Vitamin D deficiency, consequences, prevention and treatment

Paul Lips
Endocrinology/Internal Medicine
VU University Medical Center
Amsterdam
The Netherlands

Daniel Whistler 1645
Francis Glisson 1651

"morbus Anglorum"
"English disease"

rickets in children
osteomalacia in adults

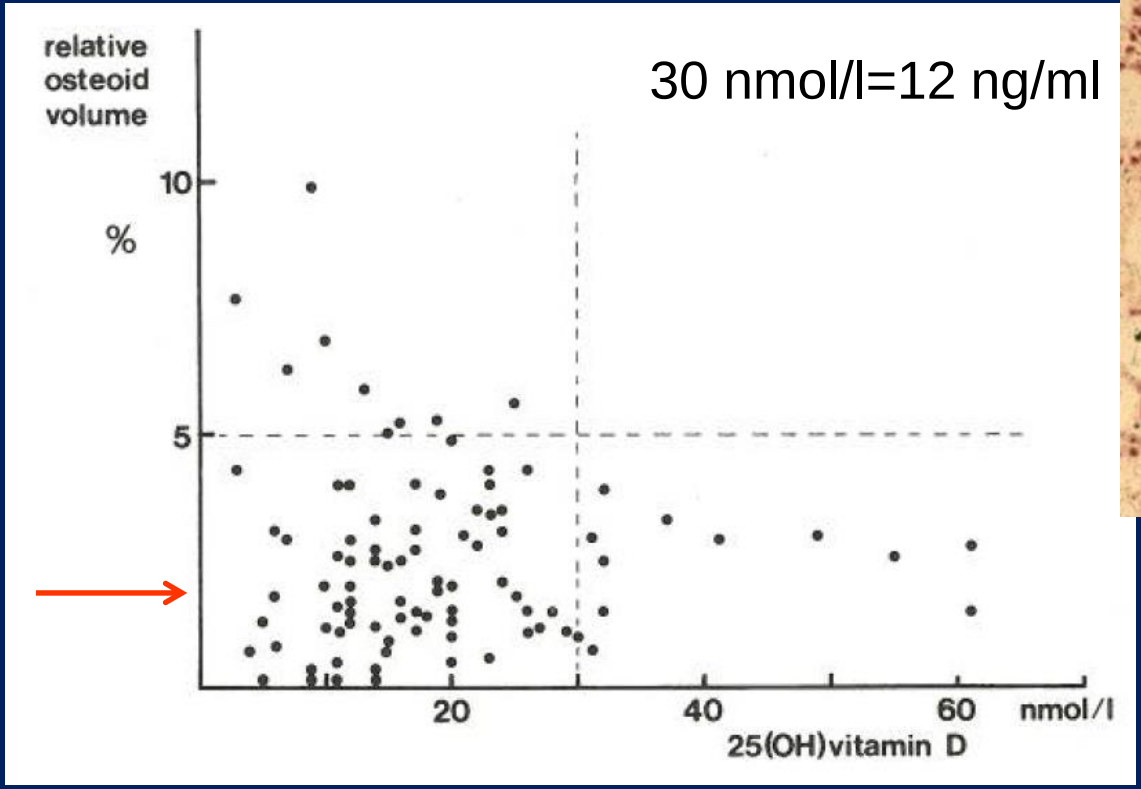
English disease (osteomalacia) in 18th and 19th century skeletons in Birmingham

M. Brickley . Am J Phys Anthropol 2007; 132: 67-79

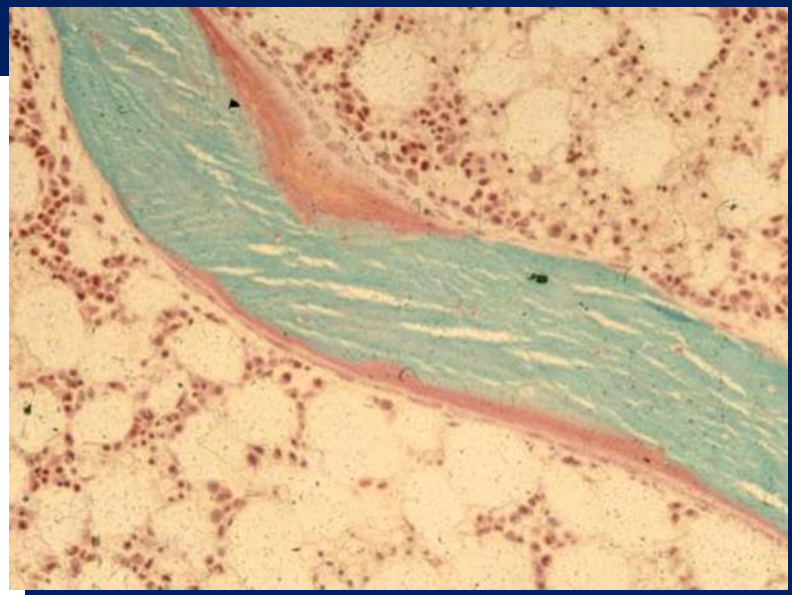
Vitamin D

- Mineralization defects
- Measurement of 25-hydroxyvitamin D
- Vitamin D and bone
- Effects outside the skeleton
- Global vitamin D deficiency
- Unsolved questions and controversial issues

A study of 119 bone biopsies and vitamin D status in patients with hip fracture
Osteoid volume and serum 25(OH)D

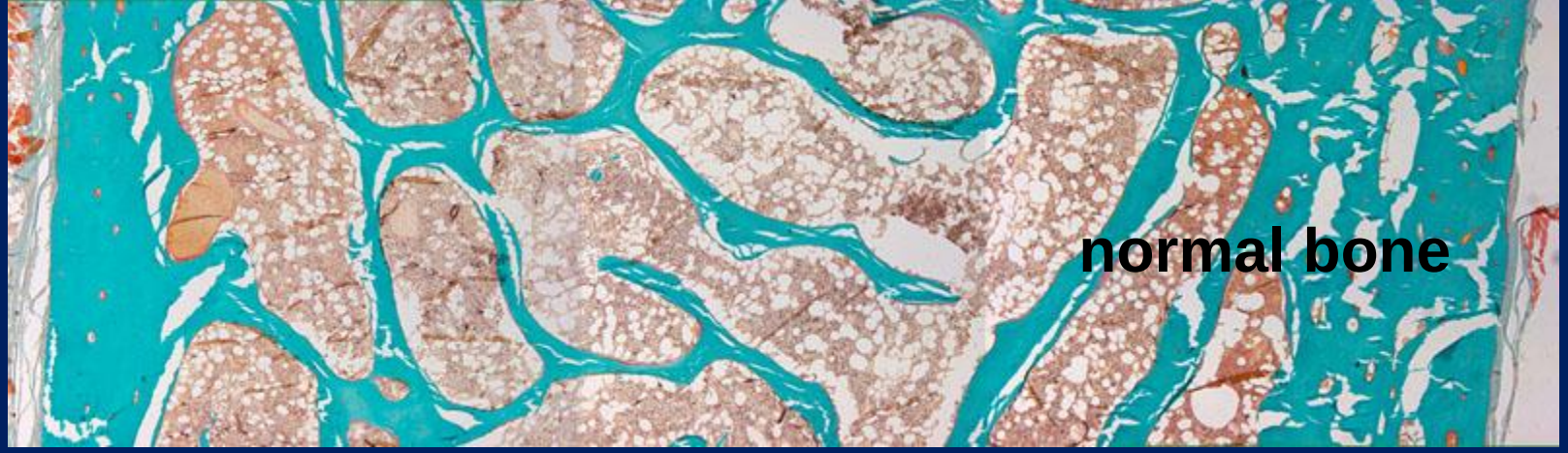


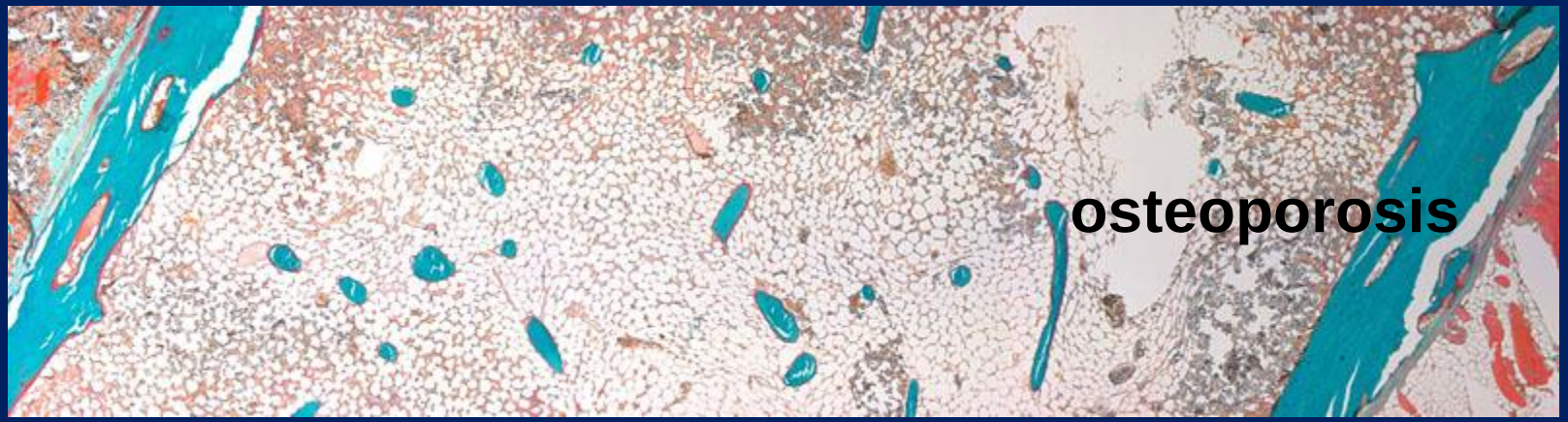
30 nmol/l=12 ng/ml

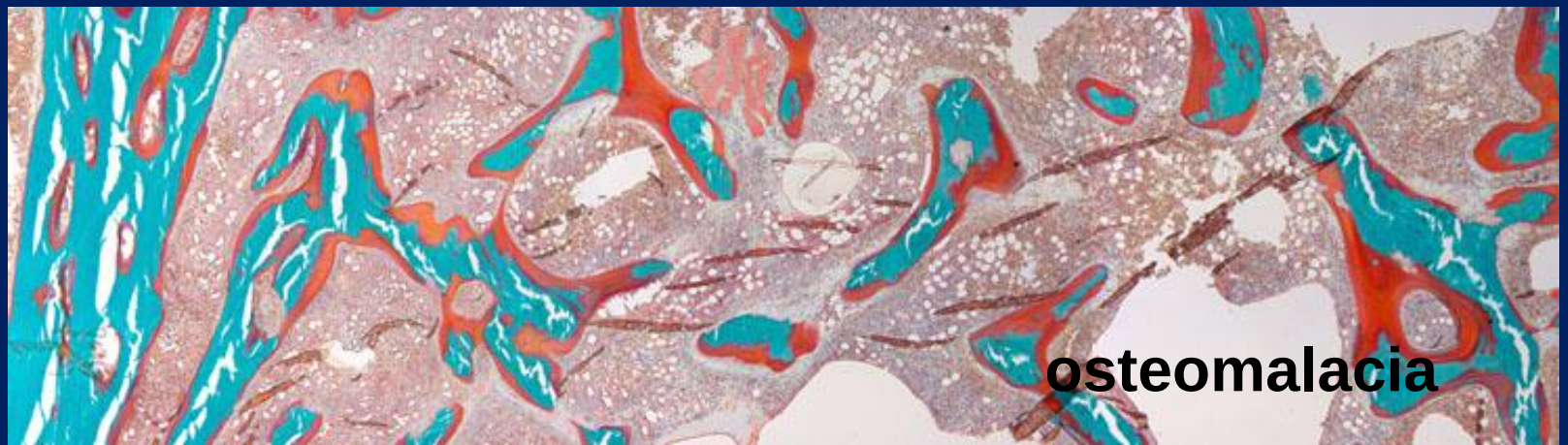


OV/BV>5% in 10 %

Lips P PhD thesis 1982, Metab Bone Dis Rel Res 1982


normal bone


osteoporosis


osteomalacia

Vitamin D-metabolism

Sun
April-sept

Nutrition

Vitamin D3

CYP2R

25(OH)-vitamin D3 (liver)

PTH

1α-hydroxylase
CYP 27B1

24-hydroxylase
CYP 24

1,25(OH)2-vitamin D3 (kidney)

24,25(OH)2 D3

Vitamin D receptor

CYP24

Function?
Callus formation?

Calcium absorption from the gut

Inactivation

Inborn errors of vitamin D-metabolism

Sun
April-sept

Nutrition

Vitamin D3

25-hydroxylase CYP2R

25(OH)-vitamin D3 (liver)

1α-hydroxylase
CYP 27B1

24-hydroxylase
CYP 24

1,25(OH)2-vitamin D3 (kidney)

24,25(OH)2 D3

Vitamin D receptor

CYP24

Function?

Low calcium absorption,
Rickets/osteomalacia

No inactivation
Hypercalcemia

Inborn errors of vitamin D metabolism

Vitamin D dependent or resistant rickets

- Type 1A: 1α-hydroxylase deficiency (CYP27B1)
- Type 1B: 25-hydroxylase deficiency (CYP2R1)
- Type 2A: true resistance, VDR mutation
- Type 2B: heterogeneous nuclear ribonucleoprotein overexpression
- Type 3: activating mutation of CYP3A4

Decreased catabolism, hypercalcemia, renal stones

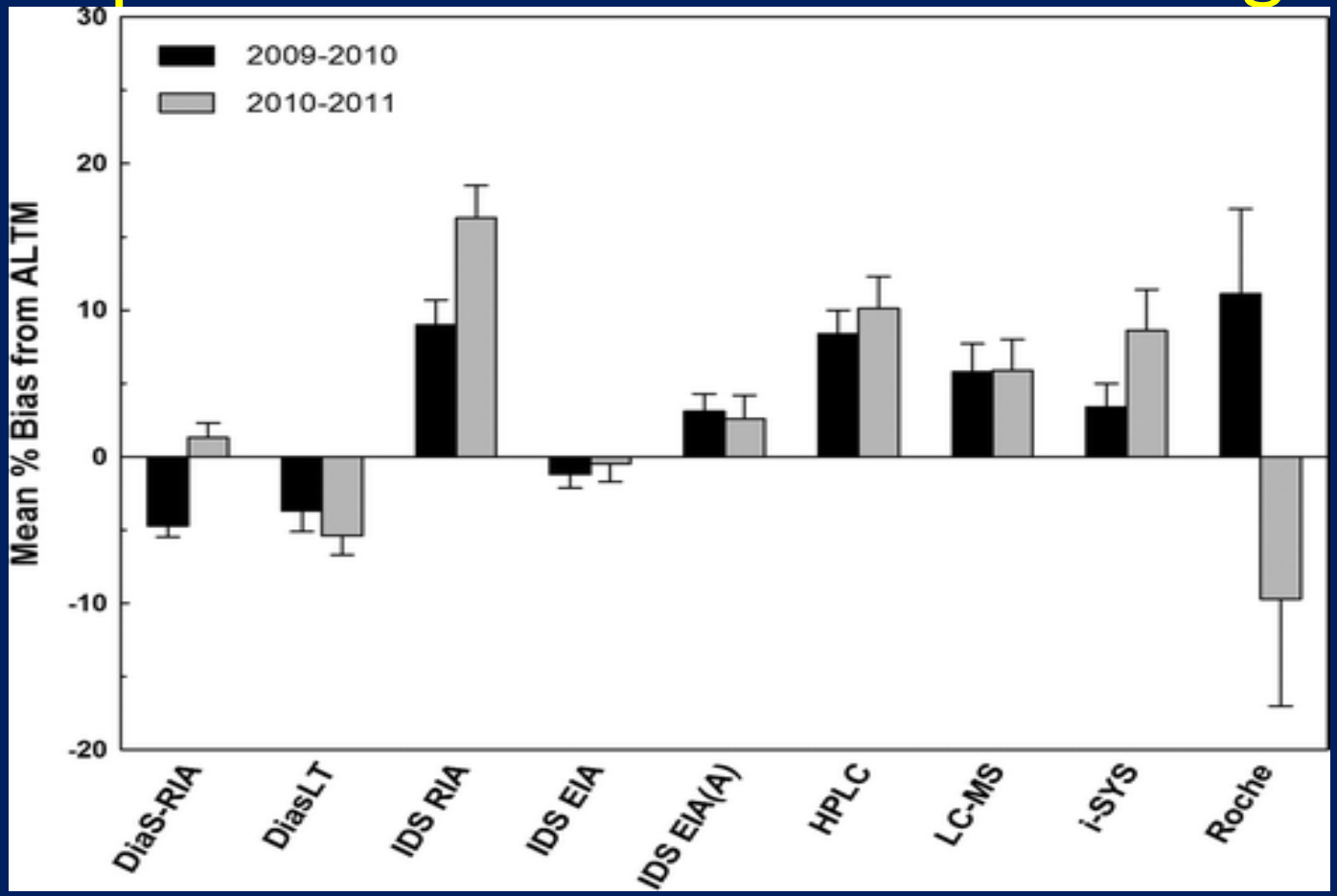
- CYP24 deficiency

Characteristics of vitamin D metabolites

	25-hydroxyvitamin D store	1,25-dihydroxyvitamin D active metabolite, hormone
Typical concentration	30-125 nmol/l 12-50 ng/ml	50-150 pmol/l 20- 60 pg/ml
Half life	25 days	7 hours
Transport protein	DBP	DBP
Free hormone level	5-40 pmol/l	1-5 pmol/l
Hormonal control	-----	PTH, calcium, phosphate,
Affinity to VDR	very low	very high
Action	??	Gut, bone, muscle
Measurement	Vitamin D status	Defects in metabolism

Lips P. J Bone Miner Res 2002

25(OH)D assay variations (DEQAS) and impact on clinical decision making



Barake M et al J Clin Endocrinol Metab 2012; 97: 835-843

25(OH)D assay variations and impact on clinical decision making

Classification 25(OH)D	IDS	Diasorin
• < 25 nmol/l	6 %	17 %
• 25-50 nmol/l	29 %	34 %
• >50 nmol/l	65 %	49 %
Needing treatment: (< 50 nmol/l = 20 ng/ml)	35 %	51 %

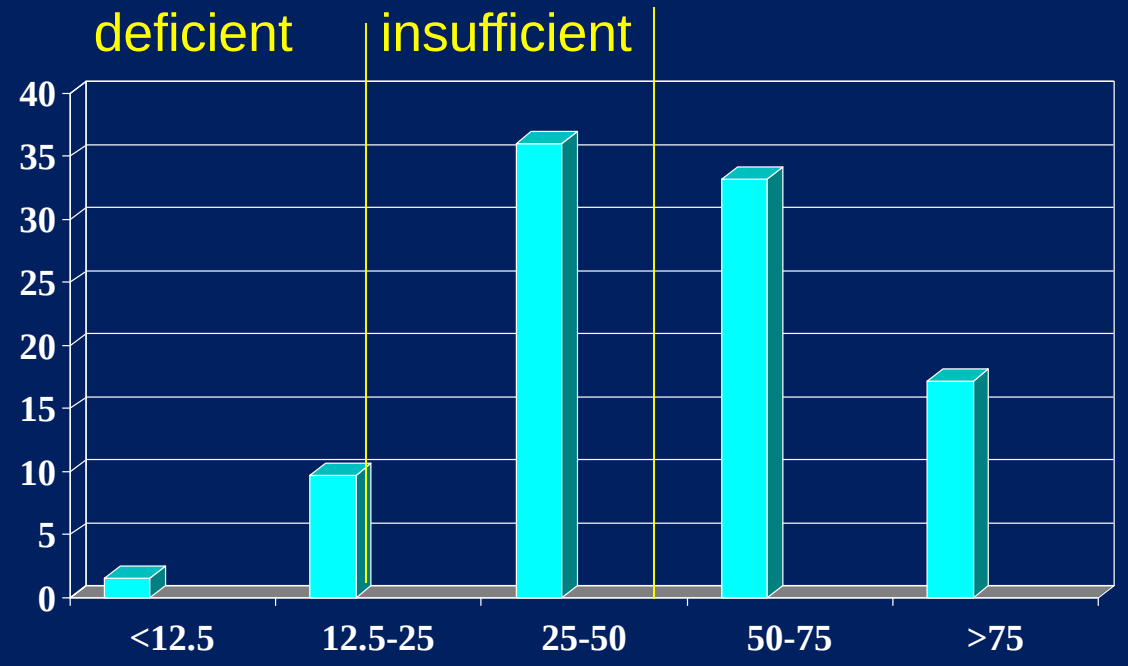
Barake M et al J Clin Endocrinol Metab 2012; 97: 835-843

Variation in 25(OH)D assays
Quality control

- International Vitamin D External Quality Assessment Scheme (DEQAS); comparison to mean value (>1000 labs participate)
- Vitamin D Standardization Program (VDSP); standardization of assays (LC-MS/MS), surveys, research with standard sera from NIST to improve accuracy.
- European ODIN study: crosscalibration of older studies with the NIST standard*.

Cashman et al. Am J Clin Nutr 2016

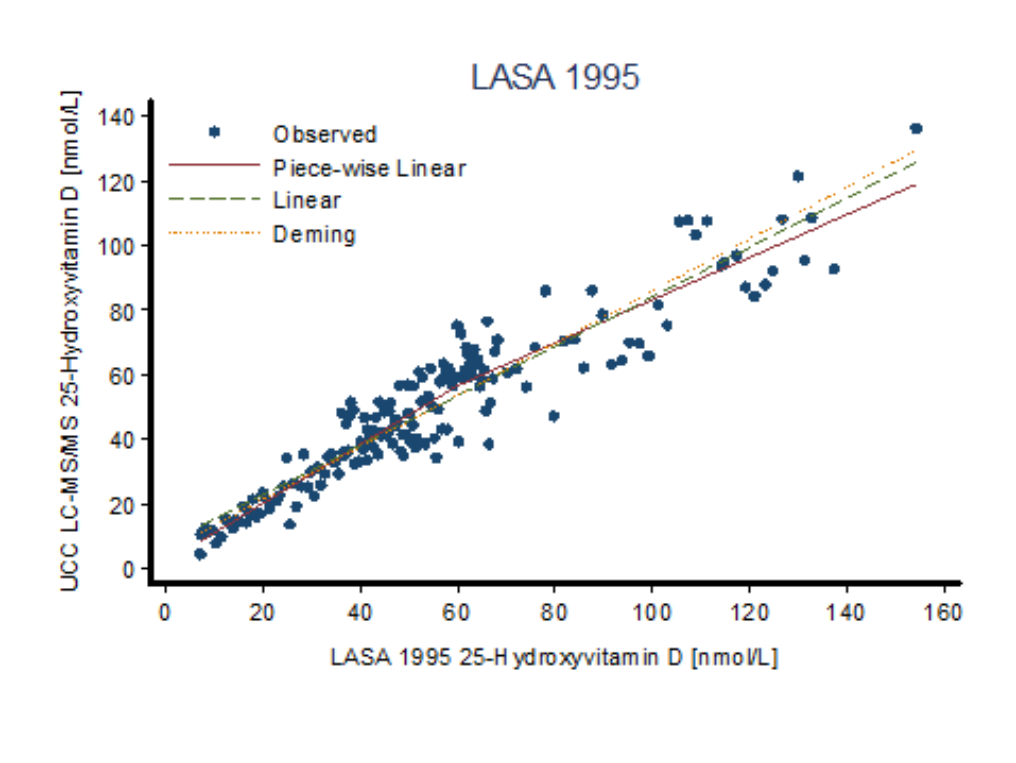
Longitudinal Aging Study Amsterdam (LASA) Vitamin D-status in 1319 participants >65 yr



25-hydroxyvitamin D concentration (nmol/l)
Values standardized in ODIN study

Fall and fracture follow-up for 3 years

ODIN: crosscalibration LASA 1995 according to Vitamin D Standardization Program

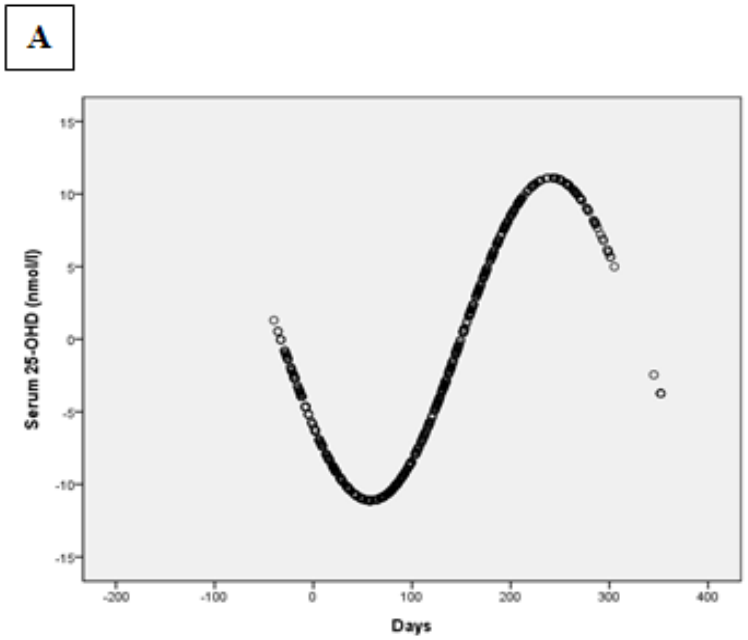


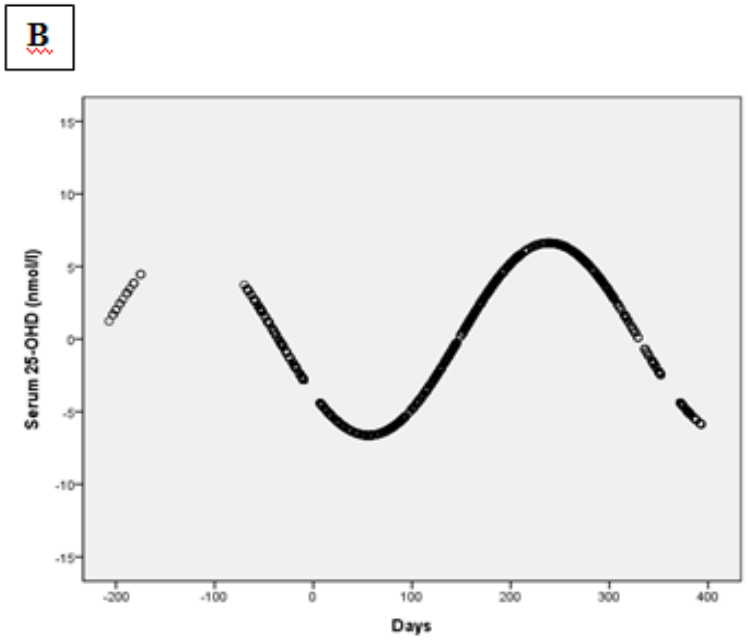
Nichols: mean 53.2; SD 24.0; median 50.9
VDSP-calibrated: mean 49.1; SD 18.7; median 48.4
Best fit: Piecewise linear regression fit (*R*2=0.89)

This project has received funding from the European Union's Seventh Framework Programme for research, technological development and

demonstration under grant agreement no. 613977

Seasonal variation of serum 25(OH)D in the Longitudinal Aging Study Amsterdam



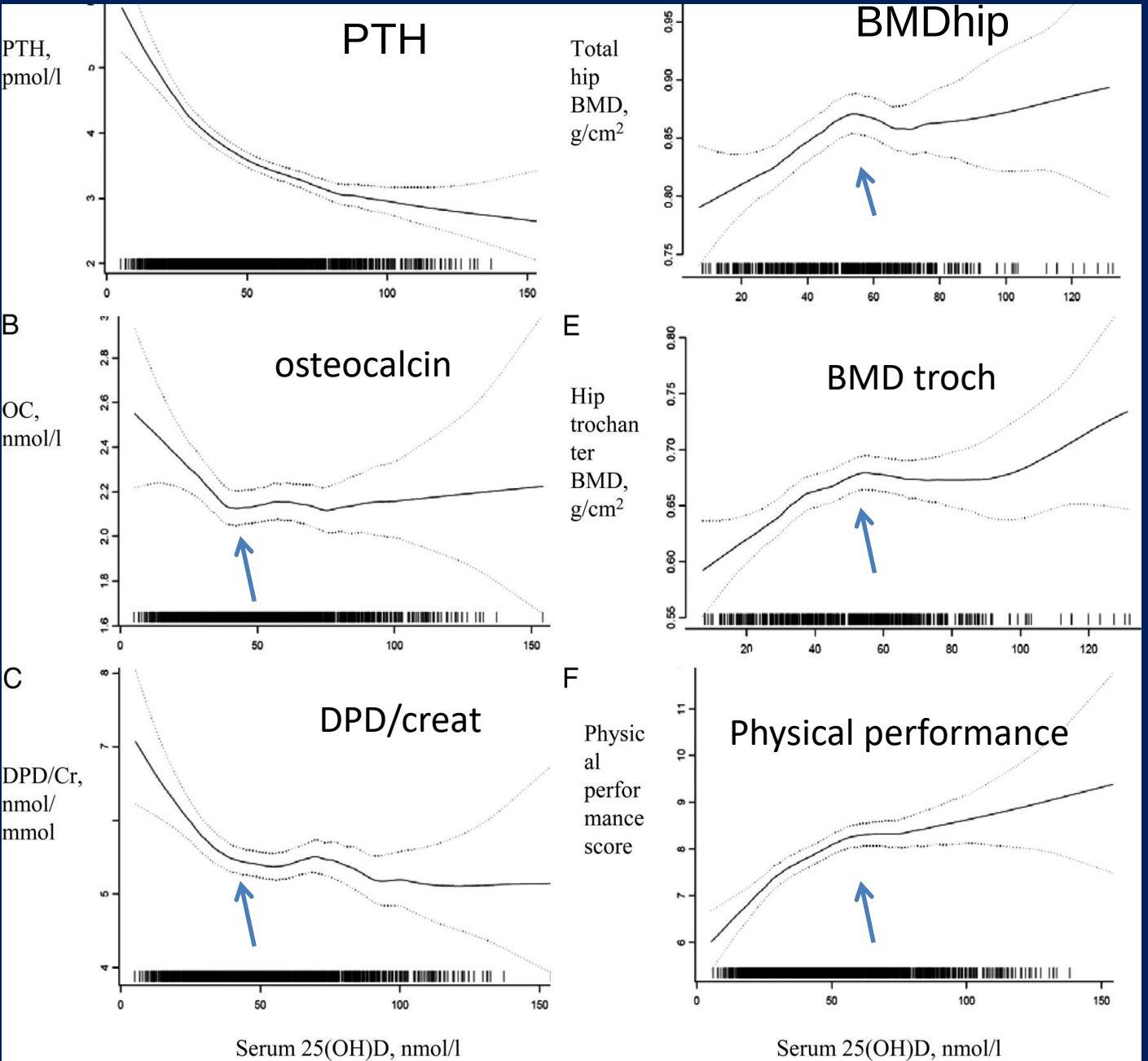


Younger cohort 55-65 yr
Mean variation 22 nmol/l

Older cohort 65-88 yr
Mean variation 14 nmol/l

Van Schoor N et al
Osteoporos Int 2014

Longitudinal Aging Study Amsterdam (LASA)



Serum 25(OH)D thresholds for PTH, BMD, bone turnover and physical performance

LOWESS plots

Kuchuk NO et al
J Clin Endocrinol Metab 2009

VDR -/- mouse

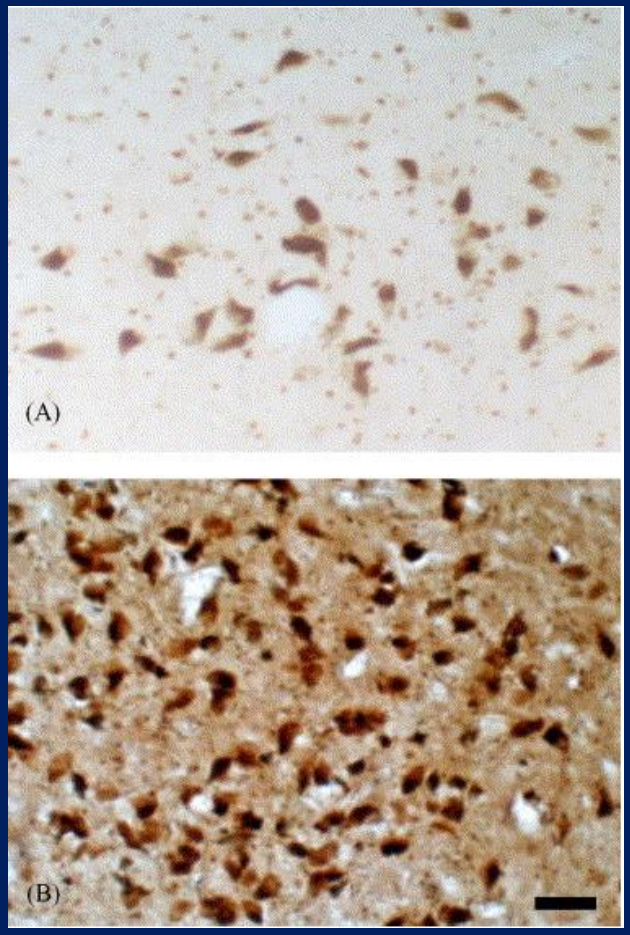
- Alopecia
- Decreased longitudinal growth, rickets
- Altered immunity
- Hypertension and cardiac hypertrophy
- Prone to chemically induced cancer
- Emotional changes

Bouillon et al Endocr Rev 2008; 29: 726-76

Extraskeletal effects of vitamin D ?

- Muscle strength and falls
- Diabetes
- Acute respiratory infections/ COPD exacerbations
- Cardiovascular diseases
- Depression
- Cancer
- Multiple sclerosis

Vitamine D receptor (A) and 1-α hydroxylase (B) in the brain (immunohistochemie)



Brain region	VDR immunoreactivity	1-OHase immunoreactivity
Caudate/putamen	+ + +	+ + +
Amygdala	+	+ +
Thalamus	+ +	+ +
Substantia nigra	+ + + +	+ + + +
Lateral geniculate nuclei	+ + +	+ + +
Hypothalamus		
Supraoptic nucleus	+ + +	+ + + +
Paraventricular nucleus	+ + +	+ + + +
Dorsal region	+ +	+ +
Lateral region	+ +	+ +
Ventromedial region	+ + +	+ +
Cerebellum	–	+ +

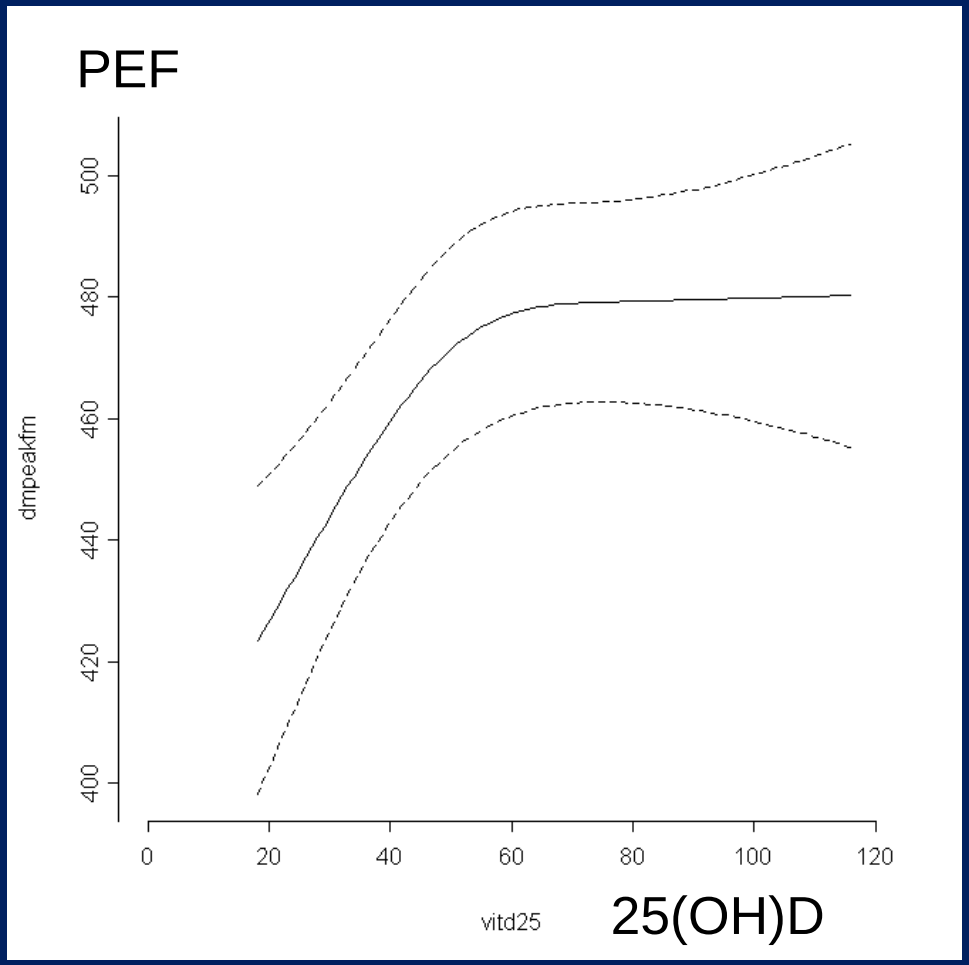
Eyles et al. J Chem Neuroanat. 2005 Jan;29(1):21-30

LASA: association studies

Vitamin D deficiency is associated with

• Fractures	van Schoor et al Bone 2008
• Bone mineral density	Kuchuk et al JCEM 2009
• Poor physical performance	Wicherts et al JCEM 2007
• Functional limitations	Sohl et al JCEM 2013
• Low muscle mass	Visser et al JCEM 2003
• Body mass index	Snijder et al JCEM 2005
• Falls	Snijder et al JCEM 2006
• Metabolic syndrome	Oosterwerff et al Clin Endocrinol 2011
• High blood pressure	Snijder et al J Intern Med 2007
• Cardiovascular disease	Sohl et al JCEM 2015
• Low peak expiratory flow	van Schoor et al JCEM 2012
• Nursing home admission	Visser et al Am J Clin Nutr 2006
• Poor quality of life	Rafiq et al JCEM 2014
• Depressive symptoms	Hoogendijk et al Arch Gen Psychiatry 2008

Vitamin D and peak expiratory flow in 454 men from the Longitudinal Aging Study Amsterdam



Multivariate association between serum 25(OH)D and PEF in men

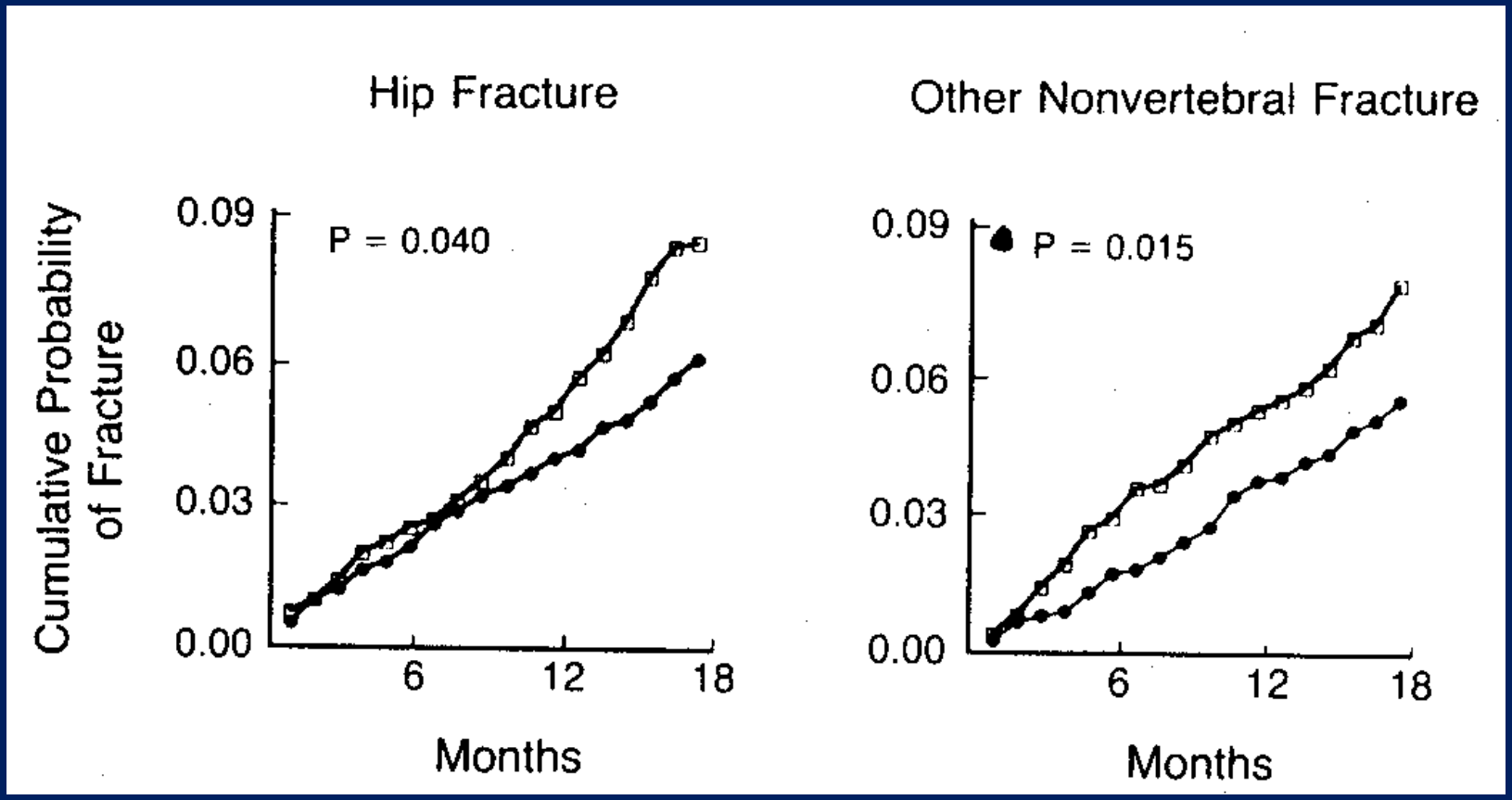
Van Schoor et al J Clin Endocrinol Metab 2012; 97:2164-71

Vitamin D deficiency: association or cause? Level of evidence

- Case-control studies
- Prospective cohort studies (LASA)
- Randomized clinical trials
- Meta-analysis of RCTs
- Individual participant meta-analysis

- Mendelian randomization studies for long term effects (cancer, multiple sclerosis, DM1)

Effect on vitamin D3 800 IU/d and calcium 1200 mg/d vs placebo on fracture incidence in 3270 French nursing home residents (mean age 84 yr)



MC Chapuy et al. N Engl J Med 1992; 327: 1637-42

The effect of vitamin D ± calcium on fracture incidence: trials and meta-analyses

- Randomized controlled clinical trials n=19
  - 5 showed decrease of fracture incidence
  - 1 borderline decrease
  - 1 decrease in per protocol analysis (WHI)
  - 10 trials no effect
  - 2 trials increase of fracture incidence (1 dose/yr)
- Meta-analyses, trial level, individual patient data n=15
- Conclusion: Vitamin D is more effective

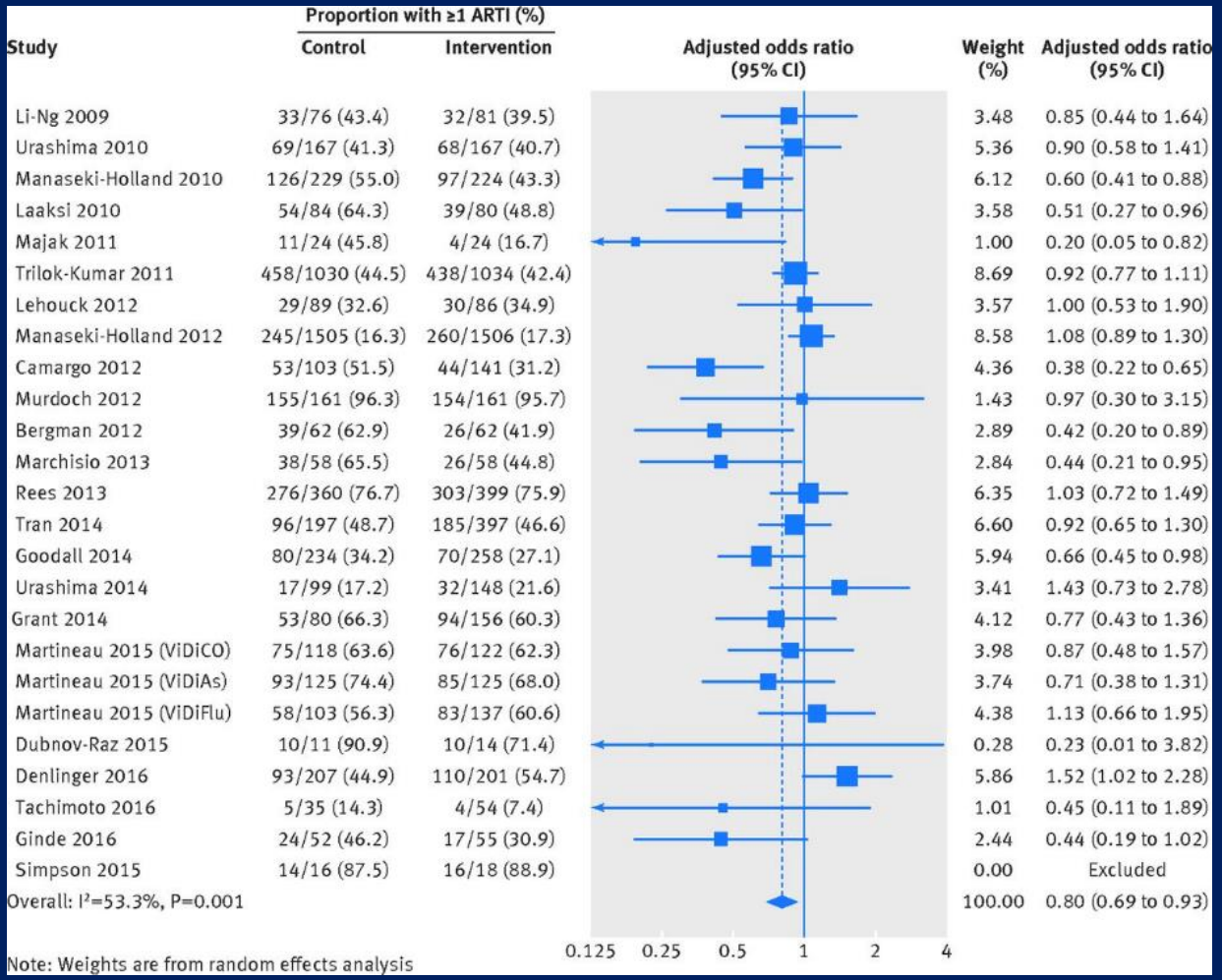
  in the institutionalized than in community–living elderly

  with a dose ≥ 800 IU/d than with < 800 IU/d

  in 80+ and 70-80 year persons than in 60-70 years.

Tang et al Lancet 2007; 370: 657-66
Bischoff-Ferrari et al N Engl J Med 2012; 367: 40-49
Bolland et al Lancet diabetes-endocrinology 2014

Vitamin D for acute respiratory infection meta-analysis



Study	Proportion with ≥1 ARTI (%) Control	Intervention	Adjusted odds ratio (95% CI)	Weight (%)	Adjusted odds ratio (95% CI)
Li-Ng 2009	33/76 (43.4)	32/81 (39.5)		3.48	0.85 (0.44 to 1.64)
Urashima 2010	69/167 (41.3)	68/167 (40.7)		5.36	0.90 (0.58 to 1.41)
Manaseki-Holland 2010	126/229 (55.0)	97/224 (43.3)		6.12	0.60 (0.41 to 0.88)
Laaksi 2010	54/84 (64.3)	39/80 (48.8)		3.58	0.51 (0.27 to 0.96)
Majak 2011	11/24 (45.8)	4/24 (16.7)		1.00	0.20 (0.05 to 0.82)
Trilok-Kumar 2011	458/1030 (44.5)	438/1034 (42.4)		8.69	0.92 (0.77 to 1.11)
Lehouck 2012	29/89 (32.6)	30/86 (34.9)		3.57	1.00 (0.53 to 1.90)
Manaseki-Holland 2012	245/1505 (16.3)	260/1506 (17.3)		8.58	1.08 (0.89 to 1.30)
Camargo 2012	53/103 (51.5)	44/141 (31.2)		4.36	0.38 (0.22 to 0.65)
Murdoch 2012	155/161 (96.3)	154/161 (95.7)		1.43	0.97 (0.30 to 3.15)
Bergman 2012	39/62 (62.9)	26/62 (41.9)		2.89	0.42 (0.20 to 0.89)
Marchisio 2013	38/58 (65.5)	26/58 (44.8)		2.84	0.44 (0.21 to 0.95)
Rees 2013	276/360 (76.7)	303/399 (75.9)		6.35	1.03 (0.72 to 1.49)
Tran 2014	96/197 (48.7)	185/397 (46.6)		6.60	0.92 (0.65 to 1.30)
Goodall 2014	80/234 (34.2)	70/258 (27.1)		5.94	0.66 (0.45 to 0.98)
Urashima 2014	17/99 (17.2)	32/148 (21.6)		3.41	1.43 (0.73 to 2.78)
Grant 2014	53/80 (66.3)	94/156 (60.3)		4.12	0.77 (0.43 to 1.36)
Martineau 2015 (ViDiCO)	75/118 (63.6)	76/122 (62.3)		3.98	0.87 (0.48 to 1.57)
Martineau 2015 (ViDiAs)	93/125 (74.4)	85/125 (68.0)		3.74	0.71 (0.38 to 1.31)
Martineau 2015 (ViDiFlu)	58/103 (56.3)	83/137 (60.6)		4.38	1.13 (0.66 to 1.95)
Dubnov-Raz 2015	10/11 (90.9)	10/14 (71.4)		0.28	0.23 (0.01 to 3.82)
Denlinger 2016	93/207 (44.9)	110/201 (54.7)		5.86	1.52 (1.02 to 2.28)
Tachimoto 2016	5/35 (14.3)	4/54 (7.4)		1.01	0.45 (0.11 to 1.89)
Ginde 2016	24/52 (46.2)	17/55 (30.9)		2.44	0.44 (0.19 to 1.02)
Simpson 2015	14/16 (87.5)	16/18 (88.9)		0.00	Excluded
Overall: I^2=53.3%, P=0.001				100.00	0.80 (0.69 to 0.93)

0.125 0.25 0.5 1 2 4

Note: Weights are from random effects analysis

Martineau et al BMJ 2016

Effect of vitamin D supplementation 1200 IU/d on insulin sensitivity in 120 overweight vitamin D–deficient non-Western immigrants in the Netherlands: a randomized placebo-controlled trial

- 120 overweight subjects with prediabetes, 25(OH)D< 50 nmol/l
- Vitamin D3 1200 IU/d, vs placebo
- Results not significant except subgroup with 25(OH) < 25 nmol/l

Effect of vitamin D 50,000 IU/month vs placebo on glycemic control in 275 patients with Type 2 Diabetes : SUNNY Trial

- 198 patients with type 2 diabetes
- Vitamin D3 50,000 IU/month vs placebo
- Results not significant except subgroup

Oosterwerff et al Am J Clin Nutr 2014; 100:152-60
Krul-Poel et al. Diabetes Care 2015;38:1420

Megatrials with multiple outcomes, currently going on

Consortium	number	dose	outcome
ViDA	5110	100,000IU/m	fract, CVD, ARI no effect
VITAL	28,875	2000 IU/d	cancer, CVD no effect
TIPS-3	5,500	60,000 IU/m	CVD, fract, cancer
FIND	18,000	3200 vs 1600 vs P	CVD, cancer
DO-HEALTH	2,152	2000 IU/om-3/exerc	fract,BP,infect/decl
D-Health	25,000	60,000 IU/m	CVD, DM, cancer
VIDI-Kids	6,750	60,000 IU/m	tuberculosis

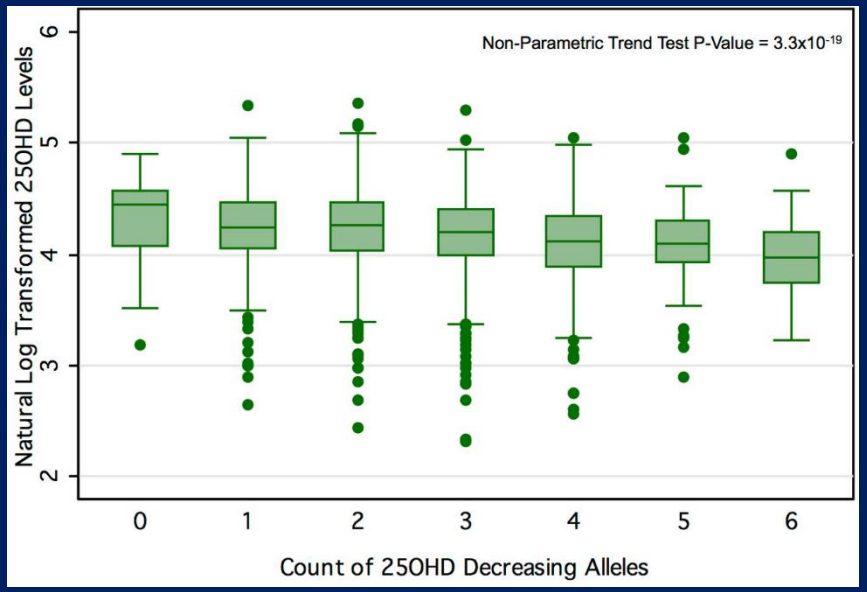
Results are expected between 2016 and 2020

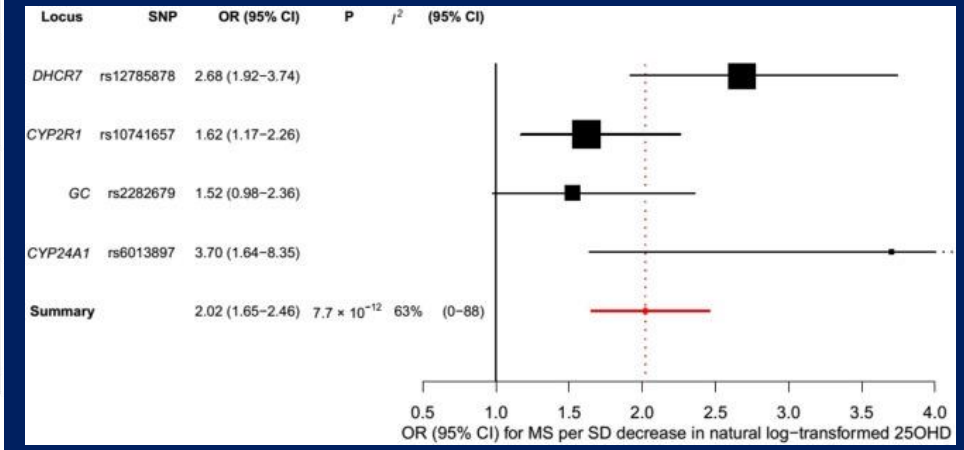
Investigators: R Scrag, JE Manson, S Yusuf, TP Tuomainen, H Bischoff-Ferrari, R Neale, A Martineau,

Why are RCTs negative, while in vitro and epidemiological studies are positive?

- Cell lines are more primitive, following dedifferentiation
- Potential functions of cells are illimited and exists for > 100 million years
- Relationships within epidemiological studies may not be causal
- Reversed causation may be important in epidemiological associations

Vitamin D and risk of multiple sclerosis: a Mendelian randomization study





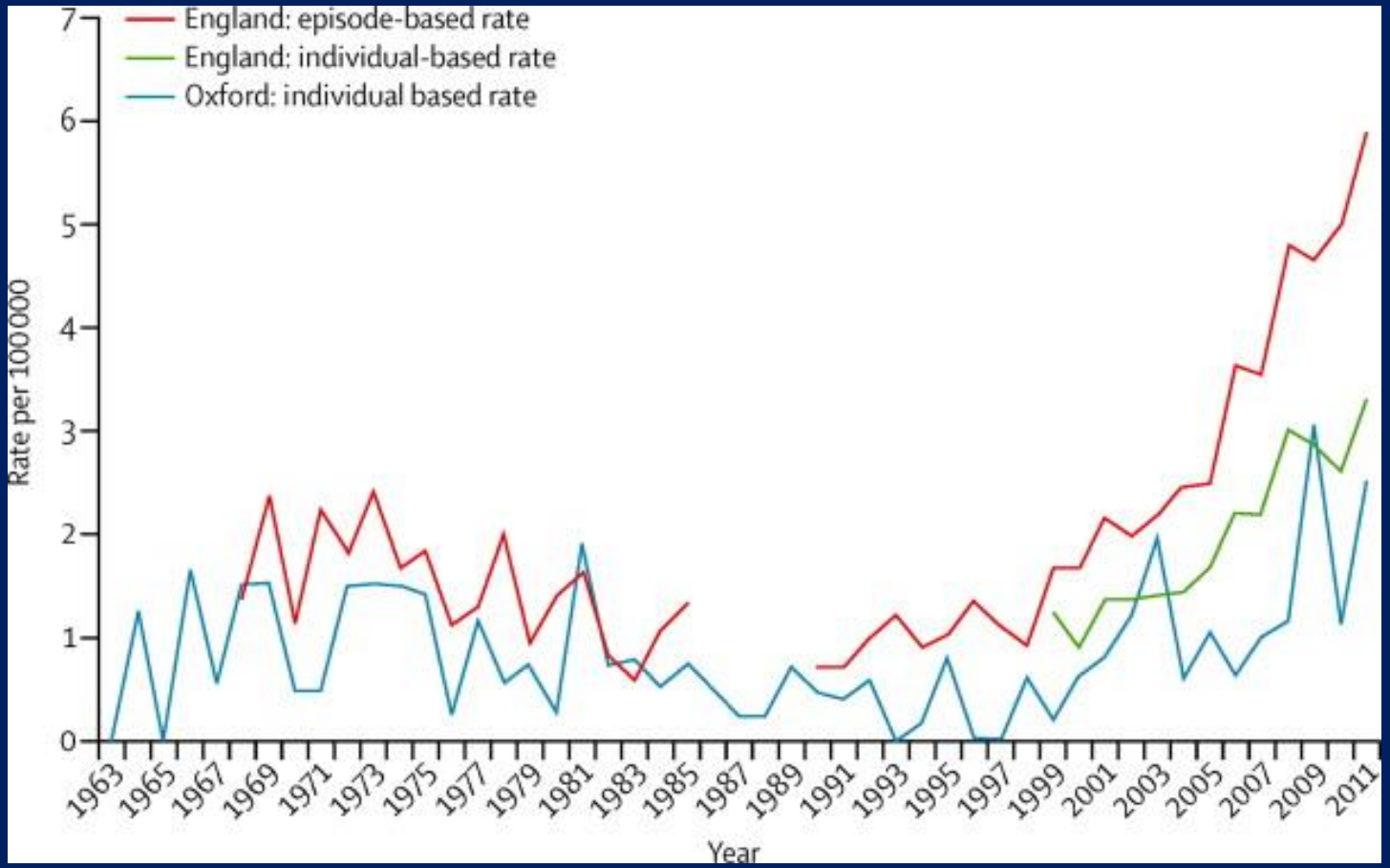
Mokry LE et al PLOS Medicine 2015 doi10.1371

Worldwide prevalence of rickets

Asia, Middle East and Africa		%
• Mongolia	1998	70
• Tibet	1994	66
• Ethiopia	1997	42
• Yemen	1987	27
• Turkey	1998	10
• Nigeria	1998	9
Europe		
• The Netherlands (macrobiotics)	1990	55
• UK – Manchester (minorities)	2002	1.6

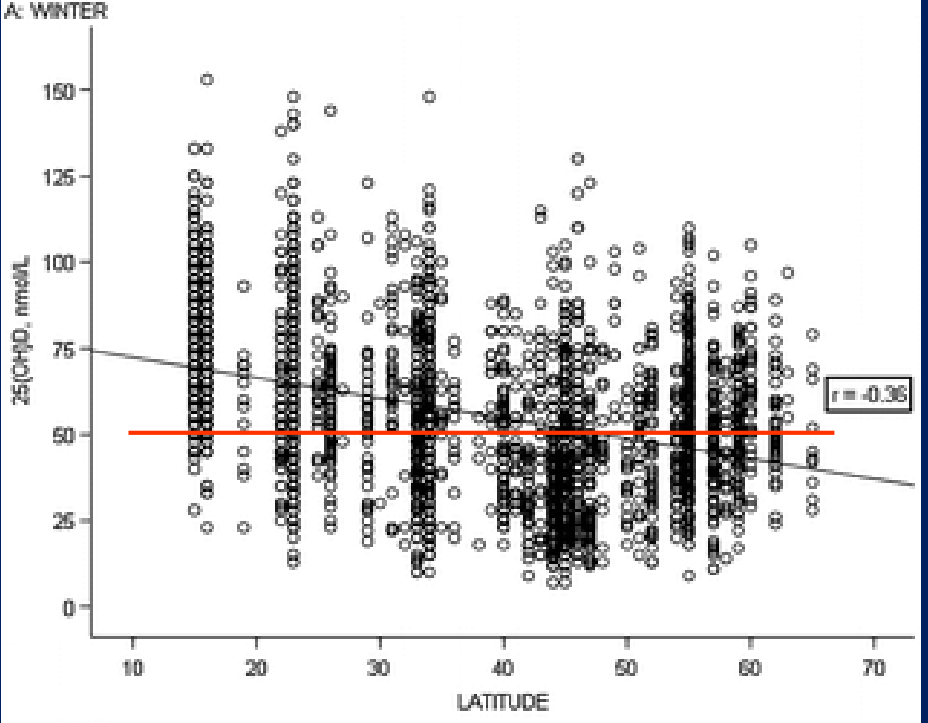
A. Prentice Nutr Rev 2008; 66 (suppl 2): S153-S164

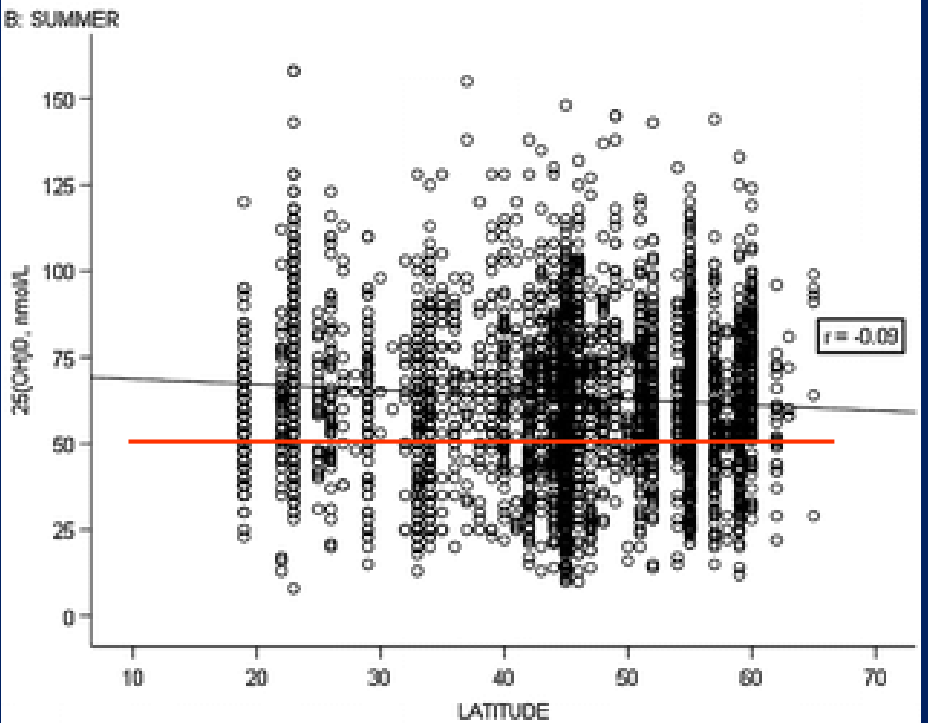
Hospital discharge data for rickets



Goldacre et al Lancet 2014

Cod liver oil for the prevention of rickets



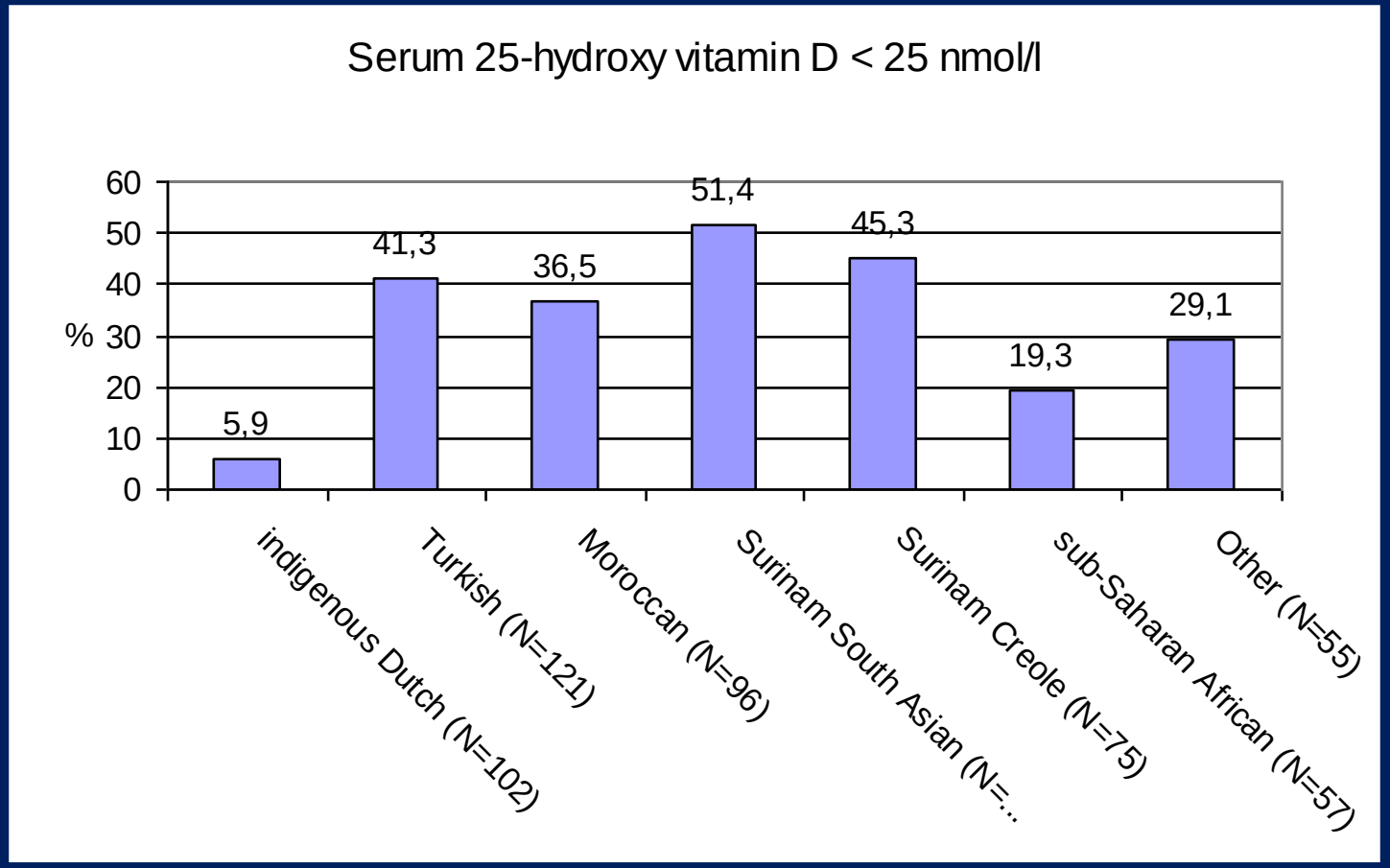


Serum 25(OH)D according to latitude in winter and summer in 7441 postmenopausal women in 6 continents

- Baseline data from the bazedoxifene study
- Central laboratory facility
- RIA: Diasorin
- 35% < 50 nmol/l in winter

Kuchuk et al J Bone Miner Res 2009; 24: 693-701

Vitamin D status in non-western immigrants



I van der Meer et al 2008 Clin Endocrinol

Required serum 25(OH)D concentration

- Institute of Medicine:

Serum 25(OH)D > 30 nmol/l prevents rickets

Serum 25(OH)D > 40 nmol/l covers requirement of 50 % of population

Serum 25(OH)D > 50 nmol/l covers requirement of 97.5 % of population

- Endocrine Society:

Serum 25(OH)D > 75 nmol/l is adequate

Position statement of the European Calcified Tissue Society

- Vitamin D deficiency:
  serum 25(OH)D < 50 nmol/l
- Severe vitamin D deficiency:
  serum 25(OH)D < 30 nmol/l
- Adequate vitamin D status
  serum 25(OH)D > 50 nmol/l

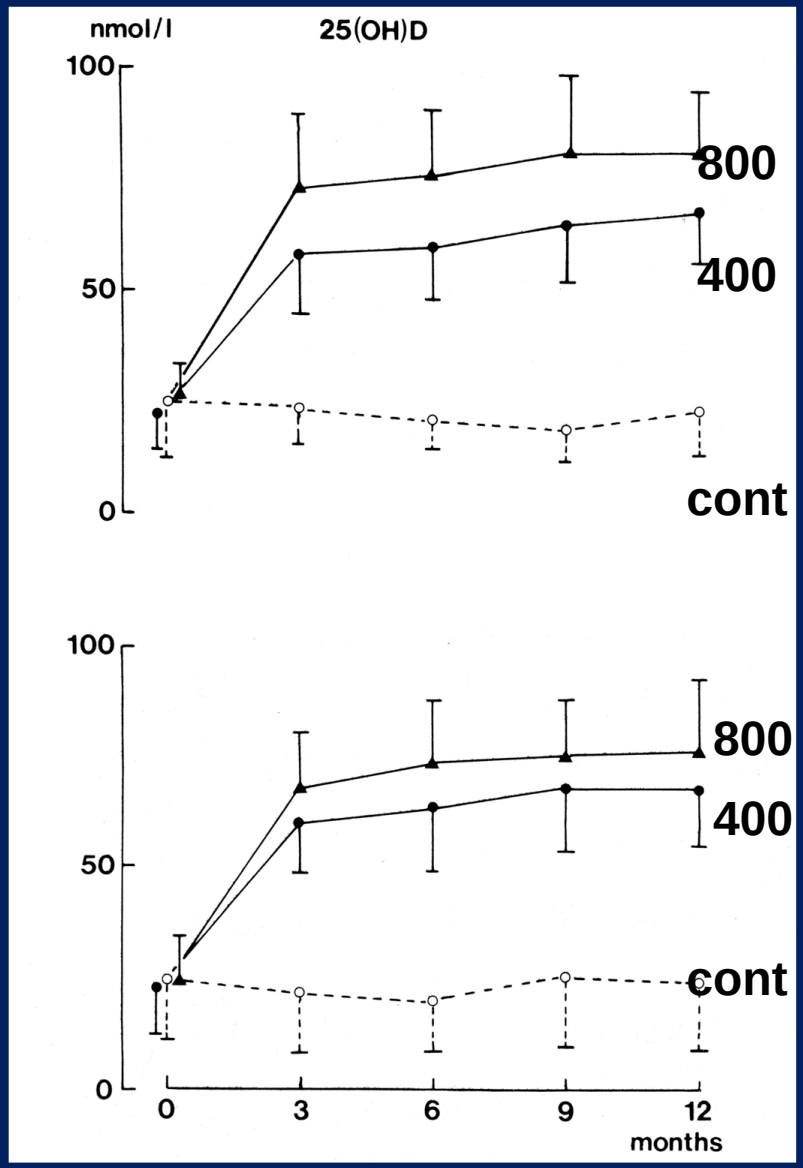
Vitamin D deficiency in Europe according to standardized serum 25(OH)D measurement

- Serum 25(OH)D < 50 nmol/l in 40%
  vitamin D deficiency in 40 %

- Serum 25(OH)D < 30 nmol/l in 12.5 %
  severe vitamin D deficiency in 12.5 %

Cashman et al Am J Clin Nutr 2016

Effect of vitamin D3 400 or 800 IU/day vs control on serum 25(OH)D and PTH in institutionalized elderly



- Randomized clinical trial
- Serum 25(OH)D by HPLC and CPB.
- No non-responders
- Non-linear increase

Lips et al J Clin Endocrinol Metab 1988

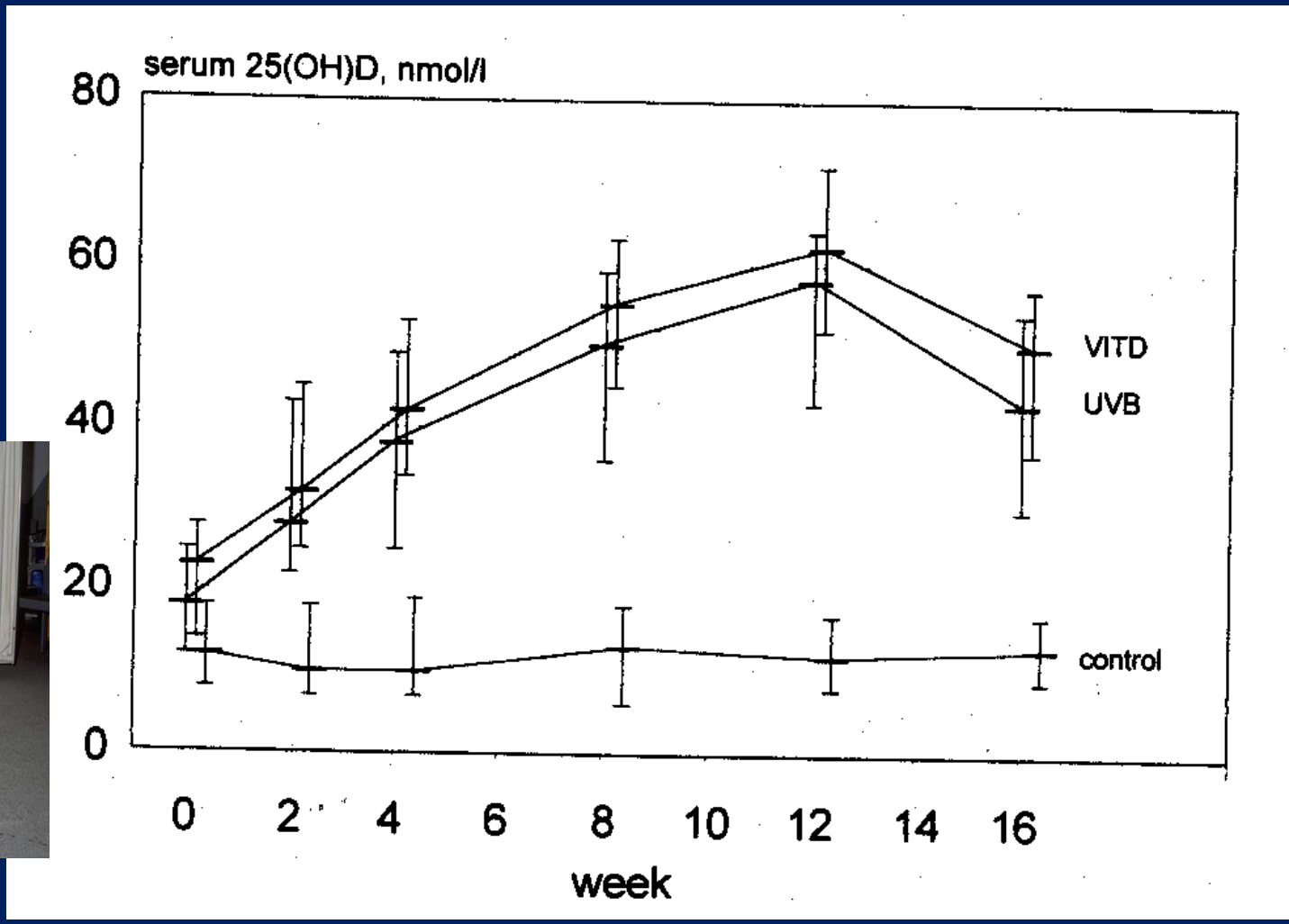
RDA, upper limit of intake (UL) according to the Institute of Medicine and requirement and UL according to the Endocrine Society.

	Inst of Med		Endocrine Soc	
Age	RDA	UL	Requirement	UL
Children 1-8 yr	600	2500	600-1000	4000
Children 9-18 yr	600	4000	600-1000	4000
Adults 19-70 yr	600	4000	1500-2000	10,000
Adults > 70 yr	800	4000	1500-2000	10,000
Pregnancy	600	4000	1500-2000	10,000
Lactation	600	4000	1500-2000	10,000

Vitamin D deficiency: strategy for prevention

- Sun
- Artificial ultraviolet light
- Oily fish (salmon, mackerel, sardines, herring)
- Cod liver oil
- Food fortification (milk products, oil, flour)
- Supplements for risk groups

Effect of UV irradiation vs. vitamin D3 400 IU/d in elderly vitamin D deficient women



V. Chel et al. J Bone Miner Res 1998; 13: 1238-42

Vitamin D in our diet

700-800 IE per herring

Mackerel, halibut, salmon: rich in vitamin D

Cod liver: much vitamin D

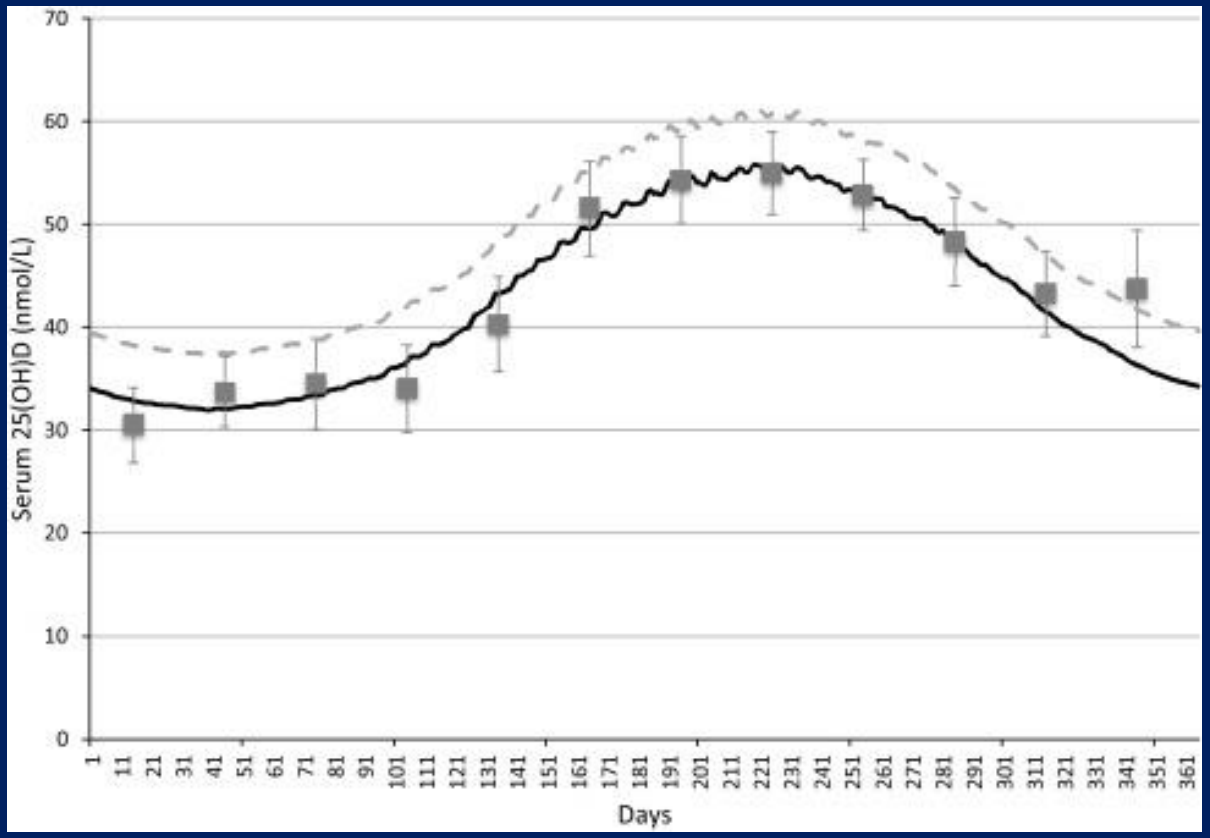
Vitamin D intake in older persons in Europe in µg/d 10 µg = 400 IU

	Data Source	M	F
Norway	Norkost 1997	15.0	12.9
Sweden	Riksmaten	7.1	6.1
Finland	Findiet 2007	9.0	6.5
Denmark	Danish National survey	3.9	3.1
Netherlands	Food consumption survey	4.8	3.6
Germany	National Nutrition Survey	4.4	3.4
Ireland	SLAN 2007	3.5	3.2
Italy	INN-CA 1996	2.5	2.4
Portugal	Epiporto	3.4	3.3
Spain	ENCAT 2002-3	0.7	0.7

Spiro and Butriss Nutr Bull 2014

Cod liver oil for the prevention of rickets in 1950
One spoon daily from September 1 till April 30

A predictive model of serum 25(OH)D for application in food fortification strategy



O'Neill CM et al J Steroid Biochem Mol Biol 2016 (on line)

Vitamin D intoxication

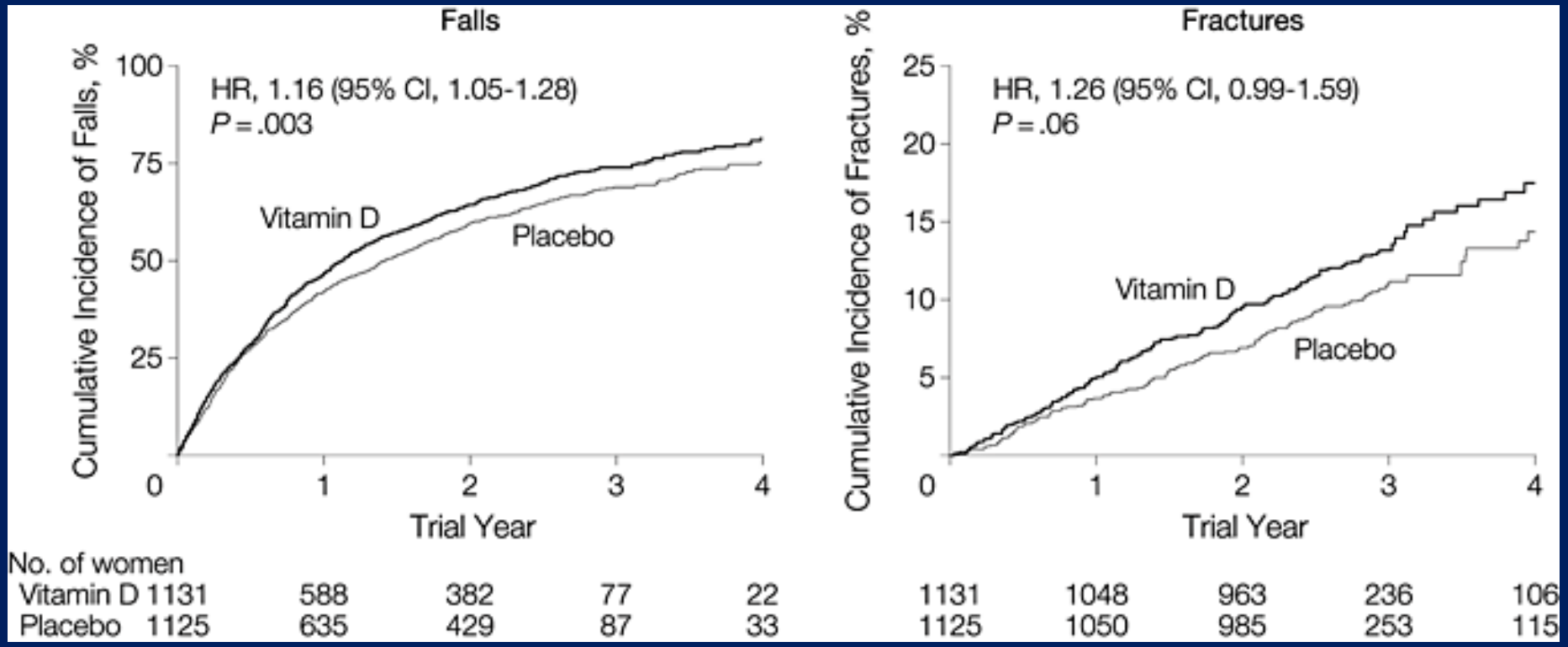
- Increased hydroxylation of 25(OH)D to $1,25(OH)_2D$ due to sarcoidose, granulomatous diseases
- Decreased hydroxylation of 25(OH)D to $24,25(OH)_2D$ due to inactivating mutation of 24-hydroxylase
- Overdose of vitamin D

Vitamin D intoxication due to overdose

- A review of 13 case reports involving 69 patients from 0 to 89 years with vitamin D intoxication due to labelling errors, inappropriate administration, and prescription errors.
- Symptoms: thirst, polyuria, nausea, vomiting, confusion
- Vitamin D doses up to 60,000,000 IU in a few months
- Serum 25(OH)D from 257 to 2900 nmol/l.
- Serum calcium from 2.75 to 5.75 mmol/l.
- Complications: deteriorated renal function, nephrocalcinosis

Galior K et al Nutrients 2018; 10: 953

Annual high-dose (500 000 IU vs placebo) oral vitamin D and falls and fractures in 2256 women >70 yrs



Sanders K et al JAMA 2010; 303: 1815-22

Vitamin D supplementation Recommendations by the ECTS

- A vitamin D supplement of **10 µg/d (400 IU/d)** is advised for **all children of 0-1 year** and preferably 0-3 year to eradicate rickets.
- A vitamin D supplement of **10-15 µg/d (400-600 IU/d)** is advised for **all pregnant women**.
- A vitamin D supplement of **10-20 µg/d (400-800 IU/d**) is advised to **all older institutionalized subjects** and should be considered for all older persons above 70 year.
- A vitamin D supplement of 10 µg/d (400 IU/d) should be considered for non-western immigrants and refugees.

Summary (1)

- The accuracy of 25(OH)D measurements still is insufficient. When reporting results, quality control (DEQAS, VDSP) should be mentioned.
- Vitamin D deficiency (serum 25(OH)D<50nmol/l) occurs in 40 % of the European population, and severe deficiency (serum 25(OH)D<30 nmol/l) in 12.5 % of Europeans.
- The optimal 25(OH)D concentration for bone and muscle function is between 50 and 75 nmol/l.

Summary (2)

- Vitamin D and calcium supplements can prevent up to 15 % of the hip and other non-vertebral fractures in older institutionalized persons.
- Vitamin D3 800 IU per day can increase the 25(OH)D concentration in 95 % of older persons to above 50 nmol/l.
- Vitamin D may have small effects on insulin secretion and on respiratory tract infections.
- Rickets still is highly prevalent in some countries and population groups. It can easily be prevented with vitamin D 400 IU/d.

Summary (3)

- Prevention of vitamin D deficiency is feasible with sunshine exposure, consumption of fatty fish or fortified foods and vitamin D supplements.
- Vitamin D supplements are advised for children 0-1 year, for pregnant women and for institutionalized older persons.
- For prevention and treatment of vitamin D deficiency high doses are not necessary and should be avoided.