High-dose Vitamin D Supplementation Improves Health (Presented in Rome, August 30, 2021)

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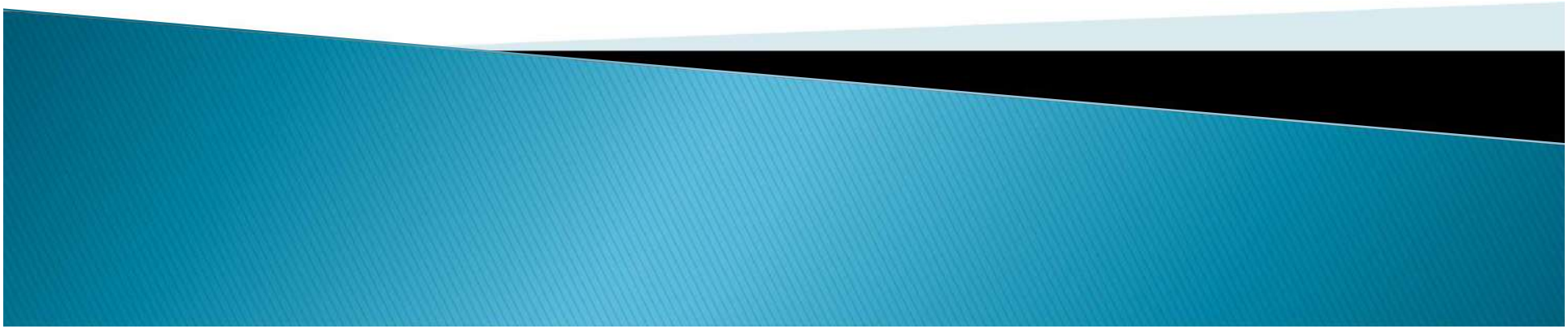


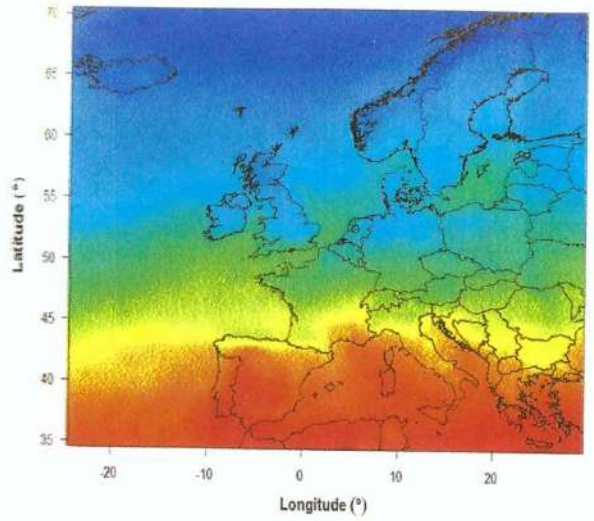
Presented at:

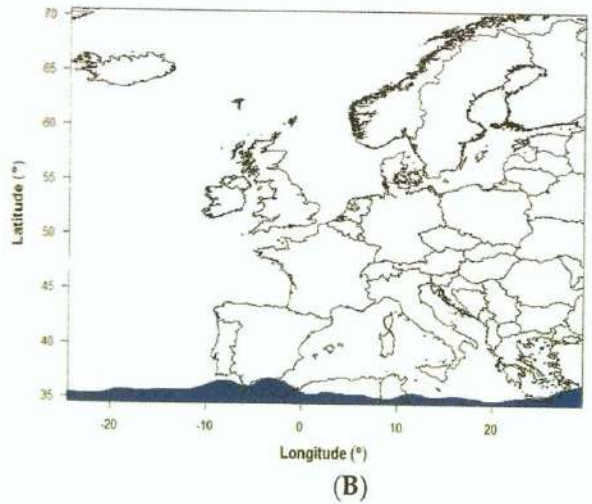
- IV International Vitamin D Mediterranean Congress
- Grand hotel Flora, Rome
-
- Monday August 30, 2021
- https://www.aicgroup.it/iv-international-vitamin-d-mediterranean-congress-rome-30-31-august-2021

Disclosure

- Sunlight, Nutrition and Health Research Center receives funding from Bio-Tech Pharmacal (Fayetteville, AR, USA), a supplier of vitamin D supplements.

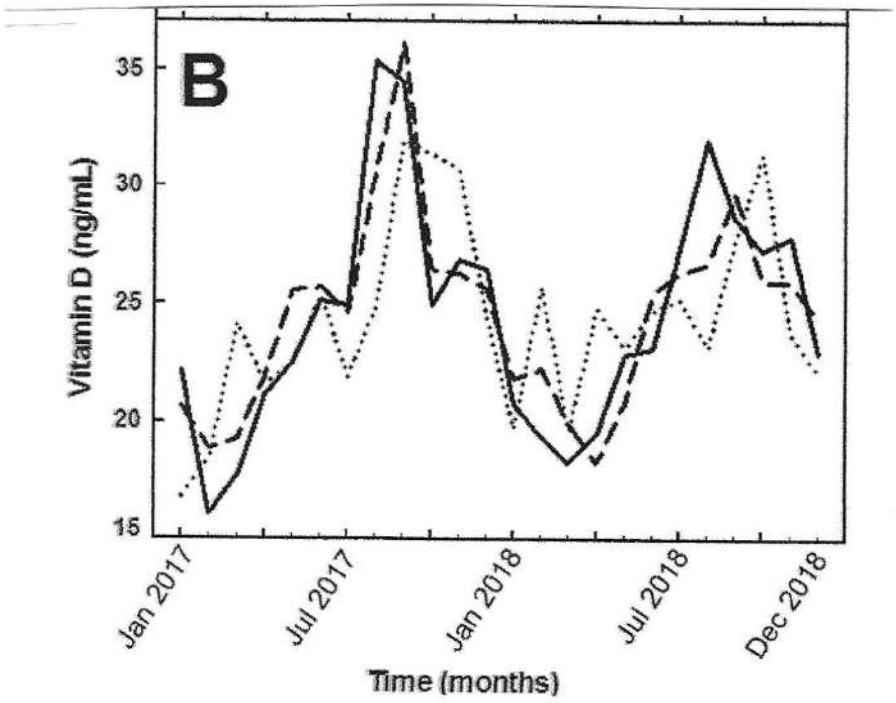
In June some Europeans get more solar UVB than others.
In December no European gets enough UVB to make vitamin D.





O'Neill CM, ….Webb AR, Cashman KD. Nutrients. 2016
https://www.mdpi.com/resolver?pii=nu8090533

Seasonal Variation of 25(OH)D_3 in Milan for Males



Ferrari, Photochem & Photobiol Sci, 2019
https://is.gd/Ul7EYy

In summer, 25(OH)D reaches 35 ng/ml, dropping to 15-20 ng/ml in winter.

One can make 10,000 to 25,000 IU/day in sunlight with full body exposure [Holick, 1993].

However,
Sunlight regulates the cutaneous production of vitamin D_3 by causing its photodegradation.
Webb, DeCosta, Holick.
J Clin Endocrinol Metab.
1989 May;68(5):882-7.
https://is.gd/EezVst

Solar UVB as a Source of Vitamin D

- Solar UVB is an important source of vitamin D.
- Vitamin D production depends on solar elevation angle. If one's shadow is the same length as one's height, vitamin D cannot be produced.
- Many factors affect vitamin D production from UVB such as clothing, time of day, skin pigmentation, age, use of sunblock, etc.
- Thus, solar UVB should not be the only source of vitamin D.

Health Effects Related to Solar UVB

- Solar UVB in summer reduces risk of many types of cancer with little seasonal dependence on incidence other than for breast cancer.

- Diseases with higher rates in winter than summer due to lower vitamin D include cardiovascular disease and many infectious diseases such as influenza and COVID-19.

Solar UVA (320–400 nm)

- Ultraviolet A (UVA) radiation induces release of cutaneous photolabile nitric oxide (NO) impacting the cardiovascular system (lowers blood pressure) and metabolic syndrome, both COVID-19 risk factors. NO also inhibits the replication of SARS-CoV2.
- Cherrie, Weller et al. Br J Dermatol. 2021 Aug; 185(2):363-370. https://is.gd/ZPruoU
- Gorman & Weller. Front Cardiovasc Med. 2020 Dec 23;7:616527. https://is.gd/Ck3qlH

Other Sources of Vitamin D

- Food: you cannot eat your way to a healthy level of vitamin D. However, meat and fish eaters have higher 25(OH)D than vegetarians and vegans in the UK.

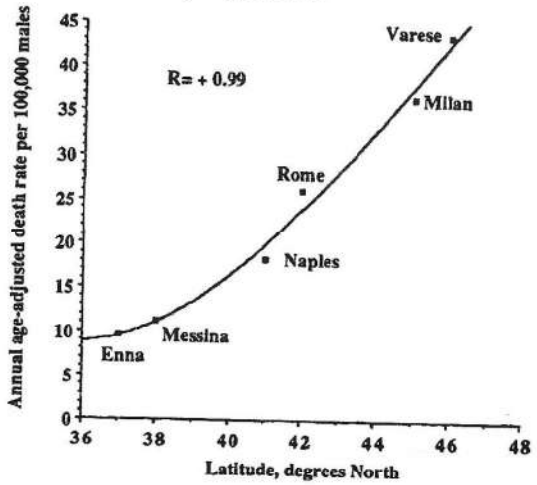
- Supplements are available, safe, inexpensive and can be taken when the sun shines, and when it doesn't. Only supplementation can reliably provide robust blood levels of 25(OH)D year-round.

Cancer

- Solar UVB and vitamin D reduce risk of 15-20 types of cancer.

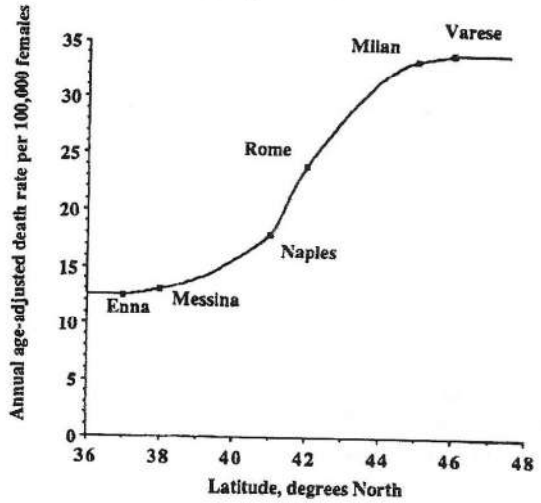
- Evidence comes from:
  - Ecological studies (historically very important)
  - Observational studies
  - Vitamin D supplementation studies
  - Studies of mechanisms of vitamin D

Figure 1. Death rates from colorectal cancer, by latitude, males, Italy, 1975-1977



Death rates for males

Figure 2. Death rates from colorectal cancer, by latitude, females, Italy, 1975-1977



Death rates for females
Colorectal Cancer Death Rates, Italy, 1975-77 [Garland, 1992]

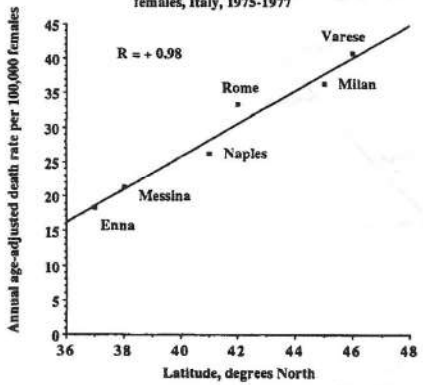
Sunlight, vitamin D, and mortality from breast and colorectal cancer in Italy: Biologic Effects of Light
CF Garland, FC Garland, ED Gorham, J Raffa - 1992 - New York: Walter de Gruyter & Co

https://is.gd/uLlm1y

Breast Cancer Mortality Rates, 1995-77 [Garland, 1992]

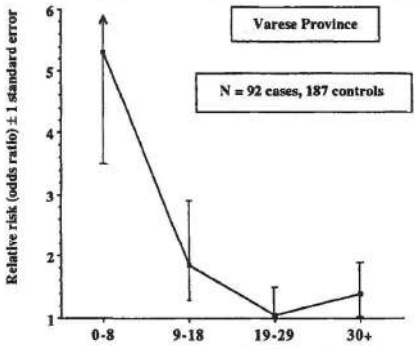
42

Figure 3. Death rates from breast cancer, by latitude, females, Italy, 1975-1977



Latitude

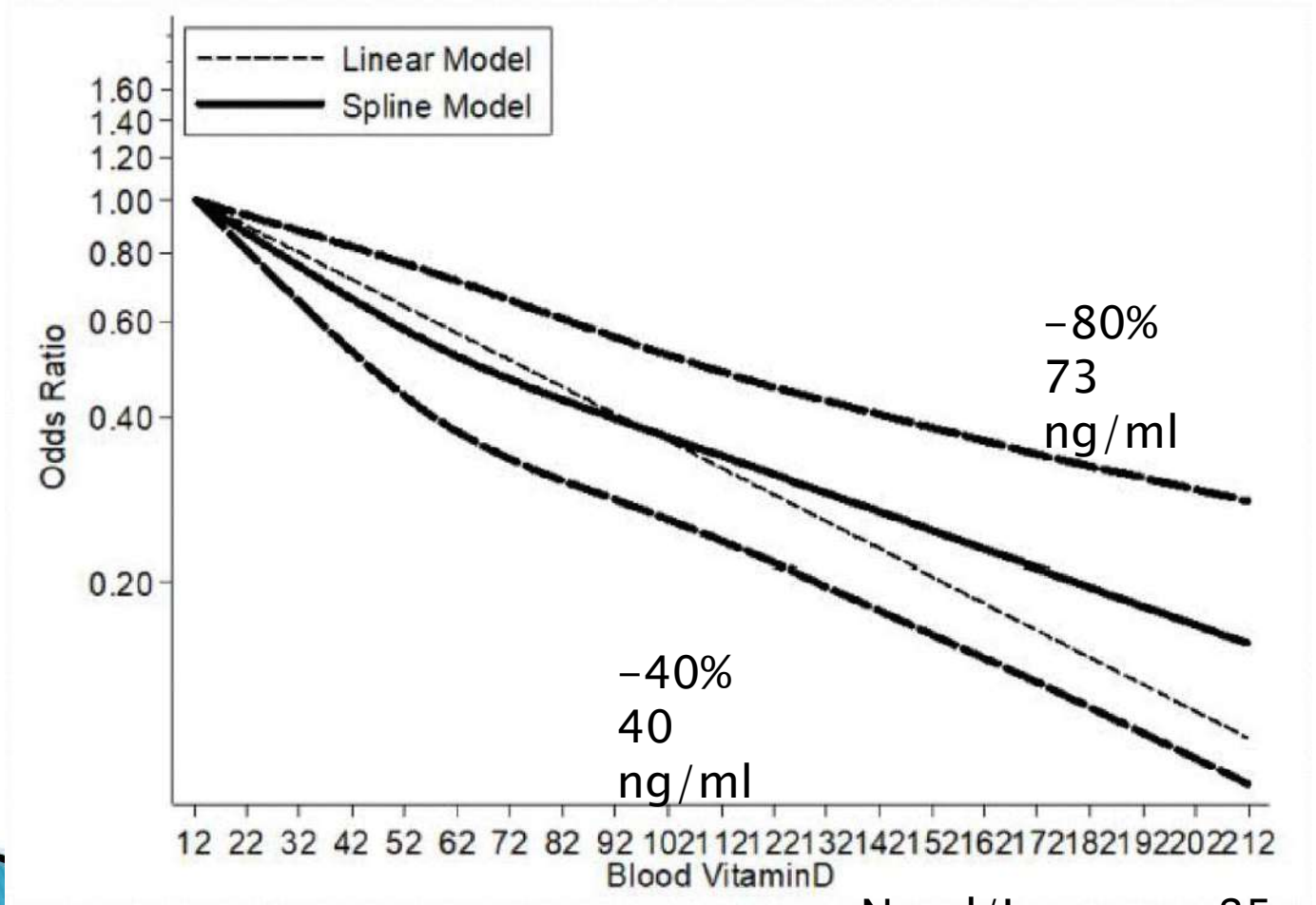
Figure 4. Relative risk of breast cancer by age at time of migration from Southern to Northern Italy, 1976-1981



Source: Berrino F. and G. Gatta. 1989. Int J Cancer, *44*, 186-187.

Women who moved to N. Italy as young children had much higher breast cancer rates than those who moved there as adults.

Breast Cancer Incidence with 25(OH)D from 36 Case-Control and 4 Cohort Studies [Song, *Aging*, 2019] https://is.gd/CxYhbG



Breast cancer risk markedly lower with serum 25(OH)D concentrations ≥60 vs <20 ng/ml

- This was a pooled study of 5038 women taking vitamin D or placebo from two Creighton University RCTs and GrassrootsHealth.net of whom 77 developed breast cancer.
- Those who achieved 25(OH)D >60 ng/ml had 80% lower risk of breast cancer than those with <20 ng/ml.
- McDonnell et al. PLoS One, 2018 Jun 15; 13(6):e0199265.
- https://is.gd/XSBedE

VITAL Vitamin D RCT, Harvard [Manson, *NEJM*, 2019]

- There were ~25,000 participants including ~5,000 black participants followed for a median of 5.3 years.
- A small vitamin D dose (2000 IU/d) reduced risk of all-cancer incidence by 25% for participants with low baseline 25(OH)D concentrations (Blacks) or low BMI <25 kg/m^2) but not the entire set of participants.
- It also reduced risk of cancer death by 25% regardless of baseline 25(OH)D.
- https://is.gd/fwuEvU

SARS-CoV-2 and COVID-19

- Observational studies
  - Having COVID-19 lowers 25(OH)D concentrations. The more severe the disease, the lower the 25(OH)D concentrations. How much 25(OH)D is lowered is not known, but those with lowest 25(OH)D probably had the lowest 25(OH)D before COVID-19.
  - Prospective studies using 25(OH)D prior to infection are better for determining the 25(OH)D-COVID-19 relationship than case-control studies.

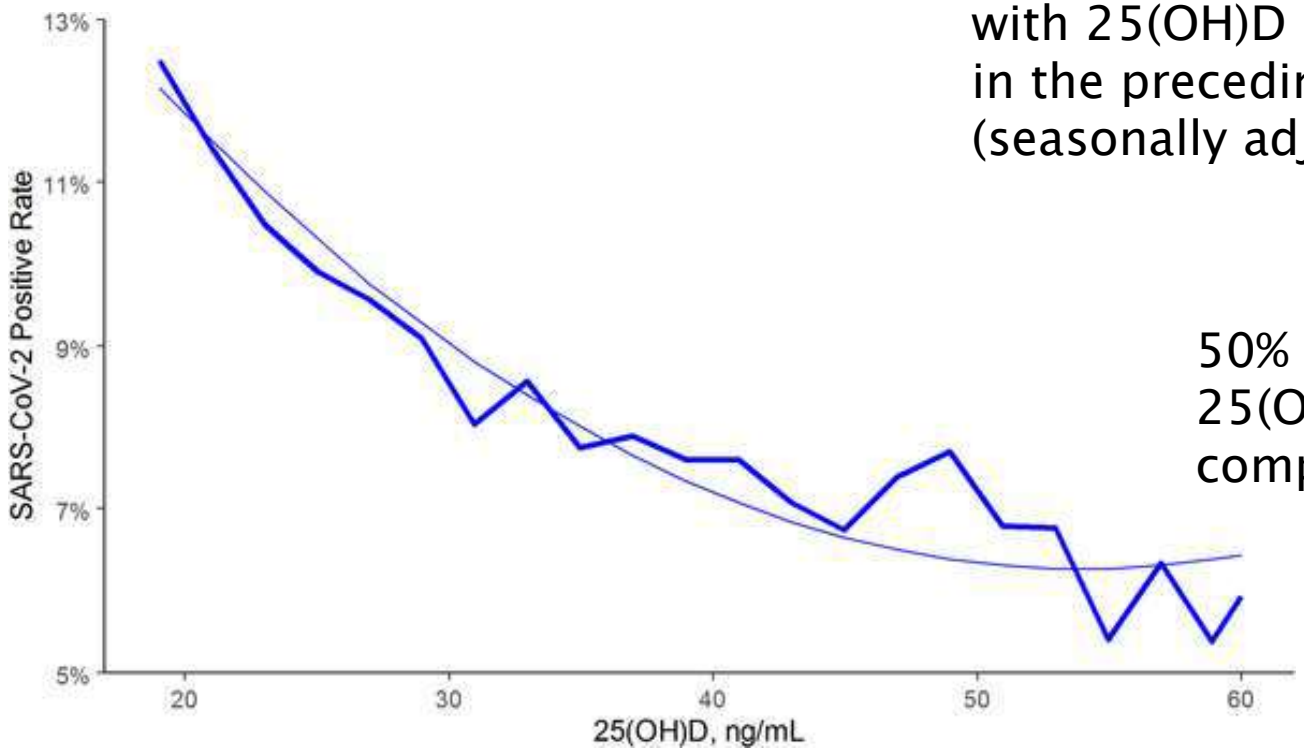
COVID-19 Treatment with Vitamin D

- It is important to treat COVID-19 at the first signs of the disease.
- Vitamin D modulates both the innate and adaptive immune systems. Vitamin D exerts this controlling influence by enhancing the production and effects of antimicrobial peptides. These peptides disrupt the fragile viral cell membrane and along with vitamin D's effects on phagocytes, they clean up the debris. Add to this the cellular repair and replacement performed by vitamin C, and we can kill the virus without regard for any variants and speed the return of each organ's function.

Human Immune Triad

- The vaccines need help. As we realize now, they may not respond well to new SARS-CoV-2 variants.
- Using vitamin D to engage the antimicrobial peptides completes the full potential of the human immune triad: antibodies, cellular defenses, and antimicrobial peptides.
- Vitamin D also reduces risk of the cytokine storm from an improper immune response that damages organs.

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



Based on 191,779 patients with 25(OH)D measurements in the preceding 12 months (seasonally adjusted).

50% reduction for 25(OH)D = 55 ng/ml compared to $\leq$20 ng/ml

Kaufman, .. Holick, PLoS One. 2020 Sep 17;15(9):e0239252 or https://is.gd/holick920

COVID-19, Prospective Observational Study from Israel

- 25(OH)D was measured prior to infection.
- Concentrations <75 nmol/L resulted in a 45% increased risk of infection and a 95% increased risk of hospitalization compared to >75 nmol/L.
- Merzon et al., FEBS J, 2020 Sep;287(17):3693-3702. https://is.gd/ssUYe9

Intervention Studies

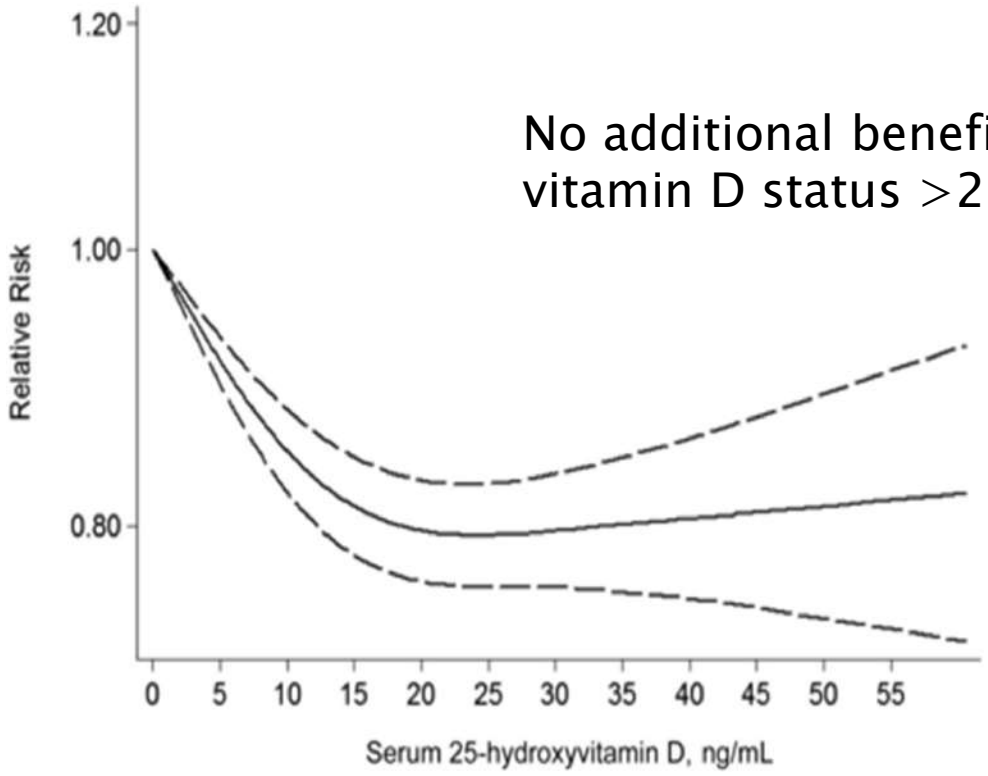
- In India, vitamin D (50,000 IU/day x 7d) was compared with placebo in COVID-19 patients. COVID viral conversion to negative in 21 days was 63% with vitamin D and only 21% with placebo. [Rastogi, 2020]. https://is.gd/hJ7gkO

- In Spain, hospitalized patients with COVID-19 were given standard care plus calcifediol [25(OH)D] therapy, compared with standard care only. Only 2% of the calcifediol-treated patients required intensive care management while 50% without the calcifediol needed ICU care ($p<0.001$). Calcifediol raises 25(OH)D more rapidly than vitamin D [Entrenas Castillo, 2020]. https://is.gd/z3UY8w

Cardiovascular Disease (CVD)

- Observational studies have long found that low 25(OH)D is associated with increased risk of CVD and that CVD rates are much higher in winter (~25%) than in summer.
- Several mechanisms have been proposed for how vitamin D can reduce risk of CVD.
- However, RCTs have consistently failed to demonstrate that vitamin D supplementation reduces risk of CVD, leading people to conclude that vitamin D does not affect risk of CVD.
- The primary reason appears to be that most participants had 25(OH)D too high.

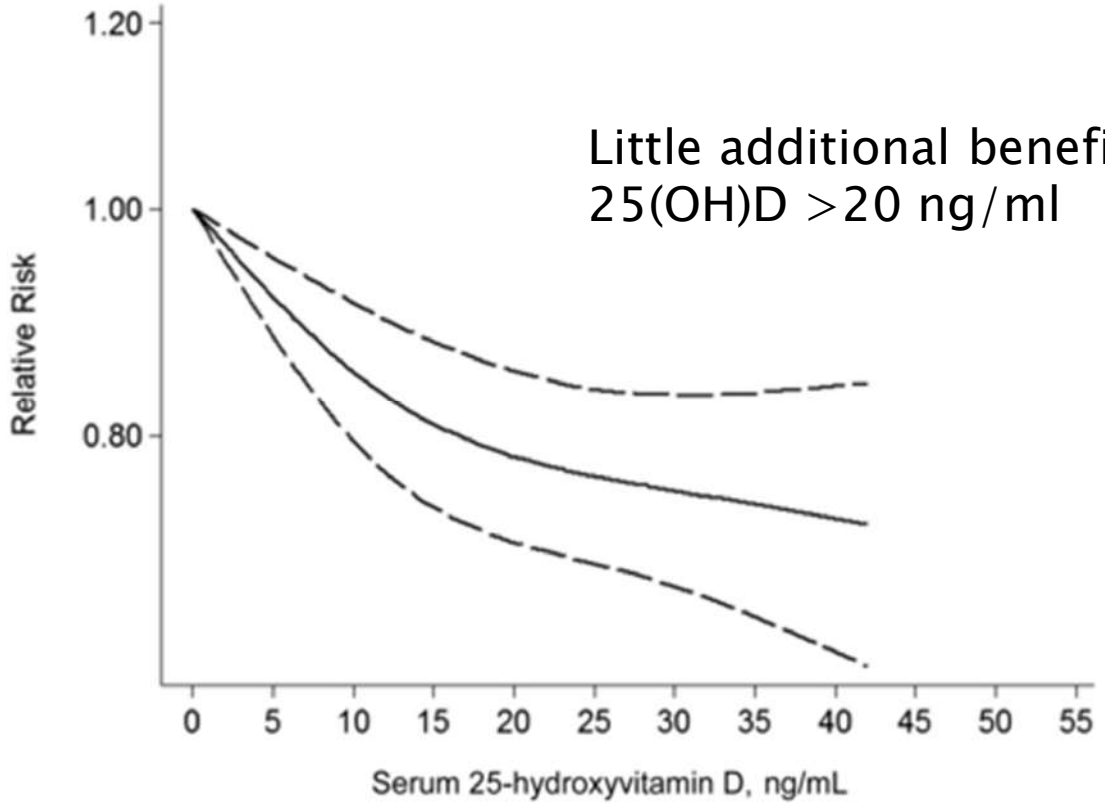
Dose-response analysis between serum 25(OH)D and the relative risk of total cardiovascular events; 1, incidence.



No additional benefit of vitamin D status >20 ng/ml

Zhang, Am J Clin Nutr 2017. https://is.gd/ObwHrg

Dose-response analysis between serum 25(OH)D and the relative risk of total cardiovascular events; 2 – mortality.



Little additional benefit of 25(OH)D >20 ng/ml

Zhang, Am J Clin Nutr 2017. https://is.gd/ObwHrg

The Effects of Vitamin D Supplementation and 25(OH)D Levels on the Risk of Myocardial Infarction and Mortality – 1

- This was a retrospective, observational, nested case-control study of 20,000 patients with low baseline25(OH)D (<20 ng/ml) who received care at the Veterans Health Administration from 1999 to 2018. Patients were divided into 3 groups:
- Group A (untreated, ≤20 ng/ml),
- Group B (treated, 21–29 ng/ml), and
- Group C (treated, ≥30 ng/ml).
- Acharya P, et al. J Endocr Soc. 2021 Jul 15;5(10):bvab124
- https://is.gd/2R3Juw

The Effects of Vitamin D Supplementation and 25(OH)D Levels on the Risk of Myocardial Infarction and Mortality – 2

- MI survival was higher by 30% for 25(OH)D >30 ng/ml than for 20–29 and <20 ng/ml.
- All-cause mortality rate was lower by 40% for 25(OH)D >30 ng/ml than for 20–29 and <20 ng/ml.

- Acharya P, et al. J Endocr Soc. 2021 Jul 15; 5(10):bvab124
- https://is.gd/acharya2021

The U.S. Veterans Administration Hospitals Treat Many Patients with 25(OH)D <20 ng/ml with Vitamin D to Save Money

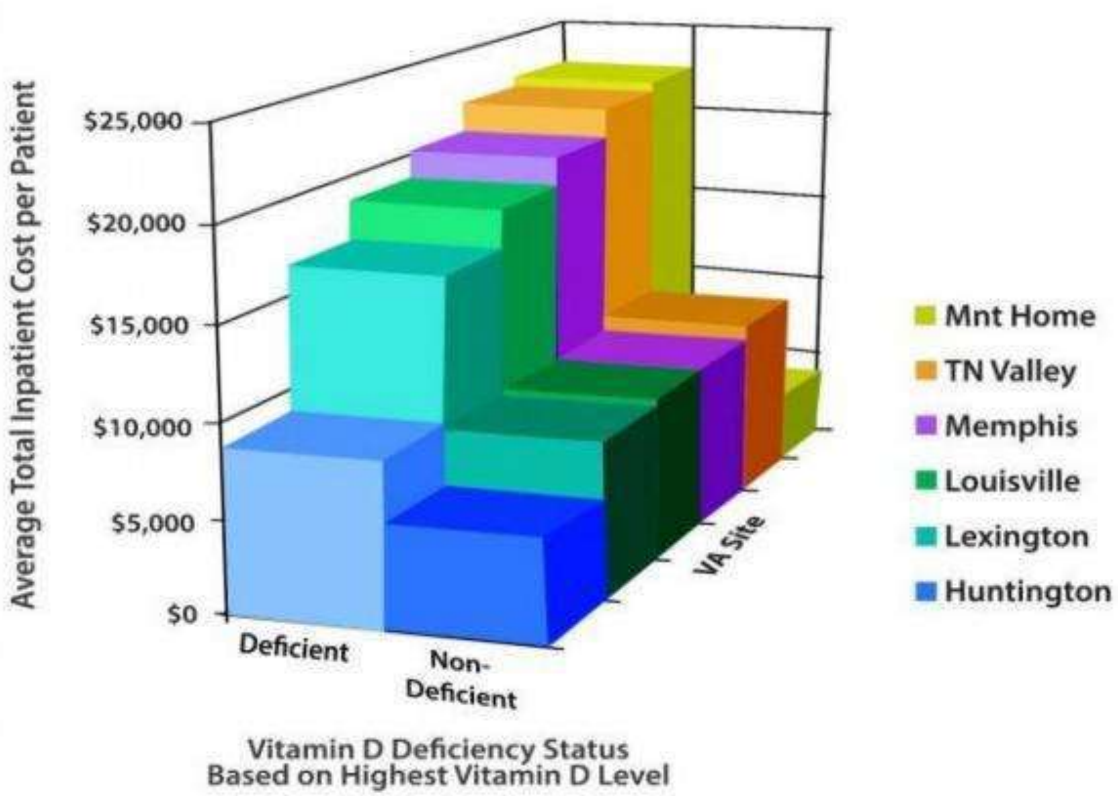


Figure 11: Total inpatient costs by VA site and vitamin D deficiency status

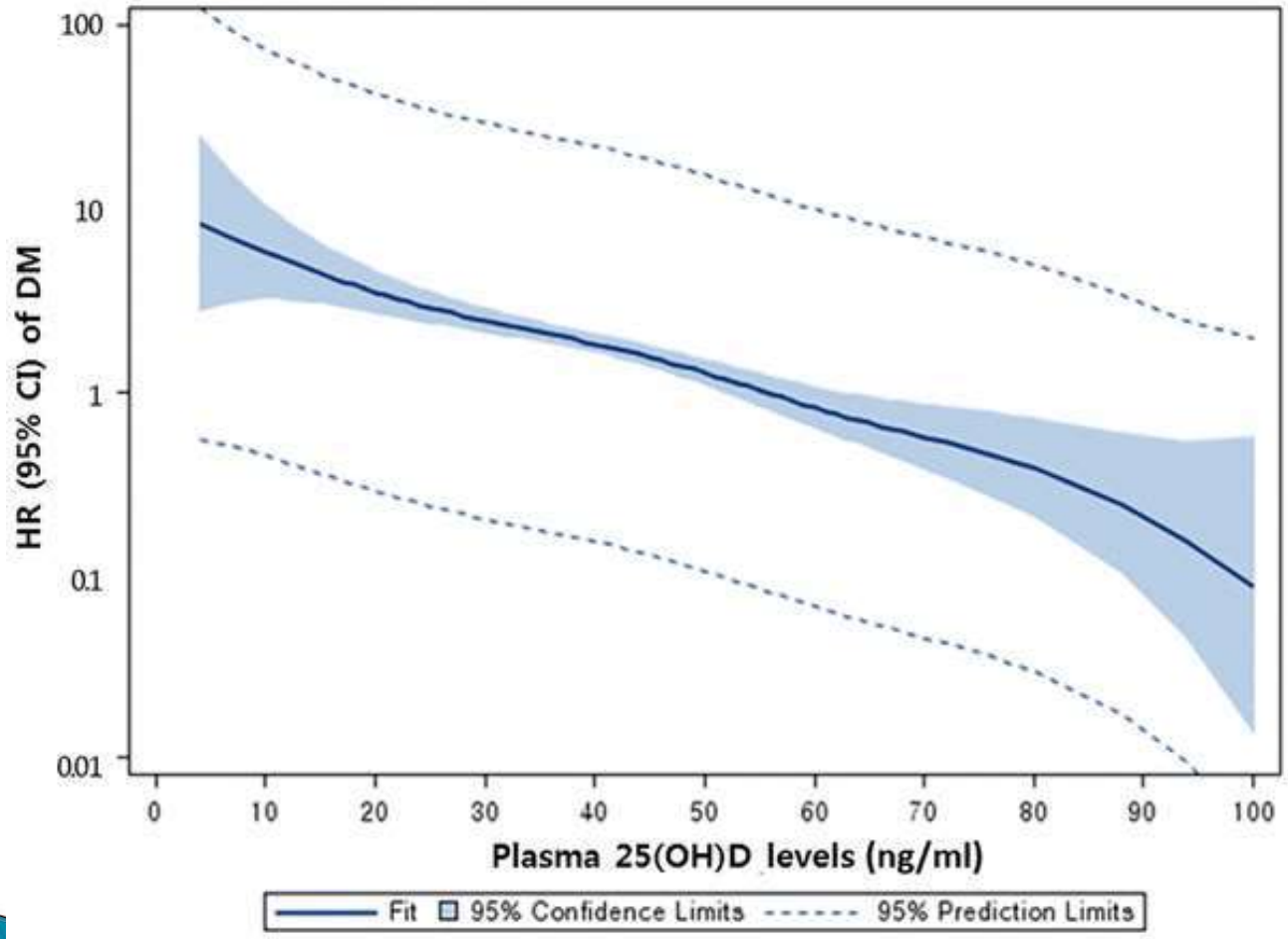
(Bailey, Manning & Peiris, 2012, p. 74).

https://is.gd/WxVVGH

Diabetes Mellitus Type 2

- Diabetes mellitus type 2 is generally considered a chronic disease caused by a bad diet.
- However, there is now strong evidence that higher 25(OH)D levels can greatly reduce risk.

Risk of type 2 diabetes incidence was reduced by 80% from 25(OH)D of <30 to >50 ng/ml



This was a 12-Year follow-up Study in sunny southern California (33° N)

Park, Garland et al.
PLoS One. 2018

https://is.gd/qm61Sp

Intratrial Exposure to Vitamin D and New-Onset Diabetes Among Adults With Prediabetes

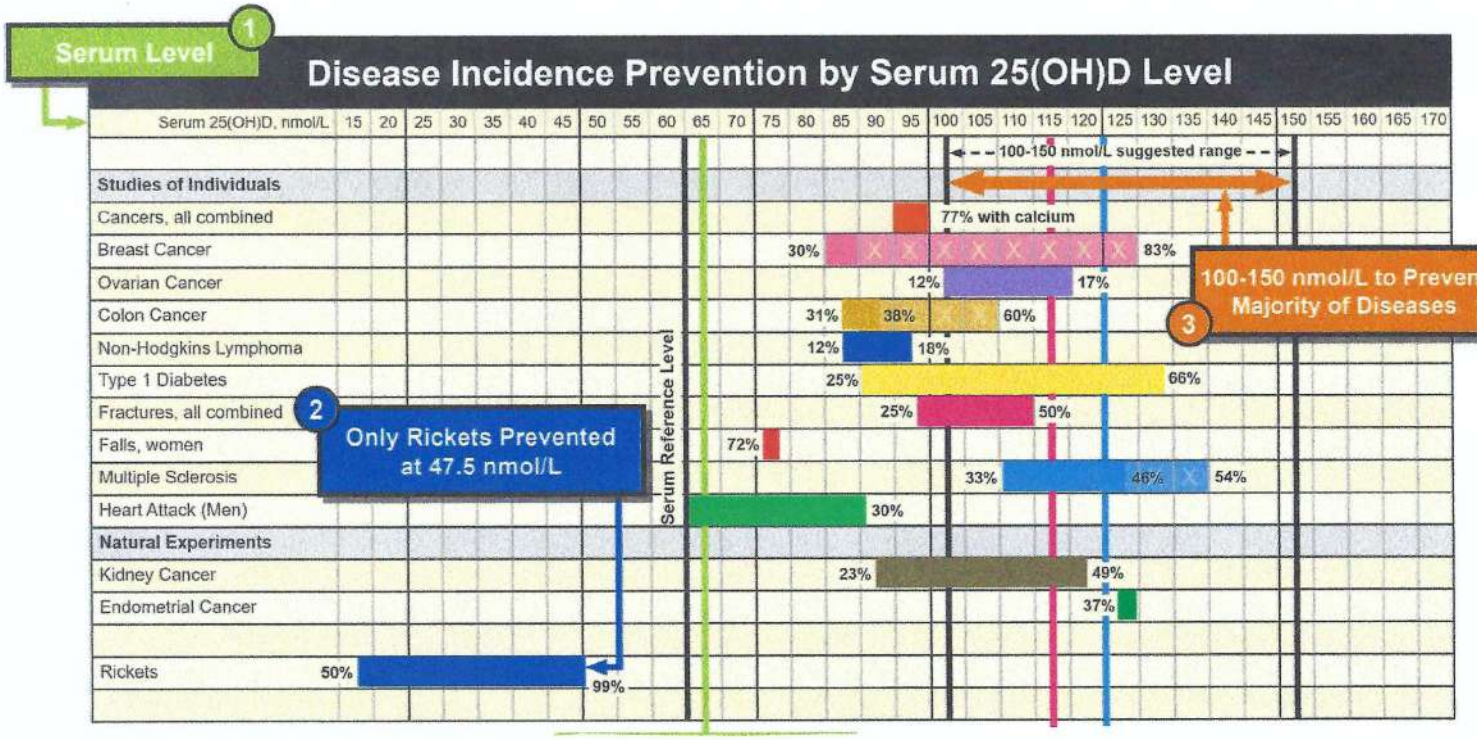
- The D2d study compared the effect of vitamin D_3 versus placebo on new-onset diabetes in adults with prediabetes.
- Every 10 ng/ml increase in 25(OH)D between 20-30 ng/ml to >50 ng/ml among those given 4000 IU/d vitamin D reduced incidence of type 2 diabetes by 25%.

- Dawson-Hughes B, ….Pittas AG; D2d Research Group. Diabetes Care. 2020;43(12):2916-2922. https://is.gd/k6vesK

History of Serum 25(OH)D Concentration Recommendations

- Institute of Medicine USA [Ross, 2011], recommended 50 nmol/L for bone health.
- https://is.gd/qaDooj
- Endocrine Society, USA, [Holick, 2011] recommended 75 nmol/L for treatment of vitamin D deficiency osteomalacia based on plateauing of PTH levels and the Priemel study.
- https://is.gd/sgFMAq
- GrassrootsHealth.net, recommended 100-150 nmol/L for optimal health in 2017.
- Based on results in this presentation, I recommend 150-200 nmol/L (60-80 ng/ml).

Chart by Grassrootshealth.net, 2017, Recommending 100-150 nmol/L



Intervention Studies with High-dose Vitamin D_3 with Good Results

- Crohn's disease
- Epilepsy
- Hemorrhagic stroke
- Hypertension
- Multiple sclerosis
- Periodontal disease
- Psoriasis
- Sepsis
- Sleep disturbance

Hypertension

- A Canadian study gave a moderate dose of vitamin D (∿4,000 IU daily) seeking 25(OH)D levels >100 nmol/L. Of the patients with hypertension at the start, 71% were no longer hypertensive 9 to 15 months later, having lowered blood pressure by 12-18 mmHg.

- Mirhosseini N, Vatanparast H, Kimball SM.
- Nutrients. 2017;9(11):1244.
- https://is.gd/OxJnsZ

Vitamin D Cofactors

- When taking high-dose vitamin D supplements, one should also consider:
  - **Vitamin C** – since vitamin D helps recycle vitamin C, people with low D levels also have low vitamin C levels. You can't recycle what you don't have.
  - **Magnesium** – activates vitamin D
  - **Vitamin K2** – to prevent calcification of soft tissue such as the vascular system
  - Reducing intake of **calcium** supplements.

Why Vitamin D

- Vitamin D is readily available, safe, and inexpensive.
- Vitamin D is the most common nutritional deficiency in the world and is one of the most studied molecules in history.
- There are over 92,000 publications on vitamin D at pubmed.gov including 5250 in 2020 by mid-August 2021.

For Further Information

- https://vitamindwiki.com/
- https://scholar.google.com/
- Sunlight, Nutrition and Health Research Center: http://www.sunarc.org/
- https://www.grassrootshealth.net/

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