

# Vitamin D and mental disorders: update on the latest evidence and focus on autism and anorexia

VITAMIN D

UpDates

2024;7(1):10-13

<https://doi.org/10.30455/2611-2876-2024-2e>

**Alessandro Cuomo, Simone Pardossi, Matteo Cattolico, Giovanni Barillà, Andrea Fagiolini**

*Department of Mental Health and Sense Organs, University of Siena*

## Summary

Vitamin D, originally associated with calcium regulation and bone health, is emerging as a crucial element within the scope of mental health, not only for disorders such as depression and schizophrenia, but also for autism and eating disorders. The presence of vitamin D receptors in several brain regions suggests that its role in neuroprotection, neurogenesis and neuroimmunological regulation is significant. Vitamin D deficiency in early life is associated with an increased risk of developing schizophrenia and low vitamin D levels have been correlated with depression, and with evidence for the use of vitamin D supplementation in reducing depressive symptoms. Although low vitamin D levels have been observed in children with autism spectrum disorders and mothers during pregnancy, causality is still complex. Patients with eating disorders show vitamin D deficiency, with implications for bone and mental health, and vitamin D may also have a link to impulsivity in these cases. Vitamin D supplementation may improve some symptoms, but further research is needed to fully understand the underlying mechanisms. This overview emphasises the importance of vitamin D for mental health and the need for further studies to clarify causal relationships and develop more effective therapies for neuropsychiatric disorders.

## INTRODUCTION OF VITAMIN D IN PSYCHIATRY AND POTENTIAL MECHANISMS OF ACTION

In recent years, vitamin D has become quite relevant to the context of mental health. Recent studies have significantly broadened knowledge of its role well beyond calcium homeostasis and bone health, exploring its implications in the neuropsychiatric field. Research has progressively elucidated the relationship between vitamin D and several mental conditions, including disorders such as depression and anxiety.

In the context of psychiatric disorders, vitamin D is involved in the region-specific expression of vitamin D receptors (VDR) in areas such as the cingulate cortex, thalamus, cerebellum, substantia nigra, amygdala and hippocampus. The presence of vitamin D, VDR and related enzymes in many regions in the brain has elucidated the role of vitamin D as a neuroactive/neurosteroid hormone as fundamental in the processes of neuroimmunomodulation, neuroprotection, neurogenesis, and normal brain function<sup>1</sup>. Indeed, vitamin D

deficiency in early life negatively affects these processes: children with low vitamin D levels, for example, have a higher risk of developing disorders such as schizophrenia<sup>2</sup>. Recently, an additional significant role of vitamin D in the differentiation of dopaminergic neurons has been identified. A 2023 study showed that continual exposure to the active vitamin D hormone increases the ability of developing neurons to produce and release dopamine, thus establishing vitamin D as an important differentiating agent for developing dopaminergic neurons.<sup>3</sup>

Therefore, vitamin D influences mental disorders such as anxiety, depression and schizophrenia through different mechanisms. Moreover, in an expansion of the understanding of its impact on mental health, recent studies have also explored vitamin D's role in relation to autism and eating disorders.

## VITAMIN D AND PSYCHIATRIC DISORDERS: THE LATEST EVIDENCE

Studies have suggested that there is a relationship between vitamin D deficiency during

### Correspondence

**Alessandro Cuomo**

[alessandrocuomo86@gmail.com](mailto:alessandrocuomo86@gmail.com)

### Conflict of interest

The authors declare no conflict of interest.

**How to cite this article:** Cuomo A, Pardossi S, Cattolico M, et al. Vitamin D and mental disorders: update on the latest evidence and focus on autism and anorexia. *Vitamin D – Updates* 2024;7(1):10-13. <https://doi.org/10.30455/2611-2876-2024-2e>

© Copyright by Pacini Editore srl



OPEN ACCESS

This is an open access article distributed in accordance with the CC-BY-NC-ND (Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International) license. The article can be used by giving appropriate credit and mentioning the license, but only for non-commercial purposes and only in the original version. For further information: <https://creativecommons.org/licenses/by-nc-nd/4.0/deed.en>

development and increased risk of schizophrenia and depression. Depression may exacerbate vitamin D deficiency by reducing exposure to sunlight, while symptoms of deficiency may in turn worsen the depressive state (Fig. 1)<sup>1</sup>.

Recently, a meta-analysis that reviewed randomised placebo-controlled trials showed that vitamin D supplementation in deficient individuals significantly reduced depressive symptoms in those diagnosed with major depressive disorder and mild depressive symptoms.<sup>4</sup> In addition, a recent cross-sectional analysis conducted in the United States examined the association between vitamin D deficiency, age and depression. The analysis took demographic features, depressive symptom characteristics and blood levels of vitamin D into consideration and revealed a significant association between vitamin D deficiency and the risk of depression<sup>5</sup>.

Similarly, a meta-analysis that summarised evidence from several randomised controlled trials showed that vitamin D supplements were significantly superior to placebo in reducing depressive symptoms in adults, with a particularly marked effect in those with more severe depression and those with lower levels<sup>6</sup>.

Other studies showed that although vitamin D supplementation could not only reduce the development of depressive symp-

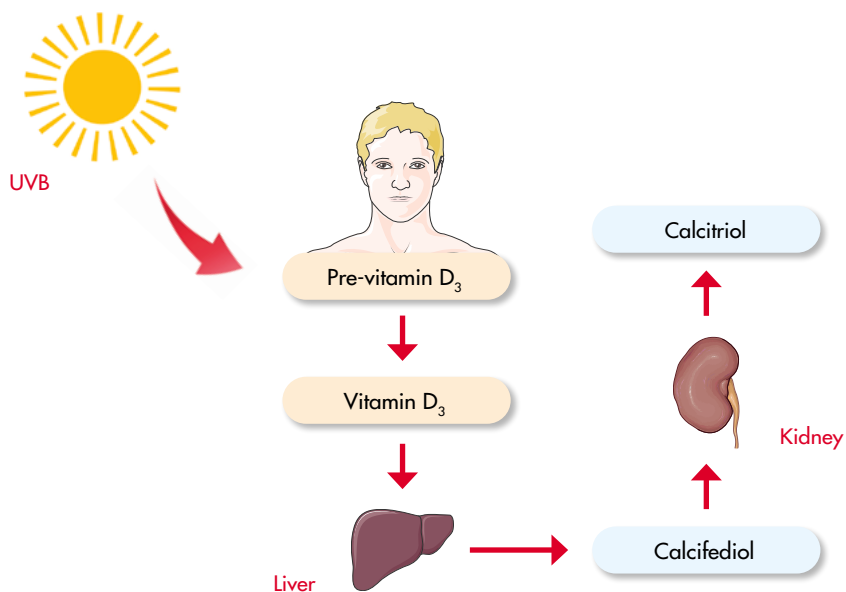
tom, higher serum levels of vitamin D could also reduce the risk of that development, which highlights that subjects with lower blood levels of vitamin D were more likely to develop depression.

Furthermore, a negative correlation has been shown between low vitamin D levels during the first trimester of pregnancy and the development of depressive symptoms in the second trimester, as well as an increased risk of peripartum depressive symptoms following Vitamin D deficiency in the second trimester<sup>7</sup>. A recent randomised controlled trial also showed that vitamin D supplementation during the first two years of life reduced the risk of disorders such as anxiety and depression at the age of 6-8 years<sup>8</sup>. There is a 70% prevalence of vitamin D deficiency among schizophrenic patients compared to a prevalence of 37.6% in the general population.

People born in winter and spring have a slightly increased risk of developing schizophrenia, which could be due to certain seasonal environmental factors such as infections being more common in the colder months and also to reduced exposure to sunlight. In particular, a correlation has been observed between vitamin D deficiency in pregnant women and infants during these months and an increased risk of schizophrenia. ultraviolet radiation during winter in high latitude

sites may not be enough to trigger the reaction necessary for the production of the vitamin D precursor<sup>9</sup>. The risk of schizophrenia is also higher in the offspring of dark-skinned migrants in some countries. Factors related to social marginalisation and migratory stress have been linked to an increased risk of mental disorders in general, including schizophrenia. However, individuals with pigmented skin living in cold climates are at higher risk of vitamin D deficiency, because pigmented skin acts as a natural sunscreen and reduces the production of the vitamin D precursor<sup>10</sup>. Additionally, it has been shown that those who migrated to the Netherlands as children have an increased risk of later schizophrenia (compared to those who have migrated as adults). This may suggest the presence of a critical exposure window, i.e. an age range in which exposure to vitamin D deficiency may increase the risk of neurodevelopmental disorders<sup>10</sup>.

Finally, a 2023 analysis showed a shared genetic architecture between schizophrenia and vitamin D levels, identifying new risk loci and highlighting a complex mechanism of genetic overlap between vitamin D deficiency and schizophrenia. These findings suggest that shared genetic variants may influence the clinical picture by contributing to the coexistence of schizophrenia and vitamin D deficiency<sup>11</sup>.



- Patients with major depression have lower blood levels of vitamin D
- Vitamin D supplementation in deficient depressive patients can improve depression symptoms

- A 70% prevalence of vitamin D deficiency is reported in patients with schizophrenia
- There is a complex genetic overlap between vitamin D deficiency and schizophrenia

**FIGURE 1.**

Vitamin D, obtained through UVB exposure and subsequent biotransformation in the liver and kidneys, may be involved in different mental disorders. Its deficiency, in fact, may be related to major depression and schizophrenia.

## VITAMIN D AND AUTISM

The aetiology and pathogenesis of autism spectrum disorders (ASD) are complex and have not been fully elucidated. Since the early 1980s, autism research has moved beyond the theory of “inadequate parental care”, focusing on biological causes. It has been discovered that ASD is a neurodevelopmental disorder caused by the interaction of genetic and environmental factors. Over 1,000 genes have been linked to ASD and there is a higher concordance between monozygotic twins than between dizygotic twins, suggesting a strong genetic role. However, only 25-30% of children with ASD show ASD-related genes, highlighting the importance of environmental factors. Factors such as nutrition, drugs, toxic substances, maternal infections during pregnancy, stress and vaccinations have also been associated with ASD. Some children with ASD have elevated serotonin levels and abnormalities in dopamine function, as well as disorders in brain structure and connections. Immunological studies have also indicated an altered immune balance. Vitamin D deficiency, linked to factors such as air pollution, climatic conditions and latitude, has been proposed as a possible cause of ASD<sup>12</sup>.

A systematic review and meta-analysis has shown that children with ASD have significantly lower serum vitamin D levels than controls without a diagnosis of ASD.<sup>13</sup> In addition, both low maternal blood vitamin D levels and low infant blood vitamin D levels correlate significantly with an increased risk of a subsequent ASD diagnosis<sup>13</sup>. Apparently, there is also an ambiguous causal relationship with vitamin D deficiency for this disorder: children with ASD have different lifestyle habits, including a more selective and less varied diet, which leads to lower vitamin D intake. These children also tend to spend less time in outdoor activities, reducing exposure to the sun's UVB rays and, consequently, reduced vitamin D synthesis in the skin. Another factor that may influence vitamin D levels is genetic, linked to variants in vitamin D metabolism and receptor genes associated with ASD risk. Finally, the use of certain medications, such as anti-epileptic drugs, may also cause a reduction in vitamin D levels.

In any case, the therapeutic potential of vitamin D supplementation in children with ASD has been explored in several studies. Specifically, though it has been shown that supplementation in deficient individuals can improve some ASD symptoms, especially

stereotypic behaviour, it does not significantly affect other major symptoms or coexisting conditions<sup>14</sup>.

The mechanisms underlying the relationship between vitamin D and ASD have yet to be fully elucidated. Vitamin D is known to play roles in brain development, immune function and inflammation, which are relevant to ASD. Vitamin D has been shown to modulate inflammatory cytokines, influence antioxidant pathways, and regulate neurotransmitters such as serotonin, all of which are crucial in the context of ASD<sup>13</sup>. Furthermore, vitamin D interacts with several ASD-associated genes and its deficiency may disrupt neurodevelopmental processes<sup>13</sup>. Nevertheless, there are limitations in current research, including heterogeneity in study designs, vitamin D dosing regimens and participant characteristics, which challenge the formulation of definitive conclusions. The variability in response to vitamin D supplementation among individuals with ASD suggests that genetic and environmental factors may influence its efficacy.

## VITAMIN D, EATING DISORDERS AND THE ROLE OF IMPULSIVITY

Patients with anorexia nervosa (AN) were shown to have significantly lower serum vitamin D levels, both in the form of 25-hydroxyvitamin D [25(OH)D] and 1,25-dihydroxyvitamin D [1,25(OH)D], than controls<sup>15</sup>.

Low serum 25(OH)D levels can lead to the bone loss typical of AN, resulting in reduced bone mineral density and a higher frequency of clinical and non-clinical fractures compared to healthy adolescents. It is therefore important to take vitamin D values into account, not only for the health of bone tissue, but also for the role vitamin D plays in other mental disorders that often afflict patients with AN<sup>15</sup>.

A meta-analysis revealed that patients with AN showed significantly lower serum vitamin D levels than controls despite similar vitamin D intake. Several elements can be taken into account to justify these data: patients with AN tend to overestimate their food intake, which could lead to an inconsistent assessment of micronutrient intake. Furthermore, not all physical activities have similar effects in maintaining optimal 25(OH)D levels. It can be the case that patients with AN spend more time indoors rather than participating in outdoor activities or that they wear clothes that cover more of the body, thus reducing light exposure and skin synthesis of vitamin D.

Although low serum 25(OH)D levels are typical in obese people due to higher fat mass, increasing research has shown that low serum 25(OH)D levels have also been associated with underweight states, such as malnutrition, neoplastic cachexia and AN<sup>15</sup>.

Finally, patients with AN also have lower serum levels of the active form of vitamin D, 1,25(OH)D. Levels of this latter form have little relation to 25(OH)D stores and are regulated mainly by parathyroid hormone (PTH) levels. Under conditions of low serum 25(OH)D levels, the active form of vitamin D usually increases, instead of decreasing, as observed in patients with AN. This imbalance between 1,25(OH)D and 25(OH)D in AN could be explained by the low serum levels of oestrogen in these patients, hormones that appear to be important 1-alpha hydroxylase agonists<sup>15</sup>.

A recent pilot study has also showed that in a population of 236 patients with eating disorders, vitamin D levels could be correlated with the presence of impulsive behaviour<sup>16</sup>. Impulsivity is considered to be implicated in the onset and outcome of several eating disorders. Specifically, neuroimaging investigations have shown an imbalance between the frontal and mesolimbic areas in patients with these disorders.<sup>16</sup> Vitamin D supplementation could be considered as part of the therapeutic approach for symptom control and relapse prevention in individuals with eating disorders, as has already been tested in patients diagnosed with attention-deficit/hyperactivity disorder (ADHD) or suicidal behaviour<sup>16</sup>.

### KEY MESSAGE ON AUTISM AND ANOREXIA

The involvement of vitamin D and its deficiency in disorders such as autism and anorexia nervosa has recently been hypothesised.

- Low levels of vitamin D in maternal and newborn blood correlate with an increased risk of a subsequent diagnosis of autism
- Supplementation in deficient individuals can improve stereotypical behaviour
- Patients with anorexia nervosa showed lower vitamin D levels than controls despite similar vitamin D intake
- Vitamin D levels correlated with the presence of impulsive behaviour

## CONCLUSIONS

A review of recent literature has sketched out a picture in which vitamin D is a potentially influential element in several mental disorders. In addition to the most studied correlations with depression and schizophrenia, recent literature has also produced evidence on the relationship between vitamin D and disorders such as autism and eating disorders. Although findings suggest a correlation between vitamin D deficiency and the manifestation and severity of these disorders, a causal relationship has not yet been clearly delineated. Specifically, in disorders such as autism and anorexia nervosa, vitamin D appears to play a role in both the development and exacerbation of symptoms. Still, it is crucial to consider that this association may not be unique. Clearly, further research is needed to understand whether vitamin D deficiency is a causal factor, a consequence or a concomitant element of these disorders. This review also highlighted how therapeutic interventions based on vitamin D supplementation may benefit mental disorders. The growing body of evidence on the relationship between mental disorders, such as schizophrenia and depression, and vitamin D lays the foundation for further investigation of the relationship between vitamin D and other psychiatric disorders, as well as the use of vitamin D supplementation in patients with mental disorders.

## References

- 1 Cuomo A, Beccarini Crescenzi B, Nitti M, et al. Vitamina D e malattie psichiatriche: analisi delle possibili relazioni di causalità. *Vitamin D – Updates* 2021;4:30-33. <https://doi.org/10.30455/2611-2876-2021-3>
- 2 Eyles DW, Burne THJ, McGrath JJ. Vitamin D, effects on brain development, adult brain function and the links between low levels of vitamin D and neuropsychiatric disease. *Front Neuroendocrinol* 2013;34:47-64. <https://doi.org/10.1016/j.yfrne.2012.07.001>.
- 3 Pertile RAN, Brigden R, Raman V, et al. Vitamin D: a potent regulator of dopaminergic neuron differentiation and function. *J Neurochem* 2023;166:779-789. <https://doi.org/10.1111/jnc.15829>
- 4 Mikola T, Marx W, Lane MM, et al. The effect of vitamin D supplementation on depressive symptoms in adults: a systematic review and meta-analysis of randomized controlled trials. *Crit Rev Food Sci Nutr* 2023;63:11784-801. <https://doi.org/10.1080/10408398.2022.2096560>
- 5 Mo H, Zhang J, Huo C, et al. The association of vitamin D deficiency, age and depression in US adults: a cross-sectional analysis. *BMC Psychiatry* 2023;23:534. <https://doi.org/10.1186/s12888-023-04685-0>
- 6 Srifuengfung M, Srifuengfung S, Pummangura C, et al. Efficacy and acceptability of vitamin D supplements for depressed patients: a systematic review and meta-analysis of randomized controlled trials. *Nutrition* 2023;108:111968. <https://doi.org/10.1016/j.nut.2022.111968>
- 7 Xie F, Huang T, Lou D, et al. Effect of vitamin D supplementation on the incidence and prognosis of depression: An updated meta-analysis based on randomized controlled trials. *Front Public Health* 2022;10:903547. <https://doi.org/10.3389/fpubh.2022.903547>
- 8 Sandboge S, Rääkkönen K, Lahti-Pulkkinen M, et al. Effect of vitamin D<sub>3</sub> supplementation in the first 2 years of life on psychiatric symptoms at ages 6 to 8 years: a randomized clinical trial. *JAMA Netw Open* 2023;6:e2314319. <https://doi.org/10.1001/jamanetworkopen.2023.14319>
- 9 Cui X, McGrath JJ, Burne THJ, et al. Vitamin D and schizophrenia: 20 years on. *Mol Psychiatry* 2021;26:2708-2720. <https://doi.org/10.1038/s41380-021-01025-0>
- 10 Albiñana C, Boelt SG, Cohen AS, et al. Developmental exposure to vitamin D deficiency and subsequent risk of schizophrenia. *Schizophr Res* 2022;247:26-32. <https://doi.org/10.1016/j.schres.2021.06.004>
- 11 Jaholkowski P, Hindley GFL, Shadrin AA, et al. Genome-wide association analysis of schizophrenia and vitamin D levels shows shared genetic architecture and identifies novel risk loci. *Schizophr Bull* 2023;49:1654-1664. <https://doi.org/10.1093/schbul/sbad063>
- 12 Wang J, Huang H, Liu C, et al. Research progress on the role of vitamin D in autism spectrum disorder. *Front Behav Neurosci* 2022;16:859151. <https://doi.org/10.3389/fnbeh.2022.859151>
- 13 Wang Z, Ding R, Wang J. The association between vitamin D status and autism spectrum disorder (ASD): a systematic review and meta-analysis. *Nutrients* 2020;13:86. <https://doi.org/10.3390/nu13010086>
- 14 Zhang M, Wu Y, Lu Z, et al. Effects of Vitamin D supplementation on children with autism spectrum disorder: a systematic review and meta-analysis. *Clin Psychopharmacol Neurosci* 2023;21:240-251. <https://doi.org/10.9758/cpn.2023.21.2.240>
- 15 Veronese N, Solmi M, Rizza W, et al. Vitamin D status in anorexia nervosa: a meta-analysis. *Intl J Eating Disorders* 2015;48:803-813. <https://doi.org/10.1002/eat.22370>
- 16 Todisco P, Meneguzzo P, Vogazianos P, et al. Relation between vitamin D and impulse behaviours in patients with eating disorder: a pilot observational study. *Euro Eating Disorders Rev* 2020;28:587-593. <https://doi.org/10.1002/erv.2740>