ALIMENTAZIONE E VITAMINA D
Roma – Hotel Mediterraneo - 9 settembre 2022
II° Modulo formativo
Fabbisogno vitamina D e "decision makers"

Supplementazione con Vitamina D: cosa indica la "EBM"

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Il sottoscritto Agostino Gaudio

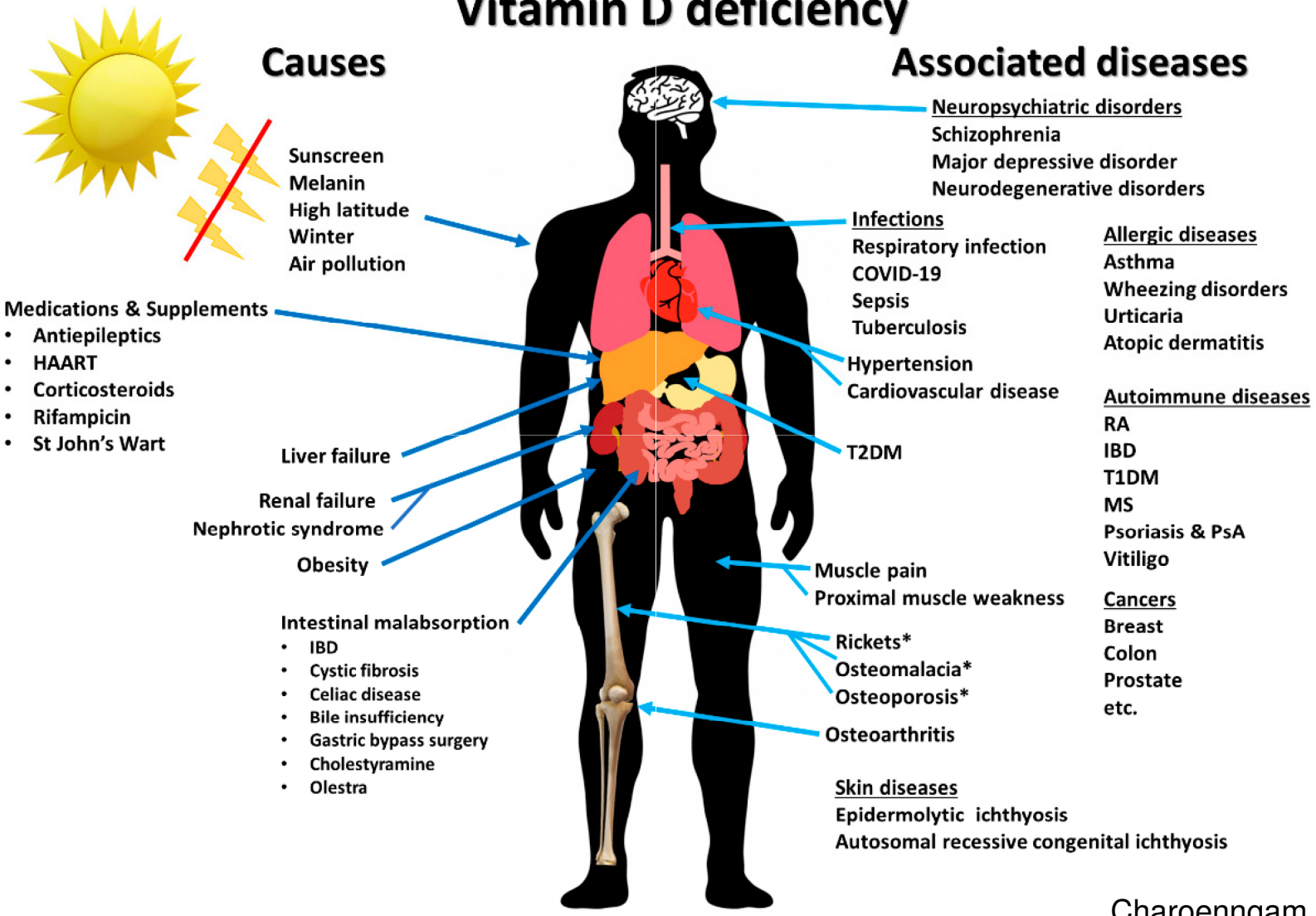
ai sensi dell’art. 76, comma 4 dell’Accordo Stato-Regioni del 2 febbraio 2017 e del paragrafo 4.5. del Manuale nazionale di accreditamento per l'erogazione di eventi ECM

dichiara che

negli ultimi due anni ha avuto i seguenti rapporti con soggetti portatori di interessi commerciali in ambito sanitario

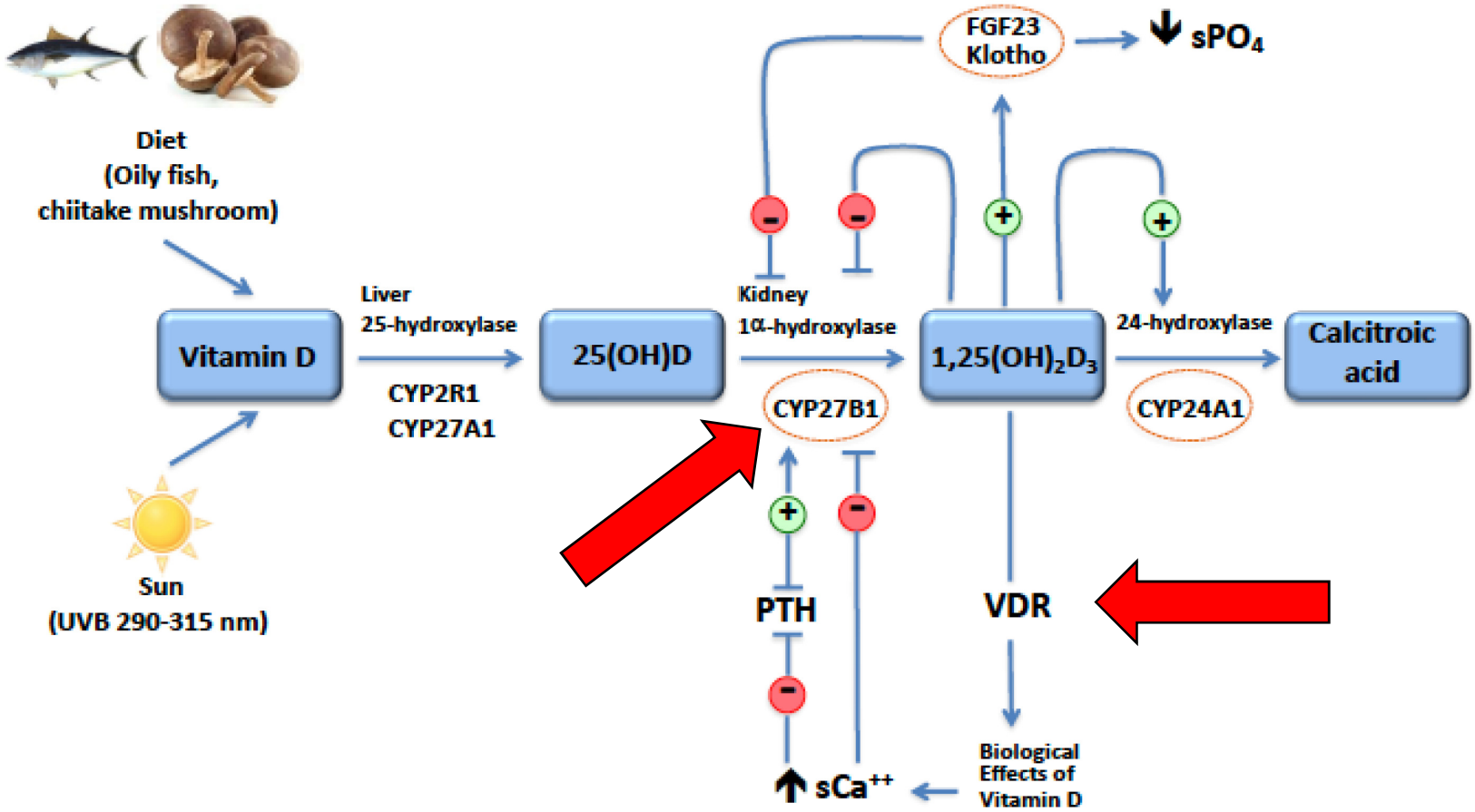
UCB, Theramex, Lilly

Vitamin D deficiency



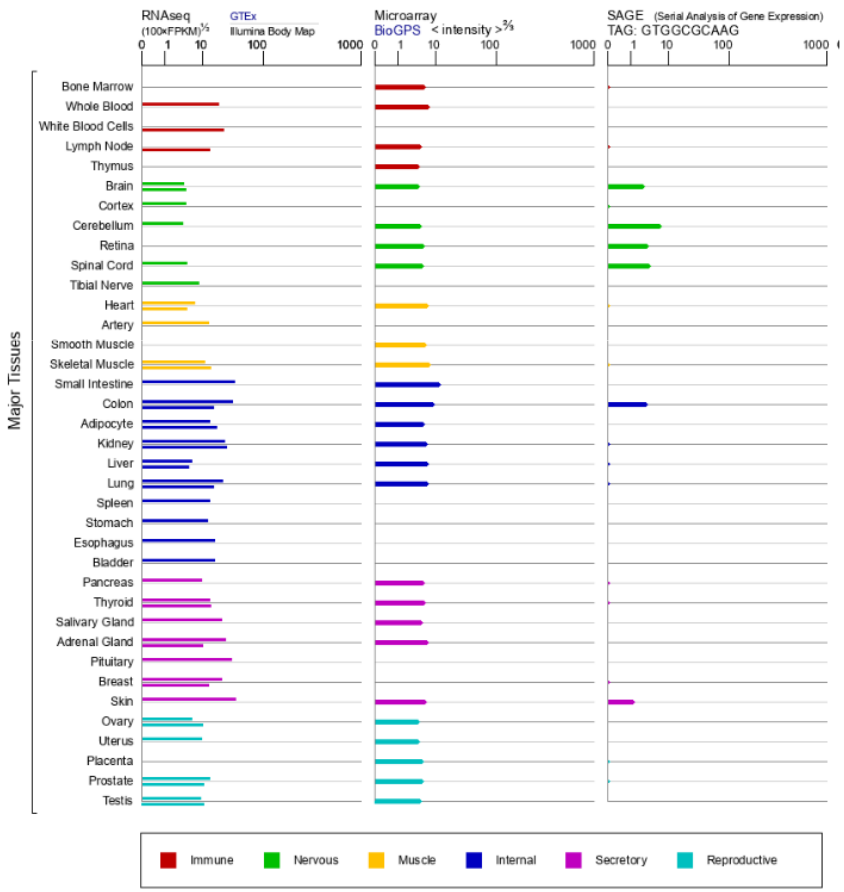
Charoenngam N, et al. Nutrients. 2

Vitamin D : Metabolism and Regulation

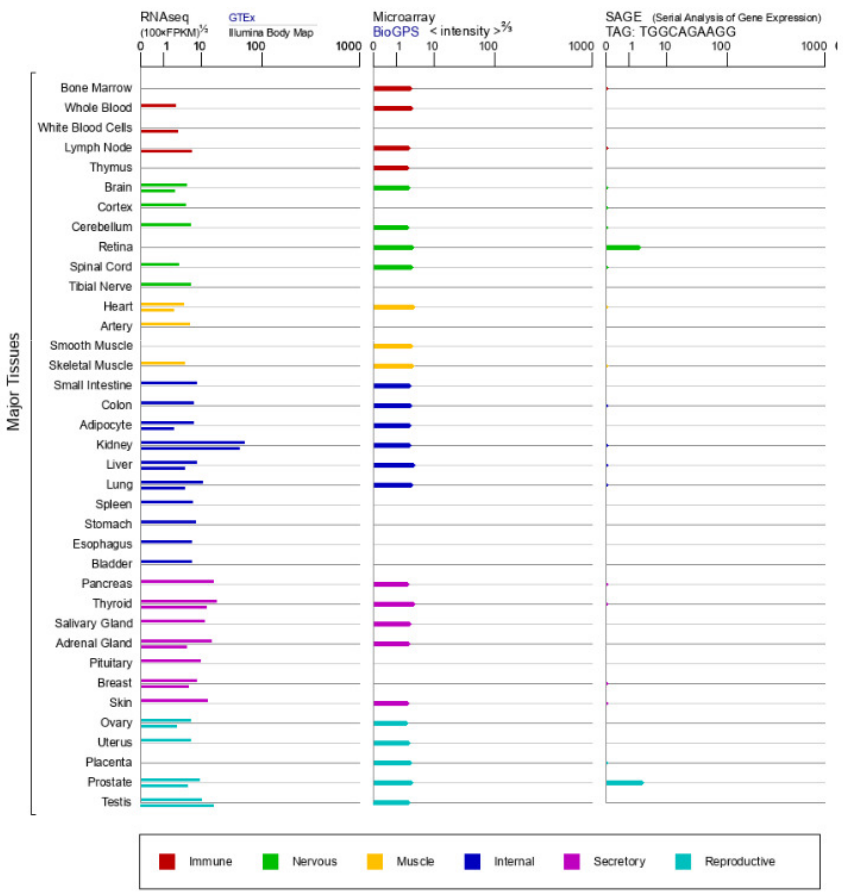


Ureña Torres PA, et al Metabolites. 2

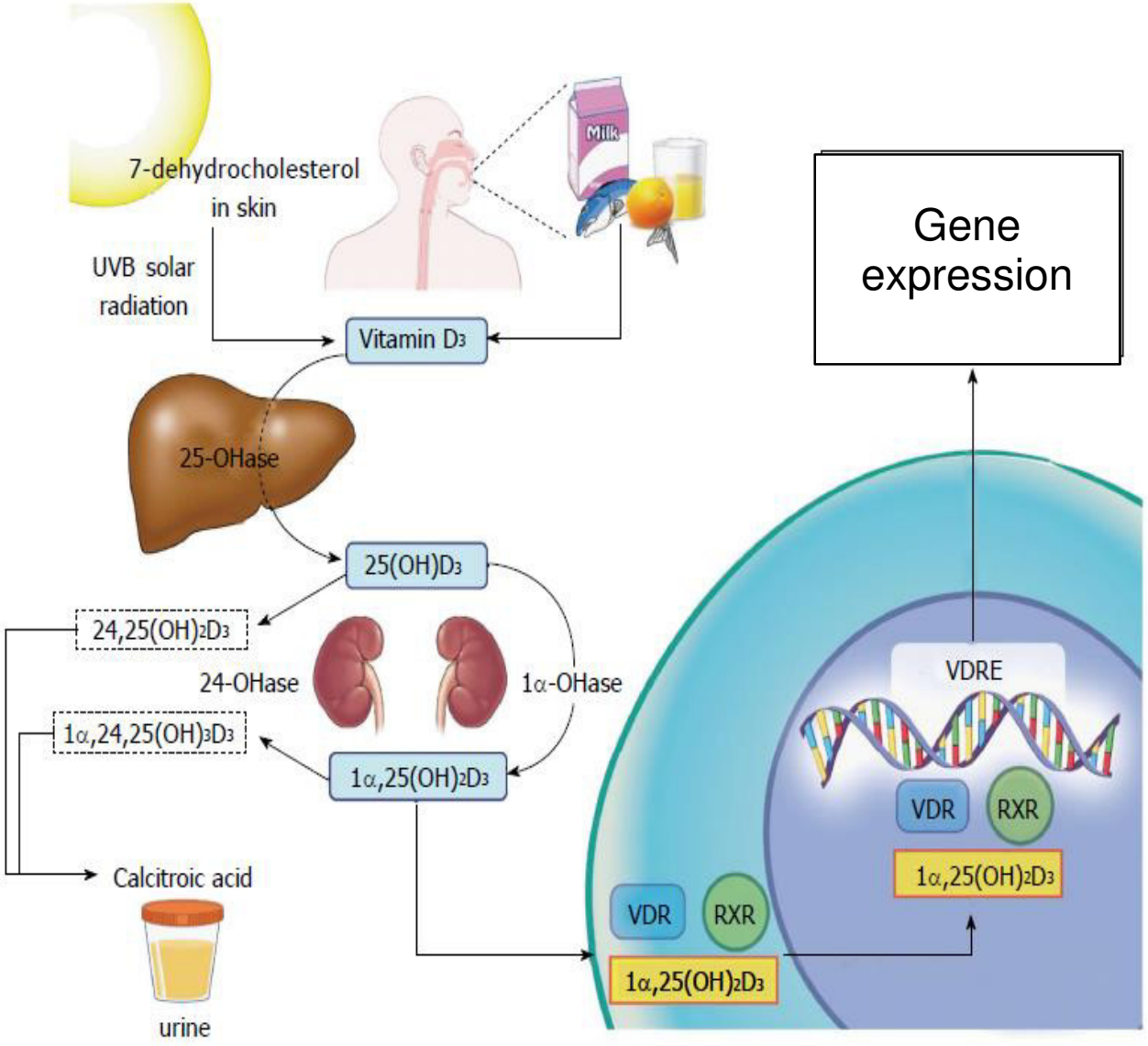
mRNA expression in normal human tissue for VDR gene



mRNA expression in normal human tissue for CYP27B1Gene



https://www.genecards



"~3% of the human and mouse genomes are under the direct o indirect control of 1,25(OH)2D3"

Modified from Rouphael C, et al. World J Gastrointest Oncol. 2

Reviews, guidelines, meta-analyses

Evidence based medicin

Quality of evidence

Table 1 | Overview of the large vitamin D supplementation clinical trials 2017–2020

Study	Country	Number of patients	Age (years, mean ± SD)	Ethnicity[a] (% white ethnicity)	Serum 25OHD (ng/ml)		Duration of follow-up (years)	Intervention (vitamin D vs placebo)	Primary outcome(s)
					Baseline	Final[b]			
VITAL[c]	USA	25,874	67 ± 7	71	30.8 ± 10	42 ± 10	5.3	2,000 IU per day	Cancer and cardiovascular disease
ViDA	New Zealand	5,110	66 ± 8	83	26.5 ± 9[d]	54 ± 16	3.3	One dose of 200,000 IU and 100,000 IU per month	Cardiovascular events and mortality
D2d	USA	2,423	60 ± 10	67	28.0 ± 10.2	54 ± 15	2.5	4,000 IU per day	T2DM
DO-HEALTH	Europe	2,157	74.9 ± 4.4	NM	22.4 ± 8.4	37.6 ± 11.3	3	2,000 IU per day[e]	Six health outcomes[f]
Calgary	Canada	373	62 ± 4	94	31 ± 8	80 ± 16[g]	3	400, 4,000 or 10,000 IU per day	BMD

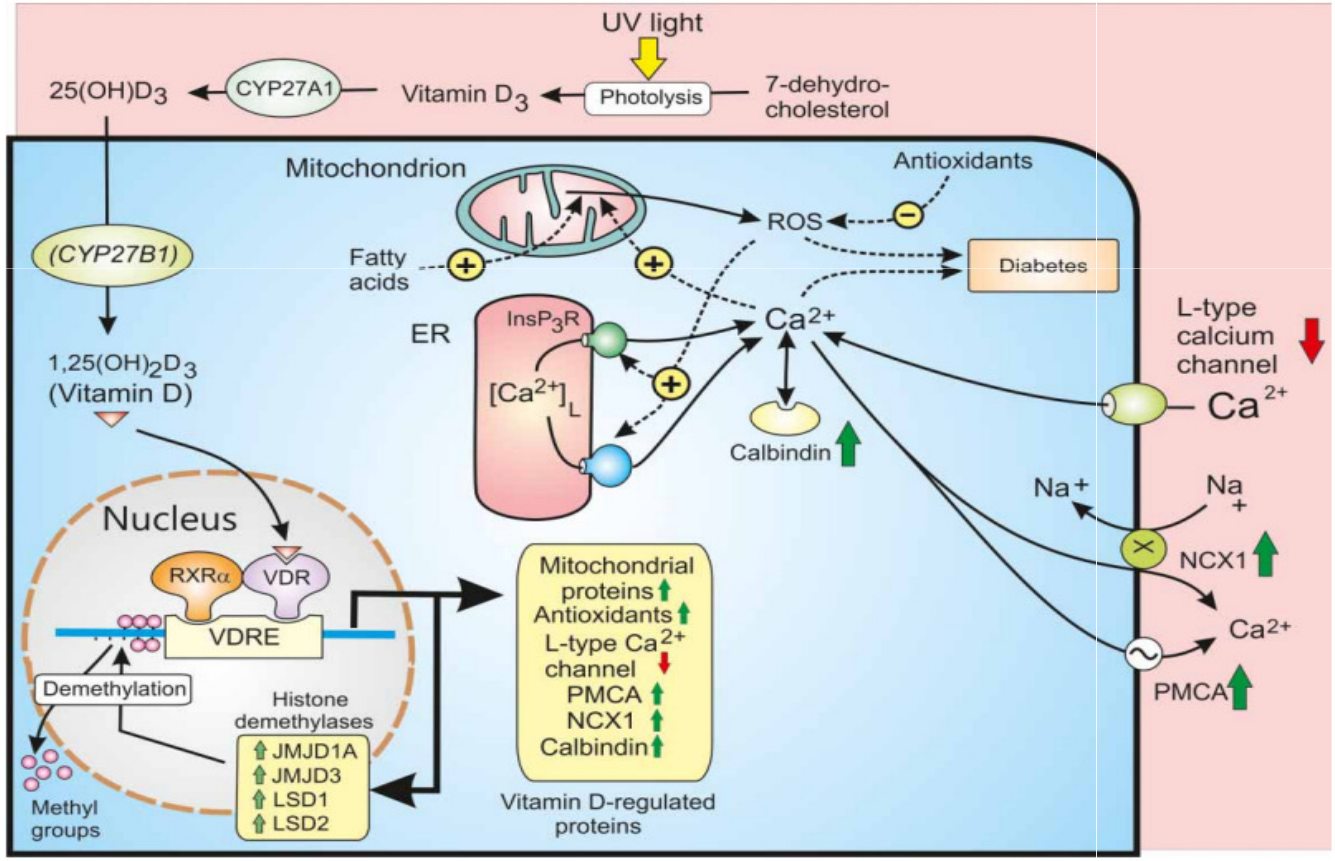
DO-Health outcomes: Systolic and diastolic blood pressure, physical and cognitive performance, non-vertebral fractures and infections

Bouillon R, et al. Nat Rev Endocrinol. 202

Effects of Vitamin D supplementation in:

- T2DM
- Cancer
- Cardiovascular disease
- Bone disease

Vitamin D and Type 2 Diabetes Mellitus



The onset of diabetes is associated with increased levels of both Ca2+ and ROS, which are normally regulated by Vitamin D, which acts to maintain low resting levels of both Ca2+ and ROS. Vitamin D increases expression of antioxidants that reduce levels of ROS, and it maintains low Ca2+ levels by increasing expression of the plasma membrane Ca2+-ATPase (PMCA) and the NCX1, which extrude Ca2+, and the Ca2+ buffer calbindin.

Berridge MJ. Biochem J. 2017

The Vitamin D and Type 2 Diabetes (D2d) trial was conducted to test whether vitamin D supplementation (4000 UI/die) reduces the risk of type 2 diabetes among adults at high risk for the disorder.

Participants met at least two of three glycemic criteria for prediabetes as defined by the 2010 American Diabetes Association (ADA) guidelines:

- fasting plasma glucose level, 100 to 125 mg/dl;
- plasma glucose level 2 hours after a 75-g oral glucose load, 140 to 199 mg/dl;
- and glycated hemoglobin level, 5.7 to 6.4%.

Exclusion criteria were any glycemic criterion in the diabetes range, factors affecting the glycated hemoglobin level, use of diabetes or weight-loss medications, or use of supplements containing vitamin D at a dose of more than 1000 IU per day or calcium at a dose of more than 600 mg per day.

Pittas AG, et al. N Engl J Med. 20

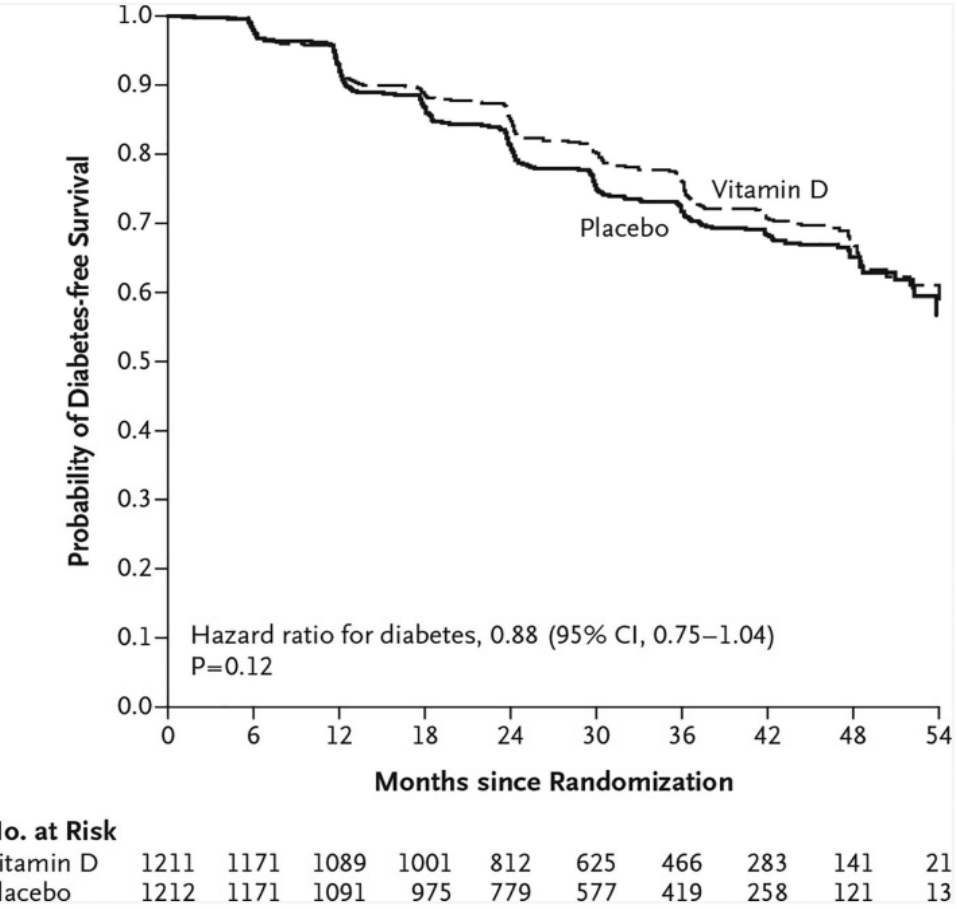
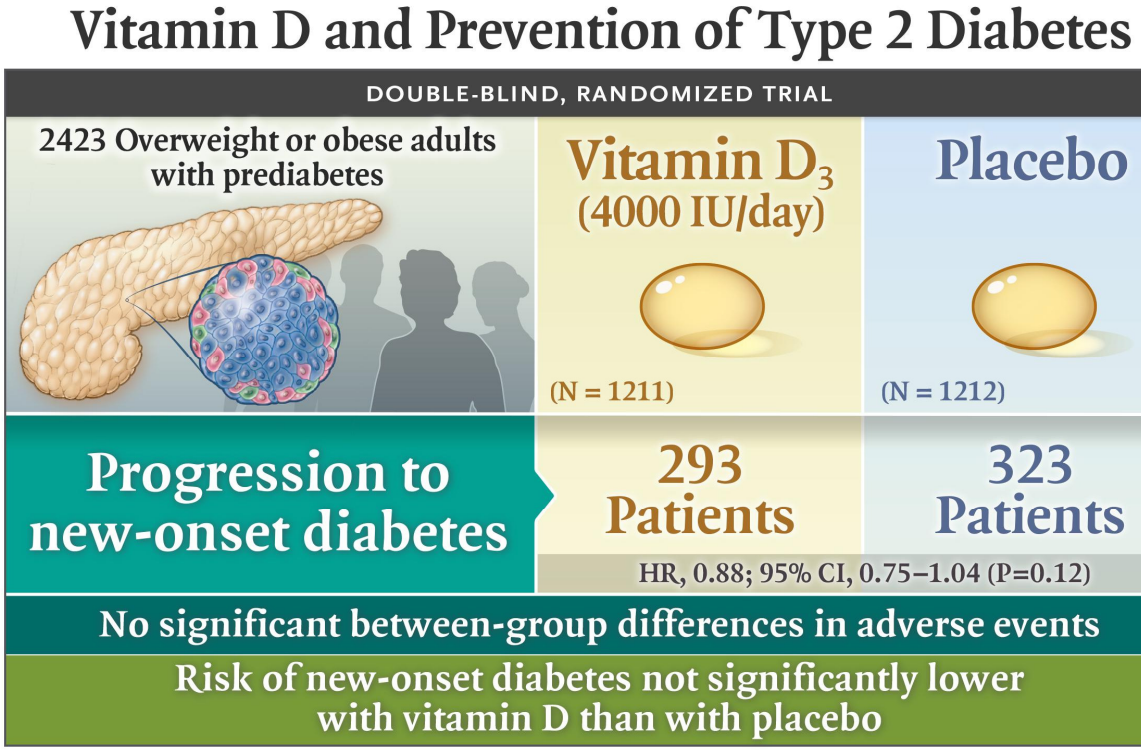


Figure 2. Kaplan–Meier Curves for Survival Free from Diabetes among Adults at Risk for Type 2 Diabetes.



Pittas AG, et al. N Engl J Med. 20

Post hoc analysis **D2d** trial

>40 ng/ml

Table 2—Hazard ratios (95% CIs) for new-onset diabetes in categories stratified by intratrial mean serum 25(OH)D level in the entire D2d cohort

	<50 nmol/L (*n* = 247)	50–74 nmol/L (*n* = 456)	75–99 nmol/L (*n* = 590)	100–124 nmol/L (*n* = 413)	≥125 nmol/L (*n* = 452)
Median level	40.0	63.8	86.3	110.0	145.2
Model 1	1.14 (0.84–1.54)	Reference	1.08 (0.84–1.38)	0.65 (0.48–0.89)	0.41 (0.29–0.57)
Model 2	1.24 (0.90–1.70)	Reference	1.01 (0.79–1.30)	0.59 (0.43–0.82)	0.38 (0.27–0.54)
Model 3	1.22 (0.89–1.68)	Reference	1.01 (0.79–1.30)	0.59 (0.43–0.82)	0.39 (0.27–0.55)
Model 4	1.24 (0.90–1.71)	Reference	0.99 (0.77–1.27)	0.58 (0.42–0.81)	0.36 (0.25–0.51)
Model 5	1.25 (0.91–1.72)	Reference	0.98 (0.76–1.26)	0.57 (0.41–0.79)	0.35 (0.24–0.50)

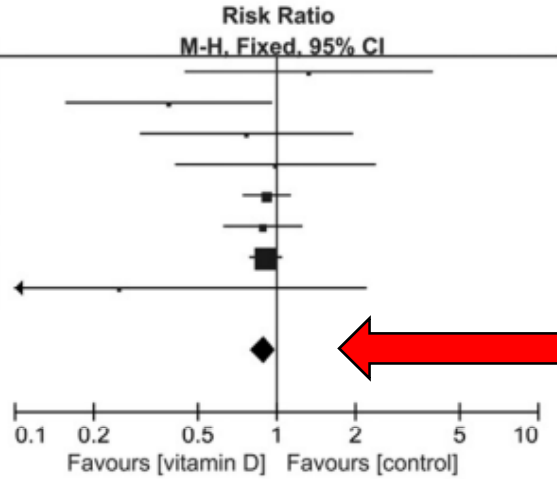
Model 1: adjusted for trial assignment (vitamin D or placebo) only. Model 2: additionally adjusted for site, BMI (at baseline), race (White, Black, other). Model 3: additionally adjusted for sex and age (at baseline). Model 4: additionally adjusted for physical activity (at baseline). Model 5: additionally adjusted for statin use (at baseline). To convert the values for 25(OH)D to ng/L, divide by 2.496.

Dawson-Hughes B, et al Diabetes Care. 2020

A Pooled Risk Ratio

Study or Subgroup	Vitamin D Events	Vitamin D Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Year
Davidson 2013	7	56	5	53	1.0%	1.32 [0.45, 3.92]	2013
Dutta 2014	6	68	13	57	2.6%	0.39 [0.16, 0.95]	2014
Kuchay 2015	7	69	9	68	1.7%	0.77 [0.30, 1.94]	2015
Barengolts 2015	9	87	9	86	1.7%	0.99 [0.41, 2.37]	2015
Jorde 2016	103	256	112	255	20.8%	0.92 [0.75, 1.12]	2016
Kawahara 2018	57	630	64	626	11.9%	0.88 [0.63, 1.24]	2018
Pittas 2019	293	1211	323	1212	59.7%	0.91 [0.79, 1.04]	2019
Niroomand 2019	1	81	4	81	0.7%	0.25 [0.03, 2.19]	2019
Total (95% CI)		**2458**		**2438**	**100.0%**	**0.89 [0.80, 0.99]**	
Total events	483		539				

Heterogeneity: Chi² = 5.42, df = 7 (P = 0.61); I² = 0%
Test for overall effect: Z = 2.14 (P = 0.03)

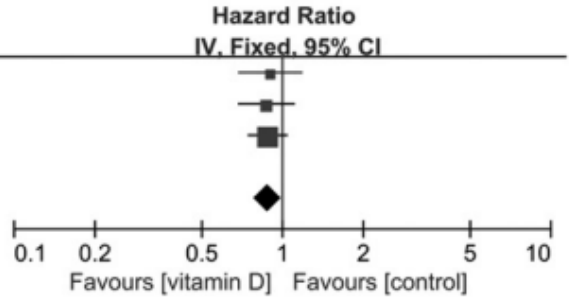


-11%

B Pooled Hazard Ratio

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Fixed, 95% CI	Year
Jorde 2016	-0.10537	0.136896	20.1%	0.90 [0.69, 1.18]	2016
Kawahara 2018	-0.13928	0.12038	25.9%	0.87 [0.69, 1.10]	2018
Pittas 2019	-0.12785	0.083402	54.0%	0.88 [0.75, 1.04]	2019
Total (95% CI)			**100.0%**	**0.88 [0.78, 0.99]**	

Heterogeneity: Chi² = 0.04, df = 2 (P = 0.98); I² = 0%
Test for overall effect: Z = 2.06 (P = 0.04)



trials with a total of 4,896 subjects

Zhang Y, et al Diabetes Care. 2020

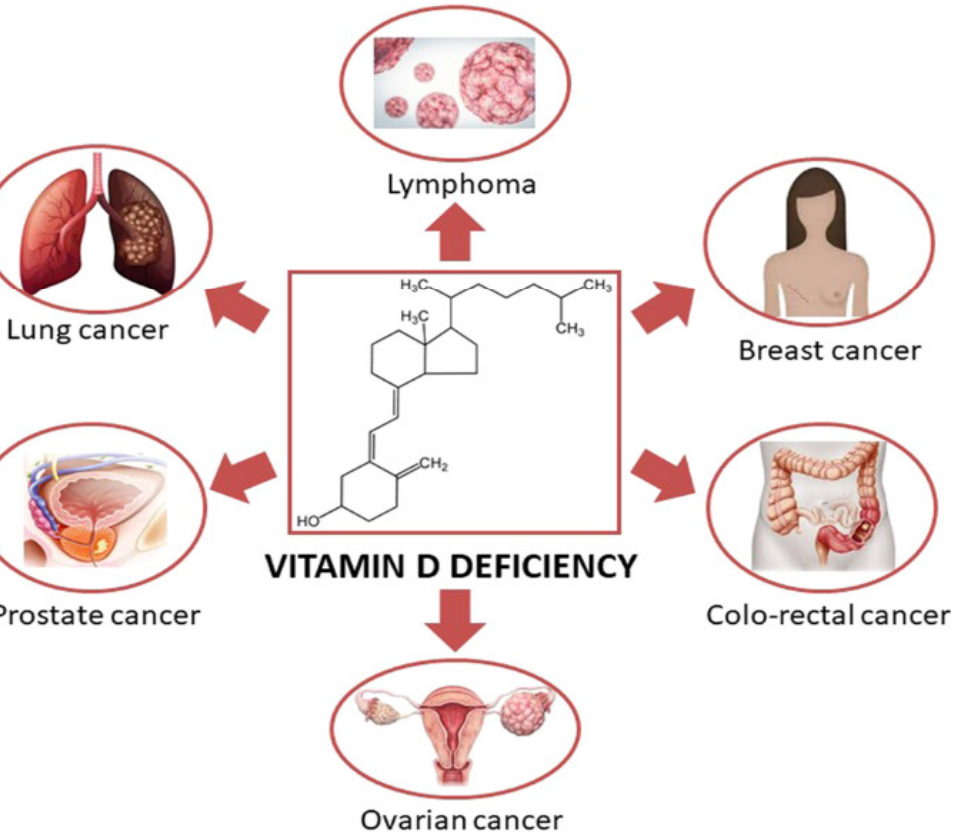
Table 3—Subgroup analysis of the effect of vitamin D on new-onset diabetes

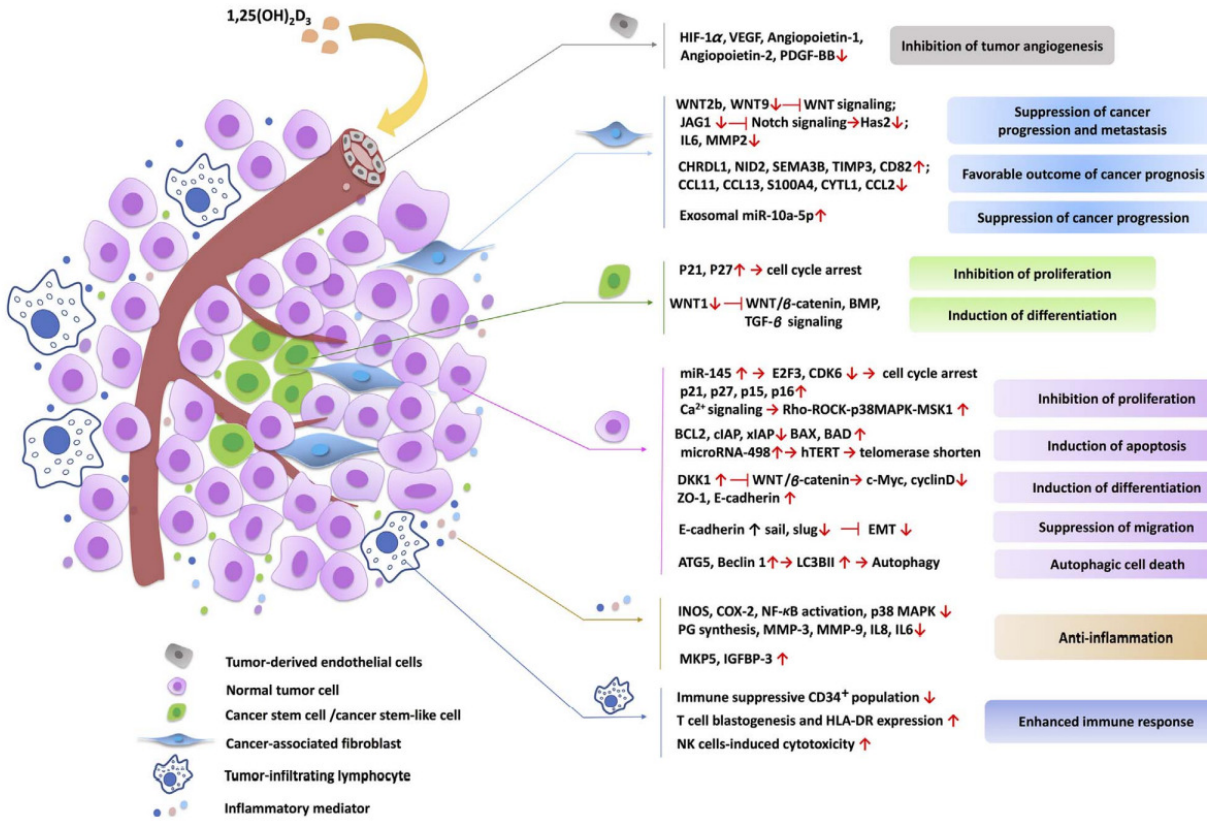
	No. of trials	No. of patients	I^2	RR (95% CI)	$P_{interaction}$
Overall	8	4,896	0%	0.89 (0.80, 0.99)	
Baseline 25(OH)D (nmol/L)					
≥50	3	2,517	0%	0.90 (0.80, 1.02)	0.79
<50	5	1,122	26%	0.87 (0.68, 1.11)	
Baseline 25(OH)D (nmol/L)					
≥30	7	3,640	0%	0.89 (0.80, 1.00)	NA
<30	0	0	NA	NA	
Achieved 25(OH)D in vitamin D group (nmol/L)					
≥75	7	4,734	0%	0.90 (0.81, 1.00)	NA
<75	0	0	NA	NA	
Type of vitamin D					
Vitamin D_3	7	4,723	0%	0.89 (0.80, 0.99)	0.81
Vitamin D_2	1	173	NA	0.99 (0.41, 2.37)	
Daily dose equivalent (IU)					
≥2,000	8	4,896	0%	0.89 (0.80, 0.99)	NA
<2,000	0	0	NA	NA	
Mean BMI (kg/m^2)					
≥30	5	2,514	0%	0.95 (0.84, 1.08)	0.048
<30	3	1,126	4%	0.73 (0.57, 0.92)	
Timing of treatment					
Daily	2	3,679	0%	0.90 (0.80, 1.03)	0.70
Intermittently	6	1,217	8%	0.86 (0.66, 1.10)	
Intervention					
Vitamin D vs. placebo	7	4,771	0%	0.90 (0.81, 1.01)	0.07
Vitamin D + calcium vs. calcium	1	125	NA	0.39 (0.16, 0.95)	
Latitude					
≥37°	3	3,557	0%	0.89 (0.79, 1.00)	0.85
<37°	6	1,339	15%	0.86 (0.63, 1.18)	
Follow-up					
≥3 years	3	4,190	0%	0.91 (0.81, 1.01)	0.28
<3 years	5	706	0%	0.70 (0.45, 1.10)	

To convert Vitamin D IU to μg, multiply by 0.0025. NA, not available.

Zhang Y, et al Diabetes Care. 202

Vitamin D and Cancer

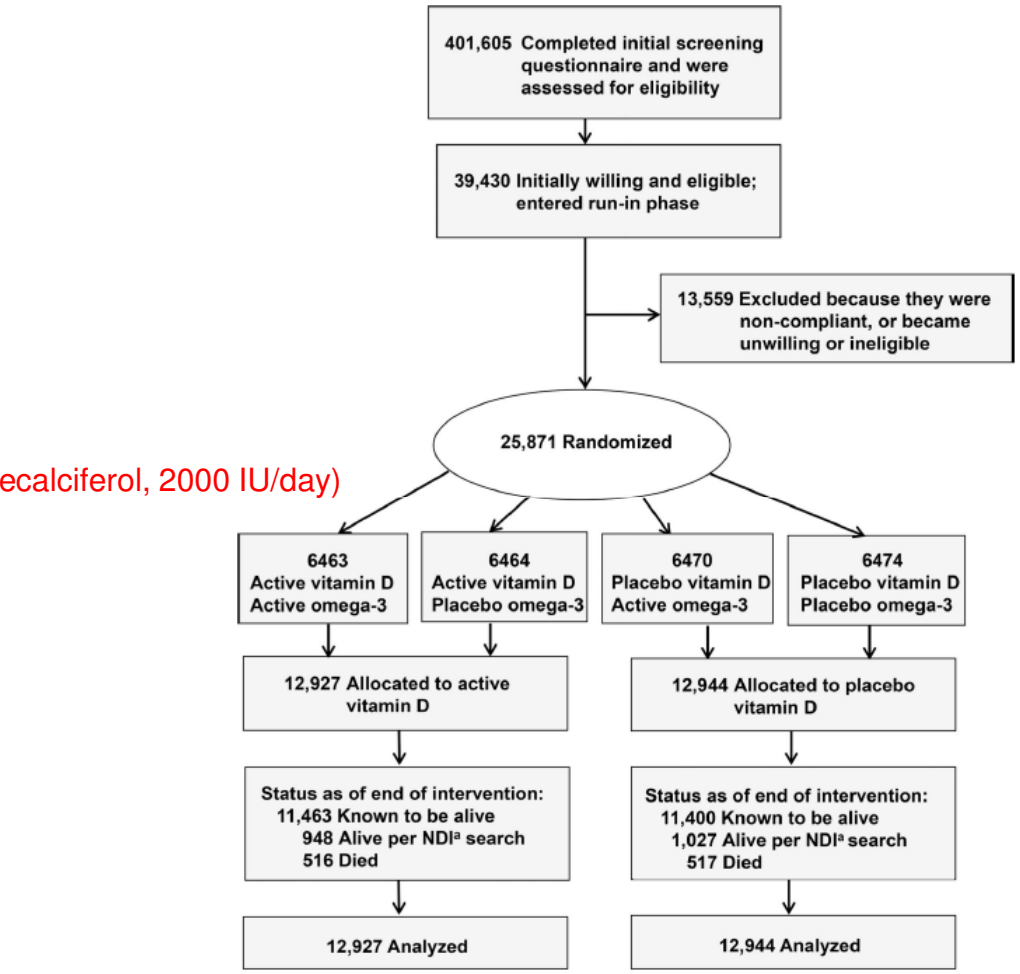




igliaccio S, et al. Int J Obes (Lond). 2022

Wu X, et al. Acta Pharm Sin B. 20

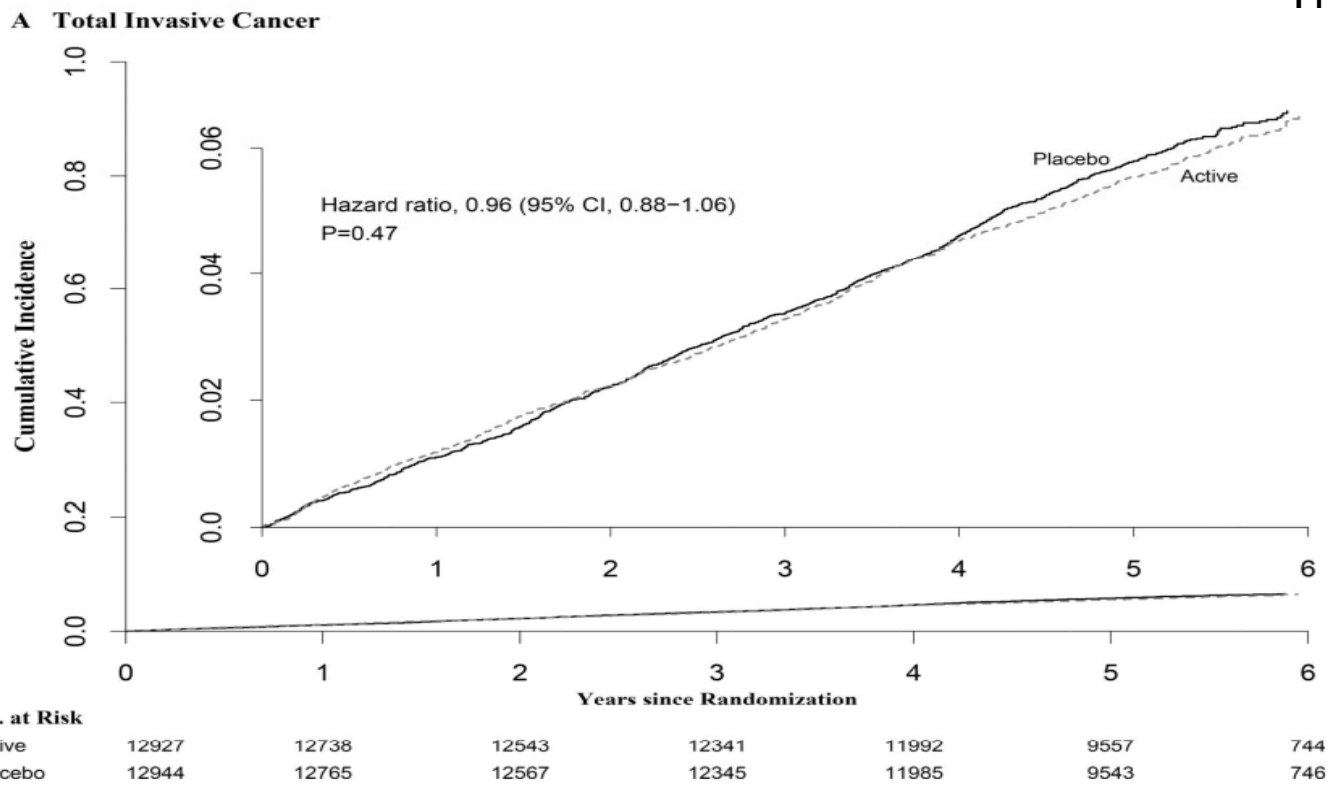
The VITamin D and OmegA-3 TriaL (VITAL)



Primary endpoints were total invasive cancer an major cardiovascular events (composite myocardial infarction, stroke, and cardiovascula mortality).

Manson JE, et al. N Engl J Med. 2019

Cancer incidence



The VITamin D and OmegA-3 TriaL (VITA

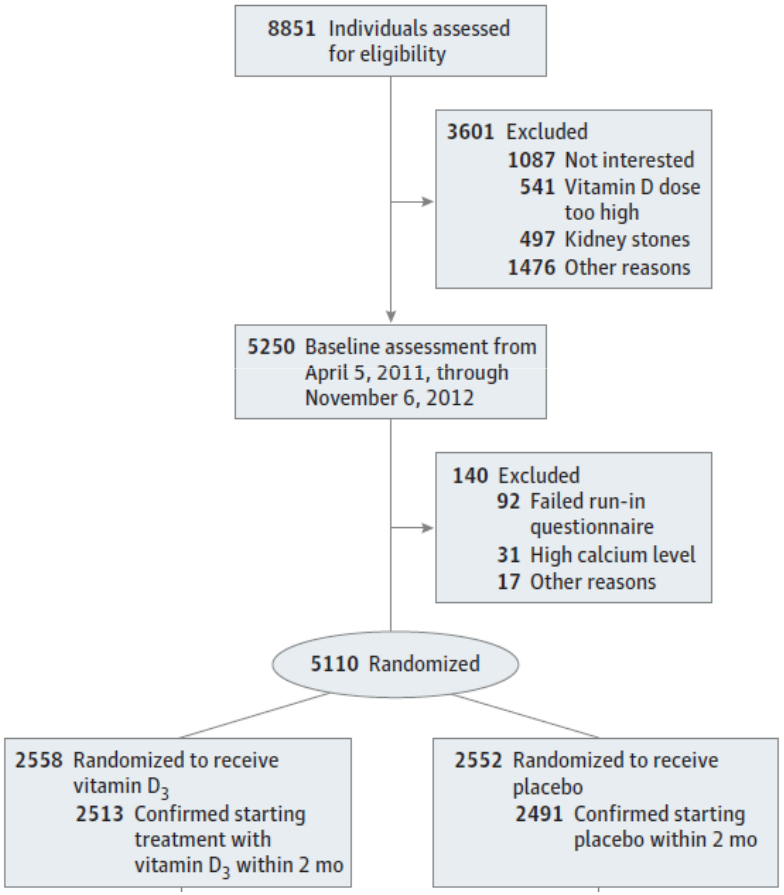
Manson JE, et al. N Engl J Med. 2019

Hazard Ratios (HR) and 95% Confidence Intervals (CI) of the Primary, Secondary, and Other Outcomes by Randomized Vitamin D Assignment in Intention-To-Treat Analyses

	No. of Events			
	Vitamin D (N = 12,927)	**Placebo (N = 12,944)**	**HR**	**95% CI**
Outcomes (1° and 2°) Total invasive cancer[a]	793	824	0.96	0.88–1.06
Breast	124	122	1.02	0.79–1.31
Prostate	192	219	0.88	0.72–1.07
Colorectal	51	47	1.09	0.73–1.62
Cancer death	154	187	0.83	0.67–1.02

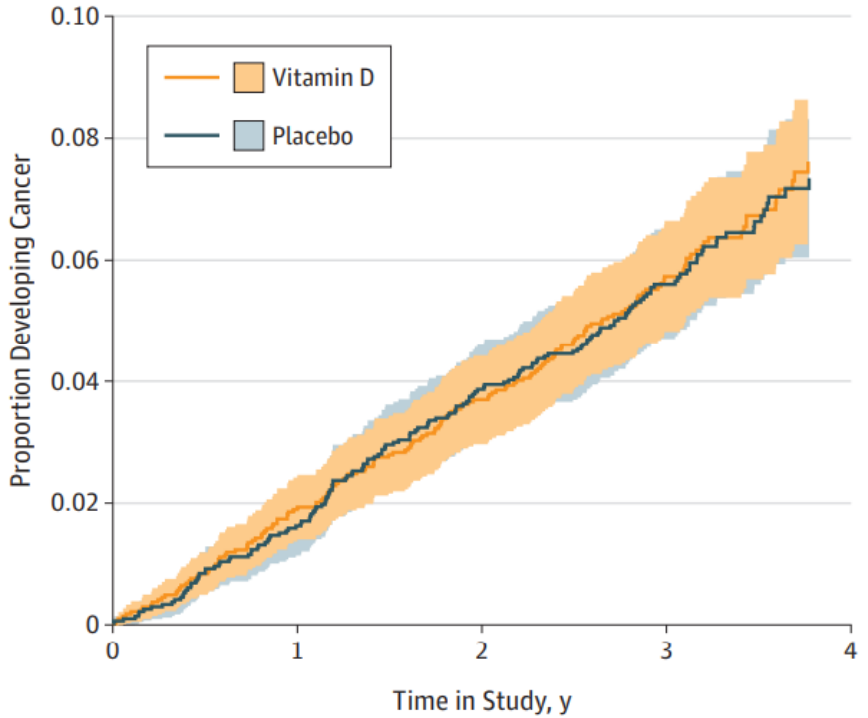
Manson JE, et al. N Engl J Med. 2019

Vitamin D Assessment (ViDA) study



cragg R, et al . JAMA Oncol. 2018

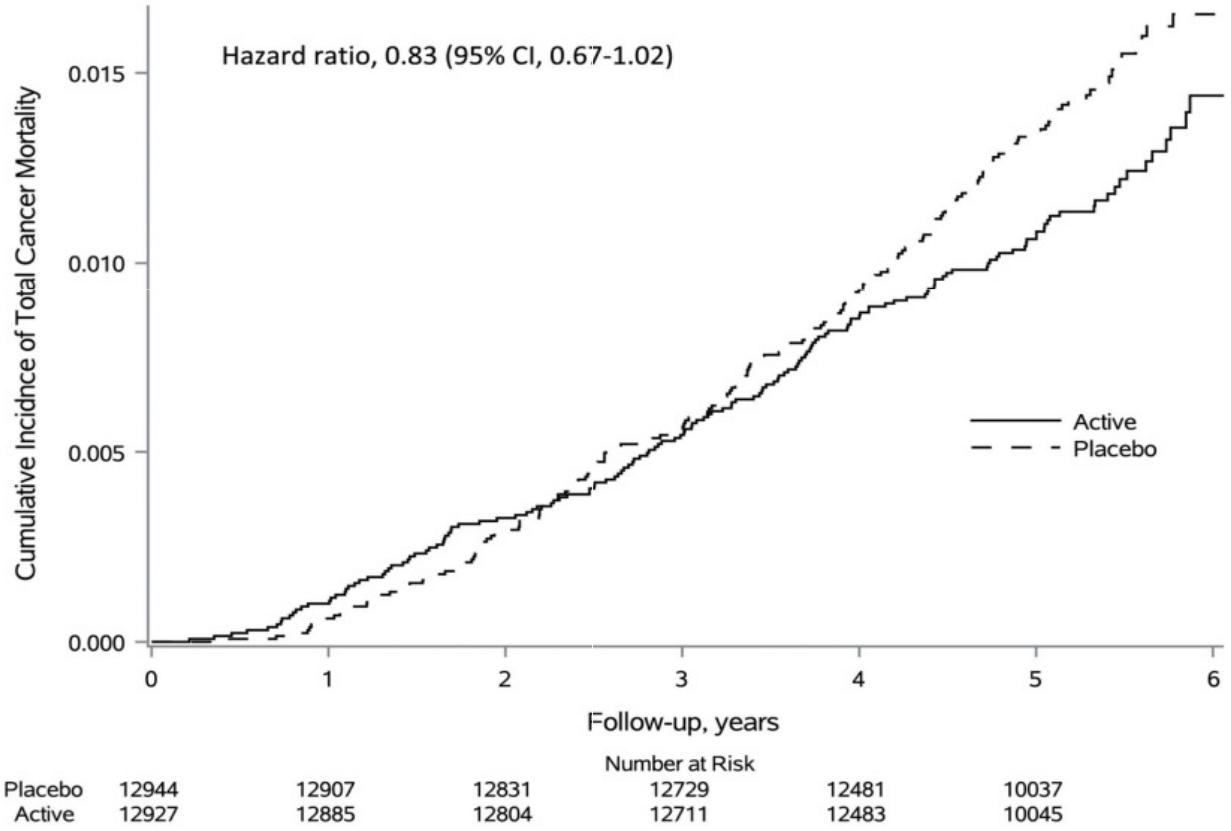
Figure 2. Proportion of Participants Developing Cancer During Follow-up From June 3, 2011, to July 31, 2015, by Study Group



No. at risk					
Vitamin D	2558	2504	2453	1760	374
Placebo	2550	2504	2447	1899	275

Shaded areas represent 95% CIs for the 2 curves.

Cancer mortality



Manson JE, et al. J Steroid Biochem Mol Biol. 2020

Endpoint	Vitamin D (N = 12,927)	Placebo (N = 12,944)	HR	95% CI
	no. of participants w/event			
Total invasive cancer[b]	793	824	0.96	0.88-1.06
Cancer mortality	154	187	0.83	0.67-1.02
Breast cancer	124	122	1.02	0.79-1.31
Prostate cancer	192	219	0.88	0.72-1.07
Colorectal cancer	51	47	1.09	0.73-1.62
Cardiovascular disease (CVD), primary and secondary outcomes				
Major CVD event[b,c]	396	409	0.97	0.85-1.12
Expanded CVD event[d]	536	558	0.96	0.86-1.08
Total myocardial infarction	169	176	0.96	0.78-1.19
Total stroke	141	149	0.95	0.76-1.20
Cardiovascular mortality	152	138	1.11	0.88-1.40
All-cause mortality	485	493	0.99	0.87-1.12
Excluding the first two years of follow-up:				
Total invasive cancer	490	522	0.94	0.83-1.06
Cancer mortality	112	149	0.75	0.59-0.96
Major CVD event	274	296	0.93	0.79-1.09
All-cause mortality	368	384	0.96	0.84-1.11

Vitamin D showed a promising signal for reduction in total cancer mortality (HR=0.83 [0.67-1.02]), especially in analyses that accounted for latency by excluding the first year (HR=0.79 [0.63-0.99]) or first 2 years (HR=0.75 [0.59-0.96]) of follow-up.

Manson JE, et al. J Steroid Biochem Mol Biol. 2020

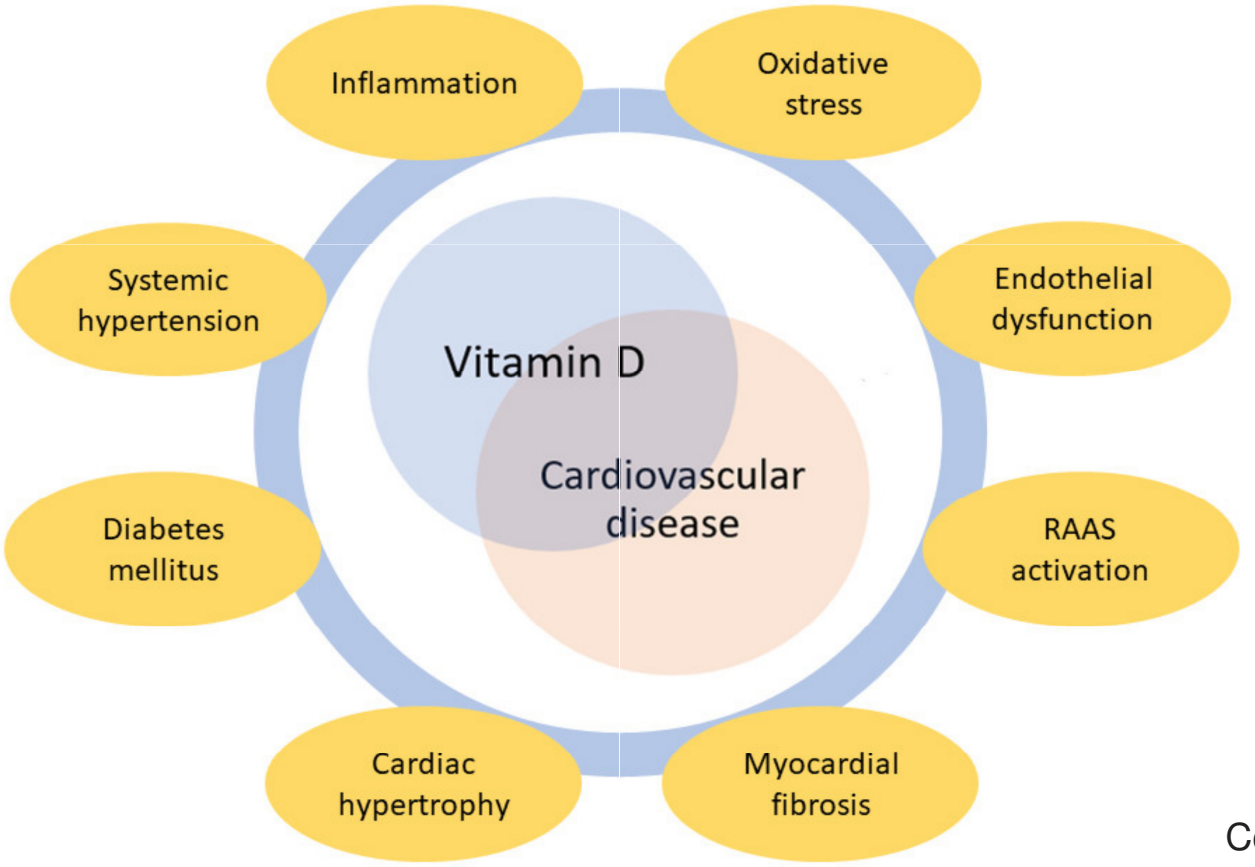
Hazard Ratios (HR) and 95% Confidence Intervals (CI) of the Primary Outcomes Comparing Vitamin D and Placebo Groups, According to Selected Prespecified Subgroups[a]

		Total Invasive Cancer			
Subgroup	**# ppts**	**Vit D**	**Placebo**	**HR (95%CI)**	**P, int.**
		# ppts with event			
Race	25,304				0.21
Non-Hispanic white	18,046	626	632	0.99 (0.89-1.11)	
African American	5,106	98	126	0.77 (0.59-1.01)	
Other	2,152	53	52	1.03 (0.70-1.51)	
Body Mass Index (kg/m²)	25,254				0.002
<25	7,843	206	278	0.76 (0.63-0.90)	
25-<30	10,122	338	323	1.04 (0.90-1.21)	
≥30	7,289	228	199	1.13 (0.94-1.37)	
Baseline serum 25(OH)D[b]	15,787				0.99
<20 ng/mL	2,001	58	63	0.97 (0.68-1.39)	
≥20 ng/mL	13,786	459	464	0.98 (0.86-1.12)	
Baseline serum 25(OH)D[b, c]	15,787				0.57
<cohort median	7,812	251	252	1.02 (0.86-1.21)	
≥cohort median	7,975	266	275	0.95 (0.80-1.12)	
Omega-3 FA randomization status[d]	25,871				0.56
Placebo group	12,938	385	412	0.94 (0.82-1.08)	
Omega-3 FA group	12,933	408	412	0.99 (0.87-1.14)	

Individuals with normal BMI (<25 kg/m2) experienced a significant treatment-associated reduction in cancer risk (HR=0.76 [0.63-0.90]), but overweight or obese individuals did not (p, interaction=0.002). African Americans assigned to vitamin D also had a suggestive reduction in cancer risk (HR=0.77 [0.59-1.01]), although the p-value for interaction by race/ethnicity was not significant

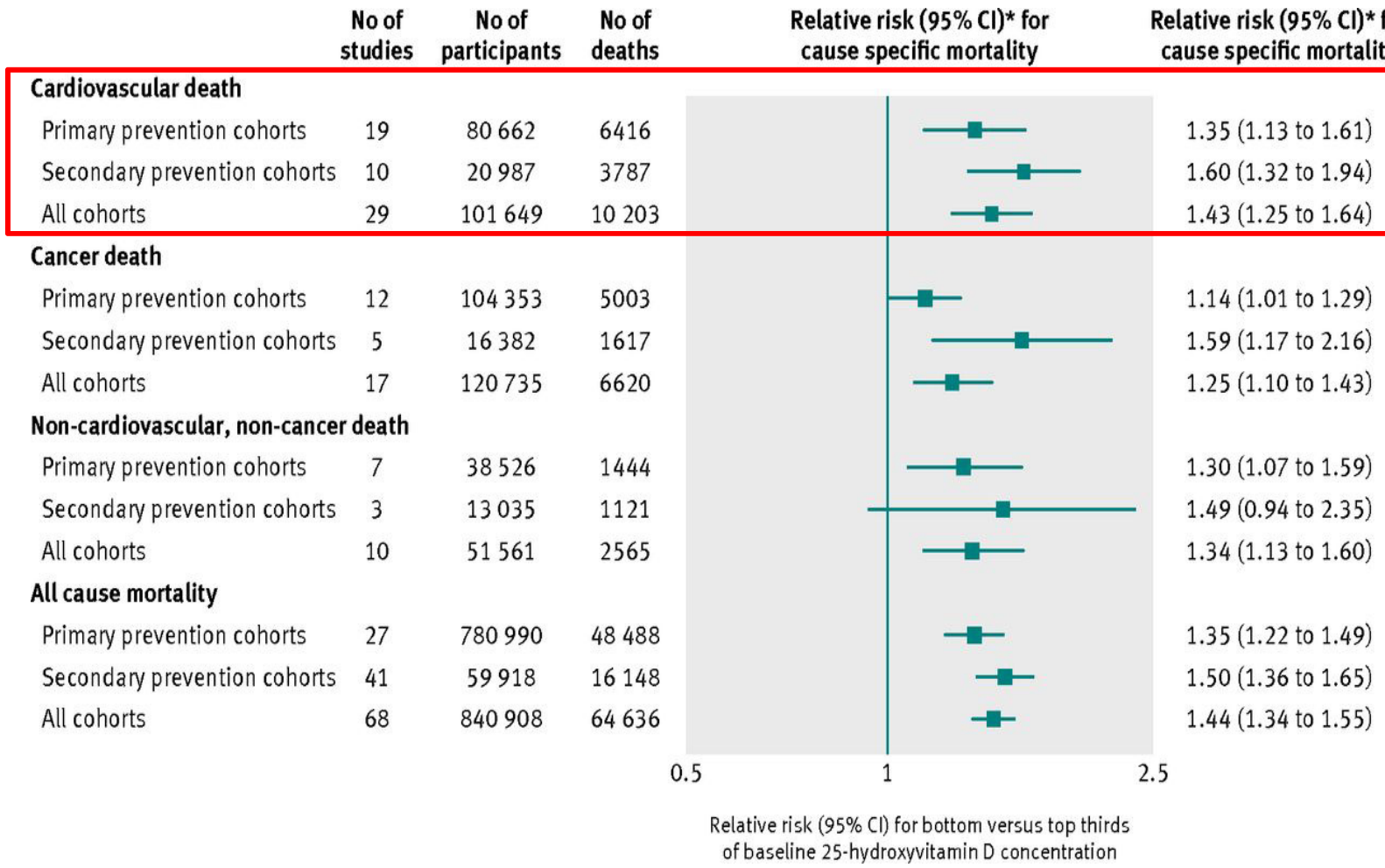
Manson JE, et al. J Steroid Biochem Mol Biol. 2020

Vitamin D and cardiovascular disease



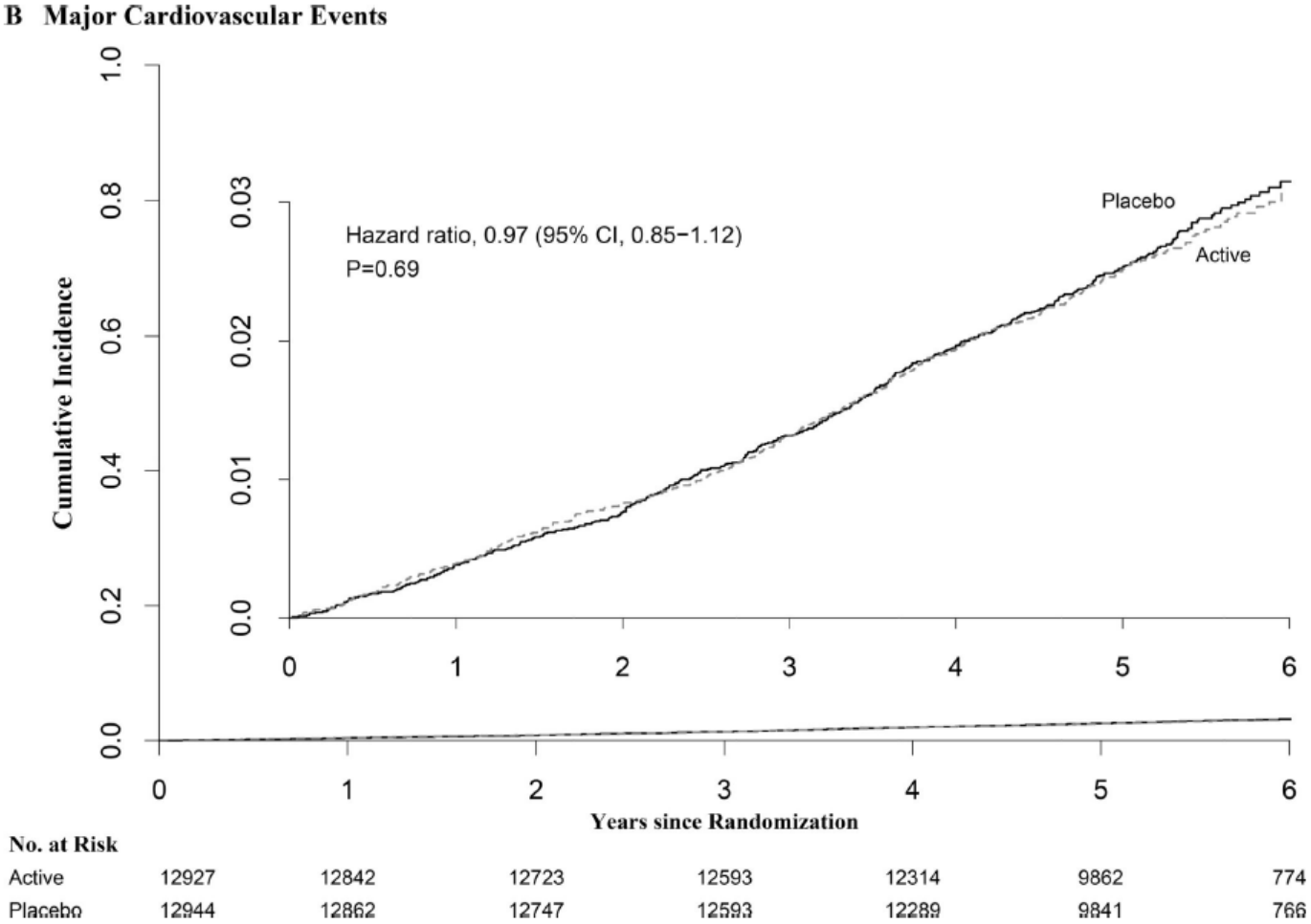
Cosentino N, et al. Nutrients. 20

n a meta-analysis of nearly 50,000 individuals, low serum 25OHD concentrations were associated with an increased risk of cardiovascular events (RR .43, comparing individuals with he lowest vitamin D status with ndividuals with a better vitamin D tatus.



Chowdhury R, et al. BMJ. 2014

The VITamin D and OmegA-3 TriaL (VITA



During the 5.3 years of follow-up in the VITAL trial, the hazard ratio for th expanded composite end point of maj cardiovascular events including corona revascularization was 0.97 (95% CI 0.85 1.12) in the vitamin D supplementatio group, compared with placebo. A simil hazard ratio was found for cardiovascul death (HR 1.11, 95% CI 0.88–1.40), death from any cause.

Manson JE, et al. N Engl J Med. 2019

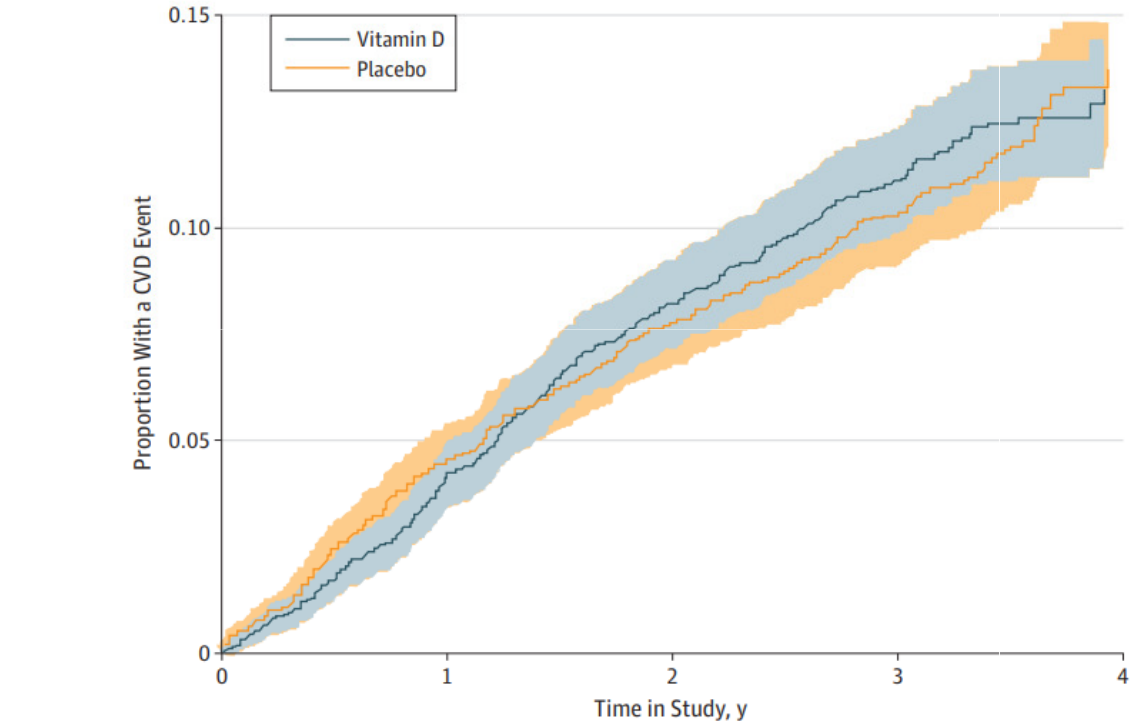
The VITamin D and OmegA-3 TriaL (VITAL

Hazard Ratios (HR) and 95% Confidence Intervals (CI) of the Primary, Secondary, and Other Outcomes by Randomized Vitamin D Assignment in Intention-To-Treat Analyses

	No. of Events			
	Vitamin D (N = 12,927)	Placebo (N = 12,944)	HR	95% CI
Cardiovascular disease (CVD) outcomes				
Major CVD events[a,b]	396	409	0.97	0.85–1.12
Expanded CVD events[c]	536	558	0.96	0.86–1.08
Myocardial infarction	169	176	0.96	0.78–1.19
Stroke	141	149	0.95	0.76–1.20
Cardiovascular mortality	152	138	1.11	0.88–1.40
Other vascular outcomes[d]				
Coronary artery bypass graft (CABG)	73	98	0.75	0.55–1.01
Percutaneous coronary intervention (PCI)	182	188	0.97	0.79–1.19
Myocardial infarction death	24	15	1.60	0.84–3.06
Stroke death	19	23	0.84	0.46–1.54

Modified from Manson JE, et al. N Engl J Med. 2

Figure 2. Proportion of Participants With a Cardiovascular Disease (CVD) Event During Follow-up



No. at risk					
Vitamin D group	2558	2432	2336	1660	205
Placebo group	2550	2453	2336	1791	239

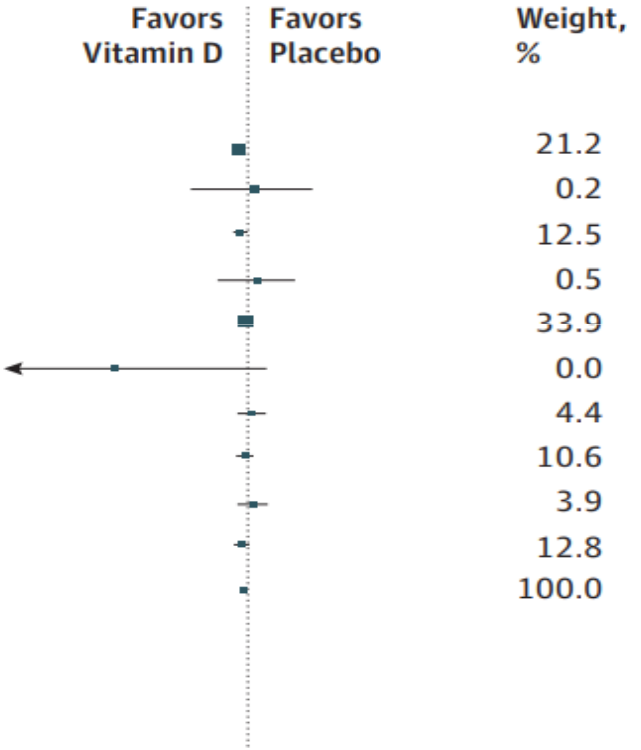
Vitamin D Assessment (ViDA) study

Similarly, in the ViDA study, the primary outcome of major cardiovascular events was not influenced by monthly vitamin D supplementation over 3.3 years.

Scragg R, et al. JAMA Cardiol. 2017

Figure 2. Forest Plot Illustrating the Results of the Primary and Secondary End Points, Part 1

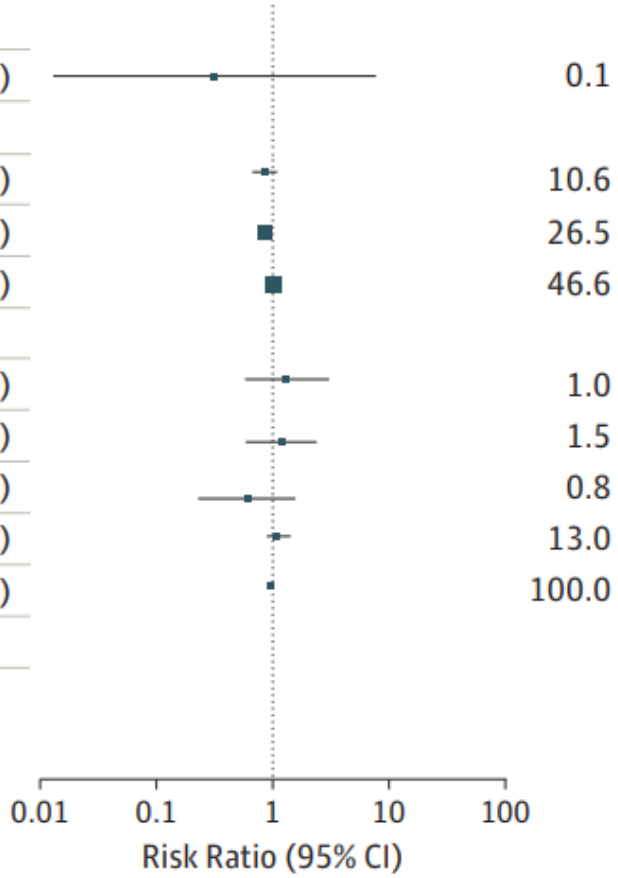
Study or Subgroup	Vitamin D Events	Vitamin D Total	Placebo Events	Placebo Total	Risk Ratio (95% CI)	Weight, %
MACE						
Trivedi et al,[35] 2003	477	1345	503	1341	0.95 (0.86-1.04)	21.2
Brazier et al,[33] 2005	6	95	5	97	1.23 (0.39-3.88)	0.2
Grant et al,[32] 2005	339	2649	363	2643	0.93 (0.81-1.07)	12.5
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: $z = 0.18$, $P = .93$						



this meta-analysis of randomized clinical trials that included more than 83 000 participants, amin D supplementation was not associated with reduced risks of major adverse rdiovascular events, myocardial infarction, stroke, cardiovascular disease mortality, or all-use mortality compared with placebo.

Barbarawi M, et al. JAMA Cardiol. 201

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: $\tau^2 = 0.00$, $\chi^2_7 = 7.11$, $P = .42$, $I^2 = 2\%$						
Test for overall effect: $z = 0.41$ ($P = .68$)						



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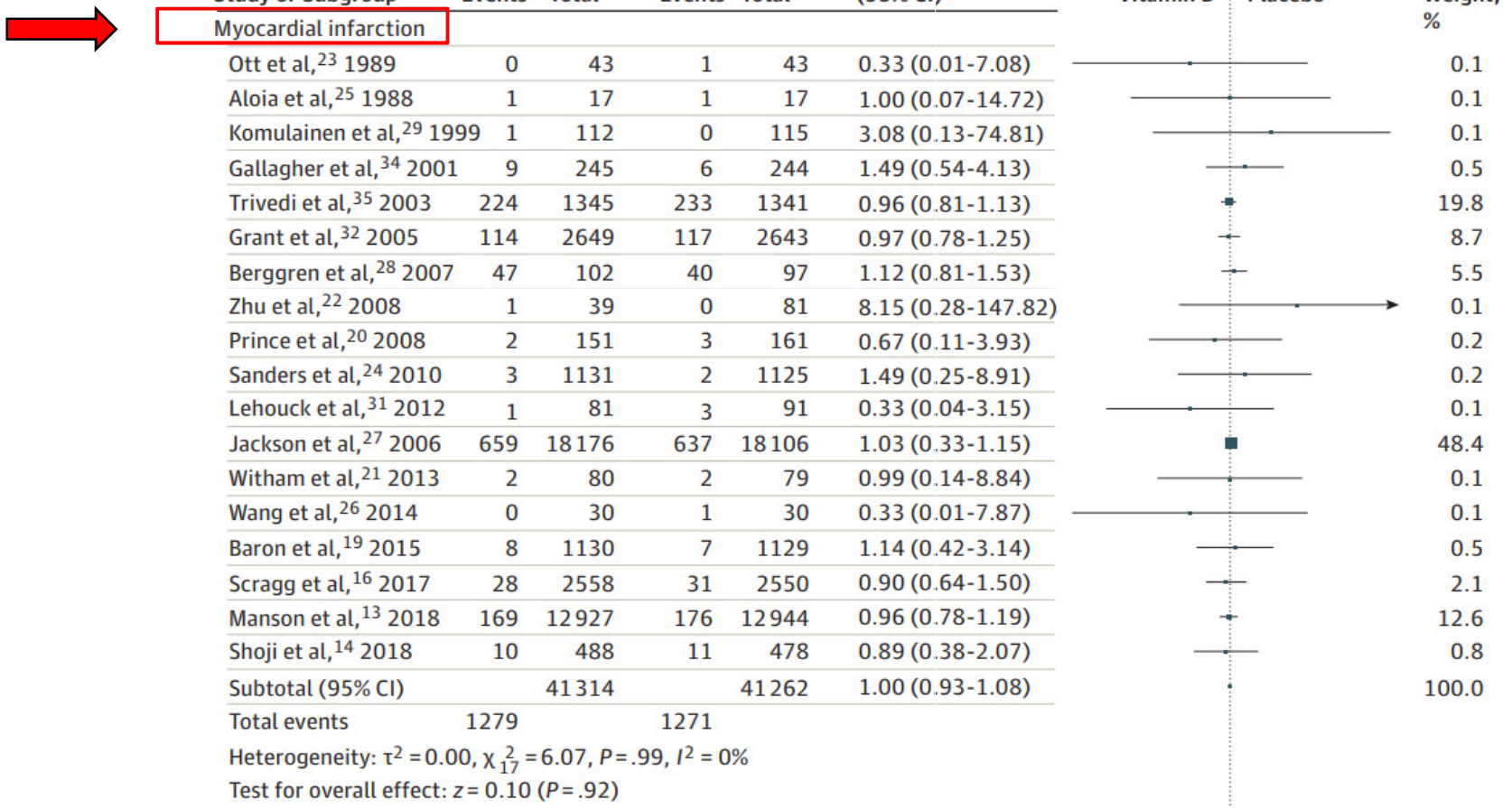


Study or Subgroup	Vitamin D Events	Vitamin D Total	Placebo Events	Placebo Total	Risk Ratio (95% CI)	Weight, %
Myocardial infarction						
Ott et al,[23] 1989	0	43	1	43	0.33 (0.01-7.08)	0.1
Aloia et al,[25] 1988	1	17	1	17	1.00 (0.07-14.72)	0.1
Komulainen et al,[29] 1999	1	112	0	115	3.08 (0.13-74.81)	0.1
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: $\tau^2 = 0.00$, $\chi^2_{17} = 6.07$, $P = .99$, $I^2 = 0\%$

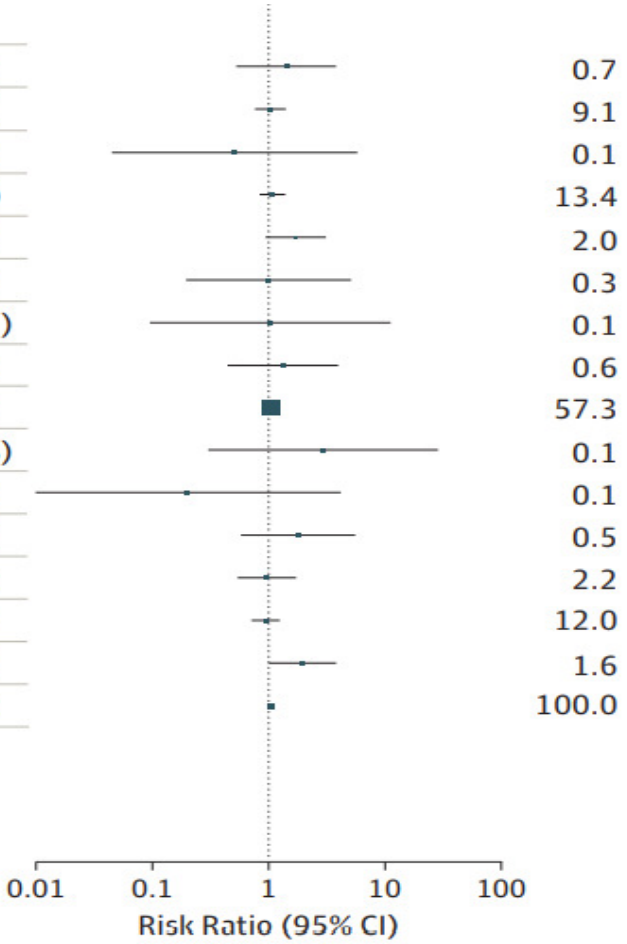
Test for overall effect: $z = 0.10$ ($P = .92$)

Barbarawi M, et al. JAMA Cardiol. 2019

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	18 176	659	18 106	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	12 927	149	12 944	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)		41 146		41 093	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: $z = 1.41$ ($P = .16$)



Barbarawi M, et al. JAMA Cardiol. 2019

The **ViDA trial** studied xtensively the effects of itamin D supplementation n a subgroup of articipants using a state of he art invasive technology suprasystolic oscillometry). After a mean follow-up of .1 years, vitamin D upplementation generated ull effects.

Table 2. Arterial Function Measures at Baseline and Follow-up (Adjusted for Age, Sex, and Ethnicity) by Treatment Group in the Total Sample (N=517)

Variable	Mean (SD)				Change From Baseline, Vitamin D Minus Placebo	
	Vitamin D Group (n=256)		Placebo Group (n=261)			
	Baseline	Follow-up	Baseline	Follow-up	Mean (95% CI)	*P* Value
Pulse rate, beats/min	63.0 (10.0)	65.7 (9.5)	63.9 (11.0)	65.7 (11.8)	0.9 (−0.7 to 2.6)	0.27
Brachial SBP, mm Hg	137.7 (18.4)	128.9 (16.1)	137.7 (16.8)	131.0 (18.9)	−2.1 (−5.2 to 0.9)	0.17
Brachial DBP, mm Hg	78.4 (10.6)	73.7 (9.9)	78.7 (9.7)	74.8 (9.9)	−0.8 (−2.5 to 0.8)	0.32
Aortic SBP, mm Hg	140.1 (18.4)	131.1 (16.2)	139.7 (17.8)	132.9 (20.2)	−2.2 (−5.4 to 0.9)	0.17
Aortic DBP, mm Hg	72.0 (6.6)	69.5 (6.1)	72.2 (6.0)	70.2 (6.1)	−0.5 (−1.5 to 0.6)	0.41
Augmentation index, %	30.0 (12.1)	27.0 (11.2)	29.9 (13.1)	26.8 (12.6)	0.0 (−2.4 to 2.5)	0.98
Pulse wave velocity, m/s	9.3 (1.7)	9.2 (1.6)	9.3 (1.7)	9.3 (1.9)	−0.1 (−0.2 to 0.0)	0.18
Peak reservoir pressure, mm Hg	124.3 (17.8)	116.5 (15.1)	124.2 (16.4)	118.4 (18.5)	−2.0 (−5.1 to 1.1)	0.21
Peak excess pressure, mm Hg	28.5 (8.3)	25.8 (7.9)	28.1 (8.5)	26.1 (8.3)	−0.7 (−2.5 to 1.0)	0.40
Reservoir pressure integral, mm Hg/s	92.1 (18.3)	83.0 (16.7)	91.7 (21.0)	85.4 (21.5)	−2.8 (−6.1 to 0.5)	0.10
Log_e(excess pressure integral, mm Hg/s)	1.57 (0.38)	1.40 (0.42)	1.54 (0.43)	1.39 (0.43)	−0.02 (−0.11 to 0.06)	0.59
Backward pressure amplitude, mm Hg	28.6 (7.3)	25.3 (6.3)	28.5 (7.5)	25.9 (8.3)	−0.8 (−2.0 to 0.5)	0.25
Forward pressure amplitude, mm Hg	40.0 (8.4)	36.8 (7.9)	39.5 (8.5)	37.5 (9.6)	−1.2 (−2.7 to 0.4)	0.14
Log_e(wave reflection index), $\times 10^{-2}$	−120.6 (35.0)	−124.5 (28.8)	−118.1 (35.9)	−125.7 (35.7)	3.7 (−4.3 to 11.8)	0.36

Sluyter JD, et al. J Am Heart Assoc. 201

Mean change at 3 y in	Vitamin D vs no vitamin D		Omega-3s vs no omega-3s		Strength exercise vs control	
	Difference (99% CI)	*P* value	Difference (99% CI)	*P* value	Difference (99% CI)	*P* value
Systolic BP, mm Hg	-0.8 (-2.1 to 0.5)	.13	-0.8 (-2.1 to 0.5)	.11	0.5 (-0.8 to 1.9)	.30
Diastolic BP, mm Hg	0 (-0.7 to 0.8)	.88	-0.5 (-1.2 to 0.2)	.06	0.3 (-0.4 to 1.0)	.32
SPPB, points	-0.1 (-0.3 to 0.1)	.26	-0.0 (-0.2 to 0.2)	.76	-0.1 (-0.3 to 0.1)	.25
MoCA, points	-0.1 (-0.4 to 0.1)	.11	-0.1 (-0.3 to 0.2)	.52	0.0 (-0.2 to 0.2)	.96
Nonvertebral fractures, IR ratio	1.03 (0.75-1.43)	.79	1.18 (0.85-1.63)	.19	1.06 (0.77-1.47)	.62
Infections, IR ratio	0.95 (0.84-1.08)	.33	0.89 (0.78-1.01)	.02	1.04 (0.92-1.18)	.38

The DO-HEALTH trial in European older adults (n. 2157) did not find any effect of vitamin D supplementation on systolic or diastolic blood pressure.

Bischoff-Ferrari HA, et al. JAMA. 202

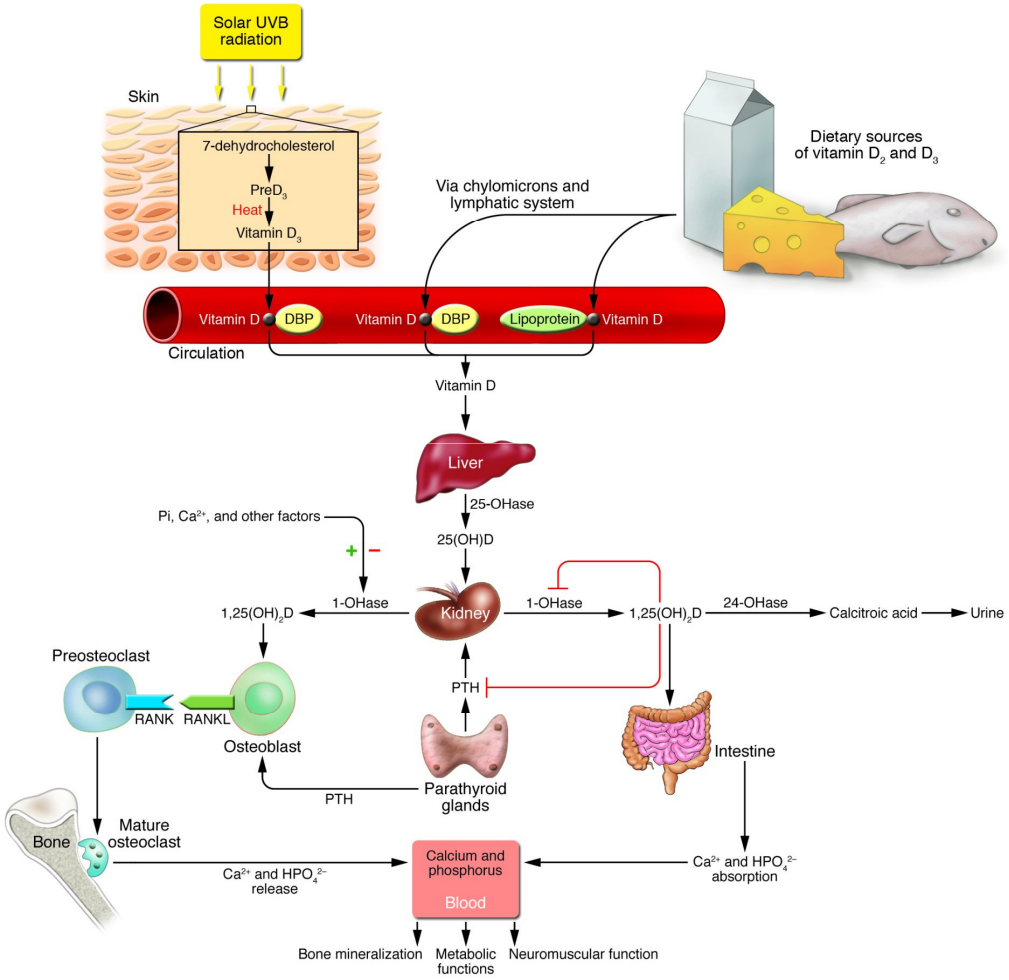
participants with vitamin D eficiency at baseline **(<50 nmol/l 20 ng/ml)**, brachial systolic and iastolic blood pressure ecreased by 3 mmHg to 5 mmHg ot significant); however, aortic ystolic blood pressure (–7.5 mmHg, P = 0.03) and other arameters (augmentation index, ulse wave velocity, peak eservoir pressure and backward ressure amplitude) improved on orrection of baseline vitamin D. eficiency.

Table 3. Arterial Function Measures at Baseline and Follow-up (Adjusted for Age, Sex, and Ethnicity) by Treatment Group Amo Those With Baseline Vitamin D Deficiency (Deseasonalized 25(OH)D <50 nmol/L; n=150)

Variable	Mean (SD)				Change From Baseline, Vitamin D Minus Placebo	
	Vitamin D Group (n=71)		Placebo Group (n=79)			
	Baseline	Follow-up	Baseline	Follow-up	Mean (95% CI)	*P* Value
Pulse rate, beats/min	62.9 (10.9)	65.7 (9.9)	66.2 (13.3)	65.4 (12.8)	3.5 (−0.0 to 7.1)	0.05
Brachial SBP, mm Hg	137.4 (16.8)	125.5 (13.0)	139.4 (18.2)	132.8 (20.1)	−5.3 (−11.8 to 1.3)	0.11
Brachial DBP, mm Hg	78.9 (10.7)	72.8 (9.2)	80.0 (11.3)	76.6 (10.8)	−2.8 (−6.2 to 0.7)	0.12
Aortic SBP, mm Hg	139.8 (18.5)	127.1 (14.1)	141.1 (18.6)	136.0 (21.4)	−7.5 (−14.4 to −0.6)	0.03
Aortic DBP, mm Hg	72.2 (6.4)	68.9 (5.5)	73.2 (7.0)	71.3 (6.5)	−1.3 (−3.7 to 1.0)	0.25
Augmentation index, %	29.7 (13.6)	22.9 (8.7)	29.1 (13.7)	28.1 (14.5)	−5.7 (−10.8 to −0.6)	0.03
Pulse wave velocity, m/s	9.2 (1.8)	8.9 (1.5)	9.2 (1.9)	9.3 (2.0)	−0.3 (−0.6 to −0.1)	0.02
Peak reservoir pressure, mm Hg	125.2 (18.0)	112.3 (12.4)	125.2 (17.9)	120.9 (20.1)	−8.6 (−15.4 to −1.9)	0.01
Peak excess pressure, mm Hg	26.5 (6.8)	25.7 (8.4)	28.6 (8.7)	27.0 (7.9)	0.7 (−2.8 to 4.1)	0.70
Reservoir pressure integral, mm Hg/s	93.0 (19.1)	81.2 (16.2)	89.5 (21.2)	87.5 (23.1)	−9.8 (−16.2 to −3.3)	0.003
Log_e(excess pressure integral, mm Hg/s)	1.51 (0.39)	1.38 (0.47)	1.54 (0.42)	1.45 (0.43)	−0.04 (−0.22 to 0.14)	0.65
Backward pressure amplitude, mm Hg	28.7 (8.0)	23.5 (6.0)	28.4 (7.7)	26.7 (9.1)	−3.6 (−6.3 to −0.8)	0.01
Forward pressure amplitude, mm Hg	39.7 (8.8)	34.7 (6.3)	40.1 (8.7)	38.4 (9.9)	−3.3 (−6.4 to −0.2)	0.04
Log_e(wave reflection index), $\times 10^{-2}$	−117.7 (34.2)	−130.6 (31.3)	−122.6 (41.8)	−125.1 (50.2)	−10.3 (−29.2 to 8.6)	0.28

Sluyter JD, et al. J Am Heart Assoc. 20

Vitamin D and bone



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HORMONE
RESEARCH IN
PÆDIATRICS

Consensus Statement

Horm Res Paediatr 2016;85:83–106
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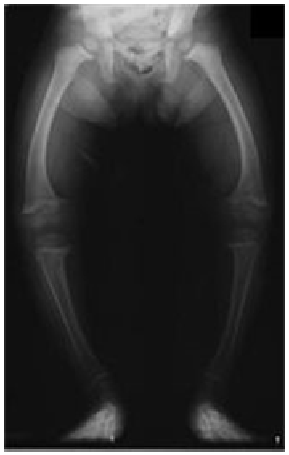
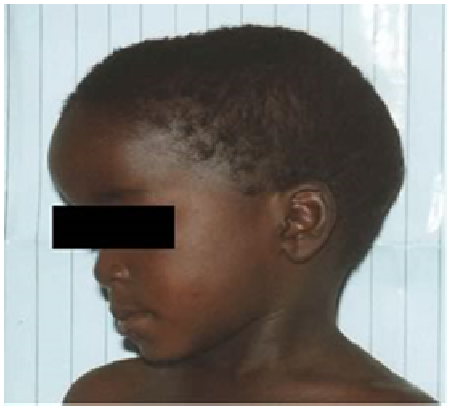
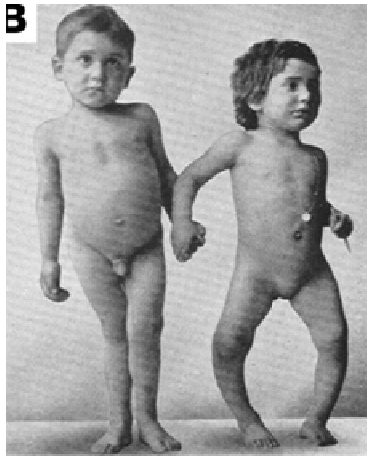
Published online: January 8, 2016

Global Consensus Recommendations on Prevention and Management of Nutritional Rickets







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Munns CF, et al. Horm Res Paediatr. 2

Guidelines for the diagnosis, prevention and management of osteoporosis

M. Rossini, S. Adami, F. Bertoldo, D. Diacinti, D. Gatti, S. Giannini, A. Giusti, N. Malavolta, S. Minisola, G. Osella, M. Pedrazzoni, L. Sinigaglia, O.Viapiana, G.C. Isaia

On behalf of the Italian Society for Osteoporosis, Mineral Metabolism and Bone Diseases (SIOMMMS)

Osteoporos Int
DOI 10.1007/s00198-012-2074-y

POSITION PAPER

European guidance for the diagnosis and management of osteoporosis in postmenopausal women

J. A. Kanis · E. V. McCloskey · H. Johansson · C. Cooper · R. Rizzoli · J.-Y. Reginster · on behalf of the Scientific Advisory Board of the European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO) and the Committee of Scientific Advisors of the International Osteoporosis Foundation (IOF)

NOTA 79

La prescrizione a carico del SSN è limitata alle seguenti condizioni di rischio di frattura osteoporotica:

- **Prevenzione secondaria in soggetti con pregresse fratture osteoporotiche**
  - **vertebrali o di femore**

Condizione	Trattamento I scelta [a]	II scelta	III scelta
1-2 fratture [b]	Alendronato (± vit.D), Risedronato, Zoledronato [d],	Denosumab [g], Ibandronato, Raloxifene, Bazedoxifene	Stronzio ranelato [f]
≥ 3 fratture	Teriparatide [e]	Denosumab [g], Zoledronato [d]	Alendronato (± vit.D), Risedronato, Ibandronato Stronzio ranelato [f]
≥ 1 frattura + T-score colonna o femore [c] ≤ -4			
≥ 1 frattura + trattamento > 12 mesi con prednisone o equivalenti ≥ 5 mg/die			
Nuova frattura vertebrale o femorale nonostante trattamento in nota 79 da almeno 1 anno			

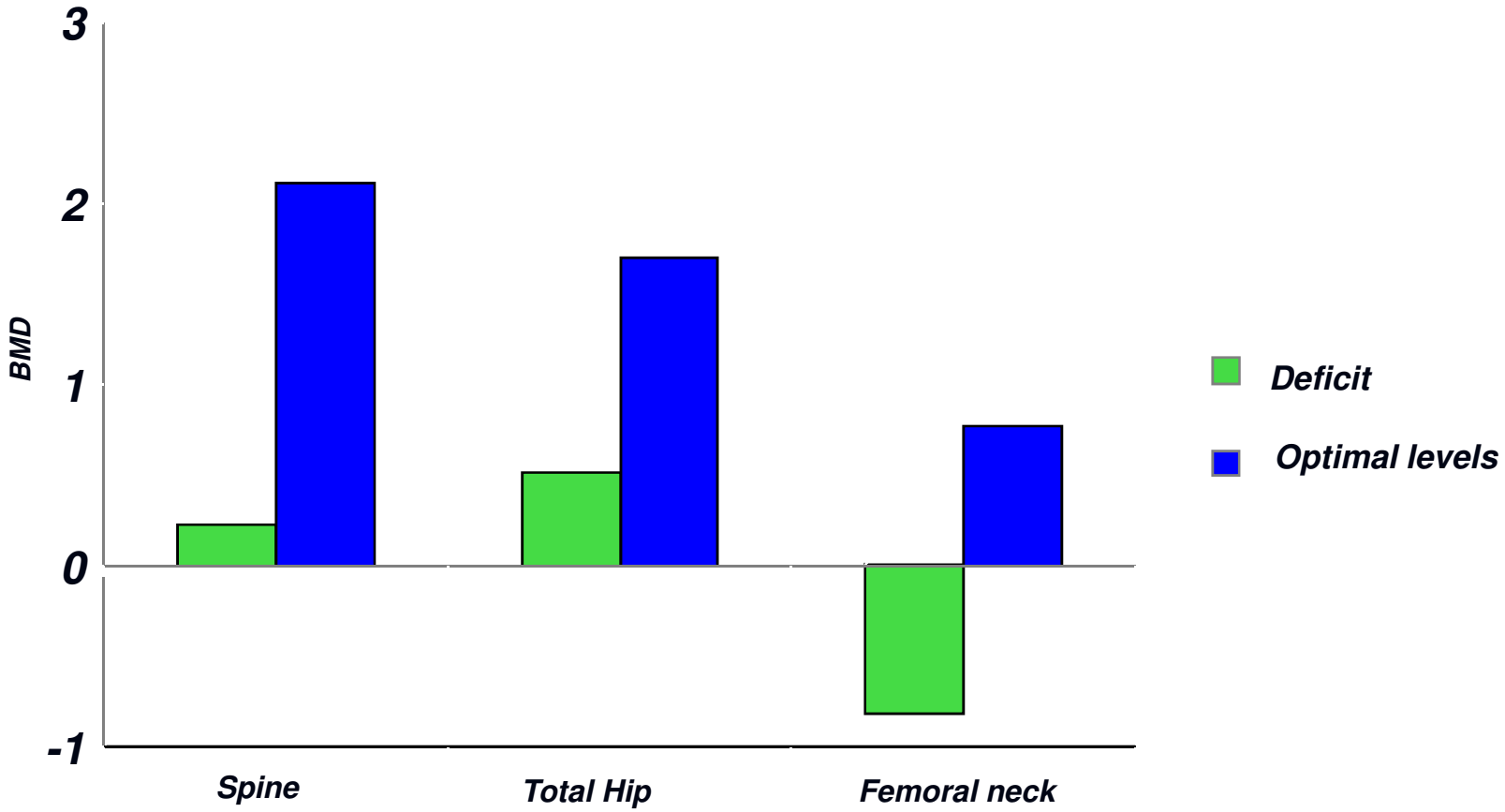
  - **non vertebrali e non femorali**

+ T-score colonna o femore ≤ -3	Alendronato (± vit.D), Risedronato, Zoledronato [d],	Denosumab [g], Ibandronato, Raloxifene, Bazedoxifene	Stronzio ranelato [f]

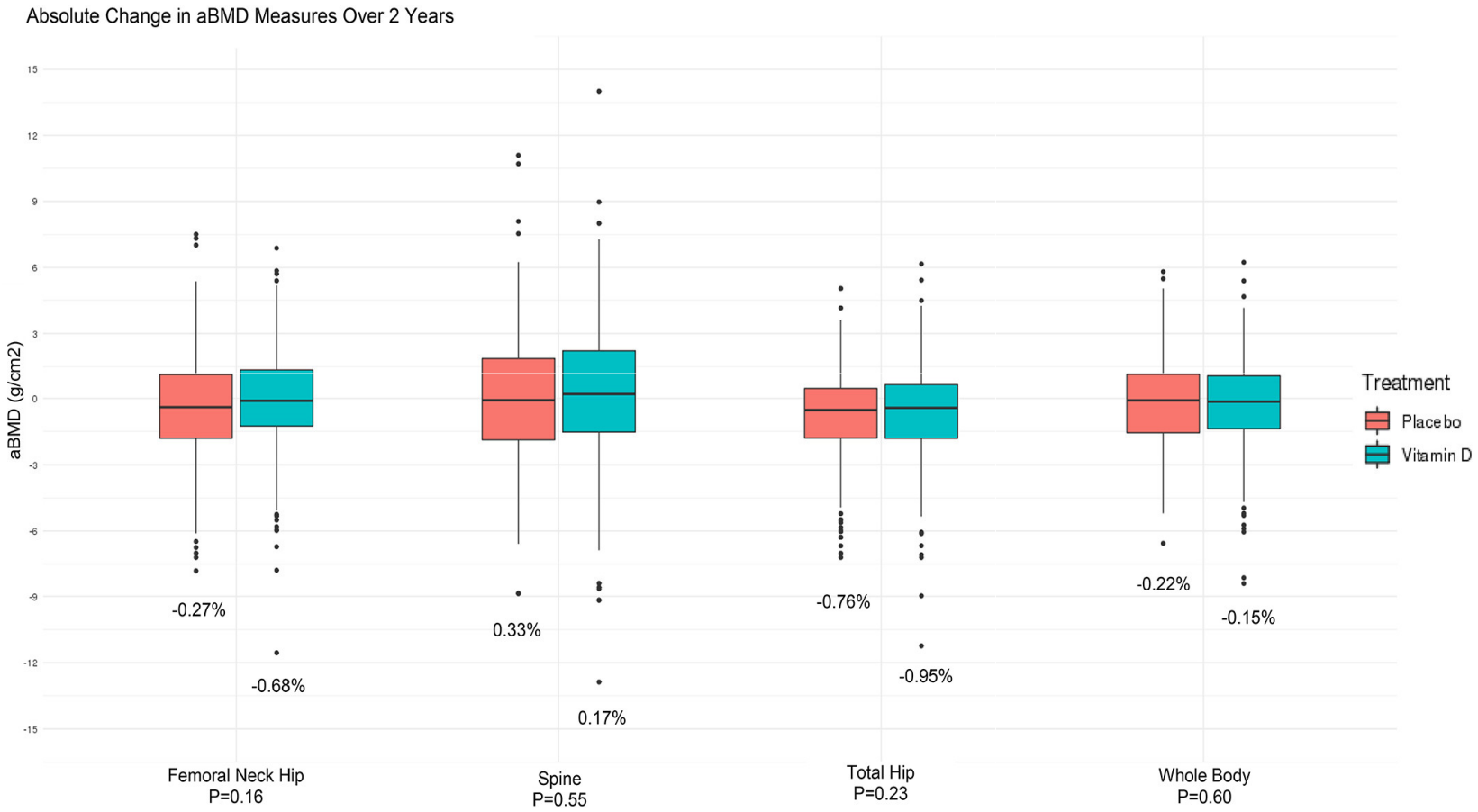
- **Prevenzione primaria in donne in menopausa o uomini di età ≥ 50 anni a rischio elevato di frattura a causa di almeno una delle condizioni sottoelencate:**

Condizione	I scelta [a]	II scelta	III scelta
Trattamento in atto o previsto per > 3 mesi con prednisone equivalente ≥ 5 mg/die	Alendronato (± vitD), Risedronato, Zoledronato [d],	denosumab	----------
Trattamento in corso di blocco ormonale adiuvante in donne con carcinoma mammario o uomini con carcinoma prostatico	Alendronato (± vitD), Risedronato, Zoledronato [d], Denosumab [g]	----------	----------
T-score colonna o femore [c] ≤ -4	Alendronato (± vit.D), Risedronato,	Denosumab [g], Zoledronato [d], Ibandronato Raloxifene, Bazedoxifene	Stronzio ranelato [f]
T-score colonna o femore [c] ≤ -3 + almeno una delle seguenti condizioni: 1) Familiarità per fratture di vertebre o femore 2) Comorbilità a rischio di frattura (artrite reumatoide o altre connettiviti, diabete, broncopneumopatia cronica			

Vitamin D status and efficacy of alendronate therapy



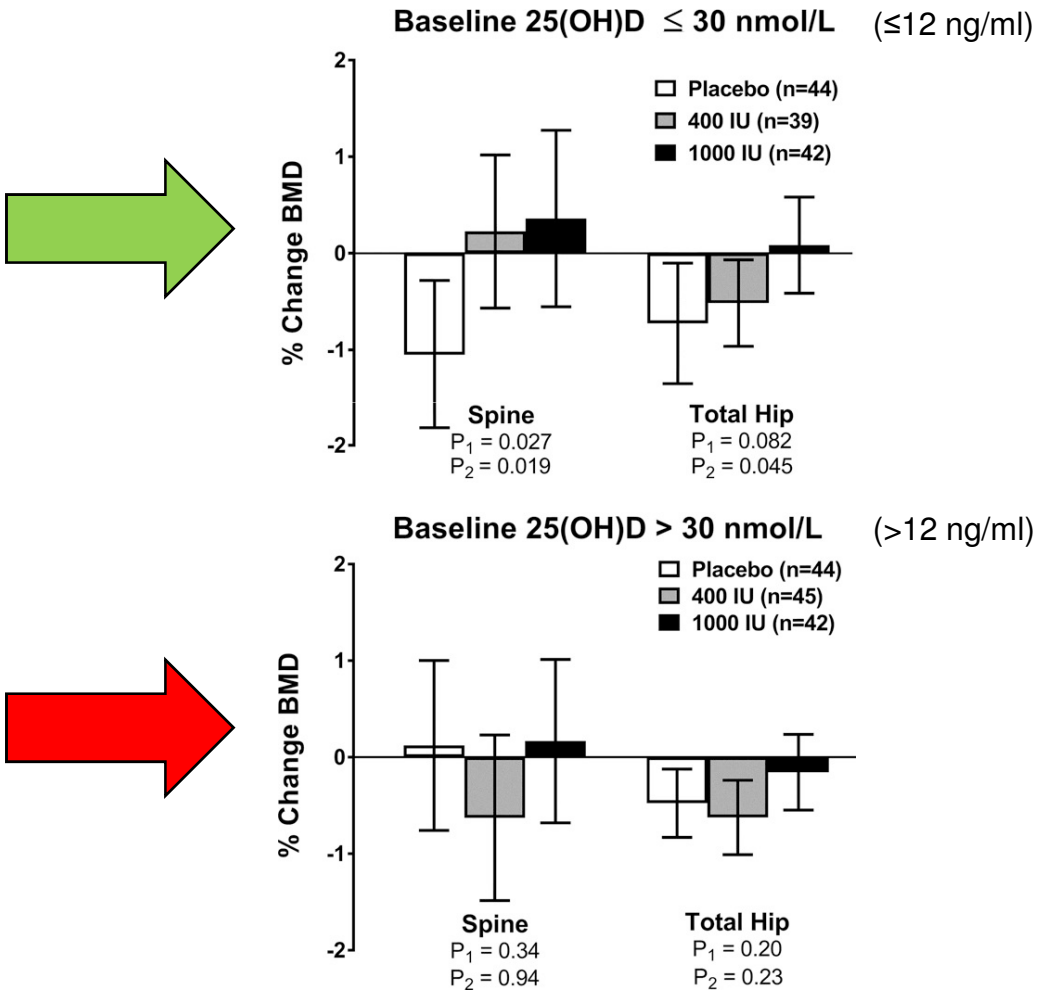
ami S. et al., Osteoporosis Int. 2008



BMD

The VITAL Bone Health stu
includes 771 participants (m
aged ≥50 years and women
aged ≥55 years; not taki
bone active medication
evaluated at baseline and aft
2 years.

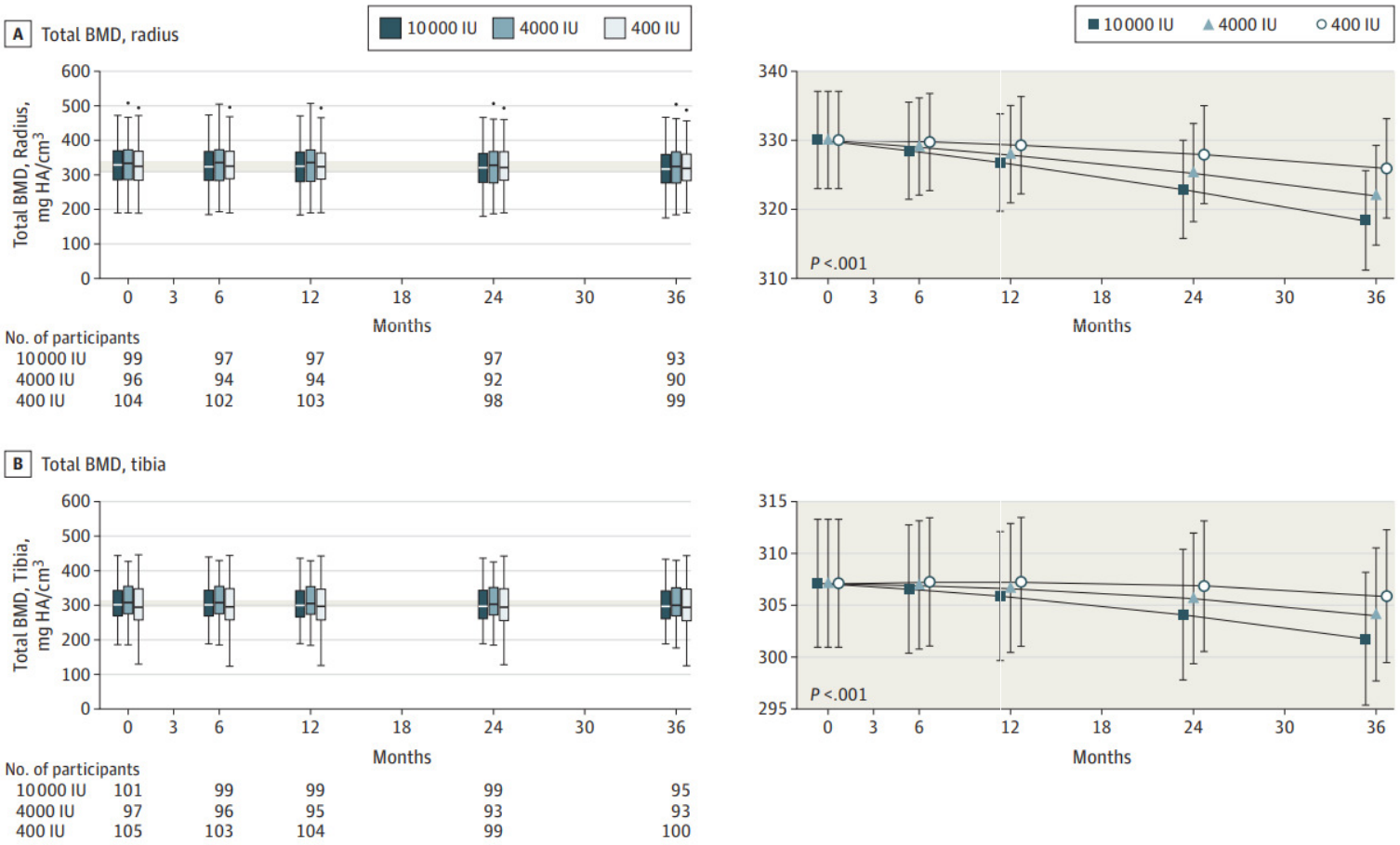
LeBoff MS, e al. J Bone Miner Res. 2



The Aberdeen study recruited 305 postmenopausal women in late winter and randomized them to receive placebo, vitamin D 400 IU/d, or vitamin D 1000 IU/d over 1 year.

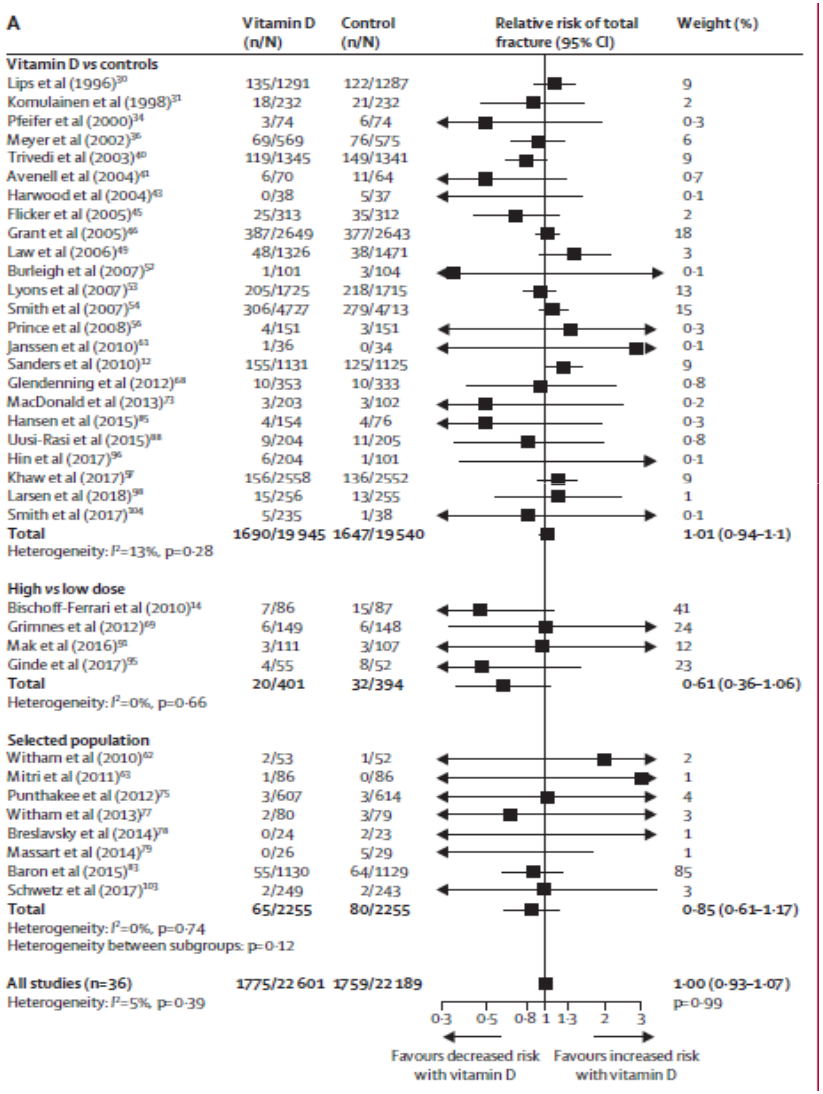
Macdonald HM, et al. J Bone Miner Res. 2018

Figure 3. Data Distribution and Change in Total Bone Mineral Density (BMD) and Failure Load During 3 Years of Vitamin D Supplementation



The Calgary study was designed evaluate the effect of long-term high-d vitamin D on bone mass and quality daily dose of 400 IU, 4,000 IU or 10,0 IU of vitamin D for 3 years in Canad adults did not increase BMD, but rat slightly decreased BMD, as measured the best available methodology (hi resolution pQCT). Indeed, BMD at radius and tibia significantly decreased 3.5% and 1.7 %, respectively in 10,000 IU per day group compared w the 400 IU per day group, whereas decrease at both sites was statistically significant in the 4,000 IU day group compared with the 400 IU day group.

Burt LA, et al. JAMA. 201

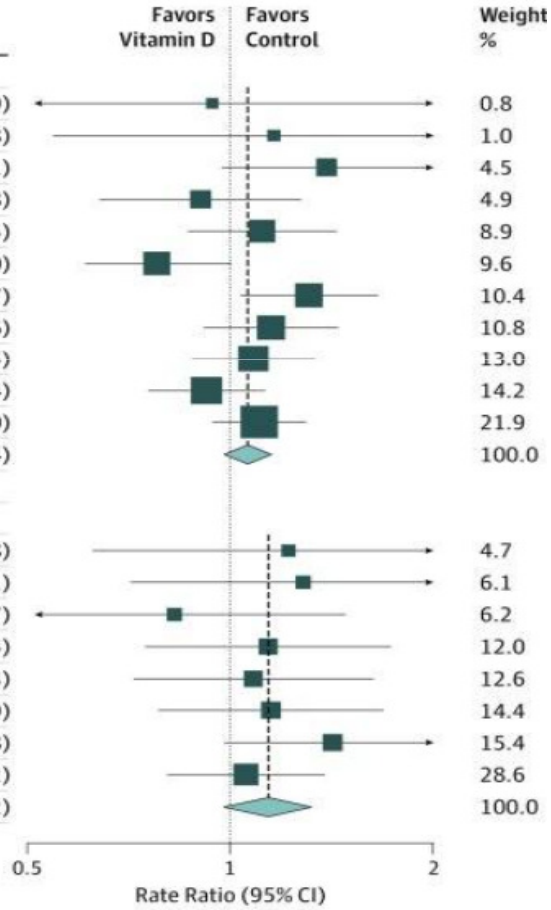


Fractures

In pooled analyses, vitamin D had no effect on total fracture (36 trials; n=44 790, relative risk 1·00, 95% CI 0·93-1·07), hip fracture (20 trials; n=36 655, 1·11, 0·97-1·26).

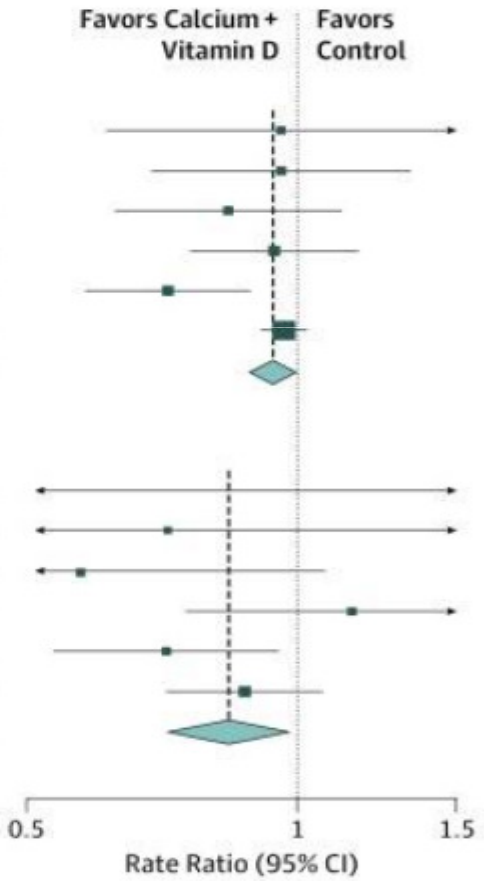
Bolland M, et al. Lancet 2018

Source	Treatment	Vitamin D Events, No./ Total Participants, No.	Control Events, No./ Total Participants, No.	Risk of Bias	Rate Ratio (95% CI)	Weight %
Any fracture						
Glendenning et al,[39] 2012	150 000 IU/3 mo	10/353	10/333	High	0.94 (0.39-2.29)	0.8
Larsen et al,[40] 2018	20 000 IU/wk	15/256	13/255	Unclear	1.16 (0.54-2.48)	1.0
Law et al,[41] 2006	100 000 IU/3 mo	66/1762	53/1955	High	1.39 (0.97-2.01)	4.5
Meyer et al,[42] 2002	400 IU/d	69/569	76/575	High	0.90 (0.64-1.28)	4.9
Lips et al,[43] 1996	400 IU/d	135/1291	122/1287	High	1.12 (0.86-1.45)	8.9
Trivedi et al,[44] 2003	100 000 IU/4 mo	119/1345	149/1341	High	0.78 (0.61-1.00)	9.6
Sanders et al,[45] 2010	500 000 IU/y	171/1131	135/1127	High	1.31 (1.03-1.67)	10.4
Khaw et al,[46] 2017	100 000 IU/mo	156/2558	136/2550	Low	1.15 (0.91-1.46)	10.8
Grant et al,[47] 2005	800 IU/d	208/1343	192/1332	High	1.08 (0.88-1.35)	13.0
Lyons et al,[48] 2007	100 000 IU/4 mo	205/1725	218/1715	High	0.92 (0.76-1.14)	14.2
Smith et al,[49] 2007	300 000 IU/y	306/4727	279/4713	High	1.11 (0.93-1.30)	21.9
All		1460/17 060	1383/17 183		1.06 (0.98-1.14)	100.0
Subtotal ($Q = 14.5$, $df = 10$, $P = .15$; $I^2 = 31.1\%$)						
Hip fracture						
Sanders et al,[45] 2010	500 000 IU/y	19/1131	15/1127	High	1.22 (0.64-2.48)	4.7
Law et al,[41] 2006	100 000 IU/3 mo	24/1762	20/1955	High	1.28 (0.73-2.41)	6.1
Trivedi et al,[44] 2003	100 000 IU/4 mo	21/1345	24/1341	High	0.83 (0.48-1.57)	6.2
Grant et al,[47] 2005	800 IU/d	47/1343	41/1332	High	1.14 (0.75-1.75)	12.0
Meyer et al,[42] 2002	400 IU/d	50/569	47/575	High	1.08 (0.71-1.63)	12.6
Lips et al,[43] 1996	400 IU/d	58/1291	48/1287	High	1.15 (0.82-1.79)	14.4
Smith et al,[49] 2007	300 000 IU/y	66/4727	44/4713	High	1.42 (1.03-2.18)	15.4
Lyons et al,[48] 2007	100 000 IU/4 mo	112/1725	104/1715	High	1.06 (0.82-1.42)	28.6
All		397/13 893	343/14 045		1.14 (0.98-1.32)	100.0
Subtotal ($Q = 3.0$, $df = 7$, $P = .89$; $I^2 = 0.0\%$)						



Yao P, et al. JAMA Netw Open. 2019

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 ($Q = 6.0$, $df = 5$, $P = .31$; $I^2 = 16.5\%$)							



-6%

-16

Yao P, et al. JAMA Netw Open. 2019

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

MS LeBoff et al. N Engl J Med 202

Discordance between observational and randomized clinical trials

Most importantly, serum 25OHD levels are a highly confounded variable. Specifically, serum 25OHD levels are affected by a host of health behaviors, the presence of obesity, socioeconomic status and education levels.

Reverse causality remains a valid rationale to explain the discordance between observational and intervention studies. The most plausible hypothesis states that individuals with any health problems are less likely to regularly engage in outdoor activity and less exposure to sunlight results in lower vitamin D status.

Modified from Bouillon R, et al. Nat Rev Endocrinol. 202

Conclusions

- The data generated by the 2017–2020 megatrials of vitamin D supplementation do not support the recommendation of vitamin D supplementation in general population for improving global health or preventing major diseases or medical events such as cancer, cardiovascular events, T2DM, falls or fractures.
- These data do not contradict the need to correct severe deficiency at any age.
- Some extra-skeletal benefits of vitamin D supplementation are largely based on subgroup or post hoc analyses and might guide the correct design of future studies.

- The 7% of the world population has a severe vitamin D deficiency and do not take or even have access to normal doses of vitamin D.
- However, many vitamin D-replete people take vitamin D supplements without clear benefits.
- Therefore, we recommend that vitamin D be used wisely and “**giveth to those who needeth**”.

Modified from Bouillon R, et al. Nat Rev Endocrinol. 202

Grazie per la vostra cortese attenzione