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Health Effects of Vitamin D supplementation: Lessons Learned from Randomized Controlled Trials and Mendelian Randomization Studies

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Abstract

Vitamin D plays an important role in calcium homeostasis and many cellular processes. Although vitamin D supplements are widely recommended for community dwelling adults, definitive data on whether these supplements benefit clinically important skeletal and extra-skeletal outcomes have been conflicting. While observational studies on effects of vitamin D on musculoskeletal and extra-skeletal outcomes may be confounded by reverse causation, randomized controlled studies (RCTs) and Mendelian Randomization (MR) studies can help to elucidate causation. In this review we summarize the recent findings from large RCTs and/or MR studies of vitamin D on bone health and risk of fractures, falls, cancer, and cardiovascular disease, disorders of the immune system, multiple sclerosis, and mortality in community-dwelling adults. The primary analyses indicate that vitamin D supplementation does not decrease bone loss, fractures, falls, cancer incidence, hypertension, or cardiovascular risk in generally healthy populations. Large RCTS and meta-analyses suggest an effect of supplemental vitamin D on cancer mortality. The existence of extra-skeletal benefits of vitamin D supplementations are best documented for the immune system especially in people with poor vitamin D status, autoimmune diseases and multiple sclerosis. Accumulating evidence indicates that vitamin D may reduce all-cause mortality. These findings, in mostly vitamin D replete populations, do not apply to older adults in residential communities or adults with vitamin D deficiency or osteoporosis. The focus of vitamin D supplementation should shift from widespread use in generally healthy populations to targeted vitamin D supplementation in select individuals, good nutritional approaches, and elimination of vitamin D deficiency globally.

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Keywords

vitamin D; randomized controlled trials; mendelian randomization

INTRODUCTION

A century ago, vitamin D was discovered to be the agent that can cure or prevent nutritional rickets in animals and children. Indeed, McCollum et al. discovered that a fat-soluble vitamin could cure rickets in dogs, and Huldschinsky, Chick and Hess proved that exposure to ultraviolet B radiation also cured or prevented rickets. (1–4) Many other scientists contributed to the full discovery of the dual origin of vitamin D. (5–7) The chemical structure of vitamin D_2 and vitamin D_3 was identified subsequently and resulted in a Nobel prize for Windaus. (8) The introduction of daily vitamin D supplements for infants and small children rapidly eliminated endemic rickets in countries that implemented such a strategy.

Vitamin D is inactive and needs to undergo two hydroxylation steps to form the active metabolite. The first of these, resulting in 25-hydroxyvitamin D [25(OH)D], occurs predominantly in the liver, mediated primarily by cytochrome P450 2R1 (CYP2R1), although there are several other hydroxylases that also play a role. The second hydroxylation at position 1α is mediated by CYP27B1, resulting in $1,25(OH)_2D$. Endocrine production of $1,25(OH)_2D$ occurs almost exclusively in the kidney, but the 1α-hydroxylase responsible for its production can also be activated in many other tissues, resulting in generation of this active metabolite in an autocrine or paracrine fashion with local effects. $1,25(OH)_2D$ binds with high affinity to the vitamin D receptor (VDR), causing it to form a heterodimer with the retinoid-X receptor. This then binds to vitamin D response elements in the promoter region of target genes, influencing gene expression. Many *in vitro* and *in vivo* studies have demonstrated that $1,25(OH)_2D$ is able to regulate a very large number of genes; about 3% of the human or mouse genome is under the direct or indirect control of the VDR system.

Vitamin D plays a critical role in calcium and phosphate metabolism and bone homeostasis. It also influences many important biological processes, suggesting potential health effects for cancer, cardiovascular disease, infectious and autoimmune diseases, among others. Many observational studies have identified associations between circulating 25(OH)D concentrations and health outcomes. However, the potential for bias due to confounding and/or reverse causation renders it difficult to infer causation. Mendelian Randomization (MR) studies can help to elucidate causation. The concept behind MR is that genetic variants, including single nucleotide polymorphism (SNPs) are randomly assigned at conception and are not influenced by environmental factors. Variants associated with the exposure of interest can be used in the analysis in place of the exposure itself. Four and later on 141 SNPs were found to predict about 5% and 10.5 %, respectively, of the genetic variation of serum 25OHD. MR studies use analysis of such SNPs in large databases as to explore whether such genetic variations are linked with relevant biological outcomes such as cancer, vascular or neurological outcomes or mortality risk. The strength of such MR studies is the absence of confounding and reverse causation, and they enable the impact on disease of variation in the exposure over a lifetime. The limitations include the assumption that the

SNPs do not modify the outcome apart from via the exposure of interest and the assumption that the association between exposure and outcome is linear. Large sample sizes are needed, particularly if the proportion of variability in the exposure explained by the SNPs is low. (9,10). Randomized controlled trials can also help to infer whether or not associations are causal, although as they investigate the effect of a particular dose for a set period at a particular stage in the life course, the absence of an effect is not proof of no association.

Here we review the findings of recent large RCTs and MR studies of vitamin D and fracture, cancer, and cardiovascular disease in community-dwelling adults. This manuscript is based on the lectures presented by the 3 authors at the ASBMR 2022 meeting in Austin, Texas.

VITAMIN D AND THE MUSCULOSKELETAL SYSTEM

Vitamin D plays a crucial role in calcium homeostasis and it is plausible that the whole vitamin D endocrine system developed during the evolution of vertebrates in response to a higher demand for adequate calcium supply. (11) $1,25(OH)_2D$ maintains a steady serum calcium concentration in concert with parathyroid hormone (PTH) and fibroblast growth factor 23 (FGF23). 1,25(OH)D acts on the small intestine and kidneys to increase calcium absorption and decrease its loss from the kidneys. When calcium concentration decreases PTH concentration increases, resulting in increased bone turnover to release calcium from bones. Low 25(OH)D concentrations are associated with elevated PTH, which can lead to increased bone turnover and bone loss. (12–16)

Vitamin D deficiency, or lack of vitamin D action due to absence of CYP27B1 or VDR, results in rickets in children (when it occurs before closure of the growth plate) or osteomalacia in adults. The 25(OH)D concentration below which rickets or osteomalacia occurs is thought to be 10–12 ng/ml (except for calcium-deficiency rickets which has a different cause). This is consistent with the threshold below which active intestinal calcium absorption, measured using reliable methods, is impaired. (17) Apart from this agreed definition of frank vitamin D deficiency, the 25(OH)D concentration that is optimal for bone health is controversial. One option is to base the definition of vitamin D adequacy on the 25(OH)D concentration that minimizes PTH concentration. Observational studies have generated inconsistent evidence, but RCTs have found that vitamin D supplementation only leads to a decrease in serum PTH concentration in people with a baseline serum 25(OH)D concentration below 20 ng/ml. (18,19)

Supplemental Vitamin D and Bone Mineral Density: Randomized Controlled Trials in Community-Dwelling Adults

Bone mineral density (BMD) is a surrogate marker for bone health and increases in BMD are associated with relatively large reductions in fracture risk. (20) Observational studies have indicated that high 25(OH)D levels are positively associated with areal bone mineral density (aBMD). (21–24) Large meta-analyses and systematic reviews that support a benefit of vitamin D supplements (without added calcium) on BMD are sparse. (25–29) The few RCTs of supplemental vitamin D alone (without added calcium) versus placebo on BMD in community-dwelling adults are described below (Table 1).

Lips and colleagues supplemented 270 men and women aged >70 years with 400 IU per day of vitamin D for 3.5 years and observed a 2.3% increase in BMD at the femoral neck, but the average baseline 25(OH)D concentration was very low, at 10.6 ng/ml. (30) A Scottish study in women with similarly low mean 25(OH)D concentration also found a small effect on BMD at the hip, albeit only with administration of 1000 IU/d of vitamin D / day; there was no effect of 400 IU / day. (31) In contrast, two studies from New Zealand and the United States, in which the mean 25(OH)D concentration was above the range often considered sufficient (i.e., ~20 ng/ml), did not find any meaningful effect on BMD. (32–35) The combined data from the studies in Scotland and New Zealand indicated that supplementation with vitamin D may have small beneficial effects on BMD at the spine and hip in community-dwelling adults with the poorest vitamin D status (<12 ng/ml). (36) Nevertheless, the small size of the effect suggests it is unlikely to have a major effect on fracture risk unless the beneficial effects could be cumulatively maintained over many years.

Detailed investigations of bone health outcomes were recently conducted as part of VITamin D and OmegA-3 TriaL (VITAL), a RCT among 25,871 men (aged ≥50) and women (aged ≥55) enrolled from 50 states of the United States, including 5,106 Black participants. Participants were randomized to vitamin D_3 (cholecalciferol, 2000 IU/d) and/or omega-3 fatty acid (1 g/d) supplements vs. double placebo in a factorial design, with primary outcomes being cancer and cardiovascular disease. (37,38) Participants were generally healthy and not preselected for vitamin D deficiency, low bone mass or osteoporosis. In a sub-study, 771 participants from the greater Boston area underwent bone health measures at baseline and two years after randomization including: areal bone density (aBMD) assessed by dual X-ray absorptiometry (DXA), and volumetric density (vBMD) and bone structure measured by peripheral computed tomography (pQCT). (33,34) Daily vitamin D supplements, compared with placebo, did not improve aBMD at the spine, hip, or whole body or vBMD or bone structure at the radius or tibia. (33) Using baseline 25(OH)D thresholds (<12, <20, or <30 ng/mL), there were no differences in changes in aBMD between vitamin D and placebo groups, although the number of participants with low 25(OH)D concentration was small. Among participants with baseline measured free 25(OH)D concentrations below the median, vitamin D_3 supplementation had a slight benefit on spine and total hip aBMD (0.75% vs. 0%, $p = 0.04$; −0.42% vs. −0.98%, $p = 0.04$). Whether free 25(OH)D levels help to identify those more likely to benefit from supplementation on BMD or fractures is currently being investigated in VITAL. (33)

Importantly, there are concerns that high doses of vitamin D could have detrimental effects on bone mineral density. A study in Calgary, which was not placebo-controlled, found that supplementing participants with 10,000 IU per day resulted in more bone loss than those supplemented with 400 IU per day. (39)

Supplemental Vitamin D and Fractures: Randomized Controlled Trials in Community-Dwelling Adults

Although vitamin D supplements are widely perceived to prevent fractures, data on whether these supplements reduce incident fractures in community-dwelling adults have

been inconsistent. (25–27,29,40–45) Many RCTs have been limited by bolus dosing, co-administration with calcium, short duration or small sample sizes.

Systematic reviews of RCTs have raised questions about whether supplemental vitamin D prevents fractures in generally healthy populations not selected for vitamin D deficiency. (46,47) We summarize the large RCTs (n=2,000–25,871 participants) of supplemental vitamin D (without added calcium) vs. placebo on fractures using intermittent dosing regimens in Table 2 and daily dosing regimens in Table 3. These studies were primary prevention trials testing whether supplemental vitamin D prevented fractures in participants living in communities around the world, including some who were found to be vitamin D replete. This contrasts secondary prevention studies in which participants might be selected on the basis of low vitamin D levels, reduced bone density or osteoporosis.

two studies that administered very high doses (300–500,000 IU of vitamin D) annually and found evidence of an increased risk of fracture. In contrast, several other studies have not found that bolus dosing increases fracture risk, In a British study, administration of a lower bolus dose of 100,000 IU of vitamin D every 4 months for 4 years reduced fracture risk by about 22–33%; the mean 25(OH)D concentration at baseline was 21 ng/ml. (48) A clinical concern is that bolus dosing of vitamin D can produce increases and then decreases in 25(OH)D concentrations and, similar to other endocrine feedback loops, bolus dosing may disrupt enzymatic regulation of vitamin D. (49) In the New Zealand ViDA study, a similar dose given monthly for 3.3 years to a population that was largely vitamin D replete at baseline generated null results (Table 2). Even in the small subgroup of subjects with a poorer vitamin D status (serum 25OHD < 20 ng/ml), no effect on fracture risk was observed [HR = 1.07 (0.91–1.25)].

In the large Australian D-Health Trial intermittent-dosing of vitamin D on fractures was explored in21,315 adults who were randomly assigned to 60,000 IU / month of vitamin D or placebo for five years.(50) Fracture outcomes were ascertained by linkage to administrative datasets, resulting in essentially complete follow-up. There was no overall effect on incident fractures, but evidence emerged of a potential beneficial effect of supplemental vitamin D on fractures after approximately 3.5 years, and a lower hazard of fractures in the vitamin D group at 5 years after randomization (hazard ratio 0.83; 95% CI 0.69–0.99).Given the inconsistency with other studies, it is unclear whether this finding reflects a real benefit, but it does provide evidence that monthly dosing with a relatively modest dose of vitamin D in vitamin D-replete population does not increase the risk of fractures.

In VITAL, the largest study of supplemental vitamin D on incident fracture outcomes, daily supplemental vitamin D 2000 IU/day vs. placebo did not decrease incident total, nonvertebral or hip fractures in midlife and older adults. Fractures were adjudicated among the 25,871 participants who were enrolled nationwide and followed for 5.3 years. (55) Effects were not modified by baseline age, sex, race, BMI, vitamin D thresholds, or use of supplemental calcium (<1200 mg/d) and/or vitamin D (<800 IU/d); only 2.4% of the VITAL cohort had 25(OHD) levels less than 12 ng/ml and there were very few fractures in this subgroup. (55) In DO-HEALTH, 2,157 community-dwelling men and women were enrolled from 5 European countries and there was no benefit of 2000 IU vitamin D/d vs. placebo

or a simple home exercise program on risk of nonvertebral fractures. (56) Thus, none of the major RCTs evaluating effects of daily vitamin D doses on incident fractures showed a reduced risk of total or site-specific fractures (Table 3). This conclusion remains valid whether the trial participants had a low vitamin D status (30) or involved mostly vitamin D-replete participants. The treatment duration lasted from 3 to more than 5 years. Studies in VITAL are determining whether free 25(OH)D levels or genetic variation in vitamin D absorption, metabolism, or receptor function may identify a subgroup of participants who may benefit from supplemental vitamin D on incident fracture outcomes. (55)

These data from large RCTs suggest there is unlikely to be a clinically relevant effect of vitamin D supplementation alone on bone health in mostly community-dwelling adults. However, these studies did not address nor contradict studies demonstrating benefits of combined vitamin D and calcium supplementation for fracture or in adults in residential communities. A recent umbrella meta-analysis concluded that combined vitamin D and calcium supplementation reduced hip or all fractures according to 8 out of 12 meta-analyses or systematic reviews in combined analyses from institutionalized and community-based individuals. However, these findings may have been underpinned by studies carried out in institutionalized participants. (45)

Vitamin D and Bone Health: Lessons from Mendelian Randomization Studies

MR studies allow evaluation of the lifelong consequences of differences in 25(OH)D concentration resulting from genetic variations. Three such studies did not find an association between genetically predicted serum 25(OH)D concentration and BMD in adults (Table 4). (59–61) A smaller study found a link between genetically predicted low vitamin D status and BMD of young children (62), but this needs to be confirmed. Two MR studies examined the link between genetically predicted serum 25(OH)D and fracture risk. One used only 6 single nucleotide polymorphisms (SNPs) as the instrument to predict 25(OH)D and found no association with risk of fracture. (63) A much larger study using the UK Biobank and 143 SNPs related to serum 25(OH)D found an increased risk of hip and leg fractures in people with a genetically predicted lower serum 25(OH)D concentration. (64) This, however, was not confirmed for all other types of fractures and there was no association with overall risk of fracture. As these studies assumed a linear effect of serum 25(OH)D concentration on fractures they are thus of limited value about the association between vitamin D deficiency and fractures.

Vitamin D, muscle strength, and falls.

Mice lacking the vitamin D receptor, either globally or specifically in muscles, have a clear phenotype of immature muscle development. (66–68) In humans, extreme vitamin D deficiency, such as occurs with vitamin D-dependent rickets or with longstanding chronic renal failure, can lead to severe muscle weakness, particularly of the proximal muscles. This condition, which sometimes results in the need for a wheelchair, responds rapidly to treatment with $1,25(OH)_2D$.

Apart from severe vitamin D deficiency, it is unclear whether there is an association between 25(OH)D concentration and muscle strength, or whether vitamin D supplementation

improves strength or reduces the risk of falls. A 2014 meta-analysis (69) concluded that vitamin D supplementation resulted in a modest increase in muscle strength, but this was not confirmed in a more recent meta-analysis that included newer studies and eliminated data that had been retracted. (70) Indeed, there was some evidence that vitamin D supplementation may modestly impair muscle strength. It is difficult to interpret these findings due to the diversity of participants and treatment schedules; importantly, most studies did not focus on proximal muscle strength, and these muscles are most affected in patients with severe vitamin D deficiency.

There are a large number of studies that have addressed the effects of vitamin D supplementation on falls. (71) A meta-analysis of RCTs demonstrated a 15% reduction in the risk of falls when people with low vitamin D status [25(OH)D <30 ng/ml] were supplemented with vitamin D (RR 0.85; 95% CI 0.73–0.98), but no effect in people with higher 25(OH)D levels. (72) A more recent meta-analysis of 21 RCTs with falls as the primary endpoint also provided evidence that a daily dose of 800–1000 IU of vitamin D reduced the risk of falls, especially in people with low vitamin D status at baseline (pooled RR 0.91; 95% CI 0.85–0.98). (71)

Two recent large RCTs including the large VITAL study did not observe an effect of the risk of falling (52,73), but both trials included participants who were largely vitamin D replete. There is some concern that high doses of vitamin D could lead to an increased risk of falling. A study of older women, in which 500,000 IU of vitamin D was administered annually, found an increased risk of falls within the first three months following administration of the dose. (74) Similarly, an increased risk of falling was also found in participants who reached high serum 25(OH)D concentrations (about 45 ng/ml) in two other trials. (75,76) In the Sturdy study, in which four different doses of daily vitamin D were compared, no benefits from daily doses of 1000 IU in comparison with 200 IU were observed, whereas there was concern about the safety of higher (2000–4000 IU) dosages. (77) In the Stop-it trial, a U-shaped relationship was observed between serum 25(OH)D concentrations and the risk of falls, with optimal 25(OH)D concentration between 20 and 40 ng/ml. (78) The large New Zealand ViDA and Australian D-Health studies did not find that monthly vitamin D increased the risk of falls (79), although in the D-Health Trial vitamin D increased the risk of falling in those with normal body mass index at baseline. A recent meta-analysis concluded that vitamin D monotherapy did not improve any sarcopenia-related parameter (including appendicular lean mass, handgrip strength and general muscle strength or physical performance. (80) Similarly, two years of vitamin D supplementation did not decrease the risk of falls in a clinical trial, whereas strength and balance training reduced such risk by more than 50%. (81)

In conclusion, despite clear evidence that severe vitamin D deficiency is associated with reduced muscle strength, vitamin D supplementation does not improve muscle strength or reduce the risk of falls in most community-dwelling adults. In contrast, there are several studies indicating that excess vitamin D may have negative effects on muscle strength or the risk of falls.

VITAMIN D AND NON-MUSCULOSKELETAL EFFECTS

Vitamin D and Cancer

In laboratory studies vitamin D influences biological processes such as cell cycling, apoptosis, and angiogenesis, suggesting a plausible effect on cancer incidence and mortality. This is evident from mouse studies, which demonstrate that mice lacking vitamin D action have an increased risk of cancer. For example, *Cyp27b1* null mice develop a variety of cancers at older age compared with their wild-type counterparts. (82) VDR-null mice exposed to at least one other carcinogenic risk factor develop more cancers than control mice, in line with a two-or-more-hit hypothesis in the etiology of cancers. (83)

Observational cohort studies in humans have consistently demonstrated associations between 25(OH)D concentration and cancer incidence, particularly for colorectal cancer. (84) However, trial data to date are somewhat limited. Neither VITAL nor ViDA found that vitamin D reduced the overall incidence of cancer. Nevertheless, in VITAL, the subgroup of participants with normal BMI (<25 kg/m^2) showed a small reduction in the incidence of cancer (OR 0.76; 95% CI 0.63–0.90), which warrants further study. A notable outcome was the finding that cancer mortality was significantly decreased in the VITAL study, at least when cancers detected within the two years after the start of the vitamin D supplementation were excluded [OR 0.75 (0.59–0.96)]. (85) This benefit on cancer mortality was confirmed in a meta-analysis of several recent RCTs using daily supplementation doses (86). A more recent meta-analysis of 14 RCTs with a total of 104,727 participants (2015 cancer deaths) yielded a statistically non-significant reduction in cancer mortality by 6% (risk ratio (RR) [95%-confidence interval (95%CI)]: 0.94 [0.86–1.02]). Subgroup analyses revealed a 12% lower cancer mortality in the vitamin D_3 group compared with the placebo group in 10 trials with a daily dosing regimen (RR [95%CI]: 0.88 [0.78–0.98]), whereas no mortality reduction was seen in 4 trials using a bolus regimen (RR [95%CI]: 1.07 [0.91–1.24]; p-value for interaction: 0.042). The individual patient data meta-analysis (RR [95%CI]: 0.93 [0.84; 1.02]) confirmed the finding of all trials. (87)

The D-Health Trial, however, found some evidence of harm (88), suggesting that it may be prudent to avoid bolus dosing for vitamin D supplementation. Multiple MR studies have evaluated the association between genetically predicted lower serum 25(OH)D concentration and cancer incidence and mortality. A 2021 review summarized 12 MR studies, all of which were negative except for one which suggested a link between low serum 25(OH)D and ovarian cancer. (89) Other studies, however, have not found a link with ovarian cancer, nor with other cancers (90–92), even when 138 SNPs were used as the instrumental variable in a large MR study using data from the UK Biobank. (93)

Vitamin D and Cardiovascular Disease

Vitamin D influences several processes within the cardiovascular system. For example, it inhibits the expression of renin, a hormone produced in the kidneys that initiates the RAAS cascade, with subsequent effects on blood pressure and vascular remodeling. *VDR* or *Cyp27b1* null mice develop renin-induced hypertension and cardiac hypertrophy. Similarly,

$1,25(OH)_2D$ regulates a variety of genes in the vascular wall that are known to be protective against cardiovascular diseases.

As with other health outcomes, observational studies in humans consistently show an inverse association between 25(OH)D concentration and cardiac outcomes such as hypertension and major cardiovascular events. However, these are arguably the outcomes most prone to confounding due to their strong associations with body mass index and physical activity which also influence 25(OH)D concentrations. Trials of vitamin D supplementation have mostly not identified any benefit of vitamin D supplementation on cardiovascular outcomes. Neither VITAL (HR 0.97; 95% CI 0.85–1.12) nor the ViDA Trial (HR 1.02; 95% CI 0.87–1.20) found any reduction in the risk of cardiovascular events. (85,94) A subgroup of ViDA participants underwent additional procedures as to evaluate a possible effect of vitamin D supplementation on blood pressure. No effect was found for usual blood pressure measurements, but a beneficial effect was found for arterial stiffness measured using an oscillometric device in participants with low vitamin D levels and a25(OH)D <20 ng/ml.(95) Whether supplemental vitamin D would have long-term health benefits on blood pressure is questionable at this time. Results from the VITAL and D-Health Trials on effects of supplemental vitamin D on blood pressure outcomes will advance understanding of this question.

MR has also been extensively used for cardiovascular disease events. At least 3 MR studies found no association between genetically predicted 25(OH)D concentration and cardiovascular diseases (myocardial infarction and stroke combined or separately), but there are also several recent MR studies with positive results in subgroups of patients such as hypertensive diabetics (96) or patients with heart failure. (97) Other MR studies examined more specific endpoints such as ischemic stroke (98) with null results, or cerebral hemorrhages (99), reporting a higher OR of 1.60 (1.05–2.43; p 0.03) for those with the lowest genetically predicted serum 25(OH)D concentrations. Zhou and colleagues (100) found a strong relationship between genetically predicted serum 25(OH)D concentration and hypertension in a group of participants with measured serum 25(OH)D concentrations below 20 ng/ml. This would indicate that lifelong lower 25(OH)D concentration in people with generally poor vitamin D status would increase the risk of hypertension. However, such conclusion needs confirmation and critical analysis of the methods used for non-linear MR studies in light of concerns about the methods raised in analyses of mortality (see below).

Vitamin D, infections and immunity

Based on preclinical data, it seems that $1,25(OH)_2D$ stimulates the native immune system and thus enhances resistance against infections. Numerous studies have confirmed a lower vitamin D status in people with infectious diseases such as HIV or tuberculosis. (101) A large number of intervention studies have been the basis of several meta-analyses confirming a small reduction in the risk of upper respiratory infections during vitamin D supplementation. (102,103) The effects were only positive where vitamin D was administered daily (not with monthly doses), more in adolescents than in other age groups, and was more pronounced in populations with poor vitamin D status at baseline, although in a meta-regression none of these factors was significantly associated with the outcome. A

large RCT in Mongolian children with severe vitamin D deficiency did not find a beneficial effect of vitamin D supplementation on the subsequent risk of subclinical or clinical tuberculosis. (104) In the D-Health study of mostly vitamin D-replete adult Australians, no effect of vitamin D supplementation on the incidence of upper respiratory infections was observed. (105) The severity of these infections, however, seemed to be somewhat milder, defined as the number of days with symptoms or with severe symptoms, in the group randomised to vitamin D. (105) In the D-Health Trial there was also a reduction in the number of antibiotic prescription episodes, irrespective of the type of infection (106), and a reduction in the number of extended-stay hospitalizations for infection. (107)

A large number of publications have addressed the question of whether vitamin D plays a role in the risk or severity of COVID-19 infection. 25(OH)D concentration has an inconsistent effect (based on meta-analyses and systematic reviews) on the incidence of COVID-19, making it unlikely that the vitamin D status is a major risk factor in comparison with other risk factors such as obesity, age, or hypertension. (108) Many studies have reported an association between low serum 25(OH)D concentration and severity or outcome of the infection. (109) A recent meta-analysis concluded that vitamin D supplementation reduced the risk of ICU admission (RR = 0.35, 95% CI: 0.20, 0.62) and mortality (RR = 0.46, 95% CI: 0.30, 0.70). (110) By contrast, an open-label phase 3 RCT in the UK involving 6,200 adults and conducted during the SARS-CoV-2 vaccine roll-out showed no effect on risk reduction of all cause acute respiratory infections or COVID-19 by implementing a test-and-treat approach to the correction of sub-optimal vitamin D status via daily oral administration of either 800 or 3,200 IU vitamin D3 over 6 months. (111) Several Spanish studies, however, have reported a benefit on ICU admission and mortality when patients with COVID-19 infections requiring hospitalization received a high dose of calcifediol at the time of admission. This metabolite allows a nearly immediate correction of vitamin D deficiency, perhaps explaining its potential efficacy. (112–114) Vitamin D supplementation did not influence the vaccine efficacy or immunogenicity in a RCT (115), in line with animal data on VDR-null mice. (116) Overall, the existing data suggest a possible influence of vitamin D status or vitamin D or calcifediol supplementation on the outcome of SARS-CoV infections, but more gold-standard RCTs are needed to define its potential clinical use. The vitamin D for COVID-19 (VIVID) trial, is an ongoing pragmatic cluster-randomized double-blinded study that is investigating effects of high daily doses of supplemental vitamin D on the severity of COVID-19 symptoms. (117) So far, no guidelines recommend using vitamin D for prevention or treatment of COVID-19 infections.

The vitamin D endocrine system also has major effects on the acquired immune system as revealed by regulation of immune genes and based on animal studies. Analogs of $1,25(OH)_2D$ with lower calcemic effects than the natural molecule have been found to reduce the severity of several autoimmune diseases such as immune diabetes, experimental allergic encephalitis (model of multiple sclerosis) or nephritis. (47) Long-term prospective studies in the United States Army demonstrated that recruits with the lowest 25(OH)D concentrations had a higher risk of developing type 1 diabetes or multiple sclerosis than those with a better baseline vitamin D status. (118,119) In a separate ancillary study in VITAL, vitamin D supplementation (2000 IU/day) reduced autoimmune disease (mostly rheumatoid arthritis and polymyalgia rheumatica) by 22% after 5 years of followup (HR

0.78; 0.61–0.99 p= 0.05). (120) In view of the age (midlife and older) of VITAL participants enrolled in this study it was not possible to evaluate the potential benefit of vitamin D supplementation on type 1 diabetes or multiple sclerosis. This result on rheumatoid arthritis is in line with the results of a MR study demonstrating a lower prevalence of autoantibodies of RA in people with a better vitamin D status. (121)

A role for the vitamin D endocrine system in autoimmune disease is strongly supported by 10 MR studies, all reporting that a higher genetically predicted 25(OH)D concentration conveys a lower risk for the development of either juvenile or adult onset multiple sclerosis.

Other MR studies however did not find such a link with other autoimmune diseases such as type 1 diabetes mellitus. (132)

Vitamin D and all-cause mortality

Observational studies have consistently observed an association between 25(OH)D concentration and all-cause mortality. (133) This finding is supported by the results of RCTs. Meta-analyses of RCTs of supplemental vitamin D have reported a small mortality risk reduction. (47)

Reanalysis of older data, including more vitamin D deficient participants, revealed a small but significant reduction in mortality. (136) Indeed, in an extensive 2014 Cochrane review, including approximately 75000 participants in 38 vitamin D supplementation trials the mortality risk was modestly reduced, RR: 0.94 (0.91–0.98). (136) The recent trials including more than 50,000 mostly vitamin D replete adults, did not find an overall effect on mortality. In contrast with the more recent RCTs, many of the participants of the older studies were more vitamin D deficient.

The results of MR studies are inconsistent. Three studies have generated null findings, whereas two studies showed a modest beneficial effect on mortality (Table 7), which was confirmed in a subsequent meta-analysis of these 5 studies.

A recent non-linear MR study did not show any association between genetically predicted 25(OH)D and mortality in the overall analysis. However, in participants with measured 25(OH)D below 20 ng/ml, lower genetically predicted 25(OH)D was associated with higher mortality. (137) Nevertheless, following comments on the methods used, the authors reanalyzed their findings and found no effect, highlighting the importance of MR assumptions in driving these results. (138)

The totality of the evidence suggests that there is a link between the vitamin D endocrine system and all-cause mortality, but it does not appear that population-wide supplementation of largely replete populations would have any benefit.

Conclusions

Activation of VDR by $1,25(OH)_2$ D regulates a large number of genes in most cells and tissues, in line with similar observations for other ligands of nuclear receptors. Many preclinical studies and observational data suggested a broad spectrum of activities related

to vitamin D. There is consensus that severe vitamin D deficiency causes nutritional rickets and osteomalacia. Introducing vitamin D supplementation has resulted in virtual elimination of endemic rickets in infants and small children in most countries. Such policy, however, still needs to be implemented in many countries or specific target groups. A poor vitamin D status decreases active intestinal calcium absorption (serum 25(OH)D <10 ng/ml) and increases serum PTH (serum 25(OH)D < 20 ng/ml) and can potentially accelerate bone loss in adults or elderly people. Recent large-scale RCTs did not show beneficial effects of vitamin D supplementation on many musculoskeletal and extra-skeletal outcomes in mostly vitamin D-replete adults. These studies, however, were not designed to define the role of vitamin D and calcium supplementation of elderly people with poor vitamin D and calcium status. Therefore, it is wise to follow most guidelines to correct such nutritional deficiencies to reduce the risk of fragility fractures. Large doses of vitamin D may have negative effects on bone density or fractures, especially when given as large bolus doses. However, monthly use of relatively modest doses of vitamin D did not increase fractures in in the large D-Health or ViDA studies, suggesting that in people where compliance with daily dosing is a problem, monthly dosing could be used.

The extra-skeletal effects of vitamin D have been the topic of hot debates. Based on the available RCTs and MR studies, there is no definitive evidence from the primary analyses that vitamin D supplementation can decrease the incidence of cancer. In the large VITAL study, however, there was a suggestion of a reduction in cancer incidence in adults with normal BMI treated with daily doses of supplemental vitamin D. Results for cancer mortality have been conflicting. Supplemental vitamin D was associated with a suggestive reduction in cancer mortality when the early follow-up was excluded in the analyses in VITAL. A large meta-analysis also confirmed a benefit of vitamin D supplementation on cancer mortality in those treated with daily, but not bolus doses of vitamin D. Vitamin D supplementation does not decrease the risk of cardiovascular events or hypertension. The recent large RCTs do not support beneficial effects of vitamin D supplementation on muscle strength or risk of falls in mostly vitamin D replete adults. Older studies in more vitamin D deficient participants suggest that vitamin D supplementation may modestly reduce the risk of falls. The existence of extra-skeletal benefits of vitamin D supplementations are best documented for the immune system as vitamin D supplementation may reduce the risk and/or severity of upper respiratory infections, especially in individuals with poor vitamin D status. There is consistent evidence from MR studies that higher genetically predicted 25(OH)D concentration is associated with lower risk of multiple sclerosis, and an effect on autoimmunity is supported by the findings of the VITAL study. Accumulating evidence from observational studies and RCTs indicates a possible role for vitamin D in all-cause mortality.

Summary

There is increasing evidence for a role of vitamin D in outcomes beyond the musculoskeletal system, particularly for all-cause mortality and outcomes related to effects on the immune system. Our summary of recent data is not intended to be a replacement for existing guidelines on the use of vitamin D and/ or calcium. The recent data do not demonstrate a benefit of vitamin D supplementation for skeletal and extra skeletal health of adults with a good vitamin D status at baseline (mean serum 25(OH)D above 25 ng/ml). Some trials,

however, generated data that long term vitamin D supplementation may have some benefit for prediabetic subjects or have modest effect on cancer mortality, but additional studies are needed to validate these data. However, avoiding low vitamin D levels (25(OH)D <50 nmol/L) is likely to have benefits beyond musculoskeletal health, particularly for infectious disease, multiple sclerosis and autoimmune diseases and in some of these clinical conditions precision preventive health may be beneficial. Implementing policies that ensure most people are vitamin D replete may have widespread benefit. In some areas of the world, infants and children do not have access to sufficient vitamin D or calcium and are therefore at risk of nutritional rickets. In some countries, with limited sun exposure and a high prevalence of vitamin D deficiency it may be better to intervene at a population level through food fortification, recognizing that, depending on the foods fortified, some people may still require individually prescribed supplements. Vitamin D testing is expensive and, in most clinical settings, not particularly accurate. Thus, rather than testing it may be better to assess a person's risk of vitamin D deficiency based on sun exposure habits and recommend a modest supplement dose (1,000 to 2,000 IU/day); this may have benefit and is unlikely to cause harm.

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TABLE 1:

Effects of Supplemental Vitamin D vs. Placebo on BMD in Community Dwelling Adults (29–31,34,37)

Study	Vitamin D Supplement	Length of Study	N	Study Population	Results
Lips P et al.	400lU/d	3.5 years	270	**Netherlands:** Women and Men >70 years **[baseline 25(OH)D 10.6 ng/mL]**	400 lU/day of vitamin D **increased** BMD at the **femoral neck by 2.3%**
Macdonald HM et al.	400 IU or 1000lU/d	1 year	305	**Scotland:** Women aged 60–70 years **[baseline 25(OH)D 13.5 ng/mL]**	1,000 lU/day of vitamin D **prevented bone loss** of ~0.6% **at the hip** but not at the spine
Hansen KE et al.	Daily 800 IU or twice monthly 50,000 IU	1 year	230	**US:** Women <75 years **[baseline 25(OH)D 21 ng/mL]**	**No effect** on BMD Preselected for vitamin D insufficiency
Reid IR et al.	100,000 lU/month	2 years	452	**New Zealand (VIDA):** Community dwelling older adults **[baseline 25(OH)D 22 ng/mL]**	**Attenuated bone loss at the hip by 0.5%; No meaningful effect on BMD**
LeBoff etal.	Daily 2000 IU	5.3 years	771	**US (VITAL):** Women aged >55 years and men aged >50 years **[baseline 25(OH)D 30.7 ng/mL]**	**No effect on aBMD** at spine, hip, or whole body or **vBMD** at radius or tibia or measures of bone structure

TABLE 2:

Previous Large RCTs Studying Bolus Dosing of Supplemental Vitamin D vs. Placebo on Incident Fractures in Community-Dwelling Adults (47,49–52)

	Study	Participants/ Duration	Intervention	25 [OH]D Levels	Key Findings
Monthly/4 -Monthly	**Trivedi DP, et al.** *BMJ. 2003*	**Great Britain:** Women and men aged 65–85 yrs (n = 2,686) Duration: 5 yrs	Oral vitamin D_3**100,000 IU** every **4 months**	Follow up (4 yrs): 30±8.3 ng/mL in vitamin D group, 21±8.5 ng/mL in placebo group	Reduced any fracture by 22% Reduced fractures at hip, wrist or forearm or vertebrae by 33%
	Vitamin D Assessment Study [VIDA] Khaw K, et al. *Lancet Diab Endo. 2017*	**New Zealand:** Women and men aged 50–84 yrs (n = 5,110) Duration: 3.3 yrs	Oral vitamin D_3**100,000 lU/ month**	Baseline: 25+9.6 ng/mL Follow-up (6 months): 52±16.8 ng/mL in vitamin D group and 30+12.4 ng/mL in placebo group	No effect on nonvertebra 1 fractures or falls
	D-Health Trial Waterhouse M, et al. *Lancet Diab Endo. 2023*	**Australia:** Adults aged 60–84 years (n=20,326) Duration: 5.1 yrs	**Oral** vitamin D_3**60,000 lU/ month**	Follow-up (5 yrs): 46.1+12 ng/mL in vitamin D group and 30.8±10 ng/mL in placebo group	No effect on total, nonvertebra 1, or hip fractures; Suggestion of a benefit on total fracture reduction after 3–5 years of follow-up
Annual	**Smith H, et al.** *Rheumatology. 2007*	**England:** Women and men >75 yrs (n = 9,440) Duration: 3 yrs	**Intramuscular** vitamin D_2**300,000 lU/yr**	Baseline: 56.5+23.7 ng/mL Follow-up (4 months): 21% increase in the vitamin D group (p = 0.15)	No effect on nonvertebra 1 or wrist fractures or falls Slight *increase* in hip or femur fractures.
	Sanders KM, et al.*JAMA. 2010*	**Australia:** Women >70 yrs at high risk of hip fracture (n=2,256) Duration: 3–5 yrs	Oral vitamin D_3**500,000 lU/yr**	Baseline: 20 ng/mL Follow up: **48 ng/mL at 1** month, 36 ng/mL at 3 months in the vitamin D group	*Increased* fractures by 26% and falls by 15% (falls and fractures in 3- month period following bolus dose)

TABLE 3:

Previous Large RCTs Studying Daily Dosing of Supplemental Vitamin D vs. Placebo on Fracture Outcomes in Community-Dwelling Adults (29,53–56)

Study	Participants/ Duration	Intervention	25 (OH}D Levels	Key Findings
Lips P, et al. *Ann Intern Med. 1996*	**Netherlands:** Women and men >70 yrs, independent/ residential facilities (n=2,578) Duration: 3.5 yrs	Oral vitamin D_3 400 lU/day	Baseline: 10.8 ng/mL in vitamin D group and 10.4 ng/mL in placebo group Follow up (3 vrs): 24.0 ng/mL in vitamin D group	No effect on hip or peripheral fractures
RECORD Grant AM, et al. *Lancet.* 2005	**UK:** Women and men >70 yrs (n=5,292) who were mobile before a low-trauma fracture Duration: 24–62 months	Oral vitamin $D_3$800 lU/ day, calcium 1000 mg/ day, or combination or placebo	Baseline: 15.2±6.5 ng/mL (n=60) Follow up (1 yr): rose by 9.7±8.7 ng/mL in vit D group and by 3.1±7.2 ng/mL in placebo group	No effect on low-trauma fractures
DO-HEALTH, Bischoff-Ferrari H et al. *JAMA 2020*	**Europe:** Women and men >70 yrs (n=2,157) Duration: 3 yrs	Oral vitamin D_3 2000 lU/day, omega-3 fatty acids 1000 mg/day, and strength- training exercise program alone and in combinations	Baseline: 22.4±8.4 ng/mL Follow up (3 yrs): 37.5 ng/mL in the vitamin D groups and 24.4 ng/mL in the non-vitamin D groups	No effect on non-vertebral fractures or falls
VITAL LeBoff MS, etal. *NEJM. 2022*	**U.S.:** Women aged >55 and men aged >50 yrs (n = 25,871) Duration: 5.3 yrs	Oral vitamin D_3 2000 lU/day	Baseline: 30.7±10 ng/mL (n=16,757) Follow up (2 yrs): 41.2 ng/mL in vit D group	No effect on total, non-vertebra 1, or hip fractures or falls

TABLE 4.

Mendelian Randomization Studies of Vitamin D and Bone Mineral Density or Fractures (59–65)

Study	Sample size (n)	SNPs	Outcome
Li, *SclRep 2016* (64)	Chinese postmenopausal women (n=1,824}	4	BMD: all p >0.1
Larsson, *JBMR 2018* (60)	2 cohorts of European descent (n=32,965 and n= 142,487)	5 linked to 4 vitamin D related genes	1 SD higher 25(OH)D BMD+ 0.02 CL-0.03 ± 0.07 p >0.1
Sun *J Cell Mol Med 2019* (58)	European ancestry (n=61,079)	6	total body BMD: p >0.05 at all ages
Kampe, *PlosGen 2019* (61)	Finish children (age 2 yrs; r=761)	2	lower 25(OH)D linked to lower BMD p <0.01
Ye, *GenEpid 2020* (63)	UK Biobark (n=326,409)	143	higher 25(OH)D linked to lower risk of leg or femur but not other fractures: OR 0.60 CL 0.45–0.SO
Colak, *Clin Chem 2020* (62)	Danish adults (n=116,335)	6	total fracture risk for 3% lower predicted 25(OH)D: OR 0.99 CL 0.981.00
Tang, *Sci Rep, 2022* (59)	European ancestry (n=67,35S)	143	predicted 25(OH)D and BMD at different sites: all p >0.05

Abbreviations: SNP: single nucleotide polymorphism, BMD: bone mineral density, NS: non-significant, BMC: bone mineral content

TABLE 5.

Mendelian Randomization Studies: Vitamin D and Multiple Sclerosis (117–126)

Study	SNP	Origin of Study	n(vs. ctr] Outcome	
Mokryetal. *2015*	4	Canada: Adult	14,49S vs. 3S,5S9	1 SD predicted higher 250HD: OR for MS: 0.5 p< 0.0000001
Rhead et al. *2016*	3	US: Non-H is panic Whites Switzerland	1,056 vs. 9,015 6,335 vs. 5,762	OR for highest predicted 250HD: 0.35, *95%* Cl 0.760.94, p=0.003
Gianfrancesco et al. *2017*	3	US: early onset MS		Higher predicted 250HD0R for MS: 0.72, 95% Cl 0.550.94, p=0.02
Jacobs et al. *2020*	5	EL nopea n ancestry: Adults and children US: Adults and children Switzerland: Adults and children	14,302 vs. 41,505 394 vs. 10,375 175 vs. 5,376	OR for MS: 0.57, 95% Cl 0.41–0.81, p=0.001
V\ian et al. *2021*	7	European ancestry	121,640	OR for MS: 0.77 (0.65–0.93)
Jiang etal. *2021*	138	European ancestry (UK Bio bank)	> 440,000	OR for MS: 0.32(0.69– 0.99)
Harroud et al. *2021*	138	European ancestry (UK Bio bank)	401,460	OR for MS: 0.72(0.60– 0.37)
Wang *2022*	20	European ancestry	14,490 vs. 24,091	OR for MS: (0.22–0.45) p< 0.001
Vandenbergh et al. *2022*	143	European ancestry	14,302 vs. 26,703	15D predicted higher 250HD: OR for MS: 0.72 (CL 0.60–033), pÔ.OOl; OR for relapse: 0.57 **(CL** 0.39–0.85), p=0.006
Zhang et al. *2023*	6	European ancestry	14,302 vs. 26,703	OR for MS: 0.81 (0.70–0.94)

TABLE 6.

All-cause mortality in major vitamin D supplementation RCTs (81,83,129,130)

Study	HR All-cause mortality	CL
WHI 2009	0.91	0.83–1.01
Record 2012	0.93	0.85–1.02
VITAL 2019	0.99	0.87–1.12
ViDA 2017	1.12	0.79–1.58
D-Health 2022	1.04	0.93–1.18

TABLE 7.

Mendelian Randomization Studies on Vitamin D Status and All-cause Mortality. (86,132,134–138)

Study	Participants (n)	SNPs	Outcome
Trummer, *Clin Chem 2013*	Patients requiring cardiac angiography (Germany; n=3,31fj)	4	NS
Afzal, *BMJ 2014*	Danish adults (n=95,766)	2	HR for 20 nmol/L lower 25(OH)D: 1.19 (1.14–1.25)
Jorde*JSBMB 2019*	Tromso study (n=6,733)	4	HR: 1.17(1.06–1.29)
Aspelund, *Nutrients 2019*	3 European cohorts (n=10,501)	4	N5
Meng, *Int JEpid 2019*	UK Biobank (n=339,256)	143	NS
Emerging risk factors, *Lancet 2021*	European ancestry (n=67,358)	3–71	Overall: NS but non-linear analysis: significant
Liu, *Adv Nutr 2022*	Meta analysis of 5 MR studies (n=95,766)	Variable	risk estimate 0.77 (0.62–0.95)