Debate on Vitamin D

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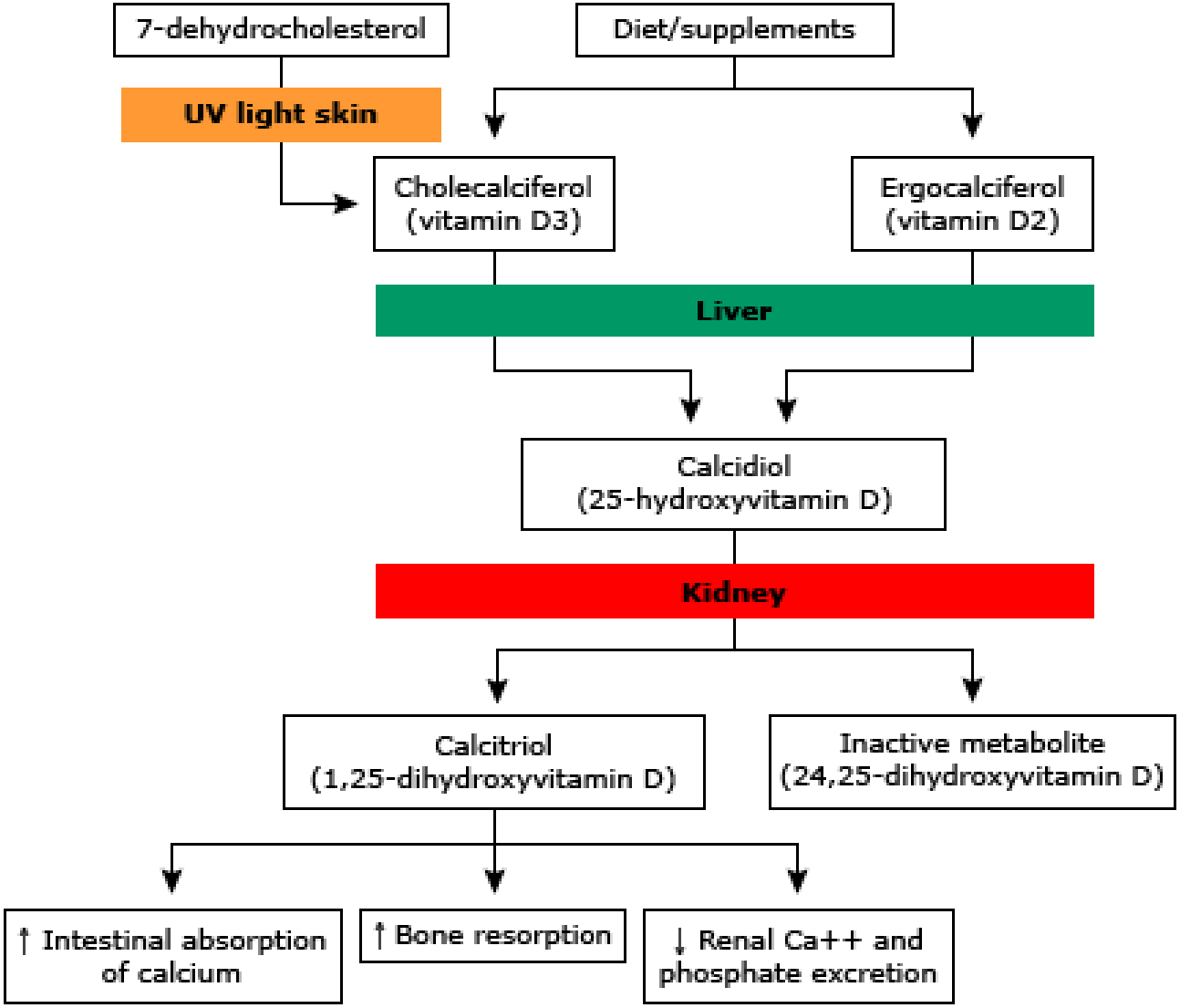
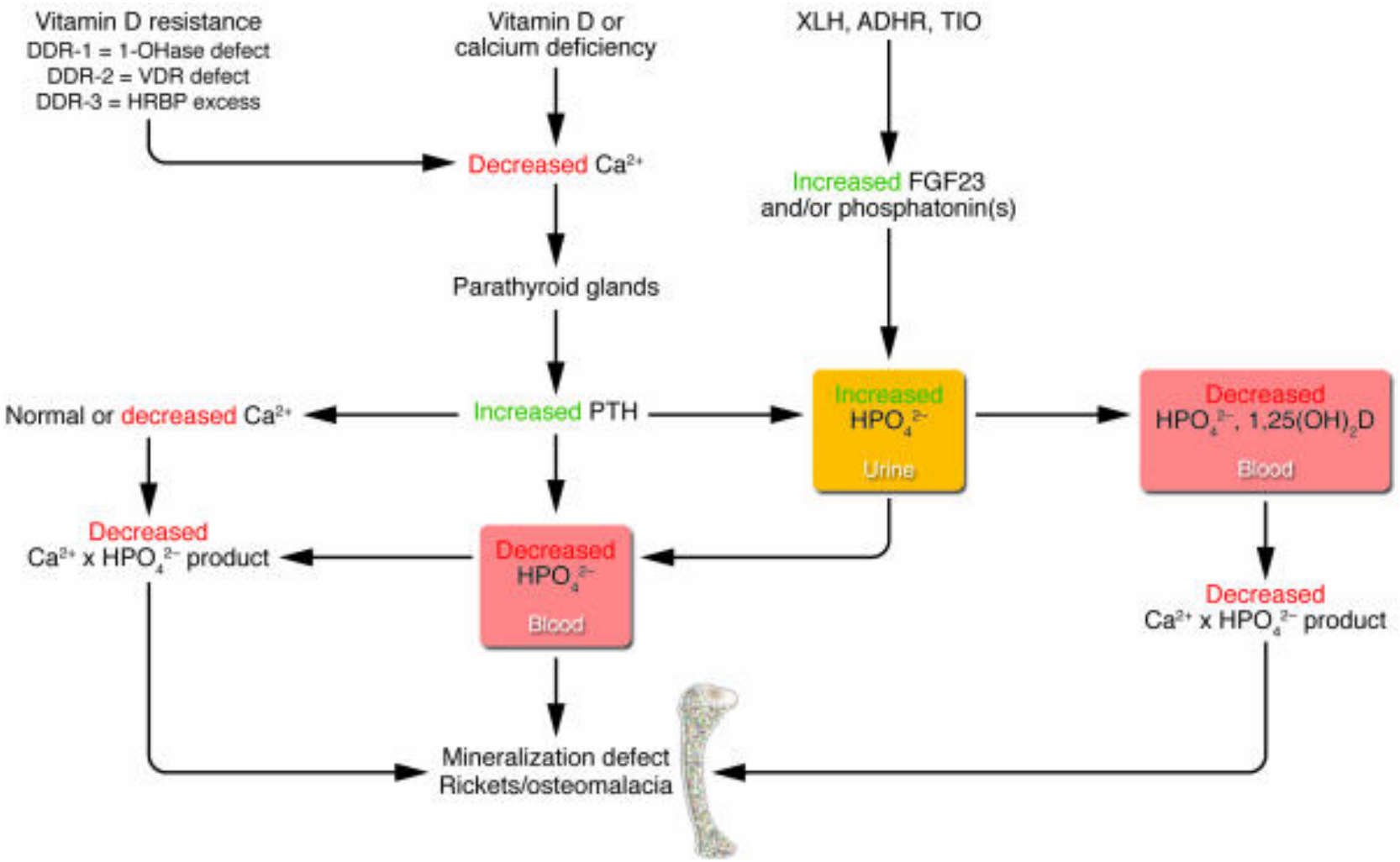
Overview

- **Background:**
  - Vitamin D metabolism
  - Proposed mechanisms for extra-skeletal benefits
- **Vitamin D in clinical outcomes and limits of available data** *(the discordance between observational studies and RCTs)*:
  - Caner
  - Cardiovascular
  - Diabetes
  - CKD
- **Summary**

Vitamin D metabolism



Skeletal action of vitamin D



M.F. Holick, JCI 2006

Vitamin D

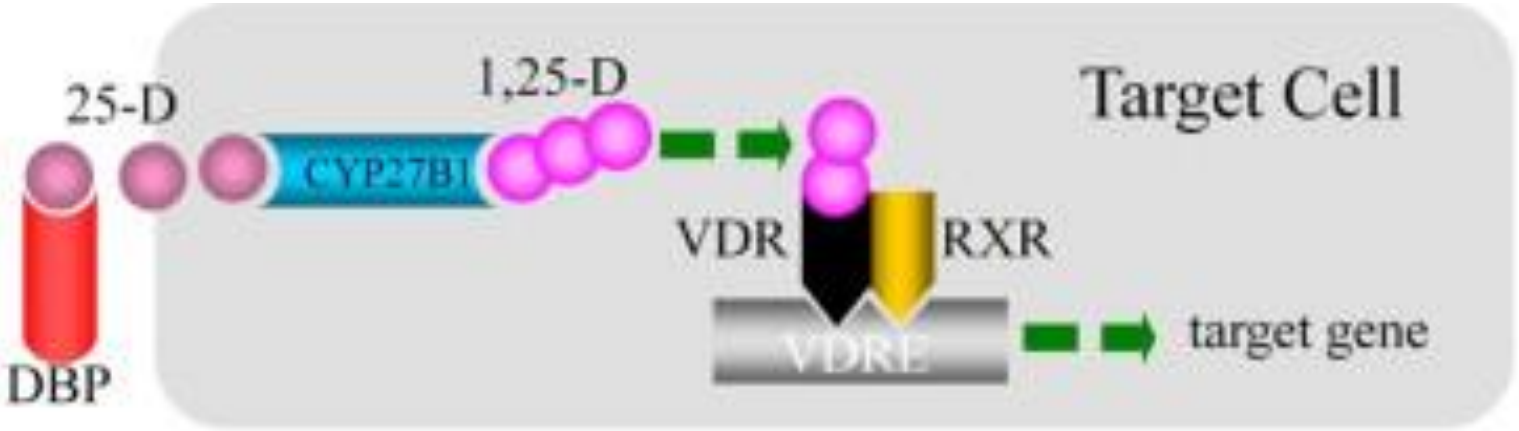
- Binds to nuclear VDR, resulting in direct or indirect regulation over a large number of genes:
  - 200-1250 (0.5-5% of total genome) genes have vit D response elements
  - Regulation over cellular proliferation/terminal differentiation, immunity, angiogenesis, insulin production, apoptosis, renin production.
- **VDR present in most cells** (including endothelial cells, pancreatic islet, neurons, T lymphocytes, cardiomyocytes, vascular smooth muscle and skeletal muscle, and hematopoietic cells)
- The local production of 1,25 (OH)2 D depends on **circulating levels of 25 OH D.**

Human cells co-expressing the CYP27B1-hydroxylase and vitamin D receptor

Macrophage	Enterocyte
Dendritic cell	Decidual stromal cell
Parathyroid cell	Fetal trophoblast
Osteoblast	Prostate epithelial cell
Osteoclast	Vascular endothelial cell
Keratinocyte	Pancreatic islet cell
Mammary epithelial cell	Renal tubular cell

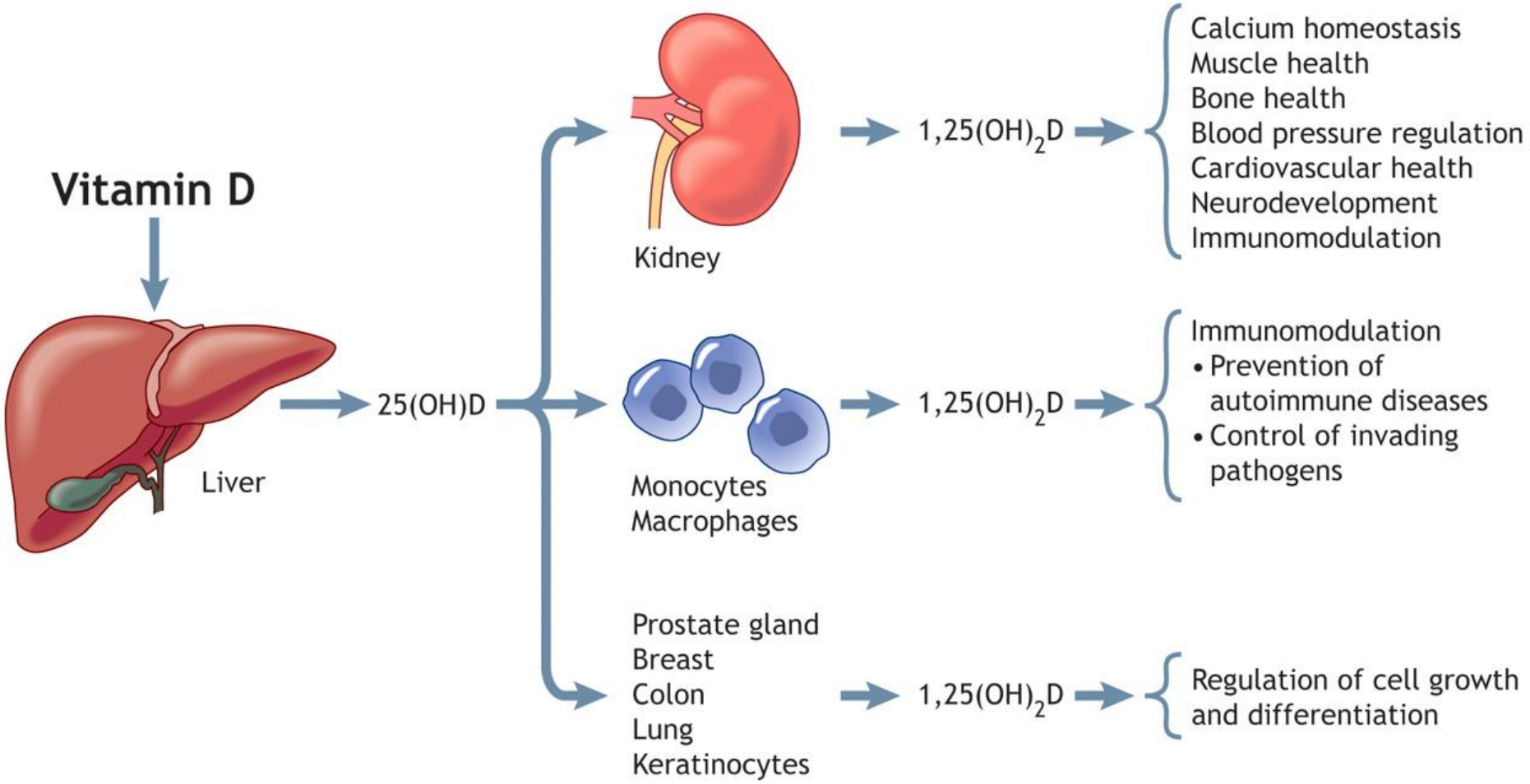
Regulation of the extrarenal CYP27B1-hydroxylase

The local production of 1,25 (OH)2 D depends on **circulating levels of 25 OH D.**



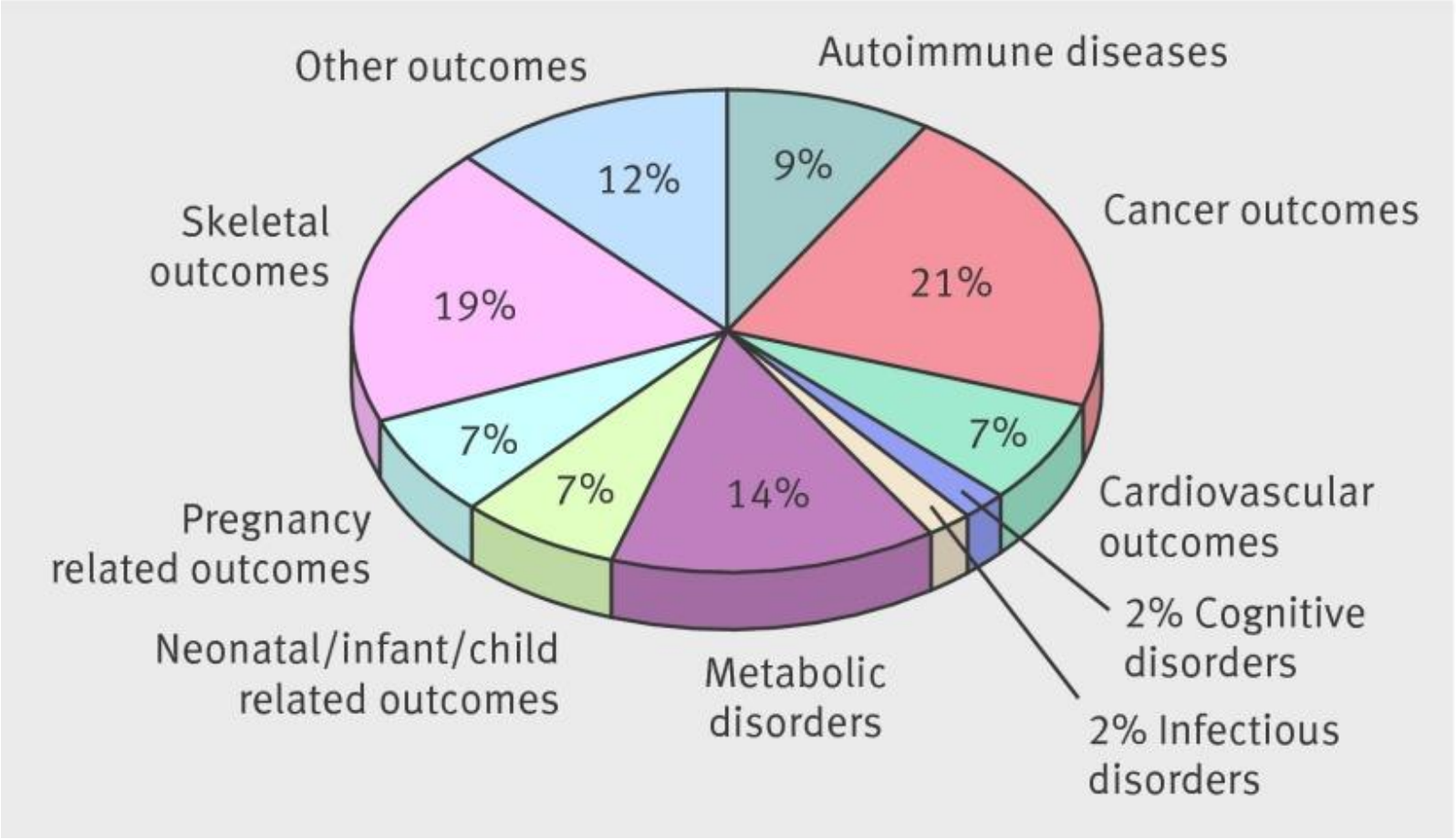
J Steroid Biochem & Molecular Biology (2014)144:22

Effects of vitamin D



CMAJ (2006)174:1287-1290

Map of vitamin D related outcomes

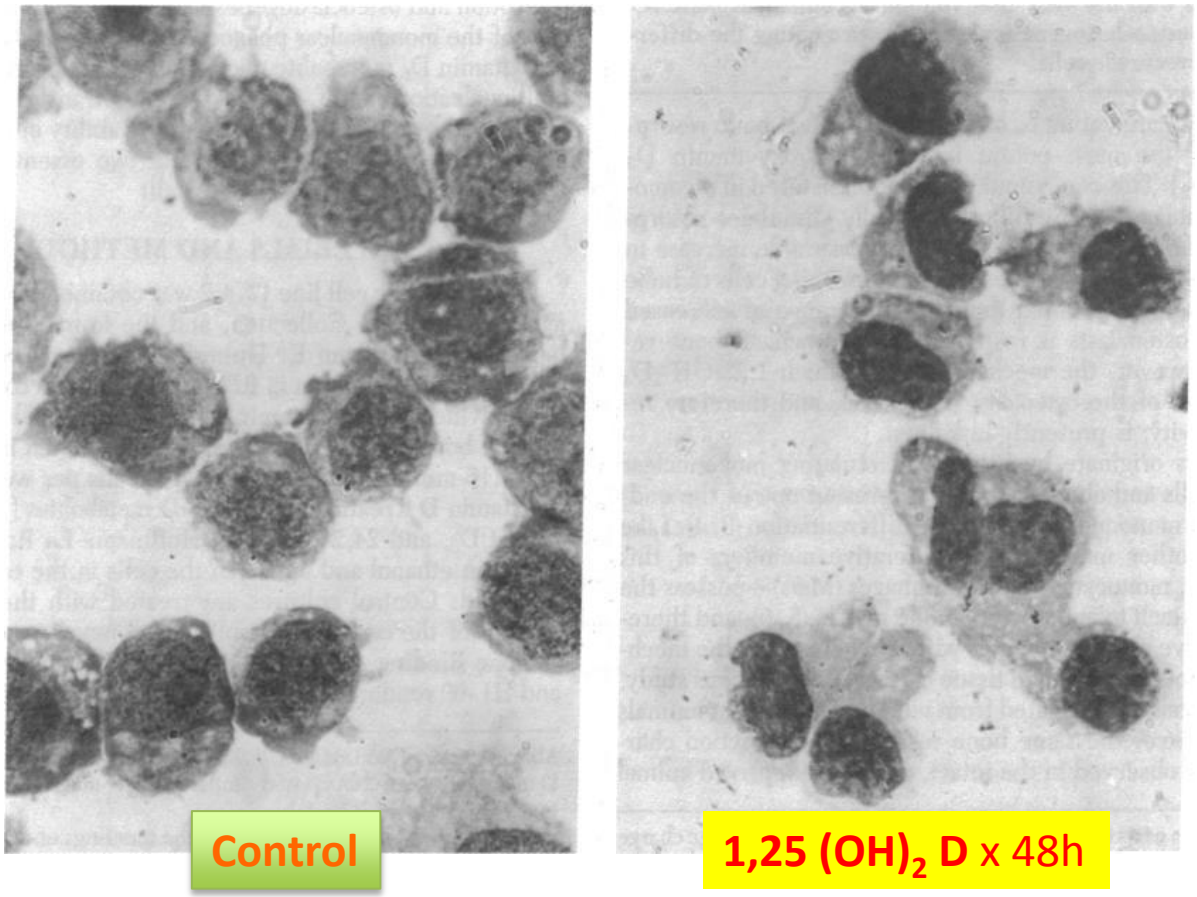


BMJ. 2014;348:g2035

Vitamin D and cancer

Vitamin D and immunology

Induction of monocytic differentiation by
1,25-dihydroxyvitamin D3 (human promyelocytic cell line)



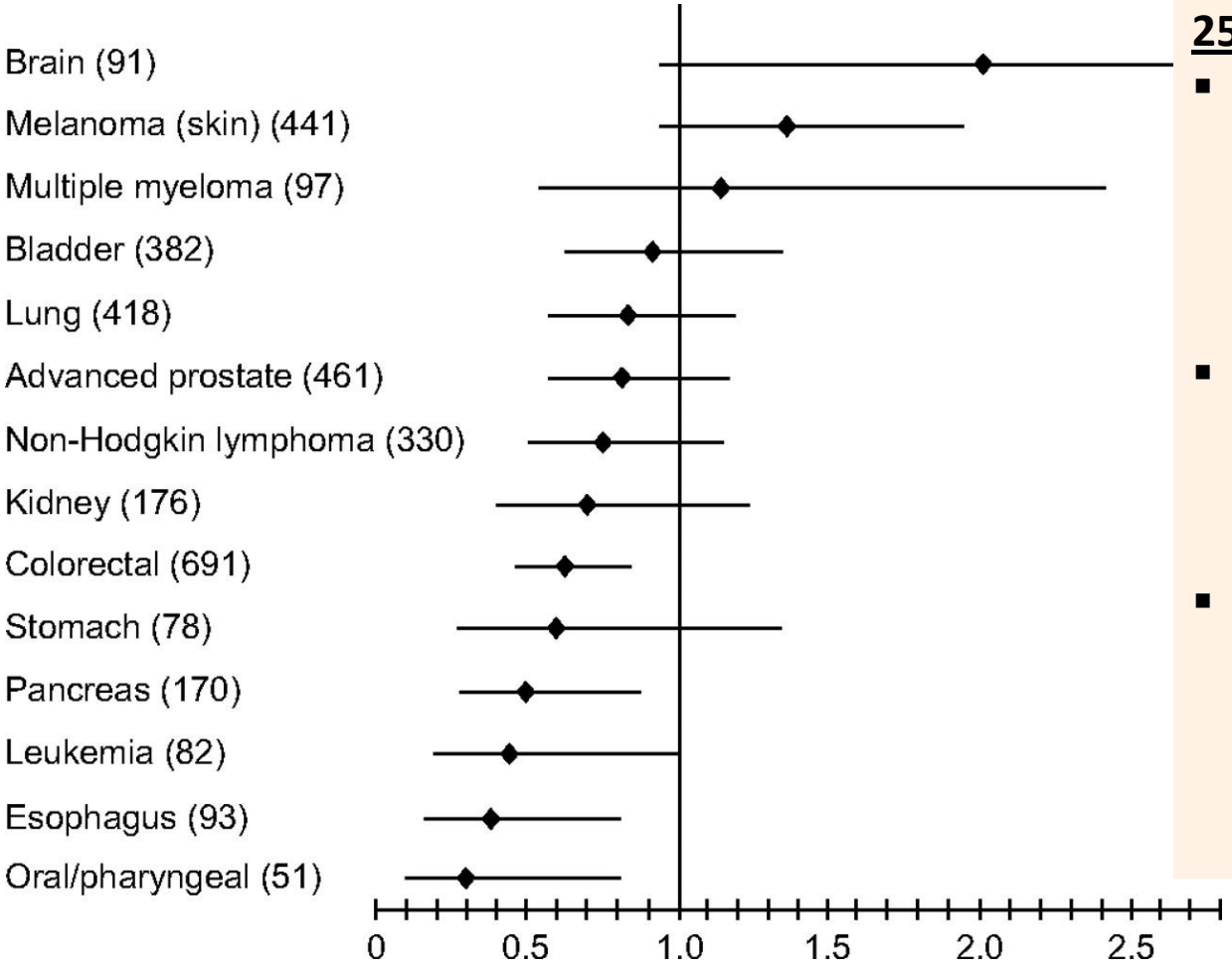
PNAS 1983

Antineoplastic effects of Vitamin D

- **Inhibition of proliferation and induction of differentiation:**
  - 1,25-(OH)2D blocks the progression of cells from the G1 to the S phase of the cell cycle either directly or through the induction of other growth factors.
- **Induction of apoptosis:**
  - induces apoptosis in a number of tumor models, including carcinomas of the breast, colon, and prostate
  - Mechanism not fully elucidated
- **Inhibition of angiogenesis and invasiveness**
  - *Effect shown in vitro* and *in vivo* experimental models

RR for cancer for an increment of 25 nmol/L in predicted plasma 25-OH D level

The Health Professional Study: N=51,529 men



25 OH D level available in 1095:

- Determinants of vit D level (sun exposure, skin color, BMI, intake, season, age) quantified through multiple linear regression model.
- The results from the model used to compute a predicted 25(OH)D level for each of 47, 800 men in the cohort.
- prospectively examined predicted 25 OH D level in relation to cancer risk with multivariable Cox proportional hazards models.

J Natl Cancer Inst (2006) 98:451

Prospective Study of 25 (OH) D3 level and cancer mortality in the US

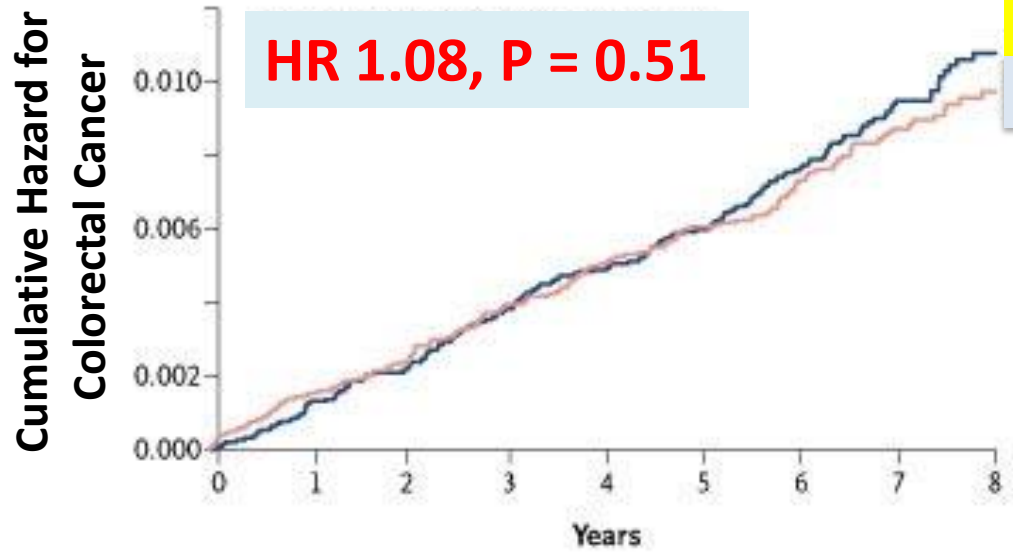
Relative Risks for cancers according to baseline vitamin D levels in NHANES III Study, 1988-2000

Cancer Site	25 (OH) D (nmol/L)				
	<50	50-<80	80-<100	≥100	P trend
Lung	1.0	0.78	0.65	1.14	0.41
Breast	1.0	0.28			0.76
prostate	1.0	0.91			0.95
Lymphoma/leukemia	1.0	1.34			0.96
Colorectal	**1.0**	**0.44**	**0.28**		**0.02**

J Natl Cancer Inst (2007) 99 (21): 1594

Vitamin D therapy does not reduce colorectal cancer risk

A RCT involving 36,282 postmenopausal women from 40 Women's Health Initiative centers (1000 mg of calcium + 400 IU D3)



Calcium+vitamin D									
No. of events	0	23	17	28	20	19	27	23	9
No. at risk	18,176	18,048	17,936	17,780	17,605	17,248	14,680	9138	4403
Placebo									
No. of events	0	27	16	27	20	18	20	17	7
No. at risk	18,106	17,967	17,832	17,663	17,471	17,093	14,530	9041	4351

Wactawski-Wende J et al. NEJM 2006;354:684

Colorectal Cancer risk according to the baseline 25-OH D Level a Nested Case–Control Study.

Table 2. Odds Ratios for Invasive Colorectal Cancer According to the Quartile of Serum 25-Hydroxyvitamin D Level at Baseline and Treatment Groups in a Nested Case–Control Study.*

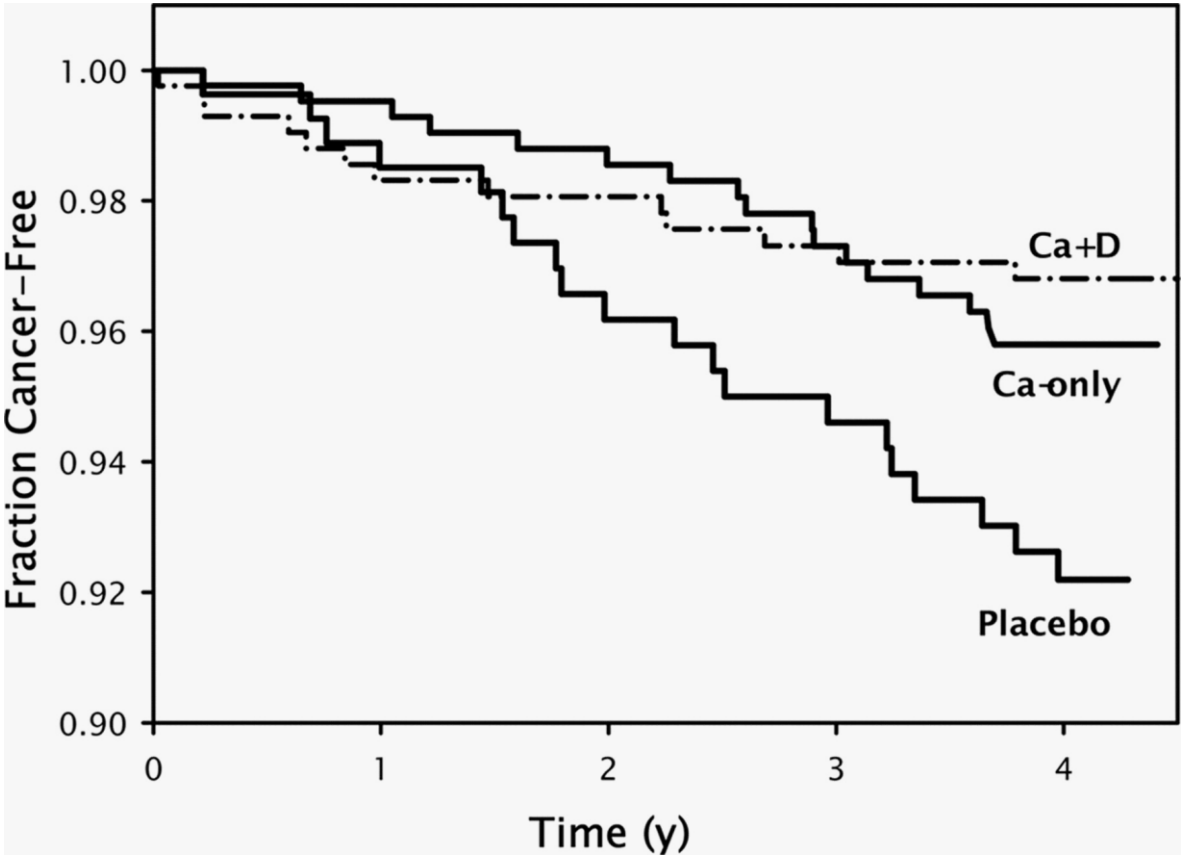
Baseline Serum 25-Hydroxyvitamin D	Main-Effect Odds Ratio (95% CI)†	Calcium + Vitamin D	Placebo	Intervention Odds Ratio (95% CI)‡
		No. with Colorectal Cancer/ No. of Controls		
≥58.4 nmol/liter	1.00	33/48	27/45	1.15 (0.58–2.27)
42.4–58.3 nmol/liter	1.96 (1.18–3.24)	44/41	34/32	1.12 (0.59–2.12)
31.0–42.3 nmol/liter	1.95 (1.18–3.24)	35/32	45/41	0.99 (0.51–1.91)
<31.0 nmol/liter	2.53 (1.49–4.32)	46/39	42/28	0.75 (0.39–1.48)

* To convert values for 25-hydroxyvitamin D to nanograms per milliliter, multiply by 0.401. CI denotes confidence interval.
† Odds ratios were derived from a logistic-regression model, conditioned on case–control pairs, estimating the main effect of the serum 25-hydroxyvitamin D level on the risk of invasive colorectal cancer (P for trend = 0.02).
‡ P for interaction = 0.54. The odds ratios were obtained from a logistic-regression model, conditioned on case–control pairs, and estimate the calcium with vitamin D intervention effect on the risk of colorectal cancer, according to serum 25-hydroxyvitamin D levels.

Wactawski-Wende J et al. N Engl J Med 2006;354:684

Vitamin D *(higher dose)* and calcium supplementation reduces cancer risk

RCT in 1179 healthy postmenopausal women in Nebraska (1500 mg Ca/1100 IU of D3)



25 (OH) D levels

	Baseline	12 mo
Placebo	72	71
Ca only	72	71
Ca + vit D	72	**96**

The first RCT that raised serum 25(OH)D >80 nmol/L for cancer outcome.

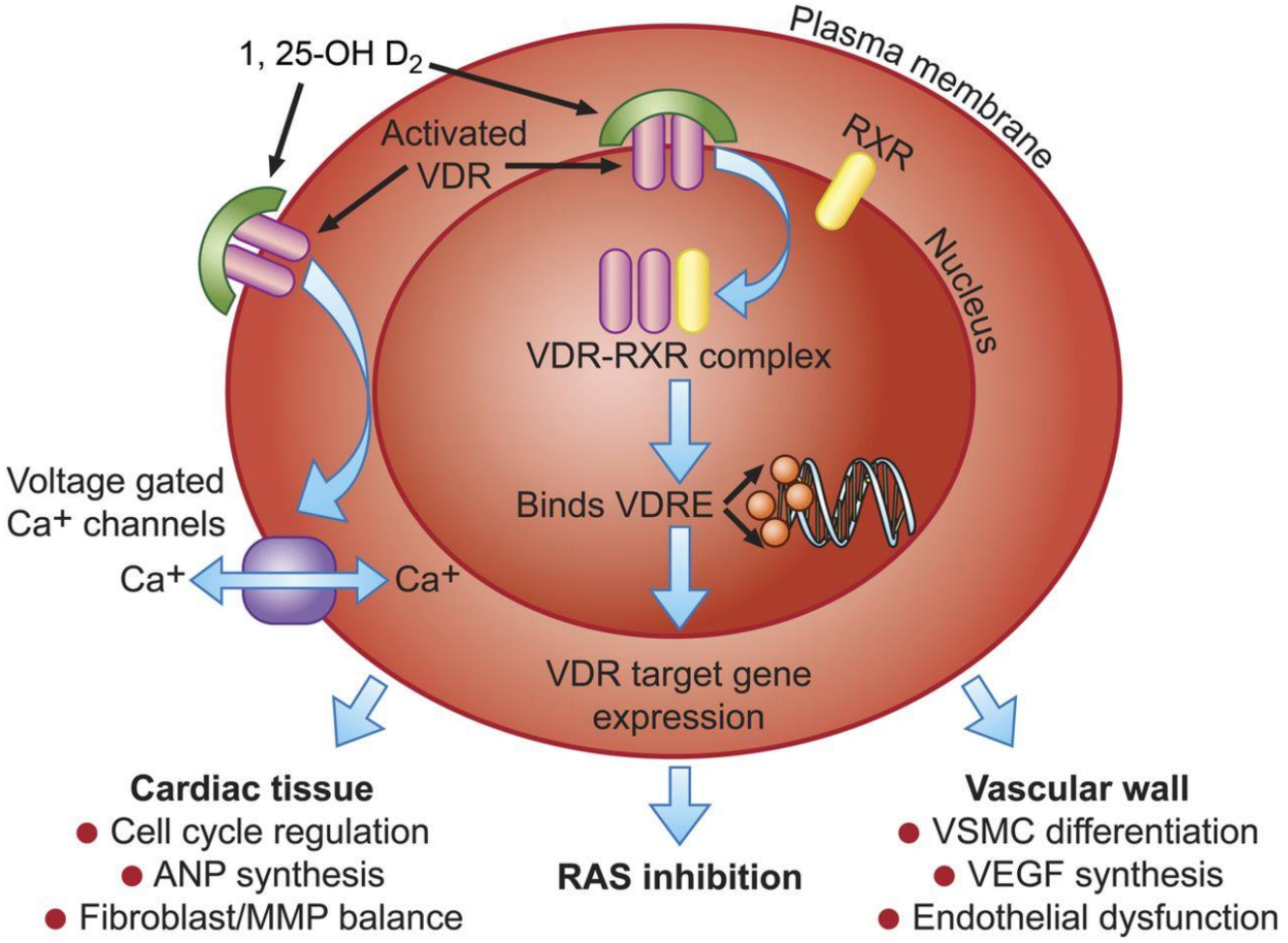
Am J Clin Nutr 2007(85):1586

Summary I: Vitamin D and cancer risk

- In contrast to experimental and epidemiologic data, no clear evidence to show that D3 therapy significantly reduces cancer incidence overall from available RCTs and meta-analyses.
  - Available data favor for possible benefit at higher dose mostly for colorectal CA.
  - Breast and prostate CA with more variable results
- Questionable dose- or level-dependent benefit? (higher dose/D3 level need to be achieved for benefit?)
- Role of VDR agonist/1,25 (OH)2 D for cancer prevention unknown.

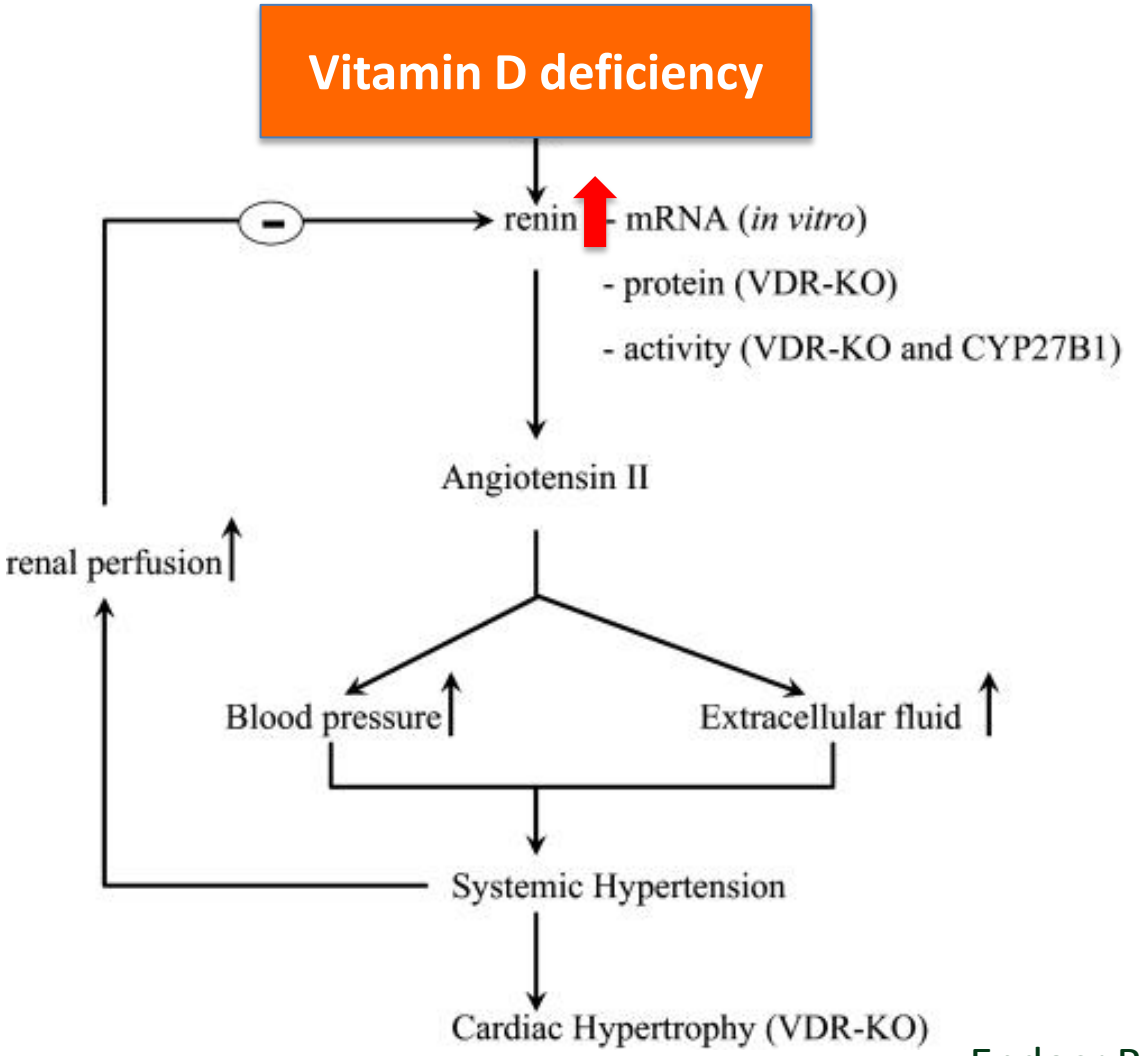
Vitamin D and the heart

Mechanisms by which vitamin D deficiency may confer cardiovascular risk



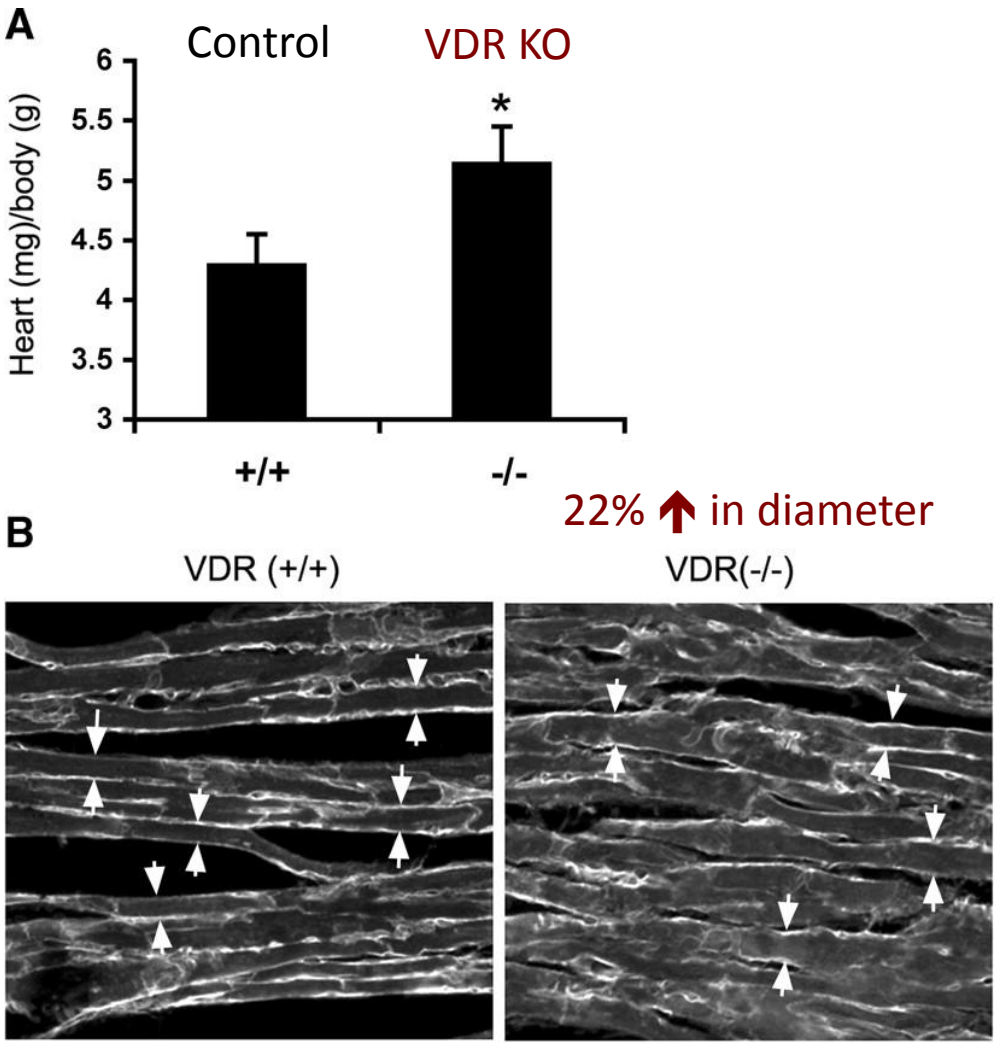
Al Mheid et al. BMJ 2013

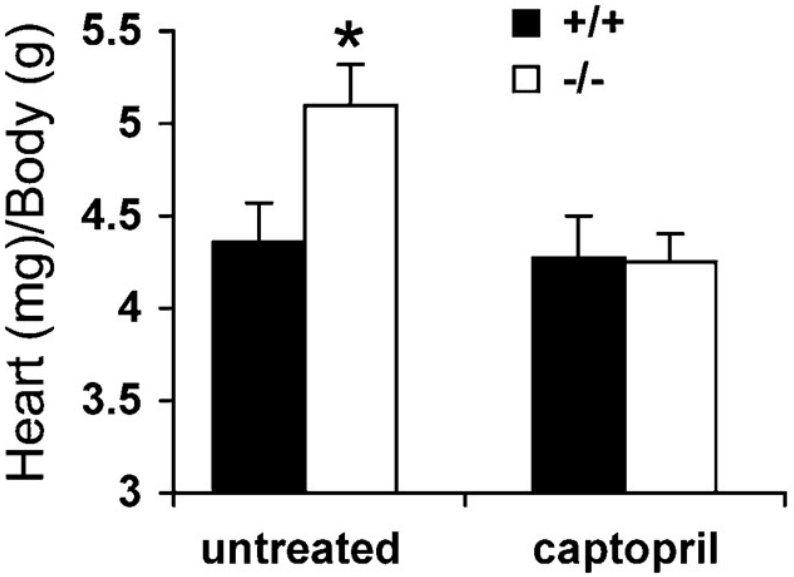
Vitamin D deficiency stimulates Renin-Angiotensin System



Endocr Rev. 2008; 29: 726

Vitamin D regulates renin biosynthesis



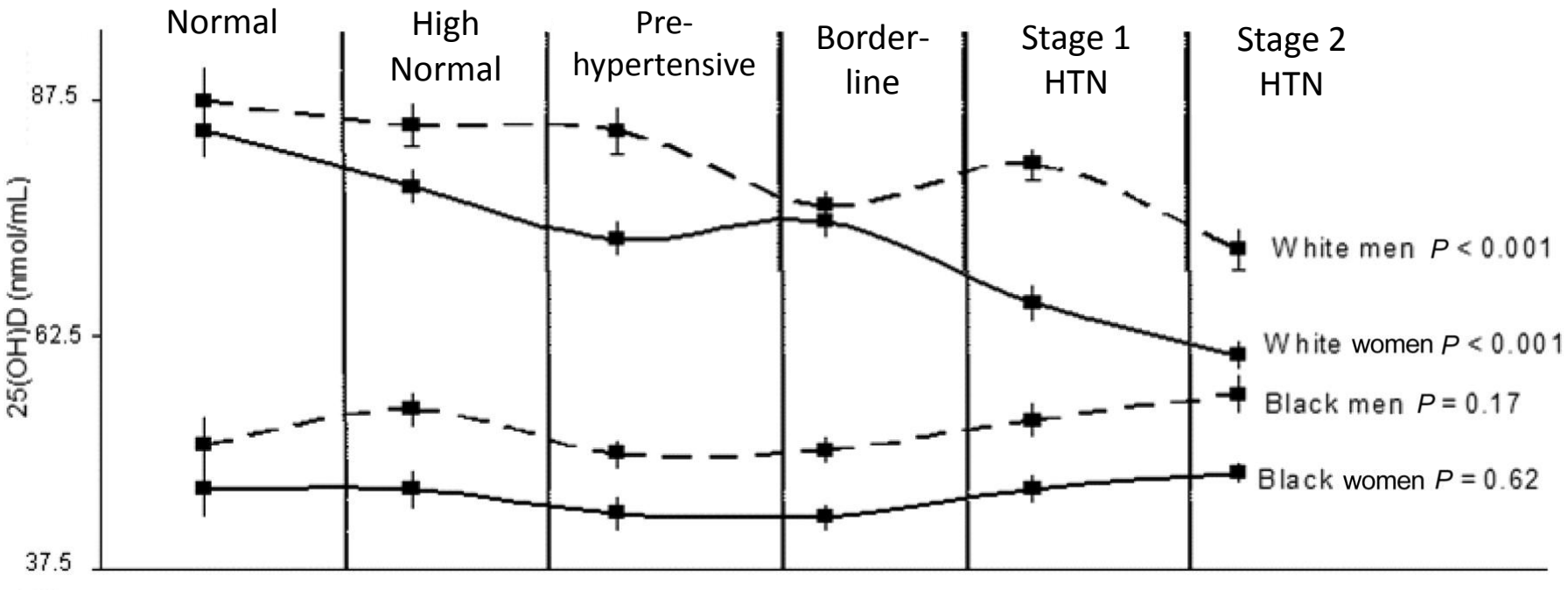


Captopril reduces cardiac hypertrophy

Am J Physiol Endocrinol Metab. 2005;288:E125

Optimal vitamin D status attenuates the age-associated increase in systolic blood pressure in white Americans: a cross-sectional study

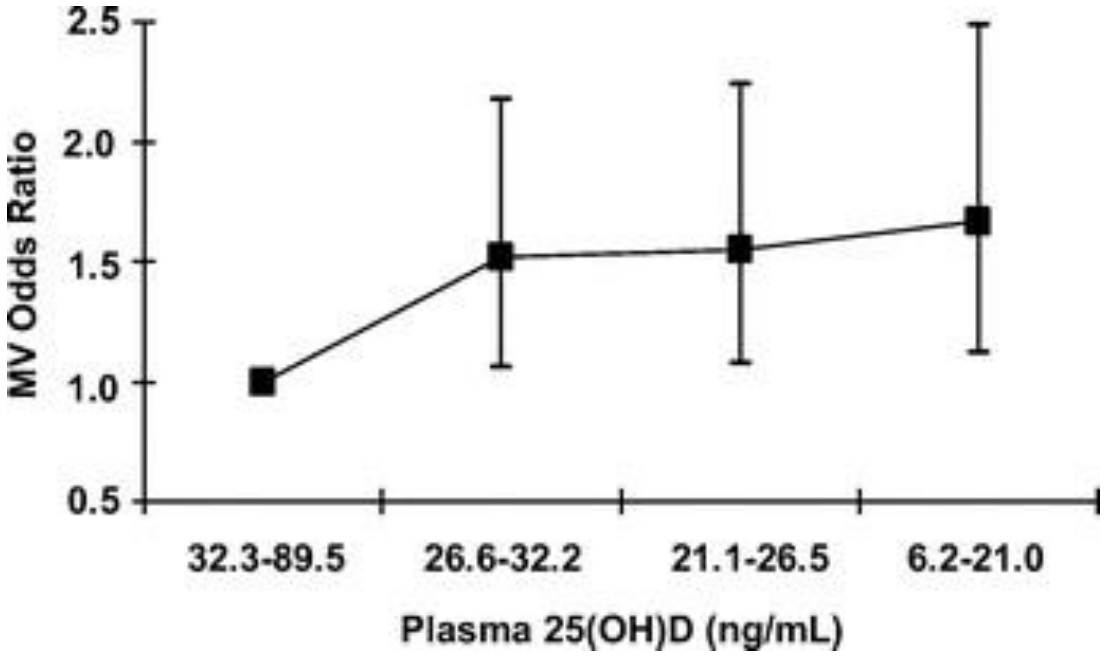
25(OH)D by SBP with the JNC 7 hypertension classifications among adults inNHANES III; 1988–1994



Am J Clin Nutr 2008(87) 136

25(OH)D levels are inversely and independently associated with the risk of developing hypertension: a prospective study

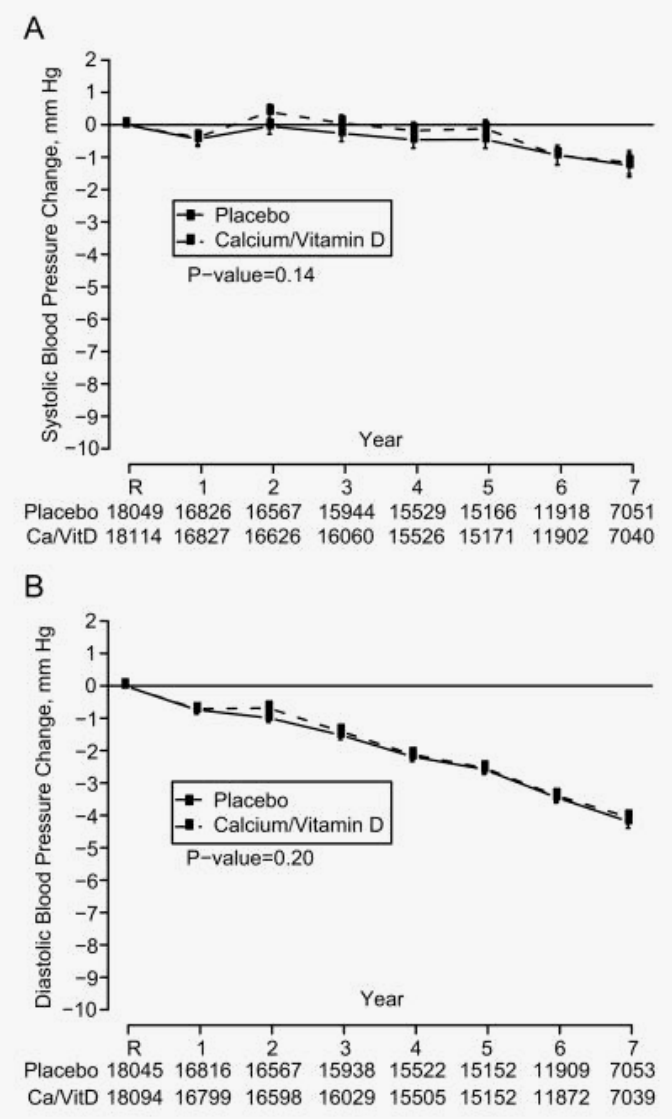
The Nurses' Health Study 2 (Nested case-control study):
N=1484, ages 32-52, no baseline HTN



- Women in the lowest compared with highest quartile of plasma 25(OH)D had an adjusted odds ratio for incident hypertension of 1.66 (P for trend=0.01)
- Vit D deficiency (<30 ng/mL, 66%) with OR of 1.47

Hypertension 2008(52):828

Low-dose D3 therapy does not prevent or improve hypertension



The Women's Health Initiative:

- a RCT of 36,282 post-menopausal women – the largest study
- 1000 mg Ca + 400 IU of D3 daily versus placebo
- Over a median of 7 yrs of follow up, no difference in mean change over time in SBP and DBP between two groups.

Hypertension 2008 (52): 847

Summary II: D3 therapy is not associated with improvement in blood pressure in interventional trials

- The second largest interventional study (N=438) randomized to weekly D3 40,000 IU, 20,000 IU, or placebo: no change in BP in all groups despite increasing D3 levels from <30 to >50 ng/mL.
  - But only 1-yr follow up.
  - Had ongoing antihypertensive therapy.
- Only 2 RCTs performed for primary HTN prevention trial without any use of antihypertensive, but with again, mixed results and limited by very short follow ups (5-8 wks)
- Over 10 interventional studies show mostly no effect of D3 therapy on BP or incident HTN.

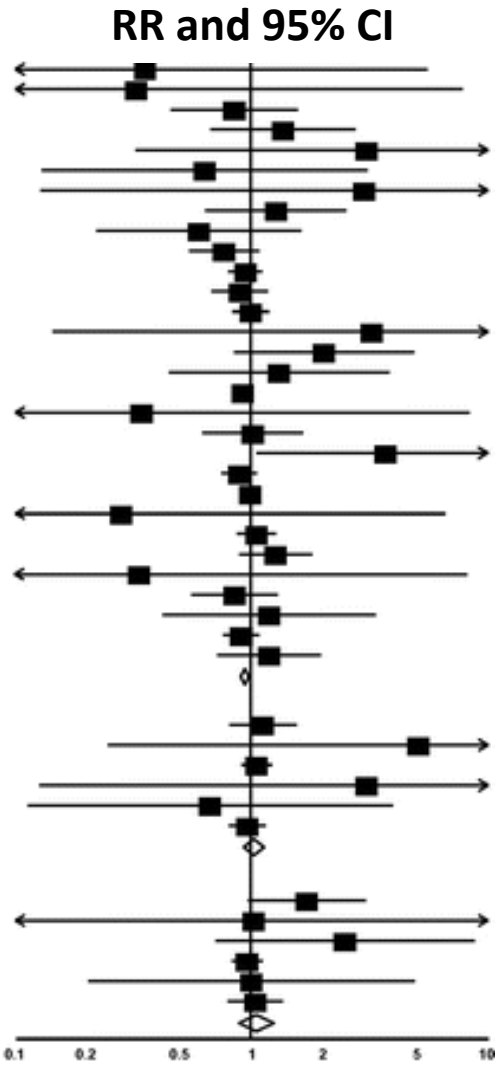
Vitamin D therapy in the setting of RCT does not improve mortality, MI, and stroke

Mortality

MI

Stroke

Study name	Relative risk	Lower limit	Upper limit	Events / Total Vitamin D	Events / Total Control
Avenell, 2004	0.35	0.02	5.50	1 / 99	1 / 35
Baeksgaard,1998	0.32	0.01	7.79	0 / 65	1 / 63
Berggren, 2008	0.85	0.46	1.56	16 / 102	18 / 97
Bjorkman, 2008	1.36	0.68	2.73	27 / 150	9 / 68
Brazier, 2005	3.06	0.32	28.93	3 / 95	1 / 97
Broe, 2007	0.63	0.13	3.07	5 / 99	2 / 25
Brohult, 1973	3.00	0.13	70.30	1 / 25	0 / 25
Burleigh, 2007	1.27	0.64	2.50	16 / 101	13 / 104
Campbell, 2005	0.60	0.22	1.61	6 / 196	10 / 195
Chapuy, 2002	0.76	0.55	1.06	71 / 393	45 / 190
Chapuy,1992	0.94	0.81	1.10	258 / 1634	274 / 1636
Flicker, 2005	0.89	0.68	1.16	76 / 313	85 / 312
Grant, 2005	0.99	0.83	1.18	217 / 1343	217 / 1332
Grove, 1981	3.23	0.14	72.46	1 / 12	0 / 13
Harwood, 2004	2.03	0.85	4.84	31 / 113	5 / 37
Inkovaara, 1983	1.31	0.45	3.80	7 / 45	5 / 42
Jackson, 2006	0.92	0.83	1.01	744 / 18176	807 / 18106
Komulainen,1999	0.34	0.01	8.31	0 / 112	1 / 115
Krieg, 1999	1.01	0.62	1.64	21 / 71	26 / 89
Latham, 2003	3.70	1.06	12.92	11 / 121	3 / 122
Lips, 1996	0.89	0.75	1.04	223 / 1291	251 / 1287
Lyons 2007	0.99	0.93	1.05	947 / 1725	953 / 1715
Meier, 2004	0.28	0.01	6.58	0 / 30	1 / 25
Meyer, 2002	1.05	0.87	1.26	169 / 569	163 / 575
Porthouse, 2005	1.26	0.90	1.79	57 / 1321	68 / 1993
Prince, 2008	0.33	0.01	8.12	0 / 151	1 / 151
Sanders, 2010	0.85	0.56	1.28	40 / 1131	47 / 1125
Schleithoff, 2006	1.19	0.42	3.33	7 / 61	6 / 62
Trivedi, 2003	0.90	0.77	1.07	224 / 1345	247 / 1341
Wejse, 2009	1.19	0.72	1.95	30 / 187	24 / 178
Mortality-Pooled estimate	**0.96**	**0.93**	**1.00**	**3209 / 31076**	**3284 / 31155**
Berggren, 2008	1.12	0.81	1.53	47 / 102	40 / 97
Brazier, 2005	5.10	0.25	104.94	2 / 95	0 / 97
Jackson, 2006	1.05	0.92	1.20	411 / 18167	390 / 18106
Komulainen,1999	3.08	0.13	74.81	1 / 112	0 / 115
Prince, 2008	0.67	0.11	3.93	2 / 151	3 / 151
Trivedi, 2003	0.96	0.81	1.13	224 / 1345	233 / 1341
Myocardial Infraction-Pooled estimate	**1.02**	**0.93**	**1.13**	**687 / 19972**	**666 / 19907**
Berggren, 2008	1.71	0.97	3.02	27 / 102	15 / 97
Brazier, 2005	1.02	0.06	16.09	1 / 95	1 / 97
Inkovaara, 1983	2.49	0.71	8.76	8 / 45	3 / 42
Jackson, 2006	0.96	0.83	1.10	362 / 18167	377 / 18106
Prince, 2008	1.00	0.21	4.88	3 / 151	3 / 151
Trivedi, 2003	1.04	0.80	1.35	105 / 1345	101 / 1341
Stroke-Pooled estimate	**1.05**	**0.88**	**1.25**	**506 / 19905**	**500 / 19834**

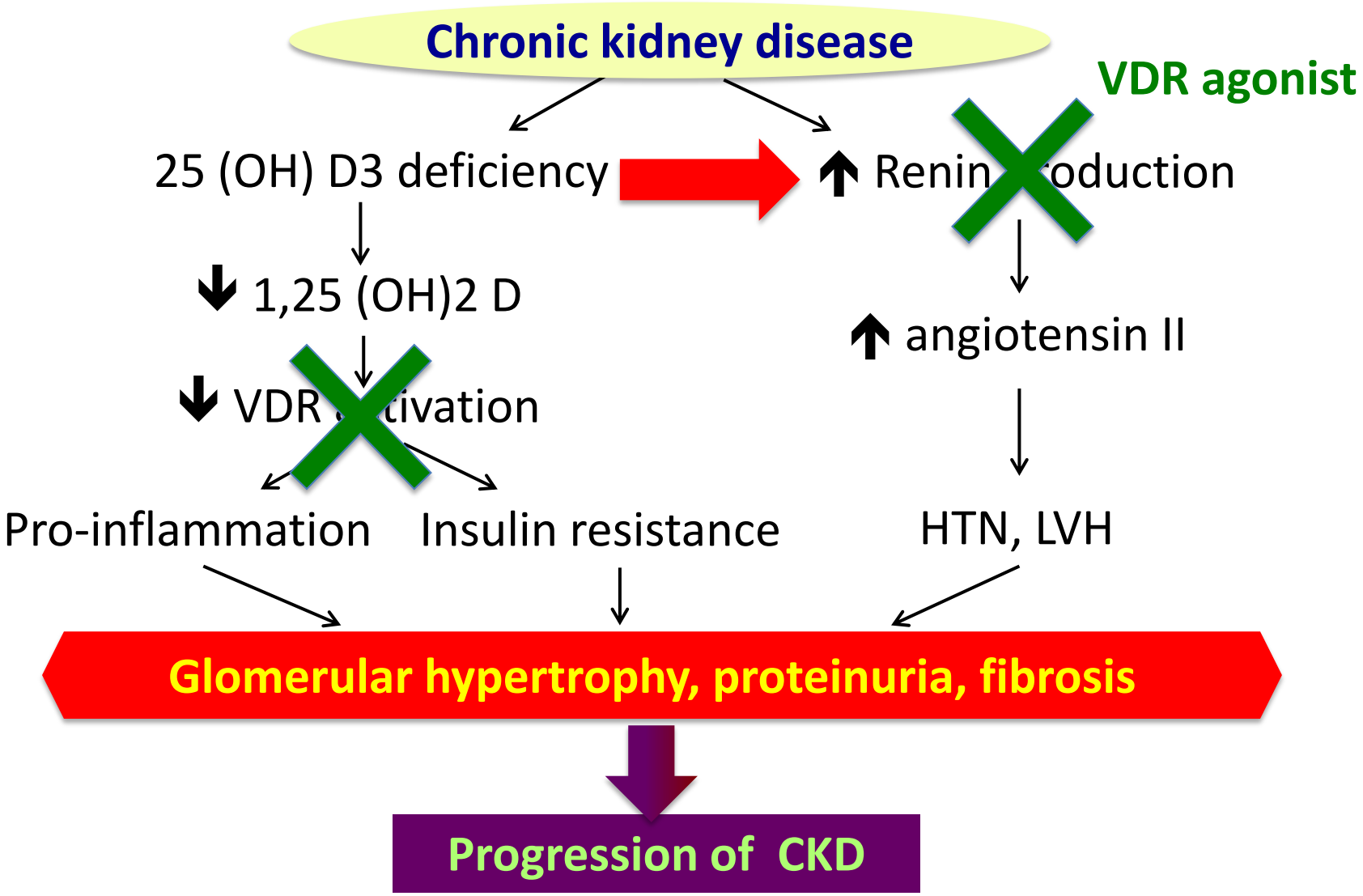


J Clin Endocrinol Metab. 2011;96:1931

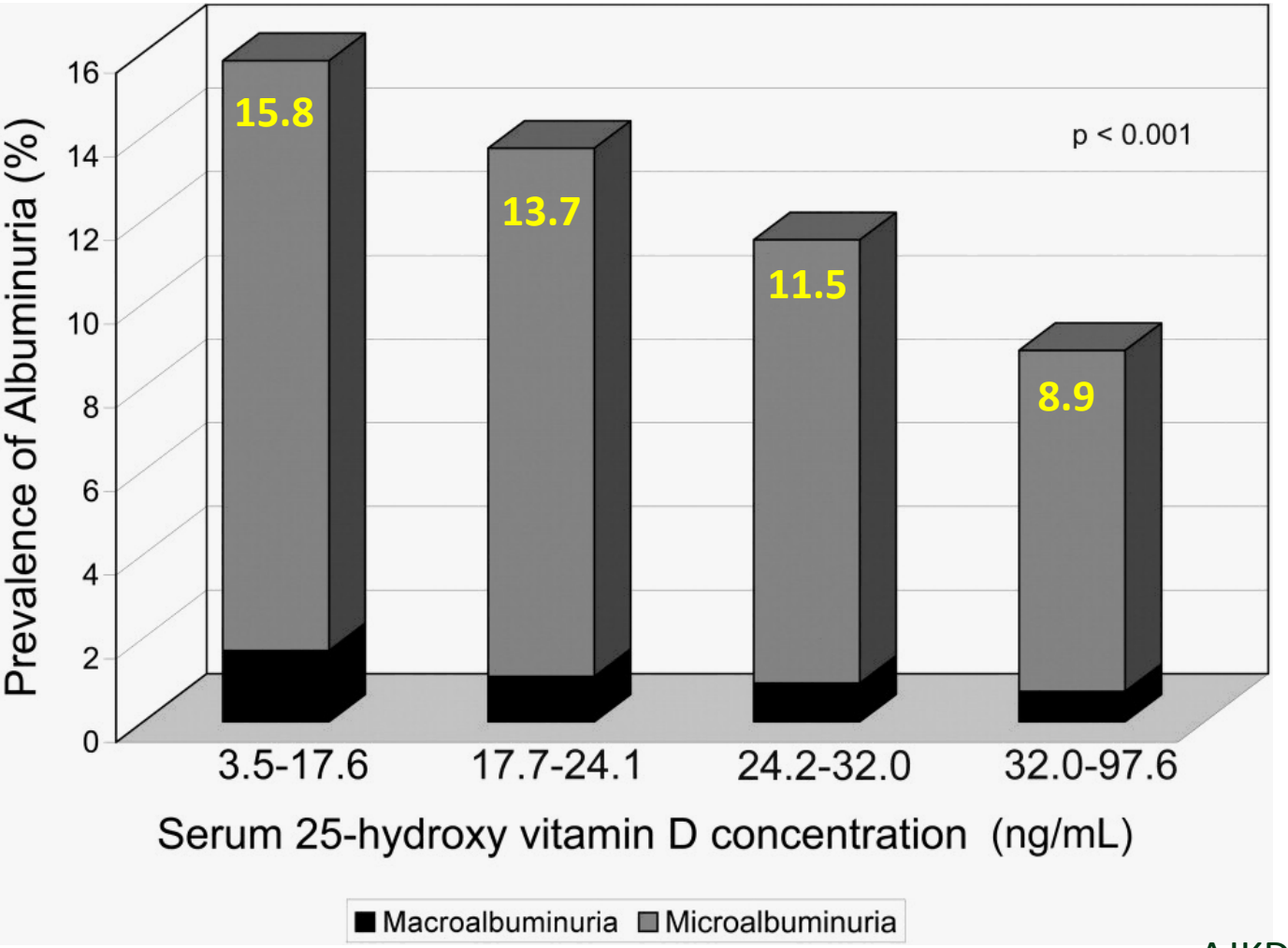
Favors vitamin D Favors control

Vitamin D and the kidney

Postulated mechanisms for the role of vitamin D in CKD progression

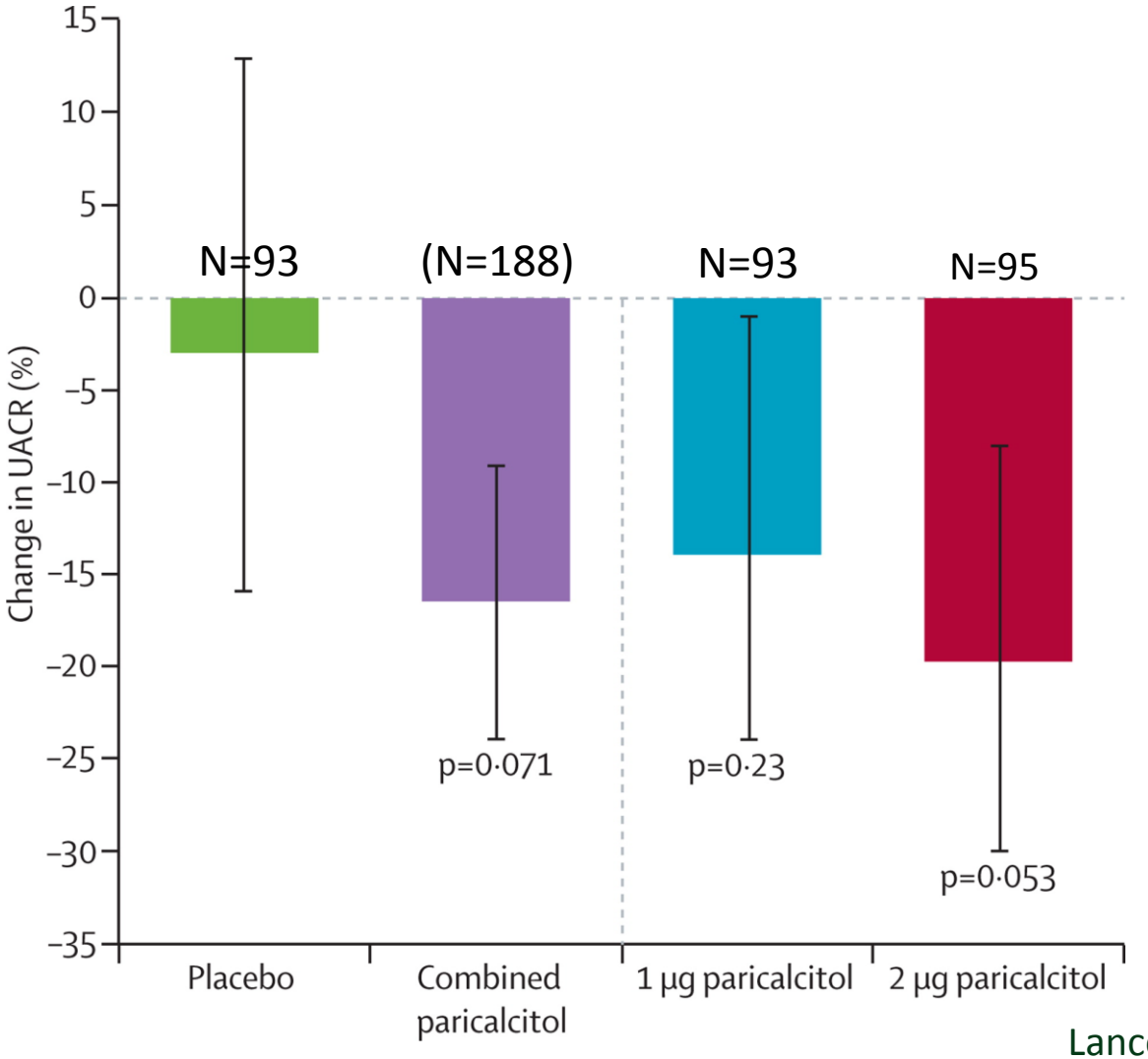


Increased prevalence of albuminuria with decreasing 25 OH D levels in NAHNES III (N=15,068)



AJKD 2007(50)69

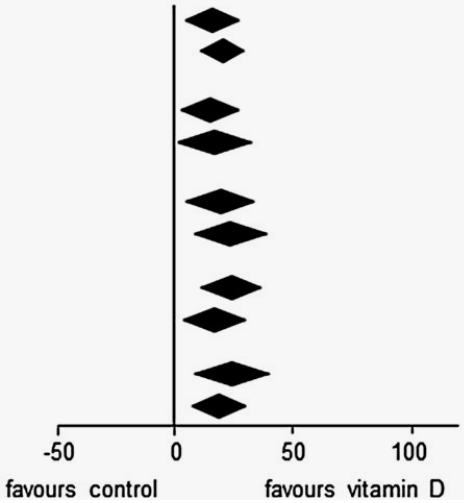
Selective VDR activation with paricalcitol lowers albuminuria in patients with type 2 diabetes (VITAL study): a randomised controlled trial (24 wks)



Lancet 2010 (376)1543

VDR agonist reduces proteinuria

		Number of studies	Number of patients (vitamin D/control)	Mean difference (95% CI)	p for subgroup differences
Study drug	paricalcitol	3	264 / 171	16% (5 to 28%)	0.16
	calcitriol	2	72 / 69	31% (14 to 48%)	
Paricalcitol dose	1 ug/day	2	123 / 118	16% (3 to 28%)	0.86
	2 ug/day	2	141 / 141	17% (1 to 34%)	
Patient population	diabetic nephropathy only	2	230 / 133	20% (4 to 35%)	0.69
	not (only) diabetic nephropathy	3	106 / 107	24% (8 to 40%)	
Duration of follow-up	<24 weeks	2	77 / 75	24% (11 to 38%)	0.46
	≥ 24 weeks	3	259 / 165	17% (3 to 31%)	
Study size	number of participants <80	3	57 / 54	24% (8 to 41%)	0.61
	number of participants ≥80	3	279 / 186	19% (7 to 31%)	



J Am Soc Nephrol. 2013;24:1863

Vitamin D therapy does not improve cardiac structure in CKD

The PRIMO Study: A RCT in CKD patients (eGFR 15-60) with mild to moderate LVH and normal EF

Change in MRI measures from baseline to 48 wks			
	Placebo (n=91)	Paricalcitol (n=88)	P
LV mass	-0.07 (-0.6 to 0.4)	0.34 (-0.1 to 0.8)	0.15
LV EF (%)	-0.54 (-2.1 to 0.1)	0.62 (-0.9 to 2.1)	0.18
Thoracoabdominal aortic plaque volume (mL)	-0.03 (-0.03 to -0.02)	-0.02 (-0.03 to -0.02)	0.09

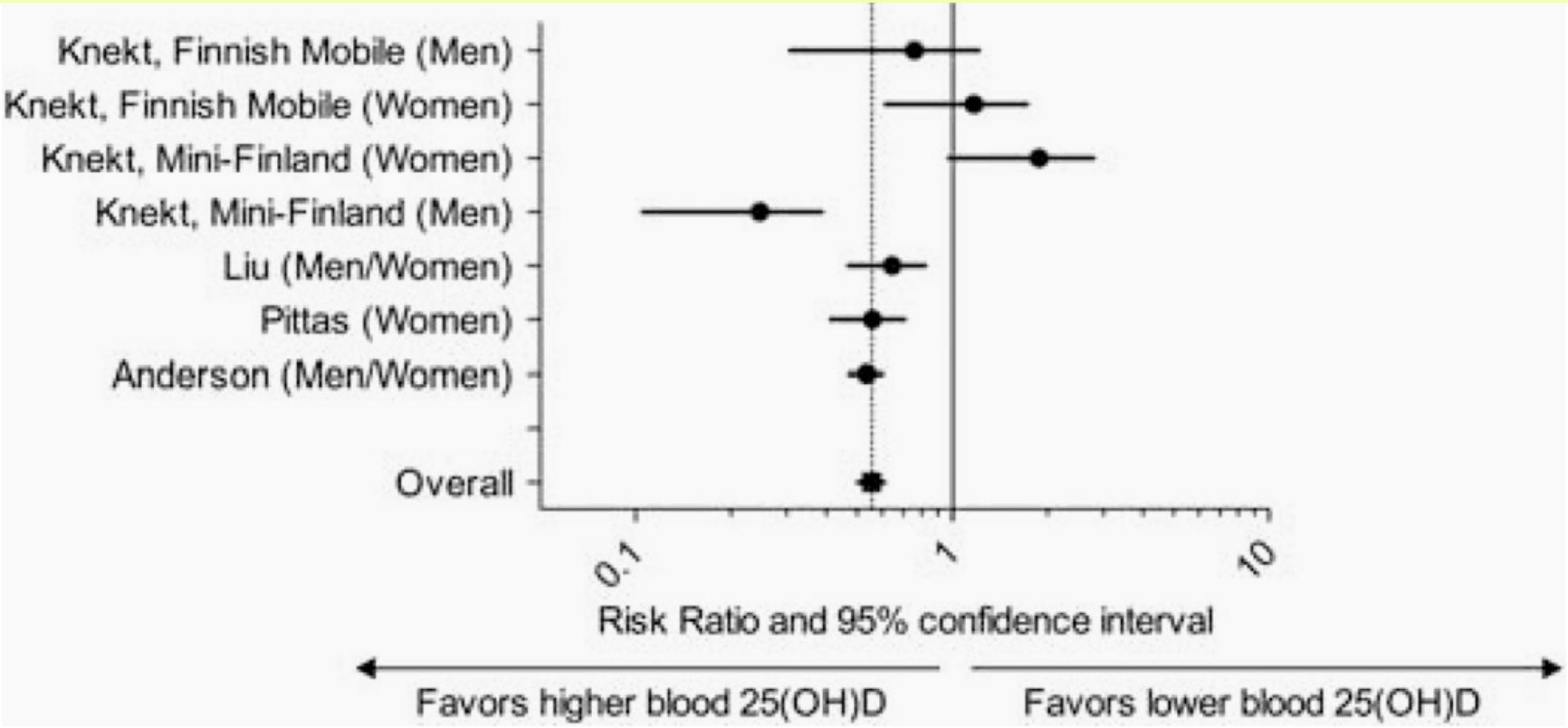
>50% with diabetes and >30% with diabetic nephropathy

JAMA 2012;307:674

Vitamin D and diabetes

Observational studies suggest protective effect of D3 on diabetic risk

25(OH)D > 25 ng/ml: a 43% lower risk of developing type 2 diabetes compared to 25(OH)D < 14 ng/ml



Eur J Clin Nutr. 2011; 65: 1005

Obesity and insufficient 25(OH)D interact to synergistically influence the risk of insulin resistance

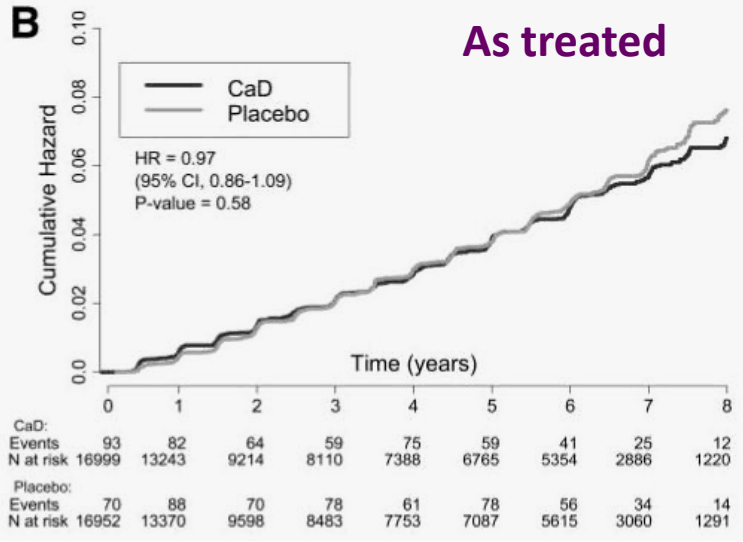
NHANES 2001-2006 (N=12,900)

OR for type 2 diabetes in adults (≥20 yrs)

BMI category	25 (OH) D level (ng/mL)	
	<20	20-50
normal	1.49	1.00
overweight	2.89	1.63
obese	6.78	3.97

Diabetes Care. 2012; 35: 2048

Calcium + vitamin D3 therapy does not reduce the risk of incident diabetes



The Women's Health Initiative:

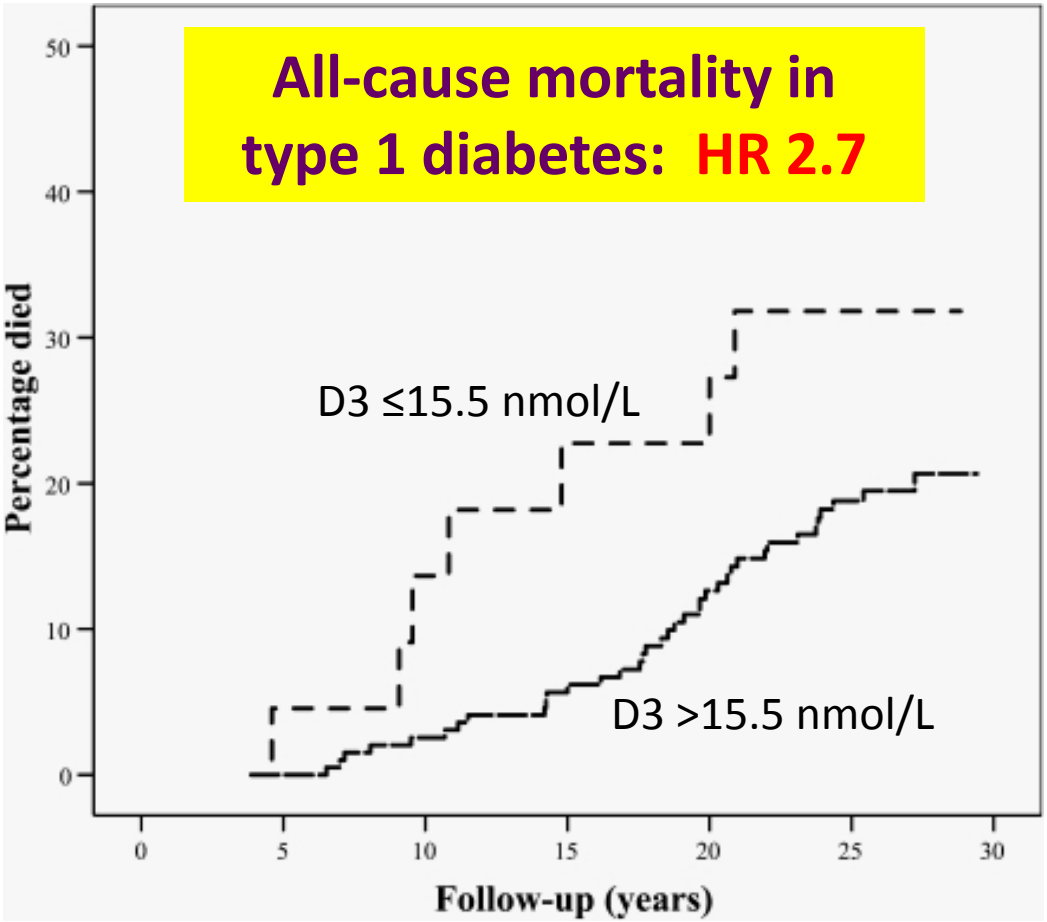
- A RCT of 33951 post-menopausal women
- D3 400 IU + 1000 mg Ca or placebo
- Median follow up of 7 yrs
- The dose too low?

Diabetes Care. 2008; 31: 701

RCT data of vitamin D and glycemic outcomes remain inconclusive

- 11 RCTs on effects of D2 or D3 on glycemia.
- Too heterogeneous for proper meta-analysis:
  - Duration 6wks to 9 yrs
  - Dose 400 to 8600 IU/d to large infrequent pulse doses
- In RCTs, vitamin D therapy had:
  - No effect in participants with normal glycemia
  - Possible beneficial effects (reduced HOMA-R) among patients with glucose intolerance or insulin resistance at baseline.

Severe vitamin D deficiency independently predicts all-cause mortality in type 1 diabetes

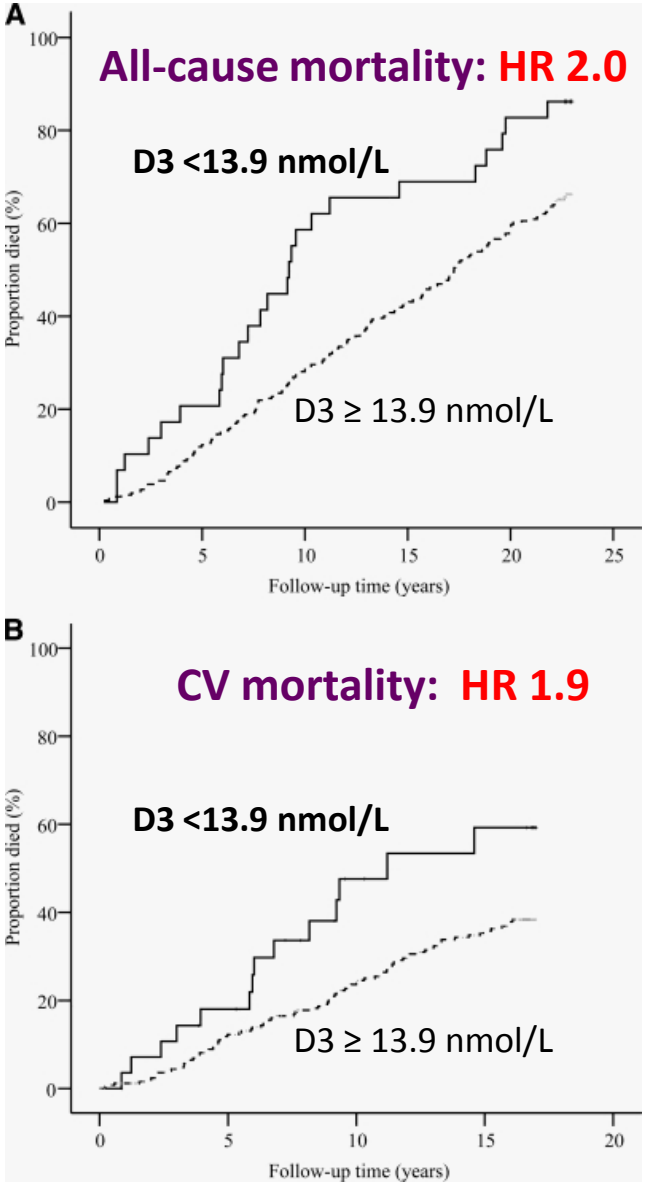


A prospective observational study (N=220) in incident type 1 diabetic patients:

- A median f/u of 26 yrs
- Severe vitamin D deficiency at baseline did not predict the development of these microvascular complications.

Diabetes Care. 2011;34:1081

Very low vit D levels (<10th percentile) independently predict mortality in type 2 diabetes



A longitudinal observational study (N=289) in type 2 diabetes:

- A median 15- yr follow up
- 60% with normo-, 25% with micro-, 15% with macroalbuminuria.
- Mortality association independent of cardiac risk factors and renal function.
- **Severe vitamin D deficiency at baseline did not predict progression to micro- or macroalbuminuria.**

Diabetes Care 2010; 33(10): 2238

Summary I

- Preclinical, cross-sectional, and observational epidemiologic studies have suggested strong association between vitamin D deficiency and increased risk of cancer, autoimmune diseases, diabetes, HTN/CV diseases, and overall mortality.

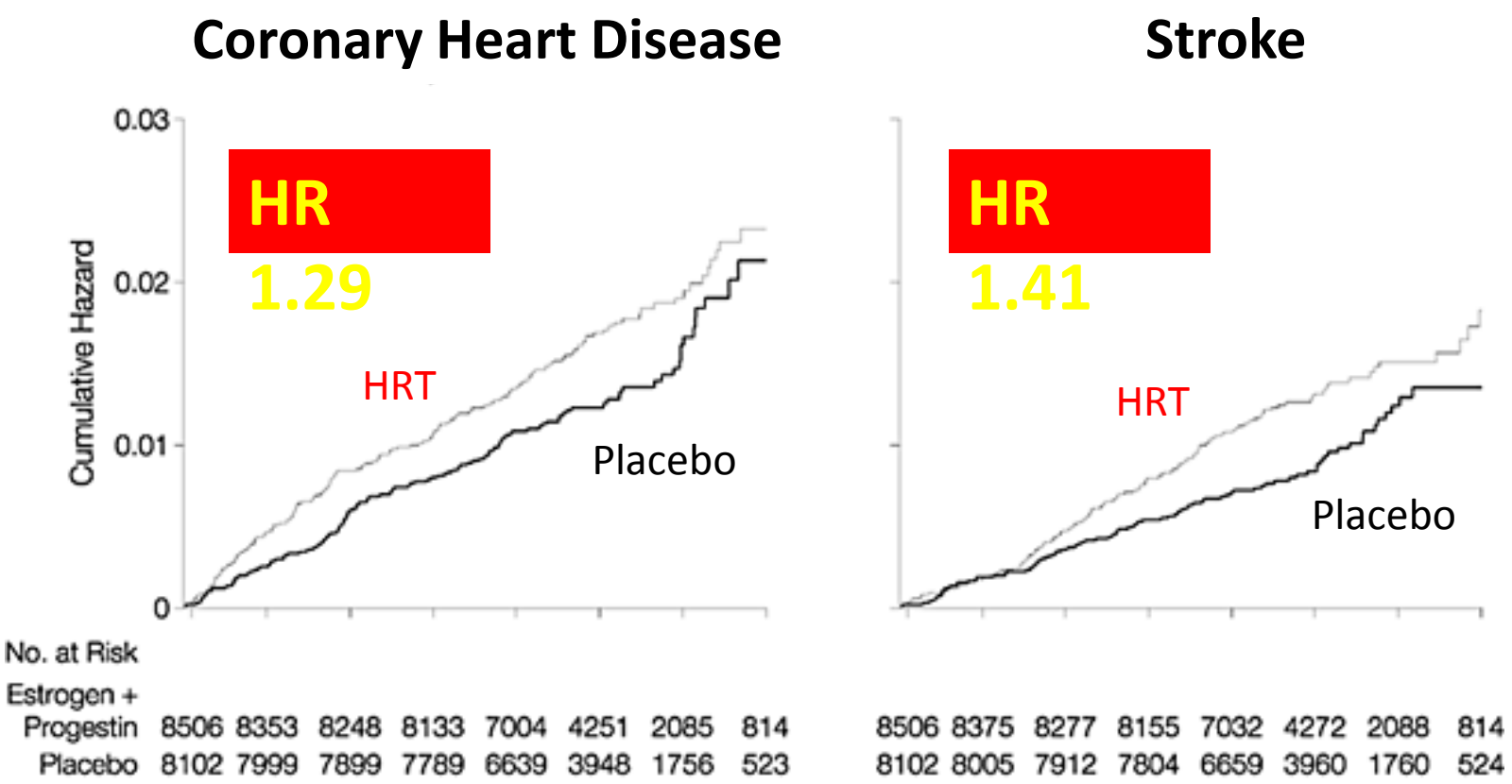
- Randomized controlled studies have yielded much more variable results, in part due to significant differences in study design, dose, and duration.

Summary II:

- *"Despite a few hundred systemic reviews and meta-analyses, highly convincing evidence of a clear role of vitamin D does not exist for any outcome, but association with a selection of outcomes are probable."*
- *The lack of concordance between observational studies and RCTs suggests that vitamin D is more likely to be a correlate marker of overall health and not causally involved in disease.*

– Theodoratou et al. BMJ 2014

Observational study vs. RCT



JAMA. 2002;288:321

Summary of benefits of vitamin D concentration or supplementation

Probable	• **Decreases dental caries in children** • **Increases birth weight** • **Increases PTH in CKD**
Suggestive	• **<u>Decreases:</u>** colorectal cancer, non-vertebral fx, HTN, CVD prevalence, CVA, metabolic syndrome prevalence, and type 2 & gestational diabetes, overall mortality in older adults • **<u>Increases:</u>** BMD in femoral neck, muscle strength, head circumference at birth

Theodoratou et al. BMJ 2014 & Chowdhury et al. BMJ 2014

Summary III: who should be screened in primary care?

- Caucasian and Asian women just before and any time after menopause, especially if they smoke or are thin.
- Women and older men with a family history of osteoporosis.
- Individuals who have had a hip, wrist, spine, or other fracture after age 50.
- Chronic steroid use.

Summary IV: Vitamin D therapy

- **<u>Suggested target serum 25(OH)D levels:</u>**
  - 20 and 40 ng/mL (50 to 100 nmol/L)
  - 30 and 50 ng/mL (75 to 125 nmol/L)
- **Ergocalciferol vs. cholecalciferol:**

	D2	D3
Source	Plant-derived	Sun exposure, fish
Potency (Δ in affinity to DBP or 25-hydroxylase)		>2-3x D2
Half life	1 d	12-30 d

- The dose and duration of supplementation remains unclear and need to be monitored for ***the risk of hypercalcemia and nephrolithiasis***.