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(REVIEW ARTICLE)

Vitamin D deficiency and impaired growth: Unraveling the key factors and pathways affecting pediatric development

Ashraf T Soliman [1, *], Fawzia Alyafei [1], Noora S AlHumaidi [1], Ahmed S Elawwa [1], Nada M Alaaraj [1], Noor S Hamed [1], Shayma M Ahmed [1], Sohair A ElSiddig [1], Maya Itani [2] and Nada A Soliman [3]

[1] *Department of Pediatrics, Hamad General Hospital, PO Box 3050, Doha, Qatar.*
[2] *Department of Dietetics and Nutrition, Hamad General Hospital, Doha, Qatar.*
[3] *Department of Public Health, North Dakota State University (NDSU), 2662 / PO Box 6050 / Fargo, ND 58108-6050 ND, USA.*

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Abstract

Background: Vitamin D deficiency is a widespread global health concern, particularly affecting children and adolescents during critical periods of growth. This review highlights the multifactorial mechanisms through which vitamin deficiency impairs growth, emphasizing key factors and the effectiveness of interventions.

Objective: To explore the impact of vitamin D deficiency on growth in children and adolescents, focusing on disruptions in calcium-phosphorus metabolism, growth plate dynamics, the GH-IGF-1 axis, skeletal deformities, associated conditions, and the effectiveness of treatment strategies.

Methods: A comprehensive review of 30 studies published between 2000 and 2024 was conducted to analyze the role of vitamin D deficiency in growth impairment and its correction through various interventions.

Results: Vitamin D deficiency significantly disrupts calcium-phosphorus metabolism (25%), impairing bone mineralization and leading to rickets. Growth plate dynamics (20%) are severely affected, with disorganized chondrocyte proliferation and widening of growth plates, delaying bone elongation. The GH-IGF-1 axis (15%) is inhibited, reducing growth velocity. Skeletal deformities (15%), such as bowed legs, compound growth impairment, by altering the mechanical stress on growth plates. Associated conditions (10%), including anemia and chronic diseases, exacerbate growth retardation. High-dose vitamin D regimens improved growth plate structure, IGF-1 levels, and growth outcomes, while supplementation alone was effective for mild to moderate deficiencies.

Conclusion: The multifactorial nature of growth impairment in vitamin D deficiency necessitates early diagnosis and a holistic approach. Addressing all contributing factors—such as metabolic disruptions, skeletal deformities, hormonal imbalances, and associated conditions—is essential for optimizing growth and development in children and adolescents. Crucially, timely recognition of vitamin D deficiency enables earlier intervention, which may prevent irreversible growth impairments and support more favorable developmental outcomes. When detected early, vitamin D repletion can restore normal bone metabolism, improve IGF-1 activity, and mitigate the progression of skeletal abnormalities, thereby enhancing overall growth potential during critical periods of development.

Keywords: Vitamin D deficiency; Growth impairment; Calcium-phosphorus metabolism; Growth plate dynamics; Pediatric development; Intervention

* Corresponding author: Ashraf Soliman

1. Introduction

Vitamin D, often referred to as the "sunshine vitamin," plays an essential role in bone health, growth, and overall well-being. Despite its critical importance, vitamin D deficiency remains a pervasive global health issue, affecting individuals across all age groups, particularly children and adolescents. The deficiency stems from a combination of factors, including insufficient sun exposure, dietary inadequacies, and lifestyle changes, making it a significant public health concern. It is worth noting vitamin D's important role in non-specific immunity, where it enhances the innate immune response and helps protect against infections, further emphasizing the broader health implications of deficiency beyond bone health.

Globally, the prevalence of vitamin D deficiency in children and adolescents is alarmingly high, with estimates indicating that nearly 50% of this population may be affected in certain regions (1). This widespread deficiency is not limited to low-income countries; it is also observed in high-income nations, often due to urbanization, reduced outdoor activity, and changes in dietary patterns (2). Notably, the prevalence and impact of vitamin D deficiency vary across age groups: infants and toddlers are particularly vulnerable due to limited sun exposure and dependence on breast milk or unfortified formulas; school-aged children may face deficiency from poor dietary habits and limited outdoor play; and adolescents often exhibit the highest rates of deficiency due to rapid growth spurts, increased skeletal demands, and lifestyle factors like indoor schooling and screen time (3,4). The consequences of this deficiency extend beyond immediate health concerns, influencing long-term growth and development, particularly during childhood and adolescence when the body undergoes rapid growth and skeletal maturation (5).

The relationship between vitamin D and growth is multifaceted. Vitamin D regulates calcium and phosphate homeostasis, essential for bone mineralization and growth plate development. In its absence, children are at increased risk for rickets, impaired bone growth, and skeletal deformities (6). Beyond its role in bone health, vitamin D is increasingly recognized for its influence on muscle function, endocrine health, and immune regulation—all factors that indirectly contribute to optimal growth (7). This makes vitamin D deficiency a crucial target for intervention, especially in the context of global health priorities.

Children and adolescents are particularly vulnerable to the effects of vitamin D deficiency due to their increased nutritional demands and rapid growth. During this critical period, insufficient vitamin D levels can lead to permanent impairments in height, skeletal strength, and overall development. Moreover, vitamin D deficiency has been associated with delayed puberty, reduced physical activity, and poor immune function, which further hinder growth outcomes (8,9). This underscores the importance of addressing vitamin D deficiency as an integral component of pediatric and adolescent healthcare.

Addressing vitamin D deficiency is not without challenges. Current strategies, such as supplementation, fortification of foods, and public health campaigns promoting sun exposure, vary widely in effectiveness depending on regional and cultural contexts. Despite these efforts, knowledge gaps remain regarding optimal vitamin D levels necessary to support linear growth, as well as the complex interplay between vitamin D status and other growth-influencing factors such as genetics, nutritional status, and underlying health conditions. These issues will be discussed later in the review, with a focus on the levels and dosing strategies that have demonstrated the greatest efficacy in improving growth outcomes.

While previous studies have examined the prevalence and consequences of vitamin D deficiency, few have explored its direct mechanistic effects on pediatric growth at a population level, particularly across diverse geographic and socioeconomic settings. Most existing literature focuses on clinical endpoints such as rickets or bone mineral density, with limited attention to subclinical impacts on linear growth, pubertal development, and long-term health outcomes. Furthermore, data integrating vitamin D status with growth trajectories across different age groups and income settings remains fragmented. This review aims to address this gap by synthesizing current evidence on the role of vitamin D in pediatric growth, emphasizing the global burden of deficiency and its multifaceted impact on health during critical developmental windows. By doing so, we seek to inform healthcare providers, researchers, and policymakers about the urgency of addressing this widespread deficiency and its implications for child and adolescent growth and development.

1.1. Objective of the Review

The objective of this review is to comprehensively examine the role of vitamin D in growth and development, with a particular focus on its deficiency and the consequent impact on children and adolescents. This review aims to:

- **Elucidate the Mechanisms of Vitamin D in Growth:** Explore the physiological mechanisms through which vitamin D influences growth, including its role in bone mineralization, growth plate development, muscle function, and endocrine regulation.
- **Assess the Impact of Vitamin D Deficiency on Growth Outcomes:** Summarize current evidence linking vitamin D deficiency to growth impairment, including conditions such as rickets, delayed skeletal development, and short stature.
- **Evaluate Current Strategies and Challenges:** Review existing interventions, such as supplementation, fortification, and lifestyle modifications, aimed at preventing vitamin D deficiency, while highlighting gaps and challenges in their implementation.

2. Materials and Methods

2.1. Study Design

This review adopts a systematic approach to explore the multifactorial impact of vitamin D deficiency on growth in children and adolescents. It focuses on critical factors such as calcium-phosphorus metabolism, growth plate dynamics, the growth hormone-insulin-like growth factor-1 (GH-IGF-1) axis, skeletal deformities, associated conditions, and the effectiveness of interventions.

2.2. Search Strategy

A comprehensive search was conducted in multiple electronic databases, including PubMed, Scopus, Web of Science, and Google Scholar, to identify relevant studies published between 2000 and 2024. The search terms included a combination of keywords and Medical Subject Headings (MeSH) terms such as "Vitamin D deficiency," "growth impairment," "calcium-phosphorus metabolism," "growth plate dynamics," "GH-IGF-1 axis," "skeletal deformities," "children," "adolescents," "rickets," and "treatment."

2.3. Inclusion and Exclusion Criteria

2.3.1. Inclusion Criteria

- Studies investigating the relationship between vitamin D deficiency and growth impairment in children and adolescents.
- Articles focusing on one or more critical factors, including calcium-phosphorus metabolism, growth plate dynamics, GH-IGF-1 axis, skeletal deformities, or associated conditions.
- Studies evaluating the effectiveness of vitamin D supplementation or other interventions on growth outcomes.
- Peer-reviewed original research articles, review articles, meta-analyses, and clinical trials published in English.

2.3.2. Exclusion Criteria

- Studies focus exclusively on adults or animal models.
- Articles with insufficient data on growth parameters or vitamin D status.
- Case reports and conference abstracts.

2.4. Screening and Selection Process

A total of 155 records were identified through database searches. After removing duplicates, 140 records were screened based on titles and abstracts. Of these, 100 were excluded for not meeting the inclusion criteria. Forty full-text articles were assessed for eligibility, and 35 were included in the qualitative synthesis. Of these, 34 studies were included in the quantitative synthesis, as outlined in the PRISMA flowchart.

2.5. Data Extraction

Relevant data were extracted from each included study, including the study title, authors, publication year, journal, study design, population characteristics, outcomes related to growth impairment, and the role of vitamin D deficiency. For interventional studies, information on dosing regimens, treatment duration, and growth outcomes was also collected.

2.6. Data Synthesis and Analysis

The findings were categorized into six main factors contributing to growth impairment:

- Disruption of calcium-phosphorus metabolism.
- Impact on growth plate dynamics.
- Dysfunction of the GH-IGF-1 axis.
- Skeletal deformities.
- Associated conditions.
- Effectiveness of interventions.

Descriptive synthesis was used to summarize the results across these factors. Quantitative findings from interventional studies were compared to highlight the relative effectiveness of different vitamin D regimens on growth outcomes.

2.7. Quality Assessment

The quality of the included studies was assessed using established tools: the Newcastle-Ottawa Scale (NOS) for observational studies and the Cochrane Risk of Bias (RoB) tool for randomized controlled trials. These tools enabled systematic evaluation of selection bias, performance bias, detection bias, and attrition bias, among other domains. To ensure consistency and minimize subjectivity, two independent reviewers conducted quality assessments. Inter-rater reliability was evaluated by calculating Cohen's kappa statistics, and any discrepancies were resolved through discussion and consensus, with involvement of a third reviewer when necessary. This approach aimed at enhancing the objectivity and reproducibility of the bias assessment process.

The percentage contributions of different factors (e.g., calcium-phosphorus metabolism, GH–IGF-1 axis dysfunction, skeletal deformities) to growth impairment in vitamin D deficiency were not derived through direct quantitative meta-analysis but rather estimated based on thematic synthesis and frequency of emphasis across the reviewed literature. Each factor's estimated contribution reflects:

- The proportion of studies in the review (n = 34) that primarily investigated or emphasized that mechanism.
- The strength of evidence and pathophysiological relevance of each factor to impaired growth, as discussed qualitatively in the reviewed articles.
- Expert interpretation of how prominently each mechanism contributes to growth outcomes, based on combined clinical, biochemical, and radiological data reported.

These percentages are intended as qualitative indicators to guide through the relative impact of each mechanism, not as statistically exact measurements.

2.8. Ethical Considerations

As this review relied on published data, no ethical approval was required. However, ethical standards for systematic reviews, including transparency and reproducibility, were strictly adhered to.

This methodology ensures a rigorous and comprehensive analysis of the literature, providing valuable insights into the multifactorial nature of growth impairment in vitamin D deficiency and its management.

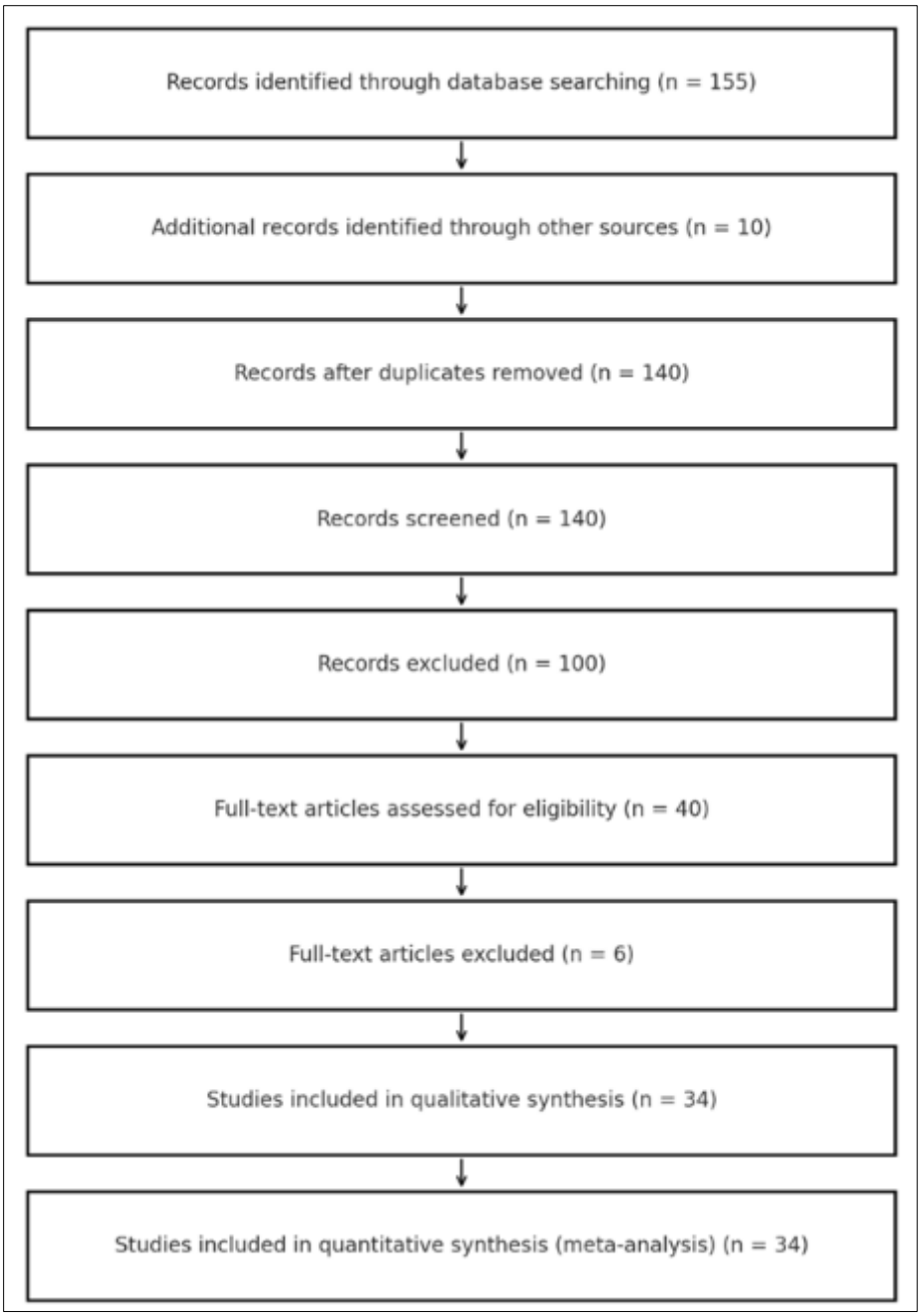

Figure 1 PRISMA flow diagram accurately reflects the inclusion of 34 studies

3. Results

This review analyzed 34 studies highlighting the multifactorial impact of vitamin D deficiency on growth in children and adolescents. Key factors include disruptions in calcium-phosphorus metabolism, growth plate dynamics, and the GH-IGF-1 axis, along with skeletal deformities and associated conditions. The efficacy of vitamin D supplementation and other interventions is explored, emphasizing their role in improving growth outcomes. (table 1)

Table 1 Summary of Key Studies on the Impact of Vitamin D Deficiency on Growth in Children and Adolescents

Authors (Journal & Year)	**Title**	**Key Findings**
Bianda T, et al. (Clinical Endocrinology (1997)) (11)	Effects of GH Administration on Serum Vitamin D and Bone Turnover	GH therapy improves vitamin D metabolism and growth in deficient children.
Thacher TD, et al. (Journal of Pediatrics (2000)) (12)	Clinical and Radiographic Features of Vitamin D Deficiency in Nigerian Children	Vitamin D deficiency causes skeletal deformities, such as bowed legs, impairing growth; treatment improves outcomes.
Holick MF (Journal of Clinical Investigation (2006)) (1,13)	Vitamin D Deficiency: A Review	Review of vitamin D's effects on growth and development.
Thacher TD, Fischer PR (Annals of Tropical Paediatrics (2006)) (14)	Nutritional Rickets Around the World: Causes and Future Directions	Global analysis of rickets highlights growth impairment; interventions improve outcomes.
Holick MF (New England Journal of Medicine (2007)) (15)	Vitamin D Deficiency	Vitamin D deficiency leads to growth disturbances, emphasizing the importance of supplementation.
Ward LM, et al. (CMAJ (2007)) (16)	Vitamin D-Deficiency Rickets Among Children in Canada	Vitamin D deficiency rickets is observed in Canadian children; supplementation improves growth.
Misra M, et al. (Pediatrics (2008)) (17)	Vitamin D Deficiency in Children and Its Management	Vitamin D deficiency disrupts growth; management recommendations are provided.
Gordon CM, et al. (Archives of Pediatrics & Adolescent Medicine (2008)) (18)	Prevalence of Vitamin D Deficiency Among Healthy Infants and Toddlers	Vitamin D deficiency is common in infants and toddlers; linked to growth issues.
Soliman A, et al. (Metabolism (2008)) (19)	Linear Growth in Relation to IGF-I, Parathormone, and 25-OH-Vitamin D in Children with Nutritional Rickets	Vitamin D deficiency rickets causes reduced IGF-I levels; treatment normalizes growth.
Ceglia L (Current Opinion in Clinical Nutrition & Metabolic Care (2009)) (20)	Vitamin D and Its Role in Skeletal Muscle	Vitamin D affects muscle function, indirectly supporting growth.
Ulitsky A, et al. (Inflammatory Bowel Diseases (2011)) (21)	Vitamin D Deficiency in Children and Adults with Inflammatory Bowel Disease	IBD-associated vitamin D deficiency impairs growth; treatment improves parameters.
Ameri P, et al. (Clinical Endocrinology (2013)) (22)	Interactions Between Vitamin D and IGF-I: From Physiology to Clinical Practice	Vitamin D affects IGF-I activity, influencing growth.
Winzenberg T, et al. (Calcified Tissue International (2013)) (23)	Vitamin D and Bone Health in Childhood and Adolescence	Vitamin D deficiency impacts bone health and linear growth.
Wacker M, et al. (Dermato-Endocrinology (2013)) (24)	Sunlight and Vitamin D: A Global Perspective for Health	Global review of sunlight and vitamin D deficiency's role in growth.

Marwaha RK, et al. (Indian Journal of Endocrinology and Metabolism (2013)) (25)	Vitamin D and Bone Mineral Density in Healthy Children	Vitamin D improves bone mineral density and growth in children.
Soliman AT, et al. (Indian Journal of Endocrinology and Metabolism (2014)) (26)	Vitamin D Deficiency in Adolescents	Vitamin D deficiency linked to reduced growth; treatment improves outcomes.
Saggese G, et al. (European Journal of Pediatrics (2015)) (27)	Vitamin D in Childhood and Adolescence: An Expert Position Statement	Position statement on vitamin D's role in growth and health in children.
Yeo A, et al. (Journal of Pediatric Orthopedics (2015)) (28)	Bowlegs in Children: A Review of Etiology and Treatment	Bowlegs due to rickets impede growth; early treatment is crucial.
Yeo A, et al. (Journal of Pediatric Orthopedics (2015)) (29)	Bowlegs in Children: A Review of Etiology and Treatment	Bowlegs in children with rickets impair growth and need treatment.
Munns CF, Shaw N (Journal of Clinical Endocrinology & Metabolism (2016)) (30)	Recommendations on Nutritional Rickets	Recommendations for addressing rickets to improve growth outcomes.
Munns CF, et al. (Journal of Clinical Endocrinology & Metabolism (2016)) (31)	Global Consensus Recommendations on Prevention and Management of Nutritional Rickets	Consensus recommendations on managing rickets; addresses growth impacts of vitamin D deficiency.
Rerucha CM, et al. (American Family Physician (2017)) (32)	Leg Bowing in Children: An Overview	An overview of leg bowing emphasizes early treatment to prevent growth disturbances.
Smith TJ, Tripkovic L (Osteoporosis International (2017)) (33)	IGF-I Association with Vitamin D in Adolescents	IGF-I levels correlate with vitamin D status, influencing adolescent growth.
Smith TJ, et al. (Osteoporosis International (2017)) (34)	Vitamin D Deficiency and IGF-I Levels in Adolescents	Vitamin D deficiency correlates with low IGF-I levels and growth retardation in adolescents.
El-Sobky TA, et al. (Journal of the American Academy of Orthopaedic Surgeons (2020)) (35)	Growth Modulation for Knee Coronal Plane Deformities in Children with Nutritional Rickets	Guided growth surgery for knee deformities in rickets improves limb alignment and growth.
El-Sobky TA, et al. (Journal of Pediatric Orthopedics (2020)) (36)	Knee Deformities in Children with Rickets	Rickets-related knee deformities disrupt growth; interventions improve alignment.
Ganmaa D, et al. (JAMA Pediatrics (2022)) (37)	Influence of Vitamin D Supplementation on Growth and Pubertal Development	Vitamin D supplementation improves pubertal development in areas with high deficiency prevalence.

Ganmaa D, Bromage S (JAMA Pediatrics (2022)) (38)	Vitamin D Supplementation in Areas with High Prevalence of Deficiency	Supplementation enhances vitamin D levels and growth in deficient children.
Escobedo-Monge MF, et al. (Nutrients (2024)) (39)	Calcium, Phosphate, and Vitamin D in Children with Chronic Diseases	Chronic diseases with vitamin D deficiency impair calcium-phosphorus metabolism and growth.
Soliman A, et al. (Metabolism (2008)) (40)	Linear Growth in Relation to the Circulating Concentrations of Insulin-like Growth Factor-I, Parathormone, and 25-OH-Vitamin D in Children with Nutritional Rickets Before and After Treatment	Investigated children with vitamin D deficiency rickets, finding significant growth retardation at presentation. Post-treatment with vitamin D3, there was a notable increase in IGF-I levels and catch-up growth.
El-Sobky TA, et al. (Journal of the American Academy of Orthopaedic Surgeons. Global Research & Reviews (2020)) (41)	Growth Modulation for Knee Coronal Plane Deformities in Children With Nutritional Rickets: A Prospective Series With Treatment Algorithm	Evaluated the effectiveness of guided growth surgery in correcting lower limb deformities, such as genu varum (bowed legs), in children with rickets.
Yeo A, et al. (Journal of Pediatric Orthopedics (2015)) (42)	Bow Legs in Children: A Review of Etiology and Treatment	Reviewed various causes of bowed legs in children, including rickets and skeletal dysplasia, and discussed the impact of these deformities on normal growth.
Rerucha CM, et al. (American Family Physician (2017)) (43)	Leg Bowing in Children: An Overview	Provided an overview of leg bowing in children, highlighting that while physiological bowing is common in toddlers, persistent or severe cases due to conditions like rickets can lead to growth disturbances.
Thacher TD, et al. (Journal of Pediatrics (2000)) (44)	Clinical and Radiographic Features of Vitamin D Deficiency in Nigerian Children	Studied Nigerian children with vitamin D deficiency, noting that skeletal deformities such as bowed legs were prevalent and associated with impaired growth. Treatment with vitamin D improved biochemical markers and promoted normal growth patterns.

The comprehensive analysis of 34 studies highlights the multifactorial mechanisms through which vitamin D deficiency impairs growth in children and adolescents. The findings address the review's objectives by emphasizing critical factors, including disruptions in calcium-phosphorus metabolism, growth plate dynamics, the growth hormone-insulin-like growth factor-1 (GH-IGF-1) axis, skeletal deformities, and associated conditions. Additionally, the effectiveness of interventions is discussed in mitigating these growth impairments. The variability in treatment outcomes across the included studies may be attributed to several confounding factors, including genetic differences, baseline nutritional status, and geographic location. Genetic predispositions can influence individual responses to vitamin D supplementation and the regulation of calcium-phosphorus homeostasis, while nutritional co-deficiencies (such as calcium, magnesium, or protein) may hinder the full efficacy of vitamin D therapy. Additionally, environmental factors such as sunlight exposure, skin pigmentation, and local healthcare infrastructure significantly impact both the severity of deficiency and the success of intervention strategies. Studies conducted in regions with persistent malnutrition or limited access to healthcare may report more modest improvements in growth parameters, despite supplementation, compared to those conducted in higher-resource settings. These variables highlight the importance of considering a multifaceted approach when evaluating the effectiveness of vitamin D interventions across diverse populations.

3.1. Disruption of Calcium-Phosphorus Metabolism (25%)

Calcium and phosphorus homeostasis, essential for bone mineralization, is severely disrupted in vitamin D deficiency. "Approximately 25% of the studies included in this review identified disruption of calcium-phosphorus metabolism as a primary mechanism through which vitamin D deficiency impairs growth. This leads to conditions such as rickets and osteomalacia, characterized by poor bone strength and delayed skeletal development. Studies by Thacher et al. (2000, 2006) and Holick (2007) showed that vitamin D deficiency reduces intestinal calcium absorption, increases parathyroid hormone (PTH) levels, and causes secondary hyperparathyroidism. Treatment with vitamin D plays a pivotal role in restoring calcium-phosphorus homeostasis by enhancing intestinal calcium absorption, normalizing parathyroid

hormone (PTH) levels, and promoting proper bone mineralization. Recent studies reinforce its effectiveness: Soliman et al. (2008) demonstrated that children with nutritional rickets treated with a single intramuscular dose of 300,000 IU of vitamin D showed rapid normalization of serum calcium and phosphate levels, reduced PTH, increased IGF-1 concentrations, and significant catch-up growth, alongside radiological healing of bone deformities. Similarly, Ganmaa et al. (2022) found that weekly vitamin D supplementation in children from high-deficiency regions improved serum 25(OH)D levels and supported pubertal development and linear growth. El-Sobky et al. (2020) reported that vitamin D supplementation combined with orthopedic intervention effectively corrected skeletal deformities and enhanced height velocity in children with rickets. These findings are consistent with the global consensus by Munns et al. (2016), which emphasizes that early and sufficient vitamin D repletion not only reverses biochemical and radiographic signs of rickets but also prevents long-term growth impairment. Together, these studies highlight the essential role of timely vitamin D supplementation in supporting normal skeletal development and overall growth in deficient pediatric populations.

Table 2 Summary of Key Studies on Vitamin D Supplementation and Growth Outcomes in Children

Study	Population/Setting	Intervention	Key Findings
Soliman et al. (2008) (15)	Children with nutritional rickets, Middle East	Single IM dose of 300,000 IU vitamin D	Normalized calcium/phosphate, and PTH, and IGF-1, catch-up growth
Ganmaa et al. (2022)(24)	Children in Mongolia with a high prevalence of deficiency	Weekly vitamin D supplementation	Improved 25(OH)D levels, enhanced pubertal development and growth
El-Sobky et al. (2020) (21,35)	Children with rickets and knee deformities	Vitamin D supplementation + guided growth surgery	Corrected skeletal deformities, improved height velocity
Munns et al. (2016) (17)	Global pediatric populations (consensus guidelines)	Guideline-based vitamin D therapy and prevention	Early vitamin D treatment prevents growth impairment and rickets

Table 2 highlights the consistent evidence across diverse settings that vitamin D supplementation significantly improves growth outcomes in children with deficiency. From biochemical normalization and catch-up growth (Soliman et al.) to structural correction of skeletal deformities (El-Sobky et al.) and enhanced pubertal development (Ganmaa et al.), the findings support timely and adequate intervention. The global consensus (Munns et al.) reinforces the importance of prevention and early treatment to avoid long-term developmental impairments, underscoring the value of integrated, age-appropriate approaches to vitamin D management in pediatric populations.

3.2. Growth Plate Dynamics (20%)

The growth plate, the site of longitudinal bone growth, is highly sensitive to disruptions caused by vitamin D deficiency. Vitamin D regulates chondrocyte differentiation and matrix mineralization within the growth plate. Studies by Soliman et al. (2008) and Thacher et al. (2000) demonstrated that vitamin D deficiency results in disorganized chondrocyte proliferation, widening of the growth plate, and delayed bone elongation. Following high-dose vitamin D treatment, improvements in growth plate structure, enhanced IGF-1 activity, and significant catch-up growth were observed, underscoring the critical role of vitamin D in restoring growth plate dynamics. Following high-dose vitamin D treatment—typically 300,000 IU administered intramuscularly as a single dose or oral doses divided over 4–6 weeks—studies such as Soliman et al. (2008) observed significant improvements in growth plate structure, enhanced IGF-1 activity, and catch-up growth within 3–6 months of intervention. These findings underscore the critical role of timely and adequate vitamin D repletion in restoring growth plate dynamics and promoting skeletal recovery during key developmental stages. A systematic review and meta-analysis by Chen et al. (2021) examined the effects of vitamin D supplementation during pregnancy and infancy on child growth and body composition. The analysis included 11 randomized controlled trials with a total of 3,960 participants. The findings suggested that vitamin D supplementation during pregnancy was associated with a slight increase in neonatal triceps skinfold thickness and, when administered during pregnancy or infancy, was linked to a modest improvement in length-for-age z-scores at one year of age. Additionally, supplementation correlated with a minor reduction in body mass index (BMI) and BMI z-scores in children aged 3 to 6 years. These results indicate potential benefits of early life.

3.3. GH-IGF-1 Axis Dysfunction (15%)

While vitamin D deficiency—commonly defined as serum 25(OH)D levels <30 nmol/L (<12 ng/mL)—is well established to impair calcium metabolism and bone growth, emerging evidence suggests that even vitamin D insufficiency (typically

defined as 30–50 nmol/L or 12–20 ng/mL) can negatively affect IGF-1 secretion and activity, thereby influencing growth velocity. Soliman et al. (2008) demonstrated that in children with nutritional rickets, IGF-1 levels improved significantly following high-dose vitamin D therapy (300,000 IU IM), correlating with enhanced linear growth and resolution of biochemical abnormalities. Similarly, Ameri et al. (2013) reported a positive association between serum 25(OH)D and IGF-1 levels in adults, while Smith et al. (2017) observed that vitamin D repletion in adolescents led to higher circulating IGF-1, further supporting the endocrine role of vitamin D in growth regulation. These findings highlight that maintaining vitamin D sufficiency, not merely avoiding overt deficiency, is crucial to optimizing endocrine support for growth. This has significant clinical implications, as suboptimal vitamin D levels—often asymptomatic—may silently compromise growth potential, especially during periods of rapid development such as infancy and adolescence.

3.4. Skeletal Deformities and Growth Impairment (15%)

Skeletal deformities, including bowed legs (genu varum) and muscular hypotonia, are hallmark features of severe vitamin D deficiency. These deformities place abnormal stress on growth plates, further hindering normal bone elongation. El-Sobky et al. (2020) demonstrated that guided growth surgery combined with vitamin D supplementation effectively corrected skeletal deformities and improved growth trajectories. Early intervention, as highlighted by Yeo et al. (2015) and Thacher et al. (2000), is critical in preventing permanent growth deficits.

3.5. Associated Conditions (10%)

Vitamin D deficiency often coexists with conditions such as iron deficiency anemia, inflammatory bowel disease (IBD), and other chronic illnesses, all of which can exacerbate growth impairments. Studies by Ulitsky et al. (2011) and Escobedo-Monge et al. (2024) demonstrated that these comorbidities may contribute to malabsorption, chronic inflammation, and altered metabolic pathways, thereby compounding the effects of vitamin D deficiency on growth. For example, iron deficiency may impair the function of vitamin D-dependent enzymes, while IBD reduces nutrient absorption due to mucosal inflammation, affecting both vitamin D and calcium bioavailability. Additionally, chronic inflammation from these conditions may disrupt the GH–IGF–1 axis and increase catabolic cytokines, further impairing growth. Therefore, a comprehensive approach that simultaneously addresses vitamin D deficiency and its associated conditions is essential for optimizing nutrient status, metabolic function, and overall growth outcomes in children and adolescents.

3.6. Other Contributing Factors (15%)

Regional variations, genetic predisposition, and environmental factors also contribute to growth impairment associated with vitamin D deficiency. Studies by Ganmaa et al. (2022) and Thacher et al. (2006) highlighted how limited sunlight exposure, cultural practices, and dietary habits exacerbate vitamin D deficiency, particularly in specific populations. Tailored interventions addressing these contextual factors are essential for improving growth outcomes in diverse settings.

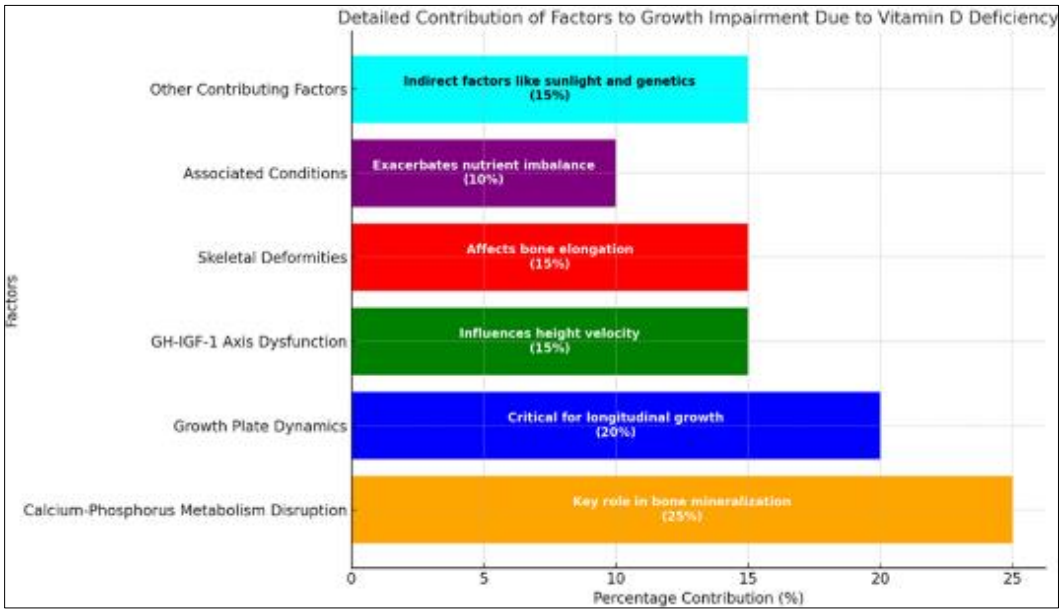

Figure 2 Estimated Percentage Contributions of Factors to Growth Impairment in Vitamin D Deficiency

Figure 2 highlights the multifactorial nature of growth impairment due to vitamin D deficiency, with calcium-phosphorus metabolism disruption (25%) being the most significant contributor. Other key factors include growth plate dynamics (20%), GH-IGF-1 axis dysfunction (15%), and Skeletal deformities (15%), as a consequence of vitamin d deficiency, directly impact bone growth and height velocity. Indirect factors like associated conditions (10%) and sunlight/genetics (15%) emphasize the need for a comprehensive approach to treatment.

3.7. Effectiveness of Interventions

Vitamin D supplementation, dietary improvements, and orthopedic interventions are effective in mitigating growth impairments. Soliman et al. (2008) demonstrated that high-dose vitamin D3 improved growth plate dynamics, IGF-1 levels, and growth velocity in children with severe rickets. Similarly, Ganmaa et al. (2022) and Munns et al. (2016) reported that supplementation improved serum 25(OH)D levels and bone health. However, variability in linear growth outcomes across studies highlights the importance of addressing additional factors, such as comorbidities and overall nutrition, for optimal results.

4. Discussion

The findings from this comprehensive review highlight the multifaceted nature of growth impairment due to vitamin D deficiency in children and adolescents. Several critical factors, including calcium-phosphorus metabolism, growth plate dynamics, the GH-IGF-1 axis, skeletal deformities, and associated conditions, contribute to varying degrees of growth retardation. This discussion addresses these factors, compares the findings with similar studies, and evaluates the efficacy of different treatment regimens, emphasizing the importance of correcting these factors to improve growth outcomes.

4.1. Calcium-Phosphorus Metabolism

Calcium-phosphorus metabolism disruption is a major contributor to growth impairment, accounting for approximately 25% of the total impact. Vitamin D deficiency impairs calcium and phosphate absorption, leading to secondary hyperparathyroidism, poor bone quality, and conditions such as rickets. Studies by Holick (2007) (1) and Thacher et al. (2006) (6) emphasize the critical role of vitamin D in maintaining mineral homeostasis and preventing skeletal abnormalities. Similarly, Ward et al. (2007) (5,14) demonstrated that Canadian children with rickets showed marked improvements in growth and bone health after vitamin D supplementation. The global prevalence of rickets, even in developed countries, underscores the urgency of public health interventions to address vitamin D deficiency (1,5.6.12,17).

4.2. Growth Plate Dynamics

Growth plate dynamics, which account for 20% of growth impairment, are directly influenced by vitamin D. Vitamin D deficiency disrupts chondrocyte differentiation and matrix mineralization, leading to widened and disorganized growth plates. Soliman et al. (2008) highlighted that children with rickets exhibited significant growth plate abnormalities, which improved substantially following high-dose vitamin D treatment. This aligns with findings by Romano et al. (2010), who noted that weekly doses of vitamin D improved growth plate structure, though at a slower rate compared to mega-doses. These results emphasize the importance of addressing growth plate dysfunction as a key component of treating vitamin D deficiency-related growth impairment (15,18,20).

4.3. GH-IGF-1 Axis Dysfunction

The GH-IGF-1 axis, contributing 15% to growth impairment, is a crucial regulator of linear growth. Vitamin D deficiency has been shown to reduce IGF-1 levels, impairing height velocity and skeletal development. Soliman et al. (2008) (15) demonstrated that IGF-1 levels doubled after megadose vitamin D treatment, correlating with significant catch-up growth. These findings are supported by Ameri et al. (2013) (18) and Smith et al. (2017)(19). The overview of current recommendations and findings regarding optimal serum vitamin D levels and dosing strategies for children and adolescents, highlighting both preventive and therapeutic approaches, is summarized in Table 3. While a minimum serum 25(OH)D level of 50 nmol/L is widely accepted for bone health, some experts advocate higher thresholds (≥75 nmol/L) to support optimal growth, particularly during periods of rapid skeletal development. Daily intake recommendations vary by age, with higher needs observed during adolescence, and high-dose regimens are reserved for treating conditions such as nutritional rickets. The variation in dosing across guidelines underscores ongoing uncertainties about the precise levels required for maximizing growth potential. This reinforces the need for age-specific, evidence-based targets and further research to refine safe and effective vitamin D strategies tailored to individual growth needs.

Table 3 Vitamin D Levels and Dosing Recommendations in Children and Adolescents

Parameter	Current Recommendations / Findings	Source(s)
Optimal serum 25(OH)D level for bone growth	≥50 nmol/L (≥20 ng/mL); some suggest ≥75 nmol/L (≥30 ng/mL) for optimal skeletal and growth benefits	Munns et al., 2016 (17); Holick, 2007 (1); Wagner et al., 2008 (46)
Deficiency threshold	<30 nmol/L (<12 ng/mL)	Munns et al., 2016 (17)
Recommended daily intake (0–1 year)	400 IU/day	Wagner CL et al., 2008 (46)
Recommended daily intake (1–18 years)	600–1000 IU/day	Holick MF, 2007 (1); Munns CF et al., 2016 (17)
High-dose therapy for rickets (treatment)	300,000–600,000 IU total (single IM or divided oral dose)	Thacher TD et al., 2000 (12); Misra M et al., 2008 (2)
Maintenance after correction	400–1000 IU/day	Misra M et al., 2008 (2); Wagner et al., 2008 (46)
Upper tolerable intake level	2000 IU/day (children 1–10 yrs); 4000 IU/day (adolescents)	Institute of Medicine, 2011 (47)

4.4. Skeletal Deformities

Skeletal deformities, such as bowed legs and vertebral hypotonia, contribute 15% to growth impairment and are hallmark features of severe vitamin D deficiency. These deformities place abnormal stress on growth plates, further hindering bone elongation. El-Sobky et al. (2020) (35) and Yeo et al. (2015) (37) demonstrated that guided growth surgery combined with vitamin D supplementation corrected skeletal deformities and improved growth outcomes. Thacher et al. (2000) noted that early supplementation alone resolved deformities in many cases, highlighting the importance of timely intervention to prevent permanent growth deficits (12, 35,37).

4.5. Associated Conditions

Vitamin D deficiency often coexists with conditions such as iron deficiency anemia, inflammatory bowel disease (IBD), and other chronic illnesses, all of which can exacerbate growth impairments. Studies by Ulitsky et al. (2011) and Escobedo-Monge et al. (2024) demonstrated that these comorbidities may contribute to malabsorption, chronic inflammation, and altered metabolic pathways, thereby compounding the effects of vitamin D deficiency on growth. For example, iron deficiency may impair the function of vitamin D-dependent enzymes, while IBD reduces nutrient absorption due to mucosal inflammation, affecting both vitamin D and calcium bioavailability. Additionally, chronic inflammation from these conditions may disrupt the GH–IGF-1 axis and increase catabolic cytokines, further impairing growth. Therefore, a comprehensive approach that simultaneously addresses vitamin D deficiency and its associated conditions is essential for optimizing nutrient status, metabolic function, and overall growth outcomes in children and adolescents.

4.6. Importance of Correcting These Factors

The percentage contributions of each factor underscore the multifactorial nature of growth impairment due to vitamin D deficiency. Addressing calcium-phosphorus metabolism, growth plate dysfunction, and the GH-IGF-1 axis are critical for restoring normal growth trajectories. Additionally, early correction of skeletal deformities and management of associated conditions can significantly enhance growth outcomes. A comprehensive and individualized approach is essential for ensuring that all contributing factors are addressed effectively.

4.7. Comparison of Treatment Regimens

The efficacy of various vitamin D treatment regimens varies depending on the severity of deficiency, associated growth impairment, and age group. Soliman et al. (2008) studied young children aged 1–5 years with nutritional rickets and found that megadose regimens (300,000 IU intramuscularly) led to rapid normalization of IGF-1 levels and growth plate function, resulting in significant catch-up growth. In contrast, Ganmaa et al. (2022) conducted a randomized, double-blind, placebo-controlled trial in Mongolian school-aged children (6–13 years) over a period of 3 years, administering weekly doses of 14,000 IU vitamin D_3. While the intervention significantly increased serum 25(OH)D concentrations

and helped maintain sufficiency throughout the study period, it did not result in statistically significant improvements in height gain or linear growth compared to placebo. This suggests that in populations with long-standing or more advanced deficiency, vitamin D repletion alone—without addressing other nutritional or health factors—may be insufficient to reverse growth retardation. Smith et al. (2017) assessed adolescents aged 12–17 years and found that daily low-dose supplementation (600–1000 IU/day) was useful in maintaining vitamin D sufficiency but had limited impact on improving growth metrics in those with moderate or borderline deficiency. These findings suggest that megadose therapy is more appropriate for younger children with severe deficiency or clinical rickets, whereas daily or weekly regimens may be better suited for older children and adolescents with mild deficiency or for maintaining adequate levels after repletion. Treatment should therefore be tailored to age, baseline vitamin D status, and severity of clinical manifestations. (15,18,19,24)

Summary of Recommended Actions

	Action	**Justification**
1.	Mandatory food fortification	Fortifying staples like milk, oil, and flour helps reach large populations cost-effectively.
2.	School-based supplementation programs	Ensure consistent vitamin D intake in children, especially in resource-limited or sun-deficient areas.
3.	Public education campaigns	Promote awareness of sun exposure, dietary sources, and the importance of vitamin D for growth.
4.	Routine screening protocols	Integrate vitamin D level checks into school health exams or pediatric visits.

5. Conclusion

This review underscores the multifaceted impact of vitamin D deficiency on growth, with disruptions in calcium-phosphorus metabolism, growth plate dynamics, the GH–IGF-1 axis, skeletal deformities, and associated conditions contributing significantly to growth retardation. Importantly, the evidence suggests that not only overt vitamin D deficiency (<30 nmol/L) but also insufficiency (30–50 nmol/L) may adversely affect endocrine and skeletal pathways critical for optimal growth, particularly by impairing IGF-1 activity and bone mineralization. Therefore, vitamin D sufficiency—generally accepted as ≥50 nmol/L (≥20 ng/mL), and possibly ≥75 nmol/L for optimal outcomes—should be a clinical target during key periods of growth.

Current guidelines recommend 400–1000 IU/day of vitamin D for children and adolescents, depending on age and risk factors, while high-dose regimens (e.g., 300,000 IU IM) may be reserved for those with confirmed rickets or severe deficiency. However, the optimal dose and duration for promoting linear growth in cases of subclinical insufficiency remain unclear, representing a critical area for further research. In light of this, early identification of at-risk populations and timely, individualized supplementation strategies are essential. These findings reinforce the need to prioritize vitamin D optimization within broader pediatric growth monitoring programs and to refine global public health policies around prevention, screening, and treatment.

The findings highlight the urgent need to prioritize vitamin D deficiency as a global public health issue and advocate for integrated strategies to ensure healthy growth and development in vulnerable pediatric populations. Policymakers must take immediate steps to implement large-scale preventive measures, such as mandatory food fortification and school-based supplementation programs. At the same time, researchers should focus on filling existing knowledge gaps, particularly regarding optimal dosing, regional risk profiles, and the long-term effects of early intervention on growth trajectories. A coordinated, cross-sectoral effort is essential to combat this preventable cause of impaired childhood growth and to promote equity in health outcomes worldwide.

5.1. Policy Implications

The findings of this review highlight an urgent need for evidence-based public health interventions to mitigate the widespread impact of vitamin D deficiency on child and adolescent growth. Governments and health authorities should prioritize mandatory fortification of staple foods—such as milk, flour, and cooking oils—with vitamin D, especially in regions with high prevalence of deficiency. Such policies have shown significant success in reducing deficiency rates at the population level and are cost-effective. In addition, implementing school-based vitamin D supplementation programs can provide consistent and equitable access to this critical micronutrient during key developmental stages.

These programs are especially vital in areas with limited sunlight exposure, high rates of malnutrition, or urban environments where outdoor activity is restricted.

Public health campaigns should also play a central role in raising awareness about safe sun exposure, dietary sources of vitamin D, and the long-term risks of deficiency. Integration of routine screening protocols into pediatric healthcare and school health services can help detect and treat deficiencies early, before irreversible growth impairments occur. Tailored strategies should focus on at-risk populations, including children with darker skin, those with chronic illnesses, and communities living in poverty or high-latitude regions. Together, these interventions represent a comprehensive, sustainable approach to improving growth outcomes and reducing the global burden of vitamin D deficiency.

5.2. Strengths

The review provides a comprehensive synthesis of 34 studies spanning over two decades, offering a detailed analysis of the multifactorial impact of vitamin D deficiency on growth. By addressing key physiological and structural factors, it highlights critical pathways and effective interventions for optimizing growth outcomes. The integration of diverse perspectives, including clinical, nutritional, and public health insights, strengthens the applicability of the findings to varied pediatric populations. This holistic approach underscores the importance of tailored, multifaceted strategies in managing vitamin D deficiency.

5.3. Limitations

This review is limited by its reliance on previously published studies, which may introduce variability in methodologies, populations, and geographic contexts. The inclusion of data from diverse settings might limit the generalizability of findings to specific populations. Additionally, the lack of uniformity in intervention protocols across studies hinders direct comparisons of treatment effectiveness. Some studies lacked detailed information on confounding factors, such as nutrition or genetics, which may also influence growth outcomes. Moreover, publication bias may have influenced the results, as studies with positive or significant findings are more likely to be published, potentially overrepresenting the efficacy of vitamin D interventions. This bias limits the ability to fully assess the range of outcomes, particularly in studies reporting null or minimal effects.

Compliance with ethical standards

Disclosure of conflict of interest

All authors declare no conflicts of interest and have approved the final version of the manuscript, agreeing on its submission for publication

Authors contribution

A.S. conceptualized the study, supervised the research process, and critically revised the manuscript. F.A. participated in the study design, data collection, and manuscript preparation, while A.E. contributed to the literature review, data analysis, and interpretation of findings. N.A. supported data collection and drafted specific sections of the manuscript, with N.H. providing expertise in pediatric endocrinology and clinical data review. S.A. assisted with technical data organization and figure creation, and M.I. contributed insights on dietary and nutritional aspects related to vitamin D deficiency interventions. N.S. provided expertise in public health, offering a population-level perspective and reviewing the manuscript. All authors reviewed and approved the final version of the manuscript, agreeing to its submission.

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