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Review Article

The Microbial Factors, Trace Elements, and Important Biological Indicators in Children with Autism Spectrum Disorder: A Meta-Analysis

Keli Qu [1]***, Zhiliang Gao*** [2]***, Cong Chang*** [3]***, *Meizhe Gao*** [1]

1. *Department of Child Healthcare, Shandong Provincial Third Hospital, Shandong University, Jinan, China*
2. *Department of Pediatric, Binzhou Hospital of Traditional Chinese Medicine, Binzhou, China*
3. *Department of Rehabilitation, Binzhou Municipal Hospital, Binzhou, China*

***Corresponding Author:** Email: gmzh2022@163.com

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Abstract

Background: We examined and compared microbiological variables, trace elements, and biological markers in autistic children.

Methods: Several databases, including the Cochrane Library, PubMed, OVID, Google Scholar, and Embase, were utilized for data collection and analysis. We studied meta-analysis data and used a continuous model with fixed or random effects to get mean differences (MD) with 95% confidence intervals (CIs). Twenty-seven studies involving 2557 children from 2014 to 2024 were analyzed.

Results: Autism spectrum disorder had significantly higher C-reactive protein (MD, 1.25; 95% CI, 0.11-2.39, *P*=0.03), interleukin 6 (MD: 2.80; 95%CI, 1.13-4.46, *P*=0.001), serotonin (MD, 111.92; 95%CI, 63.75-160.09, *P*<0.001), *Faecalibacterium* (MD, 0.48; 95%CI: 0.29-0.66, *P*<0.001), and *Parabacteroides* (MD, 0.20; 95%CI: 0.14-0.26, *P*<0.001), lower oxytocin (MD, -53.24; 95% CI, -73.39- -33.09, *P*<0.001), and serum iron (MD, -5.78; 95% CI, -9.43- -2.13, *P*=0.002) compared to control in children.

Conclusion: Autism spectrum disorder had significantly higher C-reactive protein, interleukin-6, serotonin, *Faecalibacterium*, *Parabacteroides*, lower oxytocin, and serum iron compared to control in children. Further research studies with larger sample sizes are needed.

Keywords: Microbial factor; Trace element; Important biological indicator; Serotonin; Autism spectrum disorder

Introduction

Autism spectrum disorder (ASD), as a complicated developmental illness, usually appears in toddlers and preschoolers. Problems with speech, social contact, and the development of obsessions or ritualized behaviors are hallmarks of this disorder (1). One in 44 children aged 8 years was diagnosed with autism in 2021, according to the American Centers for Disease Control and Prevention. An estimated one percent of the global population has autism (1). Boys are three to four times more likely to have autism than girls, and males with the disorder typically show more overt symptoms than their female counterparts (2).

The American Psychiatric Association's Fifth Edition of Diagnostic and Statistical Manual of Mental Disorders serves as a major source of information for the current clinical diagnosis of autism (3). Many of the most evident symptoms of ASD, e.g., a stop acquiring new abilities or a loss of previously acquired ones, frequently appear between the ages of two and three. Nevertheless, it can be challenging to make definitive predictions about future cognitive impairment in children as young as two or three years old (3). The pathogenesis of ASD remains complicated and inadequately comprehended despite extensive study (4).

According to recent biomarker studies, patients with autism disorder experienced lower levels of iron (5) and zinc (6), higher levels of inflammatory factors like C-reactive protein (C-RP) (7), and lower levels of beneficial bacterial microbiota (8) than healthy individuals. Finding biomarkers could shed light on the etiology and underlying mechanisms of the illness (9). Nevertheless, no research has comprehensively evaluated the traits of ASD patients in contrast to those in the healthy population. By thoroughly analyzing a variety of supposed biomarkers linked to ASD, e.g., biological markers, trace elements, and microbial variables, using the meta-analysis approach, this study sought to close this research gap. This approach includes trace elements (iron), microbiota-related factors (*Faecalibacterium and Parabacteroides*), and theoretical biological indicators (oxytocin, serotonin, C-RP, and interleukin 6) in autism disease. Certain biomarkers were included in this investigation based on their known functions in biological pathways related to ASD. The selection of oxytocin, serotonin, C-RP, and interleukin 6 was based on their known roles in immune system control, neurotransmission modulation, and neurodevelopmental processes—all of which are essential components linked with the pathophysiology of ASD (7).

Understanding the neurological foundations of social cognition, affective control, and behavioral responses—all of which are markedly compromised in people with ASD—requires an understanding of these biomarkers. Moreover, trace elements—iron—are included because of their vital functions as cofactors in vital enzymatic activities that are crucial for central nervous system development and synapse functions (10). Variations in its levels have been shown to correlate with characteristics associated with ASD; thus, it should be investigated in this regard. Further research explaining the mutual connection between the gut microbiota and the brain is in line with the investigation of microbiota components, e.g., *Faecalibacterium* and *Parabacteroides* (11). These factors are being investigated in relation to ASD because they may have an impact on behavior and neurodevelopment.

We aimed to expand our understanding of the molecular basis of ASD, and may help create new techniques for diagnosis and treatment by reviewing and synthesizing the literature on these biomarkers.

Methods

Meta-analysis Investigational Design

The study performed here followed the meta-analysis of observational studies in the epidemiology statement (12), which was conducted following an established protocol. Several databases, including the Cochrane Library, PubMed, OVID, Google Scholar, and Embase, were utilized for data collection and analysis. The datasets were utilized to conduct studies that compared microbiological variables, trace elements, and biological markers in autistic children to a control healthy group of children.

Data collection

Language barriers were not considered during the inclusion of research or the screening procedure for prospective participants. No limitations existed regarding the number of children in the selected studies. Because letters, reviews, and opinions do not have a place in meta-analysis, we did not include them in our study. Fig. 1 illustrates the complete inspection identification process.

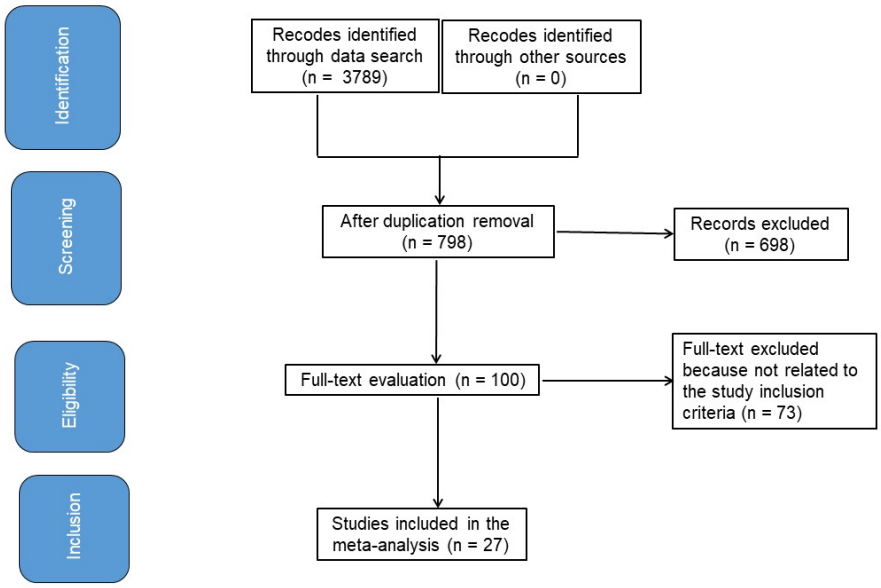

Fig. 1: Schematic diagram of the examination procedure

Eligibility of included studies

The microbial factors, trace elements, and important biological indicators in children with ASD were being studied (13). Subclass and sensitivity analyses were implemented by associating the numerous subtypes with the interference groups.

Inclusion and exclusion criteria

To identify and include studies in the analysis, the following criteria were used:

1. A prospective, observational, randomized controlled trial was conducted.
2. The selected subjects that were investigated were children.
3. Children with ASD were the interference.
4. The study highlighted the role of microbiome, trace elements, and key biological markers in children with ASD.

Study identification

A protocol of search algorithms was established and specified by the PICOS principle: P (population) was children; I (Interference) was children with ASD; C (comparison): comparing the children with ASD with a healthy group of children; O (outcome) was presence of microbiological variables, trace elements, and biological markers; and S (study design): the planned valuation was unlimited. We conducted a comprehensive search of the relevant databases up until April 2024 using the terms from Table 1. Paper replications were removed, and the rest were combined into a reference management program file, and their titles and abstracts were reassessed to avoid a study that would not have been suitable to the comparison of the meta-analysis (14).

Screening of studies

The investigation was given in a regular format, along with each of its component features. First author's last name, the study's date, the nation in which it was taking place, the type of population that was employed for meta-analysis, total number of children, clinical and treatment characteristics, demographic information, and qualitative and quantitative evaluation methods were some criteria applied to decrease the data (15). Two authors looked into the possibility of bias in the studies and the standard of approaches utilized in papers selected for supplementary analysis. The two authors conducted unbiased reviews of techniques used for each test (16).

Table 1: Database Search Strategy for inclusion of examinations

Database	Search strategy
Google Scholar	#1 "microbial factor" MD "trace element" #2 "serotonin" MD "autism spectrum disorder" MD " "C-reactive protein" MD "important biological indicator" #3 #1 AND #2
Embase	#1 'microbial factor' /exp MD 'trace element' /exp MD 'C-reactive protein' #2 'serotonin'/exp MD 'autism spectrum disorder'/exp MD 'important biological indicator' #3 #1 AND #2
Cochrane library	#1 (microbial factor):ti,ab,kw (trace element):ti,ab,kw (C-reactive protein):ti,ab,kw (Word variations have been searched) #2 (serotonin):ti,ab,kw MD (autism spectrum disorder):ti,ab,kw MD(important biological indicator):ti,ab,kw (Word variations have been searched) #3 #1 AND #2
Pubmed	#1 "microbial factor"[MeSH] MD "trace element"[MeSH] MD "C-reactive protein" [All Fields] #2 "serotonin"[MeSH Terms] MD "autism spectrum disorder"[MeSH] MD "important biological indicator "[All Fields] #3 #1 AND #2
OVID	#1 "microbial factor"[All Fields] MD "trace element" [All Fields] MD "C-reactive protein" [All Fields] #2 "serotonin"[All fields] MD "autism spectrum disorder"[All Fields] or "important biological indicator"[All Fields] #3 #1 AND #2

Statistical analyses

With the use of continuous models with random or fixed effects, the mean difference (MD) with its 95% confidence interval (CI) was obtained. A calculated I^2 index, given as a percentage, can take on values between zero and one hundred. A lower I^2 value indicates less heterogeneity, whereas a higher one indicates high heterogeneity. We used a random effect if the I^2 value was 50% or higher and a fixed effect otherwise. The two-tailed method was used to obtain *P*-values and to measure bias in quantitative analysis (Egger's tests). A *P*-value greater than 0.05 was deemed to indicate the presence of bias. Graphs and statistical analyses were generated using Review Manager 5.4 (The Nordic Cochrane Centre, Cochrane Collaboration, Copenhagen, Denmark) (17).

Results

After examining 3789 relevant publications, 27 studies that were published between 2014 and 2024 satisfied the inclusion criteria and were encompassed in this study (5-8, 18-40). 2557 children were in the selected studies, of them 1809 were ASD, and 1748 were control.

ASD had significantly higher C-RP (MD, 1.25; 95% CI, 0.11-2.39, P=0.03) with high level of heterogeneity (I^2=96%), interleukin 6 (MD, 2.80; 95% CI, 1.13-4.46, P=0.001) with high level of heterogeneity (I^2=94%), serotonin (MD, 111.92; 95% CI, 63.75-160.09, P<0.001) with high heterogeneity (I^2=96%), *Faecalibacterium* (MD, 0.48; 95% CI, 0.29-0.66, P<0.001) with no heterogeneity (I^2=0%), and *Parabacteroides* (MD, 0.20; 95% CI, 0.14-0.26, P<0.001) with no heterogeneity (I^2=0%), and lower oxytocin (MD, -53.24; 95% CI, -73.39- -33.09, P<0.001) with moderate het-

erogeneity (I^2=71%), and serum iron (MD, -5.78; 95% CI, -9.43- -2.13, *P*=0.002) with high heterogeneity (I^2=96%)compared to control in children, as shown in Figs. 2-8.

There was no evidence of bias (*P* = 0.861) in the quantitative Egger regression test or in the visual assessment of the effect's forest plot. The mainstream of relevant tests was shown to have biased selective reporting and low practical quality.

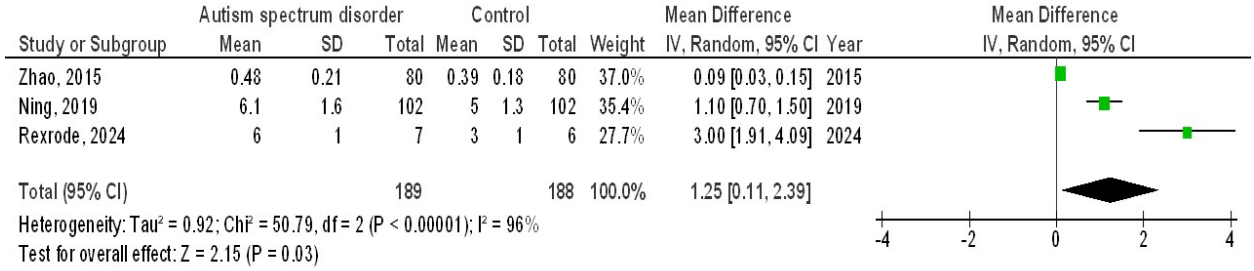

Fig. 2: The effect's forest plot of the autism spectrum disorder on C-reactive protein compared to control in children.

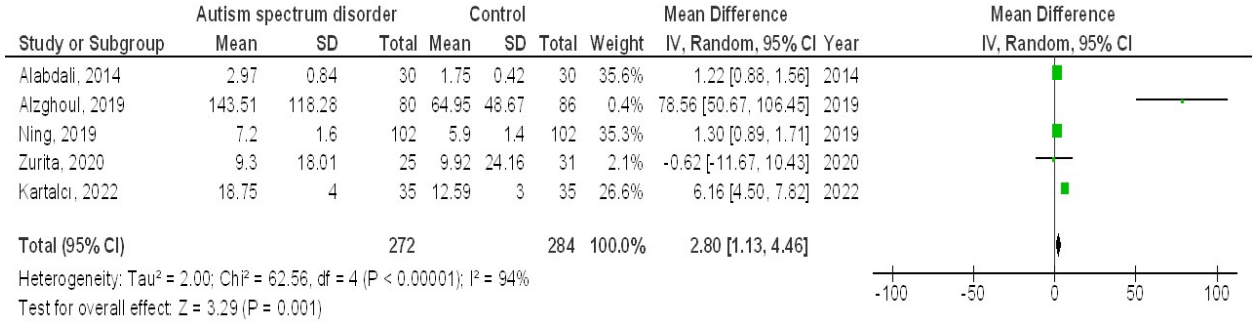

Fig. 3: The effect's forest plot of the autism spectrum disorder on interleukin 6 compared to control in children.

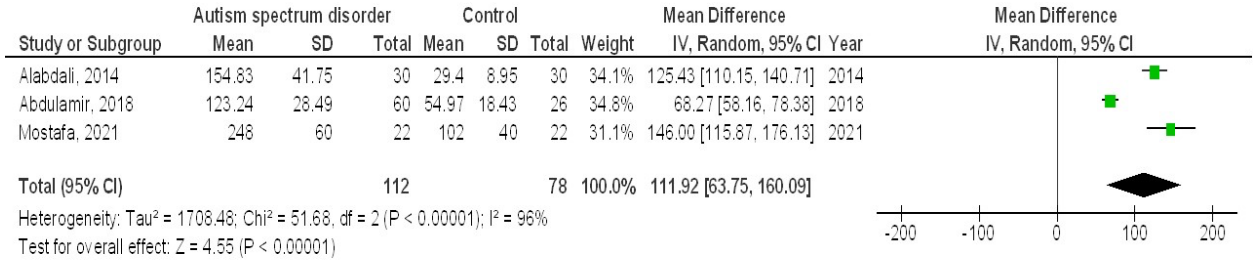

Fig. 4: The effect's forest plot of the autism spectrum disorder on serotonin compared to control in children.

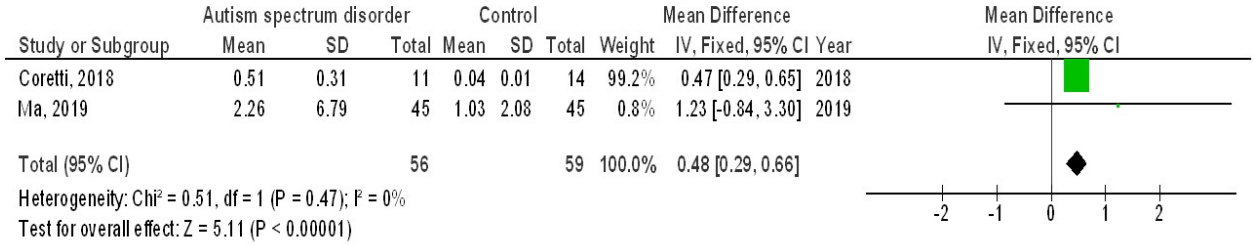

Fig. 5: The effect's forest plot of the autism spectrum disorder on Faecalibacterium compared to control in children.

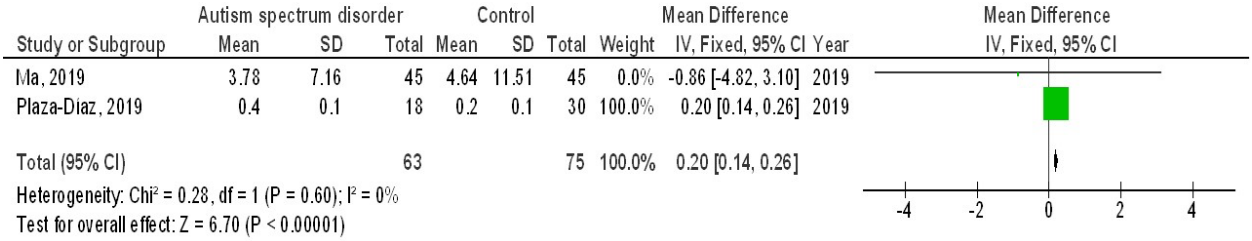

Fig. 6: The effect's forest plot of the autism spectrum disorder on Parabacteroides compared to control in children.

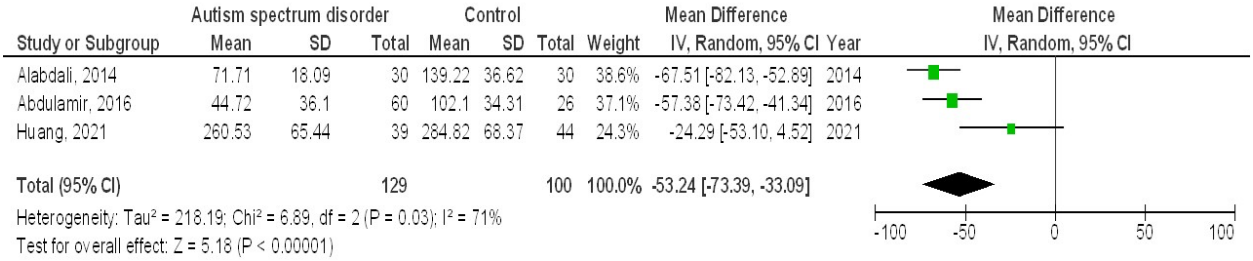

Fig. 7: The effect's forest plot of the autism spectrum disorder on oxytocin compared to control in children.

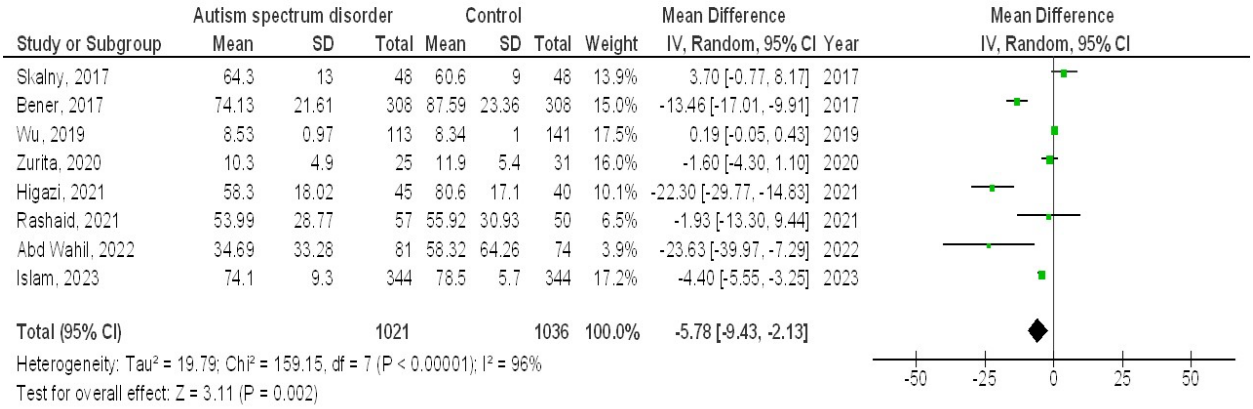

Fig. 8: The effect's forest plot of the autism spectrum disorder on iron compared to control in children.

Discussion

For the current meta-analysis, 27 studies that were published between 2014 and 2024 were included, with 2557 children; of them, 1809 were ASD, and 1748 were control (5-8, 18-40).

An analysis of the data revealed that individuals with ASD exhibited significantly elevated levels of C-RP, interleukin 6, serotonin, *Faecalibacterium*, *Parabacteroides*, and lower oxytocin and serum iron compared to control in children. Though given that most of the studies comprised a low sample size (19 studies utilizing sample sizes lower than 100 children) and some comparisons included a low number of selected studies, care must be taken when interacting with its values.

There is growing recognition that inflammatory processes may play a role in the pathophysiology of ASD. ASD patients have been shown to have changes in immune system indicators, and inflammation can have an impact on brain development and function. (41) Two of the most ex-

tensively researched inflammatory indicators, C-RP and interleukin 6, have been linked to ASD in earlier studies (42). Systemic inflammation is reflected by the acute-phase protein C-RP (43). Pro-inflammatory cytokine interleukin 6 plays a role in both immunological responses and neuronal plasticity (44). Elevated C-RP may worsen the central nervous system by increasing the paracellular permeability of the blood-brain barrier and stimulating the microglia (45). Microglia have been shown to be important in the pathophysiology of ASD in earlier research (42).

As a result, there may be a link between C-RP levels and ASD. C-RP may be a useful biomarker for the diagnosis of ASD. Increased levels of interleukin 6 have been reported in autoimmune diseases, as well as in a variety of neurodegenerative pathologies, including Alzheimer's disease (46). Furthermore, investigations have shown that interleukin 6 levels were higher during gestation in children who were later diagnosed with ASD, possibly due to interleukin 6 accumulating in the fetuses after it crossed the placental barrier (47). Additionally, a number of neurodevelopmental processes, e.g., emotional control, sensory integration, and social cognition, have been linked to neurotransmitters (48). People with ASD may have changes in these neurotransmitter levels and function (49). Oxytocin has demonstrated potential as a possible biomarker for ASD, given its well-known involvement in social bonding and attachment (50).

Studies have also looked into serotonin, which is important in mood regulation and sensory processing. They have found that people with ASD have different serotonin levels. Possible association between ASD and oxytocin receptor gene variations has been reported in a prior meta-analysis (51). Nevertheless, when taking into account the full genome, this connection falls short of the significance threshold. Furthermore, a great deal of research has been done to investigate the possibility of oxytocin therapy for people with ASDs (52). Even though the majority of these studies have produced conflicting findings, oxytocin may one day be used as a biomarker to diagnose ASD. Trace elements are essential for several biological activities, e.g., immune system function, antioxidant defense, and neurotransmitter production (53-55).

ASD patients have been found to exhibit imbalances in these trace elements, indicating a possible connection between the pathophysiology of the condition and their dysregulation (56). For example, low iron levels have been linked to the socioemotional challenges and decreased cognitive performance seen in ASD (57). We have discovered reduced iron levels in the ASD groups in this meta-analysis. Although it is known that ASD is associated with a mineral imbalance, we hope that relevant tests will be implemented and that standard trace element levels will be established as prospective biomarkers that can be useful for ASD diagnosis, prevention, and treatment.

Recent studies have also brought attention to the gut microbiome's possible role in ASD (58). The gut microbiota, a diverse community of bacteria found in the digestive tract, influences brain development and function through a two-way communication with the central nervous system. The gut microbiota may be a biomarker and potential treatment target for ASD because it is known that ASD patients have different microbial compositions and microbial metabolite abnormalities. Studies involving *Bifidobacterium* have sparked clinical studies for probiotic treatments (59). Probiotic intervention has been demonstrated to improve gastrointestinal symptoms and autistic behavioral scores in children with ASD (60, 61). Apart from the low quantity of helpful bacteria, there was also a reported rise in the quantity of bacteria such *as Bacteroides*, *Clostridium*, and *Faecalibacterium* in ASD (62). *Faecalibacterium*, a kind of bacteria that produces butyrate, has been linked to autism core symptoms and has been shown to impact gut homeostasis and physiological processes (63). Propionic acid, a neurotoxic short-chain fatty acid that has been linked to autism in animal studies, is mostly produced by the bacterium *Bacteroides* (64). Further research revealed that *Bacteroides* is what sets autistic individuals apart from control kids (65).

The study had some limitations, for example: Variety bias could have arisen because certain stud-

ies that were to be included in the meta-analysis were excluded. Nevertheless, none of the excluded studies meet the necessary criteria to be included in the meta-analysis. Still, the data was needed to determine whether influences e.g., ethnicity, age, and gender, influenced the outcomes. The objective of the study was to define the microbial factors, trace elements, and important biological indicators in children with ASD. Using inaccurate or inadequate data from a preceding study most likely made the bias worse. The children's age, gender, ethnicity, and nutritional state were the main variables that most likely contributed to bias. Values may unintentionally be modified as a result of unreported investigations and inadequate data.

Conclusion

ASD had significantly higher C-RP, interleukin 6, serotonin, *Faecalibacterium*, and *Parabacteroides*, and lower oxytocin and serum iron compared to control in children. Though given that most of the studies comprised a low sample size (19 studies utilizing sample sizes lower than 100 children) and some comparisons included a low number of selected studies, thoughtfulness ought to be given to their values.

Journalism Ethics considerations

Ethical issues (Including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc.) have been completely observed by the authors.

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Financial source of the study was negative.

Conflict of Interest

The authors declare that there is no conflict of interest.

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