FIGURE 1:

VITAMIN D SUPPLEMENTATION EVIDENCE

SKELETAL

↓ Hip fractures (NNT 200) with Ca [48-53]

↔ Falls [48-53, 111]

↔ Osteoarthritis [57]

↓ Mortality (NNT 143) with Ca [48-53]

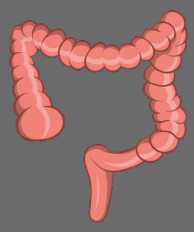
Slight ↑ BMD lumbar spine, forearm, with Ca in steroid-induced osteoporosis [55]

Skeletal outcomes better studied than other outcome areas.

OVERALL CANCER RISK

↓ Mortality (NNT 290 2-7yrs) [59]

↔ Risk (conflicting results) [27,28,58]

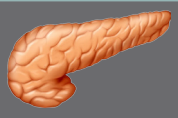


COLON CANCER

↔ Risk [60]

PROSTATE CANCER

May ↓ prostate cancer progression [62]



DIABETES

↔ T2DM prevention [68,69]

↔ Non-alcoholic fatty liver disease [67]

May ↓T1DM risk in infants [22]

BREAST CANCER

↓ Breast cancer mortality [59]

PULMONARY

↓ Asthma attacks/hospital visits in mild-mod asthma [91]

↔ Asthma symptoms/lung function [91]

↔ TB sputum culture conversion [98]

↓ COPD mod-severe exacerbation risk ONLY in Vit D deficient pts [92 (ViDiCo)]

↔ Time to 1st mod-severe exacerbation or time to 1st URTI [92 (ViDiCo)]

Small ↓ acute URTI risk (most benefit in very deficient pts and those not receiving boluses) [93]

↓ Influenza A risk/flu-related asthma attacks in children [95]

CARDIOVASCULAR

↔ CV disease risk (pts were VitD replete) [66]

↔ BP [22]

RENAL

✓ Control mineral/bone disorders D2 or calcitriol, stage 3-5 CKD [71]

May ↓ UTI risk (NNT 17 5 yrs) largest effects in males [99]

NERVOUS SYSTEM

↔ Depression treatment [78,79]

May ↓ Parkinson's progression [77]

↔ ALS prevention or prognosis [84-86]

May ↓MS relapse rate in pts on natalizumab [83]

Small ↓ in non-specific chronic pain [36]

MORTALITY

Inverse relationship with levels and mortality: threshold is 20-30ng/mL (50-75 nmol/L) for overall mortality, 30ng/mL (75 nmol/L) for CV mortality [72,94]

↔ ICU mortality, length of stay [34]

SKIN

↓ Plaque psoriasis (but more AE vs steroids) – topical vit D [39]

↓ Winter-related atopic dermatitis in children [103]

May ↓ inflammatory acne lesions [100]

Conflicting findings re: skin aging [101,102]

Rx FILES

Green Text = consistent evidence from high quality meta-analyses or RCTs

Yellow Text = evidence from RCTs or lower-quality meta-analyses

Orange Text = evidence from observational studies, or RCT evidence with limitations or inconsistency

Pink Text = lack data

This figure does not include health conditions where a correlation has been observed with Vitamin D levels but not yet tested with Vitamin D supplementation (these are outlined in Table 2).

Vitamin D: Therapeutic Overview & Evaluation of Evidence for Current Claims [1,2,3,4]

Vitamin D deficiency in Canada [5] (see Table 1 below for significance of level)	○ Statistics Canada: 32% of Canadians have levels < 50nmol/L (25% in summer, 40% in winter), and 10% are < 30 nmol/L (mean overall 64nmol/L)[42]
⇨**Symptoms**	○ muscle weakness, bone pain
⇨**Risk factors**	○ **dark skin**, lack of sunlight (northern latitude, atmospheric pollution), sunscreen use (however, sunscreen use is recommended to reduce skin cancer risk), occlusive clothing, elderly, **obese** or institutionalized, malabsorption (e.g. inflammatory bowel disease, celiac disease), **renal** disease, **medications** (anticonvulsants, thiazides,[20] corticosteroids, antiretrovirals (HIV), cholestyramine, rifampin)
Types of vitamin D - D3 (cholecalciferol) - D2 (ergocalciferol) - Other (active vitamin D analogues)	○ **vitamin D3** or **cholecalciferol:** (**preferred form**) synthesized normally in the skin via 7-dehydrocholesterol {1000IU of D3 daily will increase 25(OH)D levels by ~15-25nmol/L[6] over 8 months} ○ **vitamin D2** (or ergocalciferol) a plant based derivative; option for vegans; no longer considered bioequivalent to vitamin D3 ○ **calcitriol**: one of the active forms of Vit D in the body is calcitriol: used in patients with end-stage renal disease (ESRD) who are unable to convert vit D3 to calcitriol
⇨**Supplements available in Canada** Vitamin D2 and **D3** most useful in primary care; other analogues used in specialized areas such as chronic kidney disease.	○ vitamin D3: OTC: 400IU, 1,000 IU **tabs** Rx: 2,000 IU cap, 5,000 IU cap, 10,000 IU cap/tab; 25,000 IU cap, 50,000 IU cap, 50,000-75,000 IU manufactured cap (from powder) ○ vitamin D3: OTC: D-VI-SOL 400 IU/ml, DDROPS (600 or 1000 units/drop[5ml=180drops]) **liquid**; OTC Peds: BABY **DDROPS** : 400 units/drop (~$20 / 2.5ml bottle (~ 90 drops)) ○ vitamin D2 Rx: OSTO-D2, D-FORTE 50,000 IU/cap ○ calcitriol Rx: ROCALTROL, generics: 0.25ug, 0.5ug cap (expensive) ○ other (expensive) Rx: alfacalcidiol ONE-ALPHA 0.25 ug, 0.5 ug, 1 ug cap, 2 ug/mL
Dosage Guidelines/Considerations **Maintenance Range:** ◆ **400 IU - 2,000 IU daily** ◆ **Evidence supports efficacy & safety of 800 – 2,000 IU/day for most and possibly up to the daily upper limit of4,000 IU, especially in high risk & in winter.** (some suggest Vit D3 10,000 IU **weekly** or Vit D2 50,000 IU **monthly** to ↓ pill burden) [6] **Unit Conversion:** (1mcg = 40 IU) 400 IU = 10 mcg 800 IU = 20 mcg 1000 IU = 25 mcg 2000 IU = 50 mcg	○ Osteoporosis Canada guidelines[6]: ● **adults <50 yrs at low risk** for deficiency: vitamin D3 **400-1,000 IU once daily** ● **adults ≥ 50yrs & moderate-high risk**: vitamin D3 **800-2,000 IU once daily** - **up to 2,000 IU/day** considered safe without requiring medical supervision Max: Vit D from all sources **4000IU**/day for all older adults recommended by the American Geriatrics Society 2013 and IOM 2010} ● **adults in long-term care:** vitamin D3 **800-2,000 IU once daily** {if high fracture risk, strongly recommended, otherwise dep. on values/pref/resources}[46] ○ Canadian Cancer Society[7] ● adult (during fall & **winter**): 1,000 IU/day ●older adults, dark skin or little sun exposure: 1,000 IU/day all year ○ Canadian Pediatric Society[8]: ● **pregnancy** & lactation: consider 2,000 IU daily especially during the **winter** ● breastfed infants: 400 IU/day; 800 IU/day for northern Native communities(especially in **winter**) ● formula fed: no supplement needed; except Northern communities 400 IU/day (from Oct –Apr) ○ Scientific Advisory Committee on Nutrition (SACN, UK)[45]: ≥4 years: 400 IU once daily ○ **IOM 2010**: Recommended dietary allowance ≥1yr = 600IU/day, if ≥71yr = 800IU/day
Vitamin D Bolus doses ◆**for severe deficiency** ◆**may consider initial bolus if serum 25(OH)D level is <25-50nmol/L followed by maintenance**	○ lack of evidence and highly variable in literature and clinical practice ○ approaches vary: {D3 used more than D2; daily [9,10] e.g. 2,000 – 4,000 IU daily x 8-20 weeks; weekly [11,12] eg. 50,000 weekly x 8 wks (Vit D2 trials); monthly eg. 50,000 monthly x 9; or single bolus 10,000 - 150,000 IU x1 }; may depend on starting 25(OH)D level, BMI, effective sun exposure & other factors (eg. malabsorption) ○ single yearly high doses (500,000 IU orally or 300,000 IU IM) are not recommended in the elderly due to increased risk of fracture +/or fall esp. in the first few months post dose;[13,14] if used, vitamin D3 is preferred over vitamin D2.[47]
Vitamin D adverse effects	○ hypercalcemia [15], hypercalciuria ○ GI symptoms (may be due to combination with Ca^{++} intake) [16] ○ renal disease, **nephrolithiasis** [400 IU/day + Ca^{++}(~2,100mg/day total avg intake) HR=1.17(WHI - 7yrs)[39] ○ increased fall & fracture rates with very high single yearly doses of 500,000 IU oral vitamin D3[14], & similar increases in fractures (not falls) with 300,000 IM yearly.[15]
Food sources[17] **{Difficult to get adequate Vit D from dietary sources alone; whereas it is possible to get adequate calcium from diet alone.}**	○ fish: salmon, sardines, tuna & mackerel (200–600 IU/3.5-oz serving)[3] & fish oils ○ small amounts found in beef liver, cheese and egg yolks ○ some mushrooms may contain varying amounts of vitamin D2 ○ fortified food sources such as **fortified** milk/orange juice (8oz glass = 100 IU)

Extras: appropriate vitamin D levels may improve absorption of dietary calcium from 10-15% up to 30-40% [3,18]

Table 1: Classification of 25-hydroxyvitamin D (25(OH) D) serum levels * (ng/ml x 2.496 = nmol/L)

25(OH)D (nmol/L)	< 30[20,42]	30-50 [20,42,43]	50 – 125 [43,44]	>125[43,44]	> 375 – 500[45]
	Osteomalacia/rickets deficiency ----------	insufficiency/suboptimal	Optimal bone health	Potential adverse effects	Toxic

***Levels** ◆ **not** routinely recommended; useful if high risk of vitamin D deficiency or toxicity concerns.[6, 19,112,113] Cost: $20-60
◆ **IOM** 2010: ≥**50 nmol/L** adequate level (some controversy with US Endocrine Society recommending 75 nmol/L)[110]
◆1000IU/day of D3 will increase 25(OH)D levels by ~15-25nmol/L[6,20] over 8 months

Table 2: Claims and Evidence for Vitamin D (Abridged; for discussion, see reference link to detailed trials summary table[21])

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Category	Claims	Evidence
Skeletal	Prevents hip fractures and mortality [16,22,48-53]	**Falls/fractures** (per 1,000 treated)*: [48, 49 (CADTH umbrella review), 50-53] ◆ 5 fewer hip # (95%CI 2-8) ◆ No change in fall risk[111] ◆ 7 fewer deaths (95%CI1-14) CADTH umbrella review of 5 meta-analyses (elderly long-term care population): fall risk only reduced in 1 meta-analysis; others showed no benefit.[49] * Benefits only seen when used with Ca^{++}. Subgroups with more benefit: low vitamin D levels, community-dwelling elderly under 80 with no cognitive impairment, no Hx of fall/fracture. Toxicities for every 1,000 patients:[48-53] ◆ 8 more GI AE ◆?5 more hypercalcemia ◆ 3 more renal insufficiency or calculi ◆ 23 more MI * Most harms related to Ca^{++} component. Limit Ca^{++} to max 500 mg/day (elemental). Functional decline:[23] Higher doses (60,000 or 24,000 IU monthly) had more falls than the 24,000 IU monthly group. No benefit on lower extremity function. Single dose resulted in an increase in fracture +/or fall within the first 3 months after initial dose[15] ◆ No adverse effects noted below 200,000 IU yearly in another large-dose study (300,000-600,000 IU po yearly)[47]
	Does not prevent falls [23, 24,48-53]	
	Slightly increases femoral neck mineral density[54]	◆ 0.8% increase at femoral neck (95%CI 0.2-1.4%, with heterogeneity among trials) ◆ No effect at other sites[54]
	Steroid induced osteoporosis: Increases lumbar spine and forearm BMD[55]	2 years of Vit D + Ca^{++} increased lumbar spine and forearm BMD[55]
	Low levels related to RA disease activity [25,56]	Low vit D levels increase disease activity and bone loss. [56]
	Osteoarthritis: No benefit for pain, stiffness, or function[57]	Vit D3 (800-60,000 IU) does not improve pain, stiffness, or function (2/3 studies showed improvement in knee pain on visual analogue scale) [57]
Cancer	Conflicting findings on cancer risk[26, 58]	Cancer risk: ◆ 1,000 IU / day vitamin D + Ca^{++} 1400-1500mg/day in postmenopausal women (>55yo) had decreased rates of cancer (NNT=25/4years)$_{\text{baseline 25(OH)D=71.8 nmol/L}}$[27] ◆ 2,000IU/day vitamin D + Ca^{++} 1500 mg/day postmenopausal women (>55yo) did not sig. ↓ cancer risk[58] HR 0.70 (95%CI 0.47-1.02)(pts were Vit D replete*; mean baseline levels 32.8ng/mL (81.9 nmol/L), unknown whether Vit D would ↓ cancer risk if given to deficient pts)
	Reduces cancer mortality[59]	Cancer mortality:[59] ◆ 400-1100 IU vitamin D/day (+/- Ca^{++}) for 2-7 years sig. ↓ cancer mortality (RR 0.88) 95%CI 0.78-0.98 Risk likely related to 25(OH)D levels: In this meta-analysis, baseline 25(OH)D was 38-74.4 nmol/L; NHANES III cohort did not find cancer mortality benefit with higher 25(OH)D levels[27]
	Does not reduce colon cancer risk [28, 60-62]	◆ Prevention RCT: Vit D 1000 IU/day + Ca^{++} 1200mg/day for 3-5 years did not sig. ↓ colorectal cancer risk,[60] but genotype affects risk (AA genotype ↓ risk 64% ; 1 or 2 G alleles ↑ risk 41%[61])
	Colon cancer mortality inversely related to levels	◆ Mortality: inverse to 25(OH) D levels (observational studies)[62]
	Reduces breast cancer mortality [29, 30, 31,62,63]	◆ Observational studies: 25(OH)D levels correlated with lower progression/mortality esp. in pre-menopausal women[62,63]

Category	Claims	Evidence
		• Meta-analysis of observational studies: Higher 25(OH)D correlated with lower case-fatality rate (highest vs. lowest quantile pooled HR 0.56, 95%CI 0.4-0.7).[64] • RCT suggests safety with 10,000 IU vitamin D3 dose daily x 4 months[32] Consider Vit D dose (benefits are dose-dependent), Ca^{++} intake (harms are often related to Ca^{++} component)!
	May reduce prostate cancer progression [33,62]	• Low 25(OH)D levels related to aggressive cancer (<30ng/mL associated with adverse pathology; OR 2.64 95%CI 1.25-5.59.)[65] • Inconsistent data for progression and mortality; open-label trial suggests 4,000 IU/day may ↓ progression[62]
CV	Does not reduce cardiovascular risk [22,66]	• RCT: 200,000 IU once, then 100,000 IU monthly for 3.3 years did not reduce CV disease risk (both groups were vitamin D replete* and only half were at high CV risk; unknown if deficient or higher CV risk patients might benefit;)[66]
	Does not reduce blood pressure	• 100,000 IU q3 months x 1yr did not improve blood pressure[VitDISH]
Diabetes Mellitus (DM)	May reduce T1DM risk[22]	• Type 1 DM prevention: some benefit suggested in large cohort trial
	Does not reduce T2DM risk[68,69]	• Type 2 DM prevention: No benefit on insulin sensitivity, glucose control, or cardiometabolic risk[68,69]
	Low levels associated with CV morbidity/mortality (T2DM)	• Low 25(OH)D associated with higher risk of CV morbidity/mortality in T2DM[73]
	No benefit for non-alcoholic fatty liver disease (T2DM)[67]	• No benefit on non-alcoholic fatty liver disease in T2DM[67]
Renal	Kidney disease: reduces PTH, controls mineral and bone disorders stage 3-5CKD [22,70,71]	Chronic kidney disease: • Effective for decreasing parathyroid hormone (PTH) in patients with chronic kidney disease (but can increase calcium and phosphate) • Vitamin D3 raises 25 (OH)D levels more than D2 in non-dialysis dependent CKD patients (but levels ↓ rapidly after Tx stopped); D2 and D3 equally effective in lowering PTH.[70] • D2 and calcitriol equally effective to control mineral & bone disorders in stage 3-5 CKD.[71] Toxicity (data from Women's Health Initiative (WHI): [34] nephrolithiasis: Vit D3 400 IU/day + Ca^{++} (~2,100mg/day total intake on average) HR=1.17 95% CI 1.02-1.34 WHI - ~ 7yr
	May prevent UTI[99]	UTI: Vit D (20,000 IU/wk x 5 years) ↓ UTI risk (7% Vit D vs. 13% placebo, p<0.02)[99]
Mortality	Inverse relationship between levels and all-cause mortality [35]	•Meta-analysis (N=26, 916) : 25(OH)D levels inversely related to mortality (overall & CV mortality but not cancer mortality); effects reached a threshold at 20ng/mL (50 nmol/L) for overall mortality and 30ng/mL (75nmol/L) for CV mortality (no further benefits beyond these thresholds; may explain why trials in replete* patients did not find benefits)[72]. Another meta-analysis found the same inverse relationship, but with a threshold of 30ng/mL (75 nmol/L) for all-cause mortality.[94]
	Does not reduce ICU mortality or length of stay	• VITdAL-ICU: among critically ill pts with vit D deficiency giving 540,000 IU x1 then 90,000 IU monthly x 5 months did not reduce hospital length of stay, hospital mortality or 6 month mortality.[34]
Nervous System	Inverse relationship between vitamin D intake and Alzheimer's risk[74-76]	• Alzheimer's dementia: Proposed benefit but data lacking (inverse relationship between levels/intake and risk)[74-76]
	May slow Parkinson's disease progression[77]	• Parkinson's: RCT showing potential benefit (1,200 IU/day may slow progression)[77]

Category	Claims	Evidence
	Not effective for treating depression[78-79]	◆ Depression treatment: 2 meta-analyses showed no benefit.[78,79]
	May reduce MS relapse rate[80-83]	◆ MS: association between low neonatal and childhood Vit D and MS[80,81], placebo-controlled trial found no changes in inflammatory markers[82], but prospective cohort study found ↓ in relapse rate (in pts on natalizumab)[83]
	Does not prevent ALS or slow progrssion[84-86]	◆ ALS: Prospective cohort study found no protective effects[84], non-randomized comparative study found no change in prognosis (100,000IU/wk x 4 wks), [85] and vitamin D levels do not predict survival.[86]
	Small decrease in non-specific pain[35,87-90]	◆ Chronic pain[36]; small ↓ in non-specific pain 6 wks post 150,000 IU PO x1or2 ◆ Low vit D levels found in fibromyalgia,[87] carpal tunnel,[88] and chronic widespread pain, [89] but not low back pain. [90]
Pulmonary	Reduces asthma attacks and hospitalization[91,96]	◆ Asthma: Cochrane review - Low Vit D levels linked to asthma severity, attacks; vitamin D ↓ avg. attacks/yr (from 0.48 to 0.22, RR 0.63, 95% CI 0.45-0.88), risk of attending hospital due to attack (from 6% to 3%, OR 0.39 95% CI 0.19-0.78). No effect on lung function or day to day symptoms. Data mostly in mild-mod asthma.[91] Vit D did not influence time to exacerbation or infections upper respiratory in asthmatics. There was no sig ↓wheeze/asthma in kids when prenatal supplement given. VDAART,Chawes'16 Low Vit D levels were not found to increase the risk of atopic disease (e.g., asthma, atopic dermatitis).[96]
	COPD: reduces mod-severe exacerbation risk (only if vit D deficient) ViDiCo	◆ COPD: Correcting Vit D deficiency (120,000 IU q2mo x 6) ↓ mod-severe exacerbation risk (HR 0.57, 95% CI 0.35-0.92, p=0.021)ONLY in Vit D deficient pts (<50nmol/L) but did not affect time to 1st mod-severe exacerbation or time to 1st URTI[92 (ViDiCo)]
	Small decrease in URTI risk (mainly in vit D deficient and LTC residents)	◆ URTI: Vit D (300-2,000 IU daily or boluses of 100,000 IU monthly) ↓ acute URTI risk (OR 0.88, 95% CI 0.81-0.96) but ARR only 2% (most benefit in very deficient pts and those not receiving boluses) and definitions of URTI varied between studies (included many different conditions)[93]; reduced acute URTI in older LTC residents but more falls Ginde'16
	Reduces influenza A risk (and risk of flu-related asthma attacks)in children[95]	◆ Influenza: Vit D ↓ influenza A riskin schoolchildren (RR 0.58, 95% CI 0.34-0.99, p=0.04); ↓ risk of flu-related asthma attacks (RR 0.17, 95% CI 0.04-0.73, p=0.006)[95]
	Does not help with sputum culture conversion in tuberculosis[97]	◆ TB: Vit D deficiency increases TB risk (OR 2.57, 95% CI 1.74-3.80)[97]; Vit D did not have any significant benefits on sputum culture conversion in active tuberculosis[98]
Skin [37, 38]	Relieves symptoms of plaque psoriasis (topical vit D) [39]	◆ Psoriasis: topical vitamin D application may be useful in psoriasis but has more adverse effects when compared to corticosteroids; (ie eczema, psoriasis)
	Improves winter atopic dermatitis in children[103]	◆ Atopic dermatitis: improved winter related atopic dermatitis in children [103]
	May reduce inflammatory acne lesions[100]	◆ Acne: Low Vit D levels correlate with acne incidence/severity; 1,000 IU daily x 2 mo ↓ inflammatory lesions 34.6% (p<0.05).[100]
	Low levels may be linked to skin aging (conflicting findings)[101,102]	◆ Skin aging: Conflicting findings (some studies suggest a link, others do not; ethnic group may play a role)[101,102]

AECOPD=acute exacerbation of COPD, COPD=chronic obstructive pulmonary disease, MS=multiple sclerosis, OA=osteoarthritis, OP=osteoporosis, RA=rheumatoid arthritis, RCT=randomized controlled trial, URTI=upper respiratory tract infection

Green = consistent evidence from high quality meta-analysis or RCTs; Yellow = evidence from RCTs or lower-quality meta-analyses; Orange = evidence from observational studies, or RCT evidence with limitations or inconsistency; Pink = lack data

*Vitamin D replete = 25(OH)D levels in the 50-125 nmol/L range.

Vitamin D: What we know, what's coming next

What do we know (bottom line)?

1. **Although it is suggested that there may multiple benefits for vitamin D, the evidence for vitamin D (when used with calcium) is strongest in preventing fractures (NNT 200).**
2. **Cut-off points for 25(OH)D have not been well established.**
3. **There may be an association between low 25(OH)D and mortality, but it is unknown whether treatment will be of benefit.**

What's new since the last update (Jan 2013)?

- Concept of a threshold for the association between lower 25(OH)D levels and mortality (50-75 nmol/L)[72,94]
- New Osteoporosis Canada guidelines on preventing fracture in long-term care[46]
- New evidence (see Table 2 and Figure 1)

What are the headlines saying?

The headline	The facts
There is a vitamin D deficiency "pandemic", and most of us aren't getting enough. Nearly everyone needs a supplement.	This "hype" stems from misinterpretation of the Institute of Medicine (IOM) vitamin D recommended 25(OH)D levels of 50 nmol/L (20 ng/mL) as a "cut point" for good bone health. But this is actually the upper end of the spectrum of human need; 97.5% of people need this amount *or less*, and 50% need 40 nmol/L (16 ng/mL) or less. This means that many people whose requirement is being met are being misclassified as "deficient". Guidelines vary on who needs a supplement (generally those at high risk of deficiency or fracture; see Dosage Guidelines above). [106]
On one hand… Vitamin D is a "cure-all" that can prevent and treat a wide variety of diseases.	Correlation is not causation. Many observational studies have found relationships between low 25(OH)D levels and various diseases. But for many of these conditions, vitamin D supplementation does not result in a significant improvement.[109]
And on the other hand… Vitamin D does not live up to the "hype" – it's not as effective as we hoped.	Some news stories tout vitamin D as a cure-all, while others say it's useless and possibly harmful. The truth is somewhere in between. There is a lot of low-quality evidence linking lower levels of vitamin D to various conditions, but not much convincing evidence for supplementation except for a few key areas (see Table 2 and Figure 1). Supplementation trials may have disappointing results because vitamin D benefits are greatest in those with the lowest vitamin D levels, but many studies used patients who were vitamin D replete. Vitamin D may exhibit a "threshold effect" (only patients with levels below a certain threshold will benefit from supplementation) rather than a linear "dose response" relationship.[110] New studies are underway to help clarify the role of vitamin D supplementation (see below). [108,109,110]

What's still unclear?

1. What is the appropriate 25(OH)D level definition for vitamin D deficiency?[106]
2. Do low 25(OH)D levels increase the risk of death?
3. What is the best 25(OH)D level range for optimal health, and is it the same for all populations and disease states?[104,110]
4. Do dietary recommendations for vitamin D need to be updated?
5. Do vitamin D dosage guidelines need to be updated (guidelines have not been recently updated and recommendations differ)?[105,110]
6. How safe are large doses of vitamin D, and what is the maximum daily (or weekly, monthly or yearly) dose?
7. What is the optimal dosing regimen: would daily or weekly supplementation be more effective than monthly (which can cause fluctuations in levels) for reducing cardiovascular risk? What other conditions are sensitive to 25(OH)D level fluctuations?[107]
8. Does vitamin D supplementation reduce all-cause mortality, cancer or cardiovascular risk in people who are vitamin D deficient (most studies were in replete patients)? [72,94]
9. What are the indications for vitamin D levels?

What upcoming studies will help us answer these questions?

Study	Expected publication date	Summary
D-HEALTH **5-year RCT**	2019/early 2020's (5-year study that launched in Jan 2014)	**P**opulation: N=25,000 Australian adults aged 60-84 (no Hx of sarcoidosis, hyperparathyroidism, hypercalcemia, or kidney stones) **I**ntervention: Vit D 60,000 IU monthly x 5 years **C**ontrol: Placebo **O**utcomes: All-cause mortality (primary), total cancer incidence (secondary), colorectal cancer incidence (secondary) **T**ype of question: Prevention trial **T**ype of trial: Randomized https://dhealth.qimrberghofer.edu.au/
VITAL **RCT**	Enrollment will complete at end of 2017; Publication likely in 2018	**P**opulation: N=25,874 adults (Women 55 and over, men 50 and over, no Hx of cancer, heart attack or stroke) in Boston MA **I**ntervention: Vit D 2,000 IU daily and/or omega-3 fatty acids 1 gram daily (Vit D alone, omega-3 alone, or both)

		Control: Placebo **O**utcomes: Risk of cancer, heart disease and stroke **T**ype of question: Prevention trial **T**ype of trial: Randomized http://www.vitalstudy.org/
PRECOVID **1-year RCT**	Completion 2017; publication est. 2018	**P**opulation: N=240 COPD patients (40 and over with Vit D deficiency; 25(OH)D < 50 nmol/L) **I**ntervention: Vit D 16,800 IU weekly x 1 year **C**ontrol: Placebo **O**utcomes: Exacerbation rate (primary); physical performance, QOL **T**ype of question: Treatment trial **T**ype of trial: Randomized https://bmcpulmmed.biomedcentral.com/articles/10.1186/s12890-015-0101-4

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