

Pennsylvania Medical Directors Association:  
Annual Meeting and Symposium

## Vitamin D and Evidence-Based Medicine

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University of Maryland School of Medicine  
*Corporate Medical Director, Mid-Atlantic Health Care*  
*Multi-facility Medical Director (HCR ManorCare & FutureCare)*

## Faculty Disclosures:

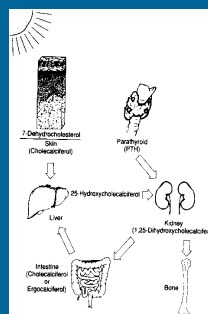
Dr. Gloth has disclosed that he has no relevant financial relationship(s).

## Learning Objectives:

*By the end of the session, participants will be able to:*

- Objective 1: Distinguish between vitamin D2 and Vitamin D3 supplementation.
- Objective 2: Recognize the contribution of vitamin D to fall and fracture reduction, improved function, combating infections, reduction in pain and mood enhancement.
- Objective 3: Develop strategies for instituting vitamin D supplementation programs in the long term care environment.

## Vitamin D Metabolism



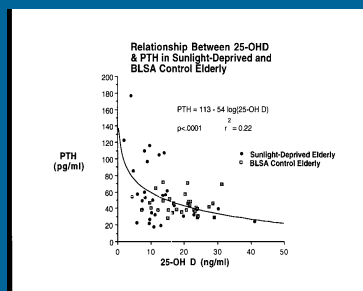
Gloth III FM, Tobin JD. A Review of Vitamin D Deficiency in the Elderly: What we know and what we don't. J Am Geriatr Soc. 1995; 43: 822-8.

## Vitamin D deficiency:

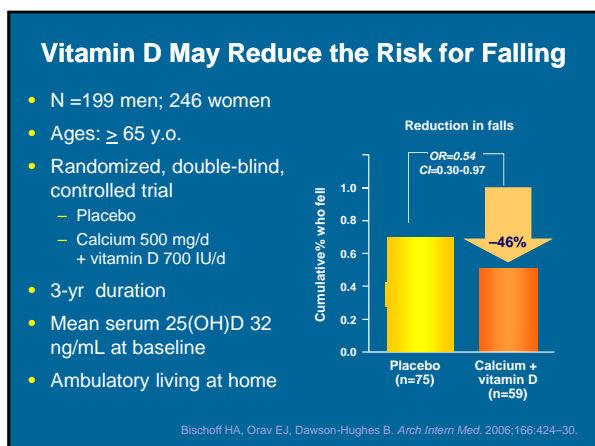
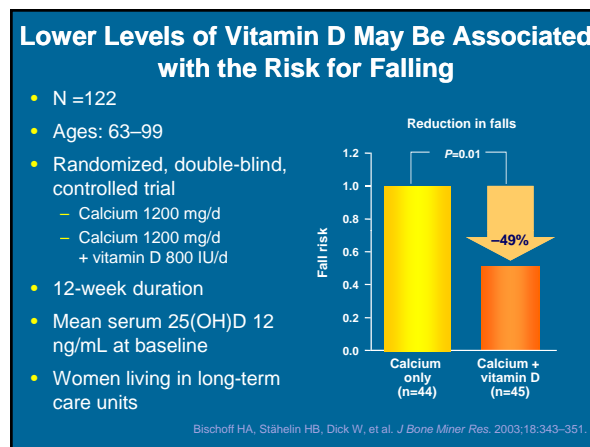
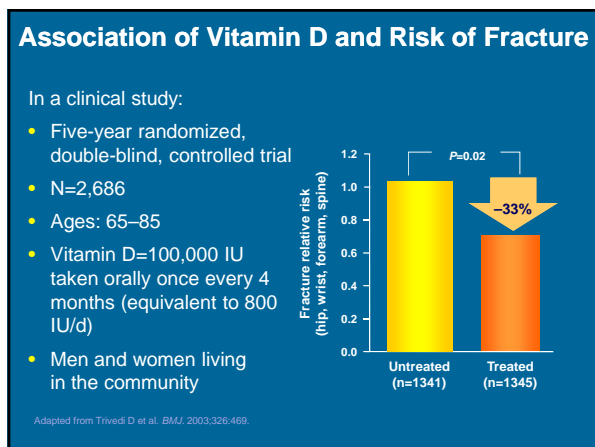
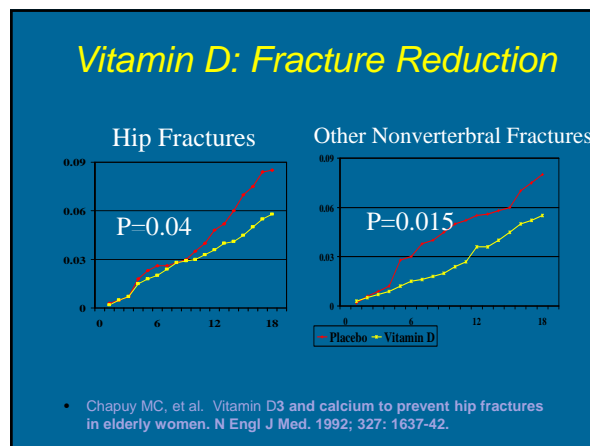
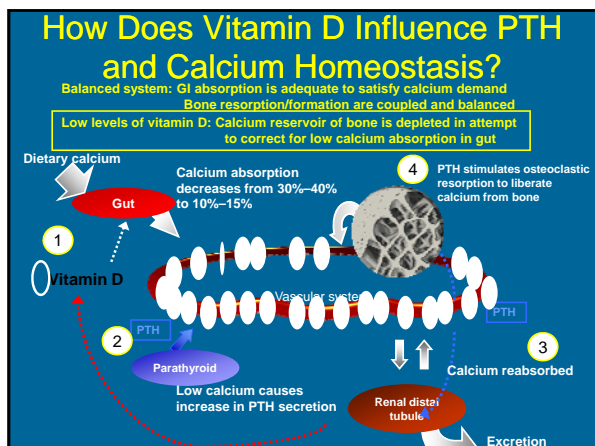
Hypovitaminosis D accompanied by physiological or biochemical abnormalities

National Academy of Science Recommended Dietary Allowances. Tenth Revised Edition, Washington, DC, The National Academy Press, 1989, 95-96.

## Low Vitamin D Status and PTH Increase



- Gloth et al. JAMA 1995. 274:1683-6

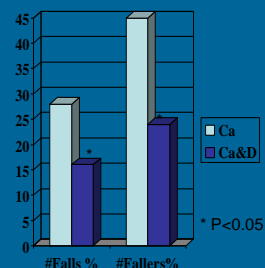


Vitamin D has been associated with a 20-30% reduction in fall rates

**Bischoff-Ferrari HA et al. Effect of vitamin D on falls: A meta-analysis. *JAMA* 2004; 291: 1999-2006**

### Vitamin D and Calcium on PTH, Sway & Falls

- 25-OHD at Baseline 25 nmol/L (10ng/mL)
- Sway frontal & saggital diam and sway area 8 wks
- PTH at 8 weeks
- Falls at one year



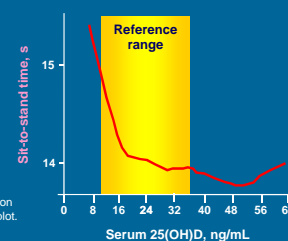
Pfeifer M et al J Bone Miner Res 2000; 15:1113-8

### Higher 25(OH)D Levels Are Associated With Better Lower Extremity Function in Ambulatory Women

- 4,100 ambulatory adults included in NHANES III
- 60 to ≥90 years
- Functional measurements used to assess lower extremity function:
  - 8-ft walking speed test
  - Timed sit-to-stand test

#### Timed Sit-to-Stand Test

LOWESS regression plot of lower extremity function vs vitamin D levels



NHANES = National Health and Nutrition Education Survey; LOWESS = locally weighted regression plot. Reference range of 22.5–94.0 nmol/L (9.0–37.7 ng/mL). N = 4,100; P < 0.001.

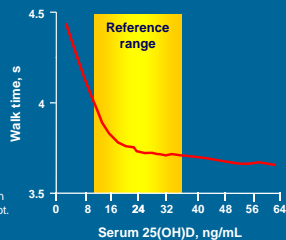
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#### 8-Ft Walking Speed Test

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### Vitamin D, Bone, and Teeth

- Vitamin D supplementation or Vitamin D Loss may have a rapid impact on bone <6 months
- Vitamin D and Calcium also reduces tooth loss
- Adding another fat-soluble vitamin, A, may impair the benefit of vitamin D on Bone (Nurses' Health Study > 3000 mcg/d retinol equivalents)

Dawson-Hughes B et al. N Engl J Med. 1997; 337: 670-6  
 Dawson-Hughes B et al. AM J Clin Nutr. 2000; 72: 745-50  
 Krall E et al. Am J Med. 2001; 111:452-6  
 Feskanich D et al. JAMA. 2002; 287: 47-54

### Vitamin D Deficiency Pain Syndrome

- Excruciating Pain with Light Pressure on Large Muscle Groups
- Pressure Sores Are Painful
- Unresponsive to Opioids or TCA's
- Marked Improvement or Resolution within 5-7 days of 100,000 I.U. Vitamin D

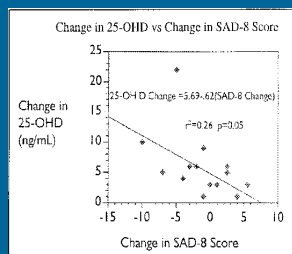
Gloth III FM, et al. Arch Intern Med. 1991; 151: 1662-1664.

### Seasonal Affective Disorder

- All patients in a small trial of SAD showed improvement on Hamilton Depression and SIGH-SAD Scales after 100,000 I.U. of Vitamin D statistically significantly better than broad spectrum light with plastic cover.
- Vitamin D status improved significantly more in Vitamin D treated group

Gloth et al. J Nutr Health Aging '99. 3(1):5-7

## Bringing Vitamin D Deficiency to Light



Gloth et al. J Nutr Health Aging '99. 3(1):5-7

## Functional Improvement with Vitamin D

- Vitamin D Deficient Subjects Treated with Vitamin D had a statistically significant improvement in FEFA scores
- Functional improvement was linearly associated with change in vitamin D status

Gloth et al. J Am Geriatr Soc. 1995; 43: 1269-71

## Vitamin D and Infection

- TLR activation of human macrophages up-regulated expression of the vitamin D receptor and the vitamin D-1-hydroxylase genes, leading to induction of the antimicrobial peptide cathelicidin and killing of intracellular Mycobacterium tuberculosis. We also observed that sera from African-American individuals, known to have increased susceptibility to tuberculosis, had low 25-hydroxyvitamin D and were inefficient in supporting cathelicidin messenger RNA induction. These data support a **link between TLRs and vitamin D-mediated innate immunity and suggest that differences in ability of human populations to produce vitamin D may contribute to susceptibility to microbial infection.**

Liu PT, Stenger S, Li H, et al. Toll-like receptor triggering of a vitamin D-mediated human antimicrobial response. Science. 2006 Mar 24;311(5768):1770-3. Epub 2006 Feb 23.

## Who gets supplements and how?

- > 800 I.U. per day if no sunlight
- Consider 100,000 I.U. once every 3 months
- Only measure levels when guidance is needed
- Consider measuring for steroid treatment (Vitamin D and Steroids competitively bind for VDRE sites on allele)

Weisman Y et al. Single oral high dose vitamin D<sub>3</sub> prophylaxis in the elderly. J Am Ger Soc 34: 515-8, 1986.

Arch Intern Med 169: 1536-7; 1806-8.

Deschasse et al. Effect of a loading dose of vitamin D<sub>3</sub> in frail elderly patients with insufficient 25-hydroxyvitamin D. J Am Ger Soc. 57: 2155-7

Malabanan A et al. Lancet. 1998; 351:805-6

## Results: 10 Individuals in the Hawaii Cohort with the **Lowest** 25OHD

- 25OHD by HPLC = 17.5\* (2.8) [33.0 (9.2)]
  - PTH = 13.5 (4.3) [13.4 (5.1)]
- Age; 20.9 (4.2) [24.5 (7.1)]
- BMI 23.0 (2.8) [23.7 (3.5)]
- No difference in serum chemistries
- 3 taking multivitamins (3, 5.5 and 7 times/week)
- Sun hours without sunscreen; 23.1 (15.6) [21.3 (15.3)]
- Sun index; 6.0\* (3.7) [11.2 (7.3)]

## The Vitamin D Autocrine/Paracrine System Functions in the Tissue-level Control of Cell Proliferation and Differentiation<sup>4,5</sup>

- Psoriasis<sup>1</sup>
- Myelodysplasia<sup>2,6</sup>
- Several colon cancer and leukemia cell lines
- Epidemiologic/ecologic evidence for human cancer<sup>3</sup>
  - Breast
  - Prostate
  - Colon

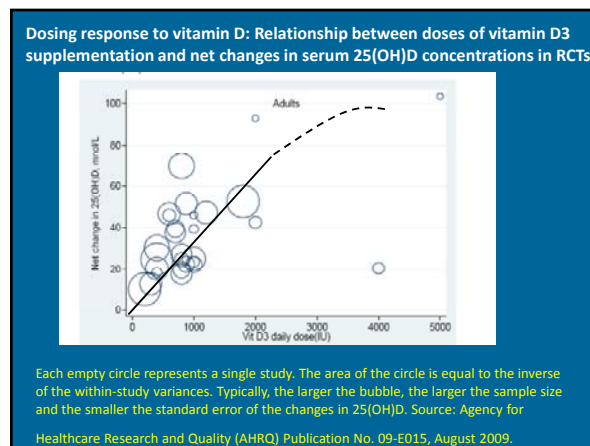
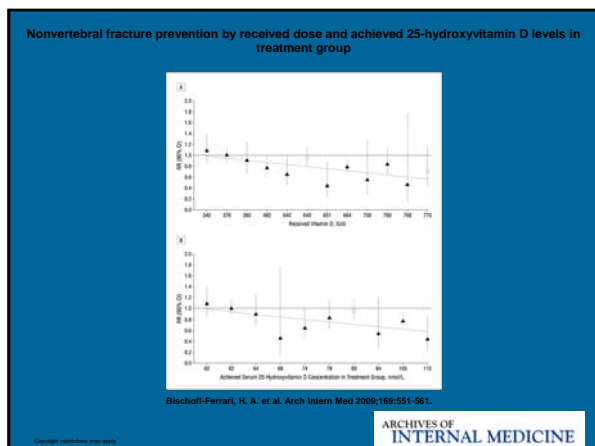
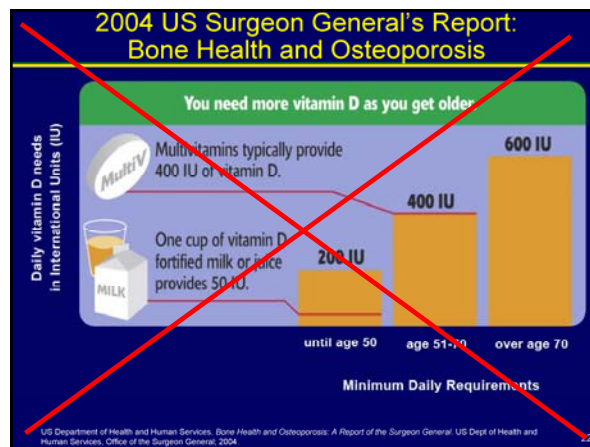
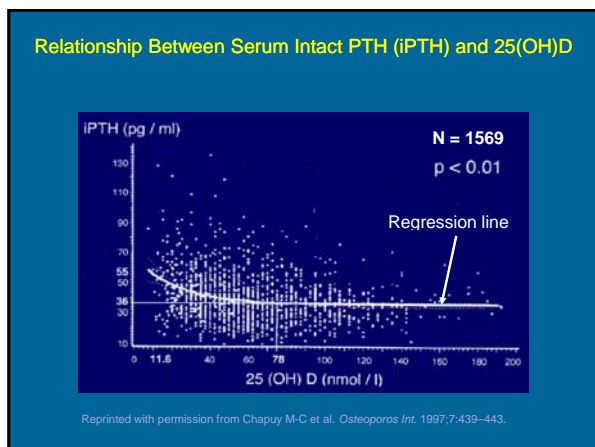
1. Stamenkovic A et al. Endocr Rev. 2000;21(5):467-487.  
 2. Boylen BD et al. Steroids. 2001;66(5-6):363-374.  
 3. Gayther RJ et al. Ann Revs. 2001;41:421-442.  
 4. Amelio SP. Steroids. 1997;62(3):155-172.  
 5. Nguyen TM et al. Am J Physiol. 1996;271(3 Pt 1):L392-L399.  
 6. vanAmerongen et al. Eur J Clin Nutr. 2004;58(8):1096-1109.

### Other Chronic Conditions Affected By Vitamin D Levels

Condition	Status of Evidence
• Osteoarthritis <sup>1</sup>	+
• Falls/neuromuscular function <sup>2</sup>	++++
• Multiple sclerosis <sup>3</sup>	++
• Fibromyalgia <sup>4</sup>	++
• Type I diabetes <sup>5</sup>	+
• Cardiovascular disease <sup>5</sup>	++
• Periodontal disease <sup>6</sup>	+


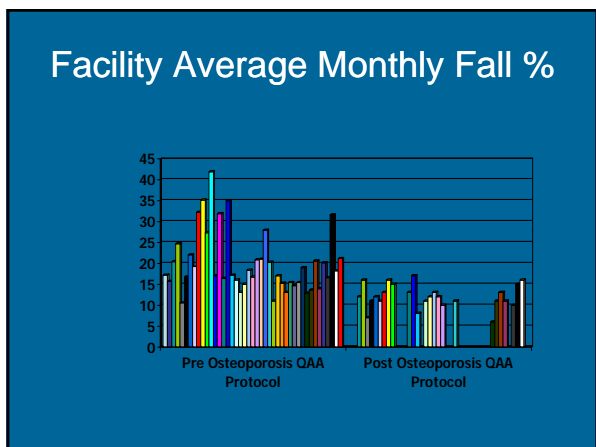
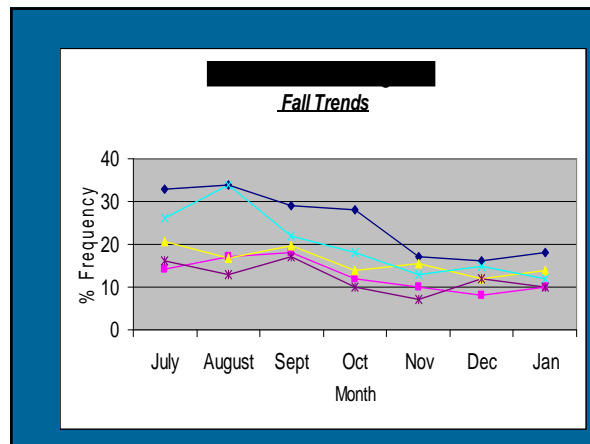
1. Lane NE et al. Arthritis Rheum. 1999;42(5):854-860.  
 2. Bischoff-Ferrari HA et al. JAMA. 2004;291(14):1999-2006.  
 3. Munger KL et al. Neurology. 2004;62(1):60-65.  
 4. Pimentel GA, Chugley JM. Mayo Clin Proc. 2003;78(12):1483-1470.  
 5. Helick ML. Ann J Clin Nutr. 2004;79:302-317.  
 6. Dietrich T et al. Ann J Clin Nutr. 2004;80(1):108-113.  
 American Neurological Association 133rd Annual Meeting, Derek Denny-Brown New Member Symposium, Presented September 23, 2008.

- ### Supporting Data for Vitamin D
- Association with Falls – Stein et al. JAGS '99
  - Increased risk in Hip Fracture trials – LeBoff et al. JAMA '99
  - Vitamin A (Cod Liver Oil) negatively impacts – JAMA '02
  - Reduction in Myocardial Infarctions – Arch Intern Med '08
  - Muscle strength is associated with vitamin D Status – JAGS '99&JBMR '97
  - Vitamin D Deficiency Pain Syndrome – Arch Intern Med '91
  - J Natl Cancer Inst 2005;97:195 – 9 *Conclusions: Sun exposure is associated with increased survival from melanoma*



- Recommended Vitamin D Input**
  - 4,000 I.U. per day input of Vitamin D<sub>2</sub> or 3
  - 100,000 I.U. Vitamin D<sub>3</sub> by mouth Monthly
  - More if diseases or medications warrant
  - Monthly monitoring is NOT needed

Kruk ME, Schwalbe N. Clin Ther 2006;28:1989-95  
 Yetley EA. AJCN 2008;88(suppl)558S-64S  
 Calvo MS. 2004  
 Hathcock JN et al. Am J Clin Nutr 2007;85:6-18  
 Jones G. AJCN 2008;88(suppl)582S-6S  
 Vieth R. Bone Miner 1990;11:267-72  
 Vieth R. Am J Clin Nutr 1999;69:842-56  
 Heaney et al. AJCN. 2003; 77: 204-210  
 Reginster JY, et al. Bone 2006;38:S2-S6

### IOM Report: Logical, Scientific, and Guidance Flaws

- Focused Solely on Bone. Nonskeletal effects were disregarded
- Skeletal Health Is Assured at 20 ng/mL
- Above 4,000 I.U. unsafe (but acknowledges that intakes up to 10,000 IU/day are probably safe for everyone)

<http://www.iom.edu/Reports/2010/Dietary-Reference-Intakes-for-Calcium-and-Vitamin-D.aspx>  
 Heaney R, Holick M. Why the IOM Recommendations for Vitamin D Are Deficient JBMR. 2011; 26:455-457 DOI: 10.1002/jbmr.328

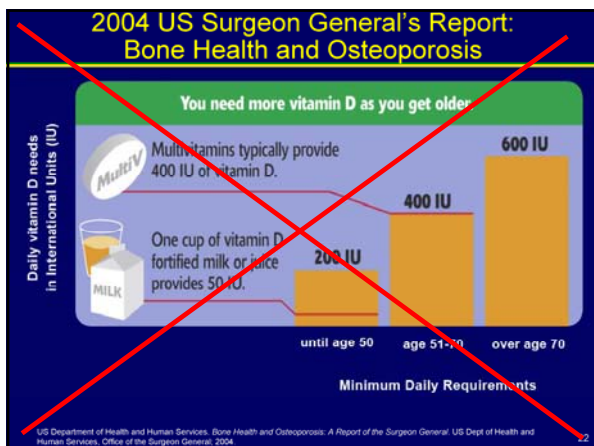
### IOM Report Logical Flaw: Focus on Bone

- Assuming that the general public does not need more vitamin D than might be sufficient for bone is a cause for concern
- The role of vitamin D for fall prevention and for immune function leaves more than sufficient data to question the adequacy of focus solely on bone.

### Vitamin D and Infection

- TLR activation of human macrophages up-regulated expression of the vitamin D receptor and the vitamin D-1-hydroxylase genes, leading to induction of the antimicrobial peptide cathelicidin and killing of intracellular Mycobacterium tuberculosis. We also observed that sera from African-American individuals, known to have increased susceptibility to tuberculosis, had low 25-hydroxyvitamin D and were inefficient in supporting cathelicidin messenger RNA induction. These data support a link between TLRs and vitamin D-mediated innate immunity and suggest that differences in ability of human populations to produce vitamin D may contribute to susceptibility to microbial infection.

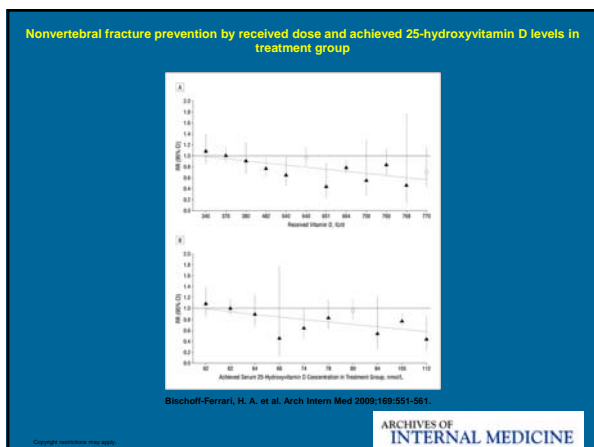
Liu PT, Stenger S, Li H, et al. Toll-like receptor triggering of a vitamin D-mediated human antimicrobial response. Science. 2006 Mar 24;311(5768):1770-3. Epub 2006 Feb 23.



### IOM Report Science Flaw: 20 ng/mL is sufficient to assure bone health

- Skeletal Health Is Assured at 20 ng/mL is simply incorrect.
- Large randomized, controlled trial in the United Kingdom that raised serum 25(OH)D level from 21 to 29 ng/mL and produced a 33% reduction in all major osteoporotic fractures combined.
- 600 IU/day would produce a value <10 ng/mL,

Trivedi DP, Doll R, Khaw KT. Effect of four monthly oral vitamin D3 (cholecalciferol) supplementation on fractures and mortality in men and women living in the community: randomized, double-blind, controlled trial. *BMJ*. 2003;326:469-474.



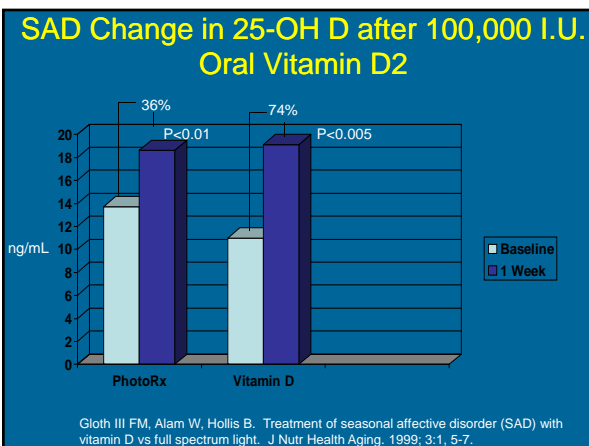
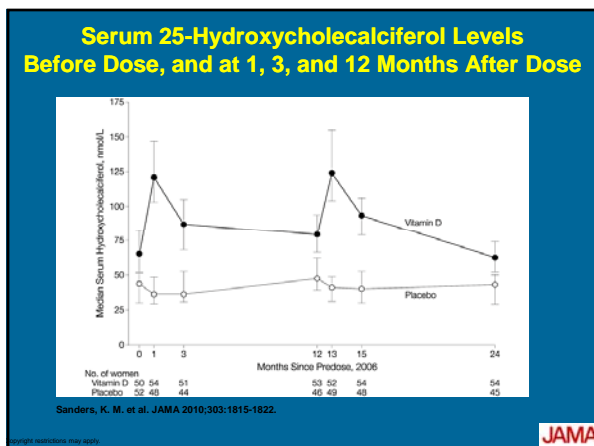
### IOM Report Guidance Flaw: 4,000 I.U. as Upper Limit of Safety

- Above 4,000 I.U. unsafe (but the report acknowledges that intakes up to 10,000 IU/day are probably safe for everyone)
- Primitive input would have been at least 4000 IU/day and probably two to three times that level, with corresponding serum 25(OH)D levels ranging from 40 to 80 ng/mL.

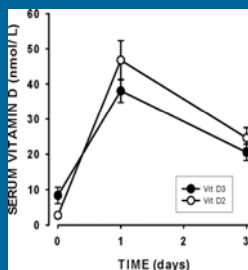
Holick MF. Environmental factors that influence the cutaneous production of vitamin D. *Am J Clin Nutr*. 1995;62(Suppl):638-645S.

Armas LAG, Dowell S, Akhter M, et al. Ultraviolet-B radiation increases serum 25-hydroxyvitamin D levels: the effect of UVB dose and skin color. *J Am Acad Dermatol*. 2007;57:588-593.

N. Binkley, R. Novotny, D. Krueger, T. Kawahara, Y. G. Daida, G. Lensmeyer, B. W. Hollis and M. K. Drezner. Low Vitamin D Status despite Abundant Sun Exposure. *J Clin Endocrin & Metab* 92:2130-2135

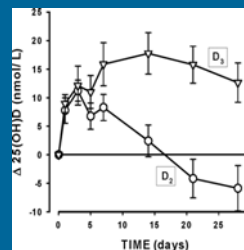


Time course of serum concentrations of vitamin D after a single oral dose of 50,000 IU of cholecalciferol (vitamin D3) or ergocalciferol (vitamin D2,) in healthy male subjects (n = 10 for each group).



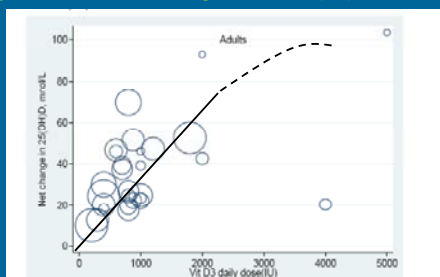
The error bars are 1 SEM.

Time course of the rise in serum 25(OH)D after a single oral dose of 50,000 IU of either cholecalciferol (vitamin D3) or ergocalciferol (vitamin D2) to two groups of 10 normal men each.



Error bars are 1 SEM. The zero-change line incorporates a correction for the seasonal rise in 25(OH)D occurring at the time this study was performed

Dosing response to vitamin D: Relationship between doses of vitamin D3 supplementation and net changes in serum 25(OH)D concentrations in RCTs



Each empty circle represents a single study. The area of the circle is equal to the inverse of the within-study variances. Typically, the larger the bubble, the larger the sample size and the smaller the standard error of the changes in 25(OH)D. Source: Agency for

Healthcare Research and Quality (AHRQ) Publication No. 09-E015, August 2009.

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1-800-345-1199

## IOM Report

“To be sure of hitting the target, shoot first and call whatever you hit the target.”

– Attributed to Ashleigh Brilliant and Patrick Toche

