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Gut microbiome differences in children with Attention Deficit Hyperactivity Disorder and Autism Spectrum Disorder and effects of probiotic supplementation: A randomized controlled trial☆

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ABSTRACT

Background: Emerging evidence suggests a significant role of gut microbiota on neurodevelopmental disorders, including Attention Deficit Hyperactivity Disorder (ADHD) and Autism Spectrum Disorder (ASD).
Aims: Our study aimed to compare gut microbiota composition between these disorders and evaluate the effect of probiotic supplementation.
Methods: We conducted a 12-week randomized, double-blind, placebo-controlled trial with 80 children aged 5–14 years (39 with ADHD, 41 with ASD). Baseline and post-intervention fecal samples were analyzed using 16S rRNA gene sequencing to identify changes in gut microbiota composition.
Results: We identified 22 taxa differentiating ADHD and ASD (AUC = 0.939), characterised by increased presence of Clostridia, Ruminococcaceae, and Lachnospiraceae in ADHD, and Bacteroides, Bacilli and Actinobacteria in ASD. These differences remained after accounting for potential confounders. ASD children receiving probiotics had significant increases in Chao 1, Fisher's alpha, and Shannon indices whereas no significant differences in α and β-diversity were

Abbreviations: ADHD, Attention Deficit Hyperactivity Disorder; ASD, Autism Spectrum Disorder; ASV, Amplicon Sequence Variant; BRIEF-2, Behavior Rating Inventory of Executive Function, Second Edition; CBCL, Child Behavior Checklist; CPT-3, Conners Continuous Performance Test 3rd Edition; DADA2, Data Analysis in Amplicon Sequencing, Version 2; DSM-5, Diagnostic and Statistical Manual of Mental Disorders, 5th Edition; GI, Gastrointestinal; KEGG, Kyoto Encyclopedia of Genes and Genomes; KOs, KEGG Orthologs; LPS, lipopolysaccharide; PAQ-C, Physical Activity Questionnaire for Children; PCoA, Principal Coordinates Analysis; PERMANOVA, Permutational Multivariate Analysis of Variance; SCFAs, short-chain fatty acids; SDSC, Bruni's Sleep Disorders Scale for Children; SRS-2, Social Responsive Scale-second edition; ZBMI, BMI z-score.

☆ This study is retrospectively registered at ClinicalTrials.gov as Nutritional Intervention for Children With ASD and/or ADHD (ProEpined), NCT05167110. Registered 22 December 2021 – http://classic.clinicaltrials.gov/ct2/show/NCT05167110

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found in ADHD. In ADHD, bacteria with potential adverse effects were under-represented. In ASD, the abundance of Eggerthellaceae, and other taxa associated with gastrointestinal problems and anxiety was decreased.
Conclusion: Variations in gut microbiota may influence responses in ADHD and ASD. Probiotic supplementation favorably altered gut microbiota composition, offering insights for future therapeutic strategies targeting the microbiome in neurodevelopmental disorders.
What this paper adds: Recent research underscores the role of gut microbiota in ADHD and ASD, indicating that diet can significantly influence microbiota composition and potentially manage these neurodevelopmental disorders. This study reveals distinct differences in gut microbiota composition between children with ADHD and ASD and demonstrates that probiotic supplementation can modulate specific microbial genera in each disorder. These findings pave the way for the development of innovative microbiome-targeted therapies, offering a new avenue for the treatment of neurodevelopmental disorders. Understanding this relationship is crucial for designing future interventions.

1. Introduction

Autism spectrum disorder (ASD) and Attention-deficit disorder (ADHD) globally affect 1.5–2.7 % (Zeidan et al., 2022) and 5–7.6 % (Ilic & Ilic, 2022) of children, respectively. Although they share specific clinical symptoms, neuroanatomic and genetic traits (Antshel & Russo, 2019; Schachar et al., 2023), they are considered as two distinct conditions. They both show a high heritability, estimated in 74 % for ADHD and 54 % for ASD, but genetics alone do not fully account for their severity, suggesting a complex interaction between genetic and non-genetic risk factors (Gaugler et al., 2014; Faraone & Larsson, 2019).

Accumulating evidence suggest that gut microbial dysbiosis is involved in the development of multiple diseases, such as obesity, type 2 diabetes, cardiovascular disease, as well as psychiatric disorders like depression (Aizawa et al., 2016), Parkinson's disease (Li et al., 2019), schizophrenia (Xu et al., 2020), and more recently, ADHD and ASD (Taniya et al., 2022; Kalenik et al., 2021). According to a recent systematic review, increased relative abundance of *Proteobacteria*, *Bacteroides*, *Barnesiella*, *Clostridium* and *Roseburia*, and reduced *Bifidobacterium*, *Coprococcus*, *Dialister*, *Faecalibacterium*, *Prevotella* and *Streptococcus* have been reported in some but not all ASD case-control studies (Bundgaard-Nielsen et al., 2020). Studies on ADHD are even more scarce, less conclusive and highly inconsistent (Bundgaard-Nielsen et al., 2020; Zhao et al., 2023). In a recent meta-analysis including children and adults, *Blautia* was the only genus found more abundant in ADHD patients, while *Coprococcus-2*, *Parabacteroides* and *Bifidobacterium* were less abundant (Wang et al., 2022). Interestingly, both ADHD and ASD appear to be associated with a lower abundance of bacteria associated with the maintenance of a healthy gastrointestinal (GI) tract (Bundgaard-Nielsen et al., 2020). Identification of specific bacteria reflecting pathophysiological processes would help to identify children who are at risk for the development of ADHD and ASD and target them for better management. Furthermore, nutritional interventions aimed at restoring gut microbial composition could be explored as a potential treatment for ADHD or ASD-associated symptoms. However, the existing evidence in the literature, although promising, is insufficient due to the heterogeneity of the studies and the medium-to-high risk of bias, making it challenging to estimate the effect sizes for prebiotics and probiotics (Martínez-González & Andreo-Martínez, 2020).

Gut microbiota may affect brain development, function, and behaviour, through the immune system, and metabolic, neuronal and endocrine pathways (Rogers et al., 2016). In this context, probiotic consumption may play a crucial role in neurodevelopment by contributing to the stability of a healthy intestinal microbiota, thereby enhancing the microbiota-brain interactions. Common strains of probiotics for prevention and treatment of neurological disorders are *Lactiplantibacillus plantarum* and *Levilactobacillus brevis*, both considered GABA- and dopamine-producing strains, which could have different effects depending on the amount, duration, and method of use (Duarte Luiz et al., 2023).

Although there is substantial evidence about the potential role of the microbiota on the onset of ADHD and ASD, only one study has compared the gut microbiota composition between children with ADHD and ASD (Bundgaard-Nielsen et al., 2023).

To address these gaps, we conducted a double-blind, controlled, randomised clinical trial involving probiotic supplementation in children with ADHD and ASD. The objectives were to assess gut microbiota diversity and composition differences between ADHD and ASD, and to investigate the effects of probiotic supplementation on their gut microbiota composition.

2. Materials and methods

2.1. Study design and participants

The current study was performed in the framework of a 12-week randomized, double-blind, placebo-controlled nutritional intervention trial conducted in children aged 5–14 years with ADHD or ASD according to the DSM-5 criteria. Eligible participants were recruited at specialized clinics and schoolchildren centres in Tarragona (Spain) between 2020 and 2022 (Canals Sans, Morales Hidalgo, Roigé Castellví, Voltas Moreso, & Hernández Martínez, 2021; Morales Hidalgo, Voltas Moreso, & Canals Sans, 2021). Children were randomized at a 1-to-1 ratio to the probiotic and placebo groups using a computer-generated randomization list in ADHD and ASD. Only AB Biotics S.A (Barcelona, Spain), who provided the probiotic and placebo capsules, and had no contact with participants, was aware of the assignment children to each group.

We included 39 children with ADHD and 41 with ASD, divided between the probiotic intervention group and the placebo group. Exclusion criteria were having probiotics 3 months before the study, were on antibiotic treatment, intolerances or allergies to the treatment excipients, and any medical condition incompatible with the intervention. Participants were randomly allocated to either the placebo or the probiotic group, both provided by AB Biotics S.A and detailed in Table S1. After 6 weeks of the intervention, parents were interviewed to monitor adherence to the intervention and ensure there were no side-effects. The institutional review board of the Institute of Health Pere Virgili approved the study protocol in May 2018 (Ref.CEIM:030/2017) and written informed consent was obtained. The trial was retrospectively registered in ClinicalTrials.gov (NCT05167110).

2.2. Measurements

Anthropometry and general clinical data were collected at baseline. Symptom severity and neuropsychological functioning were collected at the beginning and at the end of the intervention. At the two visits, parents completed a validated battery of questionnaires on the psychological, nutritional and physiological characteristics of children (See Supplementary Information S1). Children performed the computerized Conners Continuous Performance Test 3rd Edition (CPT 3) (Conners, 2014) or the Conners Kiddie Continuous Performance 2nd Edition (K-CPT 2) (Conners, 2015), based on their ages.

Stool samples were collected and delivered frozen within 1 day after collection. DNA was extracted using the QIAmp PowerFecal Pro DNA kit (Qiagen, Germantown, TN, USA) following the manufacturer's instructions with a 1-minute lysis step (FastPrep-24–5G Homogenizer, MP Biomedicals). V4 16S rRNA gene region sequencing was performed (Ion Torrent Personal Genome Machine, ThermoFisher Scientific, USA, see detailed protocol in Supplementary Information S2). Quality control, length filtering at 291 bp and denoising of forward sequences was performed in DADA2 and ASV assigned in QIIME2 (v.2019.4) (Bolyen et al., 2019) using the Naïve Bayes 138 Silva classifier (Data resources, 2023)

2.3. Statistical analyses

For the comparison of microbiota composition between the two groups at baseline, we estimated that we will have $>$ 80 % of statistical power ($\alpha = 0.05$; two-sided) to detect a difference of 0.37-fold change. We will also have $>$ 80 % statistical power ($\alpha = 0.05$; two-sided) to detect an absolute mean difference of 0.62 in relative abundances in microbiota genera between the probiotic and placebo groups, which are differences commonly observed in previous studies (Bundgaard-Nielsen et al., 2023; Inoue et al., 2019). Descriptive data of participants are presented as means and standard deviation for normally distributed variables or medians and interquartile range for non-normal distributions. Chi-square, Mann-Whitney U-test, and t-tests were conducted for categorical, non-normally, and normally distributed variables, respectively. Microbial α- and β-diversity were tested ("mia" package, v.1.7.4.). Principal coordinate analysis (PCoA) was used to compare β-diversity between interventions at baseline and at the end of the intervention by disease. A permutational multivariate analysis of variance (PERMANOVA) was conducted to assess the effect of each covariate within ADHD and ASD using the Bray–Curtis dissimilarity and 999 permutations ("vegan" package, v.2.6–4). To determine a microbiota profile corresponding to both diseases and changes between the interventions, we centered log-ratio transformed counts and regressed binary variables (ADHD or ASD, Probiotic or Placebo) against the 155 identified taxa. Due to the high dimensionality and collinearity of the data, we employed logistic regression with elastic net penalties ("glmnet" package, v.4.1–8) (Zou & Hastie, 2005). We applied the selected alpha and lambda values (Table S2) to each penalised regression for every training in a 100-iteration loop. Different signatures were built only with taxa consistently selected in 100 iterations for baseline comparisons, and at least in 80 iterations for the other comparisons. Models were further adjusted for unpenalized covariates including age, sex, BMI z-score (zBMI), and medication (psychostimulants in ADHD children, and psychostimulants and/or neuroleptics in ASD children). All analyses were conducted using R software (v.4.2.1) (R Foundation for Statistical Computing, Vienna, Austria). See supplementary information S3 for more details.

2.4. Functional enrichment analysis

We integrated the generated ASV table into the Predictive Investigation of Microbial Community Functional Potential (PICRUSt2) and employed the Kyoto Encyclopaedia of Genes and Genomes (KEGG) database as a predictive model for the functional gene layout across various microbial ecosystems using the Silva database of 16S rRNA gene sequences (Douglas et al., 2020). Predicted functionalities were further clustered in different pathway hierarchies (levels 1, 2, and 3) and analysed using Welch's *t*-test. Pathways with $P < 0.05$ after FDR correction (Benjamini-Hochberg), were considered significantly differentially expressed.

2.5. Taxa-KEGG Orthology correlation analysis

The associations between specific bacterial taxa and KEGG Orthology (KO) categories from PICRUSt2 analysis were evaluated using Spearman rank correlations. Correlations with a Spearman correlation coefficient (*rho*) greater than 0.5 and a p-value less than 0.05, following FDR correction for all comparisons, were considered significant. In the case of both disorders studied together after probiotic intervention, we used a threshold of *rho* greater than 0.4 and a p-value less than 0.05 after FDR correction. Pathways that exclusively interacted with one taxon were excluded from the analysis. The interactions between species and KO categories were visualized using Cytoscape 3.10.0.

3. Results

Of the 87 children initially assessed for eligibility (Fig. 1), 6 refused to participate and 1 did not meet the inclusion criteria. Eighty children (39 with ADHD and 41 with ASD) were finally randomised. For the present analyses, only children with available microbiota at baseline (n = 77) have been considered (Fig. 1). Baseline characteristics by disease status are shown in Table 1. No significant differences in sex, age, zBMI or medication were observed between the diseases. No significant changes were observed in zBMI after the intervention neither in ADHD (P = 0.689) nor in ASD (P = 0.347) (data not shown). No significant differences in α-diversity were observed at baseline (Fig. 2). However, after the intervention, Chao 1, Fisher's alpha and Shannon indices significantly increased in the probiotic group, but only in ASD children (PFDR<0.001, PFDR<0.01 and PFDR<0.05, respectively; (Fig. 3). Regarding β-diversity, the PCoA plots did not reveal a clear discrimination of the microbiota profiles neither between intervention groups nor within time-points (Figure S1). In contrast, when we included sex, age, zBMI and medication, the microbiota composition differed significantly between probiotic and placebo groups in ASD (P = 0.042) but not in ADHD (P = 0.147) (Table S3).

The differential abundance analyses comparing children with ADHD and ASD at baseline identified 21 microbial genera (from 5 different classes) and 1 class (Clostridia) discriminating the two diseases, 13 of them, over-represented in ADHD (Fig. 4A, Table S4). The overall predictive accuracy of the classification model (AUC) was 0.939 (95 %CI, 0.937–0.941), with a sensitivity of 0.872 (95 % CI, 0.866–0.879) and a specificity of 0.923 (95 %CI, 0.917–0.928). In ADHD, Firmicutes-related taxa were found higher compared to ASD: Clostridia class constituted a significant 84.6 % of the total microbiota, whereas the classes Bacilli and Coriobacteriia were found in lower proportions, each contributing 7.69 % to the total microbiota (Fig. 4B). Conversely, in ASD children, Actinobacteria and Clostridia classes each accounted for 11.1 % of the total microbiota. The class Bacilli was the most abundant in ASD, constituting 33.3 % of the microbiota, followed by Bacteroidia and Coriobacteriia, each contributing 22.2 %. Different relative contributions from the single genus towards the total distinctive properties are distinguished, expressed as β-coefficients.

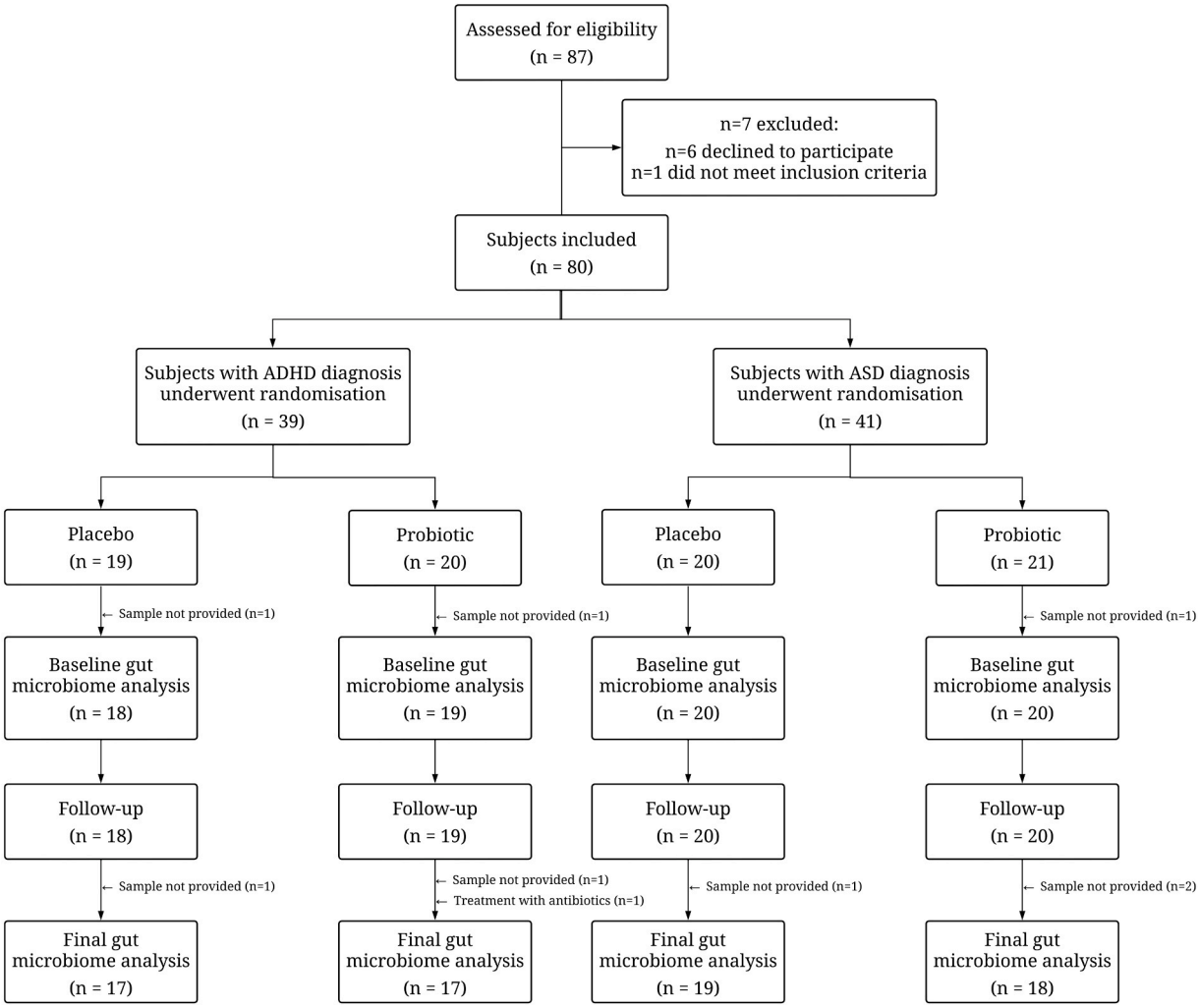

Fig. 1. Flowchart of the study.

Table 1
Baseline characteristics of study subjects.

Characteristic	ADHD	ASD	P-value
Sex, (M/F), n	28/11	34/7	0.355
Age (years)	10.00 [7.00, 12.00]	10.00 [7.50, 11.00]	0.973
Weight (kg)	34.00 [26.00, 45.90]	32.00 [26.25, 50.00]	0.832
Height (cm)	139.62 (14.51)	141.83 (16.55)	0.526
BMI (kg/m^2)	17.35 [15.44, 20.45]	17.86 [14.89, 21.21]	0.747
BMI-for-age z-score	0.59 (1.35)	0.43 (1.61)	0.640
Medication, (yes/no), n	9/30	16/25	0.195

Normal distributed continuous data is presented as a mean (standard deviation), not normal distributed continuous data is presented as median [interquartile range]. Chi-square, Mann-Whitney U-test, and t-tests were conducted for categorical, non-normally, and normally distributed variables, respectively. Abbreviations: BMI, body mass index.

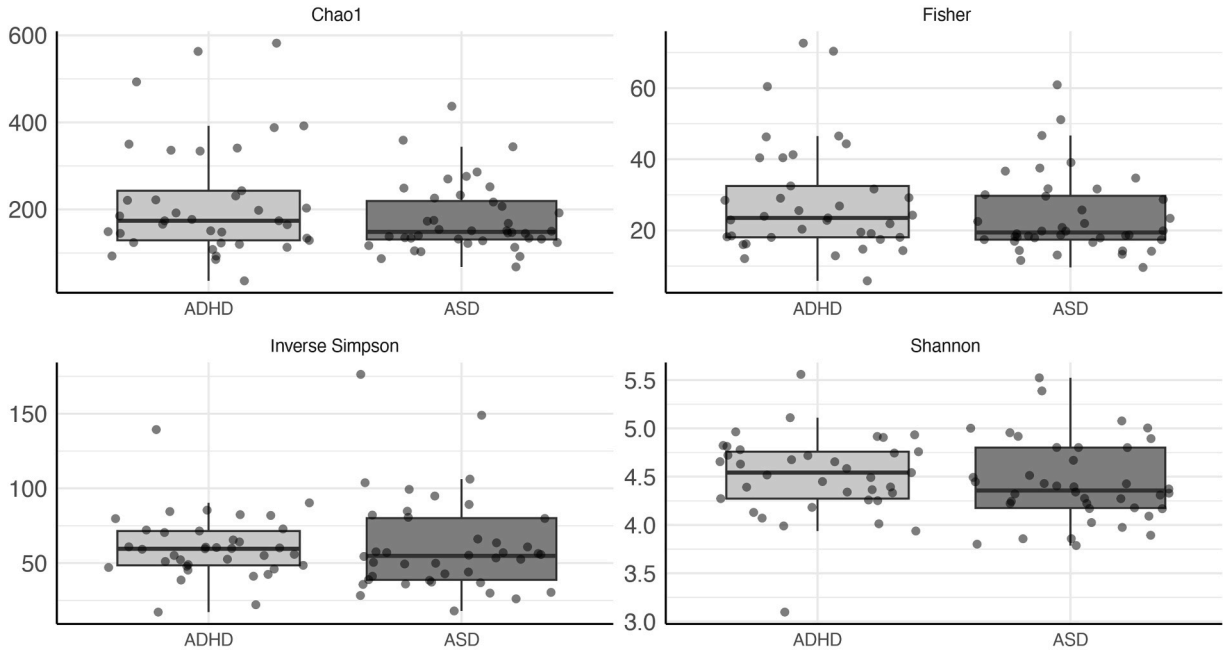

Fig. 2. Alpha diversity indexes for the ADHD and ASD groups at baseline. Box plots were generated for alpha diversity indices (Chao1, Fisher's alpha, Inverse Simpson and Shannon). No significant differences were observed.

Our analysis highlighted 3 unique microbial genera associated with the probiotic intervention in ADHD and ASD children when analyzed together. *Odoribacter* genus was over-represented after the probiotic consumption, while *Colidextribacter* and an uncultured genus from the order Rhodospirillales were under-represented in the probiotic compared to the control group (Fig. 5A.1, Table S5).

Regarding the effect of the intervention on each specific disease, within the ADHD group, the probiotic intervention resulted in an increased abundance of *Odoribacter*, while an uncultured genus from the Eggerthellaceae family and *Escherichia-Shigella* were found to be under-represented (Fig. 5B.1, Table S6). In ASD children, we identified 5 genera downregulated in the probiotic group compared to the placebo including *Coprococcus*, 2 uncultured genera (belonging to the Peptococcaceae family and Rhodospirillales order), *Phocea* and *Angelakisella* (Fig. 5C.1, Table S7). No genera were found overexpressed after the probiotic consumption in ASD. Most of the results did not change after adjusting for potential confounders (Tables S8-S11).

Analysis of the potential functional contribution of the microbiota associated with both conditions at baseline identified 33 global KEGG pathways at level 2 (Figure S2). Significant differential pathway expression between diseases (FDR-P < 0.05) encompassed 23 pathways in carbohydrate and lipid metabolism, 12 in amino acid metabolism, 6 in energy metabolism, 3 in glycan biosynthesis, 11 in cofactor and vitamin metabolism, and 1 in the immune system (Figure S3, Table S12).

Significant correlations were found between KOs categories and differentially represented taxa (Spearman's correlation, Fig. 5A.2, 5B.2, 5C.2, Tables S13-S16). At baseline, taxa differentially expressed between diseases correlated with 56 KOs. In post-probiotic intervention, 70 KO categories were correlated with the modulated taxa in ADHD and ASD when analyzed together. Although most of them showed an inverse association, 6 KOs were positively correlated with *Odoribacter*. In ADHD children, 73 KO categories exhibited positive correlations with the taxa found to be modulated by the intervention, whereas in ASD, only K07026, which is related to fructose and mannose metabolism, was negatively correlated with the lower abundance of Rhodospirillales and *Angelakisella*.

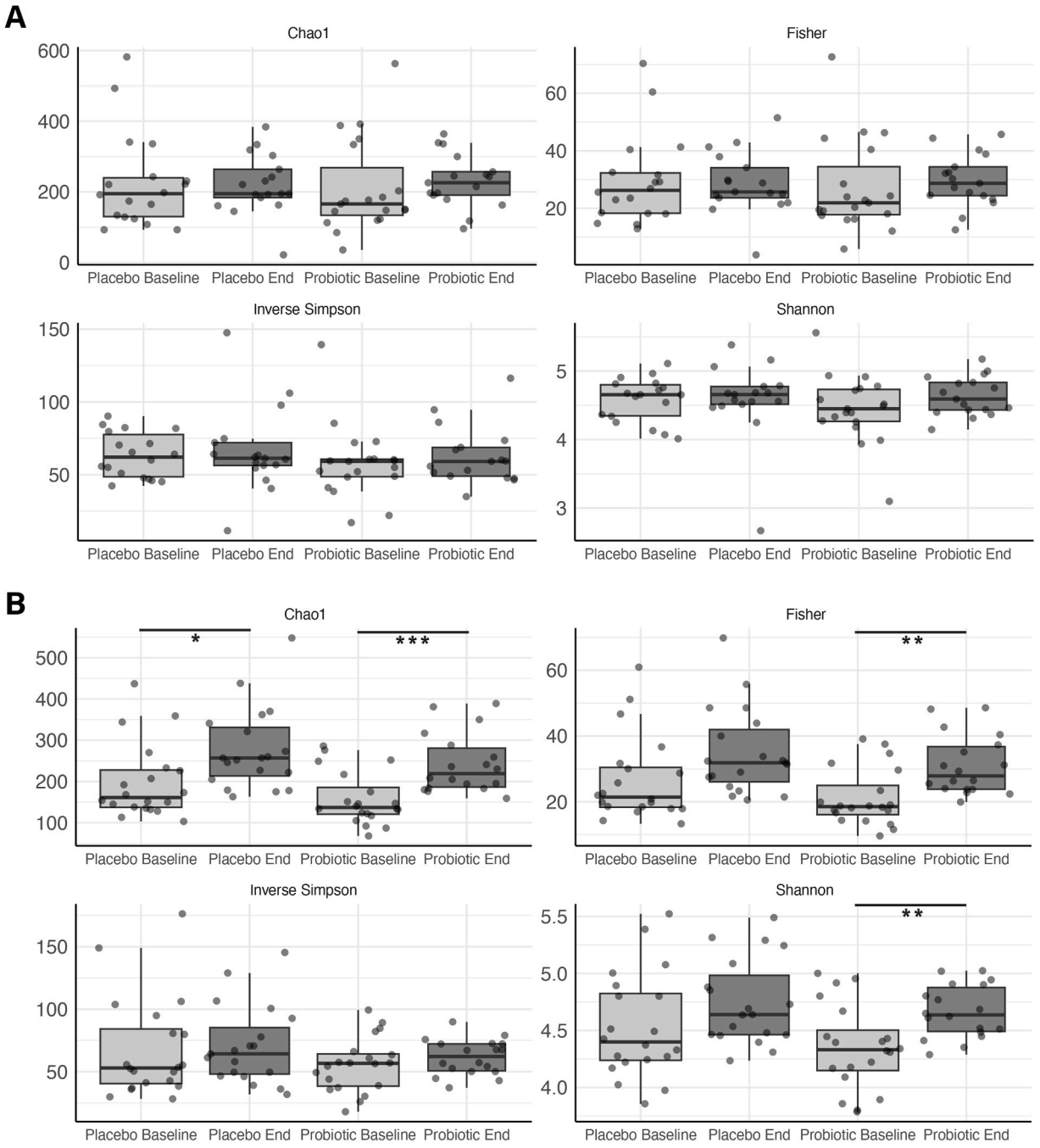

Fig. 3. Baseline and post-treatment alpha diversity in ADHD (A) and ASD (B) children across intervention groups. Box plots were generated for alpha diversity indices (Chao1, Fisher's alpha, Inverse Simpson and Shannon). P value is indicated by ***P < 0.001, **P < 0.01 and *P < 0.05.

4. Discussion

In this study, we identified, for the first time, a lower microbial diversity, with a higher abundance of Firmicutes-related taxa in ADHD children compared to ASD. Our results also demonstrate a differential effect of a 12-week probiotic intervention on gut microbiota composition in ADHD compared to ASD children.

The role of gut microbiota in mental and neurological disorders has gradually attracted attention. Gastrointestinal (GI) symptoms such as diarrhoea, constipation and abdominal pain are common in both ADHD and ASD, and positively correlated with their severity (Iglesias–vázquez et al., 2020; Ming et al., 2018). This suggests that components of the GI tract can play an important role in the

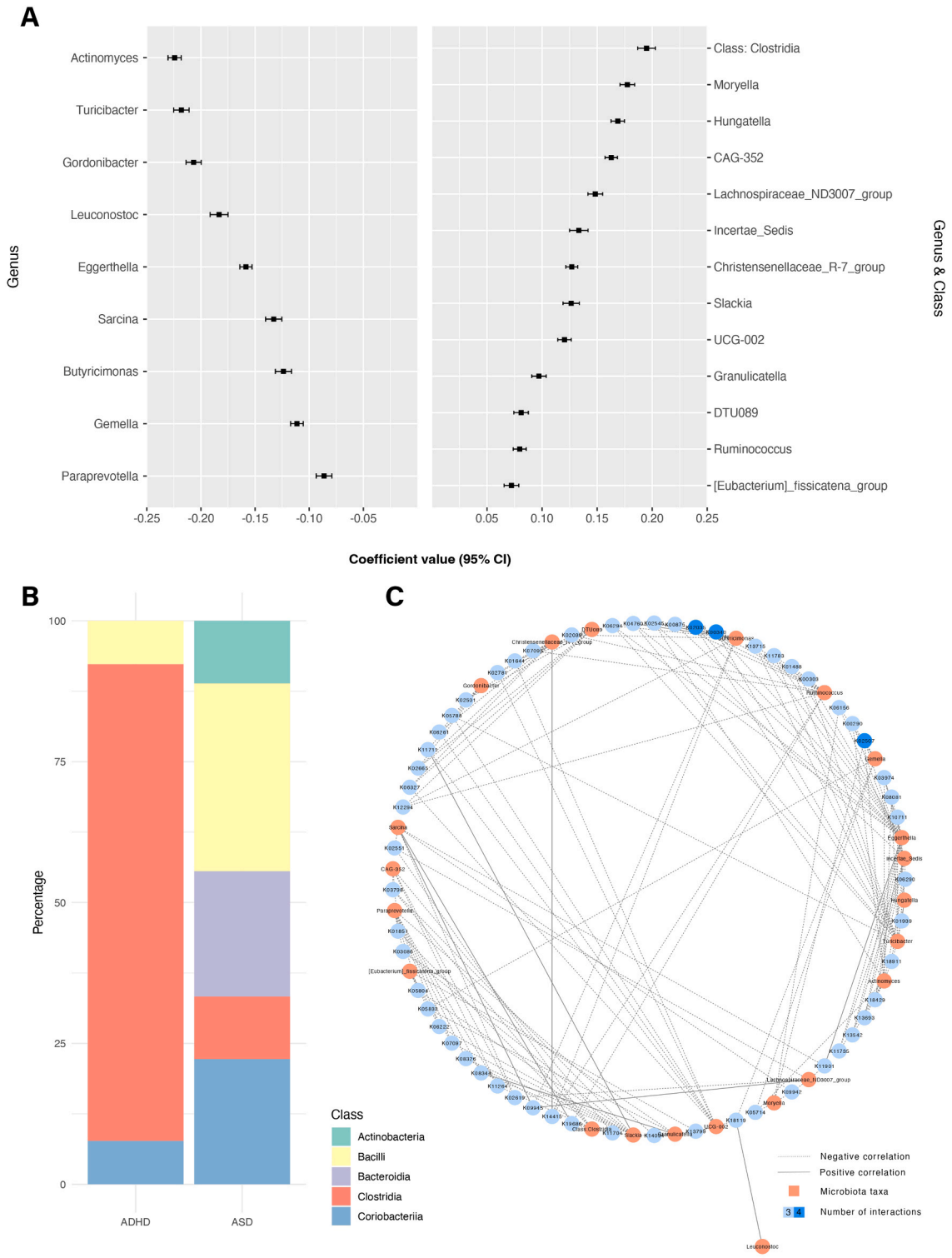

Fig. 4. Microbiota taxa differentially expressed in ADHD vs ASD at baseline, and KO categories interactions. (A) Microbiota genus and class (Clostridia) taxa ranked from the highest to the lowest elastic net positive and negative regression coefficients for ADHD vs ASD at baseline. Microbiota genus and class (Clostridia) taxa with negative coefficients (n = 9) are plotted in the left part, whereas those with positive coefficients (n = 13) are shown in the right part. (B) Frequency of classes from the identified taxa associated with ADHD and ASD. (C) Correlation network of the significant differentially expressed species and KO categories.

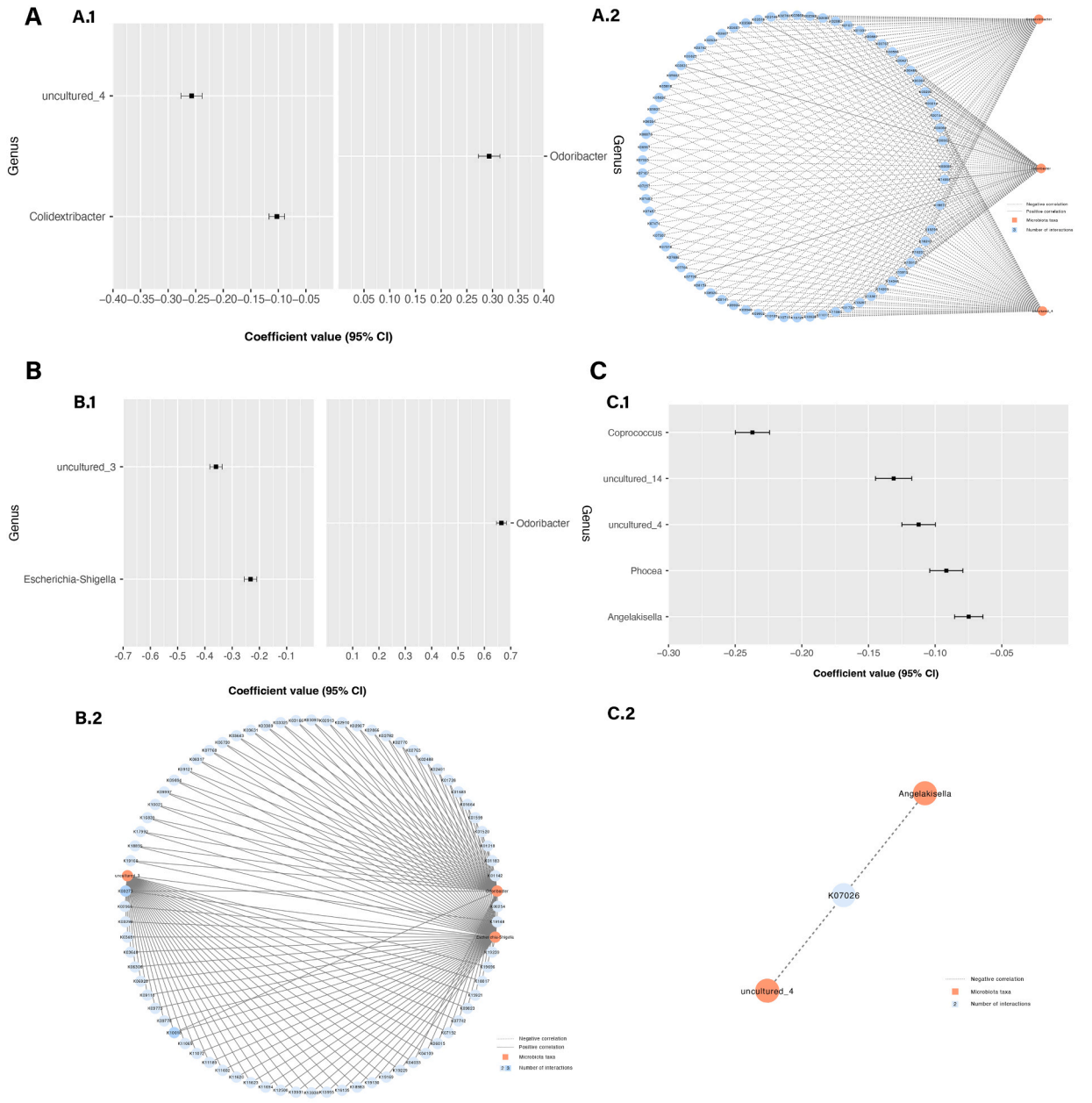

Fig. 5. Microbiota taxa differentially expressed in ADHD and ASD post-probiotic intervention, and KO categories interactions. (A.1) Microbiota genus taxa ranked from the highest to the lowest elastic net positive and negative regression coefficients for placebo and probiotic comparison using delta data (B.1) using delta data of ADHD disease and (C.1) using delta data of ASD disease. Microbiota genus taxa with negative coefficients are plotted in the left part, whereas those with positive coefficients are shown in the right part. (A.2, B.2, C.2) Correlation network of the significant differentially expressed species for each comparison and KO categories.

development and clinical progression of these disorders and have prompted research on the interplay between gut microbiota, and ADHD/ASD (Bundgaard-Nielsen et al., 2020).

Epidemiological studies consistently reported microbiota dysbiosis in ASD patients, displaying reduced levels of beneficial bacteria and increased harmful bacteria (Fattorusso et al., 2019). However, results on the specific taxonomical composition are not robust across different studies (Iglesias–vázquez et al., 2020; Xu et al., 2019; Andreo-Martínez et al., 2022). These discrepancies could be attributed to the heterogeneity of ASD phenotypes while potential confounders are not always considered (West et al., 2022). However, fecal microbiota transplantation shift the microbiota composition of ASD children towards that of healthy controls (Kang et al., 2017; Li et al., 2021), and the administration of gut microbiota-related metabolites depleted in ASD patients to mice, improved the animal ASD-like behaviors (Sharon et al., 2019), supporting the modulation of the gut microbiome as a therapeutic strategy for

improving the clinical symptoms.

Comparatively, data on gut microbiota in ADHD patients is limited and highly heterogeneous, with studies reporting different composition in ADHD compared to controls, whereas others fail to find any difference (Gkougka et al., 2022). Methodological differences and important confounder factors like age and ethnicity make the interpretation even more complicated. In our study, we identified increased *Eggerthella* abundance in ASD compared to ADHD children, and decreased *Ruminococcus* and Clostridia. *Eggerthella* has been recently found over-represented in both ADHD and ASD children (Bundgaard-Nielsen et al., 2023), and its abundance is positively correlated with depression, anxiety and stress scores (Borkent et al., 2022). Then, our findings would contribute to explain the higher anxiety and depression commonly observed in ASD patients.

In our study, Clostridia was over-represented in ADHD children when compared with ASD. Clostridia is associated with elevated gut catecholamines, particularly dopamine and norepinephrine, mirroring ADHD's dopamine pathway dysregulation and norepinephrine's attentional role (Asano et al., 2012). The gut-brain communication and brain function may be influenced by gut metabolites, predominantly short-chain fatty acids (SCFAs), and by the inflammation induced by the lipopolysaccharide (LPS), a surface marker of gram-negative bacteria (Sandhu et al., 2017). Consistently, in our study, ADHD and ASD children had a higher abundance of Clostridia and the gram-negative class Bacteroidia respectively, both recognised as key producers of SCFAs (De Angelis et al., 2013; Wang et al., 2012). In comparison with ADHD, children with ASD had an increased abundance of Bacilli and Actinobacteria consistent with findings from previous studies (Plaza-Díaz et al., 2019; Dan et al., 2020) comparing ASD subjects with healthy controls. We also found a higher abundance of Clostridia, and other robust butyrate-producers such as *Ruminococcaceae* and *Lachnospiraceae* in children with ADHD. Their association with butanoate-related pathways is consistent with the elevated butanoate pathways in ADHD reported in our study.

Previous studies have described a lower abundance of Actinobacteria in ASD compared to healthy children (Finegold et al., 2010; Adams et al., 2011), while *Actinomyces* was over-represented in ADHD children (Loo et al., 2022). In our study, we observed a lower abundance of *Actinomyces* in ADHD children. Since we did not include healthy subjects, we cannot evaluate whether this lower abundance observed in ADHD, although low, was still higher than in healthy children. Recently, Bundgaard-Nielsen et al. conducted the only study to date that evaluated differences in gut microbiota composition, as assessed by 16S rRNA gene sequencing of the V4 region, between the two diseases (Bundgaard-Nielsen et al., 2023). Similar to this previous study, we failed to find significant differences in α- and β-diversity. Contrary to their findings, we identified 13 taxa over-represented in ADHD. Interestingly, most of these taxa showed a non-significant trend to over-representation in Bundgaard-Nielsen's study (except for *CAG-352*, *Lachnospiraceae_ND3007_group* and *Granulicatella*). On the other hand, only 3 taxa found to be overexpressed in ASD in our study were also observed to be in the same direction in Bundgaard-Nielsen's study despite not being significant. The smaller number of ASD cases in their study ($n = 12$) could have limited the statistical power to detect any differences.

The probiotic intervention significantly modulated 3 taxa when children with ADHD and ASD were analysed together. Specifically, *Odoribacter*, a butyrate-producing bacterial genus related to better metabolic health in children (Yuan et al., 2021), and negatively associated with depression and fatigue in intestinal bowel disease patients (Thomann et al., 2022), was significantly over-represented in children consuming the probiotic. *Odoribacter* abundance was also significantly higher in ADHD children after the probiotic intervention but not in ASD. We also report a lower abundance of *Colidextribacter* and an uncultured genus from the order Rhodospirillales after the probiotic consumption. *Colidextribacter* has been associated with a positive response to antidepressant treatment in a mouse model of depression (Duan et al., 2021). But *Colidextribacter* abundance has also been found correlated with inflammation-related serum metabolites implying that its reduction may improve several symptoms in ADHD and ASD (Bai et al., 2021). Similarly, an uncultured bacteria of the order Rhodospirillales was found more abundant in adults with major depressive disorder compared to controls (Liu et al., 2020). Although both uncultured bacteria could be different, these findings support a beneficial effect of our probiotic through the modulation of bacteria belonging to the Rhodospirillales order. Remarkably, we found Rhodospirillales and *Colidextribacter* negatively correlated, while *Odoribacter* positively correlated with the sarcosine oxidase pathway. Sarcosine is transformed into glycine, which plays a crucial multifaceted role in human functions, such as in the formation of nucleic acids and the maintenance of the central nervous system homeostasis (Wang et al., 2013), and has been postulated to serve as a coadjuvant treatment for depression or schizophrenia (Tsai et al., 2004). Overall, these findings support the use of a probiotic intervention in children with ADHD and ASD irrespective of the type of disease.

When we analysed the effect of the intervention in ADHD children, we found a lower abundance of *Escherichia-Shigella*, two gram-negative bacteria usually associated with harmful effects. *Shigella* infection in early childhood has been related to a higher risk of having ADHD (Merzon et al., 2021), and both bacteria produce LPS and promote inflammation via toll-like receptor (TLR) or inflammasome cascades, causing gastrointestinal discomfort (Kotloff et al., 1999; Kaper et al., 2004). Furthermore, an uncultured genus from the Eggerthellaceae family was decreased in ADHD. While the specific role of this family in ADHD remains elusive, the Eggerthellaceae has been associated with depression (Radjabzadeh et al., 2022) and some psychiatric disorders such as major depressive disorder, bipolar disorder and schizophrenia-spectrum disorders (Borkent et al., 2022).

The probiotic intervention in ASD children was related to an unexpected lower abundance of *Coprococcus*, associated to the synthesis of key neurotransmitters for depression such as glutamate, butyrate, serotonin and gamma amino butyric acid (GABA) (Radjabzadeh et al., 2022; Kumar et al., 2023). The probiotic intervention was also related to a lower abundance of *Phocea* and *Angelakisella*, both belonging to the Clostridia class. A higher abundance of Clostridia has been associated with gastrointestinal problems in ASD patients (Parracho et al., 2005). Clostridia are recognized toxin-producers, including neurotoxins which could exert systemic effects (Hatheway, 1990). Moreover, *Phocea* has been correlated with comorbid anxiety as well as motor function deficits in mice (Jang et al., 2020), and with alterations in immune function. Therefore, its decreased abundance could contribute to improved specific traits in autism patients (Buie, 2015).

Our study presents several strengths. The double-blind, randomised controlled design minimizes potential bias and strengthens the robustness of the findings. Since we not only assessed the effects of probiotic supplementation on gut microbiota in both ASD and ADHD, but also we discerned the inherent differences in gut microbiota composition between these two diseases, our study offers an opportunity to enhance the biological mechanisms driving the differences between the two diseases. By investigating the influence of probiotic supplementation in the context of specific disease status (ASD or ADHD), we offered a new perspective on how these interventions could be tailored to meet the needs of distinct patient populations. Despite the strengths of our study, certain limitations must be considered. First, our results could not be extrapolated on children without this neurodevelopmental disorder. The intervention's duration does not capture the long-term gut effects. 16S rRNA sequencing does not guarantee species identity and it's increasingly evident that different species within the same genus can exhibit different activities and responses suggesting that future probiotic designs would consider other approaches to identify species. Finally, we did not directly examine microbiota activity, though we attempted to address this limitation at the predictive level.

5. Conclusion

Our study demonstrated significant differences in the abundance and composition of gut microbiota between ADHD and ASD children, pinpointing specific taxa such as Clostridia, *Ruminococcaceae*, and *Lachnospiraceae* associated with ADHD, and Bacteroides, Bacilli and Actinobacteria with ASD. Probiotic supplementation demonstrated significant potential by increasing butyrate-producing bacteria and reducing potentially harmful genera in children diagnosed with ADHD and ASD. This suggests potential therapeutic avenues targeting these specific microbial genera for each disorder. Our research also reinforces the potential for probiotic interventions to restore the microbiota composition, particularly in children with ASD. Future research is needed to validate our observations and to further understand the intricate relationship between gut microbiota and neurodevelopmental disorders.

CRediT authorship contribution statement

Bulló Mònica: Writing – review & editing, Writing – original draft, Validation, Supervision, Methodology, Investigation, Funding acquisition, Conceptualization. **Canals-Sans Josefa:** Writing – review & editing, Validation, Supervision, Methodology, Funding acquisition, Conceptualization. **Rojo-Marticella Meritxell:** Writing – review & editing, Methodology, Investigation, Data curation. **Papandreou Christopher:** Writing – review & editing, Writing – original draft, Validation, Supervision, Formal analysis. **Novau-Ferré Nil:** Writing – original draft, Validation, Methodology, Formal analysis.

Declaration of Competing Interest

The authors have declared no potential conflicts of interest relevant to this article to disclose, nor any financial ties to AB Biotics S. A. (Barcelona, Spain). AB Biotics S.A. do not have a role in the design, collection, analysis, or interpretation of the data or in the decision to submit the manuscript for publication.

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AB Biotics S.A have provided placebo and probiotics.

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Institutional review board statement

The institutional review board of the Institute of Health Pere Virgili approved the study protocol in May 2018 (Ref.CEIM:030/2017) and written informed consent was obtained. All patients included in this study were agreed and signed their Informed Consent Statements.

Authors' information

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ridd.2025.105003.

Data availability

Data will be made available on request.

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