VITAMIN D

EVALUATING THE EVIDENCE

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MY FOCI

- early life
- measuring & assessing 25(OH)D
- other

Early Life

Deficiency – a 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

CLASSICAL VIT D DEFICIENCY

- rickets in children
- caused by poor absorption of calcium
  - leading to high PTH levels,
  - lowered renal phosphate threshold
  - hypophosphatemia
- serum 25(OH)D: < 25 nmol/L
- clinically preventable by 200–400 IU D_3/day
- that dose does *not* restore full Ca absorptive function *nor* normal bone histology

RICKETS RISES AGAIN

- decreased sun exposure of babies
- maternal vitamin D deficiency
- failure to supplement infant feedings with vitamin D
- weaning infants to non-milk liquids

CRANIOTABES IN "NORMAL" INFANTS*

- 1120 consecutive neonates in Japan
- 22% had craniotabes
- median 25(OH)D at 1 mo: < 25 nmol/L

*Yorifuji et al., JCEM; 93:1784-88 (2008)

FETAL RICKETS*

- n = 424
- 3D QUS
- splay index at distal femur at 19 & 34 weeks
- (metaphyseal X-sectional area divided by femoral length)
- high ≈ rickets

*Mahon et al., (2010) JBMR 25:14–19

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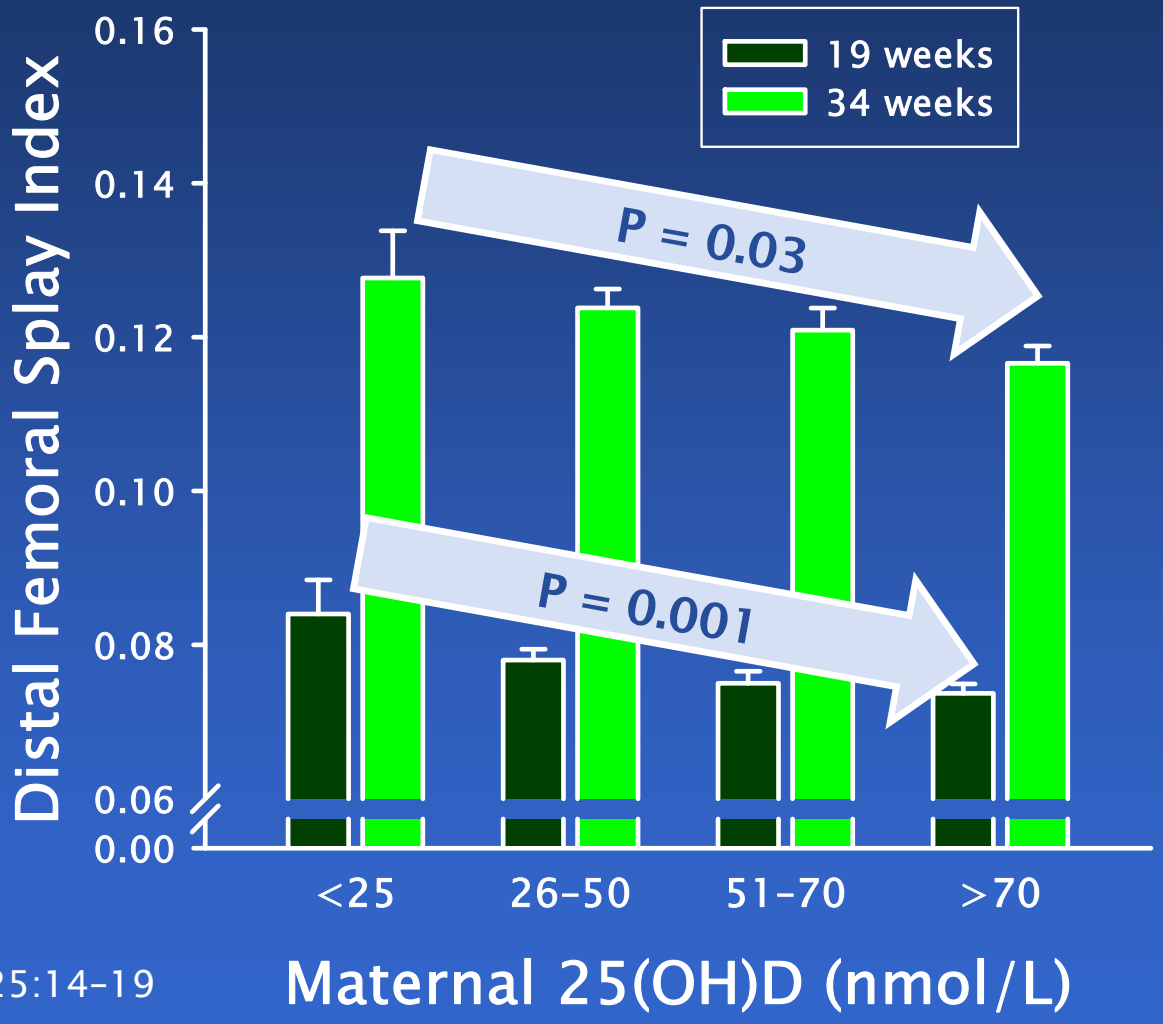
- splay index at distal femur



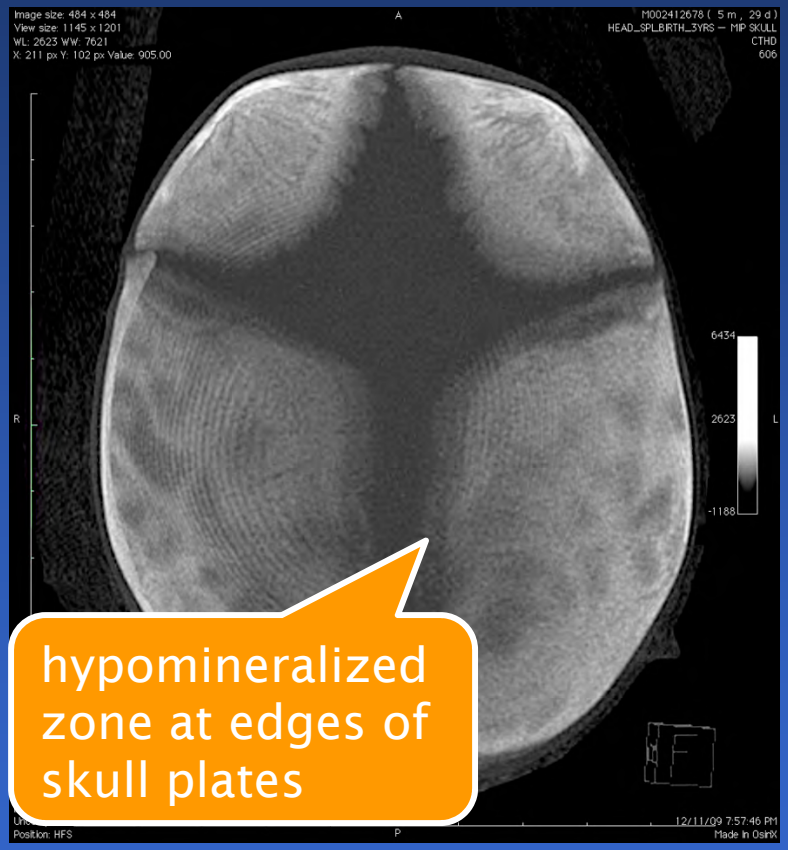
*Mahon et al., (2010) JBMR 25:14-19

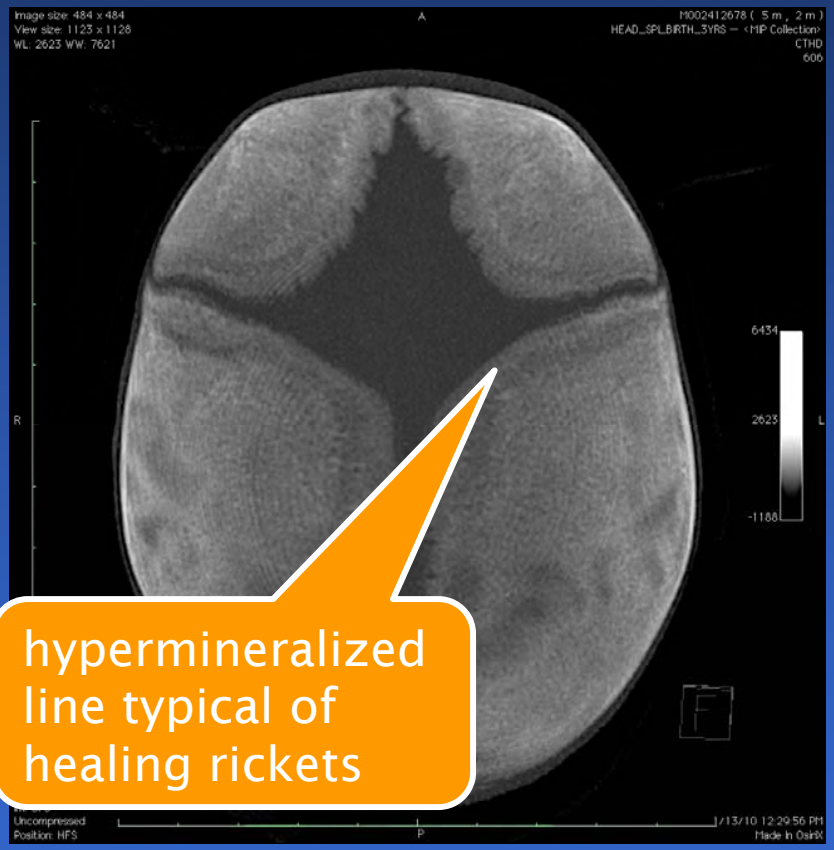
Battered child
or
unrecognized rickets?

UNDIAGNOSED METABOLIC BONE DISEASE

slide courtesy of Dr David Ayoub

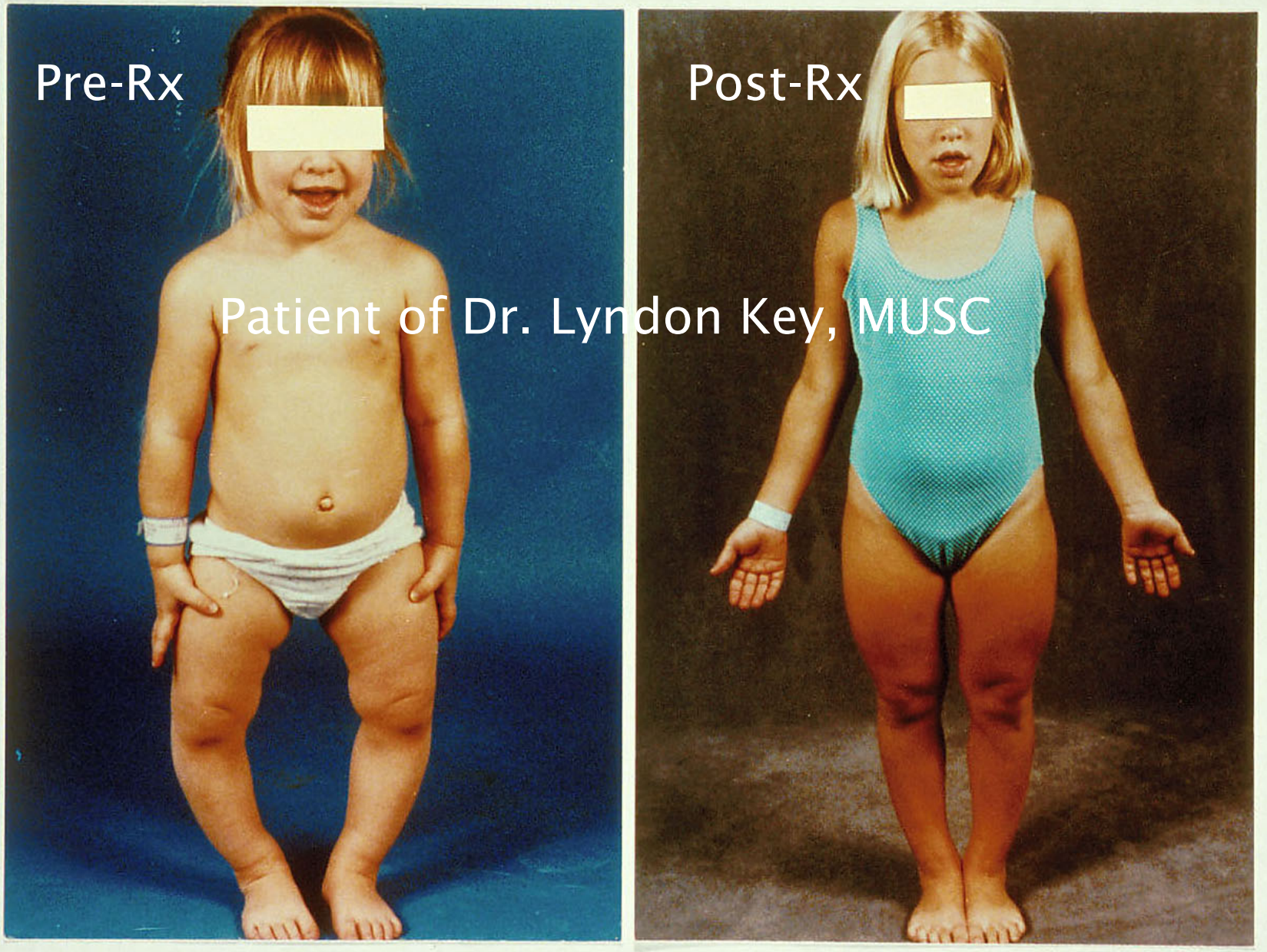
UNDIAGNOSED METABOLIC BONE DISEASE





slide courtesy of Dr David Ayoub

Cases of apparent child abuse, particularly with little or no evidence of soft tissue injury, must be evaluated for metabolic bone disease before diagnosing abuse !

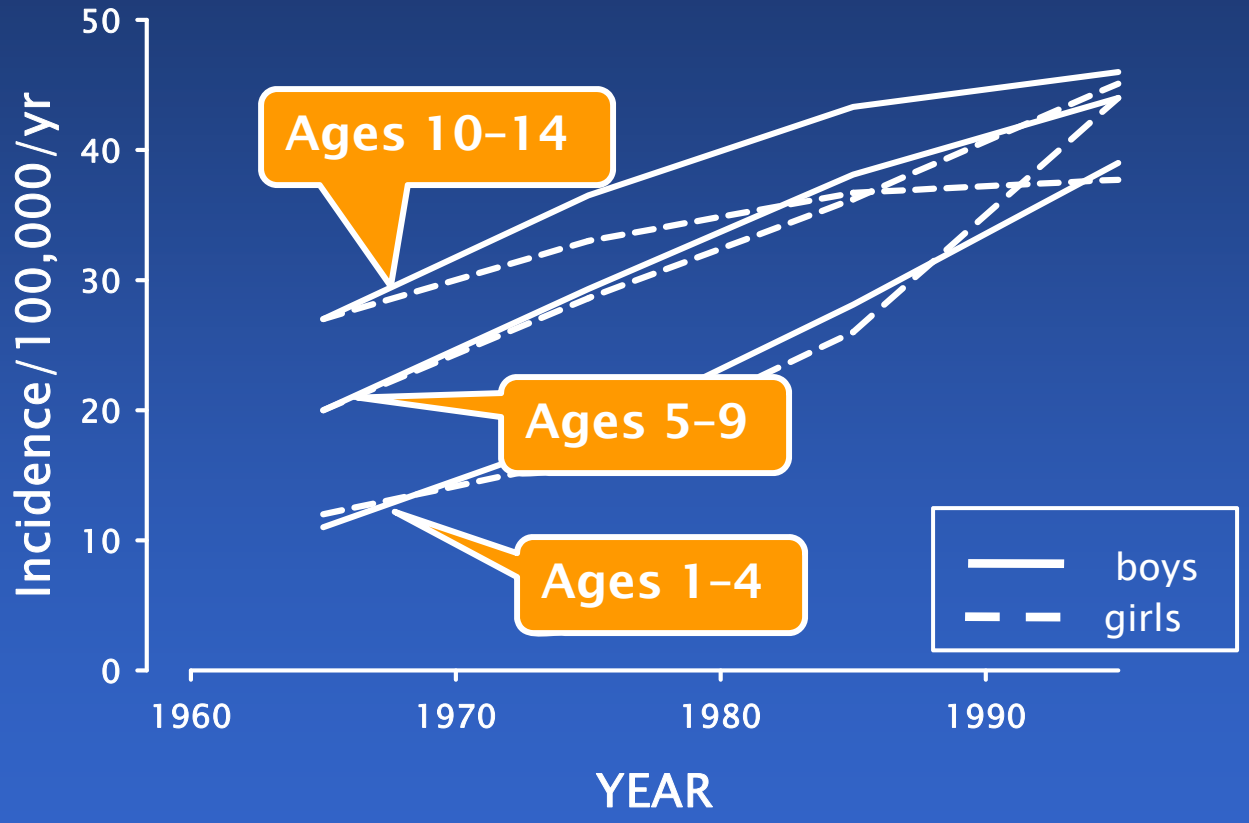

Pre-Rx
Post-Rx
Patient of Dr. Lyndon Key, MUSC

Her rickets have healed

but –

does she have subtle long-term consequences of early life vitamin D deficiency?

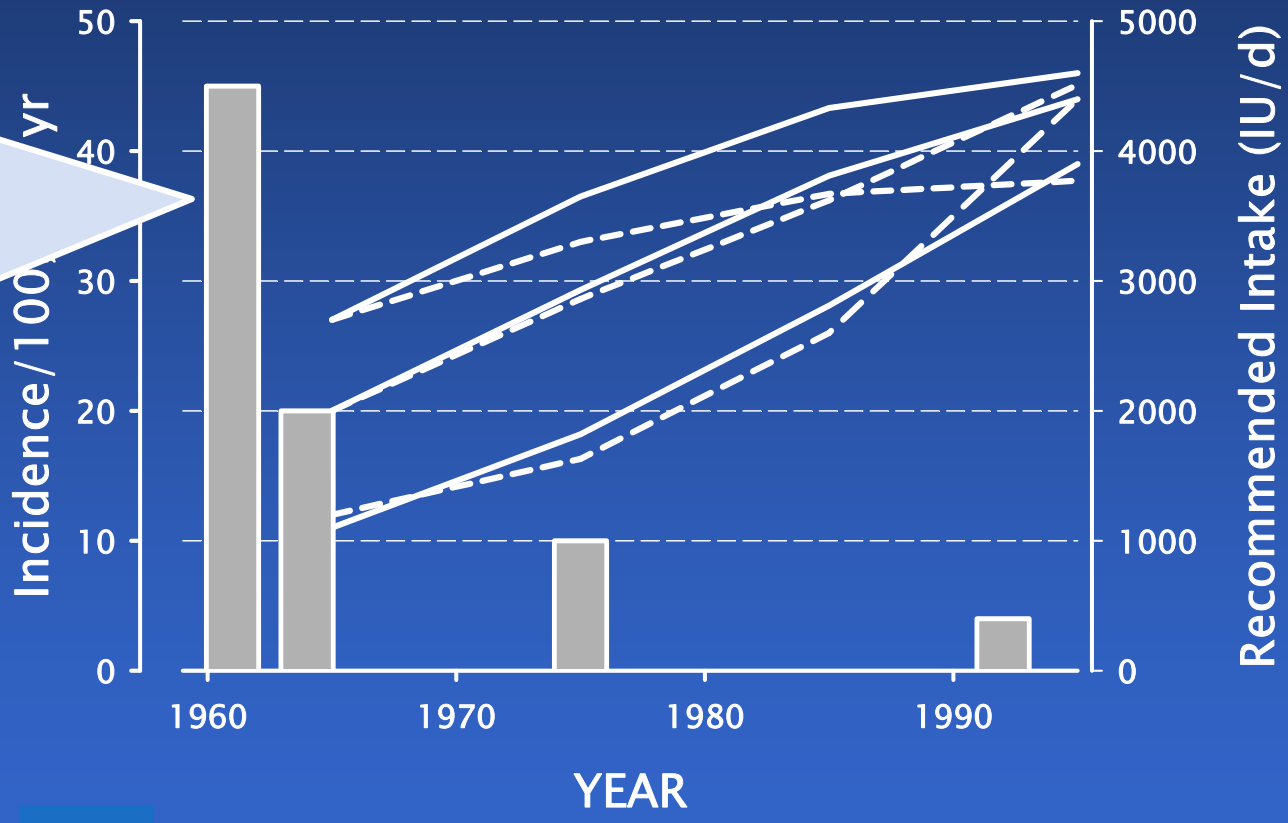
JUVENILE DIABETES IN FINLAND*



*Karvonen et al., (1999) Diabetes Care 22:1066–70

JUVENILE DIABETES IN FINLAND*

This dosage reflects the then common practice in E. Europe of giving 600,000 IU 3x per year during infancy



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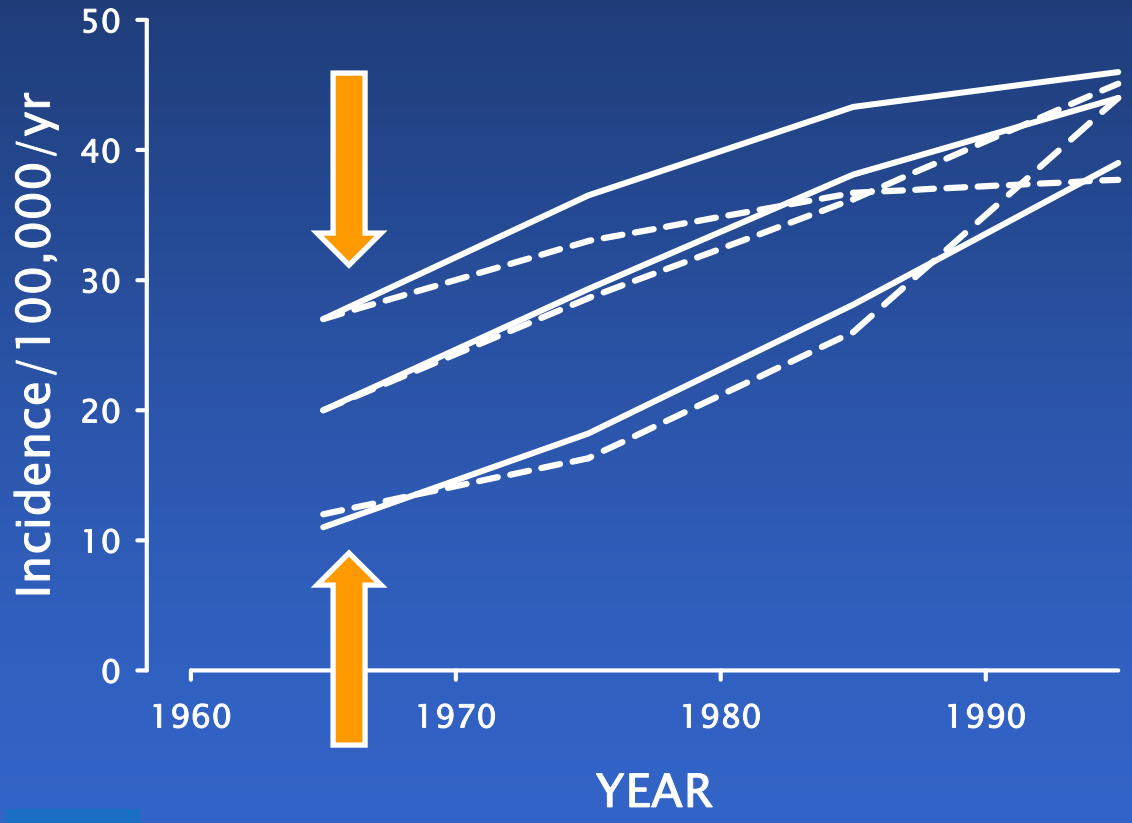

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NEONATAL VIT D & DIABETES*

- 10,366 northern Finnish children
- 2000 IU Vit D/d 1st year of life
- prevalence of type I diabetes assessed at age 31
- RR calculated vs. no supplementation

- those who got the recommended amount regularly
- those who got it sometimes
- those who got it never
- those who got little or no vit D at all & were thought to have rickets

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

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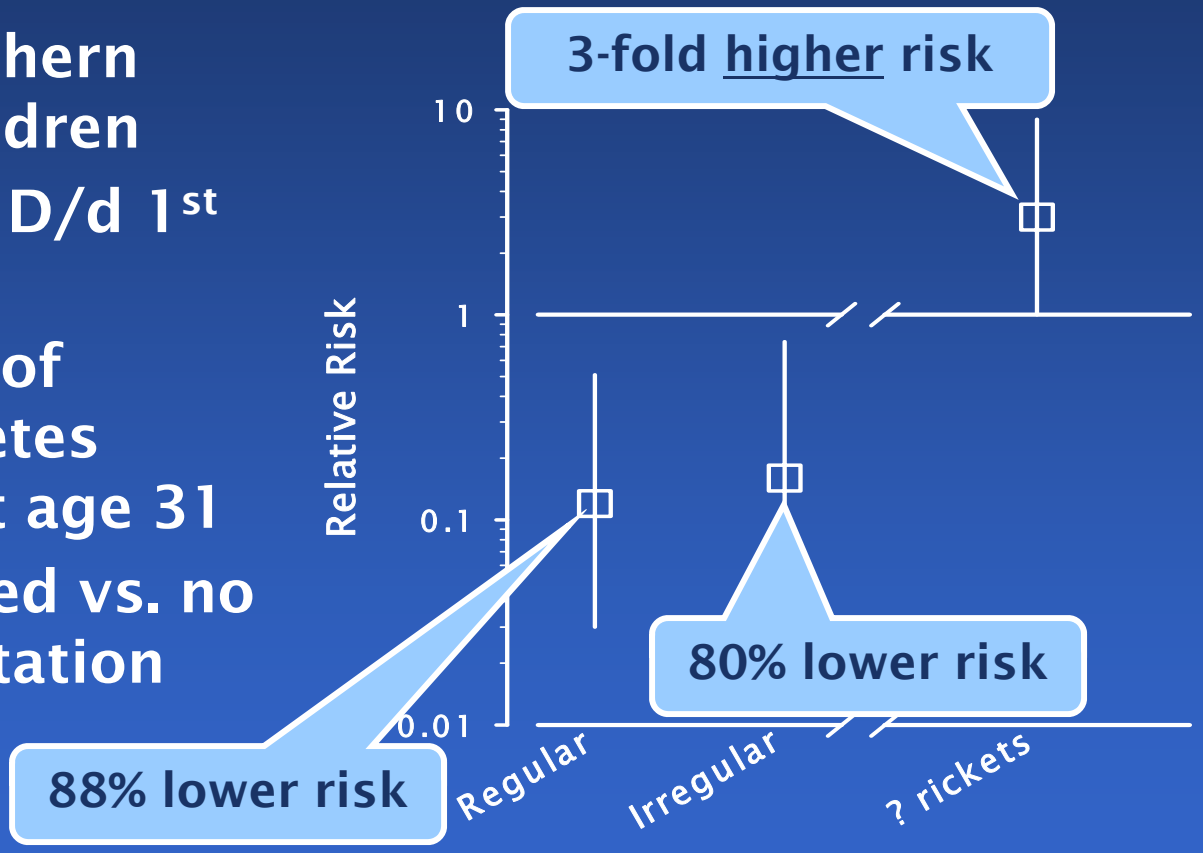

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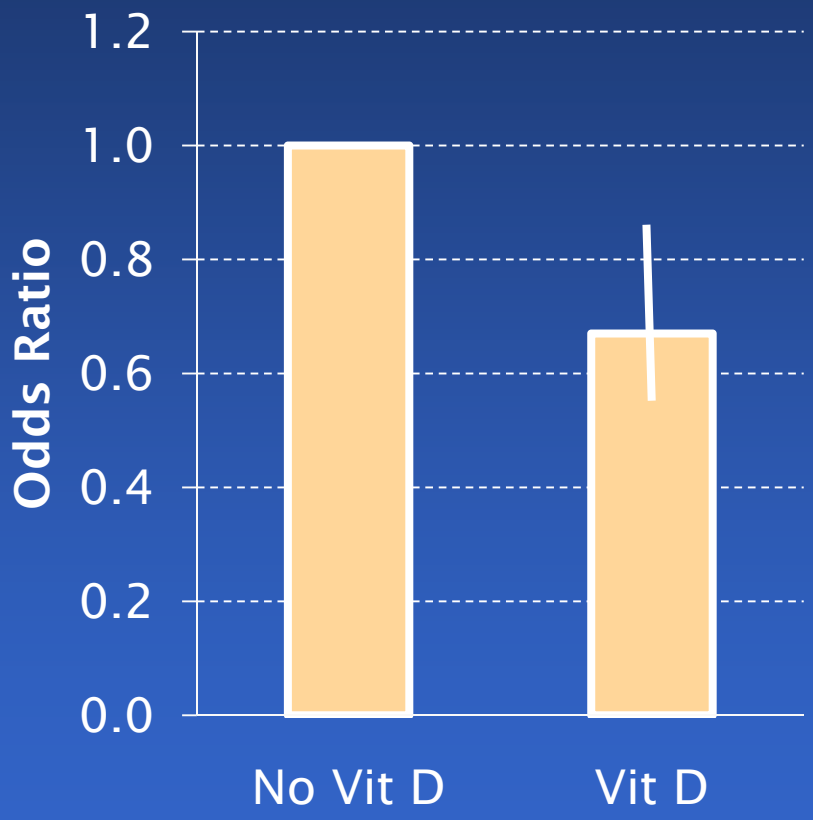
NEONATAL VIT D & DIABETES*

- EURODIAB Study
- 7 European cntrs
- case control 820 cases (~80 % eligible population)
- supplemental Vit D in infancy
- type 1 diabetes < age 15



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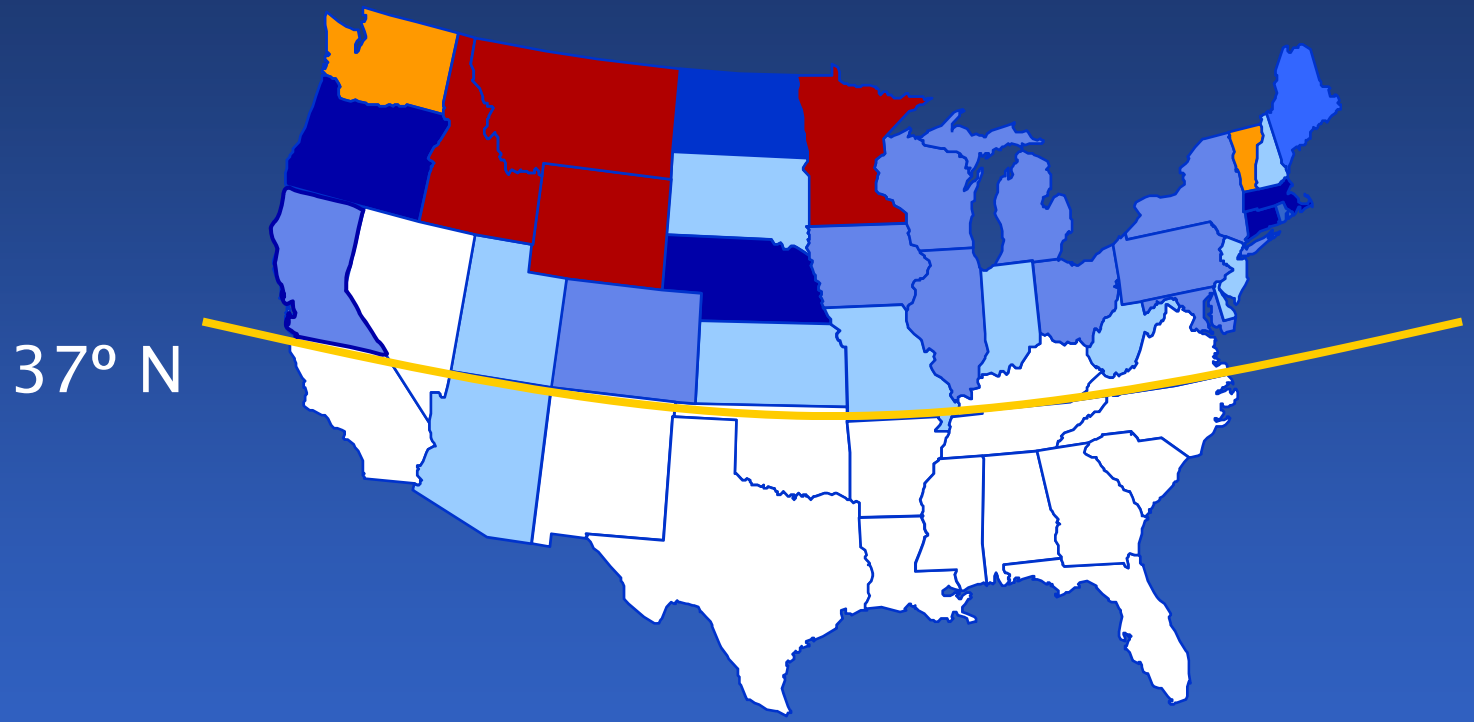
*Diabetologia 1999; 42:51-54

MS INCIDENCE MAP*



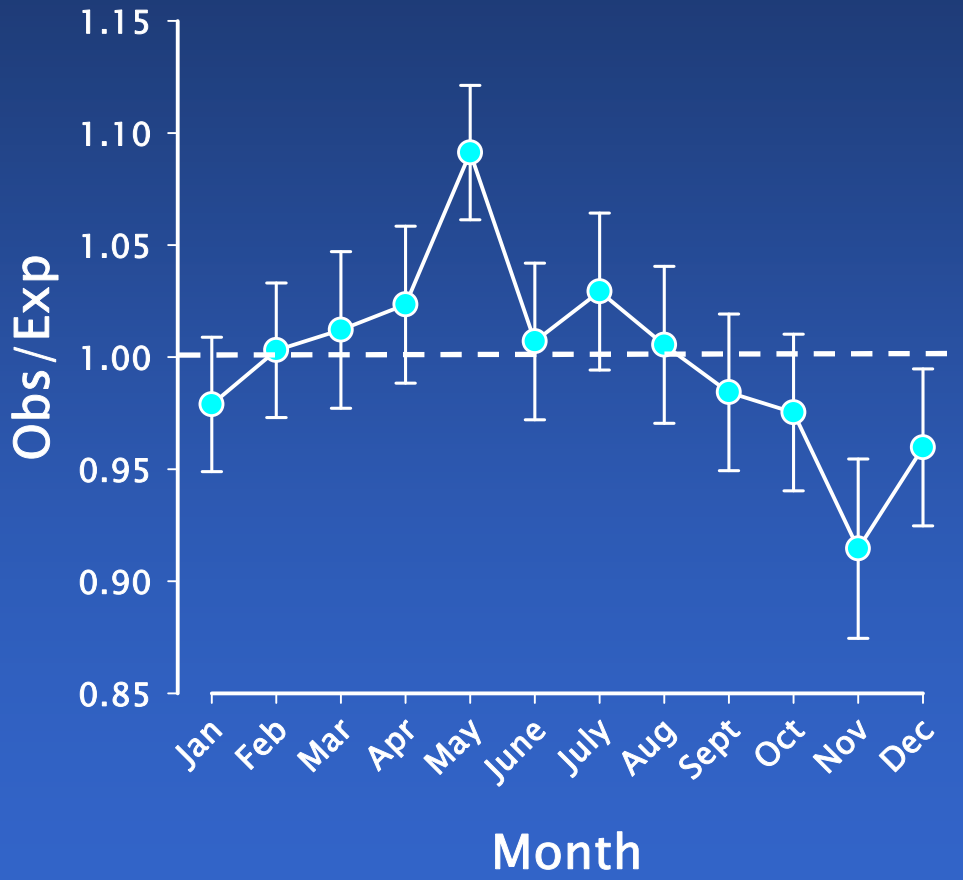
Percent national average incidence:

40–70%	70–100%	100–130%	130–160%	160–190%	190–220%

*modified from: http://mscenter.ucsf.edu/

MS RISK & BIRTH MONTH*

- 44,045 pts with MS
- populations of Canada, UK, Denmark,& Sweden
- observed cases divided by expected, by birth month



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*Willer et al., (2004) BMJ

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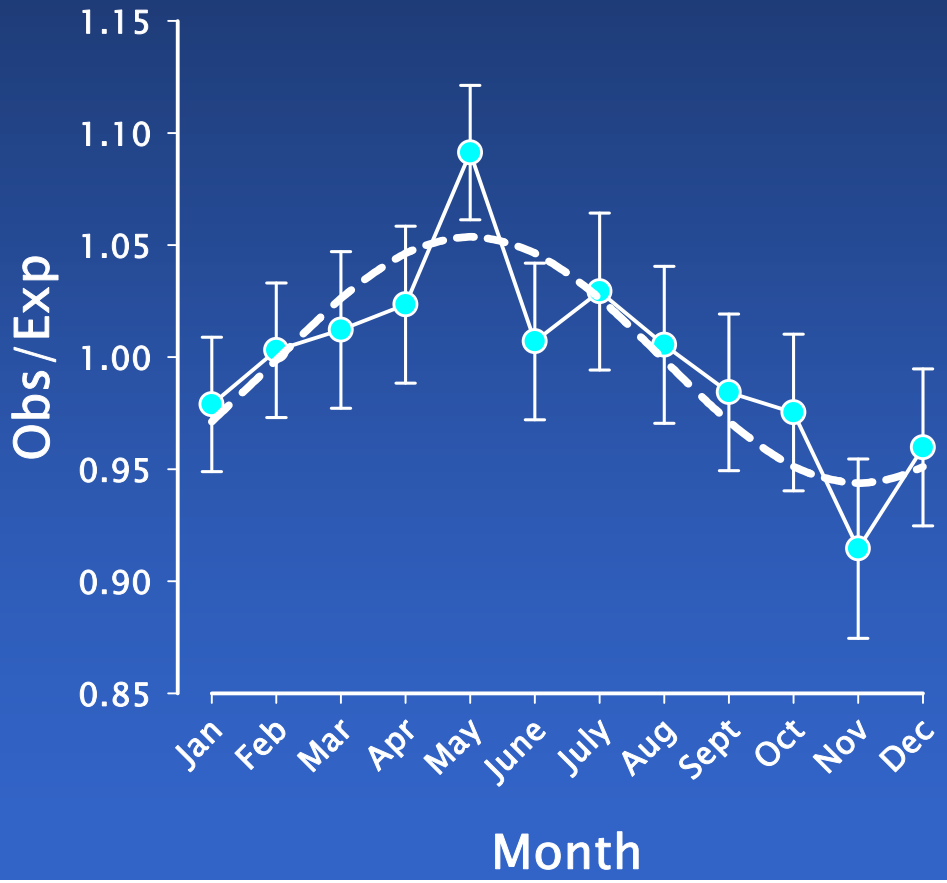
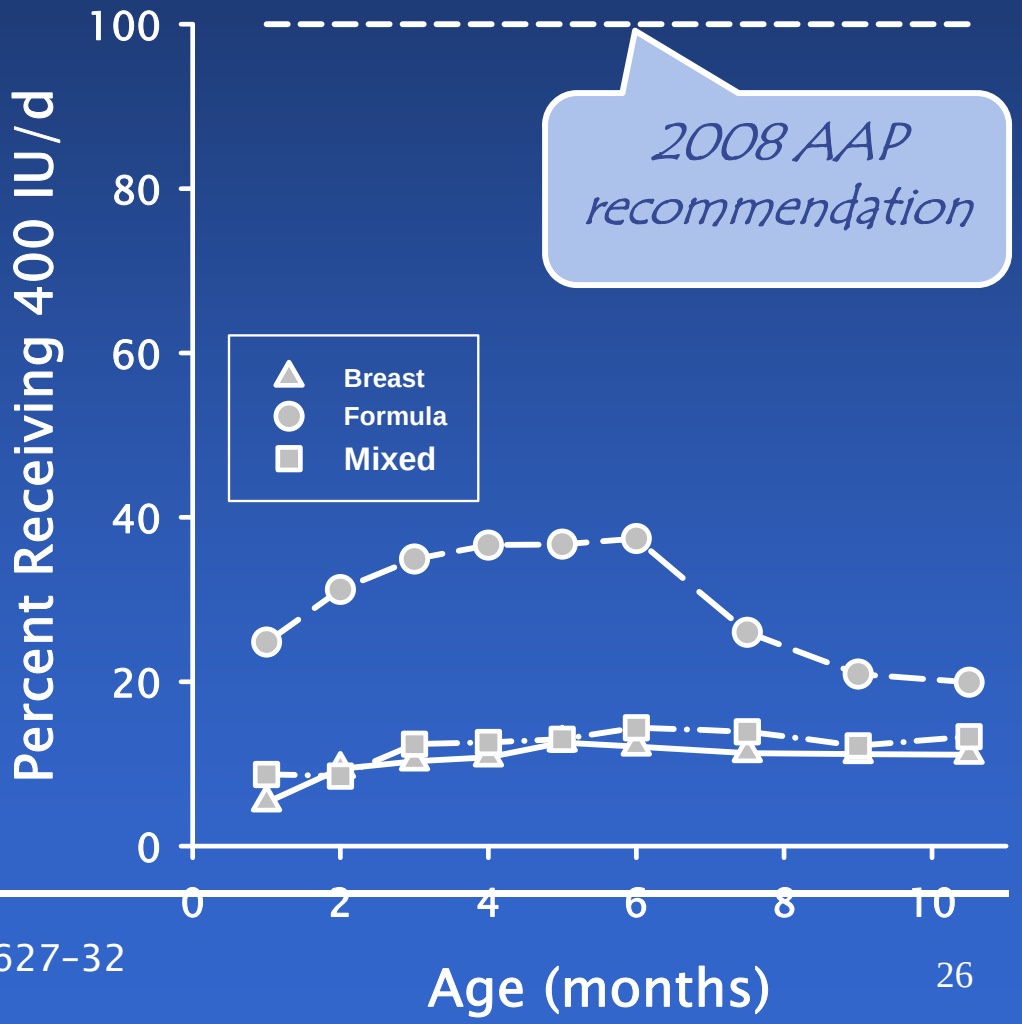


CU ORC

*Willer et al., (2004) BMJ

INFANT VITAMIN D INTAKE*

- *Infant Feeding Practices Study*
- > 33,000 infants
- 2005–2007
- Sources (1 mo):
  - breast – 43%
  - formula – 26%
  - mixed – 32%



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* Perrine et al. 2010, *Pediatrics* 125:627–32

These perinatal and early life associations are probably epigenetic in character and are believed to involve the programming of the immune system to distinguish self and non-self – a process in which vitamin D plays an essential role

VIT D & PREGNANCY OUTCOMES*

- DB-RCT; N = 690 pregnant women
- dosed with 400, 2000, & 4000 IU/d from wk 12 to delivery

*Hollis & Wagner (2009) in press

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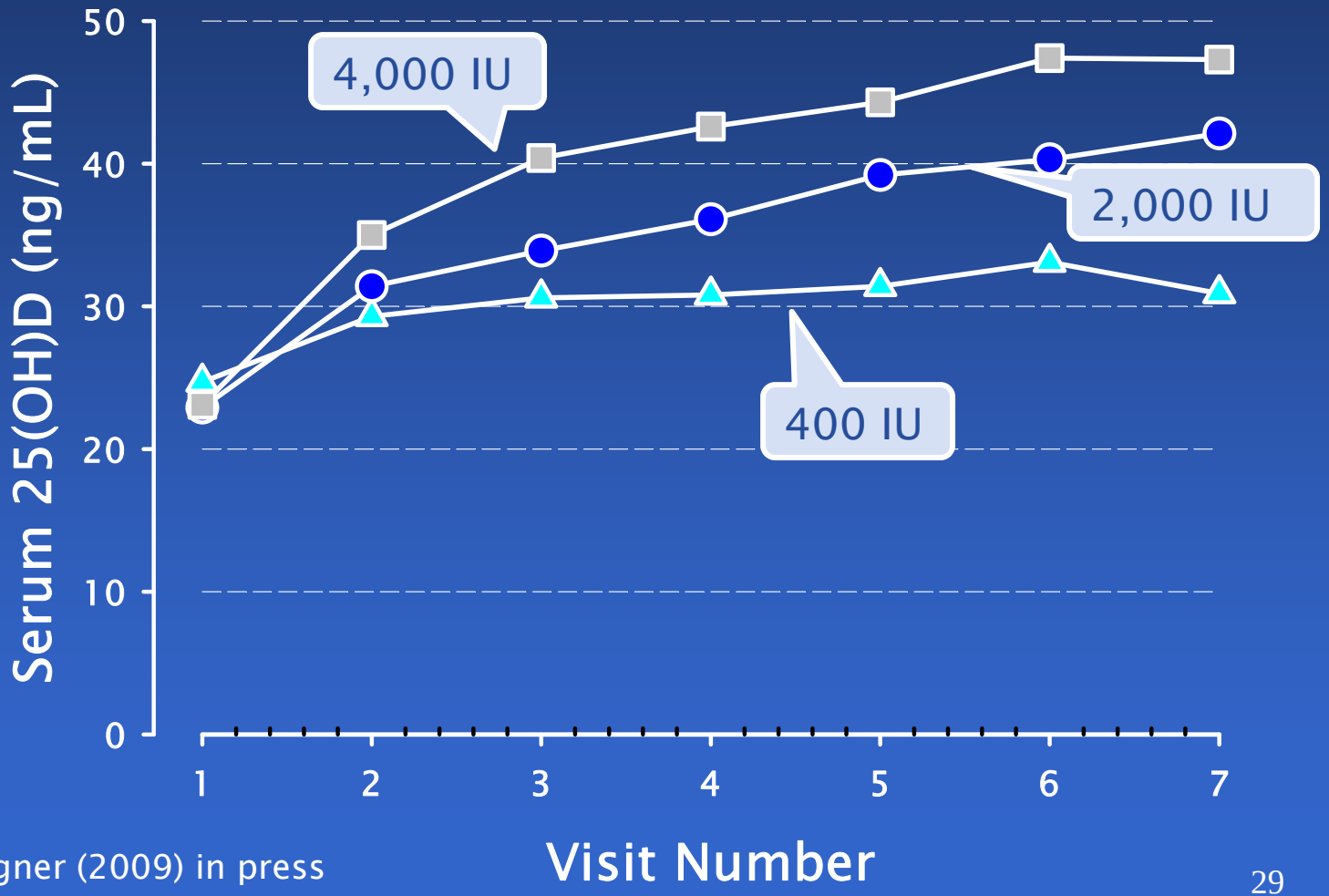

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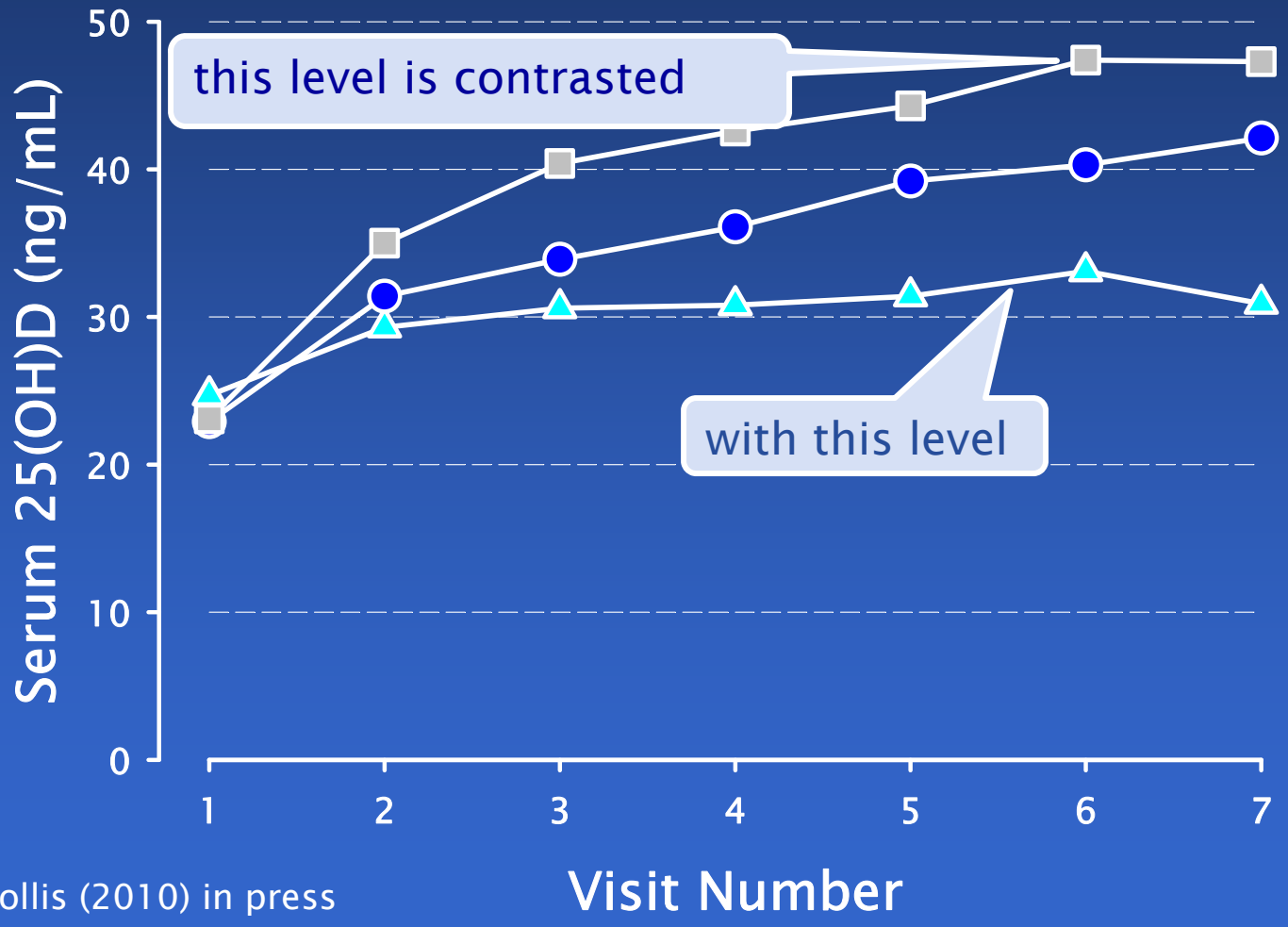


*Wagner & Hollis (2010) in press

VIT D & PREGNANCY OUTCOMES*

- DB-RCT; N = 690 pregnant women
- dosed with 400, 2000, & 4000 IU/d from wk 12 to delivery
- risk of untoward outcomes reduced by half:
  - pre-term delivery ($P < 0.01$)
  - gestational diabetes, pre-eclampsia, hypertension ($P < 0.01$)
  - periodontal disease ($P < 0.05$)
  - neonatal infection ($P < 0.05$)

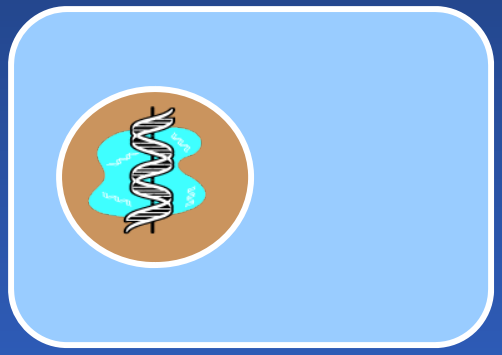
*Wagner & Hollis (2010) in press

Other

[Mechanisms]

CELL MODELS

old:



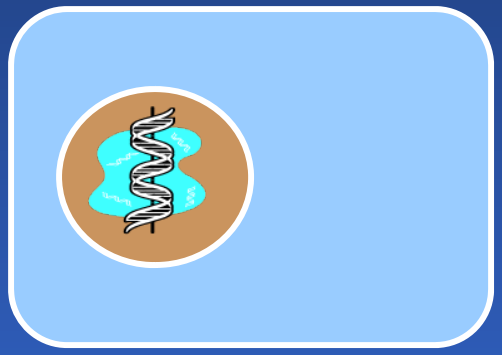
DNA in somatic cells functions mainly to make faithful copies for tissue repair or replacement

new:

DNA functions constantly in synthesis of needed cellular apparatus

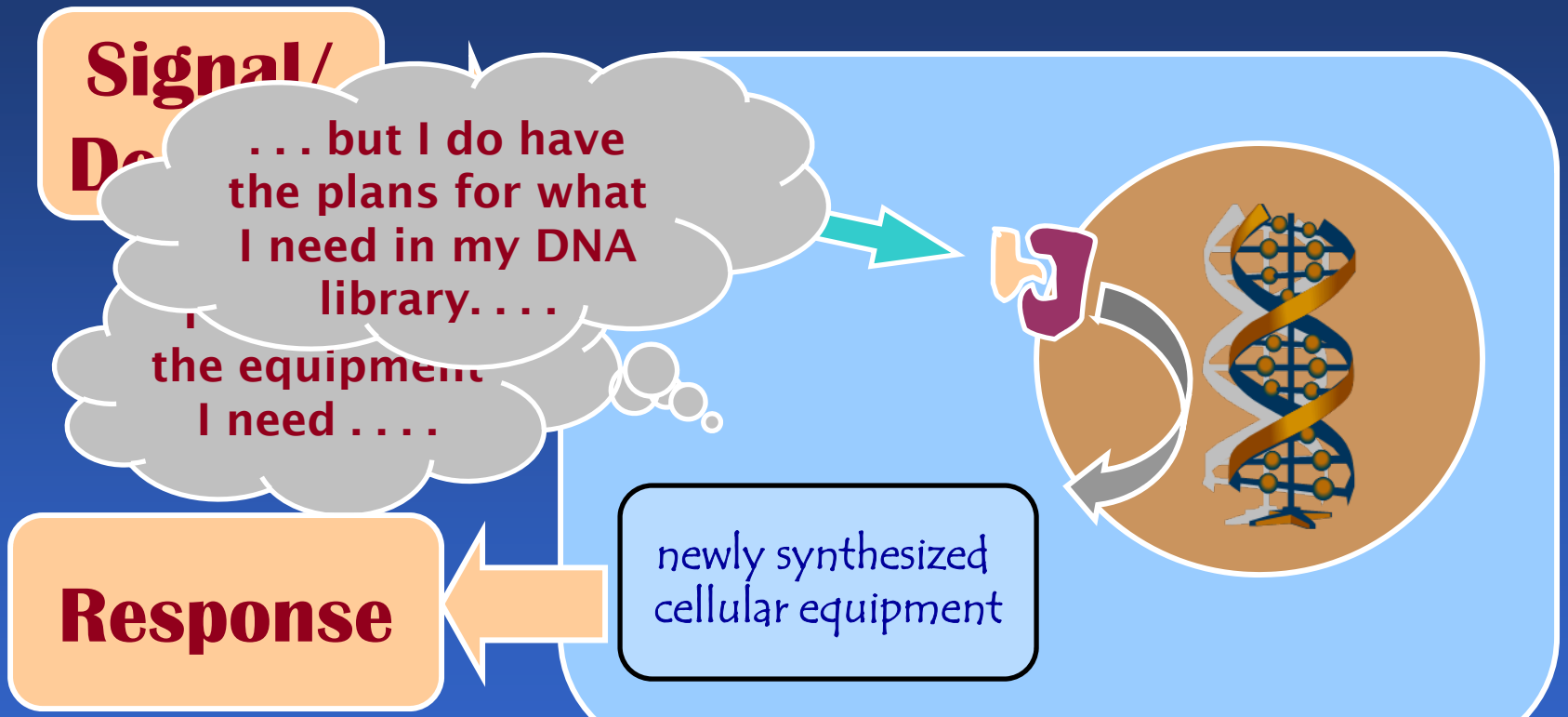
CELL MODELS

old: cell/tissue differentiation meant that each cell type contained different cytoplasmic apparatus



new: cell/tissue differentiation meant that only certain genes can be accessed in each tissue

HOW A CELL RESPONDS



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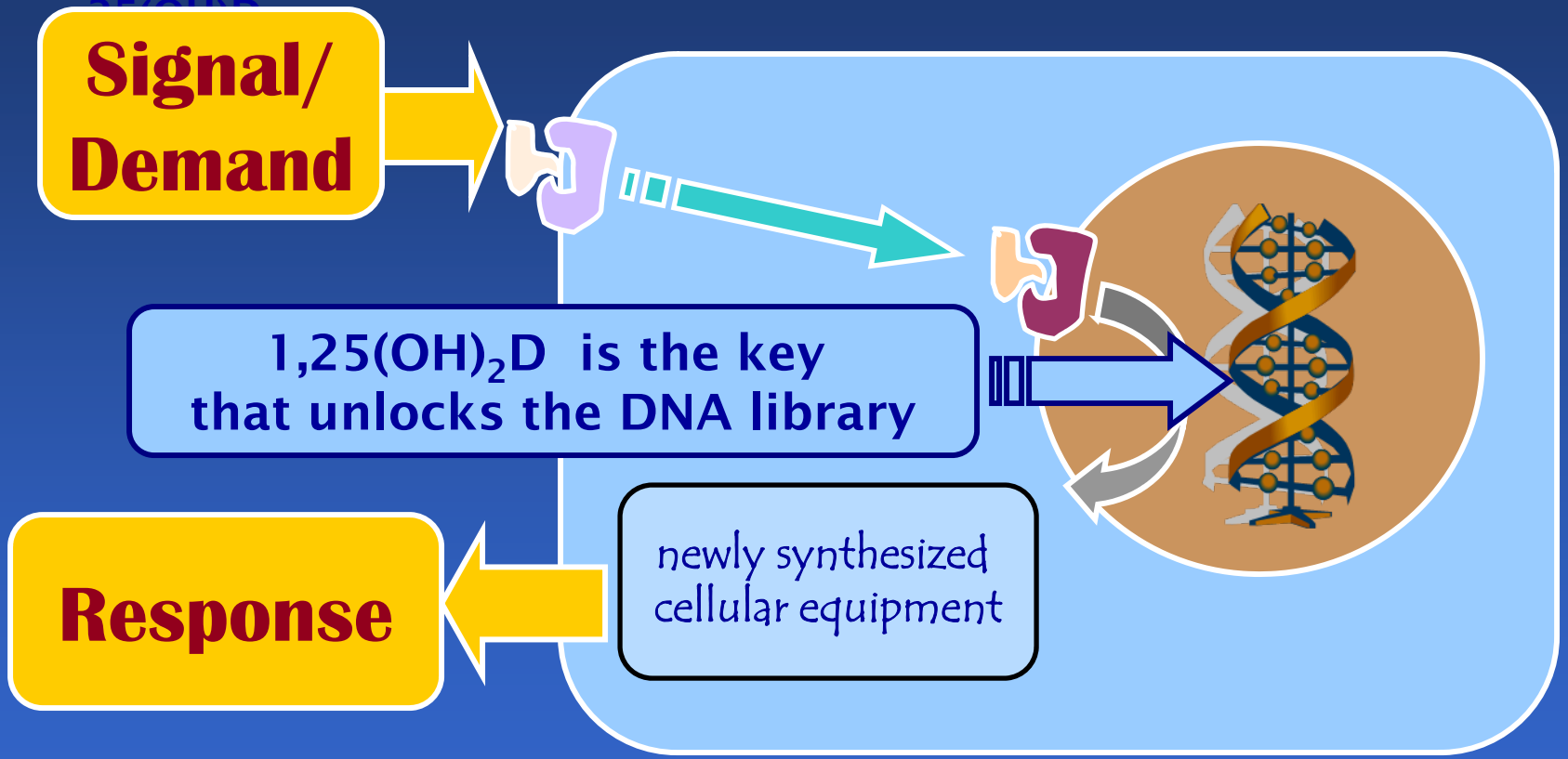

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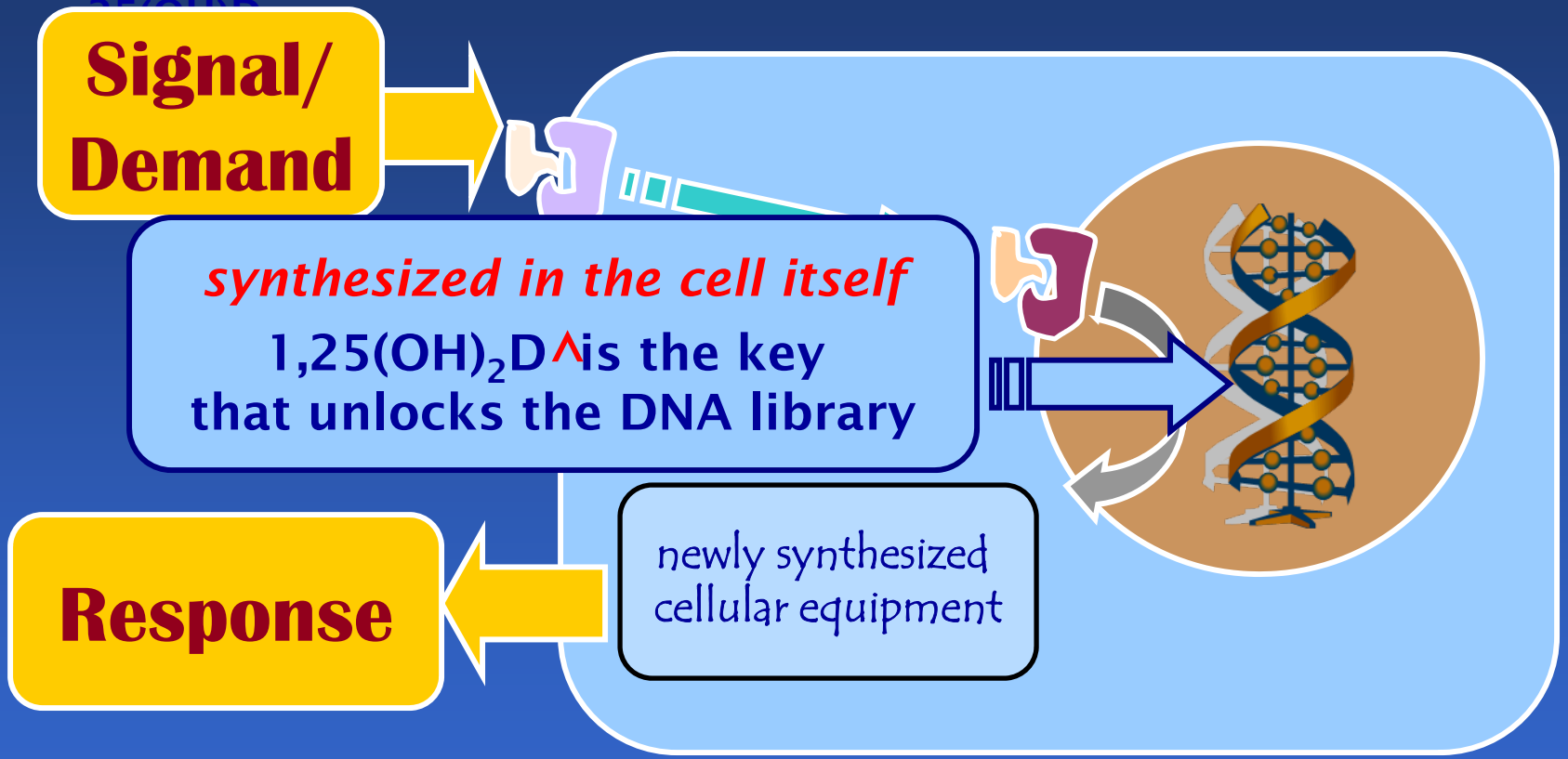

VITAMIN D & INNATE IMMUNITY*

activated Toll-like receptor

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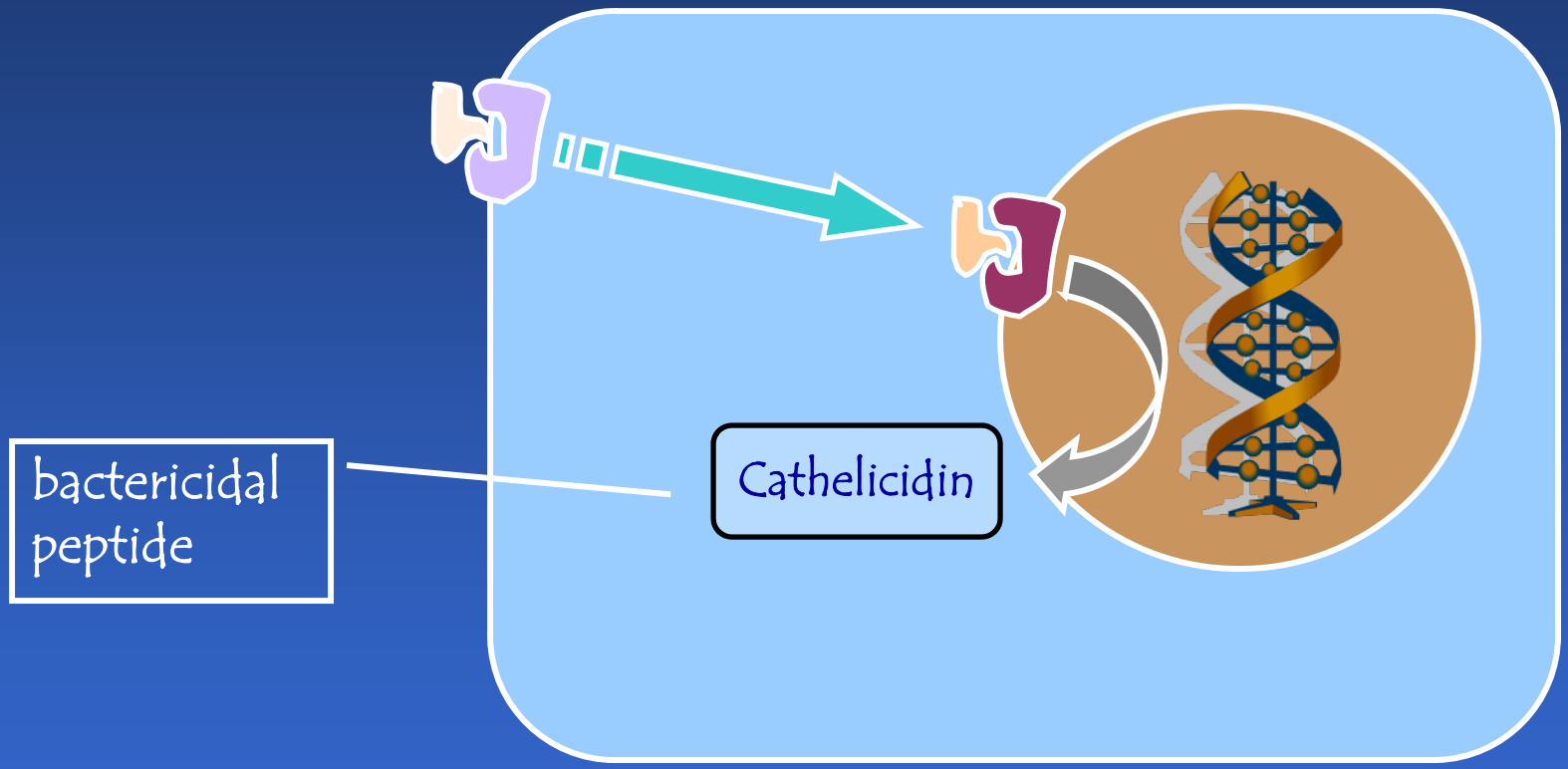
*Liu et al., Science 2006

VITAMIN D & INNATE IMMUNITY*

25(OH)D



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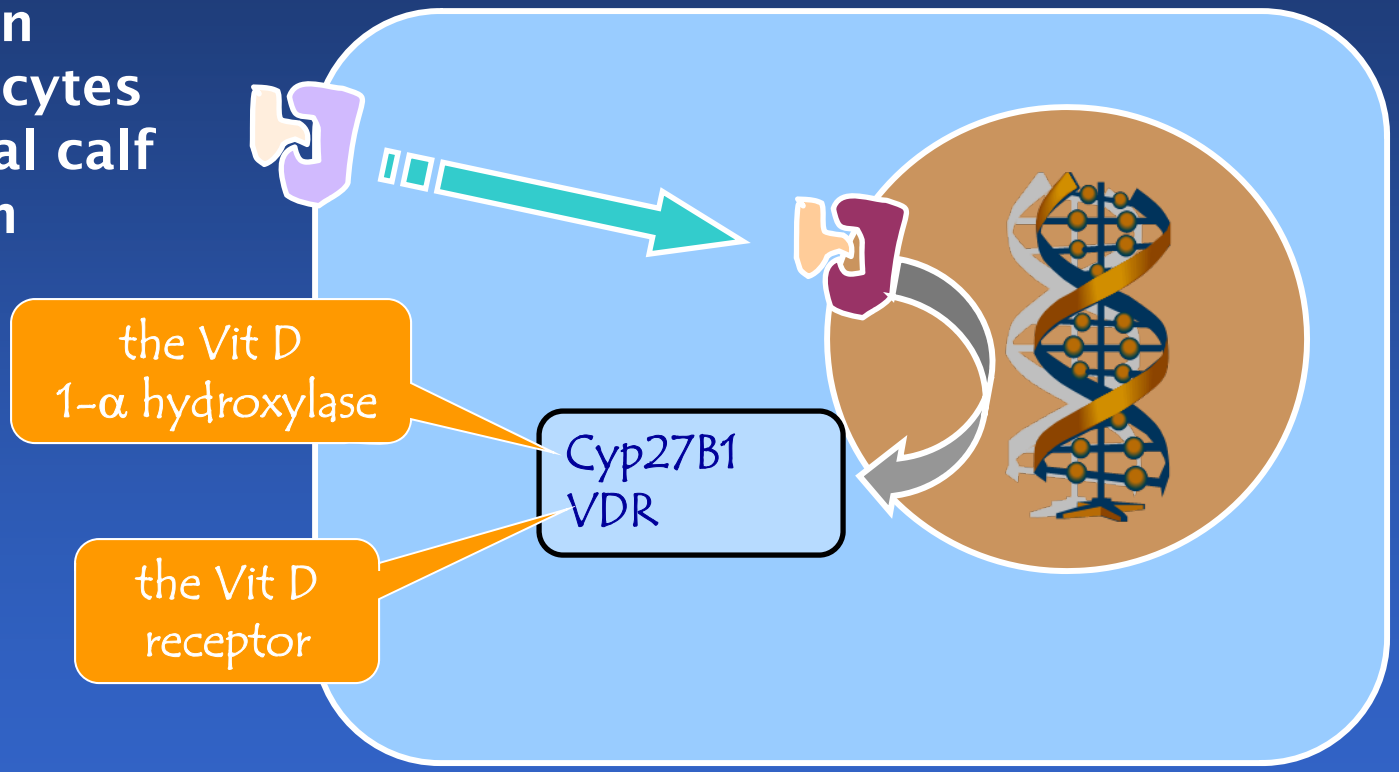
*Liu et al., Science 2006

VITAMIN D & INNATE IMMUNITY*

25(OH)D

- human monocytes in fetal calf serum



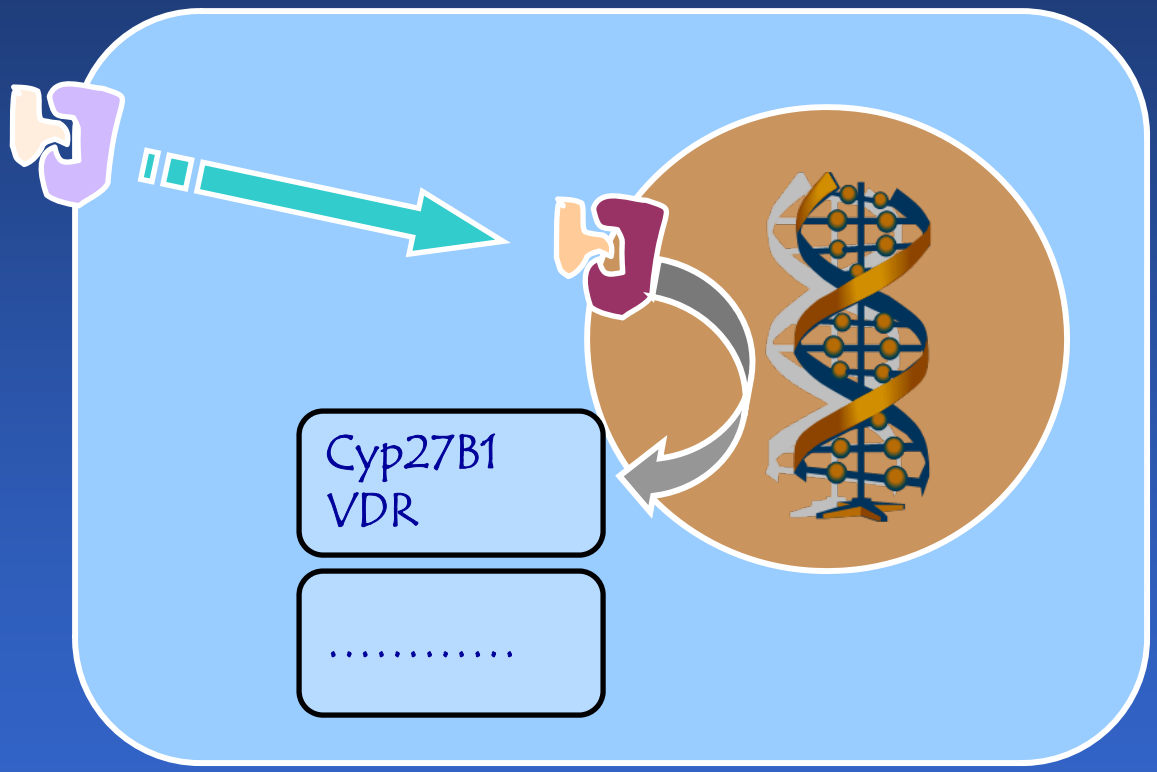
CU ORC

*Liu et al., Science 2006

VITAMIN D & INNATE IMMUNITY*

25(OH)D

- human monocytes in fetal calf serum
- fetal calf serum is low in both 25(OH)D & $1,25(OH)_2D$



CU ORC

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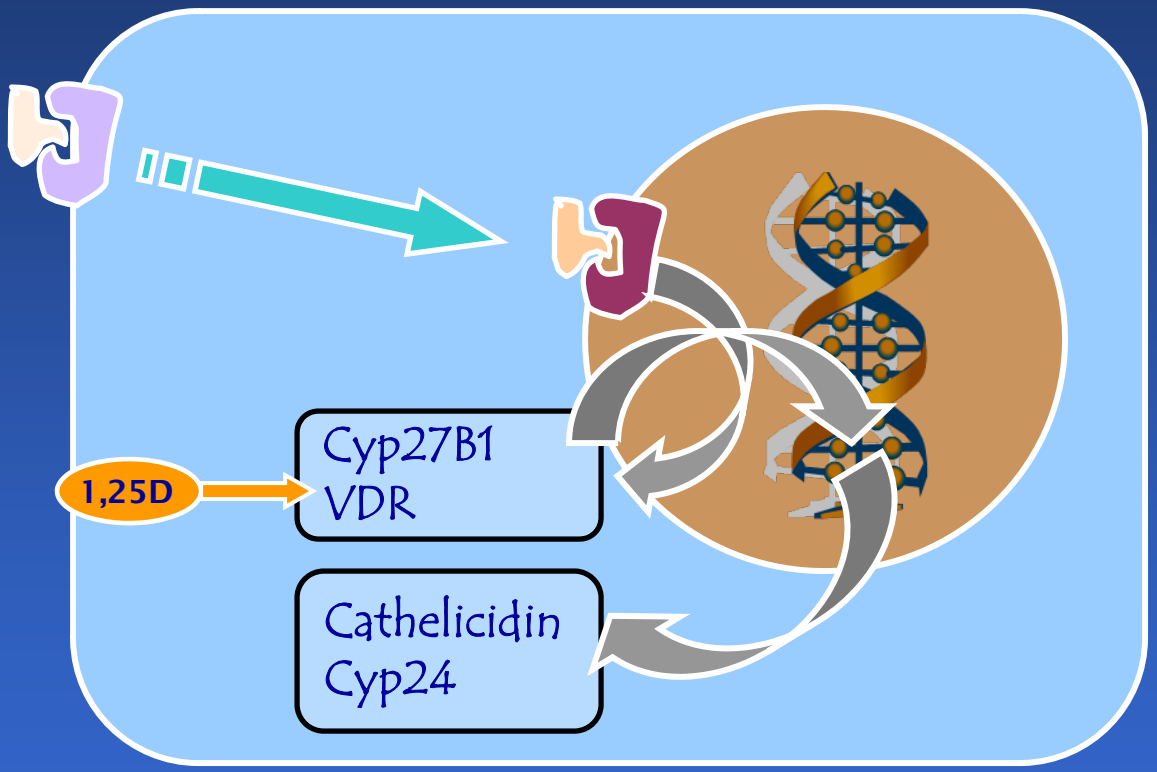
VITAMIN D & INNATE IMMUNITY*

25(OH)D

- human monocytes in fetal calf serum
- add $1,25(OH)_2D$ to the system



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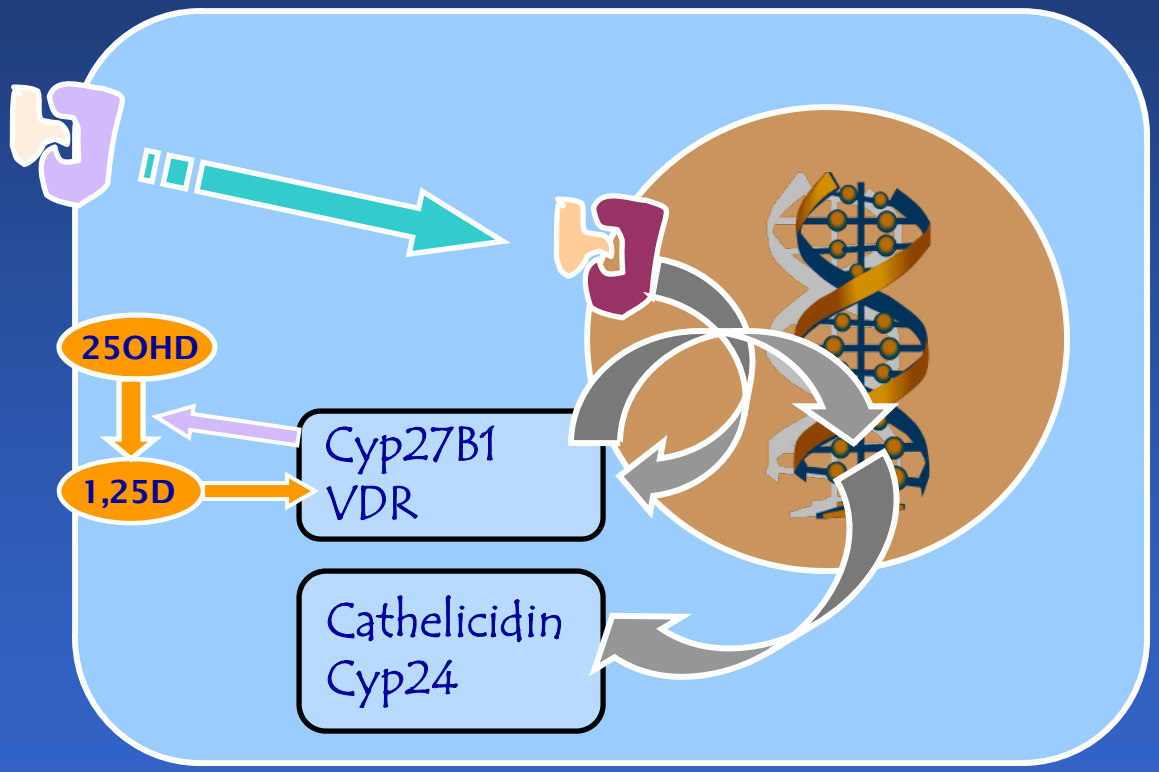
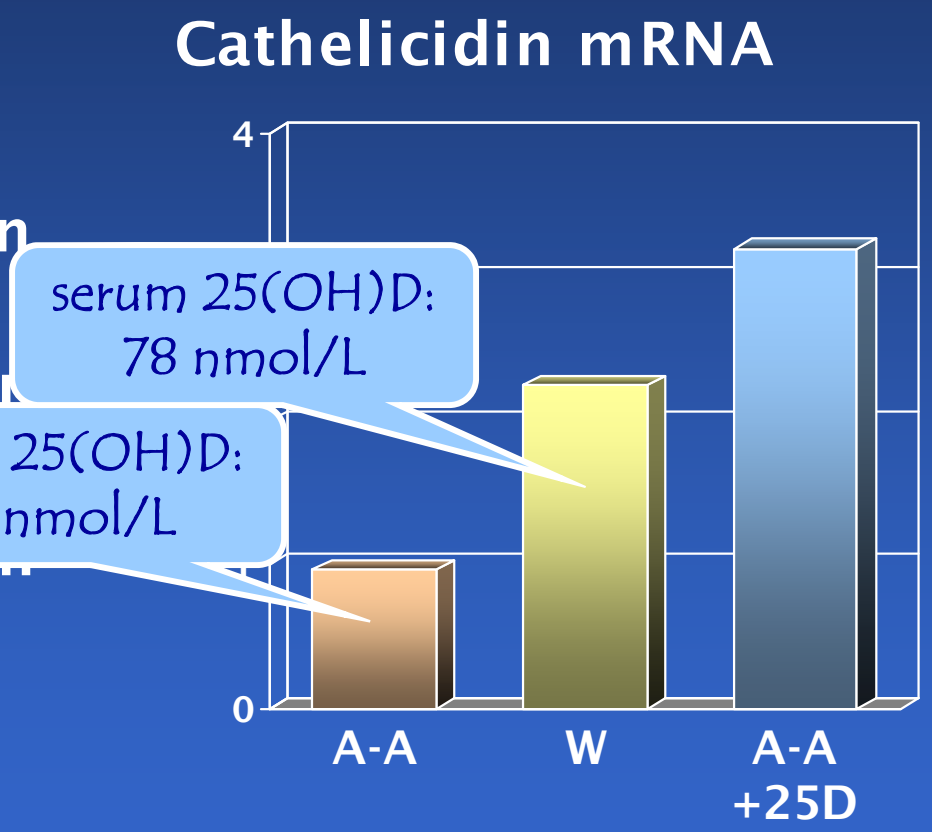


CU ORC

*Liu et al., Science 2006

VITAMIN D & TUBERCULOSIS

- human monocytes activated with *M. Tuberculosis* and incubated in human serum
  - African-American
  - White
  - African-American with added 25(OH)D



CU ORC

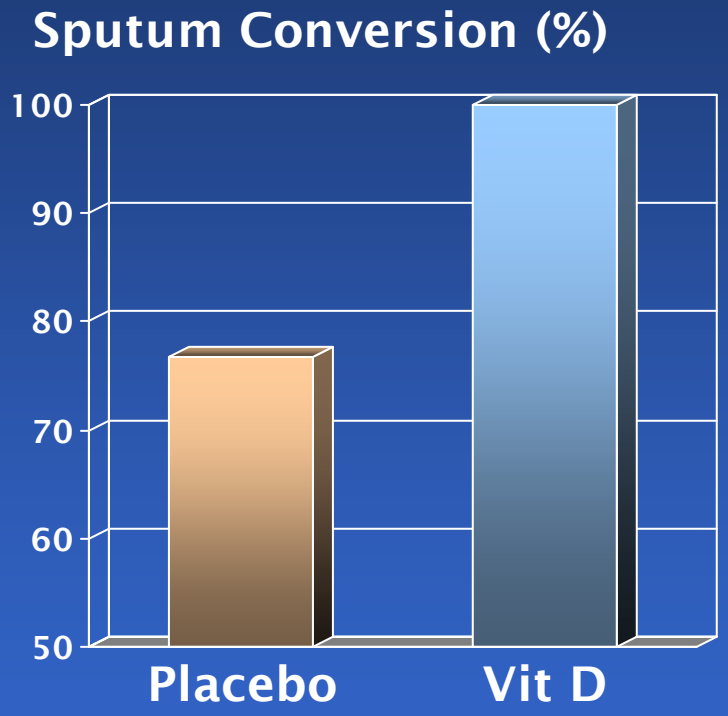
*Liu et al., Science 2006

This scheme means that each tissue

- has the amount of $1,25(OH)_2D$ it needs
- when it needs it
- and is not dependent upon a "one-size-fits all" systemic level of circulating $1,25(OH)_2D$
- every time DNA is expressed, vitamin D is consumed

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



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*Nursyam et al., Acta Med Indones 2006

Vitamin D *enables* macrophage function

It does not cause it

INNATE IMMUNITY IN INFANTS

- infection resistance in infants heavily dependent upon innate immunity
- human monocytes cultured in cord blood plasma*
  - macrophage expression of cathelicidin mRNA directly related to cord blood 25(OH)D
  - low 25(OH)D samples rescued by added 25(OH)D

*Walker et al. JCEM (in press)

Measurement & Assessment

CHRONIC DISEASE PERSPECTIVE

- chronic disease is the breakdown of structure and/or function of a body system
- its origin is usually multifactorial
  - genes
  - environment
    - ✓ nutrition
    - ✓ infection
    - ✓ toxins
    - ✓ injury

low vitamin D status impairs this protective/ reparative activity

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

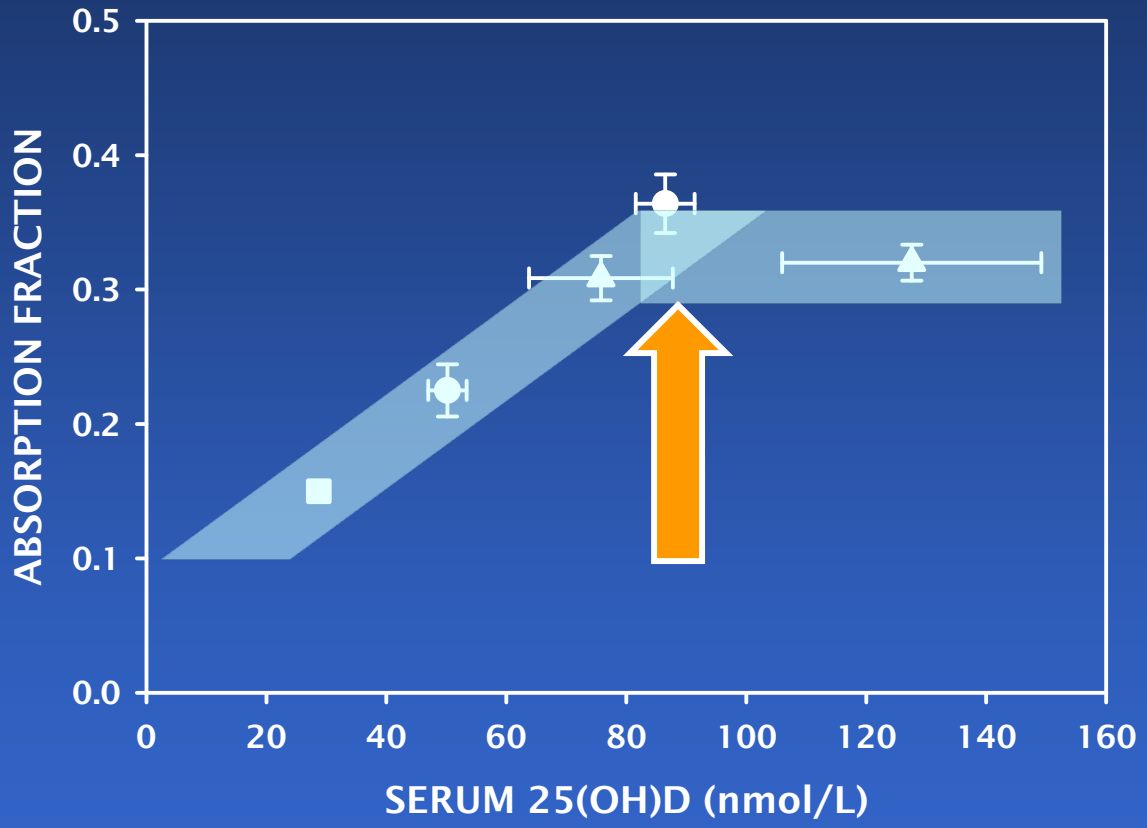
THE PREVENTIVE MAINTENANCE MODEL

- *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

VITAMIN D SHORTAGE

- when vitamin D is in short supply, the various tissues and cells of our bodies cannot make enough calcitriol to open up their DNA libraries adequately
- their functioning is thus impaired
- that, ultimately, is the basis for the multi-system manifestations of vit D deficiency

A VITAMIN D THRESHOLD



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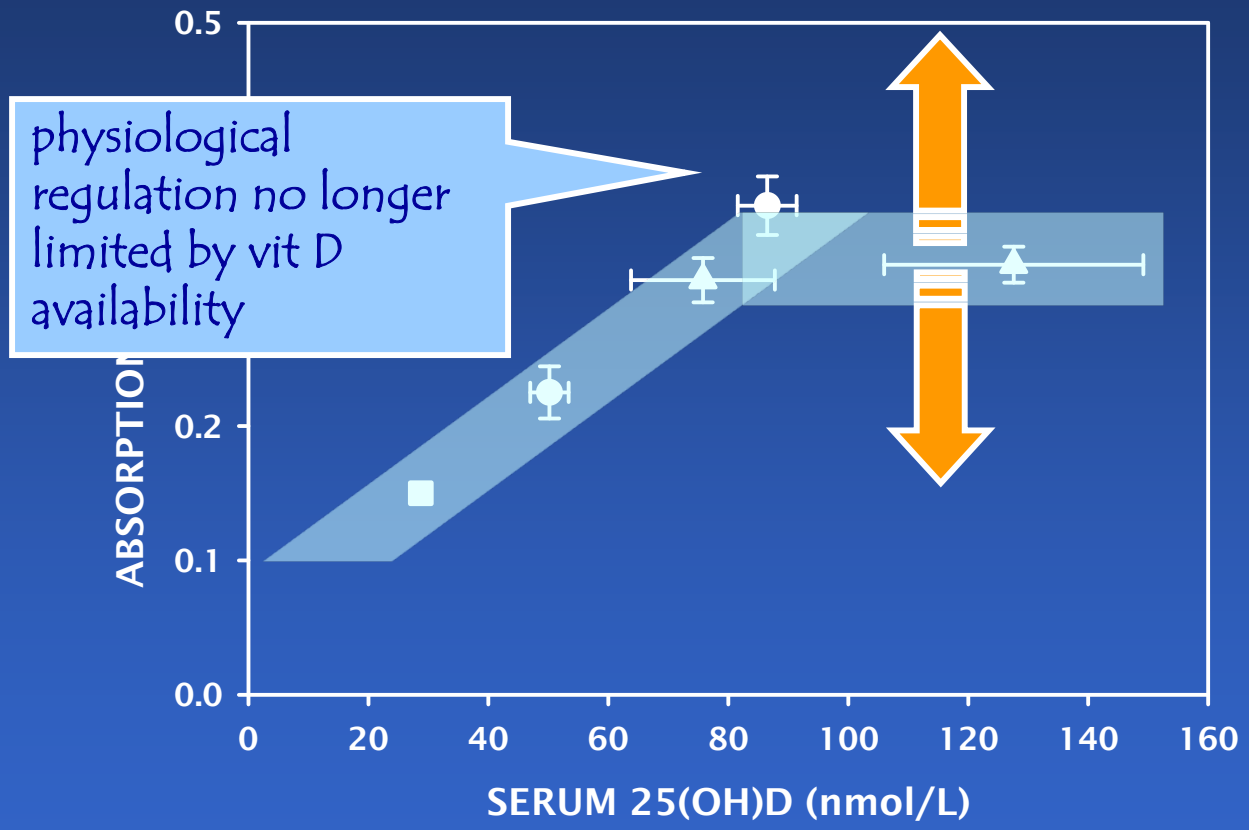

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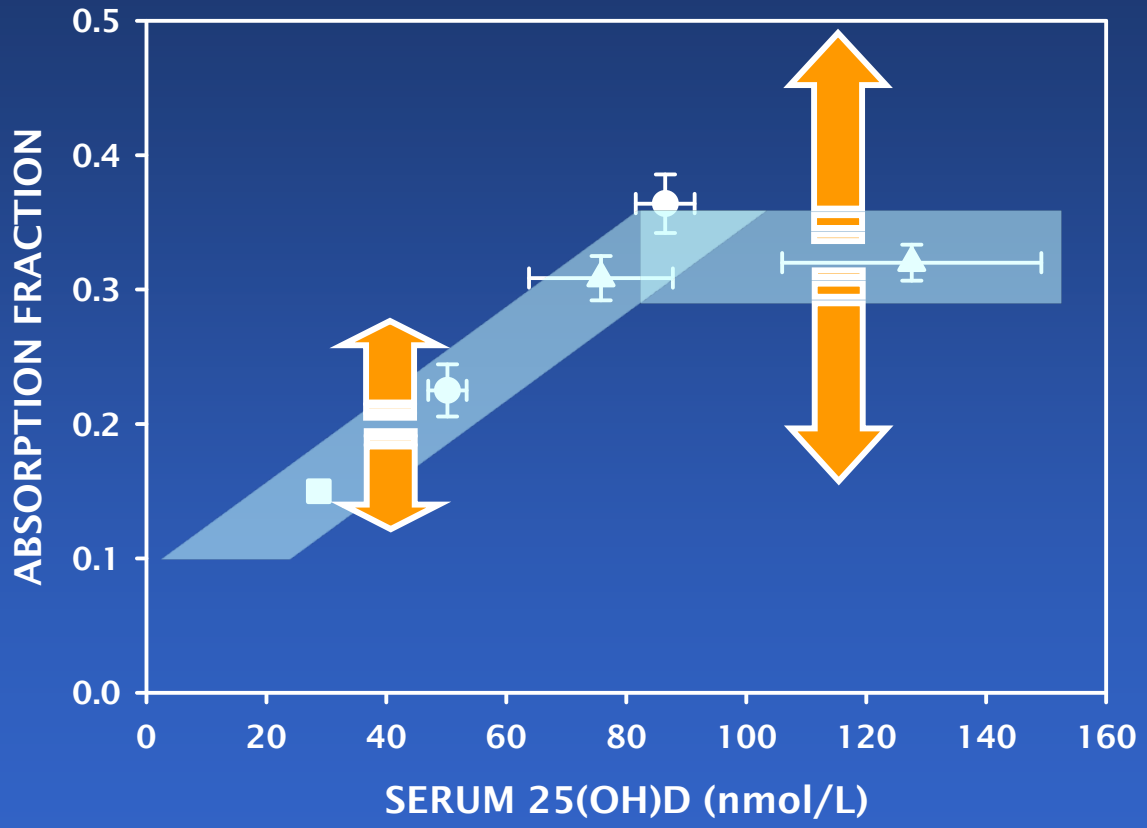

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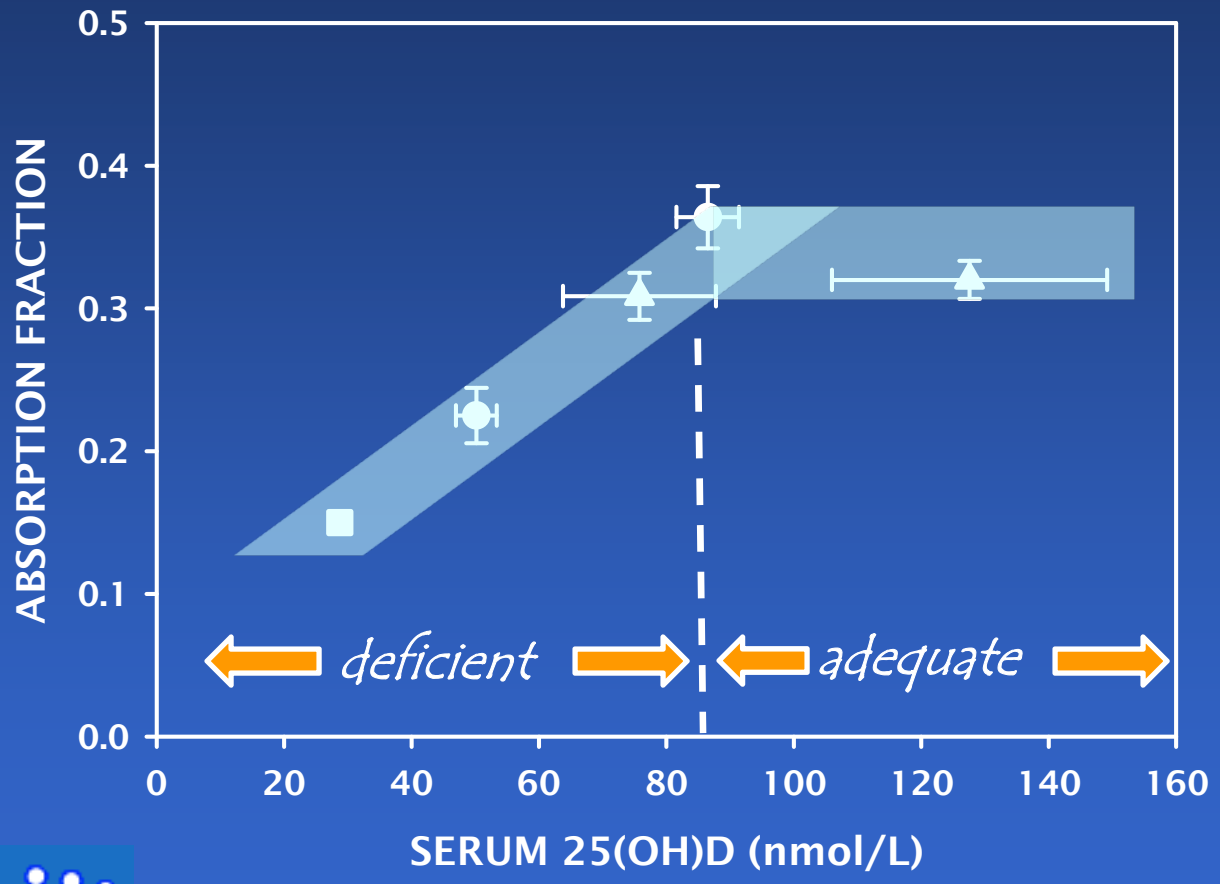

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Vitamin D *enables* Ca absorption

It does not cause it

In general vitamin D *enables* tissue response & recovery

It does not cause it

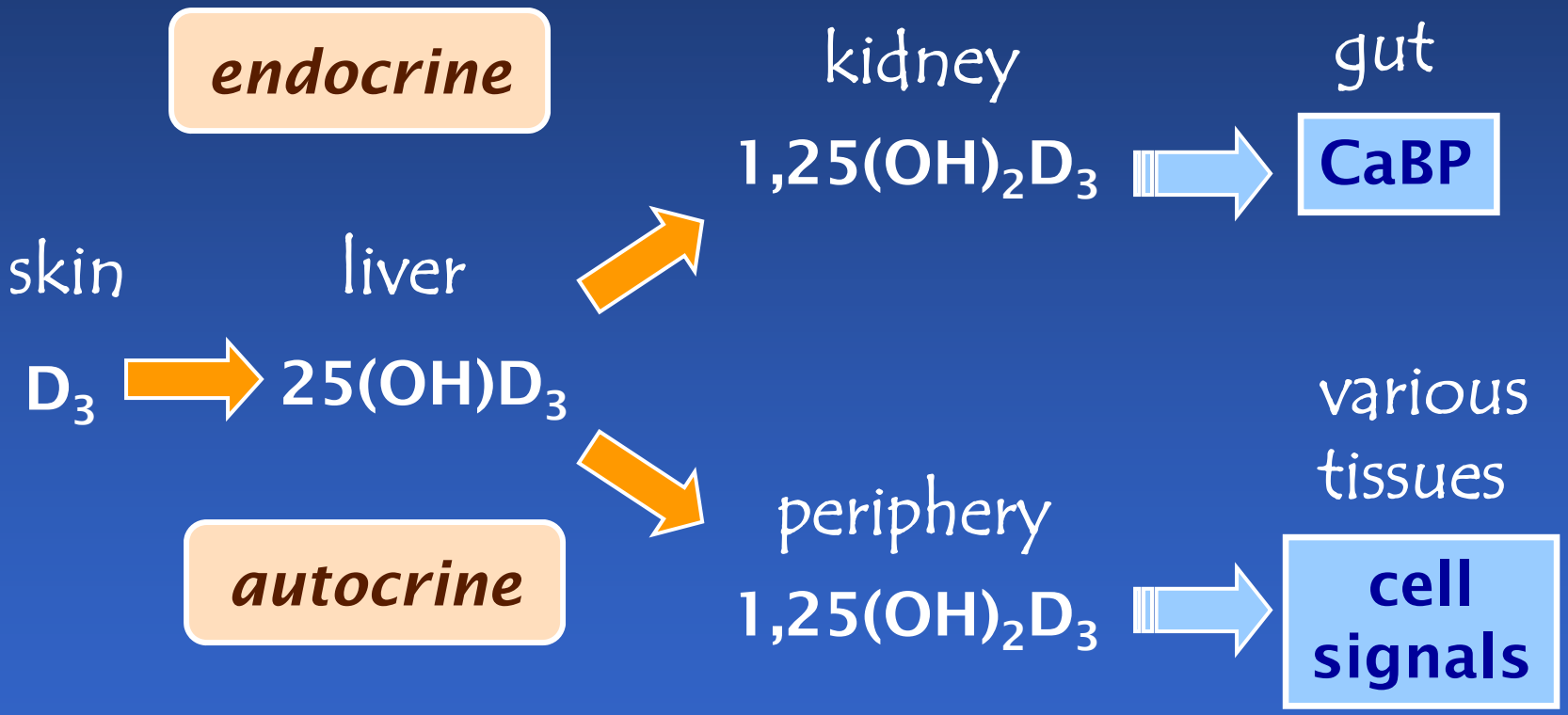
VIT D – CANONICAL SCHEME

skin liver kidney gut

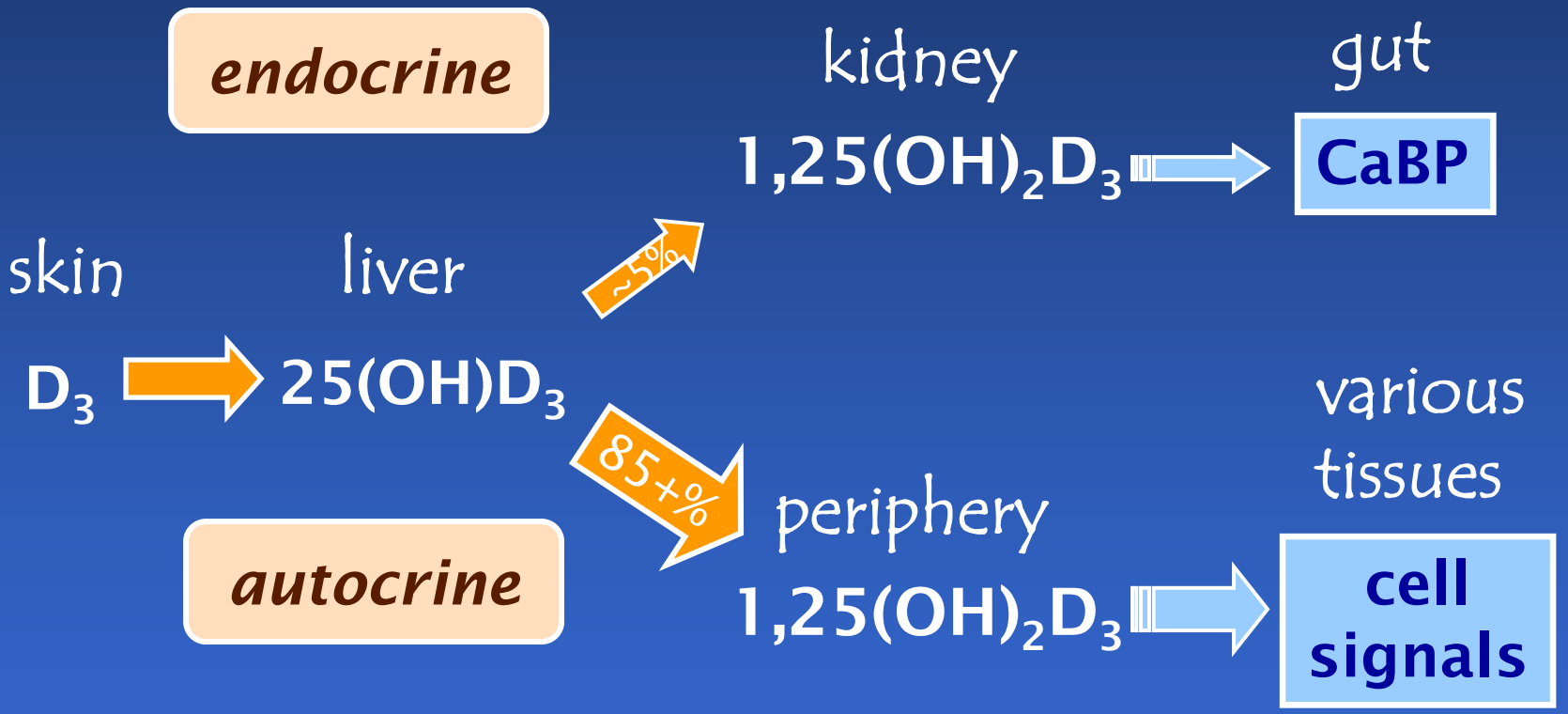
OLD
VIT D – CANONICAL SCHEME

skin liver kidney gut

VIT D – EXPANDED SCHEME



VIT D – EXPANDED SCHEME



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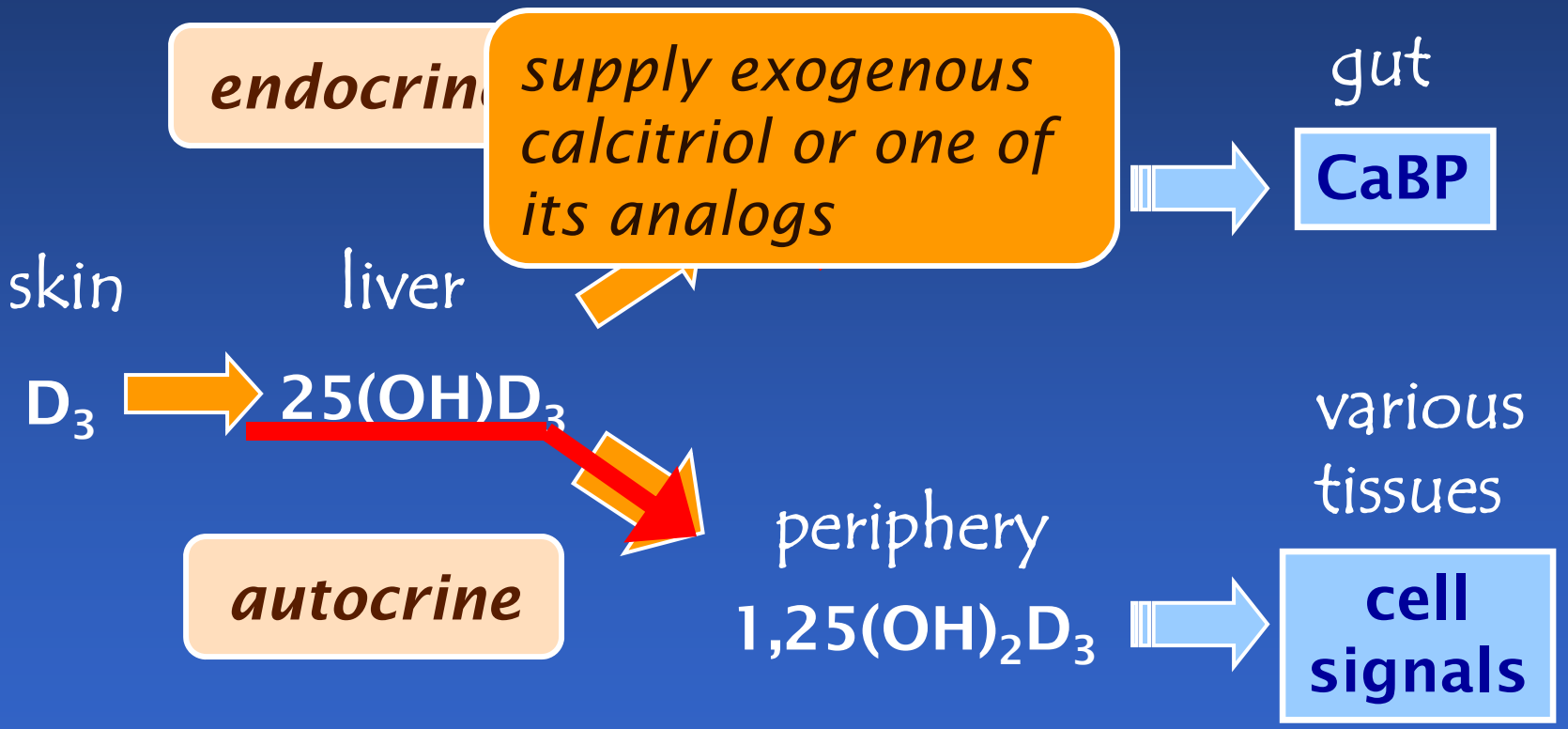
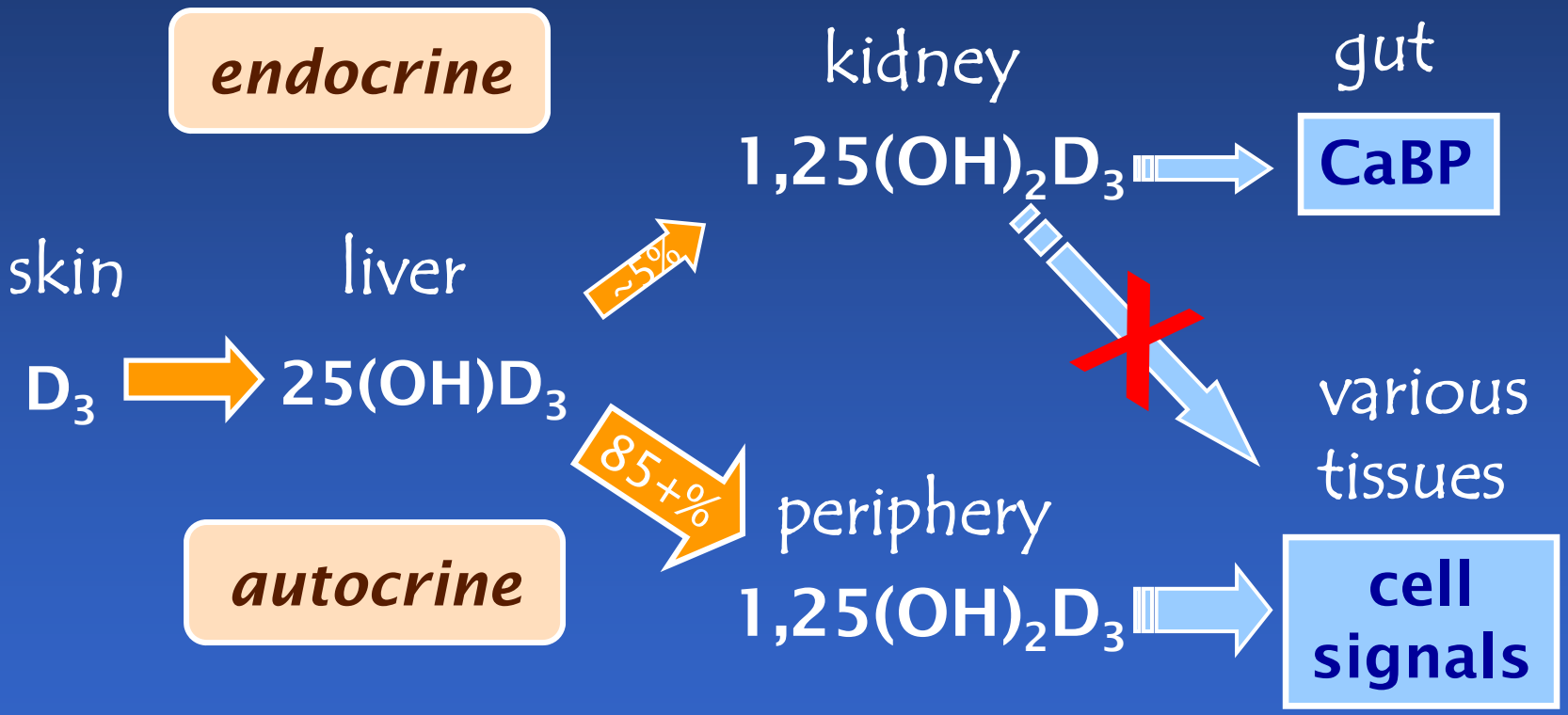


Won't calcitriol meet the body's need for vitamin D?

NO!

VIT D – EXPANDED SCHEME

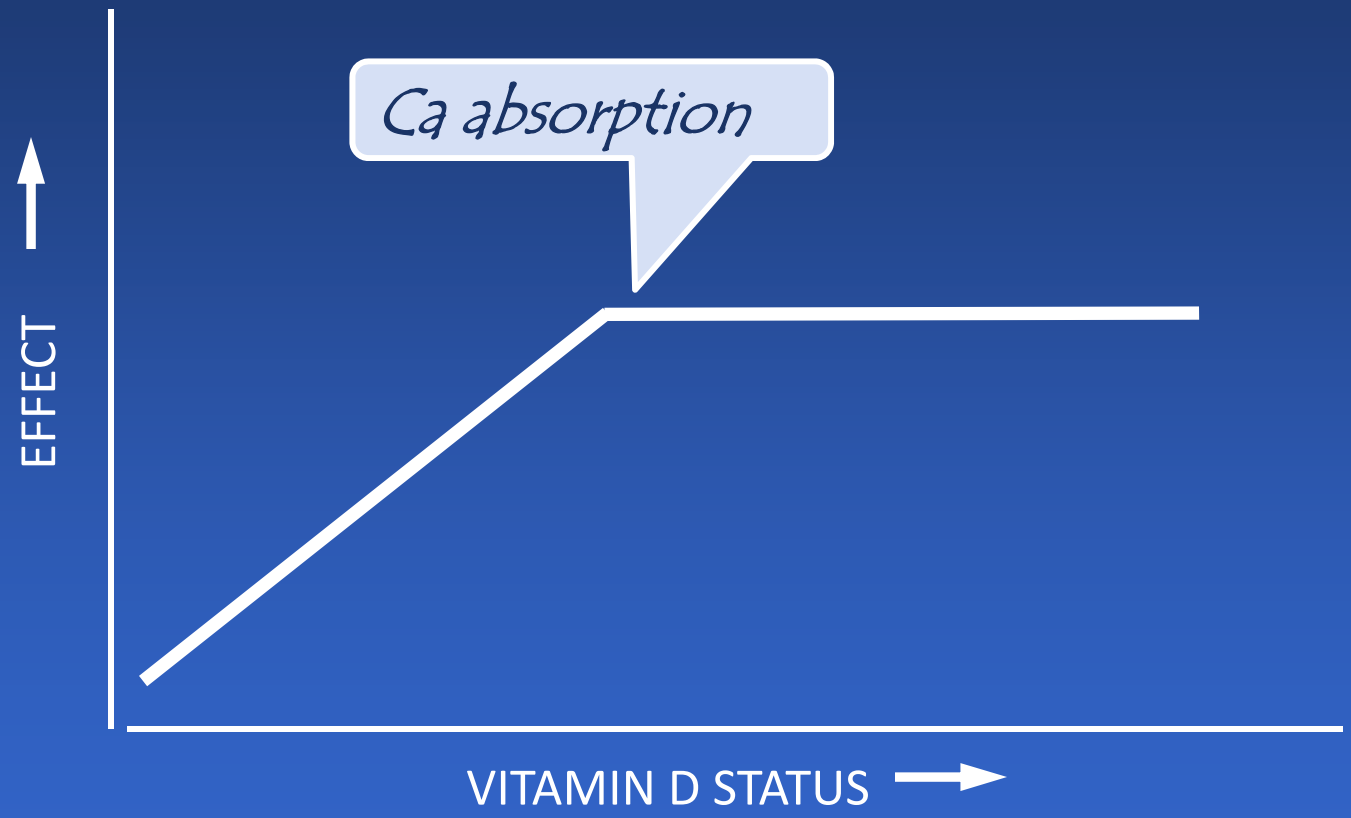


- Very recent studies have shown that, when serum 25(OH)D is normalized in patients on hemodialysis, serum $1,25(OH)_2D$ is "normalized" as well.

- Bikle showed many years ago that the skin was able to synthesize physiologically meaningful quantities of $1,25(OH)_2D$.

How much is enough?

THE RESPONSE THRESHOLD



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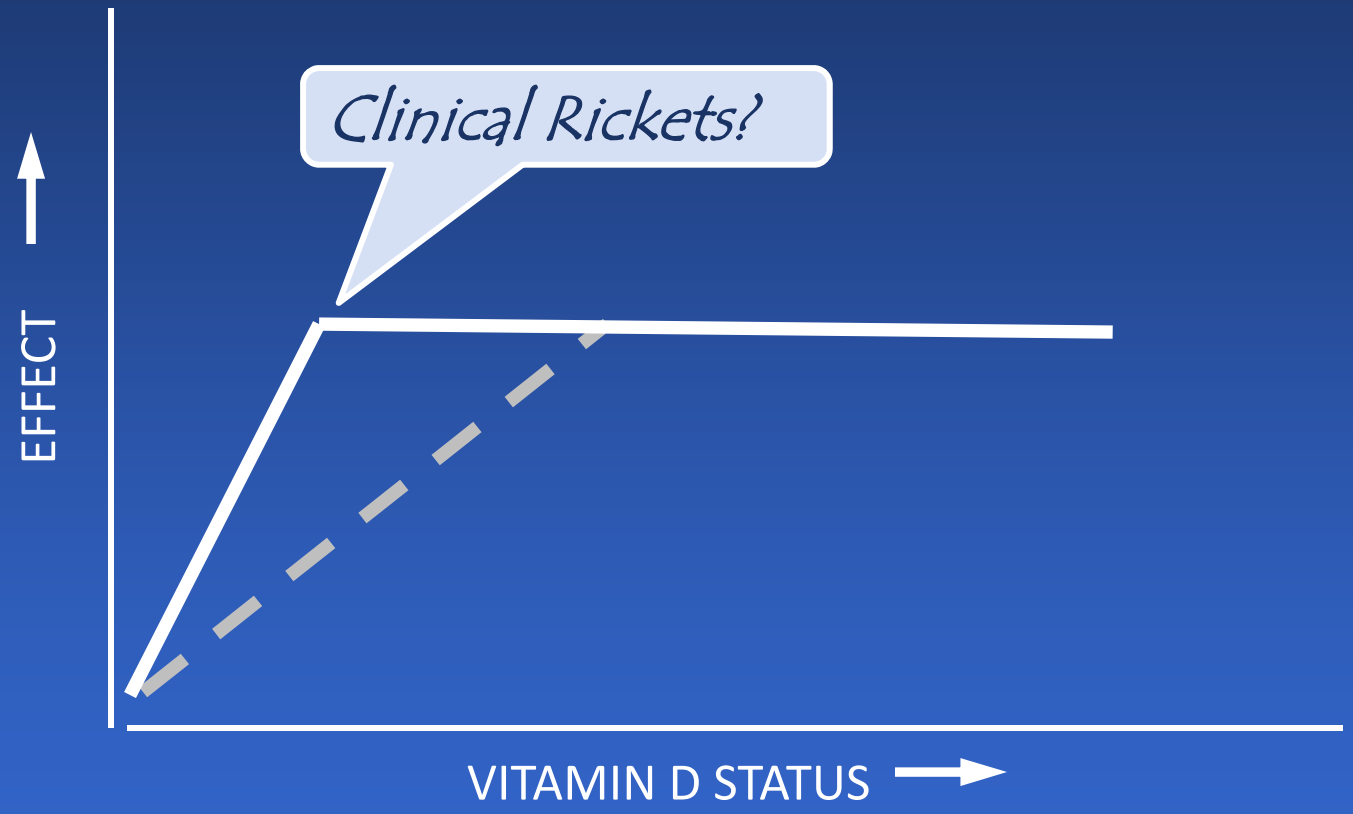

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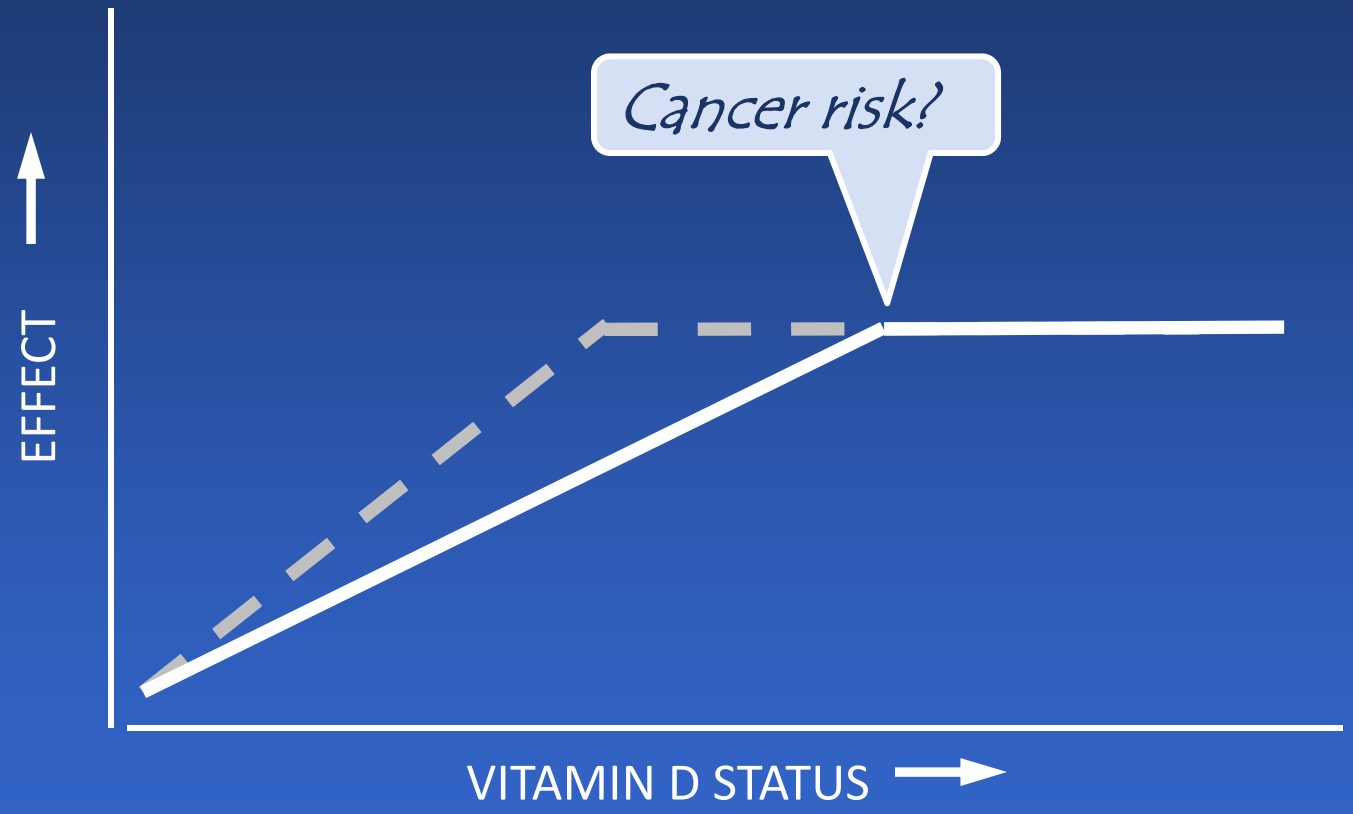
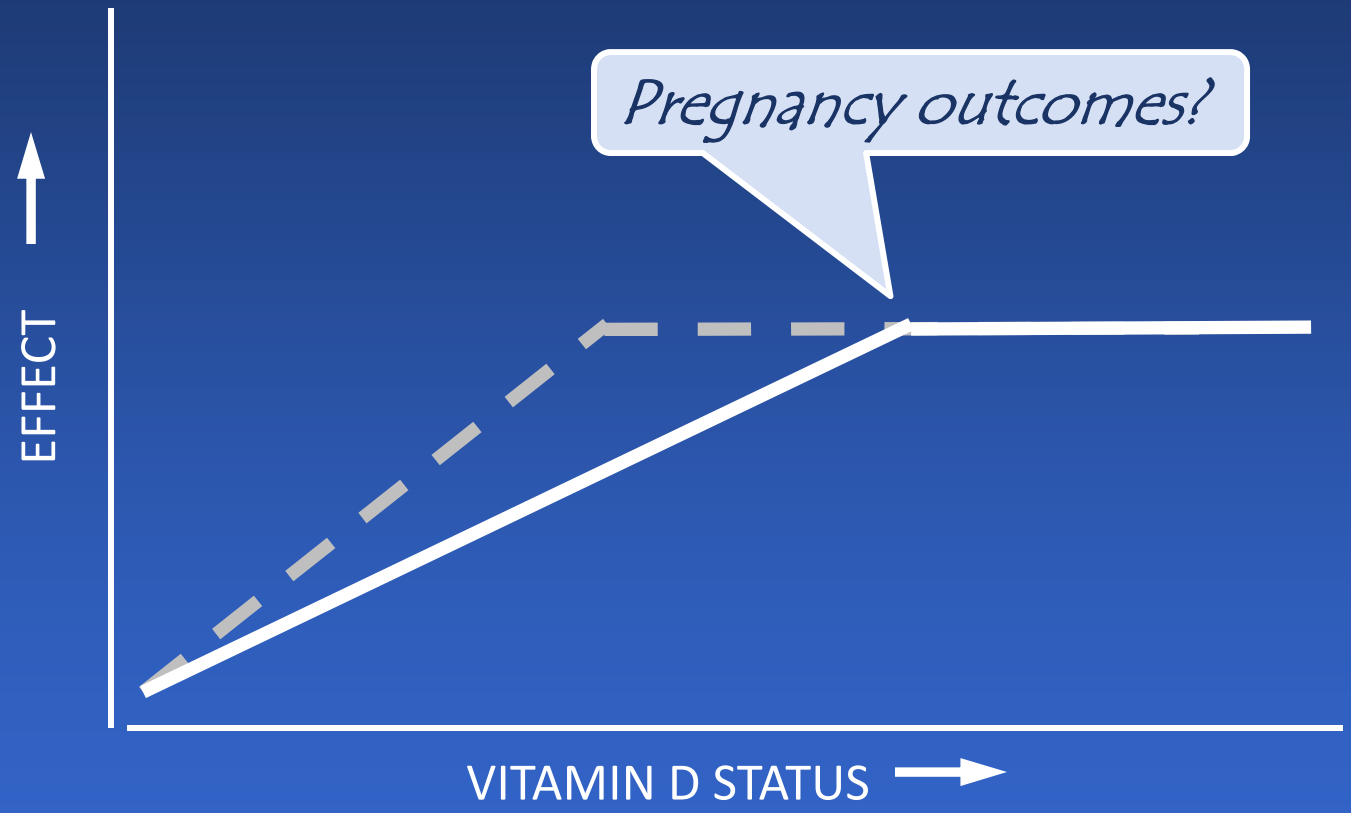


THE RESPONSE THRESHOLD



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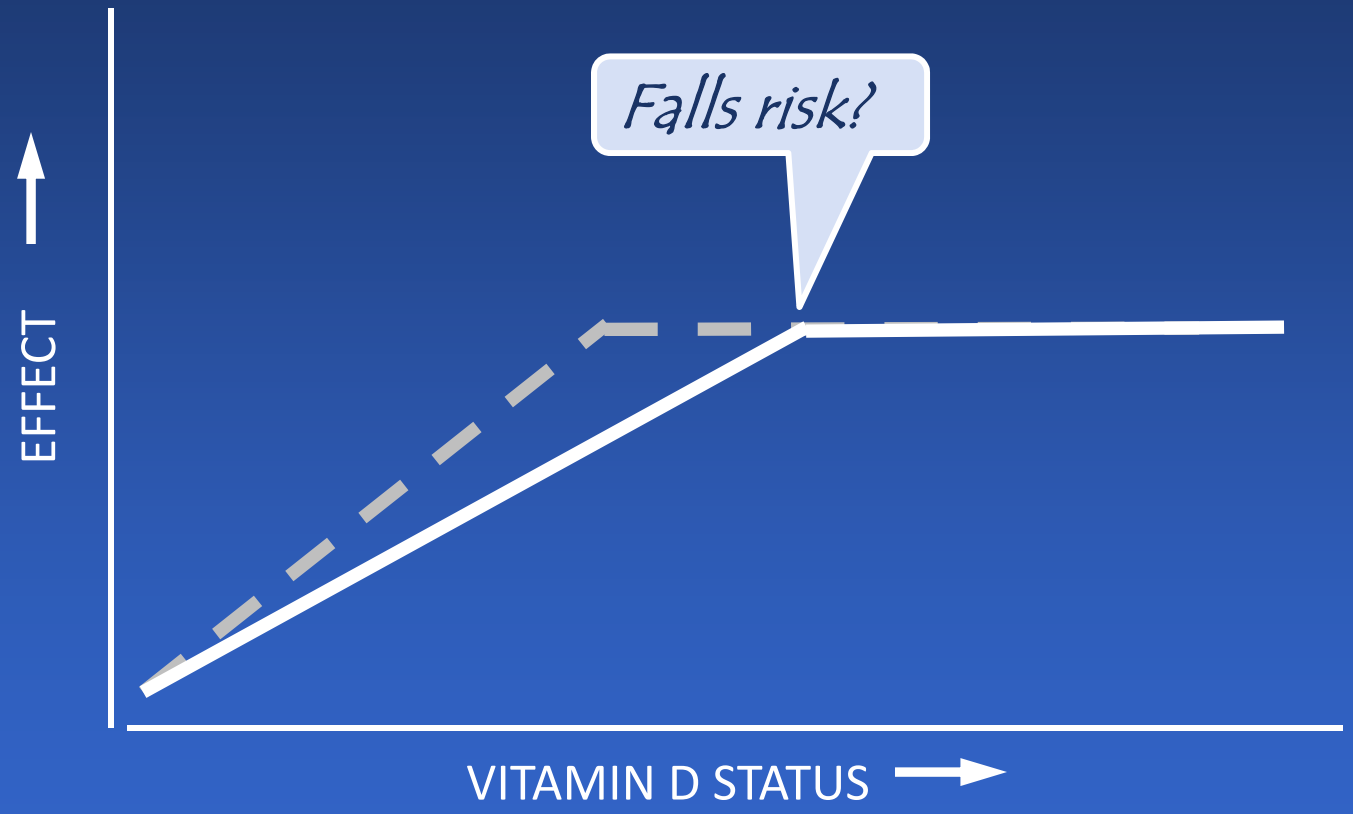

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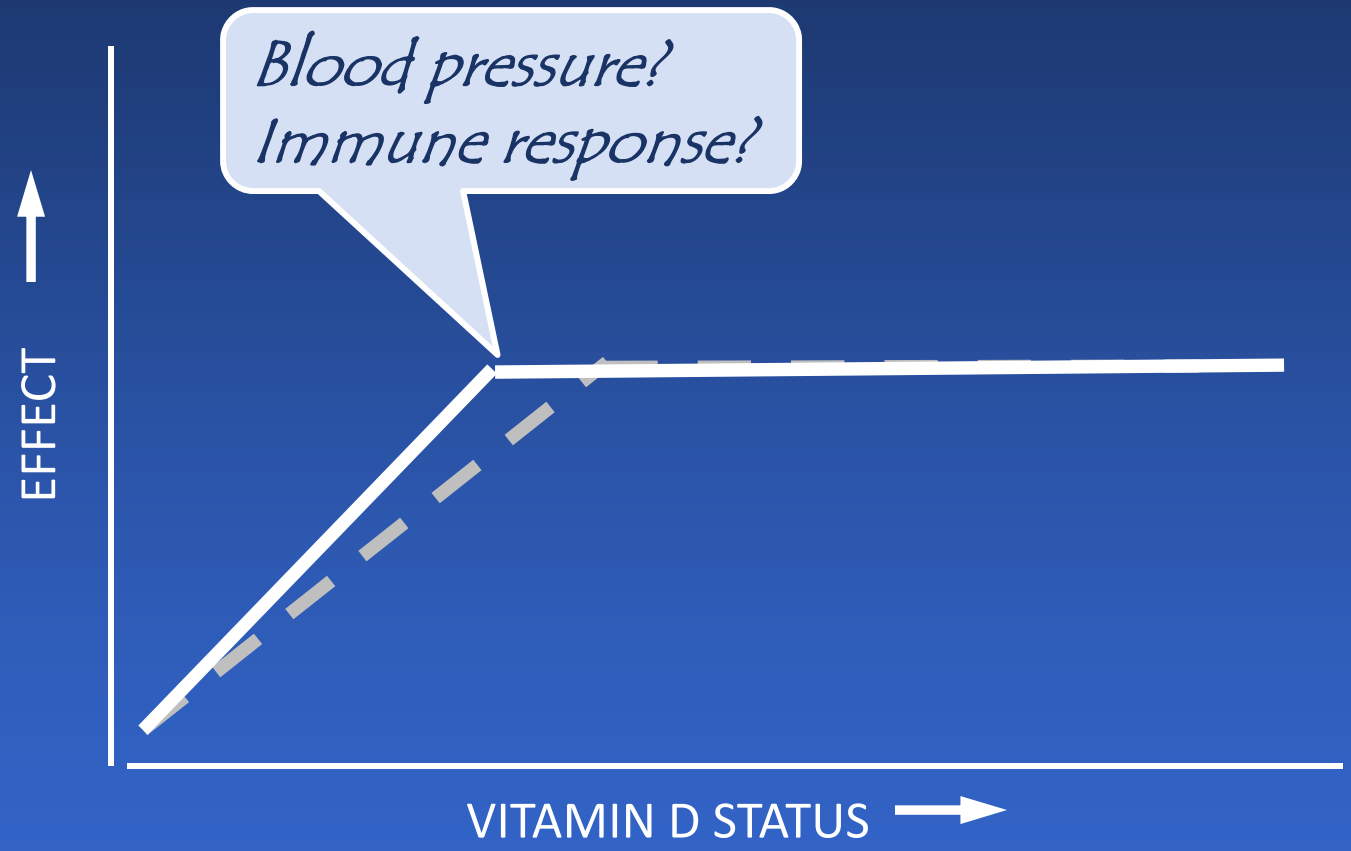
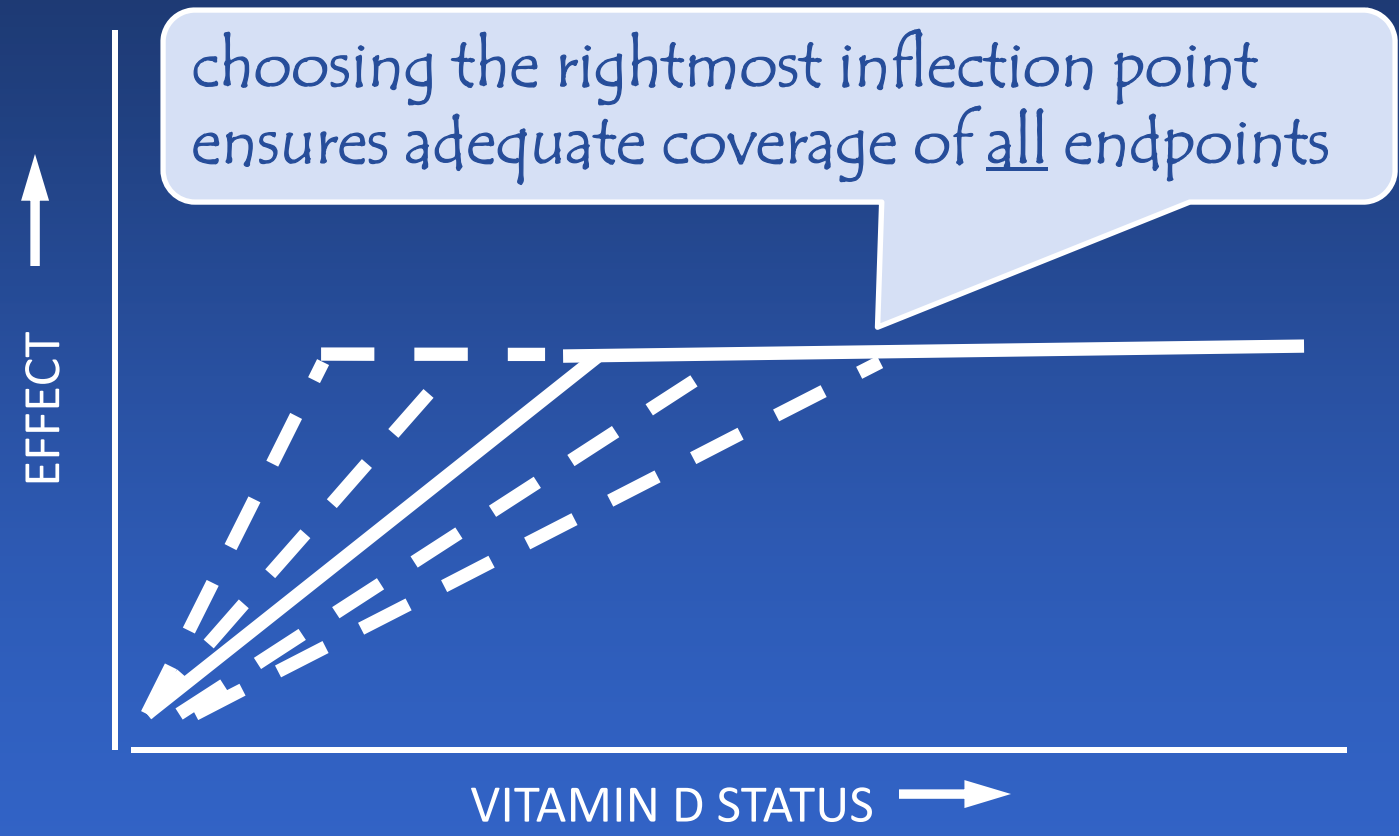


THE RESPONSE THRESHOLD



HOW MUCH IS ENOUGH?

▪ rickets & osteomalacia	
➢ clinical	25 nmol/L
➢ histological	80 nmol/L
▪ Ca absorption	80 nmol/L
▪ fracture risk	100 nmol/L
▪ pregnancy outcomes	120 nmol/L
▪ cancer	100 nmol/L
▪ other	????

STATUS OF THE EVIDENCE

- there are now more than 30 randomized controlled trials evaluating a causal connection between serum 25(OH)D levels and various health benefits
  - 13+ osteoporotic fractures
  - 5+ falls
  - 2 hypertension
  - 1 cancer
  - 1 adjuvant tuberculosis therapy
  - 3 respiratory infection/influenza risk
  - 3 pregnancy outcomes
  - 1 periodontal disease
  - 3 insulin sensitivity & diabetes

STATUS OF THE EVIDENCE

- out of this total there are, to be sure, several null trials
- in general these failed trials either –
  - used too low a dose
  - had poor compliance
  - failed to achieve a therapeutic blood level of 25(OH)D
  - failed to optimize co-nutrition
- there is only one negative trial

STATUS OF THE EVIDENCE

- there are, to be sure, several null trials as well
- in general these failed trials either –
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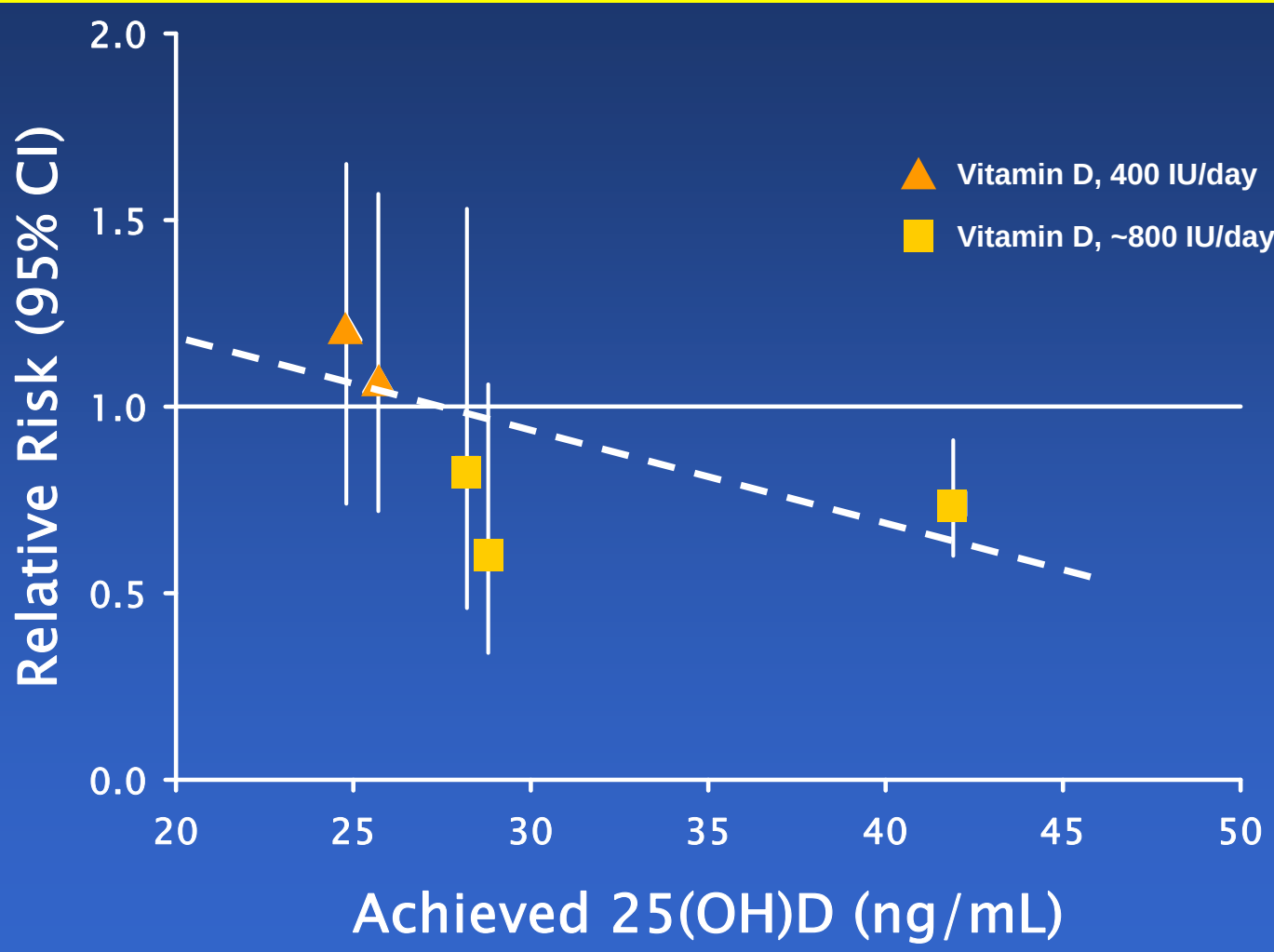
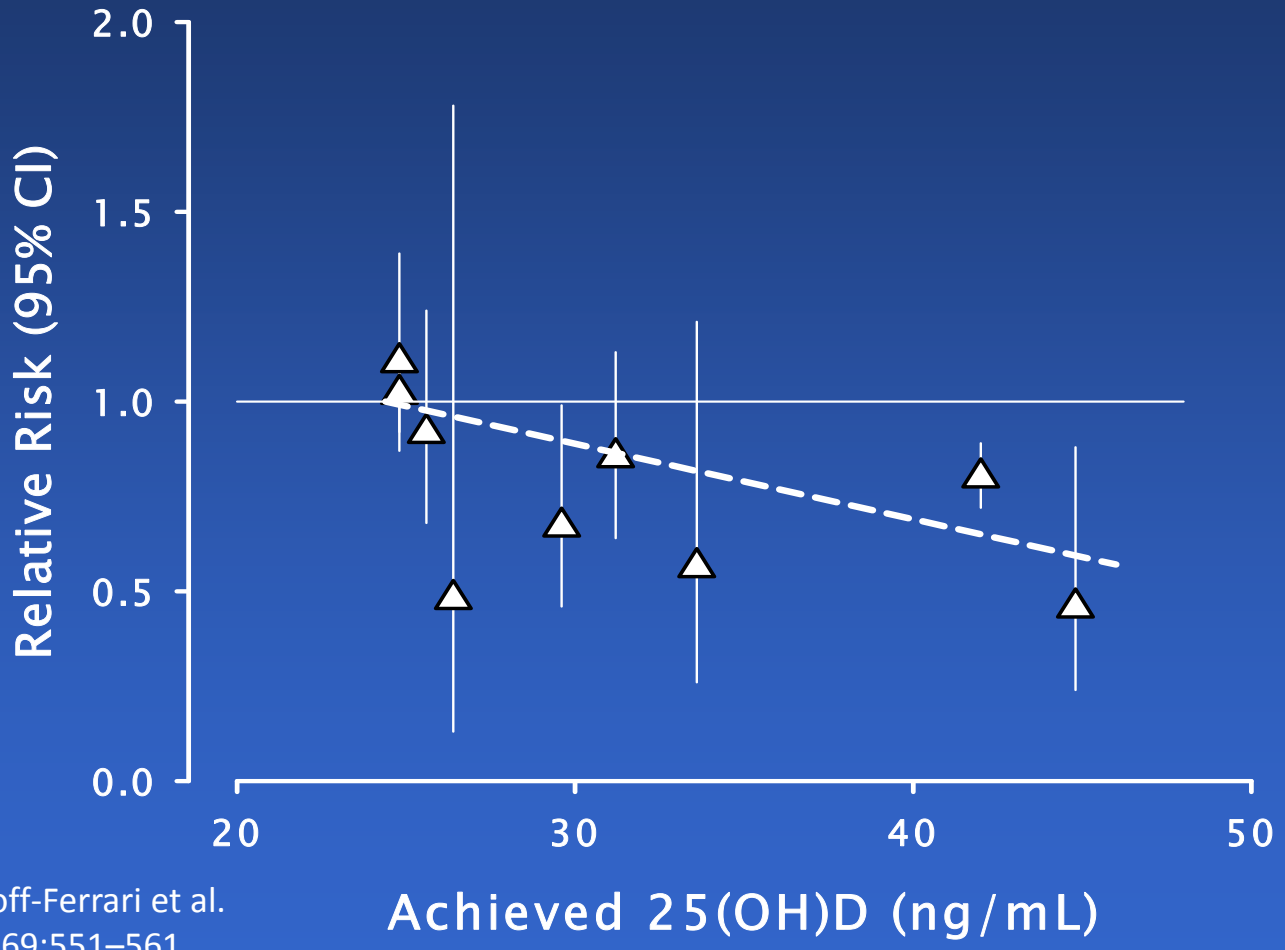
ACHIEVED 25(OH)D & HIP FRACTURE*



*Redrawn from Bischoff-Ferrari et al. *JAMA*. 2005;293:2257–2264

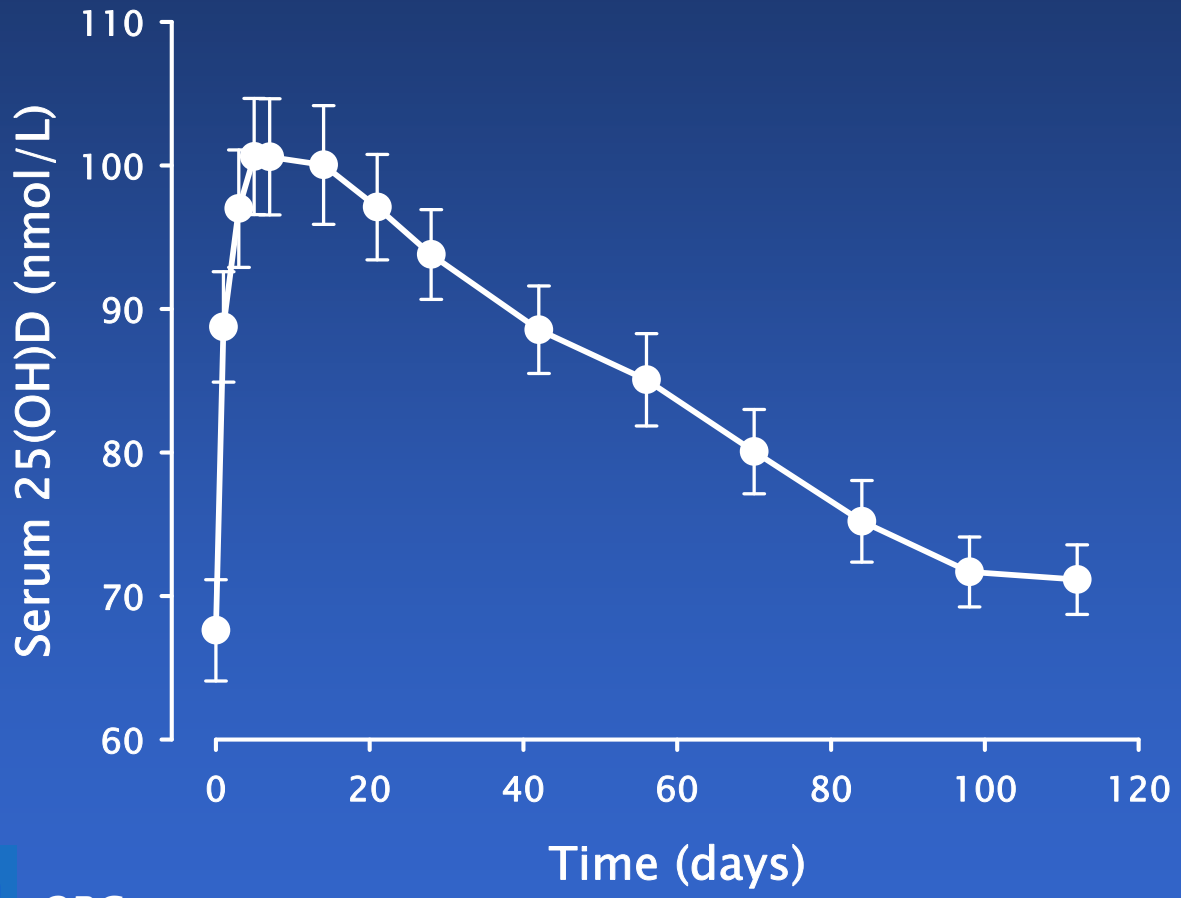
ACHIEVED DOSE & FRACTURE EFFICACY*



* Redrawn from Bischoff-Ferrari et al. (2009) Arch Int Med; 169:551–561

25(OH)D RESPONSE TO LARGE DOSES*

- 100,000 IU D_3, by mouth, once

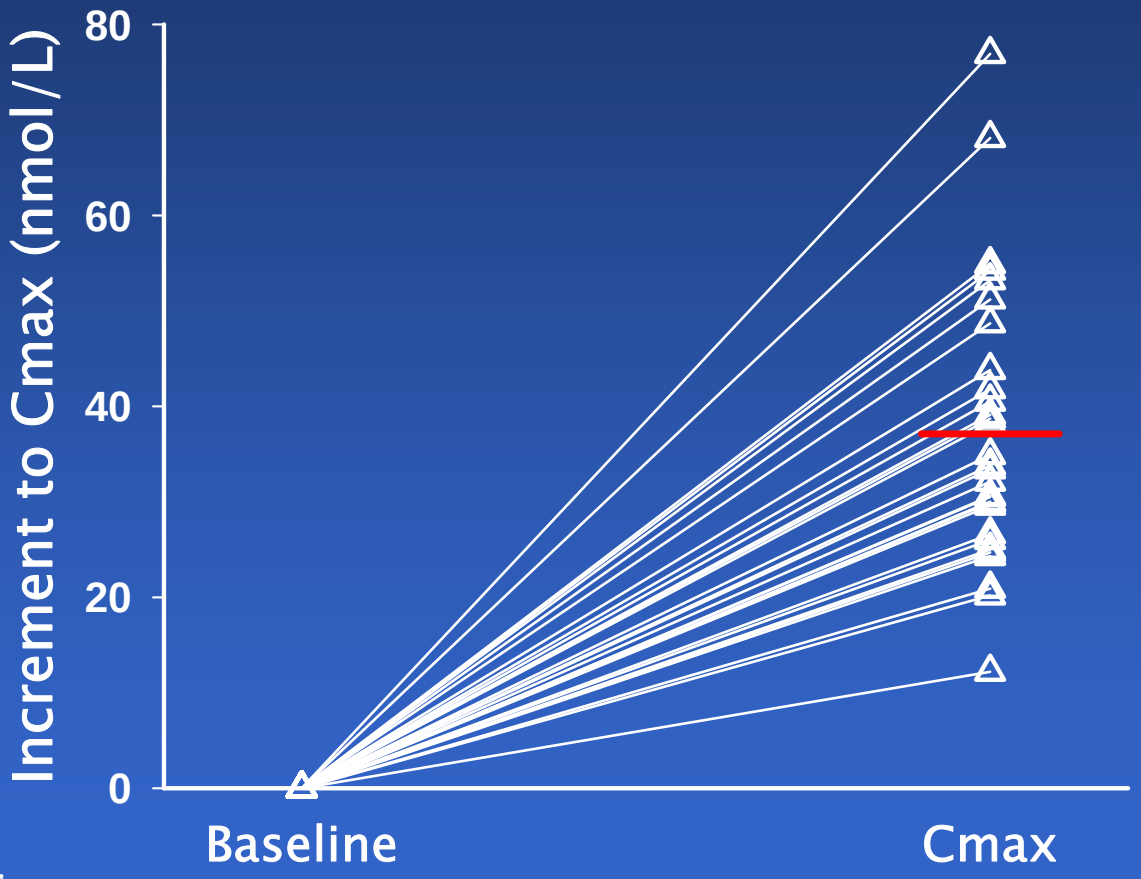


CU ORC

*Ilahi, Armas, & Heaney

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

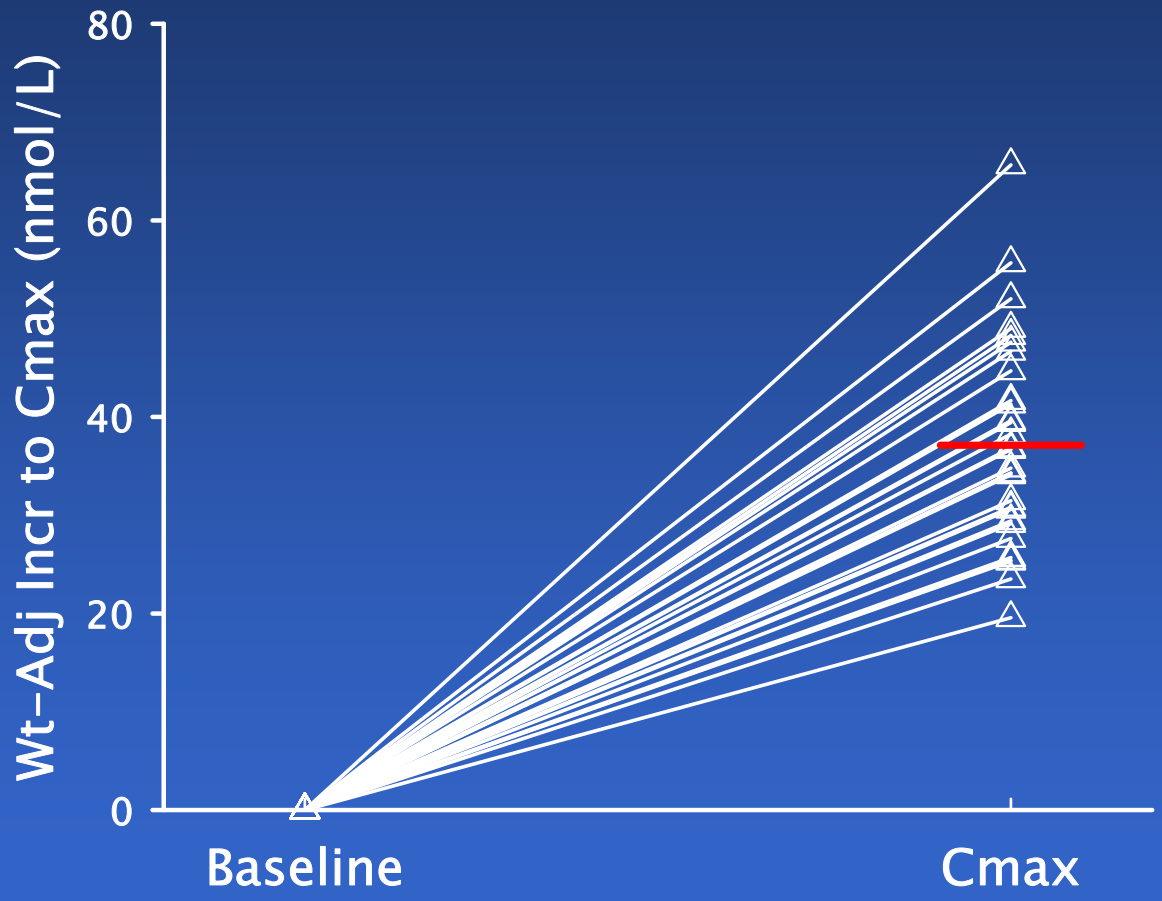


CU ORC

*Ilahi, Armas, & Heaney

VARIABILITY OF 25(OH)D RESPONSE*

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



CU ORC

*Ilahi, Armas, & Heaney

SUMMARY

- for some endpoints (e.g., pregnancy, cancer) the data suggest that 80 nmol/L is not high enough
- there is huge variability in individual response
- the emphasis must be on the achieved serum level, not on the oral dose

SUMMARY

- levels of 100 – 200 nmol/L are physiological
- given the manifest safety of such levels, we should strive to achieve at least 100 nmol/L in all our patients & clients
- whatever their primary condition, most will be vitamin D-deficient as well
- their recovery will be aided by treating that D deficiency

SUMMARY

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Thank you . . .