Supplemental e-material

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eTable 1: Definitions of outcomes

Outcomes	Definitions
All-cause Mortality	Deaths from any causes
Cancer morality	Deaths due to cancer
Cardiovascular mortality	Deaths due to cardiovascular disease
Non-cancer, non-cardiovascular mortality	Deaths from any other causes excepted cancer and cardiovascular disease
Cerebrovascular disease mortality	Deaths due to cerebrovascular disease
Ischemic heart disease mortality	Deaths due to ischemic heart disease

eTable 2: Search strategy

MEDLINE(R)		
1	exp Vitamin D/ad, ae, pd, tu [Administration & Dosage, Adverse Effects, Pharmacology, Therapeutic Use]	30296
2	((vit-d? or vitamin-d? or dihydroxyvitamin D? or dihydroxy-vitamin D? or hydroxyvitamin D? or hydroxyl-vitamin d? or dihydrotachysterol or colecalciferol or epicalcitriol or oxacalcitriol or alfacalcidol or calcifediol I or calciferol? or calcipotriol or calcitriol or dihydroxycolecalciferol or hydroxycolecalciferol or seocalcitol or tacalcitol or oxavitamin or hydroxycholecalciferol? or calcidiol or calcipotriene or dihydroxycholecalciferol? or dihydroxy-cholecalciferol or cholecalciferol? or ergocalciferol? or epiergocalciferol or dihydroxyergocalciferol or dihydroxy-ergocalciferol or hydroxyl-ergocalciferol or hydroxyergocalciferol or doxercalciferol or hydroxycalciferol or hydroxylcalciferol or dihydroxy-calciferol or dihydroxycalciferol or dihydrotachysterin or calcamine or ercalcidiol) adj5 (supplement* or therap* or treat* or prevent* or daily or receiv* or regimen or dose? or oral* or intramuscular or inject*)).mp.	23153
3	randomized controlled trial.pt.	472058
4	controlled clinical trial.pt.	92771
5	random*.mp.	1235825
6	placebo.ab.	193707
7	drug therapy.fs.	2065354
8	trial.ab.	446799
9	groups.ab.	1858094
10	or/3-9	4587425
11	exp animals/ not humans.sh.	4519948
12	10 not 11	3961476
13	(1 or 2) and 12	16982
14	limit 13 to "all adult (19 plus years)"	8430
Embase		

1	exp vitamin D/ae, ct, ad, cb, cm, cr, do, dt, ei, ce, ci, dl, du, ig, ly, im, na, os, tl, ur, ut, va, iv, vi, po, pa, oc, pd, cj, sb, li, tp, td [Adverse Drug Reaction, Clinical Trial, Drug Administration, Drug Combination, Drug Comparison, Drug Concentration, Drug Dose, Drug Therapy, Epidural Drug Administration, Intracerebral Drug Administration, Intracisternal Drug Administration, Intradermal Drug Administration, Intraduodenal Drug Administration, Intragastric Drug Administration, Intralymphatic Drug Administration, Intramuscular Drug Administration, Intranasal Drug Administration, Intraosseous Drug Administration, Intrathecal Drug Administration, Intraurethral Drug Administration, Intrauterine Drug Administration, Intravaginal Drug Administration, Intravenous Drug Administration, Intravitreal Drug Administration, Oral Drug Administration, Parenteral Drug Administration, Periocular Drug Administration, Pharmacology, Subconjunctival Drug Administration, Sublabial Drug Administration, Sublingual Drug Administration, Topical Drug Administration, Transdermal Drug Administration] ()	41677
2	((vit-d? or vitamin-d? or dihydroxyvitamin D? or dihydroxy-vitamin D? or hydroxyvitamin D? or hydroxylvitamin d? or dihydrotachysterol or colecalciferol or epicalcitriol or oxacalcitriol or alfacalcidol or calcifediol I or calciferol? or calcipotriol or calcitriol or dihydroxycolecalciferol or hydroxycolecalciferol or seocalcitol or tacalcitol or oxavitamin or hydroxycholecalciferol? or calcidiol or calcipotriene or dihydroxycholecalciferol? or dihydroxy-cholecalciferol or cholecalciferol? or ergocalciferol? or epiergocalciferol or dihydroxyergocalciferol or dihydroxy-ergocalciferol or hydroxyl-ergocalciferol or hydroxyergocalciferol or doxercalciferol or hydroxycalciferol or hydroxyl-calciferol or dihydroxy-calciferol or dihydroxycalciferol or dihydrotachysterin or calcamine or ercalcidiol) adj5 (supplement* or therap* or treat* or prevent* or daily or receiv* or regimen or dose? or oral* or intramuscular or inject*)).mp.	36502
3	randomized controlled trial/	527802
4	crossover procedure/	57606
5	double blind procedure/	156224
6	single blind procedure/	33370
7	(random* or factorial* or crossover* or placebo* or assign* or allocat* or volunteer* or (doubl* adj5 blind*) or (singl* adj5 blind*)).mp.	2330598
8	or/3-7	2330598
9	exp animal/	23506001
10	human/	19009525
11	9 not 10	4496476
12	8 not 11	2105846
13	(1 or 2) and 12	13165
14	limit 13 to (adult <18 to 64 years> or aged <65+ years>)	5251

EBM Reviews - Cochrane Central Register of Controlled Trials

1	exp Vitamin D/ad, ae, pd, tu [Administration & Dosage, Adverse Effects, Pharmacology, Therapeutic Use]	702
2	((vit-d? or vitamin-d? or dihydroxyvitamin D? or dihydroxy-vitamin D? or hydroxyvitamin D? or hydroxylvitamin d? or dihydrotachysterol or colecalciferol or epicalcitriol or oxacalcitriol or alfacalcidol or calcifediol I or calciferol? or calcipotriol or calcitriol or dihydroxycolecalciferol or hydroxycolecalciferol or seocalcitol or tacalcitol or oxavitamin or hydroxycholecalciferol? or calcidiol or calcipotriene or dihydroxycholecalciferol? or dihydroxy-cholecalciferol or cholecalciferol? or ergocalciferol? or epiergocalciferol or dihydroxyergocalciferol or dihydroxy-ergocalciferol or hydroxyl-ergocalciferol or hydroxyergocalciferol or doxercalciferol or hydroxycalciferol or hydroxyl-calciferol or dihydroxy-calciferol or dihydroxycalciferol or dihydrotachysterin or calcamine or ercalcidiol) adj5 (supplement* or therap* or treat* or prevent* or daily or receiv* or regimen or dose? or oral* or intramuscular or inject*)).mp.	7606
3	1 or 2	7688

eTable 3: Study characteristics

Trial	Intervention	Control	Primary outcome	Follow-up
Brohult 1973	vitamin D3 (100,000 IU) daily	placebo	bone mineral density	1-year
Inkovaara 1983	vitamin D3 (1000 IU) daily	placebo	Biochemistry	1-year
Corless 1985	vitamin D2 (9000 IU) daily	placebo	activities of daily living	9-month
Lips 1996	vitamin D3 (400 IU) daily	placebo	Fracture	3.5-year
Meyer 2002	vitamin D3 (400 IU) daily	placebo	Fracture	1-year
Cooper 2003	vitamin D2 (10,000 IU) weekly plus calcium (1000 mg) daily	calcium (1000 mg) daily	bone mineral density	2-year
Trivedi 2003	vitamin D3 (100,000 IU) four-monthly	placebo	Fracture	5-year
Latham 2003	vitamin D3 (300,000 IU) single dose plus exercise	placebo plus exercise	Health	6-month
Bischoff 2003	vitamin D3 (800 IU) plus calcium 1200 mg daily	calcium (1200 mg) daily	Falls	3-month
Harwood 2004	vitamin D2 (300,000 IU) single dose	placebo	bone biochemical markers	1-year
Flicker 2005	vitamin D3 (10,000 IU) weekly then vitamin D3 (1000 IU) daily plus calcium (600 mg) daily	calcium (600 mg) daily	falls and fractures	2-year
Aloia 2005	vitamin D3 (800 IU) plus calcium (1200 - 1500 mg) daily	calcium (1200-1500 mg) daily	bone mineral density	2-year
Law 2006	vitamin D2 (1100 IU) daily	no intervention	Fractures and falls	10-month
Schleithoff 2006	vitamin D3 (2000 IU) plus calcium (500 mg) daily	calcium (500 mg) daily	Biochemistry	1.25-year
Lyons 2007	vitamin D2 (100,000 IU) four-monthly	placebo	Fracture	3-year
Smith 2007	vitamin D2 (300,000 IU) yearly	placebo	Fracture	3-year
Broe 2007	vitamin D2 (800 IU, 600IU, 400IU, or 200 IU) daily	placebo	Falls	5-month
Burleigh 2007	vitamin D3 (800 IU) plus calcium (1200 mg) daily	calcium (1200 mg) daily	Falls	30-day
Lappe 2007	vitamin D3 (1000 IU) plus calcium (1400 to 1500 mg) daily	calcium (1400 to 1500 mg) daily	bone mineral density	4-year
Chel 2008	vitamin D3 (600 IU) daily, (4200 IU) weekly or (18,000 IU) monthly	placebo	25(OH)D levels	4.5-month
Prince 2008	vitamin D2 1000 IU plus calcium 1000 mg daily	calcium (1000 mg) daily	Falls	1-year

Zhu 2008	vitamin D2 (1000 IU) plus calcium (1200 mg) daily	calcium (1200 mg) daily	bone mineral density	5-year
Witham 2010	vitamin D2 (10,000 IU) tablet at baseline and 10 weeks	placebo	six-minute walk test	20-week
Sanders 2010	vitamin D3 (500,000 IU) yearly	placebo	falls and fractures	3-year
Lips 2010	vitamin D3 (8400 IU) weekly	placebo	Fracture	16-week
Janssen 2010	vitamin D3 (400 IU) plus calcium (500 mg) daily	calcium (500 mg) daily	Biochemistry	6-month
Grimnes 2011	vitamin D3 (20,000 IU) twice weekly	placebo	insulin sensitivity and secretion	6-month
Cherniack 2011	vitamin D3 (2000 IU) daily	placebo	Biochemistry	6-month
Glendenning 2012	vitamin D3 150,000 IU three-monthly	placebo	falls	9-month
Lehouck 2012	vitamin D3 100,000 IU monthly	placebo	COPD exacerbation	1-year
Punthakee 2012	vitamin D3 (1000 IU) daily	placebo	all-cause death or cancers requiring hospitalization	5-month
RECORD 2012	vitamin D3 (800 IU) daily; vitamin D3 (800 IU) plus calcium (1000 mg) daily	Placebo; calcium (1000 mg) daily	Fracture	45-month
Witham 2013	vitamin D3 (100,000 IU) three-monthly	placebo	25OHD levels	1-year
Massart 2014	vitamin D3 (25,000 IU) weekly	placebo	25(OH)D levels	13-week
Rizzoli 2014	vitamin D3 (1000 IU) daily plus strontium ranelate (2000 mg) daily	strontium ranelate (2000 mg) daily	Biochemistry	6-month
Martineau 2015	vitamin D3 (120,000 IU) two-monthly	placebo	COPD exacerbation	1-year
Hansen 2015	vitamin D3 (800 IU) daily; vitamin D3 (50,000 IU) two-weekly	placebo	bone mineral density	2-year
Uusi-Rasi 2015	vitamin D3 (800 IU) daily; vitamin D3 (800 IU) daily plus exercise	placebo; placebo plus exercise	falls	2-year
Baron 2015	vitamin D3 (1000 IU) daily plus calcium (1200 mg) daily	calcium (1200 mg) daily	adenomas incidence	3-year
Jin 2016	vitamin D3 (50,000 IU) monthly	placebo	tibial cartilage volume and pain score	2-year
Jorde 2016	vitamin D3 (20 000 IU) weekly	placebo	progression to type 2 diabetes	5-year
Arden 2016	vitamin D3 (800 IU) daily	placebo	joint space narrowing	3-year
Witte 2016	vitamin D3 (4000 IU) daily	placebo	6-min walk test distance	1-year
ViDA 2017	vitamin D3 initial (200000 IU) then vitamin D3 (100,000 IU) monthly	placebo	CVD and death	3.3-year
EVITA 2017	vitamin D3 (4000 IU) daily	placebo	all-cause mortality	3-year

Hin 2017	vitamin D3 (4000/2000 IU) daily	placebo	Biochemistry	1-year
Levis 2017	vitamin D3 (4000 IU) daily	placebo	SPPB score and gait speed	9-month
Owusu 2018	vitamin D3 (2400 IU, 3600 IU or 4800 IU) daily plus calcium (1200mg) daily	calcium (1200 mg) daily	cognitive decline	3-year
Akiba 2018	vitamin D3 (1200 IU) daily	placebo	RFS and OS	1-year
VITAL 2018	vitamin D3 (2000 IU) daily; vitamin D3 (800 IU) plus Omega-3 fatty acids (1000 mg) daily	Placebo; Omega-3 fatty acids (1000 mg) daily	cancer and major cardiovascular events	6-year

eTable 4: Population characteristics of included studies

Trial	Participants (vitamin D / no vitamin D)	Mean age (years)	Female	Baseline mean 25OHD (nmol/L) vitamin D/no vitamin D	Achieved mean 25OHD (nmol/L) vitamin D/no vitamin D
Brohult 1973	25/25	52	68%	NR/NR	NR/NR
Inkovaara 1983	45/42	79.5	17%	NR/NR	NR/NR
Corless 1985	41/41	82.4	78%	18/17	110/20
Lips 1996	1291/1287	80	74%	26/27	54/23
Meyer 2002	569/575	84.7	75%	47/51	64/46
Cooper 2003	93/94	56	100%	82/83	81/70
Trivedi 2003	1345/1341	74.7	24%	NS/NS	74/53
Latham 2003	121/122	85	100%	38/48	60/48
Bischoff 2003	62/60	85.3	100%	31/29	66/29
Harwood 2004	38/37	81.2	100%	28/30	45/32
Flicker 2005	313/312	83.4	95%	NR/NR	NR/NR
Aloia 2005	104/104	60	NS	47/43	87/NR
Law 2006	1762/1955	85	76%	59	77
Schleithoff 2006	61/62	51	17%	36/38	103/47
Lyons 2007	1725/1715	84	76%	NS/NS	80/54
Smith 2007	4727/4713	75	54%	56.5	171
Broe 2007	99/25	89	73%	48/53	63/60
Burleigh 2007	100/103	83	59%	25/22	27/22
Lappe 2007	446/445	66.7	100%	72/72	96/71
Chel 2008	166/172	84	77%	25/25	63/27
Prince 2008	151/151	77.2	100%	45/44	60/45-55
Zhu 2008	39/40	75	100%	70/67	106/64
Witham 2010	53/52	79.7	34%	21/24	NR/NR
Sanders 2010	1131/1125	76	100%	53/45	65/45
Lips 2010	114/112	78	NS	34/35	65/35
Janssen 2010	36/34	65	100%	33/34	77/42
Grimnes 2011	51/53	51.5	45%	42/39	143/43
Cherniack 2011	23/23	80	2%	71/69	107/72
Glendenning 2012	353/333	76.7	100%	65/67	75/61
Lehouck 2012	91/91	68	20%	50/50	130/55
Punthakee 2012	607/614	66.7	40%	NR/NR	NR/NR
RECORD 2012	2649/2643	77	85%	38/38	62/NR
Witham 2013	80/79	76.8	48%	45/45	65/48
Massart 2014	29/32	64	56%	43/46	88/41
Rizzoli 2014	413/105	67	90%	44/44	65/49
Martineau 2015	122/118	65	41%	45/47	67/47
Hansen 2015	154/76	61	100%	53/53	86/45
Uusi-Rasi 2015	204/205	74	100%	66/69	93/69
Baron 2015	1130/1129	58	37%	63/63	NR/NR
Jin 2016	209/204	63	50%	44/44	211/127
Jorde 2016	256/255	62	49%	60/61	122/67
Arden 2016	237/237	64	61%	21/21	76/51
Witte 2016	114/109	69	21%	38/36	115/25
ViDA 2017	2558/2552	NS	58%	64/63	135/66
EVITA 2017	199/201	55	27%	31/35	103/44
Hin 2017	204/101	72	48%	53/47	120/53
Levis 2017	66/64	72	0%	58/55	115/60

Owusu 2018	130/130	68	100%	55/56	117/52
Akiba 2018	77/78	68	38%	53/55	93/60
VITAL 2018	12927/12944	67	51%	77/77	104/ NR

NR：not reported

eTable 5: Ongoing large trial of vitamin D supplementation on mortality.

Registration	Name	Location	Participants (age)	Dose	Main outcomes	Current state	Results expected
NCT01745263	DO-HEALTH	Europe	2,152 70+	2,000 IU daily	fractures, infections, cognition, function, blood pressure; mortality	Completed; recruitment completed	Fall 2019
ACTRN12613000743763	D-Health	Australia	21,315 60-79	60,000 IU monthly	All-cause mortality; cancer	Ongoing; recruitment completed	2024
ISRCTN46328341	VIDAL	UK	20,000 65-84	60,000 IU monthly	Mortality, longevity, cancer	Ongoing; recruitment completed	2020 for the main study

eTable 6: Summary of Findings and Strength of Evidence in Studies

Outcome	No. of patients (Studies)	Risk ratio (95% CI)	I^2	Absolute effect estimates (per 1000)			Quality
				Control	Vitamin D	Difference	
All-cause Mortality	74655 (50)	RR 0.98 (0.95 to 1.02)	0%	109	107	−2 (−5 to 2)	High
Cancer morality	39197 (5)	RR 0.85 (0.74 to 0.97)	0%	24	20	-4 (-1 to -6)	High
Cardiovascular mortality	43306 (12)	RR 0.98 (0.88 to 1.08)	0%	31	30	−1 (−4 to 2)	High
Non-cancer, noncardiovascular mortality	36358 (4)	RR 1.05 (0.93 to 1.18)	0%	28	29	1 (−2 to 5)	High

eTable 7: Sensitivity analyses

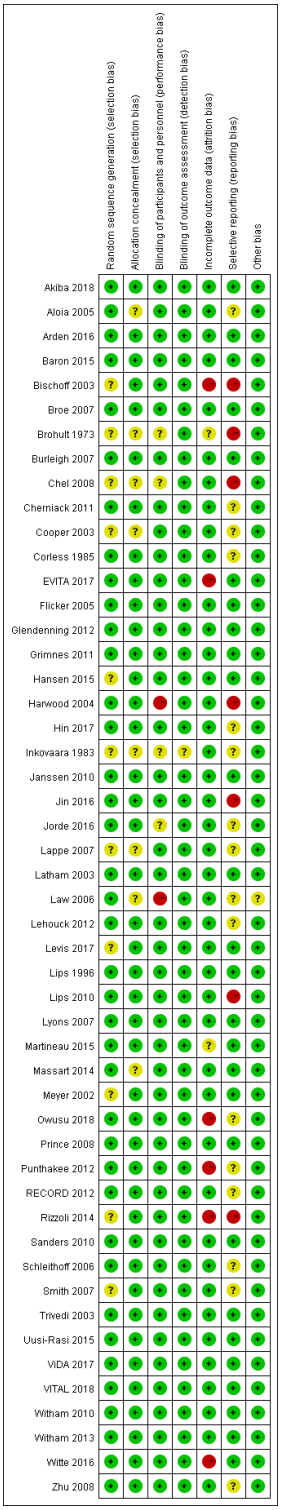
Sensitivity analyses	Risk Ratio, 95% CI	I^2	P
Excluding studies with high or unknow risk of bias	0.97 [0.92, 1.02]	0%	0.22
Excluding studies with high or unknow risk of bias of the different domains			
Sequence generation	0.99 [0.95, 1.03]	0%	0.47
Allocation concealment	0.97 [0.93, 1.01]	0%	0.14
Blinding of patients and personnel	0.97 [0.93, 1.01]	0%	0.10
Blinding of outcome assessors	0.98 [0.95, 1.02]	0%	0.40
Incomplete outcome data	0.98 [0.95, 1.02]	0%	0.41
Selective reporting	0.98 [0.93, 1.02]	0%	0.33
Other bias	0.97 [0.93, 1.01]	0%	0.09
Excluding quasi-randomized or cluster-randomized trials	0.97 [0.93, 1.01]	0%	0.09
Excluding the largest trial	0.98 [0.95, 1.02]	0%	0.43
Excluding trials with follow-up less than 1 year	0.97 [0.93, 1.00]	0%	0.08
Using random-effect models	0.98 [0.95, 1.02]	0%	0.39
Adding trials that have been excluded for vitamin D coadministered with calcium	0.96 [0.92, 1.01]	0%	0.43
Adding trials that have been excluded for hydroxylated vitamin D or vitamin D analogues	0.98 [0.93, 1.03]	0%	0.85
Using trial duration rather than long term follow-up	0.99 [0.95, 1.03]	0%	0.61

eTable 8: Subgroup analysis of the effect of vitamin D on cancer mortality

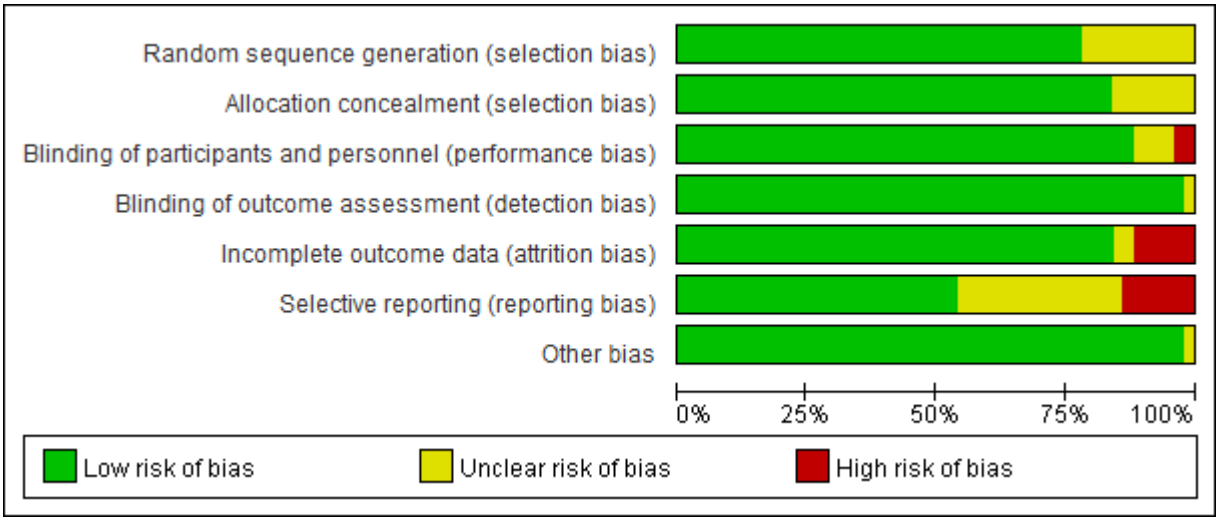
Subgroup title

	No. of trials	No. of patients	I2	Risk Ratio, 95%CI	P for interaction
Overall	5	39197	0%	0.84 [0.74, 0.96]	
No. of patients					
≥2000	4	38957	0%	0.85 [0.74, 0.97]	0.93
<2000	1	230	NA	0.97 [0.06, 15.29]	
No. of events					
≥200	2	31163	0%	0.84 [0.72, 0.97]	0.69
<200	3	8034	0%	0.89 [0.68, 1.17]	
Age					
≥70	2	7978	0%	0.85 [0.72, 1.02]	0.90
<70	3	31219	0%	0.84 [0.69, 1.02]	
Sex					
Female	0	0	NA	NA	NA
Both	5	39197	0%	0.84 [0.74, 0.96]	
Baseline 25(OH)D (nmol/L)					
≥50	2	30979	0%	0.84 [0.69, 1.02]	0.95
<50	2	5532	0%	0.85 [0.69, 1.04]	
Published year					
Before 2014	2	7978	0%	0.85 [0.72, 1.02]	0.90
In or after 2014	3	31219	0%	0.84 [0.69, 1.02]	
Type of vitamin D					
Vitamin D3	5	39197	0%	0.84 [0.74, 0.96]	NA
Vitamin D2	0	0	NA	NA	
Daily dose equivalent					
≥2000 IU	3	31219	0%	0.84 [0.69, 1.02]	0.90
<2000 IU	2	7978	0%	0.85 [0.72, 1.02]	
Timing					
Daily	2	31163	0%	0.84 [0.72, 0.97]	0.69
Intermittently	3	8034	0%	0.89 [0.68, 1.17]	
Residential status					
Community	5	39197	0%	0.84 [0.74, 0.96]	NA
Institution	0	0	NA	NA	
Follow-up					
Follow-up ≥3 y	4	39197	0%	0.85 [0.74, 0.97]	0.93
Follow-up <3 y	1	240	NA	0.97 [0.06, 15.29]	

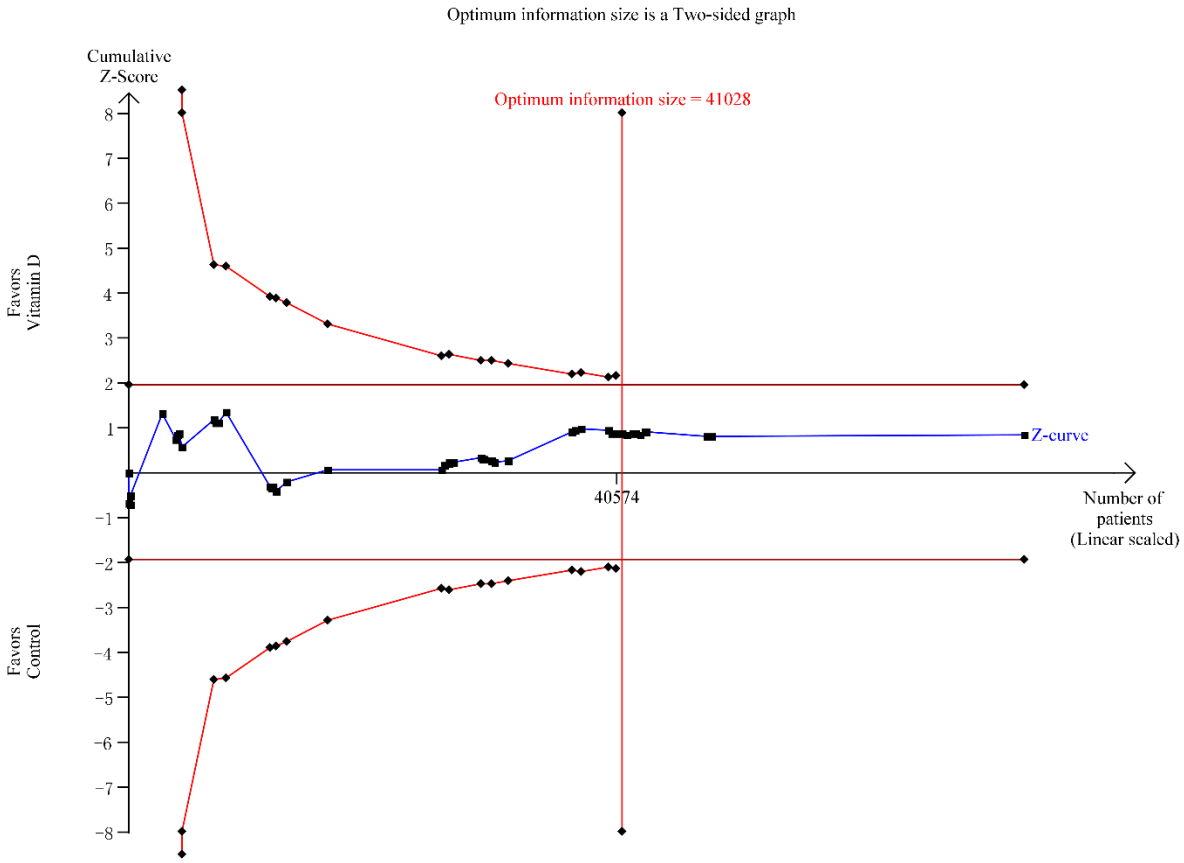
Figure 1: Risk of bias summary: review authors' judgements about each risk of bias item for each included study.


Random sequence generation (selection bias)
Allocation concealment (selection bias)
Blinding of participants and personnel (performance bias)
Blinding of outcome assessment (detection bias)
Incomplete outcome data (attrition bias)
Selective reporting (reporting bias)
Other bias
Akiba 2018
Aloia 2005
Arden 2016
Baron 2015
Bischoff 2003
Broe 2007
Brohult 1973
Burleigh 2007
Chel 2008
Cherniack 2011
Cooper 2003
Corless 1985
EVITA 2017
Flicker 2005
Glendenning 2012
Grimnes 2011
Hansen 2015
Harwood 2004
Hin 2017
Inkovaara 1983
Janssen 2010
Jin 2016
Jorde 2016
Lappe 2007
Latham 2003
Law 2006
Lehouck 2012
Levis 2017
Lips 1996
Lips 2010
Lyons 2007
Martineau 2015
Massart 2014
Meyer 2002
Owusu 2018
Prince 2008
Punthakee 2012
RECORD 2012
Rizzoli 2014
Sanders 2010
Schleithoff 2006
Smith 2007
Trivedi 2003
Uusi-Rasi 2015
ViDA 2017
VITAL 2018
Witham 2010
Witham 2013
Witte 2016
Zhu 2008

e Figure 2: Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies

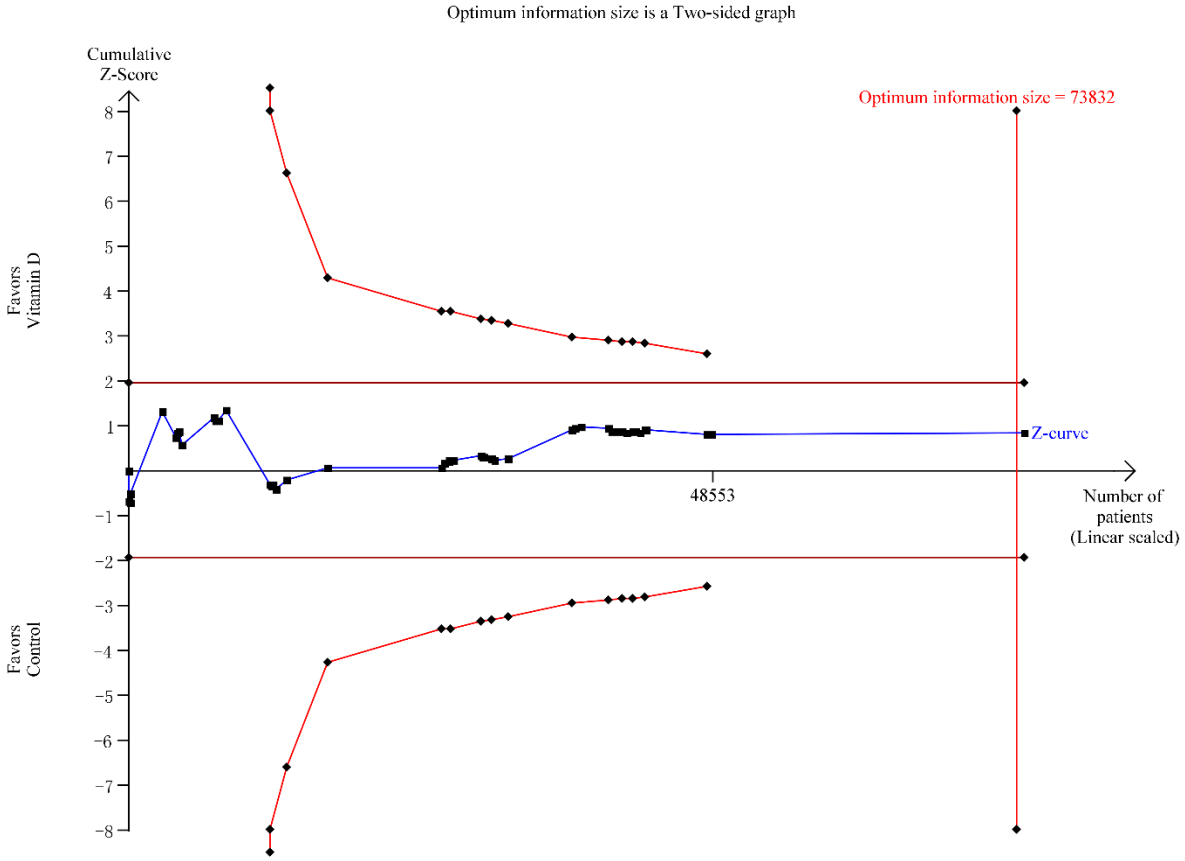


e Figure 3: Trial sequential analysis for all-cause mortality, RRR=10%



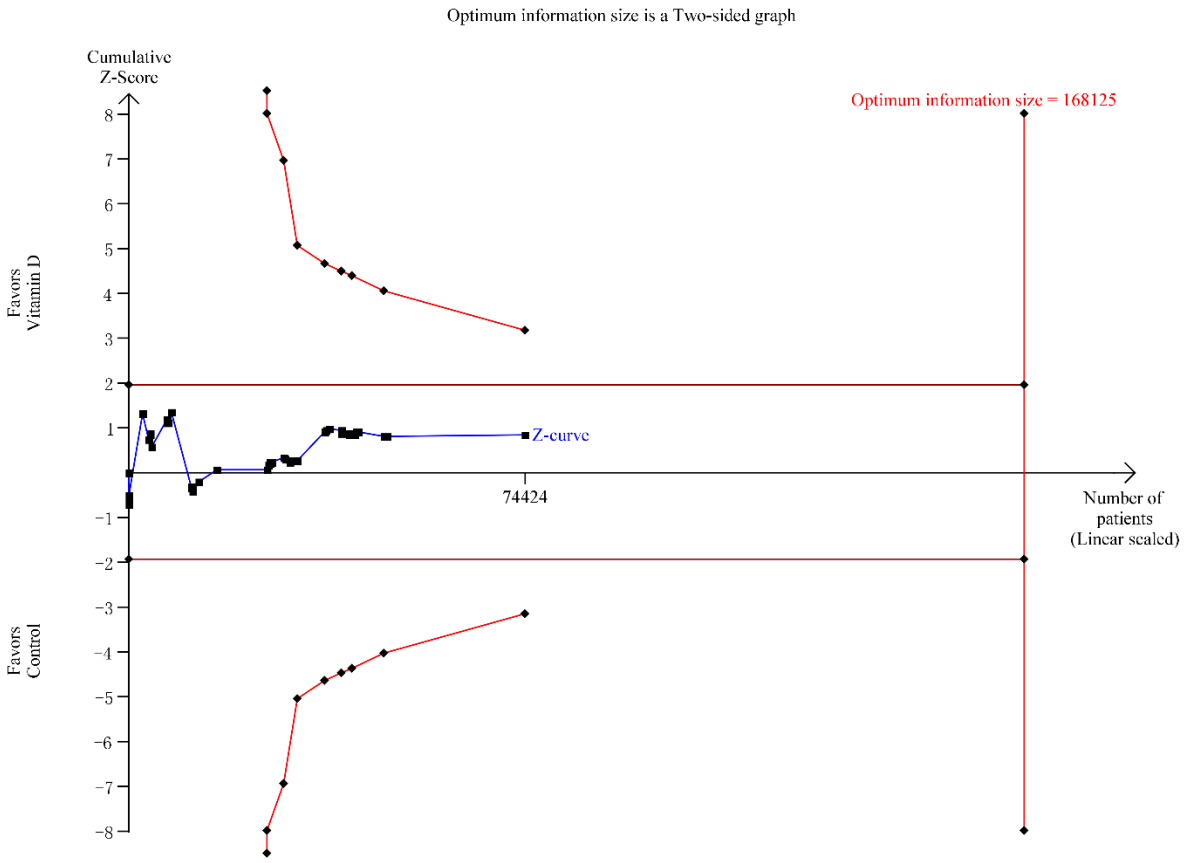
A diversity-adjusted information size (DIS) size of 41028 patients was calculated based on an anticipated relative risk reduction (RRR) of 10% (event proportion of 12% in the control arm, α=0.05 (two-sided), β=0.20 (power 80%)). The blue cumulative z-curve was constructed using a fixed-effects model and crossed the boundary for futility.

e Figure 4: Trial sequential analysis for all-cause mortality, RRR=7.5%



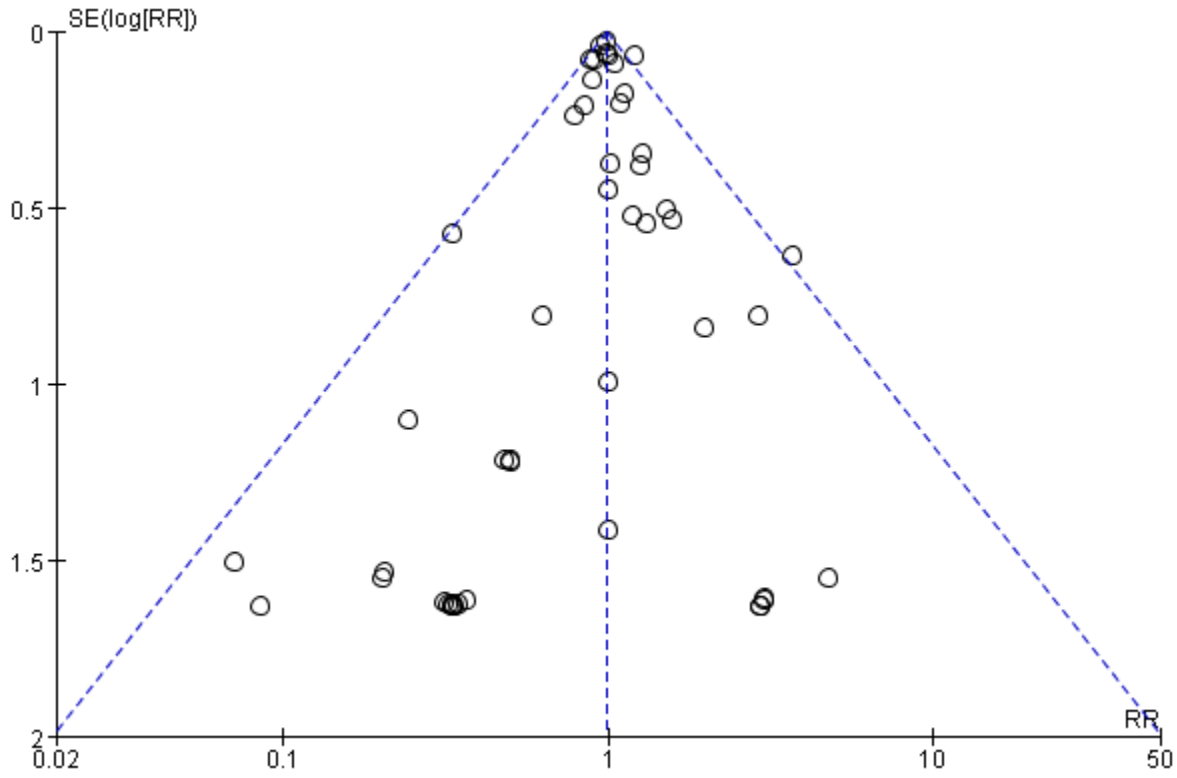
A diversity-adjusted information size (DIS) size of 73832 patients was calculated based on an anticipated relative risk reduction (RRR) of 7.5% (event proportion of 12% in the control arm, α=0.05 (two-sided), β=0.20 (power 80%)). The blue cumulative z-curve was constructed using a fixed-effects model and crossed the boundary for futility.

eFigure 5: Trial sequential analysis for all-cause mortality, RRR=5%

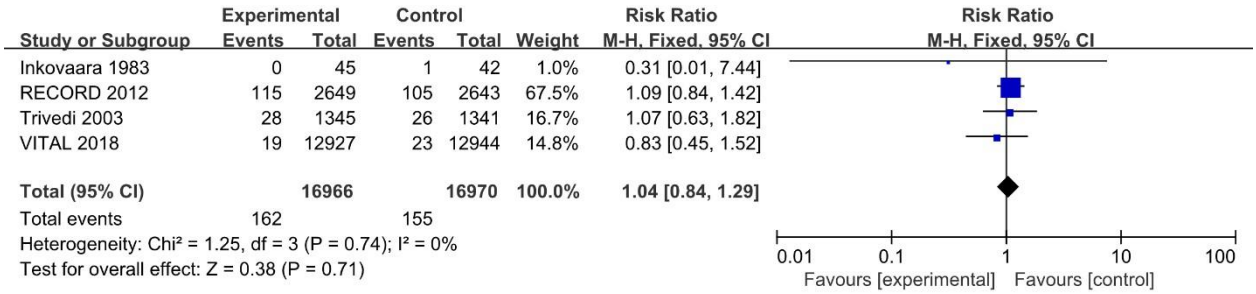


A diversity-adjusted information size (DIS) size of 168125 patients was calculated based on an anticipated relative risk reduction (RRR) of 5% (event proportion of 12% in the control arm, α=0.05 (two-sided), β=0.20 (power 80%)). The blue cumulative z-curve was constructed using a fixed-effects model and did not cross the boundary for futility.

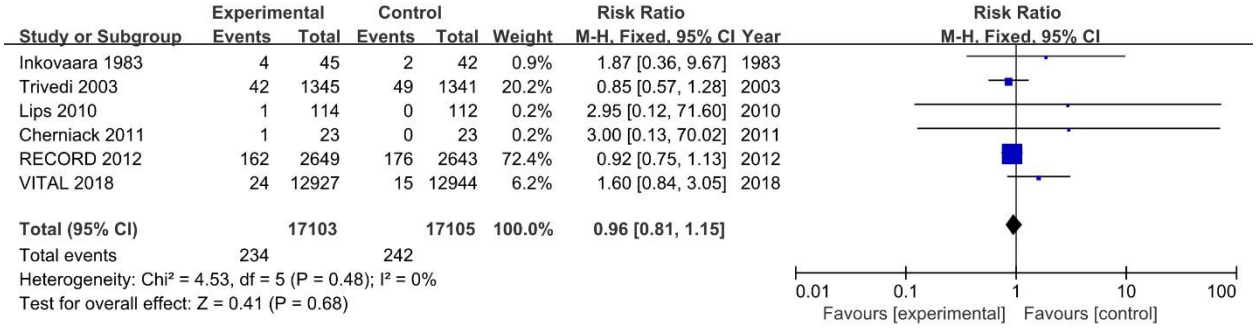
eFigure 6: Funnel plot of all-cause mortality



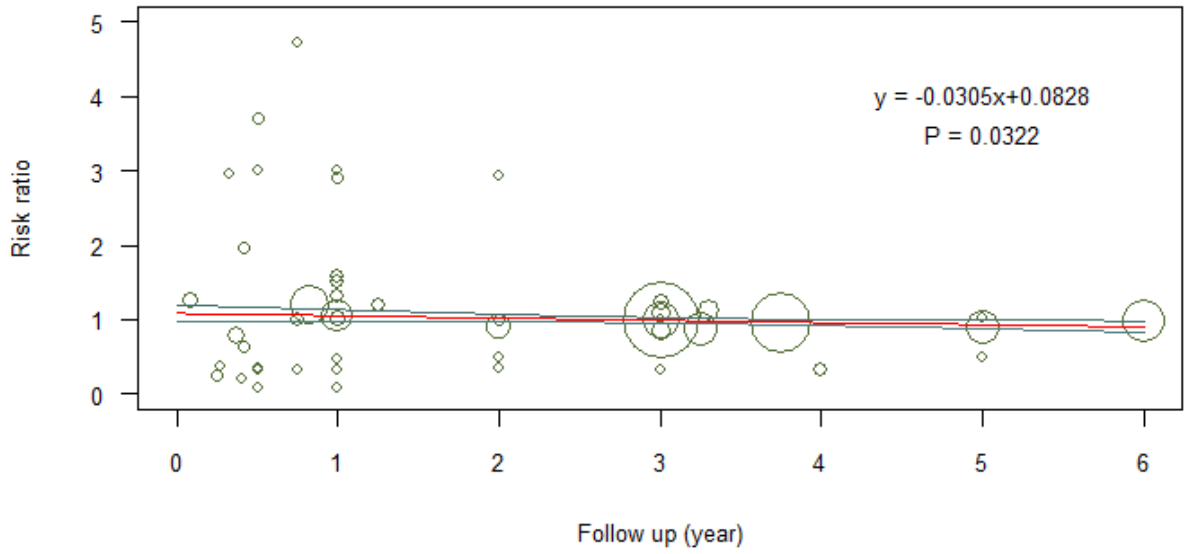
eFigure 7: Forest plot of cerebrovascular disease mortality of all trials evaluating vitamin D supplementation



eFigure 8: Forest plot of ischaemic heart disease mortality of all trials evaluating vitamin D supplementation



eFigure 9: Meta-regression for all-cause mortality by length of follow-up



eFigure 10: Meta-regression for all-cause mortality by 25(OH)D (nmol/L)