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# Nutrients deficiencies in patients with autism spectrum disorder, role of folic acid and vitamin D3 - review of literature

## Authors:

**Dominika Małachowska**

Warszawski Szpital Południowy, ul. rtm. Witolda Pileckiego 99, 02-781 Warszawa, Poland

ORCiD: 0009-0008-6305-7959

e-mail: dominika1.malachowska@gmail.com

**Aleksandra Świercz**

Warszawski Szpital Południowy, ul. rtm. Witolda Pileckiego 99, 02-781 Warszawa, Poland

ORCiD: 0009-0007-1535-1590

e-mail: aleksandra.swiercz1996@gmail.com

**Urszula Żurek**

Warszawski Szpital Południowy, ul. rtm. Witolda Pileckiego 99, 02-781 Warszawa, Poland

ORCiD: 0009-0008-3482-5381

e-mail: ula.zurek@gmail.com

**Ignacy Tołwiński**

Warszawski Szpital Południowy, ul. rtm. Witolda Pileckiego 99, 02-781 Warszawa, Poland

ORCiD: 0000-0003-1362-6734

e-mail: ignacyt233@gmail.com

**Zofia Kędzierska**
Warszawski Szpital Południowy, ul. rtm. Witolda Pileckiego 99, 02-781 Warszawa, Poland
ORCiD: 0000-0002-4181-4719
e-mail: zo.kedzierska@gmail.com

**Klaudia Antkowiak**
Szpital Średzki Serca Jezusowego z.o.o ul. Żwirki i Wigury 10, 63-000 Środa Wielkopolska, Poland
ORCiD: 0009-0008-3421-2200
e-mail: klaudia.antkowiak2021@gmail.com

**Klaudia Dadas**
Warszawski Szpital Południowy, ul. rtm. Witolda Pileckiego 99, 02-781 Warszawa, Poland
ORCiD: 0009-0007-3352-9807
e-mail: klaudia.w.2703@gmail.com

**Hubert Ciecierski-Koźlarek**
Wojewódzki Szpital Specjalistyczny w Olsztynie, ul. Żołnierska 18, 10-561 Olsztyn, Poland
ORCiD: 0009-0009-4062-6888
e-mail: hubertciecierski@icloud.com

**Kateryna Shved**
Wielospecjalistyczny Szpital Miejski im. Józefa Strusia, ul. Szwajcarska 3, 61-285 Poznań, Poland
ORCiD: 0009-0002-3773-7025
e-mail: katey.shved@gmail.com

**Abstract**

**Introduction and purpose**:

This article will discuss the relationship between nutrition deficiency, focusing on folic acid and vitamin D3 and autism spectrum disorder (ASD). Research suggests that nutrient deficiencies play a role in the development and progression of autism. This article will investigate causes of nutrient deficiencies in ASD, like dietary constraints, food choice, and

environment exposure, and their impact on ASD and related symptoms. The purpose of this article is to provide an overview of the research examining the relationship between folic acid and vitamin d3 supplementation and autism.

**Materials and methods:**

A broad search was conducted using the PubMed database in order to identify relevant studies published between 2010-2020 using keywords such as “folic acid”, “folinic acid”, "vitamin d3", "autism spectrum disorder".

**A brief description of the current state of knowledge:**

Autism spectrum disorder (ASD) is a complex neurodevelopmental disorder that in recent years has been increasingly diagnosed among children. Only between 2016 and 2014 measured prevalence in the United States has increased by 10%. [1] The exact etiology of ASD in not known. In this review we will examine a role of folic acid and vitamin D3. Research suggests that folic acid supplements can help improve verbal skills in people with ASD. Research also shows decreased levels of vitamin d3 in ASD patients. Clinical trials involving vitamin d3 present inconclusive data but lean towards positive impact of supplementation. Both folic acid and vitamin d3 supplementation is safe. Dietary changes and oral supplementation may be beneficial for patients.

**Conclusions:**

Studies with larger participant numbers should be done to prove the significance of folic acid and vitamin D3 supplementation as it shows potential in being a safe and not expensive complementary therapeutic option.

**Keywords:** autism spectrum disorder; vitamin D3; folic acid; folinic acid; verbal communication; dietary intervention,

## Introduction

Autism spectrum disorder (ASD) is a complex neurodevelopmental disorder characterized by deficits in social interaction and communication as well as restricted, repetitive behaviors and interests. It is diagnosed mostly in young children, when parents start to notice delayed development, children not hitting early milestones. That is the time when parents begin looking for a cause. Statistical research estimate that 1 in 54 children in the United States are diagnosed with ASD [1]. In Europe and Asia it is estimated that 1% of population suffers from ASD. As of now we do not know the exact etiology of ASD. Studies suggests that a

combination of genetic and environmental factors may be involved. This article will explore possible underlying causes of nutrient deficiencies in ASD, such as dietary restrictions, food selectivity, and environmental exposures, and how they may be impacting the development of autism and autism-related symptoms. Individuals along the spectrum exhibit a full range of intellectual functioning and language abilities. The deficits can be very serious, potentially affecting every aspect of an individual's life, from personal relationships to relationships with family and friends, as well as their education and career. The effects of the deficits can be observed in all situations, though they may vary depending on the context. [2]

Clinical presentation of ASD varies significantly. That was a reason for a drastic change that had occurred with classification of ASD. In new ICD-11 classification we classify individuals into 7 groups depending on the intellectual development disorder and the degree of impairment of language function.

International Classification of Diseases for Mortality and Morbidity Statistics, 11th Revision: 6A02 Autism spectrum disorder, sections/codes in this section (6A02-6A02)

- Autism spectrum disorder without disorder of intellectual development and with mild or no impairment of functional language (6A02.0)
- Autism spectrum disorder with disorder of intellectual development and with mild or no impairment of functional language (6A02.1)
- Autism spectrum disorder without disorder of intellectual development and with impaired functional language (6A02.2)
- Autism spectrum disorder with disorder of intellectual development and with impaired functional language (6A02.3)
- Autism spectrum disorder with disorder of intellectual development and with absence of functional language (6A02.5)
- Other specified autism spectrum disorder (6A02.Y)
- Autism spectrum disorder, unspecified (6A02.Z)

Autism spectrum disorder due to its complicated and varied forms of clinical presentation needs individual approach. For best results comprehensive and multidiscipline care should be provided for the families, including psychiatrists, psychologists, speech therapists, nutritional specialists. By combining knowledge and experience we can improve the quality of life not only for the individual diagnosed with ASD, but for the whole family.

## Methods

The authors conducted an extensive research using PubMed electronic database with relevant keywords and combinations such as “folic acid”, vitamin d3 deficiency”, „autism spectrum disorder”, „nutrient deficiency” „folinic acid”.

Studies investigating the effect of vitamin D3 and the effect of folic acid supplementation on patients with autism spectrum disorder were included. The selected studies were critically analyzed to assess the impact of supplementation on the behavioral patterns and general improvement on individuals with autism spectrum disorder.

The research which formed the groundwork for the article happened between March and May of 2023, and it was restricted to English and Polish language publications.

## Causes of nutrient deficiencies in patients with ASD

People with autism spectrum disorder exhibit multiple symptoms. While discussing nutrition we must say a few words about food selectivity and stimulus perception disorders, mainly hypersensitivity or hyposensitivity to oral, olfactory, and touch stimuli. Those disorders can manifest as the child’s unwillingness to eating common foods, limiting their food intake which promotes nutrients deficiencies. It can also lead to eating inedible substances [3]. Without versatile diet it is impossible to sustain healthy levels of macro and micronutrients.

## Impact of folic acid:

Folic acid, also known as Vitamin B9, is an essential vitamin that plays a significant role in many bodily processes. Most notably, folic acid is vital for proper neural development during embryonic and fetal period of life. Folate is especially important for pregnant women and growing children. [4-8] Recommended daily intake of folic acid varies. Because of the important role it plays in the neuronal development and prevention of congenital dysfunction of nervous system such as neural tube defects it is recommended to supplement folic acid before conception and during pregnancy. Centers of Disease Control and Prevention (CDC) recommends all women of reproductive age should get 400 micrograms (mcg) of folic acid every day, in addition to consuming varied diet rich in foods containing folate.

Adding folate to the diet prior to and during pregnancy has been demonstrated to reduce the chance of having a child with autism spectrum disorder (ASD).[4-8]

There is a connection between ASD and abnormalities in the way folate is metabolized. Polymorphisms in genes related to folate metabolism may be associated with ASD, and disturbances in folate processing may be related to the glutathione abnormalities seen in patients with ASD.[9]

Folic acid is found in various foods. Most notably in dark green, leafy vegetables like kale, spinach, turnip greens. Folate can also be found in fortified grains, fruits and beans. That implies that versatile diet is necessary for healthy intake of folate. This on the other hand is not easily achieved with children suffering from autism due to their picky eating habits.
Food selectivity is very common in children with autism spectrum disorder. It can be characterized as the unwillingness to consuming new foods or even common foods. Children with autism can be very inflexible, resulting in a limited diet, restricted food consumption that lead to inadequate intake of necessary nutrients. Food sensitivity in patients within the spectrum may be caused by many factors such as increased sensitivity to taste, texture or other sensory aversion. As mention before this increases the risk of malnutrition and may generate severe health problems. [10,11]

A double-blind randomized placebo-controlled study was conducted at Arkansas Children's Research Institute (Little Rock, AR, USA) from 4 June 2012 to 22 November 2013. They conducted a study with 48 participants. The purpose of the study was to determine if high-dose folinic acid supplementation is effective at improving verbal communication in children suffering from non-syndromic (idiopathic) ASD and language impairment. Forthy eight children were randomly assigned to either the high-dose folinic acid group (2mg kg -1 per day; maximum 50mg per day; n=23) or placebo n=25. It is important to note that the exclusion and inclusion criteria were strict. Exclusion criteria included: premature birth, pharmaceutical therapy with antipsychotic medication, history of kidney and liver disease, well defined genetic syndromes, supplementation exceeding the recommended daily allowance, uncontrolled gastroesophageal reflux, medications known to affect folate metabolism, sensory deficits, malformations of central nervous system or damage found on imaging studies with MRI, ongoing therapies that could interfere with the study, a clinical seizure within the last 6 months and moderate-to-severe irritability or self-abusive behavior on the aberrant behavior checklist. This type of rigorous screening promotes reliable results. The study measured the improvement using ability-appropriate instrument. Instruments used were the CELF-preschool-2, CELF-4 and the Preschool Language Scale-5 (PLS-5). Although the studied

group were not very big the results of the study found that the improvement in verbal communication was significantly greater for the participants on folinic acid as compared with participants on placebo with a medium-to-large effect size (Cohen's d = 0.70). What is also important to note, the supplementation of folinic acid also had an impact on children behavior. Irritability, lethargy, stereotyped behavior, hyperactivity, inappropriate speech and total score on the ABC (the Aberrant Behavior Checklist) significantly improved in the folinic acid group as compared with the placebo group. Stereotypic behavior and total score significantly improved for the folinic acid group as compared with the placebo group on the ASQ (Autism Symptoms Questionnaire). Internalizing problems significantly improved for the folinic acid group as compared with the placebo group on the BASC (Behavioral
Assessment System for Children 2nd Edition). [12]

Another study was conducted by University Hospital of Nancy (France) in ASD children aged between three and ten years. 19 participants were divided into two groups. The study was designed as a double-blind placebo controlled trial. Because of the placebo capsules were made separately the study was considered single-blinded. Children either were given 2x5mg folinoral (n=9) or placebo (n=10) for duration of 12 weeks. The inclusion and exclusion criteria were strict. Eligible participants could not have received any treatment that might interfere with folate metabolism, such as excessively high levels of B12 and folate intake, vitamins and minerals beyond recommended amounts, major irritability, gastroesophageal reflux, recognized liver or kidney diseases, been born before 37th gestational week or experienced lactose intolerance. Any genetic abnormality was also one of the exclusion criteria. The results were assessed using the Autism Diagnostic Observation Schedule (ADOS) and the Social Responsiveness Scale (SRS). After 12 weeks, the ADOS global score and social interaction and
communication sub scores saw a noteworthy increase in children who were taking folinic acid, but no notable change was observed in the placebo group. They observed a greater change of ADOS global score and social interactions in the folinic acid group, compared to the placebo group. The research showed that there was no increased SRS score. What is really worth emphasizing is the fact that no major negative effects were reported from folinic acid intake. [13]

Another interesting study was conducted at the autism clinic in children's outpatient clinic of Roozbeh Hospital (Tehran University of Medical Sciences, Tehran, Iran) from November

2018 to April 2019. This time the scientists investigated the role of folinic acid as an adjuvant to risperidone on inappropriate speech and other behavioral symptoms of ASD. It was a double-blind, placebo-controlled randomized clinical trial with 55 participants. Eligible to participate in the study were children between the ages of 4 and 12 who exhibited indicators of a mental disorder as outlined in the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders. Diagnosis and severity of ASD were verified by a child psychiatrist and individuals with autism who did not have severe enough symptoms that needed treatment with risperidone were not included in this research. The participants who met the inclusion criteria were divided randomly into two separate groups, one being given folinic acid (daily dosage 2 mg/kg up to 50 mg per day for the entire course of the trial n=28) and the other were receiving capsules containing placebo n=27. Both groups were given risperidone starting at a dose of 0.5 mg with a dose increase of 0.5 mg per week (for the first three weeks). The risperidone dosage was maintained at the dose of risperidone at the end of week 3 for the rest of the study. If necessary, the dose of risperidone was adjusted. Adjustments were made based on the clinical assessment of the participants. The maximum dosage of risperidone for children below 20 kg was 1 mg/day, and for children equal to 20 kg or heavier was 2 mg/day, respectively. Each enrolled patient was observed carefully beginning at the start of the study and then at 5 week and 10 week intervals. This study evaluated the changes in the score for the inappropriate speech subscale, as well as the mean changes in lethargy/social withdrawal, stereotypic behavior, hyperactivity/noncompliance, and irritability subscales of ABC-C (aberrant behavior checklist-community), and the frequency of adverse events from baseline/screening to the study endpoint. The ABC-C inappropriate speech subscale score showed a larger improvement in the group taking folinic acid than in the group taking the placebo. Differences between the folinic acid and placebo groups were evident in the ABC-C stereotypic behavior and hyperactivity/noncompliance scores between the beginning and conclusion of the study, with the folinic acid group demonstrating significant improvements in both measures. There was no significant difference in Lethargy/Social Withdrawal subscale score noticed between the patients receiving folinic acid and those taking the placebo. However, the irritability subscale score of the folinic acid group showed a significantly greater decrease. It is also important to note that no severe side effects were found during this trial. [14]

**Role of vitamin D3**

Vitamin D3 is a fat-soluble vitamin that helps regulate the calcium and phosphorus levels in the body. Vitamin D3 also stimulates the body to absorb both calcium and phosphorus more effectively and plays important role in preventing osteoporosis and decalcification of teeth. It can be found in various foods. Mainly in fatty fish such as eel, salmon, herring, mackerel and sardines. Large amounts of it are also provided by fish fats, e.g. cod liver oil and tuna [15]. Other great sources include egg yolks, fortified cereals, and dairy products. In our bodies the natural source of vitamin D is endogenous synthesis in the skin, which is able to provide up to 90% of this vitamin. It is formed under the influence of UVB radiation from the sun [16]. However, a number of factors determine how much vitamin D the skin can synthesize. Factors including: latitude, season of the year and time of day, as well as individuals' skin complexion, body weight and amount of body fat can lead to insufficient production of endogenic vitamin D [15]. Therefore, the synthesis in the skin is not always able to cover the body's need for vitamin D. The reason for this may be, for example, insufficient exposure to the sun, covering the body with clothes or using cosmetics with a protective filter that absorbs UVB7 radiation [17]. Children with autism spectrum disorder often suffer from hypersensitivity. It often presents as food selectivity which can lead to deficiency of vitamin D3. To date, several investigations have discovered that ASD patients had lower vitamin D concentrations in comparison to those healthy control groups [18,19]. These findings lead to another trials focusing on possible benefits of supplementation of vitamin D.

In 2017 scientists from Jilin University conducted a study that recruited children with Autism Spectrum Disorder from the Pediatric Neurology and Neuro-Rehabilitation Department. In this study they were trying to asses if vitamin D3 supplementation would be beneficial in improving the outcome in patients with ASD. In this trial, a total of 215 children with Autism Spectrum Disorder and 285 healthy children were recruited. Thirty-seven of those with ASD received vitamin D3 treatment, which was monitored through the use of both the Autism Behaviour Checklist (ABC) and the Childhood Autism Rating Scale (CARS) before and after a three-month period. Additionally, blood samples were taken to measure serum 25 (OH) D levels.

The results of the CARS and ABC scores indicated that vitamin D3 supplementation can reduce symptoms of ASD. The levels of 25(OH) D in the blood of ASD children was substantially lower than of that in typically developing children. Symptom scores were significantly reduced in the group receiving vitamin D supplementation. This was especially true for younger children with ASD, as they showed more pronounced treatment effects.

These findings suggest that vitamin D deficiency might be involved in ASD etiology and that providing vitamin D3 supplementation, which is a safe and economical form of treatment, might help improve the outcomes for some children with ASD, particularly the younger ones. However, the study was not a double bling, placebo controlled trial, and the number of participants was not big. Therefore, we need to consider the results with restraints. Nonetheless more research should be done as it shows great potential as an adjuvant to therapy. [20]

Another study published in 2017 was conducted as double-blind, randomized, placebo controlled trial. The study was carried out at the National Children's Hospital in Dublin, Ireland. 42 children with ASD, who met inclusion criteria, were recruited and randomly placed in placebo (n=20) or vitamin d3 group (n=22). Participants were given either daily doses of 2000 IU of vitamin D3 or a placebo for a duration of 20 weeks. The ABC Stereotypic Behavior subscale was used to measure progress after each participant's individual baseline assessment and after 20 weeks of supplement intake. This subscale was selected as the primary indicator of success. The other results of the investigation included additional subscales from the ABC, the Social Responsiveness Scale and a score on the Developmental Disabilities—Children’s Global Assessment Scale (DD-CGAS) along with the biochemistry of the total vitamin D levels. 38 children completed the trial. After taking vitamin D3 supplements, there was a marked rise in 25(OH)D to 83.8 nmol/L (p=0.0016) but it had no bearing on the main result. However, there was a visible improvement to self-care as determined by the DD-CGAS assessment (p=0.02). On the other hand, there seemed to be a decline in inappropriate conversational behavior in the placebo group. This study found that taking Vitamin D supplements did not make much of a difference when measuring the primary outcome in children with ASD, and the effects were not consistent either. Nonetheless, considering small group of participants we should conduct other trials on bigger scale. [21]

**Conclusion**

As the prevalence of ASD is still increasing, we should try and research further in hopes of better understanding the etiology and possible managements of this disorder. With more information we can provide more comfort and tools to help families and therapist who are working with patients with ASD. From this review we may conclude that both vitamin D3 and folic acid supplementation may be beneficial for communication development and

management of symptoms of ASD. However further research should be conducted on larger scale. We should focus not only on clinical trials but also conduct retrospective research on mothers, focusing on pregnancy and nutrient deficiency during this period. Given the data, supplementation and dietary changes should be implemented in patients with ASD. Dietary intervention should promote healthy, versatile diet, rich in vitamins.

## Author Contributions

Małachowska D -concept, original draft preparation; Małachowska D., Świercz A., Tołwiński I., Kędzierska Z., Shved K., Żurek U., Dadas K., Ciecierski-Koźlarek H., Antkowiak K.- writing, review and editing. All authors have read and agreed to the published version of the manuscript.

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Publicly available datasets were analyzed in this study. This data can be found here: https://www.ncbi.nlm.nih.gov/.

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## Conflicts of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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