Changing the RCT Research Paradigm for Nutrients: An Alternative to RCTs

Friday, January 23, 2015, 2:00 p.m. – 3:00 p.m. ET

Webinar

Moderator:
Karen Howard, Organic & Natural Health Association

Panelists:
Todd A. Harrison, Esq., Venable LLP
Carole Baggerly, Director, GrassrootsHealth
Dr. Robert P. Heaney, Creighton University

Clinical Research, Statistics and Other Deceptions

Defining Competent and Reliable Scientific Evidence – The Intersect of Law, Policy, and Science

Todd A. Harrison, Esq., Venable LLP

Consideration Points

- Is it time for a paradigm shift?
  - Is promoting overall health and well-being an Art or a Science?
    - Are these two concepts mutually exclusive?
- Is the legal definition of “Competent and Reliable Scientific Evidence” inflexible or flexible?
- Is the evidence based science model inflexible or flexible?
- Policy Considerations

Competent and Reliable Scientific Evidence Defined

- tests, analyses, research, studies, or other evidence based on the expertise of professionals in the relevant area, that have been conducted and evaluated in an objective manner by persons qualified to do so, using procedures generally accepted in the profession to yield accurate and reliable results
  - Is the holy grail statistical significance or clinically meaningful?
    - Bright line versus Clinical Results

RCT's Are Not The Holy Grail

- In *FTC v. QT, Inc*. 512 F.3d 858 (7th Cir. 2008), the Seventh Circuit explicitly held that "[n]othing in the Federal Trade Commission Act … requires placebo-controlled, double-blind studies. … [p]lacebo-controlled double-blind testing is not a legal requirement for consumer products." *Id*. at 861. *See FTC v. Direct Marketing Concepts, Inc*., 624 F.3d 1, 9 (1st Cir. 2010) ("To be sure, there may be other scientific evidence that could be sufficient, and we may assume for these purposes that a double-blind study is not necessarily required."); *In re POM Wonderful*, Docket No. 9344, 2012 LEXIS 106, *538-542 (May 17, 2012)

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‘Former FTC Consumer Protection Bureau Director William MacLeod criticized overly zealous state agencies and public interest groups advocating for absolute scientific certainty. He expressed a fear that, under that line of analysis, “[t]he perfect could end up being the enemy of the good.”

Statistical Significance

Nuzzo 2014: (Nature)

- Fisher introduced the P-value in 1920
- Fisher intended it to “simply be an informal way to judge whether evidence was significant in the old fashion sense” (worthy of a second look)
- Fisher intended it to be a process that blended data, and background knowledge
- “But it got swept into a movement to make evidence-based decision-making as rigorous and objective as possible”.
- Scientists who were non-statisticians, created a hybrid system that crammed Fisher’s easy-to-calculate P-value into a rigorous rule-based system.
- This is when a P value of 0.05 became enshrined as “statistically significant”
- P-value was never meant to be used the way it is used today.
- Currently, P-value encourage muddle-thinking
- Statistical significance is no indicator of practical relevance. The question we should is be asking is “how much of an effect is there”, not ”is there an effect”

Statistical Significance versus Clinical Outcome

- **Question:** What to do with clinical trials where positive clinical outcomes are observed but do not have statistical significance? Is there no value with data that shows P>0.05?
- **Question:** What other methods are there that determine efficacy, other than p-values?
- **Question:** How does one proceed with new and statistically significant and unexpected results that are primary end point but in a subgroup that was not previously identified

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Statistical Significance versus Clinically Relevant

- Statistical significance simply indicates the probability of incorrectly rejecting a true null hypothesis. Never meant to be a rigid standard
  - Is the 95% Confidence Level an Arbitrary Number
  - Can a study fail to reach statistical significance but still be considered clinically relevant?
    - Statistical significance does not give any indication of the magnitude or clinical importance of the difference
- The issue with applying statistical significance in a rigid manner
  - Studies that are statistically non-significant are ignored even though there is a true treatment effect – generally due to small sample size
  - Studies that show small difference can reach statistical significance by increasing the number of subjects in a study even though the results provide little value to the patient
  - Commercial speech concerns – 1st Amendment. Throwing the baby out with the bathwater

Statistical Significance versus Clinically Relevant

- Clinically relevant relevance is a change in an individual's clinical status that is regarded as important
  - **Minimal clinically important difference** (also known as **MCID**), attempts to define the smallest change in a treatment outcome that a patient would identify as important
    - Requires a paradigm shift
    - More consistent with 1st Amendment concerns than statistical significance

Paradigm Shift

- Statistical Significance versus Clinically Relevant
  - Is evidence based science really about the 95% confidence level
    - 95% confidence level merely validates the extreme results while ignoring the clinical results
  - Lawyers prefer bright lines because it is easier to prove their case
  - Experts may disagree on the clinical relevance of a clinical trial
    - First Amendment would permit the claim as being non-deceptive if it is clinically relevant

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Paradigm Shift from Proof of Efficacy to Proof of Probable Harm for Dietary Supplements

- For nutrients/dietary supplements, a shift in decision context be made from proof of efficacy to that of probable harm. (Heaney, 2011)
  - A calculus of benefit vs harm of an intervention should be evaluated on a nutrient-by-nutrient basis
  - Proof of harm of no intervention is already established in people who are not in disease state but have parameters suggesting a disease state trajectory
  - Without intervention, these people have a high probability of developing disease (Proof of Harm)
  - If the dietary supplement intervention can be demonstrated to be safe, through high-quality and comprehensive safety studies, calculus of benefit vs harm of the intervention shifts towards benefit
- In the context of dietary supplements, placebo group represents no intervention
  - If the surrogate biomarkers of the placebo group worsens at the end of the study while intervention group improves or maintain current levels, this outcome is of significant clinical value

Policy: Evidence Based Medicine vs. Evidence Based Nutrition

Parameter	Drugs	Nutrients
Essentiality	None	Essential
Inadequacy results in disease	No	Yes
Homeostatically controlled by the body	No	Yes
True placebo group	Yes	**No**
Baseline “status” affects response to intervention	No	**Yes**
Systemic function	Isolated	**Complex networks**
Targets	Single organ/tissue	**All cells/tissues**
Effect size	Large	Small
Side effects	Large	Small
Nature of effect	Therapeutic	Preventative

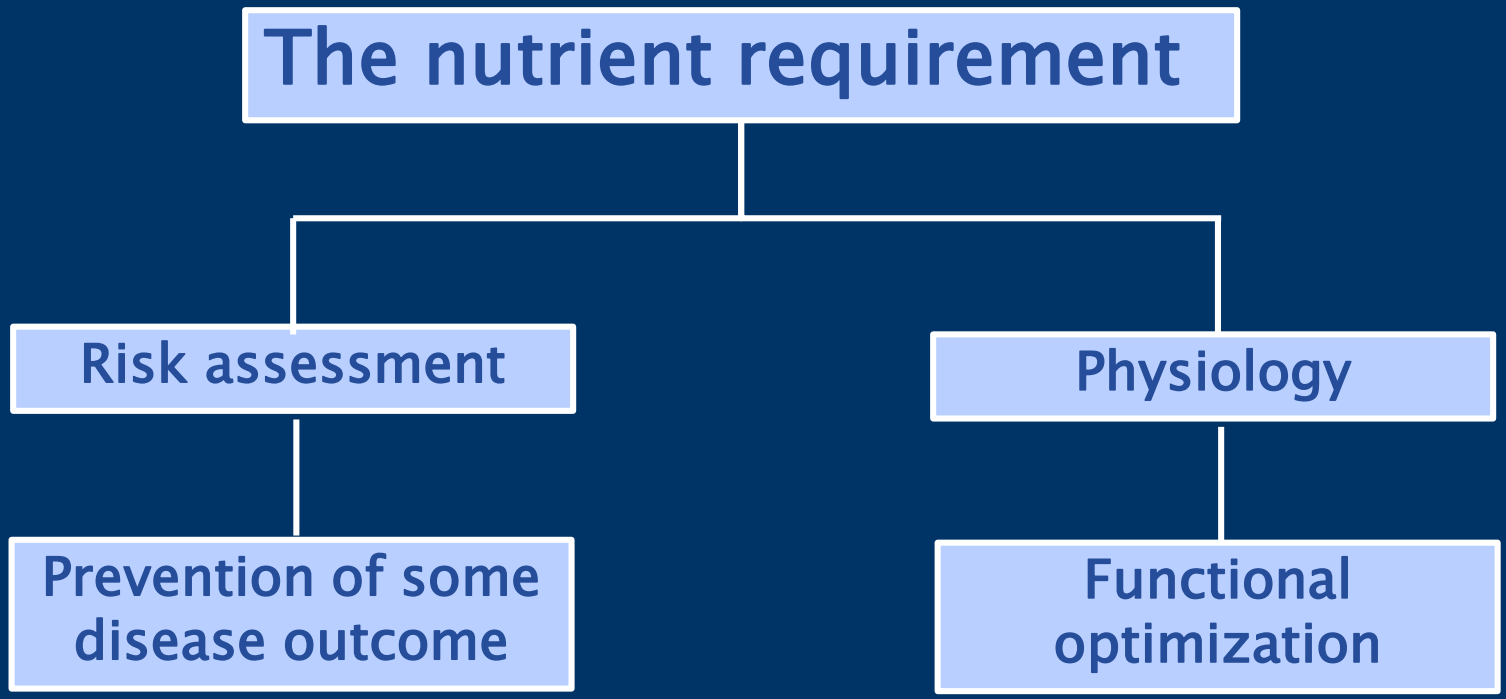
Shao and Mackay, 2010, Heaney 2010

DESIGNING NUTRIENT STUDIES

Robert P. Heaney, MD, FACP, FASN

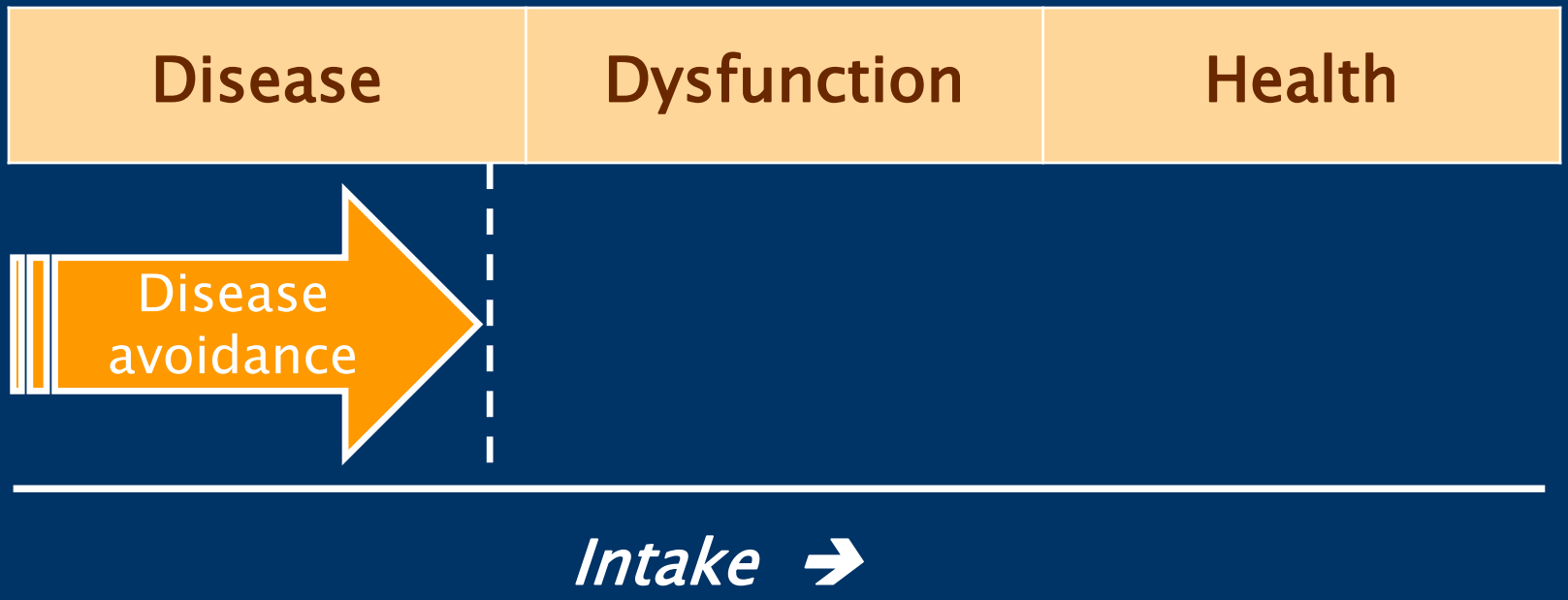
Creighton University Osteoporosis Research Center

TWO FRAMEWORKS:



DISEASE TO HEALTH CONTINUUM

"Health is more than the absence of disease"



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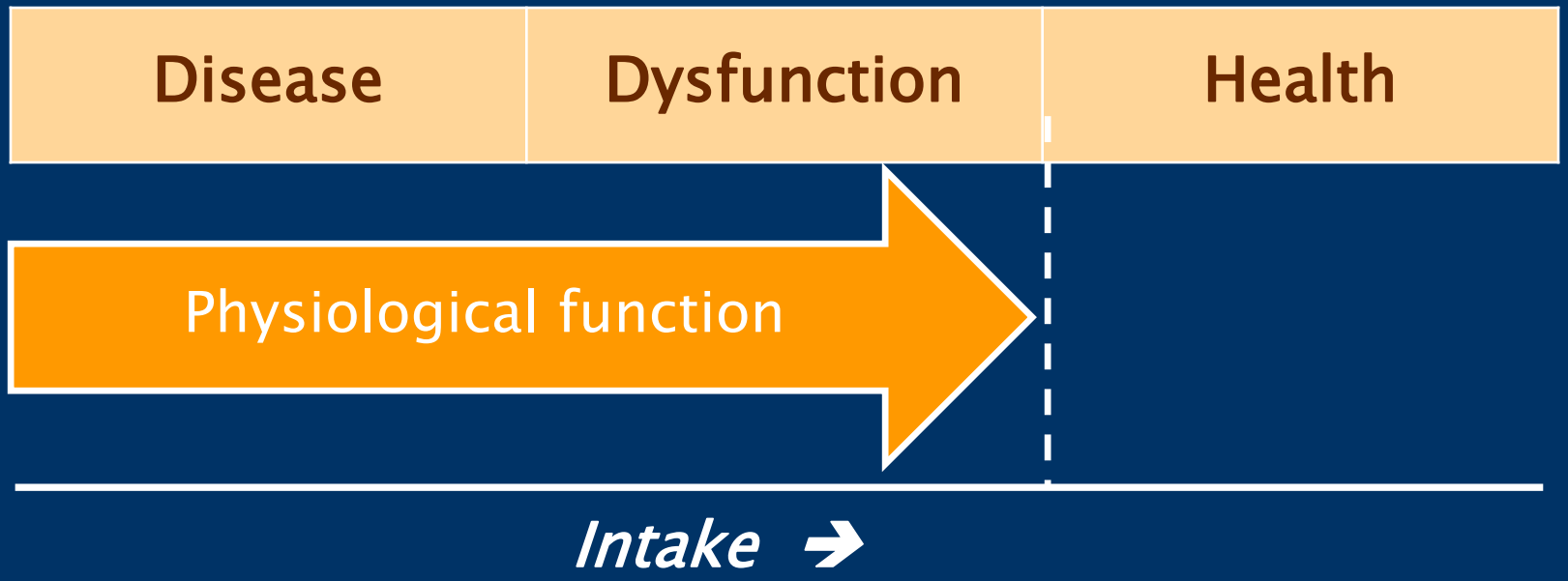


PHYSIOLOGICAL ENDPOINTS*

- setpoint feedback model
- primitive intake model
- plateau effect model
- homeostasis model
- support of a critical fun
- evolutionary mutation m

the point of

the intake to which

the intake needed

the intake that

the intake needed for a nutrient dependent function to occur

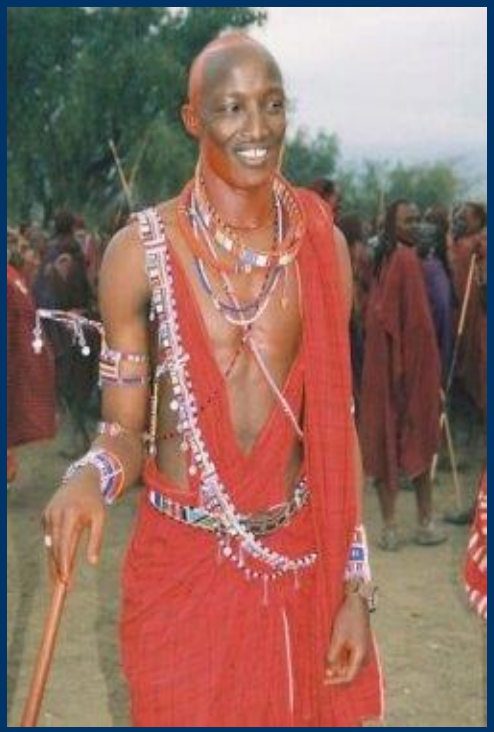
*Heaney, Nutr. Rev. 2012 70:165-169

PHYSIOLOGICAL CRITERIA – VITAMIN D

- a *physiological* requirement is the intake that:
  - calls for the least day-to-day adaptation or compensation
  - our bodies have been adapted to by natural selection
  - is needed to support one or more essential physiological functions

Matching the ancestral intake

NATIVE AFRICANS*



Masai
(pastoralists)

Hadza
(hunter-gatherers)

* Luxwolda et al., BJN 2011

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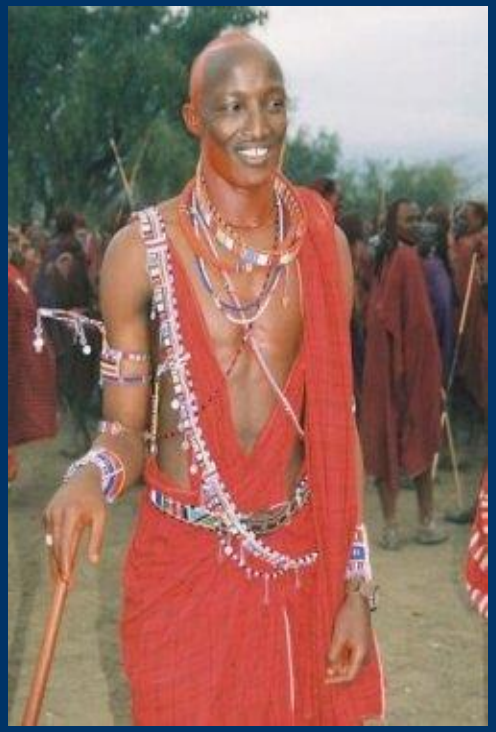


- Masai
- diet differs from the ancestral, but latitude, skin pigmentation, and skin exposure are the same as ancestral

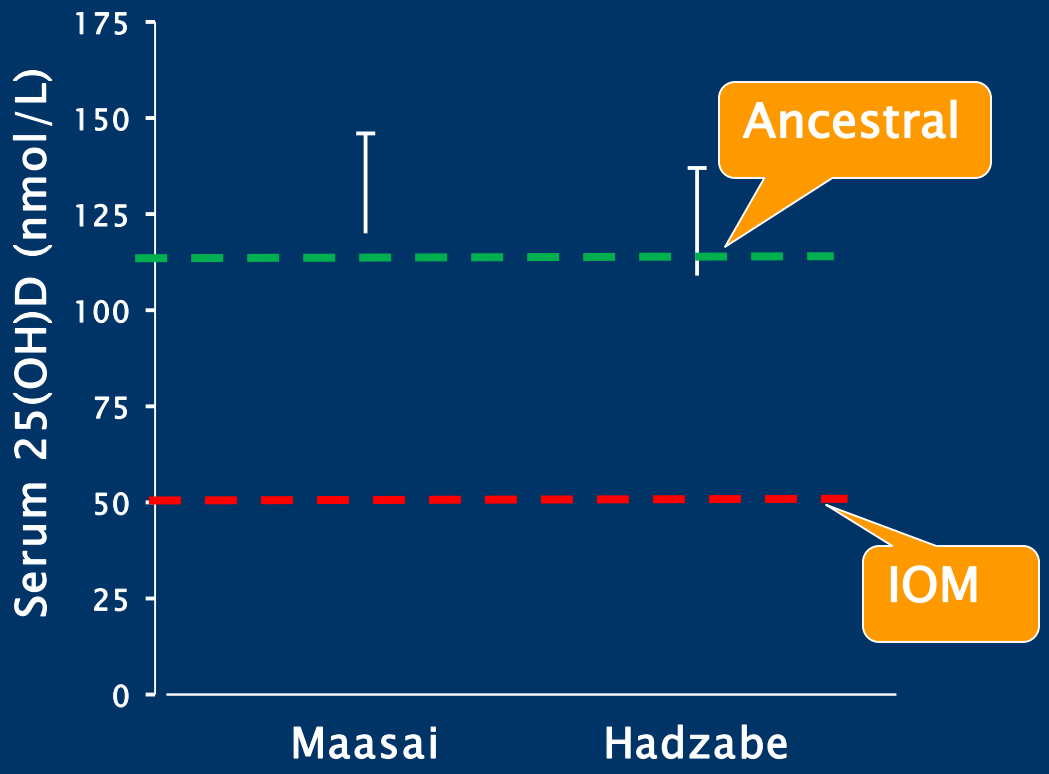
* Luxwolda et al., BJN 2011

NATIVE AFRICANS*

- Hadza (hunter-gatherers)
- diet, latitude, skin exposure, and skin pigmentation are all ancestral
- dubbed “the last of the first”

* Luxwolda et al., BJN 2011

NATIVE AFRICANS*



* Luxwolda et al., BJN 2011

Supporting a critical physiological function

LACTATION FACTS

- human milk is capable of providing all the vit. D (cholecalciferol) an infant needs
- 25(OH)D does not cross from blood into milk, while vit. D does
- but only if vit. D is present in maternal serum
- serum vit. D at prevailing intakes is close to zero
- it does not rise appreciably until the hepatic 25-hydroxylation reaction is saturated

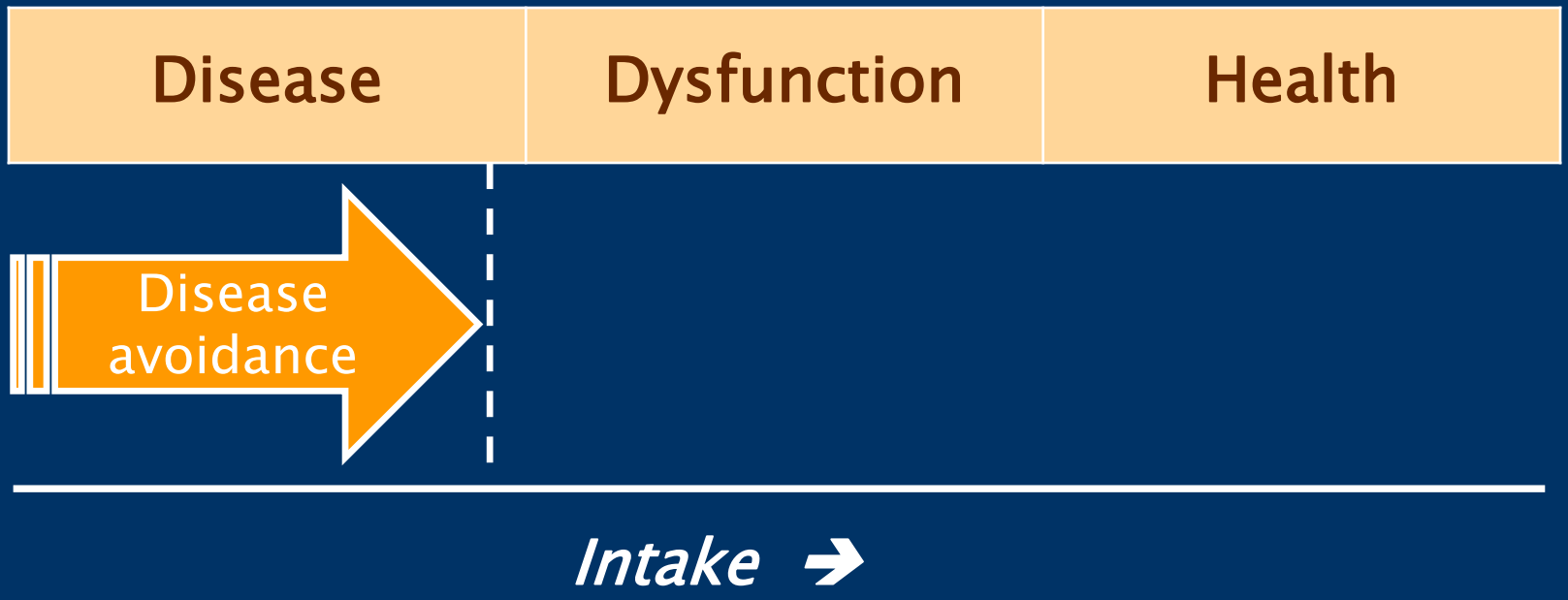
LACTATION NEED FOR D_3

- human milk D_3 concentration ≅ 28–44% serum D_3 concentration*
- to meet AAP recommendation for infants (400 IU/d) from breast milk, maternal serum D_3 would have to be about 12 ng/mL
- at that serum D_3 level, serum 25(OH)D would be ~50 ng/mL, which would require a D_3 input of 5,000–6000 IU/d
- at the IOM figure for 25(OH)D adequacy (20 ng/mL), no vitamin D gets into breast milk

*Hollis et al., (1986) JCEM

DISEASE TO HEALTH CONTINUUM

"Health is more than the absence of disease"



FEATURES OF A NUTRIENT STUDY

for a nutrient study to be informative:

- basal nutrient status must be determined and used as an inclusion criterion
- the change in intake must be large enough to change nutrient status meaningfully
- change in status must be quantified
- co-nutrient status must be optimized
- change in nutrient status, not change in intake, must be the independent variable in the hypothesis

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the study must be performed in truly deficient individuals

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- compliance must be optimized
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the dose must be big enough to make a difference

FEATURES OF A NUTRIENT STUDY

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- ch ange in int variable in the hypothesis

the change in nutrient status must be measured and reported

FEATURES OF A NUTRIENT STUDY

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- the change in intake must be large enough to change nutrient status meaningfully
- change in status must be quantified
- co-nutrient status must be optimized
- change in nutrient status must change in intake ... variable in the ...

the diet must be fully adequate in all other nutrients

BOTTOM LINE:

- **if these requirements are not – or cannot – be met, the resulting study may produce a null result – *even for an efficacious nutrient***

SUMMARY

- disease prevention & health optimization are not the same
- the latter requires more of a given nutrient than the former
- a physiology-based approach to nutrient requirements is grounded in what a nutrient actually does in the body
- efficacy studies of disease prevention must meet certain well-defined, but often ignored conditions.

GrassrootsHealth

Moving Research into Practice

Carole Baggerly, Director, GrassrootsHealth

GrassrootsHealth--Bridging the Gap

- **17+ years to get research into practice**
  - **Too big a gap between basic research and clinical practice**
- **New Population Research Model Necessary**
  - **Consumer Oriented (large population)**
  - **Safety testing in large groups**
  - **Health outcomes/nutrient measures documented**
  - **Research published *to* consumers AND in scientific journals**

GrassrootsHealth--Bridging the Gap Method with D*action Project

- Internet based, open to *everyone*
- 'Intervention' is education, vitamin D testing
- Capture health information, from standard demographics to many behaviors (exercise, sun exposure) to health outcomes
- Report My Data-My Answers
- Publish in peer-reviewed journals

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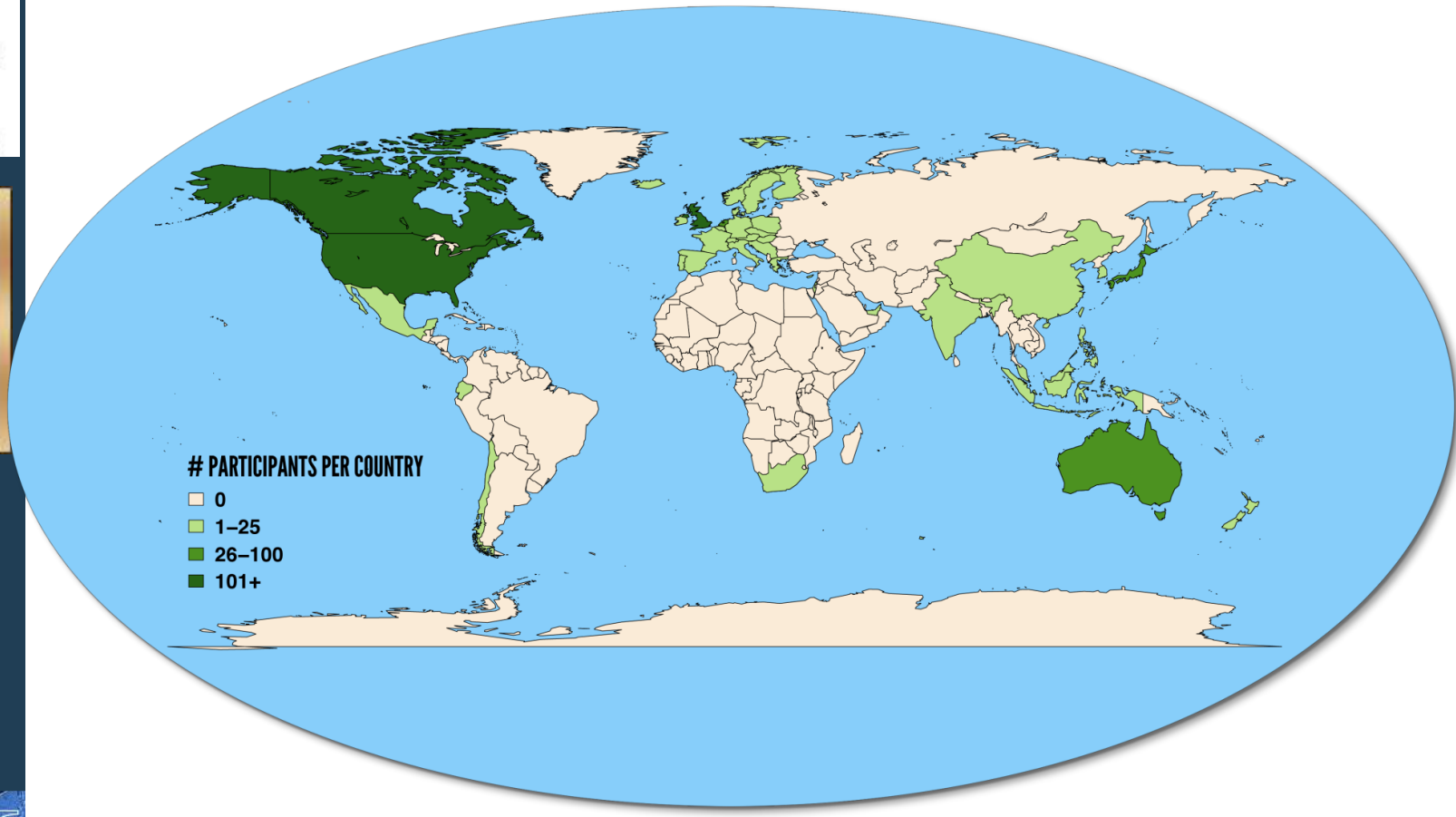
Who participates?



GrassrootsHealth--Bridging the Gap Significant Successes

- Enrollment worldwide, >10,000 people
- Average serum level >40 ng/ml
- Videos/Education
  - 250,000 views disease prevention
  - 210,000 views cancer prevention
- Publications in Peer Reviewed Journals

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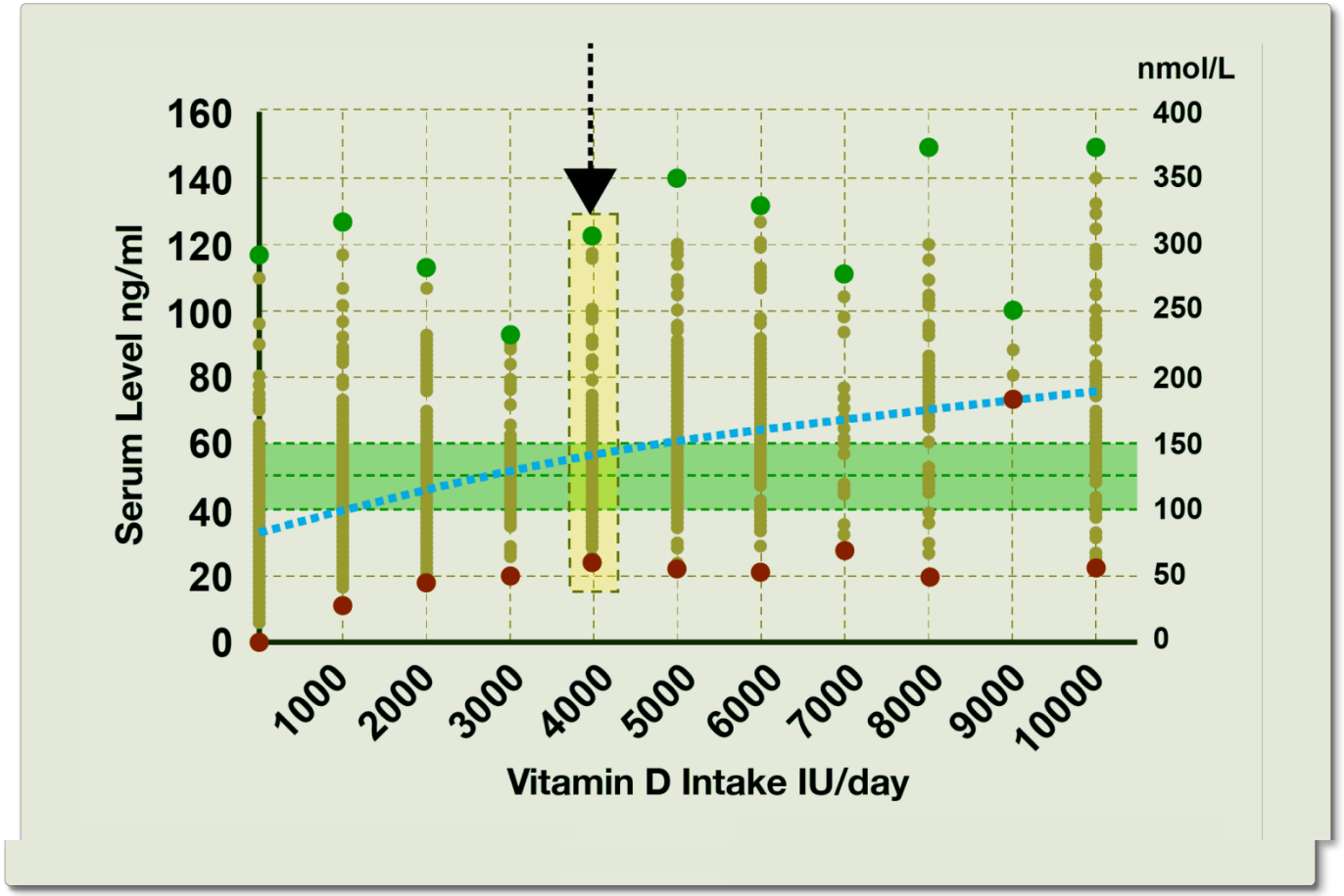
How much (D) do I take?



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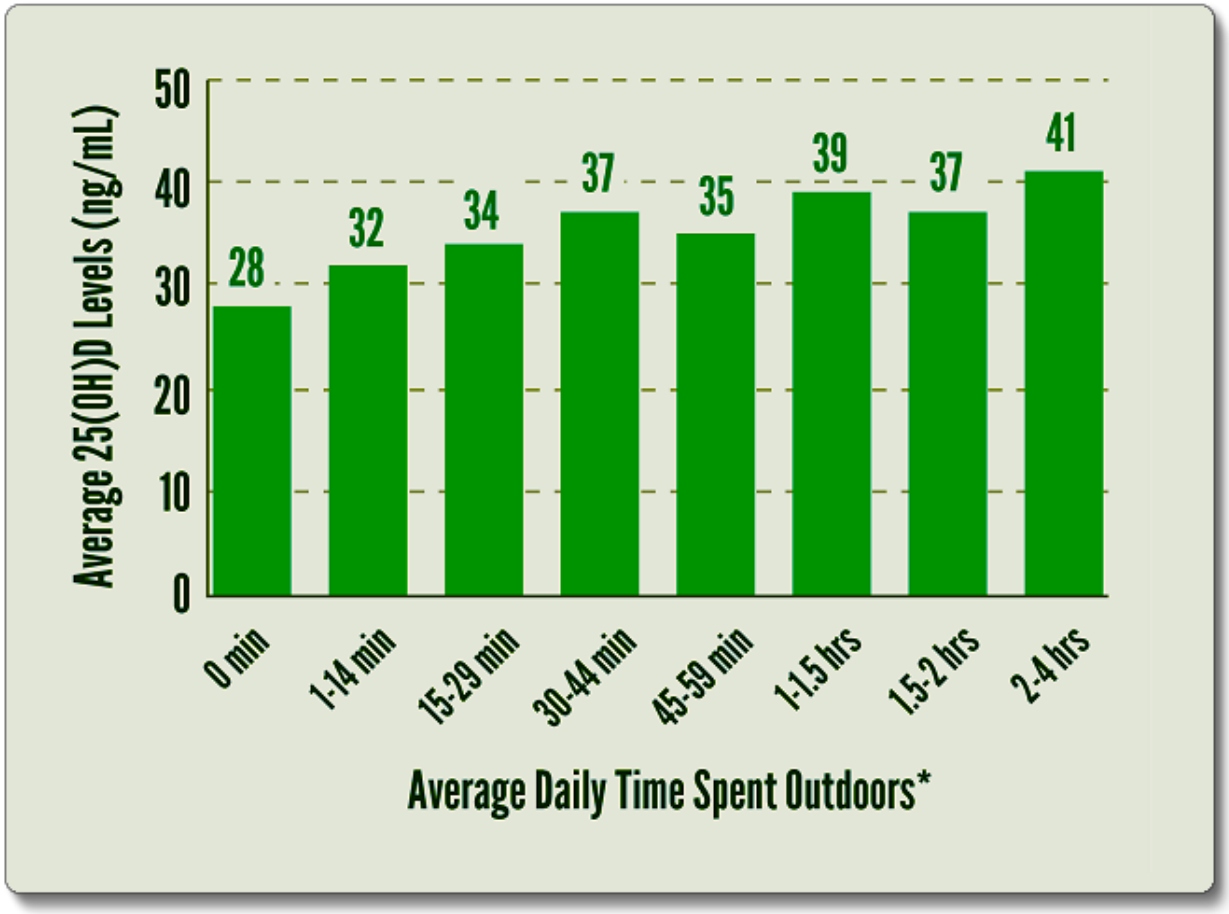
How long do I stay in the sun to achieve a specific serum level?



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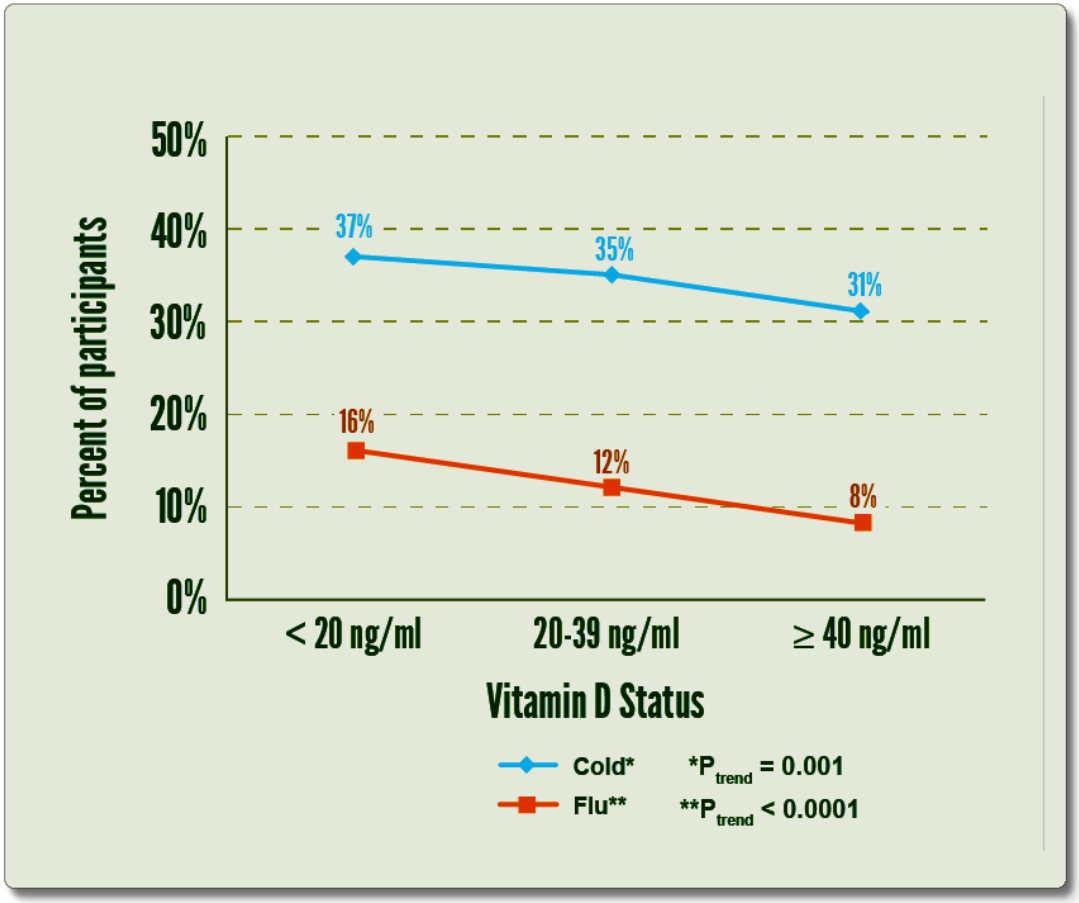
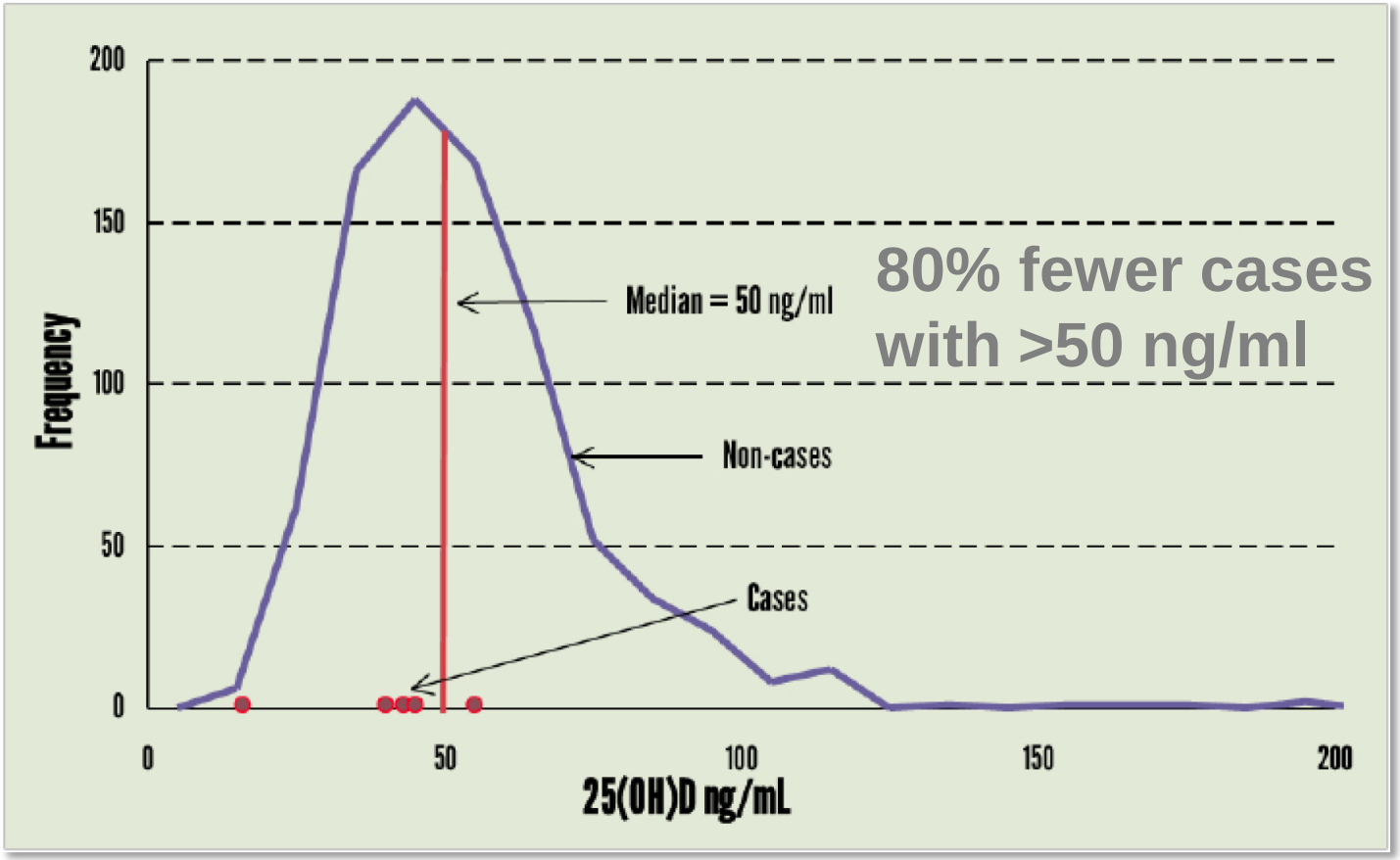
Can Vitamin D prevent flu/colds?



16% < colds

50% < flu

Might Vitamin D prevent breast cancer?



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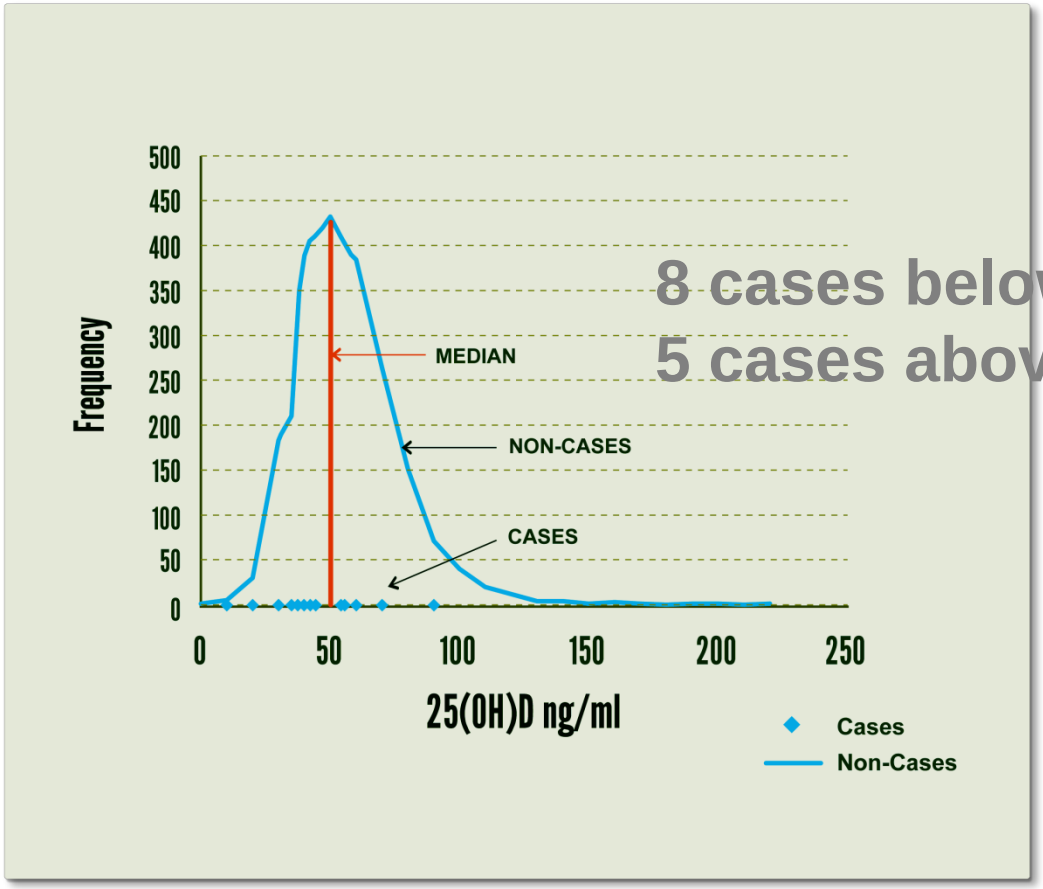
Does Vitamin D cause kidney stones?



8 cases below 50 ng/ml
5 cases above

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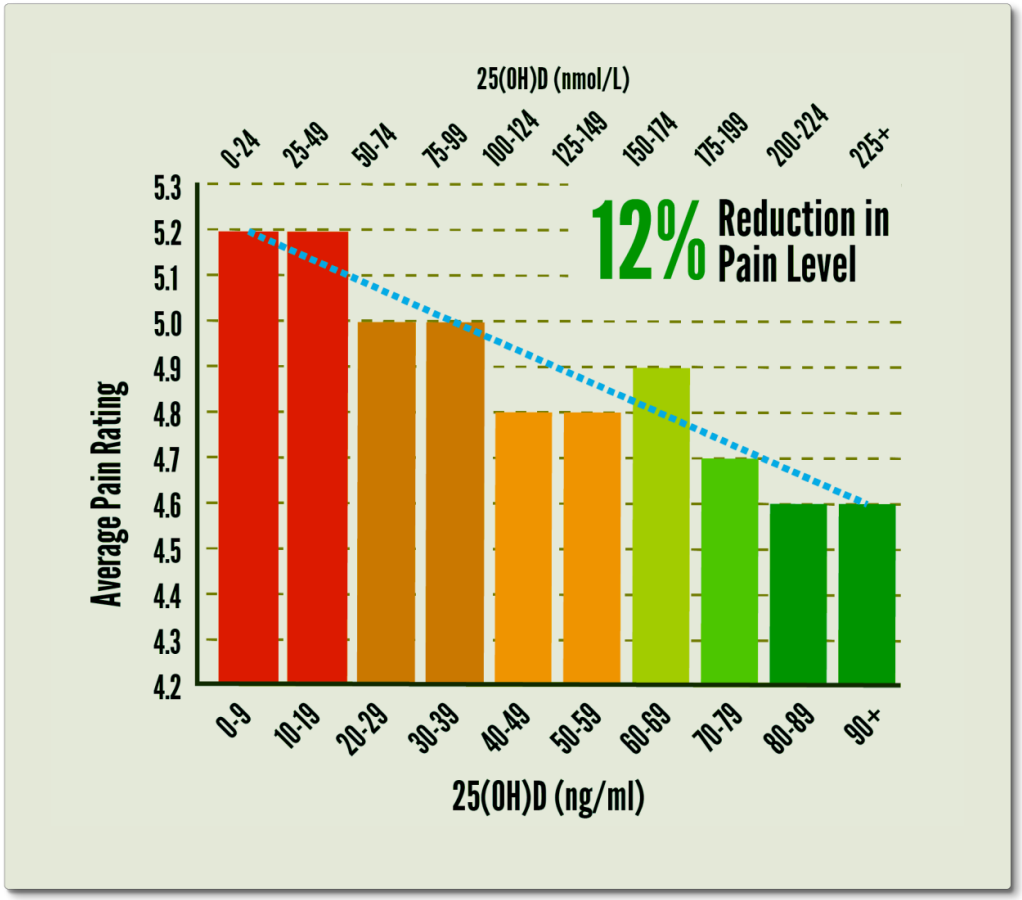
Can Vitamin D help my pain?



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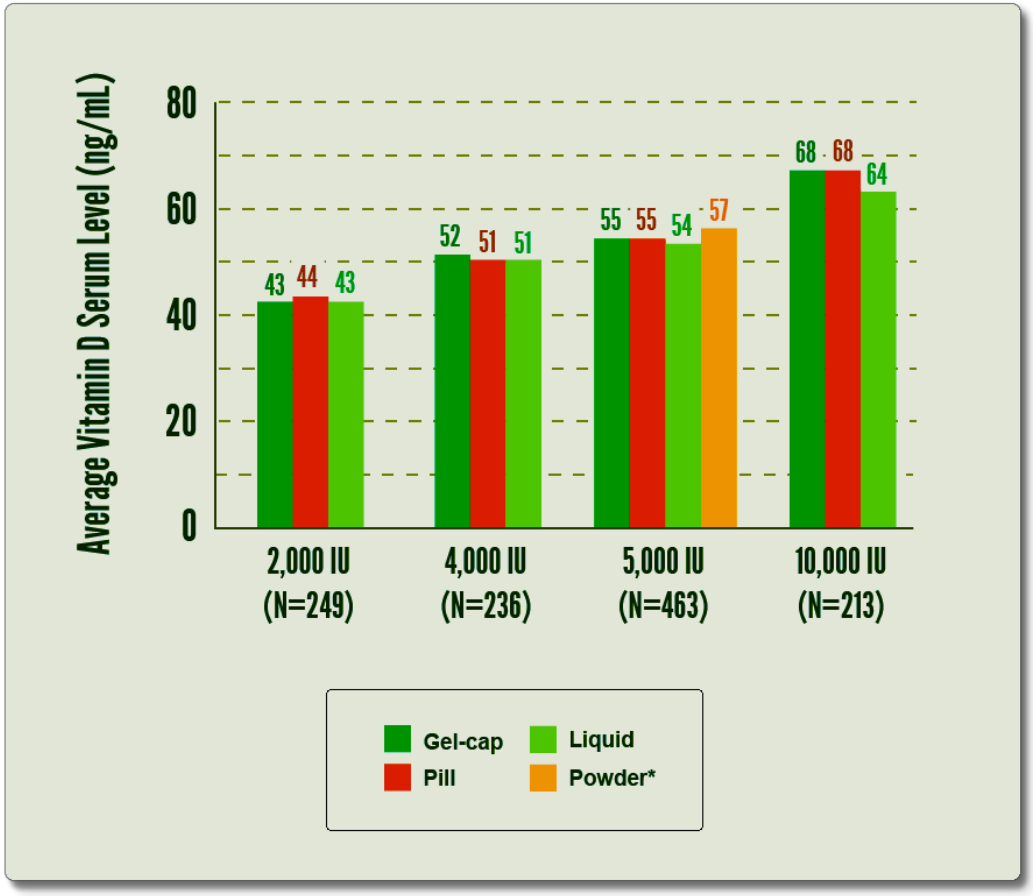
Does it matter which type of supplement I take?



Next Steps--Major Themed Projects

- **Protect our Children NOW!**
  - **To DEMONSTRATE for a community that results of a randomized trial apply to a large community base**
    - **500 pregnant women per community**
    - **12-17 weeks pregnant**
    - **Vitamin D testing 3x during pregnancy**
    - **Supplementation to reach 40 ng/ml minimum**
    - **Health outcomes measured**
    - **Publication/public health promotion in about 24 months, action!**
    - **Initiation in Charleston, SC; next Chicago, Alaska**

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Future Initiatives in Nutrition Research with Organic & Natural

- Interactions of multiple nutrients on health outcomes, e.g., vitamins D, K, C, A
- Key population groups, e.g., 'Conscious Elders' with targeted health outcomes such as falls, fractures; pain, heart attacks with nutrient sufficiency vs deficiency
- Targeted markets, e.g., Distributors, Medical Offices, Retail—What is needed to expand nutrient health?

Getting Started

- Choose a target group, area of need, benefit
- GrassrootsHealth to define project, provide quote for any custom project
- Funding is phased over duration of project

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GrassrootsHealth
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Questions & Answers

Additional Questions?

Karen Howard
khoward@organicandnatural.org
t 202.660.1345
http://organicandnatural.org/

Todd A. Harrison, Esq.
TAHarrison@Venable.com
t 202.344.4724
www.Venable.com

Carole Baggerly
carole@grassrootshealth.org
t 619.823.7062
www.grassrootshealth.net

Dr. Robert P. Heaney
rpheaney@creighton.edu
t 402.280.4029
http://blogs.creighton.edu/heaney/