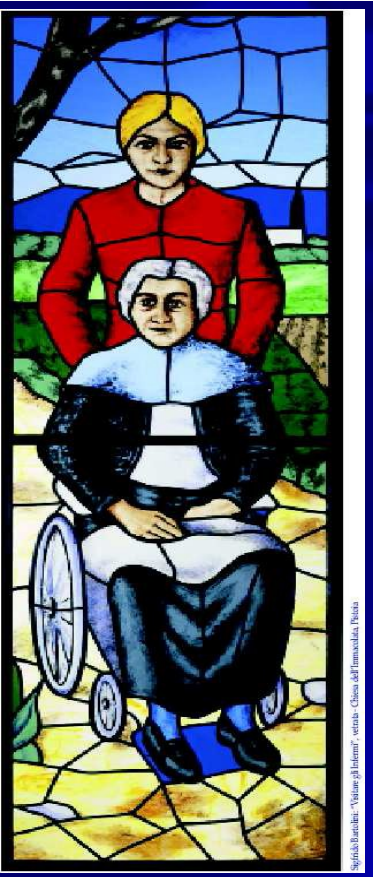


4° CONVEGNO NAZIONALE SUI CENTRI DIURNI ALZHEIMER

LA VITAMINA D
Forza muscolare, Rischio di Frattura e Cognitività

G.C. Isaia

A.O. CITTA' DELLA SALUTE E DELLA SCIENZA DI TORINO
S.C. GERIATRIA E MALATTIE METABOLICHE DELL'OSSO
Centro di Riferimento Regionale per le Malattie Metaboliche dell'osso

Pistoia, 31 Maggio - 1 Giugno 2013

Dichiarazione di conflitto di interessi

Aziende Farmaceutiche che hanno erogato finanziamenti per ricerca,formazione, sperimentazioni o consulenze (2011-2013)

- Eli Lilly
- Nycomed
- Amgen
- Abiogen
- Novartis
- Sigma Tau
- Servier Italia
- IFB Stroeder
- Merck Sharp Dhome
- SPA Società Prodotti Antibiotici
- Italfarmaco

AGENDA

- **Vitamin D and Hypovitaminosis D**
- **Vitamin D and Fragility Fractures**
- **Vitamin D and Muscle**
- **Vitamin D and Cognitive Impairment**

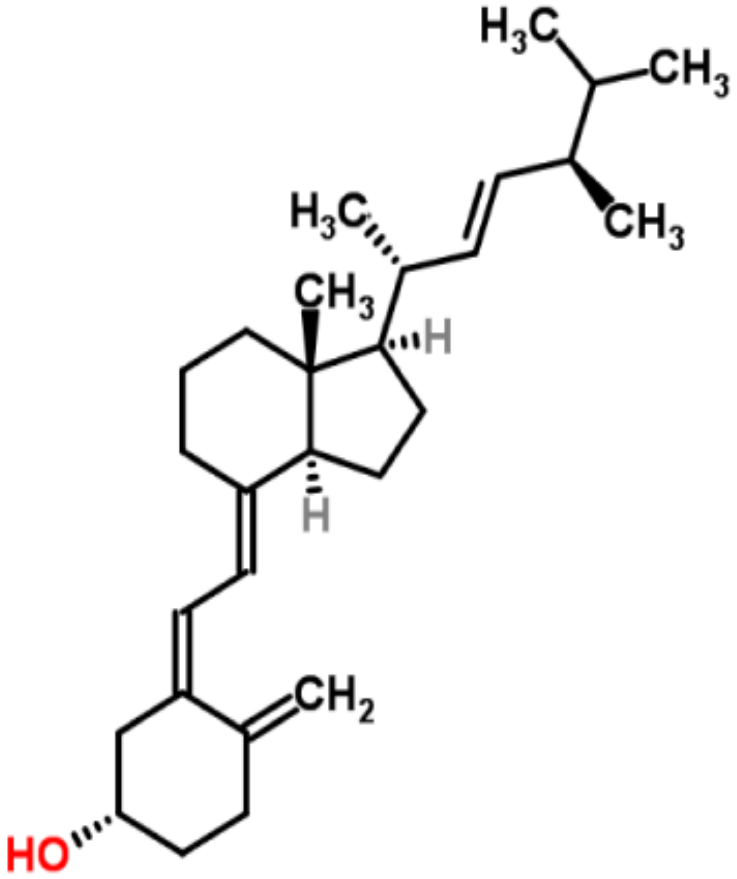
AGENDA

- **Vitamin D and Hypovitaminosis D**
- **Vitamin D and Fragility Fractures**
- **Vitamin D and Muscle**
- **Vitamin D and Cognitive Impairment**

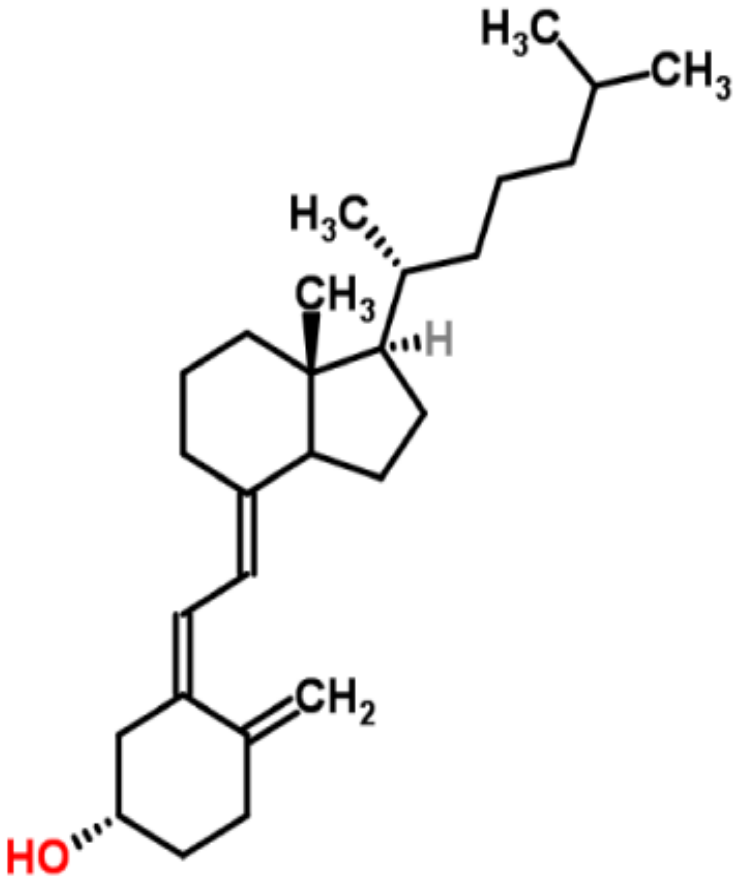
Vitamin$_s$ D (D_2 e D_3)

Chemical structure

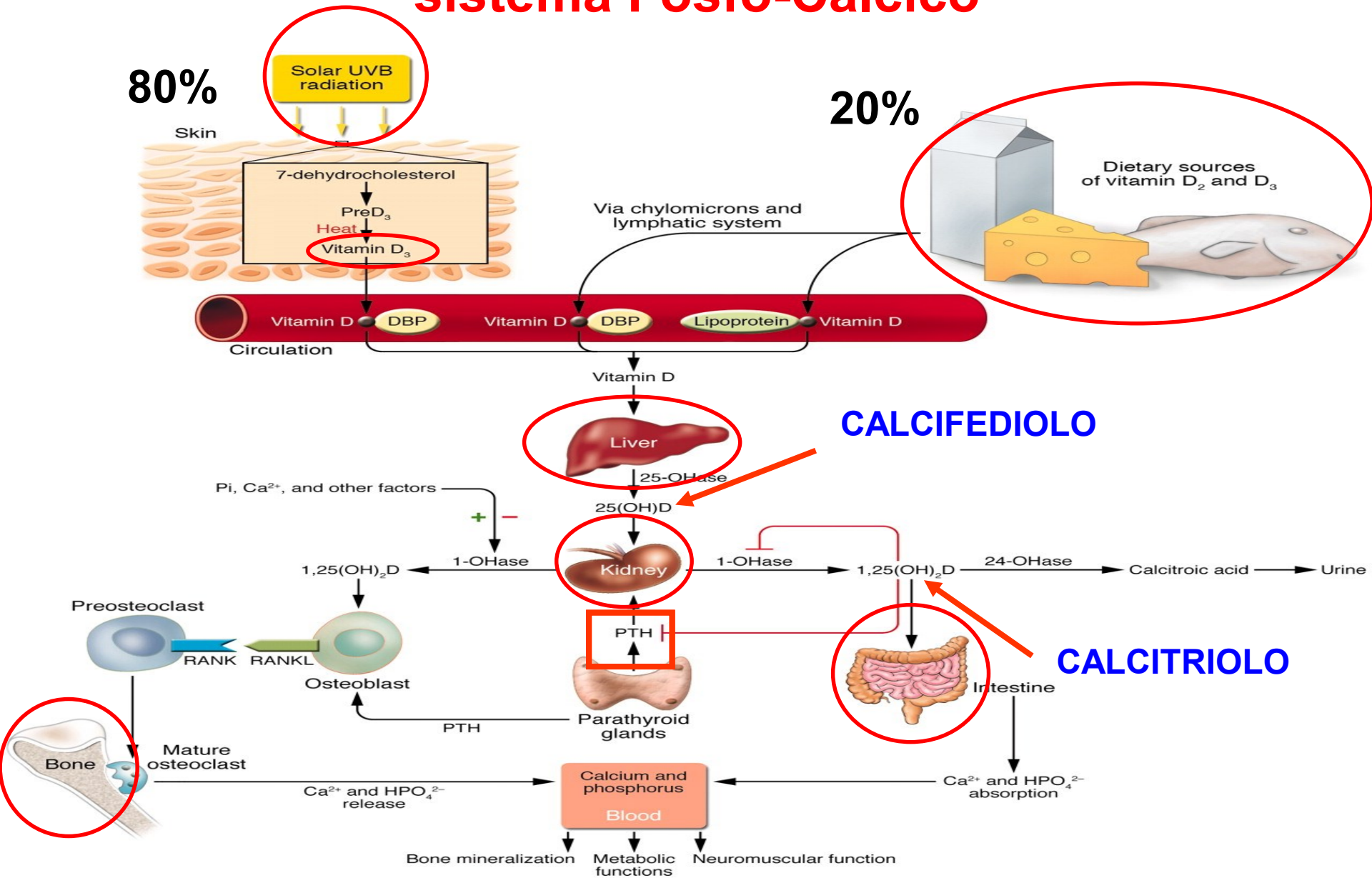
Vitamin D_2 (Ergocalciferol)



Vitamin D_3 (Cholecalciferol)



Origine, metabolismo e ruolo della Vitamina D nel sistema Fosfo-Calcico



Il dosaggio plasmatico della 25 OHD è considerato il gold standard per valutare lo stato vitaminico D

Linee guida SIOMMMS 2011

DEFINIZIONE	nmol/L	ng/ml
IPOVITAMINOSI D		
Sufficienza	75 - 250	30 - 100
Eccesso	> 250	> 100
Intossicazione	> 375	> 150

Bischoff Ferrari *Best Pract Res Clin Rheumatol* 2009
Dawson *Osteoporos Int* 2005
Holick *Drugs Aging* 2007

I livelli sierici di vitamina D e la sua produzione si riducono con l'età[1,2]

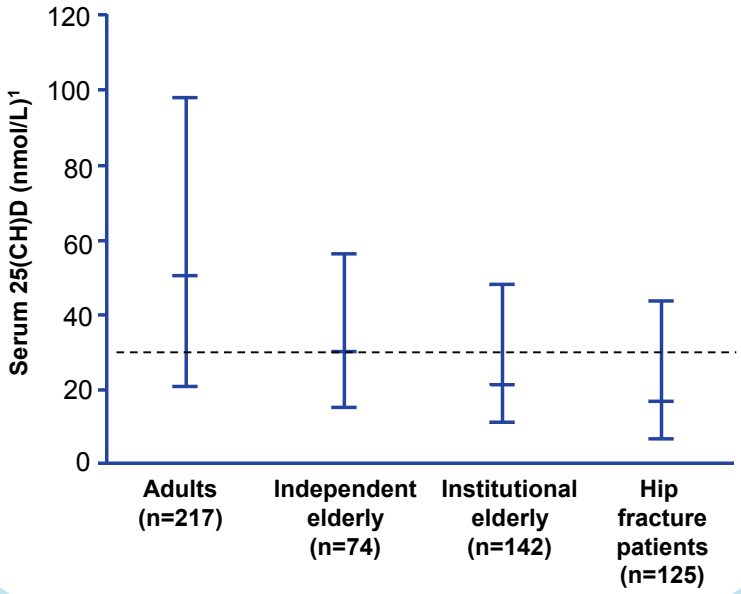


FIG. 4. Serum 25(OH)D (median, 5th-95th percentile) in 250 healthy adults (blood donors), 74 independent elderly subjects, 142 institutionalized elderly patients, and 125 patients with hip fracture. The samples in all groups were collected throughout the year. All measurements were performed by HPLC followed by competitive protein binding assay (data from Refs. 37,56,85). [Reproduced with permission from M. E. Ooms: Thesis. Vrije Universiteit Amsterdam, 1994 (105).]

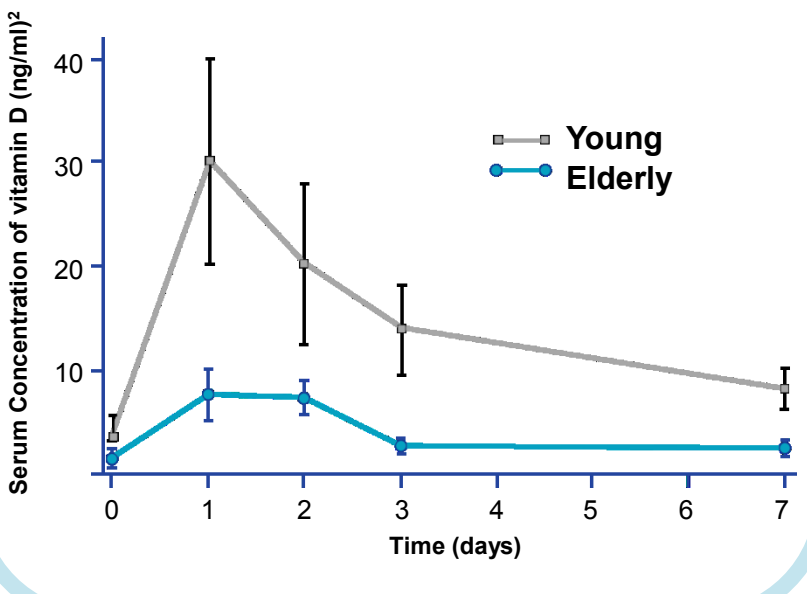
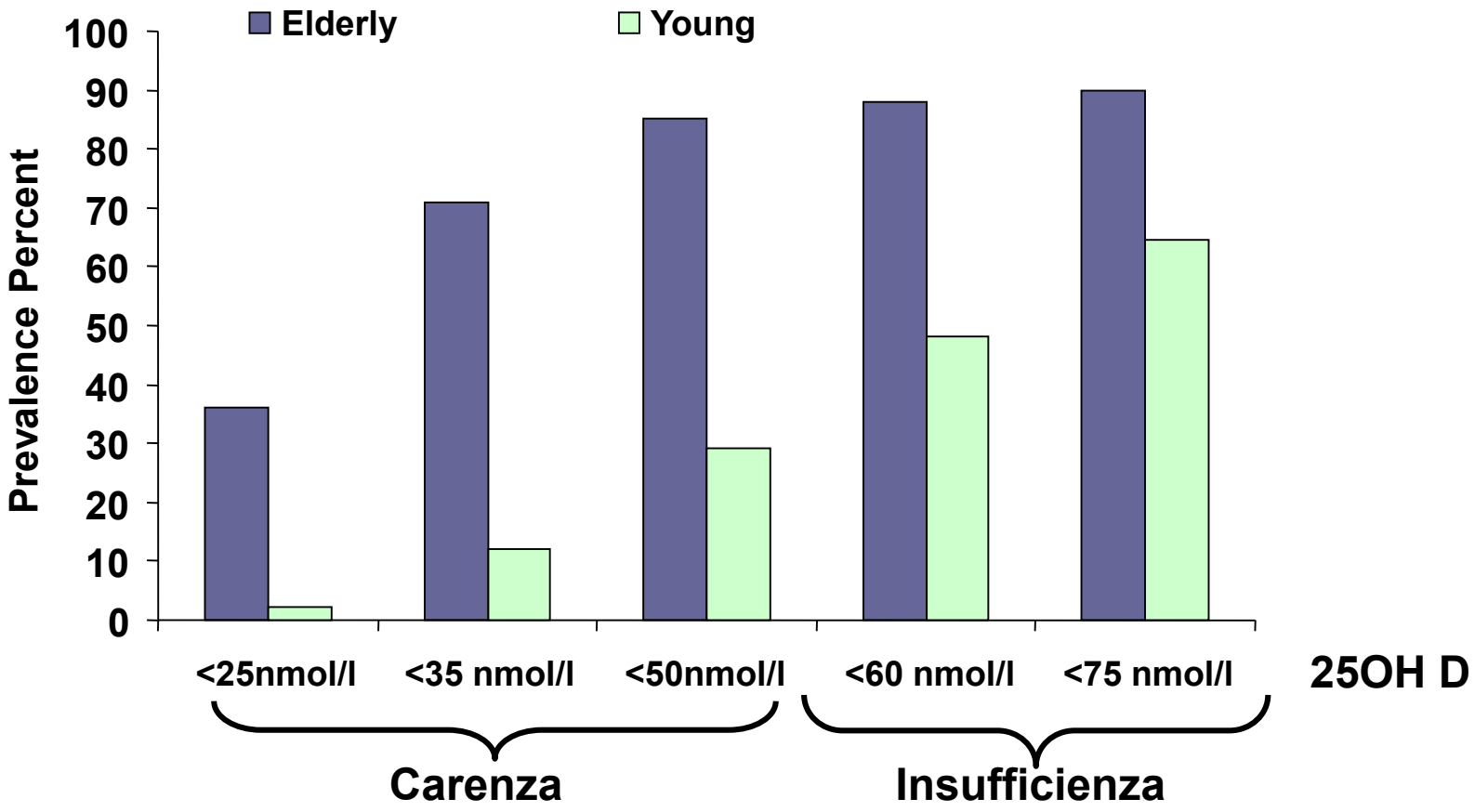


FIG. 2. Serum vitamin D_3 concentration after total body exposure to artificial sunlight (UV 260–360 nm) in six white young adults (20–30 yr) and six white elderly people (62–80 yr) with skin type III. Serum vitamin D_3 concentration was measured for 7 d. The area under the curve for serum vitamin D_3 suggests that the production of vitamin D_3 in the skin in the elderly is about 25% of that in young adults. [Reproduced with permission from M. F. Holick *et al.*: *Lancet* 2:1104–1105, 1989 (35). © The Lancet Ltd.]

1- Lips P et al. Endocr Rev 2001;22:477-501
2- Holick et al. Lancet 1989;2:1104-1105

Prevalence of Vitamin D inadequacy in Italy



Severe Vit. D deficiency is found in > 50% of elderly subjects; inadequate levels in > 95%. Inadequate Vit D values are found in > 50% of young "healthy" subjects.

Isaia GC et al Osteoporos Int 2003
Adami S et al Bone 2009
Adami S et al Bone 2008

AGENDA

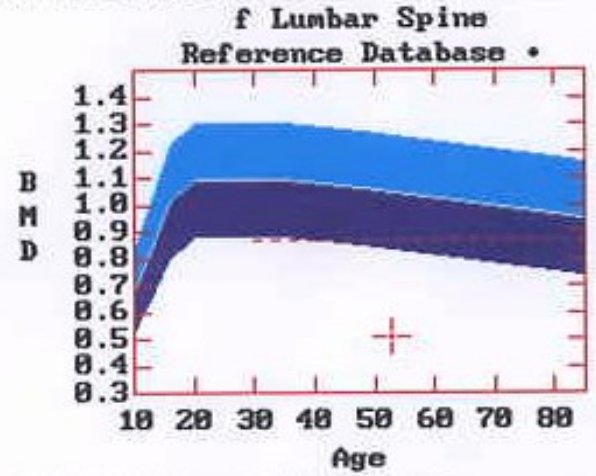
- Vitamin D and Hypovitaminosis D
- Vitamin D and Fragility Fractures
- Vitamin D and Muscle
- Vitamin D and Cognitive Impairment

Sister and brother, 4 and 6,5 years, with typical rickets deformities

Prevalence of 80-90% in early 1900s in Netherlands and Boston

Holick MF: Resurrection of Vitamina D deficiency and Rickets J Clin Invest 2006

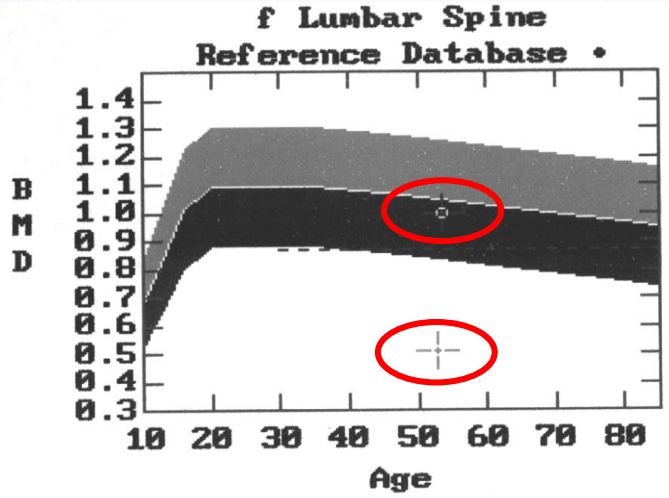
DIAGNOSI (Errata) DI OSTEOPOROSI FORMULATA SULLA BASE DEL SOLO DATO DENSITOMETRICO



BMD(L1-L4) = 0.508 g/cm^2

Region	BMD	T(30.0)		Z	
L1	0.462	-4.96	46%	-4.57	48%
L2	0.460	-5.76	42%	-5.33	44%
L3	0.529	-5.22	48%	-4.78	50%
L4	0.574	-5.19	50%	-4.74	52%
L1-L4	0.508	-5.30	47%	-4.87	49%

• Age and sex matched
T = peak BMD matched
Z = age matched TK 04 Nov 91



BMD(L1-L4) = 0.992 g/cm^2

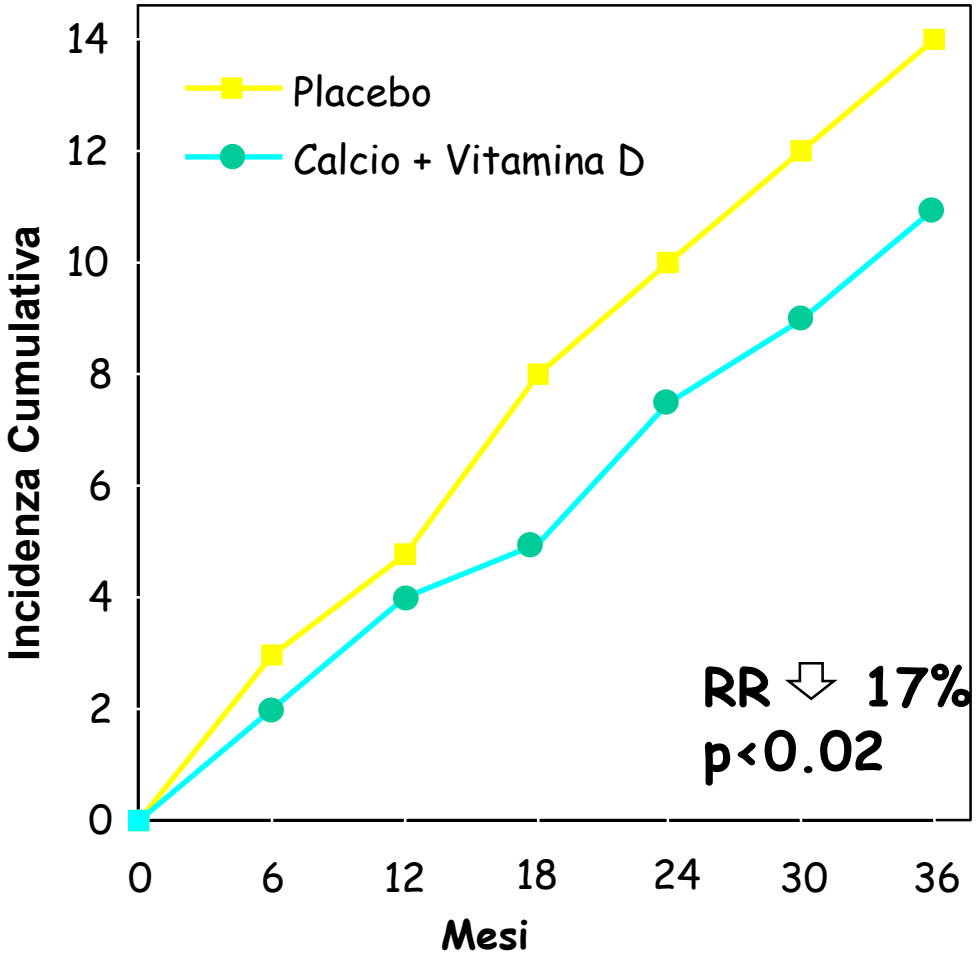
Region	BMD	T(30.0)		Z	
L1	0.940	-0.62	93%	-0.21	98%
L2	0.952	-1.29	87%	-0.84	91%
L3	1.019	-0.76	92%	-0.30	97%
L4	1.040	-0.95	91%	-0.48	95%
L1-L4	0.992	-0.90	91%	-0.45	95%

• Age and sex matched
T = peak BMD matched
Z = age matched TK 04 Nov 91

DIAGNOSI: Osteomalacia da Ipovitaminosi D

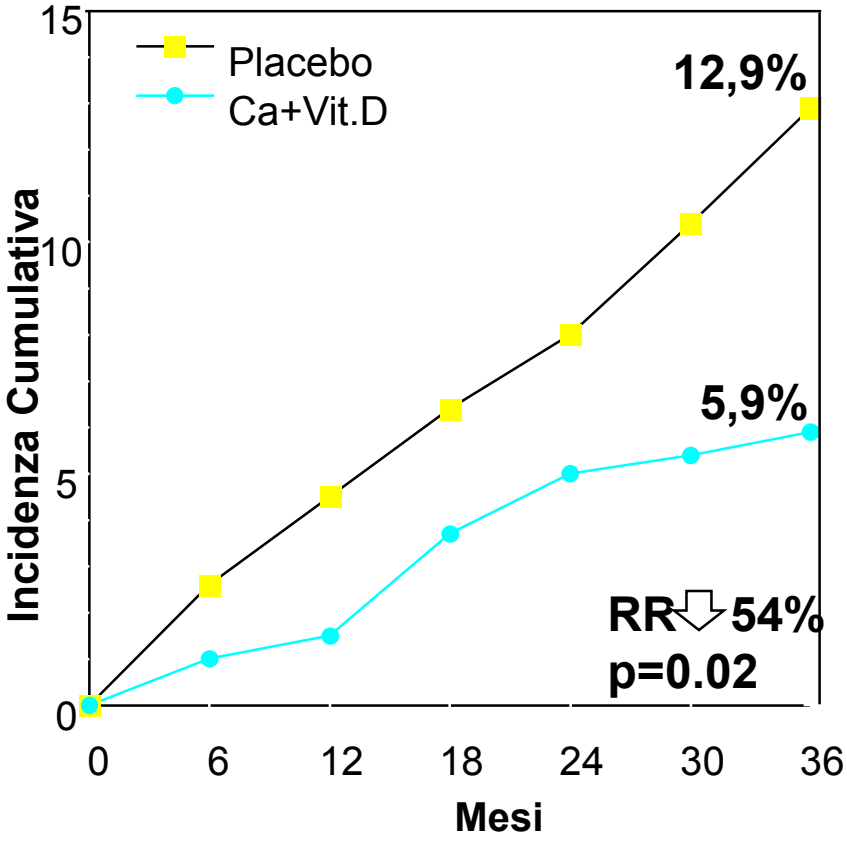
Incidenza di fratture in pazienti anziani trattati con Calcio (500 mg) e Vitamina D (700 UI)

Tutte le fratture



Meunier PJ et al. Osteop Int, 1994

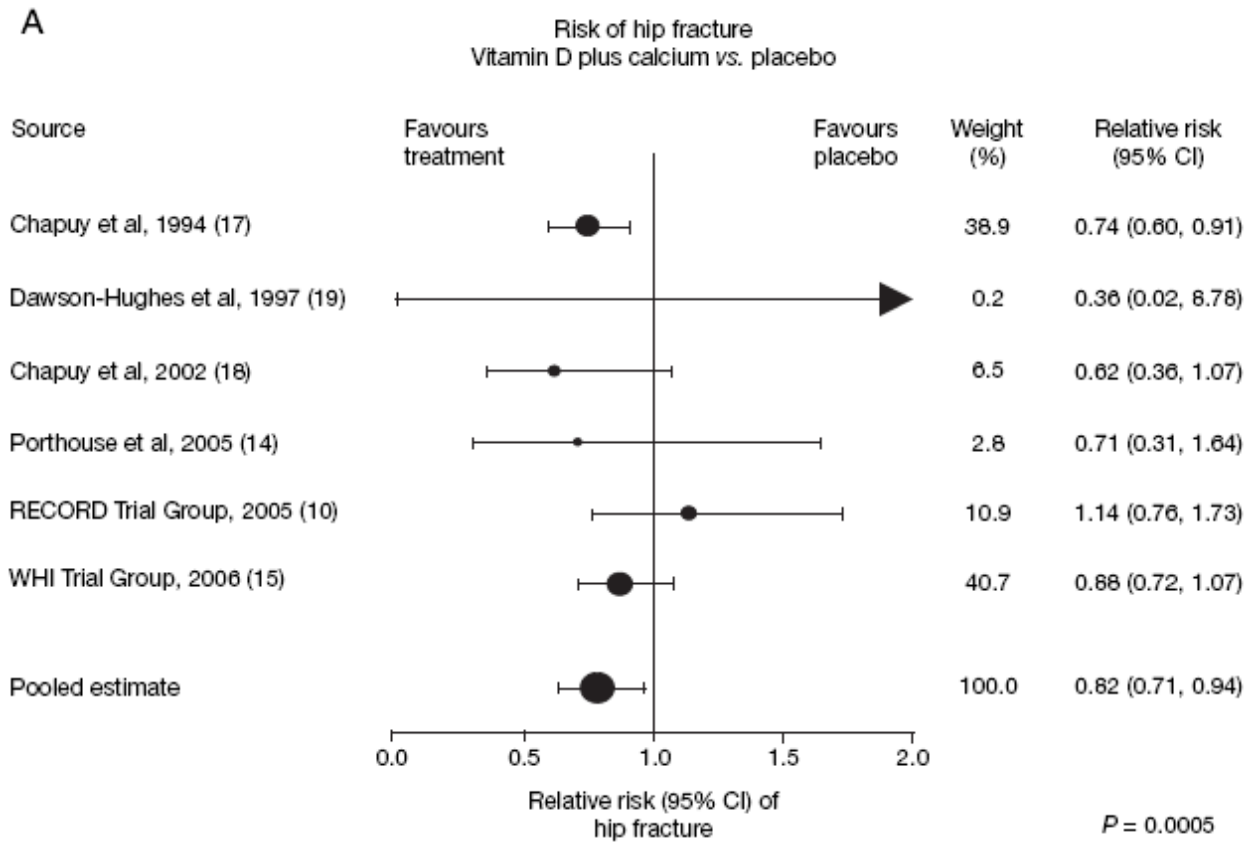
Fratture non vertebrali



Dawson Hughes *NEJM,* 1997

Calcio e Vitamina D:

Riduzione del 18% nell'incidenza di fratture di femore



Boonen *J of Clin End & Metab* 2007

Vitamin D given alone in doses of 400-800 UI/die is not effective in preventing fractures (68.500 patients)

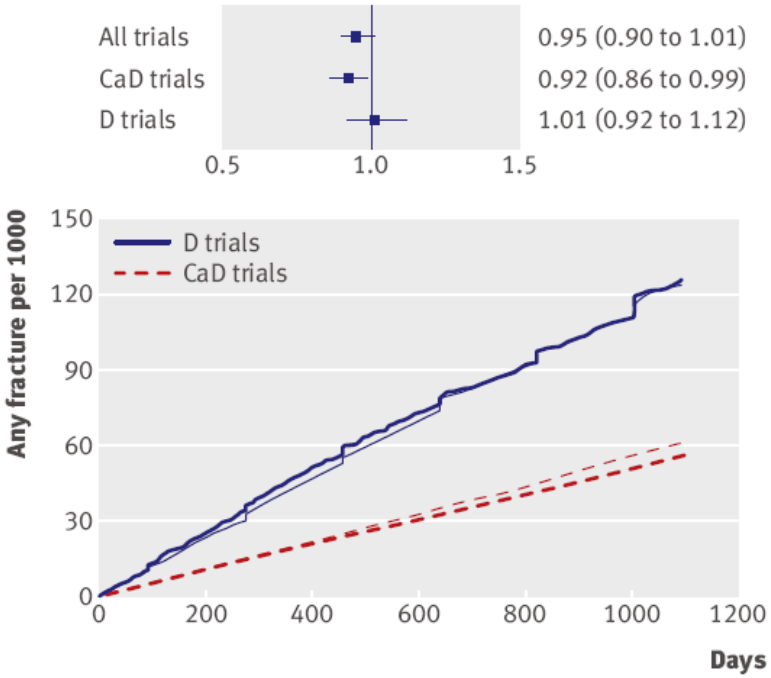


Fig 3 | Cumulative fracture incidence for vitamin D (darker lines) and controls (lighter lines). Vitamin D and calcium studies and vitamin D studies are shown separately. Inset shows treatment effect and 95% confidence intervals. CaD=calcium and vitamin D; D=vitamin D

DIPART *BMJ* 2010

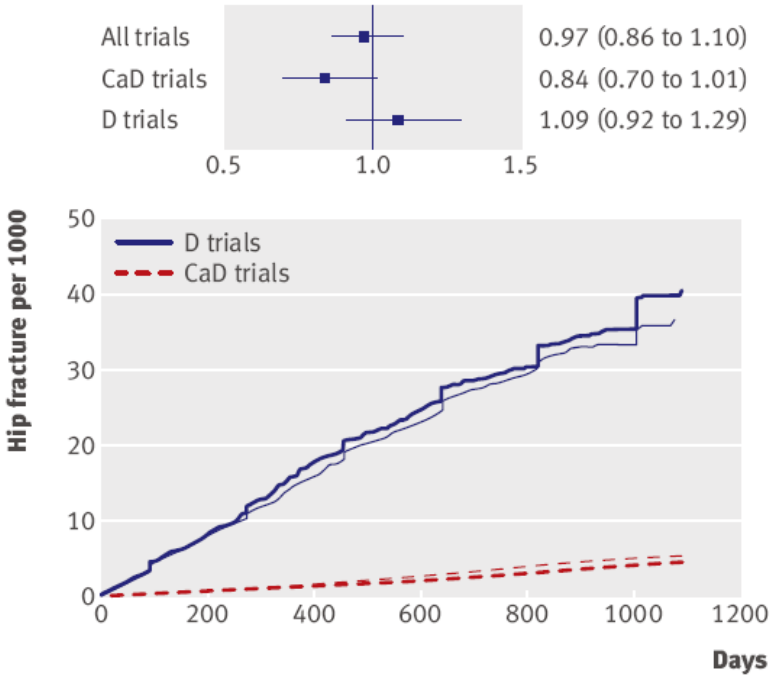


Fig 4 | Cumulative hip fracture incidence for vitamin D (darker lines) and controls (lighter lines). Vitamin D and calcium studies and vitamin D studies are shown separately. Inset shows treatment effect and 95% confidence intervals. CaD=calcium and vitamin D; D=vitamin D

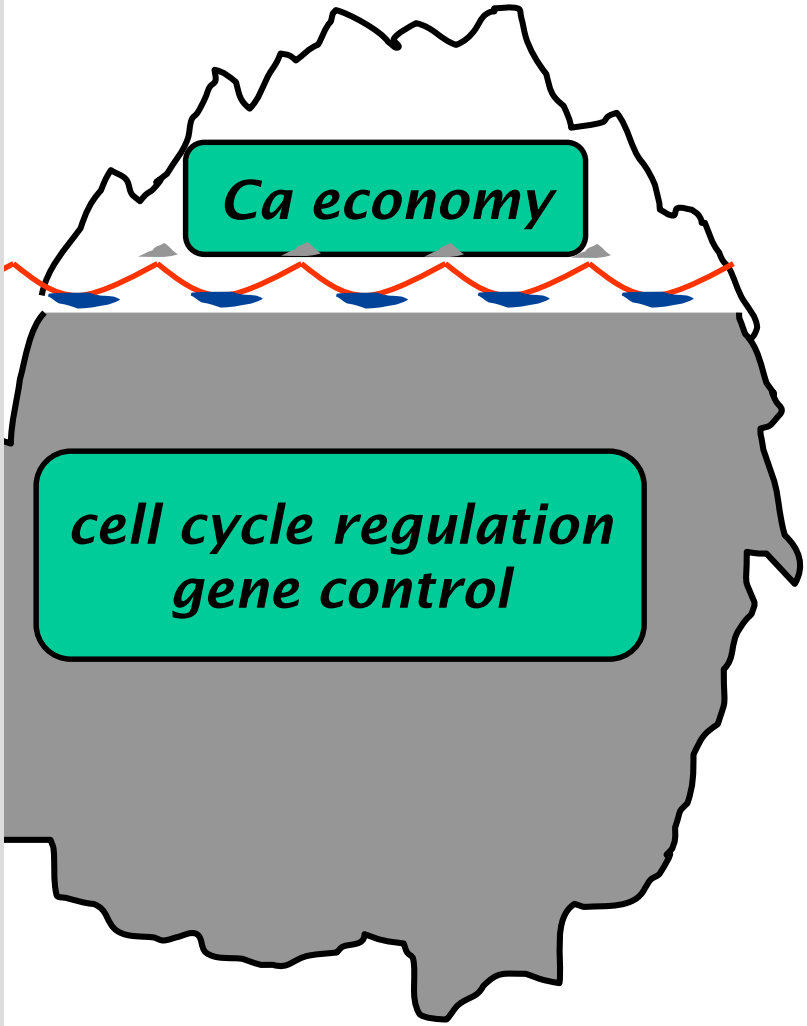
Abrahamsen *BMJ* 2010

THE VITAMIN D ICEBERG

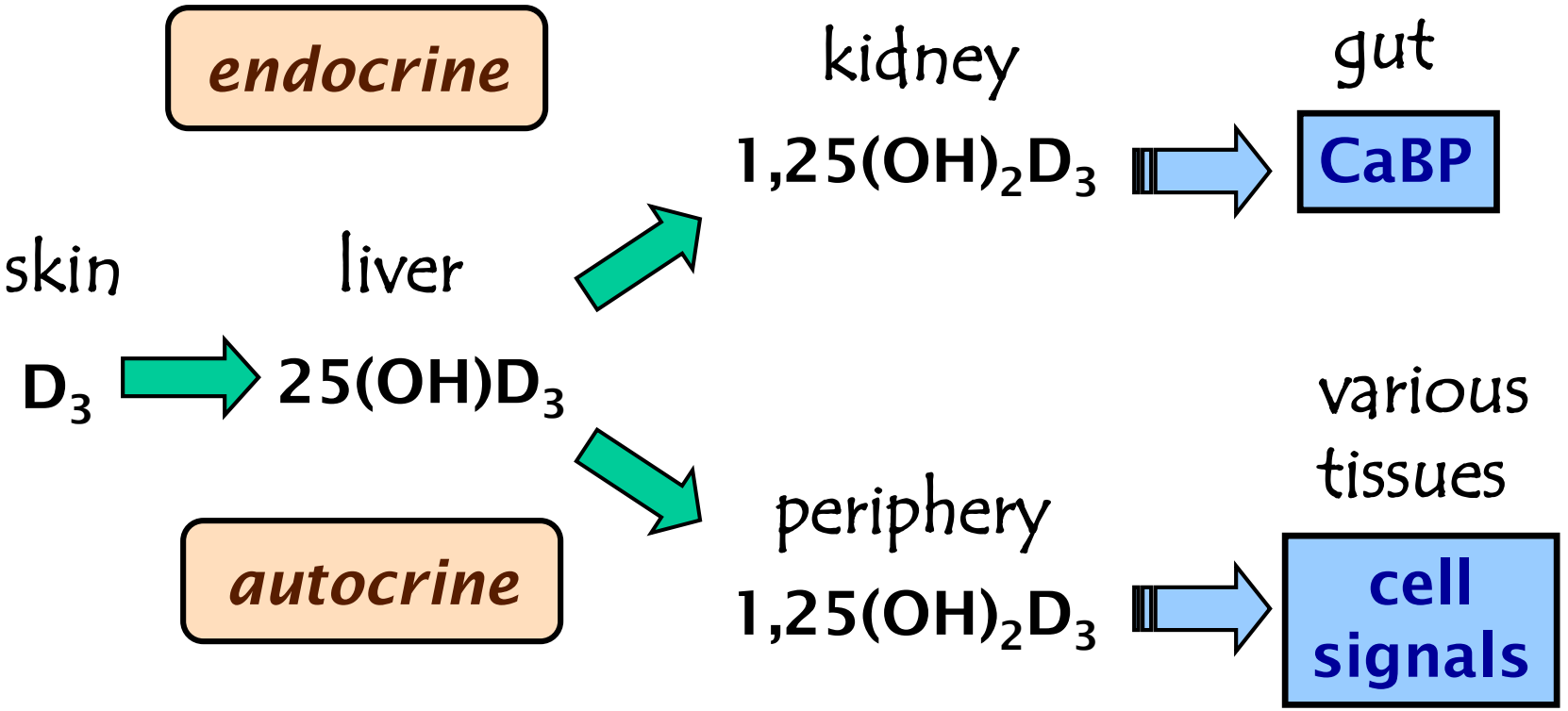
EXTRA-SKELETAL EFFECTS OF VITAMIN D

1,25-$(OH)_2D_3$target cells

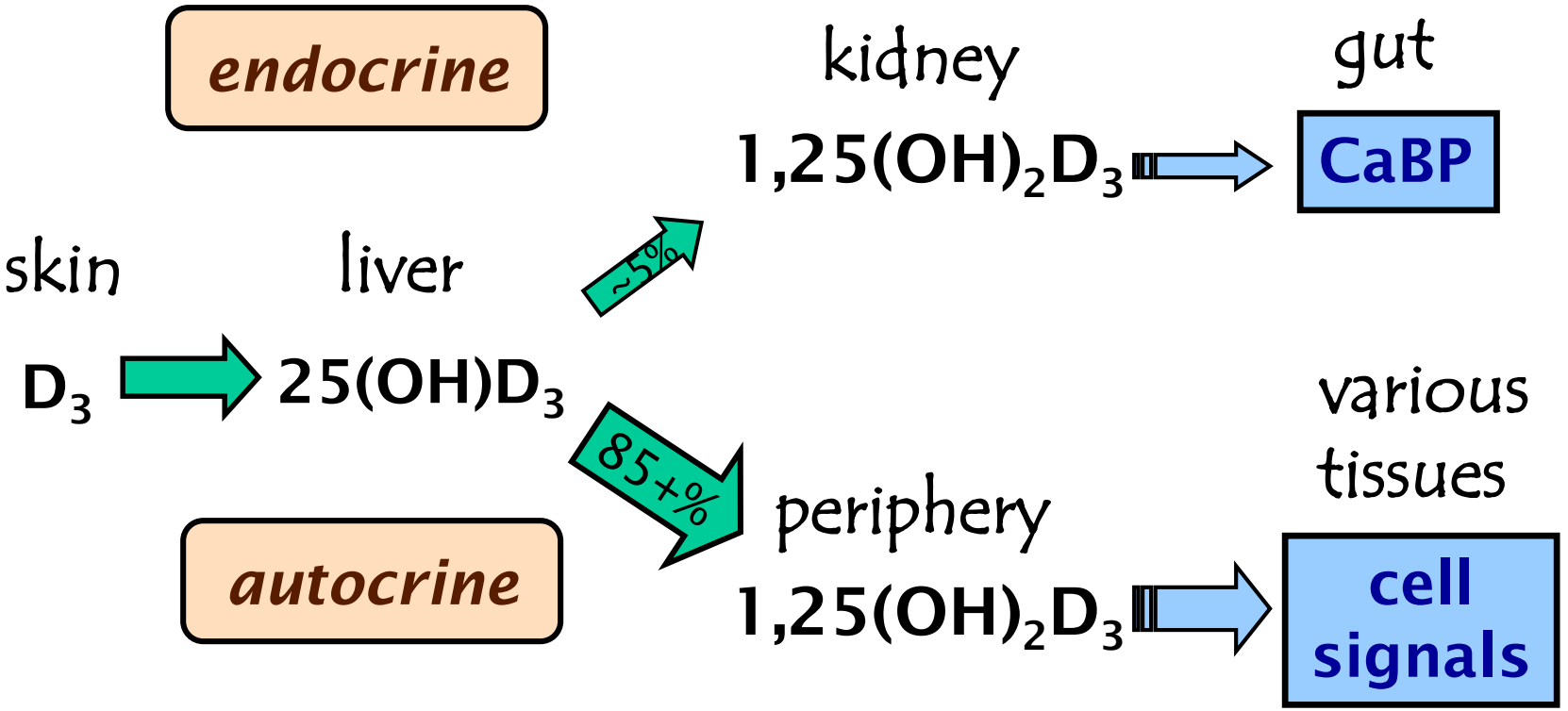
- Intestinal enterocyte
- Osteoblast
- Skeletal muscle
- Neuron and glial cells
- Distal renal cells
- Parathyroid cells
- Keratinocytes of skin
- Promyelocytes, Monocytes
- Lymphocytes
- Colon enterocytes
- Cardiomyocytes
- Vascular smooth muscle
- Shell gland
- Chick chorioallantoic membrane



VIT D – EXPANDED SCHEME



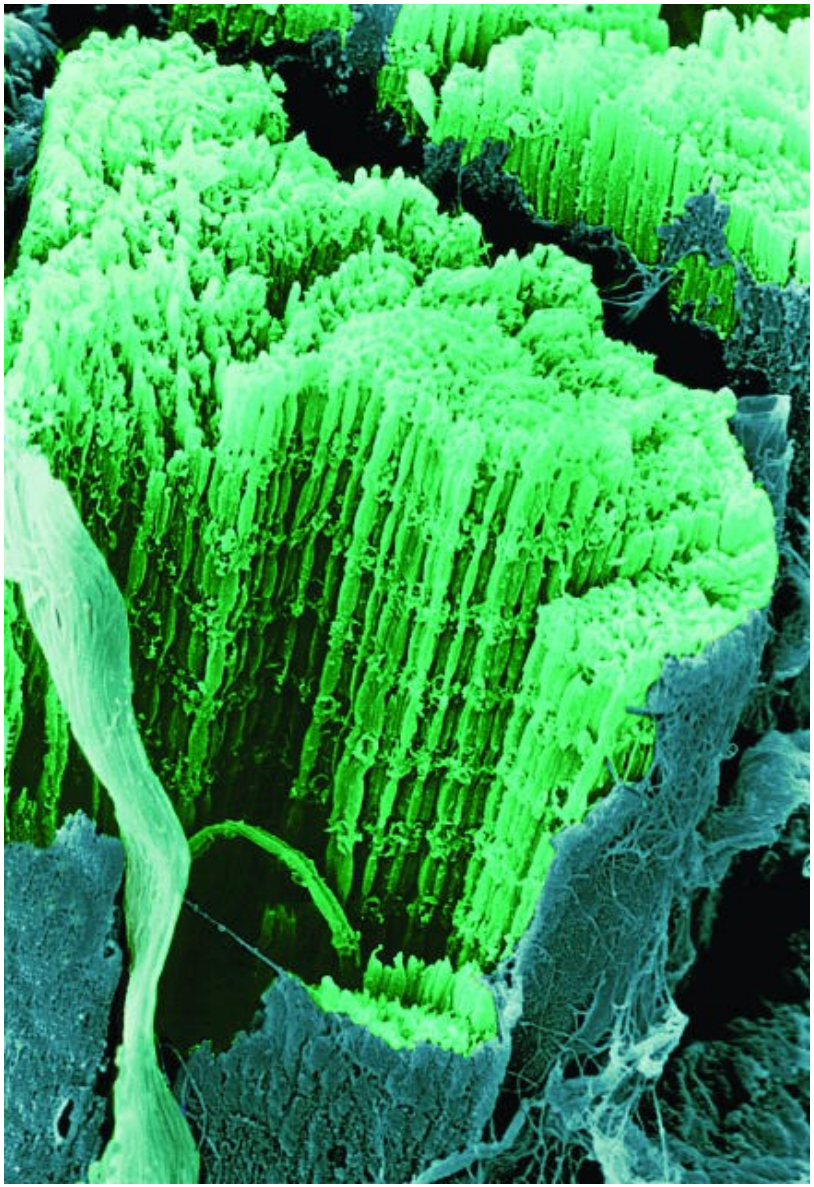
VIT D – EXPANDED SCHEME



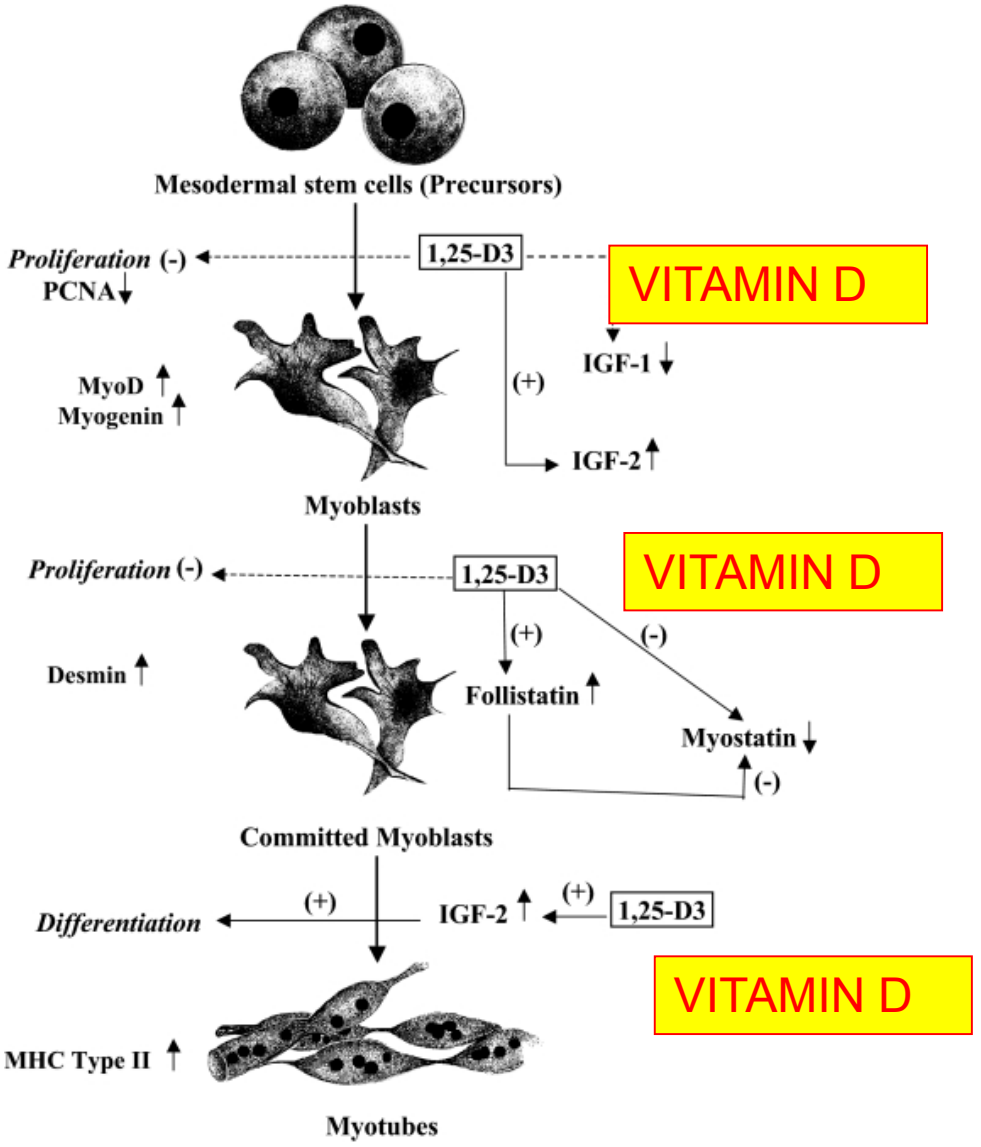
AGENDA

- Vitamin D and Hypovitaminosis D
- Vitamina D and Fragility Fractures
- Vitamin D and Muscle
- Vitamin D and Cognitive Impairment

VITAMIN D AND MUSCULAR DEVELOPMENT

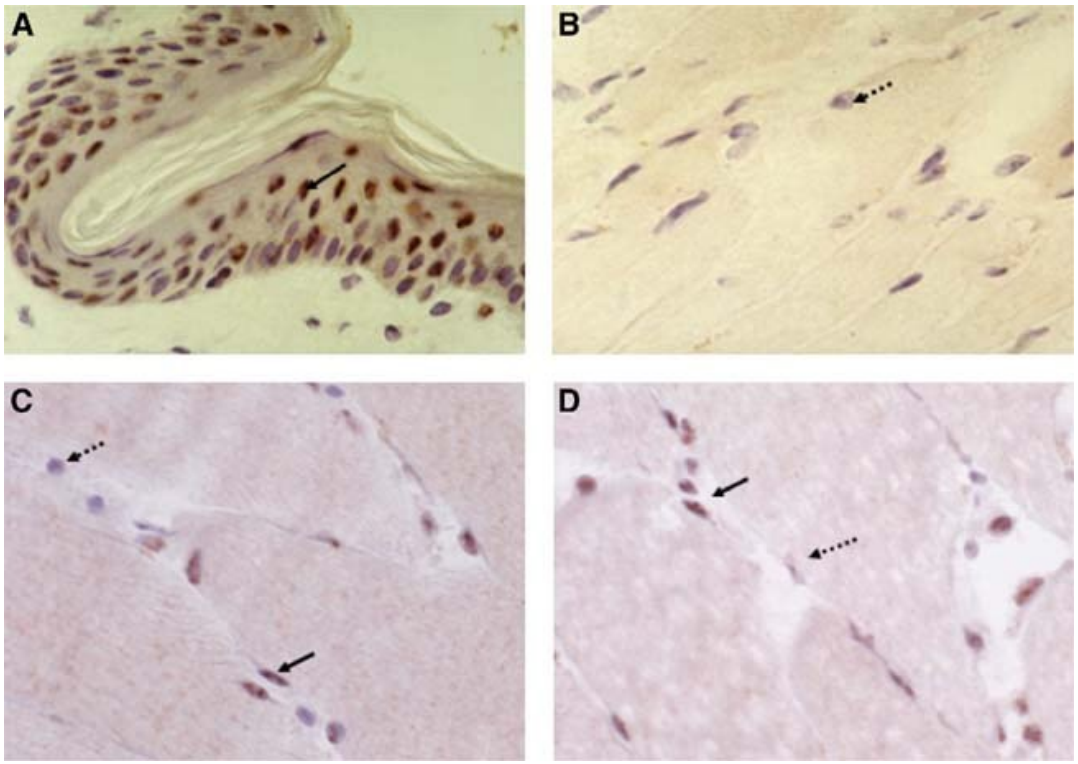


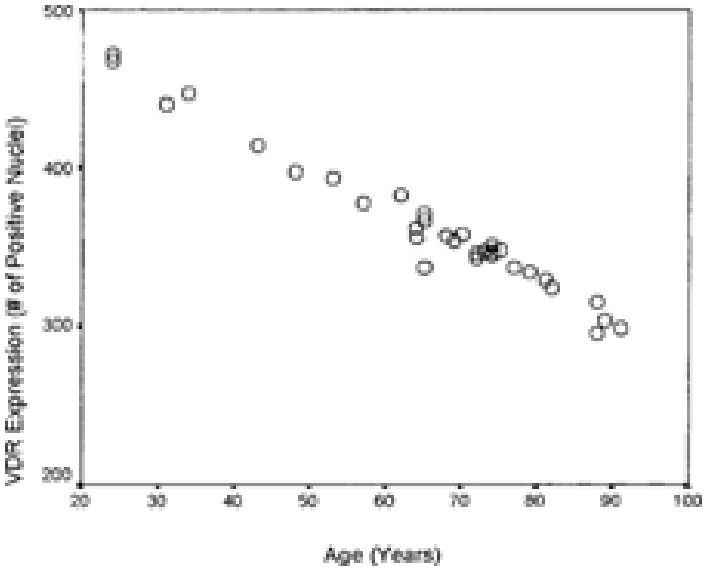
Venning G. BMJ 2005



Garcia LA et al. Endocrinology 2011

Human skeletal muscle express VDR

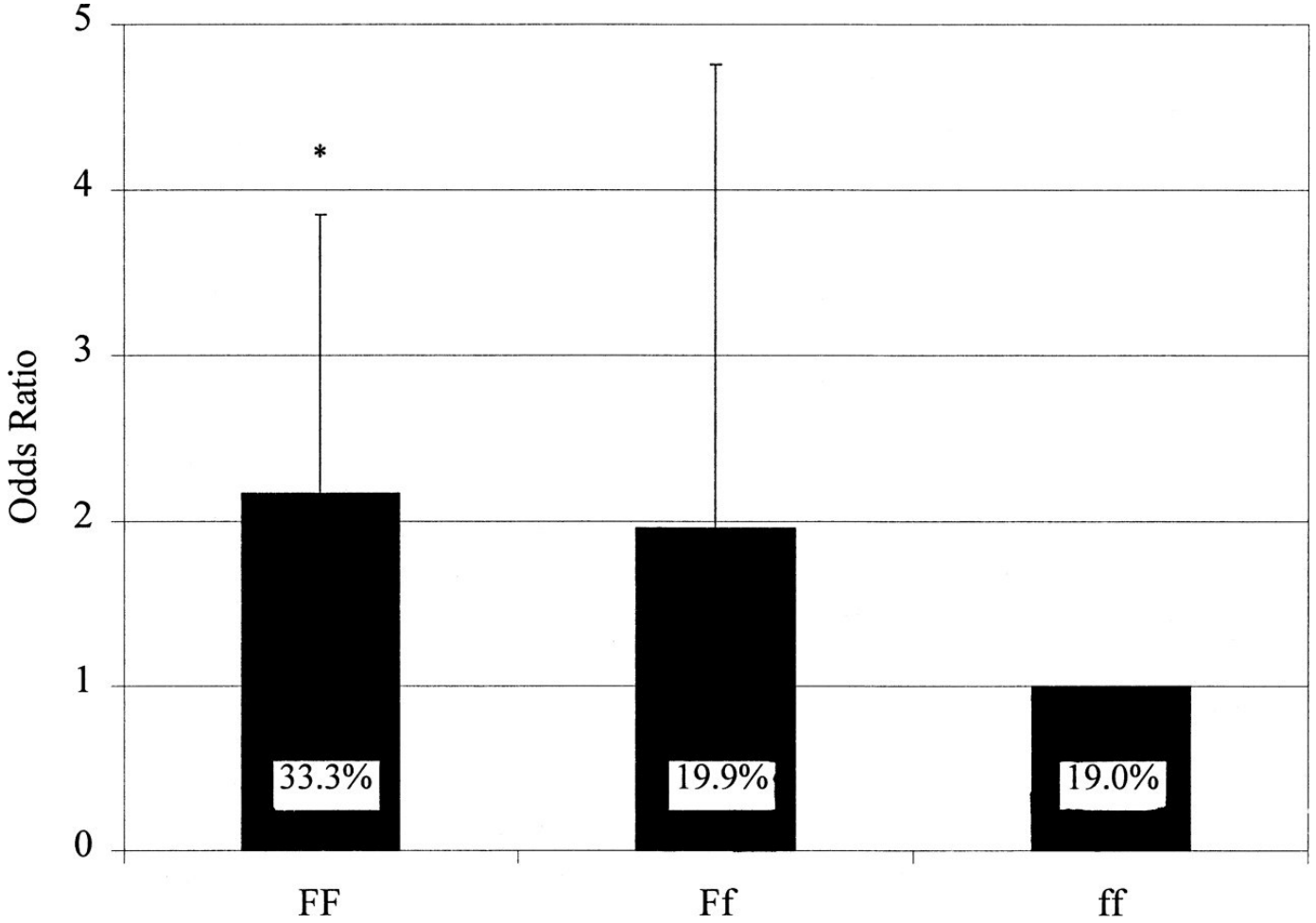




- **Regulation of calcium transport**
- **Uptake of inorganic phosphate for production of energy-rich Phosphate compounds**
- **Protein synthesis**

Pfeifer M, et al Osteoporosis Int 2012
Houston et al J Gerontol A Biol Sci Med Sci 2007

VDR genotypic variations are associated with differences in muscle strength and prevalence of sarcopenia



Roth S M et al. J Gerontol A Biol Sci Med Sci 2004

Grundberg E, et al. Eur J Endocrinol. 2004

Windelinckx A, et al. Osteoporos Int. 2007

Geusens P, et al J Bone Miner Res. 1997

How low vitamin D influence muscle trophism: fast-twitch type II

	Controls (n = 20)	Patients with hip fractures		P^a
		Sufficient 25-OHD group (n = 20)	Deficient 25-OHD group (n = 22)	
Fiber necrosis (HE)	1 (5%)	9 (45%)	11 (50%)	0.75
Inflammatory cells (HE)	0 (0%)	8 (40%)	9 (41%)	0.95
High incidence of central nuclei (HE)	0 (0%)	1 (5%)	20 (91%)	<0.0001
Rimmed vacuoles (Gomori trichrome)	0 (0%)	2 (10%)	17 (77%)	<0.0001
Routine ATPase				
Mean type I fiber diameter (μm)	47.8 ± 1.9	47.1 ± 2.8	46.5 ± 3.8	0.38
Mean type II fiber diameter (μm)	37.1 ± 4.0	38.7 ± 8.1	15.4 ± 4.2	<0.0001
Incidence of type II fiber atrophy (mean fiber diameter ratio; type II fiber/type I fiber)				
Absent	3 (15%)	4 (20%)	0 (0%)	0.0350
Mild (ratio 0.6–0.99)	11 (55%)	9 (45%)	0 (0%)	0.0007
Moderate (ratio 0.3–0.59)	6 (30%)	7 (35%)	3 (14%)	0.10
Severe (ratio ≤0.29)	0 (0%)	0 (0%)	19 (86%)	<0.0001
Type I fiber predominance	0 (0%)	0 (0%)	9 (41%)	0.0013

Sato Y et al, Bone 2002

Endocrine Abstracts (2013) 31 OC1.6
DOI:10.1530/endoabs.31.OC1.6

Society for Endocrinology

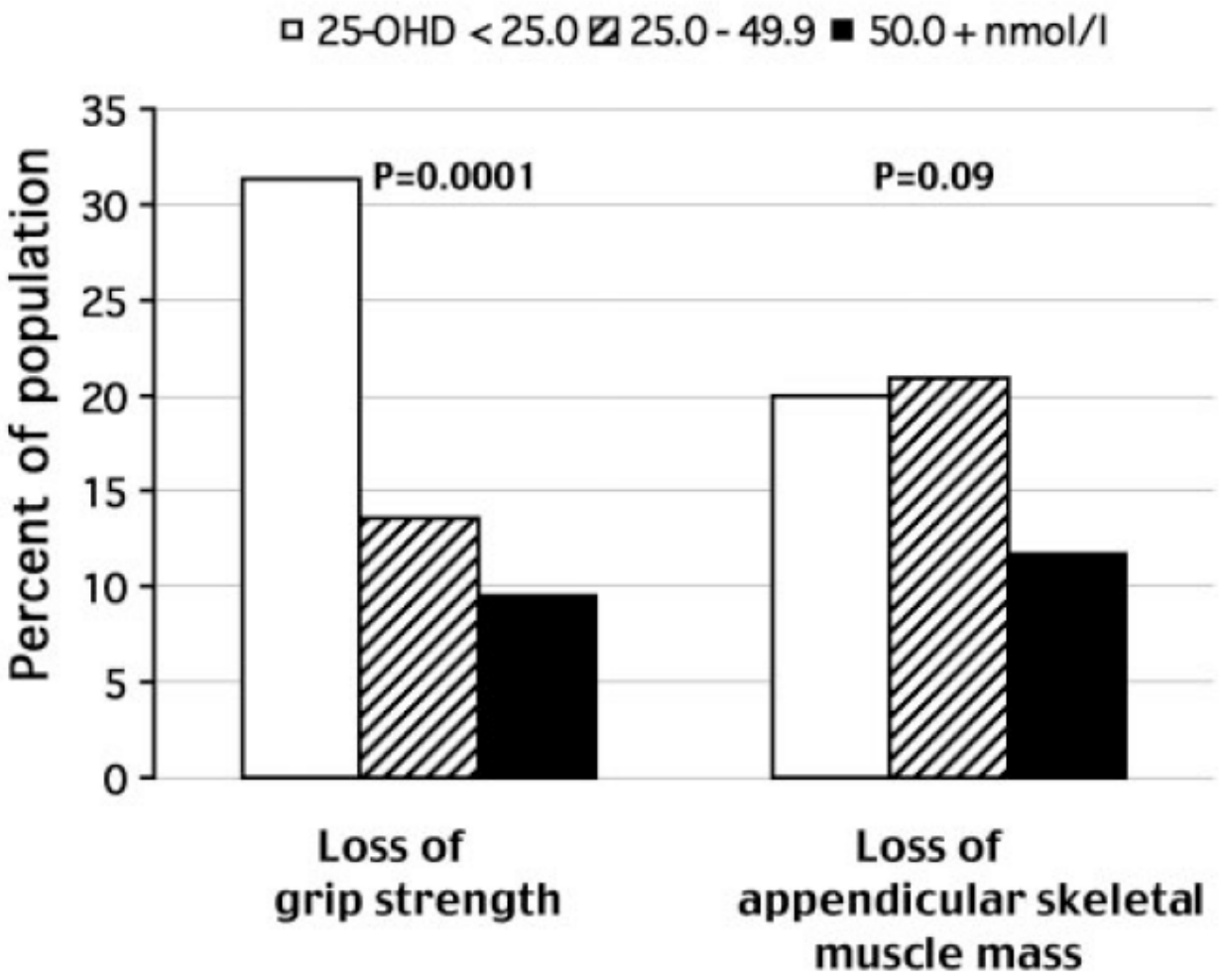
Improving the vitamin D status of vitamin D deficient adults is associated with improved mitochondrial oxidative function in skeletal muscle

Akash Sinha[1,2], Kieren Hollingsworth[3], Steve Ball[2,4] & Tim Cheetham[1,2]

Results: The phosphocreatine recovery half-time (τ1/2PCr, τ1/2ADP) was significantly reduced following cholecalciferol therapy in the subjects indicating an improvement in maximal oxidative phosphorylation ($P<0.001$, $P=0.003$). This was associated with an improvement in mean serum 25OHD levels (8.8 ± 4.2 to 113.8 ± 51.5 nmol/l, $P<0.001$). There was no difference in phosphate metabolites at rest. A linear regression model showed that decreasing serum 25OHD levels are associated with increasing τ1/2PCr ($r=-0.41$, $P=0.009$). All patients reported an improvement in fatigue following cholecalciferol therapy.

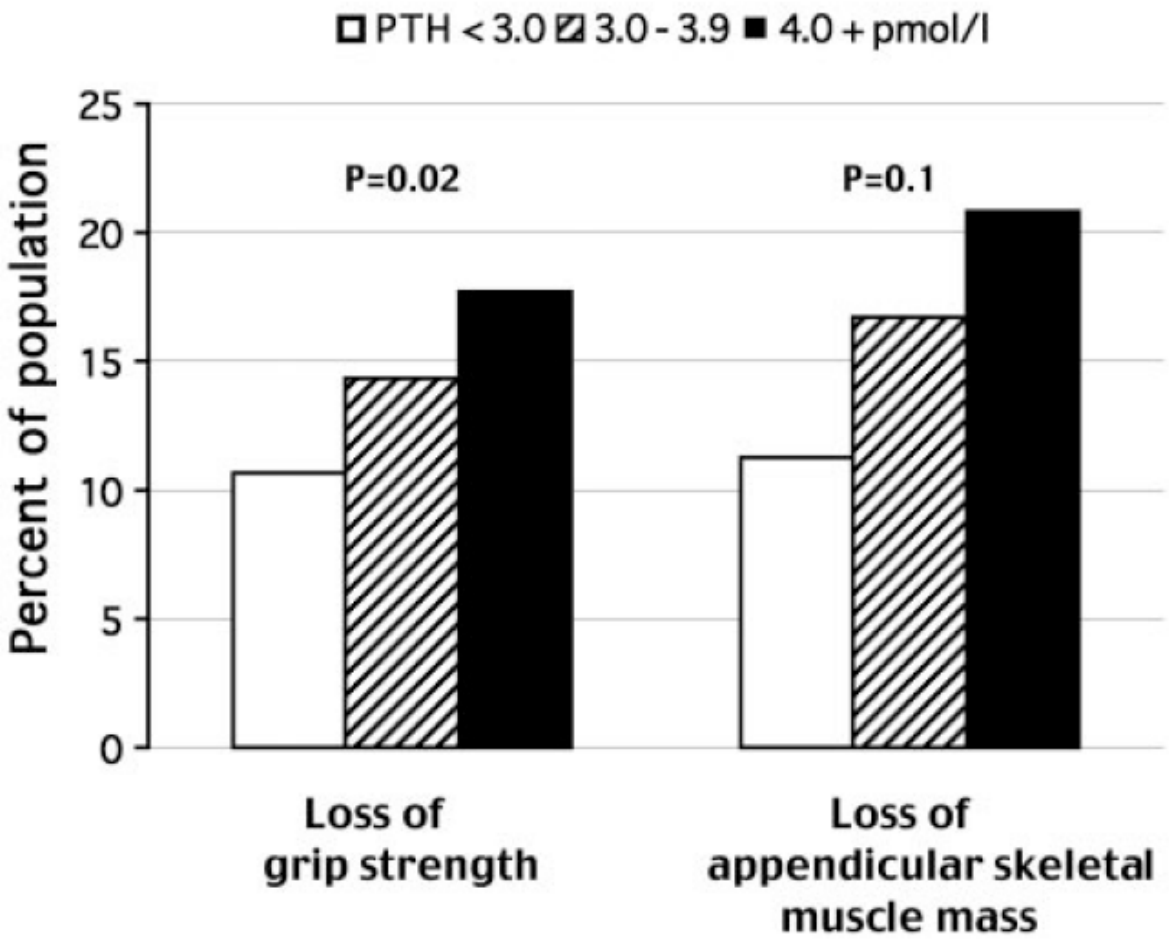
Conclusions: Cholecalciferol therapy augments muscle mitochondrial maximal oxidative phosphorylation following exercise in symptomatic, vitamin D deficient individuals. This finding suggests that changes in mitochondrial oxidative phosphorylation in skeletal muscle could at least be partly responsible for the fatigue experienced by these patients. For the first time, we demonstrate a link between vitamin D and the mitochondria in human skeletal muscle.

Low 25OH vitamin D and sarcopenia: longitudinal Aging Study Amsterdam



Visser et al JCEM 2003

High PTH and sarcopenia: longitudinal Aging Study Amsterdam



Visser et al JCEM 2003

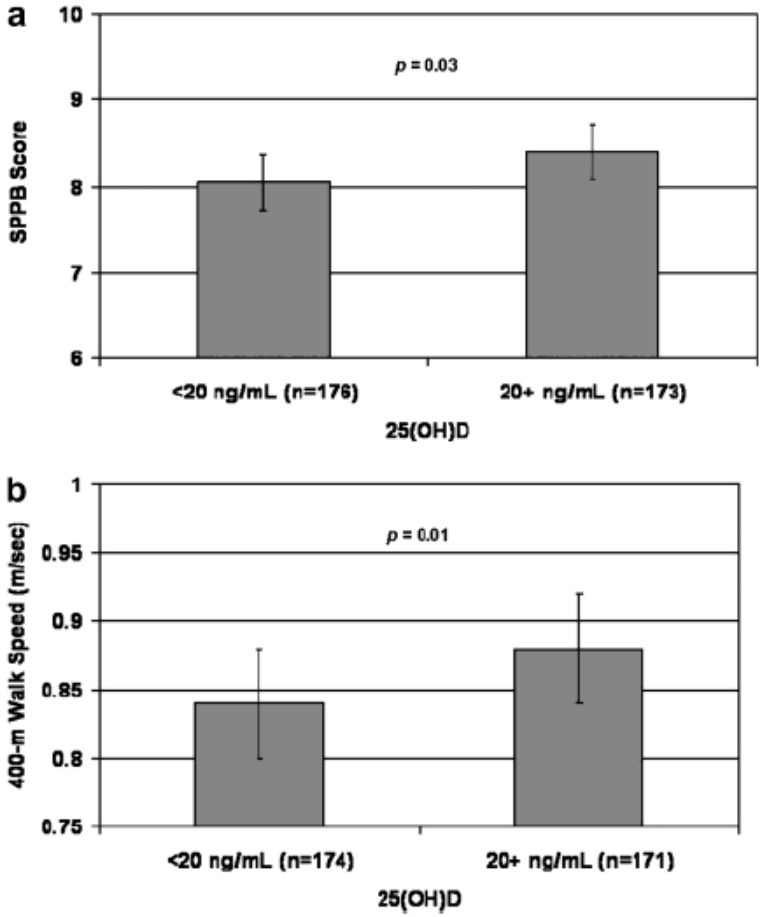
Lower 25 OH Vitamin D is associated with poorer muscular performance: the In CHIANTI studv

Conclusions—Vitamin D status was inversely associated with poor physical performance. Given the high prevalence of vitamin D deficiency in older populations, additional studies examining the association between vitamin D status and physical function are needed.

Physical Performance Measure	(nmol/L)			p value for <25 vs ≥25	p value for <50 vs ≥50	p for trend
	<25	25 to <50	≥50			
Men						
SPPB score*	10.15 (0.29)	10.73 (0.15)	10.94 (0.14)	0.03	0.10	0.04
Handgrip strength*	36.28 (1.40)	36.37 (0.71)	38.80 (0.62)	0.42	0.009	0.01
Women						
SPPB score*	9.29 (0.19)	9.85 (0.14)	9.59 (0.20)	0.03	0.74	0.58
Handgrip strength*	20.58 (0.60)	21.52 (0.41)	22.83 (0.57)	0.06	0.02	0.009

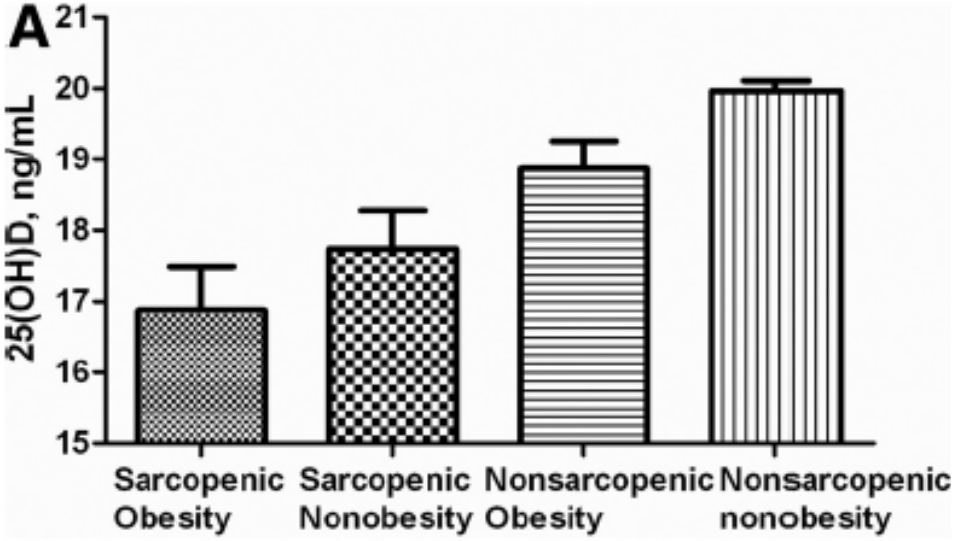
Houston et al J Gerontol A Biol Sci Med Sci 2007

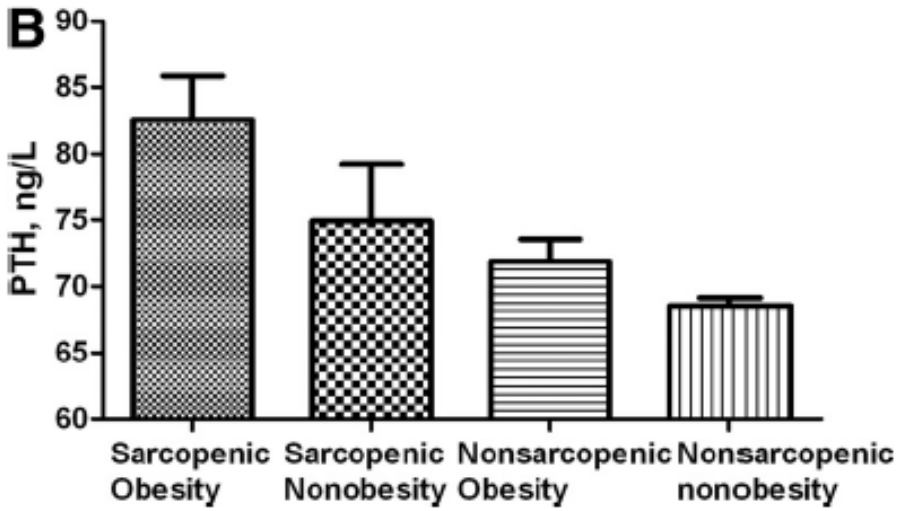
Lower vitamin D is associated with poor physical performance



Houston DK, et al J Gerontol A Biol Sci Med Sci. 2011

Vitamin D Deficiency Is Associated with Sarcopenia in Older Koreans, Regardless of Obesity: The Fourth Korea National Health and Nutrition Examination Surveys (KNHANES IV) 2009



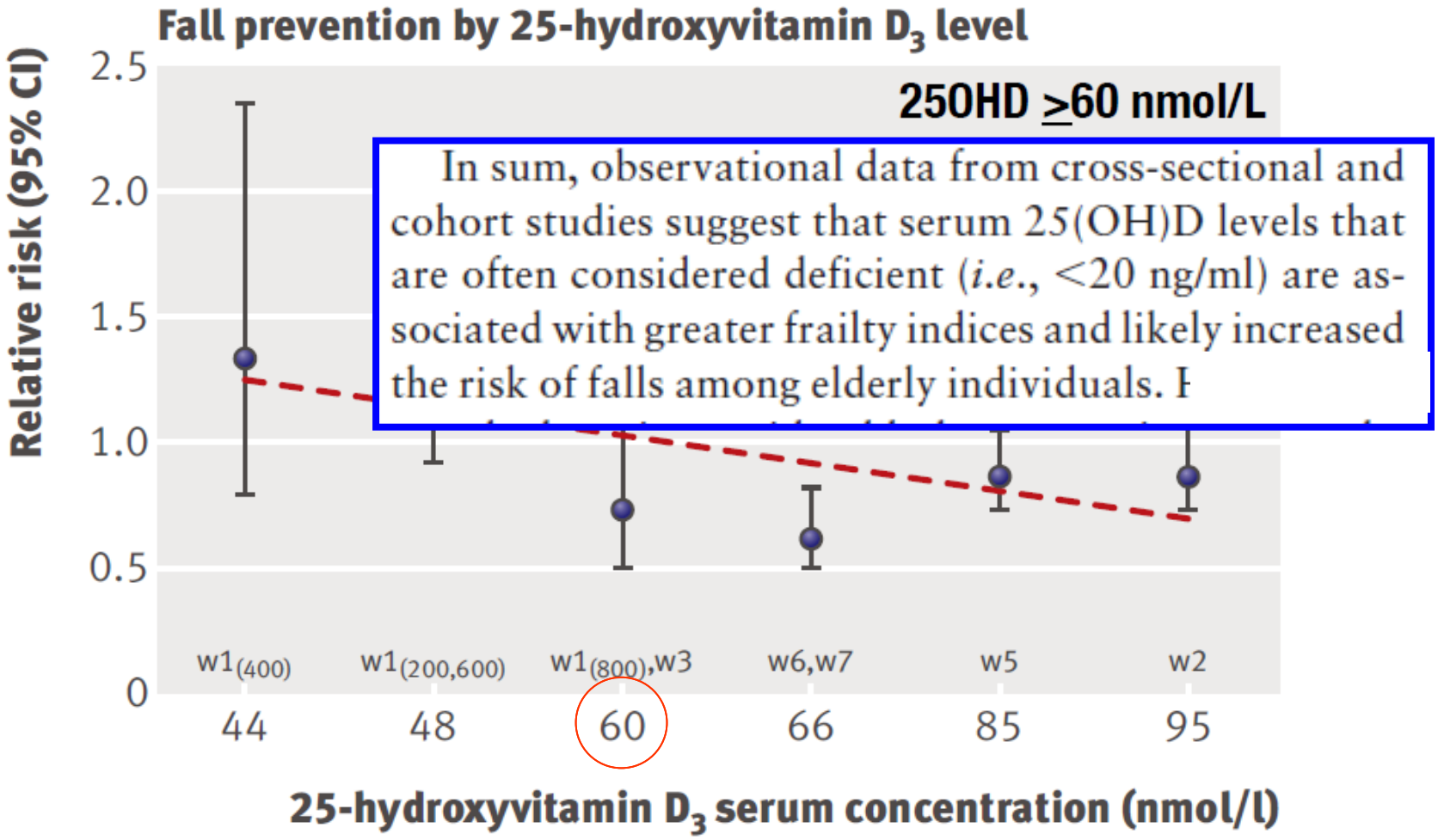


Mee Kyoung K et al, JCEM 2011

Ji AS et al JAGS 2012

Abdelouahid T et al, Age and Ageing 2013

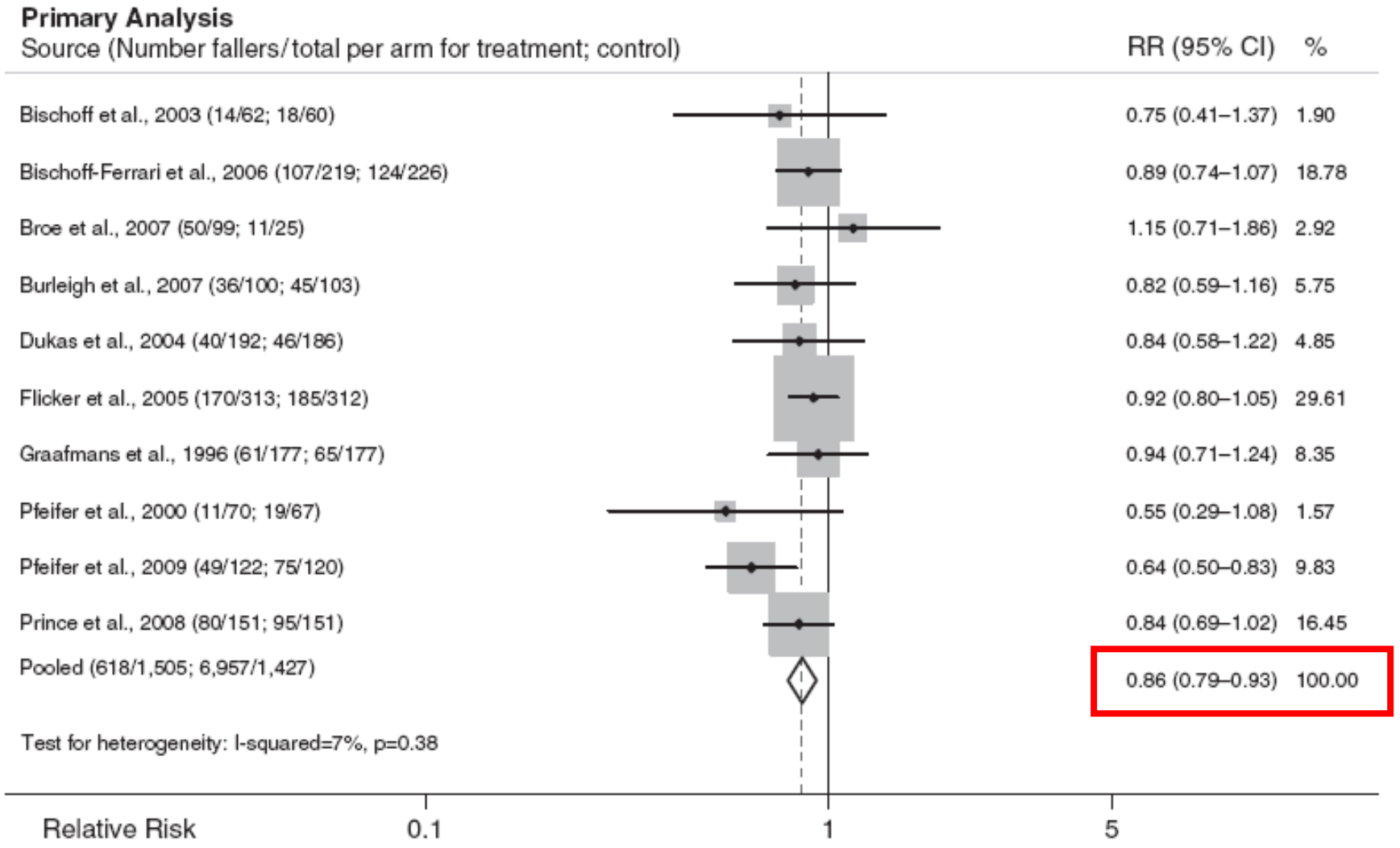
Vitamin D and the risk of falls



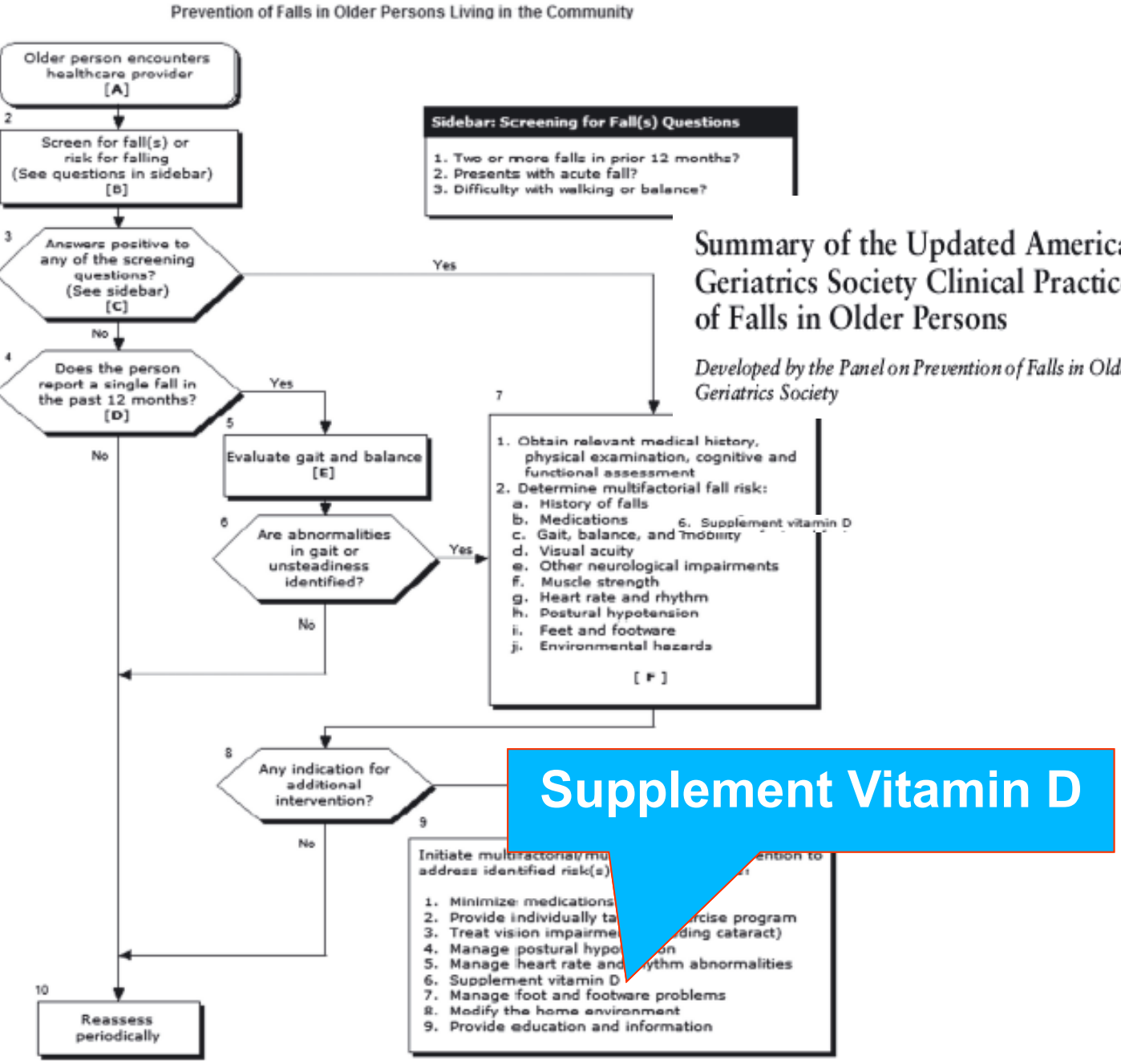
Bischoff-Ferrari et al BMJ 2009

C.J Rosen et al Endocrine Reviews 2012

Vitamin D treatment for the prevention of falls in older adults: systematic review and meta-analysis

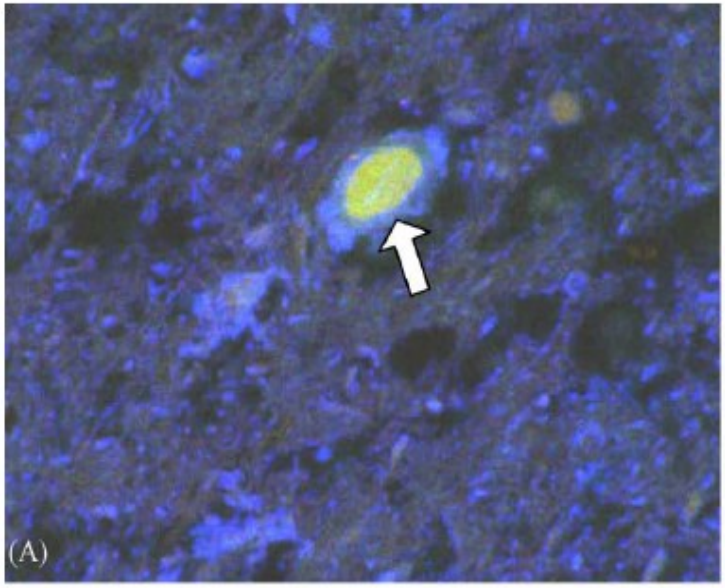


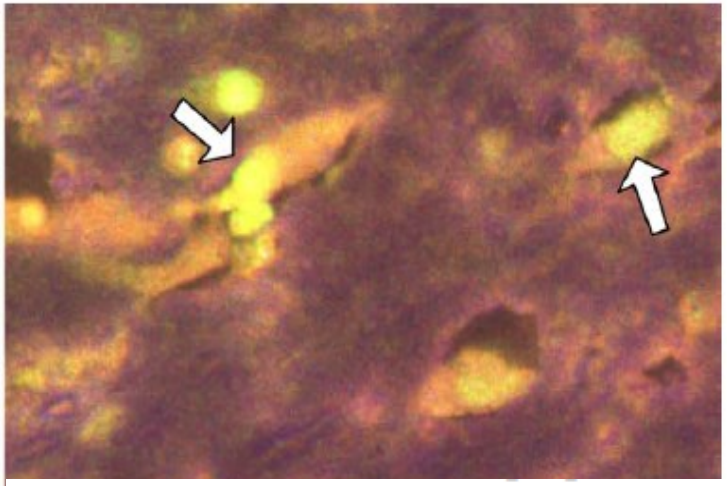
Kalyani et al, J Am Geriatr Soc 2010


Prevention of Falls in Older Persons Living in the Community
Older person encounters healthcare provider [A]
2
Screen for fall(s) or risk for falling (See questions in sidebar) [B]
Sidebar: Screening for Fall(s) Questions
1. Two or more falls in prior 12 months?
2. Presents with acute fall?
3. Difficulty with walking or balance?
3
Answers positive to any of the screening questions? (See sidebar) [C]
Yes
No
4
Does the person report a single fall in the past 12 months? [D]
Yes
No
5
Evaluate gait and balance [E]
6
Are abnormalities in gait or unsteadiness identified?
Yes
No
7
1. Obtain relevant medical history, physical examination, cognitive and functional assessment
2. Determine multifactorial fall risk:
a. History of falls
b. Medications
c. Gait, balance, and mobility
d. Visual acuity
e. Other neurological impairments
f. Muscle strength
g. Heart rate and rhythm
h. Postural hypotension
ii. Feet and footware
ji. Environmental hazards
[F]
8
Any indication for additional intervention?
No
9
address identified risk(s)
1. Minimize medications
2. Provide individually ta ercise program
3. Treat vision impairme ding cataract)
4. Manage postural hypo on
5. Manage heart rate and ythm abnormalities
6. Supplement vitamin D
7. Manage foot and footware problems
8. Modify the home environment
9. Provide education and information
10
Reassess periodically
Summary of the Updated American Geriatrics Society/British Geriatrics Society Clinical Practice Guideline for Prevention of Falls in Older Persons
JAGS, 2010
Developed by the Panel on Prevention of Falls in Older Persons, American Geriatrics Society and British Geriatrics Society
Supplement Vitamin D

AGENDA

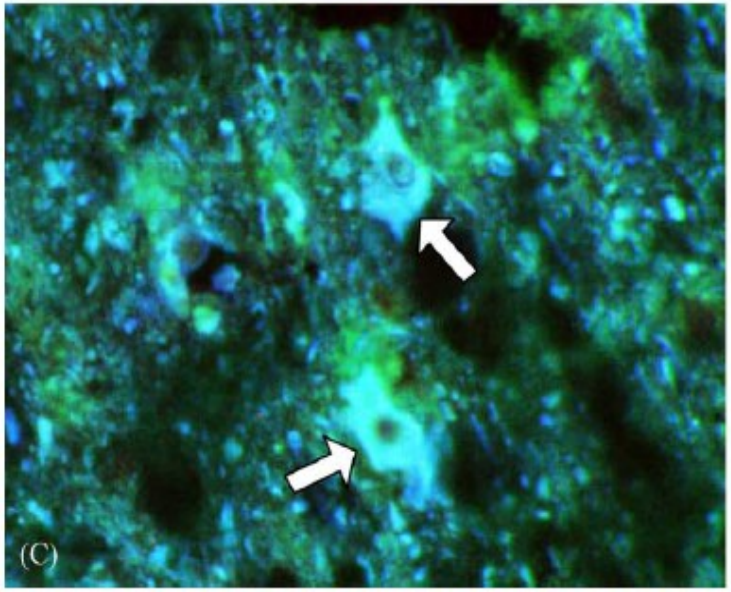
- Vitamin D and Hypovitaminosis D
- Vitamina D and Fragility Fractures
- Vitamin D and Muscle
- Vitamin D and Cognitive Impairment





Eyles DW, et al Distribution of the vitamin D receptor and 1 alphahydroxylase in human brain. J Chem Neuroanat 2005

In view of the presence of both the VDR and 1α-OHase in the human brain, and of the evidence that Vitamin D is involved in unexpectedly diverse roles in the brain, this area warrants closer scrutiny in research related to the causes and treatment of neuropsychiatric disorders.



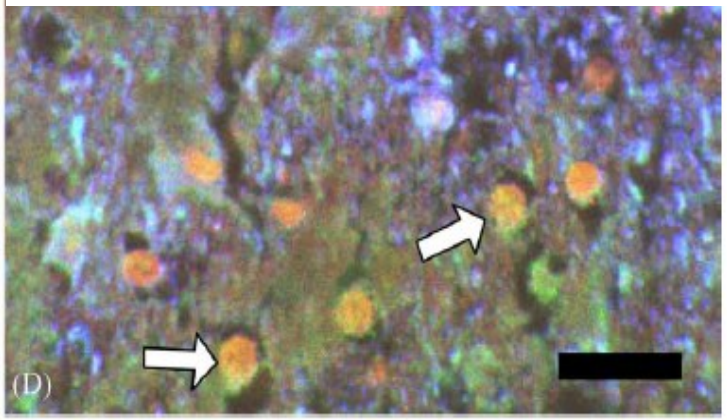


Fig. 1. Immunofluorescent detection of VDR and 1α-OH in both neurons and glia. (A) Neurofilament 200-Cy5 labeled neuron (arrow) displaying the FITC labeled VDR within the nucleus. (B) GFAP-Cy3 labeled cells also show VDR (FITC) immunoreactivity within the nucleus (arrows). (C) Neurofilament 200-Cy5 labeled neurons also express 1α-OH (FITC) within the cytoplasm producing a pale blue colour (arrows). (D) Glia labeled with GFAP-Cy3 also express 1α-OH-FITC resulting in orange colourization (arrows). Bar = 20 μm.

Brain function & Vitamin D in humans

A large body of research suggests that an inadequate dietary supply of any of a number of essential micronutrients can adversely affect brain function

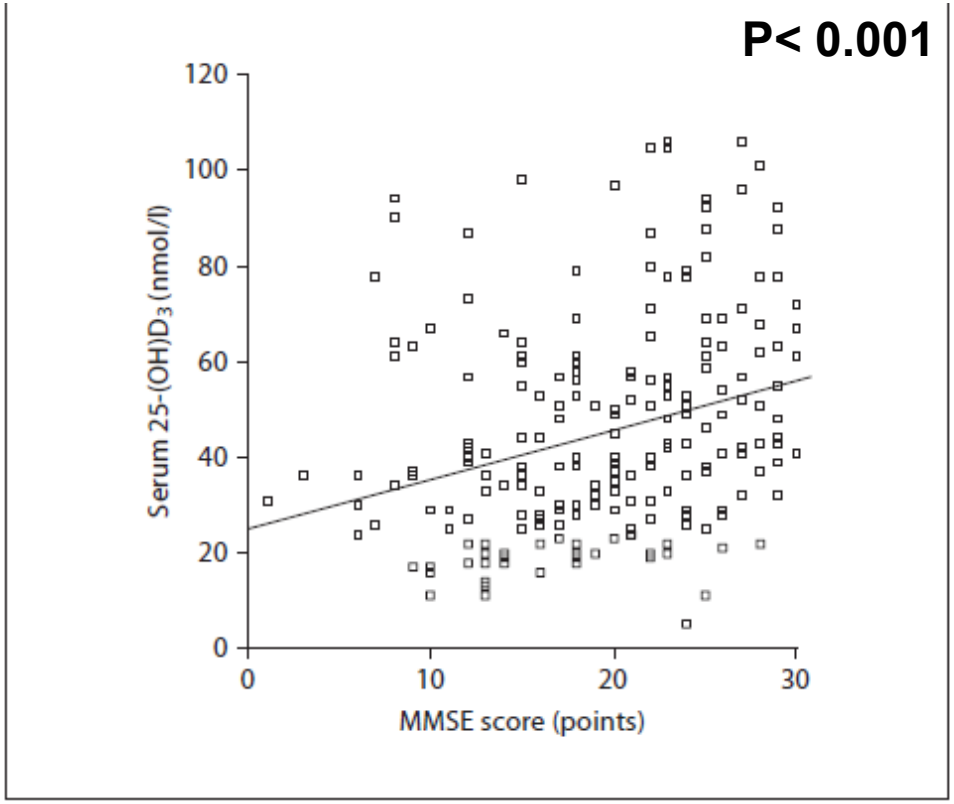
A significant positive correlation between serum 25OHD3 concentrations and scores on the minimental state examination in a retrospective chart review of data obtained on 32 older adults referred to a clinic because of symptoms of dementia

Przybelski, R. J., and Binkley, N. C. Arch. Biochem. Biophys. 2007

Higher Serum Vitamin D_3 Levels Are Associated with Better Cognitive Test Performance in Patients with Alzheimer's Disease (962 pts)

C. Oudshoorn[a] F.U.S. Mattace-Raso[a] N. van der Velde[a] E.M. Colin[b]

T.J.M. van der Cammen[a]



Dement Geriatr Cogn Disord 2008;25:539–543

Fig. 1. Scatter plot of the MMSE score versus serum 25-(OH)D_3 level.

Hypovitaminosis D and Cognitive impairment

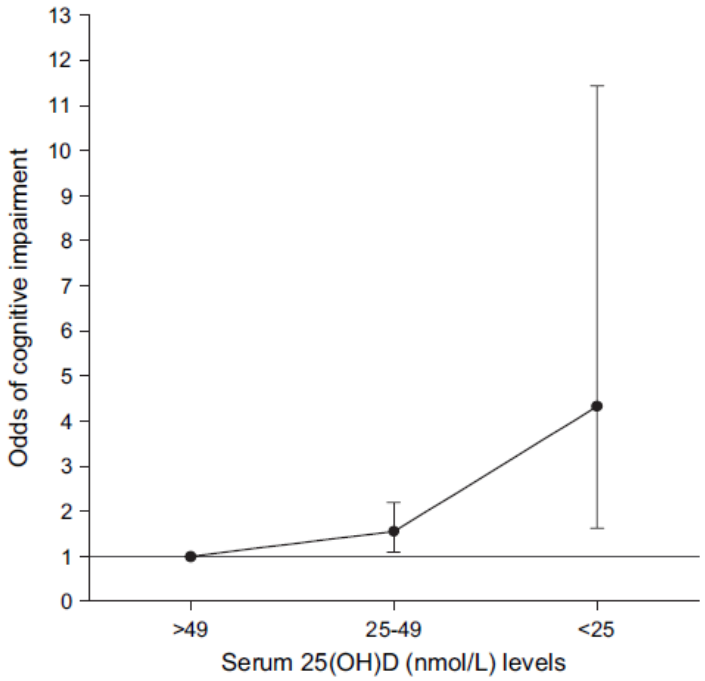


Figure 1. Odds of cognitive impairment by serum 25-hydroxyvitamin D [25(OH)D] levels. Bars indicate 95% confidence intervals. Cognitive impairment was defined as the worst 10% of the distribution of scores. Population weights are used to adjust for the sampling design. Results are also adjusted for age, sex, race/ethnicity, education, season tested, current smoking status, body mass index, alcohol consumption, serum vitamin E, combined family income, impaired mobility, and physical activity.

"…low levels of 25 (OH) D were associated with increased odds of cognitive impairment and this association remained after adjusting for a wide range of potential confounders."

Llewellyn DJ, Lang IA, Langa KM, Melzer D. Vitamin D and cognitive impairment in the elderly US population.
J Gerontol A Biol Sci Med Sci 2011

Vitamin D insufficiency and mild cognitive impairment: cross-sectional association

C. Annweiler[a,b,c], B. Fantino[b,c], A. M. Schott[d], P. Krolak-Salmon[e], G. Allali[f] and O. Beauchet[a,b,c]

European Journal of Neurology 2012, **19:** 1023–1029

Conclusions: Low 25OHD concentrations were associated with MCI status in older non-demented community-dwellers with subjective memory complaint.

Serum 25-Hydroxyvitamin D Concentration and Cognitive Impairment

David J. Llewellyn, PhD[1], **Kenneth M. Langa, MD, PhD**[2,3], and **Iain A. Lang, PhD**[4]

[1] Department of Public Health and Primary Care, University of Cambridge, Cambridge, UK

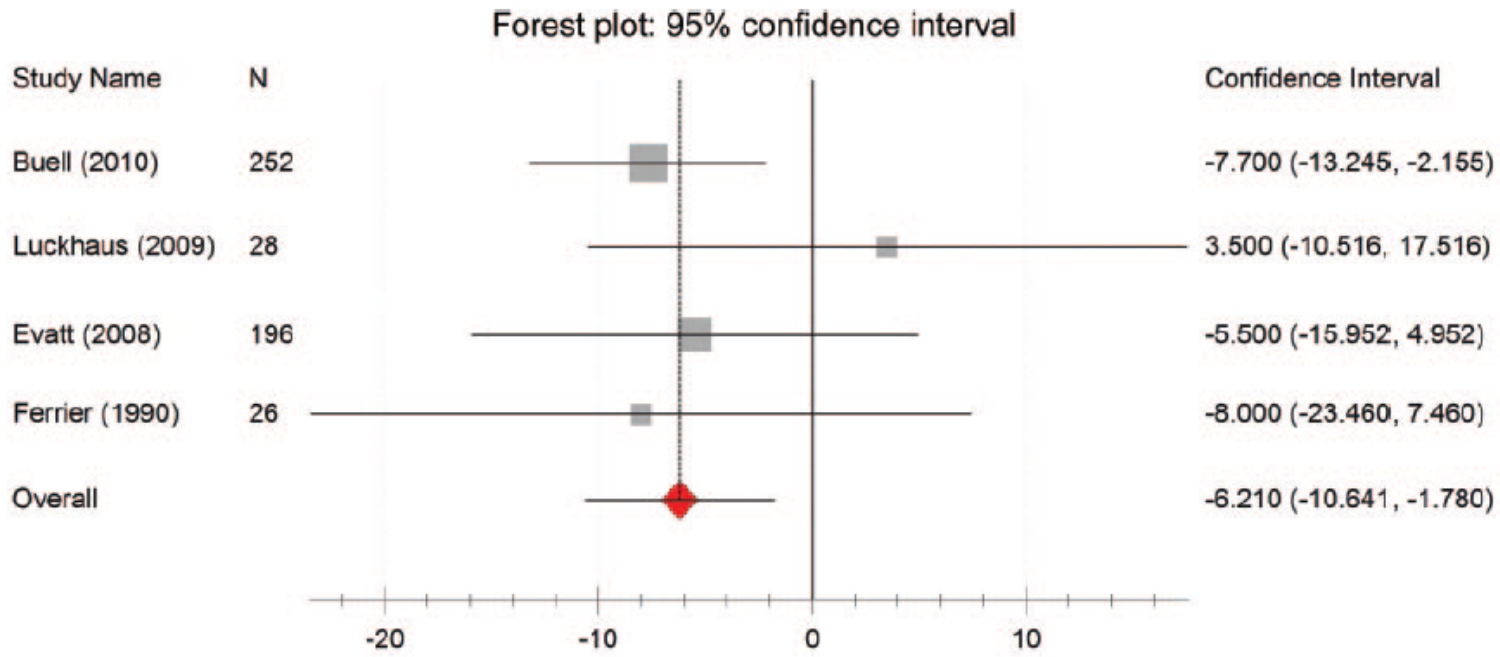
J Geriatr Psychiatry Neurol. 2009 September ; 22(3): 188–195.

In conclusion, we provide new evidence to suggest that serum 25(OH)D is related to cognitive impairment in the elderly population and a potential diagnostic aid for screening or differential diagnosis.[42] This is important because serum 25(OH)D may play an important role in the expression of neurotrophic factors, the stimulation of adult neurogenesis, calcium homeostasis,

Vitamin D, cognition, and dementia

A systematic review and meta-analysis

Figure 2 Vitamin D concentration in Alzheimer disease and control groups

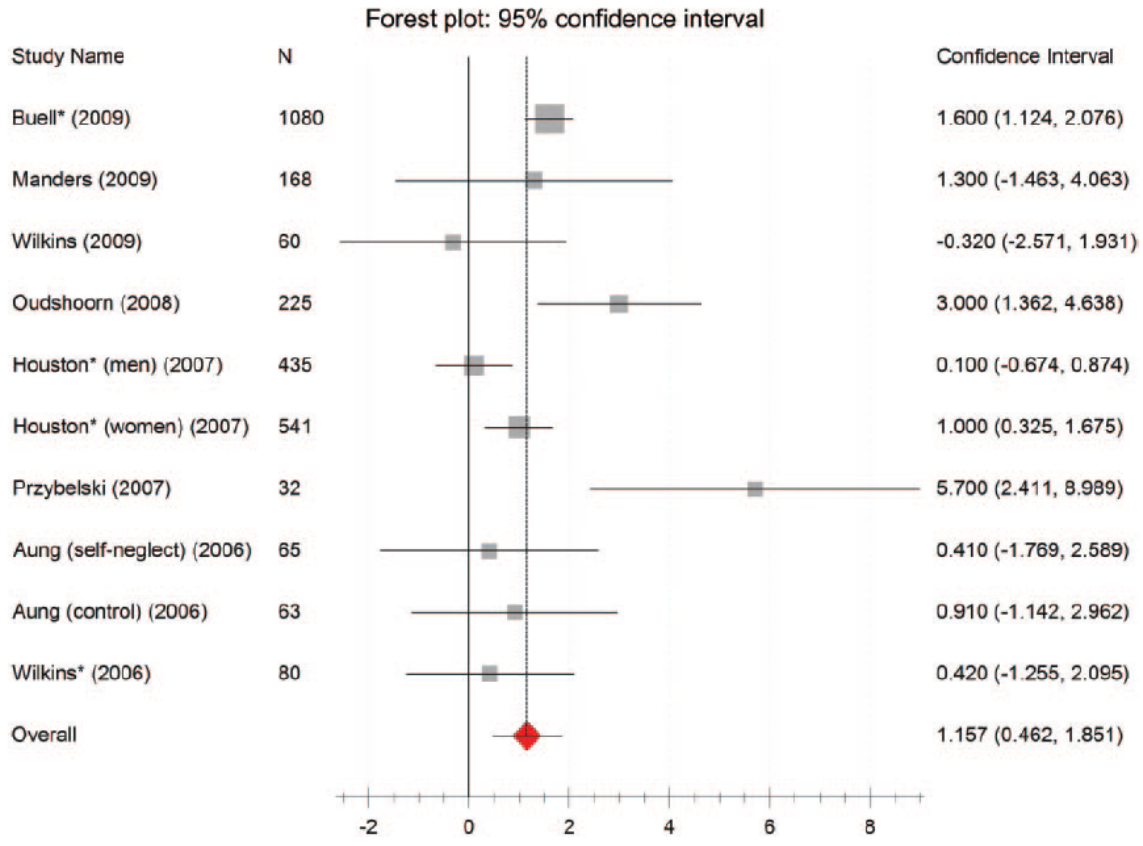


Neurology, 2012

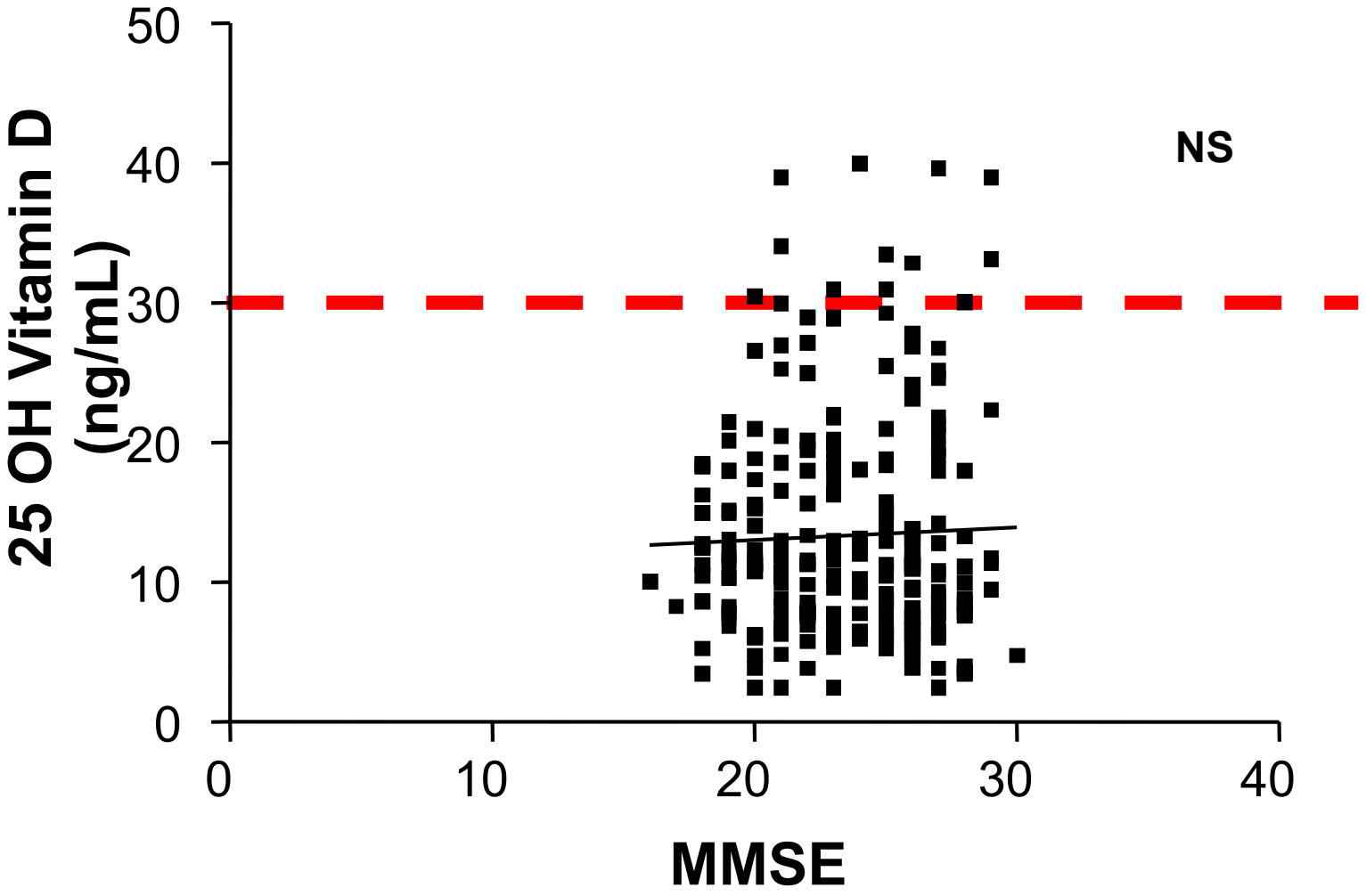
Vitamin D, cognition, and dementia

A systematic review and meta-analysis

Figure 3 Mini-Mental State Examination and vitamin D group (<50 nmol/L and ≥50 nmol/L)

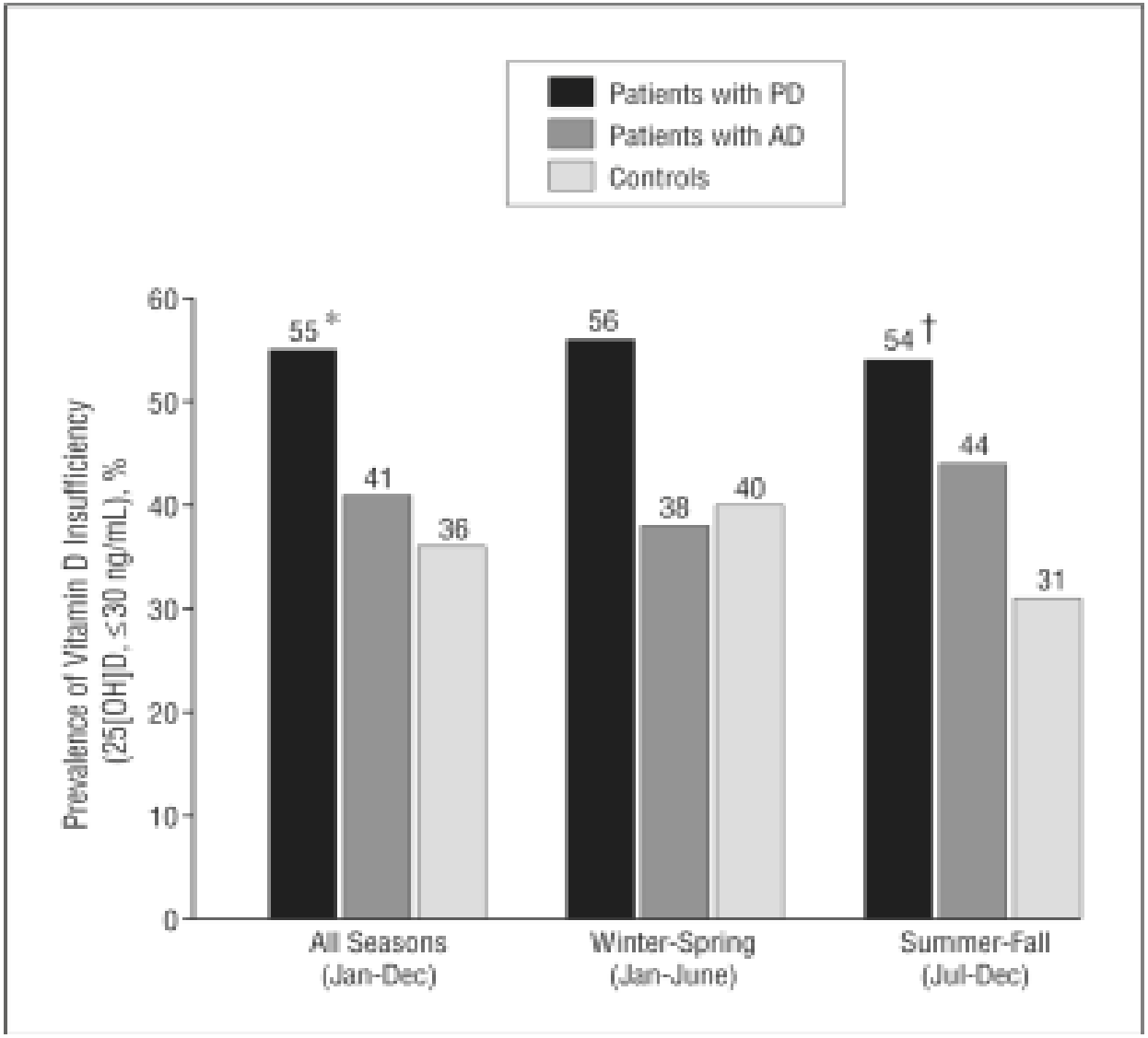


Neurology, 2012



D'Amelio P & Isaia GC personal data (252 pts)

IPOVITAMINOSI D, PARKINSON E ALZHEIMER



Marian L. Evatt, MD Arch Neurol. 2008

Hypovitaminosis D and Cognitive impairment

Several mechanism have been proposed to explain why vitamin D deficiency may increase the odds of cognitive impairment.

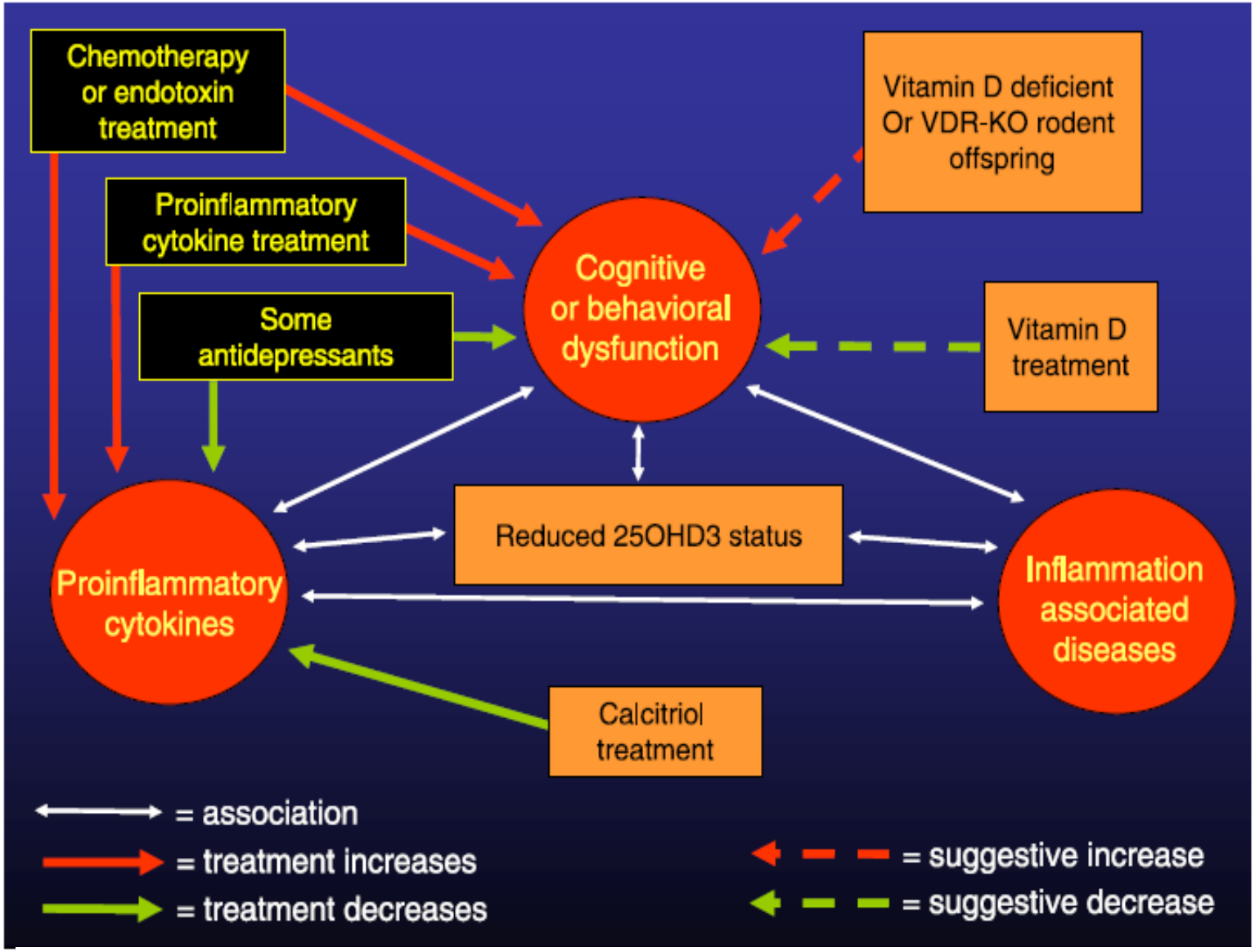
Vitamin D deficiency may increase risk of:

- Stroke
- Diabetes
- Hypertension

These conditions may in turn be associated with cognitive impairment

Vitamin D receptors are present in a wide variety of cells, including neurons and glial cells, and genes encoding the enzymes involved in the metabolism of vitamin D are also expressed in the brain

Llewellyn DJ, Lang IA, Langa KM, Melzer D.
Vitamin D and cognitive impairment in the elderly US population.
J Gerontol A Biol Sci Med Sci 2011



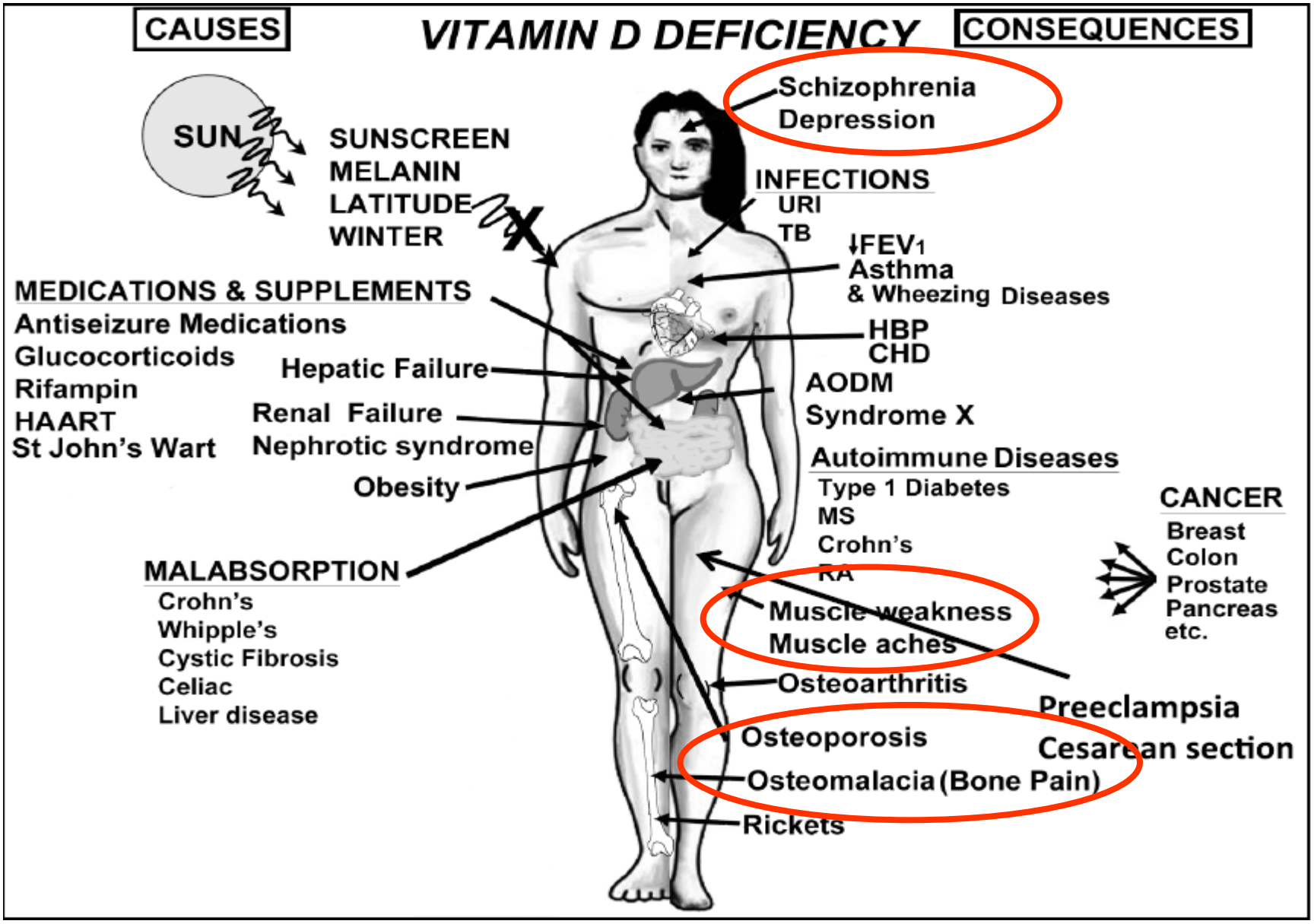
McCann JC, et al

Is there convincing biological or behavioral evidence linking vitamin D deficiency to brain dysfunction?

FASEB J 2008;

Figure 1. Vitamin D, proinflammatory cytokines, and cognitive or behavioral dysfunction. Types of evidence from human or rodent studies that link cognitive and behavioral performance to vitamin D adequacy, proinflammatory cytokine status, and inflammation-associated diseases. See text for discussion and citations.

Major Causes and Consequences of Vitamin D deficiency



Holick, M.F. The vitamin D deficiency pandemic: A forgotten hormone important for health. *Public Health Rev.* **2010**, *32*, 267–283.

CONCLUSIONI

L’ipovitaminosi D è una condizione molto diffusa in tutte le età, ma in misura più marcata negli anziani, nei quali determina sicuri effetti negativi sui tessuti scheletrico e muscolare.

Per documentare gli effetti positivi della Vitamina D a livello extrascheletrico e sulla patogenesi di numerose patologie croniche, in particolare sul deterioramento cognitivo, occorre disporre di ulteriori risultati, anche se molte evidenze suggeriscono che essa possa svolgere un ruolo significativo.

E’ comunque giustificato raccomandare, soprattutto agli anziani, di esporsi adeguatamente al sole, oppure di assumere cibi fortificati con Vitamina D e/o specifici preparati farmaceutici, i cui effetti tossici sono del tutto trascurabili alle usuali posologie di somministrazione.

Grazie per l’attenzione