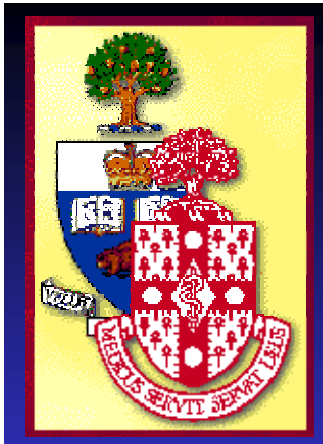


MOUNT SINAI HOSPITAL

Bright Minds. Big Hearts. The Best Medicine.

Vitamin D supplementation during pregnancy & breastfeeding

Effects on gestational diabetes, plus a review of safe and toxic blood serum levels

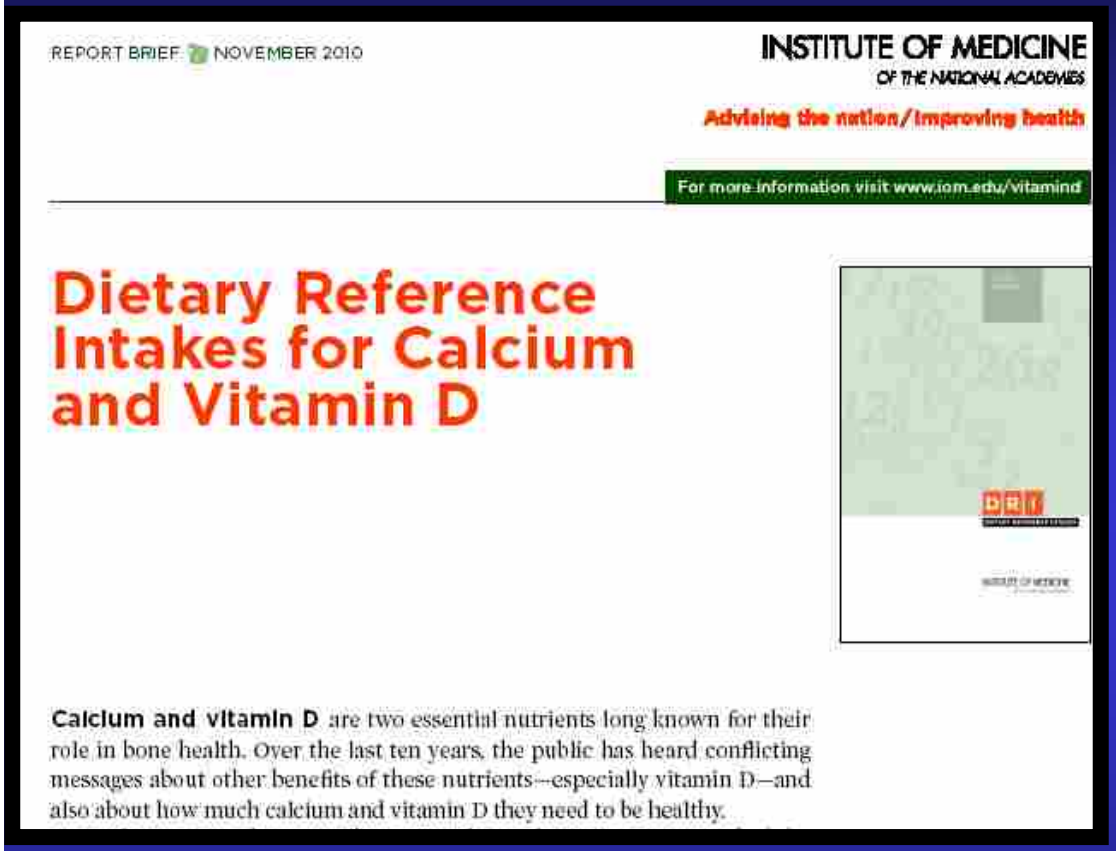
Reinhold Vieth

Professor, Departments of Nutritional Sciences and Laboratory Medicine and Pathobiology, University of Toronto, and Pathology, Mount Sinai Hospital, Toronto, Canada

LONDON MAY 17, 2011

Disclosures: I am a consultant for Ortho Clinical Diagnostics and Merck Serono. Hold a grant from Dairy Farmers of Canada. Have received payment for lectures including service on speaker bureaux from Merck and Company (MSD), Carlson Laboratories, and DiaSorin Inc, I am related to employees in the dietary supplement industry. I hold a patent for a compound for infant vitamin D supplementation.

Why is policy slow to adapt to evidence?



REPORT BRIEF NOVEMBER 2010

INSTITUTE OF MEDICINE
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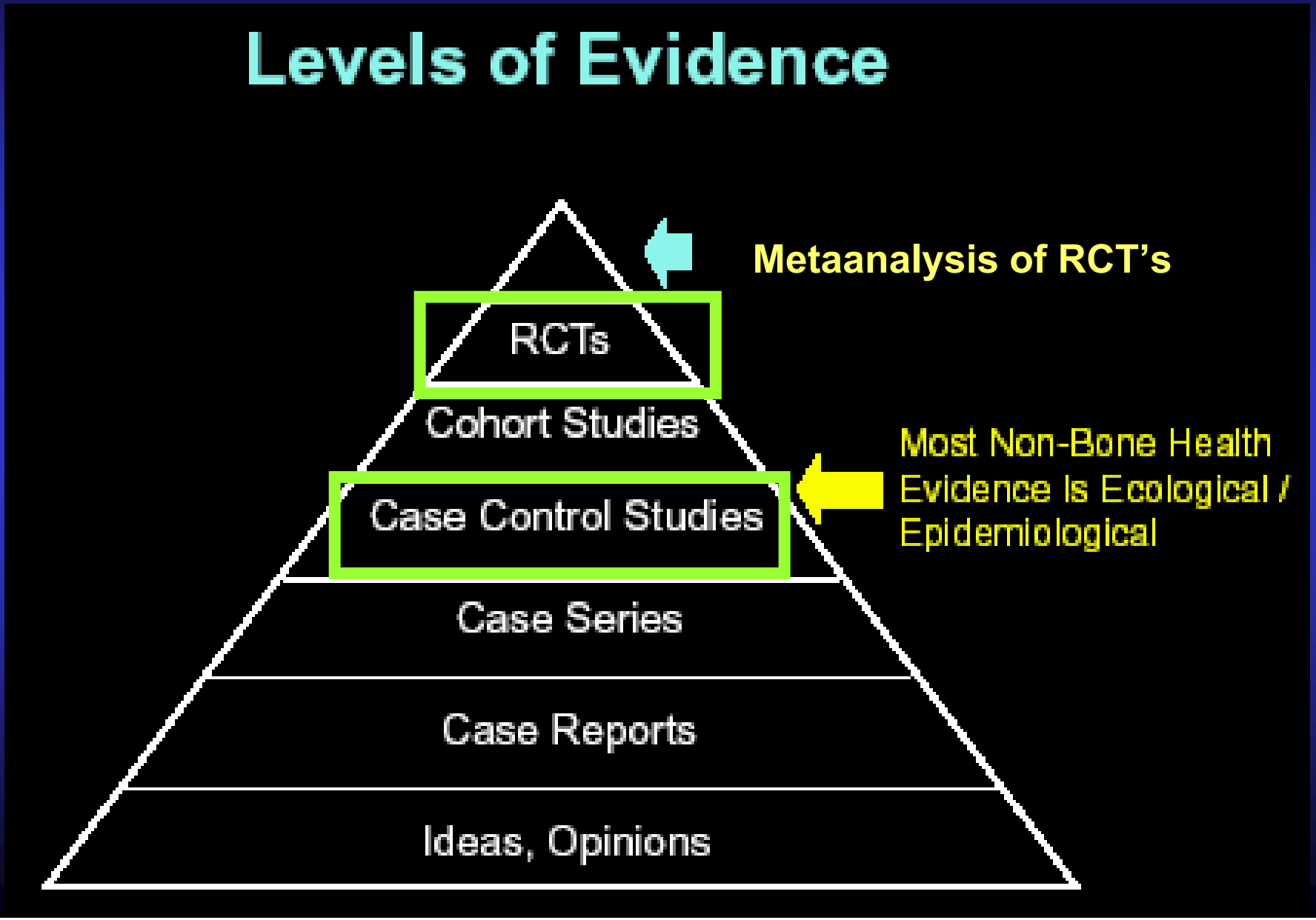
Dietary Reference Intakes for Calcium and Vitamin D

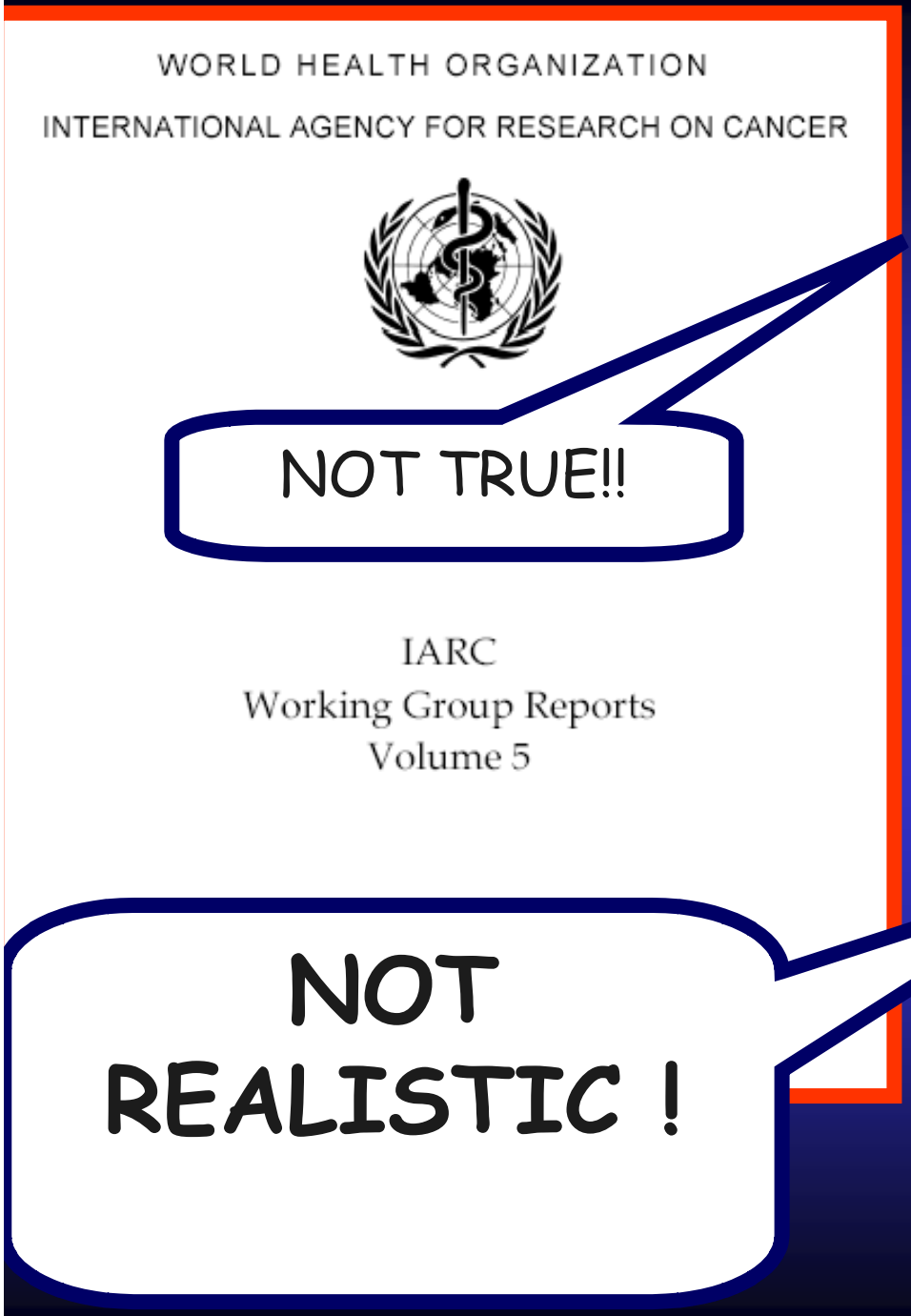
Calcium and vitamin D are two essential nutrients long known for their role in bone health. Over the last ten years, the public has heard conflicting messages about other benefits of these nutrients—especially vitamin D—and also about how much calcium and vitamin D they need to be healthy.

The Levels of Decision-Making and the Risk/Benefit Ratio

1. Personal care decisions (flexible and possibly only during sickness).
2. Physician care of patient (flexible and possibly only during sickness).
3. Government Health policy: for all society and for years to come.

Why is policy slow to adapt to evidence?

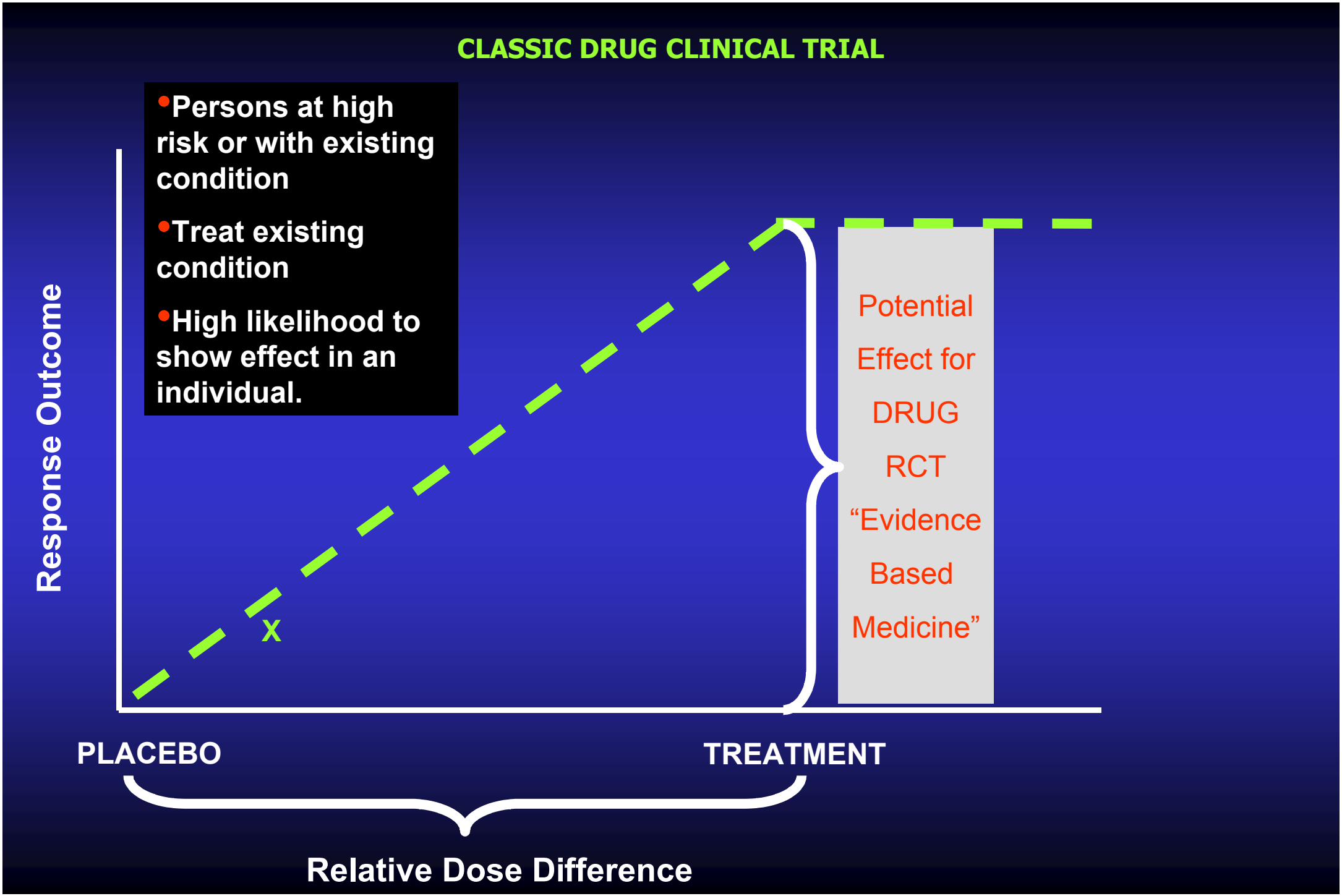


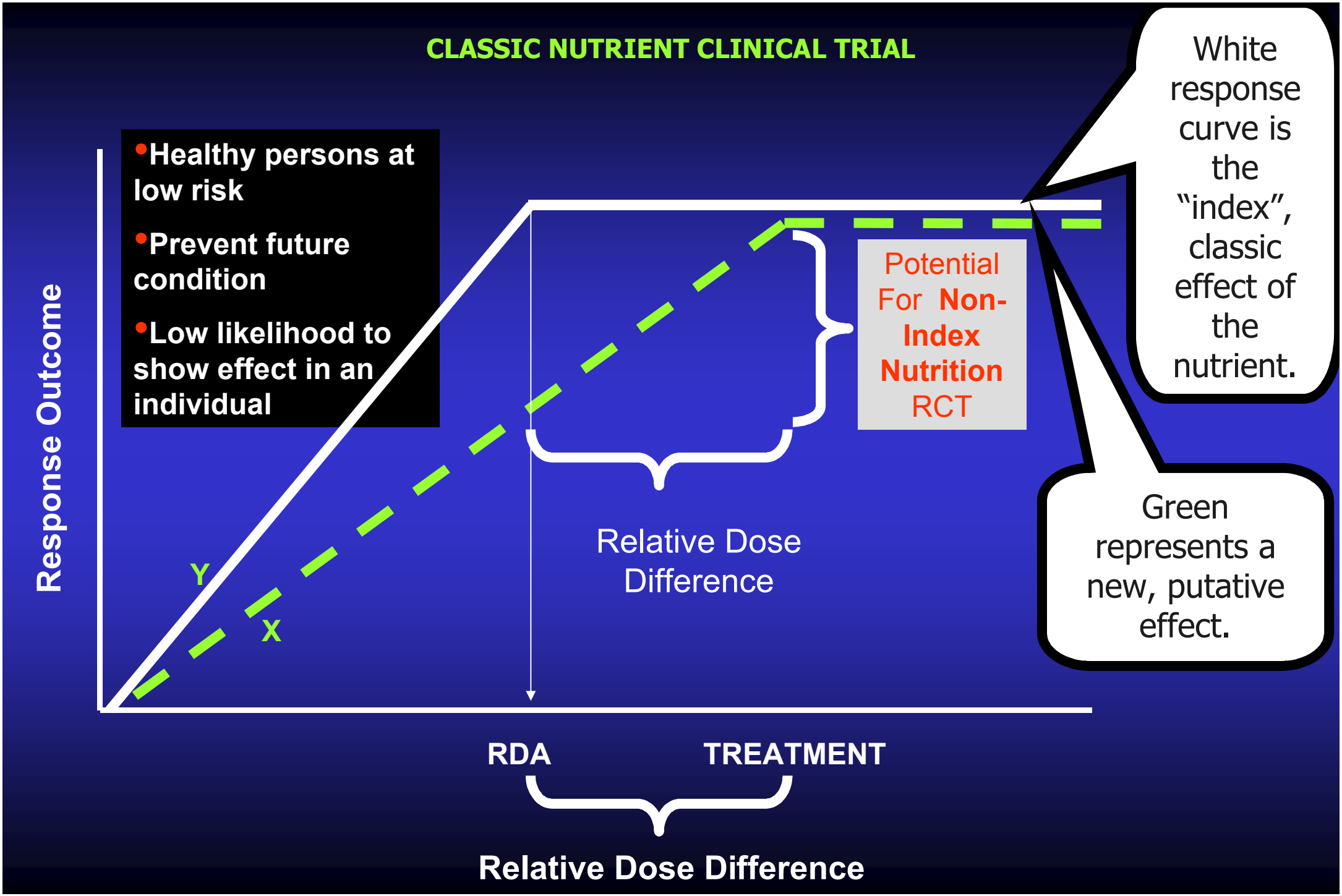


"Vitamin D is a drug, more precisely a hormone."

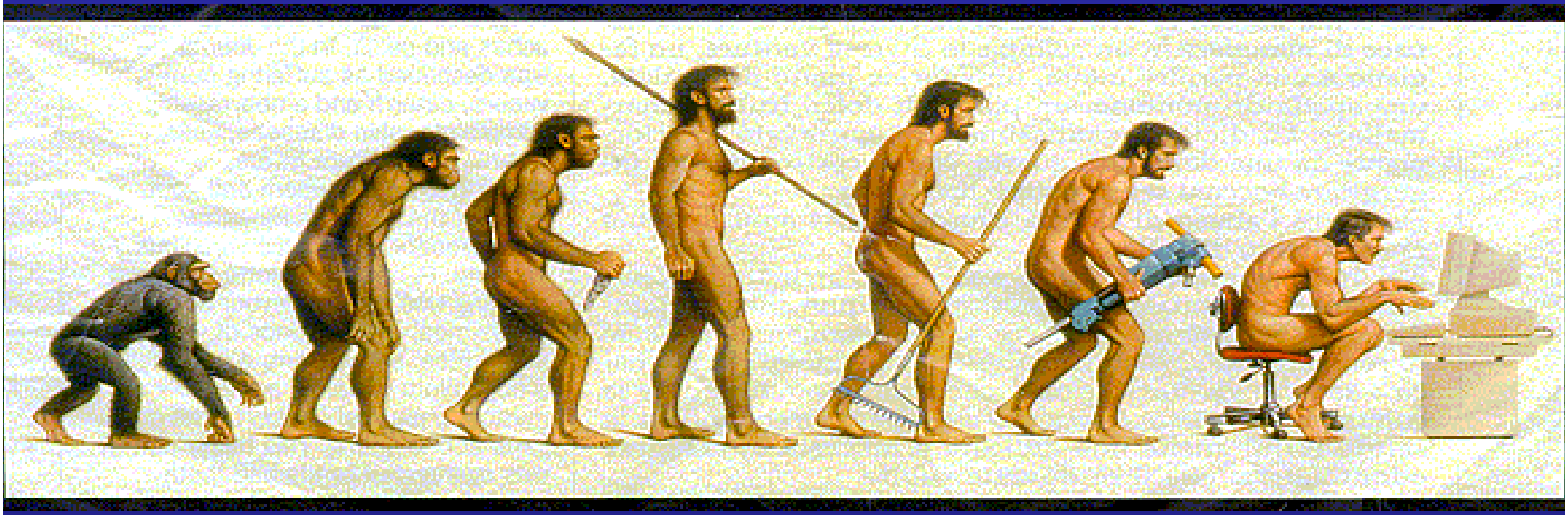
"...no compound should be recommended for cancer chemoprevention if its efficacy and side effects have not been evaluated in large, randomised trials.

Ideally, these trials should be double-blind and placebo controlled."


CLASSIC DRUG CLINICAL TRIAL
•Persons at high risk or with existing condition
•Treat existing condition
•High likelihood to show effect in an individual.
Response Outcome
X
Potential Effect for DRUG RCT "Evidence Based Medicine"
PLACEBO
TREATMENT
Relative Dose Difference


CLASSIC NUTRIENT CLINICAL TRIAL
Healthy persons at low risk
Prevent future condition
Low likelihood to show effect in an individual
Response Outcome
Potential For Non-Index Nutrition RCT
Relative Dose Difference
Y
X
White response curve is the "index", classic effect of the nutrient.
Green represents a new, putative effect.
RDA
TREATMENT
Relative Dose Difference

The conditions for which our human genome was selected offer a reasonable basis for optimal nutrition.



Anatomically "Modern" humans have existed for 100,000 years

Regions shaded white are the natural habitat of non-human primates

from; Primate Behavior: Field studies of monkeys and apes. I DeVore 1965

Natural selection can only respond to conditions that affect reproduction.

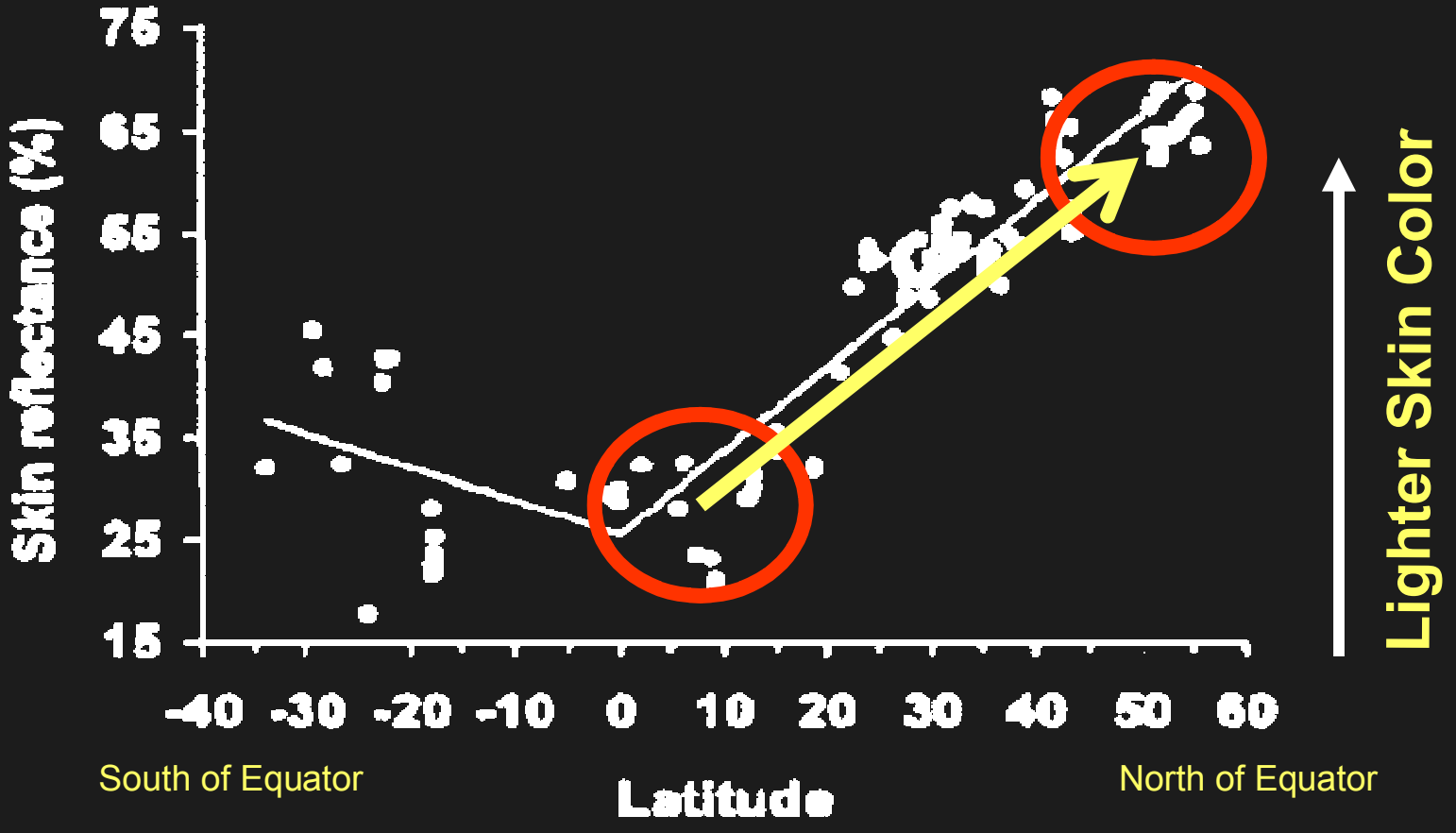
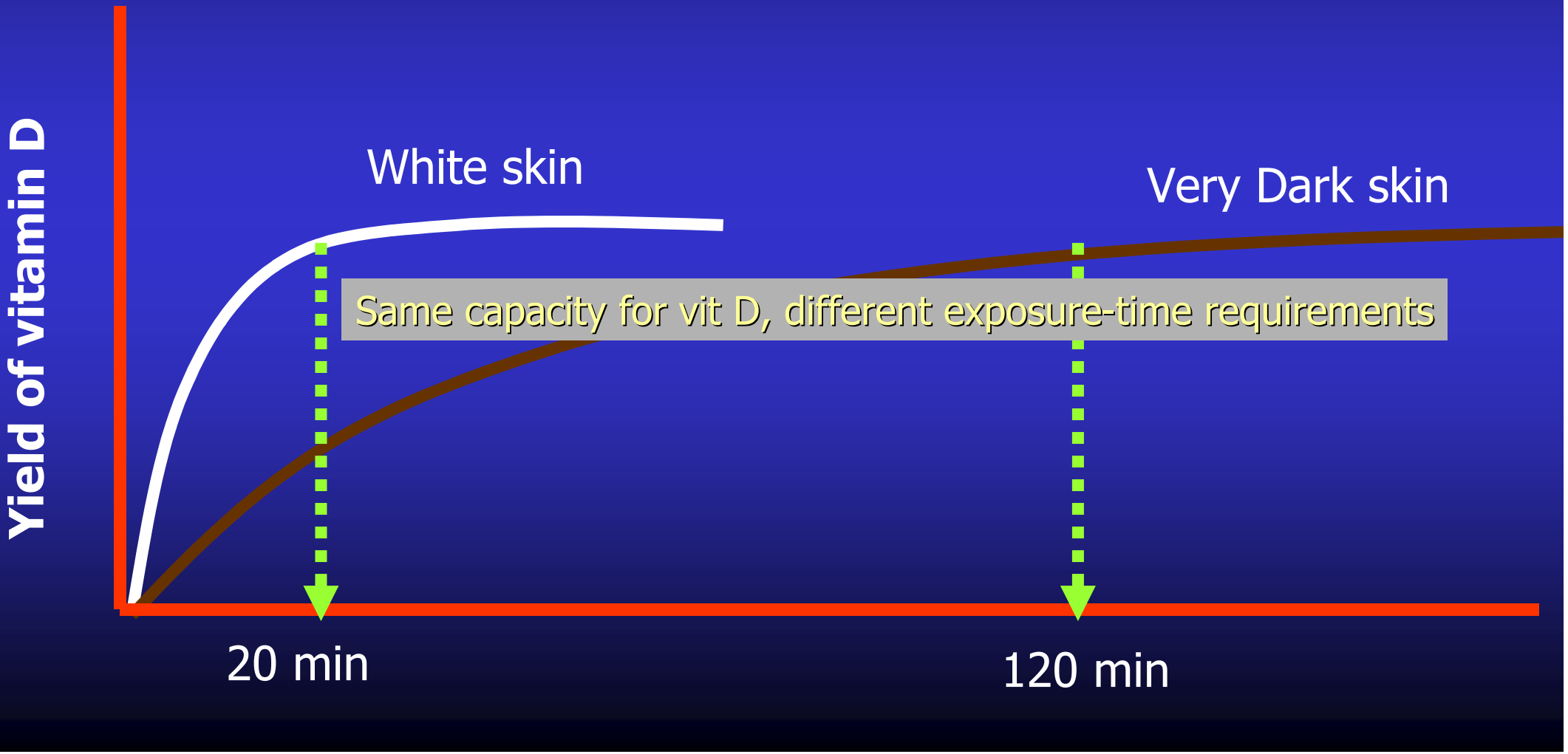


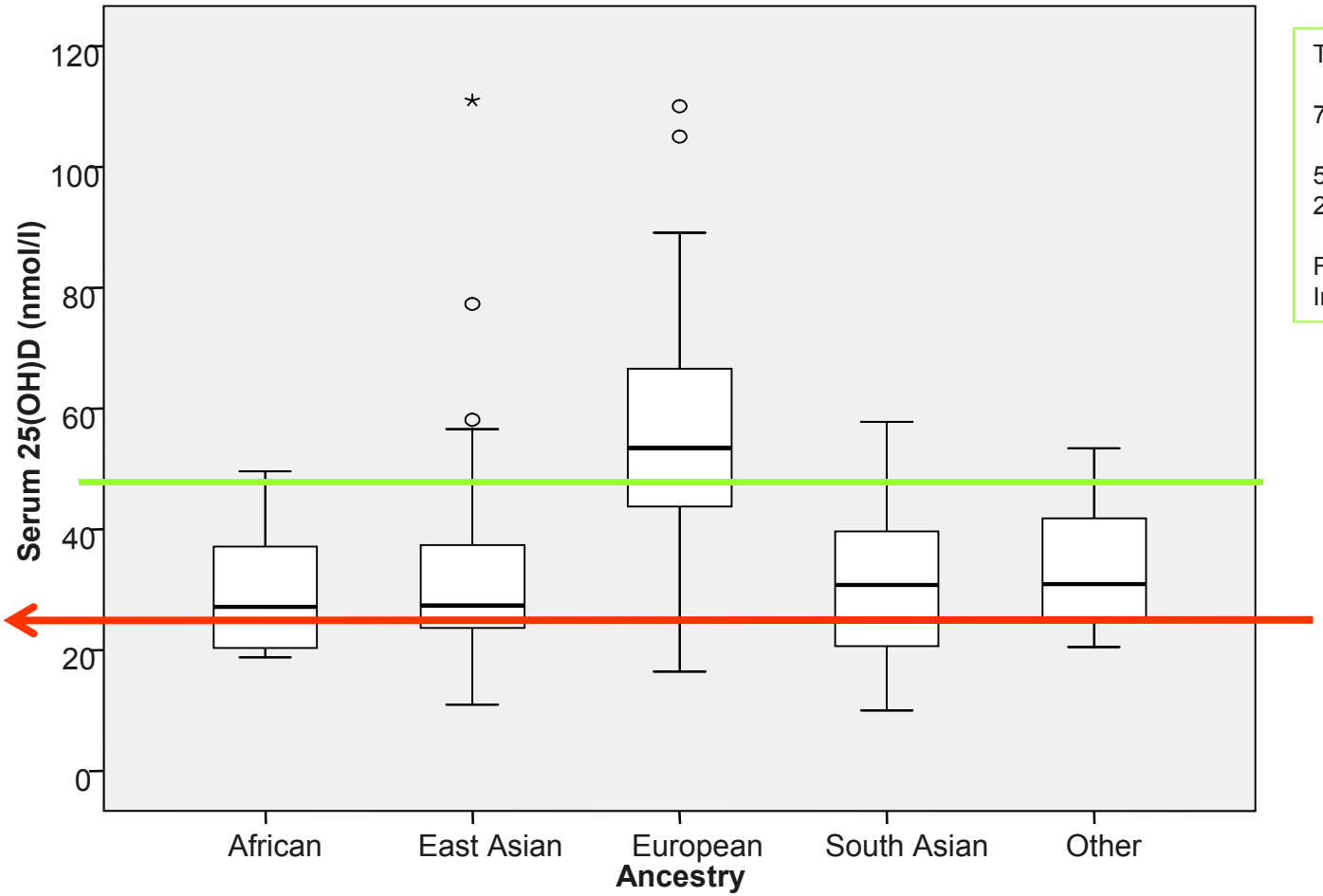
Fig. 3. Nonlinear piecewise regression results for 102 male samples ($R^2 = 0.85$) using the reduced model (equa-

From JH Rethelford, Am J Physical Anthropology 1997; 104: 449

Effect of UVB exposure time and skin colour on Vitamin D production :



Vitamin D Blood levels in University of Toronto students of various ancestries measured in winter



The box demarks:

75th percentile

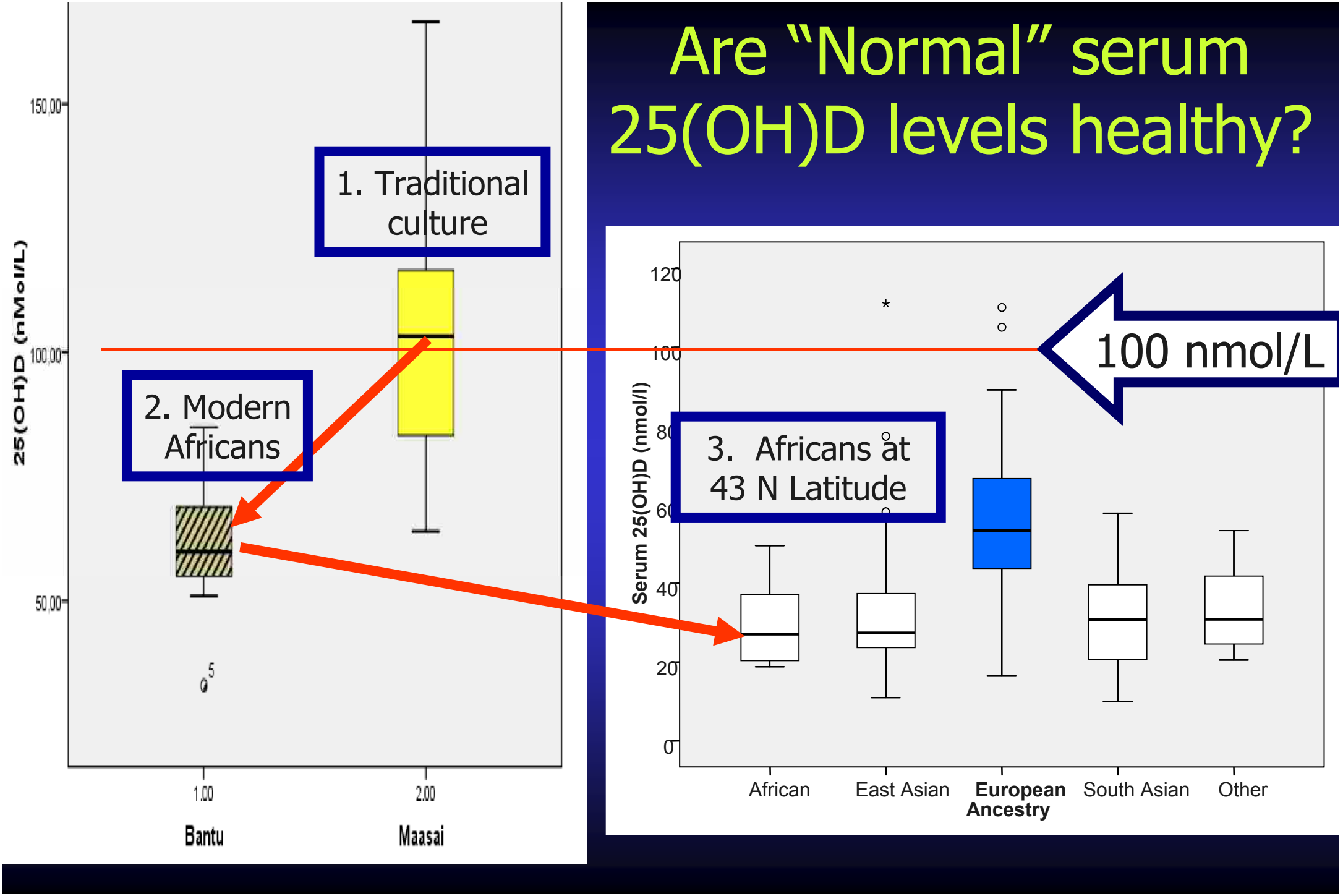
50th %ile
25th %ile

For the group
Indicated below the box

Below this is Diagnostic of vitamin D deficiency rickets in infants

Gozdik et al. *BMC Public Health* 2008, **8**:336

Are "Normal" serum 25(OH)D levels healthy?



Vitamin D myopathy with elevated 1,25(OH)2D and **very low 25-hydroxyVITAMIN D**

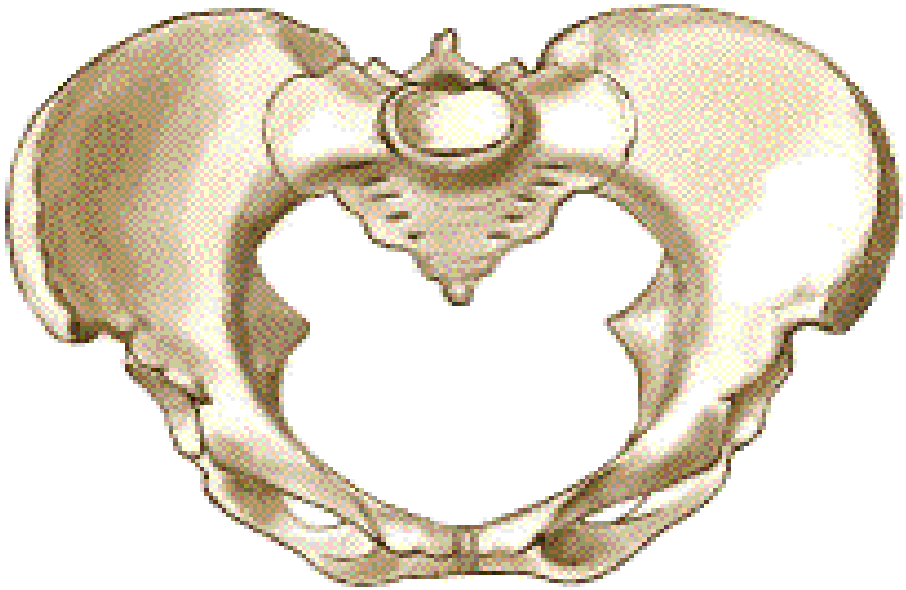
LAB TEST	HIS VALUE (NORMALS)
S.creatinine	2.13 mg/dL (-1.3)
S.calcium (corr)	**1.50 mmol/L (2.2-2.6) low**
S.phosphate	1.81 mmol/L (0.84-1.45)
S.magnesium	0.65 mmol/L (0.7-1.1)
1,25(OH)2D	163 pg/ml (30-70)
25(OH)D	**19 nmol/L (>75)**
PTH	1082 pg/ml (-65)

62 yr old patient

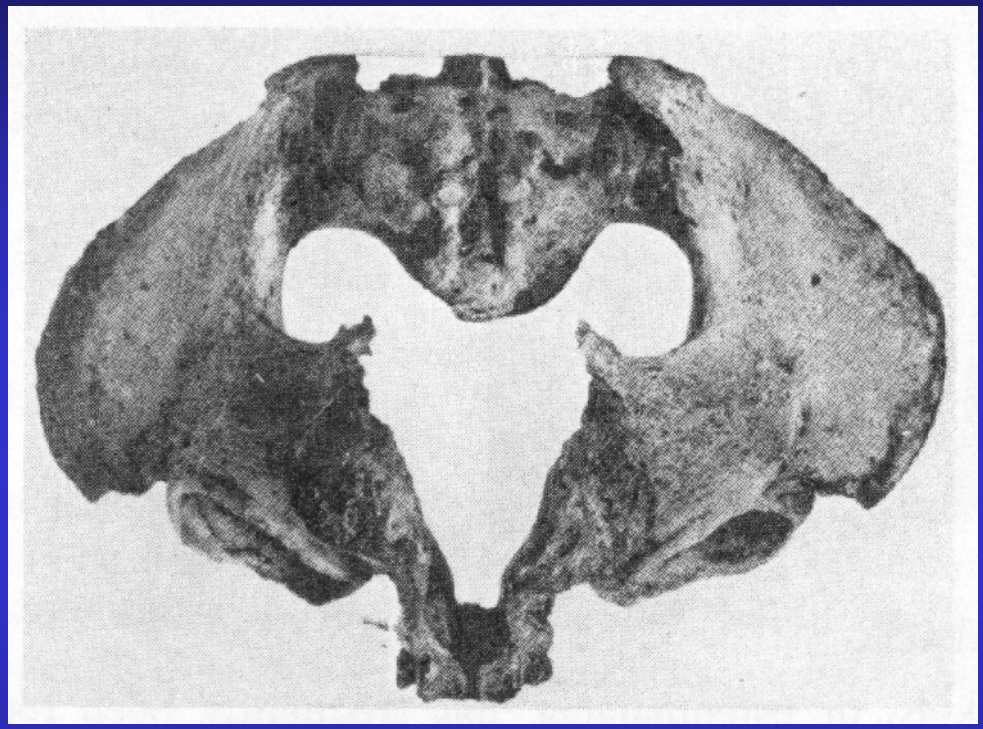
Vitamin D through Pregnancy

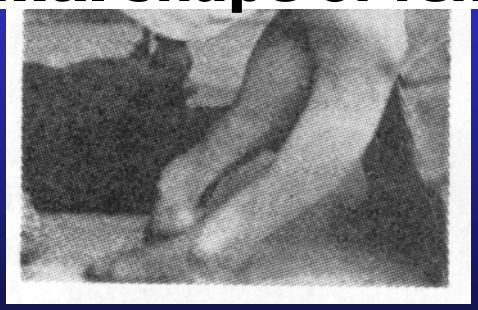
Childhood lack of vitamin D causes rickets:

Death in Childbirth was a means of natural selection for skin colour.



Normal shape of female pelvis





Contracted pelvis, in a case of osteomalacia (adult rickets). Normal childbirth would be impossible.

Vieth 2001. Nutritional Aspects of Osteoporosis, Chapter 17, ed P Burckhardt, RP Heaney, B Dawson-Hughes; Academic Press

POSITION STATEMENT (FNIM 2007-01)

Vitamin D supplementation: Recommendations for Canadian mothers and infants

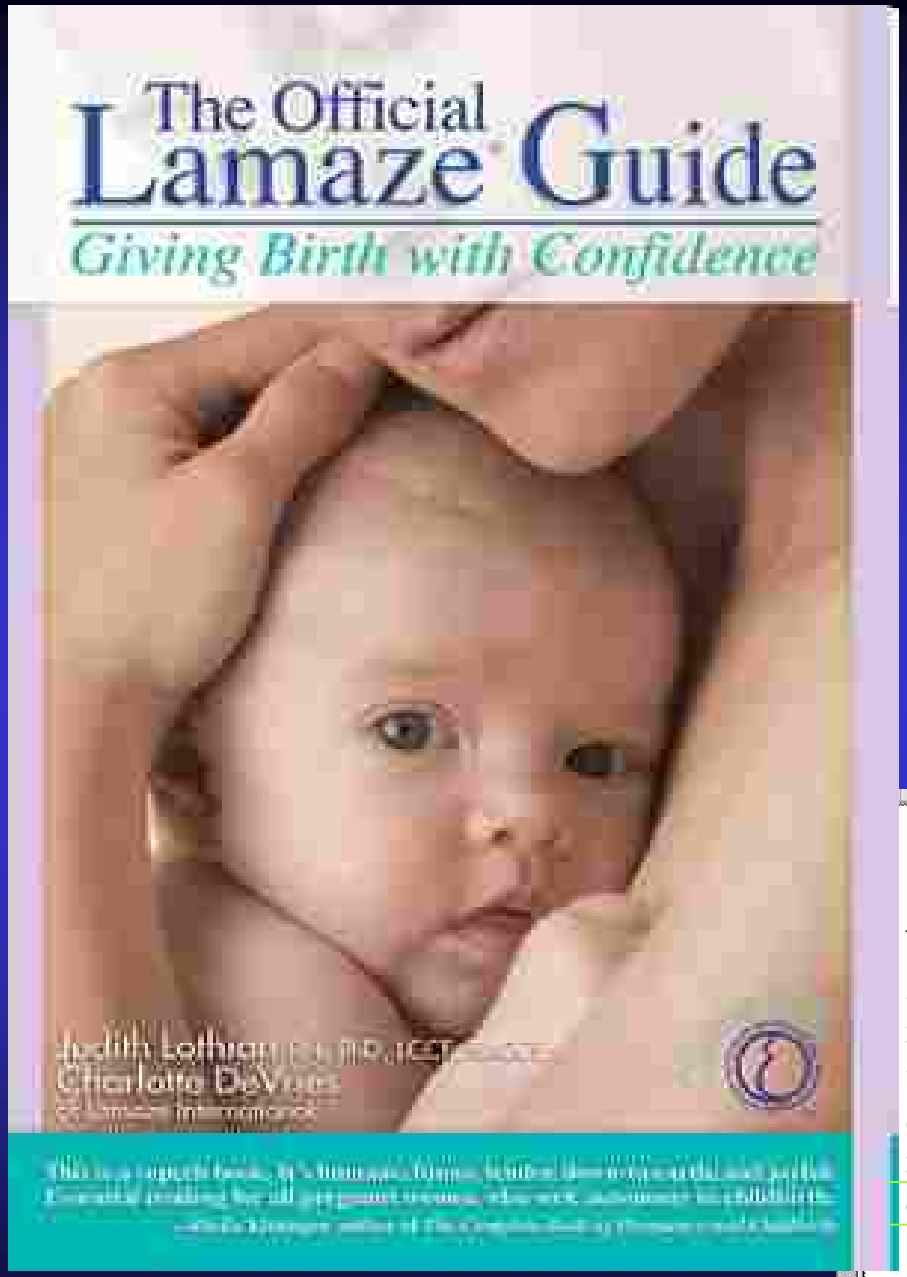
Canadian Paediatric Society

Français en page 591

The Canadian Pediatric Society Recommends
PREGNANCY: Vitamin D3 at 2000 IU/day (50mcg/d)
Why? For the health of the fetus, which is the domain of the pediatrician.

USA and Canadian Pediatric Societies:
FOR INFANTS: 400 IU/day from birth
For infants above Latitude 55, Oct-Apr: 800 IU/day

Paediatr Child Health 2007 Vol 12: 583



Pg 69. "Commercial vitamin supplements… no research confirms the need for routine use of them[2]"

3rd edition of *A Guide to Effective Care in Pregnancy and Childbirth* (Oxford University Press, 2000) authors: Murray Enkin, Marc J.N.C. Keirse, James Neilson, Caroline Crowther, Lelia Duley, Ellen Hodnett and Justus Hofmeyr.

7 Other vitamin or mineral supplementation

Vitamin D deficiency may occur in women whose diet is relatively low in the vitamin, such as vegetarians and those who either remain indoors or whose clothing leaves little exposed skin, particularly in relatively sunless climates. Controlled trials in vulnerable populations show a reduction in neonatal hypocalcemia (leading to hyper-irritability) with vitamin D supplementation. No significant effects on other substantive outcomes have been reported.

The little evidence available on vitamin B6 supplements in pregnancy suggests that they may protect against dental decay in the mother when given in the form of lozenges, but no effect has been found on other

The Lamaze motto:

A Normal Birth for Every Woman

The World Health Organization statement and standards:

Labor begins on its own

1. Mom has freedom of movement throughout labour and birth
2. Mom has continuous labour support
3. **No routine interventions**
4. Upright or side-lying positions for birth
5. No separation of mom and baby after birth.

BUT Vitamin D is intervention prevention !

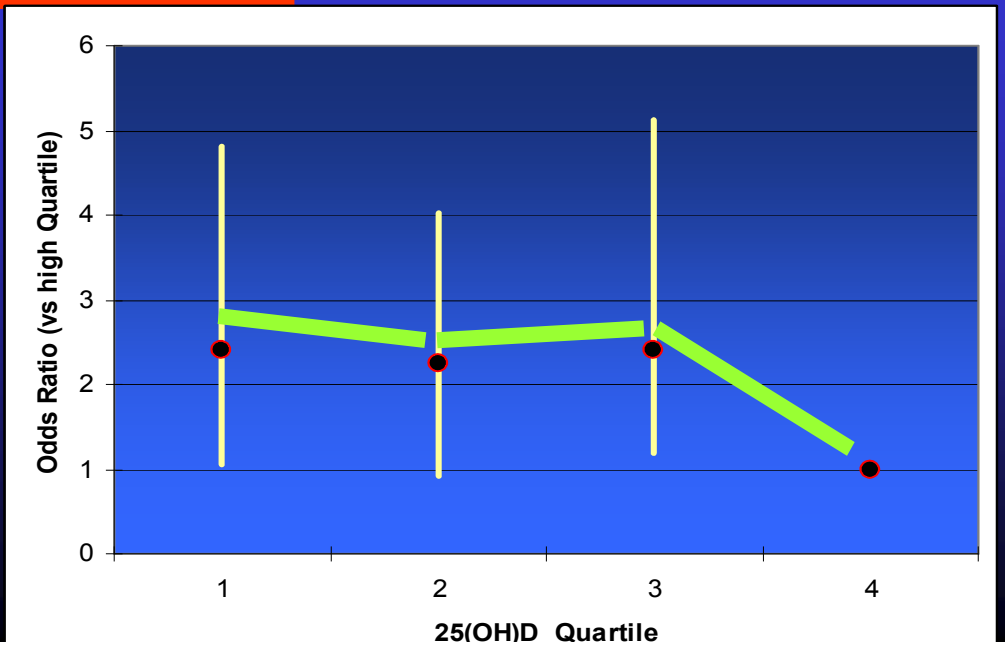
Vitamin D and Risk of Gestational Diabetes

Luciana Parlea, MD Irvin L. Bromberg, MD Denice S. Feig, MD, MSc Reinhold Vieth, PhD Erica Merman, BSc Lorraine L. Lipscombe, MD,

At 16 Weeks, blood was obtained and serum stored frozen.

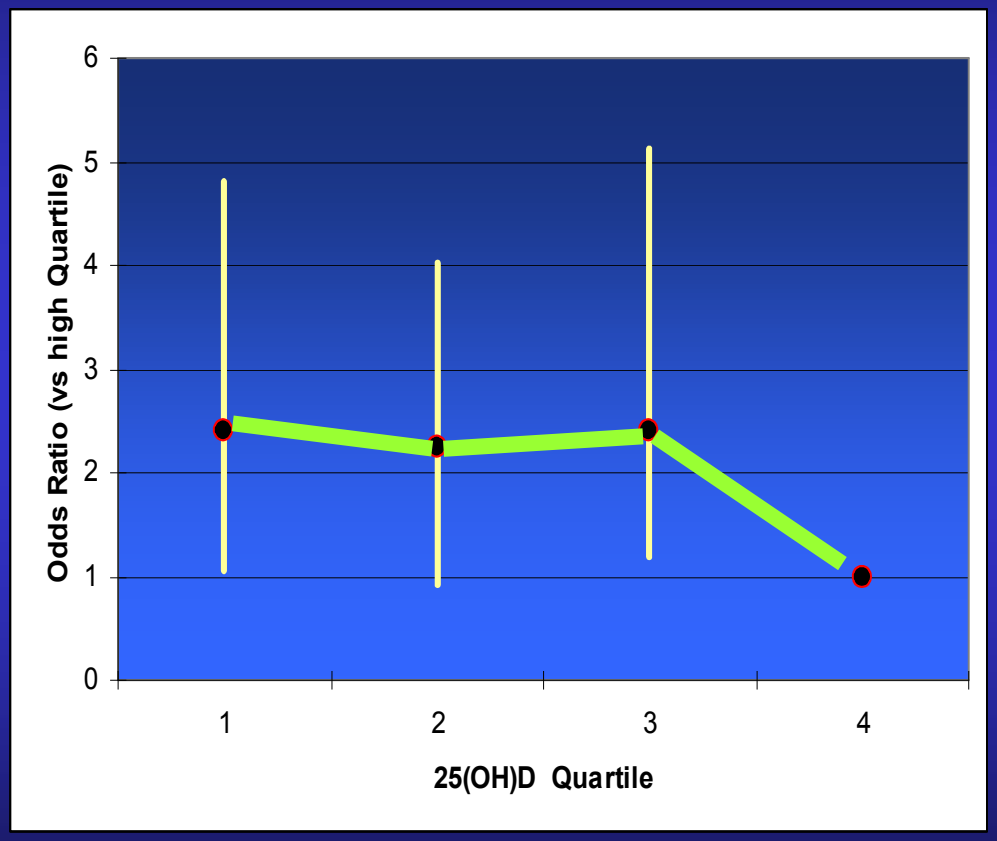
At 24 Weeks, Pregnant women with a one-hour plasma glucose value between **7.8** and 10.2 mmol/L subsequently underwent an oral glucose tolerance test (OGTT), either following a 3-hour 100-gram protocol or a 2-hour 75-gram protocol (depending on the preference of the ordering physician). GDM was diagnosed if at least two glucose criteria were met or exceeded during the OGTT. The glucose criteria for the 3-hour 100-gram protocol were fasting ≥ 5.8 mmol/L, one hour ≥ 10.6 mmol/L, two hours ≥ 9.2 mmol/L and three hours ≥ 8.1 mmol/L.

Quartile	25(OH)D nmol/L	N	GDM	Control	ODDS (GDM/Ctr)	ODDS RATIO (vs Q4)	Adjusted OR	95%CI	p-value for difference from Q4
1	<46.9	**83**	33	50	0.66	2.41	2.25	1.05 - 4.80	0.037
2	46.9-60.4	**84**	32	52	0.62	2.25	1.93	0.92 - 4.03	0.081
3	60.4-73.5	**83**	33	50	0.66	2.41	2.48	1.20 - 5.12	0.014
4	>73.5	**84**	18	66	0.27	1	-	-	-

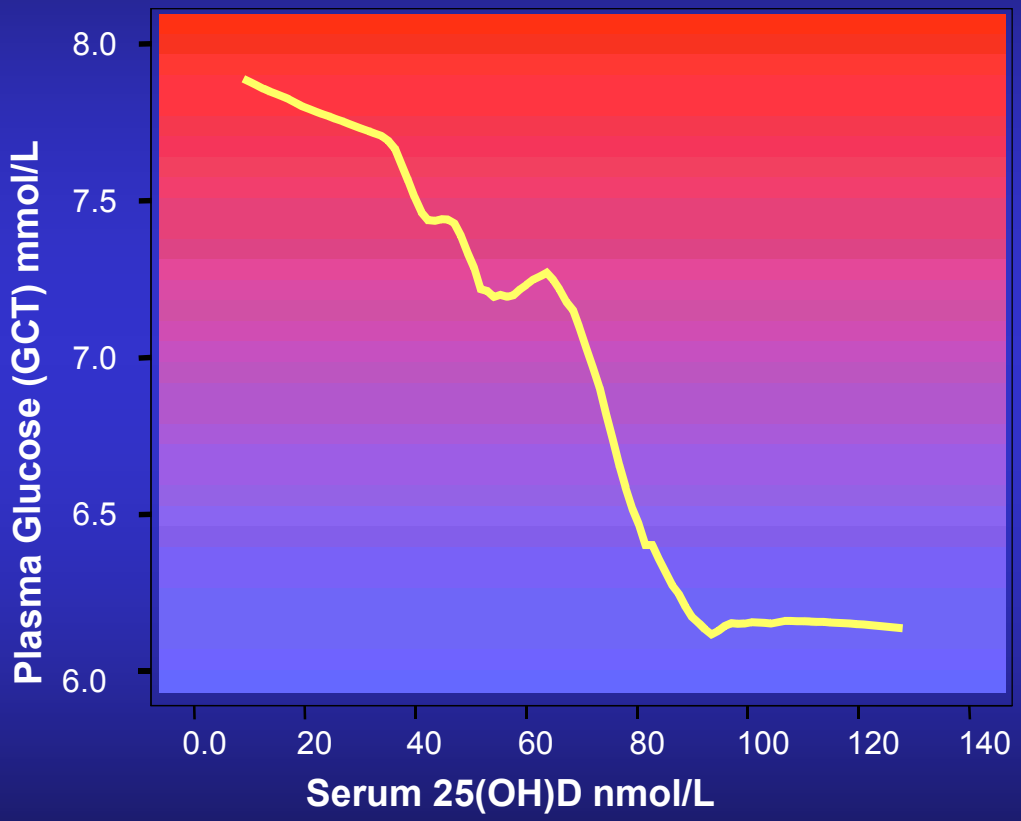


TWO WAYS OF LOOKING AT THE SAME DATA

Odds Ratios for Gestational Diabetes



1st Trimester Glucose Levels vs 25(OH)D



THE POTENTIAL FOR HARM WITH VITAMIN D

Why is vitamin D toxic? Because it works.

Paraphrasing Paracelsus:

"anything that actually works, will be harmful if the dose is high enough"

The safety of vitamin D

Traditionally

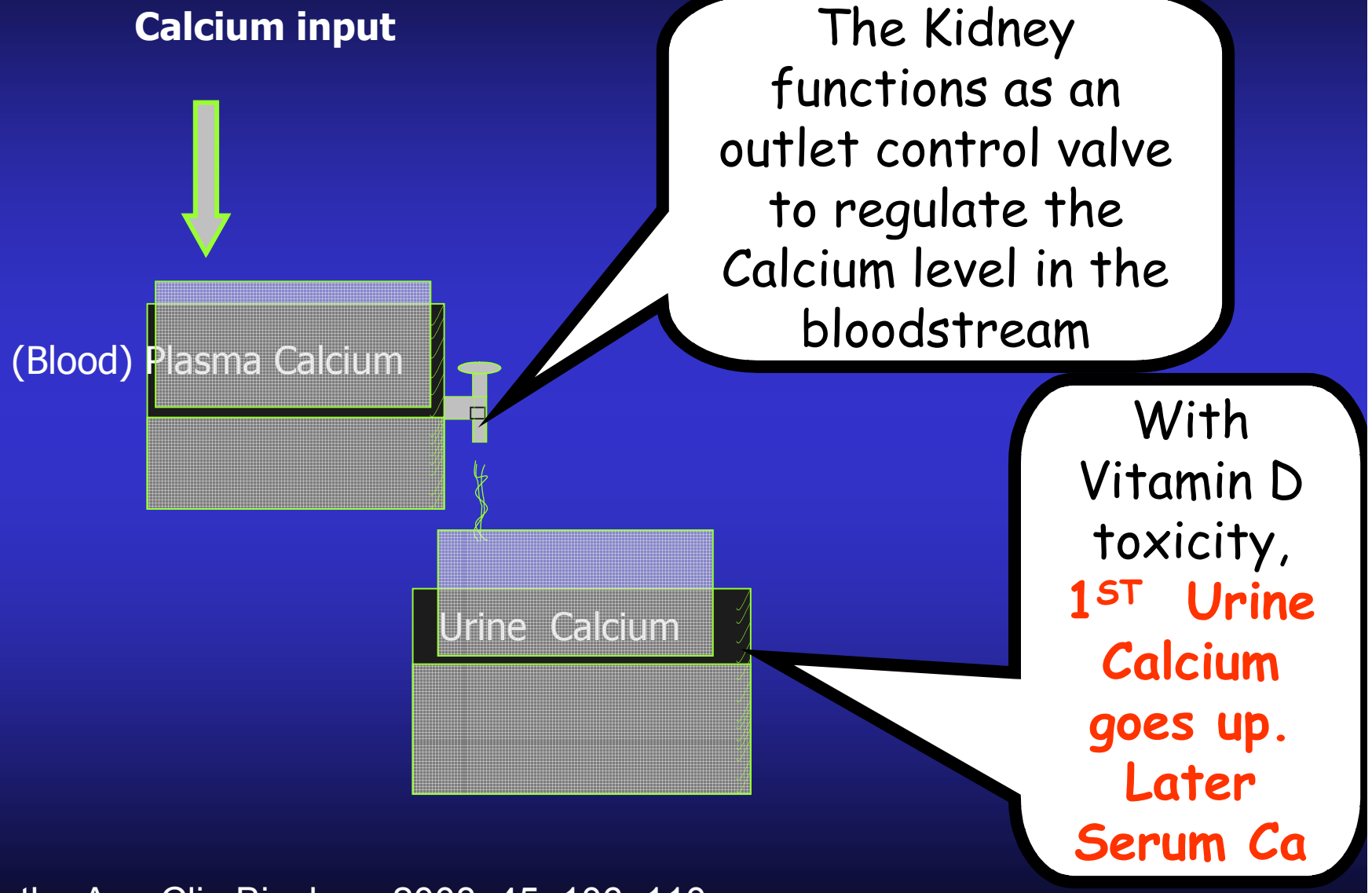
- Vitamin D safety is defined by the absence of **hypercalcemia** or hypercalciuria.

"Recent concerns":

- **RCT** → 25(OH)D 125 nmol/L → More falls and fractures

- **U-shaped risk** curves in relation to serum 25(OH)D.

Urine Calcium is the more Sensitive index of vitamin D Excess



S Kimball, R Vieth. Ann Clin Biochem 2008; 45: 106–110.

577.16–099

Quart J Med 1948, Volume 17 : 203-228

THE TOXIC EFFECTS OF CALCIFEROL[1]

By S. T. ANNING, J. DAWSON, DORIS E. DOLBY, AND JOHN T. INGRAM

(From the Departments of Dermatology and Biochemistry,

Minimum 46000 IU/d for weeks.

In 1924, Hess and Wei
that lipoid-containing

Thirst .
Anorexia .
Vomiting .
Tiredness .
Malaise .
Nausea .
Headache .
Constipation
Abdominal pain
Polyuria .

TABLE I

Summary of Published Serie

Disease	*Age*	*Preparation of vitamin D*	*Daily dose (i.u.)*	*Daily dose per kg. body-weight (approx.)*	*Period of treatment*	*Toxic symptoms*	*Renal impairment*
None	? 2–9 months	Irradiated ergosterol	50,000	800 ?	8 weeks	1	
None			5,000–50,000	7,000–10,000	1–12 weeks	1 (16 %)	Yes
Two with no disease One ? rickets	4½–7 months	Vigantol	10,000–50,000	1,500–8,300	6–15 days	3 (100 %)	Yes
Rickets	2 years	Vigantol	400,000	33,000	1 day	Yes	Yes
Arthritis	23–60 years	Viosterol	150,000–250,000	2,300–3,500	3 to 10 months	Nausea in all	In a few
Arthritis Rheumatic fever	? ?	Viosterol	200,000–300,000	3,000–4,000	? 6 months	8 (20 %)	No data
Post-operative tetany, hay-fever, asthma, arthritis, miscellaneous, and normal subjects	?	Vitamin D in corn oil	1,500–3,000	1,500–3,000		5 (100 %)	No data
			3,000–5,000	3,000–5,000	87 days	25 (4·5 %)	
			6,000–7,000	6,000–7,000	60 days	18 (14·6 %)	
				8,000–15,000		11 (15·7 %)	
				15,000–25,000	10 days	3 (18·8 %)	
				25,000–35,000	10 days	1 (20 %)	
Rheumatoid and other types of arthritis	17–64 years	Vitamin D2 in oil or propyl glycol	46,000–300,000	660–4,000	7 weeks to 10 months	13 (71 %)	Not investigated
Arthritis	32–79 years	Not specified	160,000	2,300	'Weeks to 1½ years'	None	No data
No diagnoses given	8–14 months	Irradiated ergosterol	20,000–40,000	2,000–4,000	Several months	4 (100 %)	Yes in 3
Arthritis	8–65 years	Ertron	200,000–400,000	3,000–6,000	4 to 18 months	8 (34 %)	No data
Arthritis	?	Ertron	200,000–300,000	3,000–4,000	'Months'	8 (22 %)	
Arthritis	?	Ertron	50,000	750	?	1	Yes
Osteoarthritis or fibrositis	?	Ertron	200,000–300,000	3,000–4,000	?	1 (12 %)	
Psoriasis	?	Ertron	300,000	3,000–4,000	'Months'	1 (7 %)	

Molecular Neurobiology

0893-7648/92/6/1:41–73/$6.60

Vitamin Neurotoxicity

S. Robert Snodgrass

Departments of Neurology and Pediatrics, University of Southern California School of Medicine, Los Angeles, CA 90033; and Neurology Research Laboratory, Childrens Hospital, Los Angeles, CA 90027

Contents

"Vitamin D

No evidence of vitamin D teratogenicity without effects on maternal health is known. The RDA should not be exceeded in pregnancy."

Archives of Disease in Childhood, 1984, **59**, 605–613

Original articles

Idiopathic infantile hypercalcaemia—a continuing enigma

N D T MARTIN, G J A I SNODGRASS, AND R D COHEN

The role of vitamin D remains controversial.
Metabolic balance studies have shown consistently that the infants absorbed calcium more avidly than matched controls but clinical studies, including our own, have usually **failed to find evidence of excessive vitamin D intake during infancy or of increased maternal intake during pregnancy**.
Studies of vitamin D teratogenicity in rabbits performed by Friedman et aP' 32 and in part confirmed by Chan et al used doses of vitamin D equivalent to at least 35 000 IU/week throughout a human pregnancy. To account for these facts and **to support the theory of vitamin D teratogenicity in humans, vitamin D sensitivity has been proposed.** This theory, however, would not explain adequately some of the clinical observations in this study. Firstly, of the mothers who breast fed, 52% stated that the feeding problems began before fortified milk feeds were introduced. Secondly, iatrogenic rickets may be produced in a significant minority of cases even when sunlight, the primary physiological source of vitamin D, is not restricted. Thirdly, the sporadic and transient nature of the hypercalcaemia militates against an inborn error of vitamin D metabolism. Therefore, other factors require investigation.

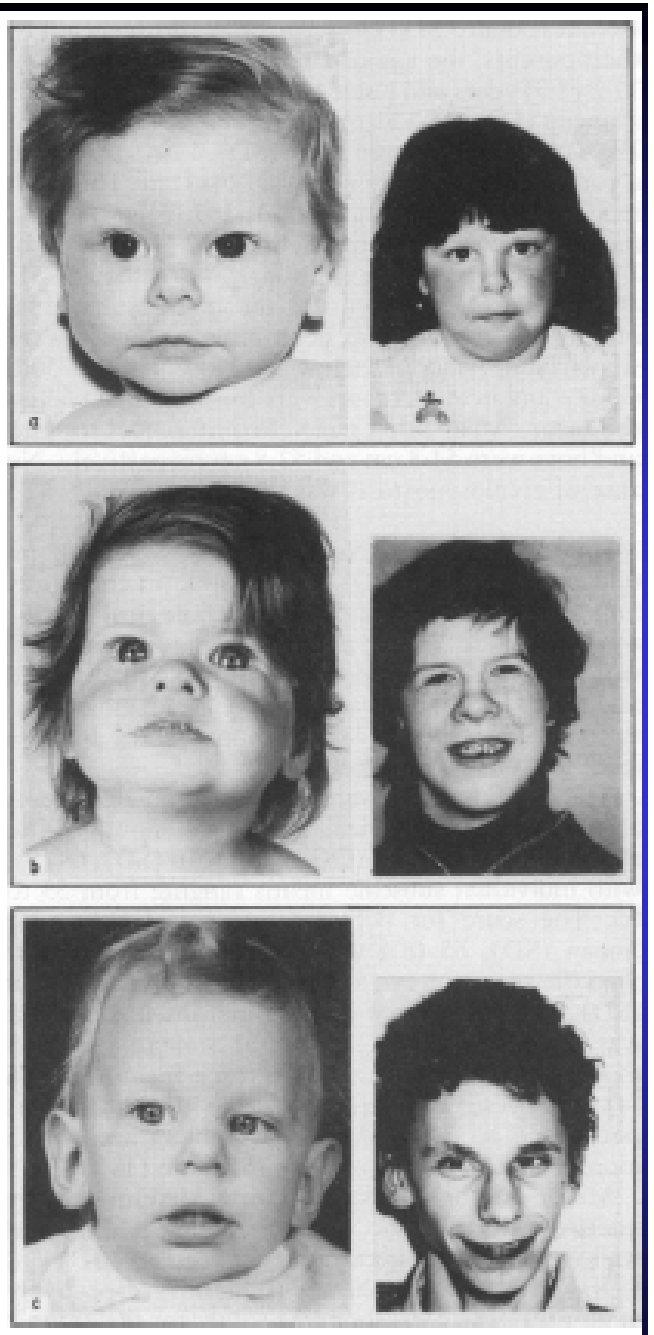


Fig. 2 *Facies of three children with Fanconi-type idiopathic infantile hypercalcaemia. Infant photographs taken around the time of diagnosis; second portrait taken at the time of study.*

Vitamin D supplements in pregnant Asian women: effects on calcium status and fetal growth

O G BROOKE, I R F BROWN, C D M BONE, N D CARTER, H J W CLEEVE, J D MAXWELL, V P ROBINSON, S M WINDER

RCT: Pregnant women with **initial 25(OH)D of 20 nmol/L**. Those randomized to 1000 IU daily of vit D2 **achieved serum 25(OH)D of 168 nmol/L** (one should wonder whether the dose or the 25(OH)D assay was wrong here).

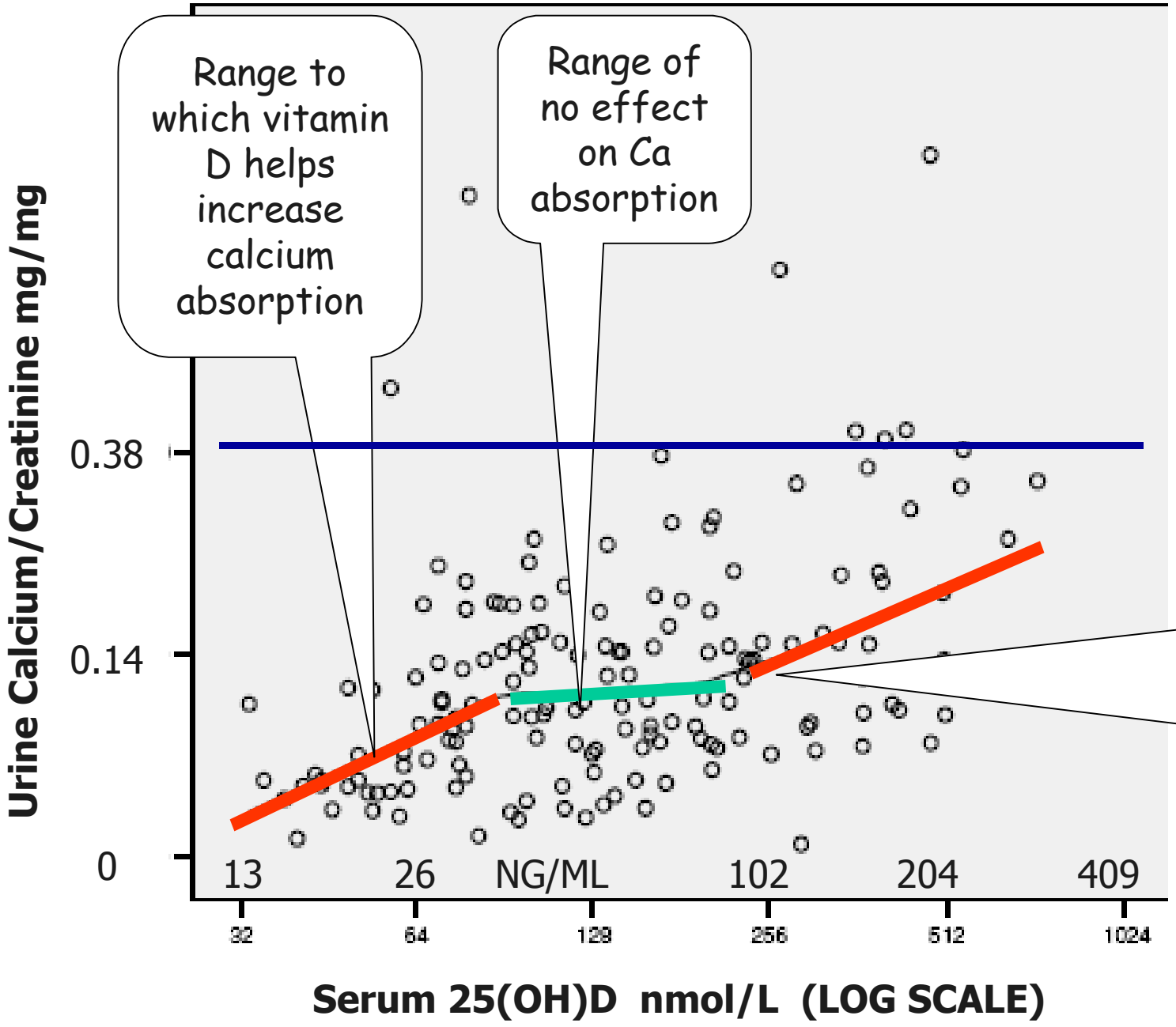
No adverse outcome, just smaller (better) fontanelle area and lower alkaline phosphatase of infants.

TABLE II—*Maternal and cord plasma biochemical results in two groups of pregnant Asian women and their infants. Results given as means ± SEM*

	At allocation (28 weeks, n = 126)	Control group (n = 67)		Treatment group (n = 59)	
		At term	Cord	At term	Cord
25 hydroxy vitamin D (nmol/l)	20·1 ± 1·9	16·2 ± 2·7	10·2 ± 2·0	168·0 ± 12·5	137·9 ± 10·8
Calcium (mmol/l)	2·42 ± 0·01	*2·51 ± 0·01	2·65 ± 0·02	*2·58 ± 0·02	2·71 ± 0·02
Phosphate (mmol/l)	0·94 ± 0·02	1·15 ± 0·06	1·84 ± 0·09	1·26 ± 0·03	2·04 ± 0·16
Albumin (g/l)	32·5 ± 0·18	29·1 ± 0·4	35·5 ± 0·5	29·4 ± 0·5	34·8 ± 0·7
Total alkaline phosphatase activity (IU/l)	83·1 ± 4·1	†136·1 ± 7·9	‡178·1 ± 15·9	†114·3 ± 6·5	‡108·1 ± 6·2
Heat-labile (placental) alkaline phosphatase activity (IU/l)	—	†77·8 ± 6·0	‡176·0 ± 15·1	†63·5 ± 3·3	‡101·0 ± 5·7
Vitamin D binding globulin (g/l)	46·8 ± 1·1	36·0 ± 1·5	24·0 ± 1·5	36·5 ± 1·8	23·5 ± 1·2

Difference between means (control group *v* treatment group) significant at: *p < 0·01, †p < 0·05, ‡p < 0·001.
Conversion: SI to traditional units—Plasma 25-hydroxy vitamin D: 1 nmol/l ≈ 0·4 ng/ml. Plasma clacium: 1 mmol/l ≈ 4 mg/100 ml. Plasma phosphate: 1 mmol/l ≈ 3·1 mg/100 ml. Plasma albumin: 1 g/l ≈ 0·1 g/100 ml.

Urine calcium / creatinine ratio vs 25(OH)D



Kimball et al. Clinical Biochem 2011 (in press)

REPORT BRIEF NOVEMBER 2010

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Advising the nation / Improving health

For more information visit www.iom.edu/vitamind

Dietary Reference Intakes for Calcium and Vitamin D

"Further, there is emerging evidence that too much of these nutrients may be harmful."

Calcium and vitamin D are two essential nutrients long known for their role in bone health. Over the last ten years, the public has heard conflicting messages about other benefits of these nutrients—especially vitamin D—and also about how much calcium and vitamin D they need to be healthy.

The safety of vitamin D

Traditionally

- Vitamin D safety is defined by the absence of **hypercalcemia** or hypercalciuria.

"Recent concerns":

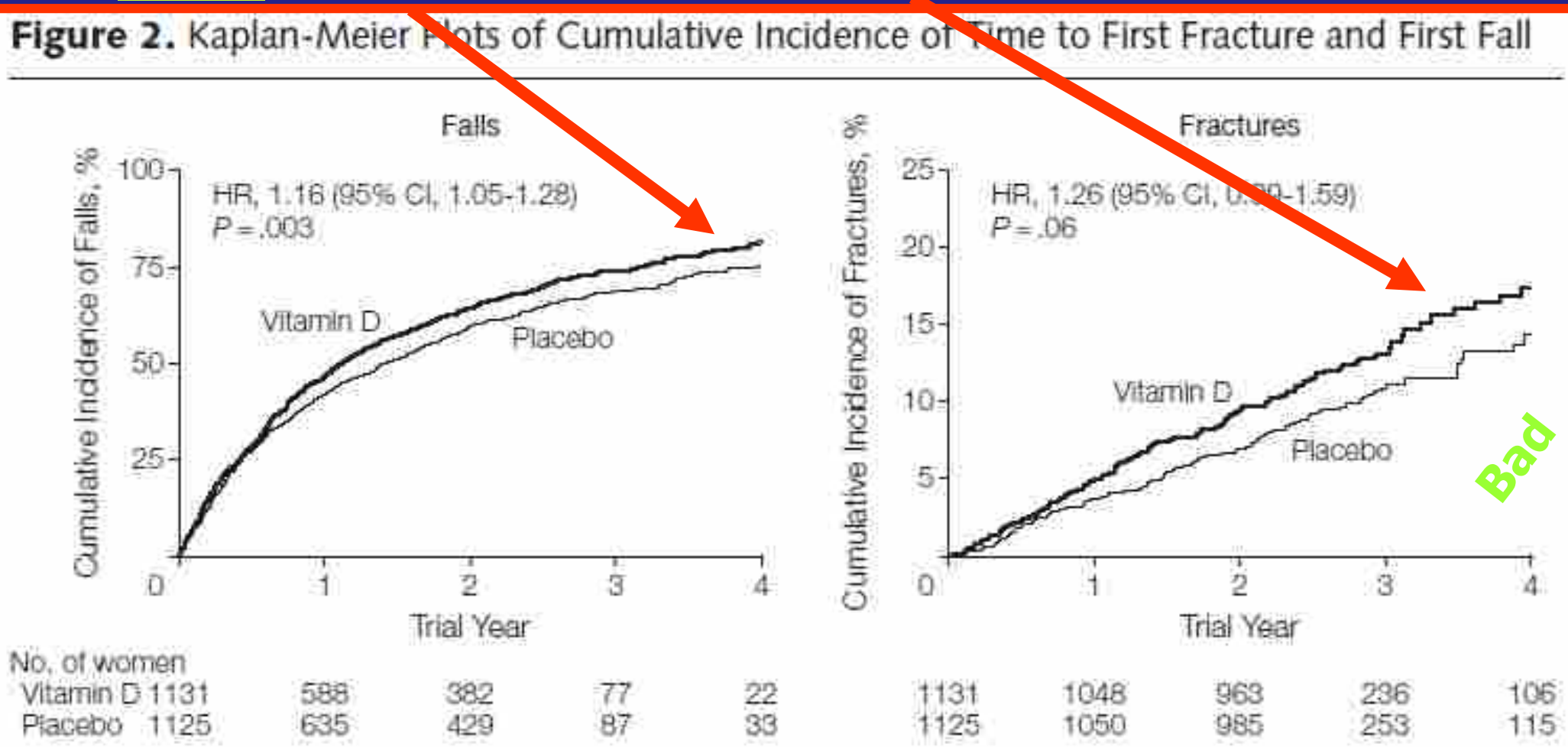
- **RCT** → 25(OH)D 125 nmol/L → More falls and fractures

- **U-shaped risk** curves in relation to serum 25(OH)D.

RCT: vitamin D3 dose, 500,000 IU once per year

(Total capacity of circulating DBP = 200,000 IU)

MORE FALLS AND FRACTURES IN THE VIT D GROUP!!



Sanders et al. *JAMA. 2010;303(18):1815-1822*

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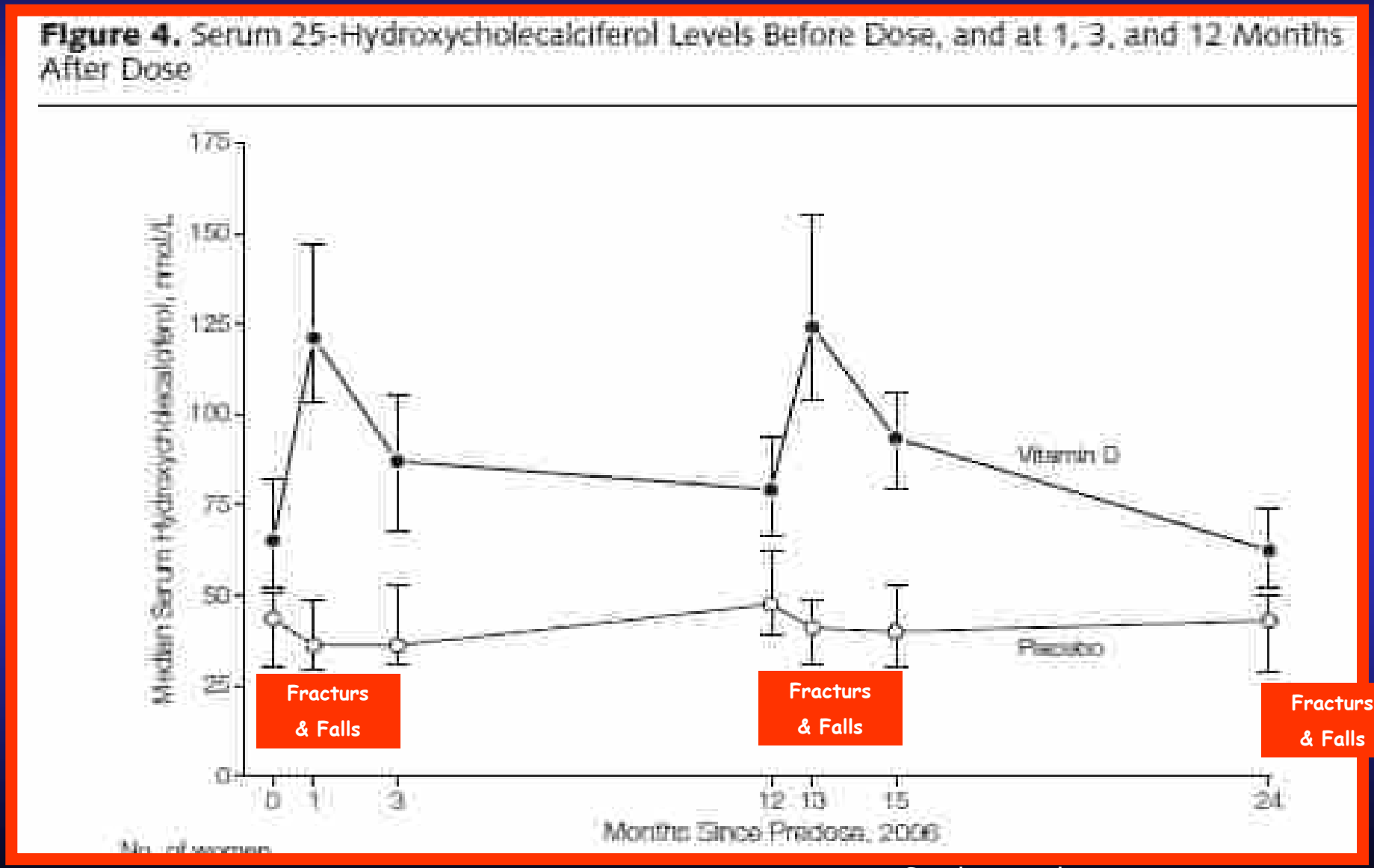


Bad

Sanders et al. *JAMA. 2010;303(18):1815-1822*

ORIGINAL ARTICLE

Endocrine Research

Effect of a Single Oral Dose of 600,000 IU of Cholecalciferol on Serum Calciotropic Hormones in Young Subjects with Vitamin D Deficiency: A Prospective Intervention Study

Cristiana Cipriani, Elisabetta Romagnoli, Alfredo Scillitani, Iacopo Chiodini, Rita Clerico, Vincenzo Carnevale, Maria Lucia Mascia, Claudia Battista, Raffaella Viti, Mauro Pileri, Cristina Eller-Vainicher, and Salvatore Minisola

Departments of Clinical Sciences (C.C., E.R., M.L.M., S.M.) and Dermatology (R.C.), University of Rome "Sapienza," 00161 Rome, Italy; Units of Endocrinology (A.S., C.B., R.V.), Internal Medicine (V.C.), and Clinical Chemistry (M.P.), Instituto di Ricovero e Cura a Carattere Scientifico (IRCCS) "Casa Sollievo della Sofferenza" Hospital, 71013 San Giovanni Rotondo, Italy; and Department of Medical Sciences (C., C.E.-V.), University of Milan, Fondazione Policlinico IRCCS, 20122 Milan, Italy

Context: Effects of vitamin D repletion in young people with low vitamin D status have not been investigated so far.

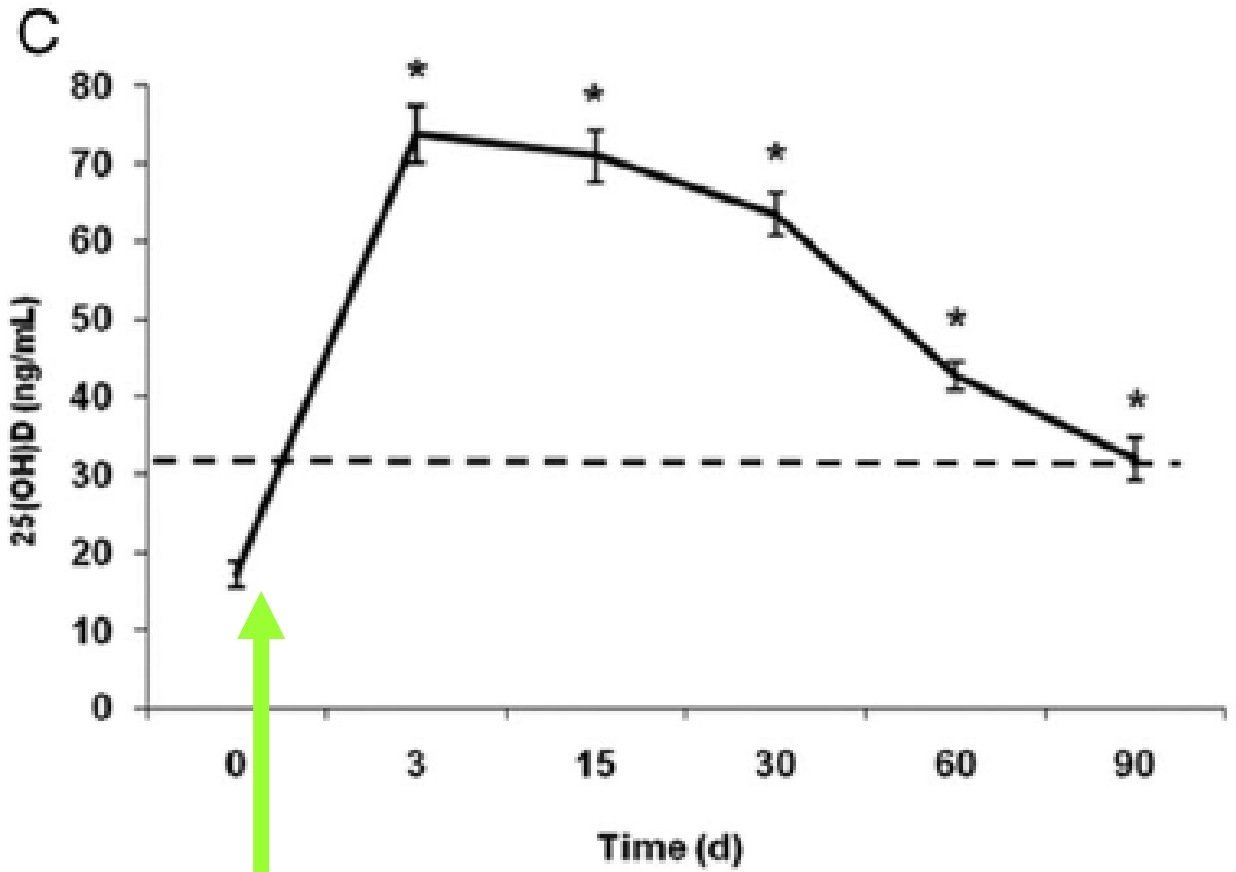
Objective: We evaluated the effect of a single massive dose of cholecalciferol on calcium metabolism at 3, 15, and 30 d, compared to baseline.

Design and Setting: We conducted a prospective intervention study in an ambulatory care setting.

Participants: Forty-eight young subjects with vitamin D deficiency participated in the study.

Intervention: A single oral dose of 600,000 IU of cholecalciferol was administered to each subject.

Main Outcome Measures: We evaluated serum changes of 25-hydroxyvitamin D [25(OH)D], 1,25-dihydroxyvitamin D, calcium, and PTH induced by a single load of cholecalciferol.



600 000 IU VitD_3

Annual High-Dose Oral Vitamin D and Falls and Fractures in Older Women

A Randomized Controlled Trial

Kerrie M. Sanders, PhD
Amanda L. Stuart, BappSc
Elizabeth J. Williamson, MA, PhD
Julie A. Simpson, PhD
Mark A. Kotowicz, MBBS, FRACP
Doris Young, MD, MBBS, FRACP
Geoffrey C. Nicholson, PhD, FRACP

Context Improving vitamin D status may be an important modifiable risk factor to reduce falls and fractures; however, adherence to daily supplementation is typically poor.

Objective To determine whether a single annual dose of 500 000 IU of cholecalciferol administered orally to older women in autumn or winter would improve adherence and reduce the risk of falls and fracture.

Design, Setting, and Participants A double-blind, placebo-controlled trial of 2256 community-dwelling women, aged 70 years or older, considered to be at high risk of fracture were recruited from June 2003 to June 2005 and were randomly assigned to receive cholecalciferol or placebo each autumn to winter for 3 to 5 years. The study concluded in 2008.

Intervention 500 000 IU of cholecalciferol or placebo.

Main Outcome Measures Falls and fractures were ascertained using monthly calendars; details were confirmed by telephone interview. Fractures were radiologically confirmed. In a substudy, 137 randomly selected participants underwent serial blood sampling for 25-hydroxycholecalciferol and parathyroid hormone levels.

Results Women in the cholecalciferol (vitamin D) group had 171 fractures vs 135 in the placebo group; 837 women in the vitamin D group fell 2892 times (rate, 83.4 per 100 person-years) while 769 women in the placebo group fell 2512 times (rate, 72.7 per 100 person-years; incidence rate ratio [IRR], 1.15; 95% confidence interval [CI]

THE RESULTS OF RANDOMIZED controlled trials investigating the effects of cholecalciferol (vitamin D) supplementation on falls and fractures have been inconsistent.[1-11] Some meta-analyses conclude that 700 to 800 IU of vitamin D daily reduces fracture risk by 13% to 26%,[1,10] whereas others conclude that vitamin D is ineffective. A Cochrane

ORIGINAL ARTICLE

Endocrine Research

Effect of a Single Oral Dose of 600,000 IU of Cholecalciferol on Serum Calciotropic Hormones in Young Subjects with Vitamin D Deficiency: A Prospective Intervention Study

Cristiana Cipriani, Elisabetta Romagnoli, Alfredo Scillitani, Iacopo Chiodini, Rita Clerico, Vincenzo Carnevale, Maria Lucia Mascia, Claudia Battista, Raffaella Viti, Mauro Pileri, Cristina Eller-Vainicher, and Salvatore Minisola

Departments of Clinical Sciences (C.C., E.R., M.L.M., S.M.) and Dermatology (R.C.), University of Rome "Sapienza," 00161 Rome, Italy; Units of Endocrinology (A.S., C.B., R.V.), Internal Medicine (V.C.), and Clinical Chemistry (M.P.), Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS) "Casa Sollievo della Sofferenza" Hospital, 71013 San Giovanni Rotondo, Italy; and Department of Medical Sciences (I.C., C.E.-V.), University of Milan, Fondazione Policlinico IRCCS, 20122 Milan, Italy

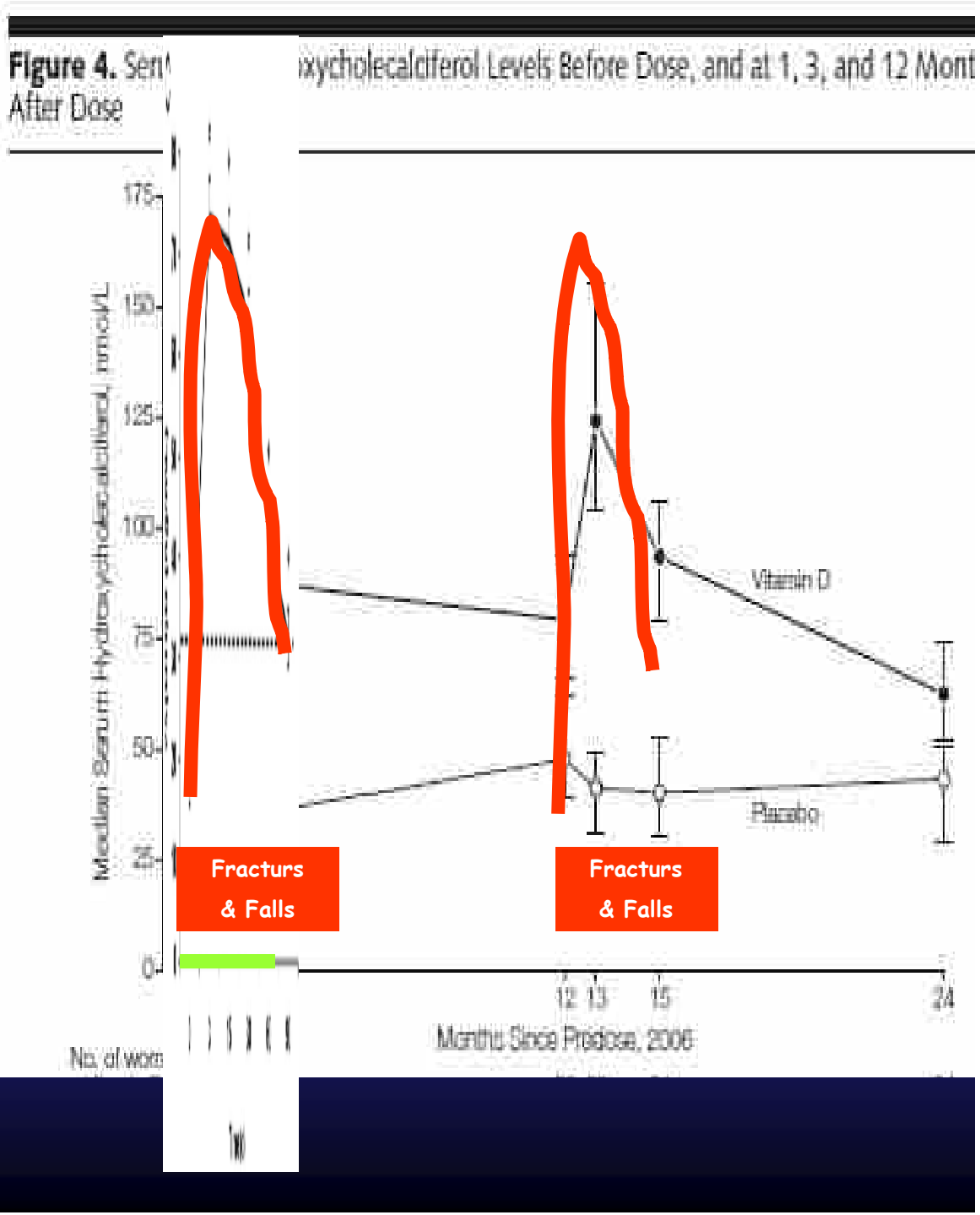
Context: Effects of vitamin D repletion in young people with low vitamin D status have not been investigated so far.

Objective: We evaluated the effect of a single massive dose of cholecalciferol on calcium metabolism at 3, 15, and 30 d, compared to baseline.

Design and Setting: We conducted a prospective intervention study in an ambulatory care setting.

Participants: Forty-eight young subjects with vitamin D deficiency participated in the study.

Intervention: A single oral dose of 600,000 IU of cholecalciferol was administered to each subject.



In New Zealand, 36 deg South Latitude, Fracture Rates cycle **annually** even without ice and snow.

JOURNAL OF BONE AND MINERAL RESEARCH
Volume 19, Number 5, 2004
Published online on January 19, 2004; doi: 10.1359/JBMR.040125
© 2004 American Society for Bone and Mineral Research

Seasonal Periodicity of Serum Vitamin D and Parathyroid Hormone, Bone Resorption, and Fractures: The Geelong Osteoporosis Study

Julie A Pasco,[1] Margaret J Henry,[1] Mark A Kotowicz,[1] Kerrie M Sanders,[1] Ego Seeman,[2] John R Pasco,[3] Hans G Schneider,[4] and Geoffrey C Nicholson[1]

ABSTRACT: In this population-based study, seasonal periodicity was seen with reduced serum vitamin D, increased serum PTH, and increased bone resorption in winter. This was associated with an increased proportion of falls resulting in fracture and an increased risk of wrist and hip fractures.

Pasco et al. J Bone Miner Res 2004;19:752–758.

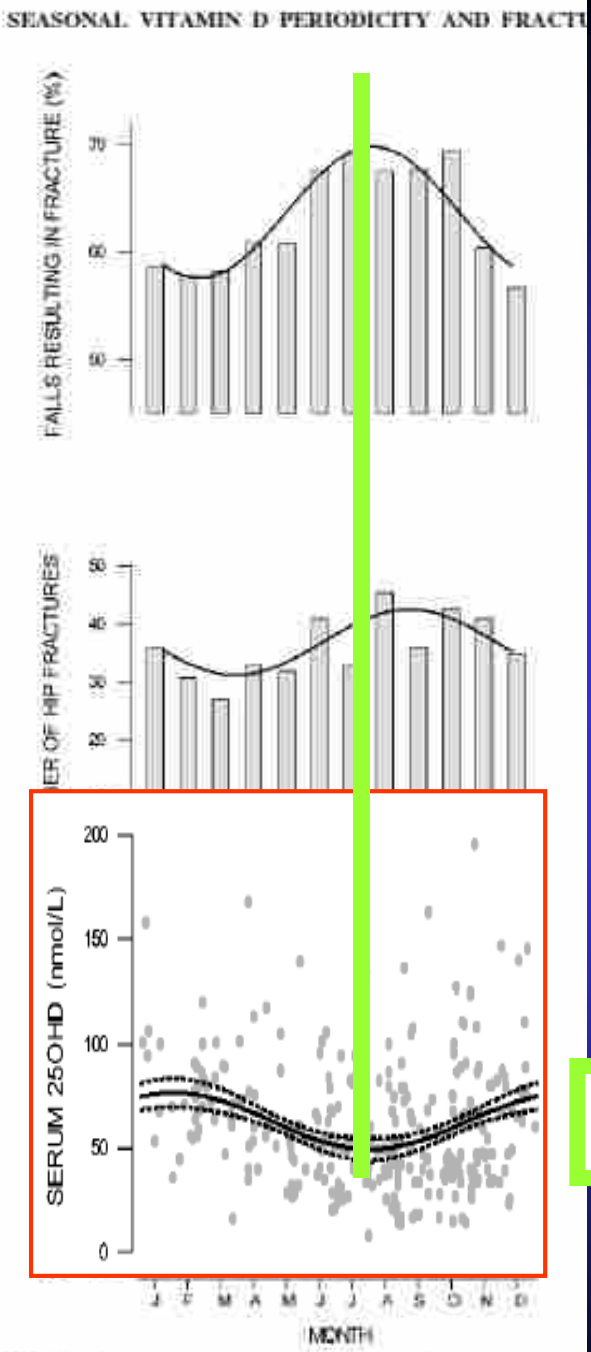


FIG. 2. Histograms showing the proportion of falls resulting in fracture and the monthly totals of hip and wrist fractures. Sine curve models describing the periodicity of the data are superimposed.

FALLS

HIP FRACTURES

25(OH)D

Musculoskeletal Health:

Fractures and falls happened with 125 nmol/L (50 ng/mL) because of the ANNUAL dosing protocol.

Basic Pharmacology of vit D:

1. dosing intervals up to 3 months are appropriate.
2. One year's total dose once annually is "**TOXIC**". → *more falls and fractures*

The safety of vitamin D

Traditionally

- Vitamin D safety is defined by the absence of **hypercalcemia** or hypercalciuria.

"Recent concerns":

- **RCT** → 25(OH)D 125 nmol/L → More falls and fractures

- **U-shaped risk** curves in relation to serum 25(OH)D.

1 U-SHAPED RISK CURVE FOR PROSTATE CANCER

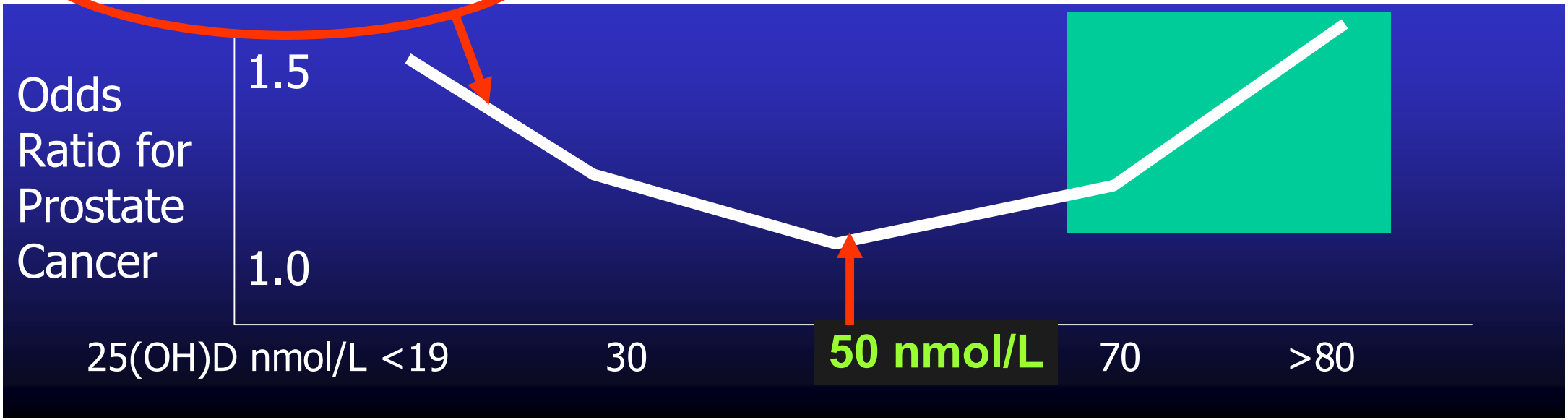
Int. J. Cancer: **108,** 104–108 (2004)

Pentti TUOHIMAA1*, Leena TENKANEN2, Merja AHONEN1, Sonja LUMME2, Egil JELLUM3, Go¨ran HALLMANS4, Pa¨r STATTIN5, Sverre HARVEI6, Timo HAKULINEN7, Tapio LUOSTARINEN7, Joakim DILLNER8, Matti LEHTINEN9 and Matti HAKAMA10

1Medical School, University of Tampere, Tampere, Finland

TABLE III – OR AND 95% CI OF PROSTATE CANCER BY 25(OH)-VITAMIN D LEVEL AND COUNTRY

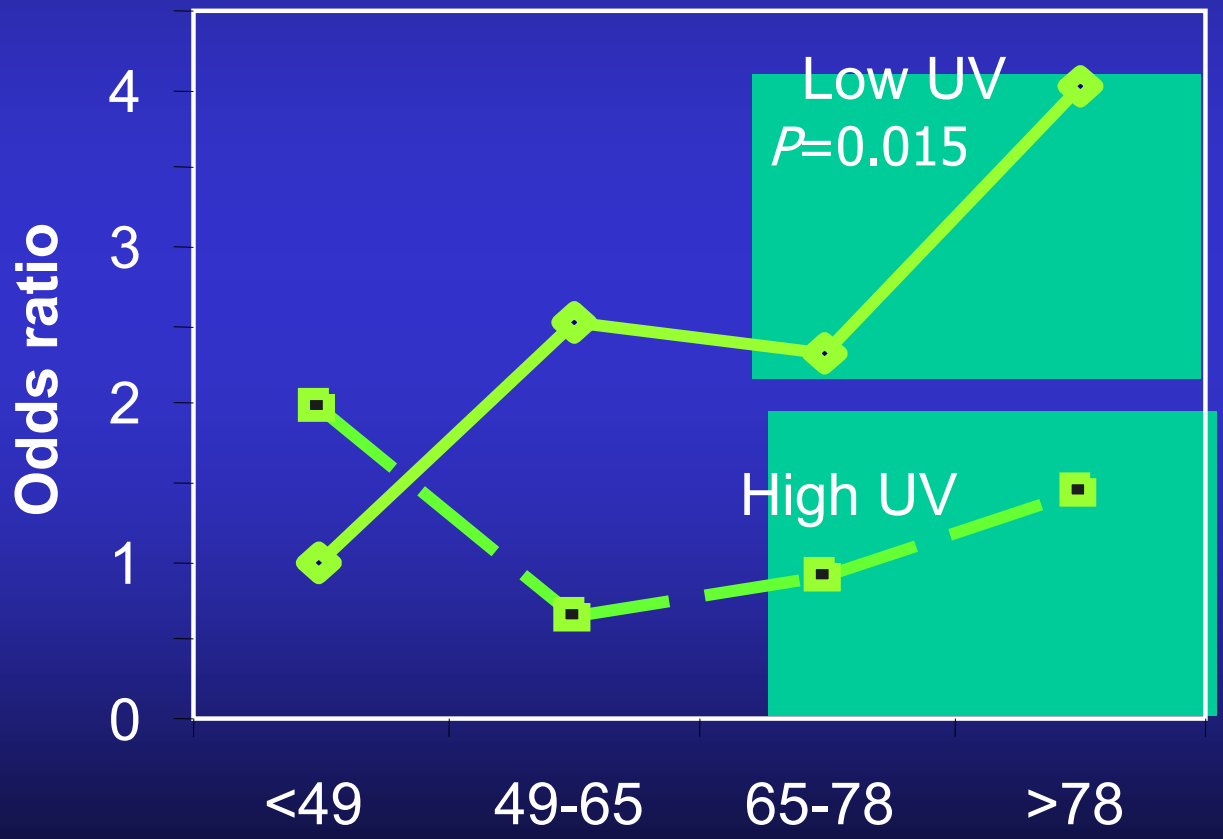
Vitamin D level (nmol/l)	All countries		Norway		Finland		Sweden	
	Number of cases	OR (CI)	Number of cases	OR (CI)	Number of cases	OR (CI)	Number of cases	OR (CI)
≤ 19	19	1.5 (0.8–2.7)	5	0.9 (0.3–2.8)	13	2.4 (1.1–5.1)	1	1.3 (0.1–12.5)
20–39	169	1.3 (0.98–1.6)	89	1.2 (0.9–1.7)	68	1.9 (1.1–3.1)	12	0.7 (0.3–1.4)
40–59 (ref.)	229	1	155	1	29	1	45	1
60–79	138	1.2 (0.9–1.5)	98	1.2 (0.8–1.7)	18	1.4 (0.7–2.8)	22	1.0 (0.5–1.8)
≥80	67	1.7 (1.1–2.4)	57	1.8 (1.1–2.8)	4	1.2 (0.4–3.8)	6	1.5 (0.5–4.4)



2

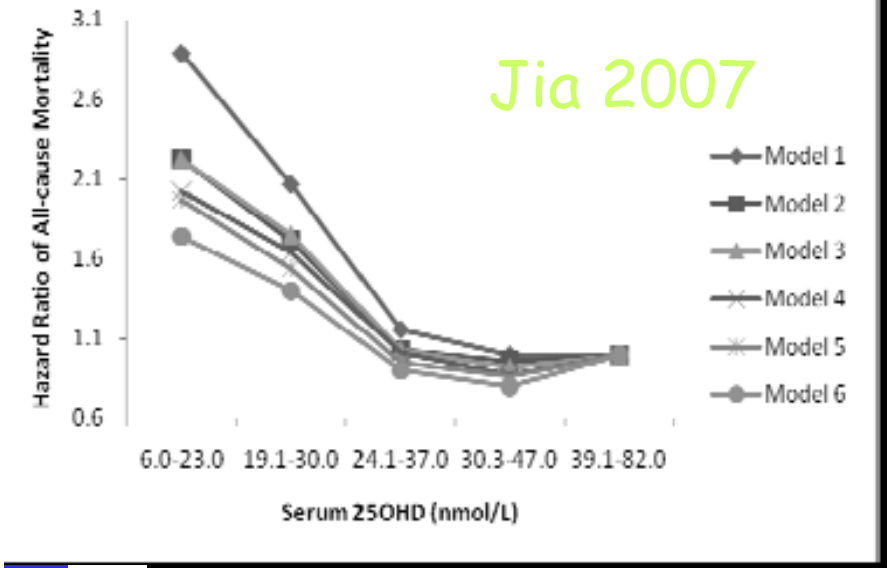
Effect of environmental ultraviolet light on the relationship between baseline serum 25(OH)D concentration and the odds of pancreatic cancer.

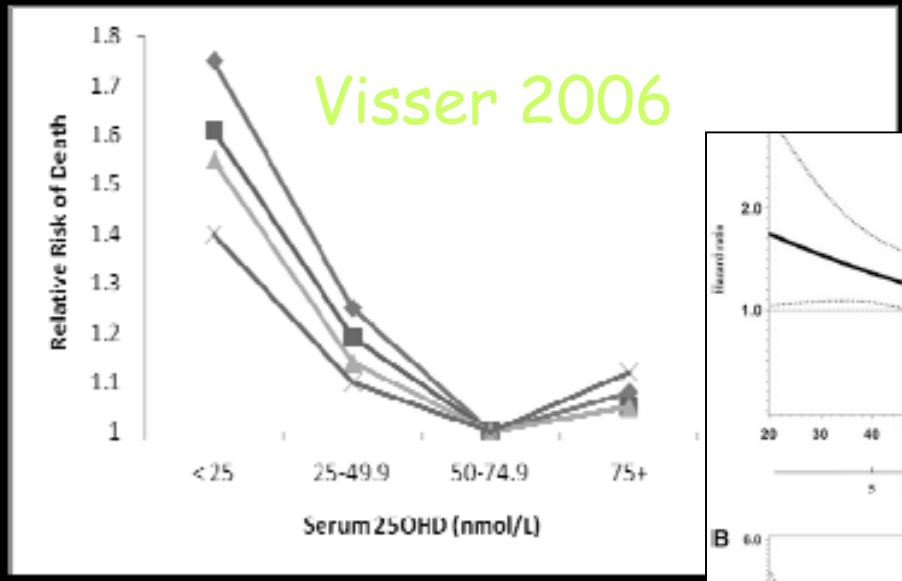
Data from Table 4 of Stolzenberg-Solomon *et al.* (Cancer Res 2009;69(4):1439–47) who reported that among subjects residing in regions of low estimated annual ultraviolet light B [UVB] exposure, higher 25(OH)D concentrations were positively associated with pancreatic cancer.

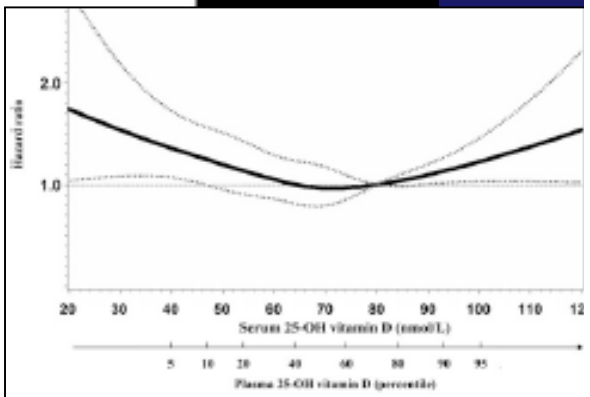


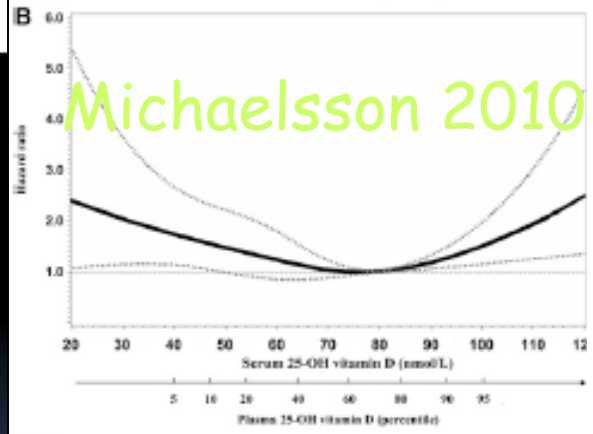
R Vieth *ANTICANCER RESEARCH* *29*: 3675-3684 (2009)

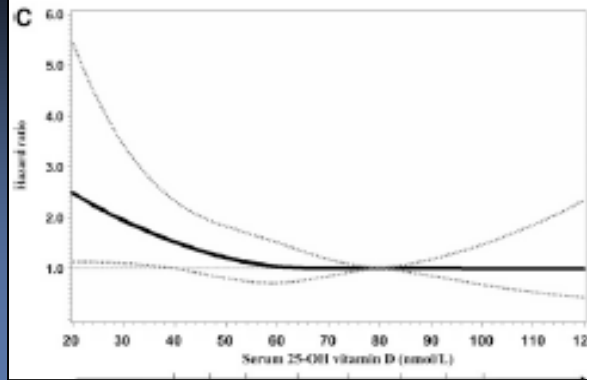
IOM Figures: U-Shaped Risk for MORTALITY











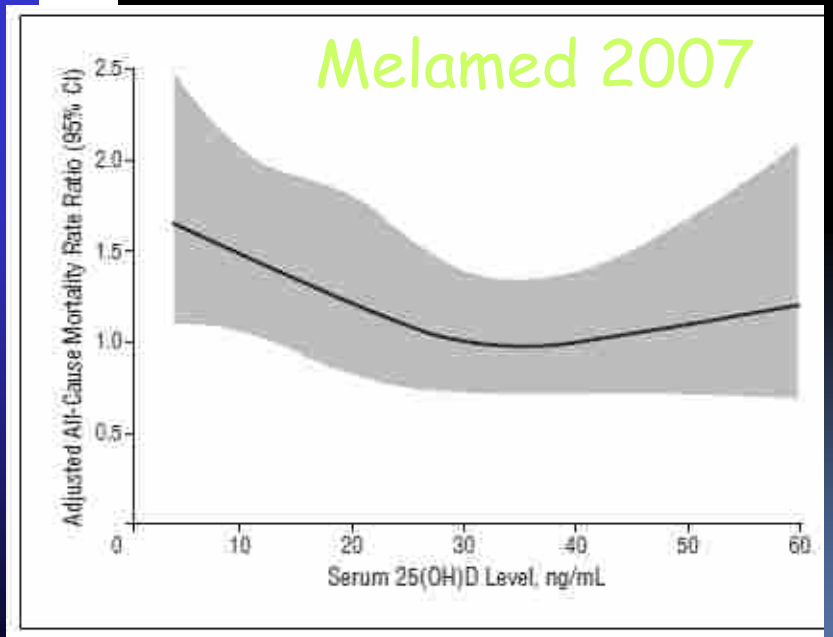


Figure 1. Restricted cubic spline showing the fully adjusted associations between serum 25-hydroxyvitamin D (25[OH]D) levels and all-cause

ANTICANCER RESEARCH 29: 3675-3684 (2009)

Review

How to Optimize Vitamin D Supplementation to Prevent Cancer, Based on Cellular Adaptation and Hydroxylase Enzymology

REINHOLD VIETH

Departments of Nutritional Sciences, and Laboratory Medicine and Pathobiology, University of Tor... Pathology and Laboratory Medicine, Mount Sinai Hospital, Toronto, M5G 1X5, ON, C...

Abstract. *The question of what makes an 'optimal' vitamin D intake is usually equivalent to, 'what serum 25-hydroxyvitamin D [25(OH)D] do we need to stay above to minimize risk of disease?'. This is a simplistic question that ignores the evidence that fluctuating concentrations 25(OH)D may in themselves be a problem*

about vitamin D and ... 25(OH)D con... that d...

INTRO...

This chapter focuses o... olecalciferol and to a les... if it were a drug. While ... drug and a dietary supplem... pharmacological perspective...

...ator ...etermining ... the "therapeutic ...xic versus beneficial

...his chapter I will return to these ques... ...n introductory overview to the topic. Table

(2004)

UICC Publication of the International Union Against Cancer

EDITOR

...hesis to Explain the U-Shaped Risk Curve for Prostate Cancer ... ...Hydroxyvitamin D in

... Medicine and Pathology, University of Toronto ... ...and Laboratory Medicine, Mount Sinai H...

...ental ...point ...$(OH)_2D$

...CLINE ...(OH)D

...plications ...erapeutics

...eywords Latitude • Seasonality • Enzyme kinetics • Pharmacokinetics • Feedback control • Regulation • Dosage interval • Cholecalciferol • Paracrine

14.1 Introduction

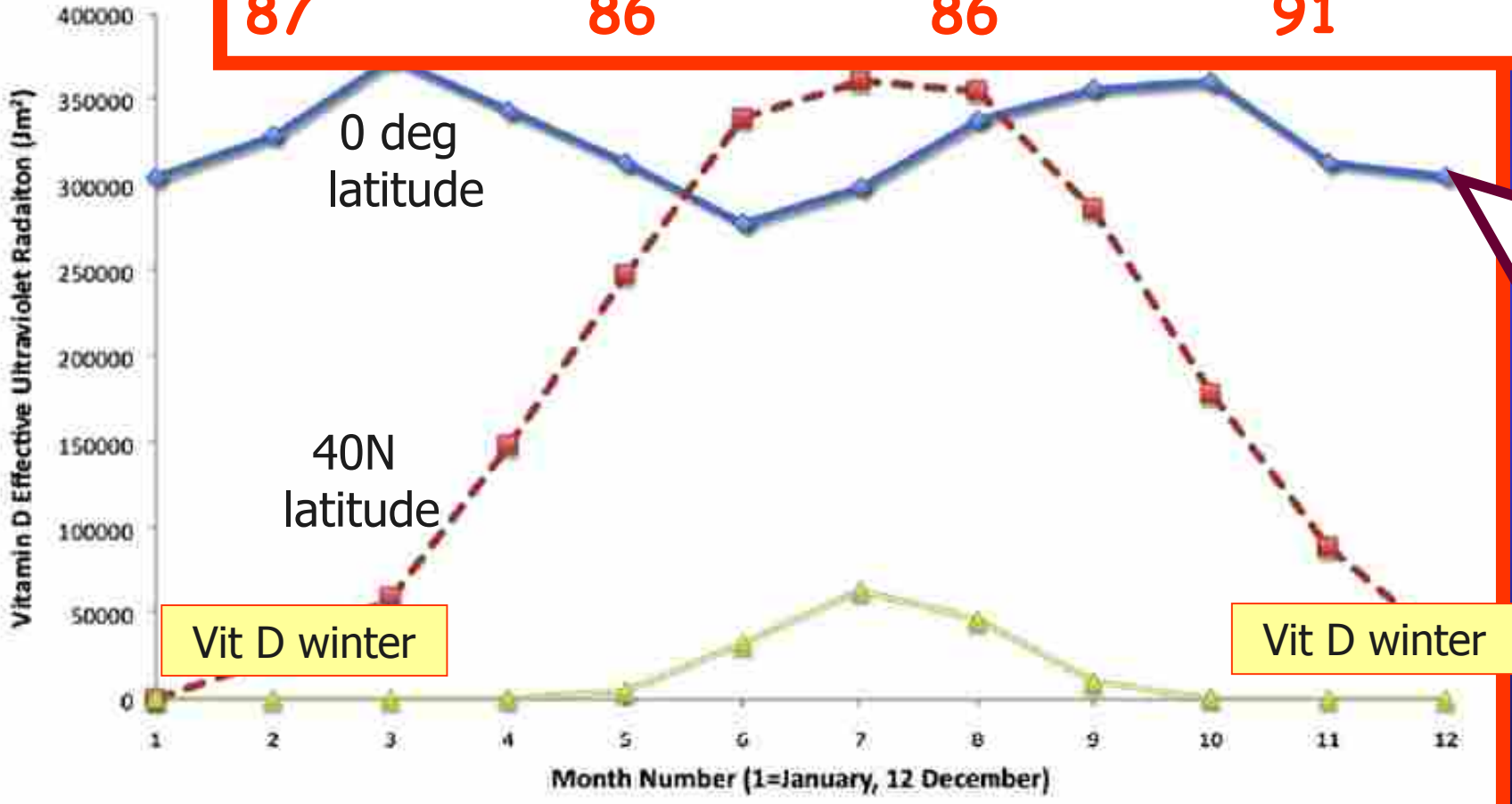
1. U-shaped 25(OH)D risk curves are specific to high latitudes.

2. Large pulse doses cause adverse, toxic effects. (RCT to "prove" this would be unethical)

Higher Latitude not only lowers total UVB for vitamin D production, but also INCREASES UVB FLUCTUATIONS

Miljkovic, Ethnicity & Disease 2011 **Men in Tobago**

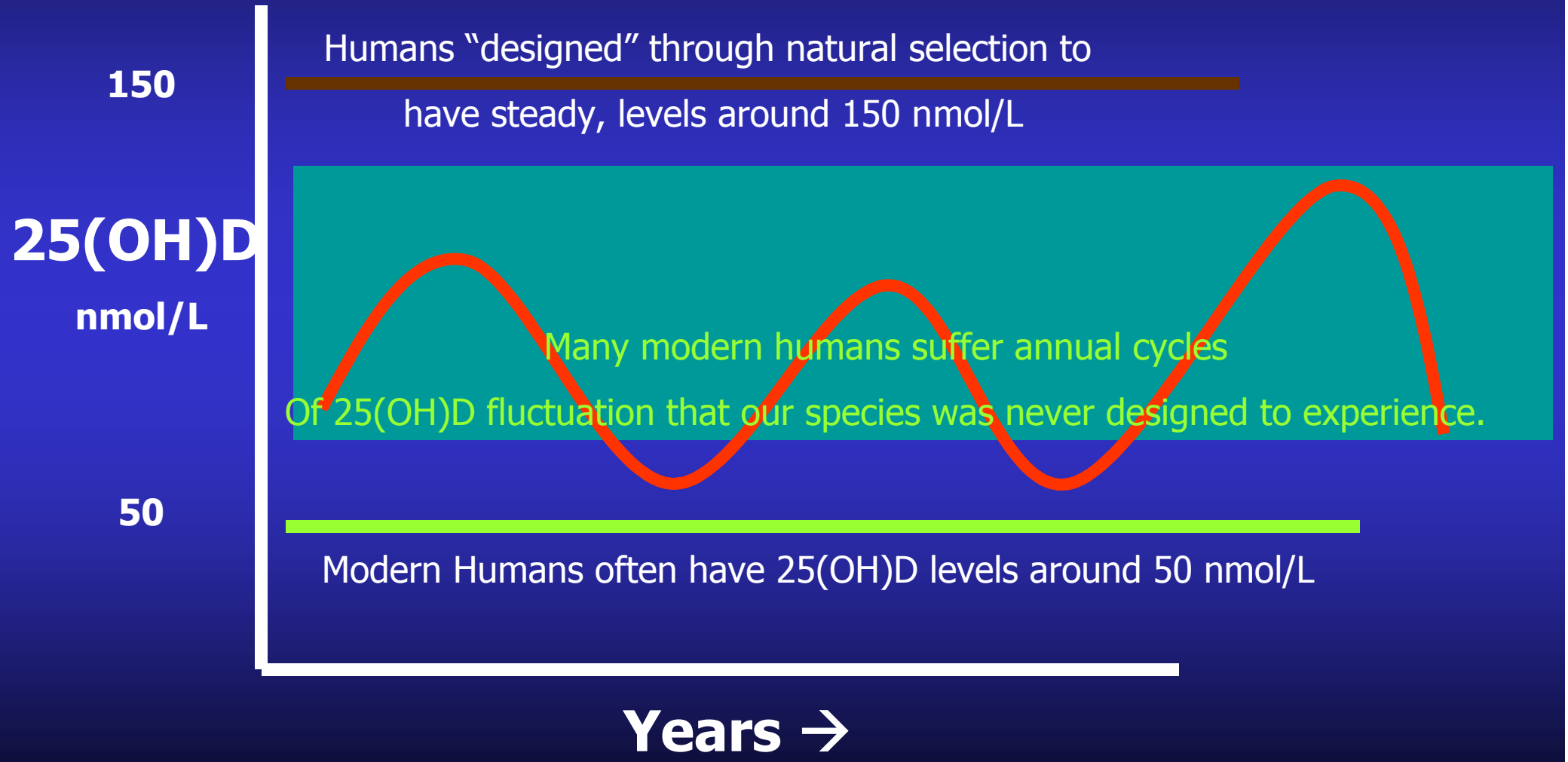
87	86	86	91	25(OH)D



The human "normal"

MG Kimlin (2008) *Molecular Aspects of Medicine* 29 453–461

Perpetually rising and falling 25(OH)D levels are adverse, and explain U-shaped risk curves for vitamin D



R Vieth *ANTICANCER RESEARCH* *29*: 3675-3684 (2009)

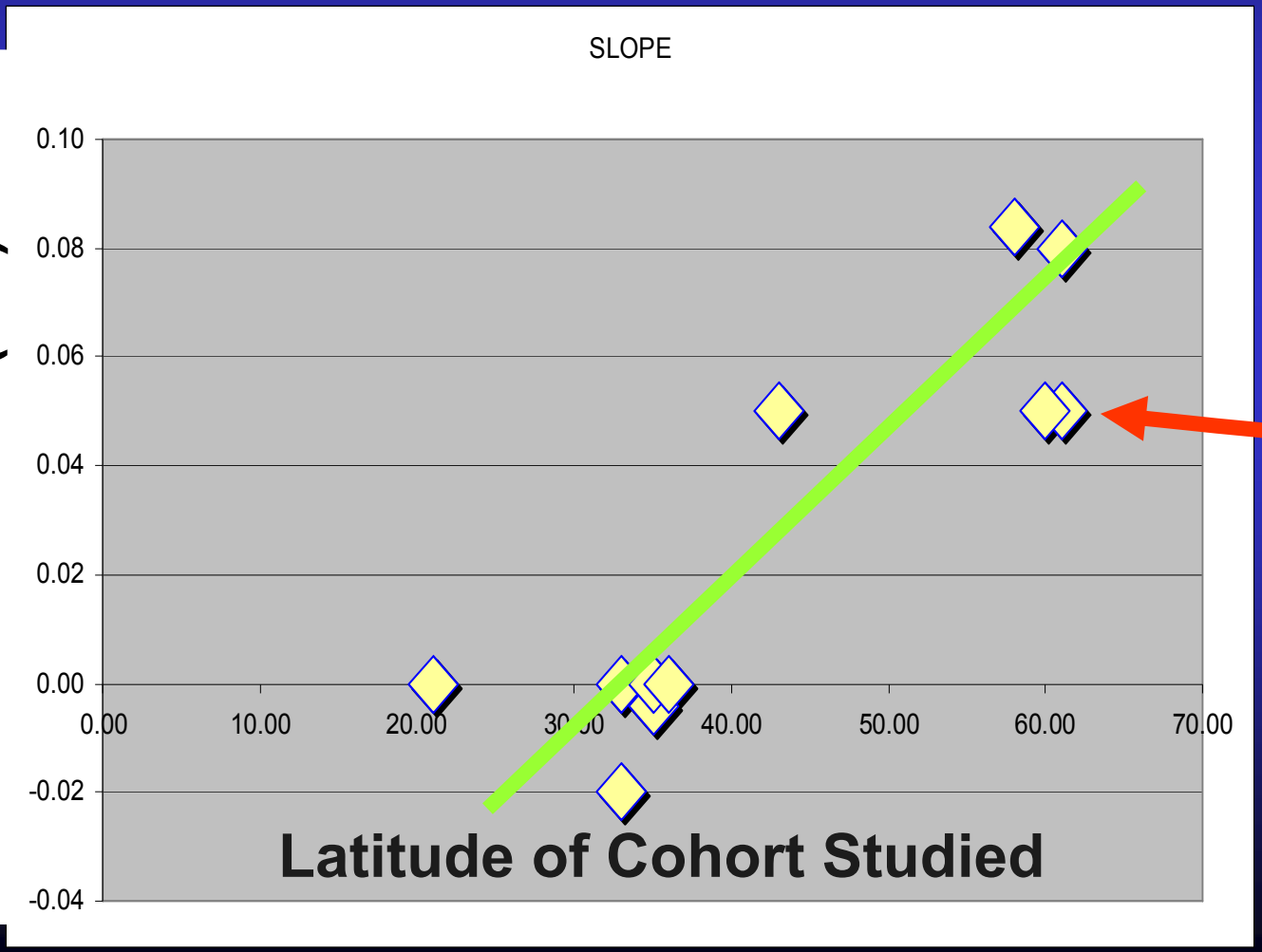
Data for Prostate and Pancreatic Cancer from IOM report on calcium and vitamin D:

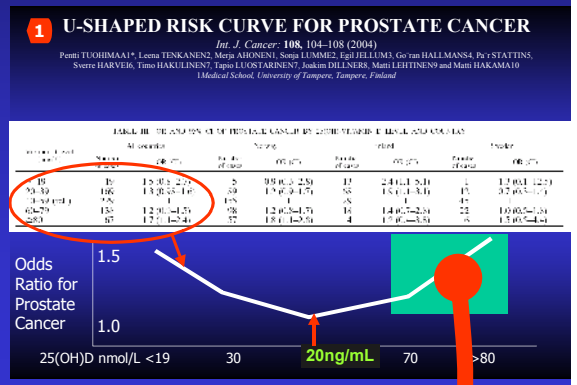
Below are the Risk Differences (Slope) for the highest 25(OH)D quartiles, for Prostate and Pancreatic cancers

RELATIONSHIPS WITH THE LATITUDE OF THE STUDY SUBJECTS

AUTHOR	CANCER	LATITUDE	SLOPE IOM	CASES	CONTROLS	WEIGHTING
Tuohiima	prostate	61.00	0.50	622.00	1,451.00	2,073.00
Ahonen	prostate	60.00	0.20	149.00	566.00	715.00
Michaels	allcancer	58.00	0.08			1,194.00
Stolzenb	pancreat	61.00	0.08	200.00	400.00	600.00
Stolzenb	pancreat	43.00	0.05	463.00	635.00	1,098.00
Stolzenb	pancreat	33.00	0.00	489.00	698.00	1,187.00
Ahn et.	prostate	35.00	-0.15	741.00	781.00	1,522.00
Jacobs	prostate	33.00	0.04	83	166	249.00
Li	prostate	35.00	0.00	492.00	664.00	1,156.00
Platz	prostate	36.00	0.42	460.00	460.00	920.00
Nomura	prostate	21.00	0.00	136.00	136.00	272.00

Highest 25(OH)D quartiles, and their Risk differences for Prostate and Pancreatic cancers: RELATIONSHIPS WITH LATITUDE





"U-Shaped Risk Curves"

- They relate to serum 25(OH)D, NOT vitamin D supplementation (unless annual doses)
- They can occur in regions with large seasonal fluctuations in UVB light and serum 25(OH)D
- The mechanism involves inappropriate breakdown of 25(OH)D and 1,25(OH)2D inside of cells, because of difficulty in turning off CYP24 enzyme

The safety of vitamin D

Traditionally

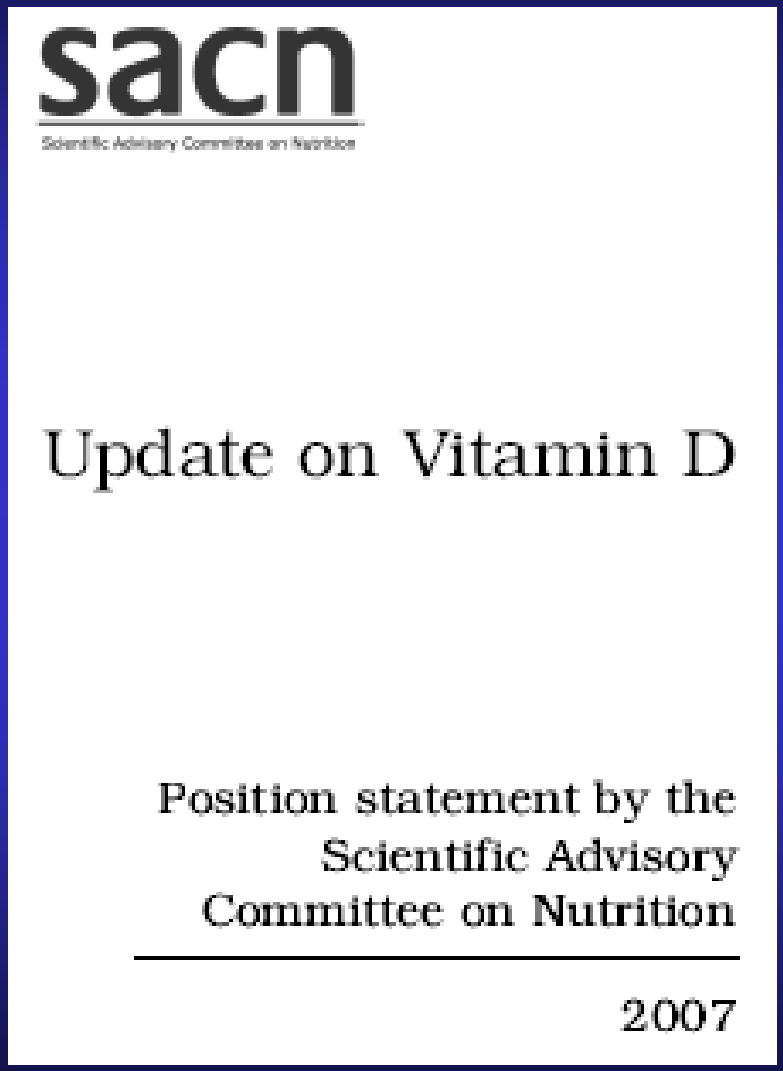
- Vitamin D safety is defined by the absence of **hypercalcemia** or hypercalciuria.

"Recent concerns":

- **RCT** → 25(OH)D 125 nmol/L → More falls and fractures

- **U-shaped risk** curves in relation to serum 25(OH)D.

Why is policy slow to adapt to evidence?



The Levels of Decision-Making and the Risk/Benefit Ratio

1. Personal care decisions (flexible and possibly only during sickness).
2. Physician care of patient (flexible and possibly only during sickness).
3. Government Health policy: for all society and for years to come.