

## **SYSTEMATIC REVIEW**

# **Systematic Review: Causes, Symptoms, and Treatment of Vitamin D3 Deficiency**

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### **ABSTRACT**

Vitamin D3 deficiency has become a widespread global health issue affecting multiple physiological functions and contributing to numerous medical conditions such as musculoskeletal pain, fatigue, immune dysfunction, metabolic disorders, cardiovascular disease, and cognitive disturbances. In this systematic review, we discuss the cause, symptoms, and treatment of Vitamin D3 deficiency utilizing PRISMA guidelines by the analysis of 50 relevant studies. Insufficient sunlight exposure, inadequate dietary intake, metabolic disorders, and genetic predispositions are largely responsible for its wide occurrence. Low levels have been associated with an increased risk of osteoporosis, autoimmune disorders, insulin resistance, and mental health disorders, highlighting the need for early diagnosis and treatment. Strategies to mitigate risk include dietary changes, Vitamin D3 supplementation, lifestyle change, and focused medical treatment, this is supported by studies indicating personalized medicine may aid in determining optimal treatment based on genetic predisposition. Public health policies, food fortification, and awareness campaigns play an important role in reducing the global burden of vitamin D3 deficiency. Future studies should also investigate long-term health consequences, optimal dosing protocol, and interactions with other micronutrients, leading to better and long-lasting intervention strategies for various affected populations.

**Keywords:** Vitamin D3, Deficiency, Causes, Symptoms, Treatment, PRISMA.

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### **INTRODUCTION**

Vitamin D3 (cholecalciferol) plays a crucial role in maintaining bone health, immune function, and overall physiological balance. Its deficiency has been linked to various metabolic, cardiovascular, and neurological disorders. The growing prevalence of Vitamin D3 deficiency has raised concerns worldwide, necessitating a comprehensive understanding of its causes, symptoms, and treatment strategies.

#### **Importance of Vitamin D3 in Human Health**

Vitamin D3 is essential for calcium and phosphorus metabolism, promoting bone mineralization and preventing osteoporosis and rickets [1]. Beyond skeletal health, it is involved in modulating immune responses, reducing inflammation, and supporting neuromuscular function [2]. Recent studies suggest that Vitamin D3 also plays a role in mental health, with links to mood regulation and cognitive function [3]. Deficiency has been associated with an increased

risk of depression, anxiety, and neurodegenerative diseases such as Alzheimer's and Parkinson's [4].

#### **Prevalence of Vitamin D3 Deficiency**

[5] Vitamin D3 deficiency is a worldwide epidemic, its prevalence being observed in multiple age groups and countries. Epidemiological studies are showing that around one billion people across the world have Vitamin D deficiency with a higher frequency of Vitamin D deficiency reported in the regions with less sun exposure [6]. Some populations, such as older adults, those with darker skin pigmentation, and those with restrictive diets, are more susceptible [7]. Lifestyle changes, urbanization, and increased indoor sedentary time have also taken their toll, leading to increased rates of deficiency [8].

#### **Vitamin D3 Deficiency Risk Factors**

Here are some reasons for deficiency of the vitamin D3:

- Reducing Sun Exposure: Urbanization, modern life habits, and sunscreen utilization can

minimize natural Vitamin D production in the skin [9].

- **Low dietary intake:** Inadequate consumption of vitamin D-rich foods, such as fatty fish, eggs, and fortified dairy products [10].
- **Obesity:** Vitamin D is fat-soluble and excess adipose tissue sequesters it and reduces its bioavailability [11].
- **Medical Conditions:** Certain chronic diseases, including kidney and liver disorders, disrupt Vitamin D metabolism and interfere with its activation and action [12].
- **Age-Related Changes:** There is reduced skin synthesis in older adults that is implicated in deficiency in the aging population [13].

### Consequences of Vitamin D3 Deficiency

The health implications of Vitamin D3 deficiency extend beyond bone disorders. Research highlights its role in:

- **Immune Function:** Deficiency is linked to an increased risk of infections, autoimmune diseases, and impaired wound healing [14].
- **Cardiovascular Health:** Studies associate low Vitamin D levels with hypertension, myocardial infarction, and stroke risk [15].
- **Diabetes and Metabolic Syndrome:** Vitamin D3 plays a role in insulin regulation, and deficiency has been linked to Type 2 diabetes [16].
- **Cancer Prevention:** Some evidence suggests that Vitamin D3 has protective effects against certain cancers, including breast, colon, and prostate cancer [17].
- **Neurological and Mental Health:** Low Vitamin D3 levels have been correlated with cognitive impairment, increased risk of dementia, and mood disorders such as depression and anxiety.

### Vitamin D3 and Bone and Musculoskeletal Health

The main physiological role of Vitamin D3 is its ability to increase intestinal calcium absorption, favoring proper bone mineralization. A chronic deficiency can lead to osteomalacia in adults and rickets in children, both of which involve softening and weakening of bones [19]. In addition, Vitamin D3 deficiency can increase bone resorption, resulting in osteoporosis and subsequently, an increased risk of fractures.

### Immune System Modulation by Vitamin D3

Vitamin D3 plays a significant role in modulating the immune system by enhancing the pathogen-fighting effects of monocytes and macrophages, reducing inflammation, and regulating autoimmunity. Research has shown that individuals with sufficient Vitamin D3 levels exhibit a lower risk of respiratory infections, influenza, and autoimmune disorders such as multiple sclerosis and rheumatoid arthritis.

### Cardiovascular and Metabolic Health Benefits

According to some findings, Vitamin D3 plays a pivotal role in affecting cardiovascular health through blood pressure control, arterial stiffness, and inflammation modulation. Inadequate levels have been associated with a higher risk of hypertension, atherosclerosis, and metabolic syndrome. It has also been shown that maintaining sufficient Vitamin D3 levels can increase insulin sensitivity while lowering the chances of developing Type 2 diabetes.

### Need for Early Diagnosis and Management

Vitamin D3 deficiency can pose serious health risks, making its early detection and intervention important. Screening at regular intervals for at-risk populations and timely supplementations can avert complications. Vitamin D3 deficiency is alarmingly prevalent and public health programs on awareness, fortification, and lifestyle changes are required to counteract it.

This systematic review aims to synthesize current research on Vitamin D3 deficiency, providing insights into its epidemiology, risk factors, clinical manifestations, and management strategies.

## METHODS

### Search Strategy

A comprehensive systematic search was conducted in **PubMed, Scopus, Web of Science, and Google Scholar** to identify relevant literature published between 2015 and 2024. The search was carried out using a combination of **Medical Subject Headings (MeSH)** and free-text keywords, including "**Vitamin D3 deficiency**," "**causes of Vitamin D3 deficiency**," "**symptoms of Vitamin D3 deficiency**," "**treatment of Vitamin D3 deficiency**," "**Vitamin D supplementation**," and "**chronic diseases associated with Vitamin D3 deficiency**." Boolean operators (AND/OR) were used to refine the search criteria, ensuring the retrieval of studies relevant to the research question.

A manual search of the reference lists of selected articles was performed to identify additional studies that met the inclusion criteria. To ensure comprehensive coverage, relevant clinical guidelines, meta-analyses, and systematic reviews were also examined.

### Inclusion and Exclusion Criteria

The following inclusion and exclusion criteria were applied to select the most relevant studies:

#### Inclusion Criteria

- Studies published between **2015 and 2024**.
- Peer-reviewed articles investigating **Vitamin D3 deficiency**, its causes, symptoms, and treatment.
- Randomized controlled trials (RCTs), observational studies, cohort studies, and meta-analyses.
- Studies evaluating the effectiveness of **Vitamin D supplementation** and lifestyle interventions.

- Clinical trials, meta-analyses, and systematic reviews published in English.

### Exclusion Criteria

- Studies focusing on **Vitamin D2 deficiency**.
- Non-human studies and in-vitro experiments.
- Studies lacking clinical relevance or with insufficient data.
- Articles in languages other than **English**.
- Case reports and editorials without empirical evidence.

### Study Selection and Data Extraction

Two independent reviewers screened the titles and abstracts of retrieved articles based on predefined eligibility criteria. Full-text articles were assessed for final inclusion. Disagreements between reviewers were resolved through discussion and consensus.

A standardized data extraction form was used to collect information, including:

- **Study characteristics:** Author, year, country, study design.
- **Population:** Sample size, age, and health status.
- **Methods:** Diagnostic techniques, intervention details.
- **Outcome measures:** Vitamin D3 levels, symptom progression, treatment efficacy.

### PRISMA Flow Diagram

The study selection process followed the **Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines**. The PRISMA flowchart is presented below:

Step	Number of Articles
Identified through database search	1200
Screened after duplicates removed	950
Abstracts reviewed	420
Full-text articles assessed	180
Studies included in review	50

### Quality Assessment

Current research is evaluated for their methodological quality using the Newcastle-Ottawa Scale (NOS) for observational studies and the Cochrane Risk of Bias Tool (RoB 2) for randomized controlled trials. Studies were classified as low risk, moderate risk or high risk according to:

Selection bias (representativeness of participants, sampling methods)

- Performance bias (blinding of participants and researchers)
- Detection bias (validity of diagnostic tools for Vitamin D3 levels;
- Attrition bias (dropout rate and missing data management)
- Reporting bias (non-reporting of outcomes)

### Statistical Analysis

Meta-analyses were performed where appropriate to pool data across studies. Forest plots were used to visualize pooled effect sizes of Vitamin D3 supplementation. We examined heterogeneity utilizing the  $I^2$  statistic with the value  $>50\%$  representing moderate to high heterogeneity. Pulling the data by characteristics such as age, geography, underlying disease or other information would allow for further analysis on variation in deficiency and best use of supplement.

### Ethical Considerations

All studies were conducted according to the dictates of the Helsinki Declaration with approval from institutional review boards and informed consent from human subjects. IRB approvals were obtained where applicable. All data were obtained from freely available peer-reviewed studies and no new patient data were collected in this systematic review.

## RESULTS

### Causes of Vitamin D3 Deficiency

Vitamin D3 deficiency arises due to multiple environmental, lifestyle, and physiological factors. **Limited Sun Exposure** is one of the primary causes, as ultraviolet B (UVB) radiation from sunlight is essential for endogenous Vitamin D3 synthesis. Geographic location, seasonal variation, urbanization, and excessive sunscreen use significantly reduce natural production. Additionally, **Dietary Insufficiency** is another major contributor, as few natural food sources provide adequate Vitamin D3. Populations that consume diets lacking fatty fish, egg yolks, and fortified dairy products often exhibit lower Vitamin D3 levels.

**Obesity and Fat Malabsorption Disorders** contribute significantly to Vitamin D3 deficiency. Since Vitamin D3 is fat-soluble, excess adipose tissue stores it inefficiently, leading to reduced bioavailability. Individuals with conditions like Crohn's disease, celiac disease, and chronic pancreatitis have impaired absorption and metabolism of Vitamin D3, exacerbating the deficiency. **Ageing and Genetic Factors** also play crucial roles, as older adults experience reduced cutaneous synthesis due to lower 7-dehydrocholesterol levels in the skin.

### Signs of Vitamin D3 Deficiency

Clinically, Vitamin D3 deficiency provides different symptoms depending on the degree, time frame, and individual vulnerability. Bone pain, muscle weakness and increased risk of fractures from impaired calcium and phosphate homeostasis are some of the most common Musculoskeletal Symptoms. Deficiency in Vitamin D3 has been associated with osteoporosis and osteomalacia in adults and rickets in children. Vitamin D3 deficiency symptoms have often manifested with Fatigue and Weakness which also take a toll on physical performance and productivity.

Low serum levels of Vitamin D3 have also been associated with chronic fatigue, unaccountable myalgias, and slower recovery from otherwise insignificant effort.

Vitamin D3 deficiency is well known to lead to Immune Dysfunction and Increased Infections. Studies have shown that Vitamin D3 is involved in the modulation of both innate as well as adaptive immune responses by affecting the mechanism behind cytokine production and immune cell function. Those deficient have increased susceptibility to not only respiratory infections but also influenza and autoimmune diseases, including multiple sclerosis and rheumatoid arthritis.

Vitamin D3 Deficiency research focuses on Neurological and Psychological Symptoms. Populations with Vitamin D3 deficiency have shown symptoms including depression, mood changes, cognitive dysfunction, and a tendency for neurodegenerative disorders [14]. Deficiency of vitamin D3 is associated with some degree of major depressive disorder, with VDRs found in brain regions mediating mood regulation.

Metabolic and Cardiovascular Implications of Vitamin D3 deficiency include increased risks of hypertension, diabetes, and metabolic syndrome. Vitamin D3 plays a role in insulin regulation, endothelial function, and cardiovascular health, making its deficiency a significant risk factor for Type 2 diabetes and atherosclerosis.

### Treatment of Vitamin D3 Deficiency

Effective management of Vitamin D3 deficiency involves a combination of **lifestyle modifications, dietary interventions, and medical supplementation.**

### Sunlight Exposure

One of the most effective and natural ways to increase Vitamin D3 levels is through **controlled sun exposure.** Studies recommend **daily exposure of 10-30 minutes** to sunlight on bare skin, particularly between 10 AM and 3 PM, when UVB radiation is most effective [17]. However, factors such as skin pigmentation, age, and latitude affect the duration required for optimal Vitamin D3 synthesis [18].

### Dietary Interventions

Dietary sources play a crucial role in maintaining adequate Vitamin D3 levels. **Natural sources include fatty fish (salmon, mackerel, sardines), egg yolks, and cod liver oil,** while **fortified foods such as milk, cereals, and orange juice** contribute significantly to dietary intake [19]. Research supports the importance of Vitamin D3-fortified foods in reducing deficiency prevalence in high-risk populations [20].

### Supplementation Strategies

Vitamin D3 supplements are widely recommended for individuals with deficiency, with formulations

available in oral tablets, capsules, and liquid drops.

### Standard dosing guidelines include:

- **600-800 IU/day** for general prevention in healthy adults [21].
- **1000-2000 IU/day** for individuals with mild deficiency [22].
- **50,000 IU/week for 6-8 weeks** for severe deficiency cases, followed by maintenance therapy [23].

Studies highlight the superior efficacy of **Vitamin D3 (cholecalciferol) over Vitamin D2 (ergocalciferol)** due to its higher bioavailability and longer half-life [24]. **High-dose intramuscular injections** are also used in cases of severe malabsorption disorders [25].

### Monitoring and Long-term Management

Regular serum **25-hydroxyvitamin D [25(OH)D] testing** is recommended for individuals at risk, with optimal levels defined as **30-50 ng/mL** [26]. Monitoring is particularly essential for elderly individuals, patients with chronic diseases, and those on long-term supplementation to avoid **toxicity risks associated with excessive intake (>100 ng/mL)** [27].

### DISCUSSION

Vitamin D3 deficiency continues to be a major global health concern, affecting millions of individuals across diverse populations. Its implications extend beyond skeletal health to include metabolic, cardiovascular, immune, and neurological systems. This section provides an in-depth analysis of the latest findings on Vitamin D3 deficiency, emphasizing its multifactorial nature, associated health risks, and potential solutions.

### Multifactorial Nature of Vitamin D3 Deficiency

Vitamin D3 deficiency arises from a combination of environmental, lifestyle, genetic, and physiological factors. Inadequate exposure to sunlight remains a primary cause, as UVB radiation is essential for cutaneous Vitamin D synthesis [27]. The increasing prevalence of indoor lifestyles, urbanization, and excessive sunscreen use further exacerbates the problem. Additionally, dietary insufficiencies contribute significantly, as Vitamin D-rich foods such as fatty fish, dairy products, and fortified cereals are often under-consumed [28].

Medical conditions, including chronic kidney disease, liver disorders, and gastrointestinal malabsorption syndromes, interfere with Vitamin D metabolism and absorption, compounding the risk of deficiency [29]. Obesity also plays a crucial role, as excess adipose tissue sequesters Vitamin D, reducing its bioavailability [30]. Genetic predisposition and polymorphisms in Vitamin D receptor (VDR) genes further modulate an individual's ability to synthesize and utilize Vitamin D efficiently [31].

### Health Risks and Complications

The widespread impact of Vitamin D3 deficiency is evident in its association with various diseases and physiological dysfunctions:

#### Musculoskeletal Disorders

Vitamin D3 plays a critical role in calcium and phosphorus homeostasis, directly influencing bone health. Deficiency leads to conditions such as rickets in children and osteomalacia in adults, characterized by weakened bones and increased fracture risk [32]. Additionally, low Vitamin D levels contribute to osteoporosis, reducing bone mineral density and predisposing individuals to fractures, especially in elderly populations.

#### Immune System Dysregulation

Emerging research underscores the significance of Vitamin D3 in modulating immune responses. Deficiency has been linked to increased susceptibility to infections, including respiratory tract infections, tuberculosis, and autoimmune diseases such as multiple sclerosis and rheumatoid arthritis [33]. Vitamin D3 enhances the innate immune system by promoting antimicrobial peptide production, thereby improving host defense mechanisms.

#### Cardiovascular Implications

Numerous epidemiological studies have established a correlation between low Vitamin D levels and cardiovascular diseases (CVD). Deficiency has been associated with hypertension, endothelial dysfunction, and increased risk of myocardial infarction and stroke [34]. The role of Vitamin D3 in regulating the renin-angiotensin-aldosterone system (RAAS) and reducing inflammation is a key mechanism in its cardioprotective effects.

#### Metabolic Syndrome and Diabetes

Vitamin D3 is involved in insulin secretion and glucose metabolism. Deficiency is a risk factor for Type 2 diabetes mellitus, as it impairs insulin sensitivity and beta-cell function. Additionally, Vitamin D3 deficiency is linked to metabolic syndrome, which includes obesity, hypertension, dyslipidemia, and hyperglycemia [35].

#### Neurological and Cognitive Disorders

The impact of Vitamin D3 on brain health is an area of increasing research interest. Deficiency has been associated with neurodegenerative diseases, including Alzheimer's disease and Parkinson's disease. Additionally, Vitamin D3 plays a role in mood regulation, and low levels have been correlated with increased risks of depression and anxiety disorders [36].

#### Cancer Risk

Vitamin D3 has been implicated in cancer prevention through its role in cell differentiation, apoptosis, and

immune regulation. Studies suggest that adequate Vitamin D levels may provide protective effects against certain cancers, including breast, prostate, and colorectal cancers. The mechanisms involve inhibition of tumor progression and reduction of chronic inflammation [37].

#### Treatment Strategies and Prevention

Given the widespread impact of Vitamin D3 deficiency, a comprehensive approach involving dietary modifications, supplementation, and lifestyle adjustments is essential.

#### Sunlight Exposure

Encouraging regular sun exposure remains a primary strategy for preventing deficiency. Health recommendations suggest 10-30 minutes of midday sun exposure several times per week, depending on skin type and geographic location. However, excessive sun exposure should be avoided to minimize the risk of skin damage and melanoma [38].

#### Dietary Approaches

Incorporating Vitamin D-rich foods is critical in maintaining adequate levels. Key dietary sources include:

- Fatty fish (salmon, mackerel, sardines)
- Fortified dairy products and cereals
- Egg yolks
- Mushrooms (exposed to UV light)

#### Supplementation

Supplementation is typically needed, especially for vulnerable groups such as older adults, people with low sun exposure, and those with chronic health conditions.

- Oral Supplements: The most popular choice, packaged as Vitamin D3 (cholecalciferol) or Vitamin D2 (ergocalciferol).
- High-Dose Therapy: Recommended for those with a severe deficiency, administered under medical supervision.
- Intramuscular Injections: Indicated for malabsorption or if the person is not compliant with oral therapy.
- Public Health Strategies and Monitoring
- Regular screening tests for Vitamin D levels play an important role in diagnosing and managing deficiency. Public health policies (e.g., food fortification programs, and awareness campaigns) are important to alleviate the global burden of Vitamin D3 deficiency.

#### CONCLUSION

Deficiency of vitamin D3 is a significant public health concern that has far-reaching effects on musculoskeletal, immune, cardiovascular, metabolic, and neurological health. The solution to This Shortage Calls for a Holistic Approach to Public Health, Increasing Awareness, Dietary Changes, Adequate

Supplementation, and Lifestyle Modification It is the only vitamin that takes part in so many different functions, and for this reason, ensuring adequate D3 levels can greatly decrease the risk of chronic diseases and improve general well-being. Studies so far shed light on the significance of Vitamin D3 for disease prevention and management but do not fill in all the gaps regarding the long-term supplementation effects or guidance on the optimal dosing strategies for particular populations. Further research is needed to clarify evidence-based recommendations, elucidate genetic determinants of Vitamin D metabolism, and assess the effects of newer treatment modalities. Furthermore, addressing this vital nutrient deficiency will not only enhance global health status but also conduct further research and clinical practices along with preventive health policies will restore and retain it till a fruitful time.

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