Calcium and Vitamin D Suppletion State of the Art

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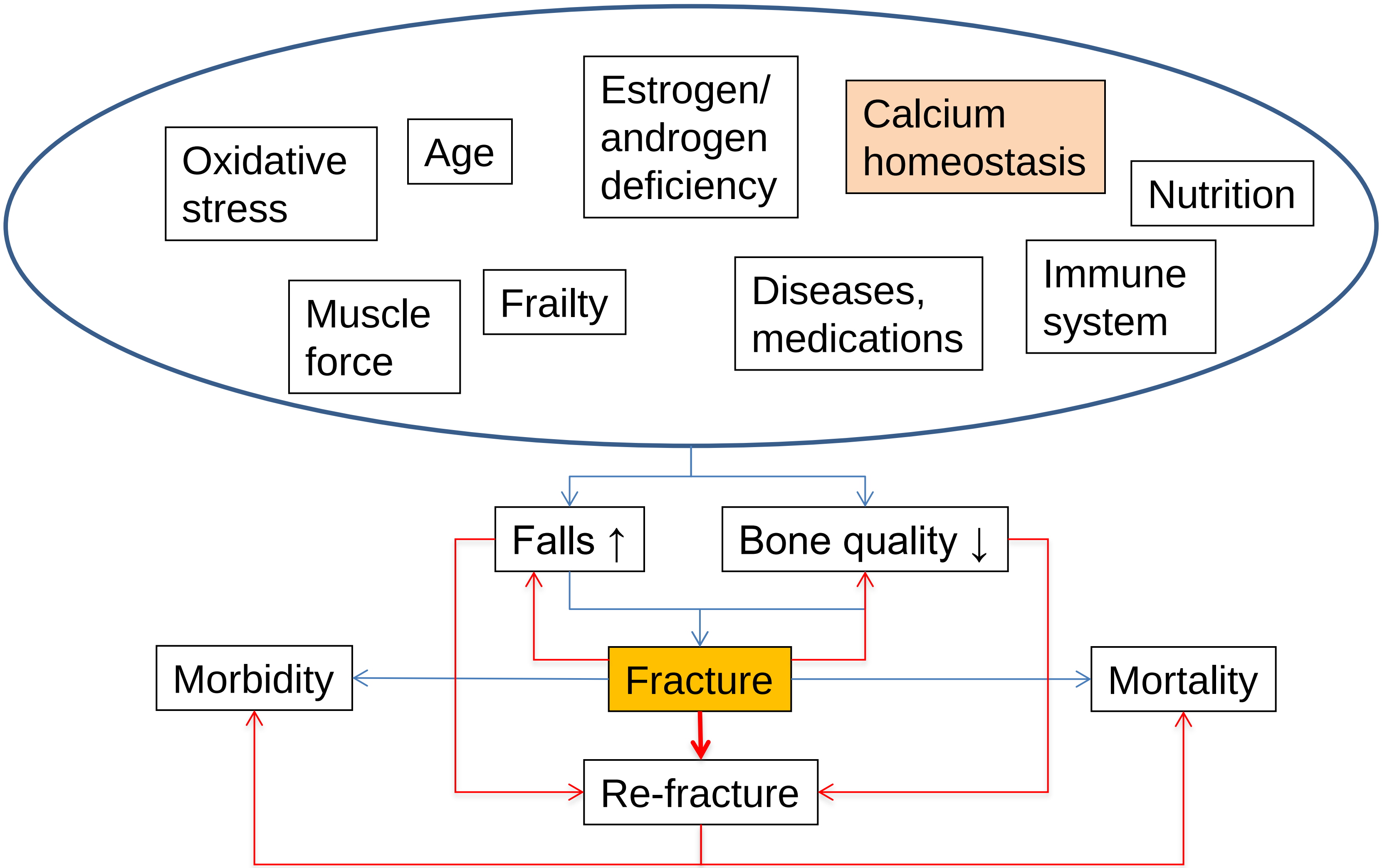
Calcium & vitamin D suppletion: the problem

- More than 50 meta-analyses published on vitamin D, with or without calcium
- Comparison of these meta-analyses highlights important differences in
  - trial selection
  - Variable baseline calcium intake and VitD levels
  - Variable doses, mostly high
  - outcome definition: fracturs, falls, BMD
  - analytical methods
- Markedly different conclusions

Calcium & vitamin D suppletion: solutions

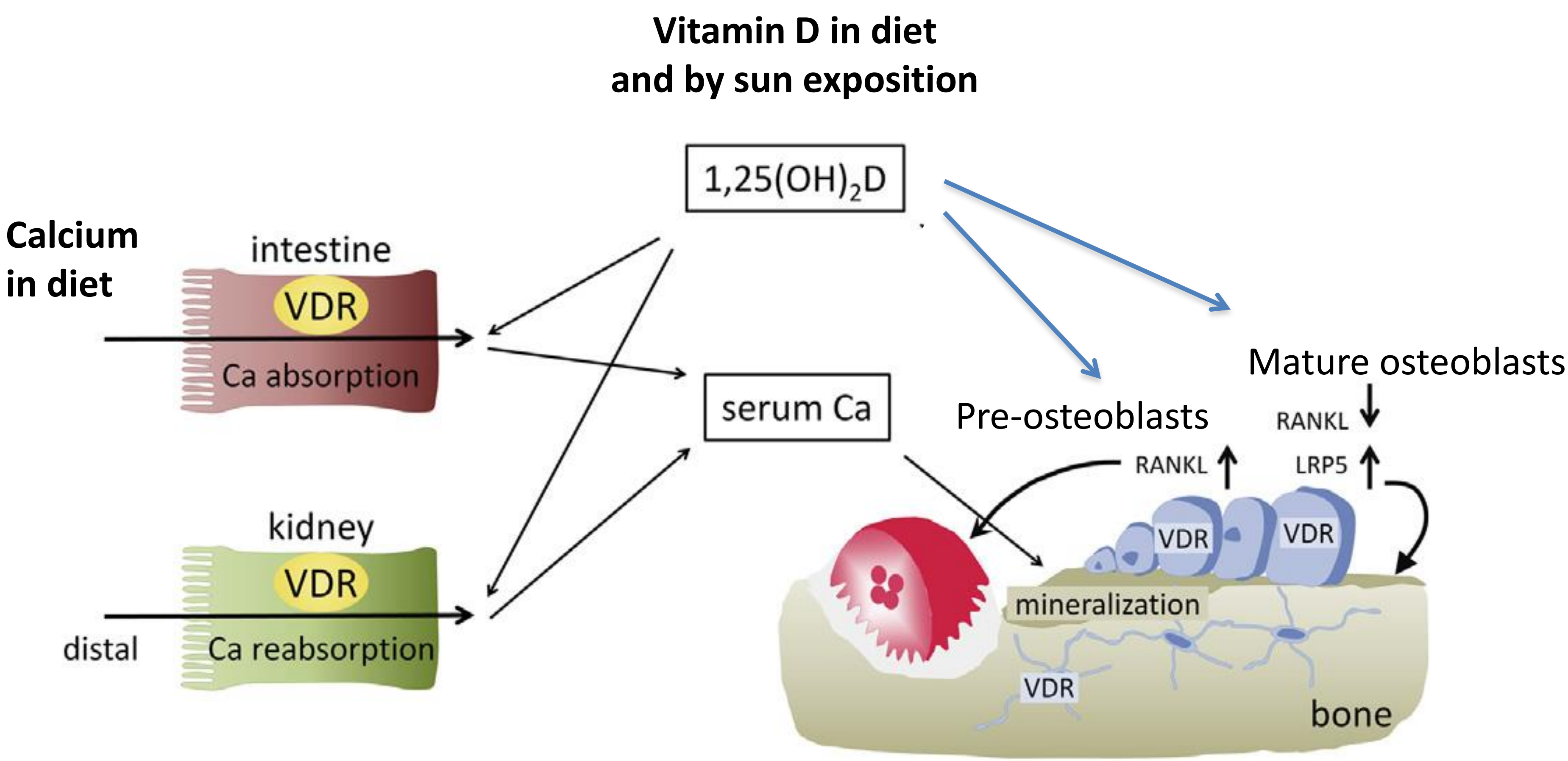
- Back to basics:
  - Calcium homeostasis
  - Bone quality
- What are the needs?
- What are the effects?
- What are the side effects?

Multifactorial etiology and multifacetted results of fractures



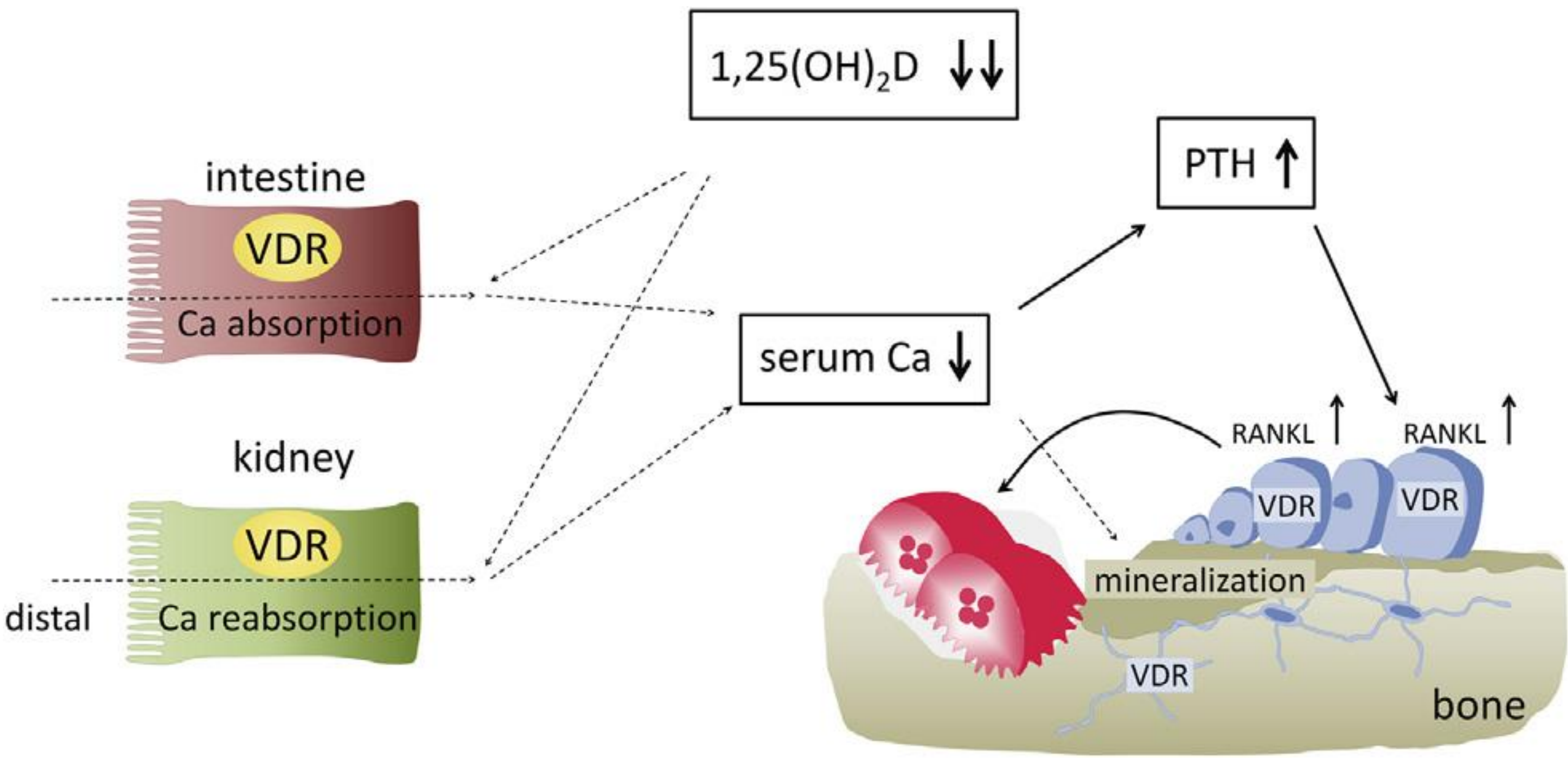
Maastricht UMC & UHasselt

Normal calcium balance

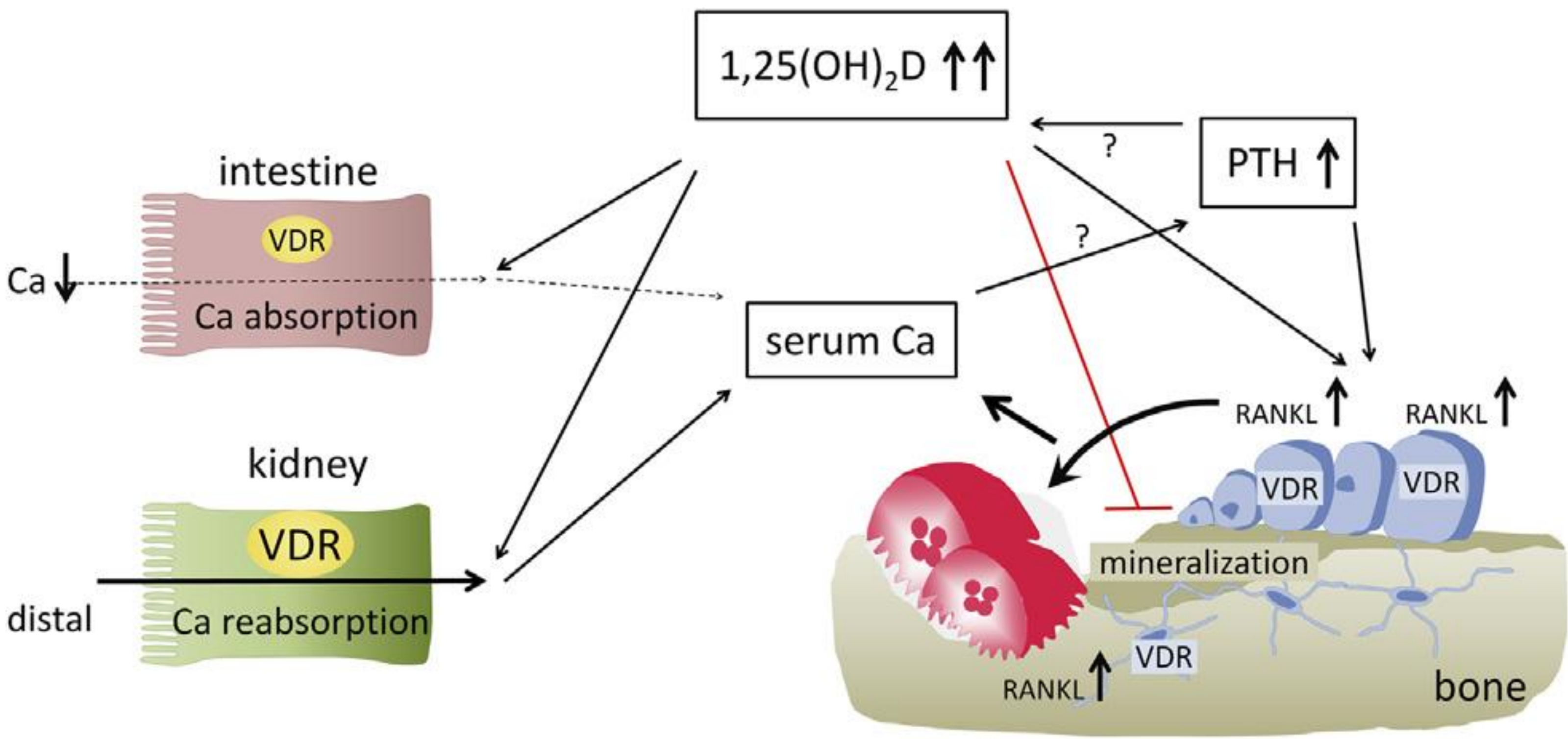


Carmeliet, Best Pract & Res Clin Endo & Metab (2015)

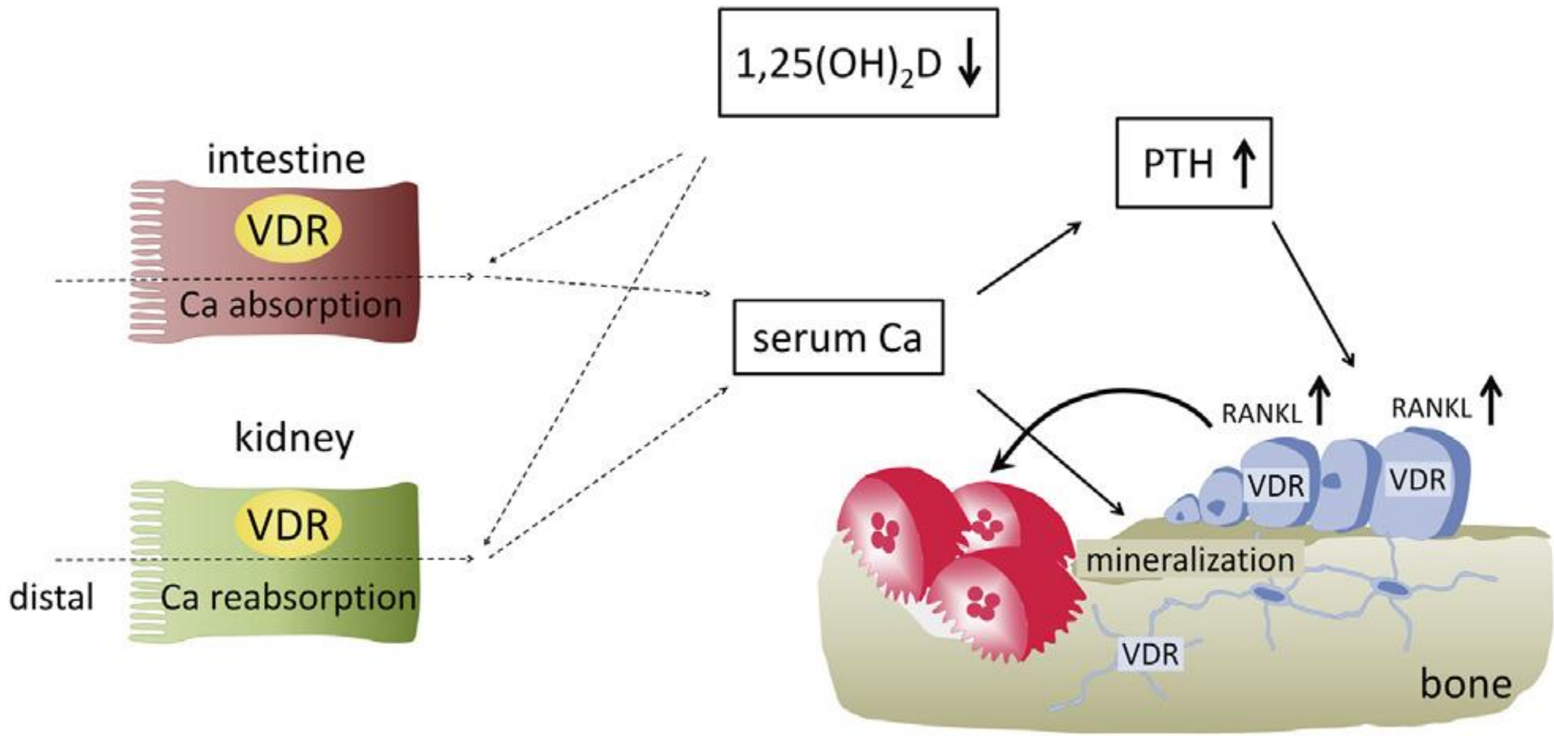
Model of Osteomalacia



Negative calcium balance

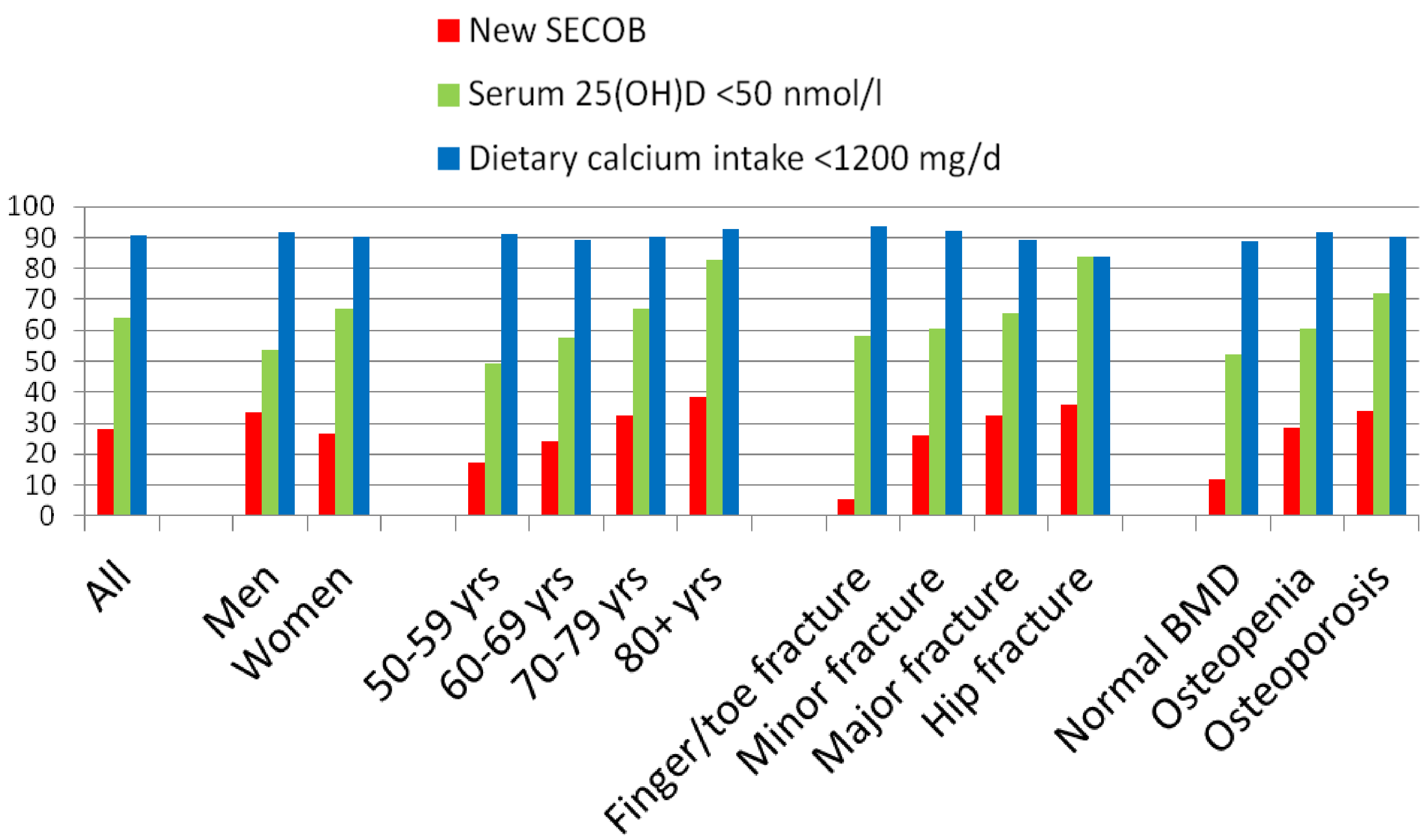


Calcium and vitamin D deficiency



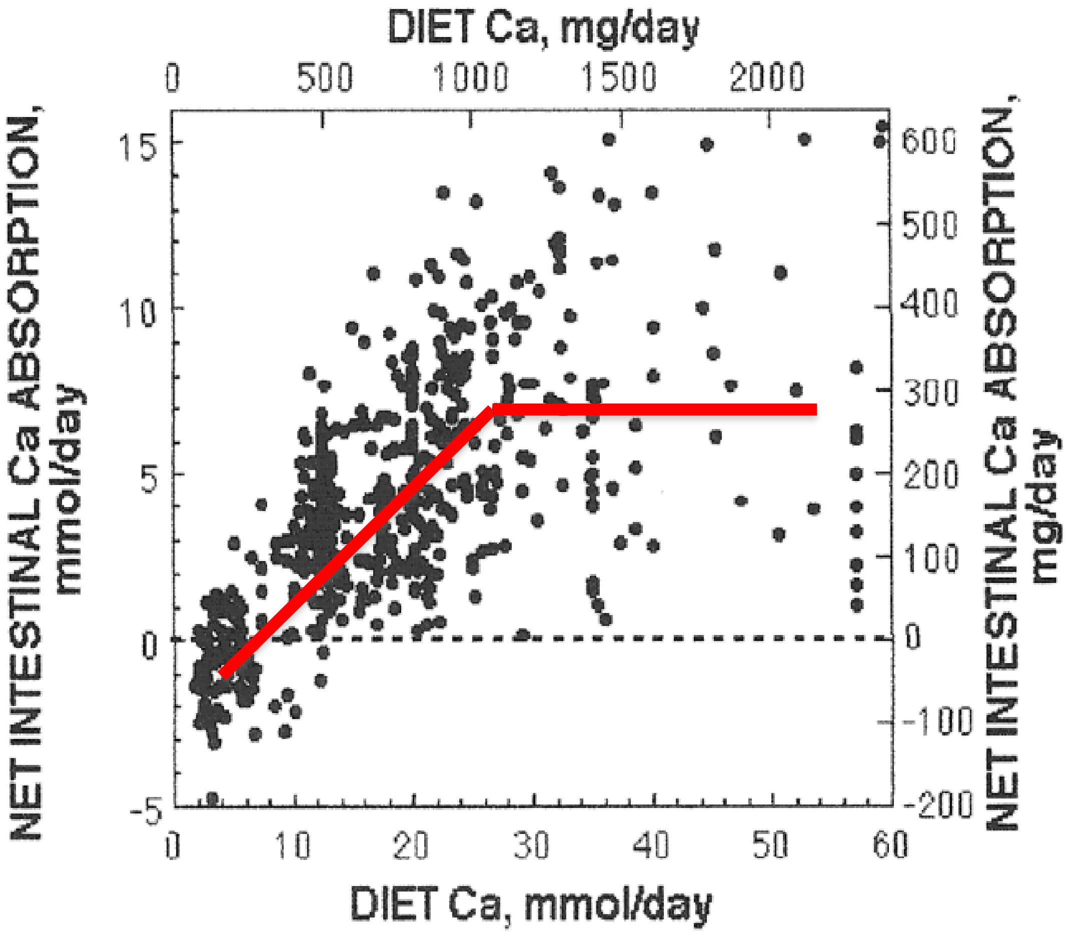
Carmeliet, Best Pract & Res Clin Endo & Metab (2015)

Secondary osteoporosis, vitamin D deficiency and calcium intake <1200 mg/d in patients with a recent fracture

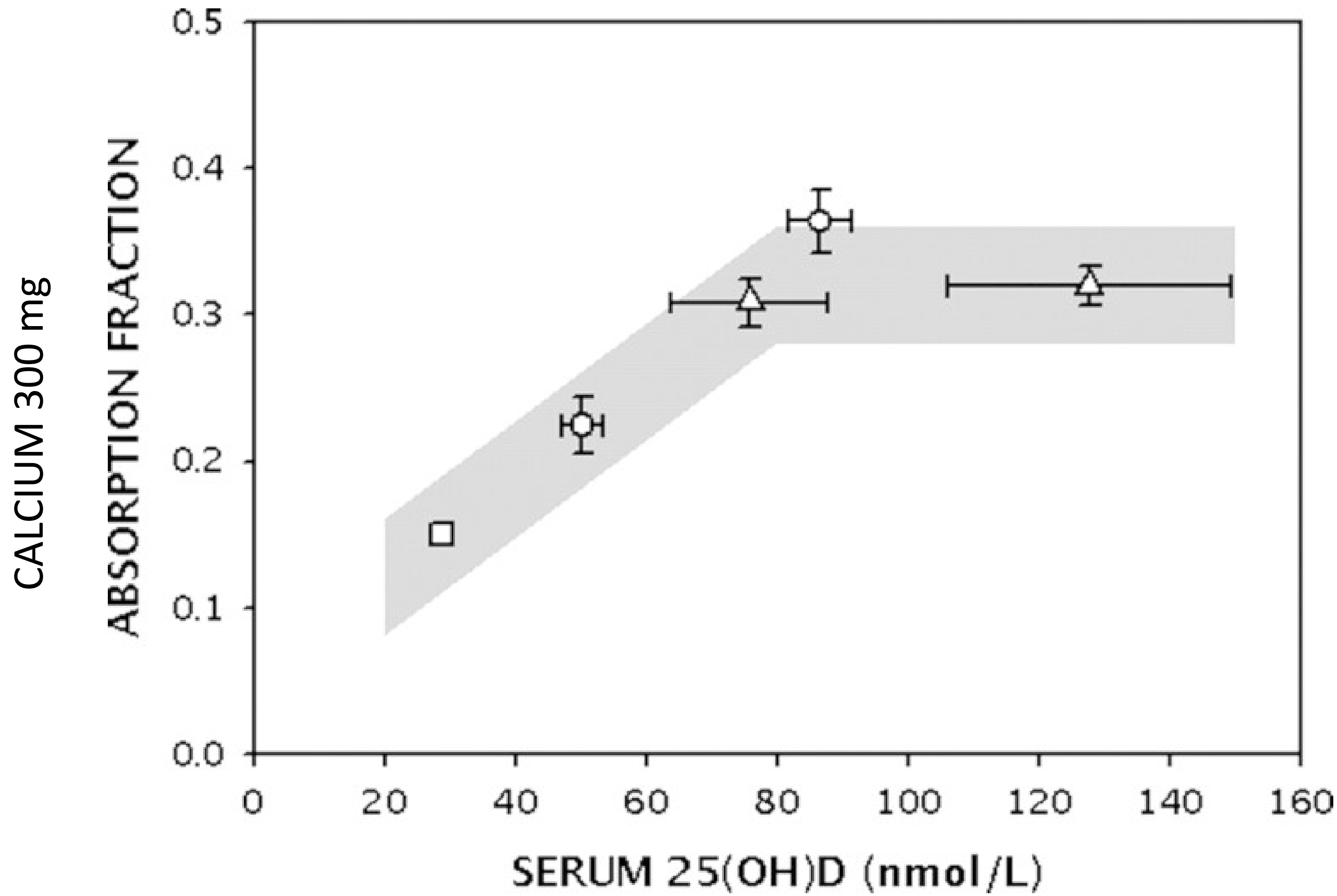


Bours, Geusens, JCEM, 2011, 1360

Net calcium absorption in relation to intake



Vitamin D and calcium absorption



Heaney, Am J Clin Nutr 2008;88(suppl):541S– 4S

Vitamin D serum levels (nmol/L)

- Sufficiency   >50
- Deficiency
  - Mild   25-49
  - Moderate   12.6-24
  - Severe   <12.5

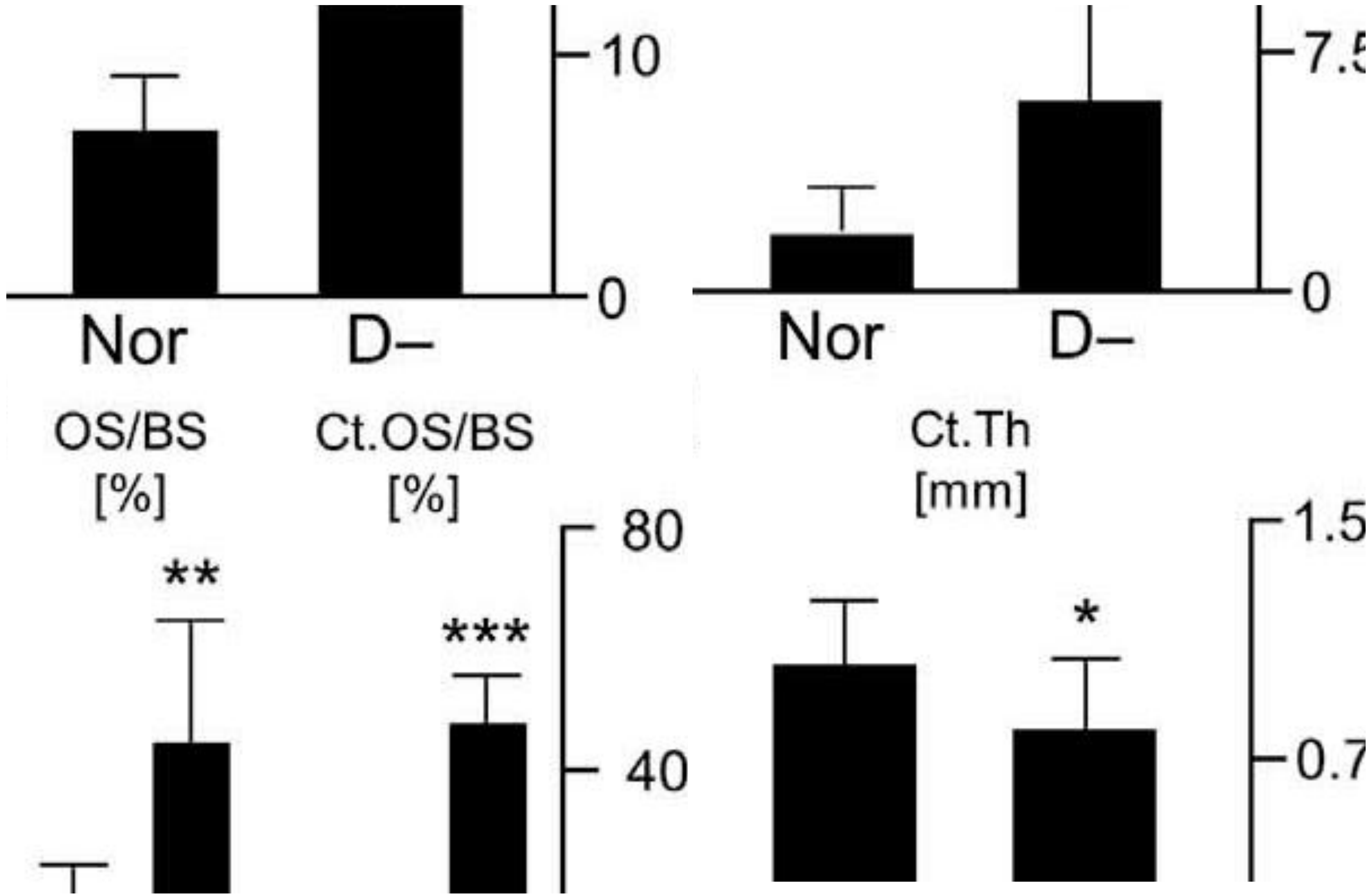
Liberman, 2014
In: De Groot, Endotext

Vitamin D in subjects with normal and low serum vitamin D

- Subjects: motor vehicle or train accidents, assaults, suicides, and other unnatural or unexpected causes
- Iliac crest biopsies

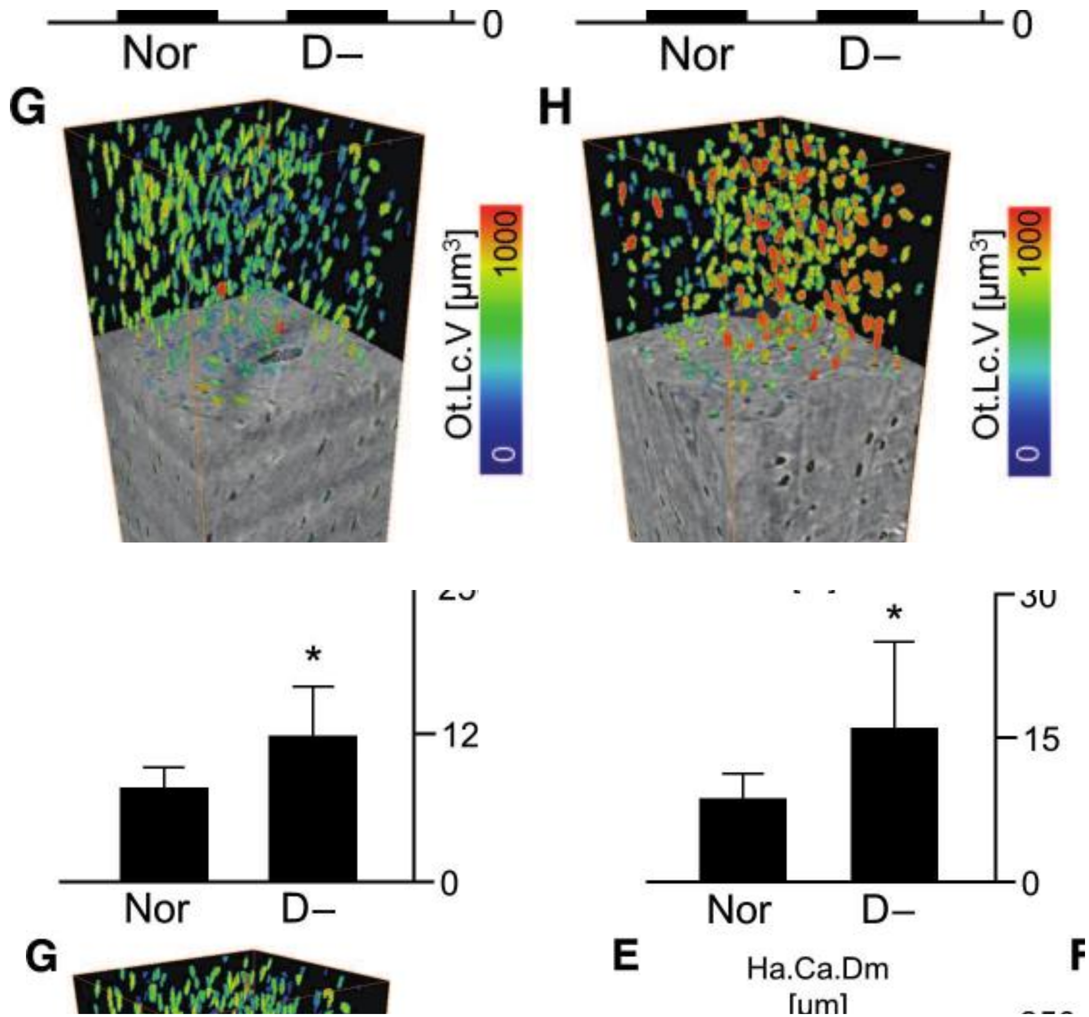
Busse, Sci Trl Med, 2013

Osteoid



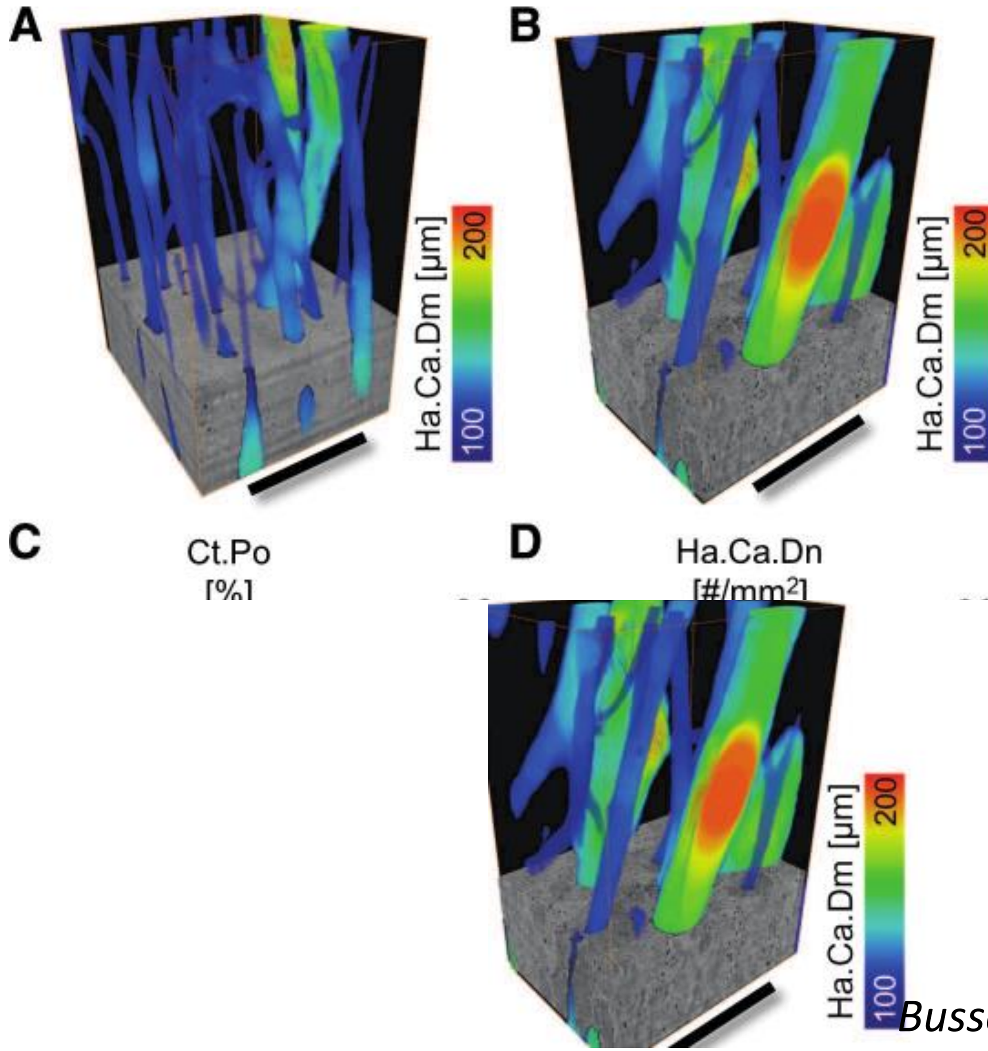
Busse, Sci Trl Med, 2013

Cortical porosity and Haversian channels



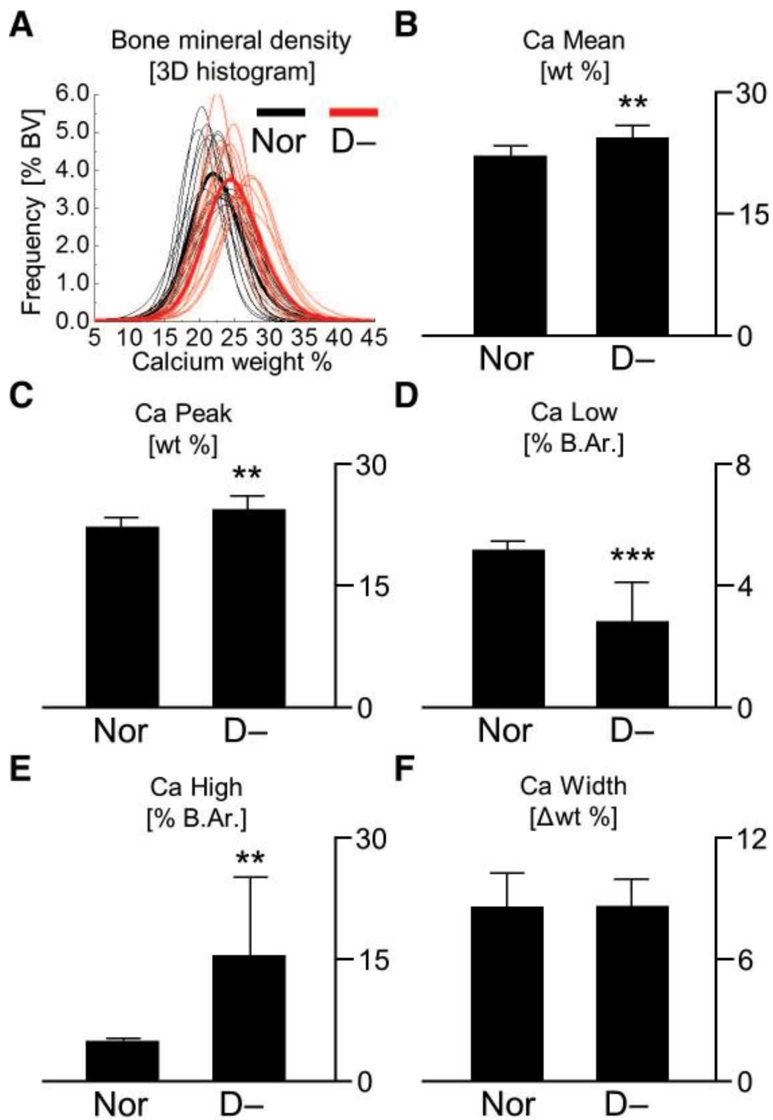
Busse, Sci Trl Med, 2013

Osteocyte lacunae



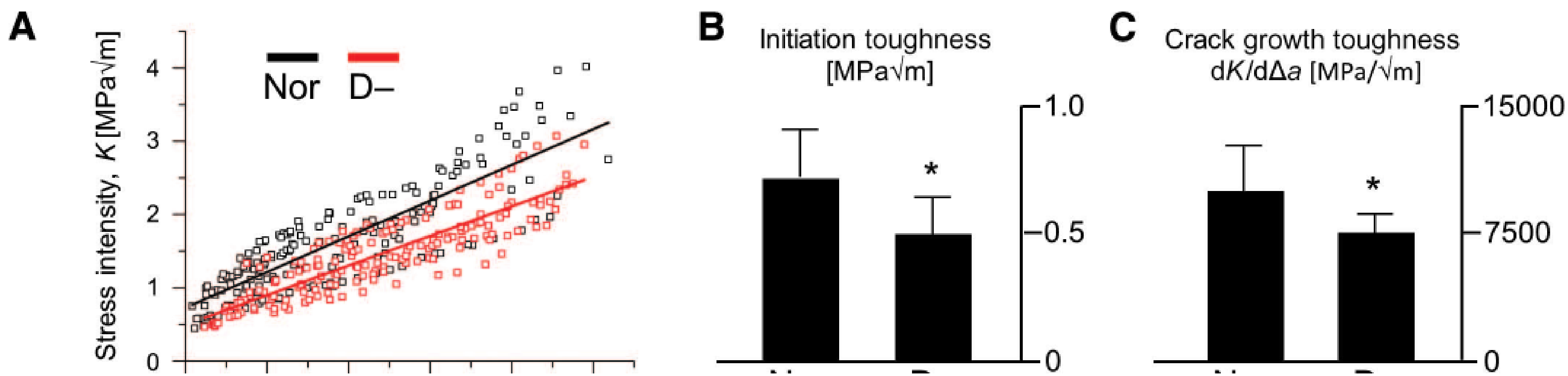
Busse, Sci Trl Med, 2013

Bone mineralisation



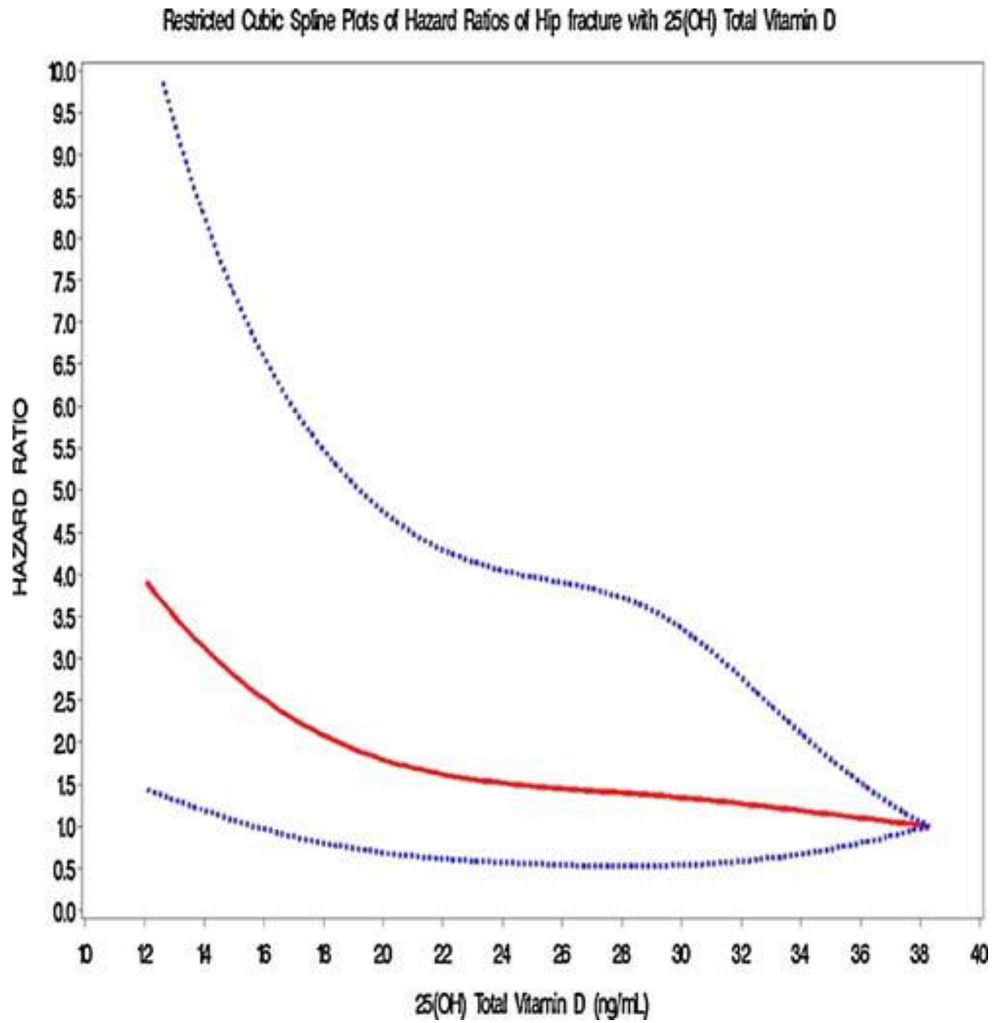
Busse, Sci Trl Med, 2013

Uncracked ligament bridges



Busse, Sci Trl Med, 2013

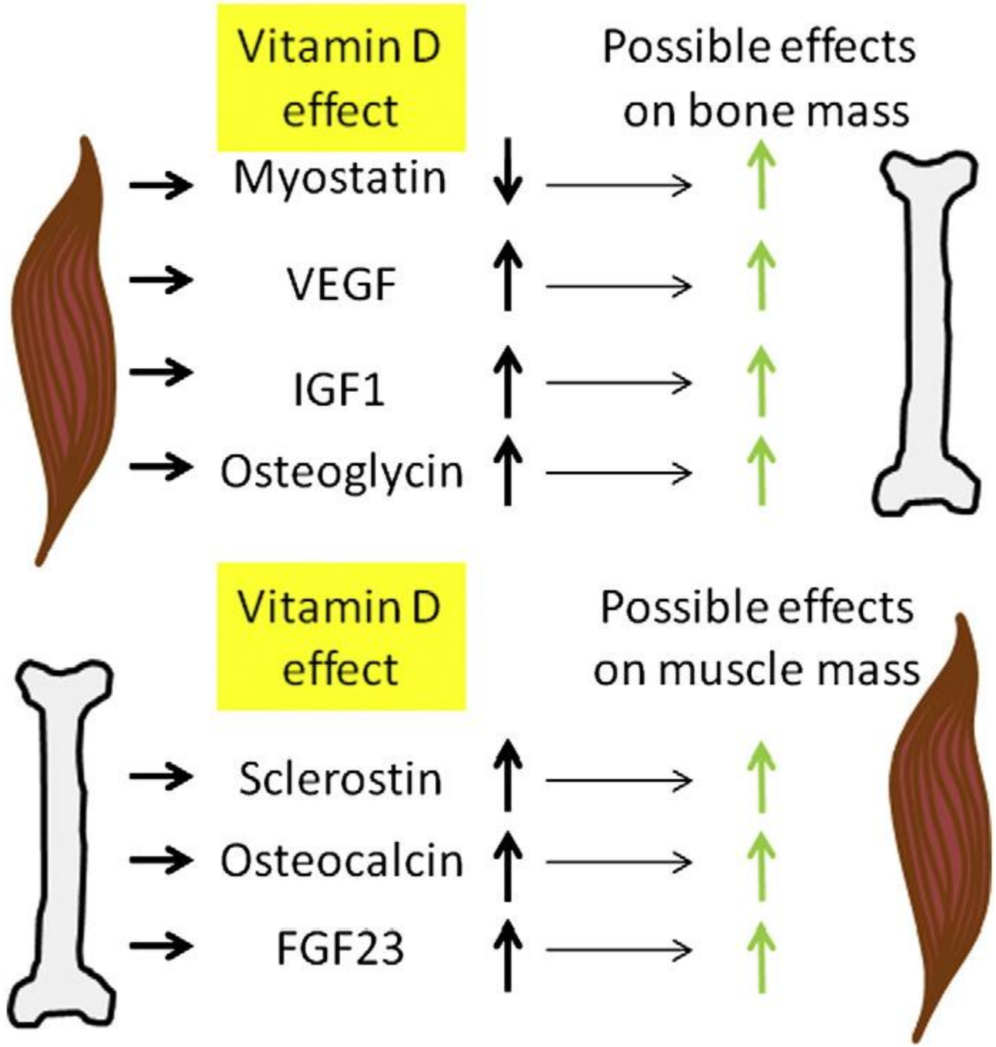
Hazard ratios of hip fracture with 25(OH)D in men



Cauley, JBMR, 2010

VITAMIN D AND MUSCLE

Potential vitamin D mediated mechanisms of bone–muscle cross-talk

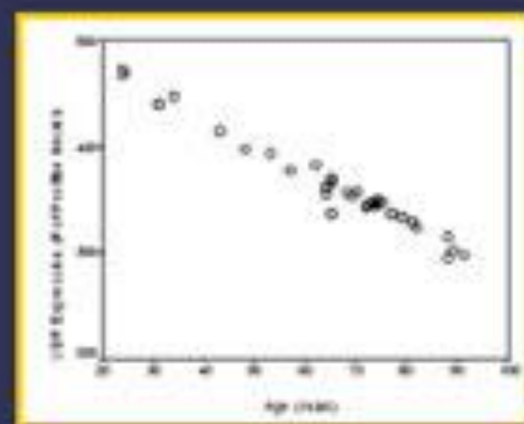


J.E. Gunton et al. / Bone 80 (2015) 89–94

Skeletal Muscle Is a Target of Vitamin D

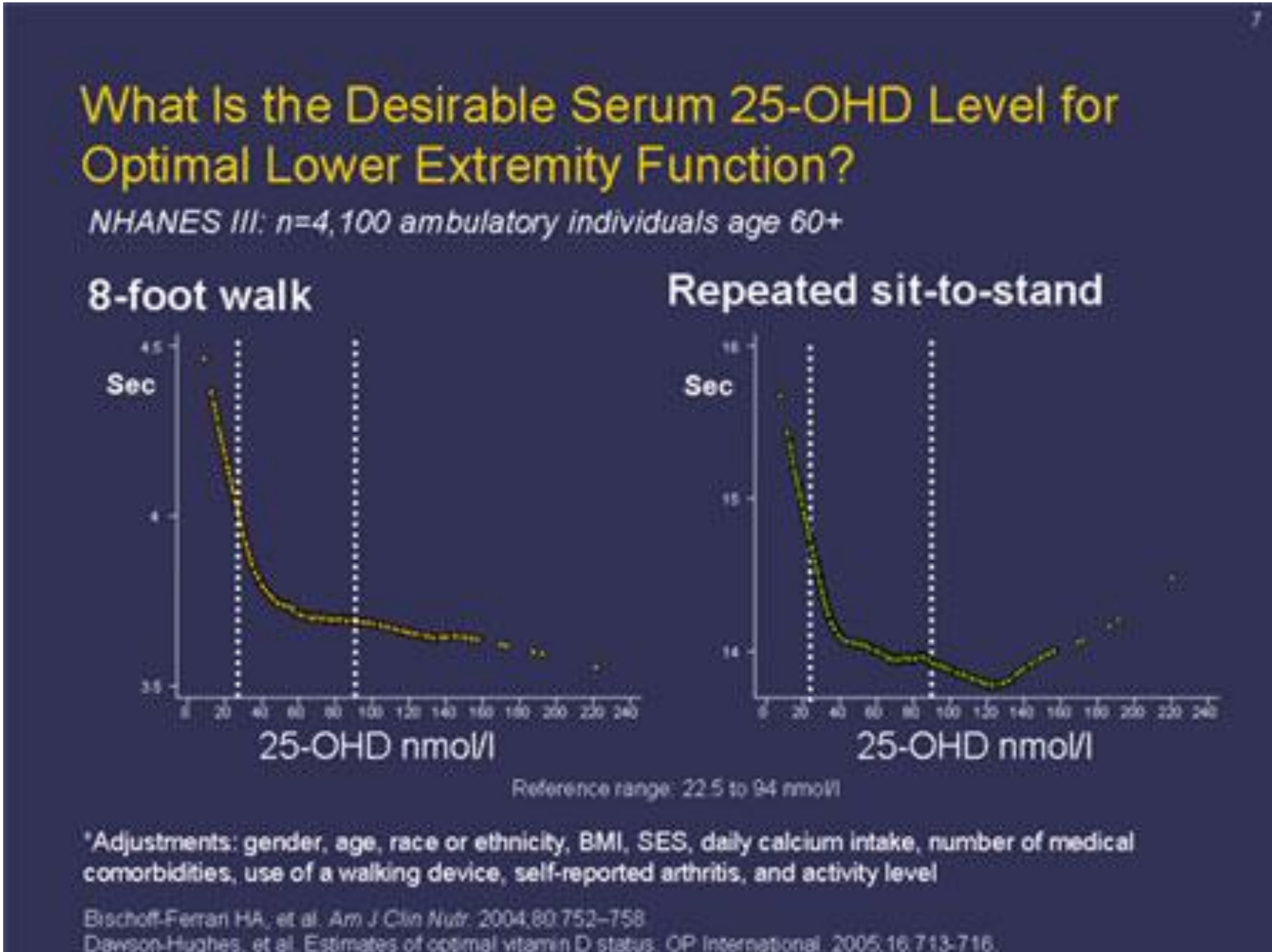
- Vitamin D nuclear receptor (VDR) is present in human skeletal muscle

- Number of VDRs decrease with age
  - 32 women ages 21 to 91 years with hip or spine surgery (p=0.047)



1. Bischoff HA, et al. *J Immunohistochem*. 2001.
2. Bischoff-Ferrari HA et al. *JBMR* 2004.

Bischoff, http://www.medscape.org



Bischoff, http://www.medscape.org

Severe Vitamin D Deficiency is a Risk Factor for Repeated Falls

Odds of falling with 25(OH)D levels less than 25 nmol/l	2+ falls OR (95% CI)	3+ falls OR (95% CI)
<75 years	5.21 (2.03-13.40)	4.96 (1.52-16.23)
≥75 years	1.24 (0.65-2.33)	1.62 (0.73-3.59)

LASA (n=1,231 men and women, ≥65 years: Model controls for age, gender, education level, region, season, physical activity, alcohol intake, and smoking

Snijder MB et al. *J Clin Endocrinol Metab.* 2006;91:2980-2985.

Bischoff, http://www.medscape.org

CALCIUM SUPPLETION STUDIES

Pooled analyses of trials of dietary sources of calcium and calcium supplements

Table 5 | Pooled analyses of trials of dietary sources of calcium and calcium supplements

	Trials of dietary sources of calcium				Calcium supplement trials				
Time point (years)	Studies	Participants	BMD difference* (95% CI)	P value	Studies	Participants	BMD difference* (95% CI)	P value	P (interaction)†
Lumbar spine									
1	11	1260	0.6 (−0.1 to 1.3)	0.08	27	3866	1.2 (0.8 to 1.7)	<0.001	0.13
2	8	816	0.7 (0.3 to 1.2)	0.001	21	6115	1.1 (0.7 to 1.6)	<0.001	0.19
>2.5	0	—	—	—	8	3861	1.0 (0.3 to 1.6)	0.003	—
Femoral neck									
1	8	1035	0.3 (−0.3 to 0.9)	0.30	19	2651	1.2 (0.7 to 1.8)	<0.001	0.02
2	7	783	1.8 (1.1 to 2.6)	<0.001	14	2415	1.0 (0.5 to 1.4)	<0.001	0.05
>2.5	0	—	—	—	5	2257	1.5 (0.2 to 2.9)	0.025	—
Total hip									
1	6	900	0.6 (0.3 to 1.0)	0.001	7	1159	1.4 (0.6 to 2.3)	0.001	0.08
2	5	689	1.5 (0.7 to 2.4)	<0.001	7	4366	1.3 (0.8 to 1.8)	<0.001	0.63
>2.5	0	—	—	—	6	3835	1.2 (0.5 to 1.9)	0.001	—
Forearm									
1	4	418	0.0 (−0.4 to 0.5)	0.85	10	791	1.0 (0.2 to 1.8)	0.014	0.04
2	2	171	0.1 (−0.3 to 0.4)	0.65	10	857	1.5 (0.5 to 2.6)	0.005	0.01
>2.5	0				5	437	1.8 (0.2 to 3.4)	0.025	
Total Body									
1	3	433	1.0 (0.3 to 1.8)	0.009	10	1255	0.7 (0.4 to 1.1)	<0.001	0.47
2	2	358	0.9 (0.5 to 1.3)	<0.001	6	3901	0.8 (0.5 to 1.1)	<0.001	0.67
>2.5	0	—	—	—	7	4164	0.8 (0.5 to 1.1)	<0.001	—

*Weighted mean difference between groups in percentage change in bone mineral density (BMD) from baseline.
†Test for interaction between subgroup of trials of dietary sources of calcium and subgroup of calcium supplement trials.

Tai, BMJ, 2015

Baseline, suppletion and total daily intake of calcium in calcium suppletion studies

Studies	Dietary calcium (mg/day)	Baseline	Suppl	Total
Dawson-Hughes[19]	406 (84)	400	500	900
Reid[21 22]	750 (290)	800	1000	1800
Riggs[24]	710 (290)	700	1600	2300
Baron[25]	880 (440)	900	1200	2100
Bonithon-Kopp[27]	980 (380)	1000	2000	3000
Grant[28]	820 (350)	800	1000	1800
Reid[15 16]	860 (390)	900	1000	1900
Prince[29]	915	900	1200	2100
Bonnick[30]	1240 (580)	1200	1000	2200
Lappe[31 32]	1070	1100	1400	2500
Reid[33]	870 (450)	900	600	1500

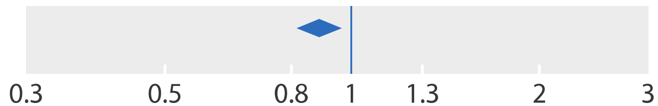
Bolland, BMJ, 2010

Calcium suppletion studies using 500-1600 mg/d average total: 1780 mg/d (range 1230-2314 mg/d)

All fractures

All studies 3246/29 115 3479/29 458 0.89 (0.81 to 0.96)

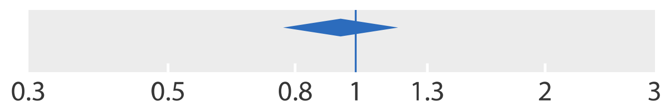
Overall: P=0.004



Hip fracture

All studies 471/28 078 510/28 570 0.95 (0.76 to 1.18)

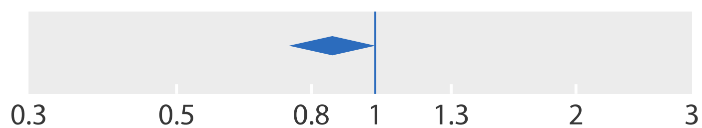
Overall: P=0.63



Vertebral fractures

All studies 309/24 506 357/24 461 0.86 (0.74 to 1.00)

Overall: P=0.04

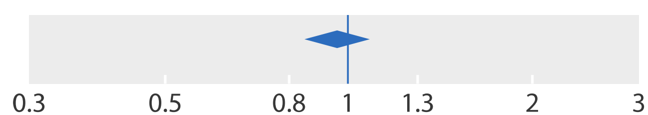


Forearm fractures

All studies 727/25 549 757/26 226 0.96 (0.85 to 1.09)

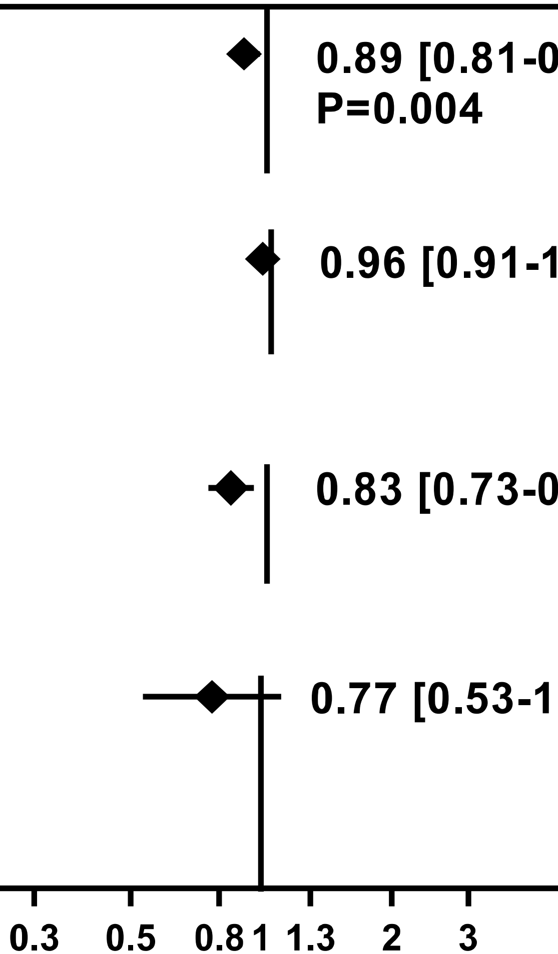
Overall: P=0.54

Test for heterogeneity: P=0.39, I^2=5%

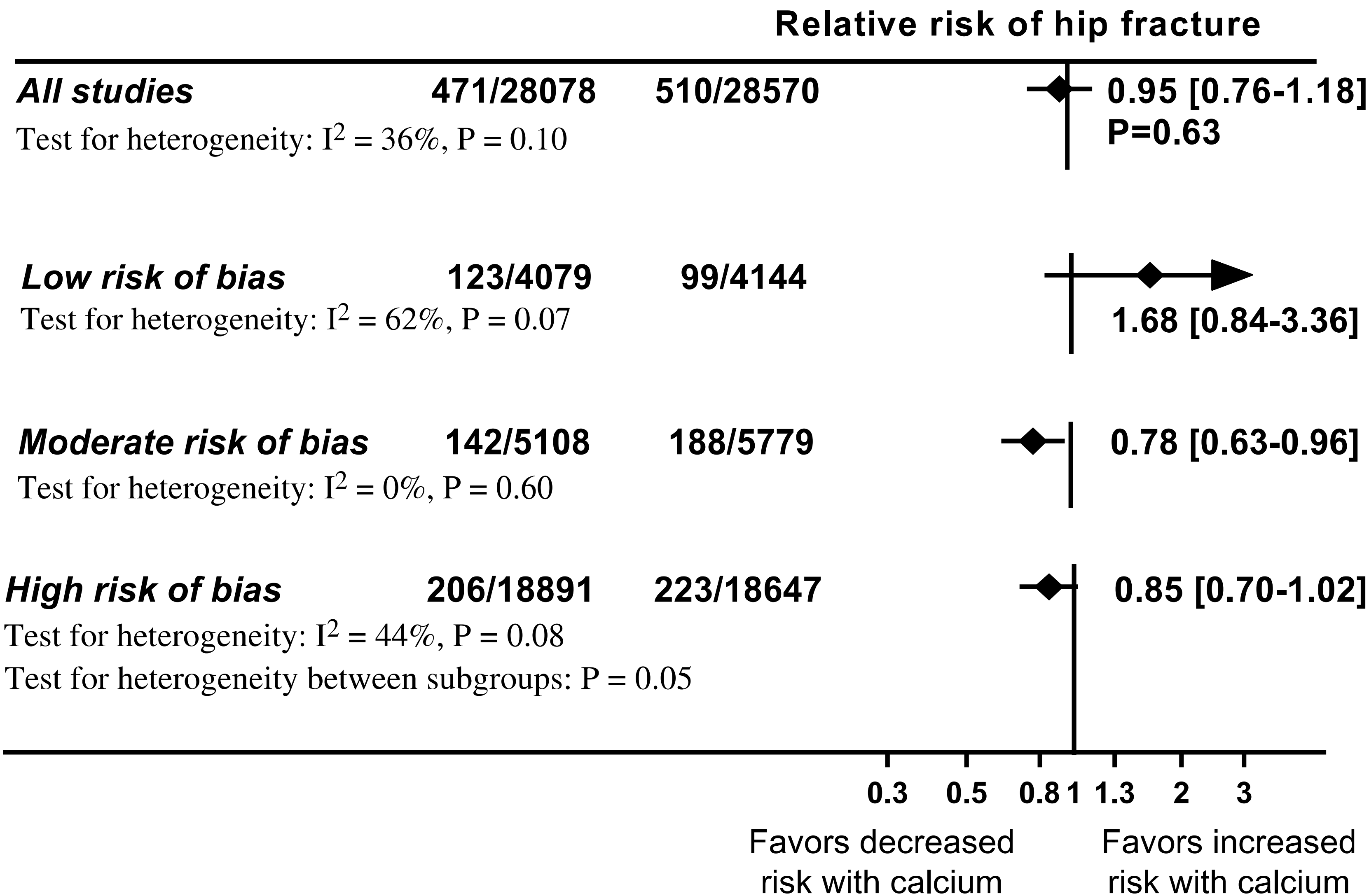


Bolland, BMJ, 2015

Study	Calcium (n/N)	Control (n/N)	Relative risk of total fracture [95% CI]	Weight (%)
All studies	**3246/29115**	**3479/29458**		**0.89 [0.81-0.96] P=0.004**
Test for heterogeneity: I^2 =27%, P = 0.17				
Low risk of bias	**2710/22255**	**2831/22250**		**0.96 [0.91-1.01]**
Test for heterogeneity: I^2 = 0%, P = 0.77				
Moderate risk of bias	**408/5505**	**521/6034**		**0.83 [0.73-0.93]**
Test for heterogeneity: I^2 = 0%, P = 0.56				
High risk of bias	**128/1355**	**127/1174**		**0.77 [0.53-1.11]**
Test for heterogeneity: I^2 = 44%, P = 0.08				
Test for heterogeneity between subgroups: P = 0.05				



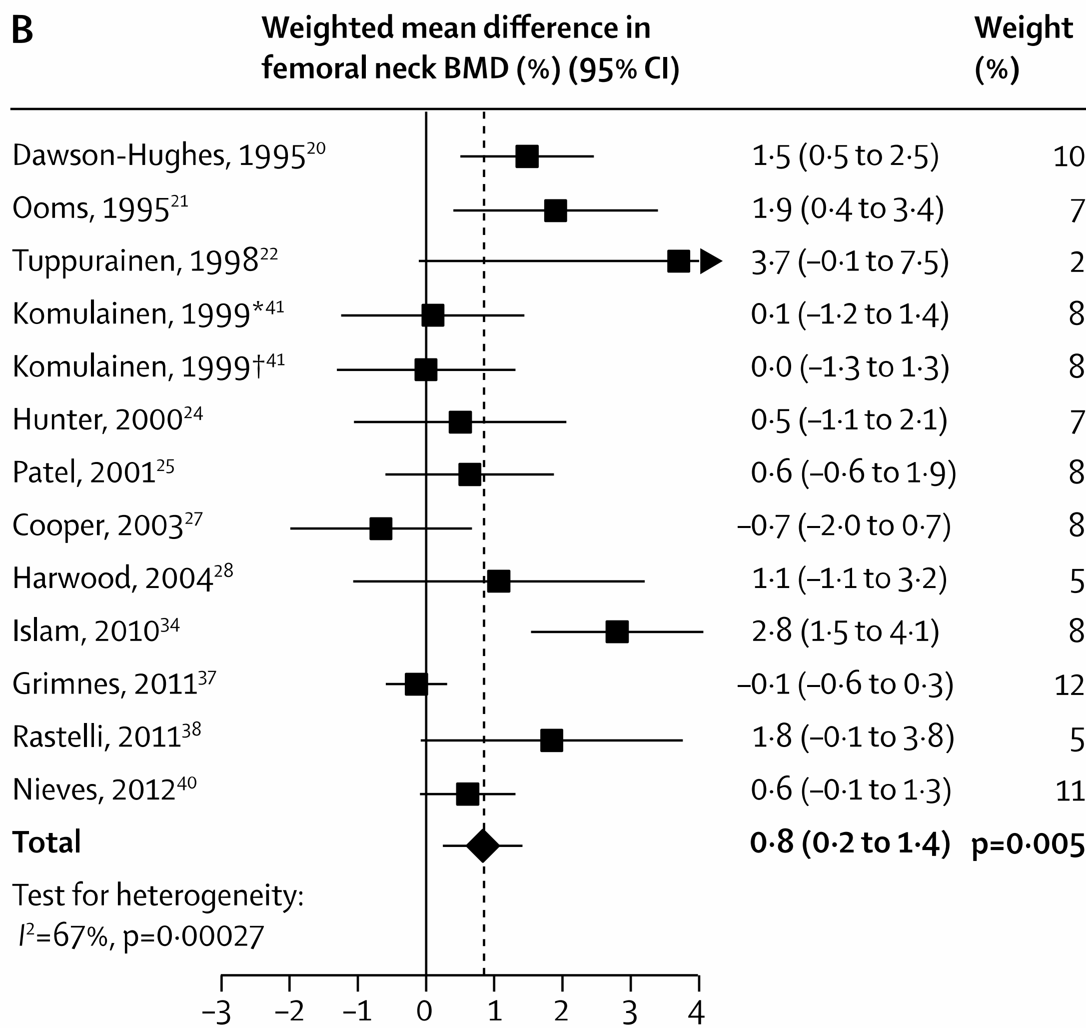
Bolland, Climactaric, 2015



Bolland, Climactaric, 2015

VITAMIN D SUPPLETION STUDIES

Effect of vitamin D on BMD in the femoral neck

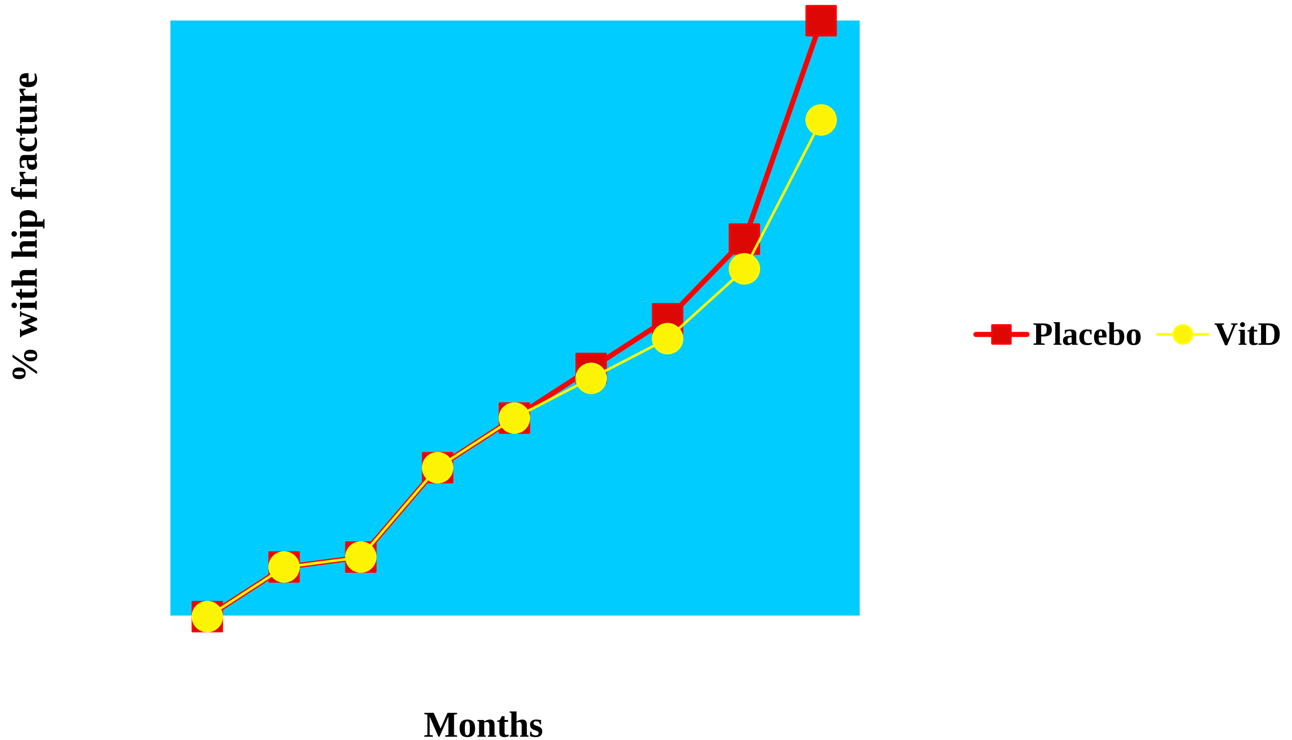


Reid, Lancet, 2014

Vitamin D 400 IU/d

Men and Women >70 yr, *n=2578*, Drop-Out: 37%

Baseline Calcium Intake: 1100 mg/d



Lips, Ann Intern Med, 1996, 400

Pooled Analysis of Vitamin D Dose Requirements for Fracture Prevention

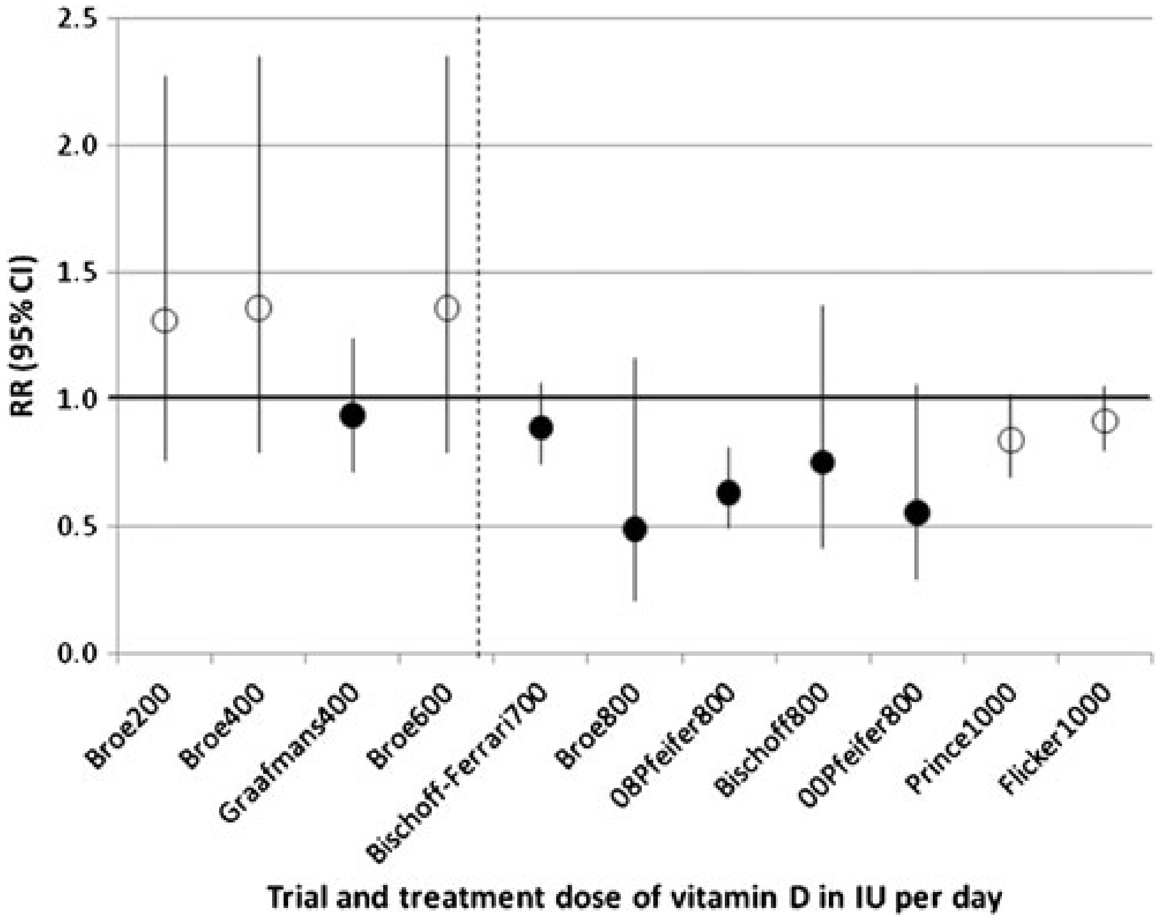
Table 2. Incidence of Fracture among 31,022 Participants, According to Vitamin D Treatment Dose and Actual Intake.*

Analysis	No. of Participants	Hip Fracture			Any Nonvertebral Fracture		
		No. of Fractures	Relative Risk (95% CI)	P Value	No. of Fractures	Relative Risk (95% CI)	P Value
Intention-to-treat analysis							
Control	15,495	586	1.00		1948	1.00	
Treatment	15,527	525	0.90 (0.80–1.01)	0.07	1822	0.93 (0.87–0.99)	0.03
Treatment-dose analysis							
Control	15,495	586	1.00		1948	1.00	
≤400 IU/day	10,111	255	0.89 (0.74–1.07)	0.20	1225	0.96 (0.89–1.05)	0.40
>400 IU/day†	5,416	270	0.91 (0.78–1.06)	0.22	597	0.89 (0.80–0.98)	0.02
Actual-intake analysis‡							
Control	15,495	586	1.00		1948	1.00	
0–360 IU/day	3,935	100	1.00 (0.79–1.26)	0.99	425	0.96 (0.86–1.07)	0.44
361–637 IU/day	3,836	110	1.03 (0.83–1.29)	0.78	520	1.01 (0.91–1.12)	0.85
638–791 IU/day	3,790	164	1.01 (0.83–1.23)	0.92	419	0.90 (0.80–1.01)	0.08
792–2000 IU/day	3,966	151	0.70 (0.58–0.86)	<0.001	458	0.86 (0.76–0.96)	0.007

Baseline serum 25(OH)D: 47-54 nmol/L

Bischoff, NEJM, 2012

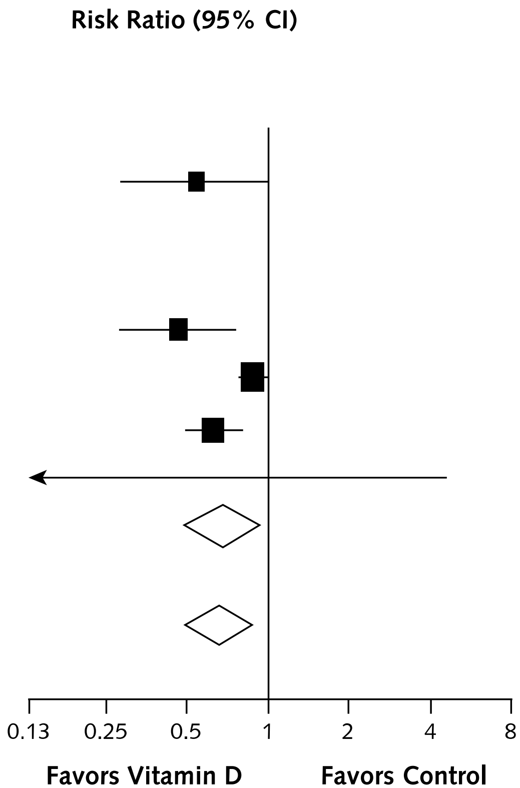
Fall prevention by dose of vitamin D



Bischoff, Rev Endocr Metab Disord (2012)

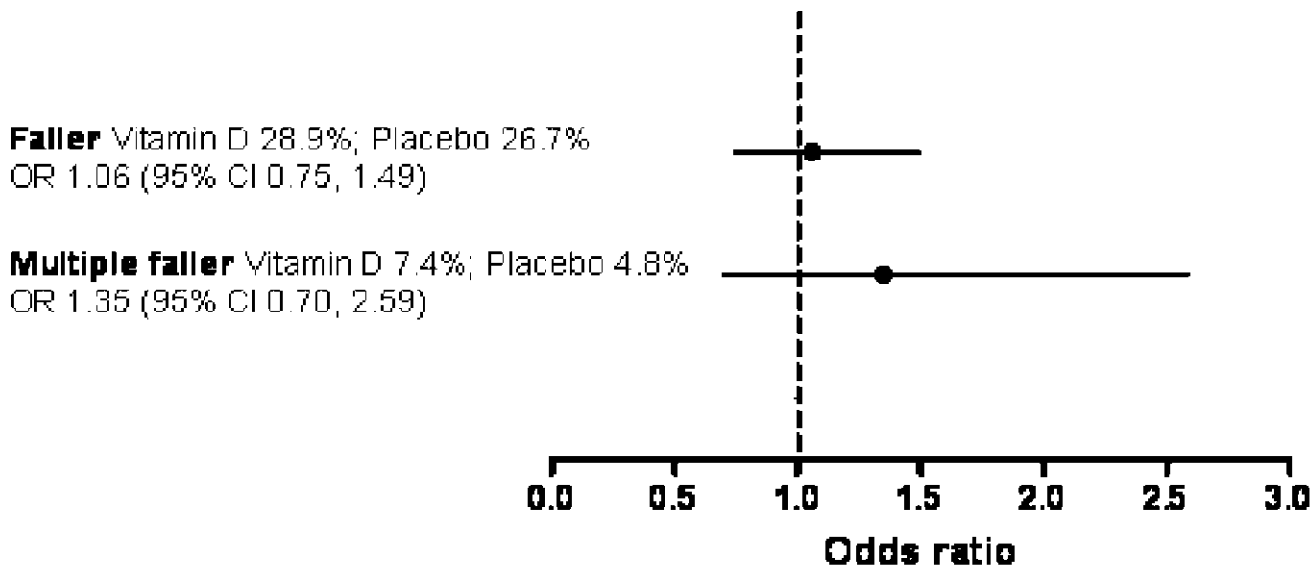
Figure 4. Meta-analysis of effects of vitamin D treatment on the number of falls per person.

Study, Year (Reference)	Vitamin D		Control		Risk Ratio (95% CI)
	Events	Falls per PY	Events	Falls per PY	
25-(OH)D <20 ng/mL*					
Pfeifer et al, 2000 (74)	17	0.24	30	0.45	0.54 (0.28–1.02)
25-(OH)D ≤30 ng/mL					
Bischoff et al, 2003 (76)†	25	1.30	55	2.81	0.46 (0.28–0.76)
Kärkkäinen et al, 2010 (78)	430	0.50	524	0.57	0.87 (0.77–1.00)
Pfeifer et al, 2009 (84)	106	0.53	169	0.84	0.63 (0.49–0.80)
Wood et al, 2012 (85)	4	0.02	3	0.03	0.67 (0.11–4.57)
Subtotal (I^2 = 69.9%; P = 0.019)					0.68 (0.50–0.93)
Total events	565		751		
Total (I^2 = 64.5%; P = 0.024)		887		922	0.66 (0.50–0.88)
Total events	582		781		



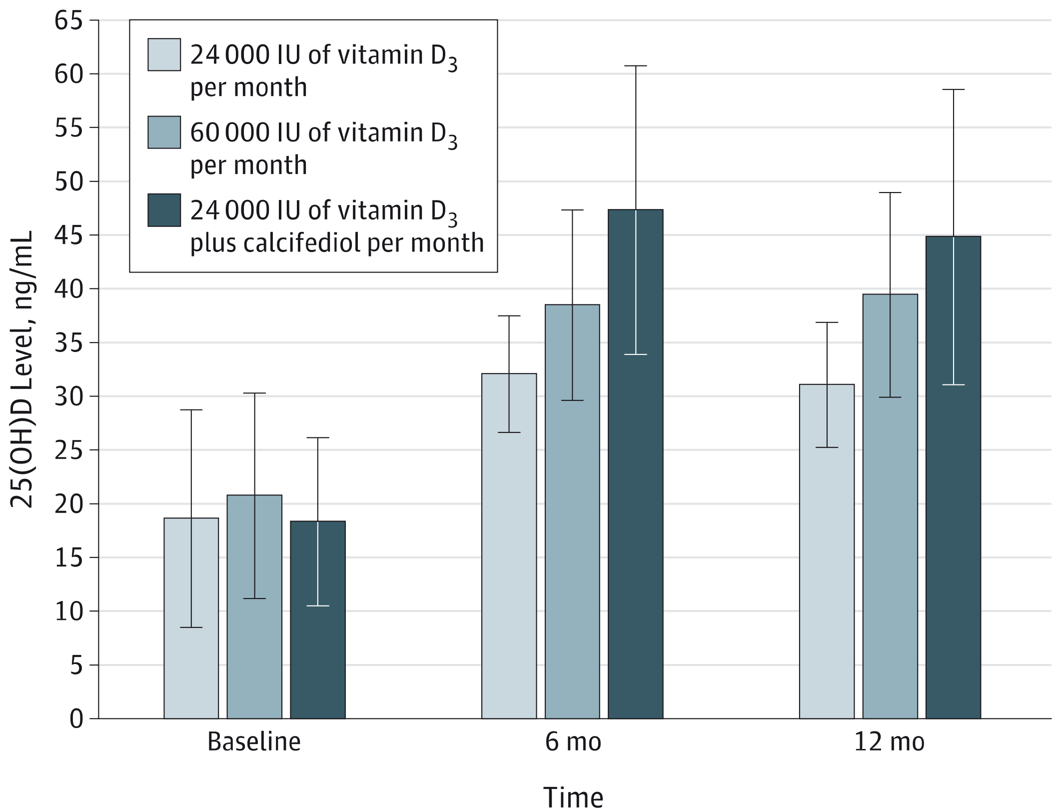
LeBlanc, Ann Int Med, 2015

Effects of cholecalciferol supplementation on falls: oral cholecalciferol 150,000 IU every 3 months



Glendenning, JBMR, 2012

Figure 2. Unadjusted 25(OH)D Levels by Treatment at Baseline, 6 Months, and 12 Months



Bischoff-Ferrari, JAMA, 2016

Table 2. Treatment Effect on the Prevention of Functional Decline and Falls[a]

Variable	24 000 IU of Vitamin D_3 per Month (n = 67)	60 000 IU of Vitamin D_3 per Month (n = 67)	24 000 IU of Vitamin D_3 Plus Calcifediol per Month (n = 66)	*P* Value for Difference Between Treatments in Change Over Time
Primary End Point of Participants With Achieved 25(OH)D Levels ≥30 ng/mL, % (95% CI)				
Unadjusted at baseline	14.9 (8.2 to 25.6)	19.4 (11.6 to 30.6)	12.1 (6.2 to 22.4)	.51[b]
Adjusted at 6 mo	63.8 (50.7 to 75.1)	83.0 (71.3 to 90.5)[c]	93.5 (84.5 to 97.4)[c]	<.001[b]
Adjusted at 12 mo	54.7 (41.6 to 67.2)	80.8 (68.5 to 89.1)[c]	83.3 (71.4 to 90.9)[c]	.001[b]
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]

Bischoff-Ferrari, JAMA, 2016

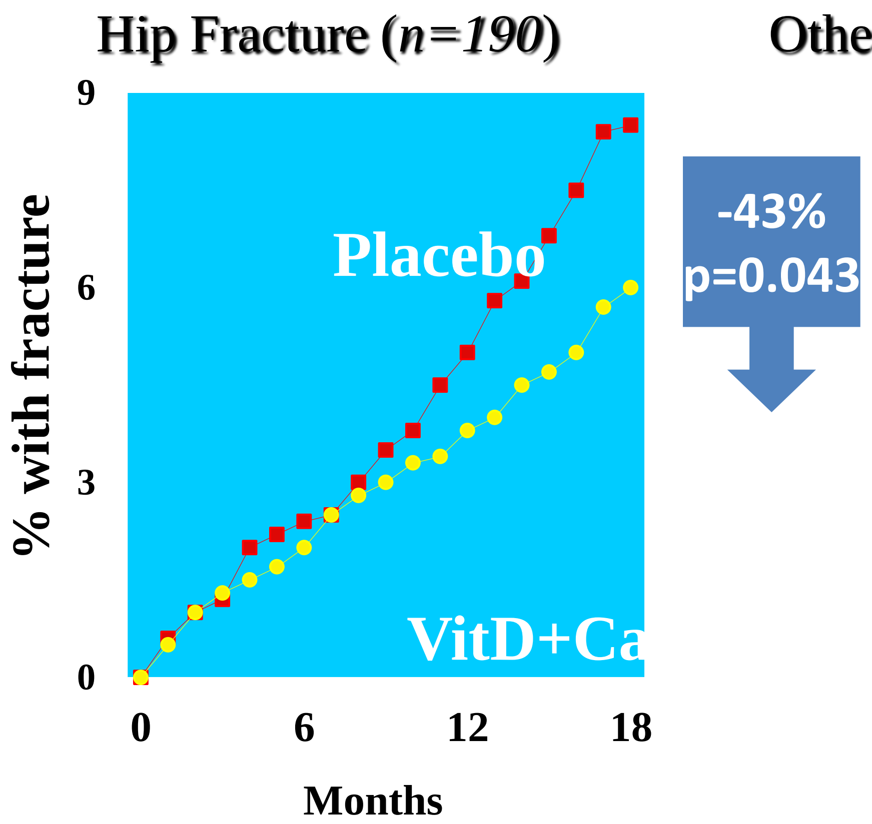
Table 3. Treatment Effect on the Prevention of Functional Decline and Falls, Stratified by Baseline Vitamin D Level[a]

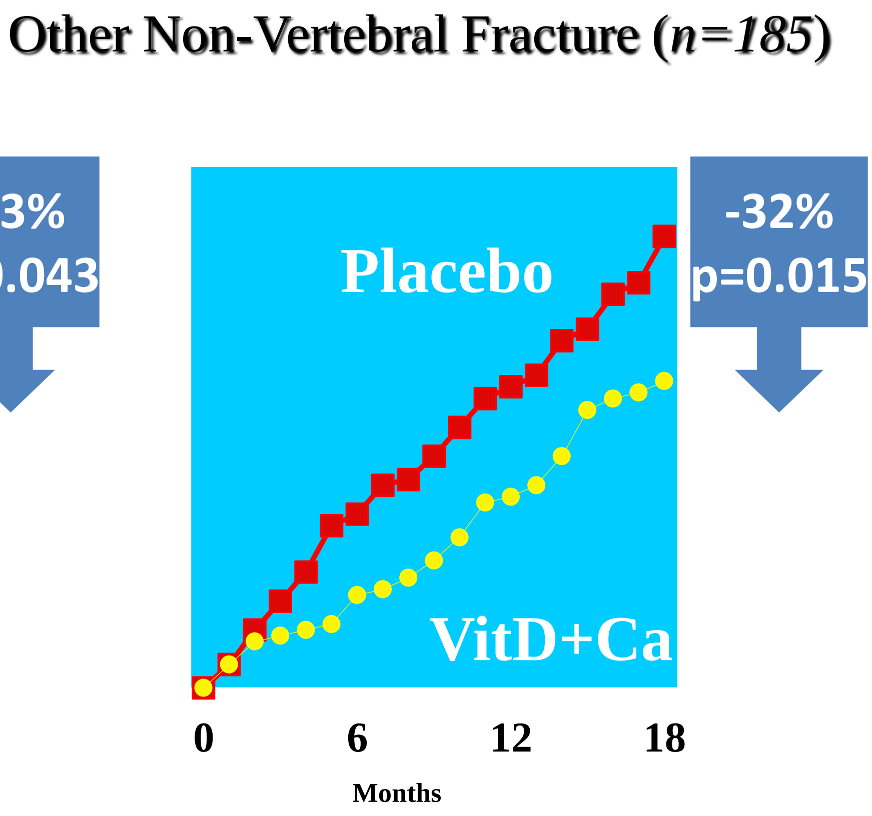
Variable	24 000 IU of Vitamin D_3 per Month (n = 67)	60 000 IU of Vitamin D_3 per Month (n = 67)	24 000 IU of Vitamin D_3 Plus Calcifediol per Month (n = 66)	*P* Value for Difference Between Treatments in Change Over Time
Primary End Point of Participants With Achieved 25(OH)D Levels ≥30 ng/mL Among Seniors With 25(OH)D Levels <20 ng/mL at Baseline, % (95% CI)				
Unadjusted at baseline	0	0	0	NA
Adjusted at 6 mo	53.3 (37.5 to 68.5)	70.4 (52.6 to 83.6)	90.8 (77.4 to 96.6)	.003
Adjusted at 12 mo	43.6 (28.4 to 60.2)	73.6 (55.1 to 86.3)	80.9 (65.0 to 90.6)	.004
Primary End Point of Participants With Achieved 25(OH)D Levels ≥30 ng/mL Among Seniors With 25(OH)D Levels ≥20 ng/mL at Baseline, % (95% CI)				
Unadjusted at baseline	23.9 (10.9 to 44.8)	28.3 (14.0 to 48.8)	21.7 (9.1 to 43.4)	.83
Adjusted at 6 mo	84.6 (63.3 to 94.6)	94.7 (80.9 to 98.7)	97.4 (80.7 to 99.7)	.14
Adjusted at 12 mo	72.8 (51.4 to 87.2)	87.1 (70.5 to 95.0)	89.2 (68.3 to 96.9)	.23
Primary End Point of Mean SPPB Functional Decline Score Among Seniors With 25(OH)D Levels <20 ng/mL at Baseline				
Unadjusted at baseline, mean (SD)	9.93 (1.44)	9.51 (1.70)	9.71 (1.50)	
Adjusted change (95% CI) at 6 mo	0.15 (−0.15 to 0.45)	0.34 (0.02 to 0.67)	0.14 (−0.16 to 0.45)	.39
Adjusted change (95% CI) at 12 mo	0.46 (0.06 to 0.87)	0.36 (−0.09 to 0.80)	0.18 (−0.23 to 0.58)	
Primary End Point of Mean SPPB Functional Decline Score Among Seniors With 25(OH)D Levels ≥20 ng/mL at Baseline				
Unadjusted at baseline, mean (SD)	10.13 (1.66)	10.11 (11.39)	10.32 (1.63)	
Adjusted change (95% CI) at 6 mo	0.34 (−0.03 to 0.71)	0.06 (−0.28 to 0.39)	0.25 (−0.16 to 0.66)	.60
Adjusted change (95% CI) at 12 mo	0.41 (0.04 to 0.86)	−0.07 (−0.49 to 0.35)	0.07 (−0.42 to 0.55)	
Secondary End Point of Prevention of Falls, Adjusted % (95% CI) of Fallers by Incidence of First Fall Among Seniors With 25(OH)D Levels <20 ng/mL at Baseline				
At 0-6 mo	38.3 (24.4 to 54.4)	43.0 (27.4 to 60.1)	43.5 (29.0 to 59.3)	.88
At 7-12 mo	25.6 (14.4 to 41.4)	38.0 (23.3 to 55.2)	49.0 (33.8 to 64.4)	.11
At 0-12 mo	44.4 (29.6 to 60.2)	67.5 (50.0 to 81.2)	75.1 (59.5 to 86.1)	.02
Secondary End Point of Prevention of Falls, Adjusted % (95% CI) of Fallers by Incidence of First Fall Among Seniors With 25(OH)D Levels ≥20 ng/mL at Baseline				
At 0-6 mo	24.8 (12.0 to 44.4)	54.2 (36.8 to 70.6)	32.0 (16.2 to 53.5)	.047
At 7-12 mo	22.0 (10.1 to 41.4)	43.2 (27.0 to 61.0)	29.8 (14.5 to 51.5)	.19
At 0-12 mo	45.1 (27.0 to 64.7)	68.0 (49.8 to 82.0)	51.5 (31.0 to 71.5)	.19
Secondary End Point of Prevention of Falls, Adjusted Mean No. (95% CI) of Falls Among Seniors With 25(OH)D Levels <20 ng/mL at Baseline				
At 0-6 mo	0.61 (0.25 to 0.97)	0.79 (0.41 to 1.17)	0.73 (0.37 to 1.08)	.79
At 7-12 mo	0.43 (0.06 to 0.80)	0.72 (0.32 to 1.11)	0.90 (0.53 to 1.26)	.20
At 0-12 mo	0.98 (0.52 to 1.44)	1.39 (0.90 to 1.88)	1.41 (0.96 to 1.86)	.33
Secondary End Point of Prevention of Falls, Adjusted Mean No. (95% CI) of Falls Among Seniors With 25(OH)D Levels ≥20 ng/mL at Baseline				
At 0-6 mo	0.39 (0.03 to 0.81)	1.03 (0.65 to 1.41)	0.60 (0.15 to 1.05)	.06
At 7-12 mo	0.42 (0.07 to 0.75)	0.73 (0.43 to 1.04)	0.46 (0.10 to 0.82)	.29
At 0-12 mo	0.78 (0.25 to 1.31)	1.65 (1.17 to 2.13)	1.03 (0.46 to 1.60)	.03

Bischoff-Ferrari, JAMA, 2016

CALCIUM + VITAMIN D SUPPLETION STUDIES

Calcium 1.200 mg/d +Vitamin D 800 IU/d





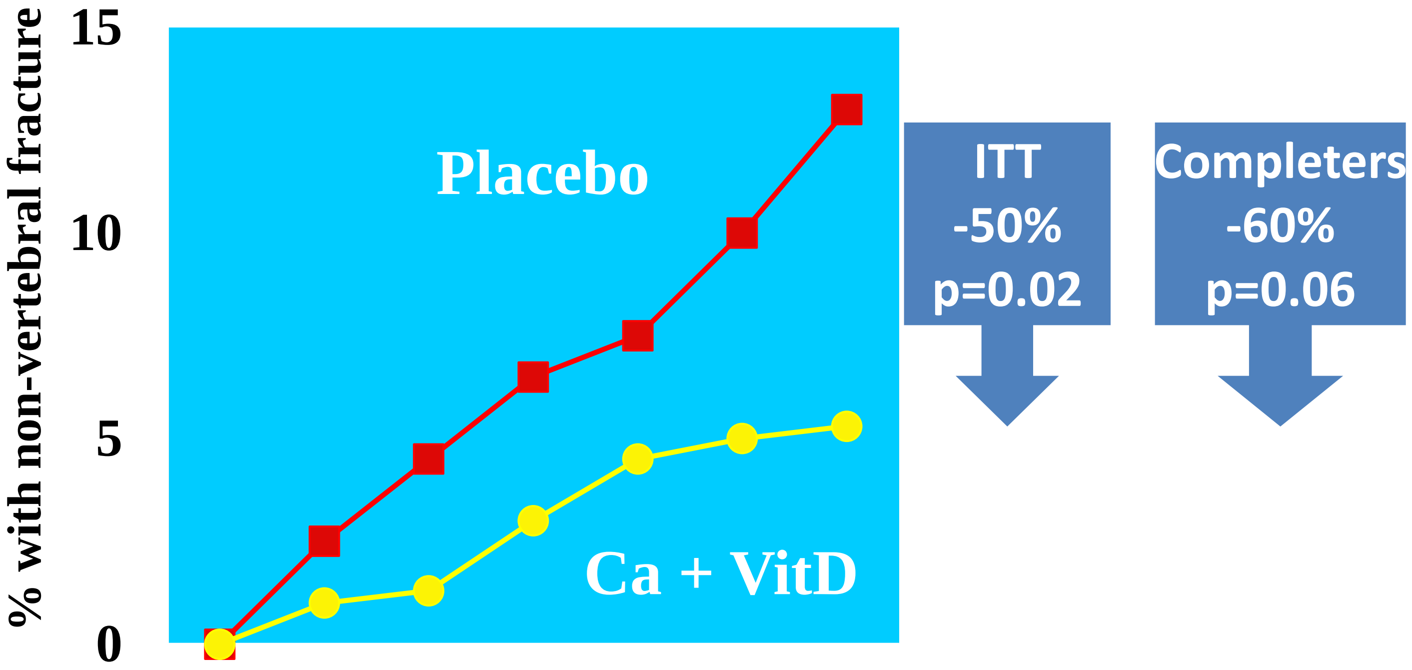
azMaastricht & UHasselt

Chapuy, NEJM, 1992, 1637

Calcium 500 mg/d and Vitamin D 700 IU/d

Men and Women >65 yr, *n=445*, Drop-Out: 29%

Baseline Calcium Intake 7-800 mg/d



(37 non-vertebral fractures)

Dawson-Hughes, NEJM, 1997, 670

Subgroup analysis for fracture prevention of calcium and calcium+ vitamin D studies

	Subtotal (n)*	RR (95% CI)	p value
Supplementation			
Calcium	6517	0·90 (0·80–1·00)	0·63
Calcium and vitamin D	46 108	0·87 (0·77–0·97)	
Previous fractures			
No	46 919	0·86 (0·78–0·95)	0·85
Yes	5706	0·93 (0·82–1·06)	
Clinical setting			
Community	49 233	0·94 (0·90–0·99)	0·003
Institutionalised	3392	0·76 (0·66–0·88)	
Serum 25(OH) vitamin D_3 concentration†			
Low	10 144	0·86 (0·78–0·93)	0·06
Normal	39 167	0·94 (0·90–0·99)	
Fracture sites			
Hip	51 935	0·87 (0·75 – 0·99)	0·72
Vertebral	45 184	0·87 (0·75 – 1·01)	
Dietary calcium intake‡			
Low	7272	0·80 (0·71–0·89)	0·008
Normal	45 241	0·95 (0·91–1·00)	
Calcium dose			
<1200 mg	47 359	0·94 (0·89–0·99)	0·006
≥1200 mg	5266	0·80 (0·72–0·89)	

Tang, Lancet, 2007

Subgroup analysis for fracture prevention of calcium and calcium+ vitamin D studies

Vitamin D dose			
<800 IU	36 671	0·87 (0·71–1·05)	0·03
≥800 IU	9437	0·84 (0·75–0·94)	
Sex			
Women-only studies	46 586	0·88 (0·80–0·97)	0·33
Men and women studies	6039	0·88 (0·80–0·96)	
Percentage change in BMD			
<1%	38 212	0·96 (0·91–1·02)	0·007
≥1%	5621	0·80 (0·70–0·91)	
Age (years)			
50–69	36 640	0·97 (0·92–1·02)	0·003
70–79	12 481	0·89 (0·82–0·96)	
≥80	3504	0·76 (0·67–0·87)	
Compliance§			
≥80%	4508	0·76 (0·67–0·86)	0·002
60–69%	3511	0·92 (0·71–1·19)	
50–59%	44 494	0·96 (0·91–1·01)	

Tang, Lancet, 2007

Calcium intake / suppletion and Cardiovascular Risk

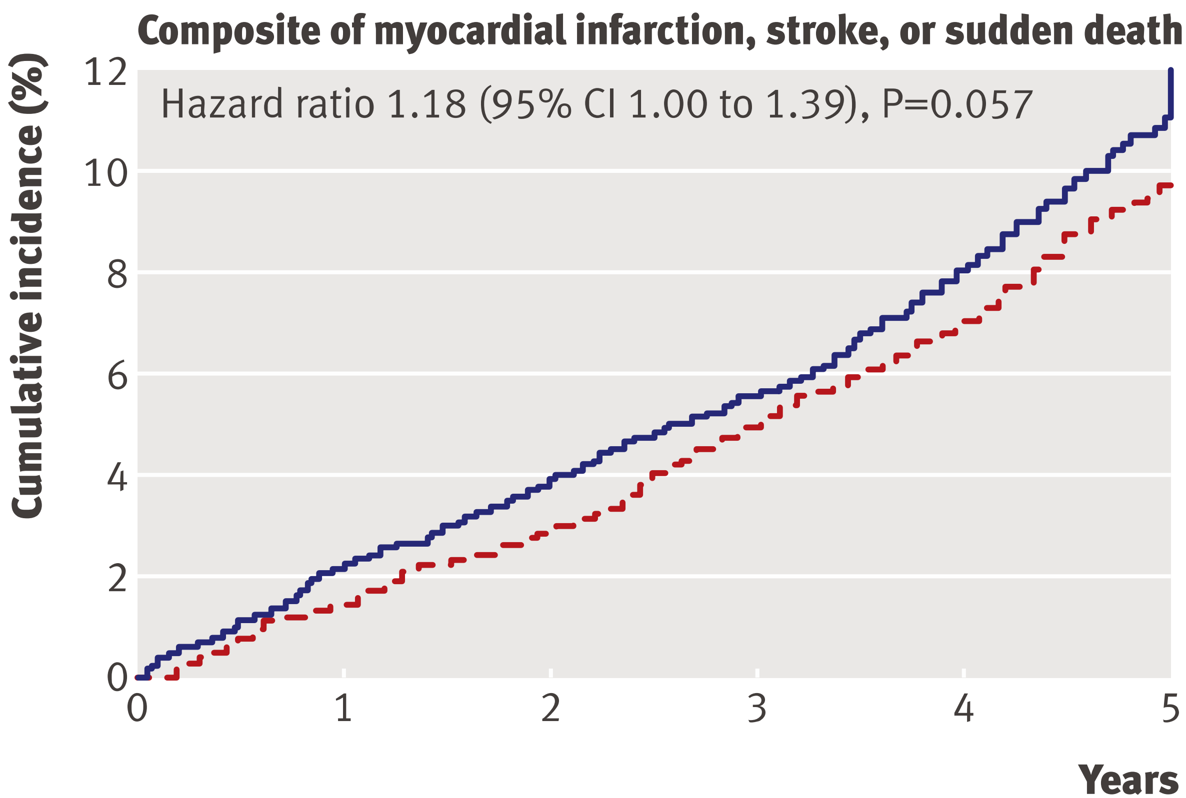
Bolland 2008

Table 2 | Potential vascular events self reported by healthy postmenopausal women assigned to calcium supplementation or to placebo or reported by family members. Values are numbers of women (numbers of events) unless stated otherwise

Vascular event	Calcium group (n=732)	Placebo group (n=739)	P value*	Relative risk (95% CI)
Angina	50 (88)	71 (99)	0.058	0.71 (0.50 to 1.01)
Myocardial infarction	31 (45)	14 (19)	0.0099	2.24 (1.20 to 4.17)
Other chest pain	16 (18)	15 (16)	0.86	1.08 (0.54 to 2.16)
Transient ischaemic attack	33 (42)	21 (27)	0.10	1.59 (0.93 to 2.72)
Stroke	40 (52)	28 (34)	0.14	1.44 (0.90 to 2.31)
Sudden death	4	1	0.22	4.04 (0.45 to 36.0)
Angina, chest pain, myocardial infarction, or sudden death	87 (155)	93 (135)	0.68	0.94 (0.72 to 1.24)
Myocardial infarction, stroke, or sudden death	69 (101)	42 (54)	0.0075	1.66 (1.15 to 2.40)
Death	34	29	0.52	1.18 (0.73 to 1.92)

*Differences between groups in numbers of women with reported events, based on Fisher's exact test.

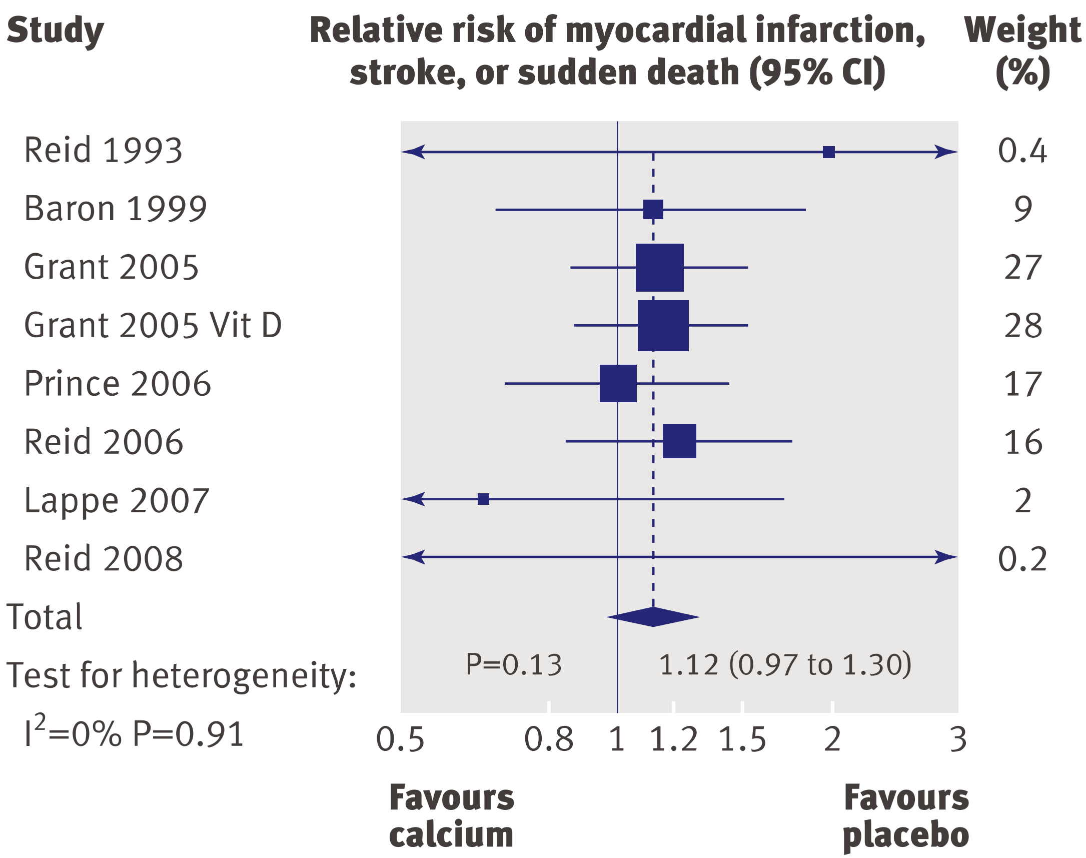
BMJ 2008;336;262-266;



No at risk

Calcium	4097	3848	3517	2635	1271	360
Placebo	4054	3848	3566	2692	1292	376

Bolland, BMJ, 2010



Bolland, BMJ, 2010

Bolland 2010

Calcium suppletion (500-2000 mg/d) were associated with:

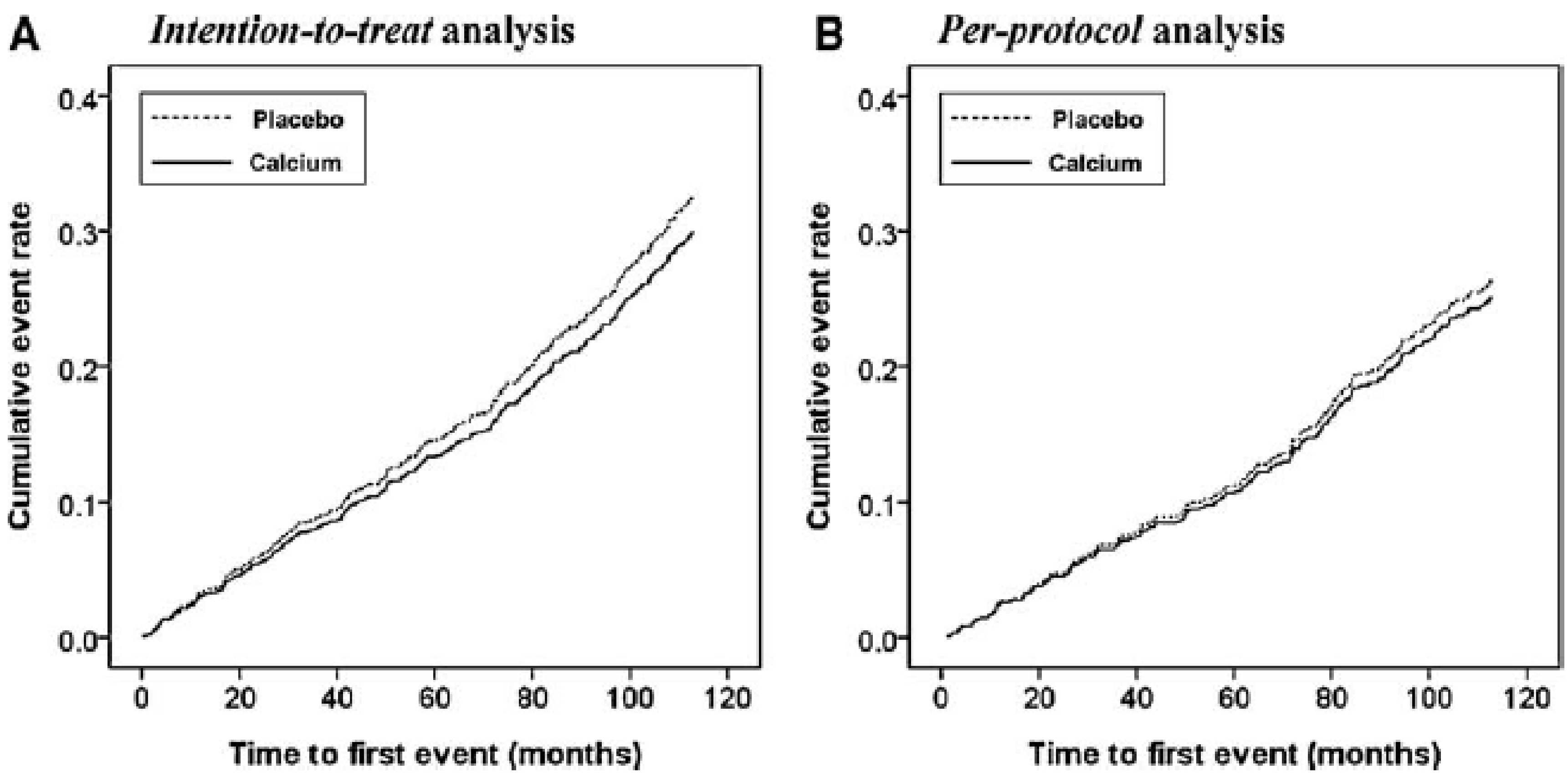
- increased risk of myocardial infarction if dietary calcium intake > 805 mg/day (HR 1.85, 1.28-2.67)
- no increased risk in those with dietary calcium intake < 805mg/day (HR 0.98, 0.69-1.38)

BMJ 2010;341:c3691

Calcium Supplementation and the Risks of Atherosclerotic Vascular Disease in Older Women: Results of a 5-Year RCT and a 4.5-Year Follow-up

Joshua R Lewis,[1,2] Janine Calver,[3] Kun Zhu,[1,2] Leon Flicker,[2,3] and Richard L Prince[1,2]

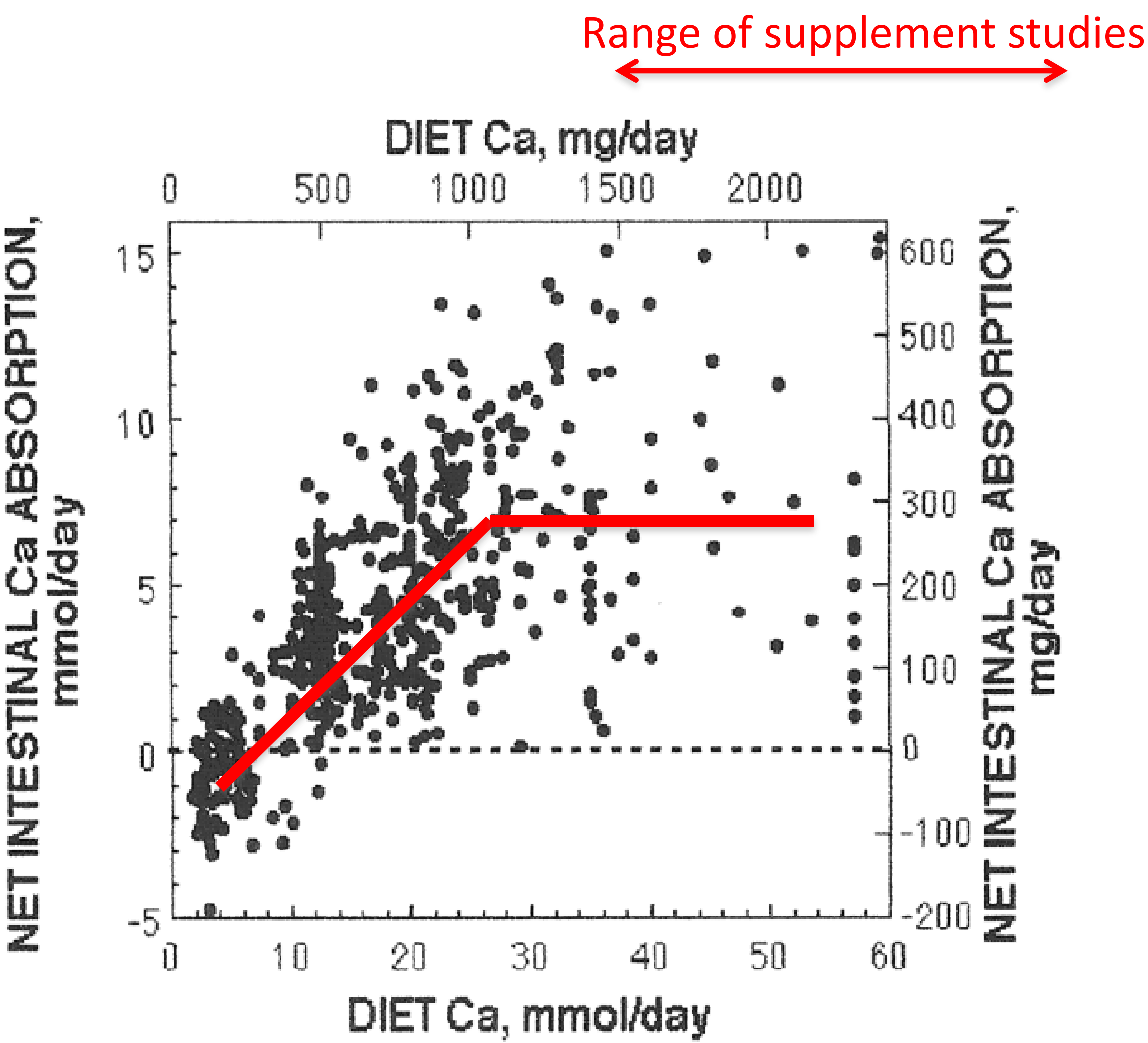
[1]Department of Endocrinology and Diabetes, Sir Charles Gairdner Hospital, Nedlands, Perth, Australia
[2]School of Medicine and Pharmacology, University of Western Australia, Crawley, Australia
[3]Western Australian Centre for Health and Ageing, University of Western Australia, Crawley, Australia



RCT 1200 mg calcium vs placebo; women ≥ 70. **Base-line dietary intake 950 mg calcium**

JBMR, Vol. 25, 2010, pp 2205–2211

Net calcium absorption in relation to intake
Doses used in studies



Baseline	Suppl	Total
400	500	900
800	1000	1800
700	1600	2300
900	1200	2100
1000	2000	3000
800	1000	1800
900	1000	1900
900	1200	2100
1200	1000	2200
1100	1400	2500
900	600	1500

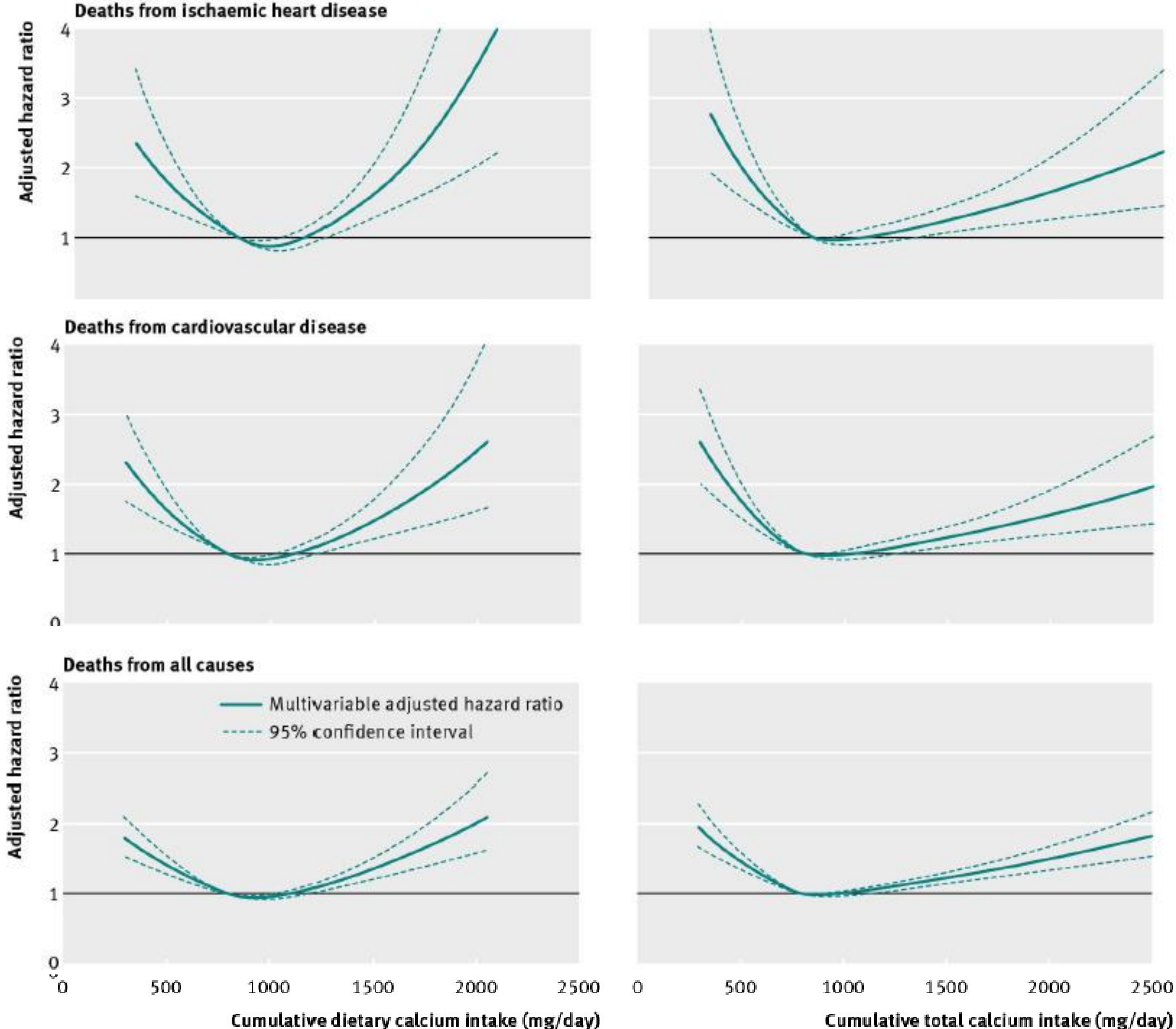
BMJ

BMJ 2013;346:f228 doi: 10.1136/bmj.f228 (Published 13 February 2013)

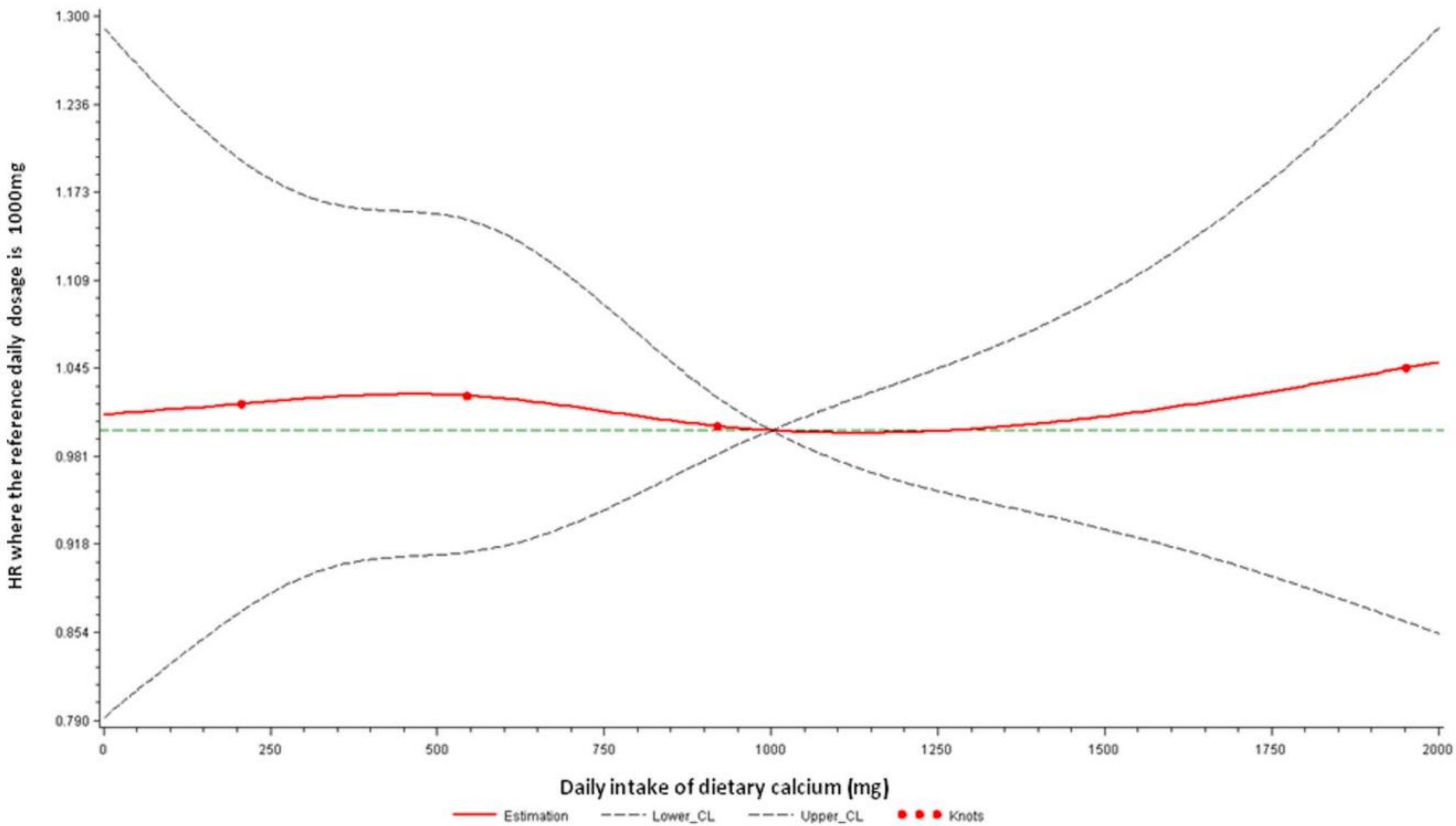
RESEARCH

Long term calcium intake and rates of all cause and cardiovascular mortality: community based prospective longitudinal cohort study

Karl Michaëlsson *professor*[1], Håkan Melhus *professor*[2], Eva Warensjö Lemming *researcher*[1], Alicja Wolk *professor*[3], Liisa Byberg *associate professor*[1]

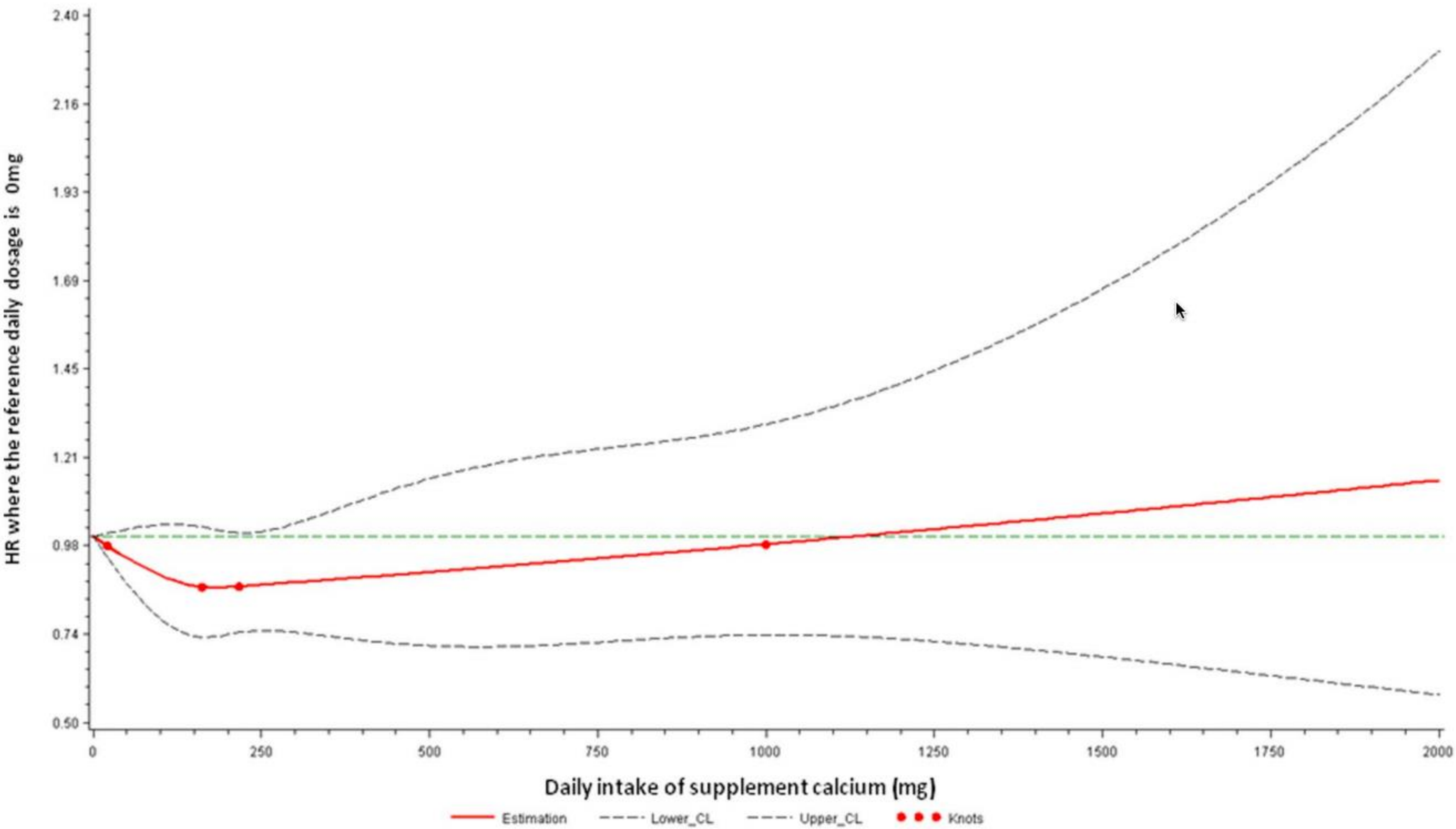

Deaths from ischaemic heart disease
Deaths from cardiovascular disease
Deaths from all causes
Adjusted hazard ratio
Multivariable adjusted hazard ratio
95% confidence interval
0
1
2
3
4
0
500
1000
1500
2000
2500
Cumulative dietary calcium intake (mg/day)
Cumulative total calcium intake (mg/day)

Adjusted dose-response association between daily dietary calcium intake and risk for cardiovascular death (NHANES III)



Plos One 2013: e61037

Adjusted dose-response association between daily calcium supplement intake and risk for cardiovascular death (NHANES III)



Plos One 2013: e61037

Table. Institute of Medicine 2011 Recommended Dietary Allowances for Vitamin D and Calcium*

Population	Recommended Daily Dose	
	Vitamin D, *IU*	Calcium, *mg*
Women		
Aged 19–50 y	600	1000
Aged 51–70 y	600	1200
Aged >70 y	800	1200
Pregnant women		
Aged <18 y	600	1300
Aged >18 y	600	1000
Breastfeeding women		
Aged <18 y	600	1300
Aged >18 y	600	1000
Men		
Aged 19–50 y	600	1000
Aged 51–70 y	600	1000
Aged >70 y	800	1200

Moyer, Ann Int Med, 2013

Cochrane 2014

- Vitamin D plus calcium can help prevent hip fracture or any type of fracture.
- The benefits need to be balanced against the risk of kidney stones, kidney disease, gastrointestinal disease or heart disease
- Vitamin D and calcium together are not associated with an increased risk of dying
- Some evidence that vitamin D3 may decrease all-cause mortality and cancer mortality in predominantly elderly participants living independently or in institutional care.

Medical treatment: calcium and vitamin D

- Optimalisation of **calcium** intake:
  - **Total intake: 1000-1200 mg calcium/day**
    - e.g.: no milk products* + 4 milk products or 1000 mg calcium supplement
    - e.g.: 2 milk products/day + 2 milk products/day or +500 mg calcium supplement
    - e.g.: 4 milk products/day no adaptation necessary
- **Vitamin D: 800 IU/day**
  - With anti-osteoporosis medication
  - In subjects in rest homes
  - In patients with a recent fracture

*milk product:
- 1 cup of milk
- or yaghourt
- or 1 slice of cheese