Βιταμίνη D - 2022

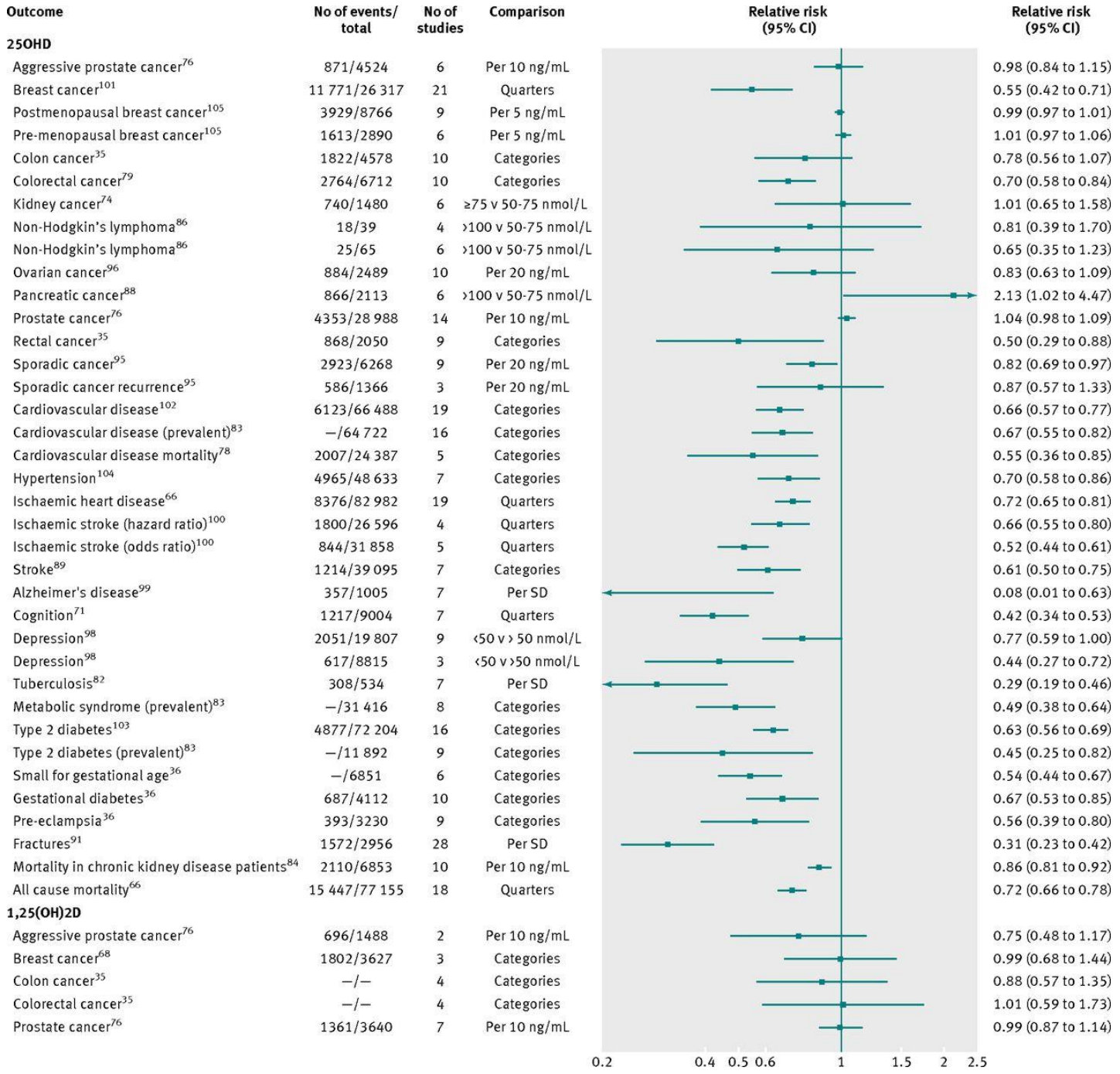
at_kout@yahoo.com

Σύγκρουση συμφερόντων

Καμία για την παρουσίαση αυτή.

"Knowing is not enough; we must apply.
Willing is not enough; we must do."

—Goethe

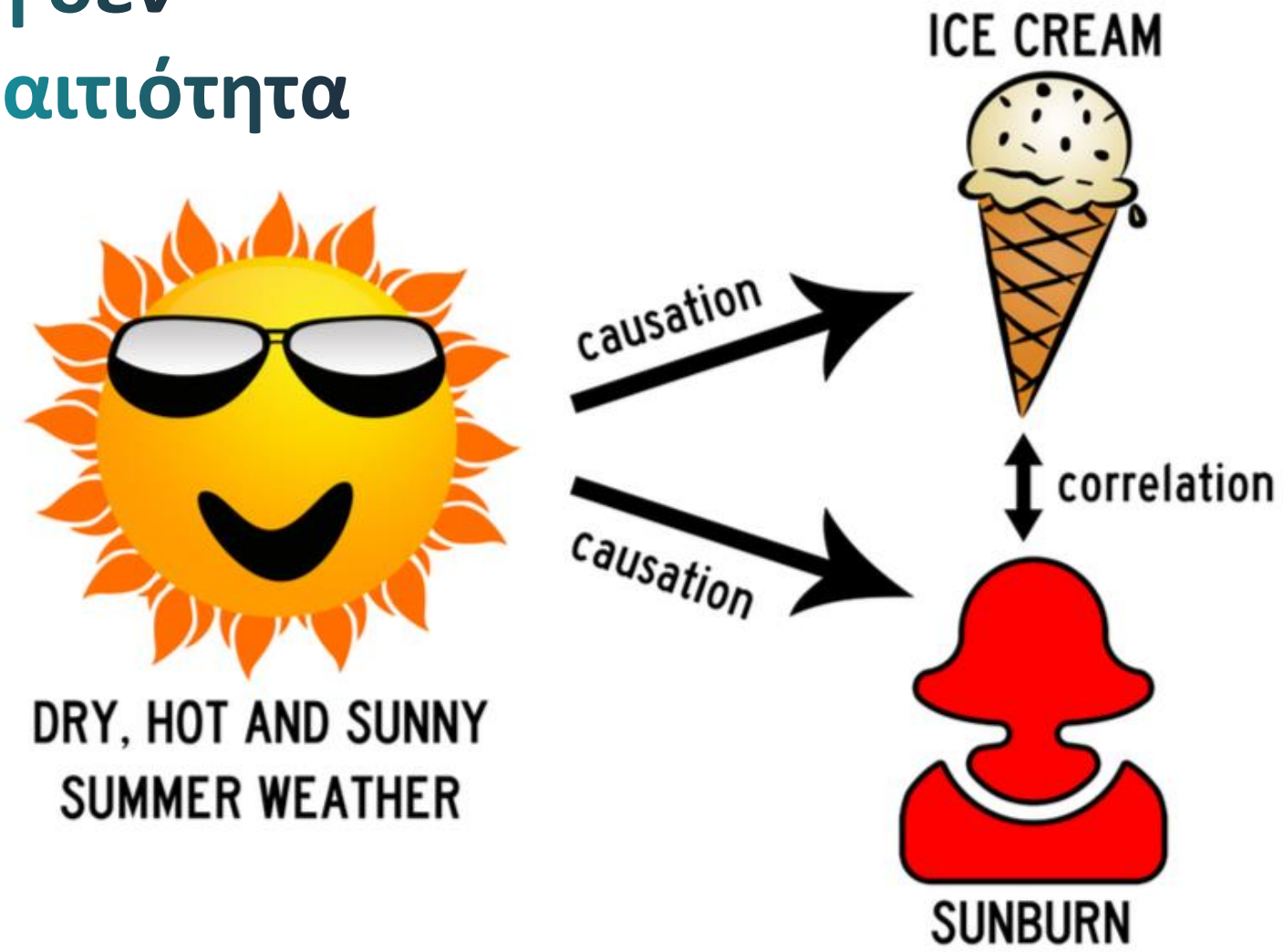


Health outcomes associated with vit D

Meta-analyses of observational studies stratified by measured biomarker with relative risk as type of metric

Theodoratou, BMJ 2014

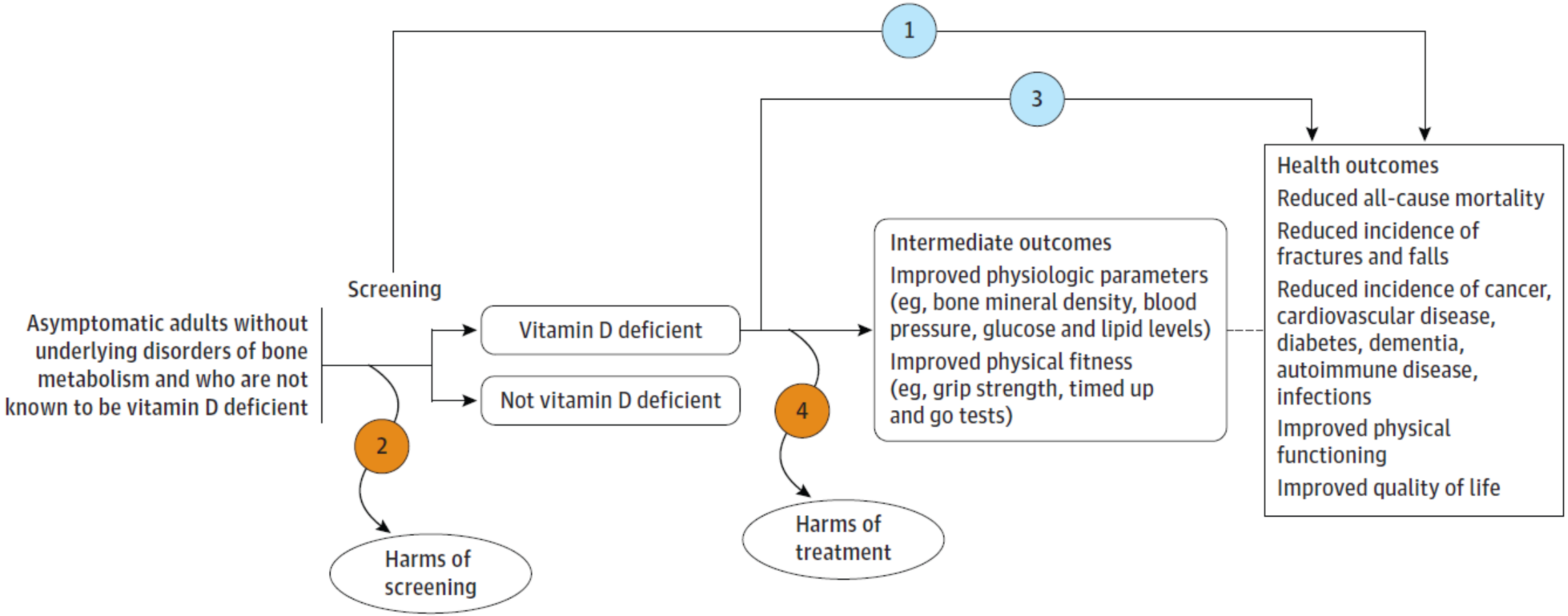
Συσχέτιση δεν σημαίνει αιτιότητα

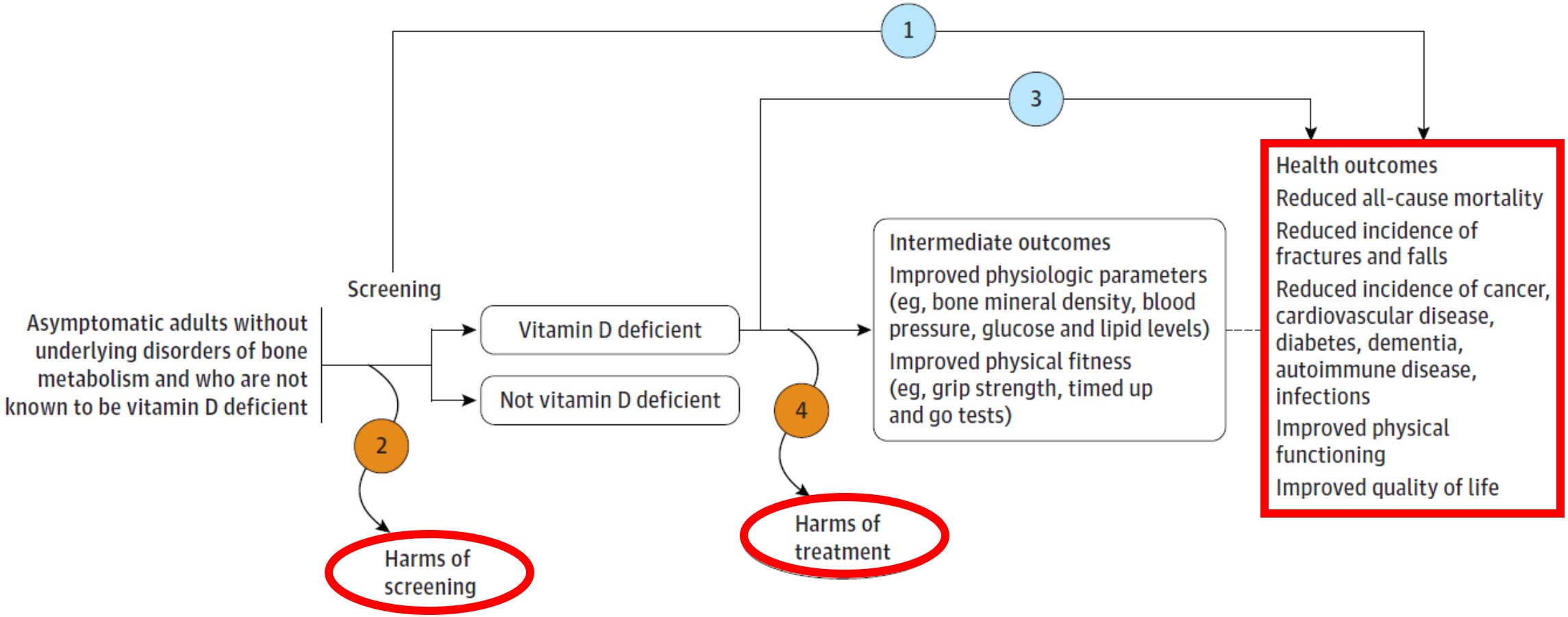


https://towardsdatascience.com/correlation-is-not-causation-ae05d03c1f53

Agenda

- Who should be screened?
- By what method?
- What time of year?
- What are the normal values?
- When should we treat?
- How should we treat?
- Does D3 supplementation prevent autoimmune disease?


1
3
Screening
Asymptomatic adults without underlying disorders of bone metabolism and who are not known to be vitamin D deficient
Vitamin D deficient
Not vitamin D deficient
2
4
Harms of screening
Harms of treatment
Intermediate outcomes
Improved physiologic parameters (eg, bone mineral density, blood pressure, glucose and lipid levels)
Improved physical fitness (eg, grip strength, timed up and go tests)
Health outcomes
Reduced all-cause mortality
Reduced incidence of fractures and falls
Reduced incidence of cancer, cardiovascular disease, diabetes, dementia, autoimmune disease, infections
Improved physical functioning
Improved quality of life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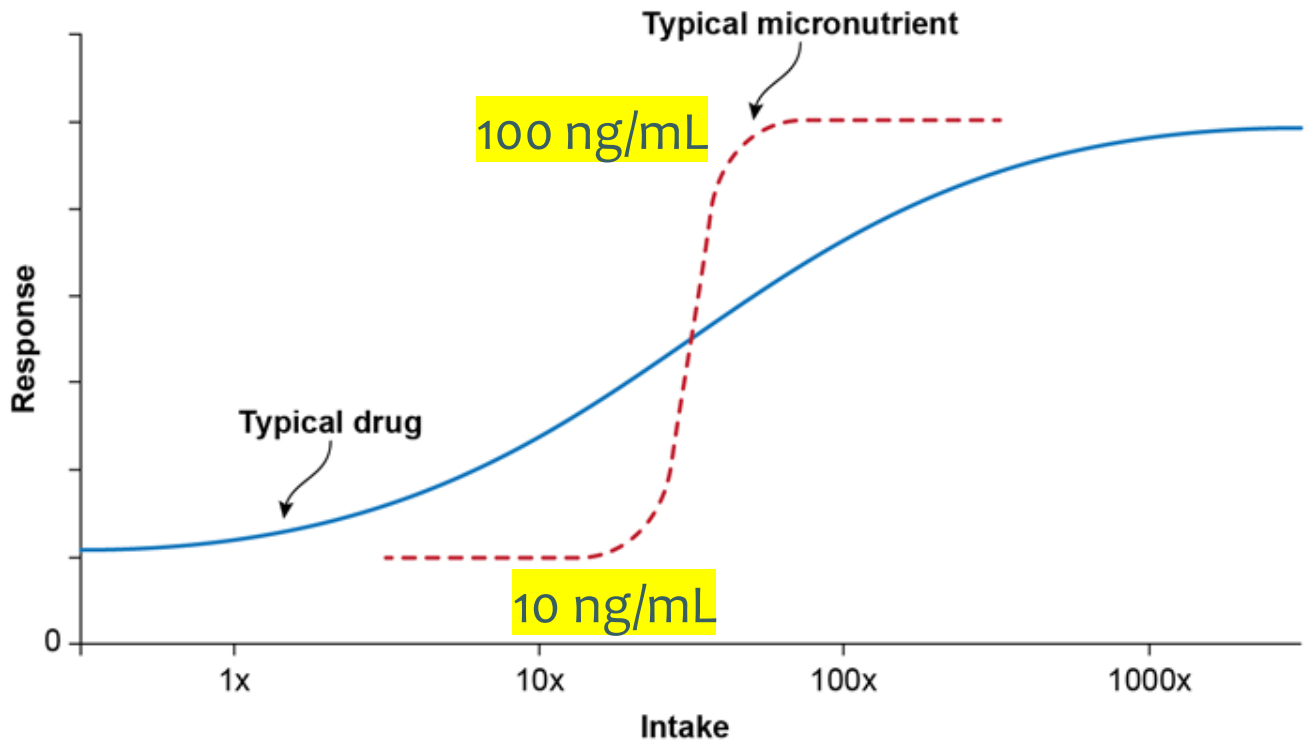
Vitamin D deficient
Not vitamin D deficient
2
4
Harms of screening
Harms of treatment

Limitations of RCTs, observational studies and meta-analyses

1. Wrong dose (too high or too low)
2. Wrong part of the dose-response curve
3. Low compliance rate
4. Contamination (placebo group)
5. Wrong part of natural history
6. Insufficient duration

Vitamin D: Moving Toward Evidence-based Decision Making in Primary Care December 2-3, 2014 Summary of Conference Presentations and Discussions, NIH



Καμπύλη δόσης-ανταπόκρισης Φάρμακα vs συμπληρώματα θρεπτικών συστατικών

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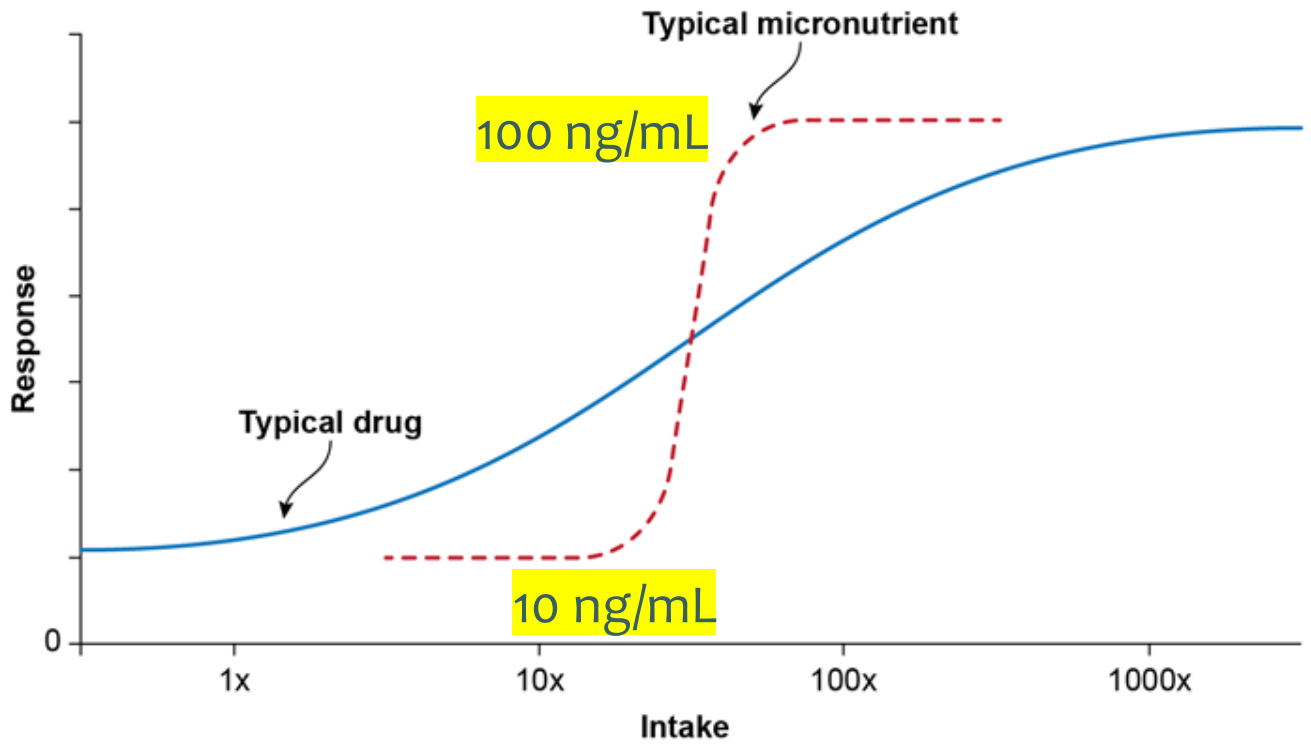

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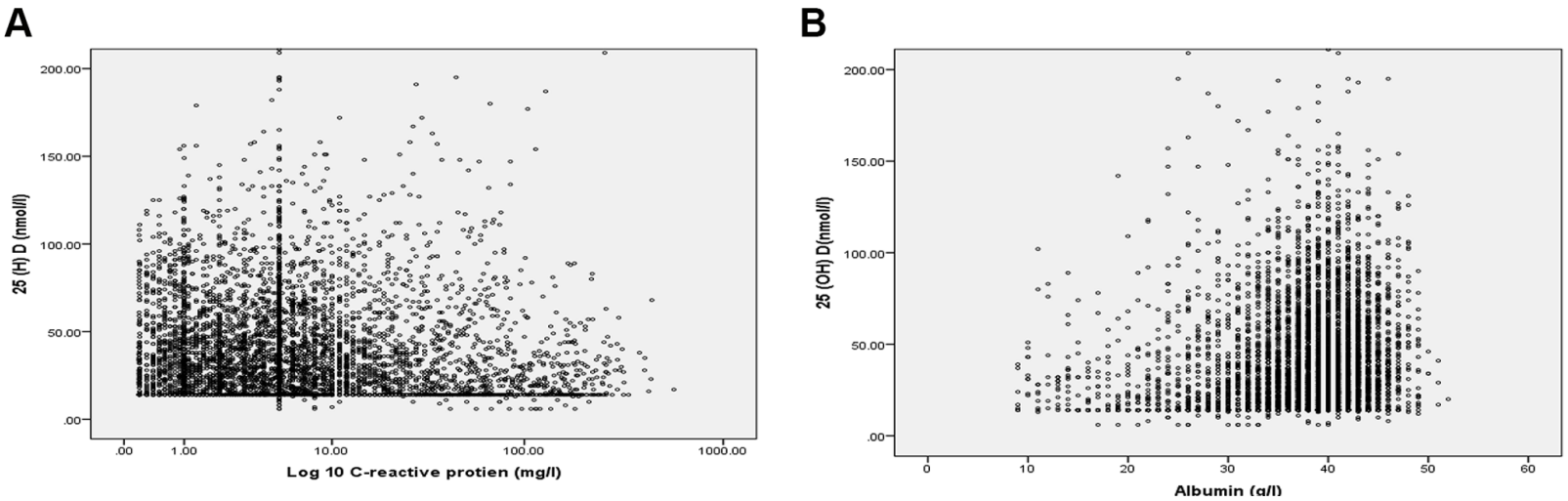
Vitamin D: Moving Toward Evidence-based Decision Making in Primary Care December 2-3, 2014 Summary of Conference Presentations and Discussions, NIH

Dose to maintain 10 ng/mL: 1000 IU/day

Vit D is a negative acute phase reactant

Ghushut, Plos One 2014



Who should be screened?

Who should be screened?

All individuals at risk (not everyone)

Those more likely to benefit from vit D supplementation

Holick, J CLin Endocrinol Metabol 2011

TABLE 2. Indications for 25(OH)D measurement (candidates for screening)

- Rickets
- Osteomalacia
- Osteoporosis
- Chronic kidney disease
- Hepatic failure
- Malabsorption syndromes
  - Cystic fibrosis
  - Inflammatory bowel disease
  - Crohn's disease
  - Bariatric surgery
  - Radiation enteritis
- Hyperparathyroidism
- Medications
  - Antiseizure medications
  - Glucocorticoids
  - AIDS medications
  - Antifungals, *e.g.* ketoconazole
  - Cholestyramine
- African-American and Hispanic children and adults
- Pregnant and lactating women
- Older adults with history of falls
- Older adults with history of nontraumatic fractures
- Obese children and adults (BMI > 30 kg/m^2)
- Granuloma-forming disorders
  - Sarcoidosis
  - Tuberculosis
  - Histoplasmosis
  - Coccidiomycosis
  - Berylliosis
- Some lymphomas

US Endocrine Society guideline,
Holick et al,
J Clin Endocrinol Metabol 2011

Use 25 (OH) D for screening, rather than total vit D or 1,25 (OH)2 D

Use 1,25 (OH)2 D only in:

chronic kidney disease,

hereditary phosphate-losing disorders,

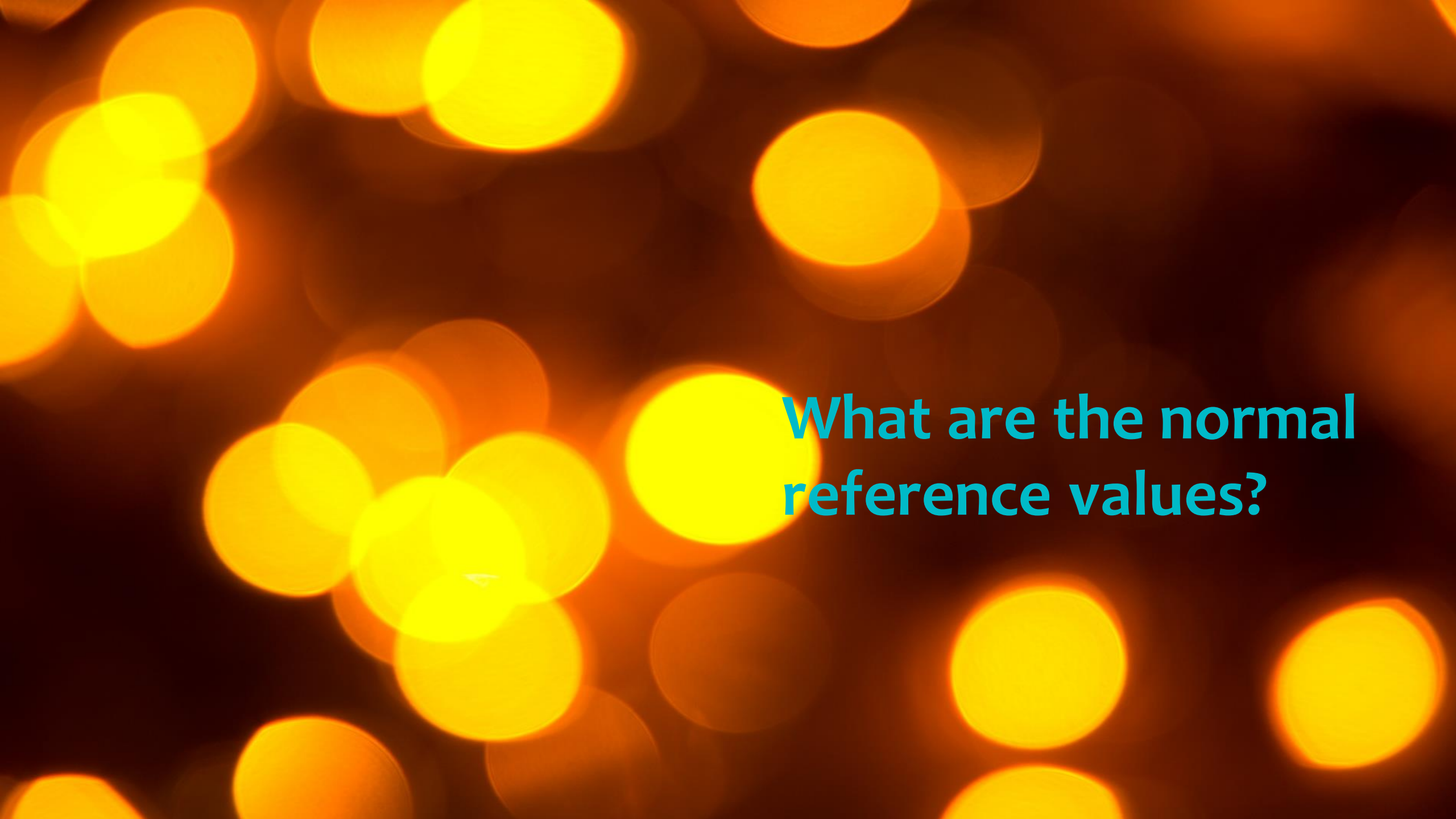
oncogenic osteomalacia,

pseudovitamin D-deficiency rickets,

vitamin D-resistant rickets,

Chronic granuloma forming disorders such as sarcoidosis and some lymphomas

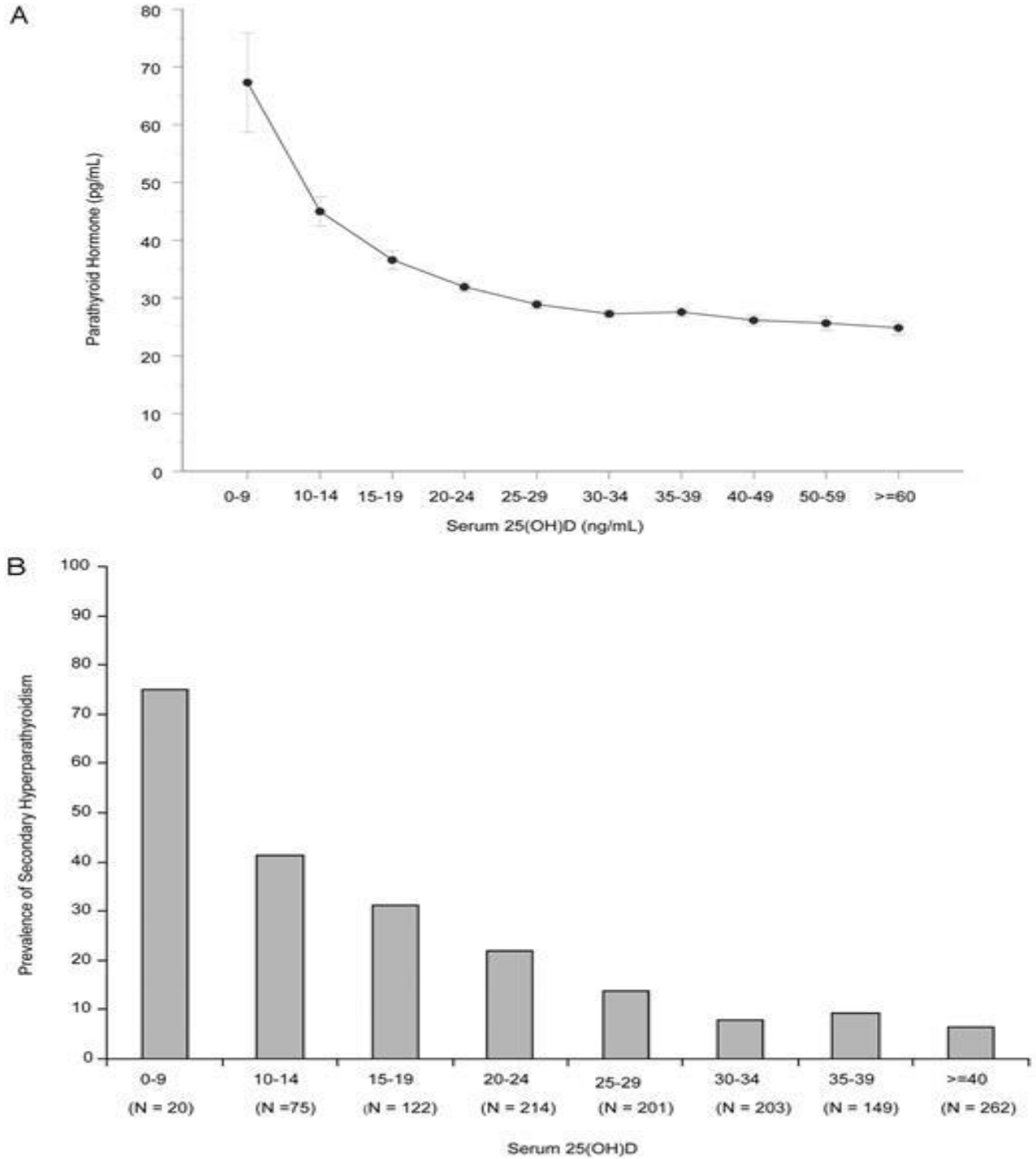
Holick, J CLin Endocrinol Metabol 2011


What are the normal reference values?

Normal reference values

Physiologic

The 25(OH)D3 concentration that allows for better calcium absorption and lower PTH stimulation



Holick, J Clin Endocrinol Metabol 2005

Normal reference values

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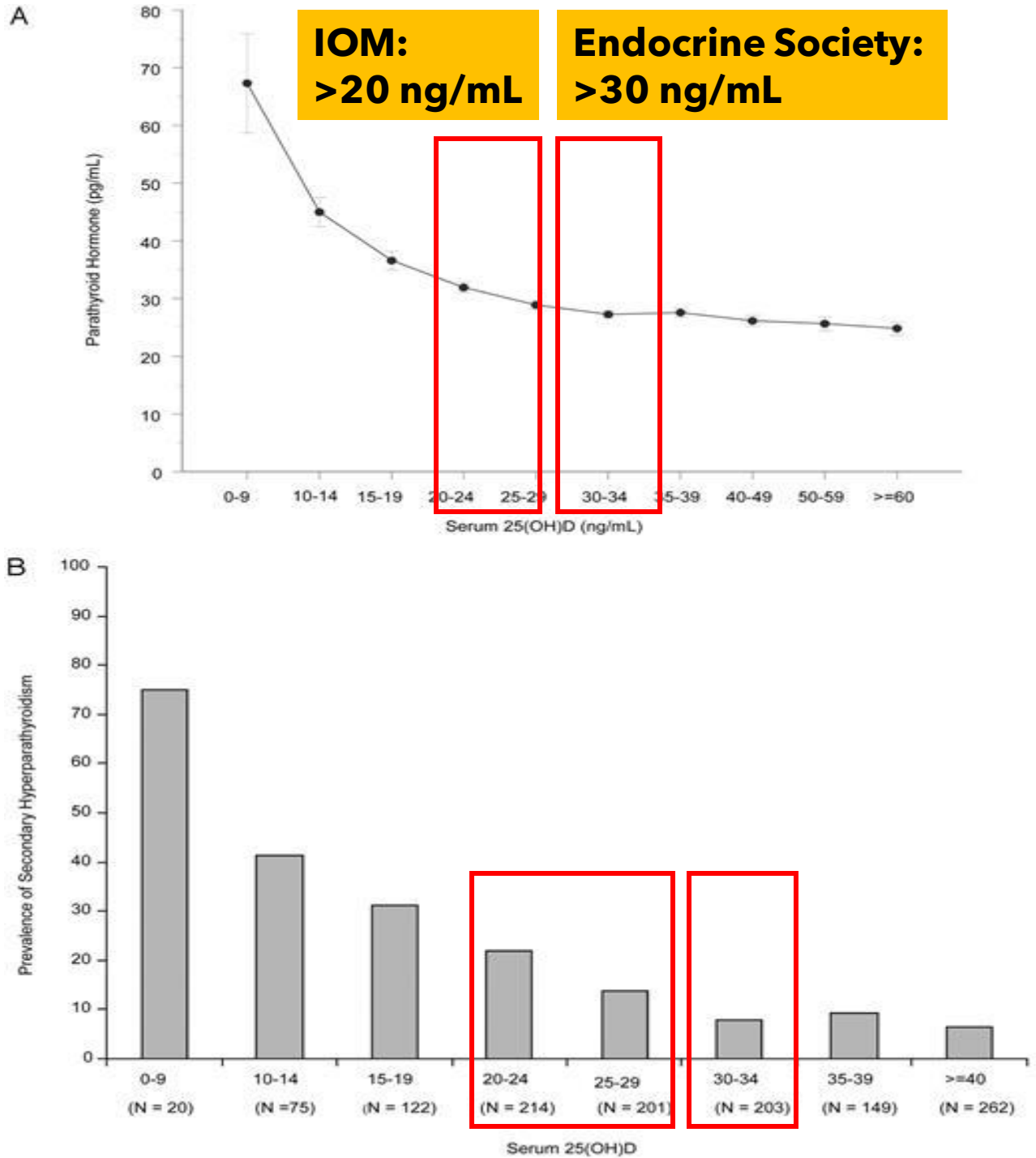
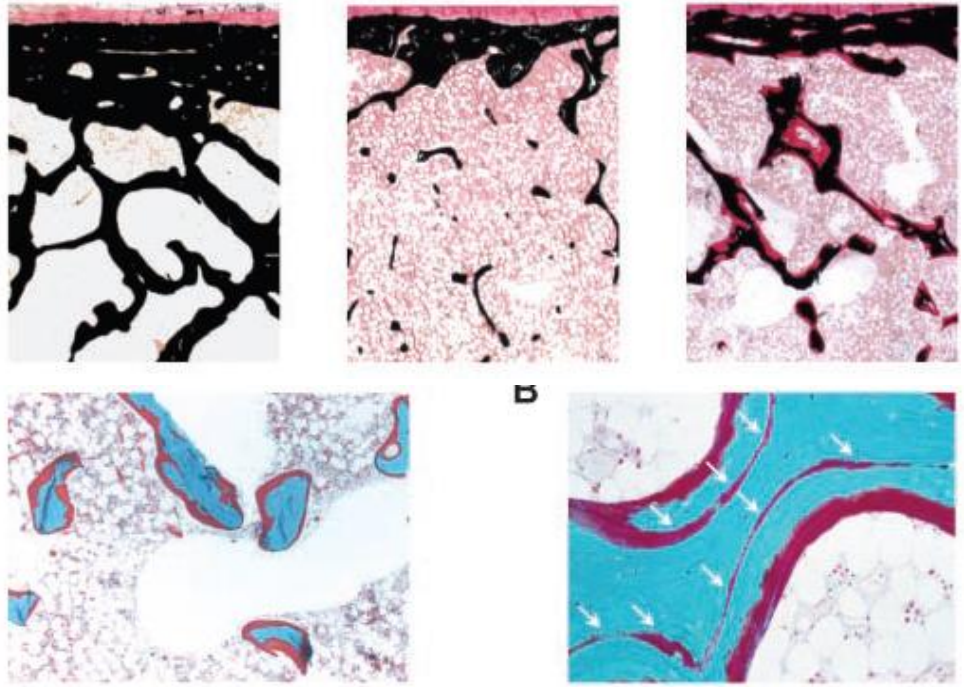


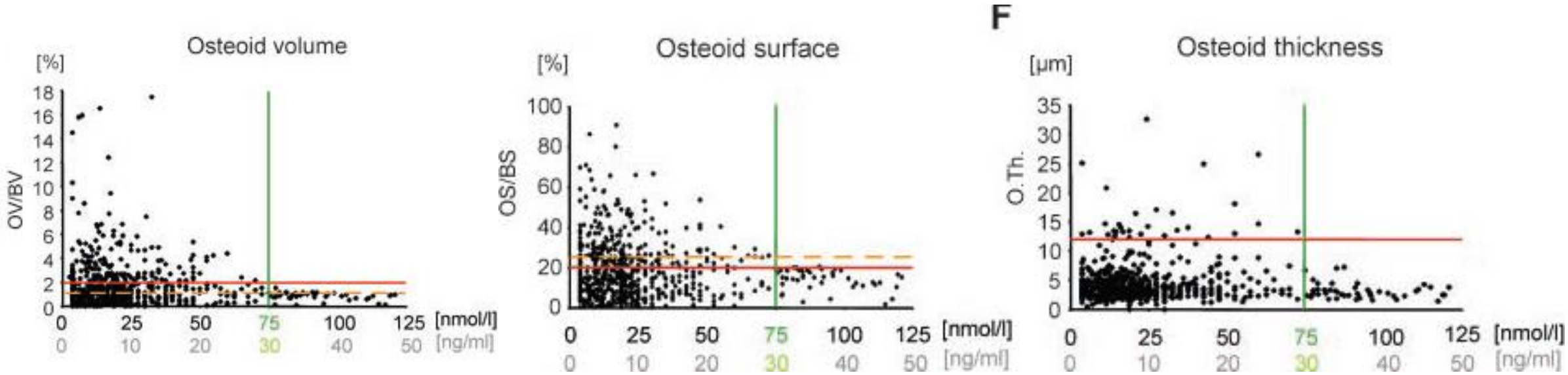
Holick, J Clin Endocrinol Metabol 2005

Bone mineralization defects in relation to 25 (OH)D3 levels in 675 iliac crest biopsies.

Priemel, J Bone Mineral Res 2010



While there is no threshold under which mineralization defects appear, no mineralization defects are evident with 25(OH)D3 levels of 30 ng/ml and higher



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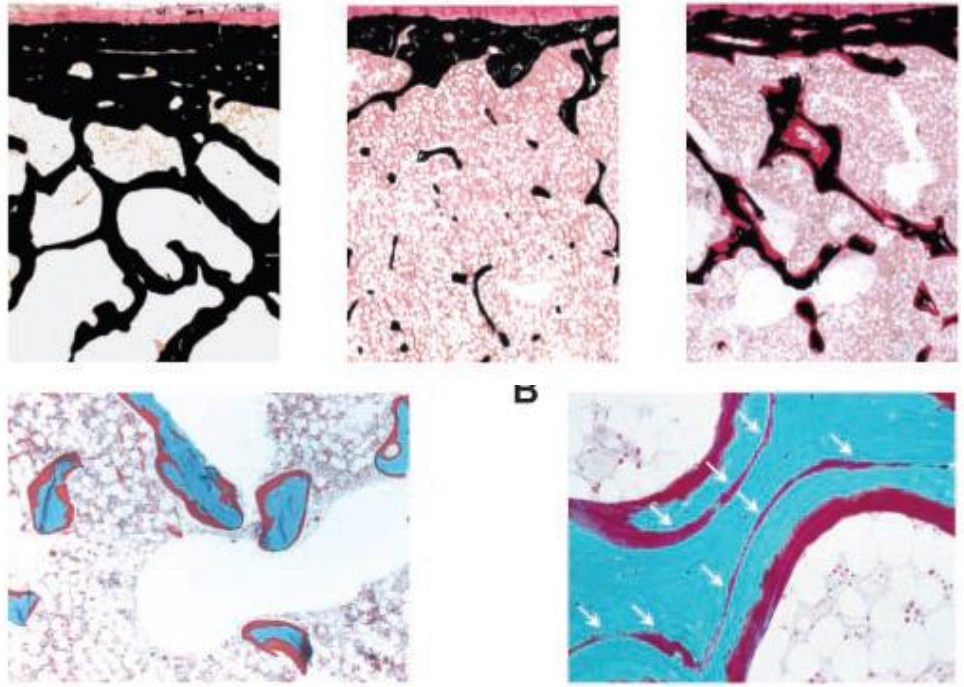

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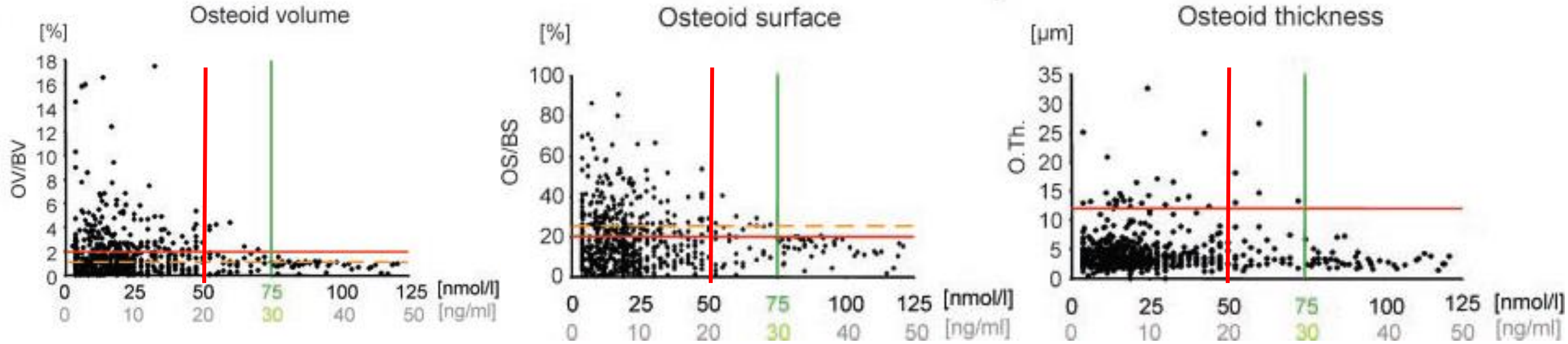
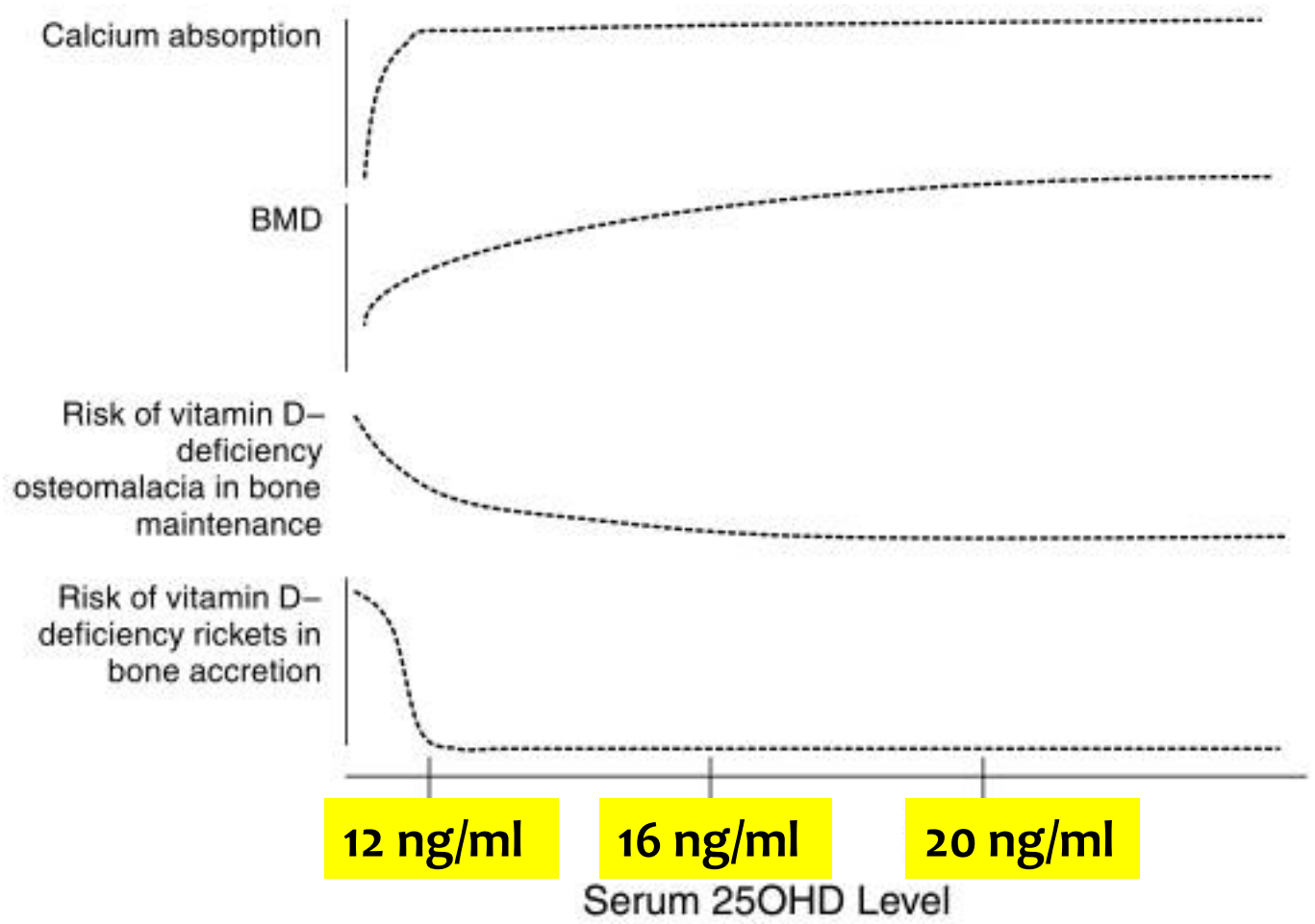


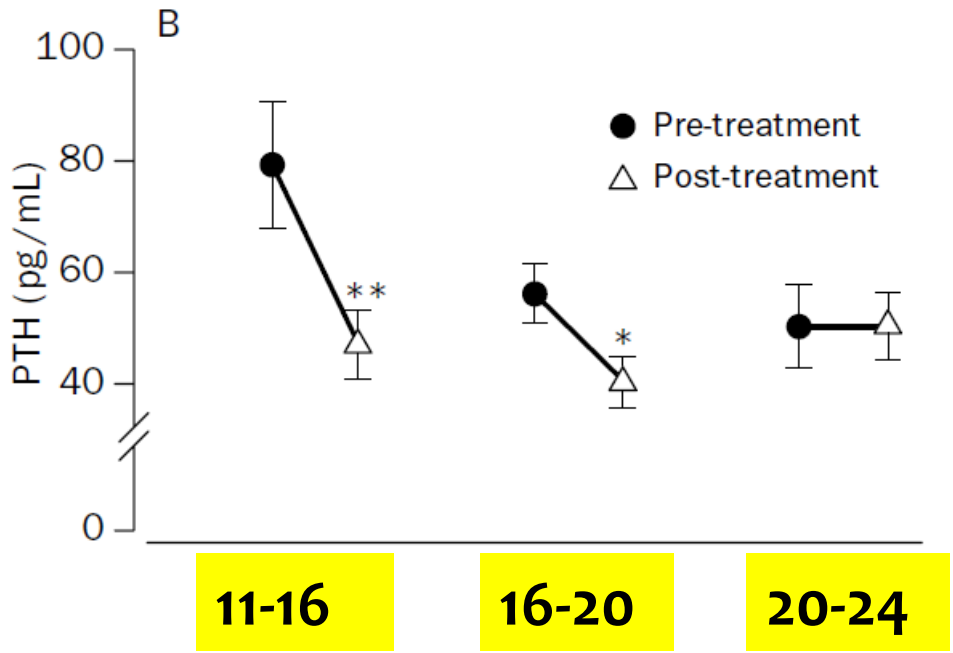


Conceptualization of integrated bone health outcomes and vitamin D exposure.

IOM Guideline

Dietary Reference Intakes for Calcium and Vitamin D
Institute of Medicine (US) Committee to Review Dietary Reference Intakes for Vitamin D and Calcium; Editors: A Catharine Ross, Christine L Taylor, Ann L Yaktine, and Heather B Del Valle.
Washington (DC): National Academies Press (US); 2011.

A minimum of 20 ng/ml is required to achieve optimum PTH levels



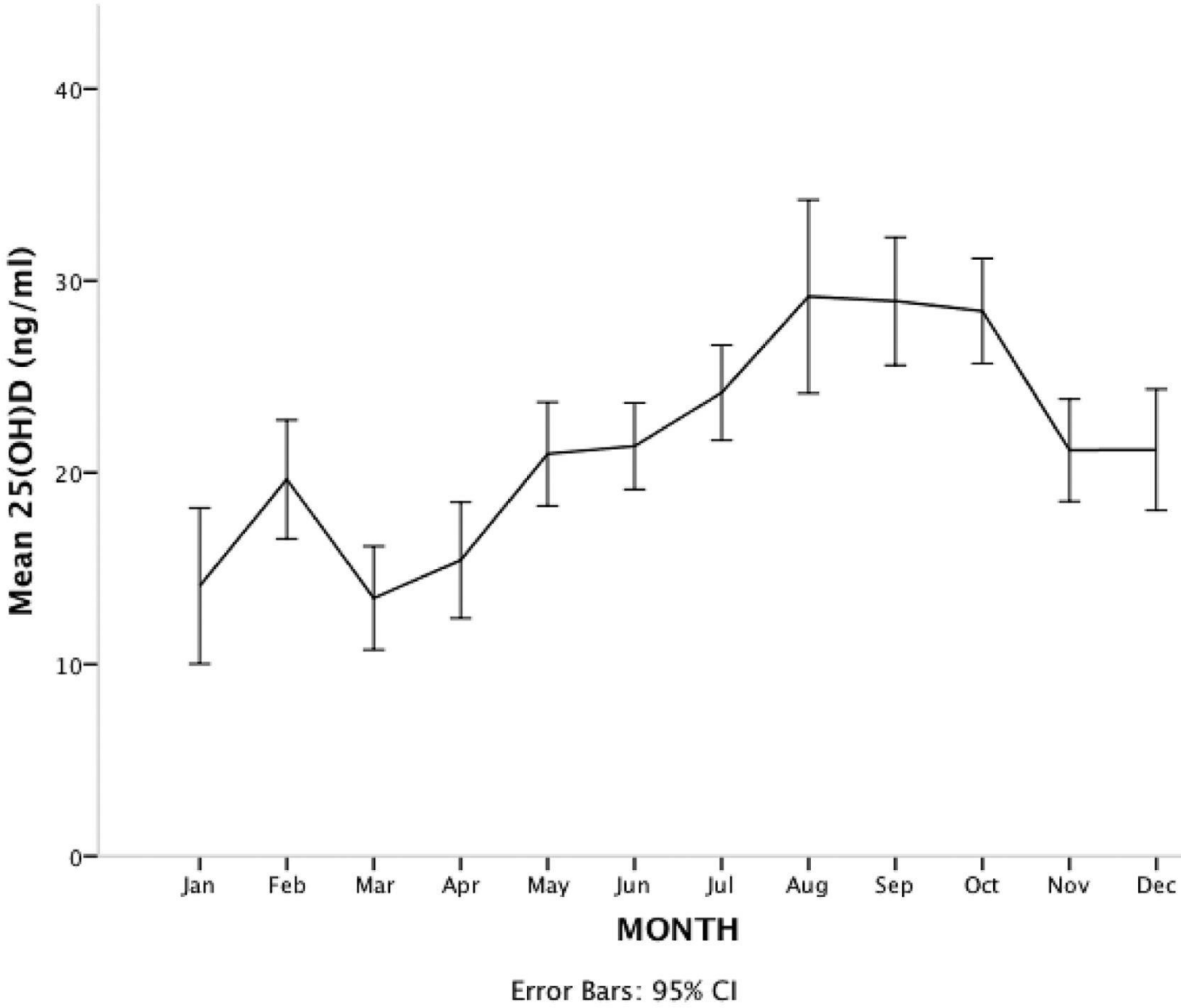
Relations between 25(OH)D and PTH before and after therapy with 50 000 IU of vitamin D, and calcium supplementation once a week for 8 weeks

Malabanan, Lancet 1998

Normal reference values

	Endocrine society	IOM
Normal	>30 ng/mL	20-50 ng/mL
Insufficient	21-29 ng/mL	12-20 ng/mL
Deficient	<20 mg/mL	<12 ng/mL

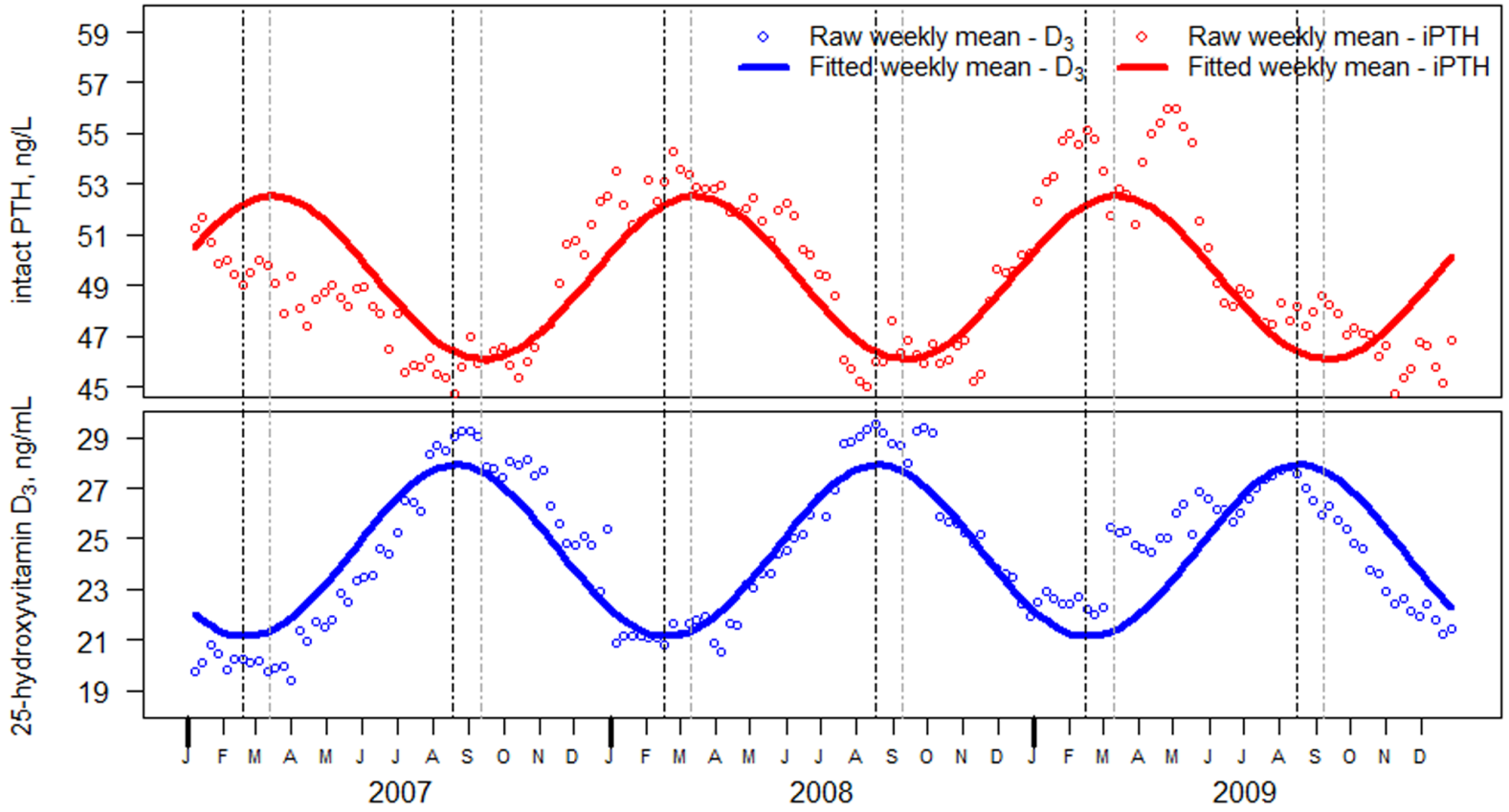
Holick, J CLin Endocrinol Metabol 2011, Institute of Medicine Guidelines, 2011



Εποχικές διακυμάνσεις επιπέδων βιτ D

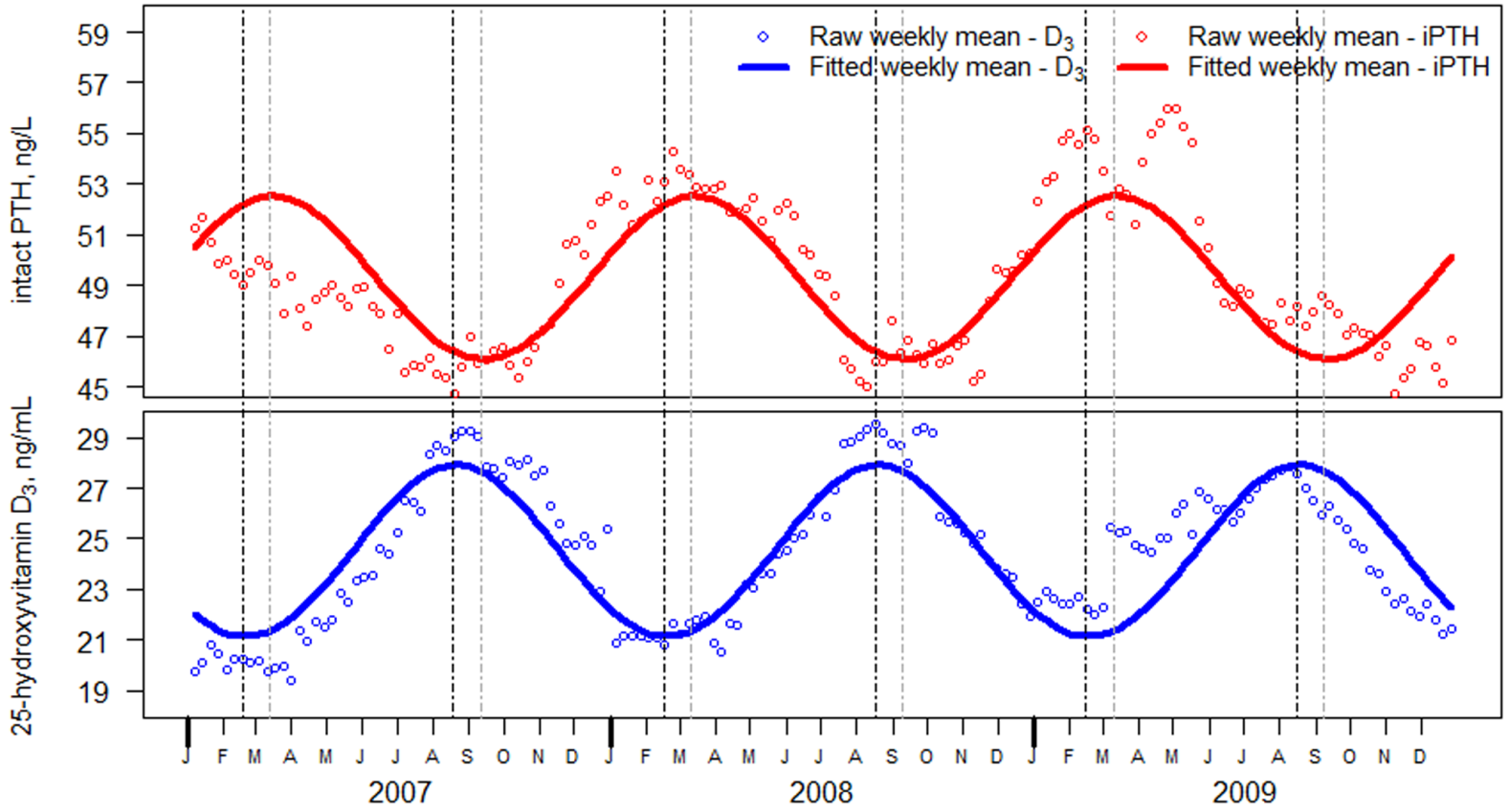
Papadakis, In Vivo 2015

Εποχικές διακυμάνσεις



Kroll, Plos One 2015

Εποχικές διακυμάνσεις



Εχει σημασία η διακύμανση της PTH;

Kroll, Plos One 2015

Who should be treated?

Who should be treated?

- Rickets/ osteomalacia
- Osteoporosis
- Secondary hyperparathyroidism, due to low vit D
- Deficiency (<20 ng/ml? Or <12 ng/ml?)
- Patients at high risk of falls? (with calcium)
- Frail, elderly patients with muscle weakness?
- **Institunionalised**, elderly patients
- Malabsorbing states


How should we treat?

Vit D deficiency

50000 IU D3 / week for 8 weeks

Or

6000 IU / day

To achieve a 25(OH)D level of >30 ng/ml

Followed by maintenance therapy

1500-2000 IU / day

Holick, J CLin Endocrinol Metabol 2011

TABLE 3. Vitamin D intakes recommended by the IOM and the Endocrine Practice Guidelines Committee

Life stage group	IOM recommendations				Committee recommendations for patients at risk for vitamin D deficiency	
	AI	EAR	RDA	UL	Daily requirement	UL
Infants						
0 to 6 months	400 IU (10 μg)			1,000 IU (25 μg)	400–1,000 IU	2,000 IU
6 to 12 months	400 IU (10 μg)			1,500 IU (38 μg)	400–1,000 IU	2,000 IU
Children						
1–3 yr		400 IU (10 μg)	600 IU (15 μg)	2,500 IU (63 μg)	600–1,000 IU	4,000 IU
4–8 yr		400 IU (10 μg)	600 IU (15 μg)	3,000 IU (75 μg)	600–1,000 IU	4,000 IU
Males						
9–13 yr		400 IU (10 μg)	600 IU (15 μg)	4,000 IU (100 μg)	600–1,000 IU	4,000 IU
14–18 yr		400 IU (10 μg)	600 IU (15 μg)	4,000 IU (100 μg)	600–1,000 IU	4,000 IU
19–30 yr		400 IU (10 μg)	600 IU (15 μg)	4,000 IU (100 μg)	1,500–2,000 IU	10,000 IU
31–50 yr		400 IU (10 μg)	600 IU (15 μg)	4,000 IU (100 μg)	1,500–2,000 IU	10,000 IU
51–70 yr		400 IU (10 μg)	600 IU (15 μg)	4,000 IU (100 μg)	1,500–2,000 IU	10,000 IU
>70 yr		400 IU (10 μg)	800 IU (20 μg)	4,000 IU (100 μg)	1,500–2,000 IU	10,000 IU
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Pregnancy						
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Lactation[a]						
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AI, Adequate intake; EAR, estimated average requirement; UL, tolerable upper intake level.

[a] Mother's requirement, 4,000–6,000 IU/d (mother's intake for infant's requirement if infant is not receiving 400 IU/d).

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Holick, J CLin Endocrinol Metabol 2011


How does vit D supplementation affect health outcomes?

Effect on community-dwelling or institutionalized asymptomatic populations-mortality

JAMA Network

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

JAMA. 2021;325(14):1443-1463. doi:10.1001/jama.2020.26498

Source	Treatment duration	Calcium received	Vitamin D: No. with event	Vitamin D: No. without event	Control: No. with event	Control: No. without event	Absolute risk difference (95% CI)	Weight, %	Relative risk (95% CI)	Weight, %
Community										
Grimnes et al,[25] 2011	26 wk	None	0	49	1	44	-0.022 (-0.080 to 0.037)	2.00	0.32 (0.01-7.42)	11.65
Hin et al,[27] 2017	52 wk	None	0	204	3	98	-0.030 (-0.065 to 0.006)	5.39	0.10 (0.01-1.36)	16.70
Hansen et al,[26] 2015	52 wk	None	0	154	0	76	0.000 (-0.018 to 0.018)	21.13	1.00 (0.02-63.94)	6.61
Kärkkäinen et al,[39] 2010	3 y	Active intervention	3	287	1	312	0.007 (-0.006 to 0.020)	38.84	3.24 (0.34-30.95)	22.42
Brazier et al,[18] 2005	52 wk	Active intervention	3	92	1	95	0.021 (-0.019 to 0.062)	4.11	3.03 (0.32-28.63)	22.66
Gallagher et al,[21] 2014	52 wk	Both groups	0	100	0	28	0.000 (-0.036 to 0.036)	5.14	1.00 (0.01-112.49)	5.12
Lips et al,[43] 2010	16 wk	Both groups	1	113	0	112	0.009 (-0.015 to 0.033)	11.71	2.98 (0.12-73.14)	11.16
Gallagher et al,[22] 2012	52 wk	Both groups	0	196	0	33	0.000 (-0.024 to 0.024)	11.68	1.00 (0.00-262.10)	3.68
Subtotal							0.003 (-0.006 to 0.011) I^2 = 0.0%, P = .56	100.0	1.13 (0.39-3.28) I^2 = 0.0%, P = .55	100.0
Institutionalized										
Lips et al,[44] 1996	3-3.5 y	None	223	1068	251	1036	-0.022 (-0.052 to 0.008)	78.78	0.89 (0.75-1.04)	74.54
Krieg et al,[42] 1999	2 y	Active intervention	21	103	26	98	-0.040 (-0.138 to 0.057)	7.42	0.81 (0.48-1.36)	7.37
Chapuy et al,[19] 2002	2 y	Active intervention	71	322	45	145	-0.056 (-0.128 to 0.015)	13.80	0.76 (0.55-1.06)	18.09
Subtotal							-0.028 (-0.055 to -0.002) I^2 = 0.0%, P = .67	100.0	0.86 (0.74-0.99) I^2 = 0.0%, P = .74	100.0

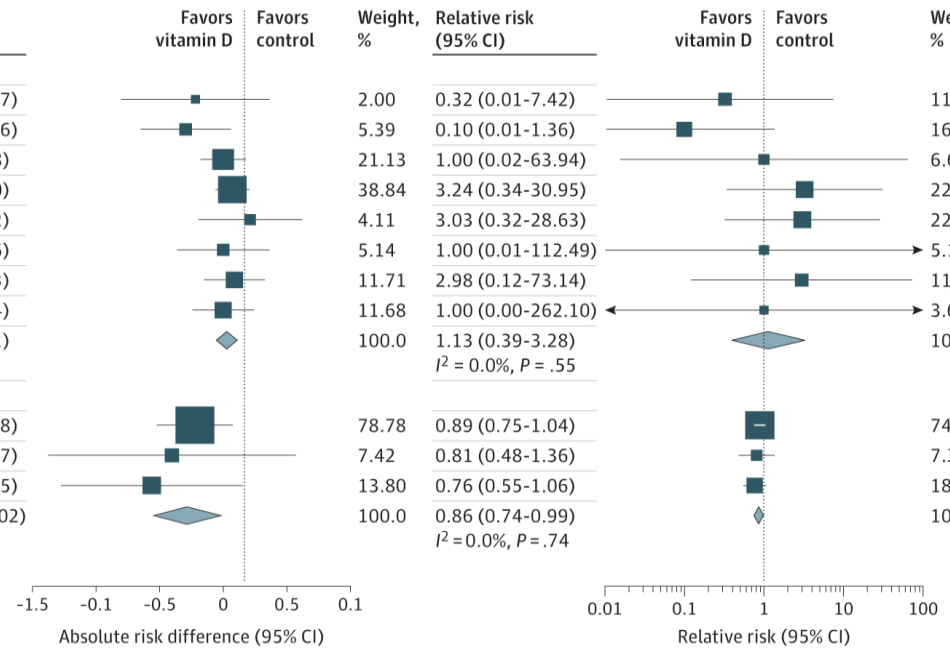

Figure Legend:

Effect of Vitamin D Treatment on Mortality Stratified by SettingSize of each data marker indicates the weight of the study in the analysis. Weights are from random-effects analysis. To calculate the absolute risk difference in percentage points, multiply value by 100 (eg, 0.009 multiplied by 100 = 0.9 percentage points).

JAMA Network

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

JAMA. 2021;325(14):1443-1463. doi:10.1001/jama.2020.26498

Effect on community-dwelling or institutionalized asymptomatic populations-mortality

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Hin et al,[27] 2017	52 wk	None	0	204	3	98	-0.030 (-0.065 to 0.006)
Hansen et al,[26] 2015	52 wk	None	0	154	0	76	0.000 (-0.018 to 0.018)
Kärkkäinen et al,[39] 2010	3 y	Active intervention	3	287	1	312	0.007 (-0.006 to 0.020)
Brazier et al,[18] 2005	52 wk	Active intervention	3	92	1	95	0.021 (-0.019 to 0.062)
Gallagher et al,[21] 2014	52 wk	Both groups	0	100	0	28	0.000 (-0.036 to 0.036)
Lips et al,[43] 2010	16 wk	Both groups	1	113	0	112	0.009 (-0.015 to 0.033)
Gallagher et al,[22] 2012	52 wk	Both groups	0	196	0	33	0.000 (-0.024 to 0.024)
Subtotal							0.003 (-0.006 to 0.011) $I^2 = 0.0\%$, $P = .56$
Institutionalized							
Lips et al, [illegible] 1996	3-3.5 y	None	223	1068	251	1036	-0.022 (-0.052 to 0.008)
Krieg et al,[42] 1999	2 y	Active intervention	21	103	26	98	-0.040 (-0.138 to 0.057)
Chapuy et al,[19] 2002	2 y	Active intervention	71	322	45	145	-0.056 (-0.128 to 0.015)
Subtotal							-0.028 (-0.055 to -0.002) $I^2 = 0.0\%$, $P = .67$

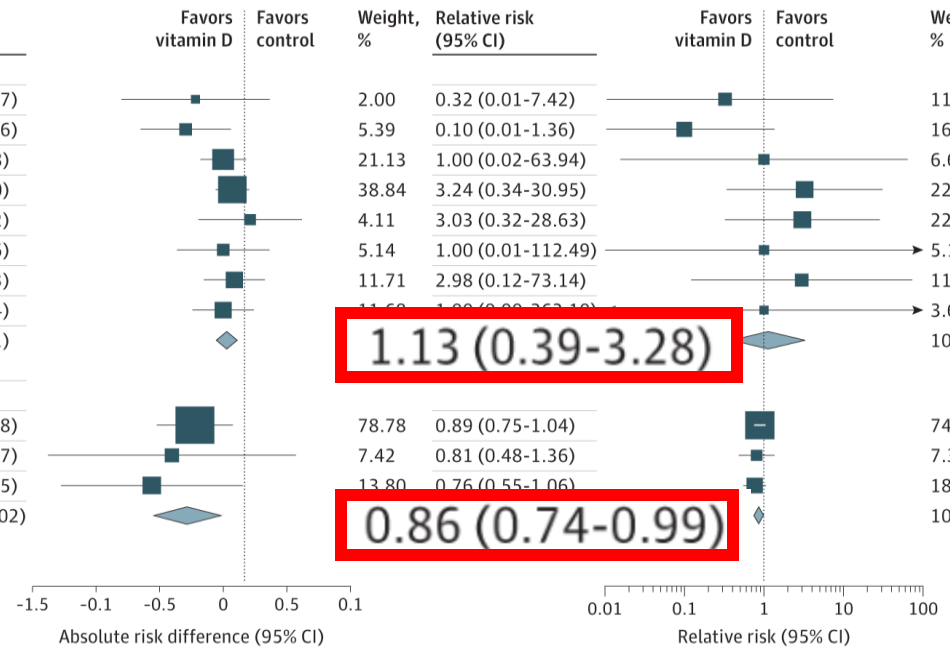
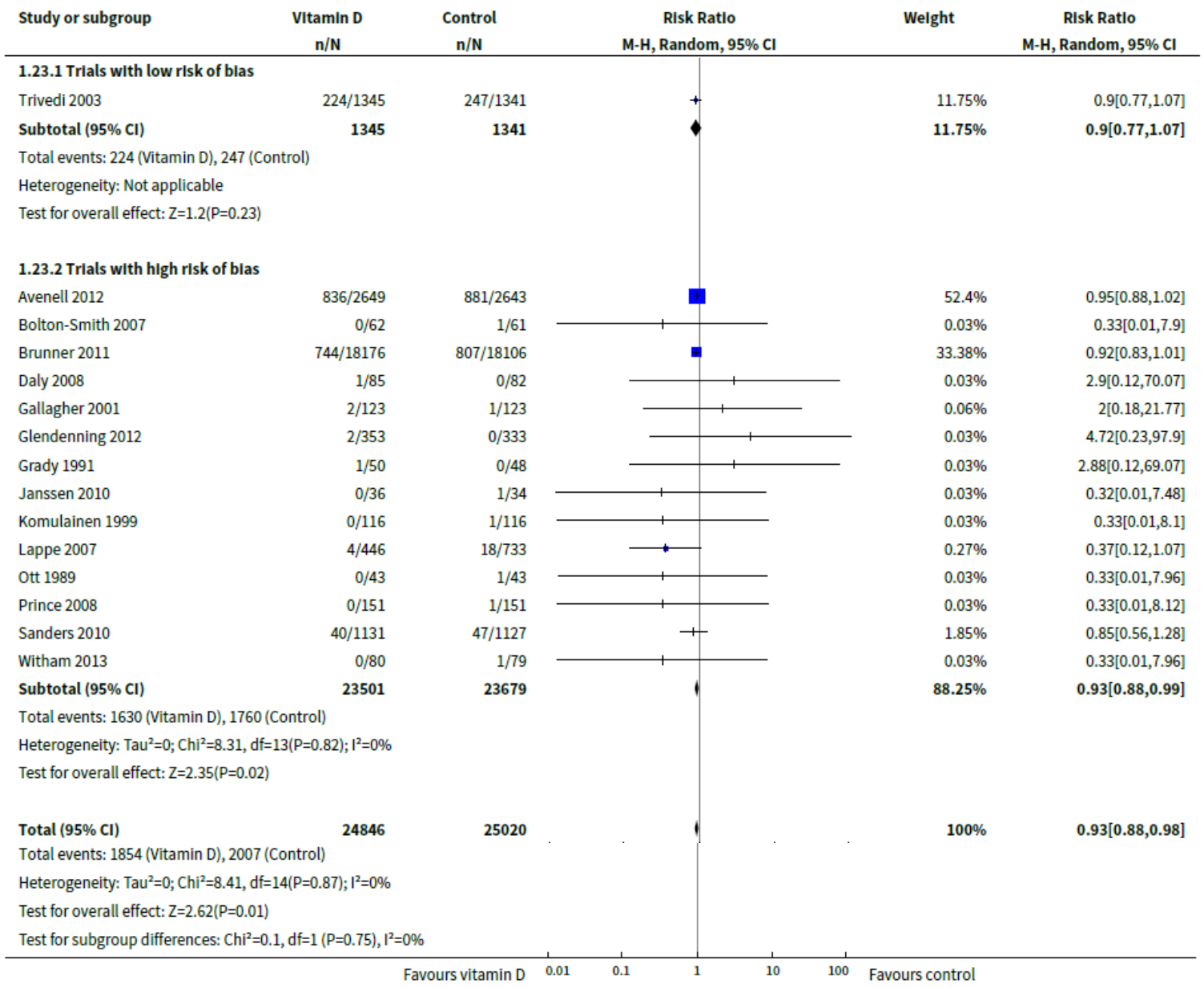


Figure Legend:

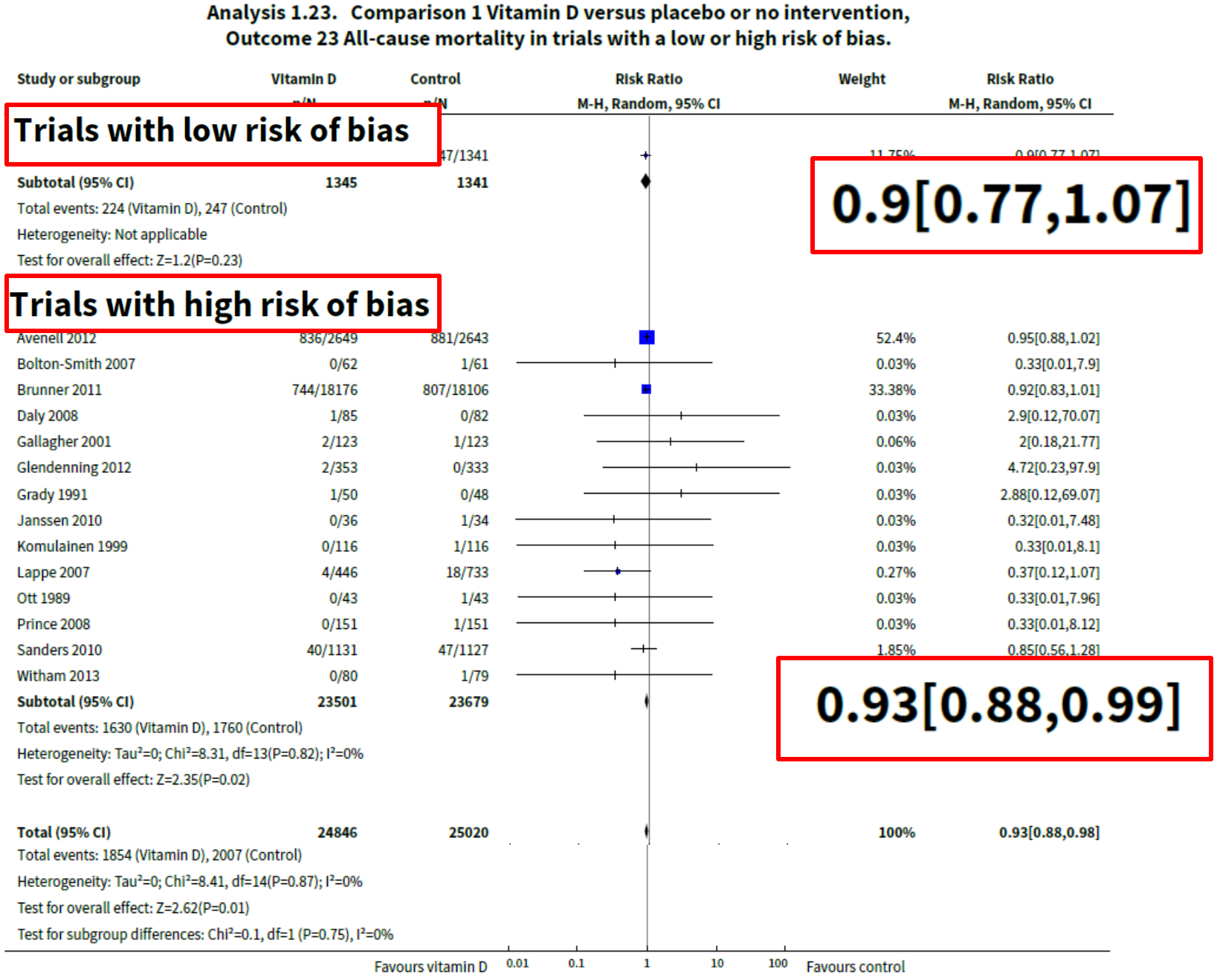
Effect of Vitamin D Treatment on Mortality Stratified by SettingSize of each data marker indicates the weight of the study in the analysis. Weights are from random-effects analysis. To calculate the absolute risk difference in percentage points, multiply value by 100 (eg, 0.009 multiplied by 100 = 0.9 percentage points).

Analysis 1.23. Comparison 1 Vitamin D versus placebo or no intervention, Outcome 23 All-cause mortality in trials with a low or high risk of bias.



Effect on community-dwelling or intitutionalized asymptomatic populations- mortality

Bjelakovic, Cochrane Rev Database 2014



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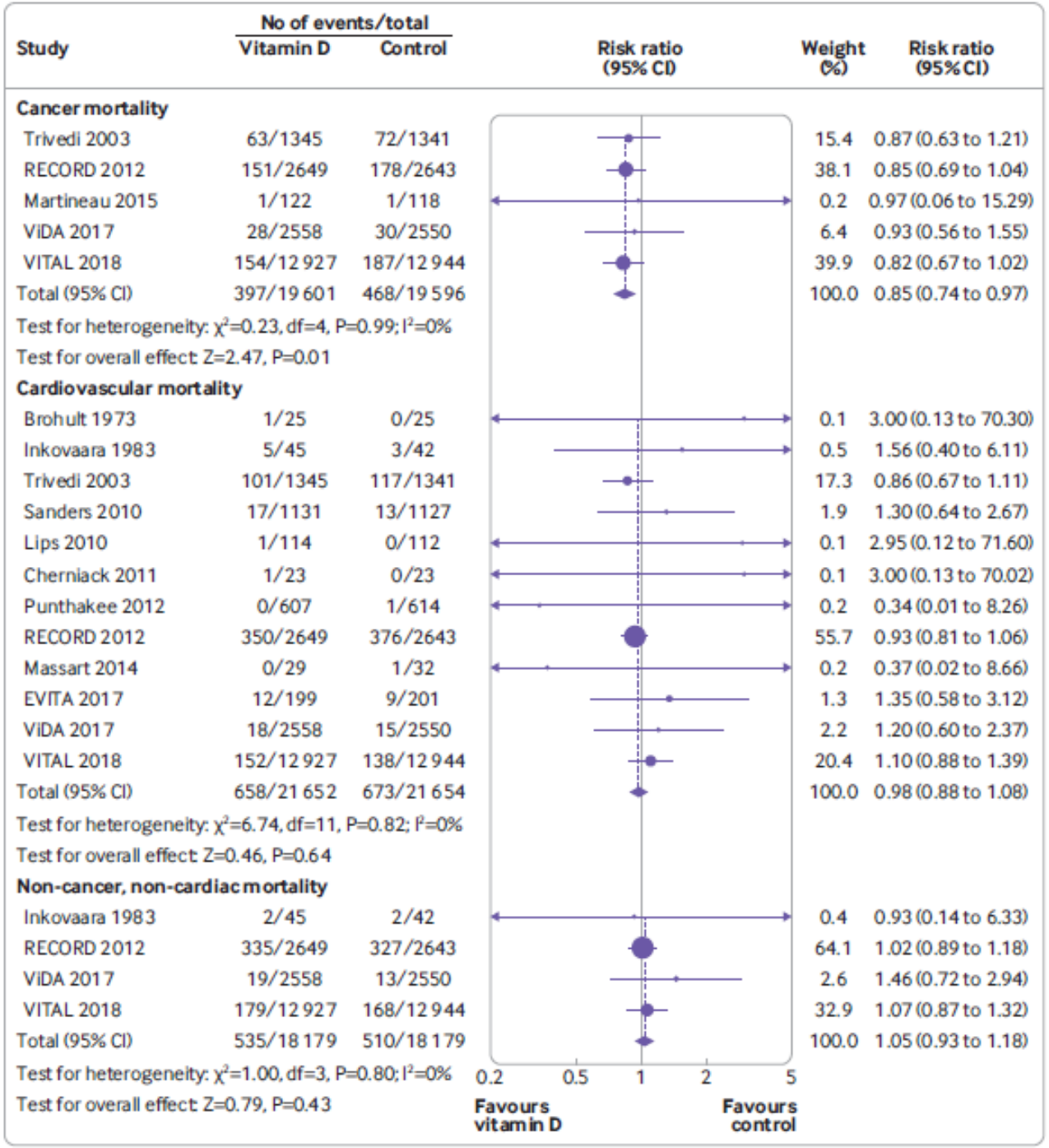
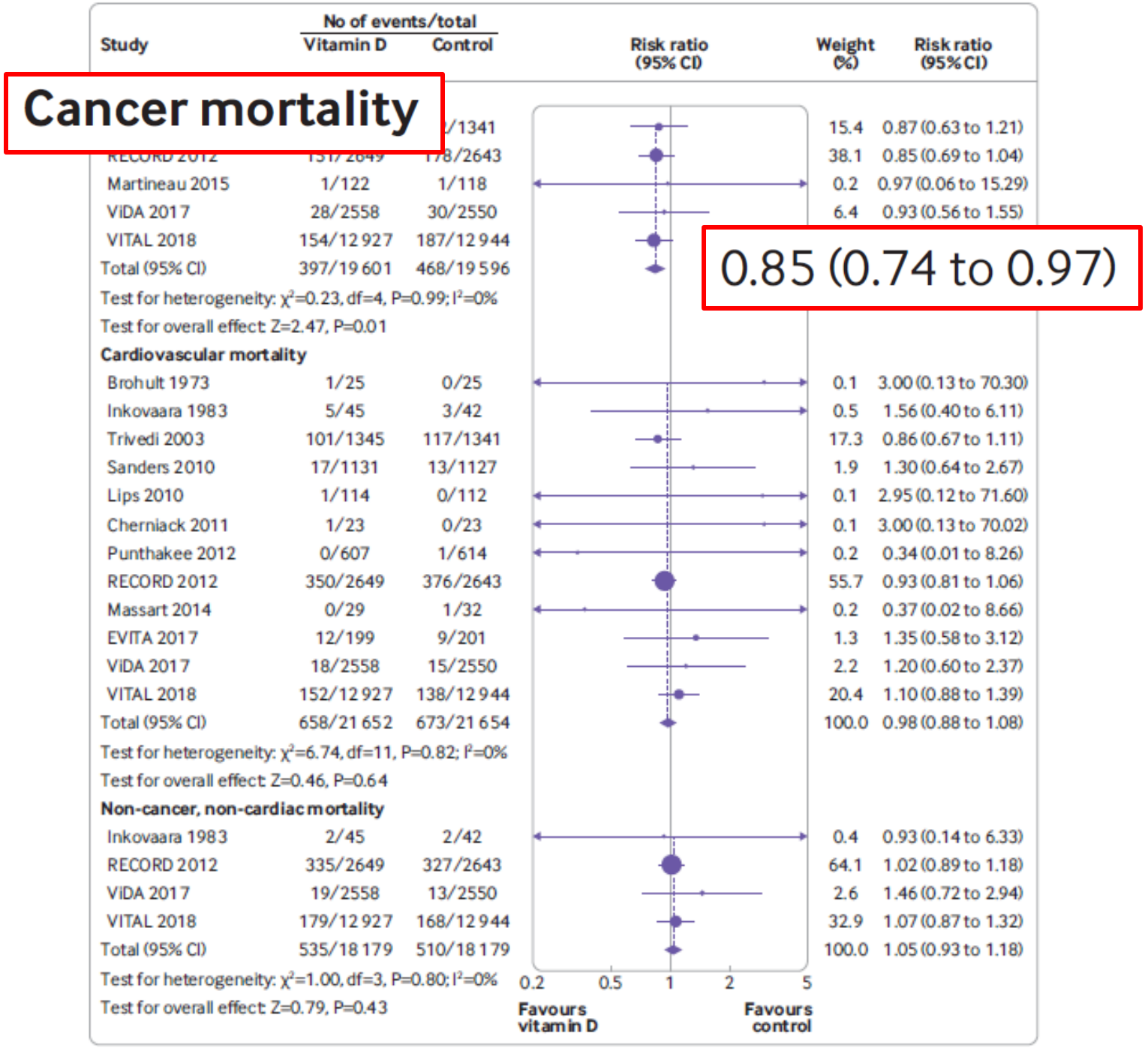


Mortality by cause (cancer, CV, else)

Zhang, BMJ 2019

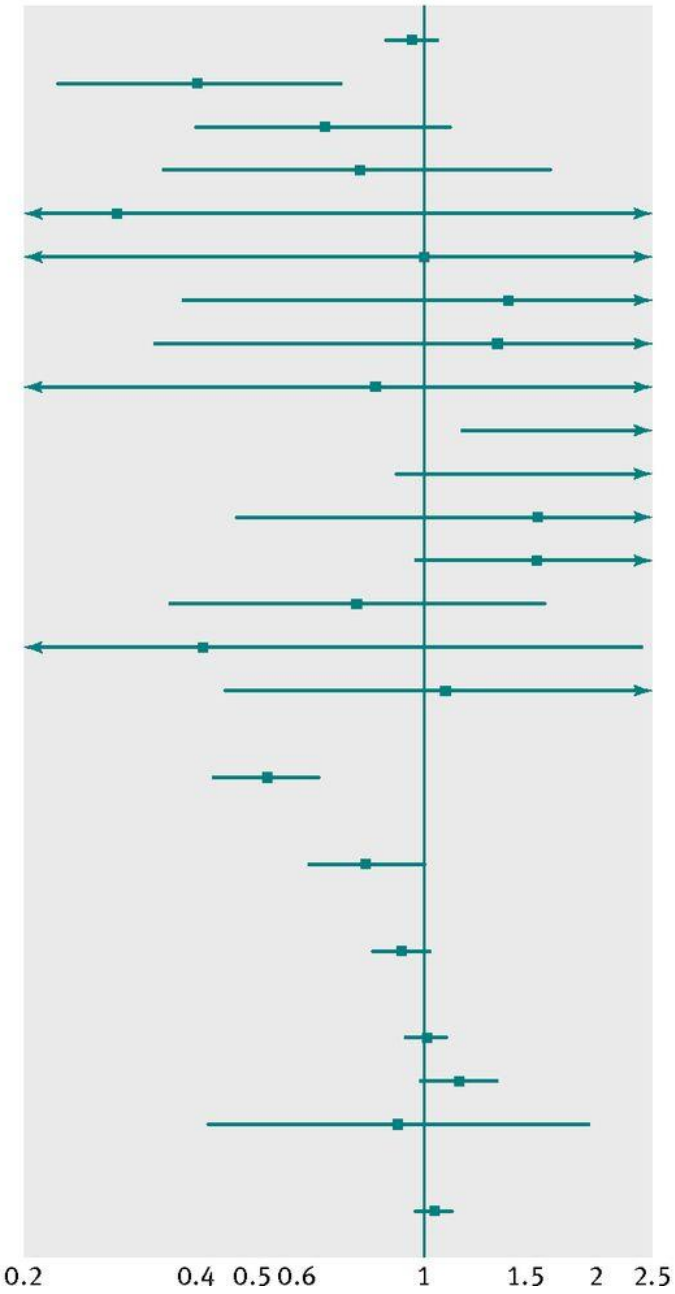


Mortality by cause (cancer, CV, else)

Zhang, BMJ 2019

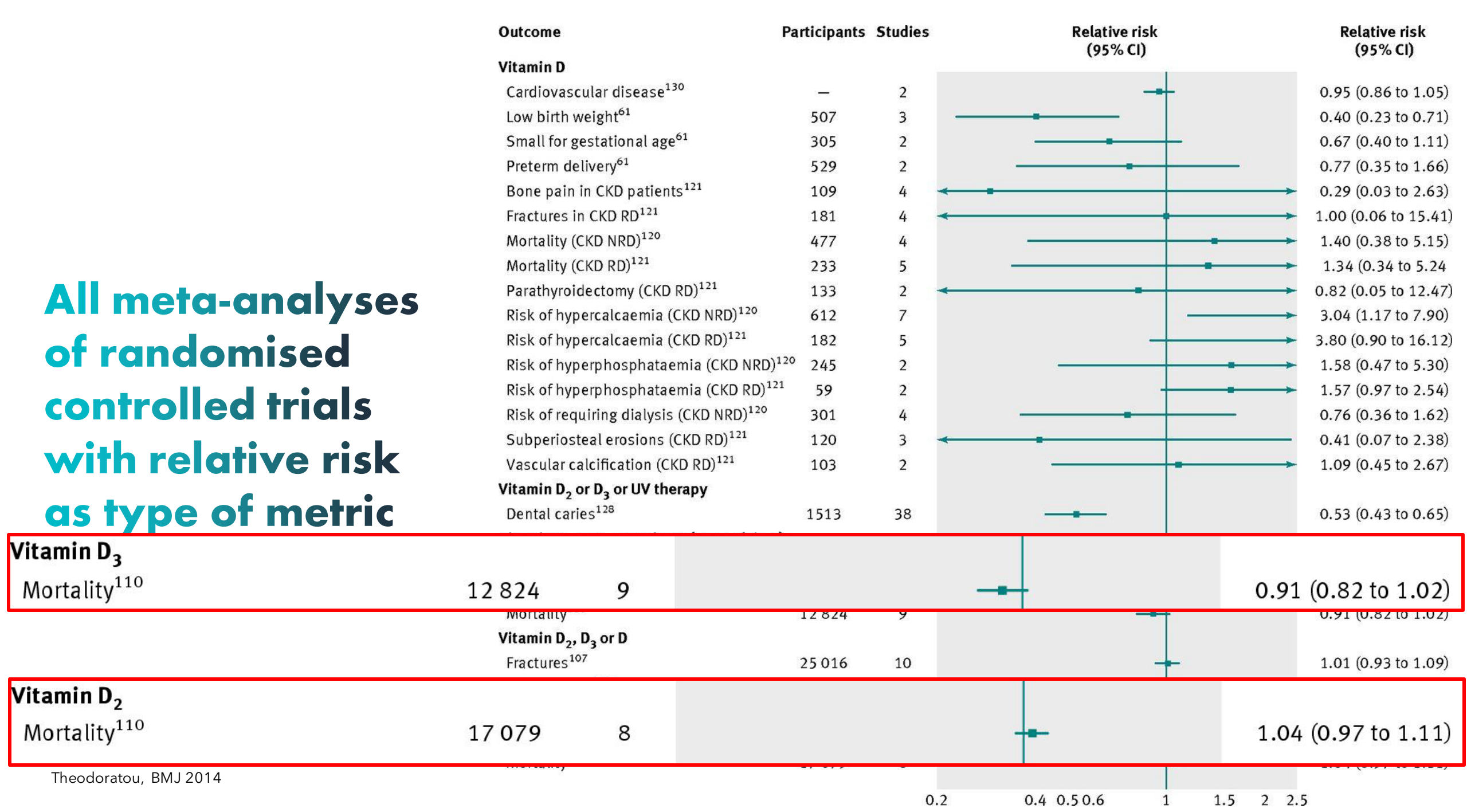
All meta-analyses of randomised controlled trials with relative risk as type of metric

Outcome	Participants	Studies	Relative risk (95% CI)
Vitamin D			
Cardiovascular disease[130]	—	2	0.95 (0.86 to 1.05)
Low birth weight[61]	507	3	0.40 (0.23 to 0.71)
Small for gestational age[61]	305	2	0.67 (0.40 to 1.11)
Preterm delivery[61]	529	2	0.77 (0.35 to 1.66)
Bone pain in CKD patients[121]	109	4	0.29 (0.03 to 2.63)
Fractures in CKD RD[121]	181	4	1.00 (0.06 to 15.41)
Mortality (CKD NRD)[120]	477	4	1.40 (0.38 to 5.15)
Mortality (CKD RD)[121]	233	5	1.34 (0.34 to 5.24
Parathyroidectomy (CKD RD)[121]	133	2	0.82 (0.05 to 12.47)
Risk of hypercalcaemia (CKD NRD)[120]	612	7	3.04 (1.17 to 7.90)
Risk of hypercalcaemia (CKD RD)[121]	182	5	3.80 (0.90 to 16.12)
Risk of hyperphosphataemia (CKD NRD)[120]	245	2	1.58 (0.47 to 5.30)
Risk of hyperphosphataemia (CKD RD)[121]	59	2	1.57 (0.97 to 2.54)
Risk of requiring dialysis (CKD NRD)[120]	301	4	0.76 (0.36 to 1.62)
Subperiosteal erosions (CKD RD)[121]	120	3	0.41 (0.07 to 2.38)
Vascular calcification (CKD RD)[121]	103	2	1.09 (0.45 to 2.67)
Vitamin D_2 or D_3 or UV therapy			
Dental caries[128]	1513	38	0.53 (0.43 to 0.65)
Vitamin D_2 or D_3 or active D (or + calcium)			
Non-vertebral fractures[5]	7130	5	0.79 (0.63 to 0.99)
Vitamin D_3			
Mortality[110]	12 824	9	0.91 (0.82 to 1.02)
Vitamin D_2, D_3 or D			
Fractures[107]	25 016	10	1.01 (0.93 to 1.09)
Hip fractures[107]	24 749	9	1.15 (0.99 to 1.33)
Vertebral fractures[107]	9138	5	0.90 (0.42 to 1.92)
Vitamin D_2			
Mortality[110]	17 079	8	1.04 (0.97 to 1.11)



Theodoratou, BMJ 2014

All meta-analyses of randomised controlled trials with relative risk as type of metric



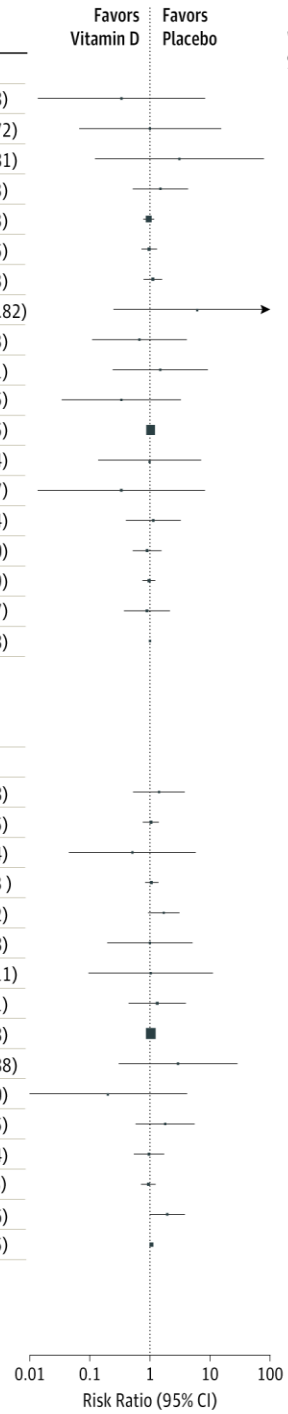
Theodoratou, BMJ 2014

CV outcomes

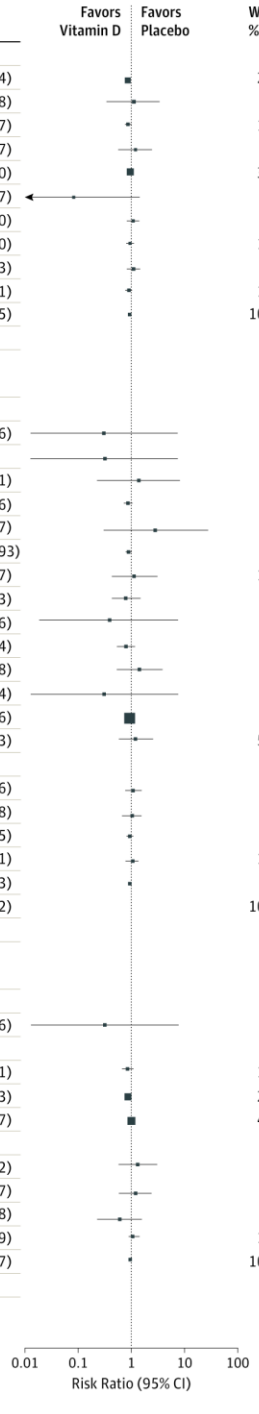
(MACE, All-cause mortality, CV death , cerebrovascular accident, myocardial infarction)

Barbarawi, JAMA Cardiol 2019

Study or Subgroup	Vitamin D Events	Vitamin D Total	Placebo Events	Placebo Total	Risk Ratio (95% CI)	Weight, %
Myocardial infarction						
Ott et al,[23] 1989	0	43	1	43	0.33 (0.01-7.08)	0.1
Aloia et al,[25] 1988	1	17	1	17	1.00 (0.07-14.72)	0.1
Komulainen et al,[29] 1999	1	112	0	115	3.08 (0.13-74.81)	0.1
Gallagher et al,[34] 2001	9	245	6	244	1.49 (0.54-4.13)	0.5
Trivedi et al,[35] 2003	224	1345	233	1341	0.96 (0.81-1.13)	19.8
Grant et al,[32] 2005	114	2649	117	2643	0.97 (0.78-1.25)	8.7
Berggren et al,[28] 2007	47	102	40	97	1.12 (0.81-1.53)	5.5
Zhu et al,[22] 2008	1	39	0	81	8.15 (0.28-147.82)	0.1
Prince et al,[20] 2008	2	151	3	161	0.67 (0.11-3.93)	0.2
Sanders et al,[24] 2010	3	1131	2	1125	1.49 (0.25-8.91)	0.2
Lehouck et al,[31] 2012	1	81	3	91	0.33 (0.04-3.15)	0.1
Jackson et al,[27] 2006	659	18176	637	18106	1.03 (0.33-1.15)	48.4
Witham et al,[21] 2013	2	80	2	79	0.99 (0.14-8.84)	0.1
Wang et al,[26] 2014	0	30	1	30	0.33 (0.01-7.87)	0.1
Baron et al,[19] 2015	8	1130	7	1129	1.14 (0.42-3.14)	0.5
Scragg et al,[16] 2017	28	2558	31	2550	0.90 (0.64-1.50)	2.1
Manson et al,[13] 2018	169	12927	176	12944	0.96 (0.78-1.19)	12.6
Shoji et al,[14] 2018	10	488	11	478	0.89 (0.38-2.07)	0.8
Subtotal (95% CI)		41314		41262	1.00 (0.93-1.08)	100.0
Total events	1279		1271			
Heterogeneity: $\tau^2 = 0.00$, $\chi^2_{17} = 6.07$, $P = .99$, $I^2 = 0\%$						
Test for overall effect: $z = 0.10$ ($P = .92$)						
Cerebrovascular accident						
Gallagher et al,[34] 2001	10	245	7	244	1.42 (0.55-3.68)	0.7
Trivedi et al,[35] 2003	105	1345	101	1341	1.04 (0.60-1.35)	9.1
Brazier et al,[33] 2006	1	95	2	97	0.51 (0.05-5.54)	0.1
Grant et al,[32] 2005	160	2649	149	2643	1.07 (0.88-1.33)	13.4
Berggren et al,[28] 2007	27	102	15	97	1.71 (0.97-3.02)	2.0
Prince et al,[20] 2008	3	151	3	151	1.00 (0.21-4.88)	0.3
Zhu et al,[22] 2008	1	39	2	81	1.04 (0.10-11.11)	0.1
Sanders et al,[24] 2010	8	1131	6	1125	1.33 (0.48-3.81)	0.6
Jackson et al,[27] 2006	690	18176	659	18106	1.04 (0.94-1.18)	57.3
Witham et al,[21] 2013	3	80	1	79	2.96 (0.31-27.88)	0.1
Wang et al,[26] 2014	0	30	2	30	0.20 (0.01-4.00)	0.1
Baron et al,[19] 2015	9	1130	5	1129	1.80 (0.60-5.35)	0.5
Scragg et al,[16] 2017	26	2558	27	2550	0.96 (0.56-1.54)	2.2
Manson et al,[13] 2018	141	12927	149	12944	0.95 (0.75-1.18)	12.0
Shoji et al,[14] 2018	28	488	14	476	1.96 (1.04-3.86)	1.6
Subtotal (95% CI)		41146		41093	1.06 (0.98-1.15)	100.0
Total events		1212	1142			
Heterogeneity: $\tau^2 = 0.00$, $\chi^2_{14} = 11.35$, $P = .86$, $I^2 = 0\%$						
Test for overall effect: $z = 1.41$ ($P = .16$)						



Study or Subgroup	Vitamin D Events	Vitamin D Total	Placebo Events	Placebo Total	Risk Ratio (95% CI)	Weight, %
MACE						
Trivedi et al,[35] 2003	477	1345	503	1341	0.95 (0.86-1.04)	21.2
Brazier et al,[33] 2005	6	95	5	97	1.23 (0.39-3.88)	0.2
Grant et al,[32] 2005	339	2649	363	2643	0.93 (0.81-1.07)	12.5
Sanders et al,[24] 2010	17	1131	13	1125	1.30 (0.63-2.67)	0.5
Jackson et al,[27] 2006	1405	18176	1363	18106	1.03 (0.96-1.10)	33.9
Wang et al, [26] 2014	0	30	5	30	0.09 (0.01-1.57)	0.0
Zitterman et al, [15] 2017	85	199	73	201	1.18 (0.92-1.50)	4.4
Scragg et al,[16] 2017	303	2558	293	2550	1.03 (0.89-1.20)	10.6
Shoji et al,[14] 2018	103	488	85	476	1.18 (0.91-1.53)	3.9
Manson et al,[13] 2018	396	12927	409	12944	0.97 (0.85-1.11)	12.8
Subtotal (95% CI)		39598		39513	1.00 (0.95-1.05)	100.0
Total events	3131		3112			
Heterogeneity: $\tau^2 = 0.00$, $\chi^2_9 = 10.07$, $P = .35$, $I^2 = 8\%$						
Test for overall effect: $z = 0.18$, $P = .93$						
All-cause mortality						
Ott et al,[23] 1989	0	43	1	43	0.33 (0.01-7.96)	0.0
Aloia et al,[25] 1988	0	17	0	17	Not estimable	
Komulainen et al,[29] 1999	0	112	1	115	0.34 (0.01-8.31)	0.0
Gallagher et al,[34] 2001	3	245	2	244	1.49 (0.25-8.86)	0.1
Trivedi et al,[35] 2003	224	1345	247	1341	0.90 (0.77-1.07)	7.8
Brazier et al,[33] 2005	3	95	1	97	3.09 (0.32-28.93)	0.0
Grant et al, [32] 2005	438	2649	460	2643	0.95 (0.84-1.07)	14.8
Schleithoff et al,[30] 2006	7	61	6	62	1.19 (0.42-3.33)	0.2
Berggren et al,[28] 2007	16	102	18	97	0.85 (0.46-1.56)	0.6
Zhu et al,[22] 2008	0	39	2	81	0.41 (0.02-8.34)	0.0
Sanders et al,[24] 2010	40	1131	47	1125	0.85 (0.56-1.28)	1.2
Lehouck et al,[31] 2012	9	91	6	91	1.50 (0.56-4.04)	0.2
Witham et al,[21] 2013	0	80	1	79	0.33 (0.01-7.96)	0.0
Jackson et al,[27] 2006	1775	18176	1823	18106	0.97 (0.91-1.03)	54.8
Wang et al,[26] 2014	0	30	0	30	Not estimable	
Baron et al,[19] 2015	15	1130	12	1129	1.25 (0.59-2.66)	0.4
Scragg et al,[16] 2017	85	5658	58	2550	1.12 (0.79-1.58)	1.7
Zitterman et al,[15] 2017	39	199	36	201	1.09 (0.73-1.65)	1.3
Manson et al,[13] 2018	485	12927	493	12944	0.99 (0.87-1.11)	14.0
Shoji et al,[14] 2018	89	488	80	476	1.09 (0.82-1.43)	2.8
Subtotal (95% CI)		41518		41541	0.97 (0.93-1.02)	100.0
Total events		3208		3294		
Heterogeneity: $\tau^2 = 0.00$, $\chi^2_7 = 7.25$, $P = 0.98$, $I^2 = 0\%$						
Test for overall effect: $z = 1.19$ ($P = .23$)						
Cardiovascular death						
Ott et al,[23] 1889	0	43	1	43	0.33 (0.01-7.06)	0.1
Aloia et al,[25] 1988	0	17	0	17	Not estimable	
Trivedi et al,[35] 2003	101	1345	117	1341	0.86 (0.87-1.11)	10.6
Grant et al,[32] 2005	256	2648	291	2643	0.80 (0.75-1.03)	26.5
Jackson et al,[27] 2006	549	18178	525	18106	1.04 (0.93-1.17)	46.6
Wang et al,[26] 2014	0	30	0	30	Not estimable	
Zitterman et al,[15] 2017	12	199	9	201	1.35 (0.58-3.12)	1.0
Scragg et al,[16] 2017	18	2558	15	2550	1.20 (0.50-2.37)	1.5
Shoji et al,[14] 2018	7	488	11	476	0.82 (0.24-1.58)	0.8
Manson et al,[13] 2018	152	12927	138	12944	1.10 (0.88-1.39)	13.0
Subtotal (95% CI)		38432		38351	0.98 (0.90-1.07)	100.0
Total events	1095		1107			
Heterogeneity: $\tau^2 = 0.00$, $\chi^2_3 = 7.11$, $P = .42$, $I^2 = 2\%$						
Test for overall effect: $z = 0.41$ ($P = .68$)						



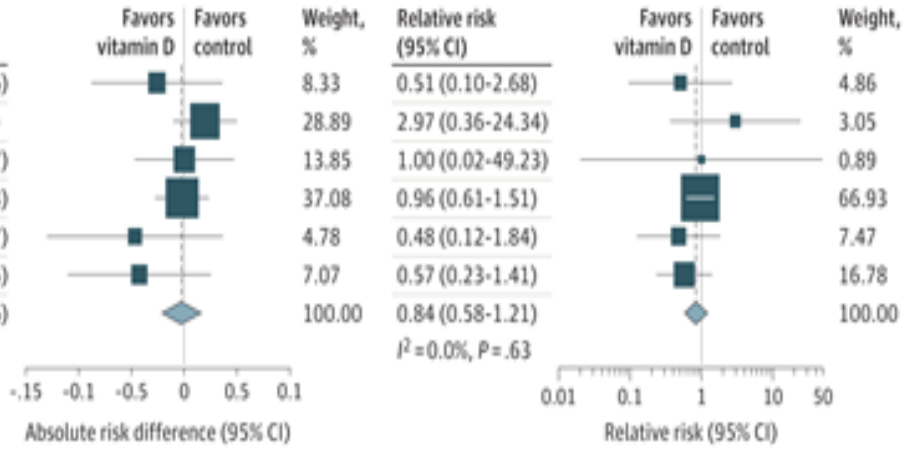
JAMA Network™

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

JAMA. 2021;325(14):1443-1463. doi:10.1001/jama.2020.26498

Effect on community-dwelling, asymptomatic populations- any fractures

Source	Treatment duration	Fracture type	Calcium received	Vitamin D: No. with fracture	Vitamin D: No. without fracture	Control: No. with fracture	Control: No. without fracture	Absolute risk difference (95% CI)	Weight, %	Relative risk (95% CI)	Weight, %
Hansen et al,[26] 2015	52 wk	Undefined	None	2	73	4	72	-0.026 (-0.088 to 0.036)	8.33	0.51 (0.10-2.68)	4.86
Hin et al,[27] 2017	52 wk	Undefined	None	6	198	1	100	0.020 (-0.011 to 0.050)	28.89	2.97 (0.36-24.34)	3.05
Bislev et al,[17] 2019	12 wk	Undefined	None	0	40	0	41	-0.000 (-0.047 to 0.047)	13.85	1.00 (0.02-49.23)	0.89
Khaw et al,[54] 2017	3.3 y	Nonvertebral	None	34	578	38	620	-0.002 (-0.028 to 0.023)	37.08	0.96 (0.61-1.51)	66.93
Pfeifer et al,[52] 2000	1 y	Any	Both groups	3	67	6	61	-0.047 (-0.130 to 0.037)	4.78	0.48 (0.12-1.84)	7.47
Pfeifer et al,[51] 2009	1.75 y	Any	Both groups	7	115	12	108	-0.043 (-0.110 to 0.025)	7.07	0.57 (0.23-1.41)	16.78
Overall								-0.003 (-0.021 to 0.016)	100.00	0.84 (0.58-1.21)	100.00
								I^2 = 13.0%, P = .33		I^2 = 0.0%, P = .63	



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Hansen et al,[26] 2015	52 wk	Undefined	None	2	73	4	72	-0.026 (-0.088 to 0.036)
Hin et al,[27] 2017	52 wk	Undefined	None	6	198	1	100	0.020 (-0.011 to 0.050)
Bislev et al,[17] 2019	12 wk	Undefined	None	0	40	0	41	-0.000 (-0.047 to 0.047)
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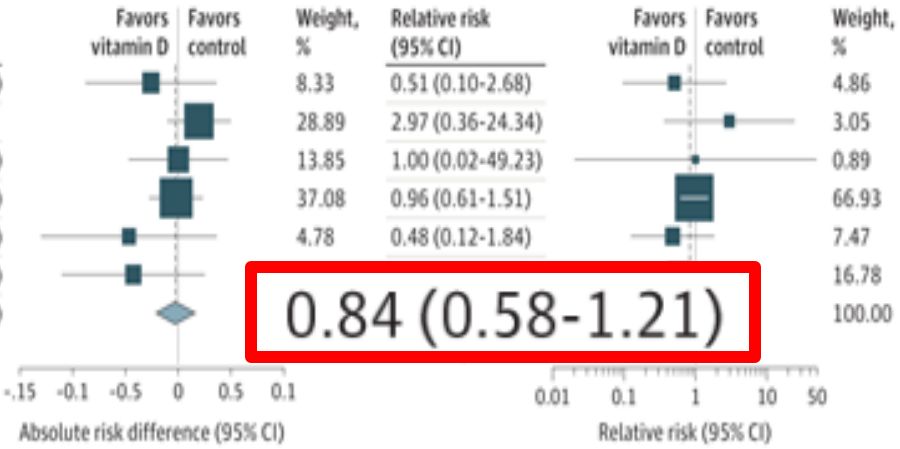
Overall								-0.003 (-0.021 to 0.016)
								I^2 = 13.0%, P = .33



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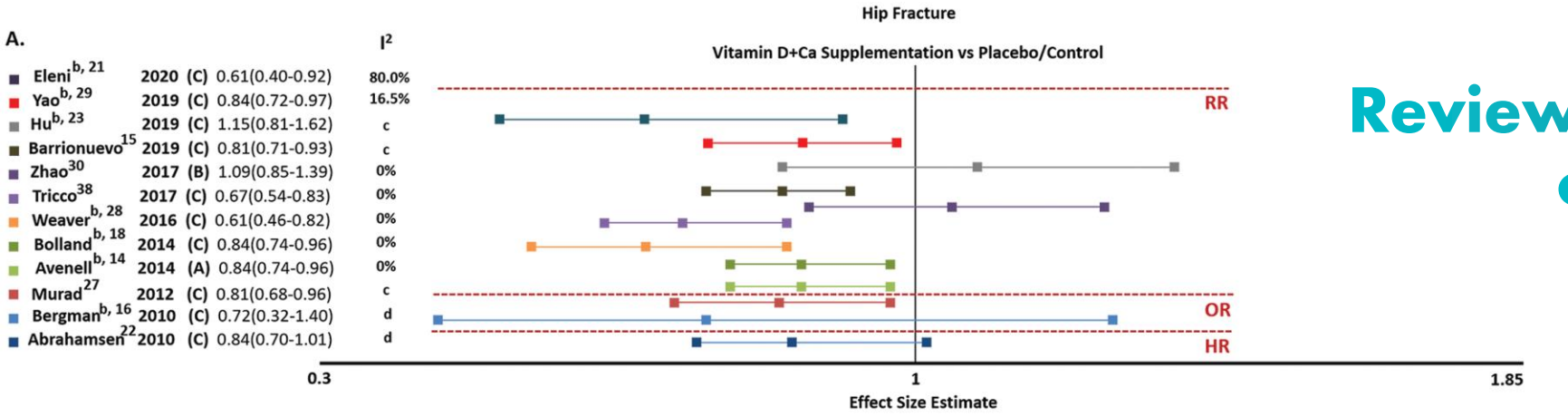
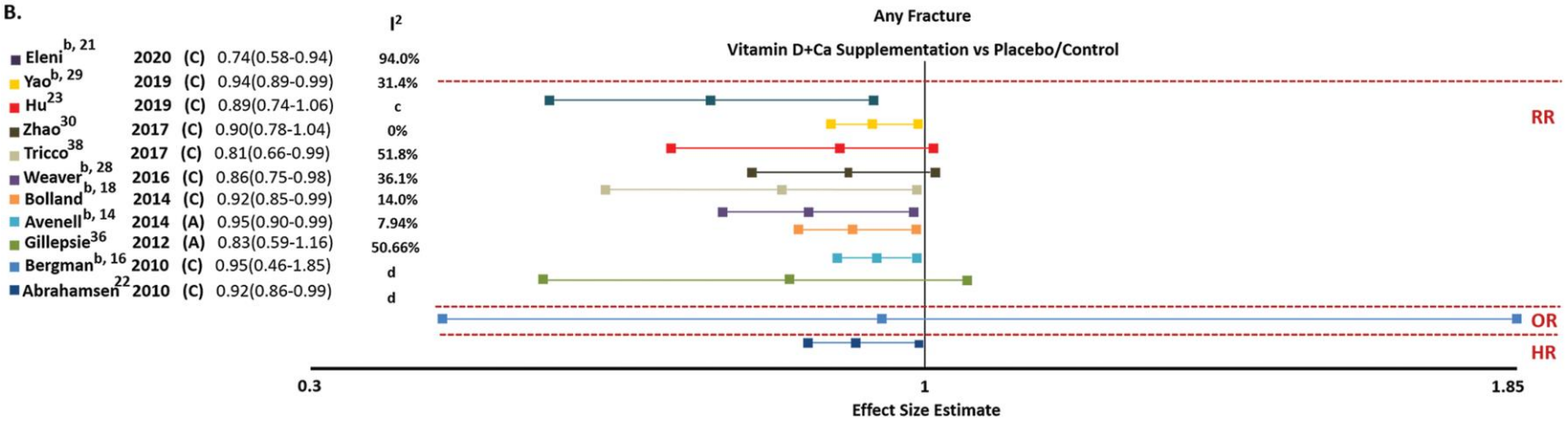
Review of meta analyses of RCTs on fracture prevention





Quality Assessment Using the AMSTAR-2 Tool: (A)-Moderate Quality; (B)-Low Quality; (C)-Critically Low Quality

a: Abbreviations: RR: Risk Ratio, OR: Odds Ratio, HR: Hazard Ratio

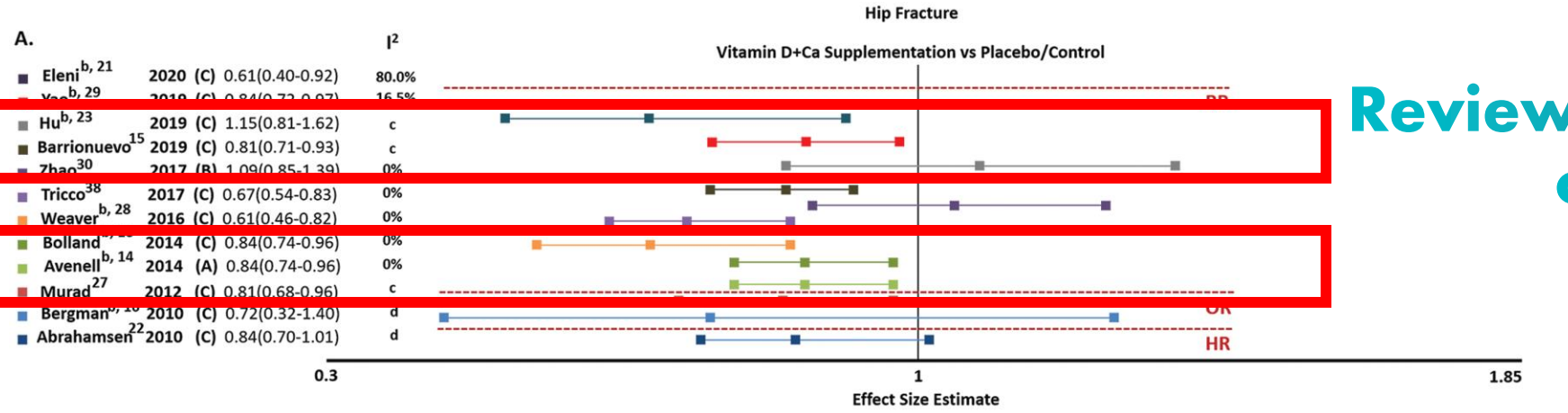
b: Meta-Analysis including institutionalized trials

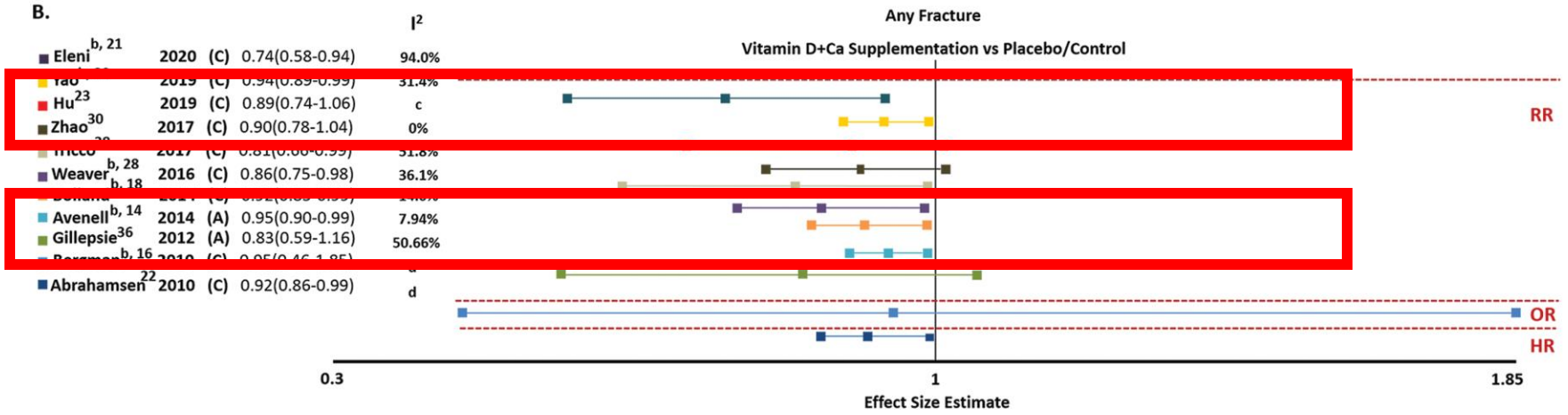
c: Network Meta-Analysis

d: Not available

Chaktoura, J Endocrinol Metabol 2022

Review of meta analyses of RCTs on fracture prevention





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a: Abbreviations: RR: Risk Ratio, OR: Odds Ratio, HR: Hazard Ratio
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d: Not available

Fracture risk reduction is possibly driven by effect on institunionalized individuals

Chaktoura, J Endocrinol Metabol 2022

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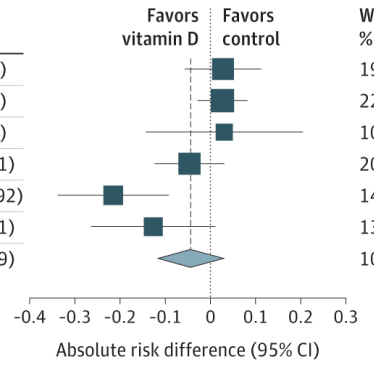
JAMA. 2021;325(14):1443-1463. doi:10.1001/jama.2020.26498

Effect on community-dwelling, asymptomatic populations- falls (incidence of falls)

Source	Treatment duration	Calcium received	Vitamin D No. with event	Vitamin D No. without event	Control No. with event	Control No. without event	Absolute risk difference (95% CI)
Hin et al,[27] 2017	1 y	None	34	170	14	87	0.028 (-0.057 to 0.113)
Khaw et al,[54] 2017	3.3 y	None	307	295	316	338	0.027 (-0.029 to 0.082)
Shea et al,[57] 2019	1 y	None	14	35	13	38	0.031 (-0.143 to 0.205)
Kärkkäinen et al,[39] 2010	3 y	Active intervention	179	108	205	101	-0.046 (-0.123 to 0.031)
Pfeifer et al,[51] 2009	1.75 y	Both groups	49	72	75	46	-0.215 (-0.338 to -0.092)
Pfeifer et al,[52] 2000	1 y	Both groups	11	59	19	48	-0.126 (-0.264 to 0.011)
Subtotal							-0.043 (-0.116 to 0.029)
							I^2 = 70.1%, P = .005



Weight, %	Relative risk (95% CI)
19.09	1.20 (0.68-2.14)
22.45	1.06 (0.94-1.18)
10.34	1.12 (0.59-2.14)
20.00	0.93 (0.83-1.05)
14.78	0.65 (0.51-0.84)
13.35	0.55 (0.29-1.08)
100.0	0.90 (0.75-1.08)
	I^2 = 66.8%, P = .01

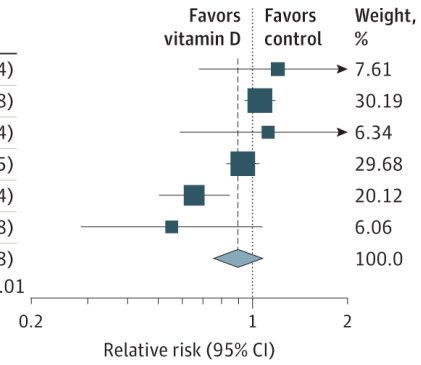


Figure Legend:

Effect of Vitamin D Treatment on Mortality Stratified by SettingSize of each data marker indicates the weight of the study in the analysis. Weights are from random-effects analysis. To calculate the absolute risk difference in percentage points, multiply value by 100 (eg, 0.009 multiplied by 100 = 0.9 percentage points).

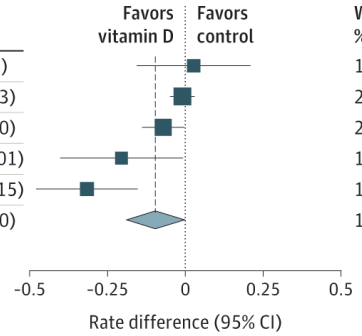
JAMA Network™

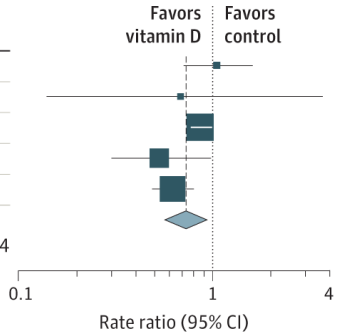
From: **Screening for Vitamin D Deficiency in Adults: Updated Evidence Report and Systematic Review for the US Preventive Services Task Force**

JAMA. 2021;325(14):1443-1463. doi:10.1001/jama.2020.26498

Effect on community-dwelling, asymptomatic populations- falls (number of falls)

Source	Treatment duration	Vitamin D: No. of falls	Vitamin D: Person-years	Vitamin D: No. of falls per person-year	Control: No. of falls	Control: Person-years	Control: No. of falls per person-year	Rate difference (95% CI)	Weight, %	Rate ratio (95% CI)	Weight, %
Hansen et al,[26] 2015	52 wk	71	154	.46	33	76	.43	0.03 (-0.16 to 0.21)	14.33	1.06 (0.71-1.62)	11.72
Wood et al,[58] 2012	52 wk	4	193	.02	3	100	.03	-0.01 (-0.05 to 0.03)	29.54	0.69 (0.14-3.70)	1.04
Kärkkäinen et al,[39] 2010	3 y	430	861	.50	524	918	.57	-0.07 (-0.14 to 0.00)	26.83	0.87 (0.77-0.99)	37.10
Pfeifer et al,[52] 2000	1 y	17	70	.24	30	67	.45	-0.20 (-0.40 to -0.01)	13.16	0.54 (0.30-0.98)	17.24
Pfeifer et al,[51] 2009	1.75 y	106	199.5	.53	169	199.5	.85	-0.32 (-0.48 to -0.15)	16.13	0.63 (0.49-0.80)	32.90
Subtotal								-0.10 (-0.19 to 0.00) I^2 = 76.9%, P = .002	100.0	0.76 (0.57-0.94) I^2 = 59.9%, P = .04	100.0





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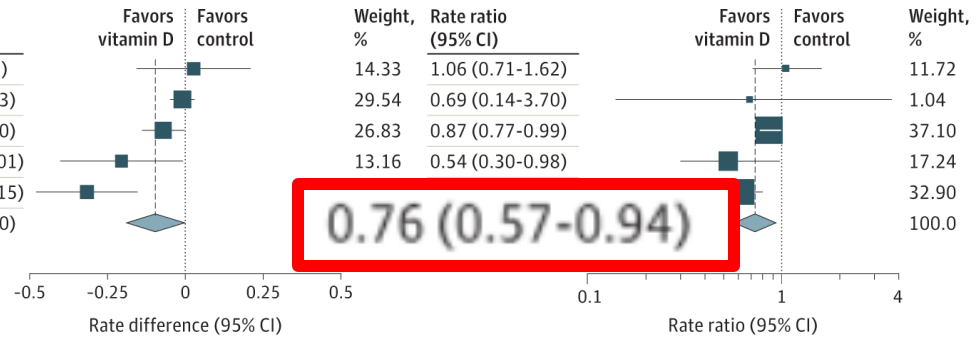

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Table 1. Components of Interventions to Prevent Falls

Intervention Component	Abbreviation
Basic falls risk assessment	bf
Calcium	ca
Cognitive behavioral therapy	cb
Clinic-level quality improvement	cl-qi
Comprehensive podiatry assessment and treatment	cp
Device—alarm	de-al
Device—hip protector	de-hp
Device—orthosis	de-or
Dietary modifcations	di
Environmental assessment and modification	ea
Electromagnetic field therapy and whole-body vibration	em + wb
Exercise	ex
Flooring	fl
Lavender	la
Multifactorial assessment and treatment	mf
Osteoporosis treatment	op-tx
Patient-level quality improvement	pa-qi
Social engagement	so
Surgery—cataract	su-ey
Surgery—hip	su-hi
Surgery—pacemaker	su-pm
Health system-level quality improvement	sy-qi
Usual care	uc
Vision assessment and treatment	va
Vitamin D	vi-d

Fall prevention is a multifactorial task

Tricco, JAMA 2017

Box 2. Interventions Associated With Reduction of Outcome Compared With Usual Care in Network Meta-analysis

Outcomes

Number of Injurious Falls
Exercise

Combined exercise and vision assessment and treatment

Combined exercise, vision assessment and treatment, and environmental assessment and modification

Combined clinic-level quality improvement strategies, multifactorial assessment and treatment, calcium supplementation, and vitamin D supplementation

Number of Fallers
Exercise

Combined exercise, patient-level quality improvement strategies, clinic-level quality improvement strategies, and multifactorial assessment and treatment

Combined exercise, patient-level quality improvement strategies, hip protectors, and environmental assessment and modification

Combined patient-level quality improvement strategies, clinic-level quality improvement strategies, dietary modifications, calcium supplementation, and vitamin D supplementation

Combined orthotics and exercise

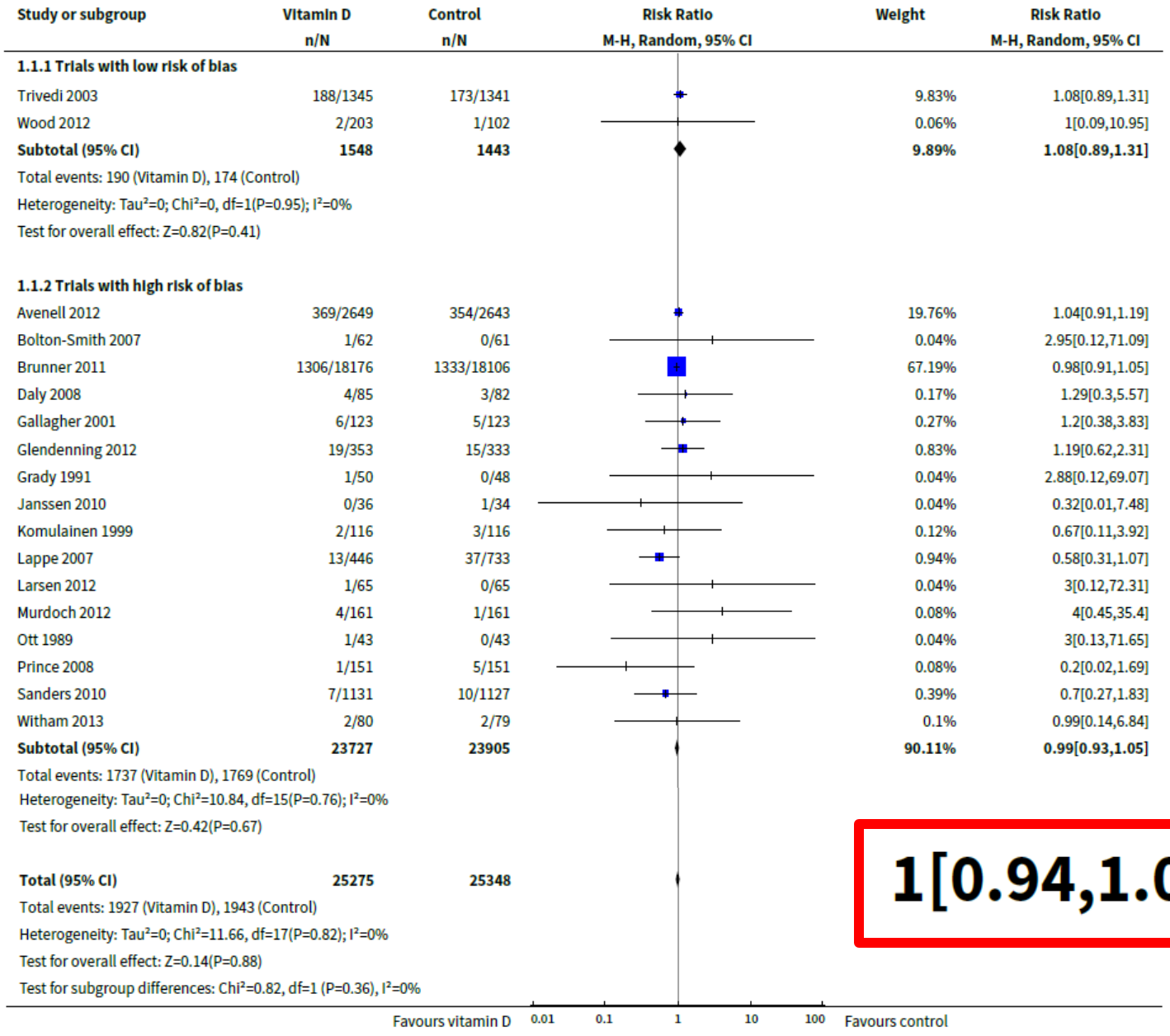
Number of Fractures
Combined osteoporosis treatment, calcium supplementation, and vitamin D supplementation

Number of Hip Fractures
Combined osteoporosis treatment, calcium supplementation, and vitamin D supplementation

Fall prevention is a multifactorial task

Tricco, JAMA 2017

Analysis 1.1. Comparison 1 Vitamin D versus placebo or no intervention, Outcome 1 Cancer occurrence in trials with a low or high risk of bias.



1[0.94,1.06]

Effect on community-dwelling, asymptomatic populations- cancer incidence

Bjelakovic, Cochrane Rev Database 2014

Meta analyses: methodological considerations

Do not preclude effect on patient subgroups (elderly, frail, institutionalized individuals etc)

Overlapping populations

Different inclusion criteria reflect different populations and methods

Outcome definitions and analytic approaches

Chakhtoura, J Clin Endocrinol Metabol 2022, Bolland, Plos One 2014

Vit D supplementation may reduce risk of incident autoimmune disease- The VITAL trial

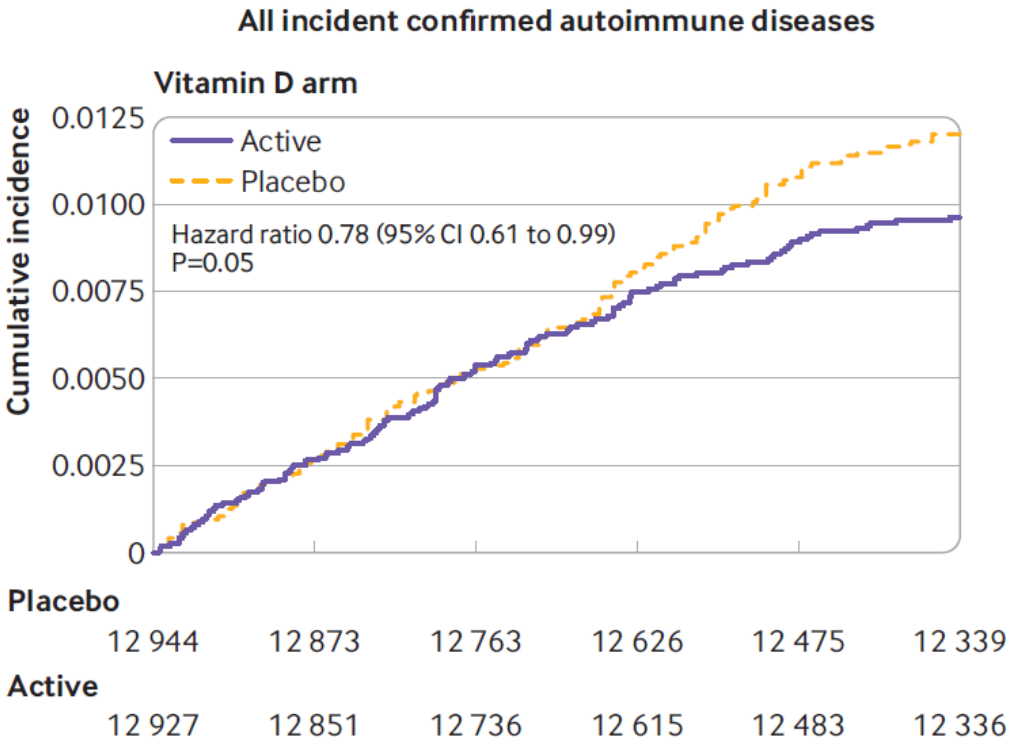


Table 2 | Hazard ratios and 95% confidence intervals for primary and secondary endpoints according to randomized assignment to vitamin D or placebo

Endpoint	Vitamin D group (n=12 927)	Placebo group (n=12 944)	Hazard ratio (95% CI)	P value
Primary endpoint				
Confirmed autoimmune diseases	123	155	0.78 (0.61 to 0.99)	0.05
Secondary endpoints				
Confirmed+probable autoimmune diseases	210	247	0.85 (0.70 to 1.02)	0.09
Analyses excluding all prerandomization autoimmune diseases				
Confirmed autoimmune diseases	102	128	0.79 (0.61 to 1.03)	0.08
Confirmed+probable autoimmune diseases	170	209	0.81 (0.66 to 1.00)	0.05
Analyses excluding first two years of follow-up				
Confirmed autoimmune diseases	54	87	0.61 (0.43 to 0.86)	0.005
Confirmed+probable autoimmune diseases	94	133	0.69 (0.53 to 0.90)	0.007
Individual autoimmune diseases				
Confirmed rheumatoid arthritis	15	24	0.58 (0.30 to 1.13)	0.11
Confirmed+probable rheumatoid arthritis	18	27	0.63 (0.34 to 1.15)	0.13
Confirmed polymyalgia rheumatic*	31	43	0.70 (0.44 to 1.12)	0.14
Confirmed+probable polymyalgia rheumatica	32	43	0.72 (0.46 to 1.15)	0.17
Confirmed autoimmune thyroid disease	21	11	1.63 (0.77 to 3.45)	0.20
Confirmed+probable autoimmune thyroid disease	99	94	1.05 (0.78 to 1.41)	0.74
Confirmed psoriasis†	15	23	0.72 (0.37 to 1.39)	0.32
Confirmed+probable psoriasis	17	25	0.70 (0.37 to 1.32)	0.27
Confirmed other autoimmune disease	40	56	0.74 (0.49 to 1.11)	0.15
Confirmed+probable other autoimmune disease	45	63	0.73 (0.50 to 1.08)	0.12

Analyses were from Cox regression models controlled for age, sex, race, and omega 3 fatty acid randomization group.
*Fourteen participants had confirmed polymyalgia rheumatica without giant cell arteritis, 18 had confirmed giant cell arteritis without polymyalgia rheumatica, and two were confirmed with both.
†No participants had psoriatic arthritis.

Hahn, BMJ 2022

Vit D supplementation may reduce risk of incident autoimmune disease- The VITAL trial

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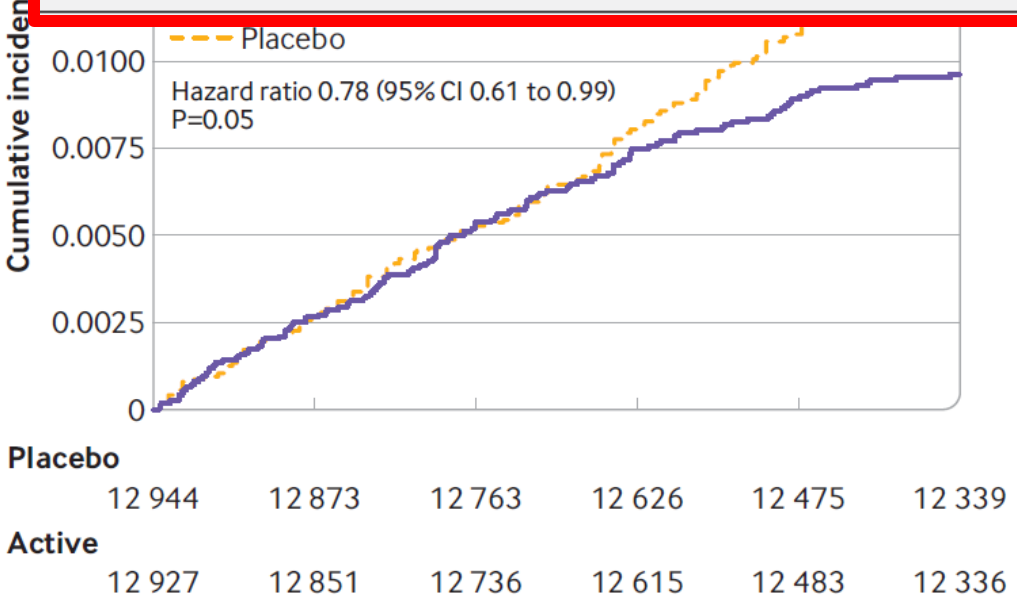

Hahn, BMJ 2022

Summary

All meta-analyses: **reduced** mortality from cancer

Most meta-analyses: **reduced** falls (with Ca)

Probably **reduce** fractures (with Ca)

No effect on extra-skeletal outcomes (cancer incidence, infections, CV disease or death)

Final considerations

Screen individuals at risk (not everyone)

Treat accordingly

Uncertain health benefits beyond musculoskeletal system

Consider outcomes in the long-term: low treatment adherence, unknown long-term benefits and harms


To D or not to D? That is (still) the question...