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A REVIEW OF DIETARY AND NUTRITIONAL INTERVENTIONS AVAILABLE FOR MANAGEMENT OF AUTISM SPECTRUM DISORDER SYMPTOMS IN CHILDREN AND ADOLESCENTS - KENYA

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ABSTRACT

Research on the challenges of raising a child with autism is mostly reported from Europe, North America and Australia. There is limited autism spectrum disorder (ASD) research in Kenya and families lack support as the etiology is linked to witchcraft and sorcery. Research indicates an increase in ASD prevalence globally and in Africa. Malnutrition and neuro-disability are major public health problems in Africa. Approximately one billion people, 15% of the world's population, have a disability of some kind and 80% live in Low- and Middle-Income countries (LMICs). Of these, 53 million are children aged below 5 years living in sub-Saharan Africa. In Kenya, 2.2% (0.9 million people) live with some form of disability. Children diagnosed with autism spectrum disorder (ASD) suffer from neuro disabilities eliciting: altered sensory processing, restricted interests, and behavioral rigidity. Autism spectrum disorders have no cure, management is by use of interventional targeting autistic symptoms such as linguistic development, non-verbal cognitive development, and motor development. The objectives of this review were: to identify dietary and nutritional interventions available for the management of ASD symptoms in children and adolescents - Kenya, and to analyze the results of existing research in this area in order to understand and describe the characteristics and results of these studies to enable their use in the management of ASD symptoms. Cochrane Library, PubMed, PMC, Google scholar, and Free Full databases were searched to identify studies published between September 2011 and September 2021. Included were studies on nutrition or dietary interventions given to ASD children and adolescents that assessed autistic behavior and/or gastrointestinal symptoms. Excluded were those articles that evaluated surrogate outcomes as the primary outcome such as urinary peptide excretion and other neuro-disabilities other than ASD. Eighteen articles were included: 12 randomized case-control trials, 3 open-label trials, one 2×2 factorial study, and 2 cross-over trials. The following dietary and nutritional interventions were evaluated: gluten and casein-free diet, ketogenic diets; probiotic supplements, specific carbohydrate diets, polyunsaturated fatty acids, vitamin and mineral supplantation (A, B6, B12, D, magnesium, folic acid), and alternative diets. Authors report improvements in the symptoms associated with ASD individuals receiving nutritional interventions such as vitamin and mineral supplementation however, their safety and efficacy needs to be evaluated. The study findings will help policymakers and implementers to understand the consistency and precision and impact of these interventions. These findings will contribute to improving the safety and efficacy of these interventions, positively impacting the health and nutrition outcomes of children and adolescents with ASD. These study findings indicate that more research targeting ASD dietary and Nutritional Interventions for management of ASD symptoms is required in Kenya and other resource constrained settings.

Key words: autism spectrum disorder, nutritional intervention, diet therapy, child, adolescent, Kenya



INTRODUCTION

Research on the challenges of raising a child with autism is mostly reported from Europe, North America and Australia and has revealed that parents have to come to terms with living with a child who has a lifelong developmental disability [1]. There is limited ASD research in Kenya and families lack support as the etiology is linked to witchcraft and sorcery. These children are therefore hidden instead of treatment being sought [2].

Research on ASD in Kenya indicates that parents, caregivers, and special needs providers encounter various challenges in the diagnosis, and treatment. There is lack of awareness and limited research in ASD matters. Research in ASD matters are hindered by cultural factors, and there is a lack of treatment protocols, lack of institutional and government support. The ASD treatment is expensive for the families already facing a lot of social stigmas, isolation and brokenness [3].

Dietary interventions such as restrictive diets or supplements are common treatments for young people with autism spectrum disorder (ASD)[4]. There is no cure for ASD hence its management is mainly interventional centered around speech and behavioral therapies to improve social functioning and communication [5].

The Autism Society of Kenya estimates the number of children with autism to be about 800,000, whereby 25,000 of these children are found in Nairobi. It has been estimated that 10% of children with a disability are those of school-going age [6].

Currently of the world's total population, 15% have a disability of some form, and 80% of them live in Low and Middle-Income Countries (LMICs). Of these, 53 million are children under five years living with a developmental disability. Although the prevalence of developmental disabilities among children younger than 5 years has decreased recently in all countries except in North America between 1996 and 2016, the numbers of those with developmental disabilities are increasing significantly in sub-Saharan African countries for example in Zambia and South Africa (Western Cape). Globally, 71.3% of these children have vision loss while the other 28.7% have: hearing loss, intellectual disability, and autism spectrum disorder, respectively [7].

Malnutrition and neuro-disability are both major public health problems in Africa. Both macro and micronutrient malnutrition can both cause or be caused by neuro-disability. Maternal malnutrition affects fetal neurodevelopment in various ways

including neural tube defects, impaired cognitive function, birth asphyxia and neuro-disability. Mechanisms include decreased food intake, increased nutrient losses, and increased nutrient requirement [8].

In the USA, currently the prevalence in 8-year-olds is one in every 54 children [9]. Autism Spectrum Disorder prevalence rate increases are attributed to increased awareness and improvements in diagnosis and data capacity. Autism spectrum disorder diagnostic criteria have undergone refinement to include autism, Asperger's syndrome, Rett's syndrome, and childhood disintegrative disorder [10].

Autism spectrum disorder (ASD) is a neural developmental syndrome characterized by: a defect in social reciprocity such as emotion and affection, restricted communication such as difficulty in establishing verbal and non-verbal communication, difficulties in establishing relationship interests, and activities, stereotypical movements, inflexible adherence to routines such as food behaviors[11].

The diagnosis of ASD is made using the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) which was updated in 2013. However, there are no specific laboratory tests that are used in ASD identification [12].

Autism etiology is multifactorial including: genetics, drugs, environmental chemicals, infectious agents, dietary factors, and physical and psychological stresses [13]. Some of the environmental factors which are directly associated with Autism include smoking, alcohol consumption, air pollution, pesticides, endocrine-disrupting chemicals, heavy metals, and some fatty acids [14].

In trying to explain the autism pathophysiology to aid in making diagnoses, several studies have investigated changes in physiology and different biomarkers. Autism spectrum disorder individuals have several biological changes: greater circulation of inflammatory cytokines: modifications and nonspecific intestinal inflammation: high concentrations of amino acids peptides from incomplete protein breakdown, and cerebrospinal fluid, and urine. These factors combined lead to a theory about the connection between autism and problems in metabolizing substances from food [15].

Children diagnosed with this condition elicit intolerances to various foods such as milk and milk products, wheat, rye, barley, and oats necessitating gluten and casein dietary elimination[16].

Autism has no known cure hence its management is mainly Interventional to help ASD individuals adjust effectively to their environment. These interventions include behavioral therapy, medication, pharmacotherapy, and nutritional management methods. Dietary interventions in the form of gluten and casein-free (GFCF) diet administration have been used with great success in the management of ASD symptoms[17].

Individuals with ASD also suffer from gastrointestinal (GI) disturbances hence the interest in nutritional interventions to alleviate these gastrointestinal and behavioral symptoms. Current nutritional interventions for ASD, include gluten-free and casein-free diets, ketogenic diets, and specific carbohydrate diets, as well as probiotics, polyunsaturated fatty acids, and dietary supplements (vitamins A, C, B6, and B12, magnesium and folate as shown in (Table 1) in appendix A.

The objectives of this systematic review were to identify dietary and nutritional interventions available for the management of ASD symptoms in children and adolescents in Kenya and to analyze the results of existing research in order to understand and describe the characteristics and results of these studies for use in the management of ASD symptoms.

MATERIALS AND METHODS

This paper is a systematic review based on quantitative and qualitative data. The Cochrane Library, PubMed, Google Scholar, and Free Full databases were searched.

The search syntax was built using the following key words: (autism spectrum disorder[MeSH Terms] OR (autism[All Fields] AND spectrum [All Fields] AND disorder[All Fields]) OR autism spectrum disorder[All Fields]) AND (diet therapy[MeSH Terms] OR (diet[All Fields] AND therapy[All Fields]) OR diet therapy[All Fields] OR (nutrition[All Fields] AND interventions[All Fields]) OR nutrition interventions[All Fields]) AND (child[MeSH Terms] OR child [All Fields] OR children[All Fields]) AND (adolescent[MeSH Terms] OR adolescent[All Fields] OR adolescents[All Fields]) AND (africa [MeSH Terms] OR Africa [All Fields]) AND (open access[filter] AND has associated data[Filter]) AND 2011/09/14[PDat] : 2021/09/10[PDat]).

The study was conducted through a research strategy that considered the terms that characterize the research question structured by the Population, Intervention, Comparison, and Outcome (PICO) method as shown in (Table 2) in Appendix A.

The main criteria for inclusion of selected papers were:

- Include at least one person aged 1 year to 18 years diagnosed with ASD, including autism, Asperger's syndrome, or invasive developmental disorder, not otherwise specified.
- Relevance to ASD nutrition interventions in children and adolescents
- The intervention implemented had to include diet changes of the research participants
- The dependent variable is associated with behavioral symptoms of ASD and/or gastrointestinal symptoms
- The search covered the period 2011 to 2021.
- There was no limit on the geographical location

The criteria for exclusion of selected papers were:

- Articles that evaluated surrogate outcomes as their only primary outputs without involving other variables.
- Other neuro-disabilities other than ASD.

The articles found were submitted to the Mendeley website, and the bibliographic reference manager and duplicates were removed. The review process was performed in various steps. From the 368 documents originally found using the above syntax and words, 251 articles were excluded after associated data screening, hence 117 documents with relevant titles were retained. Subsequent screening for open access excluded 15 articles allowing the selection of 102 articles. Screening focusing on studies done in the above-mentioned 10-year period excluded 29 articles allowing for the retention of 73 articles. Subsequently, abstract screening to determine the suitability and relevance of article and compliance to all inclusion and exclusion criteria led to the exclusion of 55 papers. Finally, the abstract screening included looking at factors such as: a population with children and adolescents, relevant interventions, the comparison group with no placebo or treatment, and an outcome that include changes in ASD symptoms, allowed the final selection of 18 papers relevant for the review as shown in Figure 1.

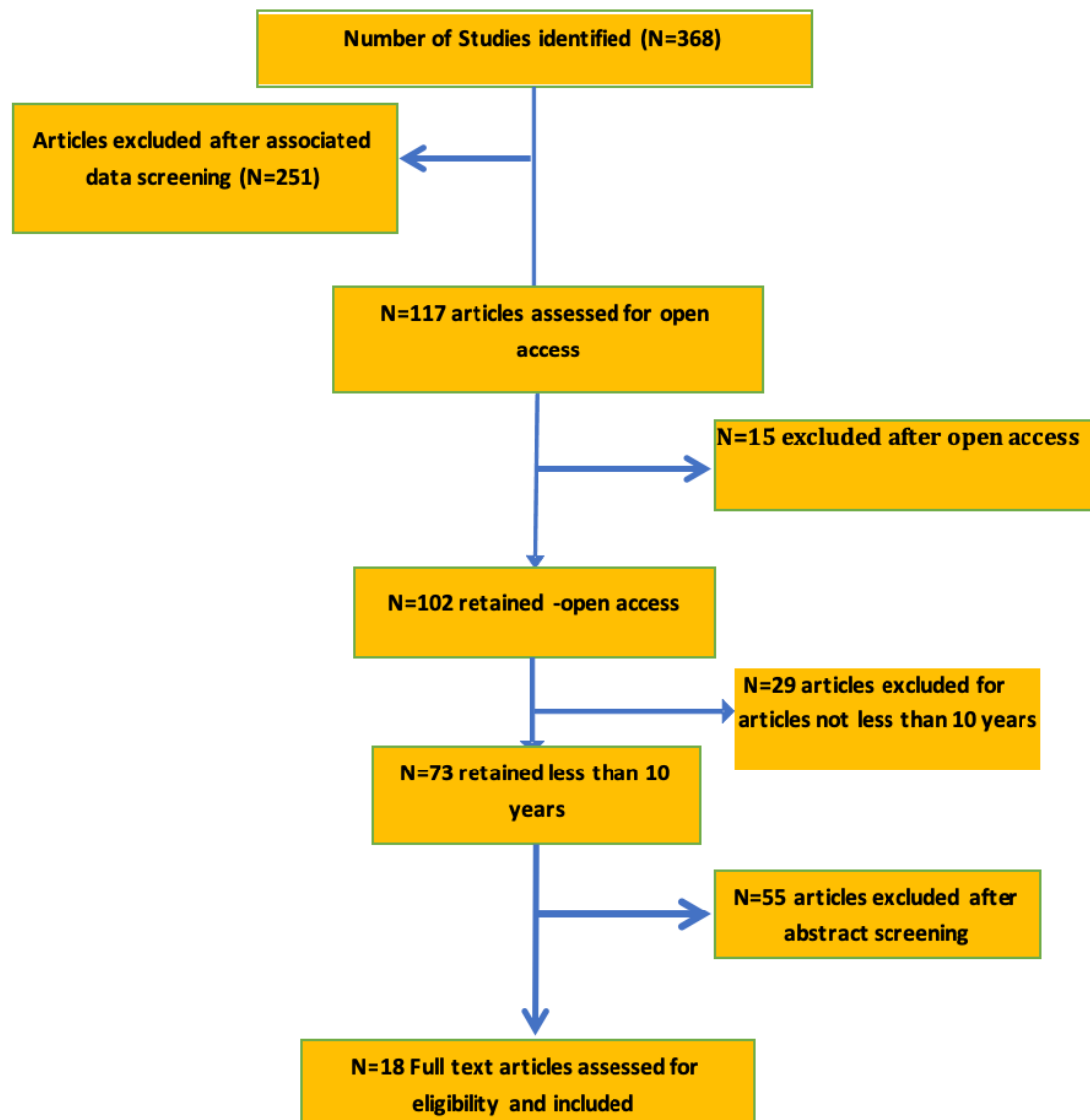


Figure 1: Flowchart of studies selected for review

For the articles included in the review, a clinical data extraction form was used to synthesize the following information: study design, characteristics of the population studied, description of the intervention, as well as its duration, outcome measures, evaluation tools, and country or study region of interest.

RESULTS AND DISCUSSION

Overview of currently available dietary and nutritional interventions

Of the eighteen articles assessed, 15 were randomized controlled trials (RCT's) [20 - 35] and three used the open-label model [24, 26, 35]. One study used the 2×2 factorial double-blind model [22]. One study used the cross-over trial model [23].

This review established that majority of the studies, 83% of the total studies under review used the randomized controlled trial (RCT) as the study design. Monteiro *et al.* [19] conducted a systematic review about nutritional interventions in Brazil and established similar results.

The total number of participants in the interventions in this review was 1298, the participants' ages ranged from 1 year [32] to 18 years [25]. The intervention time ranged from 3 months to 12 months showing a diverse duration between interventions.

Regarding the location or origin of each study, it was observed majority of the studies were conducted in the United States and Asia constituting 66.6% of the total. Whereas, the remaining 33.4 % of the studies constituted those carried out in Europe, sub-Saharan Africa, Australia, and New Zealand, respectively.

This systematic review established limited existence of studies on dietary and nutritional interventions available for use in ASD symptom management in children and adolescents conducted in Africa. It was established that of the total studies included in the review, only 11.1% of studies were conducted in Africa, and none had been conducted in Kenya.

The summary of the studies in this review on dietary and nutritional interventions for ASD children and adolescents have been summarized in a clinical form indicating: country where research was conducted, the type of study design, the sample characteristics, type of intervention, duration of intervention, and the main study findings. This summary of nutrition interventions is as shown in (Table 3) in the Appendix B.

Management of ASD symptoms using dietary and nutritional interventions

Regarding the interventions which were evaluated in this review, the following were analyzed: a gluten and casein-free diet, ketogenic diets, probiotic supplements, specific carbohydrate diets, polyunsaturated fatty acids, vitamin and mineral supplementation (A, B6, B12, D, magnesium, folic acid) and alternative diets.

This review found six articles that performed the nutrition interventions related to gluten and/or casein-free diet [20, 23, 25, 27, 28, 29]. The longest study in this gluten and casein free diet (GFCF) review took one year whereas the shortest study took 6 weeks. The review established that five out of the six GFCF studies representing 83% of the studies, translated to improvements in: communication,

stereotypical movements, aggressive behavior, language hyperactivity, tantrums, attention deficit hyperactivity disorder (ADHD) and gastrointestinal disorders. Karlu *et al.* [5] performed a systematic review on current clinical and experimental literature on nutritional interventions available for management of ASD symptoms in the United States of America (USA). Karlu's review established that gastrointestinal disturbances were the most commonly encountered comorbidities and played an important role in modulating expression of social and behavioral symptoms. This review established a benefit of use of GFCF diet on gastrointestinal symptoms of ASD.

One of the articles in this review established that one study [31] used omega 3 supplementations as an intervention to improve the clinical condition of children and adolescents with ASD. Keim *et al.* [31] established in a study conducted in the United States of America (USA) that the use of omega 3 supplementation had clinically significant improvements in ASD symptoms in the treatment compared to controls. These improvements were measured using the Brief Infant Toddler Social Emotional Assessment (BITSEA) scale.

In this review, seven articles [20, 22, 32, 33, 34, 35, 36] had interventions related to micronutrient supplementation to improve the clinical picture of ASD. Adams *et al.* [20] in a study on dietary and nutritional interventions in Arizona (USA) gave a combined vitamin A, B2, B5, B6, B12, and folic acid to the treatment group for 12 months, and there was an improvement in the nutritional status, non-verbal intellectual ability (IQ), autism symptoms, and other symptoms in the treatment group than in the controls.

In a study conducted by Mazahery *et al.* [22] in New Zealand, vitamin D and omega-3 long chain polyunsaturated fatty acids were used in the treatment of irritability and hyperactivity among children with ASD. In this study the intervention group was given vitamin D supplements and Omega 3 combined for 12 months. There was observed a significant reduction in hyperactivity and irritability in the treatment group compared to the controls, the outcome was measured using the Aberrant Behavior Checklist (ABC) tool.

A study on nutritional interventions for ASD was conducted by Liu *et al.* [22] in China. In this study vitamin A was given as an intervention to 1–8-year-old ASD children for 6 months, this study found an improvement in the ASD-related symptoms as measured using the Childhood Autism Rating Scale (CARS).

Xia *et al.* [33] in the United States of America conducted a study on nutrition supplements for reducing ASD symptoms. The intervention gave vitamin B6 to the ASD intervention group for 5 months. The study by Xia reported an improvement in ASD-related symptoms.

Hendren *et al.* [34] conducted a RCT trial in the USA by giving vitamin B12 to the intervention group for 8 weeks. There was reported an improvement in clinical related ASD symptoms.

In a study done by Sun *et al.* [36] in China, folic acid as an intervention was given to the ASD intervention group for 3 months. The results showed a significant improvement in sociability, cognitive verbal/preverbal, receptive language and affective expression and communication in the treatment group compared to the controls.

In this review, four studies [21, 24, 26, 37] gave probiotics and prebiotic treatment interventions for the treatment of ASD symptoms. The longest study duration was 6 months and the shortest duration among the four studies was 28 days. There was improvement in: gastrointestinal symptoms of ASD, sensory functioning, defiance behavior, and aberrant ASD behaviors. Santocchi *et al.* [21] in Italy conducted a RCT on effects of probiotic supplementation on gastrointestinal, sensory and Core ASD symptoms. There was established an improvement in gastrointestinal, sensory and core ASD symptoms in the treatment group compared to controls.

Two other studies by El-Rashidy and Lee performed interventions related to Ketogenic diets combined with GFCF diets and mid-chain triglycerides. Lee *et al.* [28] in Hawaii (USA) conducted a study where the intervention was a modified ketogenic gluten free diet with mid chain triglycerides for 3 months. Improvements were observed in cognition, sociability, and irritability.

Opportunities for improving dietary and nutritional interventions

Monteiro *et al.* [19] established that better results from interventions would be obtained when: rigorous methodologies are developed, interventions are longer than 6 months, and adequate sample sizes are obtained, and standard evaluation measures and results are obtained.

Karlu *et al.* [5] in a review done in the USA established need for GFCF efficacy studies and uniform outcome measurement indicators. The review recommended the need for ensuring dietary adequacy in the subjects due to ASD food selectivity.

This review confirmed widespread use of dietary and nutritional treatments. However, the review noted a lack adequate scientific evidence to support their efficacy and safety. It was recommended that an analysis should be done to identify limitations such as insufficient sample size, heterogeneity, short study duration and lack of comparison groups, and lack of standardized methodologies leading to difficulty in validating the approaches.

Gona *et al.* [1], investigating challenges and coping strategies of parents of children with autism on the Kenya coastland established that diet management was one of the coping strategies employed by parents in ASD symptom management. The study established that health professionals advised that avoidance of certain foods given to children with autism could control autistic behaviors such being hyperactive. The foods the parents of children with ASD on the Kenyan coast avoided or eliminated included sugar and sugary foods, cow milk, and pawpaw. This study underlined the need for more research in dietary and nutrition interventions for ASD symptom management.

Sathe *et al.* [39] systematically reviewed the effectiveness of different nutritional interventions in individuals with ASD. The review established that there were positive associations between nutritional interventions and ASD symptoms; however, several limitations in the design of research make this evidence insufficient such as small and short-term studies and lack of standardized populations.

A study by Liu *et al.* [32] in China conducted research in correlation of nutrition and ASD symptoms in children. This study identified various limitations in dietary and nutritional intervention studies. The study identified that sample size determines the significance levels of findings, hence the sample needs to be large enough to make generalizations. This study also emphasized on the need to have standard ASD measuring tools to obtain similar findings in different study settings.

CONCLUSION, AND RECOMMENDATIONS FOR DEVELOPMENT

This review established that vitamin and mineral supplementation was the most widely used dietary and nutritional intervention for the management of ASD symptoms. The second most widely used interventions in ASD symptom management were Gluten-free Casein-free (GFCF) diets and probiotics, respectively. This review also established that there are limited or no studies on dietary and nutritional interventions in Kenya. Hence more studies on dietary and nutrition interventions for use in management of ASD symptoms that have rigorous

methodologies such as: ample duration, adequate sample size, and well-evaluated dosage measures are required. These will help policymakers and implementers of these interventions to understand the consistency and precision and impact of these interventions. This will improve the safety and efficacy of these interventions positively impacting the health and nutrition outcomes of children and adolescents with ASD.

LIMITATION

The unavailability of ASD dietary and nutritional intervention studies specific to Kenya may have limited the deep analysis of the interventions in the local context. However, inclusion of other studies from resource constrained settings in the sub-Saharan region has covered a little bit of this gap.

DECLARATION OF CONFLICT OF INTEREST

The authors declare that they have no competing interests.

FUNDING

This study did not receive any funding.

Table 1: A summary of Dietary and Nutritional Interventions for Autism Spectrum Disorders

Nutritional interventions	Clinical implications or advantages	Limitations or disadvantages
Gluten-free casein-free diet [20, 23, 25, 27, 28, 29]	RCTs provided evidence of behavioral and GI symptom improvement; no reported adverse effects or nutritional deficiencies.	The long treatment time required for response; adherence difficulty; may only be effective in a subset of patients.
The ketogenic diet [27, 28]	Animal studies and limited cohort studies demonstrate potential for behavioral symptom improvement.	Few existing studies, restrictive diet, and potentially unpalatable, limited sampling can cause nutritional deficits.
Probiotics [21, 24, 26, 37]	Significant potential for improvement of GI and ASD symptoms	Limited studies and unproven mechanistic theories; mixed reaction by parents and ASD community to current research.
Specific carbohydrate diet [30]	Anecdotal reports of symptom improvement.	Very few existing studies; no RCTs; a very restrictive diet and difficult adherence.
Polyunsaturated fatty acids supplementation [20, 31]	Implicated as a pathophysiologic pathway for ASD; potential for combining with other therapeutic modalities	Mixed results regarding supplement; lack of consistent RCTs.
Vitamin A supplementation [20, 32]	The potential mechanism linking vitamin A deficiency to ASD pathophysiology	Correction of vitamin A deficiency via supplementation has proven ineffective and may lead to adverse effects associated with excess vitamin A intake
Vitamin C supplementation	None	ASD nutritional deficiency has been linked to scurvy and other vitamin C- related adverse effects, but there is no apparent link between deficiency and pathophysiology or supplementation and therapy
Vitamin B6 and magnesium supplementation [20, 33]	Proposed mechanism for therapy via supplementation	No conclusive data demonstrating therapy via supplementation; statements against supplementation from scientific bodies (American Psychiatric Association and American Academy of Pediatrics)
Vitamin B12 supplementation [20, 34]	Encouraging early results may demonstrate improvement in ASD symptoms	The paucity of data and studies; ultimately, effects are inconclusive and warrant additional study.
Folic acid supplementation [35, 36]	Folic acid supplementation in pregnant mothers may prevent ASD; potential future in screening for ASD related to folate-dependent 1-carbon metabolism and sulfuration pathways.	Results are only gestational, no evidence in therapy for ASD symptoms after birth

Abbreviations: ASD: autism spectrum disorder; GI: gastrointestinal; RCT: randomized controlled trial (Karhu 2020) [5]

Table 2: Description of the Population, Intervention Comparison, and Outcome Method

Population	Children and adolescents with ASD
Intervention	Dietary/Nutritional intervention
Comparison	No treatment, placebo, or conventional therapies such as serotonin, music therapies
Outcome	Change in ASD symptoms, behavioral, gastrointestinal symptoms
Study type	Randomized controlled trials, prospective, and retrospective cohort studies, case-control, and non-randomized controlled trials

KEY: ASD- autism spectrum disorder [18]

[19]

Table 3: Results summary of Systematic Review of Dietary and Butritional Interventions

Authors/Ref/Country	Condition	Type of Study	Sample size and Age	Types of diet/Intervention	Duration of intervention	Main findings
Adams <i>et al.</i> [20] (Arizona USA)	ASD	-single-blind children/adults randomized case-controlled trial	n=67 ASD n=50 Controls 3-18 years	vitamin /mineral supplement essential fatty acids, Epsom salts, carnitine, digestive enzyme, GFCF diet	12 months	improved non-verbal intellectual ability in ASD treatment group than in controls improvements in: carnitine, vitamin A, B2, B6, B12, Folic acid and co-enzyme Q10
Santocchi <i>et al.</i> [21] (Italy)	ASD	RCT-double blind randomized Placebo-controlled trial	n=85	probiotics [de-simone formulation n=42, and placebo n=43]	6 months	Autism diagnostic observation schedule-for calibrated severity score improved in the treatment group compared to the control group improved in GI symptoms, Adaptive functioning, and sensory profiles
Mazahery <i>et al.</i> [22] (New Zealand)	ASD	2 × 2 factorial-double blind controlled trial	n=73	Vitamin D 2000 IU, n-3 LCPFA's 722 mg Both 2000 IU and 722mg, or placebo (4 randomized treatments)	12 months	reduced inflammation in the group given both vitamin D and n-3 LCPFA's

Authors/Ref/Country	Condition	Type of Study	Sample size and Age	Types of diet/Intervention	Duration of intervention	Main findings
Gonzalez <i>et al.</i> [23] (Spain)	ASD	crossover trial	n=28	normal diet +GFCF diet GFCF diet alone	3 months 3 months	no significant change in behavior symptoms were noticed after the GFCF diet
Liu <i>et al.</i> [24] (Taiwan)	ASD	4-week randomized double-blind Placebo-controlled study	unspecified 7-15 years	Lactobacillus plantarum PS 128	28 days	improvement in opposition/defiance autism-associated behavior in the ASD group compared to the control group
Alamri <i>et al.</i> [25] (Saudi Arabia)	ASD	9 RCT studies	n=521 2-18 years	Gluten-free casein-free diet	unspecified	n=4 studies- showed no significant improvements in Symptoms n= 5 studies showed improvements in communication, stereotypical behavior, aggressiveness, language, hyperactivity, tantrums, and ADHA Compared to the control
Sanctuary <i>et al.</i> [26] (USA)	ASD	Randomized double-blind controlled trial	n=8 2-11years	combined treatment probiotic/prebiotic Bifidobacterium infantis) and Bovine colostrum product	12-week study	combined treatment well tolerated I both groups, reduction in the frequency of GI symptoms, as well as a reduction in particular aberrant behavior.

Authors/Ref/Country	Condition	Type of Study	Sample size and Age	Types of diet/Intervention	Duration of intervention	Main findings
El-Rashidy <i>et al.</i> [27] (Egypt)	ASD	Randomized controlled trial	n=45 3-8years	15- ketogenic diet + modified Atkins diet 15- gluten free casein free diet 15- control (balanced nutrition)	unspecified	both groups showed improvements in childhood autism rating scale and autism treatment evaluation test ketogenic diet scored better results in cognition and sociability compared to the GFCF diet group
LEE R <i>et al.</i> [28] (Hawaii USA)	ASD	Open-label clinical trial	n= 15 2-17years	modified ketogenic GFCF with Mid chain triglycerides	3 months	no improvements in restrictive and repetitive behavior there were improvements in imitation, body use, nervousness
Ghalichi <i>et al.</i> [29] (Iran)	ASD	A randomized clinical trial Case-control study	n=80	n=40 Gluten-free diet n=40 normal diet	6 weeks	significant reduction in the gastrointestinal symptoms in the treatment group but increased in the control group significant reduction in behavioral symptoms in the treatment the group compared to the control group
BARNHILL <i>et al.</i> [30] USA	ASD	RCT	n=1 4 years	specific carbohydrate diet	4 months	improvements in nutrition status, gastrointestinal problems, and behavioral symptom improvements

Authors/Ref/Country	Condition	Type of Study	Sample size and Age	Types of diet/Intervention	Duration of intervention	Main findings
KEIM <i>et al.</i> [31] (USA)	ASD	randomized fully blinded placebo controlled trial	n=31 18-36 months born at <29 weeks	n= 15 omega 3-6-9 n=16 canola oil placebo	90 days	significant reduction of autism-related symptoms in the treatment the group compared to controls
LIU <i>et al.</i> [32] (China)	ASD	RCT	n=64 1-8 years	vitamin A supplementation n=20 controls n=44 treatment group	6 months	improvements in ASD-associated symptoms
XIA <i>et al.</i> [33] (USA)	ASD	RCT	n=1 9 years	vitamin B6	5 months	improvements in ASD-related symptoms
HENDREN <i>et al.</i> [34] (USA)	ASD	Randomized controlled placebo Trial	n=57	Methyl B12	8 weeks	Improved clinical rated ASD symptoms
FRYE <i>et al.</i> [35] (USA)	ASD	Double-blind controlled placebo	n=48 7 years	folic acid n=23 high dose folic acid n=25 placebo	12 weeks	improvement in verbal communication in treatment compared to control improvements in autism-related symptoms
Authors/Ref/Country	Condition	Type of Study	Sample size and Age	Types of diet/Intervention	Duration of intervention	Main findings

SUN <i>et al.</i> [36] (China)	ASD	Open-label trial	n=66	n=44 folic acid n=22 placebo	3 months	folic acid improved ASD symptoms toward sociability, cognitive verbal receptive language improved folic acid concentrations
SHABAAN <i>et al.</i> [37] (Egypt)	ASD	Prospective open-label non controlled Trial	n=60 5-9 years	n=30 ASD Lactobacteria acidophilus, L.rhamosus and bifidobacteria longum	3 months	improved GI symptoms in treatment than controls

KEY: ASD -autism spectrum disorders, RCT- randomized controlled trial, GFCF-Gluten free casein free diets

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