

Cognitive Vitality Reports® are reports written by neuroscientists at the Alzheimer's Drug Discovery Foundation (ADDF). These scientific reports include analysis of drugs, drugs-in-development, drug targets, supplements, nutraceuticals, food/drink, non-pharmacologic interventions, and risk factors. Neuroscientists evaluate the potential benefit (or harm) for brain health, as well as for age-related health concerns that can affect brain health (e.g., cardiovascular diseases, cancers, diabetes/metabolic syndrome). In addition, these reports include evaluation of safety data, from clinical trials if available, and from preclinical models.

Vitamin D

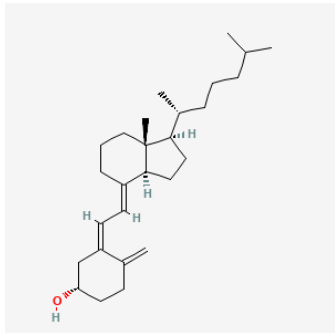
Evidence Summary

Observational studies are compelling with regards to higher vitamin D levels and lower risk of dementia and age-related diseases, but clinical trials of vitamin D have generally not produced protective benefits.

Neuroprotective Benefit: While observational studies have shown strong links between low vitamin D levels and higher dementia risk, vitamin D treatment trials have mostly reported a lack of cognitive benefit in healthy people and in people with dementia.

Aging and related health concerns: Vitamin D supplementation has shown a lack of benefit for prevention of cardiovascular diseases or cancer. Small biomarker benefits have been observed in metabolic conditions and rheumatoid arthritis.

Safety: Large, long-term clinical trials have reported that vitamin D is generally safe when used as directed. Prolonged sun exposure does not cause vitamin D overdose. Excessive supplementation can lead to renal failure, cardiac arrhythmias, and other conditions.

Availability: in food and as over-the-counter supplements	Dose: The recommended dietary allowance for adults is 600 IU (15 mcg) daily. For adults >70 years old, it is 800 IU (20 mcg) daily.	Chemical formula: C ₂₇ H ₄₄ O ₅ MW: 384.6 (vitamin D3)  Source: PubChem
Half-life: vitamin D3 stored in fat tissue has a half-life about 2 months; 25-hydroxy-vitamin D, the main circulating form measured in blood tests, has a half-life of 2-3 weeks	BBB: penetrant	
Clinical trials: The largest meta-analyses have included 80+ randomized controlled trials enrolling a total of 160,000+ participants.	Observational studies: Large meta-analyses of observational studies have included over 2M participants.	

What is it?

Vitamin D is a fat-soluble vitamin and hormone that the body needs to build strong bones, absorb calcium, and support the immune and nervous systems. Vitamin D binding to vitamin D receptors results in various regulatory roles, including maintaining calcium balance, the regulation of parathyroid hormone, the promotion of kidney reabsorption of calcium, increased absorption of calcium and phosphorus by the intestine, and increased calcium and phosphorus mobilization from bone to plasma to maintain balanced levels ([DrugBank.com](#)). Vitamin D receptors are also found throughout the brain and vitamin D appears to play a role in neuroprotection and anti-inflammatory effects [1].

There are two forms of vitamin D: D2 and D3. While some vitamin D2 is present in mushrooms, it is pharmacologically less potent than vitamin D3, which we get predominantly from a photochemical conversion of the vitamin D3 precursor 7-dehydrocholesterol in the skin via exposure to ultraviolet B wavelengths of sunlight ([DrugBank.com](#); [PubChem](#)). Our skin can produce up to 10,000 IU (international units) of vitamin D3 with just 20-30 minutes of sunlight exposure. The skin's ability to produce vitamin D3, however, declines with age and vitamin D deficiency is common in older adults. Severe vitamin D

deficiency can increase one's risk of bone pain, muscle pain, and fatigue, with some impacts on respiratory and cardiovascular conditions (<25 nmol/L of 25-hydroxy-vitamin D in the blood; equivalent to <10 ng/mL). Vitamin D levels can vary across seasons, often decreasing in the winter due to less sun exposure. Some foods that contain vitamin D3 include fatty fish (e.g., salmon, trout, and mackerel), cod liver oil, and egg yolk.

Vitamin D treatment is indicated for use in the treatment of hypoparathyroidism, refractory rickets, and familial hypophosphatemia ([DrugBank.com](https://www.drugbank.com)). Vitamin D supplementation is also used for treatment of vitamin D-deficient states in adults and children, which can occur due to insufficient sunlight exposure, insufficient dietary intake, increased age, and weight loss surgery ([Drugs.com](https://www.drugs.com)).

Neuroprotective Benefit: While observational studies have shown strong links between low vitamin D levels and higher dementia risk, vitamin D treatment trials have mostly reported a lack of cognitive benefit in healthy people and in people with dementia.

Types of evidence:

- 4 meta-analyses of randomized controlled trials examining the effects of vitamin D treatment on cognitive functions
- 9 meta-analyses of observational studies examining the link between vitamin D levels and cognitive functions or dementia risk
- 3 large randomized clinical trial testing the effects of vitamin D in healthy individuals
- 1 double-blind randomized controlled trial testing vitamin D intervention in people with mild cognitive impairment
- 3 randomized controlled studies testing the effects of vitamin D in people with dementia
- 1 Mendelian randomization study examining the relationship between genetically predicted vitamin D levels and dementia risk or neuroimaging markers
- 8 observational studies examining links between vitamin D levels and cognitive function/decline
- Numerous preclinical studies on possible mechanisms of action

Human research to suggest prevention of dementia, prevention of decline, or improved cognitive function:

Numerous observational studies, including Mendelian randomization studies, have found that people with low vitamin D levels are more likely to develop dementia, or higher blood levels of vitamin D are

associated with lower risk of mild cognitive impairment or dementia [2; 3; 4; 5; 6; 7]. A 2025 meta-analysis of 22 studies including a total of 53,122 participants reported a dose-response relationship between vitamin D levels and dementia risk such that people in the lowest vitamin D category had a 49% higher risk of dementia compared to those in the highest category (RR=1.49; 95% CI, 1.32 to 1.67; $p=0.039$) [8]. Each 10 nM/L increase in vitamin D levels was associated with a 1.2% lower risk of dementia (RR=0.988; 95% CI, 0.982 to 0.994; $p=0.007$). In a 2024 meta-analysis of 30 observational studies including a total of 525,714 people with a mean follow-up of 2 to 21 years, vitamin D deficiency (25-hydroxy-vitamin D levels of 25-50 nmol/L, or 10-20 ng/ml) was associated with a 42% higher risk for dementia (RR=1.42; 95% CI, 1.21 to 1.65), a 57% higher risk for Alzheimer's disease (RR=1.57; 95% CI, 1.15 to 2.14), and a 34% higher risk of cognitive impairment (RR=1.34; 95% CI, 1.19 to 1.52) [9]. 25-hydroxy-vitamin D levels associated with the lowest dementia risk was approximately between 77.5-100 nmol/L.

Despite the numerous observational studies showing a consistent relationship between vitamin D levels and dementia risk (or cognitive function), these are only designed to show associations and not definitive causation. Randomized controlled trials are needed to confirm causality.

There have been numerous randomized placebo-controlled clinical trials aiming to prove that higher vitamin D levels (through supplementation) prevent dementia; however, these have generally not produced positive results.

The largest and longest randomized clinical trial to date testing vitamin D was part of the Women's Health Initiative, where 4,143 women over age 65 were randomized to a combination of vitamin D3 (400 IU/day) and calcium (1,000 mg/day) vs placebo, with a mean follow-up of 7.8 years [10]. This trial found that vitamin D + calcium supplementation did not significantly alter risk of mild cognitive impairment or dementia, or affect global or domain-specific cognitive function.

Two ancillary studies of the VITAL trial (VITamin D and Omega-3 Trial), VITAL-Cog (n=3,424) and CTCS-Cog (n=794), tested a high-dose vitamin D3 (2000 IU/day) and fish oil against placebo for 2-3 years in people over 60 years old with no cardiovascular disease or cancer at baseline, to determine whether vitamin D3 or fish oil affects cognitive functions [11]. The primary outcome was the global composite score, which showed no mean difference in annual rate of decline for vitamin D3 versus placebo in the VITAL-Cog study (mean difference [MD]=0.01; 95% CI, -0.01 to 0.02) or the CTCS-Cog study (MD=0.05; 95% CI, -0.04 to 0.14). A meta-analysis of the 2 trials also showed no significant benefits of vitamin D3 supplementation on annual rate of decline of the global composite (MD=0.01; 95% CI, -0.01 to 0.02),

verbal composite (MD=0.01; 95% CI, -0.01 to 0.02), executive function/attention composite (MD=0.01; 95% CI, -0.01 to 0.02), and telephone interview of cognitive status (MD=0.03; 95% CI, -0.03 to 0.09). No between-group differences were seen after multivariable-adjustment of the global composite score or any of the secondary outcomes for either of the trials. There were also no significant interactions between cognitive outcomes and baseline 25-hydroxy-vitamin-D levels. There was, however, an interaction with race such that Black participants assigned to vitamin D3 had better cognitive maintenance (MD=0.04; 95% CI, 0.01 to 0.08) compared to placebo, while other races showed no significant effects. Cognitive function in people receiving vitamin D3 was comparable to participants 1.2 years younger, suggesting an overall modest effect. The beneficial effect of vitamin D3 in Black participants was stronger for executive function/attention score, where the benefit was equivalent to being 3.8 years younger. These subgroup findings regarding race are preliminary and need to be confirmed in future studies.

In a secondary analysis of the VITAL trial described above, plasma biomarkers from 929 participants were evaluated [12]. Compared to placebo, neither vitamin D3 treatment (2,000 IU/day) nor omega-3 treatment (1 g/day) significantly reduced Alzheimer's disease-related biomarkers over 4 years. These biomarkers included plasma N-terminal tau fragment (NT1), A β 40:42 ratio, neurofilament light (NfL), and glial fibrillary acidic protein (GFAP). Among Black participants, vitamin D3 supplementation resulted in a 16.2% reduction in plasma NfL levels, and omega-3 supplementation resulted in a 12.4% reduction in GFAP levels; however, these analyses were uncorrected for multiple comparisons and need to be interpreted cautiously as hypothesis-generating signals requiring further study.

In a double-blind randomized controlled trial of 2,492 Finnish people (mean age, 68.2 years old) free of dementia at baseline, vitamin D3 treatment (1,600 or 3,200 IU/day, orally; Galena Pharma Ltd., Kuopio, Finland) for up to 5 years did not affect dementia incidence [13]. The participants were largely vitamin D-sufficient. Using the placebo arm as the reference, the age- and sex-adjusted hazard ratios for all-cause dementia were not significantly different for the 1,600 IU/day group (HR=0.77; 95% CI, 0.38 to 1.55; p=0.46) or for the 3,200 IU/day group (HR=0.72; 95% CI, 0.35 to 1.48; p=0.37). During the extended follow-up of 7.7 years, hazard ratios of all-cause dementia compared to placebo were 0.95 and 0.79 for the 1,600 IU/day arm, and 3,200 IU/day arm, respectively. The authors noted that the study did not have adequate power to detect weak or average effects of vitamin D supplementation. Both the 1,600 IU/day and 3,200 IU/day arms had significantly increased serum 25-hydroxy-vitamin D concentrations after the vitamin D intervention compared to baseline, while levels did not change in the placebo arm.



In a double-blind randomized placebo-controlled trial (VitaMIND) of 620 UK adults over 50 years old with mild to moderate vitamin D deficiency (≤ 50 nmol/L 25-hydroxy-vitamin D; equivalent to ≤ 20 ng/mL) and below normal cognitive function (performing 1 standard deviation below normal on cognitive test), supplementation with 4000 IU vitamin D3 (orally in hydroxypropyl methylcellulose capsules) for 24 months showed no significant benefits on cognition compared to placebo, including the primary outcome of executive function (Trail Making Test Part B; Cohen's d effect size=0.11), secondary outcome measures of numerical working memory (d=0.08), spatial working memory (paired associate learning and self-ordered search), or executive function (switching Stroop and verbal reasoning) [1]. There were also no significant effects on noncognitive outcomes, including function (instrumental activities of daily living), behavior (Mild Behavioral Inventory Checklist), and well-being (euroqol 5-Behavioral Inventory Checklist). Subgroup analyses also showed no significant effects on outcomes based on age, sex, and vitamin D deficiency severity. A few limitations of this trial include the achievement of recruitment through the PROTECT-UK cohort, which resulted in a self-selection bias toward females of White ethnicity with high educational attainment and digital engagement, which suggests that the cohort was not fully representative of the UK population. It also remains possible that a duration of intervention longer than 24 months may have shown a more favorable outcome.

In a 2020 meta-analysis of 9 randomized controlled trials including a total of 2,345 participants, vitamin D supplementation for 4 weeks to 7.8 years did not show significant benefits over the comparison group on cognitive function (MMSE), verbal fluency, verbal memory, visual ability, or attention scores [14].

Some hints of potential cognitive benefit with vitamin D treatment have been observed in smaller trials, though these may be exceptions.

A double-blind randomized controlled trial of 355 older adults with mild cognitive impairment reported that treatment with vitamin D3 alone (800 IU/day, orally) or combined with DHA (1 g/day, orally) for 12 months significantly improved cognitive scores compared to placebo treatment, measured by full-scale IQ, performance IQ, verbal IQ, and several subtests (information, comprehension, digit span, vocabulary, picture completion, block design, and picture arrangement) [15]. All 3 intervention groups (vitamin D3 alone, DHA alone, or vitamin D3 + DHA combination) demonstrated statistically significant cognitive improvements compared to the placebo group. The vitamin D3 alone group showed improvements in scores for full-scale IQ, verbal IQ, and the subtests of information, comprehension, arithmetic, digit span, vocabulary, and block design. The DHA alone group displayed improvements in verbal IQ and the specific subtests of information, similarities, digit span, and picture completion. The vitamin D3 + DHA combination group demonstrated improvements in full-scale IQ, verbal IQ, performance IQ, and the



subtests of information, comprehension, arithmetic, digit span, vocabulary, digit symbol, block design, and picture arrangement. The vitamin D3 and DHA interventions significantly increased serum levels of 25-hydroxy-vitamin D3 and erythrocyte DHA levels, respectively. With regards to Alzheimer's disease-related pathological biomarkers, the A β 42/40 ratio and the levels of APP, PS1, and PS2 showed no significant differences among the 4 groups at baseline or after 12 months of treatment. With regards to biomarkers of inflammation/pyroptosis, compared to the placebo group, significant reductions were observed in IL-1 β , NLRP3, Gasdermin D, and cleaved caspase-1 in the vitamin D3 alone group and significant reductions were observed for IL-1 β , IL-18, NLRP3, Gasdermin D, and cleaved caspase-1 in the vitamin D3 + DHA combination group. The authors noted that results should be interpreted with caution given some potential confounding factors such as baseline dietary habits, physical activity levels, and APOE genotype were not fully controlled for.

Human research to suggest benefits to patients with dementia:

In a small pilot study of 43 patients newly diagnosed with Alzheimer's disease, patients who were treated with memantine plus vitamin D showed improvement in cognitive scores after 6 months, whereas those taking memantine alone or vitamin D alone showed no changes [16]. Vitamin D supplements were taken by participants orally, either daily (ranging from 400 and 1,000 IU/day) or monthly (100,000 or 200,000 IU per month). This study lacked a placebo group, so it is not possible to rule out placebo effects with regards to cognitive changes.

In a randomized controlled trial of 32 mild-to-moderate Alzheimer's patients, high-dose vitamin D2 (3,000 IU/day; Cardinal Health, Braeside, Victoria, Australia) for 8 weeks (with dose adjustments to maintain 25-hydroxy-vitamin D levels of 135-160 nM) did not significantly alter cognition (ADAS-Cog) or disability (Disability Assessment in Dementia) [17]. All patients received 1,000 IU daily vitamin D throughout and then randomized to high-dose vitamin D2 or placebo for 8 weeks. This study was likely too short to expect any significant differences in cognitive function.

In a randomized controlled trial of 209 patients with Alzheimer's disease, vitamin D3 treatment (800 IU/day; manufactured by Aiweidi soft capsule National Medicine Health Industry Co., Shanghai, China) for 12 months improved some cognitive measures compared to placebo (full scale IQ, information, arithmetic, digit span, vocabulary, block design, and picture arrangement; $p < 0.001$ for all) while not significantly affecting others (comprehension, similarities, digit symbol, picture completion, and object assembly) [18].

Mechanisms of action for neuroprotection identified from laboratory and clinical research:

Numerous preclinical studies suggest that vitamin D may have neuroprotective actions, by decreasing amyloid and tau pathology, reducing neuroinflammation and oxidative stress, supporting cerebrovascular integrity, and preserving mitochondrial function [19; 20].

APOE4 interactions:

Observational studies suggest that vitamin D deficiency has a greater association with cognitive decline in APOE4 non-carriers than carriers. In a population-based cohort study of 1,547 cognitively normal Koreans aged ≥ 60 years, vitamin D deficiency (25-hydroxy-vitamin D < 10 ng/mL) was associated with faster cognitive decline (measured by MMSE) in APOE4 non-carriers ($p=0.001$), and this relationship was significant only in female non-carriers [21]. Male APOE4 non-carriers showed an absence of a statistically significant association between vitamin D deficiency and cognitive decline. The authors noted that the APOE4 variant is beneficial for better intestinal absorption of dietary vitamin D and reabsorption of urinary vitamin D, and these properties may mitigate the risk of cognitive decline associated with vitamin D deficiency in APOE4 carriers. The authors also discussed a few limitations of this study, including the possibility of residual confounding.

Aging and related health concerns: Vitamin D supplementation has shown a lack of benefit for prevention of cardiovascular diseases or cancer. Small biomarker benefits have been observed in metabolic conditions and rheumatoid arthritis.

Types of evidence:

- 10 meta-analyses or systematic reviews
- Numerous randomized controlled clinical trials
- Numerous observational studies

Cardiovascular diseases: LACK OF BENEFIT

The VITAL trial (VITamin D and Omega-3 Trial) tested a high-dose vitamin D3 (2000 IU/day, orally; Pharmavite) and marine omega-3 fatty acids (1 g/day, orally; Omacor) against placebo for ~ 5 years in men ≥ 50 years old and women over ≥ 55 years old with no cardiovascular disease or cancer at baseline, to determine whether vitamin D3 or fish oil can prevent major cardiovascular events, which was one of

the primary outcomes [22]. After a median follow-up of 5.3 years, vitamin D3 supplementation did not lead to a significantly lower incidence of major cardiovascular events (composite of myocardial infarction, stroke, or death from cardiovascular causes) compared to placebo (HR=0.97; 95% CI, 0.85 to 1.12; p=0.69). Vitamin D3 treatment also did not affect the risk of secondary cardiovascular end points, including the composite of major cardiovascular events plus coronary revascularization (HR=0.96; 95% CI, 0.86 to 1.08), myocardial infarction (HR=0.96; 95% CI, 0.78 to 1.19), or stroke (HR=0.95; 95% CI, 0.76 to 1.20). The vitamin D3 product was effective at significantly increasing serum 25-hydroxy-vitamin D levels in the groups receiving vitamin D3 (from 29.8 ng/mL at baseline to 41.8 ng/mL) while no changes were seen in the placebo group. The effects of vitamin D3 did not vary according to baseline serum 25-hydroxy-vitamin D levels. Because there was no statistical control for multiple comparisons, the secondary and exploratory endpoints should be interpreted with caution.

In a 2023 meta-analysis of up to 80 randomized controlled trials including a total of 163,131 participants, vitamin D supplementation for at least 1 year did not significantly lower the risk of myocardial infarction (OR=1.00; 95% CI, 0.91 to 1.09), stroke (OR=1.04; 95% CI, 0.95 to 1.13), heart failure (OR=0.94; 95% CI, 0.84 to 1.06), or major cardiovascular events (OR=1.00; 95% CI, 0.95 to 1.06) [23].

Cancer: LACK OF BENEFIT

In the VITAL trial, a high-dose vitamin D3 treatment (2000 IU/day, orally; Pharmavite) for ~5 years in men ≥50 years old and women over ≥55 years old did not significantly decrease diagnosis of cancer, which was one of the primary outcomes (any type; HR=0.96; 95% CI, 0.88 to 1.06) [22]. Vitamin D3 treatment also did not affect secondary outcomes, including risk of breast cancer (HR=1.02; 95% CI, 0.79 to 1.31), prostate cancer (HR=0.88; 95% CI, 0.72 to 1.07), or colorectal cancer (HR=1.09; 95% CI, 0.73 to 1.62). The cumulative incidence of invasive cancer of any time was also not significantly different between vitamin D3 and placebo groups.

Metabolic diseases: POTENTIAL BENEFIT IN PREDIABETES

Metabolic syndrome is defined by having 3 or more of a group of conditions that increase the risk of heart disease, stroke, and type 2 diabetes: high blood pressure, high blood sugar, excess fat around the waist, high cholesterol, and high triglycerides. In a meta-analysis of 7 randomized controlled trials in patients with metabolic syndrome and low baseline vitamin D levels (25-hydroxy-vitamin D levels <20 ng/ml), vitamin D treatment (ranging from 700 IU/day to 50,000 IU/week) for 8-48 weeks significantly



reduced triglyceride levels (MD=-12.64; 95% CI, -21.23 to -4.04; $p=0.004$), but no significant effects were seen in total cholesterol (MD=-6.04; 95% CI, -16.83 to 4.74), LDL-cholesterol (MD=-4.43; 95% CI, -11.11 to 2.25), or HDL-cholesterol levels (MD=1.41; 95% CI, -1.51 to 4.33) [24].

In a 2026 network meta-analysis of 21 randomized controlled trials in adults with prediabetes, low-dose vitamin D supplementation (<1,000 IU/day, orally) decreased fasting blood glucose compared with control [25]. With regards to fasting insulin, extremely high-dose vitamin D supplementation (≥ 4000 IU/day, orally) was more effective than control (MD=-0.30; 95% CI, -0.56 to -0.03). Extremely high-dose vitamin D supplementation was superior in reducing HOMA-IR, a measure of insulin resistance, than low-dose vitamin D treatment. The authors noted that there were only a few low-dose vitamin D studies, and more studies are needed to validate these findings.

In an umbrella review of meta-analyses of randomized controlled trials, vitamin D treatment (ranging from 400 IU/day to 200,000 IU/week) for 4-156 weeks significantly reduced inflammatory biomarkers, including CRP, TNF- α , and IL-6 levels in people with abnormal glucose homeostasis [26]. In people with type 2 diabetes, a significant reduction in hs-CRP (effect size [Hedges' g]=-0.45; $p=0.005$) and TNF- α (Hedges' g =-0.75; $p=0.05$) was observed, while reduction in IL-6 levels did not reach statistical significance.

In a 2024 meta-analysis of 11 randomized controlled trials including a total of 504 obese or overweight people with vitamin D deficiency, vitamin D supplementation (1,000-7,000 IU/day or 200,000 IU bolus) for 2-26 weeks did not significantly affect inflammation biomarkers, including CRP, IL-6, and TNF- α [27]. Results remained non-significant even when the analysis was confined to studies showing a significant increase in serum vitamin D concentrations.

Respiratory diseases: MAY REDUCE MORTALITY DUE TO COVID-19

In a 2023 meta-analysis of 17 randomized controlled trials in respiratory disease patients, vitamin D supplementation did not significantly affect the risk of all-cause mortality compared to placebo (RR=0.88; 95% CI, 0.70 to 1.13) [28]. However, a subgroup analysis indicated that vitamin D may reduce all-cause mortality among COVID-19 patients (RR=0.54; 95% CI, 0.33 to 0.88). Other subgroup analyses examining all-cause mortality in respiratory conditions, including in pulmonary tuberculosis, chronic obstructive pulmonary diseases, and pneumonia showed no significant differences between vitamin D and placebo.

Bone health: SUPPLEMENTATION ALONE DOES NOT PRODUCE BENEFIT

Some clinicians, guidelines, and regulatory agencies recommend vitamin D supplementation (with or without calcium) for musculoskeletal health. However, in a 2026 meta-analysis of up to 69 randomized controlled trials including a total of 153,902 participants reported that vitamin D supplementation over a mean follow-up of 2.0 years did not significantly affect the risk of any fracture (RR=1.00; 95% CI, 0.95 to 1.06, based on 36 trials) [29]. Vitamin D supplementation also had little to no effect on risks of hip fracture (RR=1.13; 95% CI, 1.00 to 1.27, based on 15 trials), non-vertebral fracture (RR=1.01; 95% CI, 0.95 to 1.06, based on 20 trials), vertebral fracture (RR=1.04; 95% CI, 0.66 to 1.65, based on 7 trials), falling (RR=1.01; 95% CI, 0.98 to 1.04, based on 32 trials), and total number of falls (incidence rate ratio 1.00; 95% CI, 0.95 to 1.06, based on 12 trials). Most included trials enrolled community dwelling older adults not at high risk of fractures and falls, with a median age across trials of 71.2 years old. In the same publication, they also examined the effects of vitamin D supplementation combined with calcium over a mean follow-up of 2.3 years, and this combination also had little to no effect on the risk of any fracture (RR=0.91; 95% CI, 0.84 to 0.99), hip fracture (RR=0.84; 95% CI, 0.74 to 0.96, based on 9 trials), vertebral fracture (RR=0.90; 95% CI, 0.74 to 1.09, based on 4 trials), non-vertebral fracture (RR=0.87; 95% CI, 0.78 to 0.96, based on 7 trials), risk of falling (RR=0.92; 95% CI, 0.84 to 1.00, based on 10 trials), and total number of falls (incidence rate ratio=0.95, 95% CI, 0.88 to 1.03, based on 4 trials). The authors noted that the results may not be generalizable to people with specific bone disorders or to those receiving treatment for osteoporosis or using long-term corticosteroids. The authors also recommended that clinicians, guideline panels, and regulatory agencies should re-evaluate the recommendations for vitamin D and/or calcium supplementation in light of the latest evidence.

Postmenopausal osteoporosis affects up to 70% of women over the age of 80. In a 2025 meta-analysis of 13 randomized controlled trials in postmenopausal women, vitamin D and calcium supplementation alone was compared with supplementation combined with physical interventions, including whole-body vibration, weight-bearing exercise, resistance/strength training, and mind-body or traditional Chinese exercises like Baduanjin [30]. Compared with vitamin D and calcium supplementation alone, interventions that added a physical component significantly increased lumbar spine (SMD=0.31; 95% CI, 0.06 to 0.55) and femoral neck bone mineral density (SMD=0.47; 95% CI, 0.09 to 0.84), with nonsignificant trends observed at other skeletal sites (greater trochanter, Ward's, and total hip bone mineral density). Subgroup analysis showed that whole-body vibration produced the most consistent benefits at the lumbar spine and femoral sites, while Baduanjin significantly improved lumbar spine bone mineral density. The physical intervention was typically performed 2-7 times per week for 30-75 minutes per session. The authors suggest that mechanical loads conferred by the physical interventions

amplify the osteocytic response, inducing a positive feedback loop among muscle, bone, and vitamin D/calcium metabolism, reinforcing the mineralization processes.

Periodontal health: LACK OF BENEFIT

In a meta-analysis of up to 13 randomized controlled trials in people with gingivitis an/or periodontitis, vitamin D supplementation (250-1,769 mg/day) for 6 to 156 weeks did not significantly improve probing pocket depth [31]. The authors noted that the current evidence is limited and insufficient to support a clear clinical recommendation.

Rheumatoid arthritis: MAY DECREASE PAIN AND LOWER CRP LEVELS

Vitamin D modulates inflammation by influencing diverse immune cells and reducing the production of pro-inflammatory cytokines. In a 2025 meta-analysis of 11 randomized controlled trials including a total of 1,390 people with rheumatoid arthritis, vitamin D supplementation (140-60,000 IU/week) for 6-32 weeks significantly improved pain (measured by the Visual Analog Scale; SMD=-1.54; 95% CI, -2.53 to -0.55; p=0.002), serum vitamin D levels (SMD=1.52; 95% CI, 0.86 to 2.17; p=0.001), and CRP levels (SMD=-0.88; 95% CI, -1.31 to -0.44; p=0.001) [32]. However, other outcomes, including disease activity markers (DAS28 and ESR) were not significantly affected by vitamin D treatment.

Mortality: NO BENEFIT EXCEPT IN PEOPLE WITH RESPIRATORY OR LIVER DISEASES

In the VITAL trial, a high-dose vitamin D3 treatment (2000 IU/day, orally; Pharmavite) for ~5 years in men ≥50 years old and women over ≥55 years old did not significantly alter the risk of mortality from any causes (HR=0.99; 95% CI, 0.87 to 1.12), mortality from cardiovascular causes (HR=1.11; 95% CI, 0.88 to 1.40), or mortality from cancer (HR=0.83; 95% CI, 0.67 to 1.02) [22].

In a 2023 meta-analysis of up to 80 randomized controlled trials including a total of 163,131 participants, vitamin D supplementation for at least 1 year reduced the risk of all-cause mortality slightly (OR=0.95; 95% CI, 0.91 to 0.99; p=0.013), but did not significantly alter the risk of cardiovascular mortality (OR=1.00; 95% CI, 0.92 to 1.08) or non-cardiovascular mortality (OR=0.94; 95% CI, 0.87 to 1.00; p=0.055) [23].

In a different 2023 meta-analysis that included up to 116 randomized controlled trials, vitamin D supplementation did not significantly affect the risk of all-cause mortality compared to placebo in the

general population (RR=0.99; 95% CI, 0.96 to 1.03), or in people with cardiovascular diseases (RR=1.03; 95% CI, 0.91 to 1.18) [28]. However, a meta-analysis of 17 randomized controlled trials in people with respiratory diseases found that vitamin D may reduce all-cause mortality among COVID-19 patients (RR=0.54; 95% CI, 0.33 to 0.88). Also, in people with liver cirrhosis, vitamin D treatment may reduce all-cause mortality compared to placebo (RR=0.63; 95% CI, 0.50 to 0.81).

Safety: Large, long-term clinical trials have reported that vitamin D is generally safe when used as directed. Prolonged sun exposure does not cause vitamin D overdose. Excessive supplementation can lead to renal failure, cardiac arrhythmias, and other conditions.

Types of evidence:

- Numerous meta-analyses or systematic reviews
- Numerous randomized controlled clinical trials

Clinical trials of vitamin D supplementation have reported that vitamin D is generally safe when used as directed. In the VITAL trial, a high-dose vitamin D3 treatment (2000 IU/day, orally; Pharmavite) for ~5 years in 25,871 men and women (men ≥50 years old and women over ≥55 years old) did not significantly affect the risk of hypercalcemia, kidney stones, or gastrointestinal symptoms compared to placebo [22].

A double-blind randomized controlled trial of 355 older adults with mild cognitive impairment reported that treatment with vitamin D3 alone (800 IU/day, orally) or combined with DHA (1 g/day, orally) for 12 months did not cause any adverse events throughout the intervention [15].

Toxicity due to vitamin D can occur with excessive vitamin D supplementation; prolonged sun exposure alone cannot cause vitamin D overdose because sunlight destroys excess vitamin D3 ([Drugs.com](#)). Vitamin D toxicity can cause hypercalcemia, hypercalciuria, and high serum 25-hydroxy-vitamin D concentrations ([NIH Office of Dietary Supplements](#)). In severe cases, excessive vitamin D intake (from supplements) may lead to renal failure, calcification of soft tissues, cardiac arrhythmias, and death. The tolerable upper intake level for vitamin D ranges from 25 to 100 micrograms (1,000-4,000 IU), depending on age.

Drug interactions: There are numerous drug interactions with vitamin D ([Drugs.com](#)). The use of statins may increase serum vitamin D levels. Corticosteroids decrease the metabolism of vitamin D and orlistat reduces the absorption of vitamin D. Other drugs that interact with vitamin D include aluminum

hydroxide, bile acid sequestrants, calcium salts, cardiac glycosides, danazol, erdafitinib, mineral oil, multivitamins/minerals, sucralfate, thiazide and thiazide-like diuretics, and vitamin D analogues.

Sources and dosing:

Humans synthesize vitamin D from the skin via exposure to ultraviolet B wavelengths of sunlight, which converts the vitamin D3 precursor 7-dehydrocholesterol to previtamin D3, which is then reshaped to vitamin D3 through isomerization ([DrugBank.com](#); [PubChem](#)). Vitamin D3 then moves out of the skin and enters the bloodstream. Our skin can produce up to 10,000 IU of vitamin D3 with just 20-30 minutes of sunlight exposure.

Fatty fish like salmon, trout, and herring contain high levels of vitamin D. Other food sources of vitamin D include cod liver oil, egg yolk, and mushrooms exposed to ultraviolet light.

The recommended dietary allowance for adults is 600 IU (15 mcg) daily. For adults >70 years old, it is 800 IU (20 mcg) daily.

Research underway:

Based on ClinicalTrials.gov, there are over 300 ongoing clinical trials testing vitamin D for various indications, including liver disease, diabetes, vitamin D deficiency, osteoarthritis, infertility, epilepsy, cancer, diabetes, bone loss, other diseases, and in healthy populations ([Clinicaltrials.gov](#)). Many of the interventions are combination therapies that include other compounds besides vitamin D.

One double-blind randomized placebo-controlled trial is testing the effect of vitamin D3 (800 or 1600 IU/day) and folic acid (0.4 mg/day) in 380 people with mild cognitive impairment ([NCT07486141](#)). The treatment duration is 6 months and the primary outcome is change in global cognition (MoCA). This study has completed recruitment and the study was estimated to be completed in June 2026.

A phase 2 randomized controlled trial is testing the effects of high-dose vitamin D3 (4000 IU/day) compared to the standard-dose vitamin D3 (600 IU/day) in 180 elderly people with vitamin D insufficiency ([NCT03613116](#)). They plan to enroll ~50 people with mild cognitive impairment, ~50 with mild Alzheimer's disease, and 50 with no cognitive impairment. The duration of the study is 30 months. The primary outcome is correction of vitamin D insufficiency and change in SENAS executive function score from baseline to last visit (month 42). This study is estimated to be completed in December 2026.

Search terms:

Pubmed, Google: vitamin D

- + meta-analysis, + Cochrane, + dementia, + Alzheimer, + APOE4, + cancer, + cardiovascular, + safety, + mortality

Websites visited for vitamin D:

- [Clinicaltrials.gov](https://clinicaltrials.gov)
- [Examine.com](https://examine.com)
- [DrugAge](https://drugage.com)
- [Drugs.com](https://drugs.com)
- [WebMD.com](https://webmd.com)
- [PubChem](https://pubchem.ncbi.nlm.nih.gov)
- [DrugBank.ca](https://drugbank.ca)
- [Labdoor.com](https://labdoor.com)
- [ConsumerLab.com](https://consumerlab.com)

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