VITAMIN D

How Much Do We Make?
How Much Do We Need?
For What Endpoints?

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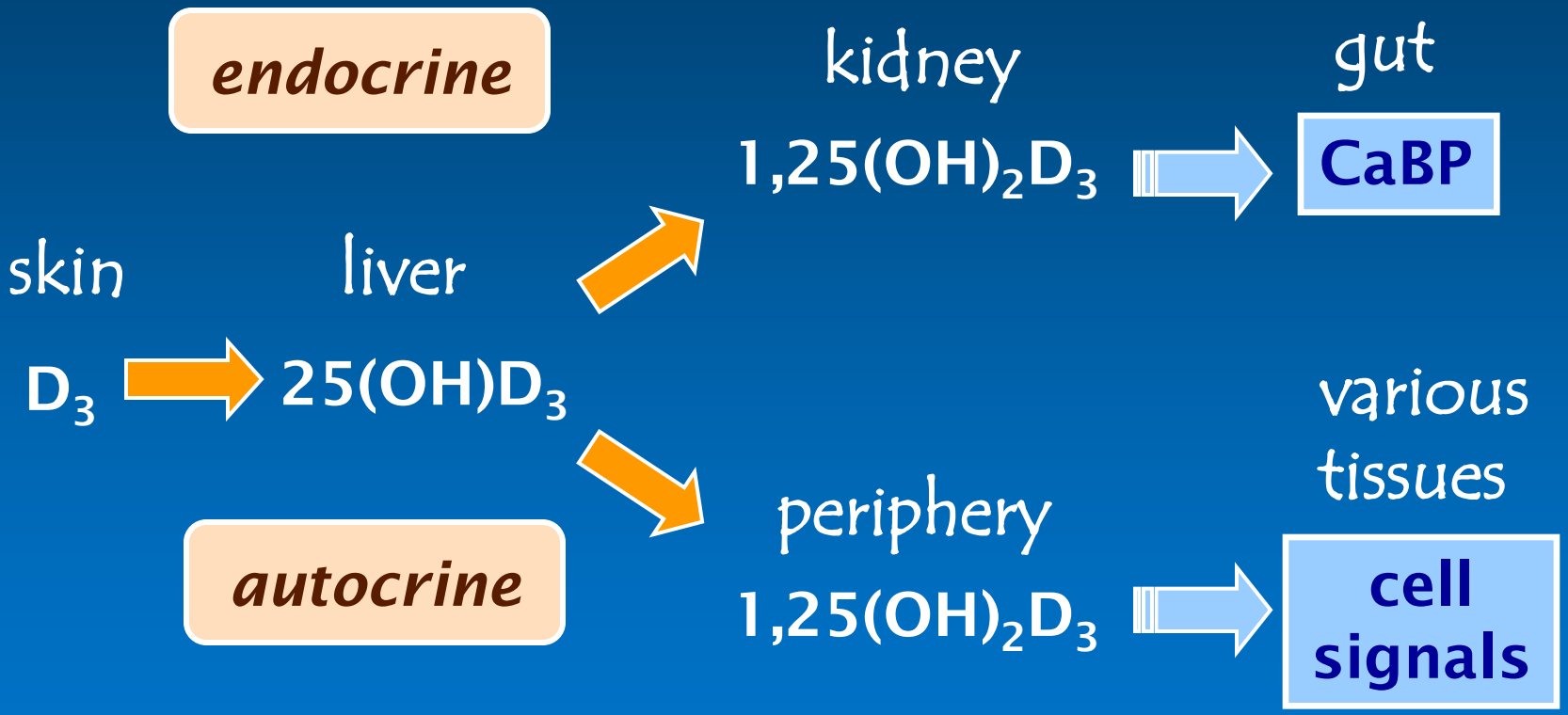
OBJECTIVES

1. describe the D_3 to 25(OH)D conversion
2. cite four systems in which vitamin D inadequacy may contribute to disease
3. cite evidence with respect to the serum level of 25(OH)D that minimizes these effects
4. describe the skin vitamin D response to UV-B radiation
5. recall the amount of additional D needed to raise serum 25(OH)D by any given amount

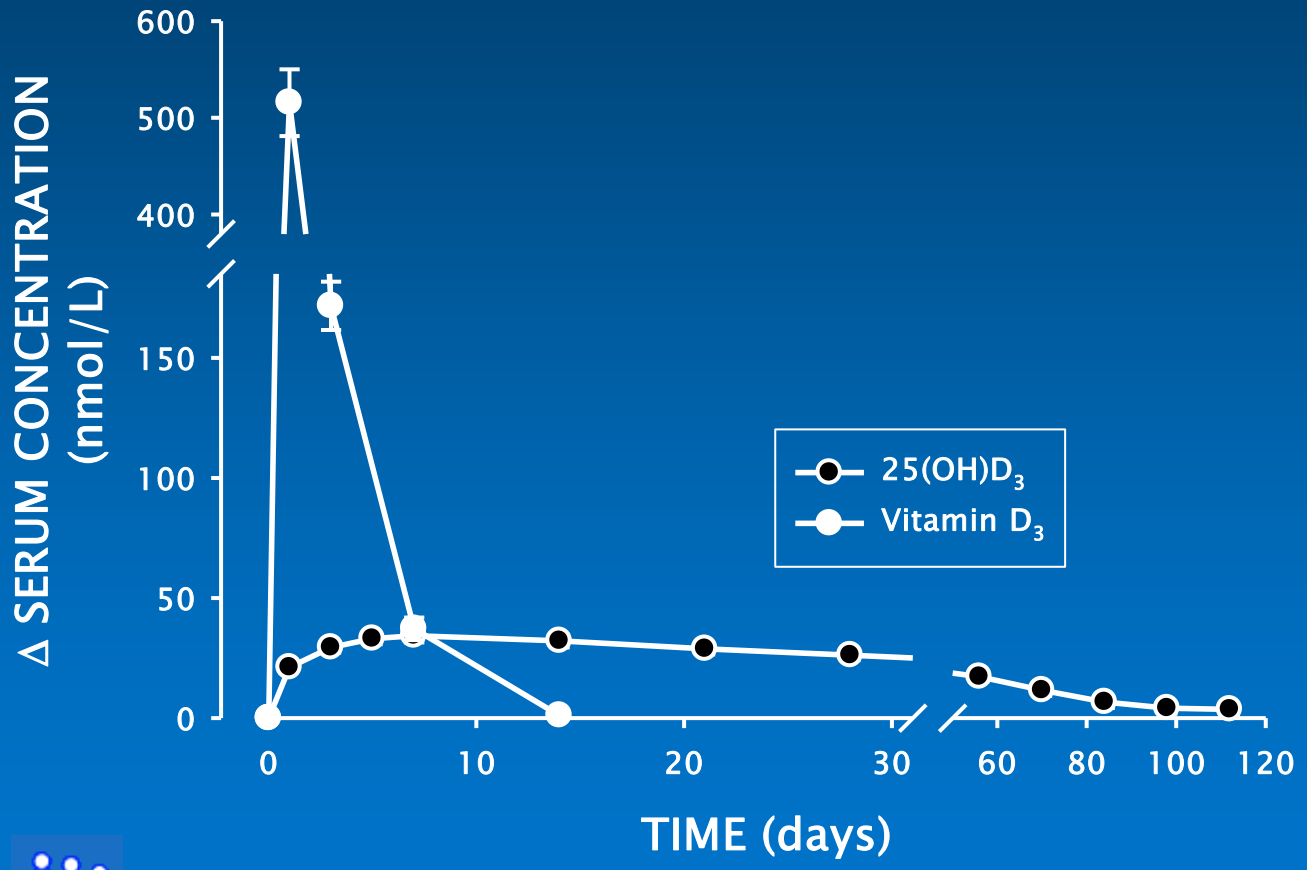
VIT D – CANONICAL SCHEME

skin liver kidney gut

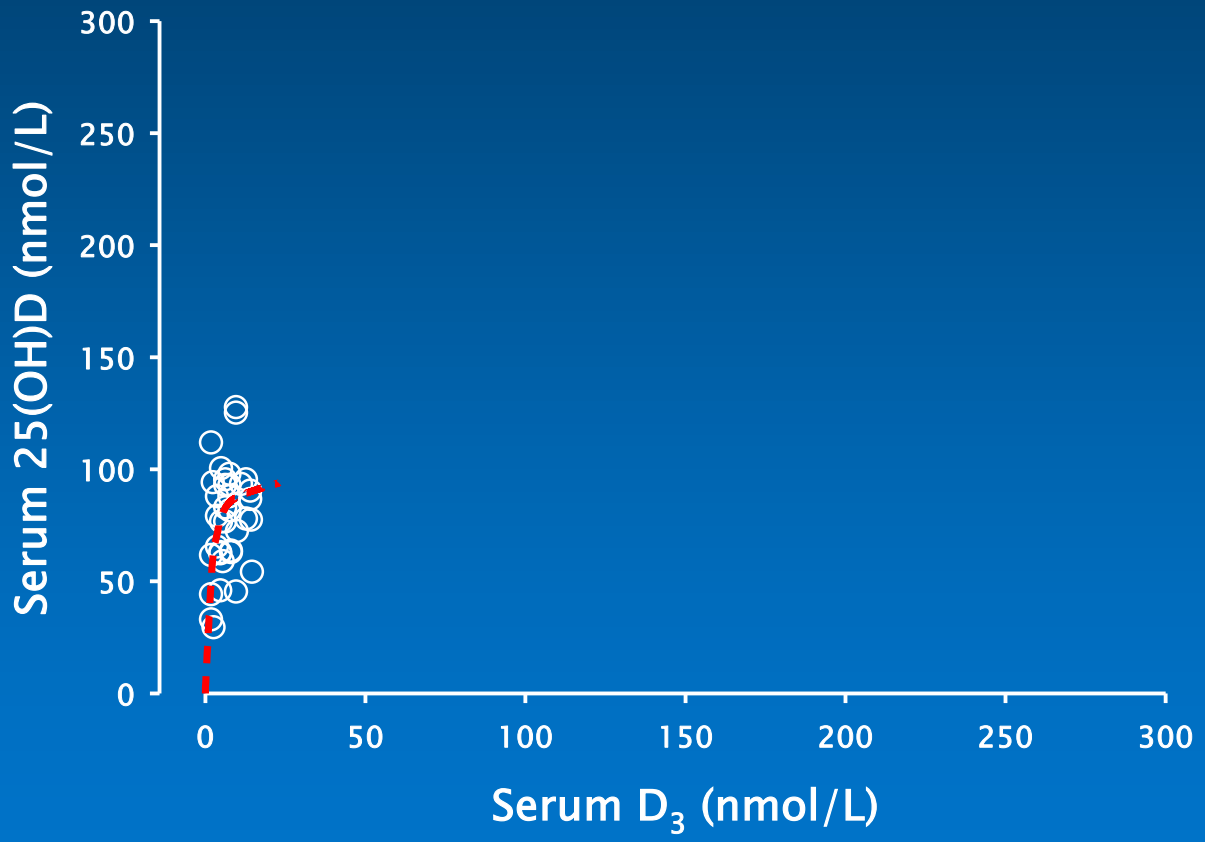
VIT D – EXPANDED SCHEME



VITAMIN D_3 – 100,000 IU



D_3 to 25(OH)D_3 CONVERSION



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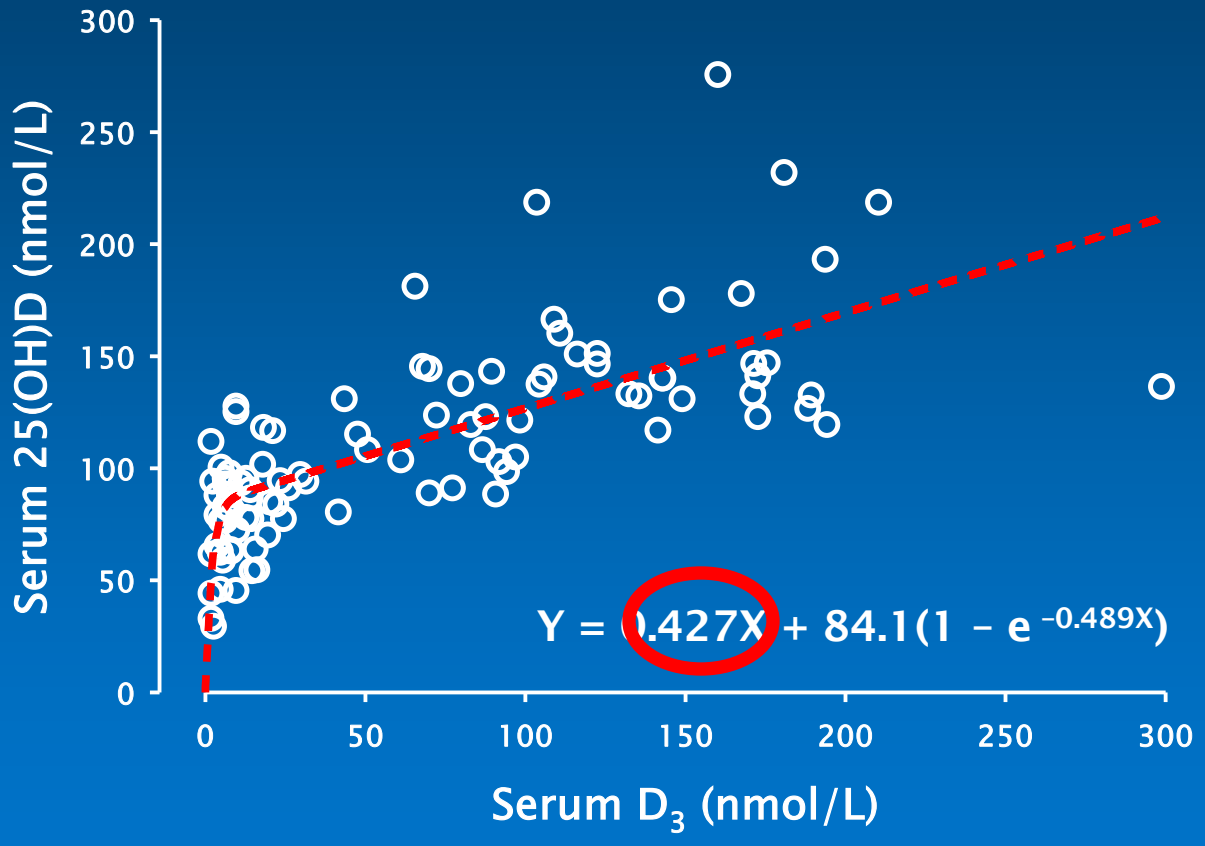
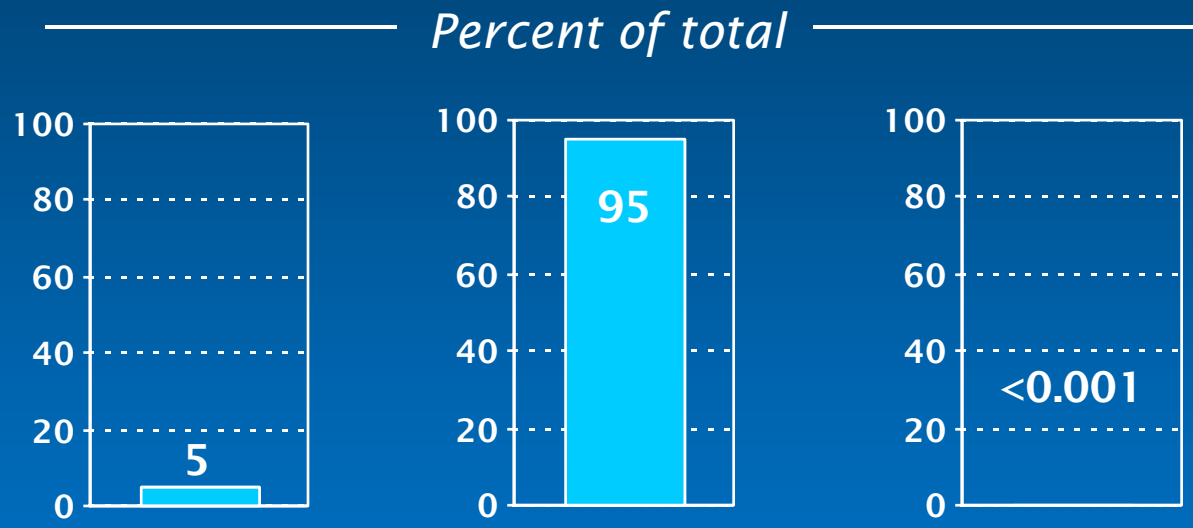


CONCLUSION

- at large inputs, vitamin D is stored – presumably in fat – because it cannot be 25-hydroxylated fast enough
- but at typical inputs, conversion to 25(OH)D is nearly quantitative, and there is essentially no storage of native cholecalciferol

VITAMIN D – HOW STORED

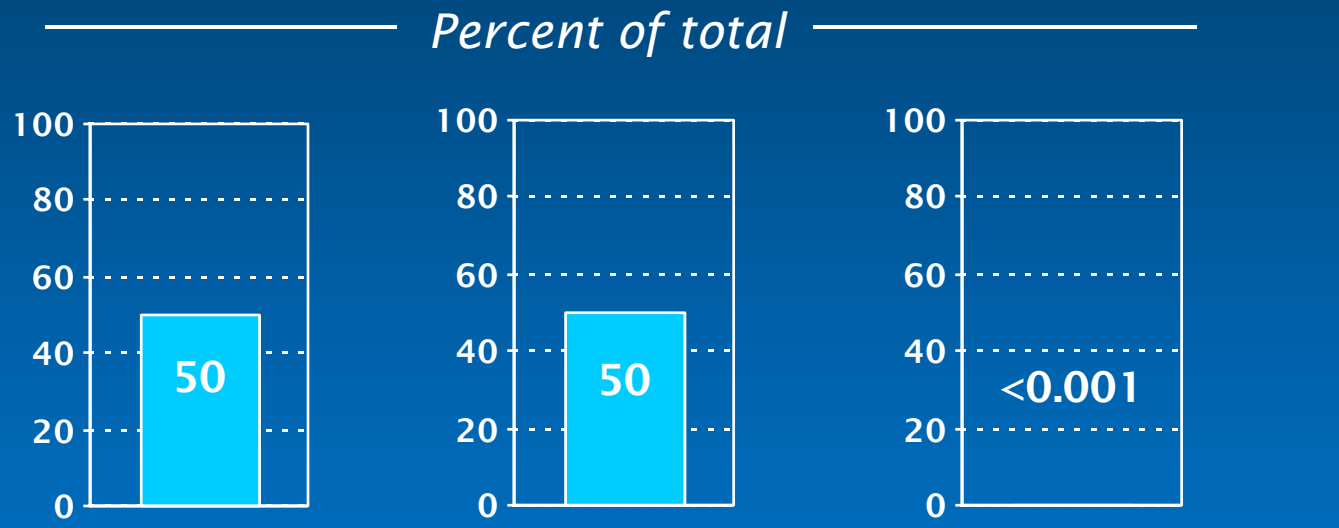
typical intakes:



D_3 → $25(OH)D_3$ → $1,25(OH)_2D_3$

VITAMIN D – HOW STORED

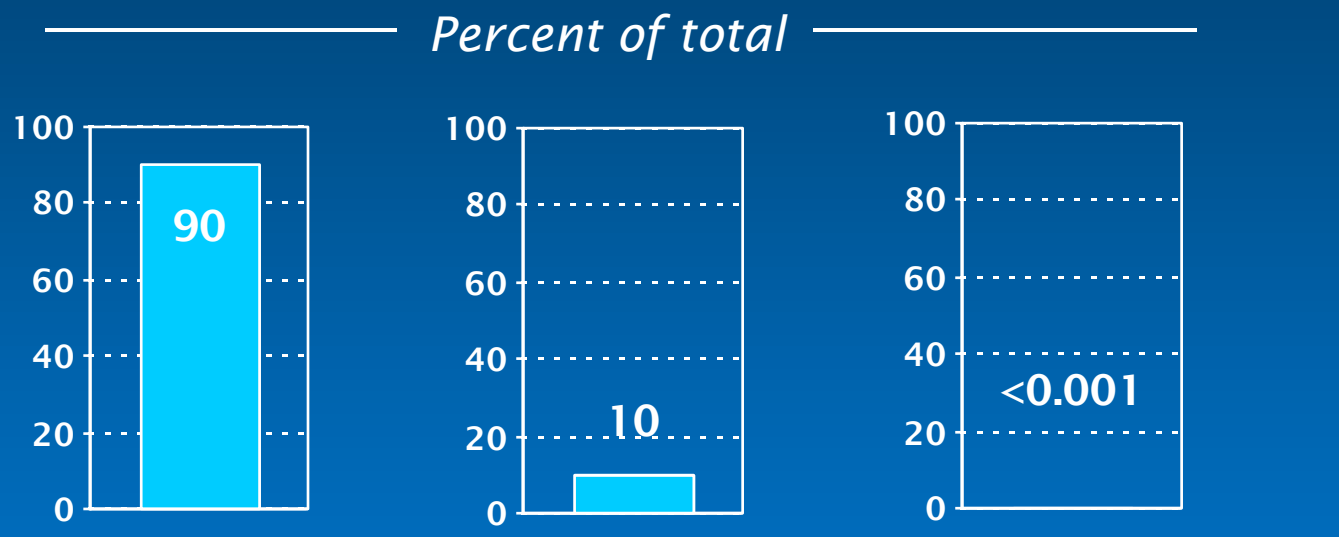
high intakes:



D_3 → $25(OH)D_3$ → $1,25(OH)_2D_3$

VITAMIN D – HOW STORED

toxic intakes:

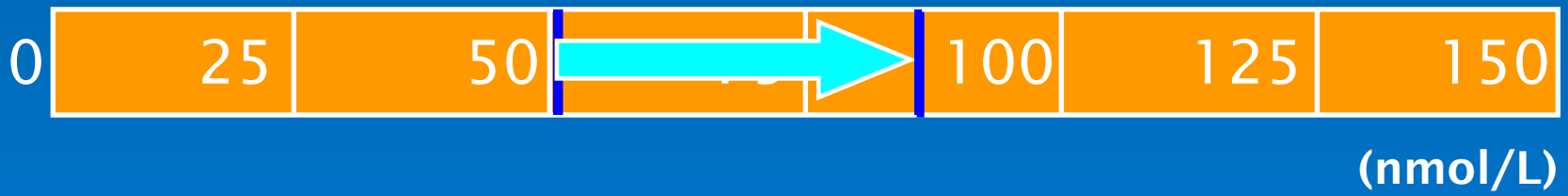


D_3 → $25(OH)D_3$ → $1,25(OH)_2D_3$

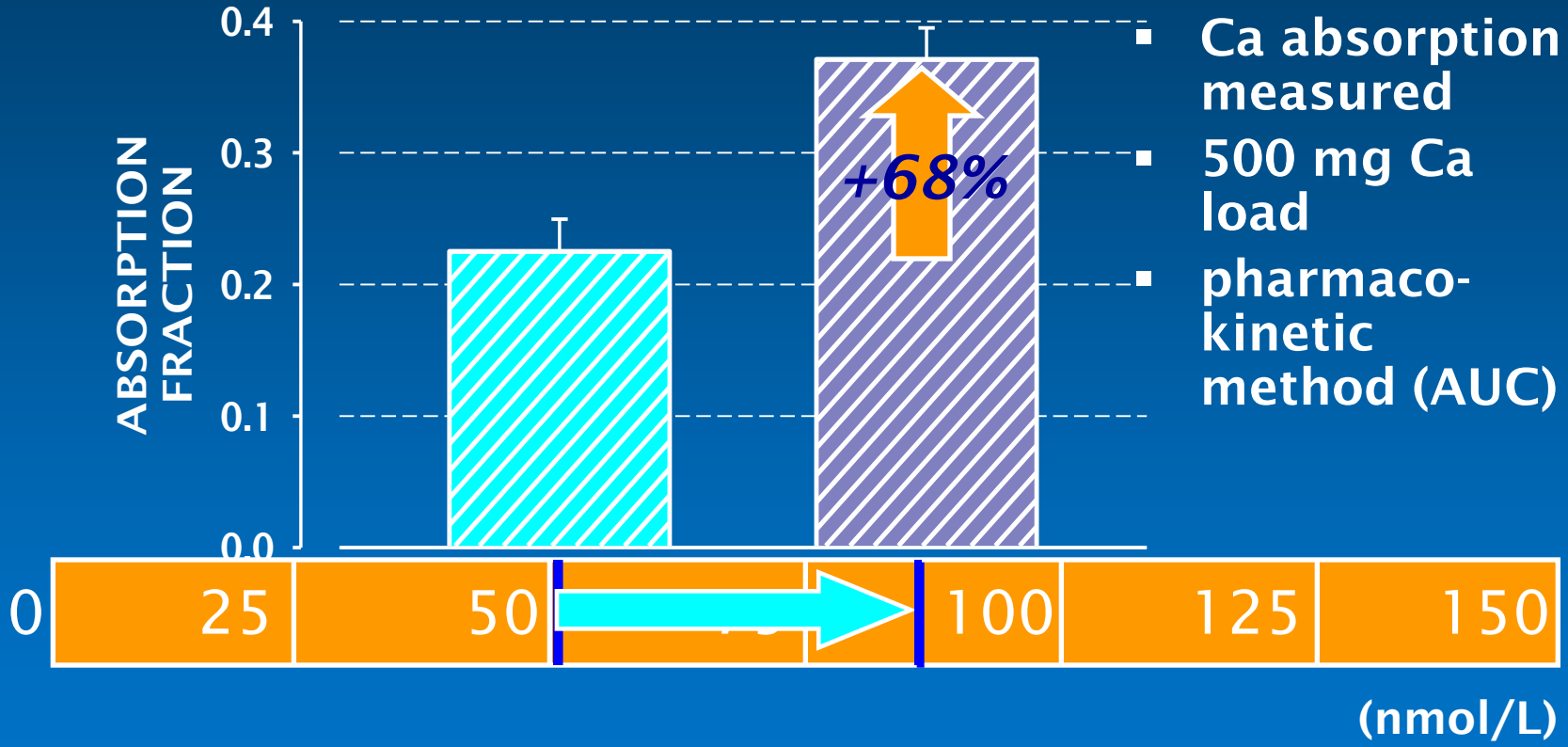
How Much Is Enough?

THE 25(OH)D CONTINUUM

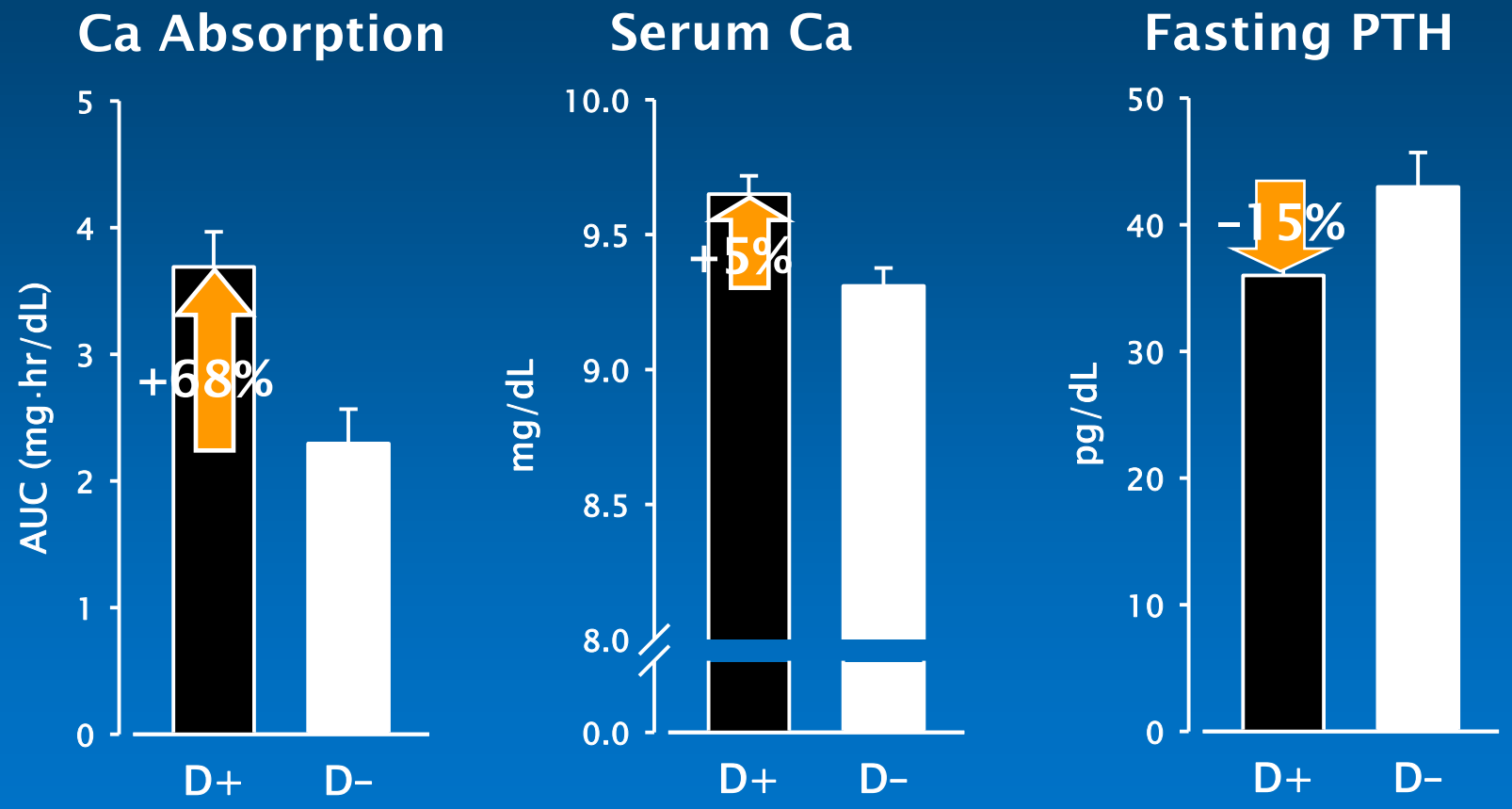
- 34 post-menopausal women
- studied twice, one yr apart, in the Spring
- given vitamin D one year & not the other
- (Heaney et al. JACN 2003; 22: 142–6)



THE 25(OH)D CONTINUUM



D STATUS & THE Ca ECONOMY



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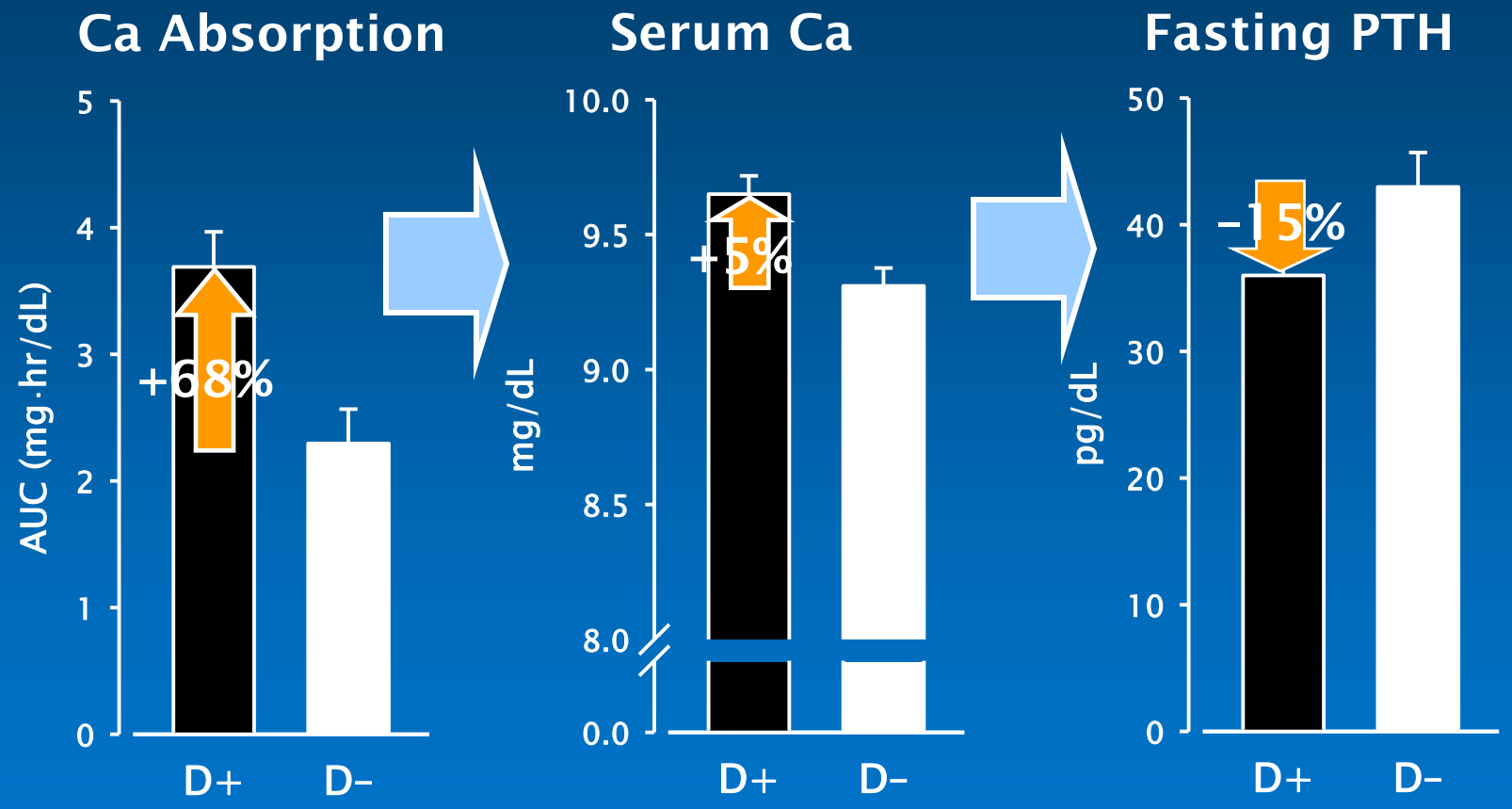
D STATUS & THE Ca ECONOMY



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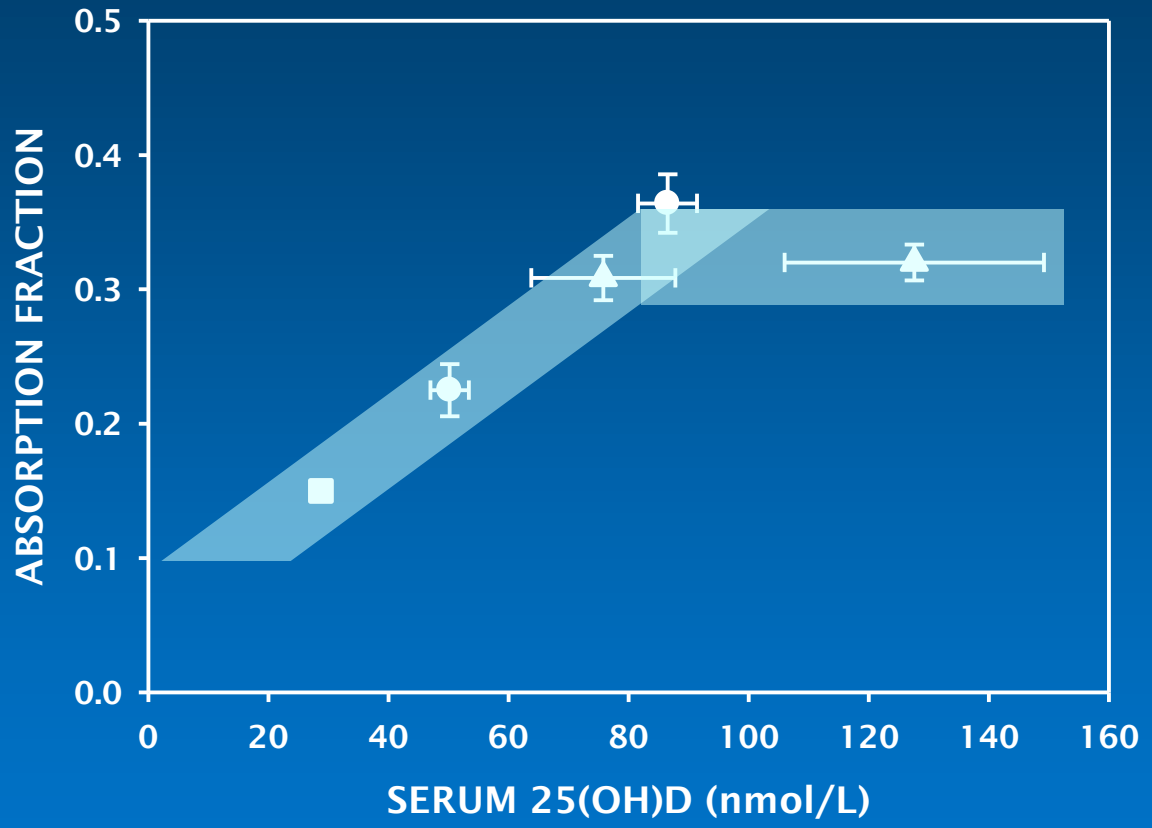
A VITAMIN D THRESHOLD



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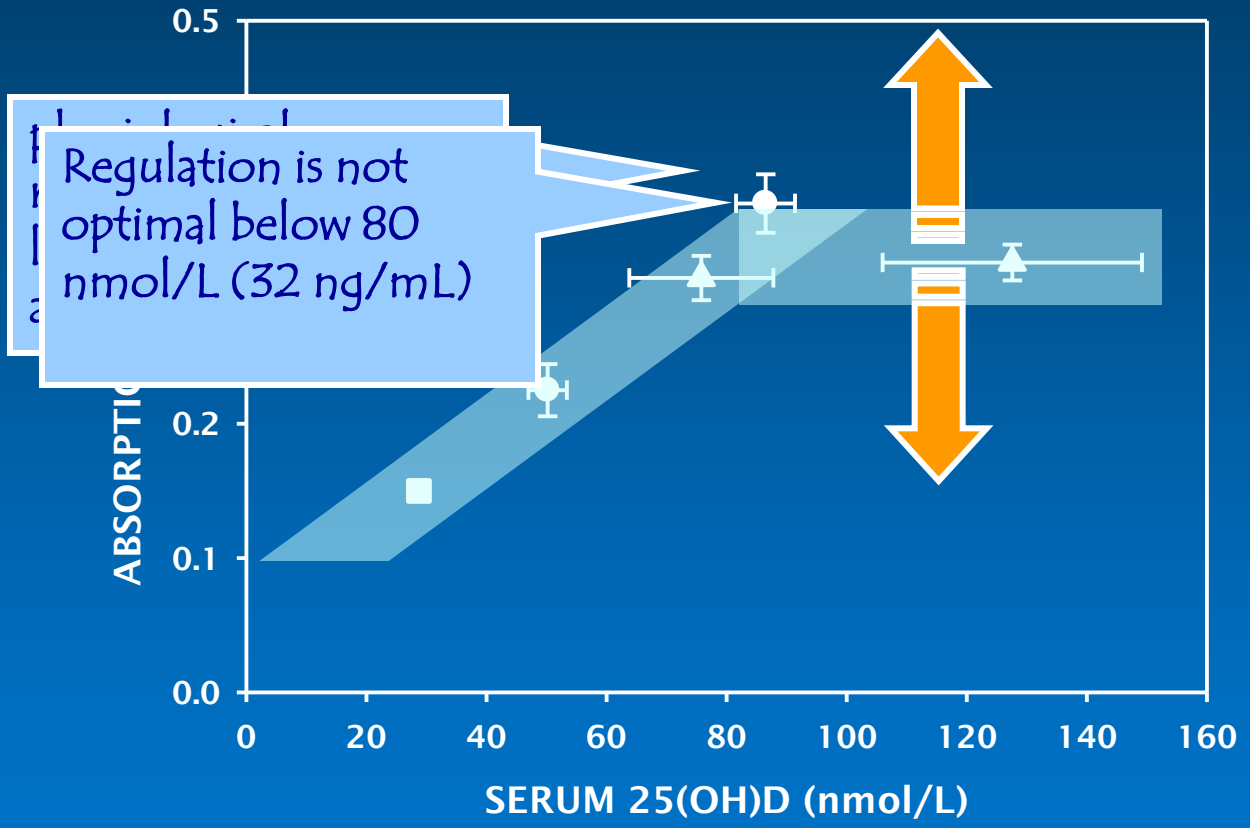

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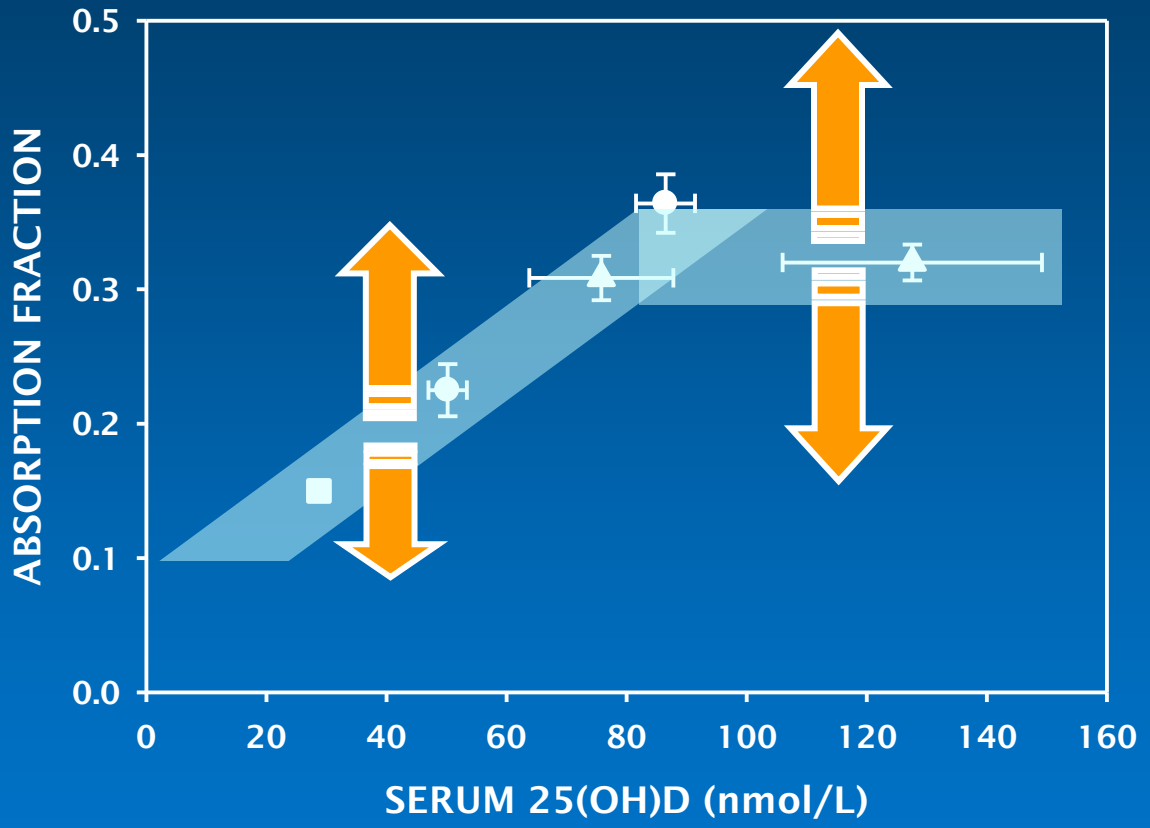
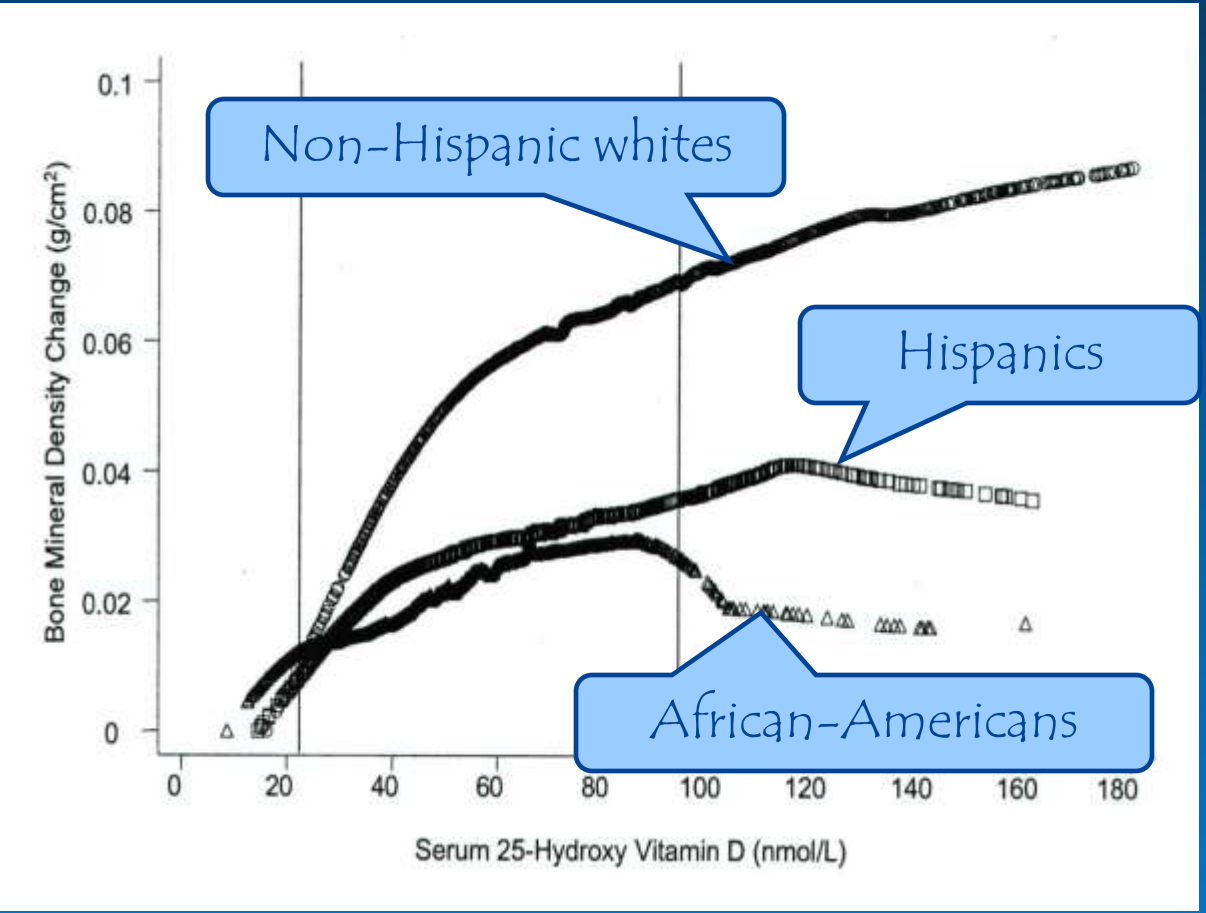


Bone Mass & Osteoporotic fractures

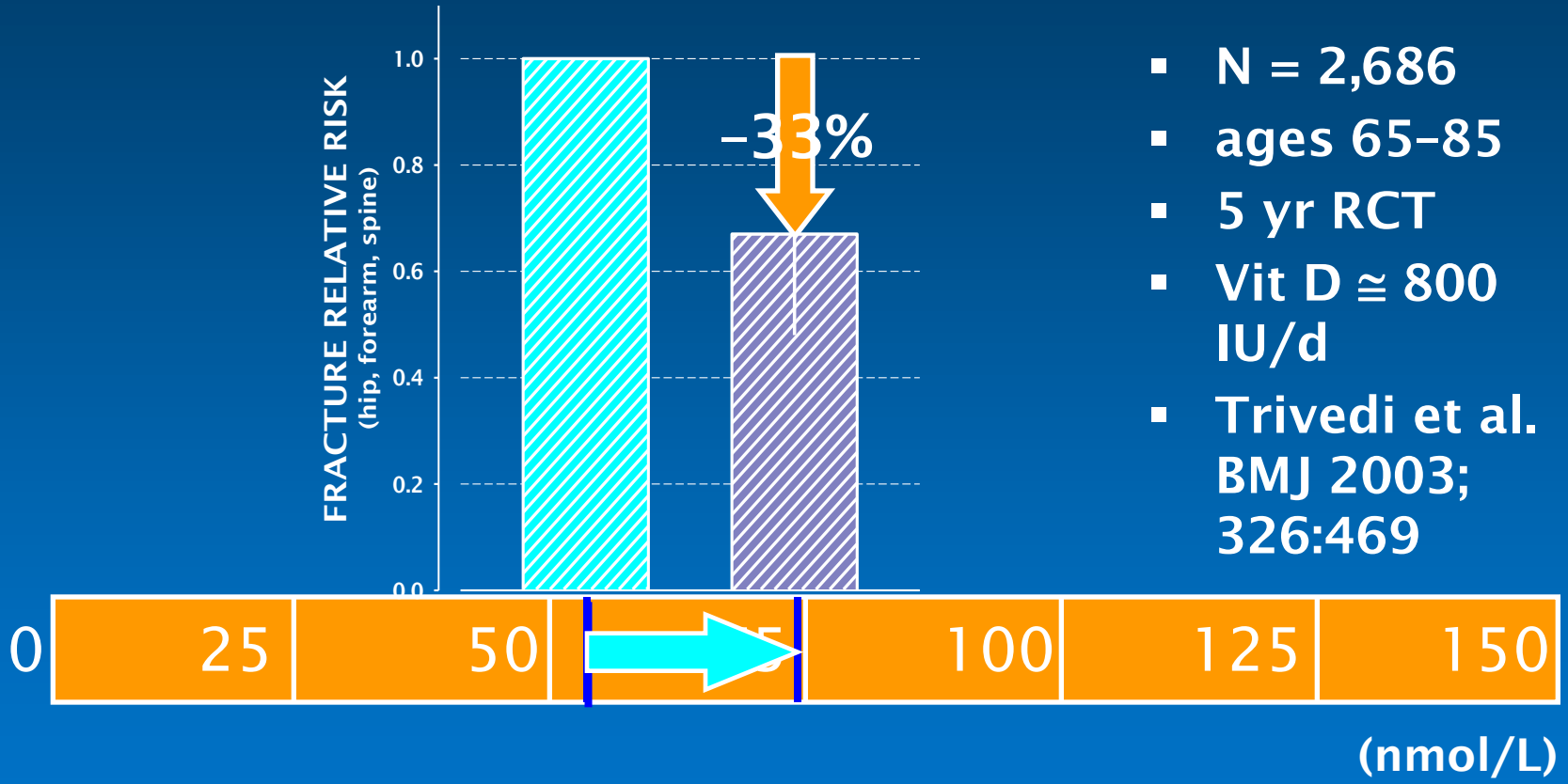
Serum 25(OH)D and Hip BMD

- NHANES-III
- Adults Age 20 – 49 yrs
- LOWESS plot of difference from lowest quantile



Bischoff-Ferrari HA. Am J Med 2004; 116: 634-9.

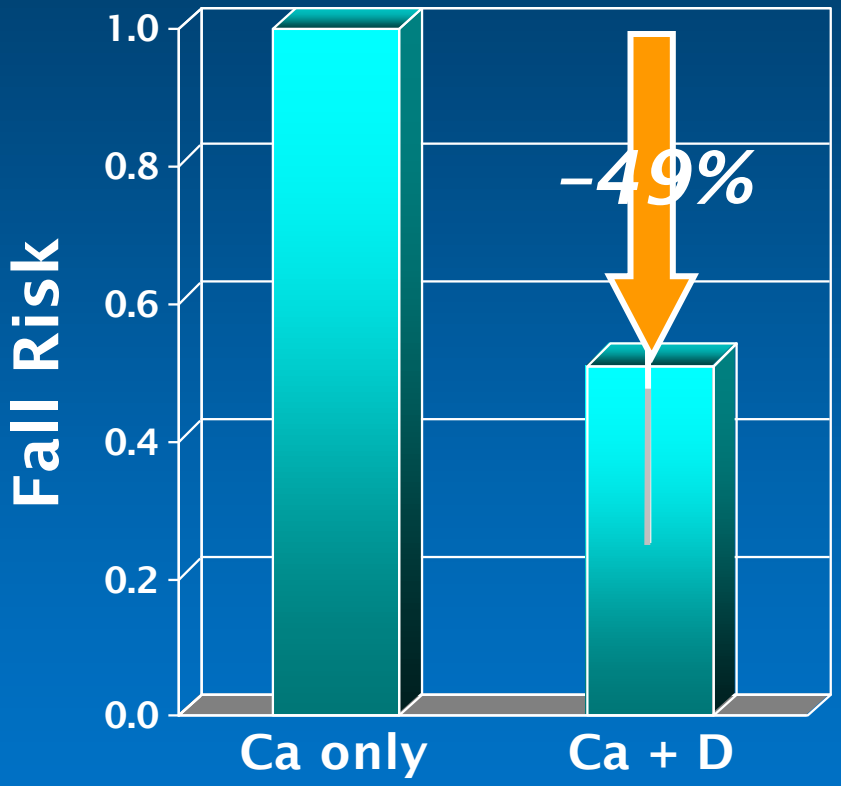
THE 25(OH)D CONTINUUM



- N = 2,686
- ages 65–85
- 5 yr RCT
- Vit D ≅ 800 IU/d
- Trivedi et al. BMJ 2003; 326:469

VITAMIN D & RISK OF FALLING*

- 122 women
- Age: 63–99
- DB-RCT
  - Ca 1,200 mg/d
  - Ca + 800 IU Vit D
- 12 week duration
- 25(OH)D 12 ng/mL at baseline



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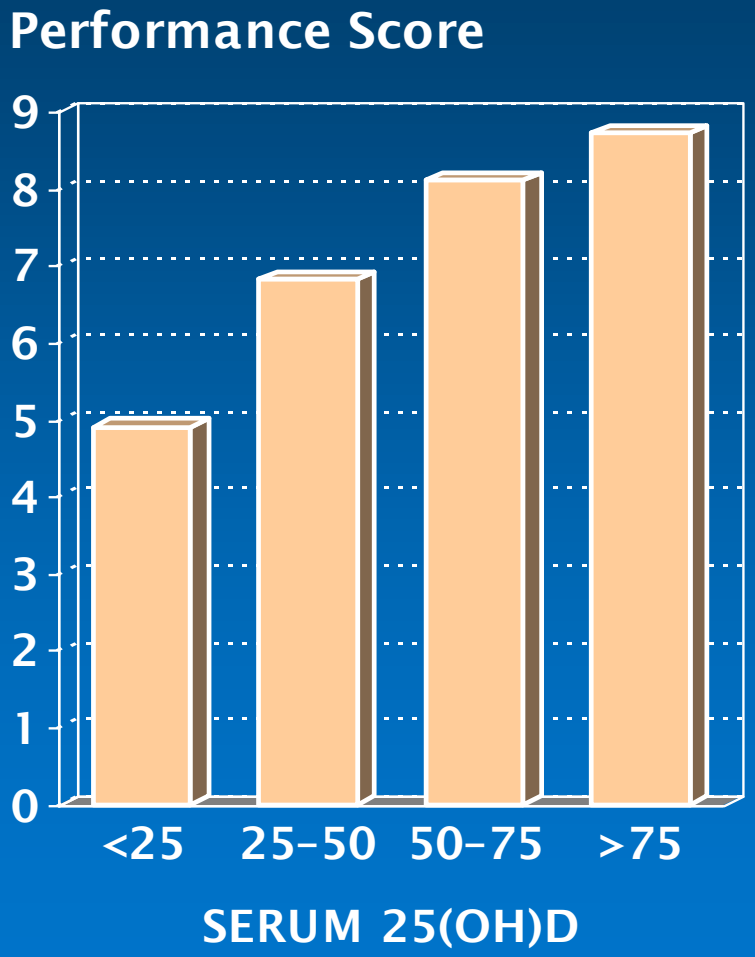
*Bischoff et al. *JBMR*. 2003;18:343–351.

VIT D & NEUROMUSCULAR FUNCTION*

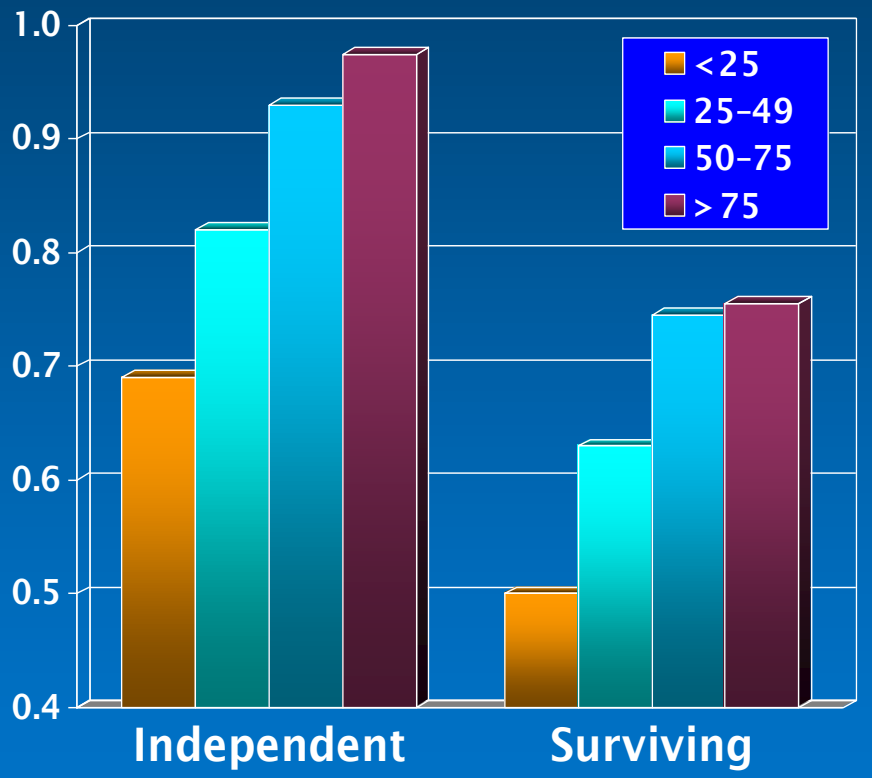
- 1359 men & women; mean age 75.5
- Amsterdam longitud. aging study
- neuromuscular performance measured on a scale of 0 to 12 (higher is better)
- each step statistically significant



*Wicherts et al. *JBMR*. 2005.

DEATH & DEBILITY

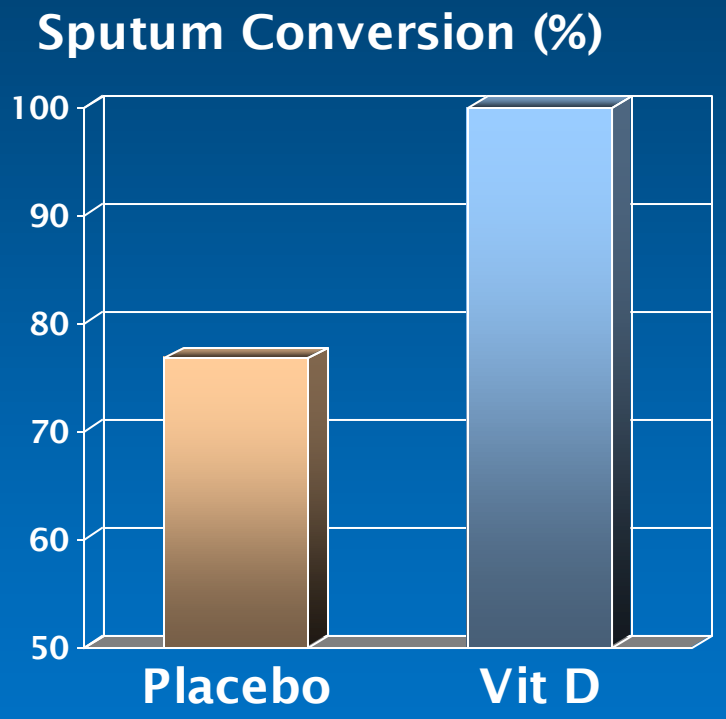
- Amsterdam Longitud. Aging Study
- N = 1509
- 6-yr followup
- evaluated likelihood of independent living & of dying
- Visser et al. (AJCN; 2006; 84:616–22)



Immune System

VITAMIN D & TUBERCULOSIS*

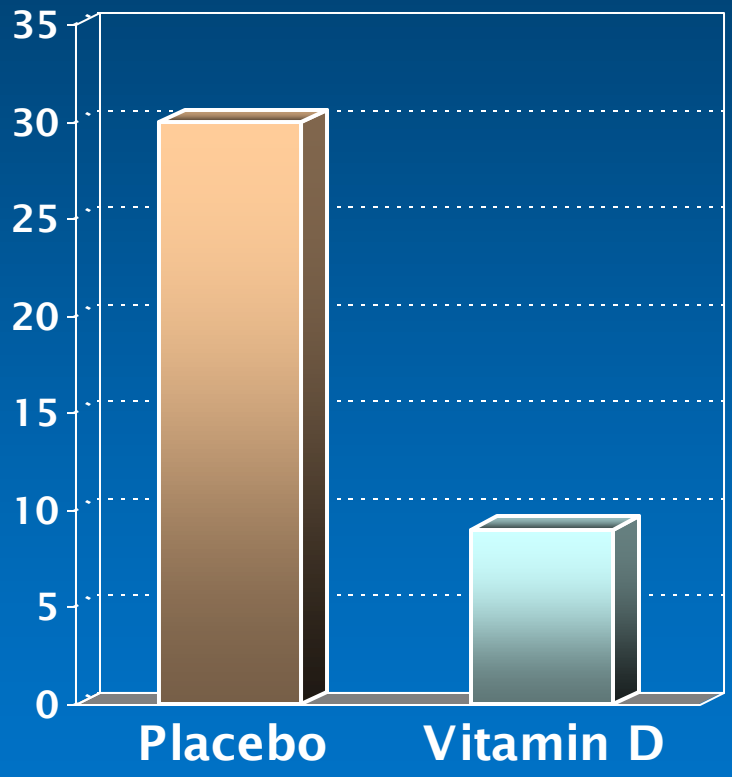
- 67 pts with pulmonary TB
- standard treatment for all
- in addition, randomized to either vit D 10,000 IU/d or placebo
- P = 0.002



*Nursyam et al., Acta Med Indones 2006

VITAMIN D & INFLUENZA*

- 208 African-American, postmenopausal women
- 3 yr DB-RCT
- placebo or vit D_3
  - 800 IU/d – 2 yrs
  - 2000 IU/d – 3rd yr
- basal 25(OH)D: 18.8 ± 7.5
- P < 0.002



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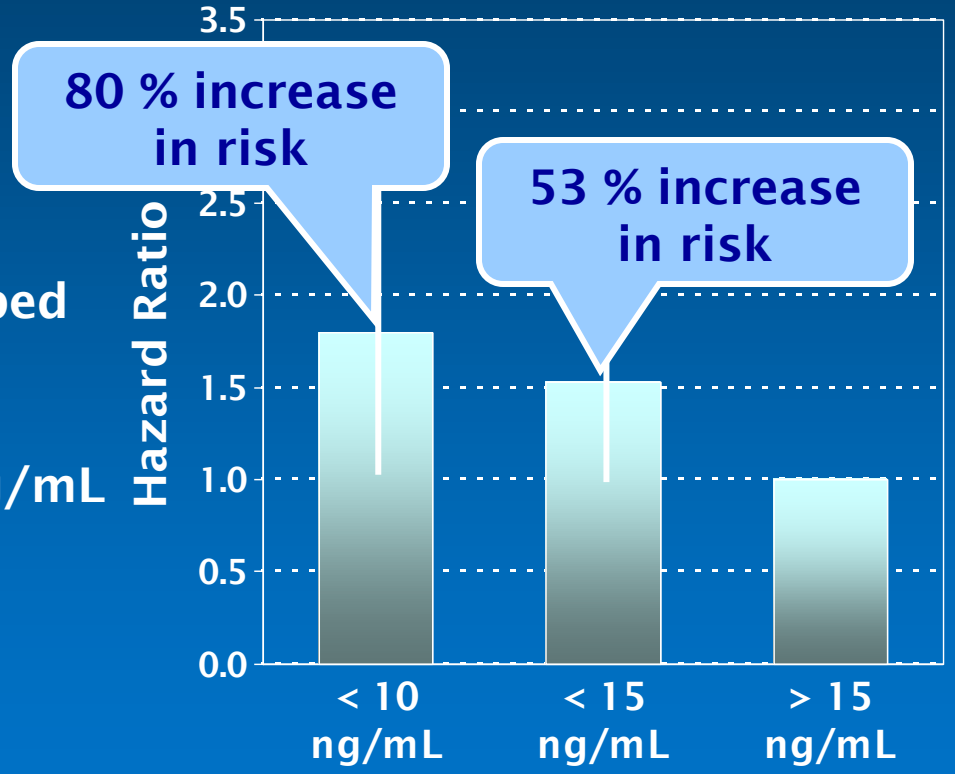
*Aloia & U-Ng (2007) Epidemiol & Infect

Cardiovascular effects

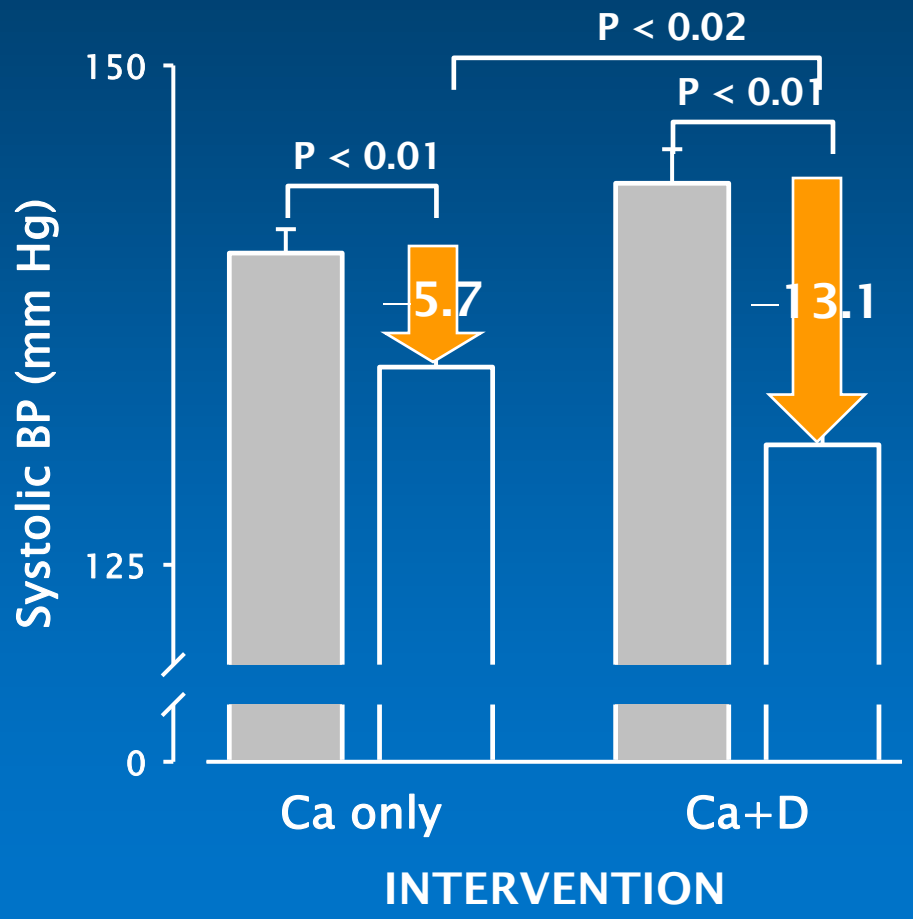
VIT D & CARDIOVASCULAR DISEASE

- 1739 Framingham Offspring members
- age: 59 yrs
- follow-up: 5.4 yrs
- 120 individuals developed a CV event
- HR calculated against 25(OH)D values > 15 ng/mL
- *Wang et al. Circulation 2008*



VIT D & BLOOD PRESSURE*

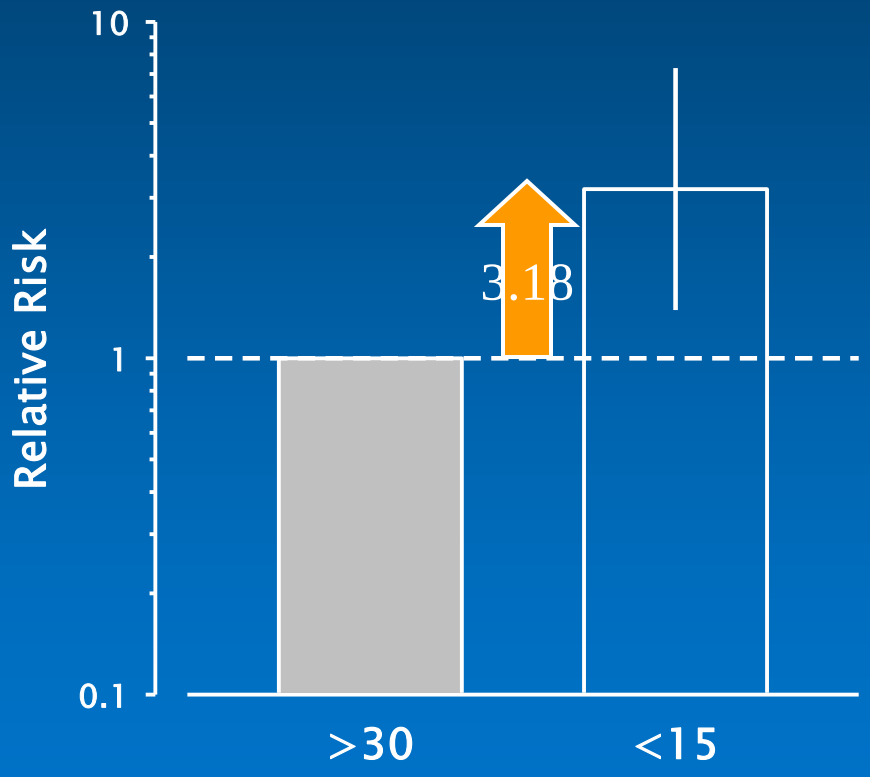
- 148 women, aged 74 ± 1
- DB–RCT
- baseline 25(OH)D < 50 nmol/L
- treated for 8 wks with:
  Ca 1200 mg/d or
  Ca + 800 IU vit D/d



*Pfeifer et al., JCEM 2001; 86:1633–37

VIT D & BLOOD PRESSURE*

- 1811 men & women with measured 25(OH)D levels**
- 4 yrs' observation
- 97 cases of incident hypertension
- RR computed for 25(OH)D <15ng/mL vs. >30 ng/mL



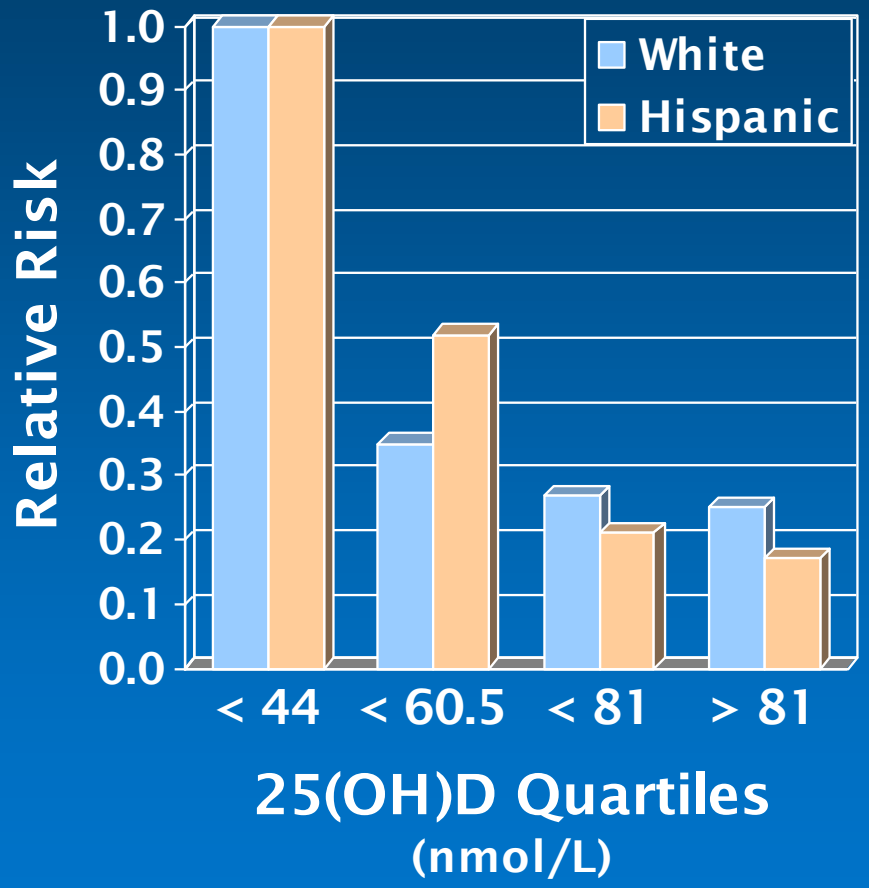
*Forman at al., 2007;Hypertension 49:1063

** Health Profs Follow-up Study & Nurses Health Study

Diabetes & Insulin Sensitivity

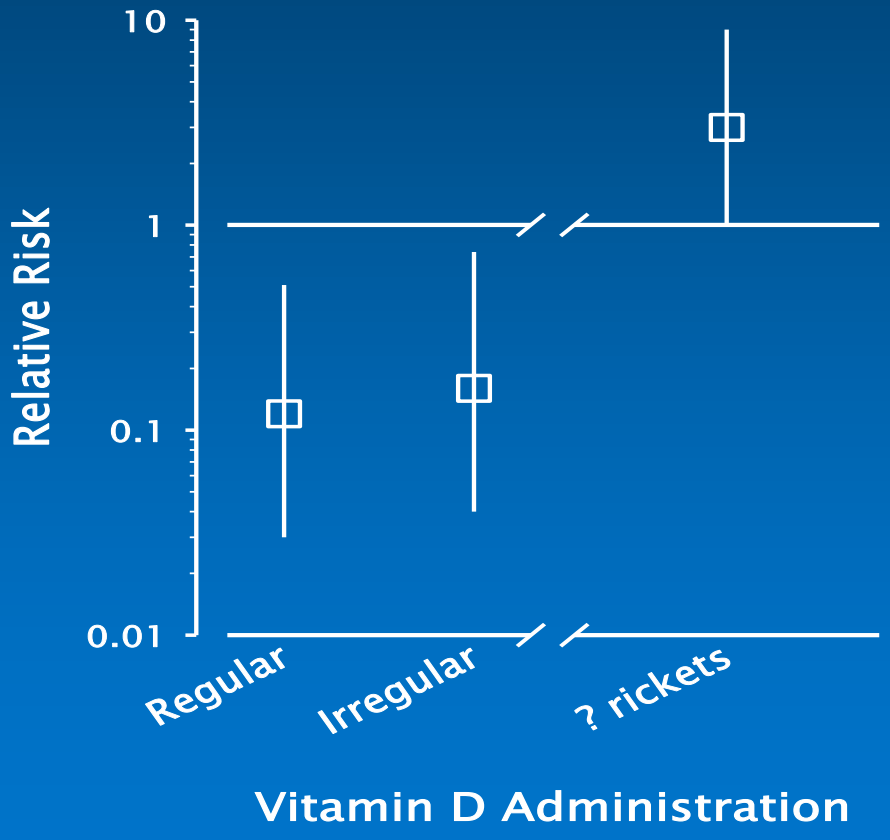
DIABETES & 25(OH)D

- Scragg et al., 2004 Diabetes Care 27:2813-18
- NHANES-III
- 6,228 adults
- plasma glucose independently predicted by BMI & serum 25OHD (fasting and 2 hr post load)



NEONATAL VIT D & DIABETES*

- 10,366 northern Finnish children
- 2000 IU Vit D/d 1st year of life
- prevalence of type I diabetes assessed at age 21
- RR calculated vs. no supplementation



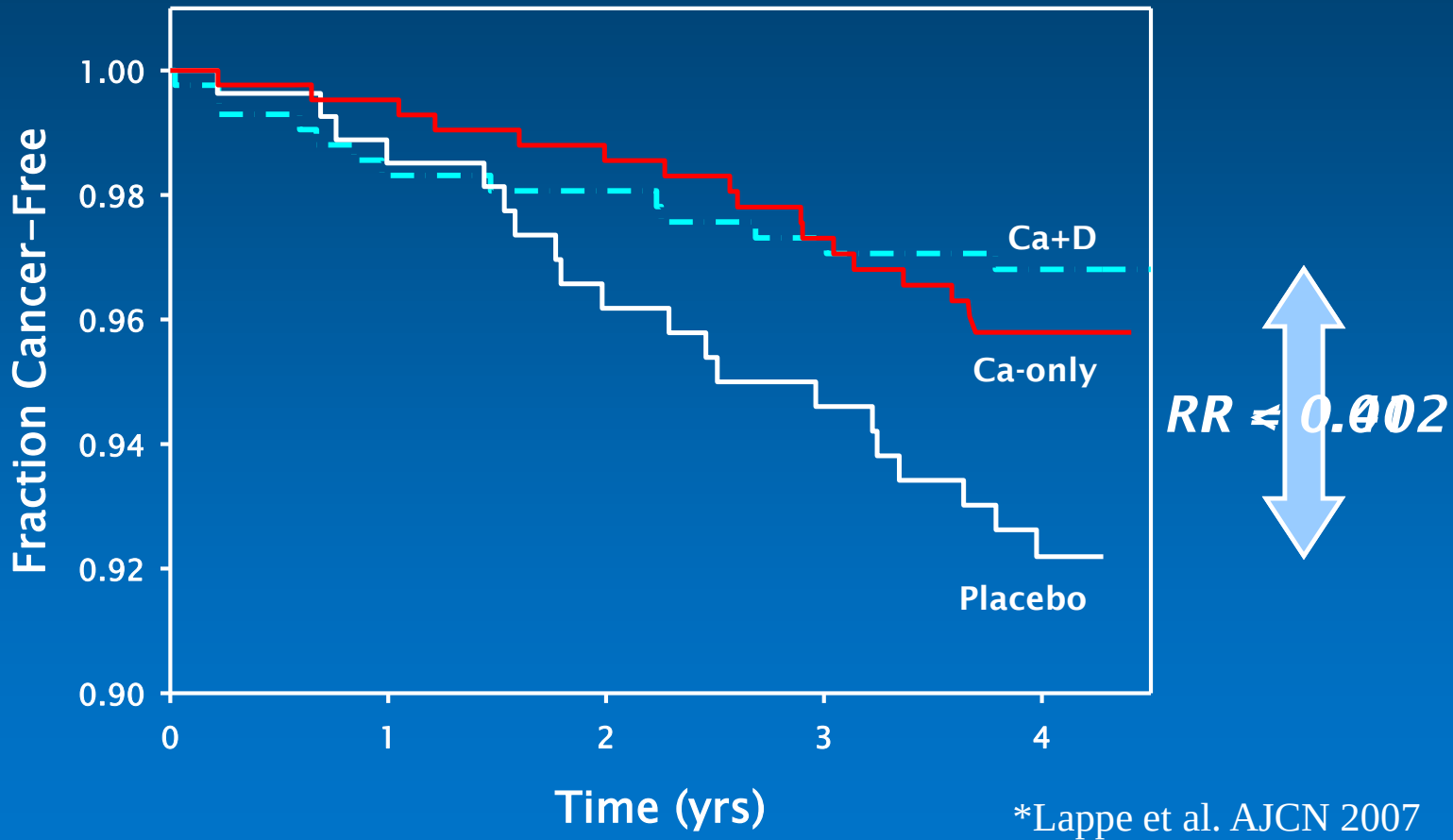
*Hypponen et al., Lancet 2001;358:1500–03

VITAMIN D & CANCER*

- 1179 healthy women
- aged 66.7 ± 7.3
- four year trial
- 1032 finished (87.5%)
- baseline 25(OH)D: 71.8 nmol/L ± 20.3
- three treatment groups:
  - control
  - Ca (1400–1500 mg/d)
  - Ca plus D_3 (1100 IU/d)
- achieved 25(OH)D: 96 nmol/L ± 21.4

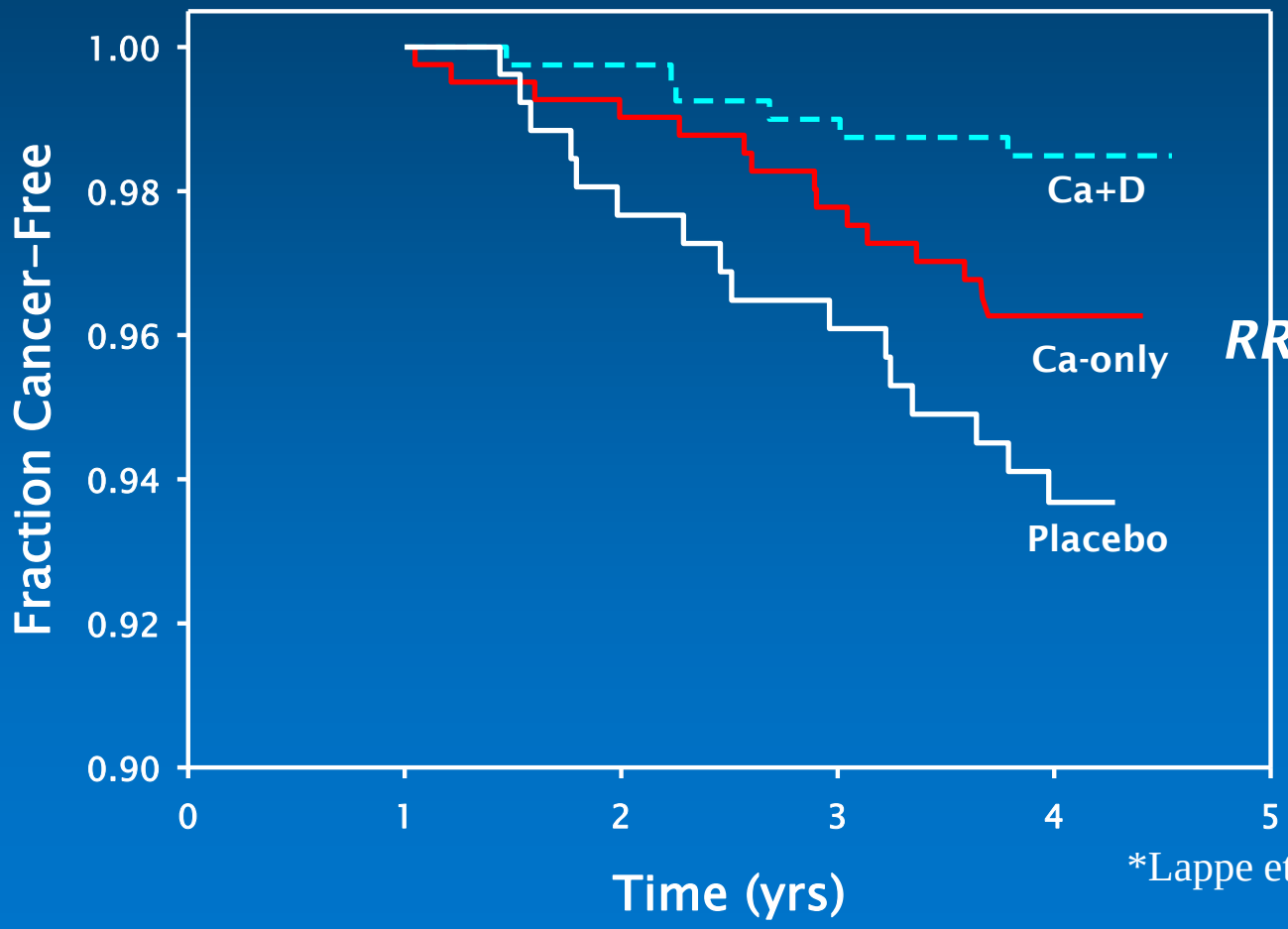
*Lappe et al. AJCN 2007

VITAMIN D & CANCER*



*Lappe et al. AJCN 2007

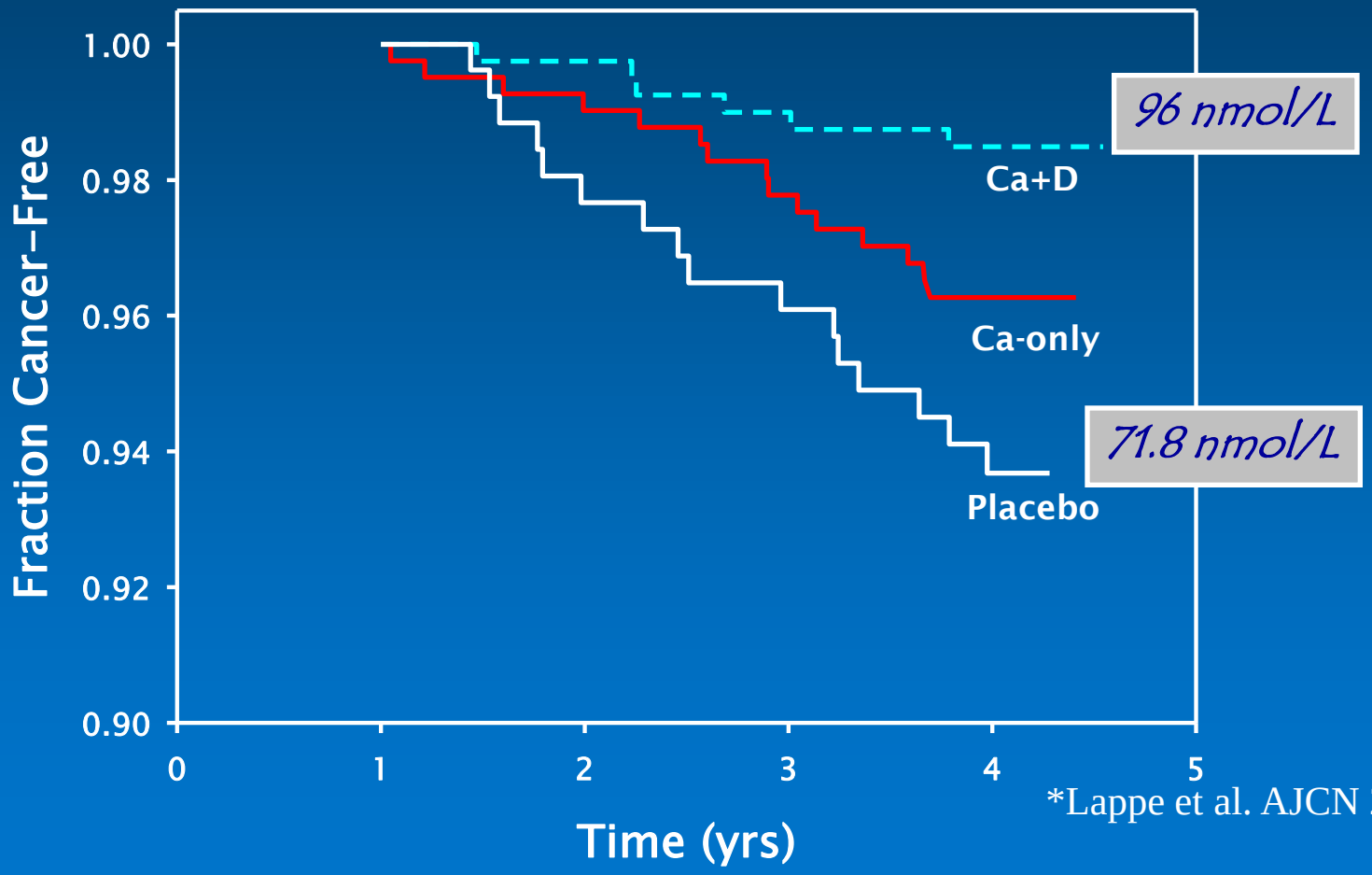
VITAMIN D & CANCER*



RR = 0.232

*Lappe et al. AJCN 2007

VITAMIN D & CANCER*



*Lappe et al. AJCN 2007

OTHER CHRONIC DISEASES?

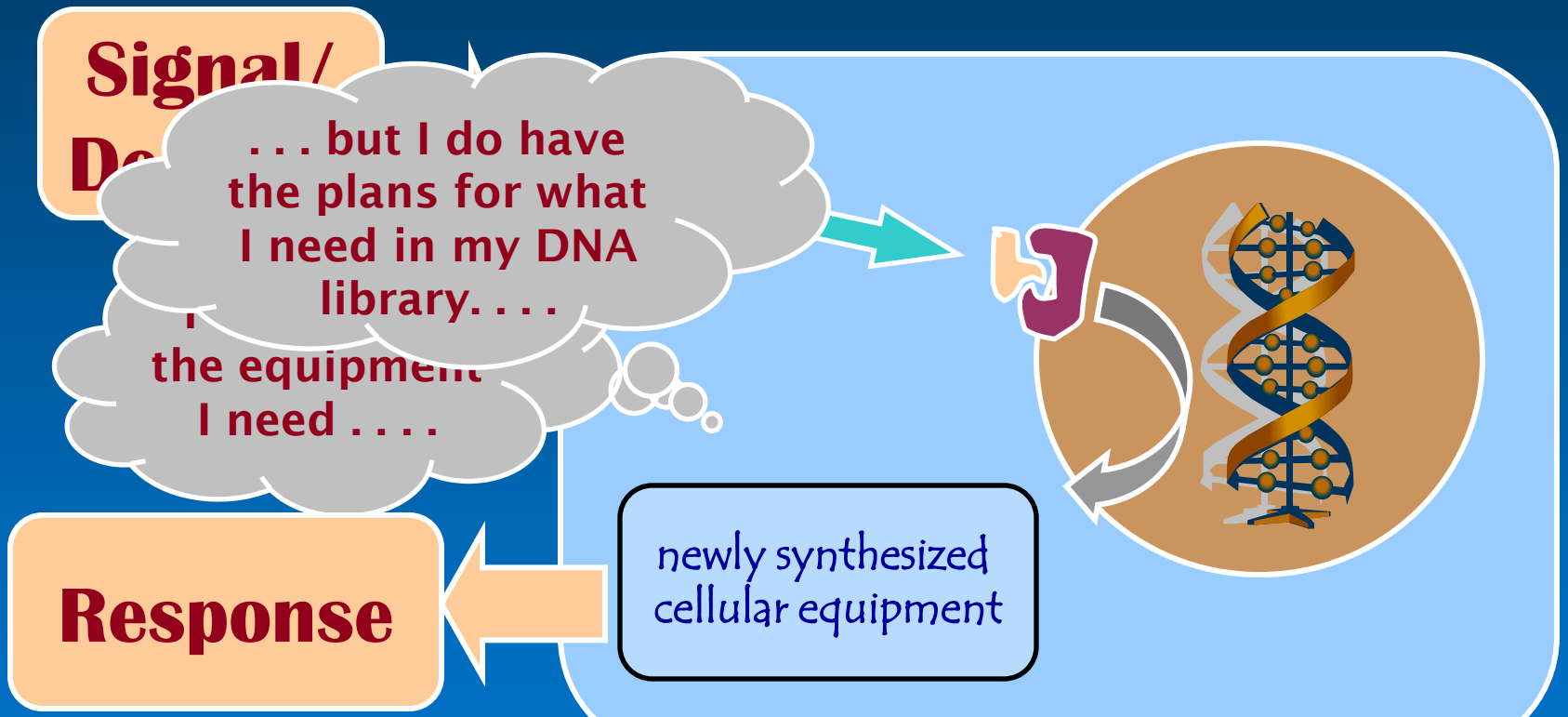
Disease	Status of Evidence
osteoarthritis	+
falls/neuromusc. fcn	++++
multiple sclerosis	++
fibromyalgia	++
type I diabetes	++
insulin sensitivity	++
cardiovascular disease	++
periodontal disease	++
various cancers	++++
tuberculosis	+++
hypertension	++++

How can deficiency of a single nutrient produce so many, and such diverse effects?

PERSPECTIVE

- vitamin D is an integral component of the mechanism whereby cells control gene transcription in response to a variety of extracellular stimuli
- adequate vitamin D status enables optimal response to a broad variety of signals

HOW A CELL RESPONDS



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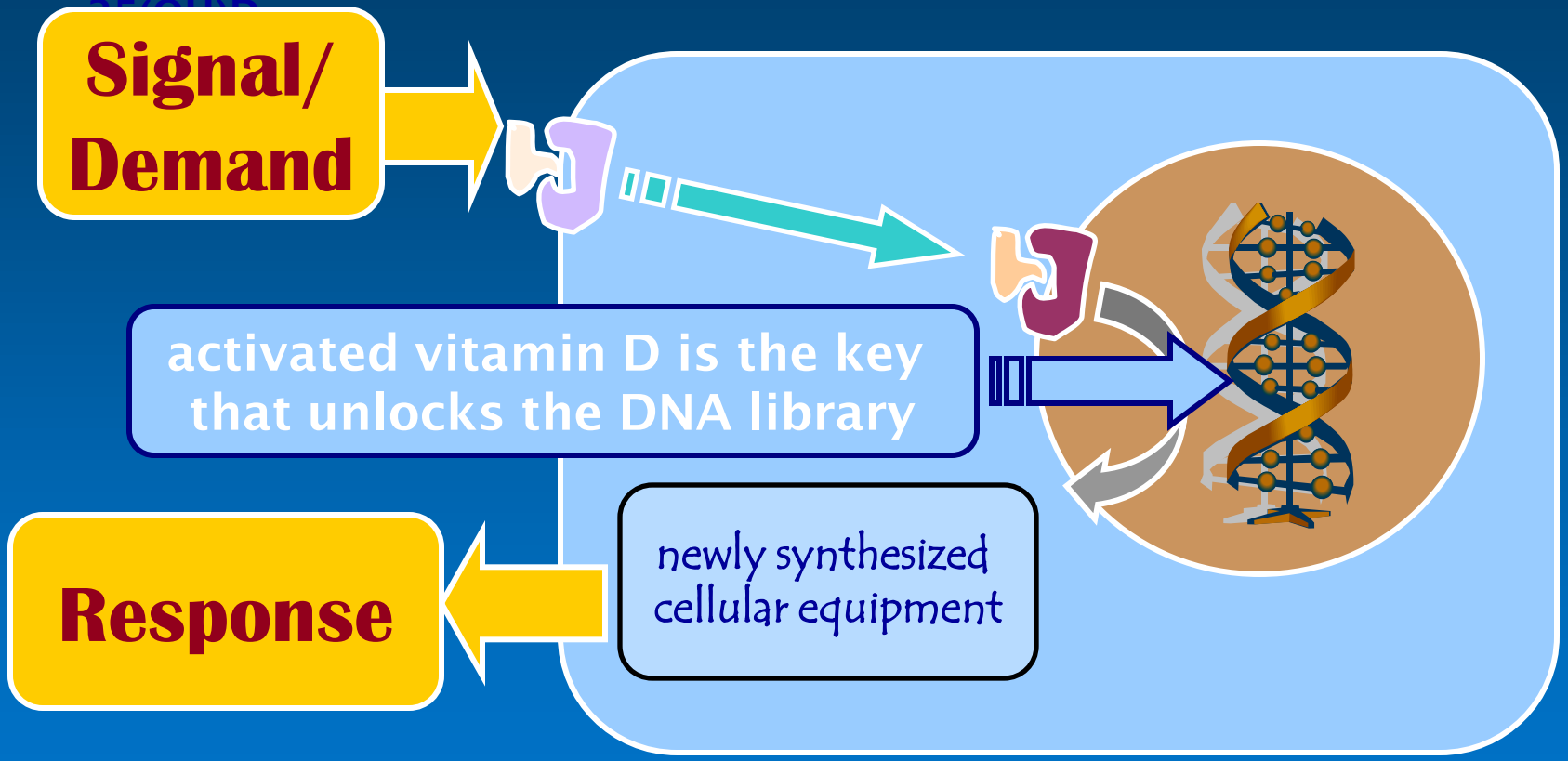
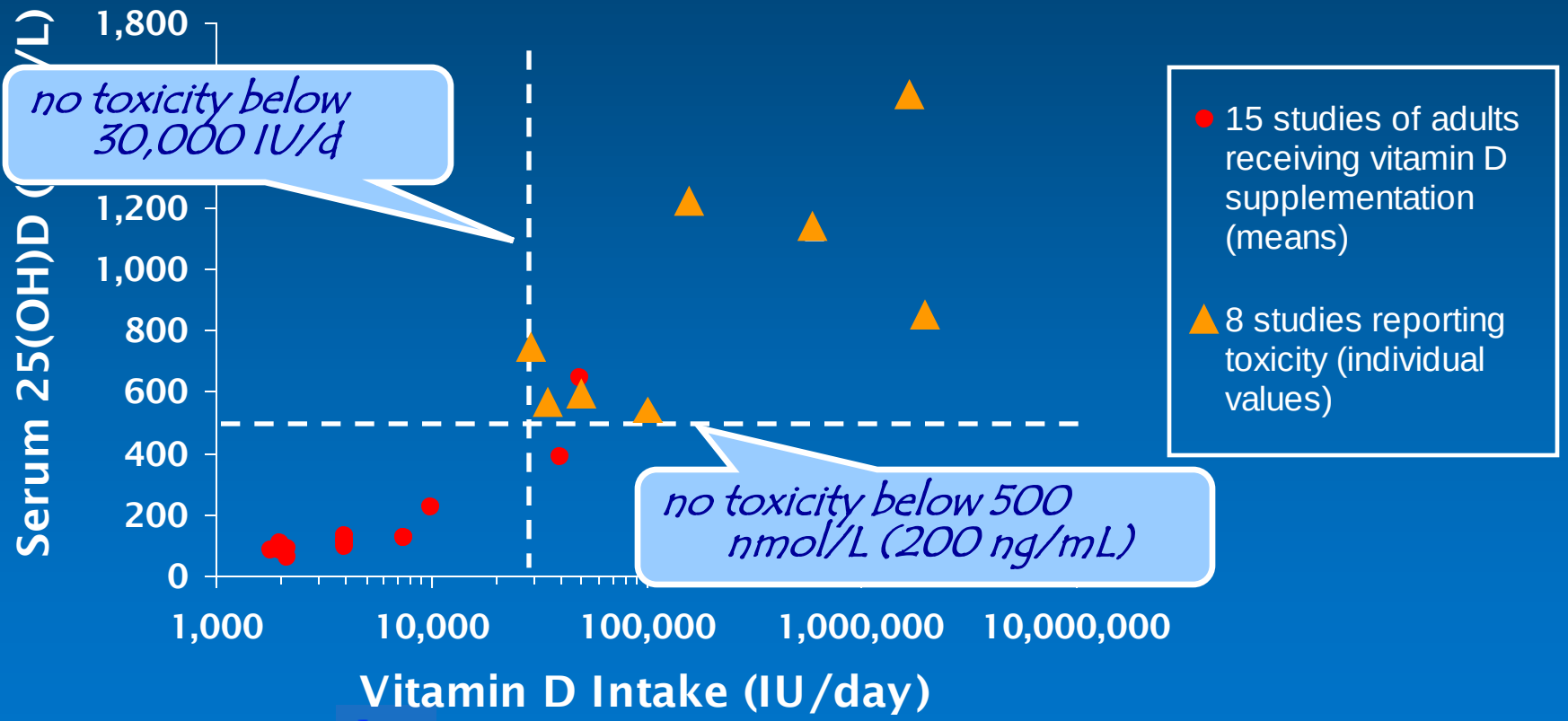


VITAMIN D INTAKE & TOXICITY*



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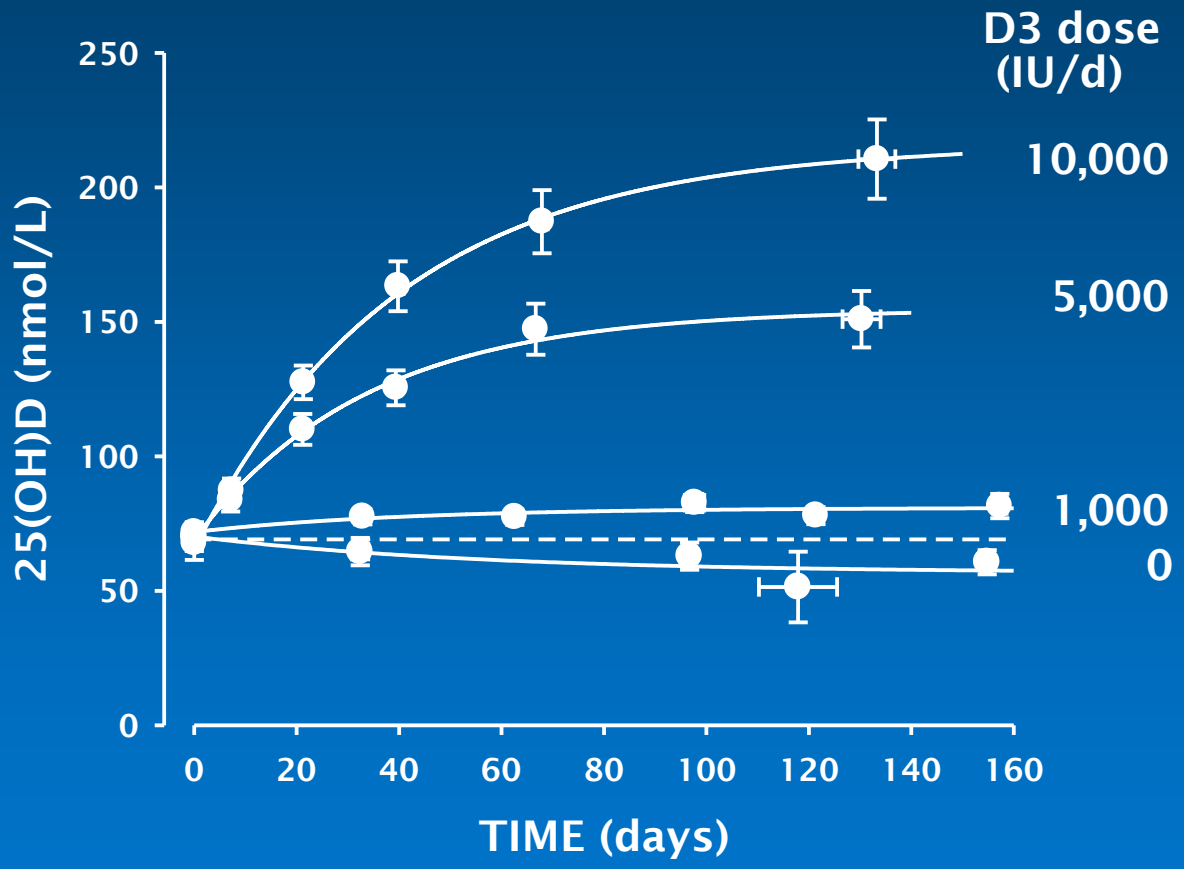
* Hathcock JN et al. *Am J Clin Nutr*. 2007;85:6–18.

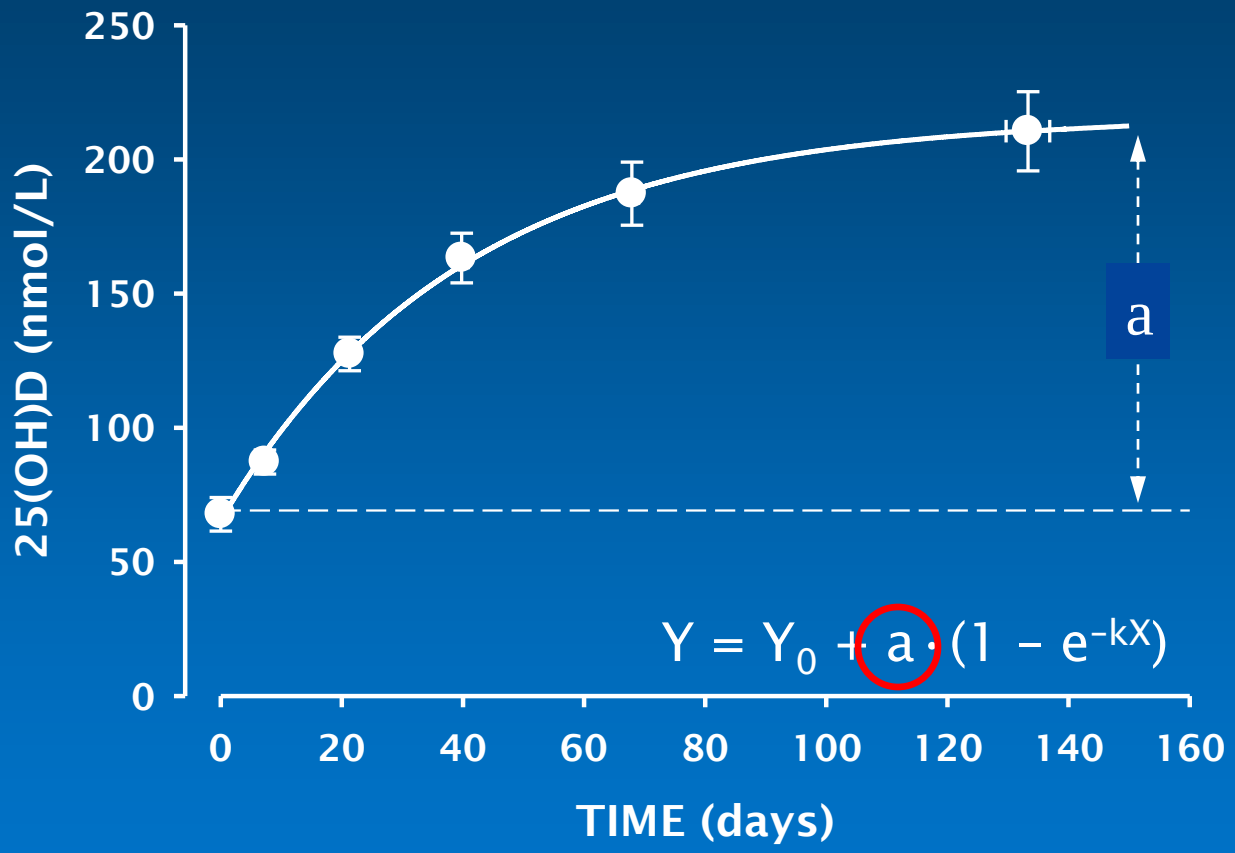
How Much Do We Need?

25(OH)D RESPONSE TO ORAL D_3

- 66 males
- aged 38.7 yr (± 11.2)
- dosed with vit D_3 from October through February

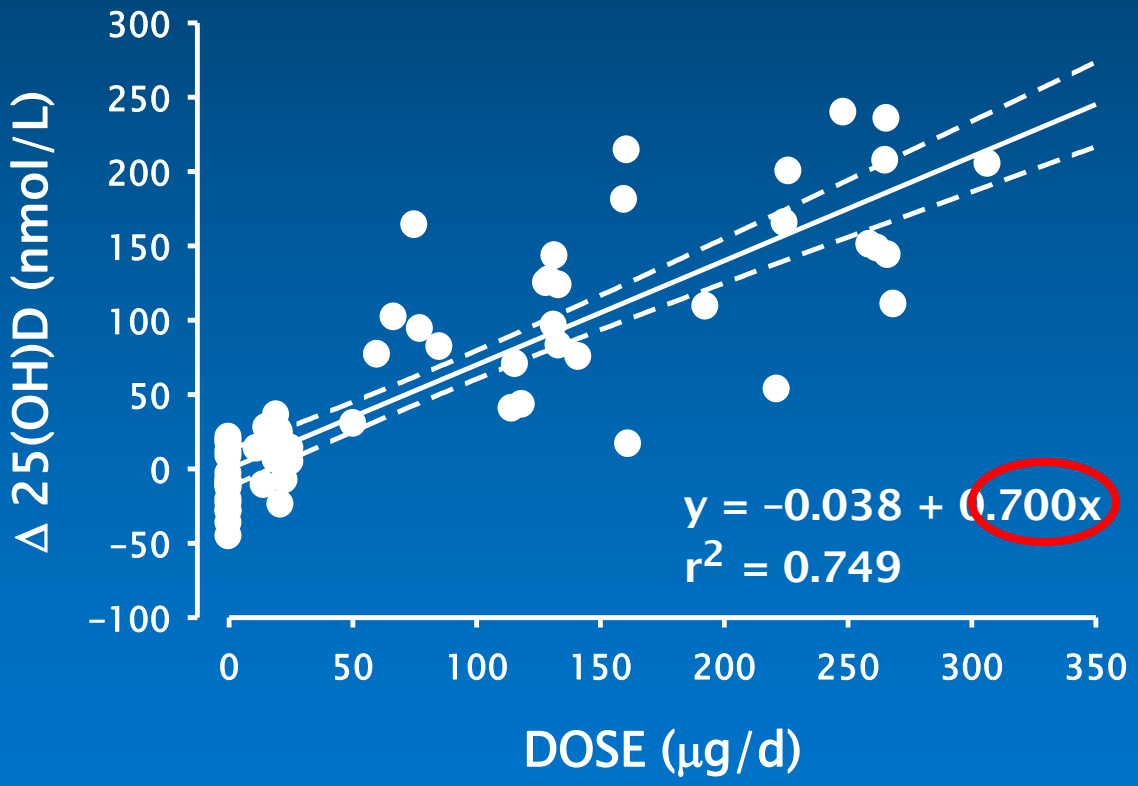


INCREMENT ESTIMATION



25(OH)D RESPONSE TO ORAL D_3

- equilibrium concentrations of 25(OH)D plotted against actual dose of vit D_3



TRANSLATION:

- steady-state serum 25(OH)D concentration rises by 0.7 nmol/L for every 1 μg (40 IU) of vit D_3, given as a *daily* oral dose
- most recent studies have produced estimates of this slope in the same range, *i.e.*, from 0.6 to 1.2 nmol/L/μg/d

TRANSLATION:

- taking a conservative figure from that range, e.g., 1.0 nmol/L/μg/d,
- 2000 IU/d *(in addition to all other inputs)* would raise serum 25(OH)D by ~50 nmol/L (20 ng/mL)
  - a rule of thumb: every *added* 100 IU/d raises serum 25(OH) by ~1 ng/mL

TWO KEY QUESTIONS

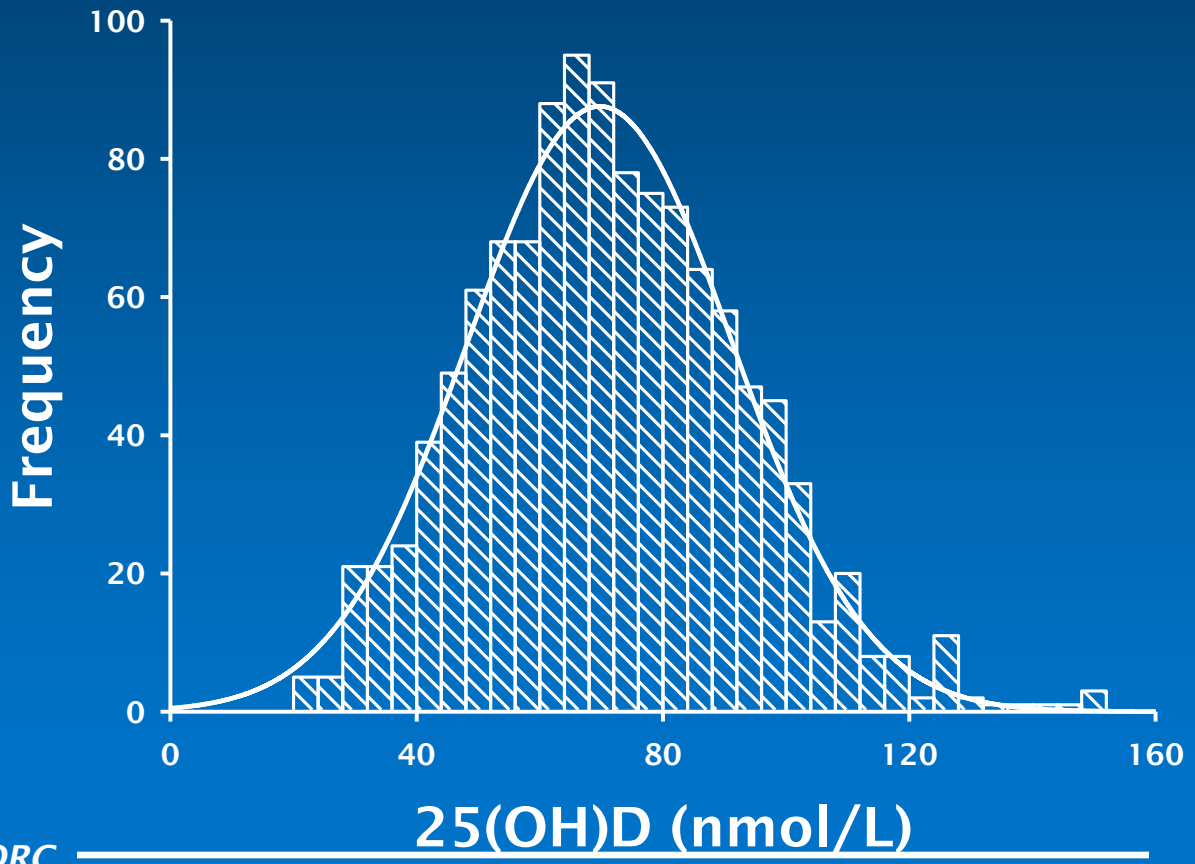
assuming a target value of 80 nmol/L:

- **how much of an increase in daily inputs would be required to ensure that no more than 2.5% of the population fell below the target value?**
- **what , if anything, is the risk of raising their 25(OH)D in those who already are at or above the target value?**

25(OH)D IN OLDER WOMEN*

*Lappe et al., JACN 2006

- 1168 women aged 55 & older
- latitude 41° N
- 25(OH)D values adjusted for season
- median vit D supplement dose = 200 IU



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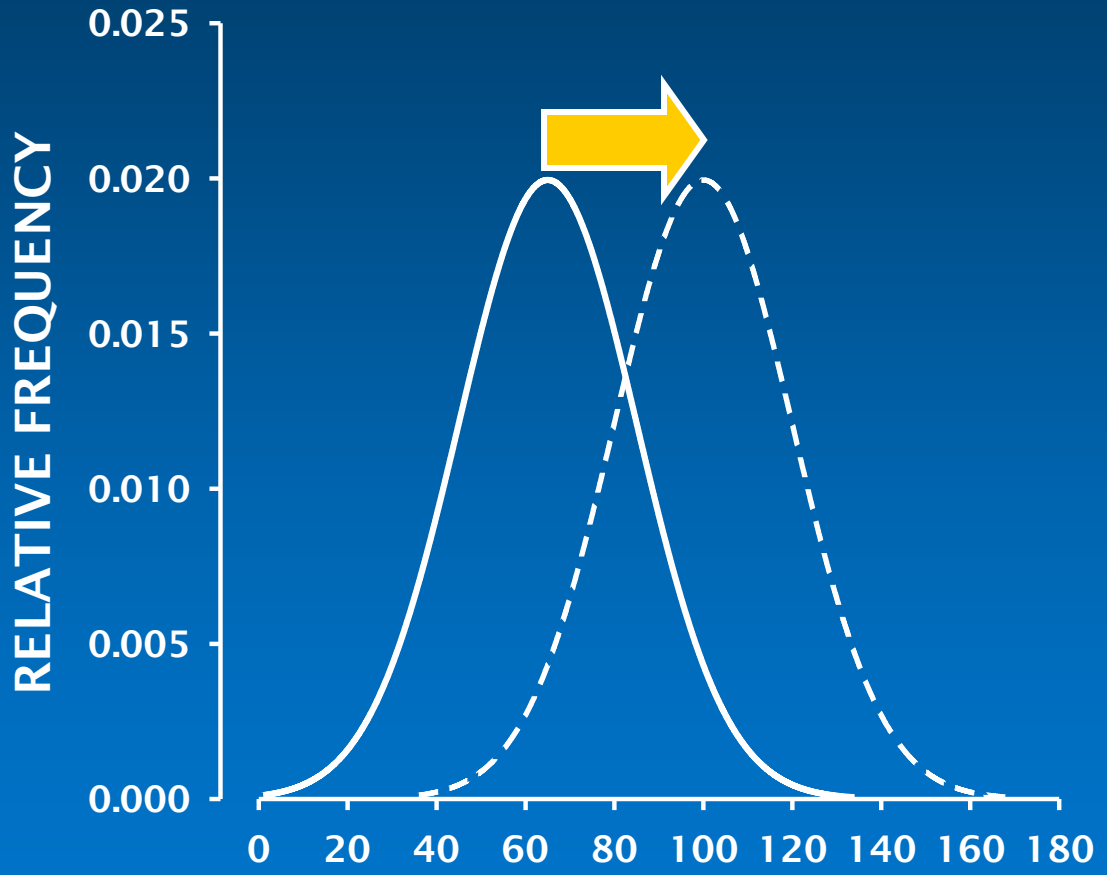
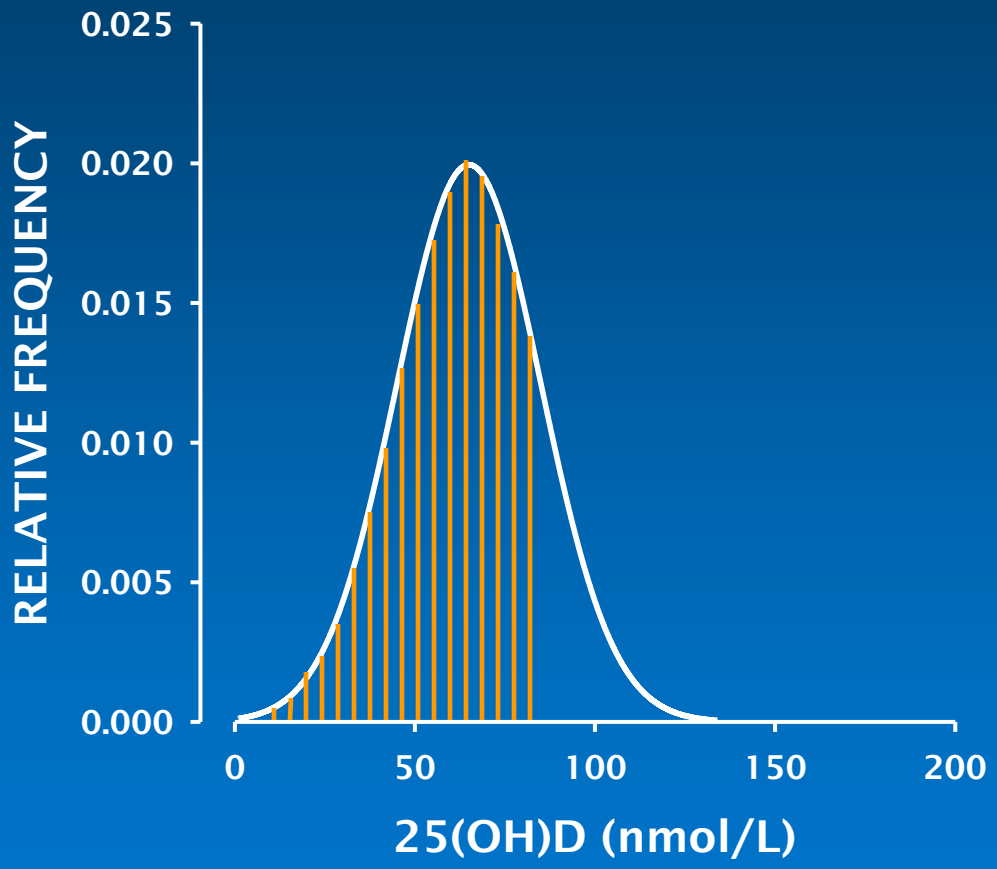
SHIFTING THE DISTRIBUTION

- improving vitamin D status at a population level means raising everybody's value, *i.e.*, moving the distribution to the right



SHIFTING THE DISTRIBUTION

- using an effect size of 1 nmol/L/μg/d
- it would require ~2000 IU of *additional* D each day to shift the distribution sufficiently to ensure that no more than 2.5 % fell below 80 nmol/L



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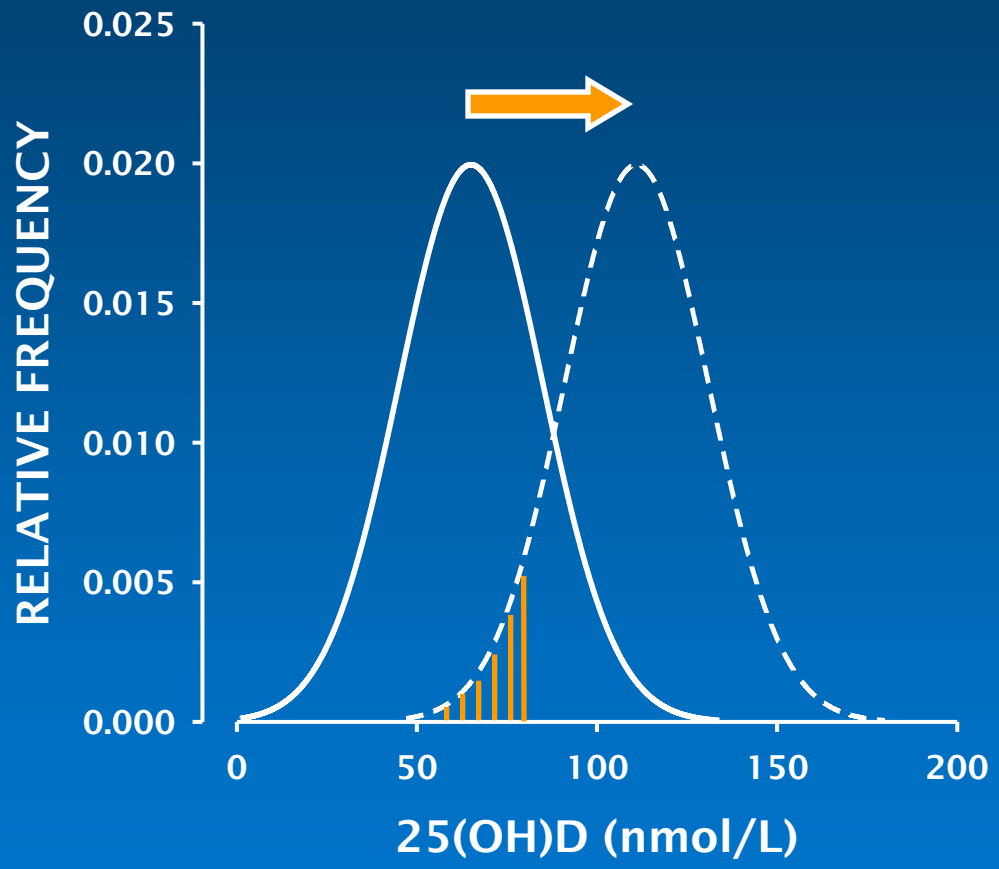
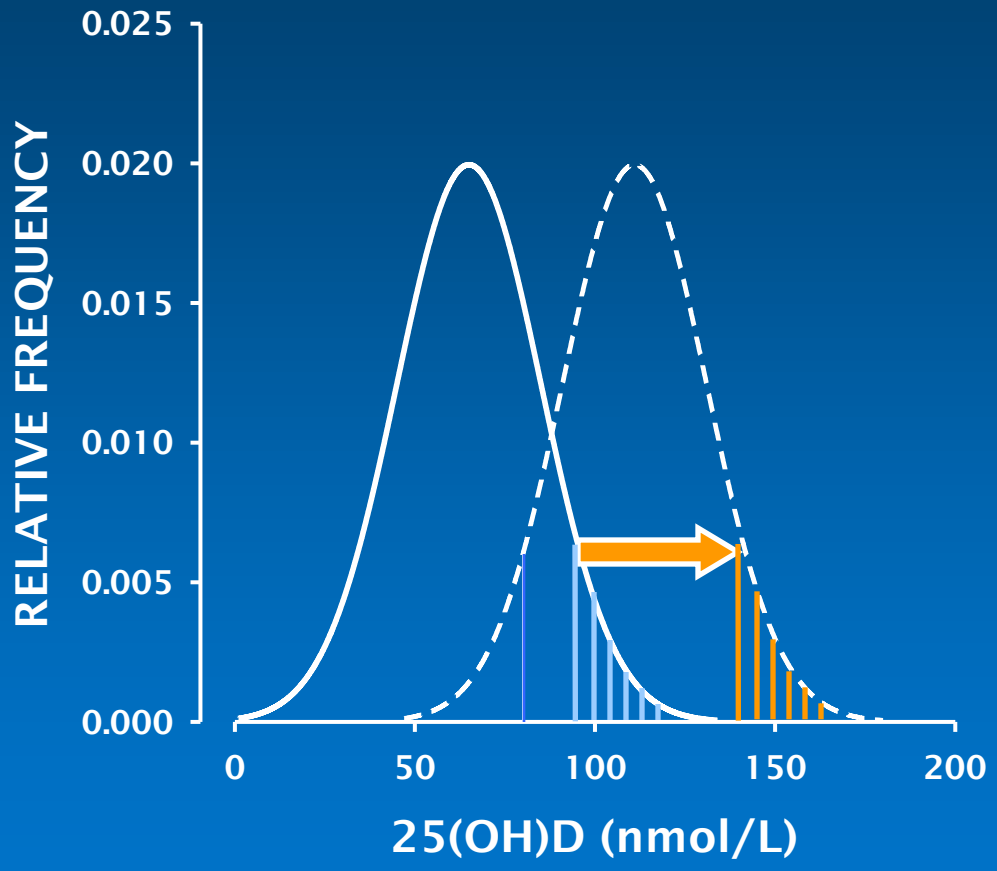


SHIFTING THE DISTRIBUTION

- what about those already 2 SD above the mean?
- the rise with an extra ~2000 IU/d would be predicted to bring them to no more than 170–180 nmol/L – well below the toxic range

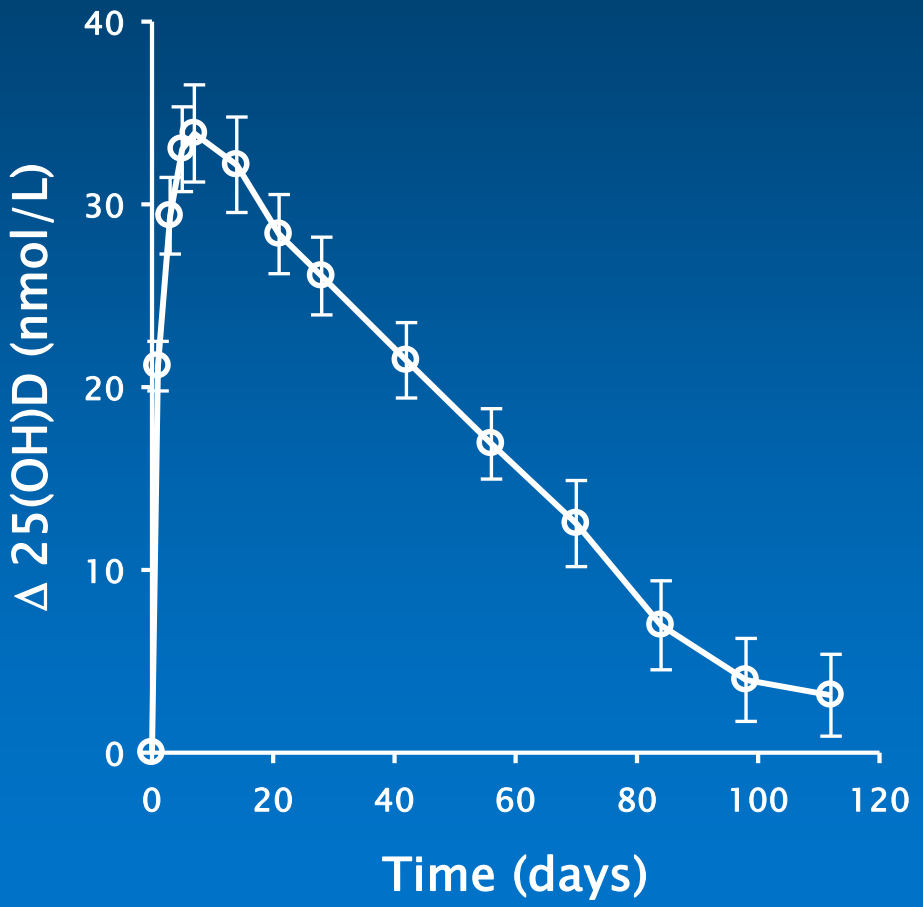


IN BRIEF

- the case is strong for raising population-level serum 25(OH)D to an extent sufficient to ensure that only ~2.5% fall below 80 nmol/L
- doing so would be safe and inexpensive
- the current TUIL (2000 IU/d) constitutes a psychological (not substantive) barrier to the needed policy changes, and must be revised upwards

RESPONSE TO 100,000 IU

- 30 healthy adults
- 100,000 iu Vitamin D_3 by mouth
- baseline 25(OH)D: 69.9 ± 19.6 nmol/L



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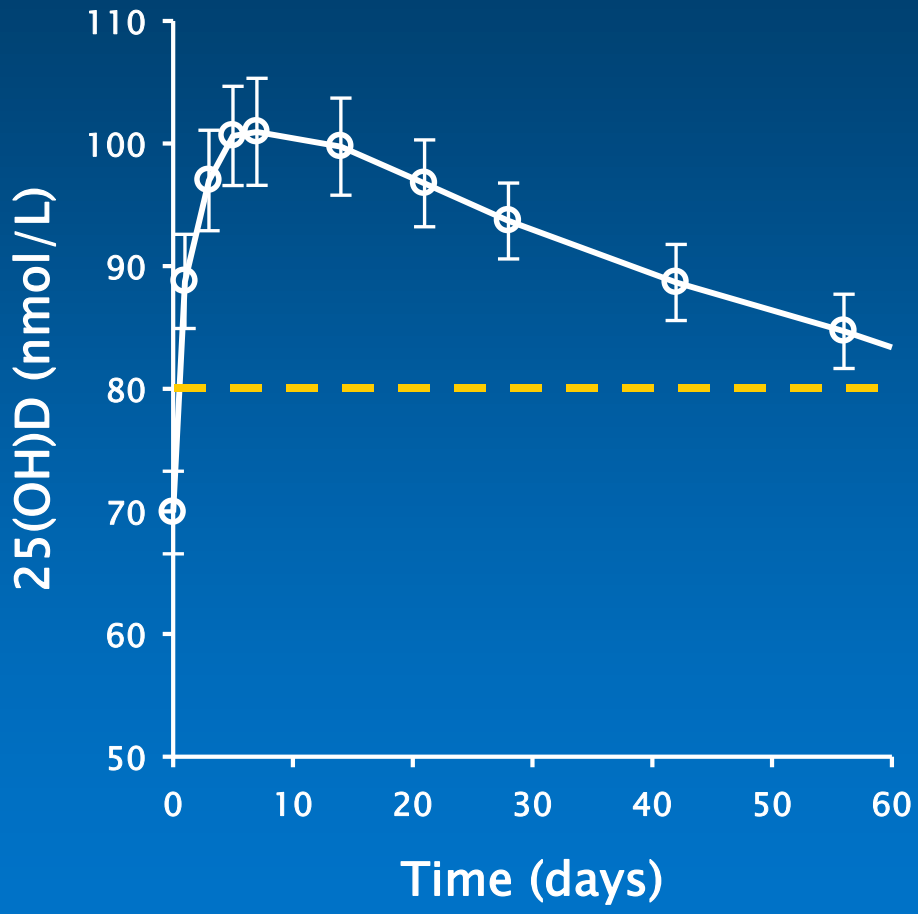
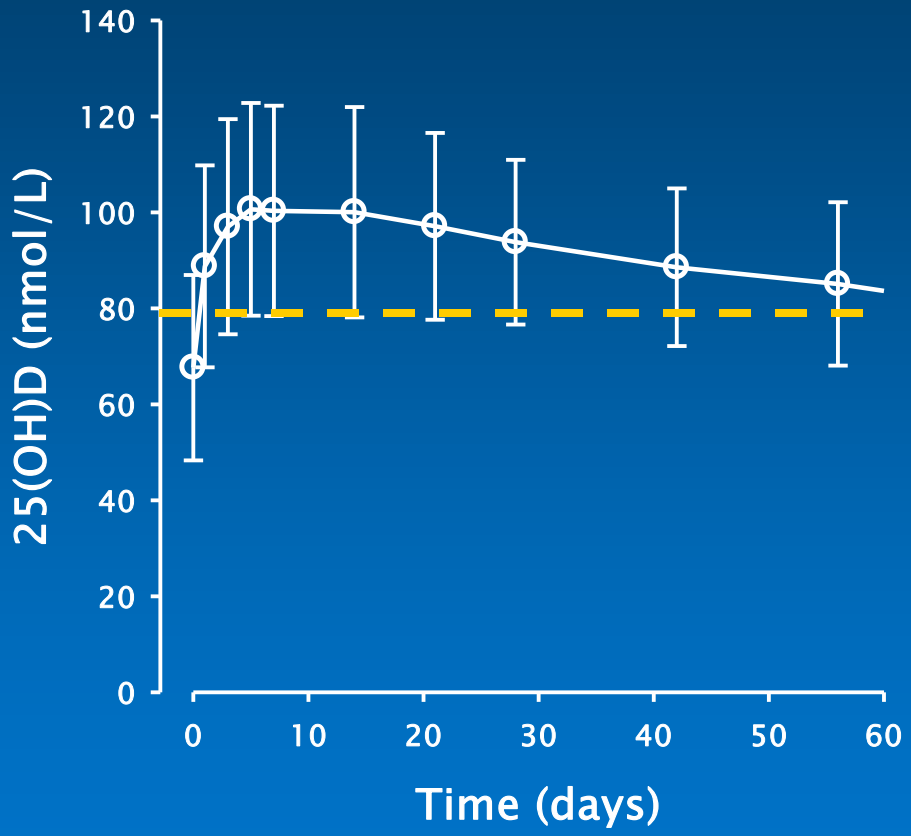
- 100,000 iu Vitamin D_3 by mouth
- baseline 25(OH)D: 69.9 ± 19.6 nmol/L



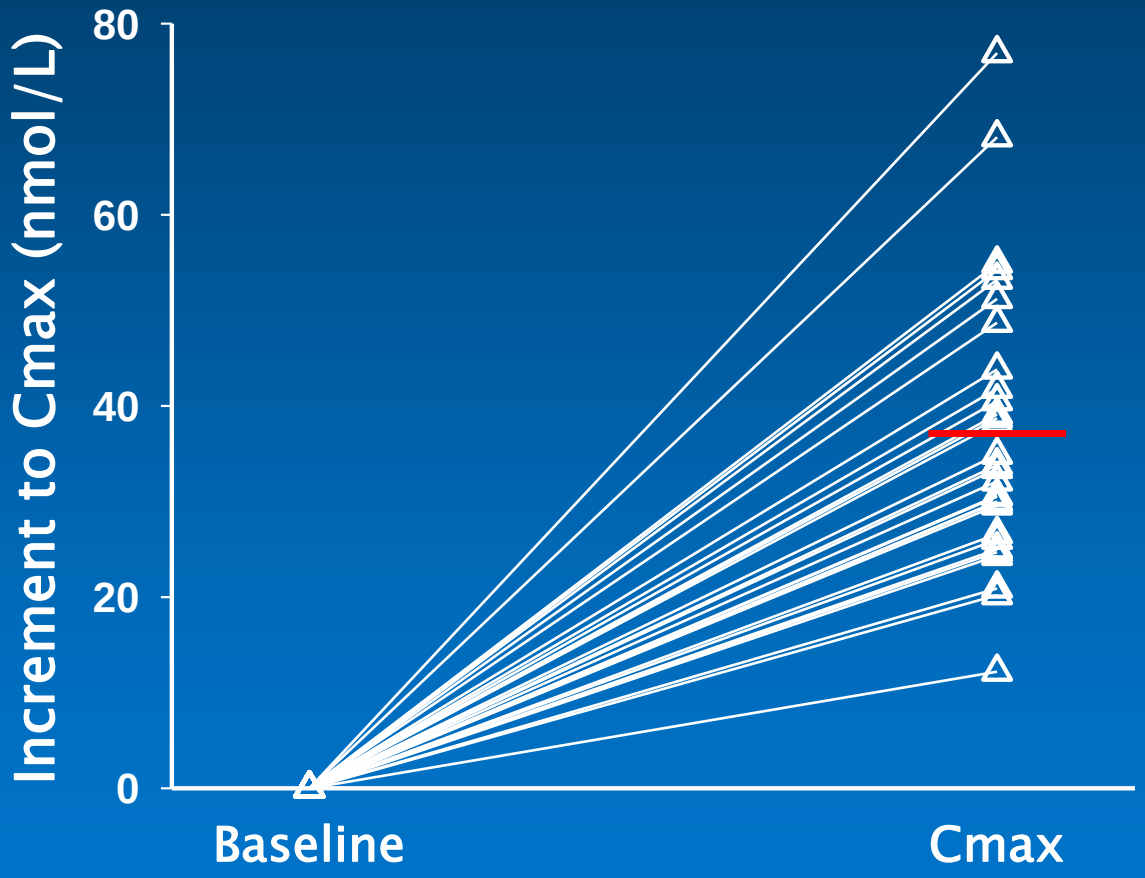
RESPONSE TO 100,000 IU

- 30 healthy adults
- 100,000 iu Vitamin D_3 by mouth
- baseline 25(OH)D: 69.9 ± 19.6 nmol/L



VARIABILITY OF 25(OH)D RESPONSE*

- Δ 25(OH)D to C_{max} ranged from +12 nmol/L to +76 nmol/L
- ~half of the variability due to body size

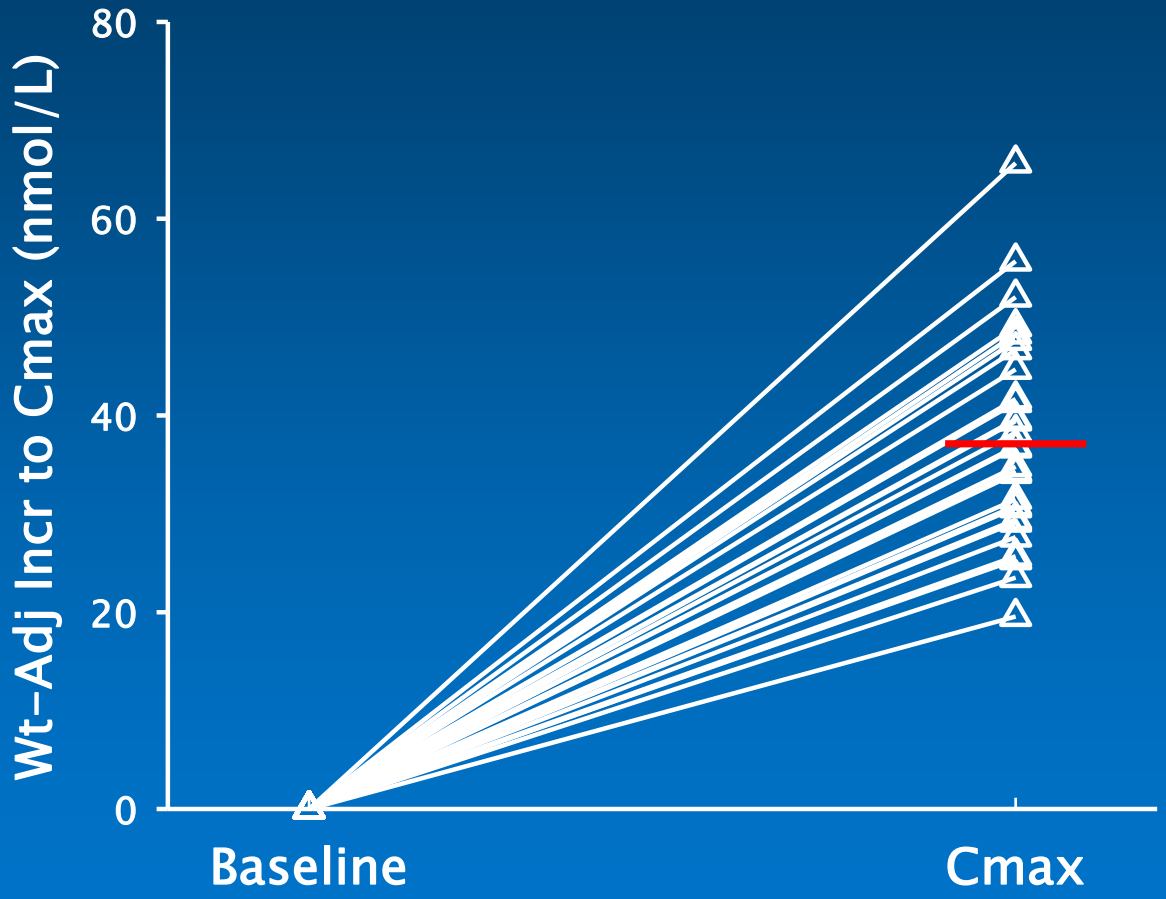


CU ORC

*Ilahi, Armas, & Heaney (2008)

VARIABILITY OF 25(OH)D RESPONSE*

- Wt-adjusted Δ 25(OH)D to C_{max} ranged from +20 nmol/L to +66 nmol/L



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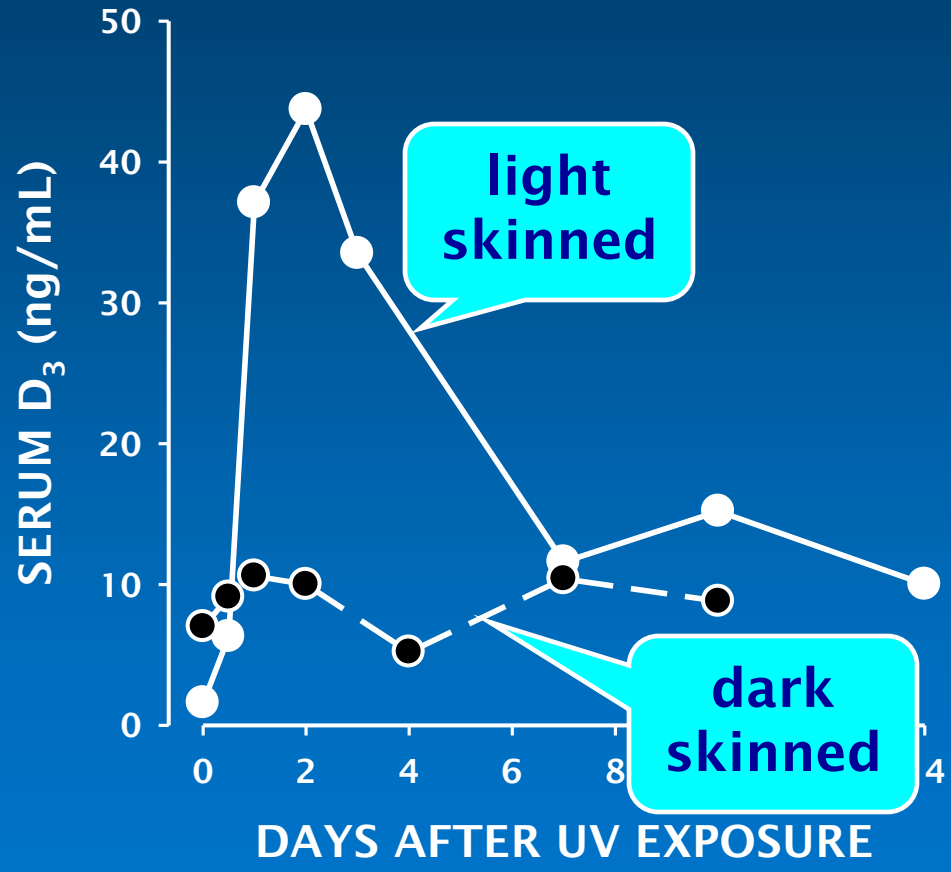
POSSIBLE EXPLANATIONS

- variable absorption of cholecalciferol
- variable 25-hydroxylation
- variable 24-hydroxylation & degradation, i.e., variation in 25(OH)D half life

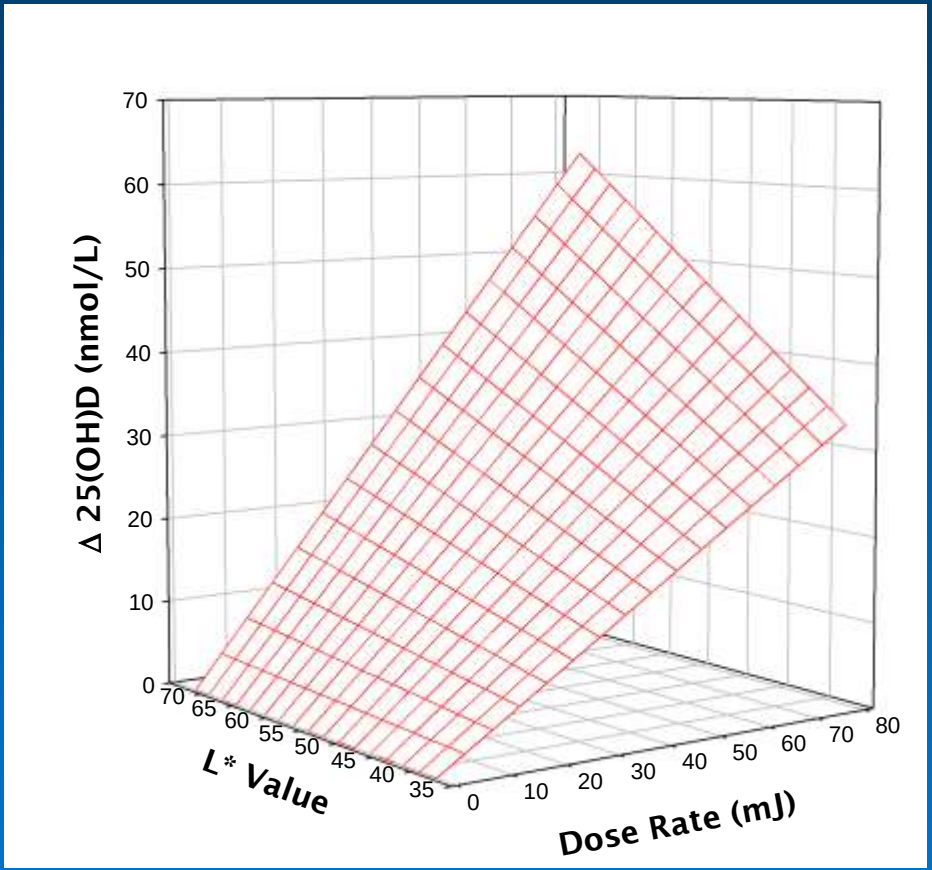
SKIN COLOR & VIT D SYNTHESIS

- total body exposure to 0.054J/cm^2 UV (1.5 MED for light skinned individuals)
- Holick *Ann NY Acad Sci* 1985



SKIN COLOR, UV-B, & RESPONSE*

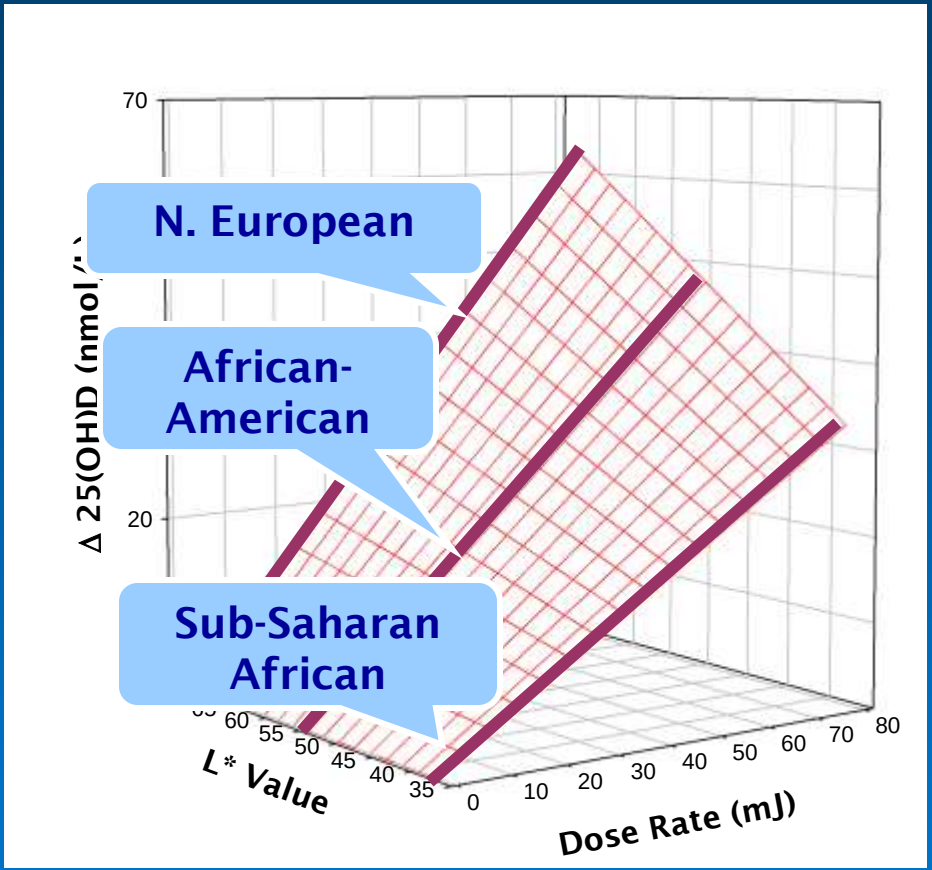
- 72 subjects
- UV-B radiation 3x/wk for 4 wks
- pigmentation measured on unexposed skin with SmartProbe® (L* value)
  - (high = light)



*Armas et al., J Am Acad Derm 2007

SKIN COLOR, UV-B, & RESPONSE*

- $Z = 0.01094*X*Y$
  - $Z = \Delta$ 25(OH)D
  - X = Lightness
  - Y = UV-B dose (mJ/cm^2)
- $R^2 = 0.794$



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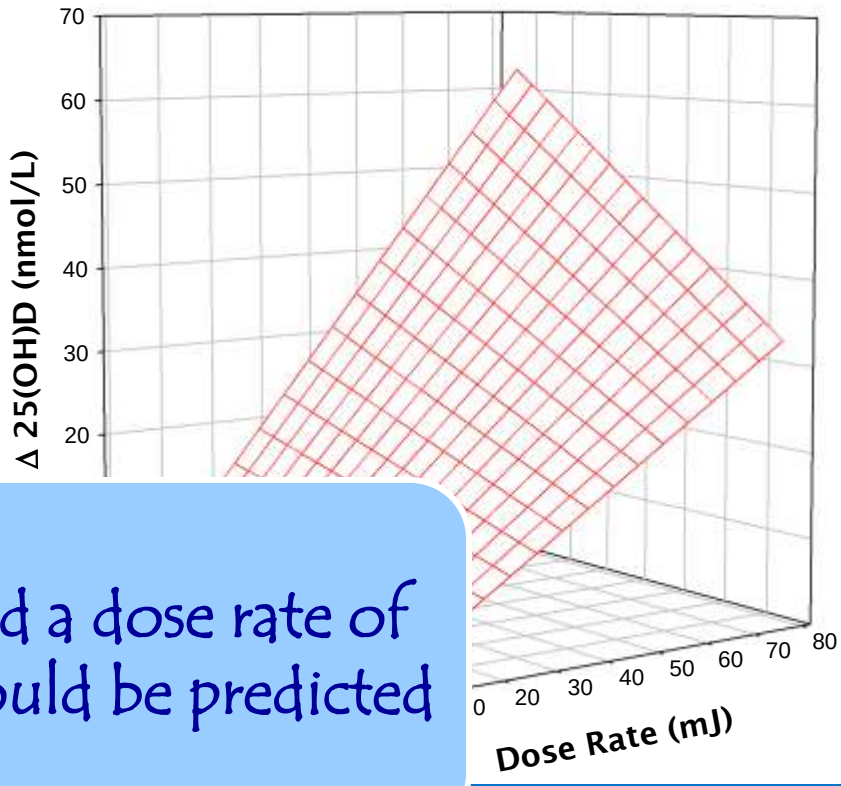
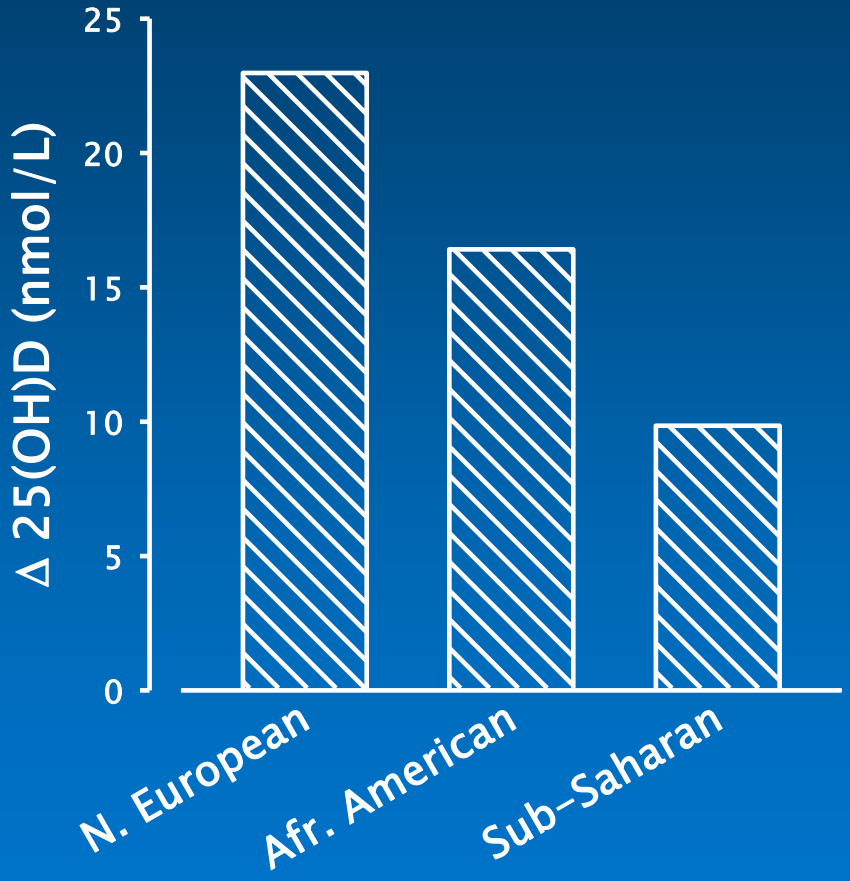


A worked example:
for a skin lightness of 60 and a dose rate of 40 mJ 3x/wk, 25(OH)D would be predicted to rise by 26 nmol/L

*Armas et al., J Am Acad Derm 2007

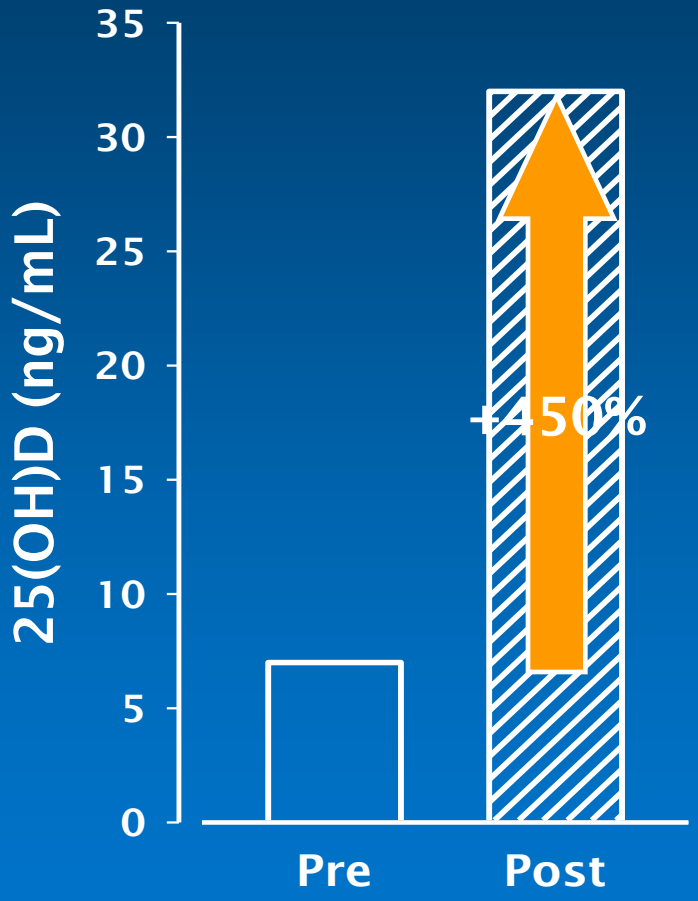
25(OH)D RESPONSE TO UV-B

- 30 mJ 3x/wk (< 1 MED)
- 90% whole body
- rise in 25(OH)D measured at 4 wks
- Armas et al. 2007



SHORT BOWEL & D STATUS*

- 57 y/o woman with Crohn's disease and short bowel
- bone pain & muscle weakness
- 25(OH)D <20 ng/ml
- failed to respond to usual D doses
- tanning bed for 10 min 3x/wk – 6 mo



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*Koutkia et al., Gastroenterology 2001;121:1485–88

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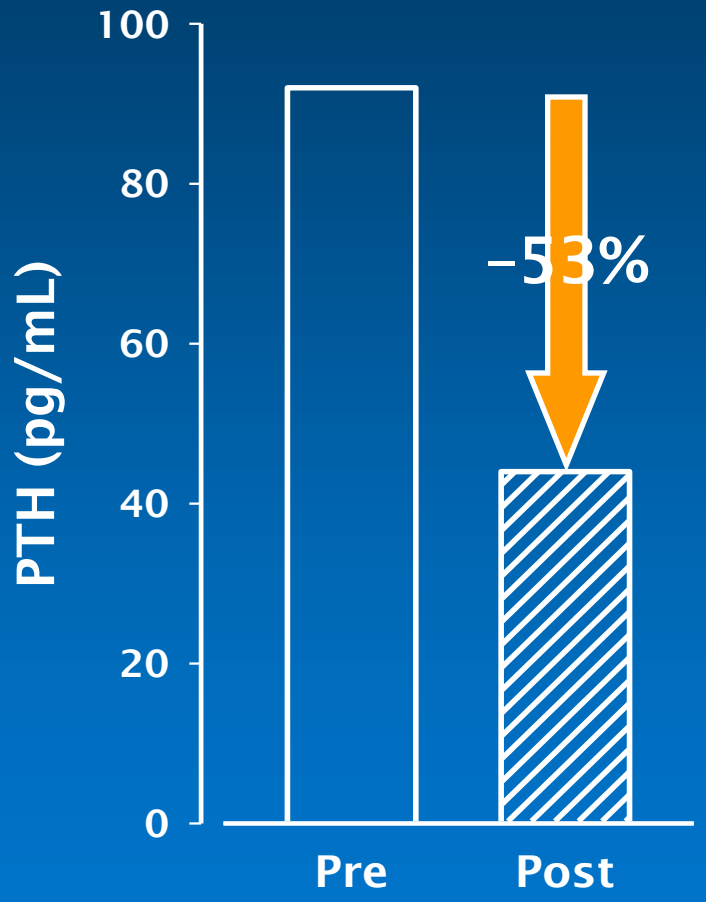

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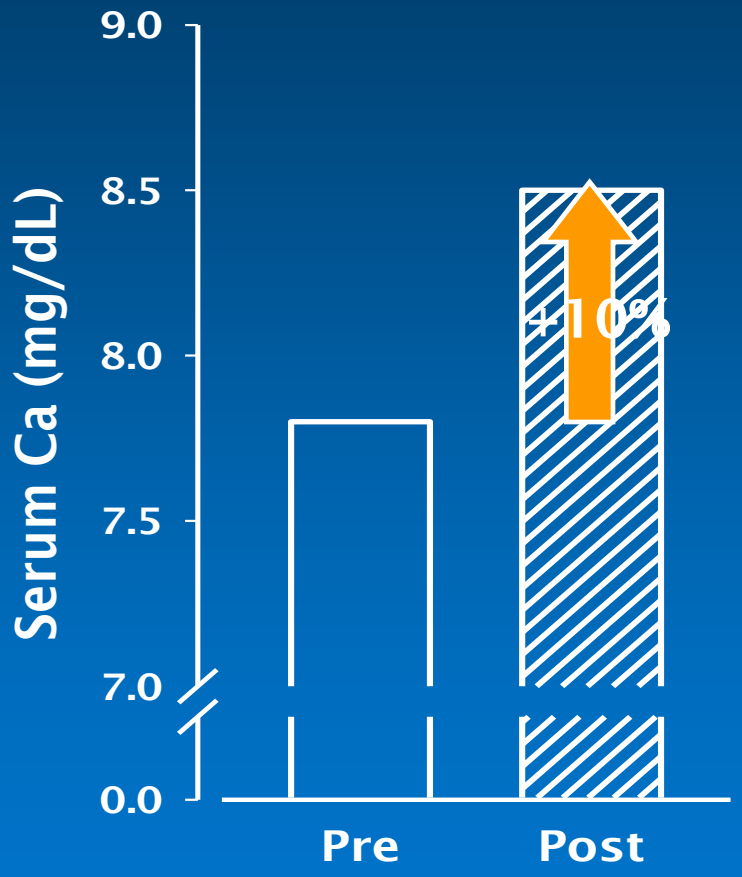

CU ORC

*Koutkia et al., Gastroenterology 2001;121:1485–88

CONCLUSIONS

- optimal serum 25(OH)D is at least 80 nmol/L [100-150 nmol/L better]
- at 80 nmol/L the body uses ~4000 IU/d
- sun exposure typically provides perhaps half of that total
- moving the population to a level so that no more than 2.5% are below 80 nmol/L will require an across-the-board increase of at least 2000 IU/d
- doing so is safe

REVIEW

1. Conversion is quantitative at typical inputs; little or no D_3 in body
2. Bone, cardiovascular, immune, cancer
3. Ca absorption suboptimal below 80 nmol/L; raising 25(OH)D to ~80 reduces fracture
4. 25(OH)D elevation is proportional to skin lightness and to UV-B dose
5. each 100 IU/d raises 25(OH)D by ~1 ng/mL