Azienda Ospedale – Università di Padova
Dipartimento di Medicina – DIMED
Clinica Medica 1

Centro Regionale Specializzato per l'Osteoporosi

Posologia, vie di somministrazione e valutazione dello stato vitaminico D

Sandro Giannini

Posologia, vie di somministrazione e valutazione dello stato vitaminico D

Vitamina D

- Quanta
- Ogni quanto
- Per os o intramuscolo
- Dosaggio della 25-OH-D sierica

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Posologia, vie di somministrazione e valutazione dello stato vitaminico D

Vitamina D

- Quanta
  - Valore-soglia di efficacia
  - Livello di partenza

European Journal of Endocrinology
(2019) **180**, P23–P54

Current vitamin D status in European and Middle East countries and strategies to prevent vitamin D deficiency: a position statement of the European Calcified Tissue Society

Paul Lips[1], Kevin D Cashman[2], Christel Lamberg-Allardt[3], Heike Annette Bischoff-Ferrari[4], Barbara Obermayer-Pietsch[5], Maria Luisa Bianchi[6], Jan Stepan[7], Ghada El-Hajj Fuleihan[8] and Roger Bouillon[9] on behalf of the Working Group on Vitamin D of the European Calcified Tissue Society

Table 1 Definitions of vitamin D deficiency and sufficiency according to different advisory bodies.

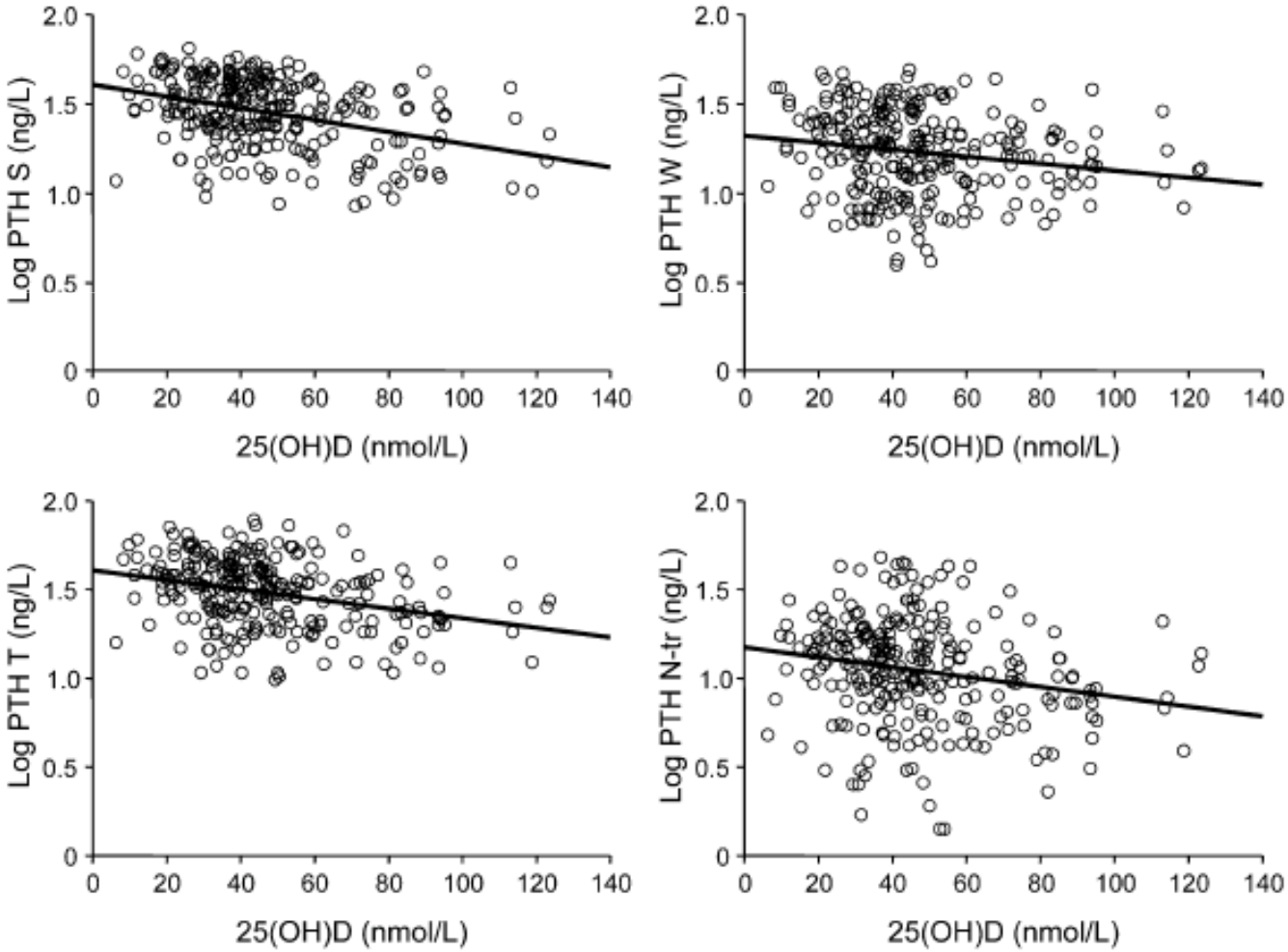
Serum 25(OH)D concentration (nmol/L)		Institute of Medicine (2)	Endocrine Society (1)	EFSA (29)	SACN (27)	ECTS (this paper)
<25/30	10-12 ng/l	Deficient	Deficient	Deficient	Deficient	Severely deficient
25–50	10-20 ng/l	Uncertain*	Deficient	Deficient		Deficient
50–75	20-30 ng/l	Sufficient	Insufficient	Sufficient		Sufficient
>75	> 30 ng/l		Sufficient			

Osteoporos Int (2005) 16: 805–812
DOI 10.1007/s00198-004-1757-4

ORIGINAL ARTICLE

Vitamin D status as the major factor determining the circulating levels of parathyroid hormone: a study in normal subjects

Jessica Pepe · Elisabetta Romagnoli · Italo Nofroni
Maria Teresa Pacitti · Simona De Geronimo
Claudio Letizia · Gianfranco Tonnarini
Addolorata Scarpiello · Emilio D'Erasmo
Salvatore Minisola

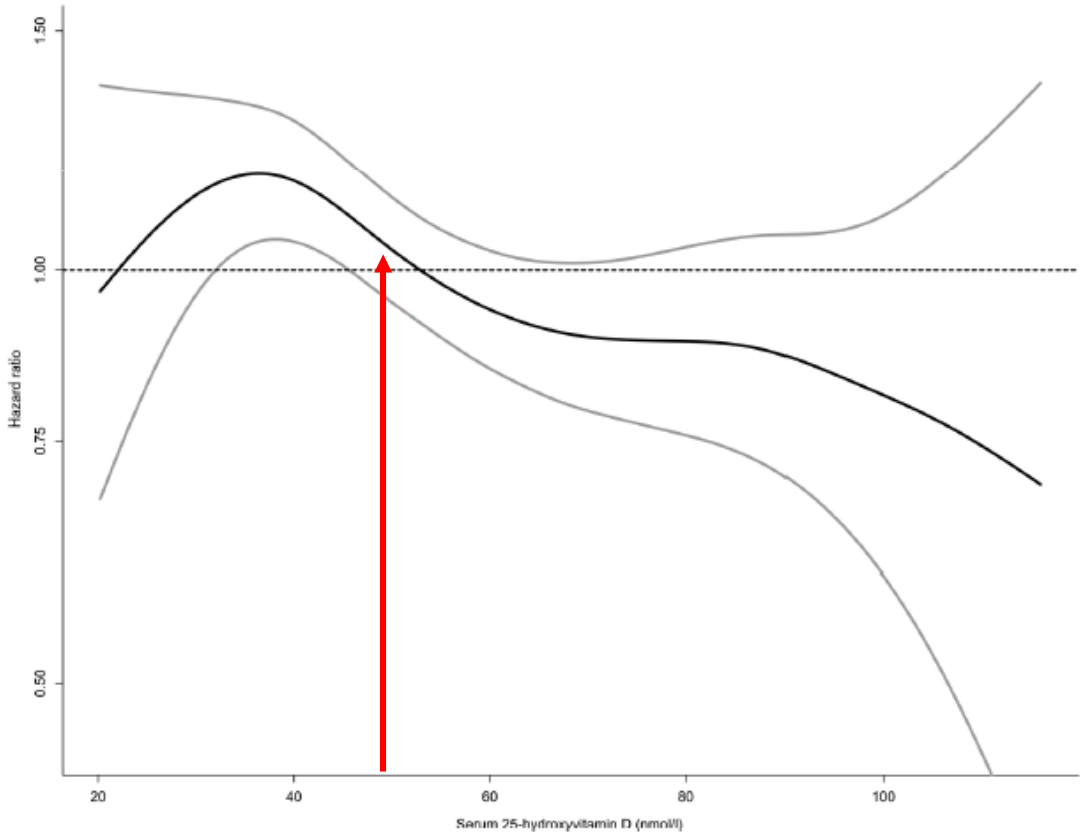


ORIGINAL ARTICLE

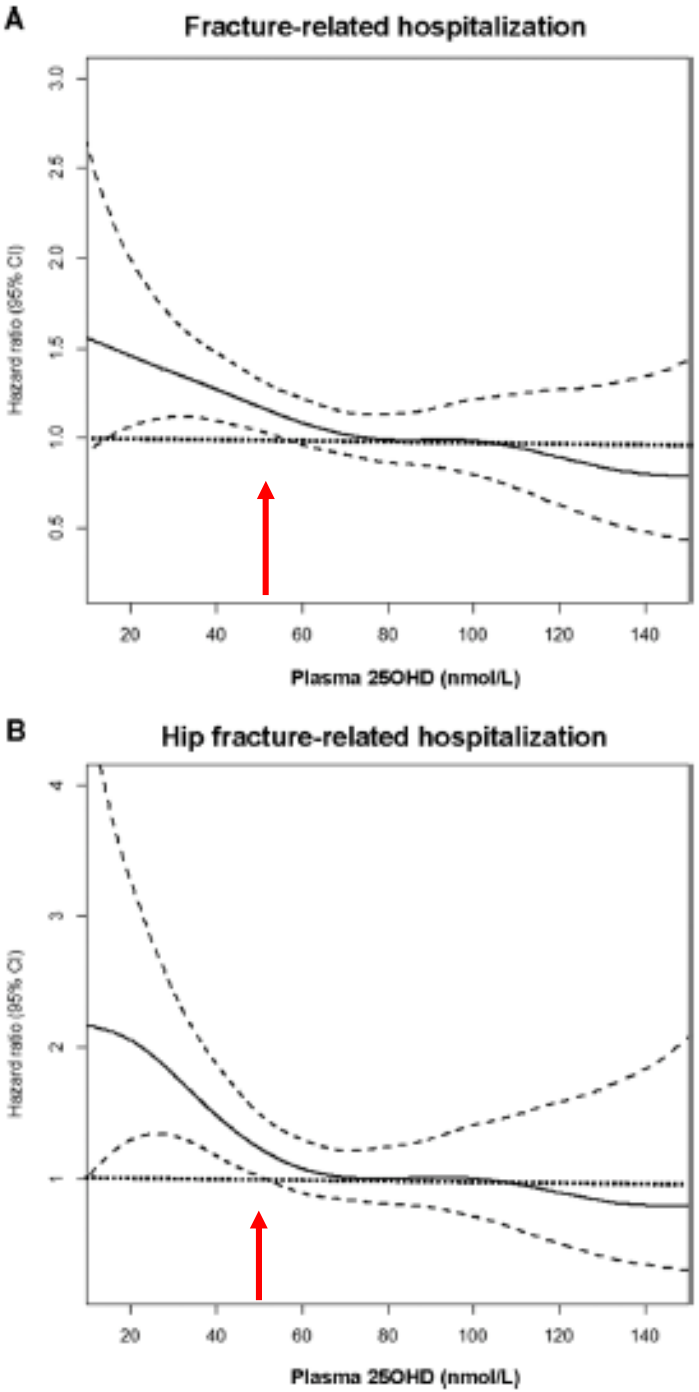
Endocrine Research

Low Serum Levels of 25-Hydroxyvitamin D Predict Hip Fracture in the Elderly: A NOREPOS Study

Kristin Holvik, Luai A. Ahmed, Siri Forsmo, Clara G. Gjesdal, Guri Grimnes, Sven Ove Samuelsen, Berit Schei, Rune Blomhoff, Grethe S. Tell, and Haakon E. Meyer



J Clin Endocrinol Metab 2013



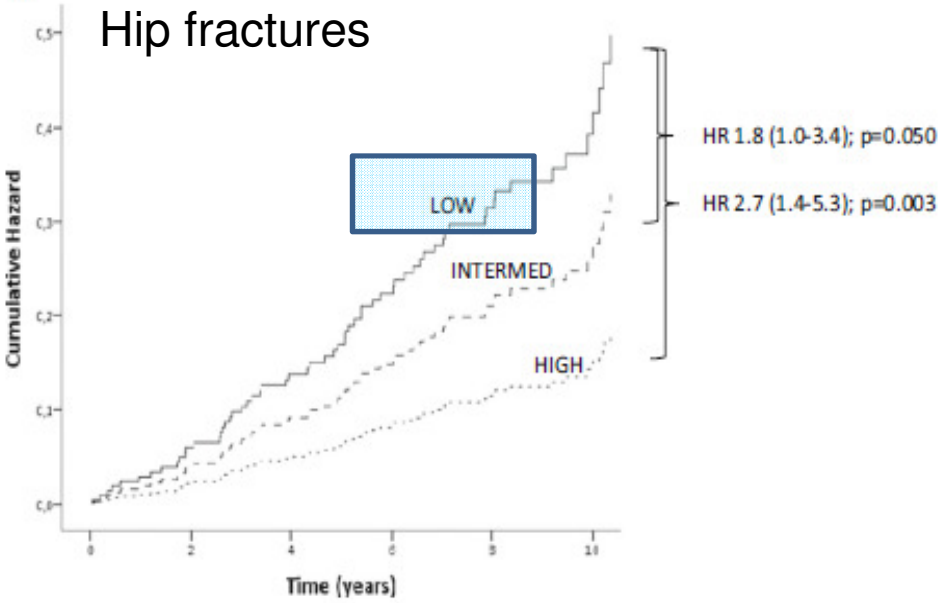
Low Vitamin D Status Is Associated With Impaired Bone Quality and Increased Risk of Fracture-Related Hospitalization in Older Australian Women

Zhu K et al., J Bone Miner Res 2019

Vitamin D insufficiency over 5 years is associated with increased fracture risk

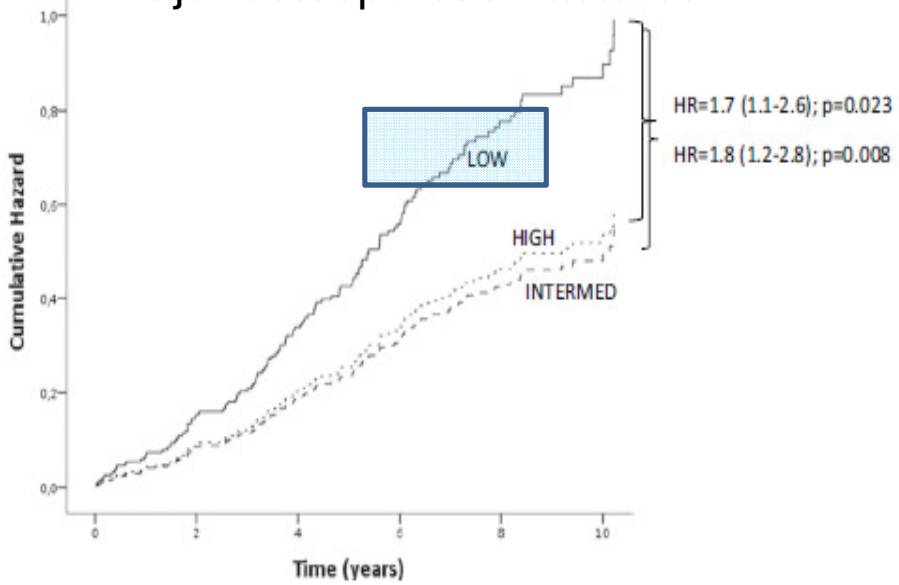
a

Hip fractures



b

Major osteoporotic fractures



- **Low = < 50 nmol/l**
- Intermediate = 50-75 nmol/l
- High = > 75 nmol/l

Buchebner D et al., Osteoporos Int 2014

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JULY 28, 2022 VOL. 387 NO. 4

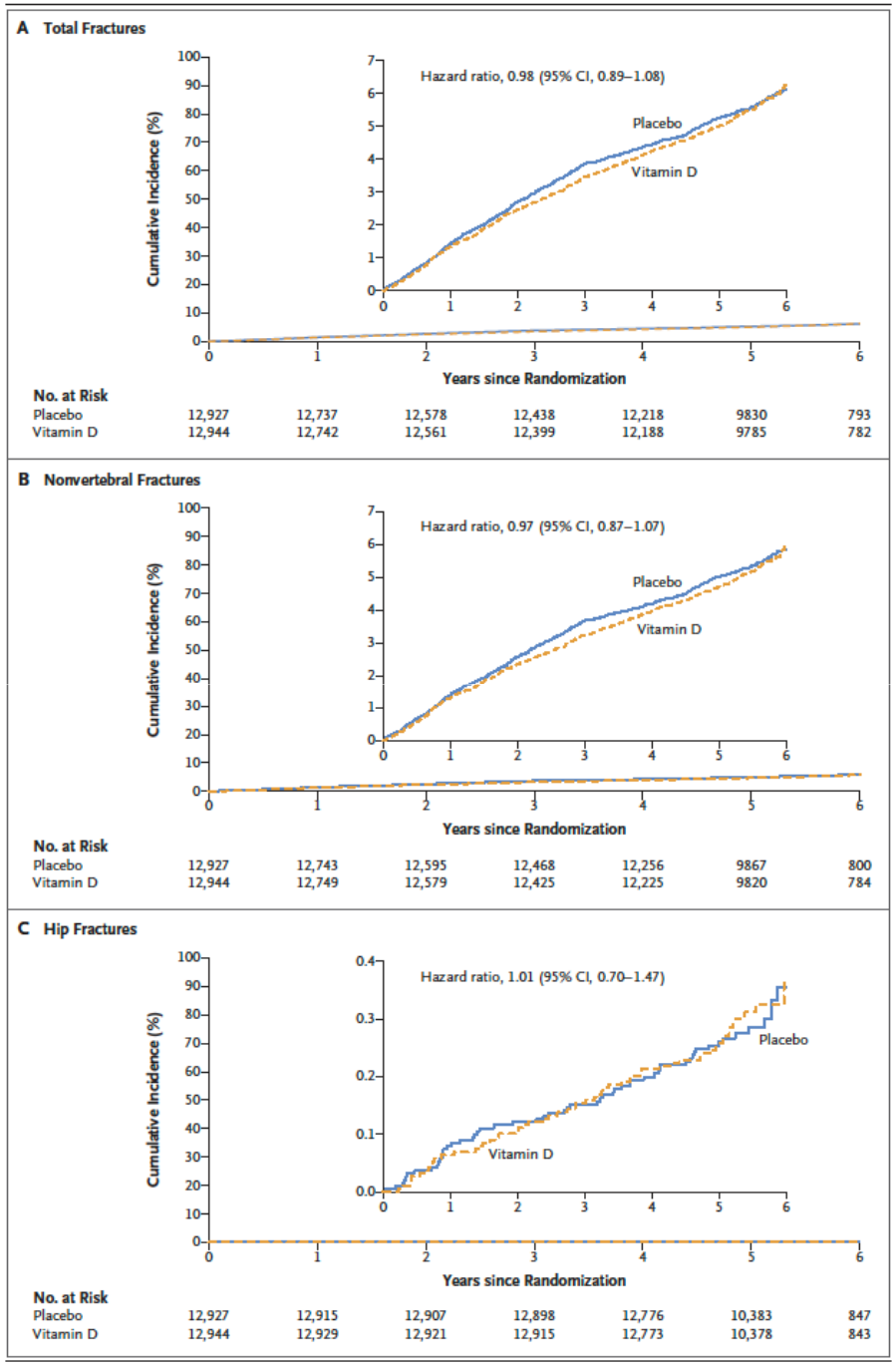
Supplemental Vitamin D and Incident Fractures in Midlife and Older Adults

Meryl S. LeBoff, M.D., Sharon H. Chou, M.D., Kristin A. Ratliff, B.A., Nancy R. Cook, Sc.D., Bharti Khurana, M.D., Eunjung Kim, M.S., Peggy M. Cawthon, Ph.D., M.P.H., Douglas C. Bauer, M.D., Dennis Black, Ph.D., J. Chris Gallagher, M.D., I-Min Lee, M.B., B.S., Sc.D., Julie E. Buring, Sc.D., and JoAnn E. Manson, M.D., Dr.P.H.

Vitamin D 2000 IU/daily

Table 1. Characteristics of the Participants at Baseline, According to Randomized Assignment to Vitamin D or Placebo.*

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
Race or ethnic group — no./total no. (%)†			
Non-Hispanic White	18,046/25,304 (71.3)	9,013/12,647 (71.3)	9,033/12,657 (71.4)
Black	5,106/25,304 (20.2)	2,553/12,647 (20.2)	2,553/12,657 (20.2)
Non-Black Hispanic	1,013/25,304 (4.0)	516/12,647 (4.1)	497/12,657 (3.9)
Asian or Pacific Islander	388/25,304 (1.5)	188/12,647 (1.5)	200/12,657 (1.6)
American Indian or Alaskan Native	228/25,304 (0.9)	118/12,647 (0.9)	110/12,657 (0.9)
Other or unknown	523/25,304 (2.1)	259/12,647 (2.0)	264/12,657 (2.1)
Body-mass index‡	28.1±5.7	28.1±5.7	28.1±5.8
Diabetes — no./total no. (%)	3,537/25,824 (13.7)	1,804/12,900 (14.0)	1,733/12,924 (13.4)
Parental history of hip fracture — no./total no. (%)	3,704/23,979 (15.4)	1,809/11,970 (15.1)	1,895/12,009 (15.8)
Rheumatoid arthritis — no./total no. (%)	1,118/25,512 (4.4)	556/12,749 (4.4)	562/12,763 (4.4)
History of fragility fracture — no./total no. (%)	2,578/25,023 (10.3)	1,287/12,513 (10.3)	1,291/12,510 (10.3)
Unintentional fall in the past year — no./total no. (%)	6,921/25,715 (26.9)	3,521/12,848 (27.4)	3,400/12,867 (26.4)
Current use of osteoporosis medication — no./total no. (%)§	1,240/25,690 (4.8)	609/12,835 (4.7)	631/12,855 (4.9)
Current smoker — no./total no. (%)	1,835/25,488 (7.2)	921/12,732 (7.2)	914/12,756 (7.2)
Current use of supplemental vitamin D — no. (%)¶	11,030 (42.6)	5,497 (42.5)	5,533 (42.7)
Current use of glucocorticoids — no./total no. (%)	461/25,427 (1.8)	239/12,705 (1.9)	222/12,722 (1.7)
Servings of milk per day	0.71±0.91	0.71±0.89	0.72±0.92
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



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STATO VITAMINICO D E SALUTE SCHELETRICA: QUALE CONSENSO?

LIVELLI COMPRESI TRA 20 E 30 ng/ml
Livelli insufficienti per particolari sottogruppi ad elevato rischio di carenza vitaminica D.

SOLO ENDOCRINE SOCIETY

LIVELLI COMPRESI TRA 10 E 20 ng/ml
- Assorbimento intestinale calcio in genere nei limiti
- Deposizione tessuto osseo in genere nei limiti
- Iperparatiroidismo secondario
- Aumento turnover osseo
- Aumento perdita ossea
- Osteoporosi accelerata
- **Aumento del rischio di frattura**

LARGO CONSENSO

LIVELLI INFERIORI A 10-12 ng/ml
- Insufficiente produzione calcitriolo
- Insufficiente assorbimento intestinale di calcio
- Calcemia e fosforemia bassi o normali-bassi
- Iperparatiroidismo secondario
- Aumento perdita ossea, riduzione BMD
- **Aumento del rischio di frattura**
- Deficit di mineralizzazione (osteomalacia/ rachitismo)
- Miopatia dei muscoli prossimali arti, cadiomiopatia

CONSENSO GENERALE

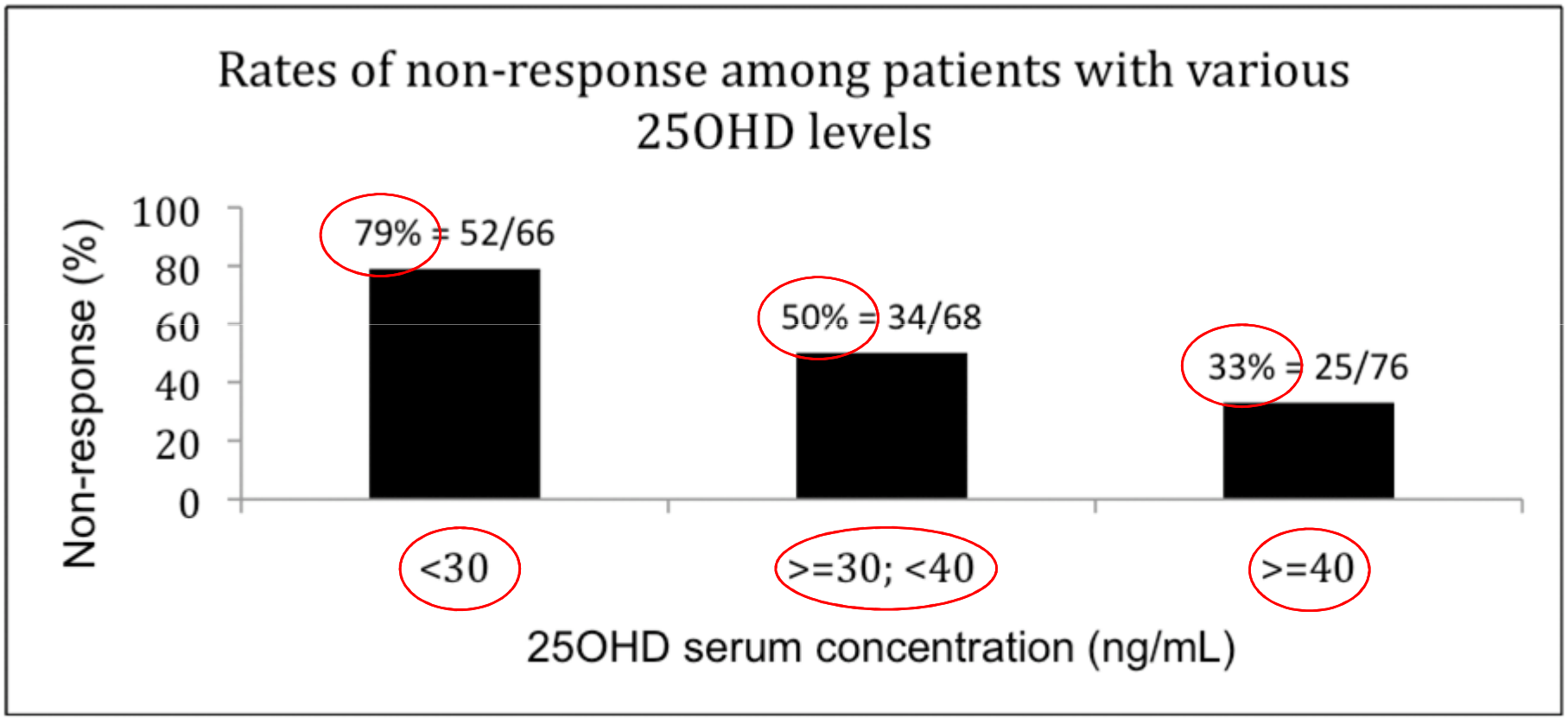
Bouillon R. Comparative analysis of nutritional guidelines for vitamin D. Nat Rev Endocrinol. 2017;13(8):466–79
Bouillon R. How much vitamin D is needed for healthy bones? J Intern Med. 2017 Nov;282(5):461-464

Special Populations

- ✓ Old people (≥ 75 yrs)
- ✓ Institutionalized subjects
- ✓ History of or risk of fall
- ✓ Metabolic bone diseases and other skeletal disorders (even if on treatment with anti-osteoporotic drugs)
- ✓ Primary Hyperparathyroidism
- ✓ Obesity
- ✓ Pregnancy and breastfeeding
- ✓ Chronic renal failure
- ✓ Cancer (in particular breast, prostate, and colon)
- ✓ Type 2 diabetes mellitus (?)
- ✓ Intestinal malabsorption and bariatric surgery
- ✓ Glucocorticoids, antiseizure medications, antiretrovirals, antifungals,
- ✓ Covid 19 (?)

Vitamin D serum levels > 30 ng/ml (75 mmol/l)

Association between 25OHD level and bisphosphonate response

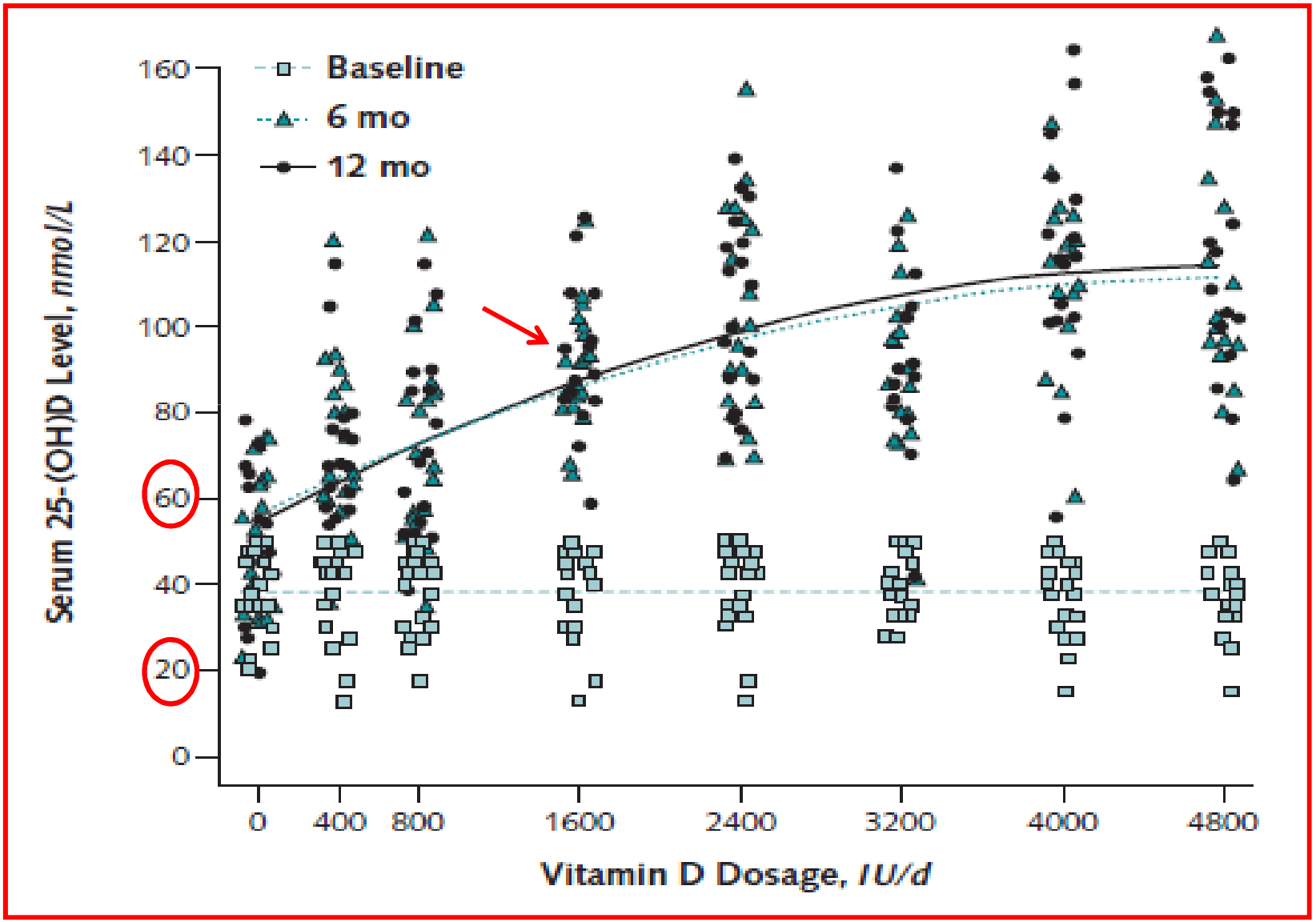


Carmel AS et al., Osteoporos Int 2012

Public Health Recommendations

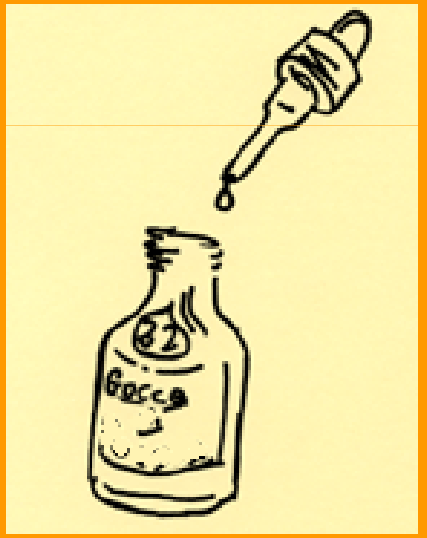
- **What dose to use?** Use a dose that brings 97.5% of population to ≥ 20 ng/mL without testing based on available data; recognize the wide inter-individual variability in response to same dose- varies by baseline level, dose, BMI
- **Guidance examples:** Adapt to local context and risk factors-in conjunction with calcium and treat without testing
  - Adults: Northern Europe: RDA 1,000 IU/day
  - Adults: Southern Europe: RDA 1,500-2,000 IU/day
  - Adults/Elderly Middle East: 3,500 IU/day
  - Children in Middle East: 2,000 IU/day
  - Diabetes, obesity: 2,000 IU/day (4,000 IU/day for target of >30 ng/mL)

Dose Response to increasing doses of Vitamin D in Postmenopausal Women



Gallagher JC et al., Ann Intern Med 2012

QUANTA VITAMINA HO			QUANTA VITAMINA MI SERVE
	nmol/L		U/die
	>60	⟷	1000
	50-60	⟷	1500
	40-50	⟷	2250
	30-40	⟷	3000
	20-30	⟷	3500
	<20	⟷	4200



Posologia, vie di somministrazione e valutazione dello stato vitaminico D

Vitamina D

- Quanta
- Ogni quanto
- Per os o intramuscolo
- Dosaggio della 25-OH-D sierica

nutrients Received: 12 May 2020; Accepted: 25 May 2020; Published: 27 May 2020

Pharmacokinetics of Oral Cholecalciferol in Healthy Subjects with Vitamin D Deficiency: A Randomized Open-Label Study

Angelo Fassio [1,*], Giovanni Adami [1], Maurizio Rossini [1], Alessandro Giollo [1], Cristian Caimmi [1], Riccardo Bixio [1], Ombretta Viapiana [1], Stefano Milleri [2], Matteo Gatti [1] and Davide Gatti [1]

Clinical Characteristics *	All Subjects (N = 75)
Age (years)	34.1 ± 10.2
Sex	
Male, *n* (%)	31 (41.3)
Female, *n* (%)	44 (58.7)
Weight (kg)	66.7 ± 12.4
BMI (kg/m^2)	23.1 ± 2.6
25 (OH)D (ng/mL)	13.7 ± 3.8
Calcium (mmol/L)	2.3 ± 0.1
Phosphate (mmol/L)	1.1 ± 0.1
Albumin (g/L)	45 ± 2.6

- Group A: once daily 10,000 International Units (IU)/day for 8 weeks, followed by 1000 IU daily for 4 weeks (Total: 588.000 IU within 12 weeks);
- Group B: 50,000 IU/week for 12 weeks (Total: 600.000 IU within 12 weeks);
- Group C: 100,000 IU every other week for 12 weeks (Total: 600.000 IU within 12 weeks)

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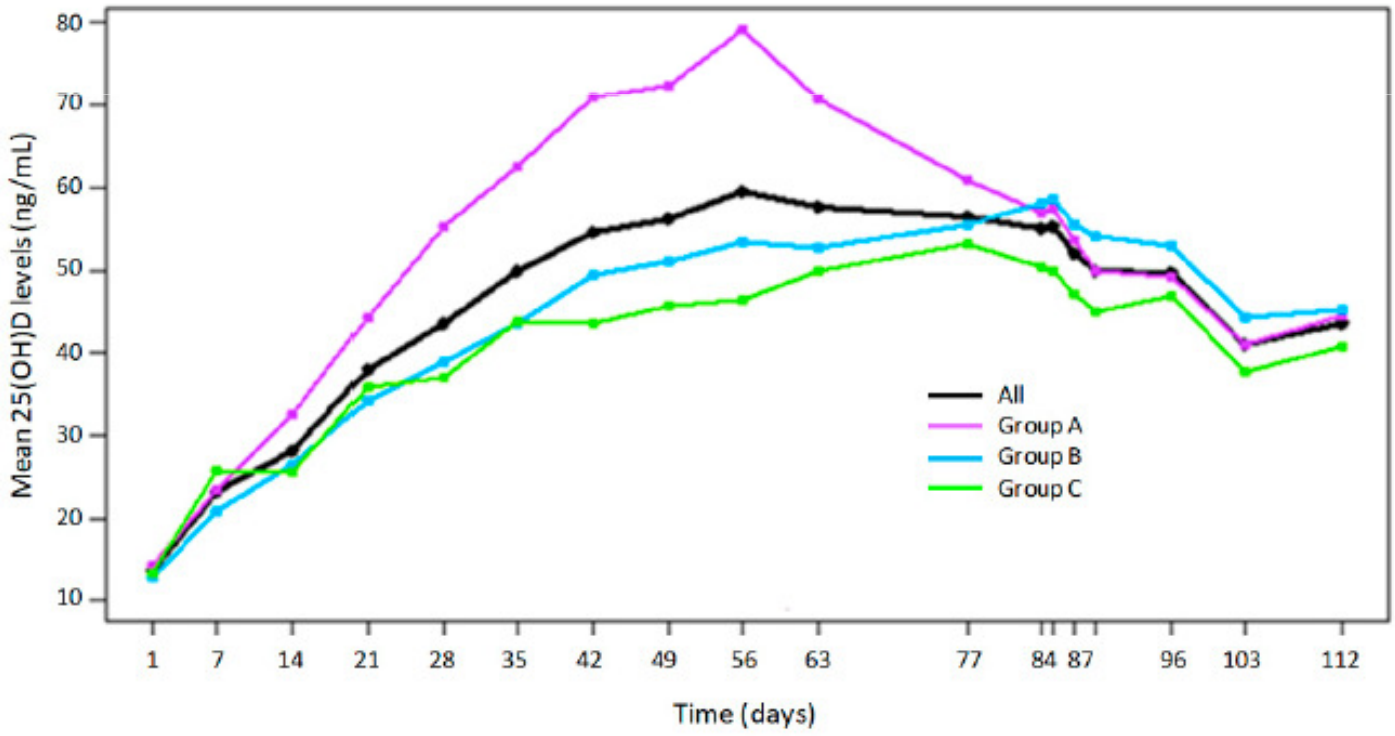

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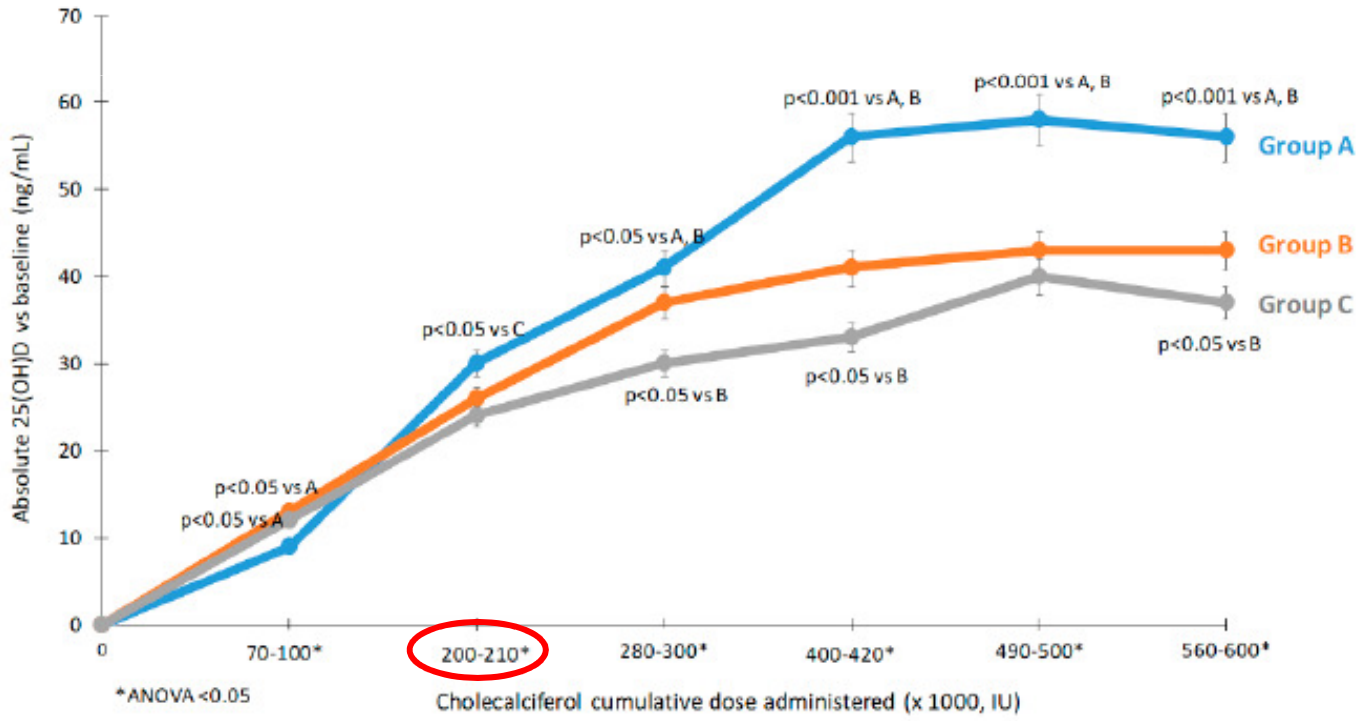

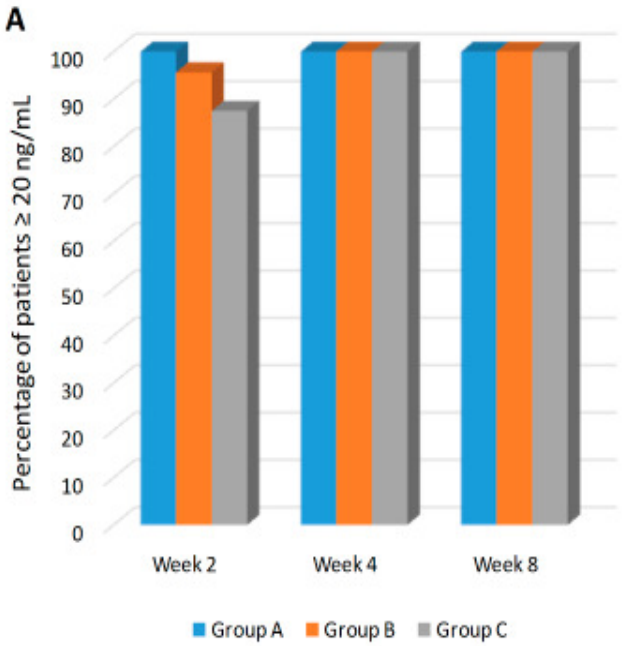

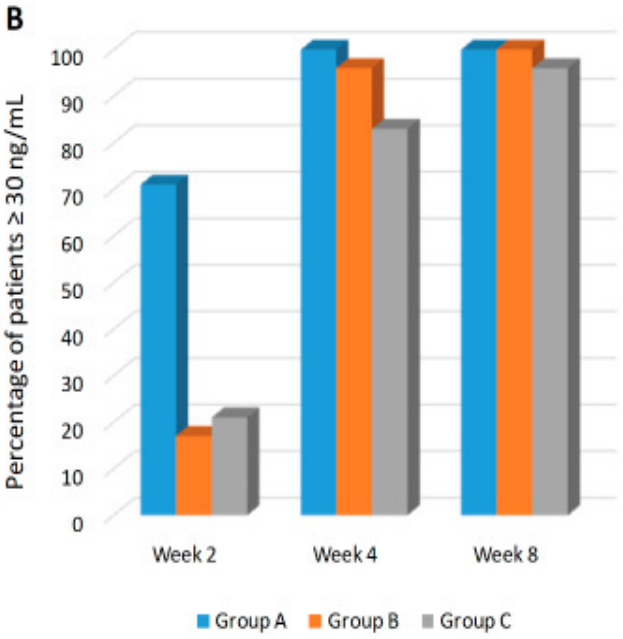

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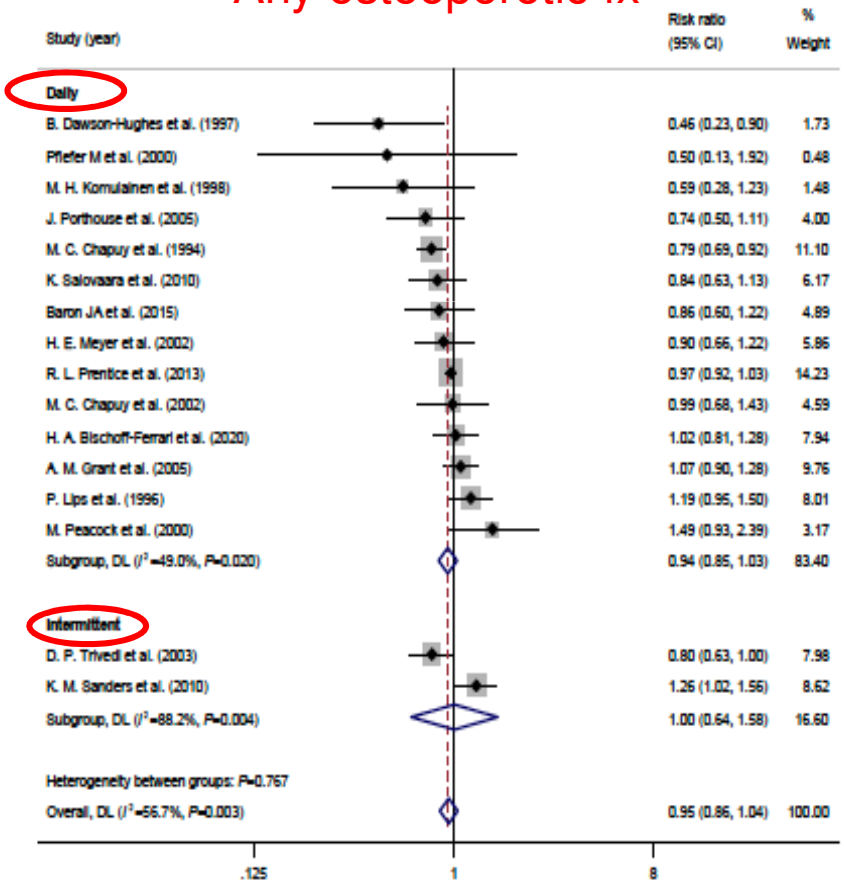
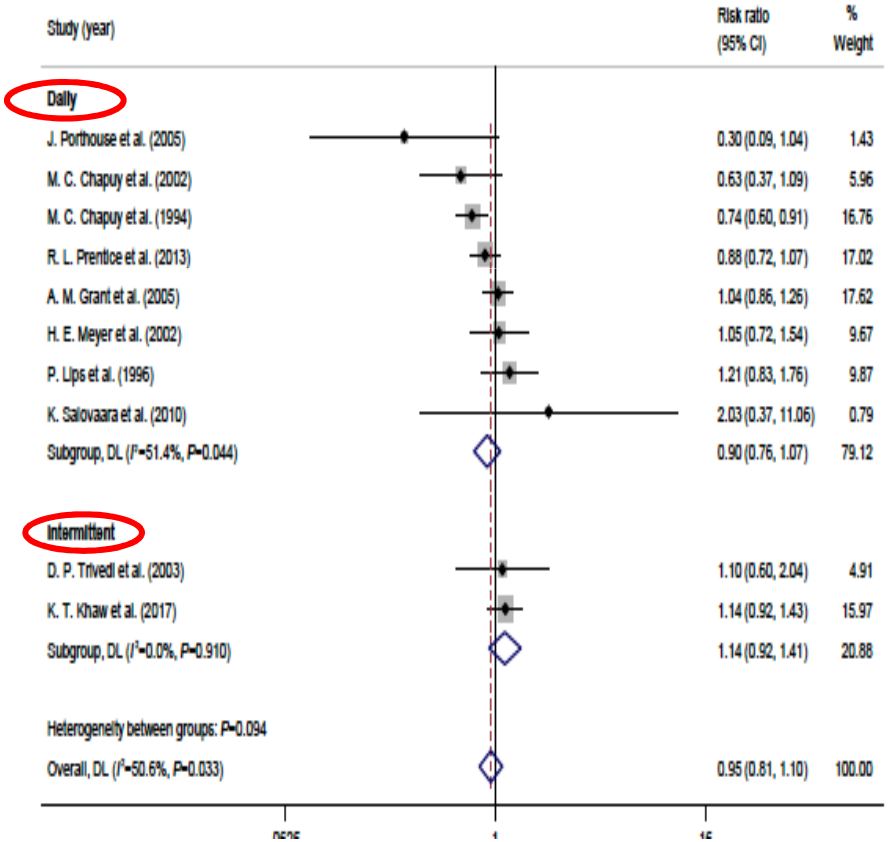
Effect of Vitamin D Supplementation on Risk of Fractures and Falls According to Dosage and Interval: A Meta-Analysis

Any osteoporotic fx



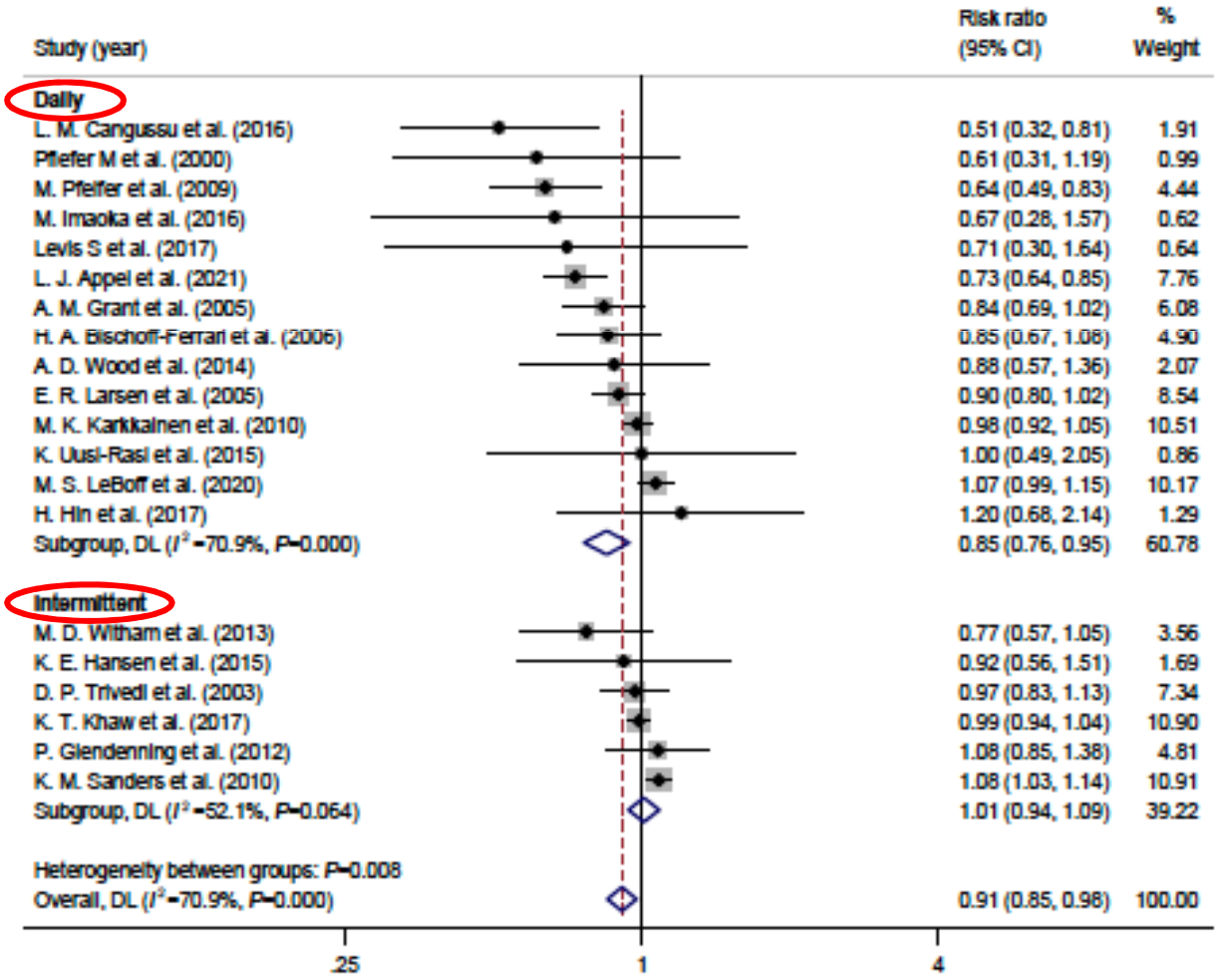
Hip fx



Kong SH et al., Endocrinol Metab 2022

Effect of Vitamin D Supplementation on Risk of Fractures and Falls According to Dosage and Interval: A Meta-Analysis

Risk of falls



Kong SH et al., Endocrinol Metab 2022

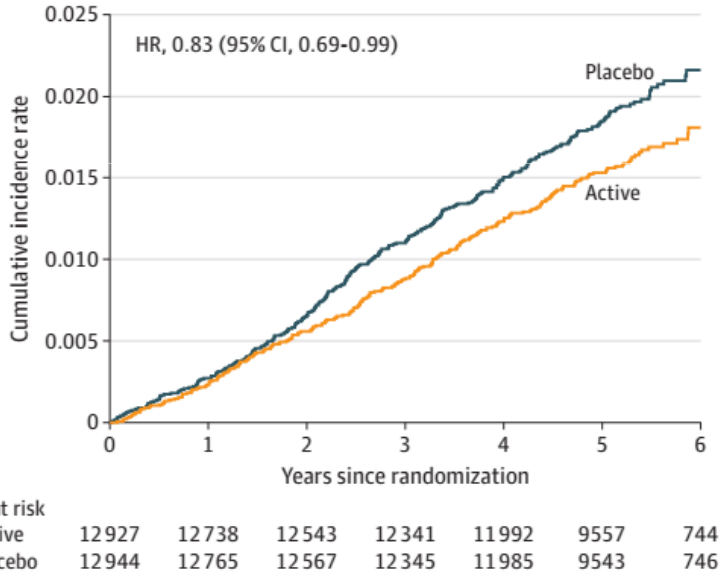
JAMA Network Open. JAMA Network Open. 2020;3(11):e November 18, 2020

Original Investigation | Oncology

Effect of Vitamin D_3 Supplements on Development of Advanced Cancer
A Secondary Analysis of the VITAL Randomized Clinical Trial

Paulette D. Chandler, MD, MPH; Wendy Y. Chen, MD, MPH; Oluremi N. Ajala, MD, MPH; Aditi Hazra, PhD, MPH; Nancy Cook, ScD; Vadim Bubes, PhD; I-Min Lee, MBBS, ScD; Edward L. Giovannucci, MD, ScD; Walter Willett, MD, DrPH; Julie E. Buring, ScD; JoAnn E. Manson, MD, DrPH; for the VITAL Research Group

Figure 2. Vitamin D (Active) and Placebo: Cumulative Incidence Rates of Metastatic and Fatal Cancer of Any Type



Cancer mortality (n = 25 254)	N	vit D	Placebo	HR	p
<25	7843	38	68	0.58 (0.39-0.86)	.007
25 to <30	10 122	66	74	0.89 (0.64-1.23)	.472
≥30	7289	46	39	1.15 (0.75-1.76)	.518

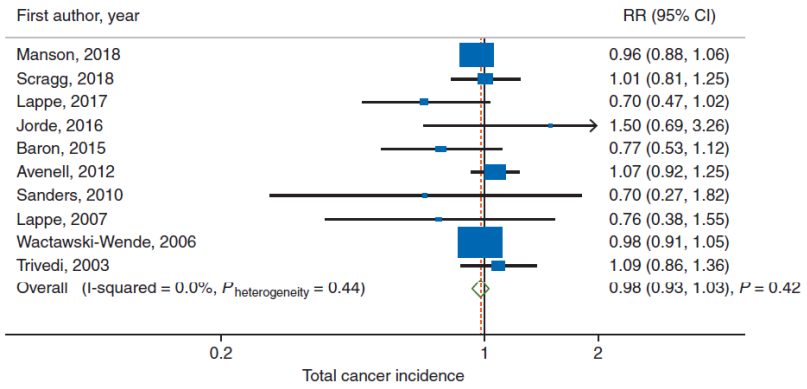
BMI

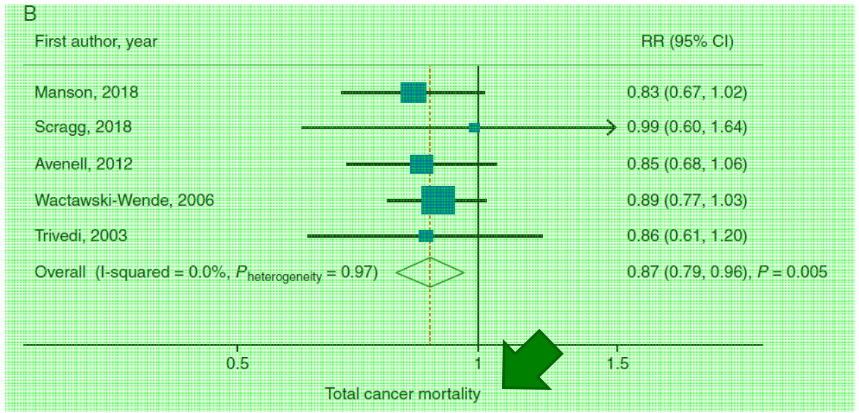
Daily dietary supplements of vitamin D3 (2000 IU)

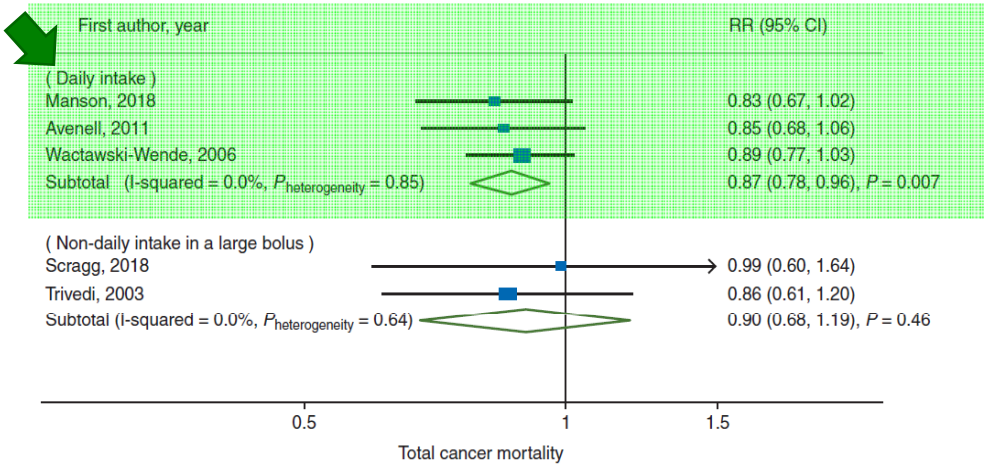
Vitamin D supplementation and total cancer incidence and mortality: a meta-analysis of randomized controlled trials

Annals of Oncology 30: 733–743, 2019

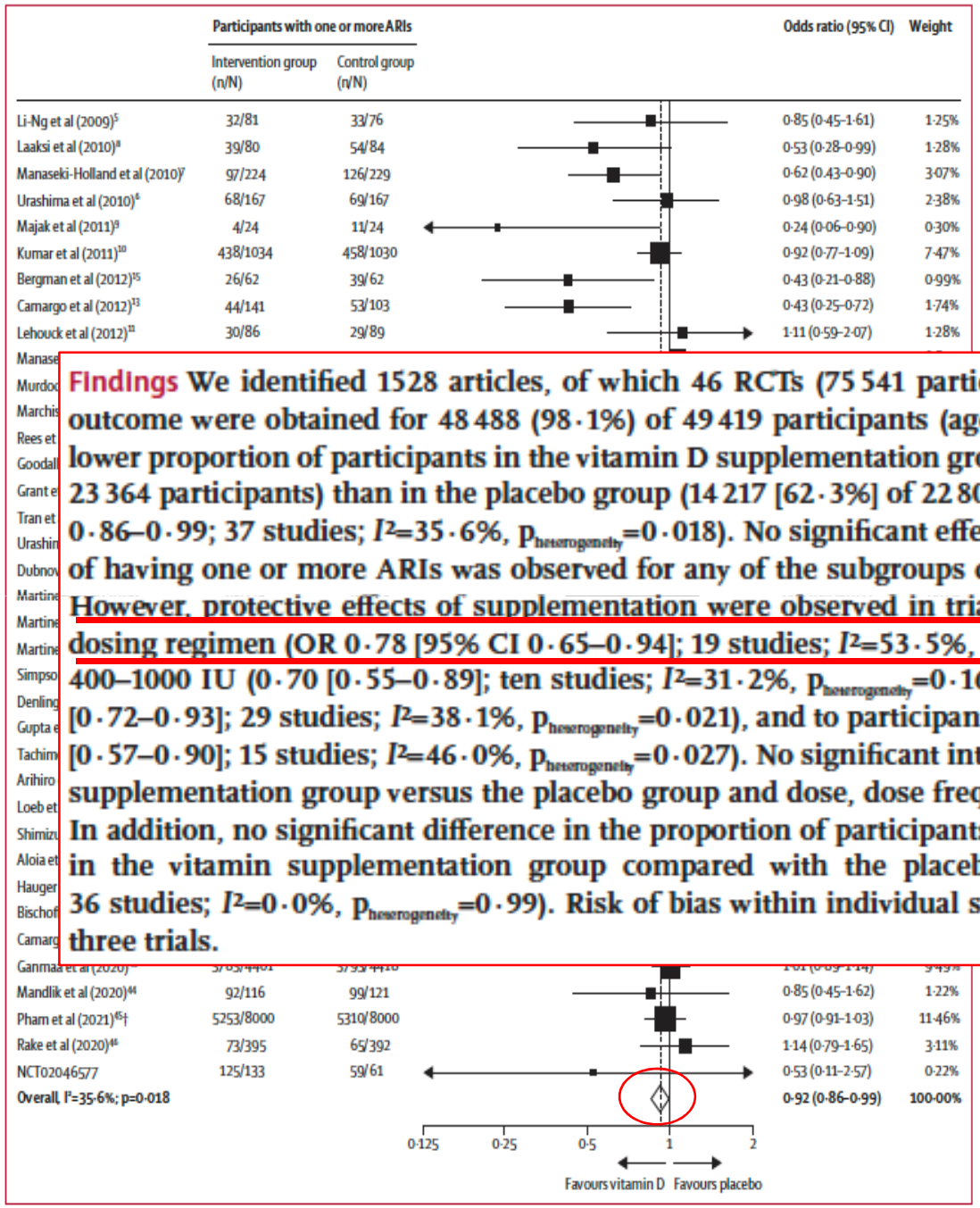
N. Keum[1,2*], D. H. Lee[1], D. C. Greenwood[3], J. E. Manson[4,5] & E. Giovannucci[1,4,5*]







Vitamin D supplementation to prevent acute respiratory infections: a systematic review



Findings We identified 1528 articles, of which 46 RCTs (75 541 participants) were eligible. Data for the primary outcome were obtained for 48 488 (98·1%) of 49 419 participants (aged 0–95 years) in 43 studies. A significantly lower proportion of participants in the vitamin D supplementation group had one or more ARIs (14 332 [61·3%] of 23 364 participants) than in the placebo group (14 217 [62·3%] of 22 802 participants), with an OR of 0·92 (95% CI 0·86–0·99; 37 studies; I^2=35·6%, $p_{heterogeneity}$=0·018). No significant effect of vitamin D supplementation on the risk of having one or more ARIs was observed for any of the subgroups defined by baseline 25(OH)D concentration. However, protective effects of supplementation were observed in trials in which vitamin D was given in a daily dosing regimen (OR 0·78 [95% CI 0·65–0·94]; 19 studies; I^2=53·5%, $p_{heterogeneity}$=0·003), at daily dose equivalents of 400–1000 IU (0·70 [0·55–0·89]; ten studies; I^2=31·2%, $p_{heterogeneity}$=0·16), for a duration of 12 months or less (0·82 [0·72–0·93]; 29 studies; I^2=38·1%, $p_{heterogeneity}$=0·021), and to participants aged 1·00–15·99 years at enrolment (0·71 [0·57–0·90]; 15 studies; I^2=46·0%, $p_{heterogeneity}$=0·027). No significant interaction between allocation to the vitamin D supplementation group versus the placebo group and dose, dose frequency, study duration, or age was observed. In addition, no significant difference in the proportion of participants who had at least one serious adverse event in the vitamin supplementation group compared with the placebo group was observed (0·97 [0·86–1·07]; 36 studies; I^2=0·0%, $p_{heterogeneity}$=0·99). Risk of bias within individual studies was assessed as being low for all but three trials.

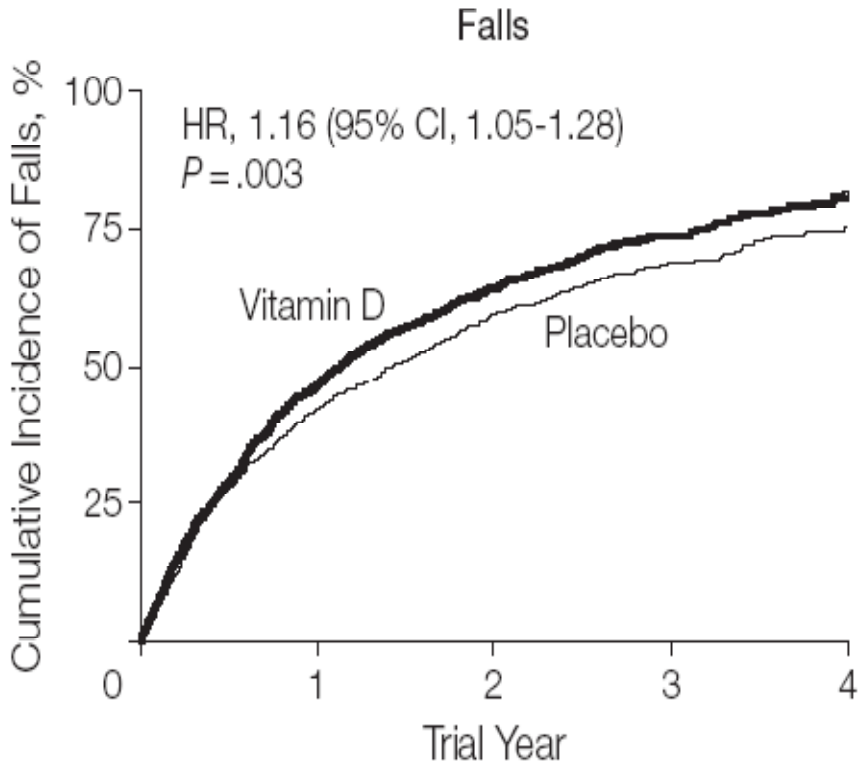
Jolliffe DA et al., Lancet Diabetes Endocrinol 2021

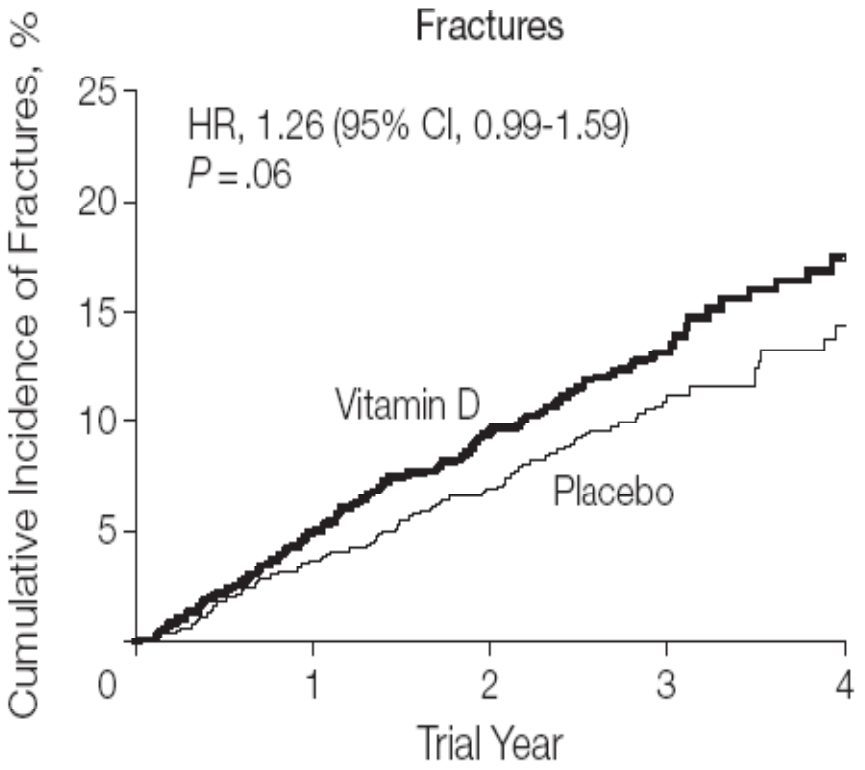
Kerrie M. Sanders, PhD
Amanda L. Stuart, BappSc
Elizabeth J. Williamson, MA, PhD
Julie A. Simpson, PhD
Mark A. Kotowicz, MBBS, FRACP
Doris Young, MD, MBBS, FRACGP
Geoffrey C. Nicholson, PhD, FRACP

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

A Randomized Controlled Trial

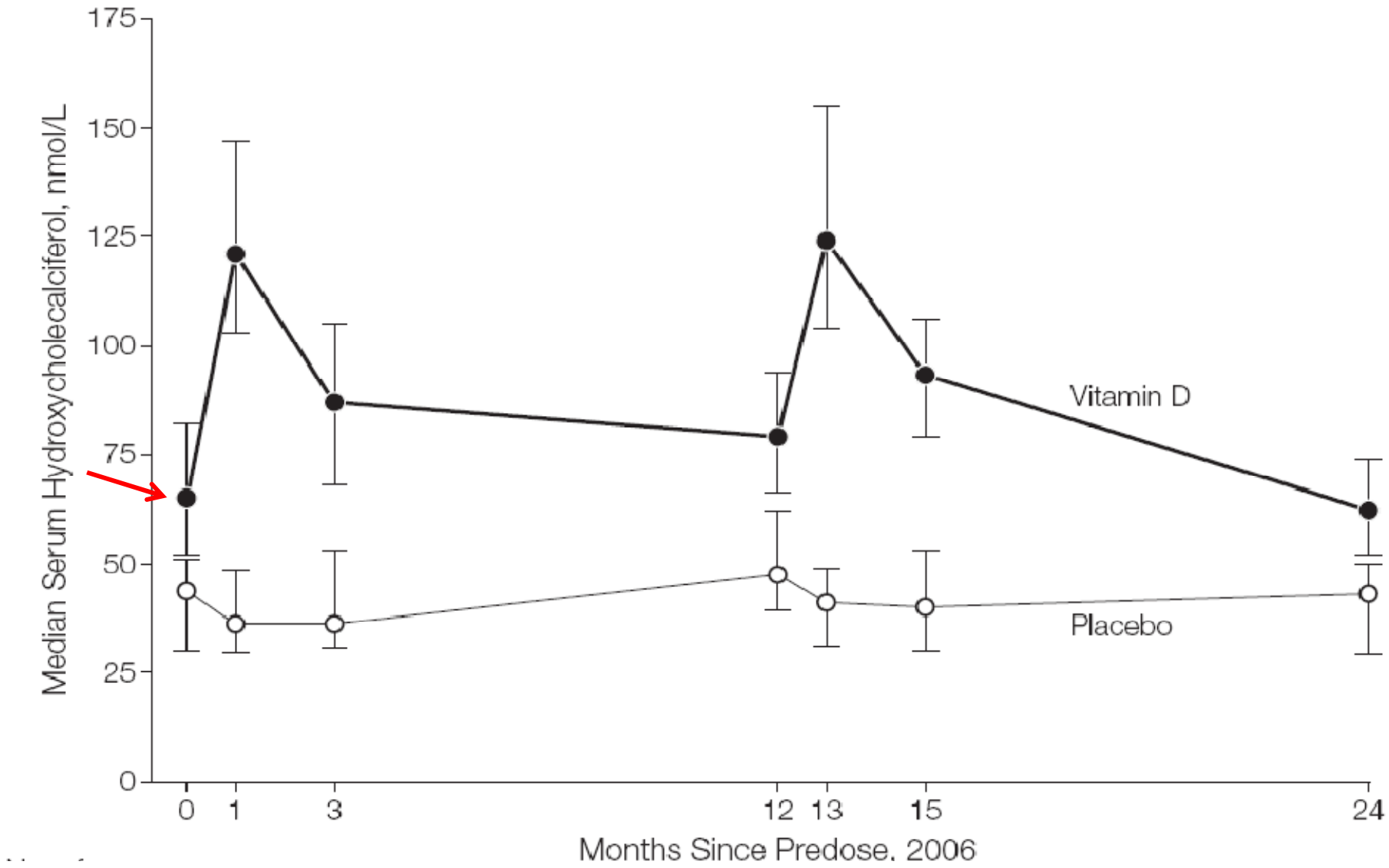
Double-blind, placebo controlled trial of 2256 community-dwelling women, aged >70 years
500000 IU of D3, orally, in autumn or winter





JAMA. 2010;303(18):1815-1822

25OHD before and after annual oral high-dose



Posologia, vie di somministrazione e valutazione dello stato vitaminico D

Vitamina D

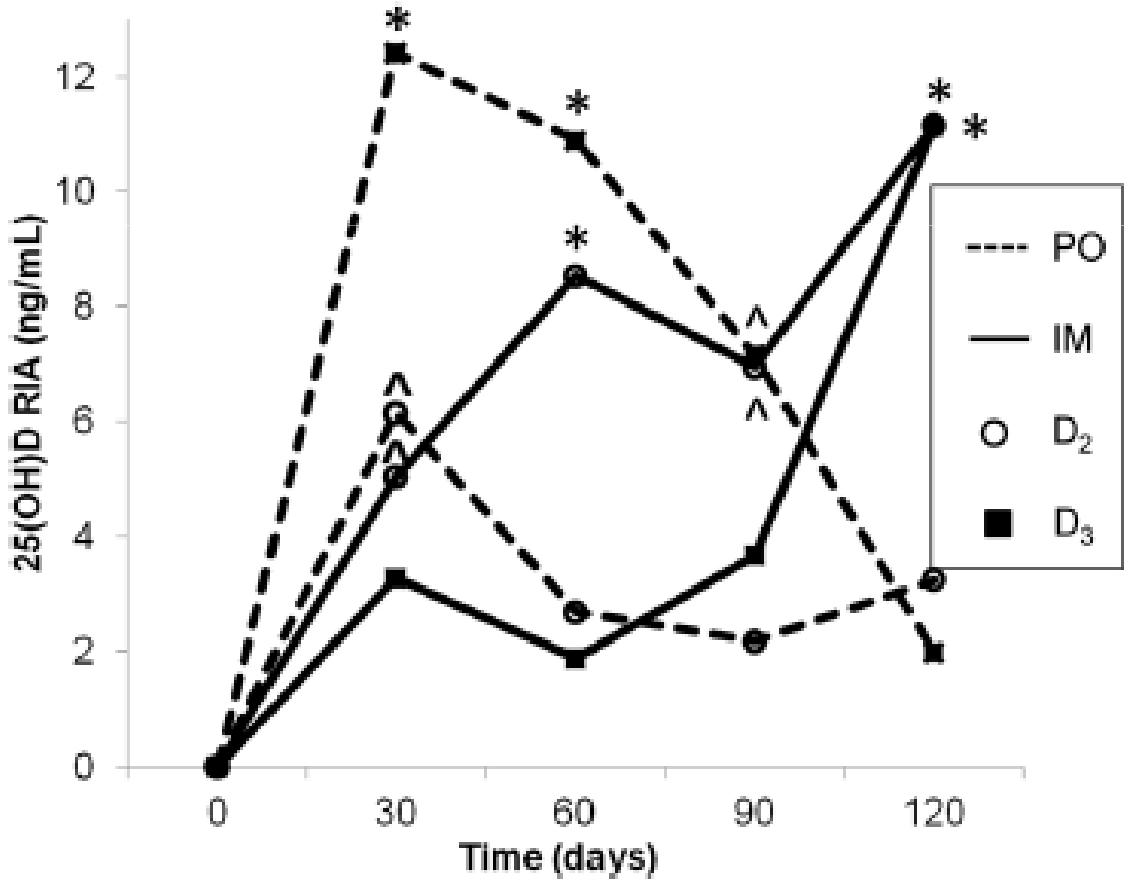
- Quanta
- Ogni quanto
- Per os o intramuscolo
- Dosaggio della 25-OH-D sierica

ORIGINAL ARTICLE

Endocrine Care

Long-Term Bioavailability After a Single Oral or Intramuscular Administration of 600,000 IU of Ergocalciferol or Cholecalciferol: Implications for Treatment and Prophylaxis

Cristiana Cipriani, Elisabetta Romagnoli, Jessica Pepe, Stefania Russo, Luciano Carlucci, Sara Piemonte, Luciano Nieddu, Donald J. McMahon, Ravinder Singh, and Salvatore Minisola



J Clin Endocrinol Metab 2013

Posologia, vie di somministrazione e valutazione dello stato vitaminico D

Vitamina D

- Quanta
- Ogni quanto
- Per os o intramuscolo
- Dosaggio della 25-OH-D sierica

JAMA | US Preventive Services Task Force | EVIDENCE REPORT

Screening for Vitamin D Deficiency in Adults Updated Evidence Report and Systematic Review for the US Preventive Services Task Force

Leila C. Kahwati, MD, MPH; Erin LeBlanc, MD, MPH; Rachel Palmieri Weber, PhD; Kayla Giger, BS; Rachel Clark, BA; Kara Suvada, BS; Amy Guisinger, BS; Meera Viswanathan, PhD

IMPORTANCE Low serum vitamin D levels have been associated with adverse clinical outcomes; identifying and treating deficiency may improve outcomes.

OBJECTIVE To review the evidence about screening for vitamin D deficiency in adults.

DATA SOURCES PubMed, EMBASE, the Cochrane Library, and trial registries through March 12, 2020; bibliographies from retrieved articles, outside experts, and surveillance of the literature through November 30, 2020.

STUDY SELECTION Fair- or good-quality, English-language randomized clinical trials (RCTs) of screening with serum 25-hydroxyvitamin D (25[OH]D) compared with no screening, or treatment with vitamin D (with or without calcium) compared with placebo or no treatment conducted in nonpregnant adults; nonrandomized controlled intervention studies for harms only. Treatment was limited to studies enrolling or analyzing participants with low serum vitamin D levels.

DATA EXTRACTION AND SYNTHESIS Two reviewers assessed titles/abstracts and full-text articles, extracted data, and assessed study quality; when at least 3 similar studies were available, meta-analyses were conducted.

MAIN OUTCOMES AND MEASURES Mortality, incident fractures, falls, diabetes, cardiovascular events, cancer, depression, physical functioning, and infection.

RESULTS Forty-six studies (N = 16 205) (77 publications) were included. No studies directly evaluated the health benefits or harms of screening. Among community-dwelling

JAMA 2021

SCIENTIFIC REPORTS

OPEN

Increase of vitamin D assays prescriptions and associated factors: a population-based cohort study

Received: 23 December 2016
Accepted: 17 May 2017
Published online: 04 September 2017

Pascal Caillet[1], Anne Goyer-Joos[1], Marie Viprey[1,2] & Anne-Marie Schott[1,2]

18.5%

	Patients with at least one 25OHD assay	*Source population (EGBS)*	p-value
Patients, n	118,509	639,163	
Female gender, n (%)	87,673 (73.9)	323,535 (50.6)	<0.001
Age at inclusion (mean, SD)	57.9 (17.8)	35.7 (23.9)	<0.001
Age at inclusion, n (%)			
0–18	0	173,072 (27.1)	<0.001
18–< 30	8,394 (70.8)	100,421 (15.7)	
30–< 40	12,036 (10.1)	87,593 (13.7)	
40–< 50	17,174 (14.5)	86,307 (13.5)	
50–< 60	23,858 (20.1)	75,546 (11.8)	
60–< 70	23,760 (20.0)	53,184 (8.3)	
70–< 80	18,120 (15.3)	39,548 (6.2)	
80–< 90	12,754 (10.8)	20,477 (3.2)	
≥90 y	2,413 (0.2)	2,982 (0.4)	
Charlson Index, mean (SD)	0.49 (1.51)	0,21 (0.92)	<0.001
Chronic disease status (*ALD* status), n (%)	41,355 (34.9)	109,187 (17.1)	<0.001
Presence of OP, n (%)	13,729 (11.6)	19,506 (3.0)	<0.001
Low economic resources status (*CMU* status), n (%)	6,872 (7.6)	80,043 (12.5)	<0.001

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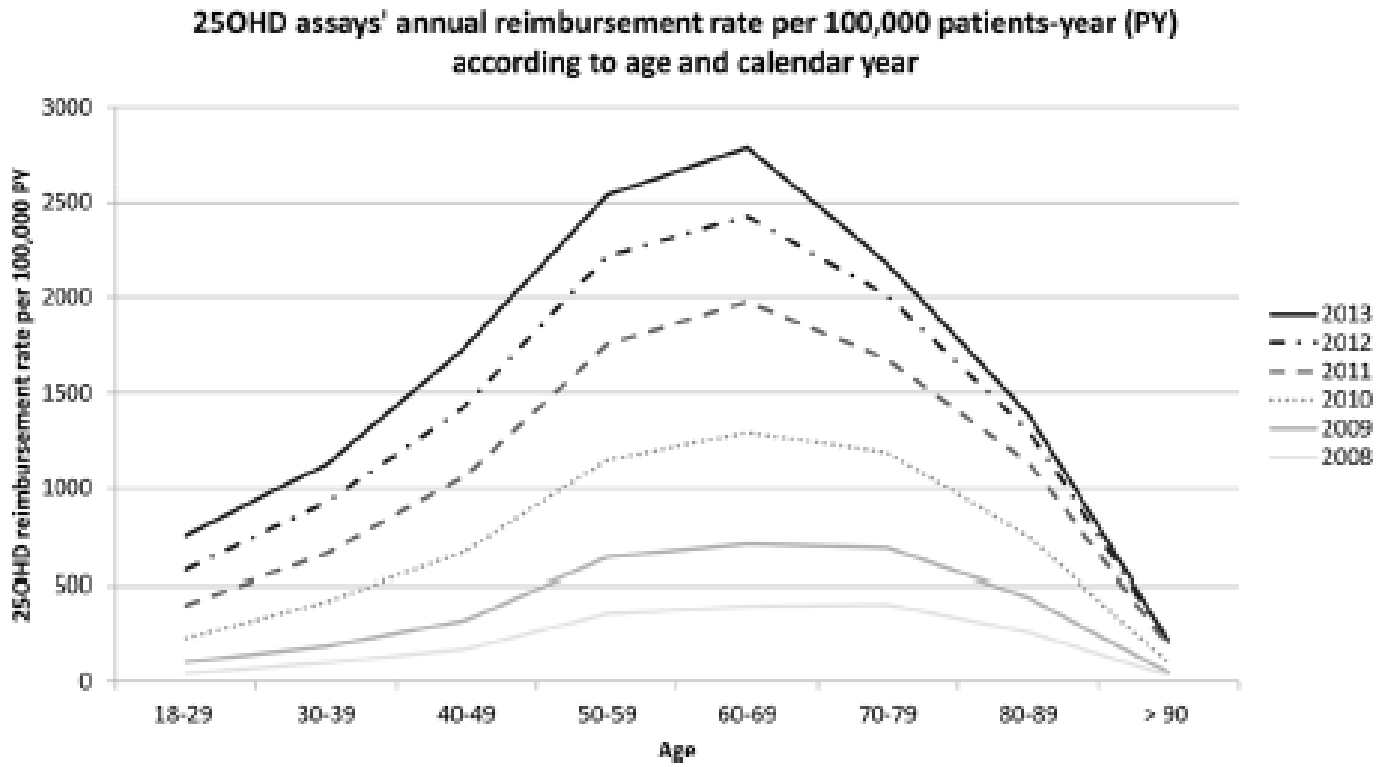

Osteoporosis International (2018) 29:1539–1547
https://doi.org/10.1007/s00198-018-4410-3

ORIGINAL ARTICLE

Prediction of insufficient serum vitamin D status in older women: a validated model

T. Merlijn[1,2] · K. M. A. Swart[1,2] · P. Lips[3] · M. W. Heymans[4,5] · E. Sohl[5] · N. M. Van Schoor[5] · C. J. Netelenbos[3] · P. J. M. Elders[1]

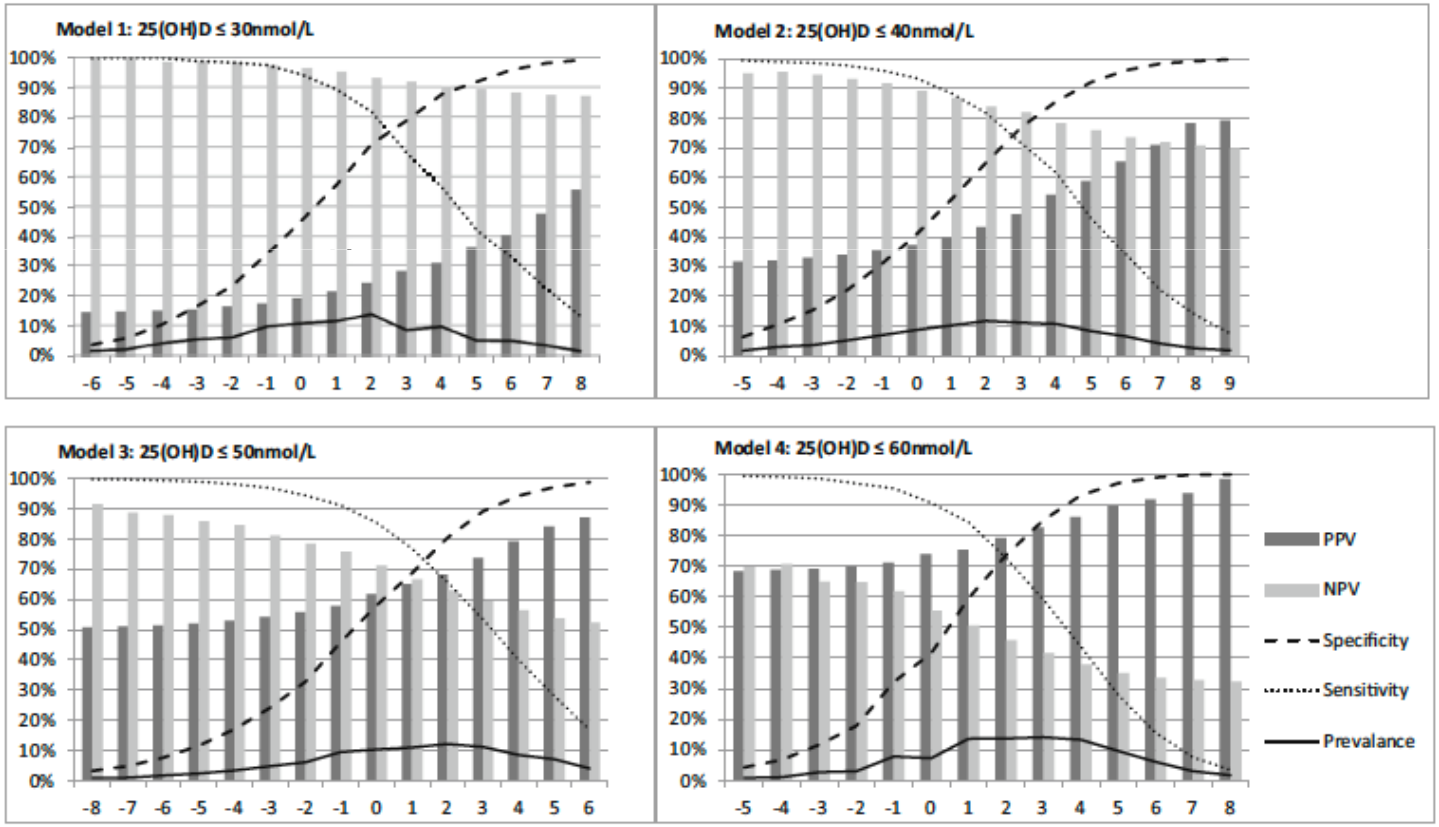

Fig. 3 Four models with different thresholds of serum 25-hydroxyvitamin D. The *Y*-axis shows the positive predictive (PPV), negative predictive value (NPV), sensitivity, specificity and prevalence for any computed risk score (*X*-axis) of participants in primary population

Prediction of vitamin D deficiency by simple patient characteristics[1–3]

Evelien Sohl, Martijn W Heymans, Renate T de Jongh, Martin den Heijer, Marjolein Visser, Thomas Merlijn, Paul Lips, and Natasja M van Schoor

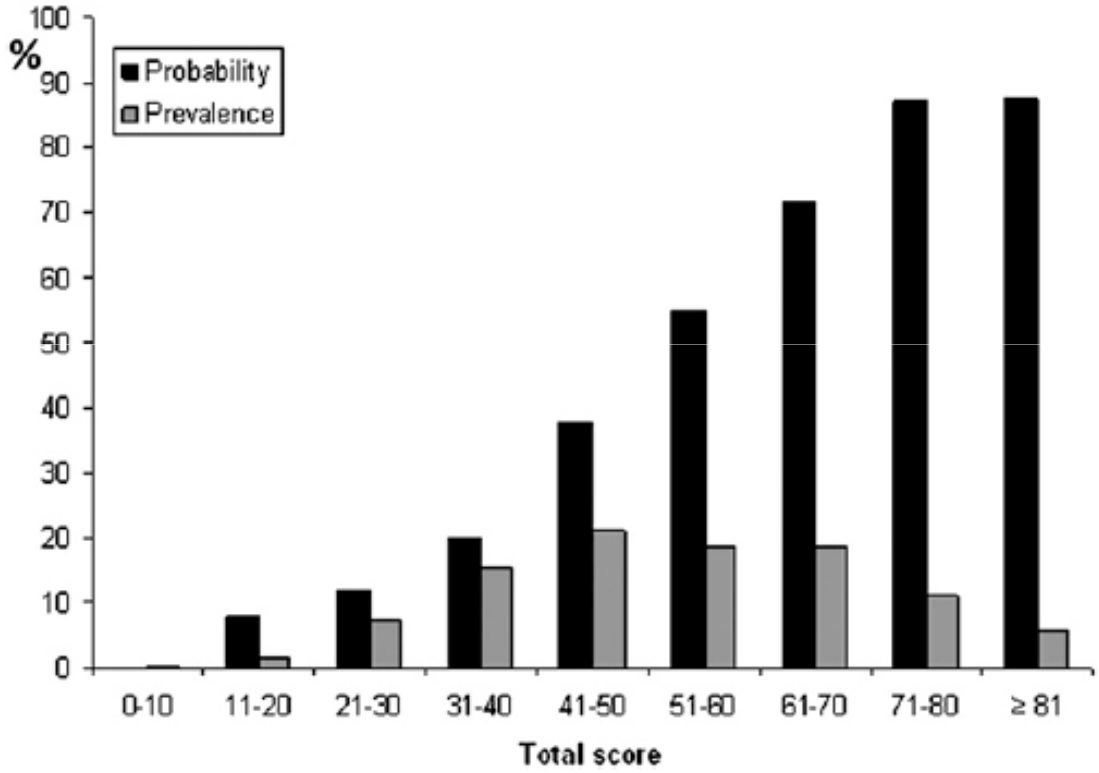

FIGURE 1. Probability and prevalence of vitamin D deficiency (<50 nmol/L) per 10-point increase in total risk score. For example, an individual with a score between 71 and 80 will have an ~90% risk of being vitamin D deficient (probability). Approximately 10% of the participants had a score between 71 and 80 (prevalence). n = 1509.

Am J Clin Nutr 2014

Allegato 1. Guida alla misurazione della 25OHD e alla successiva prescrizione della Vitamina D

Diagramma di flusso applicabile a persone > 18 anni per la determinazione della 25OH Vit D
La flowchart non è applicabile nelle seguenti condizioni per le quali è indicata una valutazione specialistica:

- insufficienza renale (eGFR<30 mmol/L),
- urolitiasi,
- ipercalcemia,
- sarcoidosi,
- neoplasie metastatiche, linfomi,

NB: La determinazione dei livelli di 25OHD NON deve essere intesa come procedura di screening è NON è indicata obbligatoriamente in tutte le possibili categorie di rischio.

(adattato da NICE 2018)

1. Esiste almeno un sintomo persistente fra quelli elencati suggestivo per carenza di vitamina D ?
   - Sintomi di osteomalacia come dolenzia in sedi ossee o dolore (anche pulsante) lombosacrale, pelvico o agli arti inferiori; senso di impedimento fisico; dolori o debolezza muscolare (anche di grado elevato) soprattutto ai quadricipiti ed ai glutei con difficoltà ad alzarsi da seduto o andatura ondeggiante;
   - Dolori diffusi di lunga durata;
   - Propensione alle cadute immotivate.
2. È prevista una terapia di lunga durata con farmaci interferenti col metabolismo della vitamina D (ed es. antiepilettici, glucocorticoidi, anti-retrovirali, anti-micotici, colestiramina, orlistat etc.) oppure esiste una condizione di malassorbimento (ad es. fibrosi cistica, celiachia, m. Crohn, chirurgia bariatrica, etc) ?
3. Esiste una patologia ossea accertata (osteoporosi, osteomalacia o malattia di Paget) che può beneficiare dal trattamento con vitamina D oppure necessita di terapia remineralizzante?
4. Esiste un riscontro di PTH elevato con calcemia normale o bassa?

SI

È appropriata la prescrizione di una determinazione della 25(OH) D.
Nell'interpretazione dei risultati considerare che il laboratorio potrebbe NON condividere i medesimi intervalli di normalità.

NO

La determinazione della 25(OH) D, NON è appropriata.