Reducing incidence and mortality rates in the UAE and related countries by raising serum 25(OH)D above 30 ng/mL

William B. Grant, Ph.D.
Sunlight, Nutrition and Health Research Center
San Francisco

Outline

- Diseases with high rates in the Middle East
- Vitamin D status in the Middle East
- Types of vitamin D studies
- Specific outcomes
  - Ischaemic heart disease
  - Stroke
  - Diabetes
  - Kidney disease, hypertension
  - Cancers
  - COVID-19
  - Dementia
  - Adverse pregnancy and birth outcomes
- Suggestions for future research

Mortality rates for leading diseases 2016 (WHO) [deaths/100,000/yr]

	Saudi M	Saudi F	UAE M	UAE F	USA M	USA F
All-cause	777	608	604	511	593	404
IHD	219	154	182	144	106	56
Stroke	86	76	74	67	24	21
Cancer	64	57	55	62	132	99
Kidney	50	41	34	27	13	9
Alzheimer	46	44	34	40	34	35
Respiratory	46	42	24	18	13	10
Diabetes	30	25	39	40	19	12

IHD, ischaemic heart disease; F, female; M, male

Processed food as a major disease risk factor

- Robert H Lustig, M.D. *Metabolical: The Lure and the Lies of Processed Food, Nutrition, and Modern Medicine*, Harper Wave, 407 pp, 2021.
  - endnotes and bibliography at Metabolical.com
- **Lustig RH.** Ultraprocessed Food: Addictive, Toxic, and Ready for Regulation. *Nutrients*. 2020;12:3401.
- **Lustig RH**, et al. Obesity I: Overview and molecular and biochemical mechanisms. *Biochem Pharmacol*. 2022;199:115012.
- **Lustig RH.** Fructose and Nonalcoholic Fatty Liver Disease. *J Calif Dent Assoc.* 2016 ;44:613-17.

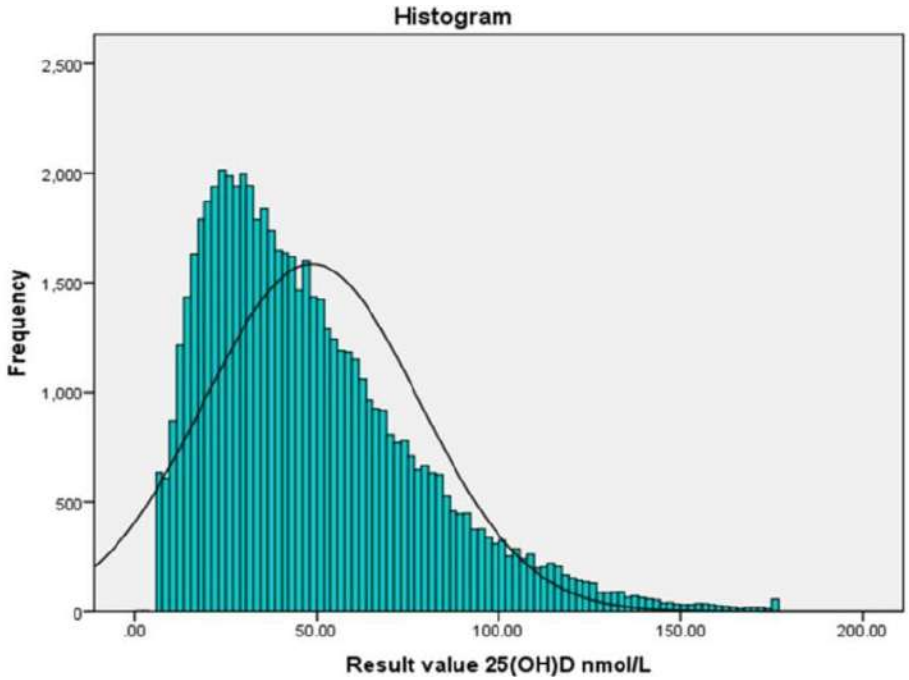
Vitamin D acts as a hormone, affecting gene expression

- 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. We observed a dose-dependent increase in 25(OH)D concentrations, decreased PTH and no change in serum calcium. A plateau in PTH levels was achieved at 16 weeks in the 4000 and 10,000 IU/d groups. 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 A, Kalajian TA, Song A, Holick MF. Sci Rep. 2019;9:17685.

Saudi Arabia

- A systematic review on the prevalence studies done in KSA from 2011 to 2016 was done and revealed that the prevalence of vitamin D deficiency (<20 ng/mL) in Saudi Arabia among different populations (adults, children and adolescents, newborns and pregnant/ lactating women) is 81% (95% CI, 68–90%), in line with most neighboring Gulf countries.
- Nasser M Al-Daghri. Vitamin D in Saudi Arabia: Prevalence, distribution and disease associations.
- J Steroid Biochem Mol Biol. 2018;175:102-107.

Abu Dhabi, [Haq, 2016]



This study was designed to determine vitamin D status of 60,979 patients admitted to the Burjeel Hospital of VPS healthcare in Abu Dhabi from October 2012 to September 2014. 26% of females and 18% of males have extreme deficiency of 25(OH)D (<10 ng/mL).

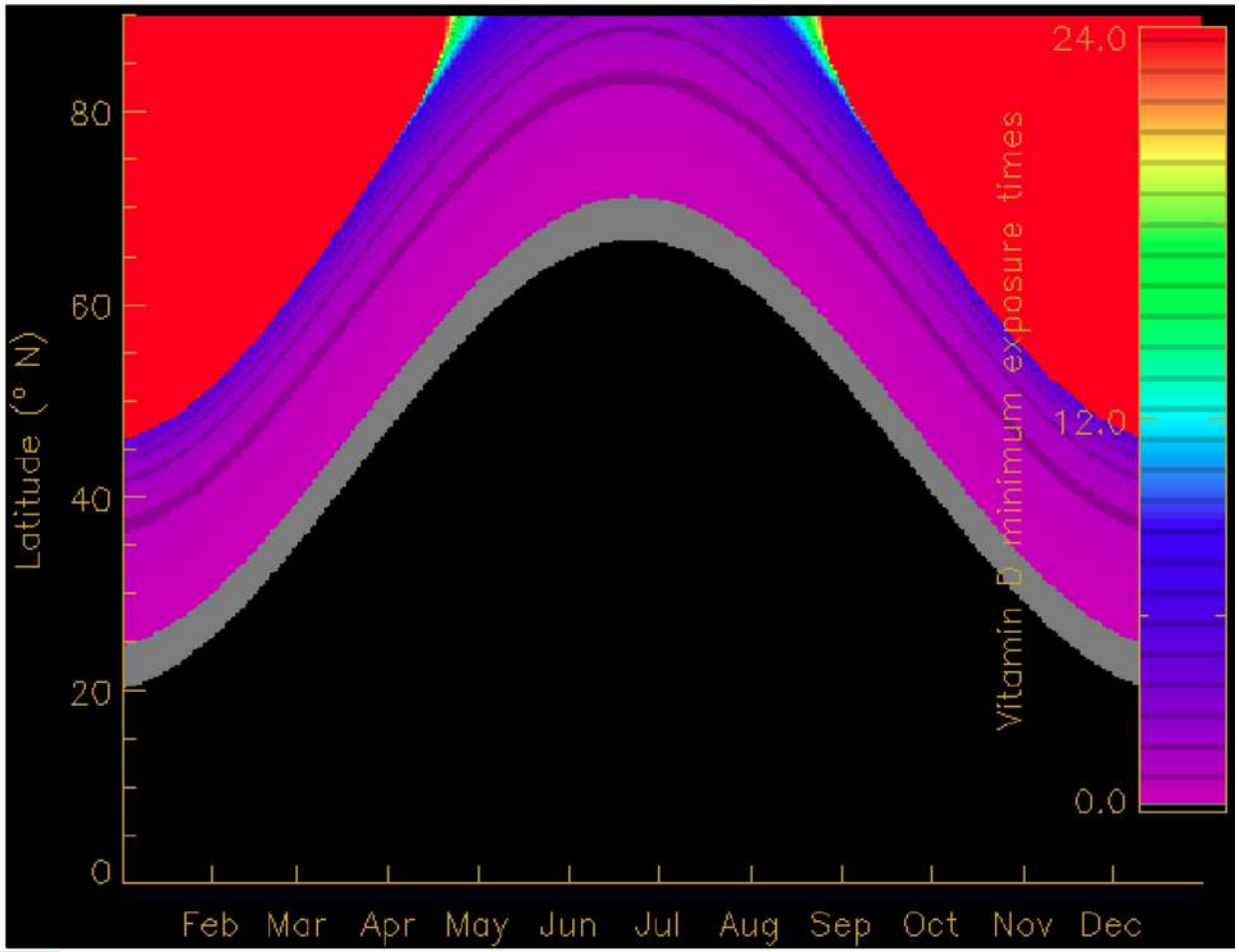
Why 25(OH)D concentrations are low in the Middle East

- 1 – a primarily plant-based diet. Meat eaters in the UK have 25(OH)D 8 ng/mL greater than vegans [Crowe, Public Health Nutr. 2011]
- 2 – often too hot in summer to be in the sun.
- 3 – wearing concealing clothing.
- 4 – lack of knowledge about vitamin D, both how to obtain it and what the health benefits are.
- 5 – food is not fortified with vitamin D.
- 6 – Big Pharma uses the Disinformation Playbook to disparage vitamin D.

Disinformation Playbook

- **Vitamin D acceptance delayed by Big Pharma following the Disinformation Playbook Commentary by William B. Grant, Ph.D.**
- Examples:
  - JAMA, Lancet and NEJM only publish disappointing articles regarding vitamin D
  - The three U.S. health agencies, CDC, FDA, and NIH are headed by Big Pharma representatives.
  - The Institute of Medicine vitamin D recommendations (600 or 800 IU/d) are very weak.
  - http://orthomolecular.org/resources/omns/v14n22.shtml

Time required to produce vitamin D vs. date and latitude [Engelsen, 2010]



Types of vitamin D studies

- Ecological, based on geography or time.
  - Considered good for hypothesis generation.
- Randomized controlled trials.
  - Limited usefulness due to enrolling participants with high 25(OH)D, using small vitamin D doses, not analyzing results with respect to baseline and achieved 25(OH)D (see Heaney RP. Nutr Rev. 2014;72(1):48–54 for guidelines for nutrients).
- Mendelian randomization studies.
  - They use alleles of genes involved in the vitamin D pathway. Require tens to hundreds of thousands of participants. This approach is able to determine causality.

Observational studies

- These are now my favorite types of study.
- Advantages
  - Can examine risk over a large 25(OH)D range.
  - Can include many confounding factors.
  - Can be relatively efficient.
  - Case-control studies are useful for non-acute inflammatory diseases.
- Disadvantages
  - Long follow-up periods degrade the findings due to temporal changes in 25(OH)D.
  - Care has to be exercised in choice of controls.

Reference for the previous two slides

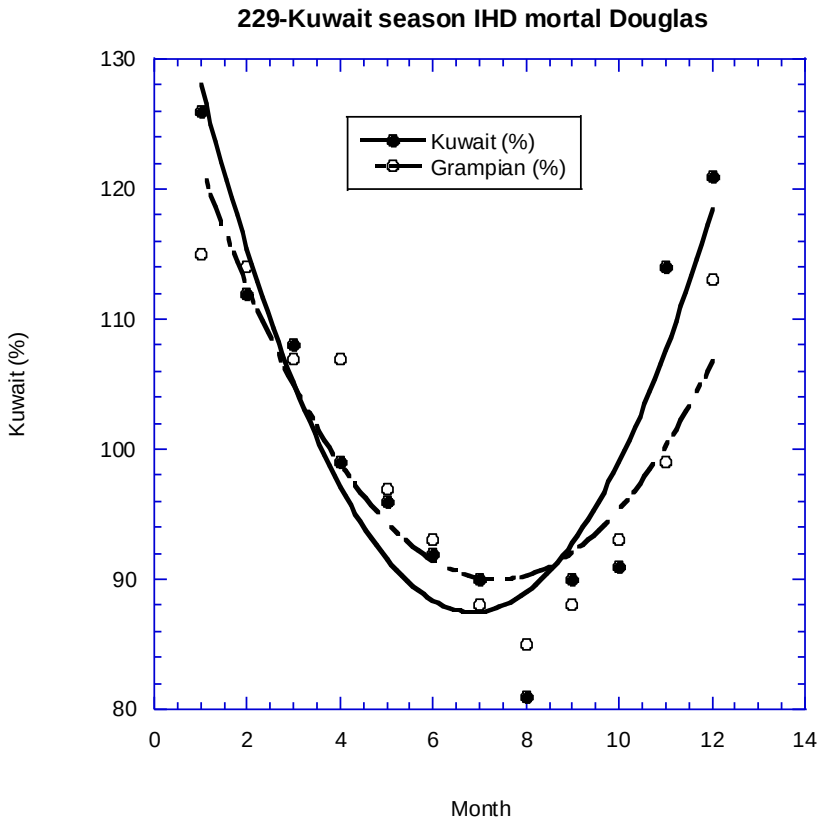
- "A promising approach for future RCT design is adjustable vitamin D supplementation based on interval serum 25(OH)D concentrations to achieve target 25(OH)D levels suggested by findings from observational studies."

- Grant WB, Boucher BJ, Al Anouti F, Pilz S. Comparing the Evidence from Observational Studies and Randomized Controlled Trials for Nonskeletal Health Effects of Vitamin **D.** Nutrients. 2022 Sep 15;14(18):3811. doi: 10.3390/nu14183811.

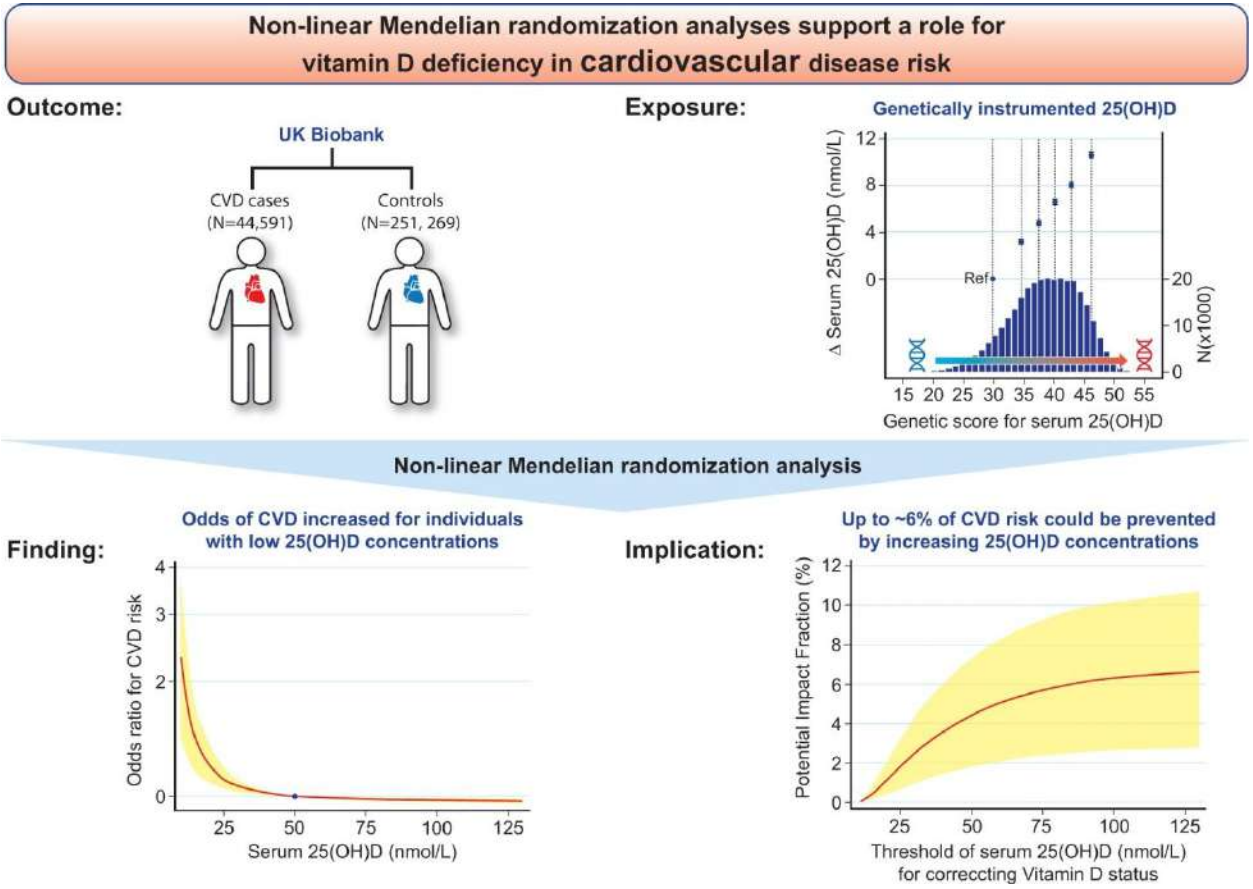
Cardiovascular disease risk factors

- •Vitamin D regulates blood pressure; and endothelial, smooth muscle cell, and cardiac functions positive influence on cardiovascular health.
- •Observational studies report associations between vitamin D deficiency with hypertension and cardiovascular deaths.
- •Epigenetic modifications subdue cellular inflammation, improve endothelial functions, and attenuate renin-angiotensin-aldosterone system.
- Wimalawansa SJ. Vitamin D and cardiovascular diseases: Causality. J Steroid Biochem Mol Biol. 2018;175:29-43.

Ischaemic heart disease; seasonal variation in mortality rate in Kuwait [Douglas, 1990]



Graphical Abstract Non-linear Mendelian randomization analyses support a L-shaped association of serum 25-hydroxyvitamin D ...



Zhou A, Selvanayagam JB, Hyppönen E.

Eur Heart J, ehab809, https://doi.org/10.1093/eurheartj/ehab809

The Effects of Vitamin D Supplementation and 25-Hydroxyvitamin D Levels on the Risk of Myocardial Infarction and Mortality. Acharya J Endocr Soc. 2021 Jul 15;5(10):bvab124.

- **Materials and methods**: This was a retrospective, observational, nested case-control study of patients (N = 20 025) with low 25-hydroxyvitamin D ([25-OH]D) levels (<20 ng/mL) who received care at the USA Veterans Health Administration from 1999 to 2018. Patients were divided into 3 groups: Group A (untreated, levels ≤20 ng/mL), Group B (treated, levels 21-29 ng/mL), and Group C (treated, levels ≥30 ng/mL). The risk of MI and all-cause mortality were compared utilizing propensity score-weighted Cox proportional hazard models.

Results after ~20 years

	<20 ng/mL	20–30 ng/mL	>30 ng/mL
Ischaemic heart disease incidence	HR = 1.00	HR = 0.73 (95% CI, 0.55–0.96)	HR = 0.65 (95% CI, 0.49–0.85)
All-cause mortality	HR = 1.00	HR = 0.59 (95% CI, 0.54–0.63)	HR = 0.61 95% CI, 0.56–0.67)

Vitamin D deficiency and incident stroke risk in community-living black and white adults Suzanne E Judd Int J Stroke. 2016;11:93-102.

- **Methods**: We examined the association of 25-hydroxyvitamin D with incident stroke in the Reasons for Geographic and Racial Differences in Stroke (REGARDS) study, a cohort of black and white adults ≥45 years of age. Using a case-cohort study design, plasma 25(OH)D was measured in 610 participants who developed incident stroke (cases) and in 937 stroke-free individuals from a stratified cohort random sample of REGARDS participants (comparison cohort).

Vitamin D deficiency and incident stroke risk in community-living black and white adults -2

- **Results:** In multivariable models adjusted for socio-demographic factors, co-morbidities and laboratory values including parathyroid hormone, lower 25(OH)D concentrations were associated with higher risk of stroke (25(OH)D >30 ng/mL reference; 25(OH)D concentrations 20-30 ng/mL, hazard ratio 1.33, 95% confidence interval (95% CI) 0.89,1.96; 25(OH)D <20 ng/mL, hazard ratio 1.85, 95% CI 1.17, 2.93).

Diabetes mellitus type 2; Observational study from an RCT

- The D2d study compared the effect of 4,000 IU/day of vitamin D_3 versus placebo on new-onset diabetes in 2423 adults with prediabetes for a median of 2.5 yrs.
- The hazard ratios for diabetes among participants treated with vitamin D who maintained intratrial 25(OH)D levels of 40–49 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;43:2916–2922

Kidney disease risk factors

- Smoking, obesity, hypertension, and diabetes mellitus can also lead to kidney disease. An uncontrolled diabetic and/or hypertensive patient can easily and quickly progress to an end-stage kidney disease patient.

- Kazancioğlu R. Risk factors for chronic kidney disease: an update. Kidney Int Suppl (2011). 2013 Dec;3(4):368-371.

Lowering blood pressure with high-dose vitamin D

- 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 >40 ng/mL.
- Mirhosseini N, Vatanparast H, Kimball SM. Nutrients. 2017;9:1244.

Lowering blood pressure with high-dose vitamin D – results

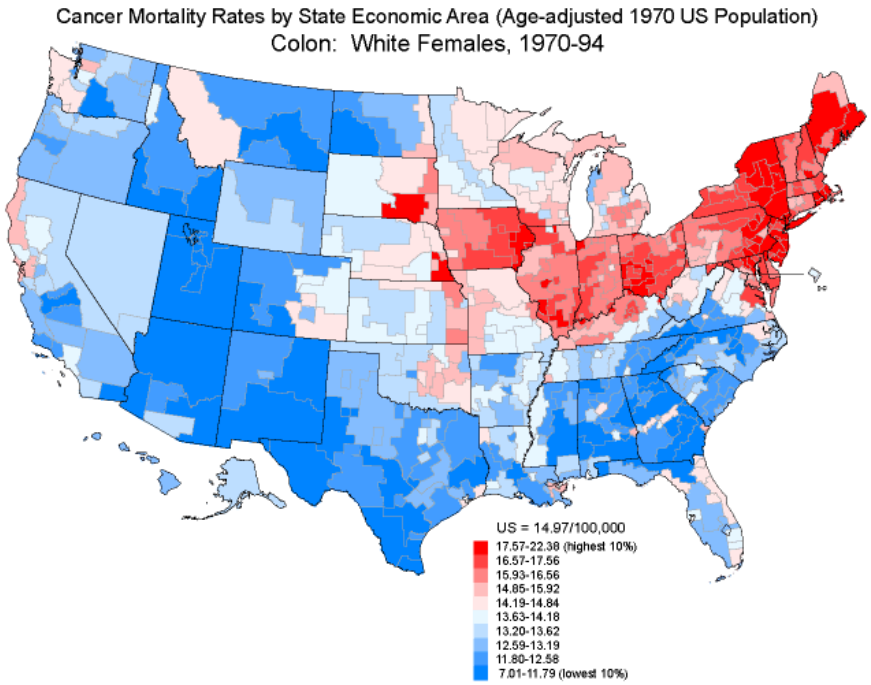
- At baseline, 592 participants (7.3%) were hypertensive; of those, 71% were no longer hypertensive at follow-up (12 ± 3 months later). There was a significant negative association between BP. For hypertensive participants who did and did not take BP-lowering medication, reduced mean systolic (−18 vs. −14 mmHg) and diastolic (−12 vs. −12 mmHg) BP were similar

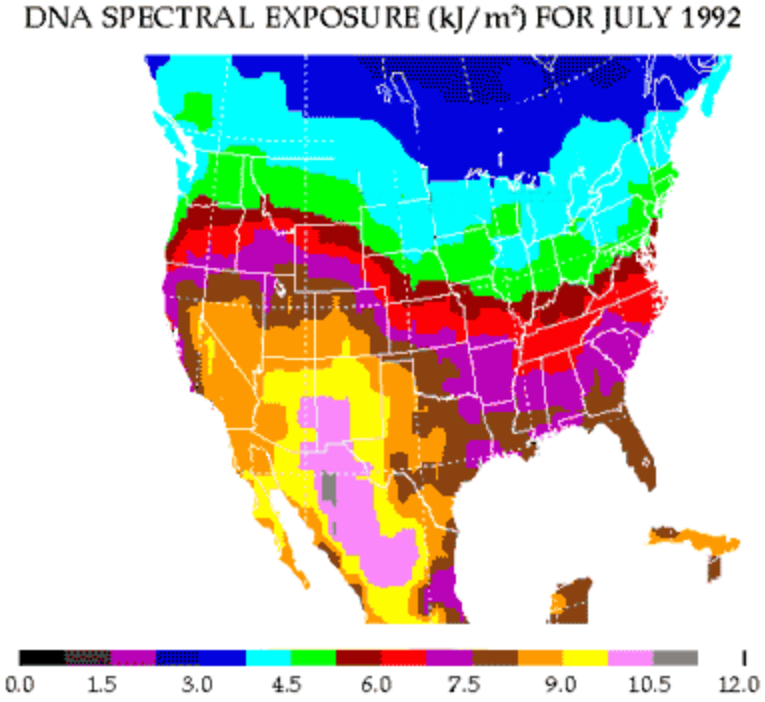
Cancer – vitamin D mecanisms

- Vitamin D reduces cancer incidence by regulating cellular differentiation, proliferation and apoptosis.
- It reduces progression by anti-angiogenesis mechanisms, and also reduces metastasis into surrounding tissues.
- Not surprisingly, vitamin D has stronger effect on cancer mortality rates than on incidence rates.

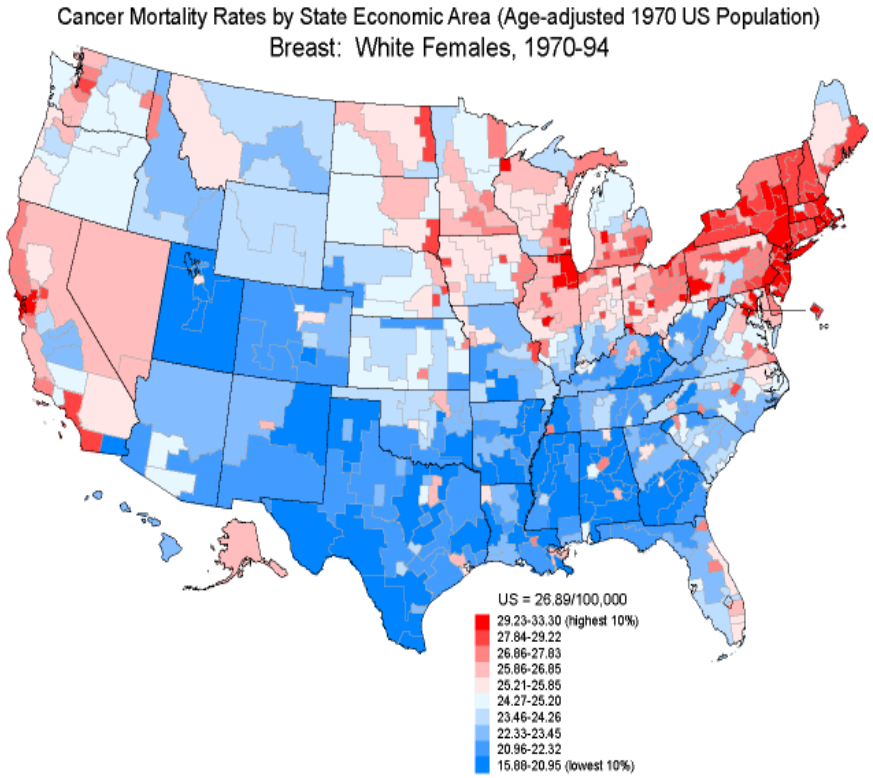
- Muñoz A, Grant WB. Vitamin D and Cancer: An Historical Overview of the Epidemiology and Mechanisms. *Nutrients*. March 14, 2022; 14(7):1448.

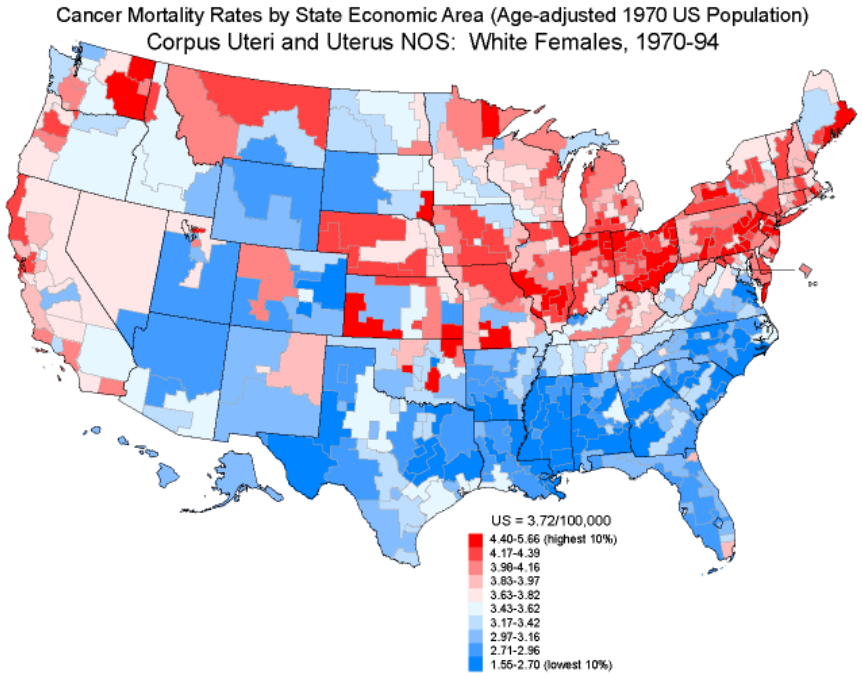
Colon cancer mortality rates (F) 1970-94 vs. solar UVB doses, July





Breast & corpus uteri cancer mortality rates 1970-94





Summary of an ecological study of cancer mortality rates in the US, 1950-94

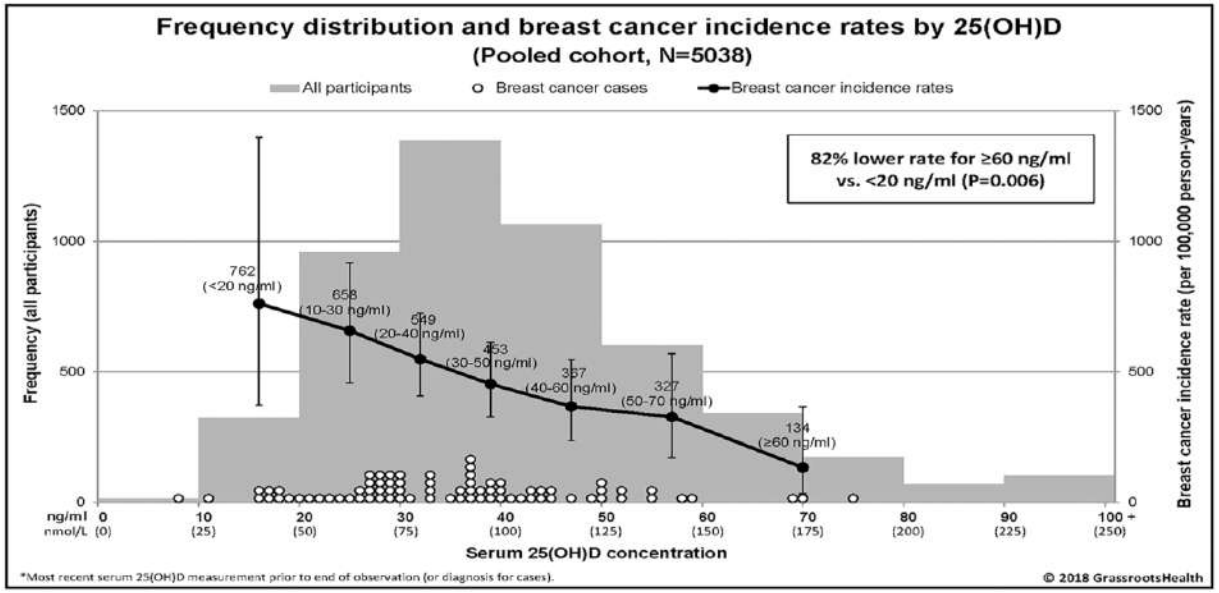
- Fifteen types of cancer were inversely-associated with UVB doses for whites:
  - Bladder, breast, cervical, colon, endometrial, esophageal, gallbladder, gastric, laryngeal, ovarian, pancreatic, rectal, renal, Hodgkin's and non-Hodgkin's lymphoma
- Confouding factors included:
  - Alcohol consumption, Hispanic heritage, poverty, smoking+diet, and urban/rural residence

- Grant WB, Garland CF. Anticancer Res. 2006;26(4A):2687-99.

VITAL: vitamin D RCT for cancer

- 25,000 participants, mean baseline 25(OH)D ~30 ng/mL, vitamin D treatment, 2000 IU/d, ~4.5 years, analyzed by intention to treat.
- For entire group, cancer incidence HR = 0.96 (0.88–1.06).
  For entire group, cancer mortality rate HR = 0.75 [95% CI, 0.59–0.96]
  For those with BMI <25 kg/m^2, cancer incidence HR = 0.76 (95% CI, 0.63–0.90)
- For African-Americans [baseline 25(OH)D = 25 ng/mL], cancer incidence HR = 0.77 (95% CI, 0.59–1.01)]

Breast cancer risk study based on participants taking vitamin D with 25(OH)D measured within one year



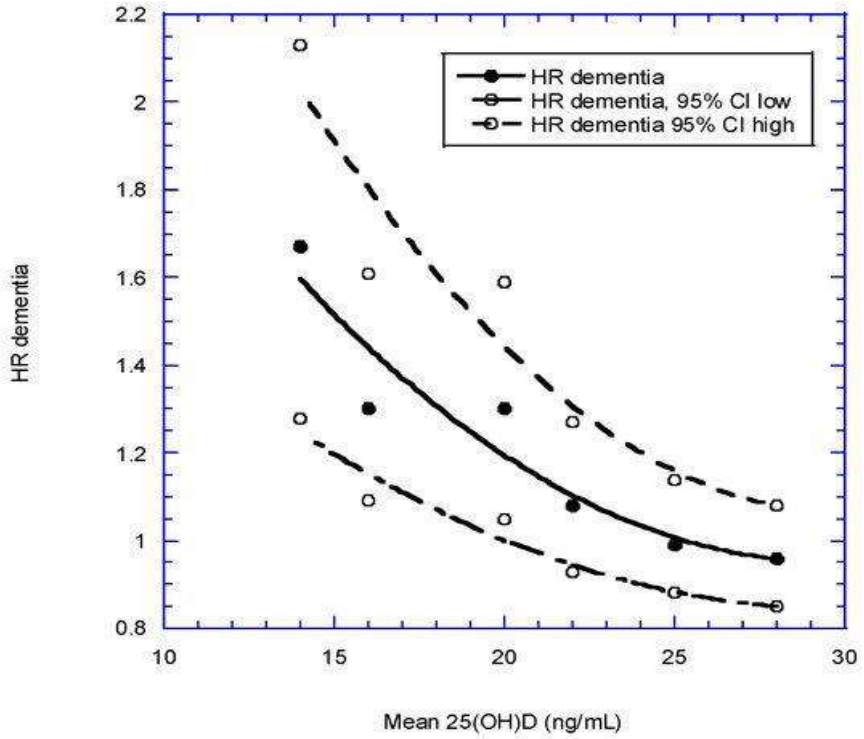
Values <40 ng/mL were mostly from two RCTs by Lappe, (1000 or 2000 IU/d vitamin D_3) while values >40 ng/mL were mostly from the GrassrootsHealth.net volunteer cohort, with choice of vitamin D dose. McDonnell et al. PLoS One. 2018;13(6):e0199265

Vitamin D supplementation and COVID-19 risk: a population-based, cohort study

- A study in Barcelona used data for vitamin D prescriptions and risk of SARS-CoV-2 or COVID-19. Most identifiable vitamin D use is by prescription rather than over-the-counter, though current usage is probably mainly over-the-counter.
  Patients on cholecalciferol treatment achieving 25(OH) D concentrations ≥30 ng/mL had lower risk of SARS-CoV2 infection, lower risk of severe COVID-19, and lower COVID-19 mortality than supplemented 25(OH)D-deficient patients (HR = 0.66 [95% CI, 0.46-0.93].
  Patients on calcifediol [25(OH)D] treatment achieving serum 25(OH)D concentrations ≥ 30 ng/mL had lower risks of SARS-CoV2 infection, of severe COVID-19, and of COVID-19 mortality than 25(OH)D-deficient patients not supplementing with vitamin D (HR = 0.56 [95% CI, 0.42-0.76]; $p < 0.001$).

- Oristrell J, Oliva JC, Casado E, Subirana I, Domínguez D, Toloba A, Balado A, Grau M. Vitamin D supplementation and COVID-19 risk: a population-based, cohort study. J Endocrinol Invest 2022 Jan;45(1):167-179.

Dementia incidence vs. 25(OH)D



Grant WB, Boucher BJ, Al Anouti F, Pilz S. Comparing the Evidence from Observational Studies and Randomized Controlled Trials for Nonskeletal Health Effects of Vitamin D. *Nutrients*. Sept. 15, 2022; 14(18):3811.

Adverse pregnancy and birth outcomes

- 25(OH)D concentration <30 ng/mL increases risk of Cesarean-section delivery, gestational diabetes, pre-eclampsia, preterm birth, maternal mortality as well as adverse neurological and physical outcomes in early life.
- Vitamin D_3 supplementation of 4000-5000 IU/d is recommended to raise 25(OH)D to above 30-40 ng/mL.
- Hollis BW, Wagner CL. Substantial Vitamin D Supplementation Is Required during the Prenatal Period to Improve Birth Outcomes. Nutrients 2022;14(4):899.

Summary

- 25(OH)D concentrations >30 or 40 ng/mL are associated with reduced risk of many types of conditions and diseases. Vitamin D_3 supplementation should be 2000–4000 or 5000 IU/d for adults in the Middle East due to widespread vitamin D deficiency. Loading doses can be used at first to rapidly increase 25(OH)D concentrations. There are very few risks associated with these doses.

Recommendations

- Physicians might devise their own observational studies to assess the importance of higher 25(OH)D concentrations. For example, patients could be counseled on the importance of vitamin D supplementation and 25(OH)D concentrations could be measured annually and at diagnosis of disease. (Acute inflammatory illnesses lower 25(OH)D, but most diseases do not.) Such measurements will help establish the correlation between 25(OH)D and diseases in the Middle East.

For more information

- 30+ of my open-access publications on vitamin D
- https://www.mdpi.com/search?authors=william+b+grant&journal=nutrients
- My website: http://sunarc.org/
- My Twitter account: @wbgrant2
- My email address: wbgrant@infionline.net