8th National Congress on Osteoporosis, Osteoarthritis and Musculoskeletal Diseases
Antalya November 2024

Vitamin D: for Whom and How

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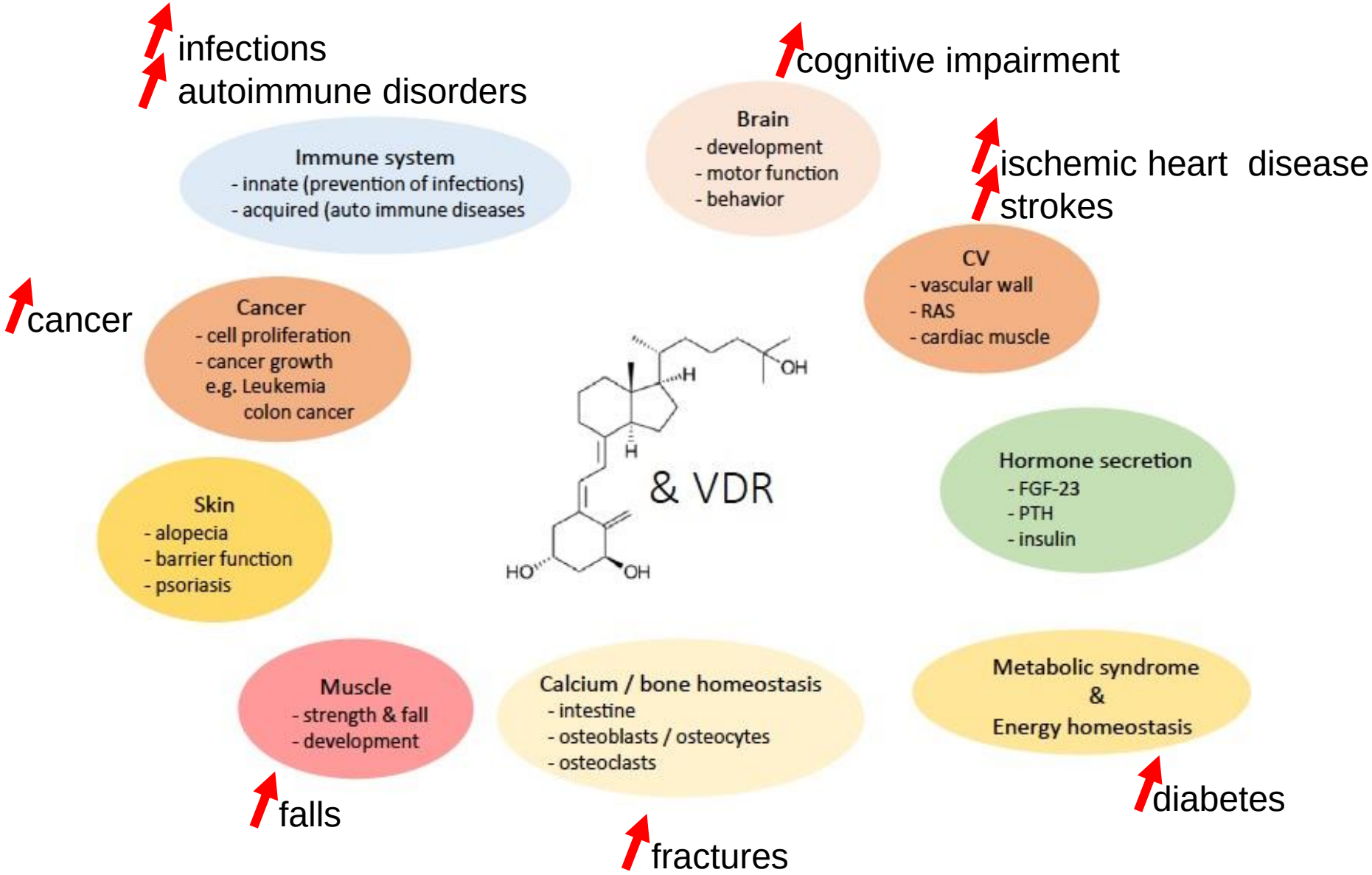
Disclosure

Speaker Bureau or Member of Scientific Advisory Boards for Abiogen, Naturex, Theramex, Viatris

Vitamin D **Deficiency**



Bouillon & Carmeliet Best Pract Res Clin Endocr Metab 2018

Large Randomized Trials on the Effects of Vitamin D Supplementation

Study	Region	Number	Mean Age (Yrs)	Duration (Yrs)	Vitamin D Supplements	Primary Outcomes
VITAL	USA	25’874	67	5.3	2’000 IU daily	Cardio-vascular events, cancer
VIDA	New Zealand	5’110	66	3.3	200’000 IU, then 100’000 IU monthly	Cardio-vascular events, mortality
D2D					4’000 IU daily	T2DM
Do-Health	Europe	2’157	75	3	2’000 IU daily	6 Outcomes
D-Health	Australia	21’315	> 60	5	60’000 IU monthly	Mortality
FIND	Finland	2’495	≥ 65	5	1’600, 3’200 IU daily	Cardio-vascular events, cancer

All negative

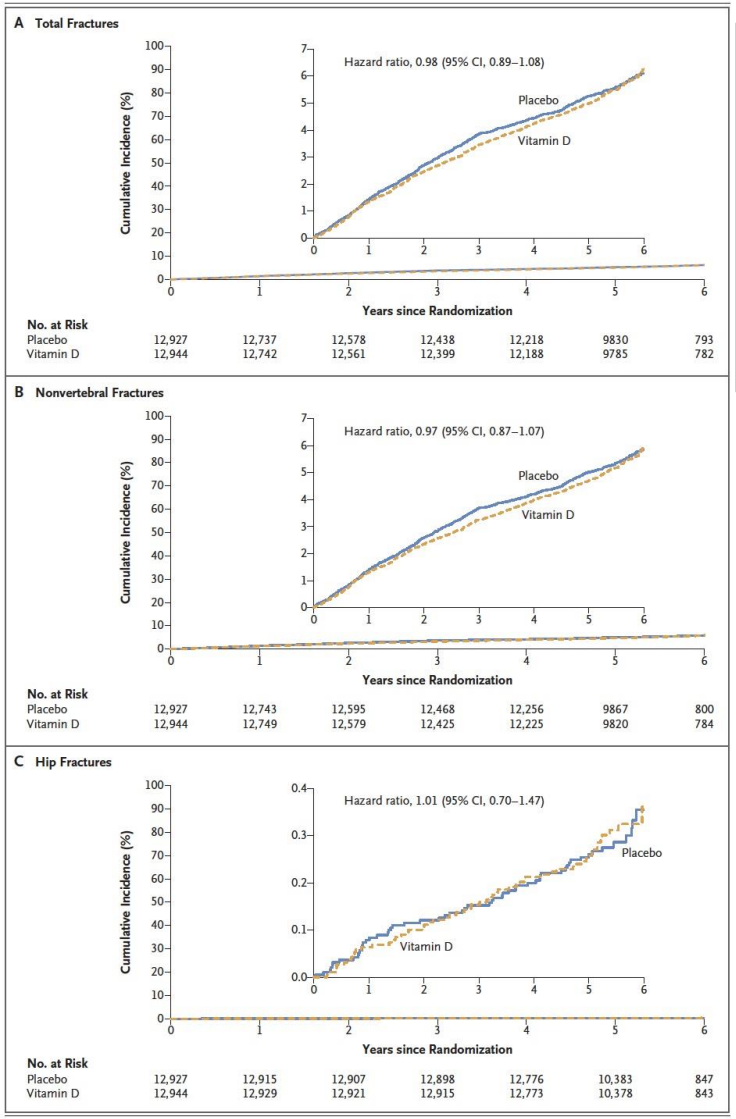
Supplemental Vitamin D and Incident Fractures in Midlife and Older Adults

VITamin D and OmegA-3 TriaL (VITAL): Effects of Vitamin D Supplements on Risk of Falls in the US Population

All

Non-vert

Hip fractures

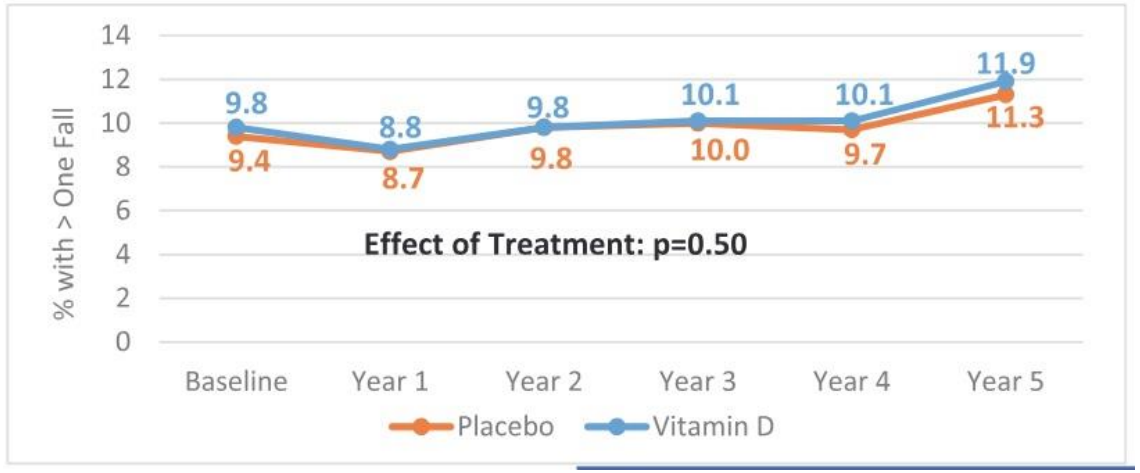


Leboff et al NEJM 2022

VITAL trial
n = 25’871 (50.6 % W)
67 Yrs
± 2’000 IU/day, 5.3 Yrs
Baseline 25OHD 30.7 ng/ml
(76 nmol/l)

2a. Percent with Two or More Falls

Group	Baseline	Year 1	Year 2	Year 3	Year 4	Year 5
Placebo	1207/12867	1059/12119	1158/11861	1130/11334	1048/10764	1127/9960
Vitamin D	1260/12848	1075/12168	1167/11879	1155/11410	1102/10914	1202/10099



LeBoff et al JCEM 2020

Issues in Interpreting Randomized Controlled Trials on Vitamin D

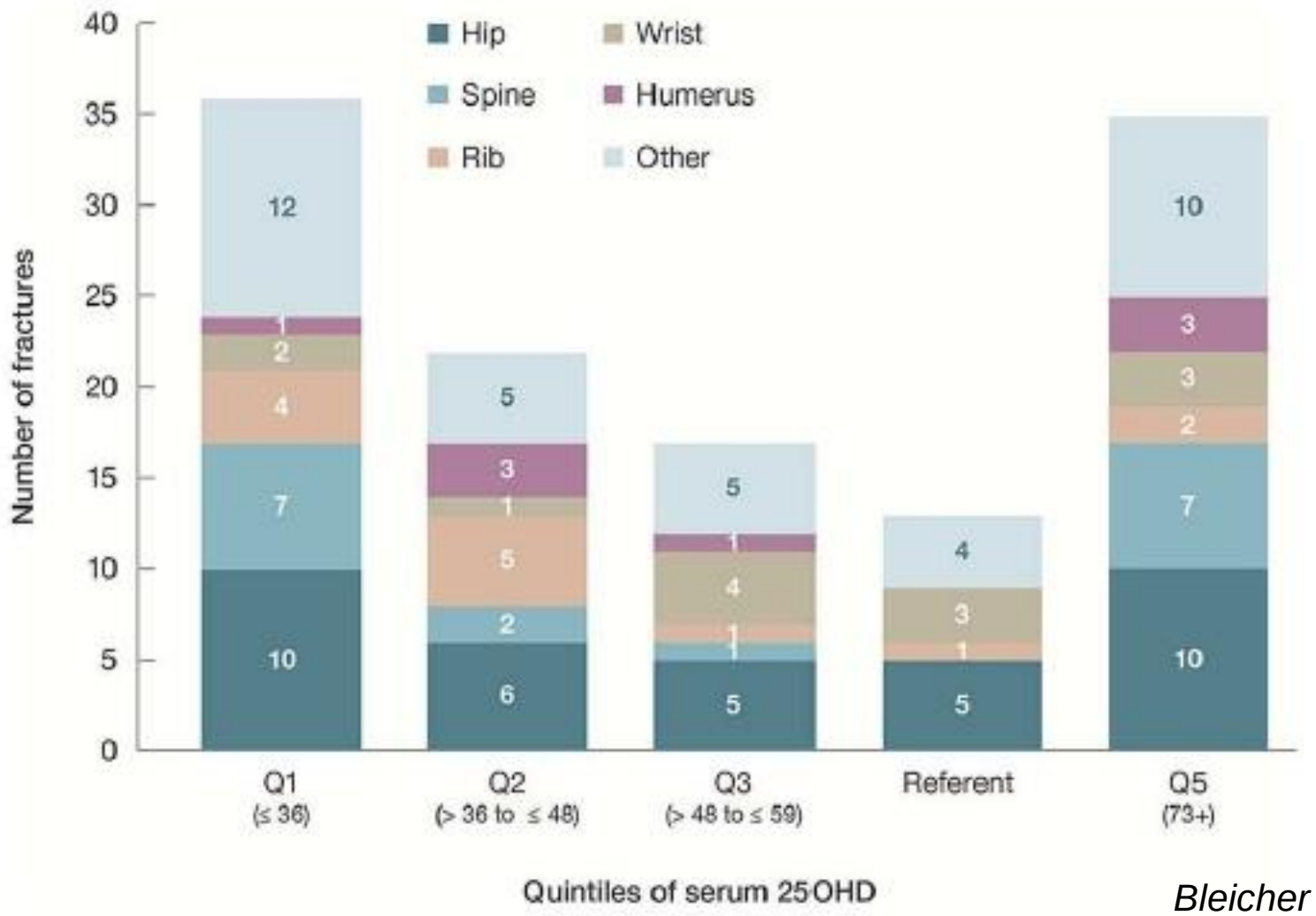
1. **P**opulation Studied
2. **I**ntervention
   - Dose
   - Schedule of Administration
3. **C**omparison
4. **O**utcome

5. Role of Concommitant Treatments

Large Randomized Trials on the Effects of Vitamin D Supplementation

Study	Region	Number	Mean Age (Yrs)	Baseline 25OHD (ng/ml)	Duration (Yrs)	Vitamin D Supplements	Primary Outcomes
VITAL	USA	25'874	67	**30.8 (77)***	5.3	2'000 IU daily	Cardio-vascular events, cancer
VIDA	New Zealand	5'110	66	**26.5 (66)***	3.3	200'000 IU, then 100'000 IU monthly	Cardio-vascular events, mortality
D2D	USA	2'423	60	**28 (70)***	2.5	4'000 IU daily	T2DM
Do-Health	Europe	2'157	75	**22 (55)***	3	2'000 IU daily	6 Outcomes
D-Health	Australia	21'315	> 60	**30.3 (76)***	5	60'000 IU monthly	Mortality
FIND	Finland	2'495	≥ 65	**30 (75)* * nmol/l**	5	1'600, 3'200 IU daily	Cardio-vascular events, cancer

U-Shaped Association Between Serum 25-Hydroxyvitamin D and Fracture Risk in Older Men: Results From the Prospective Population-Based CHAMP Study



1’662 Men,
70-97 Yrs
4.3 Yrs

Bleicher et al JBMR 2014

Issues in Interpreting Randomized Controlled Trials on Vitamin D

1. Population Studied
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   - Dose
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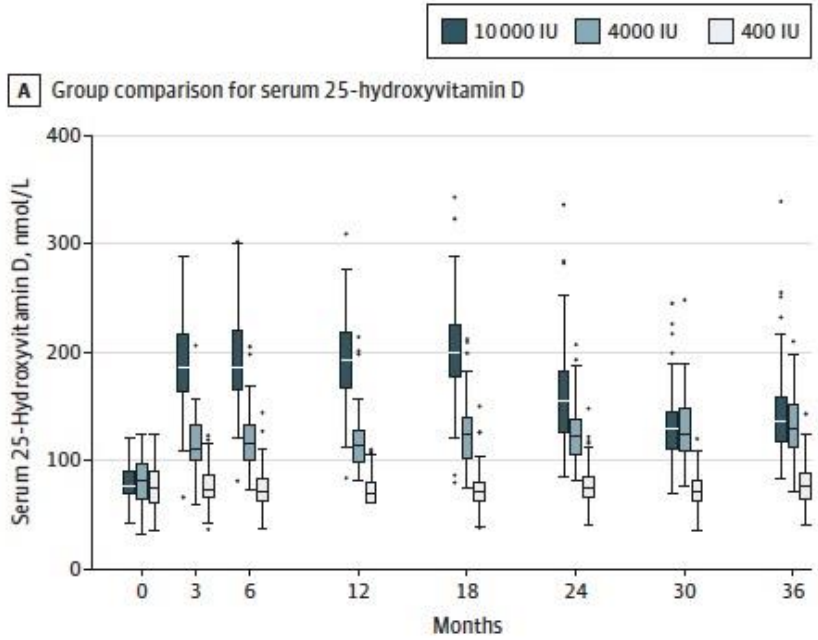
5. Role of Concommitant Treatments

Effect of High-Dose Vitamin D Supplementation on Volumetric Bone Density and Bone Strength
A Randomized Clinical Trial

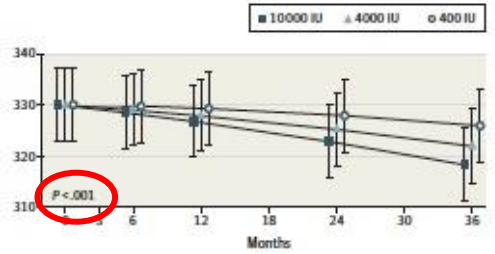
61-yr, Men & Women (46%)
Baseline 25OHD: 79 nmol/l
3 yrs, Vit D 400 - 4'000 - 10'000 IU/d



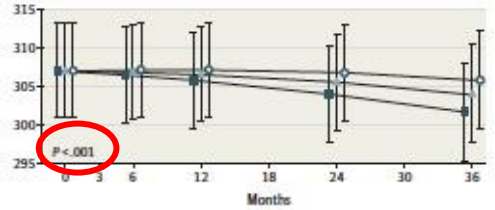
	Vit D 400	4'000	10'000 IU/d
Hypercalcemia	0	4	9 %
Hypercalciuria	17	22	33 %
Falls	4	10	5 %

Burt et al JAMA 2019

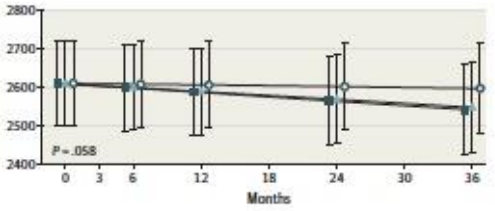
Radius Total BMD



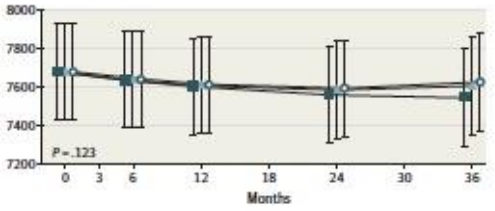
Tibia total BMD



Radius Failure Load

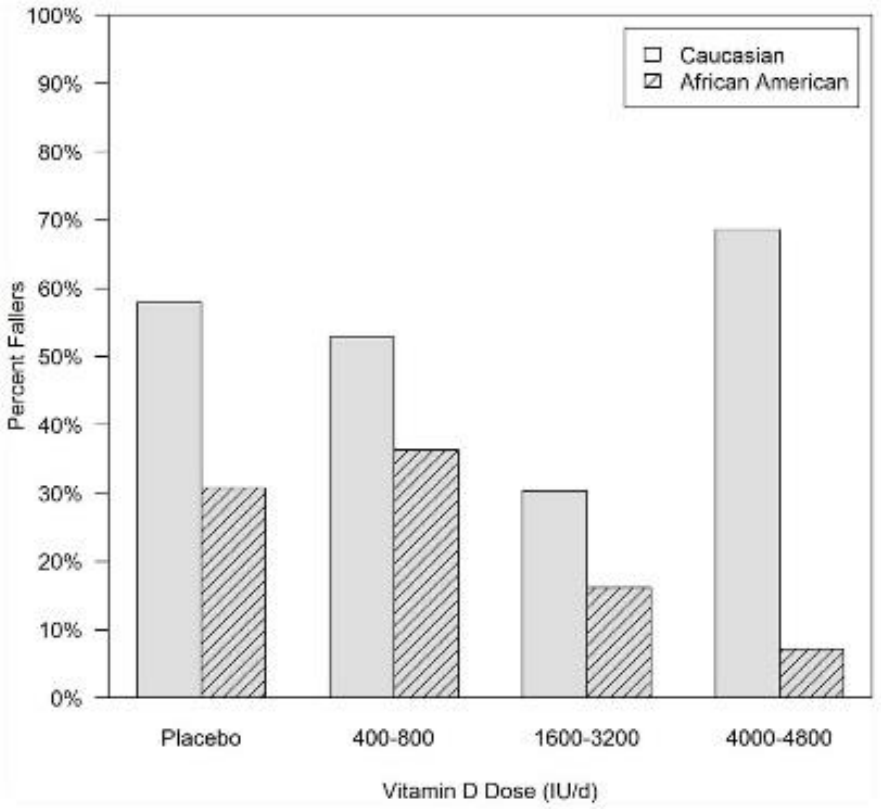


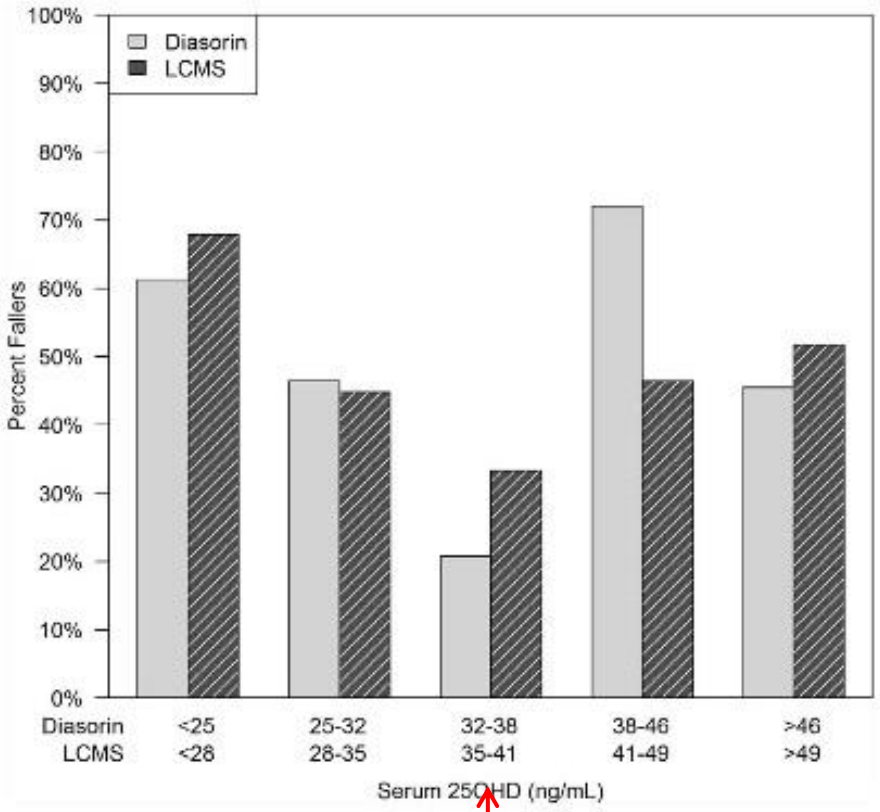
Tibia Failure Load



Medium doses of daily vitamin D decrease falls and higher doses of daily vitamin D3 increase falls: A randomized clinical trial

12 Months





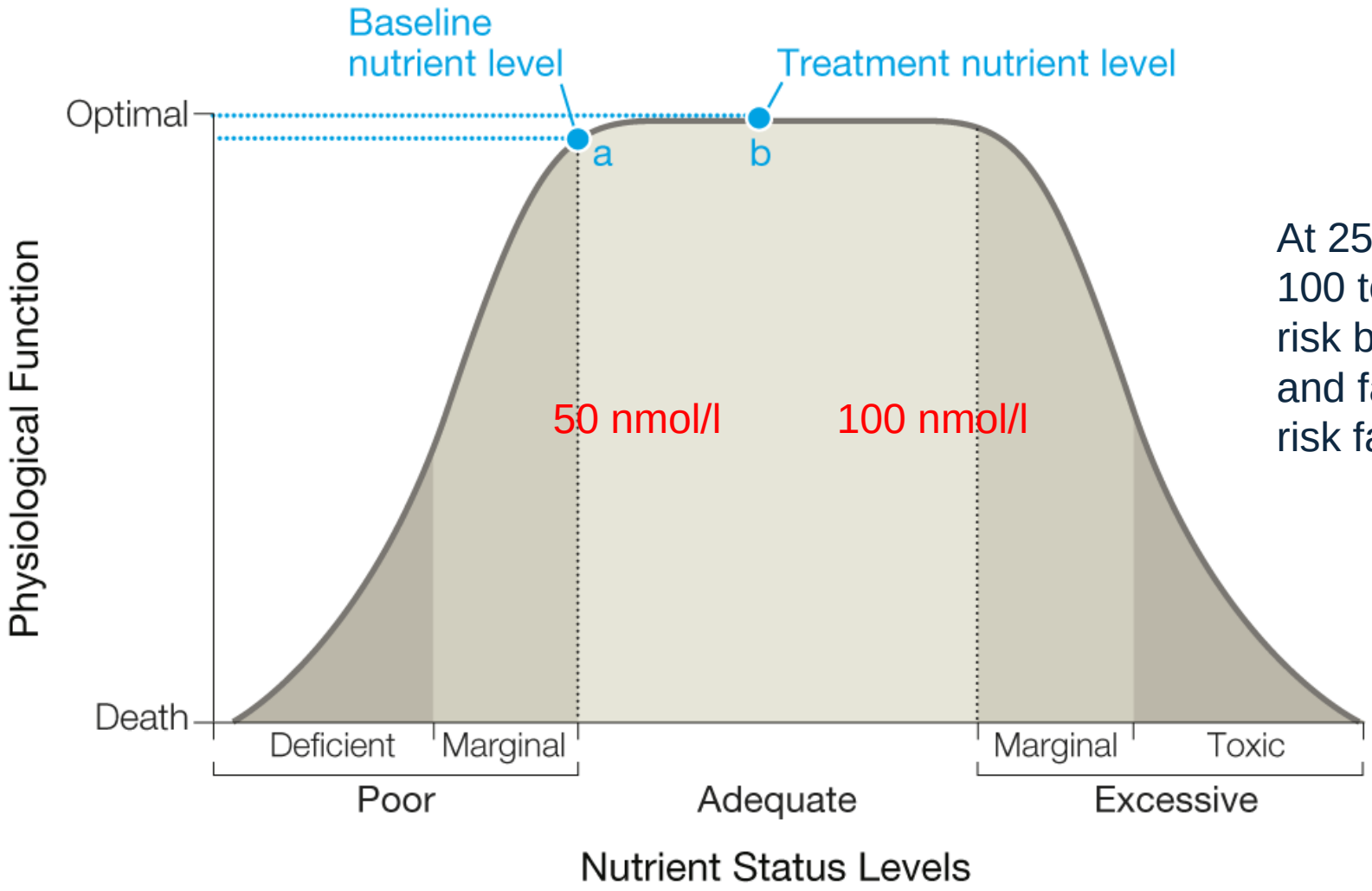
Baseline 25OHD: 38 nmol/l

75-100 nmol/l

Smith et al J Ster Bioch Mol Biol 2017

U-shaped association of falls with 25(OH)D

Levels under 50 nmol/l are considered insufficient.

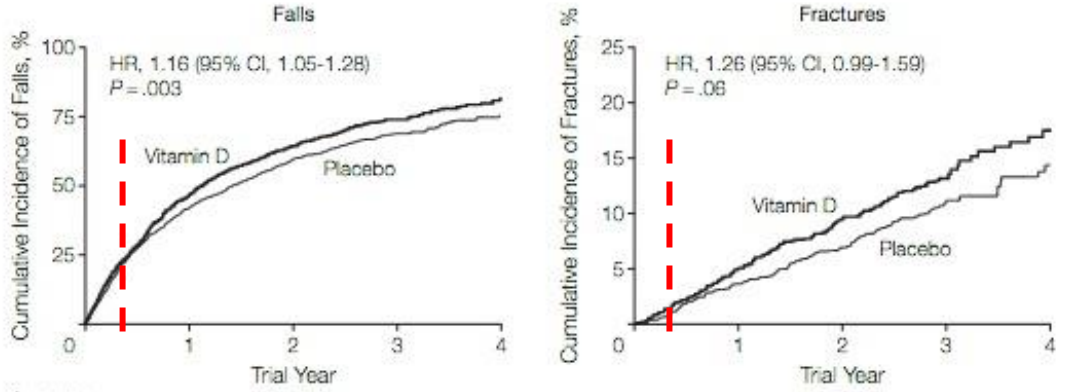


At 25(OH)D levels above 100 to 150 nmol/l, fall risk begins to increase and falls are the major risk factor for fracture.

Morris et al. JAMA 2011.

Annual High-Dose Oral Vitamin D and Falls and Fractures in Older Women- A Randomized Controlled Trial

Figure 2. Kaplan-Meier Plots of Cumulative Incidence of Time to First Fracture and First Fall



No. of women

Vitamin D	1131	588	382	77	22	1131	1048	963	236	106
Placebo	1125	635	429	87	33	1125	1050	985	253	115

This analysis censors data after first fall or fracture. Time to first fracture and fall was analyzed using Cox proportional hazards models. CI indicates confidence intervals; HR, hazard ratio.

Table 4. Temporal Pattern of Risk in Falls and Fracture 0 to 3 Months and 4 to 12 Months After Treatment

	Incidence Rate Ratio for Vitamin D Group, Estimate (95% Confidence Interval)[a]	*P* Value
Time after treatment, mo		
Falls		
Within 3	1.31 (1.12-1.54)	.001
After 3	1.13 (0.99-1.29)	.08
Fracture		
Within 3	1.53 (0.95-2.46)	.08
After 3	1.18 (0.91-1.54)	.21

[a] The incidence rate ratio refers to the risk ratio of the vitamin D group compared with the placebo group. The rate ratio within 3 months after treatment is significantly different from the rate ratio of the remaining 9 months after treatment for falls ($P = .02$) but not for fracture ($P = .36$).

Sanders et al JAMA 2010

Meta-analysis of 23 RCTs:
High doses of vitamin D increase circulating FGF23 levels

Zittermann A. Europ J Clin Nutr 2021

- Vitamin D doses ≥ 2000 IU/d and bolus doses increase FGF-23 levels.
- FGF-23 downregulates 1α-hydroxylase (CYP27B1) in the kidney.
- FGF-23 upregulates 24-hydroxylase (CYP24A1), converting $1,25(OH)_2D$ to the inactive calcitroic acid $1,24,25(OH)_3D$.

=> inadequate $1,25(OH)_2D$ despite adequate or high levels of 25(OH)D.

Christakos S. Endo Metab Clinics NA 2010

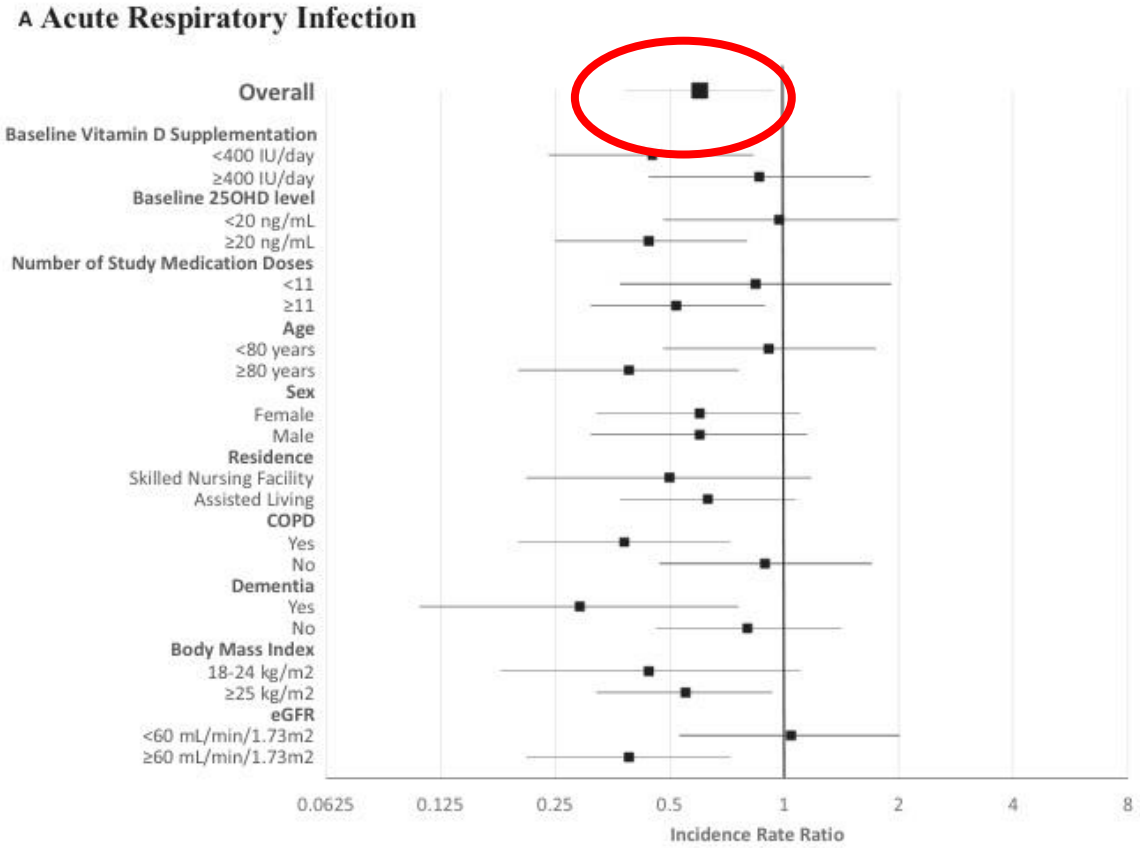
Issues in Interpreting Randomized Controlled Trials on Vitamin D

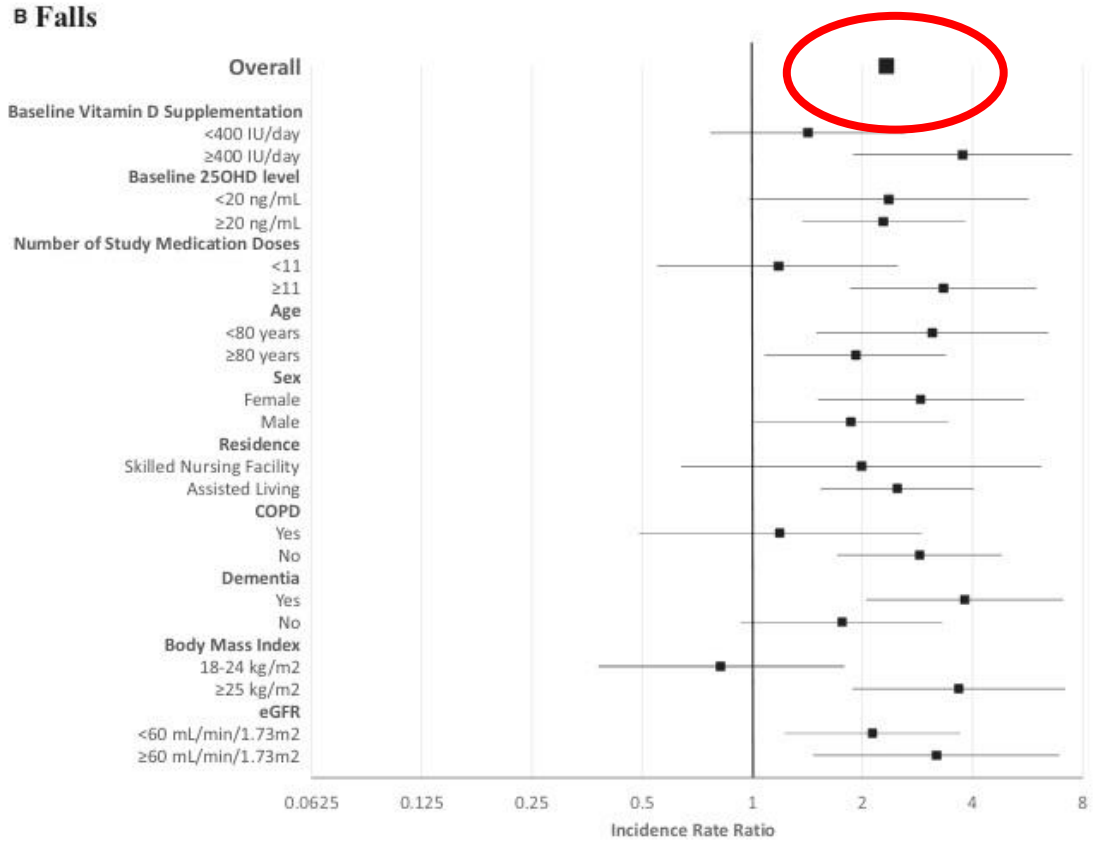
1. **P**opulation Studied
2. **I**ntervention
   - Dose
   - Schedule of Administration
3. **C**omparison
4. **O**utcome

5. Role of Concommitant Treatments

High-Dose Monthly Vitamin D for Prevention of Acute Respiratory Infection in Older Long-Term Care Residents: A Randomized Clinical Trial

N= 107, 81 Yrs, 3’000-4’000 vs 400-1’000 IU/day equivalent





Ginde et al JAGS 2017

Issues in Interpreting Randomized Controlled Trials on Vitamin D

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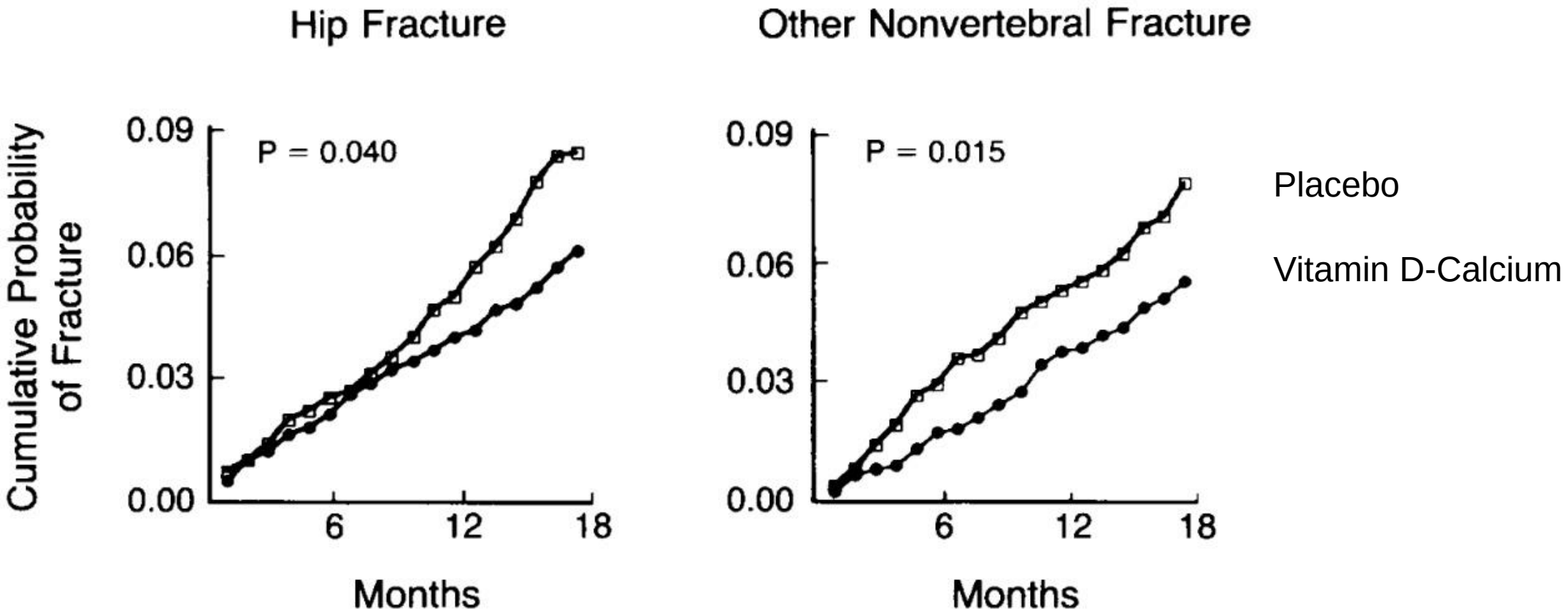
5. Role of Concommitant Treatments

Vitamin D3 and calcium to prevent hip fractures in elderly women

n=3270, 84 yrs, 25OHD: 40 nmol/l, calcium intake: 511 mg/d
± 800 IU/d vitamin D-1200 mg/d calcium



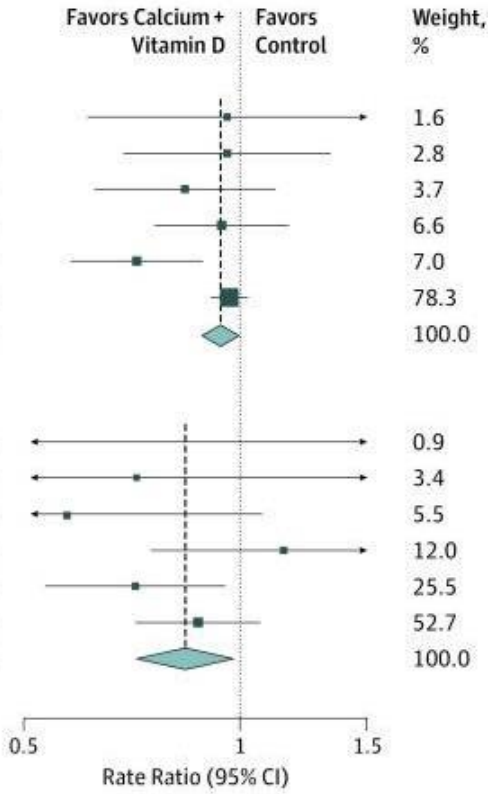
Chapuy et al NEJM 1992

Vitamin D and Calcium for the Prevention of Fracture

A Systematic Review and Meta-analysis

Meta-analysis of **Randomized Clinical Trials** of Supplementation **With Calcium Plus Vitamin D** vs Placebo or No Treatment for Prevention of Any Fracture or of Hip Fracture

Source	Calcium + Vitamin D: Calcium, mg/d	Calcium + Vitamin D: Vitamin D, IU/d	Calcium + Vitamin D: Events, No./ Total Participants, No.	Control: Events, No./ Total Participants, No.	Risk of Bias	Rate Ratio (95% CI)	Weight, %
Any fracture							
Chapuy et al,[50] 2002	1200	800	70/393	35/190	High	0.96 (0.61-1.51)	1.6
Porthouse et al,[51] 2005	1000	800	58/1321	91/1993	High	0.96 (0.69-1.34)	2.8
Salovaara et al,[52] 2010	1000	800	86/1586	103/1609	High	0.84 (0.63-1.13)	3.7
Grant et al,[47] 2005	1000	800	179/1306	192/1332	High	0.94 (0.76-1.17)	6.6
Chapuy et al,[53] 1992	1200	800	160/1634	215/1636	High	0.72 (0.58-0.89)	7.0
Jackson et al,[54] 2006	1000	400	2102/18176	2158/18106	Low	0.97 (0.91-1.03)	78.3
All			2655/24416	2794/24866		0.94 (0.89-0.99)	100.0
Subtotal ($Q = 7.3$, $df = 5$, $P = .20$; $I^2 = 31.4\%$)							
Hip fracture							
Salovaara et al,[52] 2010	1000	800	4/1586	2/1609	High	1.98 (0.40-9.81)	0.9
Porthouse et al,[51] 2005	1000	800	8/1321	17/1993	High	0.72 (0.32-1.61)	3.4
Chapuy et al,[50] 2002	1200	800	27/393	21/190	High	0.58 (0.31-1.08)	5.5
Grant et al,[47] 2005	1000	800	46/1306	41/1332	High	1.15 (0.75-1.76)	12.0
Chapuy et al,[53] 1992	1200	800	80/1634	110/1636	High	0.72 (0.53-0.96)	25.5
Jackson et al,[54] 2006	1000	400	175/18176	199/18106	Low	0.87 (0.71-1.07)	52.7
All			340/24416	390/24866		0.84 (0.72-0.97)	100.0
Subtotal ($Q = 6.0$, $df = 5$, $P = .31$; $I^2 = 16.5\%$)							



Yao et al JAMA Netw Open 2019

Vitamin D: for Whom and How ?

The ESCEO/IOF viewpoint

Meta-analyses of studies on vitamin D supplementation and fractures (continued)

Author, year	Trials	Outcome : vitamin D	Outcome : vitamin D and calcium
Bolland et al. 2018	81 unblinded and blinded randomized trials among (*n*= 44,790)	– Authors *excluded trials that combined vit D with calcium* and thereby 40% of the literature that contributed to current guidelines – Authors *included large bolus doses* that have consistently increased the risk of falls and fractures	No benefit on fractures **Re-analysis of 800–1000 IU vit D trials of this meta-analysis and excluding bolus trials suggests a significant 14% reduction in total fractures**
Hu Z et al. 2019	25 RCTs N=43,510		No reduction of the risk of total, hip and vertebral fractures using different doses of vit D, calcium or their combination compared with placebo or no treatment
Yao P et al. 2019	11 RCTs N=34,243 6 RCTs N=49,282	Vit D alone : no reduction of risk of any fracture (RR: 1.06; 95%CI, 0.98-1.14) or hip fracture (RR: 1.14; 95%CI, 0.98-1.32)	**↓ 6% of any fracture (RR, 0.94; 95%CI, 0.89-0.99) and ↓ 16% of hip fractures (RR, 0.84; 95%CI, 0.72-0.97)**
Eleni A et al. 2020	10 RCTs N=74,325	Patients aged 50 years or older Reported on fractures as a primary outcome	**RR 0.74 [CI: 95% 0.58–0.94] for total fractures.** **RR: 0.61 [CI 95% 0.4–0.92] for hip fractrures 8 RCTs, N=68,957**
Thanapluetiwong et al. 2020	26 RCTs N=40,209	Vit D alone : no fracture lowering benefit, RR=0.949 (95% CI 0.846-1.064).	**Vit D +calcium: lower fracture rates, RR=0.859 (95% CI 0.741-0.996)**
Li S et al. 2021	33 RCTs N=83,083	Vit D alone : no reduction of the risk of total fractures (RR ¼ 0.96, 95%CI ¼ 0.87–1.05)	**Vit D3 (700–800IU/d) + calcium : significant reduction of total (RR=0.85, 95% CI =0.77-0.95), hip (RR=0.81, 95% CI =0.68-0.97), and non-vertebral fractures (RR=0.84, 95% CI =0.74-0.95), in the pairwise meta-analysis.**
Chakhtoura M et al. 2022	Umbrella review of Meta-Analyses 25 RCTs	No fracture risk reduction in SRs/MAs exclusively evaluating community-dwelling individuals or in those on vit D alone compared to placebo/control	**Vit D + calcium : ↓ risk of hip fractures in 8/12 SRs/MAs [RR] 0.61-0.84) ↓ risk of any fractures in 7/11 SRs/MAs [RR] 0.74-0.95)**
Kong SH et al. 2022	.32 RCTs n=104,363 16 RCTs n=36,793 for fracture outcome	**Vit D 800 to 1,000 IU/d : Pooled relative risk [RR], 0.87; 95% [CI], 0.78 to 0.97) for osteoporotic fractures** No reduction of hip fractures RR, 0.84; 95% CI, 0.64 to 1.10	**Vit D 800 to 1,000 IU/d + calcium : pooled RR, 0.88; 95% CI, 0.78 to 1.00) for osteoporotic fractures**

Chevalley et al ACER 2022

Indications for vitamin D supplementation

Daily vitamin D (800-1000 IU)

- At risk of osteoporosis
- Concurrent osteoporosis treatment
- Fragility fracture
- At risk of falling
- Obesity
- Pigmented skin
- Limited sun exposure
- Insufficient vitamin D intake
- Malabsorption *
- After bariatric surgery *
- Anticonvulsants
- Glucocorticoids

*Higher doses may be needed
(as well as in obeses)

Loading dose (25,000 or 50,000 IU/week for 4 to 6 weeks)

- Low 25-hydroxyvitamin D levels
- Need for a rapid correction of vitamin D deficiency
- After bariatric surgery
- Malabsorption
- Severe obesity

Chevalley et al ACER 2022

Summary and Conclusions

1. Doses of 800 – 1’000 IU Daily of vitamin D are Safe
2. Intermittent Regimens are not Recommended
3. The Risk of Overdosing Expression is Related to the Outcome Evaluated
4. Upper Limit of Safety for Clinical Outcomes (for both Dose and Circulating Levels) should still be better Evaluated and Defined
5. Vitamin D and calcium should be considered for fracture prevention and in patients on anti-osteoporosis treatment

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