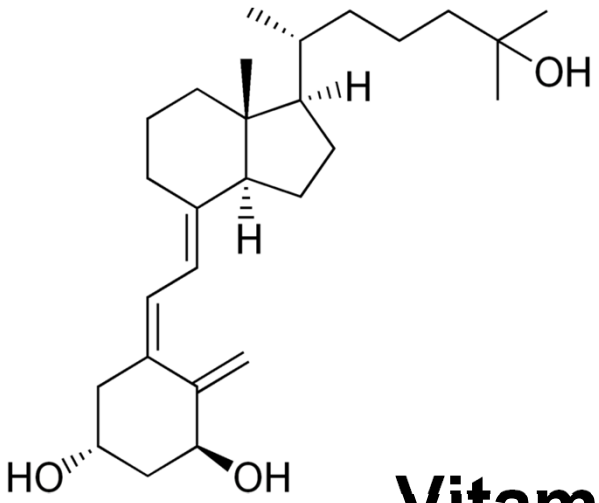

Vitamin D and Inflammation

Susan Harris, D.Sc.

Jean Mayer USDA Human Nutrition Research Center on Aging at Tufts University

Boston, MA

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Liver

Vitamin D

25(OH)D

storage form

nmol/l=ng/ml x 2.5

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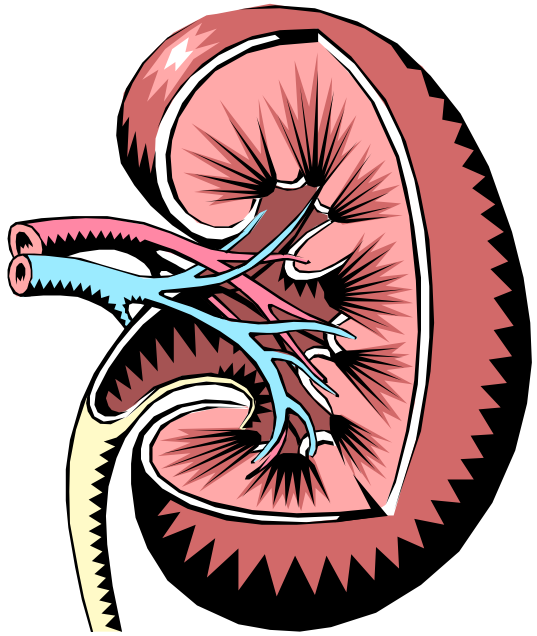
Renal $1,25(OH)_2D$ Production

25(OH)D



$1,25(OH)_2D$

active form

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Extra-Renal $1,25(OH)_2D$ Production

25(OH)D

$1,25(OH)_2D$

active form

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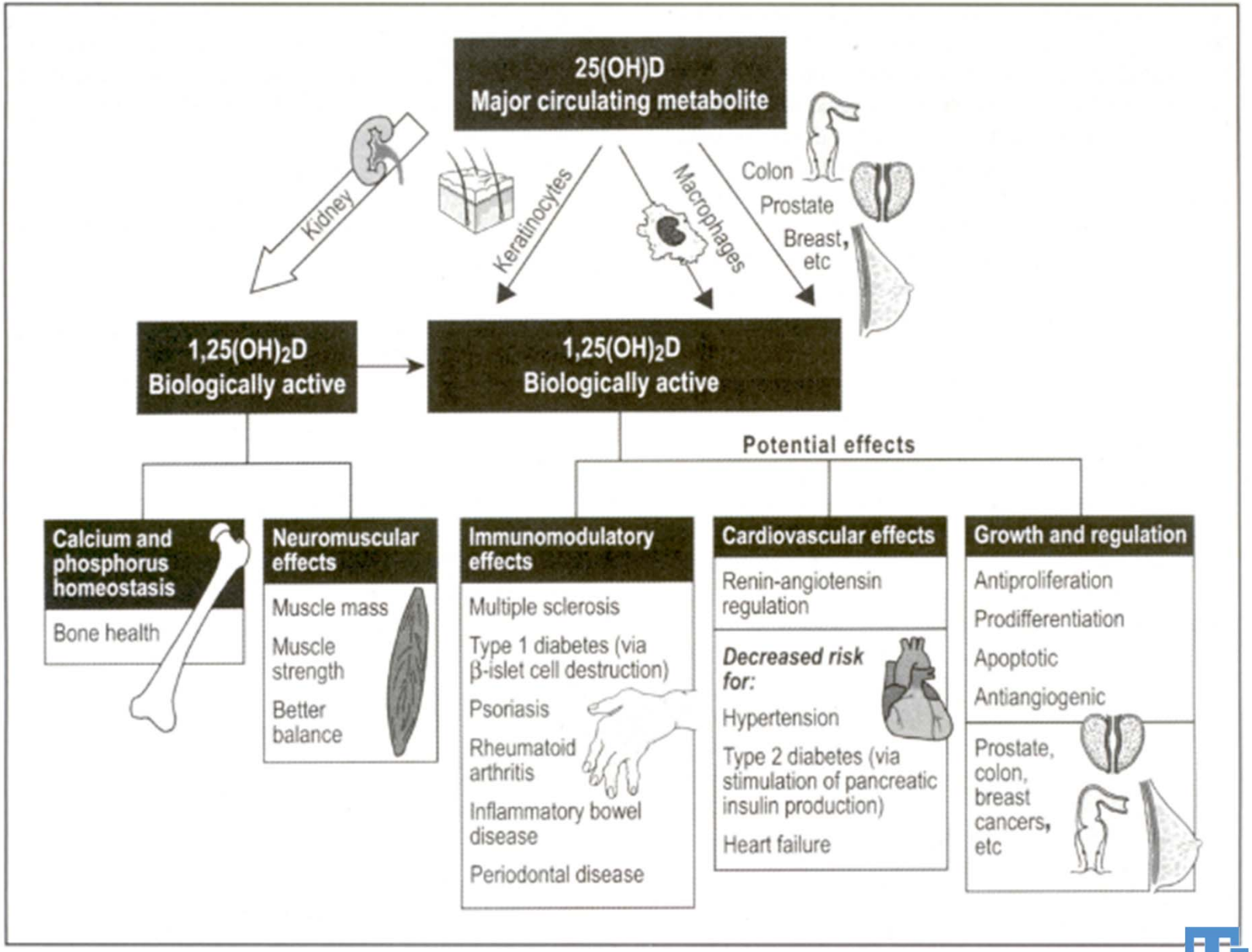

Holick MF, Mayo Clin Proc 2006:353

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Vitamin D and Inflammation: Cell and Animal Studies

Good evidence that $1,25(OH)_2D$ contributes to regulating the immune response and inflammation

- VDR in immune system cells and $1,25(OH)D_2$ hydroxylase in dendritic cells and macrophages suggest autocrine/paracrine actions at site of inflammation

- cell culture evidence suggests that $1,25(OH)_2D$ can down regulate production of pro-inflammatory cytokines by immune cells

- VDR KO mice develop chronic inflammation in GI tract

Yu et al. PNAS 105:20834-20839, 2008
Flores M. Nutr Res Rev 18:175-82, 2005
Cantorna et al AJCN 2004; Mahon et al J. Cell Bio 2003;
Zitterman Brit J Nutr 2003

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Vitamin D and Inflammation: Human Studies

- Much less direct evidence in human studies
- Extensive evidence from observational studies that vitamin D influences risk for conditions having an inflammatory component
- BUT uncontrolled confounding is a possibility because many third factors are associated with both vitamin D levels and disease risk, e.g. obesity, time spent outside, age
- Limited and often flawed trial data

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Evidence from Human Studies of Vitamin D Associations with Autoimmune and Inflammatory Conditions

- multiple sclerosis
- rheumatoid arthritis
- inflammatory bowel disease
- Crohn's disease
- systemic lupus erythematosus
- periodontal disease
- hypertension/arteriosclerosis/other CVD
- type 2 diabetes mellitus

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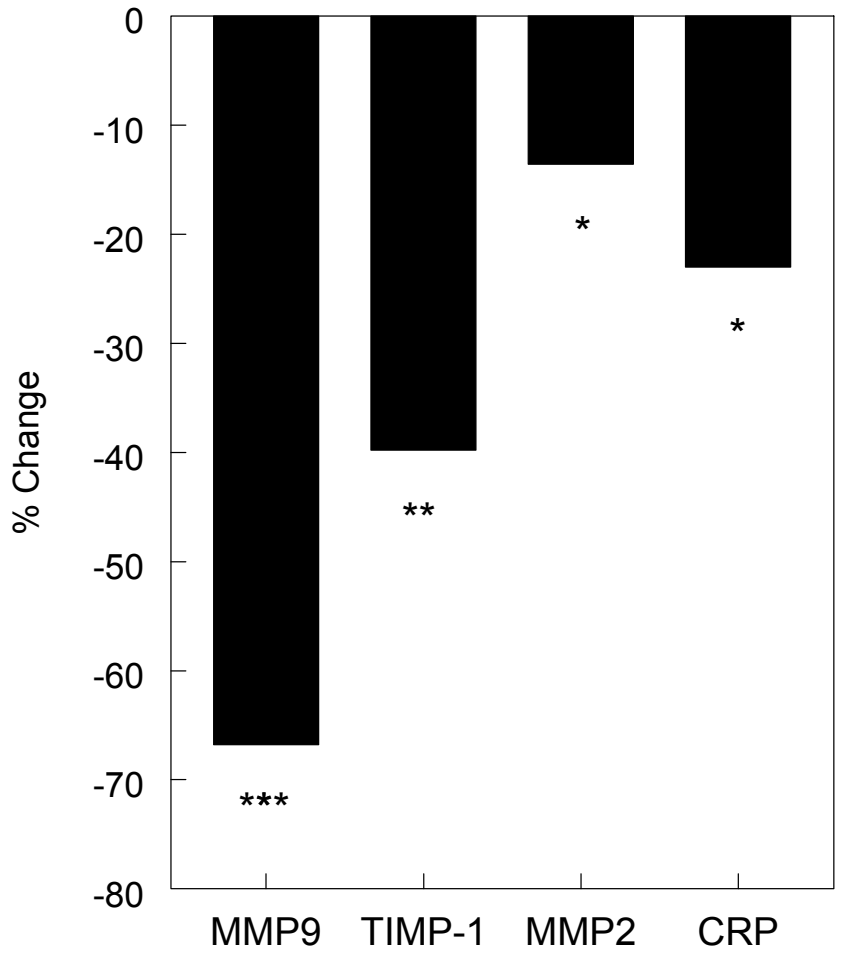
Changes in Markers of Inflammation



- 38 vitamin D deficient Bangladeshi-British adults age 35-65
- 25(OH)D
  pre: 8.6 ng/ml (21 nmol/l)
  post: 14.1 ng/ml (35 nmol/l)
- 1 year supplementation with 3-monthly vitamin D injection
- no control group
- (n=24-38)

Timms PM et al., Q J Med 95:787, 2002

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Inflammatory Bowel Disease

Retrospective study in 504 patients with inflammatory bowel disease

50% deficient, 11% severely deficient

In Crohn's disease and ulcerative colitis, vitamin D deficiency associated with higher disease activity and poorer quality of life.

Presented by A. Ulitsky at 2009 meeting of the American College of Gastroenterology

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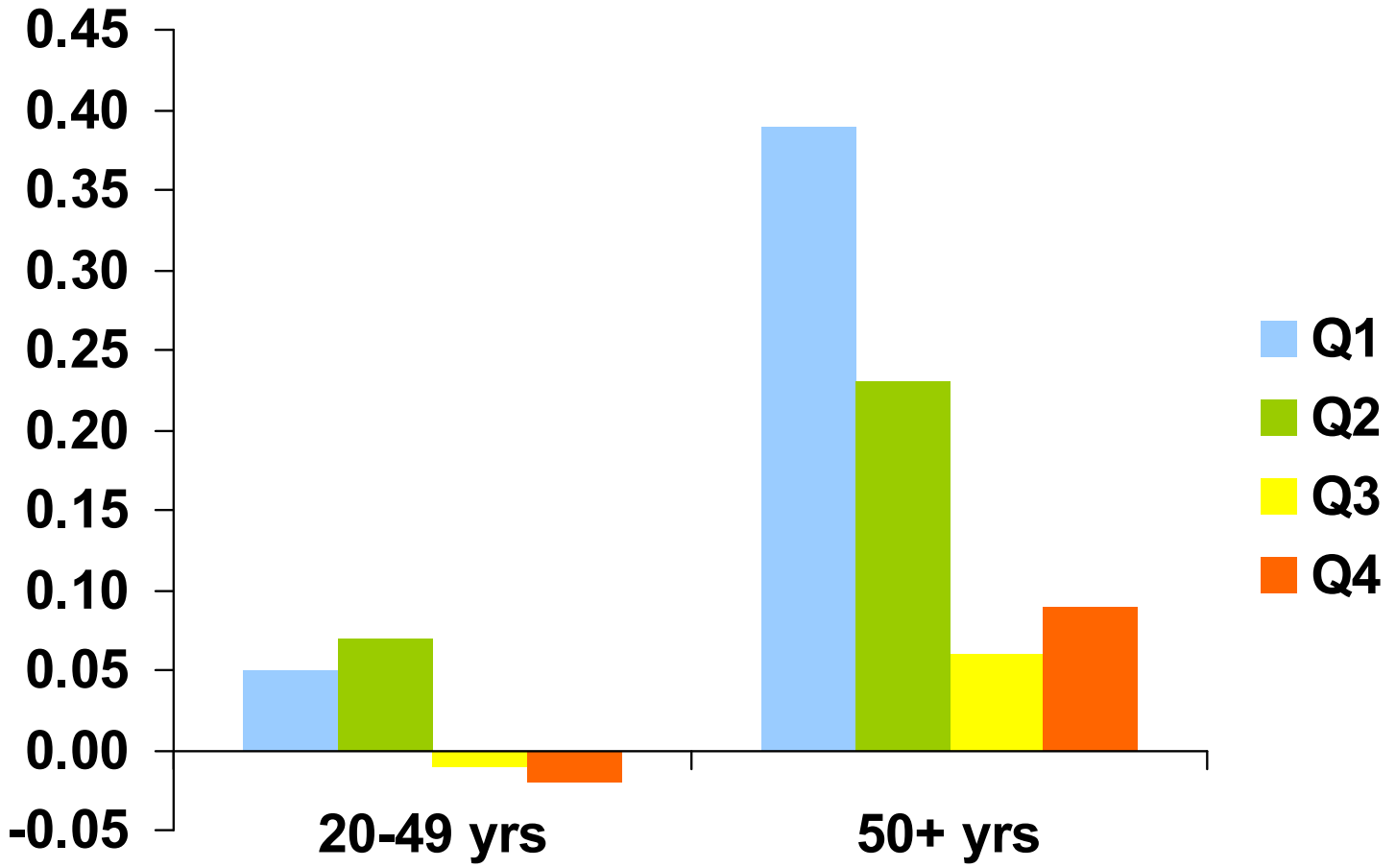
PERIODONTAL DISEASE: Adj. B (mm) for Periodontal Attachment Loss by Quintile of 25(OH)D (relative to Q5)

NHANES III



Dietrich T et al. Am J Clin Nutr 80:108, 2004

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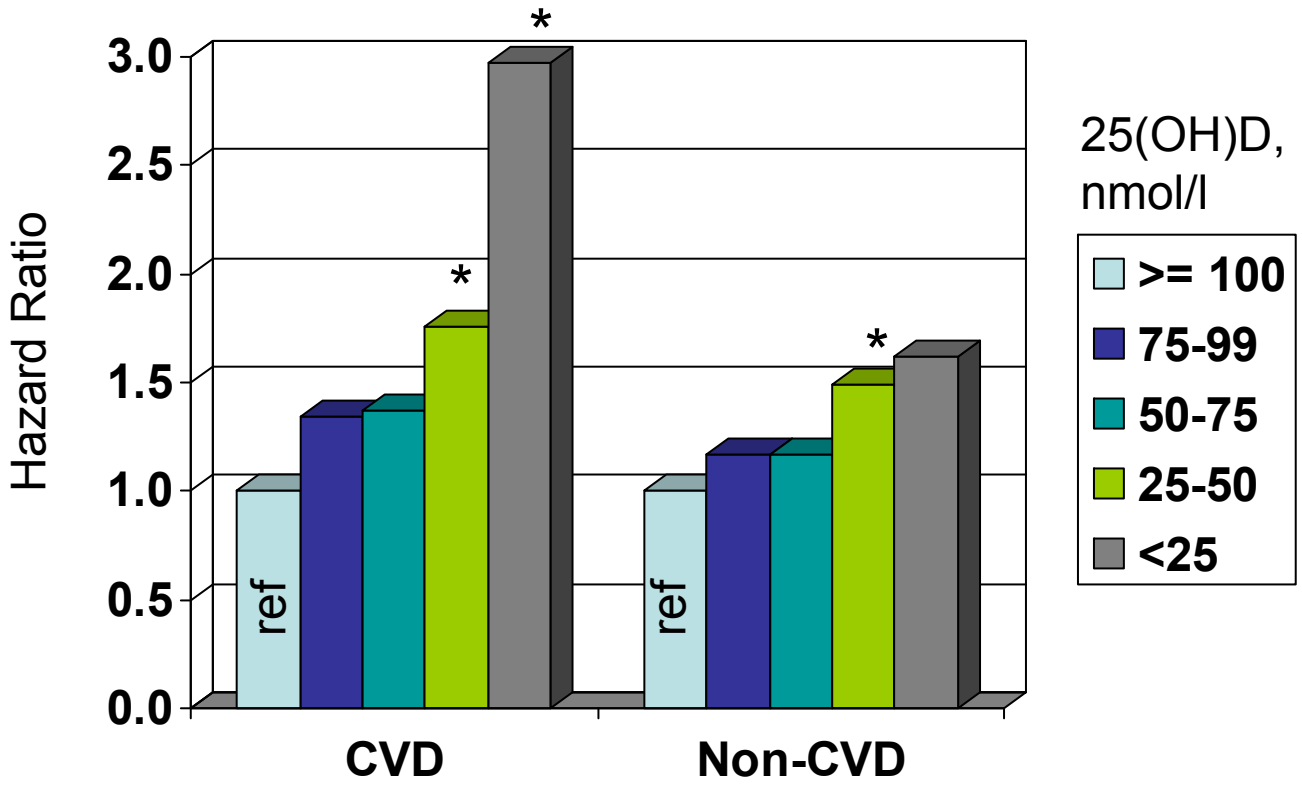
Risk of CVD and Non-CVD Mortality by 25(OH)D



NHANES III linked to mortality files

3408 adults age 65+ followed median 7.3 years

Ginde AA et al., JAGS 57:1595, 2009

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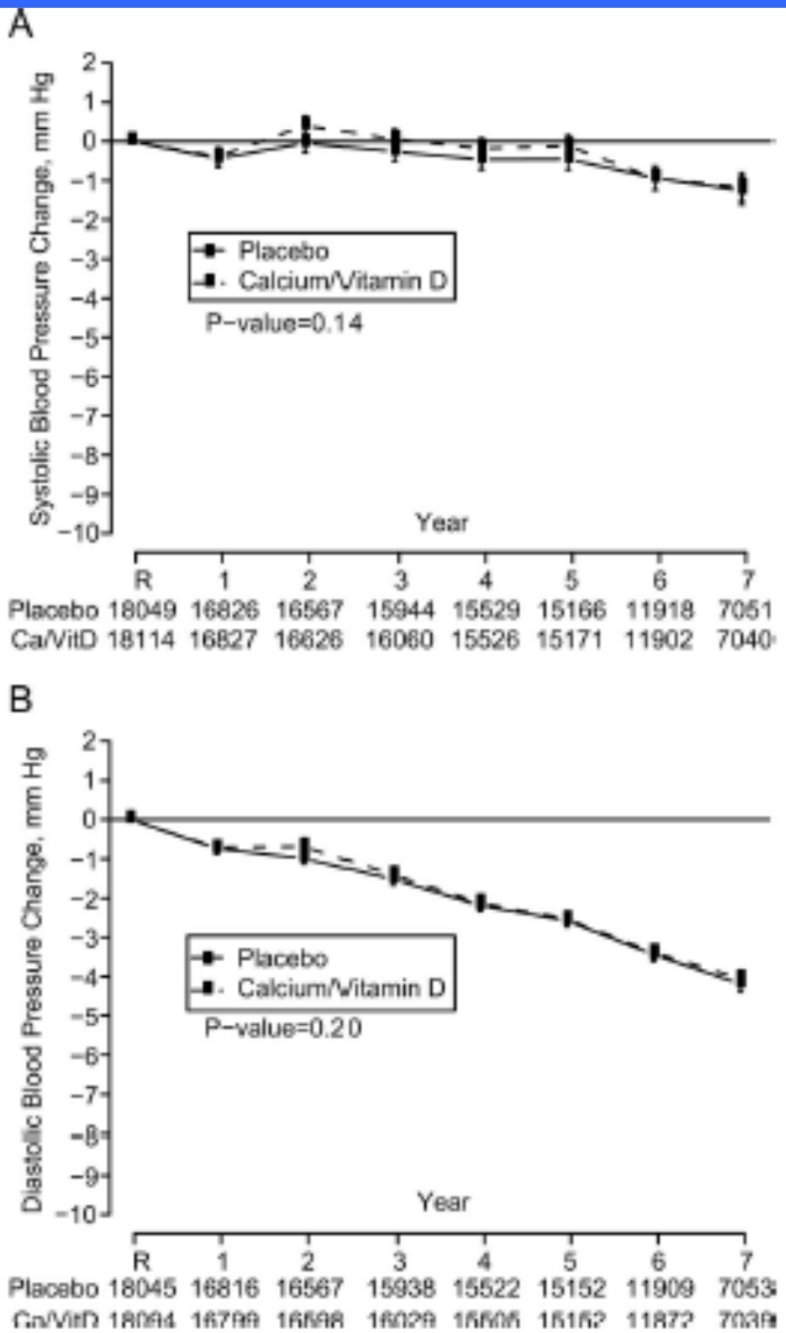

Women's Health Initiative[1]

36,282 women age 50-79

randomized to placebo or
1000 mg/d Ca + 400 IU/d D3

followed for 7 years

Lappe et al.[2] estimate
25(OH)D increase to have
been ≈ 2 ng/ml

[1]Margolis KL et al., Hypertension 52:847-55, 2008.

[2]Lappe JM, et al., Am J Clin Nutr 85:1586-91, 2007.

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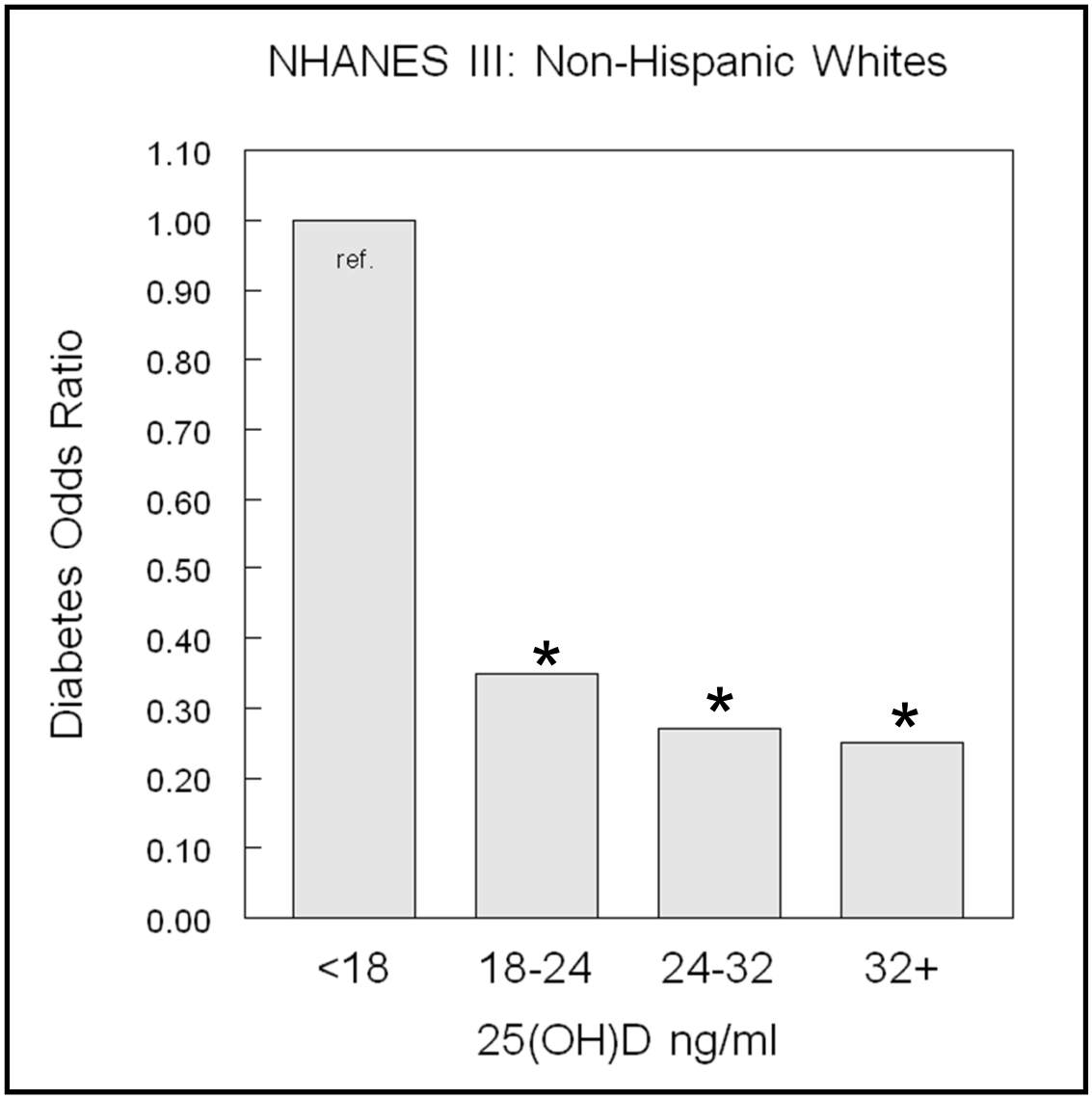

R Scragg, Diab Care 27:2813, 2004

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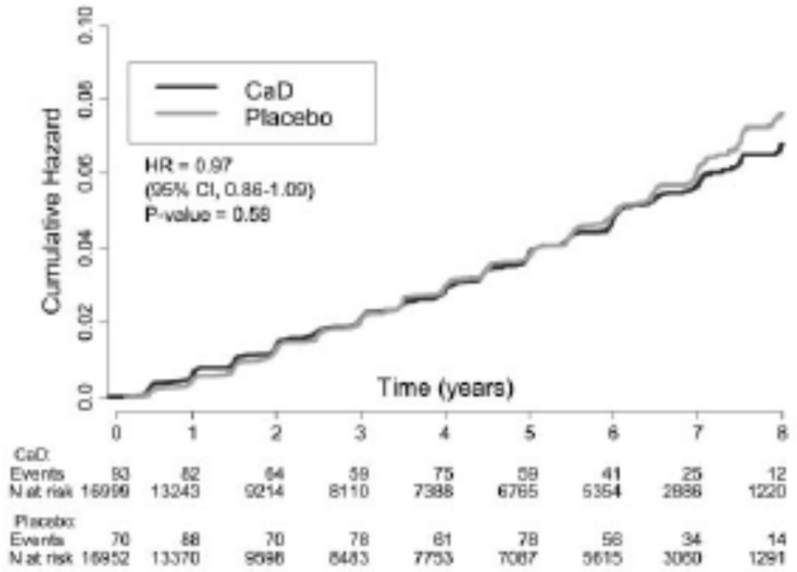
Cumulative Incidence of Diabetes



Per-protocol results above.
ITT results, P=0.72

Women's Health Initiative

33,951 women age 50-79

randomized to placebo or
1000 mg/d Ca + 400 IU/d D3

followed for 7 years

de Boer et al., Diabetes Care 31:701-7, 2008.

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The Association of Vitamin D with Physical and Cognitive Function

- good evidence from observational studies and some trials

- effects may be due to actions of vitamin D that are independent of its anti-inflammatory role

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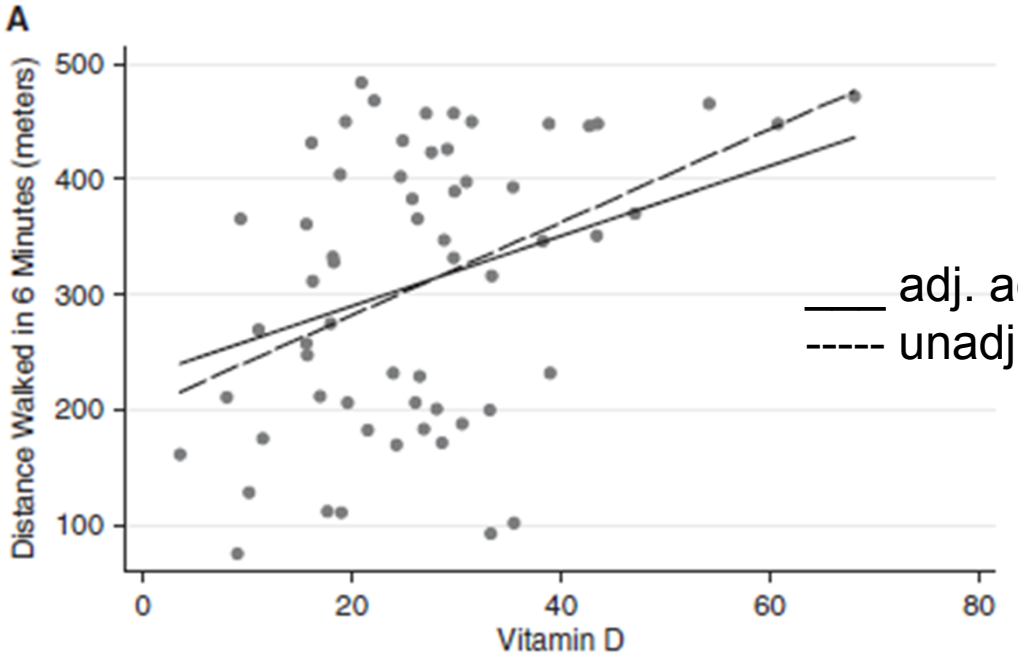
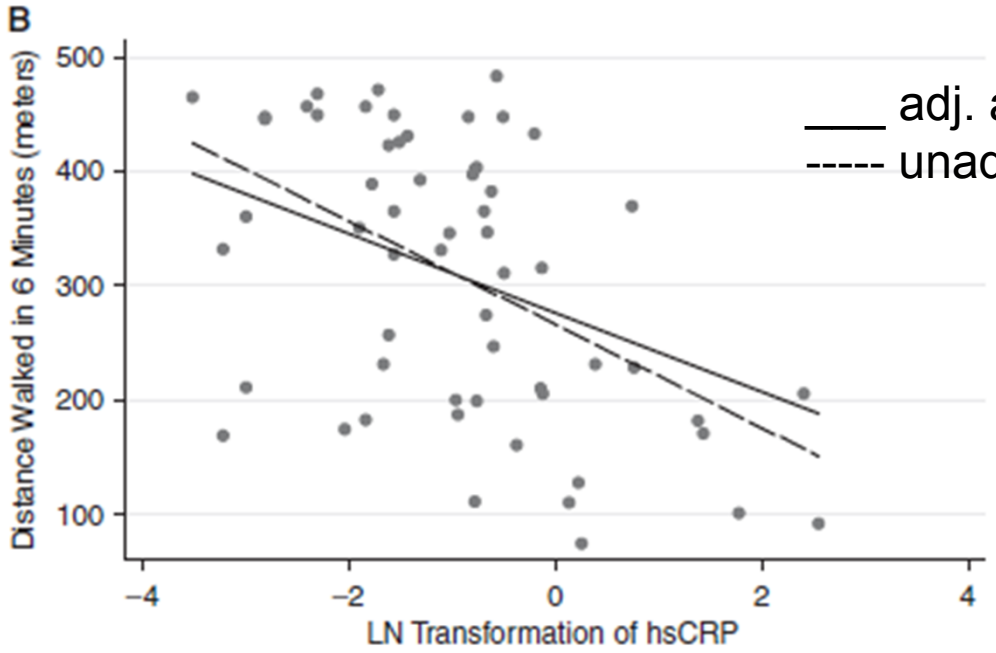


60 older men and women

____ adj. age, sex, hs-CRP
----- unadjusted



____ adj. age, sex, 25(OH)D
----- unadjusted

Boxer RS et al., JAGS 56:454, 2008

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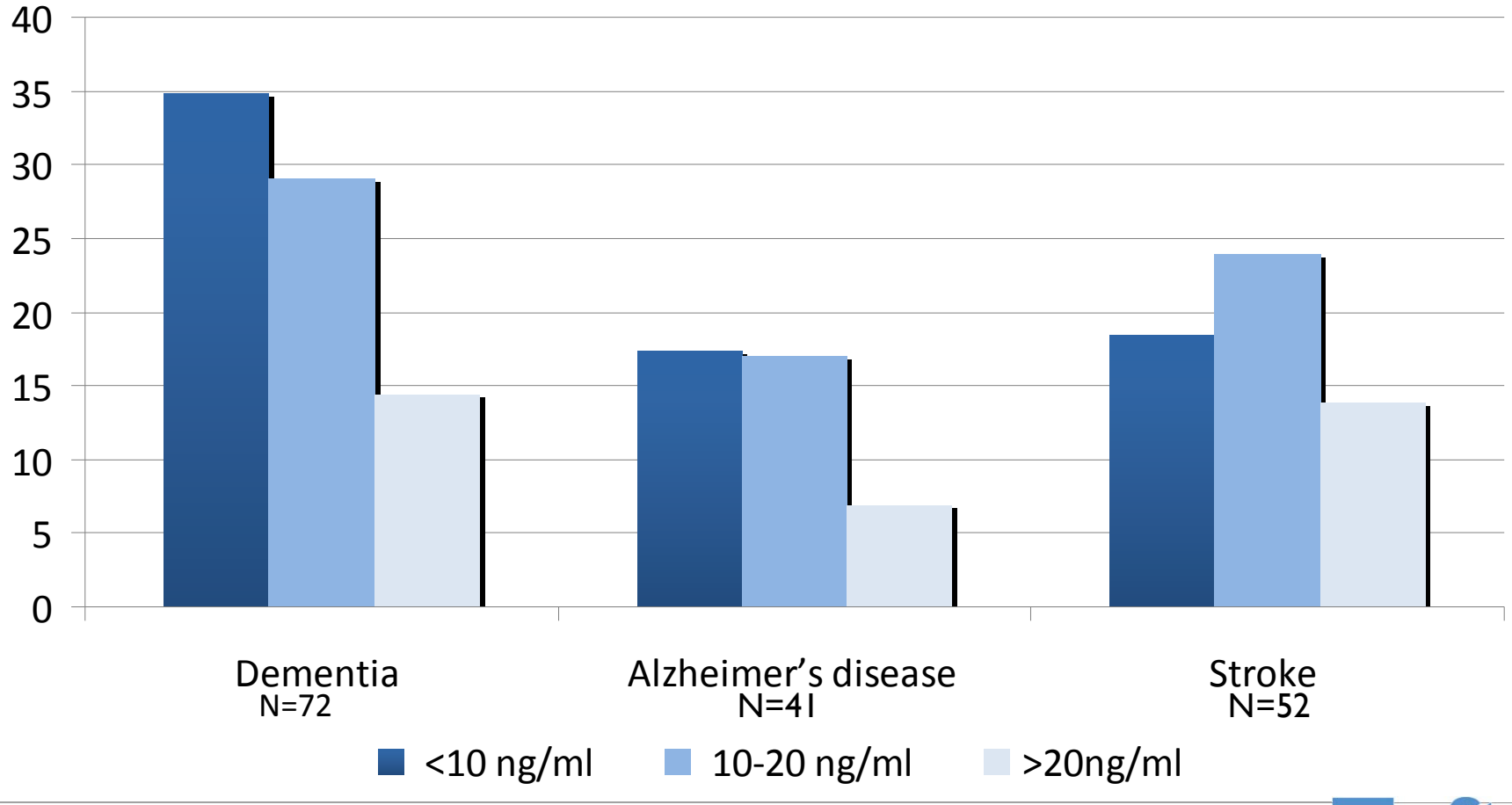
Prevalence of Dementia, AD, and Stroke by 25(OH)D Status



J.S. Buell

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Patient Populations

- Few studies except in chronic kidney disease
- Many effects may be more pronounced in patient populations due to
  - more profound D deficiency
  - potential need for greater 25(OH)D substrate

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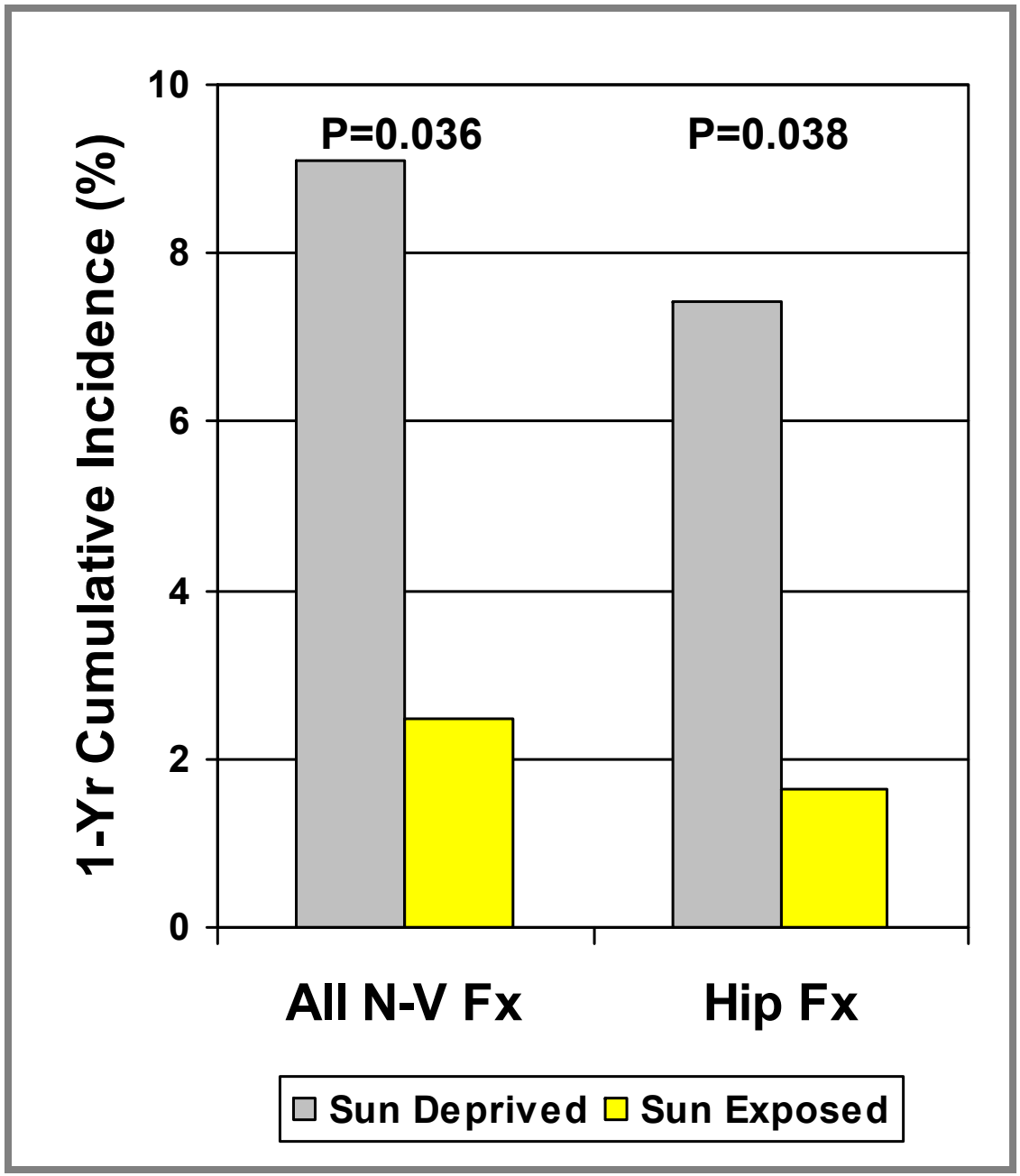

264 Hospitalized Alzheimer's patients mean age 72 yrs Japan, latitude 32 N (≈ San Diego)

Sunlight exposure for 15 min. per day on clear days vs.

Usual low sun exposure (83% had none)

Sato et al., J Bone Miner Res, 2005

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Vitamin D in Chronic Kidney Disease

- $1,25(OH)_2D$ declines in kidney disease due to reduced renal mass for conversion of 25(OH)D and also because of increased fibroblast growth factor-23
  - Gal-Moscovici, J Bon Miner Res, 22:V91, 2007
- Large observational studies demonstrate reduced mortality with administration of $1,25(OH)_2D$ or analogs
  - Kovesdy Arch Int Med 168:397, 2008
  - Tentori, Kidney Int 70:1858, 2006
- It may also be desirable to supplement these patients with 25(OH)D as substrate for autocrine/paracrine functions – this has received much less research attention

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Association of Calcitriol Treatment with Mortality in CKD

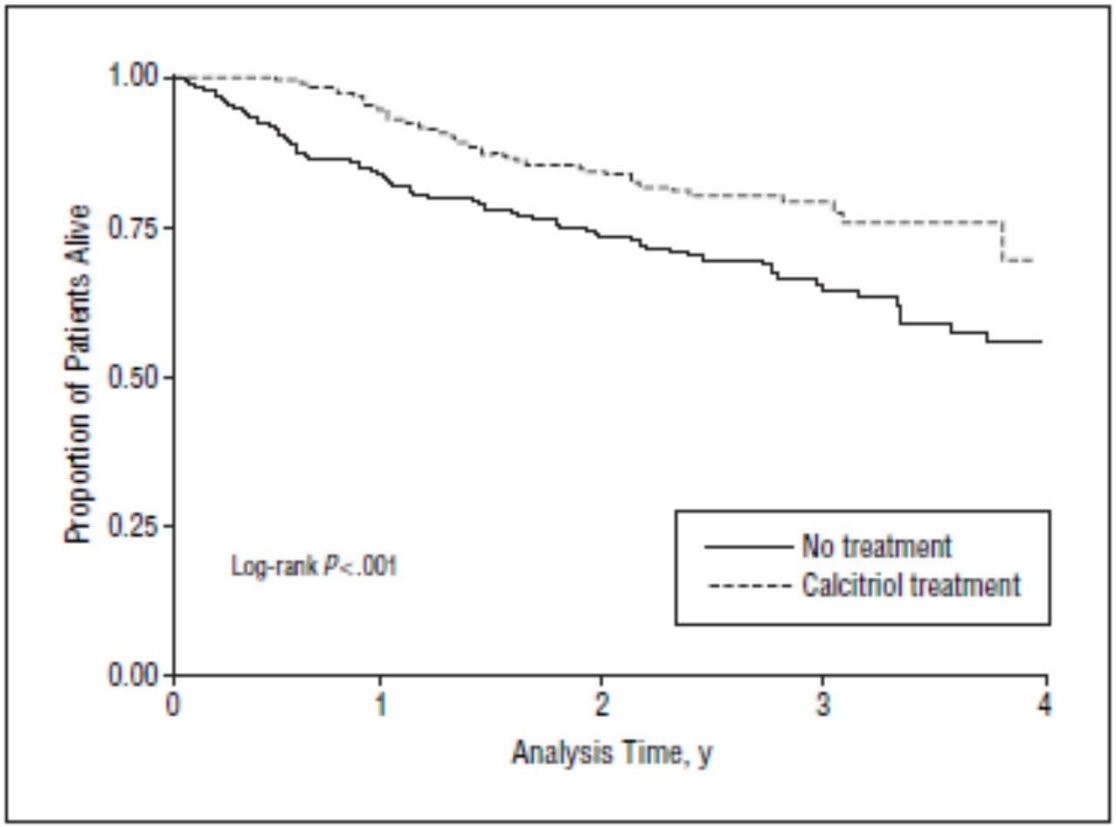

Figure 2. Kaplan-Meier curves for all-cause mortality, comparing calcitriol-treated vs untreated patients.

520 male US veterans, mean age 69.8

CKD stage 3-5, not yet receiving dialysis

Kovesdy CP, Arch Intern Med 168:397, 2008

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Summary of Evidence

Hypothesis	**Evidence from Observational Studies**	**Evidence from Vitamin D Intervention Studies**
Vitamin D affects immune response and inflammation in cells, animals	--	strong – many, varied studies
Vitamin D affects markers of inflammation in human studies	limited – few studies	limited – few studies
Vitamin D affects markers/precursors for diseases with inflammatory component	moderate – many studies, some large	limited – few studies, most small
Vitamin D affects prevalence/incidence of diseases with inflammatory component	moderate – many studies, some large	limited except for bone & falls
Vitamin D affects patient survival	good for CKD patients, otherwise limited	very limited to non-existent

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Ongoing Trials

Trials of vitamin D supplementation in older adults are now underway to look at effects on

- Cardiovascular Disease
  - Hypertension
  - Hypercholesterolemia
  - Metabolic Syndrome
- Type 2 Diabetes Mellitus
  - Insulin Resistance
  - Glucose Intolerance
- Systemic Lupus Erythematosus
- Asthma
- Chronic Obstructive Pulmonary Disease

Clinicaltrials.gov

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Considerations for Future Intervention Studies

- Lack of effect in prior studies may often have been due to inclusion of subjects with relatively high baseline 25(OH)D – focus should be on those with known or suspected deficiency
- Lack of effect also results from inadequate 25(OH)D step up – critical to chose high enough dose and attain high adherence rates
- Frail, ill elderly are the most likely to benefit but have been little studied except with respect to bone and falls

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Multiple Sclerosis Risk

Vitamin D levels (nmol/L)	OR (95% CI)
15.2 – 63.2	1.0
63.3 – 75.3	0.57 (0.30-1.07)
75.4 – 84.8	0.57 (0.30-1.07)
84.9 – 99.1	0.74 (0.40-1.36)
99.2 – 152.9	0.38 (0.19-0.75)*

White men & women only. Black & Hispanic: not significant (potentially due to lower numbers of cases).

Case Control: 148 cases, 296 controls

*P = .006

Munger KL et al. JAMA 2006.

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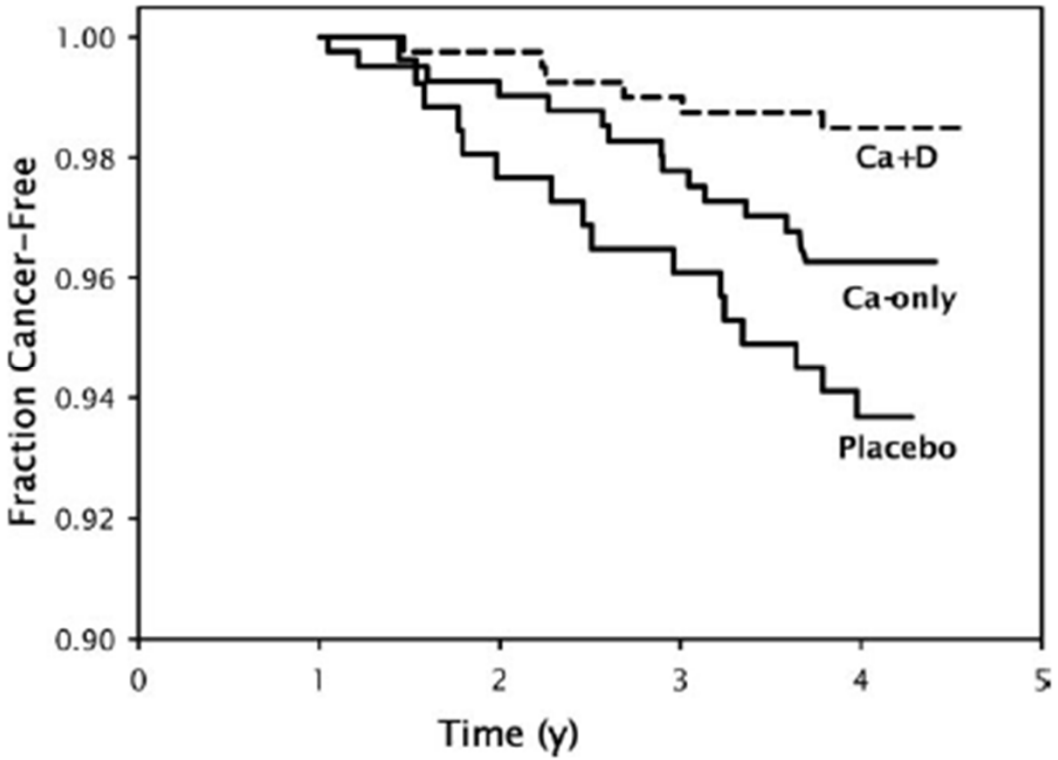
RCT: Calcium, Vitamin D and Cancer Incidence



Ca + 1100 IU vit D / day
RR=0.23

1400-1500 mg Ca / day
RR=0.59

Placebo
reference

1179 healthy postmenopausal women

Lappe JM et al., Am J Clin Nutr 2007:1586

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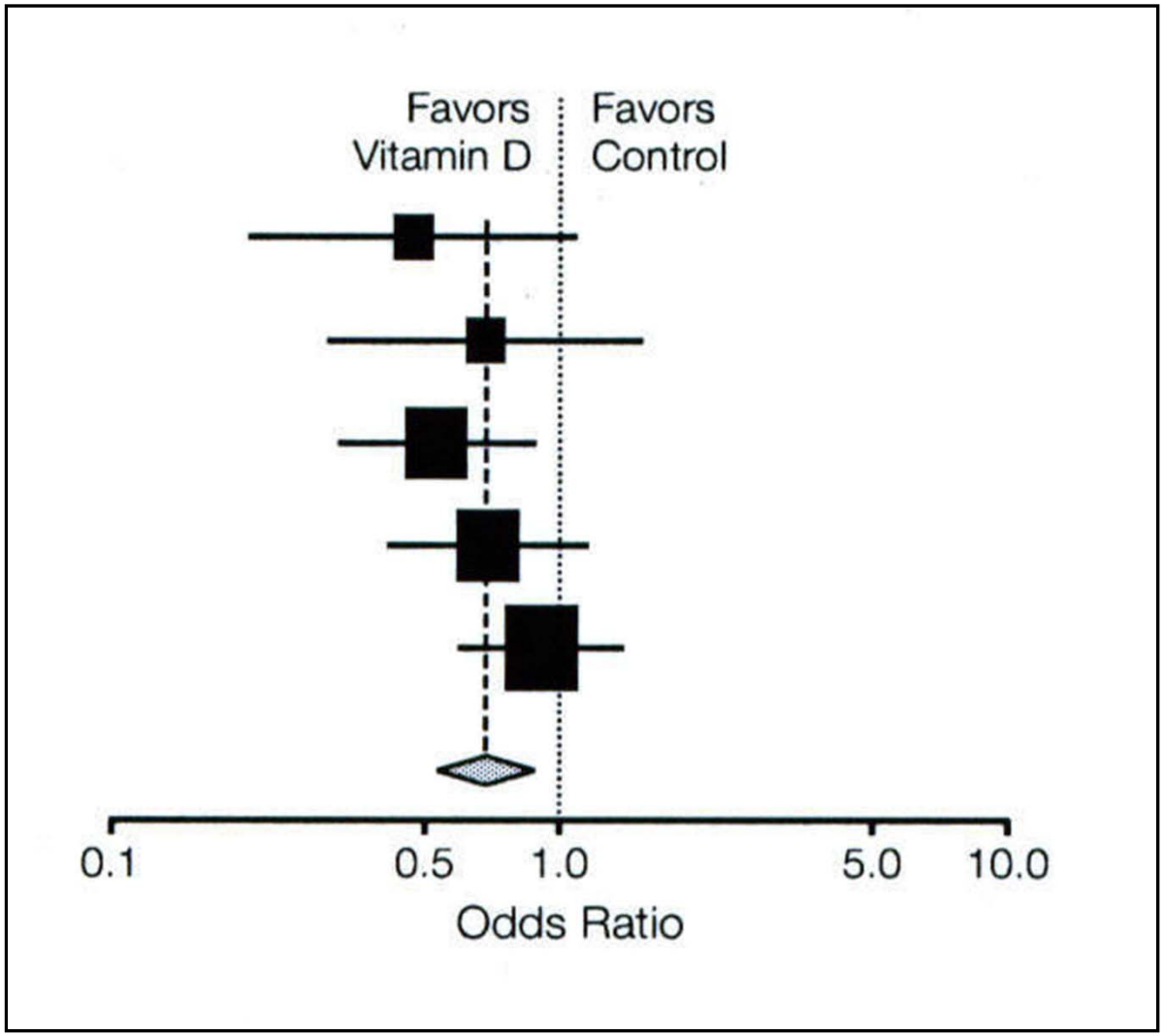
Meta-Analysis of Vitamin D and Falls



Bischoff-Ferrari, Dawson-Hughes. JAMA 2004.

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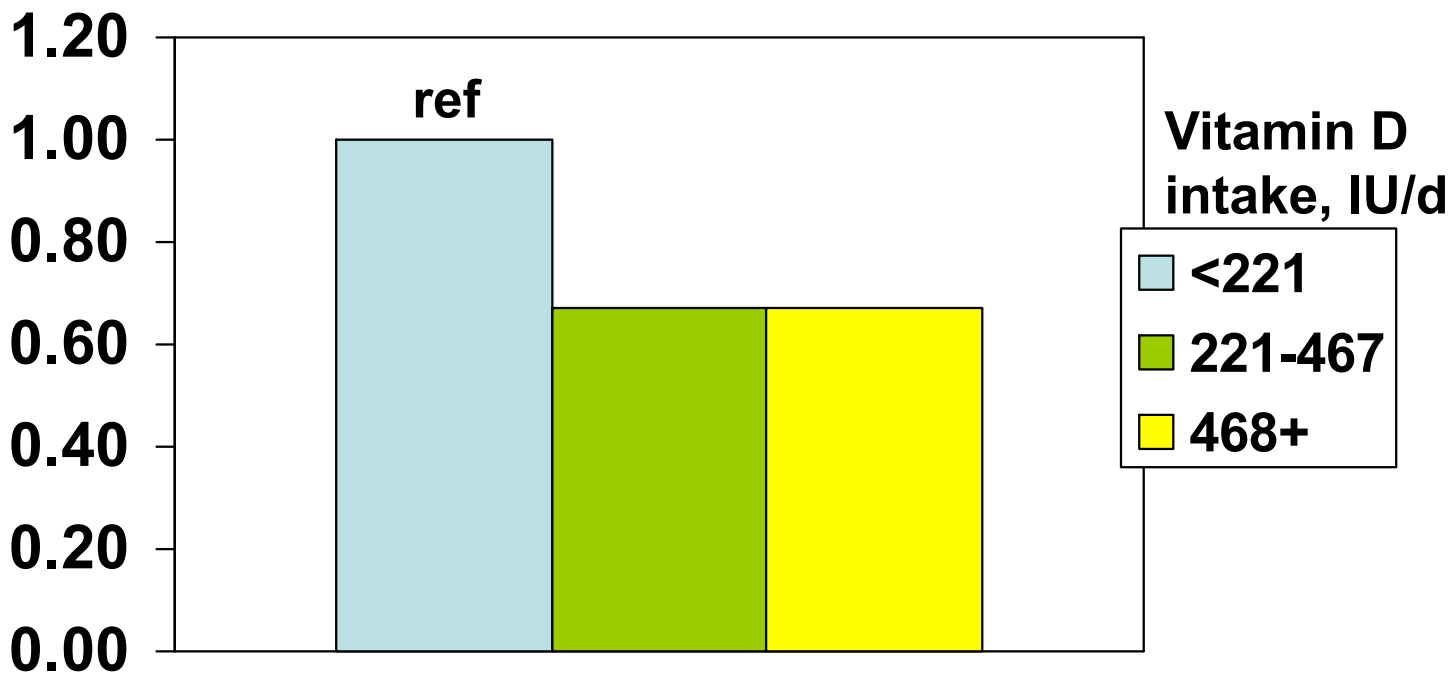
Iowa Women's Health Study: Adj. RR of Rheumatoid Arthritis



Merlino LA et al., Arthritis and Rheumatism 50:72, 2004

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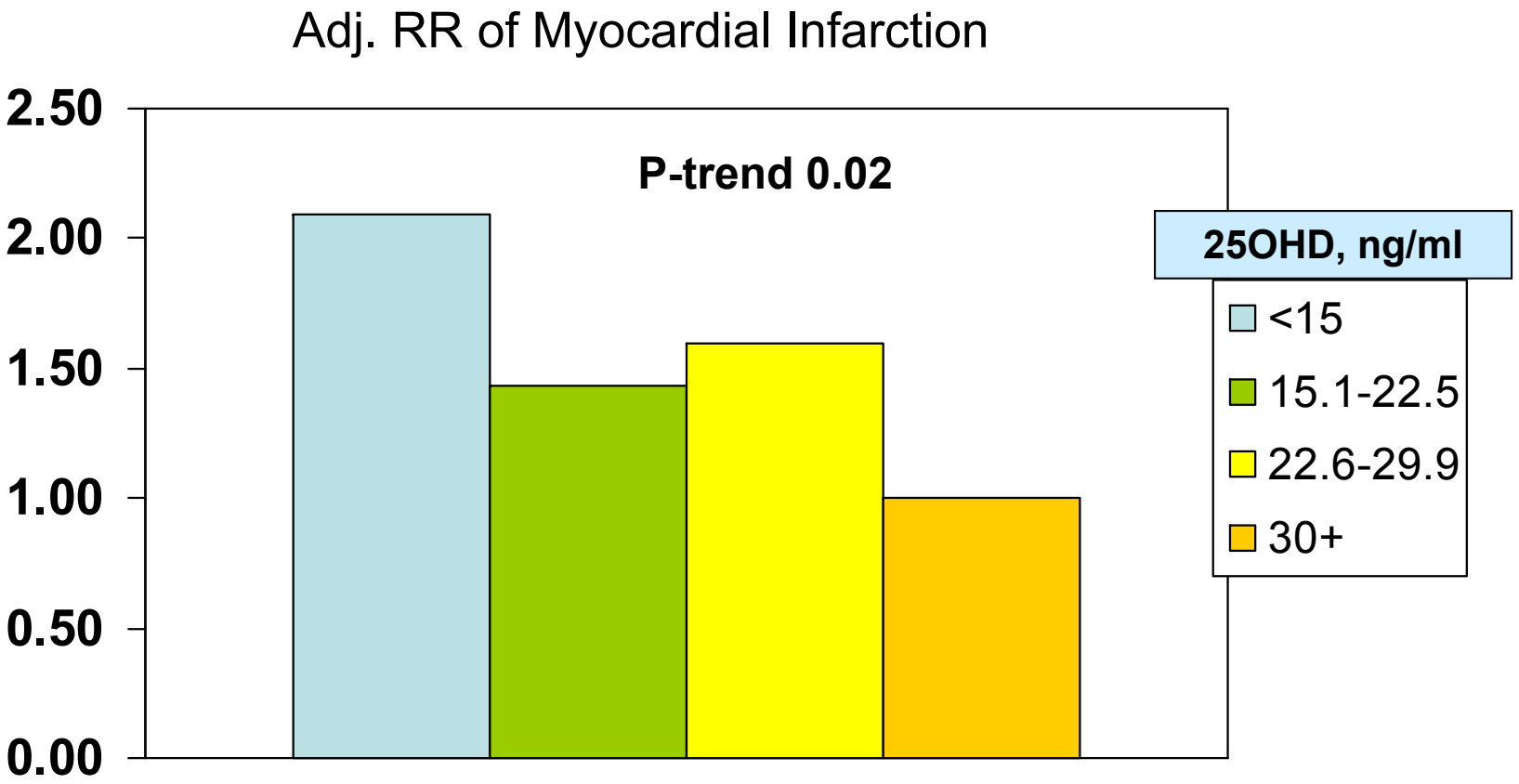
Health Professionals Follow-Up Study



Nested case-control in 18,225 men followed for 10 years

Giovannucci et al, Arch Int Med 2008

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Falls

- Considerable trial data supports protective effect of vitamin D supplementation ≥ 800 IU/d on falls in elderly
  - Bischoff-Ferrari JAMA 293:2257, 2005 (meta-analysis)
  - Broe JAGS 55:234, 2007
- No effect seen in some large, well-conducted studies possibly due to
  - low baseline risk of falls
  - small 25(OH)D step-up due to high starting value, low dose or poor compliance (e.g. RECORD Trial: Grant, Lancet 365:1621, 2005)

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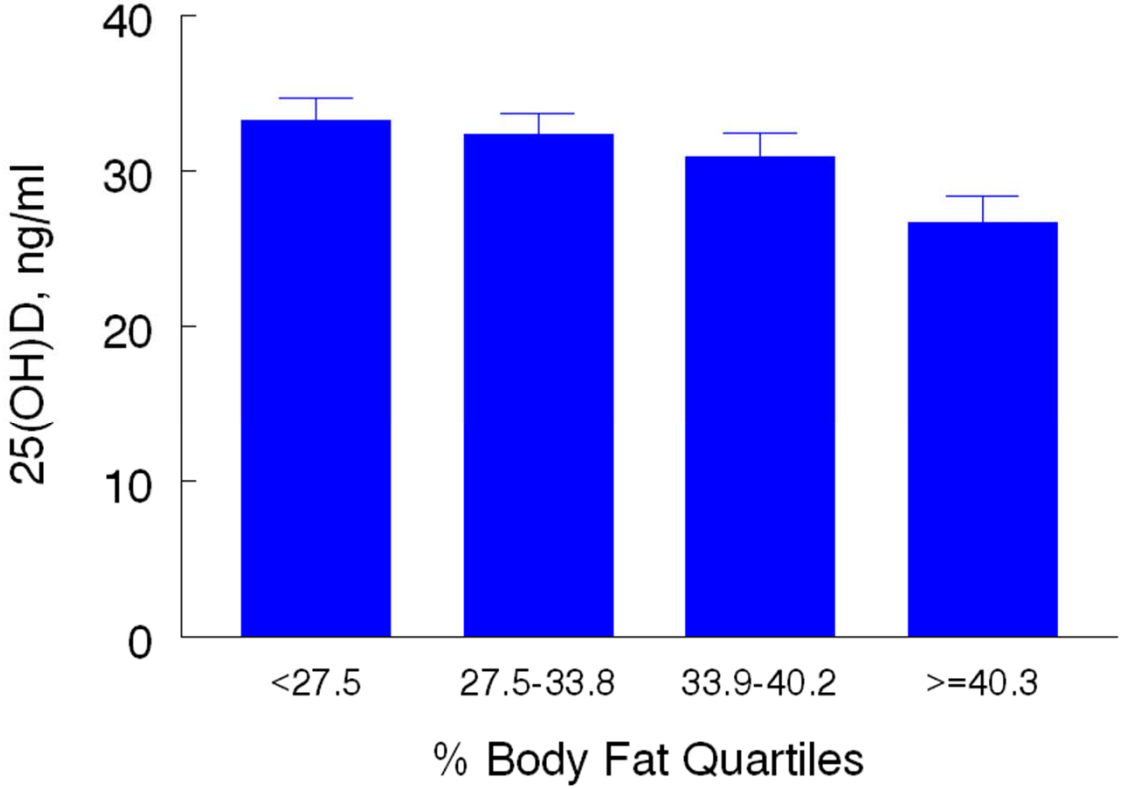
Obesity and Vitamin D Status



381 healthy adults
>= 65 yrs

adjusted for sex, age, vitamin D intake, season, sun exposure

Harris SS & Dawson-Hughes B, JCEM 2007:3155

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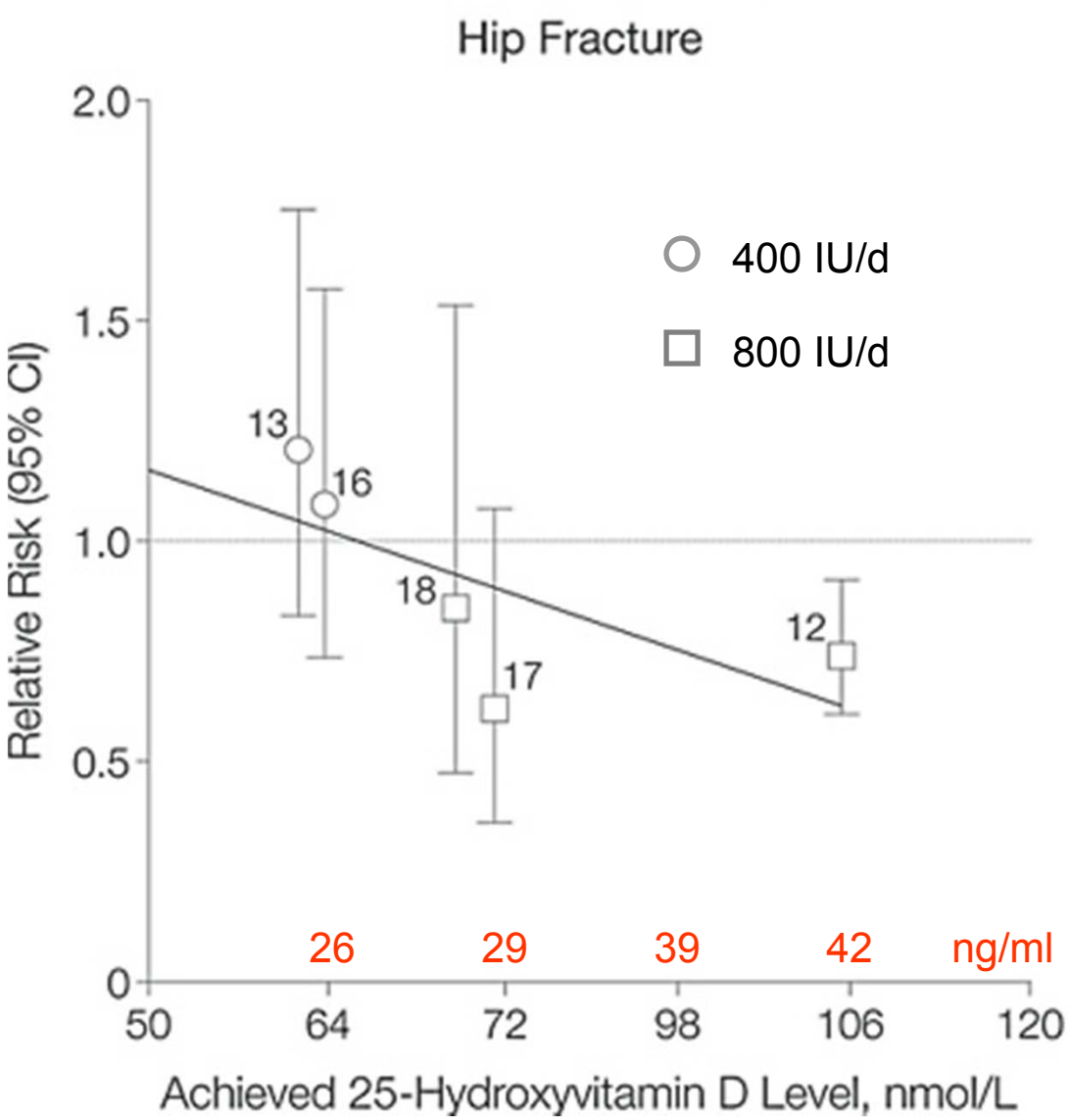

Meta-Analysis:

RCTs of oral vitamin D supplementation

Adults age 65+

Bischoff-Ferrari et al. JAMA 2005

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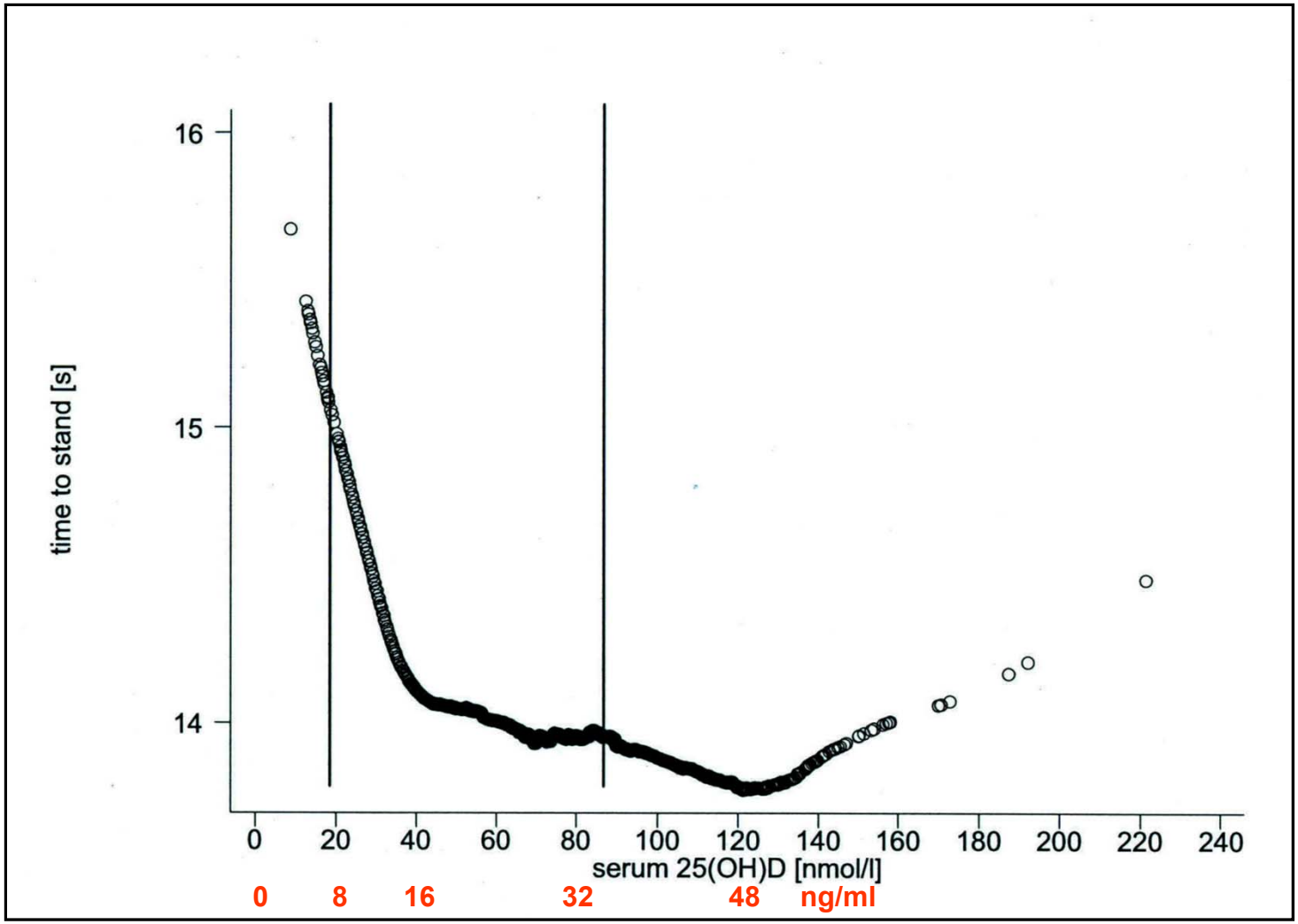
NHANES III: Time to Stand



Bischoff-Ferrari, Dawson-Hughes. Am J Clin Nutr 2004;80:752-8.

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