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REVIEW

The Effectiveness of the Gut Microbiota Modulation on ADHD in Adults: A Systematic Review

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Abstract

Purpose of Review To critically assess the effectiveness of gut microbiota modulation (GMM) as a complementary approach for managing Attention Deficit Hyperactivity Disorder (ADHD) in adults.

Methods A systematic review was conducted following the JBI Manual for Evidence Synthesis, with searches in PubMed, Web of Science, Cochrane Database, ClinicalTrials.gov, EMBASE/Ovid, and APA PsycInfo.

Results Among 3,591 identified studies, only three randomized controlled trials met the inclusion criteria. One study reported improvements in inattention, while another found benefits in hyperactivity. Additionally, synbiotics and probiotics showed positive effects on emotional dysregulation, inflammatory markers, and gastrointestinal symptoms, reinforcing the link between gut microbiota and ADHD. However, the evidence remains inconsistent, and the studies are heterogeneous in methodology and outcomes.

Summary This review highlights the potential of GMM, particularly to enhance the management of refractory ADHD or for patients who experience significant side effects from conventional treatments. However, due to the very limited evidence, further high-quality, standardized trials are needed to determine its effectiveness, identify optimal bacterial strains and dosages, and develop more personalized treatment approaches, for better patient outcomes and functioning.

Keywords ADHD · Adults · Gut Microbiota Modulation · Probiotics · Synbiotics · Efficacy Assessment

Introduction

Attention Deficit Hyperactivity Disorder (ADHD) is a common neurodevelopmental disorder that is characterized by persistent inattention and/or hyperactivity/impulsivity [1]. While ADHD is regularly diagnosed in childhood, it is estimated that 30–60% of cases persist into adulthood [2]. However, a significant proportion of adults are not diagnosed during childhood but rather receive their diagnosis later in life [3]. In adults, the global prevalence of ADHD has increased significantly in recent years and is currently estimated to affect 3–4% of the global population [4, 5].

Despite the similarities between childhood and adult ADHD, there are important differences. In adults, hyperactivity or impulsivity tend to be less overt. When present, individuals with ADHD often report feeling fidgety or restless as a manifestation of hyperactivity, while impulsivity is more likely to appear in verbal behaviors rather than physical actions (e.g., quitting a job without having an alternative) [6]. In contrast, inattention becomes more prominent in adulthood, typically presenting as difficulty remaining focused on a task, especially over long periods, leading to challenges in time management and task completion [7]. According to the DSM- 5 diagnostic criteria, ADHD can present in different forms: predominantly inattentive, predominantly hyperactive/impulsive, or combined, and its severity can vary from person to person. It is also characterized by executive dysfunction, inattention, impulsivity, restlessness, and emotional dysregulation, all of which contribute to significant functional impairments [1, 8]. Although

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emotional dysregulation is not exclusive to ADHD, it refers to the inability to manage uncomfortable emotions when necessary and to engage in appropriate behaviors (e.g., going to work, maintaining social relationships) despite emotional discomfort, often resulting in irritability [9].

Adults with ADHD face challenges in multiple aspects of life, including educational underachievement, difficulty maintaining stable employment, an increased likelihood of criminal behavior, divorce, traffic accidents, and financial difficulties, all of which reduce their quality of life [8, 10]. In terms of life expectancy, these individuals have higher mortality rates, leading to a shorter lifespan [11]. In addition, adult ADHD often has psychiatric comorbidities, such as anxiety, mood disorders, and substance use disorders, which are present in approximately 80% of cases, complicating both diagnosis and treatment [12].

Adequate treatment is crucial to reduce the risk of comorbidities and improve functional outcomes [13]. For most adults, the first-line treatment typically involves a combination of psychostimulant medication (e.g. methylphenidate), and cognitive-behavioral therapy (CBT) targeting executive dysfunction [14–16]. Despite their positive effects, psychostimulants have limitations: they only address symptoms, without targeting underlying causes, are often prescribed for long periods, have a lack of response in up to 30% of individuals, and can cause adverse effects such as irritability, reduced appetite, and cardiovascular issues [17]. Concerns about these side effects, limited access to CBT, poor compliance, and reduced efficacy in adults with comorbidities took many individuals to seek alternative treatment options [16, 18].

Recently, the Microbiome-Gut-Brain Axis (MGBA) has gained attention as a potential target for novel ADHD interventions [19]. The gastrointestinal tract hosts a vast number of bacteria, remarkably, humans have almost as many bacterial cells as human cells [20]. Collectively, these bacteria form what is called the microbiome. Over the last decades, the microbiome has been suggested to influence our mood and behavior through the MGBA. The MGBA is a bidirectional communication between the intestinal tract and the central nervous system (CNS) [19]. Key pathways involved are the vagus nerve, the immune system, tryptophan metabolism, neurotransmitter regulation, such as dopamine, serotonin, gamma-aminobutyric (GABA), norepinephrine or acetylcholine, and the hypothalamic–pituitary–adrenal (HPA) axis, which modulates the stress response via cortisol secretion [21, 22]. Additionally, this communication is influenced by the bacterial fermentation products, the short-chain fatty acids (SCFAs) [23, 24].

Although the exact etiology of ADHD remains unclear, its development appears to be related not only to a high heritability rate (estimated at 76%) but also to several environmental risk factors, including alterations in the gut microbiome/dysbiosis [25]. Research has linked the pathophysiology of ADHD to immune and inflammatory processes, as well as to alterations in neurotransmission [26]. Supporting this, there is an increased incidence of immune-mediated conditions, such as asthma and celiac disease, in patients with ADHD [27, 28]. Additionally, studies have shown a high co-occurrence of gastrointestinal symptoms in ADHD. For instance, a recent study found a higher prevalence of irritable bowel syndrome (IBS) in a large cohort of adults with ADHD [29, 30]. Furthermore, differences in the gut microbiota composition between individuals with ADHD and neurotypical controls have been identified. Specifically, a recent meta-analysis demonstrated that adults with ADHD exhibit a higher abundance of *Ruminococcus* (associated with inflammation and hyperactivity/impulsivity symptoms) and a lower abundance of *Eubacterium xylanophilum* (associated with anti-inflammatory properties) [31]. Therefore, considering the connection between gut microbiota and ADHD, the gut microbiota modulation (GMM) may constitute a promising therapeutic approach.

According to the International Scientific Association for Probiotics and Prebiotics, probiotics are defined as "live microorganisms that, when administered in adequate amounts, confer a health benefit on the host" [23, 32, 33]. The most commonly used bacterial genera are lactic acid bacteria, primarily *Lactobacillus* and *Bifidobacterium* [33]. These "friendly bacteria" naturally inhabit the human gut and are also present in fermented foods, products made through microbial fermentation and enzymatic conversion of food components, such as yogurt, kefir, sauerkraut, miso, and tempeh [34]. Prebiotics, on the other hand, are non-digestible dietary fibers, that selectively stimulate the growth of beneficial gut bacteria [35, 36]. It is represented mainly by the oligosaccharides such as fructans (fructooligosaccharides (FOS) and inulin) commonly found in fruits and vegetables, and galactans (galactooligosaccharides or GOS) which are naturally present in human milk [23, 36]. Synbiotics combine probiotics and prebiotics to enhance their complementary effects [37].

These GMM interventions are collectively referred to as "psychobiotics," a term that has expanded to include any external influence whose impact on the brain is mediated by bacteria [38]. Psychobiotics can produce neurotransmitters, regulate immune responses, and generate SCFAs [39]. SCFAs, including butyrate, acetate, and propionate, act as messengers for MGBA, and are mainly produced by anaerobic colonic bacteria through the fermentation of dietary fibers, and they are crucial for the gut health [40, 41]. Another possible GMM is fecal microbial transplantation (FMT), which involves transferring fecal material from a healthy donor to the intestinal tract of an individual to restore gut microbiome balance [23, 42].

Recent studies and reviews have demonstrated that GMM has positive effects on ADHD-related symptoms in children [19, 34, 43–45]. For instance, an open-label trial demonstrated that an 8-week supplementation with Bifidobacterium bifidum (Bf- 688) improved inattention and hyperactivity/impulsivity symptoms in 30 children with ADHD [46]. Similarly, a long-term study by Pärtty and colleagues found that supplementation with Lactobacillus rhamnosus GC in at-risk infants (aged 3 months) reduced the incidence of an ADHD diagnosis, during a 13-year follow-up period [47].

Nevertheless, recent research, like Wang et al. emphasize the need to be cautious when extrapolating findings from pediatric to adult ADHD [48]. Although psychobiotics seem to provide some advantages for children with ADHD, it is important to note that these have not been definitively established. Consequently, the impact on both populations remains unclear and needs more investigation [49].

Previous reviews on this topic have either included multiple psychiatric diagnoses or combined children and adults within the same analysis. Moreover, many reviews have focused exclusively on specific types of psychobiotics, often limiting their scope of GMM. Although systematic reviews have been conducted on GGM in children with ADHD, there is a gap in the literature, specifically regarding adults.

To the best of our knowledge, no comprehensive review to date has focused exclusively on adults with ADHD, a population with distinct characteristics. Therefore, we intend to contribute new insights into the possibilities of complementary therapies for ADHD in adults and advance our understanding of the efficacy of GMM interventions with the potential for clinical application in the future.

This review aims to evaluate the efficacy of gut microbiota modulation (including prebiotics, probiotics, fecal microbial transplantation and short-chain fatty acids) in reducing Attention Deficit Hyperactivity Disorder (ADHD)-related symptoms in adults.

Methods

This systematic review was conducted using The JBI Manual for Evidence Synthesis [50] and PRISMA guidelines [51]. The protocol was registered in the International Prospective Register of Systematic Reviews on 8 November 2024 (PROSPERO, registration No.: CRD42024611600).

Eligibility Criteria

Type of Studies

Randomized or observational studies (cohort and case–control) were eligible for inclusion. Any publication date was considered. Studies in languages other than English, Portuguese, French, and Spanish were excluded. Only studies with human participants were included.

Population

Adult patients (≥ 18 years old) diagnosed with ADHD. ADHD was required to be defined according to the Diagnostic and Statistical Manual of Mental Disorders (DSM), the Diagnostic Interview for ADHD in Adults (DIVA 2.0), or other recognized diagnostic criteria (e.g., ICD- 10, International Classification of Diseases- 10). Clinical judgement by a psychiatrist for diagnosis confirmation was also acceptable. Studies that included both adults and children were accepted, provided they met the diagnostic criteria and reported the outcomes adapted for each age group. Studies including participants with other psychiatric conditions (such as depression or borderline personality disorder) were considered, as long as these conditions were specified and differentiated when needed. This unrestricted search approach was adopted because of the anticipated limited number of studies as the field is in its early stages.

Intervention(s)/Exposure(s)

We included studies that assessed the effects of GMM interventions, such as prebiotics, probiotics, synbiotics, psychobiotics, fecal microbial transplantation, or short-chain fatty acids. A minimum intervention duration of eight weeks was required to allow sufficient time for measurable effects.

Comparator(s)/Control

It had to be either a placebo or conventional psychiatric treatments for ADHD.

Main Outcome(s)

Studies had to include at least one symptom: inattention, hyperactivity/restlessness, impulsivity, emotional dysregulation/irritability, and executive function impairment.

Reduction of ADHD-related symptoms in adults should be assessed through validated scales, including the Wender-Fitzgerald Adult Attention Deficit Disorder Scale (WURS-25), Conners Adult ADHD Rating Scale (CAARS-S), Adult Self-Report Scale (ASRS), ADHD Rating Scale (ADHD-RS), and the Difficulties in Emotion Regulation Scale (DERS- 16). Additional tools addressing ADHD-related symptoms and associated domains were also considered, such as the Strengths and Difficulties Questionnaire (SDQ), the MOXO Continuous Performance Test (MOXO-CPT), among others.

Additional Outcome(s)

Effect on functional impairment related to ADHD symptoms, assessed through validated instruments such as: Daily functioning (Weiss Functional Impairment Rating Scale – WFIRS), general functioning (Functioning Assessment Short Test – FAST), and perceived stress levels (Perceived Stress Scale – PSS).

Search Strategy

A comprehensive electronic literature search was conducted from 15 th October 2024 until 4 th January 2025 using six bibliographic databases: PubMed, Web of Science, Cochrane Database, ClinicalTrials.gov, EMBASE/Ovid and APA PsycInfo.

A standard search strategy based on PICO elements was designed in PubMed using free-text keywords and Medical Subject Headings (MeSH) terms, with the following combination: *Attention Deficit Hyperactivity Disorder (ADHD), Attention Deficit Disorder (ADD), neurodevelopmental disorder, adults, gut microbiota modulation, psychobiotic, prebiotic, fructo-oligosaccharides, oligofructose, oligosaccharide, inulin, galactooligosaccharides, trans-galacto-oligosaccharides, probiotic, Lactobacillus, Bifidobacterium, fermented food, yogurt, kefir, sauerkraut, miso, tempeh, synbiotic, fecal microbial transplantation, short-chain fatty acids (SCFAs) and butyrate.* This is detailed further in Supplemental Table 1. This strategy was then adapted and replicated across the syntax of each database, under the guidance of the academic librarian. The complete search strategy is shown in Supplemental Table 2. The reference lists of previously published relevant systematic reviews and selected primary studies were checked, and no additional searches were performed.

Study Screening and Selection

After a systematic search of the literature, all citations were downloaded in supported formats and uploaded to Rayyan, where duplicates were removed. Then, two independent reviewers (AG and CS) proceeded to the initial screening of the titles and abstracts, separately and in "blind mode" (where neither reviewer could see the screening decisions made by the other), using Rayyan. If different data were available for the same trial, the most recent publication was considered.

The included references were then assessed for full-text screening by the two independent reviewers according to the eligibility criteria. Decisions to include or exclude studies in the review were made by consensus. When uncertainties arose, they were resolved through discussion with a third author (FN or PP). The results were displayed in the PRISMA flow diagram of the selection process.

Critical Appraisal

To assess the methodological quality of the included studies and the possibility of bias in their design, conduct and analysis, we subjected the studies to a rigorous appraisal. An independent critical appraisal was performed by the two reviewers (AG and CS), and there were no uncertainties over the retrieved studies. The risk of bias was evaluated using The JBI Critical Appraisal Checklist for Randomized Controlled Trials [52], a tool that includes 13 questions structured into two main categories: internal validity, and statistical conclusion validity. The internal validity section involves five domains: (1) bias related to the selection and allocation, (2) bias related to administration of intervention/exposure, (3) bias related to assessment, detection and measurement of the outcome, and (4) bias related to participant retention. We decided to score one point for each question rated "yes". To distinguish between low-to-moderate and high-quality studies, we established a cutoff point of 9 out of 13 questions. Any study scoring below this threshold, classified as low-to-moderate methodological quality, was excluded.

The results of the critical appraisal were presented in a traffic light plot, where "yes" responses were interpreted as "high judgement" (indicating low risk of bias), "maybe" responses as "some concerns", and "no" responses as "low judgement" (indicating high risk of bias). An overall risk of bias assessment for the entire set of included studies was also provided. The findings were also reported in a narrative form for use in the synthesis phase to critically evaluate how the methodological quality of the studies influenced the results.

Data Extraction

The same reviewers (AG and CS) independently extracted data from each report, and any discrepancies were resolved through team consensus. The JBI Mastari Data Extraction Tool for Quantitative Research [53] was used to create a standardized data extraction table, facilitating comparison and summarizing key information relevant to the research question. Extracted information included: study references, location, design and follow-up period; diagnostic and inclusion criteria; study settings, interventions (type and dosage), comparators; only the study population relevant to the PICO question (adults with ADHD), including the number of participants per arm; outcome measures for ADHD-related symptoms and additional outcomes and measures; results and limitations.

Data Synthesis

Given the heterogeneous nature of the study interventions and outcome measurements, conducting a statistical meta-analysis was not feasible. Instead, the reviewers opted for a narrative synthesis, extracting relevant information from the primary literature and qualitatively analyzing it. A descriptive analysis was also performed to summarize the results, which were presented in a data extraction table.

Results

Study Inclusion

The search of electronic databases retrieved 3591 records, 255 of which were removed as duplicates, leaving 3336 for screening. After evaluating titles and abstracts against the inclusion criteria, 6 studies were selected for full-text assessment. From this full-text analysis, 3 records were excluded: one ongoing study, one duplicate record, and one due to insufficient outcomes, as the study only assessed biological markers/SCFAs and did not include measurements of any ADHD-related symptoms. A total of 3 studies met the inclusion criteria [49, 53, 54], as shown in the PRISMA flow diagram (Fig. 1).

The included studies underwent a methodological quality assessment, revealing an overall high quality (≥ 9 for randomized controlled trials). The results of the risk of bias assessment, which examined various aspects of methodological quality such as randomization, blinding, measurement, and statistical analysis, are displayed in Table 1. The detailed answers and justifications from The JBI Critical Appraisal Checklist for Randomized Controlled Trials [52] are presented in the Supplementary Material.

In terms of internal validity, there was no evidence of bias in the participant selection and allocation (1) or intervention administration (2) in any of the included studies. However,

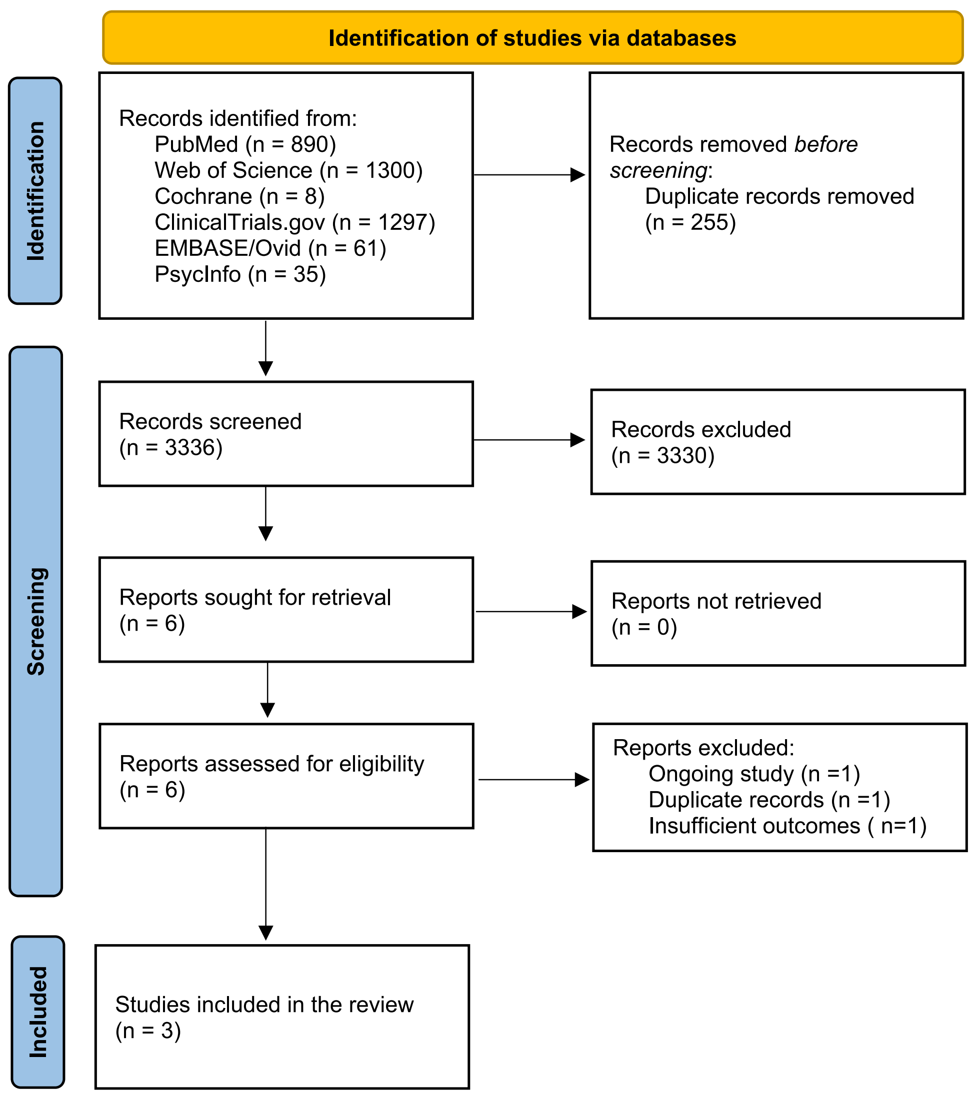

Fig. 1 PRISMA flow diagram of the selection process [55]

Table 1 Critical appraisal results for included studies using the JBI-critical appraisal checklist for randomized controlled trials presented as a traffic light plot of risk of bias [52]

Risk of bias domains

Study	D1	D2	D3	D4	D5	D6	D7	D8	D9	D10	D11	D12	D13	Overall
Schwartz et al. [55]	High	High	High	High	High	High	Low	High	Low	Some concerns	High	High	High	High
Arteaga-Henríquez et al. [56]	High	High	High	High	High	High	Low	High	Low	Some concerns	High	High	High	High
Skott et al. [51]	High	High	High	High	High	High	Some concerns	High	Some concerns	Some concerns	Some concerns	High	High	High

Domains:
(1) D1-D3: Bias related to the selection and allocation
(2) D4-D6: Bias related to administration of intervention/exposure
(3) D7-D9: Bias related to assessment, detection and measurement of the outcome
(4) D10: Bias related to participant retention
(5) D11-D13: Bias related to Statistical Conclusion Validity

Judgement:
High
Some concerns
Low

Domains:
(1) D1-D3: Bias related to the selection and allocation
(2) D4-D6: Bias related to administration of intervention/exposure
(3) D7-D9: Bias related to assessment, detection and measurement of the outcome
(4) D10: Bias related to participant retention
(5) D11-D13: Bias related to Statistical Conclusion Validity
Judgement:
High
Some concerns
Low

certain limitations were observed in the assessment, detection, and measurement of the outcomes (3). In 2 out of 3 studies [53, 54], the self-reported component of some outcome measures made full blinding impossible, resulting in a "No" answer for assessor blinding. Despite the validity of the outcome measures, this led to an unreliable outcome measurement process, partly due to the lack of information on the number of raters, their training, and other relevant details in the same two studies. The remaining study [49] did not specify whether assessors were blinded, resulting in an "Unclear" classification, which further affected confidence in the reliability of the outcome assessment. There were some concerns about participant retention (4), with 3 out of 3 studies not providing a sensitivity analysis to evaluate the impact of dropouts on the results.

Regarding the statistical conclusion validity, 1 out of 3 studies [49] was unclear, as it appears that only participants who completed the intervention were analyzed (per-protocol analysis) and it does not explicitly state whether an Intention-to-Treat (ITT) analysis was used, i.e., whether all randomized participants were included regardless of adherence. However, overall, the 3 studies applied appropriate statistical tests.

In general, the included studies demonstrated a high quality in participant selection/allocation, a high quality of intervention administration, some concerns regarding the assessment, detection, and measurement of outcomes, as well as participant retention criteria, and an overall high quality of statistical conclusion validity.

Characteristics of Included Studies

The three included studies were published between 2020 and 2024, with two from 2024 [49, 54]. Schwartz et al. [49] was set in Israel, Arteaga-Henríquez et al. [54]. in three countries, Hungary, Spain, and Germany, and the first one, Skott et al. [53], in Sweden. All included studies were prospective, double-blind, randomized, and placebo-controlled trials, with two out of three being multicenter [53, 54] and the remaining one [49] single-center.

Arteaga-Henríquez et al. [54] was considered a “basket” trial, as it evaluated the effect of the targeted therapy on a specific symptom (irritability) in two diseases with a presumably common biological background: ADHD and Borderline Personality Disorder (BPD). Two of the studies [53, 54] recruited outpatients from clinics and through advertising, whereas Schwartz et al. [49] recruited participants via institutional emails in an academic support center. They used the ADHD RS-based questionnaire (MATAL) as a diagnostic criterion, while the other studies used the DSM-5. The MATAL is a computerized didactic assessment with a standardized battery of tests commonly used in Israel and was confirmed by a psychiatrist or neurologist. Additionally, Skott et al. [53] used the ICD- 10, while Arteaga-Henríquez et al. [54] confirmed the diagnosis with the DIVA 2.0.

All studies included male and female patients aged at least 18 years, with a predominance of female participants. However, Skott et al. [53] also included children (> 5 years), but we focused only on the adult population for the descriptive analysis. They restricted inclusion to adult participants up to 55 years old, requiring stable pharmacological treatment (no changes in the last four weeks) and the ability to read Swedish, as the questionnaires were in Swedish. They also included a healthy control group, with no ADHD diagnosis, to compare the biomarkers. Schwartz et al. [49] included only non-medicated ADHD participants aged between 19 and 30 years. Arteaga-Henríquez et al. [54] included individuals with ADHD and/or BPD, aged between 18 and 65 years, with high levels of chronic irritability (i.e., ARI-S ≥ 5 + CGI-S ≥ 4, moderately ill).

Regarding the interventions, two studies [53, 54] evaluated the effect of nearly identical Synbiotic 2000 formulations, each containing a total of 4×10^{11} colony-forming units (CFU) per dose. Skott et al. [53] used a probiotic component composed of three lactic acid bacteria—*Pediococcus pentosaceus 5–33:3/16:1, Lactobacillus casei ssp. paracasei F19,* and *Lactobacillus plantarum 2362*—combined with a prebiotic component consisting of 2.5 g of each of the fermentable fibers: β-glucan, inulin, pectin, and resistant starch. Meanwhile, Arteaga-Henríquez et al. [54] used Synbiotic 2000 Forte, only with the addition of just one bacteria strain, *Leuconostoc mesenteroides 77:1*. Both studies used the same placebo—oligosaccharide maltodextrin—designed to be identical in sachet form and administered orally once daily. Participants received the same instructions to mix the powder with drinks or food (not exceeding 40 °C). Skott et al. [53] stored the sachets at − 20 °C and participants took them for 9 weeks, while Arteaga-Henríquez et al. [54] stored them at a refrigerated temperature of 4–6 °C, with a follow-up period of 10 weeks. On the other hand, Schwartz et al. [49] used a probiotic formulation containing *Lactobacillus helveticus, Bifidobacterium animalis ssp. lactis, Enterococcus faecium, Bifidobacterium longum, and Bacillus subtilis* (8×10^9 CFUs each), with a placebo composed of potato starch, magnesium stearate, and ascorbic acid. Both were administered as two capsules daily at room temperature for three months.

All studies assessed changes in ADHD-related symptoms, from baseline to end-of-trial, using different but validated scales. Two studies [49, 54] used the ADHD Rating Scale (ADHD RS), while two studies [53, 54] employed the Difficulties in Emotion Regulation Scale (DERS- 16). In addition, Schwartz et al. [49] assessed ADHD symptoms through the MOXO Continuous Performance Test (MOXO-CPT), whereas Skott et al. [53] used the Adult ADHD Self-Report Scale (ASRS). Additional outcomes varied across studies. Findings are presented by intervention type: synbiotics and probiotics, in the following subchapters.

The total sample of this systematic review comprised 300 individuals with ADHD. The range of adult age was 18 to 65 years old. The follow-up periods range from 9 to 12 weeks. The number of adult participants, after dropouts, ranged from 60 to 126, with an adequate proportion between intervention and placebo. Overall, the genera *Lactobacillus spp.* were the most used bacterial genera across the different interventions. Table 2 represents the summary of the findings.

Synbiotics and Adults ADHD

As mentioned, two studies [53, 54] investigated the effects of synbiotics. Regarding core ADHD symptoms, although Skott et al. [53] observed an improvement in inattention and hyperactivity/impulsivity based on ASRS, the effect was similar for both arms, Synbiotic 2000 and placebo (0.180; 0.174), with no statistically significant difference (95% CI: − 0.153 to 0.263 for total symptoms). However, Arteaga-Henríquez et al. [54] found significant between-group differences in inattention improvement with Synbiotic 2000 Forte, as measured by ADHD-RS (− 1.8, 95% CI: − 3.2 to − 0.4; $\eta 2p = 0.04$; $p = 0.01$), but no effect was observed on impulsivity.

Regarding emotion regulation, both studies reported positive effects, both using DERS- 16. Skott et al. [53] assessed this outcome exclusively in adults and found an improvement, particularly in goal-directed behavior (95% CI: − 2.07 to − 0.014, $\eta^2 = 0.040$). Arteaga-Henríquez et al. [54] observed significant improvements in emotion dysregulation (− 3.6, 95% CI: − 6.8 to − 0.3; $\eta 2p = 0.03$; $p = 0.03$) and emotional symptoms (Strengths and Difficulties Questionnaire-SDQ, − 0.6, 95% CI: − 1.2 to − 0.05; $\eta 2p = 0.03$; $p = 0.03$).

Irritability was another key symptom evaluated in the “basket” study, by Arteaga-Henríquez et al. [54]. They used an end-of-treatment response outcome defined as a $\geq$ 30% decrease in the Affective Reactivity Index Self-Report

Table 2 Summary of findings table

Authors and year of publication	Study Location	Study Design and duration	Diagnostic criteria	Inclusion criteria	Setting	Arms and Number of Participants per Arm (only adults with ADHD)	Outcome measures	Results	Limitations referred by the studies
Skott et al. (2020) [53]	Sweden	RCT; 9 weeks	DSM- 5 or ICD- 10	ADHD, a stable treatment (minimum of at least 4 weeks); swedish speaking/reading; aged 5–55 years;	Outpatient pshychiatric clinics in Stockholm and via advertising	**Intervention 1:** 57 Synbiotic 2000 Lactic acid bacteria: Pediococcus pentosaceus 5–33:3/16:1, Lactobacillus casei ssp paracasei F19, Lactobacillus plantarum 2362 (4 × 10^11 CFU total) + Fermentable fibers: β-glucan, inulin, pectin and resistant starch (2.5 g/dose each); 1 sachet daily **Intervention 2:** 57 Placebo: maltodextrin	**ADHD-related symptoms:** ASRS DERS- 16 **Additional outcomes:** sVCAM- 1 levels and plasma CRP WFIRS-SA (Daily functioning); FFQ (Dietary changes); Others related to children population	Equally improvement between arms (0.180, 0.174; 95% CI: − 0.153 to 0.263 for total symptoms) Improvement in symbiotic arm (95% CI: − 2.07 to − 0.014, $\eta^2 = 0.040$) Higher baseline sVCAM- 1 levels in ADHD patients (95% CI: 26,648.2 to 107,603.2 pg/mL), and associated with better results in emotion regulation (95% CI: − 17.0 to − 2.40, $\eta^2 = 0.209$). No differences in CRP levels No significant differences No significant differences	Unassessed effects on inflammatory markers and ADHD comorbidities; Absent multiple testing correction, increasing the risk for type I errors; Potential confounding from medication (49%) and dietary supplements (72%); Retrospective dietary assessment;

Table 2 (continued)

Authors and year of publication	Study Location	Study Design and duration	Diagnostic criteria	Inclusion criteria	Setting	Arms and Number of Participants per Arm (only adults with ADHD)	Outcome measures	Results	Limitations referred by the studies
Arteaga-Henríquez et al. (2024) [54]	Hungary, Spain and Germany	RCT "basket"; 10 weeks	DSM- 5 and DIVA 2.0	ADHD and/or BPD with high levels of chronic irritability (ARI-S ≥ 5 + CGI-S ≥ 4); aged 18–65 years	Outpatient clinics in three European clinical centers and via advertising	**Intervention 1:** 61 Synbiotic 2000 Forte Lactic acid bacteria: Pediococcus pentosaceus 5–33:3/16:1, Lactobacillus casei ssp paracasei F19, Lactobacillus plantarum 2362 and Leuconostoc mesenteroides 77:1 (4 × 10^11 CFU total) + Fermentable fibers: β-glucan, inulin, pectin, and resistant starch (2.5 g/dose each); 1 sachet daily **Intervention 2:** 65 Placebo: maltodextrin	**ADHD-related symptoms:** ADHD-RS DERS- 16 SDQ End-of-treatment response of irritability (ARI-S, CGI-I)	Superiority of the symbiotic group in improvement of: inattention (− 1.8, 95% CI: − 3.2 to − 0.4; η2p = 0.04; *p* = 0.01) without significant effect on impulsivity, emotion dysregulation (− 3.6, 95% CI: − 6.8 to − 0.3; η2p = 0.03; *p* = 0.03) and emotion symptoms (− 0.6, 95% CI: − 1.2 to − 0.05; η2p = 0.03; *p* = 0.03) Higher proportion of responders, 11%, in the synbiotic group (OR: 0.2, 95% CI: 0.1 to 0.7; *P* = 0.01)	High loss to follow-up, likely due to COVID-19 lockdowns; Short 10-week follow-up; Blinding not formally assessed; No healthy control; No analysis of immune or microbiota effects; Underpowered for secondary outcomes
							Additional outcomes: 72 Inflammation-related markers FAST (Global and psychological functioning); PSS (Perceived stress levels) BMI, nutrient intake IPAQ (physical activity) Body System Questionnaire (Safety)	Higher response rates associated with lower baseline RANK-L levels (OR = 0.10, 95% CI: − 4.33 to − 0.33, *p* = 0.02). In the placebo group, higher baseline IL- 17 A levels associated with improvement in emotion dysregulation, in placebo group (B = − 7.16, SE = 3.38, 95% CI: − 14.02 to − 0.31, *p* = 0.04) Improvements in the symbiotic group, particularly on peer relationship problems (− 2.7, 95% CI: − 5.2 to − 0.2; η2p = 0.03; *p* = 0.03) Reduced levels in the symbiotic group (− 0.6, 95% CI: − 1.2 to − 0.05, η2*p* = 0.03; *p* = 0.03) No differences No differences No significant differences between groups	

Table 2 (continued)

Authors and year of publication	Study Location	Study Design and duration	Diagnostic criteria	Inclusion criteria	Setting	Arms and Number of Participants per Arm (only adults with ADHD)	Outcome measures	Results	Limitations referred by the studies
Schwartz et al. (2024) [49]	Israel	RCT; 3 months	ADHD RS based questionaire (MATAL) + confirmed by a psychiatrist/ neurologist	ADHD non-medicated in students; aged 19–30 years	Students from the Tel Hai Academic College Support Center	**Intervention 1:** 30 Probiotic: L. helveticus, B. animalis ssp. lactis, Enterococcus faecium, B. longum and Bacillus subtilis (8 × 10^9 CFUs each); 2 capsules daily **Intervention 2:** 30 Placebo: potato starch, magnesium stearate and ascorbic acid	**ADHD-related symptoms:** MOXO-CPT ADHD-RS based questionaire (MATAL) **Additional outcomes:** GI symptoms (questionnaire) Cortisol levels (FCC) Academic performance (records) FFQ (Dietary intake) SSHS (sleep patterns) FEAHQ (eating and activity habits) Anthropometrics (BIA device, tape measure and calibrated scale)	Reduction in hyperactivity in the probiotic arm (− 1.0 ± 0.6 to − 0.2 ± 0.35, p = 0.012), particularly among individuals with low baseline functioning (− 1.5 ± 0.6 to − 0.4 ± 0.35, p = 0.0074). No significant changes in inattention, impulsivity Detect no significant differences Reduced gastrointestinal (GI) symptoms (p = 0.007) in probiotics arm Negative correlation between FCC and inattention, impulsivity in the probiotic group, among the "low-functioning" (rs = − 0.478, p = 0.038; rs = − 0.731, p < 0.001) Positive correlation between the average final grades and hyperactivity and impulsivity (rs = 0.554, p = 0.005; rs = 0.520, p = 0.009) No significant differences No significant differences No significant differences	Small sample size (n = 60); Low adherence (50–75%), with 12 exclusions; No formal blinding assessment; Lack of inflammatory biomarker and gut microbiome measurements

(ARI-S) total score plus a Clinical Global Impression-Improvement (CGI-I) score of 1 or 2 at week 10. The ARI-S is a self-administered questionnaire designed to evaluate irritability and has been validated for use in adult populations. The CGI-I, on the other hand, is a clinician-rated scale utilized as an effectiveness measure in clinical drug trials, assessing the improvement in a patient's overall clinical condition compared to baseline. They found that a higher proportion of responders (11%) showed a clinically meaningful improvement in irritability in the synbiotic group (OR: 0.2, 95% CI: 0.1 to 0.7; $P = 0.01$).

Concerning inflammation-related protein markers, Skott et al. [53] assessed plasma C-reactive protein (CRP) and sVCAM- 1 levels at baseline in ADHD patients and also in the healthy control group, using a sandwich immunoassay with Meso Scale Discovery (MSD). They found that ADHD patients had higher baseline sVCAM- 1 levels compared to controls (95% CI: 26,648.2 to 107,603.2 pg/mL), but no differences in CRP levels were detected. Among individuals with higher sVCAM- 1 levels, Synbiotic 2000 led to greater improvements in emotion regulation scores (95% CI: − 17.0 to − 2.40, $\eta^2 = 0.209$). Arteaga-Henríquez et al. [54], analyzed a broader panel of 72 inflammation-related markers, using Olink Target 96. The findings revealed that lower baseline RANK-L levels were significantly associated with higher treatment response rates in the synbiotic group (OR = 0.10, 95% CI: − 4.33 to − 0.33, $p = 0.02$). In the placebo group, higher baseline IL- 17 A levels were significantly associated with greater improvement in emotion dysregulation (B = − 7.16, SE = 3.38, 95% CI: − 14.02 to − 0.31, $p = 0.04$).

As for additional outcomes, Skott et al. [53] found no significant differences in daily functioning between groups (95% CI: − 0.149 to 0.085; $p > 0.05$), measured by Weiss Functional Impairment Rating Scale (WFIRS-SA). They also evaluated dietary changes using a food-frequency questionnaire, detecting no differences between baseline and follow-up, suggesting that dietary factors did not confound the results.

On the other hand, Arteaga-Henríquez et al. [54] observed improvements in global and psychological functioning (Functioning Assessment Short Test-FAST, − 2.7, 95% CI: − 5.2 to − 0.2; $\eta 2p = 0.03$; $p = 0.03$), particularly on peer relationship problems. They also reported reduced perceived stress levels (Perceived Stress Scale-PSS, − 0.6, 95% CI: − 1.2 to − 0.05, $\eta 2p = 0.03$; $p = 0.03$). Additionally, potential major alterations in BMI, nutrient intake, and physical activity (based on International Physical Activity Questionnaire-IPAQ) were assessed, but none of these factors influenced the findings. Adverse effects were evaluated as well, using a Body System Questionnaire. The most common reported effects were gastrointestinal symptoms, but no significant differences between groups were found.

Regarding Skott et al. [53], the researchers referred that the dropout rate was 34 out of 114, mainly due to loss to follow-up and discontinued intervention (disliked the powder, changed medication, or started antibiotic treatment), but the clinical characteristics of dropouts were similar to completers. Also, they identified several limitations. The CRP, sVCAM- 1 levels were only measured at baseline, so it was not possible to observe effects of the synbiotic on the inflammatory makers. Multiple testing corrections were not made, increasing the risk of type I errors. Nearly half (49%) of adults used melatonin, antipsychotics, or antidepressants, and 72% took dietary supplements (vitamins, omega- 3, probiotics), which could have influenced gut microbiota and intervention effects. Additionally, dietary intake was assessed retrospectively, limiting the detection of minor or dynamic changes over 9 weeks.

Related to Arteaga-Henríquez et al. [54], the researchers referred limitations: a high loss to follow-up, particularly in the placebo group, likely due to the study being conducted during the strictest months of the COVID- 19 pandemic in Europe, when national lockdowns were in place. Although the exact dropout rate between ADHD patients is unavailable, the characteristics were similar to the completers. Short follow-up period of 10 weeks, which may not have been sufficient to reveal long-term benefits or side effects. Blinding was not formally assessed, and a healthy control group was not included. Additionally, the study did not analyze the intervention effects on anti-inflammatory or immune parameters, nor did it confirm changes in gut microbiota composition. While multiple measures were performed, the study was underpowered for secondary outcomes, increasing the risk of Type I error.

Probiotics and Adults ADHD

As mentioned before, Schwartz et al. [49] assessed the impact of probiotics. The referred ADHD outcome measure, MOXO-CPT, is a computerized assessment tool with a high sensitivity (90%) and specificity (85%) for ADHD diagnosis. They divided participants into “normal-functioning” and “low-functioning”, based on baseline MOXO performance. The MATAL questionnaire evaluates symptom severity using ADHD RS and is commonly used in Israel for educational and psychological assessments.

Related to the core ADHD symptoms, using the MOXO-CPT, in the probiotic arm, a significant reduction in hyperactivity (− 1.0 ± 0.6 to − 0.2 ± 0.35, $p = 0.012$) was observed, particularly among individuals with low baseline functioning (− 1.5 ± 0.6 to − 0.4 ± 0.35, $p = 0.0074$). However, no significant changes were found in inattention or impulsivity.

On the other hand, the MATAL questionnaire did not detect significant differences between groups ($p > 0.05$).

Several additional outcomes were evaluated, including the long-term activity of the hypothalamic–pituitary–adrenal axis, through fingernail cortisol concentrations (FCC). Although no significant differences were found, correlation analyses revealed a negative correlation between post-intervention FCC levels and inattention and impulsivity, in the probiotic group among “low-functioning” participants (rs = − 0.478, $p = 0.038$; rs = − 0.731, $p < 0.001$, respectively). This negative correlation suggests that lower FCC levels were associated with greater reductions in these symptoms, especially with impulsivity.

It was also evaluated academic achievement. Despite showing an increase in average grades in the probiotic group, the p-value of 0.4181 and an effect size (Cohen’s d) of − 0.307 indicate that the result is not statistically significant. Correlations were also explored, and there was a significant positive correlation between average final grades and changes in hyperactivity and impulsivity (rs = 0.554, $p = 0.005$; rs = 0.520, $p = 0.009$, respectively). This suggests that high levels of improvement in hyperactivity and impulsivity are associated with higher average final grades.

No significant differences were found in dietary intake (assessed through the Food Frequency Questionnaire-FFQ), or in sleep patterns (assessed via the School Sleep Habits Survey-SSHS questionnaire), nor in eating and activity habits (evaluated using the Family Eating and Activity Habits Questionnaire-FEAHQ). Interestingly, probiotics significantly reduced gastrointestinal (GI) symptoms ($p = 0.007$), with baseline values being similar between participants, as assessed using the GI questionnaire. Anthropometrics was also evaluated, with a bioelectric impedance analysis (BIA) device, a tape measure, and a calibrated scale, and were not significantly different.

Also, a multivariate analysis predicting the Composite Benefit Score was done, and it was identified age as a significant predictor, indicating that younger participants experienced greater overall benefits from the intervention (coefficient = − 0.654, $p = 0.013$), while treatment, gender, weight, and height were not significant predictors.

The study acknowledged limitations: the small sample size of 60 college students, which restricts the ability to generalize the findings to the extended adult ADHD population; low adherence rates (e.g., 75% or 50%), with 12 participants excluded from the analysis—5 started drug treatment, and 7 failed to consume at least 80% of the supplements; there was no formal assessment of blinding; and the absence of measurements of inflammatory biomarkers or gut microbiome profiles, before and after treatment, which could have provided valuable insights into the underlying biological mechanisms.

Discussion

Summary of Findings

To the best of our knowledge, this systematic review is the first one examining the relationship between GMM exclusively in adults with ADHD.

This systematic review summarizes the findings from 3 prospective, double-blind, randomized, placebo-controlled trials, focusing on the evidence of the effectiveness of GMM interventions for ADHD in adult patients. The pharmacological interventions assessed in the included studies encompassed different agents, including synbiotics and probiotics, administered for 10,3 weeks of mean follow up.

ADHD-Core Symptoms

Our narrative synthesis suggests that synbiotics may be beneficial, as observed in both studies with the symbiotic intervention. Moreover, Arteaga-Henríquez et al. [54] reported improvements in inattention and irritability, while Skott et al. [53] found no significant effects on any core ADHD symptoms. Probiotics showed a more pronounced impact restricted to hyperactivity. However, neither study found significant effects on impulsivity. Furthermore, some findings suggest potential benefits for non-core ADHD symptoms and highlight possible associations between inflammatory markers, gastrointestinal symptoms, cortisol levels, and ADHD.

These different observed effects may be explained due to the big heterogeneity, as suggested by Schwartz et al. [49]. Primarily, the heterogeneity of the different bacterial strains used, which may have distinct effects, by targeting different neurotransmitter systems. Since the neurobiological pathophysiology of ADHD involves distinct neural pathways for each symptom, certain interventions are more likely to have a more pronounced effect on some circuits than on others [56]. For instance, some approaches may influence more directly circuits related to cognitive domains such as attention, while others may modulate motor activity associated with hyperactivity. As well as for the dosage of the interventions. Secondly, the heterogeneity in symptom assessment tools. Core ADHD symptoms were evaluated using ASRS, ADHD-RS, MOXO-CPT, and MATAL (ADHD-RS-based). It is possible that some tools were more sensitive to detecting changes in specific symptoms than others. Future studies should incorporate a large range of validated assessment tools, particularly for measuring attention and impulsivity, such as the Conners’ Adult ADHD Rating Scale (CAARS) and the Wender Utah Rating Scale (WURS- 25), which demonstrate more robust psychometric statistics and content validity, as suggested in a systematic review [57]. Another important factor is the considerable clinical heterogeneity in

ADHD itself, with different presentations, as well as different symptom severity. None of the included studies accounted for these differences. Also, individual microbiome composition could play a crucial role, as each gut microbiome is unique and may lead to a variability of treatment responses. Since baseline microbiome data was not assessed in any study, it remains unknown how it could have influenced outcomes. This emphasizes the importance of microbiome analysis before and after intervention to better understand individualized responses to gut microbiome modulation.

Bacterial Strains

The selected interventions were almost identical in symbiotic composition in the two studies [53, 54]. In the first study, Skott et al. [53] justified their choice based on their anti-infectious, anti-inflammatory properties and the ability to prevent leaky gut, since these synbiotics have shown benefits in other conditions, including critically ill patients [58].

As mentioned, the most frequently used bacteria were *Lactobacillus spp.* This genus is a typical inhabitant of the human gut and has been widely investigated for its psychobiotic effects [33]. For instance, *Lactobacillus casei* has been linked to increased colonic serotonin synthesis in mice [59], while *Lactobacillus plantarum* has been associated with reduced stress and anxiety in adults, likely through modulation of serotonin, dopamine, and norepinephrine pathways [60, 61]. These findings corroborate the gut-brain axis mechanism, particularly regarding neurotransmitter pathways.

A recent systematic review on ADHD in children [43] shows that, despite reporting heterogeneous results, the strains that showed the most consistent positive effects were *Lactobacillus rhamnosus GG* and *Lactobacillus plantarum PS128*. Additionally, *Bifidobacterium bifidum* was associated with improvements in hyperactivity/impulsivity symptoms and modulation of gut microbiota composition [46]. Similarly, a recent systematic review on psychiatric disorders, identified major depressive disorder (MDD) as the most studied condition, with the strongest evidence supporting the use of *Bifidobacterium* and *Lactobacillus* strains [34]. Given these findings, future trials in adults with ADHD could benefit from testing similar bacteria strains with a more comprehensive formulation, considering their potential therapeutic effects.

One approach that could help identify the ideal strategy for restoring a healthier gut microbiota in individuals with ADHD is to first understand the specific gut dysbiosis patterns associated with the condition, which would allow for more targeted GMM interventions. In fact, several studies have already attempted to characterize these differences. However, according to a recent review, the overall evidence remains inconsistent across studies, and has not yet confirmed any specific bacterial strains consistently linked to ADHD [62].

Another GMM we considered in our search strategy, but for which no studies met the inclusion criteria, was fecal microbiota transplantation (FMT). However, in the primary research, we found a case report on this topic, which we excluded due to its study design [63]. Still, it is worth mentioning as a potential future GMM intervention. The report provides preliminary evidence on the use of FMT in a patient with Clostridium difficile infection, which coincidentally alleviated ADHD symptoms. The authors suggested that changes in the gut microbiome, whether through the gain or loss of specific bacterial species, could play a role in ADHD and may be worth exploring as a potential treatment approach.

Other ADHD Symptoms

There is evidence that psychobiotics contribute to the improvement of non-core symptoms in various psychiatric disorders [34]. Our research observed some positive effects, especially in emotion dysregulation. Both studies that assessed this outcome reported improvements. Emotion regulation is a complex process involving the modulation of emotions to guide behavior toward goals, relying on various strategies. Its impairment is a common feature of ADHD and contributes to additional suffering in affected individuals [64]. Notably, as noted by Skott et al. [65], this symptom is not typically improved by standard stimulant treatment, which makes psychobiotics a promising option to bridge this gap. Another symptom that improved was irritability, as reported by Arteaga-Henríquez et al. [54], with robust findings. Irritability is often linked to emotion dysregulation and manifests as an increased tendency toward anger relative to peers [66, 67].

Functioning was also evaluated in both studies, but only study [54] revealed improvements. Individuals with ADHD frequently experience functional impairments, leading to significant personal and societal costs [10].

Another finding was the negative correlation between post-intervention fingernail cortisol concentrations (FCC) and core ADHD symptoms, particularly impulsivity, reported by Schwartz et al. [49]. This reinforces the role of the HPA axis as a key pathway of the MGBA, suggesting that its involvement in stress regulation and executive function may contribute to impulsivity in ADHD [22]. This study also assessed gastrointestinal symptoms, showing a positive effect in the probiotics arm. This supports the frequent co-occurrence of gastrointestinal symptoms in ADHD patients and highlights the potential of GMM interventions in alleviating these symptoms, emphasizing the connection between ADHD and gut health [29, 30].

Inflamatory Markers

Regarding inflammatory markers, they were assessed in two studies [53, 54]. However, since the evaluations were conducted only at baseline, the potential effects of synbiotics on these markers could not be observed. This was noted as a limitation in both studies.

In Skott et al. [53], sVCAM- 1 levels showed significant variations. Specifically, researchers found that ADHD patients had higher baseline sVCAM- 1 levels compared to controls. Moreover, improvements in emotion regulation were more pronounced in individuals with higher baseline sVCAM- 1 levels. This molecule is an indirect plasma marker of VCAM- 1 expression, which is predominantly expressed by endothelial cells [68].

Additionally, there is a follow-up to this clinical trial with different outcomes. However, we excluded that article due to its lack of eligibility criteria, as it did not include any measurements of ADHD-related symptoms [69]. In that study, they reported that, at baseline, adults had higher sICAM- 1 levels and lower SCFA levels compared to healthy controls. Interestingly, Synbiotic 2000 also appeared to reduce several additional pro-inflammatory markers in the adult cohort.

In Arteaga-Henríquez et al. [54] lower baseline RANK-L levels were significantly associated with a higher treatment response in the synbiotic group. RANK-L is a member of the tumor necrosis factor (TNF) family and plays a key role in immune system regulation. As noted in the study, some research suggests it may have neuroprotective effects by reducing microglial activation [70]. Besides that, they also found that higher baseline IL- 17 A levels were significantly linked to greater improvements in emotion dysregulation. This marker interacts with IL- 23, which is primarily produced by dendritic cells and macrophages. As commented by Schwartz et al. [49], research suggests that emotion dysregulation may be associated with dysfunction in the IL- 23/IL- 17 axis [71]. Also, some bacterial strains, such as *Lactobacillus casei* and *Lactobacillus plantarum*, have been suggested to reduce IL- 17 levels, though the evidence remains uncertain [72].

These findings reinforce the known anti-inflammatory properties of the Synbiotic 2000 constituents, particularly with more effect in individuals with greater dysregulation of inflammatory markers. This also connects to a key pathway of the microbiota-gut-brain axis (MGBA), the immune pathway. Beyond its potential benefits for ADHD itself, this could also be relevant for autoimmune comorbidities reported in research [27, 28]. Future studies assessing immune markers at baseline and after intervention will be crucial to clarify these relationships further.

Limitations

This systematic review faces several constraints related to both the included studies and the review process. Firstly, a small number of trials met the inclusion criteria, with only three studies, increasing the risk of spurious findings and limiting the robustness of the conclusions. Secondly, there is a possible language bias, as despite a comprehensive literature search, studies published in languages other than English, Portuguese, French, or Spanish may not have been found, introducing potential bias. Another limitation relates to methodological quality, as several aspects of study design posed risks of bias, particularly in outcome assessment, detection, and measurement. Many studies relied on self-reported assessments, which reduces reliability compared to more objective measures. Additionally, participant retention was a concern, as no trial conducted a proper sensitivity analysis to assess the impact of dropouts on results. To ensure consistently high methodological quality, only studies with a quality score of 9 or higher were included.

Heterogeneity among the included studies also posed challenges, with variations in bacterial strains, strain combinations, dosage, and follow-up duration. The rationale for strain selection was often incomplete, and in some cases, intervention durations may have been too short to induce meaningful changes in the gut microbiota and, consequently, the human brain. Currently, there is still no consensus on the optimal duration of these interventions, as this remains a relatively new field [73, 74]. However, evidence suggests that the MGBA operates slowly, meaning longer studies might yield more pronounced results [75]. Nevertheless, extended follow-up periods are likely to be associated with higher dropout rates and increased costs. Moreover, ADHD diagnosis varied across studies, using different criteria such as DSM- 5, ICD- 10, DIVA 2.0, or ADHD-RS-based questionnaires (e.g., MATAL), confirmed by a psychiatrist or neurologist, potentially introducing discrepancies.

Furthermore, the broader eligibility criterion posed another challenge, as this review did not impose strict conditions regarding comorbidities or concomitant medication use. For instance, in the first study, nearly half of the participants used melatonin, antipsychotics, or antidepressants, while the "basket" study also included individuals with borderline personality disorder, potentially influencing results given the effects of psychotropic medications and comorbidities on the gut microbiome. Additionally, some co-adjuvant treatments were not clearly reported. However, this broader inclusion criterion enhances the external validity of the findings, as ADHD is frequently associated with comorbidities, and real-world patients often take multiple medications. Lastly, publication bias remains a concern, as studies reporting positive outcomes are more likely to be published, which may lead to an overestimation of treatment efficacy.

In summary, this diversity and few articles restricted our ability to perform meaningful comparisons and meta-analysis. The limitations outlined may have influenced the results and should be carefully considered when interpreting and applying them to clinical practice.

Implications for Practice and Research

From a clinical perspective, GMM interventions could be a promising adjunctive strategy for adults with ADHD, particularly in the management of emotional dysregulation, an issue frequently observed in these patients. Additionally, GMM may contribute to functional improvement, which has both personal and societal cost implications, and potentially alleviate core ADHD symptoms. Given the limited treatment options currently available for these symptoms, our findings suggest that GMM could have meaningful clinical and therapeutic implications.

The small number of trials and their recent publication highlight the novelty of this field, while also emphasizing its potential and the need for future adequately powered studies.

Ideally, randomized controlled trials should be larger and multicenter, including only adults with a confirmed ADHD diagnosis and a comprehensive assessment of core symptoms using modern, validated, and robust tools. These studies should differentiate ADHD presentations, combined, predominantly inattentive, or hyperactive/impulsive, and consider disease severity based on DSM- 5 criteria. The therapeutic intervention should be clearly described and standardized, including detailed information on ADHD medications taken by participants. Additionally, biological markers as well as gut microbiota composition should be assessed at baseline (compared to a healthy control group) and post-intervention, to better understand underlying mechanisms. Primary outcomes should extend beyond core ADHD symptoms to include executive function and emotional dysregulation. Secondary outcomes could include gastrointestinal symptoms, cortisol levels, nutrition intake, sleep, and physical activity. Furthermore, studies should implement formal blinding checks and sensitivity analyses of dropouts to minimize the risk of bias.

Identifying the most effective bacterial strains, dosages, probiotic combinations, and the minimum effective intervention duration will be key to optimizing and standardizing GMM as a viable therapeutic strategy. Further research should also explore which ADHD subgroups stand to benefit the most from these interventions, ultimately advancing this promising approach in clinical practice.

Currently, there is one ongoing multicenter randomized double-blind placebo-controlled parallel trial (Clinicaltrials.gov identifier: NCT03495375, PROBIA) investigating the effects of Synbiotic2000 Forte on impulsivity, compulsivity, and aggression in adults with ADHD and/or BPD.

Conclusion

This systematic review highlights the potential of GMM as a complementary approach for adults with ADHD, especially for those who may not respond well to existing treatments or experience significant side effects. While preliminary findings suggest some benefits, especially in emotional dysregulation, the evidence remains highly inconsistent, and the studies are heterogeneous across various domains. Therefore, due to the very low certainty of the evidence, high-quality, standardized trials are needed to better determine the effectiveness of these interventions.

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Declarations

Human and Animal Rights and Informed Consent This article contains no studies with human or animal subjects performed by authors.

Competing interests The authors declare no competing interests.

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