

The role of vitamin D deficiency in the development of paediatric diseases

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ABSTRACT

Children's Vitamin D (VitD) fortification and supplementation are diminishing due to less outdoor exercise and insufficient VitD intake (low exogenous intake and endogenous malabsorption induced by gastrointestinal disease). Consequently, children in many developed countries suffer from VitD deficiency, which may contribute to many paediatric disorders. Our review briefly introduced the metabolic process of VitD, summarized the role of VitD in paediatric diseases such as autism, obesity, rickets and asthma. We sought to identify the link between VitD deficiency and these diseases.

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The metabolic process of VitD

Vitamin D (VitD) is a sterol derivative. In humans, it is mainly obtained from exposure to ultraviolet rays (UVR) or food sources (fishes or mushrooms) [1]. 7-dehydrocholesterol is converted into pro-VitD3 by exposure to UVR. Next, the pro-VitD3 is thermally restructured into VitD3. After binding to the VitD binding protein (VDBP), it is transported to the liver [2]. 25-hydroxyVitD3 (25(OH)D₃) is hydroxylated by cytochrome P-450 enzymes (CYP2R1 and CYP27A) in the liver, their gene mutations may result in VitD deficiency [3]. The concentration of 25(OH)D₃ is a marker of VitD status *in vivo*, the bloodstream transports it into other organs, such as the brain, intestines, kidneys, lungs and heart [4]. It is mainly the kidneys that activate VitD in the second step. In the kidneys, 25(OH)D₃ is converted to 1,25-dihydroxy VitD₃ (calcitriol, 1,25-(OH)₂D₃) by the 1 α -hydroxylase [5]. Since other tissues also contain 1 α -hydroxylase, 1,25-(OH)₂D₃ could also be synthesized in them (Figure 1) [6]. In the human brain, 1,25-(OH)₂D₃ acts upon the prefrontal cortex, hippocampus, cingulate gyrus, thalamus, hypothalamus, and substantia nigra [7]. The role of 1,25-(OH)₂D₃ in neuroprotection is attributed to its abilities

to inhibit oxidative stress and inflammation and regulate many neurotrophic factors [8].

In the VitD family, VitD3 (cholecalciferol) and VitD2 (ergocalciferol) are essential for human health. VitD3 is the initial product of VitD metabolism in liver cells. In a double-blind experiment, adults with insufficient VitD took oral VitD3 stool samples for eight weeks. The results showed that serum 25(OH)D increased, beneficial bacteria in the intestine increased, and pathogenic bacteria decreased [9]. Recent studies have shown that VitD3 levels of 40–60 ng/ml may reduce the risk of various types of cancer [10]. Furthermore, researchers found that VitD3 inhibited inflammation and oxidative stress in cognitive impairment rats, alleviated the symptoms of memory dysfunction, and improved learning abilities [11]. In natural world, VitD2 is a steroid derived chiefly from ergosterol, which is commonly present in fungi and certain plants [12]. In recent years, people gradually paid more attention to the researches on VitD2. Studies have shown that oral administration of VitD2 in rats had anti-anxiety, anti-depressant and memory-enhancing effects after noise stimulation [13]. According to Balachandar, VitD3 had higher efficacy in improving total 25(OH)D and reducing serum parathyroid level, comparing to VitD2 [14].

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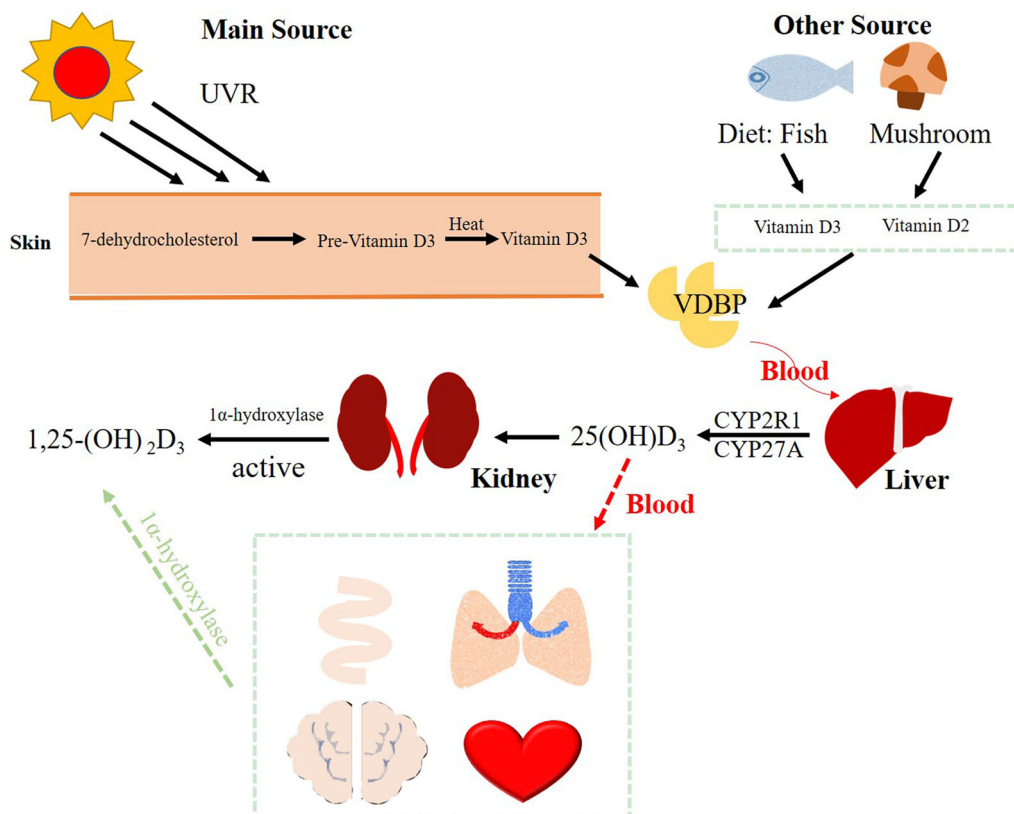


Figure 1. VitD metabolism. The synthesis of VitD₃ in the skin is triggered by ultraviolet radiation (UVR) or by food consumption. By combining with VitD-binding protein (VDBP), VitD₃ is transported into the liver. Cytochrome P-450 enzymes (CYP2R1 and CYP27A) are responsible for converting VitD₃ to 25-hydroxyvitamin D₃ (25(OH)D₃) in the liver. The 25(OH)D₃ is converted into 1,25-dihydroxyvitamin D₃ (1,25-(OH)₂D₃) in the kidneys, liver, lungs, brain, intestines and heart by 1 α -hydroxylase.

Correlation of VitD deficiency with paediatric diseases

VitD is measured by the level of 25(OH)D in serum in the body. If the 25(OH)D concentrations are below 75 nmol/L (or 30 ng/ml), it is considered VitD deficiency. While concentrations are below 25 or 30 nmol/L (or 10/12 ng/ml), it is considered severe VitD deficiency [15]. While standards vary from different countries, the Institute of Medicine (United States) and the Endocrine Society VitD Working Group offer 50 nmol/L as a critical threshold [16].

The distribution of VitD levels in children aged 0–4 years in Yunnan Province, China, showed that children's VitD levels were highest in summer and lowest in winter, and VitD deficiency was more common in girls than boys [17]. Over the last two decades, global VitD deficiency increased. It is estimated that VitD deficiency ranged from 6.9% to 81.8% in European countries and from 2.0% to 87.5% in Asian countries [18]. The majority of these surveys were conducted in cities. In mountainous areas of the northern Persian Gulf, VitD deficiency was prevalent at 78%

[19]. Important underlying factors associated with VitD deficiency in this population included dark skin, domestic and sedentary periods, insufficient sun exposure, air pollution, clothing style, obesity, sunscreen using, and lack of VitD supplementation [20]. In addition, taking antiepileptic drugs (carbamazepine) and anticonvulsant drugs (levetiracetam) would lead to decreasing of VitD *in vivo* [21]. The atrophy of the intestinal villi patients with coeliac disease led to nutrient absorption, reduced the absorption of VitD, calcium and magnesium [22].

It has become apparent that VitD deficiency contributes to the occurrence or aggravation of many paediatric diseases. VitD deficiency could cause osteomalacia and rickets in children [23]. Children's Hospital in the United Arab Emirates showed 35% of patients with VitD deficiency [24]. VitD deficiency was common in Egyptian children with allergic rhinitis [25]. Evidences suggested that VitD supplementation could treat related childhood illnesses. Inflammatory markers IL-12, IL-17, IL-23, and TNF- α were significantly reduced after VitD supplementation in children with

inflammatory bowel disease, and the frequency of hospitalizations and the number of emergency department visits were significantly lower [26]. Clinical data showed that VitD supplementing effectively relieved osteomalacia in children and adolescents [27]. However, there were also conflicting findings on whether VitD deficiency was associated with paediatric diseases. Thus, the primary purpose of this review was to summarize the current status of researches on VitD metabolism and to clarify its roles in paediatric diseases.

VitD and childhood autism

Autism Spectrum Disorder (ASD) is a neurodevelopmental disorder characterized by impaired social communication and interaction, and repetitive and stereotyped behaviours and interests [28]. Autism is a multifactorial disease caused by the interaction of genetic and environmental factors. Hundreds of autism risk genes and various environmental factors (neonatal hypoxia and gestational diabetes) have been found [29]. ASD children are known to exhibit various behaviour problems, including aggression, self-harm, attention deficit hyperactivity disorder, sleep disorders, and obsessive-compulsive disorder, which may prevent them from getting the same life and educational opportunities as other children have [30]. VitD plays an important role in the regulation of gene expression in ASD. One study showed that 223

ASD risk genes in the SFARI database were VitD3-sensitive genes [31]. A study by Wang et al. showed that the VitD levels of ASD children were lower than those of healthy children [29]. It has been demonstrated that VitD levels in ASD children were lower also when compared with children with other neuropsychiatric disorders [32]. In a randomized controlled trial, allergy and hyperactivity behaviours were improved after VitD and omega-3 long-chain polyunsaturated fatty acids were used to treat ASD children [33]. Some studies observed that VitD supplementation significantly reduced the severity of ASD [34]. But others showed that this effect was not consistently different between treatment and control groups [35]. VitD supplementation was beneficial for hyperactivity but not core symptoms of ASD or other co-existing behaviours and conditions [36]. Many factors could affect the experiments, including the small sample size of children with ASD, and the possible influence, such as sun exposure, race and skin colour, dietary habits and nutritional status [37]. The impact of VitD on ASD is still under discussion. In addition to theoretical support that the effects of VitD on ASD may be related to signalling pathways involving whole blood arginine and nitric oxide, researchers also found that ASD is associated with disorders of the dopamine system and abnormalities of the serotonin-melatonin axis, which are caused by insufficient amounts of VitD (Figure 2) [38].

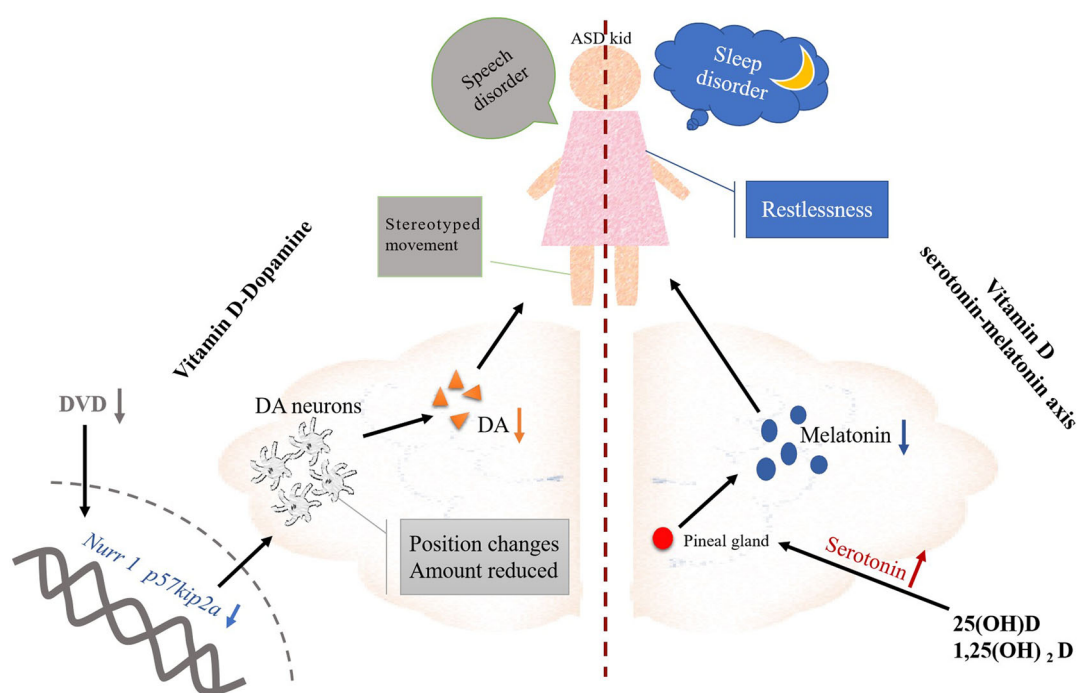


Figure 2. ASD children's behaviours may be affected by VitD regulating the secretion of dopamine and serotonin/melatonin. DVD: development VitD; DA: dopamine neurons.

VitD-dopamine hypothesis

A significant number of VDR have been found in the cortex and hippocampus [39]. A study by Harms found that mice lacking developmental VitD (DVD) severely reduced hippocampus size [40]. And insufficient DVD reduced the synthesis of dopamine (DA). In the embryonic brains of individuals with DVD deficiency, the gene expressions of *Nurr1* and *P57kip2a* were reduced, the maturation of DA neurons and DA distribution within the midbrain were inhibited [41]. The study found that 28 gene polymorphisms were associated with ASD, including the dopamine receptor D1 [42]. Among 2084 children with ASD (age under six-year-old) in Vineland, 35% were found to have obvious movement difficulties. 44% displayed poor skills with sports stereotypes (hand slap, rotation, body shaking) and non-verbal behaviour [43]. VitD and omega-3 long-chain polyunsaturated fatty acids reduced symptoms of dysphoria, and VitD also relieved symptoms of hyperactivity in ASD children³³. Brandenburg discovered that changes in the basal ganglia were associated with alterations in biochemistry or cellular processes, causing impaired language development and stereotyped movement patterns in ASD patients [44]. Additionally, the dopamine receptors within the basal ganglia circuit were crucial to motor control [45]. Consequently, ASD patients might suffer from a severely damaged dopaminergic system and neurochemical imbalance. Due to the lack of DVD, DA neurons were being damaged, the level of DA was reduced, and the growth of the striatum and the basal nucleus were abnormal, leading to speech disorder and stereotyped movements in ASD children.

VitD-serotonin-melatonin axis

Melatonin is an indoleamine produced by the pineal gland mostly found in the suprachiasmatic nucleus of the hypothalamus and the cerebrospinal fluid. Melatonin is essential for regulating sleep/wake cycles and biological rhythms [46]. According to literature, the prevalence of sleep disorders in ASD children ranged from 40 to 93%, as recently reported by Petruzzelli MG [47]. Melatonin is clinically used to treat sleep disorders. In the clinical trial, 104 weeks of melatonin therapy were administered to ASD children and adolescents. Melatonin therapy significantly improved their sleep disorders and sleep quality [48]. Researchers proposed that VitD inhibited serotonin production by regulating melatonin levels outside the blood-brain barrier [49]. In the evening, the levels of 25(OH)D and 1,25(OH)₂D in serum and peripheral *TPH1* gene expression increased, which stimulated

melatonin production [50]. ASD children with sleeping issues may benefit from low-dose melatonin due to its addictive properties. Therefore, it is still necessary to investigate the effects of melatonin combined with VitD in treating ASD children on sleeping problems.

VitD and childhood obesity

Children's diets are full of high sugar and fatty junk food. Reduced exercise also contributed to children's obesity. There were 14 million obese children in the United States [51]. Childhood obesity has been associated with type 2 diabetes, orthopaedic diseases and psychological problems such as anxiety and autism [52]. The meta-analysis showed that overweight children and adolescents had a higher prevalence of VitD deficiency, which they believed was due to the excessive absorption of fat soluble VitD by adipose tissue [53]. Serum 25(OH)D of 80.4% children aged 4 to 14 years in Chile were too low [54]; 64% morbidly obese children and adolescents were VitD deficient [55]. Akter revealed that childhood obesity associated with VitD deficiency and VDR gene polymorphisms such as single nucleotide polymorphisms (SNPs) *TaqI*, *BsmI*, *Apal*, *FokI* and *Cdx2* [56]. VDR genes' polymorphisms were associated in body weight, insulin sensitivity, and susceptibility to type 1 or type 2 diabetes [57].

Obesity inhibited CYP2R1 in the liver and consequently reduced VitD levels. In The research of Mahamoud et al. they found that obesity affected CYP2R1 gene expression in liver and kidneys, and the plasma 25(OH)D was decreased in mice [58]. They also found that obesity repressed expression of the VDR in brown adipose tissue in mice. However, no effect was observed in the human subcutaneous adipose tissue. A study on 44 Brazilian children aged 4 to 11 years old with hypertriglyceridaemia who were supplemented with cholecalciferol observed that the blood lipid level in the children's body was improved, but the change in weight was not significant [59]. In another study of 73 obese children taking oral VitD3, 50% improved their VitD levels and BMI level, all had significantly lower percentages of fat mass, but they were still obese [60]. Based on the above results, the therapeutic effect of simply supplementing VitD in the treatment of childhood obesity is not significant.

VitD and childhood asthma

Asthma is a chronic respiratory condition characterized by airway inflammation and hyperreactivity [61]. Asthma is further complicated by smoke and chemical

gas particles [62]. It is the most frequent cause of acute admissions in children and a major source of morbidity for adults with asthma, causing mild wheezing or life-threatening airway obstruction [63]. VitD had the ability to prevent airway inflammation in asthmatic mice by promoting Th17/Treg balance and inhibiting NF- κ B-mediated inflammation [64]. By activating VDR, VitD could influence various immune cells such as dendritic cells, monocytes, macrophages and T cells [65]. A meta-analysis showed that asthmatic children had significantly lower 25(OH)D levels than non-asthmatic children [66]. In a cross-sectional study in southern Jordan, 76.5% of 98 children with bronchial asthma were VitD deficient [67]. VitD deficiency was associated with increased asthma exacerbations per year and length of stay per admission [68]. According to Fergeson et al., the anti-inflammatory drugs used for the treatment of asthma were corticosteroids and β 2-adrenergic receptor agonists [69]. Taking steroid drugs would also reduce the VitD content in asthma children.

There are four types of gene polymorphisms in VDBP: GC1, GC2, GC1F and GC1S. Some studies showed that GC2 was closely related to asthma risk, and GC1 had therapeutic effect on asthma [70]. VDR gene polymorphism is also a part of asthma susceptibility genes. A meta-analysis found that VDR *FokI* and VDR *TaqI* might be risk factors for childhood asthma [71]. The VDR *FokI* polymorphism would result in a new isomer of VDR: VDRA. VDR *TaqI* will not alter the structure of VDR. However, it will affect the stability of VDR mRNA and directly affect protein transcription [72]. The polymorphisms of the VDBP gene and VDR gene might have a role in the etiopathogenesis of childhood asthma.

Diverging opinions exist regarding the effects of VitD on asthma children. Some researchers suggested that VitD supplementation may not be protective against asthma. A clinical trial conducted by Chirag Thakur reported that VitD levels increased during 12 weeks of VitD supplementation, but asthma indicators such as the Childhood Asthma Control Test (C-ACT) and the number of asthma exacerbations did not improve [73]. To determine the effectiveness of VitD supplementation, Forno's clinical study showed that VitD3 supplementation in chronic asthmatic children with low VitD levels failed to significantly improve the time to severe asthma exacerbations [74]. Systematic reviews and meta-analyses concluded that VitD supplementation had a small effect size and a low level of certainty. It was ineffective in reducing asthma attacks or systemic steroid levels, nor did it

significantly improve emergency room visits or hospitalizations of asthma children [75]. We couldn't find consistent evidence that supplementing VitD reduces asthma exacerbations in a paediatric population. Therefore, more extensive clinical trials and preclinical medical experiment are necessary to determine the effectiveness of VitD in children with asthma.

VitD and rickets

Skeletal development problems occur in children and adolescents during their growth and development. In children with rickets, low calcium levels resulted in skeletal deformities, including pectus excavatum, X-legs and O-legs [76]. Vitamin D is a key regulator of calcium and bone homeostasis. Low calcium levels symptoms were proved to be related to VitD deficiency. VitD deficiency rickets and other severe VitD deficiency manifestations, such as cardiomyopathy and hypocalcemic seizures, continued to be diagnosed in Canada [77]. This is due to the disruption of calcium metabolism caused by low VitD levels. There are three main steps involved in the active transport of calcium across the cell membrane of the proximal intestine with VitD [78] (Figure 3):

1. Luminal calcium enters the intestinal epithelial cells through transient receptor potential vanilloid type 6 (TRPV6);
2. In intestinal epithelial cells, VDR and VitD increase calcium binding to the calbindin-D9k protein and diffusing through the cytoplasm;
3. Calcium is transported from the basolateral membrane to blood vessels and bones through blood ATPase (PMCA1b) and Na⁺-Ca²⁺ exchanger 1 (NCX1) in a translational transport, or through claudin 2 and claudin 12 protein in a paracellular transport [79].

In Figure 3, the VitD and VDR enhanced calcium transport by paracellular transport and translational transport in the epithelial cells of villi and crypts, respectively [80].

VitD is an essential medium for calcium intake in multiple organs. Studies have shown that lacking adequate amounts of VitD suffered a 75% reduction in intestinal calcium absorption [81]. The kidney is also the main excretion pathway for phosphorus. Phosphate and calcium are simultaneously regulated by VitD3, parathyroid hormone (PTH) and calcitonin [82]. PTH increased the activity of 1-hydroxylase, promoted the conversion of calcidiol into calcitriol, and

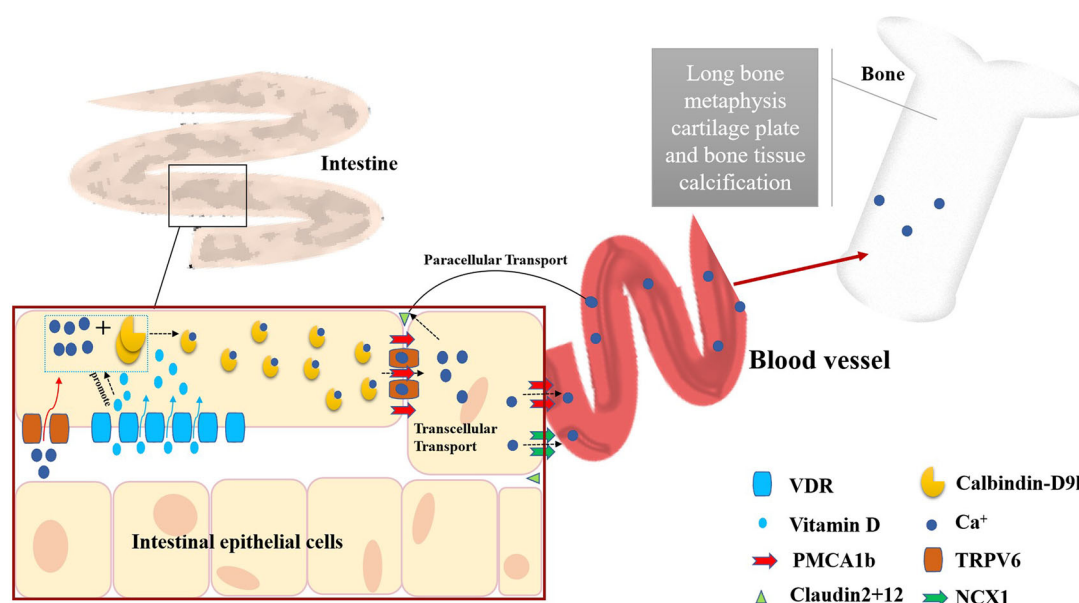


Figure 3. Calcium is absorbed in the proximal intestine and transported to bones *via* paracellular transport and transcellular transport. VDR: VitD receptor; TRPV6: transient receptor potential vanilloid type 6; NCX1: Na⁺-Ca²⁺ exchanger 1.

increased the calcium secretion of calcitriol [83]. Casselbrant et al. found, that heat shock protein in the bile could also regulate calcium transport *via* the VDR [84]. Therefore, some researchers found that the prevalence of VitD deficiency in healthy children was also common, and suggested timely supplementation of VitD for early prevention of related diseases [85].

Conclusion

It is important to underline that despite it is well known that VitD deficiency affects a big number of children, and could be associated with important childhood health problems, with VitD playing a potential role in their etiopathogenesis, nowadays data about the role of prevention and vitamin D supplementation are inconclusive.

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Author contributions

ZL did the writing, reviewing and editing of this review. YNL did the conceptualization, methodology and literature search. XLY and YW assembled the data and performed the

analysis. JZ and SMH revised it critically for intellectual content and the final approval of the version to be published. All authors agree to be accountable for all aspects of the work.

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Data availability statement

Data sharing is not applicable to this article as no new data were created or analysed in this study.

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