Is Vitamin D the Fountain of Youth?

Neil Binkley, M.D.

University of Wisconsin - Madison
steoporosis Clinical Center
& Research Program

It is Time to Think Clearly and Objectively About Vitamin D….

Can Vitamin D Help Prevent Swine Flu and Other Diseases?

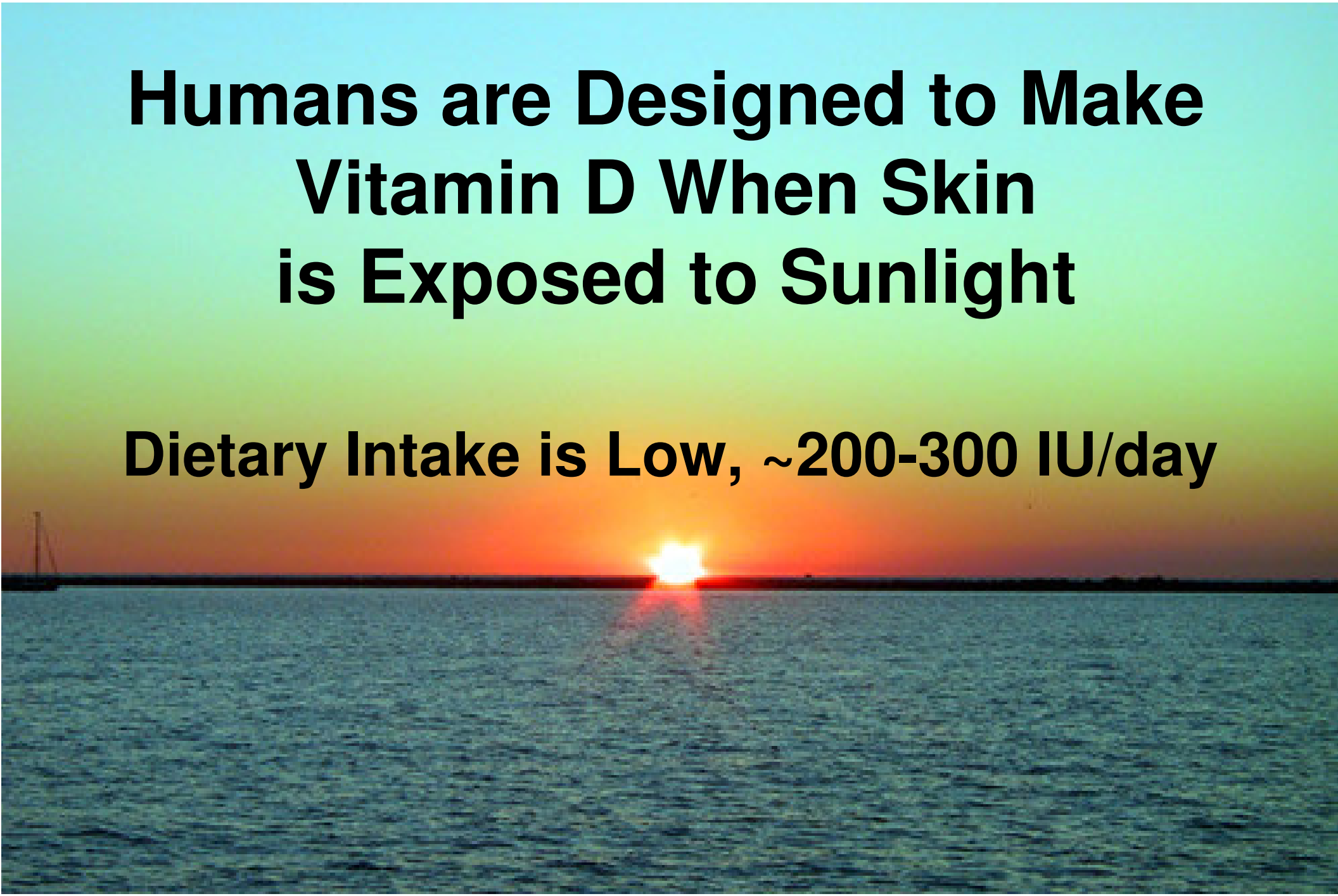
April 29, 2009 in Cold & Flu Prevention, Diabetes, Did You Know?, Educational, Empowering,

Vitamin D 'may help slow ageing'

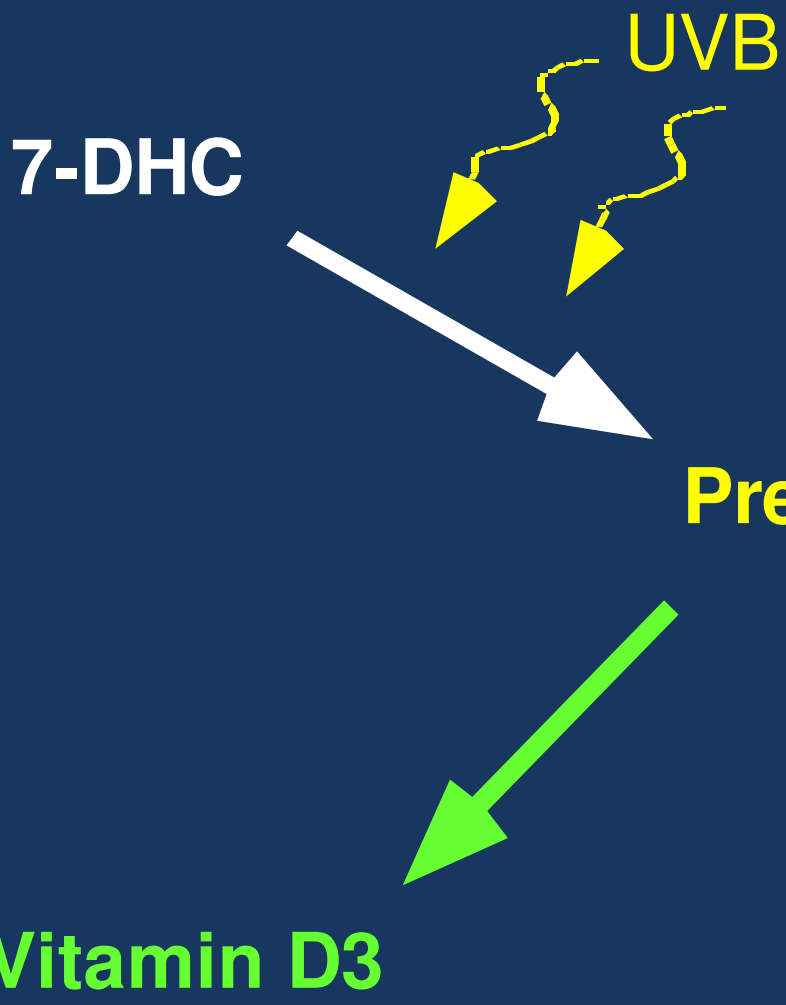
A vitamin made when sunlight hits the skin could help slow down the ageing of cells and tissues, say researchers.

A King's College London study of more than 2,000 women found those with higher vitamin D levels showed fewer ageing-related changes in their DNA.

Vitamin D may have far-reaching effects in the body


Humans are Designed to Make
Vitamin D When Skin
is Exposed to Sunlight
Dietary Intake is Low, ~200-300 IU/day

UVB (~280-315 nm) Produces Vitamin D



Holick, Ann NY Acad Sci, 435:1-13, 1985

Human Lifestyle Required Physical Activity, Sun Exposure and a Hunter-Gatherer Diet

Eaton S, Osteoporos Int, 17(suppl 2): S2-3, 2006

We are “Cavemen”

Humans Were Not D Deficient Until the Industrial Revolution

www.nettlesworth.durham.sch.uk/time/victorian/vindust.html

In the late 1800's estimated that ~90% of children who lived in industrialized cities of Europe and North America had rickets

Signs of rickets include; growth retardation, widening of the ends of the long bones and bowing and bending of the legs

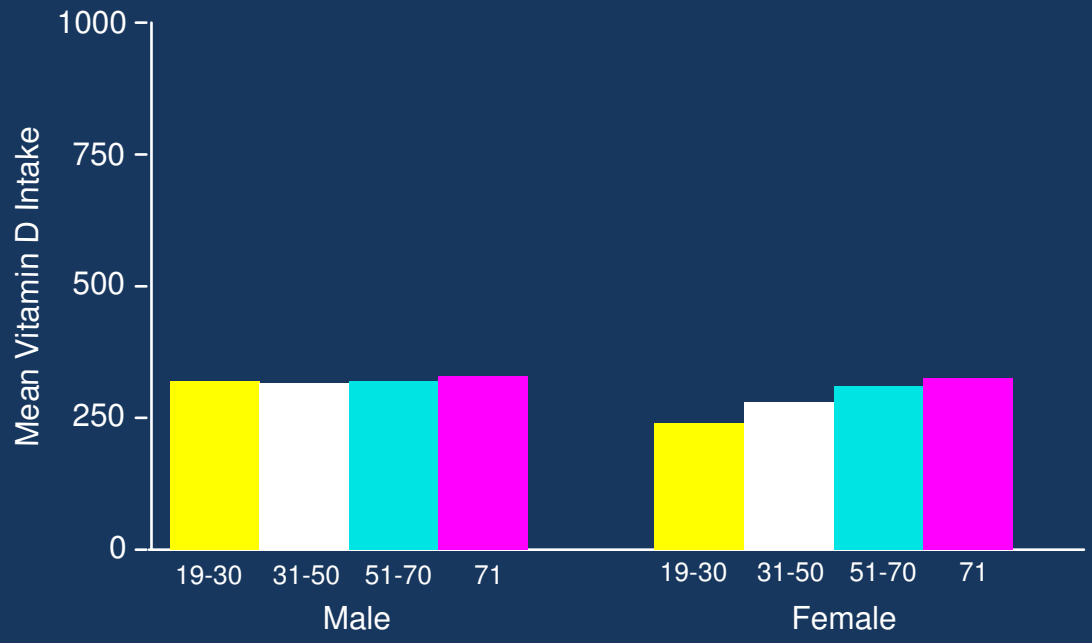
The Induction of Growth-Promoting and Calcifying Properties in a Ration by Exposure to Light

"By irradiation with the quartz mercury vapor lamp, rat rations can be activated, making them growth promoting and bone-calcifying, to the same degree as when the rats are irradiated directly."

Steenbock, J Biol Chem, 1924

Vitamin D is Rare in Food; as a Result, Intake is Low At All Ages

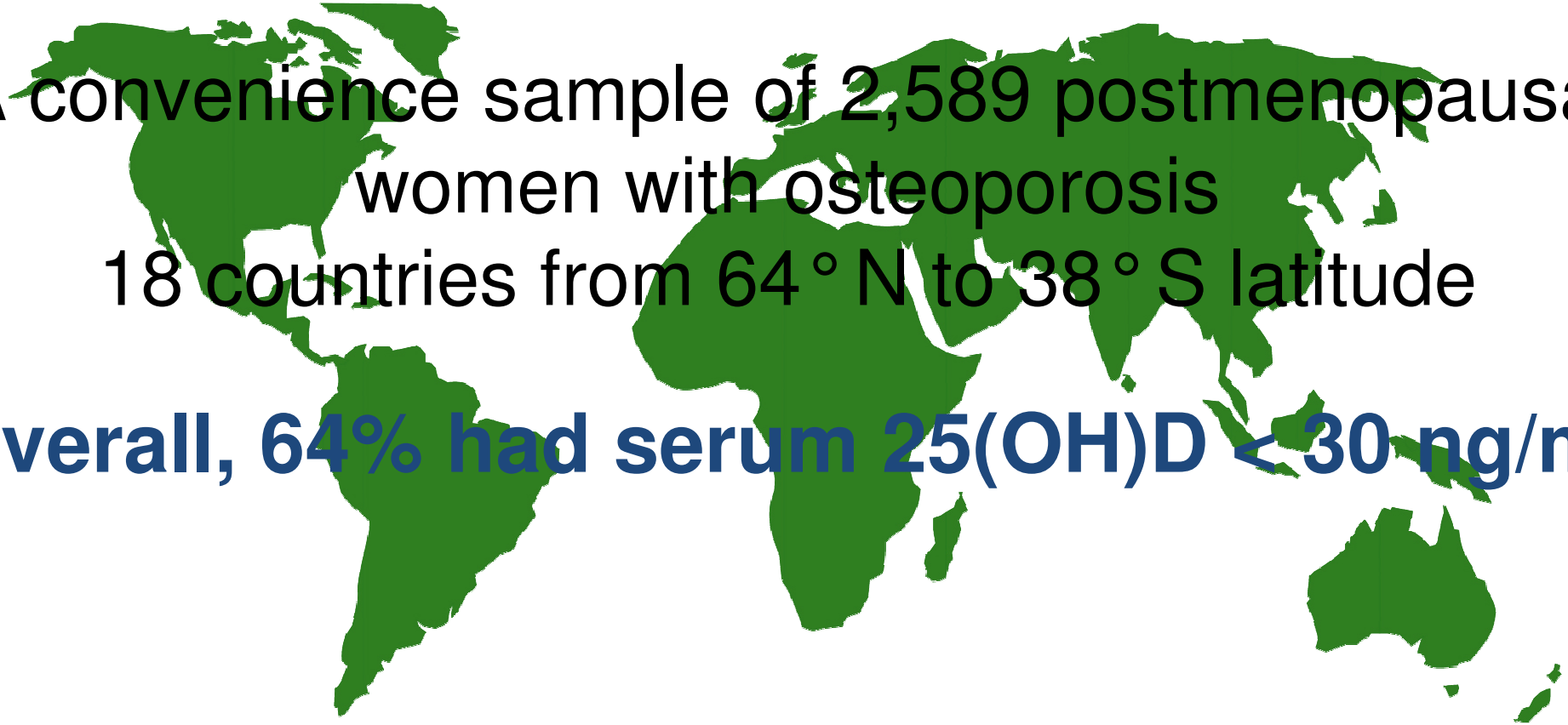
Food	IU
Cod Liver Oil, 1 Tbs	1360
Salmon, 3.5 oz	360
Mackerel, 3.5 oz	345
Milk, 1 cup	100
Fortified cereal, 3/4 cup	50
Liver, 3.5 oz	30
Egg, one whole	25



NHANES III data; mean vitamin D intake from food plus supplements

Moore, et. al., Am Diet Assoc, 104;980-983, 2004

Vitamin D Inadequacy is Common Worldwide



A convenience sample of 2,589 postmenopausal women with osteoporosis
18 countries from 64° N to 38° S latitude

Overall, 64% had serum 25(OH)D < 30 ng/ml

Adapted from Lips, et. al., J Intern Med, 260; 245-254, 2006

What's Our Target 25(OH)D?
How Much Vitamin D Do We Need?

"For five of the six authors, the minimum desirable 25(OH)D concentration clusters between 70 and 80 nmol/L." (28-32 ng/ml)

This requires ~1000 IU/day

Dawson-Hughes, Heaney, Holick, Lips, Meunier & Vieth, Osteoporos Int, 16;713-716, 2005

1,000-2,000 IU Daily is Conservative

"…..it would require input of an additional 2,600 IU/day of oral vitamin D3 to ensure that 97.5% of older women have 25(OH)D values at or above desirable levels."

Heaney RP, J Nutr 136;1123-1125, 2006

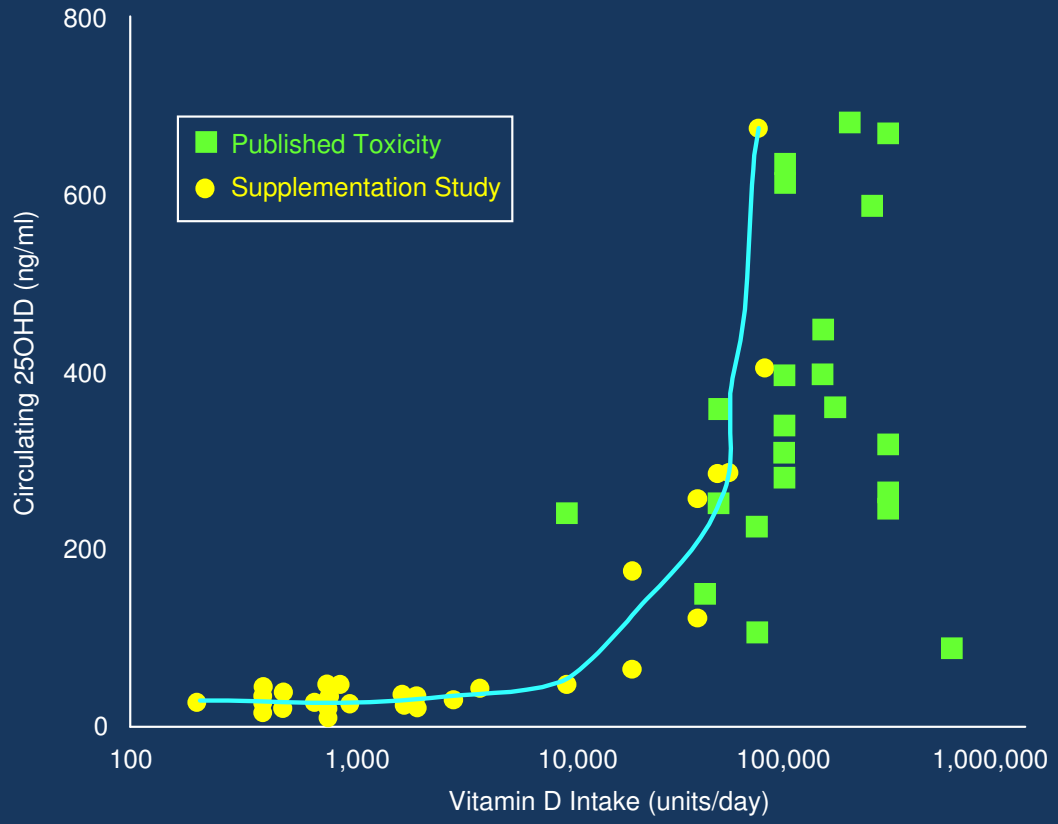
*"Current recommendation among experts is between **2,000 and 4,000 units per day** to reduce risks of cancer and autoimmune disease."*

DeLuca H, October, 2007

No Toxicity Until Very High Doses

Assembled data from many vitamin D supplementation studies & published cases of toxicity

Toxicity cases all Involve intake **>40,000 IU/day**

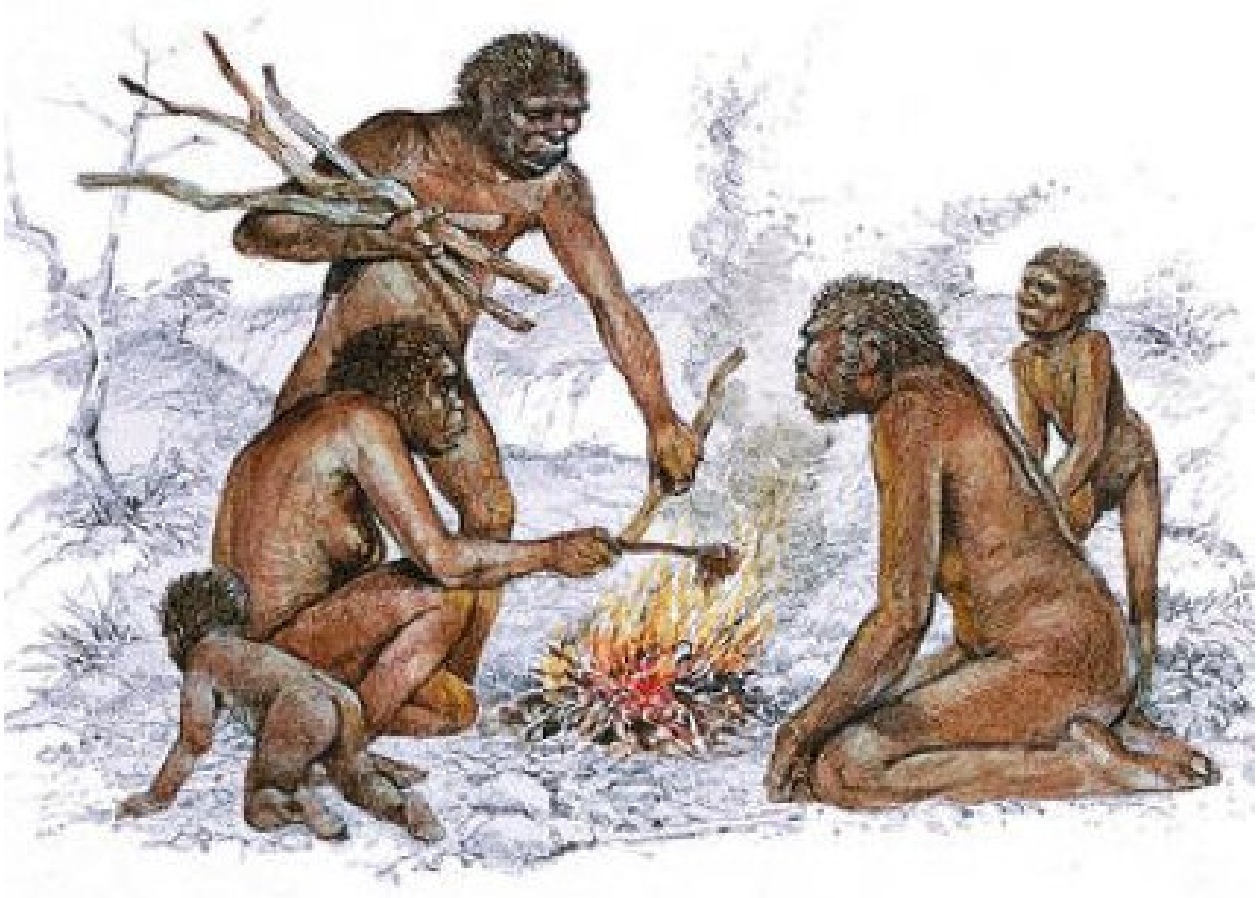


Veith, Am J Clin Nutr, 69;842-856, 1999

"All known poisonings of adults with vitamin D_3 reflect misuse on an industrial scale."

Veith, Lancet, 359;672, 2002

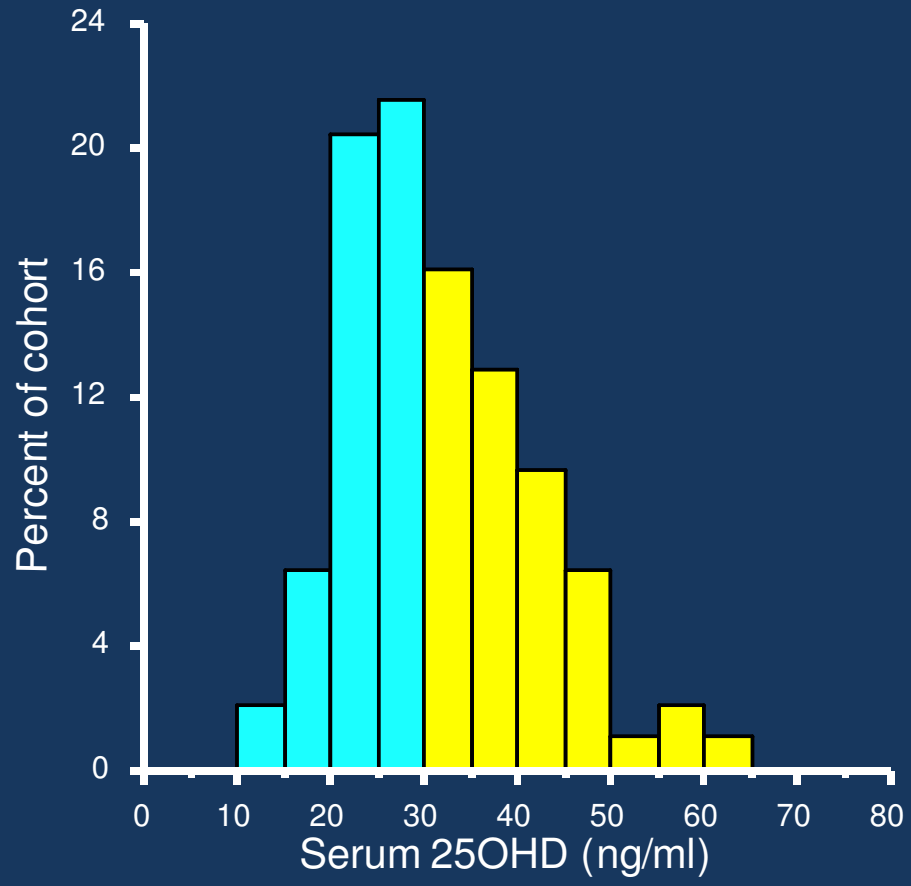
"I suggest that the 25(OH)D levels in the lifeguards are normal and the "normals" are actually vitamin D deficient." Hollis, J Nutr, 135:317-325, 2005



If we use highly sun exposed people to define a goal 25(OH)D concentration what is our target when prescribing vitamin D treatment?

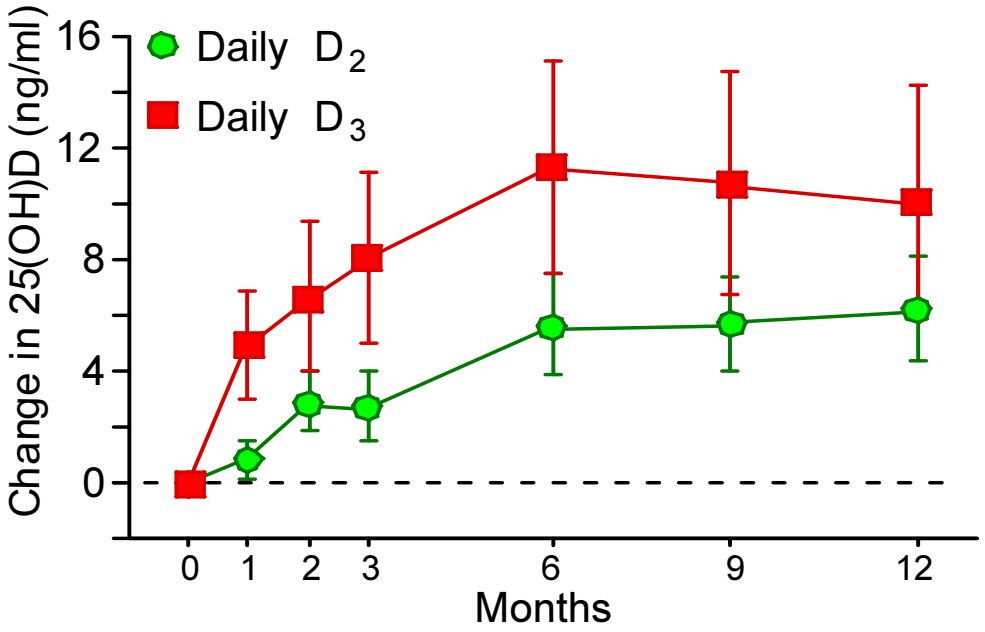
Even Major Sun Exposure Does Not Guarantee Vitamin D Adequacy

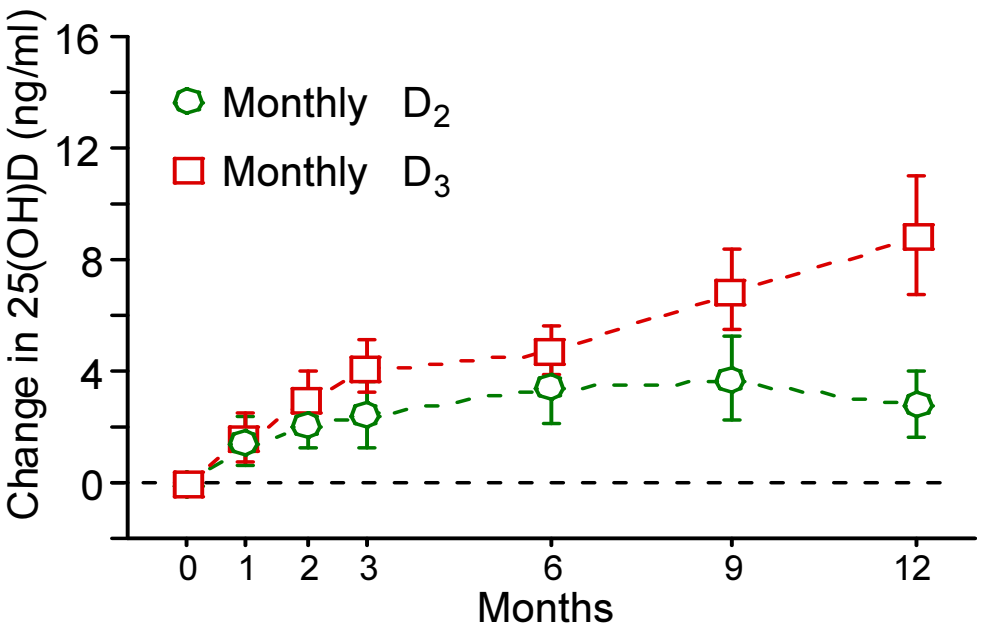
Mean sun index = 11.1



Binkley, et al, J Clin Endocrinol Metab, 92:2130-2135, 2007

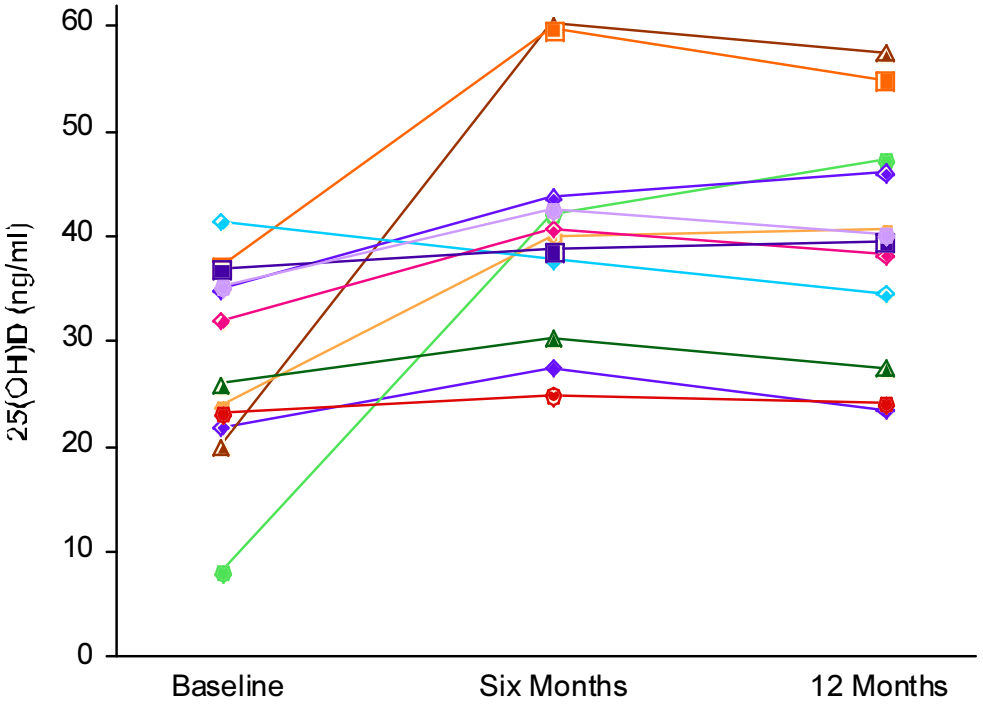
Vitamin D_3 (Cholecalciferol) or Vitamin D_2 (Ergocalciferol)?



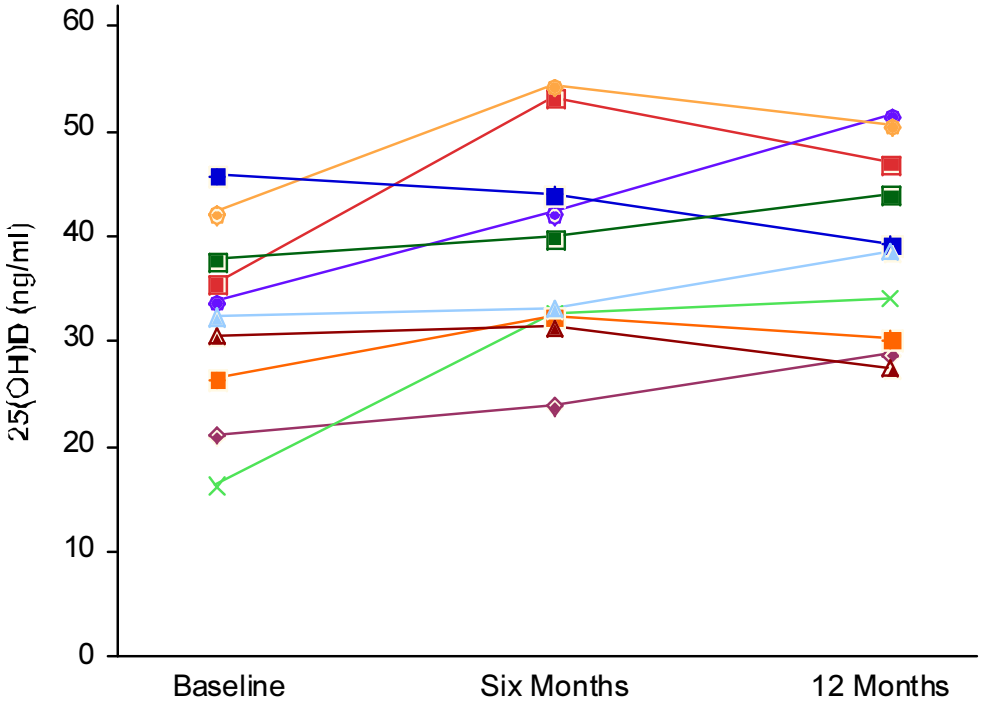


Binkley, et. al, J Bone Miner Res, 23 (suppl 1);S350, 2008

Individual Variability in Response to Vitamin D



1,600 IU D_3 Daily



1,600 IU D_2 Daily

Binkley, et. al, ISCD Annual Meeting, March 2009

Reasonable Approaches to Vitamin D Repletion

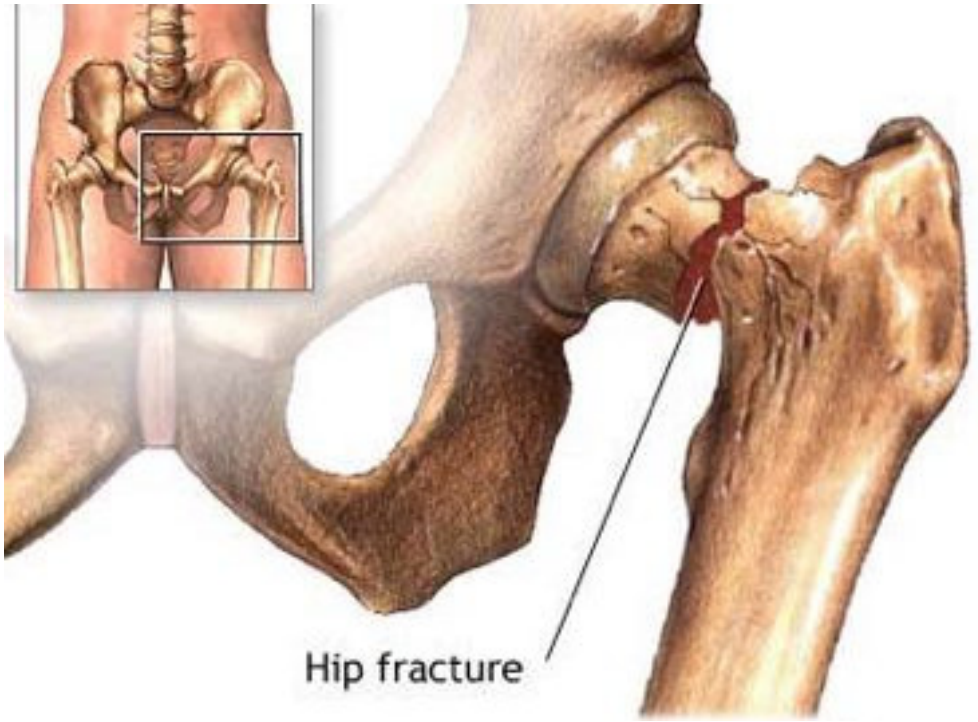
- 50,000 IU once per week for eight weeks
- 50,000 IU three times per week for four weeks

30-40 ng/ml; increase supplemental D_3 by 1,000 IU/day
20-30 ng/ml; increase supplemental D_3 by 2,000 IU/day
< 20 ng/ml; 50,000 IU D_2 3x/week for 4 weeks (or other) and increase supplemental D_3 by 2,000 IU/day, repeat 25(OH)D ~3-6 months later

Pepper, et. al, Endocrine Pract, 15;95-103, 2009

Increasing the Amount of Vitamin D in "Fortified" Foods Seems Like The Logical Approach to Correcting Vitamin D Deficiency on a Population Basis

Vitamin D: Falls and Fractures



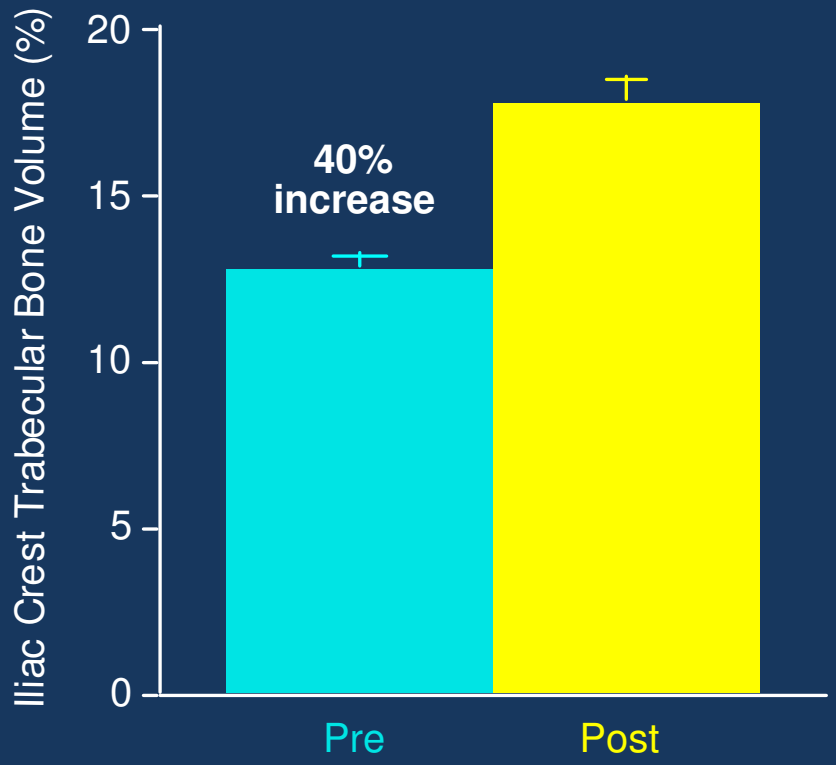
"Low serum 25(OH)D concentrations are associated with a higher risk for hip fracture."

Cauley, et. al., Ann Int Med; 149:242-250, 2008

That High-dose Vitamin D is Safe and Good For Bones is NOT a New Idea

13 postmenopausal women
Radiographic osteopenia
11 with vertebral fx (mean = 3.8)
1 with hip fx, 1 with low BMD

Rx 2-6 years (mean 3.5)
Calcitonin 40 IU SC 3x/week
50,000 IU vitamin D 3x/week
$CaC0_3$ 1000 mg/day



"No hypercalcemia or hypercalciuria was observed in any of the patients."

Palmieri, et. al, Calcif Tissue Int, 45: 137-141,1989

Vitamin D Has Local Effects

- Vitamin D receptors are present in > 30 tissues
- Essentially all tissues have 25 hydroxylase
- Many tissues (not just kidney) possess 1 α-hydroxylase
  - Intestine, muscle, islet cells, monocytes, B & T cells, neurons, chondrocytes, colonic enterocytes, prostate, ovary, endothelial cells…..
- 1, 25 di(OH)D can be produced locally in many tissues
- Reasonable that low D status impairs local 1, 25 production
- *"The nonclassical actions of vitamin D are cell specific and provide a number of potential new clinical applications for $1,25(OH)_2D_3$ and its analogs."*

Bikle, J Clin Endo Metab, 94:26-34, 2009

Diseases/Conditions Associated With Low Vitamin D Status

- Osteomalacia/Osteoporosis
- Muscle functionand falls
- Cancer
- Multiple sclerosis
- Hypertension
- Diabetes
- Inflammatory bowel disease
- Rheumatoid arthritis
- TB
- Macular degeneration
- Cognitive impairment
- Cardiovascular events
- Peripheral vascular disease
- Polymyalgia rheumatica
- Chronic pain
- Autism
- Infection
- Athletic performance
- Depression
- Seasonal affective disorder
- Pulmonary function
- Incontinence
- Aging
- Overall mortality

The Lancet 1999; **353**:806

DOI:10.1016/S0140-6736(98)10206-4

A woman who left her wheelchair

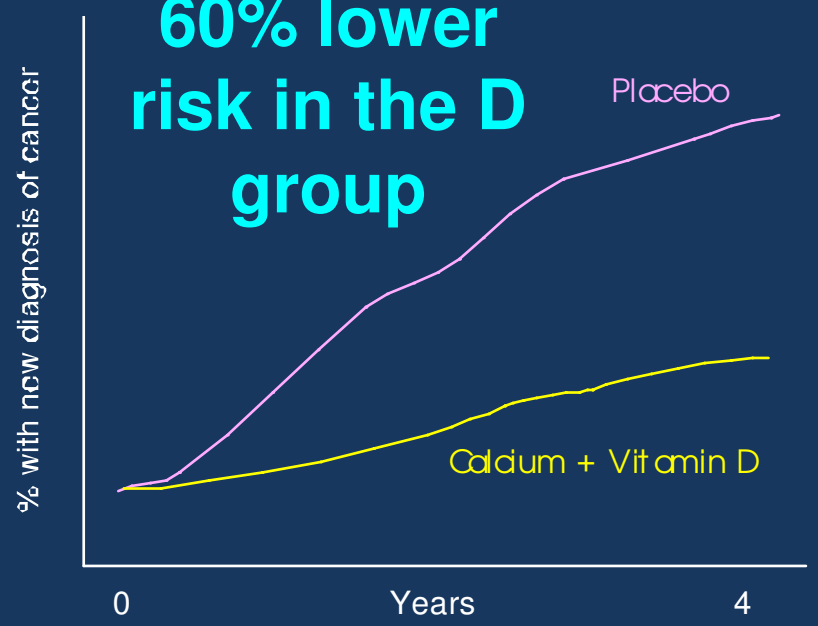
MD, Dr G Mingrone [a], MD AV Greco [a], MD M Castagneto [b], G Gasbarrini [a]

- 32 year old woman with progressive muscle weakness and diffuse bone pain
- Crohn's disease; s/p bowel resection with fat malabsorption
- 25(OH)D = 2.4 ng/ml
- Treated with 1, 25 diOHD_3
- *"After 3 weeks she could walk again, and muscle weakness and bone pain had disappeared."*

Vitamin D Supplementation Reduces Cancer Risk

1179 women ave age 67 years; 4-year study
Pbo, calcium 1500 mg or calcium + vitamin D 1100 IU

25OHD increased from 28 ng/ml to 38 ng/ml



".. improving vitamin D nutritional status substantially reduced all-cancer risk in postmenopausal women."

Lappe, et. al., Am J Clin Nutr, 85:1586-1591, 2007

Could a Reduction in Cancer Risk be Related to Effects on Immune Function?

- Helper T cells (Th) central to antigen-specific immune responses
- The microenvironment in which Th cells develop determines which of the 2 subtypes predominate
- The balance between Th1 and Th2 response dictates the immune system outcome
- Th1 and Th2 are direct targets of 1, 25 di(OH)D

Cantorna, et. al., Am J Clin Nutr, 80(suppl):1717S-1720S, 2004

Vitamin D and Diabetes

- Beta cells contain the vitamin D receptor
- 1, 25 stimulates insulin release
- Insulin release is reduced in vitamin D deficient animals
- 1, 25 prevents development of diabetes in the NOD mouse
- Recent meta-analyses associate low vitamin D status with increased risk of type 1 and type 2 diabetes

Vitamin D and Vascular Disease

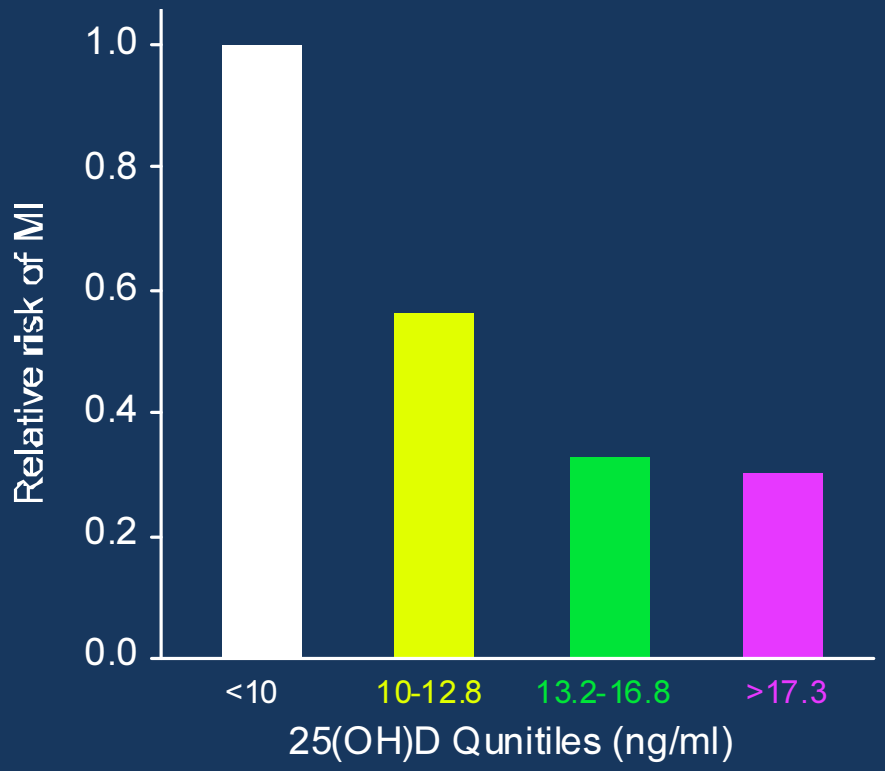
- CVD death rate increases with latitude
- Higher CVD deaths in winter months
- Vitamin D receptors in myocytes
- Vitamin D impacts renin-angiotensin and blood pressure
- Vitamin D involved in inflammation

Vitamin D Status and MI Risk

Case control study; 179 MI
Controls matched by age, sex and date of blood draw

25(OH)D by CPB
Mean 25(OH)D lower (p <0.5) in cases 12.8 ng/ml
Vs. controls 14.0 ng/ml

Differed also in chol, BMI and smoking



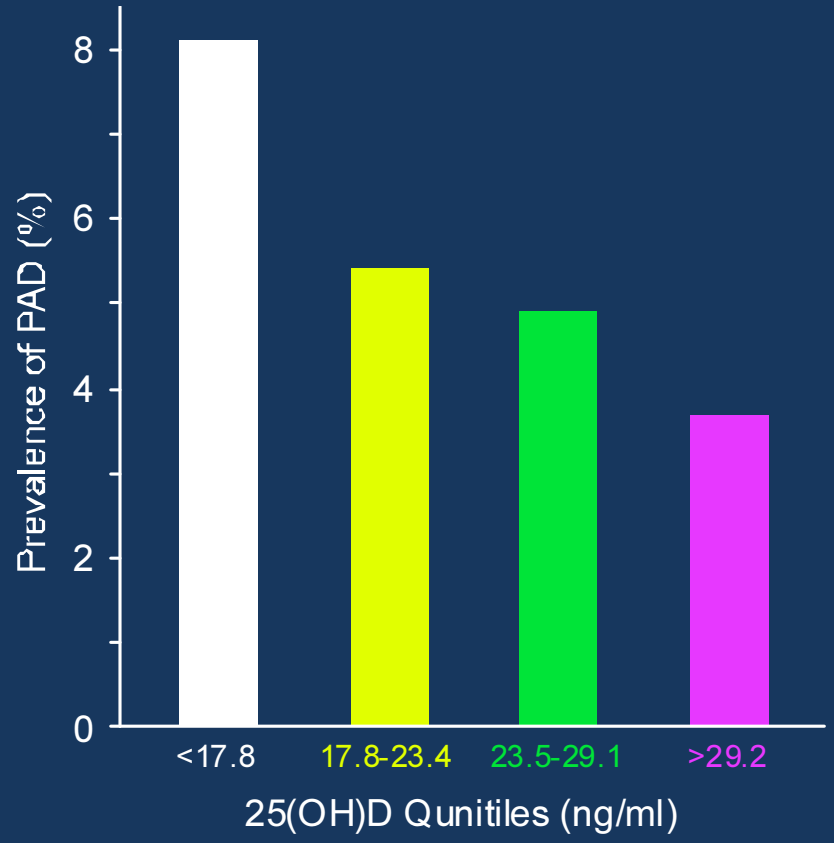
"…provides support for the hypothesis that increased exposure to sunlight is protective against CHD."

Scragg, et. al., Int J Epidemiol:559-563, 1990

25(OH)D and Peripheral Arterial Disease

4,839 participants in NHANES
PAD defined as ankle-brachial index < 0.9

25(OH)D by Diasorin RIA
Adjusted for age, gender, race, BMI, DM, activity, CKD and MI



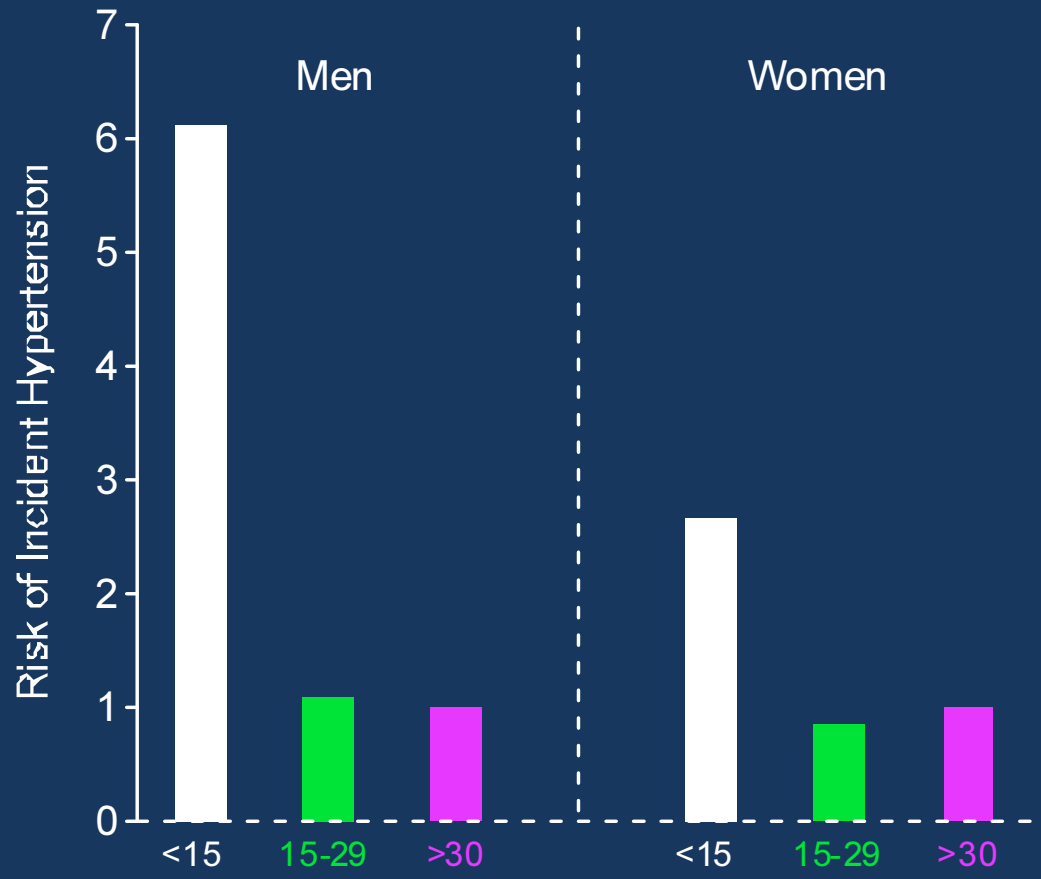
"Low 25(OH)D levels are associated with a higher prevalence of PAD." This association was strong, graded and present after adjustment for multiple CV risk factors."

Melamed, et. al., Arterioscler Thromb Vasc Biol, 28:1179-1185, 2008

25(OH)D and Blood Pressure

Two prospective cohort studies; 613 men; Health Professionals follow up study and 1198 women; nurses health study
Followed for 4-8 years

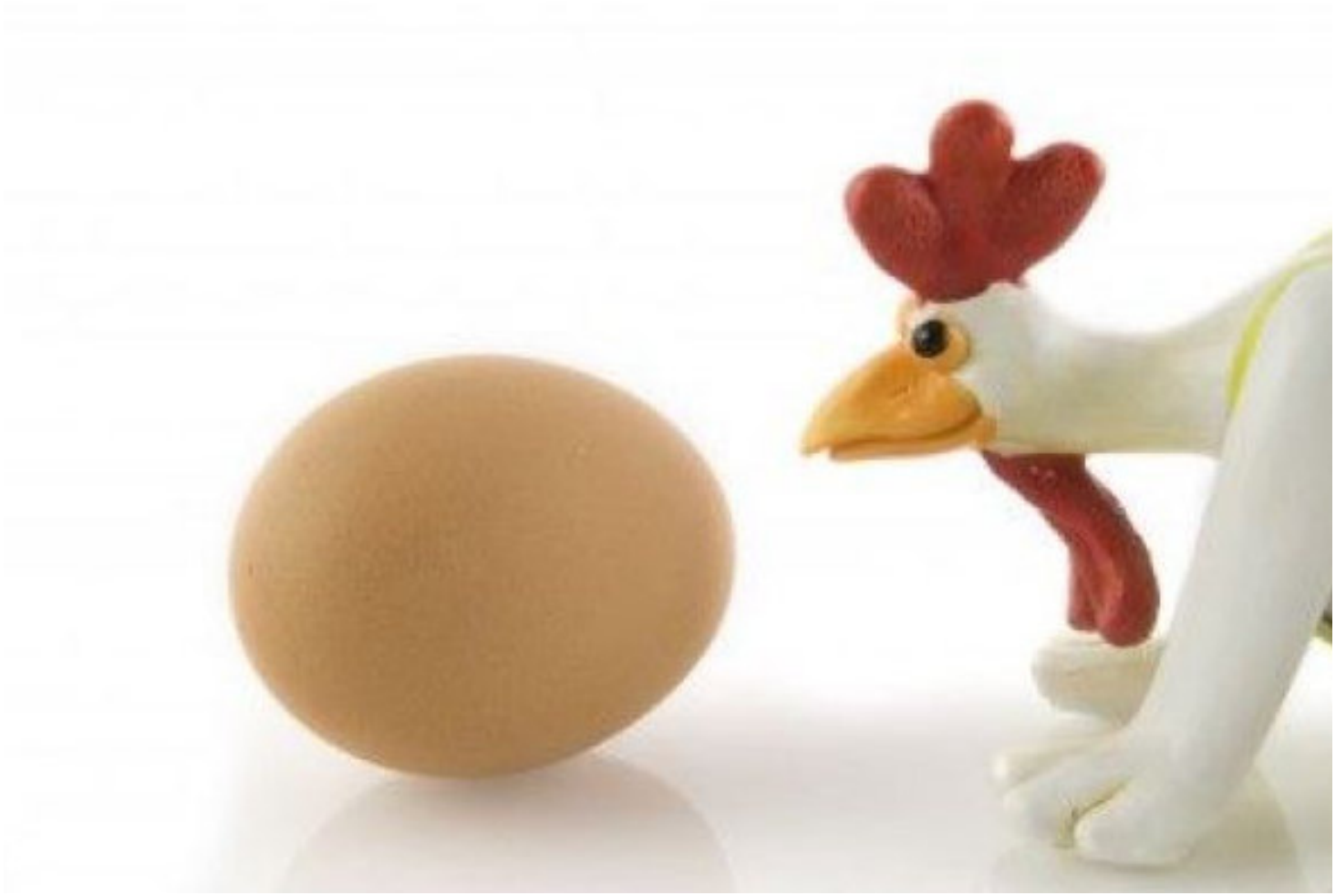
25(OH)D by Diasorin RIA
Adjusted for multiple variables including age, BMI, activity and race



"Plasma 25(OH)D levels are inversely associated with risk of incident hypertension."

Forman, et. al., Hypertension, 49:1063-1069, 2007

Vitamin D and Age-Related Diseases Chicken or Egg?



"For every complex problem, there is a solution that is simple, neat, and wrong."

H. L. Mencken

Association Does Not Prove Causation

Vitamin D Conclusions; 2009

- Vitamin D inadequacy is common
- Prudent to recommend D_3
- We need at least 1,000-2,000 IU/day
- These “higher” doses are safe
- Not everyone needs the same dose
- Casual sun exposure is not enough
- Vitamin D adequacy will reduce osteoporotic fractures, falls, probably cancer and potentially other diseases