2-29-2020

Vitamin D for Skeletal & Non-Skeletal Health: Myths, Hype & Facts

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Henry Ford Health System, srao1@hfhs.org

Vitamin D for Skeletal & Non-Skeletal Health

Myths, Hype & Facts

7th HFH Osteoporosis & Bone & Mineral Symposium

Saturday, February 29th, 2020

Troy Marriott

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Section Head, Bone & Mineral Metabolism

Director, Bone & Mineral Research Laboratory

Disclosures

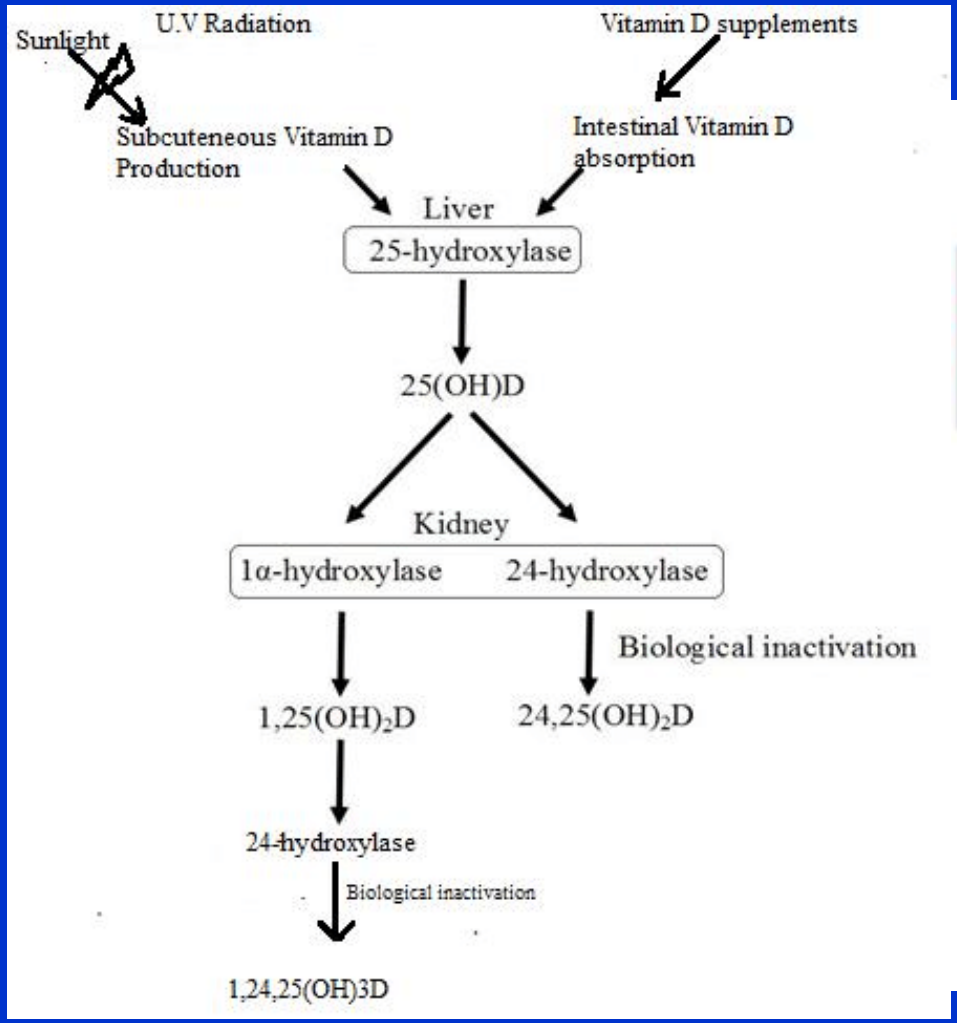
- Grant Supports: NIH, DoD, & Radius Health
- I am not on any speaker's bureaus
- *I will not discuss proprietary, off label or investigational uses.*
- *I serve on an Advisory Board for DiaSorin Inc.*

Objectives

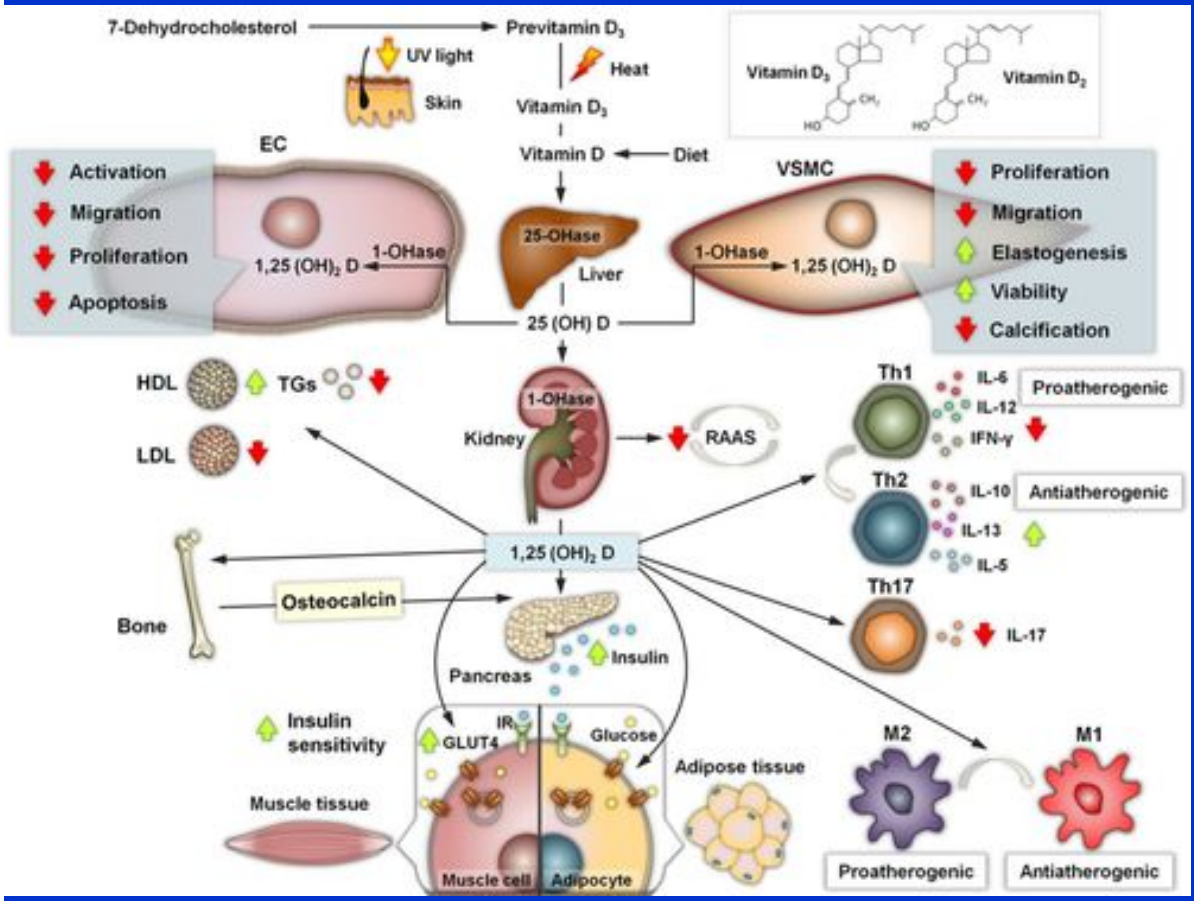
- Review of vitamin D production, metabolism & functions
- Definitions of deficiency, insufficiency, & sufficiency
- Current “State of vitamin D nutrition” in populations
- Role of vitamin D in Bone & Mineral Disorders
- Role of vitamin D in Non-Skeletal Health
- Assessment of vitamin D nutrition
- Vitamin D repletion strategies
- Vitamin D toxicity
- Concluding Remarks
- Comments & Questions

Vitamin D Metabolism & Its Functions

When I graduated from medical school, things were quite simple

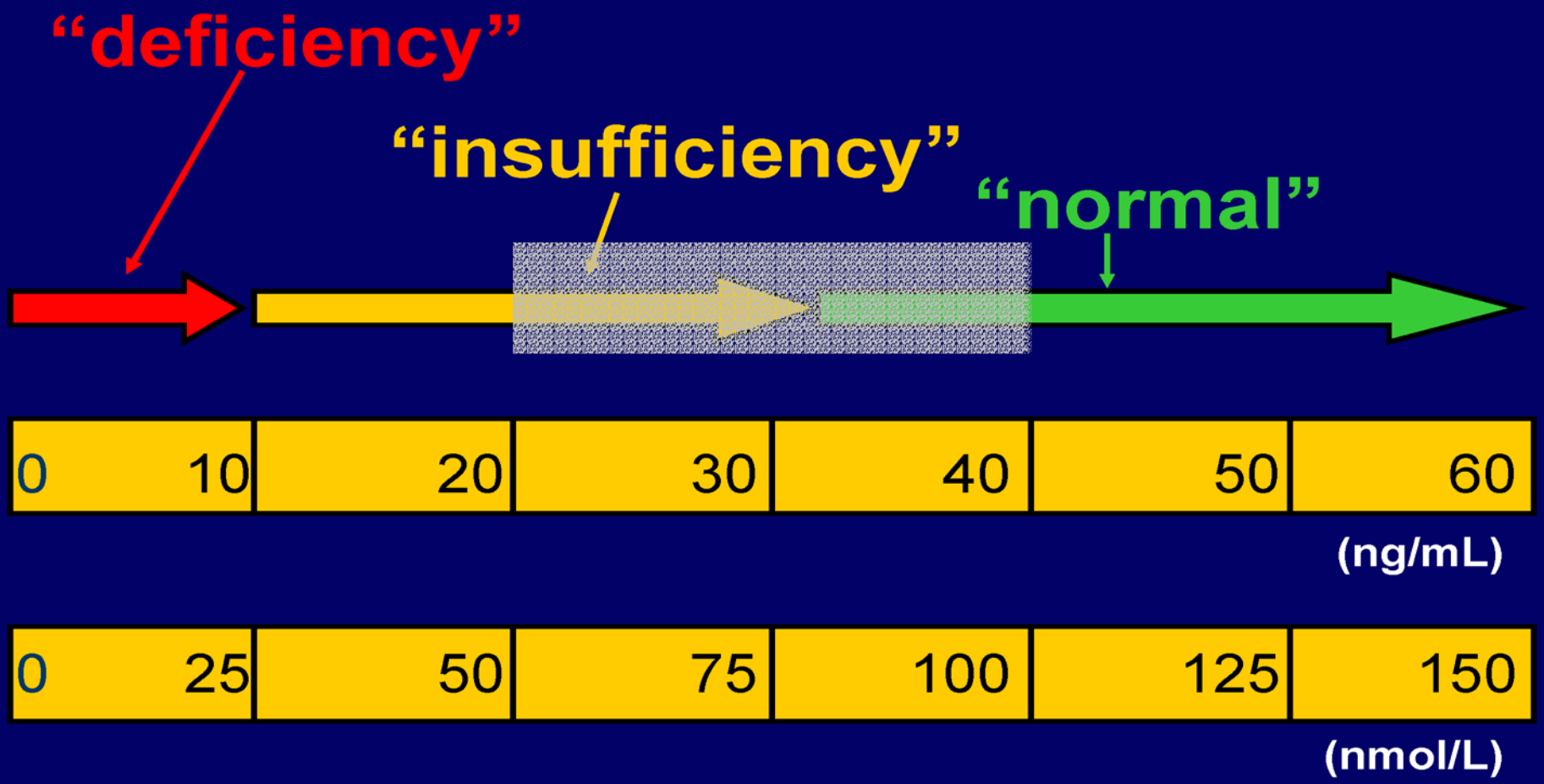


But became quite complex since!



The 25(OH)D Continuum Controversy

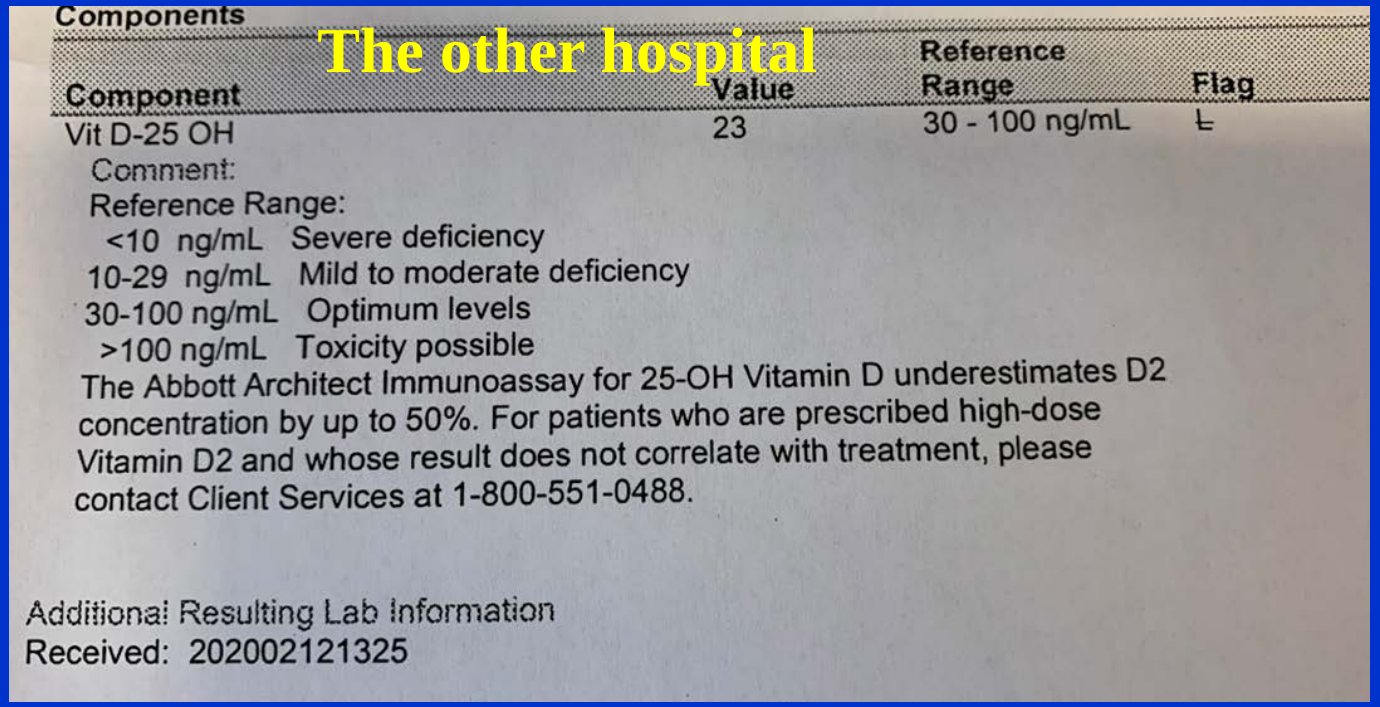
How do we define Vitamin D Nutritional Adequacy



1. Boonen S et al. *Osteoporos Int.* 2004;15:511–519.
2. Lips P. *Endocr Rev.* 2001;22:477–501.
3. Heaney RP. *Osteoporos Int.* 2000;11:553–555.
4. Heaney RP. *Am J Clin Nutr.* 2004;80(suppl):1706S-1709S.
5. Thomas MK. *N Engl J Med.* 1998;338:777–783.

How do labs define vitamin D nutritional status?

Resulting lab: HENRY FORD HOSPITAL LABORATORY
Reference range: >20 ng/mL Value: 32
Comment: Vitamin D deficiency < 10 ng/mL
Vitamin D insufficiency 10 to 20 ng/mL
Vitamin D toxicity (possible) >150 ng/mL



Components

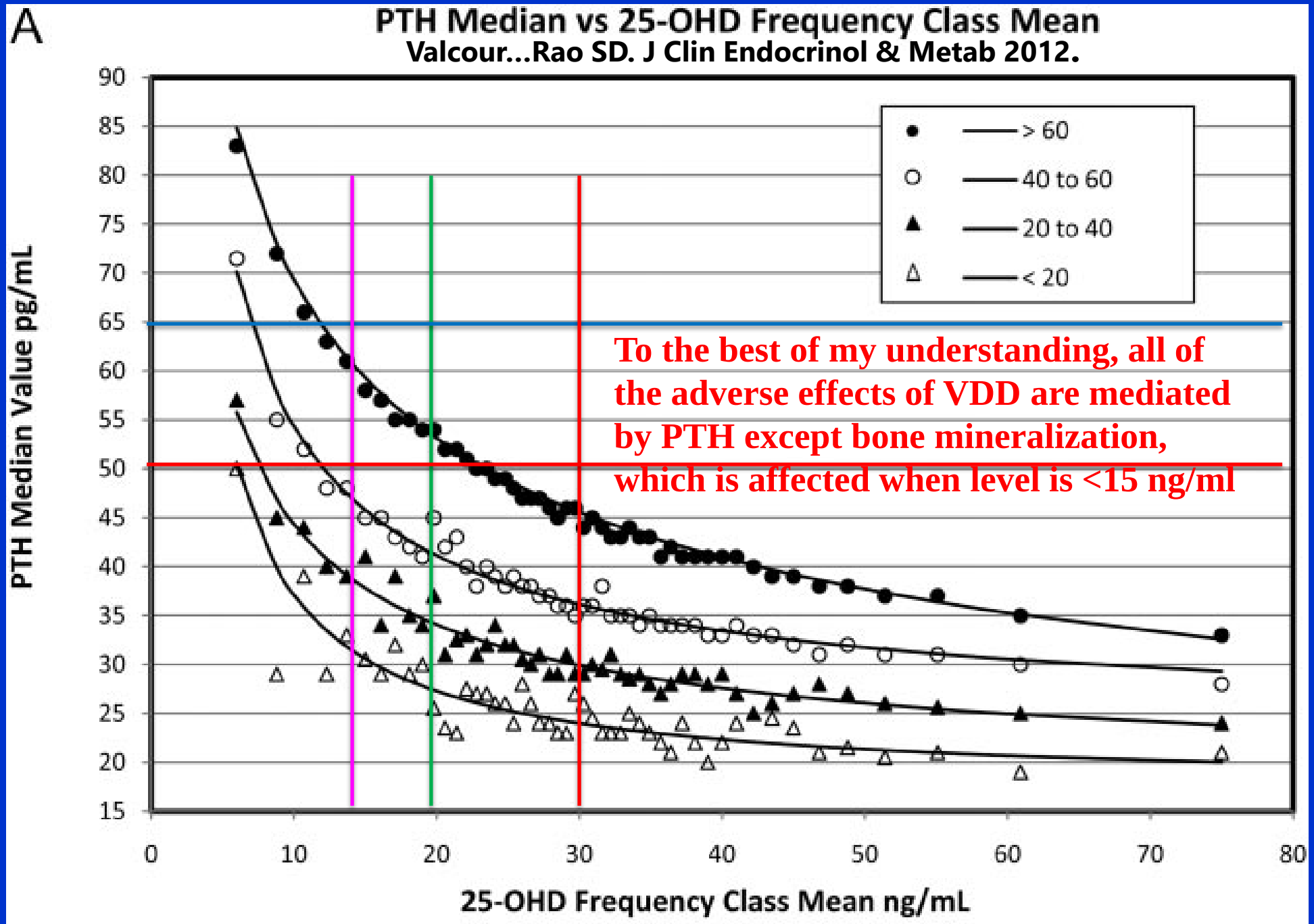
The other hospital

Component	Value	Reference Range	Flag
Vit D-25 OH	23	30 - 100 ng/mL	L

Comment:
Reference Range:
<10 ng/mL Severe deficiency
10-29 ng/mL Mild to moderate deficiency
30-100 ng/mL Optimum levels
>100 ng/mL Toxicity possible
The Abbott Architect Immunoassay for 25-OH Vitamin D underestimates D2 concentration by up to 50%. For patients who are prescribed high-dose Vitamin D2 and whose result does not correlate with treatment, please contact Client Services at 1-800-551-0488.

Additional Resulting Lab Information
Received: 202002121325

A


PTH Median vs 25-OHD Frequency Class Mean
Valcour...Rao SD. J Clin Endocrinol & Metab 2012.
PTH Median Value pg/mL
25-OHD Frequency Class Mean ng/mL
> 60
40 to 60
20 to 40
< 20
To the best of my understanding, all of the adverse effects of VDD are mediated by PTH except bone mineralization, which is affected when level is <15 ng/ml

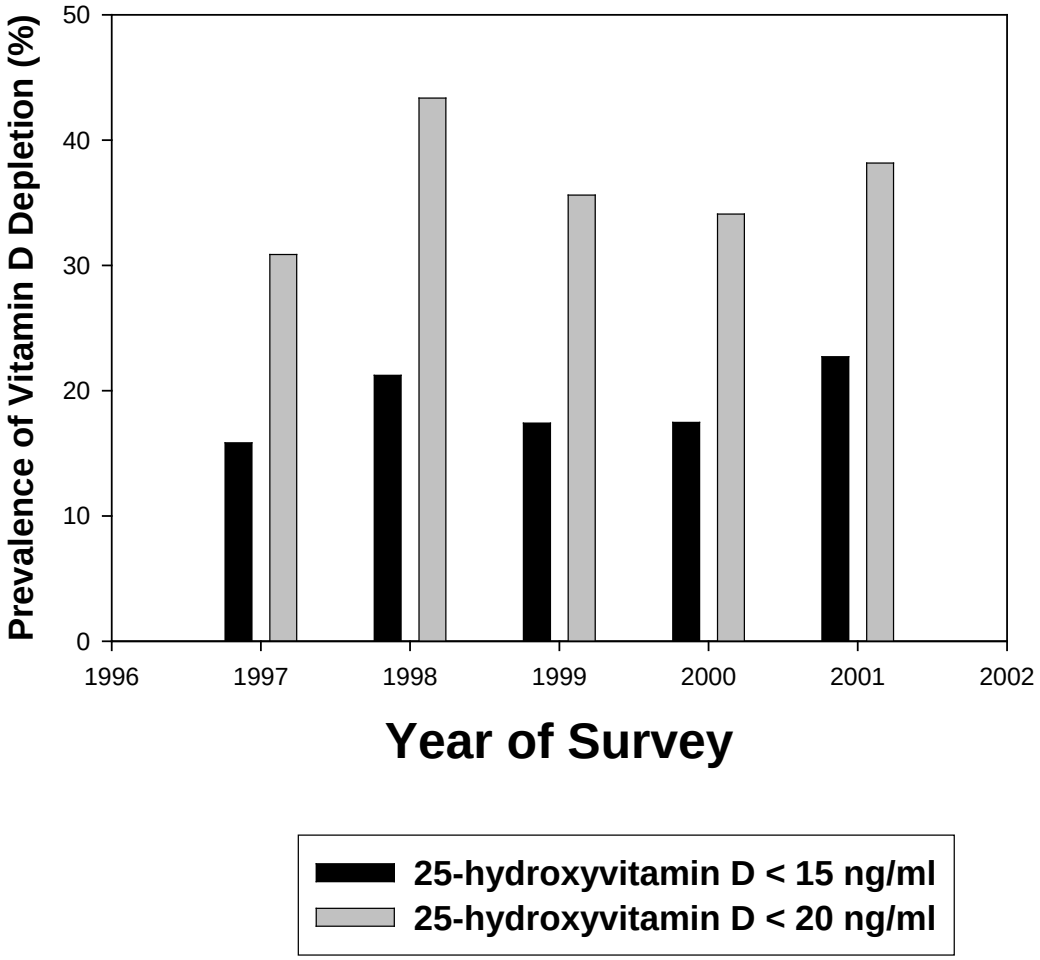
Role of vitamin D in Skeletal Health

- Patients with osteoporosis before and during treatment
- VDN & hip fracture risk relationship
- VDN & muscle strength relationship
- Patients with primary hyperparathyroidism
- Patients with secondary hyperparathyroidism)

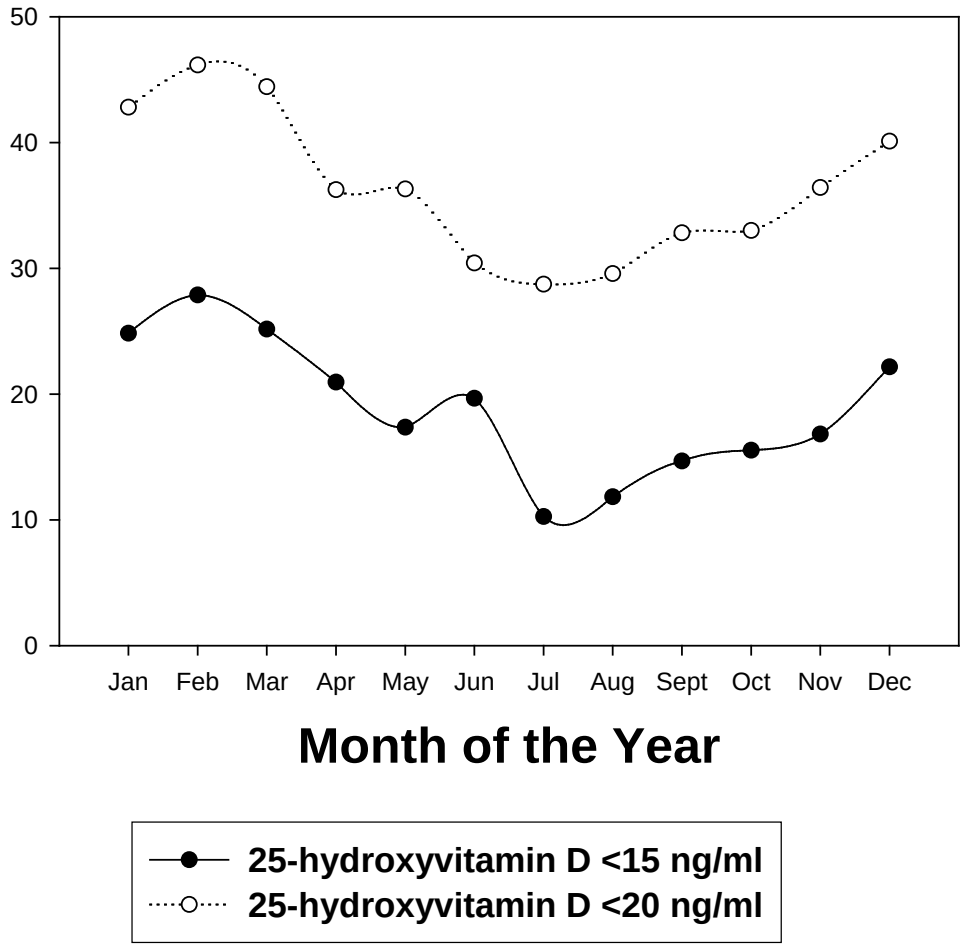
Prevalence of VDD among women before receiving OP-Rx

Guardia…Rao et al, Osteoporosis International 2008

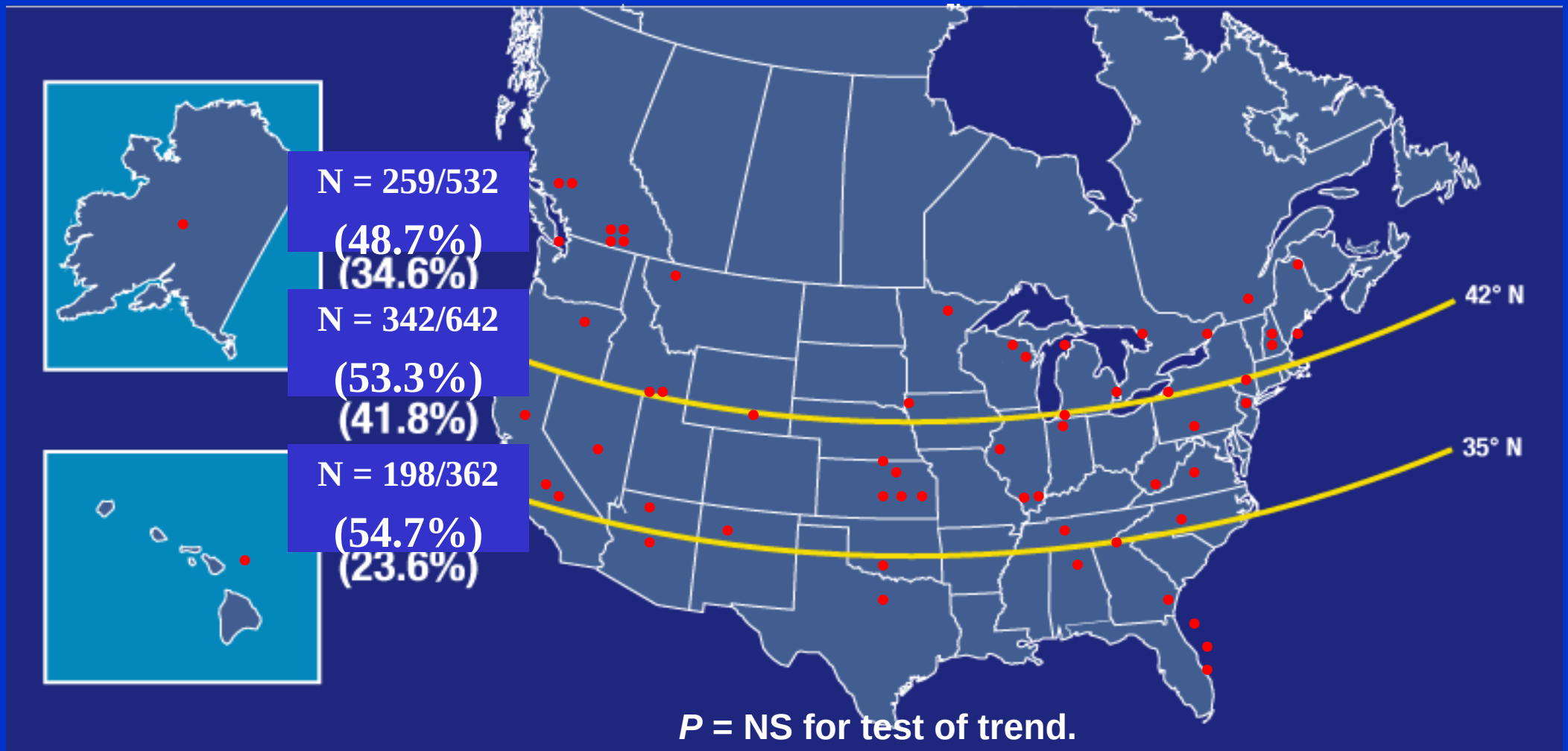
Prevalence of Vitamin D Depletion According to Year of Survey



Prevalence of Vitamin D Depletion According to Calendar Months of the Year



VDN Status (<30 ng/ml) in women receiving OP-Rx Across all latitudes in the US



Holick MF et al. *J Clin Endocrinol Metab*. 2005;90:3215–3224.

Does vitamin D prevent fractures?

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

A Pooled Analysis of Vitamin D Dose Requirements for Fracture Prevention

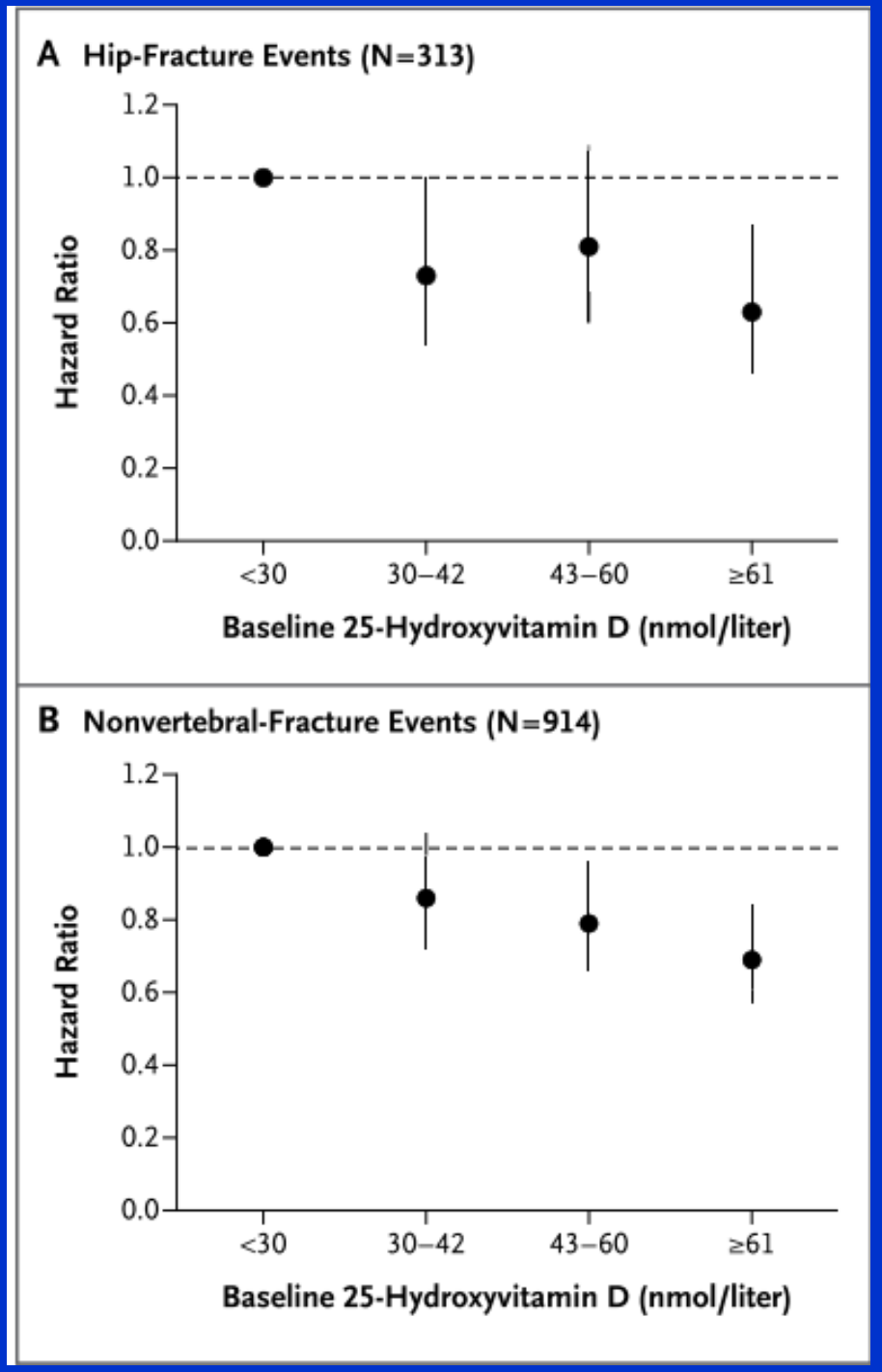
Heike A. Bischoff-Ferrari, M.D., Dr.P.H., Walter C. Willett, M.D., Dr.P.H.,

CONCLUSIONS

High-dose vitamin D supplementation (≥800 IU daily) was somewhat favorable in the prevention of hip fracture and any nonvertebral fracture in persons 65 years of age or older. (Funded by the Swiss National Foundations and others.)

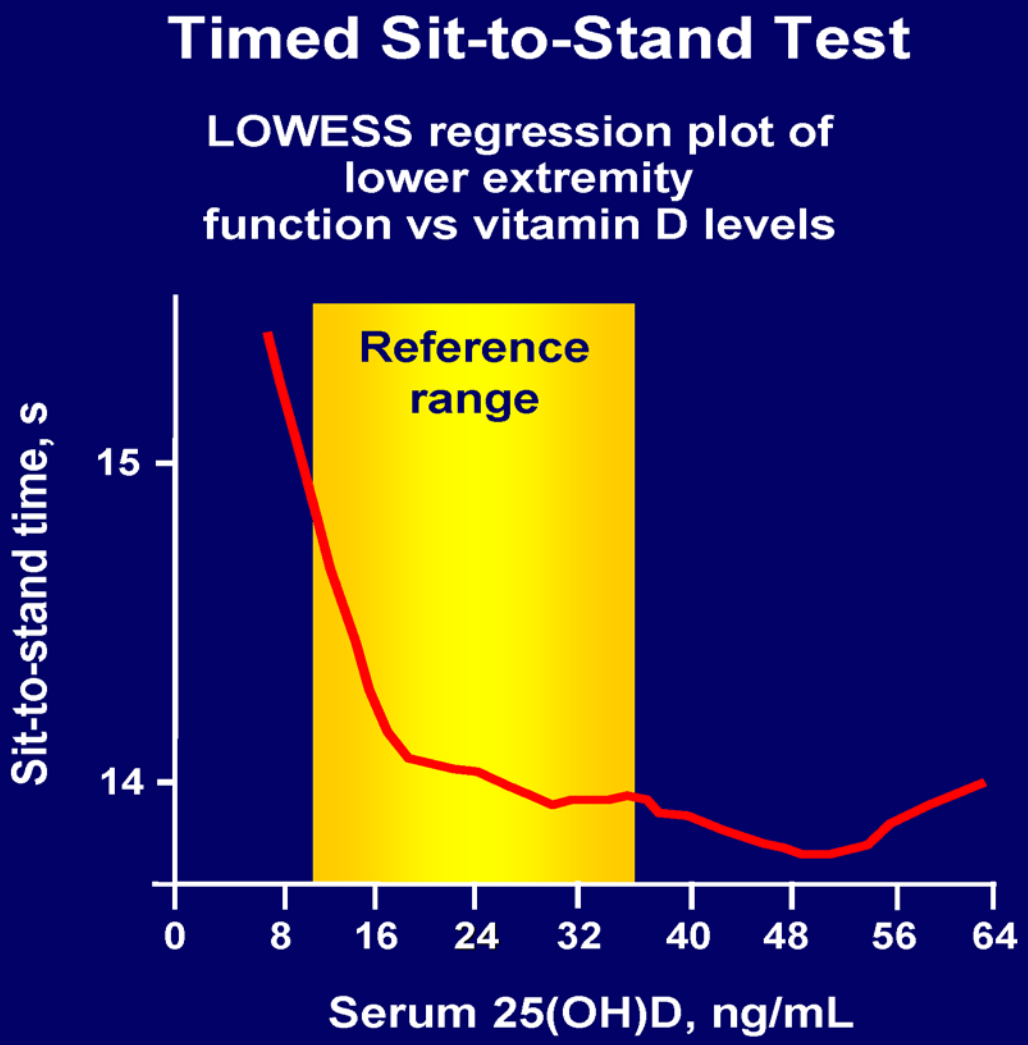
Vitamin D Supplementation in Older Adults: is the hype definitely over? Bischoff-Ferrari HA. Dtsch Med Wochenschr. 2019 Aug;144(15):1018-1021

Based on critical review of the 4 meta-analyzes 2016-2019 vitamin D with or without Ca is still useful in older adults (>65y), with an increased risk of VDD & increased fracture risk.



Higher 25(OH)D Levels Are Associated With Better Lower Extremity Function in Ambulatory Women

- 4,100 ambulatory adults included in NHANES III
- 60 to ≥90 years
- Functional measurements used to assess lower extremity function:
  - 8-ft walking speed test
  - Timed sit-to-stand test



LOWESS = locally weighted regression plot.

Reference range of 22.5–94.0 nmol/L (9.0–37.7 ng/mL).

N = 4,100; $P<0.001$.

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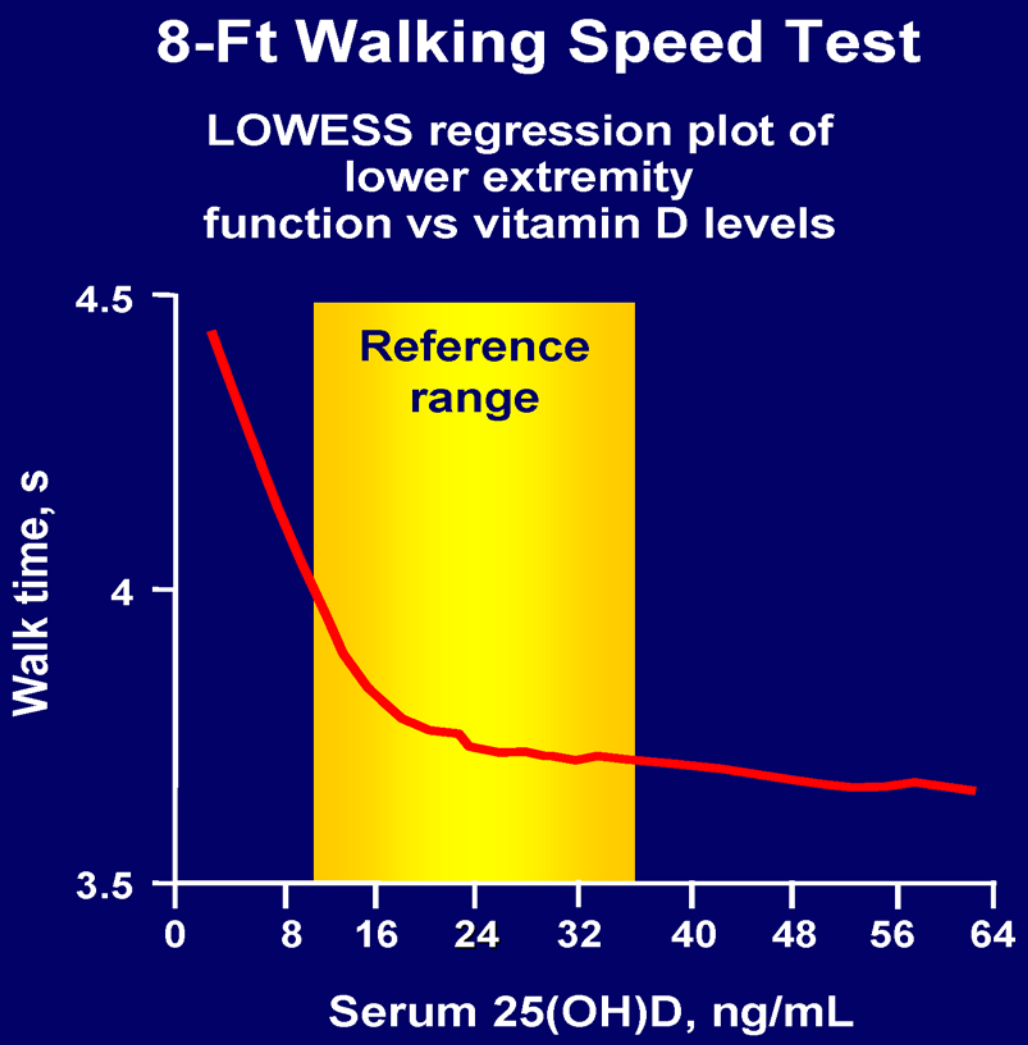


LOWESS = locally weighted regression plot.

Reference range of 9.0–37.7 ng/mL(22.5–94.0 nmol/L).
N = 4,100; *P*<0.001.

Role of Vitamin D In Hip Fracture Prevention

STRENGTH OF BONE

Bone Turnover

Bone Mass

Bone Quality

Fall-Related Trauma

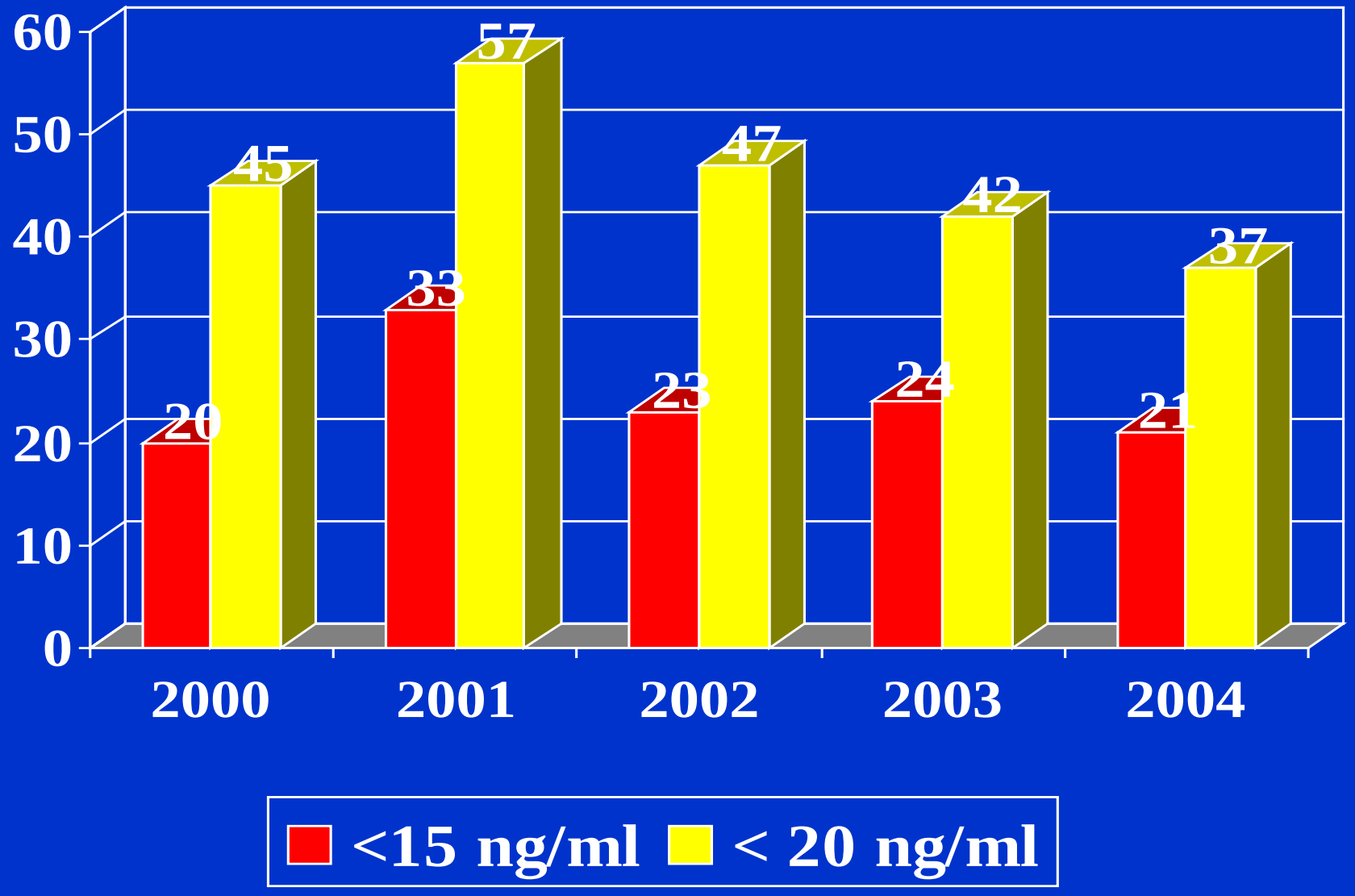
Risk of Fall
Neuromuscular Function
Environmental Hazards
Time Spent at Risk

Force of Impact
Type of Fall
Protective Responses
Energy Absorption

Adequate Calcium & Vitamin D Nutrition

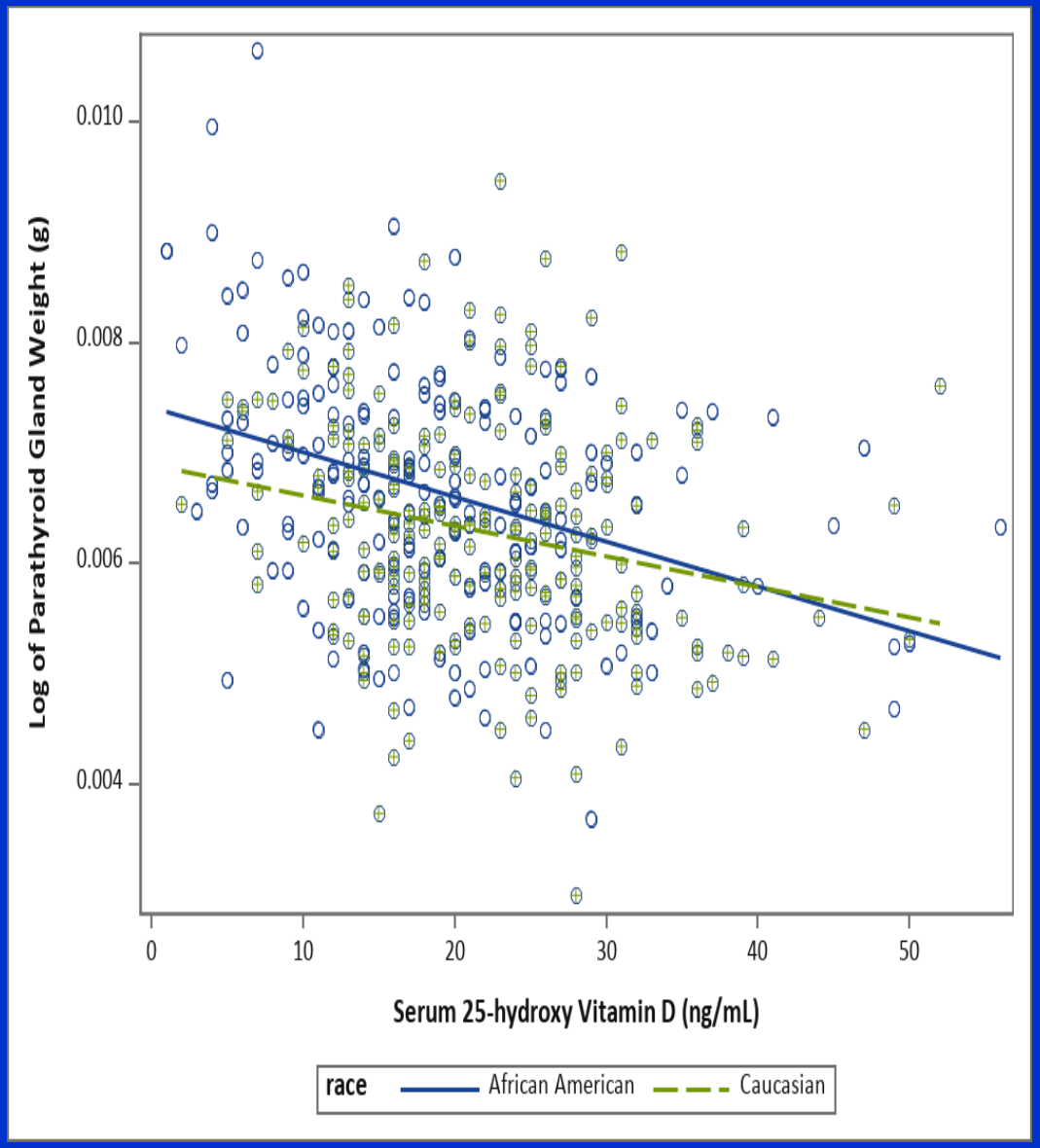
Prevalence (%) of Vitamin D Depletion in PHPT

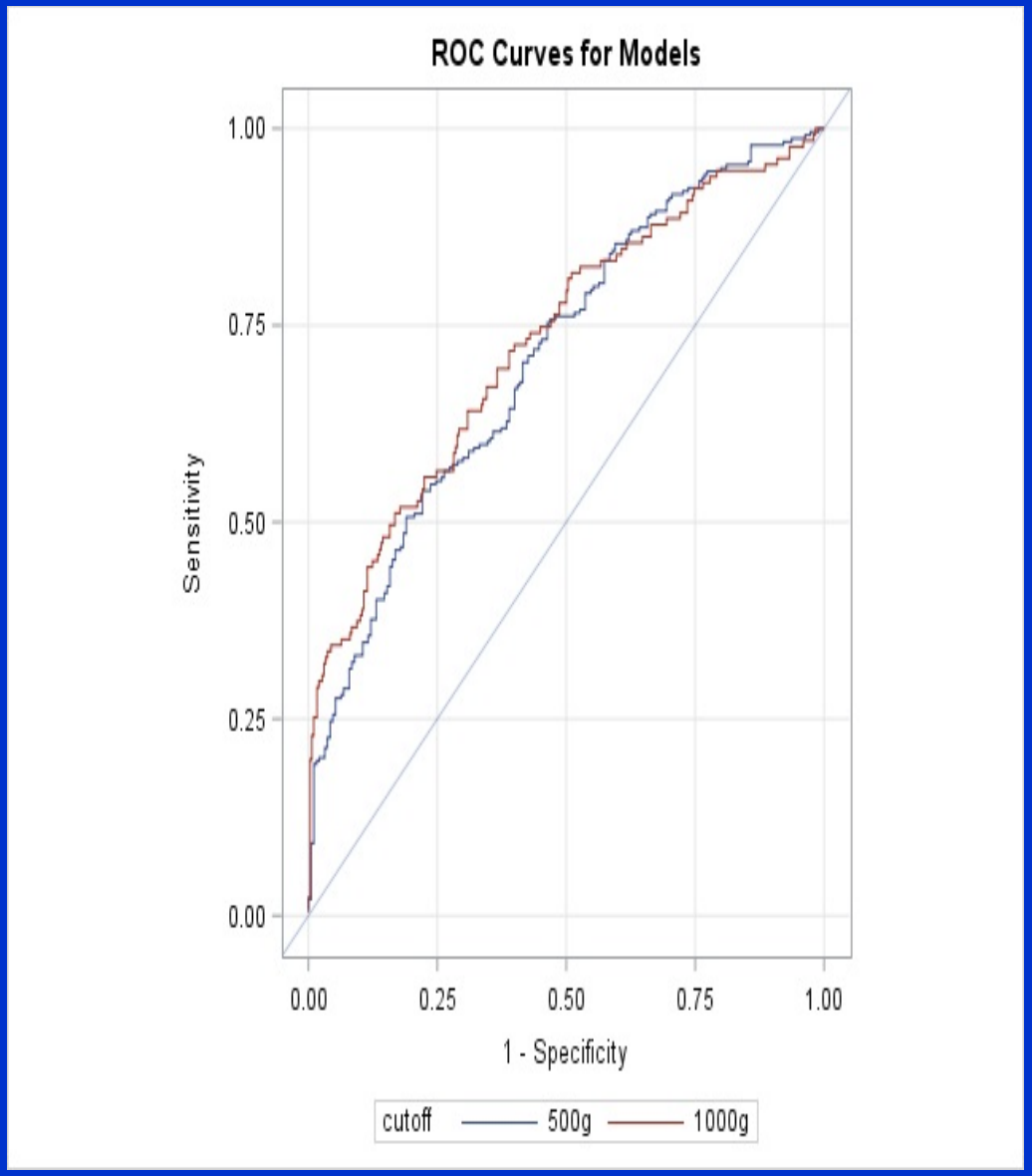
(Rao et al ASBMR, Cincinnati, 2005)



Relationship between VDN and Parathyroid Tumor weight

(Rao et.al., Steroid Biochem Mol Biol (in press)

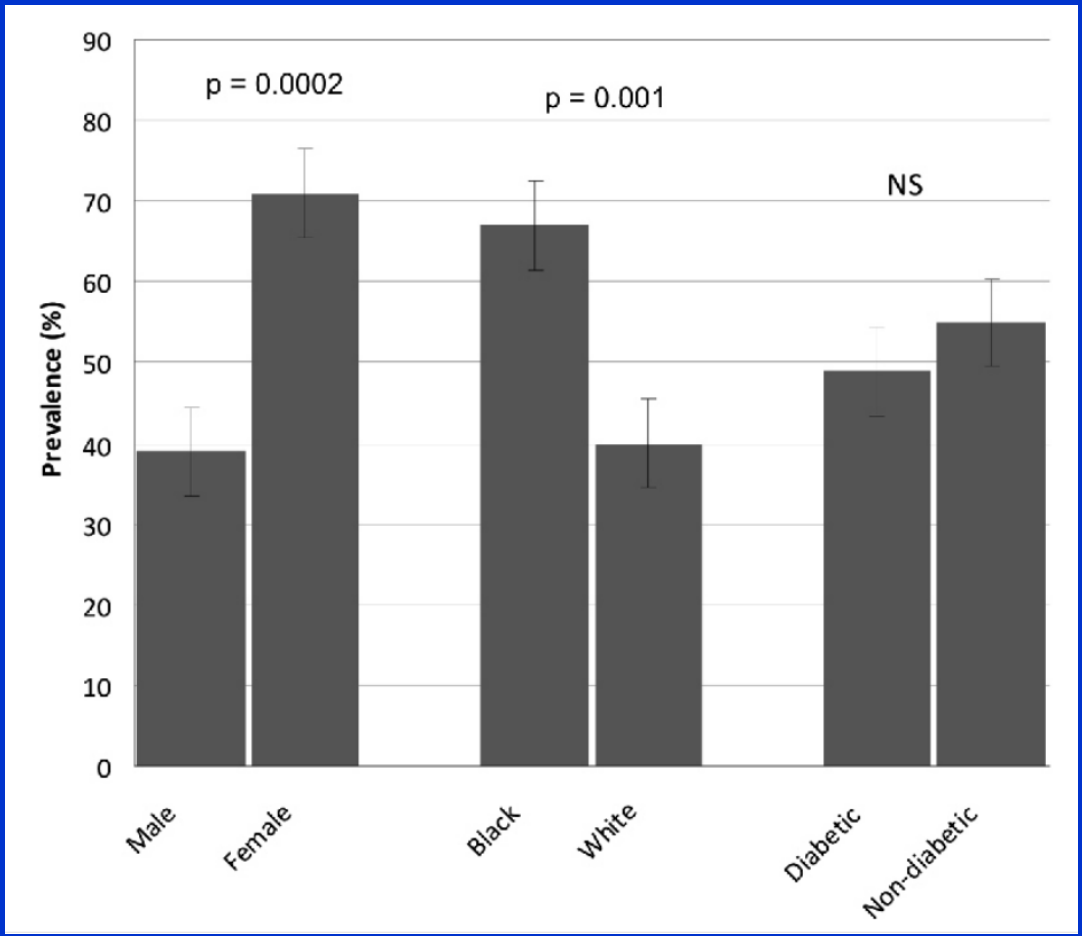




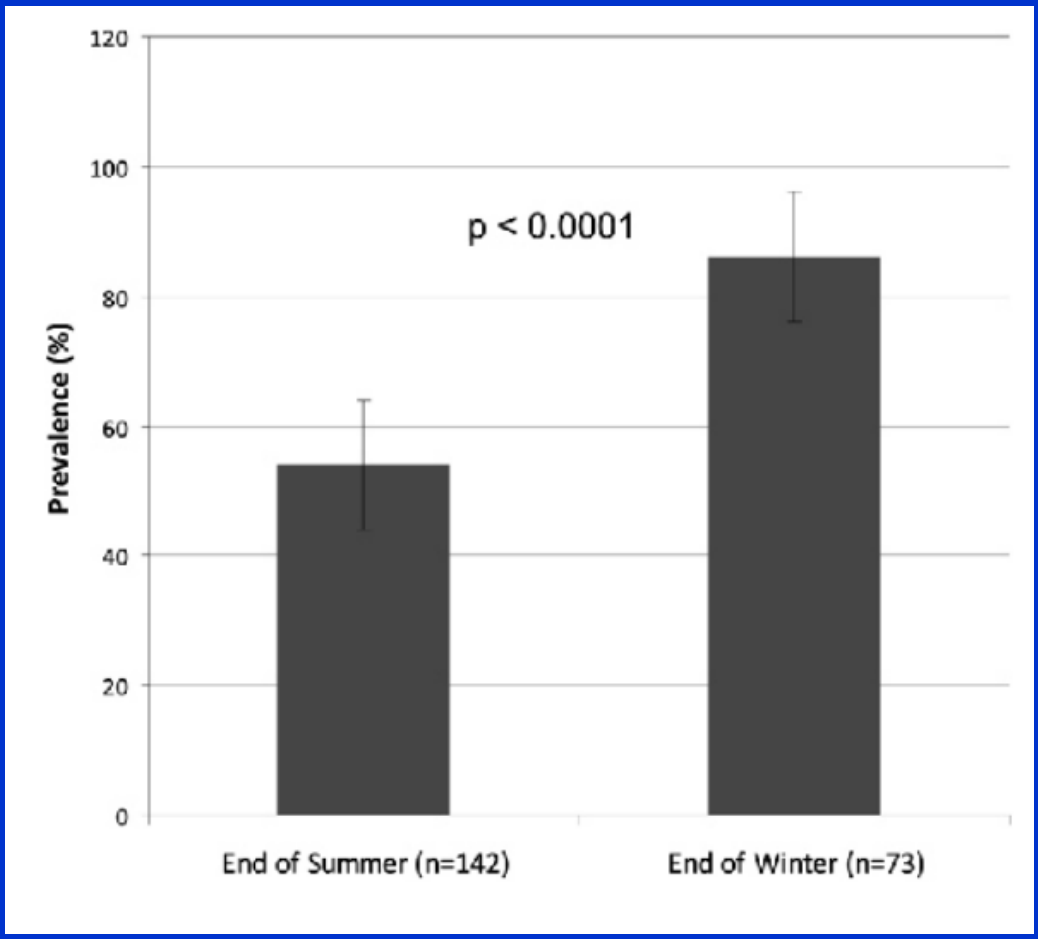
Prevalence of Vitamin D Depletion in Dialysis Patients

(Tolouian, Rao et al; Clin Nephrol 2010)

Over all

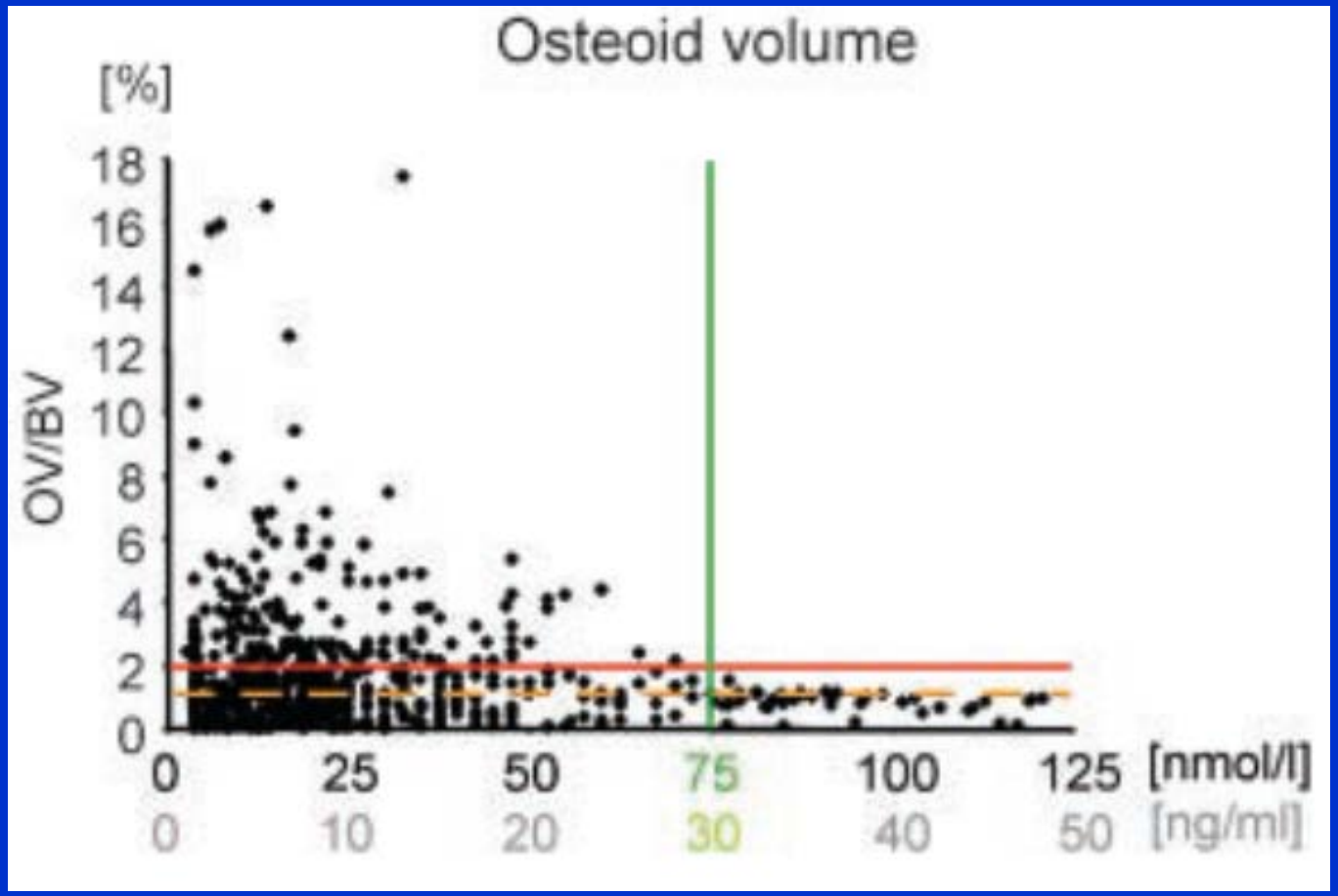


By season

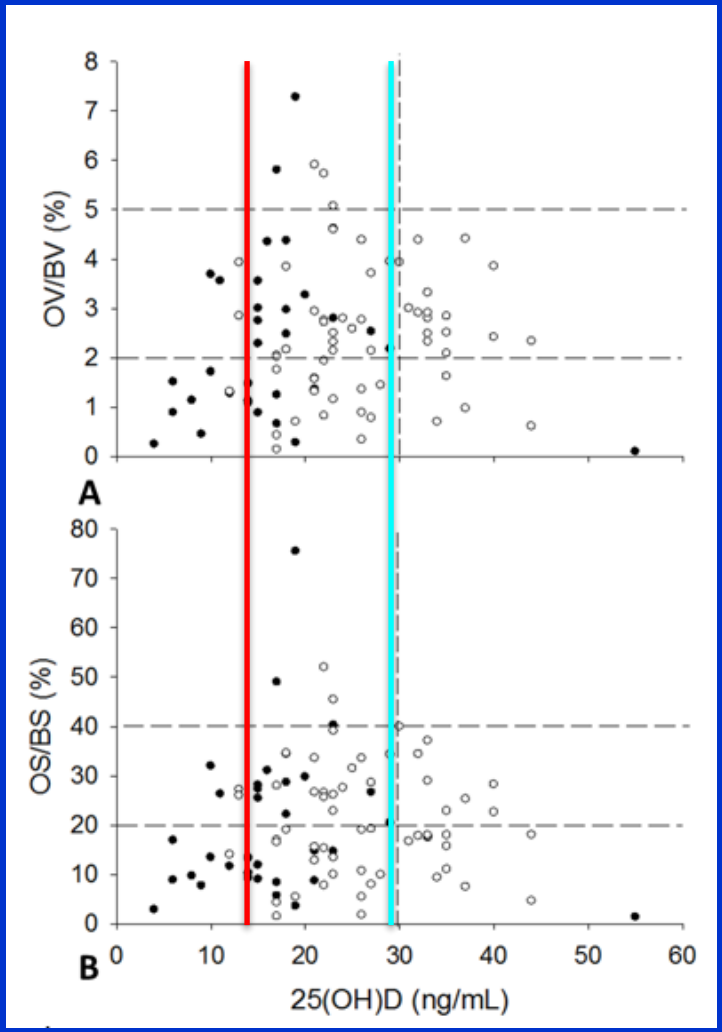


What is the minimal 25-OHD for optimal bone mineralization?

Priemel et al, JBMR, 2010



Qiu & Rao et al,
Steroid Biochem Mol Biol (in press)

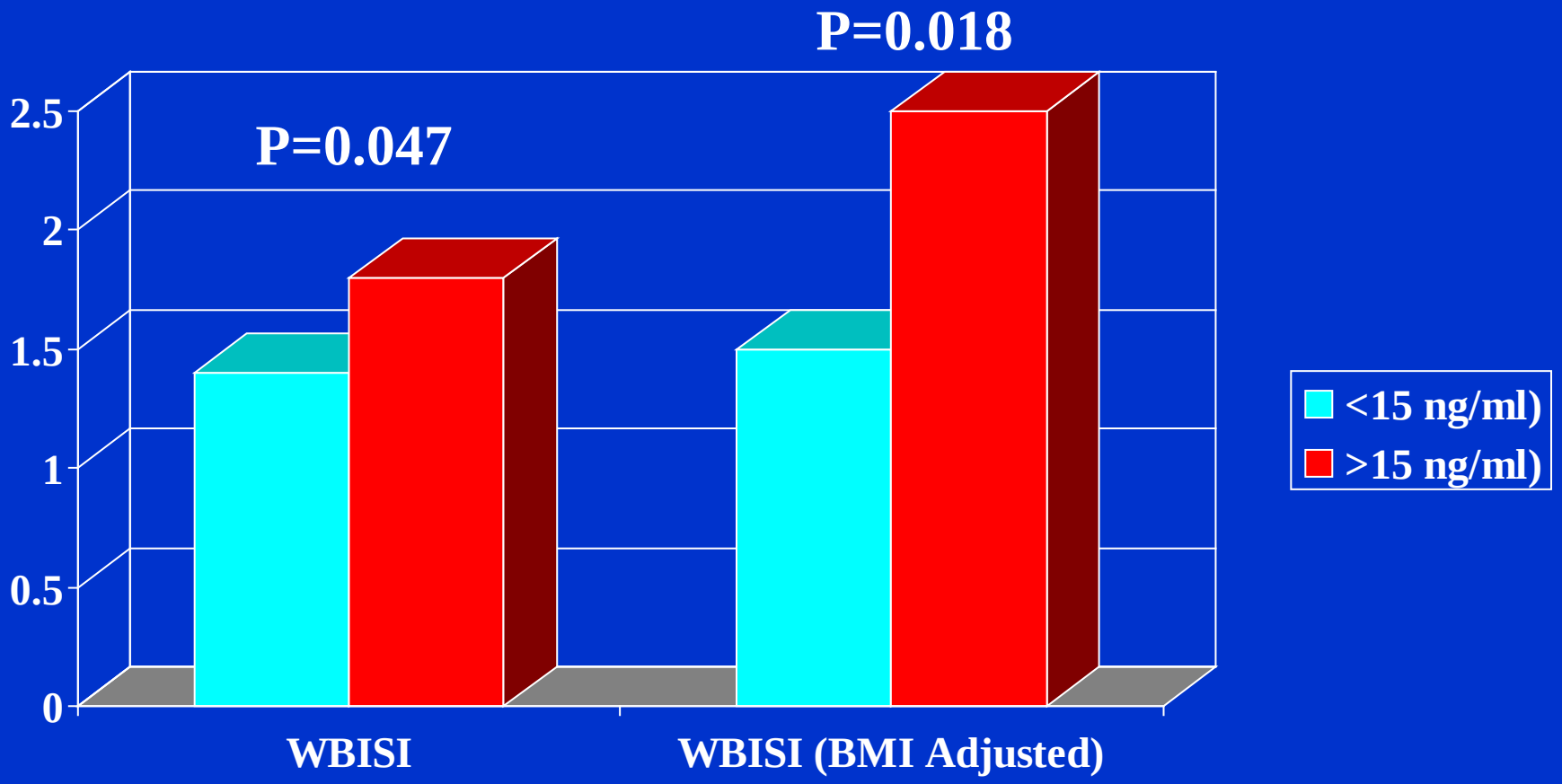


Role of Vitamin D in Non-Skeletal Health

- Autoimmunity
  - Type 1 DM
  - Rheumatoid Arthritis (*50,000 IU/day)
  - Childhood allergy & asthma, bronchitis etc
- Cardiovascular
  - Myocyte apoptosis, Hypertension, Cholesterol, RAAS
- Diabetes
  - Insulin secretion & insulin resistance
  - Risk of developing DM; both Type 1 & 2
- Cancer
  - Breast, Prostate, Colon, Lung, Leukemia etc.
- Others:
  - Multiple sclerosis
  - Psoriasis
  - Tuberculosis: (Revolving Sanitaria)

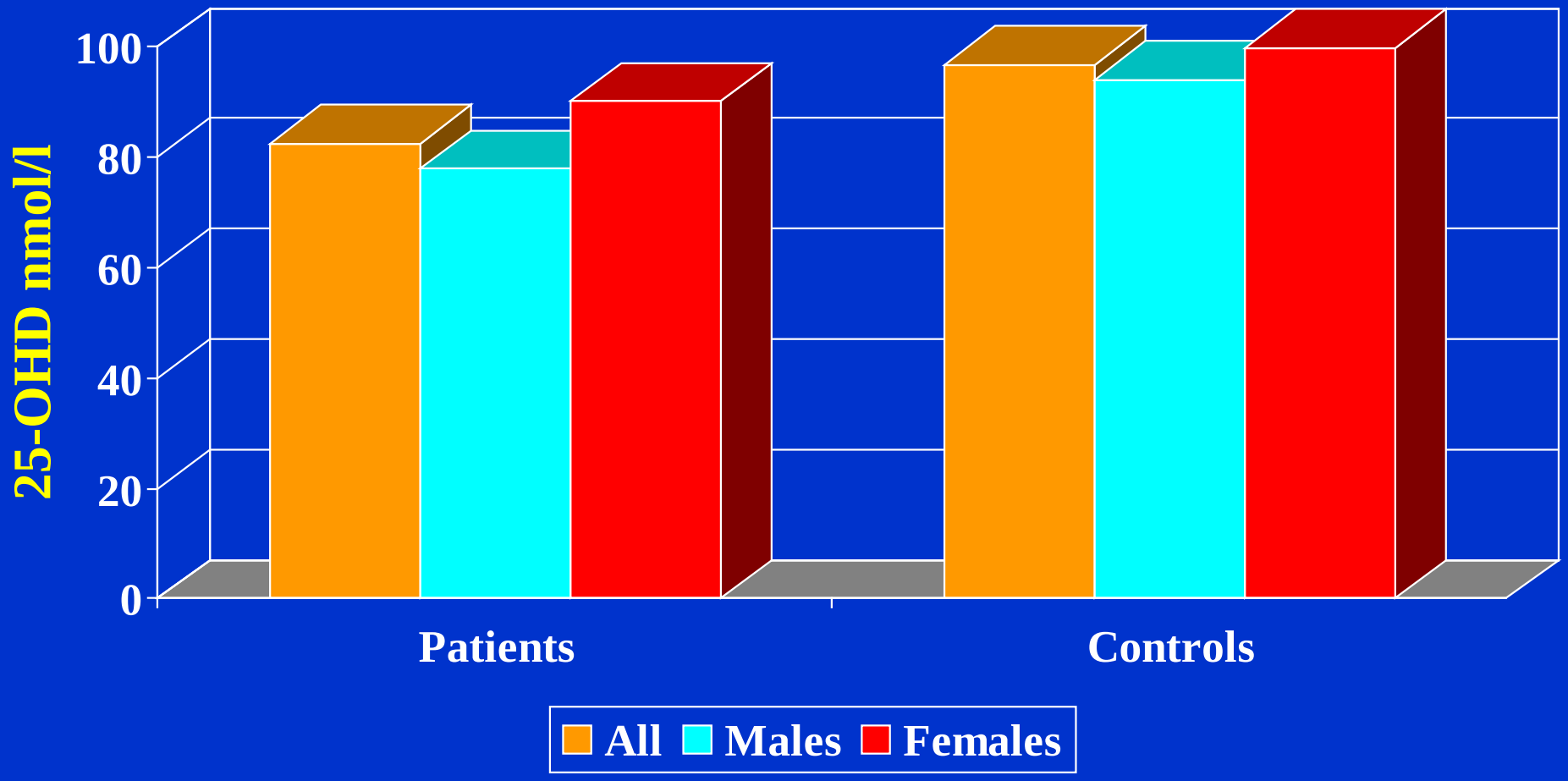
Whole Body Insulin Sensitivity Index (WBISI) in Blacks (Higher the better)

Ambika Ashraf et., al. J Clin Endocrinol Metab 94: 3200-3206; 2009



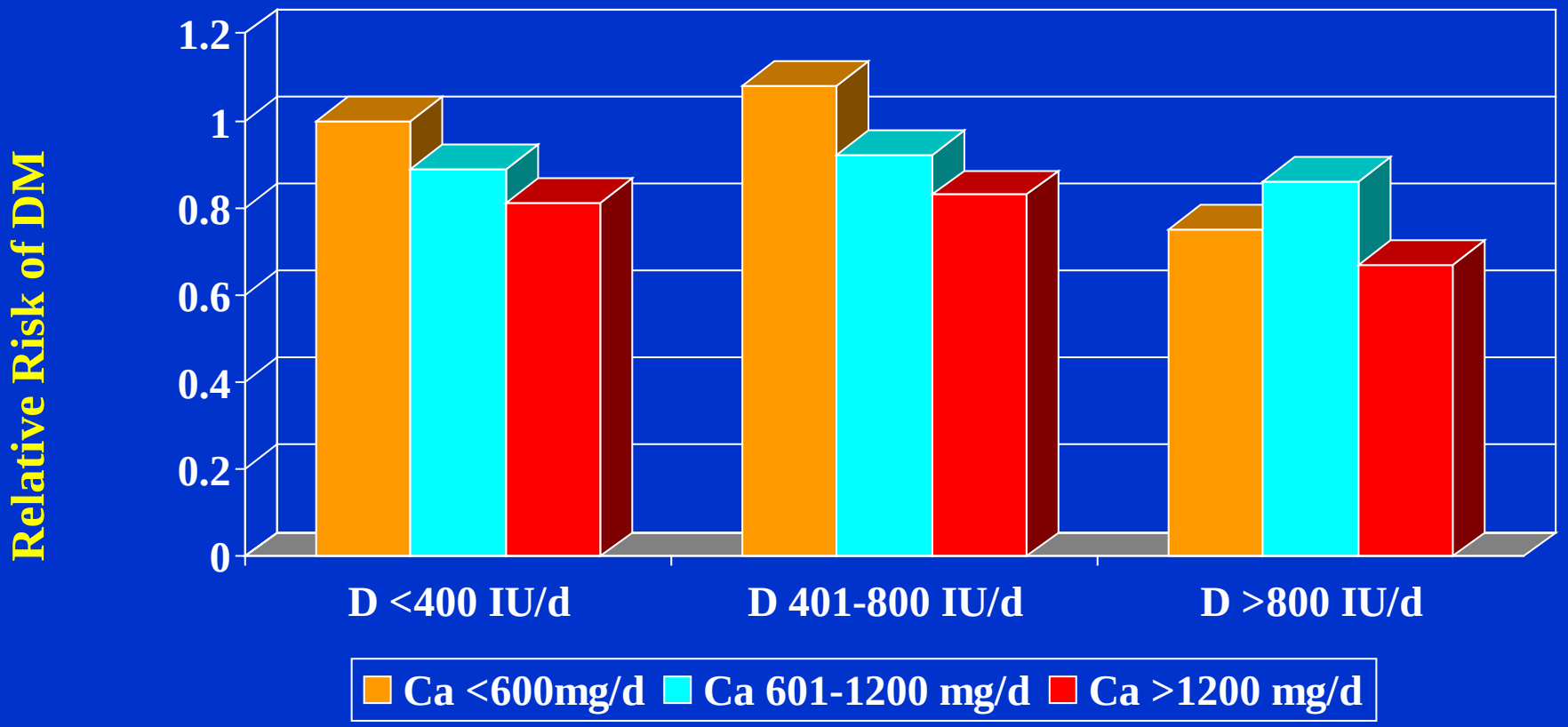
Serum 25-OHD Levels in Type 1 DM

Diabetes Incidence Study in Sweden (DISS); Diabetalogia, 2006; 49:2847



RR of Type 2 DM Based on Ca & D Intakes

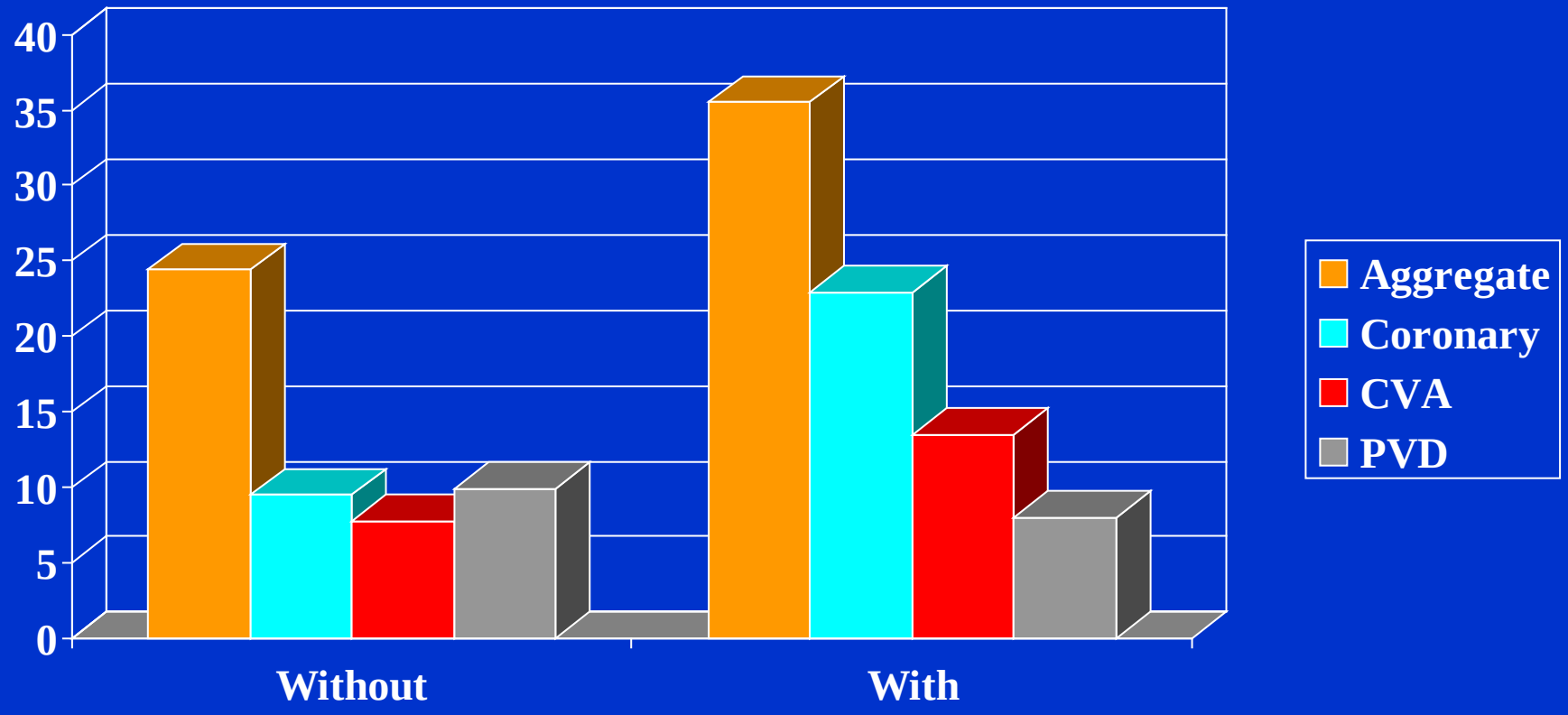
Nurses Health Prospective Observational Study; Pittas et., al. Diabetes Care, 2006



“Effect of VDN” on Events

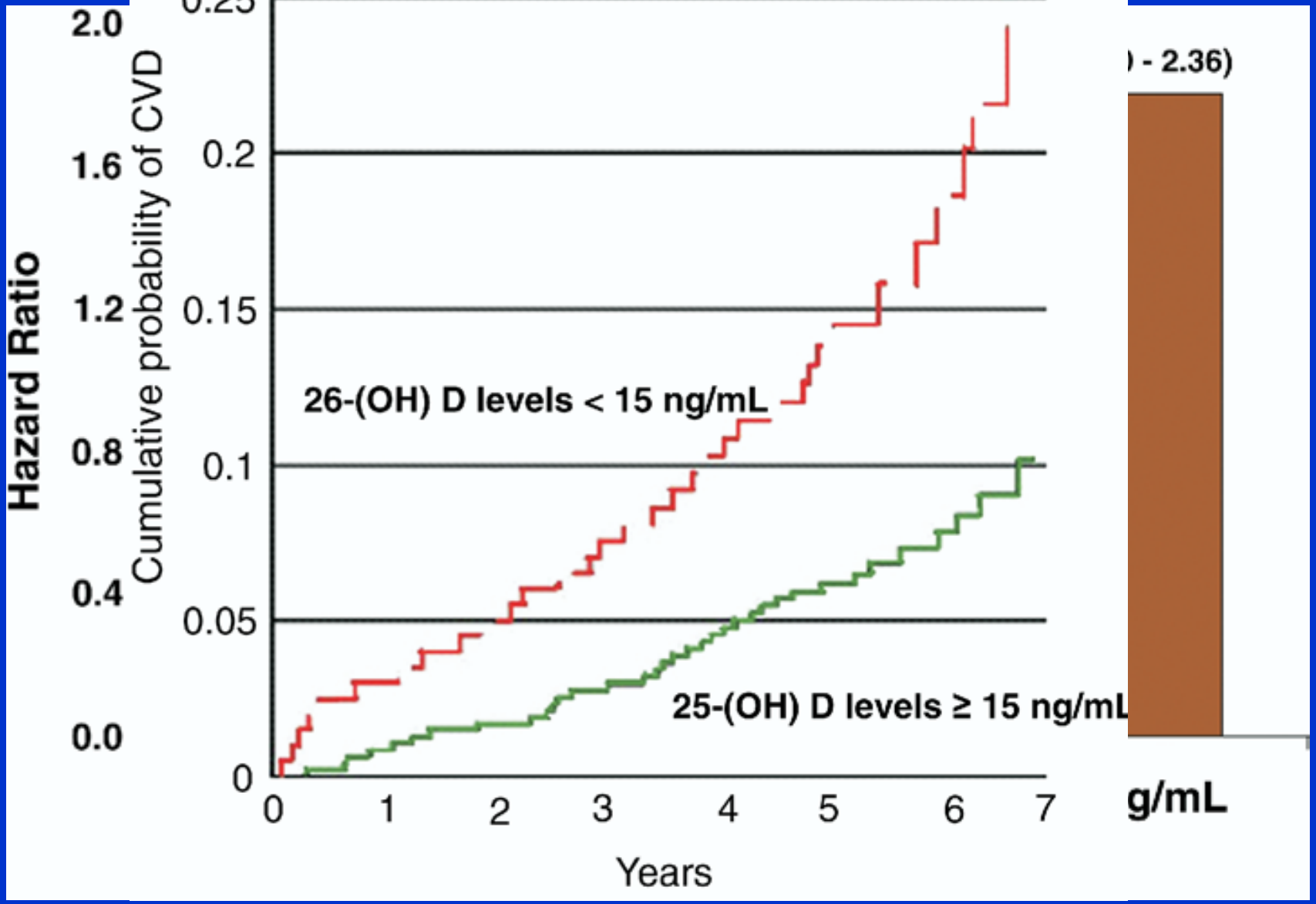
25-OHD & Cardiovascular disease among Type 2 DM patients

Cigolini et. al, Diabetes Care; 2006; 29:722



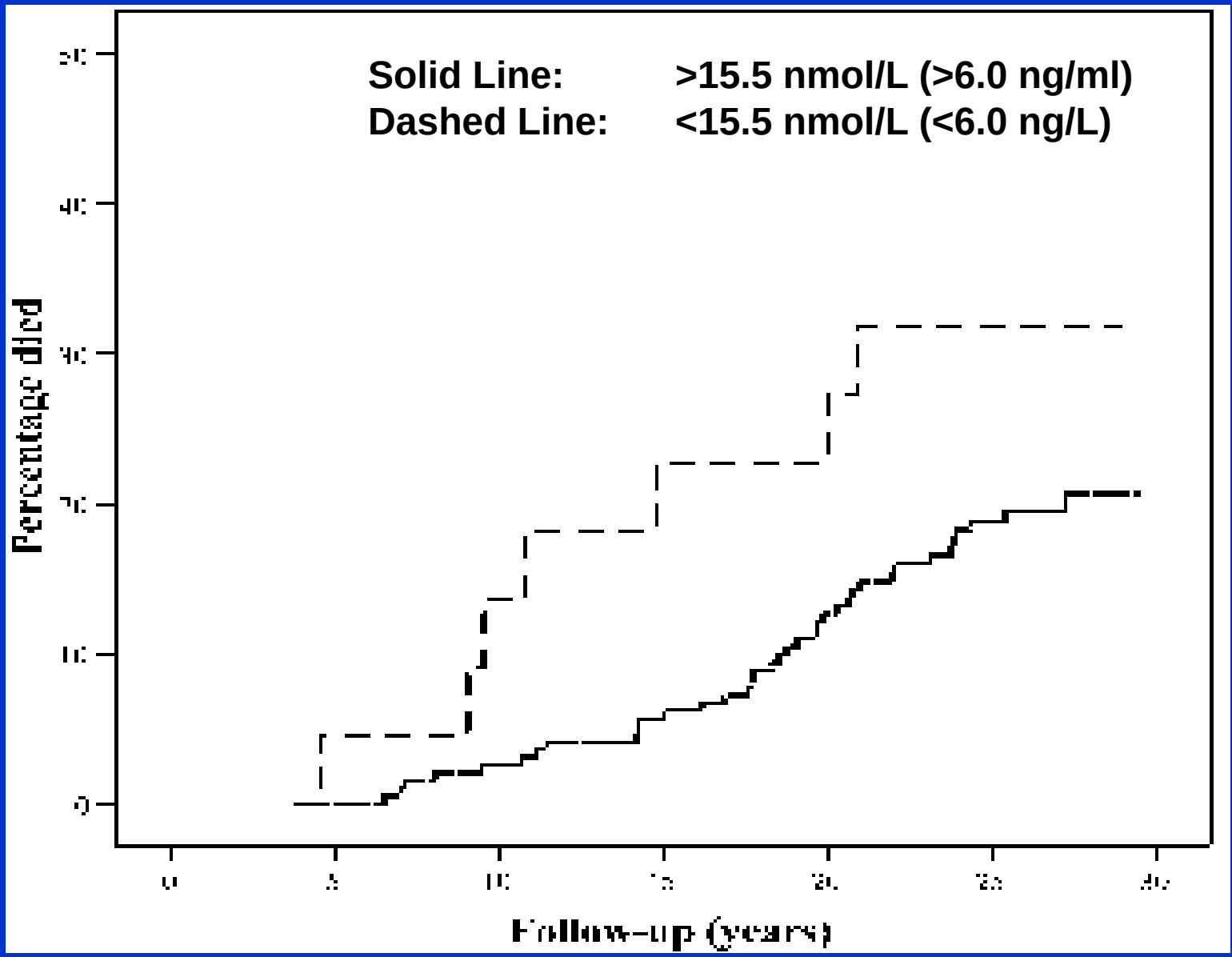
Vita CVD

But only in patients with hypertension

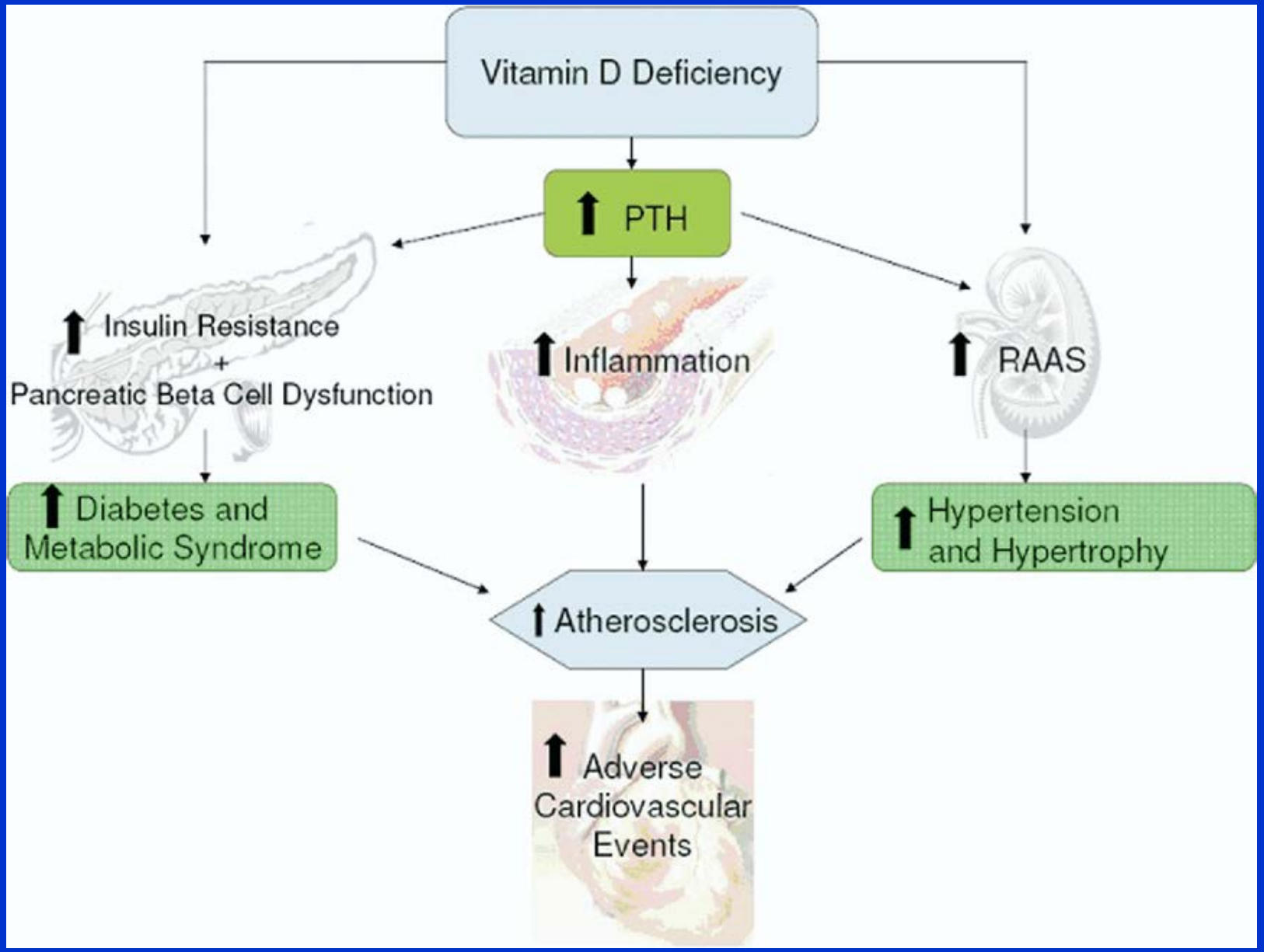


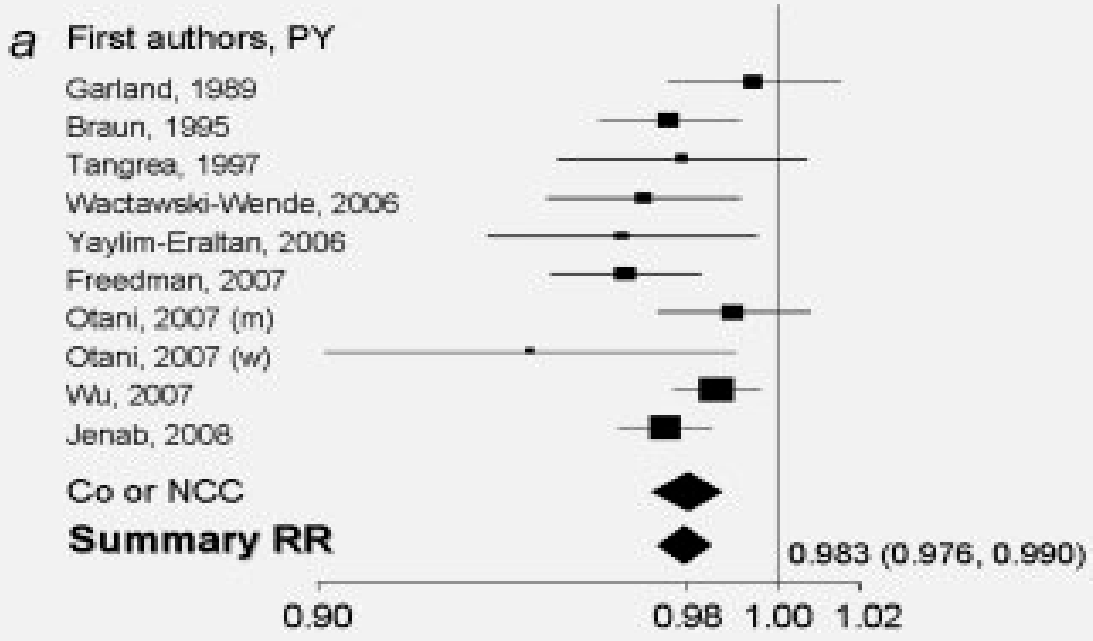
25-OHD Levels & Mortality

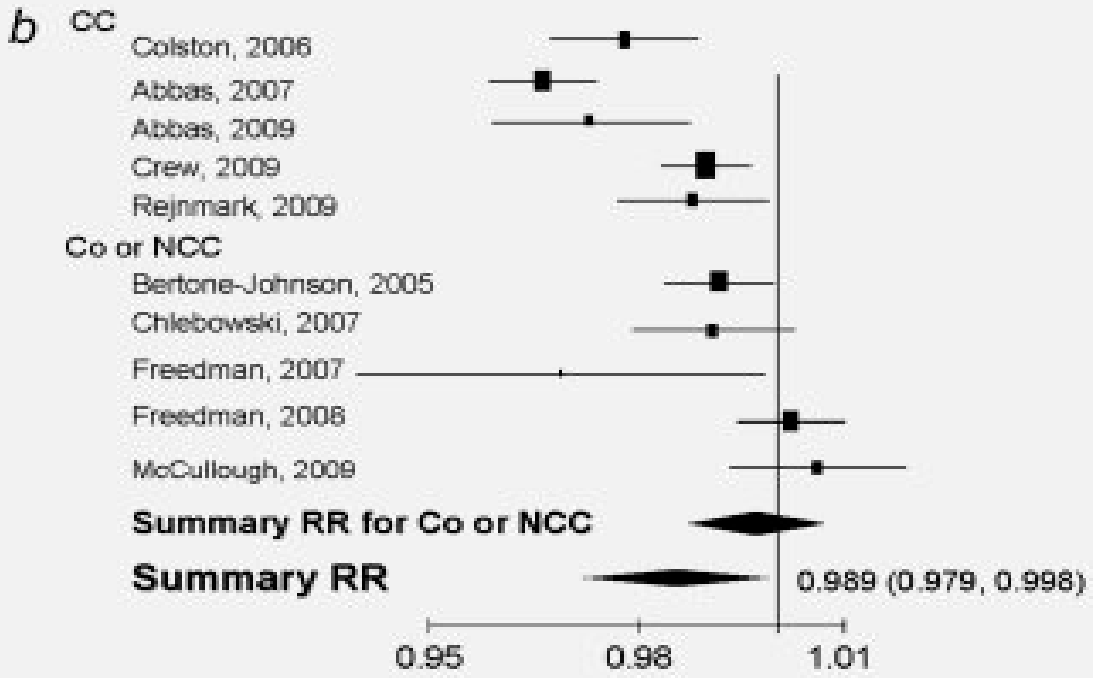
Joergensen et al; Diabetes Care, 2011; 34:1081



Potential Mechanism for VDD & CVD Risk







Meta-Analysis of VDN & Cancer Risk
Gandini et al, Int J Cancer. 2011; 128:1414-24

Despite potential ascertainment bias or self-self selection, for 3 cancers there was a "dose-response"

Disease	Units of increase	Summary relative risk	95% CI
Colorectal cancer			
All studies	10 ng/ml	0.85	0.79; 0.91
NCC and cohort studies[1]	10 ng/ml	0.85	0.79; 0.92
Breast cancer			
All studies	10 ng/ml	0.89	0.81; 0.98
NCC and cohort studies	10 ng/ml	0.97	0.92; 1.03
Prostate cancer			
All studies[2]	10 ng/ml	0.99	0.95; 1.03

Vitamin D Nutritional Status and Antenatal Depressive Symptoms in African American Women

Andrea E. Cassidy-Bushrow, Ph.D., M.P.H.,[1] Rosalind M. Peters, Ph.D., R.N., FAAN,[2] Dayna A. Johnson, M.P.H., M.S.W., M.S.,[1] Jia Li, Ph.D.,[1] and D. Sudhaker Rao, MBBS[3]

TABLE 2. ASSOCIATION OF LOG-TRANSFORMED 25-HYDROXYVITAMIN D (LOG (25-OHD)) WITH ELEVATED DEPRESSION SYMPTOMS (CES-D ≥ 16)

Log (25-OHD) (per 1 unit increase)	*Odds ratio (95% CI)*	p
Unadjusted	0.49 (0.28-0.87)	0.014
Adjusted for maternal age, ≥ high-school education, and marital status	0.55 (0.30-0.98)	0.041
Adjusted for maternal age, ≥ high-school education, marital status, season of 25-OHD measure, and number of days between 25-OHD and CES-D measure	0.54 (0.29-0.99)	0.046

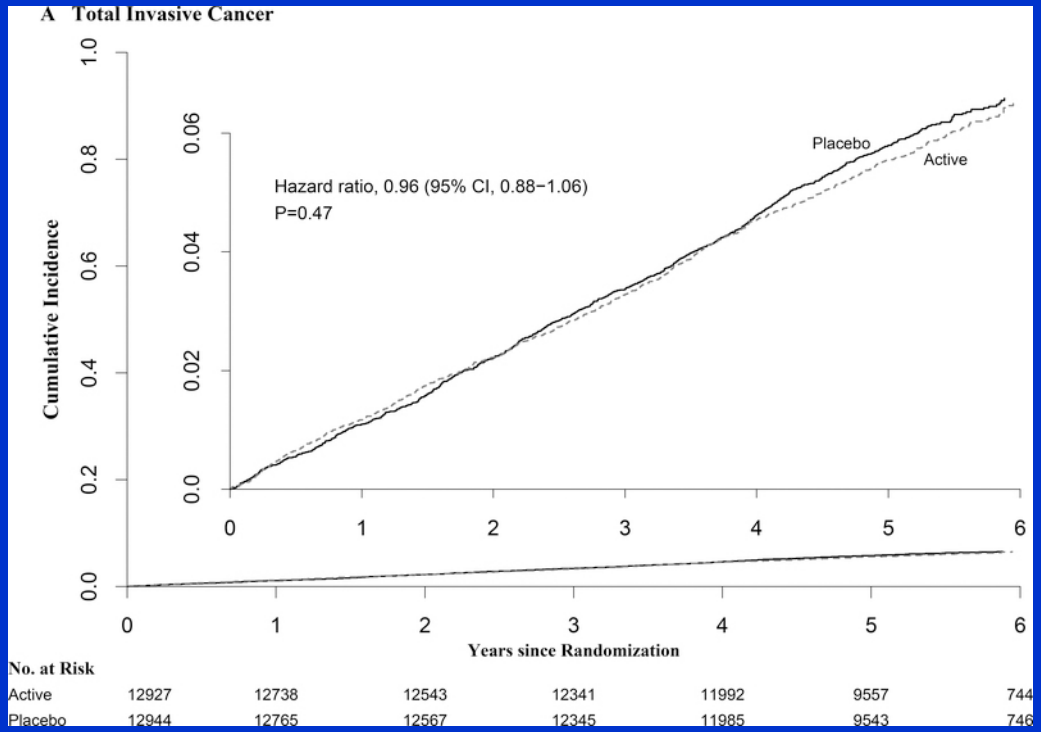
CES-D, center for epidemiological studies depression scale; CI, confidence interval.

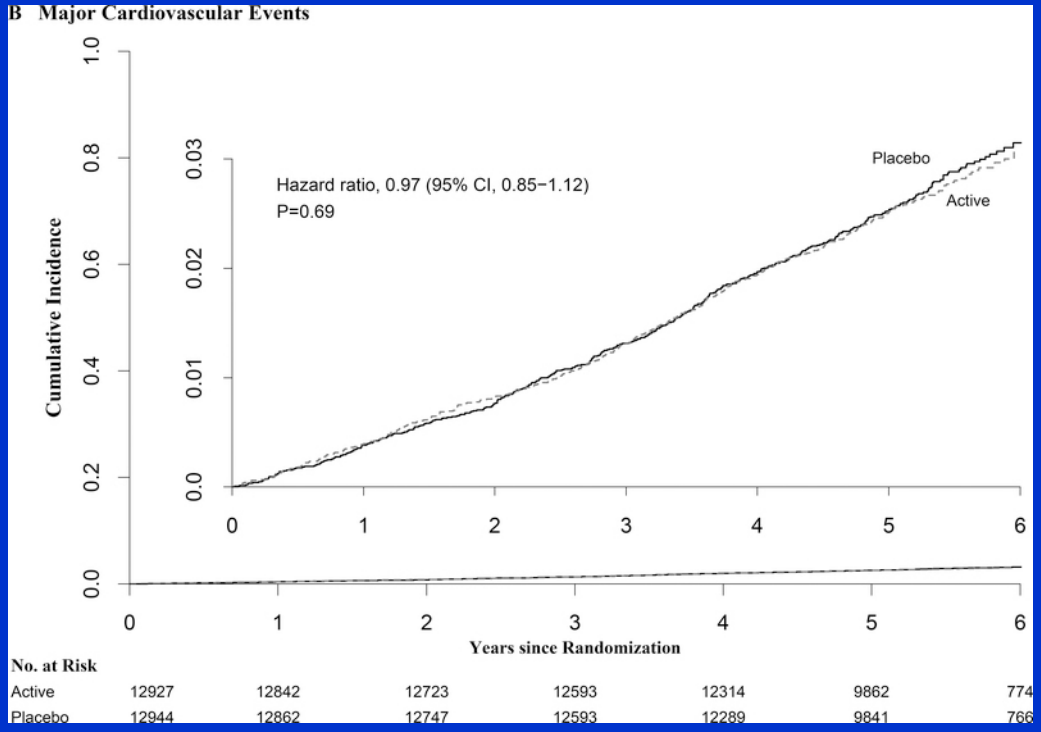
Role of Vitamin D in Non-Skeletal Conditions

&

Welcome to the Million $$ RCTs

Vitamin D Supplements and Prevention of Cancer and Cardiovascular Disease.
Manson et al for the VITAL Research Group. N Engl J Med. 2019 Jan 3;380(1):33-44.

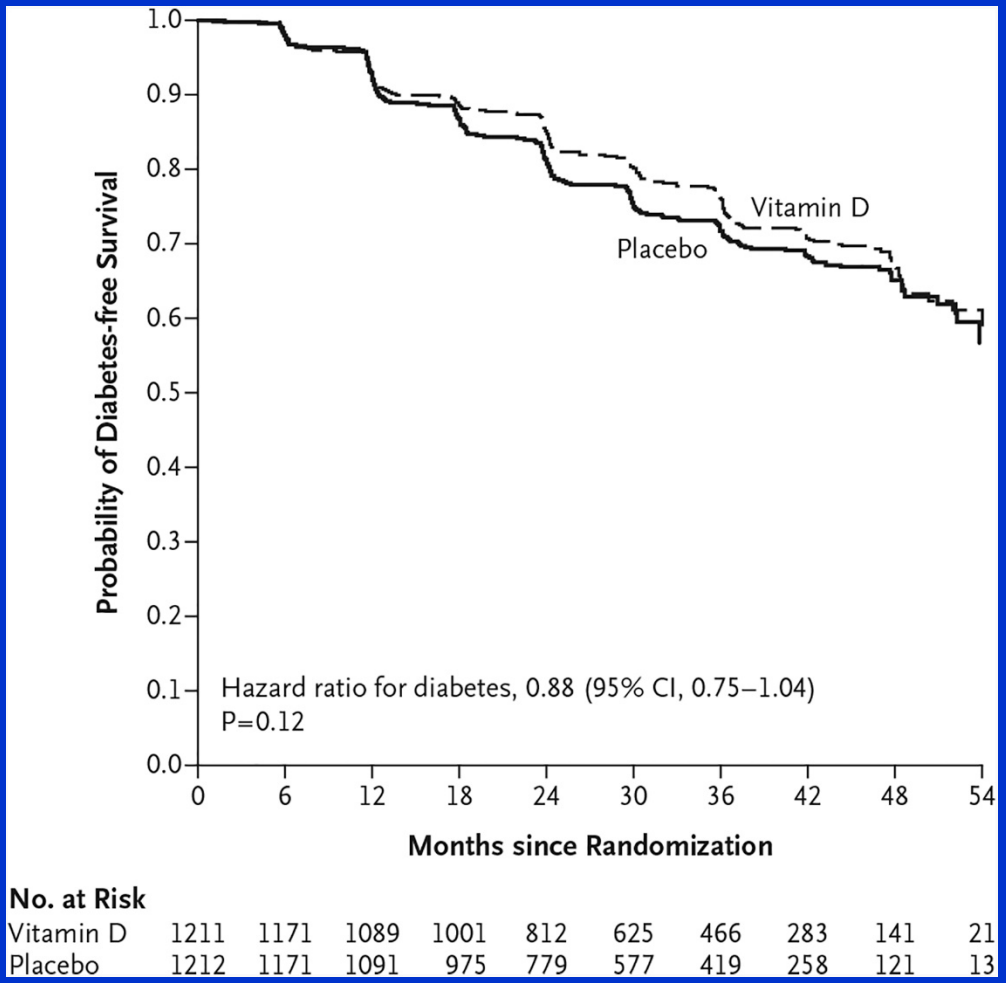


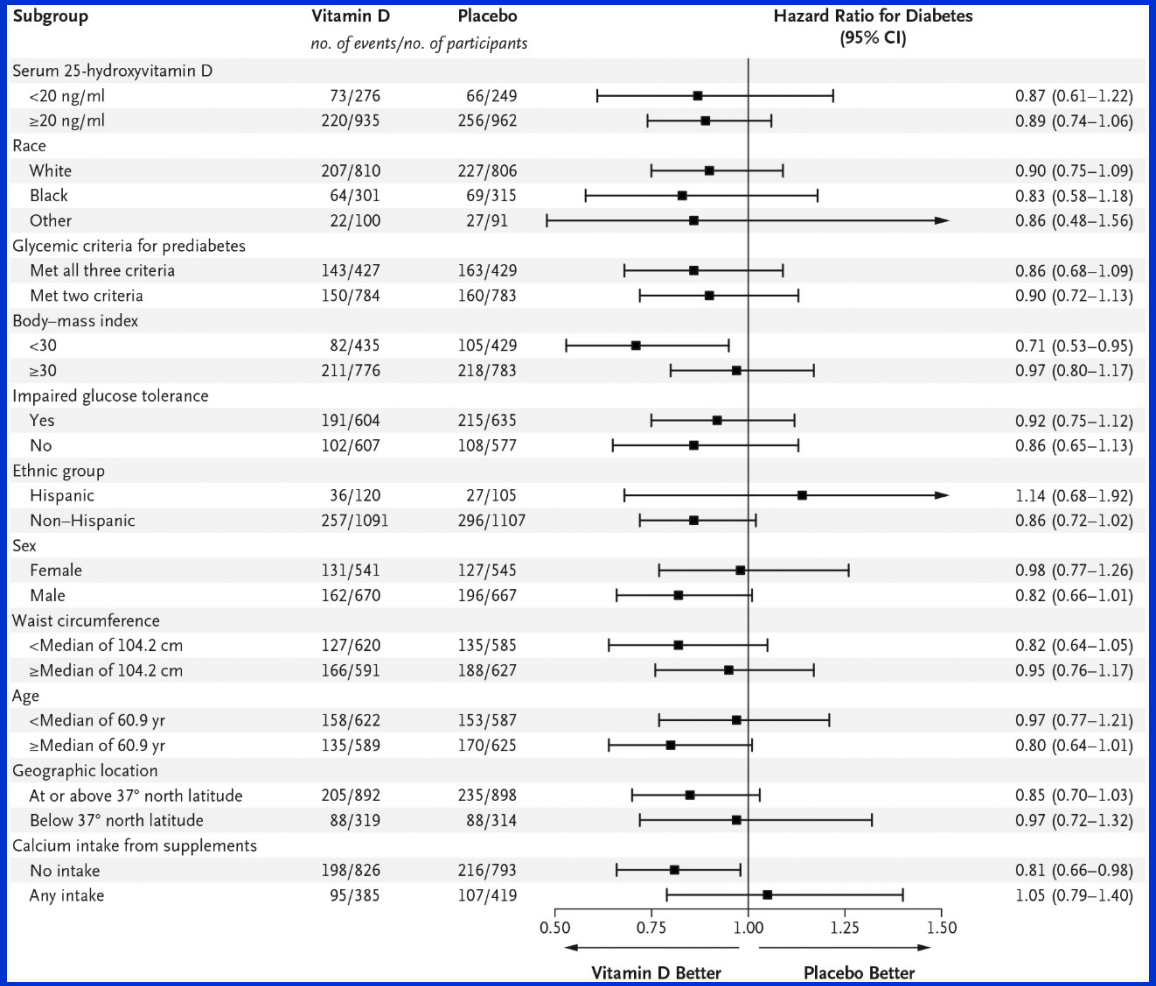


CONCLUSIONS: Supplementation with vitamin D did not result in a lower incidence of invasive cancer or cardiovascular events than placebo.

Vitamin D Supplementation and Prevention of Type 2 Diabetes.

Pittas AG, et., al; N Engl J Med. 2019 Aug 8;381(6):520-530.





CONCLUSIONS: Among persons at high risk for type 2 diabetes not selected for vitamin D insufficiency, vitamin D_3 supplementation at a dose of 4000 IU per day did not result in a significantly lower risk of diabetes than placebo.

Effects of Supplemental Vitamin D on Bone Health Outcomes in Women and Men in the VITamin D and OmegA-3 TriaL (VITAL)

Meryl S LeBoff,[1,2] Sharon H Chou,[1] Elle M Murata,[1] Catherine M Donlon,[1] Nancy R Cook,[2,3,4] Samia Mora,[2,3,5] I-Min Lee,[3,4] Gregory Kotler,[3] Vadim Bubes,[3] Julie E Buring,[2,3,4] and JoAnn E Manson[2,3,4]

Supplemental vitamin D3 Vs. placebo had no effect on 2-year changes in BMD at the spine, femoral neck, total hip, or whole body, or on bone structure.

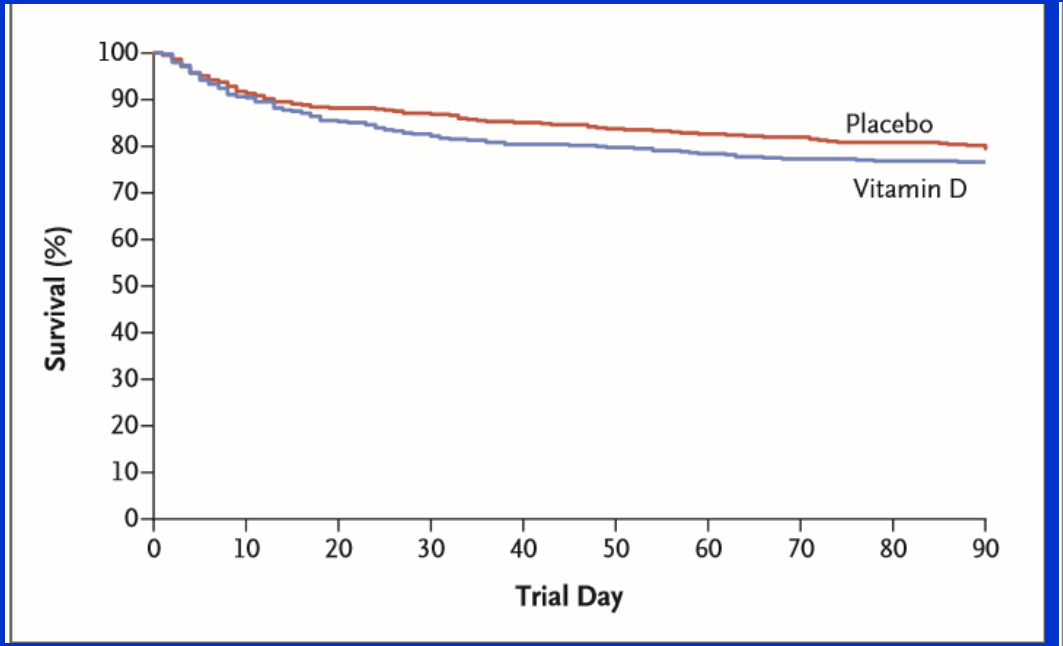
Effects did not vary by sex, race/ethnicity, BMI, or 25(OH)D levels.

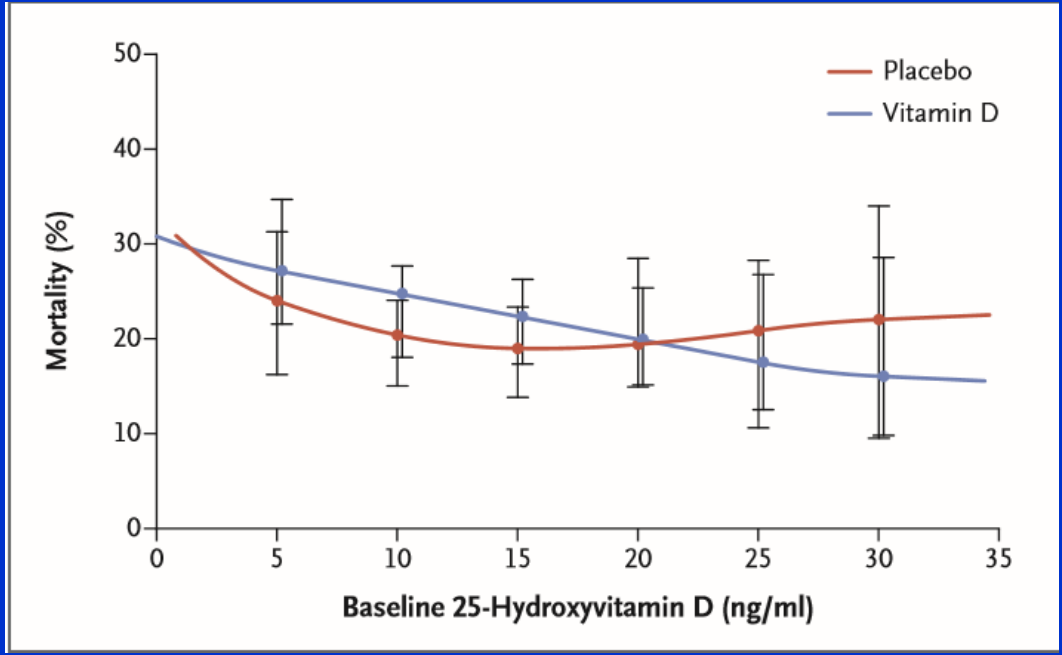
Conclusions:

Supplemental vitamin D3 Vs. placebo for 2 years in generally healthy adults not selected for vitamin D insufficiency did not improve BMD or structure.

Early High-Dose Vitamin D_3 for Critically Ill, Vitamin D-Deficient Patients.

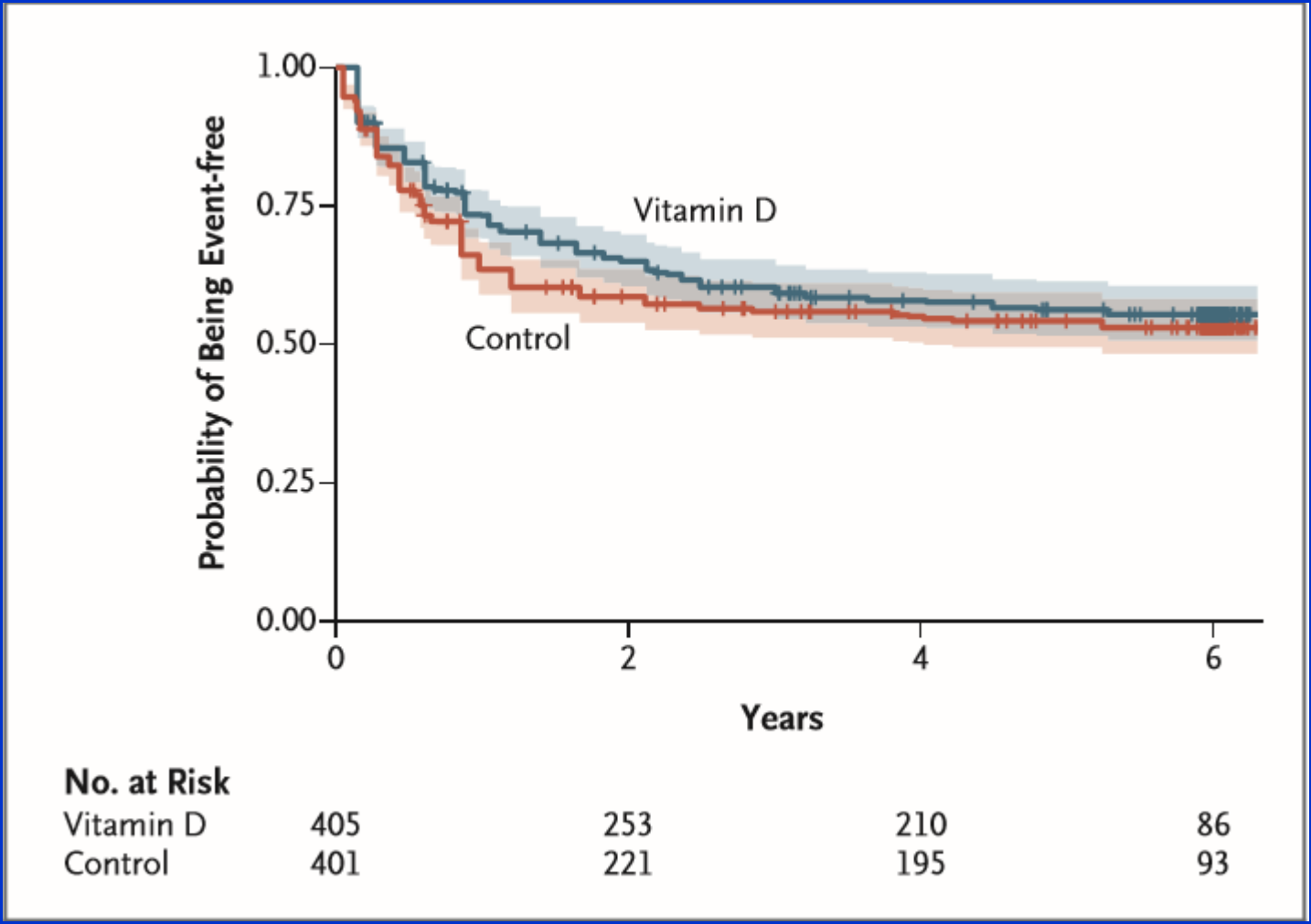
NHLBI-PETAL Clinical Trials Network, N Engl J Med. 2019;381:2529-2540.





CONCLUSIONS: Early administration of high-dose enteral vitamin D_3 did not provide an advantage over placebo with respect to 90-day mortality or other, nonfatal outcomes among critically ill, vitamin D-deficient patients.

Six-Year Follow-up of a Trial of Antenatal Vitamin D for Asthma Reduction.
Litonjua AA, et., al. N Engl J Med. 2020 Feb 6;382(6):525-533.



CONCLUSIONS: Vitamin D supplementation during the prenatal period alone did not influence the 6-year incidence of asthma and recurrent wheeze among children who were at risk for asthma.

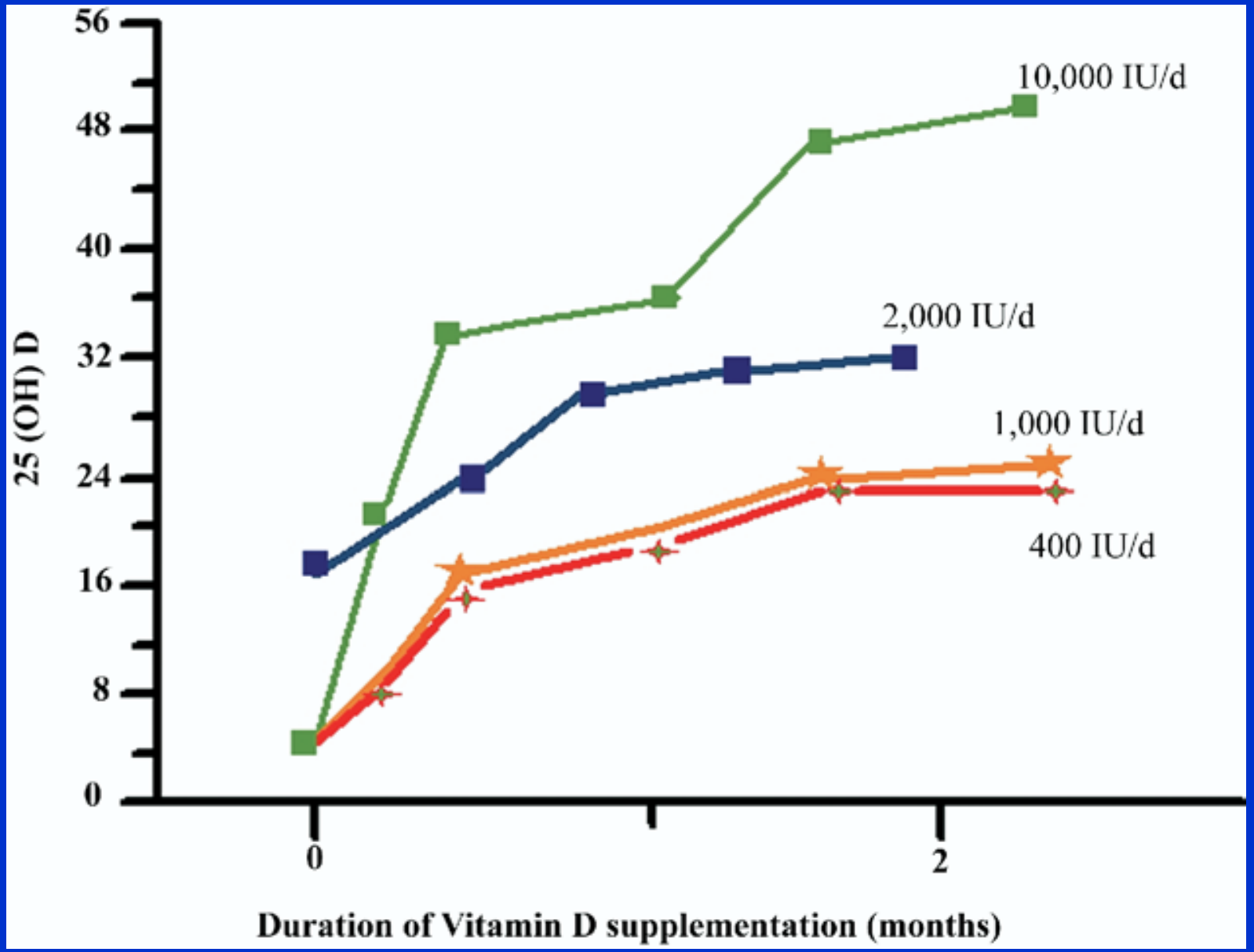
Institute of Medicine (IOM) & The Endocrine Society (TES) Controversy
(20 ng/ml Vs. 30 ng/ml)

- Global health (IOM) versus select populations (TES)
- Effect on PTH & Bone (TES)
- Effect on bone mineralization (Priemel Paper; TES)
- Potential non-skeletal benefits (TES)
  - Cancer, CV, DM, muscle strength, fall risk etc.
- Concerns about accuracy 25-hydroxyvitamin D assays
  - ICMA Vs. LC-MS/MS (IOM & TES)
- Who to screen? (IOM & USPSTF)
- High risk populations (IOM & USPSTF)

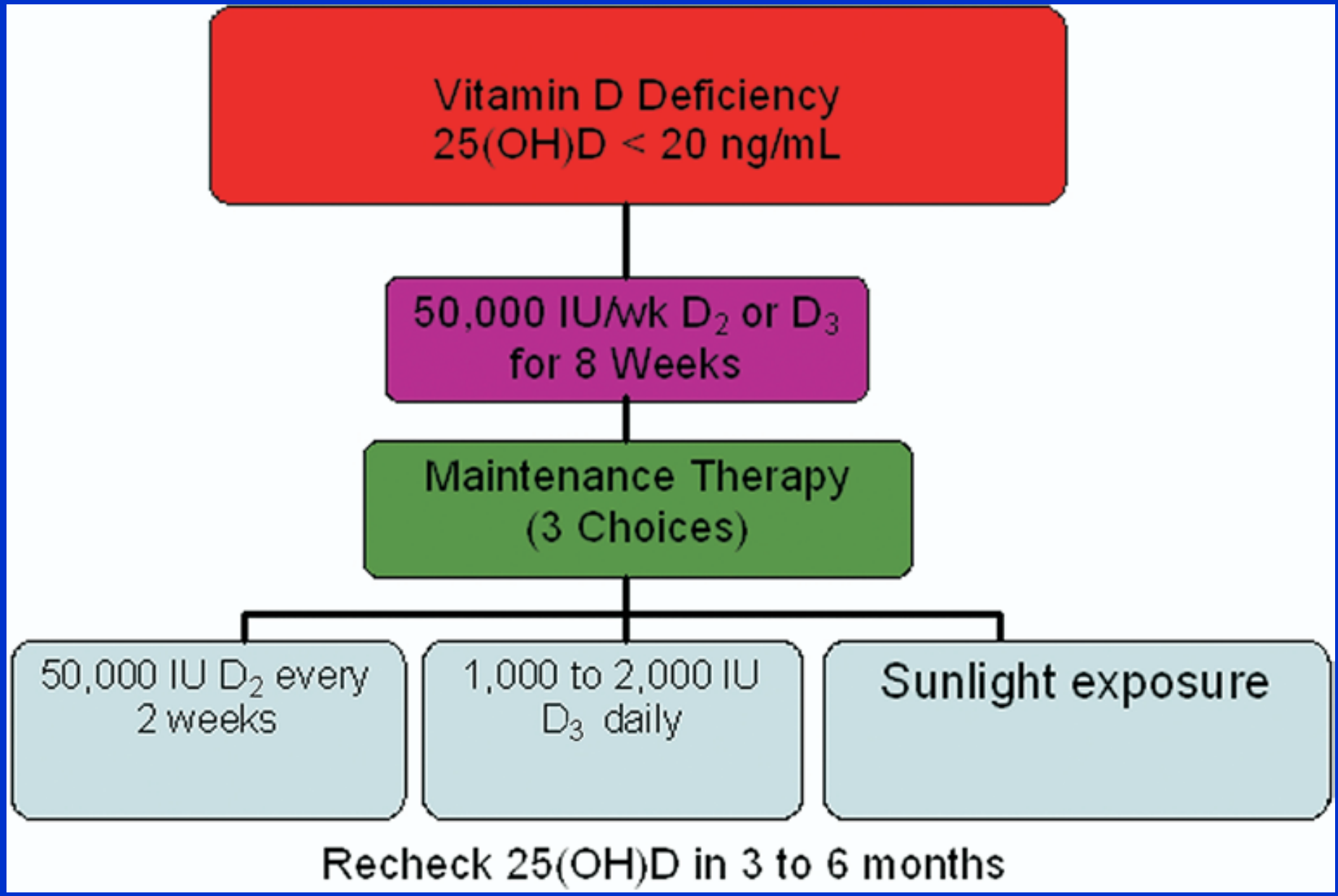
Vitamin D Repletion Strategies

25-OHD Rise with Vitamin D Supplements

Note:
Rise in 25-OHD is much faster than fall in PTH, often months to years



The Ian Reid's Method



The Other Methods (?The Emory Methods)

- 300,000 IU once a year and a maintenance dose of 800-1000 IU indefinitely
- 600 IU/d or 4,200 IU/week or 18,000 IU/month
- 50,000 IU/d for 10 days, then once/month
- 500,000 IU followed by regular supplements
- 100,000 IU every 4 months
- **Special Circumstances:**
  - **What about intramuscular preparations?**
  - **What about in bariatric surgery patients?**
  - **Can we use calcitriol?**

…and the Rao's Method

- Needless to say, this is the best, most efficient & safest method, because it is my method!
  - If 25-OHD <15ng/dl & PTH is elevated (>100 pg/ml)
    - 50,000 IU (1.25 mg)/week for 12 weeks followed by 1000 IU/day or 50,000 IU/month indefinitely
  - If 25-OHD <20ng/dl & PTH <100 pg/ml
    - 50,000 IU (1.25 mg)/week for 8 weeks followed by 1000 IU/day or 50,000 IU/month indefinitely
- Cautious approach in
  - Patients with a history (or active) of sarcoidosis
  - Patients with primary hyperparathyroidism with Ca>12 mg/dl

Vitamin D Toxicity…does it occur?

- Probably not...
- Large latitude between optimal & toxic levels
  - 20/30 ng/ml & >150 ng/ml
  - Cumulative input of >1,000,000 IU
- Cases of vitamin D toxicity have been reported with >10,000/day for at least >1 month
- However, no toxic effects with 4000 IU/day for 5 months
- Critical control step ~ product-substrate feedback
- Redundant catabolic pathway ~ inert metabolites

My Unbiased opinions

- Vitamin D "deficiency" (VDD), however one defines, is so prevalent that it is just simpler to supplement everyone with at least 1000 IU daily FOREVER!
- VDD is quite common in patients with OP, PHPT, dialysis, and blacks.
- The best available index of vitamin D nutrition is measurement of serum total 25-hydroxyvitamin D; ***1,25-DHCC level is of no clinical value or relevance***
  - **Rao, DS (1999). Perspective on assessment of VDN. J Clin Densitometry**
- For optimal bone mineralization >20 ng/ml is enough.
  - **Qiu & Rao et al, Steroid Biochem Mol Biol (in press)**
- Since combination of VDD & high PTH contributes to cortical bone loss & fractures, and since VDD may directly affect osteoblast number, function, survival, and perhaps response to specific OP therapy, greater attention to VDN is ***both necessary & essential.***
- **For non-bone purposes…who knows…but stay tuned!**

Thank you very much
for your attention