GUTMICROBIOME

REVIEW

The gut microbiome in children with mood, anxiety, and neurodevelopmental disorders: An umbrella review

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Abstract

Research on the gut microbiome and mental health among children and adolescents is growing. This umbrella review provides a high-level overview of current evidence syntheses to amalgamate current research and inform future directions. Searches were conducted across seven databases for peer-reviewed pediatric (<18 years) review literature. Studies reporting gut microbiome composition and/or biotic supplementation on depression, bipolar disorder, anxiety, attention deficit hyperactivity disorder, autism spectrum disorder (ASD), or obsessive-compulsive disorder (OCD) were included. Deduplication and screening took place in Covidence. A sensitivity analysis was conducted to assess the degree of primary study overlap. Among the 39 included review studies, 23 (59%) were observational and 16 (41%) were interventional. Most reviews (92%) focused on ASD. Over half (56%) of the observational and interventional reviews scored low or critically low for methodological quality. A higher abundance of *Clostridium* clusters and a lower abundance of *Bifidobacterium* were consistently observed in ASD studies. Biotic supplementation was associated with ASD symptom improvement. Gut microbiome-mental health evidence syntheses in child and youth depression, anxiety, bipolar disorder, and OCD are lacking. Preliminary evidence suggests an association between specific microbiota and ASD symptoms, with some evidence supporting a role for probiotic supplementation ASD therapy.

Keywords: autism; children and adolescents; mental health; microbiome; umbrella review

Background

Worldwide, approximately 15% of children and adolescents suffer from mental health and/or neuro-developmental disorders, including anxiety, depression, bipolar disorder, obsessive-compulsive disorder

(OCD), autism spectrum disorder (ASD), and attention deficit hyperactivity disorder (ADHD), contributing to lifelong morbidity and leading mental health problems among children to be of immense public health concern (Dalsgaard et al., 2002; Fergusson et al., 2007). However, the current management of mental health disorders, including pharmacological, psychological, and/or combined approaches, has frequently yielded suboptimal response rates, underscoring the need for new treatment approaches (Holmes et al., 2018).

A growing body of evidence demonstrates that diet quality may be a modifiable risk factor for mental disorders. The gut microbiome is a leading hypothesized mechanism of the diet–mental health association as its composition is driven by dietary intake (Marx et al., 2017). Loss of beneficial microbes in the gastrointestinal tract, the emergence of pathobionts (that is bacteria that cause disease only sporadically), and gut microbiome dysbiosis may influence disease progression and/or severity (Petersen and Round, 2014). Systematic reviews of observational studies have reported consistently significant associations between decreased gut microbial diversity and greater psychopathology in adults (Sanada et al., 2020; Simpson et al., 2021). Several pathophysiological mechanisms have been hypothesized to underlie these findings and require data to either support or refute these theories. Emerging paediatric research has documented disruptions to the gut microbiome across a range of chronic health conditions, including asthma (Patrick et al., 2020; Wang et al., 2021), ASD (Iglesias-Vazquez et al., 2020), ADHD (Ligezka et al., 2021), and cystic fibrosis (Nielsen et al., 2016).

Both the gut microbiome and the brain undergo significant developmental change over the first years of life, with numerous microbiota colonizing the gastrointestinal tract while simultaneous neurodevelopmental changes take place. Research has demonstrated a link between the gut microbiome and neurodevelopment in young children, suggesting that the alpha diversity of the gut microbiome as well as the level of abundance of specific gut bacteria affect cognitive functioning at an early age (Jena et al., 2020). The microbiota–gut–brain axis, an intricate communication network between the gut microbiota, the gastrointestinal tract, and the brain, is thought to be a conduit of bidirectional communication between the gut microbiome and the brain. The gut microbiota can produce neurotransmitters and neuroactive compounds that directly influence the central nervous system through the neuroendocrine pathway (Niazi et al., 2023). Additionally, the immune pathway allows immune cells and signalling molecules to affect the brain function (Verma et al., 2022). The vagus nerve pathway acts as a major route of communication connecting the gut and the brain. This bidirectional communication system plays a crucial role in regulating physiological processes and has been implicated in influencing brain function, behaviour, and overall health. Research on the microbiome–gut–brain axis is rapidly growing and has revealed several associations between the gut microbiome and neurologic and psychiatric disorders across the lifespan (Bäckhed et al., 2015; Marx et al., 2017; Dickerson et al., 2022). While the adult microbiome is relatively stable, the microbiome of a child continues to evolve through adolescence, potentially serving as a prime opportunity for preventive intervention (Agans et al., 2011; Ringel-Kulka et al., 2013; Flannery et al., 2020). Moreover, the microbial profiles associated with adult mental health disorders may differ from those for children and adolescents.

Understanding current evidence syntheses is a necessary next step in advancing knowledge in this area of research. The rigorous application of umbrella review methodology fulfils this need as it provides a high-quality overview to guide future research. This umbrella review aims to assess current knowledge about the relationship between the gut microbiome and psychiatric disorders and opportunities for future research among children and adolescents.

Methods

A protocol was created for this umbrella review following the PRISMA extension for Protocols (Rethlefsen et al., 2021) and was registered on Open Science Framework (Campisi et al., 2022). The umbrella review was conducted using the Joanna Briggs Institute Umbrella Review guidelines

and reported following the Preferred Reporting Items for Systematic Reviews and Meta-analyses (Aromataris et al., 2015).

Search methodology

The database search strategies were developed by two academic health sciences librarians (K.M. and G.B.R.) and peer-reviewed by an independent librarian following the Peer Review of Electronic Search Strategies for systematic review guidelines (McGowan et al., 2016). The search strategy was developed in Ovid Medline and translated into each database using that platform's command language, including text words, controlled vocabulary, and subject headings when possible. Searches include articles published up until February 2023. The following databases were searched: Child Development and Adolescent Studies (EBSCOhost), Ovid MEDLINE (1946 to present including Epub ahead of print, in-process, and other non-indexed citations), Ovid EMBASE (1947 to present), Ovid APA PsycINFO (1806 to present), EBSCO CINAHL Plus with Full Text (1981 to present), Scopus (Elsevier), and the Cochrane CENTRAL. A modified version of the CADTH SR / MA / HTA / ITC filter was used in the Ovid Medline and Ovid Embase search strategies (CADTH, 2023). Full search strategies can be found in Supplementary Table S1.

Inclusion and exclusion criteria

Review articles were considered eligible if they (1) examined a paediatric population (<18 years of age); (2) included participants with a diagnosis of depression, anxiety, bipolar disorder, ADHD, ASD, or OCD; (3) ensured participants did not have comorbid chronic medical conditions; (4) reported the association between the gut microbiome (i.e. alpha diversity, beta diversity, relative abundances of clusters of DNA or RNA fragment sequences commonly called operational taxonomic units [OTUs]) and mental health disorder or the effect of gut microbiome-targeted treatments (e.g. prebiotic, probiotic, and synbiotic supplementation) on symptoms of mental health disorder with or without the resulting gut microbiome composition changes, in terms of OUT abundance; (5) were peer-reviewed; and (6) were systematic reviews (observational or interventional studies). No limits were imposed on the publication date of records, geographical location, sociodemographic factors, or setting. Primary research, animal studies, narrative reviews, conference abstracts, comments, opinions, letters, and editorials were excluded. Due to the limited capacity within the study for a translator, seven non-English records were excluded.

Study selection and data collection

Deduplication of the search results took place in Covidence online software (Covidence Systematic Review Software, 2023). Screening of all references generated by the database searches occurred independently by four authors (K.R., T.Z., S.C.C., and A.S.) in a two-step process: title and abstract screening were followed by full-text screening. Discrepancies were resolved via discussion with a third author (K.R. or T.Z.). The data extraction template was pilot tested on five included systematic reviews. The following items were extracted: title, author, year, journal, mental health disorder, study review type, date range of studies included in each systematic review, number of studies in the review, sample size, age range, type of intervention and the intervention details (duration of intervention, frequency, timing, and method of intervention delivery, presence of a control group), human gut microbiota data (sequencing platform, relative abundance, richness, alpha and beta diversity), and mental health outcome data (diagnostic tool to assess mental health symptoms, symptom severity/impact). All extracted data were verified by SCC and/or AS.

Methodological quality evaluation

A MeaSurement Tool to Assess Systematic Reviews version 2 (AMSTAR-2) was used to assess the quality of the included systematic reviews and meta-analyses (Shea et al., 2017). Quality assessment was performed in duplicate (A.S. and C.Z.) and compared to ensure inter-rater reliability. Further details about individual AMSTAR-2 checklist items can be found in Supplementary Figure S1 (Shea et al., 2017). Each item on the AMSTAR-2 checklist was answered with "yes," "no," "partial yes,", or "no meta-analysis conducted"; however, only the "yes" answer counted as a point towards the total score for the assessed review. Based on the total point scores, systematic reviews and meta-analyses were categorized as *high-quality*, *moderate-quality, low-quality*, or *critically low-quality* reviews using previously established definitions (Shea et al., 2017).

Taxonomic evidence synthesis

Due to significant heterogeneity among the included systematic reviews, the findings are reported for OTUs that consistently exhibited an association or demonstrated efficacy across multiple reviews concerning mental health disorders. By focusing on the OTUs that demonstrated consistent patterns across the reviewed literature, we aimed to highlight robust signals of these particular associations or efficacies. Results are presented with phylogenetic trees and counts of OTUs reported in systematic reviews. Phylogenetic trees were created using the 'ape' package in R (Paradis et al., 2019).

Sensitivity analysis: overlap minimization

A sensitivity analysis was carried out to examine whether the strength of observed signals between mental health disorders and gut OTUs, as well as the effectiveness of prebiotic/probiotic supplementation in treating mental health disorders, were influenced by the inclusion of the same primary studies in multiple systematic reviews. This issue is particularly relevant in umbrella reviews, as the degree of overlap or inclusion of the same primary study in multiple systematic reviews can potentially introduce bias and affect the accuracy of the findings (Pieper et al., 2014).

Overlap minimization followed a multi-step procedure to align the primary studies with the current umbrella review's inclusion criteria. Initially, the primary studies were assessed to determine their alignment with our predefined inclusion criteria, excluding any studies that did not meet the criteria for inclusion. Next, the degree of overlap in primary studies was calculated using the corrected covered area (CCA) formula: $(N - r)/(rc - r)$, where N represents the number of included primary studies accounting for double counting, r is the number of index publications, and c is the number of included systematic reviews (Hennessy and Johnson, 2020). A CCA within the range of 0%–5% indicates a slight overlap, 6%–10% suggests a moderate overlap, 11%–15% indicates a high overlap, and > 15% shows a very high overlap (Hennessy and Johnson, 2020). We generated a CCA and an overlap matrix for observational and interventional systematic reviews separately with the use of the Graphical Representation of Overlap for OVErviews tool (GROOVE) (Pérez-Bracchiglione et al., 2022; Gosling et al., 2023). Whenever possible, higher quality reviews were given priority for retention. To minimize overlap and improve the CCA, systematic reviews with a primary study overlap exceeding 25% were identified, and the review with fewer primary studies was eliminated, prioritizing the retention of higher quality reviews whenever feasible (Lipsey and Wilson 2001, Lunny et al., 2018). The systematic reviews that remained after the overlap optimization were included in the taxonomic evidence sensitivity analysis.

Results

The database searches yielded 2,099 potential records for this umbrella review following the removal of duplicates (Figure 1). Among the 39 included review studies, 23 (59%) were observational and 16 (41%) were interventional. Of the included reviews, 36 (92%) examined ASD, 6 (15%) examined ADHD, 1 (3%)
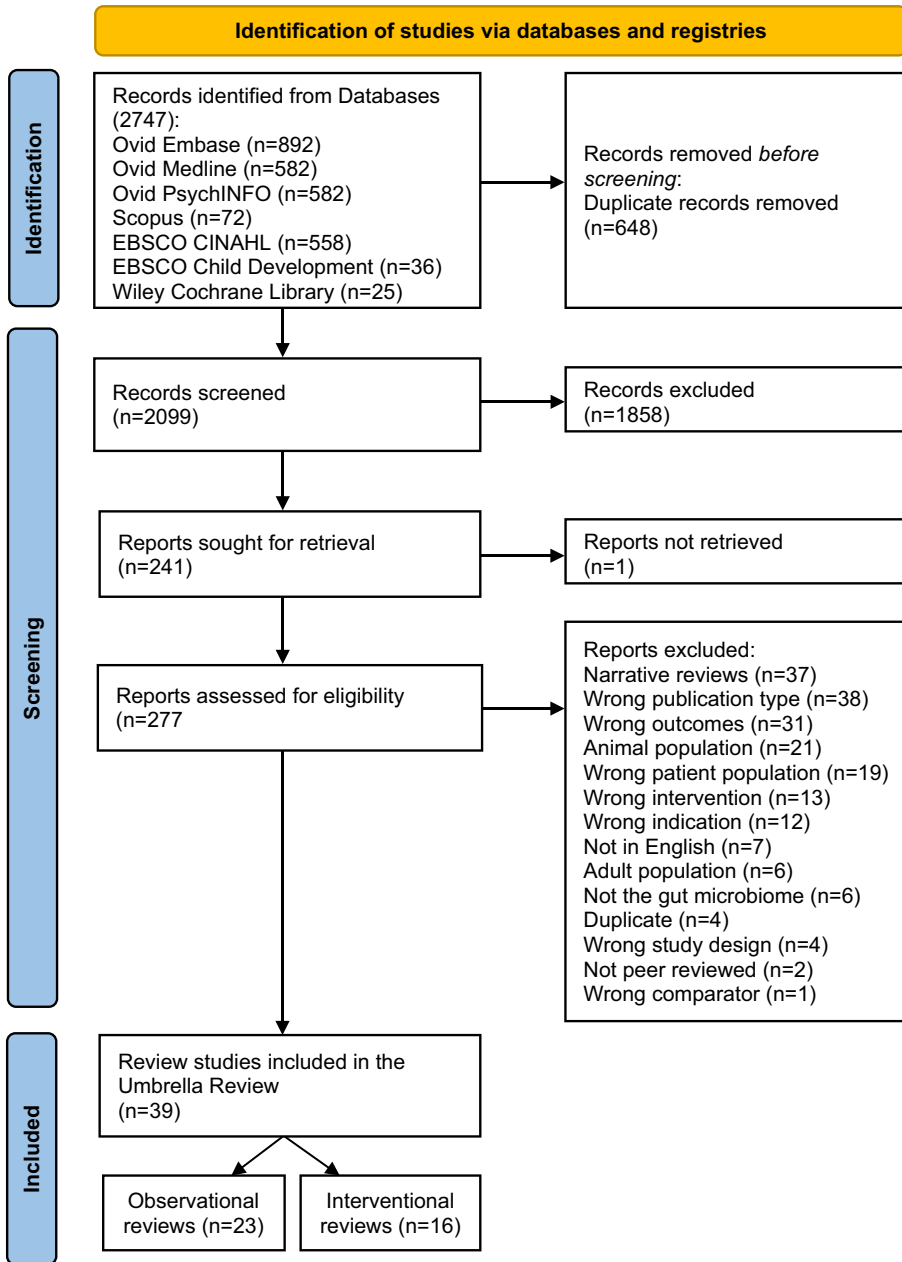
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Figure 1. PRISMA flowchart.

examined depression, 1 (3%) examined anxiety, and no reviews examined OCD or bipolar disorder [Note: totals add to more than 100% as some reviews examined more than one disorder]. The publication date for the included review studies ranged from 2013 to 2023, with 31 (80%) published between 2020 and 2023. There was significant heterogeneity among the included primary studies regarding demographics (participant characteristics, age range, sex), methodological reporting (stool collection, storage and sequencing approach that is 16S rRNA or shotgun metagenomics), statistical reporting (library preparation that is collection of DNA fragments for sequencing, choice of sequencing platform), and

intervention parameters (prebiotic or probiotic combination trialled, intervention duration). Review study characteristics can be found in Supplementary Tables S2, S3 and Table 1.

Methodological quality assessment

Methodological quality assessment was performed for observational and interventional systematic reviews. Among observational systematic reviews (n = 23), two scored in the high-quality range, eight scored in the moderate-quality range, three scored in the low-quality range, and 10 reviews scored in the critically low-quality range. Interventional systematic reviews and meta-analyses (n = 16) included seven reviews of moderate quality, two of low quality, and seven of critically low quality, using AMSTAR-2 evaluation guidelines. Several criteria of the AMSTAR-2 checklist were under-reported in the included reviews, leading to the heterogeneous outcome of the quality assessment. In detail, none of the reviews reported on the sources of funding for the included studies. Only one review (3%) provided a list of excluded primary studies, and similarly, only one review (3%) used a comprehensive literature search strategy. Furthermore, only 7 (18%) reviews had described their review methods in advance via study registration. Adequate detail regarding the included studies was described in only 9 (23%) reviews. The assessment of the risk of bias was adequately performed in 21 (54%) reviews, and 20 (51%) reviews took into consideration the risk of bias in primary outcomes when discussing the results. No systematic reviews were eliminated from further synthesis based on methodological quality since this was not one of the a priori exclusion criteria. Further detail regarding the quality assessment of individual reviews is presented in Supplementary Table S4.

Gut microbiome taxonomic evidence synthesis

Very few reviews examined the richness and diversity between the gut microbiome and mental health disorders in children. Therefore, it was not feasible to include these findings in the evidence synthesis. As a result, the focus of this umbrella review is on reported OTUs.

Observational systematic reviews – ASD

Among the 23 observational systematic reviews, there were consistent findings regarding the increased relative abundance of certain OTUs in youth with ASD. The most commonly reported OTUs across the reviews were *Clostridium clusters, Candida, Dorea, Roseburia, Bacteroides, Oscillospira, Ruminococcus, Barnesiella, Desulfovibrio*, and *Lactobacillus.*

On the other hand, a decreased abundance of specific OTUs was repeatedly observed in youth with ASD. These OTUs included *Bifidobacterium, Prevotella, Dialister, Veillonella, Escherichia, Fusobacterium, Streptococcus*, and *Coprococcus.*

It is worth noting that the remaining OTUs were only reported in one review, suggesting limited evidence regarding their association with ASD. Figures 2 and 3 offer a comprehensive overview of the OTUs reported in the observational systematic reviews for ASD and ADHD, including the specific studies that reported them and the corresponding patterns of increased or decreased abundance.

Observational systematic reviews – ADHD

Only two reviews reported an abundance of OTUs in youth with ADHD. Observational reviews consistently reported an increase in the relative abundance of OTUs belonging to the *Bacteroides* genus in youth with ADHD. On the other hand, a consistent decrease in the relative abundance of certain OTUs belonging to the *Faecalibacterium* genus was reported in observational reviews in youth with ADHD. The remaining OTUs were only reported in one review, suggesting limited evidence regarding their association with ADHD (Figure 2).

Table 1. Summary of prebiotic, probiotic, and synbiotic interventions along with reported gut microbiome and mental health outcomes among the interventional reviews (*n* = 16).

Review	Intervention			Outcome	
	Biotic	Duration/dosage	Supplement	Gut microbiome	Mental health
Autism					
Alvares et al. (2021)	Probiotic	1 month Not reported	*Lactobacillus plantarum*	Not reported	• Reduction of the total scores of Social Responsiveness Scale (SRS) (*p* = 0.04) and Swanson, Nolan and Pelham (SNAP) questionnaire version IV (SNAP-IV) (*p* = 0.02) • Improvement in anxiety and rule-breaking behaviours (*p* = 0.02) in Child Behavior Checklist • Improvement with body and object use (*p* = 0.04) in the Autism Behavior Checklist–Taiwan • Improvement in hyperactivity and impulsivity (*p* = 0.04) using Version IV, adapted for Brazil
Amadi et al. (2022)	Probiotic	3 months Not reported	*Bifidobacterium longum, Lactobacillus acidophilus, Lactobacillus rhamnosus*	Increased Bifidobacteria, Lactobacilli	• Improved behavioural pattern using Autism Treatment Evaluation Checklist
	Probiotic	4 months Not reported	3 *Lactobacillus* strains, 2 *Bifidobacterium* strains, 1 *Streptococcus* strain (species not reported)	Decreased the level of Desulfovibrio spp., Bifidobacteria, and also normalized the Bacteroidetes/Firmicutes ratio	• Beneficial effects were seen (tool unspecified)
	Probiotic	1–3 months Not reported	*L. plantarum*	Increased lactobacillus and enterococcus Decreased Clostridium cluster	• Improved behavioural pattern as well as improved total score of SNAP-IV and improvement in Total Behaviour Problem Score
	Prebiotics–	6 weeks Not reported	Galactooligosaccharide	Increased *Faecalibacterium prausnitzii*, Bacteroides spp. Decreased	• Improved anti-social behaviour (tool unspecified)

Table 1. *Continued*

Review	Intervention			Outcome	
	Biotic	Duration/dosage	Supplement	Gut microbiome	Mental health
Autism					
				Bifidobacterium spp., Veillonellaceae	
	Prebiotics–	2 months Not reported	Hydrolyzed guar gum	Not reported	• Improved behavioural irritability as per Autism Behaviour Checklist (ABC), Japanese Version
	Synbiotic	3 months Not reported	*Bifidobacterium infantis* + Bovine colostrum product	Improved gut microbiota	• Improved ASD behaviour gut microbiota
Brzóska-Konkol et al. (2022)	Probiotic	Not reported	*B. longum, L. acidophilus, Enterococcus faecalis*	Not reported	• Lower symptom severity on the Autism Treatment Evaluation Checklist scale
	Probiotic	5 weeks Not reported	*B. infantis*	Not reported	• Improved Aberrant Behavior Checklist
	Probiotic	3 weeks Not reported	*L. plantarum*	Not reported	• Lower symptom severity on the Autism Treatment Evaluation Checklist questionnaire
Vargas and Rodríguez (2022)	Prebiotic	12 weeks 0.15 g/lb of weight/day	*B. infantis* + Bovine colostrum product	Not reported	• Reduction in irritability ($p = 0.003$), stereotypy ($p = 0.006$), hyperactivity ($p = 0.007$), and total scores ($p = 0.006$), along with a trend toward a significant reduction in lethargy ($p = 0.076$) on the Aberrant Behavior Scales
	Probiotic	10 weeks Not reported	Galactooligosaccharide (GOS)	Not reported	• Improvements in anti-social behaviour of the Autism Treatment Evaluation Checklist questionnaire ($p = 0.05$)
	Probiotic	4 weeks 425 +/− 25 mg	*Bifidobacterium fragilis*	Not reported	• Reduced hyperactivity and impulsivity ($p = 0.04$), opposition and defiance ($p = 0.045$)

Table 1. *Continued*

	Intervention			Outcome	
Review	Biotic	Duration/dosage	Supplement	Gut microbiome	Mental health
Autism					
Lasheras et al. (2021)	Probiotic	3 weeks 4.5×10^{10} CFU/g	*L. plantarum*	Increased lactobacilli and enterococci, Decreased Clostridium clusters	• Lower overall behavioural/emotional disturbances scores. Scores for disruptive behaviour, anxiety, self-absorbed behaviour, and communication disturbances were lower than baseline during probiotic feeding
	Probiotic	4 months Not reported	3 *Lactobacillus* strains, 2 *Bifidobacterium* strains, 1 *Streptococcus* strain (species not reported)	Decrease in Firmicutes, which results in the increase of the Bacteroidetes/Firmicutes ratio to the level of healthy individuals. Levelling of the amount of Bifidobacterium, high in ASD children at baseline, to that of healthy controls. Increased Lactobacillus Decreased Candida, Desulfovibrio, Clostridia, Bifidobacterium, Candida	• Beneficial effects were seen (tool unspecified)
	Probiotic	2 months 11.5×10^9 CFU/g) twice a day	*L. acidophilus*	Not reported	• Improvement in concentration and ability to carry out orders on probiotic therapy
	Probiotic	1 month Not reported	*Bifidobacterium animalis*	Not reported	• Decrease in Autism Behaviour Checklist mean values after two therapeutic course treatments. Amelioration of

Table 1. *Continued*

Review	Biotic	Duration/dosage	Supplement	Gut microbiome	Mental health
		Intervention		**Outcome**	
Autism					
					communication and eye contact in 90% of ASD children, but no improvement in stereotyped behaviour
Ligezka et al. (2021)	Prebiotic	10 weeks Not reported	Galactooligosaccharide	Increased Clostridium clusters Decreased Bifidobacteria	• Improvement in anti-social behaviour (tool unspecified)
	Probiotic	5 weeks Not reported	*B. infantis*	Not reported	• Decreased score for certain aberrant behaviours based on the ABS questionnaire: irritability ($p = 0.003$), stereotypy ($p = 0.006$), hyperactivity ($p = 0.007$)
Martinez-Gonzalez and Andreo-Martinez (2020)	Probiotic	2 months 4.5×10^{10} CFU by capsule daily	*L. plantarum*	Increased Lactobacillus, Bifidobacterium	• No statistically significant effect on emotional symptoms
	Prebiotic	6 months 1.8 g: 80% GOS content	Galactooligosaccharide	Decreased Bifidobacterium spp and Veillonellaceae Increased *F. prausnitzii* and Bacteroides spp.	• Improvements in anti-social behaviour ($p < 0.05$) (tool unspecified)
	Probiotic	3 months 5 g/day; each gram contains 100×10^6 CFU	*B. longum, L. acidophilus, L. rhamnosus*	Increased Bifidobacterium and Lactobacillum	• Improvements in severity of autism ($p = 0.0001$) (tool unspecified)
	Probiotic	12 months 20 thousand million CFU/day	*B. infantis*	Not reported	• Reduced occurrence of aberrant behaviour (tool unspecified)
	Probiotic	4 months 900 thousand million bacteria/half pack in powder packs. Half pack/twice a day	*Bifidobacterium breve, B. infantis, B. longum, L. acidophilus, Lactobacillus casei, Lactobacillus delbrueckii subsp.*	Not reported	• Improvement in anxiety (tool unspecified)

Table 1. *Continued*

Review	Biotic	Intervention			Outcome	
		Duration/dosage	Supplement		Gut microbiome	Mental health
Autism						
		for the first 4 weeks. Full pack/twice a day if no effect observed at medical check at 4 weeks and 15 weeks.	*Bulgaricus, L. plantarum, Streptococcus thermophilus*			
	Probiotic	1 month 3×10^{10} CFU/capsule with microcrystalline cellulose/day	*L. plantarum*		Not reported	• A trend towards a reduction in body and object use scores ($p = 0.04$); SRS–total score ($p = 0.04$), anxiety ($p = 0.02$), hyperactivity and impulsivity ($p = 0.04$), and defiance ($p = 0.045$). (tool unspecified)
	Prebiotic	Not reported 6 g daily	Partially hydrolyzed guar gum		Increased Blautia and Acidaminococcus Decreased Streptococcus, Odoribacter, and Eubacterium	• Reduction in irritability symptoms (tool unspecified)
Mitchell and Davies (2021)	Synbiotic	108 days 10^{10} CFU/pack/day	*B. infantis, Bifidobacterium lactis, Lactobacillus paracasei L. rhamnosus* + Fructooligosaccharide		Decreased Ruminococcus and Clostridium	• Reduction in ASD severity (tool unspecified)
	Probiotic	21 days 1×10^8 CFUs 3x /day	*L. acidophilus, L. casei, L. delbrueckii, Bifidobacterium bifidum, B. longum*		Increased Bifidobacteria and Lactobacillus	• Reduction in ASD severity (tool unspecified)
	Probiotic	6 months 450 billion CFU/pack 2 packets/day in the first month; 1 packet/day for the following 5 months	*B. breve, B. infantis, B. longum, L. acidophilus, L. delbrueckii subsp. Bulgaricus, L. paracasei, L. plantarum, Streptococcus thermophiles*		No shift in gut microbiome diversity or family level composition of species	• Improved adaptive skills (repetitive, $p = 0.0104$; domestic, $p = 0.047$; coping skills, $p = 0.0115$). • Normalization of sensory profile scores

Table 1. *Continued*

Review	Biotic	Duration/dosage	Supplement	Gut microbiome	Mental health
		Intervention		**Outcome**	
Autism					
	Probiotic	2 months 5×10^9 CFU/g twice daily	*L. acidophilus*	Increased Lactobacillus, Enterococcus Decreased desulfovibrio, Clostridium clusters	• Improved some ASD symptoms (concentration and ability to follow instructions)
	Prebiotic	8 weeks Not reported	Galactooligosaccharide	Increased Bifidobacterium	• Improved ASD behaviour
	Synbiotic	12 weeks BCP — 0.15 g/lb body weight/day *B. infantis* — 2×10^9 CFU/day	*B. infantis* + Bovine colostrum product	Increased Bifidobacterium Decreased Ruminococcus, Clostridium	• Decreased total aberrant behaviour scores
Ng et al. (2019)	Probiotic	1 month Not reported	*L. acidophilus*	Not reported	• Significant improvement in the ability to concentrate and carry out orders
	Probiotic	3 weeks Not reported	*L. plantarum*	Decreased Clostridium	• No major differences in behaviour (Developmental Behaviour Checklist scores)
	Probiotic	3 months Not reported	*Bifidobacteria longum,* *L. acidophilus,* *L. rhamnosus*	Increased Bifidobacteria	• Improved behaviour after probiotics Autism Treatment Evaluation Checklist scores
	Probiotic	3 months Not reported	3 strains of *Lactobacillus*, 2 strains of *Bifidobacteria*, 1 strain of *Streptococcus* (species not reported)	Decreased Bifidobacteria and Lactobacillus	• Decreased ASD severity
Nogay and Nahikian-Nelms (2022)	Probiotic	3 weeks Not reported	*L. plantarum*	Not reported	• No effects on behavioural problems
	Probiotic	4 weeks Not reported	*L. plantarum*	Not reported	• Improved opposition/defiance behaviour, and it did so even more for the younger children than for the older ones

Table 1. *Continued*

Review	Intervention			Outcome	
	Biotic	Duration/dosage	Supplement	Gut microbiome	Mental health
Autism					
Patel et al. (2022)	Probiotic	Not reported	*L. plantarum*	Not reported	• Beneficial effects were seen (tool unspecified)
Prosperi et al. (2022)	Probiotic	2 months 5×10^9 CFU/g^2/day	*L. acidophilus*	Not reported	• Improvement in the ability to concentrate and carry out orders; no difference in reacting to other people's emotions or using eye contact
Prosperi et al. (2022)	Probiotic	3 weeks 4.5 × 1010 CFU/day	*L. plantarum*	Increased Lactobacillus, Enterococci Decreased *Clostridium coccoides*	• Improvement of the anti-social behaviours, anxiety, and communication problems
	Prebiotic	6 months 1.8 g in powder (unknown frequency)	Galactooligosaccharide	Increased Lachnospiraceae	• Improvements in anti-social behaviour
	Synbiotic	3 months 1 g = 100 × 106 CFU for each species 5 g/day	*B. longum, L. acidophilus, L. rhamnosus* + Dried carrot	Increased Bifidobacterium and Lactobacillus	• Significant improvements in ASD severity using Autism Treatment Evaluation Checklist
	Prebiotic	2–15 months 6 g/day	Partially hydrolyzed guar gum	Not reported	• Significant decrease in irritability
	Probiotic	1 month 6 g/day (36 billion CFU in total)	*B. bifidum, B. infantis, B. longum, L. acidophilus, Lactobacillus bulgaricus, L. casei*	Not reported	• Decrease in anxiety, hyperactivity, and opposition/defiance behaviours; no change in ASD symptoms
	Synbiotic	1, 2, or 3.6 months 10^{10} CFU/pack/day	*B. infantis, B. lactis, L. paracasei, L. rhamnosus* + Fructooligosaccharide	Not reported	• Decrease in total and subdomain Autism Treatment Evaluation Checklist scores
	Probiotic	6 months 3×10^{10} CFU if weight < 30 kg,	*L. plantarum*	Not reported	• Increased level of shared attention, decreased stereotyped movements,

Table 1. *Continued*

Review	Intervention			Outcome	
	Biotic	Duration/dosage	Supplement	Gut microbiome	Mental health
Autism					
		6×10^{10} CFU if weight > 30 kg			communication skills, and personal autonomy
Tan et al. (2021)	Probiotic	4 weeks 6 g/day (36 billion CFU in total)	B. bifidum, B. infantis, B. longum, L. acidophilus, L. bulgaricus, L. casei	Not reported	• Decrease in total and subdomain Autism Treatment Evaluation Checklist scores
	Probiotic	3 months 5 g/day (containing 0.5 billion CFU)	B. longum, L. acidophilus, L. rhamnosus	Not reported	• Decrease in total and subdomain Autism Treatment Evaluation Checklist scores
	Probiotic	6 weeks 20 billion CFU in total/ day	Bifidobacterium ongum, L. paracasei, L. rhamnosus	Not reported	• Decrease in total and subdomain Autism Treatment Evaluation Checklist scores
	Probiotic	3 weeks 450 billion CFU/ pack 2 packets/day in the first month; 1 packet/day for the following 5 months	B. bifidum, B. longum, L. acidophilus, L. casei, Lactobacillus delbruecki	Not reported	• Decrease in total and subdomain Autism Treatment Evaluation Checklist scores
	Prebiotic	2–15 months 6 g/day	Galactooligosaccharide	Not reported	• Decrease in autism behaviour checklist scores
	Prebiotic	6 weeks 1.8 g: 80% GOS content	Galactooligosaccharide	Not reported	• Decrease in Autism Treatment Evaluation Checklist scores, anti-sociability
	Probiotic	1, 2, or 3.6 months Not reported	B. infantis, B. lactis, L. paracasei, L. rhamnosus	Not reported	• Decrease in total and subdomain Autism Treatment Evaluation Checklist scores
	Probiotic	5 weeks 20 billion CFU/day	Bifidobacterium longum infantis	Not reported	• Decrease in autism behaviour checklist scores

Table 1. *Continued*

| Review	Biotic	Intervention		Outcome	
		Duration/dosage	Supplement	Gut microbiome	Mental health
Autism					
Yang et al. (2020)	Probiotic	3 weeks to 6 months 1 capsule 3imes a day (specific dose not reported)	*Bifidobacterium,* *Lactobacillus,* *Streptococcus* (species not reported)	Increased Bifidobacterium, Lactobacillus, Enterococcus Decreased Firmicutes, Desulfovibrio, Clostridium	• Improved ASD behaviour (tool unspeci-fied)
	Prebiotic	4–6 weeks 6 g/day	Galactooligosaccharide; Hydrolyzed guar gum	Increased *B. longum*	• Improved ASD behaviour (tool unspeci-fied)
	Synbiotic	3–4 months 10^{10} CFU/pack/day	*B. infantis, B. lactis,* *L. paracasei,* *L. rhamnosus* + Fructooligosaccharide; *B. infantis* + Bovine colostrum product	Increased *B. longum*, Bifidobacteriales Decreased Clostridium	• Improved ASD behaviour (tool unspeci-fied)
Basso et al. (2022)	Probiotic	1 month Varied: 50×10^9 CFU/ day; 15×10^9 CFU/ day; 10×10^9 CFU/ day	Multi-strains (unspecified)	Not reported	• Decreased worrying measured by the Penn State Worry Questionnaire
	Prebiotics	21 days 5500 mg/ day	Galactooligosaccharide	Not reported	• Decreased attentional bias towards negative emotion stimuli
	Prebiotics	8 days 205 mg nine times/day	Fermented ginseng	Not reported	• Decrease in total anxiety scores
	Probiotic	84 days 1×10^9 CFU/day	*L. plantarum*	Not reported	• Improvements in anxiety and stress scores using the Depression Anxiety Stress Scale (DASS-42)
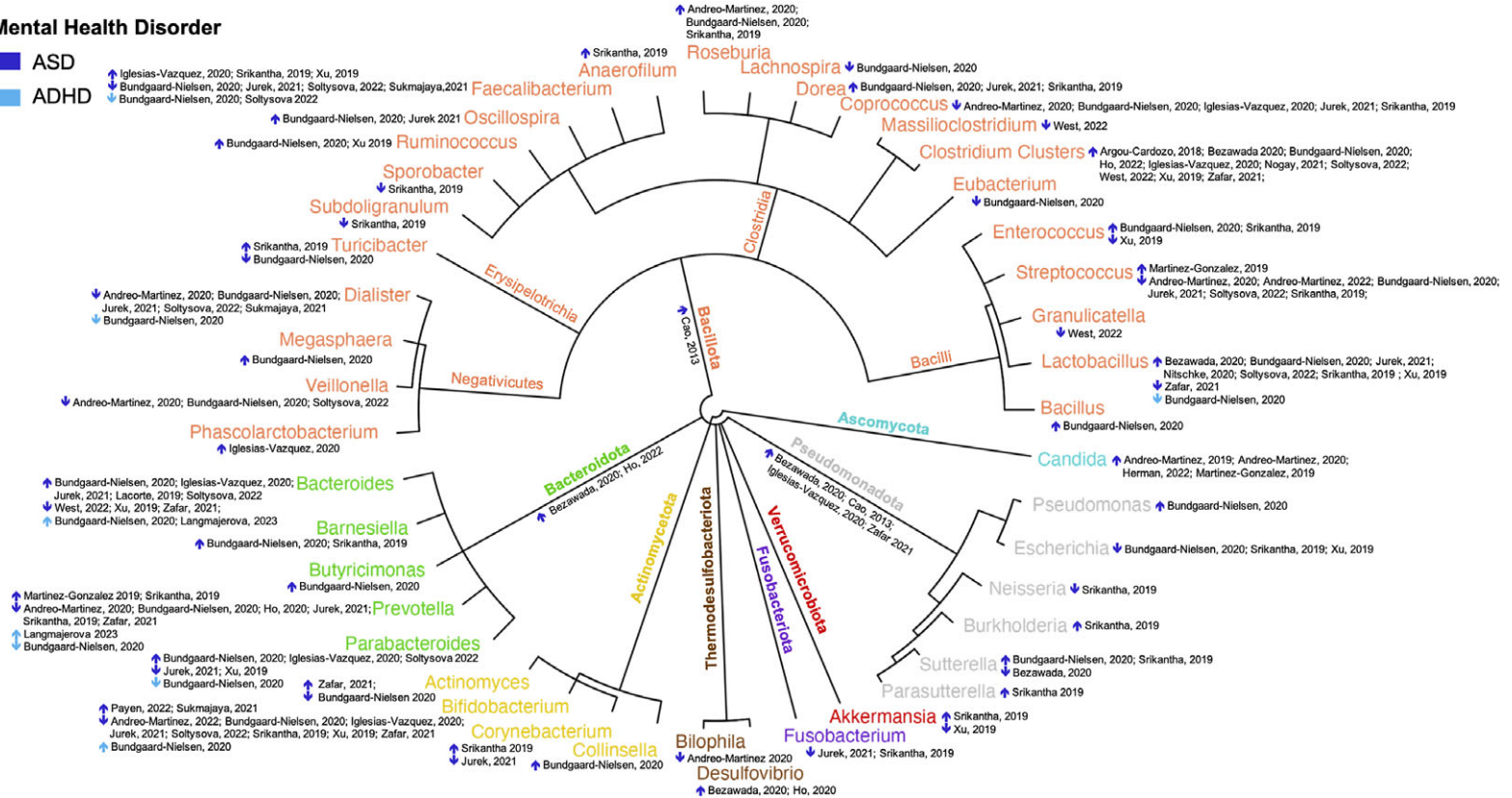
Figure 2. Reported abundance of gut operational taxonomic units in youth with ASD and ADHD (*n* = 23). The outer circle represents the genus level, with outer colours distinguishing the phylum. Dark blue arrows indicate reviews of ASD, and light blue arrows indicate reviews of ADHD. ↑ indicates higher abundance in youth with the disorder, while ↓ indicates lower abundance in the disorder.
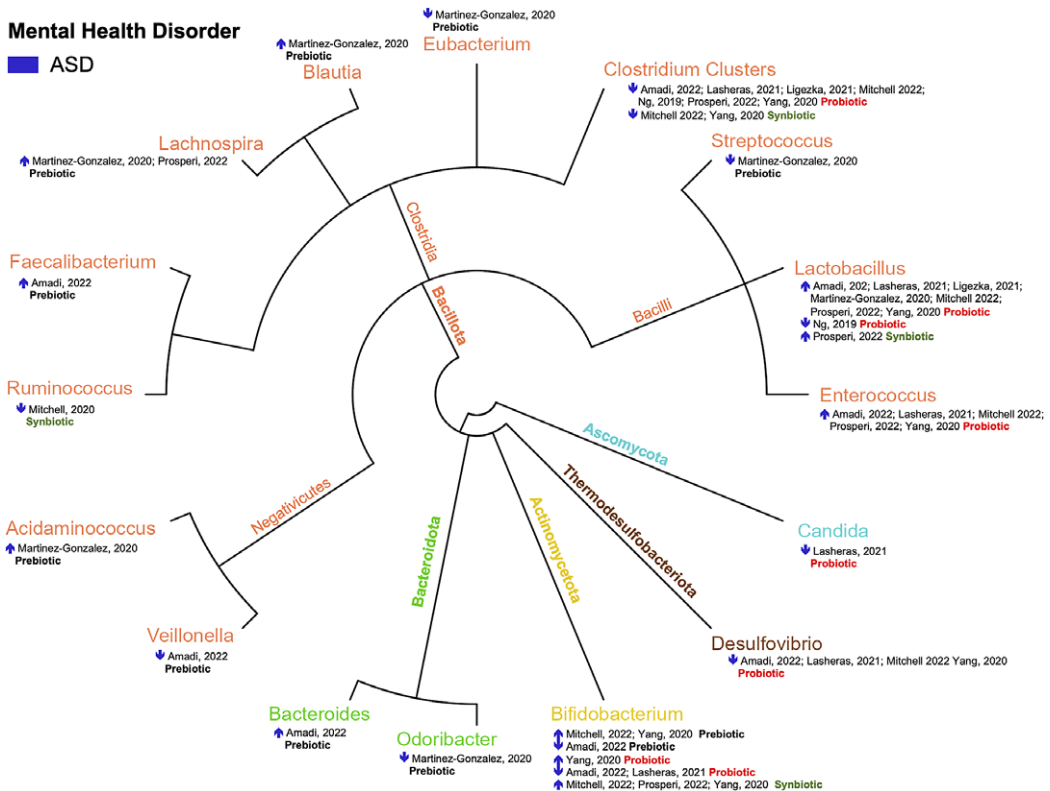
Figure 3. Reported changes in gut microbiota operational taxonomic units following prebiotic, probiotic, and synbiotic supplementation among youth with ASD (*n* = 16). The outer circle represents the genus level, with outer colours distinguishing phylum. Dark blue arrows indicate reviews of ASD. ↑ indicates higher abundance in youth with the disorder compared to baseline, while ↓ indicates lower abundance in the disorder compared to baseline.

Interventional systematic reviews

Among the 16 interventional reviews, 15 examined the efficacy of probiotics, eight examined the efficacy of prebiotics, and four examined the efficacy of synbiotics on ASD symptoms. One review examined the efficacy of probiotics and prebiotics on anxiety. All supplements were administered orally, as a capsule or packet, one, two, or three times daily, with dosages ranging from 0.5 to 90×10^{10} colony-forming units of bacteria. Treatment duration ranged from 21 days to 15 months.

Improvements in ASD symptoms were reported in all reviews following prebiotic, probiotic, and synbiotic supplementation. One review (Basso et al., 2022) reported improvement in anxiety symptoms following probiotic or prebiotic supplementation. Details regarding supplement types, duration, dosage, and species as well as gut microbiome and mental health outcomes can be found in Table 1.

Eight reviews reported changes in OTUs. Consistent findings were for the effect of prebiotics, probiotics, and synbiotics on specific bacterial groups. The use of prebiotics consistently increased the abundance of *Lachnospira*, while the use of probiotics increased the abundance of *Lactobacillus* and *Enterococcus*. Furthermore, probiotic intervention decreased the abundance of *Desulfovibrio*, and probiotics as well as synbiotic treatment consistently decreased the abundance of *Clostridium* clusters.

The impact of prebiotic, probiotic, and synbiotic supplementation on *Bifidobacterium* in the gut was inconsistent. Some studies (Yang et al., 2020; Mitchell and Davies, 2021; Prosperi et al., 2022) reported an increase in *Bifidobacterium* levels, while others reported decreased levels (Lasheras et al., 2021; Amadi et al., 2022).

The remaining OTUs were only reported in one review, indicating limited findings. Thus, the effects of prebiotics, probiotics, and synbiotics on these specific OTUs remain uncertain and require further investigation (Figure 3).

Sensitivity analysis

Reduction of overlap bias was conducted separately for observational and interventional systematic reviews.

The 23 observational systematic reviews included 92 primary studies, of which 26 were excluded for the following reasons: animal studies (n = 6), other mental health disorders (n = 15), and non-gut microbiome studies (n = 5). Forty-two primary studies were unique and 50 primary studies were reported in ≥2 systematic reviews, yielding a CCA of 12.5% and indicating a high degree of overlap (Supplementary Figure S2). Reduction methods eliminated 13 observational systematic reviews that had >25% overlap, leaving 80 primary studies (40 were unique, and 40 were reported in ≥2 systematic reviews) reported in 10 observational systematic reviews. The CCA was 8.47%, indicating a moderate degree of overlap (Supplementary Figure S3).

The overlap minimization reduced the number of reported OTUs among observational reviews of ASD youth from 43 to 32. The 11 OTUs lost were *Bacillus, Eubacterium, Lachnospira, Megasphaera, Oscillospira, Ruminococcus, Butyricimonas, Collinsella, Bilophila, Desulfovibrio*, and *Pseudomonas*. Exaggeration, the replication of primary study's findings in multiple reviews, was evident for increased and decreased abundance of OTUs. Exaggerated increased abundance was reported for *Clostridium clusters, Dorea, Enterococcus, Roseburia, Barnesiella,* and *Candida*. Exaggerated decreased abundance was reported for *Coprococcus, Dialister, Veillonella, Fusobacterium,* and *Escherichia*. Reporting inconsistencies remained for *Faecalibacterium, Lactobacillus, Prevotella,* and *Bacteroides*, while clearer signals emerged for *Streptococcus, Turicibacter, Parabacteroides*, *Bifidobacterium, Corynebacterium, Akkermansia*, and *Sutterella* (see Figure 4A,B).

The overlap minimization reduced the number of reported OTUs among observational reviews of ADHD youth from seven to three. The four OTUs lost were *Dialister, Lactobacillus, Parabacteroides*, and *Bifidobacterium*. Exaggeration in reporting was evident for increased and decreased abundance of OTUs. Exaggerated increased abundance was reported for *Bacteroides* and decreased abundance for *Faecalibacterium*. A clearer signal emerged for *Prevotella* (see Figure 4A,B).

The 16 interventional systematic reviews included 36 primary studies, of which 26 were excluded for the following reasons: not biotic supplementation (n = 11) and not a paediatric population (n = 15). Thirteen primary studies were unique and 23 primary studies were reported in ≥2 systematic reviews yielding a CCA of 18.9% indicating a high degree of overlap (Supplementary Figure S4). Reduction methods eliminated 10 interventional reviews with >25% overlap leaving 28 primary studies (17 were unique and 11 were reported in ≥2 systematic reviews) reported in six interventional systematic reviews. The CCA was 9.3%, indicating a moderate degree of overlap (Supplementary Figure S5).

The overlap minimization reduced the number of reported OTUs among ASD youth for the interventional reviews from 16 to 7. The eight OTUs removed were *Acidaminococcus, Blautia, Eubacterium, Faecalibacterium, Ruminococcus, Streptococcus, Veillonella*, *Bacteroides*, and *Odoribacter*. Exaggerated increased abundance was reported for *Enterococcus* and *Lachnospira* and decreased abundance for *Clostridium* clusters and *Desulfovibrio*. Inconsistent reporting remained for *Bifidobacterium*, and a clearer signal emerged for *Lactobacillus* (see Figure 5A,B).

Discussion

This umbrella review is the first to synthesize the current literature, to our knowledge, examining the gut microbiome and psychiatric disorders among children and adolescents. Child and adolescent psychiatric disorders were found to be unequally represented in the included systematic reviews. The majority of
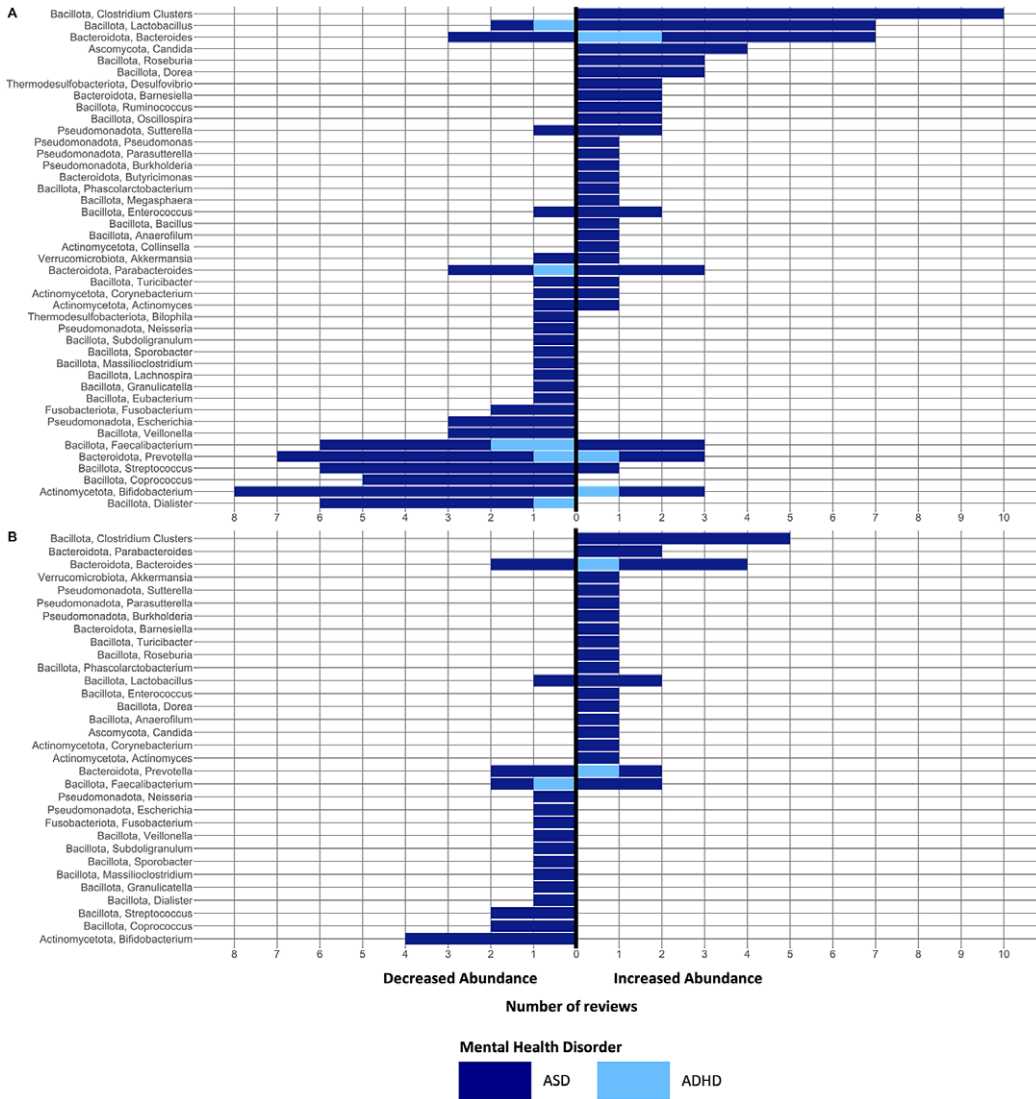
Figure 4. Reported increase/decrease in abundance of gut operational taxonomic units in youth with autism spectrum disorder (ASD) (dark blue) and ADHD (light blue) across (A) included systematic reviews (*n* = 23) and (B) after overlap bias was minimised (*n* = 10).

reviews focused on ASD, accounting for 92% of the total reviews. A smaller proportion of reviews examined ADHD, with only 15% of the reviews dedicated to this disorder. Furthermore, there was one review each on depression and anxiety, while no reviews specifically addressed OCD or bipolar disorder. The nascency of this research area was further evident as 80% of reviews were published since 2020.

Findings from observational reviews reveal consistent signals of association between specific OTUs and symptoms of ASD in youth. These findings remained following overlap minimization. The most consistent evidence points to an increased abundance of *Clostridium* clusters and a decreased abundance of *Bifidobacterium*. *Clostridium* clusters are spore-forming bacteria, known to release pro-inflammatory toxins that have the potential to reach the brain through the bloodstream (Argou-Cardozo and Zeidan-Chulia, 2018). Lower ratios of *Clostridium* clusters have been observed in vegetarians and vegans versus omnivores (Rinninella et al., 2019). Additionally, certain metabolites derived from the activity of *Clostridium*, such as short-chain fatty acids (SCFAs), are produced through the fermentation of dietary
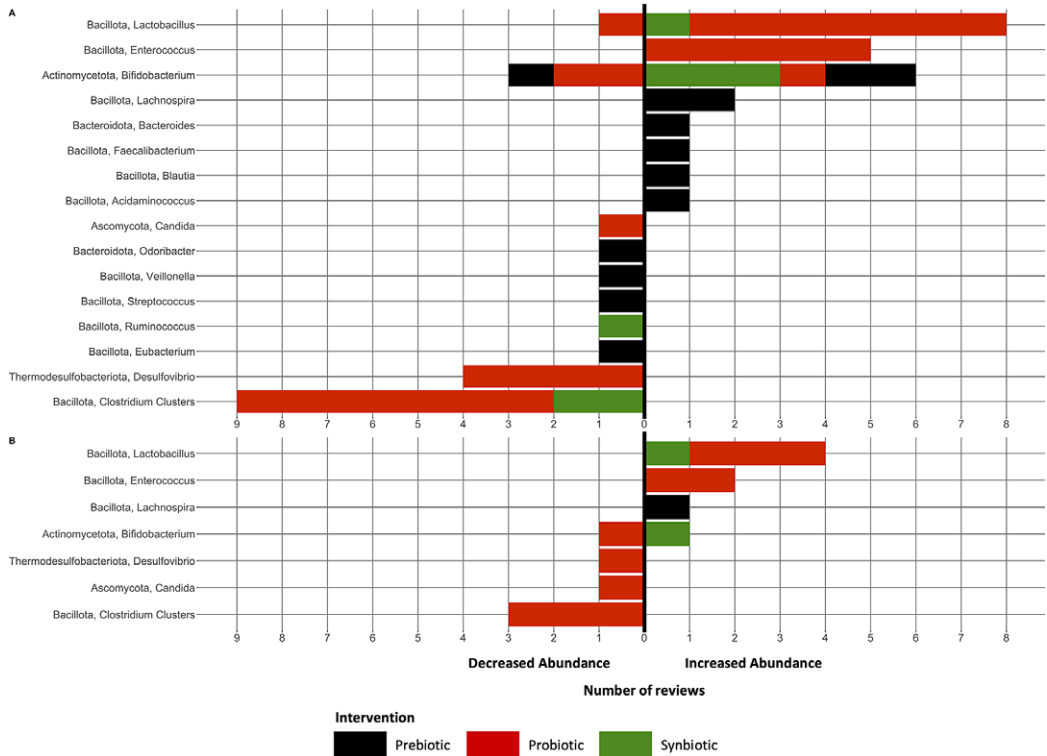
Figure 5. Reported increase/decrease in abundance of gut operational taxonomic units in youth with ASD following prebiotic (black), probiotic (red), or synbiotic (green) supplementation (A) across included interventional systematic reviews (*n* = 16) and (B) after overlap bias was minimized (*n* = 6).

fibre. SCFAs play a critical role in maintaining the proper functioning of the gut immune system by modulating gene expression. SCFAs promote gut health through increasing epithelial cell turnover and their use as sources of energy for intestinal cells (Xing et al., 2020). Imbalances in SCFA concentrations can disrupt gut homeostasis and potentially trigger peripheral inflammation. Additionally, SCFAs can reach the brain through the bloodstream, where they influence its development by modulating the production of neurotransmitters, for example, serotonin and dopamine (Srikantha and Mohajeri, 2019). *Bifidobacterium* are considered to be beneficial bacteria whose presence is consistent with a greater adherence to Mediterranean diets and lower adherence to high fat intakes similar to those seen in Western diets (Rinninella et al., 2019). Evidence from animal studies suggests that certain species of *Bifidobacterium* have a positive effect on the hypothalamic–pituitary–adrenal axis by lowering dopamine and adrenaline and may also have an anti-inflammatory effect on the gastrointestinal tract (Moya-Pérez et al., 2017). *Bifidobacterium* also has the capability to produce gamma-aminobutyric acid, an important inhibitory neurotransmitter that is closely associated with the metabolism of glutamate, the primary excitatory neurotransmitter in the brain (Perna et al., 2019).

While the full analysis may exaggerate the importance of certain species, the sensitivity analysis may potentially underestimate the importance of certain species. OTU signals remaining after the sensitivity analysis indicate a lower abundance of beneficial bacteria and higher levels of harmful bacteria in ASD youth contributing to gut dysbiosis, characterized by an imbalance or altered composition of OTUs. For example, weak but consistent increased abundance of OTUs remained for harmful bacteria in ASD youth such as *Candida*, which releases ammonia and toxins (Reichelt and Knivsberg, 2009), *Dorea* which promotes inflammation (Schirmer et al., 2016), *Bacteroides,* which produces propionic acid-neurotoxic SFCA (Abdelli et al., 2019), and SCFA producers such as *Roseburia.* Moreover, weak but consistently

decreased abundance of OTUs remained for beneficial bacteria in ASD youth such as *Coprococcus*, which are necessary for carbohydrate digestion and fermentation (Kovatcheva-Datchary et al., 2015), and *Dialister*, which are known to assist with the maintenance of the normal gastrointestinal tract function (Taylor et al., 2020).

The inconsistent findings regarding specific OTUs and their association with ASD symptoms may be attributed to several factors. Firstly, the high degree of natural variability observed in the composition of the gut microbiome across different populations can contribute to divergent results. Each individual's gut microbiome is influenced by numerous factors, including genetics, environment, and lifestyle, leading to significant variation (Vandeputte et al., 2021). Secondly, the heterogeneity of the ASD phenotype, characterized by variations in symptom severity and presentation, may also influence the composition of the gut microbiome and obscure clear associations with specific OTUs. One potential explanation for ASD-related gut dysbiosis is that children and youth with ASD have been noted to have lower vegetable intake compared with neurotypical youth. This discrepancy in vegetable consumption has been attributed to selective eating patterns and sensory disturbances commonly experienced by children with ASD (Emond et al., 2010; Siddiqi et al., 2019). The complex nature of ASD and the diverse symptoms experienced by individuals with ASD make it challenging to establish consistent relationships between specific OTUs and ASD symptoms (Jacob et al., 2019). Lastly, the variability in the age of subjects included in studies examining the gut microbiome in relation to ASD could contribute to the inconsistent findings. The gut microbiome undergoes developmental changes during childhood, and differences in age among study participants could influence the composition and functioning of the microbiome (Ronan et al., 2021). These factors collectively emphasize the complexity of studying the gut microbiome in relation to ASD and highlight the need for further research that takes these variables into account to provide more conclusive insights.

Weak signals also indicate the presence of gut dysbiosis in ADHD youth. The sensitivity analysis conducted for ADHD revealed an elevated level of replication of primary study findings in multiple reviews, which further highlights the limited primary research available in this area. Therefore, caution should be exercised when interpreting these findings. Only one review reported an increased abundance of OTUs belonging to the *Bacteroides* and *Prevotella* genus in youth with ADHD. *Bacteroides* metabolize polysaccharides and oligosaccharides, providing nutrition and vitamins to the host and other intestinal microbial residents. However, when dietary habits include the consumption of high animal protein foods, which promote the growth of *Bacteroides*, it may lead to a relative decrease in other bacterial taxa, creating an imbalance in the microbial community (Desai et al., 2016; Rinninella et al., 2019). One review also reported decreased relative abundance of beneficial OTUs belonging to the *Faecalibacterium* genus which produce butyric acid, bioactive peptides, and other anti-inflammatory substances with immuno-modulatory effects, consistent with a diet low in dietary fibre, fruit, and vegetables (Quévrain et al., 2016, Zou et al., 2021). While these weak signals suggest gut dysbiosis in ADHD youth, it is important to note that the current understanding is based on a limited number of reviews and their findings should be interpreted with caution. Additionally, the complexity of ADHD, which involves various genetic, environmental, and neurological factors, further complicates the interpretation of the results.

Interventions for ASD consistently demonstrated improvements in ASD symptoms across all reviews that evaluated biotic supplements. This trend persisted even after conducting the sensitivity analysis to account for potential overlap. These findings provide support for the hypothesis that the gut–brain axis, which involves bidirectional communication between the gut and the brain, plays a role in the manifestation of ASD. Among the reviews of interventions for ASD, the sensitivity analysis unveiled a high degree of overlap among primary studies, indicative of a reduced volume of primary research available. Therefore, when interpreting the findings, it is essential to consider the implications of minimizing the results due to overlap. Specifically, probiotic supplementation promoted a healthier state of the gut microbiota, known as gut eubiosis, as consistently reported in the reviewed studies. Enhanced gut microbiome eubiosis was characterized by an increase in the abundance of beneficial bacteria, such as *Lactobacillus and Enterococcus*, and a decrease in the abundance of detrimental bacteria, including clusters of *Clostridium*. Among this early evidence, a consistent link between enhanced gut

microbiome eubiosis and positive outcomes in ASD supports the notion that targeting the gut micro-biota through biotic supplements may hold therapeutic potential for individuals with ASD.

The effect of prebiotic, probiotic, and synbiotic supplementation on *Bifidobacterium* demonstrated inconsistent findings in interventional reviews before and after overlap minimization (Figure 5A,B). This highlights the need for additional research to provide a more comprehensive understanding of the impact of biotic supplementation on *Bifidobacterium* and to address the lack of evidence.

This umbrella review identified a significant issue of primary study overlap in the systematic evidence gathered so far. A significant amount of overlap was found in the primary studies included in observational systematic reviews and interventional reviews. Approximately 54% of primary studies in the observational reviews and 64% of primary studies in the interventional reviews were reported in two or more reviews. This overlapping inclusion of studies can introduce a high to very high level of bias when reviewing the systematic evidence. This bias was demonstrated in the sensitivity analysis, which revealed exaggerated reporting of OTUs in the included studies. Moreover, the review found that a considerable proportion (56%) of the observational and interventional reviews had low or critically low methodological quality. This was due to several factors, including missing details about excluded primary studies, failure to provide a registered a priori protocol, and inadequate use of comprehensive search strategies. These methodological shortcomings may limit the reliability and generalizability of the findings and underscore the importance of following rigorous systematic review protocols.

This umbrella review also highlights a significant issue of reporting inconsistency within the literature regarding the gut microbiota of children and adolescents with mental health disorders. Although all studies reported relative taxon abundances, very few report diversity measures such as richness, which is crucial in understanding the gut microbiome's complexity. Diversity, richness, and evenness are all vital concepts that provide a more comprehensive understanding of the gut microbiome. A greater diversity of bacteria in the gut is generally considered to be more beneficial than a less diverse microbiome (Young and Schmidt, 2008). Therefore, the lack of diversity reporting in the literature is a significant gap that needs to be addressed to better understand the relationship between the gut microbiome and mental health disorders in children and adolescents. Additionally, the compositional nature of sequence datasets may also contribute to the conflicting findings, as an increase in the relative abundance of a taxon can occur even if its absolute abundance decreases (Gloor et al., 2017). This could lead to confounding findings from many of the included reviews, possibly providing an explanation for the inconsistent results observed in different studies.

This umbrella review has several strengths. Firstly, the search and review process was rigorous, and the broad search strategy resulted in a large number of records being captured without limiting the search by date or country of publication. Secondly, this review addressed the issue of primary study overlap, which is a known source of bias in umbrella reviews. By minimizing overlap, the review was able to provide a more comprehensive and unbiased synthesis of the available evidence. Additionally, the inclusion of both observational and interventional reviews allowed for a comprehensive assessment of the literature on the gut microbiome and mental health disorders among youth.

Despite these strengths, some limitations should be considered when interpreting the results. Due to a high degree of heterogeneity, we were unable to conduct a meta-analysis. Caution should be exercised when interpreting findings related to OTUs, as the significance of certain OTUs may be overstated due to primary study overlap, while the importance of others may remain unclear or ambiguous. Additionally, due to the limitations inherent in a high-level overview, we were unable to delve into the specifics of individual treatments and their direct effects on the gut microbiome and mental health. However, our study contributes by synthesizing and presenting a broader perspective on the overall trends and implications of biotic treatments on mental health. Also, we did not report OTUs that exhibited no associations or lack of efficacy with the disorders under investigation to maintain clarity and avoid presenting conflicting or inconclusive information. It is important to note that the research field on this topic is still in its early stages, and as more studies emerge, this will improve. Additionally, the current review may under-represent research conducted in a language other than English, as our inclusion criteria led to the exclusion of seven non-English reviews. Finally, although this review focused on

alterations of gut microbiota, other research has shown that the gut–brain axis links numerous peripheral intestinal functions to brain centres through a wide range of processes and pathways, potentially in a bidirectional manner (Arneth, 2018).

To further advance our understanding of the relationship between the gut microbiome and mental health disorders among children and adolescents, future studies should consider several important methodological improvements. Researchers should consider using amplicon sequence variants (ASVs) in study analyses. ASVs allow for better comparisons across different studies and enable the identification of rare taxa that would otherwise be lost in OTU-based analyses (Amir et al., 2017; Chiarello et al., 2022). This is because OTUs can vary according to the dataset, as they rely on (and are sensitive to) clustering of sequences, while ASVs will be consistent and are not impacted by the dataset. Future research accounting for lifestyle factors and other drivers of microbiome composition such as antibiotic use is needed to determine whether putative variations in the microbiome are mechanistically important or simply non-specific correlates of psychiatric disorders. Research examining potential mechanisms of action is also needed, whereby the pathways by which the gut microbiome may influence mental health can be more clearly elucidated. Although studies using 16S analysis can provide data on species, the resolution is too limited for this purpose, given dramatic differences in gene complements even across strains of the same species. Thus, future studies should also incorporate more mechanistic approaches such as metagenomics, metatranscriptomics, and metabolomics. These technologies can provide a deeper understanding of the functional potential of the microbiome and identify specific pathways and metabolites that may be involved in mediating the relationship between the gut microbiome and mental health. Accordingly, future research should consider metabolomic changes over microbiome changes, whereby researchers can identify specific metabolites that are influenced by alterations in the gut microbiota composition or activity. These changes can be associated with various health conditions, including metabolic disorders, inflammatory bowel diseases, mental health disorders, and more. Understanding these metabolomic alterations could potentially provide valuable information about the mechanistic links between gut microbiota and host health, facilitating the development of targeted interventions or therapeutic approaches. Finally, standardization of intervention approach and reporting is needed to compare results more accurately across clinical trials.

Conclusion

The research investigating the connection between the gut microbiome and mental health disorders in children and adolescents is expanding, with the majority of studies focusing primarily on ASD. A smaller proportion of studies examined the relationship between the gut microbiome and ADHD. However, there is still a significant gap in our understanding of the gut microbiome's role in other common and debilitating mental health disorders such as depression, anxiety disorders, OCD, and bipolar disorder. Further research in these areas is crucial to gain a better understanding of the potential involvement of the gut microbiome in the development and treatment of these disorders.

In relation to ASD, this umbrella review reveals a consistent pattern across multiple reviews, indicating associations between an increased abundance of detrimental bacteria and a decreased abundance of beneficial bacteria. Although the body of review literature on interventions targeting the gut microbiome in ASD is relatively smaller, emerging evidence suggests that the use of biotic supplements can promote gut microbiome eubiosis, leading to positive impacts on ASD symptoms. These findings support the need for further investigation into the role of biotic supplementation in the management of ASD. Furthermore, considering the diverse array of clinical and microbial phenotypes found in individuals with ASD and the specificity of emerging therapies in targeting specific traits and microbial populations, it is increasingly apparent that a personalized treatment approach should be adopted to effectively address the unique requirements of each patient.

To inform the development of more targeted and effective prebiotic interventions, future research should also consider potential mediators and moderators of the gut microbiome–ASD relationship,

including the mechanisms through which the gut microbiome may contribute to ASD development and the factors that may modulate this relationship. Finally, this review highlights the need for the development of consensus reporting guidelines for a core set of gut microbiome outcome measures, which will be essential for comparing results across studies and informing future research efforts in this field.

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