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Review

# Autism and lack of D3 vitamin: A systematic review

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ABSTRACT

Autism Spectrum Disorder (ASD) is a complex neurodevelopmental disorder characterized by social communication deficits and restricted, repetitive patterns of behavior. Several medical conditions including gastrointestinal (GI) problems, asthma and allergies have been associated with ASD, and multiple risk factors, both genetic and environmental, have been proposed. Among them, vitamin D (VD) deficiency is probably associated with ASD, and may play a role in the condition.

We conducted a systematic review of the literature for the period January 1, 2010 through June 15, 2014, according to PRISMA guidelines, aiming to investigate the complex biological interplay between VD, metabolism, immune system and nervous system in ASD.

Different trends in the association between ASD and VD deficiency have been observed, and factors such as gender, ethnicity, sampling, and methodology play a role in the results and outcomes.

At present, for at least a subgroup of ASD individuals, an imbalance in VD metabolism probably exists and may be associated with the condition. In this cohort, VD replacement in these individuals might contribute to improving ASD symptoms and/or associated conditions. This topic is an important challenge for future research, and could lead to a new tailored therapeutic approach for VD in ASD.



**Contents**



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## 1. Introduction

Vitamin D (VD) is a group of several fat-soluble molecular forms of 9,10-secosteroids transformed via metabolic cascade into its active form, i.e., the multifunctional hormone calcitriol. $VD_2$ (ergocalciferol) and $VD_3$ (cholecalciferol) are the two most important molecules in humans and play a complex role in the body. They are primarily involved in bone metabolism and calcium physiology (Christodoulou, Goula, Ververidis, & Drosos, 2013), but have also been shown to modulate immune function, cell proliferation and apoptosis, brain development and function and to have neuroprotective properties (Holick, 2007).

VD and specifically $VD_3$ insufficiency is associated with osteomalacia and rickets (Ebeling, 2014; Rani, Maheshwari, Prasad, Karthik Reddy, & Reddy, 2013) with reduced mobility and bone fragility (Lippi, Sanchis-Gomar, & Montagnana, 2014), although there is no precise consensus on how long a person must be exposed to inadequately low vitamin D to result in this disease (McCarty, Chesson Jr., Jain, & Marino, 2014), probably due to the high subjectivity of physiological processes underlying this aspect. Furthermore, some evidence has associated VD insufficiency with a wide variety of medical conditions, such as autoimmune diseases (rheumatoid arthritis, systemic lupus erythematosus (SLE)) (Gentile et al., 2013), sleep disorders (McCarty et al., 2014), diabetes-type I, inflammatory bowel disease, multiple sclerosis (Al-Daghri et al., 2014; Brance et al., 2014; Delvin, Souberbielle, Viard, & Salle, 2014; Martinesi et al., 2014), cancers (Teleni et al., 2013), cardiovascular disease and thrombosis (Targher, Pichiri, & Lippi, 2012), diabetes (Mitri, Muraru, & Pittas, 2011), infections (Cannell et al., 2008; Macaluso et al., 2013), neurological and psychiatric conditions such as dementia, schizophrenia and depression (Anastasiou, Yannakoulia, & Scarmeas, 2014; Annweiler, Annweiler, Montero-Odasso, Bartha, & Beauchet, 2014; Clelland et al., 2014; Spedding, 2014), as well as some neurodevelopmental disorders, such as Rett syndrome (Motil et al., 2011; Sarajlija, Djuric, Kisic Tepavcevic, Grkovic, & Djordjevic, 2013).

VD, and in particular $VD_3$, can be taken in from food products (such as fish, egg yolk and liver), but a sufficient amount is also synthesized in the body, mainly from sun-exposed skin keratinocytes. Indeed, under the effect of ultraviolet irradiation (UV-B), the precursor 7-dehydrocholesterol is first rearranged into pre-$VD_3$ and then isomerized into $VD_3$.

Metabolic activation of $VD_3$ occurs in the liver, where $VD_3$ is hydroxylated into its pre-hormone calcifediol, also known as calcidiol, or 25(OH)$D_3$. Calcifediol is clinically measured in the serum to estimate the total amount of VD in the human body, from both skin synthesis and dietary supply. An amount of calcifediol between 30 and 74 ng/ml is considered to be within the normal range. However, it can fluctuate considerably depending on the contribution from skin synthesis. Indeed, during the summer and depending on sun exposure, circulating VD levels can increase by about one-third with respect to the levels reported in winter (Anastasiou et al., 2014; Vieth, 1999).

Calcifediol, which is still biologically inert, is finally hydroxylated into calcitriol, or 1$\alpha$,25$(OH)_2D_3$, the final biologically active form of $VD_3$. Calcitriol is mainly synthesized in the kidneys, but enzymes for activation are also present in the colon, brain, skin, lung, breast, prostate, placenta and monocytes-macrophages. In the macrophages, $VD_3$ acts locally as a cytokine, stimulating the innate immune system and showing potent immunomodulatory properties at both cellular and molecular levels (Chambers et al., 2014). VD is able to enhance regulatory T (Treg) cell subsets, which in turn have shown therapeutic potential for treating a range of immune-mediated conditions in humans. Interestingly, at different concentrations, 1$\alpha$,25$(OH)_2D_3$ is able to induce both IL-10(+) and Foxp3(+)Treg cells (the main Treg cells subsets) in cultures of human peripheral blood derived CD4+ T cells (Urry et al., 2012).

Furthermore, VD is able to promote antigen-specific tolerance. For example, 1$\alpha$,25$(OH)_2D_3$ induced mature dendritic cells (mDCs) from diabetes-prone mice expanded CD25(+)Foxp3(+) Treg cells and induced intracellular IL-10 production by T cells in vitro (Ferreira et al., 2014). A layout of the positive effects of $VD_3$ in human body is shown in Fig. 1.

### 1.1. Vitamin D and the brain: physiology and biological effects

In animal studies, it has been shown that VD metabolites can overtake the blood–brain barrier to reach the central nervous system (CNS) (Pardridge, Sakiyama, & Coty, 1985). In humans, VD metabolites have been found in the cerebrospinal fluid (Balabanova et al., 1984), deriving from both the peripheral blood circulation, which seems to be able to transport VD metabolites within the CNS, and from local synthesis and activation, which is also likely to occur as demonstrated by the presence of VD catabolism products within the CNS (Eyles, Smith, Kinobe, Hewison, & McGrath, 2005; Gezen-Ak, Dursun, & Yilmazer, 2013).

In animal models, VD can act as a neurotrophic factor in the CNS. It is able to upregulate several growth factors such as glial cell-derived neurotrophic factor and nerve growth factor (Brown, Bianco, McGrath, & Eyles, 2003) and to transform growth factor beta 2 (TGF-$\beta_2$) and neurotrophin 3 and 4 (Airavaara, Voutilainen, Wang, & Hoffer, 2012), playing an extremely

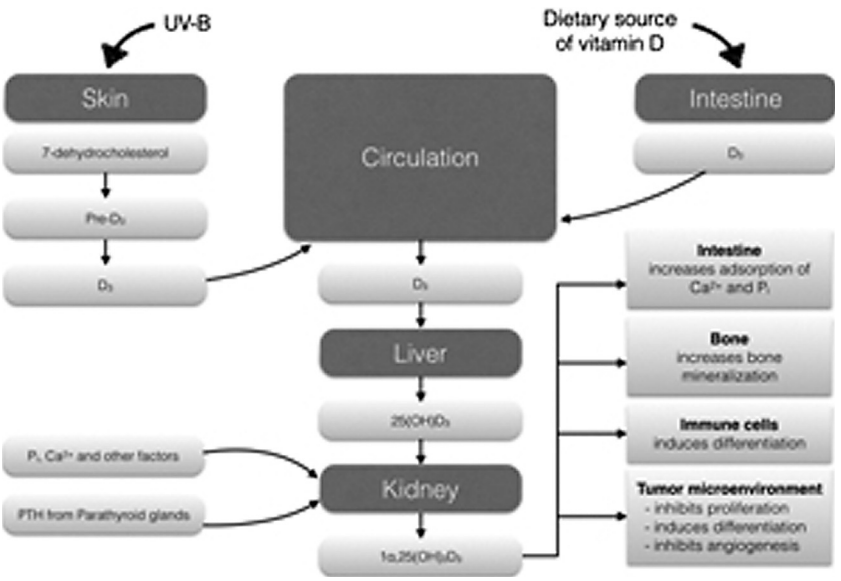


**Fig. 1.** Vitamin $D_3$ in human body.

important role in brain homeostasis and neurogenesis, as well as gene regulation (Harms, Burne, Eyles, & McGrath, 2011; Ramagopalan et al., 2010; Sigmundsdottir, 2011).

Furthermore, VD was found to have several neuroprotective effects, including a strong defense against neurodegeneration induced by inflammation, prevention of lipid peroxidation and apoptosis, and a decrease in reactive oxygen species with an overall significant reduction of the risk for the cells to become malignant (Lefebvre d'Hellencourt, Montero-Menei, Bernard, & Couez, 2003; Li et al., 2008; Lin, Chen, & Chao, 2005; Sigmundsdottir, 2011).

Animal studies showed that VD deficiency is associated with structural and functional brain modifications. In rodent models of VD depletion, altered brain morphology in the cortex, striatum and lateral ventricles has been found, possibly determining specific behavioral phenotypes (Altemus, Finger, Wolf, & Birge, 1987; Eyles, Brown, Mackay-Sim, McGrath, & Feron, 2003; Harms et al., 2012). A layout of the actions of $VD_3$ in human brain is shown in Fig. 2.

Numerous studies in animal models have found VD deficiency to be associated with multiple sclerosis (MS) risk, with some evidence demonstrating that $1\alpha,25(OH)_2D_3$ is able to prevent experimental autoimmune encephalomyelitis (EAE) in a mouse model of MS, by impeding the T Helper (TH) cells to enter the CNS parenchyma but instead maintaining them in the periphery (Grishkan, Fairchild, Calabresi, & Gocke, 2013).

Furthermore, in vivo administration of $VD_3$ in rat models of EAE led to a significant increase in CD4(+), CD25(+) and Foxp3(+) regulatory T cells in the lymph nodes, together with a significant decrease in the number of autoreactive T cells in the CNS, resulting in downregulation of the inflammatory response in the CNS (Farias et al., 2013).

In human studies, a growing body of evidence supports the hypothesis that $VD_3$ exerts immunomodulatory functions in MS and could prevent the development of MS. In a 6-month randomized controlled trial, Mosayebi et al. reported that $VD_3$ administration was significantly associated with an increase in TGF-β and interleukin-10 levels and a decrease in cell proliferation in the treatment group with respect to the placebo group (Mosayebi, Ghazavi, Ghasami, Jand, & Kokhaei, 2011).

### *1.2. Vitamin D and Autism Spectrum Disorders*

Autism Spectrum Disorders (ASD) are a heterogeneous group of early-onset neurodevelopmental conditions characterized by deficits in social communication along with restricted and repetitive interests and behaviors (World Health Organization, 1992).

Epidemiological studies are constantly reporting an increase in ASD prevalence worldwide (Atladottir et al., 2014; Blenner & Augustyn, 2014; Neggers, 2014), and posing the question whether these results depend on a real increase in the number of ASD cases or are mainly a result of more widespread screening, broadening ASD diagnostic criteria, lower age at diagnosis and intervention, greater public awareness, and parental advocacy factors (Neggers, 2014).

ASD etiology is still unknown and somewhat controversial. Although there is a large consensus regarding a key genetic role in the condition, an increasing body of evidence suggests that environmental factors may also be implied, in conjunction with the genetic factors and acting very early in development (Cannell, 2010; Coleman & Gillberg, 2011; Kinney, Barch, Chayka, Napoleon, & Munir, 2010).

The gene-environment interaction hypothesis (Freitag, Staal, Klauck, Duketis, & Waltes, 2010), investigated for several other medical and psychiatric conditions (Uher, 2014), has been recently suggested for ASD as well, and within this framework a putative role of VD deficiency has been proposed (Bakare & Munir, 2011; DeLuca, Kimball, Kolasinski, Ramagopalan, & Ebers, 2013; Neggers, 2014).

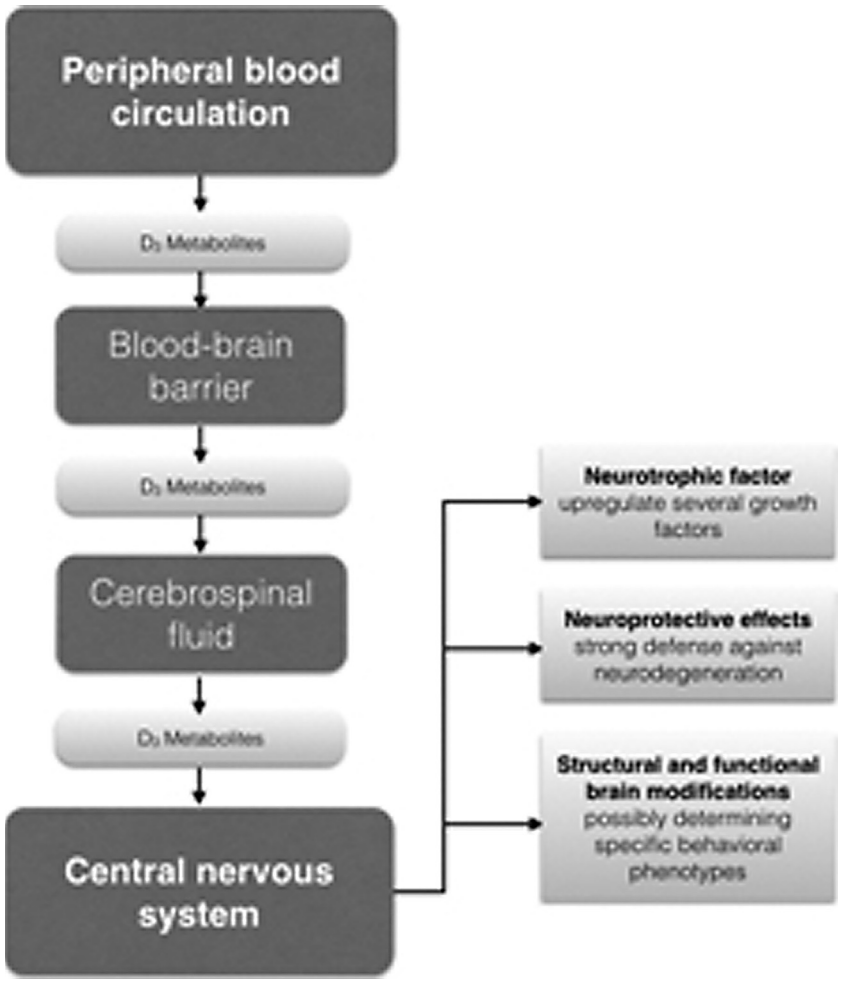


**Fig. 2.** Vitamin $D_3$ in human brain.

The assumption of a possible link between VD and ASD arose from different observational studies conducted in Northern Europe as well as North America and reporting a high rate of ASD among dark-skinned children (Barnevik-Olsson, Gillberg, & Fernell, 2008; Cannell, 2008; Eyles, 2010; Gillberg, Schaumann, & Gillberg, 1995; Goodman & Richards, 1995; Keen, Reid, & Arnone, 2010). Northern countries receive less intensive solar radiation throughout the year, but dark-skinned people need a much higher amount of UV ray exposure to synthesize VD (Clemens, Adams, Henderson, & Holick, 1982), leading to an increased risk for VD deficiency.

Furthermore, some evidence suggests that maternal VD deficiency during pregnancy is a risk factor for ASD, possibly affecting both maternal immune response and early fetal brain development (Grant & Soles, 2009).

VD deficiency in pregnant mothers has also been associated with other neurodevelopmental disorders in offspring, including language impairment (Whitehouse et al., 2012), representing a likely risk factor for ASD, even though not acting specifically on this disorder but being associated with a wider range of neurodevelopmental conditions.

## 2. Methods

A systematic review of the literature, covering the period January 1, 2010 through June 15, 2014, was conducted in PubMed, ScienceDirect, MedLine, PsycARTICLES, LILACS and Google Scholar database, according to the PRISMA guidelines (Moher, Liberati, Tetzlaff, Altman, & The PRISMA Group, 2009). The search strategy was as follows: "vitamin d or vitamin D or cholecalciferol or vitamin d3 or vitamin D3 or vitamin d 3 or vitamin D 3 or calcitriol or vitamin 1,25 D3 or vitamin 1,25 d3 or vitamin 1,25 D 3 or vitamin 1,25 d 3 or calcidiol or vitamin 25 D or vitamin 25D or 25 hydroxy vitamin d or 25-OHD or 25-hydroxyvitamin D or 25 hydroxyvitamin D or 25 hydroxy vitamin d or 25 hydroxyvitamin D AND autism or autism spectrum disorder or ASD".

The search was limited to articles published in peer-reviewed journals. After having discarded multiple-hits, the obtained results were sorted by relevance and the most significant works dealing with ASD and VD were selected. Case reports were not presented in results, but where necessary were cited in the discussion. We will first present the results from the literature review and will then critically discuss the possible implication of VD deficiency for ASD in light of the most recent findings.

## 3. Results

The systematic review of current literature, whose details are shown in Fig. 3, revealed 17 articles directly dealing with ASD and vitamin D in the period taken into consideration (Table 1).

In particular, eleven of them are focused on the determination of serum concentrations of $25(OH)D_3$ in subjects with a diagnosis of ASD, or their mothers.

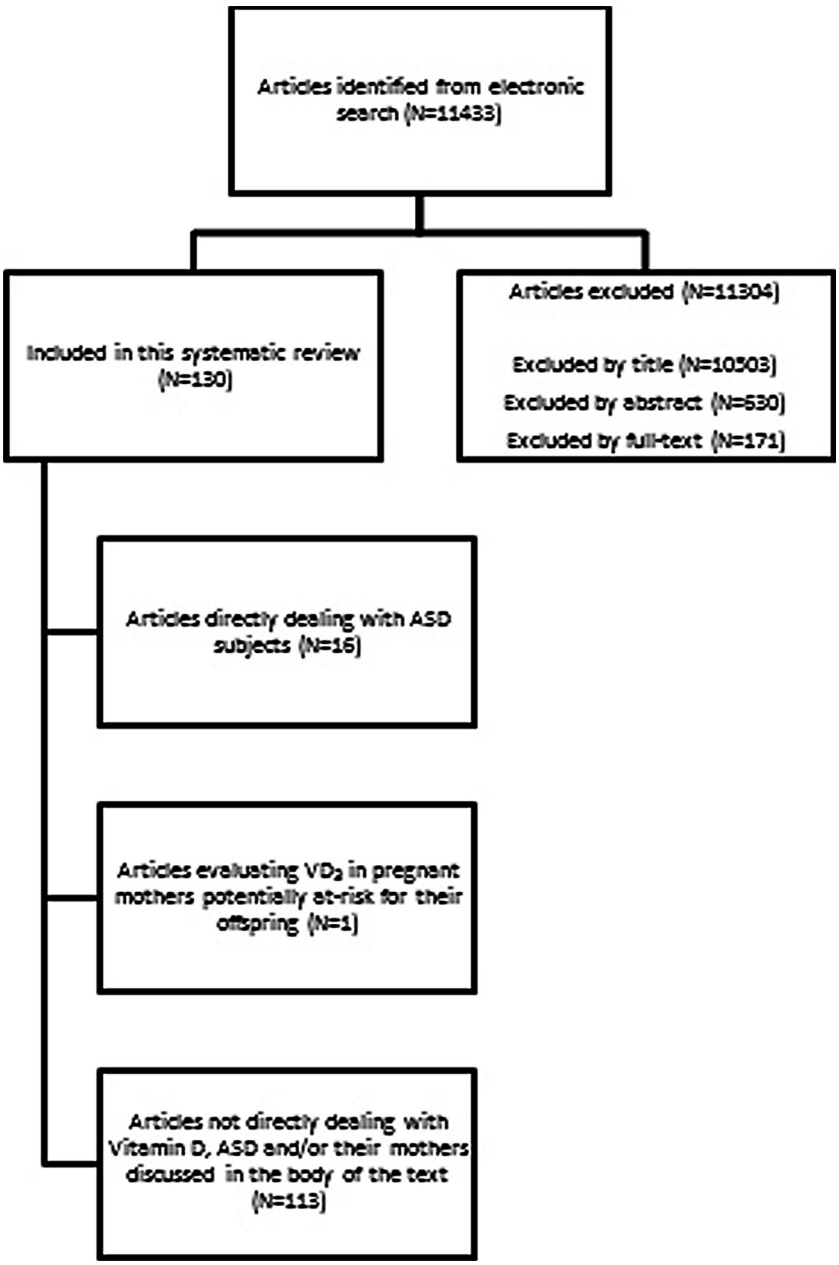


**Fig. 3.** Flow diagram of study selection.

**Table 1**
Studies measuring vitamin D or related indicators and ASD or ASD-like syndromes.

| Study | *N* (case/control) | Design | Findings |
|---|---|---|---|
| Fernell et al. (2010) Sweden | 80 (40/40) | Case–control, cross-sectional study, adult mothers involved | VD significantly higher in Swedish mothers than Somali mothers; trend of higher VD in TD subjects than in ASD |
| Humble et al. (2010) Sweden | 117 (117/0) | Cross-sectional study, only cases, European subjects with psychiatric disorders | Autism subjects show lower VD levels |
| Meguid et al. (2010) Egypt | 112 (70/42) | Case-control, cross-sectional study, ASD boys and girls, 2–8 years old | VD significantly higher in controls than in ASD |
| Molloy et al. (2010) USA | 89 (49/40) | Case–control, cross-sectional study, Caucasian ASD boys, 4–8 years old | No significant differences in VD levels |
| De Souza Tostes et al. (2012) Brazil | 48 (24/24) | Case–control, cross-sectional study, ASD boys and girls aged 7.4 ± 2.7 years | Serum levels of 25-OHD significantly lower in the ASD group |
| Hyman et al. (2012) USA | 367 (367/0) | Study based on prospective 3-day food records; 367 ASD children aged 2–11, 295 of whom completed the study. | Insufficient intake of VD in ASD children common with 87% of children younger than 4 years, 89% of those 4–8 years, and 79% of those 9–11 years below the Estimated Average Requirement (EAR) |
| Mostafa and Al-Ayadhi (2012) Saudi Arabia | 80 (50/30) | Cross-sectional study, ASD boys and girls, 5–12 years old | VD significantly higher in controls than in ASD |
| Soden et al. (2012) USA | 26 (26/0) | Cross-sectional study, ASD children aged 10–18 years | Insufficient serum 25(OH)D in ASD, increased risk of low bone mineral density and fractures |
| Bauer and Kriebel (2013) USA | N/A (probably 337,093) | Ecological study | Correlations between indicators of prenatal and perinatal paracetamol exposure and ASD |
| Brandlistuen et al. (2013) Norway | 15,256 mothers | Sibling-controlled cohort study | Paracetamol during pregnancy was associated with adverse neurodevelopmental outcomes |
| Grant and Cannell (2013) USA | N/A | Ecological study, children aged 6–17 years | ASD significantly inversely correlated with solar UVB doses |
| Neumeyer et al. (2013) USA | 37 (18/19) | Case–control study, children aged 8–14 years | Food intake of vitamin D lower in ASD, lower serum vitamin D for ASD |
| Whitehouse et al. (2013) Australia | 929 | 929 pregnant women (3 with ASD children and 926 with TD children) | No association between ASD and lower maternal 25(OH)D levels during pregnancy |
| Williams-Hooker et al. (2013) USA | 47 (47/0) | Cross-sectional, children 7–12 years old | Low VD intake than the DRI levels for ASD |
| Altbäcker et al. (2014) Hungary | N/A | Young adults assessed with Toronto Alexithymia scale | Inverse correlation between the levels of alexithymia and vitamin D |
| Gong et al. (2014) China | 96 (48/48) | Cross-sectional, case–control study, mean age = 3.67 years | Lower 25(OH)$D_3$ in ASD, significant negative correlation between 25(OH)$D_3$ and the CARS scores |
| Kočovská et al. (2014) Faroe Islands | 219 (40/179) | 40 ASD boys and girls, aged 15–24 years, compared with 62 TD siblings, 77 parents and 40 controls | Very low 25(OH)$D_3$ in the ASD group |

### 3.1. Autism and serum concentrations of 25(OH)$D_3$

Consistent results showing an association between a reduction in both 25OH$D_3$ and 1α,25$(OH)_2D_3$ and ASD were reported by Meguid and colleagues in a case-control, cross-sectional study within an Egyptian cohort (Meguid, Hashish, Anwar, & Sidhom, 2010). In this study, 112 subjects were recruited, of whom 70 had ASD and 42 were controls, within an age range between 2 and 8 years old. ASD children reported a deficiency in vitamin $D_3$ concentration, with a mean value of 28.5 ng/ml of $VD_3$ plasma level, whereas in typically developing (TD) children this value was 40.1 ng/ml, significantly higher than that of the ASD population.

Interestingly, a very similar result was found in a cross-sectional study conducted over a completely different ethnic group, represented by a Brazilian cohort (De Souza Tostes, Polonini, Gattaz, Raposo, & Baptista, 2012), composed of 24 ASD children (18 males, 6 females, mean age 7.4 ± 2.7 years) and 24 TD age- and gender-matched controls. Here, blood samples were collected after an 8-h fast, centrifuged, and frozen at −80 °C for further analysis by high-performance liquid chromatography (HPLC), in duplicate. No difference according to gender was found, neither among ASD children ($p = .293$) nor among TD ($p = .439$); serum levels of 25-OHD were reported to be significantly lower in the ASD group (26.48 ± 3.48 ng/ml vs 40.52 ± 3.13 ng/ml; $p < .001$), confirming a clear correlation between vitamin D deficiency and ASD. Moreover, the mean values obtained in the two groups were respectively very close to the ones obtained in the abovementioned study, confirming in this case a similar trend in two very different ethnic groups (Egyptians and Brazilians).

Confirming the great interest in this kind of analysis in Middle East countries, Mostafa and colleagues conducted a cross-sectional study (Mostafa & Al-Ayadhi, 2012), in a group of $n = 50$ Saudi Arabian ASD children (39 males and 11 females) aged 5–12 years and $n = 30$ (24 boys and 6 girls) TD age-matched controls.

Here, serum 25$(OH)D_3$ was analyzed by enzyme-linked immunosorbent assay (ELISA). Results showed significantly lower serum levels of 25$(OH)D_3$ in the ASD group compared with TD group (median = 18.5 ng/ml vs. 33.0 ng/ml, respectively;

$p < .001$), with values slightly lower than the ones reported in the previous two studies but still consistent and completely different between the two groups. Furthermore, 40% of children in the ASD group, but none in the TD group, displayed 25(OH)$D_3$ levels below 10 mg/dl, whereas 48% of children in the ASD group but only 20% of children in the TD group displayed 25(OH)$D_3$ levels between 10 and 30 mg/dl, showing that ASD children included in this study are at serious risk for a severe $VD_3$ deficiency.

In the same study, the Childhood Autism Rating Scale (CARS) was used to assess ASD severity (Schopler, Reichler, & Renner, 1986). When 25(OH)$D_3$ levels were correlated with the CARS scores, a significant negative correlation was found ($r = -.84$, $p < .001$), indicating that ASD severity was associated with VD serum levels, in particular with more severe cases of ASD being more seriously deficient from a VD point of view. No significant correlations were obtained with respect to age, gender and duration of weekly sun exposure, a possible co-source of VD.

Moreover, serum anti-myelin associated glycoprotein (anti-MAG) autoantibodies were also analyzed by quantitative sandwich-type enzyme immunoassay (EIA). Of ASD children, especially those reporting severe ASD, 70% displayed significantly higher serum levels of anti-MAG autoantibodies than TD children ($p < .001$), and a significant negative correlation between serum levels of 25(OH)$D_3$ and anti-MAG autoantibodies was found ($p < .001$).

VD deficiency was also found in a different geographical area, with a completely different ethnic distribution. This study was conducted in a cohort of 26 ASD patients, aged 10–18 years, in the United States (Soden, Garrison, Egan, & Beckwith, 2012). As reported by the authors, 54% of ASDs reported insufficient serum 25(OH)D levels, with fewer than 50% of subjects meeting daily reference intake of VD. The subjects with lower intake of vitamins, calcium, and calories were found to be at higher risk for occult low bone density, fractures and pain. This study highlighted the possible role of insufficient intake of vitamins and other important compounds in autistic patients.

As previously stated, one of the most important roles for vitamin D in human body concerns bone growth. This argument was explored by a recent American study that investigated the possible role of VD in bone development in peripubertal boys with ASD (Neumeyer, Gates, Ferrone, Lee, & Misra, 2013). In the study, 37 boys (18 ASD and 19 TD children, aged 8–14 years) were enrolled and investigated in terms of dietary intake of VD, bone growth and serum concentration of several compounds among which 25(OH)D. The analysis revealed a clear, though non-significant, decrease in bone age for children with autism ($10.6 \pm 0.6$ years for ASD vs $11.8 \pm 0.4$ years for TD, $p = .08$), with a significant reduction in serum levels of 25(OH)D ($26.7 \pm 1.9$ ng/ml vs $31.7 \pm 1.6$ ng/ml, $p = .05$). Dietary VD intake from food was also found to be reduced in ASD children ($199 \pm 26$ IU/d vs $340 \pm 56$ IU/d, $p = .03$), probably explaining the differences stated above and confirming the findings previously reported by other authors (Soden et al., 2012).

Further recent replications of these findings in independent cohorts were reported by Kočovská and colleagues in the Faroe Islands, Denmark (Kočovská et al., 2014) and by Gong and colleagues (Gong et al., 2014) in Beijing, China, respectively, demonstrating the worldwide interest in this topic.

In the study by Kočovská and colleagues, $n = 40$ individuals with ASD (31 males/9 females, aged 15–24 years), their TD siblings ($n = 62$, 29 brothers/33 sisters) and parents ($n = 77$, 40 mothers/37 fathers) were compared in terms of $VD_3$ concentration with a group of healthy age- and gender-matched individuals ($n = 40$, 28 males/12 females).

Both 25$OHD_3$ and 1$\alpha$,25(OH)$_2D_3$ were analyzed by liquid chromatography-tandem mass spectrometry (LC–MS/MS).

The ASD children showed significantly lower levels of 25$OHD_3$ (median 24.8 nmol/l) than their siblings (median 46.1 nmol/l, $p < .001$), parents (median 46.7 nmol/l, $p < .001$) and the control group (median 37.6 nmol/l, $p = .002$). Furthermore, a significant trend toward lower 25$OHD_3$ levels in males was reported. No associations with age, month/season of birth, IQ, ASD phenotype and Autism Diagnostic Observation Schedule (ADOS) scores were found.

Gong and colleagues analyzed serum levels of 25(OH)$D_3$ in 48 ASD and 48 typically developing children. Fasting blood samples were collected from the subjects for the measurement of serum 25(OH) $D_3$ levels, performed by E601 modular (Roche Diagnostics, Mannheim, Germany). ASD severity was assessed using the CARS scale. Significantly lower levels of 25(OH)$D_3$ were found in children with ASD ($p = .002$), and a significant negative correlation between circulating serum 25(OH)$D_3$ levels and the CARS scores after controlling for age, gender, seasonal variation, body mass index, as well as serum levels of calcium, phosphate, and magnesium effects, was found ($p < .001$).

Despite the reported evidence of VD deficiency in ASD in different cohorts and geographical areas, other studies do not find the abovementioned association. In a study conducted by Molloy and colleagues (Molloy, Kalkwarf, Manning-Courtney, Mills, & Hediger, 2010), $n = 40$ ASD Caucasian male pre-pubertal children (age 4–8 years) were compared with $n = 40$ typically developing age-, gender- and ethnicity-matched controls, having intravenous (IV) catheters placed for outpatient tonsillectomies. Within the ASD group, $n = 9$ children were on a casein-free diet. Plasma 25(OH)D concentration was measured by radioimmunoassay and no significant between-group differences were observed ($p = .4$). Anyway, in this study a noteworthy limitation concerned the season of recruitment of the different subjects. Indeed, many more TD than ASD subjects were enrolled during winter; although it did not account for a statistically significant difference, it may have affected the overall balance between the two study groups. In another study conducted in the United States (Adams et al., 2011a), 55 ASD children (49 males, 6 females), aged 5–16, and 44 controls (39 males, 5 females) reported no significant differences ($29.9 \pm 8.4$ μg/l vs. $28.6 \pm 8.4$ μg/l, $p$ = n.s.) in plasma levels of 25(OH)D measured by liquid chromatography-tandem mass spectroscopy (LC/MS/MS), adding uncertainty to this possible relationship. In this study, the authors stated that the difference between groups appeared to be due to real differences in the control groups and might be due to a variety of factors, such as sun exposure, dietary intake or factors interfering in vitamin D metabolism. Indeed, several factors such as age, sex,

sample size, possible concomitant inflammatory conditions among many others may account for the different results, as in the case of the relationship between recurrent tonsillitis and lower vitamin D levels (Nseir et al., 2012).

Other studies aimed to investigate the complex and intriguing relationship between maternal VD levels and ASD, with limited evidence. For example, Whitehouse and colleagues (2013) conducted a large population study in Perth, Australia. $N = 929$ pregnant women, randomly selected out of a cohort of $n = 2900$ subjects, were enrolled in the study. Serum 25(OH)D levels were measured by enzyme immunoassay at 18 weeks of pregnancy and the offspring were followed-up longitudinally at 5-, 8-, 10-, 14- and 17 years. $N = 3$ subjects in the cohort received a formal diagnosis of ASD, but no evidence for an association with lower maternal 25(OH)D levels during pregnancy was found, with all three values above the broader population mean (78, 63 and 65 nmol/l respectively for the mothers of the autistic, Pervasive Developmental Disorder-Not Otherwise Specified (PDD-NOS), and Asperger subjects, vs a mean value of 58.02 nmol/l for the mothers of TD children).

In the same study, 406 subjects filled out the Autism Spectrum Quotient (AQ), a self-report questionnaire providing a quantitative measure of autism traits in the general population (Baron-Cohen, Wheelwright, Skinner, Martin, & Clubley, 2001). No significant correlation between maternal 25(OH)D levels at 18 weeks of pregnancy and the total AQ scores as well as four out of five AQ subscales (social skills, communication, imagination and attention to detail) was found. However, a significant, though weak, negative correlation with the AQ attention switching domain was reported ($r = -0.13$, $p = .01$) and those offspring of mothers with 25(OH)D concentrations in the lower tertile appeared to have significantly higher scores, meaning more impairment, on the attention-switching domain than offspring of mothers in the middle and upper tertiles ($p < .01$). Overall, the study provided little evidence for an association between maternal VD deficit during pregnancy and ASD in the offspring, although limited statistical power has to be considered to interpret the findings; an indirect, complex involvement of VD in fetal brain development, with implications in some behavioral aspects related to the ASD phenotype, should not be excluded. A considerable correlation between maternal VD deficit during pregnancy and the same deficit in offspring was seen in a recent Indian study (Vadeyar, Shetye, Somani, & Shah, 2014), confirming a likely increase of this risk in the progeny.

### 3.2. Vitamin D and autism treatment

To date, pharmacological treatments for ASD core symptoms are still lacking. Several factors such as ASD severity, IQ, receptive language, imitation, motor skills as well as earlier diagnosis and treatment have been shown to be efficient, with a significant minority of ASD individuals showing an optimal outcome (Fein et al., 2013).

However, in a heterogeneous condition like ASD, both genetic and environmental factors may play a role in its pathophysiology, contributing to the ASD phenotype and accounting to some extent for the outcome.

Some anecdotal evidence reported a seasonal improvement of ASD symptoms during the summer (Hayashi, 2001), and Cannell and colleagues argued that VD might be implicated in the improvement of ASD symptoms in summer (Cannell, 2013).

Furthermore, difficulties in dietary intake of nutrients such as calcium and VD in children with ASD have been found (Hyman et al., 2012; Williams-Hooker et al., 2013; Keown, Bothwell, & Jain, 2014), even though this phenomenon is not observed in all cases (Graf-Myles et al., 2013); VD replacement has been proposed in selected cases (Cannell & Grant, 2013).

VD treatment effects have been reported in several autoimmune conditions (Berlanga-Taylor & Ramagopalan, 2013; Derakhshandi et al., 2013; Hypponen, Laara, Reunanen, Jarvelin, & Virtanen, 2001; Jankosky, Deussing, Gibson, & Haverkos, 2012; Soilu-Hanninen et al., 2012;) and immune dysregulation (Abdallah et al., 2013; Schwarz et al., 2011; Steeb et al., 2014). Moreover, autoimmune conditions have been associated with ASD (Gesundheit et al., 2013), with a few anti-neural autoantibodies associated with ASD severity (Mostafa & Al-Ayadhi, 2012; Walker, Conn, Davies, & Moore, 2006). Thus, a study published three years ago highlighted the importance of vitamin/mineral supplements in children with ASD, possibly improving their performance in the areas of hyperactivity, tantrums, overall behavior, and receptive language (Adams et al., 2011b). In this specific case, of the vitamins employed, $VD_3$ seems to be the least positively correlated with a good outcome of the health status of the children, probably because of the previously mentioned seasonal factors influencing VD concentration in all patients. Thus, at present a direct link between treatment with VD and ASD outcome improvement is still unclear.

### 3.3. Other factors associated with ASD and VD

ASD is a condition characterized by a well-known male bias. An increasing body of evidence suggests that sex steroids may play an important role in ASD, acting as environmental factors and interacting with other risk factors very early in brain development (Auyeung, Lombardo, & Baron-Cohen, 2013; Baron-Cohen et al., 2011; Hertz-Picciotto, 2011).

In a recent exploratory register-based historic birth cohort study, Baron-Cohen and colleagues reported the first direct evidence of an association between elevated steroidogenic activity in the fetus and a later ASD diagnosis (Baron-Cohen et al., 2014).

Among other complex interactions, sex-steroid hormones interact with the immune system and in particular exert effects on microglia activation (Lenz, Nugent, Haliyur, & McCarthy, 2013). Furthermore, it has been found that estrogens but not testosterone are able to increase neural $1\alpha,25(OH)_2D_3$ (Bowman & Epstein, 2005; Cannell, 2008) and indeed a potential hormone imbalance toward hyperandrogenism in ASD might be also related to lower VD levels.

Recently, another study related low levels of VD to alexithymia, a condition characterized by emotional impairment which frequently co-occurs with ASD. Scores on the Toronto Alexithymia Scale-20 were negatively correlated with VD concentration, suggesting an association between impaired emotional processing and low levels of VD (Altbäcker et al., 2014).

Environmental factors interfering with VD synthesis in relation to ASD have been also investigated. In an ecological study recently conducted in the United States, Grant and Cannell (2013) investigated the relationship between ASD and sun exposure. A negative correlation between ASD prevalence and solar UV-B doses – extracted by Total Ozone Mapping Spectrometer (TOMS) – was found (Leffell & Brash, 1996).

In another study, the association between paracetamol, VD and ASD was examined. An association between gestational paracetamol exposure and deficits in early neurodevelopment was found (Brandlistuen, Ystrom, Nulman, Koren, & Nordeng, 2013). Furthermore, prevalence of ASD was recently associated with prenatal and perinatal exposure to paracetamol (Bauer & Kriebel, 2013). The mechanism for this association is not yet clear, but it might be mediated by oxidative stress caused by paracetamol intake (Cannell, 2014). VD has been shown to have antioxidant properties (Nakai et al., 2014) and a condition of VD depletion during pregnancy might be a risk factor for increased susceptibility to oxidative stress in the fetus (Nikooyeh et al., 2014).

## 4. Discussion

ASD is a neurodevelopmental disorder with increasing prevalence in the human population (Atladottir et al., 2014; Blenner & Augustyn, 2014; Neggers, 2014), possibly due to more widespread screening performed with respect to the past, or to broadening of diagnostic criteria and greater public awareness, but likely to be related to a real increase in the number of ASD cases overall in the world, and not only in more developed countries.

Like schizophrenia and other conditions the etiology of ASD remains unknown (Eyles, Burne, & McGrath, 2013), but there are several hypotheses. According to several scientists, ASD is probably due to the interaction between several risk factors, both genetic and environmental, and VD deficiency, along with other factors acting early in brain development, may play a role in the complex neurobiology of the condition (Duan, Jia, & Jiang, 2013).

VD, whose main sources in humans are sun exposure and food intake (Anastasiou et al., 2014; Norman, 1998), is well-known to have several positive effects. Among these are bone metabolism, calcium physiology (Christodoulou et al., 2013), modulation of immune function, cell proliferation and apoptosis, and brain development and function as well as many neuroprotective properties (Holick, 2007), with important protection against cognitive impairment and neurological conditions in general (Anastasiou et al., 2014; Annweiler et al., 2014; Berquist, Schall, & Stallings, 2007). Indeed, its benefits are reported to influence a number of medical conditions, with its deficiency known to be associated with autoimmune diseases (rheumatoid arthritis, SLE, sleep disorders (McCarty et al., 2014)), diabetes-type I, inflammatory bowel disease, cancers (Teleni et al., 2013), cardiovascular disease and thrombosis (Targher et al., 2012), diabetes (Mitri et al., 2011), infections (Macaluso et al., 2013). Several neurological and psychiatric conditions were also found to be associated with a VD deficiency in both animal models and in humans. They include MS (Al-Daghri et al., 2014; Brance et al., 2014; Delvin et al., 2014; Grishkan et al., 2013; Martinesi et al., 2014), dementia, schizophrenia and depression (Anastasiou et al., 2014; Annweiler et al., 2014; Clelland et al., 2014; Spedding, 2014), as well as some neurodevelopmental disorders, such as Rett syndrome (Motil et al., 2011; Sarajlija et al., 2013).

Such important relationships are presumed to take place because of the known role of VD as a neurotrophic factor at the CNS level, upregulating a number of growth factors (e.g., glial cell-derived neurotrophic factor, nerve growth factor) (Brown et al., 2003), and transforming important compounds such as growth factor beta 2 (TGF-$\beta_2$) and the neurotrophin 3 and 4 (Airavaara et al., 2012), in this way playing a key role in brain homeostasis and neurogenesis, and gene regulation (Harms et al., 2011; Ramagopalan et al., 2010; Sigmundsdottir, 2011). Without this important role a number of neurological and neurodevelopmental conditions could occur more easily, and this could possibly explain the important link between VD deficiency and neurological disorders.

Recently, there has been growing interest in autism and ASD due to an apparently higher prevalence of the condition and to the different lifestyles of children and young people with respect to the past, possibly linked to a higher prevalence of VD deficiencies in the younger population.

Several years ago, a higher prevalence of ASD was noticed at higher latitudes (Grant & Soles, 2009), a phenomenon much more present in dark-skinned offspring born of immigrant mothers, especially those coming from East Africa to Northern Europe (Dealberto, 2011).

Indeed, dark-skinned people have more difficulty producing $VD_3$, requiring a higher dose of sun exposure to synthesize this compound, as skin pigmentation is directly correlated with the actinic production of $VD_3$ (Abrams, 2002; Holick, 1995; Kreiter et al., 2000).

Moreover, as previously reported, one of the main sources of VD is sun exposure. $VD_3$ in particular is synthesized in the body, mainly from skin keratinocytes when exposed to sun. The UV-B irradiation is able to modify the precursor 7-dehydrocholesterol, rearranging it at first into pre-$VD_3$, which is then isomerized into $VD_3$. This particular process cannot take place in absence of sun exposure, resulting in a deficiency in VD supply. This is another common feature between VD deficiency and ASD, increased winter and spring births for ASD children having been reported (Hebert, Miller, & Joinson, 2010), thus in periods when sun exposure is normally quite reduced.

The other important source of VD in humans is food. Dietary intake of VD, but also of nutrients such as calcium, was seen to be reduced in most (Hyman et al., 2012; Keown et al., 2014; Neumeyer et al., 2013; Soden et al., 2012; Williams-Hooker et al., 2013), although not all (Graf-Myles et al., 2013) cohorts of ASD children, possibly reporting another link between the two apparently different conditions.

Vitamin D is also one of the most important factors influencing the development of bone structure. Indeed, this compound regulates the formation and density of bone by promoting the absorption of key compounds such as calcium and phosphate in the intestine (Kočovská, Fernell, Billstedt, Minnis, & Gillberg, 2012). For unknown reasons, it was found that ASD subjects have a significant decrease in metacarpal bone thickness (Hediger et al., 2008), increasing the risk for occult low bone density, fractures and pain (Soden et al., 2012) and suggesting another possible indirect relationship with the deficiency of this particular compound.

In general terms, more than half of the studies found in this systematic literature review found a clear association between $VD_3$ deficiency and ASD. Such studies took place in several areas, from Brazil to China, from Faroe Islands to Egypt, involving various and heterogeneous ethnic groups. The differences found between ASD and TD controls were clear in all these studies (De Souza Tostes et al., 2012; Gong et al., 2014; Humble, Gustafsson, & Bejerot, 2010; Hyman et al., 2012; Kočovská et al., 2014; Meguid et al., 2010; Mostafa & Al-Ayadhi, 2012; Neumeyer et al., 2013; Soden et al., 2012), strengthening the hypothesis for a possible role for VD in the etiology of ASD.

On the other hand, few studies failed to replicate such results (Adams et al., 2011a; Molloy et al., 2010; Whitehouse et al., 2013), with the scientific community not fully convinced of the verisimilitude of this association (Frustaci et al., 2012). There could be various reasons for the different results obtained in such studies. First, the findings of the abovementioned studies could be affected by sample size limitations, as in the case of Whitehouse et al. (2013), where mothers possibly at risk for ASD offspring were evaluated, but only 3 out of 929 children turned out to have ASD, generating a result of poor statistical value. Second, seasonal differences could have affected the results obtained. Indeed, in the study by Molloy et al. (2010), we noticed that recruitment of the different subjects did not occur in the same season, with an evident (though not statistically significant) increase in ASD recruitment during winter, possibly affecting the overall balance in VD concentration between the two study groups.

Third, in the case of Adams et al. (2011a), the authors stated that the difference reported between the two groups appeared to be due to real differences in the control groups and might be related to several factors, such as sun exposure, dietary intake or factors interfering in vitamin D metabolism, possibly representing a limitation for these findings. Finally, ethnicity could account for differences in the studied groups, influencing VD synthesis (Barnevik-Olsson, Gillberg, & Fernell, 2010; Fernell et al., 2010; Grant & Cannell, 2013), and this factor should be carefully checked to avoid drawing inconsistent conclusions.

The reason for which this association could be considered valid include the role of VD as a CNS neurotrophic factor, as an upregulator of several growth factors, and as a key player in brain homeostasis and neurogenesis, as well as gene regulation. However, another possible role for the link between ASD and VD deficiency was found in several studies (Angelucci, Aloe, Jimenez-Vazquez, & Mathé, 2003; Humble, 2010; Pae, Marks, Han, Patkar, & Steffens, 2008; Shoval & Weizman, 2005), reporting that a predisposition for autism could result from genetic damage in spermatozoa, with some data supporting the fact that VD may prevent such damage.

On the other hand, the role of VD in treatment of ASD symptoms is under debate. Recently, this possible relationship was investigated, starting from the key facts that seasonal improvement of ASD symptoms during summer were found (Hayashi, 2001), that VD could be a factor in such improvement (Cannell, 2013), and that the effects of VD treatment have reported to be positive in the case of many autoimmune conditions (Berlanga-Taylor & Ramagopalan, 2013; Derakhshandi et al., 2013; Hypponen et al., 2001; Jankosky et al., 2012; Soilu-Hanninen et al., 2012), sometimes associated with ASD (Gesundheit et al., 2013). The importance of vitamin/mineral supplements in children with ASD, possibly improving their performance in the areas of hyperactivity, tantrums, overall behavior, and receptive language was shown (Adams et al., 2011b). Of the substances analyzed in this work, $VD_3$ seems to be the least positively correlated with a good outcome of the health status of the children, probably because of the seasonal factors influencing VD concentration in all patients. Thus, at present a direct link between treatment with VD and ASD outcome improvement is still unclear.

However, although VD deficit might be one of several risk factors for developing ASD, other aspects including genetic and other environmental factors should be taken into consideration, to pave the way toward novel, tailored treatments.

This systematic review, despite limitations concerning the inclusion of the most important – but not all – search engine methods, investigated the possible role of VD in ASD.

Positive effects of VD on the human body and especially the brain have been well-known for decades, but recently, the relationship between serum VD deficiency and neurodevelopmental disorders, including ASD, has been more thoroughly investigated, suggesting an increased ASD prevalence in dark-skinned people, decreased levels of serum VD in ASD subjects, as well as a higher ASD risk in children of mothers with VD deficiency during pregnancy. Moreover, a possible role of VD in ASD treatment was hypothesized, but findings on this topic are still debated and remain to be clarified.

Preliminary evidence suggests a putative role for VD in ASD, taking into account the etiological heterogeneity of ASD, and provides support for expanding research focus on VD in ASD, encouraging important further studies in human and animal models to clarify the potential mechanisms of VD involvement in ASD.

First, replications in independent larger cohorts are required, in order to obtain more reliable and consistent results. Such studies should clarify whether VD is implied and/or associated with the condition and whether other factors such as gender or ethnicity have implications in the VD pathway in relation to ASD.

Second, the role of maternal VD deficiency during pregnancy should be better stated, involving both animal models of maternal vitamin D insufficiency and larger birth cohorts able to provide a large enough sample size to test the hypothesis of prenatal VD deficiency in ASD. Third, the complex pathways involving VD interaction with hormones and immune function in relation to ASD should be further investigated, as well as genetic interactions. The immune intervention of $VD_3$ could be a reliable rationale for an autoimmune hypothesis regarding the origin of autism.

Finally, the possible effects of VD-based treatments should be critically considered, in order to provide evidence for additional safe, cost-effective targeted therapies for subgroups of ASD individuals.

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