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Name of Journal: *World Journal of Clinical Pediatrics*

Manuscript NO: 99649

Manuscript Type: SYSTEMATIC REVIEWS

Nutritional Management and Autism Spectrum Disorder: A Systematic Review

Diet and autism

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Abstract

BACKGROUND

Autism Spectrum Disorder (ASD) presents unique challenges related to feeding and nutritional management. Children with ASD often experience feeding difficulties, including food selectivity, refusal, and gastrointestinal issues. Various interventions have been explored to address these challenges, including dietary modifications, vitamin supplementation, feeding therapy, and behavioral interventions.

AIM

This systematic review aims to provide a comprehensive overview of the current evidence on nutritional management in ASD. We examine the effectiveness of dietary interventions, vitamin supplements, feeding therapy, behavioral interventions, and mealtime practices in addressing the feeding challenges and nutritional needs of children with ASD.

METHODS

We systematically searched relevant literature up to June 2024, using databases such as PubMed, PsycINFO, and Scopus. Studies were included if they investigated dietary interventions, nutritional supplements, or behavioral strategies to improve feeding

behaviors in children with ASD. We assessed the quality of the studies and synthesized findings on the impact of various interventions on feeding difficulties and nutritional outcomes. Data extraction focused on intervention types, study designs, participant characteristics, outcomes measured, and intervention effectiveness.

RESULTS

The review identified 316 studies that met the inclusion criteria. The evidence indicates that while dietary interventions and nutritional supplements may offer benefits in managing specific symptoms or deficiencies, the effectiveness of these approaches varies. Feeding therapy and behavioral interventions, including gradual exposure and positive reinforcement, promise to improve food acceptance and mealtime behaviors. The findings also highlight the importance of creating supportive mealtime environments tailored to the sensory and behavioral needs of children with ASD.

CONCLUSION

Nutritional management for children with ASD requires a multifaceted approach that includes dietary modifications, supplementation, feeding therapy, and behavioral strategies. The review underscores the need for personalized interventions and further research to refine treatment protocols and improve outcomes. Collaborative efforts among healthcare providers, educators, and families are essential to optimize this population's nutritional health and feeding practices. Enhancing our understanding of intervention sustainability and long-term outcomes is essential for optimizing care and improving the quality of life for children with ASD and their families.

Key Words: Feeding Therapy; Behavioral Interventions; Mealtime Practices; Autism Spectrum Disorder; Children; High-dose Methyl Cobalamine.

Al-Beltagi M. Nutritional Management and Autism Spectrum Disorder: A Systematic Review. *World J Clin Pediatr* 2024; In press

Core Tip: Effective management of feeding challenges in children with ASD requires a comprehensive approach integrating feeding therapy and behavioral interventions. Addressing oral motor skills and sensory sensitivities and establishing structured mealtime routines are crucial. Behavioral strategies like gradual exposure, positive reinforcement, and modeling can significantly improve food acceptance and mealtime behaviors. Creating a sensory-friendly environment and involving parents in meal planning are essential. This systematic review highlights the importance of multidisciplinary collaboration and tailored interventions to enhance nutritional intake and overall health outcomes for children with ASD.

INTRODUCTION

Autism Spectrum Disorder (ASD) is a neurodevelopmental disorder characterized by challenges in social interaction, communication, and repetitive behaviors. The term "spectrum" reflects the wide variability in challenges and strengths among individuals with autism. Typically diagnosed in early childhood, ASD is identified based on persistent deficits in social communication and interaction, restricted and repetitive patterns of behavior, and significant impairment in daily functioning[1]. According to the Centers for Disease Control and Prevention (CDC), approximately 1 in 36 children in the United States is diagnosed with ASD. This prevalence has increased over the past few decades due to improved awareness and diagnostic practices[2].

The etiology of ASD is not fully understood but is believed to result from a complex interplay of genetic and environmental factors. Genetic research has identified numerous genes associated with increased risk, and family studies show that having a sibling with ASD raises the risk for others[3]. Environmental factors, such as advanced parental age, low birth weight, and prenatal exposure to certain drugs, have also been linked to ASD, though no single factor has been definitively proven. Neurologically, individuals with ASD may exhibit differences in brain structure and function, affecting neuronal communication and information processing[4].

Clinically, ASD manifests in a variety of ways. Social communication challenges include difficulty understanding and using verbal and nonverbal communication, maintaining relationships, and sharing interests or emotions. Repetitive behaviors may involve movements like hand-flapping, strict adherence to routines, intense interests, and sensory sensitivities[5]. Many individuals with ASD also experience comorbid conditions such as intellectual disability, ADHD, anxiety disorders, epilepsy, gastrointestinal issues, and sleep disturbances[6].

Diagnosis of ASD involves a comprehensive evaluation by a multidisciplinary team using developmental history, direct observation, and standardized tools like the Autism Diagnostic Observation Schedule (ADOS) and the Autism Diagnostic Interview-Revised (ADI-R). While there is no cure for ASD, various interventions can significantly improve the quality of life[7]. Behavioral interventions, such as Applied Behavior Analysis (ABA), Social Skills Training, and Cognitive Behavioral Therapy (CBT), are common. Educational interventions include Individualized Education Programs (IEPs), speech and language therapy, and occupational therapy. Medical interventions often address co-occurring conditions; family support and training are crucial for empowering families to support their loved ones[8].

Understanding the dietary influences on ASD is crucial due to the significant impact diet can have on the health and well-being of individuals with autism. Many people with ASD experience sensory sensitivities that affect their food preferences, leading to limited and repetitive eating patterns, which can result in nutritional deficiencies[9]. Additionally, gastrointestinal issues, which are common in individuals with ASD, can be influenced by dietary habits and may exacerbate behavioral symptoms[10]. Exploring the relationship between diet and ASD can help identify effective nutritional interventions that may alleviate some of these challenges, improve overall health, and enhance quality of life[11]. This understanding can guide caregivers and healthcare professionals in developing personalized nutrition plans that cater to the unique needs of individuals with ASD, ultimately supporting their physical health, cognitive development, and behavioral regulation. Research into dietary influences also holds the

potential to uncover new insights into the underlying mechanisms of ASD, further contributing to the development of comprehensive treatment strategies.

This review seeks to provide an extensive overview of the current literature on nutritional challenges and management in ASD, including gastrointestinal problems, dietary interventions, vitamins, nutrients, mineral supplements, feeding therapy, and behavioral strategies. By synthesizing evidence from recent studies, this review aims to offer insights into the effectiveness of these approaches and guide clinicians and caregivers in optimizing feeding and nutritional outcomes for children with ASD.

MATERIALS AND METHODS

Study Design and Literature Search Strategy

This study employed a **systematic** approach to synthesize existing literature on feeding therapy, behavioral interventions, and mealtime practices for children with ASD. The review focused on identifying effective strategies and techniques used in clinical settings and research studies to improve feeding behaviors and expand food preferences in this population. A systematic search of electronic databases, including PubMed, Scopus, and PsycINFO, was conducted to identify relevant studies published up to July 2024. The search terms included combinations of keywords such as "autism spectrum disorder," "ASD," "feeding therapy," "behavioral interventions," "mealtime practices," "sensory integration," "oral motor skills," "food selectivity," and "nutritional intake." Only studies published in English and involving children diagnosed with ASD were included.

Selection Criteria

Studies were included if they examined feeding therapy interventions, behavioral strategies, or mealtime practices for children diagnosed with ASD, reported outcomes related to improving oral motor skills, sensory integration, food acceptance, or nutritional intake, were peer-reviewed articles, systematic reviews, meta-analyses, clinical trials, or observational studies. Studies were excluded if they focused solely on

adults with ASD or other developmental disorders, lacked clear methodology or reported relevant outcomes, and were published in a non-English language.

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Data Extraction and Synthesis and Quality Assessment

Two independent reviewers screened the titles and abstracts of identified articles based on the selection criteria. Full-text articles were retrieved to assess eligibility further. Data extraction included study design, participant characteristics (age, gender), intervention details (feeding therapy techniques, behavioral strategies), outcomes measured (changes in feeding behaviors, food acceptance, nutritional status), and key findings relevant to the study objectives. The quality of included studies was assessed using appropriate tools such as the Cochrane Collaboration's tool for assessing risk of bias in randomized trials or the Newcastle-Ottawa Scale for observational studies. Studies were evaluated based on criteria including study design, sample size, blinding, outcome measures, and statistical analysis.

Data Synthesis and Analysis and Ethical Considerations

A narrative synthesis approach was used to summarize findings from included studies. Key themes and patterns across interventions and outcomes were identified, focusing on effective strategies for improving feeding behaviors and mealtime practices in children with ASD. Quantitative data, when available, were synthesized descriptively or meta-analyzed if studies were homogeneous in methodology and outcomes. Ethical approval was not required since this study involved a review of existing literature. All data were obtained from published studies with proper ethical standards adhered to by the original researchers.

RESULTS

The systematic review identified 316 relevant studies meeting the inclusion criteria. Figure 1 shows the article's flow chart (96 research articles, 177 reviews, 24 systematic reviews, 10 meta-analyses, 6 case reports, and 3 guidelines). The included studies

encompassed a variety of study designs, including randomized controlled trials (RCTs), observational studies, and systematic reviews. Participants across studies were primarily children diagnosed with ASD, with ages ranging from early childhood to adolescence. Some studies included specific subgroups based on age, severity of ASD symptoms, or comorbid conditions.

Several studies focused on improving oral motor skills through structured exercises and sensory-motor activities. Techniques included facial massages, chewing exercises, and tongue stimulation to enhance swallowing and chewing abilities. Feeding therapists utilized sensory integration techniques to address sensory sensitivities related to food textures, tastes, and smells. Gradual exposure and desensitization strategies were commonly employed to increase tolerance to new foods. Behavioral interventions based on ABA principles were widely utilized to modify feeding behaviors. Techniques included reinforcement strategies, task analysis, and shaping to encourage positive eating behaviors and reduce food selectivity. Some studies employed modeling techniques where children observed peers or adults demonstrating appropriate eating behaviors. Social stories were used to prepare children for mealtime routines and promote understanding of expected behaviors.

Establishing consistent meal and snack times was emphasized across studies to provide predictability and reduce anxiety during meals. Visual schedules and timers were used to help children understand mealtime expectations and transitions. Modifications such as soft lighting, non-patterned tableware, and comfortable seating arrangements were implemented to minimize sensory distractions and enhance focus on eating. Many studies reported significant improvements in food acceptance and willingness to try new foods following intervention. Techniques like food chaining and gradual exposure were effective in expanding food preferences. Interventions targeting oral motor skills improved chewing, swallowing, and overall oral coordination among children with ASD. Several studies indicated that effective feeding therapy and mealtime practices improved nutritional outcomes, including increased dietary diversity and nutrient intake. Variability in intervention protocols and outcome

measures across studies made direct comparisons challenging. The diversity in participant characteristics and settings also influenced the interpretation of findings.

There was a tendency for studies to report positive outcomes, potentially leading to publication bias. Negative or null findings may be underrepresented in the literature. Studies were assessed for quality using criteria appropriate to their study design, such as the Cochrane Collaboration's risk of bias tool for RCTs or the Newcastle-Ottawa Scale for observational studies. High-quality studies with rigorous methodologies provided more robust evidence of intervention effectiveness. The synthesis of findings highlighted common themes and effective strategies across studies, including the importance of multidisciplinary approaches involving dietitians, speech-language pathologists, occupational therapists, and psychologists. Effective interventions focused on improving oral motor skills, addressing sensory sensitivities, and establishing structured mealtime routines.

DISCUSSION

Sensory Sensitivities and Food Preferences:

Individuals with Autism Spectrum Disorder (ASD) often experience heightened or diminished sensitivity to sensory stimuli, significantly influencing their food choices and eating behaviors. These sensory sensitivities can manifest in various ways. For instance, many individuals with ASD have strong preferences or aversions to specific food textures, leading them to prefer crunchy foods and avoid soft or mushy textures, or vice versa[12]. Sensitivity to smells can cause rejection of foods with strong odors, with even the smell of food being prepared or served nearby becoming overwhelming. Taste sensitivities might make certain flavors intolerable, causing individuals to avoid bitter, sour, or spicy foods and gravitate towards bland or sweet items, resulting in a limited diet lacking variety and essential nutrients[13]. Additionally, the visual appearance of food can influence acceptance, as some individuals are particular about how food is presented, preferring visually appealing foods and avoiding unfamiliar ones. Preferences for food temperature and sensitivity to the sounds associated with

eating can also affect what individuals with ASD are willing to consume. These sensory sensitivities often lead to selective eating habits, posing challenges for maintaining a balanced diet and adequate nutrition[14]. Understanding these sensory influences is crucial for developing effective strategies to broaden food acceptance and ensure nutritional adequacy in individuals with ASD.

Individuals with ASD often exhibit distinct food preferences and aversions influenced by their sensory sensitivities, significantly impacting their dietary intake and nutritional status. Commonly, they prefer bland foods with mild flavors, such as plain pasta, rice, bread, and crackers, as well as crunchy or crispy textures found in chips, crackers, and raw vegetables. Sweet and salty foods, including candies, cookies, and snack foods, are also frequently favored[14]. Familiar and predictable foods, particularly specific brands or types of packaged foods, and carbohydrate-rich items like bread, pasta, and potatoes, are often preferred due to their consistency and simplicity. Conversely, individuals with ASD often avoid foods with strong, bitter, spicy, or sour flavors, including spicy dishes, citrus fruits, and certain vegetables[9]. Soft or slimy textures, such as those found in mashed potatoes, bananas, and some cooked vegetables, are frequently rejected, as are mixed textures in dishes like casseroles, stews, or sandwiches due to their sensory complexity[15]. New or unfamiliar foods are commonly resisted, leading to a very limited diet, and foods with potent odors, such as certain cheeses, fish, and cooked cabbage, are typically avoided. These preferences and aversions result in restricted diets that may lack nutritional balance, highlighting the need for caregivers and healthcare professionals to develop strategies to gradually introduce new foods and ensure adequate nutrition for individuals with ASD[11].

The impact of sensory-based food selectivity on nutrition and health in individuals with ASD is profound and multifaceted. Many individuals with ASD exhibit selective eating patterns driven by sensory sensitivities, which often result in a limited variety of accepted foods[16]. This can lead to significant nutritional deficiencies, as essential vitamins, minerals, and dietary fiber may be lacking due to avoidance of certain

textures or flavors. Such imbalanced diets, often skewed towards carbohydrates and processed foods that meet sensory preferences, can contribute to weight management issues and increase the risk of chronic diseases like diabetes and cardiovascular conditions[17]. Moreover, inadequate nutrition can impair physical growth and development, particularly concerning bone health and cognitive function in younger individuals. Gastrointestinal problems, such as constipation and diarrhea, are also common and exacerbated by limited dietary variety and fiber intake. Behavioral challenges and emotional well-being may also be affected, with inadequate nutrition potentially contributing to increased anxiety, irritability, and difficulties in mood regulation[10]. Addressing these challenges requires tailored interventions that gradually introduce new foods, modify textures, and incorporate sensory integration techniques to broaden food acceptance and ensure optimal nutrition and overall health for individuals with ASD[18].

Gastrointestinal (GI) Issues and Autism:

Prevalence of GI Problems in Individuals with ASD:

The prevalence of GI problems in individuals with ASD is notably higher compared to the general population. Studies and clinical observations indicate that a significant proportion of individuals with ASD experience various GI issues, which can impact their overall health and quality of life[10]. Research suggests that up to 70% of individuals with ASD may have gastrointestinal symptoms, such as abdominal pain, constipation, diarrhea, bloating, and gastroesophageal reflux disease (GERD). These symptoms are often reported to occur at higher rates and with greater severity in individuals with ASD compared to neurotypical peers[19]. The exact reasons for this elevated prevalence are still under investigation. Still, they may involve factors such as altered gut microbiota, immune system dysregulation, dietary factors, and sensory sensitivities influencing food choices[20].

The presence of GI problems in individuals with ASD can complicate behavioral management and may exacerbate core symptoms of autism, such as communication

difficulties and repetitive behaviors[21]. Addressing GI issues is crucial for improving the overall well-being and quality of life of individuals with ASD. This often involves a multidisciplinary approach that includes healthcare providers specializing in both autism and gastroenterology, along with dietary interventions and behavioral strategies tailored to the unique needs of each individual[10]. Continued research into the underlying mechanisms and effective treatments for GI problems in ASD is essential for developing targeted interventions and improving outcomes for this population.

Types of Gastrointestinal Issues Commonly Observed:

Several GI issues are commonly observed in individuals with ASD, significantly impacting their overall health and well-being. Constipation is a prevalent concern, characterized by infrequent bowel movements and discomfort, often leading to abdominal pain and changes in appetite [10]. Conversely, diarrhea, marked by loose or watery stools, can also occur, potentially causing dehydration and nutrient malabsorption if persistent [10]. Gastroesophageal Reflux Disease (GERD) is another common problem in patients with autism, where stomach acid or bile refluxes into the esophagus, causing heartburn, regurgitation, and difficulty swallowing[22]. Abdominal pain is frequently reported and may stem from constipation, food intolerances, or inflammation. Bloating, characterized by abdominal discomfort and distension, is also common and may be related to dietary factors or impaired digestion[23]. Many individuals with ASD experience food intolerances or sensitivities, often to gluten or dairy, which can exacerbate GI symptoms. Feeding difficulties, such as selective eating patterns or swallowing issues, further complicate nutritional intake and digestive health management[11]. Inflammatory bowel diseases like Crohn's disease or ulcerative colitis, though less common, can also occur in individuals with ASD, necessitating careful monitoring and treatment by healthcare professionals specializing in both autism and gastroenterology[24]. Understanding and addressing these GI issues are crucial for improving the quality of life and health outcomes of individuals with ASD, often requiring tailored interventions that consider their unique sensory and dietary needs.

Constipation:

Constipation is a prevalent gastrointestinal issue among individuals with ASD, affecting a significant number of those diagnosed. It is characterized by infrequent bowel movements and difficulty passing stools, often resulting in abdominal discomfort or pain[25]. Several factors contribute to constipation in individuals with ASD, including sensory sensitivities that affect food choices and dietary habits. Many individuals with ASD have selective eating patterns, preferring certain textures or avoiding foods high in fiber, such as fruits, vegetables, and whole grains, which are essential for regular bowel movements [10]. Additionally, factors like reduced physical activity, inadequate fluid intake, and side effects from medications commonly used to manage symptoms associated with ASD can further exacerbate constipation[26]. Addressing constipation in individuals with ASD requires a multidisciplinary approach involving healthcare providers, including gastroenterologists and dietitians, who specialize in understanding the unique needs and challenges of individuals on the autism spectrum. Management typically includes dietary adjustments to increase fiber intake, hydration strategies, promoting physical activity, and, when necessary, medications to alleviate symptoms and improve bowel function. Regular monitoring and proactive management of constipation are essential to minimize discomfort, promote gastrointestinal health, and enhance overall well-being in individuals with ASD [10].

Diarrhea:

Diarrhea, though less frequently discussed compared to constipation, is a gastrointestinal issue that can affect individuals with ASD. Characterized by loose, watery stools, diarrhea can lead to dehydration and electrolyte imbalances if not managed promptly [10]. Several factors contribute to diarrhea in individuals with ASD, including sensory sensitivities that influence dietary preferences and aversions, potentially affecting digestive health[27]. Food sensitivities or intolerances, such as

reactions to gluten or dairy products, are also common triggers for gastrointestinal symptoms like diarrhea. Additionally, medications prescribed to manage symptoms associated with ASD may have side effects that include gastrointestinal disturbances. Anxiety or stress, which can be heightened in individuals with ASD, may further impact gut function and contribute to diarrhea episodes [10]. Managing diarrhea involves identifying and addressing these underlying factors, including dietary adjustments, hydration strategies, and potentially modifying medications under the guidance of healthcare providers. Monitoring and proactive management are essential to minimize discomfort, promote gastrointestinal health, and improve overall well-being in individuals with ASD affected by diarrhea [10].

Abdominal Pain:

Abdominal pain is a significant issue affecting many individuals with ASD, impacting their daily lives and overall well-being. Commonly experienced as recurrent or chronic discomfort, abdominal pain in individuals with ASD can stem from various factors. These include gastrointestinal issues such as constipation, diarrhea, bloating, and gastroesophageal reflux disease (GERD), often exacerbated by dietary preferences and sensory sensitivities [10]. Sensitivities to certain foods, like gluten or dairy, can also contribute to abdominal discomfort. Additionally, heightened levels of anxiety or stress, frequently observed in individuals with ASD, may manifest physically as abdominal pain[25]. Sensory sensitivities can further intensify the experience of pain, making individuals more sensitive to discomfort in the abdominal region. Communication challenges can complicate diagnosis and treatment, requiring caregivers and healthcare providers to rely on behavioral cues and careful observation to address underlying issues effectively[28]. Managing abdominal pain in individuals with ASD involves a holistic approach that includes addressing gastrointestinal health, managing dietary sensitivities, promoting strategies to reduce anxiety, and ensuring effective communication to improve overall quality of life. Regular monitoring and collaboration with healthcare professionals specializing in ASD and gastroenterology are essential for

developing personalized management plans that address the unique needs of individuals affected by abdominal pain [10].

Potential Links Between Gastrointestinal Issues and Dietary Habits:

There are several potential links between GI issues and dietary habits in individuals with ASD, underscoring the intricate relationship between diet and digestive health. Many individuals with ASD have sensory sensitivities that influence their food preferences and aversions. These preferences often lead to selective eating habits, where individuals may avoid foods with certain textures, flavors, or appearances that trigger discomfort or sensory overload[14]. This selective eating can limit dietary variety and potentially lead to nutritional deficiencies or imbalances contributing to GI issues. Individuals with ASD commonly experience food sensitivities or allergies, particularly to gluten, dairy, and artificial additives. These sensitivities can provoke GI symptoms such as abdominal pain, bloating, diarrhea, or constipation[29]. Managing these sensitivities through dietary modifications is crucial for alleviating GI discomfort and improving overall digestive health.

Emerging research suggests that individuals with ASD may have alterations in gut microbiota composition compared to neurotypical individuals. These microbial imbalances can influence digestion, immune function, and inflammation levels, potentially contributing to GI symptoms such as irritable bowel syndrome (IBS) or inflammatory bowel disease (IBD)[30]. Diet plays a significant role in shaping gut microbiota composition, with dietary habits affecting microbial diversity and function. Selective eating habits and restricted diets common in individuals with ASD can result in nutritional deficiencies, such as insufficient fiber intake, vitamins, and minerals. These deficiencies may exacerbate GI issues like constipation or affect overall digestive function and health[31].

Medications commonly prescribed to manage symptoms associated with ASD, such as antipsychotics or stimulants, can have side effects that impact GI function. These may include constipation, diarrhea, or changes in appetite, necessitating dietary adjustments

or additional interventions to mitigate these effects[10]. Understanding these potential links between dietary habits and GI issues is essential for developing effective management strategies tailored to the unique needs of individuals with ASD. Integrating nutritional counseling, monitoring dietary intake, addressing food sensitivities, and promoting a balanced diet are critical components of supporting digestive health and overall well-being in this population[32].

Effects of Gastrointestinal Problems on Behavior and Overall Well-being:

Gastrointestinal (GI) problems can have significant effects on behavior and overall well-being in patients with ASD, influencing various aspects of their daily lives. GI issues can exacerbate behavioral symptoms commonly associated with ASD, such as irritability, agitation, and increased repetitive behaviors[33]. Discomfort or pain from GI symptoms may lead to heightened levels of distress and difficulty in self-regulation, contributing to behavioral outbursts or withdrawal. Individuals with ASD often face challenges in communicating their discomfort or pain verbally, making it difficult for caregivers and healthcare providers to identify and address underlying GI issues promptly, potentially prolonging distress and behavioral difficulties[34]. Persistent GI symptoms, such as abdominal pain, bloating, constipation, or diarrhea, can significantly impact the overall quality of life for individuals with ASD. These symptoms may affect sleep patterns, appetite, social interactions, and participation in daily activities, leading to decreased enjoyment and engagement in their surroundings[35]. Severe or chronic GI problems can interfere with daily functioning, including disruptions in eating habits, difficulty attending school or work, and reduced participation in recreational activities. Managing GI symptoms effectively is crucial for optimizing daily functioning and promoting independence in individuals with ASD[23].

The discomfort and unpredictability of GI symptoms can contribute to heightened anxiety, stress, or mood disturbances in individuals with ASD. Addressing GI issues improves physical health and supports emotional well-being and overall mental health resilience[36]. GI symptoms may affect social interactions and participation in

community settings, as individuals with ASD may experience discomfort or embarrassment related to their symptoms. Managing GI health can enhance social engagement and improve overall social functioning[37]. Recognizing and addressing the impact of GI problems on behavior and well-being in individuals with ASD requires a comprehensive approach that includes regular monitoring, proactive management of symptoms, and collaboration among caregivers, healthcare providers, and specialists in autism and gastroenterology. Tailored interventions, such as dietary modifications, behavioral therapies, and medications, when necessary, can help alleviate GI symptoms, improve overall comfort, and enhance the quality of life for individuals with ASD affected by gastrointestinal issues[38].

Nutritional Deficiencies and ASD:

Common nutritional deficiencies in individuals with ASD:

14 Individuals with Autism Spectrum Disorder (ASD) often experience nutritional deficiencies that can impact their overall health and well-being. Here's a comprehensive review focusing on common deficiencies in vitamins, minerals, and essential fatty acids observed in individuals with ASD. *Vitamin D* deficiency is prevalent among individuals with ASD due to several factors. Many individuals with ASD may have limited outdoor activities or sunlight exposure, reducing their body's ability to synthesize Vitamin D[39]. Selective eating habits and aversions to certain foods, such as dairy products or fortified cereals, can further limit Vitamin D intake. Some individuals with ASD may have altered metabolism or absorption patterns that affect Vitamin D levels. Vitamin D deficiency can impact bone health and immune function and may exacerbate behavioral symptoms associated with ASD[16].

B vitamins are critical in neurological function, energy metabolism, and overall health. Deficiencies in B vitamins, particularly B6 (pyridoxine), B12 (cobalamin), and folate (B9), are commonly observed in individuals with ASD. Limited intake of sources rich in B vitamins, such as meats, leafy greens, and fortified grains, due to selective eating patterns or food sensitivities[40]. Increased metabolic demands or altered

metabolism in individuals with ASD may contribute to B vitamin deficiencies. B vitamin deficiencies can affect neurotransmitter synthesis and function, potentially influencing mood, behavior, and cognitive abilities in individuals with ASD. Additional vitamin deficiencies in individuals with ASD include *vitamins A, E, and C*. Vitamin A is essential for vision, immune function, and cellular growth[6]. Dietary restrictions or selective eating habits may contribute to Vitamin A deficiency. Vitamin E Acts as an antioxidant and supports immune function. Individuals with ASD may have a limited intake of sources like nuts, seeds, and vegetable oils. Vitamin C is important for immune function and collagen synthesis. Limited intake of fruits and vegetables rich in Vitamin C may contribute to deficiencies[41].

Mineral disorders, especially for zinc, iron, and calcium, in patients with ASD are commonly observed and can significantly impact their health and well-being. *Zinc* is crucial in immune function, protein synthesis, and wound healing. Zinc deficiency is prevalent among individuals with ASD due to several factors[42]. Dietary restrictions and selective eating patterns or food aversions may lead to inadequate intake of zinc-rich foods such as meats, shellfish, nuts, and seeds. Individuals with ASD may experience gastrointestinal problems that impair zinc absorption, exacerbating deficiency. Some individuals with ASD may have increased metabolic demands or higher losses of zinc due to medications or other factors[43].

Iron is essential for oxygen transport in the blood, energy metabolism, and cognitive development. Iron deficiency anemia is commonly reported in individuals with ASD. Limited consumption of iron-rich foods like red meat, poultry, beans, and fortified cereals can contribute to iron deficiency[44]. Digestive problems such as constipation or diarrhea may affect iron absorption and contribute to deficiency. In addition, preferences for certain textures or flavors may restrict dietary diversity and lead to insufficient iron intake. *Magnesium* is involved in hundreds of biochemical reactions in the body, including muscle and nerve function, energy production, and bone health. Imbalances in magnesium levels, including both deficiency and excess, have been observed in individuals with ASD[45]. Inadequate intake of magnesium-rich foods such

as nuts, seeds, whole grains, and leafy greens due to dietary restrictions or preferences. Similar to zinc and iron, gastrointestinal problems may affect magnesium absorption and contribute to imbalances. Magnesium deficiency or imbalance can impact neurological function and may exacerbate behavioral symptoms in individuals with ASD[46]. *Calcium* is crucial for bone health, muscle function, and nerve transmission. Individuals with ASD may have insufficient calcium intake. They avoid dairy products, a primary source of calcium, due to lactose intolerance or sensory issues. Calcium deficiency can affect bone density and increase the risk of osteoporosis or fractures, especially as individuals with ASD age[47].

Essential fatty acids (EFAs), particularly ³⁵omega-3 and omega-6 fatty acids, play crucial roles in brain function, inflammation regulation, and overall health. Disorders related to EFAs are often observed in patients with ASD, impacting their cognitive, behavioral, and physical well-being[48]. ²⁶*Omega-3 fatty acids*, especially eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), are essential for brain development, cognitive function, and reducing inflammation[49]. They are primarily found in fatty fish, flaxseeds, walnuts, and chia seeds. Individuals with ASD often have lower levels of omega-3 fatty acids due to selective eating habits that exclude omega-3-rich foods or metabolic differences affecting the synthesis and utilization of these fatty acids[50]. Omega-3 deficiencies are associated with various cognitive and behavioral issues in individuals with ASD, including difficulties with attention, hyperactivity, and social interactions. These fatty acids are crucial for synaptic function and neuronal communication, and deficiencies can exacerbate symptoms of ASD[51].

²*Omega-6 fatty acids*, such as linoleic acid and arachidonic acid, are important for immune function and inflammation regulation and are found in ²vegetable oils, nuts, and seeds. While necessary for health, an imbalance between omega-6 and omega-3 fatty acids is common in individuals with ASD[52]. ⁵⁰A diet high in omega-6 but low in omega-3 can promote inflammation and negatively affect brain function and behavior. Addressing EFA disorders involves increasing the intake of omega-3-rich foods and ⁴⁷reducing the consumption of omega-6-rich processed foods and vegetable oils to

balance the ratio of omega-6 to omega-3 fatty acids[53]. Omega-3 supplements, such as fish oil or algae-based supplements, can effectively increase EPA and DHA levels in individuals with ASD. It is important to choose high-quality supplements and follow recommended dosages under the guidance of healthcare providers[54]. Regular monitoring of fatty acid levels through blood tests can track the effectiveness of dietary and supplementation interventions, with adjustments made based on individual responses and progress.

Consequences of nutritional deficiencies on physical and cognitive health:

Nutritional deficiencies can have profound consequences on the physical and cognitive health of patients with ASD. These deficiencies, often stemming from selective eating habits, sensory sensitivities, and gastrointestinal issues, can exacerbate the core symptoms of ASD and lead to additional health complications.

Physical Health Consequences: Nutritional deficiencies can impair physical growth and development. For example, deficiencies in essential vitamins and minerals like Vitamin D, calcium, and zinc can lead to poor bone health, increasing the risk of fractures and osteoporosis[55]. Inadequate intake of essential nutrients can also hinder muscle development and overall physical growth. Deficiencies in vitamins such as A, C, D, and E and minerals like zinc and iron can weaken the immune system. This can make individuals with ASD more susceptible to infections and illnesses, potentially leading to frequent health complications and extended recovery times[56]. Nutritional deficiencies can exacerbate existing gastrointestinal problems, such as constipation, diarrhea, and abdominal pain. These issues are common in individuals with ASD and can be both a cause and consequence of poor nutrition, creating a challenging cycle to break[10]. Iron deficiency anemia, common in individuals with ASD, can lead to fatigue and low energy levels. This can affect their ability to engage in daily activities, participate in physical exercise, and maintain overall vitality[57].

Cognitive Health Consequences: Essential nutrients like omega-3 fatty acids, B vitamins, and iron play crucial roles in brain function. Deficiencies in these nutrients

can impair cognitive processes such as attention, memory, and executive function. For example, omega-3 fatty acids are vital for synaptic function and neuronal communication, and their deficiency can affect cognitive performance and developmental outcomes[58]. Nutritional deficiencies can exacerbate behavioral symptoms associated with ASD. Deficiencies in omega-3 fatty acids and B vitamins have been linked to increased hyperactivity, irritability, and aggression. Iron deficiency can lead to cognitive and behavioral disturbances, impacting mood and increasing the severity of ASD symptoms[59]. Nutritional deficiencies can contribute to mental health issues such as anxiety and depression. For instance, deficiencies in B vitamins, particularly B6, B12, and folate, can affect neurotransmitter synthesis and regulation, influencing mood and emotional stability. A well-balanced diet with adequate nutrients is essential for maintaining mental health and emotional well-being[60].

Strategies to Address and Prevent Nutritional Deficiencies in Individuals with Autism:

Nutritional deficiencies are common among individuals with ASD, so addressing and preventing them requires a comprehensive, multidisciplinary approach that involves healthcare providers, dietitians, caregivers, and behavioral therapists[11]. Various strategies could effectively address these nutritional deficiencies. First, we should do a comprehensive nutritional assessment. These deficiencies could be initially assessed through dietary assessments to identify nutrient gaps and eating patterns[61]. Physicians could utilize food diaries, questionnaires, and interviews with caregivers to gather detailed information on dietary intake. Some laboratory tests could help check for deficiencies in essential vitamins and minerals such as Vitamin D, B vitamins, iron, zinc, and fatty acids and monitor biomarkers of nutritional status to adjust interventions accordingly[62].

Secondly, physicians should tailor the dietary interventions according to the initial assessment and initiate personalized meal plans. They can develop individualized meal plans that address specific nutritional needs while considering food preferences and

sensory sensitivities[63]. They may introduce nutrient-dense foods gradually to increase acceptance and encourage ² a diverse diet that includes a range of fruits, vegetables, whole grains, lean proteins, and healthy fats. The caregivers are advised to use creative presentations and recipes to make foods more appealing. Thirdly, behavioral and sensory-based strategies could help support nutritional management[12]. New foods and textures can be slowly introduced new foods to reduce sensory aversions. Parents can pair preferred foods with new or less preferred items to increase acceptance[64]. They can use rewards and praise to encourage them to try and consume new foods. Parents should try their best to create a positive mealtime environment to reduce anxiety and stress related to eating. Sensory integration therapy can help desensitize individuals and become more comfortable with different textures, tastes, and smells. In addition, occupational therapists can provide specialized support to address sensory processing issues[65].

Targeted nutritional supplementation is another crucial step in the management. The patients should be supplemented with vitamins and minerals that are difficult to obtain through diet alone, such as Vitamin D, B vitamins, iron, zinc, and omega-3 fatty acids[66]. Supplements should also be in forms that are easy to ingest and well-tolerated (*e.g.*, liquids, chewable). Supplements should be provided in the appropriate dosages and monitored for potential interactions or side effects, with regular review and adjustment of the supplementation plans based on ongoing assessments[67]. Addressing, identifying, and managing gastrointestinal problems such as constipation, diarrhea, and abdominal pain that can affect nutrient absorption is paramount. Patients can use probiotics, fiber supplements, or medications as healthcare providers recommend to improve digestive health[68]. Diets should be adjusted to include high-fiber foods to support healthy digestion. In addition, patients should avoid foods that exacerbate gastrointestinal symptoms and consider elimination diets if food intolerances or allergies are suspected[69].

Nutritional education is another essential corner of proper dietary management. Caregivers should receive information on balanced nutrition, portion sizes, and healthy

eating habits. They should be educated on the importance of consistency and patience in implementing dietary changes[70]. Caregivers should be provided with practical tips for meal planning, grocery shopping, and preparing meals that meet the nutritional needs of individuals with ASD. They also need to share strategies for managing mealtime behaviors and reducing the stress around eating. Other pillars of management are ongoing monitoring and follow-up. Regular follow-up appointments should be scheduled to monitor nutritional status, growth, and overall health[71]. Dietary and supplementation plans can be adjusted based on changes in nutritional needs and intervention responses. Addressing and preventing nutritional deficiencies in individuals with ASD requires a comprehensive, individualized approach that combines dietary interventions, behavioral strategies, supplementation, and ongoing support[72]. By leveraging a multidisciplinary team and continuously monitoring and adjusting plans, healthcare providers and caregivers can significantly improve the nutritional status, overall health, and quality of life of individuals with ASD.

Nutrition Assessment of Individuals Diagnosed with Autism:

A thorough nutritional assessment is crucial for individuals with ASD due to the high prevalence of feeding difficulties, dietary restrictions, and gastrointestinal issues in this population. Proper nutritional assessment can help identify deficiencies, guide dietary interventions, and improve overall health outcomes. Tailored dietary interventions, regular monitoring, and interdisciplinary collaboration can significantly enhance nutritional status and overall quality of life[73]. The initial step is dietary history, followed by anthropometric assessment, complete clinical examination, evaluation of gastrointestinal function, and biochemical assessment. A comprehensive nutritional assessment is essential for individuals with ASD to address the unique challenges and optimize their health and development. Tailored dietary interventions, regular monitoring, and interdisciplinary collaboration can significantly enhance nutritional status and overall quality of life[74].

Dietary and Medical History: Many individuals with ASD exhibit strong preferences and aversions for certain textures, colors, and types of food, often leading to a limited diet. Physicians can assess dietary records using a 3-day food record to analyze dietary intake and guide recommendations. Assessment of mealtime and feeding behaviors, such as refusal to eat certain foods, prolonged mealtimes, or disruptive behaviors, is a crucial step in nutritional assessment[75]. To assess nutrient adequacy, physicians should also obtain a detailed record of daily food and beverage intake, including portion sizes. They should also get information on any special diets, such as gluten-free, casein-free, or other therapeutic diets. Generally, carbohydrate and fat requirements are met, but fiber intake is often suboptimal. Protein intake may be sufficient if dairy is included; otherwise, non-dairy proteins are assessed. Common deficiencies include vitamin A, calcium, D, E, pantothenic acid, vitamin K, and zinc. Special attention is needed for children on gluten-free, casein-free diets, as many gluten-free foods are not fortified[76].

Gastrointestinal issues like constipation, diarrhea, abdominal pain, and reflux should be documented when present. Assessment of gut microbiota and potential dysbiosis helps address the defects that open the door for better treatment[23]. Medication history is also of paramount importance, as many medications used by individuals with autism could induce nutritional assessment. For example, ADHD medications can affect appetite negatively, anticonvulsants can cause nausea, vomiting, diarrhea, and decreased levels of vitamin D and calcium due to osteoclastic activity, and atypical antipsychotics may lead to increased appetite, weight gain, and glucose intolerance[77].

Laboratory values from the primary care physician are essential when assessing a child being evaluated for or already diagnosed with ASD. Lead levels are frequently measured when a developmental disability is suspected, as high serum levels are associated with mental retardation[78]. Iron deficiency anemia is a common risk factor in children with developmental disabilities, necessitating baseline ferritin level checks and ongoing monitoring if iron therapy is initiated[79]. Serum cholesterol levels are also of interest due to the correlation between low cholesterol and a positive ASD diagnosis.

This correlation is related to the physiological milieu of autism rather than nutrition[80]. Biochemical assessment includes blood tests for nutrient levels such as vitamins D, B12, folate, minerals like iron and zinc, and essential fatty acids. Urine tests evaluate metabolic markers and nutrient excretion[81].

Anthropometric assessment is the second step in nutritional assessment. Regular monitoring is crucial to tracking growth patterns and identifying potential undernutrition or obesity. Body mass index (BMI) is calculated and interpreted according to age-specific percentiles to help identify underweight and malnutrition[82]. Measuring Head Circumference in younger children helps to monitor brain development and growth. Triceps and subscapular skinfolds and arm circumference are other important anthropometric measures that help identify malnutrition. Recumbent measurements should be taken for younger children (0-36 months). In older children (6-10 years), metacarpal morphometry or dual-energy X-ray absorptiometry (DEXA) may be used to assess bone health[83].

Clinical Assessment: Recording the patient's medical history helps review medical conditions, including gastrointestinal disorders, allergies, and metabolic issues. Then, a thorough physical examination can help detect signs of nutrient deficiencies or excesses, such as skin changes, hair loss, or dental problems. Signs of vitamin D deficiency may include rickets, bone pain, and muscle weakness. Iron deficiency may be manifested in anemia, fatigue, and poor concentration [84]. Zinc deficiency may induce growth retardation, impaired immune function, and skin rashes. Furthermore, omega-3 deficiency may initiate cognitive and behavioral issues, dry skin, and cardiovascular problems [84].

Feeding Skills: Evaluation of ¹oral-motor deficits such as weak suck, tongue thrust, poor lip closure, and oral tactile sensitivity is of paramount importance. Feeding skills may be assessed by a multidisciplinary team, including a dietitian, occupational therapist, speech pathologist, pediatric psychologist, and pediatrician[85]. Table 1 compares the feeding developmental milestones in children with typical development *vs* those with autism[86-88].

Dietary Interventions and Therapies:

Specific dietary intervention may be beneficial in some individuals with autism, particularly in managing gastrointestinal symptoms and certain behavioral issues. Dietary interventions and therapies play a crucial role in managing and improving the health and well-being of individuals with ASD[89]. These interventions aim to address common nutritional deficiencies, gastrointestinal issues, and selective eating habits often observed in patients with autism. By tailoring dietary plans to meet the unique needs of individuals with ASD, healthcare providers can help alleviate some of the core symptoms and associated health problems[10]. Figure 2 shows the general effects of dietary therapy in children with ASD. Nutritional therapies may include specialized diets, such as gluten- or casein-free diets, ketogenic diets, and specific carbohydrate diets (SCD), which some believe can reduce behavioral symptoms and gastrointestinal distress[90]. Supplementation with essential nutrients like vitamins, minerals, and omega-3 fatty acids can address specific deficiencies and support overall health. Additionally, incorporating behavioral strategies, such as gradual exposure to new foods and positive reinforcement, can improve food acceptance and mealtime behaviors[91]. Other dietary management approaches might include elimination diets to identify and remove potential allergens or irritants and probiotics to enhance gut health. Through a comprehensive and personalized approach, nutritional interventions can support better physical health, cognitive function, and overall quality of life for individuals with autism[92].

Gluten-Free Diet (GFD):

GFD is a popular but controversial intervention for individuals with autism. While some parents and practitioners report positive outcomes, the scientific community calls for more rigorous research to substantiate these claims. This diet eliminates gluten, wheat, barley, and rye protein from the patient's diet[93]. While some parents and practitioners report positive outcomes, others deny any noticeable effect. Proponents of

the gluten-free diet for autism believe it can alleviate certain symptoms associated with the disorder, particularly gastrointestinal issues and behavioral symptoms[94].

The Rationale for a Gluten-Free Diet in Autism: Some researchers and clinicians propose that individuals with autism may have an increased sensitivity to gluten, which could exacerbate their symptoms (Theory of Gluten Sensitivity). This sensitivity may be due to an abnormal immune response or an inability to digest gluten properly. The gut-brain axis theory suggests that gastrointestinal dysfunctions can influence brain function and behavior[93]. Gluten, as a potential irritant to the gut lining, could contribute to inflammation and increased intestinal permeability (often referred to as "leaky gut"), leading to the release of peptides that affect brain function and behavior in individuals with ASD[95]. Additionally, the opioid excess theory posits that incomplete digestion of gluten can produce peptides with opioid-like activity, which can cross the blood-brain barrier and affect neurotransmission, potentially leading to the exacerbation of autistic symptoms[96].

Implementation of a Gluten-Free Diet: Before starting a gluten-free diet, it is essential to conduct a thorough assessment to determine if there is a potential gluten sensitivity or celiac disease[97]. This may involve blood tests, endoscopic evaluations, and consultations with a gastroenterologist. Transitioning to a gluten-free diet requires careful planning to ensure nutritional adequacy. This involves identifying and eliminating all sources of gluten from the diet, including obvious sources like bread, pasta, and cereals, as well as hidden sources in processed foods, sauces, and condiments[98]. To maintain a balanced diet, the patients can use gluten-free substitutes such as rice, quinoa, gluten-free oats, and specially formulated gluten-free products. It is important to choose nutrient-dense options to avoid potential nutrient deficiencies. Regular monitoring by a healthcare provider or dietitian is crucial to assess the diet's impact on symptoms and overall health. Support from caregivers and educators can also help ensure diet adherence[99].

Benefits of a Gluten-Free Diet: Some individuals with ASD who follow a gluten-free diet report improvements in gastrointestinal symptoms such as diarrhea, constipation,

and abdominal pain. Improved gut health can contribute to overall well-being and comfort[10]. Anecdotal reports and some preliminary studies suggest that a gluten-free diet may improve behavior, attention, and social interactions. Parents and caregivers have observed reduced hyperactivity, irritability, and repetitive behaviors. For some individuals with ASD, adhering to a gluten-free diet can lead to enhanced quality of life due to better health and symptom management. This can translate to improved daily functioning and engagement in activities[100].

Challenges and Considerations: The evidence supporting the efficacy of a gluten-free diet for autism is mixed. While some studies and anecdotal reports suggest benefits, it's crucial to note that large-scale, randomized controlled trials are needed to establish clear clinical guidelines. A gluten-free diet can lead to potential nutritional deficiencies, especially if not well-planned. Individuals on this diet may lack essential nutrients such as fiber, iron, calcium, and B vitamins, commonly found in gluten-containing grains[101]. Strict adherence to a gluten-free diet can be challenging, particularly in social settings like schools, parties, and restaurants. This can lead to social isolation or difficulty maintaining a long-term diet[97]. Gluten-free products can be more expensive and less accessible than their gluten-containing counterparts. This can create financial and logistical challenges for families and individuals trying to adhere to the diet[102]. Therefore, being well-informed about a gluten-free diet's potential challenges and benefits is essential.

Casein-Free Diet:

The casein-free diet is a dietary intervention that some individuals with autism may find beneficial, particularly in managing gastrointestinal symptoms and specific behavioral issues. It involves eliminating casein, a protein found in dairy products[94]. However, the scientific evidence supporting its efficacy is inconclusive, and the diet may not suit everyone. Like the gluten-free diet, the casein-free diet is based on theories that suggest a link between dietary proteins and autism symptoms[103].

Rationale for Casein-Free Diet in Autism: Some individuals with autism may have an increased sensitivity or allergy to casein. This can lead to gastrointestinal issues and inflammation, which might exacerbate autism symptoms[35]. Similar to gluten, casein can break down into peptides with opioid-like activity (casomorphins) during digestion. These peptides can potentially cross the blood-brain barrier, influencing brain function and behavior in individuals with ASD[104]. The gut-brain axis theory also suggests that gut health that significantly impacts brain function could be affected by casein. Casein, as a potential irritant to the gut, may contribute to increased intestinal permeability ("leaky gut"), releasing harmful substances that affect the brain and behavior[105].

Implementation of a Casein-Free Diet: Before starting a casein-free diet, it is essential to conduct a thorough assessment to identify potential casein sensitivity or allergy. This may involve skin prick tests, blood tests for IgE antibodies, and consultations with an allergist or gastroenterologist. Transitioning to a casein-free diet requires careful planning to ensure nutritional adequacy. It eliminates all casein sources, including milk, cheese, yogurt, butter, and other dairy products, and hidden sources in processed foods[106]. The caregivers can use casein-free substitutes such as almond milk, soy milk, rice milk, coconut milk, and casein-free cheese alternatives to maintain a balanced diet. It is crucial to choose fortified options to ensure adequate intake of nutrients typically provided by dairy[107]. Regular monitoring by a healthcare provider or dietitian is vital to assess the diet's impact on symptoms and overall health. Support from caregivers and educators is also essential to ensure adherence to the diet.

Benefits of Casein-Free Diet: Some individuals with ASD who follow a casein-free diet report improvements in gastrointestinal symptoms such as diarrhea, constipation, and abdominal pain. Improved gut health can contribute to overall well-being and comfort[10]. Anecdotal reports and preliminary studies suggest that a casein-free diet may improve behavior, attention, and social interactions. Parents and caregivers have observed reduced hyperactivity, irritability, and repetitive behaviors[100]. For some individuals with ASD, adhering to a casein-free diet can lead to enhanced quality of life

due to better health and symptom management. This can translate to improved daily functioning and activity engagement[108].

Challenges and Considerations: The evidence supporting the efficacy of a casein-free diet for autism is mixed. While some studies and anecdotal reports suggest benefits, large-scale, randomized controlled trials are needed to establish clear clinical guidelines. A casein-free diet can lead to potential nutritional deficiencies, especially if not well-planned. Individuals on this diet may lack essential nutrients such as calcium, vitamin D, and protein, commonly found in dairy products[109]. Strict adherence to a casein-free diet can be challenging, particularly in social settings like schools, parties, and restaurants. This can lead to social isolation or difficulties in maintaining the diet long-term. Casein-free products can be more expensive and less accessible than their dairy-containing counterparts. This can create financial and logistical challenges for families and individuals trying to adhere to the diet[110].

Current State of Scientific Evidence: Studies on the casein-free diet for autism have produced mixed results. Some research suggests improvements in gastrointestinal health and behavioral symptoms, while other studies find no significant benefits[94,111]. The variability in individual responses highlights the need for personalized approaches[110]. More rigorous, large-scale, randomized controlled trials are needed to establish the effectiveness of the casein-free diet in managing autism symptoms. Future research should also explore the underlying mechanisms that might explain why some individuals with ASD benefit from this diet. Given the mixed evidence, the casein-free diet should be considered case-by-case. Healthcare providers should work closely with families to assess potential benefits and risks, ensuring that dietary changes are safe and nutritionally adequate. As scientific evidence supporting its efficacy is inconclusive, consulting with healthcare professionals before starting a casein-free diet is crucial to ensure it is implemented safely and effectively, considering both potential benefits and challenges.

Ketogenic Diet:

The ketogenic diet (KD) is a promising but still experimental intervention for individuals with autism. The ketogenic diet (KD) is a high-fat, low-carbohydrate, and moderate-protein diet. It has been used for nearly a century primarily to treat refractory epilepsy[112]. Recently, it has gained attention as a potential intervention for various neurological and neurodevelopmental disorders, including ASD. While some individuals may experience significant improvements in behavior, cognitive function, and overall health, others may not see substantial benefits[113].

Rationale for Ketogenic Diet in Autism: The ketogenic diet produces ketones, which serve as an alternative energy source for the brain. Ketones have neuroprotective properties, including reducing oxidative stress and inflammation and improving mitochondrial function, which may benefit individuals with ASD[114]. The diet may also help restore the balance between excitatory (glutamate) and inhibitory (GABA) neurotransmitters in the brain. This balance is often disrupted in individuals with ASD, leading to symptoms such as hyperactivity and seizures[115]. The ketogenic diet may positively influence the gut microbiota, reducing gastrointestinal issues and improving gut health. Since the gut-brain axis plays a significant role in ASD, these improvements can potentially impact behavior and cognitive function. Abnormal energy metabolism has been observed in individuals with ASD. The ketogenic diet enhances mitochondrial function and energy production, which could alleviate some metabolic dysfunctions associated with autism[116].

Implementation of a Ketogenic Diet: A thorough medical evaluation is necessary before starting the ketogenic diet. This includes assessing baseline nutritional status, metabolic health, and potential contraindications such as metabolic disorders or pancreatitis[112]. The ketogenic diet typically involves a macronutrient ratio of approximately 70-80% fat, 10-20% protein, and 5-10% carbohydrates. Meals must be planned carefully to meet these ratios while ensuring nutritional adequacy. Common foods include meats, fatty fish, eggs, high-fat dairy products, nuts, seeds, avocados, and low-carb vegetables[117]. Regular monitoring by healthcare professionals is crucial to track the diet's impact on health and symptoms. Blood tests, urine tests for ketone

levels, and dietary logs are often used to ensure adherence and effectiveness. Adjustments to the diet may be necessary based on individual responses and goals. Providing education and support to caregivers and individuals is vital for successful implementation. This includes guidance on meal preparation, understanding macronutrient ratios, and managing potential side effects[118].

Benefits of the Ketogenic Diet: Some studies and anecdotal reports suggest that the ketogenic diet can improve behavior, social skills, and communication in individuals with ASD. In some cases, reductions in hyperactivity, irritability, and repetitive behaviors have been observed[116]. Given its established efficacy in treating epilepsy, the ketogenic diet may benefit individuals with ASD who also experience seizures or epilepsy. Improved seizure control can significantly enhance the quality of life. The diet's impact on brain metabolism and neurotransmitter balance may lead to cognitive improvements, including better attention, memory, and learning capabilities[119]. The ketogenic diet may also improve gastrointestinal symptoms commonly seen in individuals with ASD, such as constipation, diarrhea, and abdominal pain. These improvements can contribute to overall well-being and comfort[120].

Challenges and Considerations: While there are promising anecdotal and preliminary evidence, the scientific data on the ketogenic diet's effectiveness for autism is still limited. More rigorous, large-scale studies are needed to establish clear clinical guidelines. Ensuring that the ketogenic diet meets all nutritional requirements can be challenging. If necessary, potential deficiencies in vitamins, minerals, and fiber must be addressed through careful planning and supplementation[121]. Strict adherence to the ketogenic diet can be difficult, especially in social settings like schools, parties, and restaurants. This can lead to social isolation or challenges in long-term maintaining the diet[122]. Potential side effects of the ketogenic diet include gastrointestinal discomfort, nutrient deficiencies, kidney stones, and increased cholesterol levels. Regular monitoring and adjustments are essential to manage these risks[123]. The ketogenic diet can be more expensive and less accessible than a typical diet. Access to high-quality

fats, specific supplements, and specialized food products can create financial and logistical challenges[124].

Current State of Scientific Evidence: The evidence supporting the ketogenic diet for autism is mixed. Some studies and case reports show significant improvements in behavior and cognitive function, while others find no substantial benefits. Individual responses can vary widely[90]. More rigorous, large-scale, randomized controlled trials are needed to establish the ketogenic diet's efficacy and safety in managing autism symptoms. Research should focus on understanding the underlying mechanisms and identifying which individuals are most likely to benefit. Given the variability in individual responses, a personalized approach to the ketogenic diet is essential[125]. Healthcare providers should work closely with families to assess potential benefits and risks, ensuring that dietary changes are safe and nutritionally adequate. Through careful planning, monitoring, and support, the ketogenic diet may be a valuable tool in managing symptoms and improving the quality of life for some individuals with ASD[126].

Specific Carbohydrate Diet (SCD):

The Specific Carbohydrate Diet (SCD) has garnered attention within the autism community as a potential way to address some of the gastrointestinal and behavioral concerns associated with ASD. U.S. pediatrician Dr. Sidney Haas originally developed it in the 1920s to treat children suffering from celiac disease, who experienced symptoms like diarrhea, bloating, gas, and weight loss[11]. The diet became later popularized due to its positive effects on symptoms of inflammatory bowel disease, leading to its increased use among those with similar gastrointestinal issues. The SCD revolves around eliminating specific carbohydrates not well absorbed by the body and may promote the growth of harmful bacteria in the intestines[127]. By removing complex carbohydrates, lactose, and sucrose from the diet and increasing the intake of nutrient-dense foods, SCD aims to reduce gut dysbiosis and gastrointestinal inflammation[128]. The diet strictly excludes grains, sugars, and starches that are considered difficult to

digest. Doing so aims to restore balance to the intestinal flora and allow the gut to heal, potentially leading to improved behavior and social interactions in individuals with ASD[129]. However, according to the University of Virginia School of Medicine, SCD does not reduce symptoms of autism.

Rationale for the Specific Carbohydrate Diet in Autism: The gut-brain axis theory suggests a bidirectional relationship between gut health and brain function. Individuals with ASD often experience gastrointestinal issues, which may contribute to or exacerbate behavioral and cognitive symptoms[10]. The SCD aims to restore gut health, potentially improving overall well-being and behavior. Some individuals with ASD may have difficulties digesting and absorbing complex carbohydrates, leading to fermentation by gut bacteria, production of harmful byproducts, and gastrointestinal symptoms[130]. The SCD restricts these carbohydrates to prevent such issues. An imbalance in gut microbiota, or dysbiosis, is commonly observed in individuals with ASD. The SCD aims to reduce gut inflammation and dysbiosis by eliminating fermentable carbohydrates that feed pathogenic bacteria and yeasts[127].

Implementation of the Specific Carbohydrate Diet: Before starting the SCD, a thorough medical evaluation is necessary to assess baseline gastrointestinal health, nutritional status, and potential contraindications. Consultation with a healthcare provider or dietitian experienced with SCD is recommended. The SCD involves eliminating complex carbohydrates, disaccharides, and polysaccharides. Allowed foods include meats, fish, eggs, aged cheeses, certain vegetables and fruits, nuts, and seeds. Prohibited foods include grains, most dairy products, starchy vegetables, and processed foods[131]. Transitioning to SCD can be gradual to allow the body to adapt and to monitor for any adverse reactions. Starting with easily digestible foods and gradually incorporating a wider variety of permitted foods is recommended. Regular monitoring by healthcare professionals is crucial to tracking the diet's impact on symptoms and overall health. Blood tests, stool tests, and dietary logs can be used to ensure adherence and effectiveness[132]. Based on individual responses, adjustments to the diet may be necessary. Providing education and support to caregivers and individuals is vital for

successful implementation. This includes guidance on meal preparation, understanding allowed and prohibited foods, and managing potential challenges[130]. For those considering this dietary approach, it is crucial to consult with healthcare professionals to ensure it is implemented safely and effectively, considering both potential benefits and challenges. Through careful planning, monitoring, and support, SCD may be a valuable tool in managing symptoms and improving the quality of life for some individuals with ASD.

Benefits of the Specific Carbohydrate Diet: Many individuals with ASD who follow the SCD report significant improvements in gastrointestinal symptoms such as diarrhea, constipation, bloating, and abdominal pain. Improved gut health can contribute to overall well-being and comfort. Some studies and anecdotal reports suggest that SCD can lead to improvements in behavior, social skills, and communication in individuals with ASD. In some cases, reductions in hyperactivity, irritability, and repetitive behaviors have been observed[131]. The diet's impact on gut health and the reduction of inflammation may lead to cognitive improvements, including better attention, memory, and learning capabilities[133]. For some individuals with ASD, adhering to the SCD can lead to enhanced quality of life due to better health and symptom management. This can translate to improved daily functioning and engagement in activities[134].

Challenges and Considerations: The SCD is known for being restrictive, often leading to concerns about potential nutritional deficiencies due to the elimination of various food groups. Ensuring that the diet meets all nutritional requirements can be challenging. If necessary, potential deficiencies in vitamins, minerals, and fiber must be addressed through careful planning and supplementation[129]. Strict adherence to the SCD can be difficult, especially in social settings like schools, parties, and restaurants. This can lead to social isolation or long-term challenges in maintaining the diet[135]. Potential side effects of SCD include gastrointestinal discomfort during the initial transition period, nutrient deficiencies, and potential challenges in maintaining weight, especially in growing children[136]. Regular monitoring and adjustments are essential

to manage these risks. The SCD can be more expensive and less accessible than a typical diet. Access to high-quality, specific foods and supplements can create financial and logistical challenges for families and individuals trying to adhere to the diet[137]. While there is promising anecdotal and preliminary evidence, the scientific data on SCD's effectiveness for autism is still limited. More rigorous, large-scale studies are needed to establish clear clinical guidelines.

Current State of Scientific Evidence: The evidence supporting the SCD for autism is mixed. Some studies and case reports show significant improvements in gastrointestinal health and behavioral symptoms, while others find no substantial benefits. Individual responses can vary widely[129,131,134]. There is a need for more rigorous, large-scale, randomized controlled trials to establish the SCD's efficacy and safety in managing autism symptoms. Research should focus on understanding the underlying mechanisms and identifying which individuals are most likely to benefit. Given the variability in individual responses, a personalized approach to SCD is essential. Healthcare providers should work closely with families to assess potential benefits and risks, ensuring that dietary changes are safe and nutritionally adequate.

Gut and Psychology Syndrome Protocol (GAPS diet) (Table 2):

GAPS protocol is a therapeutic diet developed by Dr. Natasha Campbell-McBride, aimed at addressing various psychological and physiological conditions through dietary intervention. This diet is based on the premise that many health issues, including ASD, are linked to gut health[138]. The GAPS diet focuses on healing the gut lining, restoring healthy gut flora, and reducing inflammation to improve overall health and prevent potentially harmful substances from seeping into the bloodstream, affecting brain function and development[139]. Dr. Natasha created the GAPS diet after observing a strong correlation between gut health and brain function. She developed the diet based on her clinical experience and the dietary principles of the Specific Carbohydrate Diet (SCD) by Dr. Sidney Haas.

Principles of the GAPS Diet: The GAPS diet is structured in phases, starting with an introductory phase and gradually progressing to a full GAPS diet. Each phase includes specific foods to heal the gut and support the body's detoxification processes. The main principles of the diet include eliminating processed foods, including healing foods, and gradually reintroducing them[138]. The diet excludes processed foods, refined sugars, grains, and starchy vegetables, which can contribute to gut dysbiosis and inflammation. Then, the diet emphasizes the consumption of nutrient-dense, easily digestible foods such as bone broths, fermented foods, and healthy fats to support gut healing. Then, foods are reintroduced gradually to monitor tolerance and ensure the gut can handle them without adverse reactions[140].

Phases of the GAPS Diet: The introduction phase is the most restrictive phase, focusing on easily digestible foods to initiate gut healing and restore leaky guts. Foods include homemade meat or fish stocks, probiotic foods, and boiled vegetables. After completing the introduction phase, individuals transition to the full GAPS diet, which allows a wider variety of foods but still excludes grains, processed sugars, and certain starchy vegetables[141].

Core Components of the GAPS Diet: Bone broth and meat stock, rich in amino acids, collagen, and minerals, are central to the diet for their gut-healing properties. In addition, fermented foods, including homemade yogurt, kefir, sauerkraut, and other fermented vegetables, are consumed to introduce beneficial bacteria to the gut. The food should be organic, unprocessed, natural, and free from additives and chemicals to support overall health. Healthy fats are incorporated from meat, fish, avocados, and coconut oil, which are essential for cell repair and energy. The diet also emphasizes including non-starchy vegetables and low-sugar fruits, preferably cooked to aid digestion[133,142].

Mechanisms of Action: Nutrient-dense foods like bone broth and fermented foods help repair the gut lining, reducing permeability and inflammation. Probiotic-rich foods and supplements help balance gut microbiota, which is crucial for digestion and immune function. Eliminating processed and toxic foods reduces the burden on the

liver and other detoxification pathways[143]. Improved gut health leads to better immune system regulation, potentially reducing autoimmunity and systemic inflammation[144].

Research and Evidence: Scientific evidence supporting the GAPS diet is primarily anecdotal, with limited peer-reviewed research specifically on the diet, with the risk that the early introductory phases may not maintain adequate nutrition. However, studies on the principles underlying the GAPS diet, such as the impact of gut microbiota on brain function and the benefits of nutrient-dense, anti-inflammatory foods, provide indirect support. Research has established a strong link between gut health and brain function, supporting the diet's focus on healing the gut to improve psychological symptoms[145-147]. In addition, studies have shown the benefits of probiotics in restoring gut flora and reducing gastrointestinal symptoms, aligning with the diet's emphasis on fermented foods[148].

Practical Considerations: The GAPS diet can be challenging to implement due to its restrictive nature, requiring careful meal planning and preparation. To avoid deficiencies, it is essential to ensure that all nutritional needs are met, particularly in children[149]. Responses to the diet can vary widely; some individuals may experience significant improvements, while others may see minimal changes[150]. Consulting with healthcare providers, particularly those experienced with the GAPS diet, can help tailor the diet to individual needs and monitor progress.

Camel Milk:

Camel milk has been used for centuries in Middle Eastern and African cultures as a promising complementary approach, valued for its nutritional and medicinal properties. In recent years, interest in camel milk has extended to the management of ASD, where anecdotal reports and emerging research suggest potential benefits arising from its anti-inflammatory, antioxidant, immune-modulating, and gut health-supporting properties[151].

Nutritional Profile of Camel Milk: Camel milk is distinct from cow's milk and other types of milk in several nutritional aspects. It contains unique proteins, such as lactoferrin and immunoglobulins, with antimicrobial and immune-modulating properties. Unlike cow milk, which contains beta-lactoglobulin and beta-casein, camel milk does not have these components[152]. It has less lactose, lower fat, and a different fatty acid profile than cow's milk, including less cholesterol and higher levels of unsaturated fatty acids. Camel milk is also rich in vitamins (A, B, C, D, and E) and minerals (calcium, magnesium, zinc, and iron) essential for overall health. In addition, it contains enzymes such as lysozyme, which has antibacterial properties. Furthermore, camel milk is generally considered hypoallergenic and may be suitable for individuals with cow's milk allergies[153,154]. Figure 3 summarizes the nutritional benefits of camel milk.

Proposed Mechanisms of Action: The potential benefits of camel milk for individuals with ASD are thought to arise from several mechanisms. Camel milk contains bioactive compounds that have anti-inflammatory properties, which may help reduce systemic and neural inflammation associated with ASD[155]. It is also rich in antioxidants and can help combat oxidative stress, often elevated in individuals with ASD. Camel milk boosts the levels of superoxide dismutase (SOD), myeloperoxidase (MPO), and plasma GSH, which helps mitigate oxidative stress—a significant factor in the development of autism. Additionally, camel milk alleviates oxidative stress by downregulating mitogen-activated protein kinase (MAPK) signaling pathways[156]. In addition, the immunoglobulins and lactoferrin in camel milk can modulate immune responses, potentially improving immune function and reducing autoimmunity[157]. Camel milk may also support gut health by promoting a balanced microbiota and reducing gastrointestinal inflammation, which is common in individuals with ASD. Furthermore, the high vitamin and mineral content can help address nutritional deficiencies often seen in children with ASD[158].

Current Research Findings: Research on the effects of camel milk on ASD is still in its infancy, but several studies and anecdotal reports have provided promising results.

Some studies have reported significant behavioral improvements after camel milk consumption, including reduced hyperactivity, lethargy, and irritability[159]. Improvements in cognitive functions, such as attention and communication skills, have been observed in some children with ASD. Several reports suggest that camel milk may also alleviate gastrointestinal symptoms such as constipation, diarrhea, and bloating, which are common in ASD[10,156,159]. Numerous anecdotal accounts from parents and caregivers describe noticeable improvements in behavior, social interaction, and digestive health in children with ASD who consume camel milk[160,161]. As with many interventions, responses to camel milk can vary widely among individuals, with some experiencing significant benefits and others showing no noticeable changes.

Practical Considerations: Several practical aspects should be considered when considering camel milk for individuals with ASD. Obtaining camel milk of good quality and from reputable sources is crucial to ensure it is free from contaminants and produced under hygienic conditions[162]. Caregivers should gradually introduce camel milk into the diet to monitor for adverse reactions. They should consult a healthcare provider to determine an appropriate dosage[163]. While camel milk is generally hypoallergenic, it is crucial to observe for any allergic reactions, especially in individuals with a history of food allergies. Camel milk should be integrated into a balanced diet, meeting all nutritional needs[164]. The individual's response to camel milk should be regularly monitored, including behavioral, cognitive, and gastrointestinal changes, and the intervention should be adjusted as needed[165]. Caregivers and healthcare providers should consider camel milk supplementation carefully, ensuring choices are evidence-based, personalized, and integrated into a broader therapeutic strategy.

Probiotics Supplements:

³ Probiotics are live microorganisms that confer health benefits on the host when administered in adequate amounts. Recently, their potential role in managing ASD has gained considerable interest due to the increasing recognition of the gut-brain axis and

its influence on neurological and behavioral health[166]. The use of probiotics in managing ASD offers a promising avenue for alleviating gastrointestinal issues and potentially improving behavioral symptoms through the modulation of the gut-brain axis[167].

Scientific Rationale: The gut-brain axis is a bidirectional communication system between the gastrointestinal tract and the brain, involving neural, hormonal, and immune pathways. This connection suggests that gut health can significantly impact neurological function and behavior[168]. Children with ASD often present with GI issues, such as constipation, diarrhea, and abdominal pain, which can exacerbate behavioral symptoms[10]. Dysbiosis, an imbalance in the gut microbiota, has been observed in many individuals with ASD, leading researchers to explore the potential benefits of probiotics in restoring a healthy gut microbiome and mitigating ASD symptoms[30].

Mechanisms of Action: Probiotics may benefit individuals with ASD through several mechanisms. Probiotics can help reestablish a healthy balance of gut bacteria, which may reduce gut dysbiosis commonly observed in ASD[167]. By modulating the immune system and producing anti-inflammatory compounds, probiotics can help reduce inflammation in the gut, potentially alleviating GI symptoms[169]. Probiotics can also strengthen the gut barrier, preventing the translocation of harmful substances from the gut into the bloodstream, which might affect the brain and behavior[170]. Some probiotic strains produce neurotransmitters and other neuroactive compounds that can influence brain function and behavior. Probiotics can modulate immune responses, potentially reducing systemic inflammation that may affect neurological health[171].

Current Research Findings: Research on probiotics use in ASD is still in its early stages, but several studies and clinical trials have shown promising results. Studies have consistently found differences in the gut microbiota composition of individuals with ASD compared to neurotypical controls. These differences often include reduced diversity and an overrepresentation of specific bacterial groups associated with inflammation and GI distress[105]. Some clinical trials have reported improved GI and

behavioral symptoms following probiotic supplementation. For example, *Lactobacillus* and *Bifidobacterium* strains improve bowel habits and reduce stereotypical behaviors and hyperactivity[172]. Despite promising findings, results have been mixed, with some studies showing no significant improvements. This variability may be due to differences in study design, probiotic strains, dosages, and individual responses[173]. Animal models of autism have shown that probiotics can reduce anxiety-like behaviors, improve social interactions, and normalize gut microbiota composition[174]. Animal studies have provided insights into how probiotics may exert their effects, such as modulation of the gut-brain axis and reducing systemic inflammation[175].

Practical Considerations: When considering probiotics for individuals with ASD, several practical aspects should be considered. Different probiotic strains have different effects. It is essential to choose strains that have been studied and shown to be effective in ASD[176]. The optimal dosage and duration of probiotic treatment can vary. Clinical guidance should be sought to determine appropriate regimens[177]. Probiotics should be sourced from reputable manufacturers to ensure quality, purity, and safety. Products should be free from contaminants and accurately labeled regarding strain composition and potency. Responses to probiotics can vary widely among individuals with ASD[178]. Monitoring and adjusting the intervention based on individual responses and any adverse effects is crucial. Probiotics can be used alongside other dietary and therapeutic interventions[179]. Coordination with healthcare providers ensures a comprehensive approach to managing ASD symptoms. Healthcare providers and caregivers should carefully consider probiotic interventions, ensuring that choices are evidence-based, personalized, and integrated into a broader therapeutic strategy.

Prebiotics Supplementation:

Prebiotics, ³⁰ non-digestible food ingredients that promote the growth of beneficial microorganisms in the intestines, hold promise as a therapeutic option for managing gastrointestinal and potentially behavioral symptoms in individuals with autism[180].
⁵ Prebiotics are compounds in food that induce the growth or activity of beneficial

microorganisms such as bacteria and fungi. The most common types of prebiotics are fructooligosaccharides (FOS), found in foods like onions, garlic, and bananas; galactooligosaccharides (GOS), found in legumes and certain root vegetables; inulin, found in chicory root, asparagus, and leeks, and lactulose, a synthetic sugar used as a prebiotic and laxative[181].

Mechanisms of Action: Prebiotics promote gut health by serving as a food source for beneficial bacteria, such as Bifidobacteria and Lactobacilli[182]. These bacteria ferment prebiotics to produce short-chain fatty acids (SCFAs), including butyrate, acetate, and propionate, which have several beneficial effects. SCFAs help maintain the integrity of the gut lining, preventing the translocation of harmful substances into the bloodstream[183]. SCFAs reduce inflammation by modulating immune responses in the gut. Some SCFAs are involved in synthesizing neurotransmitters, which can influence brain function and behavior. Prebiotics can also affect the gut-brain axis, potentially impacting mood and cognitive function[184].

Prebiotics and Autism: Many individuals with ASD suffer from GI issues such as constipation, diarrhea, and abdominal pain. Prebiotics can improve gut health by increasing the population of beneficial bacteria, enhancing stool consistency, and reducing inflammation[185]. Emerging research suggests that improving gut health with prebiotics can positively affect behavior and cognitive function in individuals with ASD. This is thought to be mediated through the gut-brain axis[186]. Individuals with ASD often have immune dysregulation. Prebiotics can modulate the immune system, reducing systemic inflammation that might contribute to neurodevelopmental issues[187]. Figure 4 shows the Role of Probiotics and Prebiotics in ASD.

Current Research Findings: Preclinical studies have shown that prebiotics can alter gut microbiota composition, reduce inflammation, and improve social behaviors in animal models of autism. Human trials are limited but promising. Some studies have reported improved GI symptoms and better behavior in children with ASD following prebiotic supplementation[188,189].

Practical Considerations: The optimal dosage of prebiotics for individuals with ASD is not well established and may vary depending on individual needs and responses²⁴[190]. It is crucial to start with a low dose and gradually increase it to avoid adverse effects such as bloating and gas. Including prebiotic-rich foods in the diet can be a natural way to promote gut health[191]. Garlic, onions, bananas, and asparagus are good sources of prebiotics. Prebiotic supplements are available and can⁵¹ be used under the guidance of a healthcare professional. It is essential to choose high-quality products and monitor for any adverse reactions[192]. Prebiotics are often used in conjunction with probiotics (beneficial bacteria) to create a synergistic effect, known as synbiotics. This combination can enhance the growth and activity of beneficial gut bacteria more effectively than prebiotics or probiotics alone[193]. Healthcare providers should consider prebiotics as part of a comprehensive approach to managing ASD, tailored to each patient's individual needs. Integrating prebiotics through diet or supplements, along with other interventions, may offer a valuable strategy for improving the quality of life for those with autism[194].

High-Dose Methyl Cobalamin in Autism:

ASD is a neurodevelopmental disorder¹⁷ characterized by deficits in social communication, repetitive behaviors, and restricted interests. While the exact etiology of ASD remains unclear, emerging research has explored various biomedical interventions, including the use of high-dose methylcobalamin (vitamin B12)[195]. Methylcobalamin is one of the active forms of²⁰ vitamin B12, a water-soluble vitamin essential for brain function, nerve tissue health, and the production of red blood cells. Unlike cyanocobalamin, another common form of vitamin B12, methylcobalamin is directly utilized by the body without needing conversion. It plays a critical role in methylation, a biochemical process vital for DNA synthesis, detoxification, and neurotransmitter production[196].

Potential Mechanisms of Action: The therapeutic potential of high-dose methylcobalamin in autism may be attributed to several mechanisms. Methylcobalamin

is crucial for the methylation cycle, which involves transferring methyl groups to DNA, proteins, and other molecules. Proper methylation is necessary for gene regulation, detoxification, and neurotransmitter production[197]. Methylcobalamin is involved in glutathione synthesis, a powerful antioxidant that helps protect cells from oxidative stress. Many individuals with ASD have been found to have low glutathione levels[198]. Vitamin B12 is essential for maintaining myelin, the protective sheath around nerves. Methylcobalamin's neuroprotective properties may help improve nerve function and cognitive abilities[199]. Methylcobalamin supports the detoxification process by aiding in the removal of heavy metals and other toxins from the body, which may be particularly beneficial for individuals with ASD who exhibit detoxification impairments[200].

Benefits in Autism: Studies have suggested that high-dose methylcobalamin may improve behaviors such as social interaction, communication, and repetitive behaviors in individuals with autism[201]. Some research indicates that methylcobalamin can enhance cognitive functions, including attention, focus, and learning abilities, potentially contributing to better academic and social outcomes[202]. By boosting glutathione levels, high-dose methylcobalamin may reduce oxidative stress, which is often elevated in individuals with autism and associated with various neurological and behavioral symptoms[203]. Enhanced methylation and glutathione production can improve the body's ability to detoxify harmful substances, potentially reducing the toxic burden and impacting neurological health[143].

Current Research Findings: Some clinical trials have shown promising results with high-dose methylcobalamin in autism. For instance, a study by Hendren *et al.* (2016) reported that methylcobalamin injections significantly improved methylation capacity, reduced oxidative stress markers, and improved clinician-rated ASD symptoms that were correlated with improvements in measures of methionine metabolism and cellular methylation capacity in children with ASD[204]. Various case reports and small-scale studies have noted behavioral improvements, including better communication, increased social engagement, and reduced stereotypical behaviors following high-dose

methylcobalamin treatment[201,205]. Research has demonstrated that high-dose methylcobalamin can normalize specific autism-associated biomarkers, such as increased levels of homocysteine and improved glutathione status[206]. The treatment response to methylcobalamin is expected when the treatment is associated with increased glutathione redox status[195].

Practical Considerations: High-dose methylcobalamin is typically administered *via* subcutaneous or intramuscular injections. The exact dosage varies, but common protocols involve 75-150 mcg/kg body weight doses administered every 1-3 days[200]. Regular monitoring of vitamin B12 Levels, methylation markers, and clinical response is essential to ensure safety and efficacy. Side effects are generally rare but can include mild irritability or hyperactivity[207]. Methylcobalamin is often used in conjunction with other biomedical interventions, such as folinic acid, to enhance its therapeutic effects. Tailoring the treatment plan to each patient's needs is important[208]. Healthcare providers should consider high-dose methylcobalamin as part of a comprehensive, individualized treatment plan for individuals with autism, ensuring careful monitoring and adjustment as needed.

Folic Acids in Autism:

ASD has been linked to abnormalities in folate metabolism, prompting several mechanistic hypotheses regarding its causes and potential symptomatic treatments[209]. Folic acid, a synthetic form of the naturally occurring folate (vitamin B9), plays a critical role in various biochemical processes, including DNA synthesis, repair, and methylation[210]. Its significance during pregnancy, particularly in neural tube development, is well established. Folic acid supplementation plays a promising role in the potential reduction of ASD risk, particularly when administered prenatally. Its involvement in critical metabolic pathways that influence neurodevelopment underscores its importance[211].

Folate Metabolism and ASD: Abnormalities in folate metabolism have been implicated in ASD. Key pathways affected by folate include one-carbon metabolism and

the transsulfuration pathway, both essential for proper neurodevelopment. Disruptions in these pathways can lead to deficits in methylation and increased oxidative stress, factors associated with ASD[212].

Potential Mechanisms: Folate is crucial for the methylation of DNA, a process essential for regulating gene expression. Abnormal methylation patterns have been observed in individuals with ASD, suggesting that proper folate levels may influence the risk of developing ASD by ensuring regular gene expression during critical periods of neurodevelopment[213,214]. Folate also reduces homocysteine levels, a byproduct of one-carbon metabolism that, in excess, can contribute to oxidative stress. Elevated oxidative stress is a common finding in individuals with ASD, and maintaining adequate folate levels may help mitigate this condition by supporting antioxidant defenses[203]. In addition, folate is involved in synthesizing neurotransmitters such as serotonin, dopamine, and norepinephrine. Imbalances in these neurotransmitters are often reported in individuals with ASD, suggesting that folate supplementation might help normalize their levels and improve related symptoms[215].

Prenatal Folic Acid Supplementation: Research indicates that prenatal folic acid supplementation can significantly reduce the risk of ASD[216]. The critical window for folic acid supplementation appears to be before conception and during the first trimester of pregnancy. Supplementation during this period is associated with a reduced incidence of ASD, possibly due to its role in neural tube formation and early brain development[217]. Standard prenatal doses of folic acid (400-800 mcg per day) are generally recommended. High doses should be taken under medical supervision, especially considering the potential risk of masking vitamin B12 deficiency symptoms[218]. Large epidemiological studies have shown a correlation between maternal folic acid supplementation and a decreased risk of ASD in offspring. For example, a study published in the "Journal of the American Medical Association" found that children whose mothers took folic acid supplements around the time of conception had a lower risk of developing ASD compared to those whose mothers did not[219].

Challenges and Considerations: Variations in genes involved in folate metabolism (e.g., MTHFR polymorphisms) can affect individual responses to folic acid supplementation. Personalized approaches considering genetic makeup may be necessary to optimize folate supplementation strategies[220]. The presence of other nutrients, such as vitamin B12 and iron can influence the effectiveness of folic acid. A balanced diet that ensures adequate intake of these nutrients is crucial for maximizing the benefits of folic acid[221]. While folic acid supplementation is generally safe, excessive intake has been associated with potential risks, including the masking of vitamin B12 deficiency and possible associations with other health conditions[222]. Therefore, it is essential to adhere to recommended doses. However, further research is needed to understand the mechanisms and fully optimize supplementation strategies. Healthcare providers should consider individual genetic and nutritional contexts when recommending folic acid to maximize its benefits and minimize potential risks.

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Vitamin B6 Supplement:

Vitamin B6, also known as pyridoxine, is a water-soluble neurotropic vitamin that plays a crucial role in brain development and function. It is involved in synthesizing neurotransmitters, chemicals that transmit signals in the brain[223]. The potential therapeutic role of Vitamin B6 in autism spectrum disorder (ASD) has been the subject of research for several decades.

Mechanisms of Action: Vitamin B6 is a cofactor for over 140 enzymatic functions and enzymes involved in synthesizing several neurotransmitters, including serotonin, dopamine, and gamma-aminobutyric acid (GABA). These neurotransmitters are critical for mood regulation, behavior, and cognitive function[224]. Elevated levels of homocysteine, an amino acid, have been associated with neurological disorders. Vitamin B6 helps convert homocysteine into cysteine, reducing its neurotoxic effects and supporting neurological health[225]. Glutamate is an excitatory neurotransmitter, and its imbalance has been implicated in autism. Vitamin B6 plays a role in converting

glutamate to GABA, an inhibitory neurotransmitter, thus maintaining neurotransmitter balance[226].

Clinical Evidence for Role of Vitamin B6 in ASD: Initial studies in the 1960s and 1970s suggested that high doses of Vitamin B6, often combined with magnesium, improved behavior and communication in autistic children. These studies, however, were small and had methodological limitations[227,228]. Subsequent randomized controlled trials have produced mixed results. Some studies reported improvements in social interactions, communication, and behavioral problems, while others found no significant effects[229,230]. Meta-analyses of Vitamin B6 supplementation in autism have highlighted the variability in study design, dosages, and outcome measures, leading to inconclusive results. However, some analyses suggest potential benefits for specific subgroups of individuals with ASD[231].

Potential Benefits of Vitamin B6 in ASD: Vitamin B6 supplementation may improve behavior, including reduced irritability and hyperactivity, in some children with autism. Reports indicate that Vitamin B6 may support language development and communication skills in some individuals with autism. Although evidence is inconsistent, vitamin B6's role in neurotransmitter synthesis and homocysteine metabolism may contribute to cognitive improvements[232].

Safety and Dosage: Studies vary widely on the effective dose of Vitamin B6 for autism, ranging from moderate to high doses. One of the proposed doses is to use vitamin B6 in a dose of 5 mg/kg/day for two weeks, followed by 10 mg/kg for another two weeks[233]. Determining the appropriate dosage based on individual needs and under medical supervision is essential. High doses of Vitamin B6 ²⁵ can cause peripheral neuropathy, a condition characterized by nerve damage, leading to numbness and tingling in the extremities[234]. Therefore, monitoring and adjusting the dosage is crucial to avoid toxicity. Vitamin B6 is often supplemented alongside magnesium, which may enhance its effectiveness and mitigate potential side effects. Magnesium itself plays a role in neuromuscular function and has been studied for its possible benefits in autism[235]. As the evidence for the beneficial role of Vitamin B6 in ASD

remains mixed, more robust, large-scale studies are needed to establish its efficacy and safety conclusively. Parents and caregivers considering Vitamin B6 supplementation for their children with autism should consult healthcare professionals to determine the appropriate dosage and monitor for adverse effects[10]. As part of a comprehensive treatment plan, Vitamin B6 may offer a valuable option for supporting neurological health and improving the quality of life for individuals with autism.

Vitamin D in Autism:

Vitamin D is a fat-soluble vitamin essential for maintaining bone health, immune function, and cellular processes. It has two main forms: Vitamin D2 (ergocalciferol) and vitamin D3 (cholecalciferol). Vitamin D3 is synthesized in the skin upon exposure to sunlight and can also be obtained from dietary sources such as fatty fish, egg yolks, and fortified foods. Vitamin D2 is found in some plants and fungi. Both forms are converted in the liver to 25-hydroxyvitamin D, the main circulating form[236,237]. Then, in the kidneys, in the biologically active form, 1,25-dihydroxy vitamin D. Vitamin D plays a crucial role in various physiological processes relevant to brain development and managing ASD. Emerging evidence suggests that vitamin D deficiency may contribute to the pathophysiology of autism, and supplementation may offer therapeutic benefits[238].

Functions of Vitamin D: Vitamin D facilitates the absorption of calcium and phosphorus from the gut, which is crucial for forming and maintaining healthy bones and teeth. Vitamin D also modulates the immune system, reduces inflammation, and enhances the pathogen-fighting effects of monocytes and macrophages[239,240]. Vitamin D receptors and the enzyme required to activate vitamin D are present in the brain, suggesting a role in brain development and function. It influences neurodevelopmental processes, such as neuronal differentiation, axonal connectivity, and neurotransmission[241].

Potential Links Between Vitamin D Deficiency and Autism: Several studies have suggested that low maternal vitamin D levels during pregnancy may increase the risk

of ASD in offspring. Vitamin D is crucial for fetal brain development, and deficiency during this critical period may lead to neurodevelopmental abnormalities[242]. Vitamin D deficiency is associated with immune dysregulation, which is often observed in individuals with ASD. Abnormal immune responses and chronic inflammation are thought to contribute to the pathophysiology of autism[243]. Vitamin D influences the production and release of neurotransmitters, such as serotonin and dopamine, implicated in mood regulation and cognitive functions. Deficiency in vitamin D may lead to imbalances in these neurotransmitters, affecting behavior and cognition. Individuals with autism often exhibit elevated oxidative stress levels[244]. Vitamin D has antioxidant properties that help reduce oxidative stress, potentially mitigating some neurobiological abnormalities in ASD[245].

Current Research Findings: ²³ Epidemiological studies have found an association between low vitamin D levels and an increased risk of autism[39]. For instance, multicentre research from Denmark, Finland, Norway, Sweden, and Western Australia indicates that children born in regions with lower sunlight exposure or during seasons with less sunlight have a higher prevalence of ASD[246]. Some clinical trials have explored the effects of vitamin D supplementation in individuals with autism. Studies measuring vitamin D levels in individuals with ASD often report lower levels compared to neurotypical controls[245]. A randomized controlled trial by Song *et al.* (2019) showed that vitamin D3 supplementation in children with ASD significantly improved autism severity scores, social interaction, and stereotypical behaviors[247]. These findings suggest a potential benefit of vitamin D supplementation in correcting deficiencies and improving symptoms.

Practical Considerations: The appropriate vitamin D dosage for individuals with autism varies based on age, baseline vitamin D levels, and individual needs[230]. General recommendations suggest a daily intake of 600-800 IU for children and adults, but higher doses may be necessary to correct deficiencies[248]. While vitamin D supplementation is generally safe, excessive intake can lead to toxicity, characterized by hypercalcemia, nausea, and kidney problems. Regularly monitoring serum 25-

hydroxyvitamin D levels is essential to ensure optimal dosing and prevent adverse effects[249]. Vitamin D supplementation is often used alongside other interventions, such as behavioral therapies and nutritional support, to maximize its potential benefits in managing autism symptoms[250]. Healthcare providers should consider evaluating and monitoring vitamin D levels as part of a comprehensive treatment plan for autism, ensuring individualized and evidence-based care.

L-Carnitine Supplement:

ASD is linked to abnormal synaptogenesis, neurotransmitter transformations, neurometabolism, and mitochondrial function[251]. L-carnitine, a naturally occurring amino acid derivative, has gained attention for its potential in managing autism due to its involvement in energy metabolism and mitochondrial health[252]. Synthesized in the liver and kidneys from lysine and methionine, L-carnitine is crucial for transporting long-chain fatty acids into mitochondria for oxidation and energy production. It also helps remove excess short- and medium-chain fatty acids, preventing their accumulation and potential toxicity[253]. Given its role in energy production, mitochondrial function, and antioxidant defense, L-carnitine is relevant to the pathophysiology of ASD[254]. Emerging evidence suggests that L-carnitine supplementation may benefit individuals with autism by enhancing mitochondrial function, reducing oxidative stress, and improving fatty acid metabolism[72].

Functions of L-Carnitine: L-carnitine facilitates the transport of fatty acids into the mitochondria, enabling their β -oxidation and subsequent production of adenosine triphosphate (ATP), the primary energy currency of cells. By promoting efficient fatty acid metabolism, L-carnitine supports mitochondrial health and function, which is crucial for maintaining cellular energy balance. L-carnitine has antioxidant properties, helping to reduce oxidative stress and protect cells from damage caused by free radicals[255].

Potential Links Between L-Carnitine Deficiency and Autism: Mitochondrial dysfunction is frequently observed in individuals with ASD. Since L-carnitine plays a

pivotal role in mitochondrial energy production, deficiency in L-carnitine could exacerbate mitochondrial abnormalities, contributing to the symptoms of autism. Increased oxidative stress is a common feature in autism[256]. L-carnitine's antioxidant properties may help mitigate oxidative stress, potentially improving cellular function and reducing neuroinflammation. Impaired fatty acid metabolism has been implicated in the pathophysiology of autism. L-carnitine deficiency can lead to the accumulation of unmetabolized fatty acids, which may adversely affect brain function and development[257].

Current Research Findings: Research has shown that individuals with autism often have lower levels of L-carnitine and its precursors in the blood. These findings suggest that L-carnitine deficiency may be a contributing factor in the development and severity of autism symptoms[256]. Studies on the metabolic profiles of individuals with autism have highlighted abnormalities in fatty acid metabolism and mitochondrial function[6]. Several clinical trials have investigated the effects of L-carnitine supplementation in children with autism[258]. A notable study by Geier *et al.* (2011) found that L-carnitine supplementation by 50 mg/kg/day for 3 months improved social behavior, communication, and overall autism severity scores in children with ASD[259]. Another study by Fahmy *et al.* (2013) reported significant improvements in speech, social interactions, and repetitive behaviors following L-carnitine supplementation[260]. L-carnitine supplementation has been shown to restore normal metabolic function and improve energy production in these individuals.

Practical Considerations: The appropriate L-carnitine dosage for individuals with autism varies based on age, weight, and individual needs. Typical dosages range from 50 to 100 mg/kg/day, divided into multiple doses[257]. It is crucial to consult a healthcare provider to determine the optimal dosage. L-carnitine supplementation is generally safe and well-tolerated. However, potential side effects include gastrointestinal discomfort, fishy body odor, and, in rare cases, seizures. Regular monitoring of blood L-carnitine levels and overall health is recommended to ensure safe and effective supplementation[261]. L-carnitine supplementation may be used

alongside other interventions, such as behavioral therapies and nutritional support, to maximize its potential benefits in managing autism symptoms[262]. Healthcare providers should consider evaluating and monitoring L-carnitine levels as part of a comprehensive treatment plan for autism, ensuring individualized and evidence-based care.

Omega 3 and 6 supplements:

Omega-3 and Omega-6 fatty acids are essential polyunsaturated fats critical for various bodily functions, including brain development and function. Omega-3 is one of the most used complementary and alternative supplements in individuals with ASD[91].
Omega-3 fatty acids include alpha-linolenic acid (ALA), eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA). They are primarily found in fish oils, flaxseeds, and walnuts. Omega-6 fatty acids, including linoleic acid (LA) and arachidonic acid (AA), are found in vegetable oils, nuts, and seeds[263]. Omega-3 and omega-6 fatty acids play critical roles in brain health and function, and their supplementation may benefit individuals with ASD. Given the unique neurological and developmental challenges faced by individuals with ASD, there has been significant interest in understanding the role these fatty acids might play in managing autism symptoms[264].

Biological Functions: Omega-3 Fatty Acids are crucial for brain function, anti-inflammatory processes, and overall neural health. DHA, in particular, is a major structural component of the brain and retina. Omega-6 Fatty Acids are essential for skin health and growth and are a precursor for inflammatory and anti-inflammatory eicosanoids[265].

Potential Benefits for Individuals with ASD: Omega-3 fatty acids, especially DHA, are vital for brain development and cognitive function. Deficiencies in these fatty acids can impair neurodevelopment, which is particularly concerning in ASD. Omega-3s have anti-inflammatory effects that may help mitigate neuroinflammation, which has been implicated in the pathophysiology of ASD[49]. Reducing inflammation can potentially improve brain function and behavior. Some studies suggest that omega-3

supplementation can improve social interaction, communication, and repetitive behaviors in children with ASD[251]. Omega-3 fatty acids influence the production and function of neurotransmitters, such as serotonin and dopamine, which play roles in mood regulation and behavior[266,267]. These fatty acids are essential components of cell membranes, influencing their fluidity and the function of membrane-bound proteins, which are crucial for cellular signaling and function[268].

Studies and Evidence: Research on omega-3 and omega-6 supplementation in ASD has shown mixed results, and more research is needed to establish definitive benefits. Some studies, such as Cheng *et al.* and Doaei *et al.*, have reported improvements in hyperactivity, social skills, and cognitive development following omega-3 supplementation[269,270]. Other studies have found no significant benefits, highlighting the variability in response among individuals with ASD[52,271].

Recommended Dosage and Safety: There is no standardized dosage for omega-3 supplementation in ASD, and recommendations can vary[272]. It's essential to consult healthcare providers to determine appropriate dosages tailored to individual needs. Omega-3 supplements are generally considered safe with few side effects. However, high doses can lead to gastrointestinal issues and an increased risk of bleeding due to their blood-thinning properties[273]. ³² Maintaining a balanced ratio of omega-3 to omega-6 fatty acids is crucial. A high intake of omega-6 relative to omega-3 can promote inflammation, counteracting the benefits of omega-3s[274]. A typical Western diet often has a disproportionately high omega-6 to omega-3 ratio, which may necessitate omega-3 supplementation to restore balance[275].

Practical Considerations: Encouraging the consumption of fatty fish, flaxseeds, chia seeds, and walnuts can naturally increase omega-3 intake. Fish oil supplements, especially DHA and EPA, are a common and effective way to ensure adequate omega-3 intake[276]. Fatty acid levels should be monitored regularly, and dietary intake or supplementation should be adjusted based on individual responses and nutritional needs[277]. While some evidence suggests potential improvements in behavior and cognitive function, the response can vary widely among individuals. Thus, omega-3

supplementation should be considered part of a comprehensive, individualized approach to managing autism, ideally under healthcare professionals' guidance. Table 3 summarizes dietary interventions, supplements, and their related details for ASD:

Role of Feeding Therapy and Behavioral Interventions in Autism:

Feeding problems are common in children with ASD, often manifesting as food selectivity, refusal, and limited dietary variety. These issues can lead to nutritional deficiencies and negatively impact overall health and development. Feeding therapy and behavioral interventions are crucial in addressing these challenges by promoting healthier eating habits and expanding food preferences[278].

Feeding Therapy:

Feeding therapy typically involves a multidisciplinary team, including dietitians, speech-language pathologists, occupational therapists, and psychologists. The primary goals are to improve oral motor skills, reduce sensory sensitivities, and establish positive mealtime behaviors[279]. Critical components of feeding therapy include oral motor skills development, sensory integration, mealtime structure, and positive reinforcement[280].

Many children with ASD have difficulty chewing, swallowing, and oral coordination. Therapists strengthen these skills through exercises and activities to improve muscle function and coordination[281]. Sensory sensitivities to textures, tastes, and smells are common in children with ASD[282]. Feeding therapists use gradual exposure techniques to desensitize children to various sensory stimuli. This may involve introducing new foods in a non-threatening way, such as through play or gradual taste testing[65]. Establishing consistent mealtime routines can help reduce anxiety and improve eating behaviors. This includes having regular meal and snack times, creating a calm eating environment, and using visual schedules to help children understand what to expect[283]. Encouraging positive eating behaviors through rewards and praise

can motivate children to try new foods and adopt healthier eating habits. This approach focuses on reinforcing desired behaviors rather than punishing undesirable ones[284].

Feeding Behavioral Interventions:

Behavioral interventions are often used in conjunction with feeding therapy to address food selectivity and refusal. These interventions are based on principles of Applied Behavior Analysis (ABA) and involve systematic techniques to modify eating behaviors[285]. Key strategies include gradual exposure and desensitization, modeling and social stories, choice, and control, reinforcement, and rewards, and task analysis and shaping[286].

Introducing new foods gradually and in small amounts can help reduce resistance. This technique involves pairing new foods with preferred ones, starting with just a touch or smell and gradually progressing to tasting and eating[287]. Children with ASD often learn through imitation. Modeling involves demonstrating appropriate eating behaviors, either by therapists, parents, or peers. Social stories are short, descriptive narratives that explain social situations and appropriate responses; helping children understand and anticipate mealtime routines and allowing children to make choices about what and how much to eat can reduce anxiety and resistance[288]. Providing a limited selection of healthy options empowers children while ensuring nutritional needs are met[289].

Positive reinforcement, such as verbal praise, stickers, or small toys, can be used to reward desired behaviors like trying a new food or sitting at the table for the duration of a meal[290]. The reinforcement should be immediate and consistently applied. Breaking down the process of eating into small, manageable steps and reinforcing each step can help children gradually build up to more complex behaviors. Shaping involves reinforcing successive approximations of the target behavior until the desired behavior is achieved[291,292].

Techniques to Expand Food Preferences:

Expanding food preferences in children with ASD involves a combination of strategies aimed at increasing acceptance and variety in their diet. Techniques include food chaining, systematic desensitization, cooking and food preparation involvement, sensory play, consistency and patience, and parental involvement and education[16].

The food Chain method involves gradually introducing new foods similar in taste, texture, or appearance to foods the child already accepts[293]. For example, if a child likes chicken nuggets, therapists might introduce breaded fish sticks, then grilled chicken, and eventually other types of protein. Similar to gradual exposure, the systematic desensitization technique involves slowly introducing new foods to reduce sensory overload[294] and, for instance, starting with a visual introduction, followed by touching, smelling, and finally tasting the food[295]. Involving children in cooking and food preparation can increase their interest in and acceptance of new foods. This hands-on approach allows children to explore new foods in a fun and non-threatening way. Encouraging sensory play with food can help children become more comfortable with different textures and smells[296]. Activities like playing with food-based sensory bins or using food in art projects can reduce sensory sensitivities[297]. Consistently offering new foods and being patient with the child's progress is crucial. It may take multiple exposures before a child is willing to try a new food. Avoid pressuring the child, which can increase resistance[298]. It is essential to educate parents about the importance of variety in the diet and provide them with strategies to encourage healthy eating at home. Parents play a critical role in modeling positive eating behaviors and creating a supportive mealtime environment[299]. By combining oral-motor skill development, sensory integration, structured mealtime routines, and behavioral techniques, therapists can help expand food preferences and improve nutritional intake, contributing to better overall health and development for children with autism.

Mealtime Environment and Practices for Children with Autism:

Creating a supportive and structured mealtime environment is crucial for children with ASD. The mealtime setting can significantly influence a child's eating behaviors, food

acceptance, and overall nutritional intake[300]. To enhance the mealtime environment for children with autism, they need to have a consistent mealtime routine, a calm and positive atmosphere, a sensory-friendly environment, positive mealtime practices, gradual introduction of new foods, managing feeding challenges, nutritional balance, collaboration with professionals, and parental support and education[301].

Establishing regular meal and snack times is essential for a consistent mealtime routine. This can create predictability and structure, reducing anxiety and resistance[302]. Visual schedules or timers can help children understand and anticipate mealtime routines, making transitions smoother. The meals should be consistent in length, typically around 20-30 minutes, to maintain structure without overstaying the child's attention span[303]. A calm and positive atmosphere is attempted by reducing background noise and distractions such as TV, loud music, or excessive conversation to help the child focus on eating[304]. Children should engage in pleasant and encouraging conversations that promote a relaxed atmosphere while avoiding discussing stressful or negative topics during meals. Children should be comfortably seated at the table with appropriate support, using adaptive seating if necessary to help them stay seated and focused[305].

Creating a sensory-friendly environment is crucial for helping children with autism focus on their food. Opting for soft, natural lighting can prevent the overwhelming effects of harsh or flickering lights, which can be distracting and distressing[306]. Additionally, using plain, non-patterned tableware helps to avoid overstimulation and aligns with the child's sensory preferences regarding textures and materials[307]. Ensuring the room temperature is comfortable is also important, as some children with ASD are sensitive to extreme temperatures, which can significantly affect their eating behavior[308]. By addressing these sensory factors, the mealtime experience can be made more comfortable and conducive to positive eating behaviors for children with autism. Positive mealtime practices are essential for fostering healthy eating habits in children with autism. Role modeling by adults and peers is crucial, as it demonstrates appropriate eating behaviors, positive food attitudes, and table manners[309].

Consistent encouragement and praise should be provided for trying new foods, using utensils correctly, or displaying other desired behaviors. Additionally, involving the child in meal planning and preparation can increase their interest in food. Simple tasks such as washing vegetables or stirring ingredients can make children more willing to try new foods[310].

Gradually introducing new foods is essential for children with autism to minimize resistance and encourage acceptance. Introducing new foods slowly and in small quantities alongside familiar and preferred foods can significantly reduce resistance[18]. Food chaining is an effective technique that involves gradually expanding the range of accepted foods by linking new foods to those the child already likes based on similarities in taste, texture, or appearance[293]. Additionally, non-pressured exposure, where new foods are offered repeatedly in a non-coercive manner, allows the child to become familiar with the food over time without feeling forced. This approach fosters a more positive and accepting attitude towards new foods[311].

Managing feeding challenges in children with autism involves several key strategies. When a child refuses food, it is essential to remain calm and remove the food without negative comments, reintroducing it later without making it a focus. For selective eating, respecting the child's preferences while gently encouraging variety is essential; a range of foods should be offered repeatedly, even if initially rejected[312]. Addressing oral-motor difficulties with appropriate therapy and techniques is crucial to improving chewing, swallowing, and overall eating skills. These approaches help create a supportive feeding environment and promote better nutritional intake[313]. Ensuring nutritional balance in children with autism involves promoting dietary diversity and monitoring for potential deficiencies. A balanced diet with various foods is essential to ensure the child receives all necessary nutrients, particularly if they have restrictive eating habits[17]. It is advisable to consult with healthcare providers about the need for nutritional supplements if the child's diet lacks essential vitamins or minerals to support their overall health and development.

Collaboration with professionals is crucial in addressing the nutritional needs and mealtime behaviors of children with autism. Working with dietitians, speech-language pathologists, and occupational therapists allows for the development of personalized strategies to improve mealtime behaviors and ensure adequate nutrition[314]. Additionally, collaborating with behavioral specialists to implement Applied Behavior Analysis (ABA) techniques can help modify eating behaviors and reduce mealtime stress, fostering a more positive and effective eating environment[315]. Parental support and education play a vital role in managing mealtime challenges for children with autism. Training parents and caregivers in effective mealtime strategies and emphasizing the importance of a structured, positive environment are essential[71]. Additionally, encouraging participation in support groups allows parents to share experiences and strategies, providing a network of support and practical advice for addressing feeding issues[316].

Recommendations

Based on the synthesis of current literature, several recommendations can be made to optimize feeding therapy, behavioral interventions, and mealtime practices for children with ASD. Firstly, healthcare professionals should prioritize multidisciplinary approaches integrating dietitians, speech-language pathologists, occupational therapists, and psychologists in designing personalized treatment plans tailored to each child's specific needs and challenges. Emphasizing early intervention is crucial, as interventions targeting oral motor skills, sensory sensitivities, and mealtime routines have shown promising outcomes in improving food acceptance and nutritional intake. Structured feeding therapy programs should focus on individualized goals that address oral motor deficits and sensory aversions, employing techniques such as oral motor exercises, sensory integration activities, and gradual exposure to new foods. Behavioral interventions grounded in Applied Behavior Analysis (ABA) principles should be utilized to reinforce positive eating behaviors, systematically desensitize sensory aversions, and promote mealtime routines that enhance predictability and reduce

anxiety. Creating a supportive mealtime environment is essential. This involves establishing consistent meal schedules, sensory-friendly settings, and visual supports to aid understanding and anticipation of mealtime routines. Parents and caregivers play a pivotal role in implementing strategies learned from professionals, emphasizing positive reinforcement, modeling appropriate eating behaviors, and gradually expanding food choices through techniques like food chaining and systematic desensitization. Further research is needed to standardize intervention protocols, assess long-term outcomes, and explore the effectiveness of emerging technologies and innovative therapies in improving feeding behaviors and nutritional status among children with ASD. Collaboration among researchers, healthcare providers, educators, and families is essential to develop evidence-based practices that enhance the quality of life and nutritional health for children with ASD.

Limitations

Several limitations should be considered when interpreting the findings of this systematic review. Firstly, the variability in study designs, intervention protocols, and outcome measures across the included studies may introduce heterogeneity and limit direct comparisons. Most studies relied on small sample sizes, which may affect the generalizability of findings to broader populations of children with ASD. Moreover, many studies lacked long-term follow-up assessments, making evaluating the sustainability of intervention effects over time challenging. The quality of evidence varied among studies, with some lacking rigorous methodologies such as randomized controlled trials or blinding of assessors. This variability in study quality could impact the reliability and strength of conclusions drawn from the collective evidence. Additionally, the reliance on parent-reported outcomes in many studies may introduce bias, as subjective perceptions of improvement in feeding behaviors and mealtime practices could influence reported outcomes. Furthermore, the complexity of ASD as a heterogeneous neurodevelopmental disorder presents challenges in identifying universally effective interventions. Children with ASD often present with diverse

sensory sensitivities, oral motor deficits, and behavioral patterns, necessitating personalized and adaptive approaches to treatment. ¹⁰ The effectiveness of interventions may vary depending on individual characteristics, comorbidities, and family dynamics, highlighting the need for tailored intervention strategies. Lastly, publication bias may influence the availability of studies included in this review, as studies reporting positive outcomes may be more likely to be published than those with null or negative findings. This potential bias could impact the comprehensiveness and representativeness of the evidence base synthesized in this review.

CONCLUSION

In conclusion, this systematic review synthesizes current evidence on feeding therapy, behavioral interventions, and mealtime practices for children with ASD. The findings highlight the multifaceted nature of interventions to improve this population's feeding behaviors and mealtime practices. Feeding therapy approaches, including oral motor skills development, sensory integration techniques, and structured mealtime routines, show promise in addressing the unique challenges faced by children with ASD. Behavioral interventions based on Applied Behavior Analysis (ABA) principles, such as gradual exposure, modeling, and positive reinforcement, offer effective strategies for reducing food selectivity and enhancing mealtime behaviors. Additionally, creating supportive mealtime environments that cater to sensory sensitivities and providing parental education and support are critical components of successful interventions. Despite the promising results observed across various studies, several limitations warrant cautious interpretation of findings, including study heterogeneity, small sample sizes, and methodological biases. The variability in intervention outcomes underscores the need for personalized, tailored approaches that consider individual differences in sensory profiles, oral motor skills, and behavioral patterns among children with ASD. ²⁹ Future research should focus on conducting well-designed randomized controlled trials with larger sample sizes and standardized outcome measures further to elucidate the effectiveness and long-term benefits of specific

interventions. Longitudinal studies are needed to assess the sustainability of intervention effects over time and to understand better the complex interplay between intervention components, individual characteristics, and family dynamics. Overall, while significant strides have been made in understanding and addressing feeding difficulties and mealtime challenges in children with ASD, continued research and clinical innovation are essential to optimize interventions and improve outcomes for this vulnerable population.

ACKNOWLEDGEMENTS

We thank the editors and the anonymous referees for their valuable suggestions.

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