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REVIEW ARTICLE

A systematic review of the beneficial effects of prebiotics, probiotics, and synbiotics on ADHD

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Abstract

Background: Children with attention deficit hyperactivity disorder (ADHD) may benefit from probiotics and prebiotics, but the effects are unclear. To determine whether probiotics and prebiotics affect children with ADHD, a systematic review was conducted.

Methods: The present systematic review analyzed cohort studies and randomized controlled trials that examined whether prebiotics and probiotics are associated with ADHD. Seven randomized controlled trials and two cohort studies met our inclusion criteria.

Results: Research on *Lactobacillus rhamnosus* GG (LGG) probiotic supplementation showed that children with ADHD had better emotional, physical, social, and school functioning, and a higher health-related quality of life compared to the placebo group.

The studies also showed that Synbiotic 2000 reduces markers of intestinal and vascular inflammation in children with ADHD, in part through increasing SCFA levels.

Conclusion: The use of probiotics and prebiotics as adjuvants therapy in patients with ADHD is beneficial. Further studies with longer duration, including more participants and a variety of age groups, and using various evaluation techniques such as in vivo observation are required to examine the effects of prebiotics and probiotics on ADHD.

KEYWORDS
ADHD, gut microbiota, prebiotics, probiotics, short-chain fatty acids (SCFA), Synbiotic

1 | INTRODUCTION

Attention deficit hyperactivity disorder (ADHD) is one of the most common neurodevelopmental disorders of childhood.[4] The behavioral symptoms of ADHD include impulsivity, inattention, and excessive movement.[6] ADHD in children is estimated to have a prevalence of 5%–6% worldwide,[8] and almost 30%–60% of these children will continue to have symptoms in adulthood.[9] Among the various factors affecting ADHD symptom severity, genetic, environmental factors, perinatal damage,[13] socioemotional condition during postnatal status,[15] and also food ingredients and micronutrients may play an important role.[16,17] Based on the theory of the "gut-brain axis," imbalances in the diversity and species of intestinal microbiota (dysbiosis) may influence the occurrence of neurodevelopmental disorders.[18,19] On the other hand, brain activity may also affect the gut microbiota environment.[20] Several studies have reported that the diversity in gut microbiota components might be related to the development of ADHD.[21]

Probiotics are live microorganisms found in fermented food products (such as yogurt, miso, or sauerkraut) or nutritional supplements that provide several health benefits to the host.[22] In addition to producing short-chain fatty acids (SCFAs) and antimicrobial compounds, probiotics as live microorganisms have a variety of effects on health including improvement of gut barrier integrity, enzyme production, and immune function.[23–25] Moreover, prebiotics are nondigestible food ingredients that act as a substrate that is selectively utilized by host microorganisms to support gut-beneficial microbes and improve the health benefits of probiotics.[26] In order to support beneficial microbes such as *Lactobacilli* and *Bifidobacteria* spp., prebiotics are required to be able to escape digestion in the upper gastrointestinal tract (GIT), be able to be fermented by the microbiota to SCFA(s), and be able to increase the abundance of bacteria which are known to be involved in human health. Good dietary sources of prebiotic carbohydrates include vegetables (including onions, garlic, and asparagus), fruits (especially bananas, apples, stone fruits, and mangos), grains, legumes, chicory, Jerusalem artichokes, soybeans, and wheat bran. Strong evidence exists that consumption of specific prebiotics benefits the GIT including inhibition of pathogens and immune stimulation, cardiometabolic support (e.g., reduction in blood lipid levels and effects upon insulin resistance), mental health benefits (e.g., metabolites that influence brain function, energy, and cognition), and bone health (e.g., mineral bioavailability).[26]

Recently, many studies have shown that manipulating the gut microbiota with probiotics and prebiotics supplementation may influence the neurodevelopmental outcomes related to ADHD symptoms and cognitive function.[27,28] Human trials found that probiotic supplementation in children with ADHD for 8 weeks could significantly reduce total ADHD rating scales (ADHD-RS).[7] According to another randomized controlled trial (RCT) study, the administration of probiotic supplementation in children aged 6–12 years with ADHD during 8 weeks considerably improved the severity and symptoms.[11] The results of another study indicated that symbiotic (combined prebiotics and probiotics) intervention improved the symptoms of ADHD, such as inattention and hyperactivity/impulsivity.[29] However, some other studies reported contradictory results. In a systematic review of randomized trials, only one of seven studies indicated a positive association between probiotic supplementation with cognitive function.[30] Another study reported no association between probiotics and gut microbiota composition.[31] To the best of our knowledge, many studies have investigated the administration of probiotic and probiotic supplementation effects in children with ADHD, whereas their results have been inconsistent. So, the present study aimed to systematically evaluate the scientific literature of randomized controlled trial studies focusing on the effect of probiotic/prebiotic interventions on ADHD in children 5–18 years.

2 | METHODS

2.1 | Search strategy

The present systematic review was carried out using Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines.[32] PubMed/MEDLINE, Scopus, EMBASE, ISI Web of Science, and Cochrane Library were searched comprehensively. In addition to searching the published literature, gray literature (ClinicalTrials.gov, Google Scholar) was also searched. The search terms described using probiotics and prebiotics in ADHD

children. Regarding PubMed, MeSH and non-MeSH terms were merged to obtain the following search strategy: "probiotics" OR "prebiotics" OR "synbiotic" AND "attention-deficit" OR "hyperactivity" OR "hyperactivity disorder" OR "ADHD" in order to avoid missing any relevant studies. In addition, we manually searched all reference lists and systematic reviews in order to find the eligible studies.

2.2 | Eligibility criteria

In this systematic review, the eligible studies were selected based on the PICO elements.[33] Clinical trials and cohort studies published in English that evaluated the effects of probiotics and prebiotics on children with ADHD were included in this systematic review. Our criteria for excluding studies were as follows: (a) studies that did not provide enough information on the outcome of interest, (b) studies with shorter than 2 weeks follow-up periods, and (c) studies conducted before 2000.

2.3 | Quality assessment of the studies

The risk of bias was assessed using the revised Cochrane risk-of-bias tool (RoB 2).[34] The following methodological domains were considered: random-sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other potential threats to validity (Table 1).

2.4 | Data extraction

For each included study, the following information was recorded: the first author's name, the publication year, the study location, the length of the study, the gender, the average age, the study design, ADHD, probiotics and prebiotics intake, and the health status of the study population. The full texts of potentially eligible articles were reviewed in order to identify relevant studies. A chief investigator (SD) attended the study selection meeting to resolve any disagreements between two researchers (PA and SAT).

3 | RESULTS

Nine studies met our inclusion criteria based on the database search. Cohorts and randomized controlled trials were included in the review to examine the associations between ADHD and probiotics and synbiotics (Table 2). Seven of the studies were randomized controlled trials (2, 4, 9, 11–13, and 16), and two were cohort studies[1,5] (Figure 1). A number of clinical studies found an association between probiotics and prebiotics with ADHD symptoms and severity.

TABLE 1 Risk of bias for randomized controlled trials, assessed according to the Revised Cochrane risk-of-bias tool for randomized trials (RoB 2).

Publications	Randomization process	Deviations from the intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported result	Overall bias
1. Anna Pärtty et al. (2015)	L	L	L	L	L	L
2 Gara Arteaga-Henríquez et al. (2020)	L	L	L	L	L	L
3. Hojka Gregoric Kumperscak et al. (2020)	L	L	L	L	L	L
4. Härtel C, Spiegler J et al. (2020)	H	L	L	L	L	H
5 Sepehrmanesh Z et al. (2021)	L	L	S	L	L	L
6 Liang-Jen Wang et al. (2022)	L	L	L	L	S	L
7 Ghanaatgar M et al. (2022)	L	L	L	L	L	L
8. Chang-Chun Wu et al. (2021)	L	L	S	L	L	L
9. Yang LL et al. (2023)	L	L	L	L	L	L

Abbreviations: H, High risk of bias; L, Low risk of bias; S, Some concerns.

TABLE 2 Characteristics of the studies on the association between ADHD with probiotics and prebiotics.

Study	Year	Country	Diagnostic criteria for ADHD	Sample size		Age	Probiotic type	Probiotic dosage	Duration of therapy	Outcome
				Probiotic	Placebo					
[1]	2015	Finland	ICD-10	40	35	13	*Lactobacillus rhamnosus*	1×10^{10}colony-forming units of *Lactobacillus rhamnosus* GG or placebo	First 6 months of life	Reduce the risk of neuropsychiatric disorder.
[2]	2020	Sweden	SNAP-IV ASRS	90	90	5–55	Synbiotic	Synbiotic 2000 daily	9 weeks	Reduction of autism symptoms in children and improved emotion regulation in adults with ADHD.
[3]	2020	Germany	The ADHD Rating Scale-IV: Home Version	18	14	4–17	*Lactobacillus rhamnosus* GG	Probiotic capsules contained the probiotic strain *Lactobacillus rhamnosus* GG (at least 10^{10} CFU)	3 months	They had better health-related QoL compared to their peers in the placebo group. This could suggest that LGG supplementation could be beneficial regarding the health-related QoL of children with ADHD.
[5]	2020	Germany	Strength and difficulties questionnaire	68		5–6	*B. infantis* and *L. acidophilus*	Daily 1 capsule $1–3\times10^{9}$ CFU L. acidophilus and $1–1.5\times10^{9}$ *B. infantis*	3 months	Reducing risk for inattention/hyperactivity and conduct problems.
[7]	2021	Iran	DSM-IV-TR	17	17	8–12	*Lactobacillus reuteri*, Lactobacillus	One probiotic sachet or placebo/day 8 weeks 8×109 CFU/day probiotic sachet with *Lactobacillus reuteri*, *Lactobacillus acidophilus*, *Lactobacillus fermentum*, and *Bifidobacterium bifidum* (each 2×10^{9})	8 weeks	Administration of probiotics in an 8-week period by children suffering ADHD could affect ADHD-RS, HAM-A, serum hs-CRP, and plasma TAC levels positively, while it neither affected CDI nor other metabolic features.
[10]	2022	Taiwan	(SNAP-IV)	30		4–16	*Bifidobacterium bifidum*	Daily bacteria count 5×10^{9}CFUs	8 weeks	Patients' inattention symptoms and hyperactivity/impulsive symptoms improved, and their weights and BMIs increased.
[11,12]	2021	Taiwan	(SNAP-IV), (CPT-2)	28	29	5–18	*Lactobacillus plantarum* PS128	One capsule 2 times a day (3×10^{10} CFU/capsule of PS128)	2 months	PS128 may be beneficial for improving the ADHD-related symptoms assessed by the SNAP-IV parent form and CPT for children with Tourette syndrome and may avoid the known side effects of taking ADHD medications.
[14]	2023	Sweden	ICD-10 DSM-5	79	75	Children and adults 5–55	Synbiotic	Synbiotic 2000 daily	9 weeks	This suggests that Synbiotic 2000, in children with ADHD, reduces markers of intestinal and vascular inflammation, the latter in part through increasing SCFA levels.

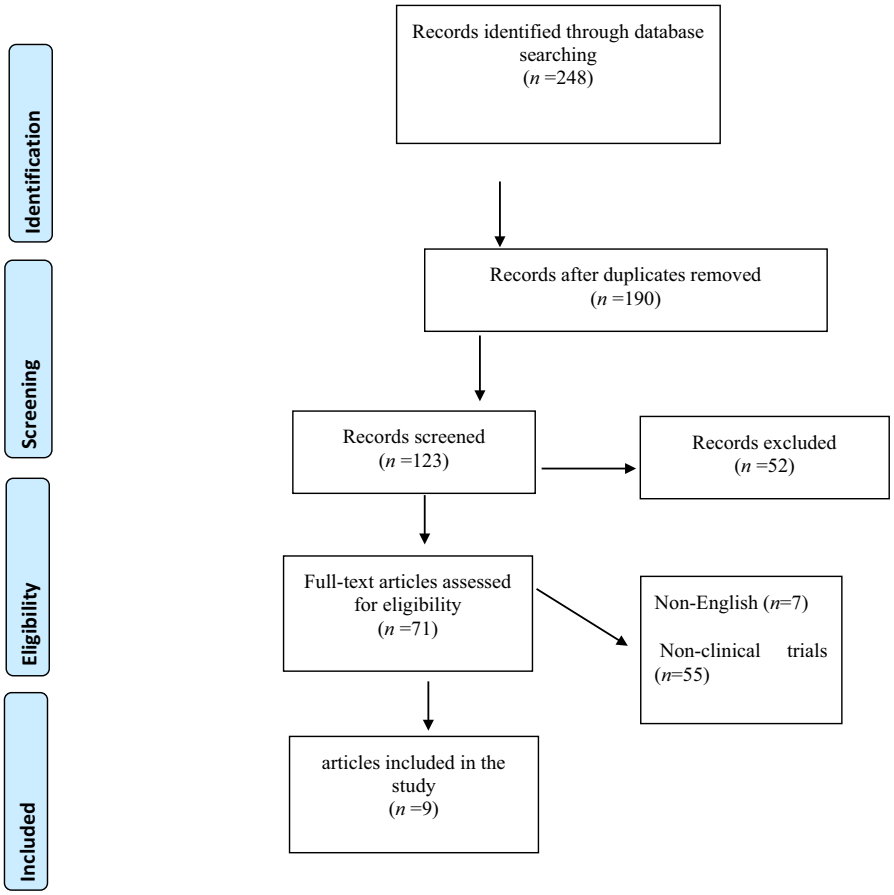

FIGURE 1 Flowchart of the included studies, including identification, screening, eligibility, and the final sample.

3.1 | Probiotics and ADHD

A total of seven studies were identified on the effect of probiotic consumption on ADHD manifestation. They consisted of clinical trials evaluating the impact of probiotics on neurocognitive and behavioral outcomes or other symptoms of ADHD. The following interventions with probiotics were considered: *Lactobacillus rhamnosus* GG ATCC53103 (LGG),[1,3] *Lactobacillus acidophilus/Bifidobacterium infantis*,[5] 8×10^9 CFU/day probiotic sachet with Lactob*acillus reuteri*, *Lactobacillus acidophilus*, *Lactobacillus fermentum*, and *Bifidobacterium bifidum* (each 2×10^9),[7] *Bifidobacterium bifidum* (Bf-688),[10] and *Lactobacillus plantarum* PS128.[11,12]

Lactobacillus rhamnosus supplementation was investigated in two studies. A study conducted by Pärtty et al. evaluated the symptoms of ADHD in a cohort of children aged 6 months to 13 years using *Lactobacillus rhamnosus* GG (ATCC 53103) or placebo and reported that ingestion of probiotics during infancy may reduce the risk of ADHD development, possibly through mechanisms other than gut microbiota composition.[1] Using 32 ADHD patients aged between 4 and 17 years, Kumperscak et al. compared daily probiotic supplementation in the form of *Lactobacillus rhamnosus* GG ATCC53103 (LGG) versus placebo for 3 months. LGG supplementation improved emotional, physical, social, and academic functioning and improved health-related quality of life for ADHD children and adolescents compared with placebos.[3] These studies showed that supplementation with LGG could benefit ADHD individuals.

The effect of breastfeeding for 3 months and prophylactic use of *Lactobacillus acidophilus* ($1–3\times10^9$ CFU) and *Bifidobacterium infantis* ($1–1.5\times10^9$) probiotics on neurocognitive and behavioral outcomes in children with very low birth weight (VLBW) from days 1 to 3 until days 14 to 35 was determined in a cohort study. Specifically, prolonged breastfeeding may lower the risks of inattention, hyperactivity, and conduct problems in highly vulnerable infants.[5]

Sepehrmanesh et al. assessed the influence of probiotic supplements on the mental health and metabolic conditions of children with ADHD. In this study, 34 subjects were randomly allocated into two groups: 17 received 8×10^9 CFU/g probiotic supplements (probiotic group), and 17 received a placebo for 8 weeks. Results showed that probiotic supplementation during an 8-week intervention in children with ADHD had positive effects on the rating scale of ADHD, hs-CRP, Hamilton Anxiety Rating Scale (HAM-A) of serum, and total antioxidant capacity (TAC) levels in plasma. Still, it neither influenced Children's Depression Inventory (CDI) nor other metabolic features.[7]

Wang et al. assessed the probiotic *Bifidobacterium bifidum* (Bf-688) (daily bacteria count 5×10^9 CFUs) on clinical characteristics and gut microbiomes among 30 ADHD children aged 4–16 years for 8 weeks. They found that children with ADHD had an increase in body weight and BMI and improved inattention symptoms as well

as hyperactivity/impulsive symptoms after taking probiotic Bf-688. Bf-688 also significantly altered gut microbiota composition. This led to a significant decrease in *Firmicutes* and *Bacteroidota*, while a significant increase in *Proteobacteria* and *Shigella*.[10]

Moreover, researchers found that probiotic supplements combined with Ritalin may reduce ADHD symptoms in children. In a recent study, 38 subjects aged 6–12 years were randomly assigned to receive either probiotics or placebos in addition to Ritalin. A probiotic supplement for 8 weeks significantly improved scores on the Clinical Global Impression–Severity Scale (CGI–S) and the Scale–short version (CPRS–RS). Prebiotics were reported to enhance ADHD symptoms and severity.[11] In another study, Wu et al. assessed the impact of probiotics *Lactobacillus plantarum* on ADHD and Tourette symptoms. In this study, 58 children aged 5 to 18 years were randomly allocated into two groups: 28 received 3×10^{10} CFU/capsule of PS128, and 29 subjects received a placebo containing only microcrystalline cellulose. SNAP-IV and Conners' continuous performance test (CPT) scores of children with Tourette syndrome improved after 2 months of taking probiotics PS128 treatment. Fifty percent of children diagnosed with ADHD have comorbid Tourette syndrome and this finding suggests probiotics as an appealing adjunctive therapy for children with ADHD.[12]

3.2 | Synbiotic and ADHD

Synbiotics supplementation and ADHD have been studied in two studies. The effects of synbiotic supplementation on 180 participants aged 18–65 with impulsive behavior and ADHD or borderline personality disorder for a period of 10 weeks were studied in a prospective, multicenter, double-blind, randomized controlled study with 180 participants. Emotion regulation was improved in patients with ADHD, according to the results.[2] Furthermore, Yang et al. conducted a double-blind randomized controlled trial of Synbiotic 2000 in children and adults with ADHD for 9 weeks to see if it affected plasma levels of immunity and inflammation markers and SCFAs. Synbiotic 2000 Forte consists of 10^{10} CFU of each of *Pediococcus pentoseceus* 5–33:3, *Leuconostoc mesenteroides* 32–77:1, *L. paracasei* ssp. *paracasei* 19, and *L. plantarum* 2362, as well as 2.5 g inulin, oat bran, pectin, and resistant starch.[35] Based on the results, Synbiotic 2000 reduces markers of inflammation in the intestine and vascular system in children with ADHD, the latter in part by increasing levels of SCFA.[14]

4 | DISCUSSION

To the researchers' knowledge, this article is the first systematic review study examining the relationship between probiotics and prebiotics in children with ADHD. A total of seven studies were identified on the effect of probiotic consumption and ADHD manifestation. Based on this systematic review, there is some evidence that confirms the impact of probiotics on neurocognitive and behavioral outcomes or symptoms of ADHD. The difference in the obtained results may be in part due to the different strains of probiotics and the dosage of the probiotic used.

However, the beneficial roles of probiotics in children with ADHD need to be further investigated by clinical research. Compared with previous studies, this study included more studies, larger sample size, less publication bias, and relatively reliable conclusions. Future studies with larger samples and longer intervention periods are needed to confirm the obtained results and to discover the underlying mechanisms of the effects of prebiotics and probiotics on patients with ADHD.

5 | CONCLUSION

ADHD in children and adolescents is reported to be associated with altered gut flora. This systematic review provides some evidence suggesting that supplementation with gut microbiota may play a role in improving ADHD symptoms. Prebiotics and probiotics are considered beneficial as adjuvant therapy because of their positive effects on the metabolic pathways involved in several psychiatric disorders. It is crucial to comprehend the function of gut microbiota in order to discover the clinical application of microbial modulation and develop microbiota-targeted treatments. Further studies with longer duration, including a more significant number of patients and a variety of age groups, and using various evaluation techniques such as in vivo observation are required to examine the effects of prebiotics and probiotics on ADHD.

AUTHOR CONTRIBUTIONS

Data collection, analysis, and manuscript drafting were performed by SD, PA, BA, ZM, MSM, MM, FA, MKM, SBS, SKH, KHAM, and HSH. This study was designed, analyzed, and critically reviewed by AH, MGH, and SD. Final approval of the manuscript was obtained from all authors.

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CONFLICT OF INTEREST STATEMENT

The authors declare that they have no competing interests.

DATA AVAILABILITY STATEMENT

Not all data are freely accessible because no informed consent was given by the participating agencies for open data sharing. However, the data are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

Not applicable.

Approval of the Research Protocol by an Institutional Reviewer Board: This study was approved by the ethics committee of Guilan University of Medical Sciences, Rasht, Iran (Code IR.GUMS.REC.1400.582).

Informed Consent: Not applicable.

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