REVIEWS

Vitamin D: A Narrative Review Examining the Evidence for Ten Beliefs

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Over the past decade, a large body of observational evidence has suggested an association between lower vitamin D status (25-hydroxyvitamin D) and multiple acute and chronic disorders, including cancer, multiple sclerosis, depression and respiratory tract infections. This evidence has fostered the hypothesis that increasing vitamin D intake may treat and prevent such disorders. Our objective was to perform a critical analysis of the highest-level evidence for ten common beliefs regarding vitamin D for the prevention of falls, fractures and respiratory tract infections, the reduction of cancer incidence/mortality and overall mortality, and the prevention or treatment of depression/mental well-being, rheumatoid arthritis and multiple sclerosis, as well as maximum dosing and regular testing. We searched the Cochrane Database of Systematic Reviews and PubMed (up to August 2014) for randomized controlled trials and systematic reviews/meta-analyses based on those studies. All searches were performed, all evidence reviewed and each section written by at least two authors. The evidence shows that vitamin D supplementation provides some benefit in fracture prevention (likely ~10–15 % relative reduction), particularly at a dose ≥800 IU and with calcium; a likely benefit in the rate of falls, though it is less clear whether the number of fallers changes; and a possible small (~5 %) relative reduction in mortality. Evidence does not support the use of vitamin D supplementation for the prevention of cancer, respiratory infections or rheumatoid arthritis. Similarly, evidence does not support vitamin D supplementation for the treatment of multiple sclerosis and rheumatoid arthritis or for improving depression/mental well-being. Regular testing of 25-hydroxyvitamin D is generally not required, and mega-doses (≥300,000 IU) appear to increase harms. Much of the evidence is at high risk of bias, with multiple flaws, including analyses of secondary endpoints, small and underpowered studies, inconsistent results and numerous other issues. Therefore, enthusiasm for a vitamin D panacea should be tempered.

Electronic supplementary material *The online version of this article (doi:10.1007/s11606-016-3645-y) contains supplementary material, which is available to authorized users.*

Received July 13, 2015
Revised November 9, 2015
Accepted February 16, 2016
Published online March 7, 2016

KEY WORDS: vitamin D; mortality; fracture; falls; depression; upper respiratory tract infection.
J Gen Intern Med 31(7):780–91
DOI: 10.1007/s11606-016-3645-y

VITAMIN D: EXAMINING THE EVIDENCE FOR TEN BELIEFS

Over the past decade, more than 1600 studies have been conducted on vitamin D, and more than half of these are cohort or observational studies demonstrating an association between deficits in vitamin D and a litany of acute and chronic disorders—cardiovascular disease, cancer, diabetes, fractures, depression and respiratory tract infections, to name a few.[1] These findings have fueled the hypothesis that vitamin D supplementation—a widely available, low-cost and mostly harmless intervention—might treat or even prevent these disorders.

Association, however, is not causation. Observational studies are not sufficient for proving that low concentrations of vitamin D (measured as 25-hydroxyvitamin D [25-OHD] level) cause disease, or that increasing levels would improve health.[1] Only high-quality randomized controlled trials (RCTs), and resulting high-quality systematic reviews and meta-analyses, can determine whether vitamin D supplementation influences clinical outcomes.

This article will explore ten common beliefs regarding vitamin D based on the available evidence. Although not always consistent, the first eight beliefs originate from observational studies or theories drawing an association between low 25-OHD level and increased risk or severity of the following medical concerns: falls,[2–4] fractures,[5,6] respiratory tract infections,[7] depression/mental well-being,[8] rheumatoid arthritis,[9,10] multiple sclerosis,[5,11–13] overall mortality[14,15] and cancer.[16] The last two beliefs involve the practical dilemmas of dosing and routine testing.

BELIEF 1: VITAMIN D REDUCES FALLS

Observational Studies

Small observational studies (3 studies, $n = 1981$) have found an association between low vitamin D levels and falls among

elderly patients in long-term care.[2–4] As a result, investigators have postulated that vitamin D supplementation may reduce the risk of falling.

Systematic Review/Meta-Analysis

Eight meta-analyses[17–24] of vitamin D levels and falls have been conducted, some with conflicting results. Online Table A provides an overview of these meta-analyses, including populations, outcomes and other methodological issues.

When considering this evidence, the analysis of "falls" rather than "fallers" in many RCTs is a key issue. An analysis of "falls" means that people who fell more than once were counted more than once in the primary outcome analysis. These studies generally lacked the statistical power to detect a significant difference in the number of "fallers" (people that fell one or more times). They relied, therefore, on repeat falls to obtain the desired number of total falls.

The most current systematic review included a trial sequential analysis[24] (a method to identify the ideal sample size of a meta-analysis and to potentially reduce false-positive results). It showed that the effect estimate for vitamin D, with or without calcium, lay within the futility boundary, i.e., that it did not alter the relative risk (RR) of falls by 15 % or more. Using a risk reduction threshold of 10 %, a sensitivity analysis (a method to assess the impact of key variables on a study's conclusions) found that the effect estimate also lay within the futility boundary.

Bottom Line

Vitamin D supplementation may reduce the number of falls among the elderly. There is also likely an overall reduction in the number of "fallers" (a less biased outcome), although these results are less consistent.

BELIEF 2: VITAMIN D REDUCES FRACTURES

Observational Studies

For the most part, more recent observational studies are consistent with older studies that have established a relationship between low vitamin D levels and fractures.[5] A systematic review and meta-analysis of observational studies (17 case–control studies, $n = 1903$ hip fracture cases and 1953 controls) found 33 % lower vitamin D levels in cases compared to controls. This difference was significantly greater in studies with population-based versus hospital-based controls.[6]

Systematic Reviews/Meta-Analyses

There are many systematic reviews of vitamin D supplementation and fracture prevention. We focus on five large reviews published within the last 5 years with meta-analyses on fracture prevention (Table 1).

Vitamin D alone did not appear to reduce hip, non-vertebral or total fractures.[25,27,28] When vitamin D was combined with calcium, the RR reductions were significant for total or non-vertebral fracture[25–29] and hip fractures,[25,28] with two results non-significant for hip fractures.[26,29]

Two of the systematic reviews[26,29] found that higher doses of vitamin D (>400 IU or a median dose of 800 IU) resulted in better and statistically significant RR reductions for non-vertebral and hip fractures. Although co-administration of calcium is important, it appears that doses <1000 mg are just as effective as higher doses.[26]

The most recent of these included a trial sequential analysis[25] showing that the effect estimate for vitamin D, with or without calcium, was less than the futility boundary of 15 % RR reduction of total fractures. Furthermore, this effect is unlikely to be meaningfully changed by future studies. However, uncertainty remains around hip fracture, with more research needed to determine whether vitamin D with calcium results in a meaningful reduction in hip fractures (≥15 %).

Bottom Line

The best available evidence shows an apparent reduction in fractures associated with vitamin D when given at moderate doses (≥800 IU/day) together with calcium at low to moderate doses (perhaps 500 mg/day). The RR reductions are approximately 10–15 % for non-vertebral/total or hip fractures. At a 15 % baseline risk of any fracture, approximately 45–67 individuals would have to take vitamin D and calcium every day for 10 years to prevent one fracture.

BELIEF 3: VITAMIN D REDUCES RESPIRATORY TRACT INFECTIONS

Observational Studies

A large cohort study ($n = 18{,}883$, age ≥12) suggested that upper respiratory tract infections (RTIs) are more common in people with low vitamin D levels and less common in those with high vitamin D levels.[7]

Systematic Reviews/Meta-Analyses

Three recent systematic reviews/meta-analyses[30–32] (Table 2) have explored vitamin D supplementation and RTIs.

The Bergman 2013[30] and Charan 2012[31] reviews concluded that vitamin D provided a protective effect against RTIs. The third, Mao 2013,[32] found no effect. All three studies have weaknesses in design and implementation, but the first two[30,31] have the greatest concerns. For example, they included RCTs from heterogeneous populations: children under the age of 3 with pneumonia from an impoverished area of Afghanistan and healthy adult volunteers from Long Island, New York. The Mao 2013 review limited some of the clinical variability by focusing on healthy subjects.[32]

Table 1 Vitamin D (With or Without Calcium) and Fracture (Systematic Reviews)

Systematic review/ Meta-analysis	Bolland 2014[25]	Bischoff-Ferrari 2012[26]	Chung 2011[27]	Avenell 2014[28]	Bischoff-Ferrari 2009[29]
Population	Mean age 56–89, 24–100 % women	Mean age 76, 91 % women	69 % post-menopausal women age ≥65	Mean age 71.3, 89 % women	89 % women
Non-vertebral fracture*	Not provided	RR 0.93 (95 % CI 0.87–0.99)	Not provided	We present total fracture (below)	RR 0.86 (95 % CI 0.77–0.96)
Total Fracture*	RR 0.95 (95 % CI 0.88–1.02)	Not provided	RR 0.88 (95 % CI 0.78–0.99)	RR 0.95 (95 % CI 0.90–0.99)	Not provided
Number of randomized controlled trials (patients)	25 (76,497)	11 (31,022)	11 (52,915)	10 (49,976)	12 (42,279)
Heterogeneity	$I^2 = 33$ %	Not provided	$I^2 = 36$ %	$I^2 = 8$ %	Q test, $p = 0.04$
Sensitivity analysis	Vitamin D alone not statistically significant, but vitamin D with calcium was: RR 0.92 (95 % CI 0.85–0.99)	Only the 800-IU/day dose showed a difference: RR 0.86 (95 % CI 0.76–0.96)	No effect of vitamin D alone	Vitamin D alone no difference in any fracture	Dose ≤400 IU/day: RR 1.02 (95 % CI 0.92–1.15) Dose >400 IU/day: RR 0.80 (95 % CI 0.72–0.89)
Hip fracture*	RR 0.97 (95 % CI 0.86–1.08)	RR 0.90 (95 % CI 0.80–1.01)	Not provided	RR 0.84 (95 % CI 0.74–0.96)	RR 0.91 (95 % CI 0.78–1.05)
Number of randomized controlled trials (patients)	21 (75,179)	11 (31,022)	Not provided	9 (49,853)	8 (40,886)
Heterogeneity	$I^2 = 14$ %	Not provided	Not provided	$I^2 = 0$ %	Q test, $p = 0.08$
Sensitivity analysis	Vitamin D alone not statistically significant, but vitamin D with calcium was: RR 0.84 (95 % CI 0.74–0.96)	Only the 800 IU/day dose showed a difference: RR 0.70 (95 % CI 0.58–0.86)	Not provided	Vitamin D alone had no effect	Dose ≤400 IU/day: RR 1.09 (95 % CI 0.90– 1.32) Dose >400 IU/day: RR 0.82 (95 % CI 0.69–0.97)
Other issues	Strengths: Included trial sequential and futility analysis (*see* text)	Weaknesses: Used patient–level data Two studies without patient-level data ("source data") excluded from primary analysis	2 studies: good quality 5 studies: fair quality 4 studies: poor quality†	Weaknesses: Population not summarized (we did with RCTs) 24 of 52 (46 %) studies lack information on randomization	Estimated non–vertebral (high-dose) number needed to treat of 93 over 12–84 months Hip (high-dose) number needed to treat of 168 over 12–84 months

RR relative risk
** Pooled results of vitamin D with or without calcium, except Avenell 2014, which is vitamin D with calcium only*
† According to AHRQ Methods Reference Guide for Effectiveness and Comparative Effectiveness Reviews

Bergman 2013[30] and Charan 2012[31] used odds ratios, which can exaggerate the relative effectiveness of interventions in common events such as upper RTIs. For example, the risk reduction from the Laaksi RCT[33] (a trial included in each of the three meta-analyses) was reported as 33 % in Bergman 2013[30] and 43 % in Charan 2012,[31] but only 12 % in Mao 2013.[32] Bergman 2013[30] and Charan 2012[31] also included the influenza A-only results (with a 47 % reduction) from one study[34] rather than all flu outcomes (with a 3 % reduction) as reported by Mao 2013.[32] All in all, the Bergman 2013[30] and Charan 2012[31] results are unreliable, particularly for healthy western populations. The Mao 2013[32] meta-analysis was not without concern—for example, 75 % of the weighting was given to one of the seven trials. Overall, however, Mao 2013[32] was likely the most reliable analysis, and found that vitamin D had no effect in reducing RTIs.

In this case, it is probably more helpful to examine the individual RCTs. A Tools for Practice article (evidence synopsis)[35] summarized 11 RCTs. The RCT of highest quality and greatest application to western populations, Murdoch 2012,[36] found that vitamin D supplementation over two winters did not reduce cold or flu illness in 322 New Zealand university and/or health care workers. The majority of other trials, including a large trial of infants in Kabul Afghanistan,[37] did not find a reduction in respiratory infections. One trial of Mongolian children with profound vitamin D deficiency (17.5 nmol/L) found a reduction of 0.35 respiratory tract infections over 3 months.[38]

Bottom Line

Vitamin D supplementation does not prevent or reduce RTIs in western populations. There may be some benefit in children

Table 2 Vitamin D and Respiratory Tract Infections (Systematic Reviews)

Systematic review/ Meta-analysis	Bergman 2013[30]	Mao 2013[32]	Charan 2012[31]
Population	50 % men, 50 % women, average age 16 years	Men and women, age range: 1.75–63 years	Adult and pediatric, male and female
Number of randomized controlled trials (patients)	11 (5660)	7 (4827)	5 (1868)
Vitamin D	1600 IU/day Dose interval: 24 h to 3 months	Range: 400–6800 IU/day 2 studies: 100,000 IU quarterly 200,000 IU quarterly	Range: 400–2000 IU/day
Duration	7 weeks to 18 months	1.75–18 months	6 months to 3 years
Outcome	Respiratory tract infections in vitamin D and placebo groups	Respiratory tract infections in vitamin D and placebo groups	Respiratory tract infections in vitamin D and placebo groups
Result	Pooled odds ratio 0.67 (95 % CI 0.50–0.88)	Pooled RR 0.98 (95 % CI 0.93–1.03)	Pooled odds ratio 0.582 (95 % CI 0.417–0.812)
Heterogeneity	Significant $Q = 35.7$; $I^2 = 72$ %	Non-significant	Significant $I^2 = 0.064$
Study quality	2 studies: high risk of bias 9 studies: low risk of bias	All high quality	2 studies: high quality* 2 studies: moderate* 1 study: poor quality*
Other issues	Strengths: Publication bias noted	Weaknesses: No evidence of publication bias noted Vitamin D dosing regimens varied widely	Weaknesses: Publication bias not checked Two studies had incomplete outcome data
	Weaknesses: Trials conducted in heterogeneous populations (Afghanistan, USA, Europe, New Zealand) and among diverse age groups with various vitamin D levels at baseline		

RR relative risk
**According to GRADE Working Group*

with profound vitamin D deficiency in developing countries, but this cannot be applied to all those countries.

BELIEF 4: VITAMIN D IMPROVES DEPRESSION AND MENTAL WELL-BEING

Observational Studies

A systematic review and meta-analysis ($n = 31{,}424$) assessed observational data on the relationship between vitamin D and depression. The systematic review included one case–control study which found that patients with depression had lower vitamin D levels than did healthy controls. The mean difference between the groups was 17.5 nmol/L. Three cohort studies also included in the review explored the association between vitamin D levels and the risk of developing depression. Results showed a significantly increased risk of depression in patients with low vitamin D levels (hazard ratio 2.21, 95 % CI 1.40–3.40).[8]

RCTs

Many of the RCTs on mental health and vitamin D are at high risk of bias, with poor randomization, lack of blinding, no description of patient characteristics, no intention-to-treat analysis and large loss to follow-up. Online Table B includes 8 RCTs that used vitamin D supplementation to improve mental well-being or depression.[39–46] Depression was not a requirement for inclusion in these studies. Based on low baseline depression scores, limited improvements in depression scales would be possible. None of the RCTs that included primarily patients without depression demonstrated a meaningful change in depression or mental well-being.

Table 3 includes three RCTs of patients with depression or depressive symptoms. Mozaffair-Khosravi 2013[47] showed a statistically and clinically significant improvement in symptoms, but had several methodological flaws, including unclear randomization and allocation concealment, and no blinding or intention-to-treat analysis. Khoraminya 2012[49] also demonstrated a statistically and clinically significant improvement in symptoms. This trial was small and of short duration, and had methodological weaknesses. Yalamanchili 2012[48] found that vitamin D had no statistically significant effect on depression. Although this was a secondary analysis, there was no indication of a positive effect.

Systematic Reviews/Meta-Analyses

Three systematic reviews of RCTs on vitamin D supplementation and depression scores have recently been completed.[50–52] The conflicting results are shown in Table 4.

Table 3 Vitamin D and Depression (Randomized Controlled Trials)

Randomized controlled trial	Mozaffari-Khosravi 2013[47]	Yalamanchili 2012[48]	Khoranimya 2012[49]
Population	Mean age ~32, vitamin D < 40 nmol/L, Iran	Community women, mean age 71, secondary analysis osteoporosis study	Major depressive disorder, mean age 39, Iran
Number of participants	120	489 (subgroup of 57 depressed)	42
Vitamin D	Intramuscular injections: 1 dose of 300,000 or 150,000 IU or nothing	0.25 g calcitriol twice/day vs. placebo	1500 IU oral daily + 20 mg fluoxetine vs. fluoxetine alone
Duration	1 year	3 years	8 weeks
Outcome and baseline	Beck Depression Inventory-II, score: ~27 (all >17)	Geriatric Depression Scale, overall: 4.8; 12 % had depression (Geriatric Depression Scale >10)	Beck Depression Inventory, score: 32 Hamilton Depression Rating Scale, score: 30
Result:			
Change in outcome score	Vitamin D 300,000 IU 26.7 to 17.4 Vitamin D150,000 IU 27.5 to 20.6 Nothing 26.4 to 24.3	Vitamin D 4.5 to 3.9 Placebo 4.6 to 4.0 Depression decreased in both groups: vitamin D 23 %; placebo 29 %	BDI: Vitamin D 32.45 to 13.2 Comparator 31.65 to 17.95 HDRS: Vitamin D 29.4 to 11.7 Comparator 30.2 to 17.2
Statistical significance	Yes: placebo vs. 300,000 IU	No	Yes
Clinical significance	Yes	No	Yes
Other issues	Weaknesses: Poor randomization (random number table) and unclear allocation concealment No power calculation No intention-to-treat analysis	Strengths: Randomization and allocation concealment described, intention-to-treat analysis done Weaknesses: Subgroup analysis (without power calculation) 15 % did not complete the Geriatric Depression Scale	Weaknesses: Unclear randomization and allocation concealment No power calculation No intention to treat analysis

Bottom Line

Vitamin D supplementation does not improve mental well-being scores in the general population without clear depression, even when 25-OHD levels are low. Vitamin D supplementation in patients with depression has conflicting, poor-quality evidence and cannot be recommended.

BELIEF 5: VITAMIN D CAN PREVENT OR TREAT RHEUMATOID ARTHRITIS (RA)

Observational Studies

In a prospective cohort study ($n = 29{,}368$) of women from Iowa (USA) aged 55–69 with no history of RA at baseline, 152 developed RA over 11 years of follow-up. When

Table 4 Vitamin D and Depression (Systematics Reviews)

Systematic review/ Meta-analysis	Shaffer 2014[50]	Li 2014[51]	Spedding 2014[52]
Number of randomized controlled trials (patients)	7 (3191)	6 (1203)	15 (not provided)
Inclusion criteria (effect of vitamin D on depression)	Patients with and without significant depression	Adults at risk of depression, with depression symptoms or with depression	No further criteria specified
Result			
Bottom Line	Reduction in depressive symptoms small and non-significant	Insufficient evidence that vitamin D supplementation can improve mood	Statistically significant improvement in 2 RCTs reporting outcomes on Beck Depression Inventory
Improvement in depression symptoms	Standardized mean difference* = −0.14 (95 % CI −0.33 to 0.05) $p = 0.16$	Standardized mean difference* = −0.14 (95 % CI −0.41 to 0.13) $p = 0.32$	Improvement on Beck Depression Inventory = 0.78 (95 % CI 0.24–1.27)
Other issues	Post hoc analysis included 2/3 RCTs of patients with depression[47,49] showing statistically significant reduction in depressive symptoms: standardized mean difference* = −0.60 (95 % CI = −1.19 to −0.01), $p = 0.046$ Weaknesses: Analysis excluded Yalamanchili 2012,[48] the one trial that found no benefit	Included 2/3 RCTs that looked specifically at patients with depression (Yalamanchili 2012[48] and Mozaffari-Khosravi 2012[47])	6 RCTs included other possibly active components in the active intervention arm[53–55] or compared vitamin D to other possibly active interventions[56–58] Beck Depression Inventory in the 2 combined RCTs statistically significant but not clinically significant (estimated to be a 4–5-point change)[59] Weaknesses: Selective reporting of studies[45] and use of per-protocol analysis[44]

** Standardized mean difference is a statistical measure used to combine different scales. It has limited clinical meaning, but it is generally agreed that differences smaller than 0.2 (or −0.2) are not clinically meaningful.*[60]

participants were divided into groups according to their vitamin D intake, those with the highest intake had a lower risk of developing RA than those with the lowest intake (RR 0.67, 95 % CI 0.44–1.00). In subgroups of vitamin D intake, both higher dietary (RR 0.72, 95 % CI 0.46–1.14) and supplemental vitamin D (RR 0.66, 95 % CI 0.43–1.00) were associated with lower risk. This study suggests a possible relationship between low vitamin D intake and increased risk of RA.[9] However, a larger cohort study ($n = 186,389$ women) failed to demonstrate a relationship between vitamin D intake and the incidence of RA or systemic lupus erythematosus.[10]

RCTs

Prevention. Participants enrolled in the Women's Health Initiative trial ($n = 36,282$, mean age 62) were randomized to a daily dose of 1000 mg calcium carbonate plus 400 IU vitamin D or placebo for an average of 5.1 years. In intention-to-treat analyses, there were no differences in RA incidence (RR 1.04, 95 % CI 0.76–1.41).[61]

Treatment. We identified three small RCTs[62–64] in patients with RA (Table 5), all with substantial issues with quality. One study[64] from Sweden, published over 40 years ago, reported that 31 % more patients on high-dose vitamin D (100,000 IU/day) had clinical improvements at 1 year. The authors, however, provided no explanation regarding the specific subjective and objective outcomes measured. The Iranian study found no effect on Disease Activity Score or any other clinical outcome.[62] The Indian study found no difference in time to pain relief (their primary outcome), but reported that patients in the vitamin D arm had greater improvement in pain at 3 months on a visual analogue scale (VAS; median 50 vs. 30 % control group, $p = 0.006$).[63] The authors mistakenly tried to convert this continuous score difference to a number needed to treat.

Overall, given the inconsistent results and high risk of bias, there is no reliable evidence that vitamin D supplementation improves outcomes in RA.

Bottom Line

Vitamin D supplementation lacks consistent and reliable evidence in preventing or treating RA.

BELIEF 6: VITAMIN D CAN TREAT MULTIPLE SCLEROSIS (MS)

Observational Studies

Observational studies have failed to demonstrate a consistent association between vitamin D levels and MS.[5] However, the association between increasing latitude and increasing prevalence of MS inevitably led some to hypothesize that lower exposure to ultraviolet radiation, and thereby lower vitamin D, at high latitudes contributes to or causes MS.[11] Furthermore, some observational studies have drawn associations between higher disease activity among MS patients and lower vitamin D levels.[12,13]

Systematic Reviews/Meta-Analyses

We could not identify any high-level evidence of vitamin D for the prevention of MS. Three systematic reviews/meta-analyses[65–67] have examined the effect of vitamin D on MS (Table 6). The systematic reviews themselves have some methodological concerns. They included up to five of six possible trials. The six trials were small and had several methodological weaknesses. Among these, one found a positive change in MRI lesions and another found one positive clinical outcome out of seven. The one systematic review[66]

Table 5 Vitamin D and Rheumatoid Arthritis Treatment (Randomized Controlled Trials)

Randomized controlled trial	Salesi 2012[62]	Gopinath 2011[63]	Brohult 1973[64]
Population	Rheumatoid arthritis patients in Iran on methotrexate, mean age 50, 91 % women	Rheumatoid arthritis patients in India on three disease-modifying antirheumatic drugs, mean age 45, 75 % women	RA patients in Sweden, mean age 52, 68 % women
Number of participants	117	121	50
Vitamin D	50,000 IU/week	500 IU/day	100,000 IU/day
Duration	12 weeks	12 weeks	1 year
Primary outcome	Reduction in Disease Activity Score	Time to pain relief	Subjective and objective improvement on 4-point scale
Result	No effect (in primary or any secondary outcome)	No effect on time to pain relief One secondary endpoint statistically better ($p = 0.006$): median pain score at trial end was 50 % better for vitamin D vs. 30 % better for placebo	Subjective and objective improvement attained in 67 % of vitamin D group (67 %) vs. 36 % of placebo group, $p < 0.01$, number needed to treat = 4
Other issues	Weaknesses: No sample size calculation Inadequate description of randomization, allocation concealment, and blinding Appears analysis was not intention-to-treat	Strengths: Analysis by intention-to-treat and sample size estimation Weaknesses: No blinding Inadequate description of randomization and allocation concealment Incorrect calculation of number needed to treat	Weaknesses: No sample size calculation Inadequate description of randomization, allocation concealment, and blinding Primary outcome (subjective and objective findings) not described Unclear whether intention-to-treat analysis done >40-year-old study may not mirror present

Table 6 Vitamin D and Multiple Sclerosis (Systematic Reviews)

Systematic review/ Meta-analysis	Pozuelo-Moyano 2013[65]	James 2013[66]	Jagannath 2010[67]
Population	Multiple sclerosis patients (primarily relapsing-remitting)	Multiple sclerosis patients	Clinically confirmed multiple sclerosis patients, mean age 40
Number of randomized controlled trials (patients)	5 (265)	5 (254)	1 (49)*
Vitamin D	Variable dosing/regimens	Approximately 3,000 to 40,000 IU/day	Escalating vitamin D dose to max 280,000 IU/week
Duration	6 months to 2 years	6 months to 2 years	1 year
Outcome	Clinical efficacy or toxicity of vitamin D in patients with multiple sclerosis	One or more relapses	Effect on relapse rate Proportion with relapse
Result	4/5 trials showed no effect on any outcome; only one trial showed improvement in magnetic resonance imaging (MRI) of lesions (but not clinical outcomes)	Vitamin D no effect on multiple sclerosis relapse (odds ratio 0.98, 95 % CI 0.44–2.17); sensitivity analyses found no effect	No statistical difference in 7 clinical outcomes, except 8 % vitamin D vs. 37.5 % placebo had higher Expanded Disability Status Scale scores
Heterogeneity	Not applicable	$I^2 = 36$ %	Not applicable
Other issues	Authors felt studies too heterogeneous for meta-analysis Strengths: Dual reviewers and assessed trial quality Weaknesses: Unclear whether allocation concealment assessed Trials underpowered	Weaknesses: Unclear whether dual reviewers and no assessment of trial quality Trials underpowered	Weaknesses: Poor randomization (draw from a hat) No allocation concealment No blinding Power calculation based on serum calcium; underpowered for clinical outcomes

* *Information drawn from the original trial*[68]

that included a meta-analysis of the results found no effect on relapse rates in either the primary or sensitivity analyses.

Bottom Line

Although the present evidence base is poor, vitamin D supplementation does not appear to provide a clinical benefit in the treatment of MS.

BELIEF 7: VITAMIN D REDUCES MORTALITY

Observational Studies

Multiple observational studies have found a positive association between low vitamin D levels and an increase in all-cause mortality.[14,15]

Systematic Reviews/Meta-Analyses

We reviewed six of the systematic reviews/meta-analyses[16,25,69–72] that examined the effect of vitamin D on mortality (Table 7). Although these are large studies, mortality was a secondary outcome for almost all included trials. A wide range of patients (community-dwelling or institutionalized, with or without chronic medical conditions or previous fractures) and doses of vitamin D_2 or D_3 (with or without calcium) were included. Overall, the relative reduction in mortality ranged from 4 to 11 %. Some of the upper confidence intervals include no effect. This is not uncommon among meta-analyses, and an interpretation of benefit should not rely entirely on statistical significance testing with confidence intervals.[73] Based on these meta-analyses, the relative change in mortality may be a 2 % increase to a 13 % reduction, but is most likely around a 5 % reduction.

Trial sequential analysis[25] suggests that optimum sample size of 130,005 participants has not been reached, indicating that the estimate could change with future studies. A number of the meta-analyses[16,69] also found that while vitamin D_3 was effective, vitamin D_2 was ineffective. The results regarding the necessity of calcium co-administration are conflicting.

Although low 25-OHD levels have been associated with increased mortality in observational studies, it should be noted that emerging observational evidence indicates that high 25-OHD levels (>120 nmol/L) are also associated with increased mortality.[74]

Bottom Line

The effects of vitamin D on mortality are not consistently statistically significant. If real, the relative reductions in mortality are likely quite small (~5 %).

BELIEF 8: VITAMIN D REDUCES CANCER INCIDENCE AND CANCER MORTALITY

Observational Studies

There is relatively consistent evidence from observational studies of an association between lower vitamin D levels and an elevated risk of cancer. Pooled data from observational studies show a correlation between populations in the bottom versus top one third of circulating vitamin D levels and a 14 % RR increase of 1.14 (95 % CI 1.01–1.29; 5003 events) in death from cancer.[16]

Table 7 Vitamin D and Mortality (Systematic Reviews)

Systematic review/Meta-Analysis	Bjelakovic 2014[69]	Chowdhury 2014[16]	Bolland 2014[25]	Rejnmark 2012[70]	Elamin 2011[71]	Autier 2007[72]
Population	Age >70 in most trials, 77 % women, wide range of healthy to institutionalized patients	Mean age 56–85	Mean age in trials 53–89, 24–100 % women	Mean age 70, 87 % women, wide range of healthy to institutionalized patients	Average age 74, 78 % women	Age 50+ in most trials
Number of randomized controlled trials (patients)	56 trials (95,286)	22 (30,716)	38 (81,173)	24 (70,528)	30 (72,231)	18 trials (57,311)
Vitamin D	Vitamin D_3, D_2 or active forms of vitamin D (alfacalcidol or calcitriol) ± calcium	Vitamin D 10–6,000 IU/day	Vitamin D (≥200 IU) ± calcium	Variable vitamin D_2 and D_3 doses and regimens, ± calcium	Majority of studies used vitamin D_3: high dose (≥800 IU) and low dose (<800 IU) ± calcium	Mean dose: 528 IU (range 300–2000 IU)/day
Duration	Weighted mean 0.9 (alfacalcidol) to 4.9 years (vitamin D_3)	Trials mean follow-up: 0.38–6.8 years	1 month to 7 years	3 years	Most (~75 %) ≥12 months	Mean 5.7 years (range 6 months to 7 years)
Primary result	Overall, vitamin D decreased mortality: RR 0.97 (CI 0.94–0.99)	Any vitamin D did not alter mortality: RR 0.98 (95 % CI 0.94–1.02)	Vitamin D reduced mortality: RR 0.96 (CI 0.93–1.00)	Vitamin D reduced mortality (hazard ratio 0.93, 95 % CI 0.88–0.99)	Vitamin D non-significantly reduced mortality: RR 0.96 (95 % CI 0.93–1.00)	Vitamin D reduced mortality (RR 0.93, 95 % CI 0.87–0.99)
Subgroup analyses	Vitamin D_3, (but not D_2 or active forms of vitamin D) reduced mortality Trials with low risk of bias and industry (or not) had similar findings Dose of D_3 or use of calcium did not alter findings	Vitamin D_3 reduced mortality [RR 0.89 (95 % CI 0.80–0.99)], but D_2 did not [RR 1.04 (95 % CI 0.97–1.11)] Dose, duration, location did not alter findings	Similar results with or without calcium (although neither reached statistical significance)	Vitamin D plus calcium reduced mortality (hazard ratio 0.91; 95 % CI 0.84–0.98) but vitamin D without calcium did not	Multiple subgroup analyses (13 total) did not alter findings (including vitamin D_3 vs. D_2)	Duration and dose of vitamin D did not alter findings
Heterogeneity	$I^2 = 0$ %	Chi-square $p = 0.34$	$I^2 = 0$ %	$I^2 = 0$–16 %	$I^2 = 0$ %	Chi-square $p = 0.52$
Other issues	Strengths: Publication bias unlikely 54 % of trials (including 71 % of participants) considered as having low risk of bias Majority of trials supported by industry	Strengths: Most included trials had low risk of bias		Strengths: Individual patient data meta-analysis performed Weaknesses: Variation in dose/regimens may have influenced results	Weaknesses: 13 subgroup analyses performed Trials generally of moderate quality	Strengths: Publication bias unlikely Weaknesses: Did not analyze vitamin D_3 or D_2 separately

RR relative risk

RCTs

A frequently cited RCT ($n = 1179$ white women over age 55)[75] demonstrated that supplementation with vitamin D plus calcium resulted in RR of developing cancer of 0.402 ($P = 0.01$) compared to placebo. The trial, however, had many limitations: industry-funded, secondary analysis of fracture trial, unclear allocation concealment, small number of events reported, efficacy of blinding not described, and outcome was patient reporting of new onset cancers.

Systematic Reviews/Meta-Analyses

Early systematic reviews[27,76,77] included limited numbers of RCTs and did not perform meta-analyses. Generally, these reviews included the RCT[75] mentioned above and non-statistically significant RCTs to conclude that possible clinically important effects could not be ruled out.

Two meta-analyses (7 trials, $n = 48,167$; 18 trials, $n = 50,623$)[25,78] have been performed more recently. Both reported that vitamin D supplementation did not alter the incidence of cancer: RR 0.99 (95 % CI 0.93–1.05),[25] and RR 1.00 (95 % CI 0.94–1.06).[78] Trial sequential analysis conducted in both meta-analyses found that the effect of vitamin D supplementation on the incidence of cancer lay within the futility boundary (15 % RR reduction), and no further studies were required.[25,78]

The larger meta-analysis[78] also assessed the effect of vitamin D supplementation on cancer mortality and found a statistically significant benefit, RR 0.88 (95 % CI 0.78–

0.98). This analysis included four trials with a total of 44,492 participants, and evidence was deemed to be of low quality. Trial sequential analysis indicated that this finding could be due to random errors and that further data were required.

Bottom Line

Vitamin D supplementation does not reduce the incidence of cancer. The impact of vitamin D supplementation on cancer mortality is less clear and has been assessed only by low-quality evidence.

BELIEF 9: VITAMIN D DOSE—MORE IS BETTER

RCTs

Two large RCTs (Table 8) provide concerning evidence that higher doses of vitamin D could increase the risk of falls and fracture.[79,80] Given the present enthusiasm for vitamin D supplementation and the pervasive belief that more is better, these trials serve as a good reminder. Even in the two clinical areas of best evidence for vitamin D supplementation (falls and fracture prevention), massive doses can increase the very outcomes we are trying to prevent. Additionally, there is some evidence (albeit observational) that higher 25-OHD levels (>120 nmol/L) are associated with increased mortality.[74]

Bottom Line

High-dose vitamin D has been shown to increase the risk of falls and fractures. Single high-dose (≥300,000 IU) supplementation should not be recommended.

BELIEF 10: VITAMIN D (25-OHD) LEVELS SHOULD BE TESTED ROUTINELY

Routine 25-OHD testing is not recommended, for several reasons. Vitamin D assays can vary by as much as 10–20 %, even when repeating the test in the same person at the same time.[5] Therefore, changes in levels may not be discernable in individuals at doses of 800 IU/day, as this dose on average changes the serum vitamin D about as much as the variance in assay.[81]

Enrollment in many vitamin D supplementation trials was not based on 25-OHD levels, and treatment of patients without screening 25-OHD level was found to be beneficial.[29,72,82]

Finally, routine screening/testing of 25-OHD levels is an onerous and costly exercise. The cost of a 25-OHD assay is $61.32,[81] two to three times the cost of a year's worth of vitamin D.

Despite recommendations to the contrary, testing 25-OHD levels has become widespread in recent years. One consequence has been confusion regarding the 25-OHD level indicative of deficiency. The "cut-points" for deficiency and sufficiency used by laboratories are neither standardized nor based on rigorous scientific studies. The number of people with vitamin D insufficiency/deficiency may be overestimated, because many labs use higher cut-points than are indicated by the evidence.[5]

Based on a systematic review of studies on health outcomes associated with vitamin D, the Institute of Medicine now recommends:

- Deficiency: <30 nmol/L places a person "at risk relative to bone health"; 30–50 nmol/L "places some, but not all, persons at risk for inadequacy."
- Sufficiency (adequate): ≥50 nmol/L meets the needs of 97.5 % of the population

The Institute of Medicine also states that "levels >75 nmol/L are not consistently associated with increased benefit."[5]

Bottom Line

Vitamin D supplementation in the general adult population is safe, and supplementation without testing is reasonable. Testing may be appropriate when clinically indicated (e.g.,

Table 8 Examples of Vitamin D Mega-Dose (Randomized Controlled Trials)

Randomized controlled trial	Sanders 2010[79]	Smith 2007[80]
Population	Age ≥70 with high risk of fracture, women only, community-dwelling	Age ≥75, 54 % women, community-dwelling
Number of participants	2256	9440
Vitamin D	500,000 IU/year (single oral dose each autumn)	300,000 IU D_2 (single intramuscular injection each autumn)
Duration	3–5 years (mean 3.1 years)	3 years
Outcome	Falls and fractures	Primary: all non-vertebral fractures Secondary: hip and wrist fractures, all falls
Result	Increased falls (rate ratio 1.15, 95 % CI 1.02–1.30) and fractures (rate ratio 1.26, 95 % CI 1.00–1.59) Statistically significant temporal pattern evident for falls—highest incidence within first 3 months of supplementation when vitamin D levels > 90 nmol/L Number needed to harm over 3.1 years of 18 for falls and 32 for fractures	Risk increased for all fractures (hazard ratio 1.09; 95 % CI 0.93–1.28) One fracture subgroup statistically significant: excess risk of hip fracture in those on vitamin D (hazard ratio 1.49; 95 % CI 1.02–2.18) No effect on falls (hazard ratio 0.98, 95 % CI 0.93–1.04)
Other issues	Strengths: Good randomization, allocation concealment and blinding Sample size calculation done Daily fall recording	Strengths: Good randomization, allocation concealment and blinding Sample size calculation done Weaknesses: 6-month recall of falls

parathyroid disease), and a variety of resources are available to direct testing.[83] When testing is performed, ≥50 nmol/L indicates vitamin D sufficiency.

CONCLUSION

Severe vitamin D deficiency causes important health problems (e.g., rickets). Additionally, lower 25-OHD levels have sometimes been associated with a long list of medical conditions and negative outcomes. However, association is not causation, and high-quality, high-level evidence for supplementation is frequently lacking. Vitamin D may prove to be a good surrogate for general well-being.

At the present time, evidence supports vitamin D supplementation to help prevent fractures (particularly if given with calcium), and possibly to prevent falls and slightly reduce mortality (particularly in older patients [>70 years of age]). No other effects are proven. For many other conditions, the evidence for vitamin D supplementation is plagued by the use of small, poor-quality trials. Lastly, testing of 25-OHD levels in the general population is not necessary, and very high doses should be avoided.

Acknowledgments: *There are no additional contributors to the manuscript. The project received no funding, and this work has not been presented previously.*

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Compliance with Ethical Standards:

Conflict of Interest: *The authors declare that they have no conflict of interest.*

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