

WHAT'S A VITAMIN D DEFICIENCY? OVERVIEW, ACTIONS

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DISCLOSURES

- Robert P. Heaney, M.D.
 - no personal financial relationships to disclose

OBJECTIVES

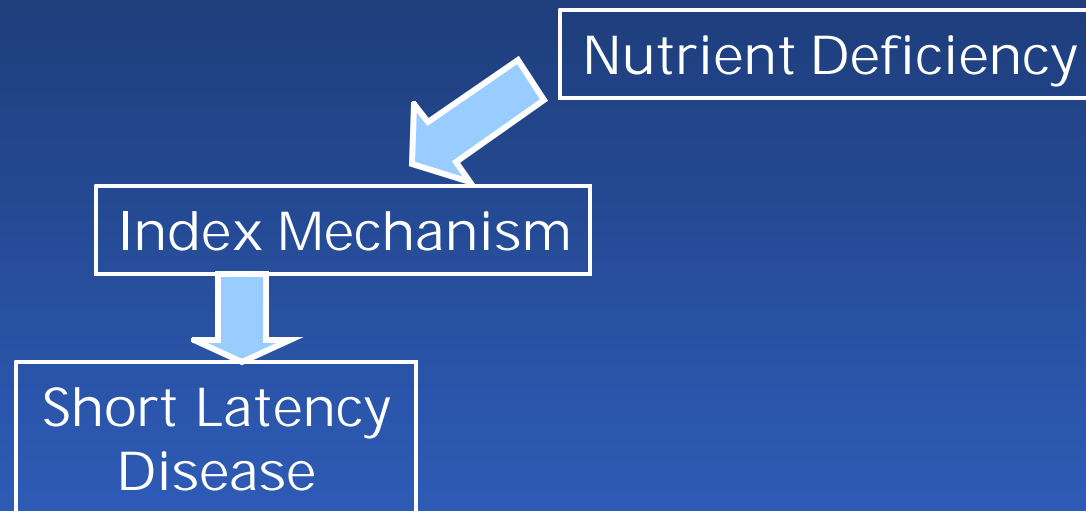
- define nutrient deficiency
- cite evidence relating to sufficiency of vitamin D
- estimate vitamin D inputs needed to sustain sufficiency
- estimate prevalence of deficiency
- characterize the effects of universal vitamin D supplementation
- define the safe upper intake of vitamin D



Working definition:

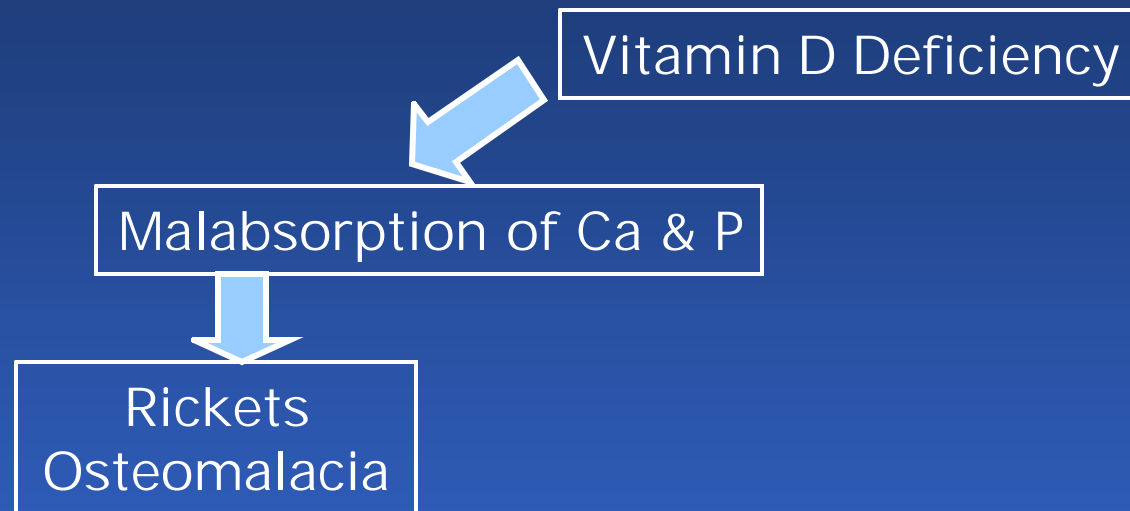
- a deficiency is any condition in which inadequate intake of a nutrient results in significant dysfunction or disease
- conversely, nutrient adequacy is the situation in which further increases in intake produce no further reduction in dysfunction or disease

RETHINKING DEFICIENCY DISEASE

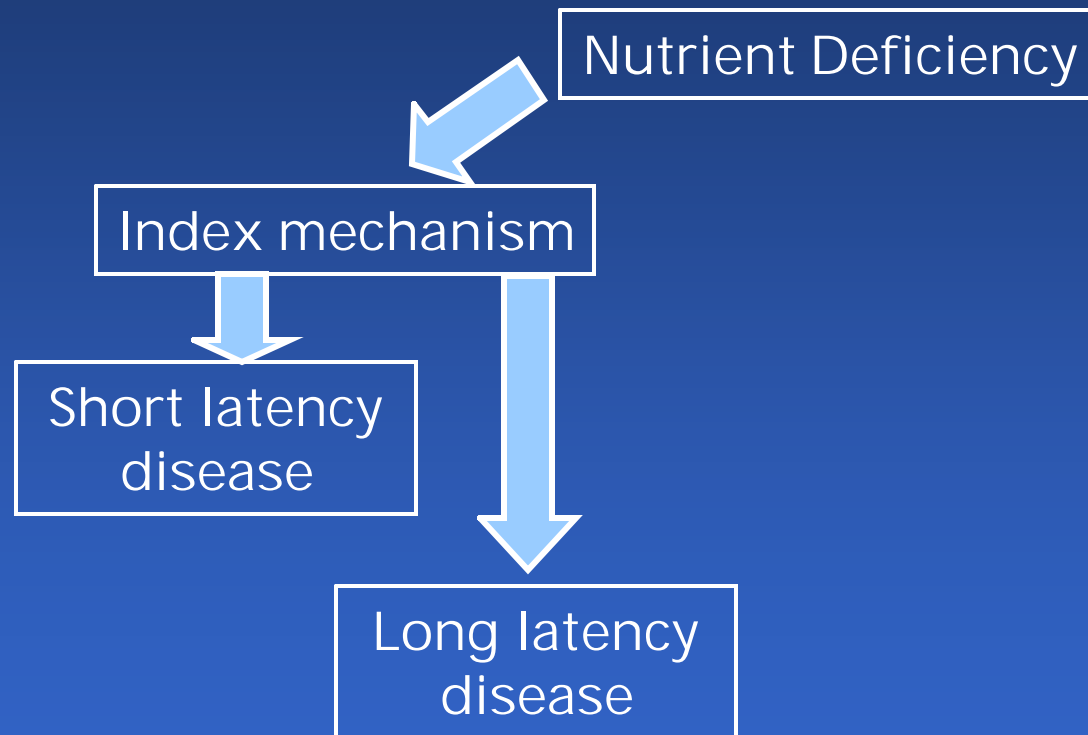


In the early days of nutrition as a science, short latency of the disease/dysfunction was necessary in order to recognize the connection between cause and effect.

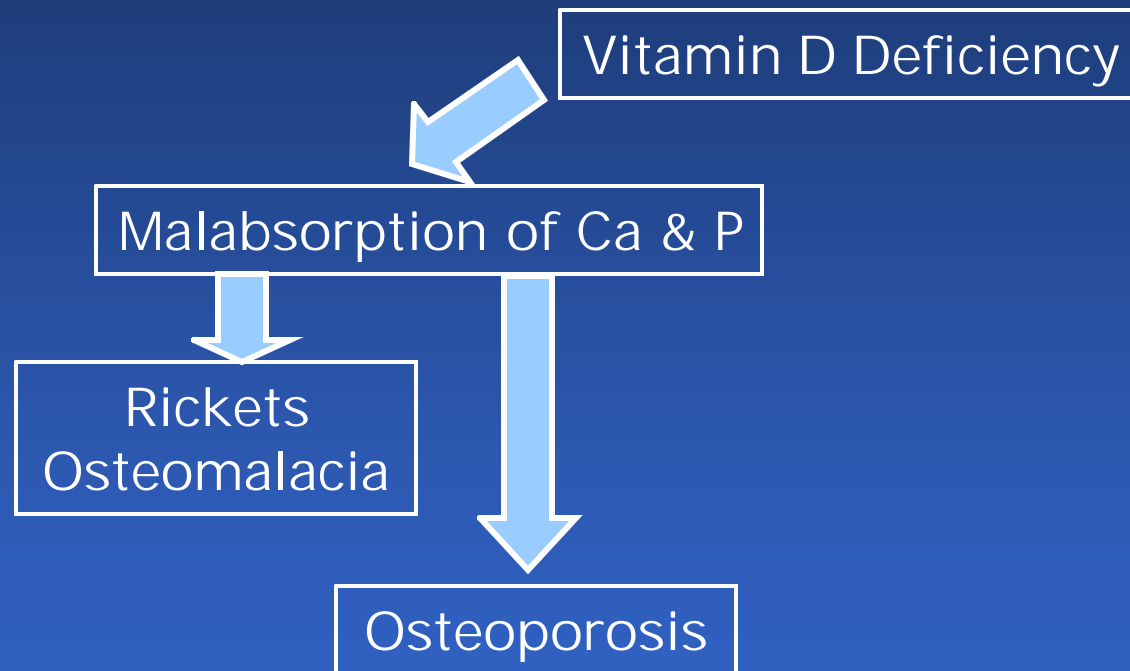
RETHINKING DEFICIENCY DISEASE



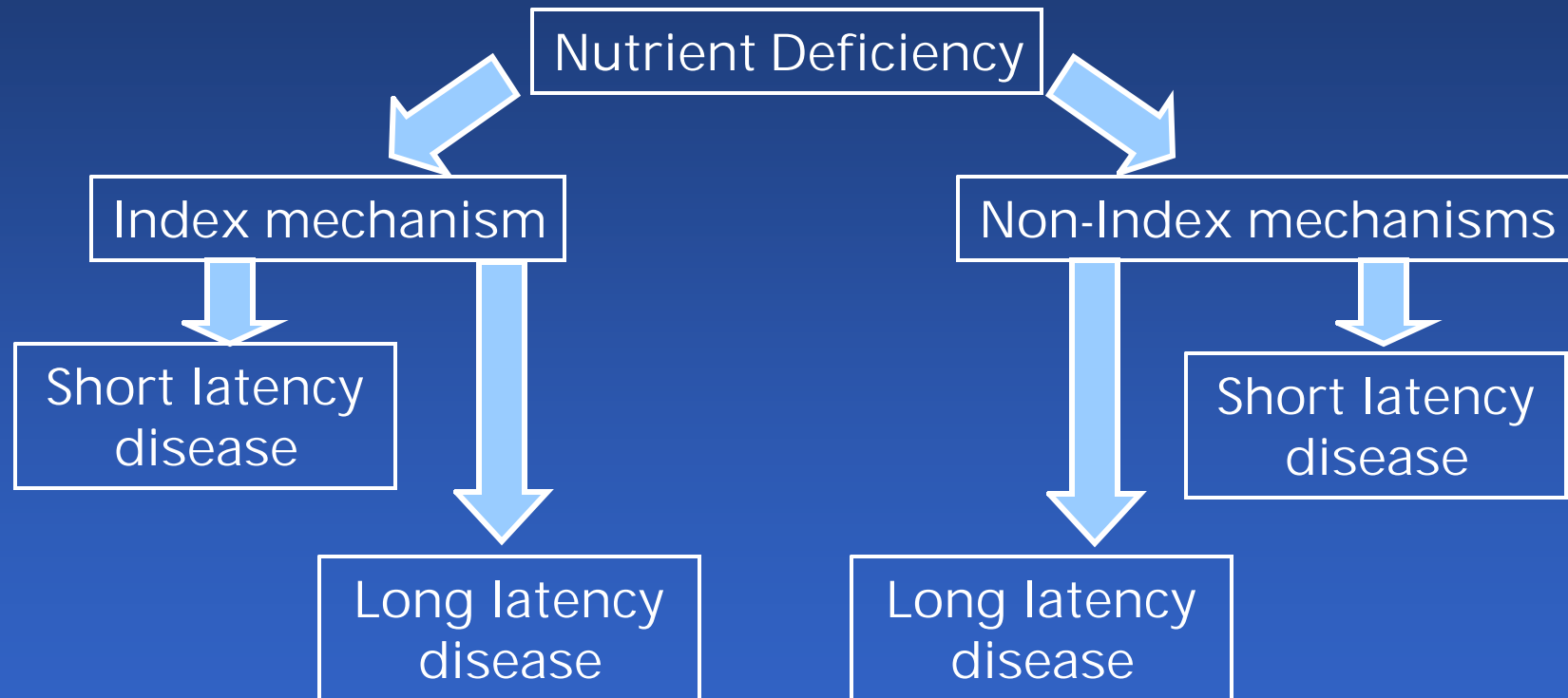
RETHINKING DEFICIENCY DISEASE



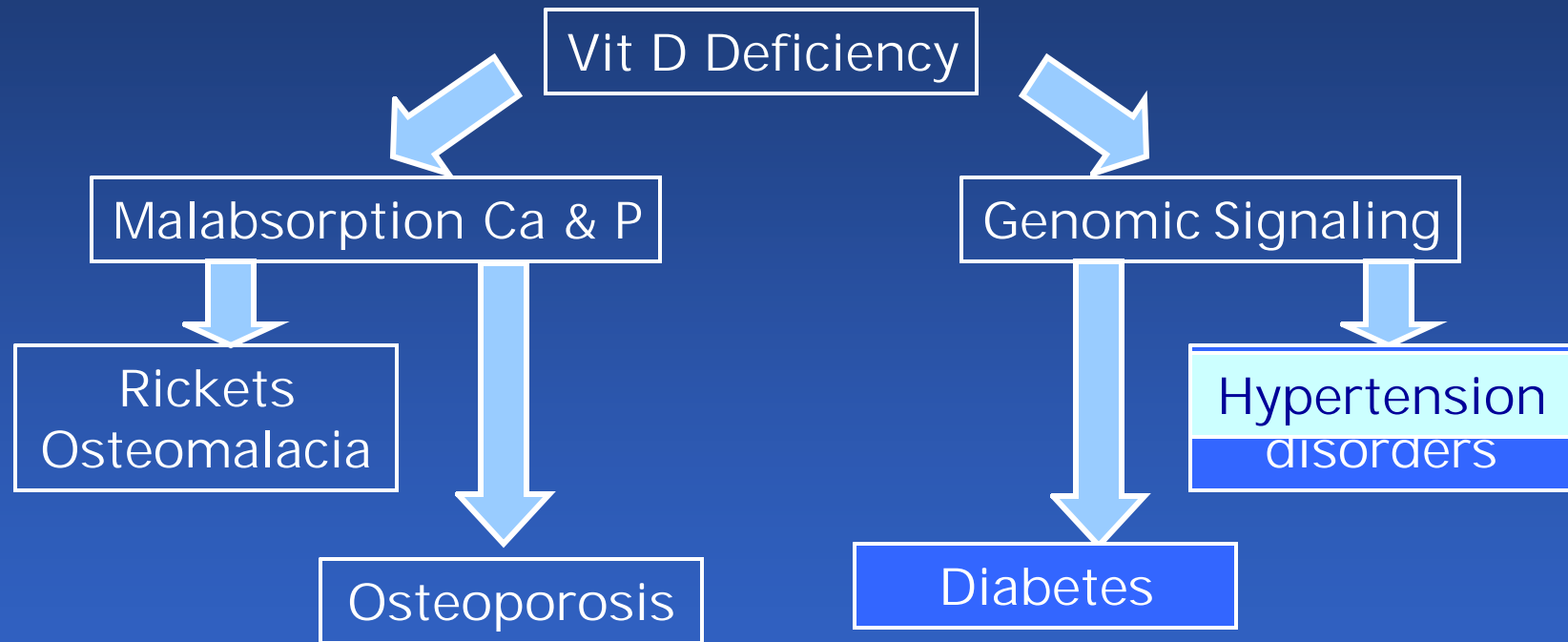
RETHINKING DEFICIENCY DISEASE



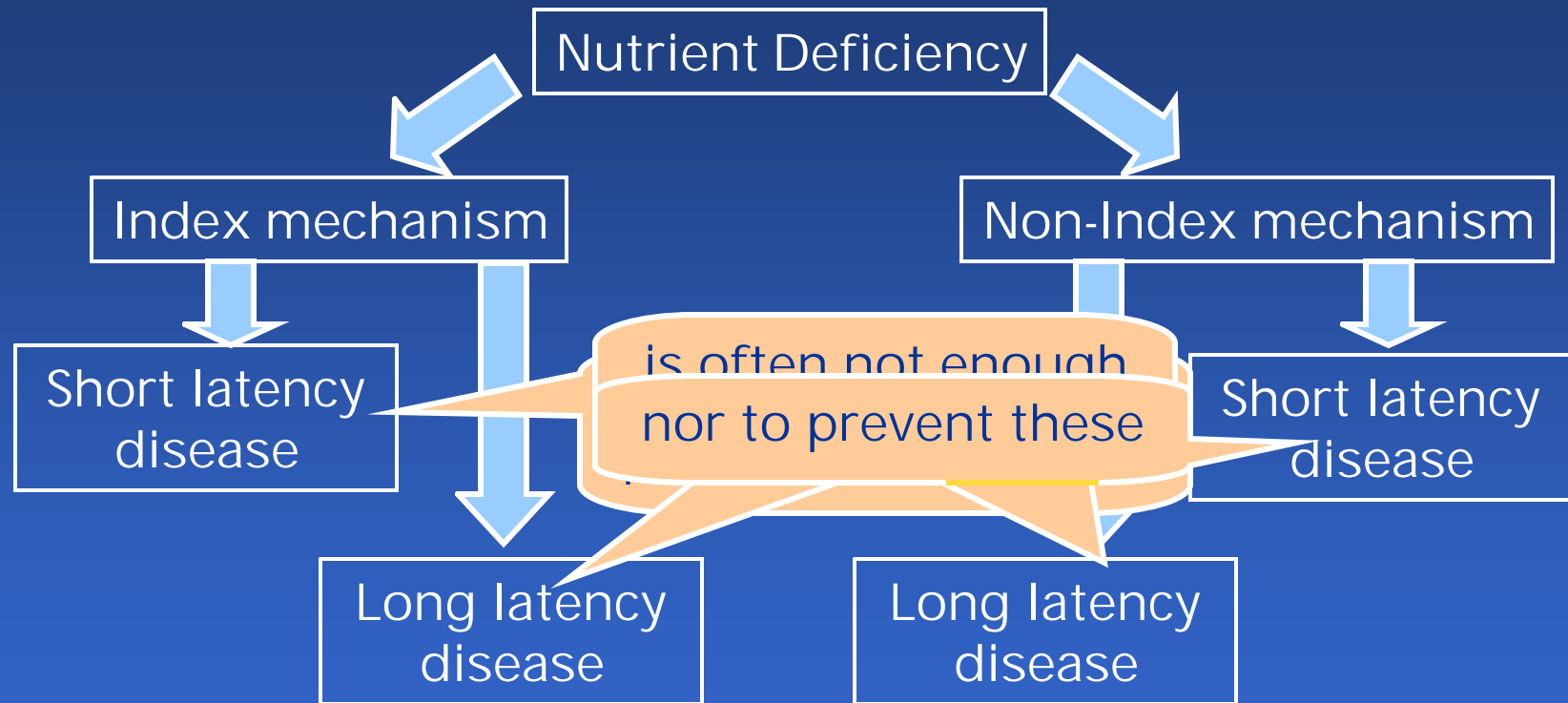
RETHINKING DEFICIENCY DISEASE



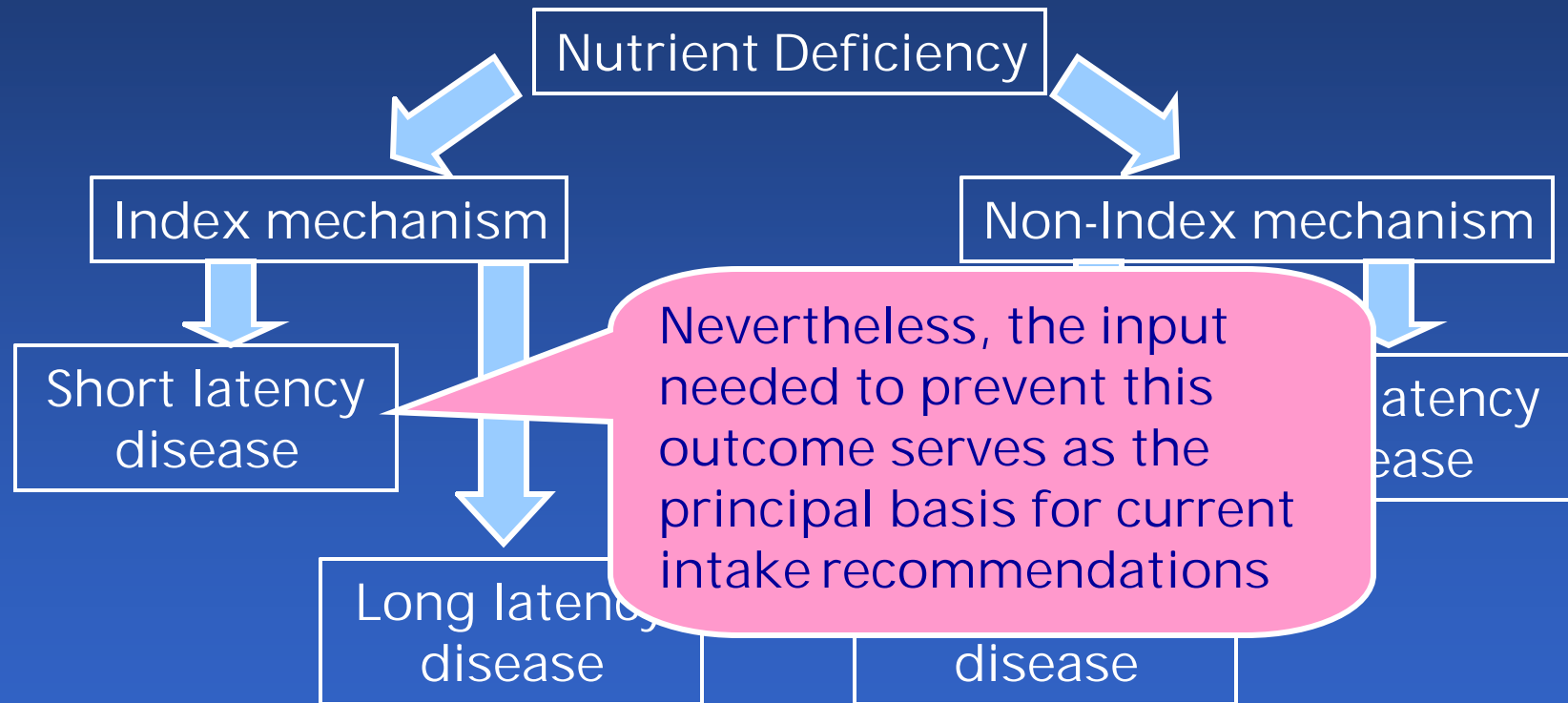
RETHINKING DEFICIENCY DISEASE



RETHINKING DEFICIENCY DISEASE



RETHINKING DEFICIENCY DISEASE



more useful

What is the ~~right~~ endpoint?

What is the operative model
for nutrition?

WHAT IS THE OPERATIVE MODEL?

- for the media?
- for regulators?
- for nutritional policy makers?
- for nutritional physiologists?

WHAT IS THE OPERATIVE MODEL?

- *for the media and for regulators*

- nutrition is about killing yourself with a fork
- it's about avoiding risks
- it's about warnings & cautions

Nutrition Facts

Serving Size 1 cup (228g)

Serving Per Container 2

Amount Per Serving

Calories 250 Calories from Fat 110

% Daily Value*

Total Fat 12g **18%**

Saturated Fat 3g **15%**

Cholesterol 30mg **10%**

Sodium 470mg **20%**

Total Carbohydrate 31g **10%**

Dietary Fiber 0g **0%**

Sugars 5g

Protein 5g

Vitamin A

Vitamin C **2%**

Calcium **20%**

Iron **4%**

* Percent Daily Values are based on a 2,000 calorie diet. Your Daily Values may be higher or lower depending on your calorie needs:

	Calories:	2,000	2,500
Total Fat	Less than	65g	80g
Sat Fat	Less than	20g	25g
Cholesterol	Less than	300mg	300mg
Sodium	Less than	2,400mg	2,400mg
Total Carbohydrate		300g	375g
Dietary Fiber		25g	30g

For a package of macaroni & cheese

<http://vm.cfsan.fda.gov/~dms/foodlab.html>

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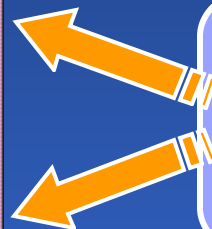
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Limit these nutrients



Get enough of these nutrients



MEDIA REPORTING

- the overwhelming majority of media reports about nutrition emphasizes harm and risk
- while the explanation is partly that harm is more newsworthy than benefit (and the media batters on controversy)
- still the impression unwittingly conveyed to the general public is one of concern and danger

WHAT IS THE OPERATIVE MODEL?

- *for nutritional policy makers*

- nutrition is about determining the least one can get by on without suffering overt disease of a specific type
- (once called MDRs)

WHAT IS THE OPERATIVE MODEL?

- *for nutritional physiologists*

- adult nutrition is about preventive maintenance of tissues and organs
- it's about keeping them from wearing out or breaking down prematurely
- its referent is the intake that prevailed when human physiology evolved

THE PREVENTIVE MAINTENANCE MODEL

foundational premises:

- all tissues need all nutrients
- shortages impair the functioning of *all* body systems
- premature organ/system “wearing out”, as a consequence of nutrient deficiency, will vary from person to person, depending on variable genetic composition; and
- therefore, expression of nutrient deficiency will usually be pluriform – both between and within individuals

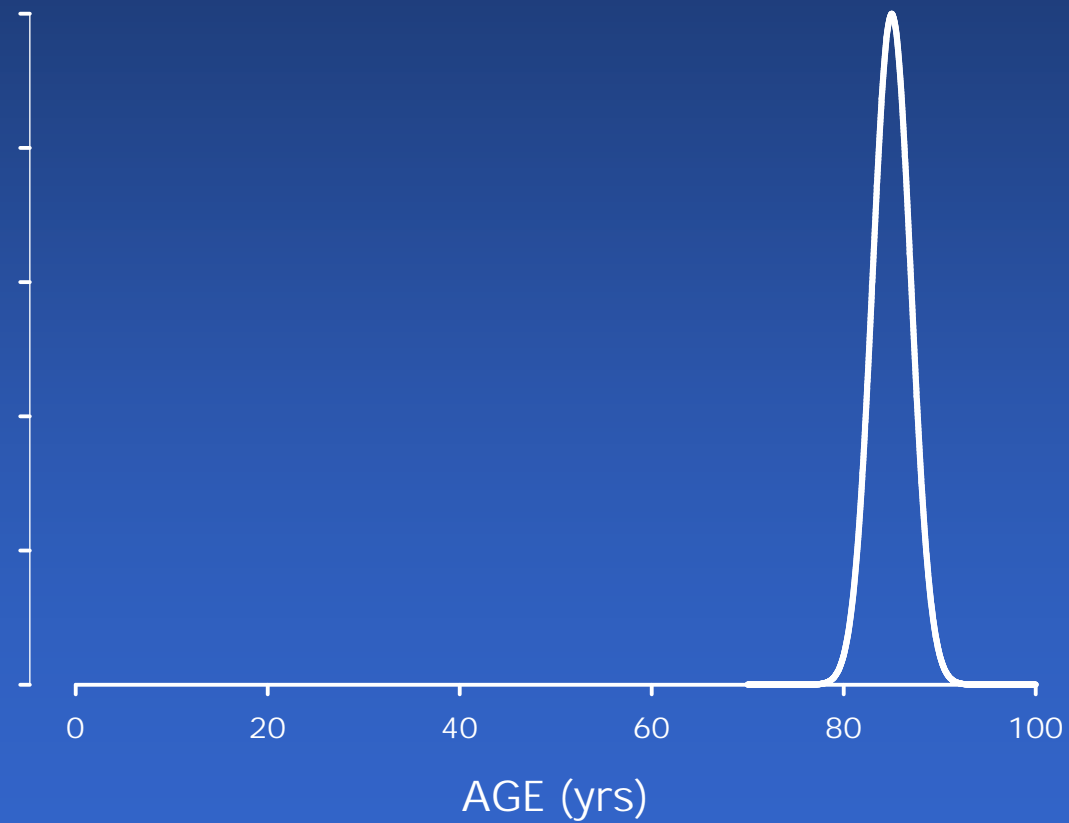
THE INTAKE REFERENT

- it is sometimes argued that primitive intakes may be ill-suited to modern conditions
- but lacking specific evidence to that effect, the presumption ought to tip toward the primitive intake
 - what is the justification for privileging the status quo?
- the burden of proof should fall on those who claim that primitive intakes are unsafe or that lower intakes are adequate

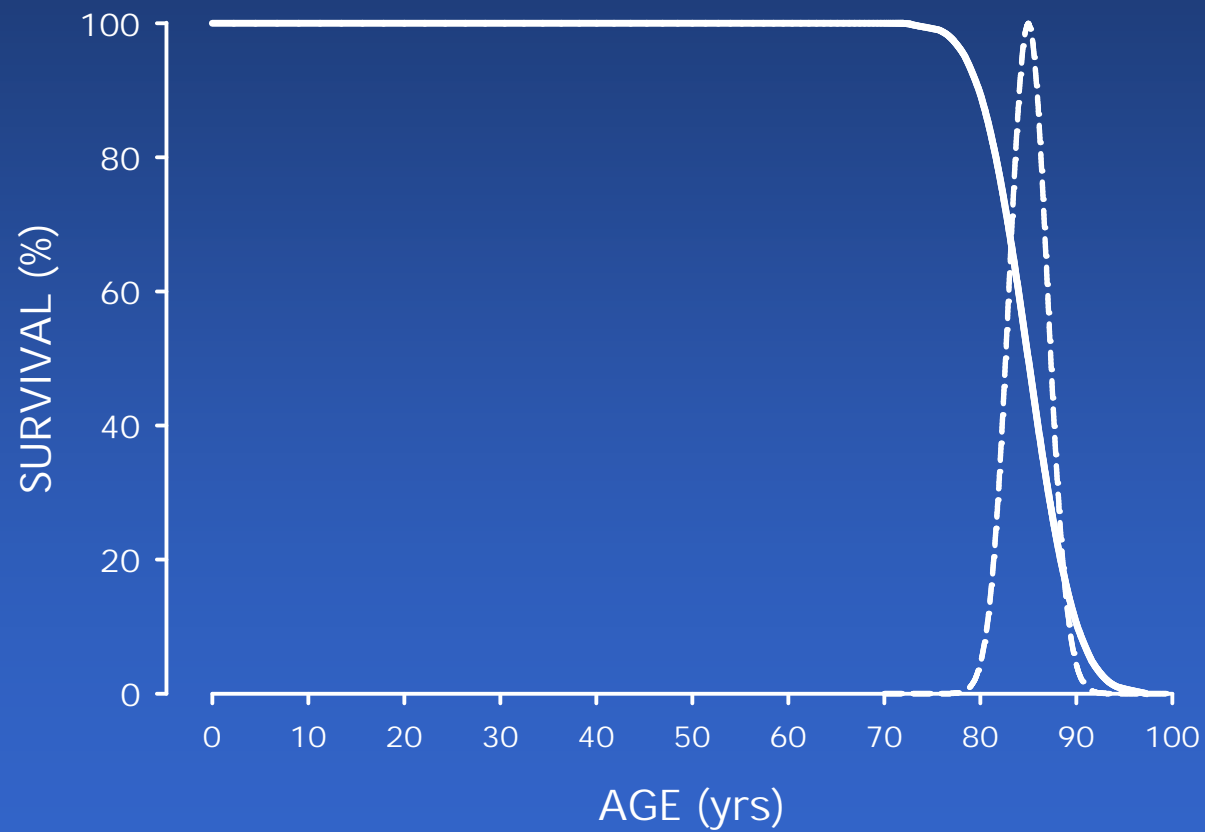
THE PREVENTIVE MAINTENANCE MODEL

- *also recognizes that:*
 - the organism will work perfectly well without maintenance – *for a while . . .*
- it thus reconciles the seeming paradox that an organism can be “deficient” without being clinically “sick”
 - *for a while . . .*
- it’s also about squaring the morbidity/mortality curve

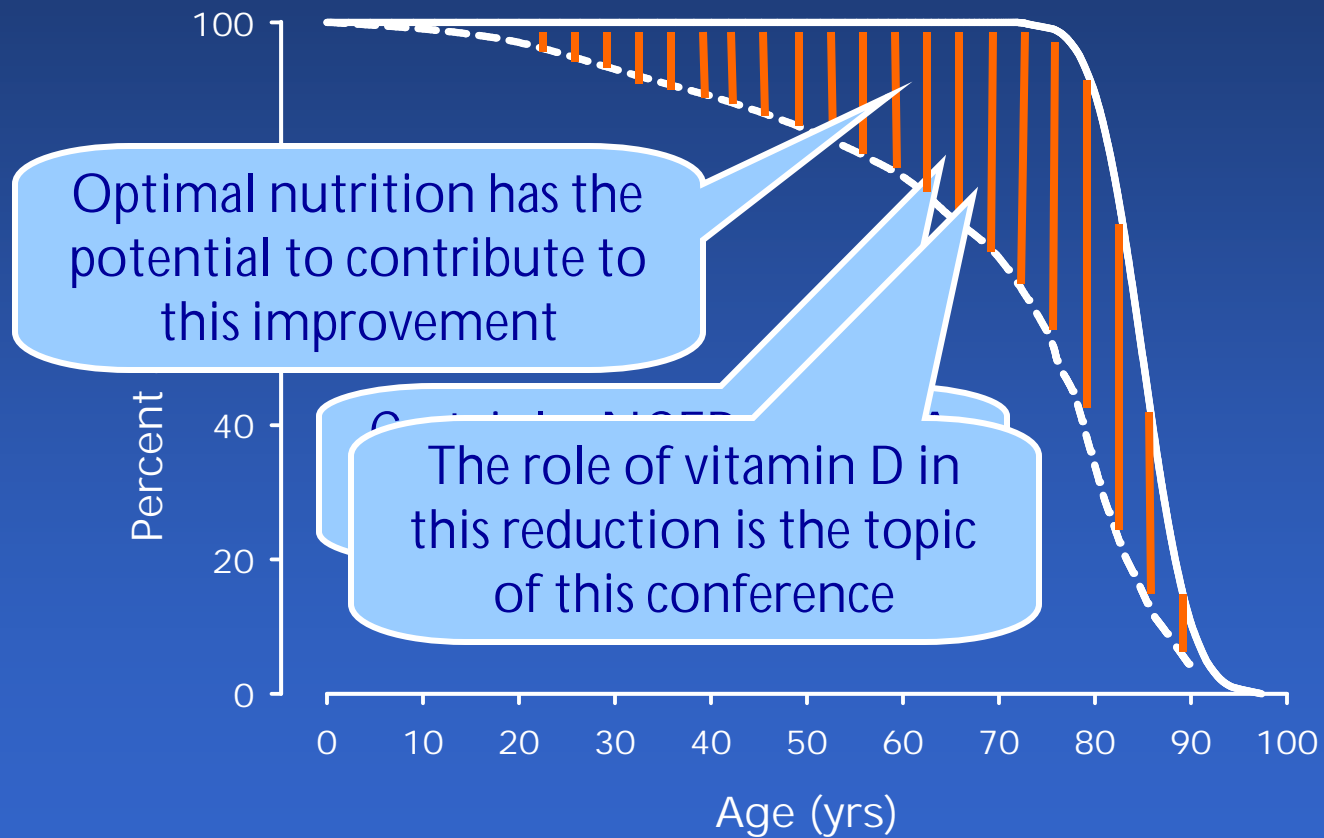
THEORETICAL MORTALITY CURVE



THEORETICAL MORTALITY CURVE



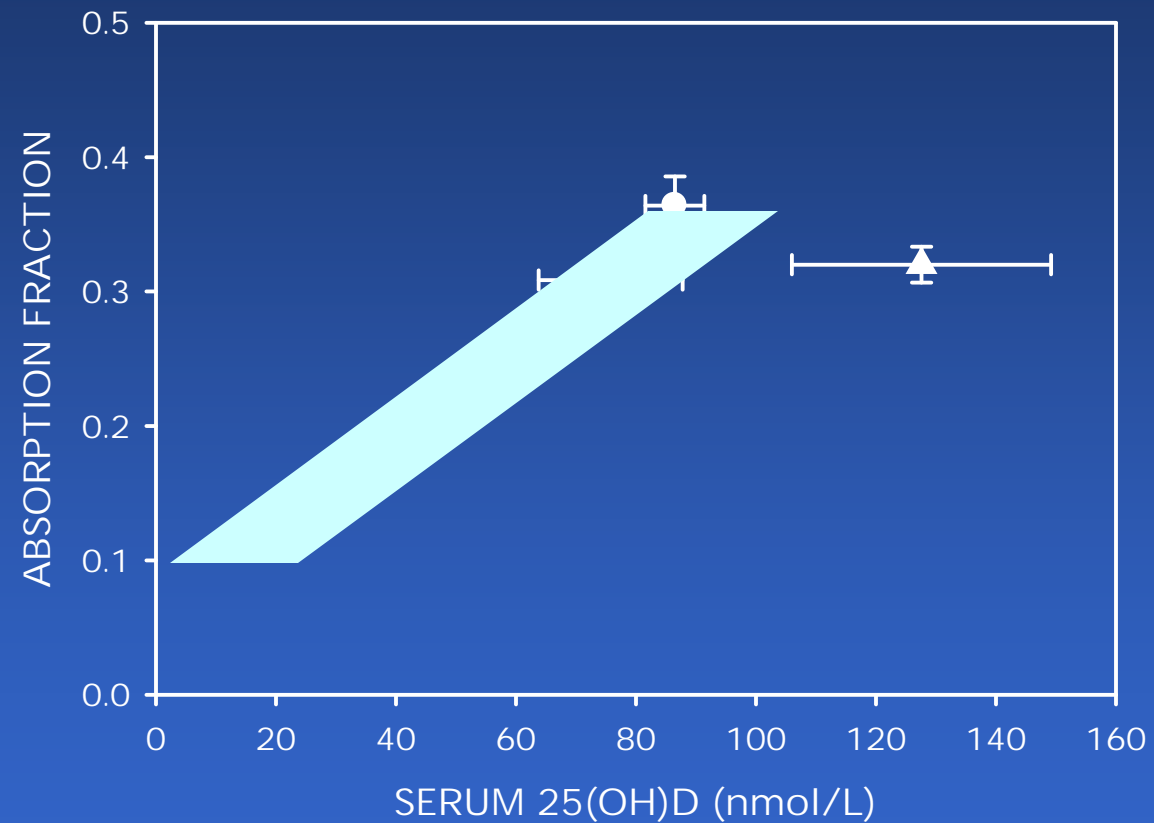
SQUARING THE MORTALITY CURVE



ASSESSING VITAMIN D DEFICIENCY

- serum *total* 25(OH)D is the: –
 - functional indicator for vit D status
 - the major storage form of vit D at typical inputs
- serum 25(OH)D₂ is of no value unless the MD is following treatment with vit D₂
- serum 1,25(OH)₂D does not measure vit D status (instead, it measures Ca need)

A VITAMIN D THRESHOLD

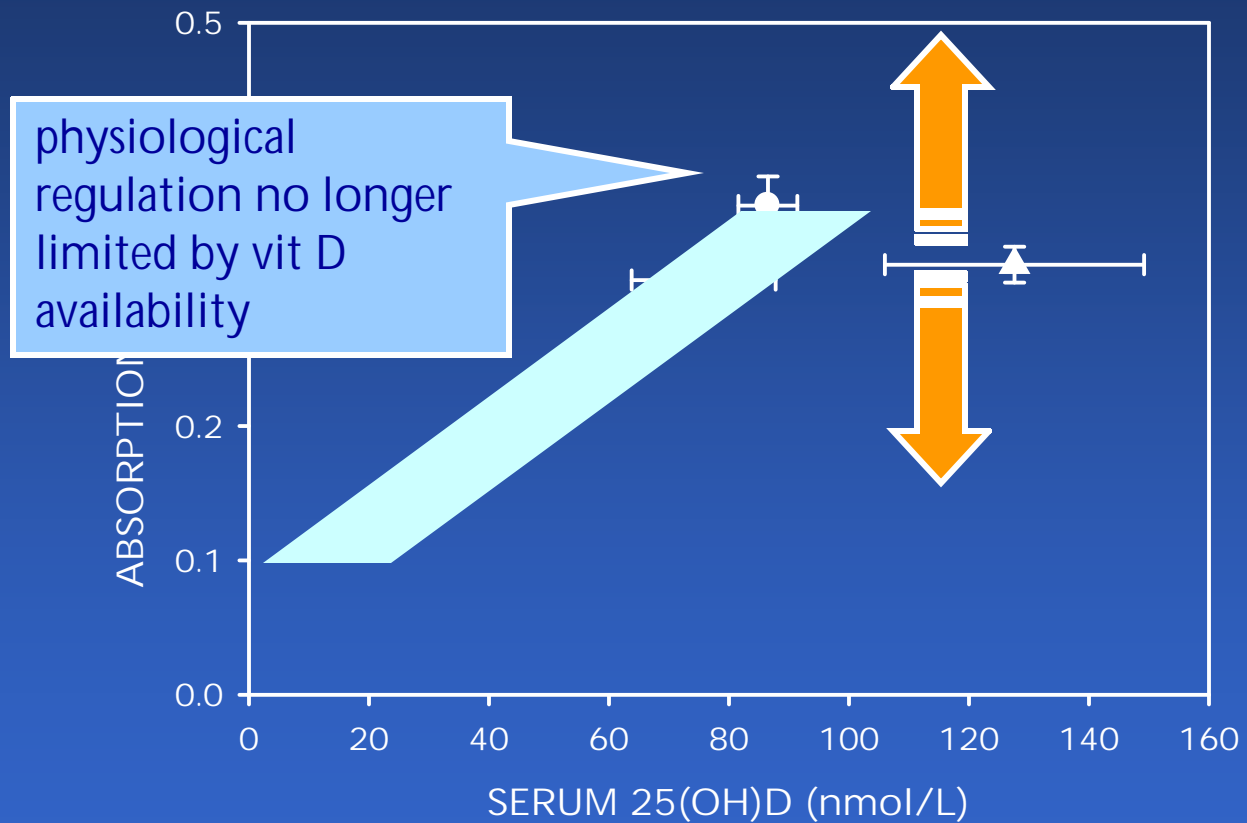


CU

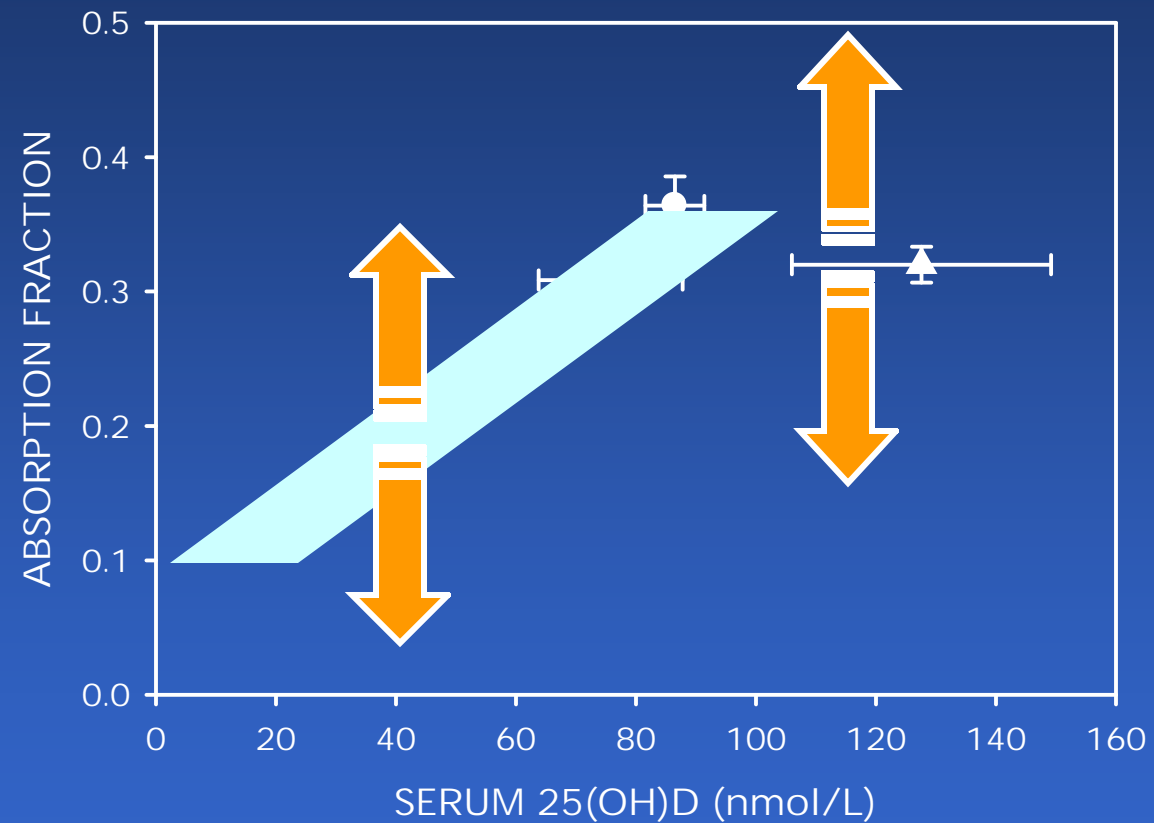


ORC

A VITAMIN D THRESHOLD



A VITAMIN D THRESHOLD



CU



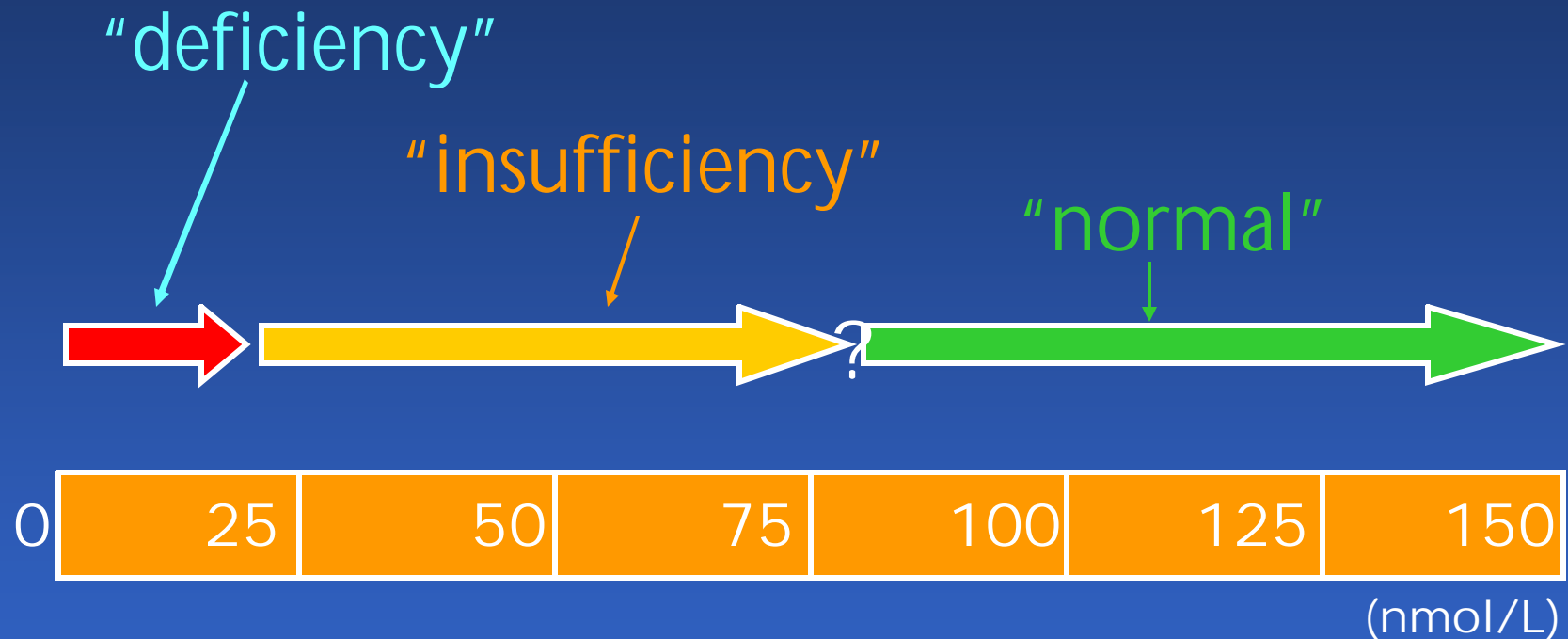
ORC

The evidence to be presented in all the papers that follow points to a requirement for serum 25(OH)D that is above 80 nmol/L* (and perhaps as much as 100–125 nmol/L**).

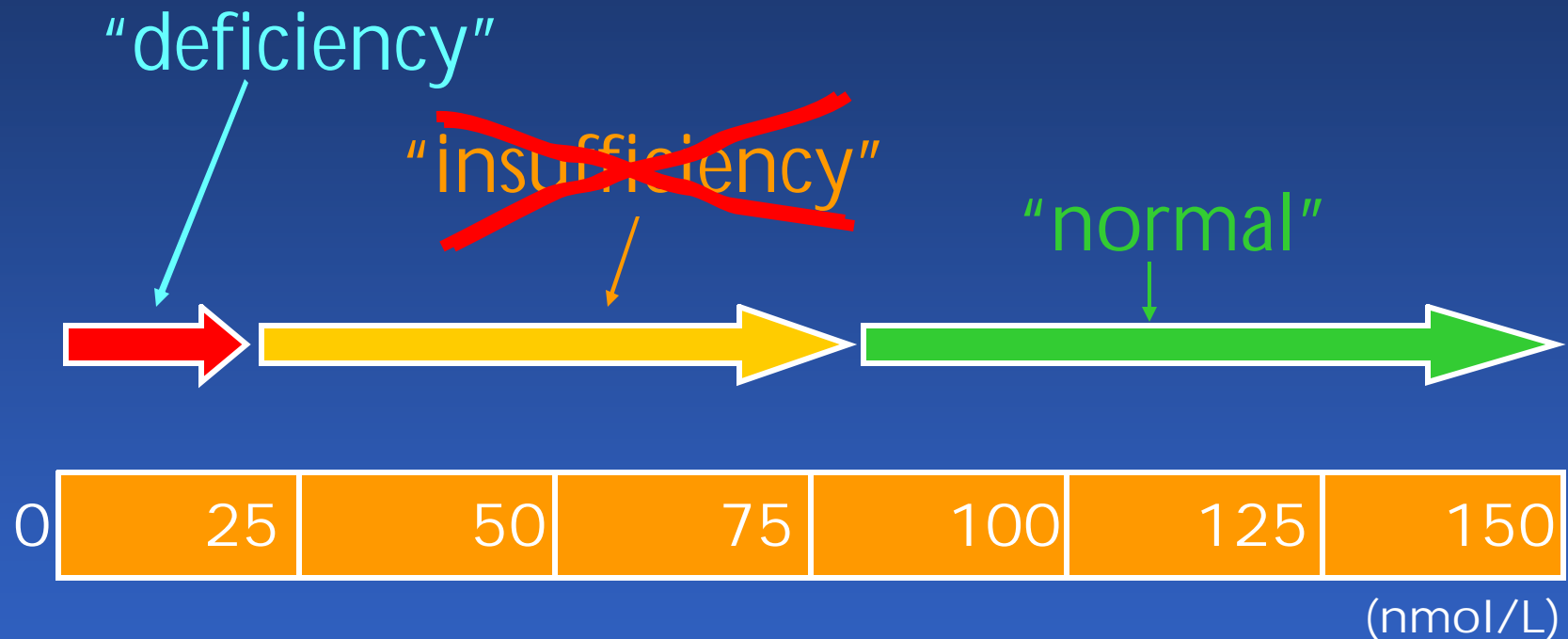
* 32 ng/mL

** 40–50 ng/mL

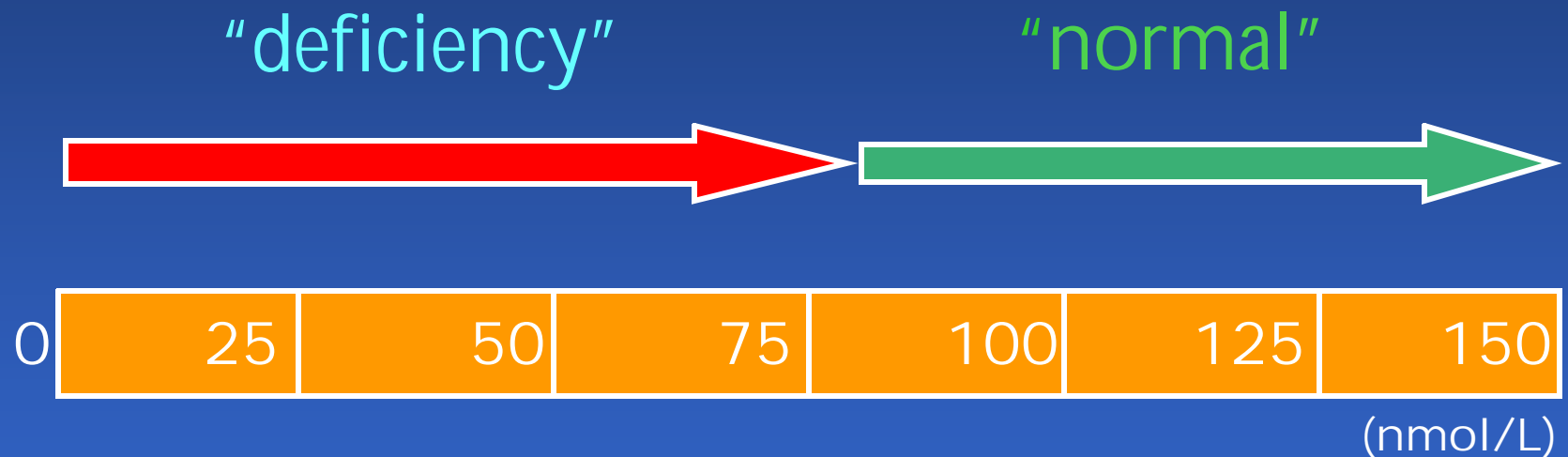
THE 25(OH)D CONTINUUM



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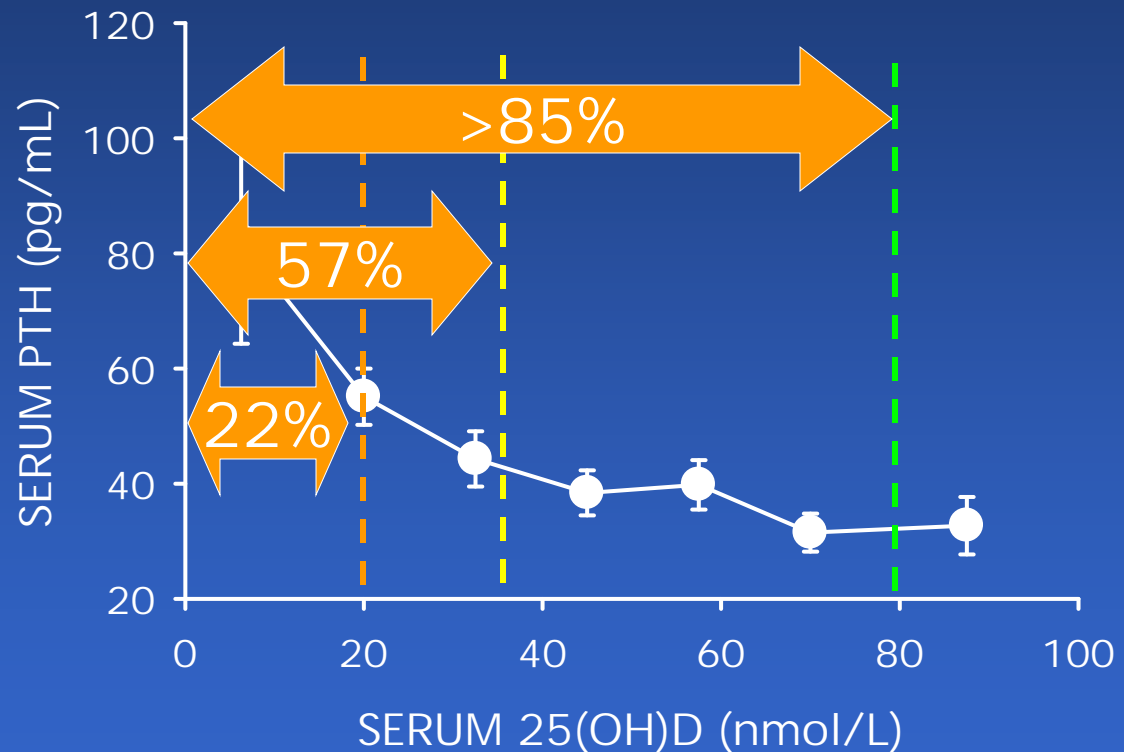


THE 25(OH)D CONTINUUM



25(OH)D & SERUM iPTH*

290
consecutive
pts. on a
general
medical
ward - MGH



CU



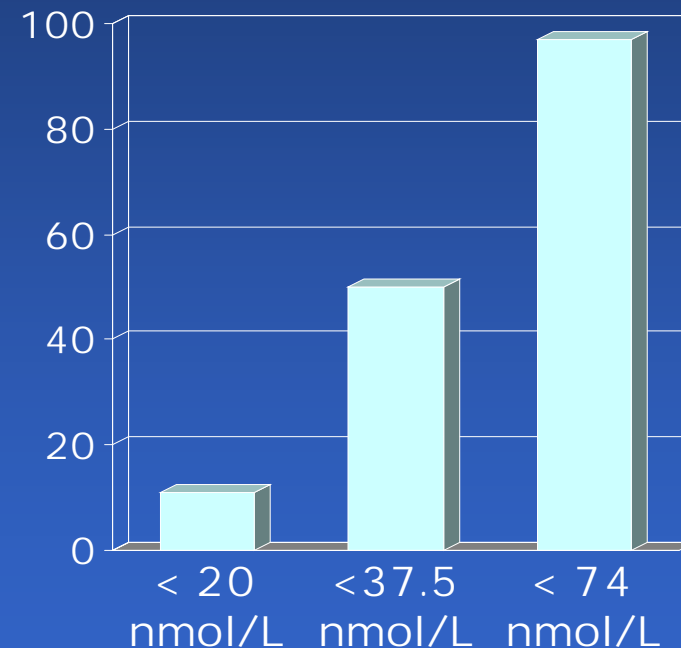
ORC

*after Thomas et al., 1998 NEJM;338:777-783

PREVALENCE IN HIP FRACTURE

- 223 new hip fractures
- SE Finland (61° N)
- 50% below 37.5 nmol/L
 - 33% late summer
 - 67% late winter
- Nurmi et al., OI (2005)
16:2018–2024

Percent Less Than



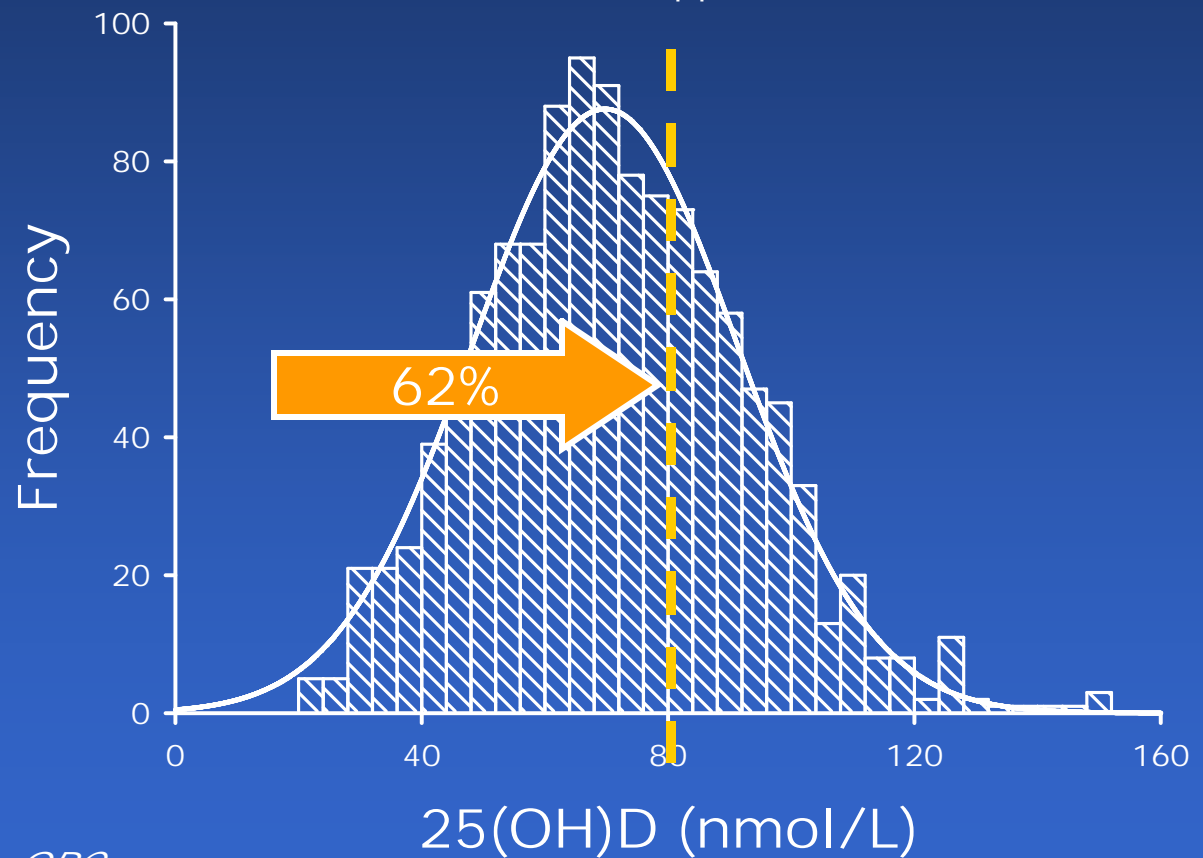
PREVALENCE IN THE OLD ELDERLY

- 104 N. Italian centenarians
 - mean age: 98 yrs
 - 90 females; 14 males
- mean 25(OH)D: 16 nmol/L
 - 99/104 unmeasurable
 - maximum: 21 nmol/L
- 14 hip fractures since age 94

25(OH)D IN OLDER WOMEN*

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

*Lappe et al., JACN 2006



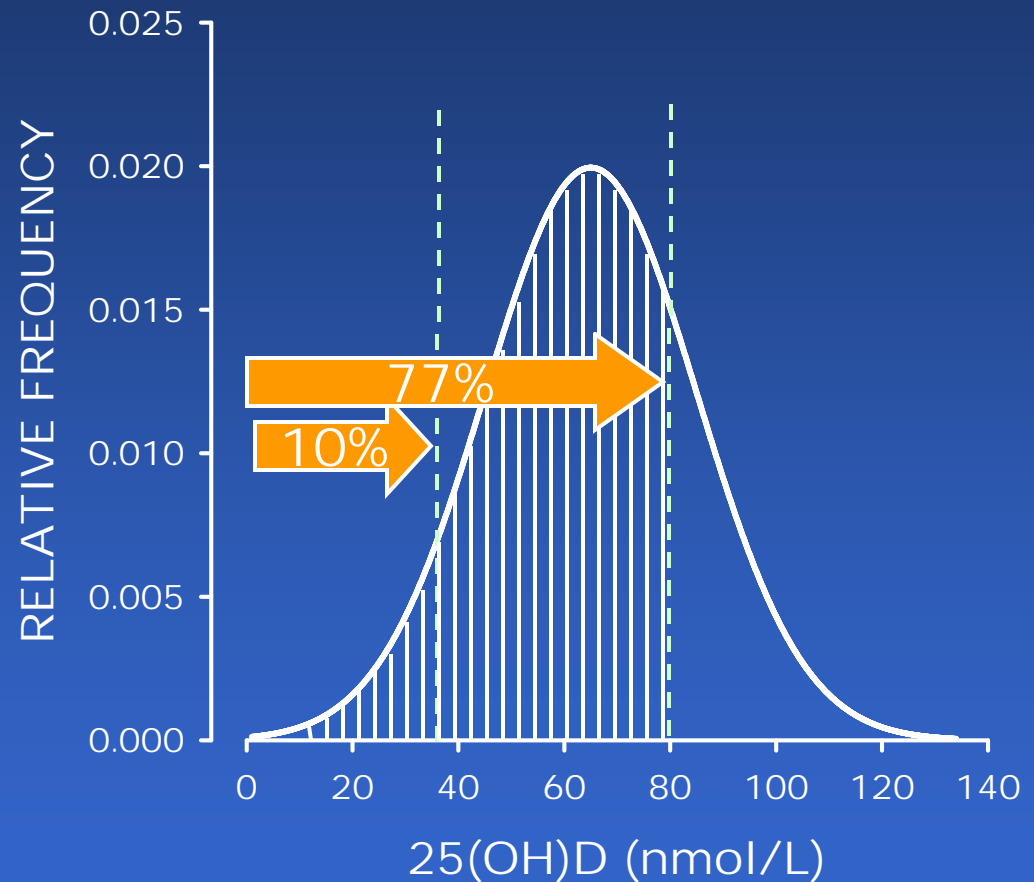
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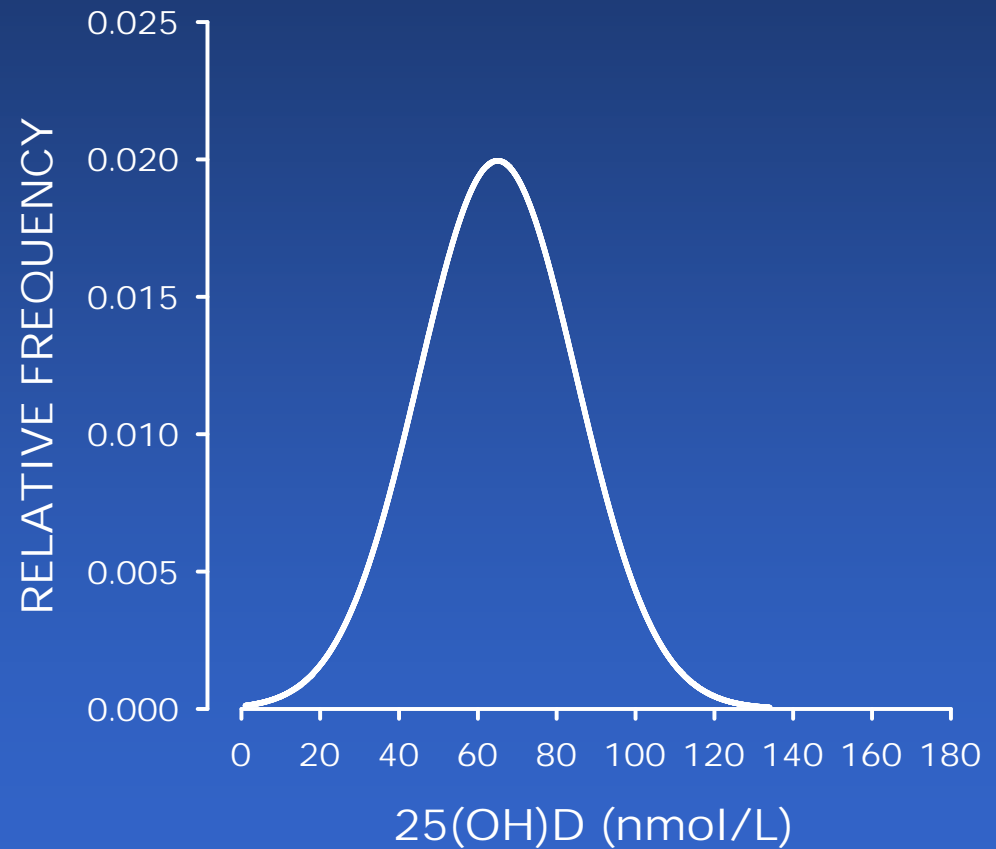
NHANES-III

- women aged 60–79
- summer, northern states
- Looker et al., (2002)
Bone 30:771–77



What would this distribution look like if the entire population were to be supplemented with vitamin D?
– say, with 2000 IU/d?

NHANES-III* + THE TUIL



CU

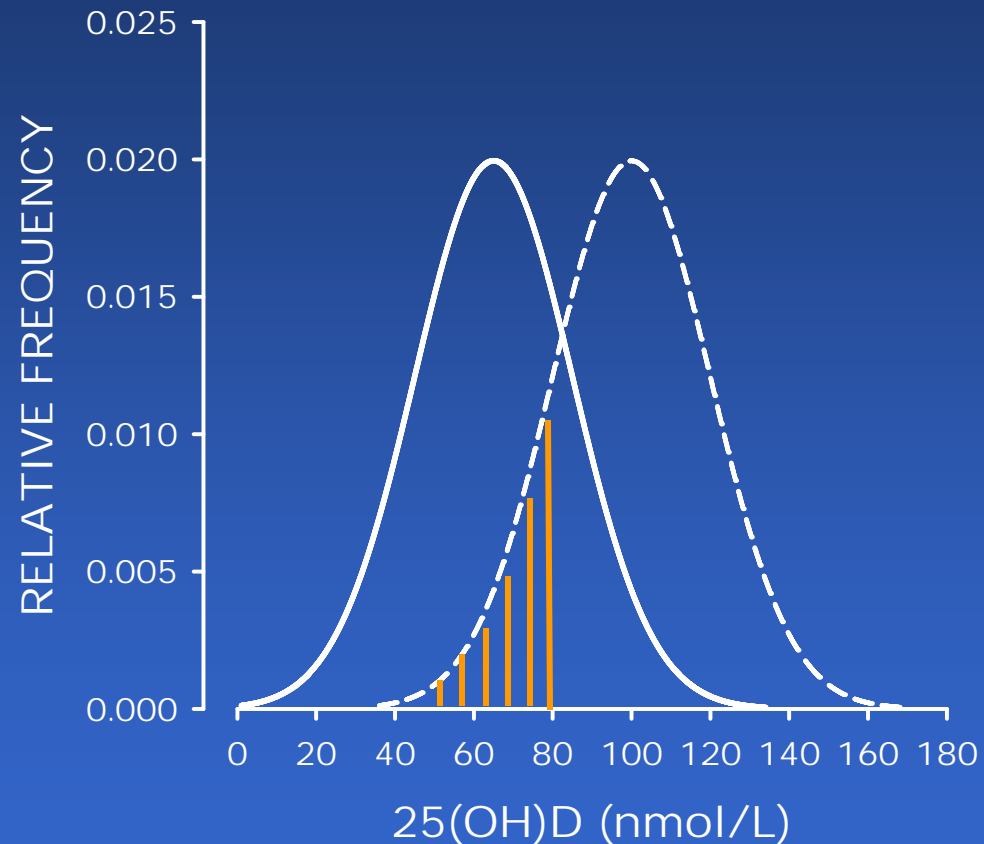


ORC

*Looker et al., (2002) Bone 30:771-77

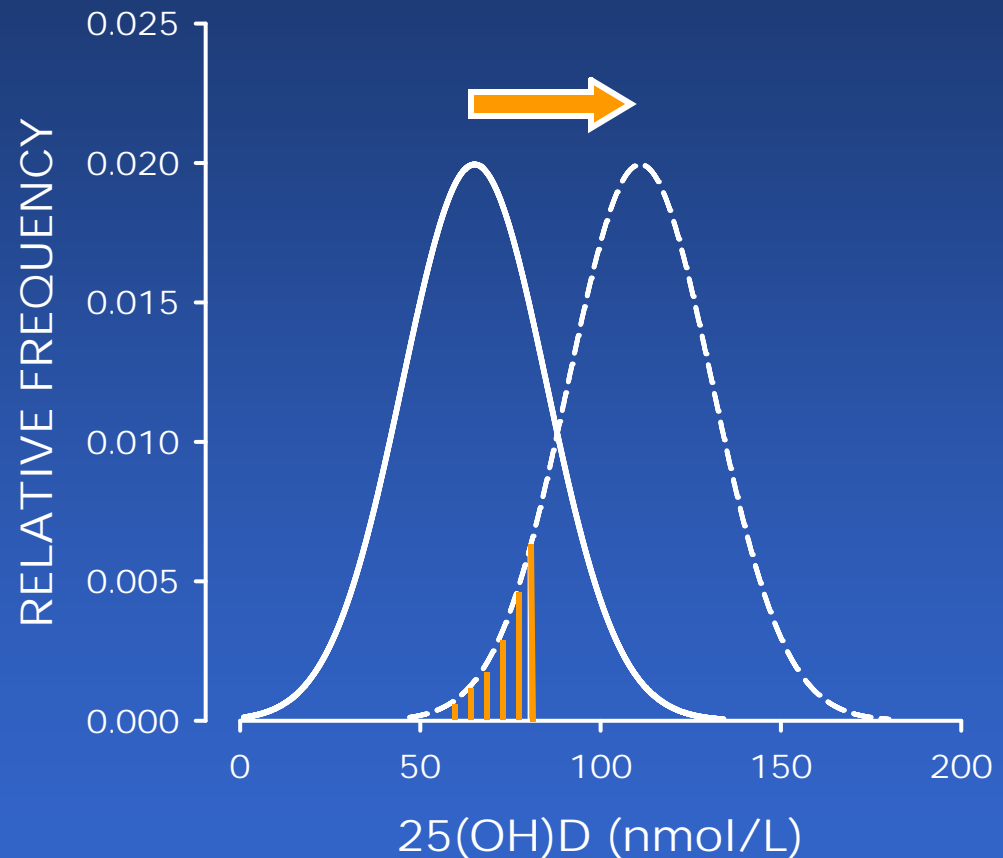
NHANES-III* + THE TUIL

- 2000 IU/d raises 25(OH)D by ~ 35 nmol/L
- 15% of older women are still below 80 nmol/L
- effectively no one would be pushed above 180 nmol/L



NHANES-III* + 2600 IU/D

- 2600 IU/d would raise 25OHD by ~ 46 nmol/L
- ~2.5 % of population still below 80 nmol/L
- thus 2600 IU/d \cong the RDA for women >60 yrs
- *but, that's over & above all current inputs*



CU

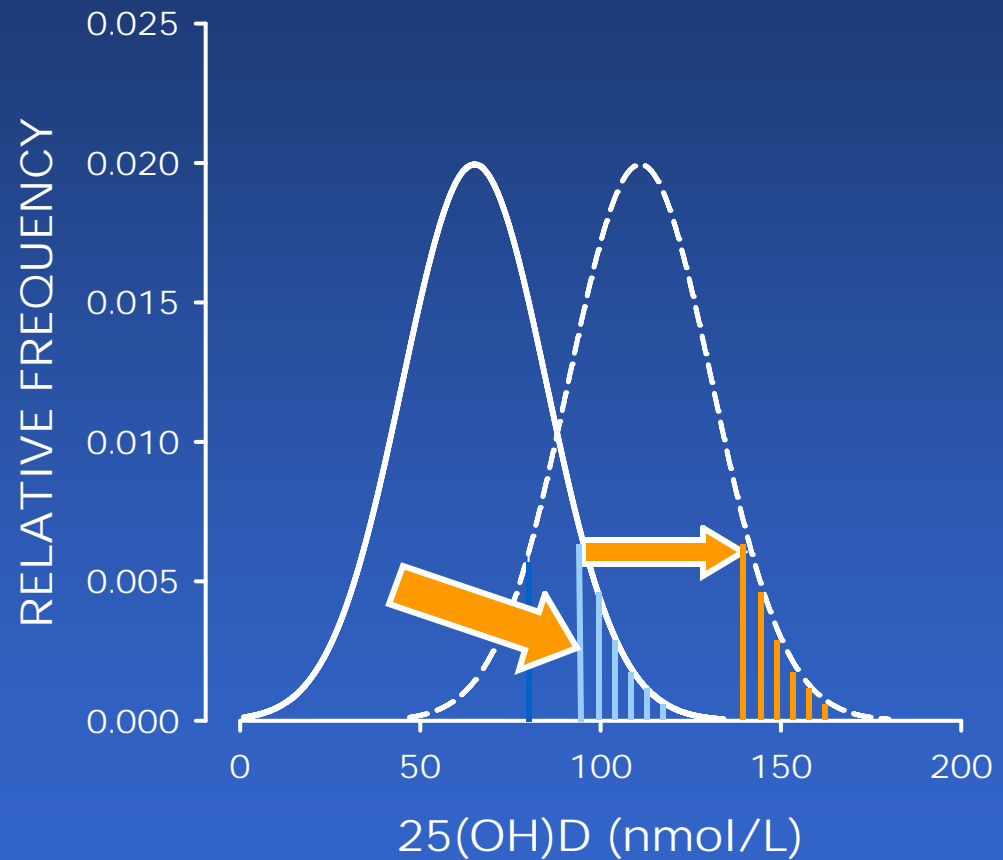


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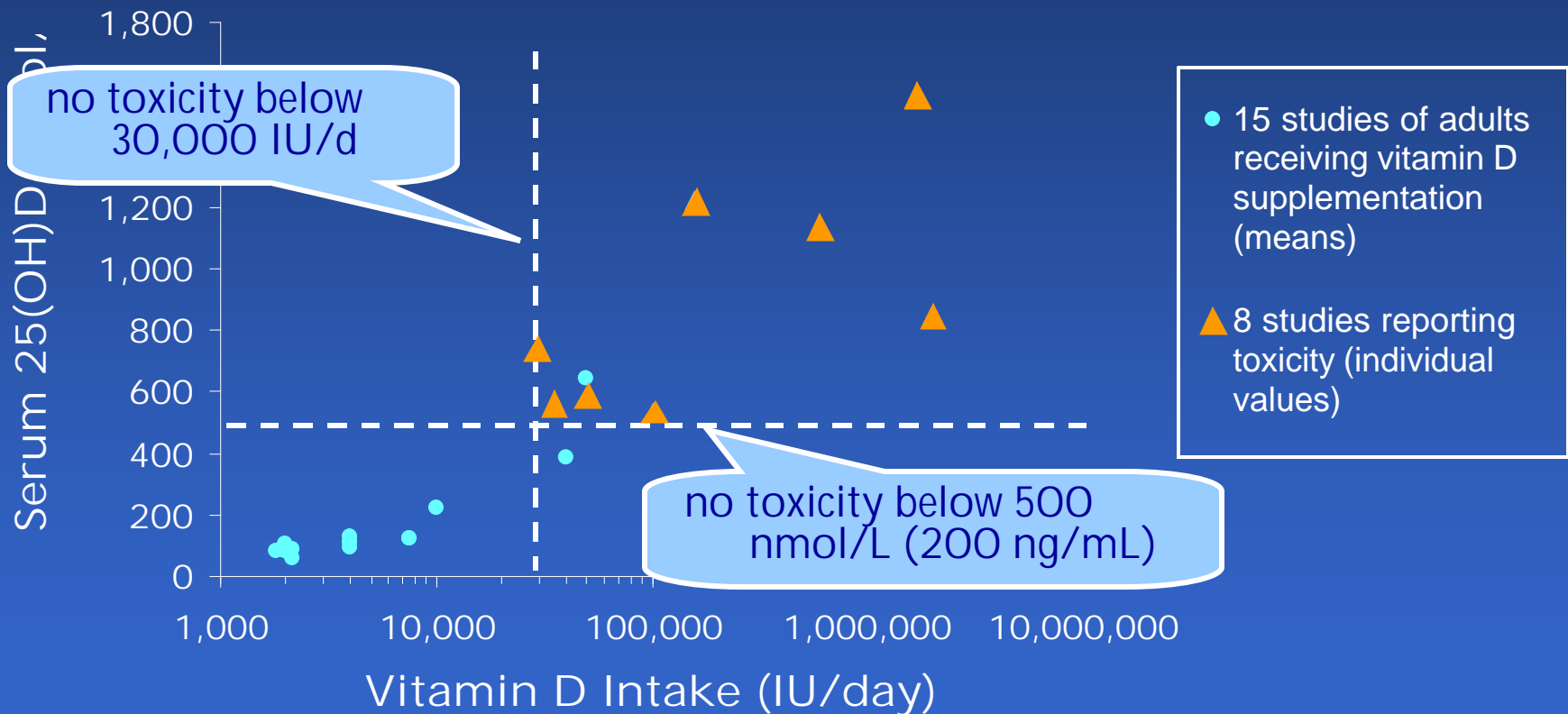
NHANES-III* + 2600 IU/D

- what about those already 2 SD above the mean?
- the rise with an extra ~2600 IU/d would be predicted to bring them to no more than 180 nmol/L – well below the toxic range



Safety

VITAMIN D INTAKE & TOXICITY*



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

TUIL: 10,000 IU/d*

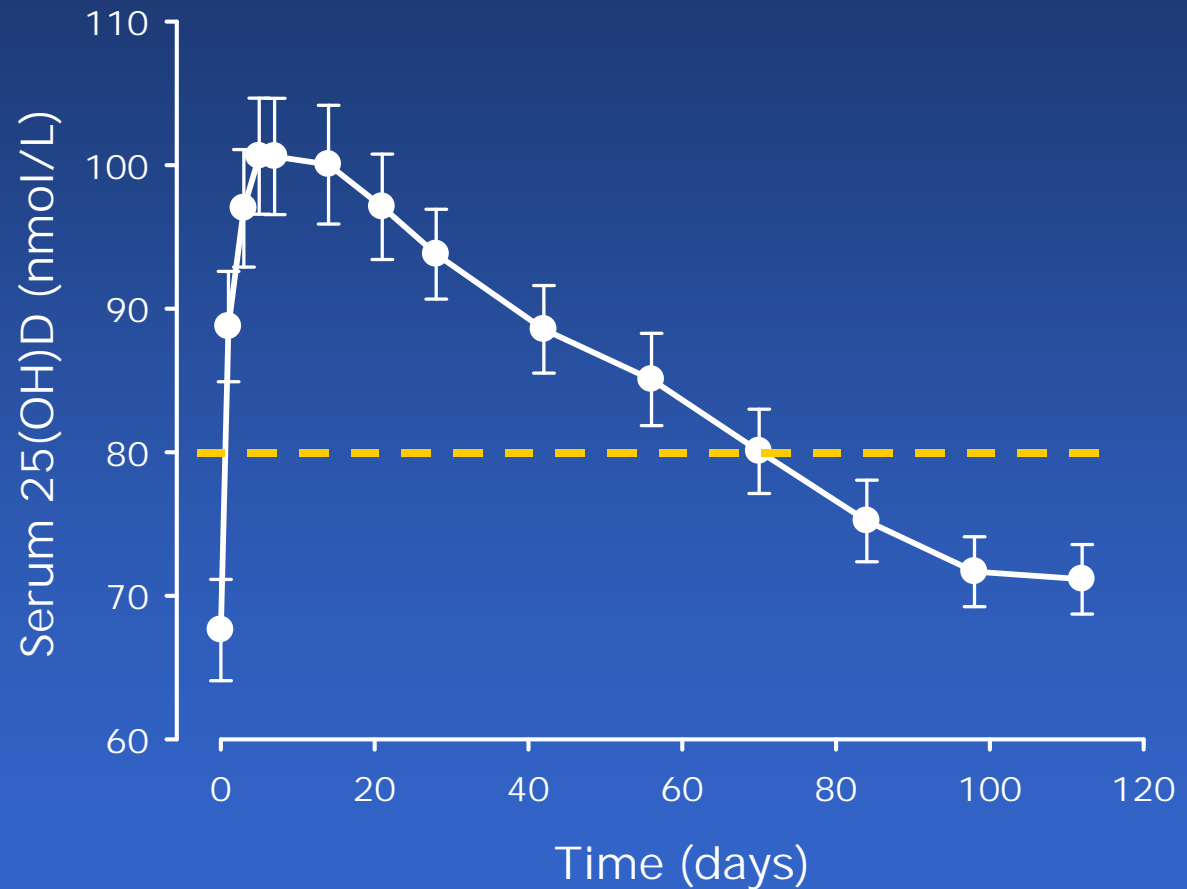
*Hathcock et al.,(2007) AJCN 85:6–18

A RULE OF THUMB

- serum 25(OH)D rises by ~ 1 ng/mL (2.5 nmol/L) for every 100 additional IU/d of vitamin D₃
- hence:
 - to raise a patient level from 15 to 30 ng/mL will typically require an additional input of 1500 IU/d
 - however there is huge variability around this average

25(OH)D RESPONSE TO LARGE DOSES*

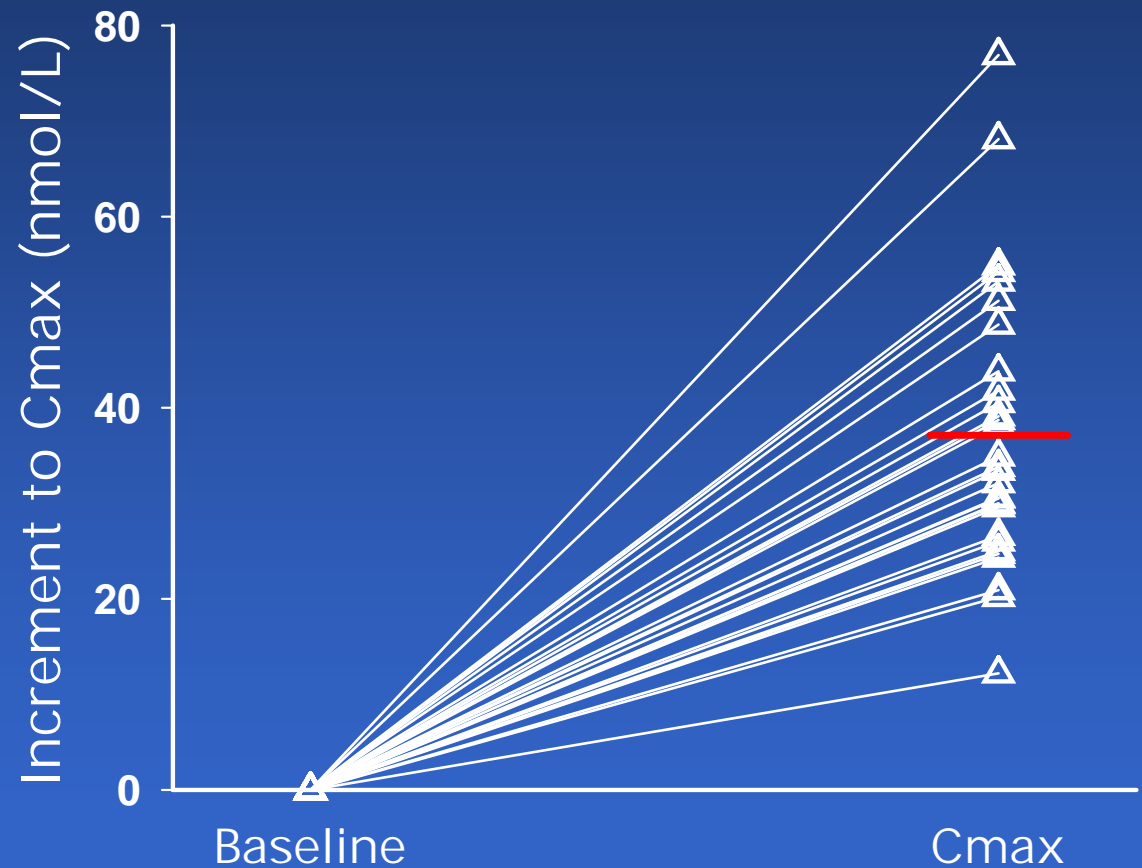
- 100,000 IU D₃, by mouth, once



*Ilahi, Armas, & Heaney (in press)

VARIABILITY OF 25(OH)D RESPONSE*

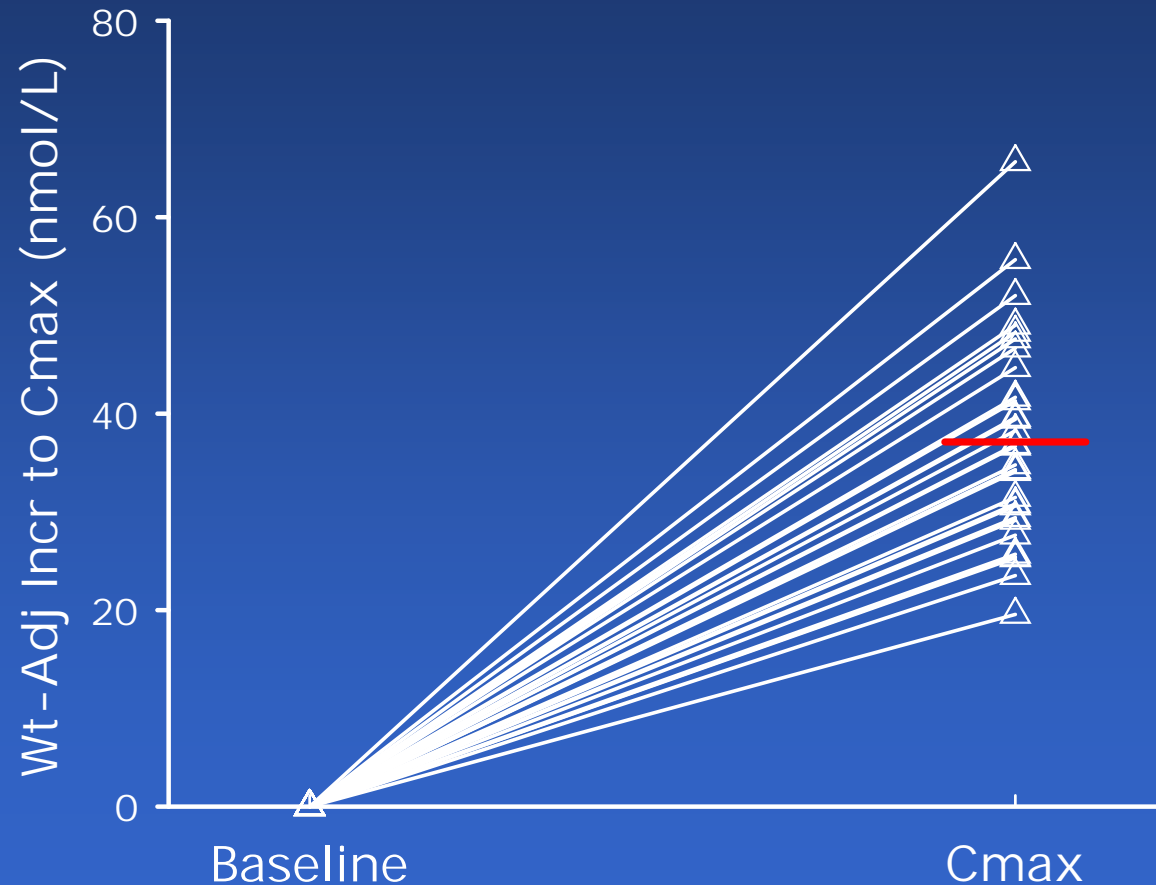
- Δ 25(OH)D to C_{\max} ranged from +12 nmol/L to +76 nmol/L
- ~half of the variability due to body size



*Ilahi, Armas, & Heaney (AJCN 2008)

VARIABILITY OF 25(OH)D RESPONSE*

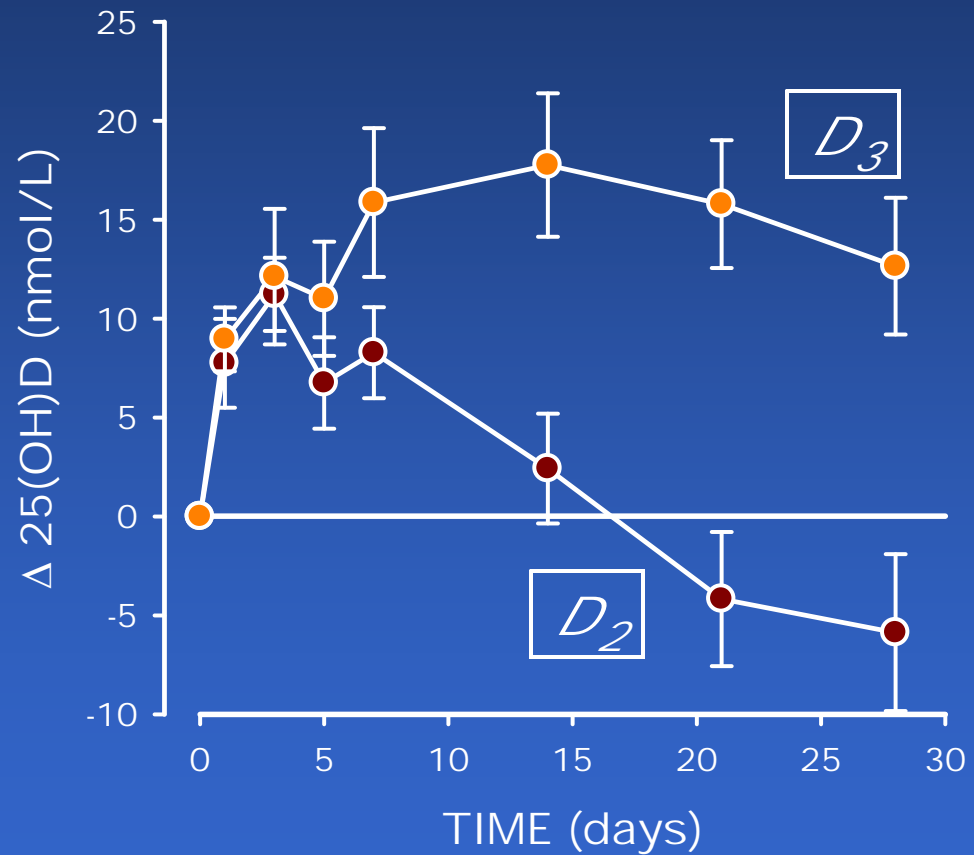
- Wt-adjusted Δ 25(OH)D to C_{max} ranged from +20 nmol/L to +66 nmol/L



*Ilahi, Armas, & Heaney (in press)

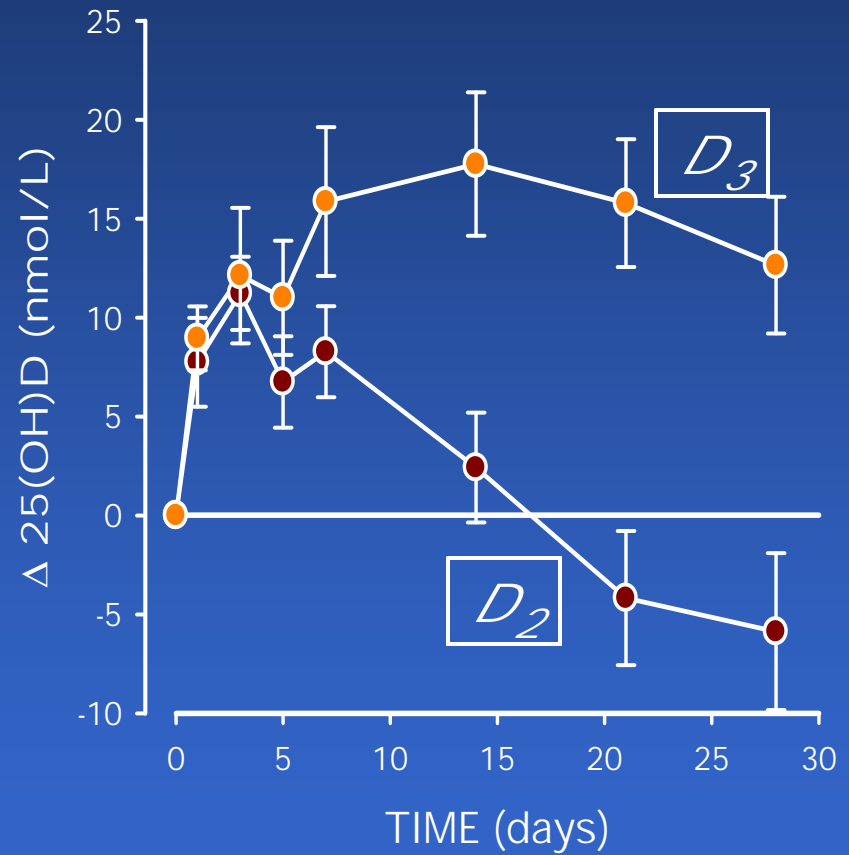
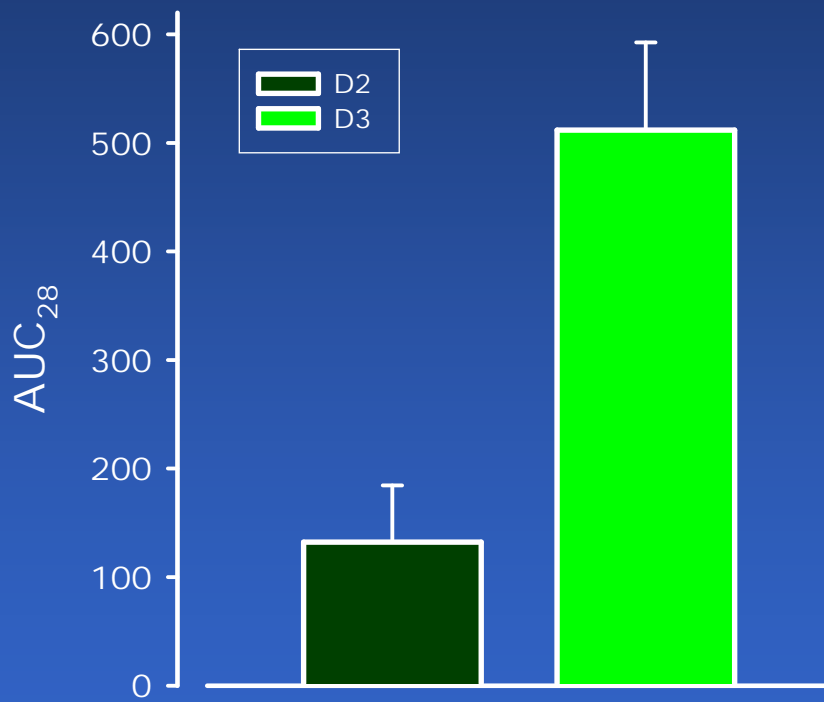
D_2 vs. D_3^*

- single oral dose
- 50,000 IU
- D_2 or D_3
- $n = 10$ in each group



*Armas et al., 2004

D_2 vs. D_3^* – AUC



*Armas et al., 2004

CONCLUSIONS

- serum 25(OH)D levels below 80 nmol/L are not adequate for any body system
- levels of as high as 120 nmol/L may be closer to optimal
- inputs from all sources combined (needed to sustain 80 nmol/L) are in the range of ~4,000 IU/d and higher
- in most healthy adults, 2000 IU/d, in addition to all other inputs, will usually suffice

OBJECTIVES

- define nutrient deficiency
- cite evidence relating to vitamin D
- estimate vitamin D intake to sustain sufficiency
- estimate prevalence of deficiency
- characterize the effects of vitamin D supplementation
- define the safe upper intake of vitamin D

disease or dysfunction due to low intake

Ca absorptive regulation suboptimal below 80 nmol/L

4000 IU/d – all sources

65–95 %

no toxicity

10,000 IU/d

Thank you

OBJECTIVES

- list 10+ vitamin D sensitive diseases
- quantify benefits of solving D deficiency
- define the dose-response relationship for osteoporosis, falls, type I diabetes, & cancer
- interpret 25(OH)D values for diagnosis & treatment
- identify & quantify risk categories for vit D treatment

