



## **Association of Vitamin D Deficiency and Child Growth and Development: A Retrospective Study of 0-12 Years Old**

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### **Authors' contributions**

*This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.*

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### **ABSTRACT**

**Objectives:** It aims to reduce the rate of vitamin D deficiency in children and enhance the importance of public and medical staff in timely supplementation of vitamin D and other healthy behaviors to recognize and promote the healthy growth of children.

**Methods:** A retrospective research method was used to collect relevant literature with the key words of "children", "vitamin D", "growth and development", and analyze the effect of vitamin D deficiency on growth and development in children aged 0-12 years and the prevention and treatment methods.

**Results:** Vitamin D deficiency can affect bone health in children, cause developmental delays, and have potentially negative effects on the respiratory tract, nervous system, and autoimmune system. Prevention and treatment of vitamin D deficiency in children is based on adequate sunlight and diet and vitamin D supplementation.

**Conclusions:** Vitamin D deficiency can have a profound impact on the healthy growth of children. To meet the vitamin D requirements of children, in addition to adequate sunshine and a healthy diet, reasonable vitamin D supplementation is essential. Therefore, in the process of children's growth, supplementation of vitamin D should be paid great attention and the 25-(OH)D3 level in children monitored regularly to reduce the incidence of vitamin D insufficiency or deficiency.

*Keywords: Children; vitamin D; growth and development; research progress.*

## 1. INTRODUCTION

Vitamin D is fat-soluble. In addition to participating in calcium and phosphorus metabolism and maintaining bone health, it also plays an important role in the growth, differentiation, and immune regulation of different tissue cells. Sources of vitamin D include endogenous (mainly sun exposure; 7-dehydrocholesterol stored in the basal layer of the skin is converted to vitamin D<sub>3</sub> after ultraviolet radiation) and exogenous (vitamin D preparations and dietary supplements). Sunlight is the main source, accounting for about 90% [1].

Vitamin D is an important nutrient for the growth and development of children. During the peak period of growth and development, the demand for vitamin D is relatively large. However, Chinese people have insufficient awareness of vitamin D and cannot provide reasonable dietary nutrition and vitamin D supplementation. At the same time, the increase of children's homework and the reduction of outdoor activities lead to insufficient or insufficient levels of vitamin D in children due to insufficient sunlight exposure, thereby increasing the risk of disease [2]. From the current research, little research has been done on the relationship between vitamin D and disease in children. This article briefly reviews the diseases caused by vitamin D deficiency in children 0 to 12 years and the research on its treatment and prevention, aiming to improve the awareness of vitamin D among the public and medical personnel, and promote the healthy growth of children.

## 2. METHODS

### 2.1 Study Population

A retrospective research method was used to collect relevant literature with the keywords of "children", "vitamin D" and "growth and development", and the research objects of the literature were determined to be children aged 0-12 years. Developmental effects, methods of prevention and treatment.

## 3. RESULTS AND DISCUSSION

### 3.1 Current Status of Serum Vitamin D Levels in Children

Vitamin D nutritional status has attracted much attention in China and the world. Serum 25-(OH)

D<sub>3</sub> level is the best indicator to evaluate vitamin D nutritional status and the basis for early diagnosis of vitamin D deficiency. However, the normal level of serum 25-(OH)D<sub>3</sub> in children is still controversial. Currently, most diagnostic criteria are defined by the American Academy of Pediatrics: children's serum 25-(OH)D<sub>3</sub> concentration >50.0 nmol/L is appropriate, 37.5 to 50.0 nmol/L is insufficient, ≤37.5 nmol/L is vitamin D deficient, and ≤12.5 nmol/L is severely deficient [3].

Relevant studies [4,5] have shown that vitamin D deficiency or insufficiency is widespread in the global population, and vitamin D deficiency is more common in Asia. Zhao Xin and colleagues conducted a survey on the status of vitamin D among children of 1 to 3 years in Wuxi in 2015; They found widespread vitamin D deficiency in infants and young children in this city, where the prevalence of vitamin D insufficiency is roughly 16.1% and the severity of vitamin D deficiency is positively correlated with age [6]. This is consistent with the trend of decreasing children's vitamin D levels with increasing age in the literature [7,8]. In recent years, lack of vitamin D in China has had large regional differences, generally related to factors such as regional living standards, latitude, and longitude. Research has shown that vitamin D deficiency affects about 10% to 40% of infants in southern China and 30% to 70% of infants in northern China [9]. This may be related to the relatively low production of vitamin D due to the lack of ultraviolet exposure due to the high northern latitudes and relatively few hours of sunlight.

### 3.2 The Significance of Vitamin D Supplementation in Children

#### 3.2.1 The impact of vitamin D deficiency on bones

Vitamin D plays a key role in calcium and phosphorus metabolism. Less than 10% of calcium is absorbed. Without vitamin D, the risk of poor bone health in children is reflected in increased odds of rickets. In severe cases, bone deformities such as chicken breast, pectus excavatum, square skull, X-shaped leg, and O-shaped leg can occur. Bone density is an important indicator of bone strength. Zhang Bing and colleagues reported in 2019 that when serum 25-(OH)D<sub>3</sub> is insufficient or deficient, children's serum 25-(OH)D<sub>3</sub> levels are positively

correlated with bone density [10]. A study on calcium, vitamin D, and the risk of fractures showed that 93% of children's vitamin D intake was below the recommended level [11]. A study conducted by Cauley and colleagues showed that for every 25 nmol/L decrease in serum 25-(OH)D3 level, the odds of hip fracture increase. For example, if the serum 25-(OH)D3 level is less than 50 nmol/L, the odds nearly double [12]. Vitamin D insufficiency or deficiency in childhood may also affect bone health in adulthood, leading to osteoporosis.

### **3.2.2 The effect of vitamin D on neurodevelopment**

In addition to its classic role in regulating bone metabolism, vitamin D can also regulate the development and function of the nervous system. Tic disorders (TDs) are neurodevelopmental disorders that begin in childhood and adolescence. The main clinical manifestations are vocal tics or motor tics. In recent years, studies have found that TDs may be related to dopaminergic abnormalities. Vitamin D plays an important role in the normal development and function of the dopaminergic system, so TDs may be associated with vitamin D insufficiency and deficiency [13]. A case-control study by Cui Shengtao on children with TD and trace elements and vitamins showed that their serum vitamin D level was significantly lower than that of children without the disease ( $P<0.05$ ) [14]. Li Honghua and colleagues showed that the serum 25-(OH)D3 level of children with TD was significantly lower than that of healthy controls and speculated that children with TD may have had low levels of vitamin D during their fetal period or after their birth. Long-term vitamin D deficiency or insufficiency induces tic symptoms [15]. Currently, there are few clinical studies on the relationship between vitamin D and TD. Autism, or autism spectrum disorder, is a widespread neurodevelopmental disorder. In the past 20 years, the prevalence of autism reported by different countries has trended upward. As early as 2008, Cannell [16] put forward the hypothesis that low vitamin D levels during the fetal period or early childhood is an important risk factor for autism. In 2017, Xu Ningang and colleagues used enzyme-linked immunosorbent assay to show that the serum 25(OH)D3 level of children with autism was significantly lower than that of healthy children. This is consistent with the research results of Dong Hanyu and colleagues [17] and confirms the above hypothesis. In addition, Dong Hanyu

has said that the vitamin D level of children with autism is negatively correlated with total score on the Child Autism Behavior Scale, indicating that the lower the vitamin D level, the higher the risk of autism and other neurological diseases.

### **3.2.3 The effect of vitamin D on the respiratory system**

Vitamin D deficiency is one of the reasons that children are prone to respiratory tract infections. Studies have shown that this is closely related to the role of vitamin D as an immunomodulator in infectious diseases. Hu Yunqing and others have pointed out that compared with children with sufficient vitamin D, children a deficiency are at significantly higher risk for different types of infection, especially those of the respiratory tract [18]. Fang Caiwen and colleagues found that immunoglobulin A (IgA) levels in children with vitamin D supplementation for 3 months rose, and the number of infections within 1 year declined [19]. A meta-analysis [20] also proposed that vitamin D supplementation can prevent acute respiratory infections. Liu ZQ [21] found that vitamin D also plays an important role in maintaining the stability of mast cells. A number of studies [22,23] have suggested that vitamin D deficiency in children can significantly increase the incidence of asthma.

A meta-analysis of children and adults with asthma showed that patients with vitamin D supplementation had fewer asthma attacks, with a reduction in the average annual incidence per person from 0.44 to 0.28 [24]. Today, COVID-19 is a global pandemic, and researchers have explored the correlation between its pathological mechanism and vitamin D level. Surveys have shown that compared with countries less affected by the epidemic, vitamin D levels are generally lower in Italy, Spain, and the United Kingdom, which have had high mortality rates from COVID-19 [25]. Grant and colleagues [26] reviewed the role of vitamin D in reducing the risk of respiratory tract infection and demonstrated epidemiologic and clinical evidence that vitamin D supplementation may reduce the risk of coronavirus pneumonia. Munshi Ruhul and colleagues [27] studied the vitamin D levels of 376 patients with COVID-19 and found that their average vitamin D level was 21.9 nmol/L and that the vitamin D levels of patients with poor prognoses were significantly lower than those with good prognoses. Therefore, giving an appropriate amount of vitamin D for prevention or

treatment may positively affect the development and prognosis of coronavirus pneumonia.

### 3.2.4 Impact of vitamin D on the immune system

In addition to regulating calcium and phosphorus, vitamin D also has a wide range of effects on the immune system. It is considered a new neuroendocrine-immunomodulatory hormone, and its importance in immune regulation is slowly becoming clear [28]. The vast majority of cells related to immune function contain vitamin D receptors (VDRs) such as mononuclear macrophages and activated T cells and B lymphocytes. In 2017, Gan Yingyan [29] and other scholars pointed out that children with autoimmune encephalitis (AIE) generally have insufficient or absent vitamin D levels and showed that a decline in vitamin D levels triggers AIE, which may be related to vitamin D. By combining with VDR in the AIE-prone brain area (cerebral limbic system), vitamin D plays a role in immune regulation and other functions. Systemic lupus erythematosus (SLE) is a T lymphocyte-dependent, immune complex-mediated autoimmune disease involving multiple systems. After studying children with SLE, researchers found that their vitamin D levels were lower than in healthy people [30]. After daily vitamin D supplementation for SLE patients for 12 consecutive months, SLE improved significantly more than that in the control group. The researchers pointed out that vitamin D supplementation should be given more attention during the active period of the disease [31].

Recent studies have shown that vitamin D levels are associated with Kawasaki disease, especially with coronary artery damage. Zhang Xiaoying and others [32] reported that the serum 25-(OH)D3 level of children with coronary artery damage was lower than that of children with no coronary artery damage and of the control group, suggesting that vitamin D deficiency may increase the risk of coronary artery damage in children with Kawasaki disease. This is consistent with the study by Zhang Yuanda and colleagues [33], who reported that children with Kawasaki disease have decrease 25-(OH)D3 levels and that the more obvious the decrease, the greater the possibility of coronary artery damage.

## 4. PREVENTION AND TREATMENT OF VITAMIN D DEFICIENCY

Pregnant and lactating women usually take part in fewer outdoor activities, spent insufficient time

in the sun, and have large changes in hormone levels and metabolism. They are prone to vitamin D deficiency, which directly affects the health of the fetus and newborn. A study on vitamin D guidelines in China and abroad suggests that [34]. All vitamin D guidelines surveyed recommend that pregnant and lactating women take vitamin D supplements to maintain an appropriate 25-(OH)D3 level. The Italian consensus in 2018 [35] recommended that all pregnant and breastfeeding women start taking 600 IU/d of vitamin D starting in the beginning of pregnancy. China recommends that pregnant women take 800 IU/d of vitamin D supplements daily during the perinatal period for them and their babies.

The prevention and treatment of vitamin D deficiency in childhood is based on adequate sunshine and dietary and vitamin D supplementation. However, excessive sun exposure can negatively affect children's health. Studies have shown that the younger the sun exposure, the greater the risk of skin cancer. The American Academy of Pediatrics recommends that babies 6 months or younger should avoid direct exposure to ultraviolet rays. Children need sunscreen and protective clothing outdoors. If the 25-(OH)D3 level cannot be reached through outdoor activities and dietary supplementation, vitamin D preparations are needed. The 2015 Recommendations for Prevention and Treatment of Vitamin D Deficiency and Vitamin D Deficiency Rickets [36] said that infants should receive at least 400 to 800 IU/d of vitamin D as soon as possible after birth and that high-risk groups (eg, premature infants, low birth-weight infants, twins) should receive 800 to 1000 IU/d of vitamin D.

After continuous vitamin D supplementation for 3 months, the guidelines changed to recommend 400 to 800 IU/d. The Global Consensus Recommendation for Nutritional Rickets Control (2016) [37] recommended supplementation with at least 400 IU/d vitamin D for infants and at least 600 IU/d for children older than 12 months. At the same time, Holick and colleagues [38] said that vitamin D should be given in a small dose once a day (400 IU/d for infants 0 to 1 year and 600 IU/d for those older than 1 year). They added that high-dose vitamin D supplementation three times a year (0 to 6 months, 1000 IU/d; 6 months to 1 year, 1500 IU/d; 1 to 3 years, 2500 IU/d; 4 to 8 years, 3000 IU/d; and 8 years and older, 4000 IU/d) can maintain the serum concentration of 25-(OH)D3 in the normal range. Although there

are differences in vitamin D supplementation in China and abroad, children 0 to 12 years can take 400 IU/d of vitamin D.

## 5. CONCLUSION

In conclusion, vitamin D deficiency can have a profound impact on the healthy development of children. To meet the needs of children for vitamin D, in addition to adequate sunlight and a healthy diet, reasonable vitamin D supplementation is also essential. Both UNICEF and the World Health Organization mentioned in their child development goals that the most direct and effective way to promote early childhood development is healthy nurturing [39,40]. Therefore, in the process of children's growth, high attention should be paid to vitamin D supplementation, and children's 25-(OH)D3 levels should be monitored regularly to reduce the incidence of vitamin D insufficiency or deficiency. In future research, attention should be paid to the establishment of individualized vitamin D supplementation programs for children aged 0-12 years and the correlation research of growth and development indicators monitoring, so as to provide children with better health services and promote healthy growth of children. The disadvantage of this study is that the included research data is not comprehensive enough, more clinical studies are included, and less basic research is included, which needs to be further improved. In addition, this study did not describe the time and method of children's sunlight exposure. Therefore, research on the relationship between children's sunlight exposure time, method and vitamin D can be carried out later.

## CONSENT AND ETHICAL APPROVAL

It is not applicable.

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## COMPETING INTERESTS

Authors have declared that no competing interests exist.

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