

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

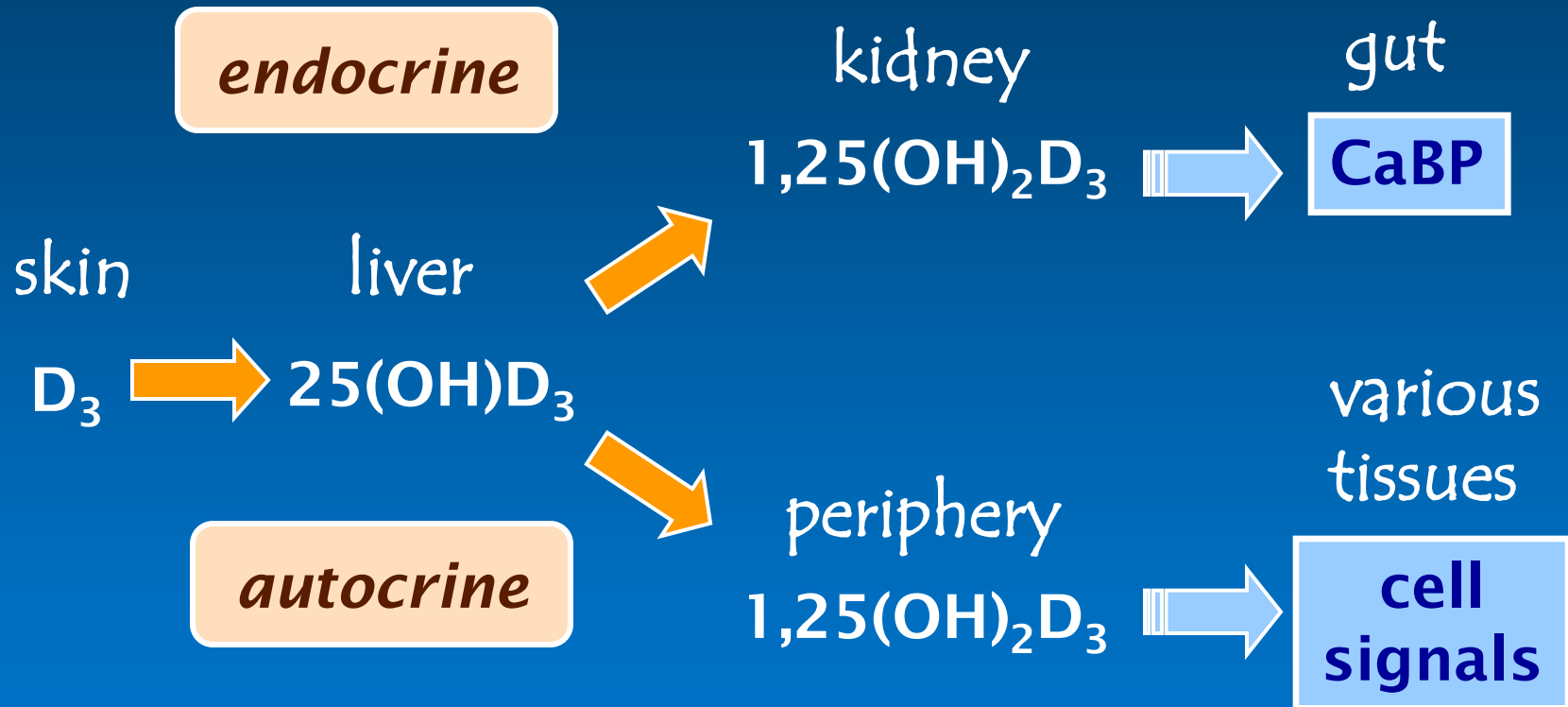
liver

kidney

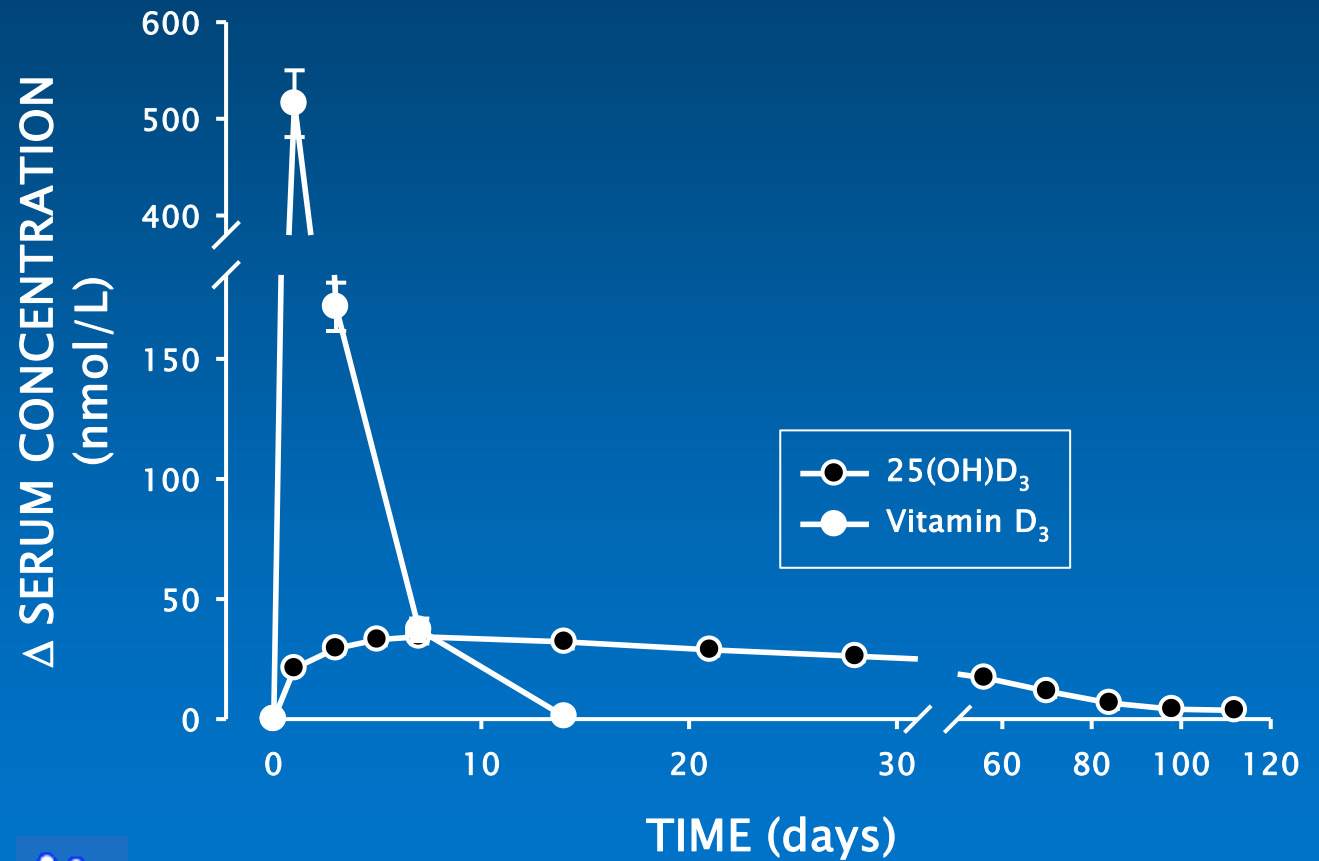
gut



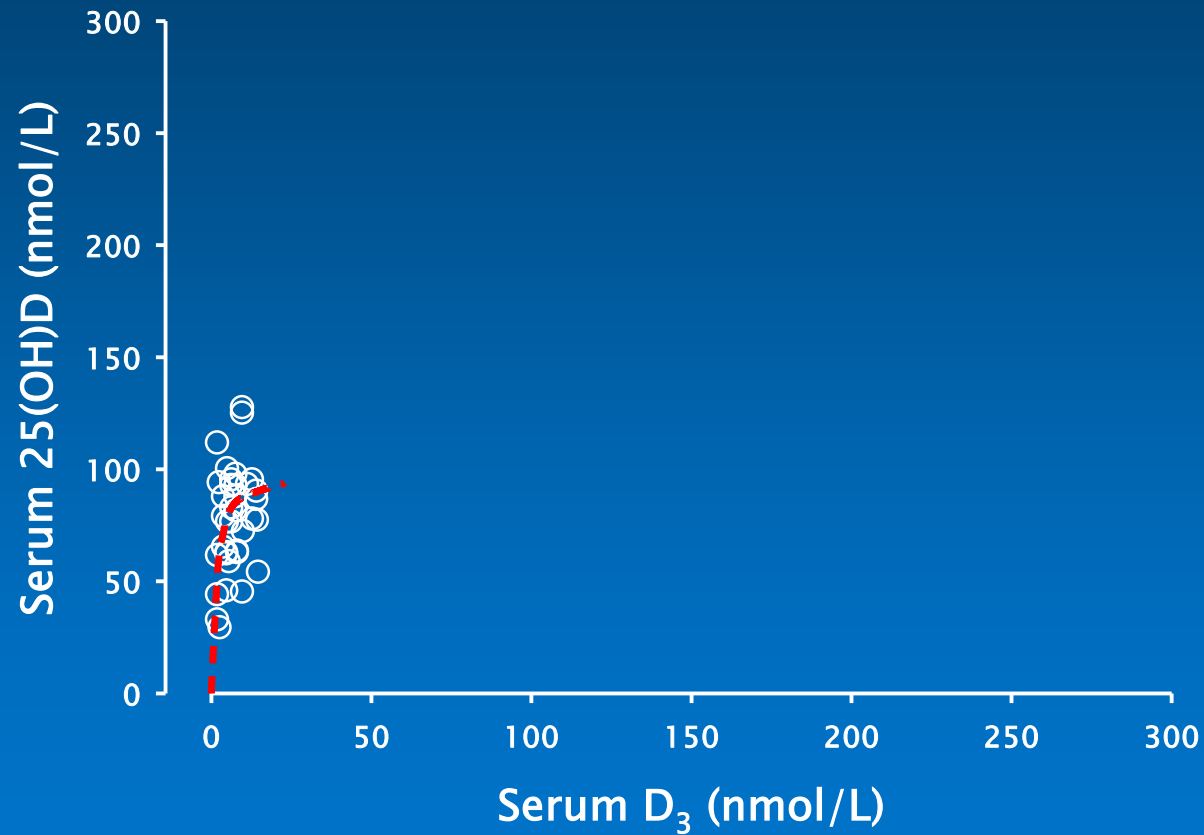
VIT D – EXPANDED SCHEME



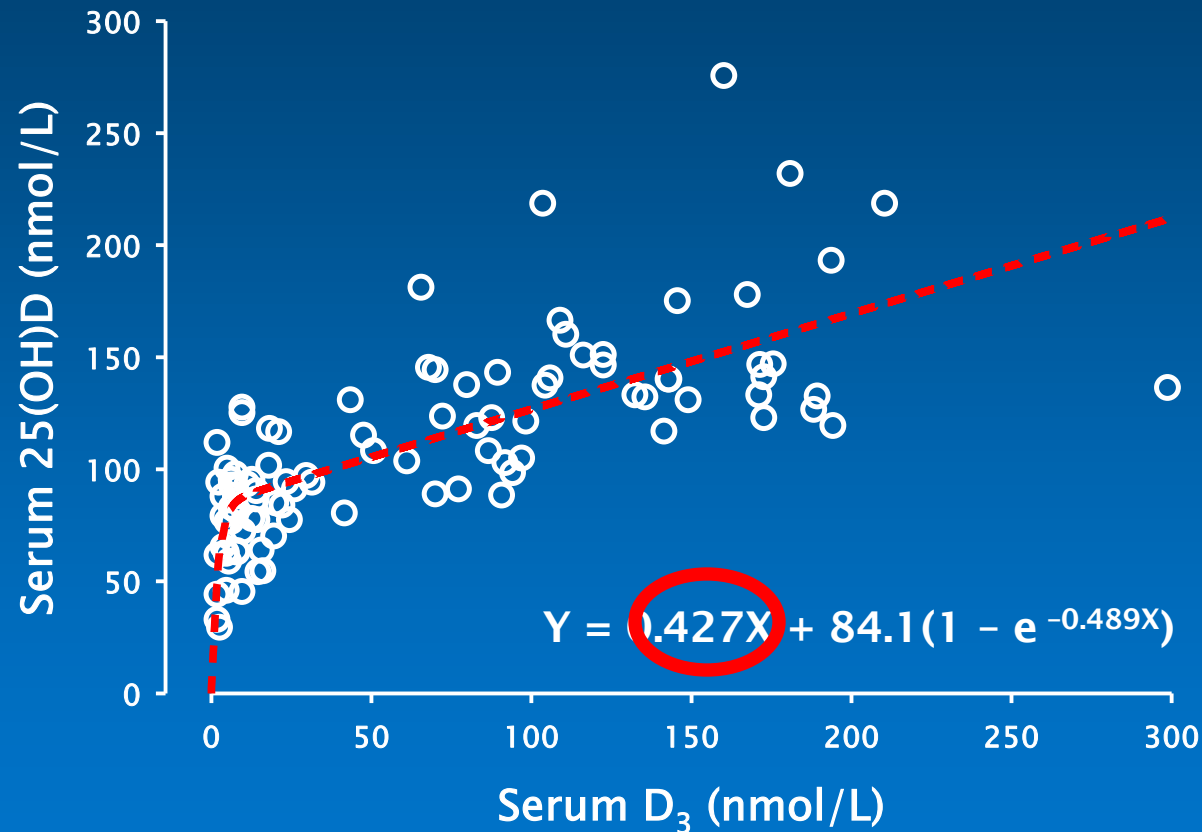
VITAMIN D₃ - 100,000 IU



D_3 to $25(OH)D_3$ CONVERSION



D₃ to 25(OH)D₃ CONVERSION

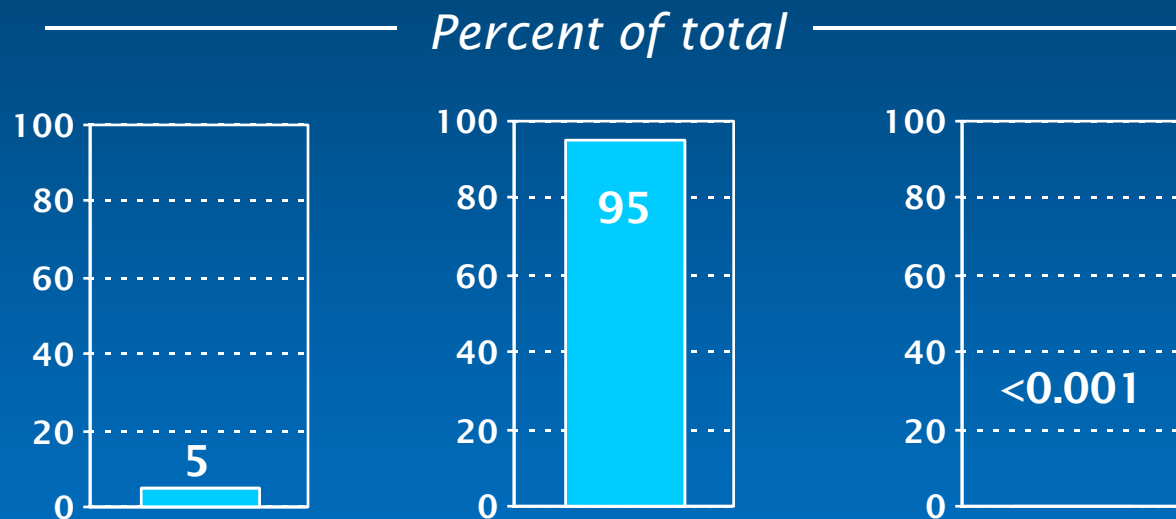


CONCLUSION

- 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

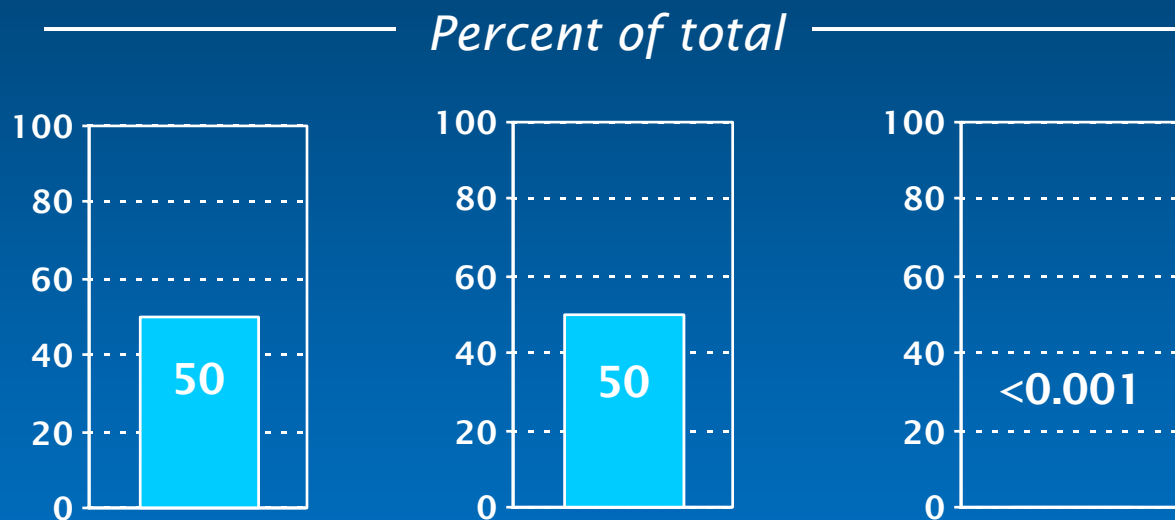
VITAMIN D – HOW STORED

typical intakes:



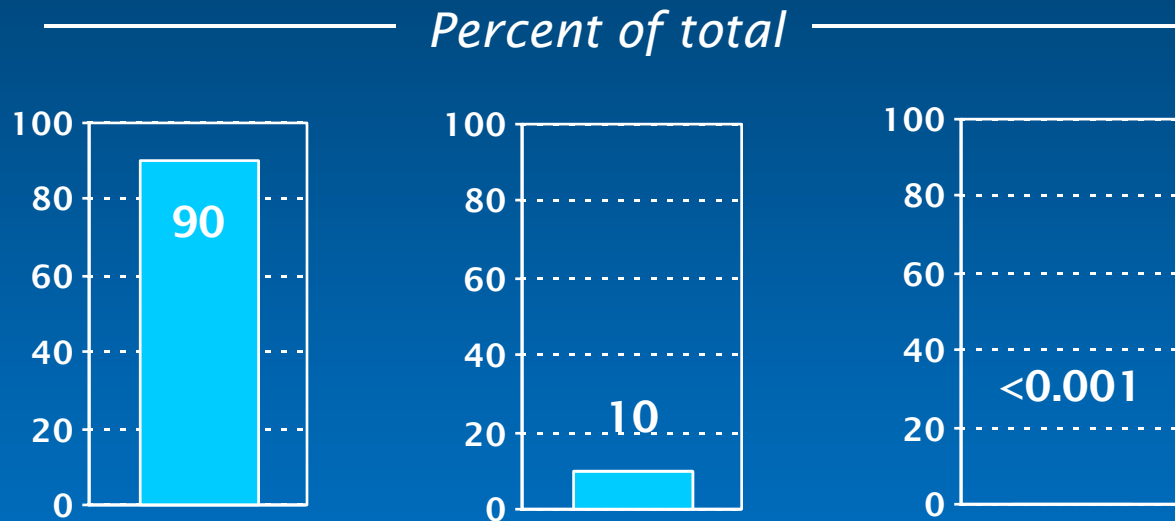
VITAMIN D – HOW STORED

high intakes:



VITAMIN D – HOW STORED

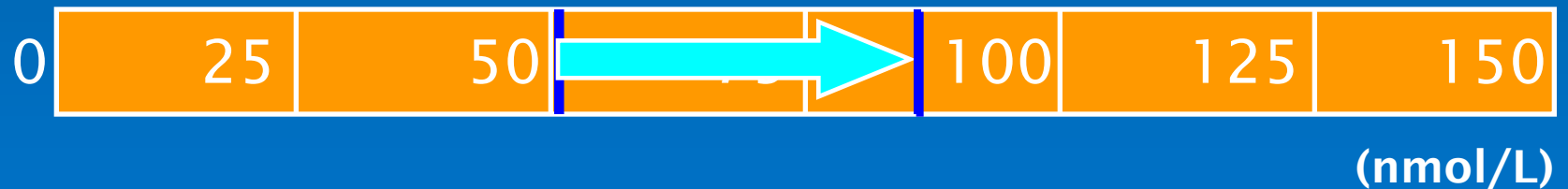
toxic intakes:



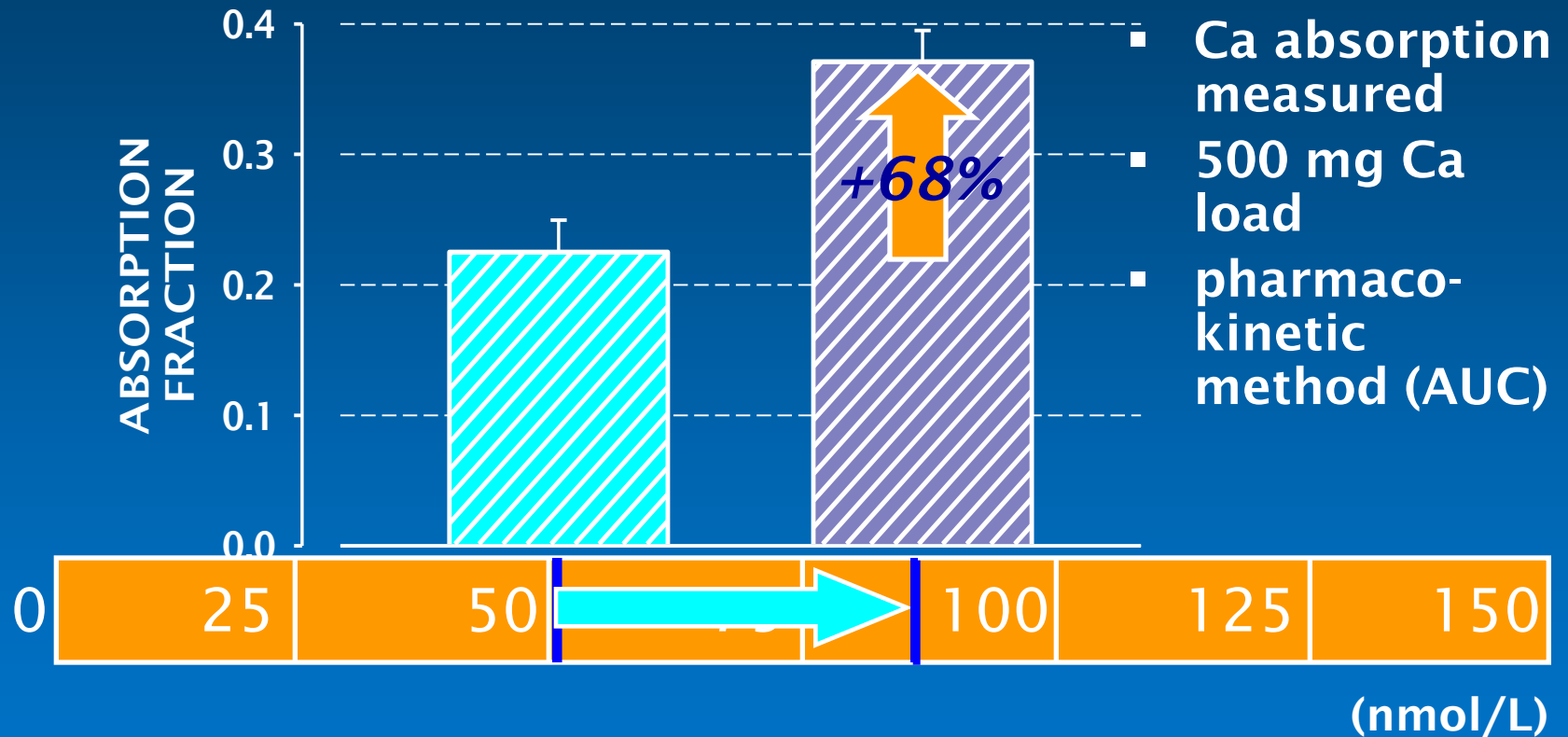
How Much Is Enough?

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)

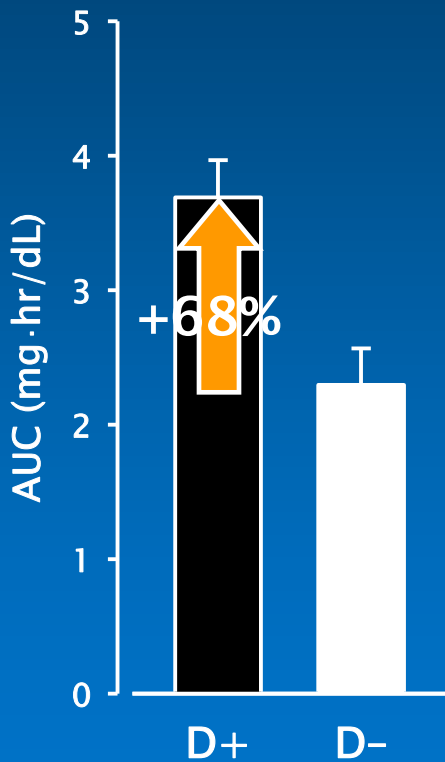


THE 25(OH)D CONTINUUM

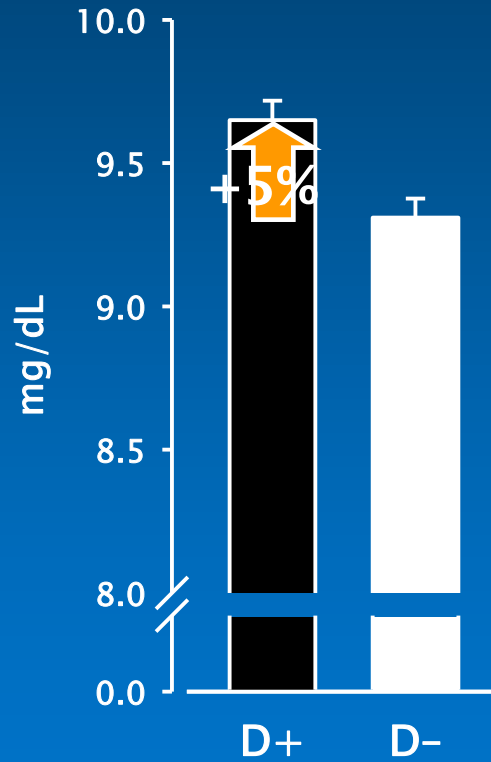


D STATUS & THE Ca ECONOMY

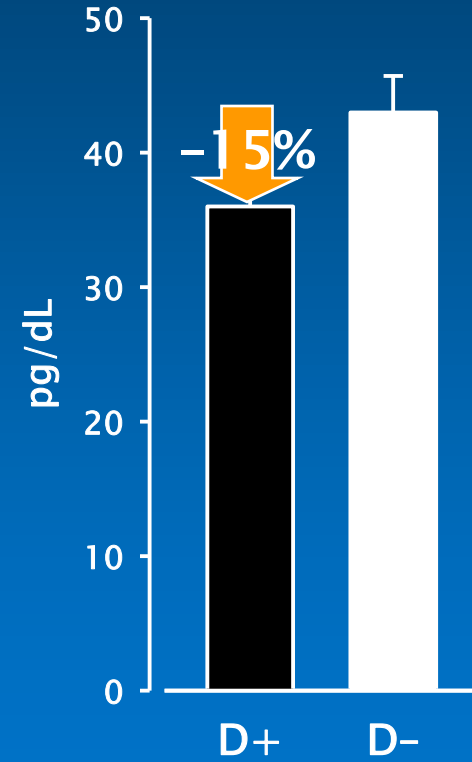
Ca Absorption



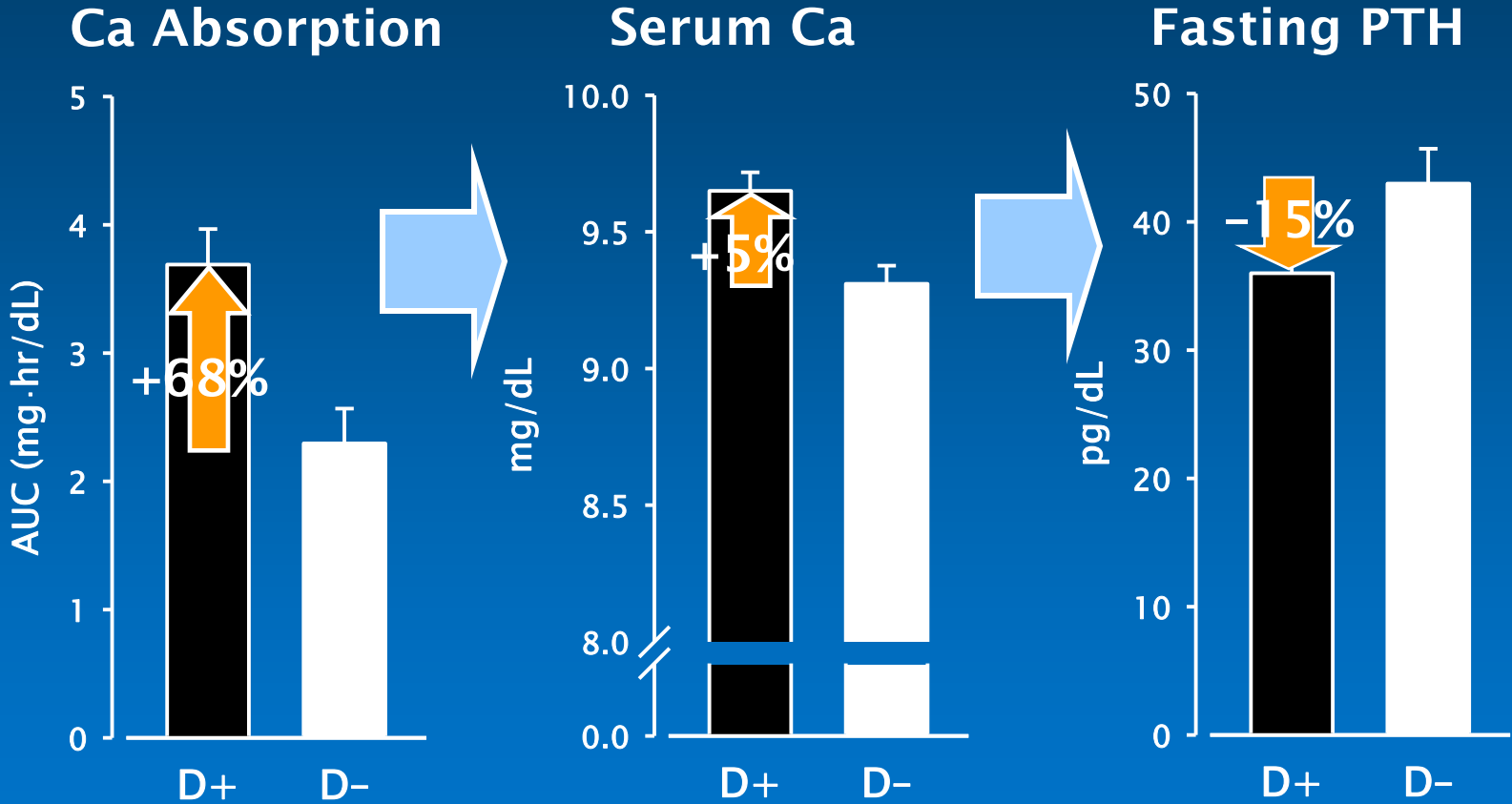
Serum Ca



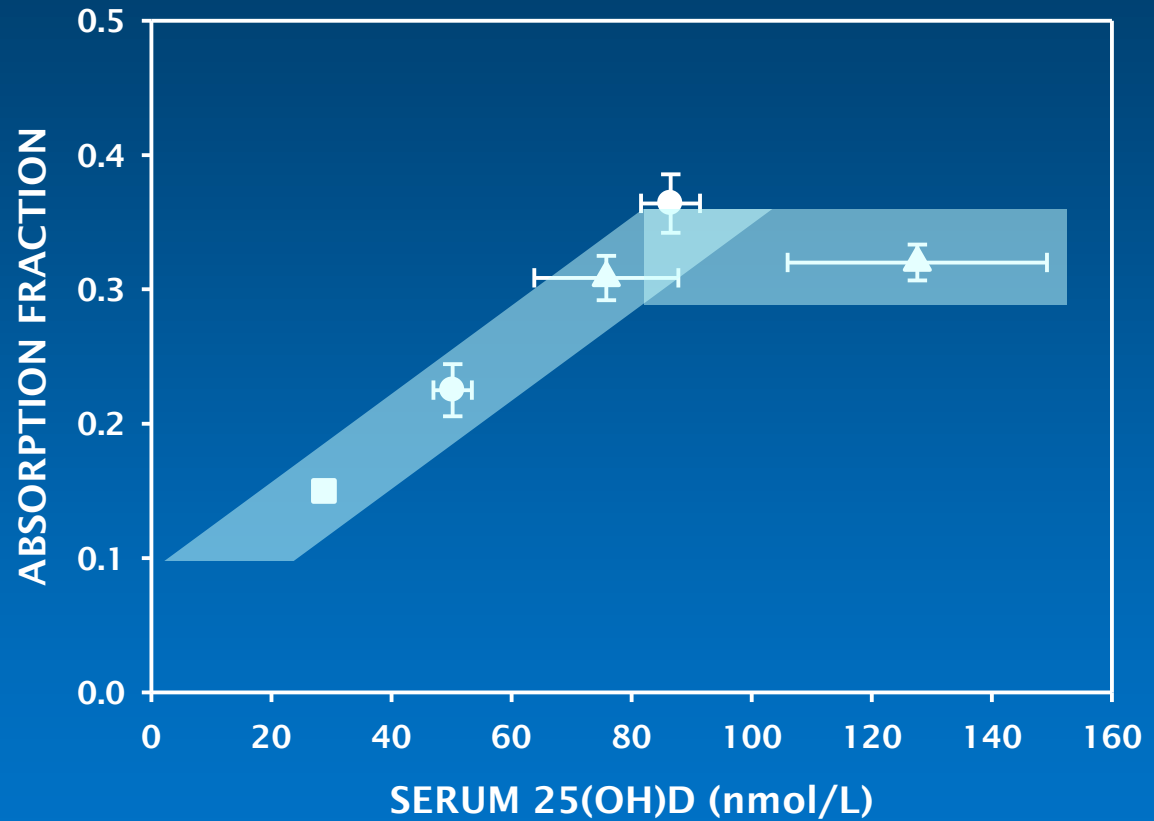
Fasting PTH



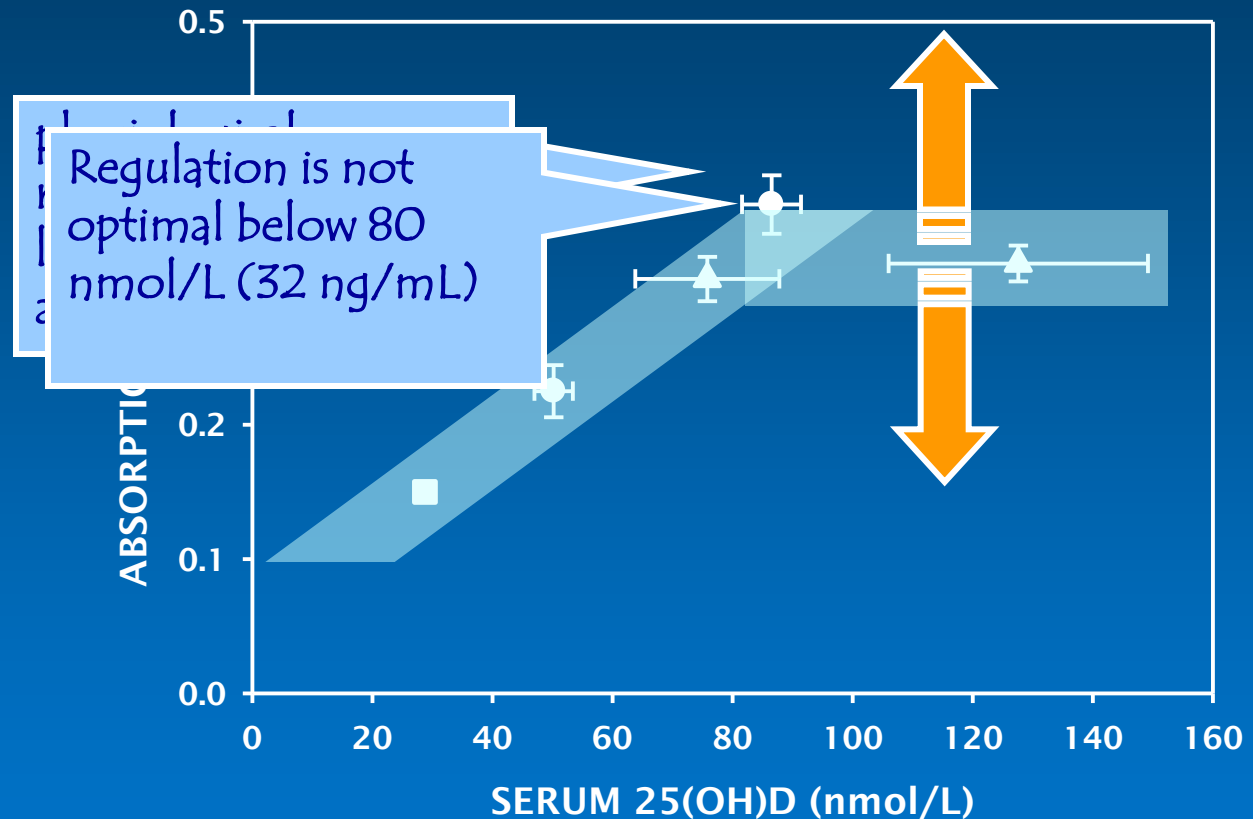
D STATUS & THE Ca ECONOMY



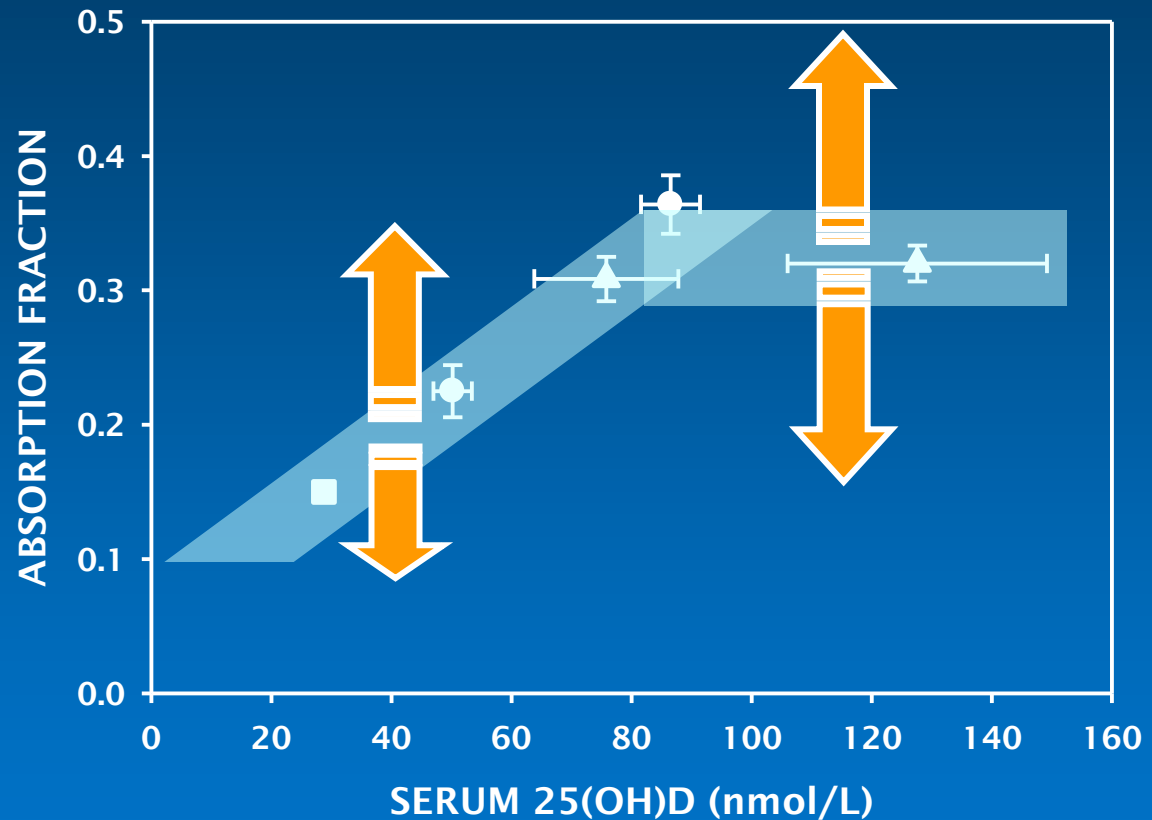
A VITAMIN D THRESHOLD



A VITAMIN D THRESHOLD



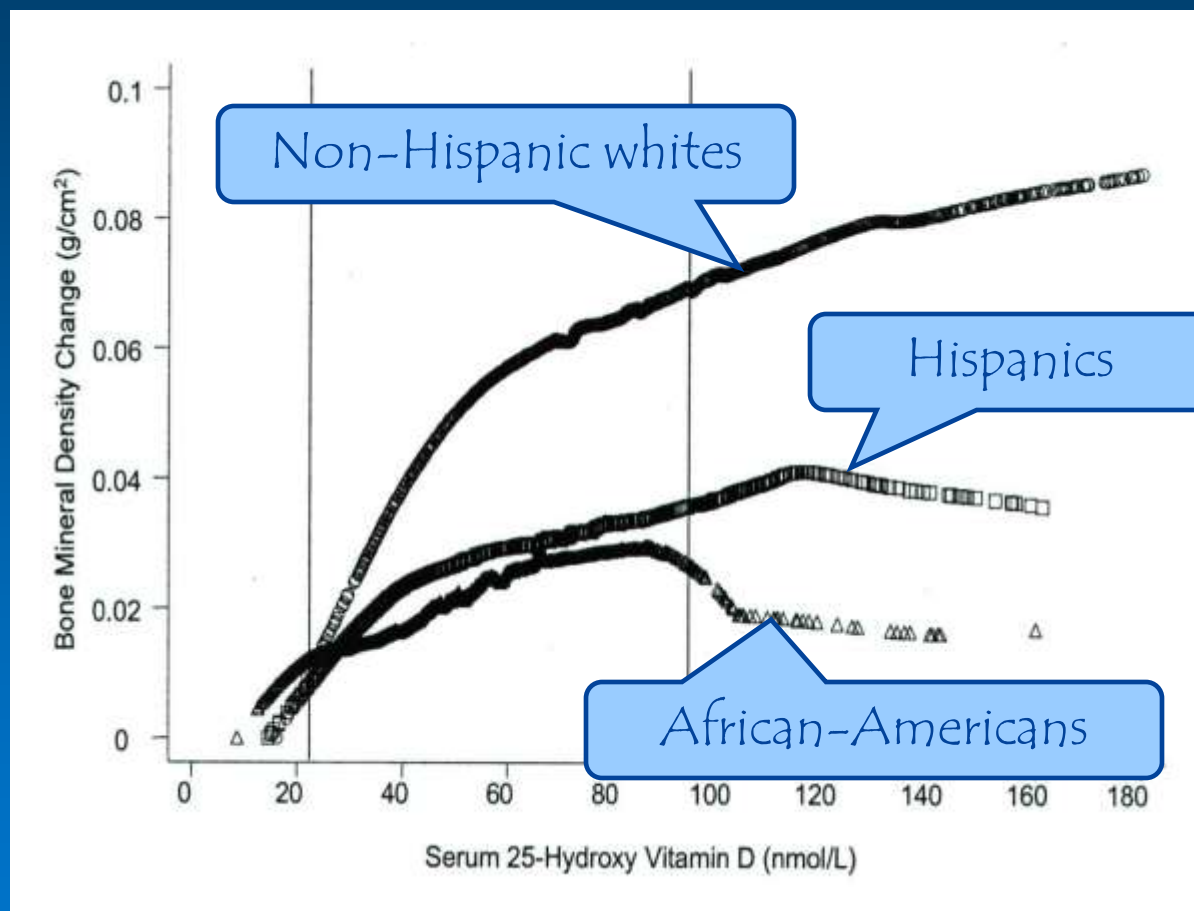
A VITAMIN D THRESHOLD



Bone Mass &
Osteoporotic fractures

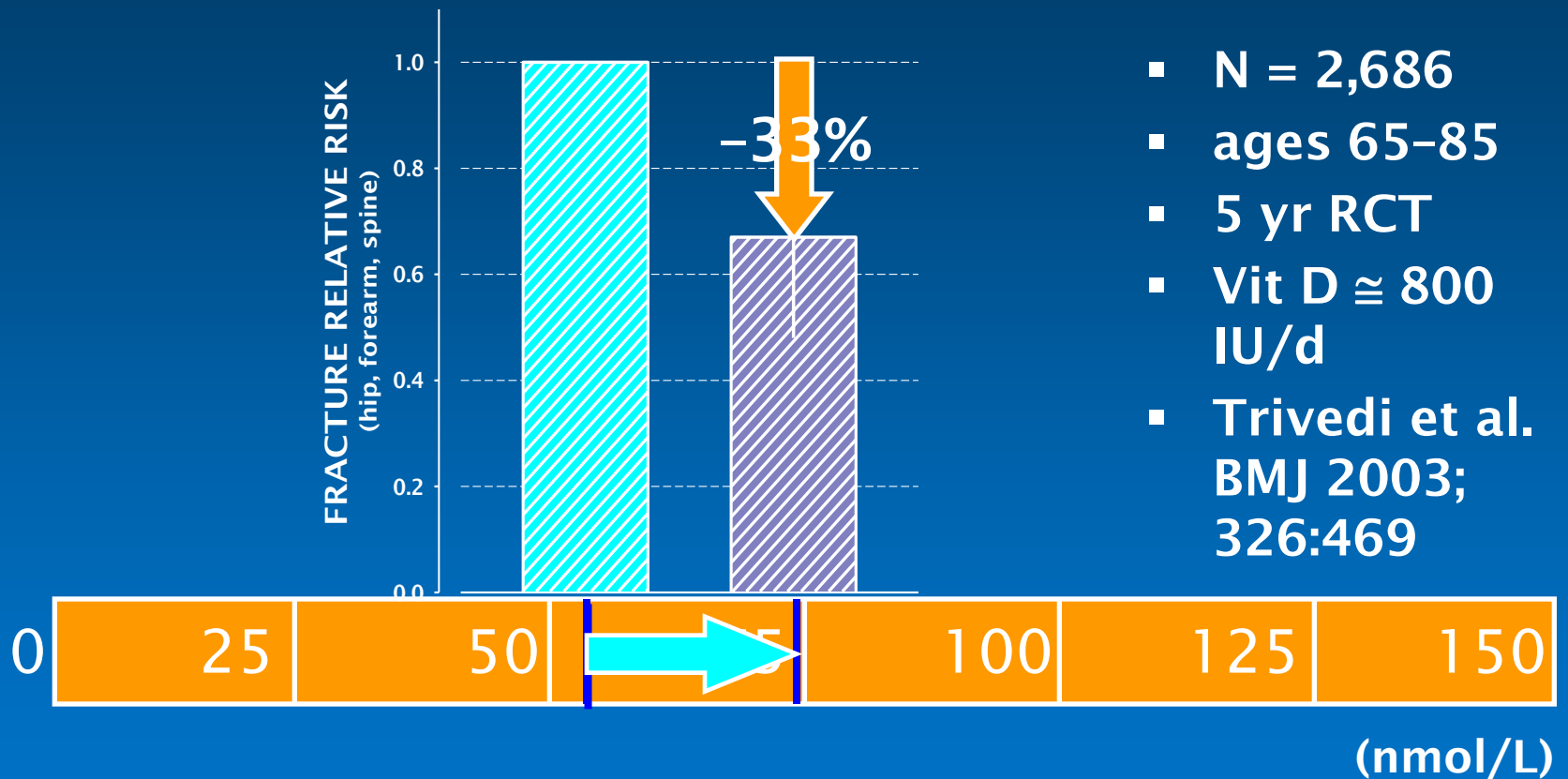
Serum 25(OH)D and Hip BMD

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



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

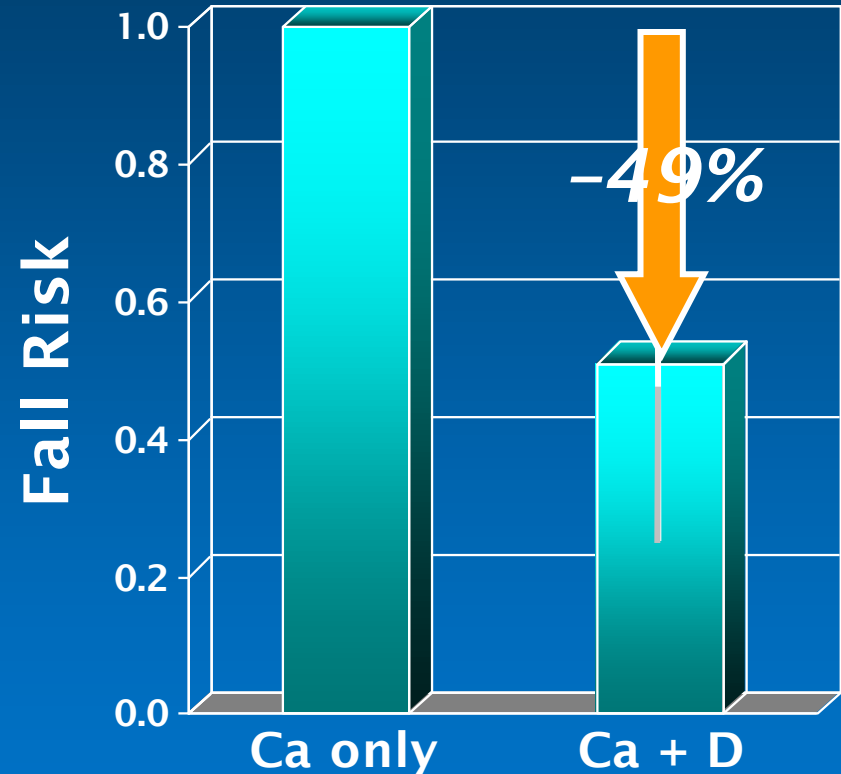
THE 25(OH)D CONTINUUM



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

VITAMIN D & RISK OF FALLING*

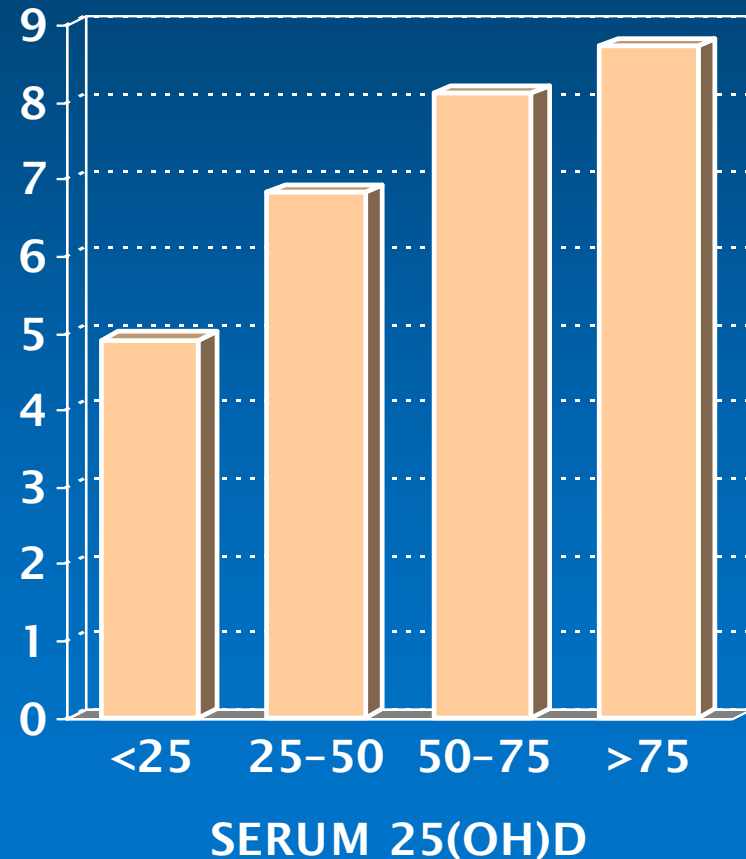
- 122 women
- Age: 63–99
- DB-RCT
 - Ca 1,200 mg/d
 - Ca + 800 IU Vit D
- 12 week duration
- 25(OH)D 12 ng/mL at baseline



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

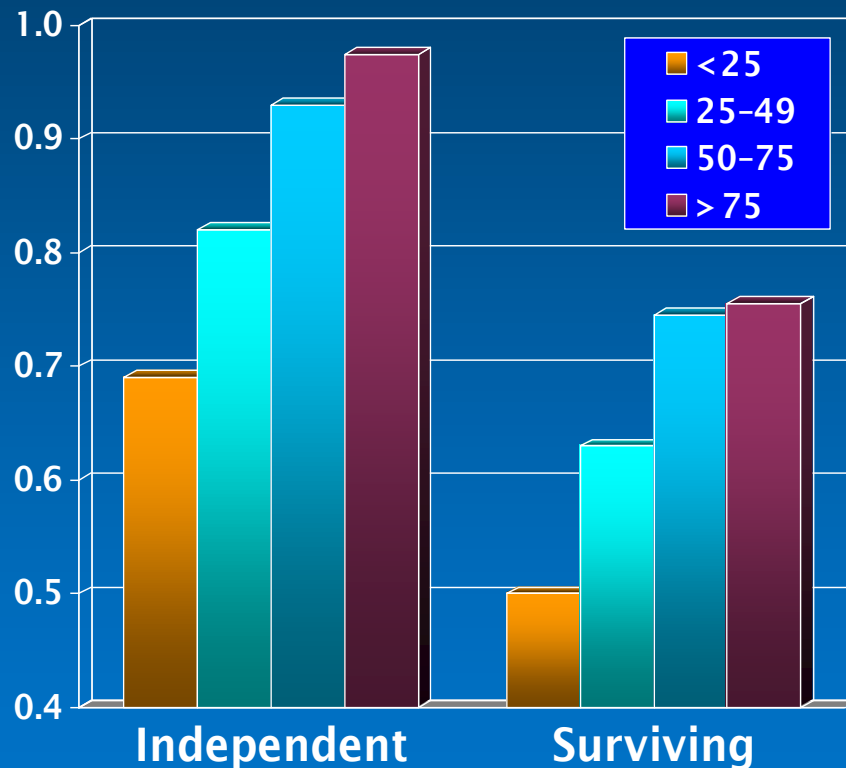
Performance Score



*Wicherts et al. *JBMR*. 2005.

DEATH & DEBILITY

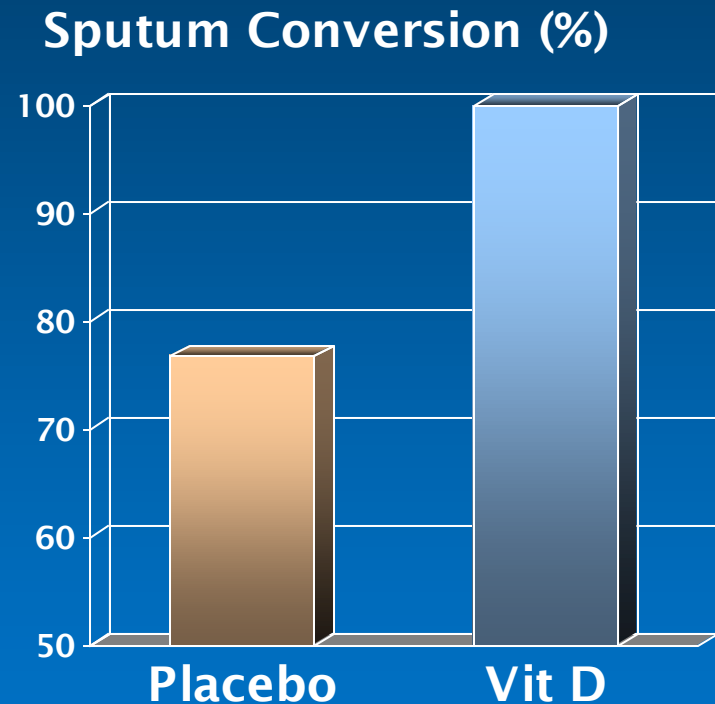
- Amsterdam Longitud. Aging Study
- N = 1509
- 6-yr followup
- evaluated likelihood of independent living & of dying
- Visser et al. (AJCN; 2006; 84:616-22)



Immune System

VITAMIN D & TUBERCULOSIS*

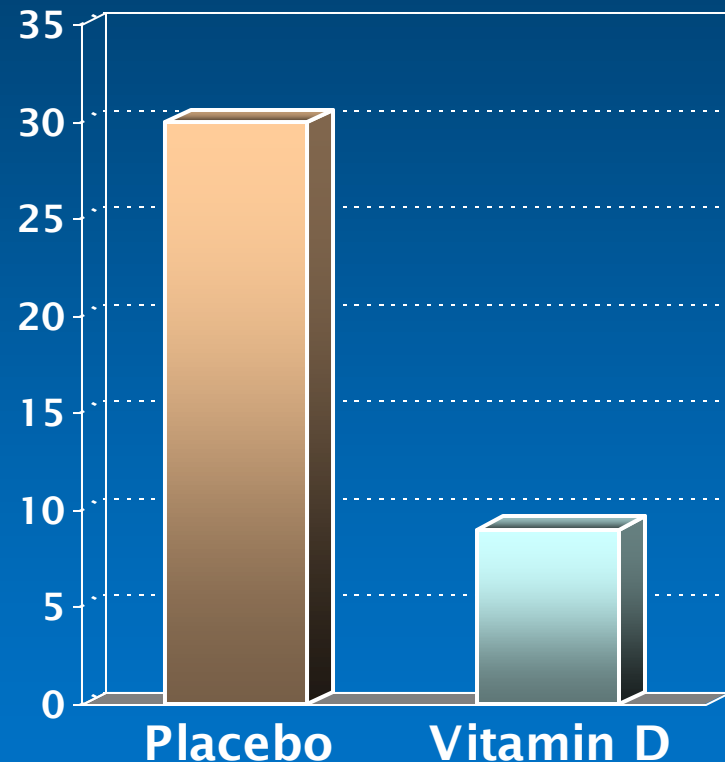
- 67 pts with pulmonary TB
- standard treatment for all
- in addition, randomized to either vit D 10,000 IU/d or placebo
- $P = 0.002$



*Nursyam et al., Acta Med Indones 2006

VITAMIN D & INFLUENZA*

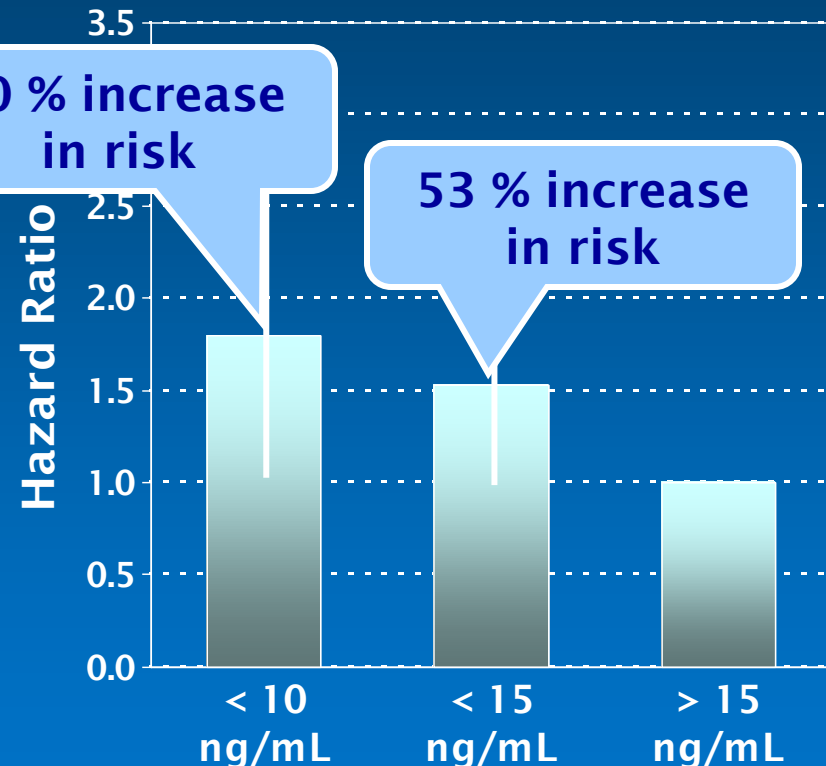
- 208 African-American, postmenopausal women
- 3 yr DB-RCT
- placebo or vit D₃
 - 800 IU/d – 2 yrs
 - 2000 IU/d – 3rd yr
- basal 25(OH)D: 18.8 ± 7.5
- P < 0.002



Cardiovascular effects

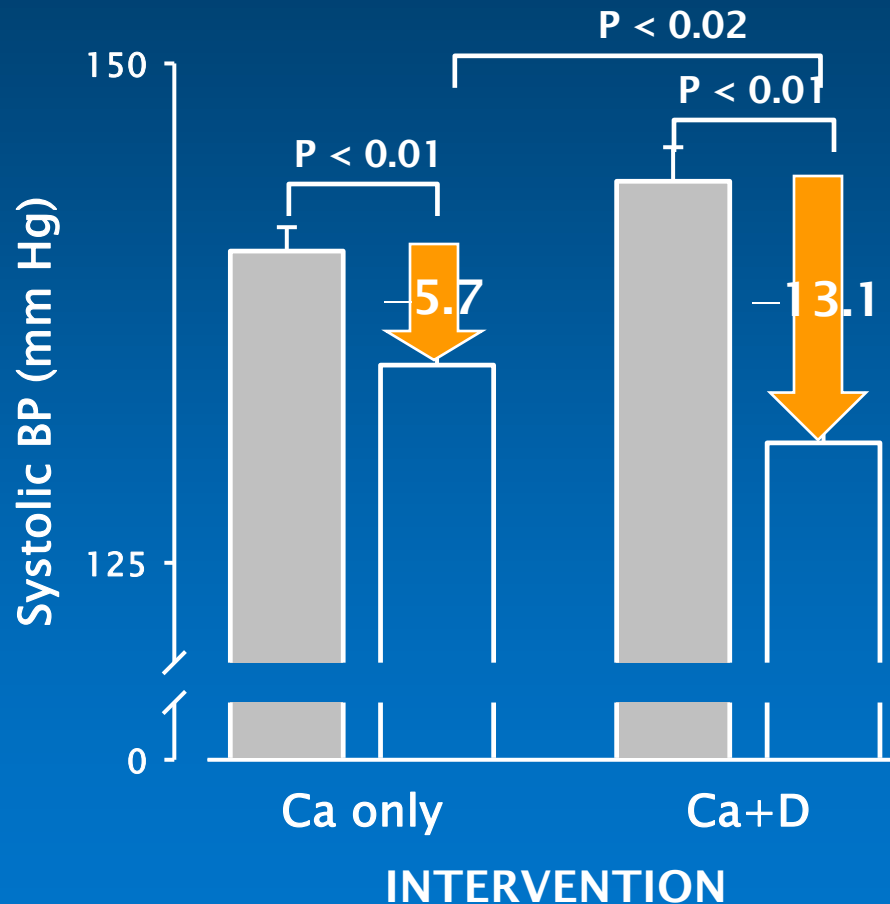
VIT D & CARDIOVASCULAR DISEASE

- 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*

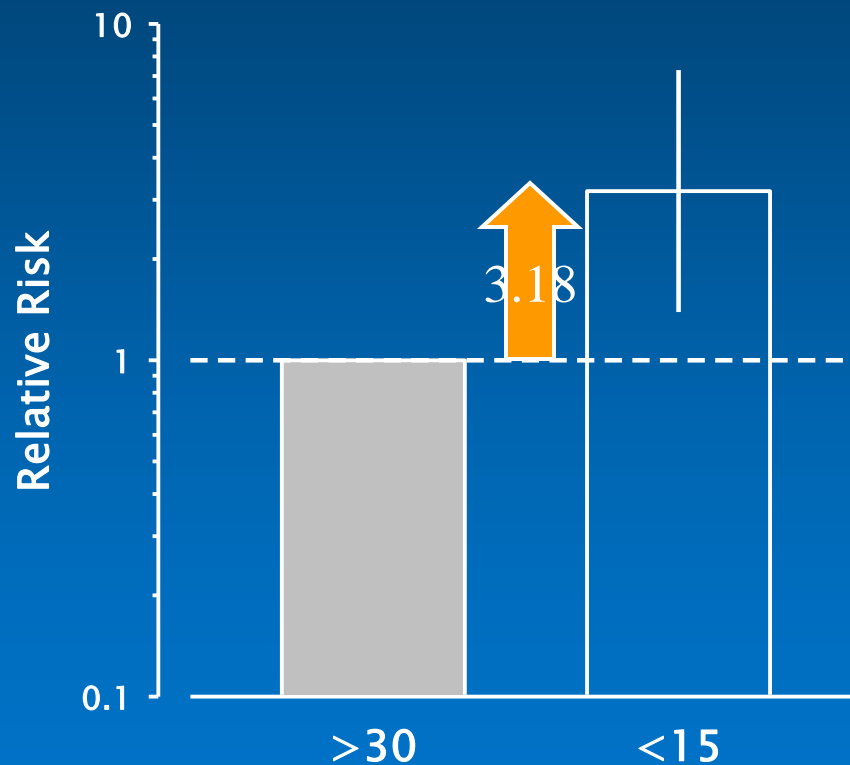
- 148 women, aged 74 ± 1
- DB-RCT
- baseline 25(OH)D < 50 nmol/L
- treated for 8 wks with:
Ca 1200 mg/d or
Ca + 800 IU vit D/d



*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



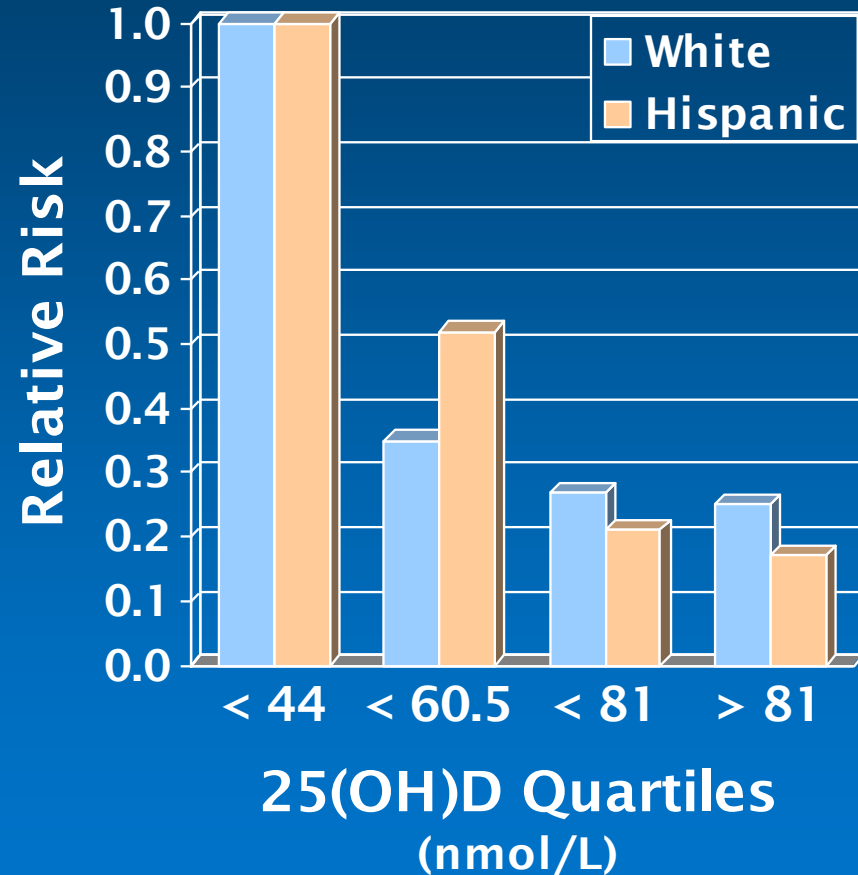
*Forman et al., 2007;Hypertension 49:1063

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

Diabetes & Insulin Sensitivity

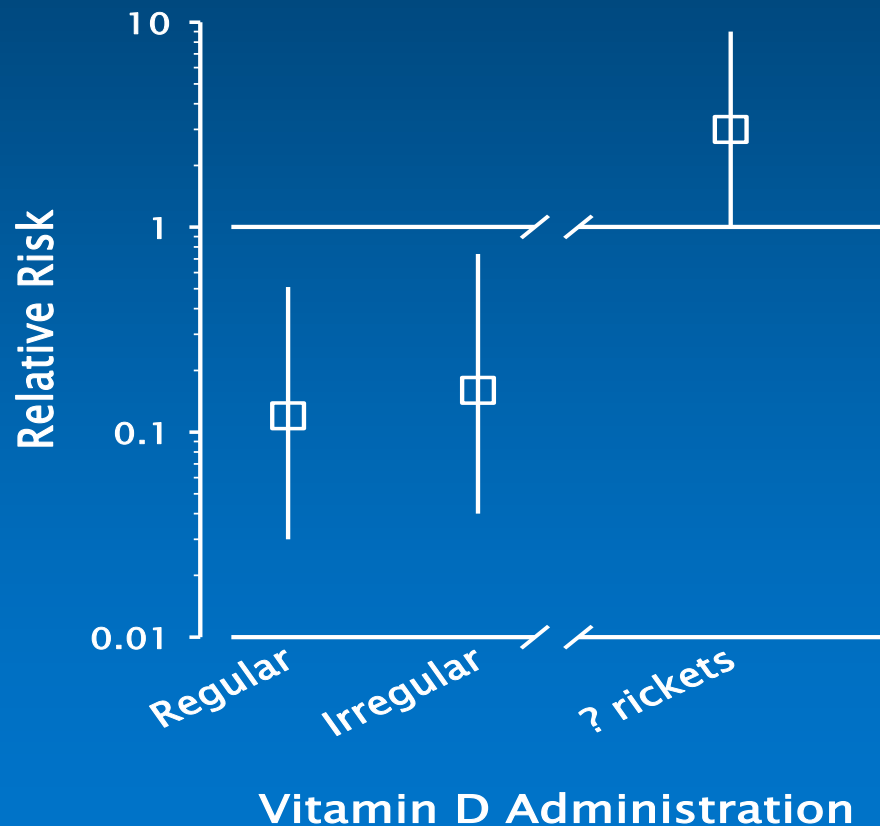
DIABETES & 25(OH)D

- 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

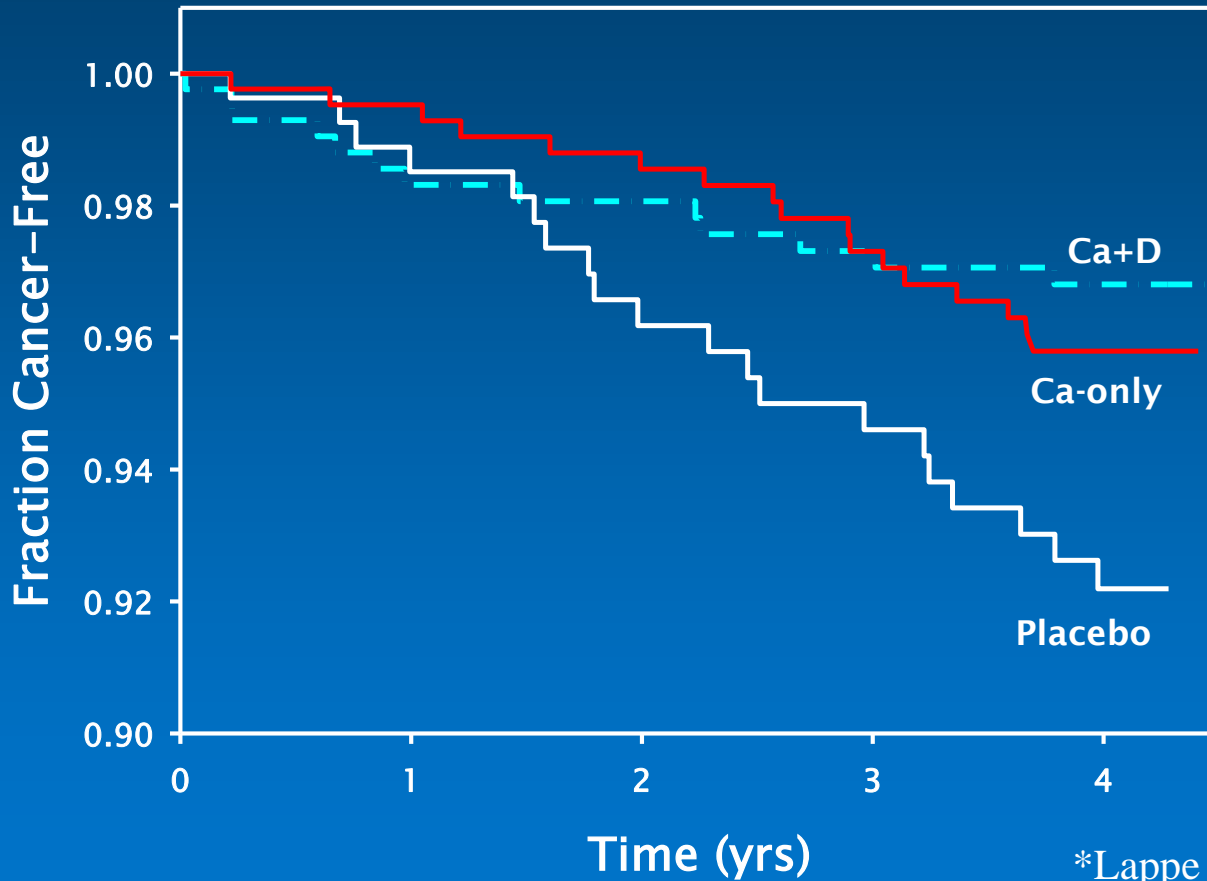


*Hypponen et al., Lancet 2001;358:1500-03

VITAMIN D & CANCER*

- 1179 healthy women
- aged 66.7 ± 7.3
- four year trial
- 1032 finished (87.5%)
- baseline 25(OH)D: $71.8 \text{ nmol/L} \pm 20.3$
- three treatment groups:
 - control
 - Ca (1400–1500 mg/d)
 - Ca plus D₃ (1100 IU/d)
- achieved 25(OH)D: $96 \text{ nmol/L} \pm 21.4$

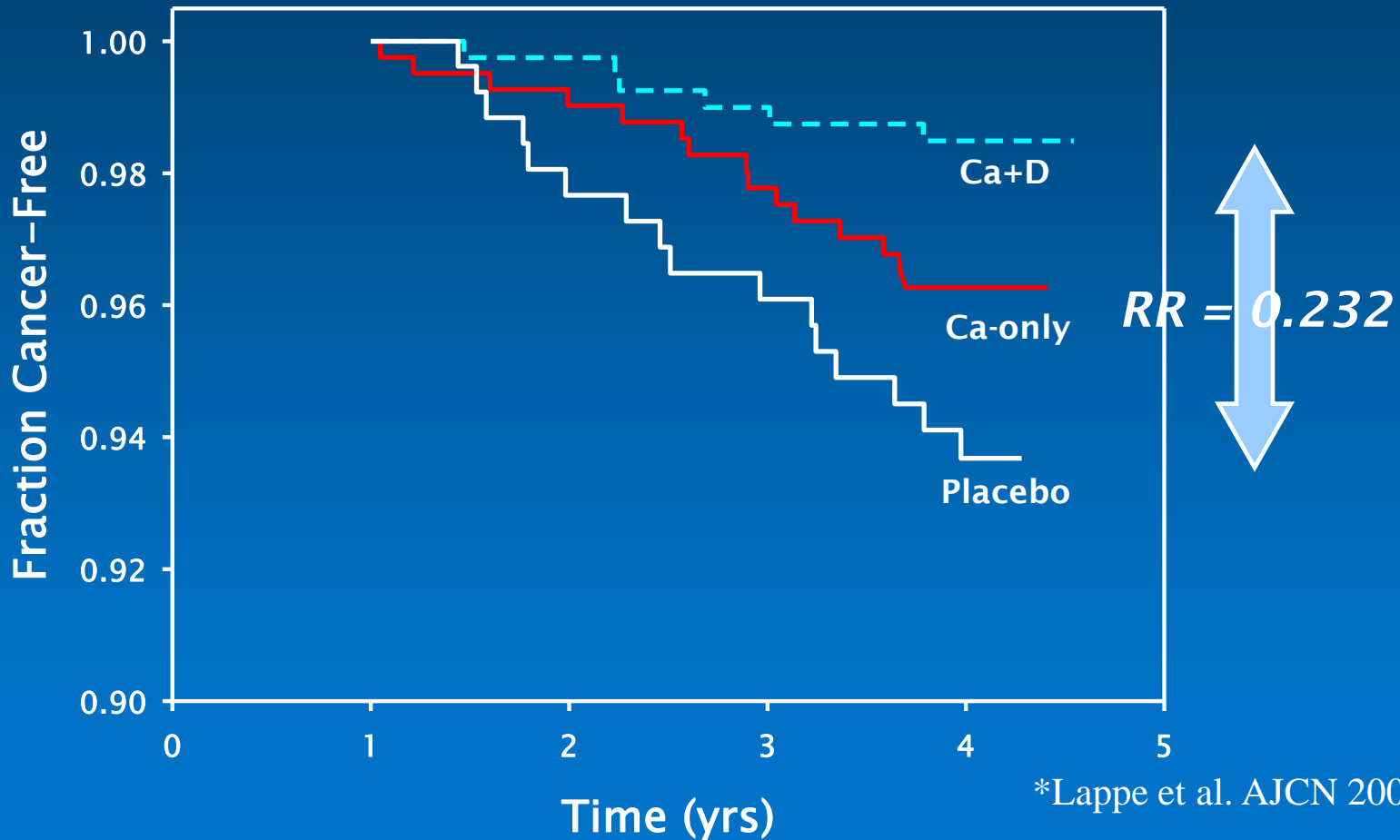
VITAMIN D & CANCER*



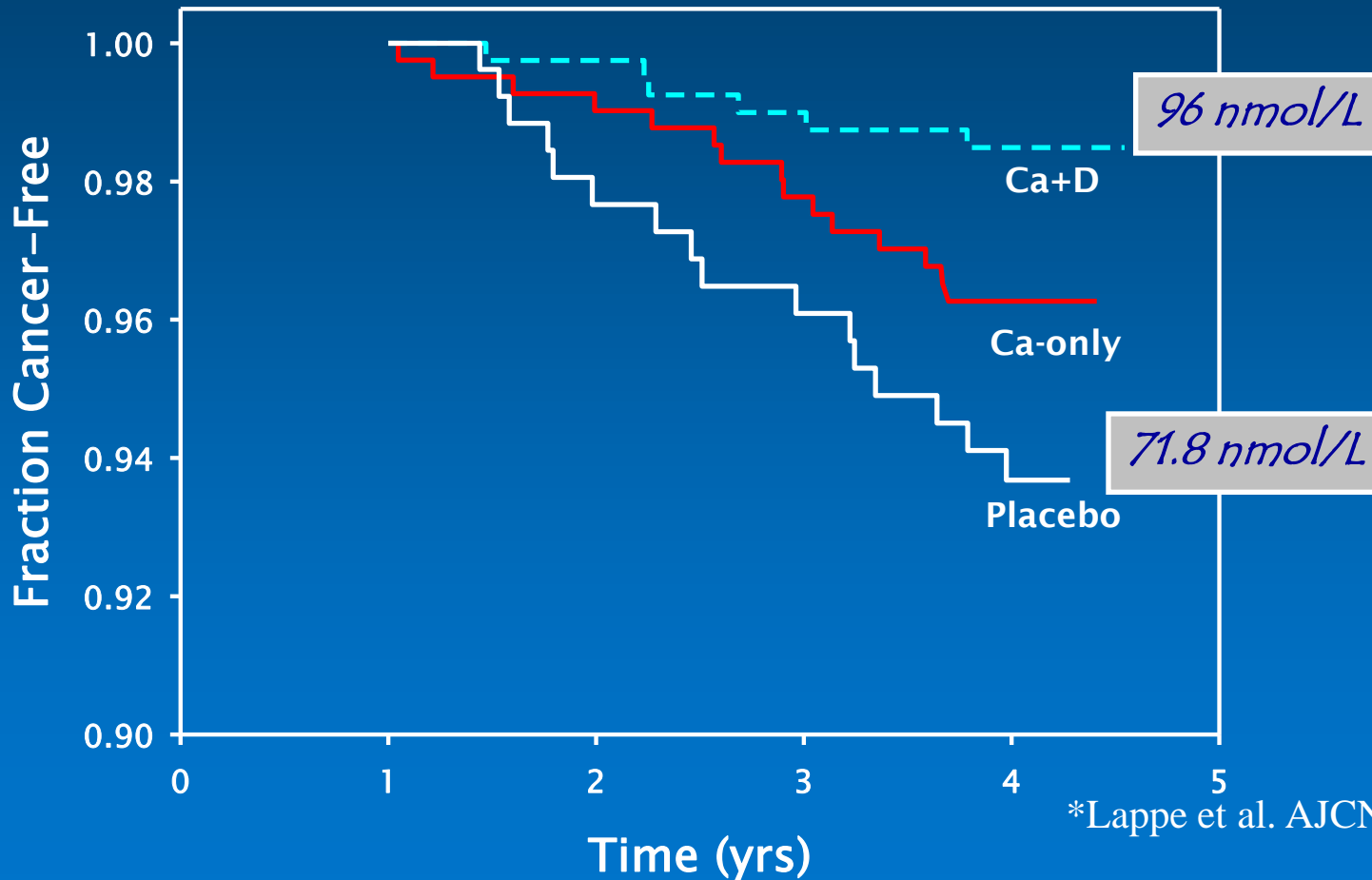
$RR \approx 0.002$

*Lappe et al. AJCN 2007

VITAMIN D & CANCER*



VITAMIN D & CANCER*



*Lappe et al. AJCN 2007

OTHER CHRONIC DISEASES?

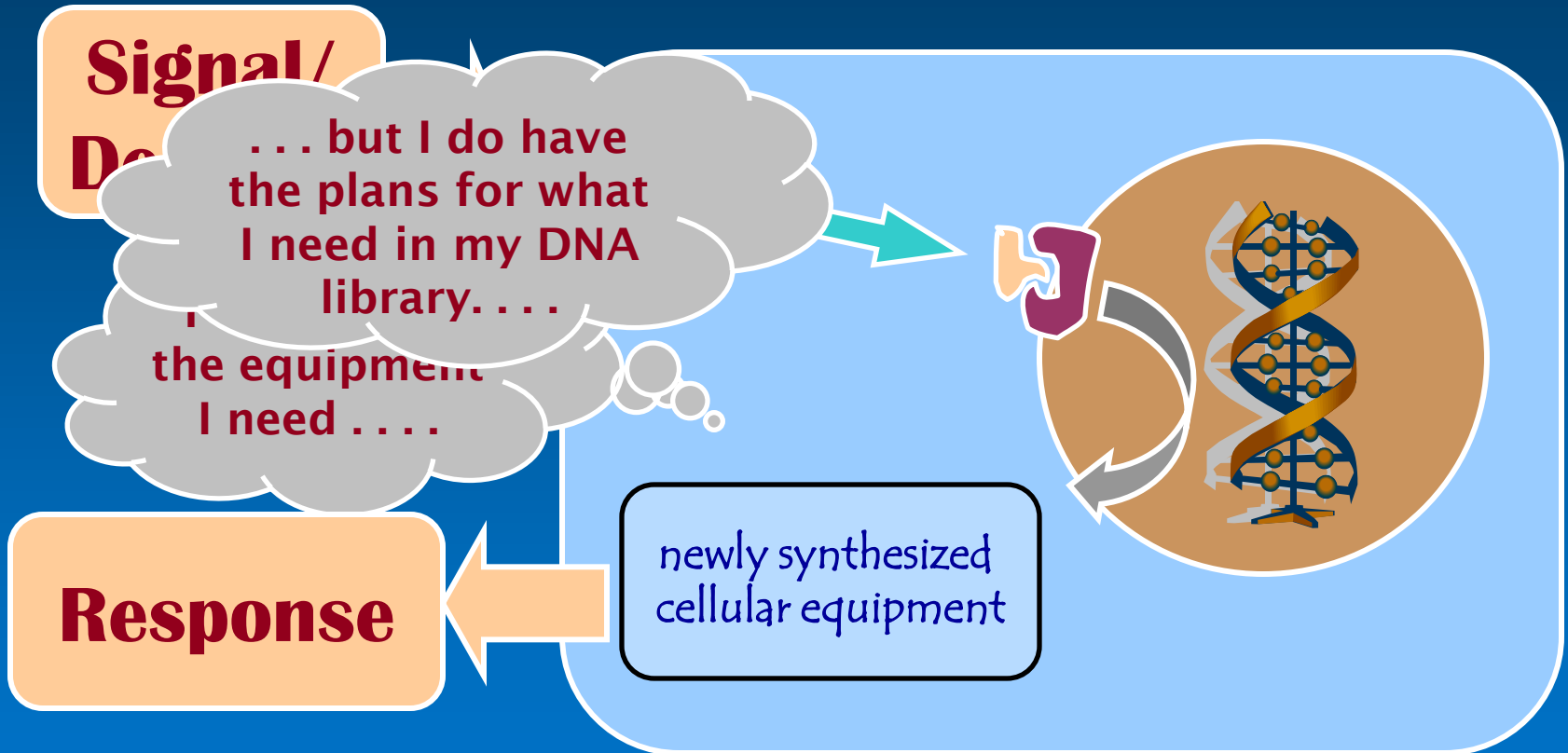
Disease	Status of Evidence
▪ osteoarthritis	+
▪ falls/neuromusc. fcn	++++
▪ multiple sclerosis	++
▪ fibromyalgia	++
▪ type I diabetes	++
▪ insulin sensitivity	++
▪ cardiovascular disease	++
▪ periodontal disease	++
▪ various cancers	++++
▪ tuberculosis	+++
▪ hypertension	++++

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

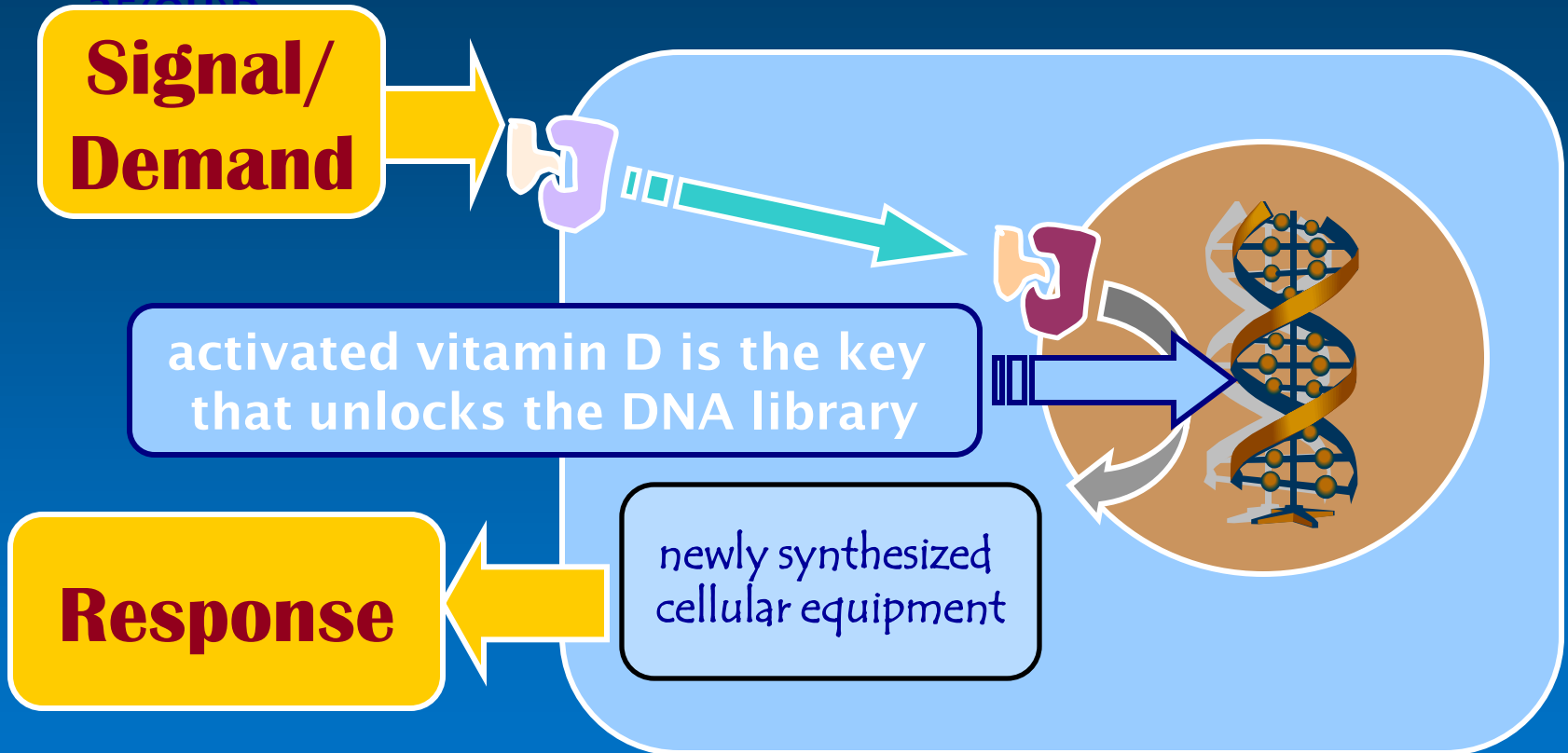
PERSPECTIVE

- **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**

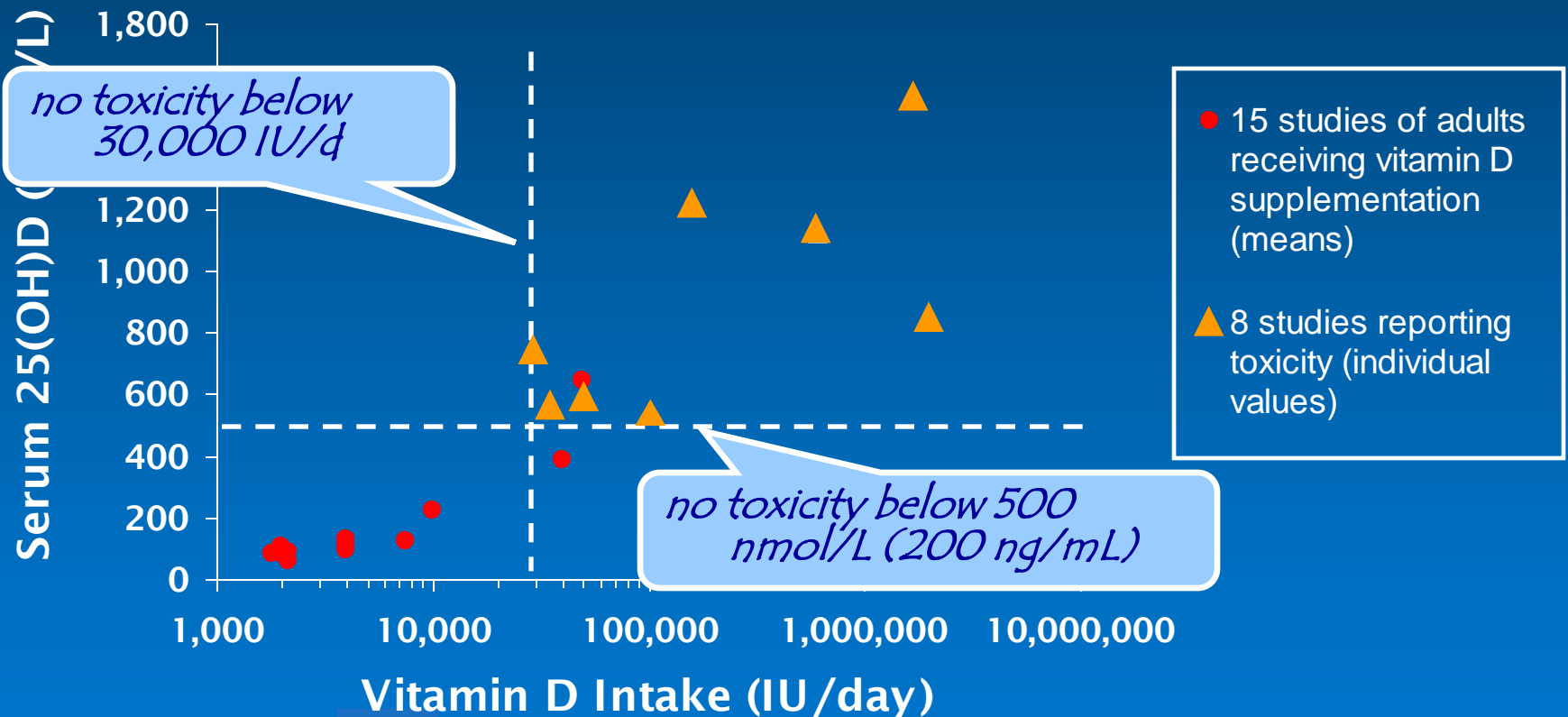
HOW A CELL RESPONDS



HOW A CELL RESPONDS



VITAMIN D INTAKE & TOXICITY*



CU



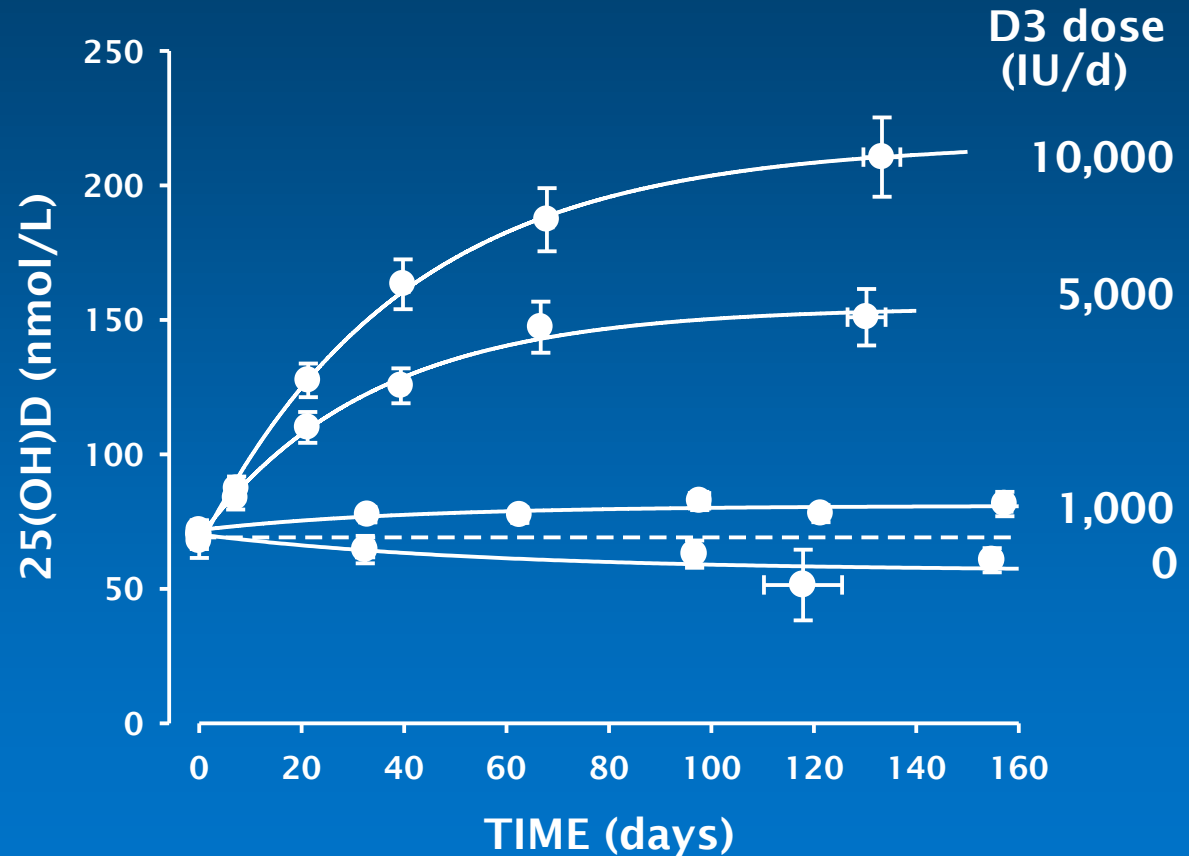
ORC

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

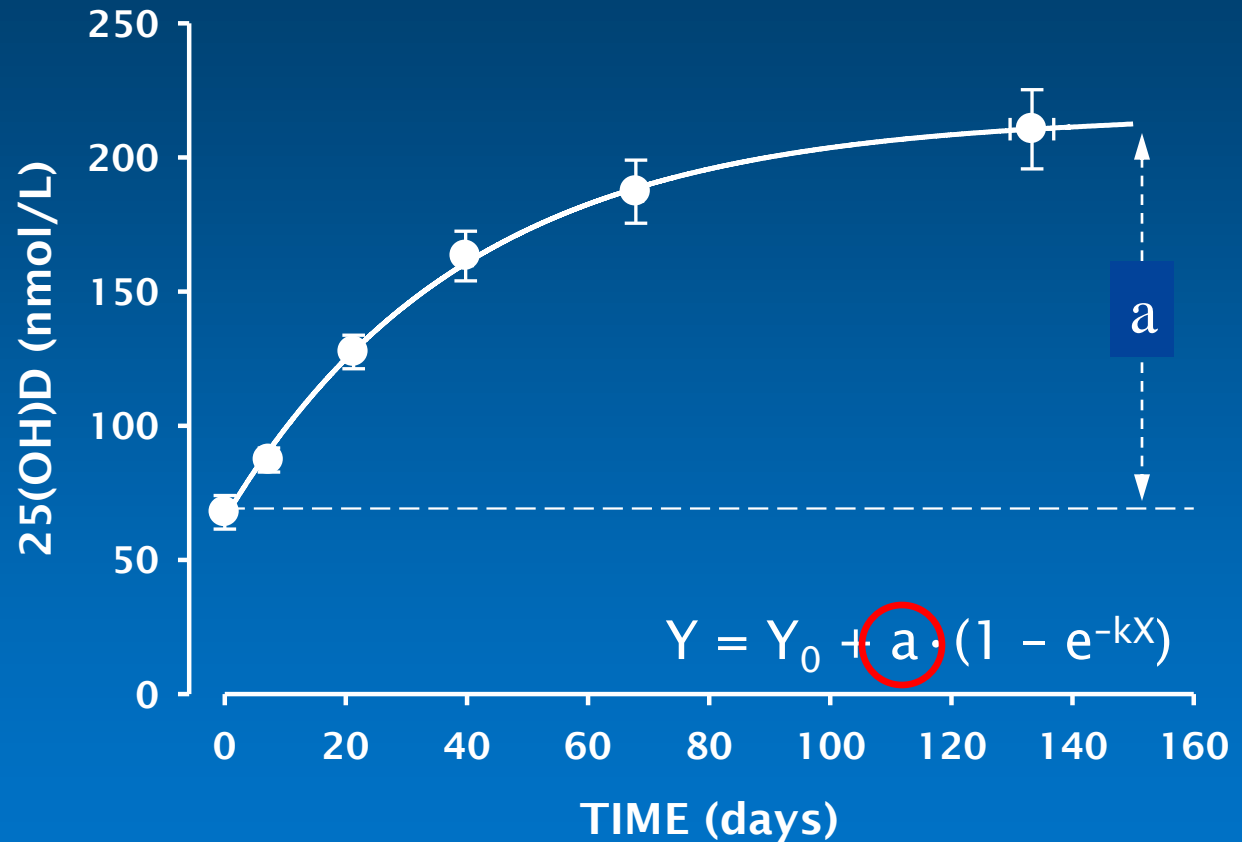
How Much Do We Need?

25(OH)D RESPONSE TO ORAL D₃

- 66 males
- aged 38.7 yr (± 11.2)
- dosed with vit D₃ from October through February

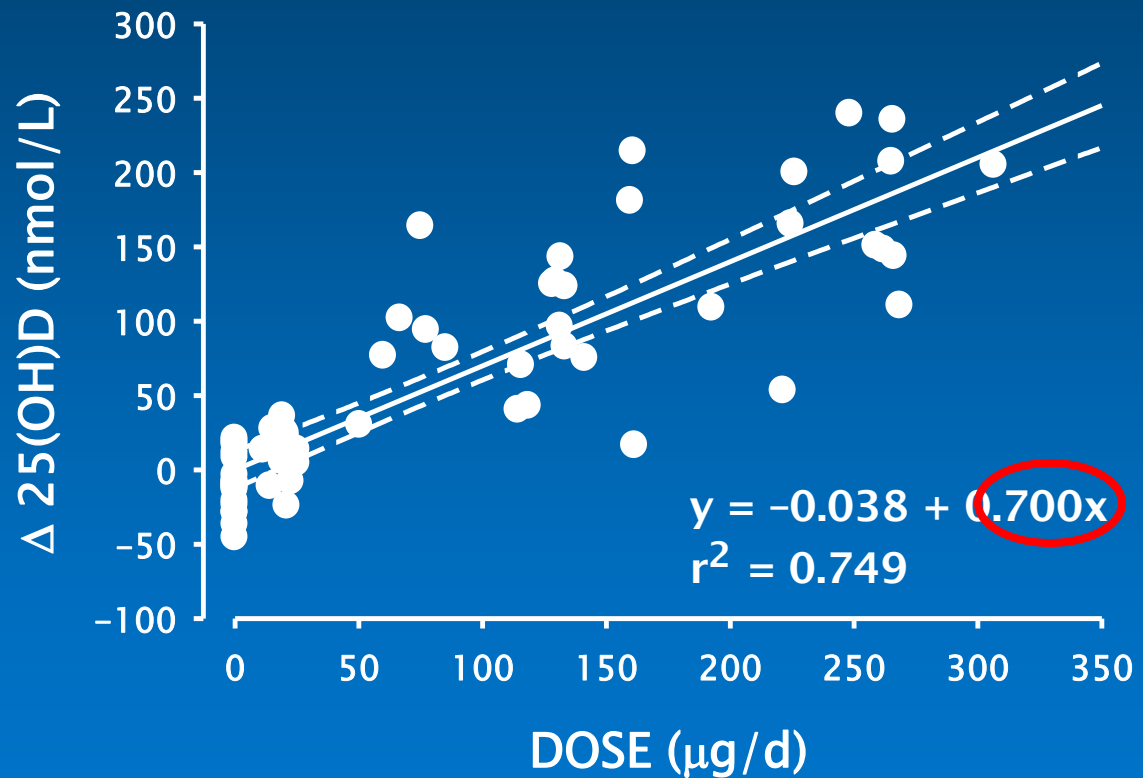


INCREMENT ESTIMATION



25(OH)D RESPONSE TO ORAL D₃

- equilibrium concentrations of 25(OH)D plotted against actual dose of vit D₃



TRANSLATION:

- steady-state serum 25(OH)D concentration rises by 0.7 nmol/L for every 1 μg (40 IU) of vit D₃, 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/ $\mu\text{g}/\text{d}$

TRANSLATION:

- taking a conservative figure from that range, e.g., 1.0 nmol/L/ μ g/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

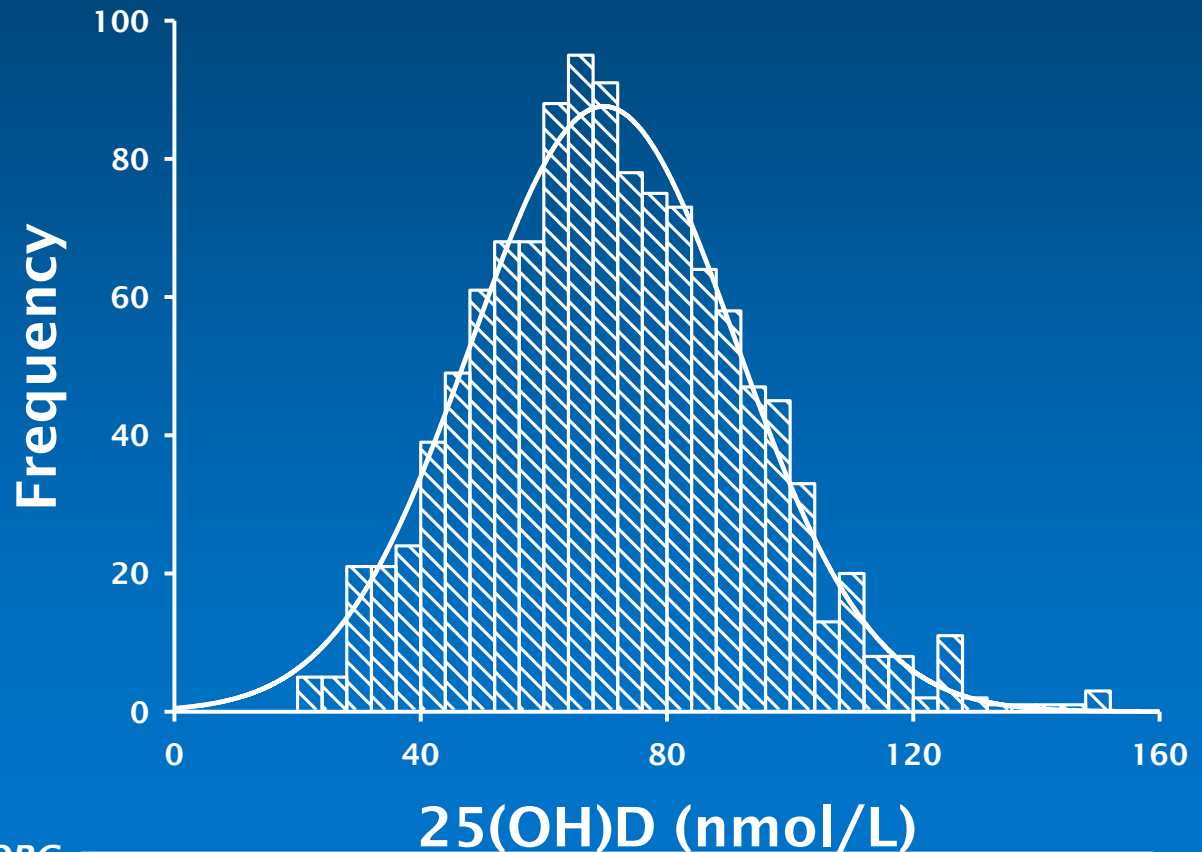
assuming a target value of 80 nmol/L:

- 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*

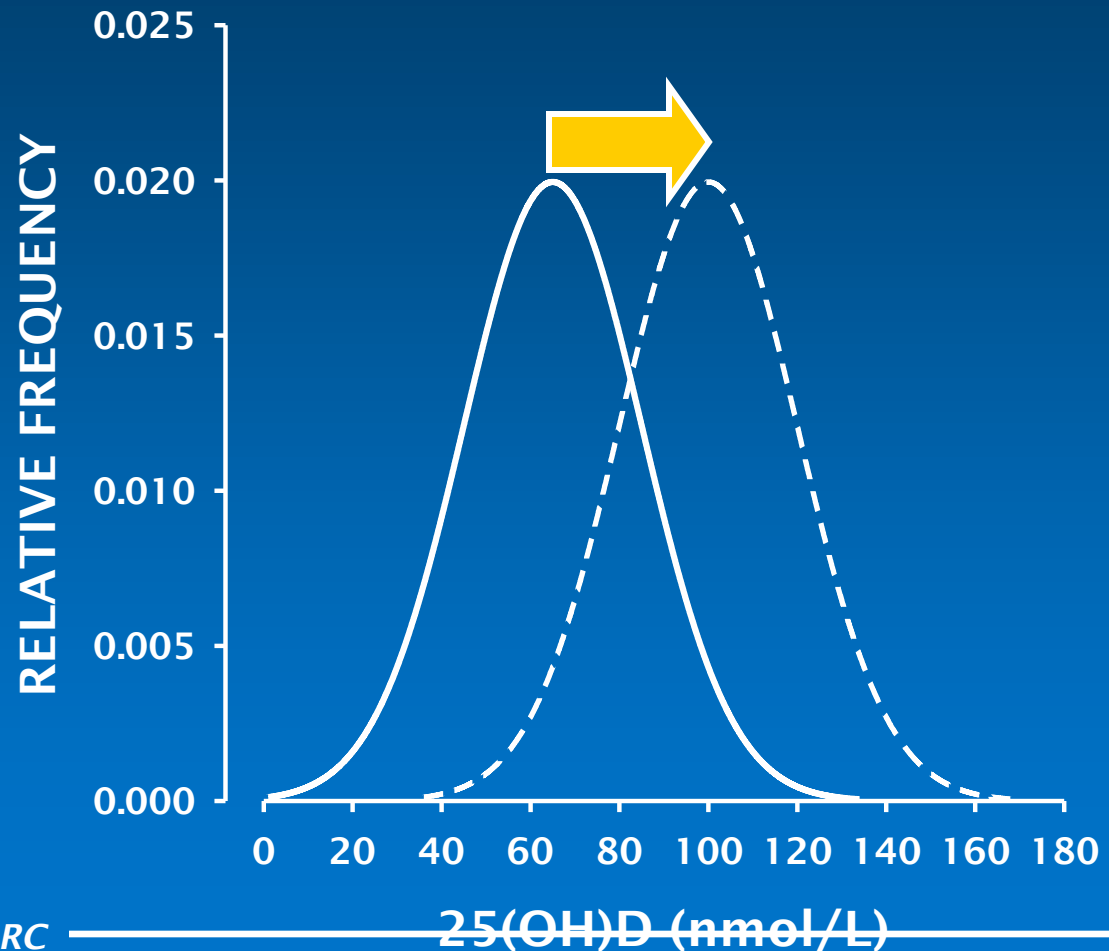
*Lappe et al., JACN 2006

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



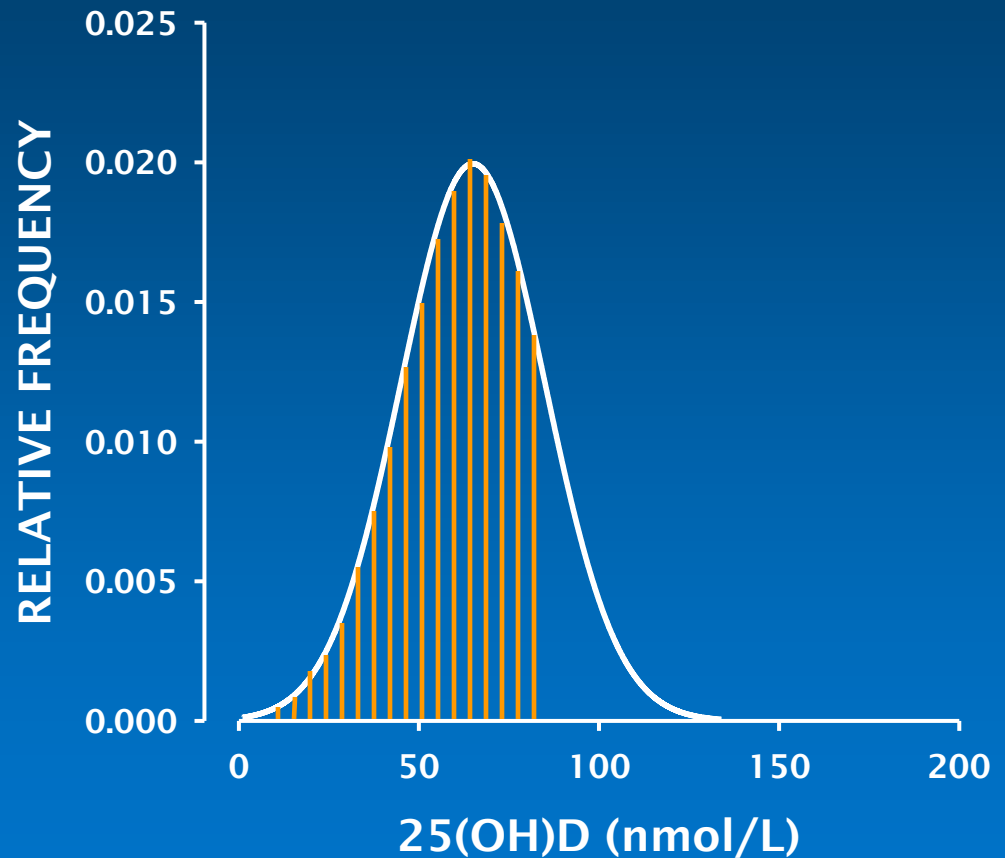
SHIFTING THE DISTRIBUTION

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



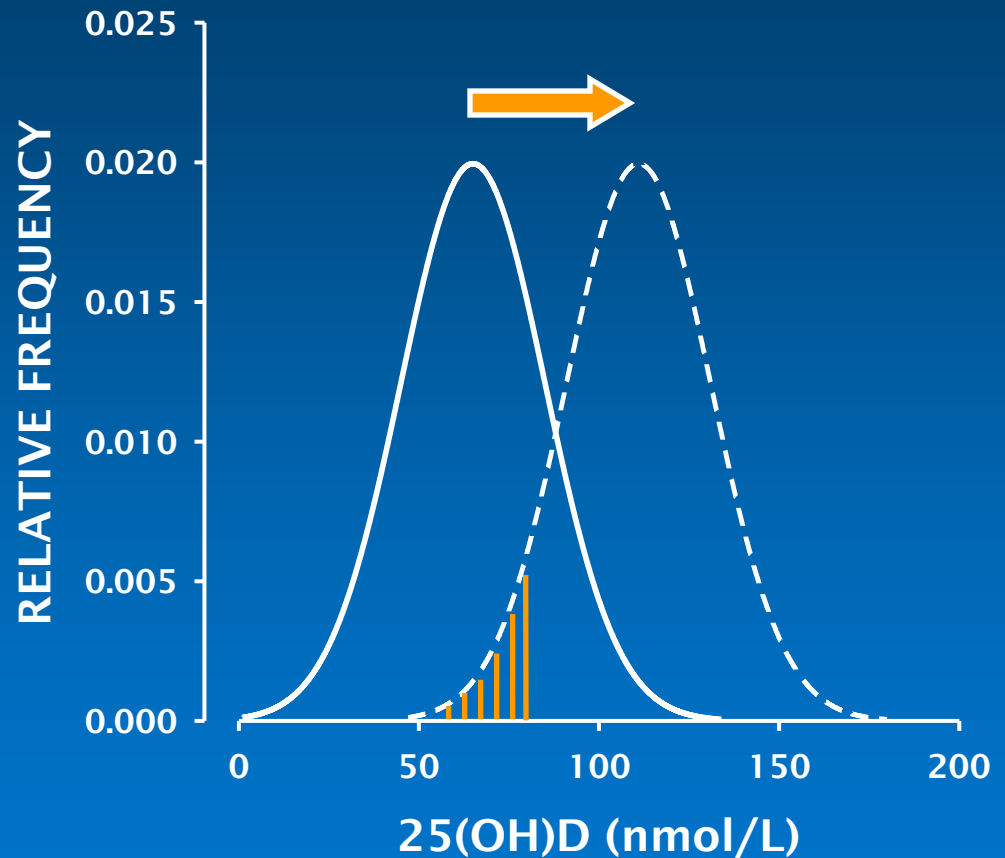
SHIFTING THE DISTRIBUTION

- using an effect size of 1 nmol/L/ μ g/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



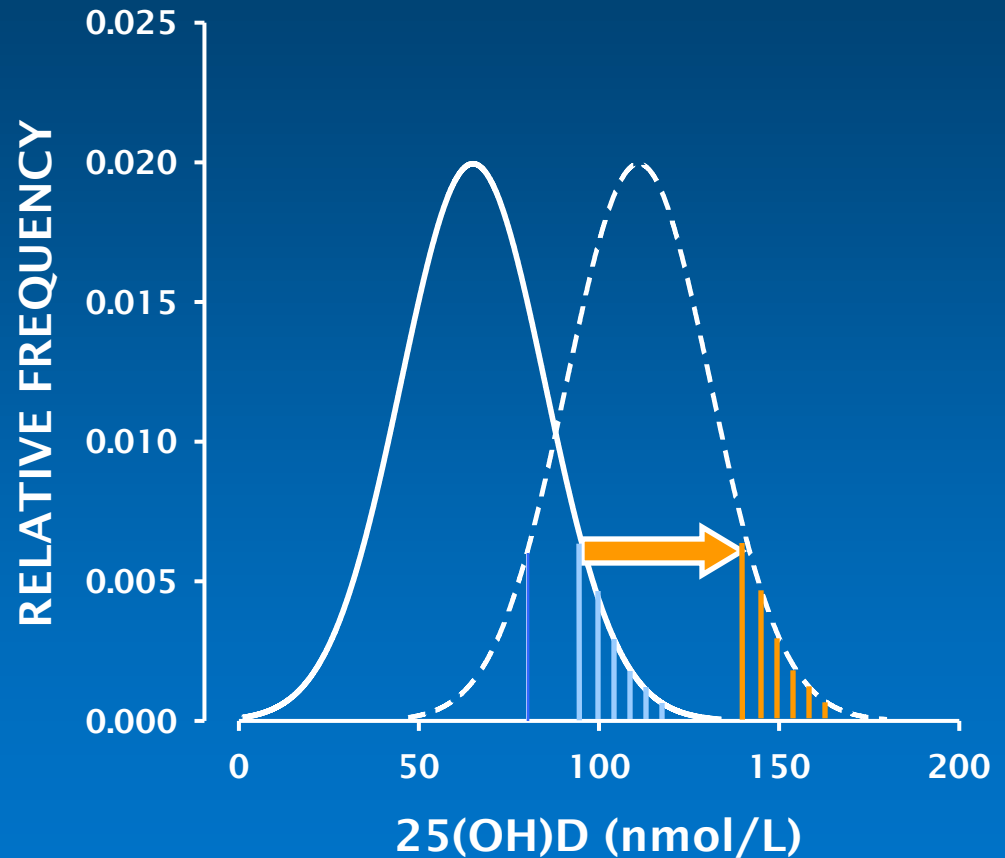
SHIFTING THE DISTRIBUTION

- taking an effect size of 1 nmol/L/ μ g/d
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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

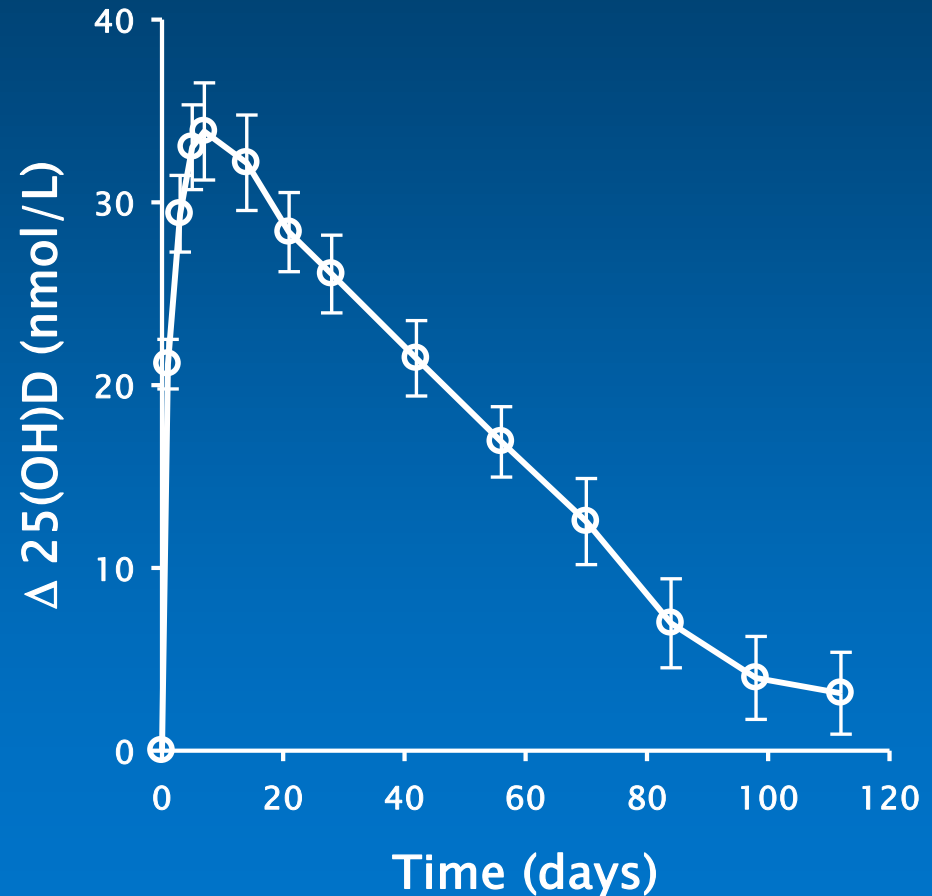


IN BRIEF

- 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

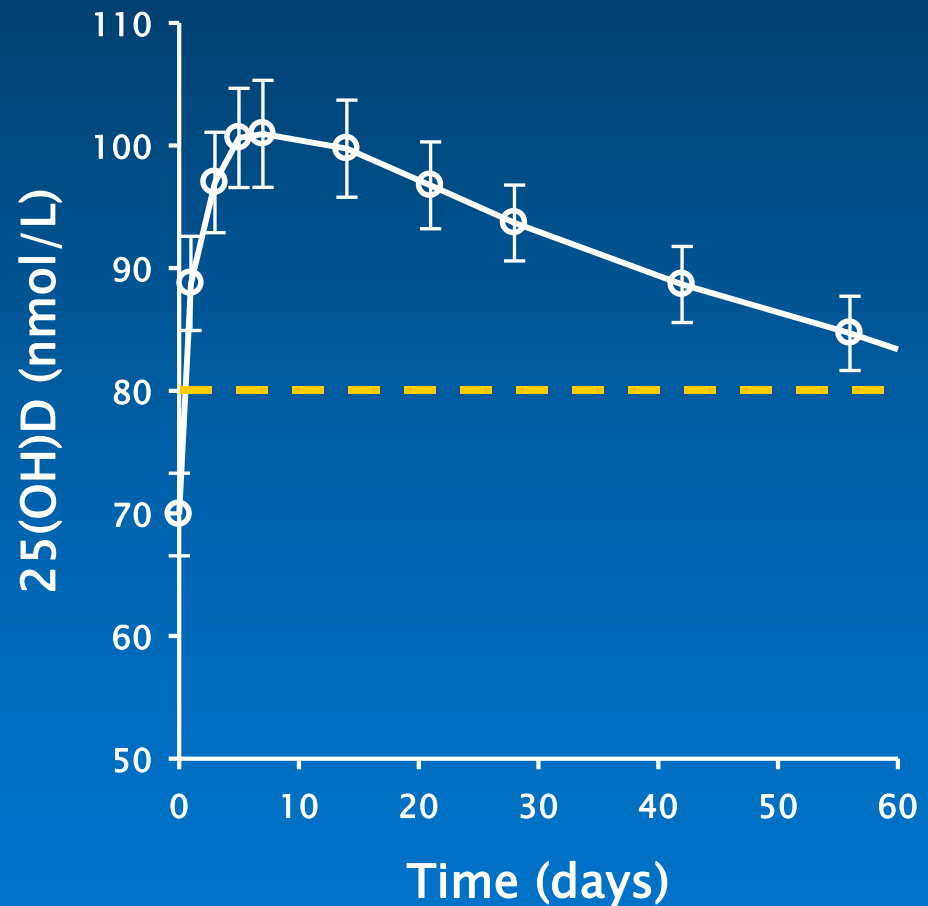
RESPONSE TO 100,000 IU

- 30 healthy adults
- 100,000 iu Vitamin D₃ by mouth
- baseline 25(OH)D: 69.9 ± 19.6 nmol/L



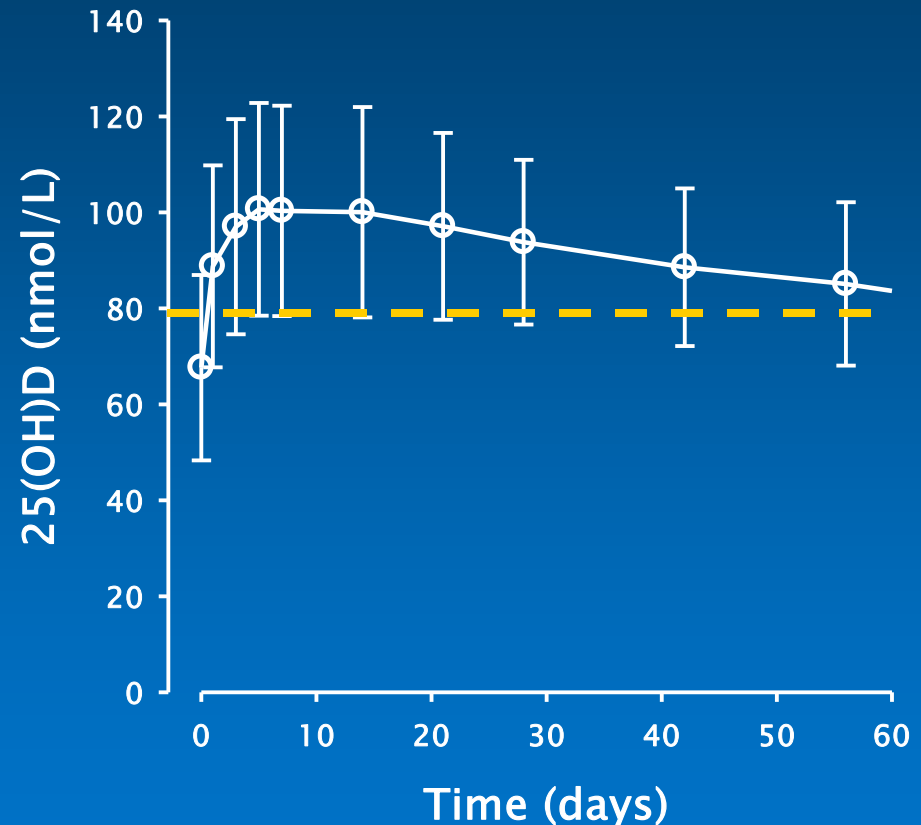
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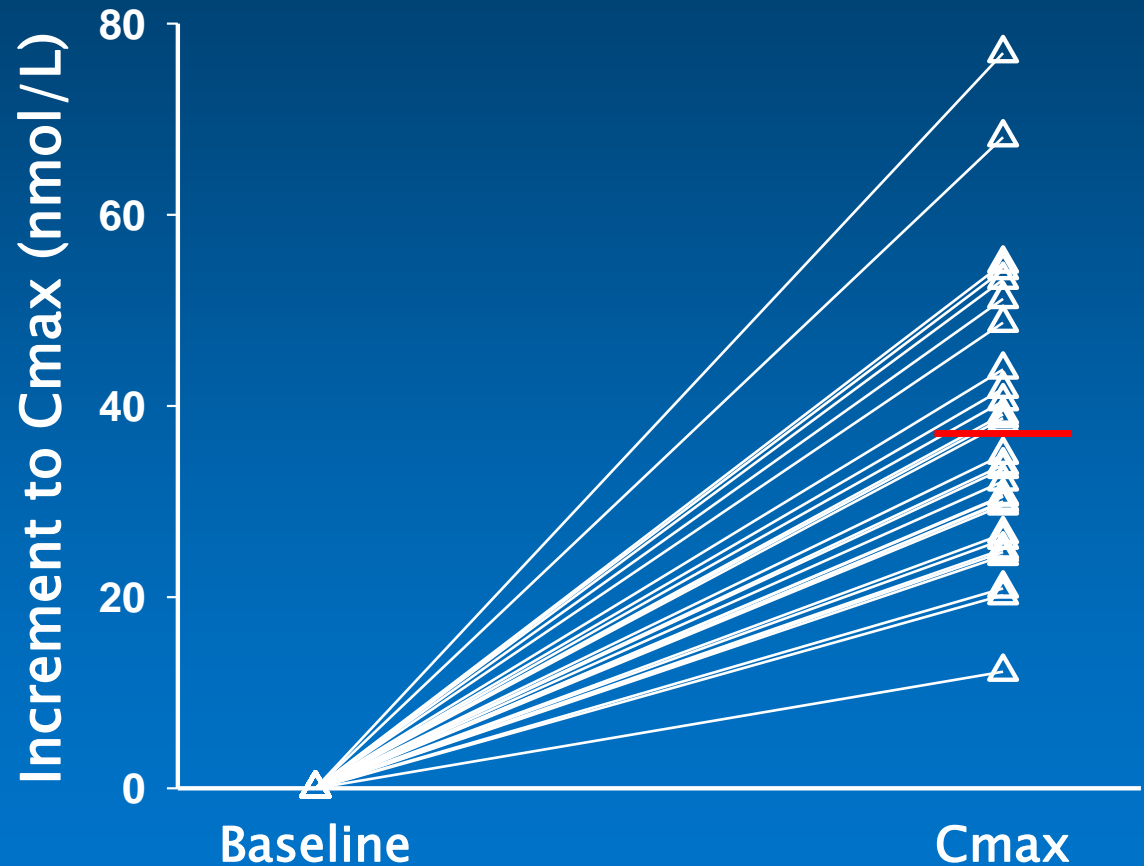
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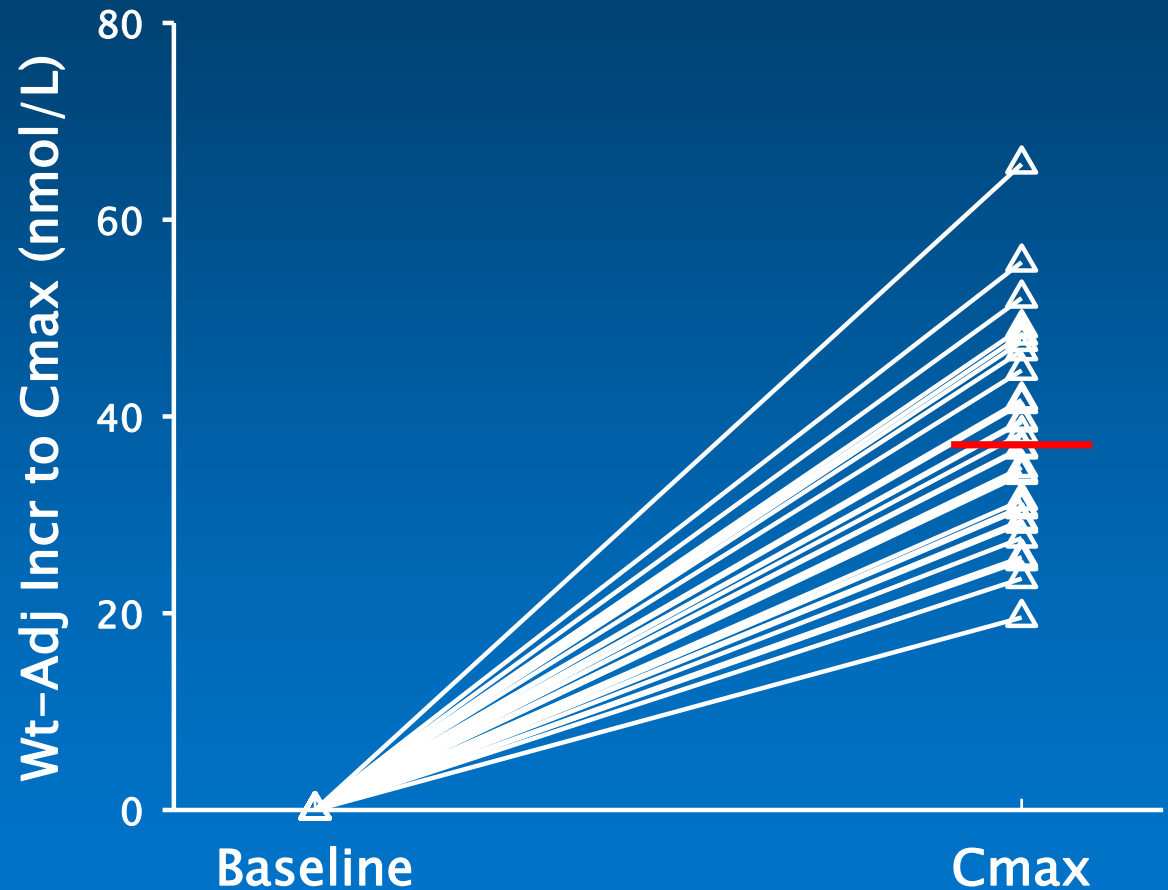
VARIABILITY OF 25(OH)D RESPONSE*

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



VARIABILITY OF 25(OH)D RESPONSE*

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

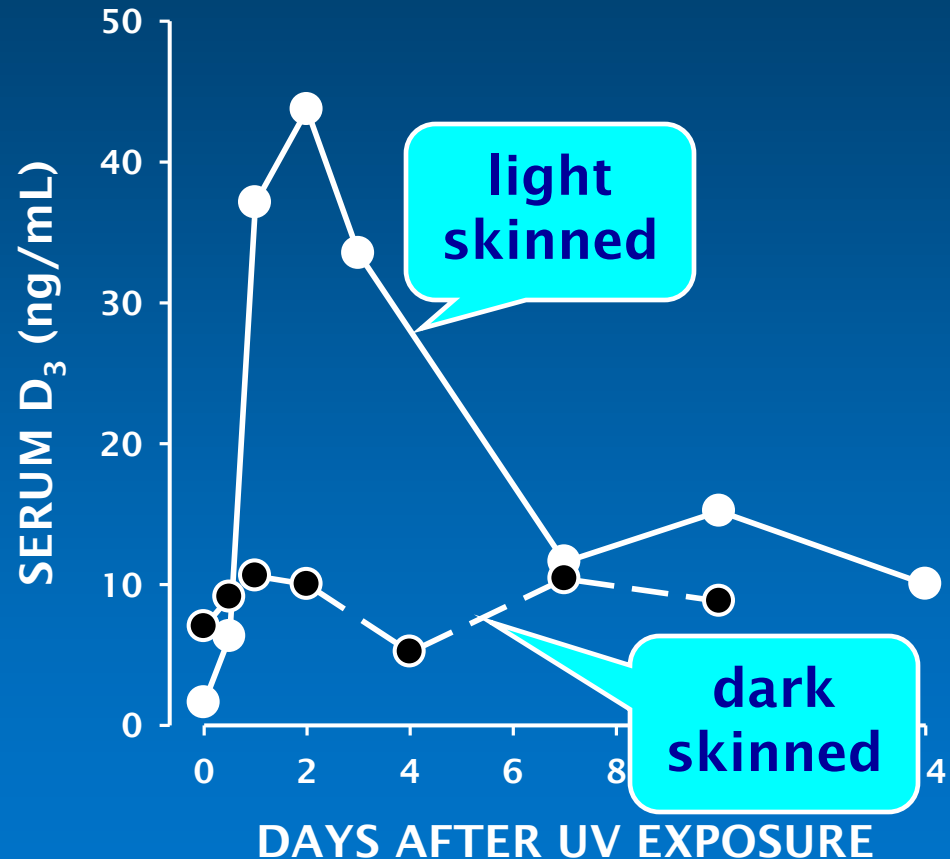


POSSIBLE EXPLANATIONS

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

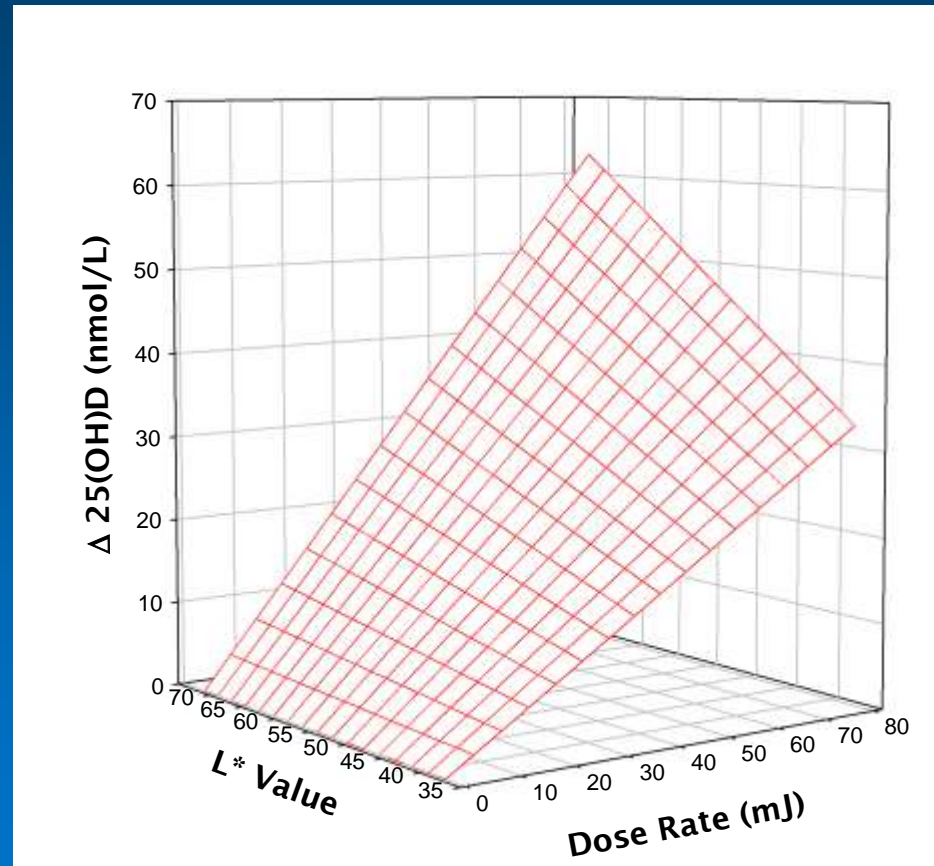
SKIN COLOR & VIT D SYNTHESIS

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



SKIN COLOR, UV-B, & RESPONSE*

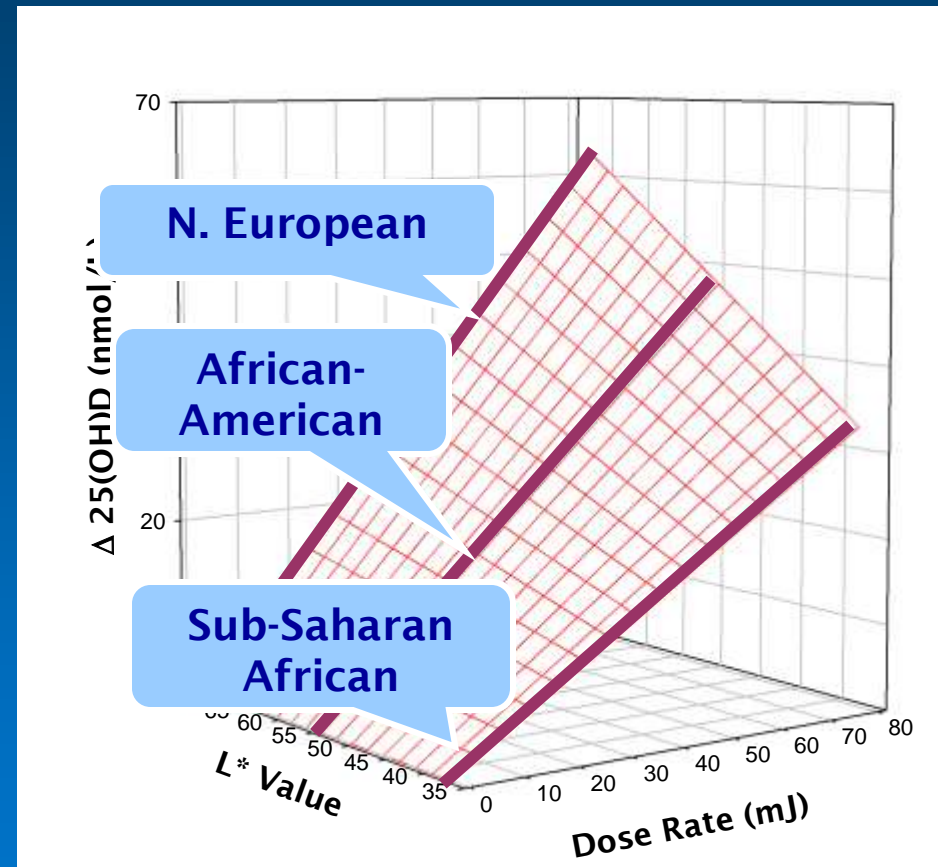
- 72 subjects
- UV-B radiation
3x/wk for 4 wks
- pigmentation
measured on
unexposed skin
with SmartProbe®
(L* value)
 - (high = light)



*Armas et al., J Am Acad Derm 2007

SKIN COLOR, UV-B, & RESPONSE*

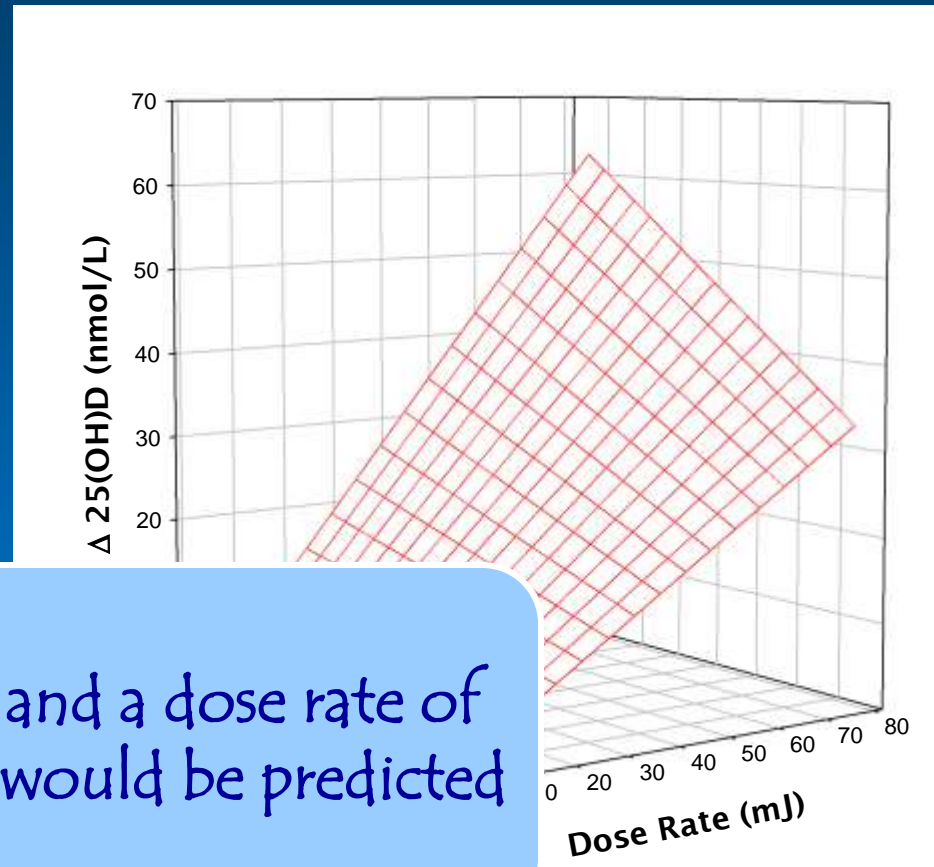
- $Z = 0.01094 * X * Y$
 - $Z = \Delta 25(\text{OH})\text{D}$
 - $X = \text{Lightness}$
 - $Y = \text{UV-B dose (mJ/cm}^2\text{)}$
- $R^2 = 0.794$



*Armas et al., J Am Acad Derm 2007

SKIN COLOR, UV-B, & RESPONSE*

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



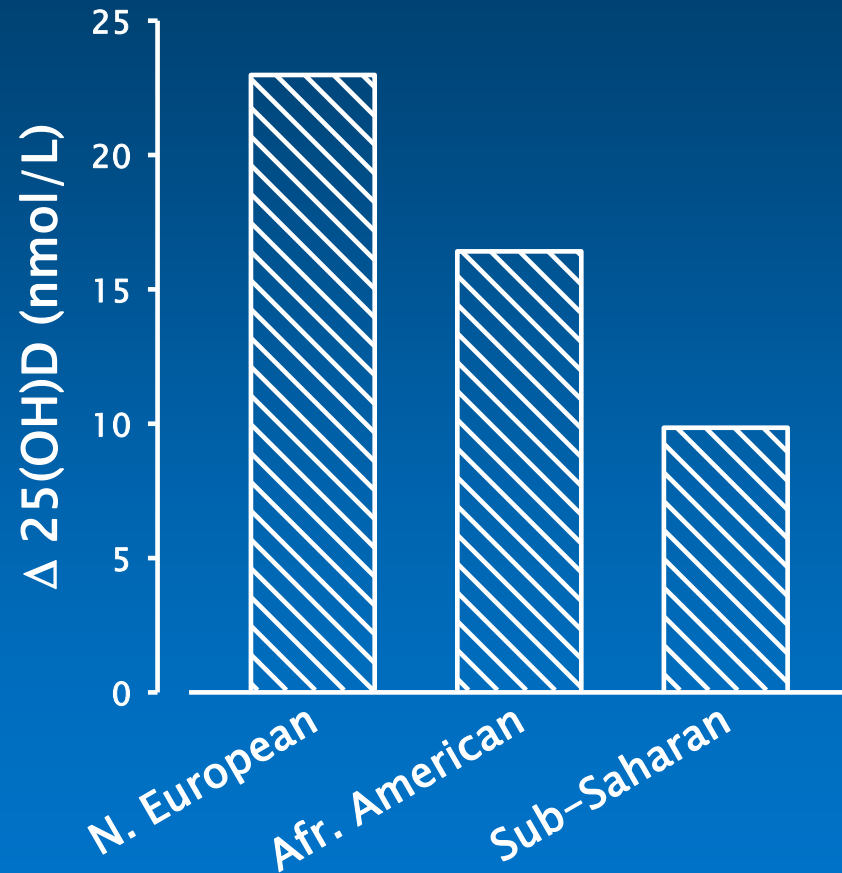
A worked example:

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

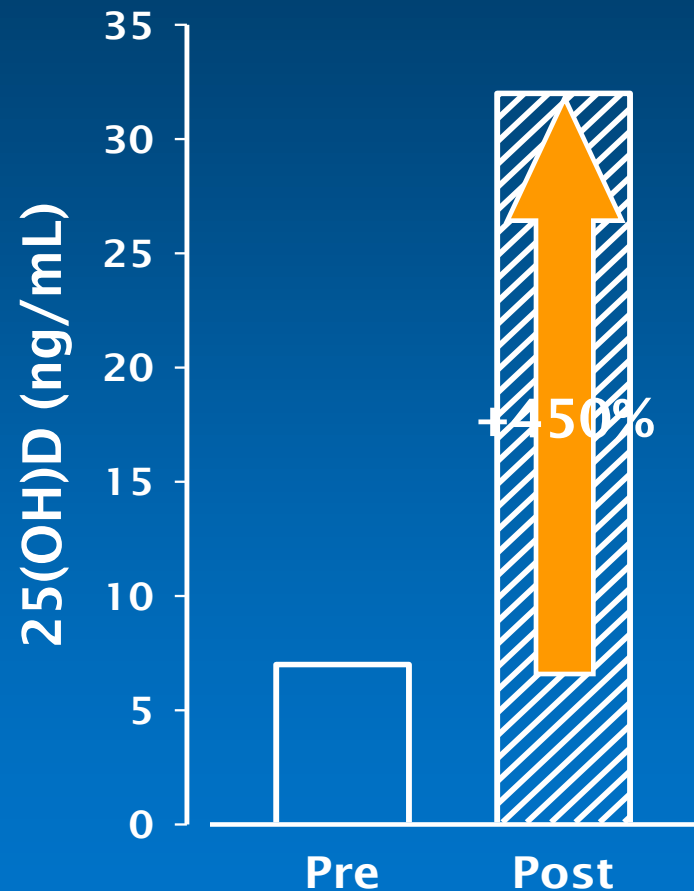
25(OH)D RESPONSE TO UV-B

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



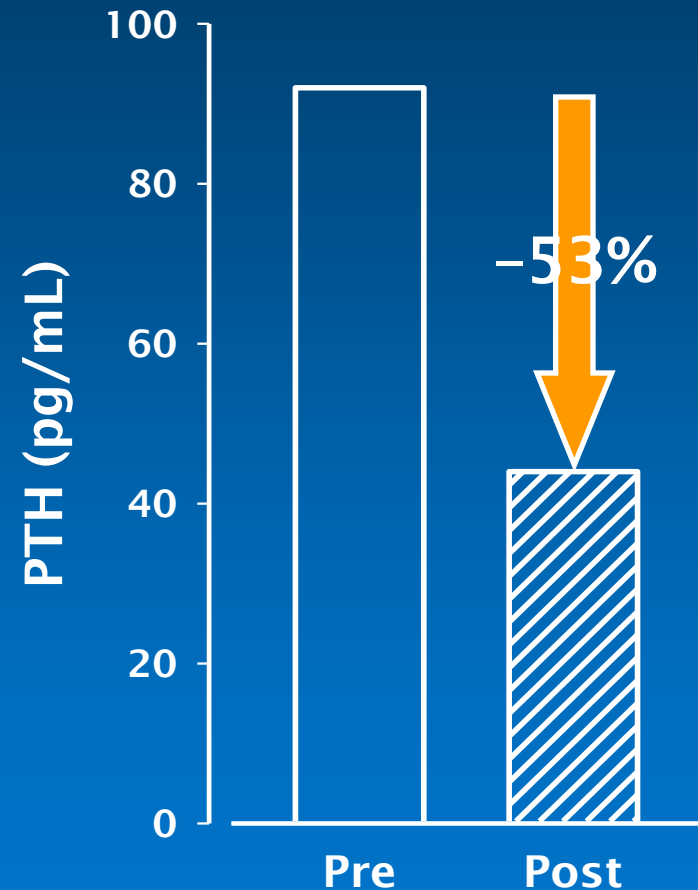
SHORT BOWEL & D STATUS*

- 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



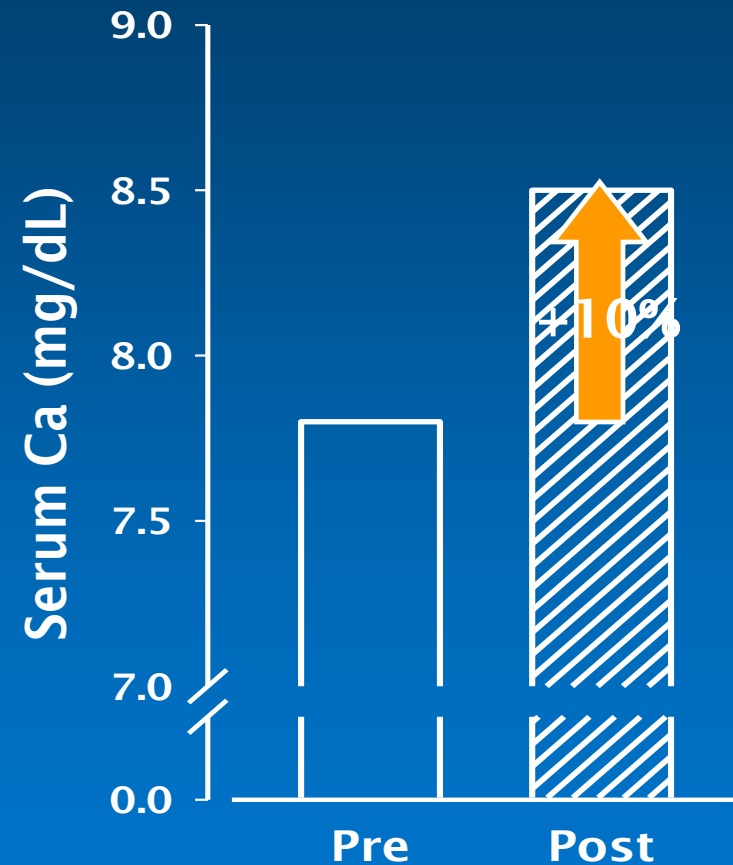
SHORT BOWEL & D STATUS*

- 57 yo woman with Crohn's disease and short bowel
- bone pain & muscle weakness
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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