Issue Rehabil. Orthop. Neurophysiol. Sport Promot. 2022; 38: 59–68. ISSN 2300-0767
DOI: 10.19271/IRONS-000161-2022-38

REVIEW ARTICLE

DIETARY INTERVENTIONS IN CHILDREN WITH ASD

INTERWENCJE DIETETYCZNE U DZIECI Z ASD

Gabriela Kędzia[1], Aleksandra Sidor[1,2], Piotr Poniewierski[1,3], Anna Kostiukow[3], Włodzimierz Samborski[3]
[1]Neurodevelopmental Student Scientific Society, Poznań University of Medical Sciences, Poznan, Poland
[2]Student Scientific Club of Clinical Dietetics, Department of the Treatment of Obesity and Metabolic Disorders and of Clinical Dietetics, Poznań University of Medical Sciences Poznan, Poland
[3]Department of Rheumatology, Rehabilitation and Internal Diseases, Poznań University of Medical Sciences, Poznań, Poland

ABSTRACT

Introduction

Autism Spectrum Disorder (ASD) is a group of disorders that are manifested primarily by difficulties in interpersonal contact. Moreover, children with ASD have specific food habits, which can disturb their proper development. Nowadays, it is suggested that appropriate dietary interventions could help in the treatment of ASD. We will consider how effective a diet could be in this role.

Aim

This review aims to estimate the effectiveness of dietary interventions used in children with ASD based on scientific research.

Material and method

This article was created on the basis of a systematic review. Articles were searched using PubMed. The applied terms were: 'diet in ASD', 'dietary interventions in Autism Spectrum Disorder', 'Autism Spectrum Disorder', 'therapies in ASD'. We searched for studies that were published in less than the last 5 years, but older references were also obtained from analyzed articles.

Results

We received a total of 227 results. After selection, It was decided to use 21 studies with dietetic interventions.

Conclusions

The most commonly performed interventions are the ketogenic diet, the gluten-free casein-free diet, and probiotic supplementation. Most studies do not have enough evidence that would allow drawing definite conclusions. Currently, modifying the diet does not appear to have a significant impact on ASD symptoms.

Author responsible for correspondence:
Gabriela Kędzia
Neurodevelopmental Student Scientific Society
Poznań University of Medical Sciences Poznan, Poland
28 Czerwca 1956 No 135/147
61-545 Poznań, Poland
E-mail: gabrielakedzia97@gmail.com
https://orcid.org/0000-0003-1416-1641

Authors reported no source of funding
Authors declared no conflict of interest

Date received: 4th August 2021
Date accepted: 25th September 2021

Keywords: Autism Spectrum Disorder ASD, diet, supplementation

STRESZCZENIE

Wstęp

Zaburzenia ze spektrum autyzmu (ASD) charakteryzują się przede wszystkim trudnościami w kontaktach interpersonalnych. U pacjentów z ASD często występują specyficzne nawyki żywieniowe oraz wybiórczość pożywienia która mogą zaburzyć prawidłowy wzrost i rozwój dziecka. Obecnie przeprowadzane jest wiele prac badawczych, które sprawdzają czy zmiana sposobu żywienia wpłynie na objawy ASD. W tym przeglądzie zbadamy, jak skuteczna mogą być interwencje dietetyczne w roli wspomagania terapii ASD.

Cel

Niniejsza praca przeglądowa ma na celu oszacowanie skuteczności interwencji dietetycznych stosowanych u dzieci z ASD.

Materiał i metody

Praca powstała zgodnie z zasadami tworzenia przeglądu systematycznego. Artykuły wyszukiwano za pomocą przeglądarki „PubMed". Stosowane terminy to: „dieta w ASD", „interwencje dietetyczne w zaburzeniach ze spektrum autyzmu", „zaburzenia ze spektrum autyzmu", „terapie w zaburzeniach ze spektrum autyzmu". Skupiono się na badaniach, które ukazały się w okresie krótszym niż 5 lat, ale pozyskano również starsze źródła z analizowanych prac.

Wyniki

Otrzymaliśmy łącznie 227 wyników. Po przeprowadzeniu selekcji zdecydowano się na wykorzystanie 21 z nich.

Wnioski

Najczęściej wykonywane interwencje to dieta ketogeniczna, dieta bezglutenowa i bezkazeinowa oraz suplementacja preparatami probiotycznymi. Większość badań nie dostarcza wystarczających dowodów, które pozwoliłyby wyciągnąć jednoznaczne wnioski. Obecnie modyfikacja diety wydaje się nie mieć znaczącego wpływu na objawy ASD.

Słowa kluczowe: Autyzm, ASD, Dieta

Introduction

Autism spectrum disorder was firstly described by Leo Kanner in 1943. Nowadays, it is estimated that approximately one child in 54 is diagnosed with ASD. Moreover, the frequency of diagnosing ASD shows an increasing tendency. ASD is four times more common among men (CDC, 2020).

ASDs are caused by disruption of a child's normal neurodevelopment. The name of the disorder originates from ancient Greek and means "alone", which corresponds very well to the clinical manifestation of the condition. Symptoms of ASD include the child's alienation and impairment of social interaction. It is said that these children live in their own world. In addition, patients present with repetitive, stereotypic behavior and very narrow and specific interests. The exact etiology of ASD remains unknown to this day. Genetic predisposition is certainly important. However, it is a well-known fact that environmental factors like late pregnancy, obesity, type 2 diabetes in the mother, and exposition to air pollution during pregnancy all contribute to an increased risk of

developing ASD in a child (Emberti – Gialloreti *et al.*, 2019; Hodges *et al.*, 2020).

A large portion of patients with ASD suffer from impairment of intestinal dysbiosis. It appears that coexisting gastrointestinal disorders are detected in 9 to 70% of patients. There is ample evidence that bacteria of the intestinal microflora may trigger certain neurobehavioral disorders (Hsiao *et al.*, 2013).

An adequate diet is an extremely important aspect in the therapy of a child with ASD and influences its proper development. Because of their food selectivity, children with ASD follow a specific, often very monotonous diet. Overall they tend to eat fewer vegetables and fruits than their healthy peers and are therefore more likely to suffer from insufficient nutrient intake.

Parents relatively often choose dietary interventions in the hope of improving their child's health status (Chistol *et al.*, 2018).

Can changing children's food habits affect the symptoms of the disease or improve their condition? In this article, we will consider how effective a diet is in the therapy of ASD.

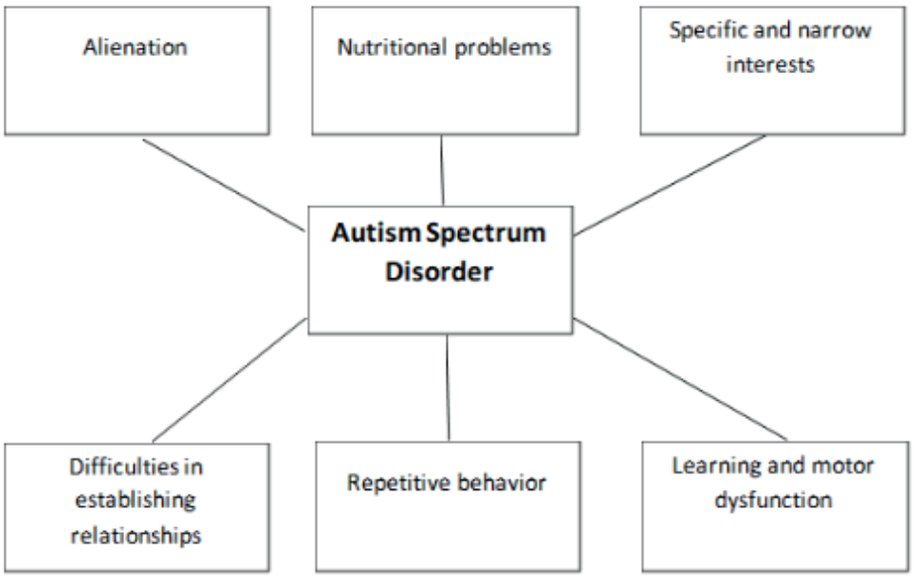

Figure 1. Syndromes of ASD.

Aim

This review aims to assess the effectiveness of dietary interventions used in children with ASD based on scientific research.

Methods and results

This review was created on the basis of a systematic review of articles, which were searched using the browser PubMed. The search terms were: 'diet in ASD', 'dietary interventions in Autism Spectrum Disorder', 'Autism Spectrum Disorder', 'therapies in ASD'.

We searched for studies that were published less in the last 5 years, but references were also obtained from reviewed articles. We received a total of 227 results. We used 21 scientific articles. We rejected all scientific publications in a language other than English. We only considered reliable scientific sources.

Gluten-free and casein-free diet (*GFCF*)

The Casein-Free Gluten-Free diet is an elimination diet that removes gluten and casein from a normal diet. Eliminating gluten means excluding all foods that contain wheat, oats, barley, rye, and elimination of casein means avoiding dairy products, including milk, yogurt, cheese, and butter. After the publication of a hypothesis stating that opioid receptors could be activated by peptides formed after the digestion of casein and gluten GFCF diet was introduced to patients with ASD. It was suspected that those peptides could affect the

behavior of children. (Shattock *et al.,* 2002; Reichelt *et al.,* 2009).

Piwowarczyk *et al.* compared and investigated all randomized control trials (RCTs) which have been performed since 2016. The study included 6 RCT's of 214 patients with ASD (107 in a sample group) (Piwowarczyk *et al.,* 2018). The results of individual RTCs are ambiguous, sometimes contradictory. This could have been influenced by the duration of the research, which varied. In four studies (Elder *et al.,* 2006; Johnson *et al.,* 2011; Navarro *et al.,* 2015; Pusponegoro *et al.,* 2015) interventions lasted 3 months or less. These studies may have been too short to display health benefits. Some data say that the GFCF diet should be followed for a minimum of 6 months to estimate the effects of the diet on ASD (Knivsberg *et al.,* 2002; Piwowarczyk *et al.,* 2018).

In the study from 2019, participants followed a diet free of gluten and casein for 6 months. It was concluded that the intervention did not make significant changes in the behavioral symptoms of ASD (González-Domenech *et al.,* 2020).

In the above studies, various scales were used to evaluate the severity of ASD. Each scale assesses ASD from a slightly different perspective, which could influence outcomes. (Piwowarczyk *et al.,* 2018; González-Domenech *et al.,* 2020).

Nowadays, there is no clear data for the effectiveness of the GFCF nutritional model in ASD. There is also a need for more studies. Moreover, it should be considered whether patients ought to follow the GFCF diet without being diagnosed with celiac disease or casein intolerance especially considering the price of the diet and the difficulty of maintaining it for a long time.

The ketogenic diet (*KD*)

KD is a low carbohydrate, norm protein, and high-fat diet. The substrates for energy production are ketone bodies which are produced from the metabolism of fatty acids. KD is widely known in the medical and outside of the medical world. It has recently reached popularity, mainly as a tool for losing weight. Medically it is used as a treatment in drug-resistant epilepsy. Recent findings, however, suggest that prolonged use of lower carbohydrate diets increases the risk of cardiovascular disease (CVD), cerebrovascular, and cancer mortality (Mazidi *et al.,* 2019).

The first-ever pilot trial to conclude whether KD could alleviate the symptoms of ASD took place in 2003 (Evangeliou *et al.,* 2003). The John Radcliffe diet (a variant of KD) was carried on for 6 months with intermissions. 7 out of 30 that participated in the study did not tolerate the diet. There was no control group. The intervention turned out to be beneficial to 60% of the probes. There was a significant improvement supported by an appraisal of the Childhood Autism Rating Scale (CARS) (Evangeliou *et al.,* 2003).

The study that was conducted in 2017 (El-Rashidy *et al.,* 2017) had patients randomly assigned to one of the three groups with different diet interventions. The first group was the control one, the second was on the GFCF diet, and the third one was on KD (modified Atkins diet). Children from the KD group presented the best improvement measured in the CARS and Autism Treatment Evaluation Test (ATEC). Out of the 15 children who were assigned to the study group, 10 were tolerant of the diet (El-Rashidy *et al.,* 2017).

Another research explores the effects of a combined ketogenic and gluten-free diet with medium-chain triglycerides supplemented. The outcome was satisfactory; however, there were only 15 patients who lasted till the end of the study, 12 had to be excluded (Lee *et al.,* 2018).

In each of the above studies, implementing a modified version of KD was not possible in all of the patients who could benefit. A significant number of the probands did not finish the plan. However, the results of those that persist show improvement. Additionally, in each study, the samples were small, and the duration of the research varied (Evangeliou *et al.,*2003; El-Rashidy *et al.,* 2017; Lee *et al.,* 2018).

n-3 Polyunsaturated Fatty Acids (*n-3 PUFA*) *supplementation*

The effect of PUFA supplementation on ASD symptoms was studied often due to a larger amount of evidence that shows their positive influence on the development of CNS. When it comes to the level of PUFA in children with ASD, it can be assumed that they show abnormal levels and possibly abnormal metabolism of fatty acids (Spahis *et al.,* 2008; Brigandi *et al.,* 2015).

In 2017, three meta-analyses were published summarizing all the RTCs that have taken place so far. The largest one covered 194 patients from 6 RTCs (Cheng *et al.,* 2017). The authors of other meta-analyses decided to exclude some of the studies (Horvath *et al.,* 2017; Mazahery *et al.,* 2017). The smallest one took into consideration the outcomes of 107 participants in the main analysis, 178 in the final interpretation (Mazahery *et al.,* 2017).

The first meta-analysis showed a positive effect on social interaction, restricted interests, and repetitive behaviors as a result of PUFA supplementation. However, there was no difference in communication (Mazahery *et al.,* 2017).

The authors of the second meta-analysis obtained different results. Overall, they did not find substantial differences between the groups, with a few exceptions. An improvement in lethargy in studies that used the ABC scale was observed but only in parents' ratings. Also, there was an increase in the Vineland Adaptive Behavior Scale-daily-living component in one RCT. (Horvath *et al.,* 2017). In the last meta-analysis, the impact of supplementation was found, but in slightly different areas than in the first meta-analysis. The change was seen in hyperactivity, lethargy, and stereotypes (Cheng *et al.,* 2017). It should be noted that despite different results, all RTCs used in meta-analyses overlap (Horvath *et al.,* 2017).

The difference in results between studies may be due to the large number of scales used to assess ASD symptoms. All researchers agreed that the results of their papers could not be extrapolated to all patients with ASD. To determine the exact effect of omega-3 fatty acids on the symptoms of ASD, more detailed researches are needed. Omega-3 fatty acids supplementation appears to be generally well-tolerated, so there is probably no reason to actively discourage parents who give it to their children as an adjunct to therapy (Perrin *et al.,* 2012; Mazahery *et al.,* 2017).

Probiotics supplementation

The enteric nervous system and vagus nerve aid a two-way communication path between an intestine and the brain, which is currently called the gut-brain axis. This relationship was first examined to understand how the central and nervous systems could influence gastrointestinal function (Cruchet *et al.,* 2016).

Scientific evidence suggests that the microflora population may be a cause of neurobehavioral disorders. The Proper composition of the microflora intestinal is considered to be 100 trillion prokaryotic cells weighing 1–2 kilograms. Numerous researches have confirmed that dysbiosis is a quite common diagnosis among patients with ASD (Rosenfeld, 2015; Tomova *et al.,* 2015).

Moreover, oftentimes, people with ASD are treated with antibiotics. In research, Bolte (Bolte, 1998) noticed a possibility of a subacute, chronic tetanus infection of the intestinal tract as the basic causes for symptoms of ASD observed in some individuals. Research by Pärtty *et al.* suggests that probiotic therapy may reduce the risk of developing neuropsychiatric disorders in later childhood (Pärtty *et al.,* 2015).

The studies that examined the behavioral changes after oral probiotics are presented in the table.

Based on data in Table 1, it can be assumed that longer-lasting studies tend to show more positive results. Due to the small amount of research, this is an unsure conclusion. More research is needed to determine the optimal time for probiotic supplementation. The outcomes may have been influenced by the fact that trials were conducted on various

Table 1. Application of probiotics in children with ASD.

Research	Sample size	Duration	Strain used	Outcome
(Shaaban *et al.*, 2018)	30	3 months	Lactobacillus acidophilus, Lactobacillus rhamnosus, Bifidobacteria longum	Improvements in the severity of autism (ATEC[1] scale)
(Santocchi *et al.*, 2016)	42	6 months	Streptococcus termophilus, Bifidobacterium breve, Bifidobacterium longum, Bifidobacterium infantis, Lactobacillus acidophilus, Lactobacillus plantarum, Lactobacillus paracasei, Lactobacillus delbrueckii	Significant decline (ADOS[2] scale)
(Parracho *et al.*, 2010)	39	Crossover study 3 week placebo and 3 weeks probiotic for each group	Lactobacillus plantarum	No significant change (DBC[3] scale)
(Wang *et al.*, 2020)	16	108 days	Bifidobacterium infantisBi-26, Lactobacillus rhamnosusHN001, Bifidobacterium lactisBL-04, and Lactobacillus paracaseiLPC-37, which contain 1010C	Improvement (ATEC scale)
(Liu *et al.*, 2019)	36 (only boys)	4 week	Lactobacillus plantarum PS128	No improvement (CGI-S[4], CGI-I[5] total ABC[6], and CBCL[7] total score) Improvement (SRS[8]-total score, and SNAP[9]-IV-total score) Also improvement in several elements from the above scales
(Slykerman *et al.*, 2018)	474	Two years	Lactobacillus rhamnosus strain HN001, Bifidobacterium animalis subsp. lactis strain HN019	No significant differences in the neurocognitive outcomes between the treatment group

1 – Autism Treatment Evaluation Checklist, 2 – Autism Diagnostic Observation Schedule 3 – Developmental Behavior Checklist 4 – The Clinical Global Impression scale 5 – The Clinical Global Impression – Improvement 6 – Autistic Behavior Checklist 7 – Child Behavior Checklist 8 – Social Responsiveness Scale (SRS) 9 – Swanson, Nolan, and Pelham IV scale.

continents and that different scales were used to assess the condition of children with ASD.

Prebiotics

The study by (Inoue 2018) showed that supplementation with prebiotic dietary fiber influenced the condition of the intestinal microflora. It has been suggested that the use of supplementation could improve the behavior of children with ASD (Inoue *et al.*, 2019).

Methyl-B12 vitamin supplementation

Methyl B12 vitamin is a cofactor in the process of DNA methylation and the transformation of homocysteine into methionine. Its deficiency may lead to a reduction in the concentration of antioxidants, which increases the body's sensitivity to oxidative stress. Children with ASD are often found to have lower levels of vitamin B12 or higher levels of Oxidative stress-related biomarkers (Adams *et al.*, 2011; Frustaci *et al.*, 2012). For this reason, it has been hypothesized that abnormal DNA methylation may be an important contributing factor in ASD etiology (Melnyk *et al.*, 2012; Zhang *et al.*, 2016; Tremblay and Jiang, 2019; Yektaş *et al.*, 2019).

Bertoglio *et al.* administered a portion of 64.5 mcg per kg of injectable methyl B12 every 3 days for 6 weeks. They noticed elevated levels of glutathione and an increase of glutathione redox status (reduced glutathione to oxidized glutathione) in children with ASD as well as in the control group. However, despite the change in laboratory test results, children with ASD did not benefit from the behavior improvement compared to the healthy group. Interestingly, this result does not agree with the observations of parents, most of whom (73%) signed up for the extension of supplementation to 6 months (Bertoglio *et al.*, 2010).

The statistically significant improvement due to methyl B12 supplementation was observed during administration of 75 μg per kg for 8 weeks. The improvement was associated with the change in the concentration of methionine and S-adenosyl-l-homocysteine (SAH) and the ratio of methionine (SAM) to SAH, but not the change in the level of GSH / GSSG ratio. The improvement may raise doubts as it was observed on a clinical scale (Clinical Global Impressions-Improvement score) but not on the parent's scale (ABC or SRS) (Hendren *et al.,* 2016).

Overall research results may indicate some role for vitamin B12 in ASD therapy, but more detailed research is needed. Currently, we have merely two, which were attended by several dozen patients and whose results are unambiguous. (Bertoglio *et al.,* 2010; Hendren *et al.,* 2016). It is also worth mentioning that there are studies that question the role of vitamin B12 in the pathogenesis of ASD. The meta-analysis (Frustaci *et al.,* 2012) did not show a statistically significant relationship between the concentration of vitamin B12, B9, and ASD.

Discussion

ASD therapy is multidisciplinary and focuses on many aspects. Due to the variety and complexity of patients' symptoms, it must be adjusted individually. There are many therapeutic trends, each focusing on a different aspect. The results of many studies are inconclusive. The ambiguity of the results occurs, among other things, because children with ASD are assessed in many scales, none of which is leading. Moreover, every scale has its own and unique scoring system. The fact that the groups in research are often small makes it hard to draw general conclusions. Communication with these children is difficult as well. The GFCF diet and PUFA supplementation are the best studied, but we cannot draw specific conclusions. Currently, no conclusive clinical studies have been published that would indicate a real impact of an elimination diet or PUFA supplementation on a patient with ASD. KD may have a positive effect, but very few patients have been studied. The results of methyl B12 supplementation are inconclusive. Research on the influence of microbiota is the most promising, carried out intensively, and we can expect discoveries in this area.

At present dietary interventions do not provide firm evidence that would allow considering diet therapy as an effective and primary treatment method.

Conclusion

Most of the research results are contradictory and do not provide a clear answer. Changing the diet does not appear to have a significant effect on ASD symptoms. Currently, we do not recommend dietary intervention as a treatment option.

REFERENCES

Adams, J.B., Audhya, T., McDonough-Means, S., Rubin, R. A., Quig, D., Geis, E., Gehn, E., Loresto, M., Mitchell, J., Atwood, S., Barnhouse, S., Lee, W. (2011). *'Nutritional and metabolic status of children with autism vs. neurotypical children, and the association with autism severity.'* Nutrition &. Metabolism, 8(1), p. 34.

Bertoglio, K., Jill James, S., Deprey, L., Brule, N., Hendren, R.L. (2010). *'Pilot study of the effect of methyl B12 treatment on behavioral and biomarker measures in children with autism'*. The Journal of Alternative and Complementary Medicine, 16 (5), pp. 555–560.

Bolte, E. R. (1998). *'Autism and clostridium tetani.'* Medical Hypotheses' 51(2), pp. 133–144.

Brigandi, S.A., Shao, H., Qian, S. Y., Shen, Y., Wu, B.-L., Kang, J. X. (2015). *'Autistic children exhibit decreased levels of essential Fatty acids in red blood cells'*. International Journal of Molecular Sciences,16(5), pp. 10061–10076.

CDC (2020). *'Data and Statistics on Autism Spectrum Disorder | CDC [WWW Document]. Cent. Dis. Control Prev. URL https://www.cdc.gov/ncbddd/autism/data.html.*

Cheng, Y.-S., Tseng, P.-T., Chen, Y.-W., Stubbs, B., Yang, W.-C., Chen, T.-Y., Wu, C.-K., Lin, P.-Y. (2017). *'Supplementation of omega 3 fatty acids may improve hyperactivity, lethargy, and*

stereotypy in children with autism spectrum disorders: a meta-analysis of randomized controlled trials'. Neuropsychiatric Disease and Treatment, 13, pp. 2531–2543.

Chistol, L. T., Bandini, L. G., Must, A., Phillips, S., Cermak, S. A., Curtin, C. (2018). *'Sensory Sensitivity and Food Selectivity in Children with Autism Spectrum Disorder'*. Journal of Autism and Developmental Disorders, 48, pp. 583–591.

Cruchet, S., Lucero, Y., Cornejo, V. (2016). *'Truths, Myths and Needs of Special Diets: Attention-Deficit/Hyperactivity Disorder, Autism, Non-Celiac Gluten Sensitivity, and Vegetarianism'*. Annals of Nutrition and Metabolism, 68, pp. 42–50.

Elder, J.H., Shankar, M., Shuster, J., Theriaque, D., Burns, S., Sherrill, L. (2006). *'The gluten-free, casein-free diet in autism: results of a preliminary double blind clinical trial'*. Journal of Autism and Developmental Disorders, 36, pp. 413–420.

El-Rashidy, O., El-Baz, F., El-Gendy, Y., Khalaf, R., Reda, D., Saad, K. (2017). *'Ketogenic diet versus gluten free casein free diet in autistic children: a case-control study'*. Metabolic Brain Disease, 32, pp. 1935–1941.

Emberti Gialloreti, L., Mazzone, L., Benvenuto, A., Fasano, A., Alcon, A.G., Kraneveld, A., Moavero, R., Raz, R., Riccio, M.P., Siracusano, M., Zachor, D.A., Marini, M., Curatolo, P. (2019). *'Risk and Protective Environmental Factors Associated with Autism Spectrum Disorder: Evidence-Based Principles and Recommendations'*. Journal of Clinical Medicine, 8(2), p. 217.

Evangeliou, A., Vlachonikolis, I., Mihailidou, H., Spilioti, M., Skarpalezou, A., Makaronas, N., Prokopiou, A., Christodoulou, P., Liapi-Adamidou, G., Helidonis, E., Sbyrakis, S., Smeitink, J. (2003). *'Application of a ketogenic diet in children with autistic behavior: pilot study'*. Journal of Child Neurology, 18(2), pp. 113–118.

Frustaci, A., Neri, M., Cesario, A., Adams, J. B., Domenici, E., Dalla Bernardina, B., Bonassi, S. (2012). *'Oxidative stress-related biomarkers in autism: Systematic review and meta-analyses'*. Free Radical Biology and Medicine, 52(10), pp. 2128–?.

González-Domenech, P.J., Díaz Atienza, F., García Pablos, C., Fernández Soto, M.L., Martínez-Ortega, J.M., Gutiérrez-Rojas, L. (2020). *'Influence of a Combined Gluten-Free and Casein-Free Diet on Behavior Disorders in Children and Adolescents Diagnosed with Autism Spectrum Disorder: A 12-Month Follow-Up Clinical Trial'*. Journal of Autism and Developmental Disorders, 50, pp. 935–948.

Hendren, R.L., James, S.J., Widjaja, F., Lawton, B., Rosenblatt, A., Bent, S. (2016). *'Randomized, Placebo-Controlled Trial of Methyl B12 for Children with Autism'*. Journal of Child and Adolescent Psychopharmacology, 26(9), pp. 774–783.

Hodges, H., Fealko, C., Soares, N. (2020). *'Autism spectrum disorder: definition, epidemiology, causes, and clinical evaluation'*. Translational Pediatrics, 9 (Supplement 1), pp. 55–65.

Horvath, A., Łukasik, J., Szajewska, H. (2017). *'Ω-3 Fatty Acid Supplementation Does Not Affect Autism Spectrum Disorder in Children: A Systematic Review and Meta-Analysis'*. The Journal of Nutrition, 147(3), pp. 367–376.

Hsiao, E.Y., McBride, S.W., Hsien, S., Sharon, G., Hyde, E.R., McCue, T., Codelli, J.A., Chow, J., Reisman, S.E., Petrosino, J.F., Patterson, P.H., Mazmanian, S.K. (2013). *'The microbiota modulates gut physiology and behavioral abnormalities associated with autism.'* Cell, 155(7), pp. 1451–1463.

Inoue, R., Sakaue, Y., Kawada, Y., Tamaki, R., Yasukawa, Z., Ozeki, M., Ueba, S., Sawai, C., Nonomura, K., Tsukahara, T., Naito, Y. (2019). *'Dietary supplementation with partially hydrolyzed guar gum helps improve constipation and gut dysbiosis symptoms and behavioral irritability in children with autism spectrum disorder.'* Journal of Clinical Biochemistry and Nutrition, 64(3), pp. 217–223.

Johnson, C.R., Handen, B.L., Zimmer, M., Sacco, K., Turner, K. (2011). *'Effects of Gluten Free / Casein Free Diet in Young Children with Autism: A Pilot Study.'* Journal of Developmental and Physical Disabilities, 23, pp. 213–225.

Knivsberg, A. M., Reichelt, K. L., Høien, T., Nødland, M. (2002). *'A randomised, controlled study of dietary intervention in autistic syndromes'*. Nutritional Neuroscience 5(4), pp. 251–261.

Lee, R. W. Y., Corley, M. J., Pang, A., Arakaki, G., Abbott, L., Nishimoto, M., Miyamoto, R., Lee, E., Yamamoto, S., Maunakea, A. K., Lum-Jones, A., Wong, M., (2018). *'A modified ketogenic gluten-free diet with MCT improves behavior in children with autism spectrum disorder.'* Physiol. Behav. 188, 205–211. https://doi.org/10.1016/j.physbeh.2018.02.006.

Liu, Y.-W., Liong, M.T., Chung, Y.-C.E., Huang, H.-Y., Peng, W.-S., Cheng, Y.-F., Lin, Y.-S., Wu, Y.-Y., Tsai, Y.-C. (2019). *'Effects of Lactobacillus plantarum PS128 on Children with Autism Spectrum Disorder in Taiwan: A Randomized, Double-Blind, Placebo-Controlled Trial.'* Nutrients, 11(4), p. 820.

Mazahery, H., Stonehouse, W., Delshad, M., Kruger, M. C., Conlon, C.A., Beck, K. L., von Hurst, P. R. (2017). *'Relationship between Long Chain n-3 Polyunsaturated Fatty Acids and Autism Spectrum Disorder: Systematic Review and Meta-Analysis of Case-Control and Randomised Controlled Trials.'* Nutrients, 9(2), p. 155.

Mazidi, M., Katsiki, N., Mikhailidis, D.P., Sattar, N., Banach, M., on behalf of the International Lipid Expert Panel (ILEP) and the Lipid and Blood Pressure Meta-analysis Collaboration (LBPMC) Group (2019). *'Lower carbohydrate diets and all-cause and cause-specific mortality: a population-based cohort study and pooling of prospective studies.'* European Heart Journal, 40(34), pp. 2870–2879.

Melnyk, S., Fuchs, G. J., Schulz, E., Lopez, M., Kahler, S. G., Fussell, J. J., Bellando, J., Pavliv, O., Rose, S., Seidel, L., Gaylor, D. W., James, S. J. (2012). *'Metabolic imbalance associated with methylation dysregulation and oxidative damage in children with autism.'* Journal of Autism and Developmental Disorders, 42, pp. 367–377.

Navarro, F., Pearson, D. A., Fatheree, N., Mansour, R., Hashmi, S. S., Rhoads, J. M. (2015). *'Are "leaky gut" and behavior associated with gluten and dairy containing diet in children with autism spectrum disorders?.'* Nutritional Neuroscience, 18, 177–185.

Parracho, H. M. R. T., Gibson, G. R., Knott, F., Bosscher, D., Kleerebezem, M., McCartney, A. L. (2010). *'A double-blind, placebo-controlled, crossover-designed probiotic feeding study in children diagnosed with autistic spectrum disorders.'* International Journal of Probiotics and Prebiotics, 5, pp. 69–74.

Pärtty, A., Kalliomäki, M., Wacklin, P., Salminen, S., Isolauri, E. (2015). *'A possible link between early probiotic intervention and the risk of neuropsychiatric disorders later in childhood: a randomized trial.'* Pediatric Research, 77(6): pp. 823–828.

Perrin, J. M., Coury, D. L., Hyman, S. L., Cole, L., Reynolds, A. M., Clemons, T. (2012). *'Complementary and Alternative Medicine Use in a Large Pediatric Autism Sample.'* Pediatrics, 130 (Supplement 2), pp. S77–S82.

Piwowarczyk, A., Horvath, A., Łukasik, J., Pisula, E., Szajewska, H. (2018). *'Gluten- and casein-free diet and autism spectrum disorders in children: a systematic review.'* European Journal of Nutrition, 57(2), pp. 433–440.

Pusponegoro, H. D., Ismael, S., Firmansyah, A., Sastroasmoro, S., Vandenplas, Y. (2015). *'Gluten and casein supplementation does not increase symptoms in children with autism spectrum disorder.'* Acta Paediatrica, 104(11), pp. e500–505.

Reichelt, K. L., Knivsberg, A. M. (2009). *'The possibility and probability of a gut-to-brain connection in autism.'* Annals of Clinical Psychiatry: Official Journal of the American Academy of Clinical Psychiatrists, 21(4), pp. 205–211.

Rosenfeld, C. S. (2015). *'Microbiome Disturbances and Autism Spectrum Disorders.'* Drug Metabolism and Disposition: the biological fate of chemicals. 43(10), pp. 1557–1571.

Santocchi, E., Guiducci, L., Fulceri, F., Billeci, L., Buzzigoli, E., Apicella, F., Calderoni, S., Grossi, E., Morales, M. A., Muratori, F. (2016). *'Gut to brain interaction in Autism Spectrum Disorders: a randomized controlled trial on*

the role of probiotics on clinical, biochemical and neurophysiological parameters.' BMC Psychiatry, 16, p. 183.

Shaaban, S. Y., Gendy, Y. G. E., Mehanna, N.S., El-Senousy, W. M., El-Feki, H. S. A., Saad, K., El-Asheer, O. M. (2018). *'The role of probiotics in children with autism spectrum disorder: A prospective, open-label study.'* Nutritional Neuroscience, 21, pp. 676–68.

Shattock, P., Whiteley, P. (2002). *'Biochemical aspects in autism spectrum disorders: updating the opioid-excess theory and presenting new opportunities for biomedical intervention.'* Expert Opinion of Therapeutic Targets, 6(2), pp. 175–183.

Slykerman, R. F., Kang, J., Van Zyl, N., Barthow, C., Wickens, K., Stanley, T., Coomarasamy, C., Purdie, G., Murphy, R., Crane, J., Mitchell, E. A. (2018). *'Effect of early probiotic supplementation on childhood cognition, behaviour and mood a randomised, placebo-controlled trial.'* Acta Paediatrica, 107, pp. 2172–2178.

Spahis, S., Vanasse, M., Bélanger, S. A., Ghadirian, P., Grenier, E., Levy, E. (2008). *'Lipid profile, fatty acid composition and pro- and anti-oxidant status in pediatric patients with attention-deficit/hyperactivity disorder.'* Prostaglandins, Leukotriens and Essential Fatty Acids, 79, pp. 47–53.

Tomova, A., Husarova, V., Lakatosova, S., Bakos, J., Vlkova, B., Babinska, K., Ostatnikova, D. (2015). *'Gastrointestinal microbiota in children with autism in Slovakia.'* Physiology & Behavior 138, pp. 179–187.

Tremblay, M. W., Jiang, Y. (2019). *'DNA Methylation and Susceptibility to Autism Spectrum Disorder.'* Annual Review of Medicine, 70, pp. 151–166.

Wang, Y., Li, N., Yang, J.-J., Zhao, D.-M., Chen, B., Zhang, G.-Q., Chen, S., Cao, R.-F., Yu, H., Zhao, C.-Y., Zhao, L., Ge, Y.-S., Liu, Y., Zhang, L.-H., Hu, W., Zhang, L., Gai, Z.-T. (2020). *'Probiotics and fructo-oligosaccharide intervention modulate the microbiota-gut brain axis to improve autism spectrum reducing also the hyper-serotonergic state and the dopamine metabolism disorder.'* Pharmacological Research, 157, p. 104784.

Yektaş, Ç., Alpay, M., Tufan, A. E. (2019). *'Comparison of serum B12, folate and homocysteine concentrations in children with autism spectrum disorder or attention deficit hyperactivity disorder and healthy controls.'* Neuropsychiatric Disease and Treatment, 15, pp. 2213–2219.

Zhang, Y., Hodgson, N. W., Trivedi, M. S., Abdolmaleky, H.M., Fournier, M., Cuenod, M., Do, K. Q., Deth, R. C. (2016). *'Decreased Brain Levels of Vitamin B12 in Aging, Autism and Schizophrenia.'* Plos One, 11, p. 0146797.