Vitamin D

SCIENTIFIC NAME

1, 25-dihydroxycholecalciferol, 25-hydroxycholecalciferol, Alfacalcidol, Calcifediol, Calcipotriene, Calcitriol, Cholecalciferol, Dihydrotachysterol, Ergocalciferol, Paricalcitol

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FAMILY

Other Common Names

Alfacalcidol: 1-alpha-hydroxycholecalciferol, 1-alpha-hydroxycholécalciférol, 1 alpha (OH)D3.

Calcifediol: 25-HCC, 25-hydroxycholecalciferol, 25-hydroxycholécalciferol, 25-hydroxyvitamin D3, 25-hydroxyvitamine D3, 25-OHCC, 25-OHD3, Calcifédiol.

Calcipotriene: Calcipotriène, Calcipotriol.

Calcitriol: 1,25-DHCC, 1,25-dihydroxycholecalciferol, 1,25-dihydroxycholécalciférol, 1,25-dihydroxyvitamin D3, 1,25-dihydroxyvitamine D3, 1,25-diOHC, 1,25(OH)2D3, Eldecalcitol.

Cholecalciferol: 7-déhydrocholestérol Activé, Activated 7-dehydrocholesterol, Cholécalciférol, Colecalciferol, Colécalciférol, Vitamin D3.

Dihydrotachysterol: DHT, Dihydrotachystérol, dihydrotachysterol 2, dichysterol, Vitamine D3.

Ergocalciferol: Activated Ergosterol, Calciferol, Ergocalciférol, Ergocalciferolum, Ergostérol Activé, Irradiated Ergosterol, Ergostérol Irradié, Viosterol, Viostérol, Vitamin D2, Vitamine D2.

Paricalcitol: 19-nor-1,25-dihydroxyvitamin D2, 19-nor-1,25-dihydroxyvitamine D2, Paracalcin.

Vitamina D, Vitamine D.

Overview

Vitamin D is an essential fat-soluble vitamin. There are several forms of vitamin D, including ergocalciferol (vitamin D2) and cholecalciferol (vitamin D3). Both ergocalciferol and cholecalciferol are metabolized in the body to calcitriol, the active metabolite (7555,16890). Commercially available vitamin D3 supplements are usually made from animal sources such as lanolin, though a vegan source of D3 made from lichen is available. Vitamin D2 supplements are primarily plant-based (114502). Vitamin D is found in dietary sources, such as fish, eggs, and fortified milk (7555). It is also made in the skin during brief exposure to sunlight (11935). In the US, foods containing at least 120 IU vitamin D are allowed to state that "adequate calcium and vitamin D as part of a well-balanced diet, along with physical activity, may reduce the risk of osteoporosis" (11940,97001).

WARNINGS

Coronavirus disease 2019 (COVID-19): Some experts suggest taking vitamin D 2000 IU (50 mcg) daily to reduce the risk for COVID-19. More recently, a joint task force has recommended 400-1000 IU (10-25 mcg) daily for those who are unable to spend 15-30 minutes in the sun each day. These doses are likely safe for most adults, but there is no strong evidence to support the effectiveness of vitamin D for COVID-19. Furthermore, clinical research suggests that a single dose of 200,000 IU is not beneficial for patients hospitalized with COVID-19. Ensure that patients considering vitamin D for COVID-19 follow healthy lifestyle choices and proven prevention methods as well.

Safety

LIKELY SAFE ...when used orally or intramuscularly and appropriately. Vitamin D has been safely used in a wide range of doses (7555,16888,16891,17476,95913,98186,104619,105209,109059). When used orally long-term, doses should not exceed the tolerable upper intake level (UL) of 4000 IU (100 mcg) daily for adults (17506,99773); however, much higher doses such as 50,000 IU (1250 mcg) weekly orally for 6-12 weeks are often needed for the short-term treatment of vitamin D deficiency (16891,17476). Monthly oral doses of up to 60,000 IU (1500 mcg) have also been safely used for up to 5 years (105726). Toxicity usually does not occur until plasma levels exceed 150 ng/mL (17476).

POSSIBLY UNSAFE ...when used orally in excessive doses, long-term. Taking doses greater than the tolerable upper intake level (UL) of 4000 IU (100 mcg) daily for adults for long periods can increase the risk of hypercalcemia (17506); however, much higher doses are often needed for short-term treatment of vitamin D deficiency. Toxicity typically occurs when levels exceed 150 ng/mL (17476).

CHILDREN: **LIKELY SAFE** ...when used orally and appropriately. When used long-term, doses should not exceed the tolerable upper intake level (UL) of 1000 IU (25 mcg) daily for those 0-6 months of age, 1500 IU (37.5 mcg) daily for those 6-12 months of age, 2500 IU (62.5 mcg) daily for those 1-3 years of age, 3000 IU (75 mcg) daily for those 4-8 years of age, and 4000 IU (100 mcg) daily for those 9 years and older (17506); however, much higher doses are often needed for the short-term treatment of vitamin D deficiency. Some research shows that giving vitamin D 14,000 IU (350 mcg) weekly for a year in children aged 10-17 years is safe (16875). A meta-analysis of clinical studies shows that 1000 IU (25 mcg) daily in those up to a year of age and greater than 2000 IU (50 mcg) daily in those aged 1-6 years does not increase the risk of serious adverse events (108424). **POSSIBLY**

UNSAFE ...when used orally in excessive doses for longer than one year. Taking doses greater than the tolerable upper intake level (UL) long-term can increase the risk of hypercalcemia (17506).

PREGNANCY: **LIKELY SAFE** ...when used orally and appropriately. Vitamin D is safe when used in doses below the tolerable upper intake level (UL) of 4000 IU (100 mcg) daily (17506,95910). **POSSIBLY UNSAFE** ...when used orally in excessive amounts. Tell patients not to use doses above the tolerable upper intake level (UL) of 4000 IU (100 mcg) daily. Hypercalcemia during pregnancy due to excessive vitamin D intake can lead to several fetal adverse effects, including suppression of parathyroid hormone, hypocalcemia, tetany, seizures, aortic valve stenosis, retinopathy, and mental and/or physical developmental delay (17506).

LACTATION: **LIKELY SAFE** ...when used orally and appropriately. Vitamin D is safe when used in doses below the tolerable upper intake level (UL) of 4000 IU (100 mcg) daily (17506). **POSSIBLY UNSAFE** ...when used orally in excessive amounts. Tell patients not to use doses above the tolerable upper intake level (UL) of 4000 IU (100 mcg) daily (17506).

Adverse Effects

General: Orally or intramuscularly, vitamin D is well tolerated.

Serious Adverse Effects (Rare):

Orally or intramuscularly: Excessive doses can lead to vitamin D toxicity with symptoms of hypercalcemia, and also sometimes azotemia and anemia.

Cardiovascular

Vitamin D intoxication can occur when vitamin D supplements are taken orally in excessive doses. Rarely, people develop hypertension (10142). An analysis of clinical research suggests that, when taken orally, vitamin D might modestly increase levels of low-density lipoprotein (LDL)-cholesterol. However, it is not clear if this increase is clinically significant (84642).

Gastrointestinal

Orally, vitamin D may cause dry mouth. In clinical research, intake of vitamin D 50,000 IU weekly for 4 weeks followed by 50,000 IU monthly for 5 months thereafter was associated with a 3.7-fold increase in reports of dry mouth compared with placebo (91348).Vitamin D intoxication can occur when vitamin D supplements are taken orally in excessive doses. Symptoms of vitamin D toxicity include pancreatitis (10142,84433). Vomiting occurred in one patient given a single dose of 200,000 IU (104624).

Genitourinary

Vitamin D intoxication can occur when vitamin D supplements are taken orally in excessive doses. Advanced symptoms may include decreased libido (10142). Vaginal discharge and itching have been reported in a clinical trial following oral use (91348).

Hematologic

Lab values of urinary and blood calcium, phosphate, albumin, blood urea nitrogen, serum cholesterol, aspartate aminotransferase, and alanine aminotransferase concentrations might increase with vitamin D use, especially with high doses (10142,91349,93943).

A case of elevated international normalized ration (INR) has been reported for an 84 year-old patient who took vitamin D 50,000 IU daily for 2 months. The patient's serum levels of vitamin D increased from <7 ng/mL to 100 ng/mL over 6 months. To resolve symptoms, vitamin D supplementation was discontinued (84433).

Musculoskeletal

Vitamin D intoxication can occur when vitamin D supplements are taken in excessive doses (10142,17506). Symptoms of vitamin D toxicity include osteoporosis in adults and decreased growth in children (10142).

Ocular/Otic

Vitamin D intoxication can occur when vitamin D supplements are taken orally in excessive doses (10142,17506). Symptoms of vitamin D toxicity include calcific conjunctivitis and photophobia (10142).

Psychiatric

Vitamin D intoxication can occur when vitamin D supplements are taken orally in excessive doses (10142,17506). In rare cases, symptoms of vitamin D toxicity include psychosis (10142,93002).

Pulmonary/Respiratory

Vitamin D intoxication can occur when vitamin D supplements are taken orally in excessive doses. Advanced symptoms of vitamin D toxicity may include runny nose (10142,17506,93002).

Renal

Vitamin D intoxication can occur when vitamin D supplements are taken orally in excessive doses. Symptoms of vitamin D toxicity include azotemia. Vitamin D may also cause hypercalcemia, with advanced symptoms including kidney stones or kidney insufficiency due to precipitation of calcium phosphate in the tubules. Symptoms of renal impairment include frequency, nighttime awakening to urinate, thirst, inability to concentrate urine, and proteinuria. Renal impairment is usually reversible with discontinuation of vitamin D supplements (10142,93002,93943,110831,110833).

Effectiveness

EFFECTIVE

Familial hypophosphatemia. Oral vitamin D in combination with phosphate is effective for bone disorders in patients with familial hypophosphatemia.
Details: Taking calcitriol or dihydrotachysterol orally in combination with phosphate supplements is effective for treating bone disorders in people with familial hypophosphatemia (11818).

Hypoparathyroidism. Oral vitamin D increases serum calcium concentrations in people with hypoparathyroidism or pseudohypoparathyroidism.
Details: Vitamin D2 (ergocalciferol) is effective in high doses for increasing serum calcium concentrations in people with hypoparathyroidism or pseudohypoparathyroidism (11820). Also, taking vitamin D (form unspecified) or calcitriol postoperatively is effective for preventing hypocalcemia in people with hypoparathyroidism due to thyroidectomy (39045).

Osteomalacia. Oral vitamin D is effective for osteomalacia.
Details: Oral calcifediol is effective for treating osteomalacia secondary to liver disease (hepatic osteodystrophy) and anticonvulsant-induced osteomalacia. Vitamin D2 (ergocalciferol) is effective for osteomalacia due to malabsorption syndromes, Fanconi syndrome, and corticosteroid-induced osteomalacia (11819,11821).

Renal osteodystrophy. Oral calcitriol prevents renal osteodystrophy in patients with chronic renal failure.
Details: Taking calcitriol orally manages hypocalcemia and prevents renal osteodystrophy in patients with chronic renal failure undergoing dialysis (11823).

Rickets. Oral vitamin D prevents and treats rickets.
Details: Vitamin D is effective for preventing and treating rickets, a consequence of vitamin D deficiency. Calcitriol should be used in patients with renal failure (11824). Clinical practice guidelines from the Endocrine Society conditionally recommend, based on low certainty of evidence, empiric vitamin D supplementation from vitamin D fortified foods, vitamin D supplements, or vitamin formulations that contain vitamin D to prevent nutritional rickets in children and adolescents aged 1 to 18 years. Empiric vitamin D supplementation is defined as supplementing with vitamin D above the Recommended Dietary Allowance without having tested serum vitamin D status (114502).

A large clinical study in pregnant adults shows that taking vitamin D 28,000 IU weekly from the second trimester up to 6 months post-partum decreases the risk of biochemical rickets by about 84% in the offspring at 6-12 months of age when compared with placebo. However, taking vitamin D 4200, 16,800, or 28,000 IU weekly from the second trimester to delivery does not decrease the risk of rickets in the offspring when compared with placebo (114503).

Vitamin D deficiency. Oral vitamin D prevents and treats vitamin D deficiency.
Details: Vitamin D is effective for preventing and treating vitamin D deficiency using a wide range of doses (7555,16888,16891,17476). Optimal blood levels of 25-hydroxyvitamin D for maintaining bone density is controversial; however, it is typically estimated that blood levels of 20-100 ng/mL are needed. Toxicity usually does not occur until levels exceed 150 ng/mL (17476,93945). Vitamin D also alleviates symptoms and syndromes associated with vitamin D deficiency. Administering vitamin D2 (ergocalciferol) intramuscularly or orally seems to help treat severe proximal myopathy associated with severe vitamin D deficiency. Several case reports suggest vitamin D therapy can provide prompt relief of muscle weakness and restore mobility (11923,84348,84687).

LIKELY EFFECTIVE

Corticosteroid-induced osteoporosis. Oral vitamin D prevents corticosteroid-induced osteopenia and osteoporosis.
Details: Taking calcifediol, cholecalciferol, calcitriol, or alfacalcidol orally prevents corticosteroid-induced osteopenia and osteoporosis (7555,83933). Vitamin D3 metabolites, including calcitriol and alfacalcidol, seem to be more effective at preventing bone loss compared to cholecalciferol in these patients, although the vitamin D3 metabolites seem to be inferior to bisphosphonates (83955). Furthermore, taking activated vitamin D or other forms of vitamin D alone or along with calcium improves bone mineral density in people with corticosteroid-induced osteoporosis (38493,38581).

Osteoporosis. Adequate intake of vitamin D in conjunction with adequate calcium intake helps to prevent the progression of osteoporosis. It might also reduce the risk of a first fracture in some patients. However, its place in the prevention of secondary fracture is unclear.
Details: The Bone Health and Osteoporosis Foundation (BHOF) recommends ensuring adequate vitamin D intake of 800-1000 IU daily along with adequate calcium intake for the prevention and treatment of osteoporosis in adults over 50 years of age. Supplementation can be used to augment dietary intake, with a target serum vitamin D level of 30 ng/mL (109425). In the US, foods that contain at least 120 IU vitamin D can be labelled with a health claim regarding the relationship between adequate vitamin D intake and a reduced risk for osteoporosis (97001). However, vitamin D supplementation is not recommended specifically for the primary prevention of osteoporosis. The US Preventive Task Force (USPSTF) states that the current evidence is insufficient to assess the balance of benefits and harms of vitamin D and calcium supplementation, alone or in combination, for the primary prevention of fractures in community dwelling adults without osteoporosis (95695).

Clinical research shows that vitamin D3 (cholecalciferol) and calcium can decrease postmenopausal bone loss, improve bone density, help prevent osteoporosis, and decrease the risk of fractures (10932,12926,12930,12934,12952) (38973,39015,39026,84003,113584). According to one analysis, taking oral vitamin D3 700-800 IU daily with or without calcium reduces fracture risk in ambulatory and institutionalized elderly people (12933). Other analyses suggest that taking vitamin D as cholecalciferol, ergocalciferol, calcifediol, calcitriol, or alfacalcidol with or without calcium can reduce the risk of all fractures by up to 17%, nonvertebral fractures by up to 49%, and hip fractures by up to 30% in older adults. However, the incidence of vertebral fractures does not appear to be reduced with vitamin D supplementation (38942,38970,38973,39015,39026,84660,109053).

Despite the majority of research showing benefit, some studies have not found a positive effect of vitamin D on fracture risk. Some analyses of clinical evidence, including patients with and without osteoporosis, show that taking vitamin D3 or vitamin D2 (ergocalciferol) alone does not reduce fracture risk, suggesting that adequate calcium intake is needed for any benefit to be realized (39015,84471). Also, some evidence suggests that vitamin D3 400 IU daily is not effective for the prevention of osteoporotic fractures in elderly nursing home residents (109053). Another clinical trial found that taking vitamin D3 800 IU daily with calcium 1200-1500 mg daily for 2 years does not increase bone mineral density (BMD) in Black postmenopausal adults. This may be due to the fact that Black females have a lower rate of bone remodeling, an increased calcium absorption efficiency, and reduced calcium excretion when compared with other ethnic groups; therefore, supplementation with vitamin D3 and calcium might not be as beneficial in these patients (16878).

There is concern that vitamin D might not be effective for secondary prevention of fractures in elderly patients. A meta-analysis of clinical studies, including many studies cited above, and a large clinical study in elderly adults with a previous osteoporotic fracture show that taking vitamin D3 400-4000 IU daily or as a single dose up to 500,000 IU orally or injected annually with or without calcium 480-1200 mg daily for up to 5 years does not reduce the risk of hip, vertebral, or other fractures when compared with placebo or no treatment (13073,112486). Another study also shows that taking vitamin D3 800 IU and calcium 1000 mg daily does not prevent a second fracture in elderly patients, or prevent a first fracture in elderly patients with other risk factors such as low body weight (under 58 kg, 127.6 pounds), smoking, family history of hip fracture, or fair or poor self-reported health (12929). However, these studies have been criticized for failing to measure vitamin D levels and low adherence to study protocol (12931). Also, one of these studies did not use a placebo control (12929).

Taking alfacalcidol orally seems to maintain BMD in prostatic carcinoma patients at risk for osteoporosis when treated with luteinizing hormone-releasing hormone analogue (LHRH-a). Alfacalcidol maintains, but does not increase, BMD in these patients (6360).

Psoriasis. Topical vitamin D or vitamin D analogues improve symptoms of psoriasis. This benefit is not seen with oral vitamin D.
^ Details: Topical application of vitamin D in the form of calcitriol or other vitamin D analogues, such as calcipotriene, maxacalcitol, and paricalcitol, effectively treats plaque psoriasis in some patients, including those with chronic plaque psoriasis (11822,84325). Applying topical vitamin D or its analogues in combination with topical corticosteroids such as betamethasone seems to be more effective for treating plaque psoriasis than either agent used alone (22283,82572,84325,84536,84647).

Despite evidence that patients with psoriasis have low baseline serum levels of vitamin D, taking oral vitamin D does not seem to prevent psoriasis, improve symptoms, or reduce the severity of psoriasis in general (11822,22283,82572,84325,84536,84647,98193,108426,112481,112482). An analysis of a large clinical study in older adults with mild psoriasis shows that taking a vitamin D3 (cholecalciferol) loading dose of 200,000 IU followed by vitamin D3 100,000 IU monthly for 1 year does not affect the severity or spread of psoriasis when compared with placebo (98193).

POSSIBLY EFFECTIVE

Allergic rhinitis (hay fever). Some research suggests that oral vitamin D reduces symptoms of allergic rhinitis in children and adults. It is unclear if oral vitamin D during pregnancy is beneficial for the prevention of allergic rhinitis in the child.
^ Details: Preliminary clinical research in adults with allergic rhinitis and vitamin D deficiency shows that taking vitamin D 50,000 IU weekly for 8 weeks along with cetirizine improves overall symptom severity when compared with placebo and cetirizine. This improvement was not significant at 4 weeks, suggesting that symptom improvement might not occur until vitamin D has been adequately replenished (102120). Another moderate-sized clinical study conducted in China in adults with moderate to severe allergic rhinitis and vitamin D levels at the low end of the normal range shows that taking vitamin D 800 IU daily for 4 weeks along with mometasone nasal spray improves runny nose, itchy nose, and nasal congestion but does not reduce sneezing when compared with placebo and mometasone (112483).

In children aged 5-15 years, 4 small- or moderate-sized clinical trials show that taking vitamin D 800 IU or 1000 IU daily for 1-6 months modestly reduces symptoms such as nasal congestion and rhinorrhea when compared with placebo or no supplementation (109728). It is unclear whether these children had vitamin D deficiency at baseline.

Vitamin D supplementation during pregnancy has also been evaluated. A meta-analysis of three large clinical studies shows that prenatal vitamin D supplementation does not reduce the risk of the child developing allergic rhinitis when compared with low-dose vitamin D, placebo, or no intervention (108438).

Dental caries. Some research suggests that oral vitamin D reduces the risk of dental caries in children.
^ Details: A meta-analysis of clinical research suggests that vitamin D3 (cholecalciferol) reduces the risk of cavities by 49%, and vitamin D2 (ergocalciferol) reduces the risk by 36% when compared with placebo in infants, children, and adolescents (84690). The validity of this finding is limited by the heterogeneity of the included trials. Also, clinical research shows an inverse correlation between cord blood vitamin D status and the number of decayed primary teeth in the infant at 12 months of age (104620). However, this same research shows that taking two oral prenatal doses of vitamin D2 50,000 IU during pregnancy does not prevent dental caries in the infant at 12 months of age or increase vitamin D levels in the cord blood (104620).

Heart failure. Limited research suggests that oral vitamin D reduces the risk of developing heart failure in some patients. However, vitamin D does not seem to improve outcomes in patients that have already developed heart failure.
^ Details: Population research has found that vitamin D levels below 15 ng/mL are associated with increased risk of developing heart failure (16615). A meta-analysis of 17 trials, including the landmark Randomized Evaluation of Calcium Or vitamin D (RECORD) trial, shows that vitamin D reduces the risk of heart failure by 21% compared to not taking vitamin D in patients 60 years or older (91343). This finding is limited because none of the included trials were designed to determine effects on cardiovascular outcomes. In contrast, a secondary analysis of data from the Women's Health Initiative trial shows that taking vitamin D 400 IU with calcium 1000 mg daily is not associated with a reduced risk of heart failure in postmenopausal adults. However, a subgroup analysis of that trial shows that taking vitamin D plus calcium is associated with a 37% lower risk of developing heart failure in postmenopausal adults classified as low-risk for heart failure at baseline. It is speculated that high-risk patients might not benefit from vitamin D plus calcium due to negative interactions with medications used to manage cardiovascular risk factors in this group (97307).

While vitamin D might be associated with a reduced risk of developing heart failure, most evidence suggests that vitamin D is not beneficial in patients already diagnosed with heart failure. In one small clinical trial, taking vitamin D3 50,000 IU weekly along with calcium citrate 800 mg daily for 6 months was not associated with an improvement in 6-minute walk test, timed get up and go test (TGUG), electrocardiographic variables, or health status when compared with placebo in adults with heart failure; mortality was not evaluated (97299,97300). In another clinical trial, taking vitamin D3 2000 IU daily did not decrease the risk of mortality when compared with placebo in New York Heart Association (NYHA) class 2 heart failure patients (16620).

Hyperparathyroidism-related bone loss. Limited evidence suggests that oral vitamin D is beneficial in patients with this condition.
^ Details: Taking vitamin D3 (cholecalciferol) orally seems to help decrease secondary hyperparathyroidism and bone turnover in females. In one study, supplementation with vitamin D3 increased serum levels of 25-hydroxyvitamin D, reduced levels of parathyroid hormone, and decreased production of markers of bone turnover (3463).

Respiratory tract infections. Clinical research shows that oral vitamin D supplementation reduces the risk for respiratory tract infections in children but not in adults or older adults. Some clinical practice guidelines recommend vitamin D supplements or fortified foods for children to potentially lower the risk of respiratory tract infections. It is unclear if oral vitamin D is beneficial for the treatment of respiratory tract infections.

^ Details: Prenatally, increased levels of vitamin D during pregnancy have been associated with a lower incidence of childhood respiratory tract infections (98197). However, two meta-analyses of small clinical studies and one meta-analysis of large clinical studies show no effect of prenatal vitamin D supplementation on the incidence of infant or childhood respiratory tract infections, including lower respiratory tract infections, when compared with control. Results related to risk of wheeze are conflicting (95910,95912,108438).

In children, most research shows that vitamin D supplementation reduces the risk of respiratory infections. A meta-analysis of clinical trials in children aged 1-16 years shows that taking vitamin D decreases the odds of having a respiratory tract infection by about 29% when compared with control, although this study also identified a high likelihood of publication bias (105721). Daily or weekly vitamin D doses seem to be more beneficial than single bolus doses, although the largest meta-analysis failed to confirm this result (84689,93766,105721). One clinical study in preterm Black infants shows that taking vitamin D3 (cholecalciferol) 200 IU daily and then 400 IU daily until 6 months of age does not affect the rate of respiratory tract infections, but does reduce wheeze by 11%, when compared with a normal diet without vitamin D supplementation (98191). This study may not have been powered to detect a difference in respiratory tract infection between groups.

Clinical practice guidelines from the Endocrine Society conditionally recommend, based on low certainty of evidence, empiric vitamin D supplementation from vitamin D fortified foods, vitamin D supplements, or vitamin formulations that contain vitamin D to potentially lower the risk of respiratory tract infections in children and adolescents aged 1 to 18 years. Empiric vitamin D supplementation is defined as supplementing with vitamin D above the Recommended Dietary Allowance without having tested serum vitamin D status (114502).

In adults, vitamin D supplementation does not seem to reduce the risk of respiratory infections. Observational research in adults has found that low levels of vitamin D are associated with worsened respiratory tract infection complications, and even increased mortality from respiratory tract infections in older adults ages 50-75 years (103659). However, meta-analyses of prospective clinical trials in adults show that taking vitamin D supplements 300-4000 IU daily for 7 weeks to 5 years or taking vitamin D 30,000-100,000 IU monthly or 96,000-120,000 IU every 2 months for 1-5 years does not reduce the odds of developing a respiratory infection or severe respiratory complications, such as emergency department utilization, hospitalization, and death, when compared with placebo. These results were similar in subgroup analyses evaluating overall vitamin D dose and baseline vitamin D status (84689,105721,114506). The largest single clinical trial, conducted in adults at least 60 years of age, shows that taking vitamin D3 (cholecalciferol) 60,000 IU once monthly for up to 5 years reduces the duration of total and severe respiratory symptoms by approximately 0.5 days, but does not reduce the incidence of respiratory illness or hospitalization, when compared with placebo (105726,110825).

A large meta-analysis of clinical studies in both children and adults shows that taking vitamin D does not reduce the risk of acute respiratory infections. While subgroup analyses revealed a reduced risk of acute respiratory infection in studies not exceeding 11 weeks' duration and with daily supplementation, these beneficial effects only persisted in studies considered to be of low quality (108435). Baseline vitamin D status was not assessed and the validity of these findings is limited by publication bias.

Vitamin D has also been evaluated for the treatment of acute respiratory infections. A large meta-analysis of clinical studies in both children and adults shows that taking vitamin D improves outcomes (e.g., sputum conversion, survival rate, therapeutic success, need for intensive care admission) by a small, but not clinically relevant, amount. In subgroup analyses, these beneficial effects only persisted in studies considered to be of low quality (108436). The validity of these findings is limited by publication bias.

Tooth retention. Oral vitamin D with calcium seems to help with tooth retention in the elderly population.

^ Details: A clinical trial in the elderly population shows that taking vitamin D3 (cholecalciferol) 700 IU daily along with calcium citrate malate 500 mg daily orally for 3 years reduces the risk of tooth loss by about 52% when compared with placebo (8816).

POSSIBLY INEFFECTIVE

Cardiovascular disease (CVD). Most research shows that taking vitamin D with or without calcium does not reduce the risk of CVD or CVD complications. There is some speculation that there might be modest benefit in the elderly, but more research is needed to confirm.

^ Details: Population research has found that low vitamin D levels, especially those below 15 ng/mL, are associated with an increased risk of developing CVD (15630,16618,93944,113588). However, taking vitamin D supplements does not seem to prevent CVD. The majority of evidence from clinical research, population research, and meta-analyses shows that vitamin D supplementation, with or without calcium, does not reduce the risk of mortality, myocardial infarction, cardiac-related hospitalizations, or stroke when compared with placebo in patients with or without CVD risk factors (91343,97296,97305,97308,98902,98916,99762,109729,110811,110827)(112021,112022,113588). The most reliable evidence comes from two meta-analyses of mainly high-quality clinical research investigating the effect of supplementation with vitamin D alone or with calcium for at least 1 year. These analyses show that vitamin D does not reduce major adverse cardiovascular events, stroke, CVD mortality, or all-cause mortality, regardless of baseline vitamin D level, vitamin D dosage, sex, formulation, or concomitant calcium supplementation (99762,109729). One large clinical trial in individuals at increased CVD risk shows that taking vitamin D as cholecalciferol 60,000 IU monthly modestly INCREASES the risk of CVD- and presumed CVD-related mortality (110827).

The effect of vitamin D supplementation in elderly adults on CVD outcomes has also been evaluated. In some research, taking vitamin D 700-1000 IU daily shows a trend towards lower CVD events and reduced risk of major adverse cardiovascular events in elderly patients (11931,98916,99762). However, another study in adults aged 70 years or older without a history of cardiovascular events and who are vitamin D replete at baseline shows that taking vitamin D 2000 IU daily for 3 years does not decrease the risk of coronary heart disease, heart failure, stroke, or hypertension when compared with placebo (113581). Larger, high-quality trials with prespecified primary outcomes are needed to determine whether or not vitamin D supplementation reduces CVD risk in elderly populations.

Critical illness (trauma). Taking vitamin D 540,000 IU as a single oral dose does not reduce death or hospital stay in critically ill patients. However, limited research suggests that taking a smaller dose of vitamin D long-term might have a modest benefit.

^ Details: The most robust evidence to date shows that correcting vitamin D levels in critically ill patients with vitamin D deficiency does not reduce mortality rate or duration of hospital stay. A large, multicenter clinical study in critically ill patients with vitamin D deficiency shows that administering a single, enteral dose of vitamin D 540,000 IU does not reduce 90-day all-cause mortality, duration of hospital stay, ventilator-free days, or other clinical outcomes when compared with placebo (103656). A previous meta-analysis of clinical research showed that vitamin D supplementation administered for a duration of 7 days or up to 6 months reduces the risk of death by 30% in critically ill hospitalized patients (95913). However, included studies were of low methodological quality, had high heterogeneity, assessed patients with and without vitamin D deficiency, and used variable vitamin D dose regimens and administrations methods (95913,95914).

Fractures. Most evidence shows that oral vitamin D alone does NOT prevent factures in people who do not have osteoporosis. Some research shows that taking vitamin D with calcium prevents fractures; however, more research is needed to determine who is most likely to benefit.
^ Details: Clinical research shows that taking vitamin D alone does not seem to prevent fractures in older adults. Most adults in these studies did not have osteoporosis, although osteoporosis status was unclear in some research (10140,12933,14282,38970,39015,84660,95822,97296,102145,104619)(109059,110827). However, several meta-analyses suggest that taking higher doses of vitamin D (about 800 IU daily) in combination with calcium might reduce overall fracture risk in older patients (38942,38970,39015,84660,102145,110809). One meta-analysis of clinical research in community- or long-term care-living males and females at least 65 years of age shows that taking vitamin D 800 IU daily in combination with calcium reduces the risk of hip and non-vertebral fractures by 25% and 20%, respectively, compared with placebo (110809). However, discrepancies exist which are possibly related to the dose and form of calcium used in combination with vitamin D and/or the patient population. Some research shows that taking vitamin D 800 IU daily in combination with calcium 1200 mg daily as tricalcium phosphate reduces fracture risk by up to 31% while taking vitamin D with calcium carbonate does not reduce fracture risk (12929,14282,16878,110809). Some individual clinical studies in postmenopausal females aged 50-79 years show that taking vitamin D plus calcium daily for 2-7 years does not prevent fractures when compared with placebo (14282,16878). Other confounding variables include the possible additional effects of hormonal therapy when given with calcium to postmenopausal adults and/or the inclusion of institutionalized patients with unclear osteoporotic status (95822,97296).

Most research shows that taking vitamin D in combination with omega-3 fatty acids does not prevent fractures. A large clinical study shows that taking vitamin D 2000 IU daily alone or with omega-3 fatty acids 1 gram daily and/or strength training three times weekly does not prevent fractures in adults over 70 years of age when compared with placebo (104619). Another large clinical trial shows that taking vitamin D 2000 IU daily, alone or with omega-3 fatty acids 1 gram daily, over approximately 5 years does not prevent overall fractures, nonvertebral fractures, or hip fractures in adults over 50 (males) or 55 (females) years old when compared with placebo. Although the osteoporosis status of the population was unclear, findings were consistent in adults at high fracture risk based on use of osteoporosis medications and/or a history of fragility fractures (109059).

As of April 2018, the US Preventative Services Task Force (USPSTF) recommends against supplementing with vitamin D 400 IU daily or less along with calcium 1000 mg daily or less for preventing primary fractures in community-dwelling postmenopausal adults. The USPSTF also concludes that there is insufficient evidence to determine whether supplementing with doses of vitamin D greater than 400 IU daily along with calcium doses greater than 1000 mg daily is safe or effective for preventing fractures in community dwelling adults without vitamin D deficiency, osteoporosis, or a history of fracture (95695). For information on patients WITH osteoporosis, refer to the Osteoporosis discussion.

There is limited research available regarding the effects of vitamin D supplementation for fracture prevention in children. Preliminary research in children aged 2 to 17 years with vitamin D insufficiency and one or more previous fractures shows that taking vitamin D 2000 IU daily with calcium 600 mg daily for 6 months modestly reduces the risk of forearm fractures over 12 months compared with children not given vitamin D or calcium (110820).

Hypertension. Overall, vitamin D does not seem to prevent or lower high blood pressure in most patients; however, it may lower blood pressure in hypertensive patients with vitamin D deficiency.
^ Details: Although population research has found that lower vitamin D levels are associated with a higher risk of developing hypertension, clinical research shows vitamin D supplementation does not prevent hypertension (15630). A large clinical trial in postmenopausal adults shows that taking vitamin D3 400 IU with calcium 1000 mg daily does not reduce the risk of developing hypertension (16714).

Most meta-analyses and clinical trials in patients with existing hypertension show that vitamin D supplementation does not lower blood pressure when compared with placebo, regardless of vitamin D formulation, dose, or duration of supplementation (16714,91340,96405,103657,104619,113583,113668). However, a meta-analysis of 5 clinical studies in patients with hypertension and vitamin D deficiency shows that supplementation with vitamin D reduces systolic and diastolic blood pressure by about 7 mmHg and 3 mmHg, respectively, when compared with placebo (100895). Another meta-analysis of 11 clinical trials in patients over 60 years of age with hypertension and vitamin D deficiency shows that taking vitamin D supplements significantly reduces systolic, but not diastolic, blood pressure when compared with placebo, especially in trials lasting more than 8 weeks where the total dose of vitamin D is above 400,000 IU (113592). An individual clinical study in patients with hypertension and vitamin D deficiency or insufficiency shows that taking vitamin D 50,000 IU weekly or 1000 IU daily reduces systolic blood pressure by about 6 mmHg and mean arterial pressure by about 4 mmHg, but does not affect diastolic blood pressure, when compared to baseline (108440).

Prostate cancer. Oral vitamin D does not appear to affect prostate cancer progression or cancer-related mortality.
^ Details: A meta-analysis of three clinical trials shows that vitamin D supplementation does not affect prostate cancer progression as measured by prostate-specific antigen (PSA), or mortality in patients with prostate cancer (99770).

Psychosis. Oral vitamin D does not seem to improve symptoms in patients with a functional psychotic disorder.
^ Details: A clinical study in adults with a functional psychotic disorder shows that taking oral vitamin D3 (cholecalciferol) 20,000 IU monthly for 6 months has no effect on total positive and negative syndrome scale score (PANSS) when compared with placebo. The majority of patients included in this study were deficient in vitamin D at baseline (107226).

Tuberculosis. Oral vitamin D seems to be ineffective for reducing the severity of tuberculosis or mortality from tuberculosis. Limited research suggests that vitamin D may have small benefits in newly diagnosed patients receiving tuberculosis treatment for the first time.
^ Details: Although population research has found that tuberculosis is associated with vitamin D deficiency, most clinical research shows that taking vitamin D does not improve clinical outcomes in people with tuberculosis infection. Meta-analyses and individual clinical studies show that taking vitamin D as a single 100,000 IU dose, or as 400 IU daily for 2 months, along with

standard care does not improve tuberculosis severity or reduce the risk of mortality in children or adults with tuberculosis, regardless of their baseline vitamin D levels (82570,82475,98913,103655,103668,104022).

However, some research has identified modest benefits in newly diagnosed patients receiving anti-tuberculosis treatment for the first time. A meta-analysis of clinical research in this population shows that taking vitamin D at a dose of 1000 IU daily or 600,000 IU monthly modestly increases the odds of sputum smear conversions by 1.2-fold, but does not improve the time to sputum smear conversions, when compared with placebo (98235). A small clinical study in treatment-naïve adults with low levels of serum vitamin D shows that taking calcitriol 0.25 mcg twice daily for up to 6 months, starting with anti-tuberculosis treatment initiation, decreases the time to sputum smear conversion and 50% lesion absorption by about 3 days when compared with not taking vitamin D (109045). Additionally, a small clinical study in children aged 6-18 years with vitamin D insufficiency receiving standard treatment for newly diagnosed pulmonary tuberculosis shows that taking vitamin D 1000 IU daily reduces the duration of fever and cough by 1 and 2 weeks, respectively, when compared with placebo (108437).

INSUFFICIENT RELIABLE EVIDENCE to RATE

Acne. It is unclear if oral vitamin D is beneficial for acne.
^ Details: A small clinical trial in patients with acne and vitamin D deficiency shows that taking cholecalciferol 1,000 IU daily for 2 months reduces the number of inflammatory lesions by about 35%, compared with 6% in those taking placebo. There was no effect on the total or non-inflammatory lesion count (106127). Other preliminary clinical research shows that taking alfacalcidol (One Alpha, LEO Company, Denmark) 0.25 mcg daily for 3 months modestly improves acne severity when compared with taking placebo (106128). In addition, population research has found that individuals with acne have modestly lower vitamin D levels than healthy controls. The odds of vitamin D deficiency were approximately three times higher in patients with acne when compared with healthy controls (106105).

Age-related cognitive decline. It is unclear if oral cholecalciferol is beneficial for preventing age-related cognitive decline.
^ Details: Pooled results of two large clinical sub-studies in community-dwelling adults aged 60 years or older show that taking cholecalciferol 2000 IU daily for 2-3 years has no effect on cognitive decline when compared with placebo. A subgroup analysis in Black patients suggests a modest effect of vitamin D when compared with placebo (108428).

Alzheimer disease. It is unclear if oral vitamin D is beneficial for this condition.
^ Details: Some population research has found that lower serum concentrations of vitamin D are associated with higher risk of Alzheimer disease, and also with decreased cognition. People with Alzheimer disease seem to have serum concentrations of vitamin D that are about 2.5 ng/mL lower than patients without Alzheimer disease (84672,103666). However, other population research has found that vitamin D deficiency (<25 nmol/L) or insufficiency (25-50 nmol/L) is not associated with increased risk of Alzheimer disease (100899).

Asthma. Oral vitamin D might reduce asthma exacerbations in adults and children with mild, but not severe or persistent, asthma. Vitamin D supplementation during pregnancy or the first 6 months of an infant's life does not seem to prevent the development of asthma later in infancy or childhood.
^ Details: Population research in patients with asthma suggests that low vitamin D levels are associated with an increased risk of exacerbations and increased need for medication therapy (94693). However, findings from clinical research are mixed. Some meta-analyses of clinical trials in adults and children with asthma show that taking vitamin D for 3 months to 1 year reduces the rate of asthma exacerbations by 31% to 36% when compared with control (92690,94686). However, findings from more recent meta-analyses show that vitamin D supplementation does not reduce the risk of asthma exacerbations when compared with placebo (109728,109732,110833). The reasons for this discrepancy are not clear. However, some clinical research suggests that vitamin D supplements might only prevent asthma in people with non-persistent asthma (92690,94685,94686,94688,104020). Also, many studies are small and do not represent patients with severe asthma exacerbations (92690,94687). Baseline levels of vitamin D may play a role. A clinical study in children aged 6-16 years with persistent asthma and low vitamin D levels shows that taking vitamin D 4000 IU daily for 48 weeks does not reduce severe asthma exacerbations when compared with placebo (104020). However, a meta-analysis including this study shows that taking vitamin D does reduce risk of asthma exacerbations in children with low baseline vitamin D levels (109728). One meta-analysis shows that taking vitamin D seems to modestly improve pulmonary function when compared with placebo (109732). Vitamin D doses have varied, with oral doses of 500-4000 IU daily, 1000 IU once weekly, 60,000 IU once monthly, 120,000 IU every 2 months, 100,000 IU 14 days apart, or 100,000 to 600,000 IU as a bolus dose followed by 400-4000 IU daily (92690,94686,104020,109728,110833).

Vitamin D supplementation for the prevention of asthma in infants has also been evaluated. A meta-analysis of 4 large clinical studies shows that taking vitamin D 400-1200 IU daily for the first 6 months of life does not reduce the risk of asthma or wheezing at 6-30 months of age when compared with control (112031).

Vitamin D supplementation during pregnancy has also been evaluated (97306,99763,102146,112031). A meta-analysis of 3 large clinical studies shows that taking vitamin D 2800-4400 IU daily during the 2nd and 3rd trimesters of pregnancy reduces the risk of recurrent wheezing by 23% but does not reduce the risk of asthma diagnosis within the first 3-6 years of life when compared with vitamin D 400 IU daily (112031). Some research suggests that the dose of vitamin D plays a role. A meta-analysis shows that prenatal vitamin D 800 IU daily reduces the odds of wheeze or asthma by 32%, while lower or higher vitamin D doses were not beneficial (103661).

Athletic performance. It is unclear if oral vitamin D is beneficial for athletic performance.
^ Details: One small clinical trial in athletes shows that taking vitamin D 20,000 or 40,000 IU once weekly for 2 doses does not affect performance on vertical jumps, sprints, or leg and bench presses when compared with placebo (98188). Another small clinical trial in professional rugby players shows that taking vitamin D3 (cholecalciferol) 50,000 IU once every two weeks over 12 weeks does not improve sprinting speed or the ability to perform bench presses, bench pulls, and chin-ups when compared with placebo (98189). Also, most research shows that taking vitamin D does not improve measures of cardiorespiratory fitness. One small study in young males undergoing resistance training shows that taking vitamin D 8000 IU daily for 12 weeks does not improve cardiorespiratory fitness compared with taking placebo (110812).

Atopic dermatitis (eczema). Most research shows that oral vitamin D reduces eczema severity in children. However, most research shows that oral vitamin D, taken during pregnancy or infancy, does not prevent eczema in the child.
^ Details: A meta-analysis of eight moderate-quality clinical trials in children shows that taking vitamin D, most commonly 1000-2000 IU daily for 4-12 weeks, modestly reduces severity of eczema when compared with placebo (109728). Most of the children in these studies were also given conventional medications.

Oral vitamin D has also been evaluated for eczema prevention. A meta-analysis of two clinical studies shows that consuming

vitamin D 2800-4400 IU daily during the 2nd and 3rd trimesters of pregnancy is not associated with a reduced risk for eczema in children during the first 3 years of life when compared with vitamin D 400 IU daily (97306). Another meta-analysis of five large clinical studies shows that prenatal or infant vitamin D supplementation does not reduce the risk of developing eczema when compared with low-dose vitamin D, placebo, or no intervention (108438).

Atrial fibrillation. It is unclear if oral vitamin D is beneficial for preventing atrial fibrillation.
^ Details: A large clinical trial in adults without cardiovascular disease shows that taking vitamin D 2000 IU daily for an average of 5 years does not reduce the incidence of atrial fibrillation when compared with placebo or fish oil 840 mg daily (105209). However, observational research in postmenopausal adults with osteoporosis found that vitamin D supplementation is associated with a lower occurrence of atrial fibrillation when compared with not taking vitamin D (98922). Also, one large observational study in vitamin D-deficient patients with no history of atrial fibrillation has found that vitamin D supplementation for at least 6 months is associated with up to a 16% decreased risk of atrial fibrillation when compared with not taking vitamin D. There were also modest improvements in atrial fibrillation-free survival. In males 65 years and older with hypertension or diabetes at baseline, blood levels of at least 30 ng/mL following vitamin D supplementation were associated with decreased risk of atrial fibrillation; a post-supplementation blood level of 21-29 ng/mL was not associated with decreased risk (109043).

Attention deficit-hyperactivity disorder (ADHD). It is unclear if oral vitamin D is beneficial for ADHD.
^ Details: A small clinical trial in children 5-12 years of age with ADHD and vitamin D insufficiency shows that taking vitamin D 2000 IU daily along with methylphenidate for 8 weeks seems to improve parental ratings of evening, but not morning or overall, symptoms of inattentiveness and impulsivity when compared with methylphenidate alone. Vitamin D insufficiency was defined as levels less than 30 ng/mL (98196). Based on these and other preliminary findings, Guidelines from The World Federation of Societies of Biological Psychiatry (WFSBP) and Canadian Network for Mood and Anxiety Treatments (CANMAT) Taskforce state that vitamin D in doses of 1500 to 4000 IU daily is weakly recommended for adjunctive use in children with ADHD, especially those with insufficient intake or skin exposure to sunlight (110318).

Autism spectrum disorder. It is unclear if oral vitamin D is beneficial for autism spectrum disorder.
^ Details: A small clinical study in children aged 2.5-8 years with autism spectrum disorder shows that taking vitamin D 2000 IU daily for 12 months modestly reduces irritability and hyperactivity when compared with placebo (99767).

Autoimmune thyroiditis. It is unclear of oral vitamin D improves outcomes in patients with Hashimoto's thyroiditis.
^ Details: A meta-analysis of 12 clinical trials in patients with Hashimoto's thyroiditis shows that taking vitamin D for at least 12 weeks increases free triiodothyronine (T3) and thyroxine (T4) levels, and reduces levels of thyroid stimulating hormone, thyroglobulin antibody, and anti-thyroid peroxidase antibody, when compared with placebo or no treatment (113593).

Bacterial vaginosis. It is unclear if oral vitamin D is beneficial for bacterial vaginosis.
^ Details: Preliminary clinical research in females at high risk for sexually transmitted disease shows that taking vitamin D along with standard therapy for bacterial vaginosis does not reduce the prevalence of bacterial vaginosis when compared with placebo. Patients in this study had been treated with metronidazole 500 mg orally twice daily for 7 days along with vitamin D3 (cholecalciferol) 50,000 IU each week for 4 weeks and then every 4 weeks for the remaining 20 weeks (91348).

Breast cancer. It is unclear if oral vitamin D is beneficial for the prevention of breast cancer.
^ Details: Some population research evaluating intake of calcium plus vitamin D suggests that higher vitamin D intake is not associated with a reduced risk of breast cancer in premenopausal or postmenopausal adults (15631). Similarly, a large observational study in females with a biological sibling with breast cancer has found that taking vitamin D recently or prior to enrollment is not associated with a reduced risk of breast cancer when compared with nonrecent vitamin D use or never taking vitamin D, respectively (107215). However, other research found that higher vitamin D intake is associated with a 17% reduced risk of breast cancer in premenopausal and perimenopausal, but not postmenopausal, adults (39001). Observational research has also examined the association between blood levels of vitamin D and risk of developing breast cancer. A meta-analysis found that those with serum levels of about 52 ng/mL had a 50% lower risk of developing breast cancer when compared with those with serum levels of less than 13 ng/mL. This high serum level of vitamin D corresponds to a high dose of about 4000 IU daily (16049). Other observational research has found that baseline vitamin D levels of more than 20 ng/mL are associated with a 48% reduced risk of developing breast cancer over approximately 9 years in Latina females in the US when compared with levels below 20 ng/mL; however, this association was not present in Black females (109058).

Despite the contradictory findings from observational research, results from clinical research are generally negative. Evidence from one large-scale clinical trial (Women's Health Initiative) shows that postmenopausal adults who take vitamin D3 (cholecalciferol) 400 IU daily plus calcium 1000 mg daily for 7 years do not have a significantly reduced risk of developing breast cancer (16715,98895). Also, a meta-analysis of two large-scale clinical trials, which did not include the Women's Health Initiative trial, shows that taking vitamin D 800-1000 IU daily, alone or with calcium, for 3-4 years does not reduce the incidence of breast cancer in postmenopausal adults, although there was a trend towards reduced risk with higher doses of vitamin D supplementation (97301). While vitamin D and calcium supplementation during the intervention period of the Women's Health Initiative trial was not associated with a reduced risk of developing breast cancer or ductal carcinoma in situ (DCIS), a precursor to breast cancer, a secondary post-hoc analysis of the data shows that supplementation reduces the risk of developing DCIS by 18% over a median follow-up of 19 years (107216). Additional research is needed regarding an optimal dose of vitamin D, timing of initiation, and whether any benefit is affected by menopausal status.

Bronchopulmonary dysplasia. Limited research suggests that vitamin D deficiency is linked with bronchopulmonary dysplasia in the infant.
^ Details: Observational research has found that vitamin D deficiency at birth is associated with about a 2-fold increased odds of developing bronchopulmonary dysplasia (104021). However, it is unclear if vitamin D supplementation is beneficial.

Cancer. Vitamin D does not seem to reduce overall cancer risk. However, some research shows that vitamin D might slightly reduce the risk of metastatic cancer and cancer-related mortality.
^ Details: There is interest in vitamin D for cancer PREVENTION, as observational research suggests that higher vitamin D intake and higher 25-hydroxyvitamin D levels are associated with a lower risk of cancer (111150). While individual clinical trials evaluating vitamin D for cancer have produced inconsistent findings, most meta-analyses and clinical trials show that taking vitamin D3 (cholecalciferol) or vitamin D2 (ergocalciferol) alone or with calcium does not significantly reduce the risk of developing cancer (15629,91344,93943,97296,98916,104024,104618,110811). However, vitamin D supplementation might reduce the risk of metastatic cancer and cancer-related mortality. A large clinical trial shows that taking vitamin D3 2000 IU daily for a median of 5.3 years slightly reduces the risk of advanced metastatic or fatal cancers when compared with placebo (104618). Additionally, meta-analyses of several large clinical trials show that taking vitamin D 400-4000 IU daily, with or without calcium,

for 1-7 years reduces the risk of cancer-related mortality by 12-13% when compared with control, while intermittent bolus dosing of vitamin D at high doses for 1-5 years does not appear to reduce the risk of cancer-related mortality (104024,111149).

The role of vitamin D in cancer TREATMENT is unclear. A meta-analysis of clinical and observational research suggests that supplementation of vitamin D after a cancer diagnosis is associated with a modest improvement in overall survival, but not progression-free or cancer-specific survival (109726). Doses used in clinical research ranged between 1200 IU and 8000 IU daily or 100,000 IU every 50 days, after surgery and/or during treatment (99195,99196,109726). Other clinical research in patients with luminal gastrointestinal cancers shows that taking vitamin D 2000 IU daily does not reduce the risk of relapse when compared with placebo (99195). It is unclear which, if any, types or stages of cancer respond best to vitamin D, and what dose of vitamin D is optimal.

Child growth. It is unclear if oral vitamin D is beneficial for improving infant growth or bone structure.
^ Details: Meta-analyses and individual clinical trials show that vitamin D supplementation during pregnancy modestly increases length at birth and bone mineral density at up to 6 years of age when compared with control, usually placebo or vitamin D 400 IU daily. However, there was no effect on length in the infant up to one year of age, weight at birth or up to one year of age, head circumference at birth or up to 6 years of age, bone mineral content at up to 6 years of age, or neonatal bone mineral density, bone mineral content, bone area, or femur or humoral length (98198,109737,112028). In the available research, vitamin D was taken in doses of 200 IU to 4400 IU daily, 4200 IU to 50,000 IU weekly, 50,000 IU every 2 weeks, or 60,000 IU every 4-8 weeks, starting from the early to late stages of pregnancy and usually continued until birth (98198,109737).

Chronic kidney disease (CKD). It is unclear if oral vitamin D is beneficial in patients with CKD. Most research suggests that it does not reduce the risk for adverse cardiovascular events.
^ Details: Population research in patients on dialysis has found that vitamin D levels less than 17.8 ng/mL are associated with a higher risk of all-cause mortality compared with higher levels (16619). A meta-analysis and individual clinical studies show that vitamin D and vitamin D analogues decrease parathyroid hormone (PTH) levels and urine protein levels in people with CKD (84376,84377,84628,98233,98236). However, taking vitamin D does not appear to decrease the risk of death or parathyroidectomy in CKD patients (84376,84377). Also, taking vitamin D increases the risk for hypercalcemia and hyperphosphatemia in this patient population (84376,84377,98236).

Vitamin D has also been evaluated for the prevention of cardiovascular events in adults with CKD. Observational research has found that vitamin D deficiency in patients with CKD is associated with adverse cardiovascular events. However, vitamin D supplementation does not seem to be beneficial. One clinical study shows that taking paricalcitol, an active form of vitamin D, titrated to maintain adequate serum calcium levels, for 48 weeks does not affect the size of the left ventricle or heart function when compared with placebo (98233). Other clinical research in Japanese patients on hemodialysis for CKD shows that adding alfacalcidol, another active form of vitamin D, 0.5 mcg daily to standard treatment for 4 years does not affect mortality or cardiovascular events such as myocardial infarctions, stroke, aortic dissection, and others compared to standard treatment only (98920). Also, a large clinical trial in patients with CKD shows that taking vitamin D as cholecalciferol 2000 IU daily, alone or with omega-3 fatty acids 1 gram daily, does not affect major cardiovascular events or invasive cancer when compared with placebo (110811).

Vitamin D has also been evaluated for musculoskeletal health in adults with CKD. A small clinical study shows that taking cholecalciferol 4000 IU daily, with or without physical activity, for 3 months improves bicep strength, but not back flexibility or aerobic fitness capacity, when compared with baseline. In patients taking cholecalciferol in combination with physical activity, musculoskeletal health was similar when compared with cholecalciferol alone (108431). However, this study was inadequately powered to detect a difference between groups, and it is unclear if the improvement from baseline differed between groups.

Vitamin D has also been evaluated for the improvement of iron status in adults with CKD and secondary hyperparathyroidism. Clinical research shows that taking Vitamin D as cholecalciferol (Vitamin D3 Forte Renapharma) 8000 IU daily for 12 weeks does not improve iron status compared with taking placebo. However, a sub-analysis shows that hemoglobin levels are modestly improved in patients with a low Vitamin D status at baseline suggesting that Vitamin D might improve iron availability in these patients (110819).

Chronic obstructive pulmonary disease (COPD). It is unclear if oral vitamin D is beneficial for COPD; benefits may be limited to patients with vitamin D deficiency.
^ Details: Population research has found an association between low vitamin D levels and reduced lung function, increased risk of developing COPD, and worsening COPD severity (17685,96401). In contrast, 2 meta-analyses of clinical research in adults with COPD and with or without vitamin D deficiency show that oral vitamin D does not have beneficial effects on mortality, rate of COPD exacerbations, pulmonary function, or most measures of symptom severity when compared with placebo (109732,112485).

However, other research suggests that vitamin D may be beneficial in patients with vitamin D deficiency. Some clinical research in patients with moderate to severe COPD and severe vitamin D deficiency shows that taking a specific vitamin D supplement (D-Cure, Laboratoires SMB) 100,000 IU once every 4 weeks for 1 year seems to reduce the rate of exacerbations by 43% when compared with placebo (98194).

Cognitive function. It is unclear if oral vitamin D is beneficial for cognitive function.
^ Details: Population research has found that low vitamin D levels are associated with worse cognitive performance and cognitive decline when compared to high vitamin D levels in healthy adults (84672,95916). However, the effect of vitamin D supplementation on cognitive function is unclear. One small meta-analysis of clinical research shows that vitamin D supplementation does not improve cognitive function (95916). However, the included trials evaluated a widely heterogeneous study population and utilized variable measures of cognitive function.

Cognitive impairment. It is unclear if oral vitamin D is beneficial for older adults with mild cognitive impairment.
^ Details: A small clinical study in older adults with mild cognitive impairment shows that taking vitamin D3 10,000 IU three times weekly for 20 weeks in addition to exercise and cognitive training does not improve cognitive function when compared with placebo and exercise with or without cognitive training. However, most participants had sufficient serum vitamin D levels at baseline (112489).

Colorectal cancer. It is unclear if oral vitamin D is beneficial for the treatment or prevention of colorectal cancer.
^ Details: Epidemiological research has found that a higher serum vitamin D level is associated with decreased risk of mortality and increased survival in patients with colorectal cancer (16101,99196). However, it is unclear whether vitamin D supplementation improves survival in patients with colorectal cancer, as research has generally involved small populations and

results are somewhat conflicting. A subgroup analysis of one clinical study shows that taking vitamin D 2000 IU daily does not reduce the risk of relapse or death, death due to any cause, or relapse over 5 years when compared with placebo in patients with colorectal cancer (99195). However, this subgroup may have been underpowered to detect between-group differences. Another small clinical trial in patients with advanced or metastatic colorectal cancer shows that taking high-dose vitamin D 8000 IU daily during the first cycle of chemotherapy, and then 4000 IU daily for subsequent cycles, does not increase median progression-free survival when compared with taking vitamin D 400 IU daily. However, patients taking high-dose vitamin D were 36% less likely to experience disease progression or death during follow-up when compared with patients taking the lower dose of vitamin D (99196). This latter result suggests that high-dose vitamin D supplementation might be beneficial for patients with advanced or metastatic colorectal cancer, but larger, multicenter studies are needed to confirm.

The role of vitamin D in colorectal cancer prevention has also been investigated. A meta-analysis of epidemiological research has found that a higher serum vitamin D level is associated with a decreased colorectal cancer risk; however, sub-analyses suggest that this association only occurs in females, not males (109740). Most studies have evaluated vitamin D supplements in combination with calcium; the effects of vitamin D supplementation alone are unclear. One meta-analysis of clinical research suggests that taking vitamin D plus calcium is not associated with a decreased incidence of colorectal cancer in people with a low baseline risk of colorectal cancer (39042). Another meta-analysis of clinical research shows that vitamin D supplementation, with or without calcium, does not reduce the incidence of colorectal cancer or colorectal adenomas (109730). Additionally, a large clinical trial suggests that postmenopausal adults who take calcium 1000 mg daily plus vitamin D 400 IU daily do not have a reduced risk of developing colorectal cancer (14290,98895). One clinical study shows that taking calcium supplements reduces the risk of colorectal adenomas, but not in people with lower than average vitamin D levels (12118).

Coronavirus disease 2019 (COVID-19). The evidence is mixed with respect to oral vitamin D supplementation for the prevention and treatment of COVID-19. Also, although some observational research has suggested a correlation between vitamin D status and risk for COVID-19, not all studies agree, and this association may be due to other confounders such as age and comorbidities.

^ Details: Clinical and observational research has evaluated vitamin D supplementation for COVID-19 prevention. A preliminary clinical trial shows that oral vitamin D 800 IU or 3200 IU daily for 6 months in individuals with lower serum levels of vitamin D does not reduce the risk of COVID-19 or any respiratory tract infection when compared with no vitamin D supplementation (109721). However, groups were not matched for baseline vitamin D status and many individuals in the untreated group took their own vitamin D supplements. Two meta-analyses of clinical and observational studies show no relationship between vitamin D supplementation and the primary prevention of COVID-19 infection, although baseline vitamin D status is unclear (109040,112488), However, an umbrella meta-analysis of clinical and observational research suggests that vitamin D deficiency is associated with a greater risk of COVID-19 infection, COVID-19 severity, and mortality (114583). Also, a quasi-experimental cohort study in Italian adults who had supplemented with vitamin D in the 3 months prior to COVID-19 diagnosis found no reduction in risk for hospitalization, as well as a trend towards increased risk for in-hospital mortality, when compared with those who had not received vitamin D supplementation (104625). However, some research disagrees. Clinical research in highly exposed healthcare workers shows that taking vitamin D as cholecalciferol 4000 IU daily for 30 days reduces the risk of COVID-19 infection by 77% when compared with placebo (109052). Also, in the UK population, observational research has found that habitual use of vitamin D supplements between 2006 and 2010 is associated with a 34% lower risk of COVID-19 infection. This finding remained positive after adjusting for baseline health status and use of other micronutrients (104717). A meta-analysis of 16 studies in various populations shows that vitamin D reduces the risk of COVID-19 infection by 40% to 60% (113590).

Vitamin D supplementation as treatment in outpatients with COVID-19 has also been evaluated. Preliminary clinical research discussed in a systematic review suggests that supplementation might be associated with less severe symptoms; however, there is inadequate information to determine if supplementation in patients with mild symptoms is associated with reduced hospital admission (109040). Conversely, a large cross-sectional study found an association between pre-hospital supplementation and increased risk for COVID-19, as well as increased rates of death and/or invasive mechanical ventilation. However, this association was no longer significant after adjusting for sex, age, and comorbidities (107205).

Most research on vitamin D supplementation has been conducted in children and adults hospitalized with COVID-19. However, meta-analyses of clinical and observational research in these patients provides conflicting results on whether vitamin D supplementation as single dose or multiple doses is associated with a reduced risk of mortality, length of hospitalization, admission to the intensive care unit (ICU), or need for ventilation when compared with placebo or standard care alone (109040,109733,112488,112490,113579,114488,114583). The quality of evidence of most individual clinical trials is low to moderate due to a lack of placebo and blinding in many of the studies. Most individual studies evaluating single doses of vitamin D, administered either after diagnosis or after hospital admission, have not identified benefit for major outcomes, such as hospital length of stay, in-hospital mortality, or ICU admission. Many of these studies were small, low quality, and conducted in heterogenous populations, with doses ranging from 80,000 IU to 500,000 IU (104624,104626,107208,108434,109051,112490). Additionally, meta-analysis of 11 clinical studies primarily in patients hospitalized with mild to severe COVID-19 shows that taking vitamin D does not reduce the risk of all-cause mortality, regardless of baseline vitamin D status, when compared with control. However, sensitivity analysis shows that multiple administration of vitamin D reduces the risk of all-cause mortality by 33% when compared with single administration (114488). One small, unblinded study in at-risk older adults admitted to the hospital or living in a long-term care facility shows that taking a single dose of 400,000 IU within 72 hours of diagnosis modestly improves survival at 14 days, but not 28 days, when compared with 50,000 IU (109039). The evidence related to multi-dose regimens in hospitalized patients is mixed. A cohort study shows that giving calcifediol 0.532 mg at hospital admission, followed by calcifediol 0.266 mg on days 3 and 7 and then weekly until discharge or ICU admission, reduces odds of in-hospital death within 30 days by 78% when compared with those not given vitamin D (106099). A small clinical trial in patients with vitamin D deficiency shows that taking vitamin D 25,000 IU daily for 4 days and then weekly for up to 6 weeks reduces length of hospital stay and duration of supplemental oxygen by 4 days and 3 days, respectively, and also reduces disease severity and ICU admission after 7 days (109050). A small, unblinded study in patients with suboptimal vitamin D status and mild to moderate COVID-19 shows that taking vitamin D3 5,000 IU daily for 2 weeks reduces the time to recovery from cough and loss of taste by 2.9 and 5.5 days, respectively, when compared with vitamin D3 1,000 IU daily. However, there was no difference in time to recovery from fever, dyspnea, body aches, or other symptoms (106117). However, some research disagrees. A small unblinded study has found that although vitamin D status at 9 days is negatively associated with the number of bed days, vitamin D 50,000 IU on days 1 and 8 does not affect the number of bed days, time to discharge, or ICU admission when compared with no supplementation (109047). An additional preliminary study in patients with severe COVID-19 and low blood levels of vitamin D shows that taking vitamin D (Plivit D3, Pliva) 10,000 IU daily while in the ICU or for at least 14 days does not reduce the number of days on respiratory support, or in the ICU or hospital, or improve survival rates when compared with no supplementation

(110813). A small, open-label study in patients hospitalized with COVID-19 pneumonia shows that taking alfacalcidol 2 mcg orally daily dose not reduce the duration of treatment or length of hospital stay (113579).

The relationship between vitamin D levels and COVID-19 has also been evaluated in pregnant patients. A meta-analysis of observational research suggests that, while lower vitamin D levels are not associated with an increased risk of COVID-19, the presence of severe COVID-19 symptoms in pregnant patients may be linked to lower vitamin D levels when compared with non-severe COVID-19 symptoms (112025).

Limited research has investigated the effect of vitamin D in combination with other ingredients. Preliminary clinical research in patients with mild to moderate COVID-19 shows that taking vitamin D3 (Davalindi, Medical Union Pharma, Cairo, Egypt) 2000 IU daily in combination with black seed (Baraka, Pharco Pharmaceuticals, Cairo, Egypt) 900 mg twice daily for 14 days modestly reduced the severity of some symptoms, including cough, diarrhea, fatigue, and pharyngitis, as well as the percent patients with viral positivity at day 7, but not headache, rhinorrhea, anosmia, or shortness of breath, or vomiting, when compared to standard care alone. However, taking vitamin D alone did not provide significant benefit (110265).

The validity of individual studies is limited by generally poor designs. More research is needed to evaluate varying vitamin D dosing levels and schedules, as well as evaluated outcomes, and whether patients with vitamin D insufficiency are more likely to benefit from vitamin D supplementation.

The relationship between vitamin D status and risk of COVID-19 infection or severe disease is unclear. Despite some observational research suggesting that low vitamin D levels are associated with an increased risk for COVID-19 mortality, development of severe disease, such as pulmonary involvement, and extended hospitalization or admission to intensive care (107206,107207,108434), several meta-analyses of observational research as well as individual observational studies have found that vitamin D deficiency in adults is not associated with a higher risk for COVID-19 infection or with disease severity or mortality (104627,107208,107209). Additional observational research has found no association between vitamin D status and hospital length of stay, need for mechanical ventilation, mortality, or experiencing persistent feelings of fatigue or reduced exercise tolerance, otherwise known as "long-COVID" (106102,106116,106120,107206). However, one meta-analysis has found that when compared with mild disease, 65% more individuals with severe disease had vitamin D deficiency. Also, vitamin D insufficiency, defined as blood levels less than 30 ng/mL, is associated with a more than 80% increased chance of hospitalization or mortality due to COVID-19. Notably, many of these studies did not control for patient age or other comorbidities (104627). A more recent observational study has found that vitamin D status in patients with severe COVID-19 symptoms is inversely correlated with both ICU admission and death, with a 1% reduction in risk of ICU admission and 4% reduction in risk of death for every 1 ng/mL increase in 25-hydroxyvitamin D (106112).

In one individual observational study, the association between vitamin D status and COVID-19 infection is no longer significant after adjusting for socioeconomic status, age, health status, body mass index, ethnicity, and other covariates (104628). In contrast, a small observational study of adults admitted to the hospital with COVID-19 has found that low vitamin D levels are associated with an increased risk of mechanical ventilation and in-hospital mortality, even after adjustment for ethnicity and pre-existing conditions, such as cardiovascular disease, respiratory disease, and diabetes. However, this study is small and does not adjust for socioeconomic factors (105720). Also, another individual observational study has found that the likelihood of testing positive for COVID-19 is increased in Black, but not White, adults who had a vitamin D level of 30-40 ng/mL at some point in the past year when compared with a level of at least 40 ng/mL, with risk decreasing as levels increased from 30 ng/mL to 40 ng/mL (104716).

Patients should be encouraged to maintain adequate vitamin D levels. A joint task force has recommended 400-1000 IU (10-25 mcg) daily for those who are unable to spend 15-30 minutes in the sun each day (103659,104629).

Crohn disease. Limited evidence suggests that vitamin D reduces relapses in patients with Crohn disease.
^ Details: A meta-analysis of small, low-quality clinical studies in patients with IBD, including Crohn disease and ulcerative colitis, shows that taking high- or low-dose vitamin D for up to 1 year reduces the rate of relapse when compared with control (98915). The validity of these findings is limited by the heterogeneity of the included studies.

Dementia. It is unclear if oral vitamin D is beneficial for dementia.
^ Details: Population research has found that patients with any type of dementia have serum concentrations of vitamin D that are about 2.5 ng/mL lower than patients without dementia (84672). However, it is unclear if vitamin D supplementation is beneficial.

Depression. It is unclear if oral vitamin D is beneficial for treating depression. Vitamin D does not seem to prevent the development of depression.
^ Details: The role of vitamin D in the treatment of depression is unclear. Earlier meta-analyses of clinical research show that vitamin D supplementation does not improve overall symptoms of depression. However, some subgroup analyses suggest that vitamin D may be beneficial for improving the symptoms of depression in people with clinically significant symptoms, as well as those with baseline vitamin D deficiency (97295,97298). More recent meta-analyses of several clinical trials, that include some of the same studies, show that vitamin D modestly improves symptoms of depression in adults; however, subgroup analysis suggests that vitamin D does not improve depressive symptoms in older adults (110832,112786). These analyses are mixed over whether baseline vitamin D status affects results (110832,112786) and one of these analyses shows no evidence that the type of depression affects findings (110832). Another meta-analysis of generally small clinical trials in patients with type 2 diabetes and depression shows that taking vitamin D modestly improves depressive symptoms when compared with placebo or no intervention (110814). Although, results of an individual clinical trial in patients with type 2 diabetes are in contrast (108423). The evaluated research implemented one-time doses of 150,000-500,000 IU, as well as daily and weekly doses ranging between 400-5000 IU daily or 5000-100,000 IU weekly for 6 weeks to 2 years, with the most evidence of benefit related to one-time high doses. Cholecalciferol was the most common form of vitamin D used (97295,97298,108423,110814,110832,112786). Significant heterogeneity between studies and the wide variability in dosing strategies limit the validity of these findings, as well as identification of an effective dose or target population.

Vitamin D has also been evaluated for the prevention of depression. One large clinical study (VITAL-DEP) in healthy patients 50 years and older shows that taking vitamin D 2000 IU daily for about 5.3 years does not prevent depression or depressive symptoms, or improve mood, when compared with placebo (103670). An analysis of a cohort of patients from the VITAL-DEP trial also shows that taking vitamin D 2000 IU daily for 2 years does not reduce the risk of major depressive disorder or improve mood scores in patients with subthreshold depression or risk factors for late-life depression when compared with placebo

(112032). In addition, a meta-analysis of several clinical studies suggests that vitamin D supplementation does not prevent depression based on subgroup analysis of patients without depression at baseline (112786).

Based on these and other preliminary findings, Guidelines from The World Federation of Societies of Biological Psychiatry (WFSBP) and Canadian Network for Mood and Anxiety Treatments (CANMAT) Taskforce state that vitamin D in doses of 1500 to 4000 IU daily is weakly recommended for adjunctive or monotherapy use in patients with depression, especially those with insufficient intake or skin exposure to sunlight (110318).

Diabetes. Oral vitamin D might improve glycemic indices in some patients with type 2 diabetes and gestational diabetes. It is unclear if oral vitamin D is beneficial for the prevention of type 1 or gestational diabetes. It is also unclear if intramuscular vitamin D is beneficial for the treatment of gestational diabetes.
^ Details: Most meta-analyses of mainly small clinical trials show that vitamin D supplementation is beneficial for measures of glycemic control in patients with diabetes. However, the best evidence of benefit is in patients with baseline vitamin D deficiency. Three meta-analyses of small trials in patients with type 2 diabetes show that vitamin D supplementation reduces glycated hemoglobin (HbA1c) by 0.20% to 0.25%, and improves serum insulin, fasting blood glucose, and measures of insulin resistance when compared with control (96403,110822,112487). Supplemental vitamin D seems to be most beneficial in patients with baseline vitamin D deficiency (96403,110822,112487). Furthermore, correlation analysis suggests an inverse relationship between serum vitamin D levels and serum insulin, fasting blood glucose, and measures of insulin resistance (112487). However, another meta-analysis of small trials in patients with vitamin D insufficiency or deficiency and type 2 diabetes shows that oral vitamin D modestly improves fasting blood glucose and postprandial blood glucose, but not HbA1c, when compared with control (107210).

Most of the evaluated research implemented daily or weekly doses of vitamin D for 4-48 weeks (96403,107210,110822). However, one meta-analysis of clinical research in patients with diabetes shows that vitamin D improves HbA1c, insulin resistance, and insulin measures in studies lasting less than 6 months, but not in studies lasting longer than 6 months (99764). An additional meta-analysis suggests that most evidence of benefit is associated with doses of more than 2000 IU daily for 4-12 weeks (110822). One small, long-term clinical study in middle-aged and elderly patients with type 2 diabetes shows that taking vitamin D 800 IU daily for 30 months reduces insulin levels and insulin resistance when compared with no supplementation. However, there was no effect on HbA1c or fasting blood glucose levels (109734). Thus, conflicting results may be related to the dose and duration of vitamin D supplementation, as well as patient characteristics at time of study entry, such as vitamin D status, baseline HbA1c levels, obesity, and medication regimen (97304,99764,109734,110822).

Vitamin D has been evaluated for the prevention of type 1 diabetes. There is preliminary evidence that daily vitamin D supplementation (form not specified) in infants during the first year of life is associated with a reduced incidence of type 1 diabetes development later in life (10139). Also, a meta-analysis of population studies has found that vitamin D supplementation in early childhood is associated with a 29% reduced risk of developing type 1 diabetes later in life (84225).

Vitamin D has been evaluated in patients with gestational diabetes. Some research has evaluated the effects of oral or intramuscular vitamin D on glycemic indices. The evidence from clinical research comparing vitamin D with placebo is mixed. Most studies show modest evidence of benefit for some markers of glycemic control. One clinical trial shows that vitamin D modestly reduces levels of insulin, as well as measures of insulin resistance, with no effect on fasting blood glucose (106125). However, other clinical research shows that taking vitamin D modestly reduces levels of fasting blood glucose and HbA1c, with no effect on insulin measures (106126). Two other trials show that taking vitamin D modestly improves all measures of glycemic indices (101775,106122). Additionally, a large clinical trial shows that taking vitamin D 1600 IU daily modestly reduces fasting blood glucose when compared with vitamin D 400 IU daily (112020). Some clinical research has also evaluated the effects of oral vitamin D on lipid indices in patients with gestational diabetes. Although some individual clinical research disagrees (106126), most research shows that taking vitamin D modestly improves levels of low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, and triglycerides when compared with control (106125,110823). Also, a meta-analysis of clinical research in patients with gestational diabetes shows that taking vitamin D reduces the risk of premature birth and neonatal hospitalization by approximately 63% and 62%, respectively (110823). Oral vitamin D 50,000 IU (eg. D-Vitin50000; Zahravi Pharm Co.) once or twice monthly, starting at week 24 of gestation and continuing for 6 weeks, 8 weeks, or until delivery, has been used in most of these studies (106122,106125,106126). One study provided oral vitamin D 500 IU twice daily in yogurt from the beginning of the second trimester for 16 weeks (101775). However, other preliminary clinical research shows that giving vitamin D 300,000 IU as a single intramuscular injection at 24-28 weeks' gestation does not affect HbA1c (106124).

Some research has examined the effect of vitamin D supplementation on insulin resistance during pregnancy in the absence of gestational diabetes. A meta-analysis of clinical research shows that taking vitamin D for 6 to 26 weeks modestly decreases measures of insulin resistance when compared with placebo. However, there was no evidence to suggest that higher doses were more beneficial than lower doses. Although this population did not have gestational diabetes, these results suggest that adequate vitamin D might be beneficial for its prevention (110821).

Vitamin D has also been evaluated in combination with omega-3 fatty acids in adults with gestational diabetes. One study evaluated vitamin D in combination with eicosapentaenoic acid (EPA) 360 mg plus docosahexaenoic acid (DHA) 240 mg twice daily. There is some evidence that this combination offers benefit over vitamin D alone and plasma triglyceride levels were also improved (106122). Other clinical research in patients with gestational diabetes shows that taking vitamin D with omega-3 fatty acids 8,000 mg twice daily for 6 weeks modestly improves glycemic indices and most lipid markers when compared with placebo (106114).

Vitamin D has also been evaluated for the prevention of gestational diabetes. A Cochrane analysis of one large clinical study shows that taking vitamin D during pregnancy does not lower the risk of gestational diabetes when compared with no supplementation (114587). In addition, a meta-analysis of population studies suggests that there is a U-shaped association between serum vitamin D concentrations and the risk of developing gestational diabetes, with serum concentrations between 40 and 90 nmol/L associated with the lowest risk (106109).

Diabetic foot ulcers. It is unclear if oral vitamin D is beneficial for diabetic foot ulcers.
^ Details: A meta-analysis of clinical research in patients with diabetic foot ulcers shows that taking vitamin D modestly reduces ulcer size and improves glycemic and lipid indices when compared with placebo (110835). This meta-analysis is limited by the availability of three small clinical trials, as well as the heterogeneous doses of vitamin D in the included studies.

Diabetic nephropathy. Limited evidence suggests that vitamin D improves some markers of kidney function in patients with diabetic nephropathy.
^ Details: A meta-analysis of small clinical studies in patients with diabetic nephropathy shows that taking vitamin D or its analogs reduces inflammatory markers and protein in the urine, but does not affect measures of kidney function such as serum creatinine or glomerular filtration rate, when compared to control (99771).

Diabetic retinopathy. It is unclear if oral vitamin D is beneficial in diabetic retinopathy.
^ Details: There is weak evidence from observational research suggesting a link between vitamin D deficiency and diabetic retinopathy (112095). However, clinical research addressing the effectiveness of vitamin D supplementation for treatment or prevention of diabetic retinopathy is lacking.

Dysmenorrhea. Limited evidence suggests that oral vitamin D reduces pain in patients with dysmenorrhea.
^ Details: A meta-analysis of 9 small clinical studies in patients with dysmenorrhea shows that taking vitamin D in doses ranging from 5000 IU daily to 300,000 IU monthly modestly reduces pain when compared with control (112029). However, the validity of these findings is limited by a high degree of heterogeneity across the studies, including differences in blinding and control interventions, vitamin D doses and frequency of supplementation, and baseline vitamin D levels. Another small clinical study in adolescent patients with dysmenorrhea shows that taking vitamin D3 50,000 IU weekly for 9 weeks modestly reduces pain when compared to baseline (98912). The validity of this finding is limited by the lack of a control group.

Erectile dysfunction (ED). It is unclear if oral vitamin D is beneficial for ED.
^ Details: Although some data suggest ED is associated with low serum 25-hydroxy-vitamin D levels, preliminary research in males aged 60-84 years shows that taking vitamin D 60,000 IU once monthly for up to 5 years does not prevent or improve ED when compared with placebo (113580).

Exercise-induced muscle damage. Small studies suggest that vitamin D does not improve exercise-induced muscle damage.
^ Details: A meta-analysis of 6 small studies shows that taking vitamin D before and/or during exercise does not improve circulating levels of creatine kinase, lactate dehydrogenase, or myoglobin when compared with placebo (107218).

Fall prevention. The role of vitamin D in fall prevention is confusing and controversial. Most clinical research shows that taking vitamin D 800-1000 IU daily decreases the risk of falls, with effects most apparent with daily over intermittent dosing and in those with vitamin D deficiency or insufficiency. Taking vitamin D at doses higher or lower than this may be associated with increased risk of falls.
^ Details: Higher serum levels of vitamin D have been associated with improved lower-extremity function in elderly adults (15636). Clinical research in older adults shows that taking vitamin D or vitamin D analogues, with or without calcium, reduces the number of people who have a fall by up to 19% (39038,84215,84374,84539,94130,104023,113595,114504). Other research shows that vitamin D, with or without calcium, reduces number of falls by 19% to 50% (11939,16275,84404,93941,109053). The beneficial effect does not appear to depend on the form of vitamin D used (ergocalciferol, cholecalciferol, calcitriol, or alfacalcidol) (39038,84374,113595). Multiple meta-analyses of clinical research show that taking vitamin D leads to a decreased rate of falls in patients with low baseline levels of vitamin D, but not in those with adequate vitamin D levels (84670,84684,109053,114504). One meta-analysis also suggests that taking vitamin D as cholecalciferol up to 1000 IU daily reduces fall risk by up to 19%, whereas higher doses do not reduce fall risk (109053). Also, daily dosing, but not intermittent dosing, seems to be associated with a reduced risk of falling (109053,114504). Similarly, another meta-analysis of clinical research shows that taking vitamin D 800-1000 IU daily, with or without calcium, lowers the risk of falls by about 15-26% when compared with placebo, no treatment, or calcium alone. However, taking vitamin D 500 IU or less daily and vitamin D 1100 IU or more daily, with or without calcium, is not associated with a lower risk of falls and may even increase the risk of falls by 22-44% (114504).

Despite the above meta-analyses, other clinical research shows that vitamin D does not reduce the risk of falling (84404,84670), the rate of falls overall (84670,93942), or the rate of injurious falls (93942) in elderly patients (93942). One study in adults over 70 years of age with a history of falling found that taking high-dose vitamin D, either as 60,000 IU monthly or 24,000 IU plus calcifediol 300 mcg monthly, increased both the risk of falling and the mean number of falls compared to a lower dose of 24,000 IU monthly (93940). One meta-analysis of 20 trials including nearly 30,000 patients shows that taking vitamin D, with or without calcium, does not reduce the risk of falling in elderly patients, regardless of baseline 25-hydroxyvitamin D levels, level of 25-hydroxyvitamin D achieved with treatment, duration of treatment, or residential status of the patients (91342). While a meta-analysis of 10 trials in nearly 6,000 patients shows that taking vitamin D 700-1000 IU daily with calcium 1000-2000 mg daily reduces the risk of falling in the elderly by 12% when compared with placebo or no treatment, a meta-analysis of 21 trials in nearly 52,000 patients shows that vitamin D alone is only associated with a reduced risk of falls in patients with baseline vitamin D levels of less than 50 nmol/L when compared with placebo or no treatment (107224). The 2018 US Preventative Services Task Force (USPSTF) guidelines for fall prevention acknowledges this research by recommending AGAINST vitamin D supplementation for fall prevention in community dwelling adults 65 years of age and older who do not have osteoporosis or vitamin D deficiency (95703).

The reasons for the disparate study results may have to do with the way in which clinical trials have reported outcomes. Clinical trials assessing the effect of vitamin D on fall risk may report results as the number of patients who experience one or more falls, the total number of falls, or the rate of falls per individual. This can affect ultimate conclusions and, in some cases, can be misleading. For example, when studies report on only the total number of falls, it is unclear if vitamin D reduces the rate of falls across the study population, or if it only reduces falls in a small subset of patients. Also, analyses of research suggest that the size of the clinical study appears to affect the trial results. Most trials showing significant reductions in fall risk have been small and of short duration (91342,94132); whereas larger and longer-term studies tend to show no benefit (13073,84399).

Fetal and premature infant mortality. Taking vitamin D during pregnancy might reduce the risk of fetal or early infant death.
^ Details: A meta-analysis of clinical research shows that vitamin D supplementation during pregnancy reduces the risk of intrauterine or neonatal death by 31% when compared with not supplementing with vitamin D. A sub-analysis shows that this benefit was limited to doses of up to 4000 IU daily (109055). However, a Cochrane review suggests that the evidence linking vitamin D supplementation to a lower risk of fetal or neonatal death is very uncertain (114587).

Clinical practice guidelines from the Endocrine Society conditionally recommend, based on low certainty of evidence, empiric vitamin D supplementation from fortified foods, vitamin D supplements, or prenatal vitamin formulations that contain vitamin D during pregnancy to potentially lower the risk of intra-uterine and neonatal mortality, preeclampsia, preterm birth, and small for gestational age (SGA) birth. Empiric vitamin D supplementation is defined as supplementing with vitamin D above the Recommended Dietary Allowance without having tested serum vitamin D status (114502).

Fibromyalgia. A small clinical study suggests that vitamin D might improve pain in patients with fibromyalgia.

^ Details: A small clinical study in fibromyalgia patients with low vitamin D levels shows that taking vitamin D3 (cholecalciferol) 1200-2400 IU daily seems to reduce pain, but not mood or quality of life, when compared with placebo (91349).

Food allergies. It is unclear if prenatal or infant oral vitamin D supplementation reduces the risk of developing food allergies.
^ Details: A meta-analysis of two large clinical studies shows that prenatal or infant vitamin D supplementation does not reduce the risk of developing food allergies when compared with low-dose vitamin D or no intervention (108438).

Frailty. It is unclear if oral vitamin D is beneficial for the prevention or treatment of frailty in older adults.
^ Details: Frailty involves a combination of muscle loss and weakness, with exhaustion and reduced ability for physical activity. Some observational research has found that low vitamin D status is associated with frailty occurrence. However, clinical research in community dwelling older adults shows that taking vitamin D as 1000 IU, 2000 IU, or 4000 IU daily for 24 months does not prevent frailty or attenuate the worsening of frailty when compared with low-dose vitamin D 200 IU daily. Baseline vitamin D status did not affect these findings. Also, a sub-analysis suggests that vitamin D 2000 IU might increase frailty; however, only a small number of participants were randomized to this dose (109046). Other clinical research in community dwelling adults at least 70 years of age shows that taking cholecalciferol 2000 IU daily for 3 years does not reduce the odds of becoming pre-frail or frail over 36 months when compared with placebo. However, when taken in combination with omega-3 fatty acids 1 gram daily and a home exercise program, the odds of becoming pre-frail is reduced by 39% (110829).

Generalized anxiety disorder (GAD). A small clinical study suggests that vitamin D may modestly improve anxiety in patients with GAD.
^ Details: A small clinical study in patients with GAD shows that taking vitamin D 50,000 IU once weekly for 3 months, in addition to taking an antidepressant and an anxiolytic, moderately reduces anxiety scores when compared with taking these medications alone (103654).

Hematopoietic stem cell transplant (HSCT). It is unclear if oral vitamin D is beneficial for improving outcomes in patients receiving HSCT.
^ Details: A small clinical study in patients who have undergone an autologous HSCT shows that taking calcitriol 0.25 mcg three times daily for 30 days can reduce the time to absolute lymphocyte count recovery, but does not affect time to recovery of absolute neutrophil and platelet counts, when compared with placebo (103665).

Hepatitis C. Low levels of vitamin D have been associated with an inadequate response to hepatitis C therapy. Adding vitamin D to standard therapy for hepatitis C may improve viral response, especially in specific genotypes.
^ Details: A small clinical trial in patients with hepatitis C genotypes 2-3 receiving standard therapy with PEG-interferon and ribavirin shows that adding vitamin D 2000 IU daily for 24 weeks results in 95% of patients achieving undetectable levels of hepatitis C RNA, compared to only 77% of patients treated with standard therapy alone (98917). Another small clinical study in patients with hepatitis C genotype 1b receiving the same standard therapy shows that adding vitamin D 1000 IU daily for 16 weeks results in about 79% of patients achieving undetectable levels of hepatitis C RNA, compared to about 55% of patients treated with standard therapy alone. The TT genotype seems to be especially susceptible to vitamin D supplementation, while TG/GG genotype does not seem to be susceptible (98923).

HIV/AIDS. It is unclear if oral vitamin D is beneficial for improving bone mineral density (BMD) in children and young adults with HIV.
^ Details: Vitamin D deficiency and hyperparathyroidism are common in children and young adults with HIV. A meta-analysis of two clinical trials in this population shows that taking cholecalciferol for 12 months does not improve spine BMD when compared with placebo. Also, an analysis of two clinical trials shows that taking doses of 1600 IU to 4000 IU daily does not improve spine BMD when compared with taking doses of 400-800 IU daily. However, taking higher dose vitamin D has a small beneficial effect on total BMD when compared with taking lower doses. There was no improvement on parathyroid hormone levels (110824). This meta-analysis is limited by the availability of small clinical trials, as well as the heterogeneous doses of vitamin D used in the included studies.

Hyperlipidemia. Although population research has found that higher vitamin D levels are associated with improved lipid levels, it is unclear if vitamin D supplementation is beneficial.
^ Details: Population research has found that higher vitamin D levels are associated with lower low-density lipoprotein (LDL) cholesterol and triglyceride levels and higher high-density lipoprotein (HDL) cholesterol levels when compared with lower vitamin D levels (15630,98919). However, supplementation might not be beneficial. A meta-analysis of small clinical studies suggests that taking vitamin D as cholecalciferol, ergocalciferol, alfacalcidol, or calcitriol slightly increases LDL cholesterol, but does not affect total cholesterol, triglycerides, or HDL cholesterol, when compared with placebo (84642). The validity of these findings is limited by the variability in patient populations, vitamin D dose and formulation, and study duration. Also, none of the included studies were prospectively designed to test the effect of vitamin D on lipid levels. Another meta-analysis of clinical studies in a mixed population of healthy patients and patients with metabolic disease shows that taking vitamin D 1400-50,000 IU weekly with calcium 500-2000 mg daily results in very modest improvements in total cholesterol, triglyceride, and HDL cholesterol levels, but not LDL or very low-density lipoprotein (VLDL) cholesterol levels, when compared with placebo. Subgroup analyses suggest that effects are more pronounced in patients with metabolic disease (107227). The validity of these findings is limited by the heterogeneity of the included studies, which persisted throughout subgroup analyses.

Hyperthyroidism. Oral vitamin D has only been evaluated in combination with other ingredients; its effect when used alone is unclear.
^ Details: Observational research suggests that serum vitamin D levels are decreased in patients with newly diagnosed Graves' disease. A small preliminary clinical trial in patients with newly diagnosed Graves' disease taking methimazole and low levels of selenium and vitamin D shows that taking vitamin D as cholecalciferol for 270 days, in combination with selenium for the first 180 days, modestly reduces levels of serum free thyroxine and improves quality of life when compared with no vitamin D or selenium. However, taking vitamin D and selenium did not affect levels of free triiodothyronine or positive thyroid stimulating hormone (TSH) receptor antibody (109049).

Hypothyroidism. It is unclear if oral vitamin D is beneficial in the treatment of subclinical hypothyroidism.
^ Details: Preliminary clinical research in patients with vitamin D deficiency and subclinical hypothyroidism shows that taking vitamin D 50,000 IU weekly for 2-12 weeks decreases mean thyroid stimulating hormone levels by about 20% when compared with placebo, or by 3.55 mIU/L when compared to baseline (107213,113589).

Ichthyosis. It is unclear if oral vitamin D is beneficial in patients with inherited ichthyosis.
^ Details: A small clinical study in patients with congenital non-syndromic ichthyosis shows that taking vitamin D 2000 IU daily for 24 weeks reduces the clinical severity of disease at 12 weeks, but not 24 weeks, when compared with baseline. When

compared with patients taking acitretin 0.5 mg/kg daily, results were similar at both 12 and 24 weeks, but it is unclear if the improvement from baseline differed between groups (108441).

IgA vasculitis. It is unclear if oral alfacalcidol is beneficial in children with IgA vasculitis.
^ Details: A clinical study in children with IgA vasculitis shows that taking alfacalcidol 0.25 mcg daily along with vitamin C, rutin, dipyridamole, cimetidine, calcium, and glucocorticoids for 4 weeks improves rates of recurrence and incidence of kidney damage when compared with those receiving the same regimen without alfacalcidol. Alfacalcidol also improves cellular immune function and reduces levels of inflammatory biomarkers (107212).

Irritable bowel syndrome (IBS). It is unclear if oral vitamin D is beneficial for IBS; the available research is conflicting.
^ Details: Although some meta-analyses show that taking vitamin D is moderately more effective than placebo for improving IBS symptom severity and quality of life, other analyses disagree. Doses of vitamin D have included 50,000 IU weekly or every 2 weeks or 2000-4000 IU daily for up to 6 months (109041,109054,109057). The reasons for these discrepancies might be attributed to the inclusion criteria related to the individual trials, the small sample sizes, and varied dosing strategies used in the available research.

Kidney transplant. It is unclear if oral cholecalciferol is beneficial for improving allograft function or preventing non-skeletal complications in kidney transplant recipients.
^ Details: Following a kidney transplant, patients are at increased risk of vitamin D insufficiency and related outcomes. A large clinical trial shows that taking a high dose of cholecalciferol for 2 years does not reduce the composite risk of developing type 2 diabetes, major cardiovascular events, or cancer, or death when compared to taking a lower dose. The high and low doses of vitamin D were 100,000 IU or 12,000 IU, respectively, every 2 weeks for 2 months, followed by monthly doses for the next 22 months (110830). The effect of a high dose of vitamin D on these outcomes individually is not clear. However, taking vitamin D does not seem to improve allograft function. A clinical study in kidney transplant recipients shows that taking cholecalciferol 4000 IU daily, beginning 1-month posttransplant and continuing for 11 months, has no effect on allograft function when compared with placebo (108425).

Kidney transplant-related bone loss. Oral vitamin D might be beneficial for preventing bone loss associated with kidney transplantation.
^ Details: A large clinical trial shows that taking a high dose of cholecalciferol for 2 years modestly reduces the odds of a fracture by 76% when compared to taking a lower dose. The high and low doses of vitamin D were 100,000 IU or 12,000 IU, respectively, every 2 weeks for 2 months, followed by monthly doses for the next 22 months (110830). A prespecified secondary analysis of a clinical study in patients at 1-month post-kidney transplant from a living donor in Japan shows that taking vitamin D (cholecalciferol) 4000 IU daily for months 1-12 posttransplant reduces whole blood parathyroid hormone levels by 15%, but does not alter levels of tartrate-resistant acid phosphatase 5-b or bone-specific alkaline phosphatase, when compared with placebo. The greatest effects on parathyroid hormone levels are observed in those with more severe vitamin D deficiency, hypocalcemia, and more preserved kidney function. Vitamin D supplementation also attenuates changes in bone mineral density (BMD) at the lumbar spine, but not the distal radius, from prior to transplant. Patients taking vitamin D had a loss of only 0.2%, compared with a loss of 2% in those receiving placebo. The greatest effects are observed in those with osteoporosis or osteopenia (107220). Conversely, a small clinical trial shows that taking calcitriol (1,25-dihydroxyvitamin D3) 0.25 mcg daily in combination with calcium carbonate 500 mg daily does not decrease bone loss associated with kidney transplantation. However, calcitriol might reduce osteoclast suppression, help maintain trabecular bone volume and wall thickness, and improve axial BMD (4823).

Impaired glucose tolerance (prediabetes). Taking vitamin D might slow prediabetes progression to diabetes in people with low baseline levels of vitamin D or in people achieving high levels of vitamin D following supplementation. It is unclear if vitamin D supplementation is beneficial in people with prediabetes and sufficient vitamin D levels.
^ Details: Observational research has found that low vitamin D levels are linked with a higher risk of prediabetes and higher dietary vitamin D is linked with a lower chance of developing diabetes (84594,103669). Meta-analyses and individual clinical studies in patients with prediabetes and unclear or sufficient vitamin D levels show that vitamin D supplementation might improve some glycemic indices, but does not seem to prevent progression of prediabetes to diabetes (84594,91347,99769,108421). However, a more recent meta-analysis of 3 clinical studies designed to evaluate the preventative effects of oral vitamin D shows that taking it in the form of cholecalciferol 4000 IU daily or 20,000 IU weekly or eldecalcitol 0.75 mcg daily reduces the risk of developing diabetes with an absolute risk reduction of 3.3% over 3 years when compared with placebo. However, the actual risk reduction is highly dependent on vitamin D status. Patients achieving the highest serum vitamin D levels have absolute 3-year risk reductions of 11.4% to 18.1% (110810). In patients with vitamin D deficiency and prediabetes, vitamin D might improve beta-cell function, suggesting reduced disease progression (99768,107210). One clinical study in adults with vitamin D deficiency shows that taking vitamin D 50,000 IU weekly for 3 months, and then monthly for 3 months, modestly improves insulin resistance and beta-cell function as measured by the Homeostatic Model Assessment of Insulin Resistance (HOMA-IR), but does not affect fasting or postprandial glucose levels when compared with placebo (99768). Further, a meta-analysis of randomized controlled trials in patients with vitamin D deficiency and prediabetes shows that oral vitamin D at a median dose of 50,000 IU weekly for 26 weeks modestly improves fasting blood glucose and some markers of islet function, but not postprandial blood glucose or glycated hemoglobin (HbA1c) levels, when compared with control. Additionally, a significantly greater proportion of patients receiving vitamin D supplementation regressed from prediabetes to normal glucose status (107210). A meta-analysis of clinical studies in overweight or obese children and adolescents shows that high doses of vitamin D, 4000 IU daily or higher for 12-52 weeks, reduce HOMA-IR and C-reactive protein levels, but do not affect body weight, cholesterol, or parathyroid hormone (113596). A study in females with vitamin D deficiency and prediabetes shows that taking vitamin D 60,000 IU weekly for 8 weeks, followed by a maintenance dose of 200 IU daily, has no effect on the incidence of type 2 diabetes at 2 years (107211).

Clinical practice guidelines from the Endocrine Society conditionally recommend, with moderate certainty of evidence, empiric vitamin D supplementation in addition to lifestyle modification for adults with high-risk prediabetes to reduce the risk of progression to diabetes. Empiric vitamin D supplementation is defined as vitamin D from supplements or fortified food above the Recommended Dietary Allowance without having tested serum vitamin D status (114502).

Infant development. It is unclear if giving oral vitamin D in doses above the recommended dietary allowance during infancy is beneficial for improving neurodevelopment. It is also unclear if oral vitamin D during pregnancy is beneficial for improving cognitive development in the offspring.
^ Details: Clinical research shows that giving vitamin D 1200 IU daily to healthy term infants of Northern European ethnicity starting at 2 weeks of age does not improve measures of neurodevelopment at 2 years of age when compared with giving the standard dose of vitamin D 400 IU (106121).

Overall, the evidence from population research is mixed as to whether vitamin D status during gestation is associated with infant developmental outcomes. However, some population research has found that increased vitamin D status during pregnancy is associated with improved anthropomorphic and neurodevelopmental outcomes (104621,105724). Two meta-analyses of observational research show that low vitamin D status during pregnancy is associated with reduced head circumference and cognitive development scores, and higher odds of the offspring developing autism and attention deficit hyperactivity disorder (105724,105725). However, one meta-analysis suggests these risks may be limited to those with very low vitamin D status (serum level < 12 ng/mL) (105724). Multiple meta-analyses show that vitamin D status during pregnancy does not appear to affect motor development (105724,105725).

In one observational study, plasma vitamin D concentrations in the second trimester of pregnancy was associated with increased IQ scores in the offspring at age 4-6 years. Each 10 ng/mL increase in vitamin D levels was associated with a 1.17-point increase in IQ (104621). In contrast, clinical research shows that taking vitamin D3 2800 IU daily during the third trimester does not improve neurodevelopmental outcomes in the first 6 years of life when compared to taking lower doses of 400 IU daily (104623).

Infertility. It is unclear if oral or intramuscular vitamin D is beneficial in females with infertility.
^ Details: Observational research in females undergoing in vitro fertilization suggests no association between dietary vitamin D intake and oocyte quality, successful embryo transfer, clinical pregnancy rate, or term pregnancy rate (112097). Additionally, a meta-analysis of clinical research in females with infertility shows that, although there was no effect of taking vitamin D on implantation rate or miscarriage, taking vitamin D increases the odds of clinical pregnancy by 49% when compared with placebo. However, sub-analyses of clinical and observational research found that benefits on clinical pregnancy rates were limited to populations with vitamin D insufficiency, but not vitamin D deficiency, and for doses between 1000 to 10,000 IU daily for 30-90 days (110818). Most studies included in the analysis used oral vitamin D; however, intramuscular vitamin D was used in one cohort study. A smaller meta-analysis of clinical studies in females with infertility and vitamin D insufficiency undergoing IVF shows that taking vitamin D increases the rate of chemical pregnancy by 50%, but has no effect on the clinical pregnancy rate (108432).

Lichen planus. It is unclear if oral vitamin D is beneficial for lichen planus.
^ Details: A small clinical study in patients with oral lichen planus and vitamin D deficiency or insufficiency shows that taking vitamin D 60,000 IU weekly in combination with systemic steroids for 1 month reduces pain severity and improves healing of lesions when compared with systemic steroids alone (114586). The validity of the study is limited by the lack of a placebo.

Low birth weight. It is unclear if oral vitamin D can reduce the risk for low birth weight; the available evidence is conflicting.
^ Details: A meta-analysis of observational research has found that a very low vitamin D status (serum level <12 ng/mL) during pregnancy is associated with lower birth weight and increased odds of SGA births. However, these risks have not been demonstrated in those with less severe vitamin D deficiency (serum level <20 ng/mL) (105724). Most research also shows that vitamin D supplementation during pregnancy reduces the risk of low birth weight. A meta-analysis of three clinical trials shows that supplementation with vitamin D 800-1000 IU daily starting between 27 and 32 weeks' gestation, or 200,000 IU administered as a single dose or in two divided doses during the seventh and eighth month of pregnancy, reduces the risk of delivering a low birth weight infant by 60% (84659). Other meta-analyses of clinical research show that supplementation with vitamin D during pregnancy results in a 31% to 60% reduced risk of low birth weight and a 103 gram greater average birth weight when compared with placebo or no intervention (99766,114587). However, some meta-analyses show that vitamin D supplementation during pregnancy does not reduce the risk of low birth weight when compared with no supplementation (95910,109055). One meta-analysis that included studies that did not directly measure birth weight shows no effect of vitamin D supplementation during pregnancy on the rate of low birth weight, despite showing an increase in overall birth weight of about 58 grams (95910).

Lung cancer. It is unclear if oral vitamin D prevents lung cancer or improves lung cancer prognosis.
^ Details: A small meta-analysis of randomized controlled trials and observational research has found that high intake of vitamin D is associated with a 10% reduction in the risk of developing lung cancer when compared with low vitamin D intake. In terms of prognosis, high vitamin D intake is associated with improvements in both overall survival and relapse-free survival (107217).

Male infertility. It is unclear if oral cholecalciferol is beneficial in males with infertility.
^ Details: A small clinical study in males with infertility shows that taking cholecalciferol 2500 IU daily for 6 months modestly improves progressive sperm motility, sperm concentration, and sperm morphology when compared with baseline (108427). The validity of these findings is limited by the lack of a comparator group.

Melanoma. It is unclear if oral vitamin D is beneficial in patients with melanoma.
^ Details: A meta-analysis of 14 observational studies suggests that vitamin D deficiency is associated with a 45% greater risk of melanoma when compared with normal vitamin D levels (112027). However, a small clinical study in patients with newly resected stage II melanoma shows that taking vitamin D3 100,000 IU every 50 days for 3 years does not improve disease-free survival when compared with placebo. Most patients in this study had vitamin D deficiency or insufficiency at baseline (106113).

Metabolic syndrome. It is unclear if oral vitamin D is beneficial for preventing or treating metabolic syndrome.
^ Details: In patients with metabolic syndrome, clinical research shows that taking vitamin D 50,000 IU weekly for 16 weeks does not affect most metabolic or anthropometric factors when compared with placebo, although there was a modest decrease in triglyceride levels (106123). However, almost all of the individuals in this study were vitamin D deficient or insufficient, and many remained in that category even after supplementation. It is unclear if vitamin D supplementation is beneficial in vitamin D sufficient patients with metabolic syndrome.

There is conflicting evidence about the association between vitamin D and metabolic syndrome (14265,16713,98234). Some population research has found that higher vitamin D levels are associated with a lower risk of metabolic syndrome, while other research found no association (14265,16713). Furthermore, a small clinical trial in patients with metabolic syndrome shows that taking vitamin D 20,000 IU or 40,000 IU weekly for 8 weeks does not affect metabolic risk factors when compared with placebo (98234).

Migraine headache. It is unclear if oral vitamin D reduces the frequency of migraine.
^ Details: A meta-analysis of three small high-quality clinical studies in patients with migraine shows that taking vitamin D 2000 or 4000 IU daily for 12-24 weeks or 500,000 IU weekly for 2 months reduces the frequency of migraines by 2-3 attacks monthly when compared with usual care or placebo (108439).

Miscarriage. Oral vitamin D has only been evaluated in combination with other ingredients; its effect when used alone is unclear.
^ Details: A small clinical study in pregnant adults with threatened miscarriage between the 6th and 13th week of gestation shows that taking a specific combination product (DAV HA, Lo.Li pharma s.r.l) containing vitamin D 50 mcg, alpha-lipoic acid, hyaluronic acid, magnesium, and vitamin B6 daily in combination with conventional treatment of vaginal progesterone over 2 weeks of observation results in a faster resorption of the subchorionic hematoma and faster decrease of patient-reported vaginal bleeding, abdominal pain, and uterine contractions when compared with vaginal progesterone alone (113893). It is unclear if these effects are due to vitamin D, other ingredients, or the combination. Additionally, the validity of these findings is limited by the lack of a placebo for the control group.

Multiple sclerosis (MS). Although vitamin D supplementation has been linked with a lower risk of developing MS, taking oral vitamin D supplements does not seem to reduce MS relapses.
^ Details: Vitamin D deficiency appears to be linked to the risk of MS development and progression. Population research suggests that long-term supplementation with vitamin D 400 IU is associated with a 40% lower risk of MS in females. The effect seems to be dose-dependent. Consumption of at least 400 IU daily, mainly in the form of a multivitamin supplement, appears to have the greatest protective effect (11356). Additional population research in over 7 million people suggests that higher levels of calcifediol are associated with a lower risk of developing MS. In white adults, for every 20 ng/mL increase in vitamin D levels, there appears to be a 41% decrease in MS risk. However, this was not found in black and Hispanic adults (15159).

Vitamin D supplementation has also been examined in patients with MS. Population research suggests that taking vitamin D supplements and the maintenance of optimal blood levels of vitamin D are associated with a reduction in the development of new areas of demyelination detected by magnetic resonance imaging (MRI) over 24 months. However, there are no correlations between vitamin D consumption or vitamin D blood levels and clinical outcomes (110816). Also, vitamin D supplementation does not seem to impact MS relapses or most symptoms in patients with MS. Meta-analyses of preliminary clinical research show that vitamin D supplementation does not affect the rate of MS relapses, overall symptoms, disability scores, or the number of MS nerve lesions detected by MRI, regardless whether the vitamin D was low-dose or high-dose (98192,98914,106119,113586). However, one meta-analysis of 6 small clinical studies shows that taking vitamin D for 8-96 weeks slightly improves fatigue scores when compared with placebo (112024). These analyses are limited by the small size and heterogeneity of most of the included studies and variability in dosing and duration of vitamin D regimens.

Muscle strength. It is unclear if oral vitamin D improves muscle strength in middle aged or older adults with low or sufficient levels of vitamin D. The available research is conflicting.
^ Details: Clinical research in healthy older adults who are not deficient in vitamin D shows that oral vitamin D3 (cholecalciferol) supplementation, with 800 IU, 1000 IU, or 2000 IU daily or 50,000 IU monthly, alone or in combination with a resistance training program, does not increase muscle strength when compared with placebo (11814,104619,108429). In patients 40-80 years of age with low vitamin D levels, taking vitamin D3 100,000 IU (2500 mcg) once, followed by 20,000 IU (500 mcg) weekly for 4 months, does not improve muscle strength when compared with placebo (103658). Similarly, meta-analyses of clinical research show that vitamin D does not increase grip strength, muscle mass, global muscle strength, or back extensor strength when compared with control (91341,113595).

However, some research has found some benefit with the use of vitamin D supplements. One meta-analysis shows that taking vitamin D increases grip strength after menopause when compared with placebo or low-dose vitamin D, although a sub-analysis shows that beneficial effects are limited to individuals aged 60-69 years, when vitamin D is taken without calcium, when baseline vitamin D levels are at least 30 ng/mL, or when the treatment consists of the vitamin D analog alfacalcidol. This suggests heterogeneity between studies (109048). Another meta-analysis in elderly adults shows that taking vitamin D as calcifediol 10-30 mcg daily for a median of 24 weeks modestly improves hand grip strength and leg extension, but not leg flexion, when compared with baseline (109042). Also, some individual clinical research in older adults with low levels of vitamin D at baseline shows that taking vitamin D3 800 IU daily or vitamin D2 (ergocalciferol) 1000 IU daily for 12 months in combination with calcium 1000 mg daily modestly improves lower extremity or hip strength by 8% to 23% when compared with calcium alone (38915,84530).

Myalgia. It is unclear if oral vitamin D is beneficial for reducing myalgia associated with obesity.
^ Details: Preliminary clinical research in obese individuals with vitamin D deficiency who are on a low-calorie diet shows that taking vitamin D 50,000 IU weekly, alone or in combination with an aerobic exercise program three times weekly for 12 weeks, modestly reduces muscle pain when compared with only aerobic exercise three times weekly (106118).

Myelodysplastic syndromes. It is unclear if oral vitamin D is beneficial for patients with myelodysplastic syndromes.
^ Details: A small observational study in patients with myelodysplastic syndromes has found that taking calcitriol or calcifediol orally is associated with slowed disease progression (11825).

Nonalcoholic fatty liver disease (NAFLD). It is unclear if oral or intramuscular vitamin D is beneficial in children or adults with NAFLD.
^ Details: Although findings from individual research are mixed, one meta-analysis of mainly small clinical trials in patients with NAFLD shows that vitamin D modestly improves insulin resistance and serum alanine aminotransferase (ALT) levels, with no effect on serum aspartate aminotransferase (AST) levels. Most studies included in the analysis used oral vitamin D 1000 IU daily or 50,000 IU weekly or biweekly for 3-6 months and compared with placebo; however, one study used a single intramuscular injection of vitamin D 600,000 IU compared with lifestyle modifications (109056). Vitamin D has also been evaluated in combination with fish oil. A clinical study in adults with NAFLD shows that taking oral vitamin D3 1680 IU daily in combination with fish oil or fish oil alone for 3 months improves serum ALT levels similarly to a control group (107186).

Vitamin D has also been evaluated for use in children with NAFLD. One clinical study in children with obesity and biopsy-proven NAFLD shows that taking oral vitamin D3 2000 IU daily for 6 months with a hypocaloric diet improves liver histopathology in terms of steatosis, lobular inflammation, and NAFLD activity score at 6 months, but not hepatocyte ballooning or fibrosis, when compared with baseline. These improvements were not seen in the group receiving placebo with a hypocaloric diet, but it is unclear if the improvement from baseline differed between groups (107222).

Nonmelanoma skin cancer. It is unclear if oral vitamin D is beneficial for preventing keratinocyte carcinomas.
^ Details: In middle aged and older adults recently diagnosed with a colorectal adenoma, clinical research shows that taking vitamin D3 1000 IU daily for 3-5 years does not reduce the incidence of keratinocyte cancer when compared with placebo over a median of 8 years. A sub-group analysis shows that taking vitamin D3 with calcium 1200 mg daily as calcium carbonate

reduces the risk of invasive cutaneous squamous cell carcinoma by a moderate amount, but has no effect on the risk of basal cell carcinoma. Vitamin D taken alone has no effect on the risk for either type of cancer (104622).

Obesity. The evidence for the use of oral vitamin D in obesity is conflicting and unclear.
^ Details: Population research has found that people with lower vitamin D levels are significantly more likely to be obese when compared to people with higher vitamin D levels (15630). Also, a large-scale, high-quality clinical trial in postmenopausal adults taking calcium 1000 mg plus vitamin D3 (cholecalciferol) 400 IU daily for 3 years shows that these patients are more likely to lose weight and maintain their weight when compared with those taking placebo. This beneficial effect is mainly seen in females who have inadequate intake of calcium, less than 1200 mg/day, before starting a calcium supplement (15604). However, other evidence suggests that vitamin D alone does not improve weight loss. One clinical trial shows that taking vitamin D3 2000 IU/day without calcium for 12 months does not increase weight loss when compared with placebo in overweight and obese postmenopausal adults who are deficient in vitamin D at baseline (91345).

Orthostatic hypotension. It is unclear if oral vitamin D is beneficial for prevention of orthostatic hypotension.
^ Details: A secondary analysis of a clinical study in older patients with vitamin D insufficiency who are at an increased risk for falls shows that taking vitamin D 1000-4000 IU daily for up to 2 years has no effect on the risk of orthostatic hypotension or orthostatic symptoms when compared with those receiving vitamin D 200 IU daily (107223).

Osteoarthritis. It is unclear if oral vitamin D is beneficial for osteoarthritis.
^ Details: The evidence for the use of vitamin D in osteoarthritis is conflicting. Some clinical research shows that taking vitamin D3 (cholecalciferol) 2000 IU daily, or at a higher dose to reach serum vitamin D levels over 36 ng/mL, for 2 years does not reduce knee pain or loss of cartilage when compared with placebo in patients with symptomatic osteoarthritis (84688). However, another clinical study shows that taking vitamin D3 daily for 10 days and then vitamin D3 60,000 IU monthly for 12 months modestly reduces pain and improves function when compared with placebo in patients with osteoarthritis and vitamin D insufficiency (98199). It is possible that higher doses of vitamin D have an effect on osteoarthritis, while lower doses do not. Due to this conflicting and low-quality evidence, the American College of Rheumatology (ACR) recommends against the use of vitamin D for any form of osteoarthritis (102114).

Otitis media. It is unclear if oral vitamin D is beneficial in patients with otitis media.
^ Details: The relationship between vitamin D status and otitis media is unclear. Population research has found that having otitis media is associated with lower blood levels of vitamin D; however, lower vitamin D levels were not associated with greater risk of otitis media (98194).

Overactive bladder. It is unclear if oral vitamin D is beneficial for overactive bladder.
^ Details: A large clinical trial in older males shows that taking vitamin D3 (cholecalciferol) 2000 IU daily for 5 years does not reduce the odds of weekly overactive bladder when compared with placebo. In males with low serum vitamin D, taking vitamin D reduces the odds of overactive bladder at 5 years by 49%, including 34% reduced odds of overactive bladder with urinary incontinence and 81% reduced odds of overactive bladder without incontinence. However, urinary incontinence while sleeping or napping was increased (109738).

Overall mortality. Taking oral vitamin D alone does not seem to reduce mortality; however, there is some evidence that taking certain forms of vitamin D with calcium might have a modest benefit.
^ Details: While higher vitamin D levels have been associated with a small reduction in mortality when compared with lower vitamin D levels (98187), clinical research shows that taking vitamin D does not reduce the risk of mortality. A comprehensive meta-analysis shows that vitamin D supplementation alone does not reduce all-cause mortality when compared to control (100900). However, giving vitamin D with calcium may modestly reduce the risk of mortality. Meta-analyses show a 4% to 9% reduced risk of mortality when trials of vitamin D alone and vitamin D with calcium are pooled together (16102,97296,98186,112022). Finally, some research suggests that the type of vitamin D supplementation might influence the results. A meta-analysis of clinical research found that vitamin D3 (cholecalciferol) with or without calcium reduces mortality risk by 6%, while alfacalcidol, calcitriol, and vitamin D2 (ergocalciferol) do not have benefit (84595,98186). Other clinical research suggests that vitamin D supplementation in older adults may reduce the risk of all-cause mortality by about 4%, with an estimated effect size of 6 fewer deaths per 1000 individuals. This finding informed the 2024 Endocrine Society Clinical Practice Guidelines on vitamin D for the prevention of disease in the general population. The Endocrine Society conditionally recommends, with moderate certainty of evidence, empiric vitamin D supplementation from fortified foods or vitamin D-containing supplements in the general population aged 75 years and older to potentially lower the risk of mortality. Empiric vitamin D is defined as vitamin D above the Recommended Dietary Allowance without having tested serum vitamin D status. For empiric supplementation and for those who have indications for vitamin D treatment or supplementation, daily lower-dose versus intermittent higher doses was suggested (114502).

Pain (chronic). It is unclear if oral vitamin D is beneficial for chronic pain.
^ Details: A meta-analysis of clinical research in patients with chronic pain shows that taking vitamin D for 1-24 months produces a 43% greater decrease in pain score when compared with placebo. However, the final follow-up pain score is similar for both groups (96402). The effect of vitamin D on pain based on pain-related diagnosis, vitamin D status, or dose is unknown.

Parkinson disease. It is unclear if oral vitamin D is beneficial for this condition.
^ Details: Population research found that higher levels of vitamin D are associated with milder Parkinson disease symptoms, while deficiency is associated with increased risk of Parkinson disease (97000,99772). One small study shows that taking vitamin D3 (cholecalciferol) 1200 IU daily for one year might modestly slow the progression of Parkinson disease based on the Hoehn and Yars staging criteria. However, there was no improvement in disease severity according to the more widely used Unified Parkinson Disease Rating Stage (UPDRS). The UPDRS includes measures of activities of daily living and non-motor symptoms. Vitamin D had no effect on most quality of life measures (95915).

Periodontitis. It is unclear if oral vitamin D is beneficial for periodontal disease.
^ Details: A meta-analysis of mostly observational research suggests that vitamin D levels are not associated with an increased or decreased risk of periodontitis (112026). Other population research suggests that higher blood levels of vitamin D may be associated with a reduced risk of periodontal disease in adults 50 years of age or older. However, this association was not found for adults younger than 50 years (15634).

Physical performance. It is unclear if oral vitamin D improves muscle strength in elderly adults.
^ Details: Some clinical research in healthy older adults who are not deficient in vitamin D shows that oral vitamin D3 (cholecalciferol) supplementation, with 800 IU, 1000 IU, or 2000 IU daily or 50,000 IU monthly, alone or in combination with a resistance training program, does not improve physical performance when compared with placebo (11814,104619,108429). Also, results from one meta-analysis of clinical research in postmenopausal females with low levels of vitamin D shows that taking

vitamin D does not improve the timed up and go test when compared with placebo or low-dose vitamin D (109048). One meta-analysis that included studies specifically evaluating the use of calcifediol in older adults shows a large benefit on gait speed; however, only one study included in the analysis used this endpoint and other measures of physical performance were not affected (109042).

Pneumonia. High-dose oral vitamin D does not reduce pneumonia severity in children.
^ Details: Although vitamin D supplementation might prevent respiratory tract infections in children, it might not prevent recurrent pneumonia. A small clinical study in children under 5 years of age with recurrent pneumonia and variable vitamin D blood levels shows that taking vitamin D 300,000 IU quarterly for 1 year does not reduce respiratory infections, severity of pneumonia, hospital admissions, or disease complications when compared with placebo (103667). However, it's unknown if vitamin D supplementation using lower and more frequent doses, or supplementation in patients with vitamin D deficiency, might be beneficial. Some observational research has found that having vitamin D deficiency is linked to a higher risk for developing community-acquired pneumonia (CAP) (102118). For information on other respiratory infections, refer to the Respiratory Tract Infection discussion.

Polycystic ovary syndrome (PCOS). It is unclear if vitamin D improves pregnancy outcomes and symptoms in patients with PCOS.
^ Details: Observational research in adults with infertility, PCOS, and insulin resistance suggests that normal vitamin D levels are associated with better embryo quality and increased pregnancy rate when compared with vitamin D deficiency or insufficiency (100834). It is unclear if supplementation with vitamin D improves pregnancy rates in patients with PCOS. A meta-analysis of clinical research shows that taking vitamin D 400-12,000 IU daily for 2-6 months improves follicular development when compared with placebo. Taking vitamin D in combination with metformin 1500 mg daily also appears to increase the number of regular menstrual cycles by 85% when compared with metformin alone, but without an effect on follicular development (96404). A meta-analysis of 9 studies also shows that combining vitamin D with metformin improves menstrual cycle regulation and reduces homeostatic model assessment for insulin resistance (HOMA-IR), body mass index, and testosterone levels when compared with metformin alone (113594). Vitamin D alone does not appear to improve menstrual cycle regularity.

A meta-analysis of several mostly low quality clinical studies in patients with PCOS and vitamin D deficiency at baseline shows that taking intramuscular or oral vitamin D 200-10,000 IU daily for up to 24 weeks in addition to fertility treatment improves pregnancy rates and reduces premature miscarriage and premature delivery, but does not impact the incidence of pregnancy complications including gestational hypertension or gestational diabetes mellitus, when compared with control. This analysis also suggests vitamin D supplementation improves certain IVF-related outcomes including ovulation rate, fertilization rate, and number of mature oocytes (112787).

The effects of vitamin D on the metabolic profile of patients with PCOS have been evaluated. A small clinical study in patients with PCOS and vitamin D deficiency or insufficiency shows that taking vitamin D 2000 IU daily in combination with diet and exercise for 12 weeks reduces insulin resistance, body mass index, waist to hip ratio, serum triglycerides, and total and low-density lipoprotein cholesterol when compared with diet and exercise alone (114580). The interpretation of these results is limited by the lack of a placebo.

Post-stroke fatigue. It is unclear if oral vitamin D is beneficial for post-stroke fatigue.
^ Details: A retrospective study in patients with post-stroke fatigue and vitamin D deficiency suggests that vitamin D (cholecalciferol) 600 IU daily is associated with improvements in fatigue severity at months 1 and 3 when compared with control. Neurologic disability also showed improvement at 3 months, but not at 1 month, when compared with control. It is unclear if improvements from baseline differed between groups (107225).

Pre-eclampsia. It is unclear if oral vitamin D during pregnancy is beneficial for the prevention or treatment of pre-eclampsia.
^ Details: While some clinical research suggests that taking vitamin D during pregnancy does not reduce the risk of pre-eclampsia (113585,114587), clinical practice guidelines from the Endocrine Society conditionally recommend, based on low certainty of evidence, empiric vitamin D supplementation from daily intake of fortified foods, vitamin D supplements, or prenatal vitamin formulations that contain vitamin D during pregnancy to potentially lower the risk of preeclampsia, intra-uterine mortality, preterm birth, small for gestational age (SGA) birth, and neonatal mortality. Empiric vitamin D supplementation is defined as supplementing with vitamin D above the Recommended Dietary Allowance without having tested serum vitamin D status (114502).

Precocious puberty. It is unclear if oral vitamin D is beneficial for the prevention or treatment of precocious puberty.
^ Details: A meta-analysis of 43 mostly observational studies from China suggests that vitamin D deficiency or insufficiency is associated with 2.25-fold greater odds of precocious puberty when compared with normal vitamin D levels. Taking vitamin D 200-1000 IU daily for 3-12 months along with a gonadotropic-releasing hormone analog (GnRHa) is associated with lower luteinizing hormone, follicle-stimulating hormone, and estradiol levels and reduced bone age when compared with GnRHa therapy alone (112019). Another meta-analysis of 15 studies, mainly from China and with high heterogeneity and publication bias, suggests that there is a negative correlation between serum 25-hydroxy-vitamin D concentrations and precocious puberty, and that vitamin D deficiency increases the risk of precocious puberty by about 53% (113578).

Pregnancy-induced hypertension. It is unclear if oral vitamin D is beneficial for patients with gestational hypertension.
^ Details: Meta-analyses of two low-quality clinical trials show that vitamin D supplementation during pregnancy does not reduce the risk for gestational hypertension when compared with control (95910,114587).

Prematurity. It is unclear if taking vitamin D during pregnancy prevents respiratory complications in preterm neonates.
^ Details: A large clinical study in pregnant patients with gestational age less than 34 weeks and at risk of preterm delivery shows that a single intramuscular injection of vitamin D 50,000 IU within 72 hours before delivery decreases the risk of respiratory distress syndrome treated by surfactant in the neonate by about 2.25-fold and increases the 5th minute APGAR scores, but not 1st minute APGAR scores, gestational age, neonatal intensive care unit admission, length of hospital stay, or delivery method, when compared with no treatment (114581).

Premenstrual syndrome (PMS). It is unclear if oral vitamin D is beneficial in patients with PMS.
^ Details: Observational research has found that increasing dietary intake of vitamin D above 706 IU daily is linked to a reduced risk of developing PMS when compared with consuming 112 IU daily (13094). Furthermore, a clinical study shows that taking vitamin D 400 IU daily in combination with calcium 1000 mg daily can decrease the severity of PMS symptoms (16869). Another clinical study in adolescent females with PMS shows that taking vitamin D3 50,000 IU weekly for 9 weeks modestly reduces PMS symptoms when compared to baseline (98912). A small clinical study in young adults with PMS and vitamin D

deficiency shows that taking vitamin D 50,000 IU every 2 weeks for 16 weeks reduces psychological symptom scores by 54% and physical symptom scores by 39% when compared with placebo (113582).

Preterm labor. It is unclear if oral vitamin D is beneficial for preterm labor.
^ Details: Vitamin D deficiency, defined as serum levels less than 20 ng/mL, during pregnancy has been associated with a 25% greater risk of preterm birth (95911). The risk seems to be especially prominent in those with darker colored skin (103662). However, meta-analyses of clinical research show that vitamin D supplementation during pregnancy does not reduce the risk of a preterm birth when compared with no supplementation with vitamin D (84659,95910,109055,114587).

The effect vitamin D specifically in vitamin D-deficient patients is still unclear. Some small, heterogeneous, and low-quality studies show that vitamin D supplementation might reduce the rate of preterm birth in vitamin D-deficient patients (84659,95910). Additional studies are needed to determine the effect of vitamin D supplementation on the risk of preterm birth.

Clinical practice guidelines from the Endocrine Society conditionally recommend, based on low certainty of evidence, empiric vitamin D supplementation from daily intake of fortified foods, vitamin D supplements, or prenatal vitamin formulations that contain vitamin D during pregnancy to potentially lower the risk of preterm birth, small for gestational age (SGA) birth, preeclampsia, intra-uterine mortality, and neonatal mortality. Empiric vitamin D supplementation iss defined as supplementing with vitamin D above the Recommended Dietary Allowance without having tested serum vitamin D status (114502).

Rheumatoid arthritis (RA). Small clinical studies suggest that oral vitamin D may not improve symptoms in patients with RA.
^ Details: Population research has found that higher intake of vitamin D from foods or supplements is associated with a lower risk of developing RA (12206,98200). However, a meta-analysis of two small clinical trials shows that vitamin D supplementation does not reduce pain or recurrence of RA when compared with placebo (98190).

Rhinosinusitis. Oral vitamin D has only been evaluated in combination with other ingredients; its effect when used alone is unclear.
^ Details: A small clinical study in patients over 12 years of age with chronic sinusitis shows that taking 1 or 2 sachets of a specific combination product (Flogostop Forte, Humana Italia) containing vitamin D 600 IU, black currant, Boswellia serrata, and bromelain along with a nasal corticosteroid daily for 15-30 days reduces symptoms of nasal hyperemia and rhinorrhea when compared with corticosteroid nasal spray alone (111501). It is unclear if these findings are due to vitamin D, other ingredients, or the combination.

Sarcopenia. It is unclear if oral vitamin D is beneficial in older adults with sarcopenia.
^ Details: A meta-analysis of randomized trials in older adults with sarcopenia shows that taking vitamin D3 (cholecalciferol) 100-800 IU daily, with protein 10-44 grams daily or amino acids 2.5-6 grams daily, for 2-6 months moderately improves muscle strength, but not muscle mass or walking speed, when compared with placebo (105727). The validity of this study is limited by high heterogeneity and an unreported baseline vitamin D status. Similarly, a small network meta-analysis of randomized trials shows that taking vitamin D 500-1600 IU daily or 2500-5000 IU weekly with protein 20-80 grams daily or amino acids 3-32 grams daily with and without exercise for 3-18 months increases hand grip strength and shortens time to chair-stand, respectively, but not gait speed or lower-limb mass when compared with usual care (107221). It is unclear if these effects are due to vitamin D, protein/amino acid supplementation, exercise, or the combinations.

Schizophrenia. It is unclear if oral vitamin D is beneficial for schizophrenia.
^ Details: Based on preliminary clinical evidence, Guidelines from The World Federation of Societies of Biological Psychiatry (WFSBP) and Canadian Network for Mood and Anxiety Treatments (CANMAT) Taskforce state that vitamin D in doses of 1500 to 4000 IU daily is not recommended for adjunctive use in patients with schizophrenia (110318).

A moderate-sized clinical study in patients with schizophrenia shows that taking a specific combination product (BioZenD, Tak Gen Zist Pharmaceutical Company) containing vitamin D 400 IU in combination with a blend of probiotics (Lactobacillus acidophilus, Lacticaseibacillus rhamnosus, Limosilactobacillus reuteri, Lacticaseibacillus paracasei, Bifidobacterium longum, Bacillus coagulans) 2 x 10^9 CFU daily for 12 weeks improves cognitive function scores but does not improve the severity of positive and negative schizophrenia symptoms when compared with placebo (114582). It is unclear if this effect is due to vitamin D, the probiotics, or the combination.

Sciatica. Oral vitamin D has only been evaluated in combination with other ingredients; its effect when used alone is unclear.
^ Details: Preliminary research in adults up to 45 years of age with discogenic sciatica shows that taking cholecalciferol 800 IU with alpha-lipoic acid, acetyl-L-carnitine, and resveratrol daily for 30 days, in combination with a 20-session rehabilitation protocol, improves pain, disability, and quality of life when compared with the supplements alone or the rehabilitation protocol alone (112933).

Seasonal affective disorder (SAD). One small study suggests that a large dose of oral vitamin D can improve symptoms of SAD.
^ Details: A small clinical study in patients with SAD suggests that a single dose of vitamin D2 (ergocalciferol) 100,000 IU improves symptoms after one month when compared to baseline (83791). The validity of this finding is limited by the lack of a control group.

Seborrheic keratosis. It is unclear if topical vitamin D analogues improve symptoms of seborrheic keratosis.
^ Details: Preliminary clinical research suggests that topical ointments containing activated vitamin D in the form of tacalcitol, calcipotriol or maxacalcitol, applied for 3-12 months, can reduce tumor volume by at least 40% in 75% of patients with seborrheic keratosis. Additionally, over 30% of patients seem to experience complete tumor resolution or a reduction in tumor volume of at least 80% (84033). The validity of this finding is limited by the lack of a control group.

Sexual dysfunction. One small study suggests that injecting a large dose of vitamin D might improve sexual function.
^ Details: A small clinical study in females with vitamin D deficiency and sexual dysfunction shows that receiving an intramuscular injection of vitamin D as cholecalciferol 300,000 IU once at baseline and a second time 4 weeks later improves sexual function at 4 and 8 weeks when compared with placebo (100896).

Sickle cell disease. One small study suggests that oral vitamin D reduces pain and improves quality of life in children with sickle cell disease with vitamin D insufficiency or deficiency.
^ Details: A small clinical study in children with sickle cell disease shows that taking vitamin D3 (cholecalciferol) 40,000-100,000 IU weekly for 6 weeks reduces days with pain and improves physical activity and quality of life for up to 6 months when compared with placebo. Of the children included in the study, 82.5% had vitamin D insufficiency, while 52.5% were deficient in vitamin D (98918). It is unclear if vitamin D is effective for patients with sickle cell disease who have adequate levels of vitamin D.

Small for gestational age (SGA). It is unclear if oral vitamin D can reduce the risk for SGA births; the available evidence is conflicting.
^ Details: Two meta-analyses of clinical research show no effect of vitamin D on the risk of SGA birth (84659,109055). However, one meta-analysis shows a 40% reduction in the risk of SGA births with vitamin D supplementation (95910). Also, one meta-analysis shows that when vitamin D supplementation is initiated before the 20th week of gestation, the risk of SGA is reduced by 54% (109055). Most individual clinical trials are small and heterogeneous. Also, the formulation of vitamin D and/or vitamin D status at baseline may explain part of the discrepant findings. For example, a meta-analysis of observational research has found that a very low vitamin D status (serum level <12 ng/mL) during pregnancy is associated with increased odds of SGA births. This association does not seem to be present with less severe vitamin D deficiency (serum level <20 ng/mL) (105724).

Clinical practice guidelines from the Endocrine Society conditionally recommend, with low certainty of evidence, empiric vitamin D supplementation from daily intake of fortified foods, vitamin D supplements, or prenatal vitamin formulations that contain vitamin D during pregnancy to potentially lower the risk of SGA births, as well as preeclampsia, intra-uterine mortality, preterm birth, and neonatal mortality. Empiric vitamin D supplementation is defined as supplementing with vitamin D above the Recommended Dietary Allowance without having tested serum vitamin D status (114502).

Statin-induced myalgia. It is unclear if oral vitamin D is beneficial for patients with statin-induced myalgia.
^ Details: Observational research has found that taking oral vitamin D supplements is associated with decreased symptoms of myalgia in patients taking statin drugs. In a small case series, patients who discontinued statins due to myalgia were able to resume statin therapy after starting vitamin D supplements. The majority of patients with myalgia were found to be vitamin D deficient, with vitamin D levels less than 12 ng/mL at baseline (16829). An observational study has also found that administering 50,000 units of vitamin D2 (ergocalciferol) once a week for 12 weeks reversed symptoms of myalgia in 92% of statin treated patients with low serum vitamin D levels of less than 32 ng/mL (16831).

Stroke. Although low vitamin D levels are associated with higher risk of stroke, taking vitamin D supplements does not seem to reduce stroke risk.
^ Details: Population research has found that low vitamin D levels are associated with an increased risk of stroke. Furthermore, increased dietary intake of vitamin D is associated with a reduced risk of stroke (15630,16618,93944,97303,106106). However, clinical research shows that vitamin D supplementation does not reduce stroke risk. Several meta-analyses and randomized controlled trials show that taking vitamin D alone or with calcium does not reduce the risk of stroke in patients with or without cardiovascular disease risk factors (16616,91343,97296,97308,106106,112022). It is difficult to draw firm conclusions from these studies, as they did not assess whether patients had adequate vitamin D levels at baseline. It is unclear if vitamin D supplementation might prevent strokes in patients with vitamin D deficiency.

Sunburn. Although there is interest in using oral vitamin D for the treatment of sunburns, there is insufficient reliable information about the clinical effects of vitamin D for this purpose.

Systemic lupus erythematosus (SLE). It is unclear if oral vitamin D is beneficial in patients with SLE.
^ Details: While some observational research has found that adults with SLE are more likely to have vitamin D deficiency than healthy controls (102119), a small cross-sectional study in females has found no association between serum levels of 25-hydroxyvitamin D, SLE disease activity, and the presence or absence of lupus nephritis (107214). A meta-analysis of three small clinical studies shows that taking vitamin D3 (cholecalciferol) 2000 IU daily or 50,000 IU weekly seems to reduce anti-dsDNA positive, a marker of disease activity, when compared with placebo in patients with SLE (98190). However, the clinical significance of this finding is unclear. A small clinical trial in females with SLE shows that taking vitamin D3 5000 IU daily for 12 weeks modestly improves overall disease activity, but not quality of life, when compared with placebo (109735).

Thyroid cancer. It is unclear if oral vitamin D is beneficial in patients with thyroid cancer.
^ Details: Observational research in patients undergoing thyroidectomy for differentiated thyroid cancer suggests that taking vitamin D daily for at least 6 months after surgery is associated with a 38% lower risk of all-cause mortality and a 33% lower risk of total cancer-related mortality when compared with no vitamin D supplementation at around 10 years' follow-up. However, vitamin D does not appear to be linked to a lower risk of thyroid cancer-related mortality in these patients (112018).

Ulcerative colitis. Limited evidence suggests that vitamin D may be beneficial in patients with ulcerative colitis.
^ Details: A meta-analysis of mainly small clinical trials in patients treated with mesalazine shows that taking vitamin D for up to 24 weeks modestly increases clinical efficacy and reduces disease score when compared with mesalazine alone (109044). Also, a meta-analysis of small, low-quality clinical studies in patients with IBD, including Crohn disease and ulcerative colitis, shows that taking high- or low-dose vitamin D for up to 1 year reduces the rate of relapse when compared with control (98915). These findings are limited because of the heterogeneity of the included studies.

Upper respiratory tract infection (URTI). It is unclear if oral vitamin D is beneficial for dementia.
^ Details: A large clinical trial shows that taking vitamin D 2800 IU daily, starting at gestational week 24 and continuing until one week after birth, reduces the risk of the child developing croup by 3 years of age by 40% when compared with olive oil as placebo. This risk reduction did not change after adjusting for the use of omega-3 fatty acids 2.4 grams daily, as well as for concomitant persistent wheeze and/or lower respiratory tract infections (109304).

Urinary incontinence. Limited evidence suggests that vitamin D may be beneficial in middle-aged, but not older, adults with urinary incontinence.
^ Details: Clinical research in middle-aged premenopausal females with stress urinary incontinence and low vitamin D status shows that taking vitamin D 5000 IU once weekly for 12 weeks has a moderate to large beneficial effect on the severity of incontinence and quality of life when compared with placebo. Kegel exercises were performed by all participants (109736). However, vitamin D supplementation does not seem to be beneficial for reducing urinary incontinence in older adults. In older females and males, a large clinical trial shows that vitamin D3 (cholecalciferol) 2000 IU daily for 5 years does not reduce the incidence or progression of urinary incontinence when compared with placebo (109738,109741). In older males with low vitamin D status, vitamin D supplementation may actually increase some types of incontinence (109738).

Urinary tract infections (UTIs). It is unclear if oral vitamin D is beneficial for the prevention of UTIs in children.
^ Details: A meta-analysis of 13 small observational studies in children suggests that lower levels of vitamin D are associated with 2.8-fold greater odds of UTI when compared with higher vitamin D levels. Further, this analysis shows that vitamin D deficiency in children is linked to 5.5-fold greater odds of UTI when compared with normal vitamin D levels (112030).

Urticaria. It is unclear if oral vitamin D is beneficial for the prevention or treatment of urticaria.

Details: A meta-analysis of population research has found that having urticaria is associated with a slightly lower vitamin D blood level and a greater likelihood of vitamin D deficiency when compared with individuals without urticaria. In addition, a meta-analysis of 6 clinical trials shows that taking high-dose vitamin D at an average daily dose of at least 4100 IU has a modest effect on the severity of urticaria symptoms (106115).

Uterine fibroids. Some evidence suggests that the risk of developing uterine fibroids is linked to vitamin D status, and that fibroid size is reduced by vitamin D supplements. However, it is unclear if oral vitamin D is beneficial for preventing the recurrence of uterine fibroids.
Details: Observational research suggests that uterine fibroids are linked to vitamin D deficiency, with normal vitamin D levels associated with 32% lower odds of developing uterine fibroids. A meta-analysis of 5 clinical trials shows that taking vitamin D for at least 8 weeks reduces uterine fibroid size when compared with placebo. One clinical study shows that the recurrence rate for uterine fibroids is about 9% with vitamin D supplementation, compared with 18% without. However, a clinical study in patients with low vitamin D levels undergoing hysteroscopic myomectomy for uterine fibroids shows that taking vitamin D 1000 IU daily for 12 months does not improve the rate of recurrence when compared with placebo (108422).

Vaginal atrophy. It is unclear if oral vitamin D is beneficial for vaginal atrophy. There is limited evidence on the topical use of vitamin D in vaginal atrophy in postmenopausal adults or patients taking tamoxifen.
Details: A small cross-sectional study in postmenopausal adults has found that taking a vitamin D supplement for at least one year improves the maturation index of superficial vaginal wall cells when compared with those who do not take vitamin D. However, symptoms of vaginal atrophy were not different between groups (16879). Vitamin D has also been evaluated for vaginal atrophy due to tamoxifen. A small clinical trial in females with breast cancer using tamoxifen shows that receiving vitamin D 1000 IU vaginal suppositories daily for 8 weeks improves maturation index of vaginal walls and self-reported symptoms when compared with placebo (99773).

Vertigo. It is unclear if oral vitamin D is beneficial in patients with vertigo.
Details: An analysis of observational research suggests that lower serum levels of vitamin D are associated with a higher risk of benign paroxysmal positional vertigo (BPPV) when compared with higher vitamin D levels (114579). However, it is unclear if vitamin D supplementation can reduce the risk of BPPV in individuals with low vitamin D levels.

Vitamin D has been evaluated in combination with other ingredients for the treatment of BPPV. A large clinical study in adults with recurrent BPPV shows that taking vitamin D 400 IU and calcium 500 mg twice daily for one year reduces the risk of recurrence by 27% when compared with no treatment. The number needed to treat to prevent vertigo was 4 (103681). It is unclear if this benefit is due to vitamin D, calcium, or the combination.

Vitiligo. Although there is interest in using oral vitamin D for vitiligo, there is insufficient reliable information about the clinical effects of vitamin D for this condition.

Warts. Although there is interest in using topical vitamin D derivatives for warts, there is insufficient reliable information about the clinical effects of vitamin D for this condition.

More evidence is needed to rate vitamin D for these uses.

Dosing & Administration

- **Adult**

  Oral:

  General: The United States Food and Drug Administration (FDA) requires that supplement labels list vitamin D content in units of micrograms (mcg). To convert from International Units (IU) to mcg, divide the IUs by a factor of 40. To convert from mcg to IUs, multiply the mcg amount by a factor of 40 (98237).

  The recommended dietary allowance (RDA) of vitamin D based on age is 600 IU (15 mcg) daily in those 1-70 years of age and 800 IU (20 mcg) daily in those 71 years and older. For those pregnant or lactating, the RDA is 600 IU (15 mcg) daily (17506). The National Osteoporosis Foundation recommends vitamin D 400-800 IU (10-20 mcg) daily for adults under age 50, and 800-1000 IU (20-25 mcg) daily for older adults (16120).

  The current RDA assumes that vitamin D2 (ergocalciferol) and vitamin D3 (cholecalciferol) are equivalent; however, some evidence indicates that vitamin D2 is less than one-third as potent as vitamin D3 and that vitamin D3 is more effective in improving vitamin D status (15263,15264,107228). Therefore, many experts now recommend using vitamin D supplements containing vitamin D3 in order to meet these intake levels (15263,15264).

  Recommendations for supplemental vitamin D doses vary greatly. In general, patients should not exceed the tolerable upper limit of 4000 IU daily, unless advised by a healthcare provider. See Effectiveness section for condition-specific information.

  Advise patients that vitamin D can be taken with or without food. When consumed with a low-fat meal, absorption of vitamin D is up to 20% higher than when consumed with a high-fat meal or no meal. However, this increased absorption does not correlate with a sustained increase in serum vitamin D levels (97302).

  Topical:

  Research is limited; typical dosing is unavailable. See Effectiveness section for condition-specific information.

- **Children**

  Oral:

  The recommended dietary allowance (RDA) for vitamin D is as follows: 1-18 years of age, 600 IU (15 mcg) daily; pregnant and lactating girls, 600 IU (15 mcg) daily. For infants ages 0-12 months, an adequate intake (AI) level of 400 IU (10 mcg) is recommended (17506). Avoid doses above the tolerable upper limit (UL), unless recommended by a healthcare provider.

The ULs for children are as follows: 1000 IU (25 mcg) daily for those 0-6 months of age, 1500 IU (37.5 mcg) daily for those 6-12 months of age, 2500 IU (62.5 mcg) daily for those 1-3 years of age, 3000 IU (75 mcg) daily for those 4-8 years of age, and 4000 IU (100 mcg) daily for those 9 years and older (17506). See Effectiveness section for condition-specific information.

The American Academy of Pediatrics increased the recommended minimum daily intake of vitamin D to 400 IU (10 mcg) daily for all infants and children, including adolescents (16614). Advise parents not to use vitamin D liquids dosed as 400 IU (10 mcg) per drop. Giving one dropperful or mL by mistake can deliver 10,000 IU (250 mcg) daily.

- **Standardization & Formulation**

  Vitamin D used in clinical research has included oral, topical, and injectable formulations. Also, inactivated, activated, and synthetic forms of vitamin D have been used in clinical research. Inactivated or unmetabolized forms of vitamin D have included cholecalciferol (vitamin D3) and ergocalciferol (vitamin D2) (11819,11820,11821). Activated forms of vitamin D have included alfacalcidol, calcitriol, and calcifediol (11818,11821,11823,39045,83933,83955). Synthetic or man-made forms of vitamin D have included dihydrotachysterol, calcipotriene, maxacalcitol, and paricalcitol (11818,11820,11822,84325).

  Some specific oral vitamin D products used in clinical research include Hydroferol (Lab Juventus), a brand of calcifediol (11825); and Rocaltrol (Roche SA), a brand of calcitriol (11825). In one clinical trial, oral vitamin D was administered via gravity-metered dropper bottles to deliver a consistent dosage (Ddrops Co, Woodbridge, ON, Canada) (91340).

  Topically, vitamin D has been used in clinical research alone or in combination with corticosteroids. Daivobet/Dovobet, a specific product used in clinical research, contains calcipotriol and betamethasone dipropionate (22283).

  In a survey of 67 multivitamins available in England for children ages 12 years and younger, 25% to 36% of the multivitamins provided at least 400 IU vitamin D daily. About 57% to 67% of multivitamins with a claim involving 'healthy bones' contained at least vitamin D 400 IU (98924).

Interactions with Drugs

ALUMINUM

Interaction Rating = **Moderate** Be cautious with this combination.
Severity = Mild • Occurrence = Probable • Level of Evidence = **B**

Vitamin D might increase aluminum absorption and toxicity, but this has only been reported in people with renal failure.

Details

The protein that transports calcium across the intestinal wall can also bind and transport aluminum. This protein is stimulated by vitamin D, which may therefore increase aluminum absorption (11595,11597,22916). This mechanism may contribute to increased aluminum levels and toxicity in people with renal failure, when they take vitamin D and aluminum-containing phosphate binders chronically (11529,11596,11597).

ATORVASTATIN (Lipitor)

Interaction Rating = **Moderate** Be cautious with this combination.
Severity = Mild • Occurrence = Probable • Level of Evidence = **B**

Vitamin D might reduce absorption of atorvastatin.

Details

A small, low-quality clinical study shows that taking vitamin D reduces levels of atorvastatin and its active metabolites by up to 55%. However, while atorvastatin levels decreased, total cholesterol, low-density lipoprotein (LDL) cholesterol, and high-density lipoprotein (HDL) cholesterol levels did not substantially change (16828). Atorvastatin is metabolized in the gut by CYP3A4 enzymes, and researchers theorized that vitamin D might induce CYP3A4, causing reduced levels of atorvastatin. However, this proposed mechanism was not specifically studied.

CALCIPOTRIENE (Dovonex)

Interaction Rating = **Moderate** Be cautious with this combination.
Severity = Moderate • Occurrence = Probable • Level of Evidence = **D**

Taking calcipotriene with vitamin D increases the risk for hypercalcemia.

Details

Calcipotriene is a vitamin D analog used topically for psoriasis. It can be absorbed in sufficient amounts to cause systemic effects, including hypercalcemia (15). Theoretically, combining calcipotriene with vitamin D supplements might increase the risk of hypercalcemia.

CYTOCHROME P450 3A4 (CYP3A4) SUBSTRATES

Interaction Rating = **Minor** Be watchful with this combination.
Severity = Mild • Occurrence = Possible • Level of Evidence = **D**

Vitamin D might induce CYP3A4 enzymes and reduce the bioavailability of CYP3A4 substrates.

Details

There is some concern that vitamin D might induce CYP3A4. In vitro research suggests that vitamin D induces CYP3A4 transcription. Additionally, observational research has found that increased UV light exposure and serum vitamin D levels are associated with decreased serum levels of CYP3A4 substrates such as tacrolimus and sirolimus, while no association between UV light exposure or vitamin D levels and levels of mycophenolic acid, a non-CYP3A4 substrate, was found (110539). A small, low-quality clinical study shows that taking vitamin D reduces levels of the CYP3A4 substrate atorvastatin and its active metabolites by up to 55%; however, the clinical effects of atorvastatin were not reduced (16828). While researchers theorized that vitamin D might induce CYP3A4, this proposed mechanism was not specifically studied.

DIGOXIN (Lanoxin)

Interaction Rating = **Moderate** Be cautious with this combination.
Severity = High • Occurrence = Possible • Level of Evidence = **D**

Theoretically, hypercalcemia induced by high-dose vitamin D can increase the risk of arrhythmia from digoxin.

Details

High doses of vitamin D can cause hypercalcemia. Hypercalcemia increases the risk of fatal cardiac arrhythmias with digoxin (15). Avoid vitamin D doses above the tolerable upper intake level (4000 IU daily for adults) and monitor serum calcium levels in people taking vitamin D and digoxin concurrently.

DILTIAZEM (Cardizem, others)
Interaction Rating = **Moderate** Be cautious with this combination.
Severity = Moderate • Occurrence = Probable • Level of Evidence = **B**
Theoretically, hypercalcemia induced by high-dose vitamin D can reduce the therapeutic effects of diltiazem for arrhythmia.
Details
High doses of vitamin D can cause hypercalcemia. Hypercalcemia can reduce the effectiveness of verapamil in atrial fibrillation (10574). Theoretically this could also occur with diltiazem. Avoid vitamin D doses above the tolerable upper intake level (4000 IU daily for adults) and monitor serum calcium levels in people taking vitamin D and diltiazem concurrently.

THIAZIDE DIURETICS
Interaction Rating = **Moderate** Be cautious with this combination.
Severity = Moderate • Occurrence = Probable • Level of Evidence = **D**
Theoretically, taking thiazide diuretics and high-dose vitamin D can increase the risk of hypercalcemia.
Details
Thiazide diuretics decrease urinary calcium excretion, which could lead to hypercalcemia if vitamin D supplements are taken concurrently (3072,11541,69580). This has been reported in people being treated with vitamin D for hypoparathyroidism, and also in elderly people with normal parathyroid function who were taking a thiazide, vitamin D, and calcium-containing antacids daily (11539,11540).

VERAPAMIL (Calan, others)
Interaction Rating = **Moderate** Be cautious with this combination.
Severity = Moderate • Occurrence = Probable • Level of Evidence = **B**
Hypercalcemia induced by high-dose vitamin D can reduce the therapeutic effects of verapamil for arrhythmia.
Details
Hypercalcemia due to high doses of vitamin D can reduce the effectiveness of verapamil in atrial fibrillation (10574). Avoid vitamin D doses above the tolerable upper intake level (4000 IU daily for adults) and monitor serum calcium levels in people taking vitamin D and verapamil concurrently.

Interactions with Supplements

CALCIUM: Vitamin D may increase the absorption of calcium in some people.
Details
Taking vitamin D along with calcium increases active absorption of calcium in the small intestine (7555). One clinical study shows that vitamin D supplementation increases true fractional calcium absorption in postmenopausal adults (98903). However, this does not seem to apply to premenopausal adults. In another clinical study in healthy young females, adding vitamin D up to 2400 IU daily to calcium did not improve absorption of calcium (98897). Theoretically, excessive intake of vitamin D and calcium might increase the risk of hypercalcemia in some people.

MAGNESIUM: Theoretically, vitamin D might increase the absorption of magnesium.
Details
The protein that transports calcium across the intestinal wall can also bind and transport magnesium. This protein is stimulated by vitamin D, which may therefore increase magnesium absorption (11595,11598). In people with low vitamin D and magnesium levels, taking vitamin D may improve magnesium status (11599). In people with normal magnesium levels, this effect does not seem to be significant, possibly because urinary magnesium excretion also increases (11598).

Interactions with Conditions

ARTERIOSCLEROSIS

High doses of vitamin D can cause hypercalcemia, which can contribute to arteriosclerosis, particularly in patients with kidney disease. Use supplemental vitamin D cautiously (11815,11816).

HISTOPLASMOSIS

Vitamin D may increase calcium levels in people with histoplasmosis. In people with this condition, the metabolism of vitamin D to calcitriol is increased, which may increase the risk for hypercalcemia and complications such as kidney stones and calcified tissue. Use supplemental vitamin D cautiously (11881).

HYPERCALCEMIA

Vitamin D supplements may precipitate and worsen hypercalcemia (11815).

HYPERPARATHYROIDISM

Vitamin D may increase calcium levels and lead to hypercalcemia in people with hyperparathyroidism. Use supplemental vitamin D cautiously (11815).

KIDNEY DISEASE

Vitamin D may increase calcium levels and increase the risk of arteriosclerosis in people with kidney failure. This must be balanced with the need to prevent renal osteodystrophy. Monitor calcium levels carefully (11816).

LYMPHOMA

Vitamin D may increase calcium levels in people with lymphoma. In some kinds of lymphoma, vitamin D is more readily converted to calcitriol and may result in hypercalcemia and complications such as kidney stones and calcified tissue. Use supplemental vitamin D cautiously (11815,11881).

SARCOIDOSIS

Vitamin D may increase calcium levels in people with sarcoidosis. In people with this condition, the metabolism of vitamin D to calcitriol is increased, which may increase the risk for hypercalcemia and complications such as kidney stones and calcified tissue. Use supplemental vitamin D cautiously (11881,110831).

TUBERCULOSIS

Vitamin D may increase calcium levels in people with tuberculosis. In people with tuberculosis infection, the metabolism of vitamin D to calcitriol is increased, which may increase the risk for hypercalcemia and complications such as kidney stones and calcified tissue. Use supplemental vitamin D cautiously (11881).

Interactions with Lab Tests

None known.

Nutrient Depletion

SOME DRUGS CAN AFFECT VITAMIN D LEVELS:

CARBAMAZEPINE (Tegretol)

Depletion Rating = **Moderate Depletion** Monitor for depletion; a supplement is needed in some patients.

Taking carbamazepine for 6 month or longer might reduce blood levels of vitamin D.

Details

Carbamazepine increases hepatic metabolism of vitamin D to inactive compounds, thereby reducing calcium absorption (2675,4430,4431). Hypocalcemia and osteomalacia have occurred, especially with prolonged therapy, concurrent use of other enzyme-inducing anticonvulsants, or when other risk factors for vitamin D deficiency are present (2675,4475,10578). Patients taking carbamazepine for 6 months or more may need vitamin D and calcium supplements. Doses of vitamin D needed range from 400-4000 IU daily (10578). For information on foods that are rich in vitamin D, see our **chart**.

CHOLESTYRAMINE (Questran)

Depletion Rating = **Moderate Depletion** Monitor for depletion; a supplement is needed in some patients.

High-dose or prolonged therapy with cholestyramine might reduce blood levels of vitamin D.

Details

Cholestyramine can reduce absorption of vitamin D. Occasionally this leads to osteomalacia, usually in patients receiving cholestyramine in doses above 32 grams daily, or prolonged therapy over 2 years, and with additional risk factors such as ileal resection or primary biliary cirrhosis, which deplete the bile acids needed for vitamin D absorption (4458,5655,5809,5838). Supplements of vitamin D, and sometimes calcium, are necessary in these patients. Use of cholestyramine (24 grams daily) for treatment of hyperlipidemia in otherwise healthy men doesn't seem to affect vitamin D and calcium levels, and supplements aren't necessary (2672).

CIMETIDINE (Tagamet)

Depletion Rating = **Insignificant Depletion** A supplement is not needed for most patients.

Cimetidine might reduce blood levels of vitamin D.

Details

Cimetidine inhibits an enzyme involved in conversion of vitamin D to its active form in the liver. However, it does not affect formation of active vitamin D metabolites in the kidneys. Clinically significant vitamin D depletion is not likely, except in people with other risk factors such as liver or kidney disease (11531,11532,22917).

COLESTIPOL (Colestid)

Depletion Rating = **Moderate Depletion** Monitor for depletion; a supplement is needed in some patients.

High-dose or prolonged therapy with colestipol might reduce blood levels of vitamin D.

Details

Colestipol can reduce absorption of fat-soluble vitamins, including vitamin D. This doesn't seem to be clinically significant when up to 20 grams daily is used for up to 2 years (4460,4461). For information on foods that are rich in vitamin D, see our **chart**.

CORTICOSTEROIDS

Depletion Rating = **Moderate Depletion** Monitor for depletion; a supplement is needed in some patients.

Corticosteroids might reduce blood levels of vitamin D.

Details

Corticosteroids, in daily doses equivalent to 7.5 mg or more of prednisone, cause significant bone loss, osteoporosis, and increased risk of fractures. The severity increases with duration of therapy. Although this is due mainly to disturbances in calcium homeostasis and bone formation, rather than vitamin D depletion, supplements of vitamin D are helpful to improve calcium absorption. Advise people taking corticosteroids in doses equivalent to prednisone 7.5 mg daily or more for 6 months or longer to maintain a daily calcium intake of 1500 mg, and to take a daily supplement of vitamin D 800 IU. Serum calcium should be monitored regularly (1832). For information on foods that are rich in vitamin D, see our **chart**.

EFAVIRENZ (Sustiva)

Depletion Rating = **Moderate Depletion** Monitor for depletion; a supplement is needed in some patients.

Efavirenz might reduce blood levels of vitamin D.

Details

Efavirenz-based antiretroviral regimens can reduce plasma levels of vitamin D. The reduction in vitamin D levels occurs within the first 6 months after initiation of antiretroviral therapy, with no subsequent reductions seen between 6 and 12 months after therapy initiation (97294). For information on foods that are rich in vitamin D, see our **chart**.

HEPARIN

Depletion Rating = **Insignificant Depletion** A supplement is not needed for most patients.

Heparin might reduce conversion of vitamin D to its active form.

Details

Unfractionated heparin is associated with reduced bone density and osteoporotic fractures, especially when doses of at least 15,000 IU daily are used for 3 months or longer (10577,10594,10595,10596). This is primarily due to direct effects of heparin on bone (increased resorption and reduced bone formation), but metabolism of vitamin D to its active form is also reduced (10577,10593,10597). Although it's not clear whether vitamin D and calcium supplements prevent bone loss associated with heparin, people needing heparin therapy for several months should maintain their recommended daily intakes of vitamin D and calcium, using supplements if necessary. For information on foods that are rich in vitamin D, see our **chart**.

LOW MOLECULAR WEIGHT HEPARINS (LMWHs)

Depletion Rating = **Insignificant Depletion** A supplement is not needed for most patients.

LMWH might reduce conversion of vitamin D to its active form.

Details

Reduced bone density has been reported with LMWHs, but probably to a lesser extent than with unfractionated heparin (10593,10598,10599,11555). The effect is primarily due to direct effects of heparins on bone (increased resorption and reduced bone formation), but metabolism of vitamin D to its active form is also reduced (10577,10593,10597). Although it's not clear whether vitamin D and calcium supplements prevent bone loss associated with LMWH, people needing therapy with LMWH for several months should maintain their recommended daily intakes of vitamin D and calcium, using supplements if necessary. For information on foods that are rich in vitamin D, see our **chart**.

MINERAL OIL

Depletion Rating = **Insignificant Depletion** A supplement is not needed for most patients.

Prolonged therapy with mineral oil might reduce blood levels of vitamin D.

Details

Mineral oil can reduce absorption of both vitamin D and calcium (4495). However, occasional or short-term use of mineral oil isn't likely to have a clinically significant effect.

ORLISTAT (Xenical, Alli)

Depletion Rating = **Major Depletion** A supplement is needed for most patients.

Orlistat decreases absorption and blood levels of vitamin D.

Details

Orlistat decreases absorption of fat-soluble vitamins including vitamin D, reducing plasma levels in some patients (1730,9595,10570). The manufacturer recommends that patients take a multivitamin supplement containing all fat-soluble vitamins, separating the dosing time by at least 2 hours from orlistat (1730).

PHENOBARBITAL (Luminal)

Depletion Rating = **Moderate Depletion** Monitor for depletion; a supplement is needed in some patients.

Taking phenobarbital for 6 month or longer might reduce blood levels of vitamin D.

Details

Phenobarbital increases hepatic metabolism of vitamin D to inactive compounds, thereby reducing calcium absorption (2675,4430,4431). Hypocalcemia and osteomalacia have occurred, especially with prolonged therapy, concurrent use of other enzyme-inducing anticonvulsants, or when other risk factors for vitamin D deficiency are present (2675,4475,10578). Patients taking phenobarbital for 6 months or more may need vitamin D and calcium supplements. Doses of vitamin D needed vary from 400-4000 IU daily (10578). For information on foods that are rich in vitamin D, see our **chart**.

PHENYTOIN (Dilantin)

Depletion Rating = **Moderate Depletion** Monitor for depletion; a supplement is needed in some patients.

Taking phenytoin for 6 months or longer might reduce blood levels of vitamin D.

Details

Phenytoin increases hepatic metabolism of vitamin D to inactive compounds, thereby reducing calcium absorption (2675,4430,4431). Hypocalcemia and osteomalacia have occurred, especially with prolonged therapy, concurrent use of other enzyme-inducing anticonvulsants, or when other risk factors for vitamin D deficiency are present (2675,4475,10578). Patients taking phenytoin for 6 months or more may need vitamin D and calcium supplements. Doses of vitamin D needed vary from 400-4000 IU daily (10578). For information on foods that are rich in vitamin D, see our **chart**.

RIFAMPIN (Rifadin)

Depletion Rating = **Moderate Depletion** Monitor for depletion; a supplement is needed in some patients.

Rifampin might reduce blood levels of vitamin D.

Details

Rifampin increases hepatic metabolism of 25-hydroxy-vitamin D, reducing its plasma levels (11561,11562,11563). This can contribute to osteomalacia after prolonged therapy (>1 year), especially if vitamin D intake is low (11562,11564). However, if isoniazid (INH, Nydrazid) is taken concurrently with rifampin there doesn't seem to be any change in vitamin D status (11561,11563). This may be because the enzyme-inducing effects on rifampin are canceled out by the enzyme-inhibiting effects of isoniazid (11563,11565). For information on foods that are rich in vitamin D, see our **chart**.

STIMULANT LAXATIVES

Depletion Rating = **Moderate Depletion** Monitor for depletion; a supplement is needed in some patients.

Prolonged therapy with stimulant laxatives might reduce blood levels of vitamin D.

^ Details

Prolonged use of high doses of stimulant laxatives can reduce dietary vitamin D and calcium absorption, leading to hypocalcemia and osteomalacia (11530). Advise patients to limit stimulant laxatives to short-term use of recommended doses.

SUNSCREENS

Depletion Rating = **Moderate Depletion** Monitor for depletion; a supplement is needed in some patients.

Frequent use of sunscreen might reduce blood levels of vitamin D.

^ Details

Frequent and extensive application of sunscreens can reduce vitamin D synthesis in the skin and plasma levels (11507,11508,11509). There is increasing concern that overuse of sunscreen can contribute to vitamin D deficiency and increased risk of some kinds of cancer (12992,12993). Tell patients that brief sun exposure is not likely dangerous and helps maintain adequate vitamin D levels. For longer exposures, recommend use of sunscreen to protect the skin. Advise people to maintain the recommended dietary intake of vitamin D. Consider supplements for people with minimal sun exposure and poor dietary intake (12992). For information on foods that are rich in vitamin D, see our **chart**.

Overdose

Presentation

Vitamin D intoxication can occur when vitamin D supplements are taken in excessive doses (10142,17506). Symptoms of vitamin D toxicity include hypercalcemia, azotemia, and anemia (10142,110831). Other symptoms of vitamin D toxicity include osteoporosis in adults, decreased growth in children, weight loss, anemia, calcific conjunctivitis, photophobia, metastatic calcification, pancreatitis, generalized vascular calcification, and seizures. Rarely, people develop hypertension and psychosis. Lab values of urinary calcium, phosphate, albumin, blood urea nitrogen, serum cholesterol, aspartate aminotransferase, and alanine aminotransferase concentrations might increase (10142).

There are two cases of vitamin D toxicity in 16-year-old males due to the inclusion of high-dose vitamin D in a creatine powder. Although vitamin D was not included on the label, the powder contained an estimated 425,000 IU per serving due to a manufacturing error. One patient consumed three servings daily for 5 days and the other consumed four servings daily for 1 week, followed by one serving daily for 3 weeks. Both patients developed acute kidney injury and hypercalcemia. Initial symptoms included fatigue, headache, and gastrointestinal symptoms. Blood levels of 25-hydroxyvitamin D were 1910 nmol/L and 1380 nmol/L (109739).

Treatment

Treatment for vitamin D toxicity may include intravenous hydration, calcitonin, and pamidronate (109739).

Commercial Products Containing: Vitamin D

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NSF Certified for Sport Products

Pharmacokinetics

Absorption: The two forms of vitamin D, cholecalciferol and ergocalciferol, are well absorbed. However, cholecalciferol appears to be more efficient in raising 25-hydroxyvitamin D serum levels, which is the best measure of vitamin D status (11937,11938,15263,15264,16119). Each mcg of cholecalciferol daily seems to increase serum 25-hydroxyvitamin D concentrations by an average of 0.78 ng/mL. Ergocalciferol yields lower increases (84652,84657). In healthy adults, the bioavailability of vitamin D from fortified food appears to be equivalent to the bioavailability of vitamin D from supplements (84246). The bioavailability of supplemental vitamin D can be affected by the accompanying beverage. When taken with milk or water, the bioavailability of cholecalciferol is greater than when taken with apple juice (110826). The bioavailability of supplemental vitamin D might also be affected by its formulation. Pharmacokinetic research in healthy adults shows that a micellar carrier-based microencapsulated vitamin D3 supplement has around 6-fold greater absorption, based on serum 25-hydroxyvitamin D concentrations, when compared with standard liquid vitamin D3 supplements, but only at doses of 1000 IU daily. Absorption of the 2500 IU daily dose is similar between formulations (114585).

Distribution: Dietary vitamin D is transported differently than vitamin D produced in the skin following exposure to the sun. Dietary vitamin D is transported primarily by chylomicron, which allows vitamin D to be distributed to peripheral tissues. If not taken up by peripheral tissue, vitamin D is transported to the liver, where it is converted to calcitriol. Vitamin D produced in the skin is transported on vitamin D binding protein (DBP) (93003).

Metabolism: Both ergocalciferol and cholecalciferol are biologically inert and require hydroxylation in the body to form the

active metabolite, calcitriol (7555,16890). Vitamin D hydroxylation first appears to occur in the liver (84242,84461). Then hydroxylation of vitamin D to calcitriol occurs in the kidneys. People with chronic renal failure may require forms of vitamin D that don't require renal hydroxylation, such as calcitriol, dihydrotachysterol, or calcifediol (7555). In people with granulomatous disorders such as tuberculosis, sarcoidosis, and histoplasmosis, vitamin D metabolism is disturbed. Vitamin D is converted to calcitriol by activated macrophages trapped in the pulmonary alveoli and granulomatous inflammation, in addition to the kidneys. This may increase the risk of hypercalcemia (7555,11881).

Excretion: Vitamin D may be cleared more rapidly in certain disease states such as diabetes, HIV, and cancer (84226).

Mechanism of Action

General: Vitamin D is a fat-soluble vitamin. The term vitamin D refers to several forms of vitamin D. There are 2 forms that are physiologically important, ergocalciferol (vitamin D2) and cholecalciferol (vitamin D3). Ergocalciferol comes from ergosterol, a plant sterol, and yeast. Cholecalciferol is synthesized in the skin via 7-dehydrocholesterol, a cholesterol precursor. Both ergocalciferol and cholecalciferol are biologically inert and require hydroxylation in the body to form the active metabolite, calcitriol (7555,16890). Since the early 1900s, ergocalciferol and cholecalciferol have been considered to be equally potent and effective in humans. However, more recently, research shows that cholecalciferol is significantly more potent than ergocalciferol and is more effective at improving total 25-hydroxyvitamin D levels (11937,11938,15263,15264,16119,107228). Ergocalciferol appears to be less than one-third the potency of cholecalciferol (11937,11938,15263,15264,16119). A blood concentration of 20 ng/mL 25-hydroxyvitamin D is considered the level to meet the bodily needs of 97.5% of the population. Lower amounts are usually considered a 'deficiency'. Higher concentrations of 32 ng/mL are preferred (15638,93945). Most laboratories consider the "normal" range to be 20 ng/mL to 100 ng/mL (16119). Very few foods naturally contain vitamin D. Dietary sources include eggs from hens that have been fed vitamin D and fatty fish such as herrings, mackerel, sardines, and tuna. In the US, Canada, and many other countries, the main source of dietary vitamin D is fortified milk and other foods. However, these are relatively minor sources of vitamin D (7555).

Brief exposure to sunlight (about 25% of the amount of time it would take to cause light pinkness to the skin) is the most efficient way to get vitamin D (11935). Skin exposure to the sun provides as much as 80% to 90% of the body's vitamin D stores (7133). Full-body sun exposure can lead to the synthesis of as much as 10,000 units of vitamin D daily (6855). Vitamin D is stored in body fat for use during periods without sun exposure. Sun exposure is an easy, reliable way for most patients to get vitamin D. Exposure of the hands, face, arms, and legs to sunlight two to three times a week for the amount of time equal to about 25% of what it would take to develop a mild sunburn will cause the skin to produce adequate vitamin D. Exposure time will vary with skin type, season, and time of day (12992). Conversely, excessive sun exposure causes photodegradation of vitamin D produced in the skin, limiting the risk of vitamin D toxicity from such exposure (11936).

Vitamin D insufficiency, based on blood levels of 25-hydroxyvitamin D below 20 ng/mL, is common in the northern latitudes such as Canada and the northern half of the US (12995). Interestingly, these levels also occur in as many as 40% of older people even in sunny climates such as South Florida (15637). Prevalence of vitamin D considered insufficient and deficient among young, healthy people appears to be increasing, possibly because of excessive use of sunscreens (12995). Exposure to sunlight might not always be sufficient to cause vitamin D synthesis in the skin. Sunlight intensity is dependent on latitude, altitude, season, cloud cover, ozone levels and other factors. During winter in some northern latitudes (e.g., northern US and Canada), little, if any, vitamin D3 is produced in the skin. For example, in Boston there is insufficient UV-B energy for vitamin D production in the skin for 4 months of the year. In Edmonton, the skin can't produce vitamin D for 5 months of the year (12998,12999,13000). Underway submariners, who get no sunlight for extended periods of time, have lowered 25-hydroxyvitamin D levels and evidence of bone resorption and turnover, even when supplemented with 400 IU daily of cholecalciferol. The capacity of UV-B mediated vitamin D synthesis is huge. Just 6 days of casual sunlight exposure without sunscreen can make up for 49 days of no sunlight exposure (12998).

Skin pigmentation affects vitamin D synthesis and 25-hydroxyvitamin D levels. A light-skinned person in a bathing suit who is not tanned would receive about 10,000 to 20,000 IU of cholecalciferol from 10-12 minutes of peak July summer sun in Boston. For a darker-skinned person, such as Asian Indian, getting this dose of vitamin D could take perhaps 30 minutes of exposure, and, for a very darkly pigmented African American, it could require 120 minutes of exposure (12997). The skin pigment melanin competes with vitamin D precursors in the skin for photons from UV-B light (6857). When serum 25-hydroxyvitamin D levels are adjusted for percent body fat, White females have serum levels 1.3-1.9 times higher than Black females (16887). This also affects vitamin D in breast milk. For example, breast milk from Black females is generally lower in vitamin D content than that from White females (35 units/L compared with 68 units/L, respectively) (6857). Black infants who are exclusively breast-fed are therefore at risk for vitamin D deficiency and rickets, even if they live in sunny climates such as the southern US (6857). Vitamin D supplements may be needed by elderly people with limited sun exposure, people living in northern latitudes, dark-skinned people, Asian Indians living in the western hemisphere, as well as people with gastrointestinal diseases leading to malabsorption of vitamin D from the diet (6855,7133).

Vitamin D deficiency, based on blood levels <20 ng/mL, is particularly common in adults over age 50 years. More than 50% of North American females receiving therapy to prevent or treat osteoporosis have inadequate vitamin D stores (12996). Factors such as lack of exposure to sunlight, reduced skin synthesis of vitamin D, lower dietary intake, impaired intestinal absorption, chronic kidney disease, and reduced metabolism to active forms of vitamin D by the kidneys increase with aging (11919,16883). Also, vitamin D receptors seem to decrease with age (11921). The risk for vitamin D deficiency in elderly adults (>65 years) is very high (12995,12996). The risk for severe vitamin D deficiency is even greater with advanced age. A survey of 104 adults older than 98 years old found blood levels of vitamin D were detectable in only 5 adults. This correlates to a blood level of less than 2 ng/mL (16874).

Body mass index seems to affect vitamin D status. There is some evidence that individuals with a body mass index (BMI) of >25kg/m2 have reduced serum vitamin D levels and/or reduced bioavailability of vitamin D from both cutaneous synthesis and gastrointestinal absorption (6856,110817). In response to similar UV-B exposures, the increase in serum vitamin D levels can be 57% less in people with obesity than in those with lower BMIs (6856). In individuals with a BMI of at least 25 kg/m2, taking cholecalciferol 2000 IU for 5 years modestly reduces the response to supplementation when compared with individuals with a BMI of up to 25 kg/m2 (110817). The content of vitamin D precursors in the skin are similar in both groups, suggesting that vitamin D synthesis is not affected by BMI, but that vitamin D is possibly sequestered into body fat, reducing its availability

(6856).

The main function of vitamin D is to regulate serum calcium and phosphorus concentrations. Vitamin D enhances the efficiency of the intestinal absorption of calcium, primarily in the duodenum and jejunum, and phosphorus, particularly in the jejunum and ilium (7555). In the absence of adequate vitamin D, only 10% to 15% of calcium is absorbed and phosphorus absorption is only 60%. In the presence of vitamin D, calcium absorption increases to 30% to 40% and phosphorus absorption to 80% (16890). Vitamin D can increase serum calcium levels, but this effect is modest in healthy people in doses less than 1200 IU daily. If dietary intake of calcium is inadequate, calcitriol in combination with parathyroid hormone mobilizes calcium stores from bone. Calcitriol also appears to have effects in the brain, heart, pancreas, mononuclear cells, activated lymphocytes, and skin, but its exact physiologic role is unclear (7555).

The hydroxylation of vitamin D to calcitriol occurs in the kidneys. People with chronic renal failure may require forms of vitamin D such as calcitriol, dihydrotachysterol, or calcifediol that don't require renal hydroxylation (7555).

In people with granulomatous disorders such as tuberculosis, sarcoidosis, and histoplasmosis, vitamin D metabolism is disturbed. Vitamin D is converted to calcitriol by activated macrophages trapped in the pulmonary alveoli and granulomatous inflammation, in addition to the kidneys. This may increase the risk of hypercalcemia (7555,11881).

Antidiabetic effects: There is interest in whether supplementing with vitamin D can impact glycemic indices in diabetes. Vitamin D impacts the function of beta-cells by mediating calcium flux. Population research found that a lower vitamin D level is associated with a higher risk of developing type 2 diabetes compared to higher vitamin D levels (15630,16713,84594). Some preliminary clinical research suggests that vitamin D insufficiency may contribute to impairment of insulin secretion and insulin action (83898). Other clinical research in patients mostly without diabetes shows that supplementing with calcium 1000 mg or more daily in conjunction with vitamin D 2000 IU or more daily lowers fasting blood glucose and reduces insulin levels and insulin resistance measured by Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) (100893).

However, it doesn't seem that vitamin D supplements can prevent or treat diabetes. Most evidence suggests that vitamin D does not significantly improve glycemic indices in patients with type 2 diabetes with adequate vitamin D status, but it may help prevent the development of type 1 diabetes when given to infants during early childhood (10139,83898,84225,84488,84594,84636,84645,84808,91347,96403)(107210,110822). Although supplementation with oral vitamin D, alone or in combination with omega-3 fatty acids, for 8 weeks actually seems to increase glycated hemoglobin (HbA1c) levels by about 0.2% or 0.4%, respectively, in patients who are vitamin D-deficient and mostly healthy when compared with control, it should be noted that more patients receiving supplementation had prediabetes at baseline when compared with control (107192).

Anti-inflammatory effects: Although some individual clinical trials disagree (110812,110828), an overarching meta-analysis of 23 individual meta-analyses shows that vitamin D supplementation in adults reduces serum levels of C-reactive protein (CRP), as well as tumor necrosis factor-alpha (TNF-alpha) and malondialdehyde. However, there were no effects on levels of interleukin-6 (IL-6) or total antioxidant capacity (109731). A meta-analysis of 7 studies in postmenopausal individuals shows that vitamin D supplements reduce CRP levels, especially at doses below 1000 IU daily for more than 3 months in subjects with lower baseline vitamin D levels (113583). A meta-analysis of clinical research and a clinical study in patients with ulcerative colitis and allergic rhinitis also shows that taking vitamin D modestly reduces levels of inflammatory cytokines TNF-alpha, CRP, and IL-6 and increases levels of anti-inflammatory cytokines interferon gamma and interleukin-10 (109044,112483). A meta-analysis of clinical research in patients with asthma also shows that taking vitamin D increases levels of IL-10 (114505). It is unclear whether these benefits are sustained in long-term studies. One large clinical trial shows that taking cholecalciferol alone or with omega-3 fatty acids reduces serum levels of CRP by 19% after 2 years, with no continued evidence of benefit after 4 years. Also, the levels of other inflammatory or anti-inflammatory mediators were not affected (110815). Vitamin D supplementation has also been found to reduce tissue and salivary levels of interferon-gamma (114586).

Anti-malarial effects: A meta-analysis of animal research suggests that vitamin D improves survival after Plasmodium infection. Researchers theorize that the benefits of vitamin D in animal models of malaria relate to its anti-inflammatory and immunologic effects (112023).

Anti-oxidant effects: There is interest in vitamin D for its potential anti-oxidant effects. Clinical research in patients with polycystic ovary syndrome (PCOS) shows that vitamin D supplementation increases total antioxidant capacity and reduces malondialdehyde when compared with a control (114584).

Anti-sepsis effects: There is interest in using vitamin D to improve outcomes in patients with sepsis. A meta-analysis of case-control studies shows that neonates and children with sepsis are more likely to have low serum levels of vitamin D than non-septic patients. However, a meta-analysis of cohort studies suggests that children with low serum vitamin D levels (< 20 ng/mL) do not have an increased risk of sepsis, mechanical ventilation, or mortality. This study may have been inadequately powered to detect a difference between groups (105722). It is unknown if treating low serum levels of vitamin D will prevent sepsis or improve outcomes in patients with sepsis.

Bone effects: Since vitamin D is important for calcium homeostasis and for bone health, it is used to help prevent osteoporosis. Early research suggested serum levels of 25-hydroxy-vitamin D (calcifediol) of at least 16 ng/mL for optimal bone health (6854). This is supported by the dietary reference intakes (93945). However, some researchers suggest serum levels of 28 to 32 ng/mL may be necessary for bone health (13276). When intake of calcium is low in healthy elderly females, 25-hydroxy-vitamin D (calcifediol) seems to be more biologically active and a more important determinant of gut calcium absorption than calcitriol (10141). Osteopenia in elderly males also seems to correlate with circulating levels of vitamin D and vitamin K (7132). There is also concern that high dose vitamin D might result in lower bone mineral density (BMD); however, research has not shown consistent results. Clinical research in healthy adults shows that taking vitamin D for 3 years at a dose of 4000 IU daily or 10000 IU daily seems to result in lower radial BMD when compared with control of taking 400 IU daily. Tibial BMD was lower only with the 10 000 IU dose when compared with control. However, there were no differences between groups in BMD of the radius or tibia (100894).

Cancer effects: There is some epidemiological evidence that people with vitamin D deficiency might be at an increased risk of colon, breast, and prostate cancer (7555). Other evidence suggests that higher serum levels of vitamin D are associated with a decreased risk of cancer (16101). Some researchers think vitamin D might have antiproliferative effects in these cancers (6855).

Prostate cancer has been associated with decreased sun exposure and vitamin D receptor activity (12994). Some evidence also suggests that vitamin D may play a role in the inhibition of cancer cell proliferation, differentiation, and apoptosis (16882).

Cardiovascular effects: There is interest in using vitamin D to prevent and treat cardiovascular disease. Vitamin D is thought to play a role in cardiovascular disease by affecting inflammatory mediators such as tumor necrosis factor-alpha (TNF-alpha) and interleukins. Vitamin D might also decrease cardiac and vascular remodeling through suppression of the rennin gene and suppression of parathyroid hormone (14614,16620,16621,16622). Some research shows that vitamin D supplementation might also suppress macrophage cholesterol uptake and decrease foam cell formation (16873). Clinical research in adults with heart failure shows that taking vitamin D with calcium reduces serum aldosterone levels, but does not alter serum levels of C-reactive protein (CRP), N-terminal pro-brain natriuretic peptide (NT-proBNP), or galectin-3 (97300). There is also interest in whether vitamin D might reduce progression of atherosclerosis. However, a meta-analysis of clinical research shows that vitamin D supplementation has no effect on measures of endothelial function such as flow-mediated dilation, pulse wave velocity, and central augmentation index (103663,103664).

Evidence in humans also suggests that taking vitamin D may result in a reduction in blood pressure. However, not all studies agree. It is possible that blood pressure lowering effects associated with vitamin D are related to direct effects on the vascular cells or a suppression of the renin-angiotensin-aldosterone system (84226,84364,84410,84554,84631,84692). There is interest in whether a mega-dose of vitamin D can decrease the resting blood pressure in elderly females with hypertension, enhance post-exercise hypotension, and improve autonomic nervous modulation. A small case control study in older females with hypertension shows that taking a single dose of vitamin D3 (cholecalciferol) 200,000 IU does not reduce resting blood pressure, but might reduce post-exercise systolic hypotension, and increase the low frequency/high frequency (LF/HF) ratio, a controversial measure of sympathovagal balance (103657).

Gastrointestinal effects: There is interest in the anti-inflammatory effects of vitamin D in patients with ulcerative colitis (UC), which involves chronic recurrent inflammation of the colon. A small clinical study in patients with mild-to-moderate UC shows that receiving a single muscular injection of 7.5 mg vitamin D3 decreases serum tumor necrosis factor (TNF)-alpha, interferon-c, and interleukin (IL)-12p70 levels, but not IL-4 and IL-10 levels, when compared with an injection of normal saline (100898). Also, a meta-analysis of clinical research in patients with UC shows that taking vitamin D modestly reduces levels of IL-6, TNF-alpha, and C-reactive protein (CRP) and improves the repair function of intestinal mucosa (109044).

Hematologic effects: An observational study in patients with vitamin D deficiency has found that supplementation with vitamin D is associated with reduced platelet concentrations (107229).

Hepatoprotective effects: There is interest in using vitamin D to treat or prevent hepatic fibrosis in patients with chronic hepatitis C. However, preliminary clinical research in adults with serum vitamin D levels <30 ng/mL and a sustained virological response after hepatitis C treatment shows that taking vitamin D2 (ergocalciferol) 60,000-100,000 IU weekly for 6 weeks does not reduce serum levels of hepatic fibrinogenesis markers, such as transforming growth factor-beta (TGF-beta), tissue inhibitor of matrix metalloproteinase-1 (TIMP-1), matrix metalloproteinase 9 (MMP-9) and amino terminal type III procollagen peptide (P3NP), when compared with placebo. However, this study did not evaluate liver biopsies for fibrosis (105723).

Hormonal effects: There is interest in using vitamin D to increase testosterone levels in males and improve the hormone profile in patients with polycystic ovary syndrome (PCOS). However, a small clinical study in middle-aged males with low testosterone levels shows that taking vitamin D 20,000 IU daily for 12 weeks does not affect levels of serum total testosterone, free testosterone, sex hormone-binding globulin, follicle-stimulating hormone, estradiol, or luteinizing hormone (103660). Clinical research in patients with PCOS shows that vitamin D supplementation reduces total testosterone levels but does not modify levels of sex-hormone binding globulin or free androgen index (114584).

Immunologic effects: Vitamin D may have immunologic activity. In models of autoimmune disease, vitamin D seems to act as an immunosuppressant. This might explain why increased vitamin D intake is associated with a lower risk of autoimmune diseases (e.g., rheumatoid arthritis) (12206,84529,107184). Additionally, people with autoimmune disease seem to have lower serum vitamin D levels than healthy controls (112482,112483). Some evidence suggests vitamin D supplementation during infancy might prevent the development of type 1 diabetes later on in life. Type 1 diabetes is believed to be an autoimmune disease. Vitamin D supplementation might inhibit an autoimmune reaction that targets the beta cells of the pancreas (10139,16886).

Vitamin D has also shown other immunologic effects. Some research shows that CD4+ T cell counts are lower in patients with tuberculosis and low vitamin D status when compared with those with normal vitamin D status, and that supplementation with vitamin D as calcitriol increases these T cell counts (109045). Another study in patients with allergic rhinitis suggests that vitamin D reduces CD4+ and CD4+/CD8+ ratio and increases CD8+ serum levels (112483). In patients hospitalized with COVID-19, taking vitamin D increases neutrophil and lymphocyte counts, decreases levels of C-reactive protein (CRP), and alters the activity of B cells (109047).

Neurologic effects: A small meta-analysis of clinical studies in a mixed population shows that taking vitamin D improves sleep quality by 2 points on the Pittsburgh Sleep Quality Index (PSQI) when compared with control (108433).

Respiratory effects: There is interest in using vitamin D for improving respiratory disorders such as bronchitis, chronic obstructive pulmonary disorder (COPD), and asthma. Epidemiological evidence suggests that 25-hydroxy vitamin D serum levels are associated with pulmonary function. People with higher levels seem to have greater pulmonary function as measured by FEV1 compared to people with lower levels. It is theorized that vitamin D might be involved in remodeling of lung tissue (14252,17685). Vitamin D might also improve lung function by decreasing immune-mediated inflammation in the airway (14253,84505,84613).

Evidence from a population based study suggests patients with low 25-hydroxy vitamin D serum levels are 27% to 55% more likely to have upper respiratory tract infections compared to patients with normal levels (16830), though clinical research has not shown that vitamin D supplementation reduces the incidence of acute respiratory infections in older adults (114506). It is also not known if taking vitamin D supplements improves pulmonary function. Vitamin D deficiency has been commonly reported in children with mild-to-moderate asthma and is also associated with increased risk of asthma exacerbations that are severe. Vitamin D receptor variants have been associated with asthma in some population studies. Additionally, population studies suggest that lower vitamin D levels are correlated with increased inhaled corticosteroid needs in children (17685).

Skeletal muscle effects: Vitamin D deficiency causes muscle pain and proximal muscle weakness with symptoms such as sensation of heaviness in the legs, rapid fatigue, and problems with climbing stairs and getting up from a chair. Some preliminary clinical research suggests that people with low vitamin D levels, considered to be less than or equal to 20 ng/mL, have more osteoarthritis pain and disability than people with adequate vitamin D stores. Vitamin D deficiency also increases postural sway and affects psychomotor function (11922,11923,11924,11925,12491). Vitamin D may prevent falls by increasing muscle strength and neuromuscular function in addition to strengthening bone. It seems to increase muscle protein synthesis, possibly by activating second messengers and phosphorylation (11919,11922). Some evidence also shows that higher serum levels of vitamin D is associated with improved lower-extremity function in people aged 60 years or older (15636). The standard dose of 400 units that is found in most multivitamin tablets appears to be too low to prevent falls or reduce fracture risk, but the optimal dose is unknown (11926,11927,11928). Fractures were reduced in clinical trials using 700 to 800 units of vitamin D daily (11930,11931). Some research suggests that sufficient calcium intake along with vitamin D is necessary to prevent falls (11932).

Thyroid effects: A meta-analysis of clinical studies in patients with Hashimoto thyroiditis shows that vitamin D supplementation reduces thyroid peroxidase antibody titers, especially when cholecalciferol is used for more than 3 months (108430).

Uterine effects: Vitamin D regulates cytochrome P450-27B1 and -24A1 enzymes, which are dysregulated in uterine fibroid disease. It also decreases growth of uterine fibroid cells, reducing expression of cyclin-dependent kinase 1 and cell proliferation nuclear antigen (113577).

Classifications

Cytochrome P450 3A4 (CYP3A4) Inducers, Fat-soluble Vitamins, Immunomodulators

References

See Monograph References

Monographs are reviewed on a regular schedule. See our Editorial Principles and Process for details. The literature evaluated in this monograph is current through 12/17/2024. This monograph was last modified on 12/17/2024. If you have comments or suggestions, please tell the editors.