





Review

# Contemporary Perspectives on the Role of Vitamin D in Enhancing Gut Health and Its Implications for Preventing and Managing Intestinal Diseases

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**Abstract:** Vitamin D, a crucial fat-soluble vitamin, is primarily synthesized in the skin upon exposure to ultraviolet radiation and is widely recognized as a bone-associated hormone. However, recent scientific advancements have unveiled its intricate association with gut health. The intestinal barrier serves as a vital component, safeguarding the intestinal milieu and maintaining overall homeostasis. Deficiencies in vitamin D have been implicated in altering the gut microbiome composition, compromising the integrity of the intestinal mucosal barrier, and predisposing individuals to various intestinal pathologies. Vitamin D exerts its regulatory function by binding to vitamin D receptors (VDR) present in immune cells, thereby modulating the production of pro-inflammatory cytokines and influencing the intestinal barrier function. Notably, numerous studies have reported lower serum vitamin D levels among patients suffering from intestinal diseases, including inflammatory bowel disease, irritable bowel syndrome, and celiac disease, highlighting the growing significance of vitamin D in gut health maintenance. This comprehensive review delves into the latest advancements in understanding the mechanistic role of vitamin D in modulating the gut microbiome and intestinal barrier function, emphasizing its pivotal role in immune regulation. Furthermore, we consolidate and present relevant findings pertaining to the therapeutic potential of vitamin D in the management of intestinal diseases.

**Keywords:** vitamin D; gut microbiome; intestinal barrier; IBD; IBS



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## 1. Introduction

Vitamin D, a fat-soluble vitamin and secosteroid hormone, is a vital nutrient that plays a crucial role in various physiological processes within the human body. It is synthesized in the skin upon exposure to ultraviolet B (UV-B) radiation from sunlight and can also be obtained through the diet, primarily from fatty fish, fortified dairy products, and supplements [1]. Beyond its well-established functions in regulating calcium and phosphorus metabolism and its importance in bone health, vitamin D has emerged as a key player in a multitude of physiological and pathological conditions.

Recent studies have provided insights into the complex connection between vitamin D and the intestinal tract, which is the largest and most intricate immunological and digestive organ in the body [2]. The gut microbiota, a complex and ever-changing community of microorganisms, resides in the intestinal tract. It plays a crucial role in breaking down nutrients, producing vitamins, and maintaining the immune balance of the gut mucosa [3]. The gut microbiota and the host's immune system maintain a delicate equilibrium, and

any disruption can potentially trigger a series of intestinal diseases, such as inflammatory bowel diseases, irritable bowel syndrome, etc. [4,5]. Emerging findings indicate that vitamin D plays a substantial role in shaping the composition of the gut microbiota and maintaining the integrity of the intestinal mucosal barrier. The existence of vitamin D receptors (VDR) throughout the intestinal tract highlights the significance of this nutrient in preserving gut equilibrium. Acting as a transcription factor, VDR governs the expression of genes associated with the biological effects of vitamin D [6]. Vitamin D exerts regulatory control over the microbiome in both health and disease states via vitamin D and VDR signal transduction pathways, crucial for maintaining gut health [7]. Vitamin D has been demonstrated to regulate the gut microbiota by stimulating the growth of advantageous bacteria and suppressing the proliferation of potentially detrimental species [8]. This modulation can augment the inherent protective function of the intestinal tract, thereby inhibiting the movement of harmful microorganisms and the subsequent triggering of the immune response. Moreover, vitamin D plays a role in regulating the immune response in the intestinal tract. It has the ability to impact both the adaptive and innate immune systems by controlling the functioning of different immune cells, such as T cells, B cells, and macrophages [9]. The immunomodulatory role is essential for maintaining a harmonized immune response and preventing excessive activation of the immune system, which can result in persistent inflammation and tissue harm in the intestinal tract.

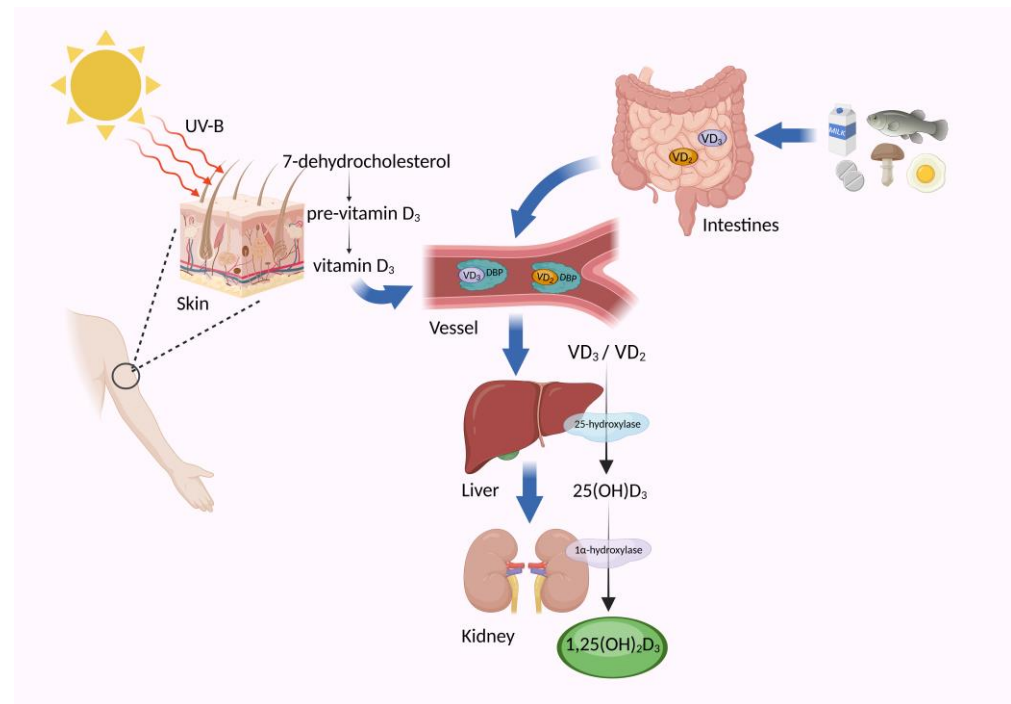
Inflammatory bowel disease (IBD) individuals, particularly those with ulcerative colitis (UC), exhibit low serum vitamin D concentrations (25-hydroxyvitamin D<sub>3</sub> [25(OH)D<sub>3</sub>] ≤ 20 ng/mL), according to a meta-analysis and systematic review [10]. Ensuring sufficient levels of vitamin D can be advantageous not only in preventing these conditions but also in managing existing intestinal diseases. The potential therapeutic efficacy of vitamin D in promoting intestinal health is a subject of increasing interest. For example, multiple studies indicate that vitamin D supplementation may enhance symptoms and decrease the recurrence rate in individuals with inflammatory bowel disease [11,12].

Comprehending the intricate relationship between vitamin D and the gut is crucial for devising innovative therapeutic approaches to enhance gut health and avert intestinal diseases. This review aims to provide an overview of the current understanding of the role of vitamin D in gut health and disease. We will discuss the mechanisms by which vitamin D influences the gut microbiota, intestinal barrier function, and immune response, and explore the clinical implications of vitamin D deficiency and supplementation in the context of intestinal diseases.

## 2. Understanding Vitamin D: Definition and Sources

Vitamin D, a steroid and fat-soluble vitamin essential for human health, plays a crucial role in various physiological processes. Its primary synthesis occurs through sunlight exposure on the skin and dietary intake. When the skin is exposed to ultraviolet radiation, 7-dehydrocholesterol is converted into pre-vitamin D<sub>3</sub>, subsequently transformed into vitamin D<sub>3</sub> with the aid of body temperature [1]. This synthesized vitamin D<sub>3</sub> enters the bloodstream, binding with the vitamin D binding protein (DBP), and then is transported to the liver. Within the liver, it undergoes conversion by microsomal 25-hydroxylase into 25-hydroxyvitamin D<sub>3</sub> [25(OH)D<sub>3</sub>]. This form of vitamin D, still bound to the DBP, is further transported to the renal tubular epithelial cells in the kidney [13]. There, mitochondrial 1 $\alpha$ -hydroxylase catalyzes its conversion into the biologically active form, 1,25-dihydroxyvitamin D<sub>3</sub> [1,25(OH)<sub>2</sub>D<sub>3</sub>], which predominates in the body. 1,25(OH)<sub>2</sub>D<sub>3</sub> circulates throughout the body via the bloodstream, reaching various tissues and organs [14–16]. In instances where endogenous synthesis of vitamin D is inadequate, dietary supplementation becomes necessary to maintain optimal levels. Vitamin D obtained from dietary sources accompanies fat into the digestive tract and is absorbed predominantly in the jejunum and ileum, facilitated by bile action. Once absorbed, vitamin D, along with chylomicrons, enters the bloodstream via the lymphatic system or binds to specific vitamin

D transporters. Eventually, it undergoes activation primarily in the liver and kidneys before entering systemic circulation [17] (Figure 1).



**Figure 1.** The synthesis, sources, and metabolism of vitamin D. Under the influence of UV-B radiation, the 7-dehydrocholesterol in the skin undergoes conversion into pre-vitamin D, subsequently transforming into vitamin D<sub>3</sub> through body temperature-mediated processes. Alternatively, dietary supplements can also serve as sources of vitamin D. Notably, vitamin D<sub>2</sub> is sourced from plants, whereas vitamin D<sub>3</sub> originates from animals. Upon entering the bloodstream, vitamin D<sub>2</sub>/D<sub>3</sub> binds to the vitamin D binding protein (DBP), facilitating its transportation to the liver and kidneys. Within these organs, it undergoes successive transformations, ultimately culminating in the formation of biologically active 1,25-dihydroxyvitamin D<sub>3</sub> (1,25(OH)<sub>2</sub>D<sub>3</sub>). This active form is then circulated throughout the body via the bloodstream, delivering its vital functions to various organs and tissues. Created with [Biorender.com](https://www.biorender.com) (accessed on 18 July 2024).

Vitamin D is integral to the regulation of calcium and phosphorus metabolism, crucial for promoting bone resorption, and pivotal in facilitating body growth and bone development. Beyond its fundamental skeletal functions, an extensive body of research underscores its intricate involvement in various physiological processes [18]. Numerous studies have elucidated the intricate relationship between vitamin D and a spectrum of health conditions, including obesity, autism, respiratory diseases, digestive tract disorders, cardiovascular ailments, cancer, and multiple sclerosis [19–23]. Furthermore, recent investigations have unveiled additional roles of vitamin D in modulating cellular proliferation and differentiation [24], orchestrating hormone secretion [25], shaping the structure of the gut microbiome [26], fortifying intestinal barrier function [27], and optimizing immune system functionality [28,29]. Thus, the multifaceted influence of vitamin D extends beyond its classical roles, highlighting its indispensable significance in maintaining overall health and well-being.

### 3. The Dynamic Interplay: Impact of Vitamin D on the Gut Microbiome and Intestinal Barrier Function

The intestinal tract, comprising the largest digestive organ in the human body, serves as a critical site for food digestion and nutrient absorption. In conjunction with endogenous digestive secretions, the gut harbors a vast array of microorganisms, pivotal in fostering gut

and overall bodily health. A thriving gut ecosystem is instrumental in the efficient breakdown and assimilation of nutrients essential for growth and maintenance. Moreover, the gut boasts extensive immunological activity, adept at discerning and combatting pathogens. Sustaining gut homeostasis bolsters immune equilibrium, averting hyperimmunity and chronic inflammation. Conversely, dysbiosis within the gut microbiome and disruption of the intestinal mucosal barrier may precipitate immune hyperactivity, culminating in inflammatory and autoimmune pathologies [30,31]. In addition, emerging research underscores the intricate interplay between the gut microbiome and various physiological processes, including lipid metabolism and communication with the central nervous system via the microbiota–gut–brain axis, thereby implicating its profound implications for mental health and neurological disorders [32,33]. Optimal levels of vitamin D are essential for maintaining gut health, influencing the composition of the gut microbiome and the integrity of the intestinal mucosal barrier. The multifaceted impact of vitamin D encompasses enhancing the stability and diversity of the gut microbiome, reinforcing the functionality of the intestinal mucosal barrier, modulating immune cell activity, and preserving mucosal integrity [34,35]. Several recent studies have identified gut-microbiota-dysbiosis-associated metabolic disorders as possible triggers or causes for dermatological conditions [36,37]. These findings suggest a broader role of vitamin D in modulating tissue functions via the gut microbiome.

### *3.1. Regulation of Vitamin D on the Composition of the Gut Microbiota*

The gut harbors a diverse and intricate microbial ecosystem known as the gut microbiome, which is inherently host-specific. Its composition and species vary across different microenvironments and species. Through continuous selection and coadaptation during the interaction between the host and its environment, the gut microbiome gradually attains dynamic stability, playing a pivotal role in host body adaptation and equilibrium. This delicate balance can be perturbed by various factors such as genetics, age, antibiotics, and environmental influences [7].

The interactions between vitamin D and the gut microbiome are complex, and studies have demonstrated the capacity of vitamin D to modulate and improve the gut microbiome under both diseased and healthy conditions [38]. For instance, a non-randomized trial supplementing 80 vitamin D-deficient women with 50,000 IU of vitamin D per week for 12 weeks significantly augmented the richness and diversity of their gut microbiomes [39]. In the obese population, a Mediterranean lifestyle intervention was able to increase serum vitamin D levels, which is associated with increased gut microbiota diversity, as well as specific gut microbiota profiles [40]. Conversely, deficiency in VDR not only precipitates metabolic disorders in mice but also alters the structure of the gut microbiome and virome, influencing virus–microbiome interactions [41,42]. Yet, conflicting evidence exists; while some studies indicate that long-term vitamin D supplementation (60,000 IU/month) does not significantly alter gut microbiome composition and diversity [43], others suggest potential effects, albeit at a lower taxonomic level [44]. It may be that factors such as the age and gender of the participants have contributed to the inconsistent effects of vitamin D and gut microbiome interactions [45,46]. Hence, the extent to which vitamin D supplementation impacts the composition of the gut microbiome remains a subject of ongoing investigation. The regulation of the gut microbiome by vitamin D is further supported by the additional evidence provided in Table 1.

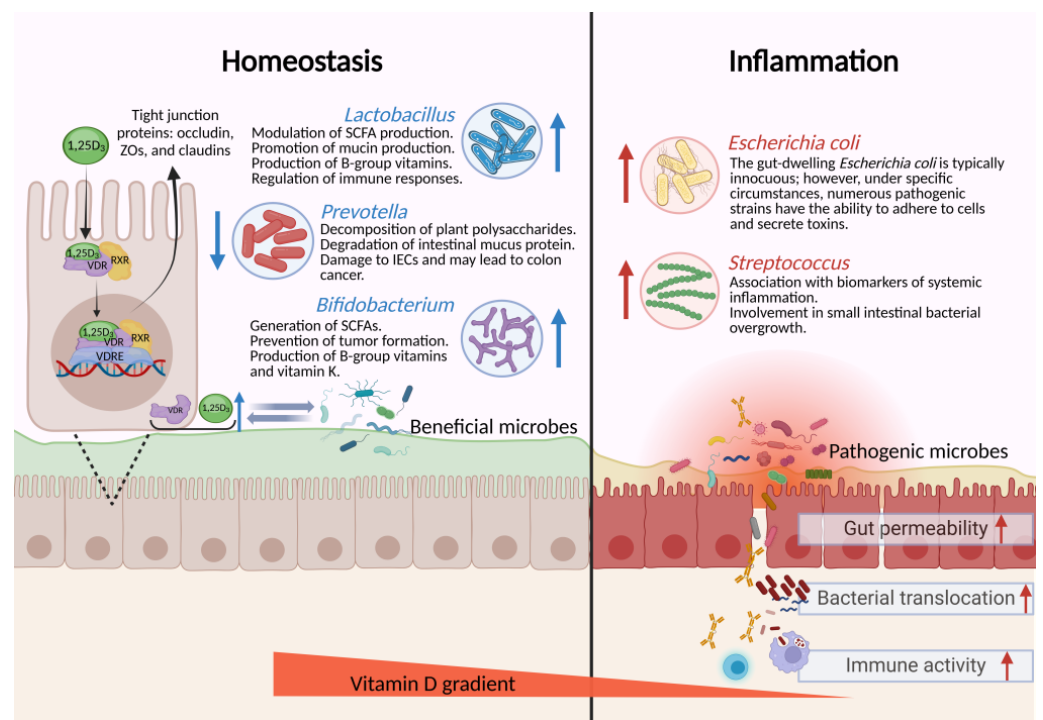
**Table 1.** Effects of vitamin D supplementation on the composition of gut microbiome in diverse populations.

Number of Participants	Country	Subject Information	Vitamin D Supplementation	Changes of Gut Microbiome	References
835	Australia	Australians aged 60–84 years	60,000 IU of vitamin D <sub>3</sub> /month for 5 years	No significant changes	[43]
36	Ireland	Healthy volunteers	60 µg vitamin D <sub>3</sub> per day for four weeks	Bacteroidetes↓; Actinobacteria↑; <i>Bifidobacterium longum</i> ↑; <i>Coprococcus</i> ↑	[47]
26	Australia	18–60 years, with vitamin D deficiency (serum 25-hydroxyvitamin D (25(OH)D) concentration ≤ 50 nmol/L)	4000 IU/day for 16 weeks	<i>Lachnospira</i> ↑; <i>Blautia</i> ↓	[44]
18	United States	Adults ≥ 18 years with vitamin D deficiency (25-hydroxyvitamin D [25(OH)D] < 20 ng/mL)	Vitamin D <sub>3</sub> (60 µg [2400 IU]/day) or 25-hydroxyvitamin D <sub>3</sub> (20 µg/day) for 8 weeks	Firmicutes↓	[48]
74	Italy	35–75 years old colorectal cancer patients with resected colorectal cancer stage I–III in the last 24 months	2000 IU vitamin D <sub>3</sub> per day for 1 year	<i>Leuconostoc pseudomesenteroides</i> ↑; <i>Bacteroides gallinarum</i> ↑; <i>Christensenella timonensis</i> ↑; <i>Ruminococcus YE78</i> ↑; <i>Faecalibacterium prausnitzii</i> ↑; <i>Holdemanella bififormis</i> ↑; <i>Eubacterium brachy</i> ↓; <i>Bacteroides coprocola</i> ↓	[49]
870	United States	10–18 weeks of gestation	4400 IU vitamin D <sub>3</sub> per day between enrollment and delivery	<i>Desulfovibrio</i> ↓	[50]
18	Korea	Patients with <i>Clostridioides difficile</i> infections (CDI) and vitamin D insufficiency (vitamin D level < 17 ng/mL)	200,000 IU vitamin D <sub>3</sub> per day for 2 weeks	Proteobacteria↓; Lachnospiraceae↑; Ruminococcaceae↑; Akkermansiaceae↑; Bifidobacteriaceae↑	[51]

Note: “↑” and “↓” represent an increase and a decrease in the abundance of the microbial community, respectively.

### 3.2. Contribution of the Gut Microbiome to Vitamin D Metabolism

Research has shown a correlation between serum 1,25(OH)<sub>2</sub>D<sub>3</sub> levels and the shifts in bacterial community composition or gut microbiota diversity, indicating a role of the microbiome in regulating vitamin D metabolism and circulation in the gut [52]. While the gut microbiome does not possess the VDR, the gut microbiota is associated with the expression of VDR, which in turn affects circulating vitamin D levels. For instance, in both murine and human intestinal epithelial cells, supplementation with *Lactiplantibacillus plantarum* and *Limosilactobacillus reuteri* increased VDR protein expression, augmented Paneth cell numbers, and bolstered mice resilience against salmonella-induced colitis in mice [53]. Moreover, human studies have shown that supplementation with *Lactobacillus reuteri* for a duration of 9 weeks led to elevated serum 25(OH) vitamin D<sub>3</sub> levels [54]. In obese patients, serum vitamin D levels were significantly positively correlated with Bifidobacteria abundance in the gut [55]. Conversely, an increase in gut pathogens has been associated with the down-regulation of VDR expression [56] (Figure 2). In addition, the gut microbiota can produce lithocholic acid (LCA), which facilitates intestinal absorption of vitamin D, consequently enhancing its bioavailability [57].



**Figure 2.** Unlocking the nexus: vitamin D, gut microbes, and epithelial cell dynamics. The vitamin D receptors (VDR) are highly abundant in intestinal epithelial cells [58]. Following the entry of vitamin D into intestinal epithelial cells, VDR can form a heterodimer with RXR. This complex translocates to the nucleus and binds to the vitamin D response element (VDRE) in the promoter region of the target genes, thereby regulating VDR expression. Interactions between vitamin D/VDR and intestinal microbes are observed. On one hand, they enhance tight junction protein expression, maintain intestinal epithelial tissue integrity, reduce bacterial translocation, promote colonization by beneficial bacteria, and alleviate mucosal damage and abnormal immune activation [59–61]. On the other hand, the gut microbiota can produce lithocholic acid (LCA), which facilitates vitamin D absorption. Created with [Biorender.com](https://www.biorender.com) (accessed on 18 July 2024).

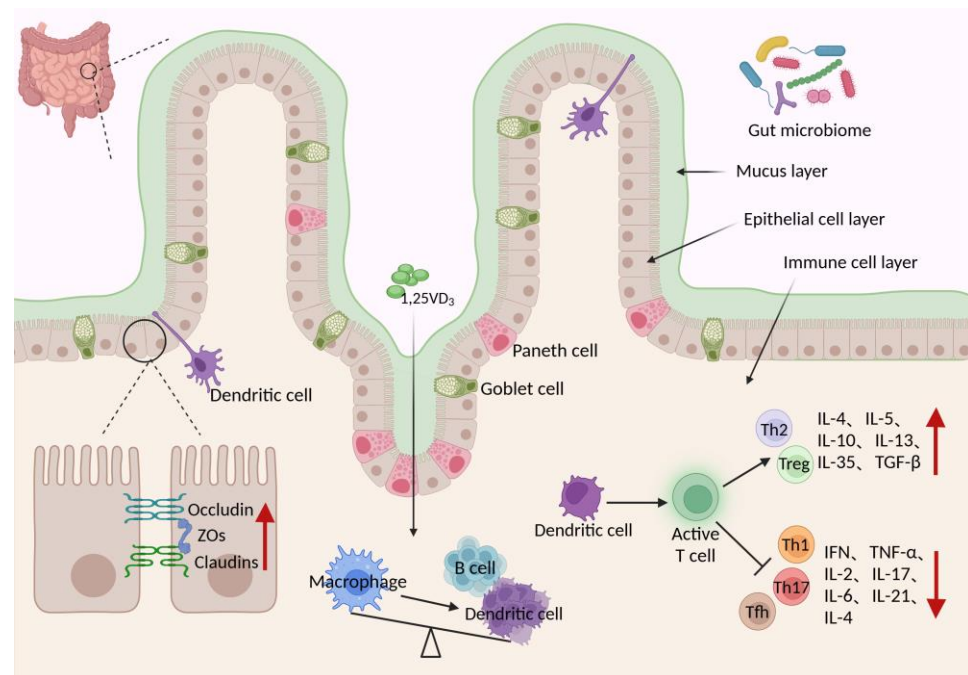
### 3.3. Role of Vitamin D in Preserving Intestinal Barrier Function

The intestinal barrier constitutes a multifaceted structure comprising the gut microbiome, mucus layer, epithelial cell layer, and immune cell layer, playing a pivotal role in both health and disease. Any impairment in barrier function or subtle alterations in microbial, mucus, epithelial, or immune components may contribute to the pathogenesis of complex diseases [62]. As the largest immune organ in the body, the gut harbors various specialized structures such as plicae circulares, intestinal villi, and crypts within the intestinal mucosa, where the mucus layer, epithelial cells, immune cells in the lamina propria, and tight junctions work in concert. The intimate association between the intestinal mucosa and the gut microbiome fosters a symbiotic relationship crucial for immune homeostasis [63,64]. The gut microbiome exerts protective effects by competitively inhibiting the attachment and proliferation of pathogenic bacteria, while also aiding in nutrient breakdown and synthesis of essential vitamins and amino acids necessary for host health [65,66]. The mucus layer, enriched with mucin, antimicrobial peptides, and secretory immunoglobulin A (sIgA), serves as the initial physical barrier encountered by luminal contents, thereby impeding direct contact between bacteria and epithelial cells and mitigating intestinal inflammation [67].

Intestinal epithelial cells play a pivotal role in maintaining the integrity of the barrier by establishing a selectively permeable interface between the luminal environment and the internal milieu. Apart from facilitating nutrient absorption and electrolyte balance, they serve as a formidable barrier against harmful substances while preserving immunological vigilance against potentially harmful compounds [67,68]. Moreover, the epithelial cell layer exhibits specialized immune and endocrine functions, further contributing to barrier integrity and immune surveillance. The immune cell layer, situated within the lamina propria beneath the epithelial cells, comprises diverse immune cells, including macrophages, dendritic cells, T cells, and mast cells, among others, each endowed with specific secretory and immunomodulatory roles, collectively orchestrating immune responses within the gut microenvironment [69].

Vitamin D exerts profound regulatory effects on immune cell development and function. It facilitates the differentiation of mononuclear macrophages into dendritic cells (DCs) and antigen-presenting cells (APCs), thereby augmenting their capacity for antigen capture and presentation [70,71]. Moreover, vitamin D promotes the differentiation of T cells into regulatory T cells (Tregs) while inhibiting the differentiation of inflammatory Th1 and Th17 cells [72,73]. Tregs, through the secretion of inhibitory cytokines such as transforming growth factor- $\beta$  (TGF- $\beta$ ) and interleukin-10 (IL-10), modulate immune responses, dampen inflammatory reactions, and mitigate autoimmune diseases [74]. Th1 and Th17 cells, on the other hand, are T helper cell subpopulations implicated in the activation of B cells, neutrophils, and macrophages, as well as the mediation of inflammatory responses by inducing various pro-inflammatory factors, chemokines, and cell adhesion molecules [75,76]. Dysregulation of Th1 and Th17 cells is associated with inflammatory and autoimmune diseases [77,78]. On the one hand, vitamin D can inhibit the activation of intestinal immune cells (such as T cells) and reduce the production of inflammatory mediators, thereby reducing the intensity and duration of the intestinal immune response [74]. Specifically, vitamin D inhibits the production of pro-inflammatory cytokines, including interleukin-6 (IL-6), interleukin-17 (IL-17), and tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), thereby curbing inflammatory damage within the gut [79,80]. Furthermore, vitamin D promotes the synthesis of the anti-inflammatory cytokine interleukin-10 (IL-10), which exerts immunosuppressive effects by dampening pro-inflammatory mediator production in macrophages and T cells, thereby enhancing immune regulation [81].

In addition to its immunoregulatory role, vitamin D enhances the integrity of the physical barrier within the intestinal mucosa. Tight junctions (TJs), composed of various proteins, including occludin, claudins, and zonula occludens (ZO), constitute crucial adhesive structures between intestinal epithelial cells, imparting a vital physical barrier for mucosal immunity [82]. Disruption of TJ integrity leads to increased cellular permeability, exposure to bacterial toxins, and heightened pro-inflammatory cytokine release, culminating in immune cell activation and chronic inflammation [83,84]. Vitamin D preserves TJ expression in epithelial cells, promotes tight junction protein synthesis, prevents epithelial cell apoptosis, fortifies intercellular connections, and shields the intestinal mucosa from harmful microorganisms and toxins, thereby mitigating inflammation [35,85] (Figure 3).



**Figure 3.** Modulation of intestinal barrier and mucosal immunity by vitamin D. Upon entering the intestine, vitamin D plays a crucial role in modulating immune responses by facilitating the differentiation of mononuclear macrophages into B cells and dendritic cells. This process significantly enhances the recognition and presentation of antigens. Furthermore, vitamin D promotes the transformation of dendritic cells into T cells, steering their differentiation towards Th2 and Treg phenotypes. This shift is accompanied by an increase in the secretion of anti-inflammatory cytokines such as IL-10 and TGF- $\beta$ , while inhibiting the differentiation into pro-inflammatory Th1, Th17, and Tfh cells. Notably, vitamin D also downregulates the secretion of pro-inflammatory cytokines, including IFN, TNF- $\alpha$ , IL-17, and IL-6, further attenuating inflammatory responses. Additionally, it upregulates the expression of tight junction proteins such as occludin, zonula occludens (ZO), and claudins, thereby reinforcing intestinal barrier integrity. Created with [Biorender.com](https://www.biorender.com) (accessed on 18 July 2024).

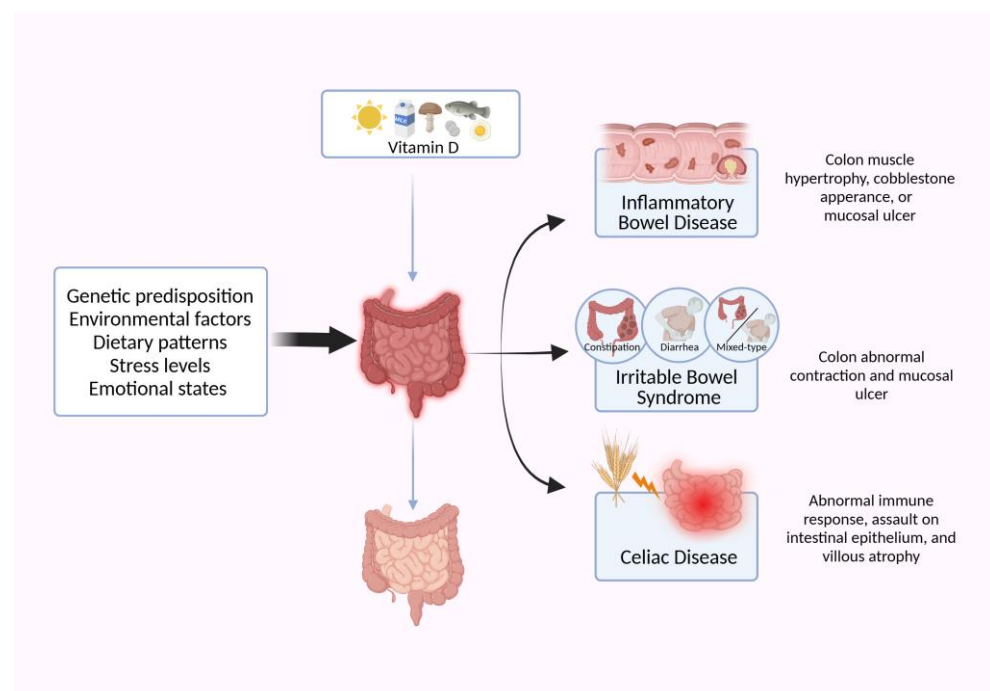
### 3.4. Consequences of Vitamin D Deficiency on Intestinal Barrier Function

An increasing body of evidence suggests that vitamin D deficiency can disrupt the integrity of the intestinal mucosal barrier [58,86–88]. Studies conducted in mouse models of induced colitis have revealed significant alterations in intestinal barrier function among mice deficient in vitamin D compared to those with sufficient levels. Specifically, deficiencies in vitamin D are associated with heightened intestinal permeability, deeper crypt mucosal hyperplasia, and increased susceptibility to viral infections [27,89]. In vitro studies further support the protective role of vitamin D supplementation, demonstrating its ability to mitigate the escalation of paracellular permeability and redistribution of tight junctions in human colonic epithelial cells induced by pathogens such as *Escherichia coli*, thereby preserving the structural and functional homeostasis of the intestinal epithelium [90]. Moreover, vitamin D deficiency not only exacerbates disease activity but also contributes to low-grade inflammation. Research findings suggest that infection with *Clostridium* induces colonic epithelial cell proliferation and perturbs paracellular permeability in rodent models. However, compared to healthy counterparts with adequate vitamin D levels, uninfected mice lacking vitamin D exhibit heightened proliferative responses, increased permeability, and elevated expression of both pro-inflammatory and anti-inflammatory cytokines in colon tissue [87]. These findings underscore the critical role of vitamin D in maintaining intestinal barrier integrity and immune homeostasis, highlighting its potential as a therapeutic target for managing intestinal diseases.



#### 4. Unraveling the Nexus: Association of Vitamin D with Gut Diseases

Vitamin D emerges as a pivotal factor in maintaining intestinal well-being and in the prevention and management of associated diseases. Apart from its recognized efficacy in ameliorating inflammatory bowel diseases (IBD), such as Crohn's disease (CD) and ulcerative colitis (UC), vitamin D demonstrates promising utility in mitigating symptoms and complications of irritable bowel syndrome (IBS) and celiac disease (CeD) [91,92]. Notably, inadequate vitamin D levels are implicated in heightened susceptibility to a spectrum of intestinal ailments, encompassing IBD, IBS, and CeD (Figure 4). Interventions involving vitamin D supplementation exhibit therapeutic potential, engendering improvements in clinical manifestations and enhancing the quality of life for affected individuals [93–95]. Consequently, maintaining optimal vitamin D status assumes paramount importance in safeguarding intestinal health and in the prophylaxis and management of intestinal diseases.



**Figure 4.** Factors affecting gut health and the role of vitamin D in gut diseases. Various factors including genetic predisposition, environmental influences, dietary patterns, stress levels, and emotional states contribute to the development of gut-related diseases. In this context, vitamin D supplementation has emerged as a promising intervention for alleviating conditions such as inflammatory bowel disease (IBD), irritable bowel syndrome (IBS), and celiac disease (CeD). IBD primarily manifests through colonic muscle hypertrophy, epithelial tissue fissures, pebble-like alterations (ulcerative colitis, UC), and mucosal injury (Crohn's disease, CD). IBS patients often experience abnormal spasms in the large intestine and mucosal damage, leading to symptoms of constipation (IBS-C), diarrhea (IBS-D), or a combination of both (IBS-M). CeD, primarily affecting susceptible individuals consuming gluten, involves abnormal activation of intestinal mucosal immunity, consequently compromising the integrity of the intestinal barrier. Created with [Biorender.com](https://biorender.com) (accessed on 18 July 2024).

##### 4.1. Vitamin D and Inflammatory Bowel Disease (IBD)

IBD comprises a group of chronic, idiopathic intestinal inflammatory conditions, notably encompassing UC and CD [96]. UC manifests as mucosal inflammation extending from the rectum to the proximal colon, typified by hemorrhagic diarrhea [97]. By contrast, CD manifests as segmental, asymmetrical, and transmural inflammation, commonly affecting the ileum and colon and presenting with symptoms such as abdominal pain, chronic diarrhea, weight loss, and fatigue [98]. The etiology of IBD remains elusive, though it is believed to result from an aberrant immune response to intestinal antigens, influenced by a

complex interplay of genetic predisposition, environmental factors, and gut microbiome dysbiosis. Notably, intestinal infection and immune dysregulation are deemed pivotal in disease pathogenesis [99,100]. Traditionally, IBD has exhibited a higher prevalence in North America, Northern Europe, and select Western nations compared to Asia, Southern Europe, and Africa. However, recent years have witnessed a rising incidence of IBD in Asian countries [101].

Beyond its classical roles in calcium and phosphorus metabolism, vitamin D assumes a critical function in modulating immune system dysregulation, rectifying gut microbiome imbalances, and preserving the integrity of the intestinal mucosal barrier [102–104]. Given its broad-spectrum antimicrobial and immunomodulatory properties, the role of vitamin D in IBD pathophysiology has garnered increasing attention and elucidation.

The biological actions of vitamin D are predominantly mediated via the VDR, which governs mucosal barrier homeostasis by upholding the integrity of junctional complexes and promoting colonic epithelial healing. Consequently, vitamin D exerts regulatory influence over intestinal barrier integrity, mucosal immunity, and gut microbiome composition [105]. Vitamin D deficiency may compromise mucosal barrier function, heightening susceptibility to mucosal injury and predisposing to IBD [88]. Indeed, studies have documented a high prevalence of vitamin D deficiency in the IBD population, with murine models of vitamin D deficiency demonstrating impaired antibacterial activity and heightened susceptibility to chemically induced colitis [106]. A comprehensive systematic review encompassing 27 studies and 8316 IBD patients corroborated the association between low vitamin D levels and disease activity, mucosal inflammation, quality of life scores, and prognostic outcomes in adult IBD patients [107].

As per the American Institute of Medicine (IOM) guidelines, vitamin D deficiency is defined by serum 25 (OH)D<sub>3</sub> levels below 20 ng/mL (50 nmol/L) [108]. Notably, individuals with IBD often struggle to attain adequate vitamin D levels through dietary sources or sunlight exposure, necessitating oral supplementation [109]. In pediatric IBD patients, vitamin D supplementation has demonstrated significant efficacy in lowering serum C-reactive protein (CRP) levels and erythrocyte sedimentation rates (ESR), concurrently elevating serum 25 (OH)D<sub>3</sub> and calcium levels. Moreover, higher supplemental doses exceeding 2000 IU per week have shown superior therapeutic outcomes [110]. Similarly, in adult IBD patients, supplementation with 40,000 IU of vitamin D weekly for 8 weeks has been shown to markedly reduce disease activity indices, fecal calprotectin levels, and serum CRP concentrations, while concurrently boosting albumin levels. This underscores the potential of vitamin D supplementation in mitigating intestinal inflammation in active colitis patients [111]. Notably, within the dosage range of 2000 IU to 50,000 IU per week, the therapeutic efficacy of vitamin D supplementation appears to be positively correlated with dosage escalation, with no reported serious adverse reactions. However, the precise optimal supplementation dosage remains to be definitively established [91,109]. Ongoing research aims to elucidate the most efficacious dosing regimen for achieving optimal therapeutic outcomes in IBD patients.

#### 4.2. Implications of Vitamin D in Irritable Bowel Syndrome (IBS)

IBS represents a multifactorial chronic disorder characterized by recurrent symptoms of intestinal dysfunction, spasms, abdominal pain, and alterations in defecation patterns [112]. Its etiology remains elusive, attributed to a complex interplay of environmental, genetic, and immune factors. Categorized by defecation habits, IBS encompasses diarrhea-predominant (IBS-D), constipation-predominant (IBS-C), and mixed-type (IBS-M) presentations [113]. Stress, depression, dysregulation of the brain–gut axis, dysbiosis of the gut microbiome, and intestinal infections are among the implicated factors contributing to IBS pathogenesis [114–118].

A considerable proportion of individuals with IBS may exhibit vitamin D deficiency, with serum vitamin D levels inversely correlating with disease severity. This underscores the potential therapeutic utility of vitamin D in IBS management [119,120]. In a randomized

clinical trial involving IBS-D patients with vitamin D deficiency, supplementation with 50,000 IU of vitamin D over 9 weeks yielded improvements in IBS symptoms and reduction in serum interleukin-6 (IL-6) concentrations [121]. IL-6, a pro-inflammatory cytokine, plays a pivotal role in acute inflammatory responses and exerts regulatory effects on nerve function, regeneration, and metabolism. Elevated serum IL-6 levels have been documented in IBS patients [122,123]. However, it is noteworthy that achieving a therapeutic effect with vitamin D supplementation may necessitate doses exceeding the established safe upper limit. Notably, within safe dosage thresholds, daily supplementation with 3000 IU of vitamin D over 12 weeks failed to yield therapeutic benefits in IBS management [124]. Thus, optimization of vitamin D supplementation strategies for IBS treatment warrants further investigation to delineate effective dosing regimens and maximize therapeutic efficacy while ensuring safety. Continued research efforts are imperative to refine our understanding and approach to utilizing vitamin D as a therapeutic modality for IBS.

#### 4.3. Influence of Vitamin D in Celiac Disease (CeD)

CeD stands as a chronic immune-mediated disorder of the small intestine, characterized by innate and adaptive immune responses triggered by dietary gluten ingestion in genetically predisposed individuals [125,126]. CeD manifests with diarrhea and mucosal damage, potentially leading to malnutrition, weight loss, growth retardation in children, and complications such as osteoporosis and intestinal lymphoma [127–129]. In recent years, the prevalence rate of CeD has been gradually increasing [130,131]. Currently, the primary treatment for CeD entails adherence to a strict gluten-free diet (GFD), which facilitates mucosal healing. However, GFD adherence may pose challenges in achieving adequate nutrition and necessitates careful dietary management in alignment with evidence-based guidelines. Studies have found that GFD can improve the composition of the gut microbiota but does not appear to safely restore the gut microbiota abundance [132]. Moreover, emerging non-dietary treatment modalities are under investigation [133–136].

Studies have suggested a correlation between the prevalence of CeD and birth season, implicating a potential association with ultraviolet B exposure and vitamin D status [137,138]. The intestinal mucosal permeability increased in patients with CeD. Gluten protein is converted into immunogenic molecules under the action of transglutaminase (TTG), which is presented to immune cells in the lamina propria to induce the production of inflammatory cytokines, resulting in intestinal villus atrophy and damage to intestinal barrier function [139,140]. Vitamin D supplementation has shown promise in ameliorating TJ barrier damage in CeD murine models and bolstering intestinal mucosal immunity [27,88,90]. Clinical studies have demonstrated that daily supplementation with 400 IU of vitamin D and 400 mg of calcium carbonate over 6 months in pediatric CeD patients on a GFD regimen effectively alleviates intestinal and systemic symptoms [141]. Furthermore, vitamin D and calcium supplementation exert notable therapeutic benefits in mitigating CeD-induced bone metabolic disorders in children [142]. These findings underscore the potential utility of vitamin D supplementation as an adjunctive therapeutic approach in CeD management, particularly in conjunction with GFD adherence and comprehensive nutritional support.

### 5. Limitations and Future Aspects

In the current landscape of vitamin D and gut health research, while numerous advancements have been made, several limitations persist. Foremost, the heterogeneity in experimental designs, sample sizes, and dosage of vitamin D across various studies poses challenges in drawing generalized and definitive conclusions. This diversity in methodologies often introduces inconsistencies and potential biases in the interpretation of results. Further research is warranted in the future to elucidate the impact of vitamin D on enhancing intestinal health across various physiological stages or in different intestinal pathological conditions, as well as determining the optimal dosage for supplementation. Furthermore, the intricate mechanisms underlying the role of vitamin D in modulating

gut health, particularly its interactions with the gut microbiome and intestinal barrier function, remain incompletely elucidated. While we have gained valuable insights, a more comprehensive understanding of these mechanisms is crucial for developing targeted therapeutic strategies.

The understanding of the role of vitamin D in gut health has made significant progress; however, there still exist ample opportunities for further research and development. Looking forward, the integration of cutting-edge technologies such as metagenomics, single-cell transcriptomics, spatial transcriptomics, and metabolomics holds great potential for further elucidating the intricate role of vitamin D in gut health. These techniques can provide us with a deeper understanding of the molecular mechanisms and signaling pathways involved. In particular, future research should focus on investigating the specific role of vitamin D in intestinal diseases, such as inflammatory bowel disease and irritable bowel syndrome. Moreover, the utilization of big data and machine learning techniques can significantly enhance our ability to analyze vast amounts of research data. These techniques can reveal new associations, identify potential targets, and facilitate the development of precision medicine approaches tailored to individual patients.

## 6. Conclusions

The intestinal mucosal barrier serves as a critical line of defense, preventing the invasion of harmful substances and maintaining internal environmental stability. Vitamin D plays a multifaceted role in regulating the integrity of this barrier. It influences the structure and diversity of the gut microbiome, modulates the proliferation and differentiation of intestinal immune cells, affects the tight junctions between intestinal epithelial cells, and regulates immune factors crucial for mucosal immunity. Insufficient levels of vitamin D can disrupt the delicate balance of the gut microbiome, impair the intestinal mucosal barrier, and predispose individuals to intestinal diseases.

Despite significant advancements in understanding the impact of vitamin D on gut health, several fundamental questions remain unanswered and warrant further research attention. The effects of vitamin D on the gut microbiome are nuanced and varied, necessitating comprehensive exploration into the underlying mechanisms and optimal dosage thresholds. Additionally, elucidating the pathogenesis of intestinal diseases and unraveling the intricate mechanisms governing microbiota responses are areas of ongoing investigation.

A comprehensive examination of the interaction between vitamin D and the gut microbiome, intestinal epithelium, and immune responses holds immense potential for the development of rational strategies aimed at protecting or restoring the intestinal barrier. By delving deeper into these interactions, researchers can formulate evidence-based approaches to mitigate intestinal diseases and identify novel therapeutic targets for enhancing intestinal health. Thus, further insights into this dynamic interplay are essential for advancing our understanding and management of intestinal disorders.

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## References

1. Wacker, M.; Holick, M.F. Sunlight and Vitamin D: A global perspective for health. *Dermato-Endocrinology* **2013**, *5*, 51–108. [[CrossRef](#)] [[PubMed](#)]
2. Fleet, J.C. Vitamin D and Gut Health. *Adv. Exp. Med. Biol.* **2022**, *1390*, 155–167. [[CrossRef](#)]
3. Thursby, E.; Juge, N. Introduction to the human gut microbiota. *Biochem. J.* **2017**, *474*, 1823–1836. [[CrossRef](#)]
4. Qiu, P.; Ishimoto, T.; Fu, L.; Zhang, J.; Zhang, Z.; Liu, Y. The Gut Microbiota in Inflammatory Bowel Disease. *Front. Cell. Infect. Microbiol.* **2022**, *12*, 733992. [[CrossRef](#)]
5. Chen, Y.; Feng, S.; Li, Y.; Zhang, C.; Chao, G.; Zhang, S. Gut microbiota and intestinal immunity—A crosstalk in irritable bowel syndrome. *Immunology* **2024**, *172*, 1–20. [[CrossRef](#)] [[PubMed](#)]
6. Sone, T.; Scott, R.A.; Hughes, M.R.; Malloy, P.J.; Feldman, D.; O'Malley, B.W.; Pike, J.W. Mutant vitamin D receptors which confer hereditary resistance to 1,25-dihydroxyvitamin D3 in humans are transcriptionally inactive in vitro. *J. Biol. Chem.* **1989**, *264*, 20230–20234. [[CrossRef](#)]
7. Kumar Singh, A.; Cabral, C.; Kumar, R.; Ganguly, R.; Kumar Rana, H.; Gupta, A.; Rosaria Lauro, M.; Carbone, C.; Reis, F.; Pandey, A.K. Beneficial Effects of Dietary Polyphenols on Gut Microbiota and Strategies to Improve Delivery Efficiency. *Nutrients* **2019**, *11*, 2216. [[CrossRef](#)]
8. Tangestani, H.; Boroujeni, H.K.; Djafarian, K.; Emamat, H.; Shab-Bidar, S. Vitamin D and The Gut Microbiota: A Narrative Literature Review. *Clin. Nutr. Res.* **2021**, *10*, 181–191. [[CrossRef](#)]
9. Martens, P.J.; Gysemans, C.; Verstuyf, A.; Mathieu, A.C. Vitamin D's Effect on Immune Function. *Nutrients* **2020**, *12*, 1248. [[CrossRef](#)] [[PubMed](#)]
10. Del Pinto, R.; Pietropaoli, D.; Chandar, A.K.; Ferri, C.; Cominelli, F. Association Between Inflammatory Bowel Disease and Vitamin D Deficiency: A Systematic Review and Meta-analysis. *Inflamm. Bowel Dis.* **2015**, *21*, 2708–2717. [[CrossRef](#)]
11. Li, J.; Chen, N.; Wang, D.; Zhang, J.; Gong, X. Efficacy of vitamin D in treatment of inflammatory bowel disease: A meta-analysis. *Medicine* **2018**, *97*, e12662. [[CrossRef](#)] [[PubMed](#)]
12. Valvano, M.; Magistrone, M.; Cesaro, N.; Carlino, G.; Monaco, S.; Fabiani, S.; Vinci, A.; Vernia, F.; Viscido, A.; Latella, G. Effectiveness of Vitamin D Supplementation on Disease Course in Inflammatory Bowel Disease Patients: Systematic Review with Meta-Analysis. *Inflamm. Bowel Dis.* **2024**, *30*, 281–291. [[CrossRef](#)] [[PubMed](#)]
13. Bikle, D.D. Vitamin D: Production, Metabolism and Mechanisms of Action. In *Endotext*; Feingold, K.R., Anawalt, B., Blackman, M.R., Boyce, A., Chrousos, G., Corpas, E., de Herder, W.W., Dhatariya, K., Dungan, K., Hofland, J., et al., Eds.; MDText.com, Inc.: South Dartmouth, MA, USA, 2000.
14. Wei, X.J.; Pandohee, J.; Xu, B.J. Recent developments and emerging trends in dietary vitamin D sources and biological conversion. *Crit. Rev. Food Sci. Nutr.* **2023**, 1–17. [[CrossRef](#)]
15. Liu, Z.; Huang, S.; Yuan, X.; Wang, Y.; Liu, Y.; Zhou, J. The role of vitamin D deficiency in the development of paediatric diseases. *Ann. Med.* **2023**, *55*, 127–135. [[CrossRef](#)] [[PubMed](#)]
16. Aggeletopoulou, I.; Tsounis, E.P.; Mouzaki, A.; Triantos, C. Exploring the Role of Vitamin D and the Vitamin D Receptor in the Composition of the Gut Microbiota. *Front. Biosci. Landmark* **2023**, *28*, 116. [[CrossRef](#)]
17. Goff, J.P.; Reinhardt, T.A.; Horst, R.L. Enzymes and factors controlling vitamin D metabolism and action in normal and milk fever cows. *J. Dairy Sci.* **1991**, *74*, 4022–4032. [[CrossRef](#)]
18. Holick, M.F. Vitamin D deficiency. *N. Engl. J. Med.* **2007**, *357*, 266–281. [[CrossRef](#)]
19. Fiamenghi, V.I.; de Mello, E.D. Vitamin D deficiency in children and adolescents with obesity: A meta-analysis. *J. Pediatr.* **2021**, *97*, 273–279. [[CrossRef](#)]
20. Luan, W.; Hammond, L.A.; Cotter, E.; Osborne, G.W.; Alexander, S.A.; Nink, V.; Cui, X.Y.; Eyles, D.W. Developmental Vitamin D (DVD) Deficiency Reduces Nurr1 and TH Expression in Post-mitotic Dopamine Neurons in Rat Mesencephalon. *Mol. Neurobiol.* **2018**, *55*, 2443–2453. [[CrossRef](#)]
21. Agarwal, P.; Agarwal, Y.; Hameed, M. Recent Advances in Association between Vitamin D Levels and Cardiovascular Disorders. *Curr. Hypertens. Rep.* **2023**, *25*, 185–209. [[CrossRef](#)]
22. Sangha, A.; Quon, M.; Pfeffer, G.; Orton, S.M. The Role of Vitamin D in Neuroprotection in Multiple Sclerosis: An Update. *Nutrients* **2023**, *15*, 2978. [[CrossRef](#)]
23. Bouillon, R.; LeBoff, M.S.; Neale, R.E. Health Effects of Vitamin D Supplementation: Lessons Learned from Randomized Controlled Trials and Mendelian Randomization Studies. *J. Bone Miner. Res.* **2023**, *38*, 1391–1403. [[CrossRef](#)] [[PubMed](#)]
24. Jin, D.; Zhang, Y.G.; Wu, S.; Lu, R.; Lin, Z.; Zheng, Y.; Chen, H.; Cs-Szabo, G.; Sun, J. Vitamin D receptor is a novel transcriptional regulator for Axin1. *J. Steroid Biochem. Mol. Biol.* **2017**, *165*, 430–437. [[CrossRef](#)] [[PubMed](#)]
25. Safari, S.; Rafraf, M.; Malekian, M.; Molani-Gol, R.; Asghari-Jafarabadi, M.; Mobasseri, M. Effects of vitamin D supplementation on metabolic parameters, serum irisin and obesity values in women with subclinical hypothyroidism: A double-blind randomized controlled trial. *Front. Endocrinol.* **2023**, *14*, 1306470. [[CrossRef](#)] [[PubMed](#)]
26. Zhu, W.; Yan, J.; Zhi, C.; Zhou, Q.; Yuan, X. 1,25(OH)<sub>2</sub>D<sub>3</sub> deficiency-induced gut microbial dysbiosis degrades the colonic mucus barrier in *Cyp27b1* knockout mouse model. *Gut Pathog.* **2019**, *11*, 8. [[CrossRef](#)]
27. Assa, A.; Vong, L.; Pinnell, L.J.; Rautava, J.; Avitzur, N.; Johnson-Henry, K.C.; Sherman, P.M. Vitamin D deficiency predisposes to adherent-invasive *Escherichia coli*-induced barrier dysfunction and experimental colonic injury. *Inflamm. Bowel Dis.* **2015**, *21*, 297–306. [[CrossRef](#)] [[PubMed](#)]

28. Liu, P.T.; Stenger, S.; Li, H.; Wenzel, L.; Tan, B.H.; Krutzik, S.R.; Ochoa, M.T.; Schauber, J.; Wu, K.; Meinken, C.; et al. Toll-like receptor triggering of a vitamin D-mediated human antimicrobial response. *Science* **2006**, *311*, 1770–1773. [[CrossRef](#)] [[PubMed](#)]
29. Agmon-Levin, N.; Theodor, E.; Segal, R.M.; Shoenfeld, Y. Vitamin D in systemic and organ-specific autoimmune diseases. *Clin. Rev. Allergy Immunol.* **2013**, *45*, 256–266. [[CrossRef](#)]
30. Saleem, M.; Masenga, S.K.; Ishimwe, J.A.; Demirci, M.; Ahmad, T.; Jamison, S.; Albritton, C.F.; Mwesigwa, N.; Porcia Haynes, A.; White, J.; et al. Recent Advances in Understanding Peripheral and Gut Immune Cell-Mediated Salt-Sensitive Hypertension and Nephropathy. *Hypertension* **2024**, *81*, 436–446. [[CrossRef](#)]
31. Liao, S.F.; Ji, F.; Fan, P.; Denryter, K. Swine Gastrointestinal Microbiota and the Effects of Dietary Amino Acids on Its Composition and Metabolism. *Int. J. Mol. Sci.* **2024**, *25*, 1237. [[CrossRef](#)]
32. Liu, X.Y.; Liu, Y.; Liu, J.L.; Zhang, H.T.; Shan, C.F.; Guo, Y.L.; Gong, X.; Cui, M.M.; Li, X.B.; Tang, M. Correlation between the gut microbiome and neurodegenerative diseases: A review of metagenomics evidence. *Neural Regen. Res.* **2024**, *19*, 833–845. [[CrossRef](#)]
33. Yang, Z.H.; Wang, Q.C.; Liu, Y.X.; Wang, L.; Ge, Z.; Li, Z.Z.; Feng, S.L.; Wu, C.M. Gut microbiota and hypertension: Association, mechanisms and treatment. *Clin. Exp. Hypertens.* **2023**, *45*, 2195135. [[CrossRef](#)] [[PubMed](#)]
34. Hamza, F.N.; Daher, S.; Fakhoury, H.M.A.; Grant, W.B.; Kviety, P.R.; Al-Kattan, K. Immunomodulatory Properties of Vitamin D in the Intestinal and Respiratory Systems. *Nutrients* **2023**, *15*, 1696. [[CrossRef](#)] [[PubMed](#)]
35. Munem, F.; Thianhlun, P.C.K.; Anderson, P.H.; Stringer, A.M. Vitamin D is a potential treatment for the management of gastrointestinal mucositis. *Curr. Opin. Support. Palliat. Care* **2023**, *17*, 247–252. [[CrossRef](#)]
36. Zhang, X.; Shi, L.; Sun, T.; Guo, K.; Geng, S. Dysbiosis of gut microbiota and its correlation with dysregulation of cytokines in psoriasis patients. *BMC Microbiol.* **2021**, *21*, 78. [[CrossRef](#)] [[PubMed](#)]
37. Stec, A.; Sikora, M.; Maciejewska, M.; Paralusz-Stec, K.; Michalska, M.; Sikorska, E.; Rudnicka, L. Bacterial Metabolites: A Link between Gut Microbiota and Dermatological Diseases. *Int. J. Mol. Sci.* **2023**, *24*, 3494. [[CrossRef](#)] [[PubMed](#)]
38. Faradina, A.; Tinkov, A.A.; Skalny, A.V.; Chang, J.S. Micronutrient (iron, selenium, vitamin D) supplementation and the gut microbiome. *Curr. Opin. Clin. Nutr. Metab. Care* **2024**, 10–1097. [[CrossRef](#)]
39. Singh, P.; Rawat, A.; Alwakeel, M.; Sharif, E.; Al Khodor, S. The potential role of vitamin D supplementation as a gut microbiota modifier in healthy individuals. *Sci. Rep.* **2020**, *10*, 21641. [[CrossRef](#)] [[PubMed](#)]
40. Boughanem, H.; Ruiz-Limon, P.; Pilo, J.; Lisbona-Montanez, J.M.; Tinahones, F.J.; Moreno Indias, I.; Macias-Gonzalez, M. Linking serum vitamin D levels with gut microbiota after 1-year lifestyle intervention with Mediterranean diet in patients with obesity and metabolic syndrome: A nested cross-sectional and prospective study. *Gut Microbes* **2023**, *15*, 2249150. [[CrossRef](#)]
41. Zhang, J.; Zhang, Y.; Xia, Y.; Sun, J. Imbalance of the intestinal virome and altered viral-bacterial interactions caused by a conditional deletion of the vitamin D receptor. *Gut Microbes* **2021**, *13*, 1957408. [[CrossRef](#)]
42. Jin, D.; Wu, S.; Zhang, Y.G.; Lu, R.; Xia, Y.; Dong, H.; Sun, J. Lack of Vitamin D Receptor Causes Dysbiosis and Changes the Functions of the Murine Intestinal Microbiome. *Clin. Ther.* **2015**, *37*, 996–1009.e7. [[CrossRef](#)] [[PubMed](#)]
43. Pham, H.; Waterhouse, M.; Rahman, S.; Baxter, C.; Duarte Romero, B.; McLeod, D.S.A.; Ebeling, P.R.; English, D.R.; Hartel, G.; O’Connell, R.L.; et al. The effect of vitamin D supplementation on the gut microbiome in older Australians—Results from analyses of the D-Health Trial. *Gut Microbes* **2023**, *15*, 2221429. [[CrossRef](#)] [[PubMed](#)]
44. Naderpoor, N.; Mousa, A.; Fernanda Gomez Arango, L.; Barrett, H.L.; Dekker Nitert, M.; de Courten, B. Effect of Vitamin D Supplementation on Faecal Microbiota: A Randomised Clinical Trial. *Nutrients* **2019**, *11*, 2888. [[CrossRef](#)] [[PubMed](#)]
45. Murdaca, G.; Tagliafico, L.; Page, E.; Paladin, F.; Gangemi, S. Gender Differences in the Interplay between Vitamin D and Microbiota in Allergic and Autoimmune Diseases. *Biomedicines* **2024**, *12*, 1023. [[CrossRef](#)] [[PubMed](#)]
46. Bellerba, F.; Muzio, V.; Gnagnarella, P.; Facciotti, F.; Chiocca, S.; Bossi, P.; Cortinovis, D.; Chiaradonna, F.; Serrano, D.; Raimondi, S.; et al. The Association between Vitamin D and Gut Microbiota: A Systematic Review of Human Studies. *Nutrients* **2021**, *13*, 3378. [[CrossRef](#)] [[PubMed](#)]
47. Pham, V.T.; Fehlbaum, S.; Seifert, N.; Richard, N.; Bruins, M.J.; Sybesma, W.; Rehman, A.; Steinert, R.E. Effects of colon-targeted vitamins on the composition and metabolic activity of the human gut microbiome—A pilot study. *Gut Microbes* **2021**, *13*, 1–20. [[CrossRef](#)] [[PubMed](#)]
48. Shieh, A.; Lee, S.M.; Lagishetty, V.; Gottleib, C.; Jacobs, J.P.; Adams, J.S. Pilot Trial of Vitamin D3 and Calcifediol in Healthy Vitamin D Deficient Adults: Does It Change the Fecal Microbiome? *J. Clin. Endocrinol. Metab.* **2021**, *106*, 3464–3476. [[CrossRef](#)]
49. Bellerba, F.; Serrano, D.; Johansson, H.; Pozzi, C.; Segata, N.; NabiNejad, A.; Piperni, E.; Gnagnarella, P.; Macis, D.; Aristarco, V.; et al. Colorectal cancer, Vitamin D and microbiota: A double-blind Phase II randomized trial (ColoViD) in colorectal cancer patients. *Neoplasia* **2022**, *34*, 100842. [[CrossRef](#)]
50. Aparicio, A.; Gold, D.R.; Weiss, S.T.; Litonjua, A.A.; Lee-Sarwar, K.; Liu, Y.Y. Association of Vitamin D Level and Maternal Gut Microbiome during Pregnancy: Findings from a Randomized Controlled Trial of Antenatal Vitamin D Supplementation. *Nutrients* **2023**, *15*, 2059. [[CrossRef](#)] [[PubMed](#)]
51. Lee, S.H.; Park, H.K.; Kang, C.D.; Choi, D.H.; Park, S.C.; Park, J.M.; Nam, S.J.; Chae, G.B.; Lee, K.Y.; Cho, H.; et al. High Dose Intramuscular Vitamin D3 Supplementation Impacts the Gut Microbiota of Patients with *Clostridioides Difficile* Infection. *Front. Cell. Infect. Microbiol.* **2022**, *12*, 904987. [[CrossRef](#)]
52. Thomas, R.L.; Jiang, L.; Adams, J.S.; Xu, Z.Z.; Shen, J.; Janssen, S.; Ackermann, G.; Vanderschueren, D.; Pauwels, S.; Knight, R.; et al. Vitamin D metabolites and the gut microbiome in older men. *Nat. Commun.* **2020**, *11*, 5997. [[CrossRef](#)]

53. Wu, S.; Yoon, S.; Zhang, Y.G.; Lu, R.; Xia, Y.; Wan, J.; Petrof, E.O.; Claud, E.C.; Chen, D.; Sun, J. Vitamin D receptor pathway is required for probiotic protection in colitis. *Am. J. Physiol. Gastrointest. Liver Physiol.* **2015**, *309*, G341–G349. [[CrossRef](#)] [[PubMed](#)]
54. Jones, M.L.; Martoni, C.J.; Prakash, S. Oral supplementation with probiotic *L. reuteri* NCIMB 30242 increases mean circulating 25-hydroxyvitamin D: A post hoc analysis of a randomized controlled trial. *J. Clin. Endocrinol. Metab.* **2013**, *98*, 2944–2951. [[CrossRef](#)] [[PubMed](#)]
55. Al-Khaldy, N.S.; Al-Musharaf, S.; Aljazairy, E.A.; Hussain, S.D.; Alnaami, A.M.; Al-Daghri, N.; Aljuraiban, G. Serum Vitamin D Level and Gut Microbiota in Women. *Healthcare* **2023**, *11*, 351. [[CrossRef](#)] [[PubMed](#)]
56. He, Q.; Ananaba, G.A.; Patrickson, J.; Pitts, S.; Yi, Y.; Yan, F.; Eko, F.O.; Lyn, D.; Black, C.M.; Igietsme, J.U.; et al. Chlamydial infection in vitamin D receptor knockout mice is more intense and prolonged than in wild-type mice. *J. Steroid Biochem. Mol. Biol.* **2013**, *135*, 7–14. [[CrossRef](#)]
57. Ishizawa, M.; Akagi, D.; Makishima, M. Lithocholic Acid Is a Vitamin D Receptor Ligand That Acts Preferentially in the Ileum. *Int. J. Mol. Sci.* **2018**, *19*, 1975. [[CrossRef](#)] [[PubMed](#)]
58. Li, Y.C.; Chen, Y.; Du, J. Critical roles of intestinal epithelial vitamin D receptor signaling in controlling gut mucosal inflammation. *J. Steroid Biochem. Mol. Biol.* **2015**, *148*, 179–183. [[CrossRef](#)]
59. Yilmaz, B.; Juillat, P.; Oyas, O.; Ramon, C.; Bravo, F.D.; Franc, Y.; Fournier, N.; Michetti, P.; Mueller, C.; Geuking, M.; et al. Microbial network disturbances in relapsing refractory Crohn’s disease. *Nat. Med.* **2019**, *25*, 323–336. [[CrossRef](#)]
60. Schirmer, M.; Garner, A.; Vlamakis, H.; Xavier, R.J. Microbial genes and pathways in inflammatory bowel disease. *Nat. Rev. Microbiol.* **2019**, *17*, 497–511. [[CrossRef](#)]
61. Prasoodanan, P.K.V.; Sharma, A.K.; Mahajan, S.; Dhakan, D.B.; Maji, A.; Scaria, J.; Sharma, V.K. Western and non-western gut microbiomes reveal new roles of *Prevotella* in carbohydrate metabolism and mouth-gut axis. *NPJ Biofilms Microbiomes* **2021**, *7*, 77. [[CrossRef](#)]
62. Untermayr, E.; Brandt, A.; Koidl, L.; Bergheim, I. The Intestinal Barrier Dysfunction as Driving Factor of Inflammation. *Nutrients* **2022**, *14*, 949. [[CrossRef](#)]
63. Liu, Q.; Yu, Z.; Tian, F.; Zhao, J.; Zhang, H.; Zhai, Q.; Chen, W. Surface components and metabolites of probiotics for regulation of intestinal epithelial barrier. *Microb. Cell Fact.* **2020**, *19*, 23. [[CrossRef](#)]
64. Hiippala, K.; Jouhten, H.; Ronkainen, A.; Hartikainen, A.; Kainulainen, V.; Jalanka, J.; Satokari, R. The Potential of Gut Commensals in Reinforcing Intestinal Barrier Function and Alleviating Inflammation. *Nutrients* **2018**, *10*, 988. [[CrossRef](#)]
65. Moens, E.; Veldhoen, M. Epithelial barrier biology: Good fences make good neighbours. *Immunology* **2012**, *135*, 1–8. [[CrossRef](#)]
66. Hooper, L.V.; Gordon, J.I. Commensal host-bacterial relationships in the gut. *Science* **2001**, *292*, 1115–1118. [[CrossRef](#)]
67. Turner, J.R. Intestinal mucosal barrier function in health and disease. *Nat. Rev. Immunol.* **2009**, *9*, 799–809. [[CrossRef](#)]
68. König, J.; Wells, J.; Cani, P.D.; García-Ródenas, C.L.; MacDonald, T.; Mercenier, A.; Whyte, J.; Troost, F.; Brummer, R.J. Human Intestinal Barrier Function in Health and Disease. *Clin. Transl. Gastroenterol.* **2016**, *7*, e196. [[CrossRef](#)]
69. Mowat, A.M.; Agace, W.W. Regional specialization within the intestinal immune system. *Nat. Rev. Immunol.* **2014**, *14*, 667–685. [[CrossRef](#)]
70. Chun, R.F.; Liu, P.T.; Modlin, R.L.; Adams, J.S.; Hewison, M. Impact of vitamin D on immune function: Lessons learned from genome-wide analysis. *Front. Physiol.* **2014**, *5*, 151. [[CrossRef](#)]
71. Piemonti, L.; Monti, P.; Sironi, M.; Fraticelli, P.; Leone, B.E.; Dal Cin, E.; Allavena, P.; Di Carlo, V. Vitamin D3 affects differentiation, maturation, and function of human monocyte-derived dendritic cells. *J. Immunol.* **2000**, *164*, 4443–4451. [[CrossRef](#)]
72. White, J.H. Vitamin D metabolism and signaling in the immune system. *Rev. Endocr. Metab. Disord.* **2012**, *13*, 21–29. [[CrossRef](#)]
73. Baeke, F.; Takiishi, T.; Korf, H.; Gysemans, C.; Mathieu, C. Vitamin D: Modulator of the immune system. *Curr. Opin. Pharmacol.* **2010**, *10*, 482–496. [[CrossRef](#)]
74. von Essen, M.R.; Kongsbak, M.; Schjerling, P.; Olgaard, K.; Odum, N.; Geisler, C. Vitamin D controls T cell antigen receptor signaling and activation of human T cells. *Nat. Immunol.* **2010**, *11*, 344–349. [[CrossRef](#)] [[PubMed](#)]
75. Badalato, G.M.; Hemal, A.K.; Menon, M.; Badani, K.K. Current role of robot-assisted pyelolithotomy for the management of large renal calculi: A contemporary analysis. *J. Endourol.* **2009**, *23*, 1719–1722. [[CrossRef](#)]
76. Iwakura, Y.; Ishigame, H.; Saijo, S.; Nakae, S. Functional specialization of interleukin-17 family members. *Immunity* **2011**, *34*, 149–162. [[CrossRef](#)]
77. Cui, H.; Wang, N.; Li, H.; Bian, Y.; Wen, W.; Kong, X.; Wang, F. The dynamic shifts of IL-10-producing Th17 and IL-17-producing Treg in health and disease: A crosstalk between ancient “Yin-Yang” theory and modern immunology. *Cell Commun. Signal.* **2024**, *22*, 99. [[CrossRef](#)] [[PubMed](#)]
78. Mori, A.; Ohno, H.; Satoh-Takayama, N. Disease pathogenesis and barrier functions regulated by group 3 innate lymphoid cells. *Semin. Immunopathol.* **2024**, *45*, 509–519. [[CrossRef](#)] [[PubMed](#)]
79. Dickie, L.J.; Church, L.D.; Coulthard, L.R.; Mathews, R.J.; Emery, P.; McDermott, M.F. Vitamin D3 down-regulates intracellular Toll-like receptor 9 expression and Toll-like receptor 9-induced IL-6 production in human monocytes. *Rheumatology* **2010**, *49*, 1466–1471. [[CrossRef](#)]
80. Miossec, P.; Kolls, J.K. Targeting IL-17 and TH17 cells in chronic inflammation. *Nat. Rev. Drug Discov.* **2012**, *11*, 763–776. [[CrossRef](#)]
81. Barbi, J.; Pardoll, D.; Pan, F. Treg functional stability and its responsiveness to the microenvironment. *Immunol. Rev.* **2014**, *259*, 115–139. [[CrossRef](#)]

82. Campbell, H.K.; Maiers, J.L.; DeMali, K.A. Interplay between tight junctions & adherens junctions. *Exp. Cell Res.* **2017**, *358*, 39–44. [[CrossRef](#)] [[PubMed](#)]
83. Odenwald, M.A.; Turner, J.R. The intestinal epithelial barrier: A therapeutic target? *Nat. Rev. Gastroenterol. Hepatol.* **2017**, *14*, 9–21. [[CrossRef](#)]
84. Al-Sadi, R.; Boivin, M.; Ma, T. Mechanism of cytokine modulation of epithelial tight junction barrier. *Front. Biosci.* **2009**, *14*, 2765–2778. [[CrossRef](#)]
85. Hausmann, A.; Steenholdt, C.; Nielsen, O.H.; Jensen, K.B. Immune cell-derived signals governing epithelial phenotypes in homeostasis and inflammation. *Trends Mol. Med.* **2024**, *30*, 239–251. [[CrossRef](#)] [[PubMed](#)]
86. Yeung, C.Y.; Chiang Chiau, J.S.; Cheng, M.L.; Chan, W.T.; Jiang, C.B.; Chang, S.W.; Liu, C.Y.; Chang, C.W.; Lee, H.C. Effects of Vitamin D-Deficient Diet on Intestinal Epithelial Integrity and Zonulin Expression in a C57BL/6 Mouse Model. *Front. Med.* **2021**, *8*, 649818. [[CrossRef](#)]
87. Assa, A.; Vong, L.; Pinnell, L.J.; Avitzur, N.; Johnson-Henry, K.C.; Sherman, P.M. Vitamin D deficiency promotes epithelial barrier dysfunction and intestinal inflammation. *J. Infect. Dis.* **2014**, *210*, 1296–1305. [[CrossRef](#)] [[PubMed](#)]
88. Kong, J.; Zhang, Z.; Musch, M.W.; Ning, G.; Sun, J.; Hart, J.; Bissonnette, M.; Li, Y.C. Novel role of the vitamin D receptor in maintaining the integrity of the intestinal mucosal barrier. *Am. J. Physiol. Gastrointest. Liver Physiol.* **2008**, *294*, G208–G216. [[CrossRef](#)] [[PubMed](#)]
89. Hetta, H.F.; Muhammad, K.; El-Masry, E.A.; Taha, A.E.; Ahmed, E.A.; Phares, C.; Kader, H.A.; Waheed, Y.; Zahran, A.M.; Yahia, R.; et al. The interplay between vitamin D and COVID-19: Protective or bystander? *Eur. Rev. Med. Pharmacol. Sci.* **2021**, *25*, 2131–2145. [[CrossRef](#)] [[PubMed](#)]
90. Stio, M.; Retico, L.; Annese, V.; Bonanomi, A.G. Vitamin D regulates the tight-junction protein expression in active ulcerative colitis. *Scand. J. Gastroenterol.* **2016**, *51*, 1193–1199. [[CrossRef](#)]
91. Huang, H.; Lu, L.; Chen, Y.; Zeng, Y.; Xu, C. The efficacy of vitamin D supplementation for irritable bowel syndrome: A systematic review with meta-analysis. *Nutr. J.* **2022**, *21*, 24. [[CrossRef](#)]
92. Vici, G.; Camilletti, D.; Polzonetti, V. Possible Role of Vitamin D in Celiac Disease Onset. *Nutrients* **2020**, *12*, 1051. [[CrossRef](#)] [[PubMed](#)]
93. Trasciatti, S.; Grizzi, F. Vitamin D and celiac disease. *Adv. Food Nutr. Res.* **2024**, *109*, 249–270. [[CrossRef](#)] [[PubMed](#)]
94. Wallace, C.; Gordon, M.; Sinopoulou, V.; Limketkai, B.N. Vitamin D for the treatment of inflammatory bowel disease. *Cochrane Database Syst. Rev.* **2023**, *10*, CD011806. [[CrossRef](#)] [[PubMed](#)]
95. Yan, C.; Hu, C.; Chen, X.; Jia, X.; Zhu, Z.; Ye, D.; Wu, Y.; Guo, R.; Jiang, M. Vitamin D improves irritable bowel syndrome symptoms: A meta-analysis. *Heliyon* **2023**, *9*, e16437. [[CrossRef](#)] [[PubMed](#)]
96. Lee, S.J.; Maizels, R.M. Inflammatory Bowel Disease. *Evol. Med. Public Health* **2014**, *2014*, 95. [[CrossRef](#)] [[PubMed](#)]
97. Ungaro, R.; Mehandru, S.; Allen, P.B.; Peyrin-Biroulet, L.; Colombel, J.F. Ulcerative colitis. *Lancet* **2017**, *389*, 1756–1770. [[CrossRef](#)] [[PubMed](#)]
98. Torres, J.; Mehandru, S.; Colombel, J.F.; Peyrin-Biroulet, L. Crohn's disease. *Lancet* **2017**, *389*, 1741–1755. [[CrossRef](#)] [[PubMed](#)]
99. McGovern, D.P.; Kugathasan, S.; Cho, J.H. Genetics of Inflammatory Bowel Diseases. *Gastroenterology* **2015**, *149*, 1163–1176.e2. [[CrossRef](#)]
100. Khanna, S.; Raffals, L.E. The Microbiome in Crohn's Disease: Role in Pathogenesis and Role of Microbiome Replacement Therapies. *Gastroenterol. Clin. N. Am.* **2017**, *46*, 481–492. [[CrossRef](#)]
101. Ng, S.C.; Shi, H.Y.; Hamidi, N.; Underwood, F.E.; Tang, W.; Benchimol, E.I.; Panaccione, R.; Ghosh, S.; Wu, J.C.Y.; Chan, F.K.L.; et al. Worldwide incidence and prevalence of inflammatory bowel disease in the 21st century: A systematic review of population-based studies. *Lancet* **2017**, *390*, 2769–2778. [[CrossRef](#)]
102. Ooi, J.H.; Li, Y.; Rogers, C.J.; Cantorna, M.T. Vitamin D regulates the gut microbiome and protects mice from dextran sodium sulfate-induced colitis. *J. Nutr.* **2013**, *143*, 1679–1686. [[CrossRef](#)] [[PubMed](#)]
103. Chen, Y.; Liu, W.; Sun, T.; Huang, Y.; Wang, Y.; Deb, D.K.; Yoon, D.; Kong, J.; Thadhani, R.; Li, Y.C. 1,25-Dihydroxyvitamin D promotes negative feedback regulation of TLR signaling via targeting microRNA-155-SOCS1 in macrophages. *J. Immunol.* **2013**, *190*, 3687–3695. [[CrossRef](#)] [[PubMed](#)]
104. Zhang, Y.G.; Wu, S.; Lu, R.; Zhou, D.; Zhou, J.; Carmeliet, G.; Petrof, E.; Claud, E.C.; Sun, J. Tight junction *CLDN2* gene is a direct target of the vitamin D receptor. *Sci. Rep.* **2015**, *5*, 10642. [[CrossRef](#)] [[PubMed](#)]
105. Vernia, F.; Valvano, M.; Longo, S.; Cesaro, N.; Viscido, A.; Latella, G. Vitamin D in Inflammatory Bowel Diseases. Mechanisms of Action and Therapeutic Implications. *Nutrients* **2022**, *14*, 269. [[CrossRef](#)] [[PubMed](#)]
106. Lagishetty, V.; Misharin, A.V.; Liu, N.Q.; Lisse, T.S.; Chun, R.F.; Ouyang, Y.; McLachlan, S.M.; Adams, J.S.; Hewison, M. Vitamin D deficiency in mice impairs colonic antibacterial activity and predisposes to colitis. *Endocrinology* **2010**, *151*, 2423–2432. [[CrossRef](#)] [[PubMed](#)]
107. Gubatan, J.; Chou, N.D.; Nielsen, O.H.; Moss, A.C. Systematic review with meta-analysis: Association of vitamin D status with clinical outcomes in adult patients with inflammatory bowel disease. *Aliment. Pharmacol. Ther.* **2019**, *50*, 1146–1158. [[CrossRef](#)] [[PubMed](#)]
108. Ross, A.C.; Manson, J.E.; Abrams, S.A.; Aloia, J.F.; Brannon, P.M.; Clinton, S.K.; Durazo-Arvizu, R.A.; Gallagher, J.C.; Gallo, R.L.; Jones, G.; et al. The 2011 report on dietary reference intakes for calcium and vitamin D from the Institute of Medicine: What clinicians need to know. *J. Clin. Endocrinol. Metab.* **2011**, *96*, 53–58. [[CrossRef](#)] [[PubMed](#)]



109. Fletcher, J.; Cooper, S.C.; Ghosh, S.; Hewison, M. The Role of Vitamin D in Inflammatory Bowel Disease: Mechanism to Management. *Nutrients* **2019**, *11*, 1019. [[CrossRef](#)]
110. Sohoul, M.H.; Farahmand, F.; Alimadadi, H.; Rahmani, P.; Motamed, F.; da Silva Magalhaes, E.I.; Rohani, P. Vitamin D therapy in pediatric patients with inflammatory bowel disease: A systematic review and meta-analysis. *World J. Pediatr.* **2023**, *19*, 48–57. [[CrossRef](#)]
111. Garg, M.; Hendy, P.; Ding, J.N.; Shaw, S.; Hold, G.; Hart, A. The Effect of Vitamin D on Intestinal Inflammation and Faecal Microbiota in Patients with Ulcerative Colitis. *J. Crohns Colitis* **2018**, *12*, 963–972. [[CrossRef](#)]
112. Ford, A.C.; Sperber, A.D.; Corsetti, M.; Camilleri, M. Irritable bowel syndrome. *Lancet* **2020**, *396*, 1675–1688. [[CrossRef](#)] [[PubMed](#)]
113. Mearin, F.; Lacy, B.E.; Chang, L.; Chey, W.D.; Lembo, A.J.; Simren, M.; Spiller, R. Bowel Disorders. *Gastroenterology* **2016**, *150*, 1393–1407. [[CrossRef](#)]
114. Hu, Z.; Li, M.; Yao, L.; Wang, Y.; Wang, E.; Yuan, J.; Wang, F.; Yang, K.; Bian, Z.; Zhong, L.L.D. The level and prevalence of depression and anxiety among patients with different subtypes of irritable bowel syndrome: A network meta-analysis. *BMC Gastroenterol.* **2021**, *21*, 23. [[CrossRef](#)] [[PubMed](#)]
115. Zamani, M.; Alizadeh-Tabari, S.; Zamani, V. Systematic review with meta-analysis: The prevalence of anxiety and depression in patients with irritable bowel syndrome. *Aliment. Pharmacol. Ther.* **2019**, *50*, 132–143. [[CrossRef](#)]
116. Mach, T. The brain-gut axis in irritable bowel syndrome—Clinical aspects. *Med. Sci. Monit.* **2004**, *10*, RA125–RA131. [[PubMed](#)]
117. Collins, S.M.; Denou, E.; Verdu, E.F.; Bercik, P. The putative role of the intestinal microbiota in the irritable bowel syndrome. *Dig. Liver Dis.* **2009**, *41*, 850–853. [[CrossRef](#)] [[PubMed](#)]
118. O'Malley, D.; Quigley, E.M.; Dinan, T.G.; Cryan, J.F. Do interactions between stress and immune responses lead to symptom exacerbations in irritable bowel syndrome? *Brain Behav. Immun.* **2011**, *25*, 1333–1341. [[CrossRef](#)] [[PubMed](#)]
119. Khayyat, Y.; Attar, S. Vitamin D Deficiency in Patients with Irritable Bowel Syndrome: Does it Exist? *Oman Med. J.* **2015**, *30*, 115–118. [[CrossRef](#)] [[PubMed](#)]
120. Williams, C.E.; Williams, E.A.; Corfe, B.M. Vitamin D status in irritable bowel syndrome and the impact of supplementation on symptoms: What do we know and what do we need to know? *Eur. J. Clin. Nutr.* **2018**, *72*, 1358–1363. [[CrossRef](#)]
121. Khalighi Sikaroudi, M.; Mokhtare, M.; Janani, L.; Faghihi Kashani, A.H.; Masoodi, M.; Agah, S.; Abbaspour, N.; Dehnad, A.; Shidfar, F. Vitamin D3 Supplementation in Diarrhea-Predominant Irritable Bowel Syndrome Patients: The Effects on Symptoms Improvement, Serum Corticotropin-Releasing Hormone, and Interleukin-6—A Randomized Clinical Trial. *Complement. Med. Res.* **2020**, *27*, 302–309. [[CrossRef](#)]
122. Pickup, J.C. Inflammation and activated innate immunity in the pathogenesis of type 2 diabetes. *Diabetes Care* **2004**, *27*, 813–823. [[CrossRef](#)] [[PubMed](#)]
123. Scheller, J.; Chalaris, A.; Schmidt-Arras, D.; Rose-John, S. The pro- and anti-inflammatory properties of the cytokine interleukin-6. *Biochim. Biophys. Acta* **2011**, *1813*, 878–888. [[CrossRef](#)]
124. Williams, C.E.; Williams, E.A.; Corfe, B.M. Vitamin D supplementation in people with IBS has no effect on symptom severity and quality of life: Results of a randomised controlled trial. *Eur. J. Nutr.* **2022**, *61*, 299–308. [[CrossRef](#)] [[PubMed](#)]
125. Kang, J.Y.; Kang, A.H.; Green, A.; Gwee, K.A.; Ho, K.Y. Systematic review: Worldwide variation in the frequency of coeliac disease and changes over time. *Aliment. Pharmacol. Ther.* **2013**, *38*, 226–245. [[CrossRef](#)] [[PubMed](#)]
126. Lindfors, K.; Ciacci, C.; Kurppa, K.; Lundin, K.E.A.; Makharia, G.K.; Mearin, M.L.; Murray, J.A.; Verdu, E.F.; Kaukinen, K. Coeliac disease. *Nat. Rev. Dis. Primers* **2019**, *5*, 3. [[CrossRef](#)]
127. Catassi, C.; Verdu, E.F.; Bai, J.C.; Lionetti, E. Coeliac disease. *Lancet* **2022**, *399*, 2413–2426. [[CrossRef](#)] [[PubMed](#)]
128. Green, P.H.; Lebowitz, B.; Greywoode, R. Celiac disease. *J. Allergy Clin. Immunol.* **2015**, *135*, 1099–1106, quiz 1107. [[CrossRef](#)] [[PubMed](#)]
129. Marsh, M.N. Gluten, major histocompatibility complex, and the small intestine. A molecular and immunobiologic approach to the spectrum of gluten sensitivity ('celiac sprue'). *Gastroenterology* **1992**, *102*, 330–354. [[CrossRef](#)] [[PubMed](#)]
130. Lohi, S.; Mustalahti, K.; Kaukinen, K.; Laurila, K.; Collin, P.; Rissanen, H.; Lohi, O.; Bravi, E.; Gasparin, M.; Reunanen, A.; et al. Increasing prevalence of coeliac disease over time. *Aliment. Pharmacol. Ther.* **2007**, *26*, 1217–1225. [[CrossRef](#)]
131. King, J.A.; Jeong, J.; Underwood, F.E.; Quan, J.; Panaccione, N.; Windsor, J.W.; Coward, S.; deBruyn, J.; Ronksley, P.E.; Shaheen, A.A.; et al. Incidence of Celiac Disease Is Increasing over Time: A Systematic Review and Meta-analysis. *Am. J. Gastroenterol.* **2020**, *115*, 507–525. [[CrossRef](#)]
132. Gorini, F.; Tonacci, A. Vitamin D: An Essential Nutrient in the Dual Relationship between Autoimmune Thyroid Diseases and Celiac Disease—A Comprehensive Review. *Nutrients* **2024**, *16*, 1762. [[CrossRef](#)]
133. Vazquez-Polo, M.; Churrua, I.; Perez-Junkera, G.; Larretxi, I.; Lasa, A.; Esparta, J.; Cantero-Ruiz de Eguino, L.; Navarro, V. Study Protocol for a Controlled Trial of Nutrition Education Intervention about Celiac Disease in Primary School: ZELIAKIDE Project. *Nutrients* **2024**, *16*, 338. [[CrossRef](#)] [[PubMed](#)]
134. Murray, J.A.; Wassaf, D.; Dunn, K.; Arora, S.; Winkle, P.; Stacey, H.; Cooper, S.; Goldstein, K.E.; Manchanda, R.; Kontos, S.; et al. Safety and tolerability of KAN-101, a liver-targeted immune tolerance therapy, in patients with coeliac disease (ACeD): A phase 1 trial. *Lancet Gastroenterol. Hepatol.* **2023**, *8*, 735–747. [[CrossRef](#)] [[PubMed](#)]

135. Tye-Din, J.A.; Daveson, A.J.M.; Goel, G.; Goldstein, K.E.; Hand, H.L.; Neff, K.M.; Popp, A.; Taavela, J.; Maki, M.; Isola, J.; et al. Efficacy and safety of gluten peptide-based antigen-specific immunotherapy (Nexvax2) in adults with coeliac disease after bolus exposure to gluten (RESET CeD): An interim analysis of a terminated randomised, double-blind, placebo-controlled phase 2 study. *Lancet Gastroenterol. Hepatol.* **2023**, *8*, 446–457. [[CrossRef](#)]
136. Crespo Perez, L.; Castillejo de Villasante, G.; Cano Ruiz, A.; Leon, F. Non-dietary therapeutic clinical trials in coeliac disease. *Eur. J. Intern. Med.* **2012**, *23*, 9–14. [[CrossRef](#)] [[PubMed](#)]
137. Tanpowpong, P.; Obuch, J.C.; Jiang, H.; McCarty, C.E.; Katz, A.J.; Leffler, D.A.; Kelly, C.P.; Weir, D.C.; Leichtner, A.M.; Camargo, C.A., Jr. Multicenter study on season of birth and celiac disease: Evidence for a new theoretical model of pathogenesis. *J. Pediatr.* **2013**, *162*, 501–504. [[CrossRef](#)] [[PubMed](#)]
138. Capriati, T.; Francavilla, R.; Castellaneta, S.; Ferretti, F.; Diamanti, A. Impact of the birth's season on the development of celiac disease in Italy. *Eur. J. Pediatr.* **2015**, *174*, 1657–1663. [[CrossRef](#)] [[PubMed](#)]
139. Constantin, C.; Huber, W.D.; Granditsch, G.; Weghofer, M.; Valenta, R. Different profiles of wheat antigens are recognised by patients suffering from coeliac disease and IgE-mediated food allergy. *Int. Arch. Allergy Immunol.* **2005**, *138*, 257–266. [[CrossRef](#)] [[PubMed](#)]
140. Green, P.H.; Cellier, C. Celiac disease. *N. Engl. J. Med.* **2007**, *357*, 1731–1743. [[CrossRef](#)]
141. Barera, G.; Maruca, K.; Sgaramella, P.; Di Stefano, M.; Mora, S. Short-term, low dose vitamin D supplementation in young patients with celiac disease: A pilot study. *Eur. J. Gastroenterol. Hepatol.* **2020**, *32*, 663–664. [[CrossRef](#)]
142. Blazina, S.; Bratanic, N.; Campa, A.S.; Blagus, R.; Orel, R. Bone mineral density and importance of strict gluten-free diet in children and adolescents with celiac disease. *Bone* **2010**, *47*, 598–603. [[CrossRef](#)] [[PubMed](#)]

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