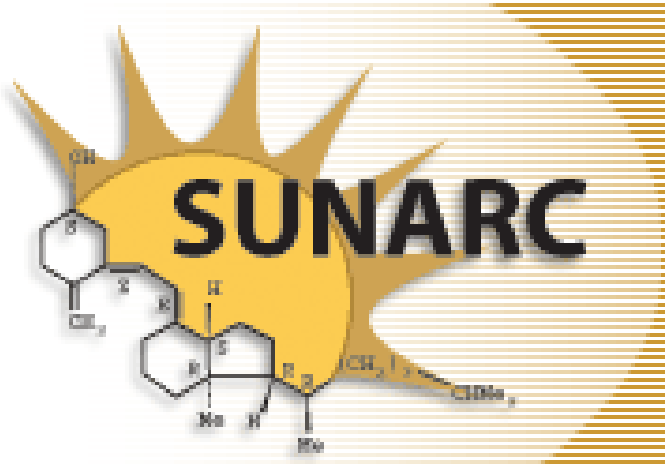

Vitamin D Update
Smart Life Forum, Oct. 19, 2017

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Sunlight, Nutrition and Health Research Center (www.sunarc.org)
San Francisco

Disclosure

- I receive funding from Bio-Tech Pharmacal, a supplier of research grade vitamin D for health professionals and consumers at
- http://www.biotechpharmacal.com/

Outline

- Vitamin D physiology
- Vitamin D recommendations
- Major health outcomes related to vitamin D
- Where is vitamin D policy headed?
- How to conduct vitamin D clinical trials
- For more information, see

Vitamin D Physiology

- Vitamin D_3 (cholecalciferol) can be made in the skin or obtained from food or supplements
- The liver converts vitamin D_3 to 25-hydroxyvitamin D_3 [$25(OH)D_3$] by adding an OH. The half life is about 2.5 weeks.
- The kidney converts $25(OH)D_3$ to $1,25(OH)_2D_3$

Serum Calcium Regulation

- $1,25(OH)_2D_3$ and parathyroid hormone (PTH) keep serum calcium within a tight range.
- $1,25(OH)_2D_3$ increases calcium absorption from the intestines
- PTH increases calcium absorption from the bones

Other Actions of Vitamin D

- Most of the action of vitamin D is through $1,25(OH)_2D_3$ entering vitamin D receptors m(VDRs), which are coupled to chromosomes in nearly all cells of the body.
- When activated, the VDRs control the expression of many genes, upregulating some, downregulating others.
- Many organs can convert $25(OH)D_3$ to $1,25(OH)_2D_3$ as needed.

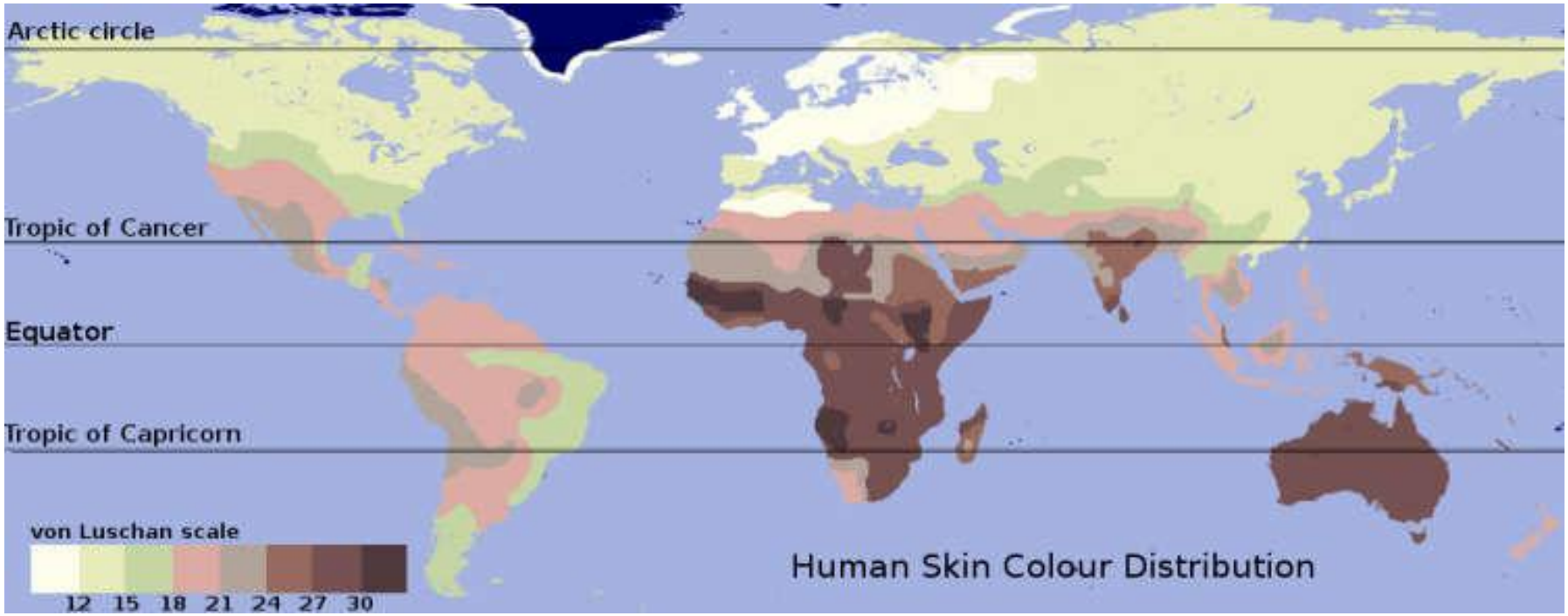
More Actions of Vitamin D

- Vitamin D fights bacterial and some viral infections by inducing production of cathelicidin, a polypeptide with antimicrobial and antiendotoxin properties.
- Vitamin D reduces inflammation by reducing production of proinflammatory cytokines (chemical messengers).

Skin Pigmentation

- Skin pigmentation varies globally depending on where people live for hundreds to thousands of years.
- Dark skin in the tropics reduces risk of free radical formation and skin cancer as well as folate destruction.
- Pale skin at high latitudes permits vitamin D production for low UVB doses.

Human Skin Color Distribution

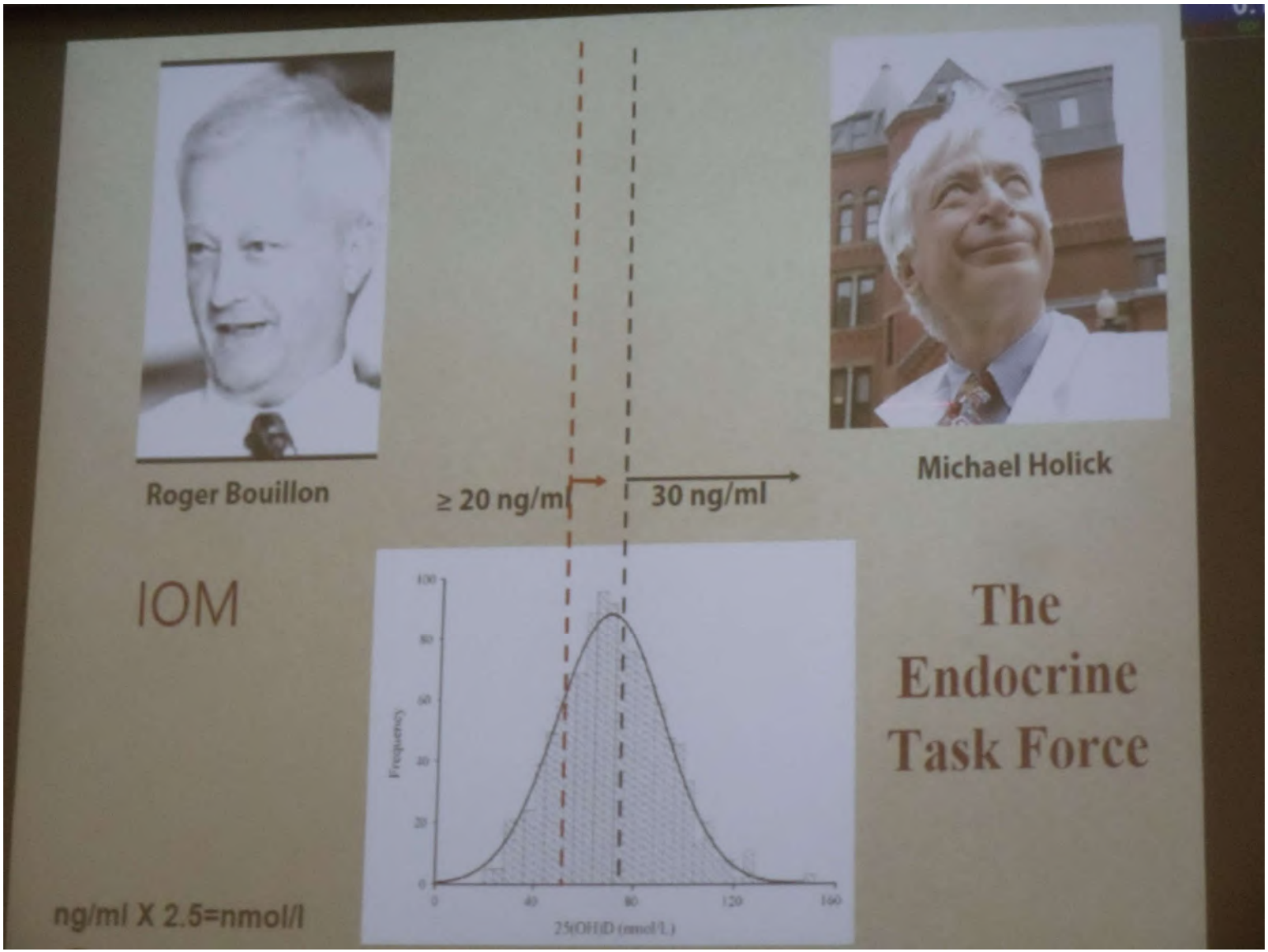


George Chaplin and Nina Jablonski

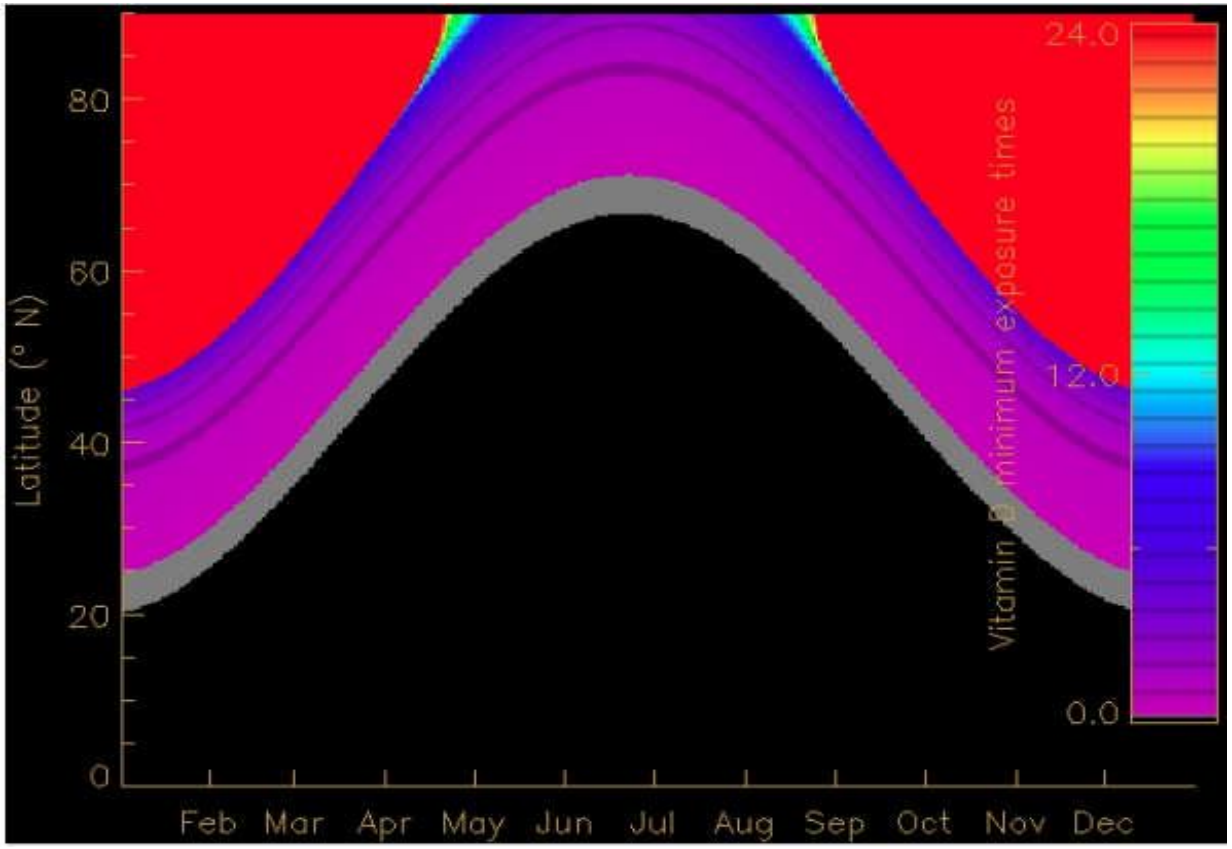
Recommendations

- Institute of Medicine (Ross, 2011)
  - 600 IU/d to 70 yrs, 800 IU/d >70 yrs
  - 20 ng/mL vitamin D
- Endocrine Society (Holick, 2011)
  - 1000-2000+ IU/d vitamin D_2 or D_3
  - 30 ng/mL
- Vitamin D advocacy organizations (2015)
  - 2000-5000 IU/d vitamin D_3
  - 40-60 ng/mL

Leaders of the Two Camps



Vitamin D from UVB Exposure



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

VÖRÖS SÜN
NÉPMŰVÉSZETI BOLT


Ergoline
0-24h
NON-STOP SZOLÁRIUM
Ergoline
0-24h
SZOLÁRIUM STÚDIÓ
ÁLLÓ ÉS FEKVŐ GÉPEK
PRÉMIUM KATEGÓRIÁS CSÖVEK
Bejárat
Ergoline
0-24h
SZOLÁRIUM STÚDIÓ
pepsi
GYROS
650-

Other Effects of UV Exposure

- Production of beta-endorphins by UVB, resulting in desire to get more UVB.
- Release of nitric oxide from subcutaneous nitrogen compounds, leading to lower blood pressure.
- Reduced risk of multiple sclerosis, in addition to vitamin D.

Those Most Likely to Have Low 25(OH)D Concentrations

- Those spending most time indoors.
- Not being in sun near solar noon with sufficient body surface exposed.
- Dark-skinned people.
- The overweight and obese.
- Those wearing sunscreen.
- Older folks (vitamin D production decreases in older age due to less 7-dehydrocholesterol).

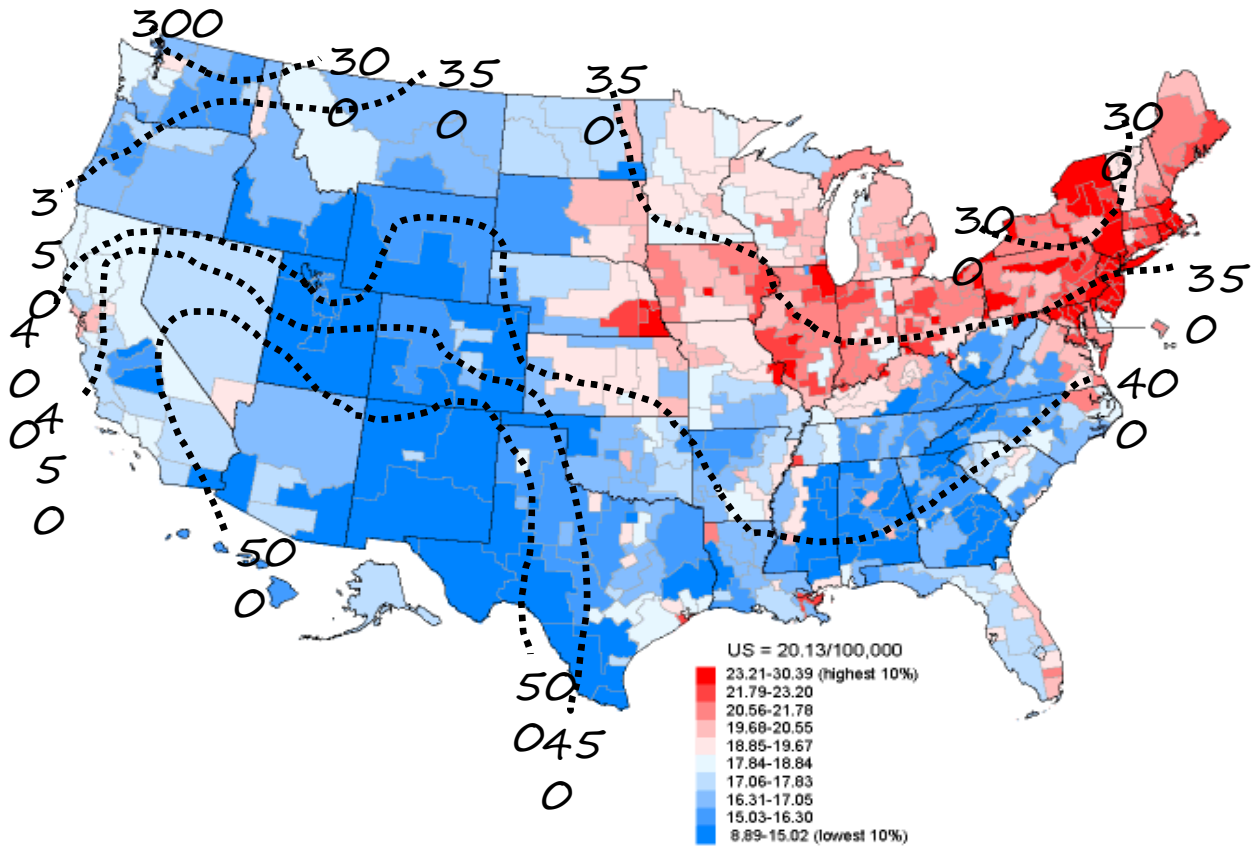
Value of Measuring 25(OH)D

- Since modern life makes it difficult to obtain vitamin D from solar UVB exposure and since 25(OH)D concentrations vary widely with respect to oral vitamin D intake, it is wise to measure 25(OH)D prior to starting supplementation and after a few months.
- www.GrassrootsHealth.net
- www.VitaminDCouncil.org

Benefits of Higher 25(OH)D (Partial List)

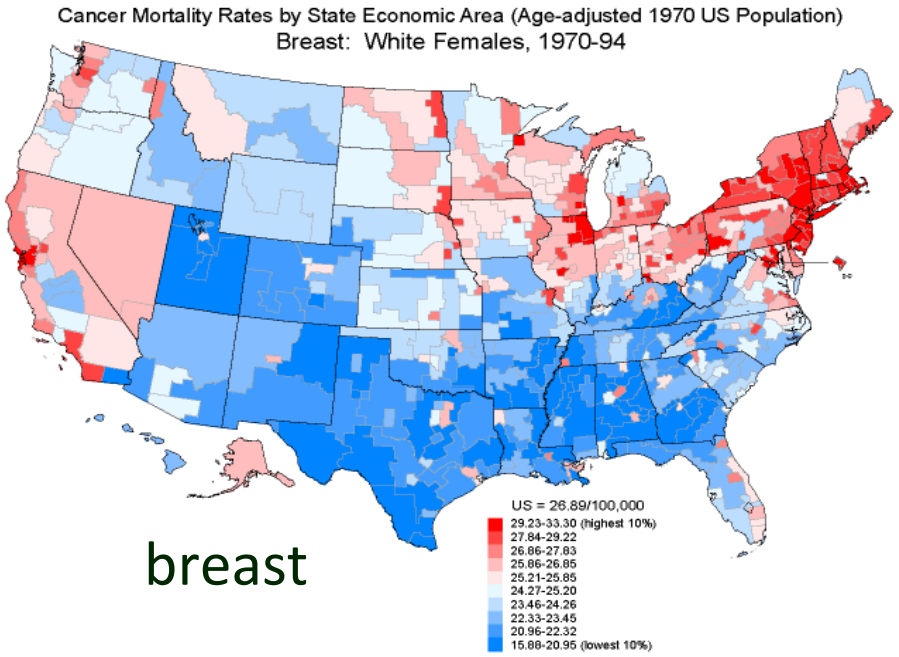
- Risk reduction for
  - Cancer
  - Respiratory tract infection
  - Adverse pregnancy and birth outcomes
  - Premature death
  - Autism and ADHD
  - Dental caries
  - Poor sleep
  - Cognitive dysfunction, Alzheimer's disease
  - Erectile dysfunction and low testosterone

Colon Cancer Mortality Rates, White Males, 1950-69

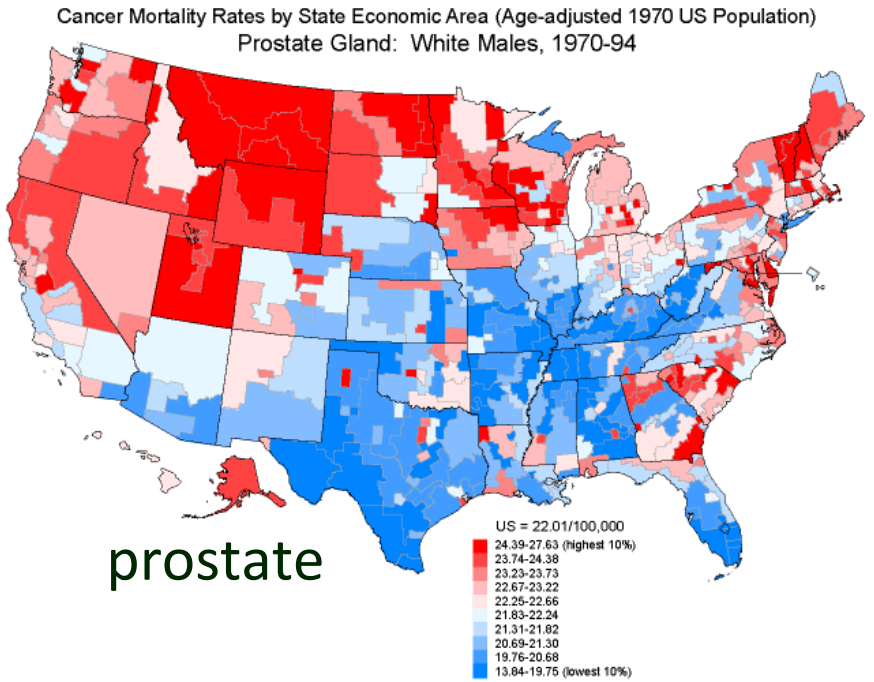


First proposed by Cedric and Frank Garland in 1980

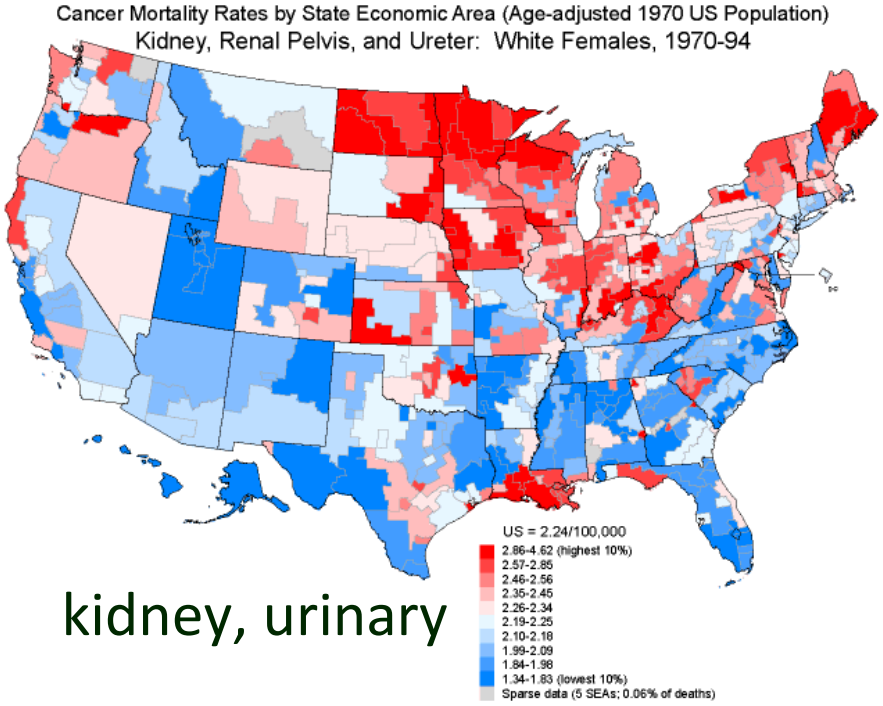
Dotted lines indicate annual solar radiation doses



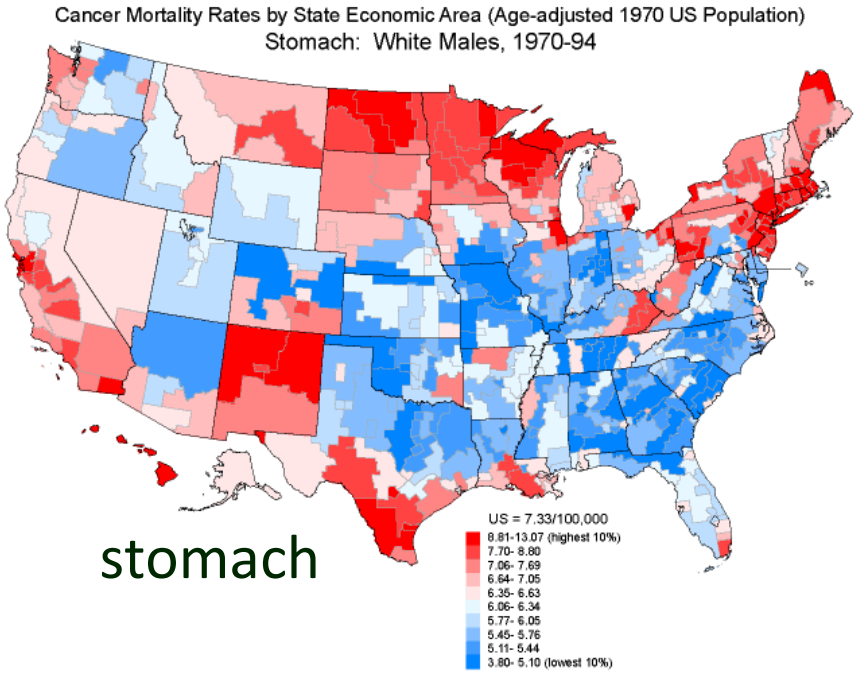
breast



prostate

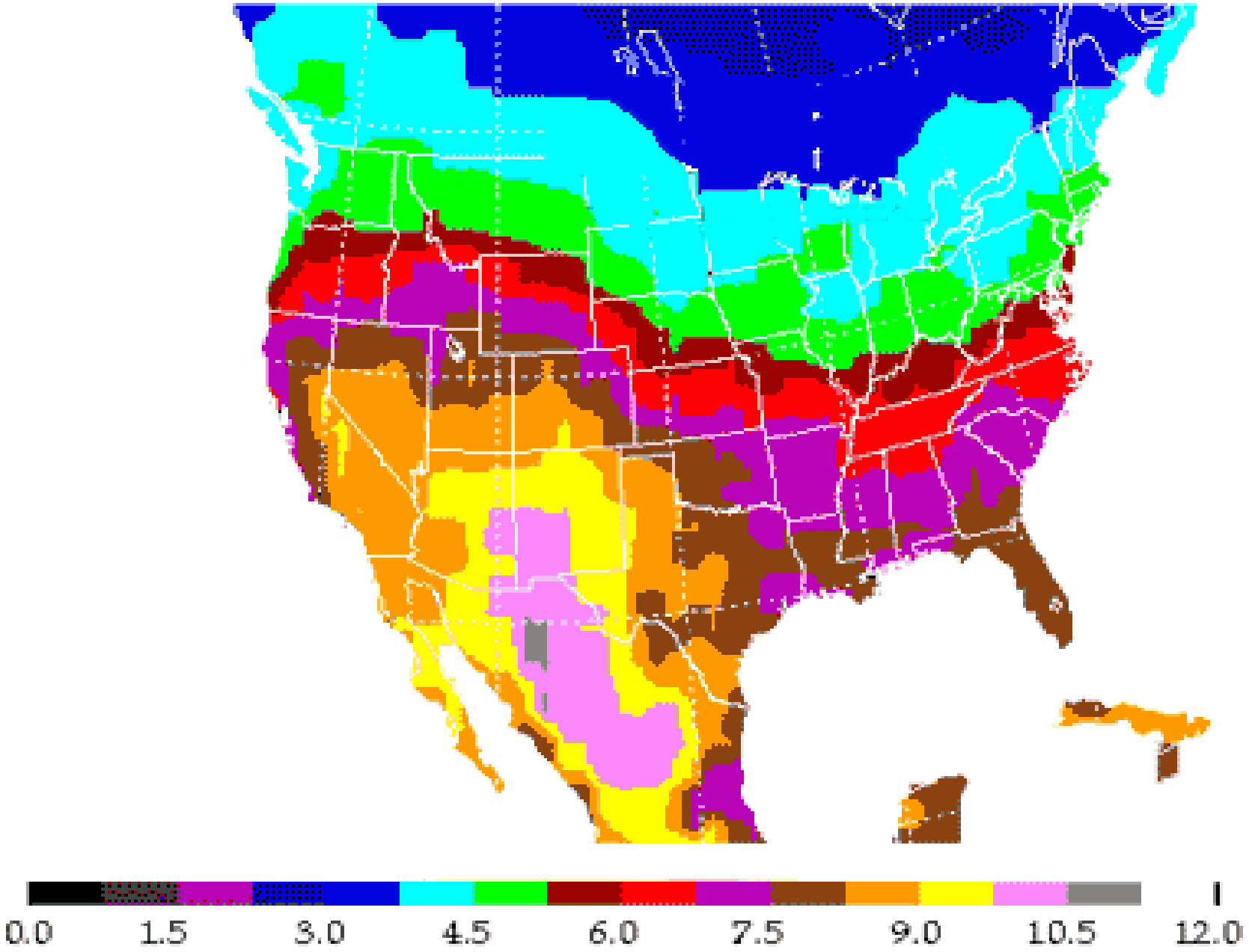


kidney, urinary



stomach

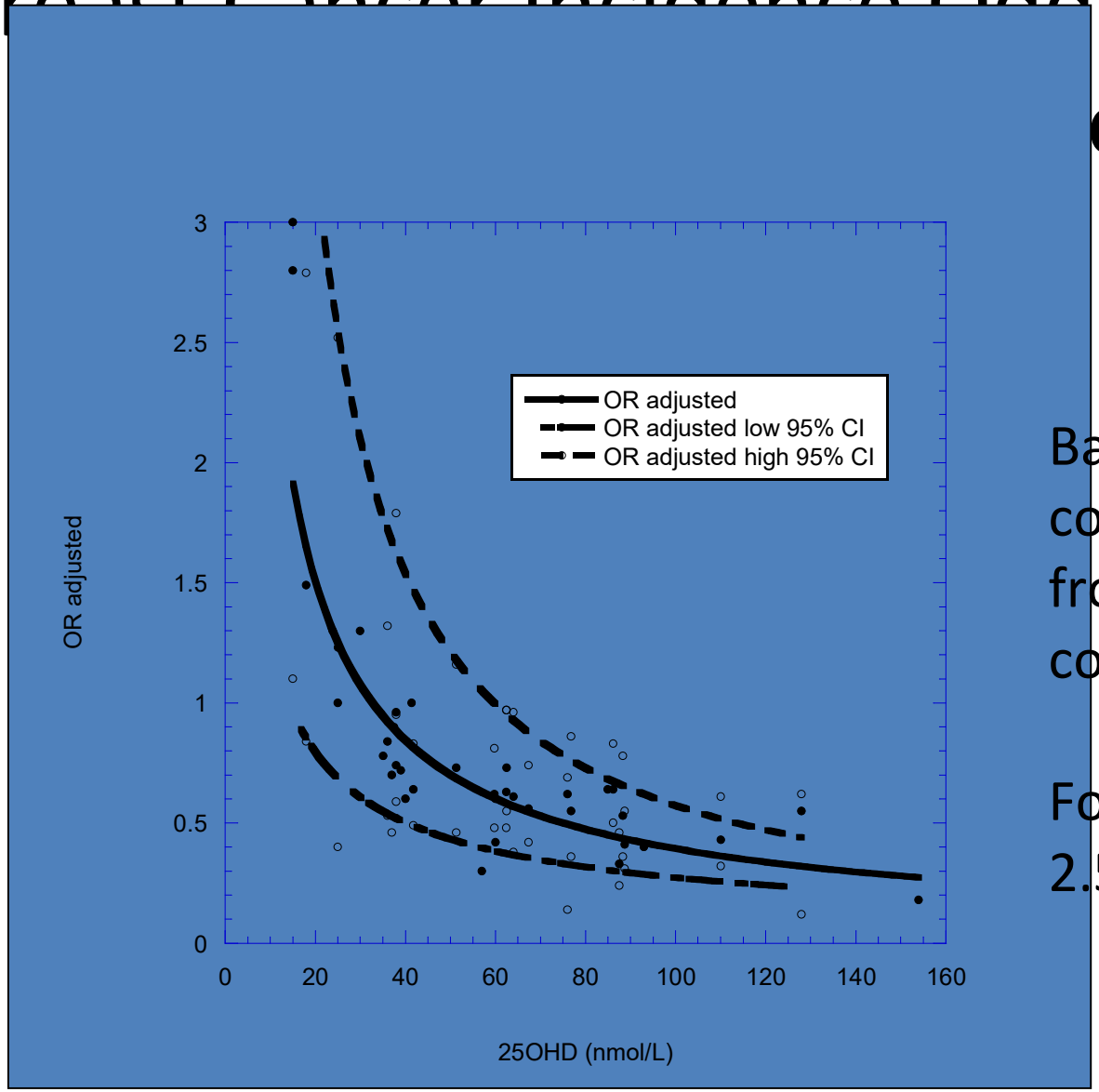
DNA SPECTRAL EXPOSURE (kJ/m^2) FOR JULY 1992



Types of Cancer Reduced by UVB Exposure in the U.S.

- Digestive tract: Colon, esophageal, laryngeal, oral, pharyngeal, rectal, small intestine
- Female: breast, endometrial, ovarian, vulvar
- Urogenital: bladder, kidney, prostate, testicular
- Miscellaneous organs: gallbladder, lung, pancreatic, thyroid
- Blood: Hodgkin's lymphoma, leukemia, non-Hodgkin's lymphoma

Breast Cancer Incidence Odds Ratio vs. 25OHD Concentration

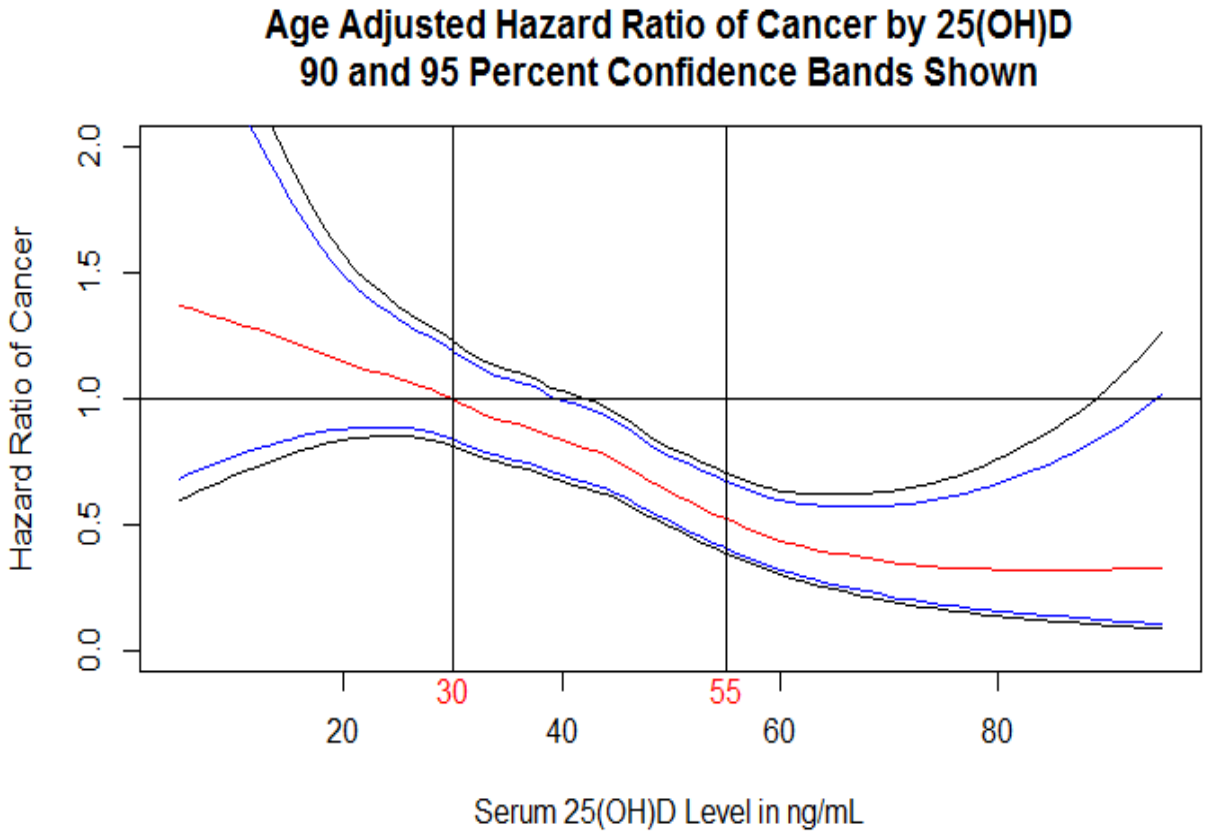


Based on 11 case-control studies from seven countries

For ng/ml, divide by 2.5

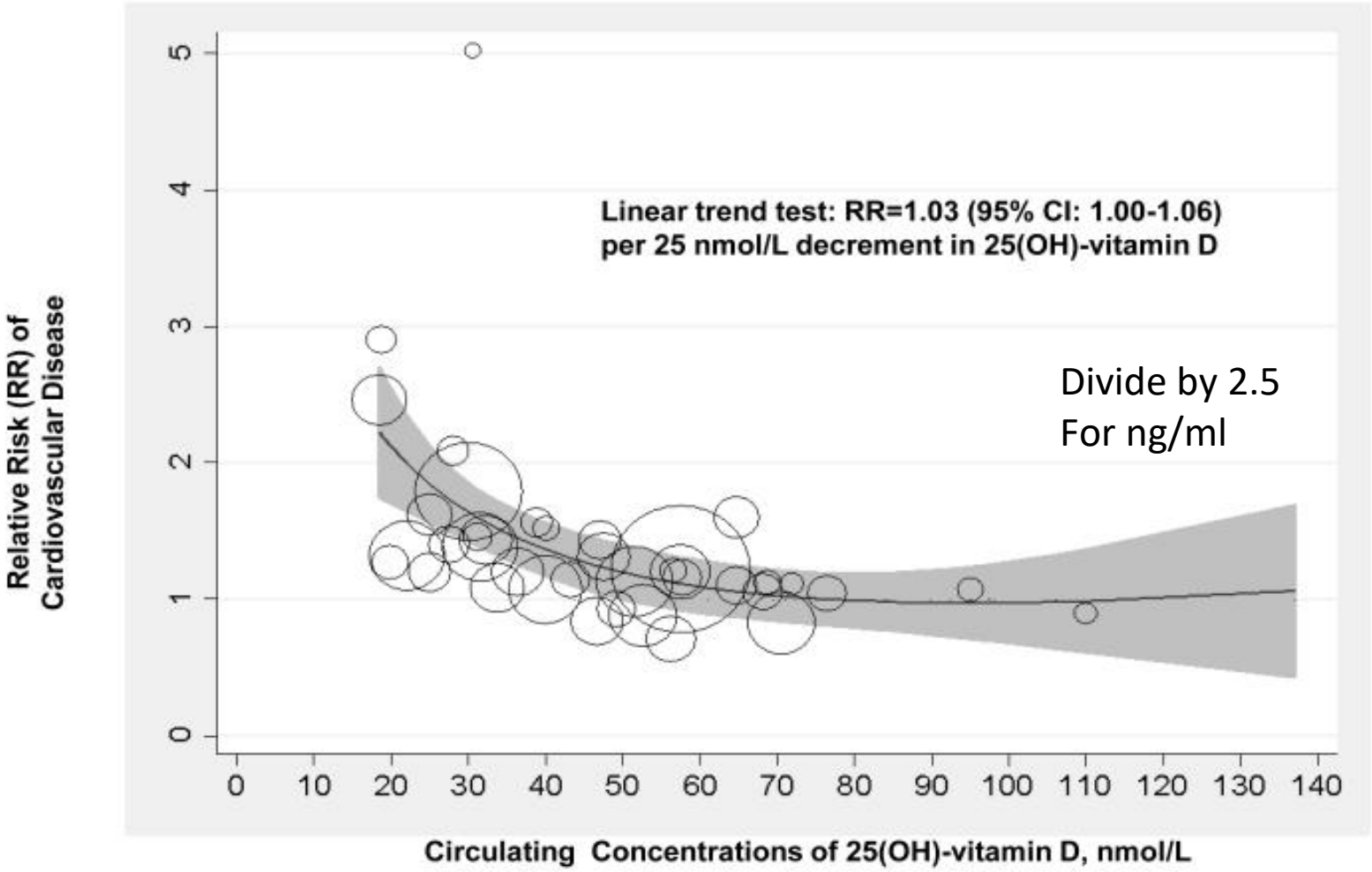
Grant WB, Boucher BJ. PLoS One. 2017 May 1;12(5):e0176448

Results from the Lappe Study Based on 25(OH)D Concentrations (online only)



Lappe J, Watson P, Travers-Gustafson D, Recker R, Garland C, Gorham E, Baggerly K, McDonnell SL. JAMA. 2017 Mar 28;317(12):1234-1243.

Cardiovascular Disease Meta-analysis [Wang, 2012]



Seasonal Influenza

- John Cannell proposed that influenza was largely seasonal due to seasonal variations in solar UVB doses.
- Two clinical trials, one involving post-menopausal African-American women, the other involving Japanese school children (Type A only), supported that hypothesis.
- (Cold temperature and low humidity also contribute to the seasonality.)

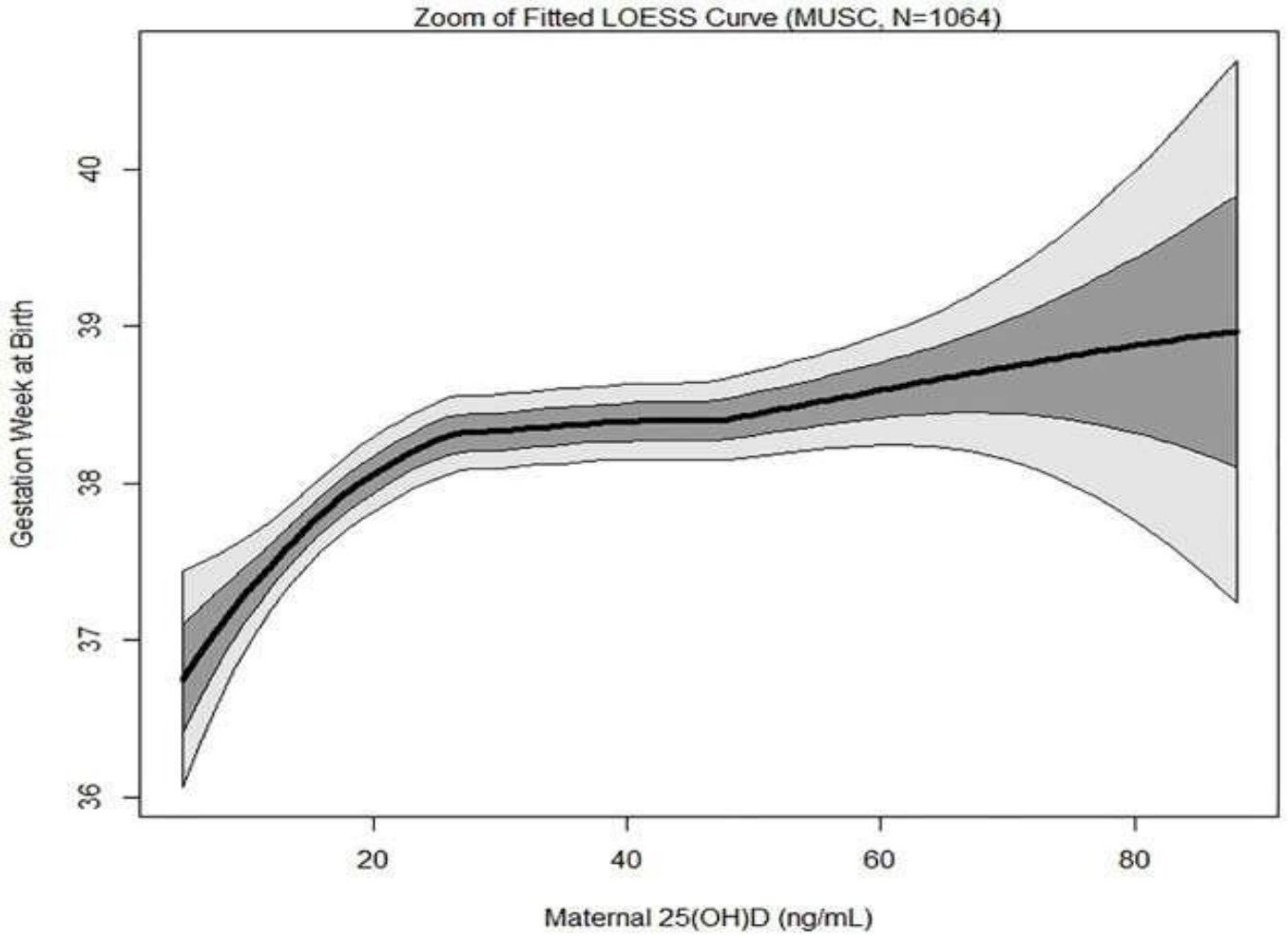
Pregnancy

- Clinical trials in South Carolina found that pregnant women have better pregnancy and birth outcomes by taking 4000-6400 IU/d vitamin D_3 and reaching >40 ng/mL 25(OH)D.
- For 25(OH)D >40 ng/mL, $1,25(OH)_2D_3$ concentrations stabilize, leading to improved gene expression.

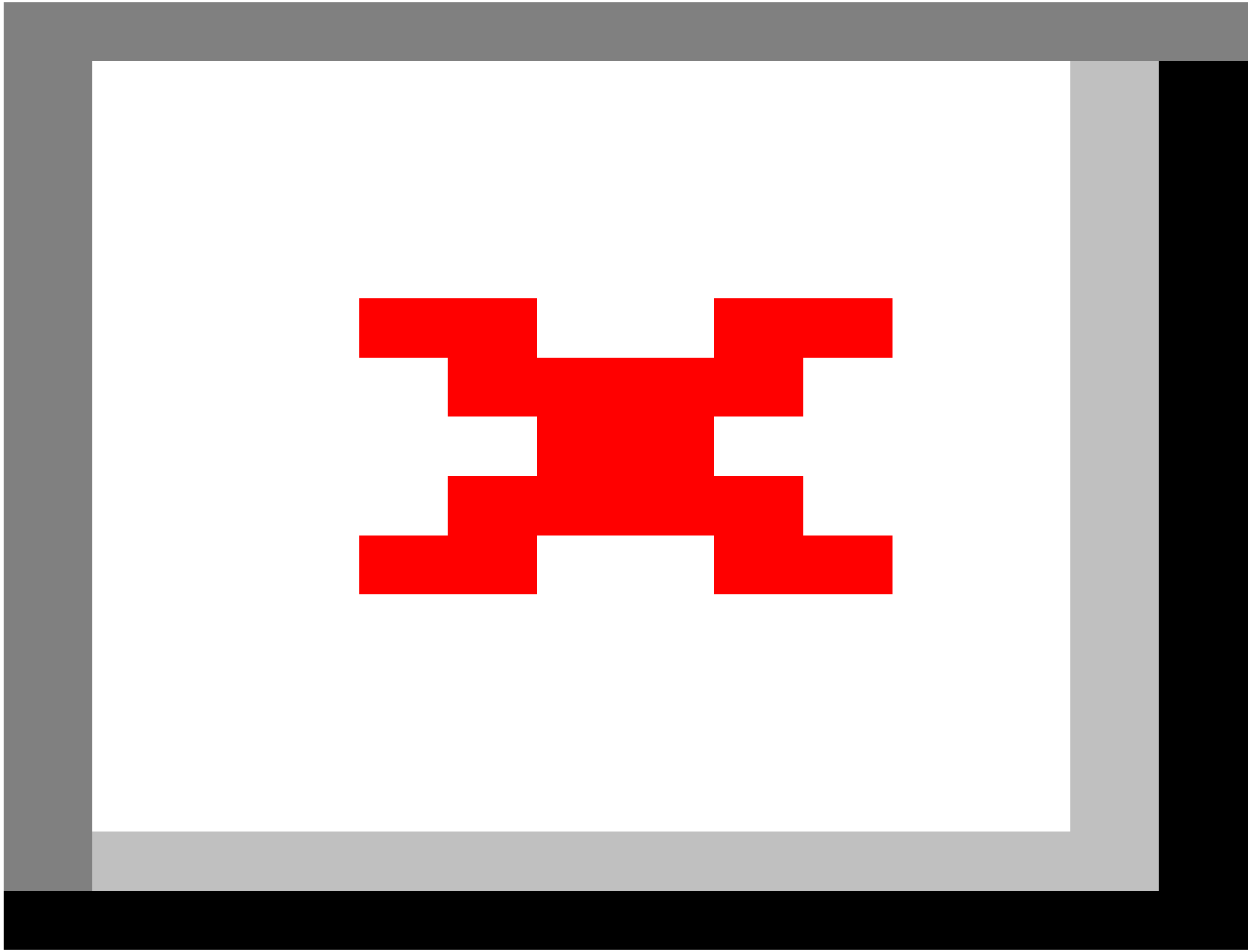
Benefits of Vitamin D during Pregnancy

- Reduced risk of primary C-section delivery
- Reduced risk of gestational diabetes.
- Reduced risk of preterm birth.
- For infants
  - Reduced risk of low-for-gestational weight.
  - Reduced risk of autism.
  - Reduced risk of asthma

Birth Week vs. 25(OH)D Concentration



McDonnell SL, Baggerly KA, Baggerly CA, ….. Hollis BW, Wagner CL. PLoS One. 2017 Jul 24;12(7):e0180483.



An estimate of the global reduction in mortality rates through doubling vitamin D levels.

- The vitamin D-sensitive diseases that account for more than half of global mortality rates are CVD, cancer, respiratory infections, respiratory diseases, tuberculosis and diabetes mellitus. Additional vitamin D-sensitive diseases and conditions that account for 2 to 3% of global mortality rates.
- Increasing serum 25(OH)D levels from 22 to 44 ng/ml could reduce the vitamin D-sensitive disease mortality rate by an estimated 20%, increasing life expectancy by 2 years.
- Grant, Eur J Clin Nutr. 2011

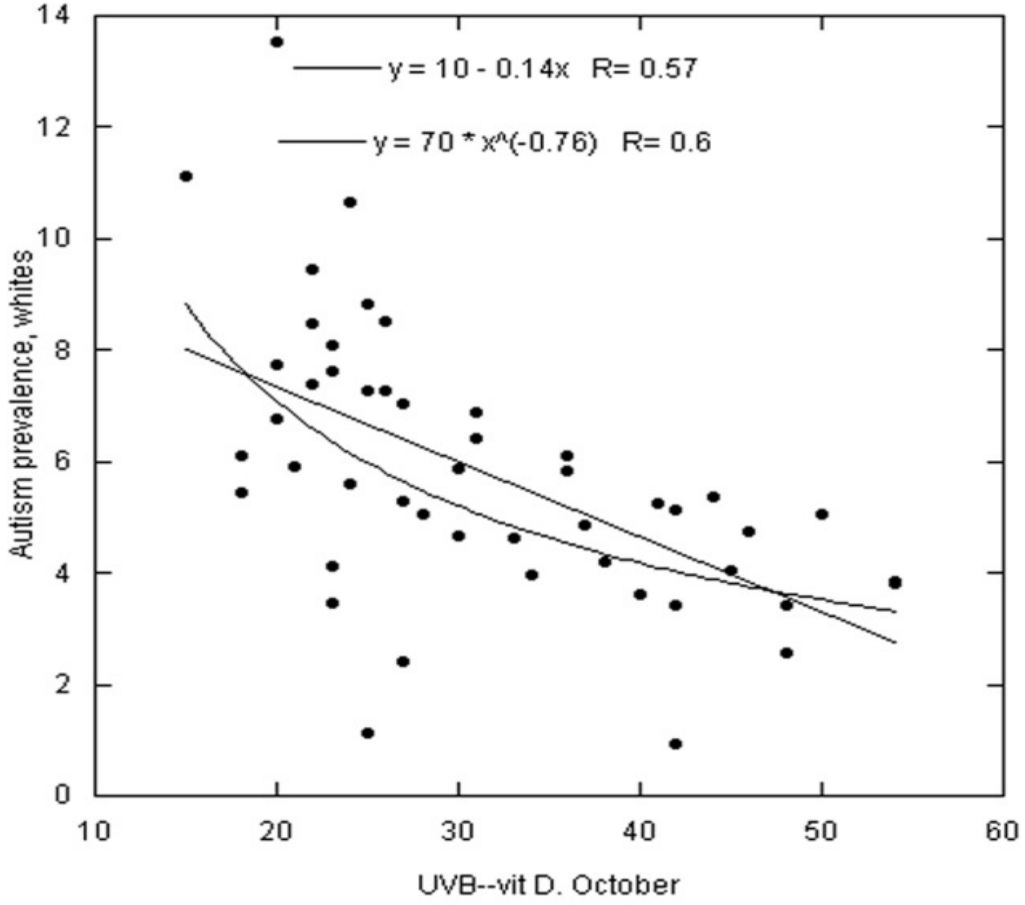
Athletic Performance

- Vitamin D may improve athletic performance in vitamin D-deficient athletes.
  Peak athletic performance may occur when 25(OH)D levels approach those obtained by natural, full-body, summer sun exposure, which is at least 50 ng/mL. Such 25(OH)D levels may also protect the athlete from several acute and chronic medical conditions.
- Cannell et al., 2009

From VitaminDCouncil.org by John Cannell (2010)

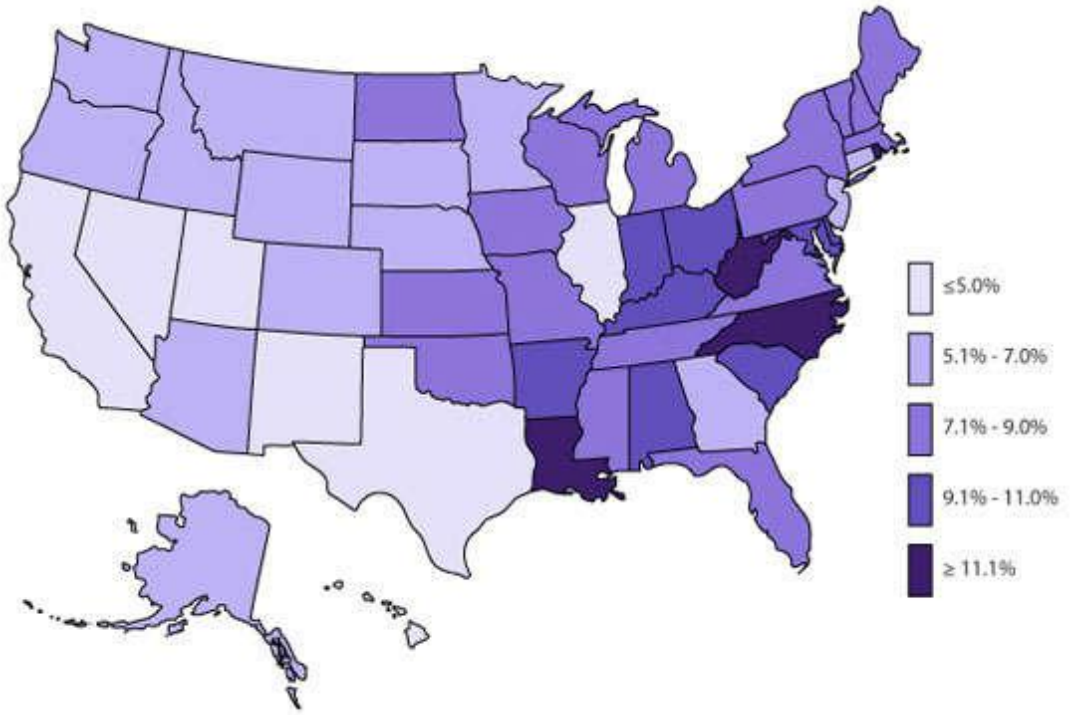
- The Chicago Blackhawks are the first vitamin D team in modern professional sports history.
- According to my sources, the Chicago Blackhawk team physicians began diagnosing and treating vitamin D deficiency in all Blackhawk players about 18 months ago. Apparently, most players are on 5,000 IU per day.
- After many losing seasons, last year the Blackhawks came out of nowhere to get to the Western conference finals. This year they are playing even better.

Autism Prevalence, White Children, vs. UVB dose for October

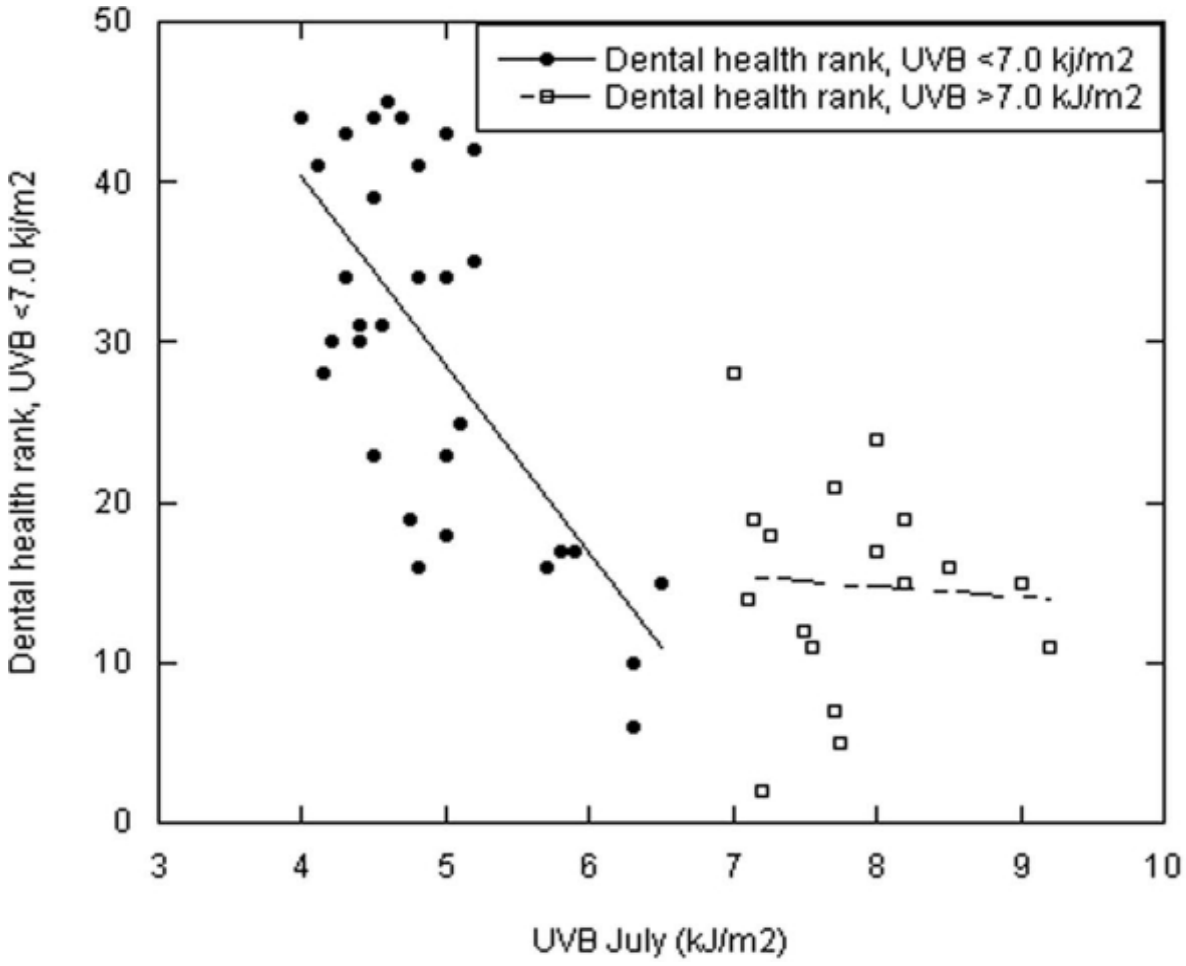


Grant and Cannell, Dermato-Endocrinolgy, 2013

ADHD Prevalence 2007
From the CDC

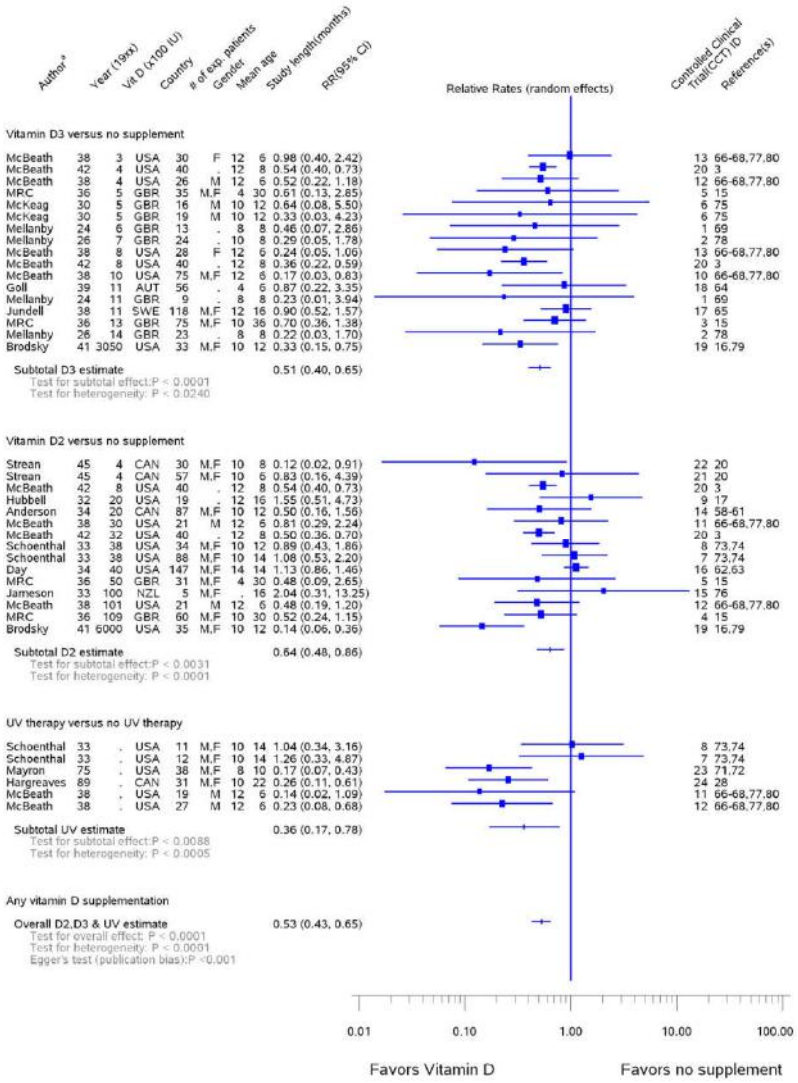


Dental Caries Rate for Servicemen, 1918-1934 vs. UVB Dose



Grant, Dermato-Endocrinology, 2011

Dental Caries – Vitamin D Clinical Trials
Hujoel, 2012



Sleep

- Raising 25OHD to 60-70 ng/ml improves sleep.
- However, after two years, systemic pain develops – due to depletion of some of the gut biome involved in B vitamin production.
- Solution: at that point, supplement with B100 for a couple of months.

- Gominak, Med Hypothesis. 2016

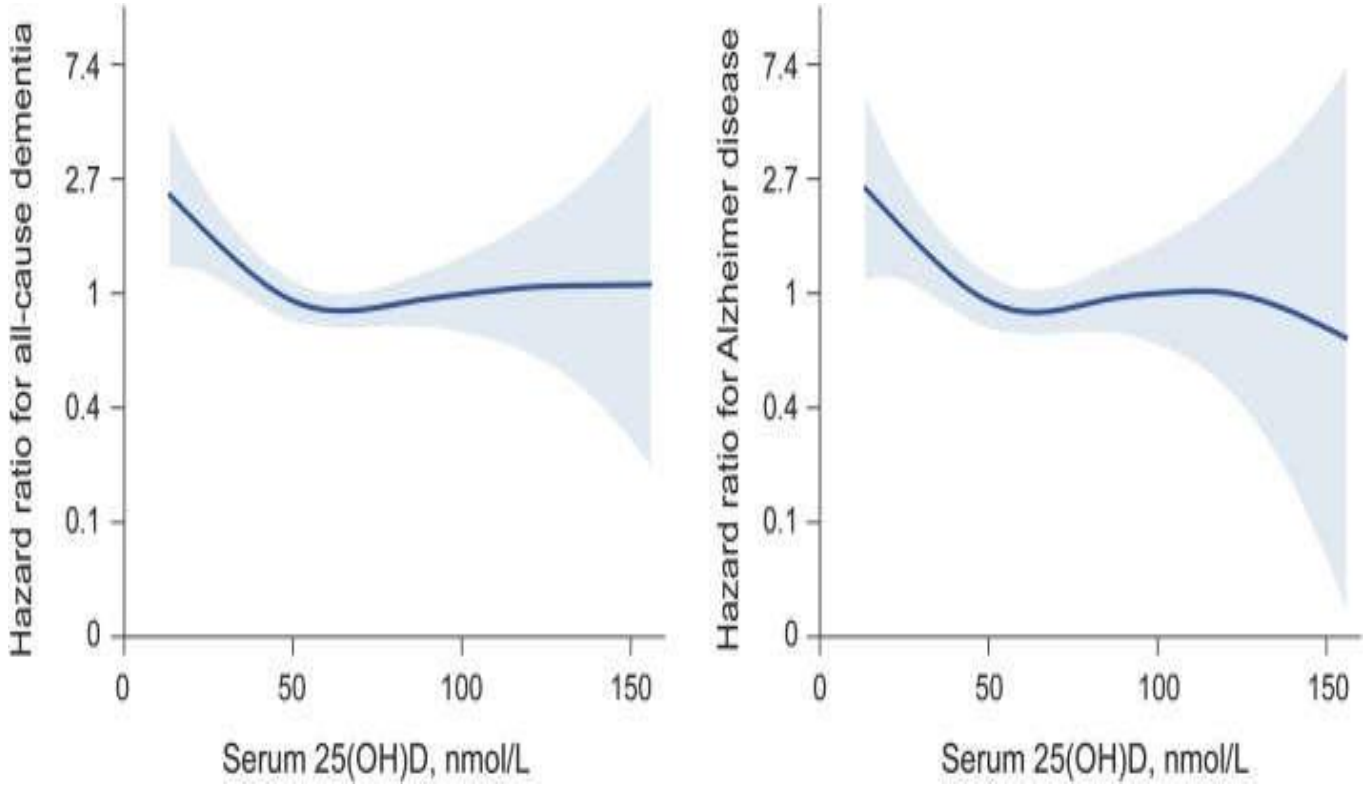
Vitamin D and Verbal Fluency

- Performance on verbal fluency, differed by vitamin D status. Specifically, participants with supratherapeutic levels provided a greater number of words than those with insufficient
- Similarly, vitamin D status was a significant independent predictor of verbal. Spline analyses revealed that there is a positive, near-linear association between verbal fluency and 25(OH)D levels up to and exceeding 40 ng/ml.
- Pettersen, JCEN, 2016

Vitamin D Status and Rates of Cognitive Decline in a Multiethnic Cohort of Older Adults

- Rates of decline in episodic memory and executive function among VitD-deficient participants were greater than those with adequate status after controlling for age, sex, education, ethnicity, body mass index, season of blood draw, vascular risk, and apolipoprotein E4 genotype.
- Miller et al., JAMA Neurol, 2015

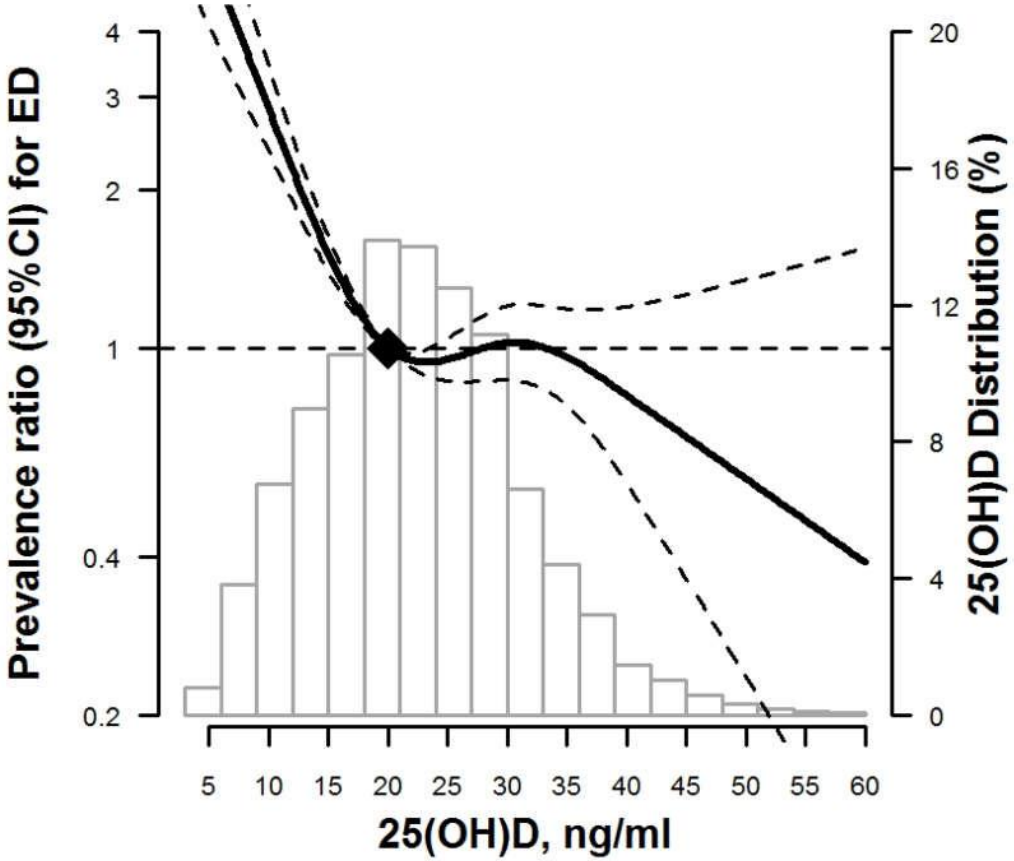
Alzheimer's and Dementia Prospective Study 5.6 yrs



Littlejohns et al., Neurology, 2014

Divide by 2.5 for ng/ml

Erectile Dysfunction



Farag et al., 2016

Testosterone - 1

- Participants received either 83 µg (3,332 IU) vitamin D daily for 1 year (n = 31) or placebo (n =2 3). Initial 25(OH)D concentrations were in the deficiency range (< 20 ng/ml) and testosterone values were at the lower end of the reference range (9.1-55.3 nmol/l for males aged 20-49 years) in both groups. Mean circulating 25(OH)D concentrations increased significantly by 21 ng/ml in the vitamin D group, but remained almost constant in the placebo group.

Testosterone - 2

- Compared to baseline values, a significant increase in total testosterone levels (from 10.7 ± 3.9 nmol/l to 13.4 ± 4.7 nmol/l; $p < 0.001$), bioactive testosterone (from 5.2 ± 1.9 nmol/l to 6.3 ± 2.0 nmol/l; $p = 0.001$), and free testosterone levels (from 0.22 ± 0.08 nmol/l to 0.27 ± 0.09 nmol/l; $p = 0.001$) were observed in the vitamin D supplemented group.
- Pilz et al., 2011

Surgery

- The mean length of stay in the Surgical Intensive Care Unit for the severe vitamin D-deficient group was 13 ± 20 days versus 7 ± 15 days and 5 ± 7 days for the moderate and mild vitamin D-deficient groups, respectively, which was clinically significant (P = 0.002).
- Matthews et al., Am J Surg, 2012

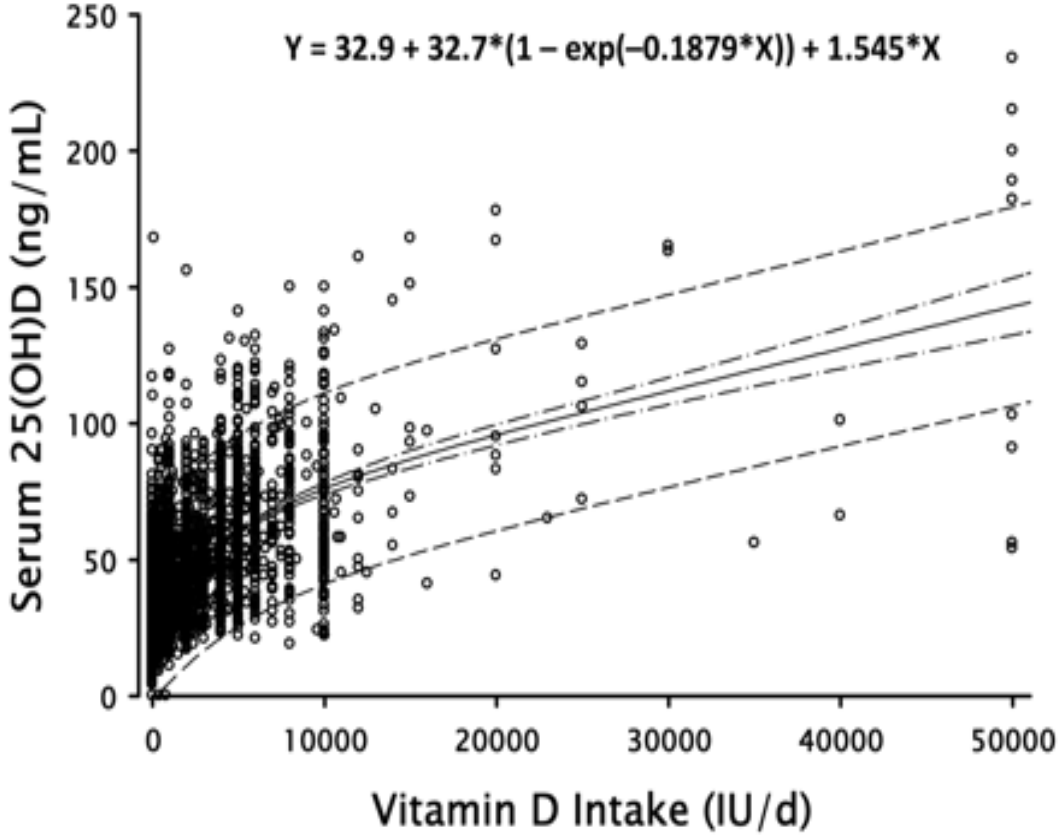
Where is Vitamin D Policy Headed?

- The IOM recommendation of 2010 is now considered incorrect.
- Several major vitamin D supplementation trials will complete data collection soon.
- They generally used 2000 IU/d or 100,000 IU/mo vitamin D_3, perhaps with calcium.
- The results of these studies will provide much of the basis for next recommendations.

Why Vitamin D Clinical Trials Should Be Based on 25(OH)D Concentrations

- Most trials used principles designed to test pharmaceutical drugs:
  - the trial is the sole source of the agent, and
  - dose-response relationships are linear.
- However, neither assumption is true for vitamin D since neither vitamin D dose-responses or health outcome-serum 25(OH)D concentration relationships are linear.

Variation of 25(OH)D Concentration with Oral Vitamin D Intake



Garland CF, French CB, Baggerly LL, Heaney RP. Anticancer Res. 2011 Feb;31(2):607-11.

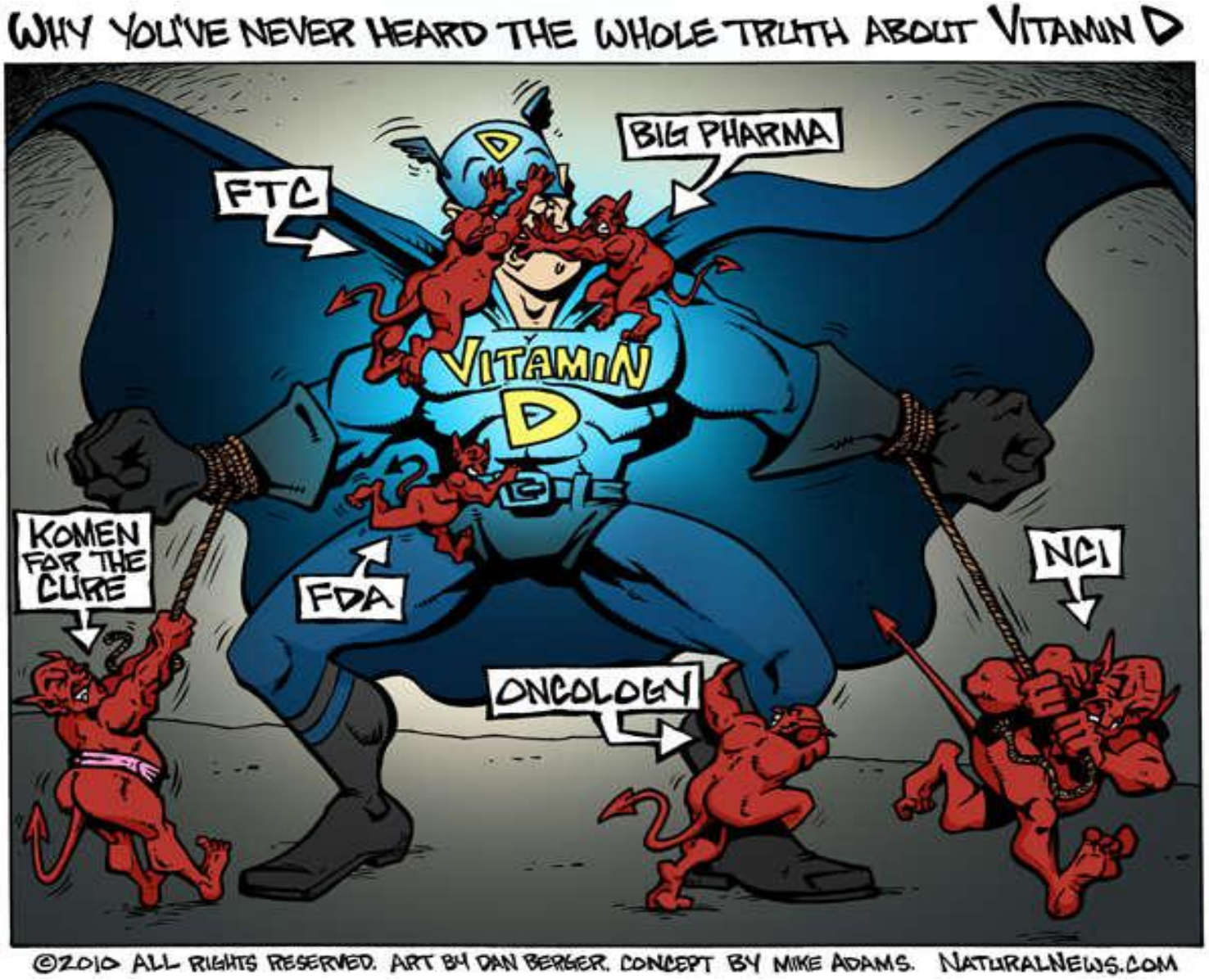
Necessity for Vitamin D Clinical Trials

- Observational studies could be using 25(OH)D concentration as an index of diet [e.g., meat eaters get 25(OH)D from meat] or UVB exposure.
- Findings of mechanisms does not tell how important vitamin D is in reducing risk.
- Health systems look to clinical trials as the “gold standard”.


REX CIBORUM
GOOSE AND
DUCK LIVER
850

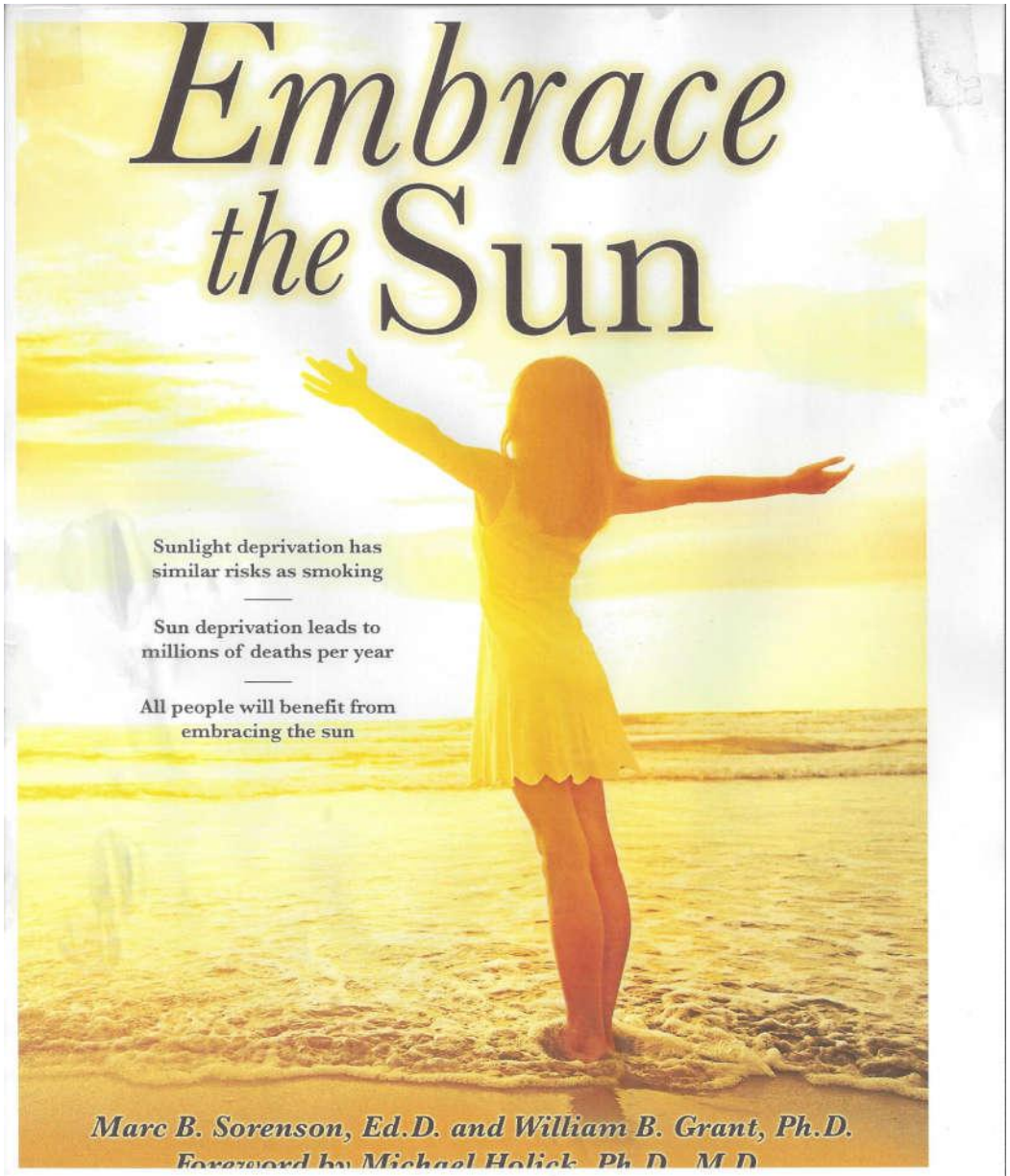
Why vitamin D clinical trials should be based on 25(OH)D concentrations - 2

- We propose a hybrid observational approach to vitamin D RCT design, based primarily on serum 25(OH)D concentration, requiring an understanding of serum 25(OH)D concentration-health outcome relationships, measuring baseline 25(OH)D values, recruiting non-replete subjects, measuring serum 25(OH)D during the trial for adjustment of supplemental doses for achievement of pretrial selection of target 25(OH)D values, where possible, and analyzing health outcomes in relation to those data rather than solely to vitamin D dosages.
- Grant et al., JSBMB, 2017



http://www.naturalnews.com/028353_vitamin_D_sunlight.html

Embrace the Sun



Sunlight deprivation has similar risks as smoking

Sun deprivation leads to millions of deaths per year

All people will benefit from embracing the sun

Marc B. Sorenson, Ed.D. and William B. Grant, Ph.D.
Foreword by Michael Holick, Ph.D., M.D.

For More Information

- www.ncbi.nlm.nih.gov/pubmed/
- scholar.google.com/
- grassrootshealth.net/
- www.vitamindwiki.com/VitaminDWiki
- www.vitamindcouncil.org
- vitamindsociety.org/