Vitamin D:
A Potential Role in Diabetes

Collaborative Diabetes Education Conference
Jan 22, 2011

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Disclosures/Conflict of Interest

None

Is Vitamin D Deficiency Important in Diabetes Pathogenesis and/or Prevention/Treatment??

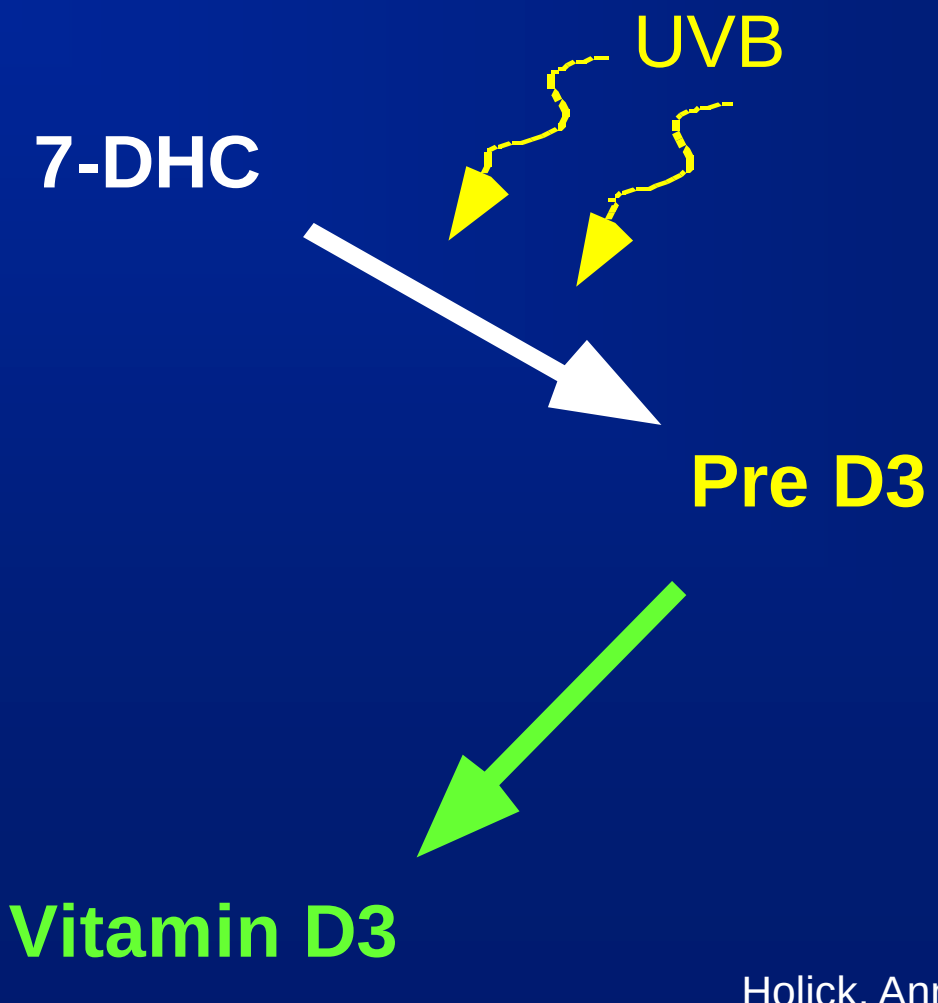
No One Knows…

Remember That Association Does Not Prove Causation…

- Brief vitamin D history
- Prevalence of low vitamin D status
- Measurement of 25(OH)D
- Correction
  - How much vitamin D do we need?
  - Are vitamins D_2 and D_3 equivalent?
  - Approaches to correcting low vitamin D status
- Importance of low vitamin D in diseases, including diabetes

Historically, Humans Obtained Vitamin D from the Sun

UVB (~280-315 nm) Produces Vitamin D



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

Humans Were a Highly Sun-exposed Species

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

Vitamin D Deficiency Accompanied the Industrial Revolution

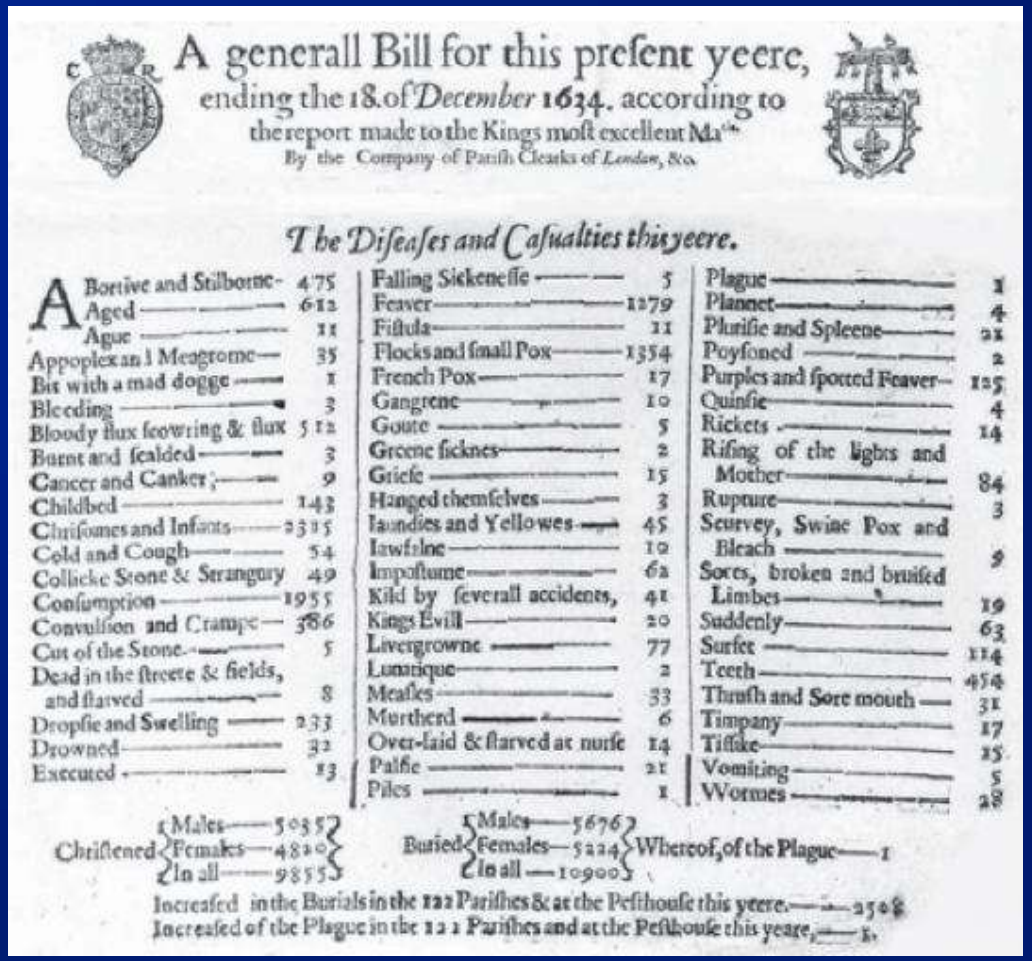
www.nettlesworth.durham.sch.uk/time/victorian/vindust.html

“Rickets” First Used in Print 1634

Annual Bill of Mortality for the City of London; 441 deaths in 1659

Described by Whistler in his thesis for the doctor of medicine degree in 1645; believed Rickets to be a new disease that appeared ~20 years previously

Crow liver considered as a possible treatment



A generall Bill for this prefent yeere, ending the 18. of *December* 1634. according to the report made to the Kings moſt excellent Ma^tie By the Company of Parish Clerks of *London*, &c.

The Diſeaſes and Caſualties this yeere.

Abortive and Stillborne	475	Falling Sickeneſſe	5	Plague	1
Aged	612	Feaver	1279	Planet	4
Ague	11	Fiſtula	11	Pliriſie and Spleene	21
Appoplex and Meagrome	35	Flocks and ſmall Pox	1354	Poyſoned	2
Bit with a mad dogge	1	French Pox	17	Purples and ſpotted Feaver	125
Bleeding	3	Gangrene	10	Quinſie	4
Bloody flux fcowring & flux	512	Goute	5	Rickets	14
Burnt and ſcalded	3	Greene ſickneſs	2	Riſing of the lights and Mother	84
Cancer and Canker	9	Griefe	15	Rupture	3
Childbed	143	Hanged themſelves	3	Scurvey, Swine Pox and Bleach	9
Chriſomes and Infants	2345	Iaundies and Yellowes	45	Sores, broken and bruiſed Limbes	19
Cold and Cough	54	Iawfalne	10	Suddenly	63
Collicke Stone & Strangury	49	Impoſtume	62	Surfet	114
Conſumption	1955	Kild by ſeverall accidents	41	Teeth	454
Convulſion and Cramp	386	Kings Evill	20	Thruſh and Sore mouth	31
Cut of the Stone	5	Livergrowne	77	Timpany	17
Dead in the ſtreete & fields, and ſtarved	8	Lunatique	2	Tiſſike	25
Dropſie and Swelling	233	Meaſles	33	Vomiting	5
Drowned	32	Murthered	6	Wormes	28
Executed	13	Over-laid & ſtarved at nurſe	14		
		Palſie	21		
		Piles	1		

Chriſtened: Males 5035, Females 4820, In all 9855

Buried: Males 5676, Females 5224, In all 10900. Whereof, of the Plague 1

Increaſed in the Burials in the 122 Parishes & at the Peſthouſe this yeere 2508

Increaſed of the Plague in the 122 Parishes and at the Peſthouſe this yeare 1.

O’Riordan, J Bone Miner Res, 21; 1506-1510, 2006

In the late 1800's estimated that ~80-90% of children who lived in industrialized cities of Europe and North America had rickets

Holick, J Clin Invest 116:2062-2072, 2006

Have We Returned to the 1890's?

wikiHow
The How-to Manual That You Can Edit

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- Be Energetic when You Are Playing a Sport
- Beat Boredom over the Summer
- Be Energetic and Fun Loving

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How to Play Outside

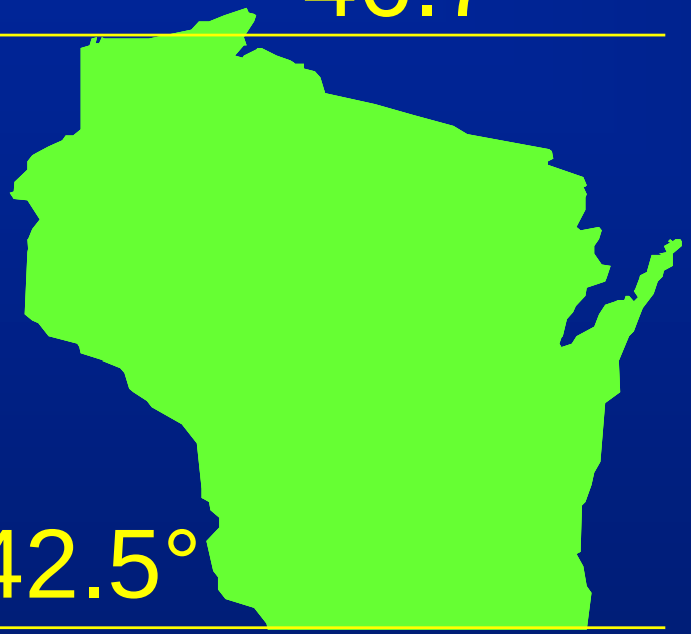
Summer is here, and the kids need to get outside for exercise, sun, and fresh air, but playing outside seems for many to be a lost art. There is television and video games to compete with, but with some imagination, playing outside can result in hours of fun.

Have fun outside!

Messages to “Avoid the Sun” are Widespread and Powerful

No Skin Production of Vitamin D At Northern Latitudes from November Through February

46.7°



42.5°

41.8°

32.7°

There is virtually **NO** skin synthesis in Boston (latitude 42.3° N) from November thru February

Chen, et. al., 1998

Cavemen?

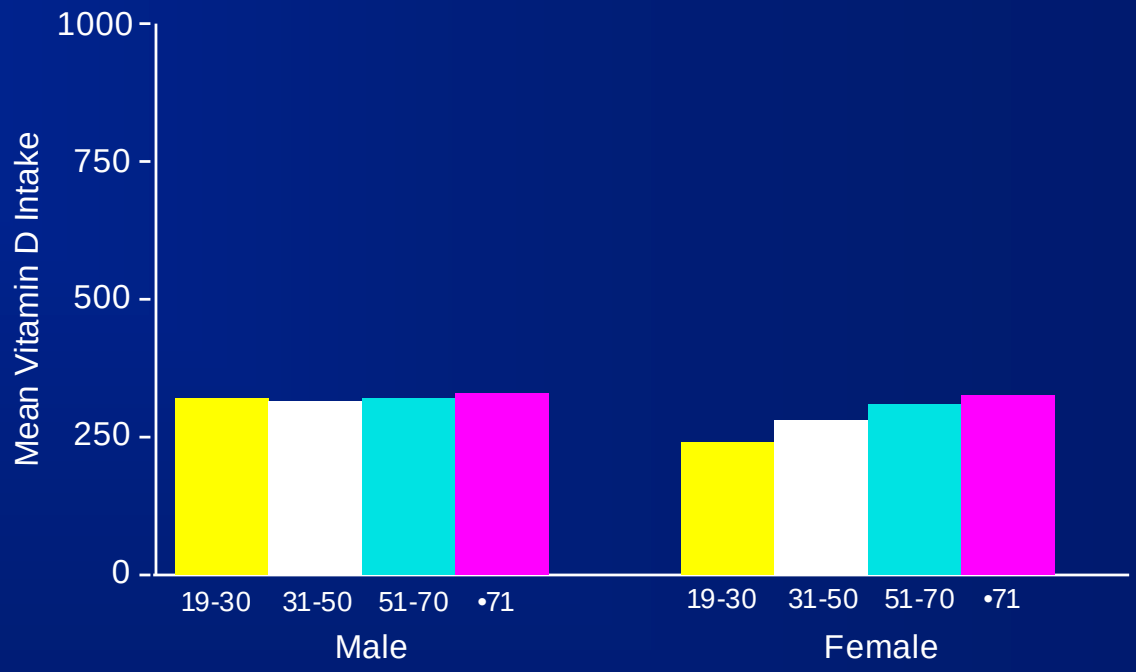
Caveman

We No Longer Make Vitamin D in the Skin…
What About Food?

Vitamin D is Uncommon in Food

Intake Low At All Ages

Food	IU
Cod liver oil, 1 tbs	1360
Salmon, 3.5 oz	360
Milk, 1 cup	100
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

Recognized in the 1920's That Irradiating Food Cured Rickets

"By irradiation with the quartz mercury vapor lamp, rat rations can be activated, making them growth promoting and bone-calcifying..."

Steenbock, J Biol Chem, 61:405-1924

What Foods Are Fortified?

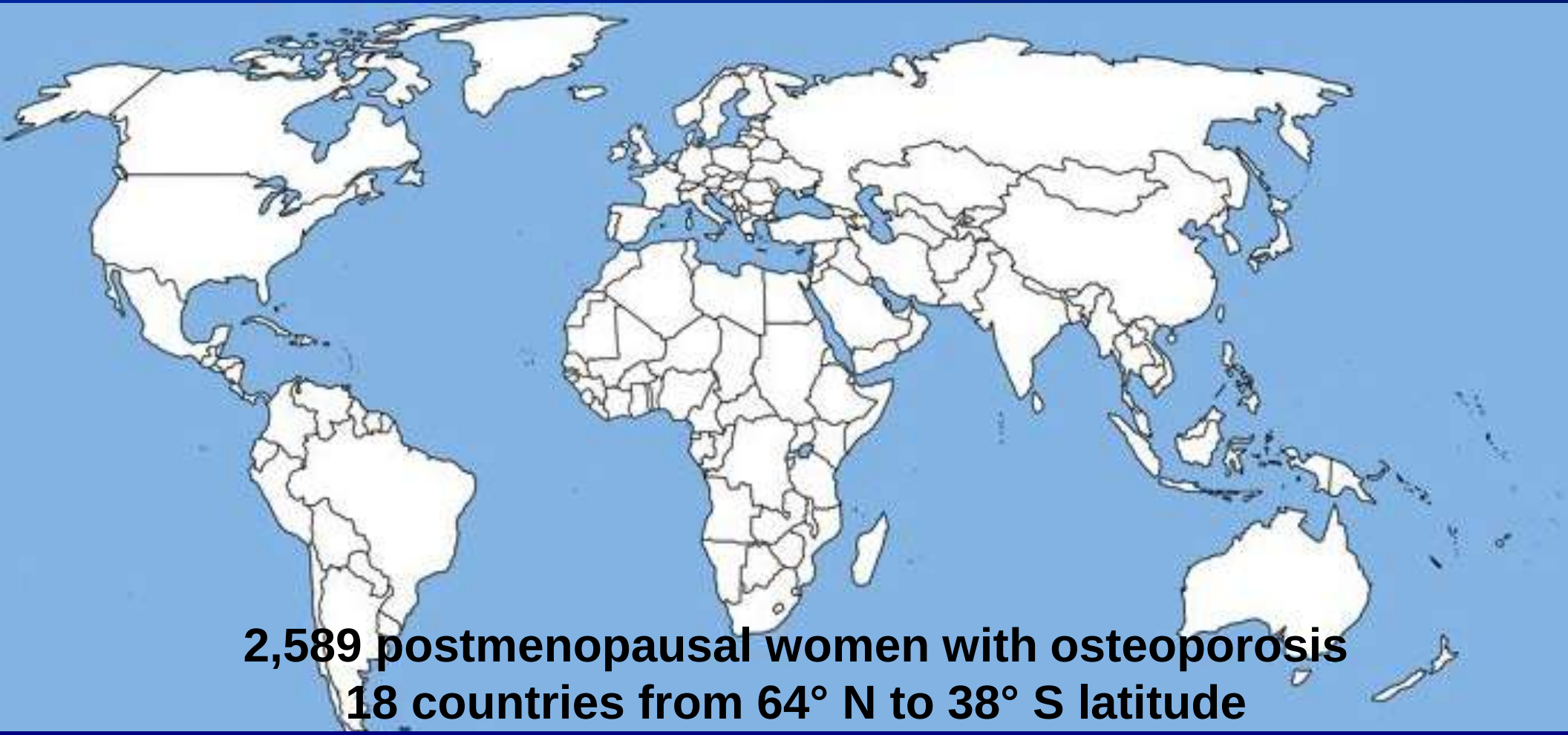
Current Status, USA

Food Label and Package Survey

- Milk (almost all)
- Breakfast cereals (~75%)
- Milk substitutes (~50%)
- Yogurts (~25%)
- Cheeses, juices (8-14%)
- Most use D_3
- Some milk substitutes use D_2
- **40-100 IU/serving**

Yetley, EA, Am J Clin Nutr; 88(suppl):558S-564S, 2008

Vitamin D Inadequacy is Common Worldwide



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

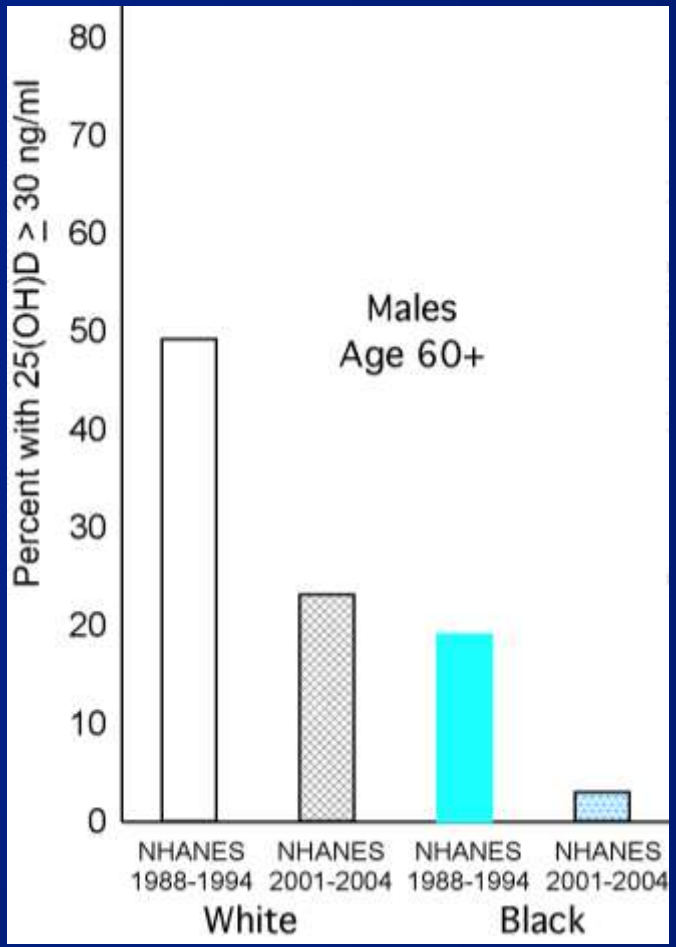
64% had serum 25(OH)D < 30 ng/ml

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

How Can Vitamin D Inadequacy Be So Common?

- Lifestyle; lack of sunlight exposure
  - Clothing habits
  - Living arrangements/work environment
  - Use of sunscreen
- Vitamin D is not readily available in the diet
- Lack of supplement use/inadequate food fortification
- Skin ability to synthesize vitamin D declines with age

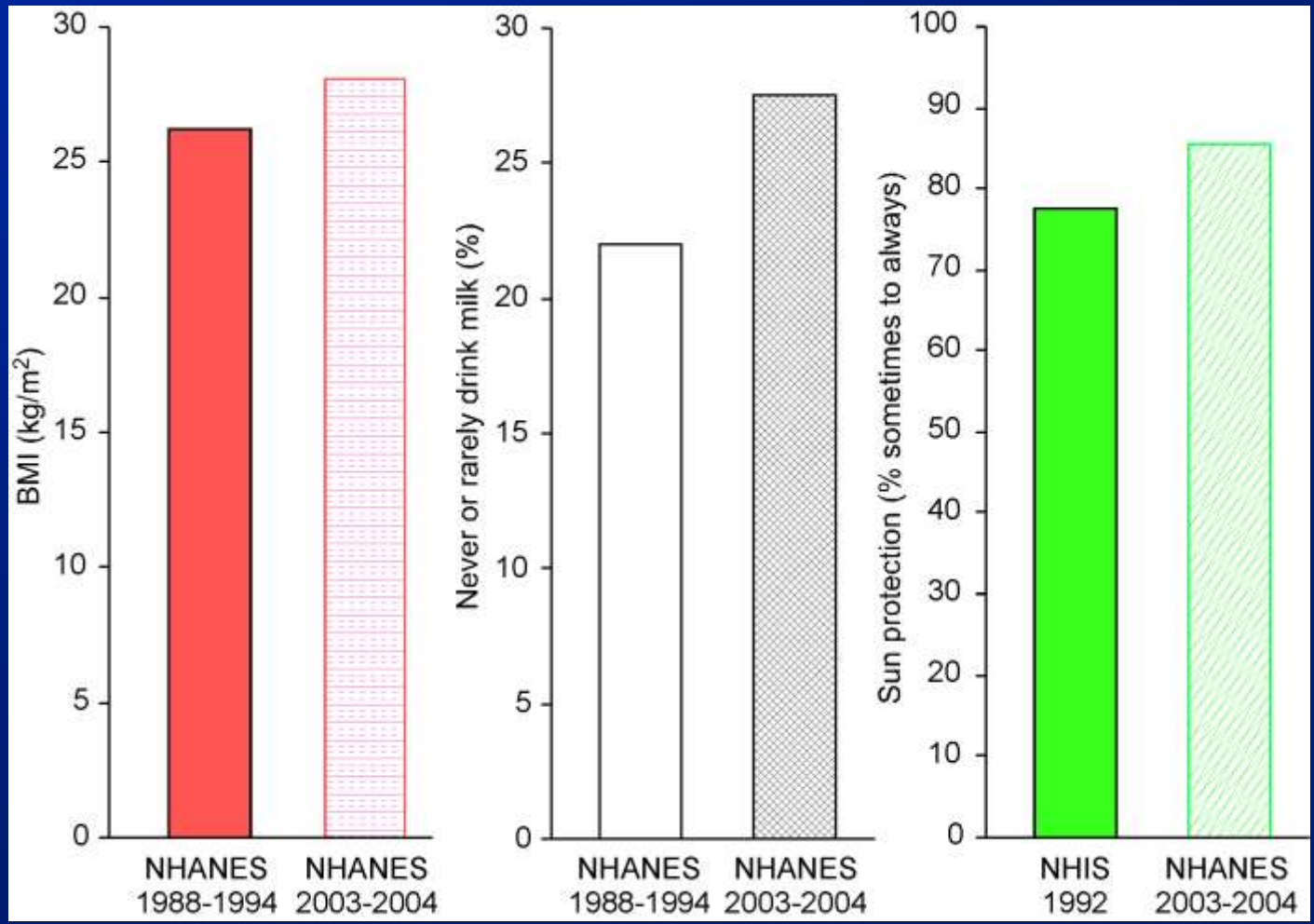
Vitamin D Deficiency is Getting Worse



"Current recommendations for vitamin D supplementation are inadequate to address the growing epidemic of vitamin D insufficiency."

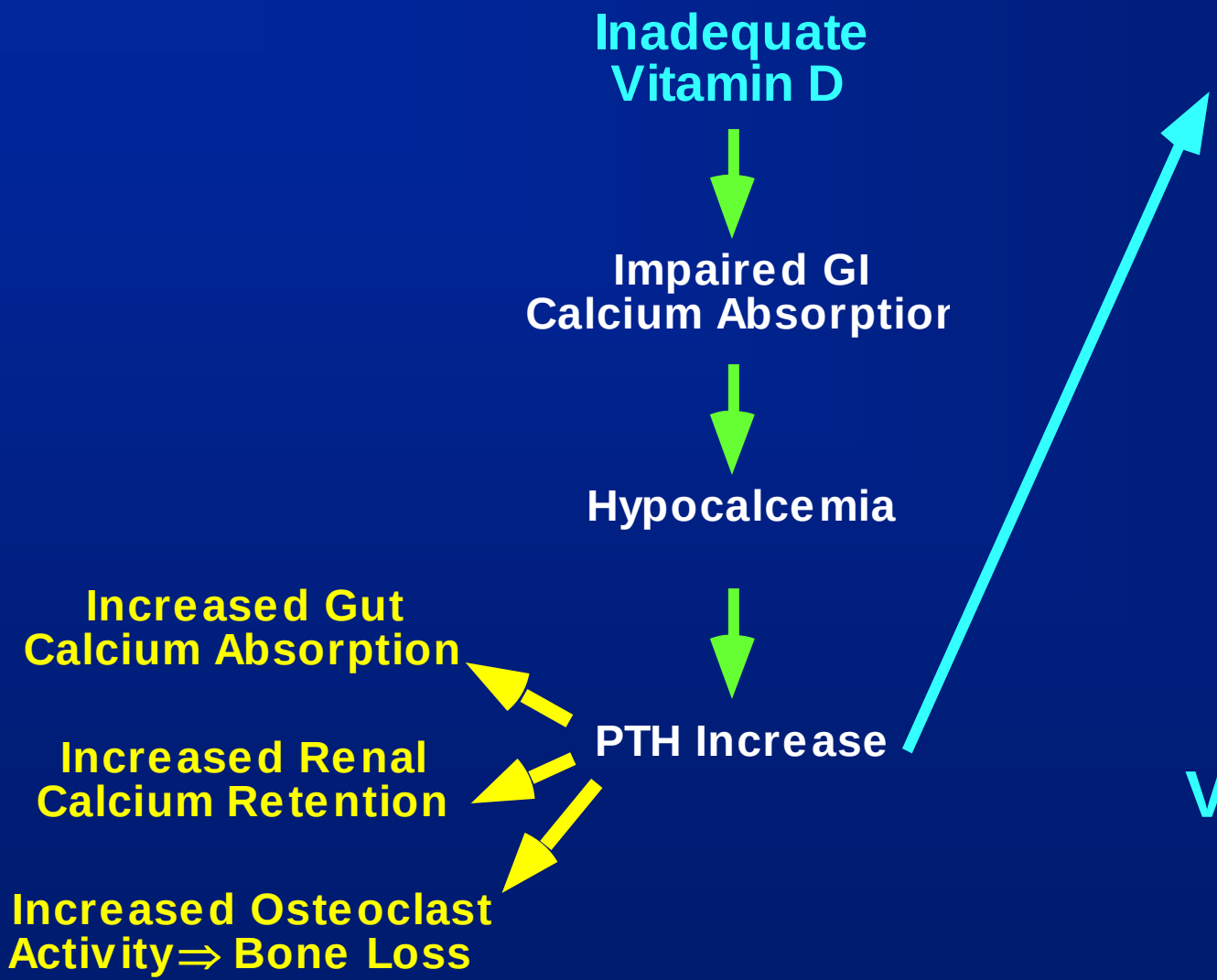
Adapted from Ginde, et. al, Arch Intern Med 169:626-632, 2009

Worsening 25(OH)D Due to Increasing BMI, Less Milk and More Sunscreen



Looker, et. al., Am J Clin Nutr, 88; 1519-1527, 2008

Classic Vitamin D Insufficiency



Increased Activity of 1 a-hydroxylase

Converts Available 25OHD to 1, 25 diOHD

Thus, 25OHD, Not 1,25 is the Best Clinical Measure of Vitamin D Status

Assessment of Vitamin D Status: Measure 25(OH)D

The Vitamin D Continuum

Deficiency

~10 ng/ml

Insufficiency

30 ng/ml

Optimal

What's Our Target 25(OH)D?

"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

The Target 25(OH)D Remains Controversial

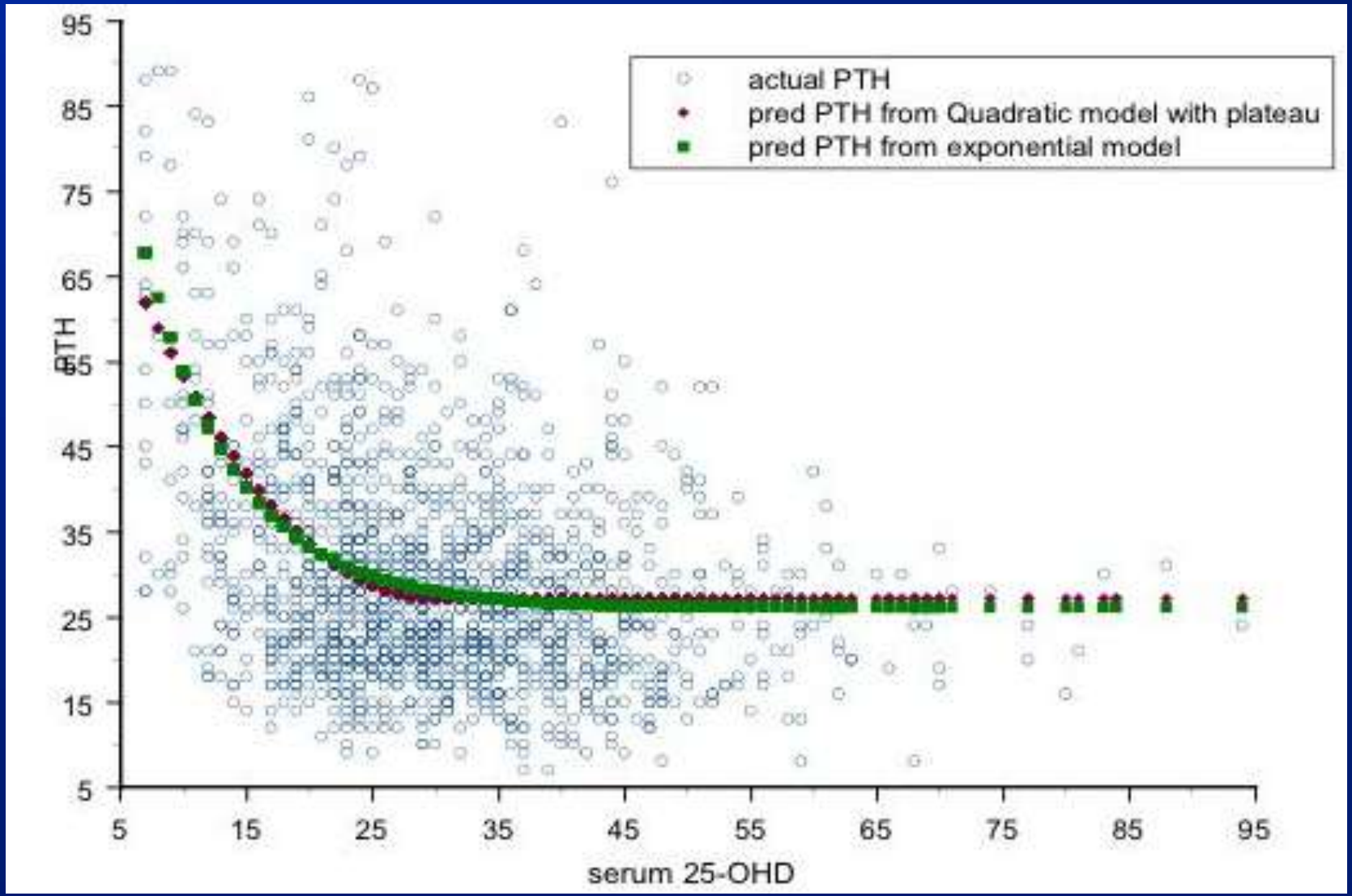
13th Workshop consensus for vitamin D nutritional guidelines

"There was a general consensus that the blood concentration of vitamin D should at the very least meet or hopefully exceed a minimum desirable serum concentration of 50 nM or 20 ng/ml."

Norman, et. al., J Steroid Biochem Mol Biol, 103;204-205, 2007

Why ~20-30 ng/ml??

Optimizes Calcium Absorption and Suppresses PTH



Data from Holick, et al., JCEM, 2005

How Much Vitamin D Do We Need?

How Much Vitamin D Do We Need?

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The 2011 Report on Dietary Reference Intakes for Calcium and Vitamin D from the Institute of Medicine: What Clinicians Need to Know

A. Catharine Ross, JoAnn E. Manson, Steven A. Abrams, John F. Aloia, Patsy M. Brannon, Steven K. Clinton, Ramon A. Durazo-Arvizu, J. Christopher Gallagher, Richard L. Gallo, Glenville Jones, Christopher S. Kovacs, Susan T. Mayne, Clifford J. Rosen, and Sue A. Shapses

TABLE 1. Calcium and vitamin D dietary reference intakes by life stage

Life-stage group (age and gender)	Calcium		Vitamin D		
	RDA (mg/d) (intake that covers needs of ≥97.5% of population)	UL (mg/d)[a]	RDA (IU/d) (intake that covers needs of ≥97.5% of population)	Serum 25OHD level (ng/ml) (corresponding to the RDA)[b]	UL (IU/d)[a]
1–3 yr (M+F)	700	2500	600	20	2500
4–8 yr (M+F)	1000	2500	600	20	3000
9–13 yr (M+F)	1300	3000	600	20	4000
14–18 yr (M+F)	1300	3000	600	20	4000
19–30 yr (M+F)	1000	2500	600	20	4000
31–50 yr (M+F)	1000	2500	600	20	4000
51–70 yr (M)	1000	2000	600	20	4000
51–70 yr (F)	1200	2000	600	20	4000
71+ yr (M+F)	1200	2000	800	20	4000
Pregnant or lactating (F)					
14–18 yr	1300	3000	600	20	4000
19–50 yr	1000	2500	600	20	4000
Infants					
0–6 months (M+F)	200[c]	1000	400[c]	20	1000
6–12 months (M+F)	260[c]	1500	400[c]	20	1500

J Clin Endocrinol Metab, Jan 2011 epub doi:10.1210/jc.2010-2704

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- "… bone health was the only outcome that satisfied criteria for use as an indicator.."
- "….future research may elucidate clear benefits and possibly even different requirement levels… existing data cannot support such conclusions."
- "… a margin of safety for public health recommendations is prudent."

J Clin Endocrinol Metab, Jan 2011 epub doi:10.1210/jc.2010-2704

Expert Reviews of the Available Data Appear to be Reaching Differing Conclusions

Preliminary Daily Recommendations

CPME — Comité Permanent des Médecins Européens / Standing Committee of European Doctors	600-800 IU
Institute of Medicine of the National Academies — Food and Nutrition Board	800-1,000 IU
An Endocrine Organization	1,500-2,000 IU
A Geriatrics Organization	4,000 IU

- "…it would be appropriate to use a range from 30-50 ng/ml for most patients as an optimal and safe range."
- "For many patients, 1000-2000 IU of vitamin D daily is required to maintain a 25-OH vitamin D level at 30 ng/ml or above."
- "…the common use of vitamin D in the 1000-2000 IU daily dosing range would be reasonable."
- "For now, it is important to use the recommendations in conjunction with clinical judgement to determine the proper calcium and vitamin D requirements for any given patient."

800-1,000 IU Daily is Conservative

"…..it would require input of an additional 2,600 IU/day of oral vitamin D_3 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."

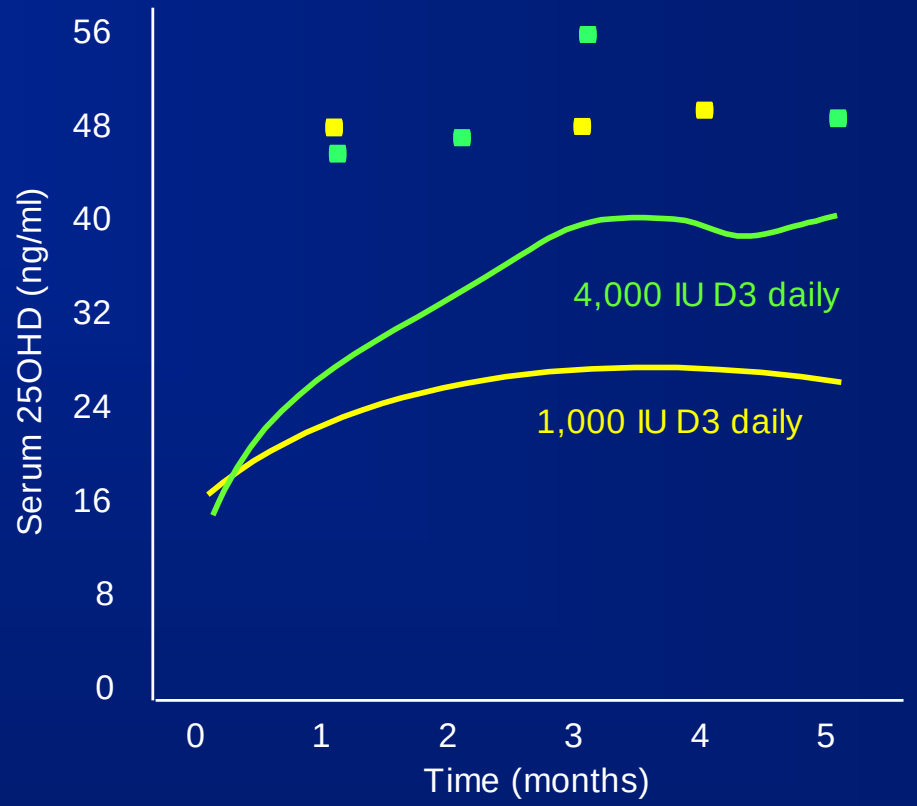
DeLuca H, October, 2007

Are Higher Doses Safe?

Five Month Safety Data

61 Canadian M/F age 41
Rx with **1000** or **4000** IU
D_3 daily for 5 months

Serum 25OHD peaked
at 3 months
Serum calcium normal in all
No significant change from
baseline in urinary Ca/Cr



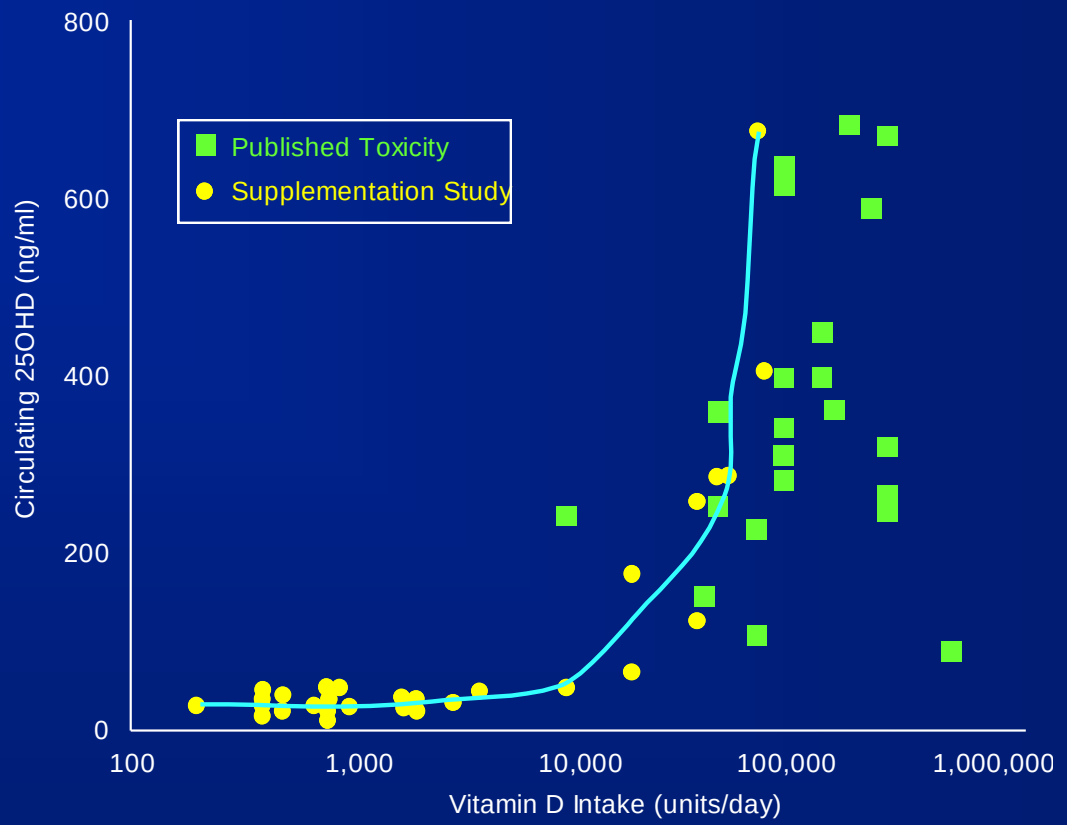
"Consumption of vitamin D_3 at intakes ≥ 4000 IU causes no harm."

Veith, et. al., Am J Clin Nutr, 73:288-294, 2001

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."

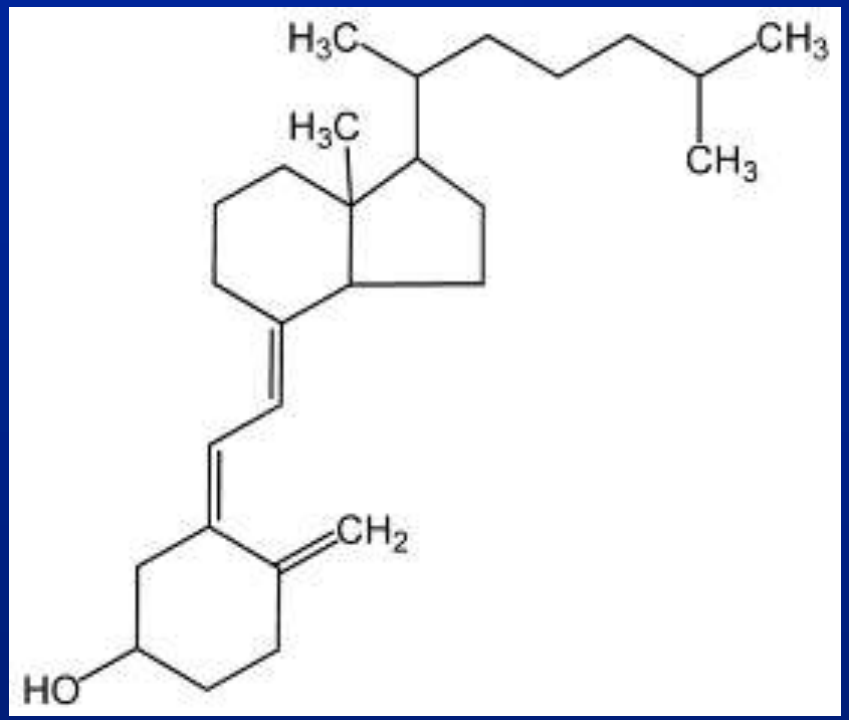
Veith, Lancet, 359;672, 2002

1,000 IU of Daily Vitamin D_3 Increases Circulating 25(OH)D By ~ 6 ng/ml

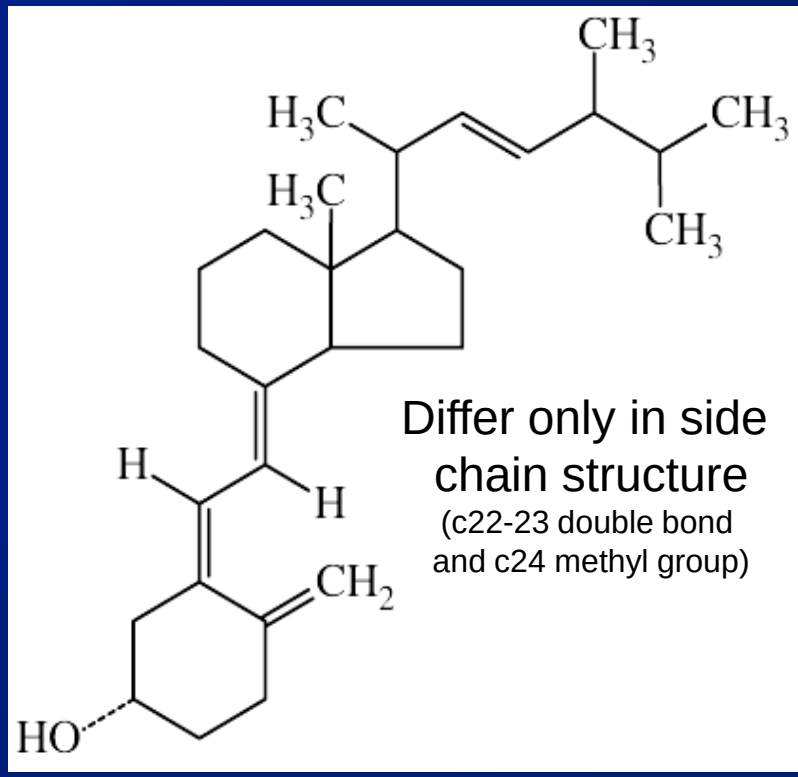
- 7.0 ng/ml
  - Heaney, et. al., Am J Clin Nutr; 87:1952-1958, 2008
- 6.6 ng/ml
  - Aloia, et. al., Am J Clin Nutr; 87:1952-1958, 2008
- 5.9 ng/ml
  - Haller, et. al, ASBMR 2009, SA036
- 5.8 ng/ml
  - Binkley, et. al., ASBMR 2009, #1596
- 5.6 ng/ml
  - Vieth, et. al., Am J Clin Nutr; 73:288-294, 2001

A “Rule of Thumb” is 1,000 IU of D_3 Daily Will Increase 25(OH)D by ~ 10 ng/ml

Vitamin D_2 vs. D_3?

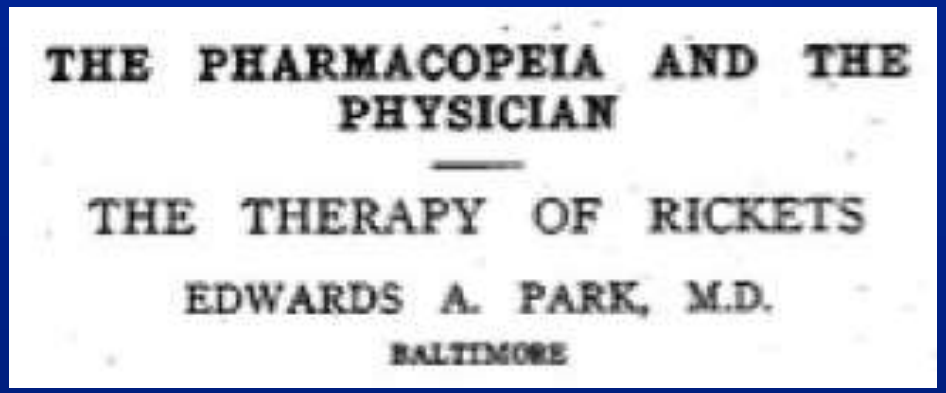


Cholecalciferol
Vitamin D_3



Ergocalciferol
Vitamin D_2

Vitamin D_2 and D_3 Appear to be Equally Effective in Treating Rickets



THE PHARMACOPEIA AND THE PHYSICIAN

THE THERAPY OF RICKETS

EDWARDS A. PARK, M.D.

BALTIMORE

"More than forty studies have been made in order to determine whether the two forms of vitamin D are equally effective…."

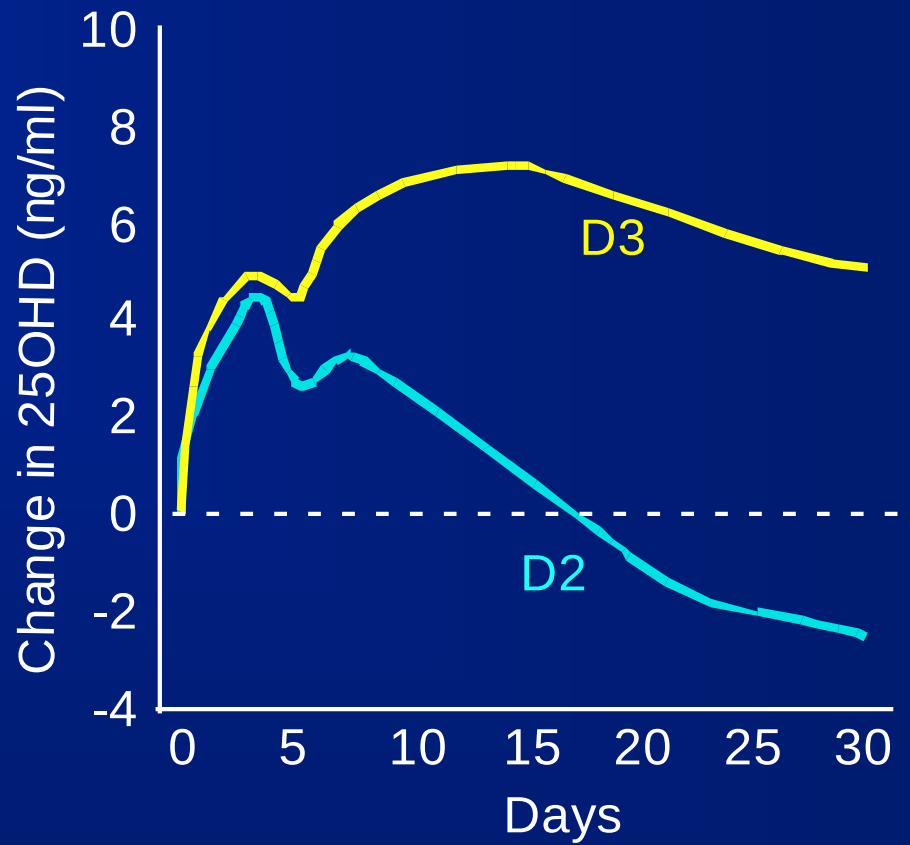
"Only generalizations of an uncertain nature can be drawn from the conflicting and confusing data obtained. For practical purposes the vitamin D in viosterol may be regarded as being equal to the vitamin D of cod liver oil."

Park E, JAMA, 115:370-379, 1940

D_2 is Less Effective than D_3

2 groups of healthy men
Age 20-61
Received 50,000 IU
D_2 or D_3

Suggests more rapid metabolism; Possibly related to different DPB affinity



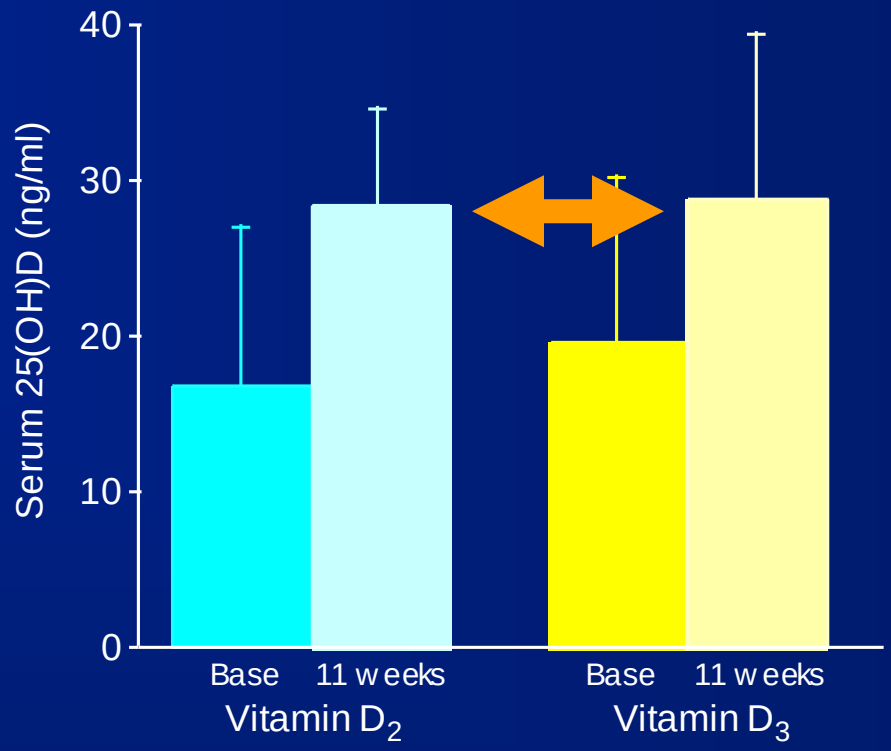
"Vitamin D_2 potency is less than one third that of vitamin D_3."

Adapted from Armas et. al., J Clin Endo Metab, 89:5387-5391, 20

D_2 and D_3 Are Equally Effective

68 healthy adults
Age 18-84 years

Randomly assigned to
1000 IU D_2, D_3, D_2+D_3
or placebo
daily for 11 weeks

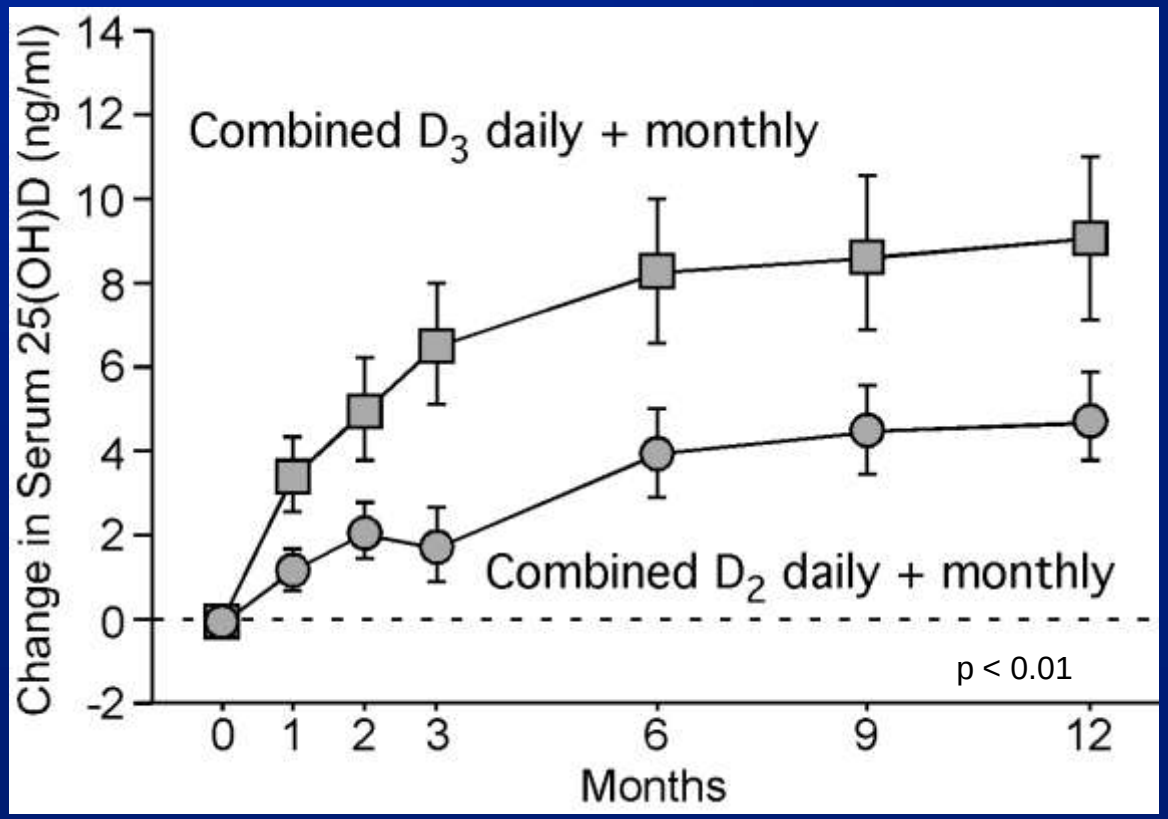


"Vitamin D_2 is equally as effective as vitamin D_3 in maintaining 25-hydroxyvitamin D status."

Adapted from Holick et. al., J Clin Endo Metab, 93:677-681, 2008

In My Opinion…. Both Work, But Vitamin D_3 is a Little Better than D_2

Effect of 1600 IU daily or 50,000 IU once per month for one year



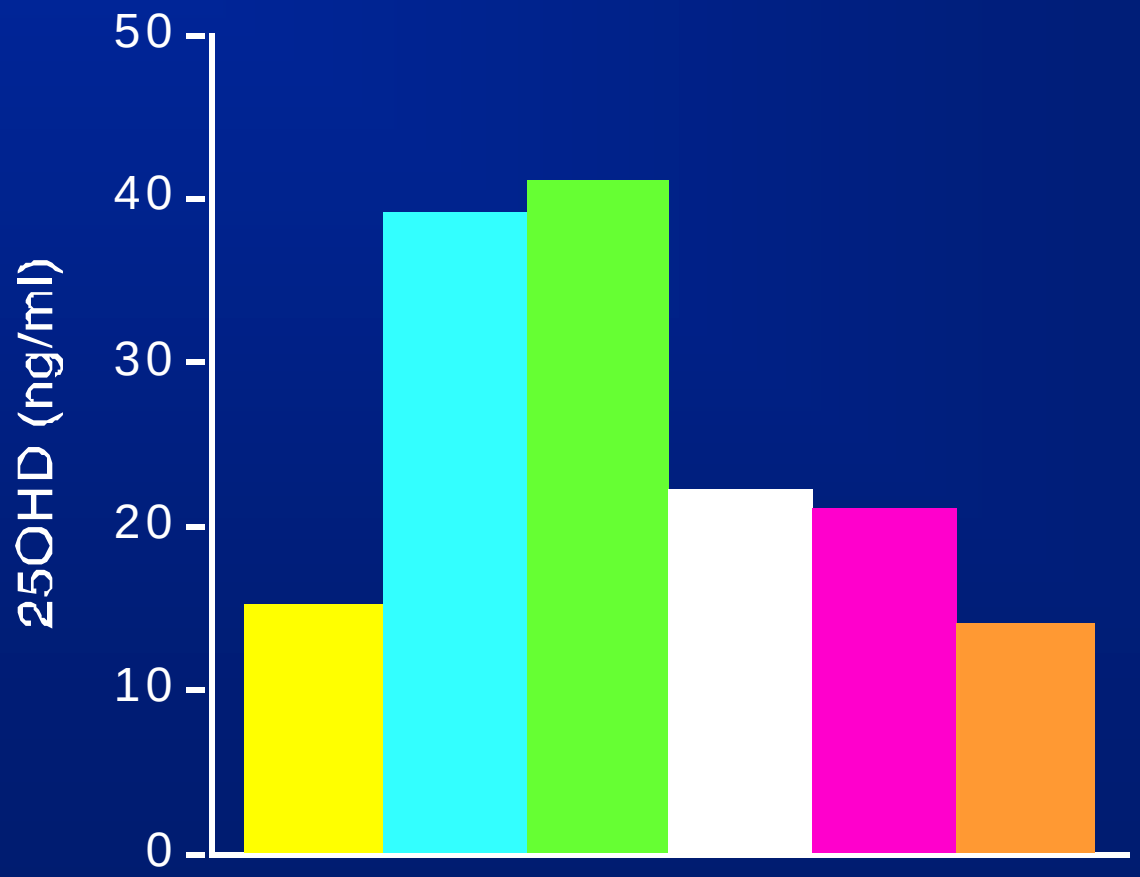
9.1 ng/ml

4.8 ng/ml

Binkley, et. al., J Clin Endocrinol Metab; in press

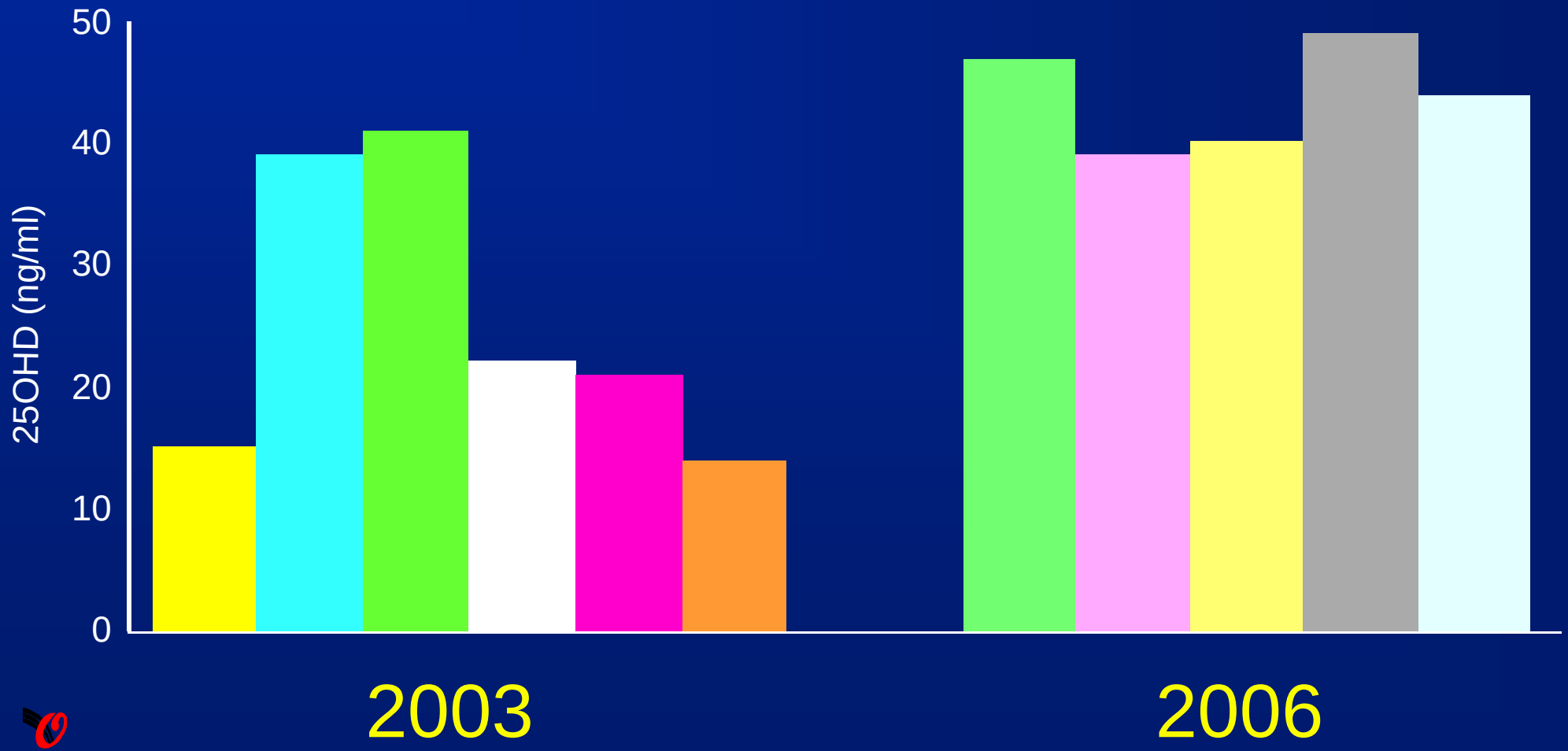
“I’ve heard that the vitamin D assays are no good. Is that true?”

Individual 25OHD Values Have Been Extremely Lab-Dependent



Binkley, et. al., JCEM, 89: 3152-3157, 2004

25(OH)D Clinical Measurement



How Are We Doing With 25(OH)D Measurement Clinically Today?

Data from DEQAS

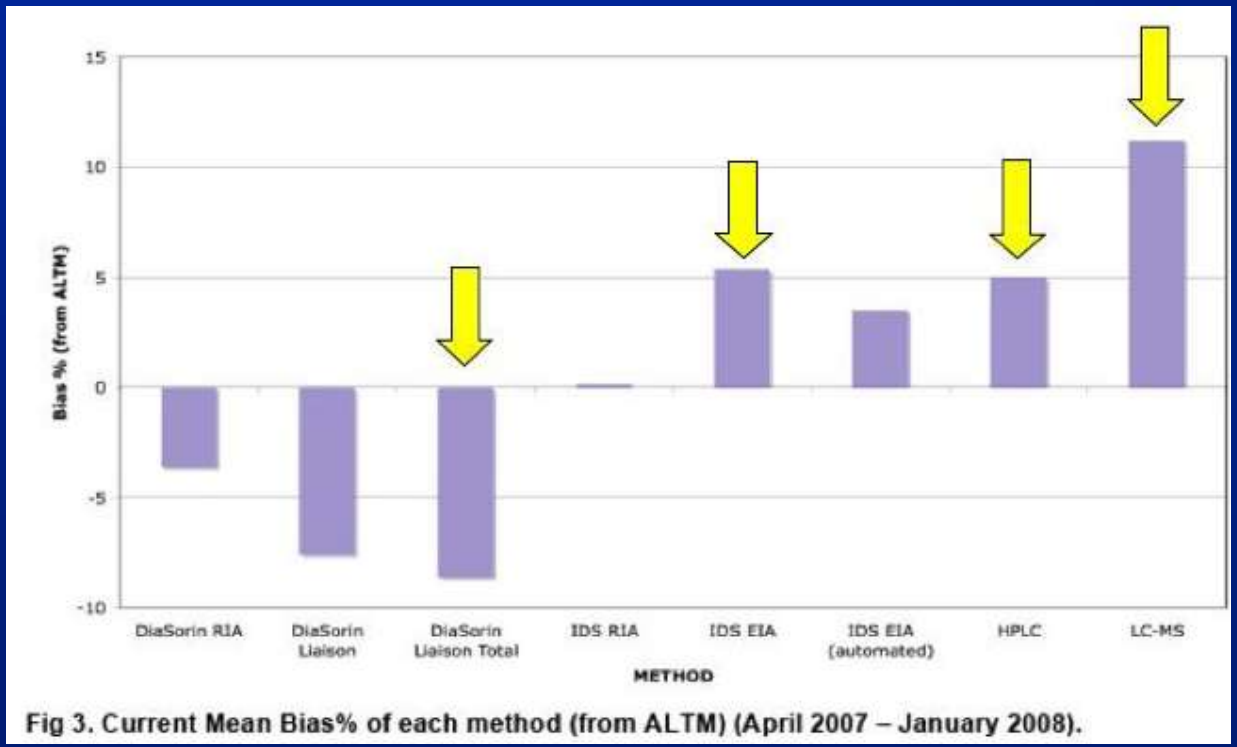
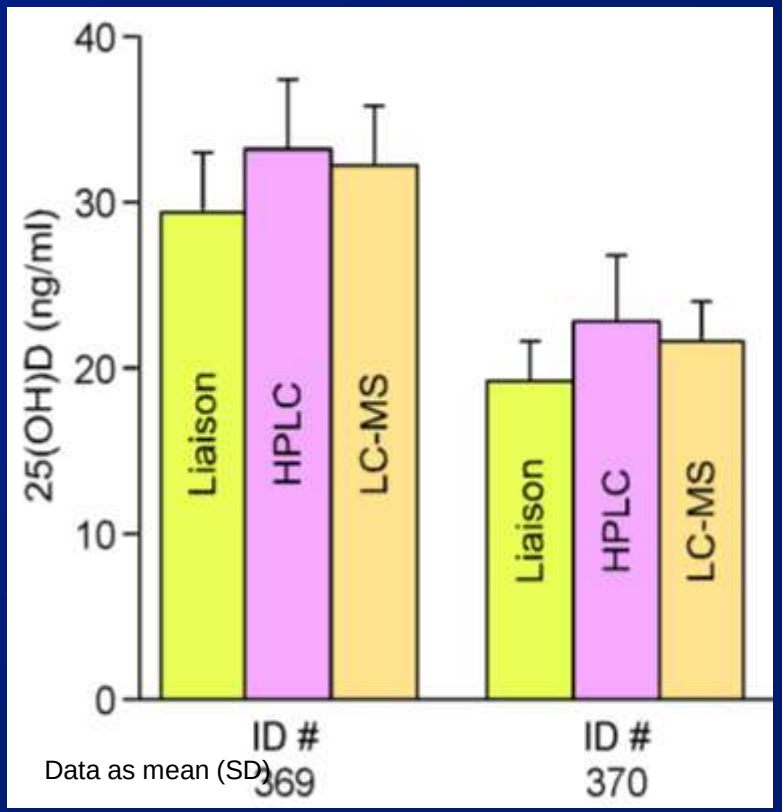
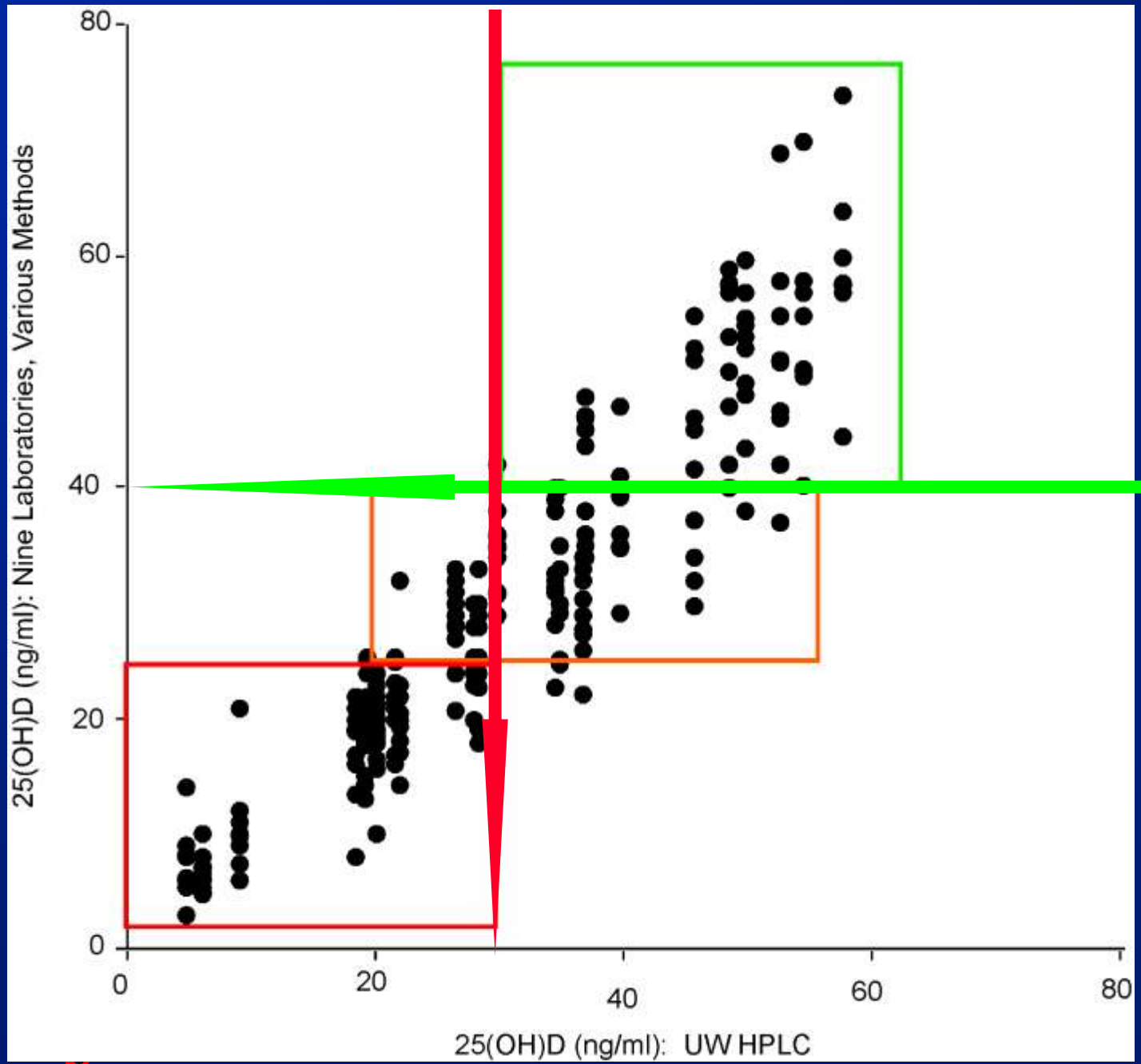


Fig 3. Current Mean Bias% of each method (from ALTM) (April 2007 – January 2008).



Data as mean (SD)

Data from DEQAS Jan 2010 distribution



IF You Are Aiming for 30 ng/ml, Reasonable to Target ~40 ng/ml

Binkley, et. al., ASBMR, 2009; poster SA 394

Who Should Have Their 25(OH)D Measured?

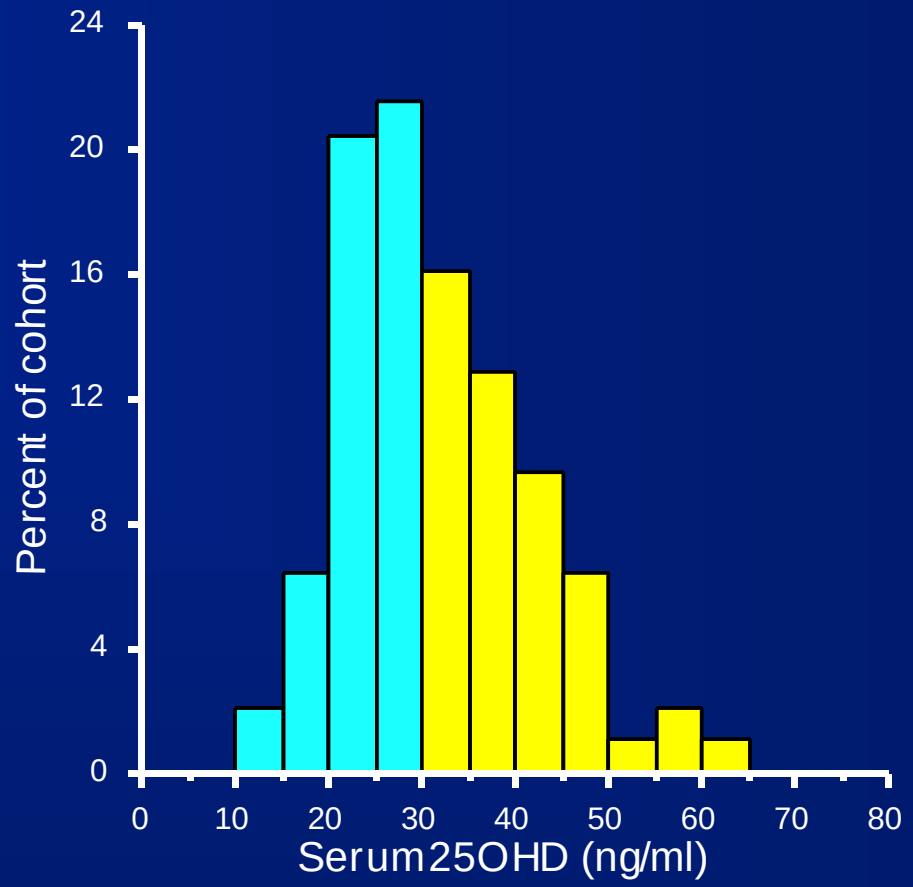
- *"It is reasonable for everyone to have his or her 25(OH)D concentration measured once a year."*
  Holick, Am J Clin Nutr, 76:3-4, 2002
  - $100 x 305 million = $30.5 billion
    - ~7.5% of total Medicare budget)
- Osteoporosis
- Falls/falls risk
- Malabsorption
- Medications that alter D metabolism
- Cancer?
- Diabetes mellitus??

“Let’s Correct Vitamin D Deficiency by Brief Sun Exposure.”

We Are Not All The Same….

Even Major Sun Exposure Does Not Guarantee Vitamin D Adequacy

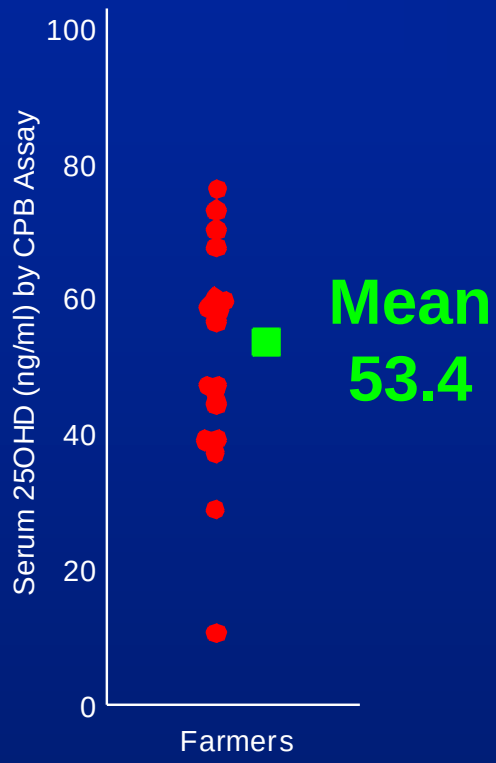
Mean sun index = 11.1

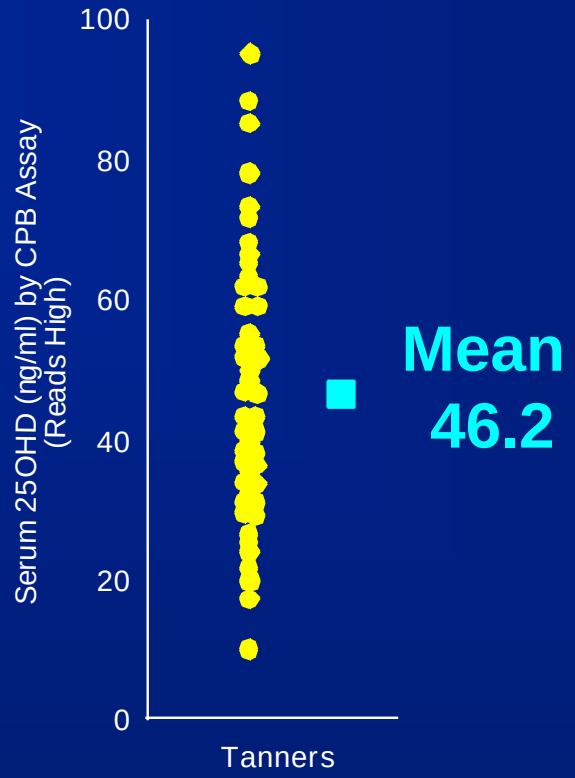


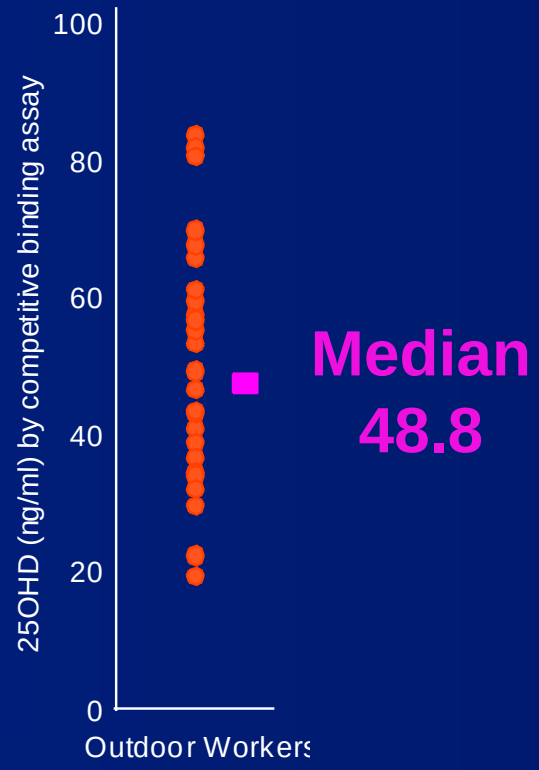
Binkley, et al, J Clin Endocrinol Metab, 92:2130-2135, 2007

The "Surfer Study" is Not Unique

25(OH)D Status in UV Exposed Adults







18 farmers sun exposure from 32-70 hours/wk

Haddock, PR Health Sci J, 1982

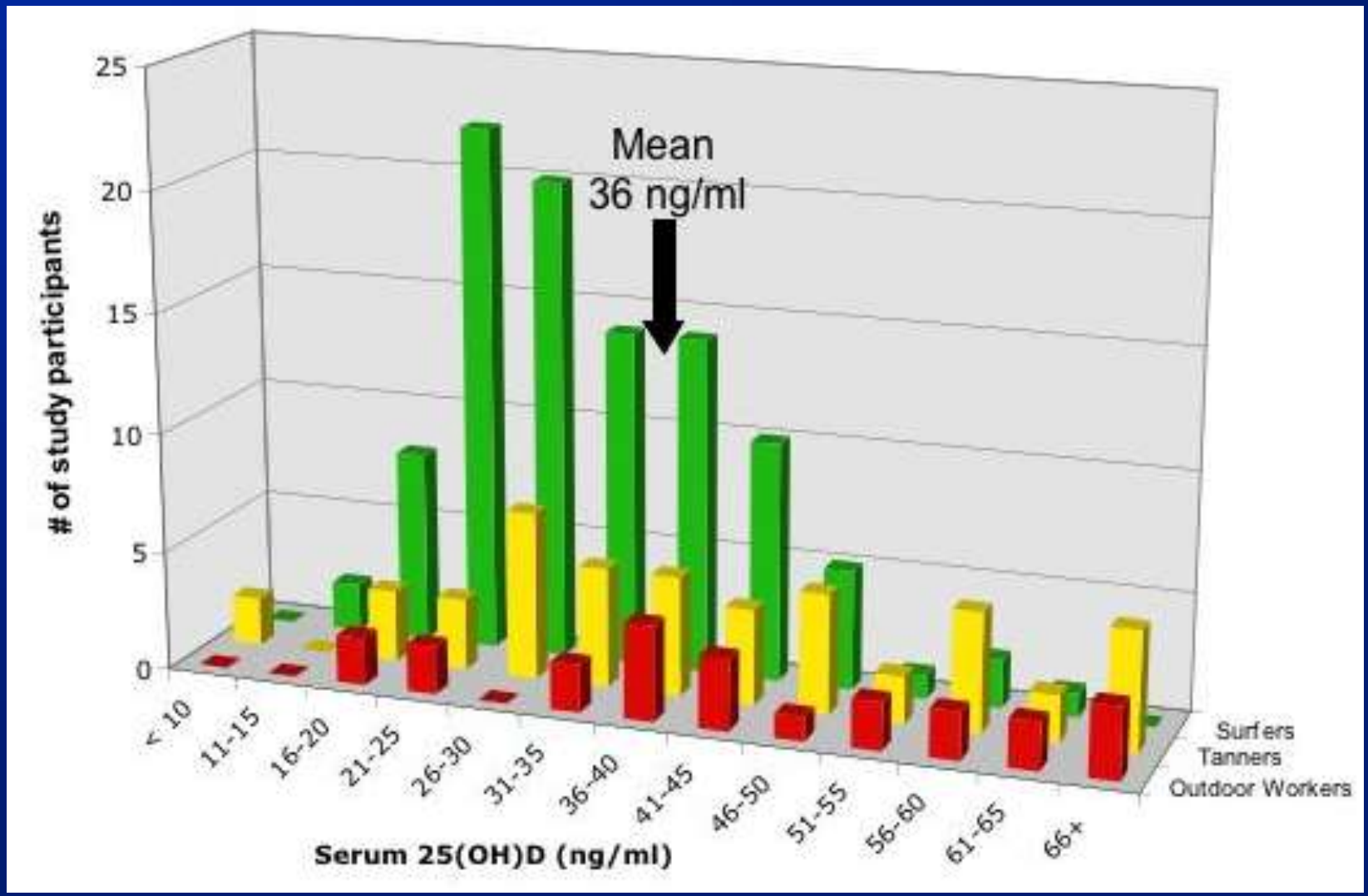
50 subjects tanning bed ≥ 1x/wk for 6 mo

Tangpricha, Am J Clin Nutr 2004

30 outdoor workers Sun index = 11.5

Barger-Lux, JCEM 2002

Combining These Studies, ~35 ng/ml Seems a Reasonable Goal and 20 ng/ml Seems Low



Data from: Barger-Lux, JCEM 2002, Tangpricha, Am J Clin Nutr 2004 and Binkley JCEM 2007

“Casual” Sun Exposure Does Not Guarantee Optimal D Status

We Need to Utilize Vitamin D Supplements

How and What??

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

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

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 3,000 IU/day, repeat 25(OH)D ~3-6 months later

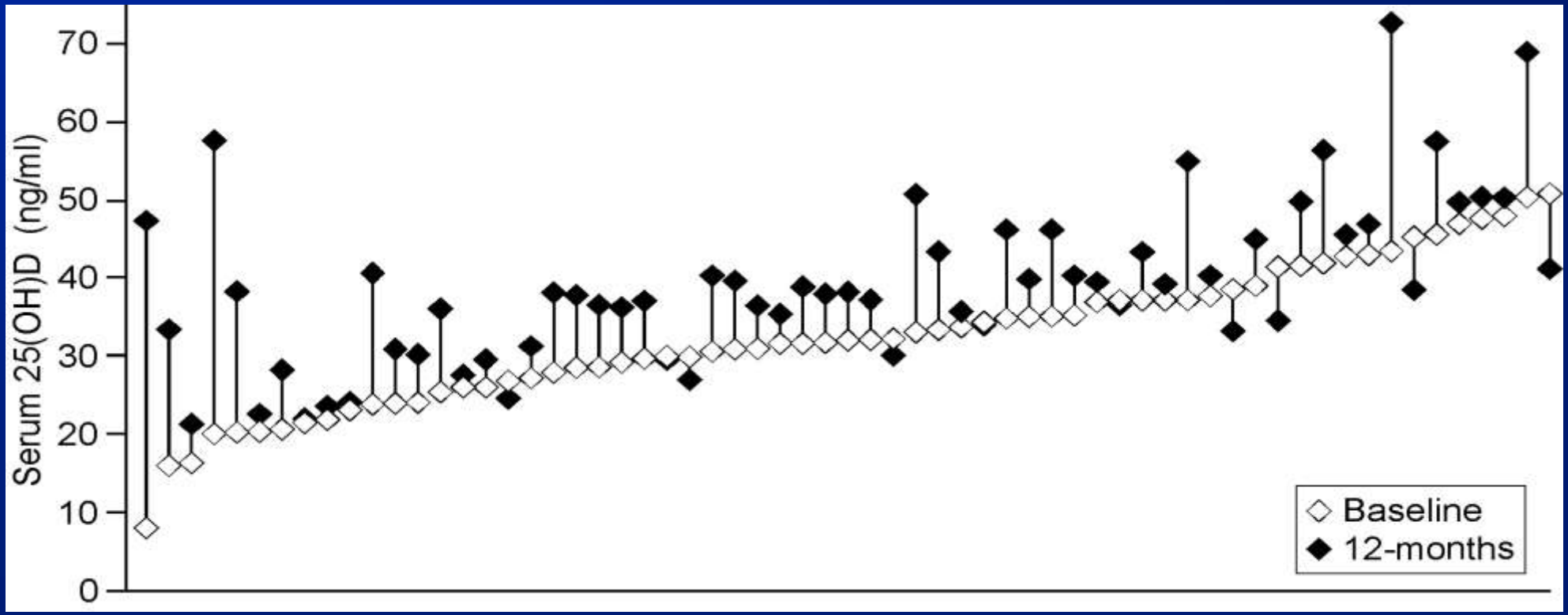
As With Sun Exposure: Substantial Variability Exists in Response to Oral Vitamin D Dosing

"A striking finding in this study was the high variability in the slopes for the dose-response curves."

"… a single dose of vitamin D may not be satisfactory for achieving a range of 75-220 nmol/L for serum 25(OH)D in almost everyone."

Aloia, et. al., Am J Clin Nutr, 87:1952-1958, 2008

Example of Between-Individual Variability in Response to Vitamin D

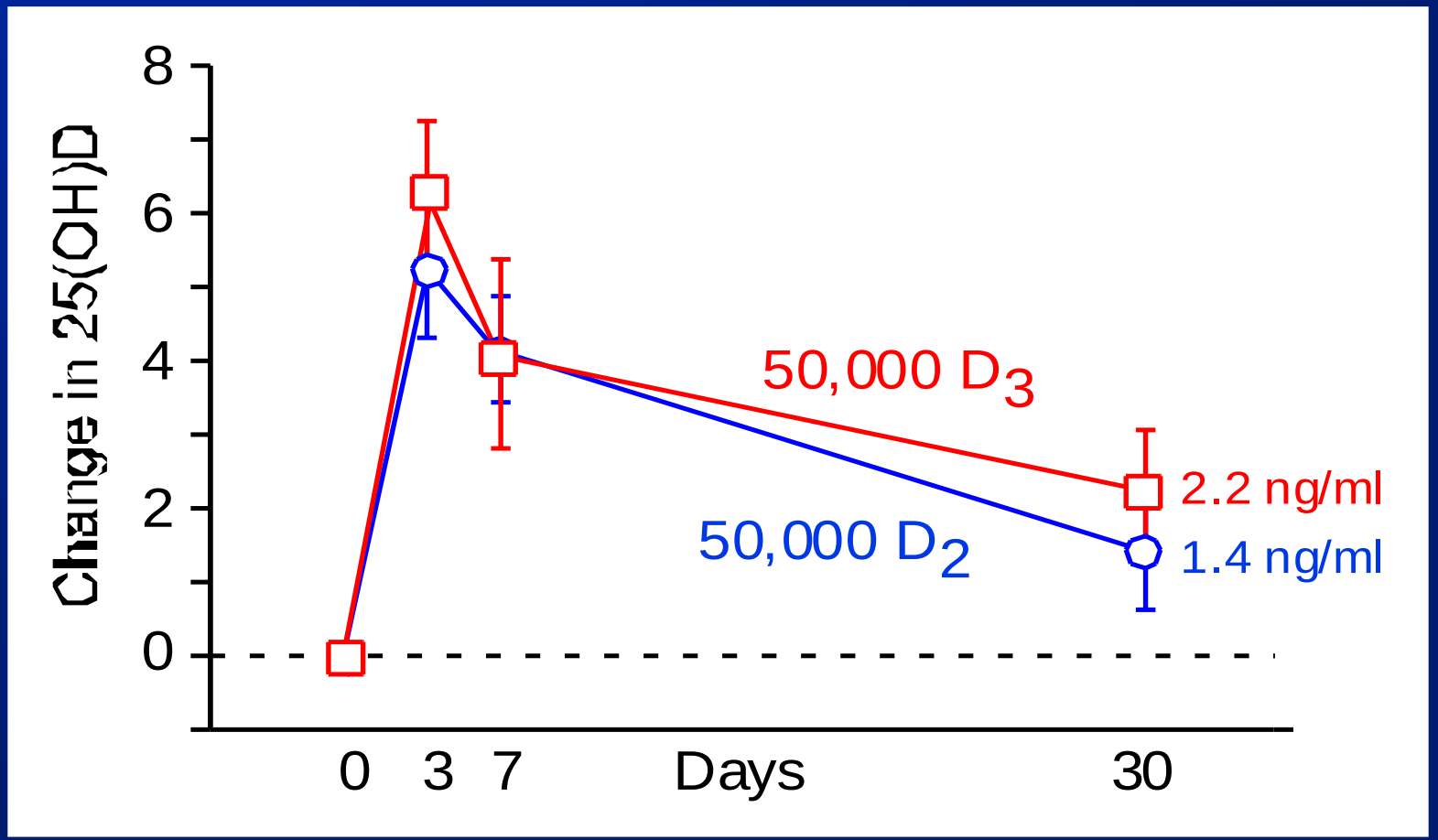


To assure adequacy, either you need to give **a lot** or measure 25(OH)D

Binkley, et. al., Presented at ASBMR, 2009, #1281

50,000 IU Once Monthly Is Not "A Lot"

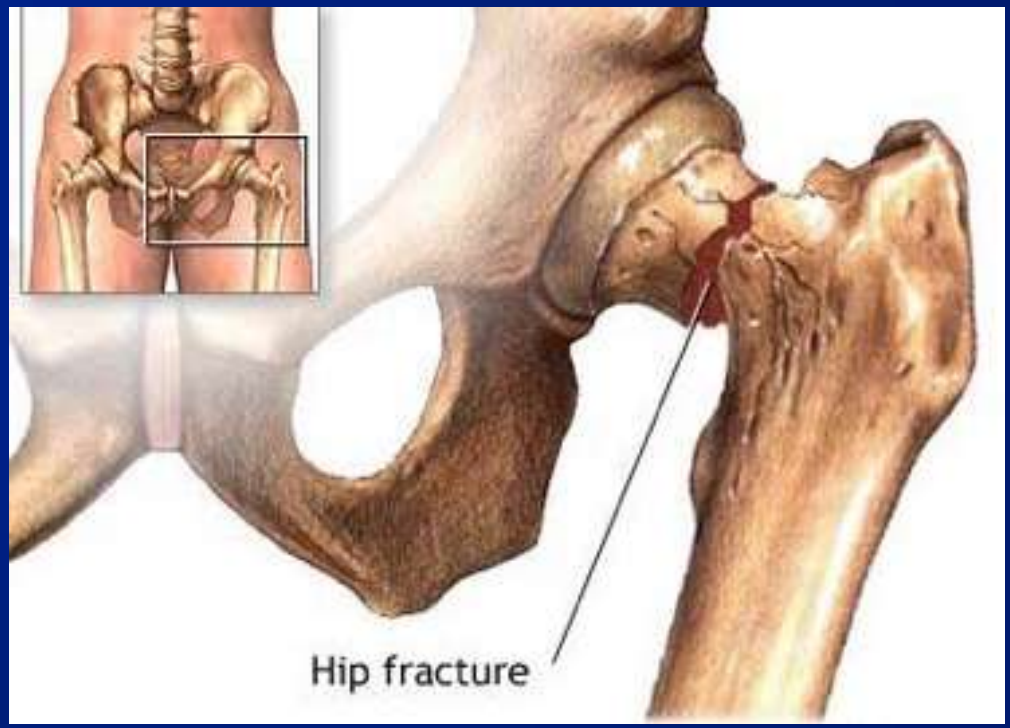
Also, Note the Peak/Trough Effect



Binkley, et. al, submitted for publication

What Will Result From Optimizing Vitamin D Status??

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

Vitamin D and Muscle

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]

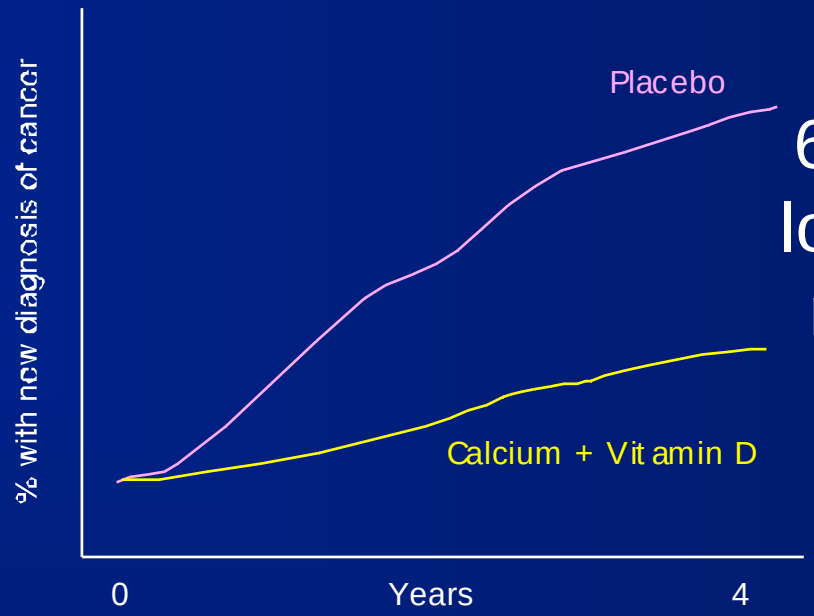
- Myocytes possess vitamin D receptors
- D deficiency associated with myopathy
  - 32 year old woman with progressive muscle weakness and diffuse bone pain
  - Fat malabsorption; s/p bowel resection
  - 25(OH)D = 2.4 ng/ml
- Treated with 1, 25 diOHD$_3$
- *"After 3 weeks she could walk again, and muscle weakness and bone pain had disappeared."*

Boonen, et. al, Calcif Tissue Int, 78:257-270, 2006
Sorenson, et. al, Clin Sci, 56:157-161, 1979

Vitamin D Reduces Cancer Risk

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

25(OH)D increased from 28 ng/ml to 38 ng/ml



60% lower risk

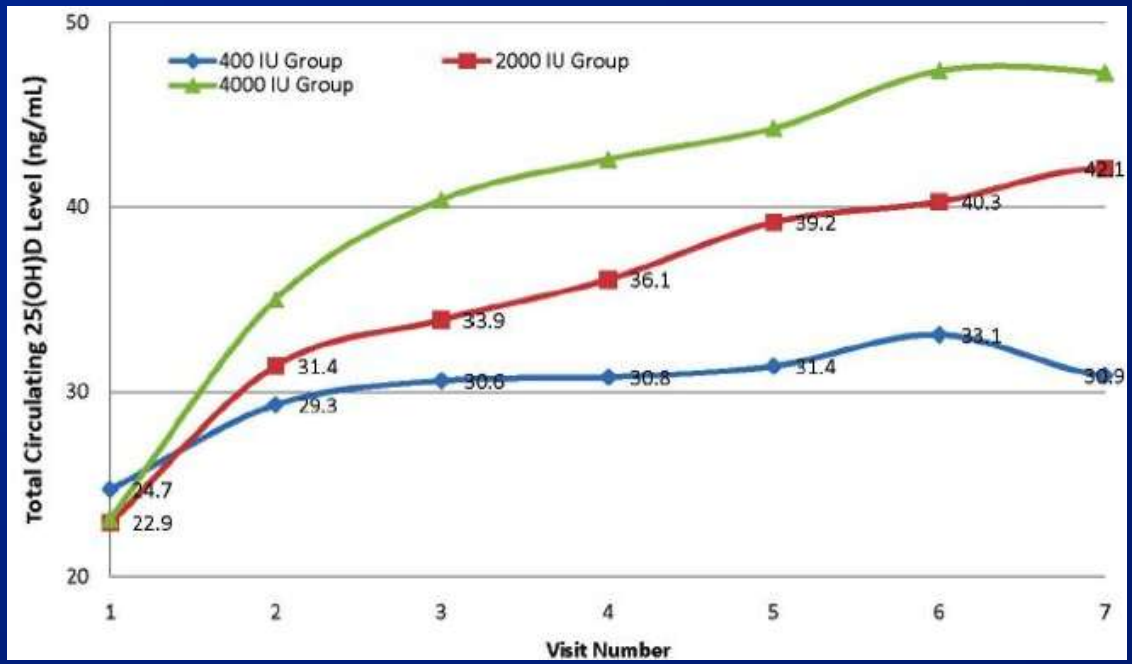
".. improving vitamin D nutritional status substantially reduced all-cancer risk in postmenopausal women."

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

Reducing the Risk of Osteoporosis and Fracture, Falls and Cancer is Good Enough for Me….

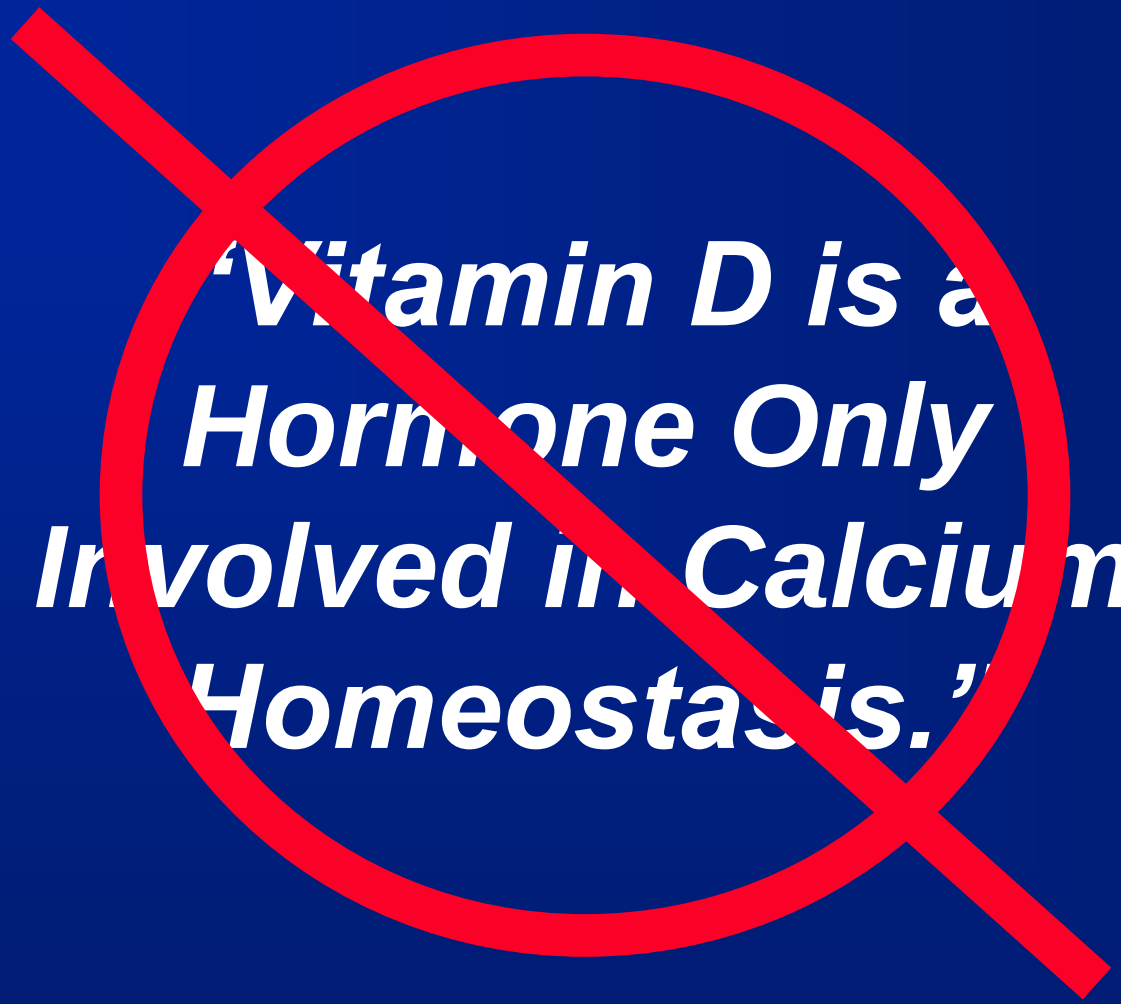
Vitamin D and Pregnancy

- 350 pregnant women, 12-16 weeks gestation randomly received 400, 2000 or 4000 IU vitamin D_3 daily until delivery
- 99 AA, 137 Hisp, 115 Cauc
- No effect on serum calcium, creatinine, phos or urine ca/cr
- Preterm labor, premature birth and infection inversely related to 25(OH)D and lowest ($p < 0.0001$) in the 4000 IU group



"We recommend 4000 IU/day for all pregnant women."

Wagner, et. al, Presented at Pediatric Academic Societies Ann Meeting 2010, Vancouver


“Vitamin D is a
Hormone Only
Involved in Calcium
Homeostasis.”

Vitamin D Has Local Effects

- Vitamin D receptors are present in many 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 $(OH)_2D$ 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 mellitus**
- 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
- Obesity
- Incontinence
- Aging
- Overall mortality

We Need 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

Vitamin D and Diabetes

Potential Mechanisms

- Beta cells contain the vitamin D receptor and the 1 alpha hydroxylase. Bland, et. al., J Steroid Biochem Mol Biol, 121:9-, 2004
- Vitamin D improves beta cell function
  - Direct effect on insulin secretion
    - Impaired insulin secretion in VDR deficient mice
    - 1, 25 $(OH)_2D$ stimulates insulin release
    - Reduced insulin secretion in D deficiency
    - Supplementation with vitamin D restores insulin secretion in animals
  - Indirect effect on insulin secretion; potentially via a calcium effect on insulin secretion
    - Hypocalcemia associated with impaired insulin secretion

Pittas, et. al, J Clin Endo Metab, 2007; 92:2017*2029

Vitamin D and Diabetes

Potential Mechanisms

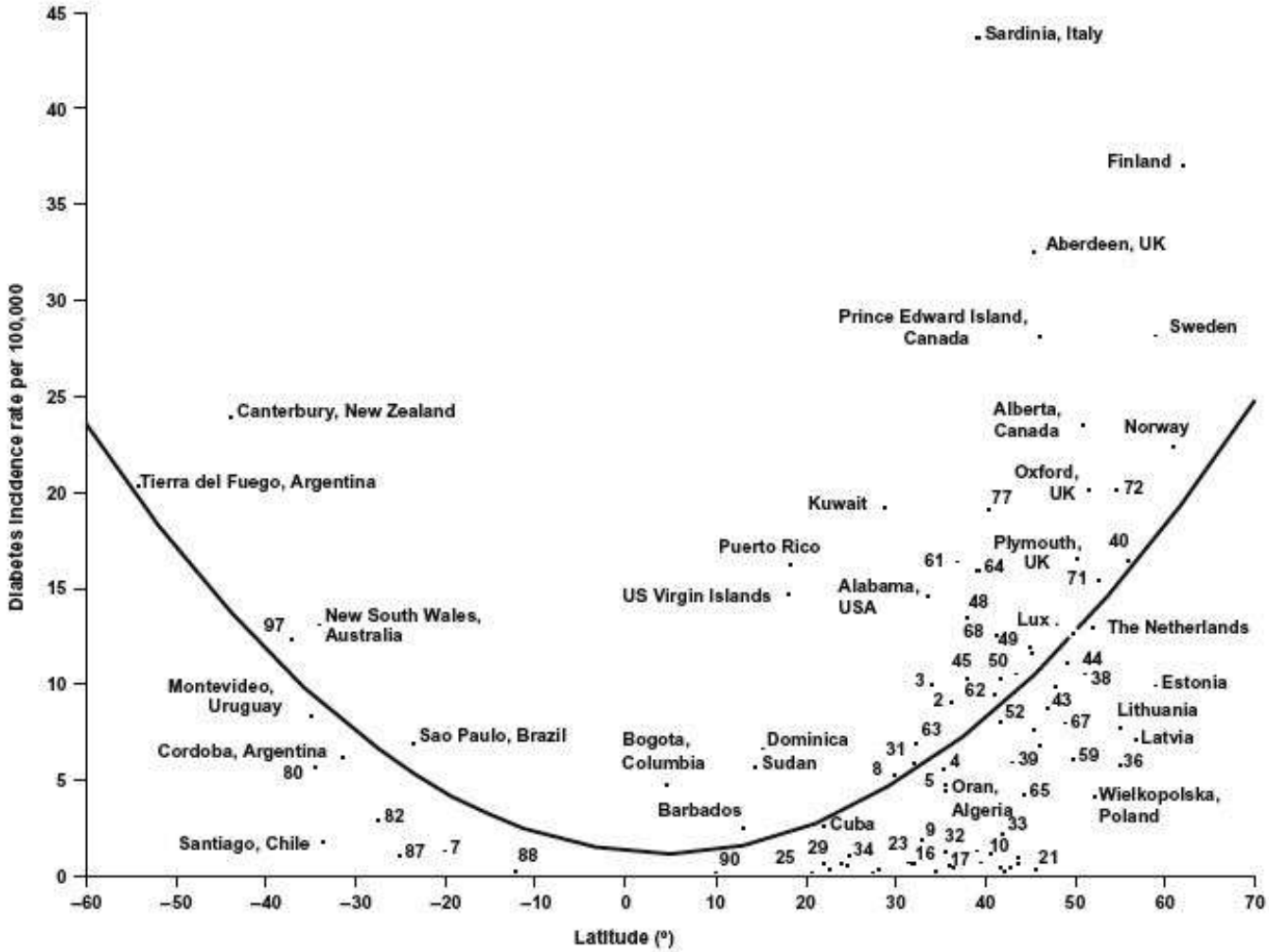
- Improvement in insulin action
  - Direct effect on insulin action
    - Stimulates expression of insulin receptor
    - Enhances insulin responsiveness for glucose transport
  - Indirect effect on insulin action
    - Potentially via a calcium effect on insulin secretion
- Calcium effect on insulin action
  - Calcium essential for insulin-mediated intracellular processes
  - Impairment of insulin receptor phosphorylation, a calcium dependent process, leads to impaired insulin signal transduction
- Improvement in systemic inflammation
  - Direct effects on cytokines
  - Effect of calcium on cytokines

Pittas, et. al, J Clin Endo Metab, 2007; 92:2017*2029

Observational Studies Suggest That Low Vitamin D Status May Be Associated With Increased Diabetes Risk

Geographic Variation Type 1 Diabetes Incidence

Greater incidence at higher latitudes



Mohr, et. al., Diabetologia, 2008; 51:1391-1398

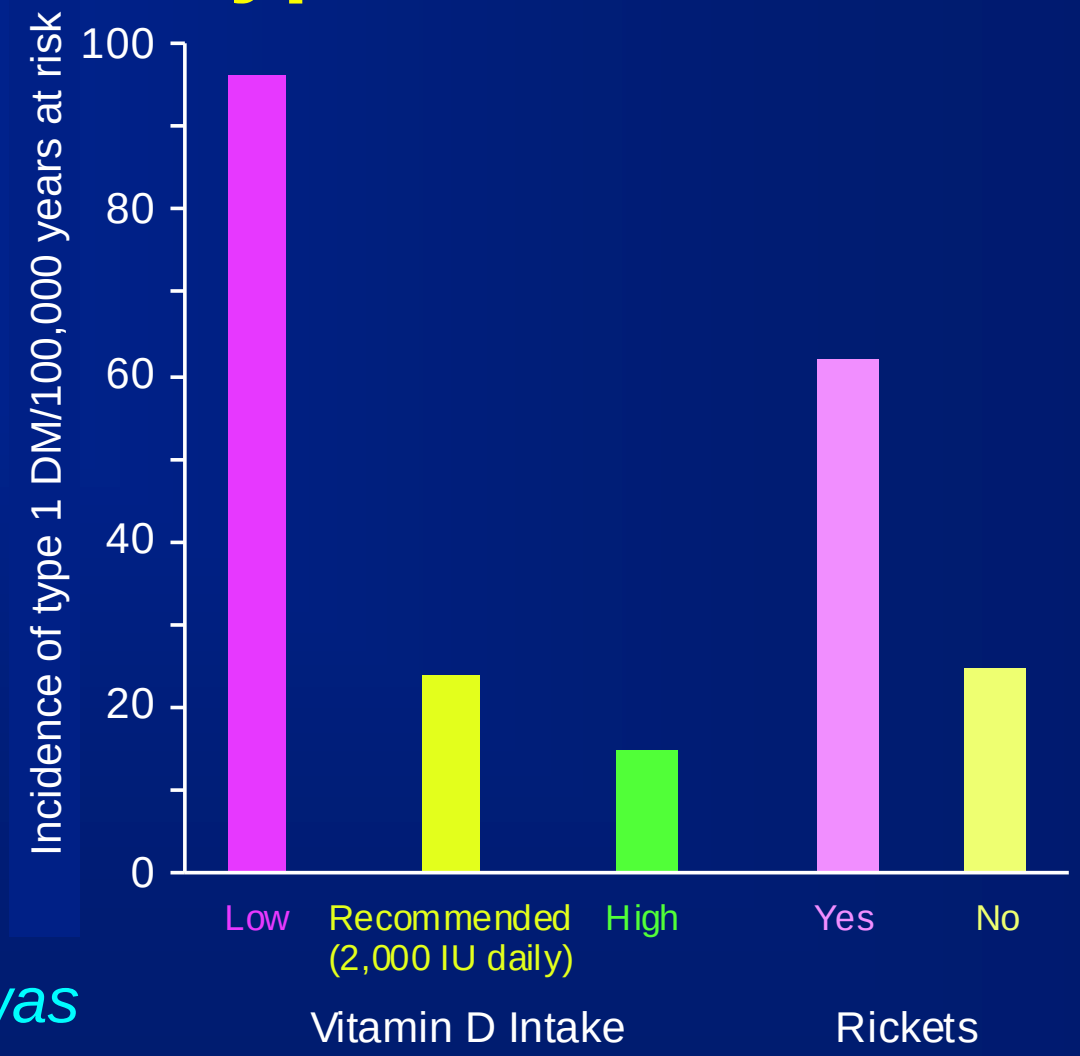
Vitamin D Supplementation in Infancy Reduces the Risk of Type 1 Diabetes

All women in 2 northern Finland towns who gave birth in 1966 (n = 10, 366)

Data collected in 1st year of life re: vitamin D supplementation and presence of Rickets

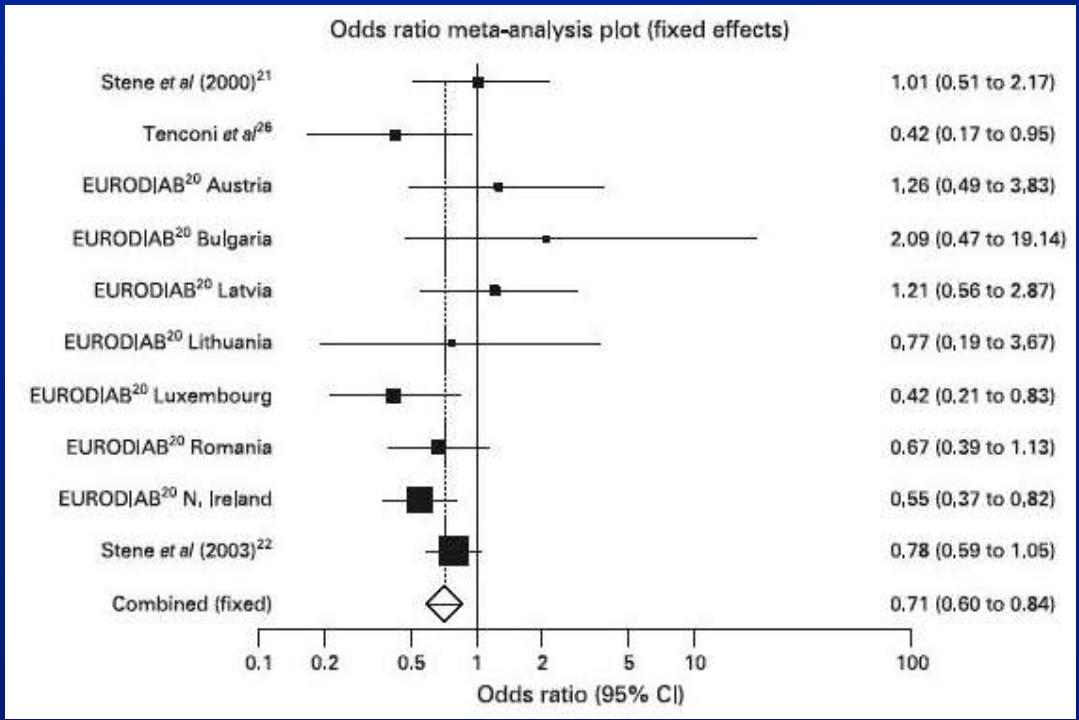
Primary outcome Dx of DM type 1 by 1997; n = 81

"In children who received vitamin D regularly, the risk was reduced by about 80%"



Hypponen, et. al., Lancet. 2001; 358:1500-1503

Vitamin D Supplementation in Early Childhood and Risk of Type 1 Diabetes



29% reduction in risk of developing type 1 diabetes compared with their peers who were not supplemented

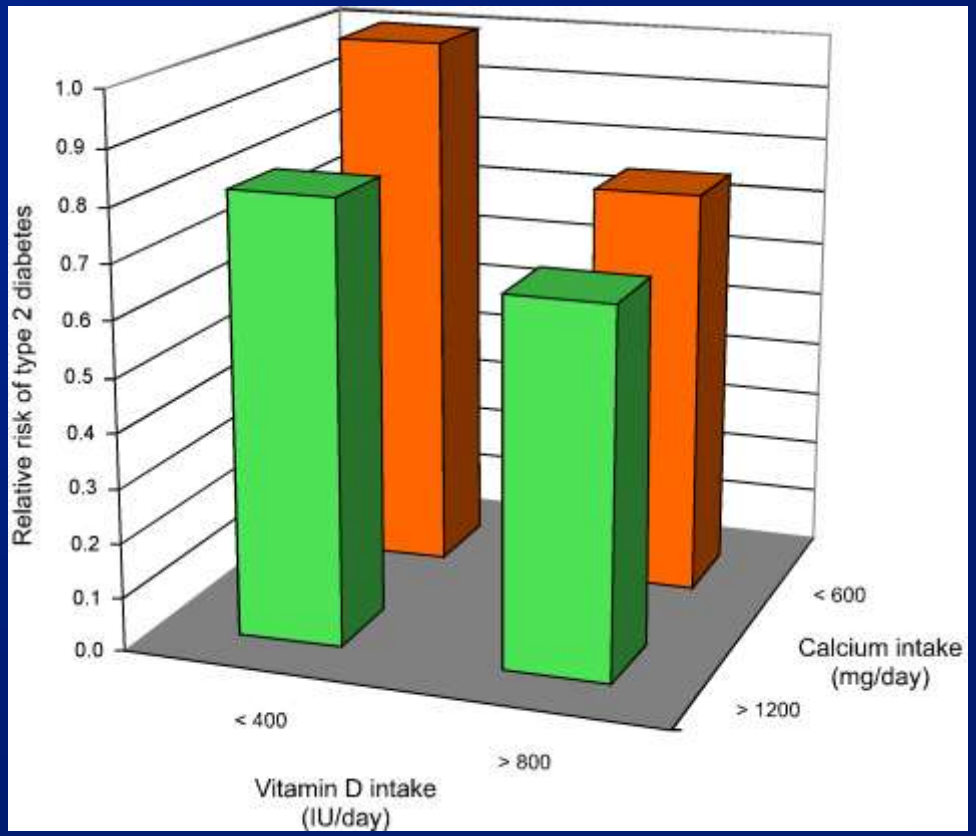
…the risk of type 1 diabetes was significantly reduced in infants who were supplemented with vitamin D compared to those who were not….” “There was also some evidence of a dose-response effect”

Zipitis and Akobeng, Arch Dis Child. 2008; 93:512-517

Observational Studies Find an Association Between Low Vitamin D Status and Risk of Type 2 DM

Nurses Health Study
83,779 women; 20 year f/u
4,843 new cases type 2 DM

"A combined daily intake of >1,000 mg calcium and >800 IU vitamin D was associated with a 33% lower risk of type 2 diabetes"



Pittas, et. al, Diabetes Care, 2006; 29:650-656

Meta-Analysis: Association of Low Vitamin D and Risk of Type 2 DM

"Combining data from all studies that reported the association between 25(OH)D and prevalent type 2 DM, the summary OR was 0.54 for the highest vs. the lowest 25(OH)D concentration…
When we excluded blacks… OR = 0.36"

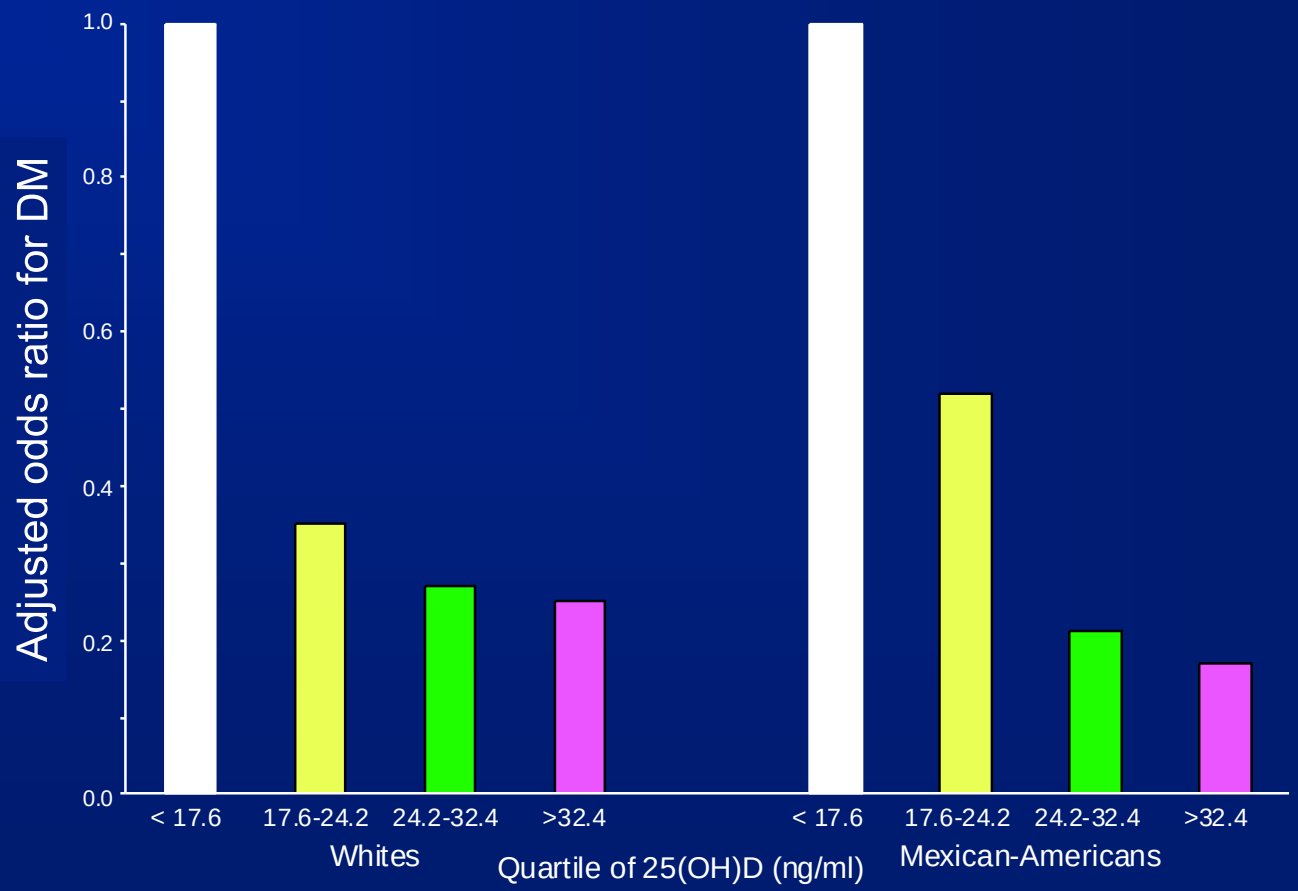
Pittas, et. al, J Clin Endo Metab, 2007; 92:2017-2029

NHANES III (1988-1994)

Strong inverse association between 25(OH)D and diabetes prevalence

25(OH)D 2,766 white, 1,736 black and 1,726 Mexican Americans

Adjusting for sex, age, BMI, activity and season, the odds ratios varied inversely with 25(OH) quartiles in whites and Mexican Americans

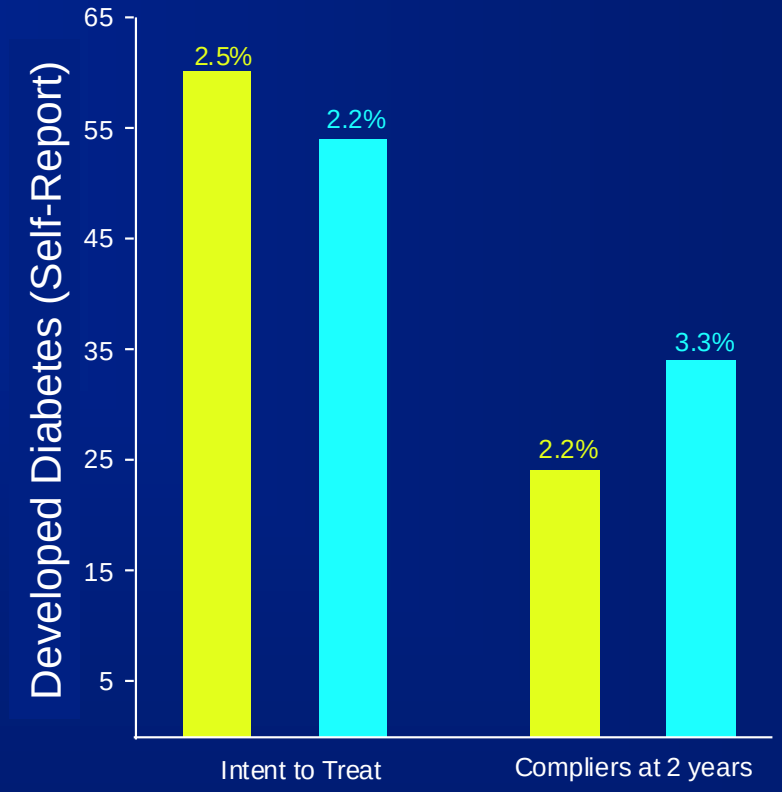


Scragg, et. al., Diabetes Care. 2004; 27:2813-2818

Prospective Studies of Vitamin D Supplementation and Diabetes Are Very Limited

Post Hoc Analysis: RECORD Trial

5,202 (84% female)
age 70+
Randomized to
800 IU D3
Calcium 1000 mg
Both or PBO
Followed for 24-62 mo

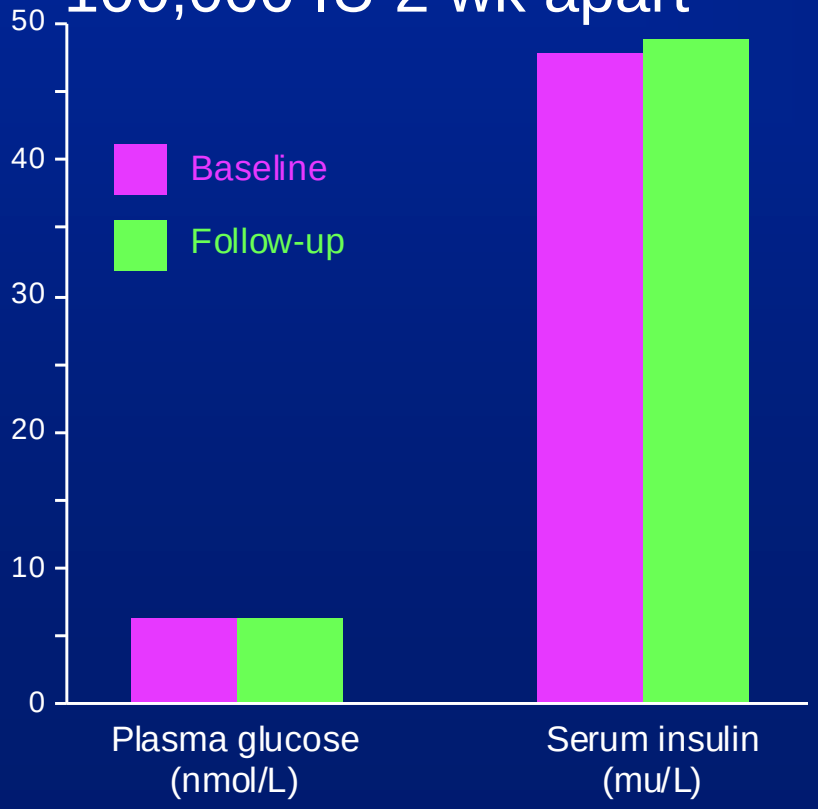


…800 IU vitamin D_3 did <u>not</u> suggest a protective effect against the development of type 2 diabetes…"

Avenell et. al., Age Ageing. 2009; 38:606-609

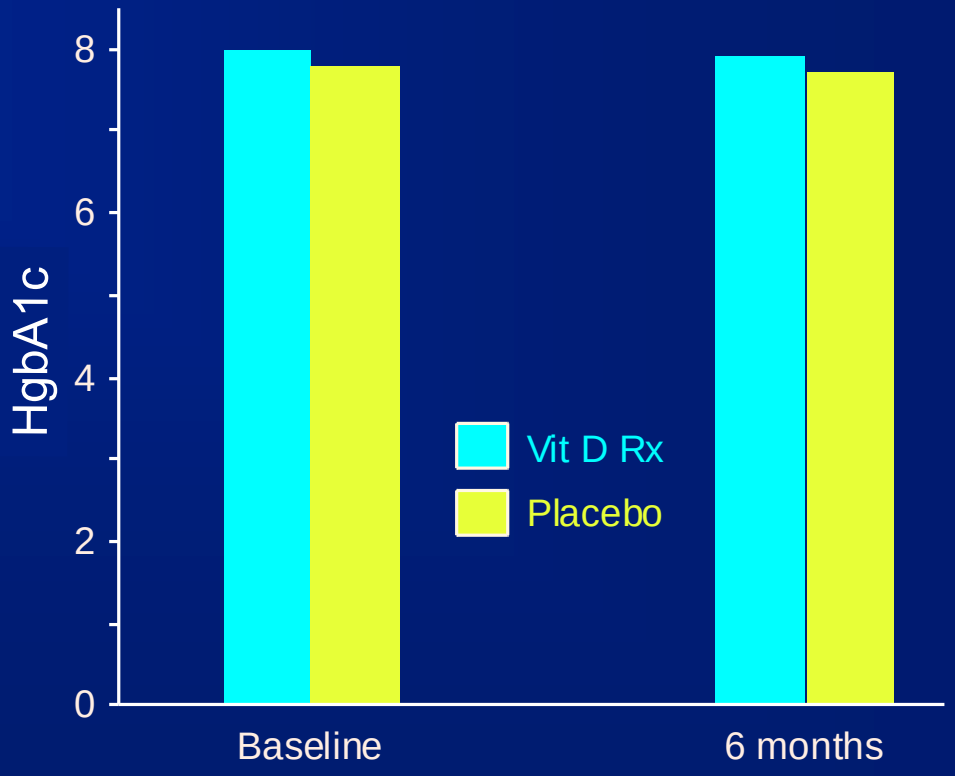
Two Small Prospective Studies Found No Effect of Vitamin D Supplementation

Low vit D (<20 ng/ml)
n = 36; 2 doses of D_3
100,000 IU 2 wk apart



Tai, et. al, Nutrition, 2008; 24:950-956

Treated DM; n = 36
D_3 40,000 IU/wk vs PBO

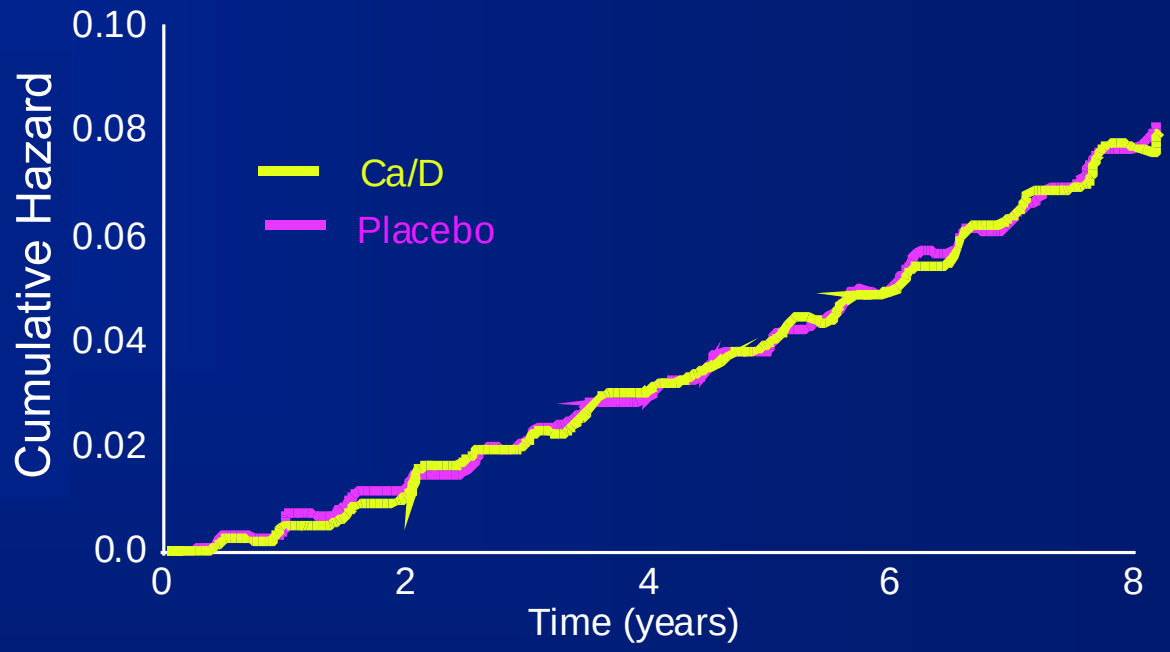


Jorde & Figenschau, Eur J Nutr, 2009; 48:349-354

Calcium + Vitamin D Had No Effect on DM Risk: Women's Health Initiative

Participants without prevalent diabetes at study enrollment (n = 33,951)

Randomized to 1000 mg calcium + 400 IU D_3 or PBO
Median follow-up 7 years



Problems: Self-reported diabetes
Low vitamin D dose
25(OH)D not measured at follow up

De Boer et. al., Diabetes Care. 2008; 31:701-707

The Prospective Trials of Vitamin D Supplementation Are Too Small or Used Inadequate Amounts of Vitamin D

Larger Studies With Higher Vitamin D Dose are Needed

Vitamin D May Protect Against DM Nephropathy

Mice

- 1, 25-dihydroxyvitamin D suppresses renin in mice and reduce proteinuria
- Diabetic VDR knockout mice develop more severe albuminuria and glomerulosclerosis and have increased renin

"Our study suggests that receptor-mediated vitamin D actions are renoprotective in diabetic nephropathy."

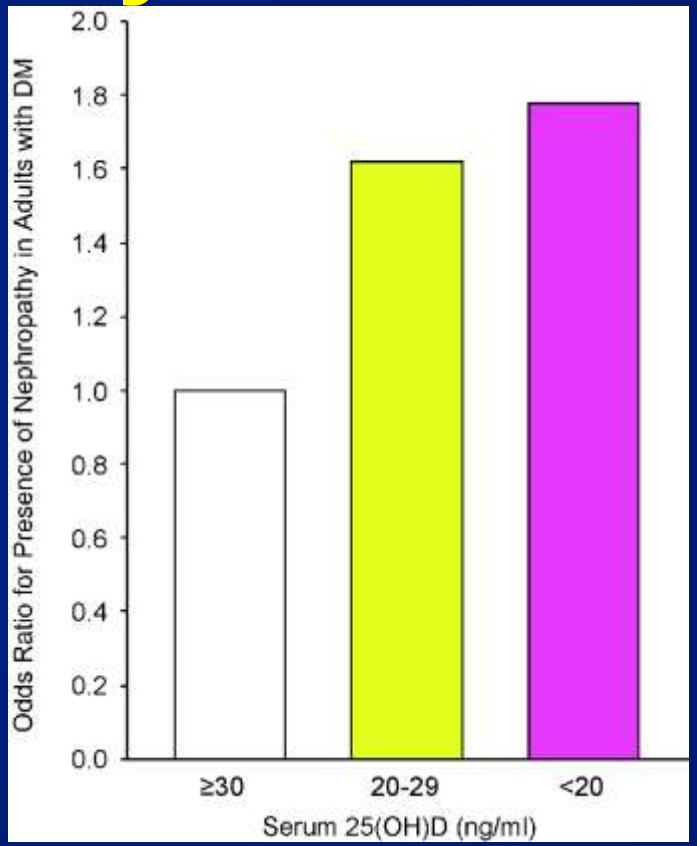
Zhang et. al., Kidney Int. 2008; 73:163-171

Vitamin D May Protect Against DM Nephropathy

Humans

NHANES; 1216 adults with DM Nephropathy; defined as urine albumin to creatinine ratio ≥ 30 mg/g in spot urine

OR adjusted for age, gender, race, hypertension, cholesterol, smoking, ACE use and obesity



"There is an independent association between vitamin D deficiency with the presence of nephropathy."

Diaz et. al., J Am Board Fam Med. 2009; 22:521-527

Vitamin D and Diabetes: Summary

"Animal and human studies support the notion that adequate vitamin D supplementation may decrease the incidence of type 1 and possibly also of type 2 diabetes mellitus and may improve the metabolic control in the diabetes state. However, the exact mechanisms… are not clear and need further investigation."

Danescu et. al., Endocr. 2009; 34:11-17

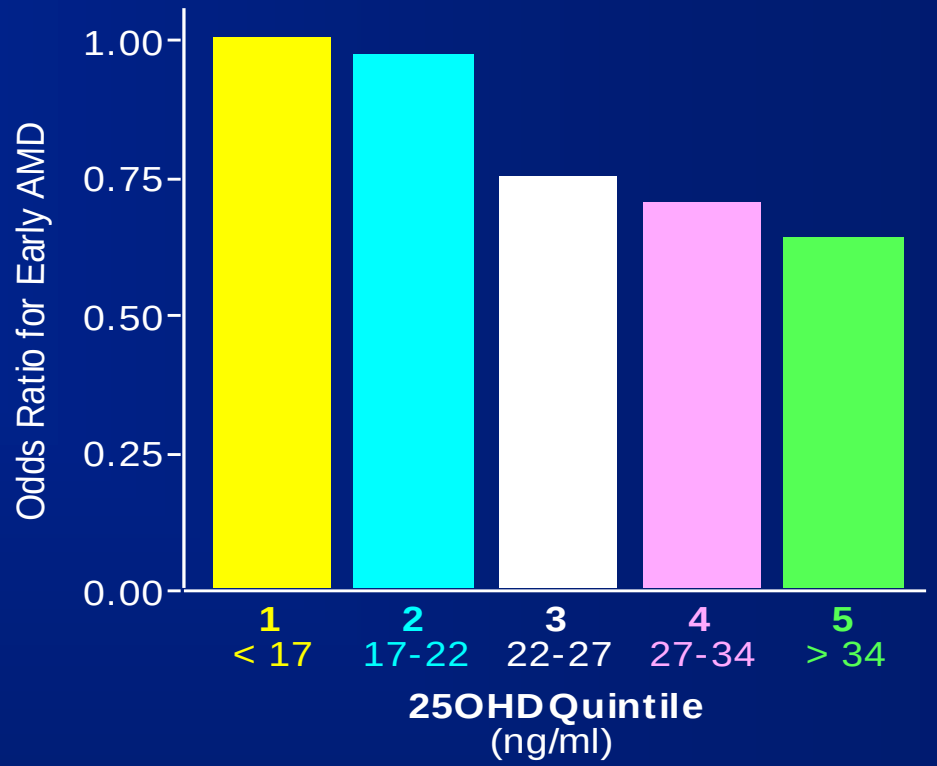
"Much work remains to be done in this new field before the role of vitamin D in the pathogenesis of diabetes mellitus is completely understood."

Alfonso et. al., Diabetes Metab Res Rev, 2009; 25:417-419

What About Vitamin D Inadequacy And Other "Age-Related Morbidities???

Vitamin D Status & Macular Degeneration

Evaluated association of 25(OH)D and prevalent age-related macular degeneration in NHANES III (n = 7752, 11% with AMD)
25(OH)D by RIA
AMD identified by fundus photographs



"This study provides evidence that vitamin D may protect against AMD. Additional studies are needed …."

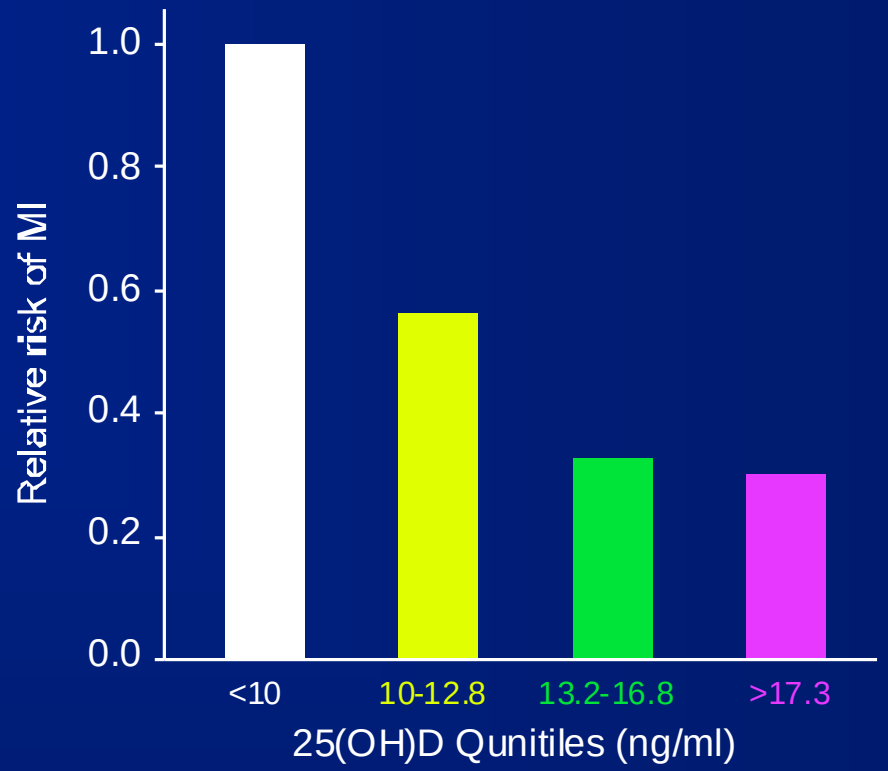
Adapted from Parekh, et. al., Arch Ophthalmol,125:661-669, 2007

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



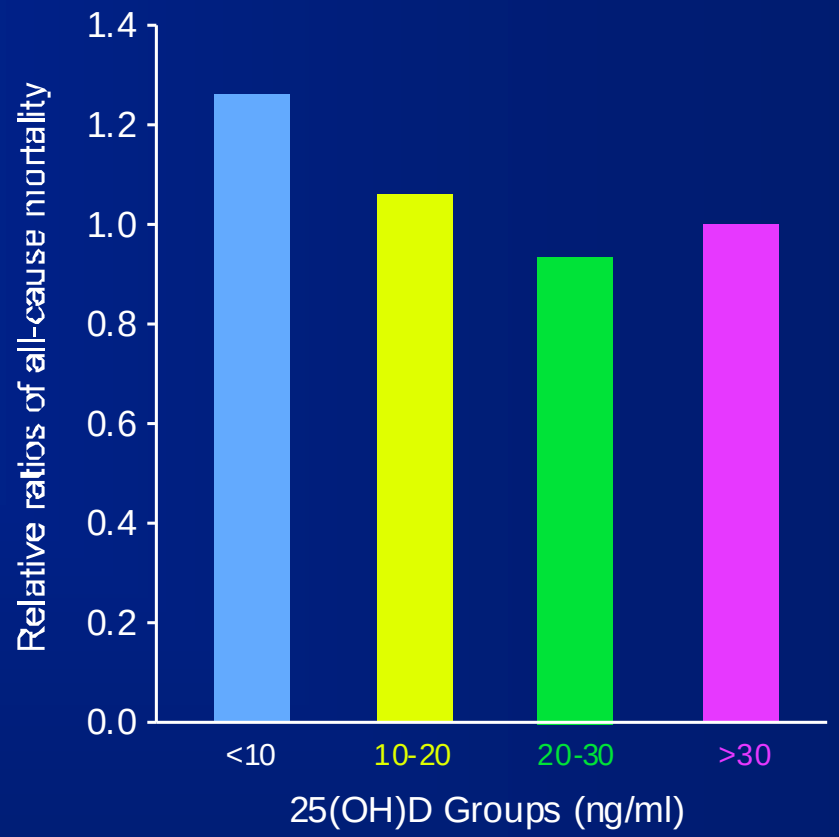
"…provides support for the hypothesis that increased exposure to sunlight is protective against CHD."

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

25(OH)D Levels and Mortality

NHANES; 13,331 adults followed for mortality from 1988-1994 to 2000
Median follow up of 8.7 years
1806 deaths; 777 from CVD

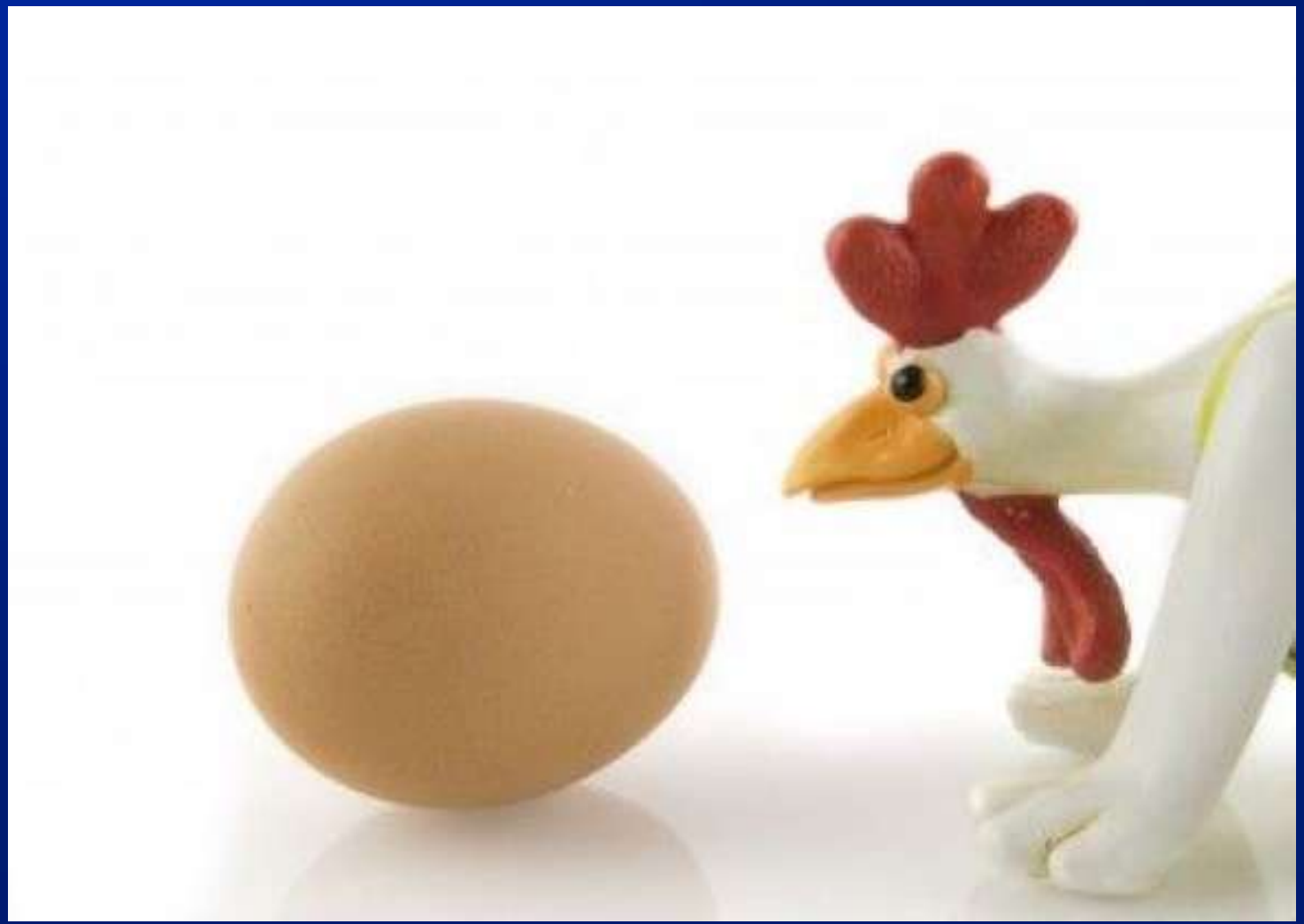
25(OH)D by Diasorin RIA
Hazard ratios multiply adjusted



"The lowest quartile of 25(OH)D (<17.8 ng/ml) is independently associated with all-cause mortality in the general population."

Mclamed, et. al., Arch Intern Med, 168:1629-1637, 2008

Vitamin D and Chronic Disease
Chicken or Egg?



It is Attractive to Speculate that Vitamin D Insufficiency Contributes to the Development of Multiple Diseases.

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

H. L. Mencken

Association Does Not Prove Causation

"…it remains unclear whether vitamin D deficiency is a cause or a consequence of a poor health status."

Pilz, et. al, Clin Endo, 2009

"We know an insufficient amount about vitamin D insufficiency."

M.K. Drezner, M.D.

Vitamin D Conclusions; 2011

- Vitamin D inadequacy is very common
- No downside to aiming for 25(OH)D ~40 ng/ml
- Need at least 1,000-2,000 IU/day
  - Not everyone needs the same dose
  - Prudent to recommend vitamin D_3
  - These “higher” doses are safe
- “Casual” sun exposure is not enough
- Unlikely that vitamin D is the fountain of youth
- Vitamin D adequacy will reduce osteoporotic fractures, falls, probably cancer and **potentially** a multitude other diseases

Thank You!