



4° CONGRESSO NAZIONALE FRAGILITY FRACTURE NETWORK - ITALIA

*Appropriatezza, Qualità e Sostenibilità delle
Cure nel Percorso Ortogeriatrico*



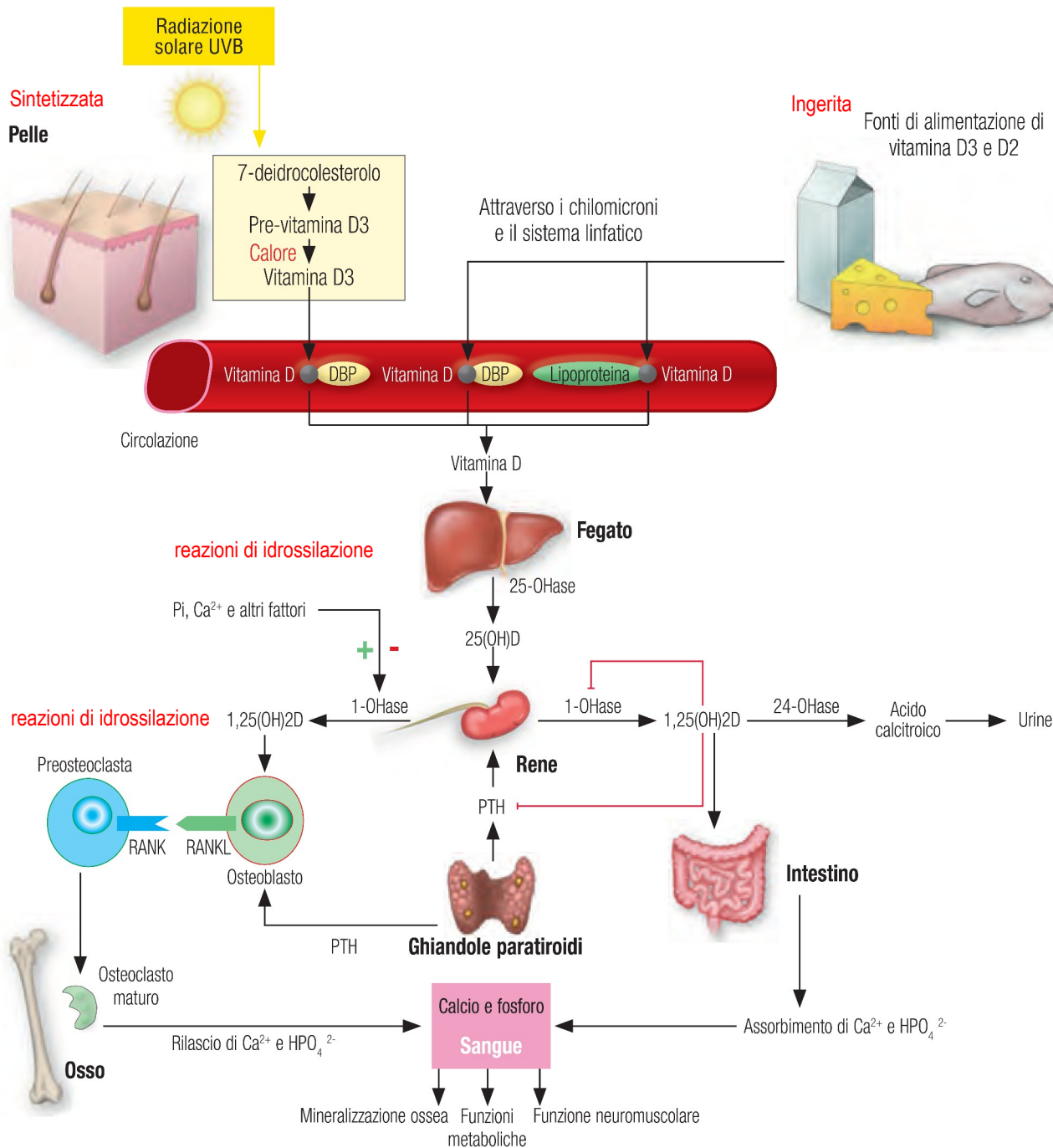
VII Sessione: Curare l'osteoporosi e prevenire le fratture

Vitamina D: vecchi e nuovi protagonisti

Carla Caffarelli

Università di Siena

Vitamina D

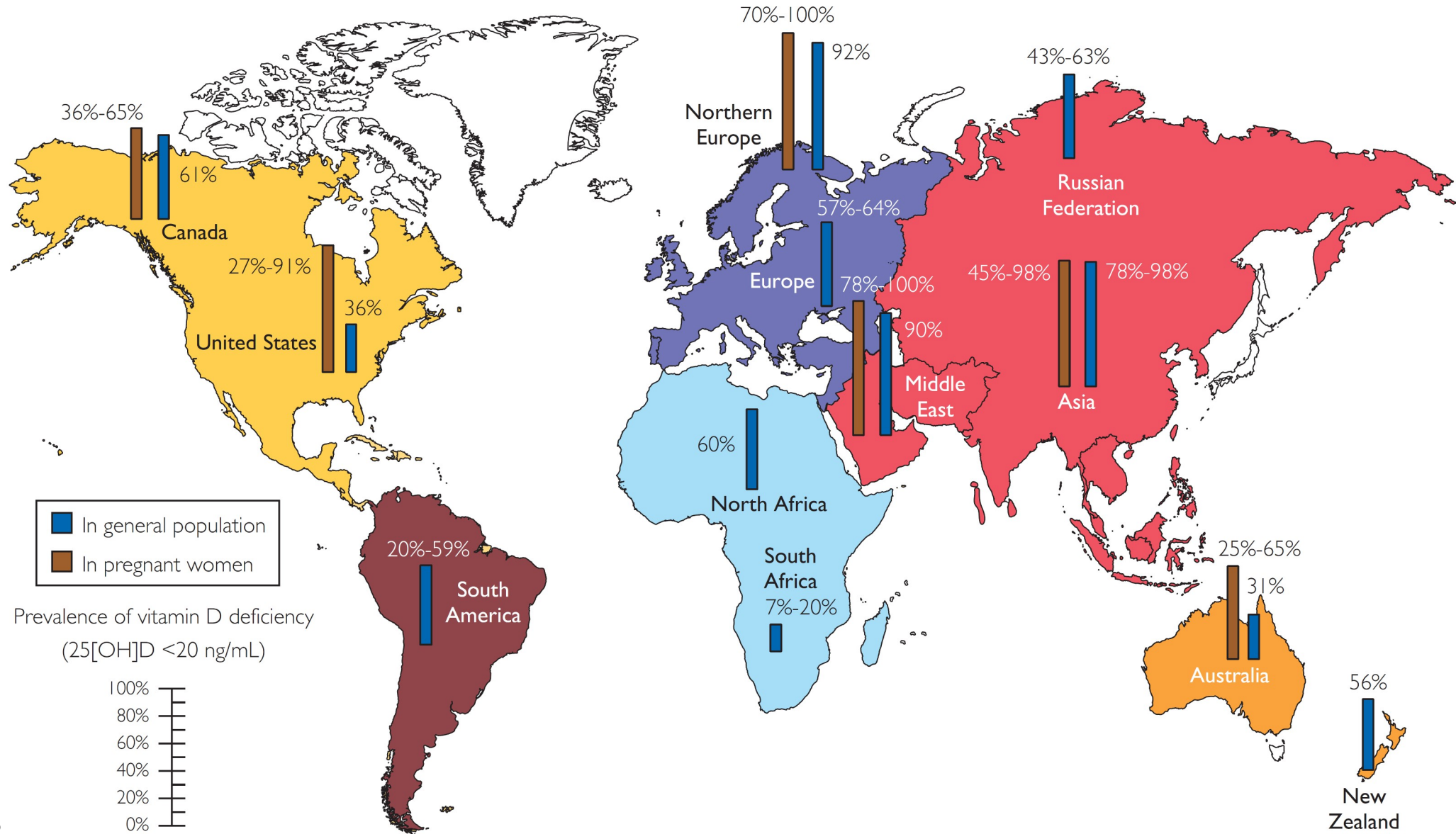


La **vitamina D** è un ormone fondamentale per mantenere l'omeostasi del calcio attraverso l'azione della sua forma attiva plasmatica (**1,25-(OH)₂VitD** o **calcitriolo**) e del recettore della vitamina D (**vitamin D receptor, VDR**).

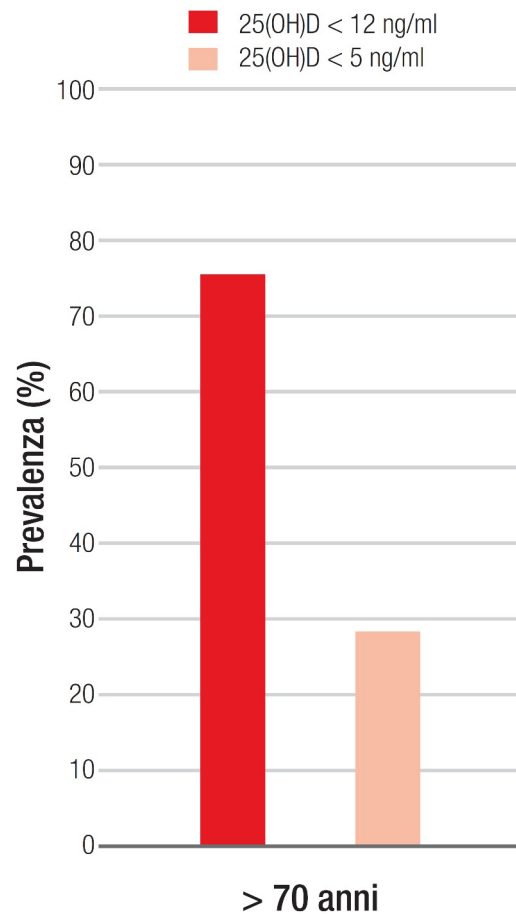
- **Intestino** – aumento dell'assorbimento di Ca^{2+} con meccanismo attivo e passivo
- **Tessuto osseo** – L'1,25(OH)₂D interagisce con R sugli OB producendo Osteocalcina e induce sugli OC attivazione RANK-RANKL
- **Tessuto muscolare** - L'1,25(OH)₂D stimola la produzione di proteine muscolari attiva alcuni meccanismi di trasporto del Ca^{2+} a livello del reticolo sarcoplasmatico essenziali per la contrazione muscolare.

Stato Vitaminico D

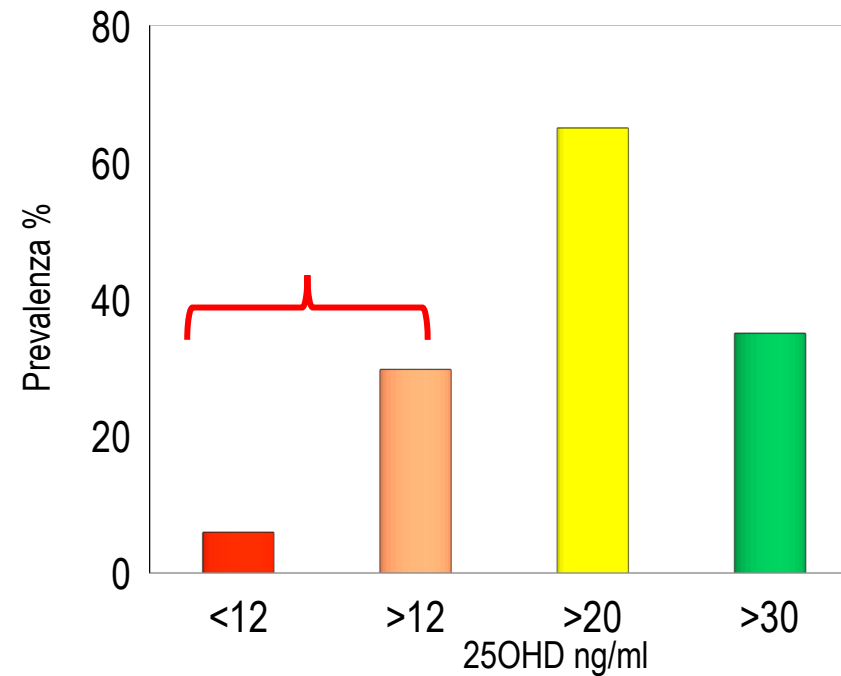
► Prevalenza di livelli sierici di Vitamina D < 20 ng/ml



Prevalenza dell'ipovitaminosi D nella popolazione italiana

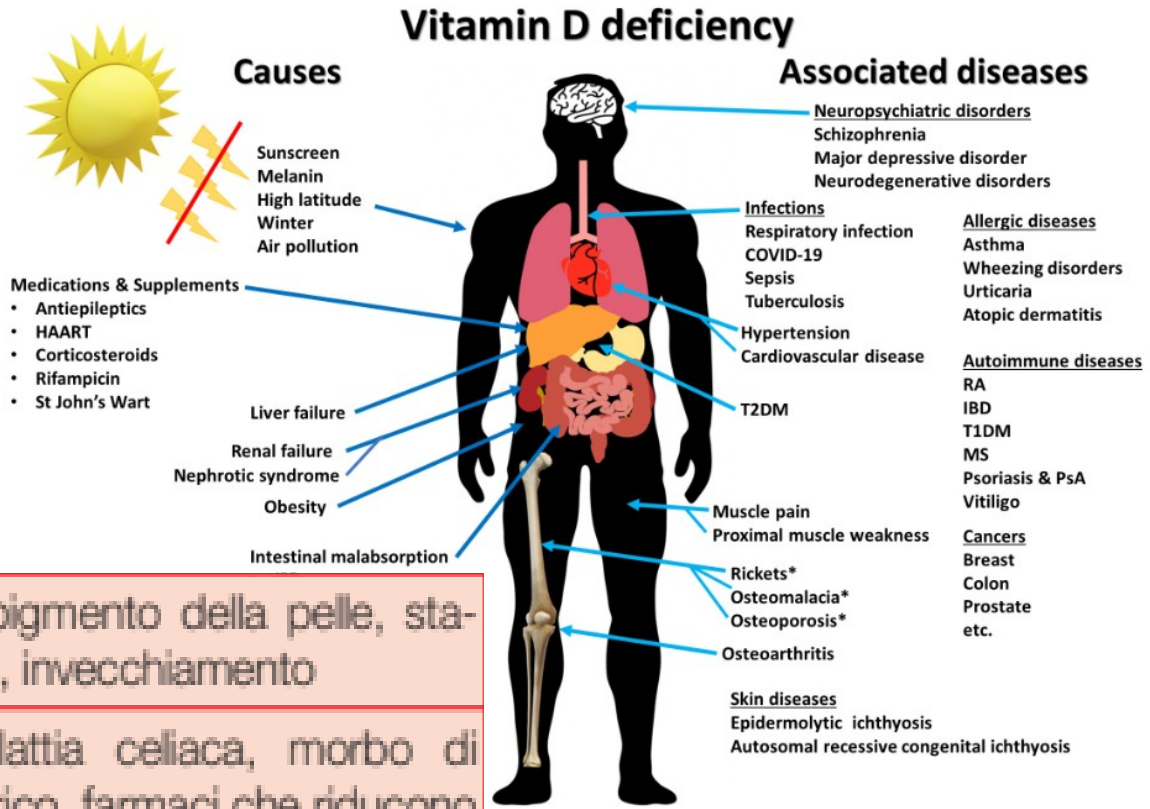


❖ **76%** delle donne italiane con > 70 aa aveva livelli sierici di 25OHD < 12 ng/ml al termine del periodo invernale



❖ **36%** delle donne italiane (età media 35 aa) aveva livelli sierici di 25OHD < 20 ng/ml

Le principali cause di ipovitaminosi D

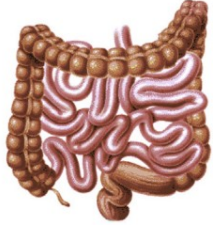


Sintesi cutanea ridotta	Protezione solare, pigmento della pelle, stagione/ora del giorno, invecchiamento
Diminuzione assorbimento	Fibrosi cistica, malattia celiaca, morbo di Crohn, bypass gastrico, farmaci che riducono l'assorbimento del colesterolo
Aumento del sequestro	Obesità (BMI > 30)
Aumento del catabolismo	Anti-convulsivanti, glucocorticoidi
Allattamento al seno	Senza supplementazione di vitamina D
Diminuzione della sintesi di 25-idrossivitamina D	Insufficienza epatica
Aumento della perdita urinaria di 25-idrossivitamina D	Proteinuria nefrosica
Diminuzione della sintesi di 1,25-diidrossivitamina D	Insufficienza renale cronica
Malattie ereditarie	Resistenza alla vitamina D



Vitamin D deficiency in the elderly

Resistance to 1,25(OH)₂D
 ↓ VDR
 postreceptor defects eg. in calcium transport proteins



↓ VDR
 ↓ CYP27B1 activity
 ↓ effect 1,25(OH)₂D on osteoblast differentiation
 ↑ adipocytes

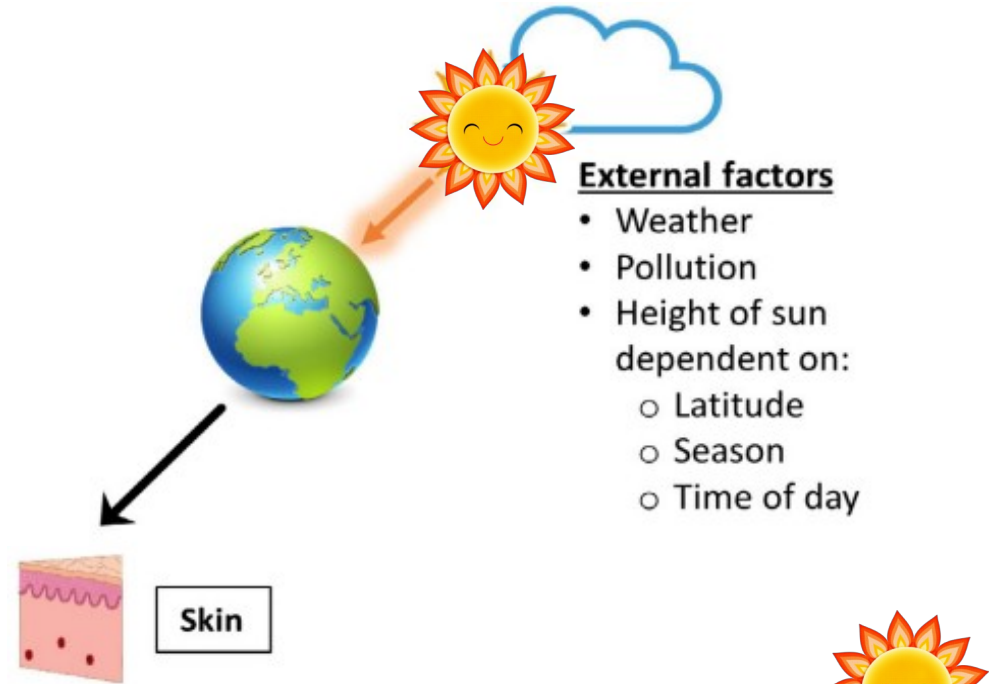
Aging

PTH resistance
 ↓ VDR
 ↓ CYP27B1 activity
 ↑ CYP24A1 activity
 ↓ calcium transport proteins



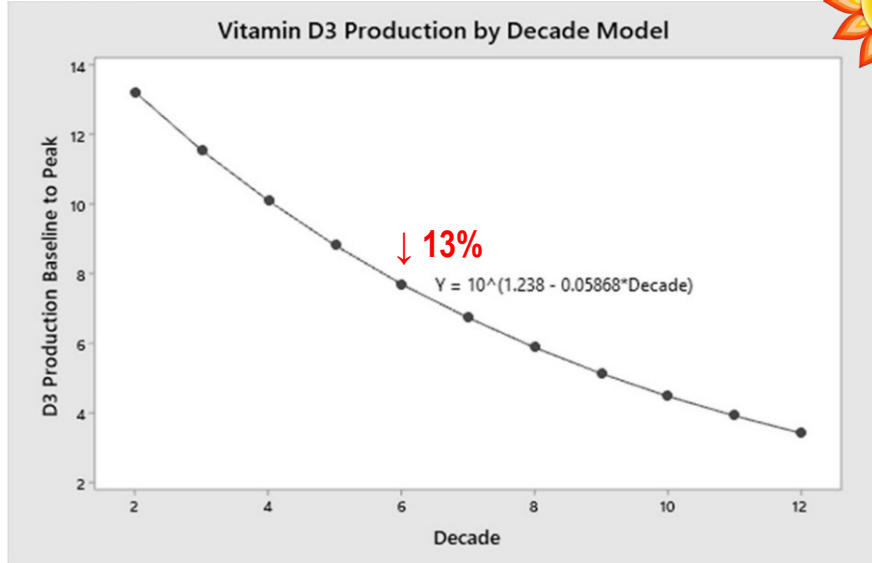
↓ VDR
 ↑ adipocytes
 ↑ protein turnover

Aging
Effects on the Vitamin D Endocrine System
 ↓ Intestinal calcium absorption (↓ TRPV6 and ↓ Calbindin)
 Vitamin D resistance
 ↓ Synthesis of 1,25(OH)₂D₃
 ↑ 24(OH)ase expression (↑ Catabolism of 1,25(OH)₂D₃)
 (↑ Age related bone loss)



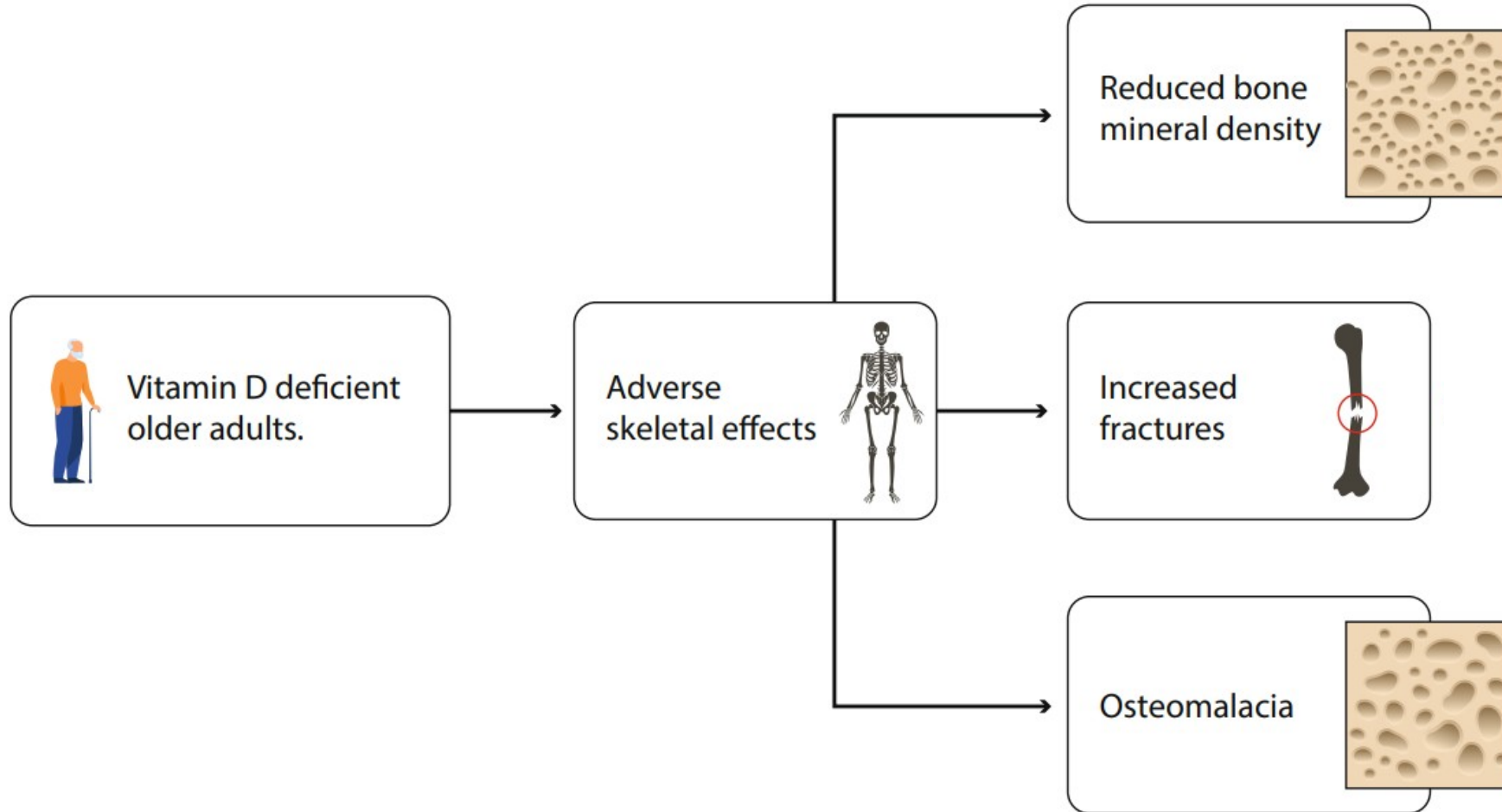
External factors

- Weather
- Pollution
- Height of sun dependent on:
 - Latitude
 - Season
 - Time of day

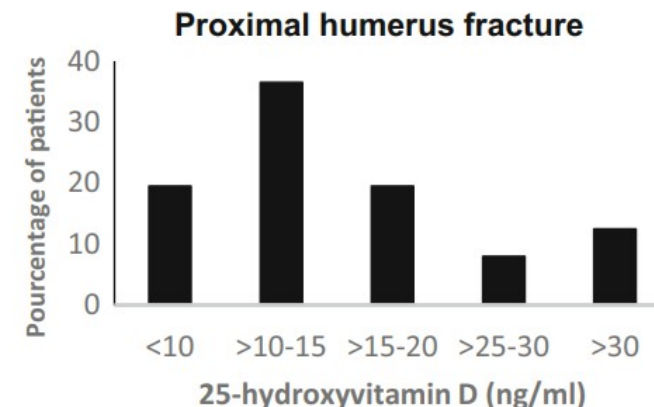
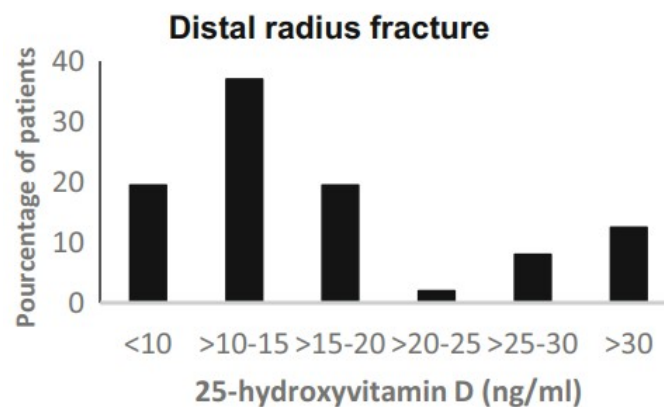
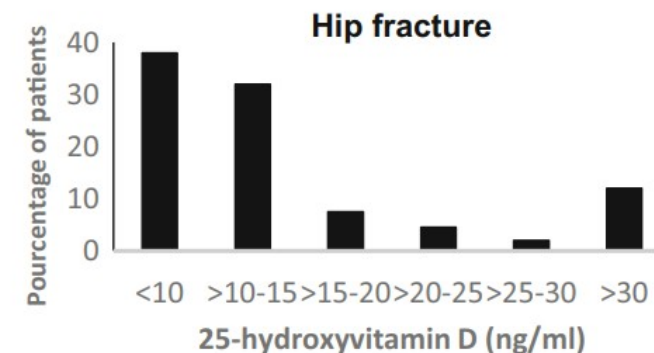
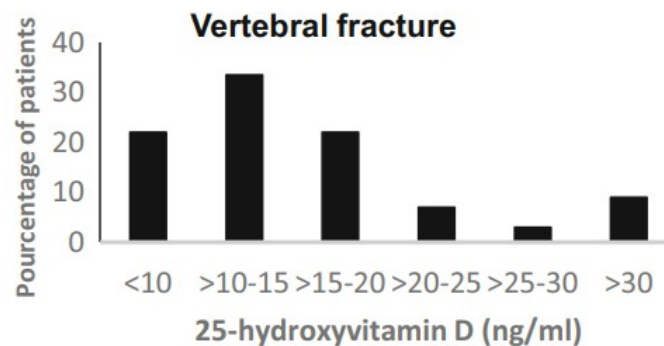




Skeletal effects of vitamin D deficiency in the elderly



Calcifediol (25-OHD) levels by fracture type

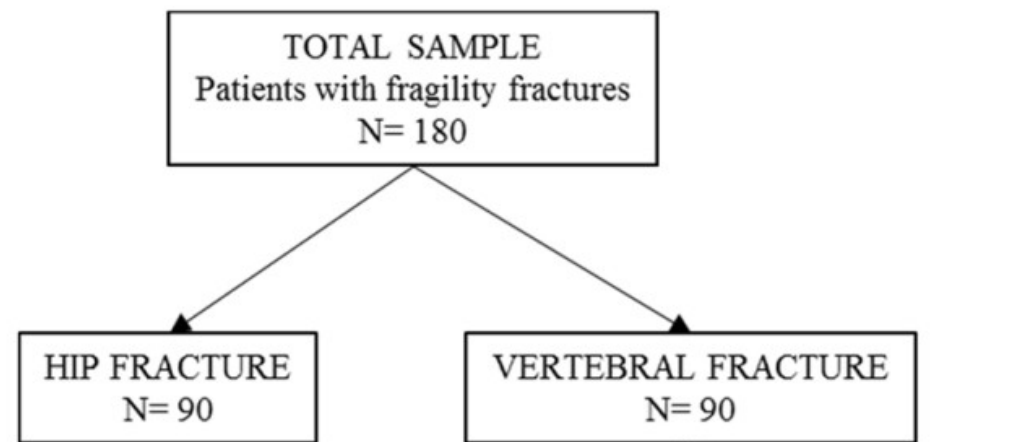


Study	Country	Population (% female)	Mean (SD) age, years	Mean (SD) 25(OH)D nmol/l	% 25(OH)D < 50 nmol/l
Awal et al. [40] [#]	Australia	313	79.5		34
Hao et al. [14] [*]	USA	290 (73)	82 (7)	55 (24)	46
Bischoff-Ferrari et al. [12] [*]	Switzerland	222 (77)	86	34.6 (community) 24 (nursing homes)	80
Cher et al. [41] [*]	Singapore	801 (71)	77.7 (8)	-	47.4
Niikura et al. [44] [*]	Japan	360 878)	84.7 (8.2)	41.3 (18)	71.7
Papaiannou et al. [45] [*]	Canada	65 (56)	78.5 (10.3)	52.3	-
Ish-Shalom et al. [46] [*]	Israel	48 (100)	81 (89)	39.3 (25.3)	-
Mak et al. [47] [*]	Australia	218 (77)	83.9 (7.2)	52.7 (23.5)	47
Moo et al. [48] [*]	Singapore	796 (71)	77.7 (8)	50.1 (18.5)	53.9

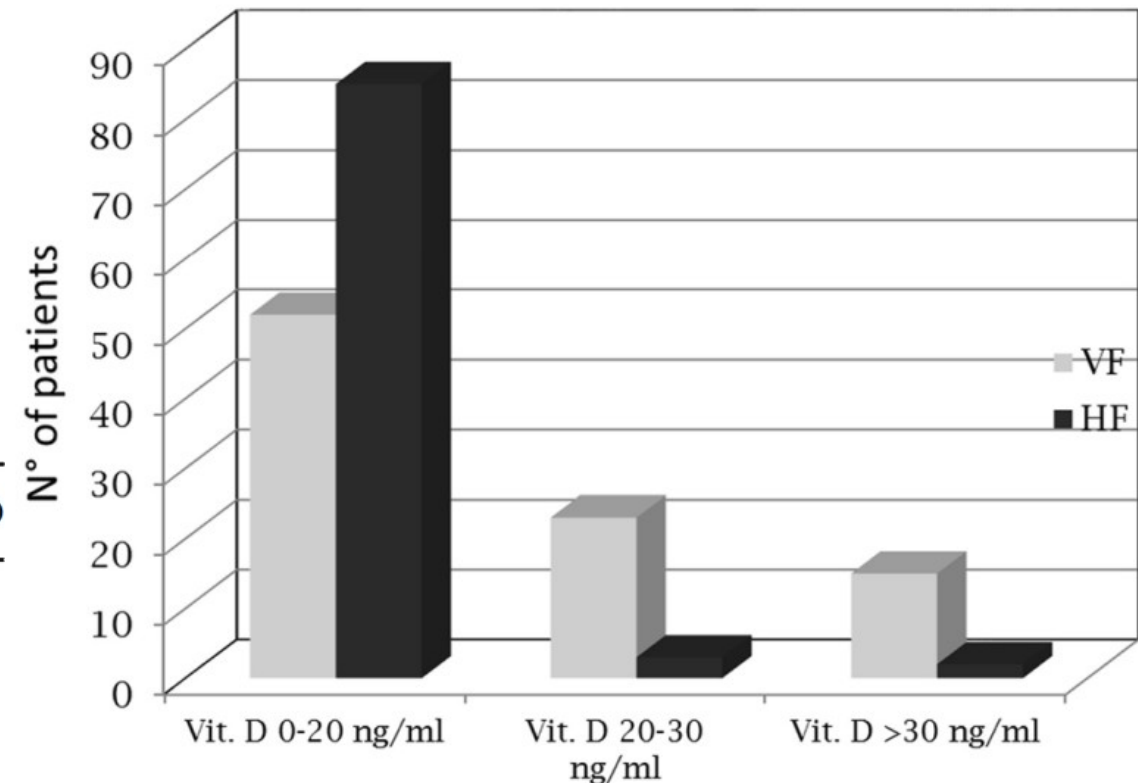


Hypovitaminosis D: comparison between patients with hip fracture and patients with vertebral fractures

S. Giordano¹ · A. Proietti¹ · T. Bisaccia¹ · P. Caso¹ · A. Martocchia¹ · P. Falaschi¹ · L. Tafaro¹ 



	Total average ± SD	VF average ± SD	HF average ± SD
Age	77.1 ± 6,7	76,6 ± 6,5	77.6 ± 6.8
Vitamin D ng/ml	13.2 ± 9,6	18.7 ± 9.7	7.9 ± 5.7*
PTH pg/ml	67.5 ± 54,9	55.8 ± 27.3	78.7 ± 70.3 *





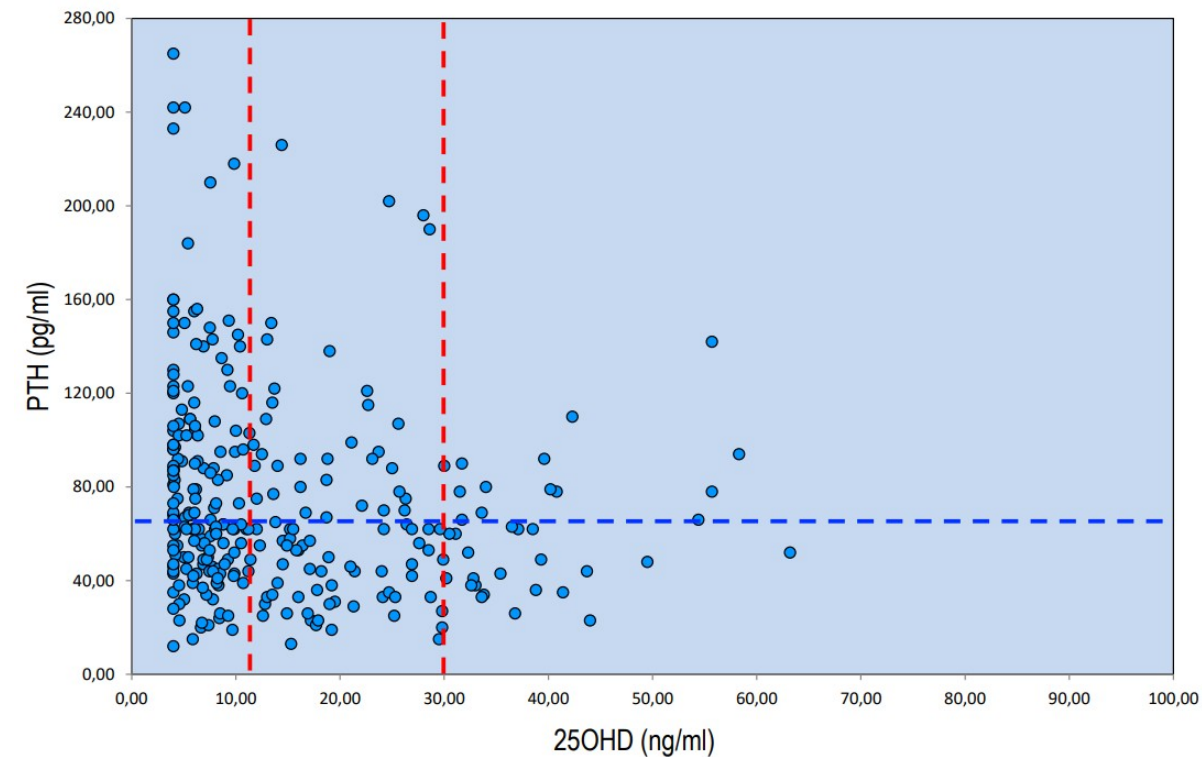
Article

The Phenotype of Bone Turnover in Patients with Fragility Hip Fracture: Experience in a Fracture Liaison Service Population

Carla Caffarelli ¹, Nicola Mondanelli ² , Eduardo Crainz ³, Stefano Giannotti ², Bruno Frediani ⁴ and Stefano Gonnelli ^{1,*}

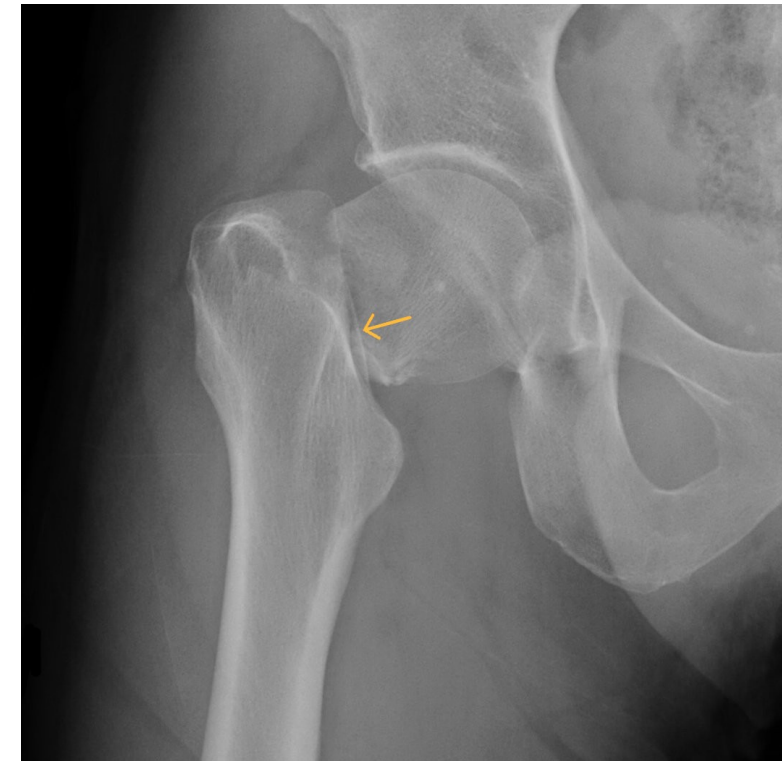
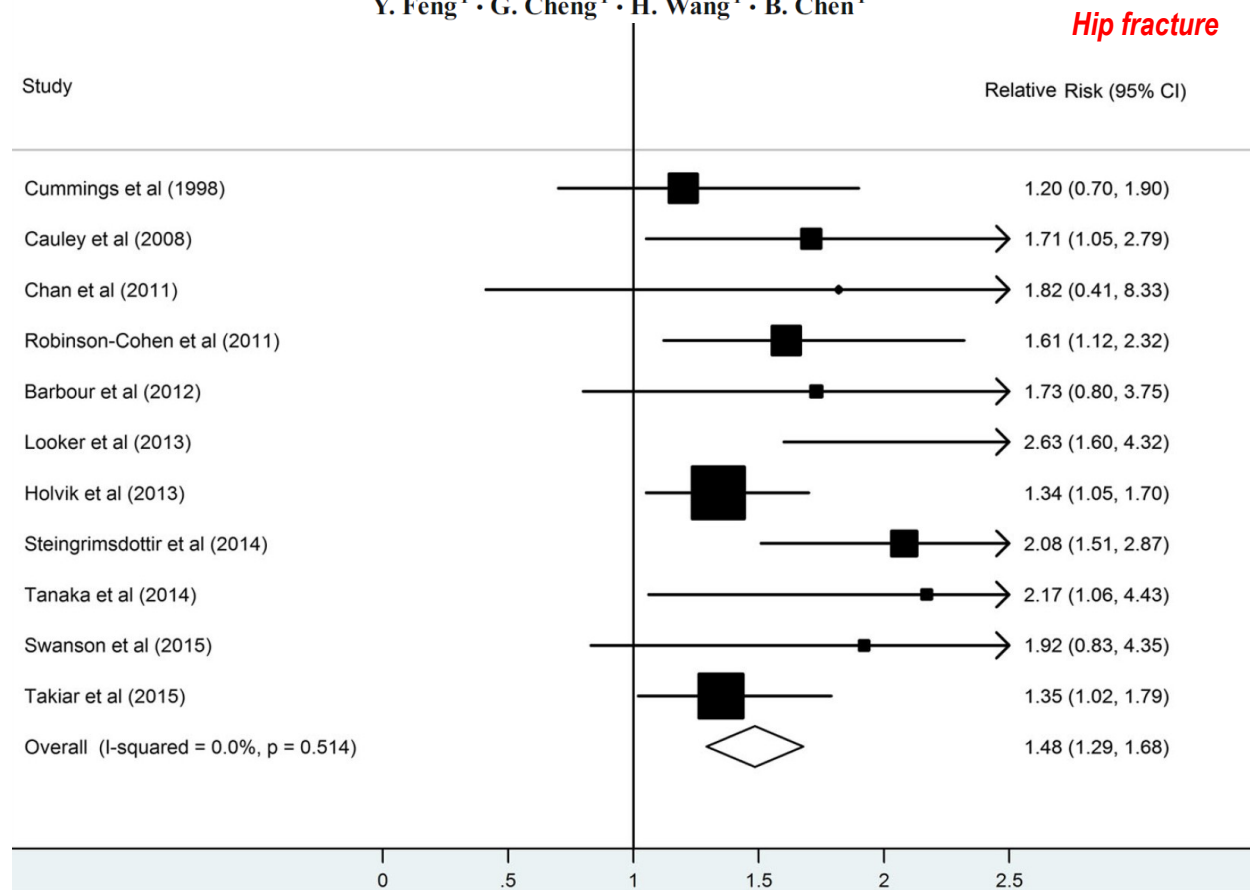
	Fratture di femore (N = 363)	Controlli (N = 194)
Sesso (F/M)	289/74	140/54
Età (anni)	84. ± 9.2	72.8 ± 2.6**
BMI (Kg/m ²)	24.1 ± 4.9	25.9 ± 2.9**
Creatinina (mg/dl)	0.92 ± 0.32	0.95 ± 0.20*
Calcio (mg/dl)	8.24 ± 0.56	9.24 ± 0.52**
Fosforo (mg/dl)	2.98 ± 0.82	3.31 ± 0.60**
➔ ALP (UI/L)	83.62 ± 42.19	75.84 ± 28.66
➔ 25OHD (ng/ml)	14.90 ± 13.88	24.70 ± 9.10**
PTH (pg/ml)	77.80 ± 55.01	23.99 ± 13.60**
B-ALP (µg/L)	11.60 ± 7.10	11.80 ± 5.43
β-CTX (ng/L)	1.250 ± 0.500	0.616 ± 0.296**

* p<0.05; ** p< 0.01 Fratture di femore vs controlli



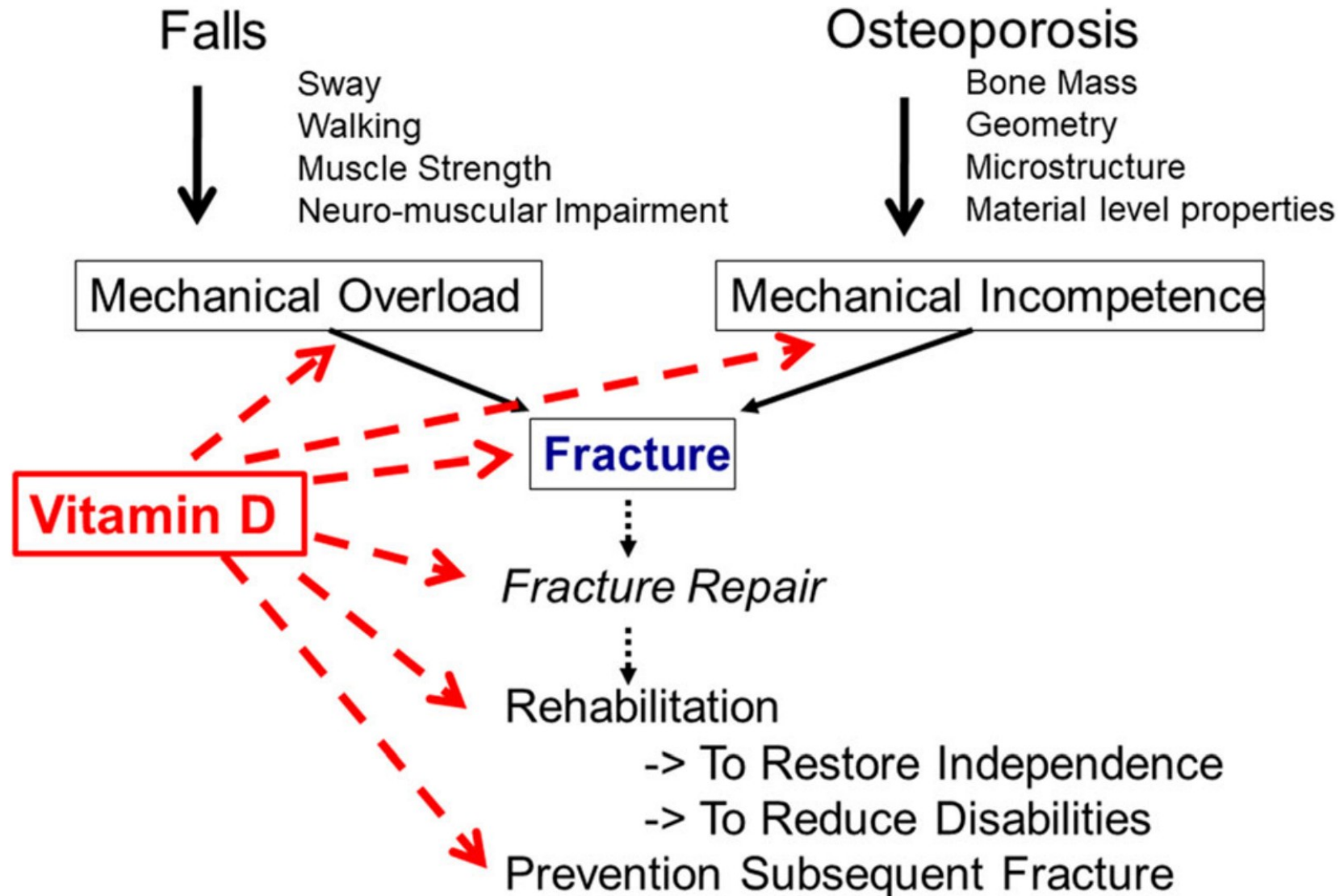
The associations between serum 25-hydroxyvitamin D level and the risk of total fracture and hip fracture

Y. Feng¹ · G. Cheng¹ · H. Wang¹ · B. Chen¹



❖ Valori inferiori a 20 ng/ml (50 nmol/l) sono indicativi di un aumento del 40% del rischio di frattura di femore per ogni calo di una DS dei valori di 25(OH)D

Role of vitamin D in the pathogenesis and management of osteoporotic fractures



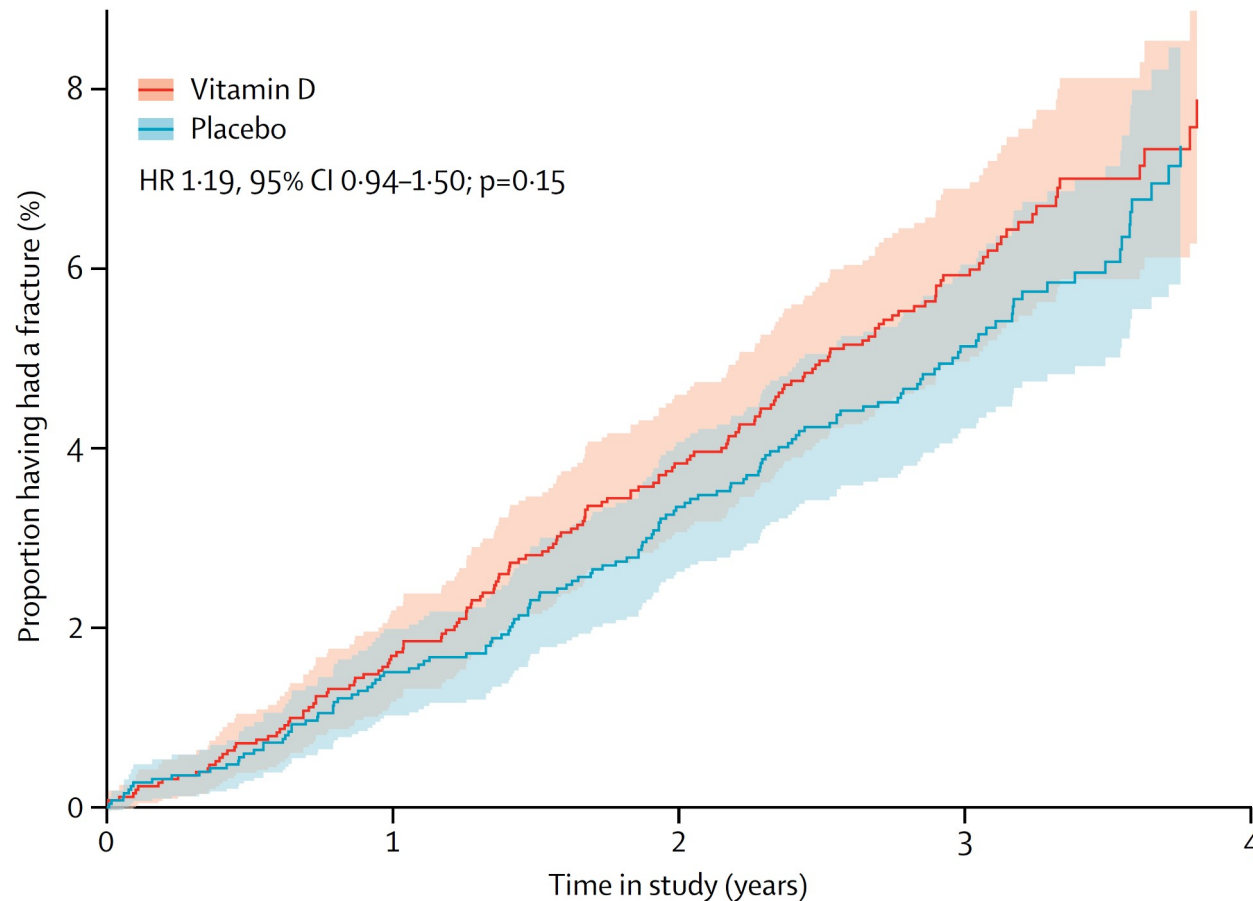


Effect of monthly high-dose vitamin D supplementation on falls and non-vertebral fractures: secondary and post-hoc outcomes from the randomised, double-blind, placebo-controlled ViDA trial



Kay-Tee Khaw, Alistair W Stewart, Debbie Waayer, Carlene M M Lawes, Les Toop, Carlos A Camargo Jr, Robert Scragg

Lancet Diabetes Endocrinol 2017



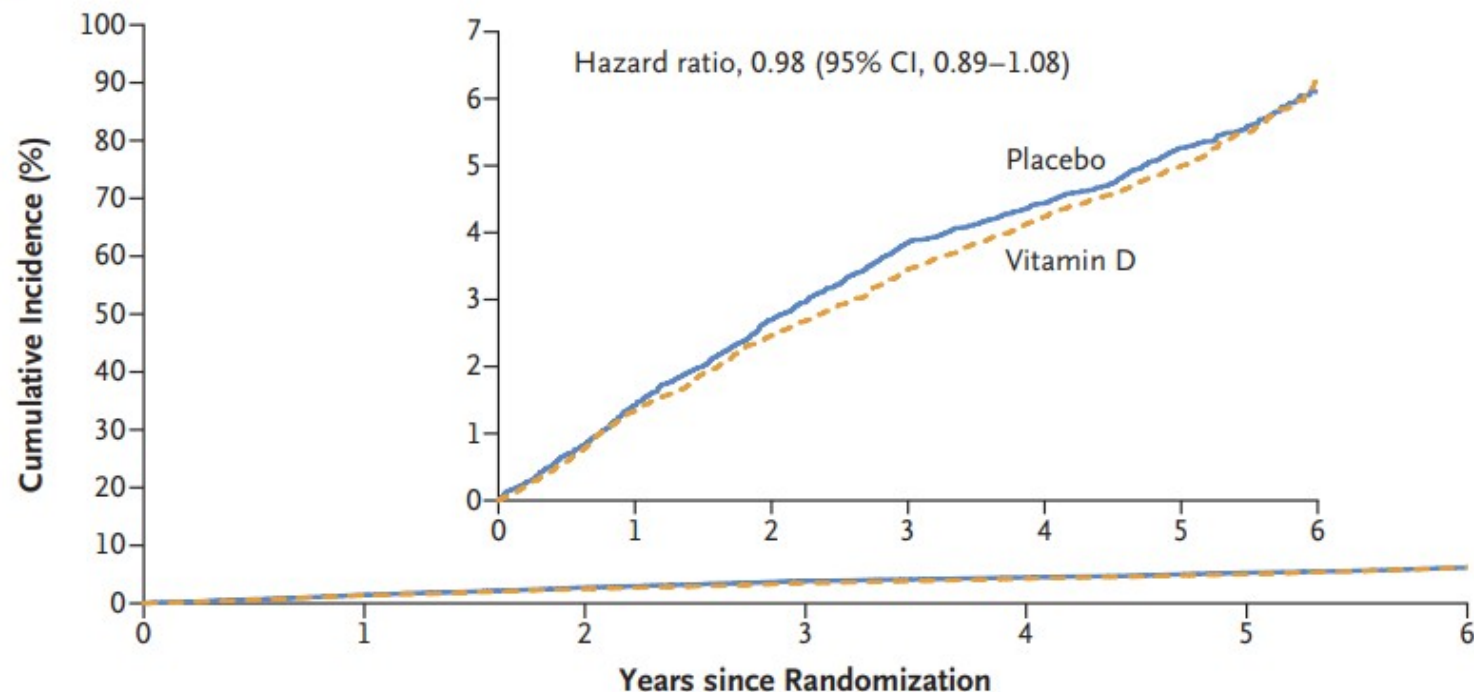
In un ampio studio clinico randomizzato e controllato su **adulti sani**, dosi pur elevate di colecalciferolo (pari a 100.000/UI al mese) per circa 4 anni non comportavano alcun vantaggio in termini di rischio di cadute e di frattura rispetto al braccio del placebo. L'80% della popolazione studiata aveva valori basali di **25OHD > 25 ng/ml**.

Non vi sono evidenze che valori di **25(OH)D > 20 ng/ml** comportino vantaggi sulla salute dello scheletro (BMD o fratture) nella popolazione generale.

Supplemental Vitamin D and Incident Fractures in Midlife and Older Adults

Meryl S. LeBoff, M.D., Sharon H. Chou, M.D., Kristin A. Ratliff, B.A., Nancy R. Cook, Sc.D., Bharti Khurana, M.D.,

Total Fractures



No. at Risk

Placebo	12,927	12,737	12,578	12,438	12,218	9830	793
Vitamin D	12,944	12,742	12,561	12,399	12,188	9785	782

The NEW ENGLAND JOURNAL of MEDICINE

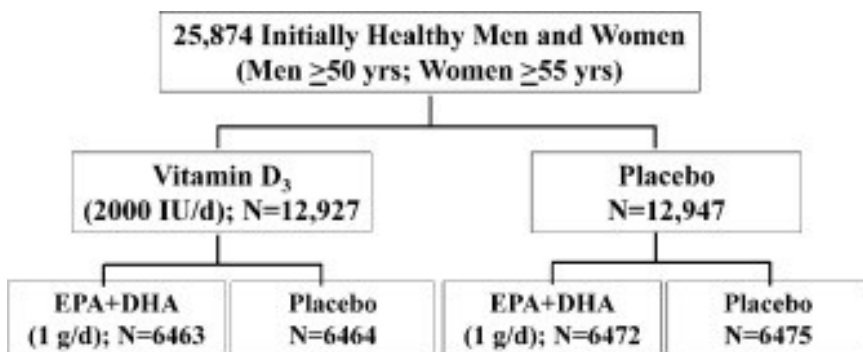
ESTABLISHED IN 1812

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Supplemental Vitamin D and Incident Fractures in Midlife and Older Adults

Meryl S. LeBoff, M.D., Sharon H. Chou, M.D., Kristin A. Ratliff, B.A., Nancy R. Cook, Sc.D., Bharti Khurana, M.D.,



Mean Treatment Period = 5.0 years

Blood collection in 16,956, follow-up samples in ~6000

Primary Outcomes: Cancer (total) and CVD (MI, stroke, CVD death)

Characteristic	Total (N=25,871)	Vitamin D Group (N=12,927)	Placebo Group (N=12,944)
Female sex — no. (%)	13,085 (50.6)	6,547 (50.6)	6,538 (50.5)
Age — yr	67.1±7.1	67.1±7.0	67.1±7.1
Baseline 25-hydroxyvitamin D level — ng/ml	30.7±10.0	30.7±10.0	30.7±10.0
Baseline calcium level — mg/dl**	9.00±1.61	9.00±1.61	9.00±1.61

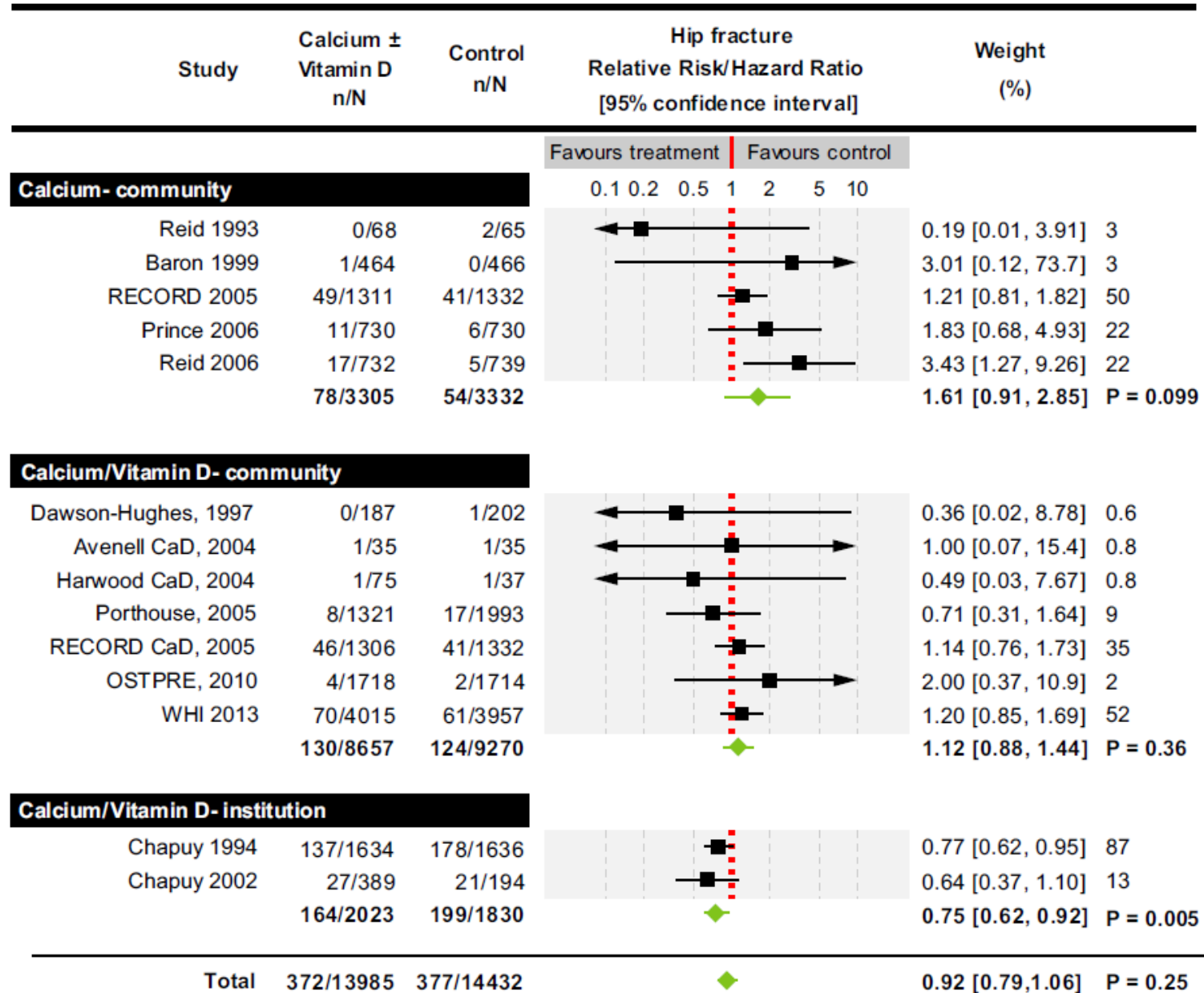
Health Effects of Vitamin D Supplementation: Lessons Learned From Randomized Controlled Trials and Mendelian Randomization Studies

Roger Bouillon,¹ Meryl S LeBoff,² and Rachel E Neale³

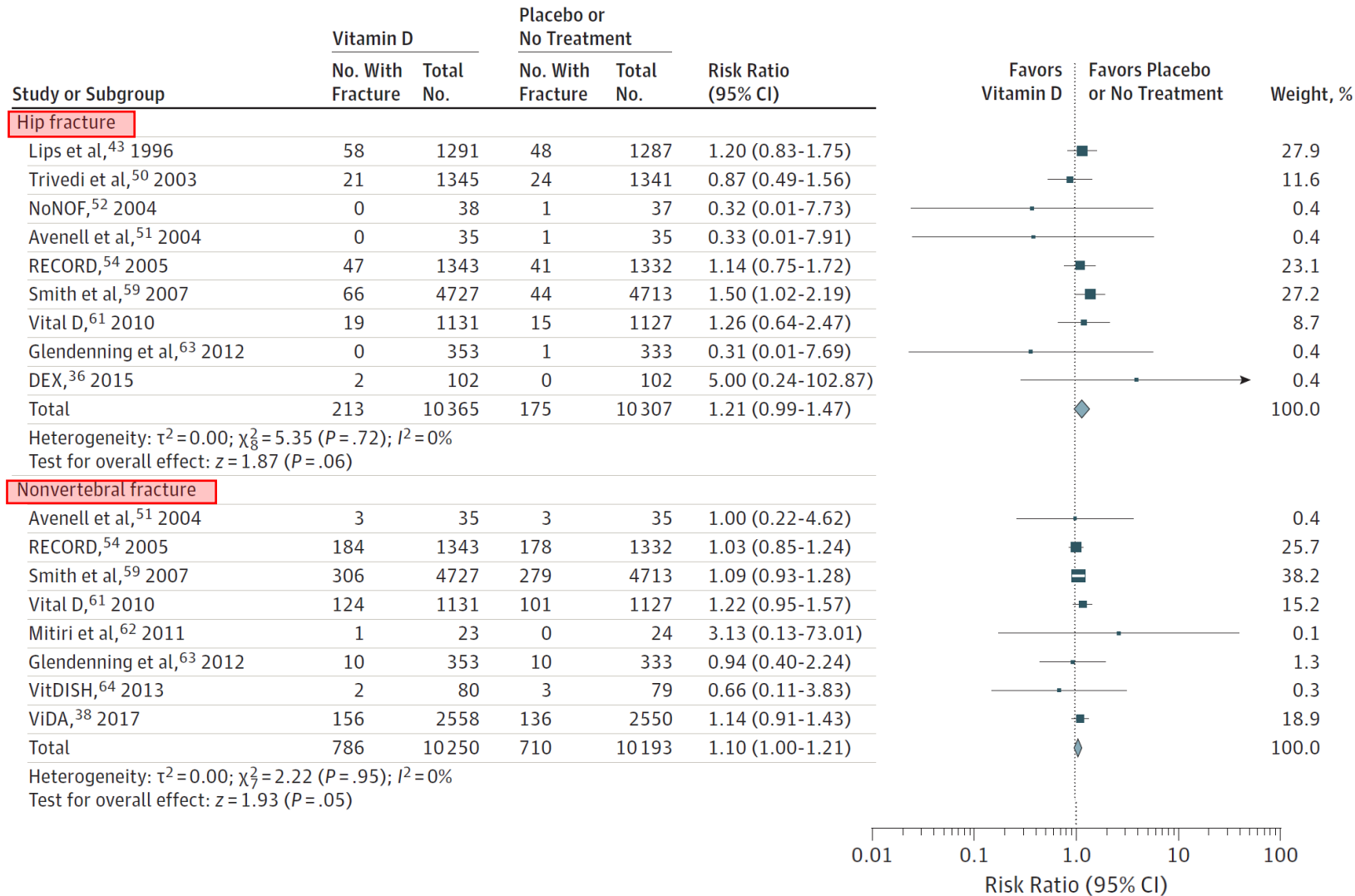
Summary

There is increasing evidence for a role of vitamin D in outcomes beyond the musculoskeletal system, particularly for all-cause mortality and outcomes related to effects on the immune system. Our summary of recent data is not intended to be a replacement for existing guidelines on the use of vitamin D and/or calcium. The recent data do not demonstrate a benefit of vitamin D supplementation for skeletal and extraskeletal health of adults with a good vitamin D status at baseline (mean serum 25(OH)D above 25 ng/mL). Some trials, however, generated data that long-term vitamin D supplementation may have some benefit for prediabetic subjects or have modest effect on cancer mortality, but additional studies are needed to validate these data. However, avoiding low vitamin D levels (25(OH)D <50 nmol/L) is likely to have benefits beyond musculoskeletal health, particularly for infectious disease, multiple sclerosis, and autoimmune diseases, and in some of these clinical conditions precision preventive health may be beneficial. Implementing policies that ensure most people are vitamin D replete may have widespread benefit. In some areas of the world, infants and children do not have access to sufficient vitamin D or calcium and are therefore at risk of nutritional rickets. In some countries, with limited sun exposure and a high prevalence of vitamin D deficiency, it may be better to intervene at a population level through food fortification, recognizing that, depending on the foods fortified, some people may still require individually prescribed supplements. Vitamin D testing is expensive and, in most clinical settings, not particularly accurate. Thus, rather than testing, it may be better to assess a person's risk of vitamin D deficiency based on sun exposure habits and recommend a modest supplement dose (1000–2000 IU/d); this may have benefit and is unlikely to cause harm.

The effects of calcium alone or with vitamin D on hip fracture risk



Meta-analysis Results of Vitamin D Supplementation for the Incidence of Hip, Nonvertebral Fractures



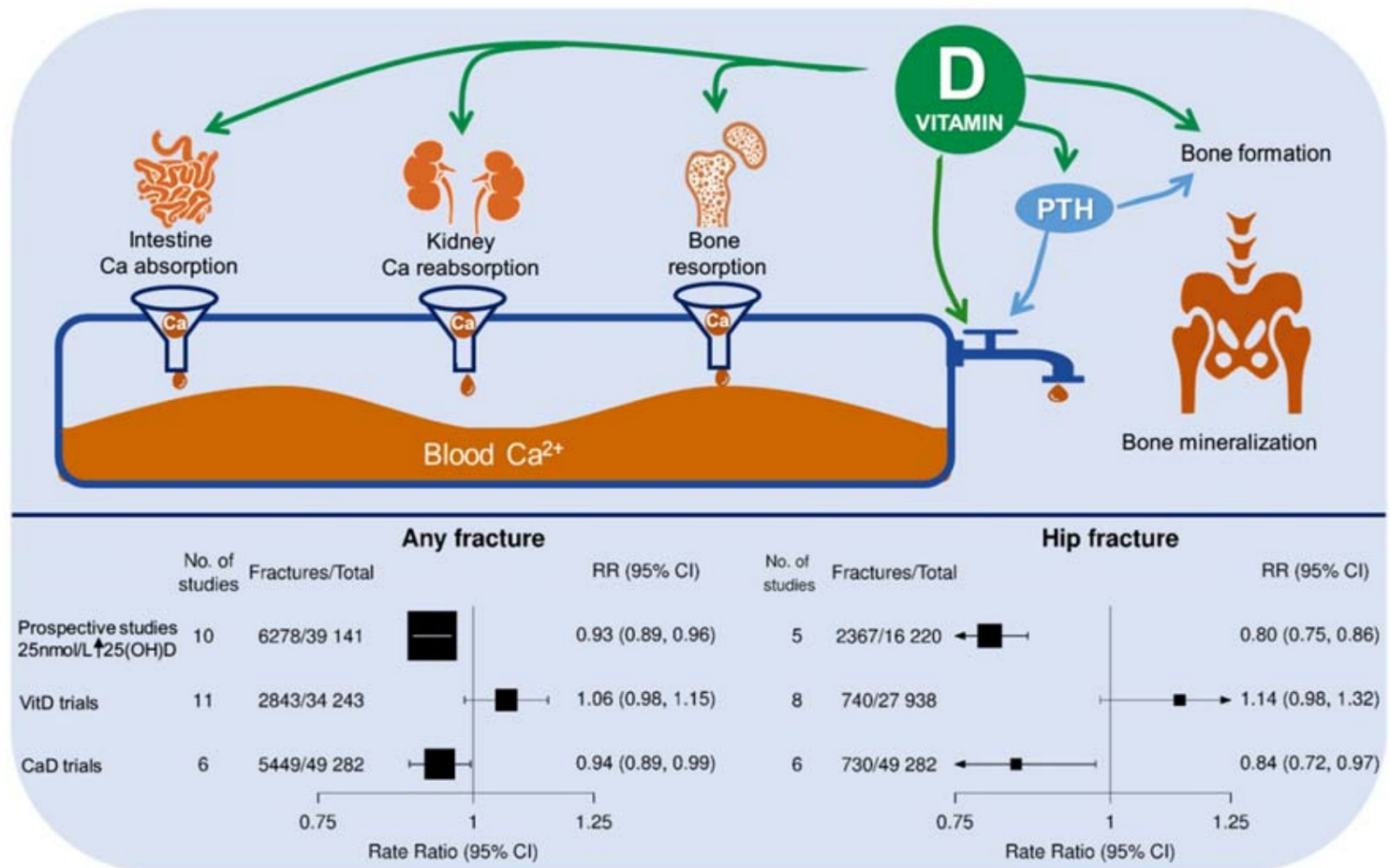
Original Investigation | Public Health

Vitamin D and Calcium for the Prevention of Fracture

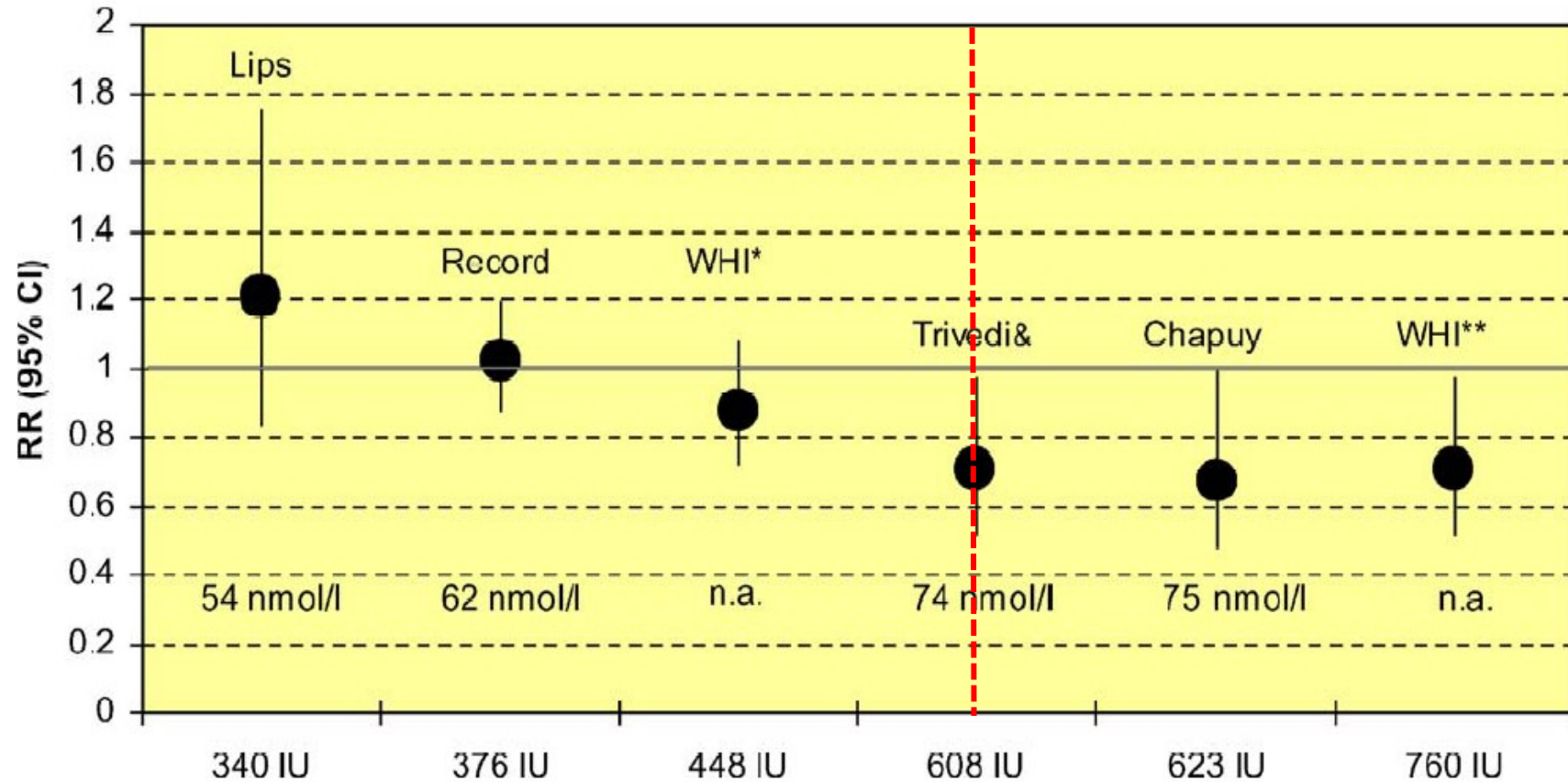
A Systematic Review and Meta-analysis

Pang Yao, PhD; Derrick Bennett, PhD; Marion Mafham, MD; Xu Lin, MD, PhD; Zhengming Chen, DPhil; Jane Armitage, FRCP; Robert Clarke, FRCP, MD

- **11 observational studies** (39 141 participants, 6278 fractures, 2367 hip fractures)
- **11 RCTs** (34 243 participants, 2843 fractures, 740 hip fractures) of vitamin D
- **6 RCTs** (49 282 participants, 5449 fractures, 730 hip fractures) of Vitamin D + calcium

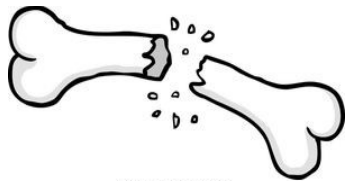


Hip fracture risk and estimated vitamin D intake



- ❖ L'effetto antifratturativo aumenta con l'aumento della dose di Vit D assunta
- ❖ Studi che hanno avuto dimostrato una riduzione delle fratture si è verificato per valori > 600 UI/die da raggiungere livelli medi di 25(OH)D ≥ 75 nmol/l.





Use of antiosteoporotic drugs and calcium/vitamin D in patients with fragility fractures: impact on re-fracture and mortality risk

Luca Degli Esposti¹ · Anna Girardi¹ · Stefania Saragoni¹ · Stefania Sella⁴ · Margherita Andretta² · Maurizio Rossini³ · Sandro Giannini⁴ · on the behalf of the Study group

Study design

Administrative Database:

- Hospital Discharge Database (Napoli³, Verona, Udine, Frosinone, Pescara)

Enrollment criteria:

- At least one hospitalization discharge diagnosis of vertebral or femoral fracture from January 1, 2011 to June 30, 2015 (the date of the first discharge diagnosis is defined index-date).

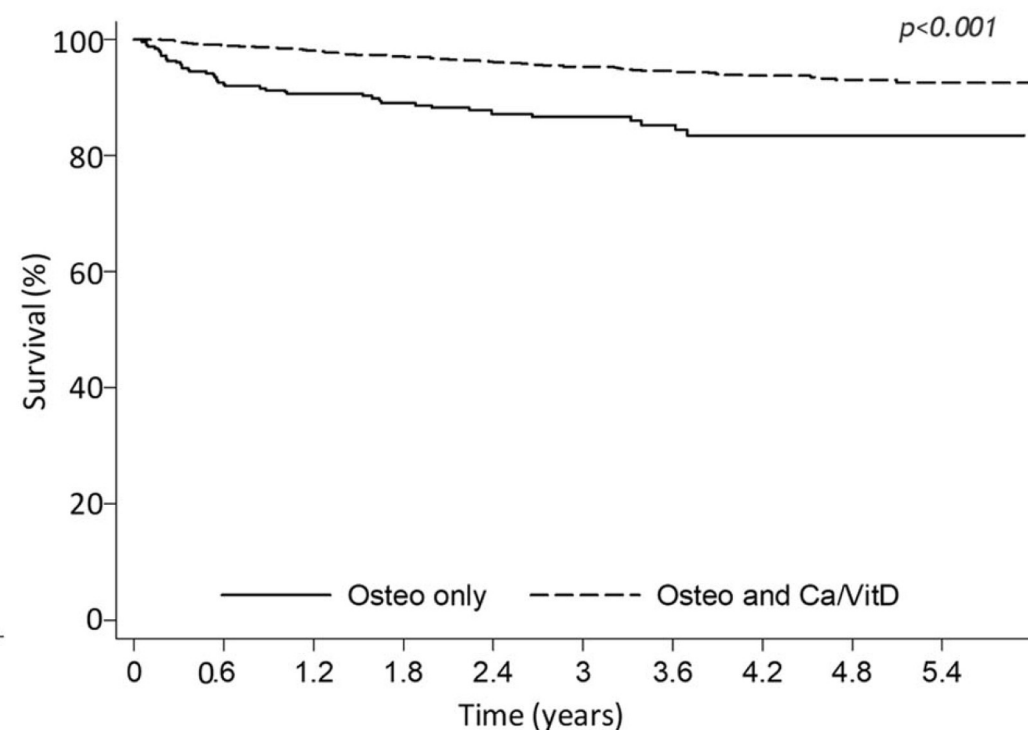
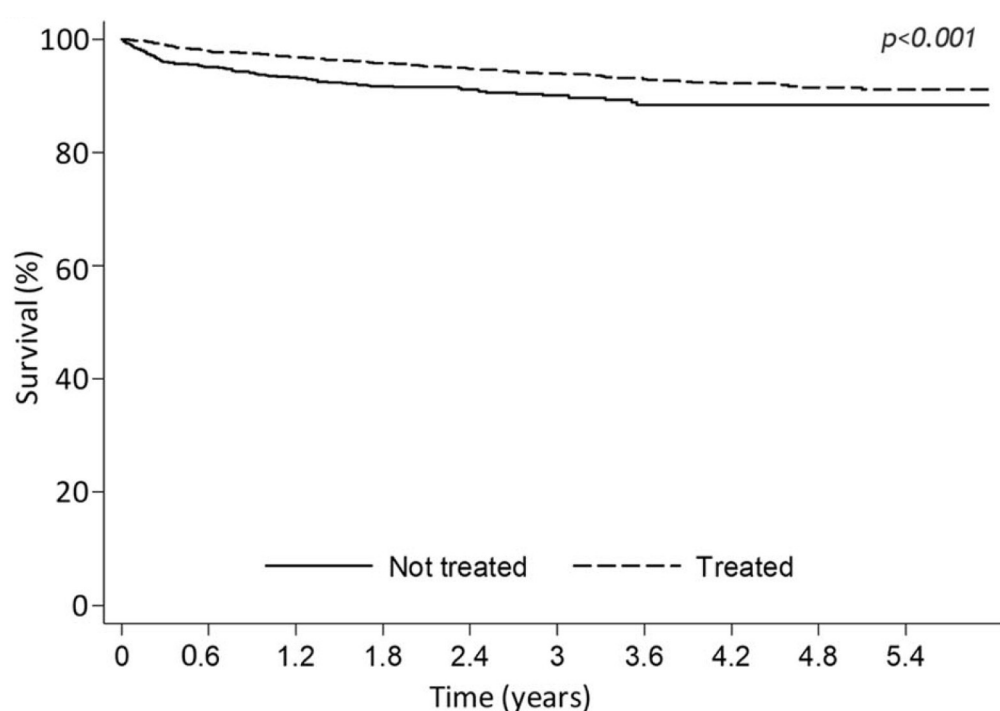
Outcomes:

- Re-fracture episodes or death up to June 30, 2016



Use of antiosteoporotic drugs and calcium/vitamin D in patients with fragility fractures: impact on re-fracture and mortality risk

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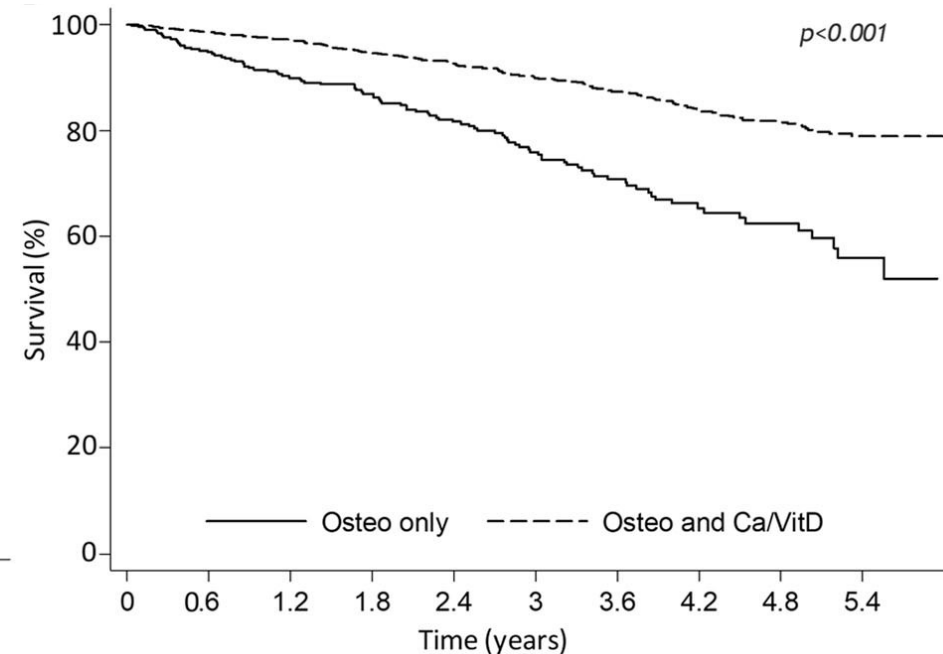
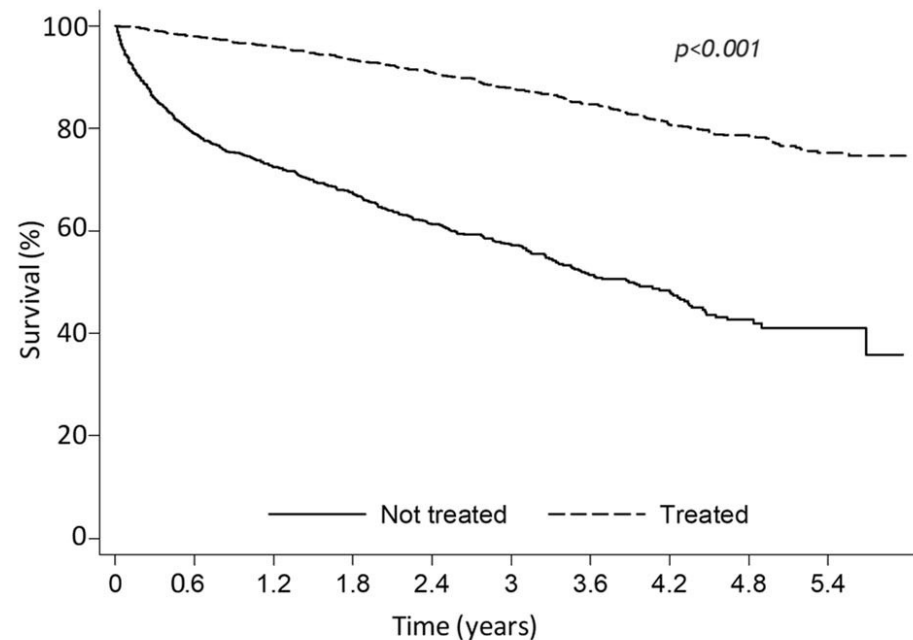


- Pz **non trattati** hanno un rischio superiore del **55,6%** per ri-frattura rispetto ai pazienti trattati con farmaci anti-osteoporosi.
- Pz che assumono Ca/VitD hanno avuto un rischio di ri-frattura inferiore del **64,4%** rispetto ai pz trattati senza supplementazione.



Use of antiosteoporotic drugs and calcium/vitamin D in patients with fragility fractures: impact on re-fracture and mortality risk

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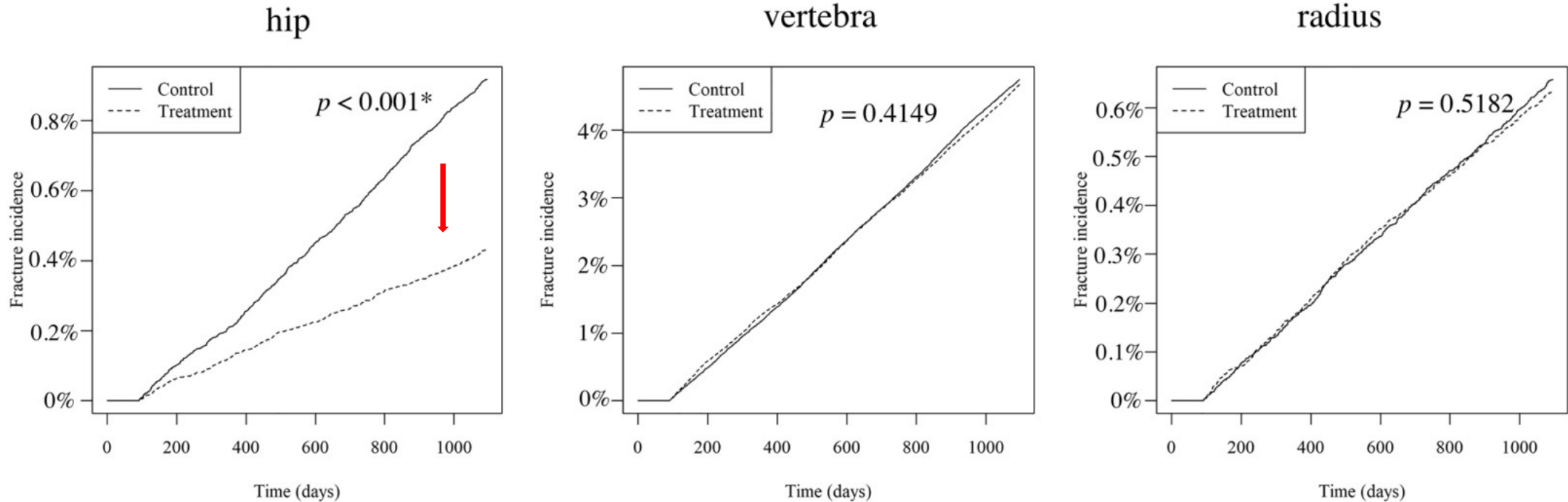
- Pz **non trattati** hanno un rischio superiore del **36%** per la mortalità rispetto ai pazienti trattati con farmaci anti-osteoporosi.
- Pz che assumono Ca/VitD hanno **avuto un rischio di mortalità inferiore del 47.1%** rispetto ai pz trattati senza supplementazione.



OPEN

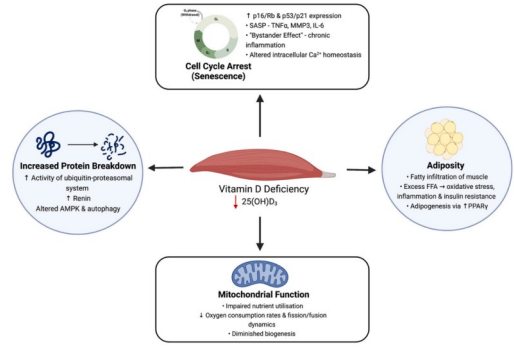
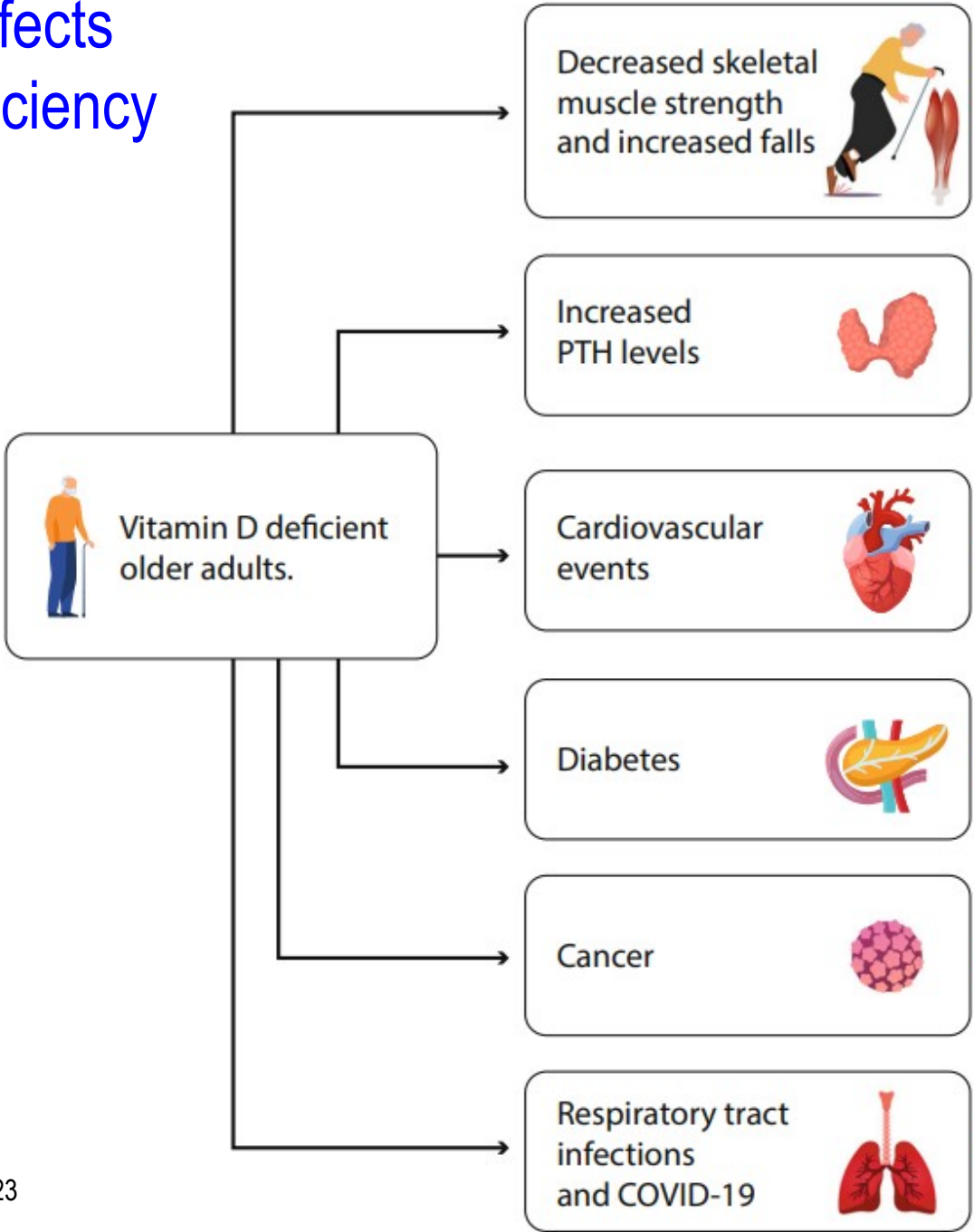
Prescription of vitamin D was associated with a lower incidence of hip fractures

Mitsutaka Yakabe¹, Tatsuya Hosoi¹, Shoya Matsumoto¹, Kenji Fujimori^{2,8}, Junko Tamaki^{3,8},



- The data of osteoporotic patients from the nationwide health insurance claims database of Japan.
- The follow-up period was 3 years after entry.
- The untreated patients were ($n = 422,454$), and the treated patients had a vitamin D medication possession ratio of ≥ 0.5 at all time points ($n = 169,774$).

Extra skeletal effects of vitamin D deficiency in the elderly



Vitamin D and Omega-3 Trial, VITAL : 2.000 UI/die di colecalciferolo non si associa ad una minore incidenza di eventi cardiovascolari (MACE) rispetto al gruppo placebo,

Trial D2d: 4.000 UI/die di colecalciferolo non determina una significativa riduzione del rischio di sviluppare DM2 in individui adulti con prediabete.

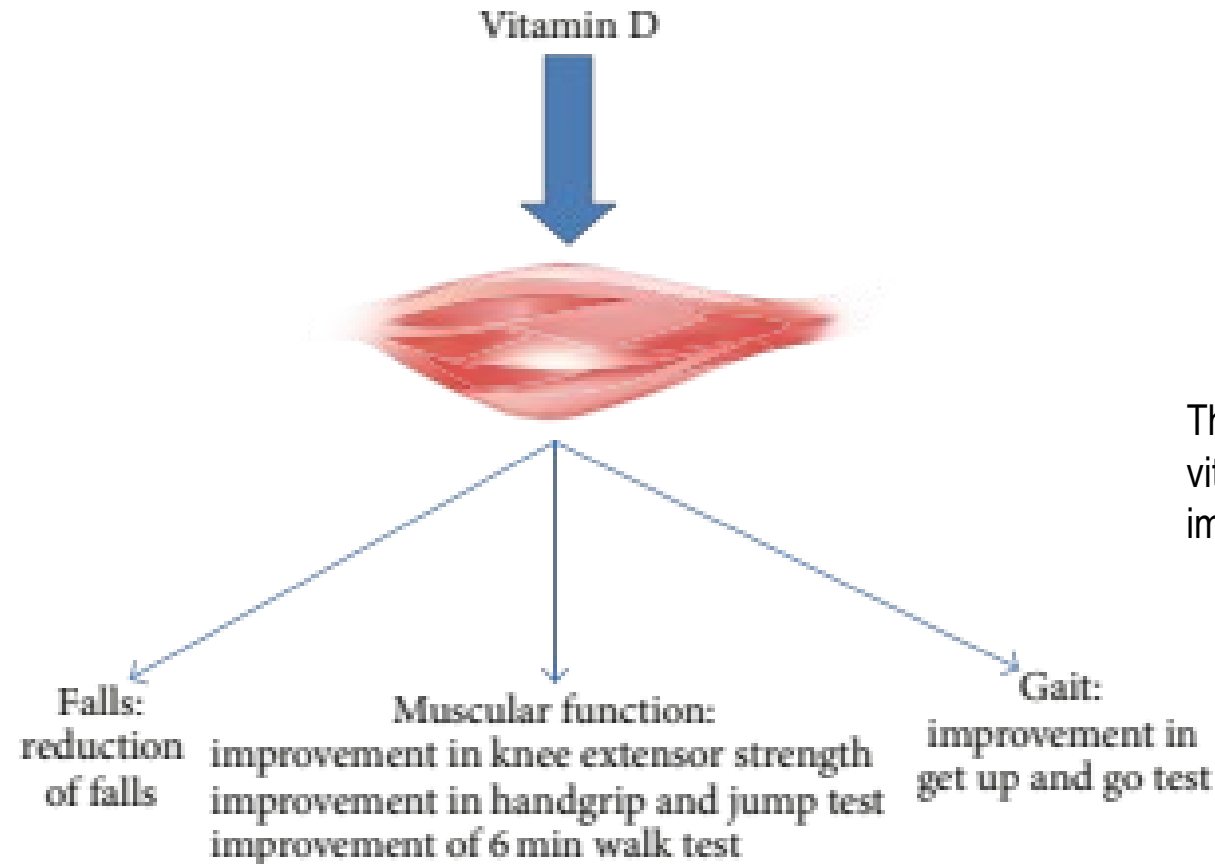
Vitamin D and Omega-3 Trial, VITAL : 2.000 UI/die di colecalciferolo non si associa ad una minore incidenza di neoplasie (tutti i tipi) rispetto al gruppo placebo,

Effects of vitamin D supplementation on musculoskeletal health: a systematic review, meta-analysis, and trial sequential analysis

Mark J Bolland, Andrew Grey, Alison Avenell



Lancet Diabetes Endocrinol 2018



There is little justification to use vitamin D supplements to maintain or improve musculoskeletal health.

Fall prevention with high dose and low dose of supplemental vitamin D

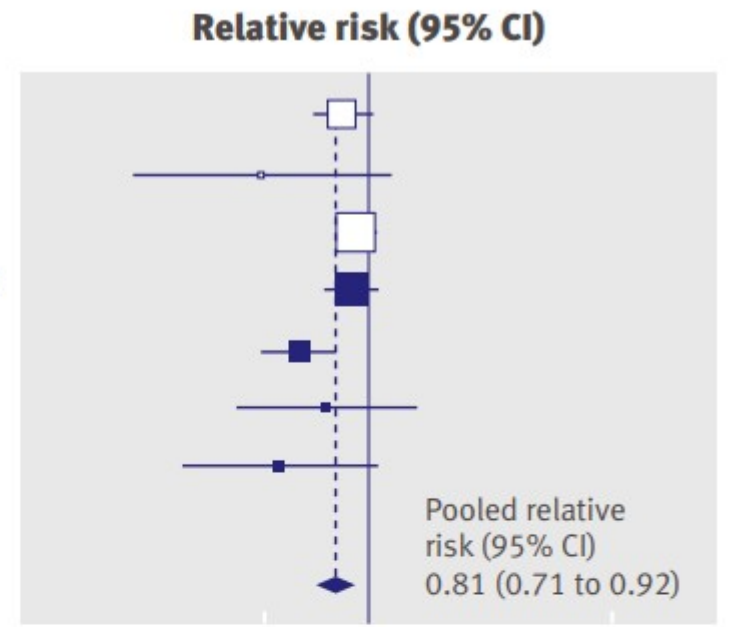
- Supplemental vit D in a dose of 700-1000 IU a day reduced the risk of falling among older individuals by 19% and to a similar degree as active forms of vit D.
- Doses of supplemental vit D of less than 700 IU or serum 25-OHD concentrations of less than 60 nmol/l may not reduce the risk of falling among older individuals.

High dose vitamin D

(700-1000 IU a day)

- Prince et al^{w3}
- Broe et al^{w1}
- Flicker et al^{w4}
- Bischoff-Ferrari et al^{w2}
- Pfeifer et al^{w5}
- Bischoff et al^{w6}
- Pfeifer et al^{w7}

Combined

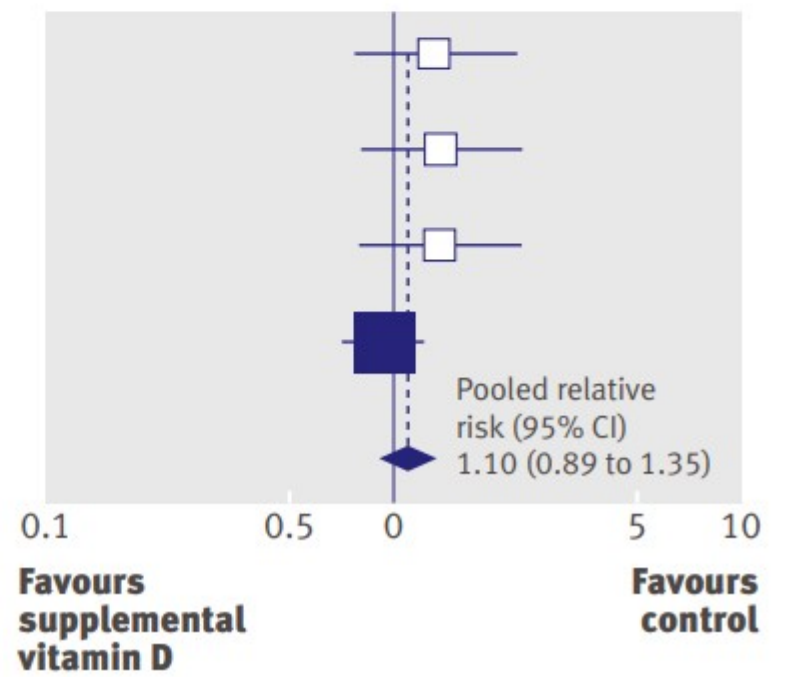


Low dose vitamin D

(200-600 IU a day)

- Broe et al^{w1} (200 IU D₂/day)
- Broe et al^{w1} (400 IU D₂/day)
- Broe et al^{w1} (600 IU D₂/day)
- Graafmans et al^{w8}

Combined





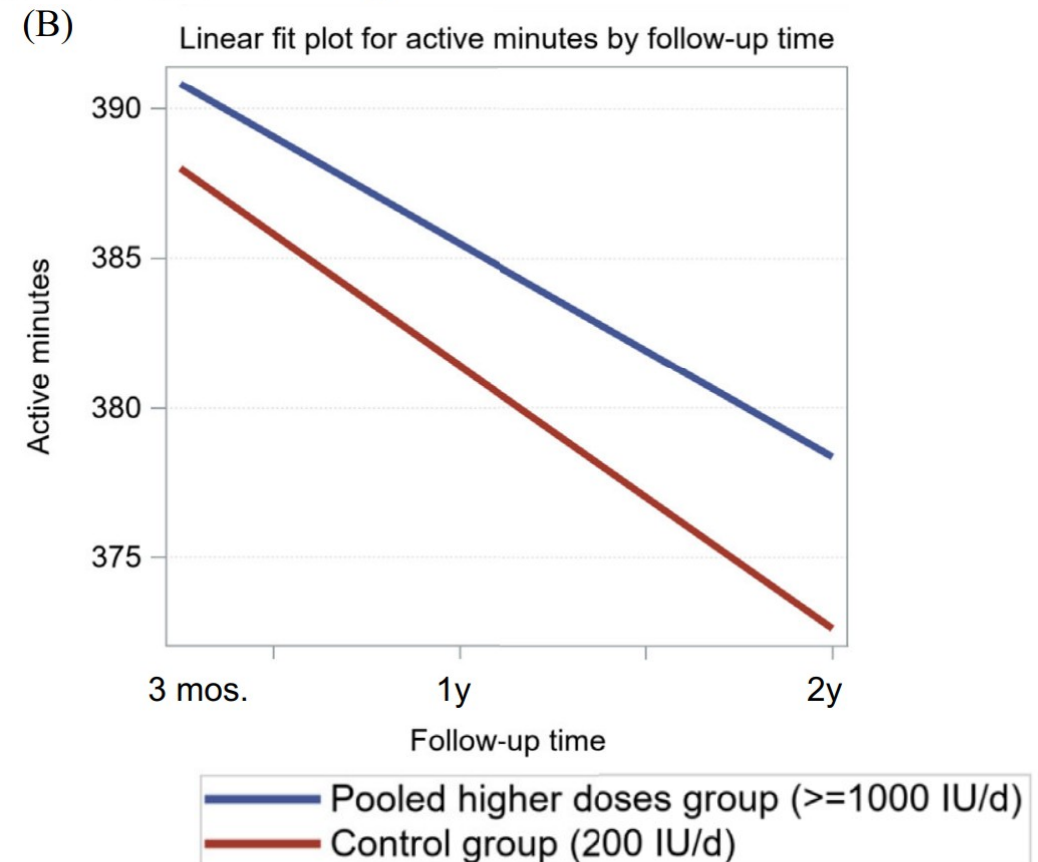
The association of vitamin D supplementation and serum vitamin D levels with physical activity in older adults: Results from a randomized trial

Jennifer A. Schrack PhD, MS^{1,2} | Yurun Cai PhD^{1,3} | Jacek K. Urbanek PhD^{2,4} |

► To assess whether vitamin D3 supplementation attenuates the decline in daily physical activity in low-functioning adults at risk for falls.

Key points

- Low serum 25-hydroxyvitamin [25(OH)D] is associated with low daily physical activity in older adults.
- Decline in physical activity over up to 24-months of follow-up was greater among those with serum 25(OH)D <20 ng/mL compared to serum 25(OH)D of 20–29 ng/mL; Vitamin D supplementation did not attenuate this decline.












Recommended vitamin D supply in women older than 50 years

Authority and/or country (year)	Recommended intake of vitamin D (IU/d)		
	Age 50–60 years	Age 61–70 years	Age > 70 years
IOF (2010) [108]	800	800	800-1000; up to 2000 IU/day if needed to achieve sufficient vitamin D level
IOM (2011) [106]	600	600	800
Endocrine society (2011) [107]	600	600	800 ; up to 1500–2000 IU/day if needed to achieve sufficient vitamin D level
DACH (2012) [101]	800	800	800
Nordic countries (2012) [102]	400	400	800 (> 75 years)
ESCEO (2013) [100]	800	800	800
EFSA (2016) [103]	600	600	600
UK (SACN 2016) [104]	400	400	400
ESCEO-IOF (2019) [105]	800	800	800

IOF (International Osteoporosis Foundation); IOM (Institute of Medicine) ; DACH (Germany (D), Austria (A) and Switzerland (CH)); ESCEO (European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases); EFSA (European Food Safety Authority); UK SACN (United Kingdom-Scientific Advisory Committee on Nutrition)

Review

Definition, Assessment, and Management of Vitamin D Inadequacy: Suggestions, Recommendations, and Warnings from the Italian Society for Osteoporosis, Mineral Metabolism and Bone Diseases (SIOMMMS)

Francesco Bertoldo ¹, Luisella Cianferotti ², Marco Di Monaco ³, Alberto Falchetti ^{4,*}, Angelo Fassio ⁵,
Davide Gatti ⁵, Luigi Gennari ⁶, Sandro Giannini ⁷, Giuseppe Girasole ⁸, Stefano Gonnelli ⁶,
Nazzarena Malavolta ⁹, Salvatore Minisola ¹⁰, Mario Pedrazzoni ¹¹, Domenico Rendina ¹², Maurizio Rossini ⁵
and Iacopo Chiodini ^{13,14}

4. Come dovrebbe essere integrata la vitamina D in soggetti con ipovitaminosi D o candidati a trattamento farmacologico con terapia per la fragilità scheletrica?

Si suggerisce l'uso di una dose iniziale di carico, seguita da dose di mantenimento in pazienti con osteomalacia sintomatica e/o valore sierico di 25(OH)D < 10 ng/mL o in pazienti che iniziano terapia con bisfosfonati per endovena o denosumab con 25(OH)D < 20 ng/mL

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Si suggerisce, come dose di carico, colecalciferolo 3000-10.000 UI/die (media 5000 UI/die) per 1-2 mesi, o colecalciferolo in una singola dose di 60.000 a 150.000 UI seguita dalla dose di mantenimento (2000 UI/die). In alternativa, si suggerisce calcifediolo 20-40 mcg/die (4-8 gtt/die) per 20-30 giorni, prima di passare alla dose di mantenimento*

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Effect of Vitamin D Deficiency on Voice: A Review of the Literature

Abdul-Latif Hamdan, Jad Hosri, Patrick Abou Raji Feghali, Yara Yammine, Christophe Abi Zeid Daou, and Christopher Jabbour, *Beirut, Lebanon*

Summary: Objective. The purpose of this study is to review the current literature on the effect of hypovitaminosis D on voice.

Study design. Narrative review.

Methods. The literature search from electronic databases included PubMed/MEDLINE, EMBASE, SCOPUS, and Google Scholar. Search terms included voice, voice quality, voice disorders, larynx, laryngology, acoustic analysis, vitamin D, calcitriol, cholecalciferol, vitamin D deficiency, and vitamin D insufficiency. All studies on patients with vitamin D deficiency, which included subjective and objective voice assessments, were reviewed.

Results. A total of 39 studies were retrieved. Only four studies met the above-mentioned inclusion criteria and hence were included in this review. The total number of subjects analyzed was 466. The subjective voice outcome measures used were the Voice Handicap Index-10 (VHI-10), self-reported phonatory symptoms, and the GRBAS scale. Objective voice outcome measures included fundamental frequency, jitter, shimmer, noise-to-harmonic ratio, maximum phonation time, and dysphonia severity index.

Conclusion. Vitamin D deficiency has no significant effect on laryngeal muscles. There was no statistically significant difference in VHI-10 score, self-reported dysphonia, perceptual voice evaluation scores, or any of the acoustic measures between those with or without vitamin D deficiency.

Key Words: Vitamin D deficiency–Voice–Laryngology–Vitamin D insufficiency.



25.000 UI di
Vitamina D al
giorno a tutti i
cantanti !

