Vitamin D: A cloudy state
Why nutrition science is so challenging

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Vitamin D is flying off shelves

Photo by AG Pittas at local pharmacy, October 2012

Definitions

Deficiency

Various syndromes

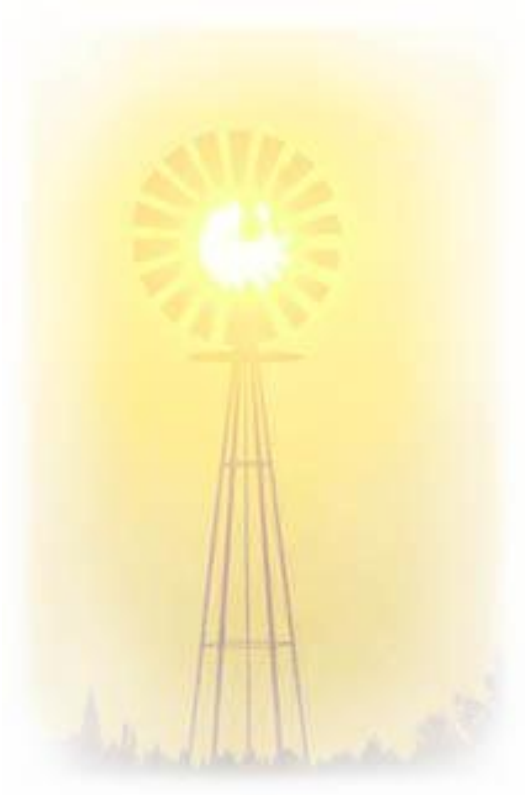
Rickets,
Osteomalacia

Vitamin D Dietary Sources are Limited

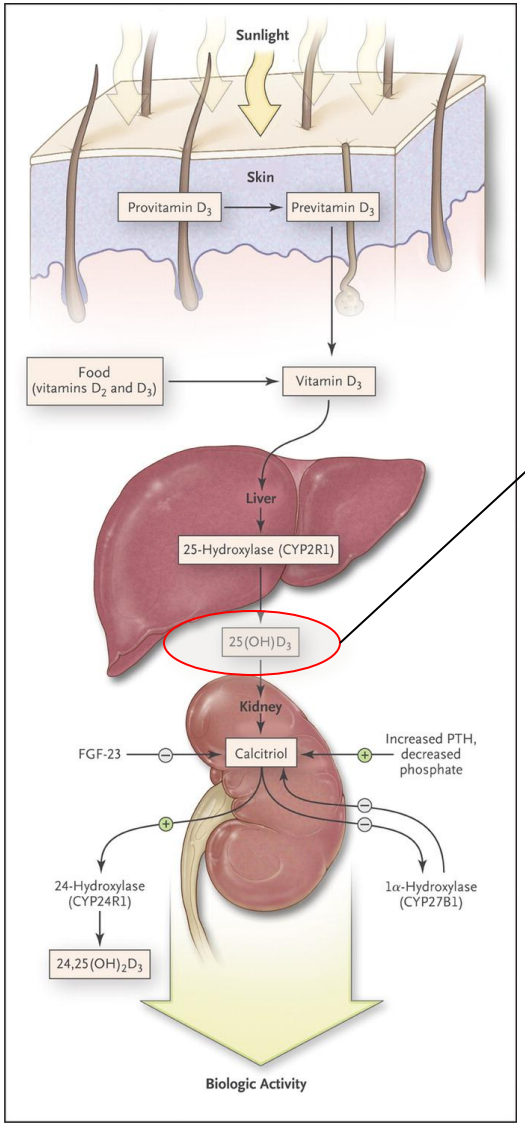
- Natural resources
  - Cod liver oil
  - Oily fish (e.g. swordfish, salmon, tuna)
  - Egg yolks
- Fortified foods
  - Milk, orange juice
  - Some yogurt
  - Many cereal
- Dietary supplements

* Disclaimer : There is no fruit in “Fruity” Pebbl

Evolutionary appropriate source of vitamin D
Solar UVB exposure (lately… in decline)



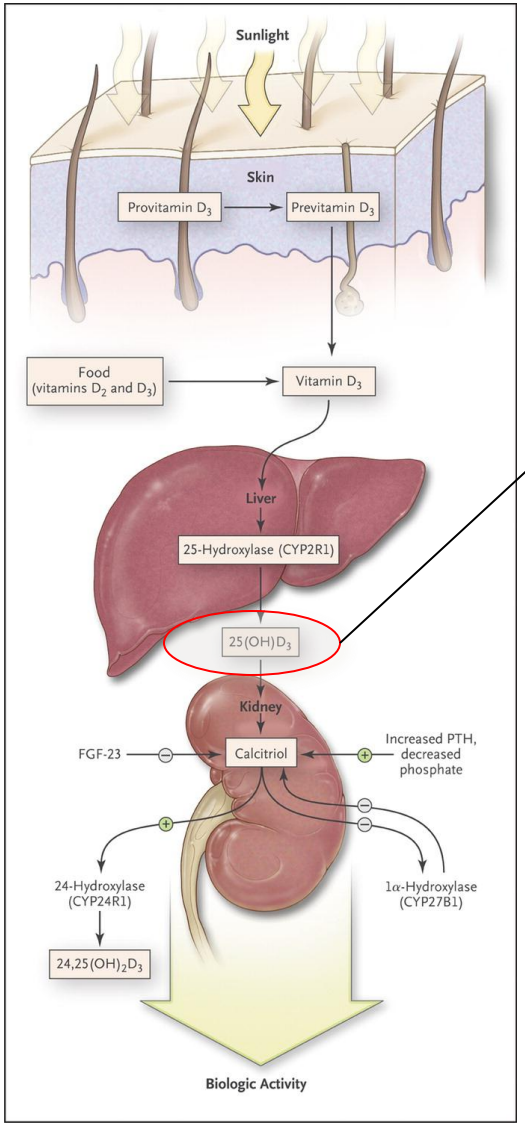
Vitamin D Homeostasis



25OHD, a biomarker of vitamin D status

Rosen NEJM 2011

Vitamin D Homeostasis



Rosen NEJM 2011

25OHD, a biomarker of vitamin D status

25OHD (ng/mL) trend over time

1988-1994 ➔ 2001-2006

~28 ➔ ~24

Looker et al AJCN 2008:88:1519
Looker et al NCHS Data Brief, No 59, March 2011

Population 25OHD is lower than it used to be… *is that important*?

Definitions of Biomarker

- Biomarker of exposure
  - Validated measure to reflect intake or exposure
  - Example: *25OHD*
- Biomarker of effect (=causal association)
  - Validated measure that is causally related to and predictive of important health outcomes
  - Example: *LDL*

Biomarker of Exposure $\neq$ Biomarker of Effect

Prerequisites for Causal Association of Vitamin D with Disease

- Plausible mechanism
- Temporal relationship: longitudinal studies
- Strength of the association: high relative risk
- Dose response (except in thresholds)
- Experimental evidence
  - Cessation/removal of exposure, intervention [RCT]
- Consideration of alternative explanations
- Coherence [consistency among studies]

Bradford Hill's Guidelines, Howick et al JRSocMed 2009

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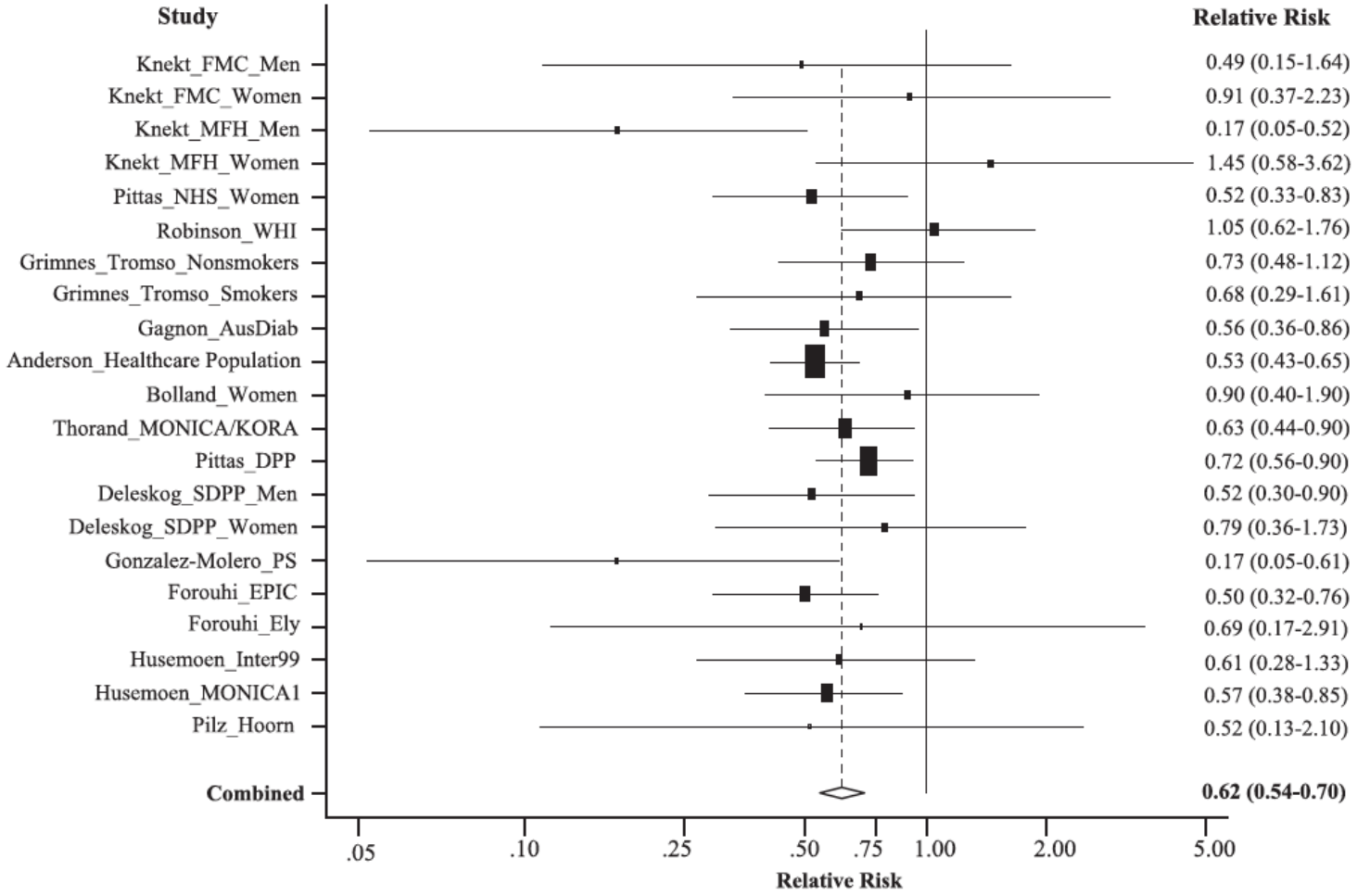
Association of 25OHD with Incident Diabetes
Meta-analysis of Longitudinal Observational Studies

for 25OHD (ng/mL) >25-30 vs. <8-20
Risk is lower by 35%



Song et al Diabetes Care March 2013

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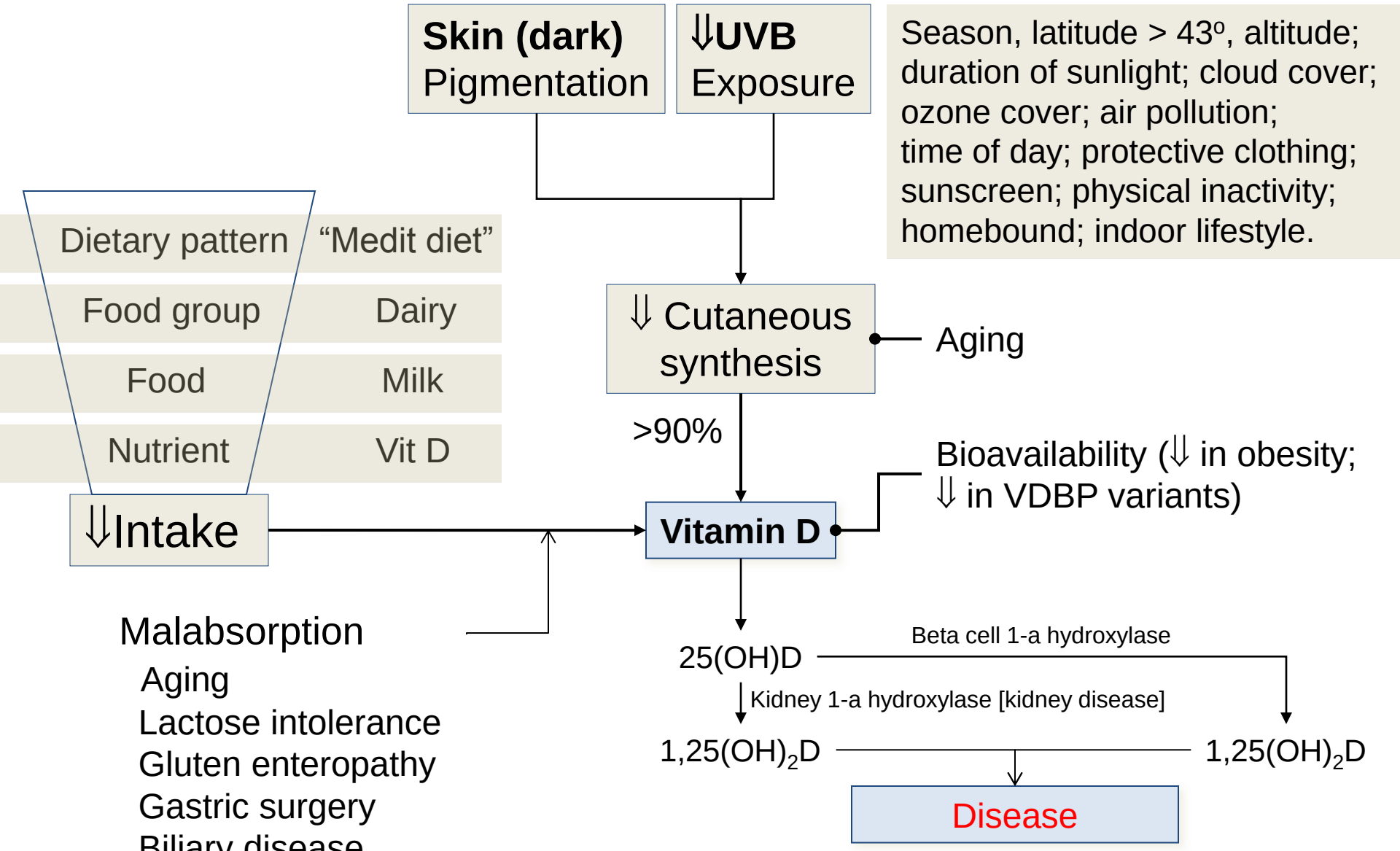
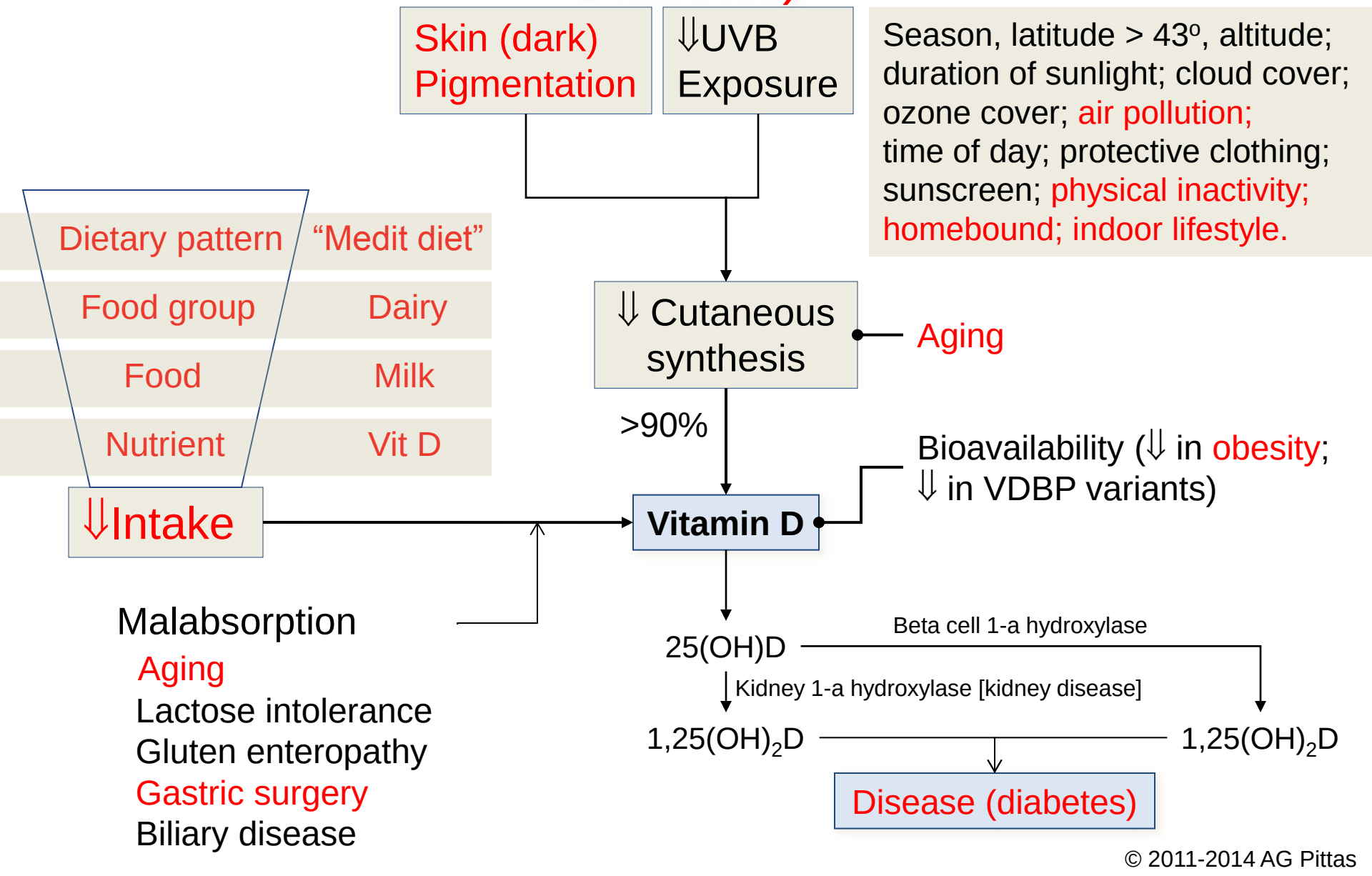
Factors that Contribute to Vitamin D Deficiency/Insufficiency



Factors that Contribute to Vitamin D Deficiency/Insufficiency & Disease (e.g. Diabetes)



(Residual & Unmeasured) **Confounding**

Is vitamin D status [i.e., blood 25OHD] simply a marker of increased risk for disease?

Association ≠ "supplementation would be beneficial"

Randomized Clinical Trials

Vitamin D Recommended Intake
Institute of Medicine (U.S.) 2011 Report *

	RDA [1]	Upper Limit [2]
≤ 70 years	600 IU	4,000 IU
> 70 years	800 IU	4,000 IU

* RDA for skeletal outcomes (fractures and falls) ONLY
Under conditions of minimal sun exposure
Applicable to normal healthy population groups

[1]**Recommended Dietary Allowance**, intake that meets needs of **97.5% of healthy** population

[2]**Tolerable Upper Intake Level**, above which potential **risk of adverse effects may increase with chronic use.**

UL is not highest dose recommended

Vitamin D Recommended Intake (units)
IOM (U.S.) vs. Endocrine Society (U.S.)

Life stage group	IOM recommendations				Committee recommendations for patients at risk for vitamin D deficiency	
	AI	EAR	RDA	UL	Daily requirement	UL
Infants						
0 to 6 months						
6 to 12 months						
Children						
1–3 yr						
4–8 yr						
Males						
9–13 yr			600 IU (15 μg)	4,000 IU (100 μg)	600–1,000 IU	4,000 IU
14–18 yr			600 IU (15 μg)	4,000 IU (100 μg)	600–1,000 IU	4,000 IU
19–30 yr			600 IU (15 μg)	4,000 IU (100 μg)	1,500–2,000 IU	10,000 IU
31–50 yr			600 IU (15 μg)	4,000 IU (100 μg)	1,500–2,000 IU	10,000 IU
51–70 yr			600 IU (15 μg)	4,000 IU (100 μg)	1,500–2,000 IU	10,000 IU
>70 yr			800 IU (20 μg)	4,000 IU (100 μg)	1,500–2,000 IU	10,000 IU
Females						
9–13 yr			600 IU (15 μg)	4,000 IU (100 μg)	600–1,000 IU	4,000 IU
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Pregnancy						
14–18 yr			600 IU (15 μg)	4,000 IU (100 μg)	600–1,000 IU	4,000 IU
19–30 yr			600 IU (15 μg)	4,000 IU (100 μg)	1,500–2,000 IU	10,000 IU
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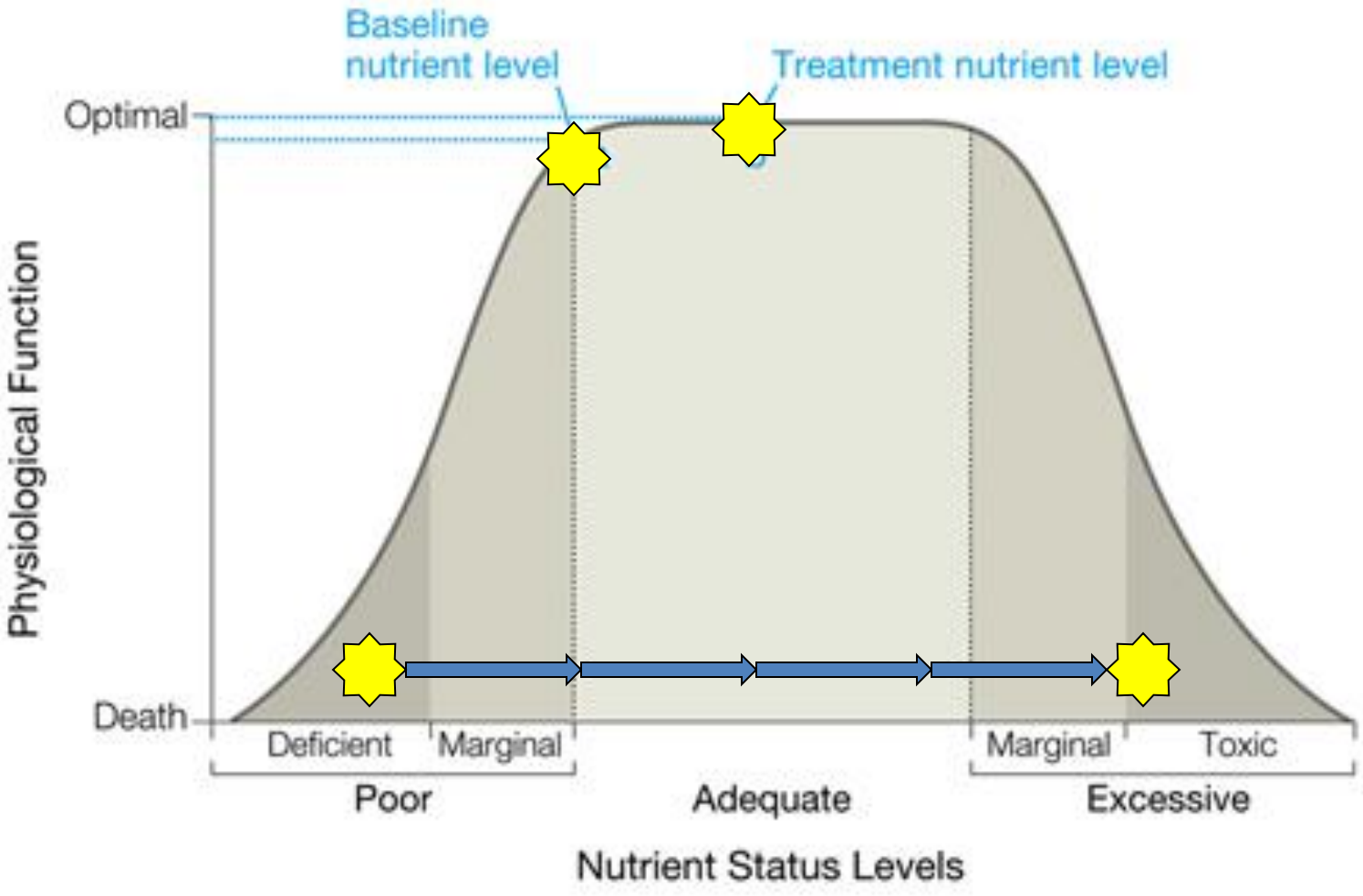
Is more (vitamin D) better?
Intake-Response Relationship for Nutrients



= specific dose of vitamin D (e.g. 1000 units)

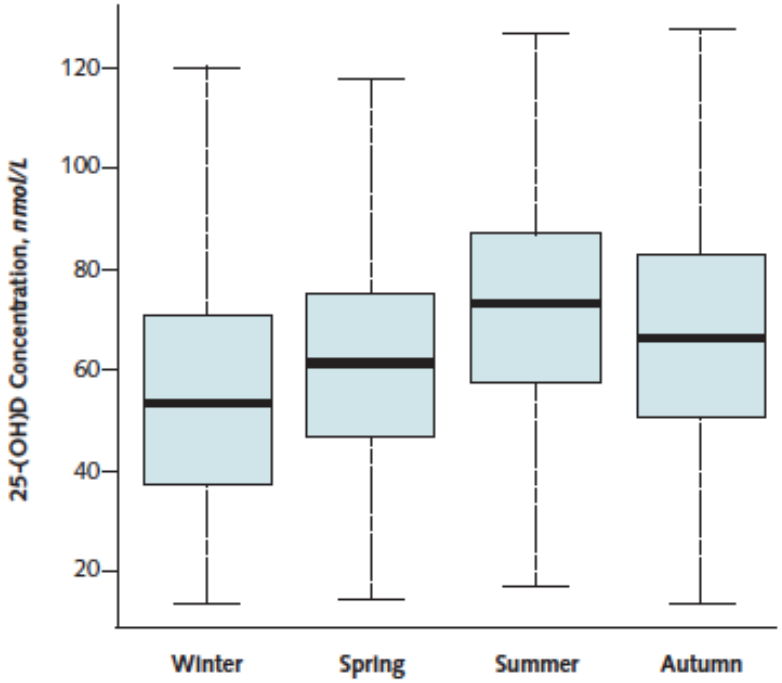
Optimal 25OHD Concentration

	ng/mL	
Deficiency	< 12	Rickets, Osteomalacia

Optimal 25OHD Concentration
Institute of Medicine (U.S.) vs. Endocrine Society c. 2011

	ng/mL		
Deficiency	< 12	Rickets, Osteomalacia	
"Inadequacy"	12 - 19		
"Sufficiency"	20 - 29	✓ Skeletal Outcomes **ONLY**	IOM
"Sufficiency"	> 30	✓ Skeletal & Non-skeletal Outcomes	Endo Society

Seasonal variability of blood 25OHD concentration



~22 ng/mL

~30 ng/mL

Measure 25OHD in Fall or Spring

de Boer et al Ann Intern Med. 2012;156(9):627-634