

# Vitamin D in Childhood Beyond Bone Health: A Review of Its Roles in Immunity, Metabolism, and Neurodevelopment

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## Abstract

*Vitamin D has long been known as a basic modulator of calcium and phosphorus metabolism, and a critical modulator of skeletogenesis in childhood. However, in recent years, molecular studies of vitamin D have revealed that vitamin D action is far from skeletal. The vitamin D receptor (VDR) is found in many non-skeletal tissues, such as immune cells, pancreatic  $\beta$ -cells, adipose tissue, skeletal muscle and developing nervous system. These tissues undergo genomic and nongenomic vitamin D signaling pathways that regulate the antimicrobial response, inflammation, metabolic homeostasis, neuronal differentiation, oxidative stress and synaptic function. The biological window in childhood is of special relevance since immune maturation, metabolic programming, rapid somatic growth and neurodevelopment are all happening at the same time. The relationship between vitamin D status and respiratory infections, allergic and inflammatory disorders, obesity, insulin resistance, cardiometabolic risk, cognition, behavioral development, autism spectrum disorder, and other neurodevelopmental outcomes have thus been explored. There is good biological plausibility from mechanistic and observational evidence, but a mixture of clinical evidence. Evidence from recent randomized trials does not consistently show the reduction of acute respiratory infections with vitamin D supplementation, and the effect of vitamin D on insulin resistance and cardiometabolic outcomes in children with overweight or obesity has been variable. Likewise, some associations of vitamin D with neurodevelopment have been reported, but evidence is still limited. This review explores the mechanisms of vitamin D action in childhood, beyond bone development, including its effects on immune function, metabolic physiology, neurodevelopment, critical windows of development and clinical implications. A special focus is provided on the difference between correction of deficiency and the use of vitamin D as a disease-modifying intervention. Knowing the difference will make it easier to determine more specific and evidence-based methods for assessing and supplementing vitamin D in children.*

**Keywords:** Vitamin D; Childhood; Vitamin D Receptor; Immunity; Metabolism; Neurodevelopment

## Introduction

The importance of vitamin D in the nutrition of children is no longer new, given its well-known actions in calcium absorption, phosphate metabolism, skeletal mineralization and nutritional rickets prevention. This classical function is still important, especially in times of fast skeletogenesis [1]. However, there has been a great deal of evolution in the definition of vitamin D in the past few decades. The identification of vitamin D receptors (VDRs) in a variety of tissues and the fact that several extra-renal cells have the ability to locally activate vitamin D have shifted the interest on the potential role of vitamin D as a systemic signaling hormone instead of a bone nutrient [2].

It is now recognized that vitamin D signaling activates cellular pathways that regulate innate and adaptive

immunity, inflammation, glucose control, adipose biology, neuronal differentiation, oxidative stress and synaptic function [3]. The observations are especially significant for childhood because the maturation of multiple physiological systems occur at the same time. The immune system is gradually becoming more complex and ordered, metabolic pathways are becoming programmed, body composition is rapidly changing, and the central nervous system is extensively ordered and developing in structure and function [4,5].

The first 1,000 days of life have been suggested as a critical window when nutrition exposures could have long-term effects on developmental outcomes [6]. Biologically plausible links between early-life vitamin D status and immunological, metabolic and neurodevelopmental pathways have been recently reviewed and the evidence obtained in the clinical setting has been variable [7].

But importantly, the detection of VDR in tissue or the demonstration of molecular effects of vitamin D by itself should not be taken as proof of the beneficial impact of vitamin D supplementation on clinical parameters [8]. This is important because observational studies often have found links between low vitamin D levels and the development of disease, while randomized trials have often yielded less definitive or less significant findings [9].

Thus, the present review explores the vitamin D as a development signaling molecule in multiple organs and systems during childhood, emphasizing three key biological systems: immunity, metabolism, and neurodevelopment, as well as critically assessing the robustness and weaknesses of the current evidence.

## Materials and Methods

This study employed a narrative review approach to synthesize current evidence regarding the extraskeletal roles of vitamin D during childhood, with particular emphasis on immune regulation, metabolic homeostasis, and neurodevelopment. Relevant peer-reviewed literature, including original studies, randomized controlled trials, systematic reviews, meta-analyses, and mechanistic investigations, was examined to describe vitamin D metabolism, vitamin D receptor (VDR) signaling, tissue-specific activation, and their potential clinical implications in pediatric populations. The evidence was organized thematically into three major domains: immune function, including innate and adaptive immunity and respiratory infections; metabolic function, including obesity, adipose tissue biology, insulin resistance, and cardiometabolic risk; and neurodevelopment, including neuronal differentiation, oxidative stress, neuroinflammation, cognition, behavior, and developmental outcomes. Particular attention was given to differences between mechanistic and observational evidence and findings from randomized clinical studies. Evidence was also interpreted according to developmental stages, including infancy, early childhood, school age, and adolescence, while considering potential modifying factors such as baseline 25-hydroxyvitamin D [25(OH)D] status, obesity, dietary intake, sunlight exposure, season, inflammation, and chronic disease. The synthesis was subsequently used to distinguish the established role of correcting vitamin D deficiency from the less certain use of supplementation as a disease-modifying intervention in childhood.

## Result and Discussion

### Results

#### From a “Bone Vitamin” to a Multisystem Hormonal Signal

#### The Vitamin D Metabolic Pathway: More Than Calcium Regulation

Vitamin D is mainly synthesized in the skin after exposure to ultraviolet B but also comes from food and supplements. Vitamin D is inactive in its natural state and is converted to biologically active 25-hydroxyvitamin D [25(OH)D], which is the major circulating metabolite that is clinically used to assess vitamin D status. The hormonally active metabolite 1,25-dihydroxyvitamin D [1,25(OH)<sub>2</sub>D] is formed by a subsequent hydroxylation, mainly by CYP27B1 [10].

Renal synthesis of  $1,25(\text{OH})_2\text{D}$  and control of calcium and phosphate metabolism is a classical endocrine pathway. But there are a number of other non-renal tissues that contain CYP27B1 and are therefore capable of converting  $25(\text{OH})\text{D}$  to active vitamin D locally. This tissue-specific activation offers a significant explanation as to the extraskeletal effects of vitamin D: Rather than elevating systemic levels of calcitriol, individual tissues can locally activate vitamin D to meet tissue physiological needs [11].

### VDR as a Molecular Gateway

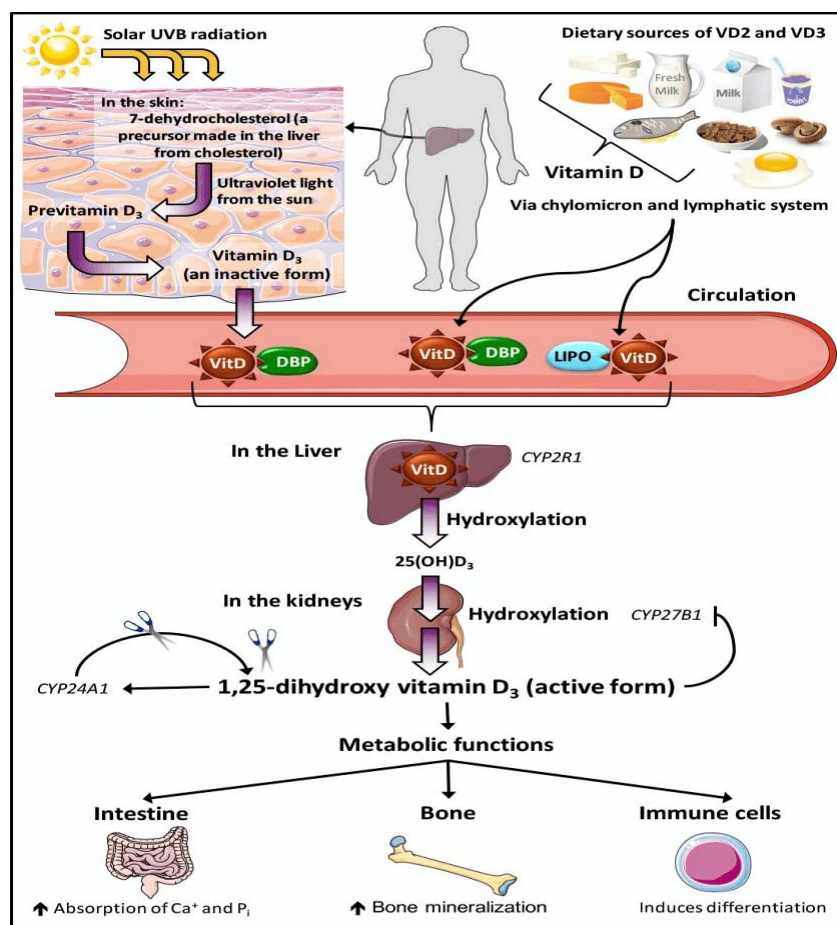
Active vitamin D effects mainly occur through the Vitamin D Receptor (VDR). VDR is a member of the nuclear receptor family of transcription factors that are activated by a ligand. VDR then binds to  $1,25(\text{OH})_2\text{D}$  to create a heterodimer with retinoid X receptor and binds to vitamin D response elements in DNA, altering the transcription of target genes [12].

The expression of the VDR in immune cells gives a molecular basis for immunomodulation, expression in pancreatic and adipose tissues gives a molecular basis for metabolic effects, and expression in neural tissues gives a plausible mechanism by which vitamin D can affect neurodevelopment [13].

### Childhood as a Unique Biological Window

Children's understanding of the importance of these pathways would be enhanced by their physiology, which includes the development of bone, immune competence, metabolic regulation and neuronal networks. Vitamin D may then play a role in multiple developmental systems, and not just in one such physiological compartment (Figure 1) [14].

The recent studies on nutritional programming during the first 1000 days validate this multi-system approach and describe potential Vitamin D pathways in the placenta, immune, metabolic, skeletogenesis and neurodevelopment pathways. The authors also point out that data from humans is not consistent, and that clinical causation does not necessarily follow from the plausibility of a biological mechanism [15].



**Figure 1.** From Sunlight to Cellular Signaling: Vitamin D Metabolism, Tissue-Specific Activation, and VDR-Mediated Multisystem Effects During Childhood.

## Vitamin D and the Immune System: Programming Defense Without Excessive Inflammation

### Vitamin D as a Regulator of Innate Immunity

Among the most explored extraskelatal targets of vitamin D is the immune system, where VDR is found in macrophages, dendritic cells, lymphocytes and other immune-cell types. Importantly, activation of the immune system may also lead to an increase in the local activity of CYP27B1, and so immune cells may generate 1,25(OH)D from the circulating 25(OH)D [16].

A major effect is the control of antimicrobial peptides such as cathelicidin and  $\beta$ -defensins. These molecules play a role in maintaining the integrity of the epithelial barrier and in defense against invading microorganisms. Vitamin D may also modulate early cell responses to pathogens via its interactions with pattern recognition pathways such as mechanisms involving Toll-like receptors [17].

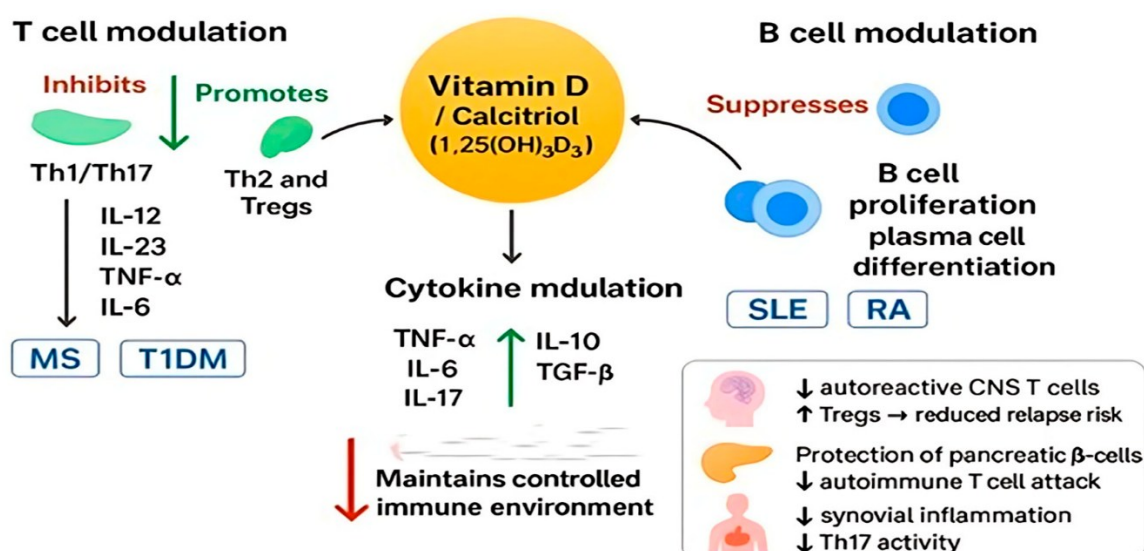
This pathway is of particular importance when children are young, when they are exposed to a number of respiratory and gastrointestinal microbes. Vitamin D may thus play a role in normal host defense, particularly for those with sub-optimal baseline vitamin D status [18].

### Adaptive Immunity and the Balance Between Defense and Tolerance

Vitamin D is also involved in adaptive immune responses. It may have a role in the maturation of antigen presenting-cells and in the modulation of the ratio of various T-cell subsets. There is experimental evidence that vitamin D may help to dampen the inflammatory activity that is associated with the Th1 and Th17 cells, while promoting the activity of the regulatory T cells (Figure 2) [19].

A state of immunological balance is of great importance in childhood. The immune system needs to be activated enough to destroy pathogens, but too much or chronic inflammation can lead to tissue damage, allergies and auto-immune disease. Vitamin D can thus be considered a biological modulator, which helps regulate immune activation and tolerance, in a delicate balance [20].

This idea has spurred studies on vitamin D for asthma, allergic disease, autoimmune disorders, and inflammatory disorders. But there is much more mechanistic evidence than clinical evidence that support supplementation as a therapy for these disorders [21].



**Figure 2.** The Vitamin D–Immune Defense Network in Childhood: Antimicrobial Peptides, Barrier Protection, Dendritic Cells, T-Cell Polarization, Cytokine Regulation, and Immune Tolerance.

### Respiratory Infections: Why the Biology Is Convincing but the Clinical Evidence Is Mixed

Respiratory infections are an example of biological plausibility vs therapeutic efficacy. Both the antimicrobial function of epithelia and inflammatory response is supposed to be improved by vitamin D theoretically, and many observational studies have demonstrated vitamin D association with respiratory infections [22].

But, there has been less randomized evidence. Systematic review and meta-analysis of 17 randomized trials including 18,372 children found that vitamin D supplementation did not significantly reduce incidence of acute respiratory infections in children, nor length of hospital stay, time to recovery or all-cause mortality in children [23].

However, these findings do not imply that vitamin D is not a factor in immunity. Instead, they speculate that any clinical effect of supplementation might be affected by factors such as baseline vitamin D levels, dosage, frequency, age, pathogen exposure, and health status. If one child is severely deficient, he or she might not respond to vitamin D as a child with adequate levels will respond. Thus, the current evidence is complex: vitamin D is an important component of a healthy immune system but supplements are not a magic bullet to prevent and treat infections [24].

### **The Vitamin D–Obesity Connection: From Adipose Sequestration to Metabolic Signaling**

#### **Why Obesity and Vitamin D Deficiency Frequently Coexist**

There has been a large number of studies on vitamin D and obesity related to vitamin D metabolism in children. 25(OH)D levels are lower in adolescents and children who are obese. A meta-analysis of 24,600 children and adolescents showed obesity to be associated with higher risk of vitamin D deficiency (pooled relative risk 1.41) [25].

There are a number of possible reasons why these two are connected. The distribution of fat-soluble vitamin D can be modified as well as its blood level by the growth of the adipose tissue. Low vitamin D status may also be contributed to by lower outdoor activity and differences in diets [26]. Furthermore, obesity may also have adverse effects on vitamin D metabolism because of metabolic dysfunction [27].

That doesn't necessarily mean one way though. The role of vitamin D signaling on adipocyte biology, inflammatory pathways and metabolic regulation implies a possible vitamin D/obesity-related dysfunction feedback loop [28].

#### **Vitamin D and Insulin Resistance**

VDR is present in pancreatic  $\beta$ -cells and in various insulin sensitive tissues. The effects of vitamin D on insulin secretion could depend on calcium-mediated pathways and could involve interactions with inflammatory and oxidative pathways that impact  $\beta$ -cell function [29].

Vitamin D has been proposed to have anti-inflammatory and effects on insulin sensitivity in skeletal muscle and fat tissue. These mechanisms offer a mechanism to explain the epidemiological relationships among low vitamin D status and insulin resistance [30].

But, the findings of intervention research have been inconsistent. In a systematic review and meta-analysis, 23 studies of supplementation in overweight and obese children and adolescents were included, finding that supplementation increased circulating levels of 25(OH)D, but there was discussion of the effects on metabolism and cardiovascular parameters [31].

Similarly, in a recent meta-analysis of 2025, which comprised 9 randomized controlled trials involving 440 people, supplementation as a whole did not significantly affect BMI, fasting glucose, insulin, HOMA-IR or some lipid parameters [32].

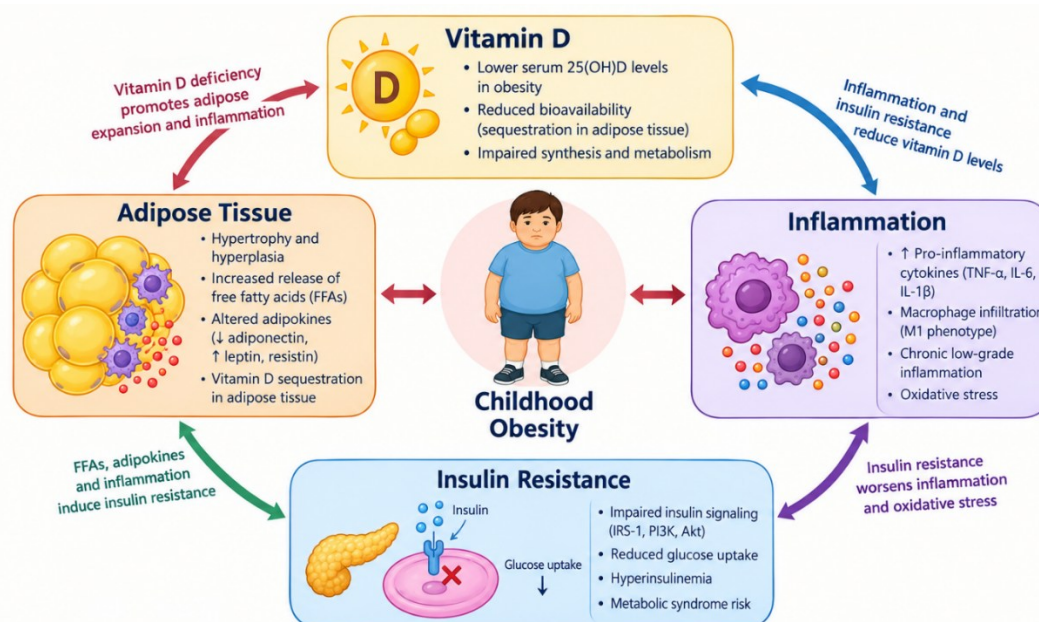
#### **The Emerging Concept of a Vitamin D–Adipose Tissue–Inflammation Axis**

Adipose tissue is an endocrine and immune active organ. Obesity is characterized by hypertrophy of adipocytes with infiltration of macrophages, secretion of adipokines and chronic low-grade inflammation. These processes could be influenced by vitamin D signaling by regulating inflammatory transcription pathways and adipocyte differentiation [33].

Such a model is thus more complex than just “obesity causes vitamin D deficiency.” It proposes a possibly linked set of biological links between adipose tissue, Vitamin D metabolism, inflammation, insulin signaling and energy homeostasis (Figure 3) [34].

At present, however, there are no sufficient data to suggest that vitamin D supplements are effective in treating pediatric obesity. Instead, vitamin D should be regarded as a part of the nutritional and metabolic

evaluation, especially in children with a high risk of deficiency.



**Figure 3.** Beyond Sequestration: The Bidirectional Vitamin D–Adipose Tissue–Inflammation–Insulin Resistance Axis in Childhood Obesity.

### Vitamin D and the Developing Brain: A Nutritional Signal at the Neurodevelopmental Interface

#### Why the Brain Responds to Vitamin D

One of the most exciting new areas of vitamin D research is the developing nervous system. The presence of VDR and vitamin D-metabolizing enzymes in neural tissues suggest that vitamin D has local action within the brain [35].

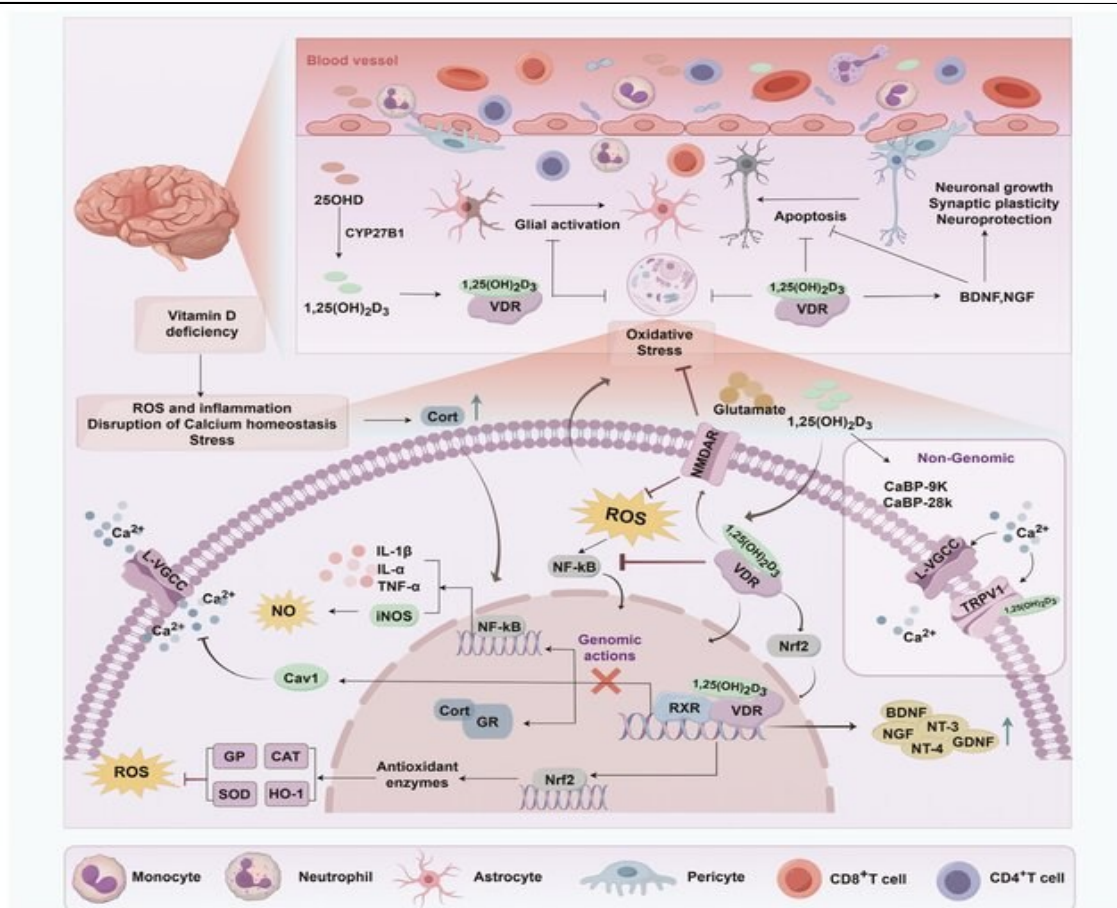
The coordinated and precise execution of neuronal proliferation, migration, differentiation, axonal growth, formation of synapses and maturation of networks are essential for neurodevelopment. Several of these processes have been implicated in vitamin D. Its potential actions include regulation of neurotrophic signaling, calcium homeostasis, anti-oxidant defense, neuronal differentiation and inflammatory pathways [36]. These mechanisms are especially relevant at the time of fetal development, infancy, and early childhood when neural circuits are undergoing tremendous structural and functional modifications.

#### Neurotrophic Signaling, Oxidative Stress, and Neuroinflammation

Vitamin D's involvement in neurotrophic factors and/or neuronal survival pathways is investigated. It can also impact oxidative stress and neuroinflammation—two areas of biology that can impact neural development [37].

The brain is a very special tissue because it has a high metabolic rate and the lipid-rich cell membranes make it particularly sensitive to oxidative imbalance (Figure 4). Too much oxidative stress can result in harm to proteins, lipids, and nucleic acids and inflammatory activation can cause changes in the signaling and organization of neurons. Vitamin D can regulate these pathways by modulating inflammatory mediators and/or by transcriptional regulation [38,39].

These mechanisms are biologically attractive as reasons for vitamin D to play a role as a neurodevelopmental factor. However, most mechanistic evidence is only available from experiments and extrapolation to the pediatric population is incomplete.



**Figure 4.** Vitamin D at the Neurodevelopmental Interface: VDR Signaling Linking Neuronal Differentiation, Neurotrophic Support, Calcium Homeostasis, Oxidative Stress, Neuroinflammation, and Synaptic Plasticity.

### Cognition, Behavior, Autism, and Attention-Related Outcomes

The relationship between human vitamin D and cognitive, language, motor, behavioral and developmental outcomes, such as autism spectrum disorders (ASD) and attention-related disorders (ARD), has been studied. Several studies have found a link between lower vitamin D levels and poorer neurodevelopmental outcomes, whereas none have found any strong correlation [40].

There were 31 studies with 31,375 subjects that were included in a systematic review which showed a very mixed body of evidence [41,42]. Association of low vitamin D status with neurobehavioral outcomes has been reported to be both positive and negative in both maternal and childhood studies [43,44]. The evidence available for pediatrics from this review did not show a definite causal link.

It's really a big difference in science. A low vitamin D level can occur in conjunction with other factors that impact neurodevelopment such as maternal health, socioeconomic status, nutrition, physical activity, chronic diseases, and environmental exposures. So, at the present time, decreased levels of vitamin D are not a known cause of autism, ADHD or cognitive dysfunction [45].

So far, the most intriguing hypothesis is that vitamin D may be a potential neurodevelopmental signaling molecule, but the extent and significance of the effect of vitamin D in humans has yet to be determined.

### One Molecule, Different Developmental Windows: Vitamin D From Infancy to Adolescence

Infancy is one of the most dynamic periods of human growth and development. The skeleton is mineralizing rapidly, immune response is developing, and there is significant brain synaptic development. Therefore, adequate vitamin D levels in infants may play a role in numerous physiological systems [46].

The early 1000 days of a child's life has been suggested as a critical period of nutritional programming. Existing literature indicates that vitamin D may play a role in skeletal, immune, metabolic and

neurodevelopmental functions during this time. There are, however, non-consistent long-term extra-skeletal benefits of supplementation [47].

Vitamin D status in school-aged population is influenced by the outdoor activity, seasonal variation, dietary intake, body composition, geographic location, and chronic disease. In this period, continual exposure to infectious pathogens and continued cognitive and behavioral development [48].

Children with reduced exposure to sunlight and/or reduced dietary intake of vitamin D may be at risk for Vitamin D deficiency. Likewise, children who are obese might be at risk for deficiency. But the overall picture of the nutrition status, physical activity, sleep, socioeconomic factors and overall health should be taken into account when interpreting vitamin D status [49].

Adolescence is one of the critical stages of development. Rapid skeletal growth and hormonal changes, adiposity in some, and lifestyle changes might influence vitamin D status. Not doing as much outside activity and spending more time in front of screens may reduce exposure to the sun [50].

However, insulin resistance, dyslipidemia and hypertension may begin to occur as risk factors linked with the heart and blood sugar. This has led to the vitamin D being recognized as a metabolic modifier [51].

However, there is not clear evidence for randomization. Meta-analyses of overweight and obese children and adolescents have found mixed results for BMI, but consistent improvements for vitamin D levels, no improvements for other cardiometabolic markers [52]. So, developmental stage is likely to be an important modifier of vitamin D biology. Vitamin D status during infancy does not necessarily correspond to that during adolescence.

### **From Deficiency Correction to Precision Pediatric Vitamin D: What Should Come Next?**

Serum 25(OH)D is the most commonly used parameter of vitamin D status. There are, however, important considerations of assay method, biological variability, season, age, obesity and clinical setting to be taken into account before making the interpretation [53].

One of the limitations in the extraskeletal literature is that different concentrations of an agent are probably needed for optimal activity in immune, metabolic and neurological functions compared to the activity in skeletal disease. But there's no definite evidence that higher amounts are beneficial, meaning that "more vitamin D" does not equate to better health [54].

The most evidence-based indication for giving vitamin D to kids is to prevent vitamin D deficiency and its skeletal manifestations. The cases for supplementation are much less clear when directed to the prevention of infection, treatment of obesity, treatment of insulin resistance, and modification of neurodevelopment (Figure 5) [55].

This is certainly emphasized in the literature of the respiratory system. In a meta-analysis of 18,372 children from 20 pediatric randomized trials, there was no overall evidence of a reduction in the incidence of acute respiratory infections and clinical outcomes [56,57].

There is some conflicting evidence in the metabolic category, too. The current evidence suggests that vitamin D doesn't have a cardiometabolic benefit in children overall, although there were some sub-groups that provided some evidence of potential benefit, including children with obesity and a child's low vitamin D status [58].

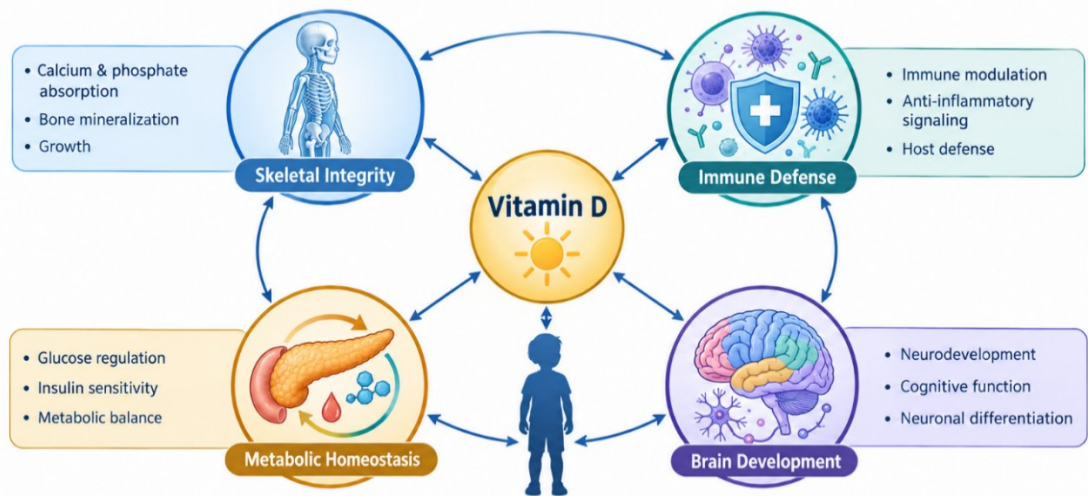
So the right scientific answer is not to say that vitamin D doesn't have any extraskeletal effects. Instead, the data suggests that in not every child, biological activity is correlated to clinically-relevant response to supplementation [59].

In the future, studies should be directed towards developing a precision model (Figure 6). Children are not all equal and it is important that baseline 25(OH)D levels, age, developmental stage, obesity, diet, season, genetic variation, inflammatory status, and chronic disease status shall be considered when interpreting the results of studies.

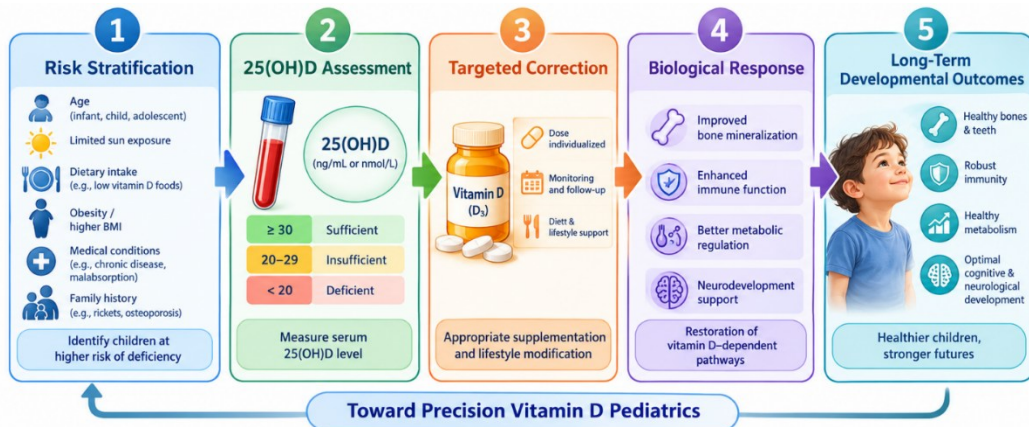
This may be why some trials report good results and others don't. The effect of vitamin-D supplementation may vary between a vitamin-D deficient child with chronic inflammation and a child who is vitamin-D

sufficient, however. Primary prevention, Vitamin-D.

Designing large randomized trials should thus be based on clinically well-defined biological phenotypes and not merely supplementing vitamin D and comparing it with a placebo group in a heterogeneous pediatric population.



**Figure 5.** The Integrated Vitamin D–Childhood Health Network: Connecting Skeletal Integrity, Immune Defense, Metabolic Homeostasis, and Brain Development.



**Figure 6.** Toward Precision Vitamin D Pediatrics: Risk Stratification → 25(OH)D Assessment → Targeted Correction → Biological Response → Long-Term Developmental Outcomes.

## Discussion

The findings of this review indicate that vitamin D should be considered not only a regulator of skeletal mineralization but also a biologically active signaling molecule involved in several developmental systems during childhood. The widespread expression of VDR and the capacity of extra-renal tissues to locally activate vitamin D provide a plausible molecular basis for its involvement in immune regulation, metabolic homeostasis, and neurodevelopment. In the immune system, vitamin D influences antimicrobial peptide production, epithelial defense, antigen presentation, T-cell differentiation, and inflammatory regulation; however, these mechanistic effects have not consistently translated into clinical benefits from supplementation. Notably, evidence summarized in the manuscript shows that randomized trials involving children did not demonstrate a consistent reduction in acute respiratory infections or related clinical outcomes following vitamin D supplementation. Similarly, although obesity in children and adolescents is frequently associated with lower 25(OH)D concentrations and vitamin D signaling may interact with

adipose inflammation and insulin-related pathways, supplementation has produced inconsistent effects on BMI, glucose regulation, insulin resistance, and other cardiometabolic indicators. 16983\_Naskah\_Utama In neurodevelopment, the presence of VDR and vitamin D-metabolizing enzymes in neural tissues supports potential roles in neuronal differentiation, neurotrophic signaling, calcium homeostasis, oxidative defense, and neuroinflammatory regulation, yet available human evidence remains heterogeneous and does not establish vitamin D deficiency as a direct cause of autism spectrum disorder, attention-related disorders, or cognitive dysfunction. Collectively, these findings highlight an important distinction between biological activity and therapeutic efficacy: the existence of vitamin D-dependent molecular pathways does not necessarily mean that universal supplementation will improve extraskelatal clinical outcomes. Therefore, the strongest current rationale remains the prevention and correction of vitamin D deficiency and its skeletal consequences, while extraskelatal supplementation should be interpreted cautiously. Future research should adopt a more individualized or precision-based approach by considering baseline vitamin D status, developmental stage, obesity, diet, season, inflammatory status, genetic variation, and chronic disease when identifying children who may derive measurable extraskelatal benefits from vitamin D intervention.

## Conclusion

Previous ideas about the role of vitamin D as a bone mineralization hormone are no longer the only ones that are in the realm of possibility. From a molecular perspective, more and more evidence is emerging to support the notion that vitamin D signaling is an integral component of a complex multisystem network of immune regulation, metabolic homeostasis, adipose biology, neuronal development, oxidative stress and synaptic function. These actions have a strong biological basis as VDR is expressed in a variety of tissues and extra-renal cells can locally activate vitamin D.

One of the most apparent extraskelatal vitamin D actions is the immune system. The role of vitamin D in the production of antimicrobial peptides, epithelial immunity, antigen presentation, T-cell differentiation and regulation of inflammatory response. However, there is no randomized evidence of the effectiveness of universal supplementation to reduce ARI in children at present. Reminder: Efficacy (therapeutic effect) does not always equal physiological importance.

This vitamin D – childhood obesity link is also puzzling. Vitamin D deficiency is far more prevalent in children who are overweight and there are potential interactions between vitamin D metabolism, inflammatory pathways and adipose tissue. The effects of supplementation on BMI, insulin resistance, glucose regulation and cardiometabolic risk, however, are not always observed in children.

A special area of interest is neurodevelopment. It is suggested that Vitamin D signaling in neural tissues exerts a neurotrophic effect, oxidative stress, neuroinflammation and promotes neuronal differentiation and synaptic development through Vitamin D. However, there is some conflicting human evidence and at this time there is no direct evidence that vitamin D deficiency is a cause of neurodevelopmental disorders.

The concept that emerges is not just that vitamin D “prevents disease,” however, but that vitamin D is a developmental signaling component with biologic effects that are dependent on the context. Other factors to consider in addition to developmental stage are age, baseline vitamin D levels, obesity, inflammation, diet, sun exposure and genetic variations.

Moving from universal supplementation to precision pediatric vitamin D medicine, in which vitamin D would be targeted based on biological need, should consequently be the next step of research. This may help identify children that would be identified as benefiting and may suggest whether or not correction of the deficiency would likely impact immune, metabolic or neurodevelopmental pathways.

Last but not least, the “bone vitamin” role of Vitamin D should not be considered solely for its activity in bone development but as a multisystem developmental signal, linking the skeleton, the immune system, the metabolic organs and the developing brain. Current pediatric research should not be limited to establishing the vitamin D beyond bone benefits, but should also focus on who the people are, in which context the

vitamin D effects are beneficial, and when it is possible for vitamin D intervention to change that in order to make a difference.

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