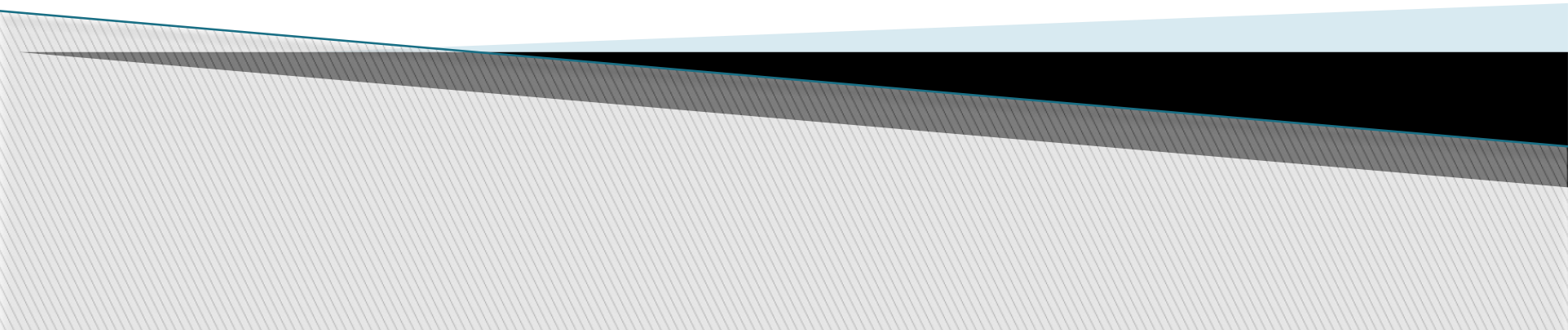


Vitamin D for Disease Prevention and Treatment

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Disclosure

- ▶ I receive funding from Bio-Tech Pharmacal, Inc. (Fayetteville, AR, USA), a supplier of vitamin D and other supplements.

Outline

- ▶ Introduction to vitamin D
 - ▶ Types of studies
 - ▶ Findings for major diseases
 - Cancers
 - Cardiovascular disease
 - Diabetes mellitus type 2
 - Dementia and Alzheimer's disease
 - COVID-19
 - Pregnancy and birth outcomes
 - ▶ Hill's criteria for causality in a biological system
 - ▶ Where additional research is needed
 - ▶ Recommendations
 - ▶ Where to find information regarding vitamin D
- 

We Are in the “Golden Age” of Vitamin D Research

- ▶ Vitamin D has gone from being associated with bone health prior to ~2000 to being associated with up to 300 conditions and diseases.
- ▶ Publications with vitamin D in the title/abstract:
 - ▶ 1950–1999: 14,168
 - ▶ 2000–2009: 12,339
 - ▶ 2010–2019: 34,980
 - ▶ 2020–2026: 31,765

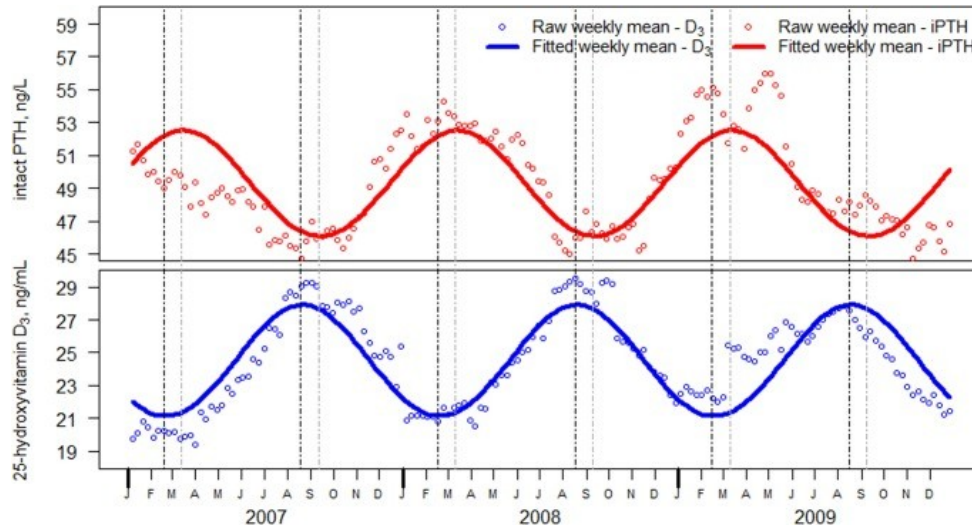
Introduction to Vitamin D

- ▶ Vitamin D₃ (cholecalciferol) is obtained from solar UVB exposure, diet, and/or supplements.
- ▶ It is converted in the liver to 25-hydroxyvitamin D [25(OH)D], which is measured as the “vitamin D level”.
- ▶ It is converted in the kidneys and other organs as needed to 1,25-dihydroxyvitamin D (1,25-(OH)₂D₃).
- ▶ It acts primarily through 1,25-(OH)₂D₃ binding to vitamin D receptors found in nearly every cell in the body where it affects gene expression, upregulating some genes, downregulating others.

Disassociation of Vitamin D's Calcemic Activity and Non-calcemic Genomic Activity and Individual Responsiveness

- ▶ Thirty healthy adults were randomized to receive 600, 4,000 or 10,000 IU/d of vitamin D₃ for 6 months. There was a dose-dependent 25(OH)D alteration in broad gene expression with 162, 320 and 1289 genes up- or down-regulated in their white blood cells.
- ▶ Shirvani A, Kalajian TA, Song A, Holick MF. *Sci Rep.* 2019;9(1):17685.

Seasonal Variations in Serum 25(OH)D and PTH in the U.S.



Nearly half of the US population had vitamin D deficiency in winter! Temporal relationship between vitamin D status and parathyroid hormone in the United States. Kroll MH, Bi C, Garber CC, Kaufman HW, ...Holick MF. *PLoS One*. 2015;10(3):e0118108.

Winter 25(OH)D concentrations are about 70% of summer concentrations due to 25(OH)D stored in muscle cells released back into the serum. (Rebecca S Mason, Mark S Rybchyn, 2019, 2020)

Seasonal Variations of U.S. Deaths, 1979–2004

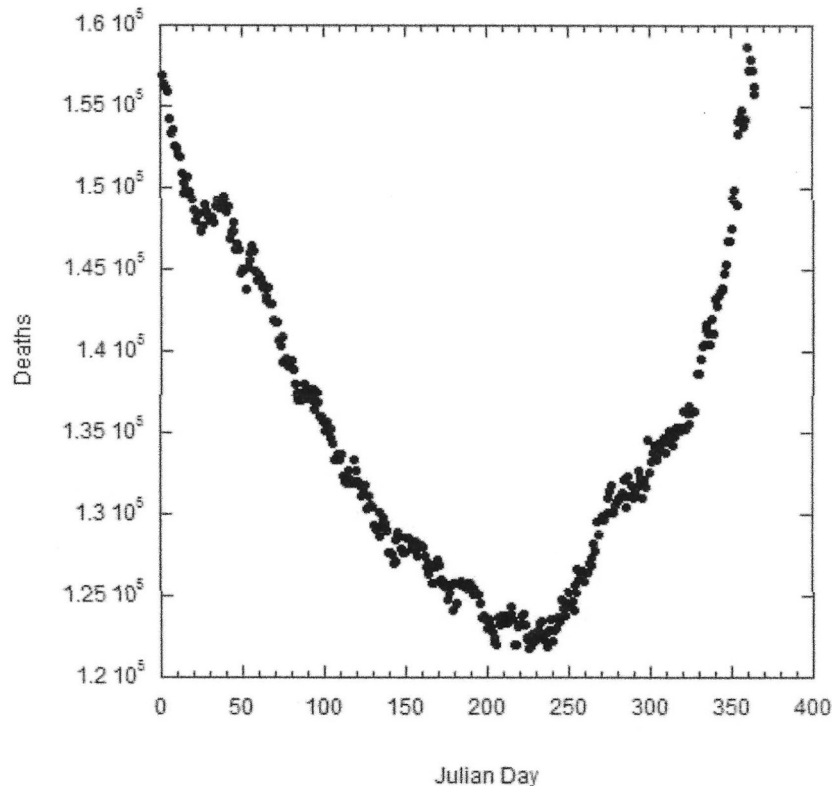


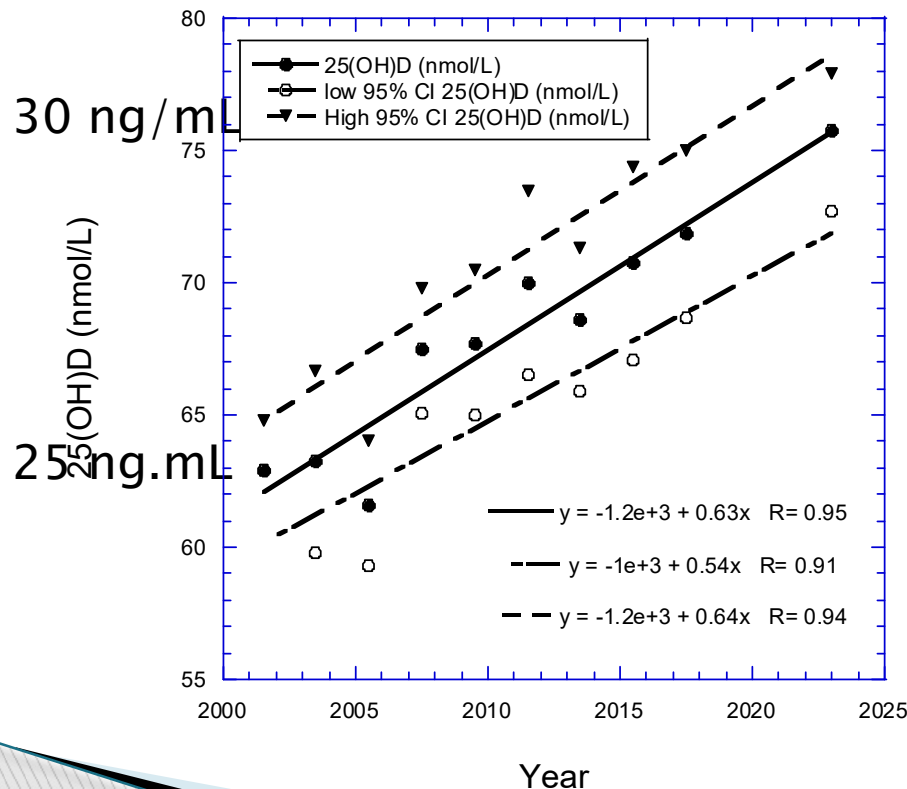
Figure 1. Deaths per day of the year, according to all official U.S. death certificates for 1979–2004 from Phillips et al., 2010.

Year end deaths were 30% higher than late summer deaths.

Seasonal variations are mostly due to cardiovascular disease and infectious diseases.

Seasonal variations of U.S. mortality rates: Roles of solar ultraviolet-B doses, vitamin D, gene expression, and infections. Grant WB, Bhattoa HP, Boucher BJ. *J Steroid Biochem Mol Biol.* 2017;173:5–12.

Population-Level Changes in 25(OH)D from NHANES in the US



Likely due to reports from observational studies reporting many diseases reduced at higher 25(OH)D concentrations.

Fazili Z, Zhang M, Mineva EM, Jarrett JM.
Curr Dev Nutr.
2026 Apr 8;10(5):107687

Types of Studies for Vitamin D's Effects

- ▶ Observational studies
 - Ecological studies
 - Prospective cohort studies
 - (Cross-sectional studies)*
 - (Case-control studies)*
- ▶ Randomized controlled trials
- ▶ (Mendelian randomization studies)*
- ▶ (Animal studies)*
- ▶ Mechanistic studies
- ▶ * Not discussed in this presentation

Ecological Studies

- ▶ Ecological studies consider populations in geographical regions as entities.
 - ▶ Disease outcomes are compared statistically with different geographical regions or different times.
 - ▶ Indices for solar UVB doses are used along with indices for important confounding factors.
 - ▶ Such studies have provided early findings regarding vitamin D and disease rates.
- 

Prospective Cohort Studies

- ▶ Participants are enrolled and baseline data are obtained.
- ▶ Participants are followed for years.
- ▶ Health outcomes are generally related to baseline data such as 25(OH)D concentrations.
- ▶ Such studies are subject to “regression dilution”.
- ▶ Underestimation of risk associations due to **regression dilution** in long-term follow-up of prospective studies. Clarke R, Shipley M, Lewington S, Youngman L, Collins R, Marmot M, Peto R. *Am J Epidemiol.* 1999 ;150(4):341–53

Regression Dilution

Data are from the Framingham Study (Framingham, Massachusetts) and Whitehall Study (London, England).

They show that values of variables for participants change over time, shown for 26 years.

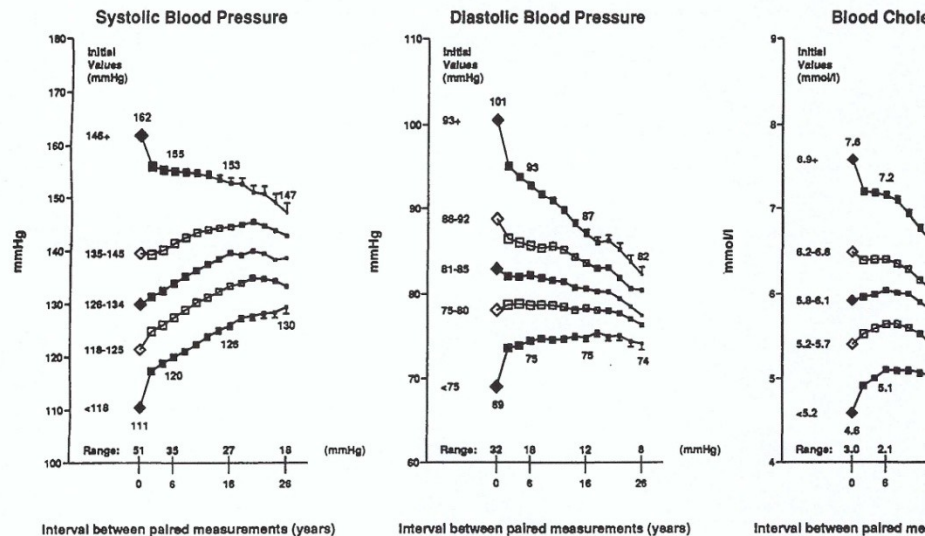
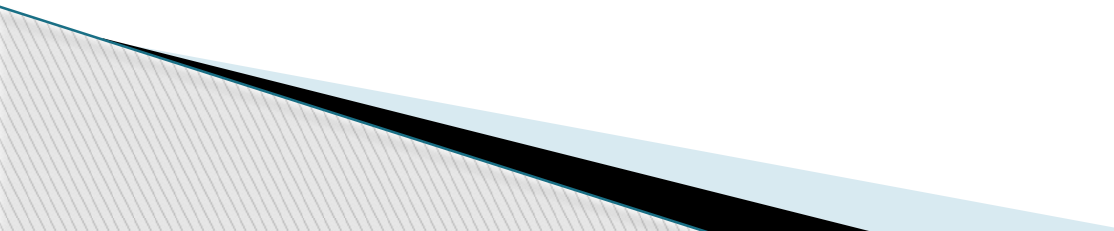


FIGURE 1. Serial shrinkage of the ranges for blood pressure and cholesterol values in groups defined by the first of a pair of measurements in the Framingham Study and at subsequent follow-up are plotted for persons subdivided into five similar-sized groups according to the value of just the first of each pair of measurements. The size of the square is proportional to the quantity of statistical information available, and the 95% confidence intervals for the top and bottom groups are represented by the top and bottom squares, and the absolute differences (ranges) between them, are given at year 0 (i.e., the initial measurement of the pairs) and at approximate midpoints of the first, second, and third decades, respectively, after the initial measurement.

Underestimation of risk associations due to regression dilution in long-term follow-up of prospective studies. Clarke R, ...Peto R. *Am J Epidemiol.* 1999;150(4):341-53.

Randomized Controlled Trials

- ▶ In RCTs, participants are randomly assigned to treatment or control groups.
 - ▶ The treatment group is given the agent and the control group is generally given a placebo.
 - ▶ Results are generally analyzed according to intention to treat.
 - ▶ While this approach works well for pharmaceutical drugs, it often does not for vitamin D.
- 

Problems with Vitamin D RCTs

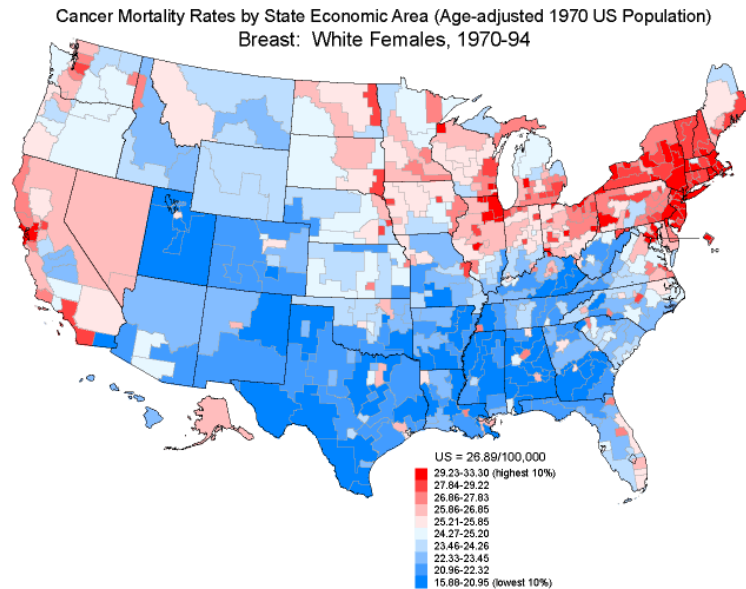
Differences between Drugs and Nutrients

- ▶ The main problems with most vitamin D RCTs are:
 - ▶ 1 – failure to include mostly participants with low 25(OH)D concentrations;
 - ▶ 2 – giving the treatment group low vitamin D doses;
 - ▶ 3 – not analyzing the results according to achieved 25(OH)D concentration.
- ▶ Guidelines for optimizing design and analysis of clinical studies of nutrient effects. Heaney RP. *Nutr Rev.* 2014;72(1):48–54.

Vitamin D and Cancer

- ▶ The role of vitamin D in reducing risk of cancer was proposed in 1980 by the Garland brothers based on an ecological study in the US.
- ▶ Ecological studies in the early 2000s increased the number of cancer types linked to low solar UVB/vitamin D to 13.
- ▶ Other types of studies have increased the evidence.
- ▶ Garland CF, Garland FC. Do sunlight and vitamin D reduce the likelihood of colon cancer? *Int J Epidemiol.* 1980;9(3):227–31.

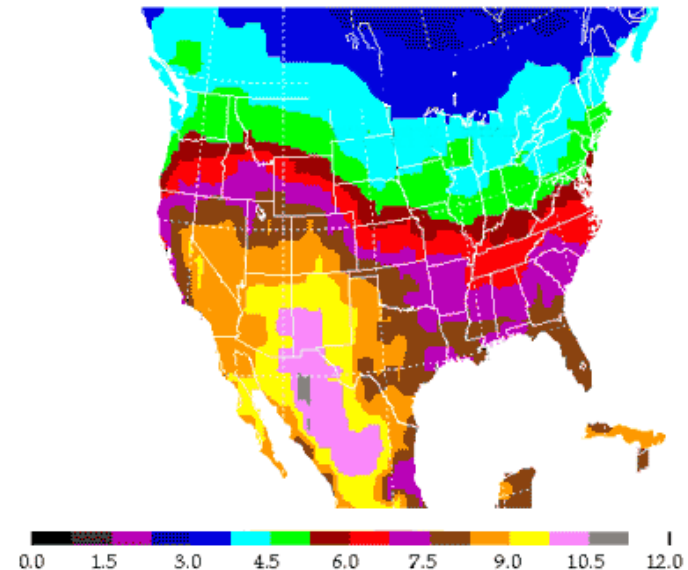
Breast Cancer Mortality Rates, 1970–1994 and Solar UVB Surface Doses, July 1992



A time when obesity rates were low, people spent more time in the sun, and cancer treatment was limited.

Atlas of cancer mortality in the United States, 1950–94, Devesa SS, NIH, National Cancer Institute, 1999

DNA SPECTRAL EXPOSURE (kJ/m^2) FOR JULY 1992

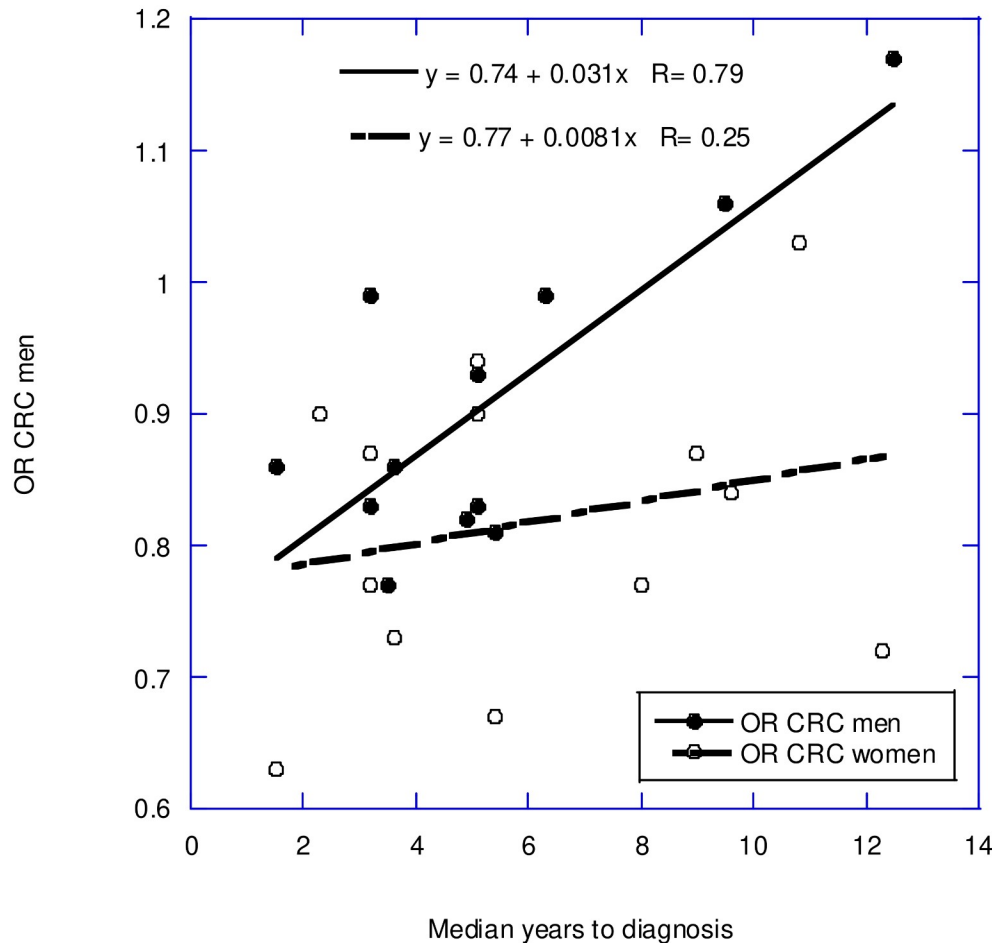


Solar UVB doses are higher in the west due to higher surface elevation and thinner stratospheric ozone layer due to westerly winds crossing the Rocky Mountains. Data obtained from NASA's Total Ozone Mapping Spectrometer (TOMS)

Additional Ecological Studies

- ▶ Adding these confounding factors to the analysis did not change the effect of solar UVB from 1950–1994: alcohol consumption, Hispanic heritage, poverty, smoking, urban–rural residence (Grant, Garland, 2006).
- ▶ However, an ecological study in the U.S. for 2016–2020 found obesity more important than solar UVB for incidence of breast, colon, and renal cancers (Grant, 2024).
- ▶ Grant WB, Garland CF. *Anticancer Res.* 2006;26(4A):2687–99.
- ▶ Grant WB. *Nutrients.* 2024;16(10):1450.

High vs. Low 25(OH)D Concentration Reduces Risk of Colorectal Cancer by 25%

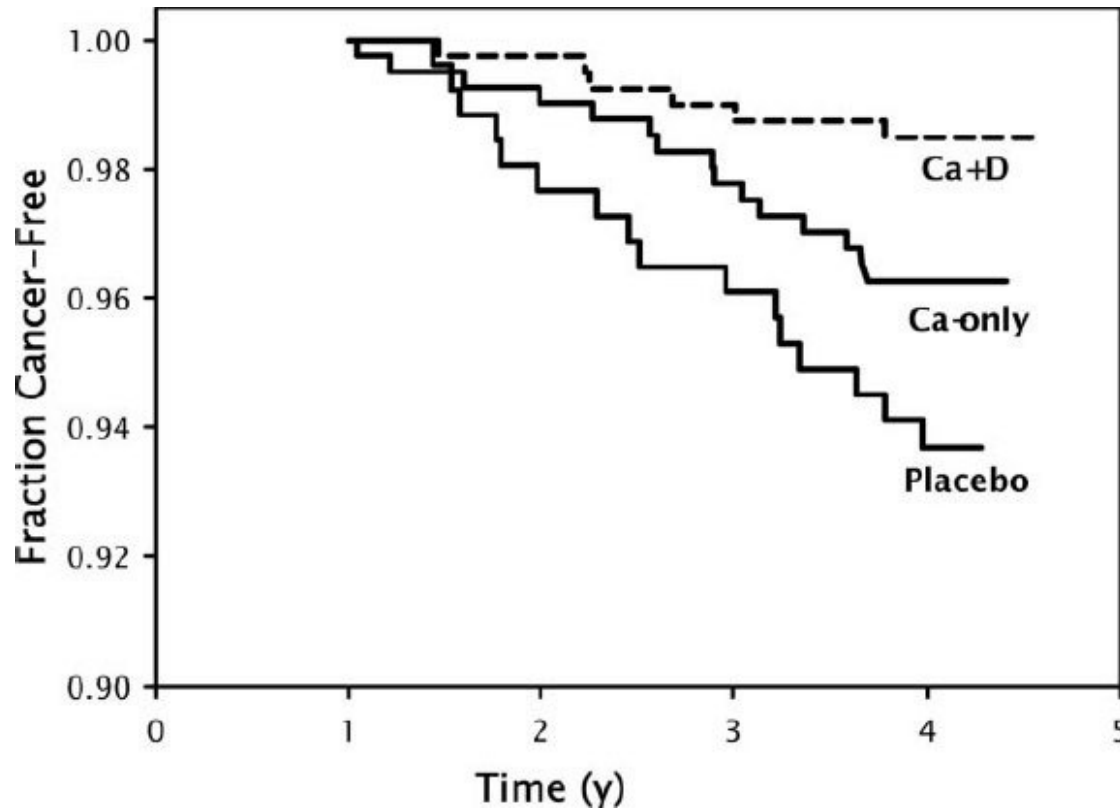


Median 25(OH)D in the control groups:
22 (95% CI, 16–34) ng/mL.

This plot shows the effect of “regression dilution” involving many studies.

Vitamin D and Cancer: An Historical Overview of the Epidemiology and Mechanisms. Muñoz A, Grant WB. *Nutrients*. 2022;14(7):1448.

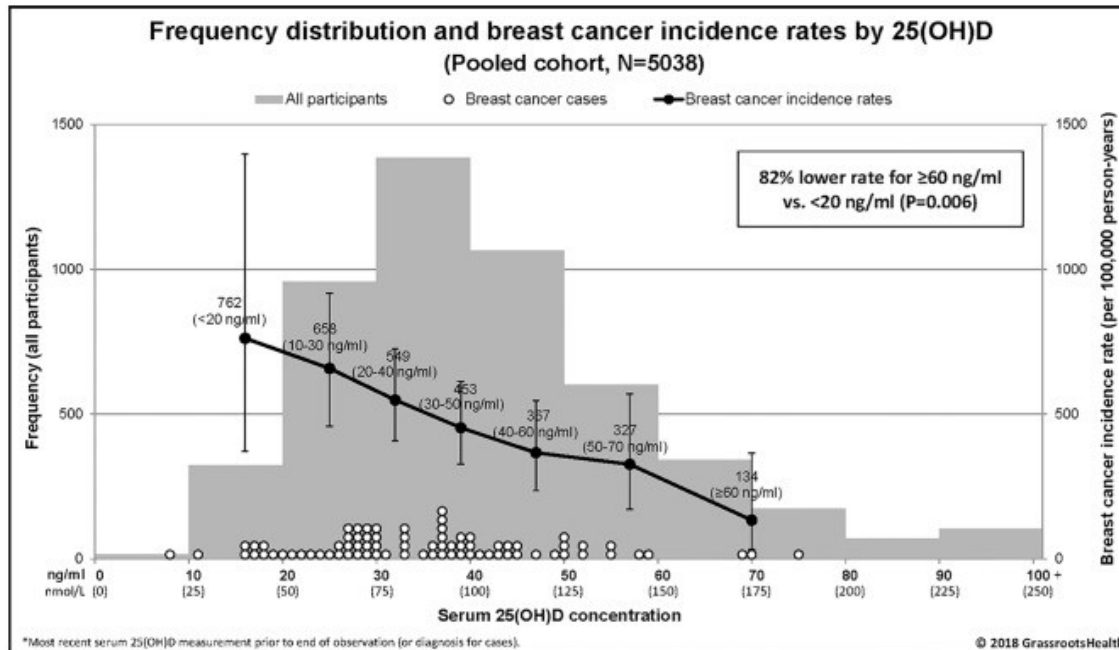
Vitamin D and calcium supplementation reduces cancer risk: results of a randomized trial



This was a 4-year, population-based, RCT. The subjects were 1179 community-dwelling of healthy postmenopausal women aged >55 y, mean baseline 25(OH)D = 33 ng/mL, mean BMI = 30 kg/m² in Nebraska centered at latitude 41.4 degrees N. Subjects were randomly assigned to receive 1400–1500 mg supplemental calcium/day alone (Ca-only), supplemental calcium plus 1100 IU vitamin D3/d (Ca + D), or placebo.

Am J Clin Nutr. 2007;85(6):1586–91.

Breast cancer risk markedly lower with serum 25-hydroxyvitamin D concentrations ≥ 60 vs <20 ng/ml (150 vs 50 nmol/L): Pooled analysis of two randomized trials and a prospective cohort



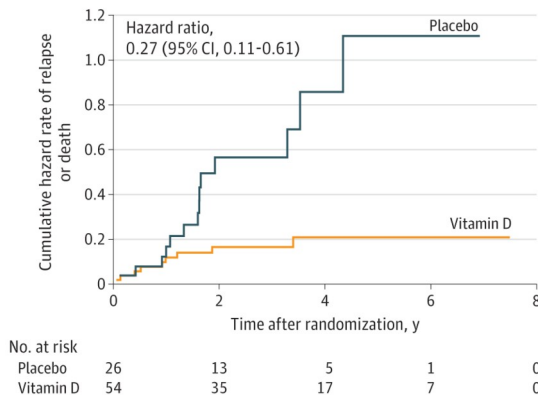
McDonnell et al.
PLoS One.
2018;13(6):e0199265.

Vitamin D Supplements and Prevention of Cancer and Cardiovascular Disease

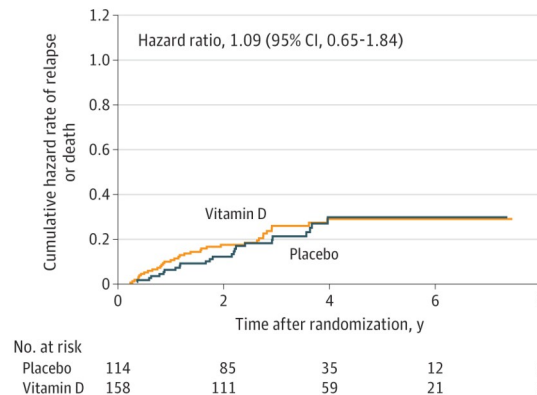
- ▶ 25,000 M+F participants
- ▶ Mean age, 67 years; mean BMI 28 kg/m²
- ▶ 2000 IU/day vitamin D₃ for 5 years
- ▶ All participants permitted to take 600–800 IU/day vitamin D₃
- ▶ Only those with BMI <25 kg/m² had a reduced incidence of all cancer (25%)
- ▶ Why did this RCT not find results similar to those by Lappe et al.?
- ▶ Manson et al. *N Engl J Med.* 2019;380(1):33–44.

Effect of Vitamin D Supplements on Relapse or Death in a p53–Immunoreactive Subgroup With Digestive Tract Cancer

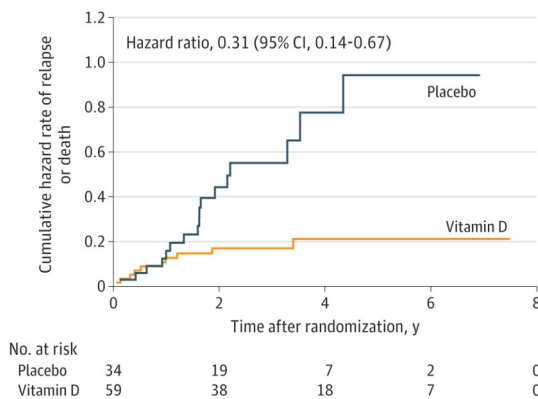
A p53-Ab (+) and p53-IHC (3+) subgroup



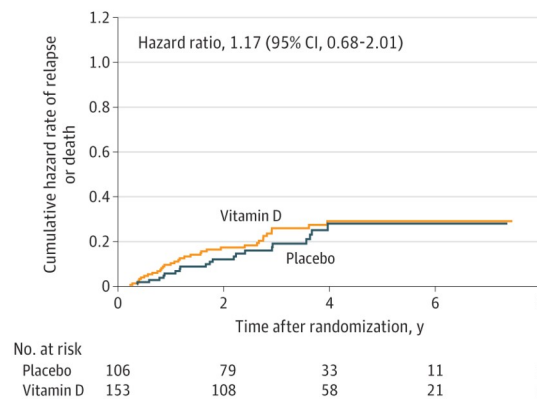
B p53-Ab (-) or p53-IHC (2+ or 1+ or 0) subgroup



C p53-Ab (+) and p53-IHC-positive subgroup



D p53-Ab (-) or p53-IHC-negative subgroup



Kanno K, Akutsu T, Ohdaira H, Suzuki Y, Urashima M. JAMA Netw Open. 2023;6(8):e2328886.

Vitamin D and Cancer – Unresolved Issue – Effect of Obesity on Role of Vitamin D

- ▶ We critically summarize emerging biological mechanisms linking obesity to cancer encompassing insulin resistance and abnormalities of the IGF-I system and signaling; sex hormones biosynthesis and pathway; subclinical chronic low-grade inflammation and oxidative stress; alterations in adipokine pathophysiology; factors deriving from ectopic fat deposition; microenvironment and cellular perturbations including vascular perturbations, epithelial-mesenchymal transition, endoplasmic reticulum stress and migrating adipose progenitor cells; disruption of circadian rhythms; dietary nutrients; factors with potential significance such as the altered intestinal microbiome; and mechanic factors in obesity and cancer.
- ▶ Obesity and cancer risk: Emerging biological mechanisms and perspectives. Avgerinos KI, et al. *Metabolism*. 2019;92:121–135.

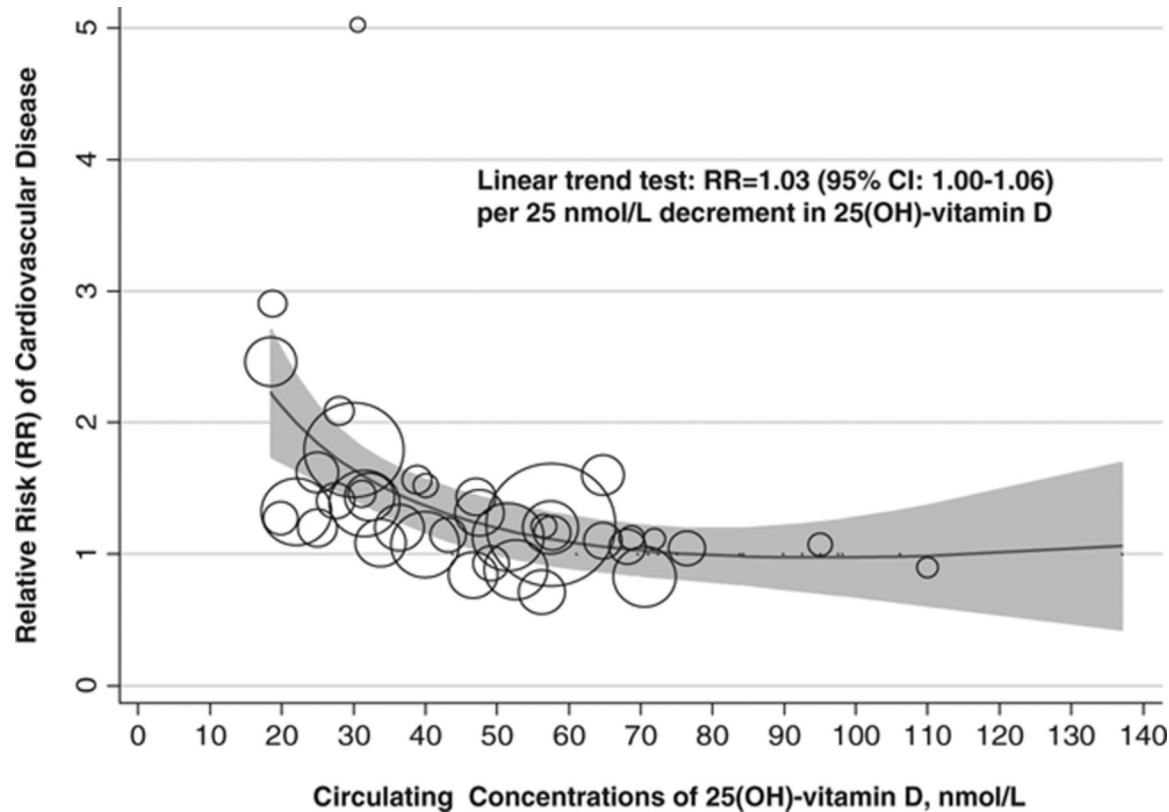
Vitamin D and Cancer – Present Understanding

- ▶ Ecological studies of cancer with respect to indices of solar radiation found a reduced risk of incidence and mortality for approximately 23 types of cancer. Meta-analyses of observational studies reported the inverse correlations of serum 25(OH)D with the incidence of 12 types of cancer.
- ▶ Studies show the inhibition of tumor cell proliferation, dedifferentiation, and invasion together with the sensitization to proapoptotic agents. Vitamin D reduces angiogenesis around tumors. Moreover, 1,25-(OH)₂D₃ modulates the biology of several types of stromal cells in a way that interferes with metastasis.
- ▶ Vitamin D and Cancer: An Historical Overview of the Epidemiology and Mechanisms. Muñoz A, Grant WB. *Nutrients*. 2022;14(7):1448.

Vitamin D and Cardiovascular Health: A Narrative Review of Risk Reduction Evidence

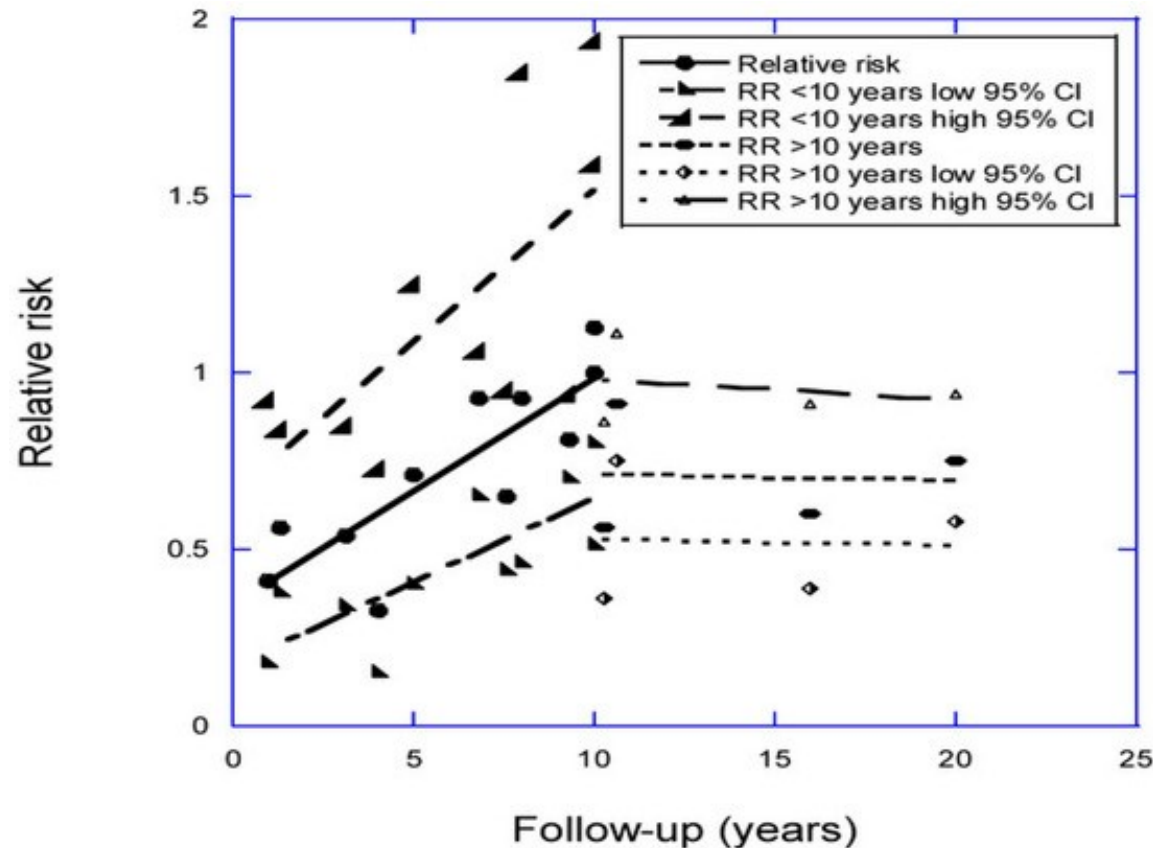
- ▶ Vitamin D supplementation studies have found modest reductions in several CVD risk factors. Observational studies of vitamin D supplementation have reported reduced CVD risks (e.g., ischemic heart disease, hypertension, and myocardial infarction). Temporal ecological studies further support this relationship, revealing that CVD incidence rates are lowest in summer and CVD mortality rates are significantly higher in late winter—when 25(OH)D concentrations are lowest—compared to late summer.
- ▶ A previously reported analysis using eight of Hill's criteria further strengthens the biological plausibility of vitamin D's role in CVD risk reduction. Its role in modulating inflammation and oxidative stress, improving endothelial function, and reducing several cardiometabolic risk factors supports its inclusion as part of a comprehensive, multi-modal approach to cardiovascular health.
- ▶ Therefore, vitamin D should be considered an integral component in the prevention and management of CVD. Preferably, it should be used in combination with other nutritional supplements, a heart-healthy diet, and prescription medications to reduce the risk of CVD incidence.
- ▶ Grant WB, Boucher BJ, Cheng RZ, Pludowski P, Wimalawansa SJ. *Nutrients*. 2025;17(13):2102.

CVD Incidence vs. Serum 25(OH)D



Wang L, et al. Circulating 25-hydroxy-vitamin D and risk of cardiovascular disease: a meta-analysis of prospective studies. *Circ Cardiovasc Qual Outcomes*. 2012;5(6):819-29.

How Follow-Up Period in Prospective Cohort Studies Affects Relationship Between Baseline Serum 25(OH)D Concentration and Risk of Stroke and Major Cardiovascular Events.



Grant, W.B.; Boucher, B.J. *Nutrients* 2024, 16, 3759.

Risk of stroke vs. follow-up period

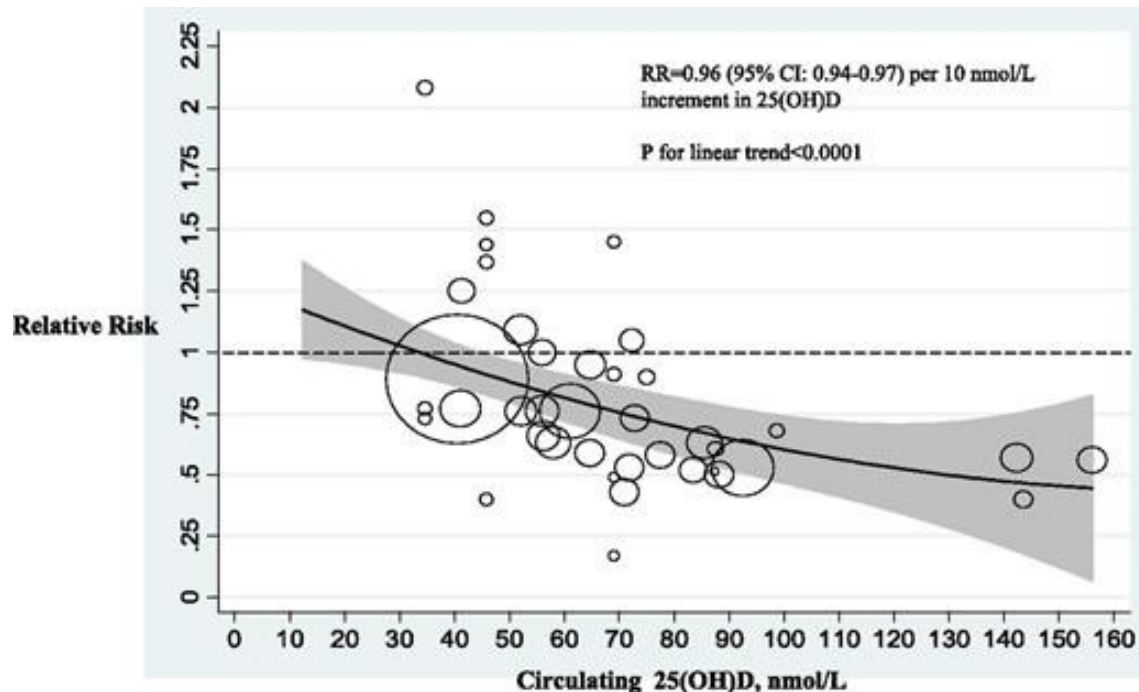
Vitamin D₃ and Ischemic Stroke: A Narrative Review

- ▶ Recently, vitamin D₃ has emerged as a potential treatment adjunct for ischemic stroke, as it interferes with the key prosurvival pathways and shows neuroprotective, anti-inflammatory, regenerative and anti-aging properties in both neuronal and vascular tissue. Moreover, the stimulatory effect of vitamin D₃ on brain-derived neurotrophic factor (BDNF) signaling and neuroplasticity may play a role not only in the recovery of neurological functions, but also in ameliorating post-stroke depression and anxiety.
- ▶ Lasoń et al. *Antioxidants* **2022**, 11(11):2120

The Association between Serum 25(OH)D Status and Blood Pressure in Participants of a Community-Based Program Taking Vitamin D Supplements

- ▶ We assessed 8155 participants in a community-based program to investigate the association between serum 25(OH)D status and blood pressure (BP) and the influence of vitamin D supplementation on hypertension.
- ▶ Participants were provided vitamin D₃ supplements to reach a target serum 25(OH)D >100 nmol/L.
- ▶ At baseline, 592 participants (7.3%) were hypertensive; of those, 71% were no longer hypertensive at follow-up (12 ± 3 months later).
- ▶ Reduced mean systolic (−18 vs. −14 mmHg) and diastolic (−12 vs. −12 mmHg) BP, pulse pressure (−5 vs. −1 mmHg) and mean arterial pressure (−14 vs. −13 mmHg) were not significantly different between hypertensive participants who did and did not take BP-lowering medication.
- ▶ Mirhosseini N, Vatanparast H, Kimball SM. *Nutrients*. 2017;9(11):1244.

Blood 25(OH)D Levels and Incident Type 2 Diabetes: A meta-analysis of prospective studies



Relation between the risk of type 2 diabetes and baseline levels of 25(OH)D in 18 independent prospective studies included in the meta-analysis.

Song Y, Wang L, Pittas AG, Del Gobbo LC, Zhang C, Manson JE, Hu FB. Diabetes Care. 2013;36(5):1422-8

Vitamin D Supplementation for People with Prediabetes – 2019

- ▶ A total of 2423 participants underwent randomization (1211 to the vitamin D group and 1212 to the placebo group). By month 24, the mean serum 25(OH)D level in the vitamin D group was 54.3 ng/mL (from 27.7 ng/mL at baseline), as compared with 28.8 ng/mL in the placebo group (from 28.2 ng/mL at baseline).
- ▶ After a median follow-up of 2.5 years, the primary outcome of diabetes occurred in 293 participants in the vitamin D group and 323 in the placebo group (9.39 and 10.66 events per 100 person-years, respectively). **The HR for vitamin D as compared with placebo was 0.88 (95% confidence interval, 0.75 to 1.04; $p = 0.12$).**
- ▶
- ▶ Vitamin D Supplementation and Prevention of Type 2 Diabetes Pittas AG, Dawson-Hughes B, ...; D2d Research Group. *N Engl J Med*. 2019;381(6):520–530.

Vitamin D Supplementation for People with Prediabetes – 2020

- ▶ There was an interaction of trial assignment with intratrial 25(OH)D level in predicting diabetes risk (interaction $p = 0.02$). **The HR for diabetes for an increase of 25 nmol/L in intratrial 25(OH)D level was 0.75 (95% CI 0.68–0.82) among those assigned to vitamin D and 0.90 (0.80–1.02) among those assigned to placebo. The HRs for diabetes among participants treated with vitamin D who maintained intratrial 25(OH)D levels of 100–124 and ≥ 125 nmol/L were 0.48 (0.29–0.80) and 0.29 (0.17–0.50), respectively, compared with those who maintained a level of 50–74 nmol/L.**
- ▶ Dawson–Hughes B, ... Pittas AG; D2d Research Group. **Intratrial Exposure to Vitamin D and New-Onset Diabetes Among Adults With Prediabetes: A Secondary Analysis From the Vitamin D and Type 2 Diabetes (D2d) Study.** *Diabetes Care*. 2020;43(12):2916–2922.

Effect of High BMI/Visceral Obesity on Vitamin D for Diabetes

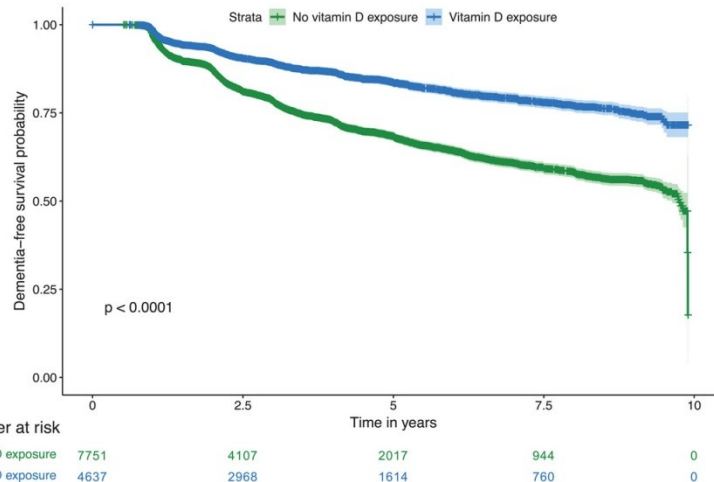
- ▶ There is evidence that obesity represses vitamin D bioactivation by CYP2R1, leading to reduced production of 25(OH)D, and that weight loss upregulates CYP2R1 expression. When we examined data from the 2 trials that administered cholecalciferol, which requires activation first by CYP2R1 and subsequently by CYP27B1, there was an interaction by BMI such that participants with baseline BMI below the median (31.3 kg/m²) had a 26% lower risk for diabetes with cholecalciferol versus placebo, whereas among participants with a BMI at or above the median, there did not seem to be an effect.
- ▶ Pittas et al., *Ann Intern Med.* 2023;176:355–363

Vitamin D Reduces Risk of Insulin Resistance

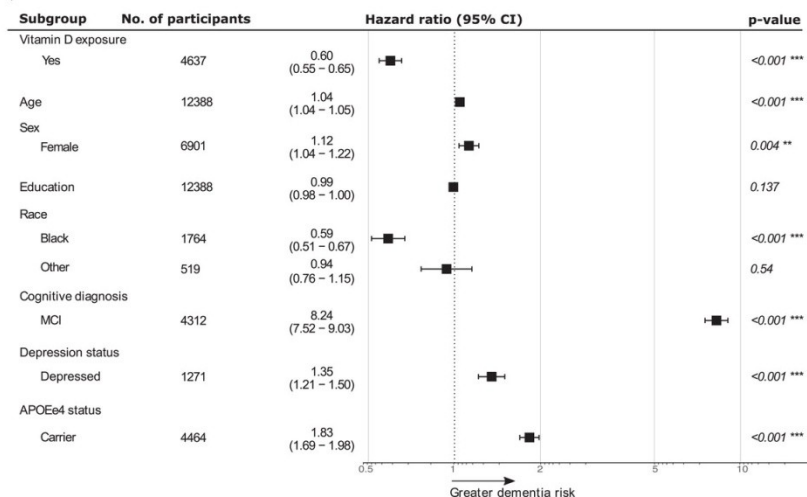
- ▶ Vitamin D deficiency can compromise the capacity of β cells to convert pro-insulin into insulin (Schmitt, 2018).
- ▶ Supplementation with 5000 IU daily of vitamin D for 6 months increased insulin sensitivity and pancreatic β -cell activity (Lemieux, 2019)
- ▶ Vitamin D directly binds to vitamin D receptors (VDR) within β -cells, promoting insulin gene transcription via genomic pathways. It also exerts non-genomic effects, such as regulating intracellular calcium levels, which are essential for insulin exocytosis.
- ▶ In peripheral tissues, vitamin D enhances insulin sensitivity by stimulating insulin receptor (IR) gene expression, thereby strengthening insulin signaling and promoting glucose uptake in muscle, liver, and adipose tissue
- ▶ Chronic low-grade inflammation is a central driver of insulin resistance and metabolic syndrome, and vitamin D exerts notable anti-inflammatory effects (Al Argan, 2026)
- ▶ Al Argan et al. *Obesity Medicine*, 2026, 59, 100680
- ▶ Lemieux et al. *Eur. J. Endocrinol.* 2019, 181, 287-299.
- ▶ Schmitt et al. *Maturitas* 2018, 107, 97-102.

Vitamin D supplementation and incident dementia: Effects of sex, *APOE*, and baseline cognitive status

(A)



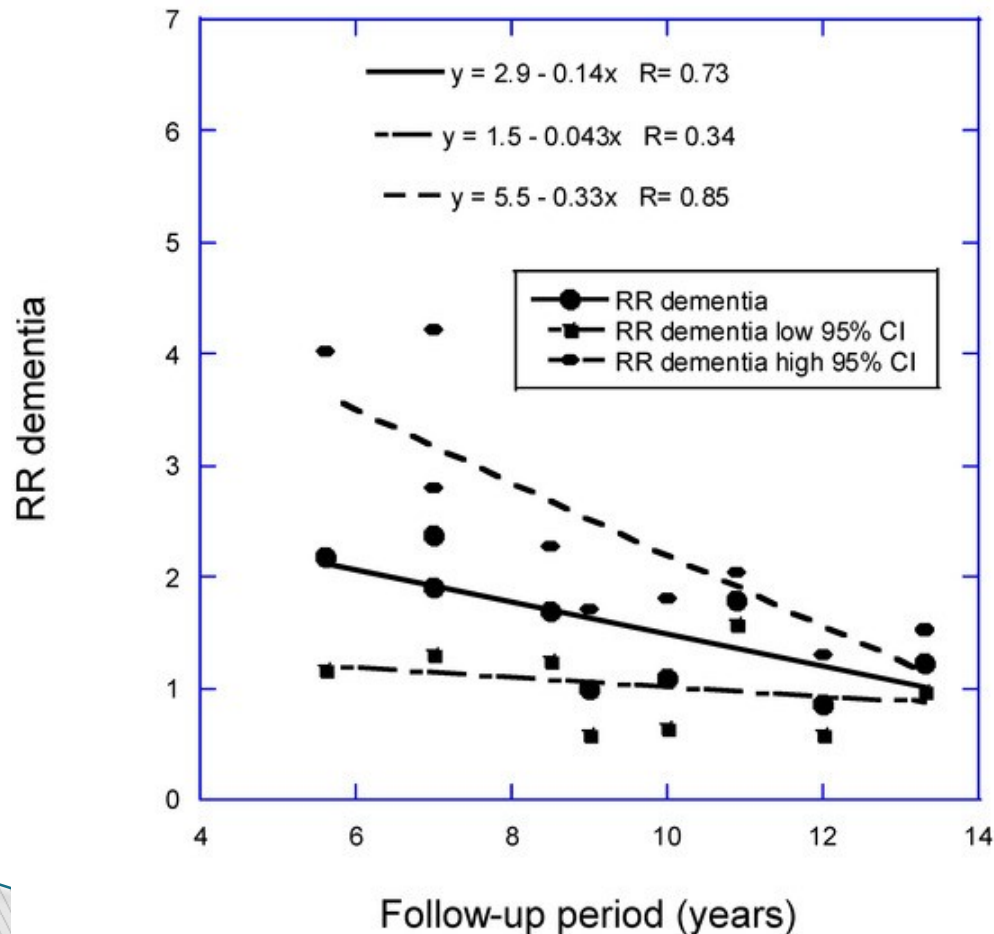
(B)



In a prospective cohort study, we assessed effects of Vitamin D on dementia incidence in 12,388 participants from the USA National Alzheimer's Coordinating Center dataset. Vitamin D exposure was associated with 40% lower dementia incidence versus no exposure. Vitamin D effects were significantly greater in females versus males and in normal cognition versus mild cognitive impairment. Vitamin D effects were significantly greater in apolipoprotein E ε4 non-carriers versus carriers. Vitamin D has potential for dementia prevention, especially in the high-risk strata.

Ghahremani et al. *Alzheimers Dement (Amst)*. 2023;15(1):e12404.

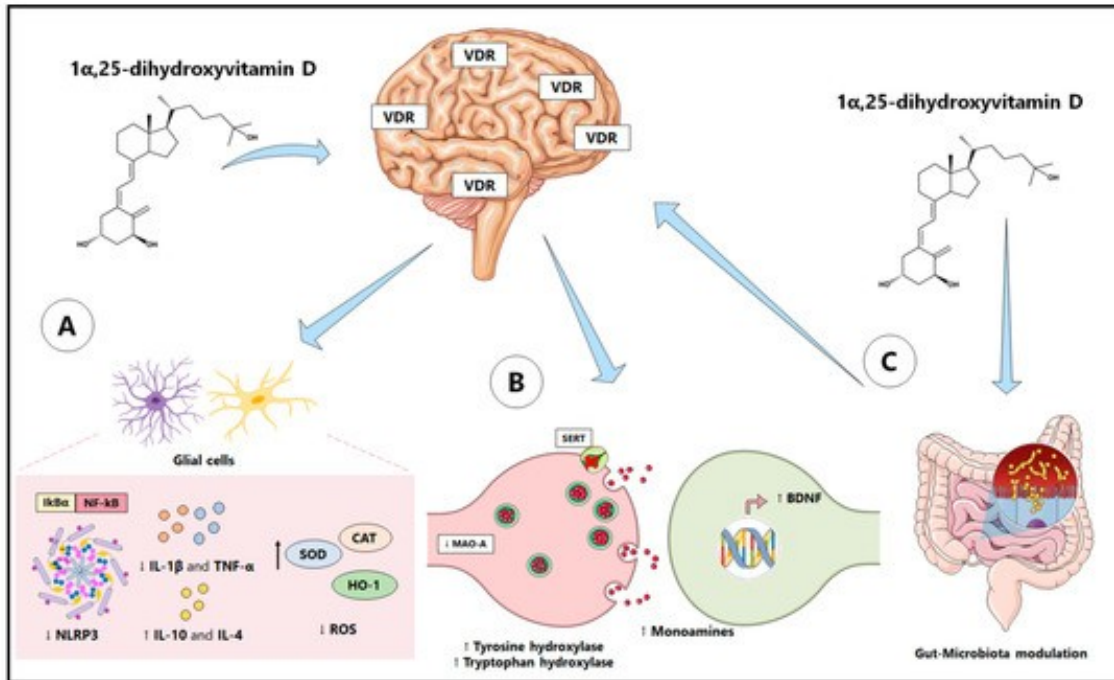
Follow-Up Period Affects the Association between Serum 25(OH)D Concentration and Incidence of Dementia, Alzheimer's Disease, and Cognitive Impairment



A plot of dementia risk vs. follow-up period for low vs. high 25(OH)D concentrations.

Grant WB. *Nutrients*. 2024;16(18):3211.

Molecular Basis Underlying the Therapeutic Potential of Vitamin D for the Treatment of Depression and Anxiety



Kouba et al.
Int. J. Mol. Sci.
2022;23:7077

Antioxidant, anti-inflammatory, and neuromodulatory properties of vitamin D. Neurons and glial cells are able to express VDR in regions such as the prefrontal cortex and hippocampus. In these regions, the positive modulation of antioxidant enzymes, such as HO-1, CAT, and SOD, by calcitriol contributes to redox homeostasis and, consequently, to the attenuation of the neuroinflammatory process. Calcitriol is also able to increase the expression of IkBα, thus, inhibiting the nuclear translocation of NF-κB.

Prevagen for Brain Health



AI Overview

Prevagen contains two active ingredients: apoeaquorin (a protein originally found in jellyfish) and Vitamin D3.

Active Ingredients

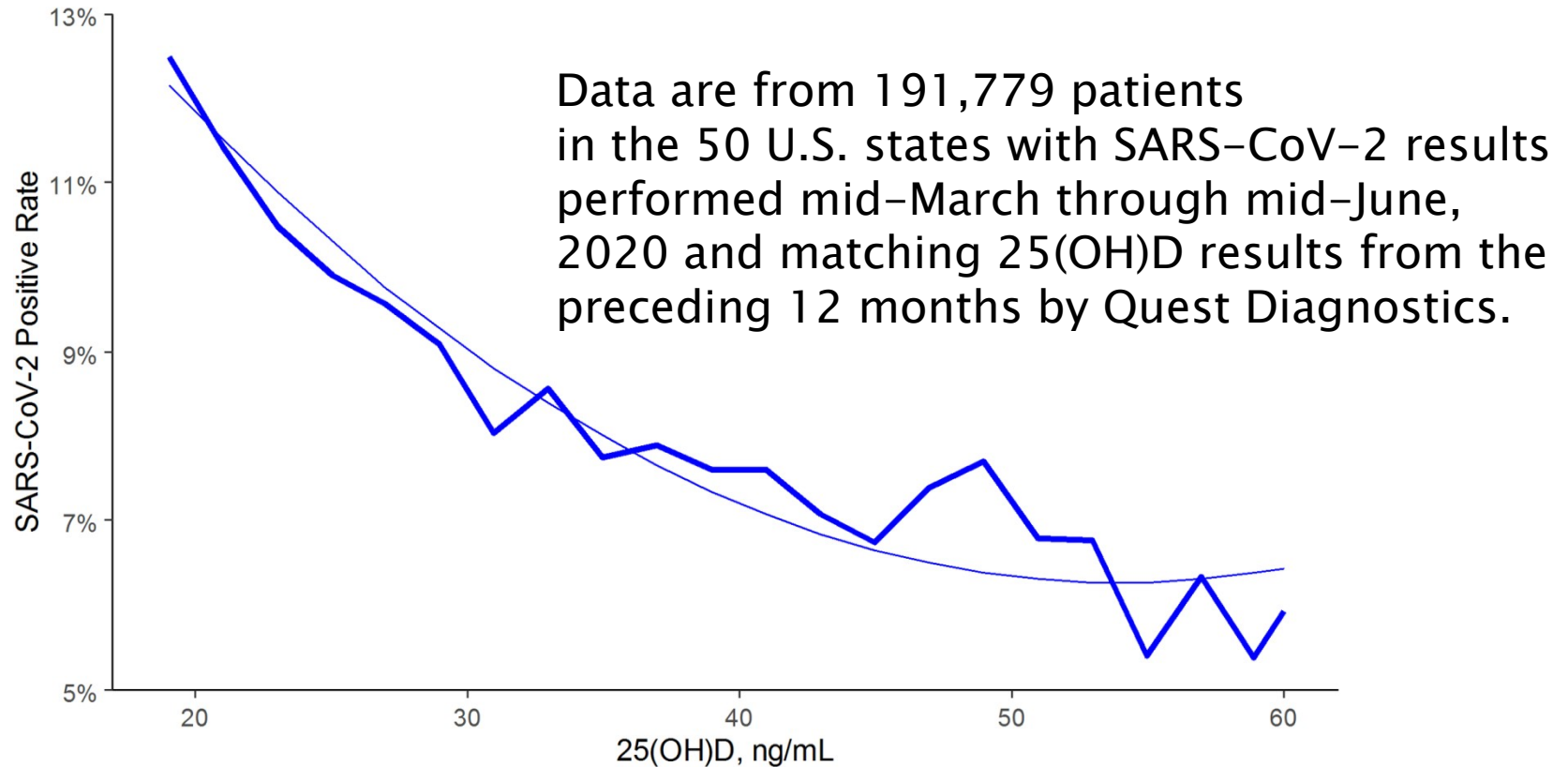
Apoaequorin: A calcium-binding protein ranging from 10 mg to 40 mg per serving. It is manufactured via fermentation rather than harvested directly from jellyfish.

Vitamin D3: 50 mcg (2,000 IU) included in each serving.

Cost/supplement: \$1.33 US

2024 Estimated Revenue: for 2024 was \$206 million.

SARS-CoV-2 positivity rates associated with circulating 25(OH)D levels

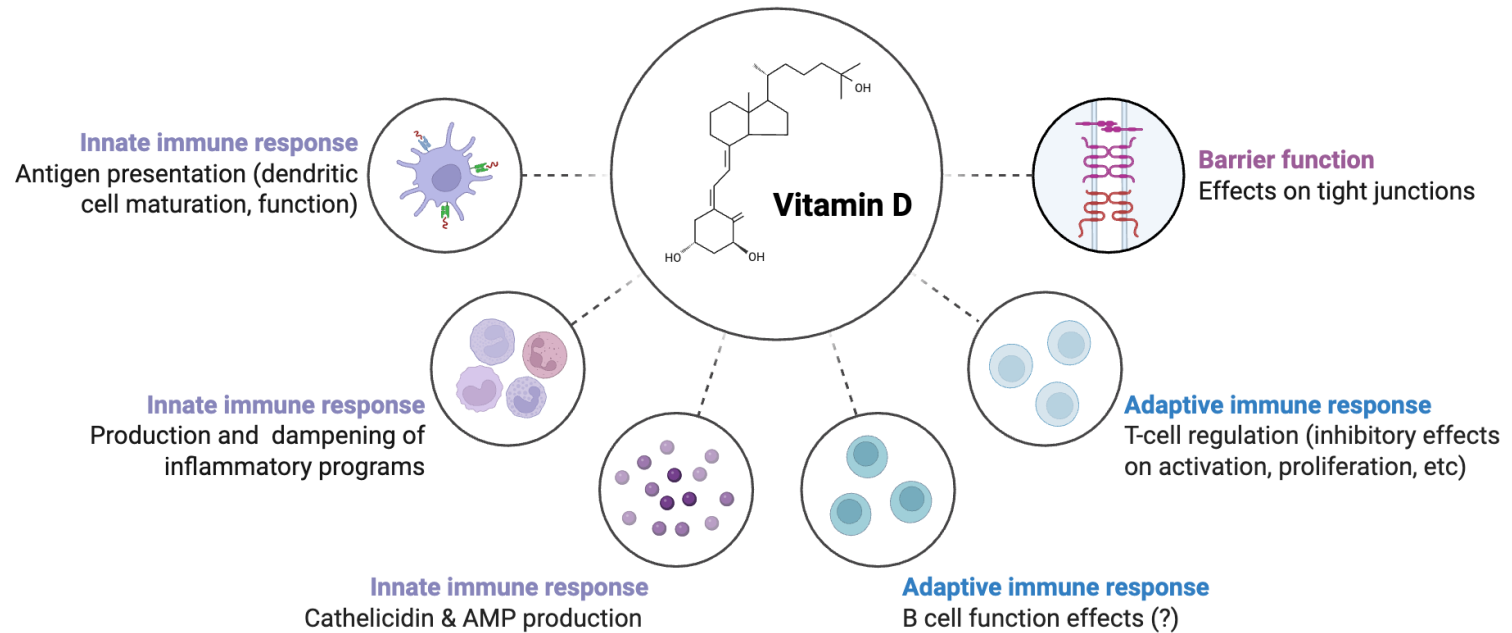


Kaufman, Niles, Kroll, Bi, Holick, *PLoS One*. 2020;15(9):e0239252.

Calcifediol [25(OH)D] Treatment and COVID-19-Related Outcomes

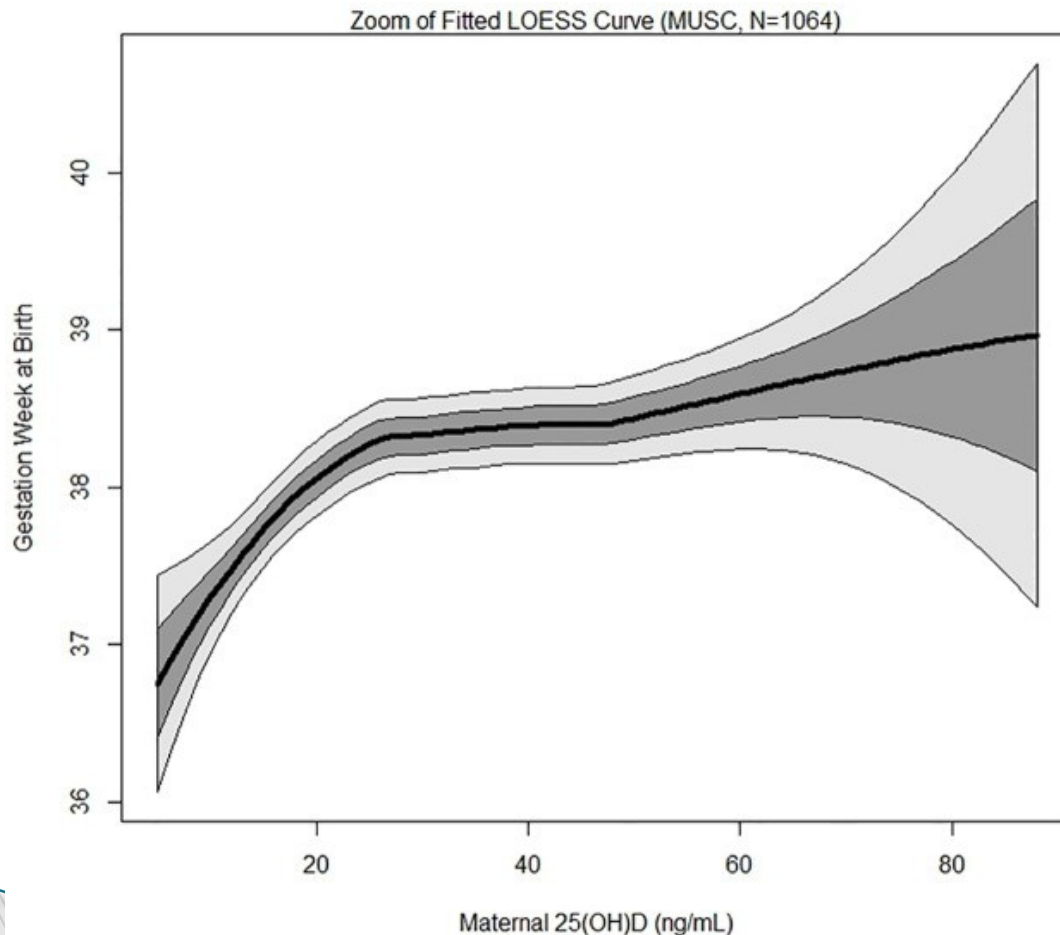
- ▶ This observational cohort study was conducted from March to May 2020, among patients admitted to COVID-19 wards of Hospital del Mar, Barcelona, Spain.
- ▶ Out of 447 patients treated with calcifediol at admission, 20 (4.5%) required the ICU, compared to 82 (21%) out of 391 nontreated ($P < .001$). Logistic regression of calcifediol treatment on ICU admission, adjusted by age, sex, linearized 25(OH)D levels at baseline, and comorbidities showed that treated patients had a reduced risk of requiring the ICU (odds ratio [OR] 0.13; 95% CI 0.07–0.23). In the intention-to-treat analysis, 21 (4.7%) out of 447 patients treated with calcifediol at admission died compared to 62 patients (15.9%) out of 391 nontreated ($P = .001$). Adjusted results showed a reduced mortality risk with an OR of 0.21 (95% CI, 0.10–0.43).
- ▶ Nogues et al. *J Clin Endocrinol Metab.* 2021;106(10):e4017–e4027.

Effects of Vitamin D on the Immune System



Created by Scott Tillman Weiss, PhD BioRender Team

Maternal 25(OH)D concentrations ≥ 40 ng/mL associated with 60% lower preterm birth risk among general obstetrical patients at an urban medical center



Medical record data were obtained for pregnant patients aged 18–45 years between September 2015 and December 2016 at the Medical University of South Carolina. During this time, a protocol that included 25(OH)D testing at first prenatal visit with recommended follow-up testing was initiated. Free vitamin D supplements were offered and the treatment goal was ≥ 40 ng/mL. McDonnell et al. *PLoS One*. 2017;12(7):e0180483.

Effectiveness of Prenatal Vitamin D Deficiency Screening and Treatment Program: A Stratified Randomized Field Trial

- ▶ **Design:** Two cities of Masjed-Soleyman and Shushtar from Khuzestan province, Iran, were selected as the screening and nonscreening arms, respectively. Within the screening arm, a randomized controlled trial was conducted on 800 pregnant women [mean 25(OH)D = 11 ng/mL]
- ▶ **Patients or participants:** Pregnant women aged 18 to 40 years.
- ▶ **Intervention:** Women with moderate [25(OH)D, 10 to 20 ng/mL] and severe [25(OH)D, <10 ng/mL] deficiency were randomly divided into four subgroups and received vitamin D3 (D3) until delivery.
- ▶ **Main outcome measure:** Maternal concentration of 25(OH)D at delivery and rate of pregnancy complications.
- ▶ **Results:** After supplementation, only 2% of the women in the nonscreening site met the sufficiency level (>20 ng/mL) vs 53% of the women in the screening site. Adverse pregnancy outcomes, including preeclampsia, gestational diabetes mellitus, and preterm delivery, were decreased by 60%, 50%, and 40%, respectively, in the screening site. A D3 injection in addition to monthly 50,000 IU maintenance therapy contributed the most to achievement of sufficient levels at delivery.
- ▶ Rostami M, Tehrani FR, Simbar M, Bidhendi Yarandi R, Minooee S, Hollis BW, Hosseinpanah F. *J Clin Endocrinol Metab.* 2018;103(8):2936–2948.

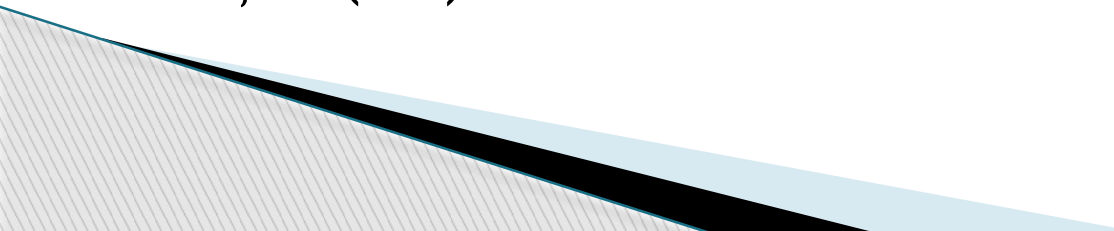
Vitamin D: Evidence–Based Health Benefits and Recommendations for Population Guidelines

- ▶ Based mostly on findings from observational studies, serum 25(OH)D concentrations above 30 ng/mL (75 nmol/L) can significantly reduce the burden of disease for eight of the top ten causes of death in the US (**these 8 accounted for 90% of all deaths in 2021 and 2022**):
- ▶ Heart disease, cancer, COVID–19, stroke, chronic lower respiratory diseases, Alzheimer’s disease and other dementias, diabetes mellitus, and kidney disease.
- ▶ Grant WB, Wimalawansa SJ, Pludowski P, Cheng RZ. *Nutrients*. 2025;17(2):277

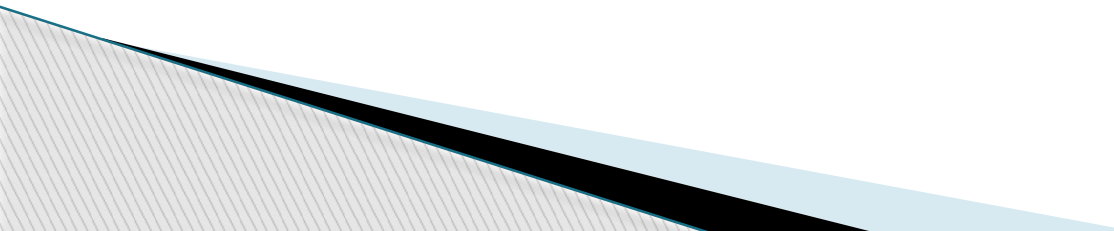
Vitamin D and Health: Establishing Causal Relationships Through Observational Evidence and Hill's Criteria in a Biological Framework

- ▶ This is an alternate scientific way to examine causality. The criteria appropriate for vitamin D:
 - Strength of association
 - Consistency of findings in different populations
 - Temporality
 - Biological gradient
 - Plausibility (e.g., mechanisms)
 - Coherence with the science of the day
 - Experiment (e.g., vitamin D supplementation)
 - Analogy
 - (consider confounding factors, remove bias).
 - Not all criteria need to be satisfied to claim causality, but the more that are, the better.
- ▶ Observational studies can be used to examine most of these criteria.

Vitamin D and Health: Establishing Causal Relationships Through Observational Evidence and Hill's Criteria in a Biological Framework

- ▶ This narrative review critically evaluates the evidence for cancer, CVD, blood pressure, COVID-19, type 1 and type 2 diabetes, periodontal disease, multiple sclerosis, and dementia. For these diseases, the authors concluded that the evidence satisfies Hill's criteria for causality and aligns with current understanding of vitamin D biology and nutrient–health relationships.
 - ▶ Grant WB, Wimalawansa SJ. *Nutrients*. 2026 Sep 4;18(17):2902.
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Suggestions for Additional Vitamin D Research

- ▶ More observational studies of the effects of vitamin D supplementation
 - ▶ Health effects of 100–175 nmol/L (40–70 ng/mL)
 - ▶ Importance of cofactors such as calcium, magnesium, and vitamin K₂
 - ▶ Effects of vitamin D supplementation as an adjuvant during treatments
 - ▶ Effects of obesity/visceral adiposity on effects of vitamin D
 - ▶ More evaluations of causality of vitamin D using Hill's criteria for causality
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Recommendations

- ▶ Adults should consider supplementing with 1000–5000 IU/day (25–125 mcg/day) vitamin D₃ to achieve 25(OH)D concentrations to at least 75–100 nmol/L (30–40 ng/mL) but preferably 100–150+ nmol/L (40–60+ ng/mL) .
- ▶ Serum 25(OH)D concentrations should be measured to help guide dose.
- ▶ Physicians should research the journal literature regarding the role of vitamin D for the health conditions they treat, recommend vitamin D supplementation to their patients, and monitor the effect of increasing serum 25(OH)D concentrations.

Where to Find Information Regarding Vitamin D and Health

- ▶ Google Scholar (Scholar.Google.com)
- ▶ Pubmed.gov
- ▶ GrassrootsHealth.net
- ▶ <https://vitamindwiki.com/>

