

## CLINICAL REVIEW

# An Evidence-Based Review of Vitamin D for Common and High-Mortality Conditions

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**Background:** Vitamin D is a fat-soluble vitamin available from food and sun exposure. Vitamin D receptors are present in cells throughout the body and cause it to act like a hormone. Observational studies document the association of low vitamin D levels with multiple health conditions. This article reviews the evidence for vitamin D in prevention and treatment in primary care.

**Methods:** We performed a literature review of randomized controlled trials, meta-analyses, systematic reviews, and large prospective trials looking at the role of vitamin D deficiency in the most common conditions seen in primary care and the top 10 causes of mortality since 2010.

**Results:** Vitamin D supplementation in patients with known cardiovascular disease does not reduce risk of stroke or heart attack. Vitamin D supplementation does not seem to have an effect in the treatment of hypertension or in cancer prevention. There is emerging evidence that supplementation reduces COVID-19 severity and risk of mechanical ventilation. Vitamin D at more moderate levels may reduce the risk of falls, but higher doses may cause increased fall risk. There does not seem to be a link between vitamin D supplementation and improved cognition. Vitamin D supplementation may be helpful in patients with major depression. High dose vitamin D may improve pain in people with fibromyalgia. Supplementing patients with prediabetes reduced the risk of progression to type 2 diabetes mellitus. Vitamin D supplementation in addition to standard emollient treatment helped to reduce symptoms in people with atopic dermatitis.

**Conclusion:** Prospective studies of vitamin D supplementation demonstrate variable impact on disease specific and patient-oriented outcomes, suggesting a correlation but not a causal relationship between low vitamin D levels and disease pathogenicity. Future research should determine dosing standards and timing of vitamin D in treatment and prevention. (J Am Board Fam Med 2022;00:000–000.)

**Keywords:** Atopic Dermatitis, Cardiovascular Diseases, Child Health, Chronic Pain, COVID-19, Dementia, Depression, Dietary Supplements, Family Medicine, Geriatrics, Hypertension, Meta-Analysis, Obstetrics, Prenatal Care, Primary Health Care, Type 2 Diabetes, Vitamin D

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## Introduction

Vitamin D is a fat-soluble vitamin with receptors on cells throughout the body that is available from

food as well as from sun exposure. Although a vitamin, it can act as a hormone with metabolic activity on a variety of organ systems.<sup>1,2</sup> It is important for its role in bone development and growth and possesses anti-inflammatory, antioxidant, and neuro-protective properties.<sup>1</sup> An estimated 50 to 70% of patients in the United States do not consume the recommended daily value of vitamin D,<sup>3</sup> and about 6% of the US population is vitamin D deficient with serum 25(OH)D concentrations less than 30 nmol/L as defined by National Academies of Sciences, Engineering, and Medicine.<sup>4–6</sup> Research has documented the association of hypovitaminosis D with myriad health conditions and has evaluated whether vitamin D supplementation improves these

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conditions.<sup>7</sup> This article summarizes evidence since 2010, the last time a vitamin D review article was published in this journal and focuses on frequently encountered diseases in Family Medicine. Combining a list of common conditions in Primary Care and a list of leading causes of death, we focused this article on 12 disease processes and their relationship to vitamin D.<sup>8,9</sup> In 2016, the US Food and Drug Administration (FDA) released a significant regulatory update pertaining to vitamin D when it changed the units of vitamin D from international unit (IU) to microgram (mcg; see Table 1).<sup>10</sup> This article will use micrograms when referring broadly, but may still report IUs if such units are used in referenced studies.

## Methods

A PubMed search was completed in Clinical Queries using the key terms “vitamin D” and “mortality” “cardiovascular disease” “hypertension” “resistant hypertension” “cancer” “COVID-19” “falls” “chronic pain” “depression” “anxiety” “dementia” “cognition” “diabetes mellitus” “dermatitis” “pregnancy” “lactation” and “prevention.” We also searched Cochrane Library, Trip Database, Essential Evidence Plus, Clinical Evidence, Google Scholar, the Agency for Health care Research and Quality evidence reports, and the National Guideline Clearinghouse database. Our literature review placed emphasis on meta-analyses, systematic reviews, randomized controlled trials (RCTs), and large observational trials published since 2010. Search dates: 01/25/2022, 06/03/2022

### Vitamin D and Mortality

A large randomized controlled trial in Australia compared vitamin D3 supplementation (60,000 IU monthly) to placebo in over 21,000 community dwelling, healthy adults over 60 years old. The

participants were observed for 5 years, and vitamin D supplementation did not reduce all-cause mortality.<sup>11</sup> A large systematic review and meta-analysis of 50 studies with over 74,000 participants did not find that vitamin D supplementation affected all-cause mortality in adults.<sup>12</sup> However, subgroup analysis demonstrated decreased mortality in people who received vitamin D3 supplements as compared with vitamin D2.<sup>12</sup>

Observational studies have demonstrated an association between vitamin D deficiency and poor outcomes in critically ill patients.<sup>13</sup> However, whether vitamin D supplementation affects mortality in critically ill patients is less clear.<sup>14</sup> A 2021 systematic review and meta-analysis included 14 studies (2324 patients in total) and did not find an effect of vitamin D supplementation on mortality in critically ill patients.<sup>15</sup>

### Vitamin D and Cardiovascular Disease

Low vitamin D levels are associated with an increased risk of myocardial infarction, stroke and overall cardiovascular disease (CVD) related mortality. A 2012 meta-analysis of 19 prospective studies with 6123 CVD cases in 65,944 participants found a linear and inverse association between vitamin D levels and CVD risk.<sup>16</sup> Observational studies have also consistently linked low vitamin D levels and hypertension. A meta-analysis of 11 prospective studies that included 2,83537 individuals concluded that for every 10 ng/mL incremental increase of circulating 25(OH)D, the future risk of hypertension is lowered by 12%.<sup>17</sup>

Due to the strong association between vitamin D deficiency and risk of cardiovascular disease and hypertension, multiple trials have examined whether supplementation impacts cardiovascular morbidity and mortality. A 2019 RCT looked at the effect of vitamin D supplementation on cardiovascular disease prevention, randomizing 25,871 participants (men over age 50 and women over age 55) to 2000 IU daily of vitamin D3 and 1 g of omega-3 fatty acids vs placebo.<sup>18</sup> After a median of 5.3-year follow-up, there was no difference in the incidence of major adverse cardiovascular events (MACE) between the 2 groups (396 events in the supplemented group vs 409 events in the placebo group; 95% CI, of 0.85 to 1.12).<sup>18</sup> There was also no difference in the secondary end points of myocardial infarction, stroke, or death from cardiovascular causes. A 2019 meta-analysis included 41,669 participants who received vitamin D supplementation

**Table 1. The United States Food and Drug Administration (FDA) Updated Units for Dosing Equivalentents of Vitamin D**

Old Units (International Units [IU])	New Units (Micrograms [mcg])
400 IU	10 mcg
800 IU	20 mcg
1000 IU	25 mcg
2000 IU	50 mcg
5000 IU	125 mcg
50,000 IU	1250 mcg

and 41,622 who received placebo and found that vitamin D supplementation was not associated with reduced MACE when compared with placebo (RR 1.00 with 95% CI, 0.95–1.06).<sup>19</sup> These findings were consistent by age, sex, baseline vitamin D level and the presence or absence of concurrent calcium administration.

A double-blind, randomized trial enrolled 534 individuals between age 18 to 50 with vitamin D less than 25 ng/mL and systolic blood pressure of 120 to 150 mmHg.<sup>20</sup> Participants were randomized to high dose (4000 IU/d) and low dose (400 IU/d) and measured 24-hour systolic blood pressure at baseline and 2-month intervals for 6 months. At the end of the study, there was no change in 24-hour systolic pressure measurement ( $P=.71$ ) between the 2 groups despite patients in the high dose arm having improved serum vitamin D levels at 2-month follow-up.<sup>20</sup> This data are further consistent with a 2020 meta-analysis of 11 cohort studies and 27 randomized controlled trials that did not show any effect of vitamin D supplementation on diastolic or systolic pressure despite.<sup>21</sup> Observational studies highlight the risk of treatment resistant hypertension in patients with low vitamin D levels.<sup>22</sup> A double-blind, placebo-controlled randomized control trial of 64 patients with persistent blood pressure  $\geq 140/90$  and on 3 blood pressure medications were randomized into 2 groups of 32 who received either 100,000 IU vitamin D every 2 months or placebo. There was no change in ambulatory or office blood pressure readings at 2, 4 and 6 months.<sup>23</sup>

### **Vitamin D and Cancer**

Observational studies have demonstrated an association between cancer risk and vitamin D deficiency. A 2015 review combined a case control study with 14 observational studies and found an inverse relationship between circulating vitamin D levels and risk of colorectal cancer (odds ratio [OR], 0.68; 95% CI, 0.54–0.82).<sup>24</sup> A 2019 study pooled data from 17 cohort studies including 5706 participants with colorectal cancer and 7107 control participants and found that for every 10 ng/mL increase in circulating 25-hydroxyvitamin D levels, colorectal cancer risk was 19% lower in women (95% CI, 0.75–0.87) and 7% lower in men (95% CI, 0.86–1.00).<sup>25</sup> A 2019 systematic review of 8 observational studies included 2916 cases of colorectal cancer and 6678 controls and found that higher levels of vitamin D were associated

with decreased risk of colorectal cancer in Asian countries (95% CI, 0.64–0.97).<sup>26</sup>

However, randomized prospective trials have not demonstrated an association between vitamin D supplementation or levels and cancer incidence. A Cochrane review published in 2014 looked at 18 randomized trials with 50,623 participants and found no benefit to vitamin D supplementation to prevent cancer (95% CI, 0.94–1.06).<sup>27</sup> This review also noted that of the 18 trials, many “had a high risk of bias, mainly for-profit bias” and that all the trials came from high-income countries. A 2019 study of healthy and cancer-free men  $\geq 50$  and women  $\geq 55$  years old randomized 25,871 people to supplementation with 2000 IU of vitamin D and 1 g of omega-3 fatty acid or placebo. After a median follow-up of 5.3 years, there was no difference in the rates of invasive cancer in the supplementation vs placebo groups (95% CI, 0.87–1.12).<sup>18</sup> In addition, there was no statistical significance with subgroup analyses that looked at specific types of cancer (breast, prostate and colorectal) between the 2 groups or cancer mortality. Another RCT randomized 2496 participants to 3 different study arms (placebo, 1600 IU daily, 3200 IU daily). After 5 years, vitamin D supplementation did not lower the rates of invasive cancer in the 1600 IU (95% CI, 0.75–1.72) or 3200 IU groups (95% CI, 0.61–1.47).<sup>28</sup>

A 2017 randomized trial attempted to determine if circulating concentrations of vitamin D are causally associated with risk of 7 different cancer types using a Mendelian randomization design.<sup>29</sup> Over 70,500 cancer cases (among them 22,898 prostate, 15,748 breast, 12,537 lung, 11,488 colorectal, 4369 ovarian, 1896 pancreatic and 1627 neuroblastoma cancers) were compared with 84,418 controls. Increasing levels of 25-hydroxyvitamin D concentrations were not associated with risk reduction of any of the 7 cancers studied.

While observational evidence suggests a link between vitamin D deficiency and risk of malignancy, especially in the case of colorectal cancer, randomized, prospective trials do not support vitamin D supplementation to reduce overall cancer risk and thus as a strategy for cancer prevention.

### **Vitamin D and COVID-19**

Vitamin D is an important modulator of inflammatory and immune responses. Respiratory macrophages and epithelial cells display vitamin D receptors, and variations in vitamin D receptors may contribute to

susceptibility to respiratory infections.<sup>30,31</sup> Vitamin D deficiency is associated with increased risk of COVID-19 infection.<sup>32–34</sup> A 2021 meta-analysis including data from 612,601 patients demonstrated that among patients with vitamin D deficiency, the risk of COVID-19 infection was higher than in vitamin D replete individuals, with an odds ratio of 1.26 (95% CI, 1.19–1.34;  $P \leq .01$ ).<sup>32</sup> This finding was confirmed by subsequent meta-analyses.<sup>33,34</sup> Chiodini and colleagues showed that severe deficiency, deficiency and insufficiency of vitamin D were all associated with COVID-19 related hospitalization, ICU admission, and mortality,<sup>35</sup> where Bassatne et al found similar trends that did not reach statistical significance.<sup>33</sup> Preliminary evidence from a single RCT of frontline health care workers randomized to vitamin D supplementation ( $n = 94$ ) vs placebo ( $n = 98$ ) suggests supplementing vitamin D could prevent COVID-19 infection.<sup>36</sup> These results are consistent with a large meta-analysis of 25 RCTs including 11,321 participants demonstrating that vitamin D supplementation is associated with a small reduction in risk of acute URI.<sup>37</sup> A Cochrane review did not find evidence that vitamin D supplementation in all patients with COVID-19 affected outcomes.<sup>38</sup> A more recent meta-analysis showed decreased COVID-19 severity, as assessed by pooled relative risk of mechanical ventilation, ICU requirement and symptoms severity, with oral vitamin D supplementation. Vitamin D preparation, dosage and duration of therapy varied considerably between studies.<sup>39</sup> Shah and colleagues demonstrated a lower relative risk of ICU admission with vitamin D supplementation using oral vitamin D, though formulation, dosing and duration of therapy again varied considerably between studies.<sup>40</sup> Vitamin D supplementation has not been shown to be associated with decreased COVID-19 mortality.<sup>38–40</sup>

### ***Vitamin D and Unintentional Injuries/Falls***

Falls are a source of considerable morbidity and mortality in the elderly population and evidence continues to grow demonstrating a reduced risk of falls with vitamin D supplementation. One proposed mechanism relates to improved muscle function from vitamin D supplementation within the normal range, vitamin D excess can also impair muscle function.

Several meta-analyses have evaluated the effect of vitamin D on falls finding that only in combination

with calcium is there evidence to support a reduction in fall risk.<sup>41,42</sup> A meta-analysis in 2021 reviewed 31 studies (57,867 participants), 21 of which involved vitamin D alone (51,984 participants) and 10 of which included vitamin D plus calcium (5883 participants).<sup>43</sup> Vitamin D alone (with wide dose range from daily doses of 400 IU or higher to intermittent doses up to 60,000 IU) was not associated with a reduced fall risk in all participants, however the subgroup of patients with a baseline 25(OH)D level below 20 ng/mL (50 nmol/L) did show a 23% reduction in fall risk. In the groups with vitamin D plus calcium there was a 12% reduction in falls.<sup>43</sup>

More recent studies have evaluated intermittent high doses of vitamin D ranging from 90,000 to 600,000 IU from every 3 months to once annually. While these extremely high doses present opportunities to improve treatment adherence, data suggests that they might increase fall risk. A randomized controlled trial in 2010 found that the risk of falling with high annual dosages was increased 15% and found that serum 25(OH)D levels were at or above 45 ng/mL during the increased fall period after bolus dosing.<sup>44</sup> A subsequent RCT showed a trend of increasing falls risk with higher doses of vitamin D.<sup>45</sup>

An RCT compared different doses of vitamin D in 273 postmenopausal women and found a dose response effect with the lowest fall risk occurring at doses between 1600 to 3200 IU daily.<sup>46</sup> Doses of 4000 IU per day and higher were associated with an increase in the fall risk as was a post treatment 25 (OH)D level of 41 ng/mL or higher. The reduction in fall risk was most prominent in those with a history of falls.<sup>46</sup>

### ***Vitamin D and Dementia***

Data links low vitamin D levels with poor cognition and increased risk of dementia.<sup>47–49</sup> A 2017 meta-analysis evaluating 26 observational studies ( $n = 20,750$ ) and 3 intervention studies ( $n = 314$ ) found that there was a strong correlation between low vitamin D status and cognitive impairment due to dementia.<sup>49</sup> However, there was no demonstrated benefit of improved cognition with vitamin D supplementation.<sup>49</sup> A limitation of many studies included a short study interval.<sup>50</sup> While the effects of vitamin D supplementation on dementia are still uncertain, an international expert review committee recommends correcting known hypovitaminosis D



in individuals with cognitive impairment and dementia.<sup>51,52</sup>

### ***Vitamin D and Depression and Anxiety***

Due to neuromuscular mechanisms of vitamin D and its theorized effects on behavior, research has explored the role of vitamin D in mental health disorders.<sup>53</sup> Low vitamin D levels are a risk factor for development of depression and anxiety,<sup>54</sup> and observational studies demonstrate that vitamin D deficiency is associated with depressive symptoms.<sup>55</sup>

Evidence does not support the use of vitamin D supplementation for prevention of depression in adults  $\geq 50$  years old.<sup>56</sup> There is no role for vitamin D supplementation for universal prevention nor does supplementation reduce the risk for depression or anxiety.<sup>56,57</sup> However, there is limited evidence to support vitamin D supplementation to treat depressive and anxious symptoms when present.<sup>57,58</sup> Subgroup analysis of a meta-analysis of 7 RCTs representing 3,191 patients demonstrated that vitamin D use is most effective when used for patients who have a formal major depressive disorder diagnosis (95% CI,  $-1.19$  to  $-0.01$ ;  $P = 0.046$ ).<sup>58</sup> In this population, 2 studies observed a moderate reduction in depressive symptoms.<sup>58</sup> These studies were limited by significant heterogeneity with type, dosage, frequency, and duration varying across studies.

### ***Vitamin D and Chronic Pain***

A 2018 systematic review and meta-analysis of 81 observational studies including 50,834 participants demonstrated an increased risk of vitamin D deficiency in participants with arthritis, muscle pain, and chronic widespread pain, as compared with the general population. However, there was considerable heterogeneity of the evidence, with some authors finding no difference in prevalence of vitamin D deficiency in people with and without chronic pain.<sup>59,60</sup>

Vitamin D modulates neurotransmitter function, inhibits prostaglandin synthesis, and promotes down regulation of proinflammatory T cells, leading some authors to suggest that vitamin D deficiency promotes a chronic pain state.<sup>61</sup> However, UVB exposure, which facilitates synthesis of vitamin D, also promotes the production of endogenous opioids. Therefore, adequate vitamin D stores may only point to UVB exposure, with this exposure being the actual therapeutic agent.<sup>61</sup>

A 2015 Cochrane review of 10 studies ( $n = 811$  participants) that did not select for baseline vitamin D deficiency, did not demonstrate that vitamin D supplementation was better than placebo in any chronic painful condition.<sup>62</sup> However, a 2017 article summarized the efficacy of vitamin D for chronic pain management and concluded that in patients with 25(OH)D levels  $\leq 30$  nmol/l, there is evidence of benefit with supplementation, while in patients with adequate vitamin D stores ( $\geq 50$  nmol/l), there is no clear evidence of benefit.<sup>61</sup> In addition, in a 2016 RCT ( $n = 58$ ), patients with chronic nonspecific widespread musculoskeletal pain and vitamin D deficiency at baseline demonstrated statistically significant improvements in serum vitamin D levels, pain scores, tender point counts, and depression symptoms with oral vitamin D supplementation at a dose of 50,000 IU once weekly over the 3-month study period.<sup>63</sup> Other studies of participants with fibromyalgia and vitamin D deficiency have yielded similar results.<sup>64</sup> In patients with vitamin D deficiency and fibromyalgia, high vitamin D3 doses of 50,000 international units weekly may improve pain.<sup>62,64</sup>

### ***Vitamin D and Diabetes***

Type 2 diabetes mellitus (T2DM) is an increasingly common chronic disease and confers significant morbidity and mortality.<sup>65,66</sup> Vitamin D has been linked to diabetes through a number of possible mechanisms beyond its role in calcium homeostasis including modulating inflammation and reducing  $\beta$  cell death.<sup>67</sup> BMI is an independent predictor of the risk for development of T2DM<sup>68</sup> and a meta-analysis of 45 studies (26,325 patients) found an association between low vitamin D levels and higher BMI in nondiabetic patients.<sup>69</sup>

To understand the causal association between vitamin D and diabetes a number of studies have evaluated the impact of supplementing vitamin D in patients with prediabetes. A meta-analysis of 9 randomized controlled trials representing 43,559 patients found that in subgroup analysis, patients with prediabetes who received high dose ( $\geq 1000$  IU/day) of vitamin D had a lower risk of developing T2DM (RR 0.88, 0.79 to 0.99).<sup>70</sup> The Diabetes Prevention with Active Vitamin D (DPVD) study evaluated 1256 patients with prediabetes randomized to receive vitamin D or placebo and found no significant reduction in development of T2DM over 3 years.<sup>71</sup> Studies

have also evaluated the role of vitamin D in glycemic control for patients with diagnosed T2DM. A meta-analysis of 19 studies with 1374 patients found that vitamin D supplementation had mixed results on glycemic control with no change in fasting blood glucose or hemoglobin A1c (HbA1c)<sup>72</sup> In addition a measure of insulin resistance (HOMA-IR) was significantly decreased in all 11 studies (95% CI, -0.97 to -0.53;  $P < .001$ ) as was the fasting insulin level (95% CI, -0.78 to -0.35;  $P < .001$ ).<sup>72</sup> These results are of limited utility due to variation in vitamin D dosages used in the included studies (1200 IU daily to 300,000 IU once).<sup>72</sup>

### **Vitamin D and Dermatitis**

Atopic dermatitis (AD) is an allergic condition causing chronic inflammation of the skin. Vitamin D is thought to have effects on skin barrier function as well as immune system function.<sup>73,74</sup> Atopic dermatitis seems to be correlated with low vitamin D;<sup>73,75-77</sup> however, the causation of this relationship is disputed between 2 leading theories: (1) low sun exposure leads to decreased vitamin D production which impacts AD-related cytokine activity,<sup>78</sup> (2) the chronic inflammation caused by AD produces a low vitamin D state.<sup>79</sup>

A systematic review of vitamin D supplementation for primary prevention<sup>74</sup> of atopic dermatitis found little evidence that antepartum or infant supplementation prevented development of atopic dermatitis.<sup>80</sup>

Three meta-analyses have demonstrated decreased severity and improved symptoms of pediatric and adult AD with vitamin D supplementation ranging from 25 mcg to 50 mcg daily (weighted average of 40 mcg), however the included studies were limited by small sample sizes.<sup>75,76,81</sup> The 2019 meta-analysis, which included 5 studies (n = 180), demonstrated the most significant clinical impact.<sup>75</sup> A 2022 RCT (n = 70) similarly observed beneficial effects of vitamin D supplementation specifically in pediatric participants with Fitzpatrick skin types 3 to 5.<sup>82</sup> Vitamin D supplementation in AD improves symptoms and clinical signs of AD when used as an adjuvant to standard treatment.<sup>75,76,81-83</sup>

### **Vitamin D and Pregnancy**

Low vitamin D status is common in pregnant patients worldwide.<sup>84,85</sup> Recommendations for vitamin D are no different from a nonpregnant individual, 15 mcg per day. Research documents an association between low vitamin D levels in

pregnant patients and higher incidence of complications including recurrent pregnancy loss<sup>86-88</sup>, pre-eclampsia<sup>89,90</sup>, gestational diabetes<sup>91</sup>, preterm labor<sup>92-95</sup>, low birth weight<sup>95,96</sup>, and fetal tooth defects.<sup>97</sup> A 2022 meta-analysis studied 11,082 participants who were supplemented with vitamin D during their pregnancy in doses ranging from 800 IU daily to 50,000 IU weekly.<sup>98</sup> Supplementation was associated with a significantly reduced risk of fetal death RR 0.690 (95% CI, 0.482-0.985;  $P = .04$ ).<sup>98</sup> Low birth weight, small for gestational age, and preterm birth were not significantly associated with the intervention of vitamin D supplementation.<sup>98</sup> The mechanism behind vitamin D's effects are theorized to be regulation of immunomodulation at the maternal-fetal interface, lung development, and genomic effects imparted by vitamin D.<sup>98,99</sup> The American College of Obstetricians and Gynecologists recommends consideration of checking vitamin D levels in at-risk individuals (Table 2) and supplementing those patients who are deficient (<20 ng/mL) with 25 to 50 mcg daily.<sup>100</sup>

### **Vitamin D Supplementation for the Lactating Parent and Human Milk-Fed Infant**

Breast milk is optimal nutrition for infants, as it also provides immune protection, immune modulation, growth factors, and metabolic programming.<sup>101-103</sup> All major US health organizations recommend breastfeeding.<sup>104,105</sup> All infants in the first year of life need at least 10 mcg of vitamin D daily, starting at birth, as recommended by the American Academy of Pediatrics.<sup>106</sup>

The vitamin D status of a newborn is determined by the maternal 25(OH)D status at the time

**Table 2. Risk Factors for Vitamin D Deficiency<sup>100,120</sup>**

Risk Factor	Cause
Inadequate sunlight exposure	Residing in cold climates
	Residing in northern latitudes
	Wearing sun protective clothing
	Wearing winter protective clothing
Inadequate dietary intake	Vegetarian diet
	Vegan diet
Malabsorption syndromes	Crohn's disease
	Celiac disease
Ethnic minorities, particularly those with darker skin pigmentation, have higher incidence of vitamin D deficiency.	

**Table 3. The U.S. Preventive Services Task Force (USPSTF) Recommendations**

Screening for vitamin D deficiency <sup>118</sup>	“I” Recommendation: There is insufficient evidence to recommend screening asymptomatic non-pregnant adults in the general population for vitamin D deficiency.	
Vitamin D for the primary prevention of falls <sup>121</sup>	“D” Recommendation: Evidence suggests against the use of vitamin D at any dose for the primary prevention of falls.	
Vitamin D and calcium for primary prevention of fractures <sup>122</sup>	Postmenopausal women for vitamin D doses less than 400 IU or calcium doses less than 1000 mg	“D” Recommendation. Evidence suggests against the use of vitamin D at low doses for fracture prevention in postmenopausal women.
	Postmenopausal women for vitamin D doses greater than 400 IU or calcium doses greater than 1000 mg	“I” Recommendation. There is insufficient evidence to recommend the use of vitamin D at higher doses for fracture prevention in postmenopausal women.
	Men and premenopausal women	“I” Recommendation. There is insufficient evidence to recommend the use of vitamin D at any dose for fracture prevention in men and premenopausal women.

of birth.<sup>107</sup> After birth, the infant is dependent on vitamin D from nutrition, supplementation, and from sun exposure. It is generally recommended to avoid directly exposing infants to sunlight to avoid sunburn. In addition, the amount of vitamin D generated from sun exposure is highly variable depending on latitude, season, skin pigmentation, clothing, and duration of exposure.<sup>106,108</sup>

Commercial infant formulas are fortified with sufficient vitamin D. The vitamin D content of human milk varies greatly, depending on sun exposure and vitamin D supplementation of the lactating parent, and is assumed to be low.<sup>107</sup>

Children who are fed a combination of human milk and less than 32 oz of formula daily require 10 mcg of vitamin D3 unless they are exclusively formula fed. The supplementation may cease at 1 year of age if the child is consuming sufficient dairy products or other foods to provide 10 mcg of vitamin D3.<sup>107</sup>

Because of the concern for compliance with daily dosing of vitamin D to infants, there has been significant interest in both high dose vitamin D supplementation for the lactating parent and intermittent bolus dosing for the infant. High dose supplementation of the lactating parent also has the benefit of ensuring optimal vitamin D status for the parent.

A 2021 meta-analysis of 19 trials, (n = 3337 breastfeeding mothers), evaluated the effect of maternal vitamin D supplementation on the circulating 25(OH)D levels of the lactating mother and infant and found that vitamin D supplementation in the lactating mother is associated with a nonlinear increase in 25(OH)D levels in the lactating mother, and a linear relationship with infants’ serum 25

(OH)D levels.<sup>109</sup> A maternal dose of >150 mcg of vitamin D3 was sufficient to substitute for 10 mcg of vitamin D for the infant. However, they cautioned that more research is needed to confirm this as a policy change. In addition, there is evidence that maternal BMI has an influence on the relationship between maternal vitamin D3 supplementation and maternal 25(OH)D level. Women with higher BMI require higher doses of vitamin D supplementation to achieve adequate levels of vitamin D in breastmilk.<sup>110</sup>

A systematic review of alternatives to daily infant vitamin D supplementation evaluated 9 trials of intermittent bolus dosing of vitamin D3 for the infant. The study found that there was a steady depletion of 25(OH)D level following a bolus dose, indicating that smaller quantities at more frequent intervals may be more effective in maintaining an optimal vitamin D status.<sup>107</sup>

**Table 4. National Institutes of Health (NIH) Vitamin D Recommended Daily Allowance<sup>6</sup>**

Population	Recommended Daily Allowance
Age	
0–12 months	10 mcg (400 IU)
1–13 years	15 mcg (600 IU)
14–70 years	15 mcg (600 IU)
>71 years	20 mcg (800 IU)
Special populations	
Pregnancy	15 mcg (600 IU)
Lactation	15 mcg (600 IU)
Bariatric surgery	75 mcg (3000 IU), titrate to serum level of >30 ng/mL

Abbreviation: IU, International Units.

Vitamin D3 supplements for infants are available in different forms, typically in 1 mL doses and as a single drop dose.

### **Prevention of Vitamin D Deficiency in High-Risk Groups**

According to the National Institutes of Health, there are certain populations at risk for vitamin D deficiency who could benefit from either vitamin D screening or counseling on supplementation.<sup>6</sup> These groups include breastfed infants due to low levels of vitamin D in breastmilk;<sup>106</sup> older adults, due to decreased ability to synthesize vitamin D from sun exposure and increased likelihood of being indoors<sup>111</sup>; people with limited sun exposure, such as individuals who wear full body clothing<sup>112</sup>; people with dark skin, as increased skin melanin reduces vitamin D production from sunlight<sup>4,113</sup>; people with conditions that limit fat absorption, as they may have more difficulty absorbing vitamin D from foods that are fortified, such as dairy products<sup>114</sup>; people who are obese, due to vitamin D

being sequestered in subcutaneous fat<sup>115</sup>; individuals with a history of gastric bypass, as they may have limited ability to absorb vitamin D from the upper small intestine (Table 2).<sup>116</sup>

### **USPSTF Recommendations**

The US Preventive Services Task Force has determined that current evidence is insufficient to assess the balance of benefits and harms of screening for vitamin D deficiency in asymptomatic adults.<sup>117</sup> According to the USPSTF, no professional organization in the United States recommends population screening for vitamin D deficiency (see Table 3).<sup>117,118</sup>

### **Supplementation in Vitamin D Deficiency**

Most people will not be able to obtain adequate vitamin D from food sources alone.<sup>3</sup> In foods and in dietary supplements, vitamin D has 2 main forms: D<sub>2</sub> (ergocalciferol) and D<sub>3</sub> (cholecalciferol). Both forms are well absorbed in the small intestine and raise serum 25(OH)D levels.<sup>6</sup> However, most

**Table 5. Strength of Recommendation Taxonomy (SORT) Table**

Clinical Recommendation	Evidence Rating	Comments
Patients with COVID-19 infection demonstrate reduced morbidity, but not mortality, when supplemented with vitamin D.	B	Meta-analyses showing decreased severity of illness from COVID-19 infection with vitamin D supplementation. <sup>38-40</sup>
Avoid vitamin D doses of 100 mcg (4000 IU) per day or higher as well as intermittent high dose regimens due to increased risk of falls in the elderly.	B	Several randomized controlled trials demonstrate that high dose regimens can increase the risk of falls. <sup>44-46</sup> Based on a single RCT there is suggestion that the optimal dose may be 1600 to 3200IU daily. <sup>46</sup>
In patients with vitamin D deficiency and fibromyalgia, supplement with vitamin D3 doses of 50000 international units weekly to improve pain.	B	Findings are generally consistent however, the included studies are lower quality clinical trials. <sup>63,64</sup>
In patients with dementia, correct known hypovitaminosis D.	C	Based on expert consensus despite a lack of clear evidence of benefit. <sup>51,52</sup>
For patients with symptomatic depression, supplement with vitamin D3 37.5 mcg daily to reduce depressive symptoms.	B	Two RCTs testing different doses of vitamin D in patients with clinically significant depressive symptoms showed consistent findings of improved symptoms. <sup>57,58</sup>
For patients with prediabetes, supplement with vitamin D3 1000 IU per day or greater to reduce progression to T2DM	B	Meta-analysis results showing benefit in higher dose (>1000 IU) subgroup. <sup>70</sup> Conflicting RCT results from recent study may be due to novel vitamin D formulation. <sup>71</sup>
For pediatric and adult patients with persistent atopic dermatitis, consider supplementing with vitamin D3 25 to 50 mcg daily to reduce AD symptoms in addition to standard emollient care.	B	Based on meta-analyses, limited by small sample sizes, showing reductions in AD severity scoring measures with vitamin D supplementation of 25 to 50 mcg daily. <sup>75,76,81,82</sup>
For pregnant patients with known hypovitaminosis D, supplement with vitamin D3 25 to 50mcg per day. Consider supplementing all pregnant patients with vitamin D3 25 to 50mcg per day.	B	Based on a meta-analysis demonstrating decreased fetal mortality and expert consensus despite lack of clear evidence of benefit for other pregnancy conditions. <sup>98,100</sup>
For human milk-fed infants in the first year of life, supplement 10 mcg of vitamin D3 daily to prevent vitamin D deficiency and rickets	C	Based on consensus opinion, not substantiated by most recent Cochrane review. <sup>106,107</sup>

Abbreviation: RCT, randomized controlled trials; IU, International Units.



evidence indicates that vitamin D<sub>3</sub> yields a more robust rise in serum 25(OH)D for a longer duration than vitamin D<sub>2</sub>.<sup>6</sup> Excessive vitamin D supplementation to serum levels >375 nmol/l can cause toxicity, manifesting as marked hypercalcemia and/or hypercalciuria. Vitamin D toxicity can cause renal failure, soft tissue calcification (including vascular calcification), cardiac arrhythmias, and death.<sup>6</sup> The NIH has set recommended daily allowances to reduce the risk of toxicity (Table 4).<sup>6</sup>

Monitoring vitamin D levels uses assays of 25(OH)D, which reflects vitamin D produced endogenously and that obtained from foods and supplements.<sup>6</sup> Currently, 25(OH)D is the main indicator of vitamin D status, as the more active metabolite 1,25(OH)<sub>2</sub>D has a much shorter half-life and levels do not decline until vitamin D deficiency is severe.<sup>6</sup> After initiation of a daily vitamin D supplement, measurement of serum 25(OH)D should not be done earlier than after 8 weeks because this is the minimum time required to reach a steady state.<sup>119</sup>

## Conclusion

Observational studies have consistently demonstrated an inverse correlation of serum vitamin D levels to a risk or severity of a variety of health conditions. Derived from these observational links, the initial therapeutic enthusiasm surrounding vitamin D supplementation and the hope for potential positive impact on disease prevention and treatment was high. However, when the role of supplementation and treatment with vitamin D is more closely scrutinized with higher quality, prospective, randomized controlled trials, the impact on disease specific and patient-oriented outcomes is mixed and unclear. As is shown in Table 5, there is insufficient evidence for routine screening for vitamin D deficiency, but expert opinion recommends correction of identified hypovitaminosis D.

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Sarina Schragger devised the project, the main conceptual ideas, and proof outline. All authors contributed to database searches, to summarizing the results, and to the writing of the manuscript. All authors provided critical feedback and edited the final manuscript. Sarina Schragger supervised the project.

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