Solving Vitamin D Deficiency – A Safety Profile

Identify and quantify risk levels of vitamin D

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Declaration of Potentially Perceived Conflicts:

Grant/Research Support: NCIC, Direct-MS, Dairy Farmers of Canada

Consultant: DiaSorin, Wyeth, DSM, Yoplait

Speaker's Bureau: Merck/MSD, DiaSorin, Carlson Laboratories

Rule of thumb:
each additional vitamin D3
intake of
1,000 IU/d
raises 25(OH)D by about
25. nmol/L
(10 ng/ml)

Paracelsus : Poison is in everything, and no thing is without poison. The dosage makes it either a poison or a remedy.

i.e. If something really does work, then too much of it will be bad for you.

Safety Assessment = Toxicity Assessment

For vitamin D, the classic criteria for harm pertain to hypercalcemia and hypercalciuria.

No other harmful outcomes are known… except for some epidemiologic relationships that relate higher serum 25(OH)D to higher risk of prostate and pancreatic cancers.

Safety Assessment = Toxicity Assessment

The context of calcium excess:

Safety of vitamin D_3 in adults with multiple sclerosis[1–3]

Samantha M Kimball, Melanie R Ursell, Paul O'Connor, and Reinhold Vieth

ABSTRACT

Background: Vitamin D_3 may have therapeutic potential in several diseases,including multiple sclerosis. High doses of vitamin D_3 may be required for therapeutic efficacy, and yet tolerability—in the present context, defined as the serum concentration of 24-hydroxyvitamin D [25(OH)D] that does not cause hypercalcemia—remains poorly characterized.

Objective: The objective of the study was to characterize the calcemic response to specific serum 25(OH)D concentrations.

Design: In a 28-wk protocol, 12 patients in an active phase of multiple sclerosis were given 1200 mg elemental Ca/d along with progressively increasing doses of vitamin D_3: from 700 to 7000 μg/wk (from 28 000 to 280 000 IU/wk).

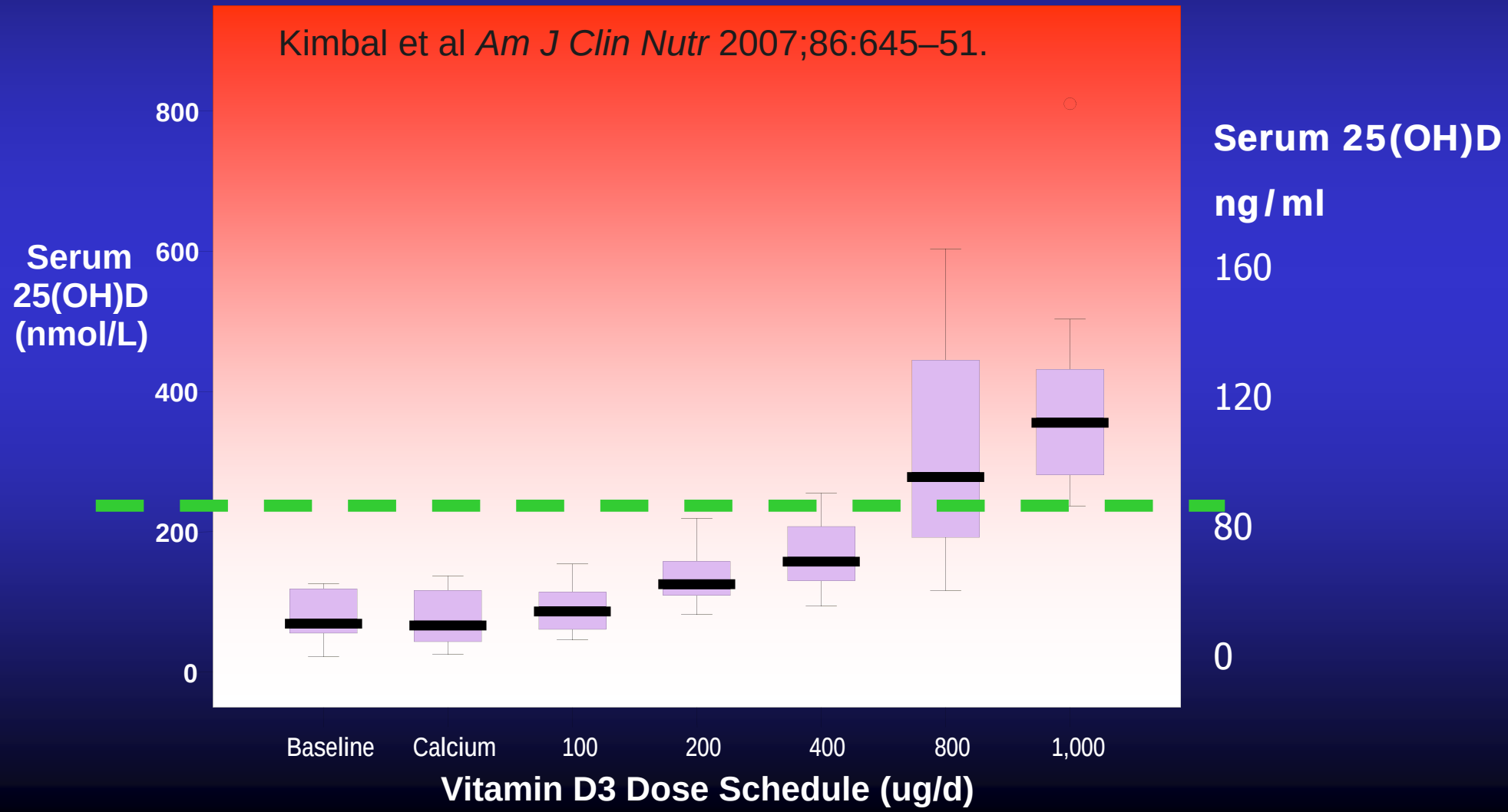
Intakes of 100 μg/d (4000 IU/d) (5) and
(6) have been shown to be safe. In f
studies suggest that the desirable seru
[25(OH)D] concentration exceeds 75
and sustain these concentrations thro
adults require vitamin D intakes of >
IU/d) (10, 11).

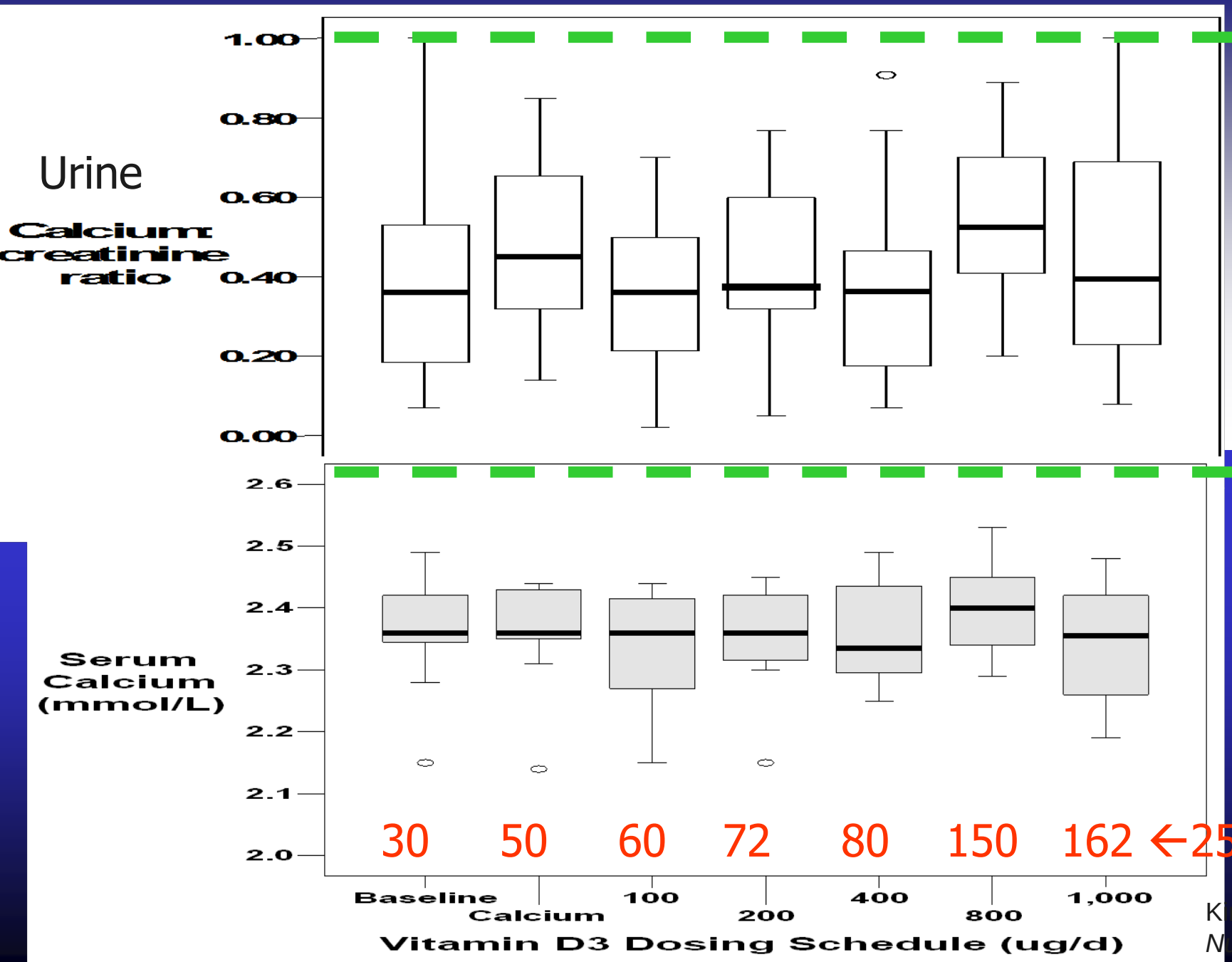
There is much interest in the role of vit
of health and disease. The rationale for
multiple sclerosis (MS) is that metabolit
as paracrine immune modulators (12),
tion of proinflammatory T lymphocytes
duction of cytokines, both of which co

Am J Clin Nutr 2007;86:645–51.

Doses of vitamin D pertinent to the UL and LOAEL, and their effects on serum calcium

MS Patients on 1200 mc Ca. EVERY MONTH THE VITAMIN D3 DOSE WAS INCREASED IN A STUDY TO CHARACTERIZE TOLERABILITY TO SPECIFIC SERUM 25(OH)D LEVELS





Kimball et al *Am J Clin Nutr* 2007;86:645–51.

ABSORPTION OF CALCIUM FROM DIET

The effect of vitamin D nutrition (based on serum 25(OH)D reaches a plateau at about 80 nmol/L)

R Heaney, *Journal of Steroid Biochemistry & Molecular Biology* xxx (2005)

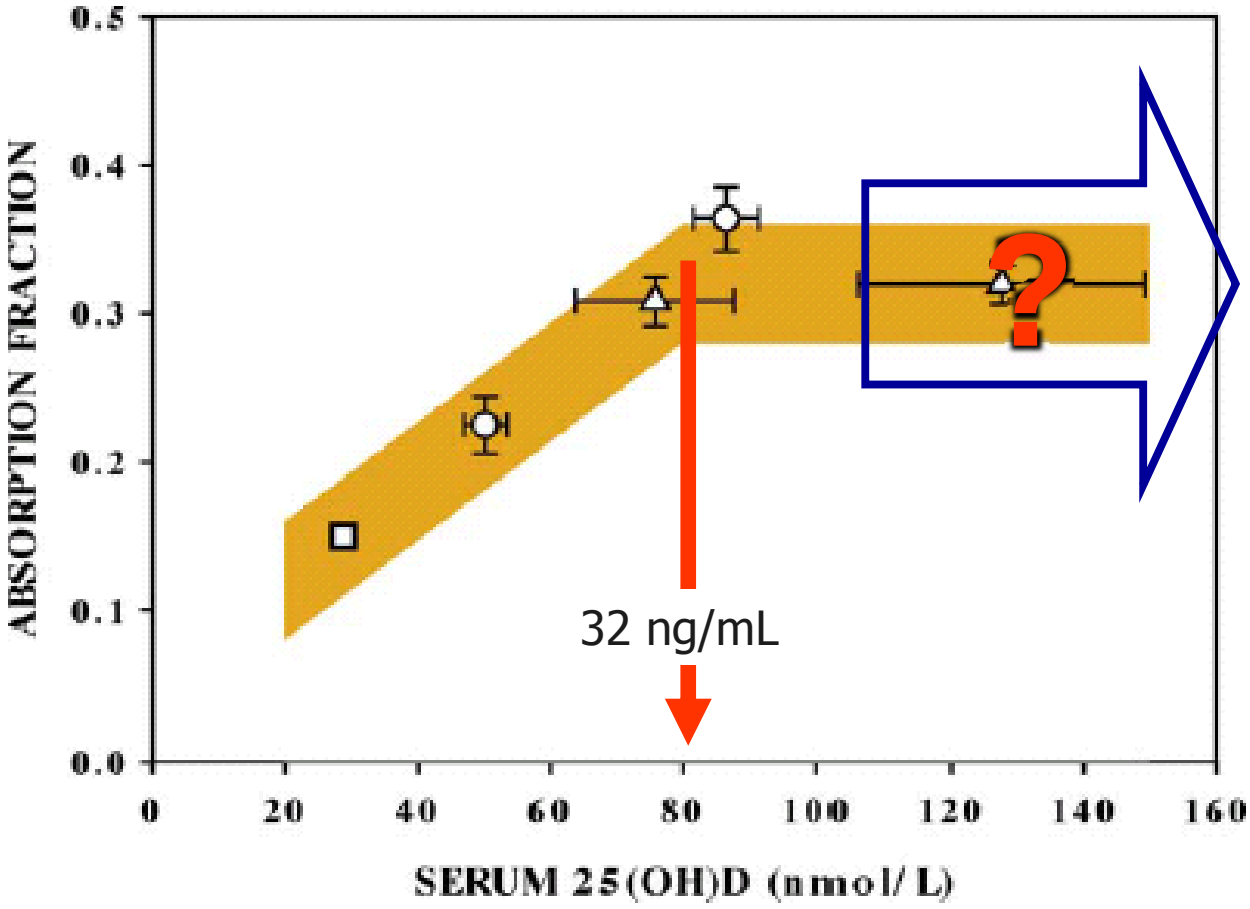
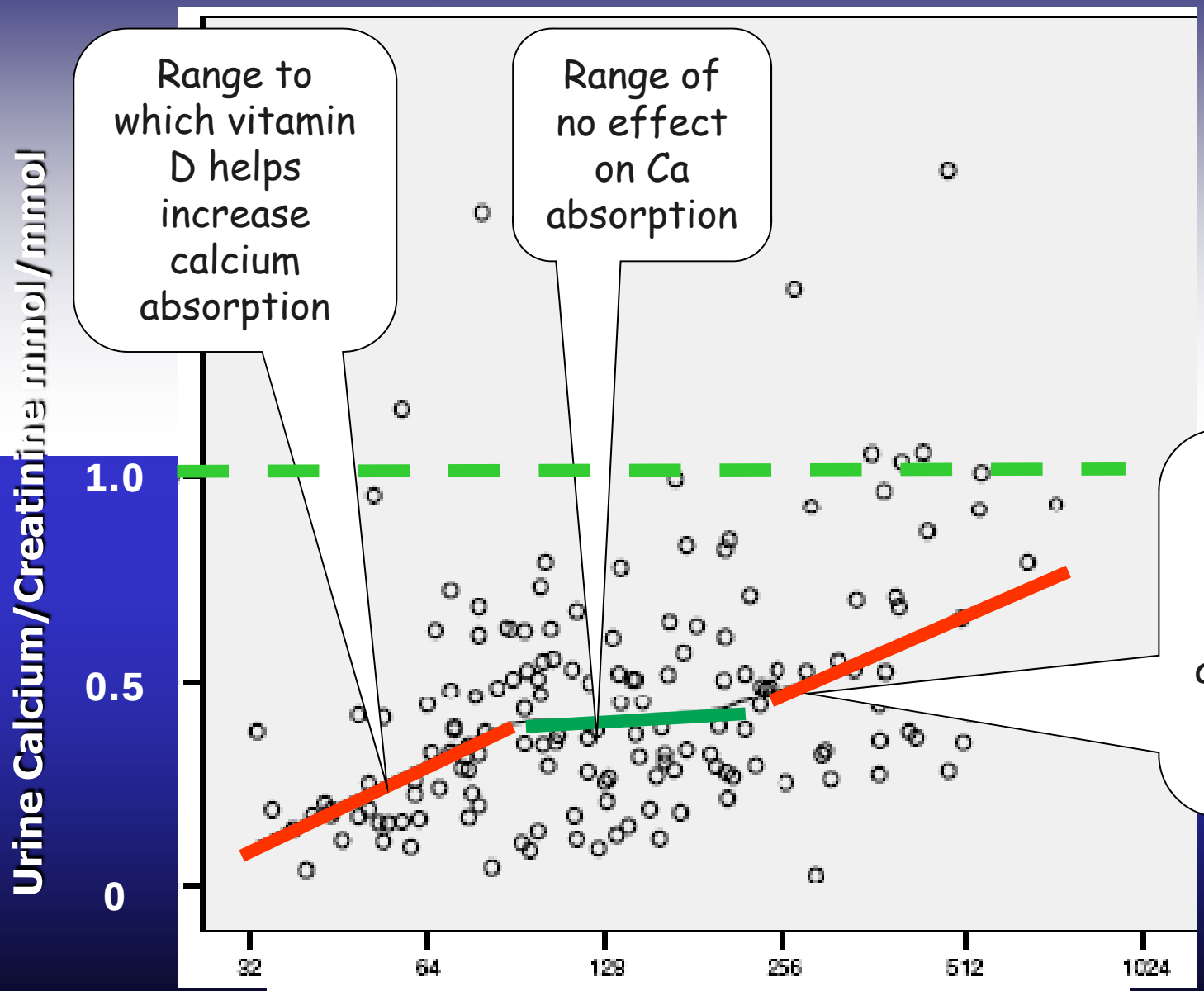


Fig. 2. Calcium absorption fraction plotted as a function of serum 25OHD concentration in three studies. The paired ○ symbols represent the data of one study [11]; the paired △ symbols, a second [12], and the □ symbol is the estimated absorption for the subjects not treated with Vitamin D in the study of Bischoff et al. [13,14]. (Copyright Robert P. Heaney, 2003. Used with permission.)

Urine calcium / creatinine ratio vs 25(OH)D



Vitamin D3 Poisoning by Table Sugar.

DOSE: 1.7 MILLION UNITS/DAY FOR 7 MONTHS!

Reinhold Vieth PhD[b], Tanya R Pinto BSc[b], Bajinder S Reen MD[a], and Min M Wong MD[a]

Lancet 2002 359: 672

June 1999, a 29-year-old man admitted to emergency with symptoms of:

- **extreme right-sided flank pain**
- **conjunctivitis** (a sign of dehydration)
- **increased thirst**
- **vomiting**
- **in acute renal failure**
- **anorexia**
- **fever, chills**

Initially treated with steroids and discharged:
presumed gastroenteritis

Vitamin D3 Poisoning by Table Sugar.
DOSE: 1.7 MILLION UNITS/DAY FOR 7 MONTHS!

October 1999, his 63-year-old father was admitted to emergency with similar complaints.

He was also in acute renal failure, and no history of stones.

Calcium VERY HIGH 3.82 mmol/L (normal, 2.20-2.65 mmol/L),

25(OH)D HIGH 1555 nmol/L (normal 20-80 nmol/L)

$1,25(OH)_2D$ NEAR NORMAL 151 pmol/L (normal, 30-140 pmol/L).
Elevated "free" 1,25(OH)2D causing toxicity.

Lancet 2002 359: 672

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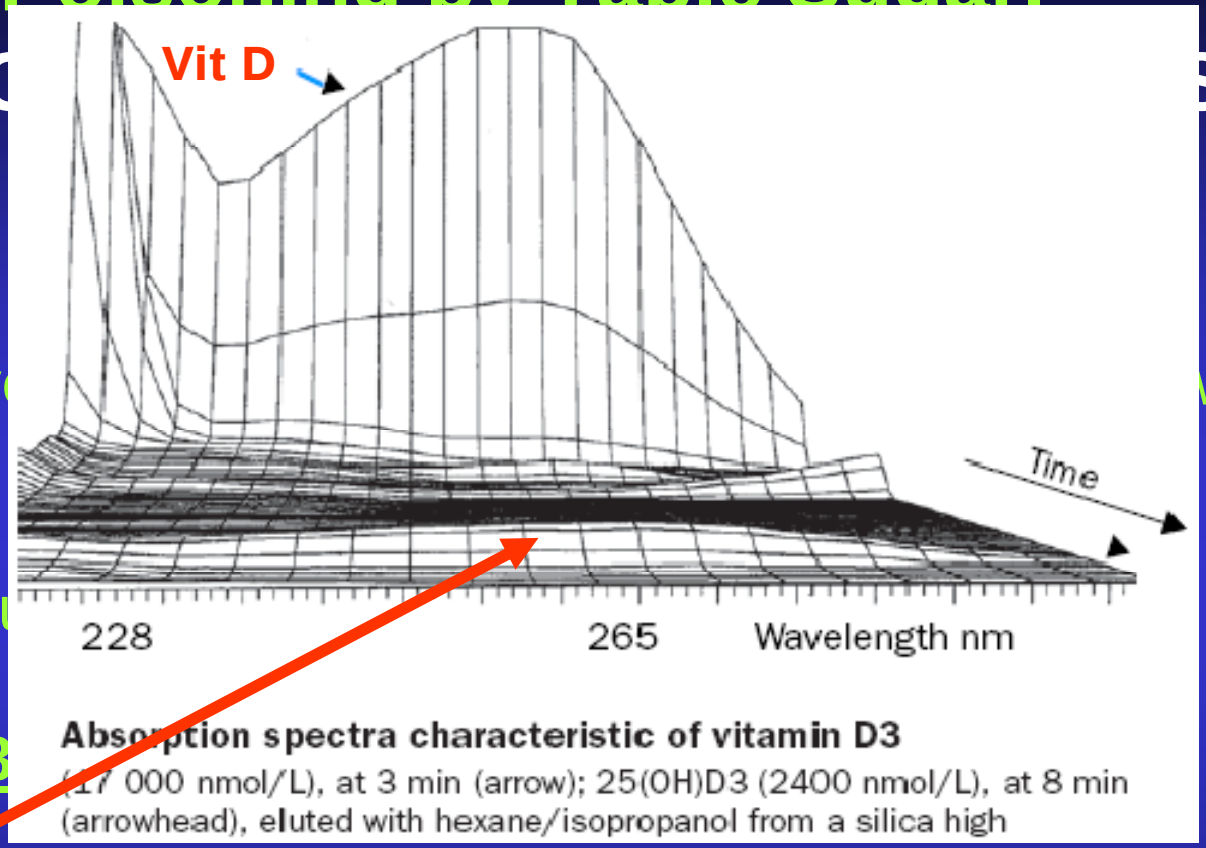


Absorption spectra characteristic of vitamin D3
(17 000 nmol/L), at 3 min (arrow); 25(OH)D3 (2400 nmol/L), at 8 min (arrowhead), eluted with hexane/isopropanol from a silica high

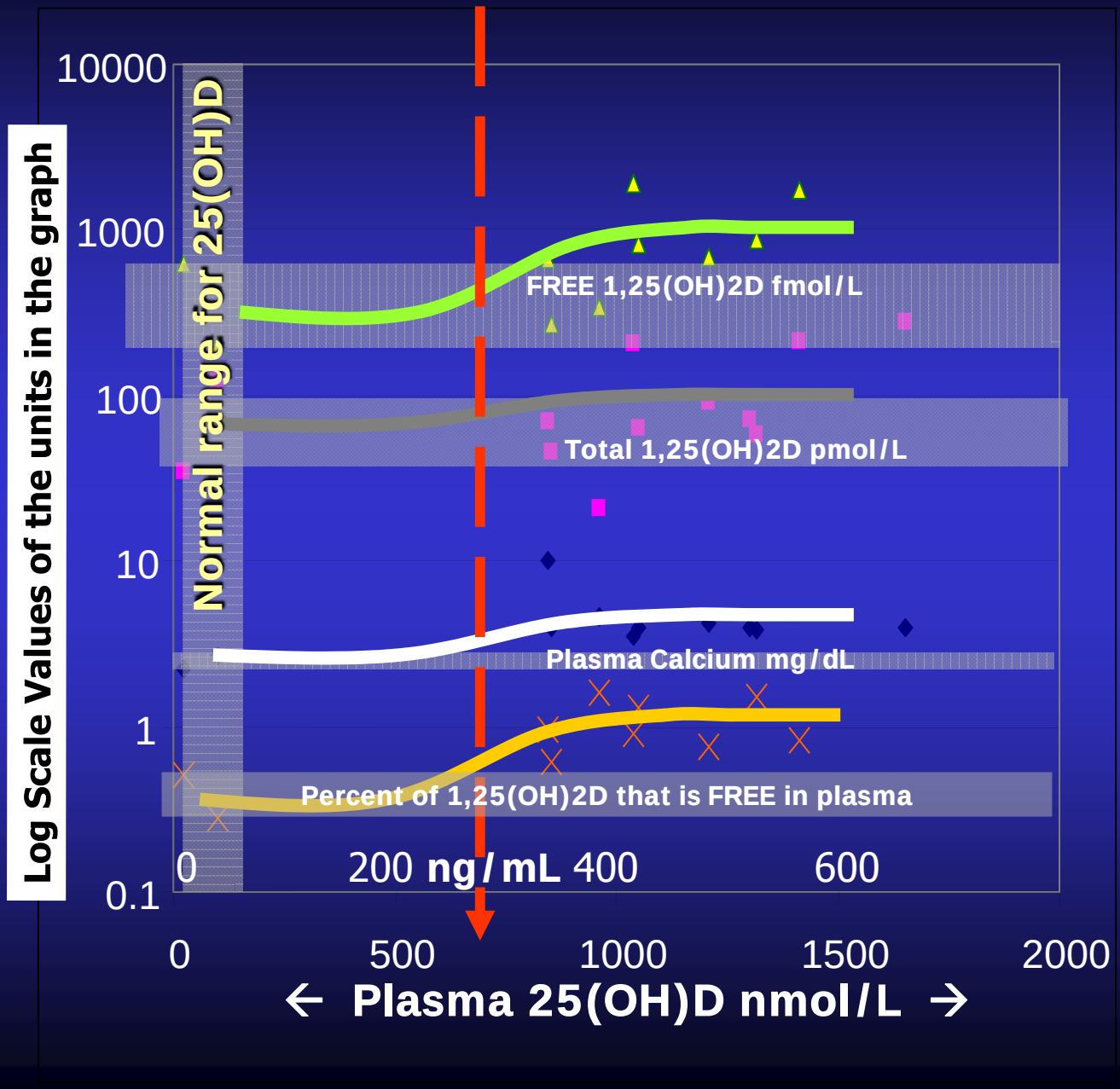
Calcium VERY HIGH 3.8

25(OH)D HIGH 1555 nmol/L (normal 20-80 nmol/L)

$1,25(OH)_2D$ NEAR NORMAL 151 pmol/L (normal, 30-140 pmol/L).
Elevated "free" 1,25(OH)2D causing toxicity.

Lancet 2002 359: 672

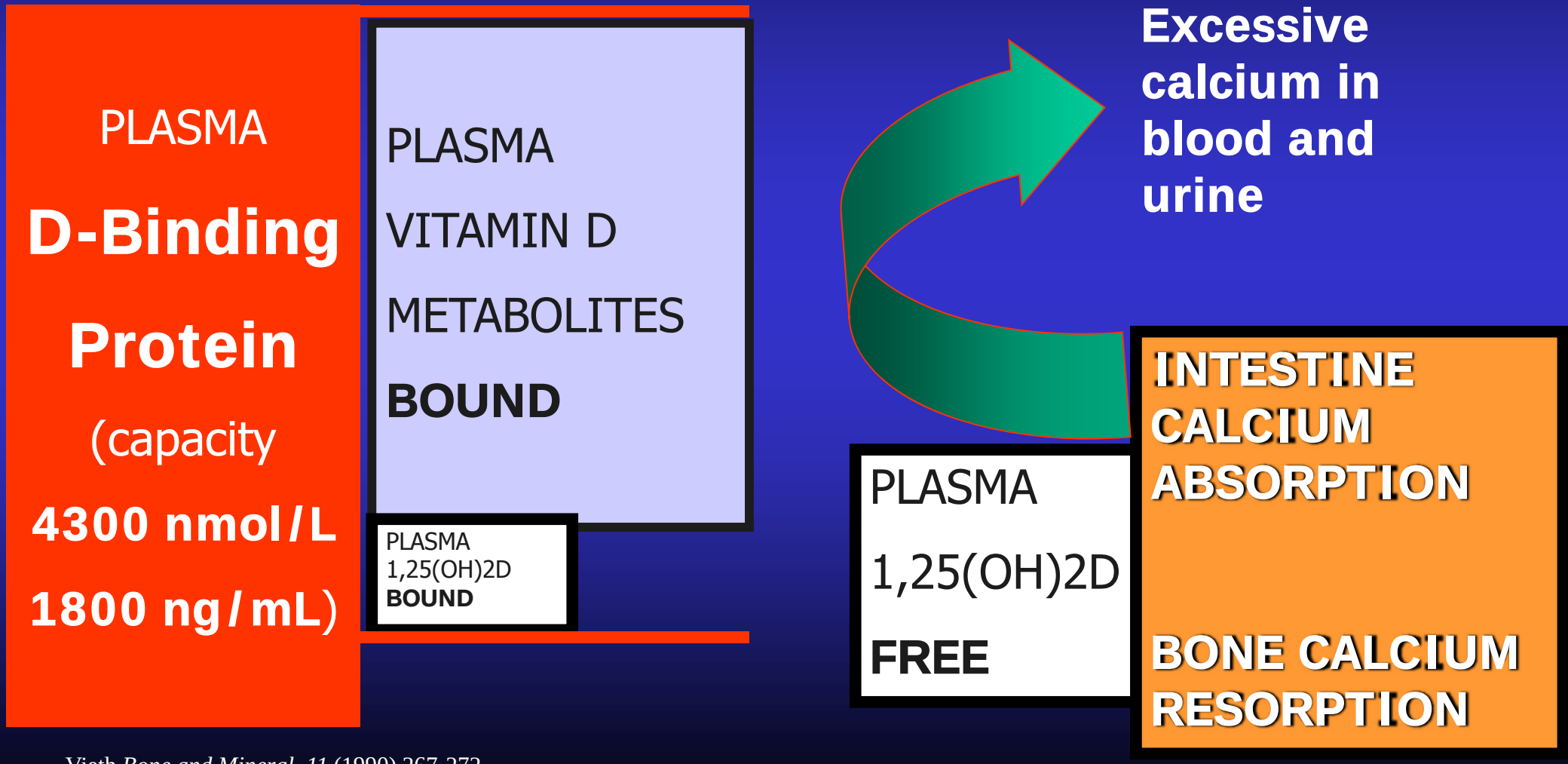
Toxic: 25(OH)D > 600 nmol/L (>240 ng/mL)



Toxic mechanism involves FREE 1,25(OH)2D

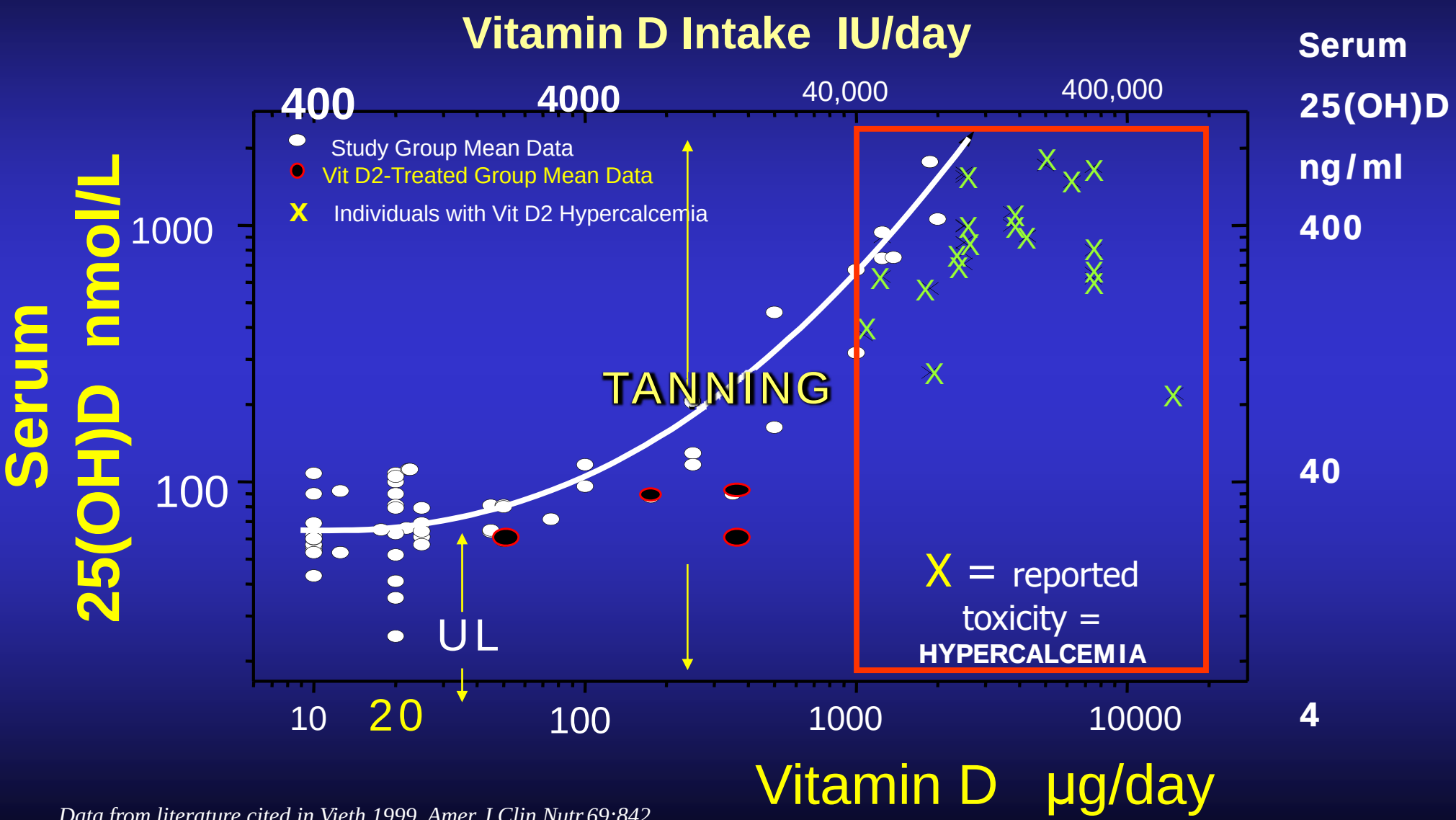
Pettifor, J. M. et. al. Ann Intern Med 1995;122:511-513

SATURABILITY OF DBP



Vieth *Bone and Mineral*, *11* (1990) 267-272

Human Dose Response for vitamin D



Data from literature cited in Vieth 1999, Amer J Clin Nutr,69:842
Hathcock JN, Shao A, Vieth R, Heaney R. Am J Clin Nutrition 2007

Safety Assessment = Toxicity Assessment

The context of Higher 25(OH)D and Higher Cancer risk

WORLD HEALTH ORGANIZATION

INTERNATIONAL AGENCY FOR RESEARCH ON CANCER

Vitamin D and Cancer

IARC 2008

Overall conclusion 6: adverse events

There is no data available on the health hazards of long-term maintenance of high 25-hydroxyvitamin D serum levels in healthy subjects over long periods.

Past experiences with other compounds (e.g., **several anti-oxidants** and **hormone replacement therapies**) have shown serious adverse effects of the chronic use of supplements or long-term maintenance of high serum levels.

Pg 306

Figure 7. Prostate cancer risk stratified by vitamin D concentration

Study	Category	25(OH)D concentration (nmol/L)	P for trend	Quality
Ahn 2008 (n=1530)	Q1 (ref)	13 - 43	0.20	B
	Q2	43 - 51		
	Q3	51 - 61		
	Q4	61 - 72		
	Q5	72 - 129		
Platz 2004 (n=920)	Q1 (ref)	nd	0.59	B
	Q2	nd		
	Q3	nd		
	Q4	nd		
Tuohimaa 2004 (n=2073)	Cat1	<19	nd	C
	Cat2	20 - 39		
	Cat3 (ref)	40 - 49		
	Cat4	50 - 79		
	Cat5	>80		
Li 2007 (n=1156)	Q1	nd	0.91	C
	Q2	nd		
	Q3	nd		
	Q4 (ref)	nd		
Ahonen 2000 (n=715)	Q1	<30	0.01	C
	Q2	31 - 40		

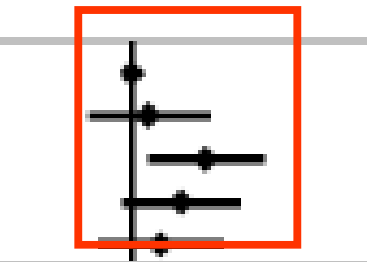
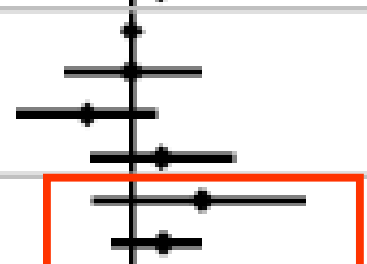
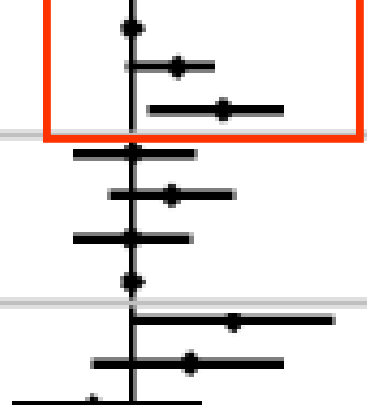
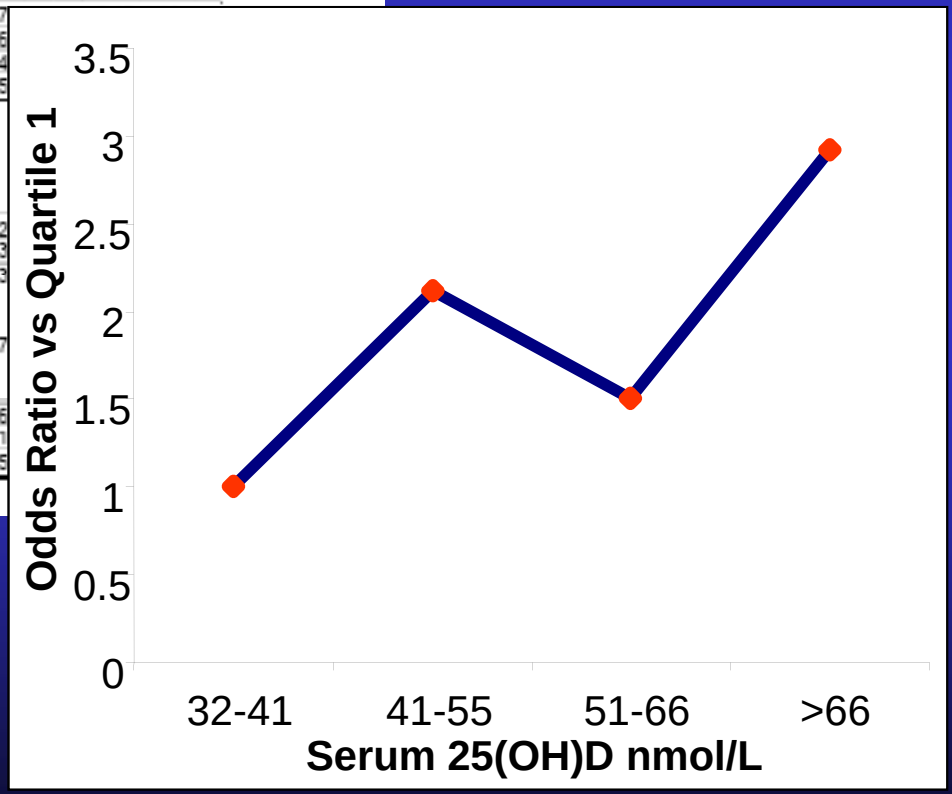




Table 29. Vitamin D and pancreatic cancer: Results of observational studies

Author Year Study Name PMID	Life Stage, y	Outcome (no. of cases; no. of control)	Time to diagnosis, y	25(OH)D concentration, nmol/L	No of cases	No. of control	Adjusted OR	95% CI	P for trend
Stolzenberg-Solomon 2006[77] ATBC Finland (50°N) [17047067]	51-70, male only	Exocrine pancreatic cancer (200; 400)	11.8 (median)						0.001
				<32	27	80	1	Reference	
				32-41.1	34	80	1.30	0.70, 2.40	
				41.1-51.1	47	80	2.12	1.15, 3.90*	
				51.1-65.5	35	81	1.30	0.01, 2.79	
				>65.5	57	79	2.92	1.56, 5.48*	
Stolzenberg-Solomon 2009[78] PLCO US (various) [19208642]	51-70, both sexes	Pancreatic cancer (184; 368)	5.4 (median), up to 11 y						0.49
				≤45.9	44	74	1	Reference	
				>45.9 to ≤60.3	40	74	0.97		
				>60.3 to ≤69.5	27	73	0.86		
				>69.5 to ≤82.3	31	74	0.84		
				>82.3	42	73	1.45		
		Pancreatic cancer: Low residential sun exposure area (91; 167)	nd						
				<49.3	22	44	1		
				>49.3 to <65.2	22	42	2.52		
				>65.2 to <78.4	21	43	2.33		
				>78.4	26	38	4.03		
		Pancreatic cancer: Moderate residential sun exposure area (91; 167)	nd						
				<49.3	33	48	1.97		
				>49.3 to <65.2	15	50	0.66		
				>65.2 to <78.4	18	49	0.91		
				>78.4	24	54	1.45		

* Statistically significant (P<0.05)

Evidence Report/Technology Assessment
Number 183 Vitamin D and Calcium: A Systematic Review of Health Outcomes
Prepared for: Agency for Healthcare Research and Quality



Stolzenberg-Solomon 2006

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				41.1-51.1	47	80	2.12	1.15, 3.90*	
				51.1-65.6	35	81	1.50	0.81, 2.76	
				>65.5	57	79	2.92	1.56, 5.46*	
Stolzenberg-Solomon 2009[78] PLCO US (various) [19208842]	51-70, both sexes	Pancreatic cancer (184; 368)	5.4 (median), up to 11 y						0.49
				≤45.9	44	74	1	Reference	
				>45.9 to ≤60.3	40	74	0.97	0.47, 1.96	
				>60.3 to ≤69.5	27	73	0.86	0.40, 1.84	
				>69.5 to ≤82.3	31	74	0.84	0.39, 1.80	
				>82.3	42	73	1.45	0.66, 3.16	
		Pancreatic cancer: Low residential sun exposure area (91; 167)	nd						P for interaction between low and moderate/high residential sun exposure = 0.015
				<49.3	22	44	1	Reference	
				>49.3 to <65.2	22	42	2.52	0.92, 6.90	
				>65.2 to <78.4	21	43	2.33	0.83, 6.48	
				>78.4	26	38	4.03	1.38, 11.79*	
		Pancreatic cancer: Moderate residential sun exposure area (91; 167)	nd						
				<49.3	33	48	1.97	0.80, 4.82	
				>49.3 to <65.2	15	50	0.66	0.22, 2.01	
				>65.2 to <78.4	18	49	0.91	0.31, 2.71	
				>78.4	24	54	1.45	0.53, 3.96	

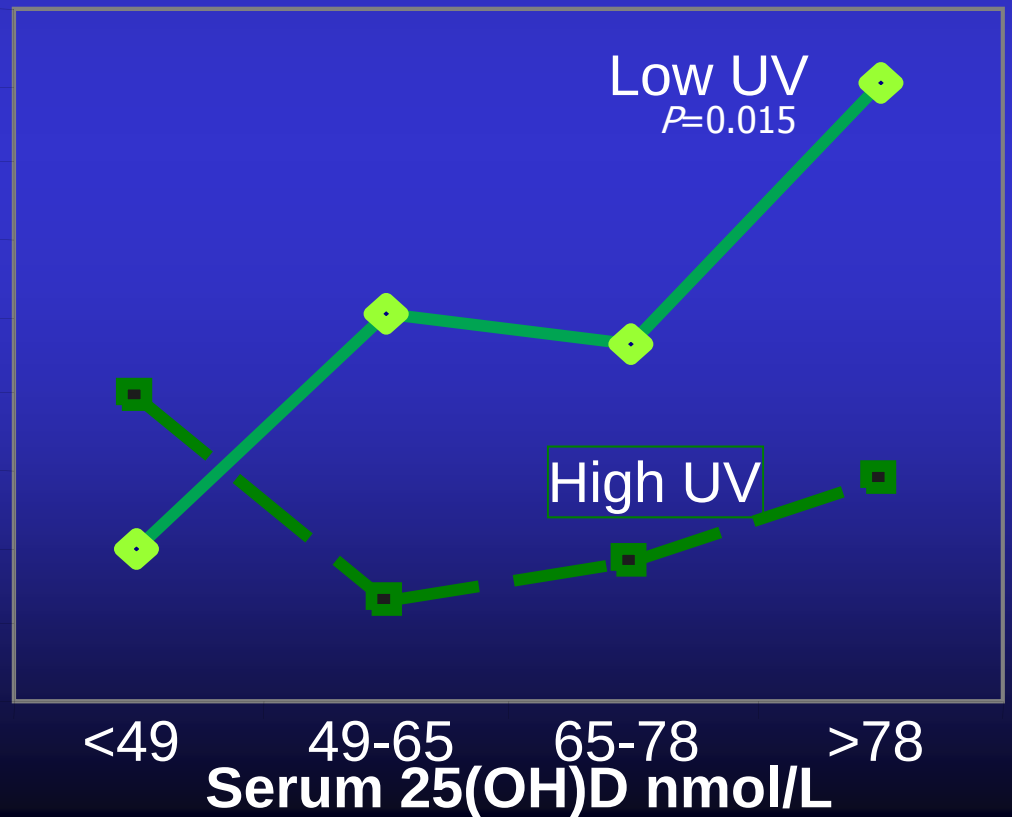
* Statistically significant (P<0.05)

Stolzenberg-Solomon *et al.* (Cancer Res 2009;69(4):1439–47)

Evidence Report/Technology Assessment

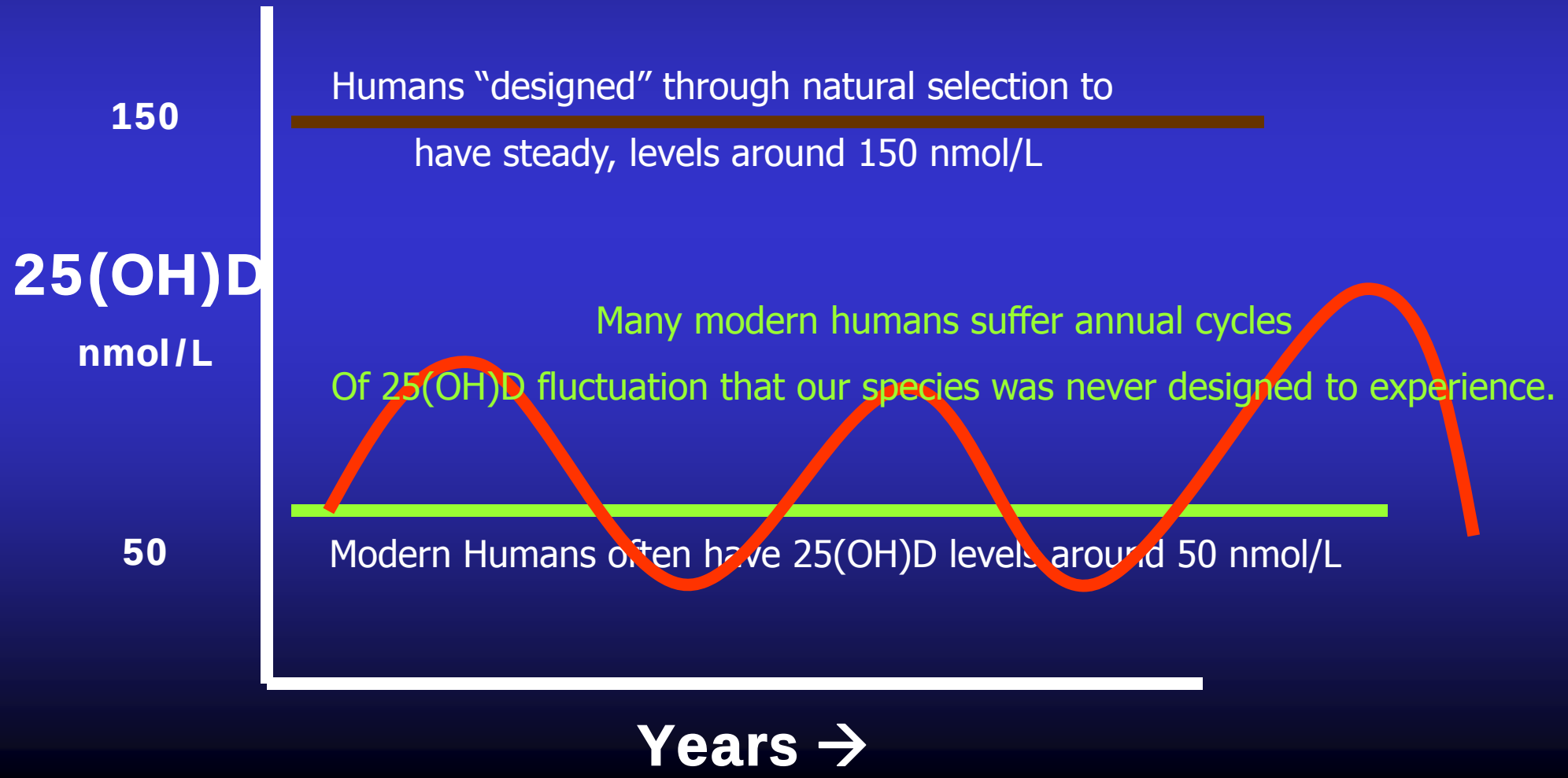
Number 183 Vitamin D and Calcium: A Systematic Review of Health Outcomes

Prepared for: Agency for Healthcare Research and Quality



Patterns of 25(OH)D levels: human design vs the modern reality.

Vieth R. *Anticancer Res.* 2009 Sep;29(9):3675-84.



Safety = Toxicity

For vitamin D, the classic criteria for harm pertain to excessive calcium in serum or urine. **TOXICITY REQUIRES AVERAGE DAILY INTAKES WELL BEYOND 10,000 IU**

Northern or low-UV environments: epidemiologic relationships with higher serum 25(OH)D and higher risk of prostate and pancreatic cancers. These may be due to **seasonal high/low fluctuations in 25(OH)D** that may be alleviated with vitamin D supplementation.

VITAMIN D CONTRADICTIONS IN TERMS OF IMMUNE RESPONSES:

DOES VITAMIN D HELP TO PROMOTE IMMUNE REACTIONS, i.e. HELPS ATTACK FOREIGN ANTIGEN ?

OR

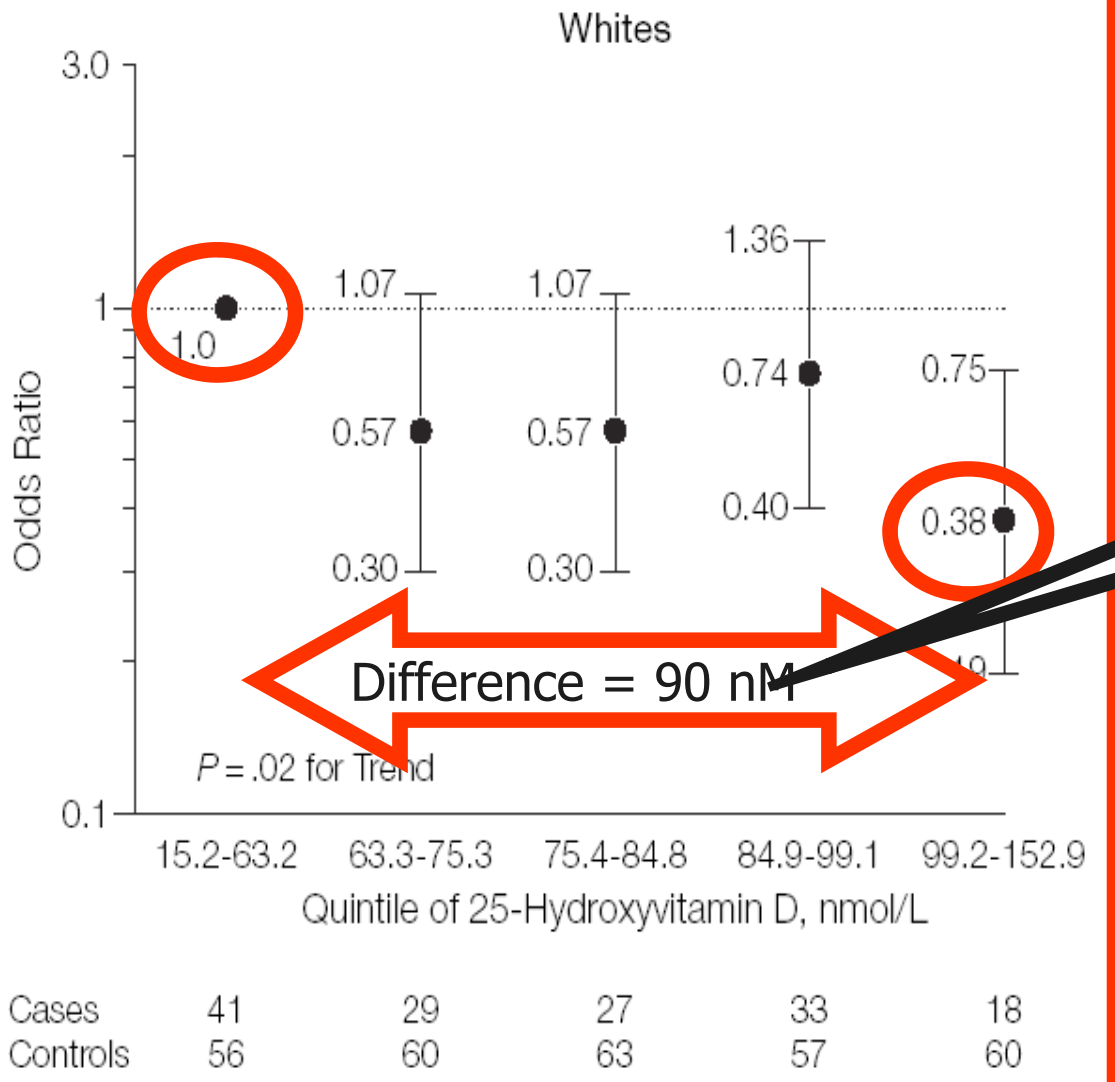
The evidence shows that it does both!

DOES VITAMIN D SUPPRESS IMMUNE ATTACK, AND PREVENT AUTO-IMMUNE DISEASE?

AUTOIMMUNE DISEASE

- JUVENILE DIABETES
- **MULTIPLE SCLEROSIS**

Low 25(OH)D predicts MS Risk
in US Military Personnel



Since 1985, the Department of Defense Serum Repository collected over 30 million serum samples leftover from routine HIV and deployment-related blood tests. All samples are cataloged and stored at −30

Th
25
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To raise an Adult's 25(OH)D by 90 nmol/L requires about 90 mcg/day of vitamin D3.

Among whites, there was a **41% decrease in MS risk for every 50-nmol/L** increase in 25(OH)D, and there was no significant difference by sex.

Munger et al *JAMA. 2006;296:2832-2838*

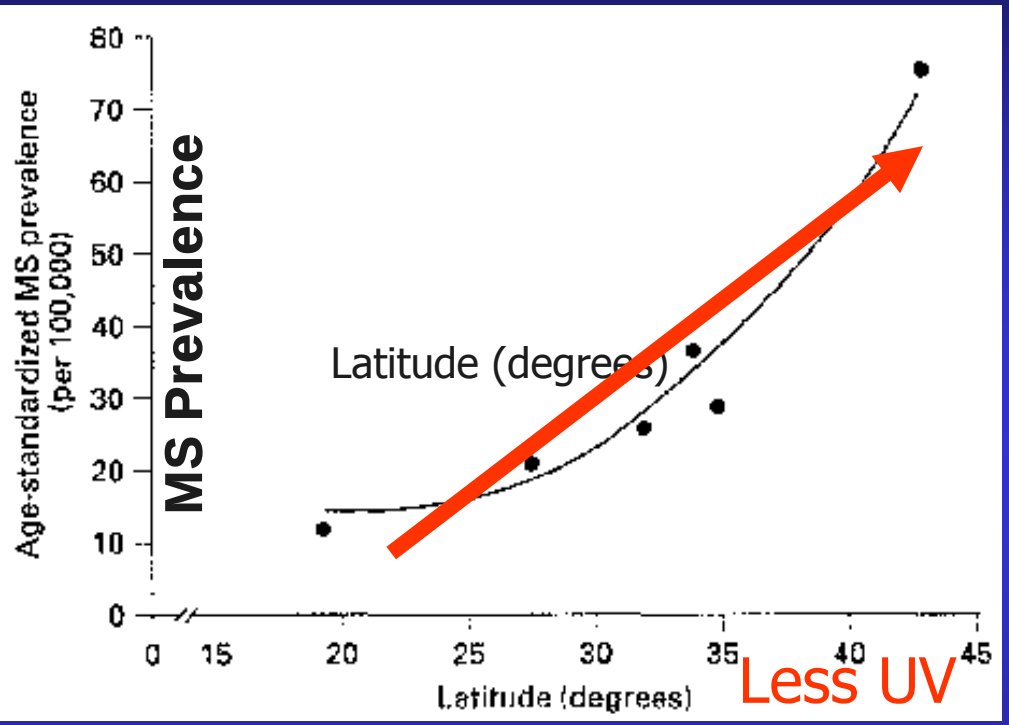
Risk of Multiple Sclerosis Decreases by 74% with Hours in the Sun when Age 6-15 yr

- Multiple Sclerosis strikes after age 20, half as common as Juvenile Diabetes
- Related to autoimmunity myelin sheath.
- Progressive loss of nerve and muscle control, often to the point of death.

Sun exposure	Adjusted odds ratio* (95% CI)
Time in sun (h/day):	
<1	
1-2	1
2-3	0.42 (0.16 to 1.09)
3-4	0.32 (0.13 to 0.80)
>4	0.26 (0.11 to 0.60)
Linear trend	P<0.01

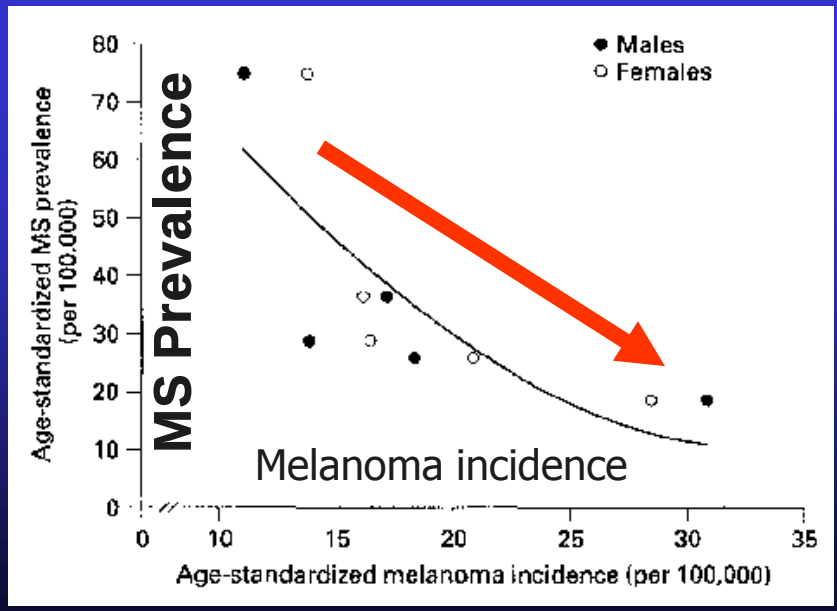
Van der Mei et al. BMJ.com 2003;327:316

Latitude, UV and Multiple Sclerosis Prevalence in Australia: Comparison across cities



MS prevalence even correlates with an indirect measure of human skin UV exposure.

i.e. MS Correlates with the Incidence of Melanoma/SkinCancer



Van der Mei et al 2001 Neuroepidemiology 20:168

Vitamin D status as a predictor of MS outcome following an initial paediatric demyelinating event.

Heather E.C. Hanwell, Reinhold Vieth, Sandra Magalhaes, Melissa McGowan, Ruth Ann Marrie, Douglas L Arnold, A Dessa Sadovnick, Amit Bar-Or, and **Brenda Banwell** on behalf of the **Canadian Pediatric Demyelinating Disease Network**

Paediatric Acquired Demyelinating Syndromes (ADS)

~15-30%

Child with ADS

Baseline

3 mos

12 mos

2 – 5 years

Serum 25(OH)D

Serum 25(OH)D

Serum 25(OH)D

Annual Visits

Child has Relapse

MS patient

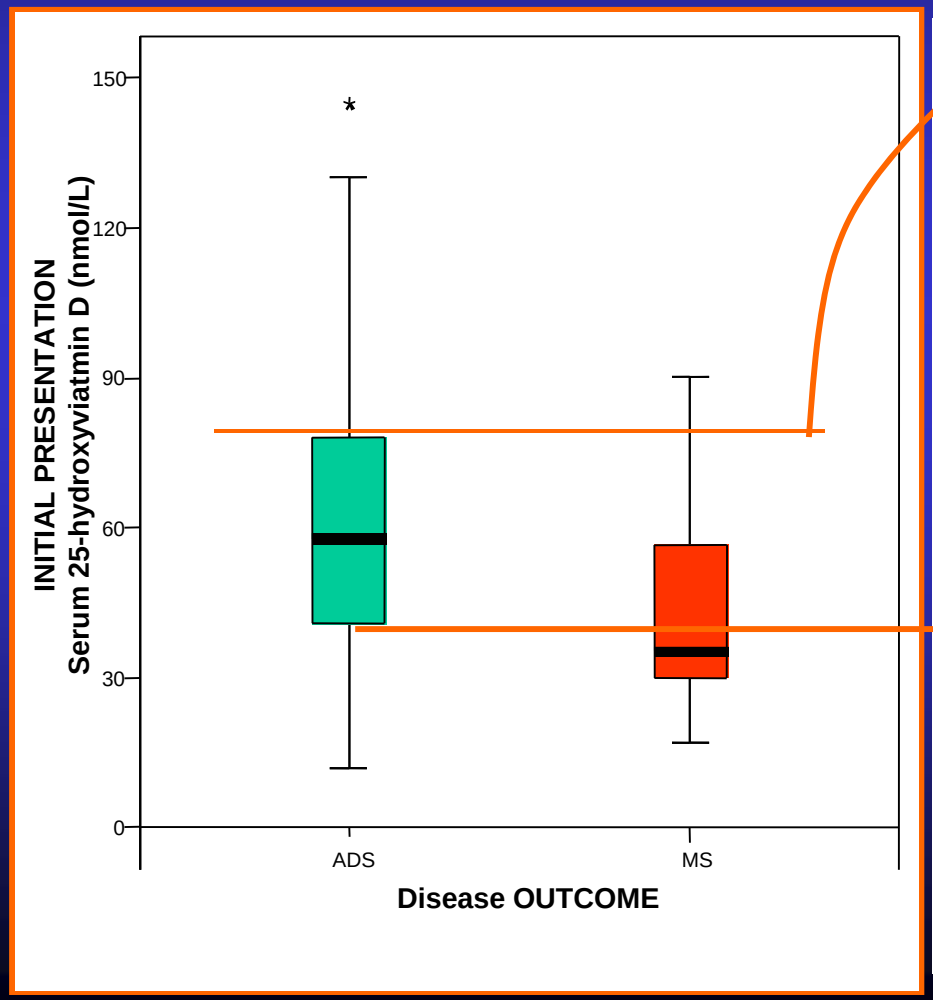
Serum 25(OH)D

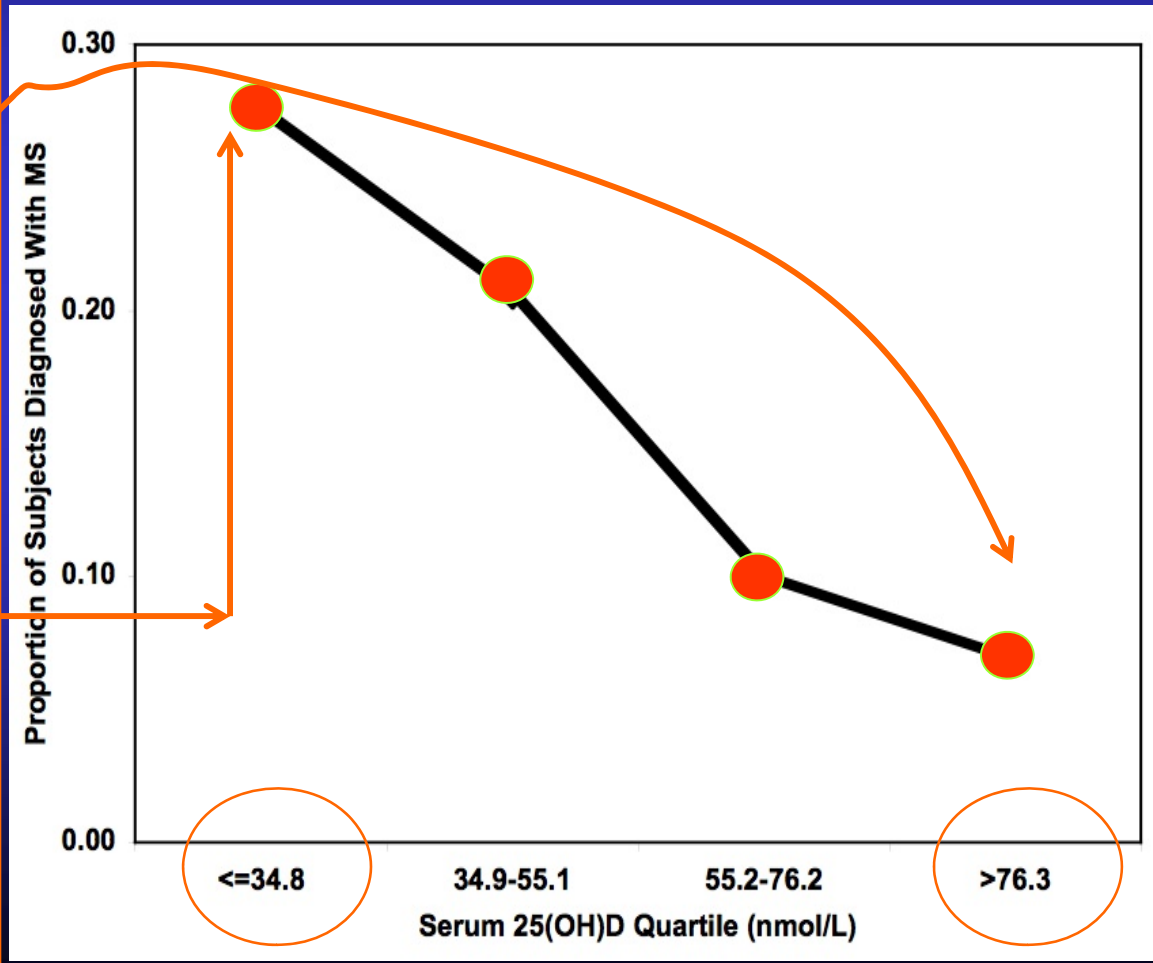
UNIVERSITY OF TORONTO

Serum 25-hydroxyvitamin D as a determinant of MS outcome following acute demyelination in children

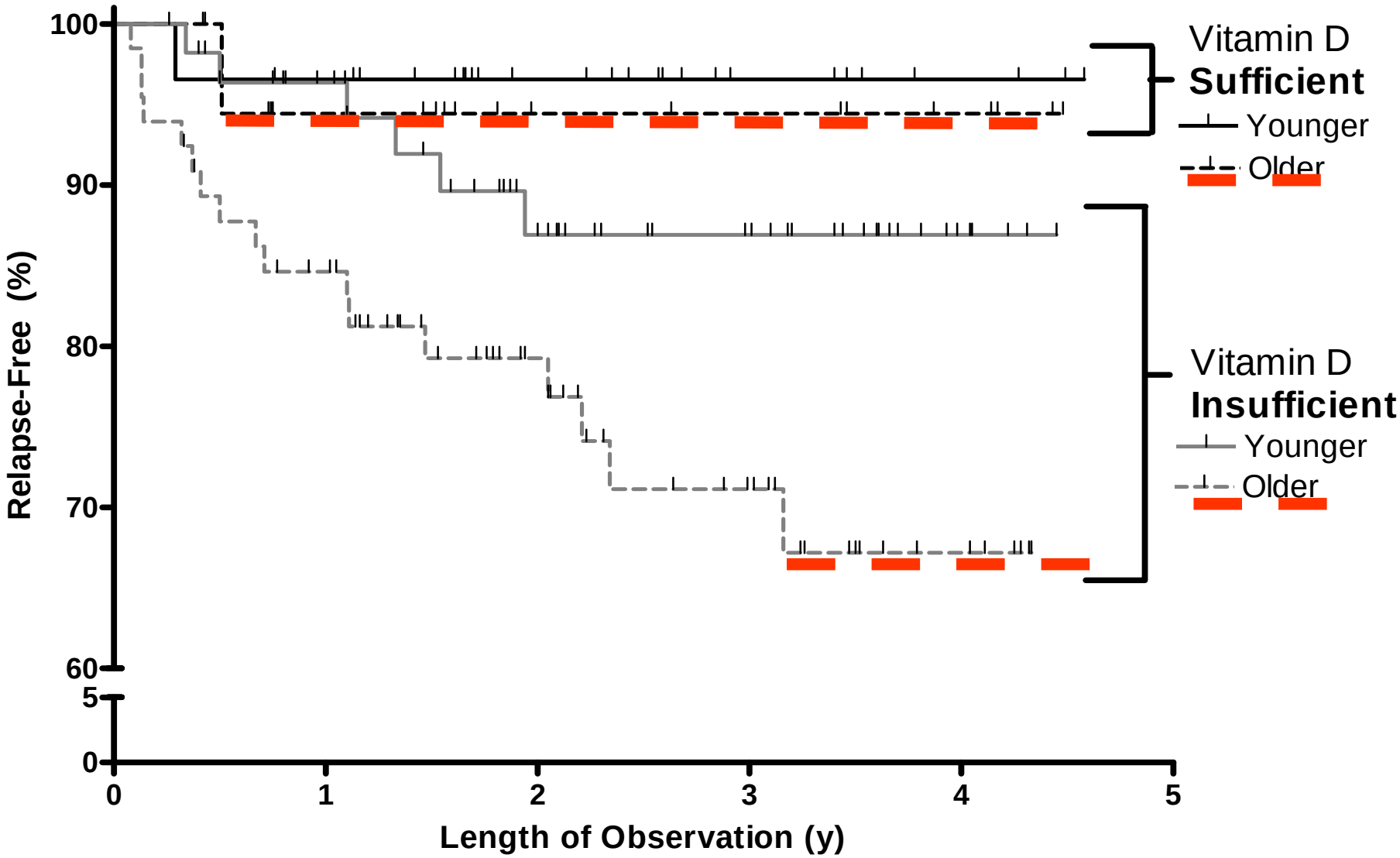
H.E.C. Hanwell[1], R. Vieth[1], A. Bar-Or[2], D. Sadovnick[3], D. Arnold[2] and B. Banwell[4] and the Canadian Pediatric Demyelinating Disease Study Group

[1]Nutritional Sciences, University of Toronto, Toronto, Ontario, [2]Montreal Neurological Institute, Montreal, Canada, [3]University of British Columbia, Vancouver, Canada, [4]Division of Neurology, The Hospital for Sick Children, Toronto, Ontario.

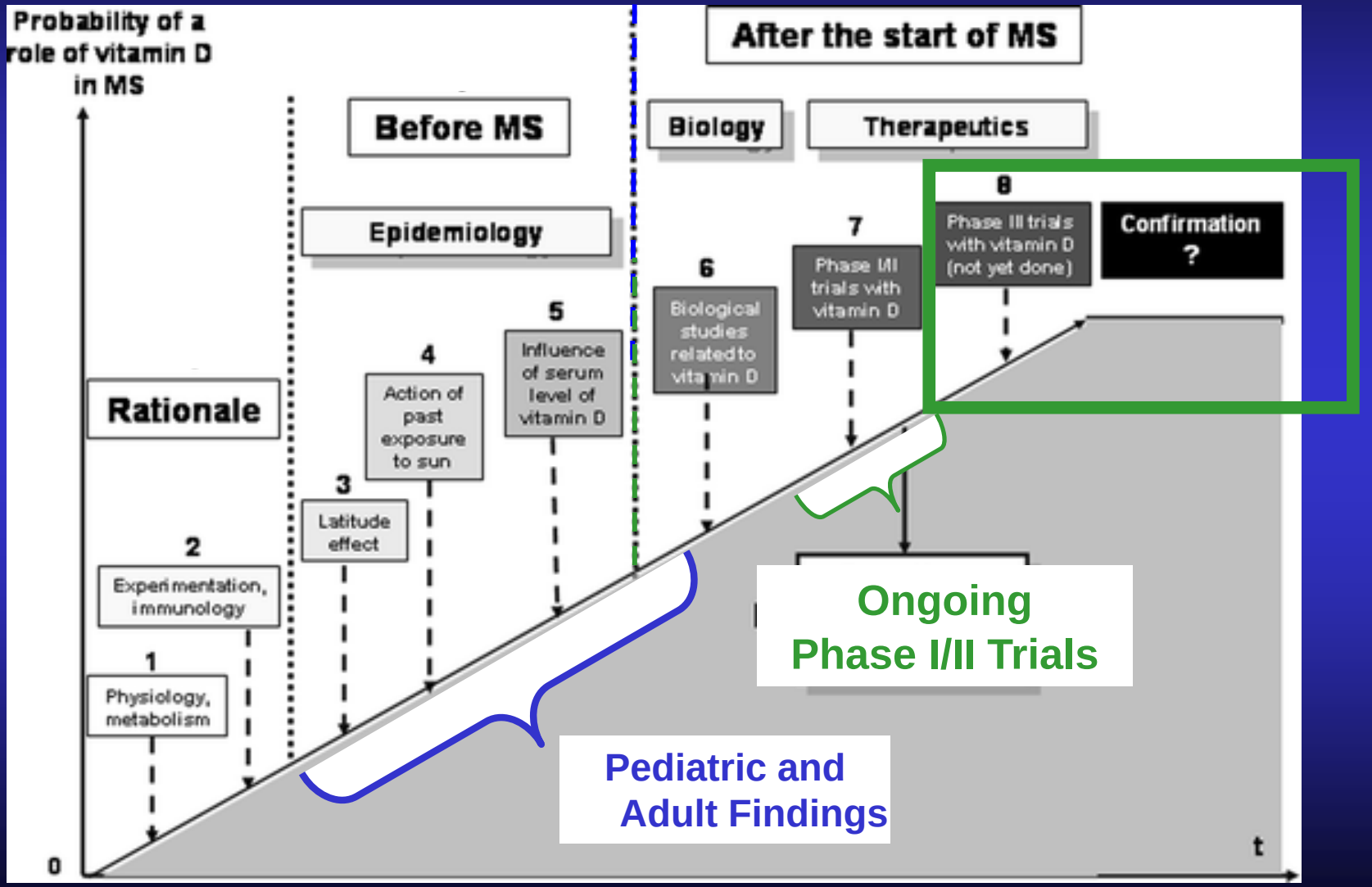




Survival Curves of theTime To MS Diagnosis: Baseline Age and Vitamin D Sufficiency



The Ascent of the Evidence Mountain for MS:

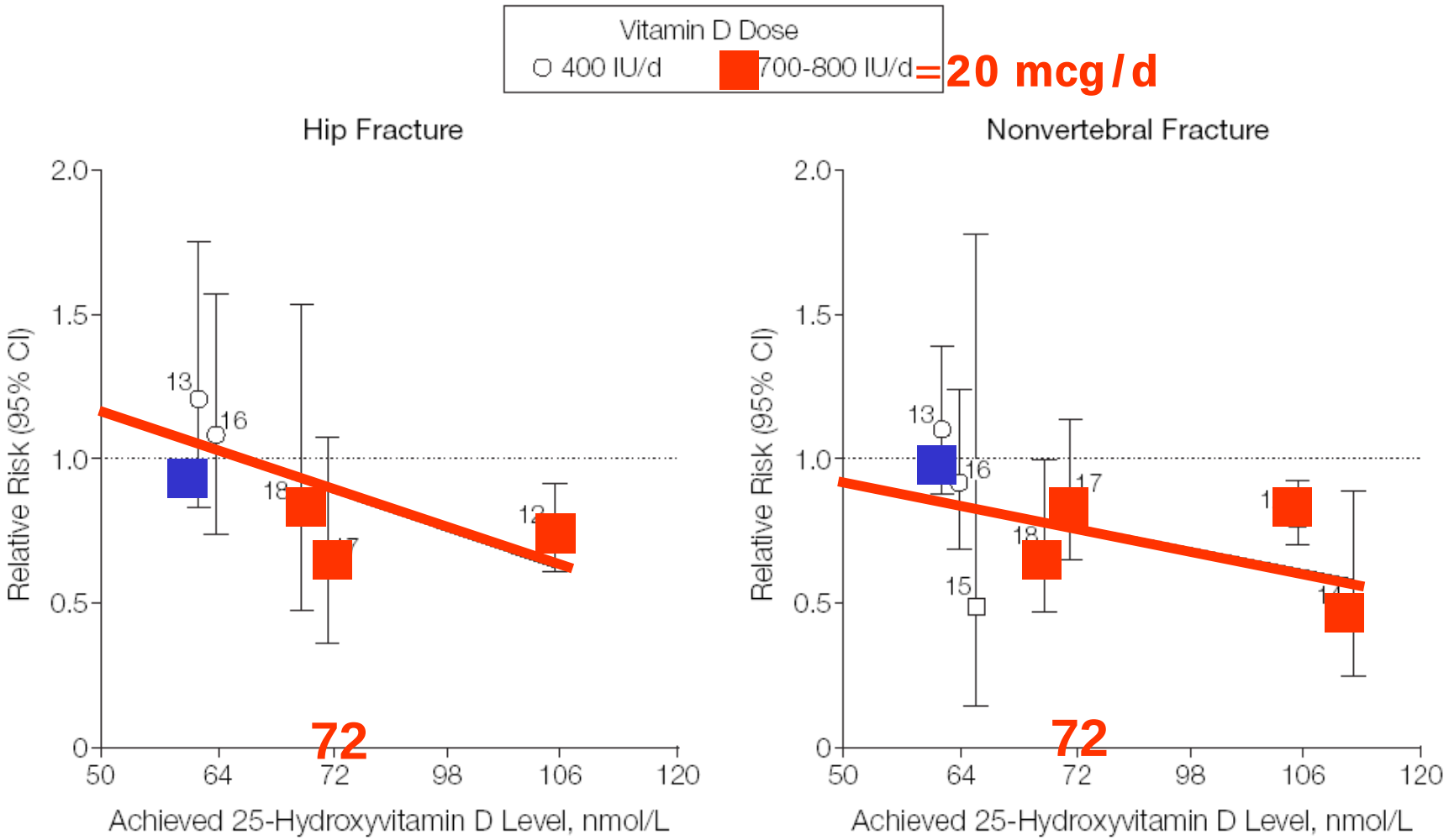


C Pierrott-Deseligny, J Neurol 2009

SUMMARY OF OUTCOMES RELATING VITAMIN D TO BONE AND OTHER HEALTH OUTCOMES

FRACTURE-PREVENTION STUDIES WITH VITAMIN D3

Figure 3. Hip and Nonvertebral Fracture Efficacies by Achieved 25-Hydroxyvitamin D Levels in 400 IU/d and 700-800 IU/d Vitamin D–Treated Groups

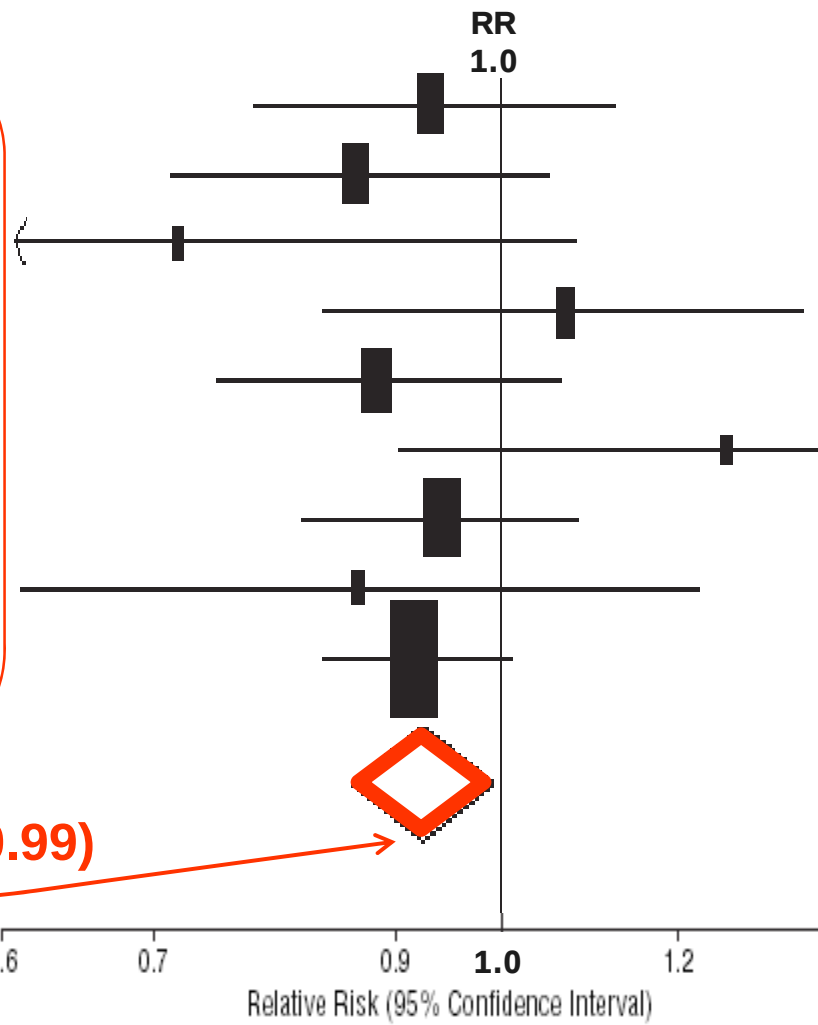


Bischoff-Ferrari et alJAMA. 2005;293:2257-2264

Meta-analysis of data on all-cause MORTALITY in randomized controlled trials with vitamin D.

Study	Therapy	PLACEBO
Chapuy et al, 1992	258/1634	274/1636
Lips et al, 1996	223/1291	251/1287
Chapuy et al, 2002	71/393	45/190
Meyer et al, 2002	169/569	163/575
Trivedi et al, 2003	224/1345	247/1341
Porthouse et al, 2005	57/1321	68/1993
RECORD Trial, 2005	438/2649	460/2643
Flicker et al, 2004	76/312	85/313
Jackson et al, 2006	744/18 176	807/18 106

Summary relative risk (95%). **0.92 (0.86-0.99)**



Autier and Gandi 2007 *Arch Intern Med;167(16):1730-1737*

Estimation of optimal serum 25-hydroxyvitamin D levels for multiple health outcomes Bischoff-Ferrari HA, 1,3Giovannucci E, 1,3Willett WC, 4Dietrich T, 5Dawson-Hughes B