Vitamin D and Health for The Real Truth About Health
April 9, 2026

William B. Grant, PhD
Sunlight, Nutrition and Health Research Center
San Francisco, CA, USA

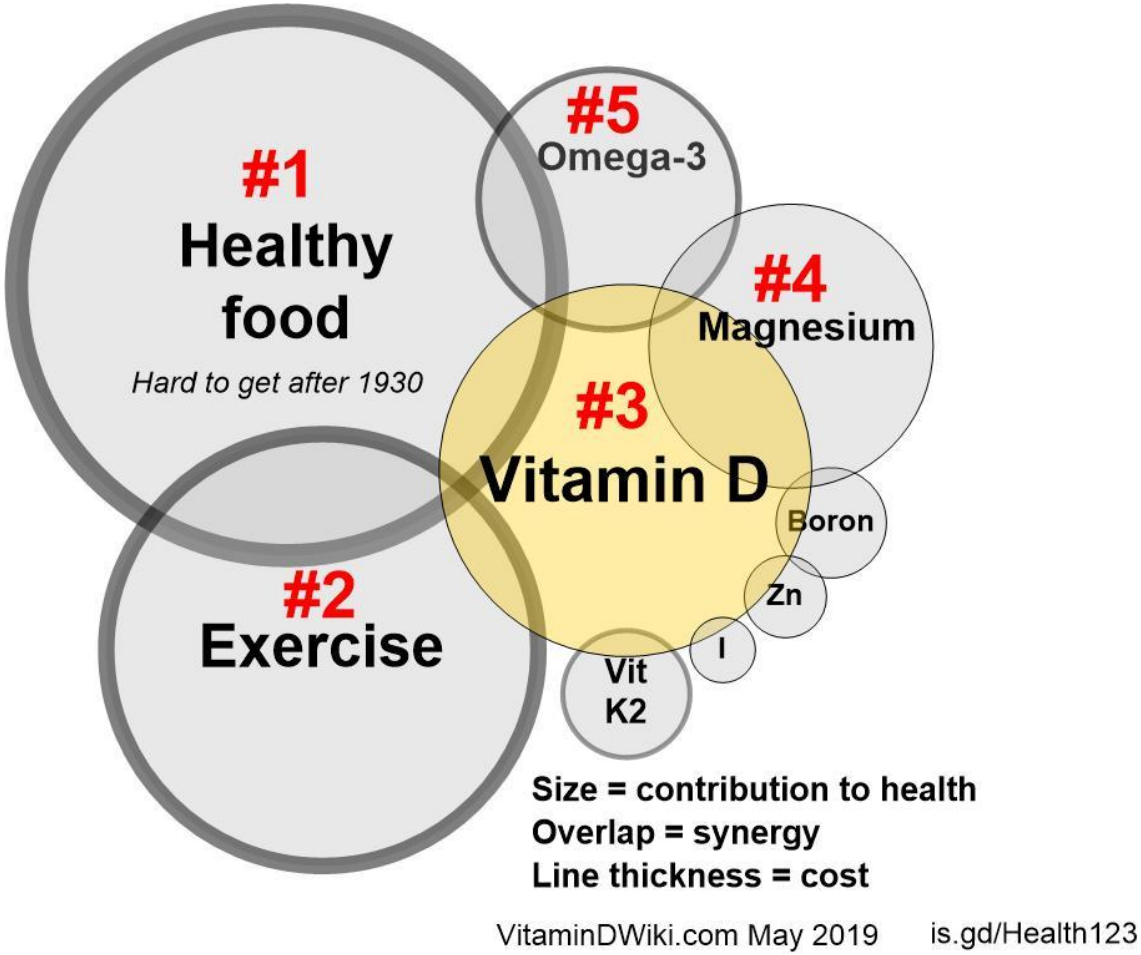
Background and Disclosures

- I have a PhD in Physics from UC Berkeley, 1971.
- I had a 30-year career in developing and using laser-remote sensing systems to study the atmosphere. The final 15 years were at NASA Langley Research Center in Hampton, VA.
- I learned how to conduct ecological studies from a forestry professor at Miami University, Oxford, OH during a Sierra Club project to study the effects of air pollution on eastern oak and hickory forests.
- My first ecological health study was published in 1997: Grant WB. Dietary links to Alzheimer's disease. *Alz Dis Rev*,
- I receive funding from Bio-Tech Pharmacal, Inc. (Fayetteville, AR, USA), a supplier of vitamin D supplements.

Outline

- Vitamin D overview
- Types of evidence
  - Randomized controlled trials, cohort studies
  - Limitations of such studies
- Health benefits of vitamin D
  - Pregnancy and birth outcomes
  - Cancers
  - Cardiovascular disease
  - COVID-19
  - Dental caries
  - Alzheimer's and dementia and their risk factors
    - Inflammation, insulin resistance, infections, lipids, sleep
- Sun exposure
- Recommendations

Vitamin D is the Lowest-cost Major Contributor to Health



Better Living Through Vitamin D, Healthy Sun Exposure, and Exercise – Michael F. Holick

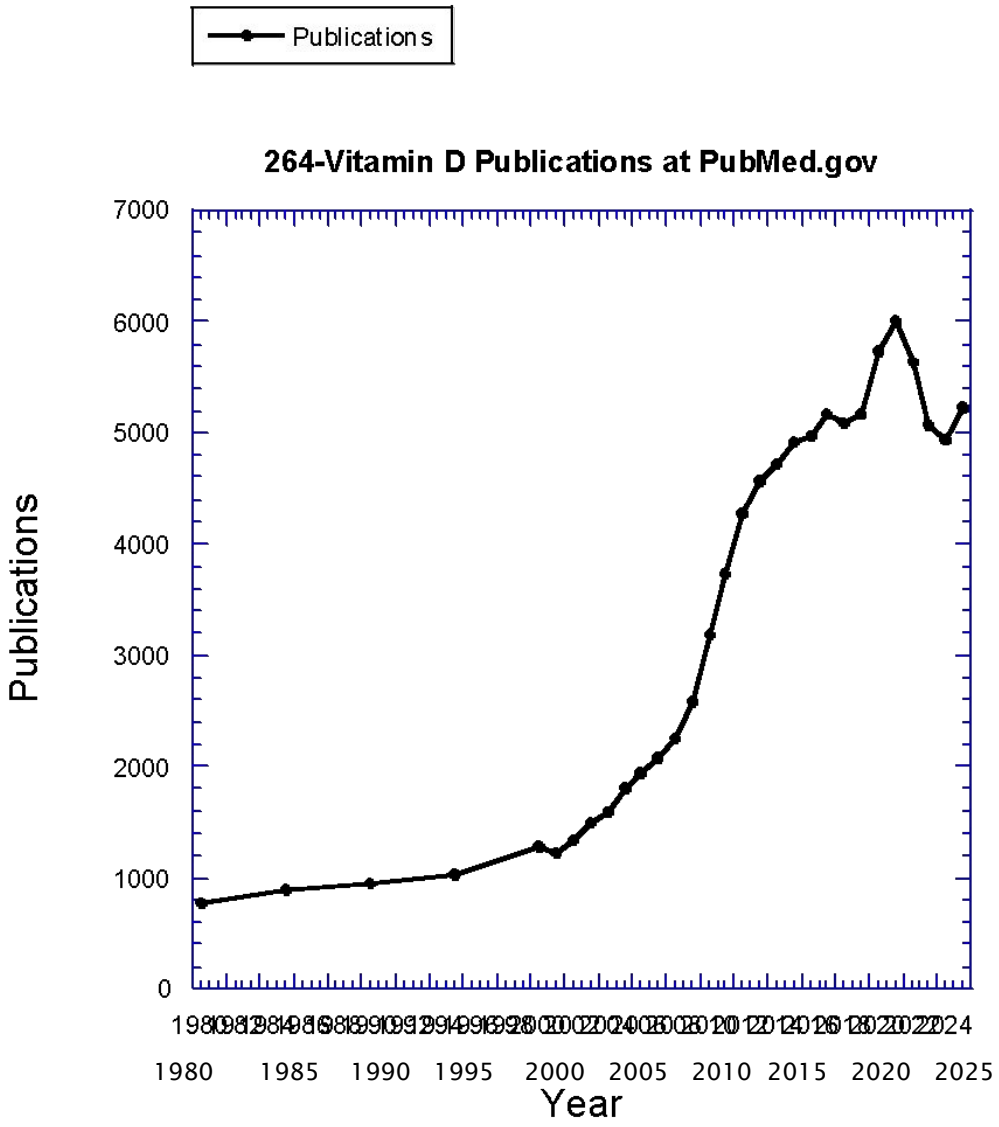
‘Refuse to stop’: 80-year-old doctor is running his third Boston Marathon

By Claire Thornton Globe Staff, Updated April 5, 2026, 6:00 a.m.

Dr. Michael Holick put on his running shoes at home in Weston for a run late last month. LANE TURNER/GLOBE STAFF

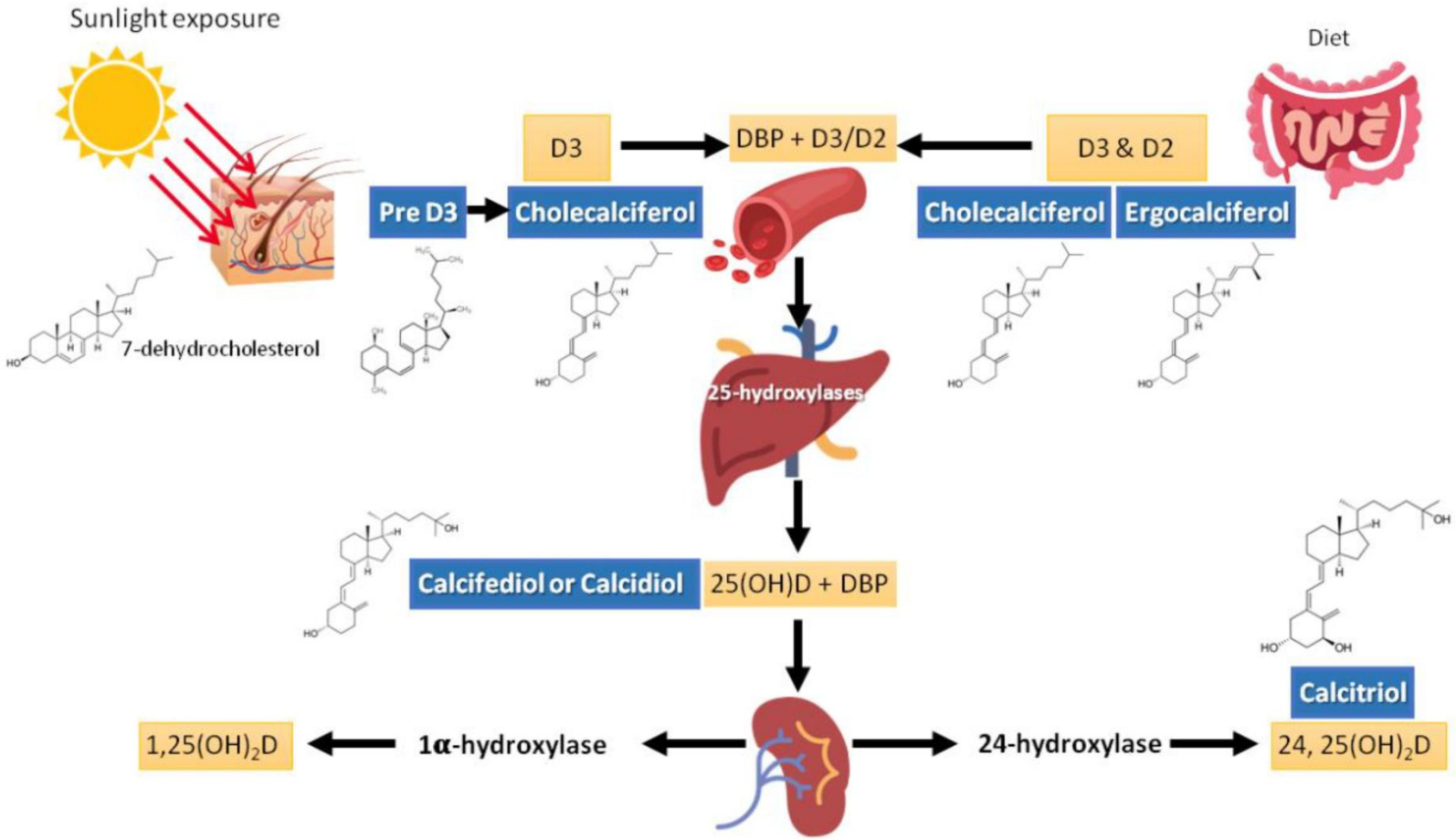
Severe hot flashes. Testosterone deficiency. Anemia. Type-2 diabetes.

Michael Holick has long battled many side effects as part of his cancer treatments. They won’t stop the 80-year-old doctor from running his third consecutive Boston Marathon



Prior to 2020, vitamin D
Was known for bone effects.
The extra-skeletal effects
Have been researched in the
Past 25 years.
Note the peak at 2020 – this
was related to COVID-19,

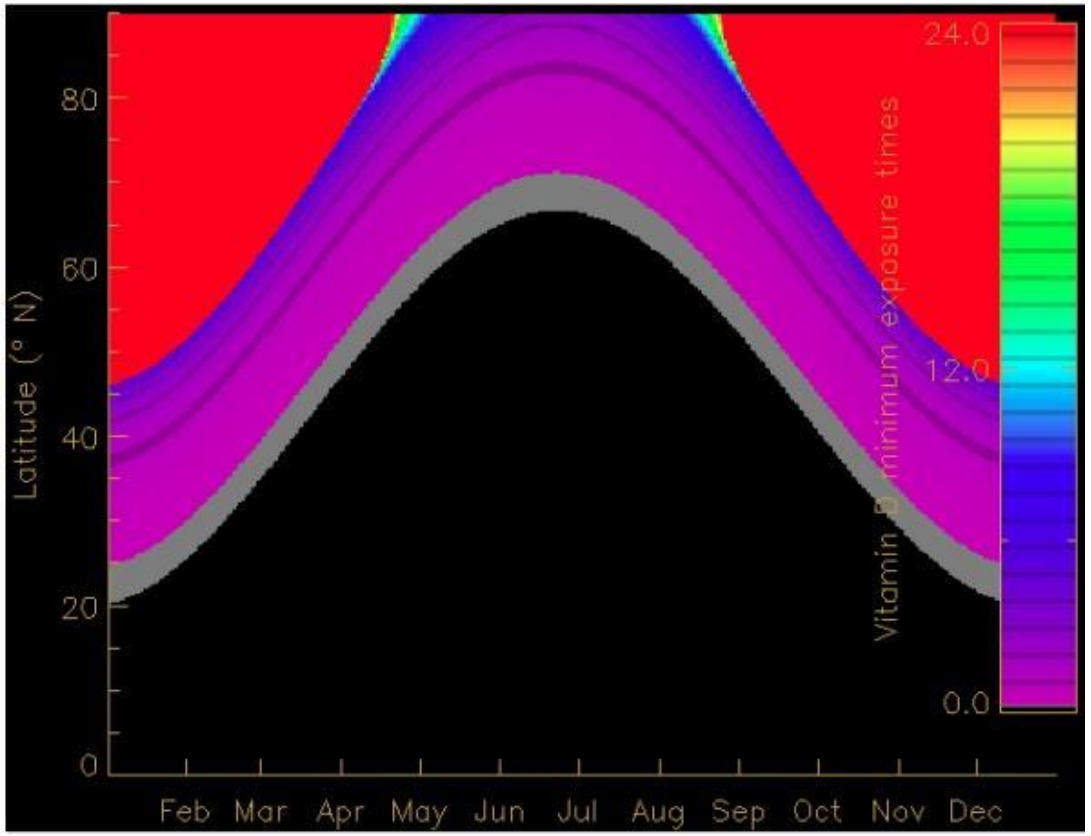
Dominguez et al. Vitamin D Sources, Metabolism, and Deficiency. M*etabolites* **2021**, *11*, 255.



An Example of Serum 25(OH)D Concentration Affecting Gene Expression

- Thirty healthy adults were randomized to receive 600, 4,000 or 10,000 IU/d of vitamin D_3 for 6 months. Circulating parathyroid hormone (PTH), 25(OH)D, calcium and peripheral white blood cells broad gene expression were evaluated. 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, respectively.
- Shirvani, Holick et al. *Sci Rep.* 2019;9(1):17685.

Time Required to Produce 400 IU of Vitamin D from Solar UVB



Lat

80

60

40

20

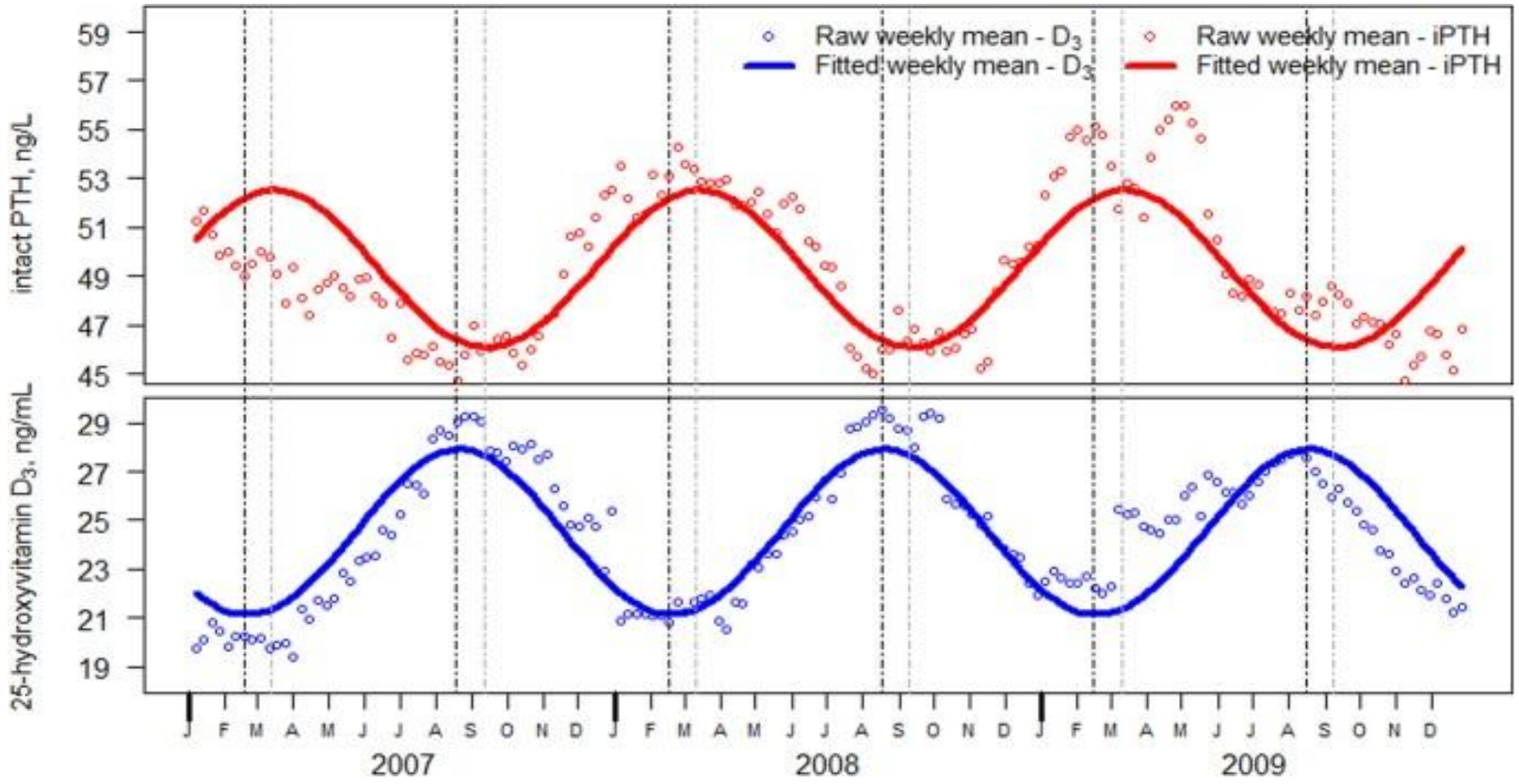
0

Feb May Aug Nov

The shadow rule: you can make vitamin D efficiently when your shadow is shorter than you are tall.

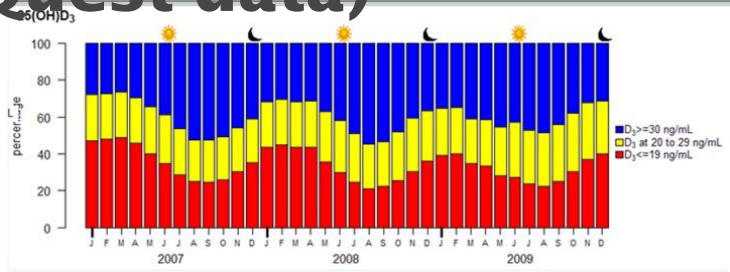
The relationship between ultraviolet radiation exposure and vitamin D status. Engelsen O. *Nutrients*. 2010;2(5):482-95.

Temporal relationship between vitamin D status and parathyroid hormone in the United States

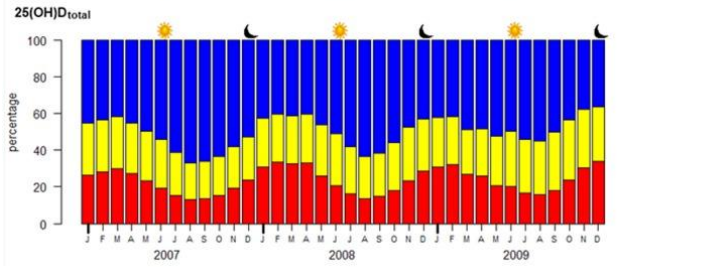


Kroll MH, et al., Holick MF. *PLoS One*. 2015;10(3):e0118108.

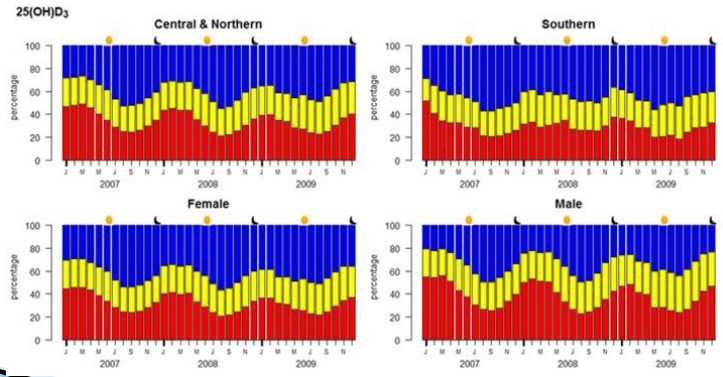
Fig 3. Percentages of patients with 25(OH)D_3 deficiency (<20 ng/mL), insufficiency (20–29 ng/mL), and sufficiency (≥30 ng/mL), by month. (Quest data)



25(OH)D_3



25(OH)D_{2+3}



Central and Northern; Southern

Female, Male

Kroll MH et al., Holick MF. *PLoS One*. 2015;10(3):e0118108

Skeletal Muscle and the Maintenance of Vitamin D Status

- Skeletal muscle cells have now been shown to incorporate the vitamin D-binding protein (DBP) from blood into the cell cytoplasm where it binds to cytoplasmic actin. This intracellular DBP provides an array of specific binding sites for 25(OH)D, which diffuses into the cell from the extracellular fluid. When intracellular DBP undergoes proteolytic breakdown, the bound 25(OH)D is then released and diffuses back into the blood. Parathyroid hormone is the most likely factor enhancing the repeated cycling of 25(OH)D between skeletal muscle and blood.
- Rybchyn MS, Abboud M, Puglisi DA, Gordon-Thomson C, Brennan-Speranza TC, Mason RS, Fraser DR. *Nutrients*. 2020;12(11):3270.

Human serum 25(OH)D response to extended oral dosing with vitamin D_3

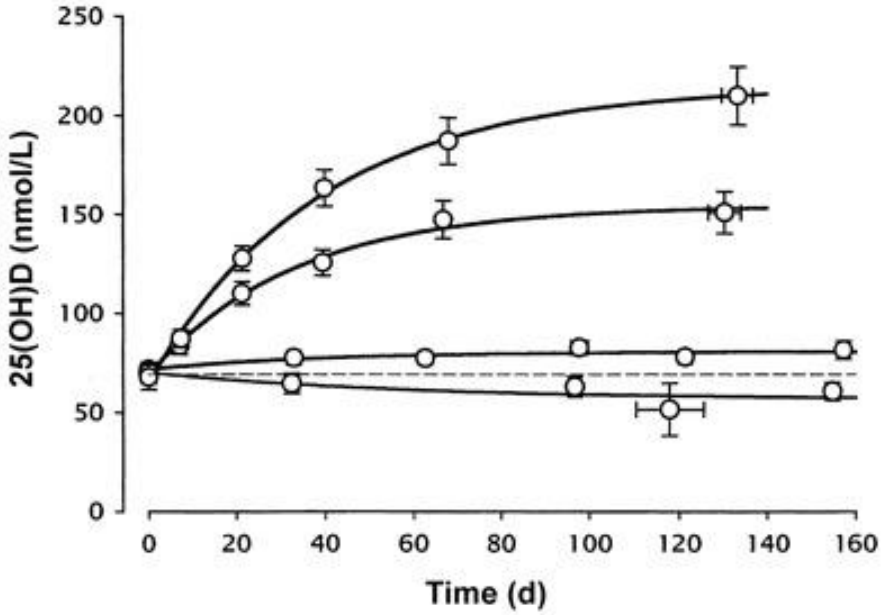
100 ng/mL

80 ng/mL

60 ng/mL

40 ng/mL

20 ng/mL



10,000 IU/day

5000 IU/day

1000 IU/day

0 IU/day

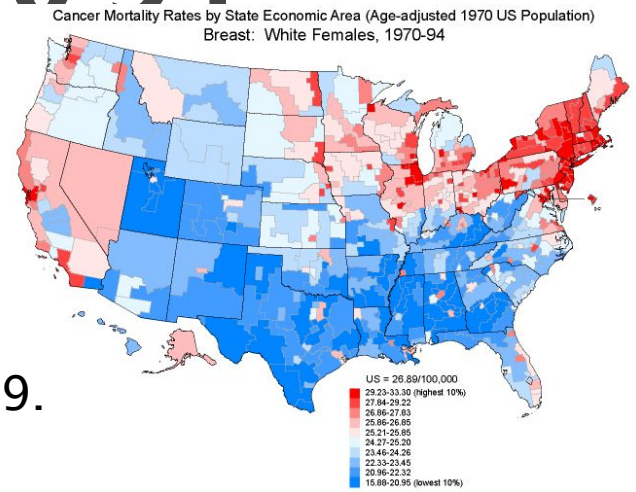
67 men, mean age 39 years, mean BMI = 27 kg/m^2
Mean baseline 25(OH)D = 70 nmol/L (28 ng/mL)
Heaney et al. *Am J Clin Nutr*. 2003;77(1):204-10.

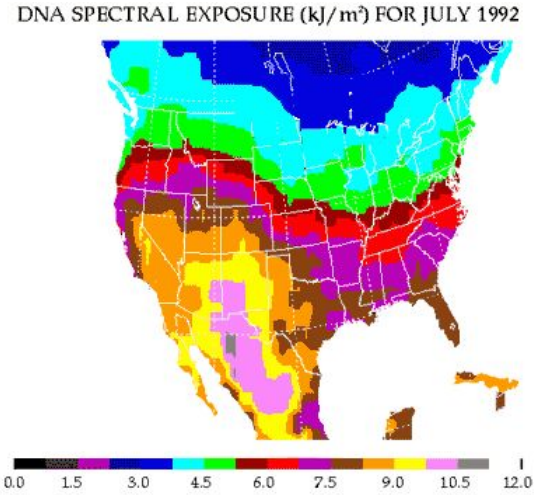
Types of Evidence re Vitamin D Benefits

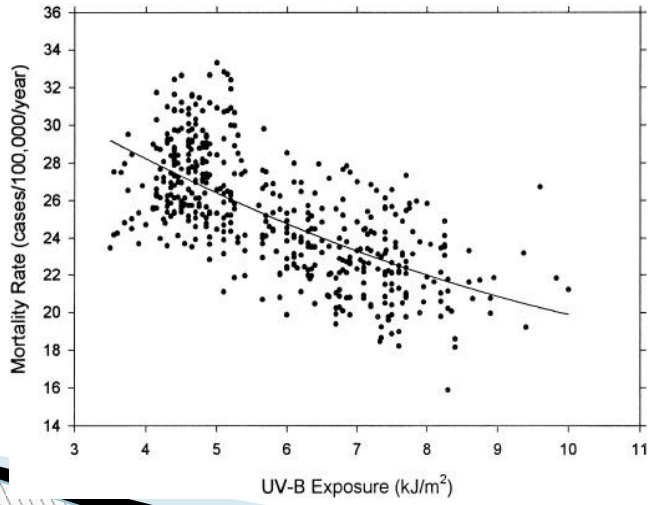
- Observational studies
  - Ecological studies
  - Prospective cohort studies
  - Cross-sectional studies
  - Case-control studies
- Randomized controlled trials (RCTs)
- Mechanisms

Ecological Studies – Breast Cancer Mortality Rates, Whites, 1970-94

Devesa et Al. Atlas of Cancer Mortality In the US 1950-1969. NIH, NCI 1999







Breast cancer mortality rate vs. solar UVB dose

Grant WB**.** An estimate of premature cancer mortality in the U.S. due to inadequate doses of solar ultraviolet-B radiation. *Cancer.* 2002;94(6):1867-75.

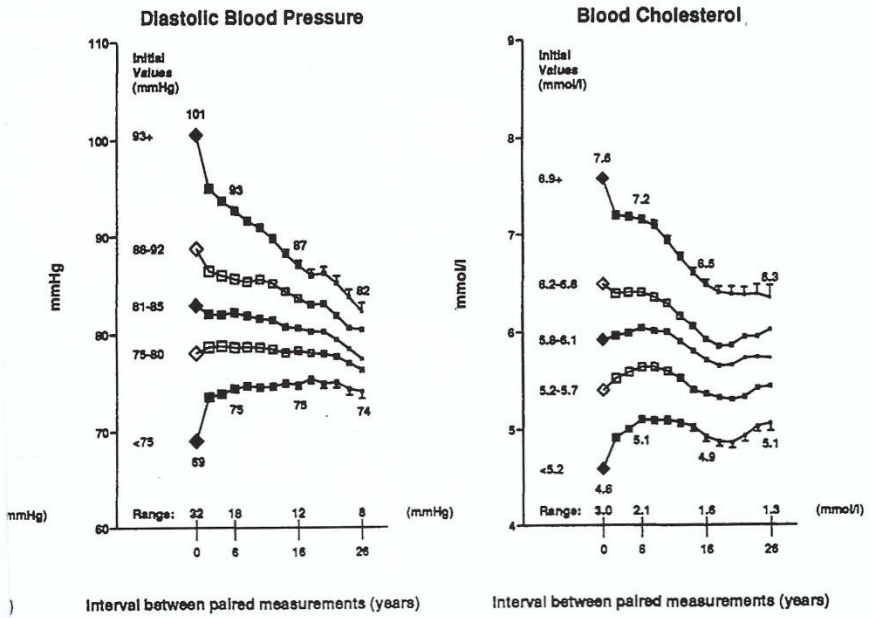
The association of solar ultraviolet B (UVB) with reducing risk of cancer: multifactorial ecologic analysis of geographic variation in age-adjusted cancer mortality rates

- Breast cancer, white females, 1970-94
- Variable, *adj.* r^2, *p*
- **UVB, – 0.71, <0.001**
- Smoking, 0.10, 0.14
- **Alcohol, 0.26, 0.001**
- **Urban, 0.31, <0.001**
- Hispanic, 0.11, 0.15
- Poverty, –0.13, 0.10
- Total, 0.84
- Grant WB, Garland CF. *Anticancer Res*. 2006;26(4A):2687-99.

Prospective Cohort Studies

- Prospective cohort studies enroll participants, measure values of the variable of most interest as well as many other variables at baseline.
  The participants are followed for any where from weeks to decades.
- Health outcomes are noted.
- Results are calculated for the variable of interest alone, and as modified by consideration of variables (adjusted value).

Underestimation of Risk Associations Due to Regression Dilution in Long-term Follow-up of Prospective Studies

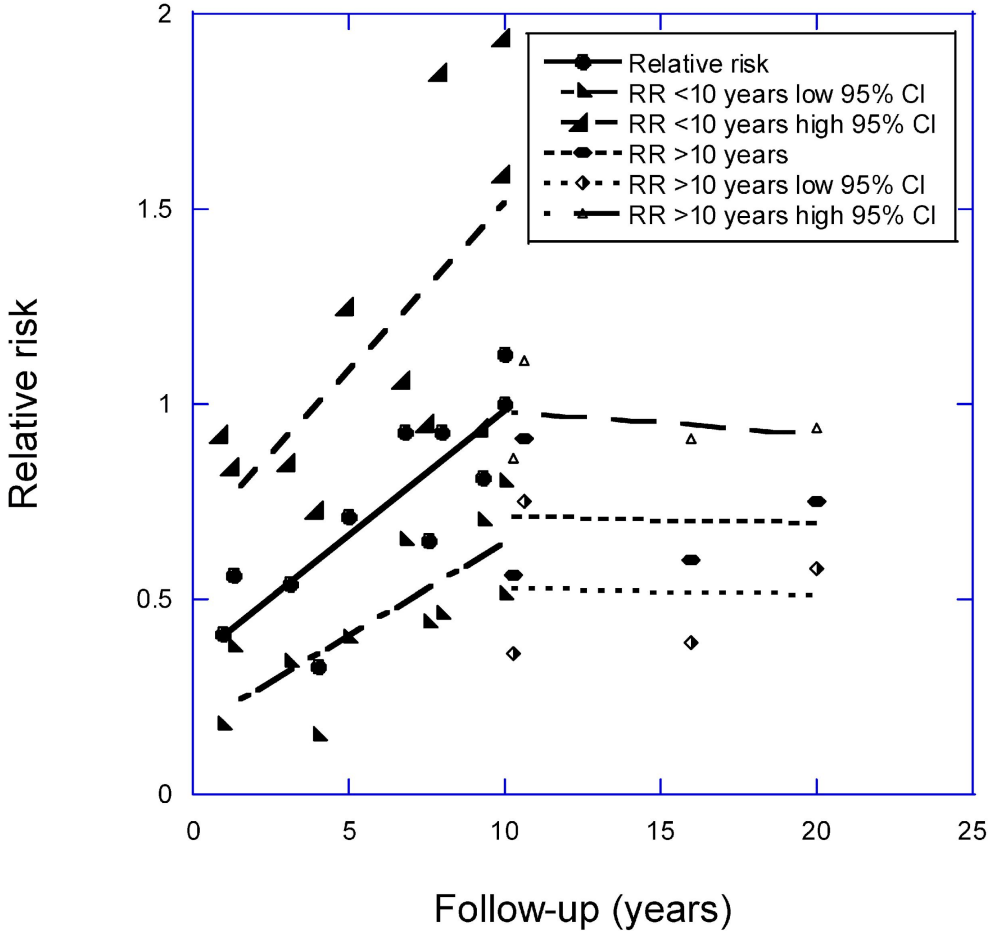


ssure and cholesterol values in groups defined by the first of a pair of measurements in the Framingham Study. Mean values ini-
s subdivided into five similar-sized groups according to the value of just the first of each pair of measurements. The size of each
ation available, and the 95% confidence intervals for the top and bottom groups are represented by the vertical bars. Mean val-
rences (ranges) between them, are given at year 0 (i.e., the initial measurement of the pairs) and at years 6, 16, and 26 (i.e., the
ades, respectively, after the initial measurement).

Blood pressure data measured every two years for quintiles at baseline. Framingham Study.

Clarke R, Shipley M, Lewington S, Youngman L, Collins R, Marmot M, Peto R. *Am J Epidemiol*. 1999;150(4):341-53.

Grant, W. B., & Boucher, B. J. (2024). 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. *Nutrients*,



Relative risk for stroke for high vs. low 25(OH)D concentration

Cross-sectional Studies

- Cross-sectional studies measure values of variables for participants at a specific time.
- It is not as useful as prospective cohort studies since causality can not be established.
- The values could have caused the disease or be a result of the disease.

Drug RCTs

- RCTs for drugs have these steps
- Preliminary studies indicate drug doses that are effective without major adverse effects.
- Volunteers not taking any drugs for the expected outcome are enrolled.
- Some are randomly assigned to the treatment arm, others to the control arm.
- Outcomes are compared for those treated with those not treated.

Nutrient RCTs Such as for Vitamin D

- Start with observational study data for the 25(OH)D dose-health outcome relationship.
- Measure 25(OH)D concentrations for all prospective participants. Include only those with low values.
- Give those in the treatment arm a dose calculated to yield important benefits.
- Do not give vitamin D to those in the treatment arm.
- Evaluate outcomes based on achieved 25(OH)D concentration.

Grant WB, Boucher BJ, Bhattoa HP, Lahore H. Why **vitamin D** clinical trials should be based on 25-hydroxyvitamin D concentrations. *J Steroid Biochem Mol Biol*. 2018;177:266-269.

Heaney RP. Guidelines for optimizing design and analysis of clinical studies of nutrient effects. *Nutr Rev*. 2014;72(1):48-54.

Why Most Vitamin D RCTs Failed

- Most vitamin D RCTs have been based on guidelines for pharmaceutical drugs. As a result, they are poorly designed, conducted, and analyzed for nutrients such as vitamin D: participants had high baseline 25(OH)D concentrations; those in the treatment arm were given low vitamin D doses; those in the control arm also took vitamin D; results were not analyzed with respect to achieved 25(OH)D concentration.

- **The failures may have been due to thoughtless adoption of guidelines for drug trials**
- **or**
- **Due to intentionally wanting to suggest that vitamin D has no important health benefits.**

Two RCTs That Found Beneficial Effects of Vitamin D Supplements

- These two RCTs will be discussed to show that it is possible to design and conduct successful vitamin D RCTs:
- One for pre-diabetes to diabetes
- The other for pregnancy and birth outcomes.
- Later, some for cancer will be presented.

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

- The D2d study compared the effect of daily supplementation with 100 µg (4,000 units) of vitamin D_3 versus placebo on new-onset diabetes in adults with prediabetes. Intratrial vitamin D exposure was calculated as the cumulative rolling mean of annual serum 25(OH)D measurements. Hazard ratios (HRs) for diabetes among participants who had intratrial 25(OH)D levels of <20, 20-30, 40-50, and ≥50 ng/mL were compared with those with levels of 20-30 ng/mL.
- The HRs for diabetes among participants treated with vitamin D who maintained intratrial 25(OH)D levels of 40-50 and ≥50 ng/mL were 0.48 (0.29-0.80) and 0.29 (0.17-0.50), respectively, compared with those who maintained a level of 20-30 ng/mL.
- Dawson-Hughes et al. *Diabetes Care*. 2020;43(12):2916-2922.

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

- 800 pregnant women from each of two health centers in Iran were enrolled. The mean baseline 25(OH)D concentration was 11 ng/mL. Those at one center were treated with variable vitamin D doses to try to achieve 25(OH)D >20 ng/mL. Those at the other center were not given any vitamin D. Outcomes were compared

- Rostami M, Tehrani FR, Simbar M, Bidhendi Yarandi R, Minooee S, Hollis BW, Hosseinpanah F. *J Clin Endocrinol Metab*. 2018;103(8):2936-2948.

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

S NS Favors VitD

Outcomes		N(%) Screening site (Masjed-Soleyman)[a]	N(%) Non-screening site (Shushtar)[a*]	OR (95% CI) (p-value)[b]	OR (95% CI)	NNS (95% CI)	P-value for interaction effect
	Moderate deficiency	29(7)	54(13)	0·5(0·3-0·8) (0·01)*		17(10-50)	
Pre-eclampsia	Severe deficiency	35(8)	75(23)	0·3(0·2-0·5) (<·001)*		7(5-11)	0·15
	Total	64(8)	129(17)	0·4(0·3-0·6) (<0·001)		11(8-17)	
	Moderate deficiency	11(3)	17(4)	0·7(0·3-1·4) (0·30)		100(-25-100)	
GDM	Severe deficiency	17(4)	30(8)	0·5(0·3-0·9) (0·02)		20(13-125)	0·42
	Total	28(4)	47(6)	0·5(0·3-0·9) (0·01)*		50(2-167)	
	Moderate deficiency	29(7)	40(9)	0·7(0·5-1·2) (0·24)		50(-50-17)	
Preterm delivery	Severe deficiency	33(7)	71(20)	0·3(0·2-0·5) (<·001)*		8(5-13)	0·02*
	Total	62(8)	111(15)	0·6(0·4-0·8) (<·001)*		20(13-50)	
	Moderate deficiency	62(16)	94(23)	0·6(0·4-0·9) (0·01)*		20(13-55)	
Composite adverse pregnancy outcomes**	Severe deficiency	71(18)	129(39)	0·3(0·2-0·5) (<·001)*[c]		8(5-13)	<0·001*
	Total	133(17)	223(29)	0·45(0·36-0·55) (<·001)*[c]		12(9-18)	

0 0·5 1·0 1·5

[a]Number of positive events in subgroups of 25(OH)D levels in intervention site
[a*]Number of positive events in subgroups of 25(OH)D level in no intervention site
[b]Odds ratio for pre-eclampsia, GDM and preterm delivery (p-value obtained from logistic regression model)
[c]OR_{CMH}: Cochran Mantel Haenszelcommon Odds Ratio

P-value obtained from subgroup analysis: the effect of intervention on the severe group compared to moderate group
*significance level was considered <0·05
** pre-eclampsia and/or GDM and/or preterm delivery
25(OH)D; 25-hydroxyvitamin D, NNS; number needed to screen, GDM; gestational diabetes mellitus

Significantly reduced risks were found for Pre-eclampsia, gestational diabetes, and preterm delivery.

Mechanisms

- Mechanisms to explain epidemiological or clinical studies provide important information and support for such studies.
- For example, Hill's criteria for causality have several criteria applicable for vitamin D:
  - Temporality
  - Strength of association
  - Consistent findings in different populations
  - Plausibility (e.g., mechanisms)
  - Experiment (e.g., RCTs)

HILL AB. THE ENVIRONMENT AND DISEASE: ASSOCIATION OR CAUSATION? Proc R Soc Med. 1965;58(5):295-300.

The Disinformation Playbook

- **Orthomolecular Medicine News Service, Oct 1, 2018**
- **Commentary by William B. Grant, Ph.D.**
- **The Disinformation Playbook (from Union of Concerned Scientists)**
- **1. <u>The Fake</u>**
  Conduct counterfeit science and try to pass it off as legitimate research.
- **2. <u>The Blitz</u>**
  Harass scientists who speak out with results or views inconvenient for industry.
- **3. <u>The Diversion</u>**
  Manufacture uncertainty about science where little or none exists.
- **4. <u>The Screen</u>**
  Buy credibility through alliances with academia or professional societies.
- **5. <u>The Fix</u>**
  Manipulate government officials or processes to influence policy inappropriately.
- **https://www.orthomolecular.org/resources/omns/v14n22.shtml**

Vitamin D Fact Sheet for Health Professionals

- Some evidence suggests that vitamin D might inhibit carcinogenesis and slow tumor progression. However, most research has found no relationship between serum 25(OH)D levels and risk of cancer. The results of clinical trials have generally failed to show that vitamin D supplementation with or without calcium supplementation reduces the incidence of cancer. Adequate or higher 25(OH)D levels might reduce cancer mortality rates, but more research is needed to determine the effects of vitamin D supplementa-tion in people with cancer.

- https://ods.od.nih.gov/factsheets/VitaminD-HealthProfessional/

NIH on Cardiovasular Disease

- Vitamin D has been linked to heart health and the risk of cardiovascular disease and vitamin D deficiency is associated with vascular dysfunction, arterial stiffening, left ventricular hypertrophy, and hyperlipidemia. While data from observational studies support an association between higher serum levels of 25(OH)D and a lower risk of cardiovascular disease incidence and mortality, clinical trials have not confirmed these results; several trials have reported that vitamin D supplementation did not reduce the risk of cardiovascular disease, even among people with low 25(OH)D status.

- https://ods.od.nih.gov/factsheets/VitaminD-HealthProfessional/

NIH on Diabetes
Updated: June 27, 2025

- Observational studies have found an inverse association between vitamin D status and blood glucose levels. However, vitamin D supplementation does not appear to help maintain glucose homeostasis, reduce the risk of progression from prediabetes to type 2 diabetes, or help manage the disease, particularly in vitamin D-replete individuals.

- https://ods.od.nih.gov/factsheets/VitaminD-HealthProfessional/

NIH on Hypecalcemia

- Vitamin D toxicity can cause hypercalcemia, hypercalciuria, and high serum 25(OH)D concentrations; in extreme cases, it may lead to renal failure, calcification of soft tissues, cardiac arrhythmias, and death. Vitamin D toxicity is almost always a result of excessive intakes of vitamin D through supplements. Taking calcium supplements in combination with vitamin D supplements may increase the risk of certain adverse effects. The Tolerable Upper Intake Level for vitamin D ranges from 25 to 100 mcg (1,000–4,000 IU), depending on age.

Vitamin D intoxication with severe hypercalcemia due to manufacturing and labeling errors of two dietary supplements made in the United States

- In both cases, repetitive inquiries were required to elicit the use of dietary supplements. Because of significant manufacturer errors and a labeling error, patients had been consuming more than 1000 times the recommended daily dose of vitamin D(3). Hypercalcemia is directly proportional to serum 25(OH)D but not 1,25-$(OH)_2$D levels. It took approximately 1 yr to normalize[2] 25(OH)D levels. However, once 25(OH)D levels decreased below 400 ng/ml, both patients became normocalcemic and asymptomatic without long-term sequelae.
- Araki T, Holick MF, et al. *J Clin Endocrinol Metab*. 2011;96(12):3603-8.

The 2011 report on dietary reference intakes for calcium and vitamin D from the Institute of Medicine: what clinicians need to know

- For extraskeletal outcomes, including cancer, cardiovascular disease, diabetes, and autoimmune disorders, the evidence was inconsistent, inconclusive as to causality, and insufficient to inform nutritional requirements. Randomized clinical trial evidence for extraskeletal outcomes was limited and generally uninformative. Based on bone health, Recommended Dietary Allowances (RDAs; covering requirements of ≥97.5% of the population) for calcium range from 700 to 1300 mg/d for life-stage groups at least 1 yr of age. For vitamin D, RDAs of 600 IU/d for ages 1-70 yr and 800 IU/d for ages 71 yr and older, corresponding to a serum 25-hydroxyvitamin D level of at least 20 ng/ml (50 nmol/liter), meet the requirements of at least 97.5% of the population.
- AC Ross, JE Manson, et al. *J Clin Endocrinol Metab*. 2011;96(1):53-8.

Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline - 2011

- Vitamin D deficiency is defined as a 25(OH)D below 20 ng/mL (50 nmol/L).
- Vitamin D insufficiency as a 25(OH)D of 21–29 ng/mL.
- They recommended supplementing people with vitamin D deficiency with enough vitamin D to raise 25(OH)D above 30 ng/mL.

- Holick et al. *J Clin Endocrinol Metab*. 2011;96(7):1911-30.

Vitamin D for the Prevention of Disease: An Endocrine Society Clinical Practice Guideline 2024

- The panel suggests empiric vitamin D supplementation [without measuring 25(OH)D] for children and adolescents aged 1 to 18 years to prevent nutritional rickets and because of its potential to lower the risk of respiratory tract infections; for those aged 75 years and older because of its potential to lower the risk of mortality; for those who are pregnant because of its potential to lower the risk of preeclampsia, intra-uterine mortality, preterm birth, small-for-gestational-age birth, and neonatal mortality; and for those with high-risk prediabetes because of its potential to reduce progression to diabetes.
- Demay MB, Pittas AG et al. *J Clin Endocrinol Metab*. 2024;109(8):1907-1947.

Vitamin D for the Prevention of Disease: An Endocrine Society Clinical Practice Guideline 2024

- The panel suggests against empiric vitamin D supplementation (without testing) above the current Dietary Reference Intake to lower the risk of disease in healthy adults younger than 75 years. No clinical trial evidence was found to support routine screening for 25(OH)D in the general population, nor in those with obesity or dark complexion, and there was no clear evidence defining the optimal target level of 25(OH)D required for disease prevention in the populations considered; thus, the panel suggests against routine 25(OH)D testing in all populations considered.

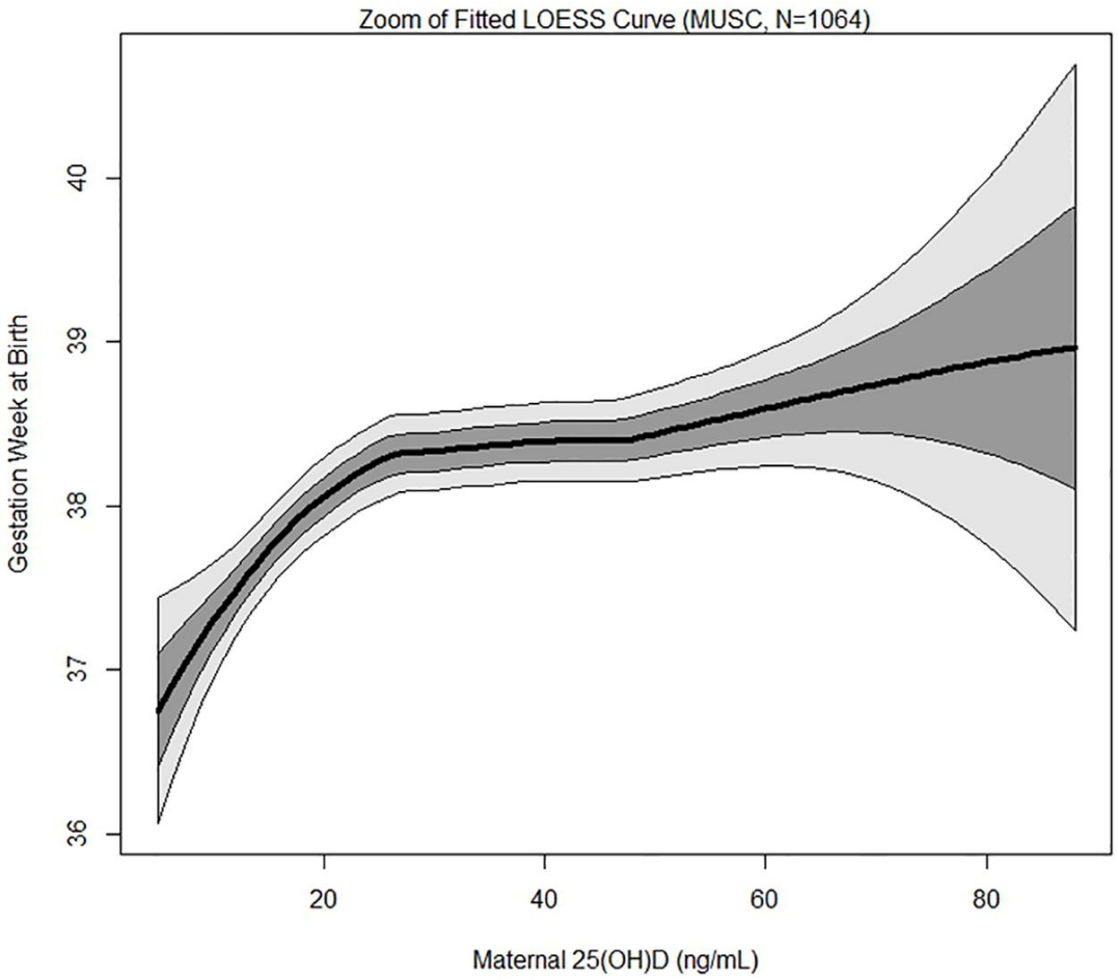
Vitamin D: Evidence-Based Health Benefits and Recommendations for Population Guidelines - 2025

- This review emphasizes the findings from prospective cohort studies showing that higher 25(OH)D concentrations reduce the risks of major diseases and mortality, including pregnancy and birth outcomes. Serum concentrations > 30 ng/mL (75 nmol/L) significantly lower disease and mortality risks compared to <20 ng/mL. With 25% of the U.S. population and 60% of Central Europeans having levels <20 ng/mL, concentrations should be raised above 30 ng/mL. This is achievable through daily supplementation with 2000 IU/day (50 mcg/day) of vitamin D_3, which reduces disease and death rates. Furthermore, a daily dose between 4000 and 6000 IU of vitamin D_3 to achieve serum 25(OH)D levels between 40 and 70 ng/mL would provide greater protection against many adverse health outcomes.
- Grant, W.B.; Wimalawansa, S.J.; Pludowski, P.; Cheng, R.Z. *Nutrients* **2025**, *17*, 277.

Vitamin D Findings for Health Benefits

- Pregnancy and birth outcomes
- Cancer
- Ecological studies, Cohort studies, RCTs
- Cardiovascular disease
- COVID-19
- Dental caries
- Alzheimer's disease and other dementia

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



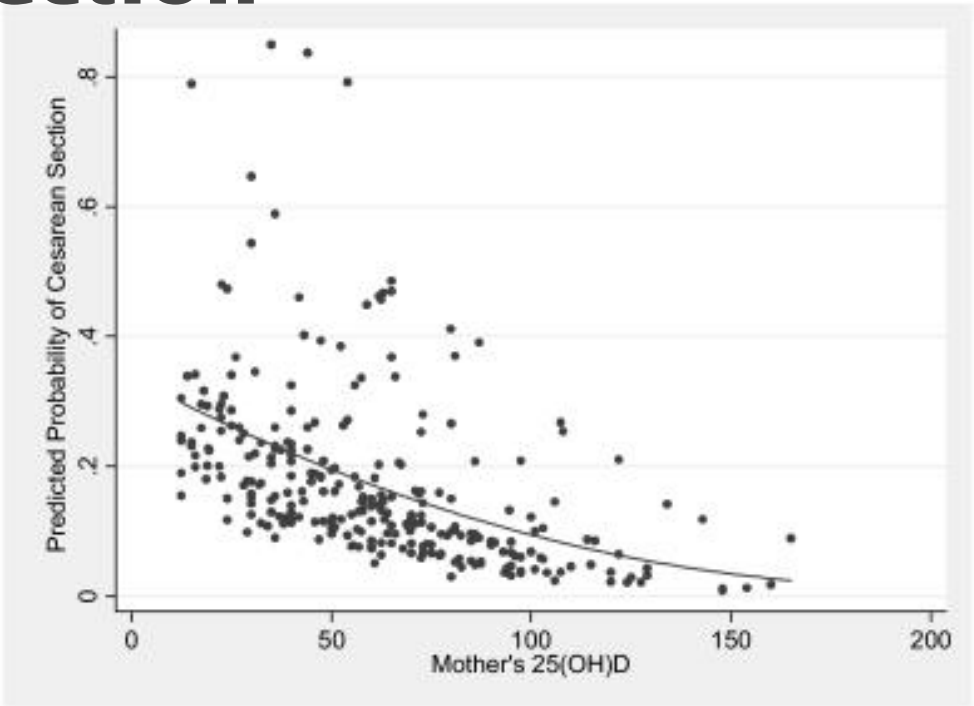
1064 Pregnant women (46% white, 37% African American) were Enrolled. Their 25(OH)D concentration was measured, they were given 5000 IU vitamin D capsules and education on the benefits of vitamin D and how to achieve 40 ng/mL 25(OH)D concentration.

McDonnell et al. *PLoS One*. 2017;12(7):e0180483

Comparison of Infant Bone Mineral Content and Density After Infant Daily Oral Vit D 400 IU Supplementation Versus Nursing Mother Oral 6,400 IU Supplementation: A Randomized Controlled Lactation Study

- Infant bone mineral content (BMC) and bone mineral density (BMD) did not differ significantly at 1, 4, or 7 months of age between direct and indirect supplementation arms. Although some differences among races were observed, this did not reflect changes in bone growth between the treatment arms. ***Conclusion:*** High-dose vitD supplementation of mothers during lactation provided an efficacious alternative to direct supplementation of infants, as evidenced by noninferior infant BMD and BMC.
- Andrews L, Phlegar K, Baatz JE, Ebeling MD, Shary JR, Gregoski MJ, Howard CR, Hollis BW, Wagner CL. *Breastfeed Med*. 2022;17(6):493-500.

Association between vitamin D deficiency and primary cesarean section



This graph shows the association between mother's increasing 25(OH)D level in nmol/L, and decreasing predicted probability of having a Cesarean section versus vaginal delivery, with a quadratically fit line. The predicted probabilities of Cesarean section are derived from a multivariate logistic regression model controlling for mother's age, education, insurance status, and race. Additionally, the model controls for reporting ever drinking alcohol during pregnancy, as this was statistically significant in univariate analysis and remained statistically significant at the $p<0.05$ level in multivariate analysis.

Merewood, Holick et al. *J Clin Endocrinol Metab*. 2009;94(3):940-5

Intake of vitamin D and risk of type 1 diabetes: a birth-cohort study (Finland)

- Children were followed-up at age 1 year. Of the 10366 children included in analyses, 81 were diagnosed with diabetes during the study. Vitamin D supplementation was associated with a decreased frequency of type 1 diabetes when adjusted for neonatal, anthropometric, and social characteristics (rate ratio [RR] for regular vs no supplementation 0.12, 95% CI 0.03-0.51, and irregular vs no supplementation 0.16, 0.04-0.74. Children who regularly took the recommended dose of vitamin D (2000 IU daily) had a RR of 0.22 (0.05-0.89) compared with those who regularly received less than the recommended amount. Children suspected of having rickets during the first year of life had a RR of 3.0 (1.0-9.0) compared with those without such a suspicion.
- Hyppönen E et al. *Lancet* . 2001;358(9292):1500-3.

Do Sunlight and Vitamin D Reduce the Likelihood of Colon Cancer?

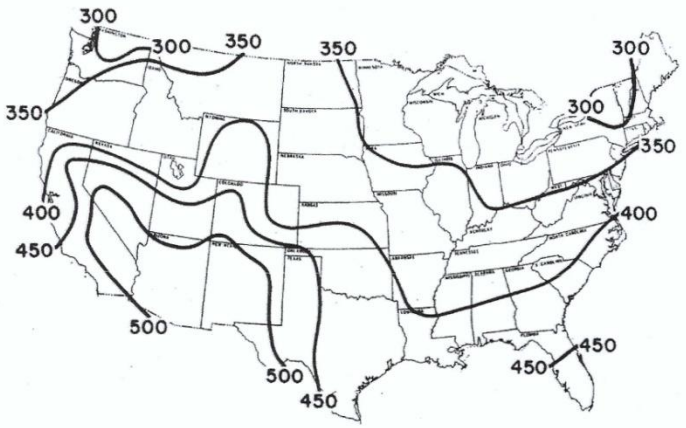


Figure 1 Annual mean daily solar radiation (gm-cal/cm^2), United States

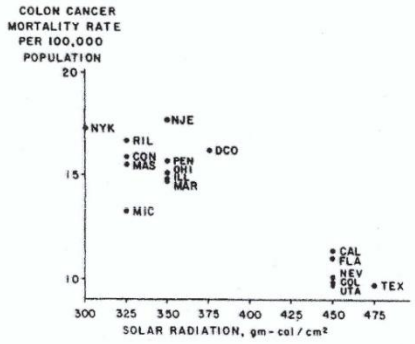


Figure 2 Annual mean daily solar radiation (gm-cal/cm^2) and annual age-adjusted colon cancer death rates per 100 000 population, white males, 17 non-metropolitan states, United States, 1959–61

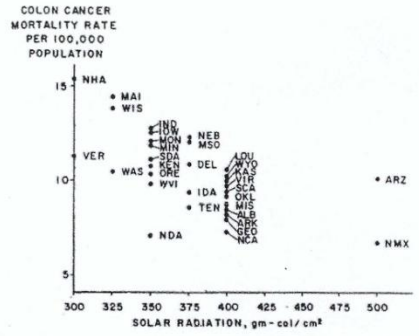


Figure 3 Annual mean daily solar radiation (gm-cal/cm^2) and annual age-adjusted colon cancer death rates per 100 000 population, white males, 32 non-metropolitan states, United States, 1959–61

Metro areas

Non-metro areas

Based on mortality rates for white males. Garland C, Garland F. *Int J Epidemiol*, 1980;9(3):227–231

DIETARY VITAMIN D AND CALCIUM AND RISK OF COLORECTAL CANCER: A 19-YEAR PROSPECTIVE STUDY IN MEN

- To investigate this possibility, the association of dietary vitamin D and calcium with 19-year risk of colorectal cancer was examined in 1954 men who had completed detailed, 28-day dietary histories in the period 1957-59. Risk of colorectal cancer was inversely correlated with dietary vitamin D and calcium. In the quartiles of a combined index of dietary vitamin D and calcium, from lowest to highest, observed risks of colorectal cancer were 38·9, 24·5, 22·5, and 14·3/1000 population. This association remained significant after adjustment for age, daily cigarette consumption, body mass index, ethanol consumption, and percentage of calories obtained from fat.
- Garland C, et al. *The Lancet*. 1985;325(8424):307-309.

SERUM 25-HYDROXYVITAMIN D AND COLON CANCER: EIGHT-YEAR PROSPECTIVE STUDY

- Blood samples taken in 1974 in Washington County, Maryland, from 25 620 volunteers were used to investigate the relation of serum 25(OH)D with subsequent risk of getting colon cancer. 34 cases of colon cancer diagnosed between August, 1975, and January, 1983, were matched to 67 controls by age, race, sex, and month blood was taken. Risk of colon cancer was reduced by 75% in the third quintile (27-32 ng/ml) and by 80% in the fourth quintile (33-41 ng/ml) of serum 25(OH)D. The results are consistent with a protective effect of serum 25(OH)D on colon cancer.
- Garland C, Garland F, et al. *The Lancet*. 1989;334(8673):1176-1178.

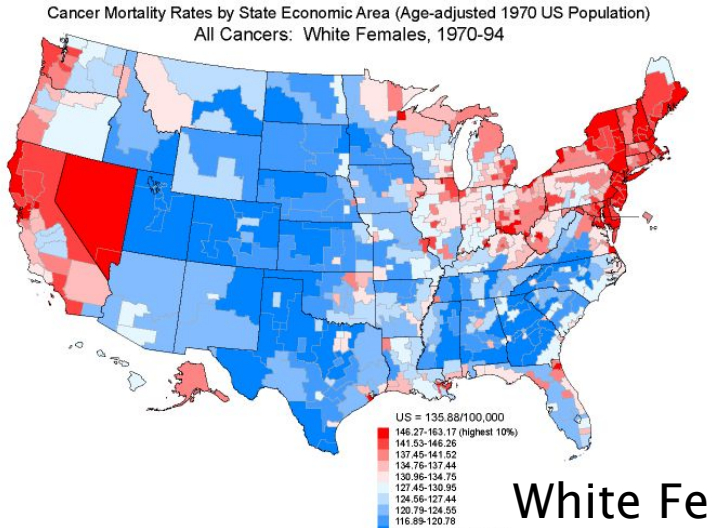
Is vitamin D deficiency a risk factor for prostate cancer? (Hypothesis)

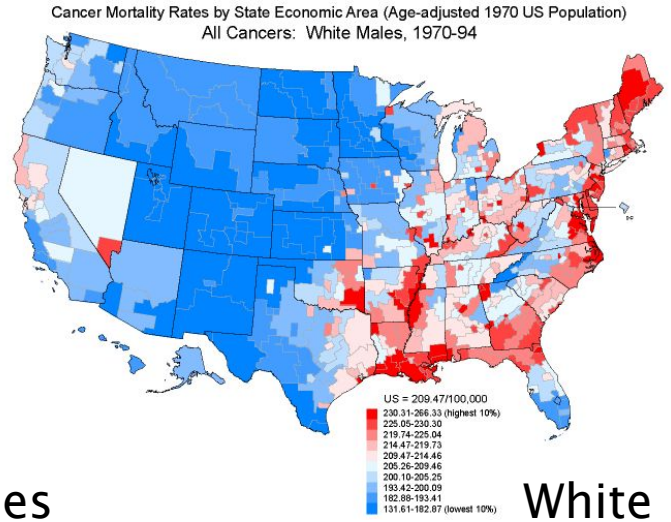
- We hypothesize that Vitamin (Hormone) D deficiency may underlie the major risks for prostate cancer, including age, Black race, and northern latitudes. These factors all are associated with decreased synthesis of Vitamin D. Mortality rates from prostate cancer in the U.S. are inversely correlated with ultraviolet radiation, the principal source of Vitamin D. This hypothesis is consistent with known antitumor properties of Vitamin D, and may suggest new avenues for research in prostate cancer.
- Schwartz GG, Hulka BS. *Anticancer Research*, 1990;10(5A):1307-1311

Vitamin D and Cancer: An Historical Overview of the Epidemiology and Mechanisms

- The first section reviews the findings from ecological studies of cancer with respect to indices of solar radiation, which 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 rates of 12 types of cancer. the correlations due to changes in 25(OH)D with time. Clinical trials have provided limited support for the UVB-vitamin D-cancer hypothesis due to poor design and execution. In recent decades, many experimental studies in cultured cells and animal models have described a wide range of anticancer effects of vitamin D compounds.
- Muñoz A, Grant WB. *Nutrients*. 2022;14(7):1448

Ecological Studies of Cancer All-cancer Mortality Rates: 1950-1969; 1970-1994

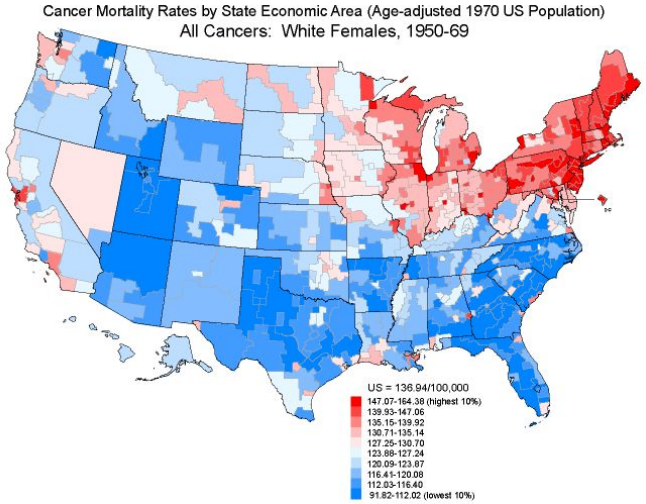


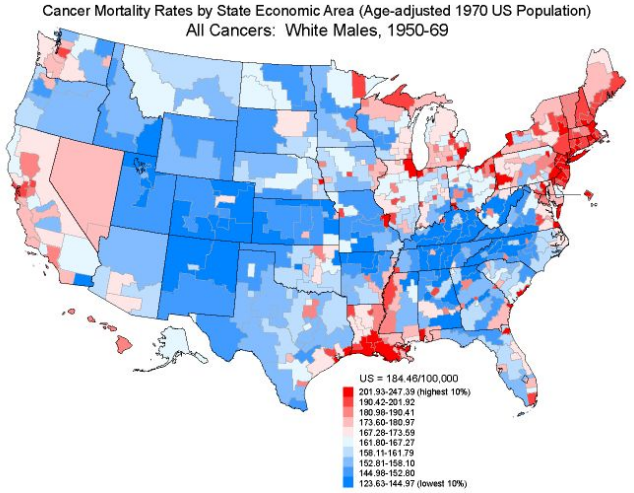


1970-1994

White Females

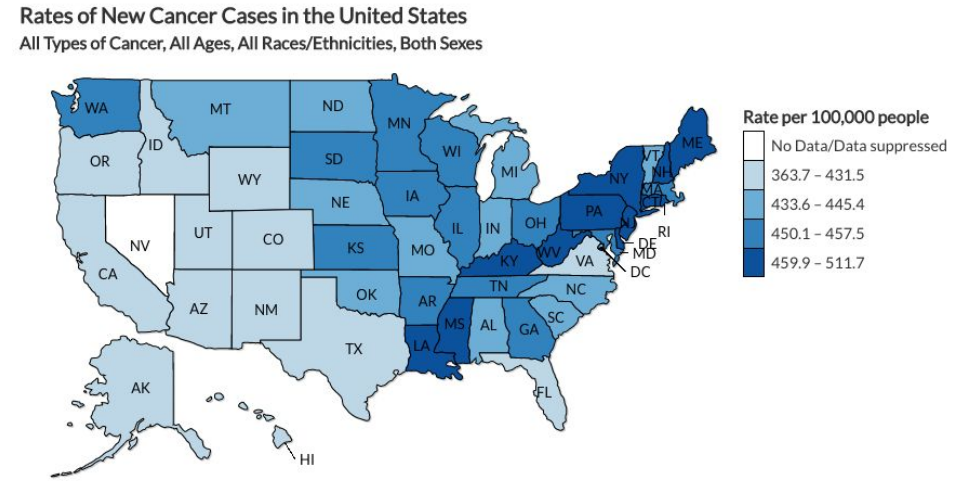
White Males





1950-1969

All-cancer Incidence and Mortality Rates, 2013



Incidence rates (mostly related to Solar UVB)

Mortality Rates
The high rates in the southeast are related to obesity, perhaps lower SES.

https://www.sciencealert.com/the-cdc-mapped-out-who-has-the-highest-rates-of-cancer-in-the-us

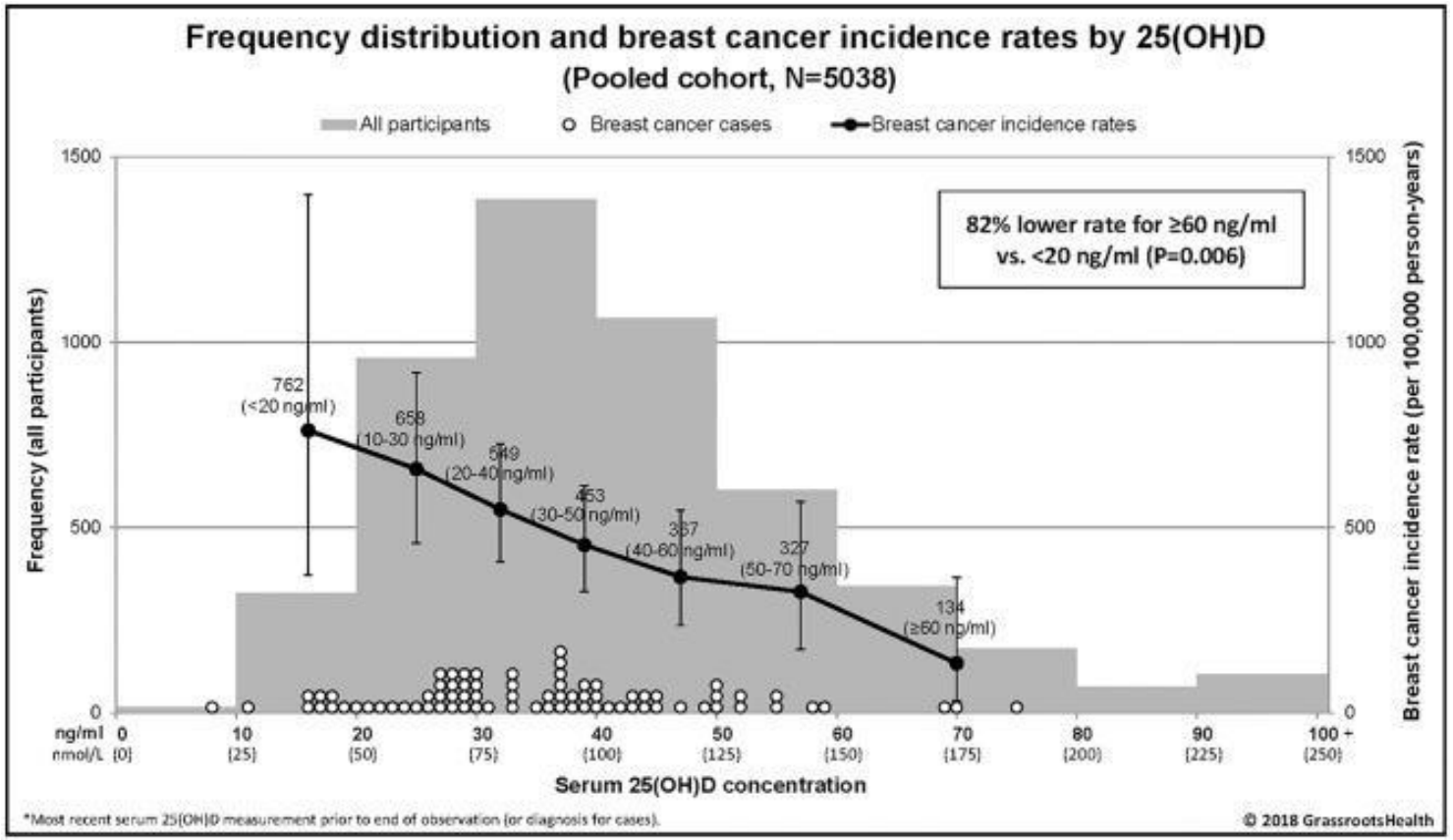
Cancer Incidence Rates in the US in 2016-2020 with Respect to Solar UVB Doses, Diabetes and Obesity Prevalence, Lung Cancer Incidence Rates, and Alcohol Consumption: An Ecological Study

- The cancers for which **solar UVB** is significantly associated with reduced incidence are bladder, brain (males), breast, corpus uteri, esophageal, gastric, non-Hodgkin's lymphoma, pancreatic, and renal cancer. **Lung cancer** was significantly associated with colorectal, laryngeal, and renal cancer. **Diabetes** was also significantly associated with breast, liver, and lung cancer. **Obesity** prevalence was significantly associated with breast, colorectal, and renal cancer. **Alcohol consumption** was associated with bladder and esophageal cancer. Thus, diet has become a very important driver of cancer incidence rates. The role of solar UVB in reducing the risk of cancer has been reduced due to people spending less time outdoors, wearing sunscreen that blocks UVB (but not UVA) radiation, and population increases in terms of overweight and obese individuals.
- Grant WB. *Nutrients*. 2024;16(10):1450

Vitamin D: What role in obesity-related cancer?

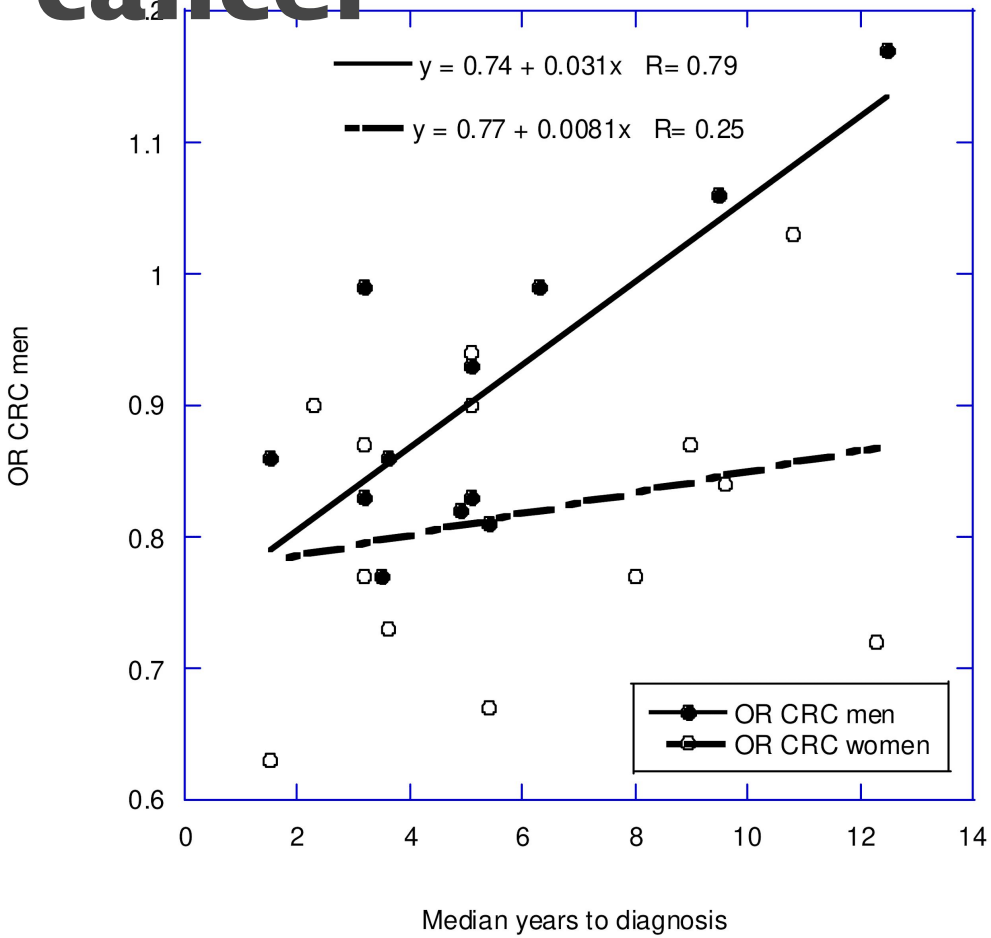
- Vitamin D is a partial ally against some of obesity's pro-carcinogenic effects, notably by reducing inflammation and regulating sex hormone receptors, leptin resistance, cellular energy metabolism, the microbiome, and hypoxia. However, it can act stronger in against the renin-angiotensin system, insulin resistance, and oxidative stress in cancer. Additionally, excess fat tissue sequesters vitamin D and, along with its dilution in increased body volume, further reduces its bioavailability and serum concentration, limiting its protective effects against cancer.
- Martinez P, Grant WB. *Semin Cancer Biol.* 2025:112:135-149.

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.

Effect of Follow-up Period on Odds Ratio for Colorectal cancer



Based on high vs. low 25(OH)D concentration.

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

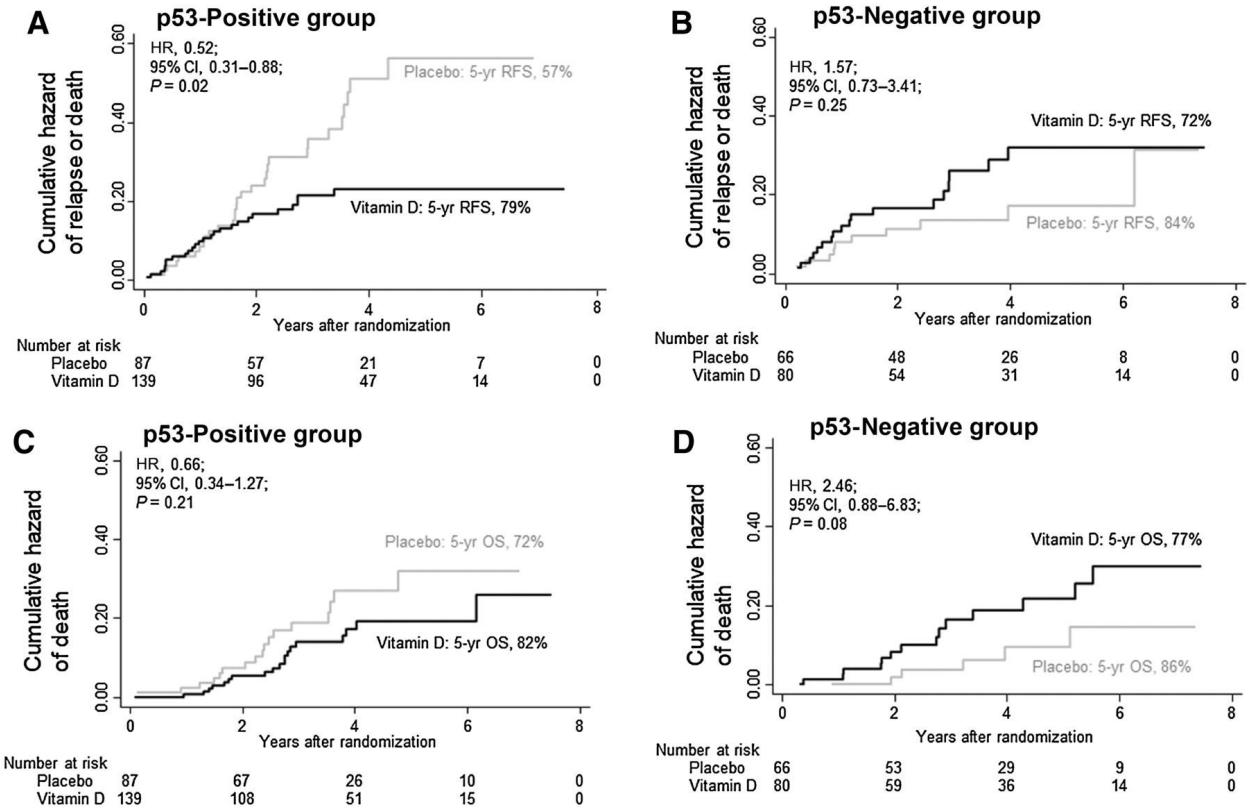
Vitamin D Supplements and Prevention of Cancer

- The VITAL study included over 25,000 participants. The mean 25(OH)D concentration for those who reported values was 31 ng/mL. Participants in the vitamin D treatment group were given 2000 IU/d vitamin D_3. Those in the control group were permitted to take 600 or 800 IU/day vitamin D.
- The relative risk (RR) of all-cancer incidence according to intention to treat was nearly unaffected.
- However, it was reduced by 25% for those with BMI <25 kg/m^2. The RR for all-cancer mortality rate was reduced by 25% after omitting the first 1 or 2 years.
- Manson JE, et al., VITAL Research Group. *N Engl J Med*. 2019;380(1):33-44.

Effect of Vitamin D on Relapse-Free Survival in a Subgroup of Patients with p53 Protein-Positive Digestive Tract Cancer: A *Post Hoc* Analysis of the AMATERASU Trial (2000 IU/day in Japan)

Relapse or Death

Death



Urashima et al. *Cancer Epidemiol Biomarkers Prev*. 2020;29(2):406-413

Impact of Vitamin D Levels on Progression-Free Survival and Response to Neoadjuvant Chemotherapy in Breast Cancer Patients: A Systematic Review and Meta-Analysis

- Neoadjuvant chemotherapy (NACT) is now standard for early-stage BC, with vitamin D (VD) emerging as a potential prognostic biomarker. All studies addressed stages II and III, with three also including stage I. The meta-analysis covered data from 722 patients regarding NACT response and 1033 patients for progression-free survival (PFS). The results revealed a 22% reduction in the likelihood of non-response to NACT associated with adequate VD levels (low/deficient VD vs. high/sufficient VD; OR: 0.78; 95% CI: 0.30–1.25; p = 0.001) and a **35% reduction in progression risk** with sufficient baseline VD levels (low/deficient VD vs. high/sufficient VD; HR: 0.65; 95% CI: 0.33–0.97; p < 0.001).
- Ottaiano*Cancers* 2024, *16*(24), 4206

Mechanisms by Which Vitamin D Reduces Risk of Cancer

- Vitamin D reduces cancer risk through several mechanisms including detecting cells that do not belong in an organ and causing apoptosis.
- Vitamin D reduces cancer progression by reducing angiogenesis around tumors.
- Vitamin D reduces mortality by reducing metastasis into surrounding tissues.
- Vitamin D is stronger at reducing cancer mortality rates than cancer incidence rates.

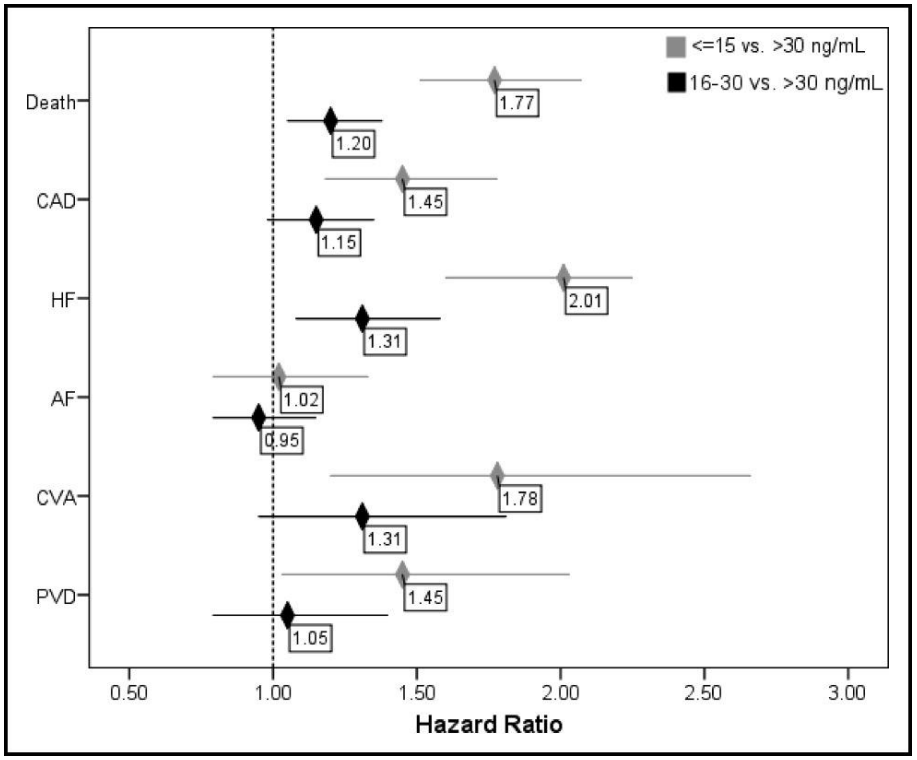
Vitamin D and Cardiovascular Health: A Narrative Review of Risk Reduction Evidence

- Prospective observational studies consistently show that low serum 25(OH)D concentrations (below 40-50 nmol/L [16-20 ng/mL]) are associated with the highest risk of CVD incidence. In addition, vitamin D supplementation studies have found modest reductions in several CVD risk factors. Other observational studies of vitamin D supplementation have reported reduced CVD risks (e.g., ischemic heart disease, hypertension, and myocardial infarction).
- Grant WB, Boucher BJ, Cheng RZ, Pludowski P, Wimalawansa SJ. *Nutrients*. 2025; 17(13):2102

Vitamin D Deficiency and Risk of Cardiovascular Disease

- We studied 1739 Framingham Offspring Study participants (mean age 59 years; 55% women; all white) without prior cardiovascular disease. Vitamin D status was assessed by measuring 25(OH)D levels. Prespecified thresholds were used to characterize varying degrees of 25(OH)D deficiency (<15 ng/mL, <10 ng/mL). Multivariable Cox regression models were adjusted for conventional risk factors. Overall, 28% of individuals had levels <15 ng/mL, and 9% had levels <10 ng/mL. During a mean follow-up of 5.4 years, 120 individuals developed a first cardiovascular event. Individuals with 25(OH)D <15 ng/mL had a multivariable-adjusted hazard ratio of 1.62 (95% confidence interval 1.11 to 2.36, *P*=0.01) for incident cardiovascular events compared with those with 25(OH)D ≥15 ng/mL.
- Wang TJ, et al. Circulation. 2008;117(4):503-511

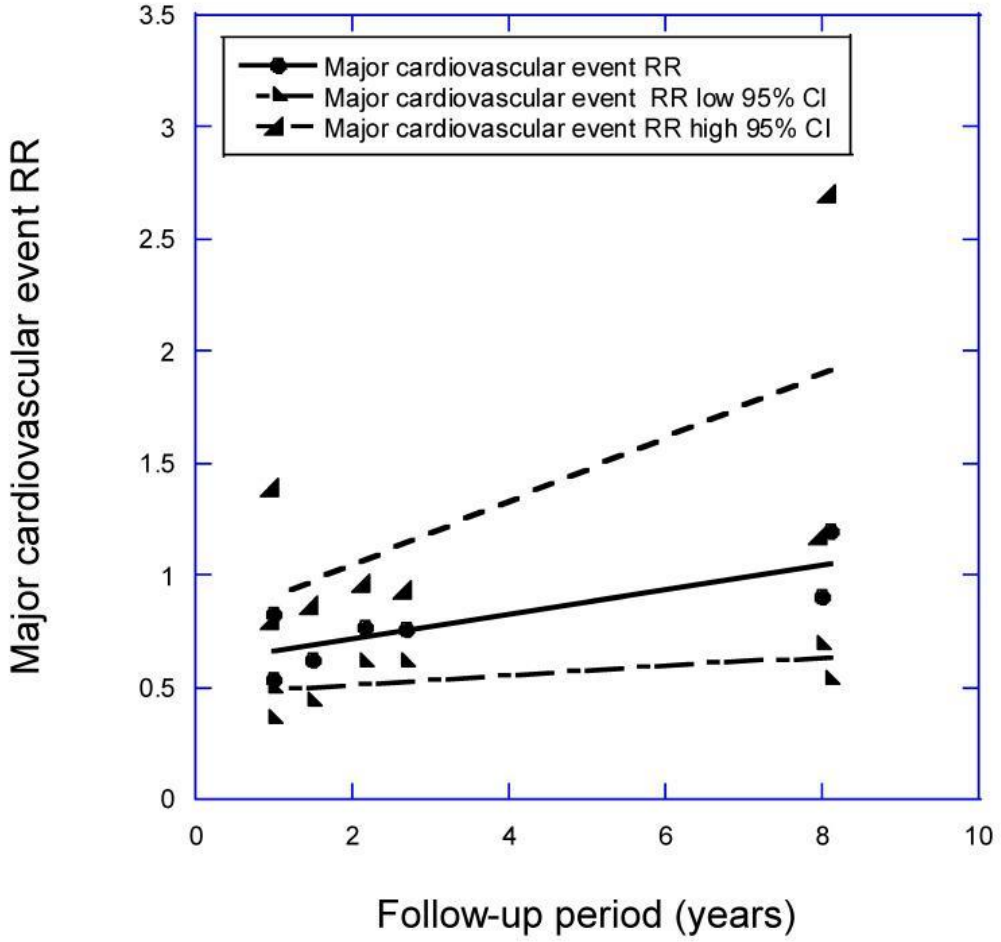
Relation of vitamin D deficiency to cardiovascular risk factors, disease status, and incident events in a general healthcare population (in Utah)



Prospectively analysis of a database containing 41,504 patient records with at least one measured vitamin D level. Patients were followed after the initial vitamin D determination for an average of 1.3 years (maximum 9.3). Vitamin D deficiency was associated with highly significant (p <0.0001) increases in the prevalence of diabetes, hypertension, hyperlipidemia, and peripheral vascular disease. The vitamin D levels were also highly associated with coronary artery disease, myocardial infarction, heart failure, and stroke (all p <0.0001), as well as with incident death, heart failure, coronary artery disease/myocardial infarction (all p <0.0001), stroke (p = 0.003), and their composite (p <0.0001).

Anderson et al. *Am J Cardiol*. 2010;106(7):963-8.

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 WB, Boucher BJ. *Nutrients*. 2024;16(21):3759.

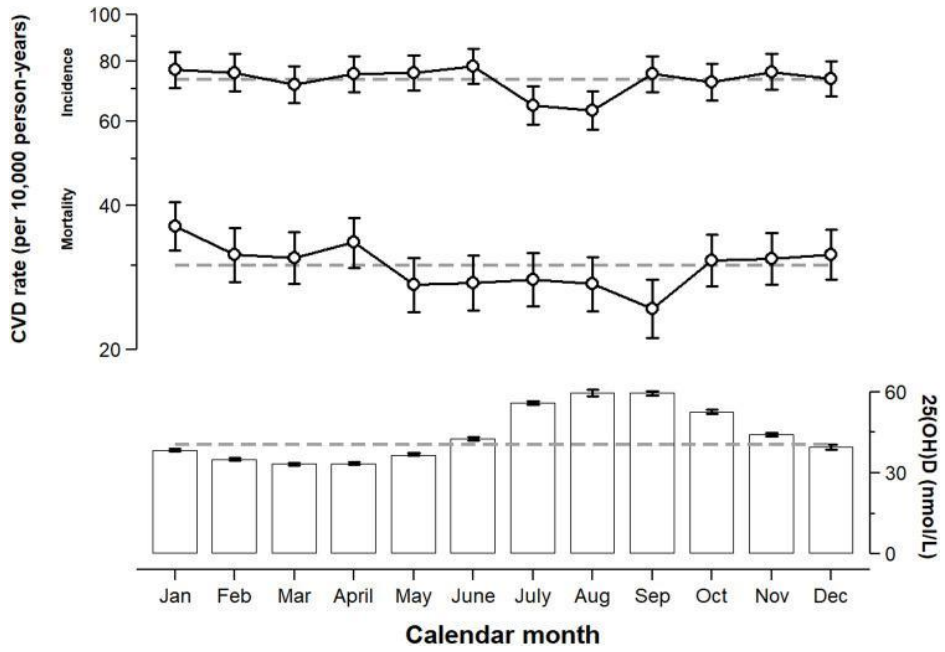
The Association between Serum 25(OH)D Status and Blood Pressure in Participants of a Community-Based Program Taking Vitamin D Supplements

- 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 D supplements to reach a target serum 25(OH)D > 100 nmol/L (40 ng/mL).
- Mirhosseini N, Vatanparast H, Kimball SM. *Nutrients*. 2017;9(11):1244.

The Association between Serum 25(OH)D Status and Blood Pressure in Participants of a Community-Based Program Taking Vitamin D Supplements - 2

- 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

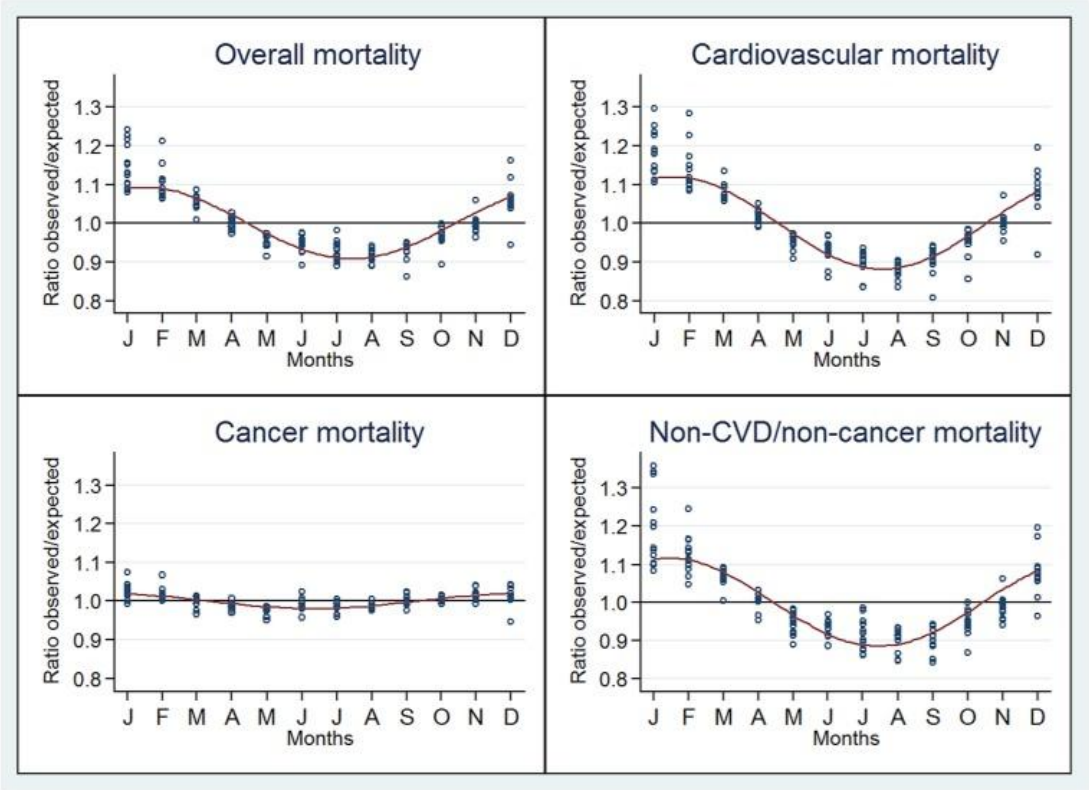
Cardiovascular disease outcomes in relation to 25-hydroxyvitamin D and its seasonal variation: Results from the BiomarCaRE consortium



The January mortality peak is the well-known Year's end holiday celebrations mortality rate increase. The April and September mortality rates show the effect of solar UVB. The highest to lowest CVD mortality rate ratio is significantly higher: (by 8 ± 5 deaths)/10,000 PYs, an increase of 30 ± 20%.

Oskarsson et al. *PLoS One*. 2025;20(4):e0319607.

Seasonal variation of overall and cardiovascular mortality: a study in 19 countries from different geographic locations



Marti-Soler et al. *PLoS One*. 2014;9(11):e113500.

Seasonal variations of U.S. mortality rates: Roles of solar ultraviolet-B doses, vitamin D, gene exp ression, and infections

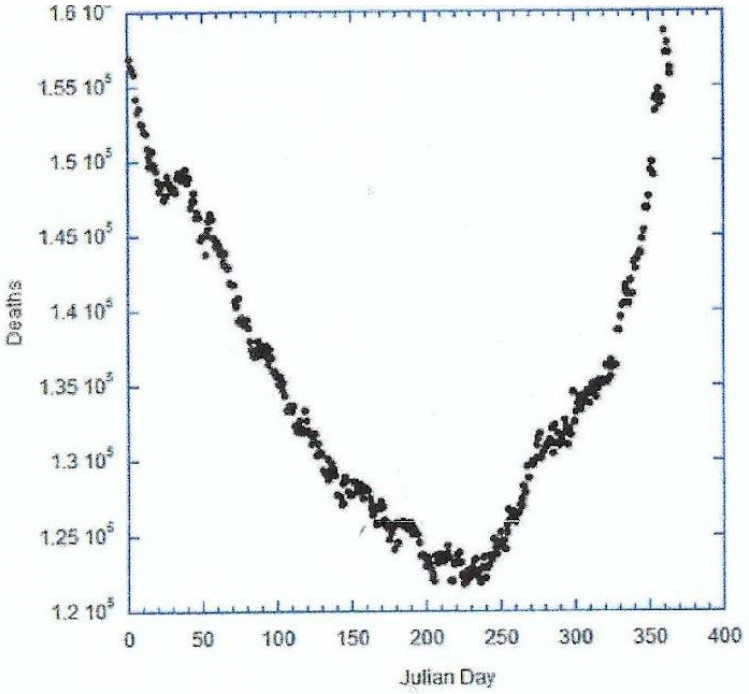


Fig. 1. Deaths per day of the year, according to all official U.S. death certificates for 1979–2004 from Phillips et al. [1].

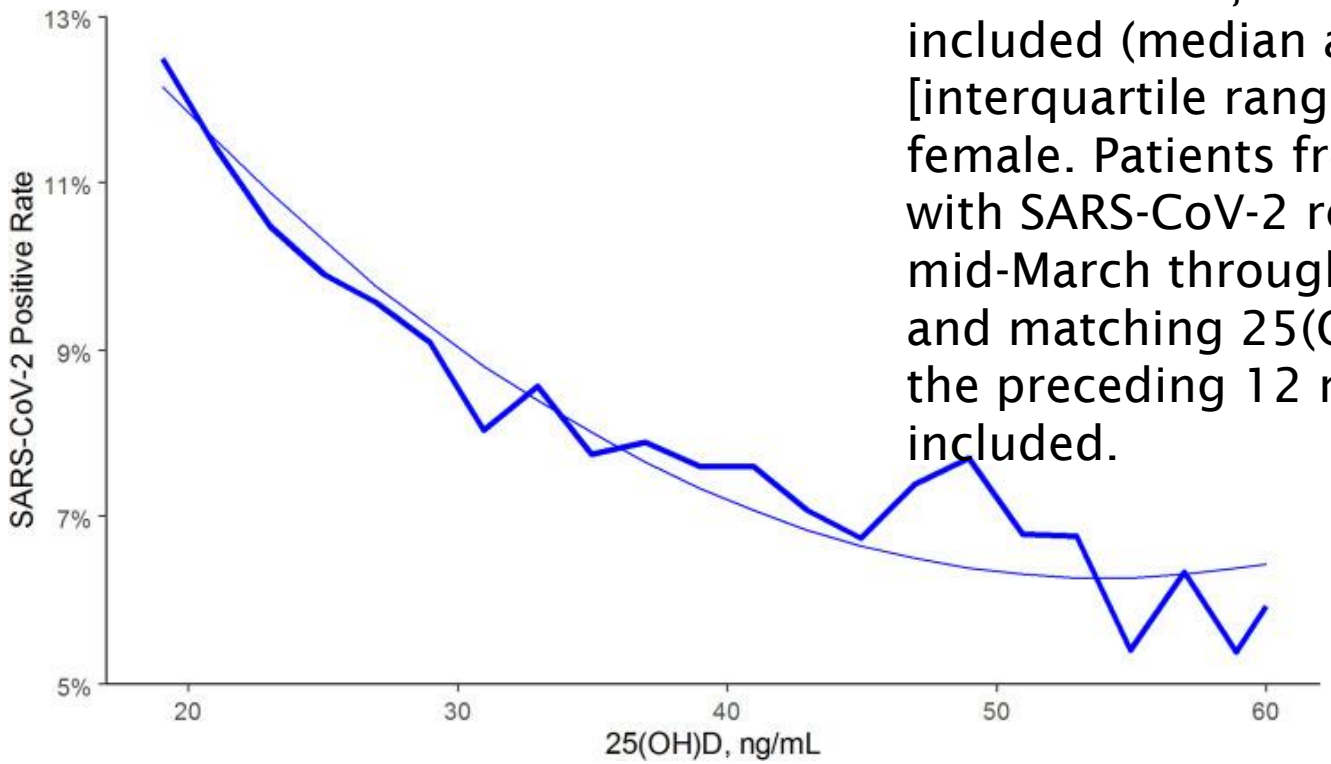
Winter death rates are about 30% higher than summer death rates. The largest contributions are from CVD and infectious diseases. Solar UVB and cold temperatures both contribute. There are also increased death rates at the time students return to school after summer vacation, likely due to infectious diseases.

rant WB, Bhattoa HP, Boucher BJ. *J Steroid Biochem Mol Biol*. 2017;173:5-12.
riginal deaths data from Phillips D, Barker GE, Brewer KM, Christmas and New ear as risk factors for death, *Soc. Sci. Med*. 2010;71(8):1463–1471.

Evidence that Vitamin D Supplementation Could Reduce Risk of Influenza and COVID-19 Infections and Deaths

- Through several mechanisms, vitamin D can reduce risk of infections. Those mechanisms include inducing cathelicidins and defensins that can lower viral replication rates and reducing concentrations of pro-inflammatory cytokines that produce the inflammation that injures the lining of the lungs, leading to pneumonia, as well as increasing concentrations of anti-inflammatory cytokines.
- Grant WB, Lahore H, McDonnell SL, Baggerly CA, French CB, Aliano JL, Bhattoa HP. *Nutrients*. 2020 April 2;12(4):988.

SARS-CoV-2 positivity rates associated with circulating 25-hydroxyvitamin D levels



A total of 191,779 patients were included (median age, 54 years [interquartile range 40.4-64.7]; 68% female. Patients from all 50 states with SARS-CoV-2 results performed mid-March through mid-June, 2020 and matching 25(OH)D results from the preceding 12 months were included.

Kaufman et al. PLoS One. 2020 Sep 17;15(9):e0239252

Vitamin D supplementation and clinical outcomes in COVID-19: a systematic review and meta-analysis

- We identified 13 studies (10 observational, 3 RCTs) pooling data retrieved from 2933 COVID-19 patients. Pooled analysis of unadjusted data showed that vitamin D use in COVID-19 was significantly associated with reduced ICU admission/mortality (OR 0.41, 95% CI: 0.20, 0.81, $p = 0.01$). Similarly, on pooling adjusted risk estimates, vitamin D was also found to reduce the risk of adverse outcomes (pooled OR 0.27, 95% CI: 0.08, 0.91, $p = 0.03$).
- Pal et al. *J Endocrinol Invest*. 2022 Jan;45(1):53-68.

The action of vitamin D in preventing the spread and promoting the arrest of caries in children

- They reported results of another study in which children were given vitamin D_2 (ergocalciferol).
- Those children taking vitamin D_2 had fewer caries and a higher degree of hardening of the enamel.
- The mechanism thought to explain the reduced development of caries was increased calcium absorption and better calcium metabolism.
- However, they noted:
- "… the dentinal tubule may contain microorganisms. These, however, are apparently inactive."
- Of course the anti-microbial properties of vitamin D were unknown at that time.

- Mellanby M. Pattison CL. *British Medical Journal*, 1928

Dental Health First Half 20th Century [Mills, 1937]

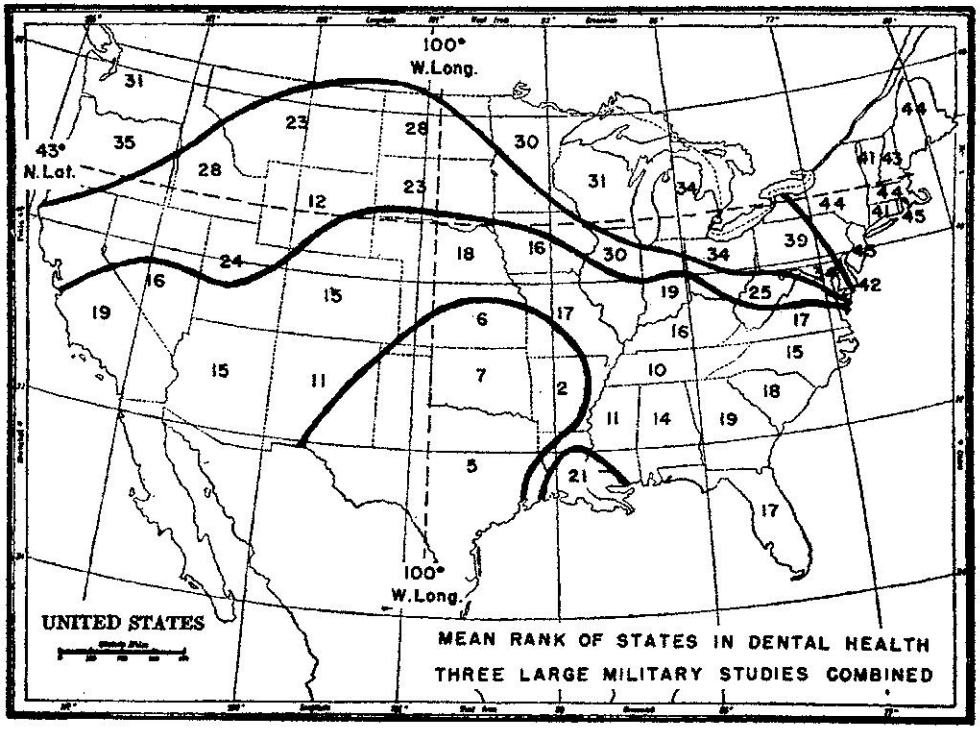


Fig. 1.

A review of the role of solar ultraviolet-B irradiance and vitamin D in reducing risk of dental caries

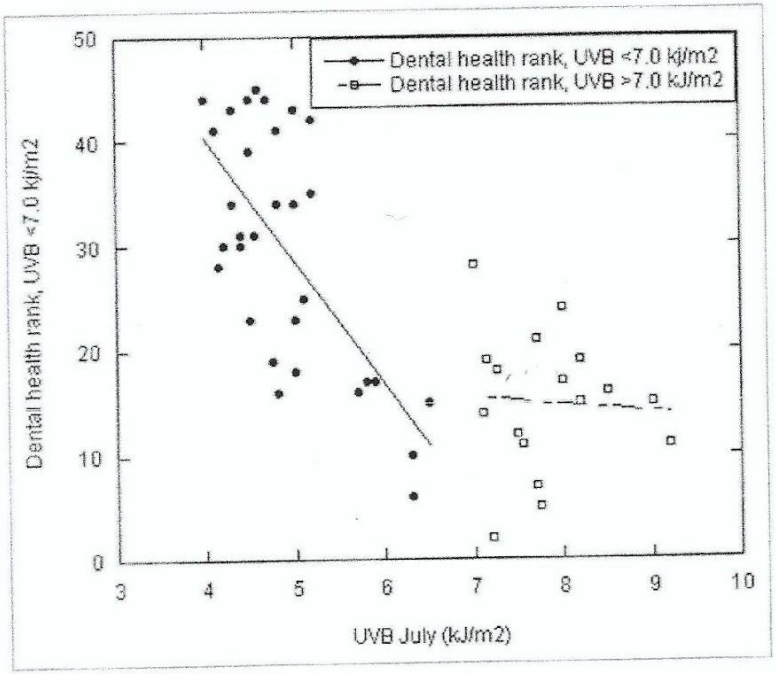
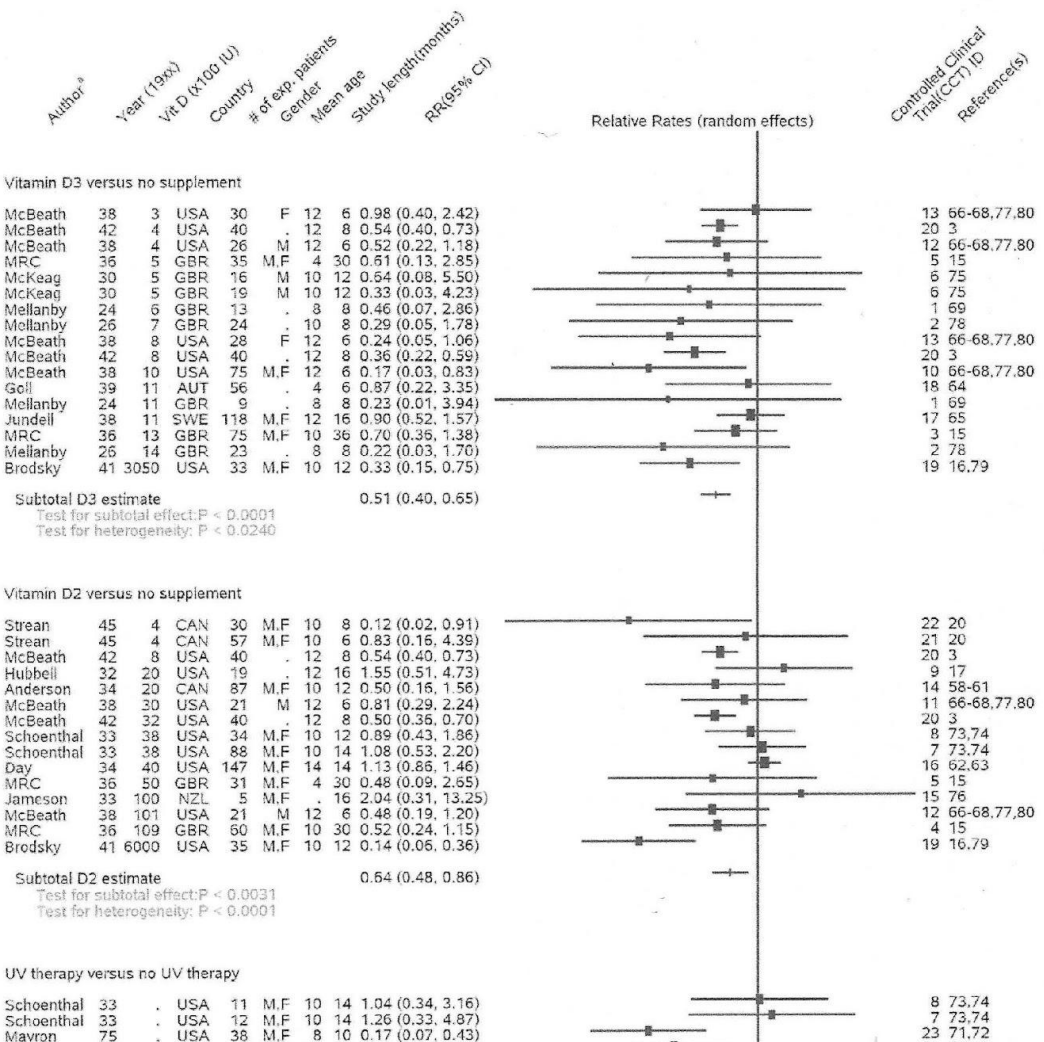


Figure 1. Dental health ranking, by state, for men entering the armed forces during World War I and II15 versus July solar UVB dose.

Grant WB.
Dermato-Endocrinology 2011;3(3)193-198;

Vitamin D and dental caries in controlled clinical trials: systematic review and meta-analysis



Hujoel PP.
Nutrition Reviews
2012;71(2):88–97

Fluoridation of Municipal Water

- T. Hadley Dean conducted his studies of the effectiveness of fluoride in the municipal water supplies in Grand Rapids, Michigan and Wisconsin in the late 1940s, early 1950s.
- This state has some nearly the lowest solar UVB doses in the country.
-

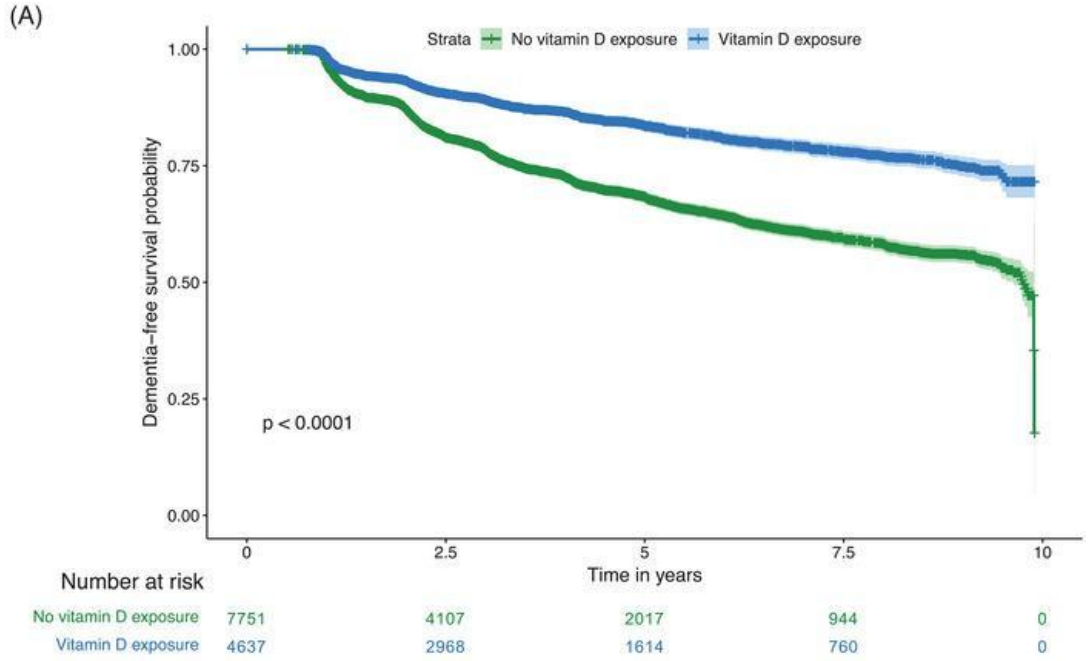
How a Nutritional Deficiency Became Treated with Fluoride

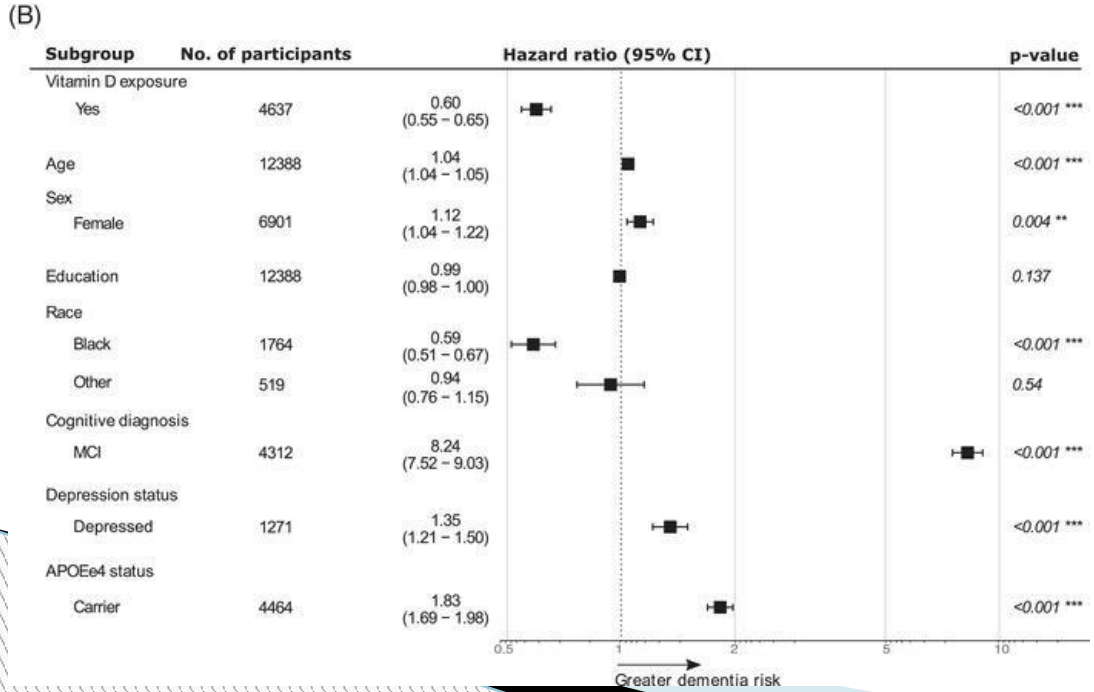
- This report explores how public health experts started to ignore evidence that pediatric vitamin D deficiencies are associated with dental caries. Historical analyses show that an organization of clinical specialists, the American Dental Association (ADA), initiated this view. The ADA was a world-leading organization and its governing bodies worked through political channels to make fluoride a global standard of care for a disease which at the time was viewed as an indicator of vitamin D deficiencies. The ADA scientific council was enlisted in this endeavor and authorized the statement saying that “claims for vitamin D as a factor in tooth decay are not acceptable”.

- Hujoel PP. *Nutrients* **2021**,*13*, 4361

How a Nutritional Deficiency Became Treated with Fluoride 2

- This statement was ghost-written, the opposite of what the ADA scientific council had endorsed for 15 years, and the opposite of what the National Academy of Sciences concluded. Internal ADA documents are informative on the origin of this scientific conundrum; the ADA scientific council had ignored their scientific rules and was assisting ADA governing bodies in conflicts with the medical profession on advertising policies. The evidence presented here suggests that professional organizations of clinical specialists have the power to create standards of care which ignore key evidence and consequently can harm public health.

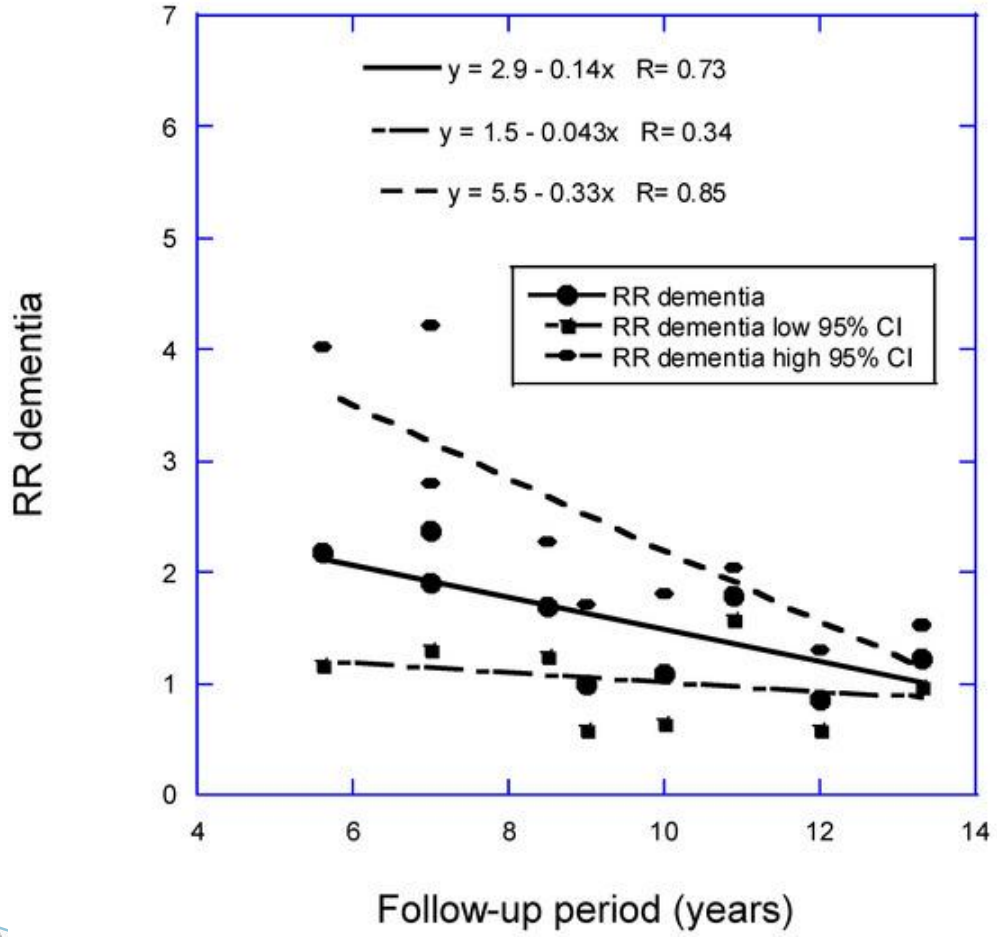




Longitudinal study involving 12,388 dementia-free persons in 40 centers in the US with mean age 71 years at baseline, followed for ten years.
Any vitamin D supplementation vs. none was associated in a 40% reduced risk of dementia (Alzheimer's disease and vascular dementia). Females, those without mild cognitive impairment, and those without ApoE ε4 had greater reductions.

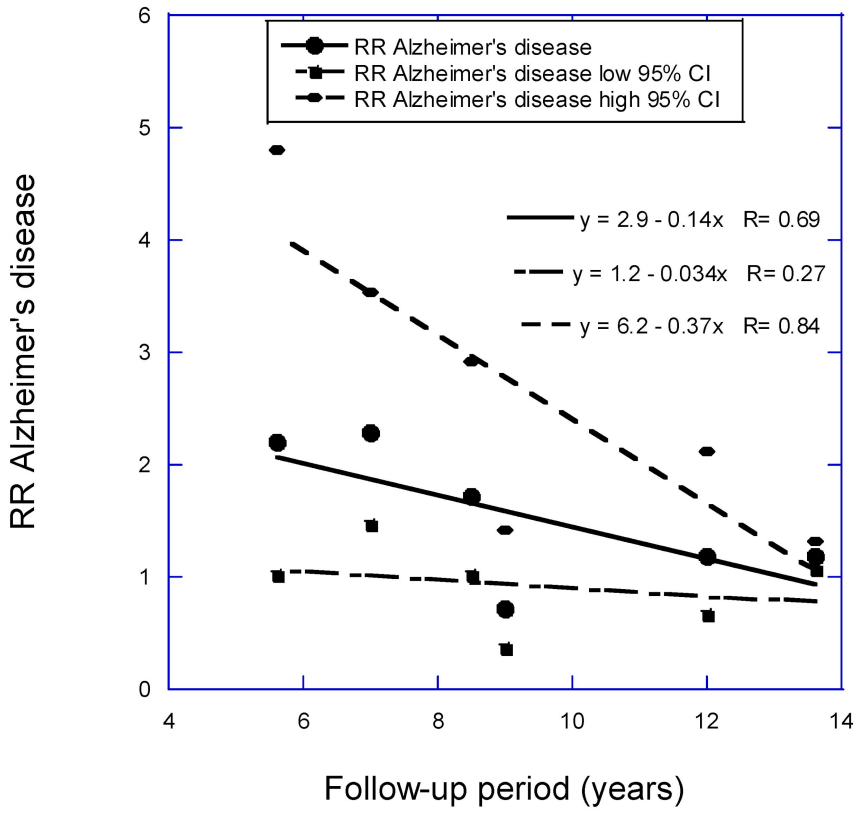
Ghahremani et al**. Vitamin D supplementation and incident dementia: Effects of sex, *APOE*, and baseline cognitive status**
Alzheimers Dement (Amst). 2023;15(1):e12404.

Grant WB. Follow-Up Period Affects the Association between Serum 25-Hydroxyvitamin D Concentration and Incidence of Dementia, Alzheimer's Disease, and Cognitive Impairment. *Nutrients*. 2024; 16(18):3211.



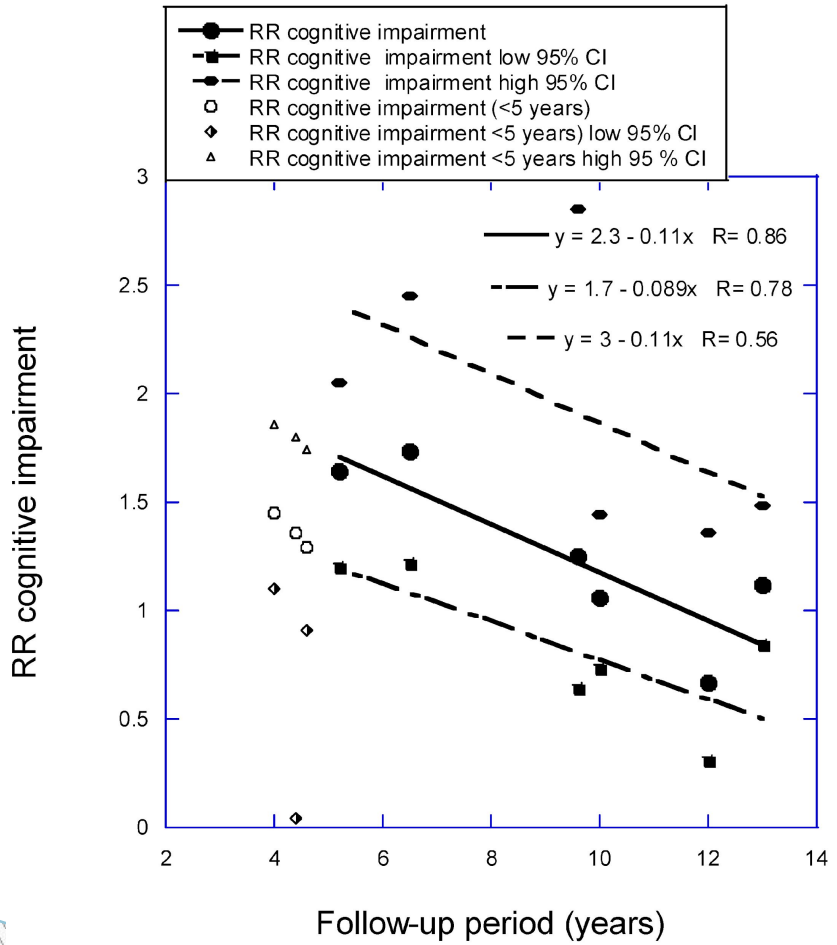
As follow-up period increases, the measured relative risk for dementia for low vs. high 25(OH)D (<25 or 50 nmol/L vs. >50 nmol/L) decreases since 25(OH)D concentrations change with time. The middle line is the regression fit to the RR; the outer two lines are the fit to the 95% confidence interval. The spread is larger for shorter follow-up times due to lower number of events. Above about 12 years, the RR is near 1.0 (i.e., no effect).

Grant WB. Follow-Up Period Affects the Association between Serum 25-Hydroxyvitamin D Concentration and Incidence of Dementia, Alzheimer's Disease, and Cognitive Impairment. *Nutrients*. 2024; 16(18):3211.



Relative risk for Alzheimer's disease for low vs. high 25(OH)D concentration (<25 or 50 nmol/L vs. >50 nmol/L) as a function of follow-up years.

Grant WB. Follow-Up Period Affects the Association between Serum 25-Hydroxyvitamin D Concentration and Incidence of Dementia, Alzheimer's Disease, and Cognitive Impairment. *Nutrients*. 2024; 16(18):3211.



Relative risk for cognitive impairment for low vs. high 25(OH)D concentration (<25 or 50 nmol/L vs. >50 nmol/L) as a function of follow-up years.

Risk Factors for Alzheimer's Disease Affected by Vitamin D

- Inflammation
- Insulin resistance
- Type 2 diabetes mellitus
- Atherosclerosis
- Infections
- Periodontal disease
- Sleep disturbance

Inflammation Context in Alzheimer's Disease, a Relationship Intricate to Define

- Importantly, Amyloid beta (Aβ) and tau species are able to activate astrocytes and microglia, which release several proinflammatory cytokines, such as tumor necrosis factor α (TNF-α) and interleukin 1β (IL-1β), together with reactive oxygen and nitrogen species, triggering neuroinflammation. However, this inflammatory response has a dual function: it can play a protective role by increasing Aβ degradation and clearance, but it can also contribute to Aβ and tau overproduction and induce neurodegeneration and synaptic loss.
- Moreover, diseases related to systemic or local inflammation, including infections, cerebrovascular accidents, and obesity, have been proposed as risk factors for the development of AD.
- Novoa et al. *Biol Res*. 2022;55(1):39.

Vitamin D as a Modulator of Neuro-inflammation: Implications for Brain Health

- Vitamin D's mechanisms of action include cytokine modulation and regulation of nuclear and mitochondrial genes. It adjusts inflammatory mediators and antioxidants, resulting in neuroprotective effects. Additionally, vitamin D impacts neurotransmitter synthesis and brain plasticity.
- Menéndez SG, Manucha W. *Curr Pharm Des*. 2024;30(5):323-332.

Insulin Resistance and Alzheimer's

- Insulin and insulin-like growth factor-1 receptors are expressed on all cell types in the central nervous system. Insulin is known to regulate glucose metabolism, support cognition, enhance the outgrowth of neurons, modulate the release and uptake of catecholamine, and regulate the expression and localization of gamma-aminobutyric acid. Insulin is also able to freely cross the blood–brain barrier from the circulation. In addition, changes in insulin signaling, caused *inter alia* insulin resistance, may accelerate brain aging, and affect plasticity and possibly neurodegeneration.
- Sędzikowska A, Szablewski L. Insulin and Insulin Resistance in Alzheimer's Disease. *Int J Mol Sci*. 2021; 22(18):9987.

Insulin Resistance

- Insulin resistance occurs when body cells fail to respond properly to insulin, forcing the pancreas to produce excess insulin to manage blood sugar, often leading to prediabetes and type 2 diabetes. Key symptoms include fatigue, increased hunger/thirst, belly fat, and skin tags. It is primarily caused by obesity, inactivity, and genetics, and treated through diet, exercise, and medication

How Vitamin D Reduces Insulin Resistance

- One of the molecular mechanisms by which vitamin D participates in insulin secretion by pancreatic β-cells is the regulation of intracellular Ca2+ concentration.
- It has also been observed that vitamin D might decrease insulin resistance indirectly via the renin-angiotensin-aldosterone system (RAAS).
- Vitamin D mediated increase in insulin sensitivity occurs via binding of 1,25(OH)2D (calcitriol) to vitamin D receptors.

- Szymczak-Pajor et al. *Int J Mol Sci*. 2020;21(18):6644.

Type 2 Diabetes Mellitus (T2DM)

- People with T2DM have a 30% increased risk of developing Alzheimer's disease.
- Athanasaki et al. *Biomedicines*, 2022:*10*(4), 778.
- It may be due to effects of T2DM or due to having shared risk factors.
- Hamzé et al. Type 2 Diabetes Mellitus and Alzheimer's Disease: Shared Molecular Mechanisms and Potential Common Therapeutic Targets. *Int J Mol Sci*. 2022; 23(23):15287.

Association between Atherosclerosis and Alzheimer's Disease: A Systematic Review and Meta-analysis

- Atherosclerosis is a disease of the arteries characterized by the deposition of plaques of fatty material on their inner walls.
- Atherosclerosis is associated with many vascular factors, such as hypertension, diabetes mellitus, dyslipidemia, and smoking.
  An analysis of the prevalence of atherosclerosis was made for ten studies (1,698 cases and 6,452 controls). Compared with controls, AD group showed a significantly higher prevalence of atherosclerosis (OR = 1.46; 95% CI, 1.26–1.68).
- Xie et al. *Brain Behav.* 2020;10(4):e01601

How Vitamin D Reduces Risk of Atherosclerosis

- **Vitamin D supplementation lowers the levels of total cholesterol, triglycerides, and LDL-cholesterol and increases the levels of HDL-cholesterol. Vitamin D is also involved in the development of atherosclerosis at the site of the blood vessels.** Deficiency of this vitamin has been found to increase adhesion molecules or endothelial activation and, at the same time, supplementation is linked to the lowering presence of adhesion surrogates. Vitamin D can also influence the vascular tone by increasing endothelial nitric oxide production. Deficiency can lead, at the same time, to oxidative stress and an increase in inflammation as well as the expression of particular immune cells that play a pivotal role in the development of atherosclerosis in the intima of the blood vessels, i.e., monocytes and macrophages. Vitamin D is also involved in atherogenesis through inhibition of vascular smooth muscle cell proliferation.
- Surdu AM, et al. Vitamin D and Its Role in the Lipid Metabolism and the Development of Atherosclerosis. *Biomedicines*. 2021; 9(2):172.

Infectious Agents and Alzheimer's Disease

- Recent reports have shown that viruses (e.g., Herpes simplex type 1, 2, 6A/B; human cytomegalovirus, Epstein-Barr virus, hepatitis C virus, influenza virus, and severe SARS-CoV-2), bacteria, as well as eukaryotic unicellular parasites (e.g., *Toxoplasma gondii*) may factor into cognitive decline within the context of AD. Microorganisms may trigger pathological changes in the brain that resemble and/or induce accumulation of Aβ peptides and promote tau hyperphosphorylation. Further, the mere presence of infectious agents is suspected to induce both local and systemic inflammatory responses promoting cellular damage and neuronal loss.
- Piekut et al. *J Integr Neurosci*. 2022;21(2):73.

Vitamin D Reduces Risk of Infections and Infectious Diseases

- Re: antiviral activity of vitamin D in a lung epithelial cell. These mechanisms include induction of cathelicidin antimicrobial peptide (CAMP) expression as well as $1,25(OH)_2D$-mediated suppression of inflammatory cytokines IL-5 and IFN-γ, ICAM-1, and PAFR. The mature form of CAMP, LL37, binds to viral dsRNA, which enables efficient binding to endosomal toll-like receptor 3 (TLR3), augmenting TLR3 signaling and subsequent viral clearance. An additional mechanism for viral removal is the induction of autophagy by $1,25(OH)_2D$.
- Ismailova A, White JH. *Rev Endocr Metab Disord.* (2022) 23:265–277

Analysis the Link between Periodontal Diseases and Alzheimer's Disease: A Systematic Review

- Five studies were included. The selected studies described in their results an increase in the bacterium *F. nucleatum* in Alzheimer's disease patients (adjusted $p = 0.02$), and its incidence was linked to two bacteria, *C. rectus* and *P. gingivalis* (adjusted HR = 1.22 [1.04-1.43]) as well as *A. naeslundii* (crude HR = 2.0 [1.1-3.8]). The presence of periodontitis at baseline was associated with a six-fold increase in the rate of cognitive decline over a 6-month follow-up period. The current review suggests an association between periodontal disease and Alzheimer's disease. The treatment of periodontal disease could be a way to explore Alzheimer's disease prevention.
- Borsa et al. *Int J Environ Res Public Health*. 2021;18(17):9312.

Vitamin D Reduces Risk of Periodontal Disease - Mechanisms

- Modulation of microbial biofilm
- Immunomodulation
- Regulation of T-cell function
- Promotion of epithelial barrier integrity
- Inhibition of osteoelastogenesis
- Reduction in oxidative stress
- Reductions ins systemic and local inflammation
- Moszura et al. *Nutrients* **2026**, *18*(4), 577

Sleep Disorders Increase the Risk of Dementia, Alzheimer's Disease, and Cognitive Decline: a Meta-analysis

- Studies reporting risk estimates for dementia, AD, or cognitive decline associated with obstructive sleep apnea, insomnia, and other sleep disorders (e.g., restless legs syndrome, circadian rhythm sleep disorders, excessive daytime sleepiness) were included. Meta-analyses were performed. Thirty-nine cohort studies were included, with subgroup analyses showing significant associations between all-cause dementia and obstructive sleep apnea (HR 1.33, 95% CI 1.09–1.61), insomnia (HR 1.36, 95% CI 1.19–1.55), and other sleep disorders (HR 1.33, 95% CI 1.24–1.43). Obstructive sleep apnea increased the risk for AD (HR 1.45, 95% CI 1.24–1.69), though its association with vascular dementia did not reach statistical significance (HR 1.35, 95% CI 0.99–1.84). Insomnia was significantly associated with increased risk for both vascular dementia (HR 1.59, 95% CI 1.01–2.51) and AD (HR 1.49, 95% CI 1.27–1.74).
- Ungvari et al. *Geroscience.* 2025.

Vitamin D Reduces Risk of Sleep Disturbance

- Over an average follow-up of 13 years, we documented 2,704 cases of sleep disorders and found that higher serum 25(OH)D concentrations were significantly associated with reduced sleep disorder risk. In fully adjusted models, sufficient serum 25(OH)D concentrations reduced sleep disorder risk by 48% in prediabetes (HR = 0.52; 95% CI: 0.41-0.65) and 52% in diabetes (HR = 0.48; 95% CI: 0.34-0.67). Subgroup analysis found that adequate 25(OH)D concentrations were associated with improved sleep health especially in people ≤60 years of age, women, BMI≥30 kg/m², and those who had never smoked.
- Liu et al. *Front Endocrinol (Lausanne).* 2025:16:1524368.

Vitamin D Protects against Depression: Evidence from an Umbrella Meta-analysis

- Ten meta-analyses of randomised controlled trials (RCTs) revealed significant reduction in depression symptoms comparing participants on vitamin D supplements to those on placebo (Pooled standardised mean difference: - 0.40; 95 % CI: - 0.60, - 0.21).
- Four meta-analyses of cohort studies (with one having two subgroups) revealed that participants with lower levels of serum vitamin D were at increased odds of depression than those with higher levels of serum vitamin D (Pooled odds ratio: 1.60; 95 % CI: 1.08, 2.36).
- Musazadeh et al. *Pharmacol Res*. 2023:187:106605

Sun Exposure for Vitamin D Production

- Approximately 80-90% of serum 25(OH)D concentrations are thought to be from solar UVB.
- In the US, food provides about 250 IU/day.
- As mentioned earlier, vitamin D production is most efficient when the sun's elevation is high enough that one's shadow is shorter than one's height.
- Most people can develop a tan that blocks 50 to 75% of the UV. Thus, people should consider spending some time in the sun every day in spring or summer to gradually develop the tan.

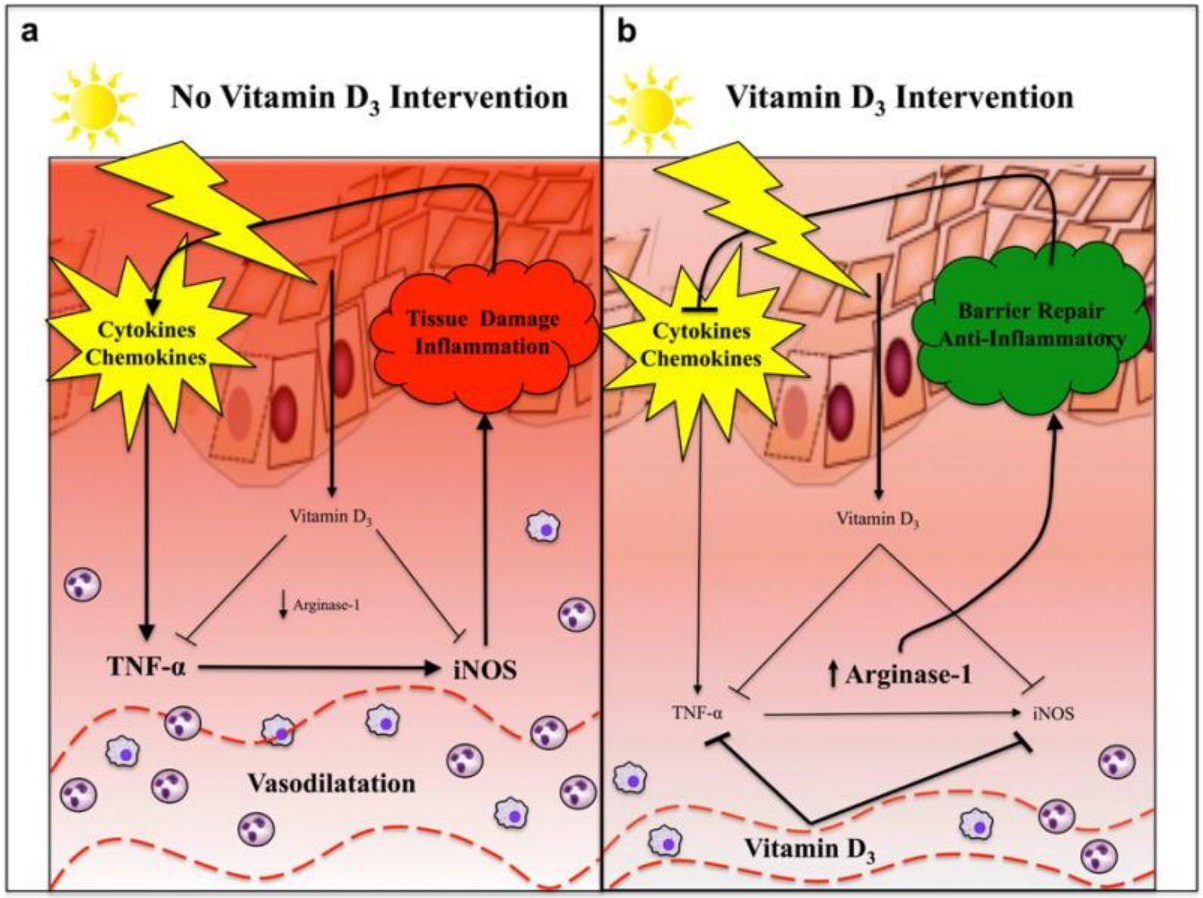
Oral Vitamin D Rapidly Attenuates Inflammation from Sunburn: An Interventional Study

- 20 healthy adults were randomized to receive either placebo or a high dose of vitamin D_3 (cholecalciferol) one hour after experimental sunburn induced by an erythemogenic dose of UVR. Compared with placebo, participants receiving vitamin D_3 (200,000 international units) demonstrated reduced expression of proinflammatory mediators tumor necrosis factor-α ($P = 0.04$) and inducible nitric oxide synthase ($P = 0.02$) in skin biopsy specimens 48 hours after experimental sunburn.
- Scott JF et al. *J Invest Dermatol.* 2017;137(10):2078-2086.

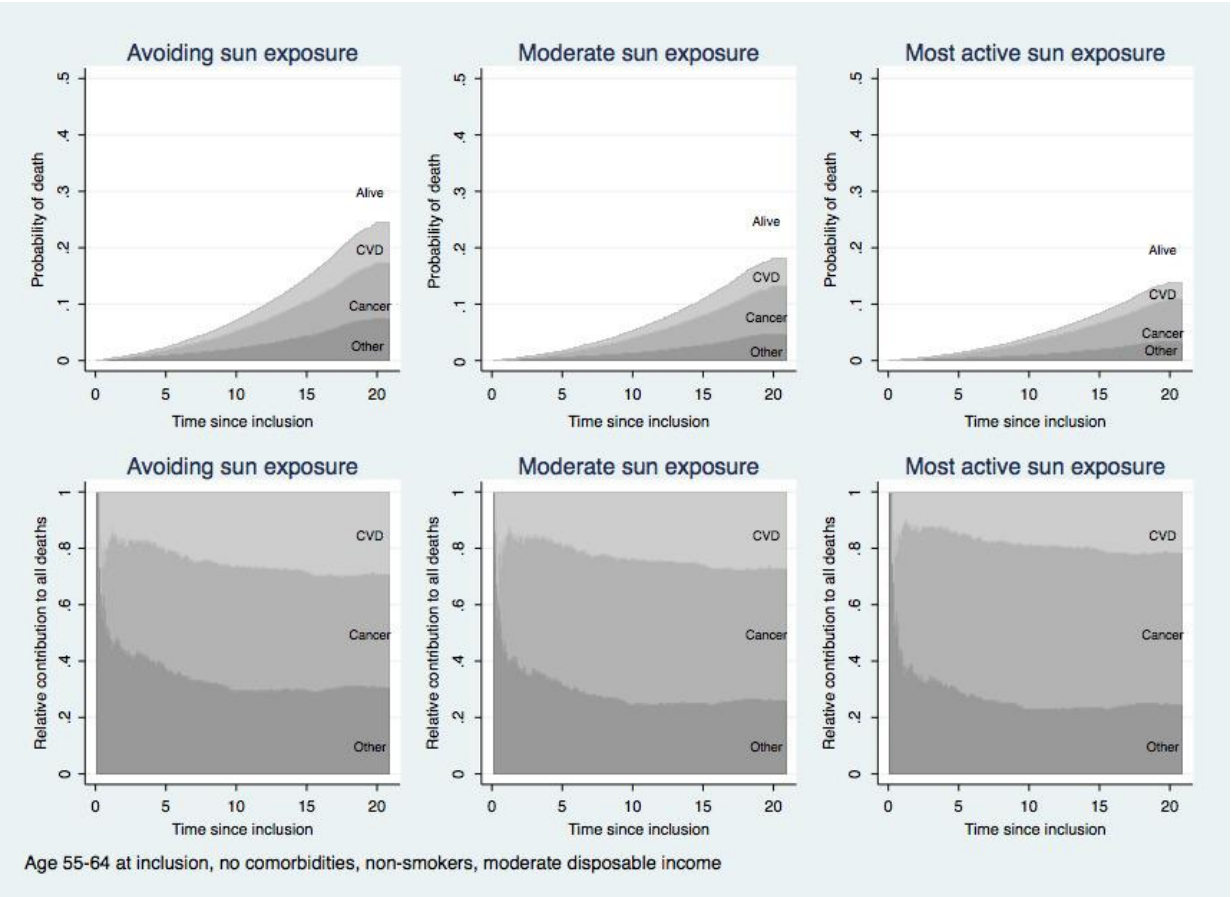
Oral Vitamin D Rapidly Attenuates Inflammation from Sunburn: An Interventional Study

- A blinded, unsupervised hierarchical clustering of participants based on global gene expression profiles revealed that participants with significantly higher serum vitamin D_3 levels after treatment ($P = 0.007$) demonstrated increased skin expression of the anti-inflammatory mediator arginase-1 ($P = 0.005$), and a sustained reduction in skin redness ($P = 0.02$), correlating with significant expression of genes related to skin barrier repair. In contrast, participants with lower serum vitamin D_3 levels had significant expression of proinflammatory genes.

Oral Vitamin D Rapidly Attenuates Inflammation from Sunburn: An Interventional Study



Avoidance of sun exposure as a risk factor for major causes of death: a competing risk analysis of the Melanoma in Southern Sweden cohort



29 518 Swedish women in a prospective 20-year follow-up of the Melanoma in Southern Sweden (MISS) cohort. Women were recruited from 1990 to 1992 (aged 25-64 years at the start of the study).
Women with active sun exposure habits were mainly at a lower risk of cardiovascular disease (CVD) and noncancer/ non-CVD death as compared to those who avoided sun exposure.

Lindqvist PG, et al. *J Intern Med*. 2016;280(4):375-87.

T A B L E 1 Estimated number of new cancer cases and deaths by sex, United States, 2026.

- Estimated New Cases Estimated Deaths
  Male Female Male Female
  All sites 1,094,070 1,020,780 327,290 298,85
- (10% reduction in cancer from UVB/vitamin D)
  -109.000 -102,000 -33,000 -30,000
- Skin (excluding basal & squamous carcinoma)
  - 70,590 49,160 9850 4720

- Siegel RL et al. Cancer statistics, 2026.
- *CA Cancer J Clin*. 2026;e70043.

Sunlight: Time for a Rethink?

- UVR is a skin carcinogen, yet no studies link sun exposure to increased all-cause mortality. Epidemiological studies from the United Kingdom and Sweden link sun exposure with reduced all-cause, cardiovascular, and cancer mortality. Vitamin D synthesis is dependent on UVB exposure. Individuals with higher serum levels of vitamin D are healthier in many ways, **yet multiple trials of oral vitamin D supplementation show little benefit**. Growing evidence shows that sunlight has health benefits through vitamin D-independent pathways, such as photomobilization of nitric oxide from cutaneous stores with reduction in cardiovascular morbidity. Sunlight has important systemic health benefit as well as risks.
- Richard Weller, J Invest Dermatol. 2024;144(8):1724-1732.

Vitamin D prevents or treats 99 health problems

- **ADHD, Alcoholic Liver Cirrhosis, ALS, Alzheimer's, Antibiotic Use in Seniors, Asthma, Autism, Autoimmune Diseases, Back pain, Blood Cell Cancer, Breast Cancer, Cardiovascular, Cholesterol, Chronic Hives, Chronic Kidney Disease, Cluster Headaches, Congestive Heart Failure (Infants), COPD, Crohn's Disease, C-Section and Pregnancy Risks, Cystic Fibrosis, Dengue Fever, Depression, Diabetes, Diabetic Neuropathy, Eczema, Epilepsy, Falls, Fatigue, Fatty Liver (Child), Fibromyalgia, Gestational Diabetes, Gingivitis, Growing Pains, Hay Fever, Heart Attack, Hemodialysis, Hepatitis-C, Hip Fractures, Hypertension, ICU survival, Influenza, Irritable Bowel Syndrome, Ischemic Stroke, Knee Osteoarthritis, Leg Ulcers, Long-COVID, Low Birth Weight, Lupus, Male Infertility, Menstrual Pain, Metabolic Syndrome, Middle Ear Infection (Infants), Mite Allergy, Multiple Sclerosis, Non-Alcoholic Fatty Liver Disease, Osteoarthritis, Parkinson's Disease, Perinatal Depression, Pneumonia (Ventilator-associated), Poor Sleep, PreDiabetes, Preeclampsia, Pre-term Birth, Prostate Cancer, Psoriasis, Quality of Life, Raynaud's Pain, Respiratory Tract Infection, Restless Leg Syndrome, Rheumatoid Arthritis, Rickets, Sarcopenia, Sepsis, Short Neonates, Sickle Cell, Stronger Senior Muscles, Survive ICU, TB, Tonsillitis, Trauma Death, Traumatic Brain Injury, Tuberculosis, Ulcerative Colitis, Urinary Tract Infection, Vaginosis, Vertigo, Warts, Weight Loss**
- **Henry Lahore, https://vitamindwiki.com/pages/proof-that-vitamin-d-works/**

Physiological Basis for Using Vitamin D to Improve Health

- Maintaining the population's vitamin D sufficiency (above 40 ng/mL) with vitamin D_3 supplements and/or daily sun exposure is the most cost-effective way to reduce chronic diseases and sepsis, overcome viral epidemics and pandemics like COVID-19, and reduce healthcare costs. Furthermore, vitamin D sufficiency improves overall health, reduces absenteeism, improves productivity, reduces the severity of chronic diseases such as metabolic and cardiovascular diseases and cancer, decreases all-cause mortality, and minimizes infection-related complications such as sepsis and COVID-19-related hospitalizations and deaths. Properly using vitamin D is the most cost-effective way to reduce chronic illnesses, infections, and healthcare costs; thus, it should be a part of routine clinical care.
- Wimalawansa SJ. *Biomedicines*. 2023; 11(6):1542.

Vitamin D: Evidence-Based Health Benefits and Recommendations for Population Guidelines - 1

- Vitamin D offers numerous under-recognized health benefits beyond its well-known role in musculoskeletal health. It is vital for extra-renal tissues, prenatal health, brain function, immunity, pregnancy, cancer prevention, and cardiovascular health. Existing guidelines issued by governmental and health organizations are bone-centric and largely overlook the above mentioned extra-skeletal benefits and optimal thresholds for 25(OH)D. In addition, they rely on RCTs, which seldom show benefits due to high baseline 25(OH)D concentrations, moderate supplementation doses, and flawed study designs.
- Grant, et al. *Nutrients*. 2025;17(2):277.

Vitamin D: Evidence-Based Health Benefits and Recommendations for Population Guidelines - 2

- This review emphasizes the findings from prospective cohort studies showing that higher 25(OH)D concentrations reduce the risks of eight major diseases and mortality, including pregnancy and birth outcomes.
- Raising 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: heart disease, cancer, COVID-19, stroke, chronic lower respiratory diseases, Alzheimer's disease and other dementias, diabetes mellitus, and kidney disease.

Vitamin D: Evidence-Based Health Benefits and Recommendations for Population Guidelines - 3

- Serum 25(OH)D concentrations above 30 ng/mL (75 nmol/L) are achievable for many people through daily supplementation with 2000 IU/day (50 mcg/day) of vitamin D_3, perhaps 4000–5000 IU/day for those obese. Furthermore, a daily dose between 4000 and 6000 IU of vitamin D_3 to achieve serum 25(OH)D levels between 40 and 70 ng/mL (100 – 175 nmol/L) would provide greater protection against many adverse health outcomes.
- Note, if a person has not been supplementing with vitamin D, a bolus dose (e.g., 10,000 IU/day for 10-15 days) could be used to rapidly increase 25(OH)D.

I Recommend Having Your 25(OH)D Concentration Measured

- That is a good way to determine how much vitamin D supplementation or sun exposure is required to reach your 25(OH)D concentration goal.
- 25(OH)D can be measured using wet blood or dried blood spots.
- Could be included in annual physical exams.
- Can be ordered online as well.

For More Information

- Search Google Scholar (Scholar.google.com)
- https://vitamindwiki.com/
- VitaminDWiki continues to be the world's most comprehensive website on Vitamin D. It has >14,400 curated pages of evidence-based studies, overviews, charts, and meta-analyses. (Click here for 340+ diseases and health topics related to Vitamin D).
- https://www.grassrootshealth.net/