Associazione Medici Endocrinologi

17° Congresso Nazionale AME
Joint Meeting with AACE Italian Chapter
Update in Endocrinologia Clinica
ROMA 8 - 11 novembre 2018

ITALIAN CHAPTER

Vitamina D:
quando, come e chi trattare

Moderatori: A. Santonati, V. Toscano

Relatore: R. Cesareo

QUANDO?

Adolf Windaus premio nobile chimica 1928

VALORI PLASMATICI DI VITAMINA D

A VOSTRO GIUDIZIO SONO OTTIMALI I VALORI DI VITAMINA D QUANDO QUESTI SONO:

> 30 ng /dl (75 nmol/l)

> 20 ng/dl (50 nmol/l)

Non lo so

Dipende da diversi fattori

Evaluation, Treatment, and Prevention of Vitamin D Deficiency: an Endocrine Society Clinical Practice Guideline

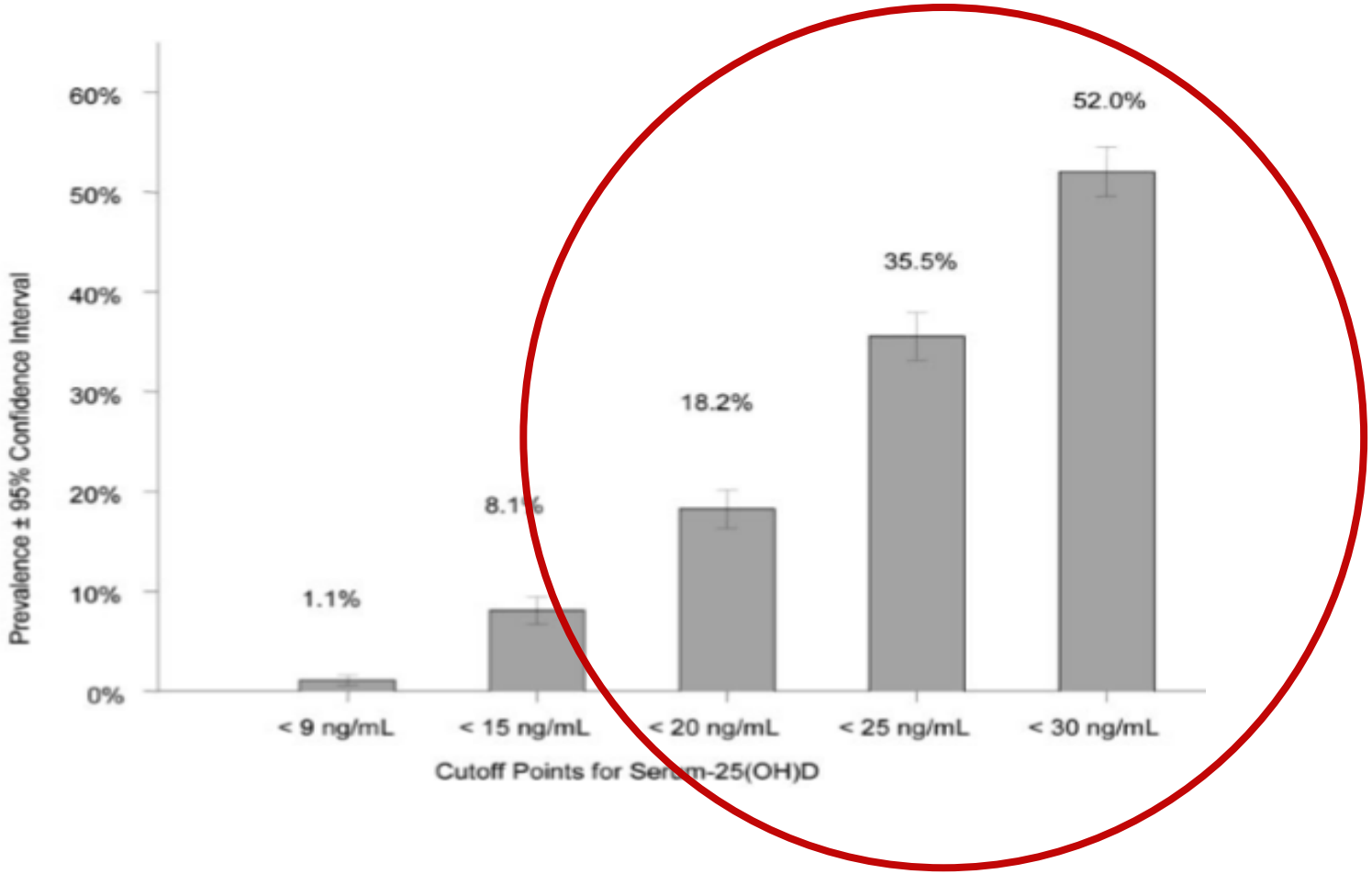
Michael F. Holick, Neil C. Binkley, Heike A. Bischoff-Ferrari, Catherine M. Gordon, David A. Hanley, Robert P. Heaney, M. Hassan Murad, and Connie M. Weaver

- ✓ **Endocrine Society 2011: "…. serum 25(OH)D levels in the range 21–29ng/mL (52.5–72.5nmol/L) are considered insufficient". Optimal 25OHD levels: >30ng/ml (>75 nmol/L)**

nmol/l	*ng/ml*	*Interpretazione*
<25	<10	Grave carenza
25-50	10-20	Carenza
50-75	20-30	Insufficienza
75-125	30-50	Range ideale
125-375	50-150	Possibili effetti indesiderati ?
>375	>150	Intossicazione

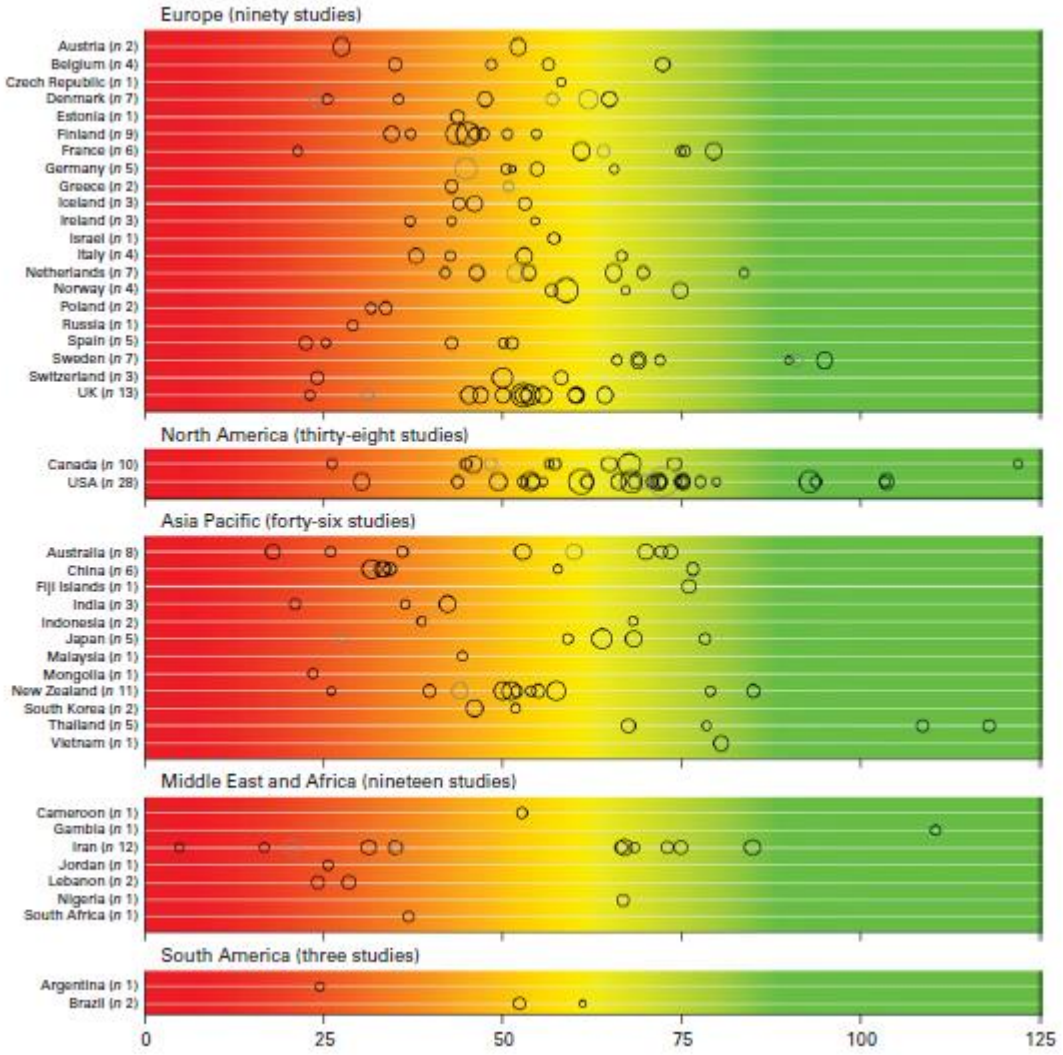
Prevalence of Vitamin D Inadequacy among Postmenopausal North American Women Receiving Osteoporosis Therapy

Michael F. Holick, Ethel S. Siris, Neil Binkley, Mary K. Beard, Aliya Khan, Jennifer T. Katzer, Richard A. Petruschke, Erluo Chen, and Anne E. de Papp



JCEM 2005

A systematic review of vitamin D status in populations worldwide



88.1% of the samples had 25(OH)D values below 30 ng/dl.

37.3% had mean values below 20 ng/dl.

6.7% had mean values below 10 ng/dl.

British Journal of Nutrition 2014

Calcium
Vitamin D

Committee to Review Dietary Reference Intakes for Vitamin D and Calcium
Food and Nutrition Board

A. Catharine Ross, Christine L. Taylor, Ann L. Yaktine, and
Heather B. Del Valle, *Editors*

INSTITUTE OF MEDICINE
OF THE NATIONAL ACADEMIES

Levels of 20 ng/ml (50 nmol/liter) cover the requirements of at least 97.5% of the population.

Serum concentrations of 25OHD above 30 ng/ml (75 nmol/liter) are not consistently associated with increased benefit

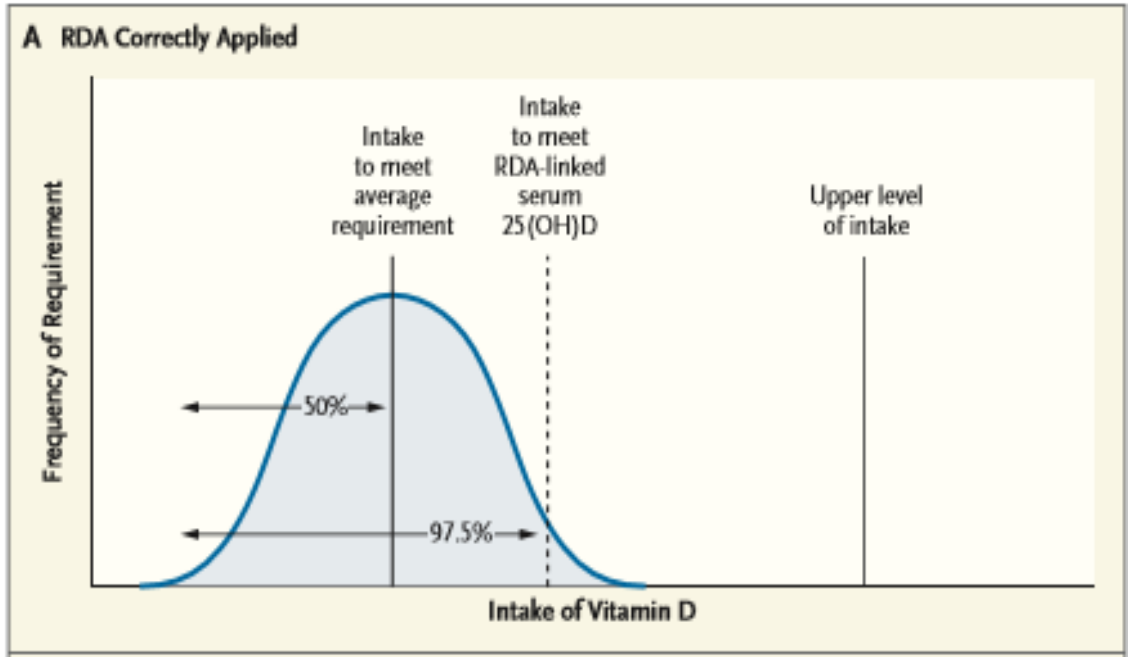
Vitamin D and health in adults in Australia and New Zealand: a position statement

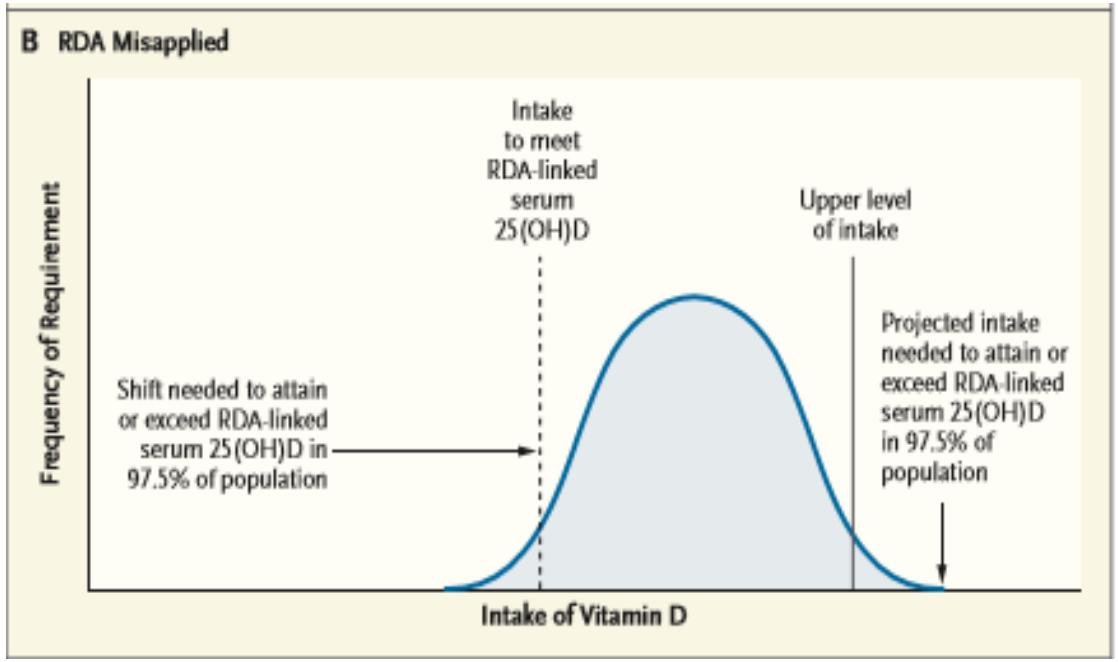
- A serum 25-hydroxyvitamin D (25-OHD) level of ⩾ 50 nmol/L at the end of winter (10–20 nmol/L higher at the end of summer, to allow for seasonal decrease) is required for optimal musculoskeletal health.
- Although it is likely that higher serum 25-OHD levels play a role in the prevention of some disease states, there is insufficient evidence from randomised controlled trials to recommend higher targets.

MJA 196 (11) · 18 June 2012

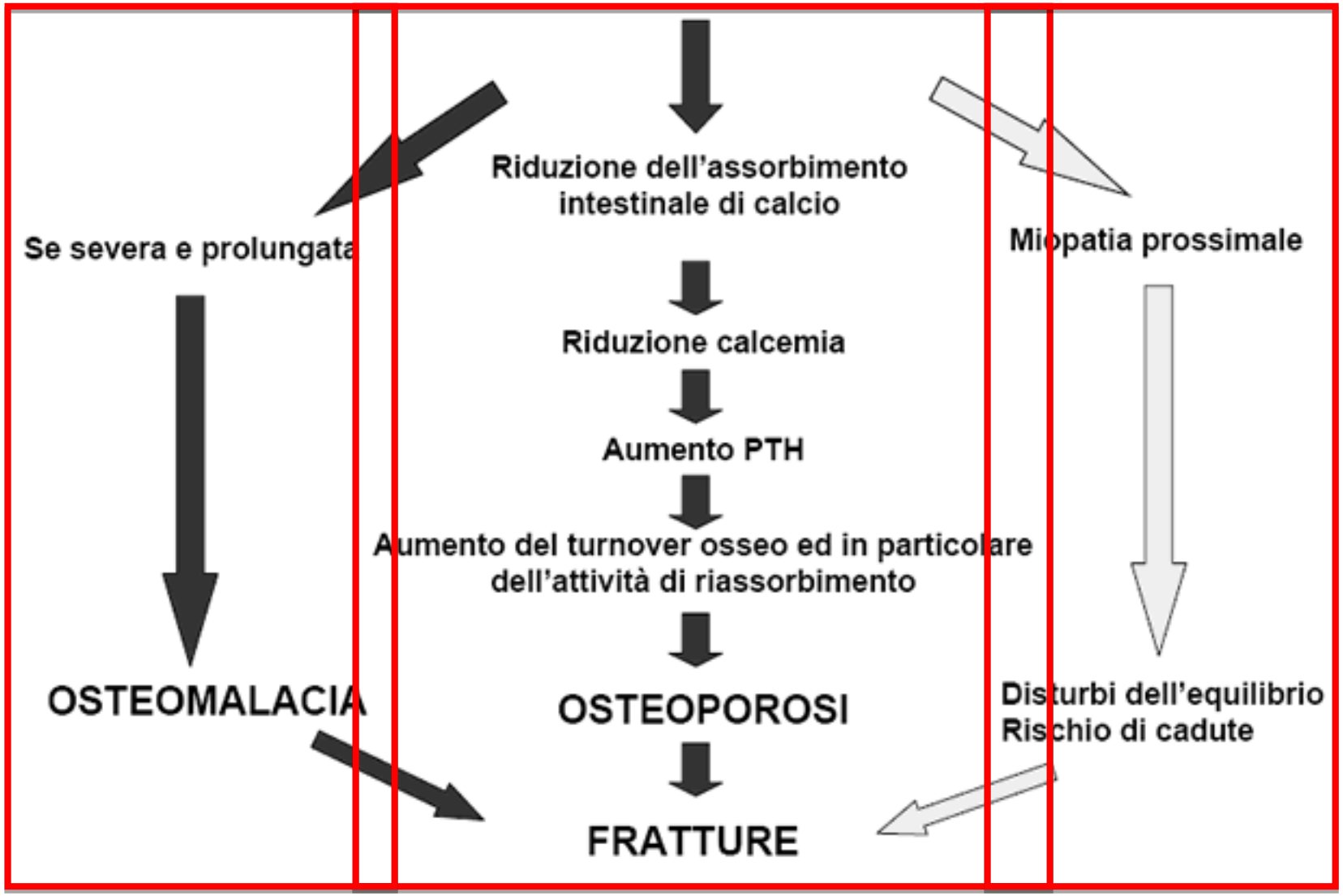
Vitamin D Deficiency — Is There Really a Pandemic?

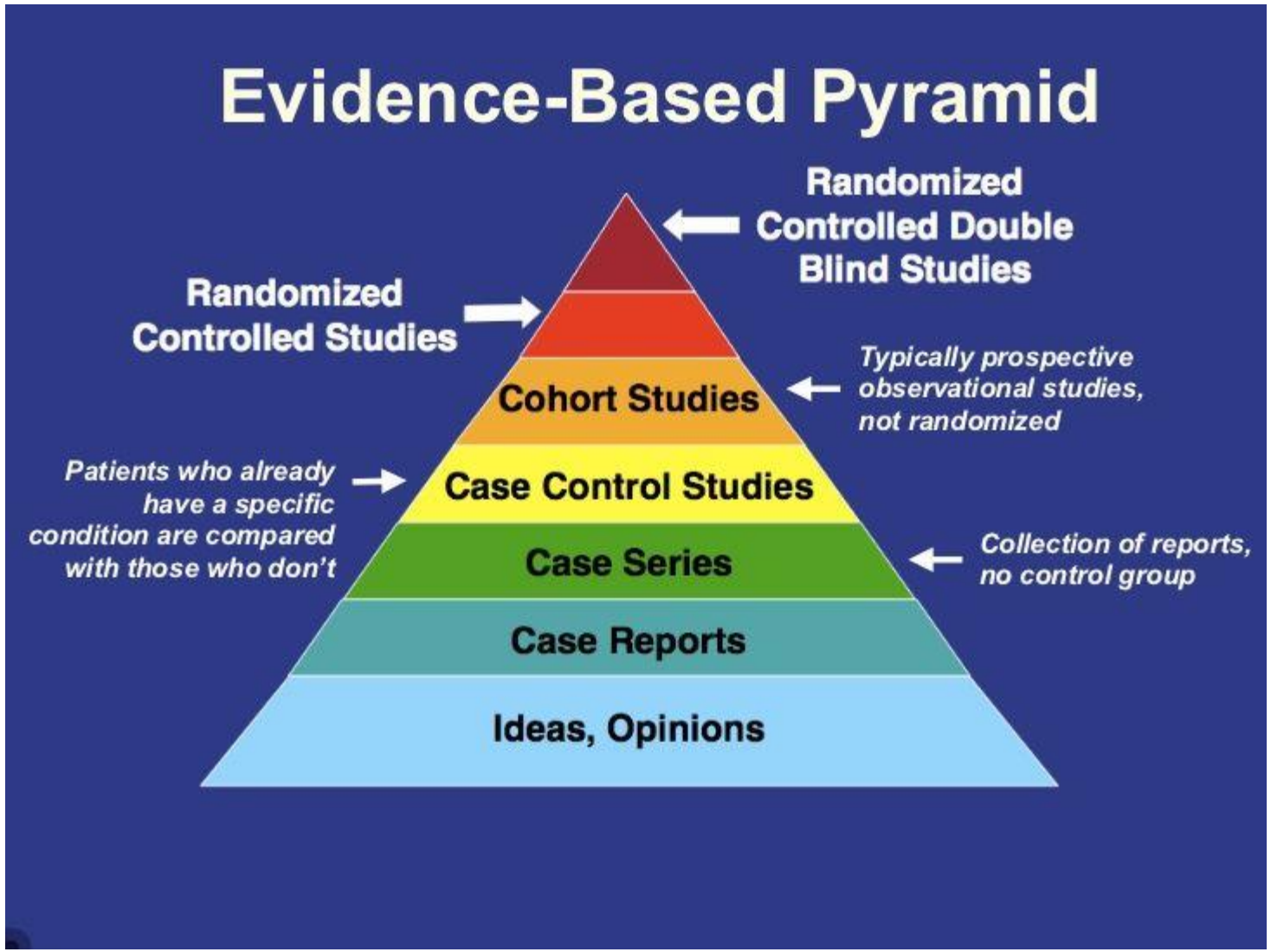
JoAnn E. Manson, M.D., Dr.P.H., Patsy M. Brannon, Ph.D., R.D., Clifford J. Rosen, M.D., and Christine L. Taylor, Ph.D.





Carenza Vitamina D




Evidence-Based Pyramid
Randomized Controlled Double Blind Studies
Randomized Controlled Studies
Typically prospective observational studies, not randomized
Cohort Studies
Patients who already have a specific condition are compared with those who don't
Case Control Studies
Case Series
Collection of reports, no control group
Case Reports
Ideas, Opinions

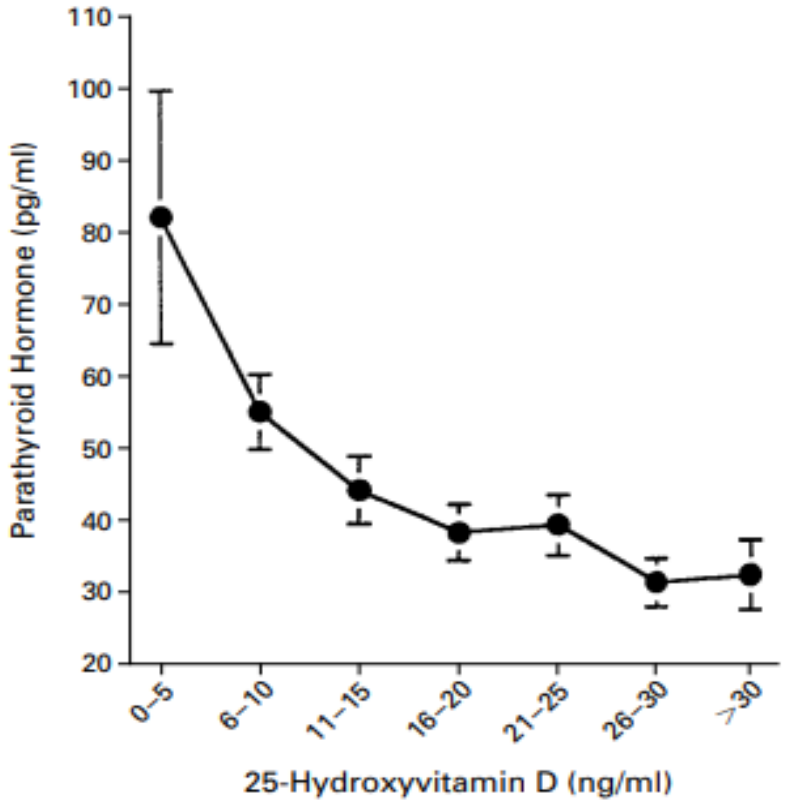
Consequences of Vitamin D Deficiency

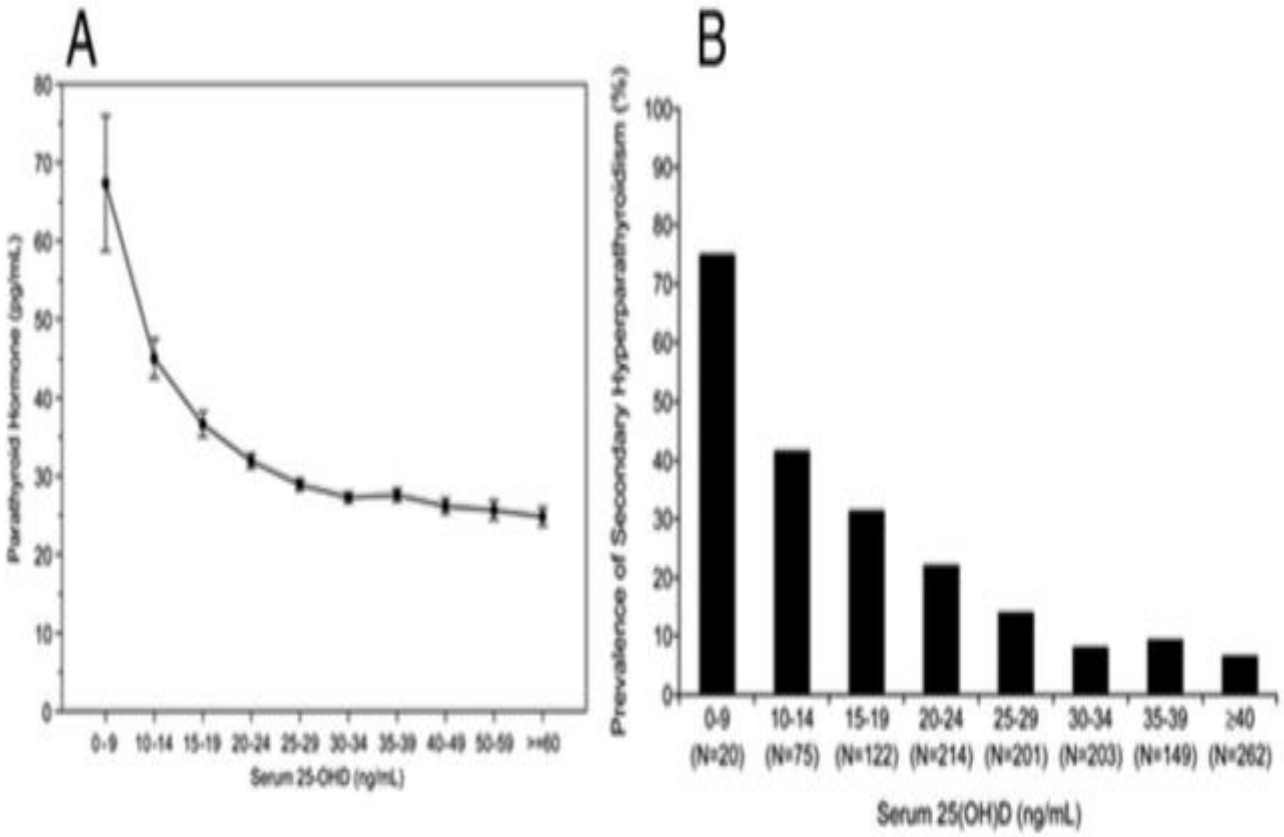
- Secondary hyperparathyroidism. The PTH-mediated increase in osteoclastic activity creates local foci of bone weakness and causes a generalized decrease in bone mineral density (BMD), resulting in osteopenia and osteoporosis

- Osteomalacia causes a decrease in BMD and is associated with isolated or generalized aches and pains in bones and muscles

- Muscle weakness; affected children have difficulty standing and walking whereas the elderly have increasing sway and more frequent falls

Guidelines for Preventing and Treating Vitamin D Deficiency and Insufficiency Revisited





N Engl J Med 1998; JCEM 2012

Consequences of Vitamin D Deficiency

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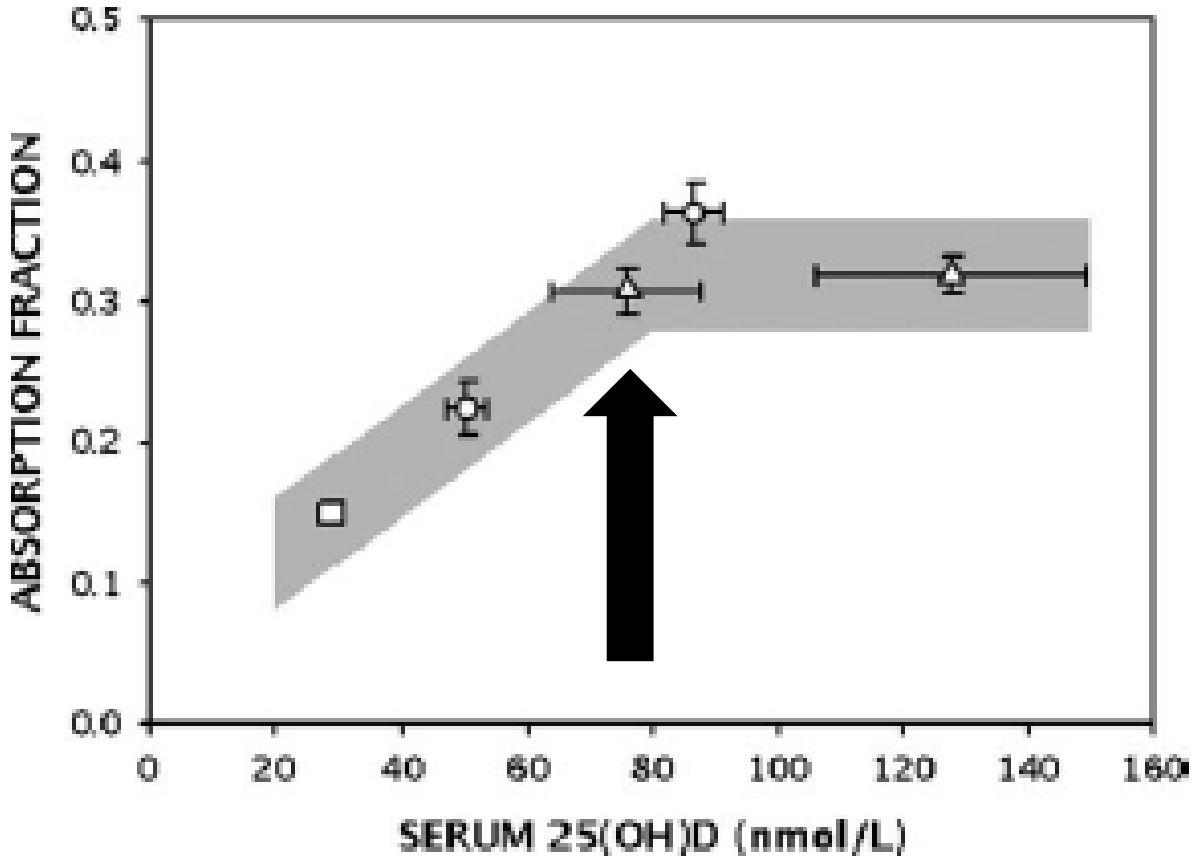
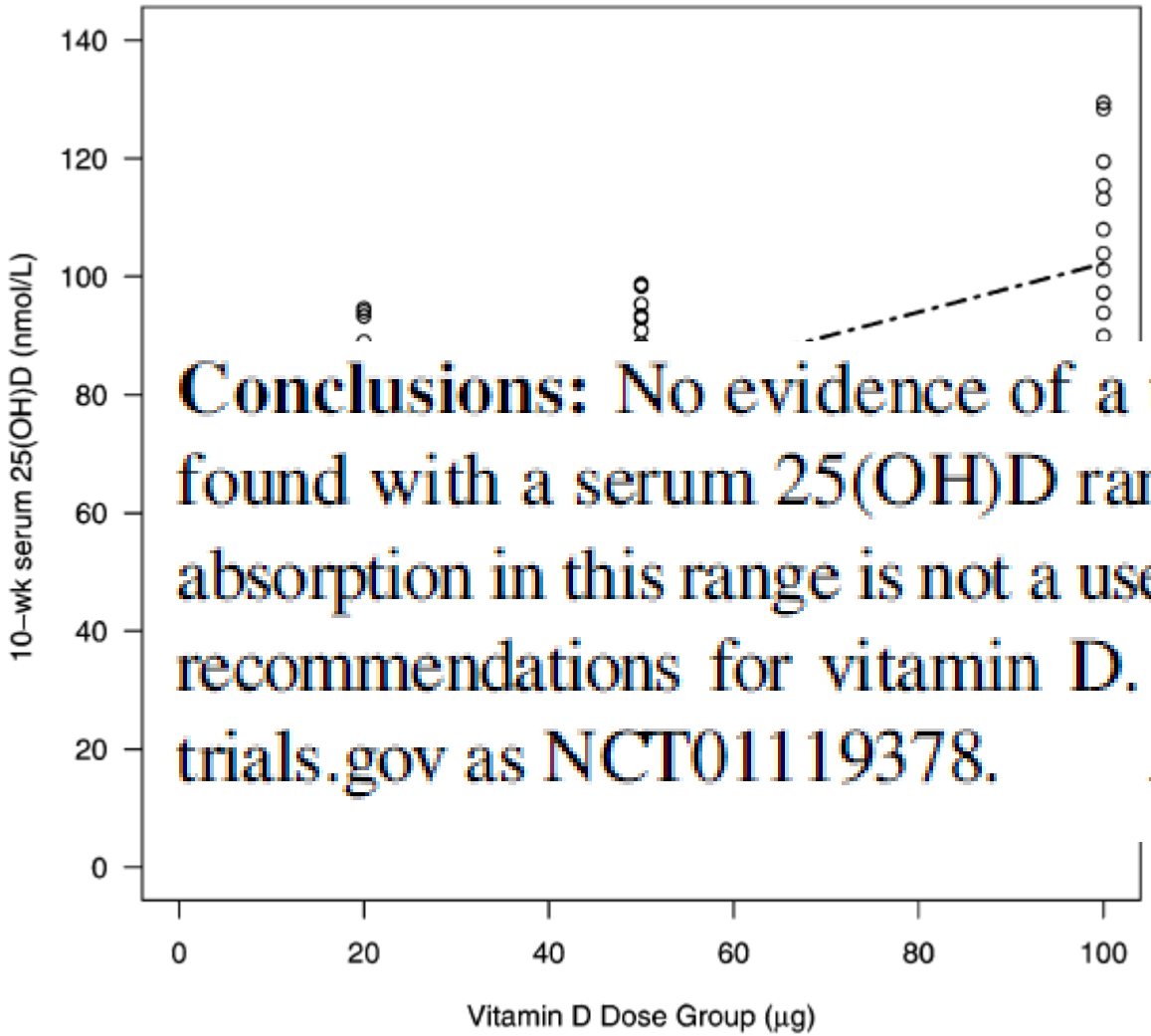
Vitamin D in Health and Disease

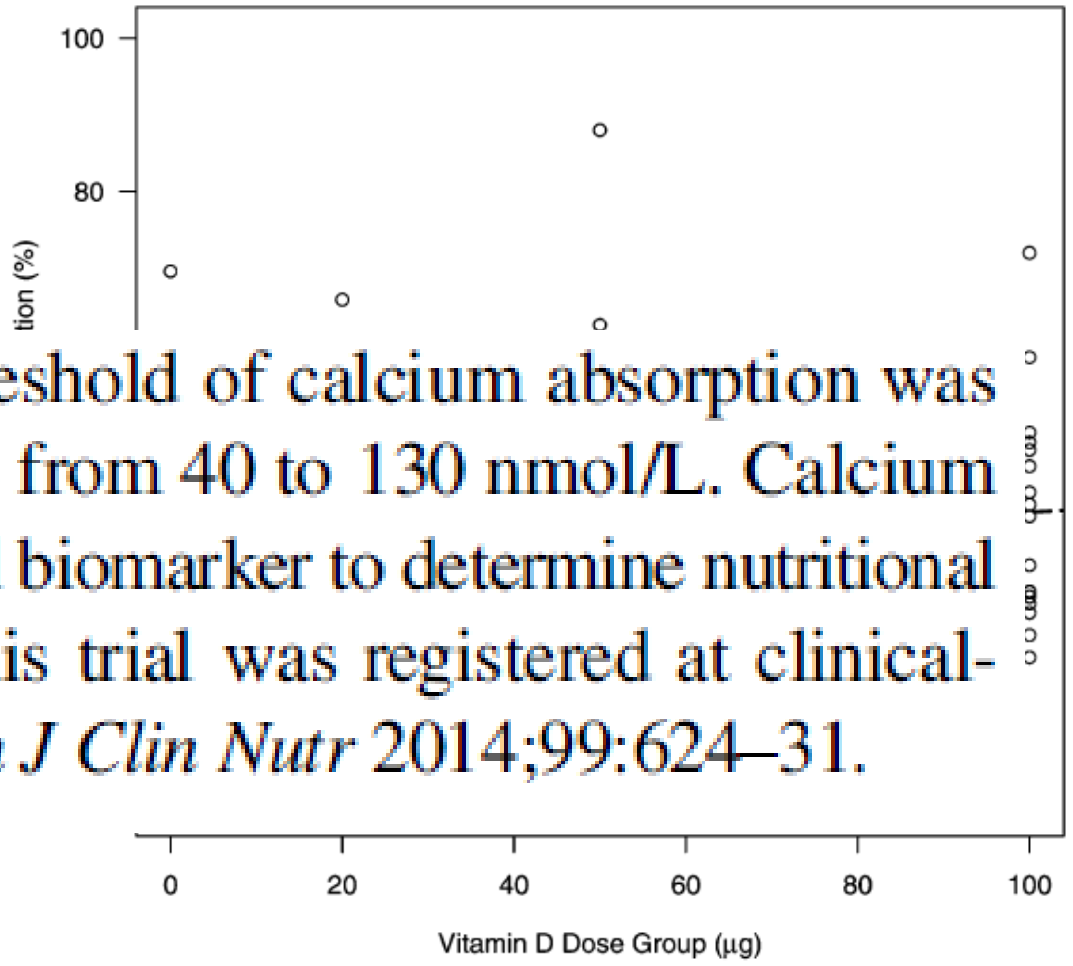
Robert P. Heaney
Creighton University, Omaha, Nebraska



Clin J Am Soc Nephrol 2008

Vitamin D supplementation increases calcium absorption without a threshold effect[1–3]

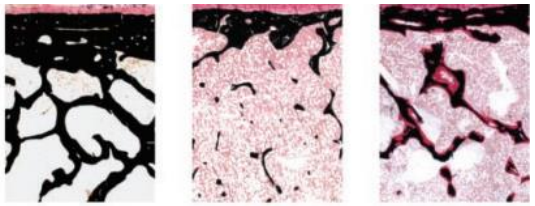


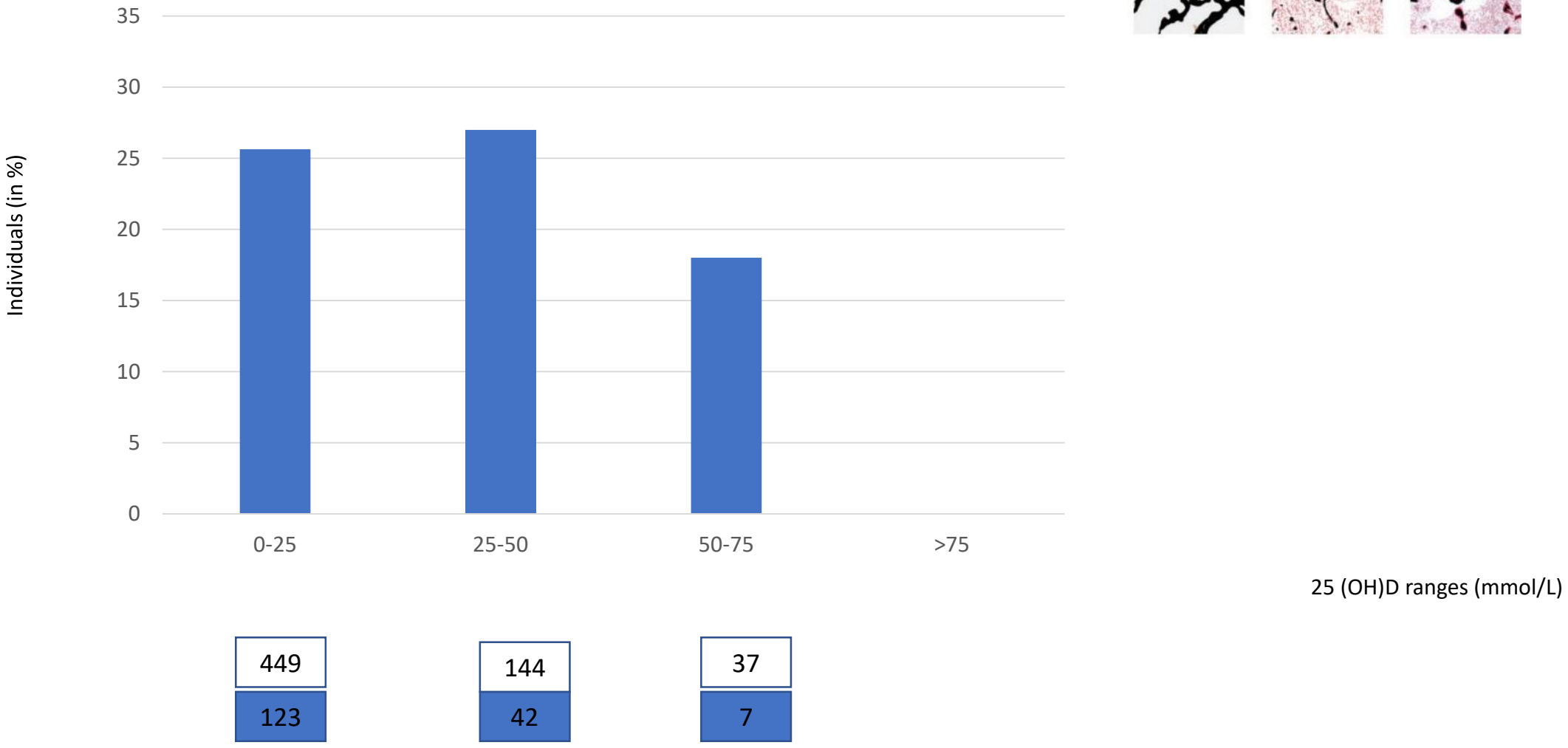


Conclusions: No evidence of a threshold of calcium absorption was found with a serum 25(OH)D range from 40 to 130 nmol/L. Calcium absorption in this range is not a useful biomarker to determine nutritional recommendations for vitamin D. This trial was registered at clinicaltrials.gov as NCT01119378. *Am J Clin Nutr* 2014;99:624–31.

Am J Clin Nutr 2014

Bone Mineralization Defects and Vitamin D Deficiency: Histomorphometric Analysis of Iliac Crest Bone Biopsies and Circulating 25-Hydroxyvitamin D in 675 Patients





Diagnostica istologica delle malattie metaboliche dello scheletro: istomorfometria ossea

Histologic diagnosis of metabolic bone diseases: bone histomorphometry

There also are, however, certain clear limitations of our study that need to be considered. First, tetracycline labeling, as one gold standard for quantification of bone formation, is missing. Second, serum analysis is limited to the assessment of 25(OH)D, whereas other laboratory data, such as serum calcium, phosphate, creatinine, PTH, and alkaline phosphatase levels, are missing owing to a lack of stability, and thus some circumstances that potentially interfere with bone mineralization, such as moderate renal dysfunction or mild primary hyperparathyroidism, might remain undetected at the tissue level. And third, one could argue that the cohort studied here

Reumatismo 2004

Vitamin D Assays and the Definition of Hypovitaminosis D: Results from the 1st International Conference on Controversies in Vitamin D

Running Title: Vitamin D Assays and Defining Hypovitaminosis D

Christopher T. Sempos[1,13], Annemieke C. Heijboer[2], Daniel D. Bikle[3], Jens Bollerslev[4]; Roger Bouillon[5], Patsy M. Brannon[6], Hector F. DeLuca[7], Glenville Jones[8], Craig F. Munns[9], John P. Bilezikian[10], Andrea Giustina[11], Neil Binkley[12].

25(OH)D values below 12 ng/mL (30 nmol/L) should be considered to be associated with an increased risk of rickets/osteomalacia

25(OH)D concentrations between 20-50 ng/mL (50-125 nmol/L) appear to be safe and sufficient in the general population for skeletal health

Br J Clin Pharmacol. 2018 May

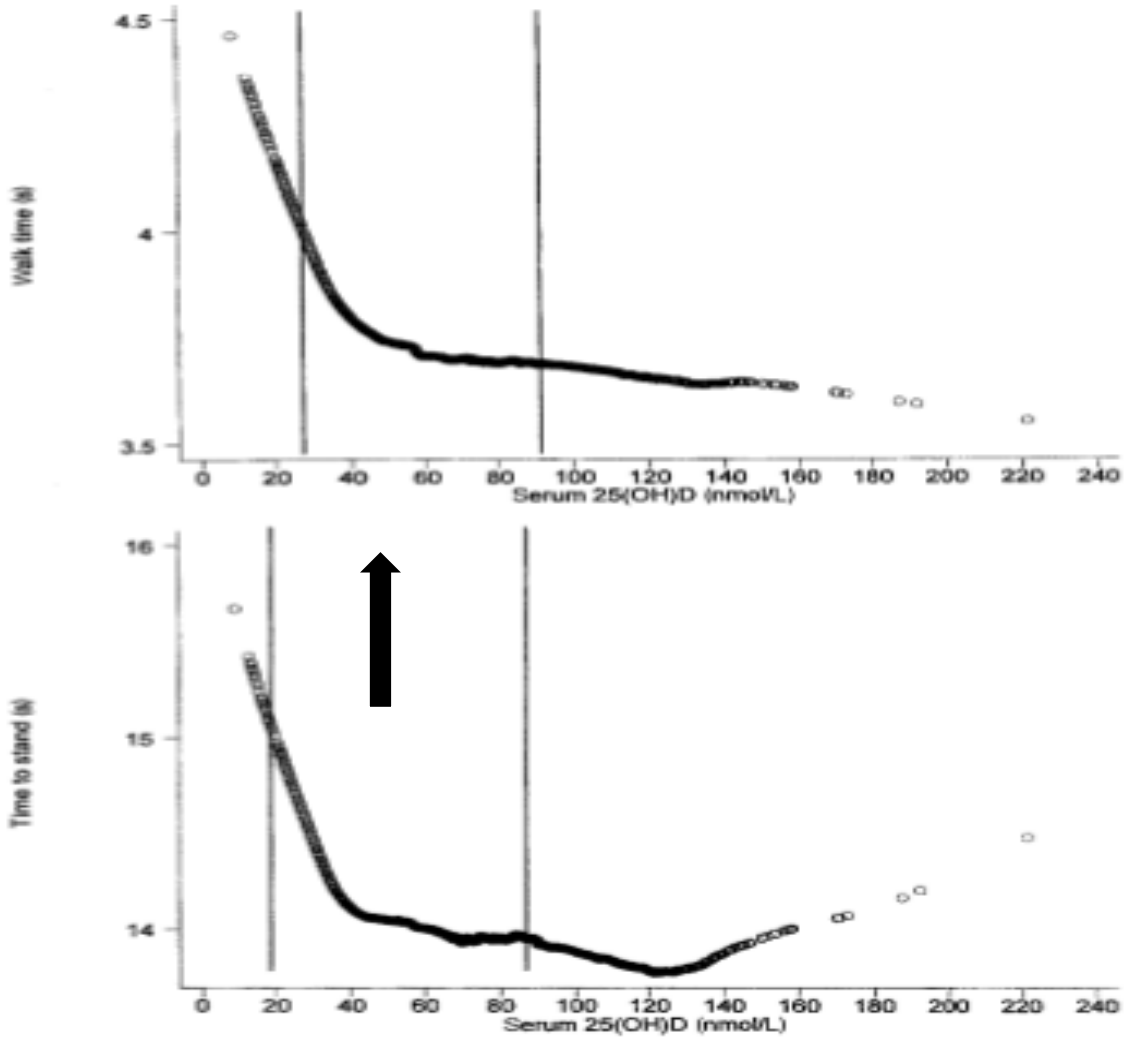
Consequences of Vitamin D Deficiency

- Secondary hyperparathyroidism. The PTH-mediated increase in osteoclastic activity creates local foci of bone weakness and causes a generalized decrease in bone mineral density (BMD), resulting in osteopenia and osteoporosis

- Osteomalacia causes a decrease in BMD and is associated with isolated or generalized aches and pains in bones and muscles

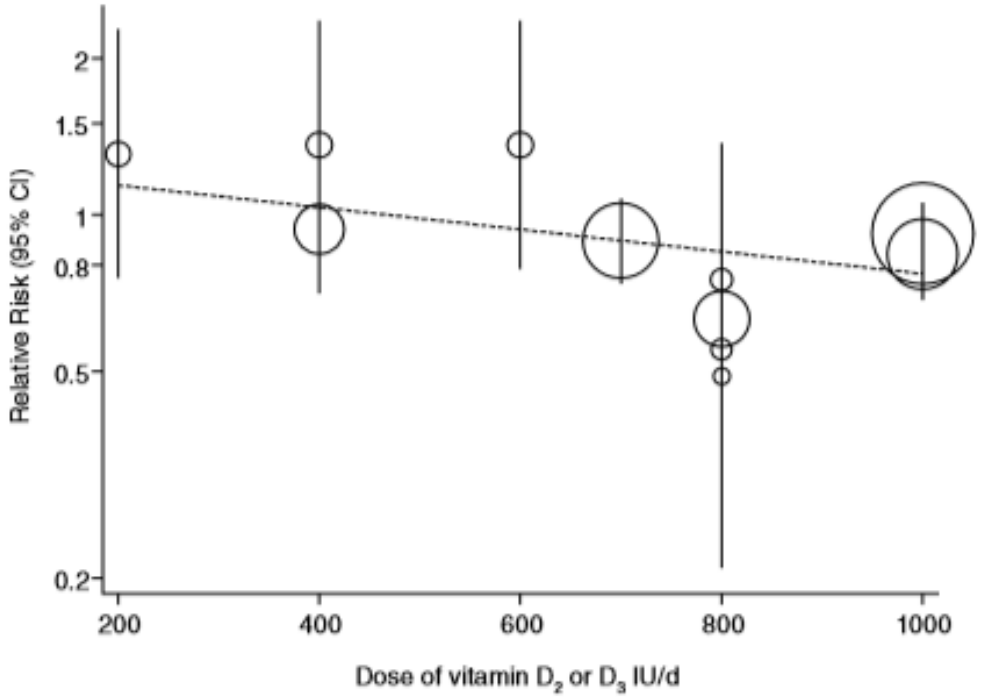
- Muscle weakness; affected children have difficulty standing and walking whereas the elderly have increasing sway and more frequent falls

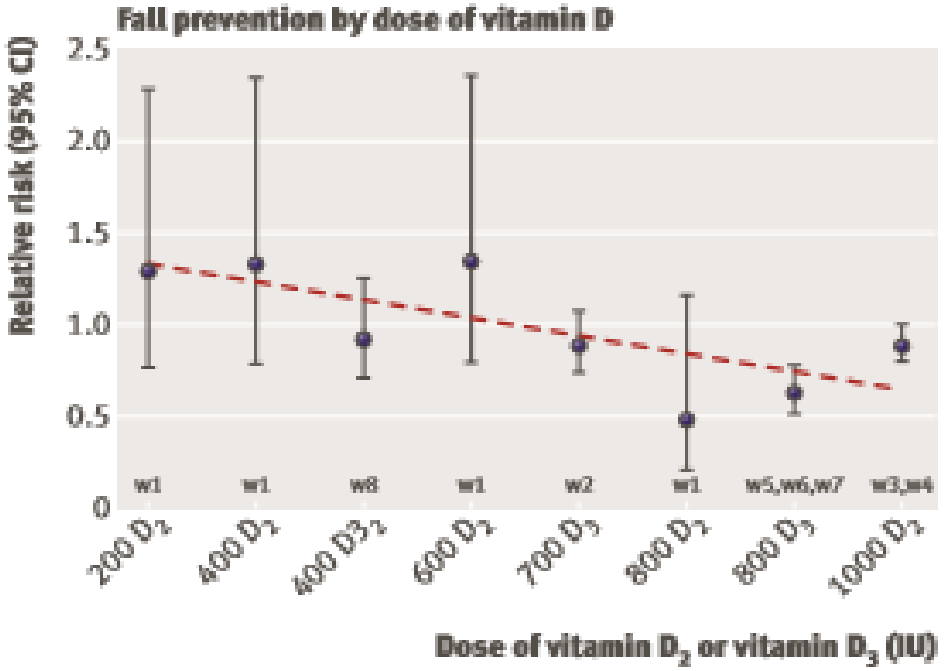
Higher 25-hydroxyvitamin D concentrations are associated with better lower-extremity function in both active and inactive persons aged ≥60 y[1–3]



AM J CLIN NUTR 2004

Fall prevention with supplemental and active forms of vitamin D: a meta-analysis of randomised controlled trials





IOM DOCUMENT 2011

BMJ 2009

A randomized, double-blind, placebo-controlled clinical trial on the treatment of vitamin D insufficiency in postmenopausal women

Objective—To compare effects of placebo, low-dose and high-dose vitamin D on one-year changes in total fractional calcium absorption, bone mineral density, Timed-Up-and-Go and 5-sit-to-stand tests and muscle mass in postmenopausal women with vitamin D insufficiency.

JAMA Intern Med. 2015

Measure		Placebo n=73 of 76	Low-Dose Vitamin D n=73 of 75	High-Dose Vitamin D n=74 of 79	High vs. Low[c]	High vs. Placebo[c]	Low vs. Placebo[c]
Timed Up and Go Test	Baseline	8.28 ± 1.69	8.04 ± 1.56	8.03 ± 1.70	0.05 (−0.42, 0.53) p=0.97	−0.03 (−0.50, 0.44) p=0.99	−0.08 (−0.56, 0.39) p=0.91
	12 months	7.92 ± 1.59	7.60 ± 1.55	7.65 ± 1.77			
	Change[a]	−0.35 (−0.70, −0.01)	−0.44 (−0.66, −0.22)	−0.38 (−0.66, −0.11)			
Five Sit-to-Stand Test	Baseline	10.32 ± 2.88	9.86 ± 2.50	9.83 ± 2.27	−0.06 (−0.83, 0.72) p=0.98	−0.49 (−1.26, +0.29) p=0.3	−0.43 (−1.21, 0.34) p=0.39
	12 months	9.77 ± 3.02	8.88 ± 2.50	8.78 ± 2.09			
	Change	−0.55 (−1.02, −0.07)	−0.98 (−1.49, −0.47)	−1.04 (−1.44, −0.63)			
Health Assessment Questionnaire	Baseline	0.13 ± 0.25	0.14 ± 0.33	0.05 ± 0.14	0.04 (−0.04, 0.12) p=0.48	0.01 (−0.08, 0.09) p=0.99	−0.03 (−0.11, 0.05) p=0.58
	12 months	0.14 ± 0.33	0.12 ± 0.32	0.06 ± 0.21			
	Change	0.01 (−0.03, 0.05)	−0.02 (−0.09, 0.04)	0.02 (−0.02, 0.05)			
Physical Activity Scale for the Elderly	Baseline	169 ± 96	167 ± 85	177 ± 83	17.6 (−13.4, 48.6) p=0.38	13.2 (−17.8, 44.3) p=0.57	−4.4 (−35.5, 26.8) p=0.94
	12 months	153 ± 86	146 ± 69	173 ± 74			
	Change	−17.25 (−39.08, 4.58)	−21.64 (−37.66, −5.63)	−4.04 (−21.40, 13.33)			
Muscle mass[b]	Baseline	7.24 ± 1.05	7.35 ± 1.24	7.29 ± 1.14	−0.05 (−0.23,0.14) p=0.83	−0.1 (−0.29,0.08) p=0.39	−0.06 (−0.24,0.13) p=0.74
	12 months	7.35 ± 1.32	7.40 ± 1.40	7.30 ± 1.28			
	Change	0.1 (−0.03, 0.24)	0.05 (−0.05, 0.14)	0.002 (−0.09, 0.10)			
Falls	n per Arm	33 falls	36 falls	35 falls	p=0.92		
Fallers	subjects	23 (30%)	24 (32%)	22 (32%)	p=0.92		

A randomized, double-blind, placebo-controlled clinical trial on the treatment of vitamin D insufficiency in postmenopausal women

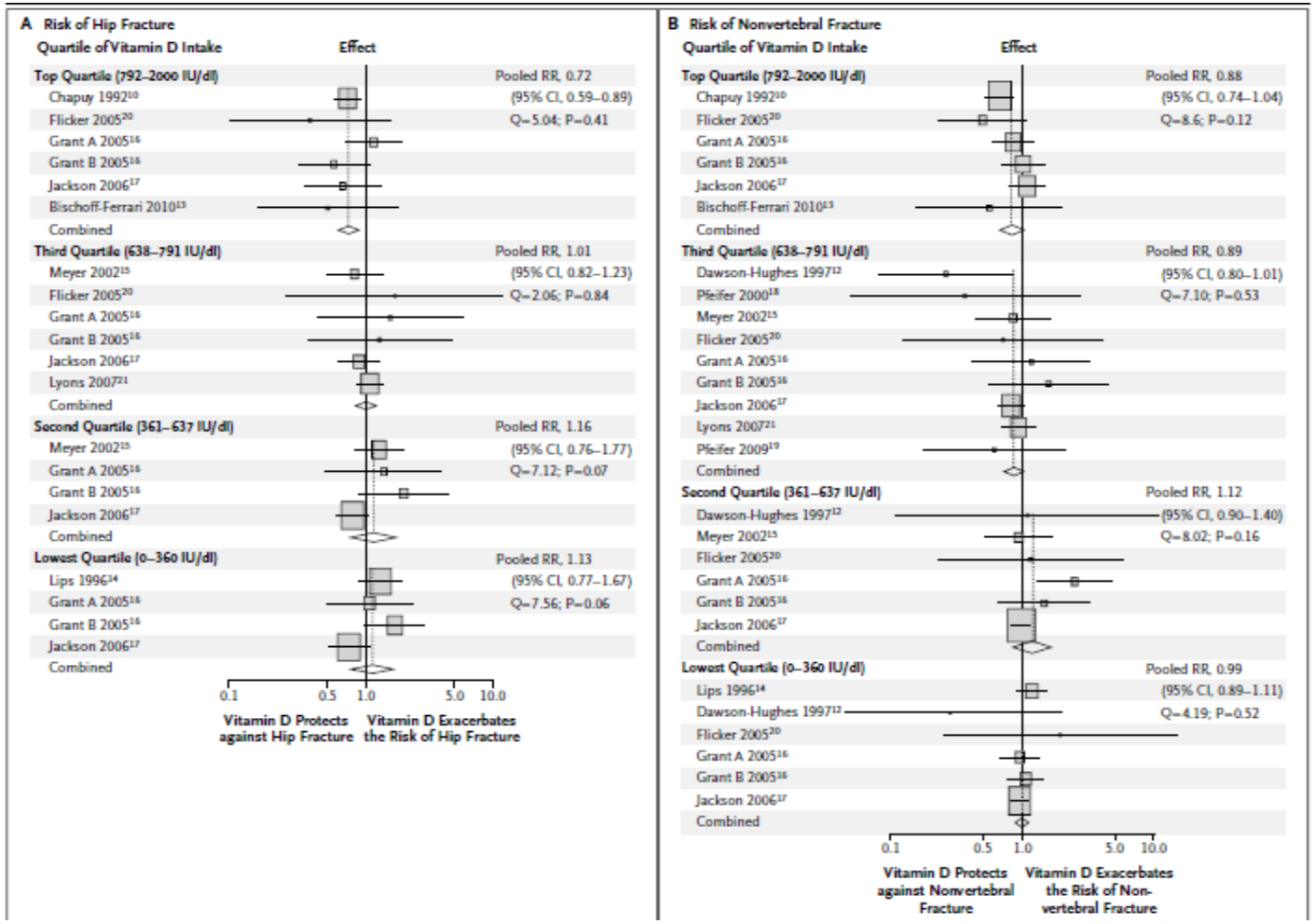
In conclusion, one year of high-dose vitamin D given to postmenopausal women with 25(OH)D levels <30 ng/mL (21 ± 3 ng/mL at baseline) had a trivial effect on calcium absorption, and no clinically meaningful beneficial effects on bone mineral density, muscle function or falls. Study results do not justify the common and frequently touted[4-6,42] practice of administering high-dose vitamin D to older adults, in order to maintain serum 25(OH)D levels ≥30 ng/mL. Rather, study results support the Institute of Medicine's conclusion that vitamin D repletion is a serum 25(OH)D level of ≥20 ng/mL.

JAMA Intern Med. 2015
IMPACT FACTOR 20

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

A Pooled Analysis of Vitamin D Dose Requirements for Fracture Prevention



Given the
NNTof 27 to 45 for any nonvertebral and hip fracture prevention, and the high morbidity, mortality, and cost of fractures, our results are compelling for general vitamin D supplementation in the range of 700 to 800 IU/d in elderly persons.

New Engl J Med 2012

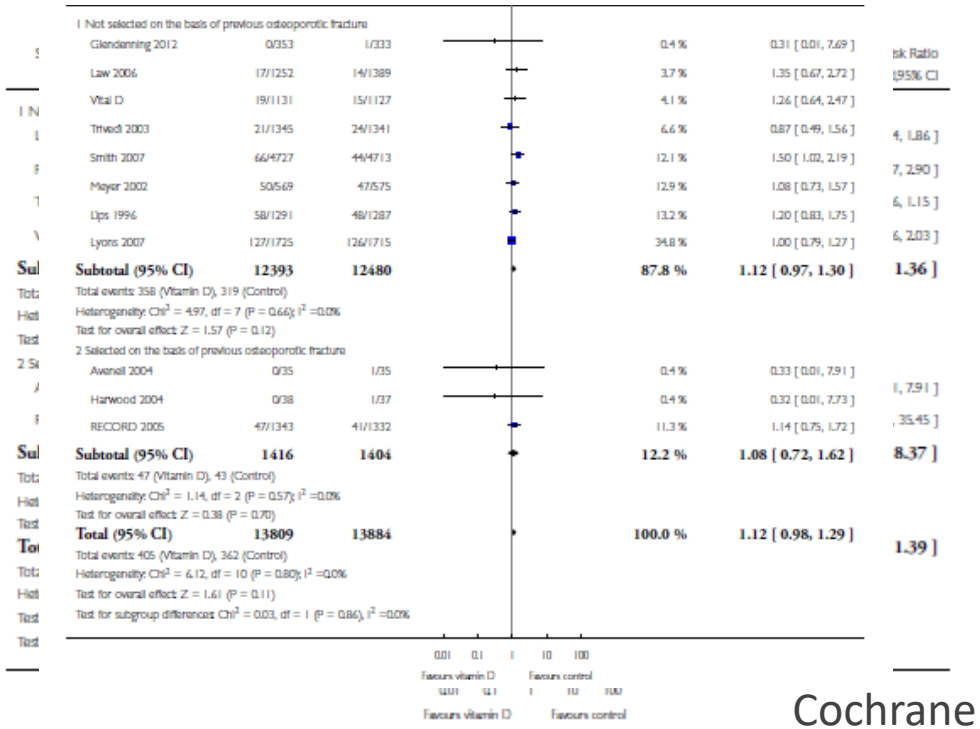
Cochrane Library
Cochrane Database of Systematic Reviews

Vitamin D and vitamin D analogues for preventing fractures in post-menopausal women and older men (Review)

Avenell A, Mak JCS, O'Connell D

Authors' conclusions

Vitamin D alone is unlikely to prevent fractures in the doses and formulations tested so far in older people.



Cochrane Database of Systematic Reviews 2014

2.1. What is the cut-off that defines vitamin D deficiency?

Italian data show that prevalence of vitamin D deficiency rises from 30% to 65% if the currently adopted cut-off should move
from 20 to 30 ng/ml

ITALIAN CHAPTER

Italian Association of Clinical Endocrinologists (AME) and Italian AACE Chapter Position Statement Clinical Management of Vitamin D Deficiency in Adults

Roberto Cesareo[1*], Roberto Attanasio[2], Marco Caputo[3], Roberto Castello[4], Iacopo Chiodini[5], Alberto Falchetti[6], Rinaldo Guglielmi[7], Enrico Papini[7], Assunta Santonati[8], Alfredo Scillitani[9], Vincenzo Toscano[10], Vincenzo Triggiani[11], Fabio Vescini[12], and Michele Zini[13]

Currently, there is consensus that 25OH-D levels lower than 20 ng/mL (50 nmol/L) are associated in adults with

- Secondary hyperparathyroidism, osteomalacia or osteoporosis;
- Proximal limb muscle weakness and ataxia;
- Increased risk of falls;
- Increased risk of fractures;
- Hampered effect of drugs used for osteoporosis.

Secondo la vostra percezione la vitamina D in italia (colecalciferolo

a) Sovrapponibili al resto dei paesi europei
b) In quantità inferiore
c) In modo sostanzialmente sovrapponibile
d) Non lo so

Analisi VitaminaD

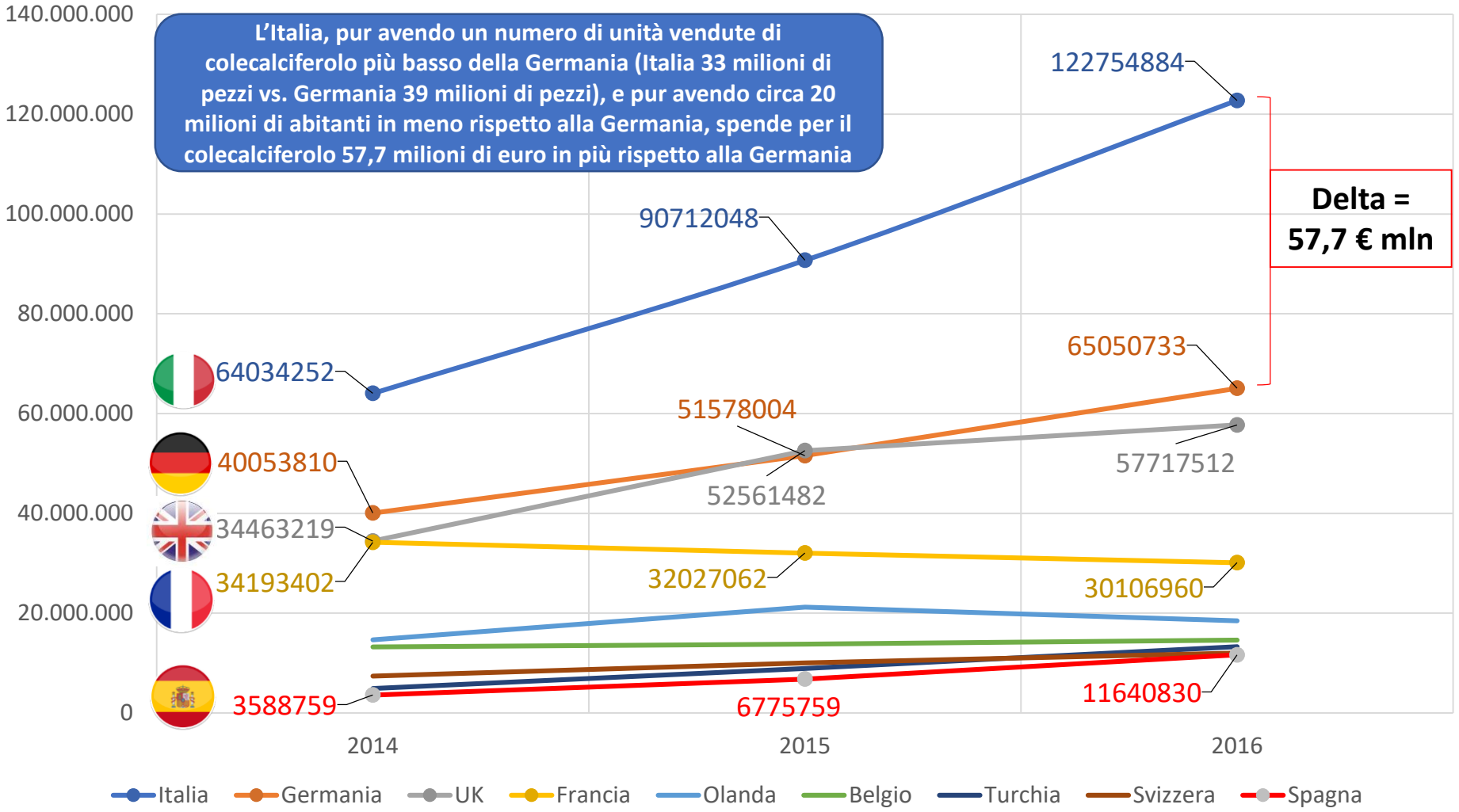
Mercato Colecalciferolo EUROPA

	UNITS 2014	UNITS 2015	UNITS 2016	VALUES 2014	VALUES 2015	VALUES 2016	Costo Medio Confezione
Italia	20.141.585	28.029.533	33.652.388	**64.034.252**	**90.712.048**	**122.754.884**	**€ 3,65**
Germania	29.588.444	34.900.197	39.036.628	40.053.810	51.578.004	65.050.733	€ 1,67
Francia	36.077.001	35.080.673	36.712.359	34.193.402	32.027.062	30.106.960	€ 0,82
Turchia	7.275.808	13.431.532	18.679.067	4.916.402	8.901.772	13.255.911	€ 0,71
Svizzera	2.035.699	2.458.921	2.970.139	7.404.326	10.050.024	12.018.005	€ 4,04
Spagna	1.758.110	2.846.533	3.567.158	3.588.759	6.775.759	11.540.830	€ 3,23
Resto EU*	169.903.846	19.975.238	23.220.167	38.541.687	46.766.511	61.273.521	**€ 2,64**

Fonte: Internal Data FAES ; *22 paesi

Analisi VitaminaD

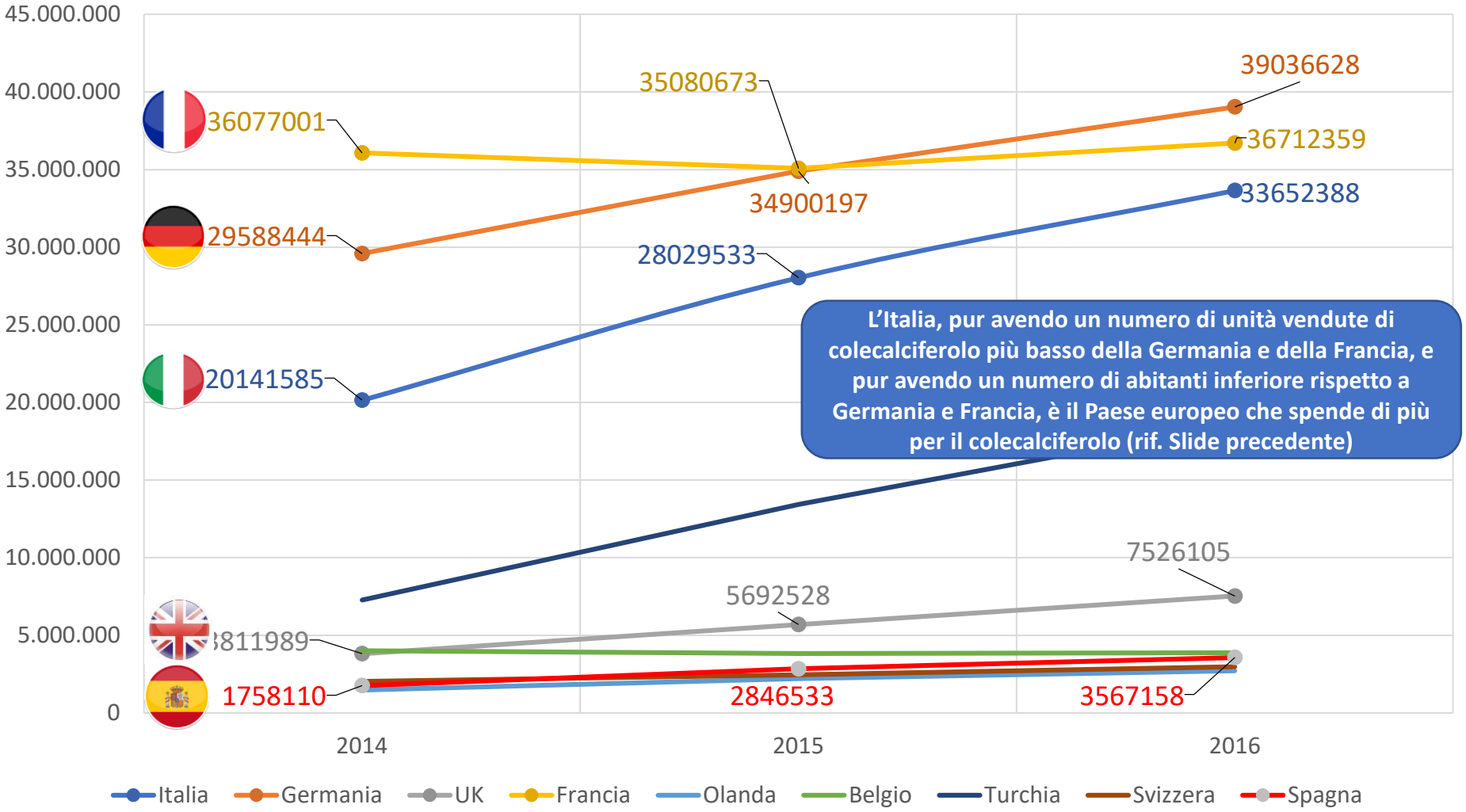
Mercato Colecalciferolo EUROPA - Valori



Fonte: Internal Data FAES

Analisi VitaminaD

Mercato Colecalciferolo EUROPA - Units



Fonte: Internal Data FAES

Tabella 2.8 Primi trenta principi attivi per spesa convenzionata di classe A-SSN: confronto 2017-2016

ATC	Principio attivo	Spesa (milioni)	%*	Spesa lorda pro capite	Rango 2017	Rango 2016
A	pantoprazolo	277,9	2,7	4,59	1	1
C	rosuvastatina	244,8	2,3	4,04	2	2
C	atorvastatina	234,5	2,3	3,87	3	3
A	colecalciferolo	233,9	2,2	3,86	4	6
C	ezetimibe/simvastatina	186,8	1,8	3,08	5	8
A	lansoprazolo	180,4	1,7	2,98	6	4
J	amoxicillina/acido clavulanico	173,7	1,7	2,87	7	7
A	omeprazolo	163,5	1,6	2,70	8	9
R	salmeterolo/fluticasone	161,3	1,5	2,66	9	5
A	esomeprazolo	149,2	1,4	2,46	10	11

Tabella 2.9 Primi trenta principi attivi* a maggiore variazione di spesa convenzionata rispetto all'anno precedente: confronto 2017-2016

ATC	Principio attivo	Spesa pro capite	Δ% 17-16	DDD/1000 ab die	Δ% 17-16
H	teriparatide	1,16	61,1	0,2	62,6
R	fluticasone/vilanterolo	1,59	30,8	2,5	25,1
J	immunoglobulina umana antiepatite B	0,52	30,7	0,0	29,1
A	colecalciferolo	3,86	26,0	10,5	25,6
C	ezetimibe	1,88	25,3	2,9	25,7
M	febuxostat	0,86	17,4	1,8	17,6
N	tapentadol	1,06	16,8	0,5	17,2
N	naloxone/ossicodone	1,06	9,1	0,4	9,9
C	olmesartan/amlodipina	1,53	8,4	4,8	13,4

DATI OSMED 2017

DOMANDA

- Nel Lazio dal 2017 la prescirizione della vitamina D è soggetta alla compilazione di piano terapeutico.

- A) si lo conosco e lo utilizzo sempre
- B) si lo conosco e lo utilizzo saltuariamente
- C) si lo conosco ma non lo utilizzo
- C) non lo conosco

ALLEGATO 3

SCHEDA REGIONALE PER LA PRESCRIZIONE DI

Colecalciferolo uso orale in pazienti adulti

Paziente: _____ Codice Fiscale: _____

Età _____ Sesso M ☐ F ☐

Regione di appartenenza dell'Assistito _____ ASL_____ Distretto_____

- **Prevenzione della carenza di vitamina D**:

☐ Gravidanza, allattamento

☐ Trattamento con anticonvulsivanti

☐ Trattamento con terapie corticosteroidee a lungo termine

☐ Altre condizioni cliniche documentate: _____

_____

☐ **Trattamento della carenza di vitamina D**:

Indagine di laboratorio: valore_____ data: _____

☐ **Osteoporosi: solo se associato a farmaci nota 79**

Farmaco associato: _____

PIANO TERAPEUTICO

FARMACO	POSOLOGIA

Durata prevista del trattamento[1] _____

☐ Primo ciclo di terapia ☐ Prosecuzione terapia

Medico Prescrittore Dr / Prof _____

Tel. _____ Data_____

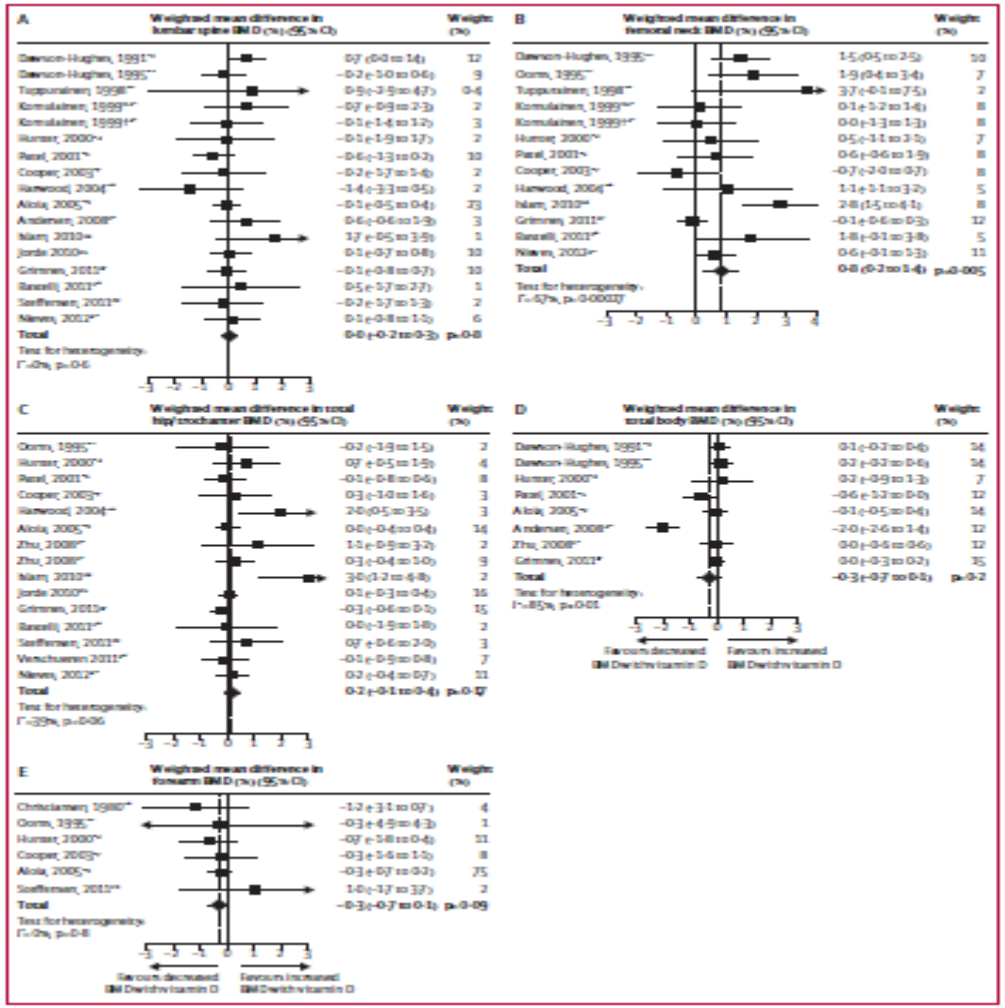
Firma e timbro del medico prescrittore[2] Timbro del Centro Prescrittore

1. Validità massima 12 mesi
2. I dati identificativi del Medico devono essere tali da permettere eventuali tempestive comunicazioni

Decreto Regione Lazio 2017

CHI TRATTARE

Effects of vitamin D supplements on bone mineral density: a systematic review and meta-analysis



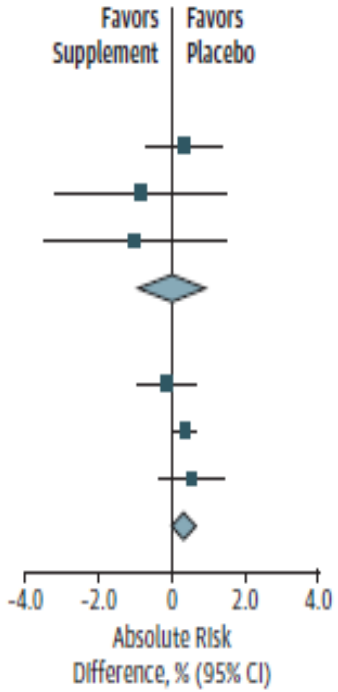
Interpretation Continuing widespread use of vitamin D for osteoporosis prevention in community-dwelling adults without specifi c risk factors for vitamin D deficiency seems to be inappropriate

Lancet 2014

Vitamin D, Calcium, or Combined Supplementation for the Primary Prevention of Fractures in Community-Dwelling Adults
Evidence Report and Systematic Review for the US Preventive Services Task Force

Figure 4. Comparison of Incident Kidney Stones in Randomized Trials Comparing Calcium or Both Vitamin D and Calcium With Placebo

Source	No. of Patients With Kidney Stones/Total No. (%)		Risk Ratio (95% CI)	Absolute Risk Difference, % (95% CI)
	Supplement	Placebo		
Calcium				
Lappe et al,[21] 2007	3/445 (0.7)	1/288 (0.4)	1.94 (0.20-18.57)	0.33 (-0.69 to 1.35)
Riggs et al,[20] 1998	0/119 (0)	1/117 (0.9)	0.33 (0.01-7.97)	-0.85 (-3.18 to 1.47)
Reid et al,[22] 2008	0/191 (0)	1/99 (1.0)	0.17 (0.01-4.22)	-1.01 (-3.50 to 1.48)
Subtotal: I^2 = 0.0%; P = .42			0.68 (0.14-3.36)	0.00 (-0.88 to 0.87)
Vitamin D with calcium				
Lappe et al,[21] 2007	1/446 (0.2)	1/288 (0.4)	0.65 (0.04-10.28)	-0.12 (-0.93 to 0.69)
WHI,[27] 2011	449/18 176 (2.5)	381/18 106 (2.1)	1.17 (1.03-1.34)	0.37 (0.06 to 0.67)
Lappe et al,[25] 2017	16/1102 (1.5)	10/1095 (0.9)	1.59 (0.72-3.49)	0.54 (-0.36 to 1.44)
Subtotal: I^2 = 0.0%; P = .69			1.18 (1.04-1.35)	0.88 (0.05 to 0.80)



Conclusions

Vitamin D supplementation alone or with calcium was not associated with reduced fracture incidence among community-dwelling adults without known vitamin D deficiency, osteoporosis, or prior fracture. Vitamin D with calcium was associated with an increase in the incidence of kidney stones.

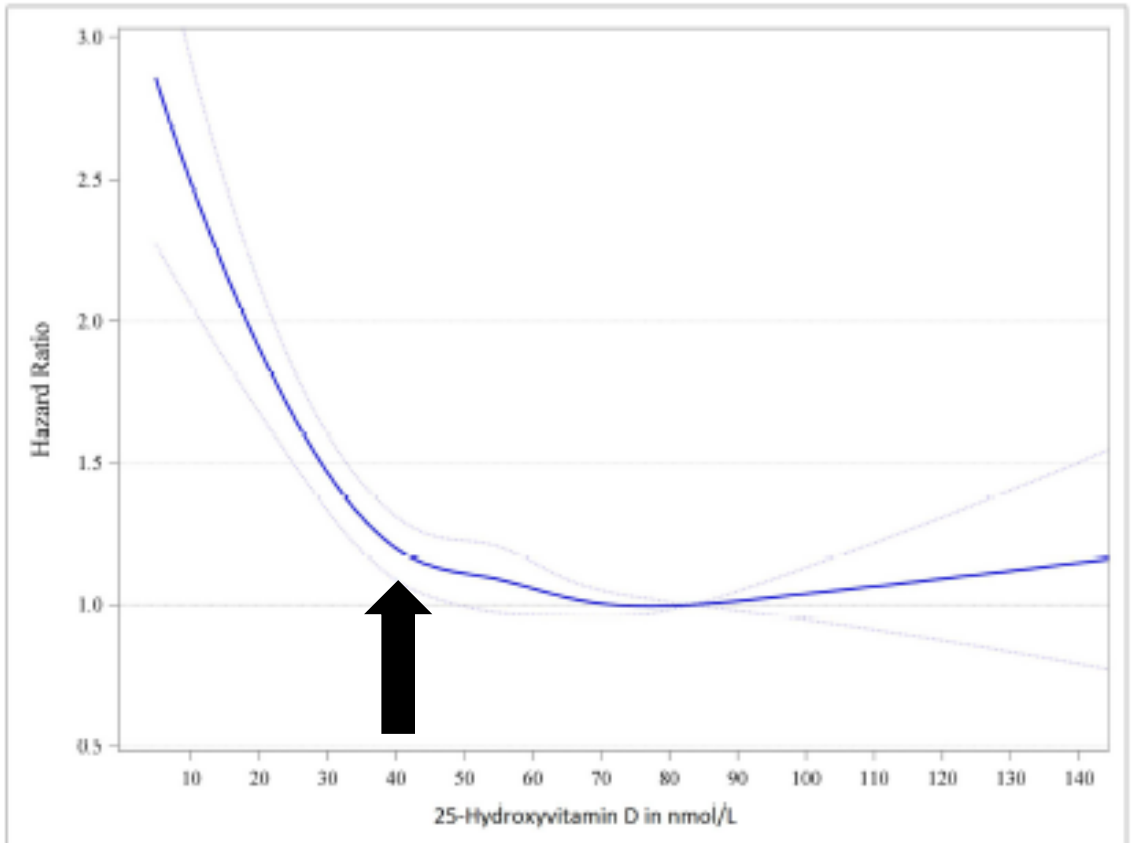
JAMA 2018

Chi di voi prescrive vitamina D per la eventuale prevenzione degli effetti extrascheletrici?

- Si la prescrivo

- No non la prescrivo mai in tali contesti clinici

Vitamin D and mortality: Individual participant data meta-analysis of standardized 25-hydroxyvitamin D in 26916 individuals from a European consortium



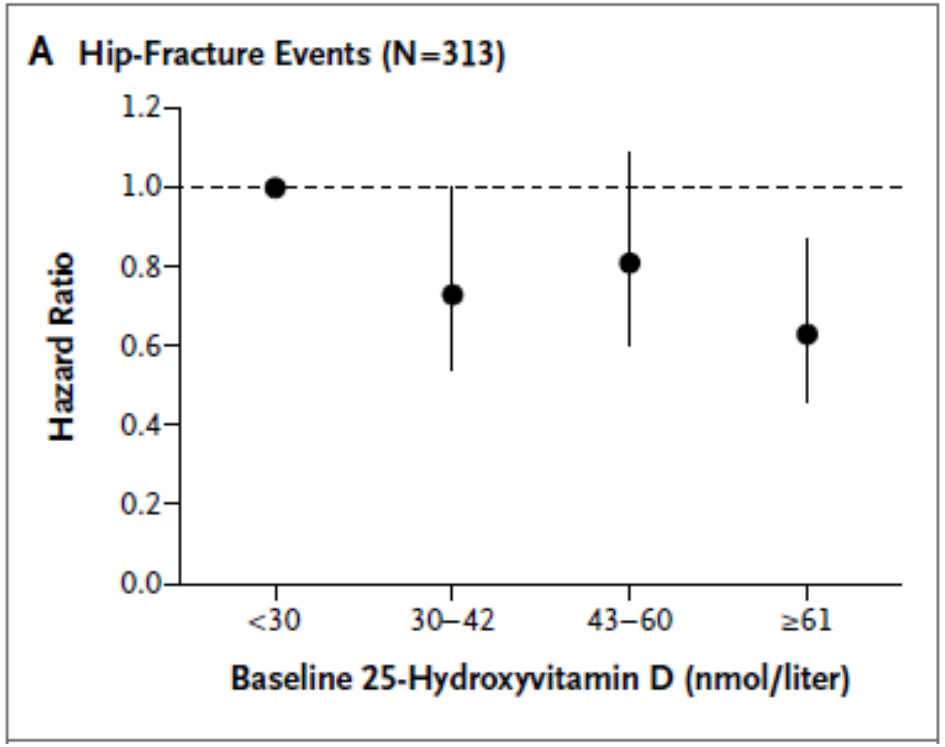
Mortalità solo cardiovasc
Aumenta sotto 40 nanomoli (16 ng/dl)
È la causa o l'effetto?

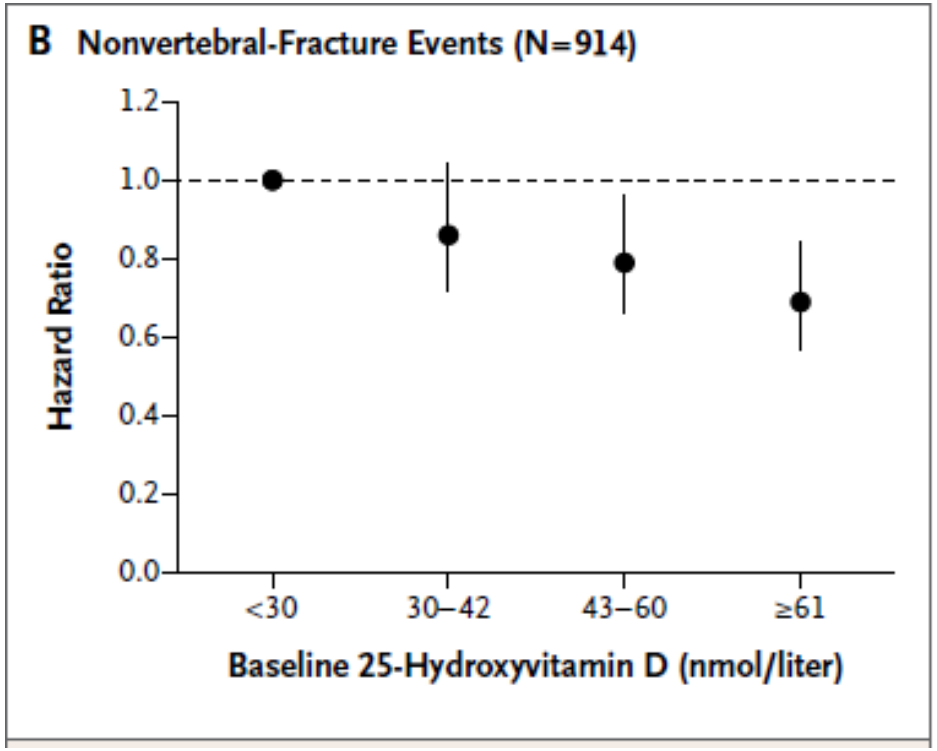
PLOS ONE, 2017

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

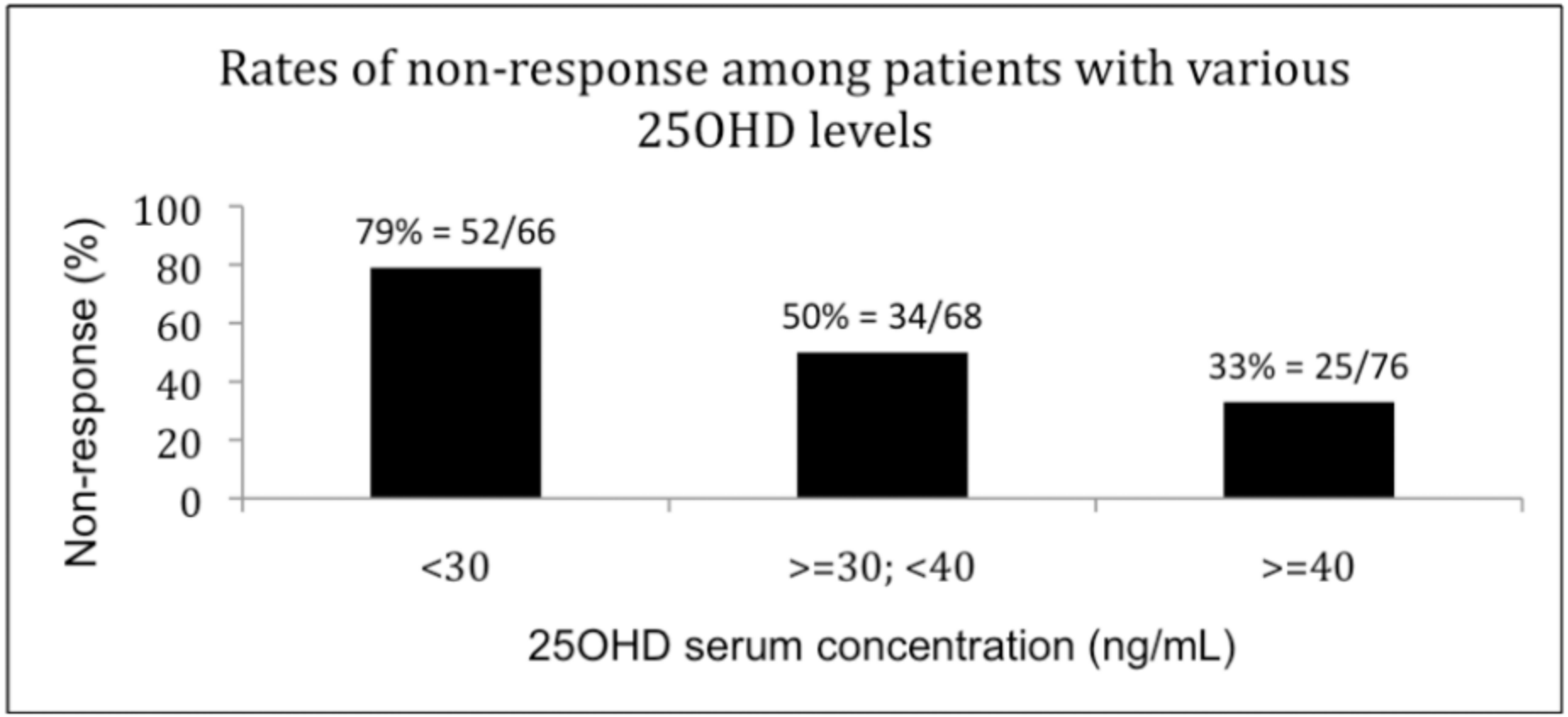
A Pooled Analysis of Vitamin D Dose Requirements for Fracture Prevention





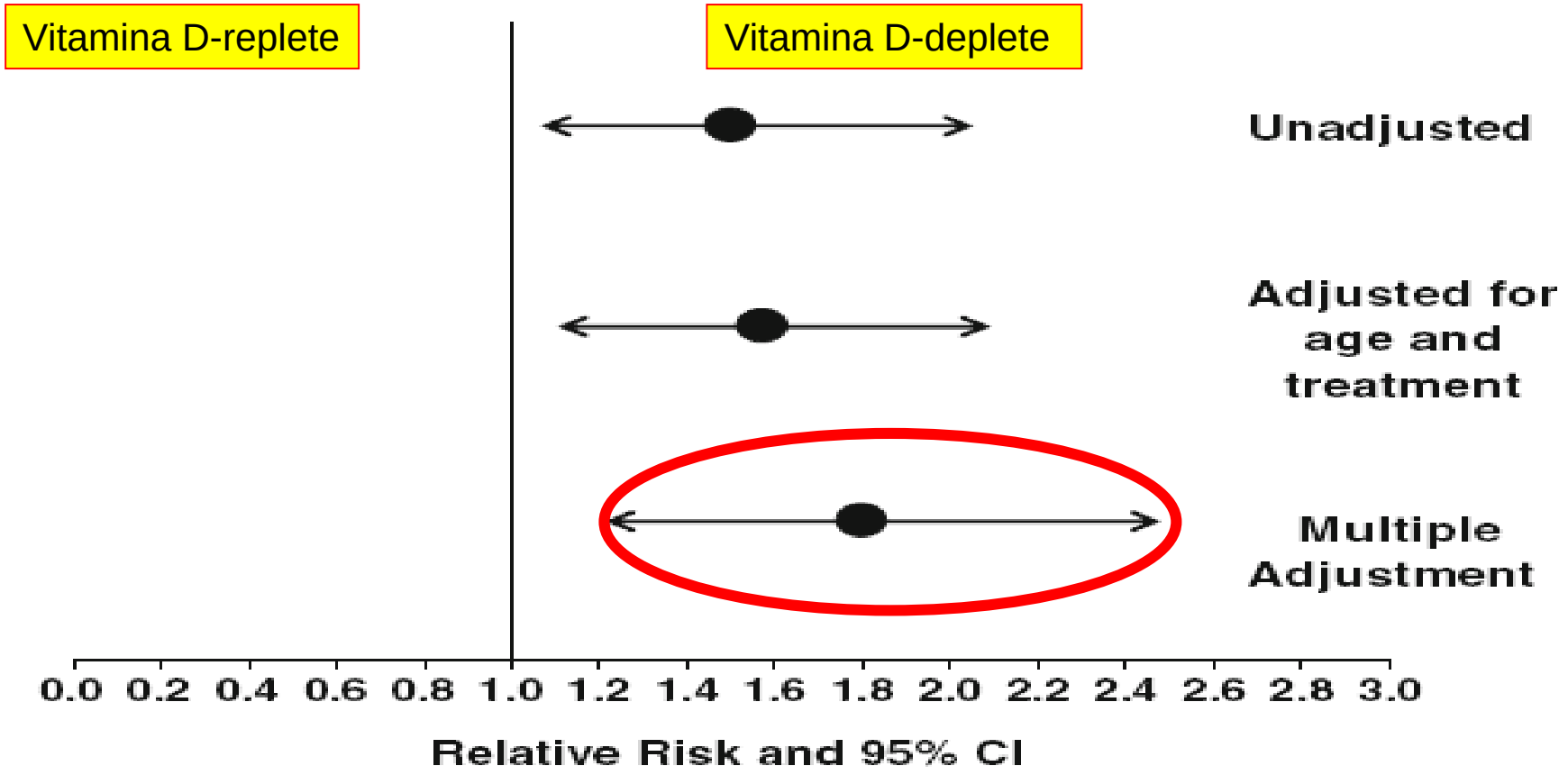
N Engl J Med 2012

The 25(OH)D Level Needed To Maintain A Favorable Bisphosphonate Response Is ≥33ng/ml



Osteop Int 2012

Il rischio di frattura è più elevato in donne osteoporotiche in trattamento con alendronato, risedronato o raloxifene ma deplete di vitamina D (vs replete)



RR corretto per tipo di trattamento, età, precedenti fratture, durata del follow-up ed intake di calcio

TABLE 1. CHARACTERISTICS OF THE RANDOMIZED PARTICIPANTS AT FLEX BASELINE

Characteristic	*Placebo (n = 437)*	*Alendronate 5 mg (n = 329)*	*Alendronate 10 mg (n = 333)*	*p Value*
Mean age ± SD (years)	73.7 ± 5.9	72.7 ± 5.7	72.9 ± 5.5	0.046

All participants were strongly encouraged to take a daily supplement containing calcium (500 mg) and vitamin D (250 IU).

The proportion of participants receiving the supplement was 97.5%; This proportion was similar at baseline and throughout the 3 years of follow-up in the three treatment groups

Bone HG, *et al*. N Engl J Med 2004

ITALIAN CHAPTER

Italian Association of Clinical Endocrinologists (AME) and Italian AACE Chapter Position Statement Clinical Management of Vitamin D Deficiency in Adults

Roberto Cesareo[1*], Roberto Attanasio[2], Marco Caputo[3], Roberto Castello[4], Iacopo Chiodini[5], Alberto Falchetti[6], Rinaldo Guglielmi[7], Enrico Papini[7], Assunta Santonati[8], Alfredo Scillitani[9], Vincenzo Toscano[10], Vincenzo Triggiani[11], Fabio Vescini[12], and Michele Zini[13]

Even though many authors found low vitamin D plasma levels in healthy people worldwide, no evidence exists as for a benefit of vitamin D deficiency screening and/or treatment at a general population level [6].

We recommend screening for vitamin D deficiency in at risk populations.
We recommend against screening for vitamin D deficiency in healthy people.

Accordingly, we believe that vitamin D determination and substitution treatment are not yet warranted to prevent or treat clinical disorders that are different from bone diseases.

We recommend to maintain 25(OH)D levels above 30 ng/mL (75 nmol/L) in subjects:

- With osteopenia, osteoporosis or fragility fractures;
- On treatment for osteoporosis;
- Who belong to at risk categories (see Section 3.1).

We suggest to consider serum PTH measurement when vitamin D values are lower than 30 ng/mL (75 nmol/L), particularly if tested in Summer and Autumn.

- Granulomatous disorders and some lymphomas (in these cases, also 1.25$(OH)_2$D should be tested)

COME TRATTARE

Forme Commerciali

PRINCIPIO ATTIVO	FORMULAZIONI	EMIVITA
colecalciferolo	orali (gtt, fl) parenterali (i.m.)	2-3 mesi
ergocalciferolo	parenterali (i. m.) orali	2-3 mesi
calcifediolo	gtt	15 giorni
α-calcidolo	orali (gtt, cp)	24 ore
diidrotachisterolo	gtt	24 ore
calcitriolo	cp	2-4 ore

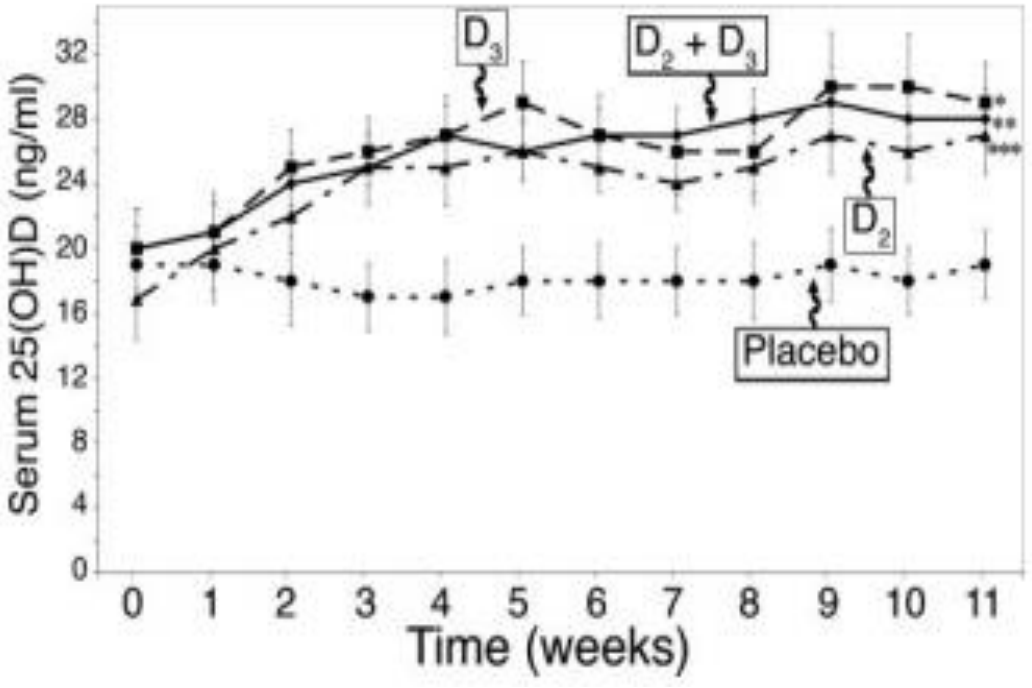
Tra i metaboliti della vitamina D usualmente prescrivete maggiormente

- Calcifediolo
- Colecalciferolo
- Alfa-1 calcidiolo
- calcitriolo

VITAMINA D2 O VITAMINA D3

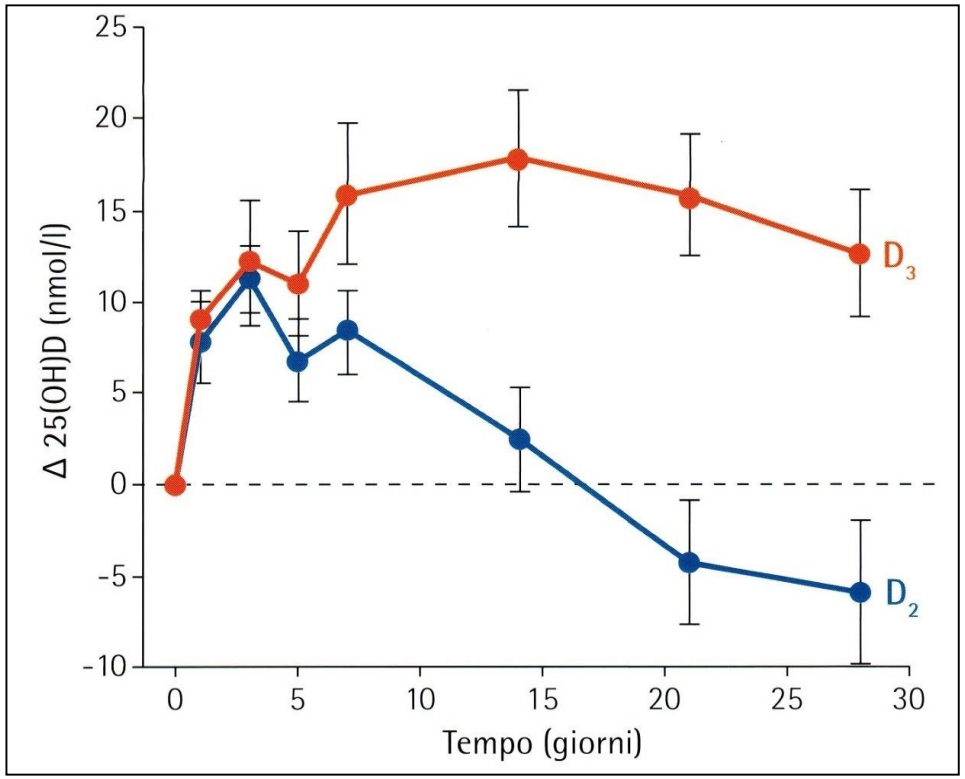
Vitamin D_2 Is as Effective as Vitamin D_3 in Maintaining Circulating Concentrations of 25-Hydroxyvitamin D

Michael F. Holick, Rachael M. Biancuzzo, Tai C. Chen, Ellen K. Klein, Azzie Young, Douglass Bibuld, Richard Reitz, Wael Salameh, Allen Ameri, and Andrew D. Tannenbaum



Vitamin D_2 Is Much Less Effective than Vitamin D_3 in Humans

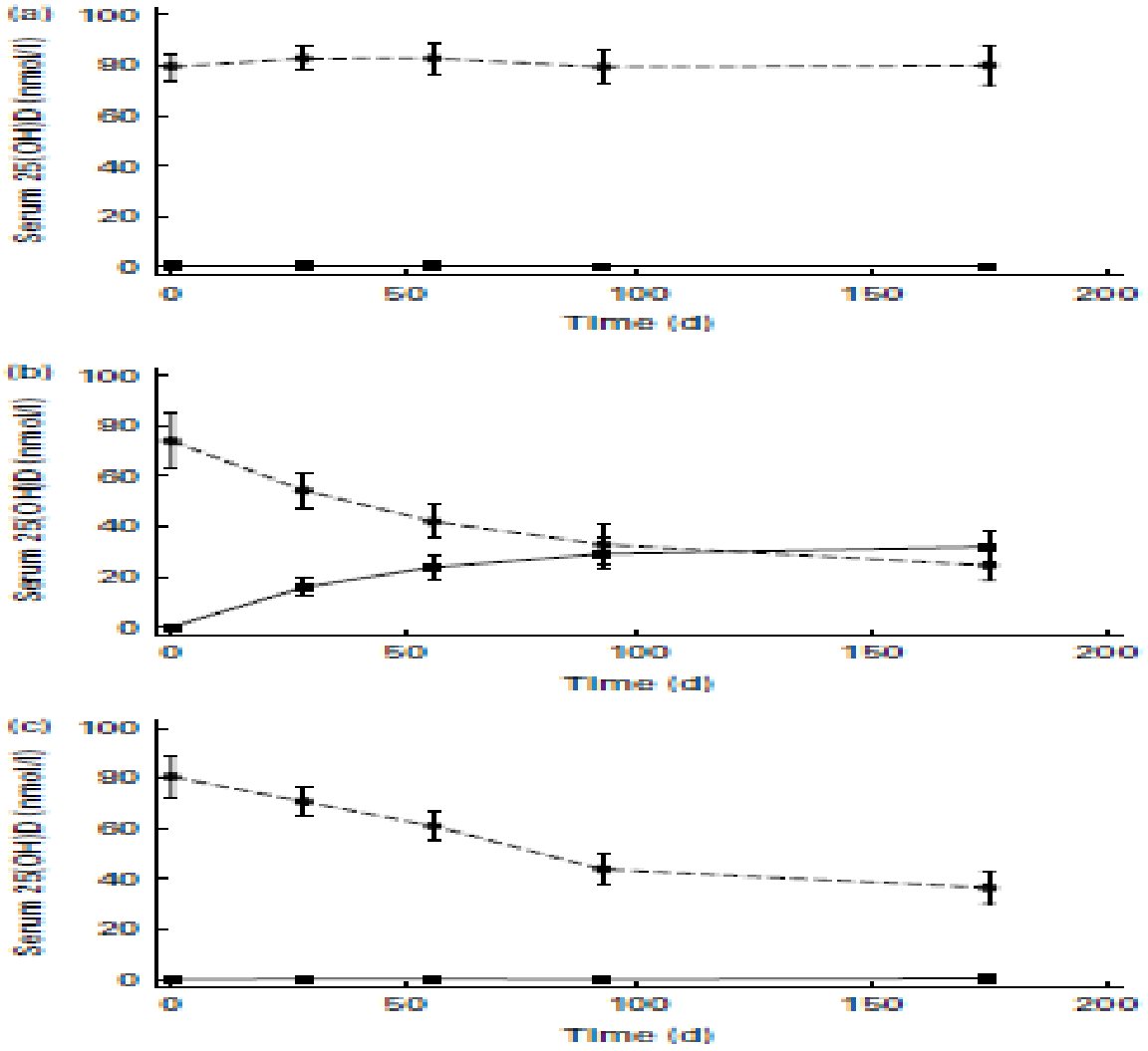
LAURA A. G. ARMAS, BRUCE W. HOLLIS, AND ROBERT P. HEANEY



50.000 UI

Jcem 2008;

Long-term vitamin D_3 supplementation is more effective than vitamin D_2 in maintaining serum 25-hydroxyvitamin D status over the winter months



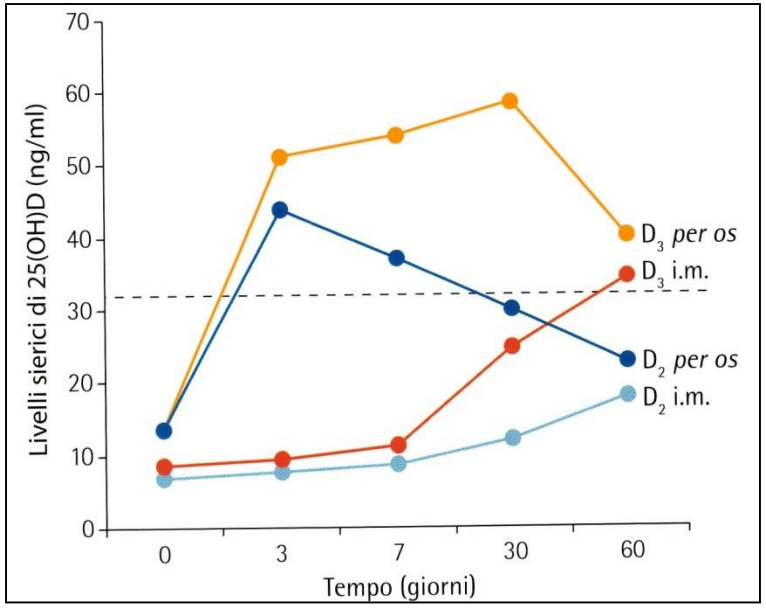
Vit-d3

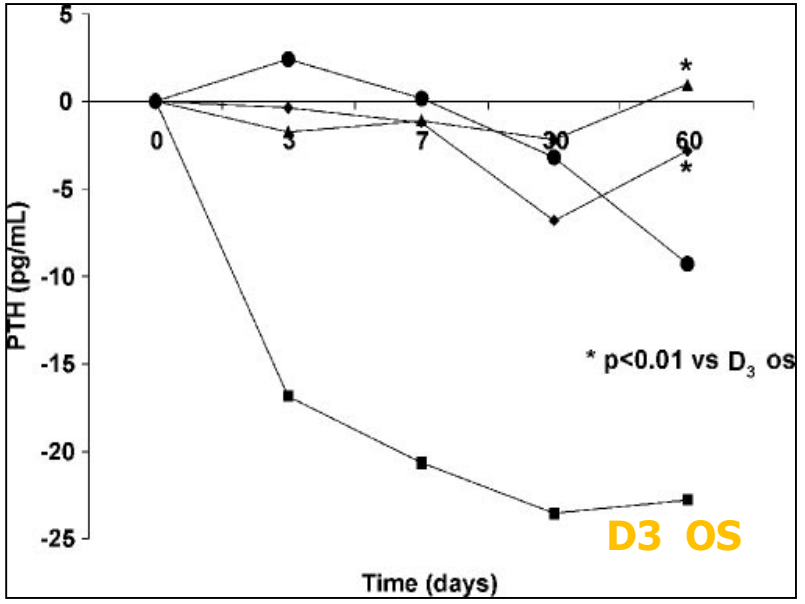
Vit-d2

Placebo

British Journal of Nutrition 2013

TERAPIA ORALE O INTRA MUSCOLO





32 donne di età tra 66 e 97 anni
Durata del trattamento 60 giorni
4 gruppi:
1) 300.000 UI colecalciferolo im
2) 300.000 UI colecalciferolo os
3) 300.000 UI ergocalciferolo im
4) 300.000 UI ergocalciferolo os

ECCEZIONE

Sindrome da malassorbimento

Patologie epato-biliari

Romagnoli JCEM 2008

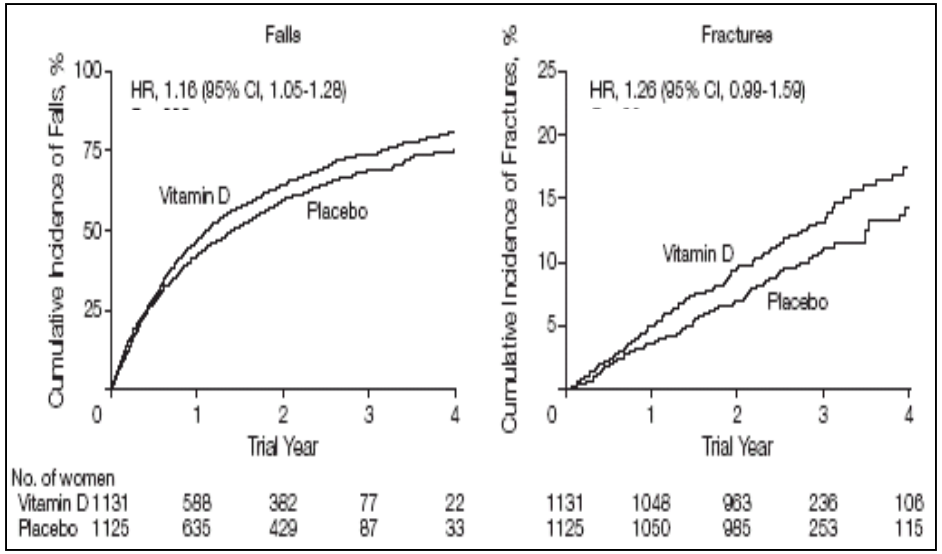
4.3. How to Supply Vitamin D?

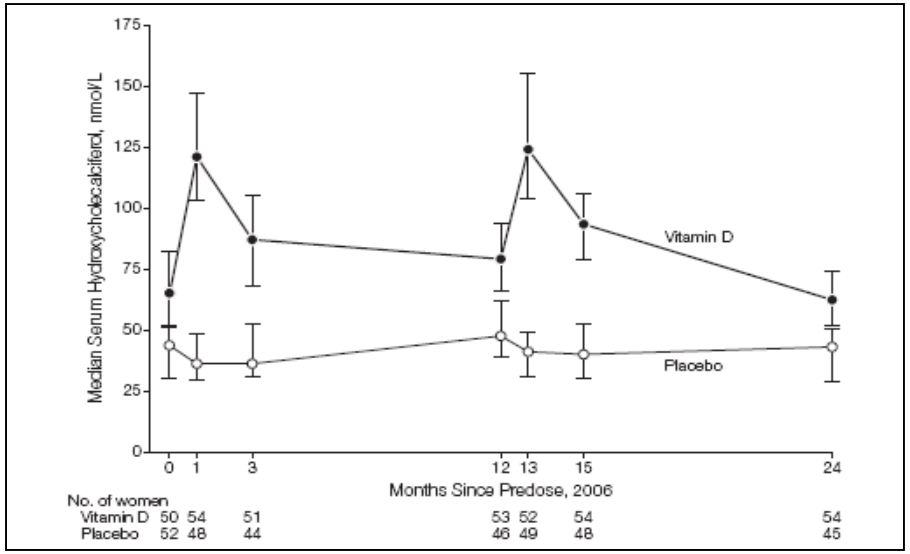
We recommend treatment with cholecalciferol by mouth as the first line therapy in most patients.

4.4. What Is the Appropriate Dosage of Vitamin D Supplementation?

Annual High-Dose Oral Vitamin D and Falls and Fractures in Older Women

A Randomized Controlled Trial





Conclusion Among older community-dwelling women, annual oral administration of high-dose cholecalciferol resulted in an increased risk of falls and fractures.

Original Investigation | LESS IS MORE

Monthly High-Dose Vitamin D Treatment for the Prevention of Functional Decline
A Randomized Clinical Trial

Heike A. Bischoff-Ferrari, MD, DrPH; Bess Dawson-Hughes, MD; E. John Orav, PhD; Hannes B. Staehelin, MD; Otto W. Meyer, MD; Robert Theiler, MD; Walter Dick, MD; Walter C. Willett, MD, DrPH; Andreas Egli, MD

rivedilo

Primary End Point of Mean SPPB Functional Decline Score				
Unadjusted at baseline, mean (SD)	9.96 (1.53)	9.81 (1.60)	9.34 (1.57)	
Adjusted change (95% CI) at 6 mo	0.17 (−0.06 to 0.41)	0.16 (−0.08 to 0.40)	0.16 (−0.08 to 0.40)	.26[d]
Adjusted change (95% CI) at 12 mo	0.38 (0.07 to 0.68)	0.10 (−0.21 to 0.41)	0.11 (−0.19 to 0.43)	
Secondary End Point of Prevention of Falls, Value (95% CI)				
Adjusted % of fallers by incidence of first fall				
At 0-6 mo	35.0 (24.3 to 47.5)	39.5 (28.1 to 52.0)	49.0 (36.9 to 61.2)	.26[b]
At 7-12 mo	26.6 (17.3 to 38.6)	41.3 (29.8 to 53.9)	38.5 (27.4 to 50.9)	.17[b]
At 0-12 mo	47.9 (35.8 to 60.3)	66.9 (54.4 to 77.5)[c]	66.1 (53.5 to 76.8)[c]	.048[b]
Adjusted mean No. of falls				
At 0-6 mo	0.52 (0.26 to 0.79)	0.86 (0.50 to 1.12)	0.67 (0.40 to 0.93)	.19[b]
At 7-12 mo	0.46 (0.20 to 0.72)	0.69 (0.43 to 0.95)	0.71 (0.45 to 0.97)	.31[b]
At 0-12 mo	0.94 (0.60 to 1.29)	1.47 (1.13 to 1.82)[c]	1.24 (0.89 to 1.58)	.09[b]

Jama Intern Med 2016

Linee guida su prevenzione e trattamento dell'ipovitaminosi D con colecalciferolo

Guidelines on prevention and treatment of vitamin D deficiency

S. Adami[1], E. Romagnoli[2], V. Carnevale[2], A. Scillitani[3], A. Giusti[4], M. Rossini[1], D. Gatti[1], R. Nuti[5], S. Minisola[2]

Valore basale di 25(OH)D	Dose terapeutica cumulativa di vitamina D	Dose giornaliera di mantenimento
<10 ng/ml o 25 nmol/l	1.000.000	2.000
10-20 ng/ml o 25- 50 nmol/l	600.000	1.000
20-30 ng/ml o 50-75 nmol/l	300.000	800

?

Reumatismo 2011

Fortification of orange juice with vitamin D_2 or vitamin D_3 is as effective as an oral supplement in maintaining vitamin D status in adults[1–4]

Rachael M Biancuzzo, Azzie Young, Douglass Bibuld, Mona H Cai, Michael R Winter, Ellen K Klein, Allen Ameri, Richard Reitz, Wael Salameh, Tai C Chen, and Michael F Holick

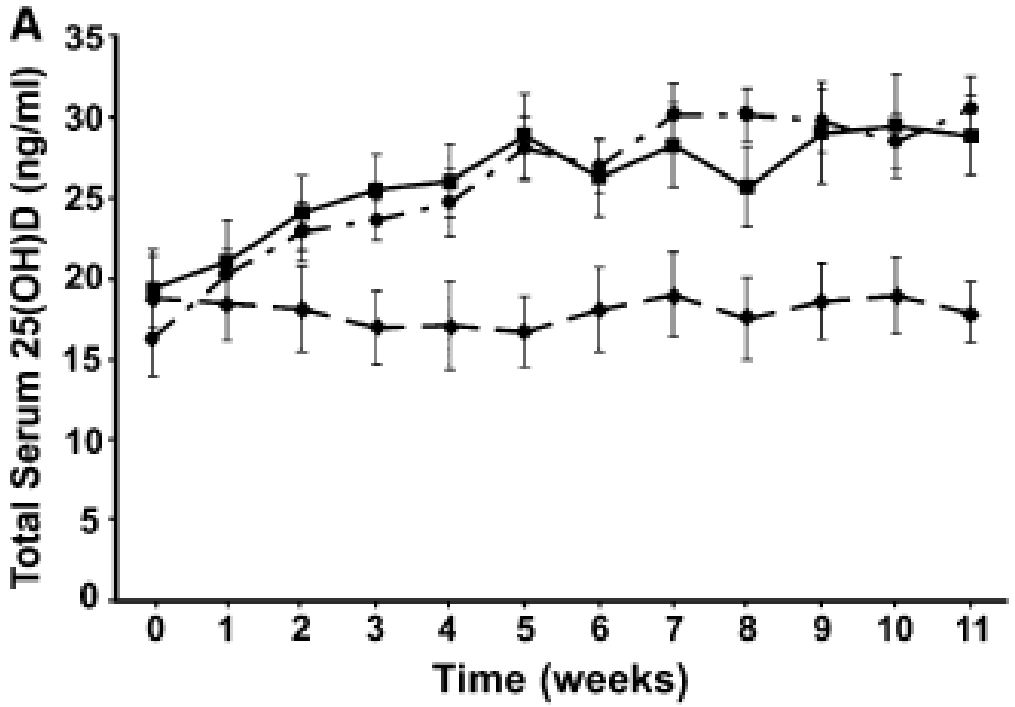
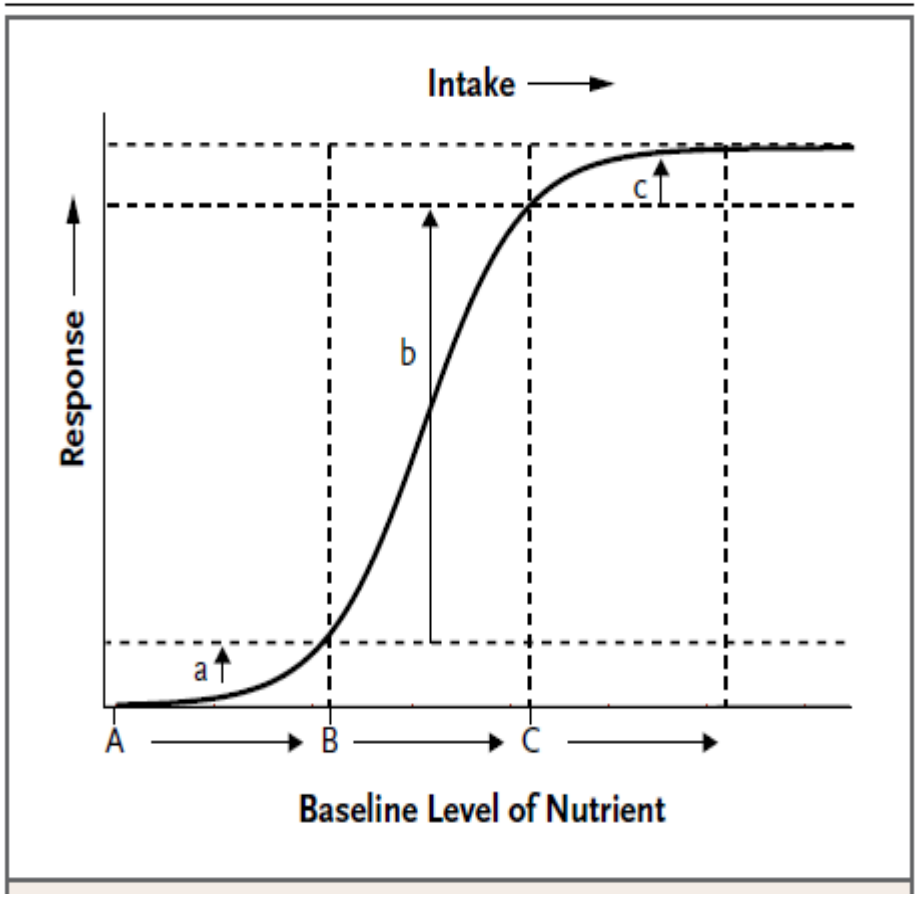


FIGURE 1. A: Mean (±SEM) total 25-hydroxyvitamin D [25(OH)D] concentrations over time after the oral administration of 1000 IU vitamin D_3 in orange juice (●; $n = 18$), 1000 IU vitamin D_3 in capsules (■; $n = 20$), or unfortified orange juice plus placebo capsules (♦; $n = 15$). No statistically significant differences were observed between areas under the curve for serum total 25(OH)D between the vitamin D_3 in orange juice and vitamin D_3 capsule groups (one-factor ANOVA, $P = 0.084$). B: Mean (±SEM) total

Vitamin D — Baseline Status and Effective Dose

Robert P. Heaney, M.D.



When baseline 25 (OH)D levels are very low it has been estimated an average 0.7-1.0 ng/ml rise for every 100 IU of daily ingested vitamin D. Subsequently, the increase slows as the 25 (OH)D levels arise

N Engl J Med 2012

4.4. What Is the Appropriate Dosage of Vitamin D Supplementation?

We suggest the following schedules for vitamin D supplementation:

- Deficiency and insufficiency: 50,000 IU once a week for 8 weeks; alternatively, a daily dose of 5000 IU for 8 weeks;
- Maintenance of sufficiency: 50,000 IU twice a month; alternatively, a daily dose of 1500–2000 IU.

We suggest an individually tailored approach for vitamin D administration, involving the patient's opinion about the schedule (daily, weekly or monthly) that may offer the best adherence.

ALLEGATO 3

SCHEDA REGIONALE PER LA PRESCRIZIONE DI

Colecalciferolo uso orale in pazienti adulti

Paziente: _____ Codice Fiscale: _____

Età _____ Sesso M ☐ F ☐

Regione di appartenenza dell'Assistito _____ ASL_____ Distretto_____

- **Prevenzione della carenza di vitamina D:**

☐ Gravidanza, allattamento

☐ Trattamento con anticonvulsivanti

☐ Trattamento con terapie corticosteroidee a lungo termine

☐ Altre condizioni cliniche documentate: _____

☐ **Trattamento della carenza di vitamina D:**

Indagine di laboratorio: valore_____ data: _____

☐ **Osteoporosi: solo se associato a farmaci nota 79**

Farmaco associato: _____

PIANO TERAPEUTICO

FARMACO	POSOLOGIA

Durata prevista del trattamento[1] _____

☐ Primo ciclo di terapia ☐ Prosecuzione terapia

Medico Prescrittore Dr / Prof _____

Tel. _____ Data_____

Firma e timbro del medico prescrittore[2] Timbro del Centro Prescrittore

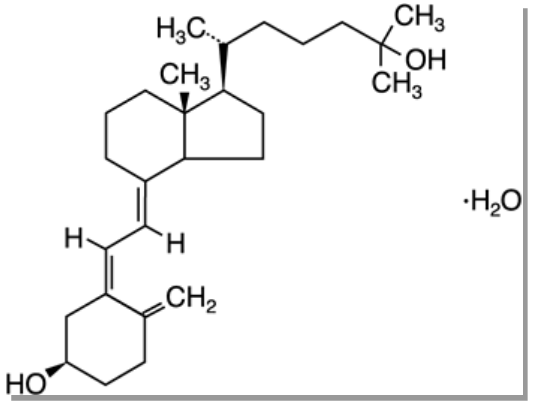
1. Validità massima 12 mesi
2. I dati identificativi del Medico devono essere tali da permettere eventuali tempestive comunicazioni

Confezionamento	Spesa Netta 2016 In €	Totale DDD (DDD: 800 UI)	Distribuzione DDD %	costo/DDD medio	Spesa se: Conversione 70 % DDD al costo del Flacone da 10 ml	Risparmio annuo	Impatto risparmio su 6 mesi
Colecalciferolo Flacone gtt 10 ml (100.000 UI)	1.627.978	47.183.875	28,5%	€ 0,0345	€ 4.284.925		
Colecalciferolo Flaconcini Monodose da 25.000 o 50.000 UI	15.211.906	118.403.406	71,5%	€ 0,1285	€ 5.318.466		
Totale Regione	**16.839.884**	**165.587.281**			**€ 9.603.391**	**€ 7.236.493**	**€ 3.618.246**

Decreto Regione Lazio 2017

4.5. When Hydroxylated Metabolites of Vitamin D Should Be Prescribed?

Calcifediolo 25-OH-VITAMINA D3



FARMACOCINETICA

Picco sierico 4h

Emivita plasmatica 18-21 giorni

Minore liposolubilità
(= minore stoccaggio nei grassi)

Seconda idrossilazione nel rene

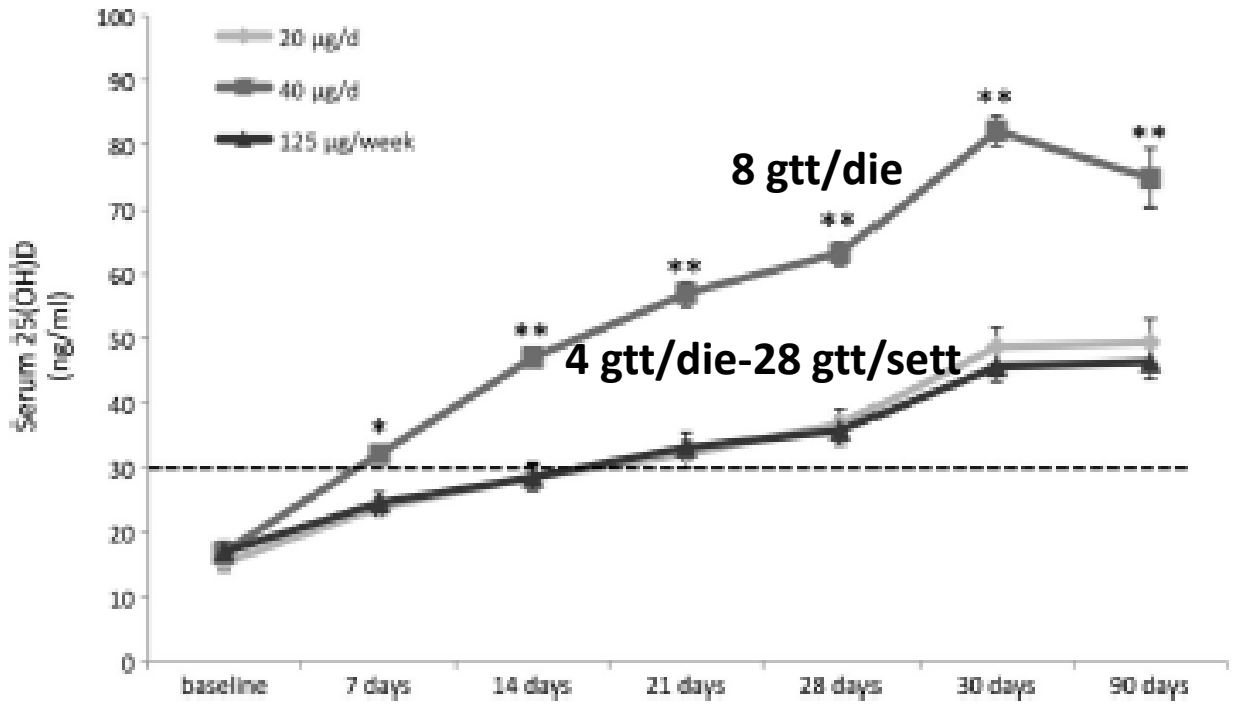
FARMACODINAMICA

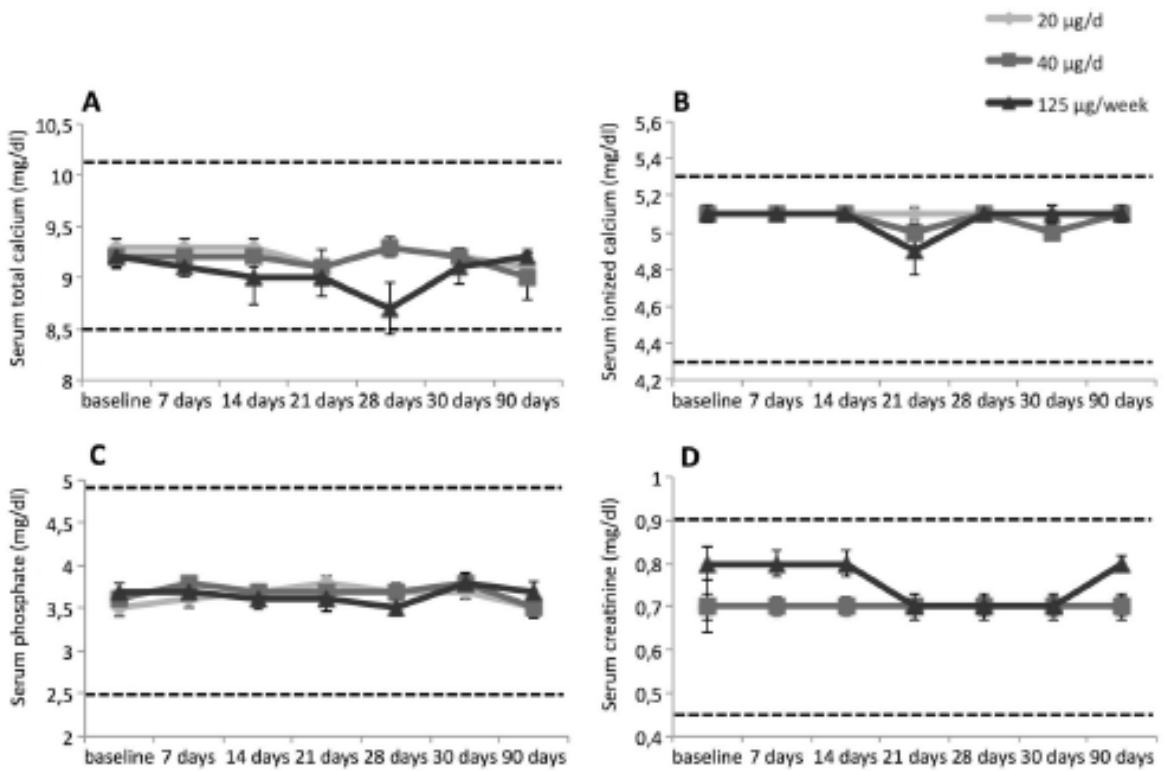
Azione più rapida

Più potente (tassi più elevati)

Correction of vitamin D status by calcidiol: pharmacokinetic profile, safety, and biochemical effects on bone and mineral metabolism of daily and weekly dosage regimens

S. Minisola[1] · L. Cianferotti[2] · P. Biondi[1] · C. Cipriani[1] · C. Fossi[2] · F. Franceschelli[2] · F. Giusti[2] · G. Leoncini[2] · J. Pepe[1] · H. A. Bischoff-Ferrari[3] · M. L. Brandi[2]





Osteop Int 2017

Relative effectiveness of oral 25-hydroxyvitamin D_3 and vitamin D_3 in raising wintertime serum 25-hydroxyvitamin D in older adults[1–4]

800UI/die
3,2 ggt/die

1,4 gtt/die

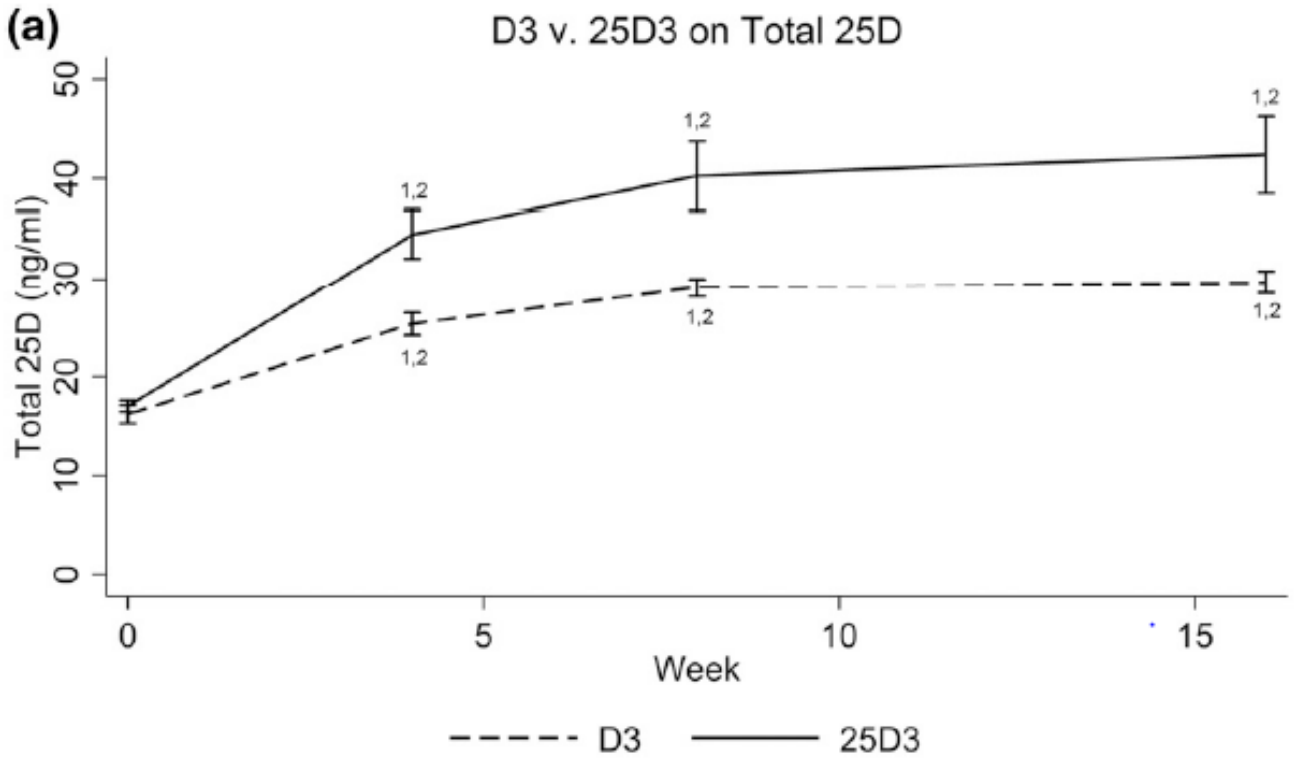
4 gtt/die

	Placebo	20 μg vitamin D_3/d	7 μg 25-hydroxyvitamin D_3/d	20 μg 25-hydroxyvitamin D_3/d	ANCOVA by intervention group (*P* value)[2]
n	16	13	14	12	—
Sex (M:F)	6:10	5:8	7:7	7:5	0.309
Dietary vitamin D (μg/d)	6.5 (2.9–7.9)[3]	7.6 (2.9–5.4)	5.1 (2.8–6.6)	4.4 (3.7–6.1)	0.161
Dietary calcium (mg/d)	970 ± 503[4]	1114 ± 494	1008 ± 415	794 ± 309	0.378
Serum 25(OH)D (nmol/L)[5]					
Before intervention[6]	42.7 ± 12.6[d]	49.7 ± 16.2[d]	42.5 ± 8.9[d]	38.2 ± 9.9[d]	0.471
During intervention	39.7 ± 11.1[a,d]	64.1 ± 9.5[b,e]	60.8 ± 8.1[b,e]	98.1 ± 20.5[c,e]	<0.0001
After intervention	41.2 ± 11.1[a,d]	69.0 ± 8.7[b,e]	70.7 ± 9.9[b,f]	134.6 ± 26.0[c,f]	<0.0001
ANOVA within group (*P*)[7]	0.01	<0.0001	<0.0001	<0.0001	
Serum calcium (mmol/L)[5,8]					
Before intervention[6]	8.4 ± 0.2	8.3 ± 0.3	8.4 ± 0.2	8.4 ± 0.3	—
During intervention	8.7 ± 0.2	8.7 ± 0.3	8.7 ± 0.2	8.7 ± 0.3	—
After intervention	8.5 ± 0.3	8.5 ± 0.2	8.5 ± 0.1	8.5 ± 0.3	—
Serum PTH (ng/mL)[5]					
Before intervention[6]	65.6 (47.4–70.2)	47.3 (41.5–57.5)	58.6 (52.8–69.9)[d]	57.9 (42.5–73.5)[d]	0.339
During intervention	66.4 (42.6–85.0)[a]	43.3 (39.8–53.3)[a,b]	49.0 (44.5–63.7)[b,e]	48.2 (39.1–66.6)[b,e]	0.013
After intervention	65.8 (54.5–87.8)[a]	44.2 (40.1–52.7)[a,b]	52.7 (41.1–62.7)[b,e]	40.5 (34.6–61.6)[b,e]	0.001
ANOVA within group (*P*)[7]	0.099	0.578	0.010	0.0004	

Am J Clin Nutr 2012

Effects of Cholecalciferol vs Calcifediol on Total and Free 25-Hydroxyvitamin D and Parathyroid Hormone

10 gtt/die (60 µgr/die) COLECALCIFEROLO
Versus
4 gtt/ die (20 µgr/die) CALCIFEDIOLO

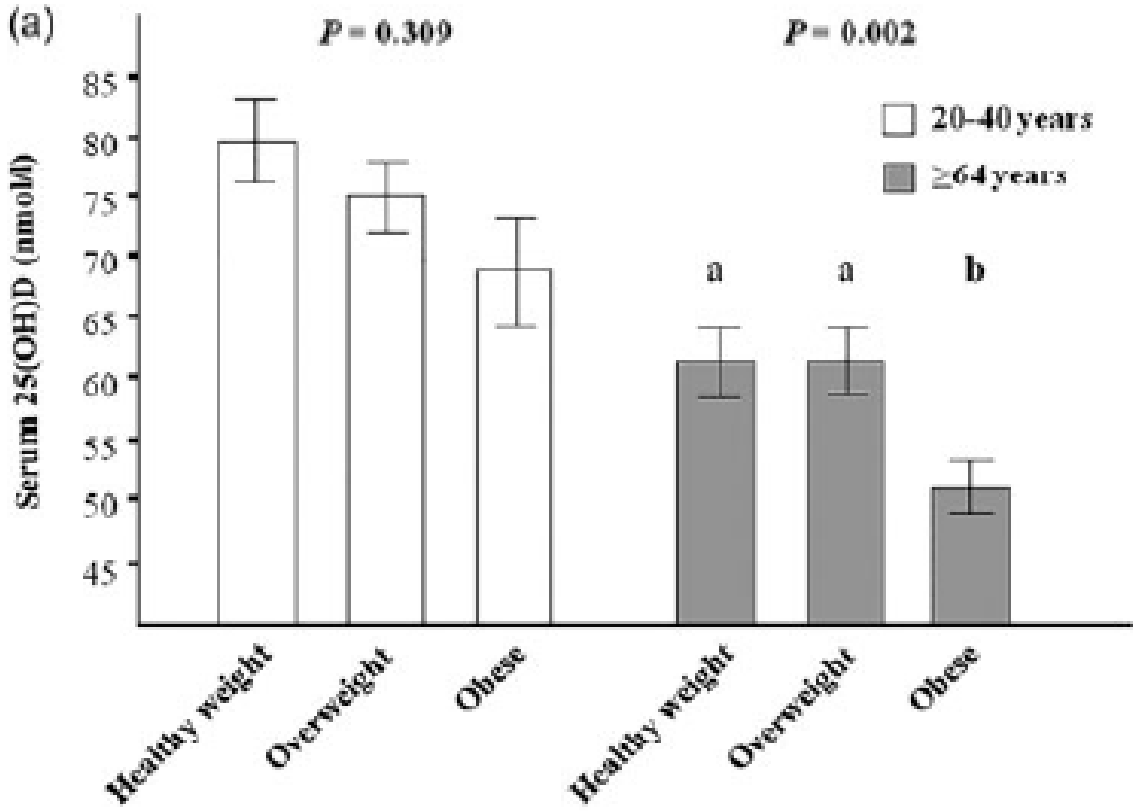


23% <30 ng/dl

JCEM 2017

Conference on 'Changing dietary behaviour: physiology through to practice'
Julie Wallace Lecture Medal Winner

Vitamin D and obesity: current perspectives and future directions



Proceedings of the Nutrition Society (2015

Evaluation, Treatment, and Prevention of Vitamin D Deficiency: an Endocrine Society Clinical Practice Guideline

Michael F. Holick, Neil C. Binkley, Heike A. Bischoff-Ferrari, Catherine M. Gordon, David A. Hanley, Robert P. Heaney, M. Hassan Murad, and Connie M. Weaver

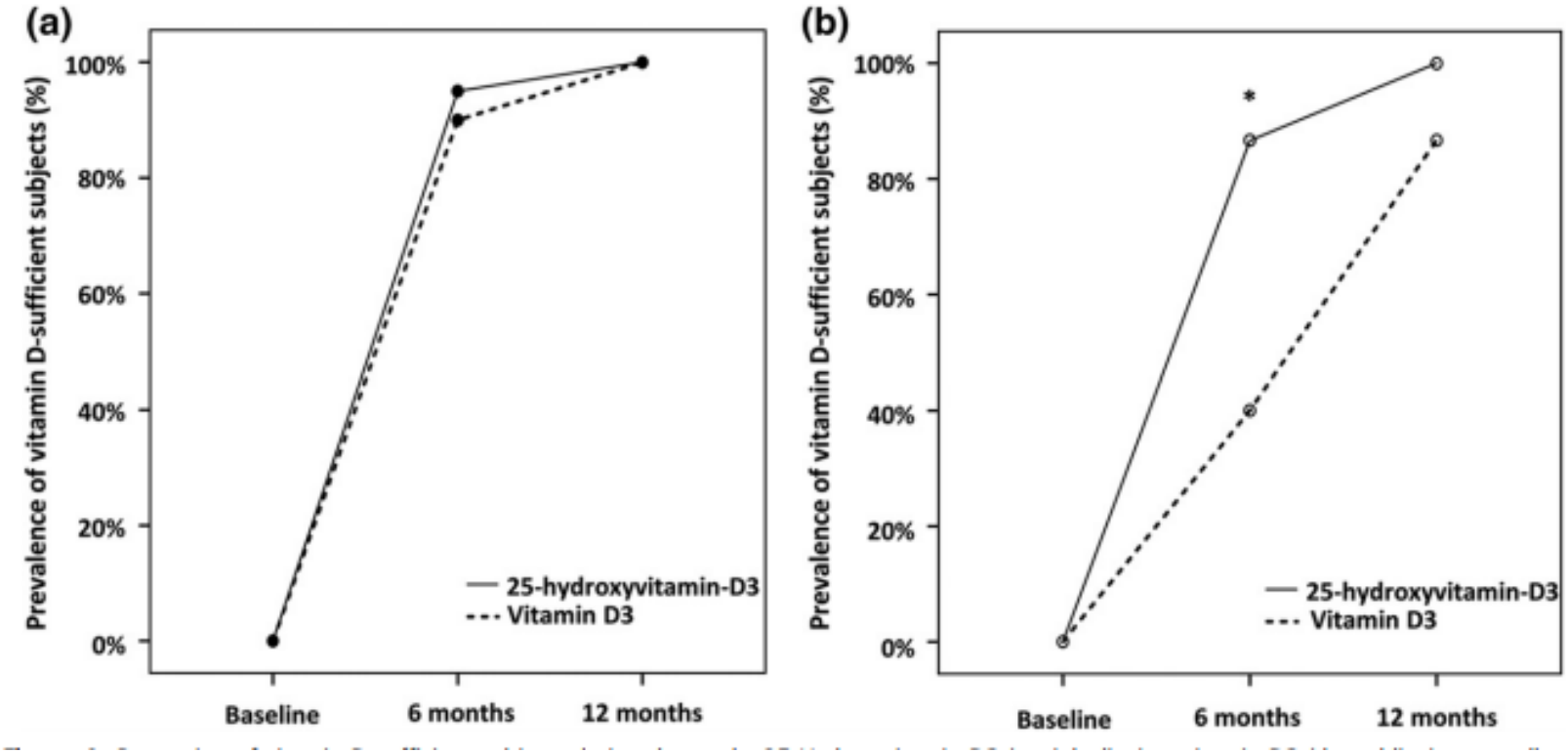
Recommendation

3.5 In obese patients, patients with malabsorption syndromes, and patients on medications affecting vitamin D metabolism, we suggest a higher dose (two to three times higher; at least 6000–10,000 IU/d) of vitamin D to treat vitamin D deficiency to maintain a 25(OH)D level above 30 ng/ml, followed by maintenance therapy of at least 3000–6000 IU/d (2|⊕⊕⊕⊕).

J Clin Endocrinol Metab 96: 1911–1930, 2011

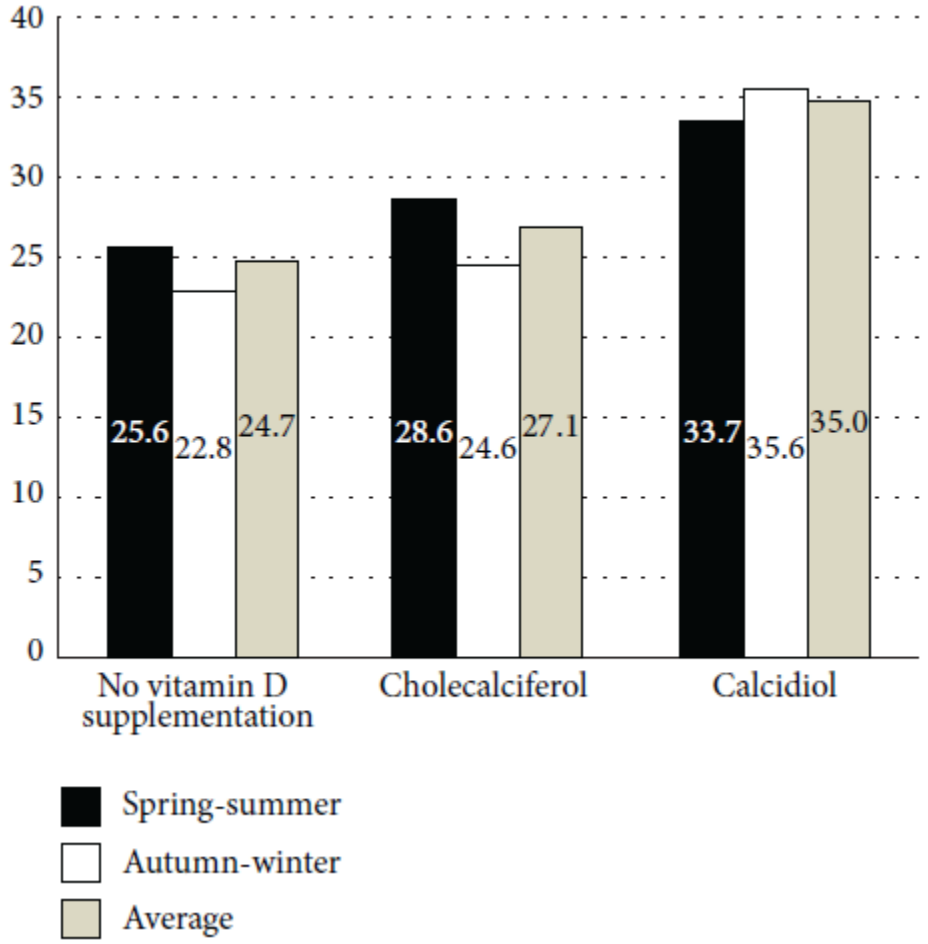
Impaired Release of Vitamin D in Dysfunctional Adipose Tissue: New Cues on Vitamin D Supplementation in Obesity

Andrea Di Nisio,[1] Luca De Toni,[1] Iva Sabovic,[1,5] Maria Santa Rocca,[1] Vincenzo De Filippis,[2] Giuseppe Opocher,[5] Bruno Azzena,[6] Roberto Vettor,[3] Mario Plebani,[4] and Carlo Foresta[1]



jcem 2017

Oral Calcidiol Is More Effective Than Cholecalciferol Supplementation to Reach Adequate 25(OH)D Levels in Patients with Autoimmune Diseases Chronically Treated with Low Doses of Glucocorticoids: A "Real-Life" Study



Rheumatology 2015

Italian Association of Clinical Endocrinologists (AME) and Italian Chapter of the American Association of Clinical Endocrinologists (AACE) Position Statement: Clinical Management of Vitamin D Deficiency in Adults

Roberto Cesareo [1,*], Roberto Attanasio [2], Marco Caputo [3], Roberto Castello [4], Iacopo Chiodini [5,6], Alberto Falchetti [7], Rinaldo Guglielmi [8], Enrico Papini [8], Assunta Santonati [9], Alfredo Scillitani [10], Vincenzo Toscano [11], Vincenzo Triggiani [12], Fabio Vescini [13], Michele Zini [14] and on behalf of AME and Italian AACE Chapter [†]

Calcifediol can be used in the general population

We suggest the use of calcifediol in case of:

- Hepatic impairment;
- Congenital abnormalities of the hepatic 25-hydroxylase enzyme;
- Malabsorption of cholecalciferol;
- Obesity.

Nutrients 2018

COLECALCIFEROLO/CALCIFEDIOLO
ANALISI DEI COSTI

CALCIFEDIOLO 10 ml gtt/os	300 gtt	**DOSAGGIO**: 20 gtt a settimana	**SOMMINISTRAZIONE**: 1 scatola ogni 4 mesi circa x os	**COSTI**: 6 mesi 8.5 euro
COLECALCIFEROLO Flacone 10 ml/os	10.000 UI	**DOSAGGIO**: 45 gtt a settimana 1600 UI/die circa	**DURATA**: 1 ml e mezzo a settimanax4 settimane = 6 mlx6 mesi =36 ml Una scatola dura 1 mese e mezzo circa	**COSTI**: 6 mesi 5.42 eurox3.5 =18.97 euro
COLECALCIFEROLO Flacone 2.5 ml/os				6 mesi = 90 euro
COLECALCIFEROLO Fiala 10 ml/os	fl 100.000 UI	**DOSAGGIO**: 1 fiala ogni 2 mesi 1600UI/die circa	**DURATA**: 1 fiala a mesi alterni x os	**COSTI**: 6 mesi 12 euro

COLECALCIFEROLO/CALCIFEDIOLO ANALISI DEI COSTI

Calcifediolo 10 ml: 1 ml = 30 gtt;

Colecalciferolo 2.5 ml: 50.000 UI; Colecalciferolo 10 ml fl 100.000 UI

- Calcefidiolo: 20 gtt a settimana = una scatola dura 4 mesi; 6 mesi = 8.5 euro
- Colecalciferolo: 45 gtt/settimana (1600 UI/die; 50.000 UI/mese); una scatola/mese = 15 euro; 6 mesi = 90 euro
- Colecalciferolo flacone 10 ml 100.000 unità; Una fiala/mese = 4 euro; 6 mesi = 12 euro (se assunto a mesi alterni)

Italian Association of Clinical Endocrinologists (AME) and Italian Chapter of the American Association of Clinical Endocrinologists (AACE) Position Statement: Clinical Management of Vitamin D Deficiency in Adults

Roberto Cesareo [1,*], Roberto Attanasio [2], Marco Caputo [3], Roberto Castello [4], Iacopo Chiodini [5,6], Alberto Falchetti [7], Rinaldo Guglielmi [8], Enrico Papini [8], Assunta Santonati [9], Alfredo Scillitani [10], Vincenzo Toscano [11], Vincenzo Triggiani [12], Fabio Vescini [13], Michele Zini [14] and on behalf of AME and Italian AACE Chapter [†]

We recommend against routine use of $1.25(OH)_2D$ or alpha-calcidiol for vitamin D deficiency.

We recommend to use $1.25(OH)_2D$ or alpha-calcidiol only when treating:

- Chronic renal failure;
- Hypoparathyroidism.

We suggest to use cholecalciferol as add on to $1.25(OH)_2D$, or alpha-calcidiol, in patients with CRF or hypoparathyroidism associated with demonstrated vitamin D deficiency.

Siobhan O'Donnell · David Moher · Kelli Thomas
David A. Hanley · Ann Cranney

Systematic review of the benefits and harms of calcitriol and alfacalcidol for fractures and falls

Side effects include hypercalcemia and hypercalciuria, so patients should be monitored closely and the dose (and/or calcium intake) adjusted as needed.

J Bone Miner Res 2008