SUN AS A MEDICINE

VITAMIN D IN HEALTH AND DISEASE

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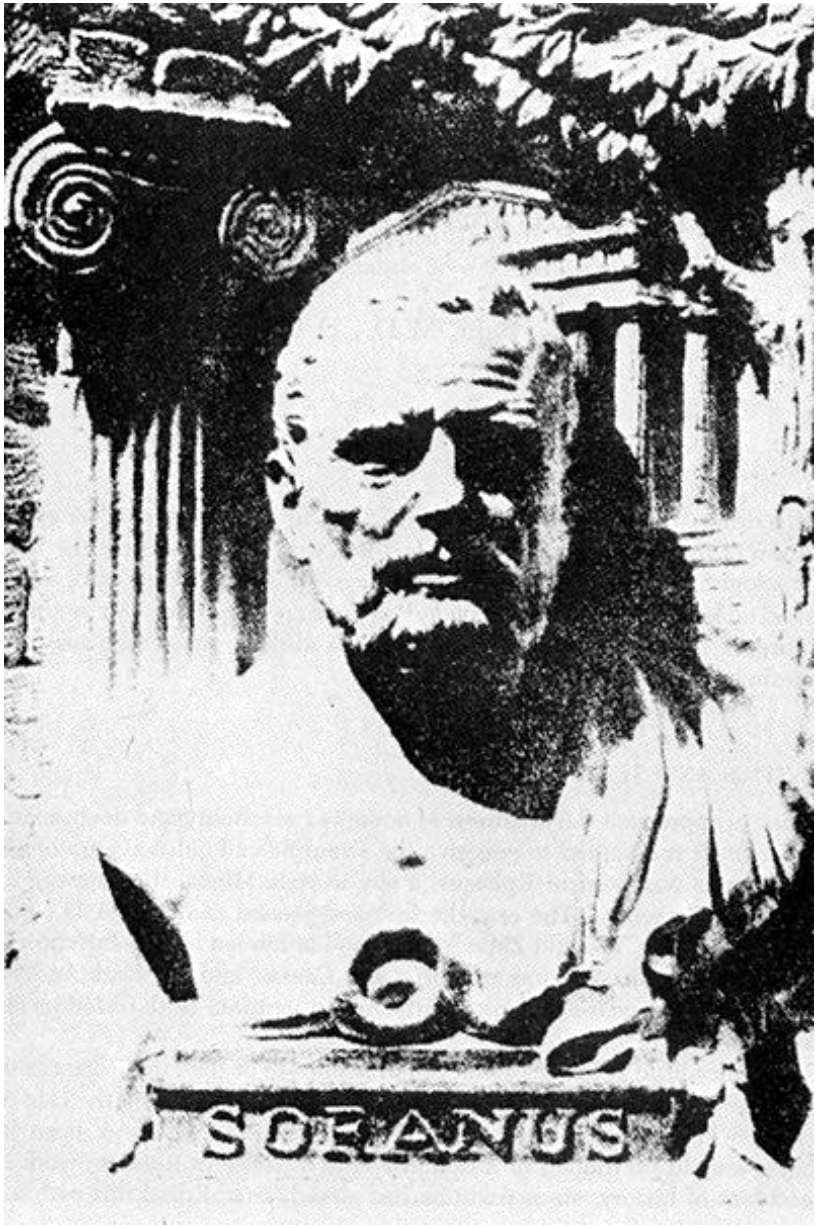
Voivodeship Hospital
OLSZTYN



Soranus of Ephesus (I – II w. n.e.)

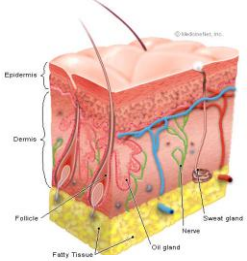
Greek physician, practiced in Alexandria and subsequently in Rome

Bone deformations are more frequent in children from Rome as compared to those from Greece – this is due to wrong diet and poorer living conditions and hygiene in Rome.

Dr. Daniel Whistler
Morbo puerilli Anglorum, quem patrio idiomate indigenae vocant the Rickets. Lugduni Batavorum 1-13, 1645

Prof. Francis Glisson
De Rachitide sive morbo puerilli, qui vulgo The Rickets diciteur. London **1 - 416**, 1650

Rickets is an endemic disease limited mostly to the south-eastern part of England (counties *Dorset* i *Somerset*)



25- hydroxylase i 1α- hydroxylase in taget cells

UV-B
290-315 nm

TARGET TISSUES

+ VDBP

7DHC
Provitamin D_3

Pre-vitamin D_3

36.6°C

Vitamin D_3

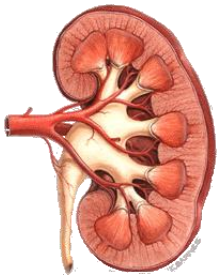
+ VDBP

Lumisterol
Tachysterol

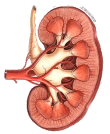
25- hydroxylase

$24.25\ (OH)_3\text{-}D_3$

$25\text{-}OH\text{-}D_3$



1α- hydroxylase



24- hydroxylase
25- $OH\text{-}D_3$

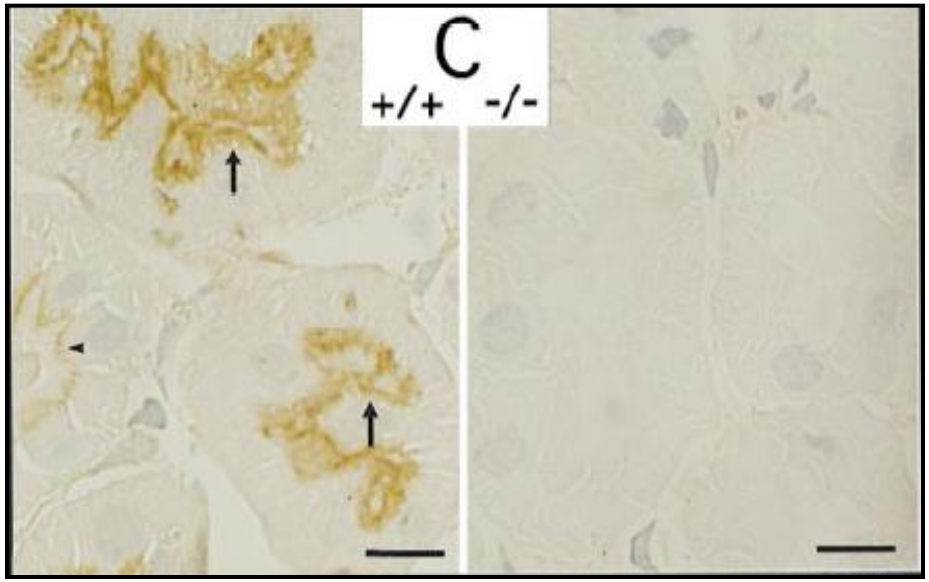
oxydation

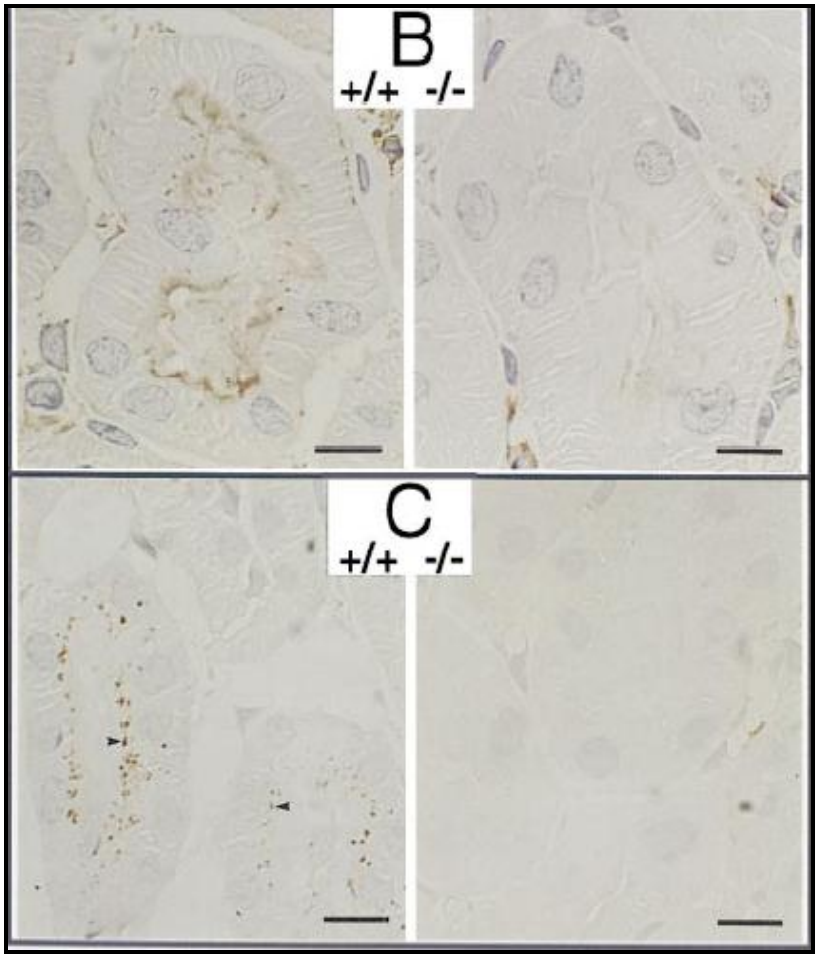
Calcitroic
acid

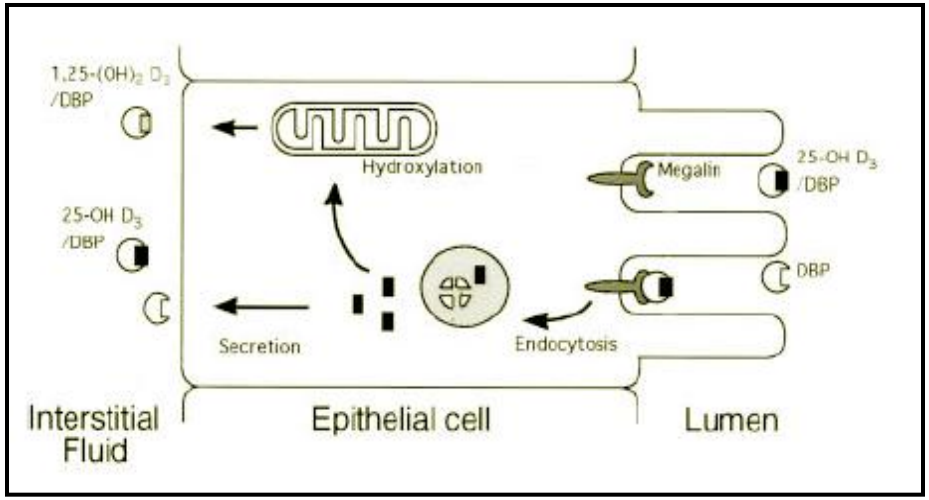
$1.24.25\ (OH)_3\text{-}D_3$

$1.25\ (OH)_2\text{-}D_3$

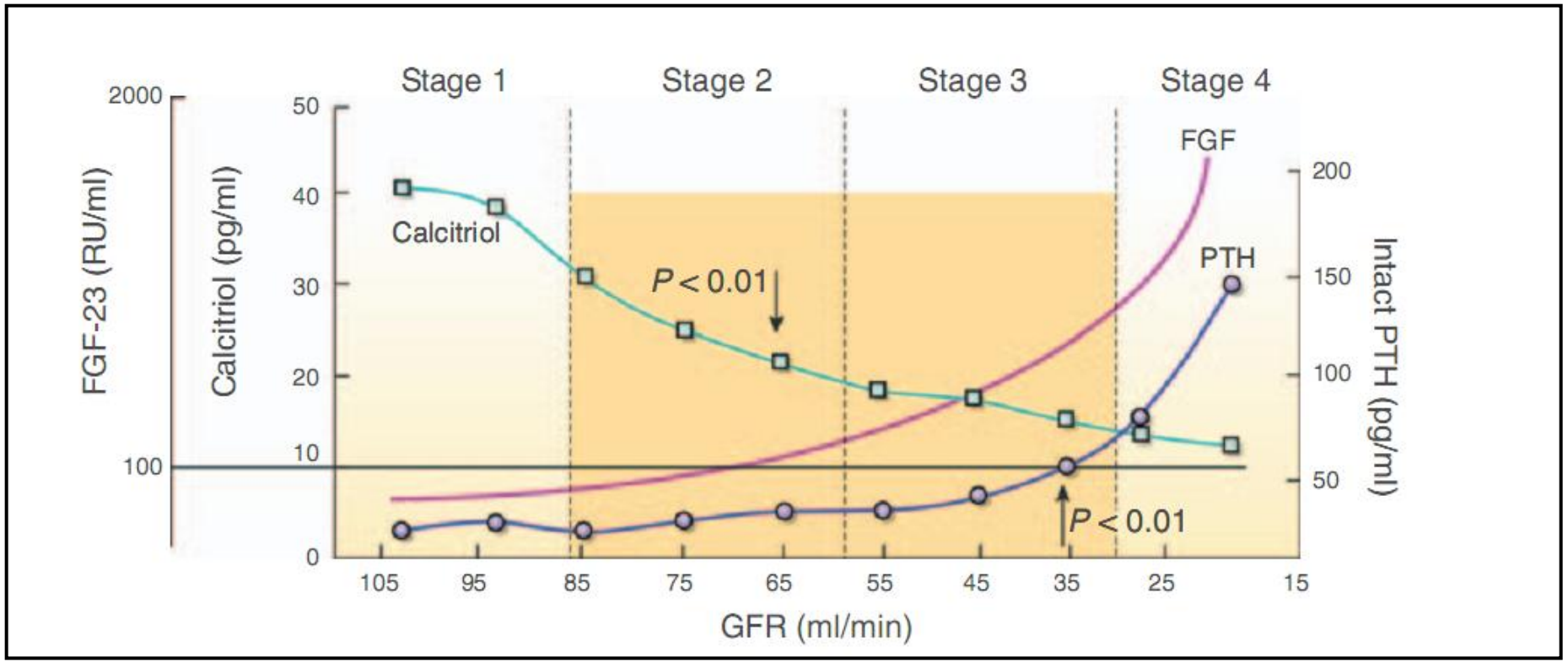
TARGET TISSUES





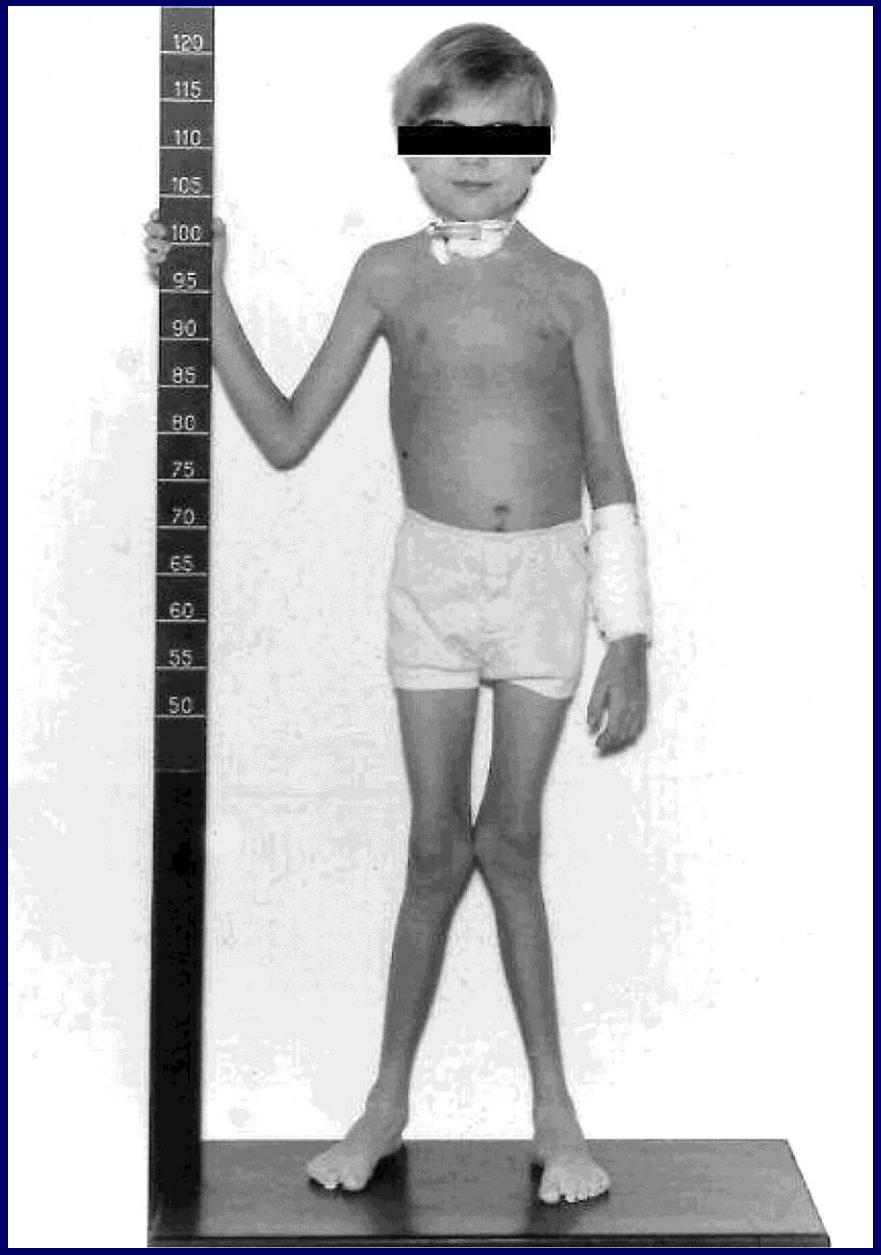


Nykjaer A, et al., Cell 1999



Gal-Moschovici A & Sprague SM. Kidney Int. 2010

‘Typical’ HD patient (aged 21, Denmark, 1971: before the therapy with vitamin D was introduced)



Olgaard K & Levin E. Nephrol Dial Transplant. 2008

Factors that impact on the rate of vitamin D synthesis in skin

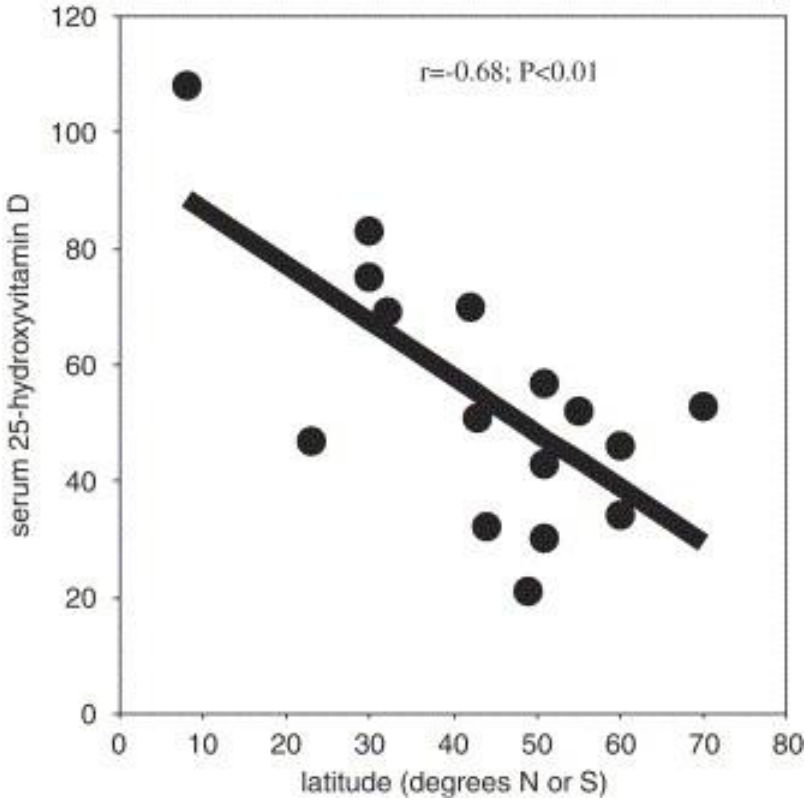
‘Individual’

- age
- race – skin color
- pigmentation
- lifestyle (work and leisure)
- cultural and religious factors
- protection against sunlight (sunscreens, cloths)

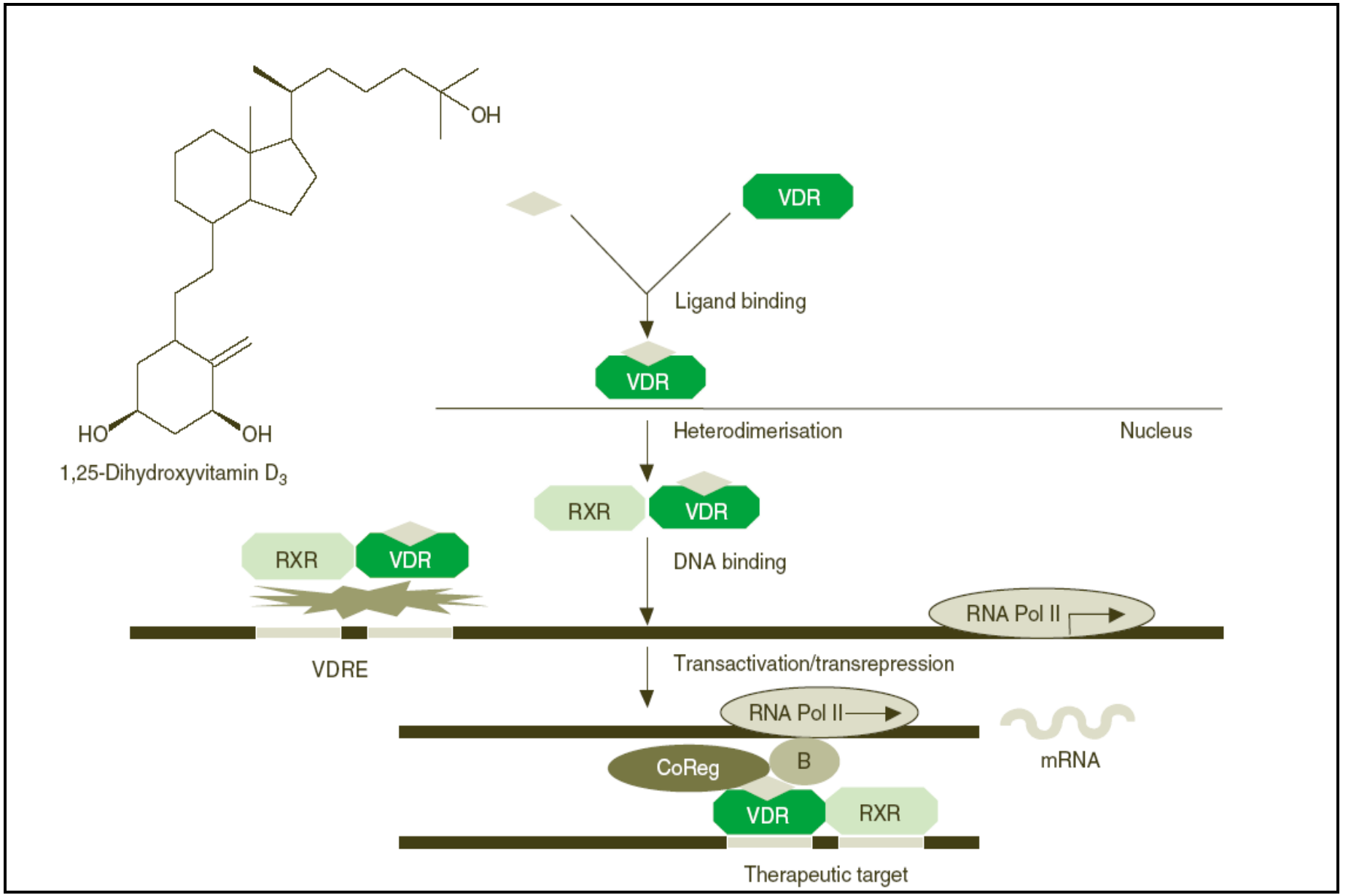
Environmental

- geographic latitude
- season of the year
- climate (clouds and rain)
- air pollution
- ozone content in the air
- ‘reflection’ surfaces (snow, water)

An association between geographic altitude and serum 25 $(OH)D_3$ concentration in young adults



Zittermann A, Progress Biophys Mol Biol 2006

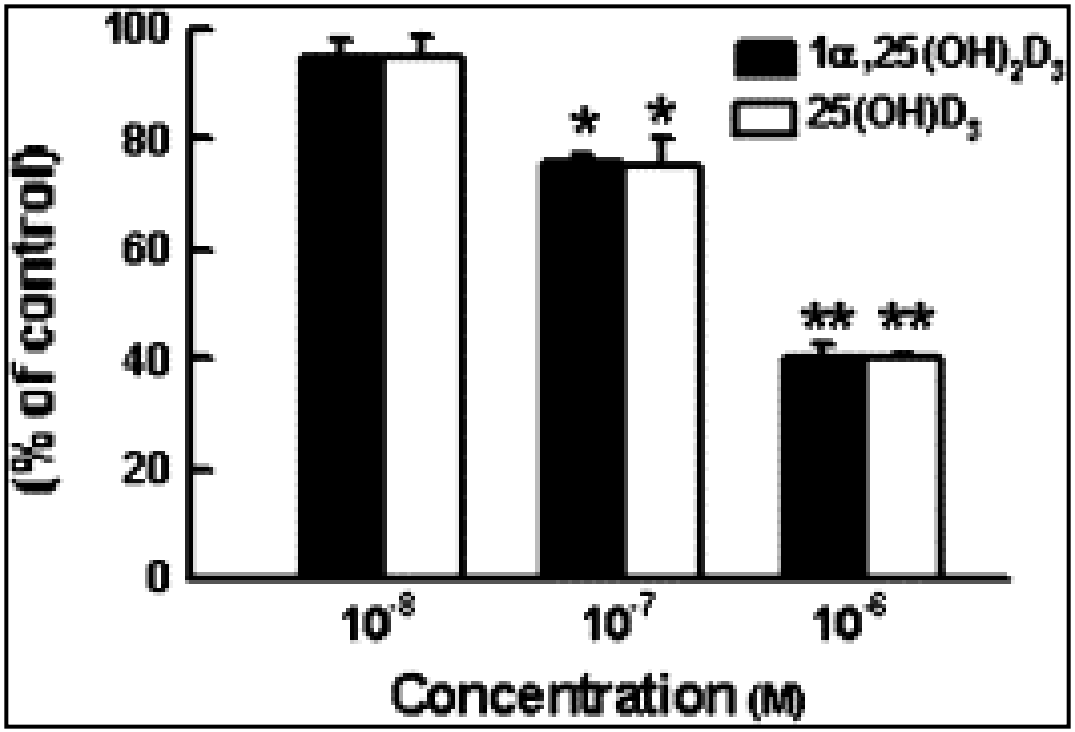


Brancaccio D, et al. Drugs. 2007

[Some] genes that are vitamin D - dependent

- RANK
- RANKL
- osteocalcin
- osteopontin
- calbindin
- Cbfa-1
- PTH
- PTHrP
- type I collagen
- alkaline phosphatase
- carbonic anhydrase
- $ECaC_1$ i $ECaC_2$
- 1α- hydroxsylase
- 24- hydroxylase 25-OH-D_3
- integrins
- C3 complement component
- CaS-R
- MGP
- GH
- p^{21}
- insulin receptor
- TNFα
- TGFβ2
- fibronectin
- bone sialoprotein
- CYP3A4

Prostate cancer cell proliferation in culture



Holick MF, Progress Biophys Mol Biol 2006

Vitamin D is ‘genoprotective’

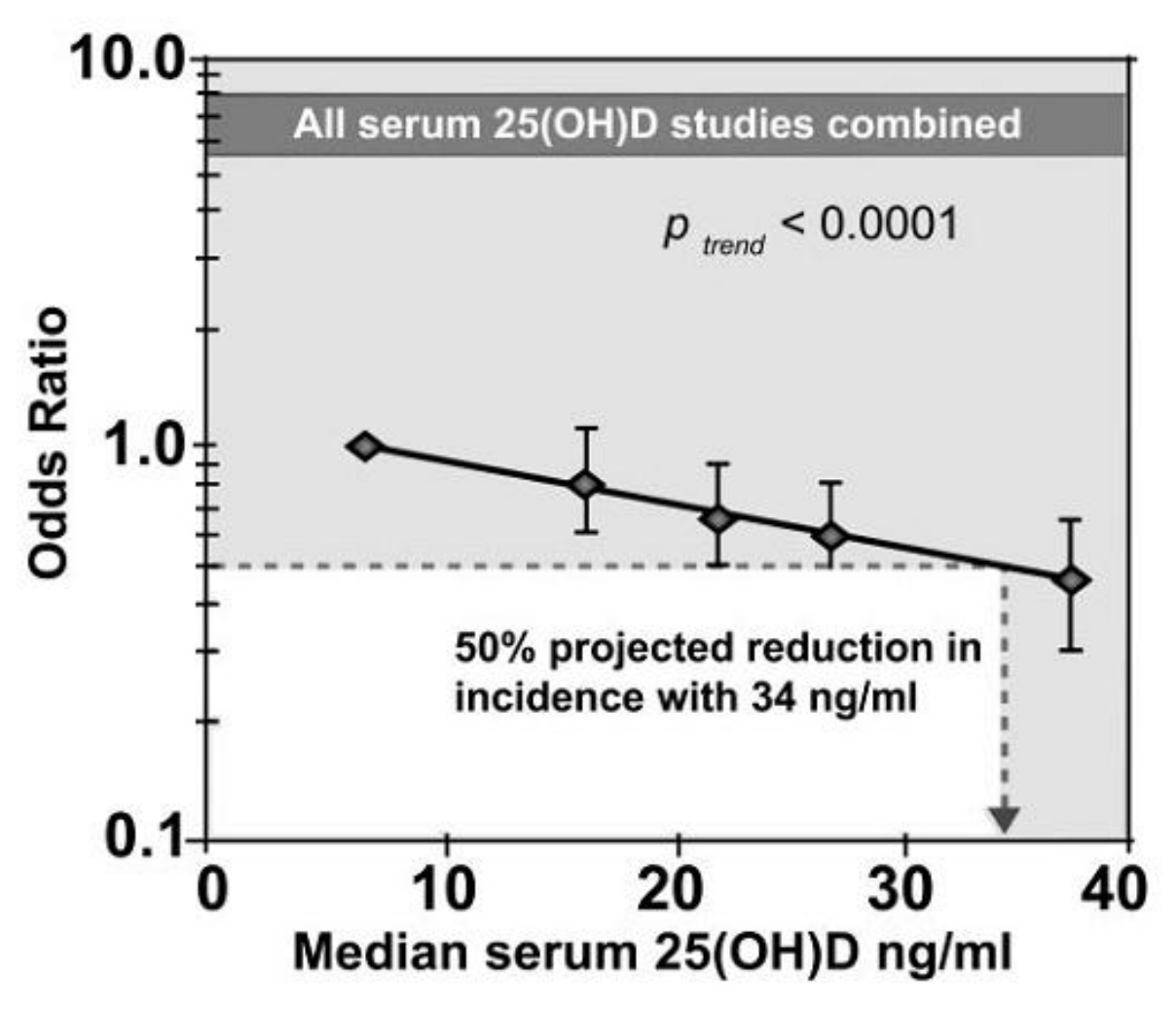
- vitamin D induces the transcription of gene for GADD45a, an enzyme that is essential for repair damaged DNA

- vitamin D protects against an oxidative stress
  - induces transcription of glukose-6-phosphate dehydrogenase
  - induces expression of metalotionein, direct reactive oxygen species scavenger

HYPOTHESIS: system of vitamin D photosynthesis in the skin has been created by God or Nature to protect against the oxidative stress that is generated after skin exposure to the sunlight

Vitamin D decreases the invasiveness of neoplasms and impairs angiogenesis

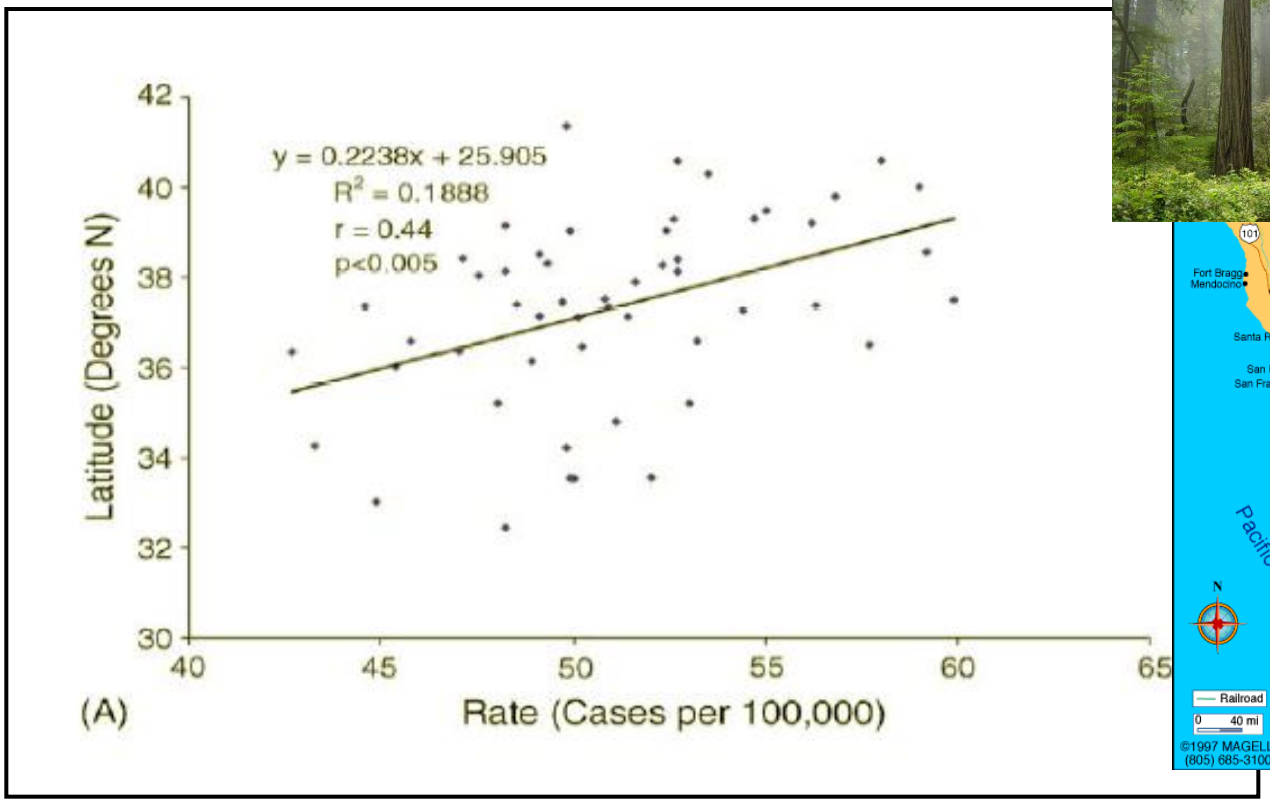
- inhibition of serine proteases (including tPA)
- inhibition of metalloproteinases
- enhanced expression of E- cadherine, factor that inhibits cancer grow
- decreased expression of tenascic C, factor that promotes growth and invasiveness of neoplasm and neo-angiogenesis
- inhibition of proliferation of endothelial cells that lay down the tumor vessels
- inhibition of new vessel budding and elongation within the tumor
- antagonism to **VEGF** effects



Risk for development of colorectal cancer and serum vitamin D

Holick MF, Clin J Am Soc Nephrol. 2008

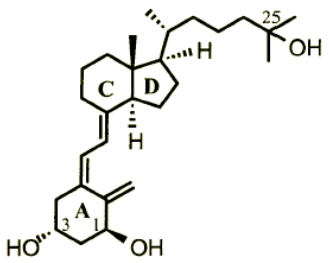
An association between the risk for development colon cancer and latitude **WITHIN** the state of California



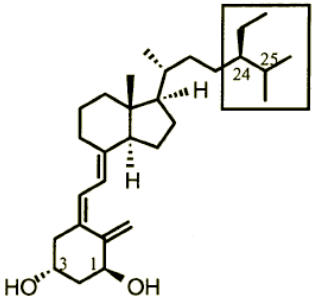
Spina C, et al., J Steroid Biochem Mol Biol. 2005

Beneficial effect of vitamin D and vitamin D derivates has been demonstrated in experiments for tumors in the following organs:

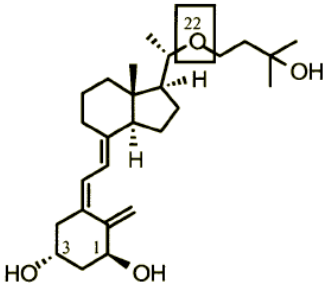
- urinary bladder
- breast
- colon
- pancreas
- *endometrium*
- kidneys
- *neuroblastoma*
- *glioma*
- ovary
- prostatic gland
- multiple myeloma
- leukemias
- squamous cell skin cancer*
- melanoma*
- *sarcoma* of bones and soft tissues
- and many others....



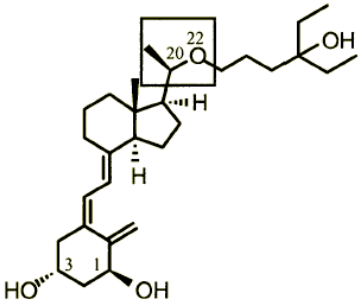
1α,25-Dihydroxyvitamin D_3
[1α,25(OH)$_2$D$_3$]



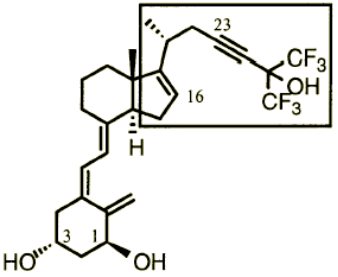
1α-Hydroxyvitamin D_5
[1α(OH)D$_5$]



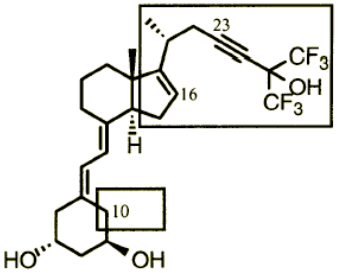
22-Oxa-1α,25(OH)$_2$D$_3$
(Chugai-OCT)



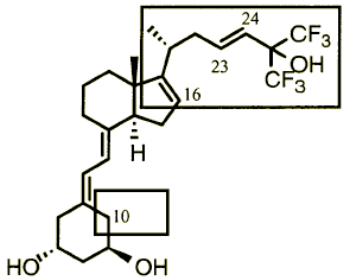
20-Epi-22-oxa-26a,27a-bishomo-1α,25(OH)$_2$D$_3$
(Leo KH-1060)



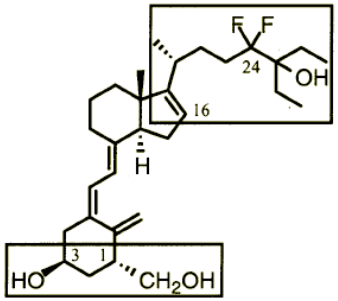
16-Ene-23-yne-26,27-hexafluoro-1α,25(OH)$_2$D$_3$
(Ro 24-5531)



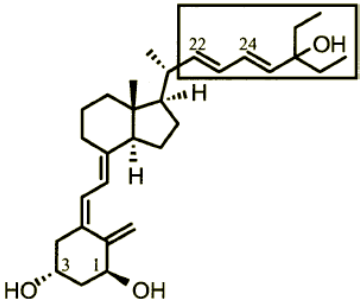
16-Ene-23-yne-19-nor-26,27-hexafluoro-1α,25(OH)$_2$D$_3$
(Ro 25-6760)



16,23E-Diene-19-nor-26,27-hexafluoro-1α,25(OH)$_2$D$_3$
(Ro 25-9022)



1β-Hydroxymethyl-3-epi-16-ene-24,24-difluoro-26a,27a-bishomo-25(OH)D$_3$
(Hopkins-QW-1624F$_2$-2)

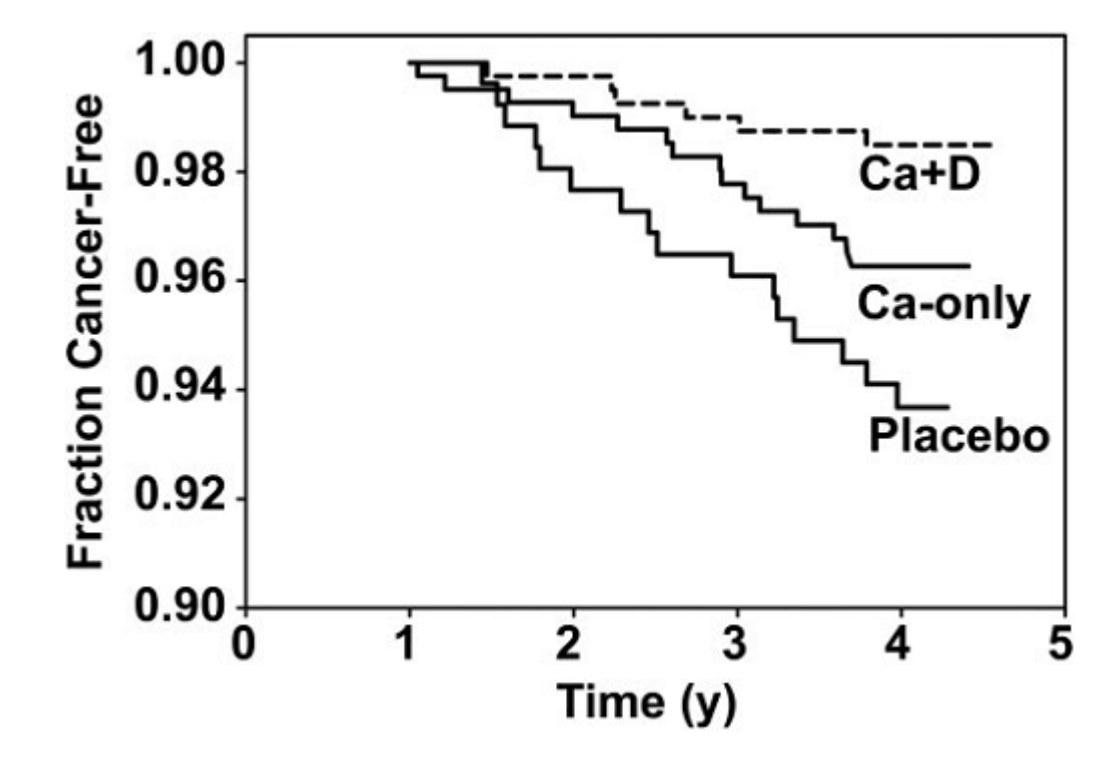


22E,24E-Diene-24,26a,27a-trihomo-1α,25(OH)$_2$D$_3$
(Leo EB-1089)

> 3000 analogues

Guyton K, et al.,
Annu Rev Pharmacol Toxicol.

Vitamin D works as an anti-cancer protective prophylaxis

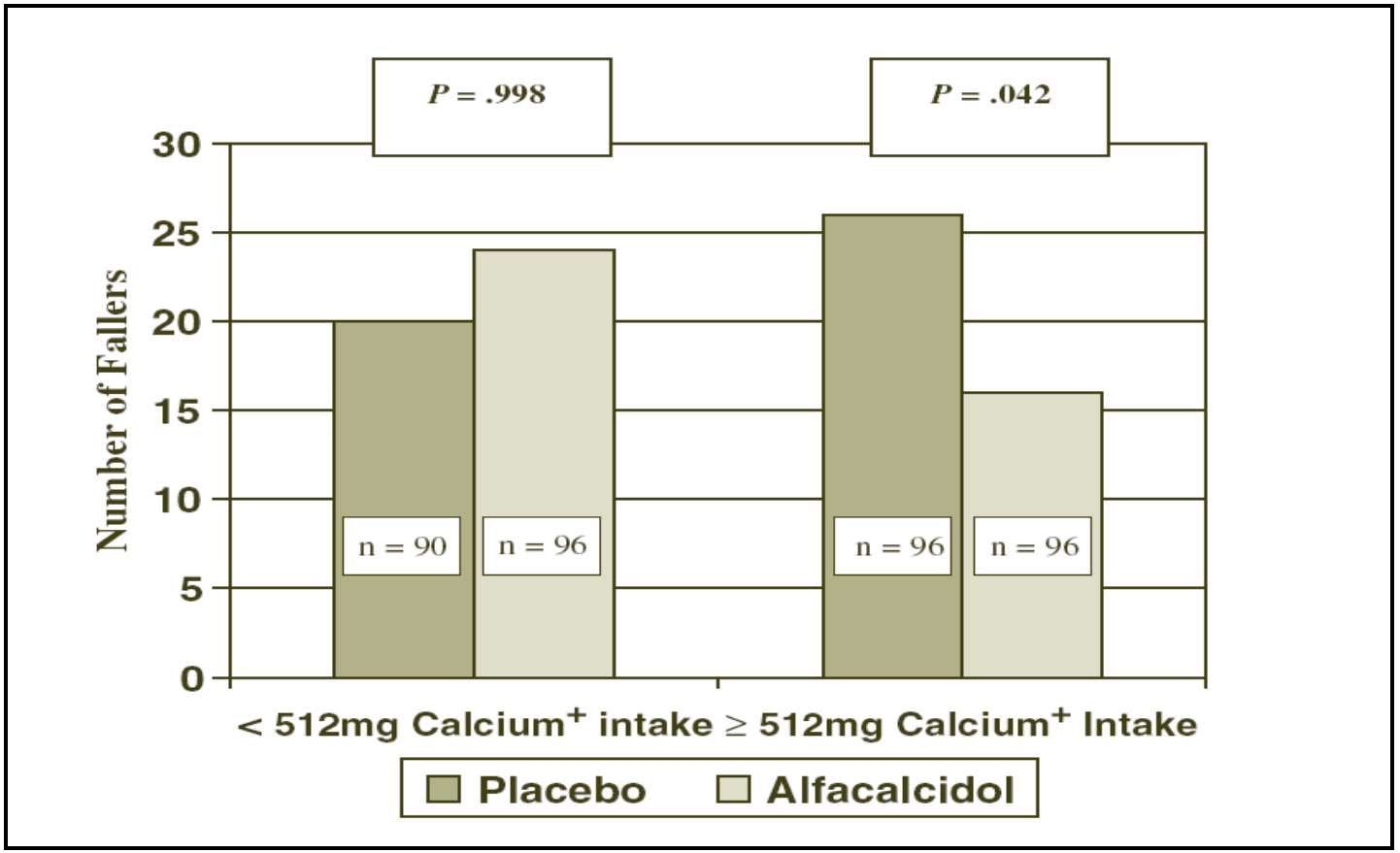


Remaining cancer-free after randomization to placebo, calcium alone or calcium with vitamin D (>1000 women)

Holick MF, Clin J Am Soc Nephrol. 2008

Vitamin D and neuro-muscular system function

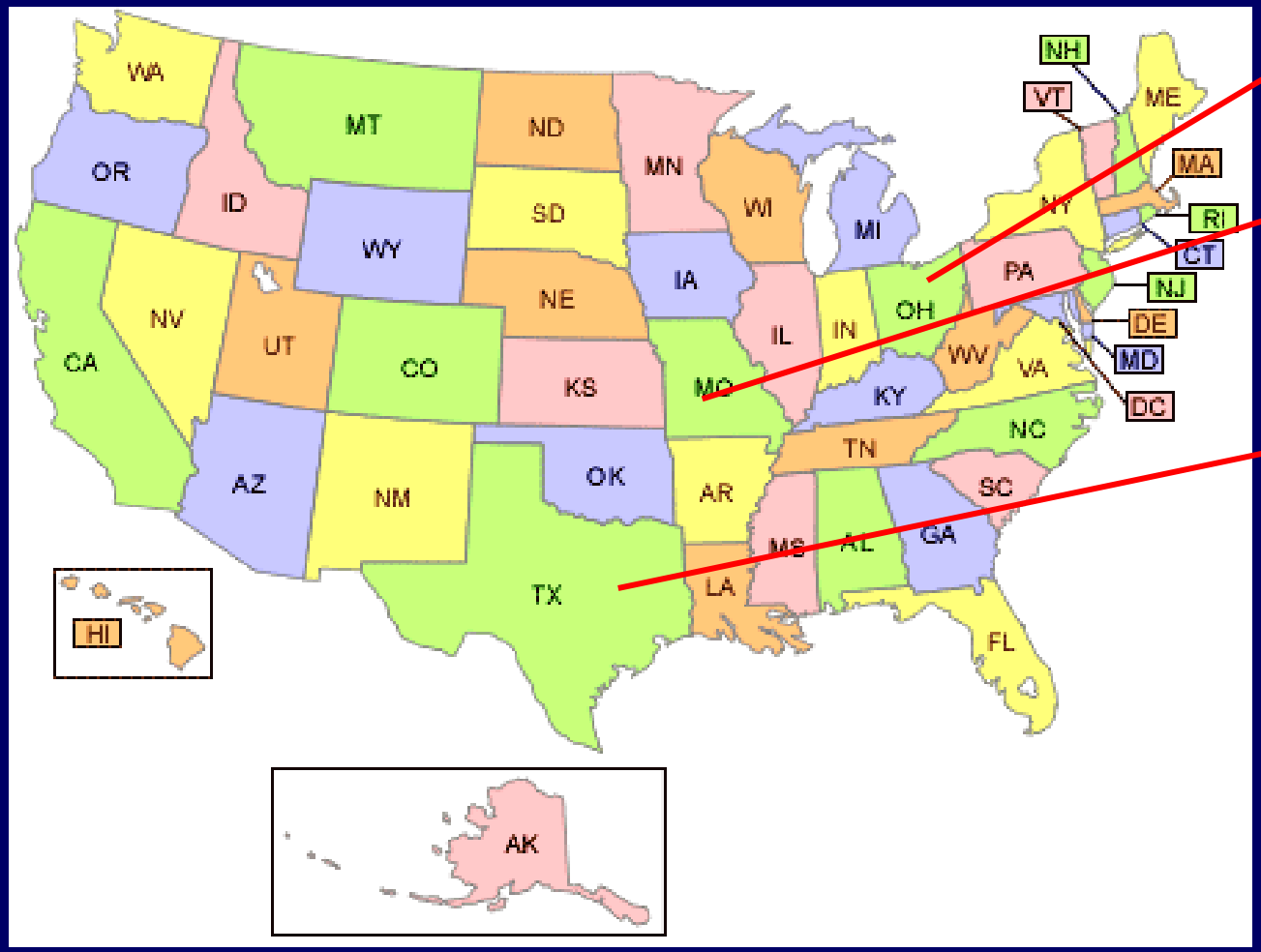
- vitamin D deficiency is one of the most frequent reasons of myopathy (sarcopenia and muscle weakness) in elderly
- vitamin D deficiency is a frequent reason of falling in elderly and fractures in post-menopausal women with osteoporosis
- studies show that vitamin D supplementation decreases the disk of falls and fractures in elderly women



Dukas L, et al. J Am Soc Geriatr. 2004

Vitamin D and nervous system

- under the experimental settings severe vitamin D deficiency leads to the development of multiple sclerosis
- north-to-south geographic latitude gradient can be noticed in the epidemiology of MS
- vitamin D reliefs some symptoms of MS and stabilizes the clinical course of a disease
- in experimental studies vitamin D can protect against the neuronal damage after stroke and other brain injury
- vitamin D protects neurons against some effects of senescence



OH – 112/100 000

MO – 87/100 000

TX - 42/100 000

Noonan CV, et al., Prev Chornic Dis. 2010

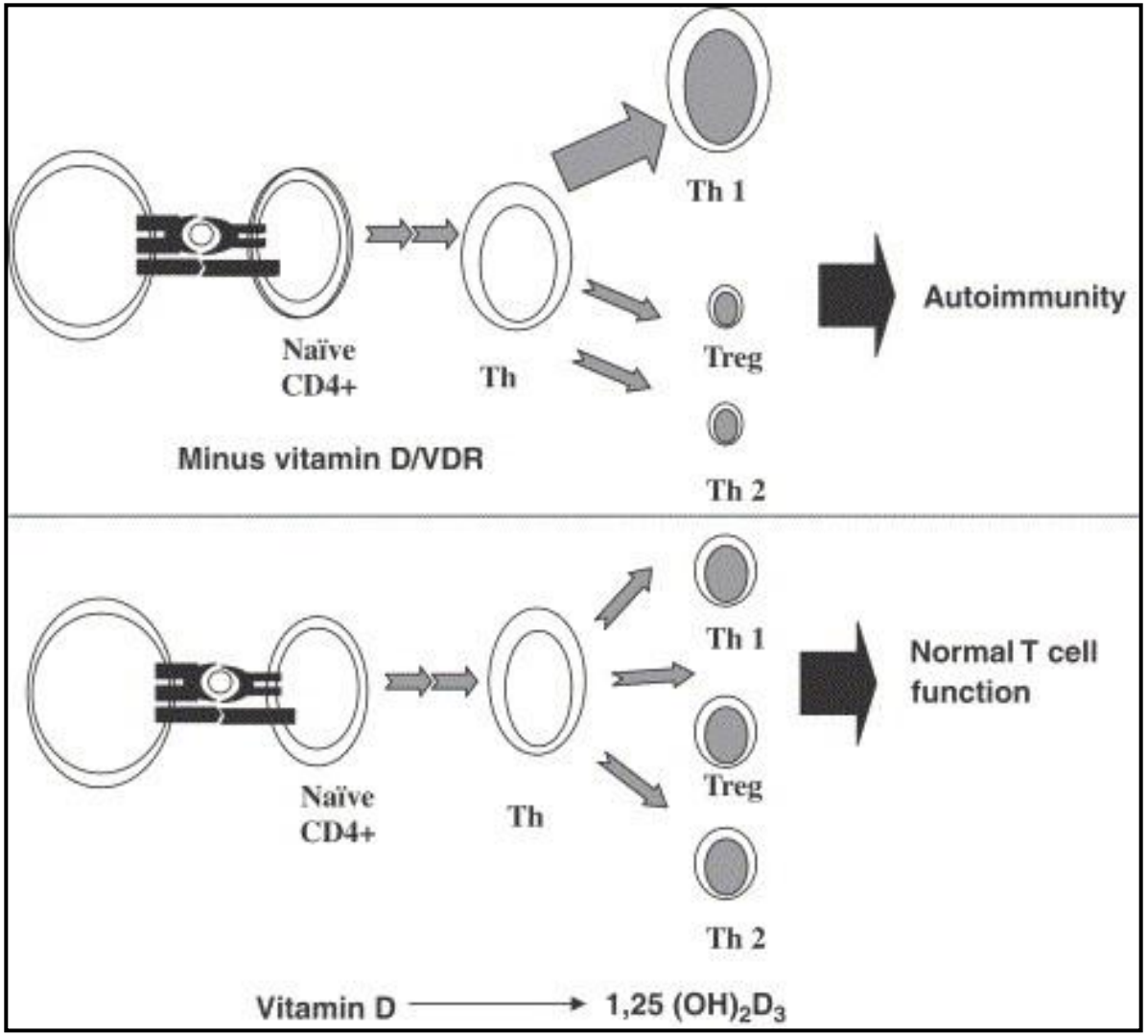
Vitamin D and immune system

- vitamin D
  - decreases expression of NF-*κ*B
  - inhibits synthesis of IL-2, 6, 12, TNFα, IFγ and *RANTES*
  - stimulates synthesis of IL-10

- activation of VDR in T- cells results in binding of VDR or VDR-RXR heterodimer to NF-AT and its inactivation (one of the key steps in activating immune reaction, including organ rejection)

- vitamin D regulates balance between Th_1 and Th_2 populations

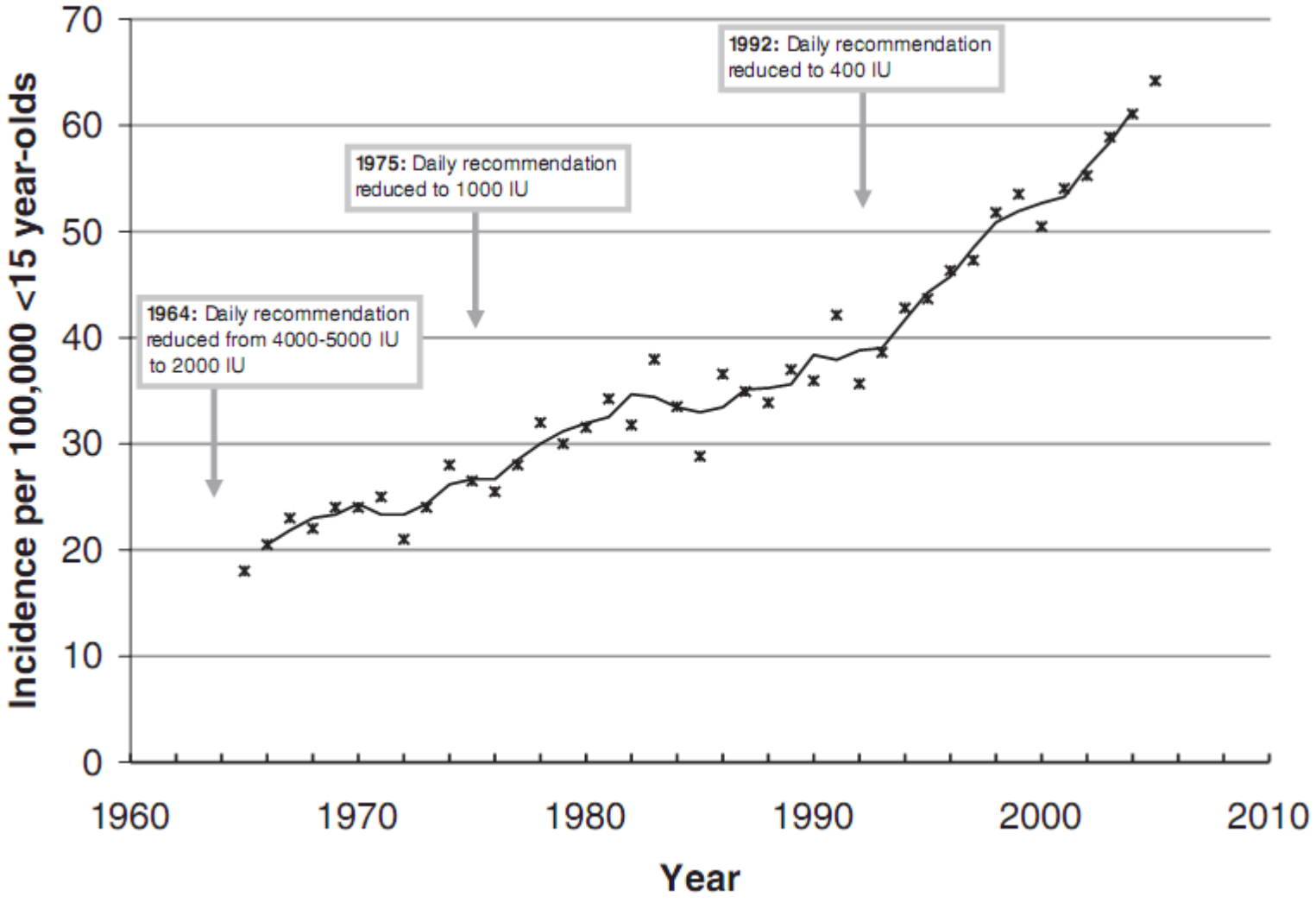
- vitamin D stimulates maturation and activity of APCs



Cantorna MT, Progress Biophys Mol Biol 2006

Following autoimmune diseases may be associated with vitamin D deficiency

- rheumatoid arthritis
- SLE
- *Crohn* disease
- ulcerous colitis
- MS
- encephalomyelitis
- thyroiditis
- insulitis
- nephritis

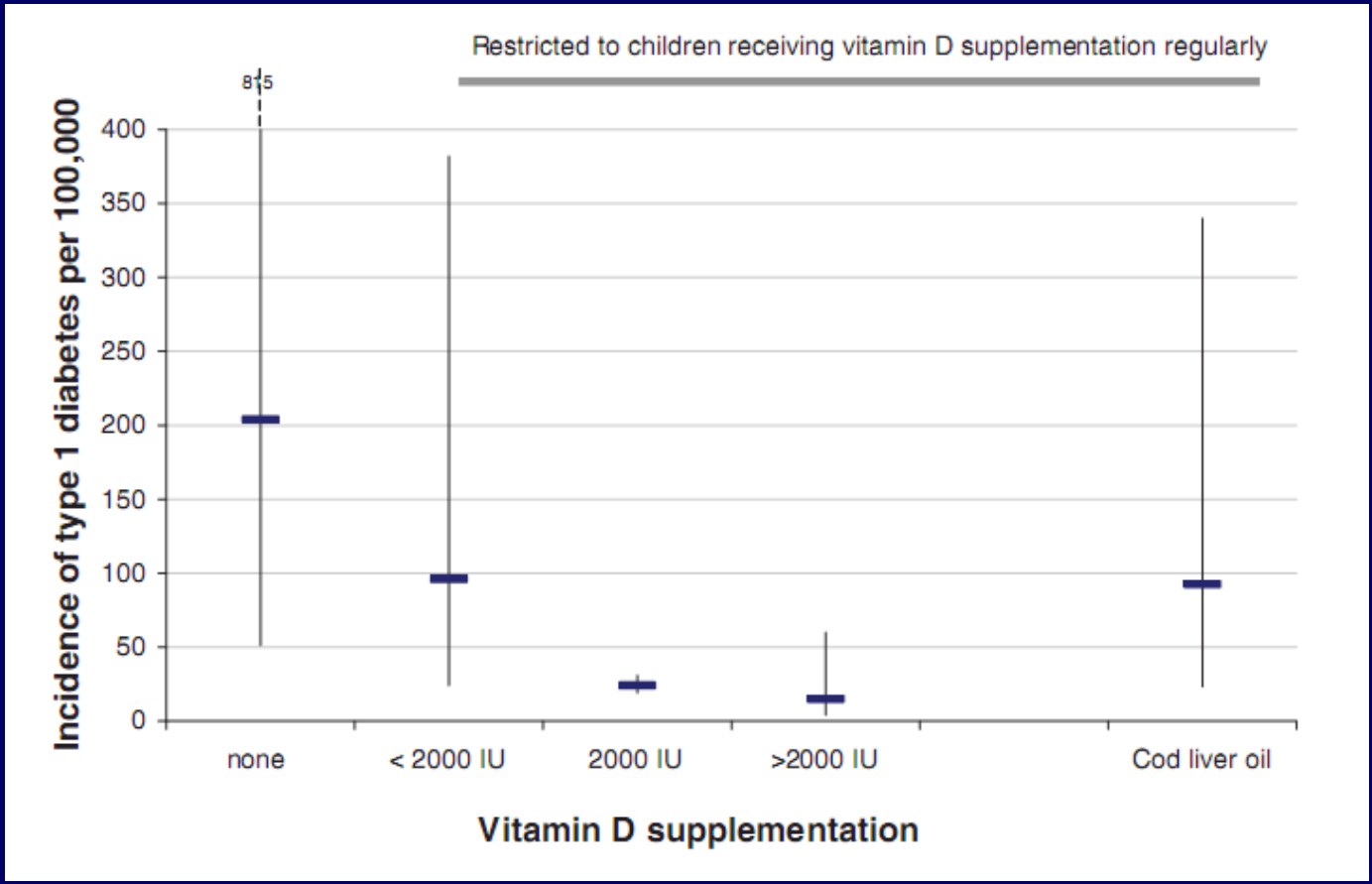


Hyppőnen E. Diab Obes Metabol. 2010

Intake of vitamin D and risk of type 1 diabetes: a birth-cohort study

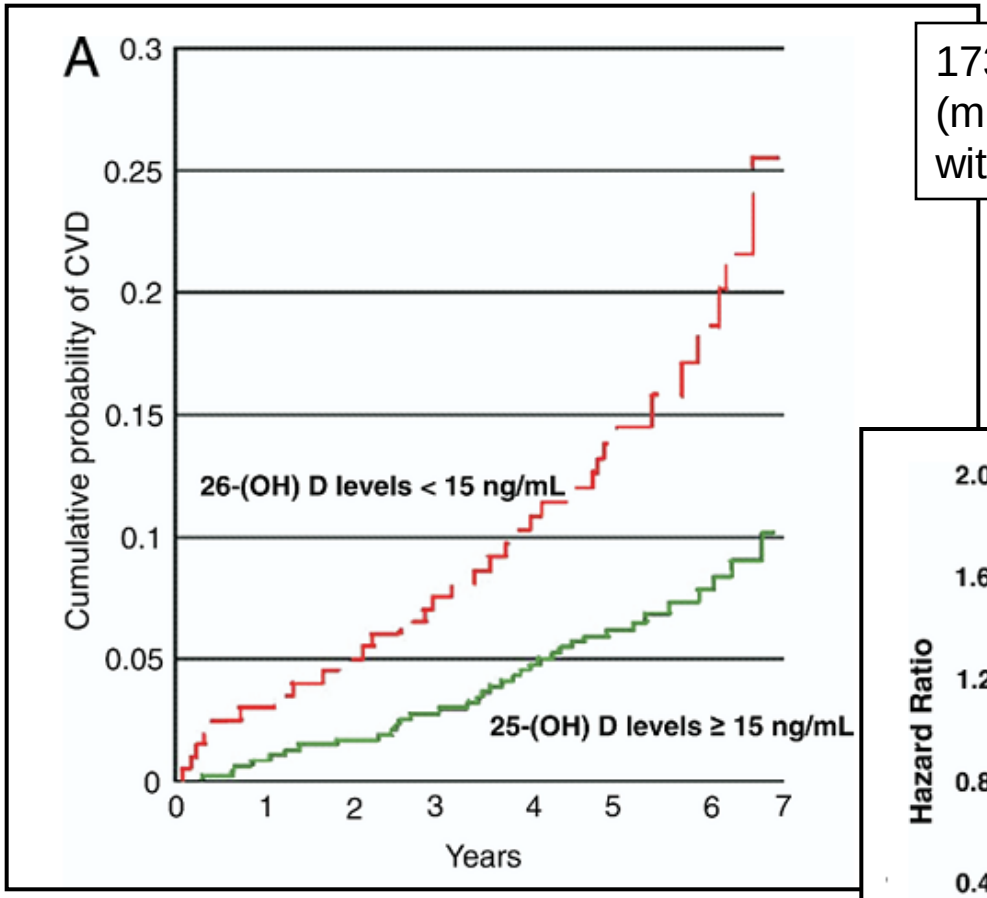
The Lancet 2001

Elina Hyppönen, Esa Läärä, Antti Reunanen, Marjo-Riitta Järvelin, Suvi M Virtanen

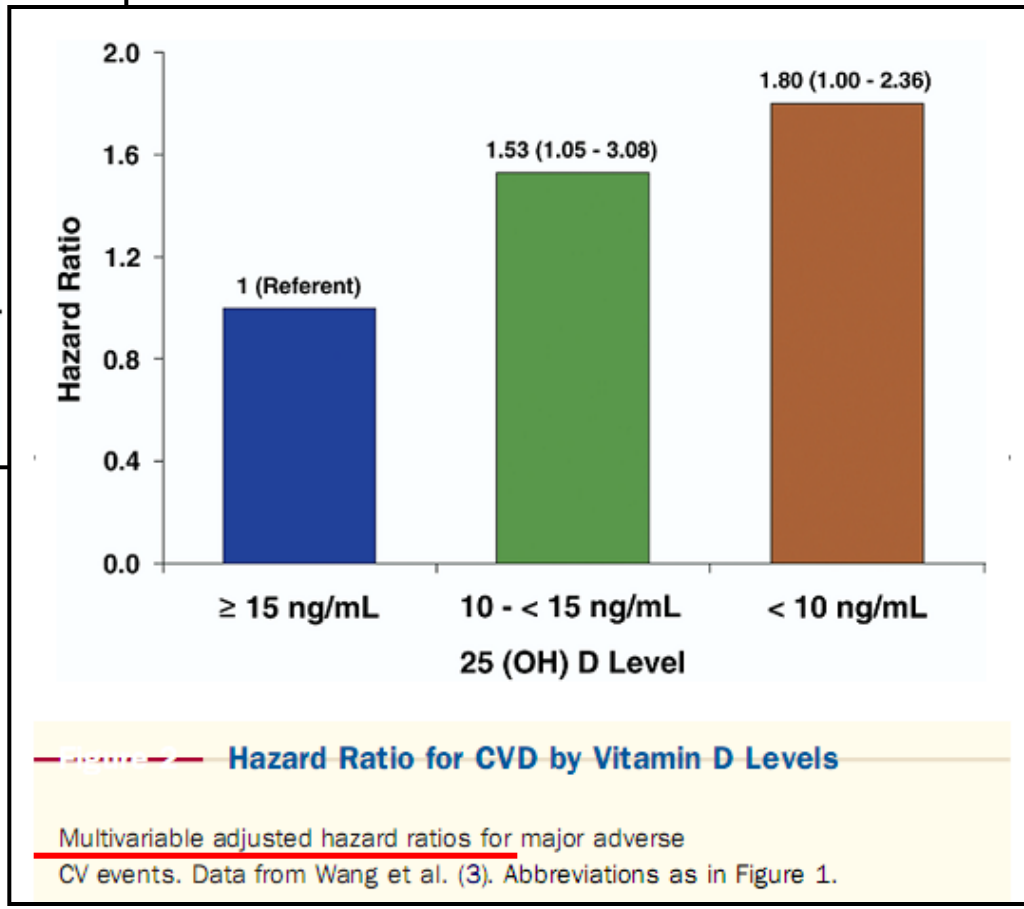


Vitamin D and CVS disease

- vitamin D decreases synthesis of proinflammatory and enhances synthesis of antiinflammatory cytokines
- vitamin D directly (via transcription control) regulates renin synthesis and release and thus controls the overall activity of renin – angiotensin – aldosteron axis
- vitamin D controls enzymatic activity of MMPs
- therapeutic measures that increase serum 25-OH-D_3 (supplementation, sunlight) may lead to reduction of LVH and lowering of blood pressure



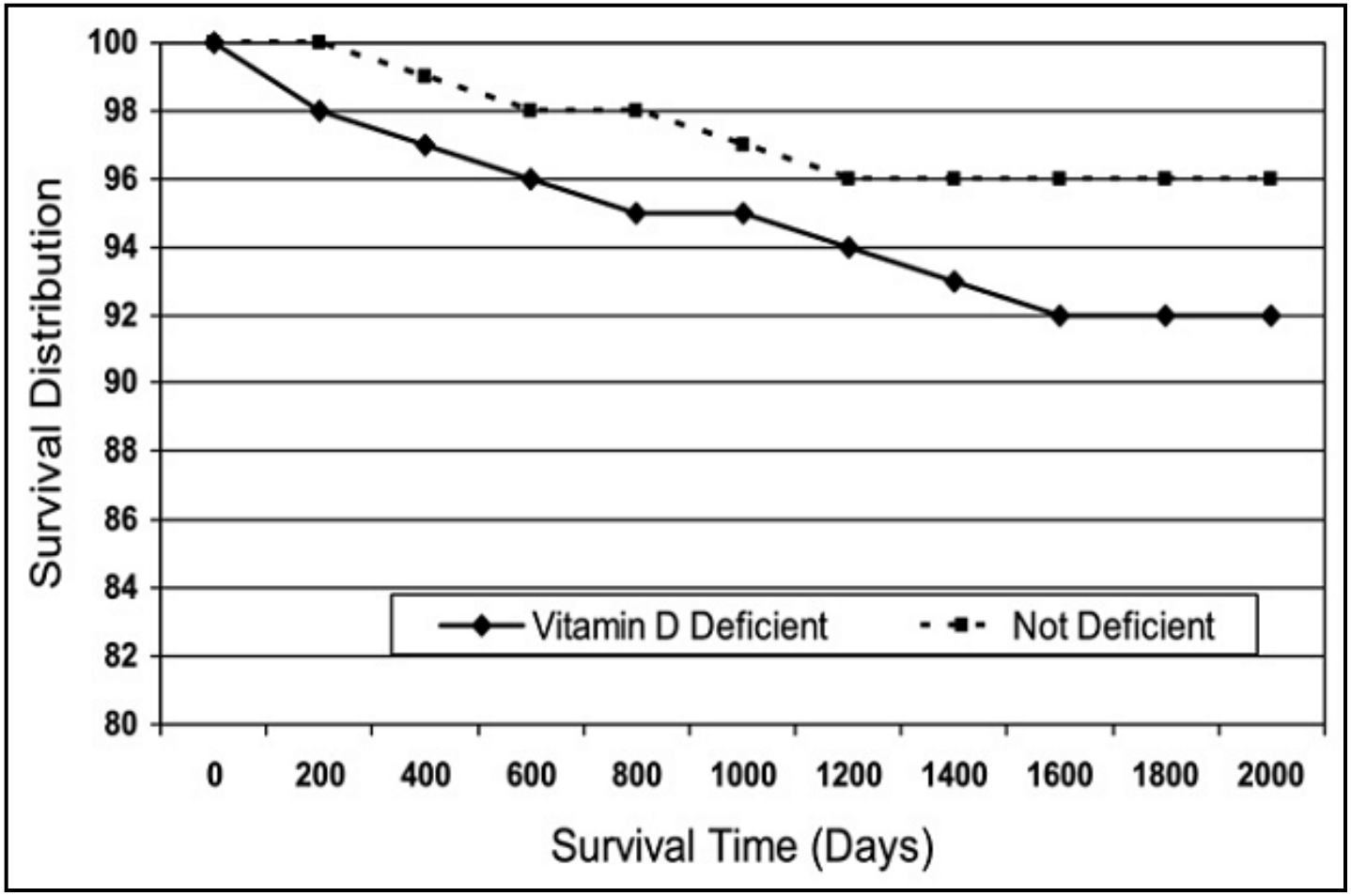
1739 Framingham Offspring Study participants (mean age 59 years; 55% women; all white) without prior cardiovascular disease



Hazard Ratio for CVD by Vitamin D Levels

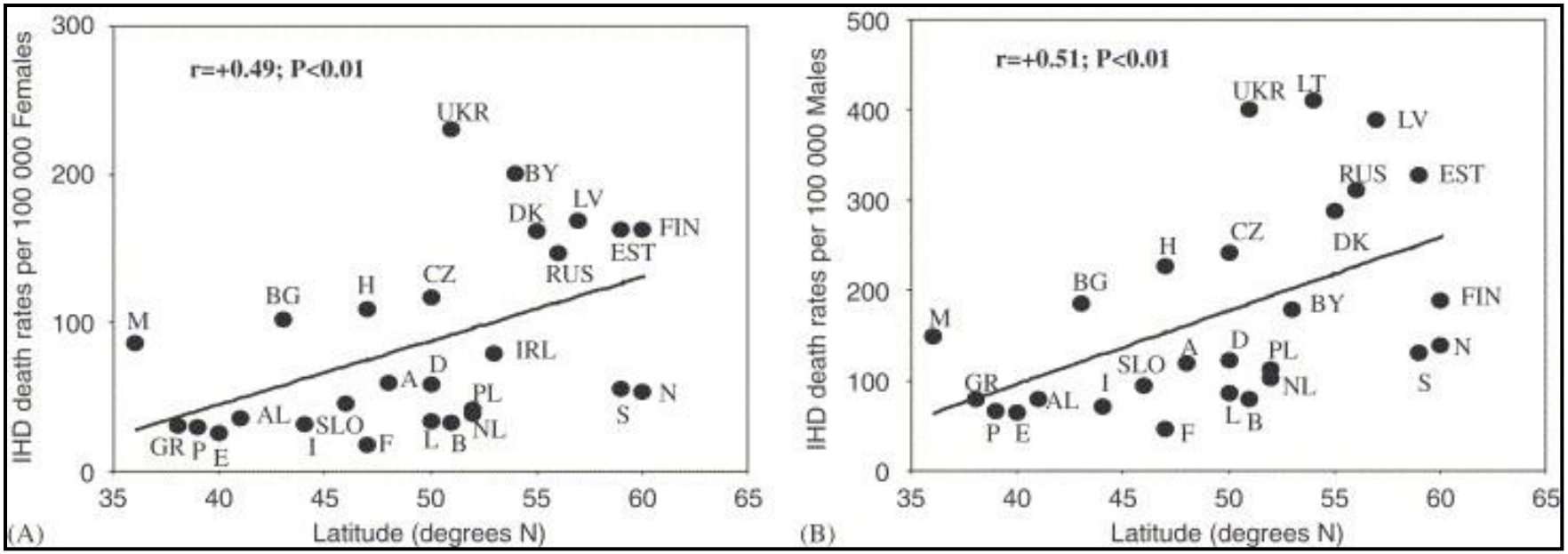
Multivariable adjusted hazard ratios for major adverse CV events. Data from Wang et al. (3). Abbreviations as in Figure 1.

Wang TJ, et al. Circulation 2008

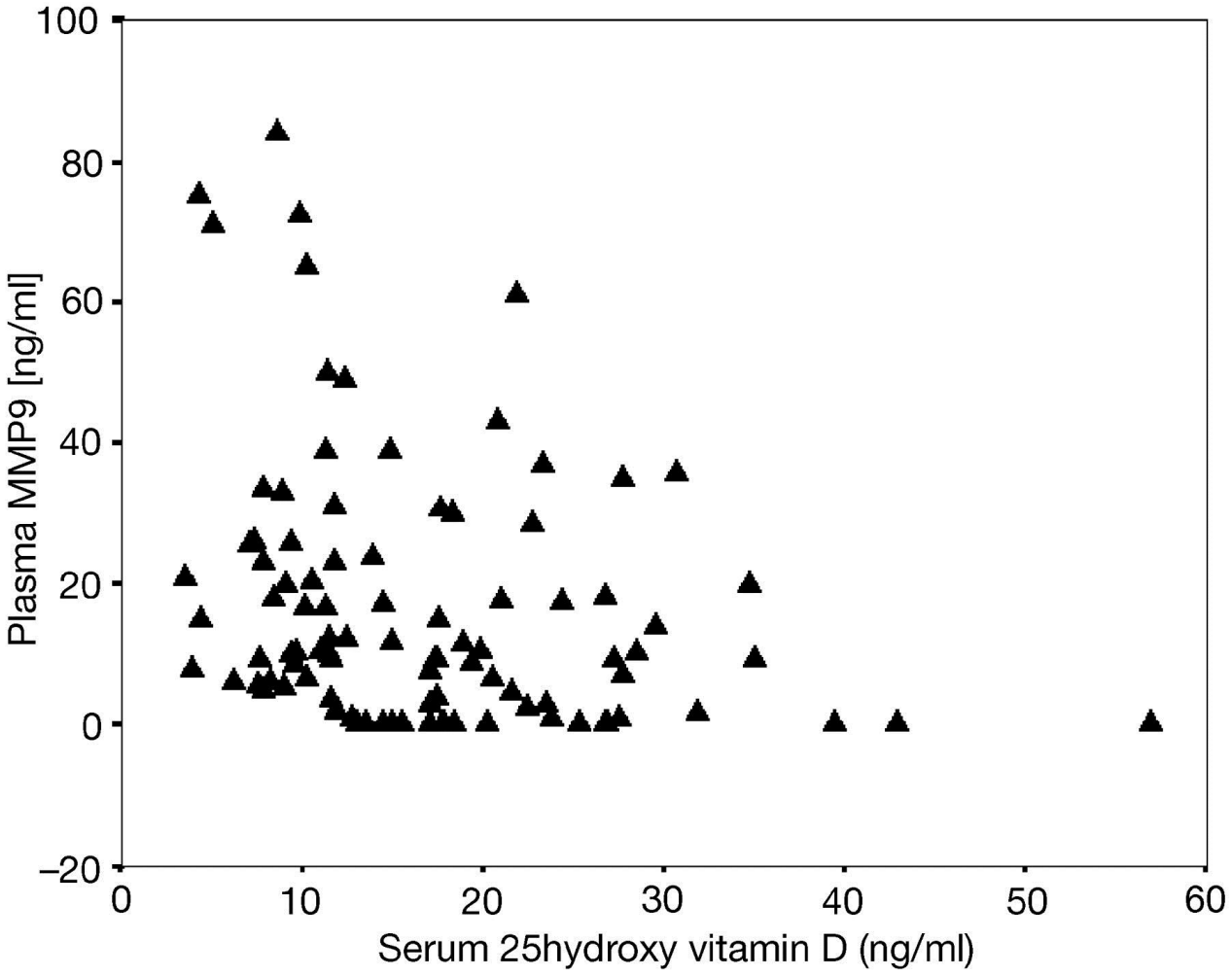


Vacek JL, et al. Am J Cardiol. 2012

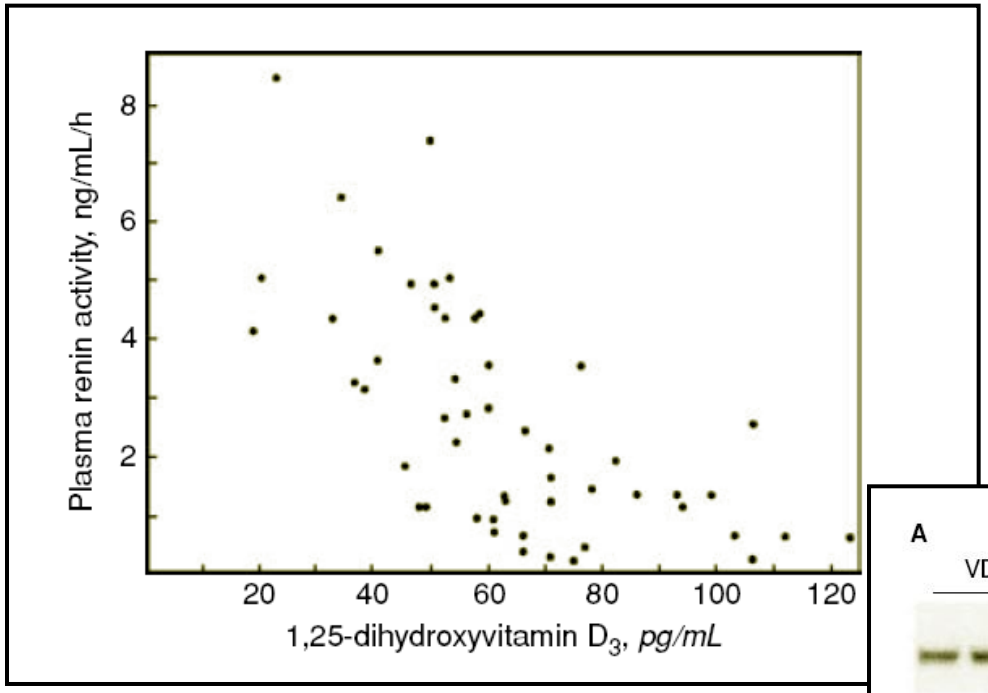
An association between frequency of death due to ischaemic heart disease and latitude in Europe

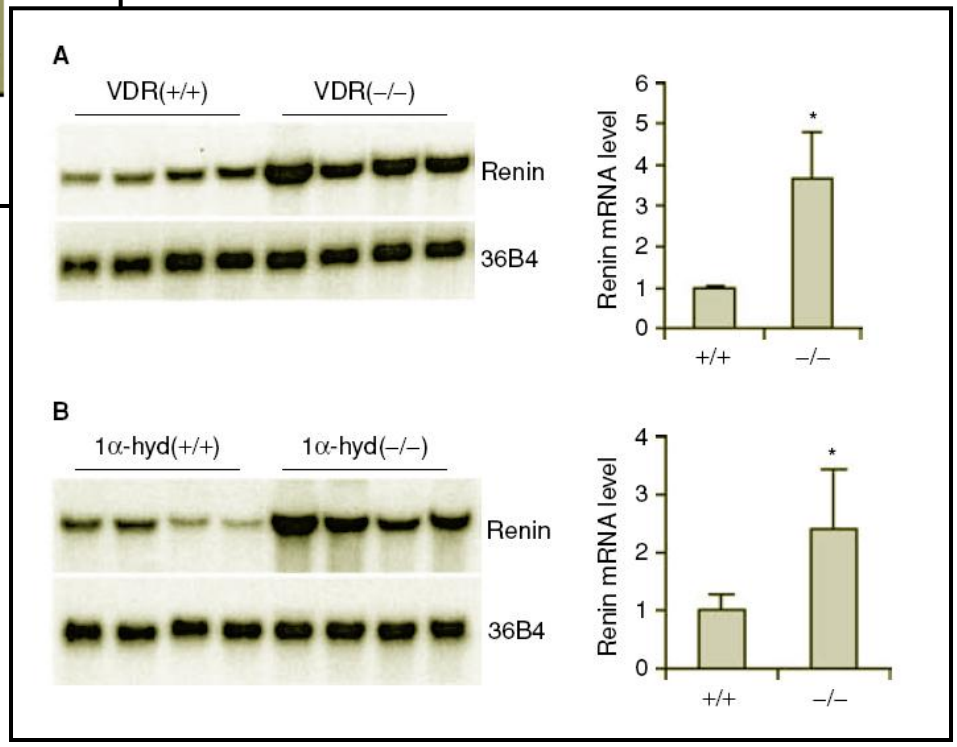


Zittermann A, Progress Biophys Mol Biol 2006



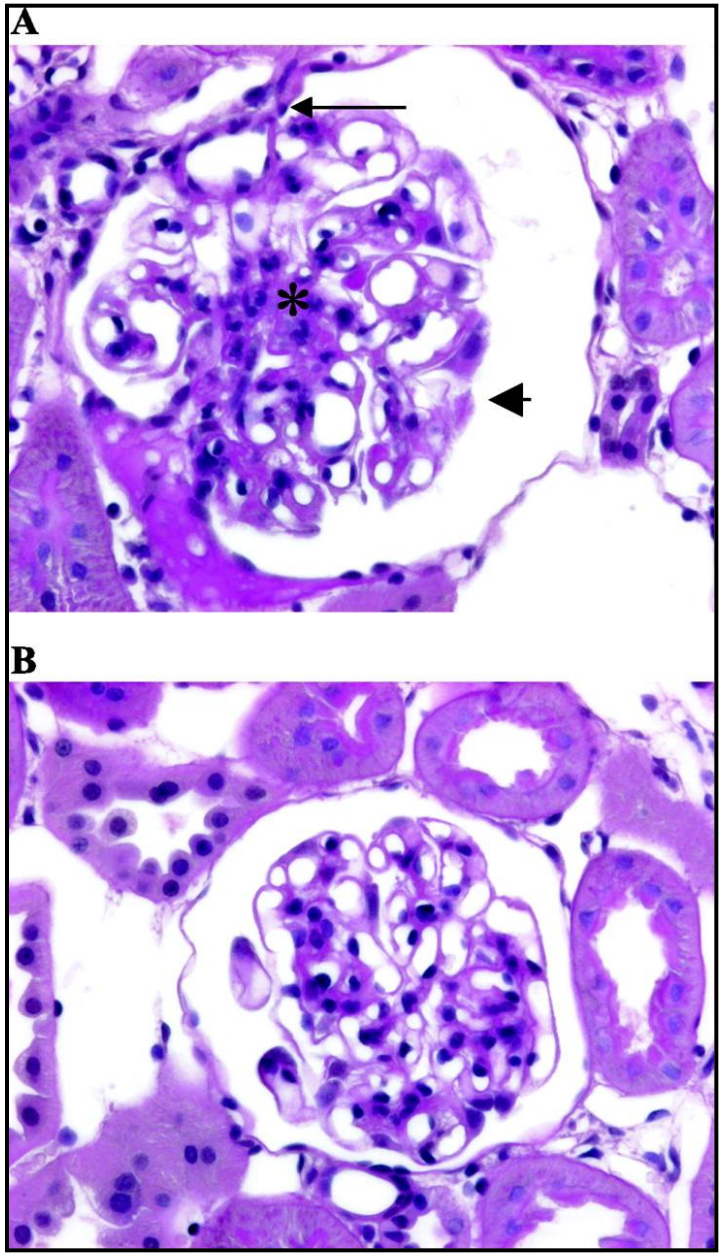
Timms PM, et al., Q J Med. 2002

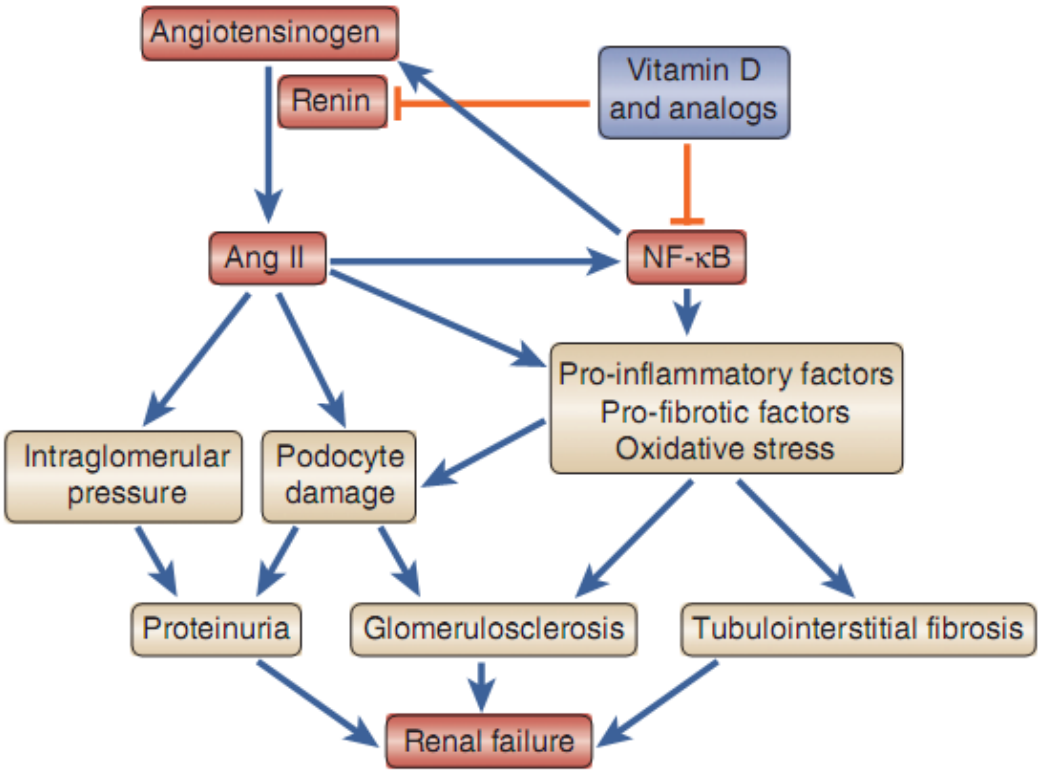




Resnick LM, et al. Ann Intern Med. 1986
Li C, et al., J Clin Invest. 2002

How about the kidneys?





Kuhlmann A, et al. Am J Physiol Renal Physiol. 2004
Li JC. Kidney Int. 2010

Cathelicidins

- cathelicidins, defensins, histatins: group of highly ‘conservative’ antibacterial peptides (AMP)
- peptides containing 20 – 60 AA which have positive electric charge and high affinity to microbial cell membranes (they built-in into the microbial cell membranes and ‘puncture’ them, thus leading to bacterial damage)
- their selectivity to bacteria is due to the fact that bacterial cell membrane has different electrical charge as compared to host cell membranes
- cathelicidins are expressed in Neu, NK cells, lympho T and B
- cathelicidins are constitutively expressed in epithelial cells (urinary tract, respiratory system, G.I.) and released to mucus; their excretion may increase upon inflammatory challenge

Cathelicidins

- cathelicidins are effective against: *Listeria monocytogenes, Staphylococcus aureus, S. epidermidis, MRSA, VREF, Bacillus subtilis, Escherichia coli, Pseudomonas aeruginosa, Salmonella typhimurium, Proteus mirabilis, Proteus vulgaris, Candida albicans* and *Mycobacterium tbc*

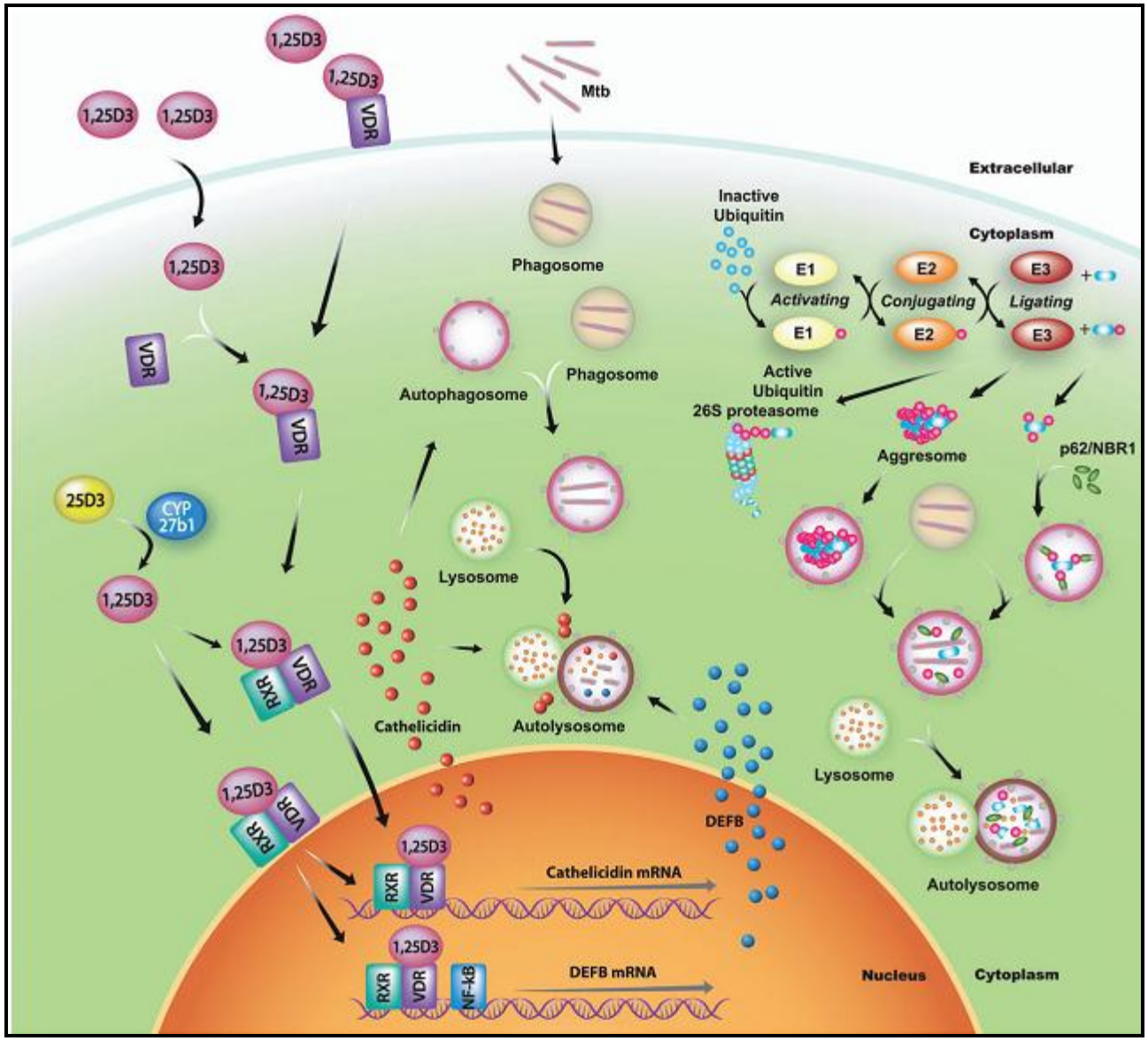
J Immunol. 2007; 179: 2060

THE JOURNAL OF IMMUNOLOGY

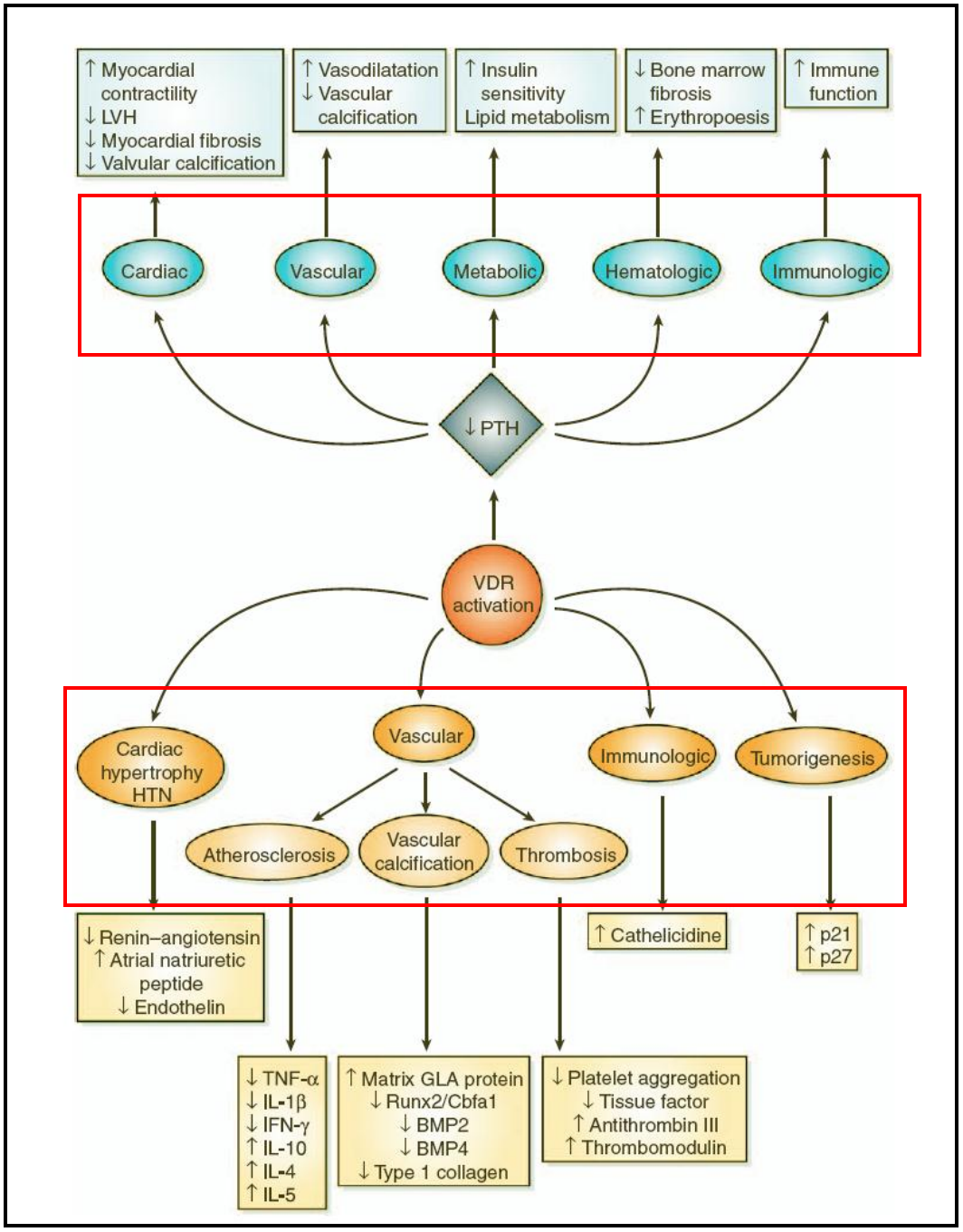
CUTTING EDGE

Cutting Edge: Vitamin D-Mediated Human Antimicrobial Activity against *Mycobacterium tuberculosis* Is Dependent on the Induction of Cathelicidin[1]

Philip T. Liu, Steffen Stenger,† Dominic H. Tang,* and Robert L. Modlin[2]**



Jo EK. Cell Microbiol. 2010



Kovesdy CP, Kalantar-Zadeh K. Kidney Int. 2008

Diseases for which the ‘latitude gradient’ as well as an association with witamin D intake and serum level were demonstrated

- ischaemic heart disease
- congestive heart failure
- *colitis ulcerosa*/*Crohn* disease
- multiple sclerosis
- rheumatoid arthritis
- type 1 DM

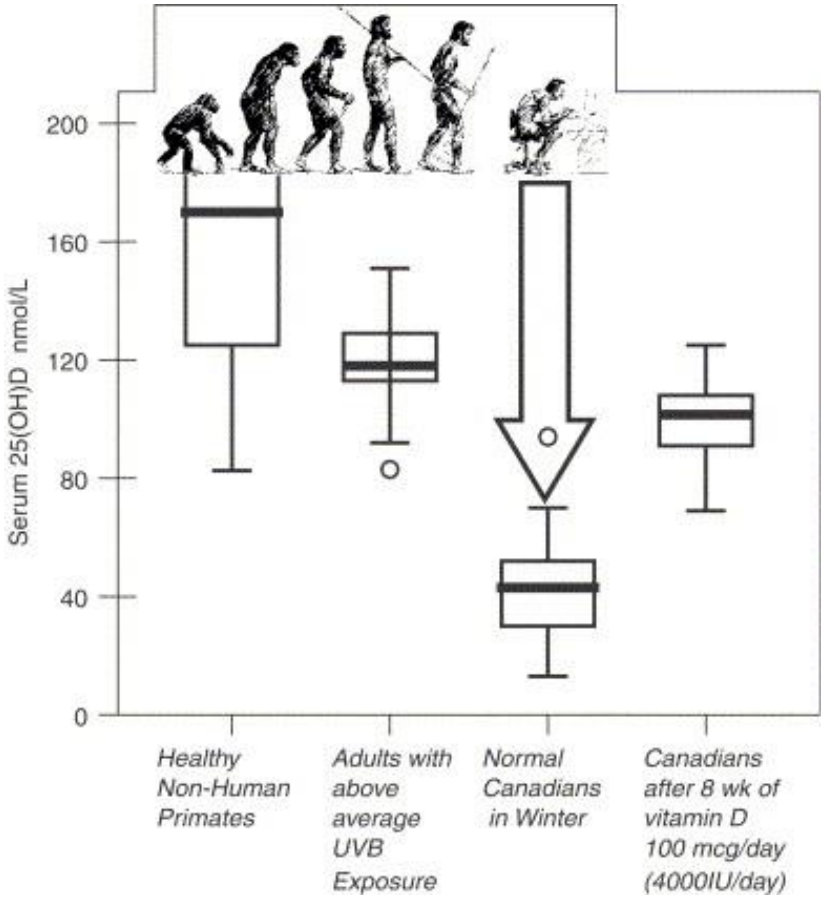
NEOPLASMS

- breast
- prostatic gland
- colon and rectum
- ovary
- stomach
- urinary bladder
- bronchus
- pancreas
- uterus
- kidney
- lymphoma
- multiple myeloma

An association between the diseases and skin ‘photosynthesis’ of vitamin D

- more frequent CVS disease and prostatic cancer among African Americans
- seasonal (autumn, winter) worsening of clinical course in otherwise stable coronary heart disease

Vitamin D deficiency as an epidemic in Western (?) countries



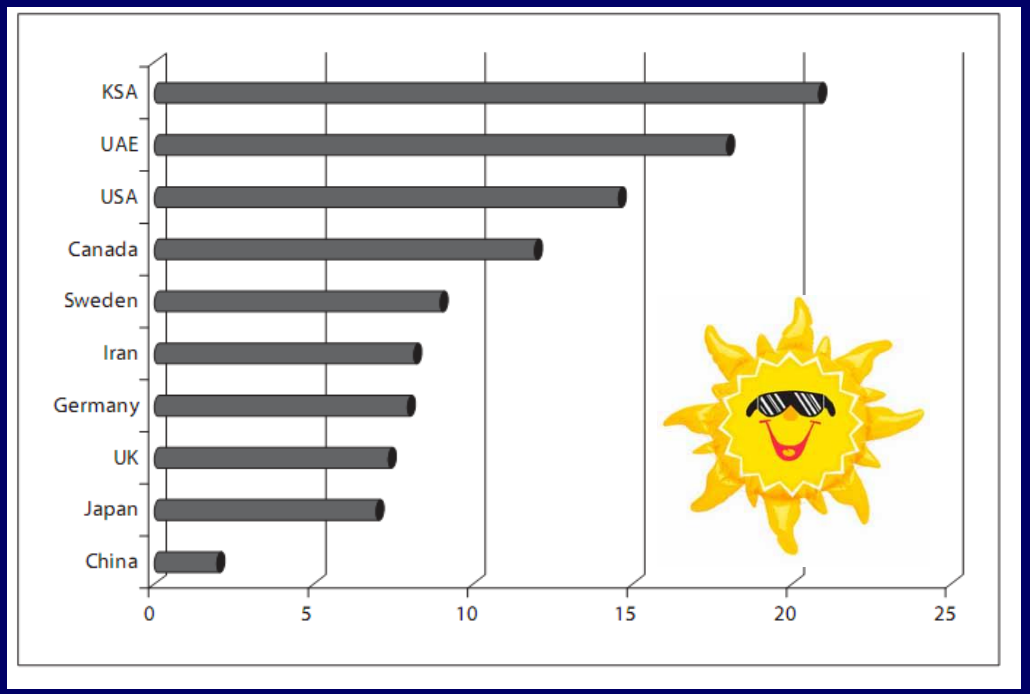
Vieth R, Progress Biophys Mol Biol 2006

Western countries only?

SHADOW SEEKING BEHAVIOUR

Epidemics of vitamin D deficiency

- an ‘average’ serum level of 25 – OH – D_3 in patients with CHF: < 40 – 50 nmol/L (and lower in winter months)
- African-American women aged 15 - 49 years (NHANES III study): vitamin D deficiency in 42%
- young Caucasian adults in Boston: vitamin D deficiency in 36%
- young Arab women living in Western Europe (Denmark) : vitamin D deficiency in 88%
- nursing home residents in the US: vitamin D deficiency in 75%



Lifetime risk for urinary tract stone development…

Johri N, et al. Nephron Clin Pract. 2010

The paradigm of TOTAL and UNCONDITIONAL PROTECTION against sunlight - we need discussion and new consensus

Several working groups, such as joint initiative of:

- *Australasian College of Dermatologists*
- *Osteoporosis Australia*
- *Australia and New Zealand Bone and Mineral Society*
- *Cancer Council Australia*

MED: minimal dose of UV-B radiation that leads to noticeable skin redness

Changing paradigm

MED: minimal dose of UV-B radiation that leads to noticeable skin redness

Exposure of 25% of skin to 25% of MED allows to synthesize 1000 IU of endogenous vitamin D

– for example: if in a person the noticeable redness after 40 min. of sun exposure, it should be enough to expose 25% of skin surface to sun for 10 minutes to synthesize 1000 IU of vitamin D (25% is face and whole upper extremities or forearms and lower legs)

UltraViolet Index (UVI): index of exposure to UV-B radiation

- 0-2: no limits
- 3-7: sunscreens needed, hat and protective cloths as well as shadow seeking necessary
- ≥ 8: no sun exposure if possible, in the middle of a day

Poland:

- October – March: 0 – 2
- April and September: 3 – 4
- May – August: 5 – 7

Kenya or Singapore: all year > 10

www.who.int/uv/intersunprogramme/activities/uv_index

Supplementation

- food products are not sufficient sources of vitamin D, unless not supplemented
- many food products are supplemented with calcium and vitamin D in USA; in Europe this has been abandoned
- pharmacological supplementation should be started when serum 25-OH-D_3 decreases below < 50 nmol/L

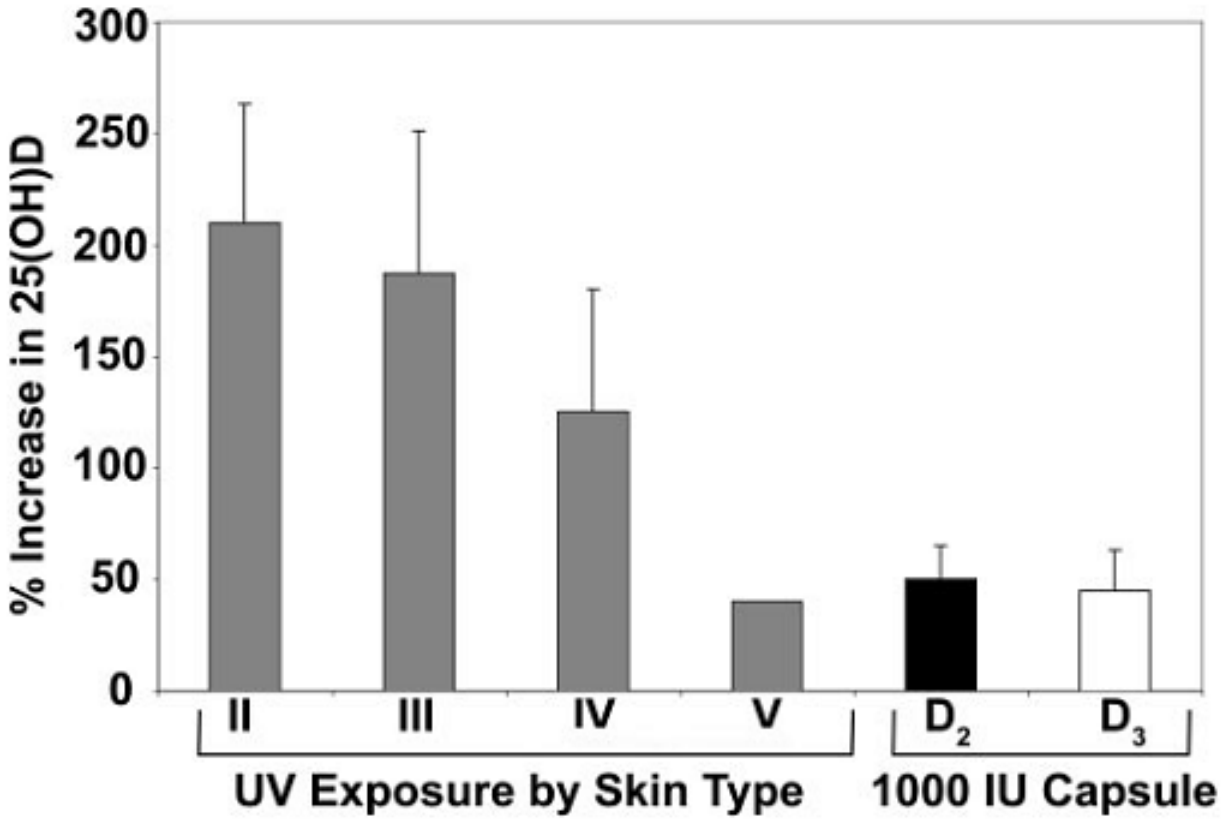
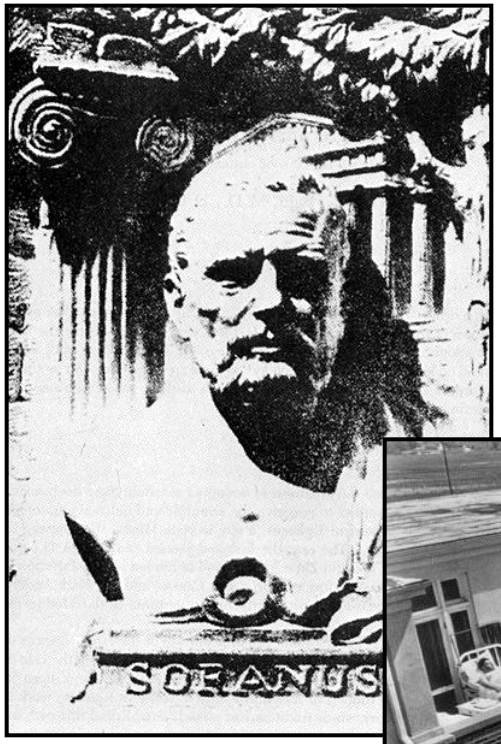


Figure 2. Comparison of the percentage increase in serum 25(OH)D levels of healthy adults who were in a bathing suit and exposed to suberythemal doses (0.5 MED) of ultraviolet B radiation once a week for 3 mo with healthy adults who received either 1000 IU of vitamin D_2 or 1000 IU of vitamin D_3

Holick MF, Clin J Am Soc Nephrol. 2008



Lekarze…
Pielęgniarki…
Dietetycy…
Ratownicy medyczni…

NIE MOGĄ DOBRZE WYKONYWAĆ SWOJEJ PRACY BEZ GRUNTOWNEGO POZNANIA MOLEKULARNEGO PODŁOŻA DZIAŁANIA WITAMINY D…