Rocz Panstw Zakl Hig 2022;73(3):247-258
http://wydawnictwa.pzh.gov.pl/roczniki_pzh/ https://doi.org/10.32394/rpzh.2022.0218

REVIEW ARTICLE

THE IMPORTANCE OF NUTRITIONAL MANAGEMENT AND EDUCATION IN THE TREATMENT OF AUTISM

Anna Mandecka[1], *Bożena Regulska-Ilow*[2]

[1]Wroclaw University of Environmental and Life Sciences, Faculty of Biotechnology and Food Sciences, Department of Functional Food Products Development, Chełmońskiego 37, 51-630 Wroclaw, Poland
[2]Wroclaw Medical University, Faculty of Pharmacy, Department of Dietetics, Borowska 211, 50-556 Wrocław, Poland

ABSTRACT
Autism spectrum disorders (ASDs) are an early-onset neurodevelopmental disorders. The key symptoms of ASD include social deficits, verbal and non-verbal communication deficits, and restricted, repetitive patterns of behaviour, interests, or activities. Dietary patterns have been evidenced to be related to maternal nutritional status that might lead to different metabolic conditions, and maternal metabolic dysfunction has been observed to be associated with ASD. Furthermore growing evidence suggests that the gut microbiota has a role in the pathophysiology of ASD. Differences in composition of the gastrointestinal (GI) microbiota in children with ASD compared to unaffected siblings and/or healthy unrelated controls have been reported in various studies. The above-mentioned ASD factors and symptoms can be regulated by proper nutrition. The importance of nutrition and its possible impact on ASD patients is key to integral therapy. According to numerous research studies, various nutritional approaches succeeded in reducing the severity of patients' core ASD symptoms. The numerous options for diet that is used in the ASD therapy, as described in the scientific literature, are related to the problem of choosing an appropriate nutritional treatment. Each nutrition programme needs to be personalised and tailored to an individual patient. The aim of the paper is to review the available literature on dietary interventions in children with ASD and provide up-to-date evidence.

Key words: *autism spectrum disorder, gut microbiota, nutritional models, special diet, nutritional education*

STRESZCZENIE
Zaburzenia ze spektrum autyzmu (ASD) są zaburzeniami neurorozwojowymi o wczesnym początku. Kluczowe objawy ASD obejmują deficyty społeczne, deficyty komunikacji werbalnej i niewerbalnej oraz ograniczone, powtarzalne wzorce zachowań, zainteresowań lub czynności. Udowodniono, że wzorce żywieniowe są powiązane ze stanem odżywienia matki, co może prowadzić do różnych stanów metabolicznych, a zaburzenia metaboliczne u matki są powiązane z ASD. Coraz więcej dowodów sugeruje, że mikroflora jelitowa odgrywa rolę w patofizjologii ASD. W różnych badaniach donoszono o różnicach w składzie mikroflory przewodu pokarmowego (GI) u dzieci z ASD w porównaniu ze zdrowym rodzeństwem i/lub zdrowymi, niespokrewnionymi grupami kontrolnymi. Czynniki i objawy ASD można regulować poprzez odpowiednie odżywianie. Znaczenie żywienia i jego możliwy wpływ na pacjentów z ASD jest kluczem do integralnej terapii. Zgodnie z licznymi badaniami naukowymi, różne podejścia żywieniowe odniosły sukces w zmniejszaniu nasilenia podstawowych objawów ASD u pacjentów. Strategie postępowania dietetycznego stosowane w terapii ASD, opisane w literaturze naukowej, wiążą się z problemem wyboru odpowiedniego leczenia żywieniowego. Każdy program żywieniowy musi być spersonalizowany i dostosowany do indywidualnego pacjenta.
Celem pracy jest przegląd dostępnej literatury na temat interwencji dietetycznych u dzieci z ASD i dostarczenie aktualnych danych naukowych.

Słowa kluczowe: *autyzm, mikrobiota jelitowa, modele dietetyczne, dieta, edukacja żywieniowa*

Corresponding author: Anna Mandecka, Wroclaw University of Environmental and Life Sciences, Faculty of Biotechnology and Food Sciences, Department of Functional Food Products Development, Chełmońskiego Str. 37, 51-630 Wroclaw, Poland. Tel.: +48 667421235; e-mail: anna.mandecka@upwr.edu.pl

INTRODUCTION

Autism spectrum disorders (ASDs) are a set of severe developmental disorders manifesting up to 30th month of life and they are associated with congenital anomalies of the nervous system. This disorder is highly variable and multiform. Difficulties in verbal and nonverbal communication and in understanding social phenomena are a common feature of ASDs [1].

In the last decade, the number of patients diagnosed with ASD doubled, rising from 6.7 to 14.7 per 1,000 children aged 8 years. It is currently estimated that approximately 1% of the world population has ASD, with a male-to-female ratio of 2.5:1 [2]. Other authors indicate that one in 88 children may exhibit developmental disorders that are characteristic of ASD, and rates describing the prevalence of the condition may be much higher, especially among males. The prevalence rate of autism among men and women can be as high as approx. 5:1 [3].

Given the epidemiologic data indicating a higher incidence of ASDs, specialists treating ASD patients attempt to understand the aetiology of the disease and they consider various factors that may affect its pathogenesis. A particular attention is drawn to the role of epigenetic, neurobiological, genetic, neurological and hormonal factors underlying this complex condition. It is emphasised that interactions between genetic and environmental factors contribute to ASDs, where genetic factors are only 10-20% of ASD cases [1, 2, 3]. According to recent epidemiological data, up to 40–50% of ASD-related symptoms may be caused by environmental factors [4].

Due to such a significant role of environmental factors in the development of ASDs, more and more specialists treating ASD patients are paying attention to the role of diet and nutrition in the treatment of ASDs, searching for the optimal model of nutritional treatment [1].

Specific selected dietary nutrients (sulphur-containing amino acids such as cysteine and methionine, folic acid, vitamins B_{12} and B_6) are of critical importance for the nutrition of ASD patients, already at the cellular level [5]. Deficiencies in antioxidants and methylation metabolites in the ASD population, which provide key epigenetic regulation of gene expression, were documented during neurodevelopment [6]. Concentrations of glutathione and S-adenosyl methionine, which are major intracellular antioxidants and methyl donors for many metabolic reactions in the body, are significantly lower in ASD patients and this is related to oxidative stress [7].

Therefore, nutrition interventions receive extraordinary attention as a complementary and unavoidable component of autism therapy, however, they are frequently omitted and treated without due consideration. Figure 1 shows an optimal procedure model in which important components of a health

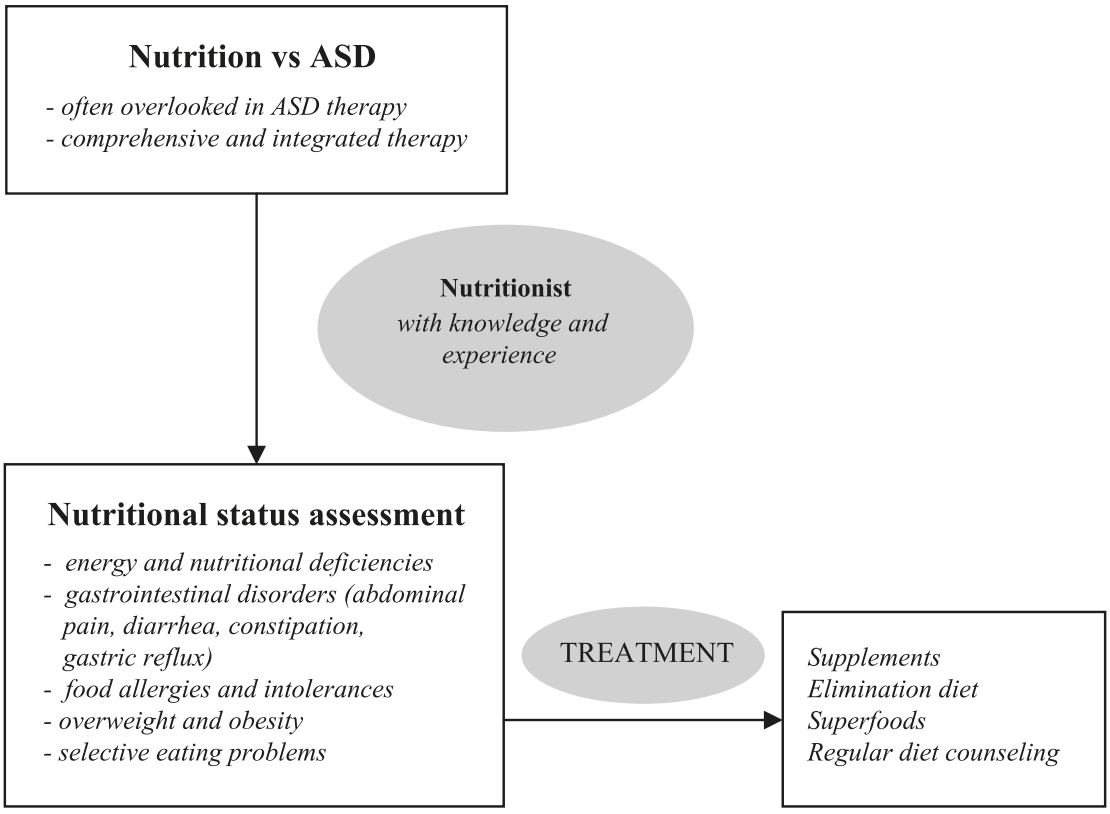

Figure 1. Integration nutrition ASD care, and the possible model of treatment [5, 8]

assessment cannot be omitted when implementing a diet therapy in ASD patients [5, 8].

The prenatal nutritional programming and prevalence of ASDs

A women's nutrition during pregnancy is crucial for fetal brain development. A pre-pregnancy diet is key to optimise the nutritional status, which plays a significant role in maintaining a healthy pregnancy and supporting a developing fetus. Nutrition at the time of conception is key to gamete function and placental development [9].

Approximately 2-3 weeks after fertilisation, the embryo undergoes organised processes of neuronal proliferation and migration, synapse formation, myelination and apoptosis for fetal brain development. During this period of rapid development, the brain exhibits increased sensitivity to the environment; its dysfunctions may predispose the fetus to postnatal neurodevelopmental disorders [10)] Provision of nutrients during the pre-conceptional and prenatal periods not only provides essential building blocks for the brain, but they may also "program" the brain through epigenetic mechanisms to confer a risk or resistance to neurological states later in life [9, 10]. The modifiable nature of nutrition during sensitive periods potentially provides opportunities for intervention. The quality of prenatal nutrition was identified as a potential risk factor for the development of ASDs.

According to the gut-brain axis (GBA) theory, early-life nutritional programming – covering pregnancy – may affect cognitive functions and predispose to the development of ASDs in genetically susceptible individuals [6]. Several studies attempted to clarify the role of nutrition in the development of ASDs. It was reported that maternal obesity might lead to fetal encephalitis [7]. The studies also stress the role of nutritional composition and dietary balance of mainly polyunsaturated fatty acids (PUFAs), whose deficiencies during pregnancy are associated with reduced learning and memory abilities and reduced cognitive functions in the offspring if PUFA dietary content has not been adjusted at an early stage of the fetal development [5].

PUFAs are structural components of cells, especially arachidonic acid (AA) of the omega-6 (n-6) family and docosahexaenoic acid (DHA) of the omega-3 (n-3) family. PUFAs rapidly accumulate in the brain from the third trimester of pregnancy until early postnatal life, and their composition in individual membranes depends mainly on the supply of DHA in the maternal diet [9, 11]. According to the Nurses' Health Study II (NHSII) [12], the total dietary n-6 PUFA content and supplementation among women prior to pregnancy was significantly and inversely associated with the risk of ASD diagnosis. Both n-3 and n-6 PUFAs are fatty acids that are essential for prenatal brain development, however, the elevated ratio of n-6 PUFAs to n-3 PUFAs, which is characteristic of the modern Western diet, may increase inflammatory processes [13]. The main dietary sources of n-3 PUFAs, especially DHA, are oily sea fish (salmon, halibut, herring, mackerel, tuna). According to the researchers there is a significant effect of adequate fish consumption by a mother on the development of ASD in her offspring. The Spanish INMA study [14] found that higher consumption of fish and seafood during the first trimester of pregnancy was associated with lower autistic traits, as measured by the Childhood Asperger Syndrome Test.

Fish and seafood are recommended dietary components; they provide complete proteins, vitamins, mineral salts and valuable omega-3 fatty acids, however, they can also be a source of dietary methylmercury. According to the authors of some studies there may be a risk of excessive mercury accumulation in ASD patients as one of the causes of ASD development [15]. Methylmercury easily crosses the blood-brain and blood-placental barriers. It also passes into breast milk, contributing to the exposure of the infant, whose body may accumulate mercury in blood cells and brain. This causes damage to the central nervous system (CNS) [16].

In many European Union countries, especially those with high consumption of fish and seafood, dietary recommendations have been implemented to limit the consumption of certain species of fish, mainly by women planning their pregnancy, pregnant women, breastfeeding mothers and children. These countries include France, Denmark, Finland, Spain, Ireland, Italy and the United Kingdom. In Poland, the consumption of fish, especially seafood, is relatively low compared to other EU countries. The European Commission has developed a special note concerning this issue, which is addressed to the most vulnerable groups of consumers, to limit the consumption of predatory fish such as a swordfish, shark, marlin and pike by pregnant women, women planning their pregnancy, breastfeeding mothers and children to one serving (approx. 100 g) per week. It is also recommended to limit tuna consumption to no more than two servings per week [17].

The U.S. Environmental Protection Agency (EPA) and the U.S. Food and Drug Administration (FDA) have recommended to limit the fish consumption by pregnant women, breastfeeding mothers and women planning their pregnancy to a serving size of 340 g per week, including no more than 170 g of tuna per week, and to completely avoid the consumption of predatory fish, i.e. a shark, swordfish, king mackerel and tilefish [17].

Although there are recommended restrictions on the consumption of selected fish species, specialists

believe that benefits for the offspring that are associated with the consumption of fish rich in omega-3 acids by women of childbearing age are more important than risks associated with their lack in the diet [15, 17]. According to *Vecchione* et al. study [15] there was no significant association between consumption of fish in the prenatal period and traits related to ASDs in children. *Vecchione* et al. noted, however, that traits associated with ASD, as measured by the Social Responsiveness Scale (SRS), were more frequently observed in children whose mothers had higher consumption of fish in the second half of pregnancy.

Moreover, a pregnant woman should pay special attention to the dietary content of folic acid and vitamin D; in case of their deficiency it should be consider to supplementation in appropriate doses. Folic acid is an essential cofactor of one-carbon metabolism that is involved in DNA and RNA synthesis and DNA methylation – processes that are particularly significant during periods of rapid growth and development. Insufficient folic acid intake is associated with altered DNA methylation and impaired fetal brain development. Supplementation with folic acid, a synthetic form of folate, before pregnancy and in early pregnancy was found to be effective in preventing neural tube defects [9, 18]. According to several studies, taking folic acid and a set of vitamins during first few months of pregnancy was associated with a lower risk of ASD. *Schmidt* et al. [19] observed that folic acid supplementation of ≥ 600 mcg/d during first months of pregnancy was associated with a reduced risk of ASD (RR=0.38; 95% Cl: 0.16; 0.90). Similar findings were obtained by other authors [20, 21].

Vitamin D deficiency is widespread worldwide, including pregnant women who are a particularly vulnerable group. It is speculated that vitamin D deficiency in a woman's body during pregnancy may be involved in the development of autism. Furthermore, there is a hypothesis that vitamin D supplementation during pregnancy and early childhood will reduce the incidence of autism recurrence in new-born's [22].

The role of the gut microbiota in ASD

Diet is one of the most influential environmental factors in determining the composition of the gastrointestinal (GI) microbiota. Intestinal dysbiosis, manifested by the appearance of intestinal disorders (intestinal gases, bloating, diarrhoea, reflux symptoms), and the influence of certain bacterial taxa on ASD symptoms are very common in ASD patients. In recent years, the GI microbiota has been identified as a potential pathway affecting symptom manifestation in cognitive and neurodevelopmental disorders such as anxiety, depression and ASD. Abnormalities in the GI microbiota of ASD children and associations between specific types of microorganisms and some ASD symptoms were observed [23, 24]. The gut microbiota of ASD patients differs in terms of composition and diversity from that of healthy developing individuals. The most diverse gut microbiome was in patients with co-occurring GI disorders, compared to the ASD group without such co-occurring disorders and healthy controls [25, 26].

The studies focusing on the evaluation of intestinal states in ASD children reported various degrees of chronic inflammatory bowel disease (IBD) with purulent secretion as well as fecal mass impaction. Moreover, there were enlarged lymph nodes that substantially occluded the intestinal lumen. The clinical image resembled inflammation in the course of *Crohn's* disease or it was atypical. The aforementioned inflammation was described as inflammation associated with ASD. Abnormalities in the intestinal microflora – dysbiosis – were identified as the cause of the development of that inflammation [27, 28].

Frequent intestinal dysfunctions and co-morbidities with microbial dysbiosis cause GI complaints that occur in up to 90% of ASD cases and thus they may play a key role in the pathogenesis of this disorder [5]. Moreover, children with ASD and GI symptoms also have immune imbalances in the gut, which may be related to an abnormal host response to microbial dysbiosis and impaired intestinal barrier integrity [29]. ASD children have a high prevalence rate of atopic diseases, including food allergy. Therefore, interventions to treat gut dysbiosis may not only help to reduce the incidence and severity of GI symptoms in ASD children, but they may also help to balance the immune system function and potentially improve some behavioural symptoms [30].

According to *Berding* et al. study [23], stool samples, food diaries from 3 days and the "Youth and Adolescent Food Frequency Questionnaire" (YAQ) were taken from ASD children. The microbiota composition of the patients was examined in relation to eating behaviours, nutrient and food group intake, as well as dietary patterns (DPs) obtained from YAQ. In ASD children, two different DPs were associated with unique microbial profiles. DP1, with a higher intake of vegetables, legumes, nuts and seeds, fruit, refined carbohydrates and starchy vegetables but a lower intake of sweets, was associated with lower abundance of *Enterobacteriaceae, Lactococcus, Roseburia, Leuconostoc and Ruminococcus.* DP2, with a low intake of vegetables, legumes, nuts, seeds and starchy vegetables, was associated with higher levels of *Barnesiellaceae, Alistipes* and lower levels of *Streptophyta,* as well as higher concentrations of propionate, isobutyrate, valerate and isovalerate. Higher concentrations of isobutyrate and isovalerate may suggest microbial metabolic changes and

increased energy food extraction from the microbiota in ASD children

In contrast, the presence of *Peptostreptococcaceae* and *Faecalibacterium* affected the development of social skills deficits in ASD children. Diet-related microbial profiles were associated with GI symptoms, however, there was no significant interaction between nutrition and microbiota in the assessment of outcomes concerning the social skills deficit. In summary, DPs associated with fecal microbiota composition and volatile chain fatty acids (VFA) concentrations were identified in ASD children [23, 31].

Creating conditions for the development of habitual, long-term (>6 months) and favorable DPs significantly improves the microbiological profile of the gut and its microbiological stability in children aged 4-8 years [23]. Adverse diet-induced changes in microbiota composition can lead to an increased risk of developing certain diseases (e.g. IBD), while a healthier long-term feeding scheme may be more beneficial for promoting a microbial profile that could potentially protect against diseases [32]. A lower ratio of *Bacteroidetes* to *Firmicutes* and higher abundance of *Clostridium* and *Desulfovibrio,* in particular, are associated with increased ASD symptoms in children [26]. There is currently growing evidence of the relationship between particular bacteria and ASD symptoms [23, 27].

The therapeutic effect of fecal microbiota transplant (FMT)

The gut microbiome is a significant environmental factor that may influence ASD symptoms, and several studies found that ASD children had distinctive gut microbiomes compared to neurotypical children [33, 34].

Modification of the gut microbiome is a potential route to improve gastrointestinal and behavioural symptoms in ASD children, and microbiota transfer therapy (MTT) may convert a dysbiotic gut microbiome into a healthy one by providing a large number of commensal microorganisms from a healthy donor. Given the connection between the gut and brain (gut-brain axis), modulating the gut microbiome using antibiotics, probiotics, prebiotics and/or FMT may be a viable therapeutic option [35].

A large diversity and number of commensal microorganisms from a healthy donor are used in FMT for converting the dysbiotic gut microbiome into a healthy microbiome. In fact, FMT is the most effective therapy for treating recurrent infections such as *Clostridium difficile* [36].

K*ang* et al. [30] conducted a pioneering trial of FMT. The MTT plan for ASD children with chronic GI problems consisted of a fortnight's treatment with vancomycin followed by intestinal cleansing, then a high-dose FMT for 1-2 days and 7-8 weeks of daily maintenance doses along with a gastric acid suppressant. After a 10-week MTT and an 8-week follow-up period (18 weeks in total), the researchers observed an 80% reduction in GI symptoms and a slow but steady improvement in baseline ASD symptoms. At the same time, the microbial diversity of the gut, including the number of potentially beneficial microbes, increased significantly after MTT.

Two years after the original clinical trial, the authors of the same study re-evaluated the participants' health status to determine whether there was continuation of observed improvements in behaviour and GI symptoms and to determine the long-term effects of MTT on the gut microbiome. The obtained results are promising because after 2 years of repeated follow-ups it was found that the improvements persisted and the composition of the beneficial gut microbiota maintained and remained altered. There was a significant reduction in GI symptoms in the patients under study, and the median of relative abundance of *Bifidobacteria* and *Prevotella* compared to baseline values increased 4-fold and 712-fold, respectively, at 10th week of the study and 5-fold and 84-fold, respectively, after two years of the study [35].

A particular attention should be drawn to an increase in abundance of *Prevotella* after MTT as its lower abundance in the faeces of ASD children, compared to neurotypical children, was confirmed in other studies. The authors of another study also showed reduced amounts of *Prevotella* in the oral microbiome of ASD children [37, 38].

Although human studies concerning the impact of the microbiome on the development of ASD are extensive, cause-and-effect relationships have not been clearly defined and it has not been determined whether changes in the gut microbiome are a consequence of ASD or they contribute to ASD symptoms. *Sharon* et al. [39] investigated whether altered human microflora might promote ASD-like behaviours in mice. Faecal samples from human donors were selected based on the Autism Diagnostic Observation Schedule (ADOS) and the GI severity index (GSI) and they were transplanted into mice. The researchers found that animals that received microbiota transplants from ASD patients developed repetitive behaviours and less interest in social behaviours. According to the transplanted material (ASD *vs.* healthy), the animals had microbiome of different composition and diversity. It was concluded that the gut microbiota regulates behaviour of mice by producing neuroactive metabolites, suggesting that gut-brain connections contribute to the pathophysiology of ASD. Factors such as altered host genetics and perinatal events, combined with altered microbiota, may together influence the aetiology of ASD by combining risks that increase the severity of symptoms.

Dietary models in ASD

The importance of nutrition and its possible impact on ASD patients is key to integral therapy. According to numerous research studies, various nutritional approaches succeeded in reducing the severity of patients' core ASD symptoms [5, 40, 41]. However, the information to date concerning the relationship between different dietary models and ASD symptoms is frequently complex, while at the same time it does not provide any specific information regarding how to initiate the nutritional therapy. Specialists attempt to explain the relationship between ASD and nutrition through various mechanisms, but the ideal diet still does not exist. However, there is lack of a practical feeding algorithm for ASD children and the presentation of some dietary models that could be implemented in therapy, immediately after an ASD diagnosis.

One of the early dietary intervention in the first stage of implementing nutritional changes may be the introduction of the principles of the Mediterranean diet (MD) in the daily diet of ASD patient. Although there are no significant studies on the relationship between ASD and the MD but it has been reported to be beneficial against the cardiovascular system, metabolism and mental diseases. MD includes fruits and vegetables, legumes, nuts, cereals, olive oil and fish. Moreover, low intake of saturated fat, red meat and sugar is also involved in MD [42]. In the study conducted by *House* et al. [43], the behaviour of the offspring of 325 pregnant women was examined concerning the mother's degree of the rate of Adherence to the Mediterranean Diet (AMD). The offspring of mothers with high AMD were found to be less likely to have depression than the offspring of other mothers. It was observed that the offspring of mothers with the lowest degree of AMD had more ASD behaviours than the offspring of other mothers with higher levels of adherence. Furthermore, the mother's high AMD has been associated with decreased methylation of the IGF2 and SGCE/PEG10 locus and increased methylation of MEG3 locus, which result in reduced adverse behaviour, and increased social relations criteria, respectively.

The numerous options for diet that is used in the ASD therapy, as described in the scientific literature, are related to the problem of choosing an appropriate nutritional treatment. Each nutrition programme needs to be personalised and tailored to an individual patient. Specialists mostly focus on several dietary models, i.e.: gluten-free, casein- free and sugar -free diets (GFCFSF), ketogenic diet (KD),special carbohydrate diet (SCD), FOODMAP diet. When choosing a specific dietary model, the following factors should be included: nutritional status of the patient, type of GI complaints, recommended supplementation, food selectivity, type of food allergies and intolerances, severity of the disease.

GFCFSF diet is the most commonly selected diet that support the ASD therapy. It is normocaloric diet, individually balanced in terms of the content of macronutrients, vitamins and minerals. From the diet should be excluded: products containing gluten, casein, sugar and highly processed products with added sugar. Hypothetical mechanisms of action of the GFCF diet in ASD are: excess opioid activity, increased autoimmunity, oxidative stress and inflammation, reactivity of antibodies to gluten products and gut microbiota perturbations [44]. GFCFSF diets are used largely due to opioid peptides released by the digestion of both gluten and casein. High concentrations of opioid peptides lower the methylation index, leading to altered patterns of DNA methylation and gene expression. Opioid peptides, derived from gluten and casein, reduce cysteine uptake by cells; because cysteine reduces the rate of glutathione synthesis (GSH), their activity results in reduced GSH levels. Moreover, lower levels of GSH in the GI tract may promote inflammation and contribute to symptoms of GI discomfort and dysfunction [5]. Although there is a belief that the GFCF diet is completely harmless, there is no clear conclusion that it has no risk at all, especially the nutrient deficiencies that may arise are of great concern. Inadequate consumption of dairy products and GFCF diets have been found to be associated with high levels of homocysteine [45, 46]. The meta-analysis, conducted by *Quan* et al. [47], showed that a GFCF diet can reduce stereotypical behaviors and improve the cognition of children with ASD. Though most of the included studies were single-blind, the benefits of a GFCF diet that have been indicated are promising.

The excessive supply of sugar-containing carbohydrate products increases intestinal inflammation and contributes to the development of adverse intestinal microflora and growth of pathological fungi. *Tarnowska* et al. study [48] aims to identify factors influencing the purchasing decisions of families with ASD children on gluten-free and/or casein-free and/or sugar-free diets and the difficulties associated with such diets. The study included a group of 40 families with ASD children (32 boys and 8 girls) aged between 3–10 years. It was found that the factors that had the greatest influence on parents' decisions concerning the purchase the products included the composition of products, the presence of a certificate confirming the absence of gluten and/or milk, and taste qualities. Furthermore, following the elimination diet was a significant obstacle when traveling or socialising, causing conflicts with family and community. In addition, the limited range of healthy gluten-free, casein-free, and sugar-free foods, poor quality of taste and unsatisfactory quality of food made it difficult to purchase and prepare varied meals.

The ketogenic diet (KD) is another type of diet that was proposed as a nutrition intervention to alleviate symptoms in ASD patients. This is a high-fat, protein-sufficient and low-carbohydrate diet, resulting in the body using fatty acid metabolites as a primary source of energy [5]. Specialists should remember to individually balanced that diet in terms of the content of macronutrients, vitamins and minerals and also constantly monitoring the concentration of ketones in the patient's body. The classic model of the ketogenic diet assumes that for 4 grams of fat there is 1 gram of protein and carbohydrates in total (distribution of the daily supply of macronutrients: fats - 90%; protein - 8%; carbohydrates - 2%). The modified Atkins diet is less restrictive than the classic ketogenic diet model, and the proportions of macronutrients are arranged as follows: fats - 60%; protein - 10%; carbohydrates - 30%. The MCT (medium chain triglycerides) diet is a variant of the ketogenic diet based on medium-chain MCT fatty acids, and the distribution of macronutrients is as follows: fats - 73% (including 30-60% MCT fatty acids); protein - 10%; carbohydrates - 17% [49, 50, 51].

The researchers of animal model studies proved that KD might be an effective intervention in alleviating ASD symptoms [52, 53]. Furthermore, larger cohort studies found that the use of KD results in noticeable improvements in: learning, social behaviour, speech, cooperation and reduction of hyperactivity in ASD patients [5, 40, 54].

Lee et al. [40] investigated the effect of a 3-month ketogenic, gluten-free diet (GF) combined with MCTs in ASD children aged between 2–17 years. The main dietary restrictions were based on: - limiting the supply of carbohydrates to 20-25 g/day, - protein requirements were determined individually, taking into account age and body weight (RDA standard), - contents of MCT was set up to 20% of energy from the daily food ration (dietary source: coconut oil or pure MCT oil), - exclusion of all gluten-containing products. After the study had ended, patients showed improved behaviour and aggression control, as well as improved social behaviours. This type of dietary intervention was identified as a potentially beneficial therapeutic option regarding ASD to improve underlying autistic disorders.

Following the SCD diet protocol can also have a positive effect on alleviating ASD symptoms. The goal of this diet is to alleviate symptoms of carbohydrate malabsorption and reduce the proliferation of pathogenic intestinal microflora resulting in dysbiosis. In SCD, it is aimed to prevent malabsorption of foods that are more difficult to digest, prevent the formation of undigested residual nutrients and, as a result, prevent the growth of pathogenic bacteria in the intestine [55]. The main principle of the SCD diet is to limit the intake of complex carbohydrates, di-, oligo- and polysaccharides, including starch. The diet should include sources of simple carbohydrates, i.e. glucose, fructose, galactose. Furthermore, an important element of the SCD diet are also milk, fermented, lactose-free probiotic products (natural yoghurts) [56].

Abele et al. [57] conducted the study to investigate the potential of a specific carbohydrate diet and selected dietary supplements in reducing some autistic spectrum disorder (ASD) symptoms in children. This was a quantitative, non-blinded, non-randomized three-month pilot study of a dietary and nutritional intervention. The intervention group received a specific carbohydrate dietary plan - Specific Carbohydrate Diet/ Gut and Psychology Syndrome diet (SCD / GAPS) – and a few dietary supplements (omega-3 essential fatty acids, ascorbyl-palmitate, probiotics, vitamin D, and vitamin C). The analyzed diet (SCD/GAPS) enriched with some specific supplements were found to be a safe and effective approach for reducing some symptoms of ASD in children.

Studies confirm that the GI symptoms in ASD children are related to behavioural problems. FODMAP-restricted diets are used for alleviating irritable bowel syndrome (IBS) symptoms such as abdominal pain, bloating, constipation and diarrhoea. The diet should be followed by a 6-8 week to relieve inflammation in the gut, then expanding the diet to include foods with increasingly higher amounts of FODMAPs [41, 58]. *Nogay* et al. pilot study [41] aims to evaluate the effect of the diet of low fermentable oligosaccharides, disaccharides, monosaccharides and polyols (FODMAPs) on gastrointestinal and behavioural problems in ASD children. The researchers found that the study group following the FODMAP diet experienced significant relief in terms of some GI problems compared to baseline in this group and the control group. Fermentable oligo-di-monosaccharides and polyols (FODMAPs) form a heterogeneous group of poorly absorbed short-chain carbohydrates that are later fermented in the small or large intestine. FODMAPs include fructose (e.g. fruit and high-fructose corn syrup), lactose (e.g. milk and dairy products), fructans (e.g. cereals, vegetables and fruit), galactans (e.g. legumes and vegetables) and sugar alcohols (polyols such as sorbitol, fruit and vegetables) [58].

Other types of diets or product eliminations are selected based on specialised tests recommended by a doctor and dietician. This may include such diets as a Feingold, anti-inflammatory, oxalate-free, low-histamine or purine-free diet, according to the child's status of the organism, for example, problems with fat digestion or elevated serum ammonia levels. When following a specific diet, highly processed foods that contain food additives and preservatives should not be consumed. Food needs to be as natural as possible,

preferably cooked at home using simple products. The diet should be light and varied, so as to relieve the affected intestine while providing the body with essential nutrients [59].

Moreover, the elimination-rotation diet, which consists of excluding products that cause (delayed) IgG food allergies, may improve behaviour of ASD patients. Therefore, a food allergy test needs to be performed to indicate harmful food products. Self-monitoring can be difficult because the body's reaction may occur as long as 3 days after eating a particular food product. Moreover, symptoms typical of an IgE allergy, such as rash, are not present in IgG food allergies. However, such symptoms as abdominal pain, bloating, intestinal gases and headache may indicate IgG food allergies. In the first stage of the diet, harmful food products should be eliminated based on the test results, then they should be reimplemented into the diet after a set period of time, in rotation (as a rule, every 4th day). The elimination-rotation diet needs to be followed under the supervision of a dietitian to ensure the provision of all nutrients for the child, which are necessary for their growth and development [3].

Food selectivity in ASD *vs.* nutrition education

ASD patients may exhibit higher food selectivity (i.e. eating a narrow range of food products and/or rejecting one or more food groups), which limits the intake of certain foods and it may lead to nutritional deficiencies. Mild to severe food selectivity affects up to 95% ASD children [60]. Children with mild food selectivity may not require treatment. However, children with moderate to severe food selectivity will require intervention to promote dietary diversity and reduce the risk of nutritional deficiencies, bone density loss and constipation [60, 61].

Food selectivity also increases the challenges of parenting the ASD child. Parental attempts to introduce new, previously unfamiliar food products or dishes into a child's diet may result in crying, aggression, self-injury, throwing objects, spitting and pushing food away as a result of self-defence and protest [62]. Such destructive behaviours may also occur at the mere sight or smell of unfamiliar and unwanted foods. Parents may also be concerned that the persistent introduction of new foods and dishes into their child's diet may lead to further dietary restrictions and worsening of nutritional deficiencies [63].

In ASD patients, achieving adequate food intake is a challenge, and some nutrient deficiencies were identified. The authors of a meta-analysis, which determines the differences in terms of nutrition between ASD children and a group of typically developing children, found that participants with ASD consumed less protein, phosphorus, selenium, vitamin D and calcium, thiamine, riboflavin and vitamin B12. Moreover, ASD children consumed less omega-3 PUFAs and more fruit and vegetables, compared to controls [64].

Combined behavioural and medical interventions, in highly organised inpatient units or day treatment programmes, are well supported in the case of ASD children with strong food selectivity. These intensive programmes, however, are expensive and thus they are not available to all social groups [65]. Furthermore, ASD children with moderate food selectivity may not require such advanced treatment. Parent training appears to be useful for moderate food selectivity in ASD children [66]. The high prevalence of food selectivity in ASD and associated health risks determine the need to develop and test therapies tailored to the severity of the condition.

Sharp et al. [67] developed a meal plan specifically designed for ASD children with moderate food selectivity. A key component of this programme was the development of a multidisciplinary model of care that combines behavioural intervention and nutrition education. The dietitian assessed anthropometric measurements and dietary needs of each child based on a food diary assessment. The dietitian also participated in food selection to increase meal variety. Moreover, dietitians provided nutrition education for participants to promote principles of healthy eating and reduce the risk of nutritional deficiencies due to food selectivity. The implemented educational programme was also aimed at improving the mealtime behaviour. Parents of ASD children, who participated in the study, learnt how to select meal portions and how to give praise/attention to their child to shape target mealtime behaviours. The combination of behaviour management strategies and nutrition education was designed to promote health and a healthy, balanced diet.

It was found that the implemented educational programme was acceptable to both parents and ASD children. Parents expressed great satisfaction with the programme. Dietitians individually prepared food plans for each patient, which further demonstrated the high reliability of the programme. The authors of the study concluded that such educational programmes may improve the mealtime behaviour and promote dietary expansion in ASD children with moderate food selectivity [68].

Matching symptom severity to intervention based on a specific criterion, such as the degree of dietary restriction, meets the call for designing educational programmes that address patient-specific requirements. This is particularly significant in patients with multiple diseases, which is frequently a characteristic of ASDs [68].

Park et al. [69] conducted an analysis of the relationship between age and BMI as well as the mealtime behaviours and food preferences of ASD

students to identify problematic mealtime behaviours. The researchers proved that students with ASD could be divided according to the degree of problematic eating behaviours, and food preferences were not significantly different from those of typically developing students. The conclusion that age and BMI values mediated the differences in meal behaviours of students with ASD seems to be particularly important, suggesting that personalised programmes of nutrition education are necessary. It was found that younger children were choosier about food and they needed a separate educational programme to experience a wider variety of foods, while older children needed an educational programme focused on obesity prevention and treatment.

A particular attention should be drawn to frequently overlooked fact that autism, although observed in early childhood, is not an exclusively childhood disorder. Typically, autistic adults are significantly less frequent subject of interest than autistic children. Meanwhile, children with autism grow and change, becoming autistic adolescents and adults who, in many cases, are able to compensate for their deficits [70].

The high prevalence of food selectivity of varying intensity in ASD patients is a flagrant need to develop and test methods of treatment that can be implemented on a broader scale and be age-appropriate and appropriate to severity of the disease. Early childhood, multilevel education, including nutrition education that may influence the way the ASD symptoms manifest themselves in later developmental periods, is one of the most significant factors.

CONCLUSIONS

The ASDs definition are used to group disease entities that are neurodevelopmental abnormalities. Many biological and environmental factors have been identified, potentially leading to the development of ASD.

Maternal nutrition is a potentially modifiable factor important for fetal neurodevelopment. Understanding the sensitive window of exposure and gene-diet interactions may help inform precise intervention and prevention. Future studies that comprehensively quantify maternal nutrient intake from both food and supplements and integrate more objective measures of biomarkers reflecting intake and metabolism are warranted.

The gut microbiota is believed to play a crucial role in human health and disease through involvement in physiological homoeostasis, immunological development, glutathione metabolism, amino acid metabolism, etc., which in a reasonable way explain the role of gut-brain axis in autism. Based on the studies conducted so far, it is estimated that the incidence of gastrointestinal disorders among patients with autistic disorders is much higher than in the population of healthy people, i.e. without the presence of neurodevelopmental disorders.

Gastrointestinal problems that are seen associated with most of the autism cases suggest that it is not just a psychiatric disorder as many claim but have a physiological base, and alleviating the gastrointestinal problems could help alleviating the symptoms .

The importance of nutrition and its possible impact on ASD patients is key to integral therapy. According to numerous research studies, various nutritional approaches succeeded in reducing the severity of patients' core ASD symptoms. The diet of ASD patients is also a key factor for the worsening of ASD symptoms. Children with autism have food selectivity and limited diets due to smell, taste, or other characteristics of foods.

Various dietary interventions are tried to alleviate the symptoms of ASD. Furthermore, utrition plays an important role in healing gastrointestinal problems that patients with ASD suffer from. Accordingly, individual-specific arrangements can be made on existing dietary protocols. Overall, more studies are needed for proving the effectiveness of the proposal diets in individuals with ASD.

Conflict of interest

Authors declare no conflict of interest.

REFERENCES

1. *Peretti S, Mariano M, Mazzocchetti C, Mazza M, Pino MC, Verrotti Di Pianella A, Valenti M.* Diet: the keystone of autism spectrum disorder? Nutr Neurosci. 2019;22(12):825-839. doi: 10.1080/1028415X.2018.1464819.
2. *Lai MC, Lombardo MV, Baron-Cohen S.* Autism. Lancet 2014;383:896-910. doi.org/10.1016/S0140-6736(13)61539-1.
3. *Cekici H, Sanlier N.* Current nutritional approaches in managing autism spectrum disorder: A review. Nutr Neurosci. 2019; 22(3): 145-155. doi: 10.1080/1028415X.2017.1358481.
4. *Modabbernia A, Velthorst E, Reichenberg A.* Environmental risk factors for autism: an evidence-based review of systematic reviews and meta-analyses. Mol Autism 2017;8:13. doi: 10.1186/s13229-017-0121-4.
5. *Karhu E, Zukerman R, Eshraghi RS, Mittal J, Deth RC, Castejon AM, Trivedi M, Mittal R, Eshraghi AA.* Nutritional interventions for autism spectrum disorder. Nutr Rev. 2020;78(7): 515-531. doi: 10.1093/nutrit/nuz092.
6. *Moody L, Chen H, Pan YX.* Early-life nutritional programming of cognition–the fundamental role of epigenetic mechanisms in mediating the relation between early-life environment and learning and memory process. Adv Nutr. 2017;8(2):337–350. doi:10.3945/an.116.014209.

7. *Vargas DL, Nascimbene C, Krishnan C, Zimmerman AW, Pardo CA.* Neuroglial activation and neuroinflammation in the brain of patients with autism. Ann Neurol. 2005;57(1):67-81. doi: 10.1002/ana.20315.
8. *Liu J, Amat M, Kong X.* Missing components in current management of Autism Spectrum Disorders (ASD): nutrition, dental care, and house-call programs. Rev J Autism Dev Disord. 2020;7:219-225. doi.org/10.1007/s40489-019-00182-x.
9. *Li M, Francis E, Hinkle SN, Ajjarapu AS, Zhang C.* Preconception and Prenatal Nutrition and Neurodevelopmental Disorders: A Systematic Review and Meta-Analysis. Nutrients 2019;11(7):1628. doi: 10.3390/nu11071628.
10. *Lyall K, Schmidt RJ, Hertz-Picciotto I.* Maternal lifestyle and environmental risk factors for autism spectrum disorders. Int J Epidemiol. 2014;43(2):443–464. doi: 10.1093/ije/dyt282.
11. *Lauritzen L, Brambilla P, Mazzocchi A, Harsløf LBS, Ciappolino V, Agostoni C.* DHA effects in brain development and function. Nutrients 2016;8(1):6. doi: 10.3390/nu8010006.
12. *Lyall K, Munger KL, O'Reilly EJ, Santangelo SL, Ascherio A.* Maternal dietary fat intake in association with autism spectrum disorders. Am J Epidemiol. 2013;178(2):209–220. doi.org/10.1093/aje/kws433.
13. *Patterson E, Wall R, Fitzgerald GF, Ross RP, Stanton C.* Health implications of high dietary omega-6 polyunsaturated fatty acids. J Nutr Metab. 2012;2012:539426. doi: 10.1155/2012/539426.
14. *Julvez J, Mendez M, Fernandez-Barres S, Romaguera D, Vioque J, Llop S, Ibarluzea J, Guxens M, Avella-Garcia C, Tardón A, Riaño I, Andiarena A, Robinson O, Arija V, Esnaola M, Ballester F, Sunyer J.* Maternal consumption of seafood in pregnancy and child neuropsychological development: A longitudinal study based on a population with high consumption levels. Am J Epidemiol. 2016;183(3):169–182. doi: 10.1093/aje/kwv195.
15. *Vecchione R, Vigna C, Whitman C, Kauffman EM, Braun JM, Chen A, Xu Y, Hamra GB, Lanphear BP, Yolton K, Croen LA, Fallin MD, Irva Hertz-Picciotto, Newschaffer CJ, Lyall K.* The Association Between Maternal Prenatal Fish Intake and Child Autism-Related Traits in the EARLI and HOME Studies. Rev J Autism Dev Disord. 2021;51(2):487-500. doi: 10.1007/s10803-020-04546-9
16. *Farina M, Rocha JBT, Aschner M.* Mechanisms of methylmercury-induced neurotoxicity: evidence from experimental studies. Life Sci. 2011;89(15-16):555-563. doi: 10.1016/j.lfs.2011.05.019.
17. FAO/WHO: Report of the Joint FAO/WHO Expert Consultation on the Risks and Benefits of Fish Consumption. Rome, Food and Agriculture Organization of the United Nations; Geneva, World Health Organization 2011, 50 pp.
18. *Lee HS.* Impact of maternal diet on the epigenome during in utero life and the developmental programming of diseases in childhood and adulthood. Nutrients 2015;7(11):9492–9507. doi: 10.3390/nu7115467.
19. *Schmidt RJ, Iosif AM, Angel EG, Ozonoff S.* Association of maternal prenatal vitamin use with risk for autism spectrum disorder recurrence in young siblings. JAMA Psychiatry 2019;76(4):391–398. doi: 10.1001/jamapsychiatry.2018.3901.
20. *Levine SZ, Kodesh A, Viktorin A, Smith L, Uher R, Reichenberg A, Sandin S.* Association of maternal use of folic acid and multivitamin supplements in the periods before and during pregnancy with the risk of autism spectrum disorder in offspring. JAMA Psychiatry 2018;75(2):176–184. doi: 10.1001/jamapsychiatry.2017.4050.
21. *Li YM, Shen YD, Li YJ, Xun GL, Liu H, Wu RR, Xia K, Zhao JP, Ou JJ.* Maternal dietary patterns, supplements intake and autism spectrum disorders: A preliminary case-control study. Medicine 2018;97(52):e13902. doi: 10.1097/MD.0000000000013902.
22. *Stubbs G, Henley K, Green J.* Autism: Will vitamin D supplementation during pregnancy and early childhood reduce the recurrence rate of autism in newborn siblings? Med Hypotheses 2016;88:74-78. doi: 10.1016/j.mehy.2016.01.015.
23. *Berding K, Donovan SM.* Diet can impact microbiota composition in children with autism spectrum disorder. Front Neurosci. 2018;12:515. doi: 10.3389/fnins.2018.00515.
24. *Tomova A, Husarova V, Lakatosova S, Bakos J, Vlkova B, Babinska K, Ostatnikova D.* Gastrointestinal microbiota in children with autism in Slovakia. Psychol Behav. 2015;138:179-187. doi: 10.1016/j.physbeh.2014.10.033.
25. *Coretti L, Paparo L, Riccio MP, Amato F, Cuomo M, Natale A, Borrelli L, Corrado G, Comegna M, Buommino E, Castaldo G, Bravaccio C, Chiariotti L, Berni Canani R, Lembo F.* Gut Microbiota Features in Young Children With Autism Spectrum Disorders. Front Microbiol. 2018;9:3146. doi: 10.3389/fmicb.2018.03146.
26. *Chaidez V, Hansen RL, Hertz-Picciotto I.* Gastrointestinal problems in children with autism, developmental delays or typical development. J Autism Dev Disord. 2014;44(5):1117–1127. doi: 10.1007/s10803-013-1973-x.
27. *Sanctuary MR, Kain JN, Chen SY, Kalanetra K, Lemay DG, Rose DR, Yang HT, Tancredi DJ, German JB, Slupsky CM, Ashwood P, Mills DA, Smilowitz JT, Angkustsiri K.* Pilot study of probiotic/colostrum supplementation on gut function in children with autism and gastrointestinal symptoms. PLOS ONE. 2019;14(1):e0210064. doi: 10.1371/journal.pone.0210064.
28. *Leader G, Tuohy E, Chen JL, Mannion A, Gilroy SP.* Feeding Problems, Gastrointestinal Symptoms, Challenging Behavior and Sensory Issues in Children and Adolescents with Autism Spectrum Disorder. J Autism Dev Disord. 2020;50(4):1401-1410. doi: 10.1007/s10803-019-04357-7.
29. *de Magistris L, Familiari V, Pascotto A, Sapone A, Frolli A, Iardino P, Carteni M, De Rosa M, Francavilla R, Riegler G, Militerni R, Bravaccio C.* Alterations of the intestinal barrier in patients with autism spectrum disorders and in their first-degree relatives. J Pediatr Gastroenterol Nutr. 2010;51(4):418–424. doi: 10.1097/MPG.0b013e3181dcc4a5.

30. *Kang DW, Adams JB, Gregory AC, Borody T, Chittick L, Fasano A, Khoruts A, Geis E, Maldonado J, McDonough-Means S, Pollard EL, Roux S, Sadowsky MJ, Lipson KS, Sullivan MB, Caporaso JG, Krajmalnik-Brown R.* Microbiota transfer therapy alters gut ecosystem and improves gastrointestinal and autism symptoms: an open label study. Microbiome 2017;5(1):10. doi: 10.1186/s40168-016-0225-7.
31. *Wang L, Christophersen CT, Sorich MJ, Gerber JP, Angley MT, Conlon MA.* Elevated fecal short chain fatty acid and ammonia concentrations in children with autism spectrum disorder. Dig Dis Sci. 2012; 57(8): 2096-2102. doi: 10.1007/s10620-012-2167-7.
32. *Albenberg LG, Wu GD.* Diet and the intestinal microbiome associations, functions, and implications for health and disease. Gastroenterology 2014;146(6):1564-1572. doi: 10.1053/j.gastro.2014.01.058.
33. *Gondalia SV, Palombo EA, Knowles SR, Cox SB, Meyer D, Austin DW.* Molecular characterization of gastrointestinal microbiota of children with autism (with and without gastrointestinal dysfunction) and their neurotypical siblings. Autism Res. 2012;5(6):419-427. doi: 10.1002/aur.1253.
34. *Son JS, Zheng LJ, Rowehl LM, Tian X, Zhang Y, Zhu W, Litcher-Kelly L, Gadow KD, Gathungu G, Robertson CE, Ir D, Frank DN, Li E.* Comparison of Fecal Microbiota in Children with Autism Spectrum Disorders and Neurotypical Siblings in the Simons Simplex Collection. PLoS One. 2015; 10(10): e0137725. doi: 10.1371/journal.pone.0137725.
35. *Kang DW, Adams JB, Coleman D, Pollard EL, Maldonado J, McDonough-Means S, Caporaso JG, Krajmalnik-Brown R.* Long-term benefit of Microbiota Transfer Therapy on autism symptoms and gut microbiota. Sci Rep. 2019;9(1):5821. doi: 10.1038/s41598-019-42183-0.
36. *Bagdasarian N, Rao K, Malani PN.* Diagnosis and treatment of *Clostridium difficile* in adults a systematic review. JAMA 2015; 313(4):398–408. doi: 10.1001/jama.2014.17103.
37. *Kang DW, Ilhan ZE, Isern NG, Hoyt DW, Howsmon DP, Shaffer M, Lozupone CA, Hahn J, Adams JB, Krajmalnik-Brown R.* Differences in fecal microbial metabolites and microbiota of children with autism spectrum disorders. Anaerobe 2018; 49: 121-131. doi: 10.1016/j.anaerobe.2017.12.007.
38. *Qiao Y, Wu M, Feng Y, Zhou Z, Chen L, Chen F.* Alterations of oral microbiota distinguish children with autism spectrum disorders from healthy controls. Scient Rep. 2018;8(1):1-12. doi: 10.1038/s41598-018-19982-y.
39. *Sharon G, Cruz NJ, Kang DW, Gandal MJ, Wang B, Kim YM, Zink EM, Casey CP, Taylor BC, Lane CJ, Bramer LM, Isern NG, Hoyt DW, Noecker C, Sweredoski MJ, Moradian A, Borenstein E, Jansson JK, Knight R, Metz TO, Lois C, Geschwind DH, Krajmalnik-Brown R, Mazmanian SK.* Human Gut Microbiota from Autism Spectrum Disorder Promote Behavioral Symptoms in Mice. Cell 2019;177(6):1600-1618. doi: 10.1016/j.cell.2019.05.004.
40. *Lee RWY, Corley MJ, Pang A, Arakaki G, Abbott L, Nishimoto M, Miyamoto R, Lee E, Yamamoto S, Maunakea AK, Lum-Jones A, Wong M.* A modified ketogenic gluten-free diet with MCT improved behavior in children with autism spectrum disorder. Physiol Behav. 2018;188:205-211. doi: 10.1016/j.physbeh.2018.02.006.
41. *Nogay NH, Walton J, Roberts KM, Nahikian-Nelms M, Witwer AN.* The Effect of the Low FODMAP Diet on Gastrointestinal Symptoms, Behavioral Problems and Nutrient Intake in Children with Autism Spectrum Disorder: A Randomized Controlled Pilot Trial. J Autism Dev Disord. 2021;51(8): 2800-2811. doi: 10.1007/s10803-020-04717-8.
42. *Ventriglio A, Sancassiani F, Contu MP, Latorre M, Di Slavatore M, Fornaro M, Bhugra D.* Mediterranean Diet and its Benefits on Health and Mental Health: A Literature Review. Clin Pract Epidemiol Ment Health. 2020;16 (Suppl-1):156–164. doi: 10.2174/1745017902016010156.
43. *House JS, Mendez M, Maguire RL, Gonzalez-Nahm S, Huang Z, Daniels J, Murphy SK, Fuemmeler BF, Wright FA, Hoyo C.* Periconceptional maternal mediterranean diet is associated with favorable offspring behaviors and altered CpG methylation of imprinted genes. Front Cell Dev Biol. 2018;6:107. doi: 10.3389/fcell.2018.00107.
44. *Lange KW, Reissmann A.* Is the gluten-free and casein-free diet efficacious in the treatment of childhood autism spectrum disorder? JFB. 2021;15. doi.org/10.31665/JFB.2021.15277.
45. *Lutsey PL, Steffen LM, Feldman HA, Hoelscher DH, Webber LS, Luepker RV, Lytle LA, Zive M, Osganian SK.* Serum homocysteine is related to food intake in adolescents: the Child and Adolescent Trial for Cardiovascular Health. Am J Clinic Nutr. 2006;83(6):1380–1386. doi: 10.1093/ajcn/83.6.1380.
46. *Valente FX, Campos Tdo N, Moraes LF, Hermsdorff HH, Cardoso Lde M, Pinheiro-Sant'Ana HM, Gilberti FA, Peluzio Mdo C.* B vitamins related to homocysteine metabolism in adults celiac disease patients: a cross-sectional study. Nutr J. 2015;14:110. doi: 10.1186/s12937-015-0099-8.
47. *Quan L, Xu X, Cui Y, Han H, Hendren RL, Zhao L, You X.* A systematic review and meta-analysis of the benefits of a gluten-free diet and/or casein-free diet for children with autism spectrum disorder. Nutr Rev. 2022;80(5):1237-1246. doi: 10.1093/nutrit/nuab073.
48. *Tarnowska K, Gruczyńska-Sękowska E, Kowalska D, Kozłowska M, Majewska E, Winkler R.* Difficulties and factors influencing purchase decision. The perspective of families with children with autism spectrum disorders on a gluten-free and casein-free diet. Preliminary study. Rocz Panstw Zakl Hig. 2020;71(3):321-328. doi: 10.32394/rpzh.2020.0122.
49. *Ruskin DN, Murphy MI, Slade SL, Masino SA.* Ketogenic diet improves behaviors in a maternal immune activation model of autism spectrum disorder. PloS one. 2017;12(2):e0171643. doi: 10.1371/journal.pone.0171643.
50. *Castro K, Faccioli LS, Baronio D, Gottfried C, Schweigert Perry I, dos Santos Riesgo R.* Effect of a ketogenic diet on autism spectrum disorder: A systematic review. Res Autism Spectr Disord. 2015;20:31-38. doi.org/10.1016/j.rasd.2015.08.005.

51. *El-Rashidy O, El-Baz F, El-Gendy Y, Khalaf R, Reda D, Saad K.* Ketogenic diet versus gluten free casein free diet in autistic children: a case-control study. Meta. Brain Dis. 2017;32(6):1935-1941. doi: 10.1007/s11011-017-0088-z.
52. *Mychasiuk R, Rho JM.* Genetic modifications associated with ketogenic diet treatment in the BTBR+ Tf/J mouse model of autism spectrum disorder. Autism Res. 2017;10(3):456-471. doi: 10.1002/aur.1682.
53. *Newell C, Johnsen VL, Yee NC, Xu WJ, Klein MS, Khan A, Rho JM, Shearer J.* Ketogenic diet leads to O-GlcNAc modification in the BTBRt+Tf/J mouse model of autism. Biochim Biophys Acta Mol Basis Dis. 2017;1863(9):2274-2281. doi: 10.1016/j.bbadis.2017.05.013.
54. *Varesio C, Grumi S, Zanaboni MP, Mensi MM, Chiappedi M, Pasca L, Ferraris C, Tagliabue A, Borgatti R, De Giorgis V.* Ketogenic Dietary Therapies in Patients with Autism Spectrum Disorder: Facts or Fads? A Scoping Review and a Proposal for a Shared Protocol. Nutrients 2021;13(6):2057. doi: 10.3390/nu13062057.
55. *Suskind DL, Wahbeh G, Gregory N, Vendettuoli H, Christie D.* Nutritional therapy in pediatric Crohn disease: the specific carbohydrate diet. J Pediatr Gastroenterol Nutr. 2014;58(1):87-91. doi: 10.1097/MPG.0000000000000103.
56. *Obih C, Wahbeh G, Lee D, Braly K, Giefer M, Shaffer ML, Nielson H, Suskind DL.* Specific carbohydrate diet for pediatric inflammatory bowel disease in clinical practice within an academic IBD center. Nutrition 2016;32(4):418-25. doi: 10.1016/j.nut.2015.08.025.
57. *Ābele S, Meija L, Folkmanis V, Tzivian L.* Specific Carbohydrate Diet (SCD/GAPS) and Dietary Supplements for Children with Autistic Spectrum Disorder. In: Proceedings of the Latvian Academy of Sciences. Section B. Natural, Exact, and Applied Sciences 2021;75(6):417-425. doi.org/10.2478/prolas-2021-0062.
58. *Nanayakkara WS, Skidmore PM, O'Brien L, Wilkinson TJ, Gearry RB.* Efficacy of the low FODMAP diet for treating irritable bowel syndrome: the evidence to date. Clin Exp Gastroenterol. 2016;9:131–142. doi: 10.2147/CEG.S86798.
59. *Madzhidova S, Sedrakyan L.* The use of dietary interventions in pediatric patients. PMC. 2019; 7(1): 1-13. doi: 10.3390/pharmacy7010010.
60. *Sharp WG, Berry RC, McCracken C, Nuhu NN, Marvel E, Saulnier CA, Klin A, Jones W, Jaquess DL.* Feeding problems and nutrient intake in children with autism spectrum disorders: A meta-analysis and comprehensive review of the literature. J Autism Dev Disord. 2013;43(9):2159–2173. doi: 10.1007/s10803-013-1771-5.
61. *Sharp WG, Postorino V, McCracken CE, Berry RC, Criado KK, Burrell TL, Scahill L.* Dietary intake, nutrient status, and growth parameters in children with autism spectrum disorder and severe food selectivity: An electronic medical record review. J Acad Nutr Diet. 2018;118(10):1943–1950. doi: 10.1016/j.jand.2018.05.005.
62. *Curtin C, Hubbard K, Anderson SE, Mick E, Must A, Bandini LG.* Food selectivity, mealtime behavior problems, spousal stress, and family food choices in children with and without autism spectrum disorder. J Autism Dev Disord. 2015;45(10): 3308–3315. doi: 10.1007/s10803-015-2490-x.
63. *Schreck KA, Williams K.* Food preferences and factors influencing food selectivity for children with autism spectrum disorders. Res Dev Disabil. 2006;27(4): 353–363. doi: 10.1016/j.ridd.2005.03.005.
64. *Esteban-Figuerola P, Canals J, Fernández-Cao JC, Arija Val V.* Differences in food consumption and nutritional intake between children with autism spectrum disorders and typically developing children: A meta-analysis. Autism 2019;23(5):1079-1095. doi: 10.1177/1362361318794179.
65. *Sharp WG, Volkert VM, Scahill L, McCracken CE, McElhanon B.* A systematic review and meta-analysis of intensive multidisciplinary intervention for pediatric feeding disorders: How standard is the standard of care? J Pediatr. 2017;181:116–124. doi: 10.1016/j.jpeds.2016.10.002.
66. *Cosbey J, Muldoon D.* EAT-UP™ Family-Centered Feeding Intervention to Promote Food Acceptance and Decrease Challenging Behaviors: A Single-Case Experimental Design Replicated Across Three Families of Children with Autism Spectrum Disorder. J Autism Dev Disord. 2017;47(3): 564–578. doi: 10.1007/s10803-016-2977-0.
67. *Sharp WG, Burrell TL, Berry RC, Stubbs KH, McCracken CE, Gillespie SE, Scahill L.* The Autism Managing Eating Aversions and Limited Variety Plan vs Parent Education: A Randomized Clinical Trial. J Pediatr. 2019;211:185-192. doi: 10.1016/j.jpeds.2019.03.046.
68. *Smith SM, Bayliss EA, Mercer SW, Gunn J, Vestergaard M, Wyke S, Salisbury C, Fortin M.* How to design and evaluate interventions to improve outcomes for patients with multimorbidity. *J Comorb.* 2013;3:10–17. doi: 10.15256/joc.2013.3.21.
69. *Park HJ, Choi SJ, Kim Y, Cho MS, Kim YR, Oh JE.* Mealtime Behaviors and Food Preferences of Students with Autism Spectrum Disorder. Foods 2020;10(1):49. doi: 10.3390/foods10010049.
70. *Hyman SL, Levey SE, Myers SM.* Council on children with Disabilities, Section on Developmental and Behavioral Pediatrics. Identification, Evaluation, and Management of Children With Autism Spectrum Disorder. Peditarics 2020;145(1):e20193447. doi: 10.1542/peds.2019-3447.

Received: 15.06.2022
Accepted: 20.07.2022
Published online first: 05.08.2022