

# **The association of low Vitamin D levels with Autism Spectrum Disorder**

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## **Abstract**

Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by social communication and interaction impairment and repetitive behaviors and has lifelong impacts (1). ASD is likely to have both genetic and environmental components, and more than 1,000 genes are registered in SFARI (Simon's Foundation Autism Research Initiative) gene database related to this disorder (1, 2). SFARI uses human genetics to develop studies identifying additional genes involved in ASD (3). Autism is very complex and many environmental and epigenetic factors also involved but the role of all these factors to ASD etiology are incompletely understood (1, 2). Vitamin D as an important factor for brain functions like neuronal differentiation, maturation and growth has been researched as an important factor in the development of autism recently (4, 5).

## **Introduction**

Autism is a multifactorial complex disorder with both genetic and environmental components (6). The number of diagnosed cases of autism has increased greatly in recent years and its prevalence has become worrying; due to this high prevalence of ASD, many large epidemiological studies have been conducted in recent years and it has been observed that ASD prevalence has increased on all continents (6, 7). Autism is a complex and diverse behavioral disorder with various phenotypes and symptoms, which have been divided into several subgroups: Autistic Disorder (AD), Asperger Syndrome (AS) and Pervasive Developmental Disorder Not Otherwise Specified (PDD-NOS) (8). Most autistic children show symptoms during the first three years of life but sometimes the disorder becomes diagnosable later in life (8). ASD is a behaviorally defined disorder with patients exhibiting abnormal eye contact, lack of social smiling, poor attention, lack of appropriate facial expressions, problems with expressing and understanding certain emotions, difficulty in understanding other's moods, preferring minimal changes to routines, impaired expressive language, preferring to play individually and having restricted ways of using toys. Generally autism also involves general difficulty having relationship with others and preferring to live independently, having repetitive behaviors, and hypo- or hypersensitivity to environmental stimulus (5, 8-10). Studies suggest that 75% of autistic children have learning difficulties (9).

Autism is a very challenging disorder to diagnose due to its variable range and level of function, some of which not becoming obvious until mid-childhood. As a result of this frequently delayed diagnosis, children often have inadequate medical care (9, 11). Besides genetics, many environmental factors have been found to be associated with ASD including folic acid deficiency, neonatal hypoxia, maternal obesity, gestational diabetes mellitus, exposure to infection during prenatal and early life periods, obstetric

complications, exposure to toxins, and many nutritional triggers. Recent studies have suggested that gestational vitamin D deficiency is another environmental risk factor (5, 6, 10). In 2008, Cannel published his hypothesis that low vitamin D status during fetal period or childhood could be an environmental factor for ASD (8). The interaction between genetics and environmental factors for ASD is the subject of many recent studies; most studies show that children with ASD have low levels of 25-hydroxy Vitamin D (25(OH)D), so Vitamin D deficiency can be an environmental factor (4).

The active form of Vitamin D is 1, 25-dihydroxyvitamin D (calcitriol) (2). A large number of genes associated with autism (223 out of 1053) are regulated by calcitriol (2). The most well-known role of Vitamin D is in bone health and skeletal systems via calcium homeostasis, but normal levels of VD also required for healthy functioning of immune, reproductive, epithelial, cardiovascular, muscular and nervous systems. It is important for regulation of calcium and phosphate metabolism, auto-antibody production and deficiency has been linked to the development of some autoimmune disorders (5, 12, 13).

Vitamin D is a fat-soluble secosteroid hormone that regulates the expression of 900 genes with many important roles in the human body (2, 14). Vitamin D comprises two compounds: Vitamin D2, which comes from diet, and Vitamin D3 which comes from both diet and endogenous synthesis (14). 90% of Vitamin D3 synthesis occurs in the skin with exposure to sunlight. Some sources of Vitamin D are fatty fish, fish oil, egg yolk and margarines, but dietary sources are limited (12, 15). The role of sunlight exposure, i.e., level of UV-B light, is very important for Vitamin D synthesis, and this can be affected by seasons, geography, the weather, skin pigmentation and age. Vitamin D deficiency is logically more common in winter and in dark-skinned persons but it is increasing and common in all over the world, especially in pregnant women (12, 15).

Vitamin D2 (ergocalciferol) and Vitamin D3 (cholecalciferol) are biologically inactive pre-vitamins necessary for the production of the biologically active calcitriol. Vitamin D2 and vitamin D3 undergo modification in the liver and produce 25-hydroxy vitamin D (calcidiol). Calcidiol is the circulating form of vitamin D and has a 6-8 weeks biological half-life and can be stored in body. Measurements of calcidiol are standard for determining vitamin D deficiency. Calcidiol is biologically inactive and is converted into the fully active 1, 25-dihydroxymetabolite (calcitriol) in the kidneys by 25-hydroxy vitamin D-1a hydroxylase, an enzyme induced by parathyroid hormone (PTH). Calcitriol is biologically active but is only stable for a few minutes. The stable form is very important for calcium/phosphate homeostasis, regulation of cell proliferation and degeneration in many tissues and organs like immune cells (13, 14, 16).

Although Vitamin D has a crucial role in early life on brain development, it also has important roles in adulthood and acts as a neurosteroid that regulates immunomodulation and brain function, among other things (14).

### **Vitamin D's role in brain development**

Recent research has suggested a link between vitamin D deficiency and many neurological diseases like multiple sclerosis (MS), depression, schizophrenia, autism, Alzheimer's and Parkinson's (2, 16). Based on many animal and human studies, the vitamin D receptor is found abundantly in the brain, particularly in the cortex, hippocampus, amygdala, thalamus, substantia nigra (6, 14, 17). Variants in genes coding for subunits of calcium channels are linked to risk of schizophrenia and ASD, and the active form of vitamin D affects the function of these calcium channels (5). Vitamin D is important for DNA repair and protects DNA from oxidative stress-associated damage. Interestingly, autistic children often exhibit increased oxidative stress (13).

It's hypothesized that hyperactivation of mTOR signaling affects the expression of autism-related genes and also core symptoms of autism. Vitamin D deficiency could be a reason for this hyperactivation. About 79% of high scored genes from SFARI gene database are connected to mTOR signaling activity and are dependent on vitamin D3 availability (directly or indirectly). The mTOR signaling pathway regulates intra- and extracellular signals like growth factors, nutrients, stress, infections, immune response, cell and tumor growth, long-term synaptic plasticity and memory formation. mTOR signaling plays a pathogenic role in numerous neurological disorders like epilepsy, autism, intellectual disability, dementia, traumatic brain injury, brain tumors and hypoxic-ischemic injury (2).

In this study, we investigate the quality and quantity of evidence for a significant role of vitamin D as a neurosteroid in brain development relevant to Autism Spectrum Disorder.

### **Methods**

For this study I examined a diverse range of articles on the association between low Vitamin D levels with Autism Spectrum Disorder and conduct a systematic review using NCBI/PubMed as a research tool using key words like "Autism", "Autism and Vitamin D deficiency", "Vitamin D and neurological development". I include articles from diverse countries and include meta-analyses, systematic and clinical reviews, and research articles, targeting the period from 2011 to 2020.

## Results

Many studies have described associations of vitamin D serum levels with autism spectrum disorder. Vinkhuyzen *et al*/ studied the levels of 25(OH)D in the gestational period, finding that 25(OH)D deficiency at mid-gestation and at birth is related to autism and can increase the risk of ASD in 6 year-old children (5). In another study by the same group done in 2017 on vitamin D levels at mid-gestation and at birth found more vitamin D deficiency in ASD children than non-ASD children (18). In 2019, a Swedish population-based cohort study was published showing that low vitamin D levels in maternal and neonatal blood samples were associated with increased risk of ASD (15). Another study published in 2012 on autistic children showed that 25(OH)D serum levels are significantly lower in autistic children than healthy controls and healthy children didn't have vitamin D deficiency (13). Likewise, a Brazilian study found that 25(OH)D serum levels in autistic children were low and they frequently were vitamin D deficient (10). An Egyptian study published in 2010 measuring the vitamin D levels in autistic children found that the levels of both 25(OH)D and 1,25(OH)<sub>2</sub>D were lower in autistic children (19).

According to Bener *et al*/, vitamin D supplements can decrease the risk of autism and can be very effective for the prevention of autism and also autoimmune diseases (4). Some studies also demonstrate that vitamin/mineral supplementation can improve metabolic status in children with autism and reduce symptoms (20).

## Discussion

Autism spectrum disorder (ASD) is increasing in all over the world and this trend is very worrying. ASD has both hereditary and environmental components. Vitamin D deficiency as an environmental risk factor that has attracted widespread attention. Vitamin D has important roles in brain development and function whereas vitamin D deficiency nowadays is very common and an increasing problem around the world especially among pregnant women.

Many studies investigating the role of vitamin D deficiency as a risk factor for neurodevelopmental disorders especially ASD and many animal and human studies confirm the role of VD in processes involved in ASD and also its importance in normal brain development(8, 10). Many studies on vitamin D concentrations during the fetal period, early childhood and also autistic children, comparing them with healthy control groups, demonstrate relationships between low serum levels of 25(OH)D and the risk of ASD (5, 6, 12, 13).

In conclusion, there have been many studies demonstrating a relationship between VD levels and autism, but more case-control studies are necessary to prove

causation (6). It should be noted that some studies have not observed statistical differences in Vitamin D levels in autistic children, an example being a study by Bicikova *et al* in 2019 (16, 18). Additional molecular studies are also needed to better understand the role of vitamin D in brain development, the relationship of vitamin D deficiency with autism and the role of vitamin D supplementation in decreasing ASD symptoms in patients.

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