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**

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.[1,2] It is important for its role in bone development and growth and possesses anti-inflammatory, antioxidant, and neuroprotective properties.[1] An estimated 50 to 70% of patients in the United States do not consume the recommended daily value of vitamin D,[3] 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.[4–6] 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.[7] 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.[8,9] 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).[10] 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 Healthcare 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.[11] 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.[12] However, subgroup analysis demonstrated decreased mortality in people who received vitamin D3 supplements as compared with vitamin D2.[12]

Observational studies have demonstrated an association between vitamin D deficiency and poor outcomes in critically ill patients.[13] However, whether vitamin D supplementation affects mortality in critically ill patients is less clear.[14] 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.[15]

Table 1. The United States Food and Drug Administration (FDA) Updated Units for Dosing Equivalents 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

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.[16] 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%.[17]

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.[18] 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).[18] 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

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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).[19] 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.[20] 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.[20] 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.[21] Observational studies highlight the risk of treatment resistant hypertension in patients with low vitamin D levels.[22] A double-blind, placebo-controlled randomized control trial of 64 patients with persistent blood pressure ≥ 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.[23]

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).[24] 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).[25] 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).[26]

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).[27] 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 ≥50 and women ≥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).[18] 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).[28]

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.[29] 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

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susceptibility to respiratory infections.[30,31] Vitamin D deficiency is associated with increased risk of COVID-19 infection.[32–34] 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; $P \leq .01$).[32] This finding was confirmed by subsequent meta-analyses.[33,34] 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,[35] where Bassatne et al found similar trends that did not reach statistical significance.[33] 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.[36] 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.[37] A Cochrane review did not find evidence that vitamin D supplementation in all patients with COVID-19 affected outcomes.[38] 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.[39] 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.[40] Vitamin D supplementation has not been shown to be associated with decreased COVID-19 mortality.[38–40]

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.[41,42] 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).[43] 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.[43]

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.[44] A subsequent RCT showed a trend of increasing falls risk with higher doses of vitamin D3.[45]

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.[46] 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.[46]

Vitamin D and Dementia

Data links low vitamin D levels with poor cognition and increased risk of dementia.[47–49] 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.[49] However, there was no demonstrated benefit of improved cognition with vitamin D supplementation.[49] A limitation of many studies included a short study interval.[50] While the effects of vitamin D supplementation on dementia are still uncertain, an international expert review committee recommends correcting known hypovitaminosis D

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in individuals with cognitive impairment and dementia.[51,52]

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.[53] Low vitamin D levels are a risk factor for development of depression and anxiety,[54] and observational studies demonstrate that vitamin D deficiency is associated with depressive symptoms.[55]

Evidence does not support the use of vitamin D supplementation for prevention of depression in adults ≥ 50 years old.[56] There is no role for vitamin D supplementation for universal prevention nor does supplementation reduce the risk for depression or anxiety.[56,57] However, there is limited evidence to support vitamin D supplementation to treat depressive and anxious symptoms when present.[57,58] 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; $P = 0.046$).[58] In this population, 2 studies observed a moderate reduction in depressive symptoms.[58] 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.[59,60]

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.[61] 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.[61]

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.[62] However, a 2017 article summarized the efficacy of vitamin D for chronic pain management and concluded that in patients with 25(OH)D levels ≤30 nmol/l, there is evidence of benefit with supplementation, while in patients with adequate vitamin D stores (≥50 nmol/l), there is no clear evidence of benefit.[61] 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.[63] Other studies of participants with fibromyalgia and vitamin D deficiency have yielded similar results.[64] In patients with vitamin D deficiency and fibromyalgia, high vitamin D3 doses of 50,000 international units weekly may improve pain.[62,64]

Vitamin D and Diabetes

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

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 (≥1000 IU/day) of vitamin D had a lower risk of developing T2DM (RR 0.88, 0.79 to 0.99).[70] 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.[71] Studies

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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)[72] 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; $P < .001$).[72] 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).[72]

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.[73,74] Atopic dermatitis seems to be correlated with low vitamin D;[73,75–77] 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,[78] (2) the chronic inflammation caused by AD produces a low vitamin D state.[79]

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

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.[75,76,81] The 2019 meta-analysis, which included 5 studies (n = 180), demonstrated the most significant clinical impact.[75] A 2022 RCT (n = 70) similarly observed beneficial effects of vitamin D supplementation specifically in pediatric participants with Fitzpatrick skin types 3 to 5.[82] Vitamin D supplementation in AD improves symptoms and clinical signs of AD when used as an adjuvant to standard treatment.[75,76,81–83]

Vitamin D and Pregnancy

Low vitamin D status is common in pregnant patients worldwide.[84,85] 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[86–88], pre-eclampsia[89,90], gestational diabetes[91], preterm labor[92–95], low birth weight[95,96], and fetal tooth defects.[97] 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.[98] Supplementation was associated with a significantly reduced risk of fetal death RR 0.690 (95% CI, 0.482–0.985; $P = .04$).[98] Low birth weight, small for gestational age, and preterm birth were not significantly associated with the intervention of vitamin D supplementation.[98] 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.[98,99] 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.[100]

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.[101–103] All major US health organizations recommend breastfeeding.[104,105] 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.[106]

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[100,120]

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.	

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

Screening for vitamin D deficiency[118]	"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[121]	"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[122]	Postmenopauasal 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.
	Postmenopauasal 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.[107] 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.[106,108]

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.[107]

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.[107]

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.[109] 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.[110]

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.[107]

Table 4. National Institutes of Health (NIH) Vitamin D Recommended Daily Allowance[6]

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.

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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.[6] These groups include breastfed infants due to low levels of vitamin D in breastmilk;[106] older adults, due to decreased ability to synthesize vitamin D from sun exposure and increased likelihood of being indoors[111]; people with limited sun exposure, such as individuals who wear full body clothing[112]; people with dark skin, as increased skin melanin reduces vitamin D production from sunlight[4,113]; 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[114]; people who are obese, due to vitamin D being sequestered in subcutaneous fat[115]; individuals with a history of gastric bypass, as they may have limited ability to absorb vitamin D from the upper small intestine (Table 2).[116]

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.[117] According to the USPSTF, no professional organization in the United States recommends population screening for vitamin D deficiency (see Table 3).[117,118]

Supplementation in Vitamin D Deficiency

Most people will not be able to obtain adequate vitamin D from food sources alone.[3] In foods and in dietary supplements, vitamin D has 2 main forms: D_2 (ergocalciferol) and D_3 (cholecalciferol). Both forms are well absorbed in the small intestine and raise serum 25(OH)D levels.[6] 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.[38–40]
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.[44–46] Based on a single RCT there is suggestion that the optimal dose may be 1600 to 3200IU daily.[46]
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.[63,64]
In patients with dementia, correct known hypovitaminosis D.	C	Based on expert consensus despite a lack of clear evidence of benefit.[51,52]
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.[57,58]
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.[70] Conflicting RCT results from recent study may be due to novel vitamin D formulation.[71]
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.[75,76,81,82]
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.[98,100]
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.[106,107]

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

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evidence indicates that vitamin D_3 yields a more robust rise in serum 25(OH)D for a longer duration than vitamin D2.[6] 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.[6] The NIH has set recommended daily allowances to reduce the risk of toxicity (Table 4).[6]

Monitoring vitamin D levels uses assays of 25 (OH)D, which reflects vitamin D produced endogenously and that obtained from foods and supplements.[6] Currently, 25(OH)D is the main indicator of vitamin D status, as the more active metabolite 1,25 (OH)2D has a much shorter half-life and levels do not decline until vitamin D deficiency is severe.[6] 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 is the minimum time required to reach a steady state.[119]

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.

Sarina Schrager 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 Schrager supervised the project.

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References

1. Ellison DL, Moran HR. Vitamin D: vitamin or hormone? Nurs Clin North Am 2021;56:47–57.
2. Wang Y, Zhu J, DeLuca HF. Where is the vitamin D receptor? Arch Biochem Biophys 2012;523:123–33.
3. Cashman KD. Vitamin D deficiency: defining, prevalence, causes, and strategies of addressing. Calcif Tissue Int 2020;106:14–29.
4. Schleicher RL, Sternberg MR, Looker AC, et al. National estimates of serum total 25-hydroxy vitamin D and metabolite concentrations measured by liquid chromatography—tandem mass spectrometry in the US population during 2007–2010. J Nutr 2016;146:1051–61.
5. Holick MF. Vitamin D: a D-lightful solution for health. J Investig Med Off Med 2011;59:872–80.
6. National Institutes of Health, Office of Dietary Supplements. Vitamin D: Fact Sheet for Health Professionals. Published March 2, 2018. Updated August 12, 2022. Accessed February 9, 2022. Available from: https://ods.od.nih.gov/factsheets/VitaminD-HealthProfessional/.
7. Kulie T, Groff A, Redmer J, Hounshell J, Schrager S. Vitamin D: an evidence-based review. J Am Board Fam Med 2009;22:698–706.
8. Finley CR, Chan DS, Garrison S, et al. What are the most common conditions in primary care? Can Fam Physician 2018;64:832–40.
9. Ahmad FB, Anderson RN. The leading causes of death in the US for 2020. JAMA 2021;325:1829–30.
10. Food and Drug Administration. Comments to the Proposed Rule and the Supplemental Proposed Rule, Our Responses, and a Description of the Final Rule. Published May 27, 2016. Accessed June 9, 2022. Available from https://www.govinfo.gov/content/pkg/FR-2016-05-27/pdf/2016-11867.pdf.
11. Neale RE, Baxter C, Romero BD, et al. The D-Health Trial: a randomised controlled trial of the effect of vitamin D on mortality. Lancet Diabetes Endocrinol 2022;10:120–8.
12. Zhang Y, Fang F, Tang J, et al. Association between vitamin D supplementation and mortality: systematic review and meta-analysis. BMJ 2019;366:l4673.
13. Moraes RB, Friedman G, Wawrzeniak IC, et al. Vitamin D deficiency is independently associated with mortality among critically ill patients. Clinics 2015;70:326–32.
14. Heath AK, Kim IY, Hodge AM, et al. Vitamin D status and mortality: a systematic review of observational studies. IJERPH 2019;16:383.
15. Shen H, Mei Y, Zhang K, Xu X. The effect of vitamin D supplementation on clinical outcomes for critically ill patients: a systemic review and meta-analysis of randomized clinical trials. Front Nutr 2021;8:664940.
16. Wang L, Song Y, Manson JE, et al. Circulating 25-hydroxy-vitamin D and risk of cardiovascular disease: a meta-analysis of prospective studies. Circ Cardiovasc Qual Outcomes 2012;5:819–29.

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17. Kunutsor SK, Apekey TA, Steur M. Vitamin D and risk of future hypertension: meta-analysis of 283,537 participants. Eur J Epidemiol 2013;28: 205–21.
18. Manson JE, Cook NR, Lee IM, et al. Vitamin D supplements and prevention of cancer and cardiovascular disease. N Engl J Med 2019;380:33–44.
19. Barbarawi M, Kheiri B, Zayed Y, et al. Vitamin D supplementation and cardiovascular disease risks in more than 83,000 individuals in 21 randomized clinical trials: a meta-analysis. JAMA Cardiol 2019;4:765–76.
20. Arora P, Song Y, Dusek J, et al. Vitamin D therapy in individuals with prehypertension or hypertension: the DAYLIGHT trial. Circulation 2015; 131:254–62.
21. Zhang D, Cheng C, Wang Y, et al. Effect of vitamin D on blood pressure and hypertension in the general population: an update meta-analysis of cohort studies and randomized controlled trials. Prev Chronic Dis 2020;17:E03.
22. Alagacone S, Verga E, Verdolini R, Saifullah SM. The association between vitamin D deficiency and the risk of resistant hypertension. Clin Exp Hypertens 2020;42:177–80.
23. Witham MD, Ireland S, Houston JG, et al. Vitamin D therapy to reduce blood pressure and left ventricular hypertrophy in resistant hypertension: randomized, controlled trial. Hypertension 2014;63: 706–12.
24. Choi YJ, Kim YH, Cho CH, et al. Circulating levels of vitamin D and colorectal adenoma: A case-control study and a meta-analysis. World J Gastroenterol 2015;21:8868–77.
25. McCullough ML, Zoltick ES, Weinstein SJ, et al. Circulating vitamin D and colorectal cancer risk: an international pooling project of 17 cohorts. J Natl Cancer Inst 2019;111:158–69.
26. Zhang L, Zou H, Zhao Y, et al. Association between blood circulating vitamin D and colorectal cancer risk in Asian countries: a systematic review and dose-response meta-analysis. BMJ Open 2019;9:e030513.
27. Bjelakovic G, Gluud LL, Nikolova D, et al. Vitamin D supplementation for prevention of cancer in adults. Cochrane Database Syst Rev 2014;CD007469.
28. Virtanen JK, Nurmi T, Aro A, et al. Vitamin D supplementation and prevention of cardiovascular disease and cancer in the Finnish Vitamin D Trial—a randomized controlled trial. Am J Clin Nutr. Published online January 4 2022;nqab419.
29. Dimitrakopoulou VI, Tsilidis KK, Haycock PC, et al. Circulating vitamin D concentration and risk of seven cancers: Mendelian randomisation study. BMJ 2017;359:j4761.
30. Zdrenghea MT, Makrinioti H, Bagacean C, Bush A, Johnston SL, Stanciu LA. Vitamin D modulation of innate immune responses to respiratory viral infections. Rev Med Virol 2017;27.
31. Jolliffe DA, Greiller CL, Mein CA, et al. Vitamin D receptor genotype influences risk of upper respiratory infection. Br J Nutr 2018;120: 891–900.
32. Petrelli F, Luciani A, Perego G, Dognini G, Colombelli PL, Ghidini A. Therapeutic and prognostic role of vitamin D for COVID-19 infection: A systematic review and meta-analysis of 43 observational studies. J Steroid Biochem Mol Biol 2021;211:105883.
33. Bassatne A, Basbous M, Chakhtoura M, El Zein O, Rahme M, El-Hajj Fuleihan G. The link between COVID-19 and vitamin D (VIVID): A systematic review and meta-analysis. Metabolism 2021;119:154753.
34. Teshome A, Adane A, Girma B, Mekonnen ZA. The impact of vitamin D level on COVID-19 infection: systematic review and meta-analysis. Front Public Health 2021;9:624559.
35. Chiodini I, Gatti D, Soranna D, et al. Vitamin D status and SARS-CoV-2 infection and COVID-19 clinical outcomes. Front Public Health 2021; 9:736665.
36. Villasis-Keever MA, López-Alarcón MG, Miranda-Novales G, et al. Efficacy and safety of vitamin D supplementation to prevent COVID-19 in frontline healthcare workers. A randomized clinical trial. Arch Med Res 2022;53:423–30.
37. Martineau AR, Jolliffe DA, Hooper RL, et al. Vitamin D supplementation to prevent acute respiratory tract infections: systematic review and meta-analysis of individual participant data. BMJ 2017;356: i6583.
38. Stroehlein JK, Wallqvist J, Iannizzi C, et al. Vitamin D supplementation for the treatment of COVID-19: a living systematic review. Cochrane Database Syst Rev 2021;CD015043.
39. Varikasuvu SR, Thangappazham B, Vykunta A, et al. COVID-19 and vitamin D (Co-VIVID study): a systematic review and meta-analysis of randomized controlled trials. Expert Rev Anti Infect Ther 2022; 20:907–13.
40. Shah K, Saxena D, Mavalankar D. Vitamin D supplementation, COVID-19 and disease severity: a meta-analysis. QJM Mon J Assoc Physicians 2021; 114:175–81.
41. Thanapluetiwong S, Chewcharat A, Takkavatakarn K, Praditpornsilpa K, Eiam-Ong S, Susantitaphong P. Vitamin D supplement on prevention of fall and fracture: A meta-analysis of randomized controlled trials. Medicine (Baltimore) 2020;99: e21506.
42. Dhaliwal R, Aloia JF. Effect of vitamin D on falls and physical performance. Endocrinol Metab Clin North Am 2017;46:919–33.
43. Ling Y, Xu F, Xia X, et al. Vitamin D supplementation reduces the risk of fall in the vitamin D

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deficient elderly: an updated meta-analysis. Clin Nutr 2021;40:5531–7.
44. Sanders KM, Stuart AL, Williamson EJ, et al. Annual high-dose oral vitamin D and falls and fractures in older women: a randomized controlled trial. JAMA 2010;303:1815–22.
45. Bischoff-Ferrari HA, Dawson-Hughes B, Orav EJ, et al. Monthly high-dose vitamin D treatment for the prevention of functional decline: a randomized clinical trial. JAMA Intern Med 2016;176:175.
46. Smith LM, Gallagher JC, Suiter C. Medium doses of daily vitamin D decrease falls and higher doses of daily vitamin D3 increase falls: A randomized clinical trial. J Steroid Biochem Mol Biol 2017; 173:317–22.
47. Balion C, Griffith LE, Strifler L, et al. Vitamin D, cognition, and dementia: A systematic review and meta-analysis. Neurology 2012;79:1397–405.
48. Yang T, Wang H, Xiong Y, et al. Vitamin D supplementation improves cognitive function through reducing oxidative stress regulated by telomere length in older adults with mild cognitive impairment: a 12-month randomized controlled trial. JAD 2020;78:1509–18.
49. Goodwill AM, Szoeke C. A systematic review and meta-analysis of the effect of low vitamin D on cognition. J Am Geriatr Soc 2017;65:2161–8.
50. Jorde R, Kubiak J, Svartberg J, et al. Vitamin D supplementation has no effect on cognitive performance after four months in mid-aged and older subjects. J Neurol Sci 2019;396:165–71.
51. Annweiler C, Dursun E, Féron F, et al. Vitamin D and cognition in older adults: updated international recommendations. J Intern Med 2015;277: 45–57.
52. Annweiler C. Vitamin D-mentia: Is vitamin D optional or essential for preventing late-life cognitive decline? J Am Geriatr Soc 2017;65:2155–7.
53. Casseb GAS, Kaster MP, Rodrigues ALS. Potential role of vitamin D for the management of depression and anxiety. CNS Drugs 2019;33:619–37.
54. Kim SY, Jeon SW, Lim WJ, et al. The relationship between serum vitamin D levels, C-reactive protein, and anxiety symptoms. Psychiatry Investig 2020;17: 312–9.
55. Anglin RES, Samaan Z, Walter SD, McDonald SD. Vitamin D deficiency and depression in adults: systematic review and meta-analysis. Br J Psychiatry J Psychiatry 2013;202:100–7.
56. Okereke OI, Reynolds CF, Mischoulon D, et al. Effect of long-term vitamin D3 supplementation vs placebo on risk of depression or clinically relevant depressive symptoms and on change in mood scores: a randomized clinical trial. JAMA 2020; 324:471–80.
57. Jorde R, Kubiak J. No improvement in depressive symptoms by vitamin D supplementation: results from a randomised controlled trial. J Nutr Sci 2018;7:e30.
58. Shaffer JA, Edmondson D, Wasson LT, et al. Vitamin D supplementation for depressive symptoms: a systematic review and meta-analysis of randomized controlled trials. Psychosom Med 2014;76:190–6.
59. Wu Z, Malihi Z, Stewart AW, et al. The association between vitamin D concentration and pain: a systematic review and meta-analysis. Public Health Nutr 2018;21:2022–37.
60. Ali OME. Prevalence of vitamin D deficiency and its relationship with clinical outcomes in patients with fibromyalgia: a systematic review of the literature. SN Compr Clin Med 2022;4:38.
61. Helde-Frankling M, Björkhem-Bergman L. Vitamin D in pain management. IJMS 2017;18: 2170.
62. Straube S, Derry S, Straube C, Moore RA. Vitamin D for the treatment of chronic painful conditions in adults. Cochrane Database Syst Rev 2015;CD015043.
63. Yilmaz R, Salli A, Cingoz HT, et al. Efficacy of vitamin D replacement therapy on patients with chronic nonspecific widespread musculoskeletal pain with vitamin D deficiency. Int J Rheum Dis 2016;19:1255–62.
64. Pagliai G, Giangrandi I, Dinu M, et al. Nutritional interventions in the management of fibromyalgia syndrome. Nutrients 2020;12:12092525.
65. Ogurtsova K, da Rocha Fernandes JD, Huang Y, et al. IDF diabetes atlas: global estimates for the prevalence of diabetes for 2015 and 2040. Diabetes Res Clin Pract 2017;128:40–50.
66. Huang Y, Cai X, Mai W, et al. Association between prediabetes and risk of cardiovascular disease and all-cause mortality: systematic review and meta-analysis. BMJ 2016;i5953.
67. Berridge MJ. Vitamin D deficiency and diabetes. Biochem J 2017;474:1321–32.
68. Narayan KMV, Boyle JP, Thompson TJ, et al. Effect of BMI on lifetime risk for diabetes in the U.S. Diabetes Care 2007;30:1562–6.
69. Rafiq S, Jeppesen P. Body mass index, vitamin D, and type 2 diabetes: a systematic review and meta-analysis. Nutrients 2018;10:1182.
70. Barbarawi M, Zayed Y, Barbarawi O, et al. Effect of vitamin D supplementation on the incidence of diabetes mellitus. J Clin Endocrinol Metab 2020; 105:2857–68.
71. Kawahara T, Suzuki G, Mizuno S, et al. Effect of active vitamin D treatment on development of type 2 diabetes: DPVD randomised controlled trial in Japanese population. BMJ. 2022; e066222.
72. Hu Z, Chen J, Sun X, et al. Efficacy of vitamin D supplementation on glycemic control in type 2

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diabetes patients: A meta-analysis of interventional studies. Medicine (Baltimore) 2019;98:e14970.
73. Palmer DJ. Vitamin D and the development of atopic eczema. J Clin Med 2015;4:1036–50.
74. Williams H, Chalmers J. Prevention of atopic dermatitis. Acta Derm Venereol 2020;100:adv00166.
75. Hattangdi-Haridas SR, Lanham-New SA, Wong WHS, et al. Vitamin D deficiency and effects of vitamin D supplementation on disease severity in patients with atopic dermatitis: a systematic review and meta-analysis in adults and children. Nutrients 2019;11:1854.
76. Kim MJ, Kim SN, Lee YW, et al. Vitamin D status and efficacy of vitamin D supplementation in atopic dermatitis: a systematic review and meta-analysis. Nutrients 2016;8:789.
77. Wang SS, Hon KL, Kong AP, et al. Vitamin D deficiency is associated with diagnosis and severity of childhood atopic dermatitis. Pediatr Allergy Immunol 2014;25:30–5.
78. Vähävihu K, Ala-Houhala M, Peric M, et al. Narrowband ultraviolet B treatment improves Vitamin D balance and alters antimicrobial peptide expression in skin lesions of psoriasis and atopic dermatitis. Br J Dermatol 2010;163:321–8.
79. Mangin M, Sinha R, Fincher K. Inflammation and vitamin D: the infection connection. Inflamm Res Off Res 2014;63:803–19.
80. Yepes-Nuñez JJ, Brożek JL, Fiocchi A, et al. Vitamin D supplementation in primary allergy prevention: Systematic review of randomized and non-randomized studies. Allergy 2018;73:37–49.
81. Kim G, Bae JH. Vitamin D and atopic dermatitis: A systematic review and meta-analysis. Nutrition 2016;32:913–20.
82. Raj KAP, Handa S, Narang T, et al. Correlation of serum vitamin D levels with severity of pediatric atopic dermatitis and the impact of vitamin D supplementation on treatment outcomes. J Dermatolog Treat 2022;33:1397–400.
83. Mansour NO, Mohamed AA, Hussein M, et al. The impact of vitamin D supplementation as an adjuvant therapy on clinical outcomes in patients with severe atopic dermatitis: A randomized controlled trial. Pharmacol Res Perspect 2020;8: e00679.
84. Kiely ME, Wagner CL, Roth DE. Vitamin D in pregnancy: Where we are and where we should go. J Steroid Biochem Mol Biol 2020;201:105669.
85. Urrutia RP, Thorp JM. Vitamin D in pregnancy: current concepts. Curr Opin Obstet Gynecol 2012;24:57–64.
86. Sharif K, Sharif Y, Watad A, et al. Vitamin D, autoimmunity and recurrent pregnancy loss: More than an association. Am J Reprod Immunol N Immunol 2018;80:e12991.
87. Ji J, Zhai H, Zhou H, et al. The role and mechanism of vitamin D-mediated regulation of treg/Th17 balance in recurrent pregnancy loss. Am J Reprod Immunol N Immunol 2019;81:e13112.
88. Tamblyn JA, Pilarski NSP, Markland AD, et al. Vitamin D and miscarriage: a systematic review and meta-analysis. Fertil Steril 2022;118:111–22.
89. Mirzakhani H, Litonjua AA, McElrath TF, et al. Early pregnancy vitamin D status and risk of preeclampsia. J Clin Invest 2016;126:4702–15.
90. Khaing W, Vallibhakara SAO, Tantrakul V, et al. Calcium and vitamin D supplementation for prevention of preeclampsia: a systematic review and network meta-analysis. Nutrients 2017;9:1141.
91. Yue CY, Ying CM. Sufficience serum vitamin D before 20 weeks of pregnancy reduces the risk of gestational diabetes mellitus. Nutr Metab (Lond) 2020;17:89.
92. Kalok A. Maternal serum vitamin D and spontaneous preterm birth. Clin Exp Obstet Gynecol 2020; 47:16–20.
93. McDonnell SL, Baggerly KA, Baggerly CA, et al. Maternal 25(OH)D concentrations ≥40 ng/mL associated with 60% lower preterm birth risk among general obstetrical patients at an urban medical center. PloS One 2017;12:e0180483.
94. Wagner CL, Taylor SN, Dawodu A, et al. Vitamin D and its role during pregnancy in attaining optimal health of mother and fetus. Nutrients 2012;4:208–30.
95. Zhao R, Zhou L, Wang S, et al. Effect of maternal vitamin D status on risk of adverse birth outcomes: a systematic review and dose-response meta-analysis of observational studies. Eur J Nutr 2022;61:2881–907.
96. Qureshi S, Wilkinson JE. Vitamin D supplementation for women during pregnancy. Am Fam Physician 2013;87:314.
97. Nørrisgaard PE, Haubek D, Kühnisch J, et al. Association of high-dose vitamin D supplementation during pregnancy with the risk of enamel defects in offspring: a 6-year follow-up of a randomized clinical trial. JAMA Pediatr 2019;173: 924–930.
98. Liu Y, Ding C, Xu R, et al. Effects of vitamin D supplementation during pregnancy on offspring health at birth: a meta-analysis of randomized controlled trails. Clin Nutr Edinb Nutr 2022;41: 1532–1540.
99. Hollis BW, Wagner CL. Substantial vitamin D supplementation is required during the prenatal period to improve birth outcomes. Nutrients 2022;14:899.
100. American College of Obstetricians and Gynecologists. ACOG Committee Opinion No. 495: Vitamin D screening and supplementation during pregnancy. Obstet Gynecol 2011;118:197–198.

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101. Gila-Diaz A, Arribas SM, Algara A, et al. A review of bioactive factors in human breastmilk: a focus on prematurity. Nutrients 2019;11:1307.
102. Chatterton DEW, Nguyen DN, Bering SB, Sangild PT. Anti-inflammatory mechanisms of bioactive milk proteins in the intestine of newborns. Int J Biochem Cell Biol 2013;45:1730–1747.
103. Andreas NJ, Kampmann B, Mehring Le-Doare K. Human breast milk: a review on its composition and bioactivity. Early Hum Dev 2015;91:629–635.
104. Breastfeeding, Family Physicians Supporting (Position Paper). Published 2001. Updated April 2021. Accessed March 9, 2022. Available from: https://www.aafp.org/about/policies/all/breastfeeding-position-paper.html.
105. American College of Obstetricians and Gynecologists. ACOG Committee Opinion No. 756. Optimizing support for breastfeeding as part of obstetric practice. Obstet Gynecol 2018;132:e187–e196.
106. Wagner CL, Greer FR. Prevention of rickets and vitamin D deficiency in infants, children, and adolescents. Pediatrics 2008;122:1142–1152.
107. O'Callaghan KM, Taghivand M, Zuchniak A, et al. Vitamin D in breastfed infants: systematic review of alternatives to daily supplementation. Adv Nutr 2019;nmz098.
108. Tung KTS, Wong RS, Tsang HW, et al. An assessment of risk factors for insufficient levels of vitamin D during early Infancy. Nutrients 2021; 13:1068.
109. Kazemain E, Ansari S, Davoodi SH, et al. The effect of maternal vitamin D supplementation on vitamin D status of exclusively breastfeeding mothers and their nursing infants: a systematic review and meta-analysis of randomized clinical trials. Adv Nutr 2021;nmab126.
110. Sen S, Penfield-Cyr A, Hollis BW, Wagner CL. Maternal obesity, 25-hydroxy vitamin D concentration, and bone density in breastfeeding dyads. J Pediatr 2017;187:147–152.
111. Chalcraft JR, Cardinal LM, Wechsler PJ, et al. Vitamin D synthesis following a single bout of sun exposure in older and younger men and women. Nutrients 2020;12:2237.
112. Nadeem S, Munim TF, Hussain HF, Hussain DF. Determinants of vitamin D deficiency in asymptomatic healthy young medical students. Pak J Med Sci 2018;34:1248–1252.
113. Brown LL, Cohen B, Tabor D, et al. The vitamin D paradox in Black Americans: a systems-based approach to investigating clinical practice, research, and public health expert panel meeting report. BMC Proc 2018;12:6–6.
114. Vavricka SR, Rogler G. Intestinal absorption and vitamin levels: is a new focus needed? Dig Dis 2012;30:73–80.
115. Ekwaru JP, Zwicker JD, Holick MF, et al. The importance of body weight for the dose response relationship of oral vitamin D supplementation and serum 25-hydroxy vitamin D in healthy volunteers. PLoS ONE 2014;9:e111265.
116. Aarts E, van Groningen L, Horst R, et al. Vitamin D absorption: consequences of gastric bypass surgery. Eur J Endocrinol 2011;164:827–832.
117. LeFevre ML. Screening for vitamin D deficiency in adults: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med 2015; 162:133–140.
118. Burnett-Bowie SAM, Cappola AR. The USPSTF 2021 recommendations on screening for asymptomatic vitamin D deficiency in adults: the challenge for clinicians continues. JAMA 2021;325:1401–1402.
119. Pilz S, Zittermann A, Trummer C, et al. Vitamin D testing and treatment: a narrative review of current evidence. Endocr Connect 2019;8:R27–R43.
120. Parva NR, Tadepalli S, Singh P, et al. Prevalence of vitamin D deficiency and associated risk factors in the US population. Cureus 2018;10:e2741.
121. US Preventive Services Task Force. Interventions to prevent falls in community-dwelling older adults: US Preventive Services Task Force recommendation statement. JAMA 2018;319(16):1696–1704.
122. US Preventive Services Task Force. Vitamin D, calcium, or combined supplementation for the primary prevention of fractures in community-dwelling adults: US Preventive Services Task Force recommendation statement. JAMA 2018;319:1592–1599.

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