SUPPLEMENTARY MATERIAL

eTable 1. General characteristics of 73 unique observational cohort studies of circulating blood 25-hydroxyvitamin D included in the current review*

Lead author, year of publication	Name of the study	Location	Population source	Baseline population	Average age, yrs	Male (%)	Sample type	Vitamin D assay method (source)	Average level of vitamin D (ng/ml)	No of total participants	Average follow up, yrs	No of total deaths	Study quality
Durup D, 2012	CopD	Denmark	Healthcare register	Community-dwelling population	51.0	34.8	Serum	LIAISON & OCTEIA (DiaSorin & IDS)	18.8	247,574	3.1	15,198	9
Dror Y, 2013	CHS-Israel	Israel	Healthcare register	Community-dwelling population	64.2	31.0	Serum	CIA (DiaSorin)	19.14	422,822	4.5	12,280	8
Anderson JL, 2010	Intermountain	United States	Healthcare register	Individuals enrolled in insurance database	66.6	25.0	Serum	CIA	28.0	27,686	1.3	1,193	7
Melamed ML, 2008	NHANES III	United States	Population register	Community-dwelling population	44.8	45.5	Serum	RIA (DiaSorin)	24.6	13,331	8.7	1,806	9
Kitamura K, 2010	Yamato	Japan	Population register	Community-dwelling population	83.6	30.8	Serum	CIA	NR	205	2	42	8
Brøndum-Jacobsen P, 2012	CCHS	Denmark	Population register	Community-dwelling population	57.0	44.0	Plasma	CIA (DiaSorin)	17.7	10,170	29.0	6,747	9
Skaaby T, 2012	MONICAI/ INTER99	Denmark	Population (MONICA) & trial register (INTER99)	Community-dwelling population	48.8	49.5	Serum	INTER99: HPLC MONICA10: CIA (IDS)	20.55	8,329	4.3	633	8
Ford ES, 2011	NHANES 2001-4	United States	Population register	Community-dwelling population	45.9	49.3	Serum	RIA (DiaSorin)	24.3	7,531	3.8	347	8
Hutchinson MS, 2010	Tromsø Heart	Norway	Population register	Community-dwelling population	58.9	10.2	Serum	Immunometry (ECLIA)	23.6	7,161	11.7	1,359	9
Tretli S, 2012	JANUS	Norway	Population register	Community-dwelling population	56.5	39.1	Serum	RIA (DiaSorin)	10.0	658	24	399	8
Pilz S/Hoorn, 2009	Hoorn	The Netherlands	Population register	Community-dwelling population	69.8	49.3	Serum	RIA (DiaSorin)	21.4	614	6.2	51	9
Kritchevsky SB, 2012	Health ABC	United States	Population register	Community-dwelling population	74.7	48.8	Serum	RIA (DiaSorin)	25.8	2,638	8.5	691	8
Kestenbaum B, 2011	CHS-US	United States	Population register	Community-dwelling population	74.0	29.0	Serum	HPLC-MS (Waters Quattro)	25.2	2,312	14.0	1,226	9
Eaton CB, 2011	WHI	United States	Healthcare register	Healthy post-menopausal women	65.8	0.0	Serum	RIA (DiaSorin)	19.6	2,429	7.1	224	7
Fang F, 2011	HPFS/ PHS	United States	Population register	Community-dwelling population	62.5	100.0	Plasma	RIA	25	1,822	10.0	595	8
Jia X, 2007	-	Scotland	Population register	Community-dwelling population	80.0	51.4	Serum	RIA (DiaSorin)	30.0	398	5.8	129	8
Cawthon PM, 2010	MrOS	United States	Population register	Community-dwelling men	73.0	100.0	Serum	MS	25.2	1,490	7.3	330	8
Bolland MJ, 2010	Auckland	New Zealand	Trial register	Healthy post-menopausal women	74.0	0.0	Serum	RIA (DiaSorin)	20.2	1,471	5.0	63	7
Vrieling A, 2011	MARIE	Germany	Healthcare register	Community-dwelling population	63.4	0.0	Serum	ELISA (IDS)	17.9	1,265	5.8	174	8
Visser M, 2006	LASA	The Netherlands	Population register	Community-dwelling population	74.3	48.9	Serum	CPBA (Nichols Diagnostics)	20.8	1,260	6.0	380	9
Michaelsson K, 2010	ULSAM	Sweden	Population register	Community-dwelling men	71.0	100.0	Plasma	HPLC-MS (Hewlett-Packard)	27.5	1,194	12.7	584	8
Virtanen JK, 2011	KIHD	Finland	Population register	Community-dwelling population	61.8	48.6	Serum	HPLC-MS (Shimadzu)	17.5	1,136	9.1	87	8
Szulc P, 2009	MINOS	France	Population register	Community-dwelling men	65.4	100.0	Serum	RIA (Incstar Corp)	27.1	782	10.0	182	7

Lead author, year of publication	Name of the study	Location	Population source	Baseline population	Average age, yrs	Male (%)	Sample type	Vitamin D assay method (source)	Average level of vitamin D (ng/ml)	No of total participants	Average follow up, yrs	No of total deaths	Study quality
Semba RD (2), 2009	WHAS	United States	Healthcare register	Community-dwelling post-menopausal women	74.0	0.0	Serum	CPBA (Nichols Diagnostics)	20.4	714	6.0	100	8
Bates CJ, 2012	NDNS	United Kingdom	Population register	Community-dwelling population	76.6	51.0	Plasma	CPBA (Incstar)	21.7	1,054	13.5	717	8
Semba RD (1), 2009	InCHIANTI	Italy	Population register	Community-dwelling population	74.0	75.0	Serum	RIA (DiaSorin)	16.0	1,006	6.5	228	8
Lin SW, 2012	Linxian	China	Population register	Healthy adults	56.5	55	Serum	ELISA (IDS)	12.7	1,101	24	793	8
Signorello LB, 2012	SCCS	United States	Population register	Healthy adults	40-79	58	Serum	CIA (DiaSorin)	16.2	3,704	3.6	1,852	8
Welsh P, 2012	MIDSPAN	Scotland	Population register	Healthy adults	45.1	44.2	Plasma	HPLC-MS (Chromsystems GmbH)	18.6	1,492	14.4	70	8
Schierbeck LL, 2012	DOPS	Denmark	Population register	Healthy post-menopausal women	50	0	Serum	RIA (Incstar Corp)	25	2,013	16	135	8
Jassal SK, 2010	Rancho Bernado	United States	Population register	Healthy older adults	76	38.3	Serum	CIA	42	1,073	6.4	111	9
Kilkkinen A, 2009	Mini-Finland	Finland	Population register	Healthy adults	49.4	45.3	Serum	RIA (DiaSorin)	17.4	6,219	27.1	933	8
Schottker B, 2013	ESTHER	Germany	GP register	Healthy adults	62	43.8	Serum	Automated Immunoassay (DiaSorin-Liaison)	20.5	9,578	9.5	1083	7
Jean G, 2011	ARNOS	France	Healthcare register	Chronic Kidney Disease patients	67.1	60.0	Serum	CIA (DiaSorin)	18.0	648	3.5	330	7
Krause R, 2012	-	Germany	Healthcare register	Chronic Kidney Disease patients	71.0	58.6	NR	CPBA (In-house & Nichols)	17.0	6,518	9.0	3,010	6
Liu LCY, 2011	COACH	The Netherlands	Healthcare register	Heart Failure Patients	74.0	61.0	Plasma	ELISA (IDS)	14.7	548	1.5	155	7
Zittermann A, 2009	-	The Netherlands and Germany	Healthcare register	Heart failure patients	53.6	69.0	Serum	RIA (DiaSorin)	13.8	510	1.0	82	8
Drechsler C, 2010	4D	Germany	Trial register	Chronic Kidney Disease patients	66.0	54.0	Serum	CIA (IDS)	24.3	1,108	4.0	545	7
Joergensen C, 2010	Hvidore	Denmark	Healthcare register	Type 2 Diabetes patients	54.0	61.0	Plasma	LC-MS/MS	14.3	289	15.0	196	8
Wang AY, 2008	-	China	Healthcare register	Chronic Kidney Disease patients	55.0	51.0	Plasma	ELISA (IDS)	18.3	230	3.0	70	6
Jorgensen C, 2010	STENO	Denmark	Healthcare register	Type 1 Diabetes patients	29.2	59.5	Plasma	HPLC-MS	17.9	220	26.0	44	6
Navaneethan SD, 2011	Cleveland	United States	Healthcare register	Chronic Kidney Disease patients	71.5	33.2	Serum	CIA (DiaSorin)	NR	12,427	1.4	767	7
Ravani P, 2008	-	Italy	Healthcare register	Chronic Kidney Disease patients	70.1	63.1	Serum	ELISA (IDS)	18.1	168	4.0	78	7
Barreto DV, 2009	Amiens	France	Healthcare register	Chronic Kidney Disease patients	67.0	61.0	Serum	CIA (Liaison)	16.7	140	1.7	25	7
Pecovnik-Balon B, 2009	-	Slovenia	Healthcare register	Chronic Kidney Disease patients	60.5	56.9	Serum	ELISA (IDS)	23.2	102	2.0	27	6
Gracia-Iguacel C, 2010	-	Spain	Healthcare register	Chronic Kidney Disease patients	65.1	61.5	Serum	CIA (DiaSorin)	13.8	94	1.1	18	6
Bilcher TM, 2012	Copenhagen	Denmark	Hospital	Older Hospitalized patients	77.4	25.2	Serum	RIA (IDS)	NR	5,147	2.7	1,689	6
Wolf M, 2007	ArMORR	United States	Healthcare register	Chronic Kidney Disease patients	63.0	53.0	Serum	RIA (DiaSorin)	21.0	984	0.3	244	7

Lead author, year of publication	Name of the study	Location	Population source	Baseline population	Average age, yrs	Male (%)	Sample type	Vitamin D assay method (source)	Average level of vitamin D (ng/ml)	No of total participants	Average follow up, yrs	No of total deaths	Study quality
Naesgaard PA, 2012	ARRA-RACS	Argentina	Healthcare register	Acute coronary syndrome patients	62.2	59.8	Serum	LC-MS/MS (Waters Quattro)	21.7	982	2.0	119	7
Kendrick J, 2011	HOST	United States	Trial register	Chronic Kidney Disease patients	69.0	98.0	Plasma	CIA (DiaSorin)	21.0	1,099	2.9	453	6
Drechsler C	NECOSAD	The Netherlands	Healthcare register	Chronic Kidney Disease patients	59.0	61.0	Plasma	CIA (DiaSorin)	18.0	762	3.0	213	7
Grandi NC, 2010	KAROLA	Germany	Healthcare register	Coronary heart disease patients	60.0	84.0	Serum	CIA (Roche)	22.0	1,125	8.0	121	8
Bittner V, 2012	TNT	United States	Trial register	Clinically evident CHD patients	61.1	83.1	Plasma	RIA (IDS)	NR	1,509	4.9	160	6
Fedirko V, 2012	EPIC	Multi-country	Population register	Colorectal Cancer patients	62.1	49.6	Serum	ELISA (OCTEIA, IDS)	23.4	1,202	6.1	541	8
Ng K, 2011	Intergroup	United States	Trial register	Colorectal Cancer patients	61	59	Plasma	RIA	20	515	5.1	475	6
Mezawa H, 2010	-	Japan	Healthcare register	Colorectal Cancer patients	65	36	Serum	RIA	12	257	2.7	39	6
Ren C, 2012	-	China	Healthcare register	Gastric Cancer patients	NR	68	Serum	ELISA (IDS)	19.97	197	5	106	6
Jacobs ET, 2011	WHEL	United States	Healthcare register	Breast Cancer survivors	51.3	0	Serum	CIA (DiaSorin)	24.4	500	7.3	250	6
Goodwin PJ, 2009	-	Canada	Healthcare register	Breast Cancer Patients	50.4	0	Plasma	RIA	23.3	512	11.6	106	6
Zhou W, 2007	NSCLC	United States	Healthcare register	Lung Cancer patients	68.8	50	Serum	RIA	16.5	447	6	234	6
Newton-Bishop JA, 2009	LMC	United Kingdom	Healthcare register	Melanoma patients	NR	NR	Serum	LC-MS/MS	21.3	872	4.7	141	6
Drake MT, 2010	SPORE	United States	Healthcare register	Non-Hodgkin's Lymphoma patients	62	54.9	Serum	LC-MS/MS	NR	370	2.9	100	6
Shanafelt TD, 2010	SPORE (2)	United States	Healthcare register	Chronic Lymphocytic leukemia patients	63	68.5	Serum	LC-MS/MS	30.7	390	3	34	6
Pardanani A, 2011	-	United States	Healthcare register	Myeloproliferative Neoplasm patients	63	68	Plasma	LC-MS/MS	25	247	2.8	129	6
Gugatschka M, 2011	-	Austria	Healthcare register	Head and neck Cancer patients	66	86	Serum	ELISA (IDS)	22.5	88	1.2	29	6
Meyer F, 2011	-	Canada	Healthcare register	Head and neck Cancer patients	62.5	79	Serum	RIA (DiaSorin)	25.5	540	8	223	6
Tomson J, 2013	Whitehall	United Kingdom	Population register	Older civil servants	76.9	100	Plasma	Automated Immunoassay (IDS)	22.4	5,409	13	3215	8
Ensrud K.E, 2010	SOF	United States	Population register	Post-menopausal older women	76.7	0	Serum	LC-MS/MS	23.2	4,551	4.5	432	8
Dobnig H, 2008	LURIC	Germany	Healthcare register	Acute coronary syndrome patients	63.7	69.8	Serum	RIA (DiaSorin)	17.4	3,258	7.7	737	8
Kuroda T, 2009	-	Japan	Healthcare register	Ambulatory post-menopausal women	63.9	0	Serum	CPBA	NR	1,232	6.9	107	6
Holmgaard D.B, 2013	-	Denmark	Trial register	Chronic Obstructive Pulmonary Disease patients	71	49.8	Serum	LC-MS/MS	22.4	462	10	353	6
Villasenor A, 2013	HEAL	United States	Healthcare register	Breast Cancer patients	55.8	0	Serum	RIA (DiaSorin)	24.8	585	9.2	110	6
Alele J.D, 2013	VADT	United States	Trial register	Type 2 diabetes patients	59.7	96.9	Serum	RIA	NR	936	3.7	62	6
Total†					*63.4*	*49.9*			*20.4*	*849,412*	*7.6*	*66,511*	

*Includes exclusively the observational cohort studies that measured (that is, not predicted) levels of circulating 25-hydroxyvitamin D in bloodstream. 66ArMORR, Accelerated Mortality on Renal Replacement; ARRA-RACS, Argentinean Risk Assessment Registry in Acute Coronary Syndrome; CCHS, Copenhagen City Heart Study; CHS-Israel, Clalit Health Services-Israel; CHS-US, Cardiovascular Health Study-US; CIA, Chemiluminescent immunoassay; COACH, Coordinating study evaluating Outcomes of Advising Counselling in Heart Failure; CPBA, Competitive protein-binding assay; DOPS, Danish Osteoporosis Prevention Study; EPIC, European Prospective Investigation into Cancer and Nutrition; GP, General Practioner; 4D, German Diabetes and Dialysis Study;Health ABC, Health, Aging, and Body Composition; HPFS, Health Professionals Follow-up Study; HOST, Homocysteine in Kidney and End Stage Renal Disease; InCHIANTI, Invecchiare in Chianti, Aging in the Chianti Area; KAROLA, Langzeiterfolge der KARdiLogischen Anschlussheilbehandlung; KIHD, Kuopio Ischaemic Heart Disease Risk Factor Study; LASA, Longitudinal Aging Study; LMC, Leeds Melanoma Cohort; LURIC, Ludwigshafen Risk and Cardiovascular Health; MARIE, Mamma Carcinoma Risk Factor Investigation; MrOS, Prospective Osteoporotic Fractures in Men; MS, mass spectrometry; NHANES, National Health and Nutrition Examination Survey; NDNS, National Diet and Nutrition Survey; NECOSAD, Netherlands Cooperative Study on the Adequacy of Dialysis; NSCLC, Non-small-cell lung cancer; PHS, Physicians Health Study; RIA, Radioimmunoassay; SCCS, Southern Community Cohort Study; SOF, Study of Osteoporotic Fractures; SPORE, Specialized Program of Research Excellence; TNT, Treating to New Targets; ULSAM, Uppsala Longitudinal Study of Adult Men; WHAS, Women's Health and Aging Study; WHEL, Women's Healthy Eating and Living; WHI, Women's Health Initiative; †, Total based on unique studies

eTable 2. List of adjustment factors employed in the 73 observational cohort studies included in the current review

Lead author, year of publication	Name of the study	Location	Adjustment factors
Durup D, 2012	CopD	Denmark	Age, sex, season
Dror Y, 2013	CHS-Israel	Israel	Age, gender, sector, prior IHD, HbA1C, LDL-cholesterol, smoking status, SBP, BMI
Anderson JL, 2010	Intermountain	United States	Age, gender, hypertension, hyperlipidemia, diabetes, peripheral vascular disease
Melamed ML, 2008	NHANES III	United States	Age, sex, race, season, hypertension, history of CVD, diabetes, smoking, lipids, statins, eGFR, albumin, CRP, BMI, physical activity, vitamin D supplements, SES
Kitamura K, 2010	Yamato	Japan	Age, SES, BMI, season, serum albumin
Brøndum-Jacobsen P, 2012	CCHS	Denmark	Age, BMI, pack-years smoked, alcohol consumption, plasma total cholesterol, HDL-cholesterol, SBP, estimated GFR
Skaaby T, 2012	MONICAI/ INTER99	Denmark	Study group, gender, education, season of blood sample, intake of fish, physical activity, smoking habits, BMI, alcohol consumption
Ford ES, 2011	NHANES 2001-4	United States	Age, ethnicity, CaD-trial indicator, education, smoking status, current aspirin use, history of fracture at >54y of age, waist circumference, BMI, physical activity, and use of vitamin D supplements
Hutchinson MS, 2010	Tromsø Heart	Norway	Age, gender, BMI, physical activity score, diabetes, hypertension, serum creatinine, prior CVD, and prior cancer
Tretli S, 2012	JANUS	Norway	Age at diagnosis, sex and season of blood sampling
Pilz S/Hoorn, 2009	Hoorn	The Netherlands	Age, sex, dibetes, smoking, hypertension, HDL-C, GFR, WHR, PTH
Kritchevsky SB, 2012	Health ABC	United States	Age, gender, race (for total sample only), education (less than high school, high school or more), season, field center, smoking status (current, former, never), pack-years, alcohol consumption (none in past year, seven or fewer drinks per week, more than one drink per day), BMI, time walking (0, 1–149, or 150 min/wk), usual 20-m walking speed, estimated glomerular filtration rate, PTH, cognition (3MS score), depressive symptoms (CES-D score 16), IL-6 (picograms per milliliter), cholesterol (milligrams per deciliter), and prevalent diabetes, hypertension, CVD, cancer, or lung disease
Kestenbaum B, 2011	CHS-US	United States	Age, race, sex, season of the year, clinic site, diabetes, antihypertensive medications, smoking , education, kilocalories of physical activity, body mass index, systolic blood pressure, levels of C-reactive protein, total and high-density lipoprotein cholesterol, calcium, phosphorus, glomerular filtration ratecystatin
Eaton CB, 2011	WHI	United States	Month, age, ethnicity, CaD-trial indicator, education, smoking status, current aspirin use, history of fracture at >=55 y of age, waist circumference, BMI, physical activity, and use of vitamin D supplements
Fang F, 2011	HPFS/ PHS	United States	Age, BMI, PA, smoking, Gleason score, TNM stage
Jia X, 2007	-	Scotland	Age, sex, taking five or more kinds of medicine, self-perceived health status, having heart problem, diabetes at baseline
Cawthon PM, 2010	MrOS	United States	Age, clinic, season of blood draw, serum calcium and phosphate, GFR, percentage body fat, weight, race, health status, presence of at least one medical condition, alcohol use, education, activity level (PASE score), marital status, and presence of a functional or mobility limitation
Bolland MJ, 2010	Auckland	New Zealand	Treatment allocation (calcium or placebo) and baseline age, body weight, smoking status, systolic blood pressure, and history of ischemic heart disease, stroke or transient ischemic attack, dyslipidemia, and diabetes
Vrieling A, 2011	MARIE	Germany	Stratified by age at diagnosis, season and adjusted for tumor size, nodal status, metastases, tumor grade, estrogen/progesterone receptor status, diabetes, mode of detection
Visser M, 2006	LASA	The Netherlands	Age, sex, education, partner status, hx of chronic diseases, creatinine status, cognitive status, depressive symptoms, BMI, smoking, alcohol consumption, and physical activity
Michaelsson K, 2010	ULSAM	Sweden	Age, weight, height, calcium intake, season of blood draw, social class, smoking status, leisure physical activity, self-perceived health, diabetes mellitus, other endocrine disease, hematologic diseases, dermatoses, infectious disease, musculoskeletal disease, psychiatric disease, respiratory disease, kidney or urinary disease, gastrointestinal disease, supplemental vitamin D use, total vitamin D intake, fish intake, plasma parathyroid hormone, plasma cystatin C, plasma CRP, serum calcium, serum phosphate, plasma troponin I, plasma N-terminal pro brain natriuretic peptide, plasma cholesterol, plasma triglycerides, plasma HDL cholesterol, plasma retinol, plasma insulin, total energy intake, and alcohol intake and systolic blood pressure, diastolic blood pressure, lipid-lowering treatment, and antihypertensive treatment

Lead author, year of publication	Name of the study	Location	Adjustment factors
Virtanen JK, 2011	KIHD	Finland	Age, gender, examination year, examination month, diabetes, treated hypertension, body mass index, smoking, education years, and medication for hyperlipidemia
Szulc P, 2009	MINOS	France	Age, BMI, log transformed Aortic Calcification Score, smoking, physical performance score, leisure physical activity, IHD, diabetes, Parkinson's disease, vitamin D supplementation, log-transformed creatinine clearance
Semba RD (2), 2009	WHAS	United States	Age, race, education, season, BMI, smoking, supplement use, physical activity, lipids and history of chronic diseases
Bates CJ, 2012	NDNS	United Kingdom	Age
Semba RD (1), 2009	InCHIANTI	Italy	Age, sex, education, season, BMI, smoking, aspirin use, physical activity, lipids, MMSE score and history chronic diseases
Lin SW, 2012	Linxian	China	Stratified by age group and sex, and adjusted for continuous age, sex, hypertension, tobacco smoking, body mass index, and alcohol consumption
Signorello LB, 2012	SCCS	United States	Matched on sex, race (black/white/other), age at enrollment (±3 years), community health center enrollment site, and date of blood collection (±6 weeks), adjusted for body mass index, smoking, physical activity, and
Welsh P, 2012	MIDSPAN	Scotland	Age, sex, and season, diabetes, glucose, smoking, systolic blood pressure, total cholesterol, high-density cholesterol, and BMI, triglycerides, waist circumference, creatinine, C-reactive protein, insulin, highest educational level (tertiary level or other), social class, deprivation category, percent fat from diet, alcohol intake, high and low fiber in diet, current medication (angiotensin-converting enzyme inhibitors, antihypertensives, aspirin, insulin, oral hypoglycemics, sartans, and statins), baseline coronary heart disease, low baseline physical activity, and percent predicted FEV1.
Schierbeck LL, 2012	DOPS	Denmark	Age, smoking, blood pressure, family history of MI, education and hip/waist ratio.
Jassal SK, 2010	Rancho Bernado	United States	Age, sex, BMI, systolic BP, LDL-cholesterol, fasting glucose, physical activity, log(urine albumin/creatinine ratio), glomerular filtration rate, prevalent CVD, season, use of diuretics, calcium channel blockers, β-blockers, and angiotensin-converting enzyme inhibitors
Kilkkinen A, 2009	Mini-Finland	Finland	Age (as a continuous variable), sex, marital status (unmarried, married or in a committed relationship, widowed, divorced), education (low, high), body mass index (weight (kg)/height (m)2; continuous variable), alcohol consumption (ethanol intake, g/week; continuous variable), smoking (nonsmoker or smoker with a low, average, or high cotinine level), leisure-time physical activity (inactive, occasionally active, regularly active), and season of baseline examination (winter, summer).
Schottker B, 2013	ESTHER	Germany	Age, sex, season, multivitamin use, fish consumption, education, PA, smoking, SBP, CKD, CRP, TC, diabetes, hypertension, CVD, Cancer
Jean G, 2011	ARNOS	France	Age, sex, diabetes, calcemia, phosphatemia, peripheral vascular and cardiac disease, dialysis vintage
Krause R, 2012	-	Germany	Gender, year of incidence, age at incidence and diabetes type I/II as primary renal disease.
Liu LCY, 2011	COACH	The Netherlands	Age, type 2 diabetes, estimated GFR, N-terminal pro-brain natriuretic peptides
Zittermann A, 2009	-	The Netherlands and Germany	Age, BMI, smoking, renal function, CRP, TNF-alfa, aspirin use, prior CVD, hypertension, and diabetes
Drechsler C, 2010	4D	Germany	Age, sex, atorvastatin treatment, season, coronary artery disease, congestive heart failure, systolic blood pressure, smoking, duration of dialysis, ultrafiltration volume, body mass index, levels of LDL-, HDL-cholesterol, CRP, HbA1c, use of beta-blockers, ACE inhibitors, diuretics, PTH, calcium, and phosphate.
Joergensen C, 2010	Hvidore	Denmark	Age, sex, smoking, systolic blood pressure, history of cardiovascular disease, duration of diabetes, total cholesterol, kidney function (eGFR, UAER)
Wang AY, 2008	-	China	Age, sex
Jorgensen C, 2010	STENO	Denmark	Age, sex, history of CVD, SBP, total cholesterol, estimated GFR, log transformed urinary albumin excretion rate, smoking, diabetes duration
Navaneethan SD, 2011	Cleveland	United States	Age, sex, race, BMI, estimated GFR, diabetes, hypertension, hyperlipidemia, congestive heart failure, cerebrovascular disease, coronary artery disease, season of 25(OH)D testing, serum albumin, haemoglobin
Ravani P, 2008	-	Italy	Age, smoking, heart failure, albumin, CRP, GFR, angiotensin-converting enzyme inhibitors or angiotensin receptor blockers
Barreto DV, 2009	Amiens	France	Age, gender, diabetes, albumin, haemoglobin, phosphate, systolic arterial pressure, smoking habit, vitamin D supplementation, CKD, Aortic Calcification Score, pulse wave velocity
Pecovnik-Balon B, 2009	-	Slovenia	Not stated

Lead author, year of publication	Name of the study	Location	Adjustment factors
Gracia-Iguacel C, 2010	-	Spain	Sex, PTH, Ph, Charlson comorbidity index
Bilcher TM, 2012	Copenhagen	Denmark	Age (per 10 year increase), sex, serum PTH per pmol/L increase, serum 25(OH)D per 10 nmol/L decrease, serum Ca (2+) per mmol/L increase
Wolf M, 2007	ArMORR	United States	Age, sex, race, Prior CVD, SBP, PTH, calcium, albumin, creatinine, phosphorus, haemoglobin
Naesgaard PA, 2012	ARRA-RACS	Argentina	Age, gender, smoking, hypertension, index diagnosis, DM, CHF, history of previous CHD, hypercholesterolemia/use of statins, TnT.0.01 ng/mL, estimated GFR, CRP, BNP, BMI, months of the year and beta-blockers prior to enrolment
Kendrick J, 2011	HOST	United States	Age, gender, race
Drechsler C	NECOSAD	The Netherlands	Age, sex, dialysis modality, ethnicity, primary kidney disease, diabetes mellitus, CVD, BMI, SBP, smoking, cholesterol, use of vitamin supplements, levels of albumin, haemoglobin and creatinine, seasonal variation in vitamin D, PTH, calcium, phosphate, alkaline phosphatase
Grandi NC, 2010	KAROLA	Germany	Age, gender, season, smoking, BMI, TG, LDL-cholesterol, HDL-cholesterol, number of affected vessels, history of MI, creatinine clearance, treatment with beta blockers, calcium antagonists, aspirin, lipi-lowering drugs, ACE inhibitors, or diuretics, CRP, history of hypertension, history of diabetes
Bittner V, 2012	TNT	United States	Treatment group, age at baseline, gender, smoking status, race (white or nonwhite), baseline systolic blood pressure, CKD, BMI, diabetes, season, and baseline total cholesterol to HDL-C ratio
Fedirko V, 2012	EPIC	Multi-country	Age at diagnosis (in years as a continuous variable), sex (men or women), cancer stage (I to IV, unknown), grade of tumor differentiation (well differentiated, moderately differentiated, poorly differentiated, or unknown),
Ng K, 2011	Intergroup	United States	Age (in years as a continuous variable), season of blood collection (summer, autumn, winter, spring), sex (male, female), baseline performance status (0-1, 2), treatment arm (IFL, FOLFOX4, IROX), body mass index (in kg/m2 as a continuous variable), and metastatic sites (liver only, liver + any other site, single non-liver, multiple non-liver).
Mezawa H, 2010	-	Japan	Age at diagnosis (years), gender, calendar month of blood sampling, cancer stage (I, II, III, and IV), residual tumor after surgery (R0, no residual tumor; R1, microscopic residual tumor; R2, macroscopic residual tumor), time period of surgery, location of tumor, adjuvant chemotherapy, and number of lymph nodes with metastasis
Ren C, 2012	-	China	Tumour size and position, Bormann type, T classification, Distant metastasis, Symptom duration
Jacobs ET, 2011	WHEL	United States	Matched on clinical site, cancer stage, age at cancer diagnosis, date of random assignment into the WHEL Study, and date of original cancer diagnosis. Adjusted for BMI (continuous), ethnicity (white compared with nonwhite), intervention group, calcium intake, and tumor grade
Goodwin PJ, 2009	-	Canada	Vitamin D (categorical), age, tumor stage, nodal stage, estrogen receptor, and grade
Zhou W, 2007	NSCLC	United States	Age, sex, stage, pack-years of smoking, chemotherapy/radiation therapy, and surgery season
Newton-Bishop JA, 2009	LMC	United Kingdom	Age, sex, townswend score, site of tumour, Breslow thickenss, BMI and stratified by season of sample
Drake MT, 2010	SPORE	United States	Stage and performance status
Shanafelt TD, 2010	SPORE (2)	United States	Age, sex, Rai stage, CD38 status, ZAP-70 status, immunoglobulin heavy chain variable (IGHV) gene mutation status, CD49d status, and cytogenetic abnormalities
Pardanani A, 2011	-	United States	Disease-specific prognostic variables
Gugatschka M, 2011	-	Austria	Age and sex matched, adjusted for BMI and tumour size.
Meyer F, 2011	-	Canada	Trial arm, adjusting for season of blood collection, age, site, stage, smoking, alcohol consumption and body mass index
Tomson J, 2013	Whitehall	United Kingdom	Smoking, drinking, recall of diagnosis of IHD, stroke, cancer, self-reported health/frailty, employment grade, LDL, HDL, ApoA1, ApoB, BMI, albumin, fibrinogen, CRP, Medication use, SBP, DBP, estimated GFR
Ensrud K.E, 2010	SOF	United States	Age, clinic site, season of blood draw, BMI, health status, education, smoking, alcohol, comorbid conditions, cognitive function, frailty status
Dobnig H, 2008	LURIC	Germany	Age, sex, body mass index, physical exercise, smoking, diabetes, blood pressure, albumin, cystatin C, N-terminal pro-brain natriuretic peptides, lipids, medication usage
Kuroda T, 2009	-	Japan	Age

Lead author, year of publication	Name of the study	Location	Adjustment factors
Holmgaard D.B, 2013	-	Denmark	Age, BMI<20, COPD stage, Charlson score, treatment group, Neutrophils, pack-years>40
Villasenor A, 2013	HEAL	United States	Age, tumour stage, BMI, race-ethnicity/study site, Tamoxifen use, season of blood draw, treatment used, PA, smoking
Alele J.D, 2013	VADT	United States	Age, minority, treatment arm, prior event

ApoA1,apolipoprotein A1; ApoB, apolipoprotein B, ArMORR, Accelerated Mortality on Renal Replacement; ARRA-RACS, Argentinean Risk Assessment Registry in Acute Coronary Syndrome; BMI, body mass index; CCHS, Copenhagen City Heart Study; CHS-Israel, Clalit Health Services-Israel; CHS-US, Cardiovascular Health Study-US; CIA, Chemiluminescent immunoassay; CKD, chronic kidney disease; COACH, Coordinating study evaluating Outcomes of Advising Counselling in Heart Failure; COPD, chronic obstructive pulmonary disease; CPBA, Competitive protein-binding assay; CRP, C-reactive protein; CVD, cardiovascular disease; DBP, diastolic blood pressure; DOPS, Danish Osteoporosis Prevention Study; EPIC, European Prospective Investigation into Cancer and Nutrition; GFR, glomerular filtration rate; GP, General Practioner; 4D, German Diabetes and Dialysis Study;Health ABC, Health, Aging, and Body Composition; HPFS, Health Professionals Follow-up Study; HDL, high density lipoprotein; HOST, Homocysteine in Kidney and End Stage Renal Disease; IHD, ischaemic heart disease; InCHIANTI, Invecchiare in Chianti, Aging in the Chianti Area; KAROLA, Langzeiterfolge der KARdiLogischen Anschlussheilbehandlung; KIHD, Kuopio Ischaemic Heart Disease Risk Factor Study; LASA, Longitudinal Aging Study; LDL, low-density lipoprotein; LMC, Leeds Melanoma Cohort; LURIC, Ludwigshafen Risk and Cardiovascular Health; MARIE, Mamma Carcinoma Risk Factor Investigation; MrOS, Prospective Osteoporotic Fractures in Men; MS, mass spectrometry; NHANES, National Health and Nutrition Examination Survey; NDNS, National Diet and Nutrition Survey; NECOSAD, Netherlands Cooperative Study on the Adequacy of Dialysis; NSCLC, Non-small-cell lung cancer; PA, physical activity; PHS, Physicians Health Study; PTH, parathyroid hormone; RIA, Radioimmunoassay; SBP, systolic blood pressure; SCCS, Southern Community Cohort Study; SOF, Study of Osteoporotic Fractures; SPORE, Specialized Program of Research Excellence; TC, total cholesterol; TG, triglycerides; TNT, Treating to New Targets; ULSAM, Uppsala Longitudinal Study of Adult Men; WHAS, Women's Health and Aging Study; WHEL, Women's Healthy Eating and Living; WHI, Women's Health Initiative; WHR, waist-to-hip ratio

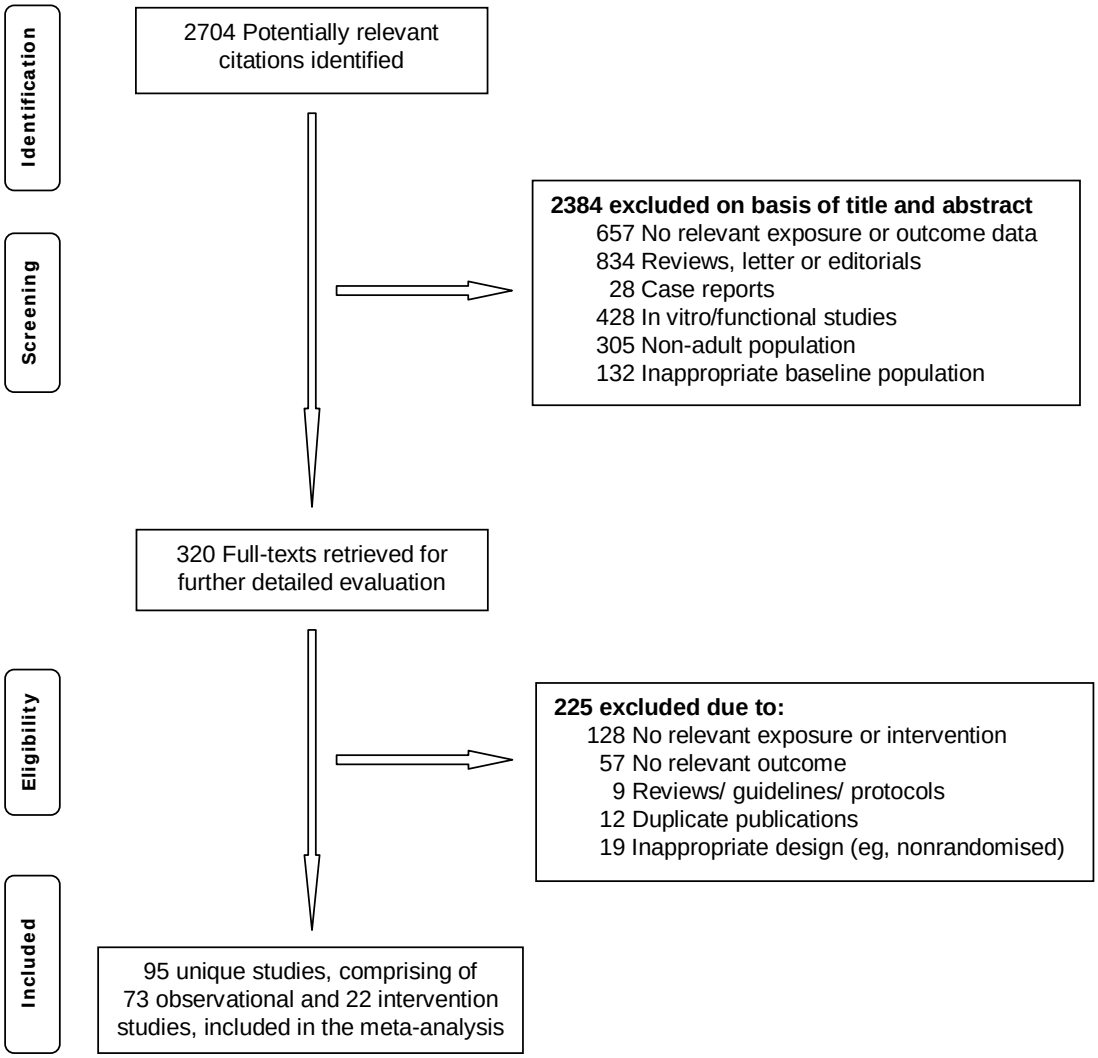
eTable 3. Summary of 22 unique randomised controlled trials included in the present review

Lead Author (Study name), publication year	Location	Baseline population	Age group, years	Sex	Allocation concealment	Blinding to subjects	Blinding to carers	Intervention form	Intervention Type	Dose per day, IU‡	Intervention period (yrs)	Control	No of total participants†	Average Follow up, yrs	No of all cause mortality events
Broe KE, 2007	United States	Care home residents	68-104	Both	Yes	Yes	Yes	Tablet	D2	208	0.417	Placebo	124	0.42	7
Corless D, 1985	United Kingdom	Hospital patients	82*	Both	Yes	Yes	Yes	Tablet	D2	4,500	0.458	Placebo	82	0.46	16
Harwood RH (NoNOF), 2004	United Kingdom	Hip fracture patients	67-92	Female	Yes	No	No	Injection	D2	822	0.003	No treatment	75	1	12
Law M, 2006	United Kingdom	Care home residents	85*	Both	No	No	No	Tablet	D2	880	0.833	No treatment	3,717	0.83	669
Lyons RA, 2007	United Kingdom	Care home residents	84*	Both	Yes	Yes	Yes	Tablet	D2	3,288	3	Placebo	3,440	5	1,428
Smith H, 2007	United Kingdom	Community-based elderly	≥ 75	Both	Yes	Yes	Yes	Injection	D2	2,466	3	Placebo	9,440	3	709
Witham MD, 2010	United Kingdom	Heart failure patients	≥ 70	Both	Yes	Yes	Yes	Tablet	D2	548	0.38	Placebo	105	0.38	6
Sato Y, 2005	Japan	Hospitalized stroke patients	74*	Female	Yes	Yes	Yes	Tablet	D2	4,000	2	Placebo	96	2	3
Avenell A (RECORD), 2012	United Kingdom	Hospitalized patients with fragility fractures	≥ 70	Both	Yes	Yes	Yes	Tablet	D3	6,000	3.75	Placebo	2,675	6.75	855
Campbell AJ, 2005	New Zealand	Community-based elderly	≥ 75	Both	Yes	No	Yes	Tablet	D3	2,137	1	No treatment	391	2	16
Chel V, 2008	Netherlands	Care home residents	≥ 70	Both	Yes	NR	NR	Tablet	D3	200	0.333	Placebo	338	0.38	58
Gallagher JC, 2004	United States	Community-based elderly	72*	Female	Yes	Yes	Yes	Tablet	D3	60	3	Placebo	246	3	3
Grady D, 1991	United States	Community-based elderly	> 69	Both	NR	Yes	Yes	Capsule	D3	10	0.5	Placebo	98	0.5	1
Latham NK (FITNESS), 2003	New Zealand & Australia	Frail hospital patients	≥ 65	Both	Yes	Yes	Yes	Tablet	D3	4,932	0.003	Placebo	243	0.5	14
Lips P, 1996	Netherlands	Community-based elderly	≥ 70	Both	Yes	Yes	Yes	Tablet	D3	1,292	3.23	Placebo	2,578	3.5	588
Ooms ME, 1995	Netherlands	Care home residents	≥ 70	Female	Yes	Yes	Yes	Tablet	D3	800	2	Placebo	348	2	32
Sanders KM (Vital D), 2010	Australia	Community-based elderly	≥ 70	Female	Yes	Yes	Yes	Tablet	D3	5,479	4	Placebo	2,258	5	87
Trivedi DP, 2003	United Kingdom	Community-based elderly	65-85	Both	Yes	Yes	Yes	Tablet	D3	5,479	5	Placebo	2,686	5	471
Beer (ASCENT), 2007	United States	Prostate cancer patients	≥ 18	Male	Yes	Yes	Yes	Tablet	D3	271	NR	Placebo	250	1.53	109

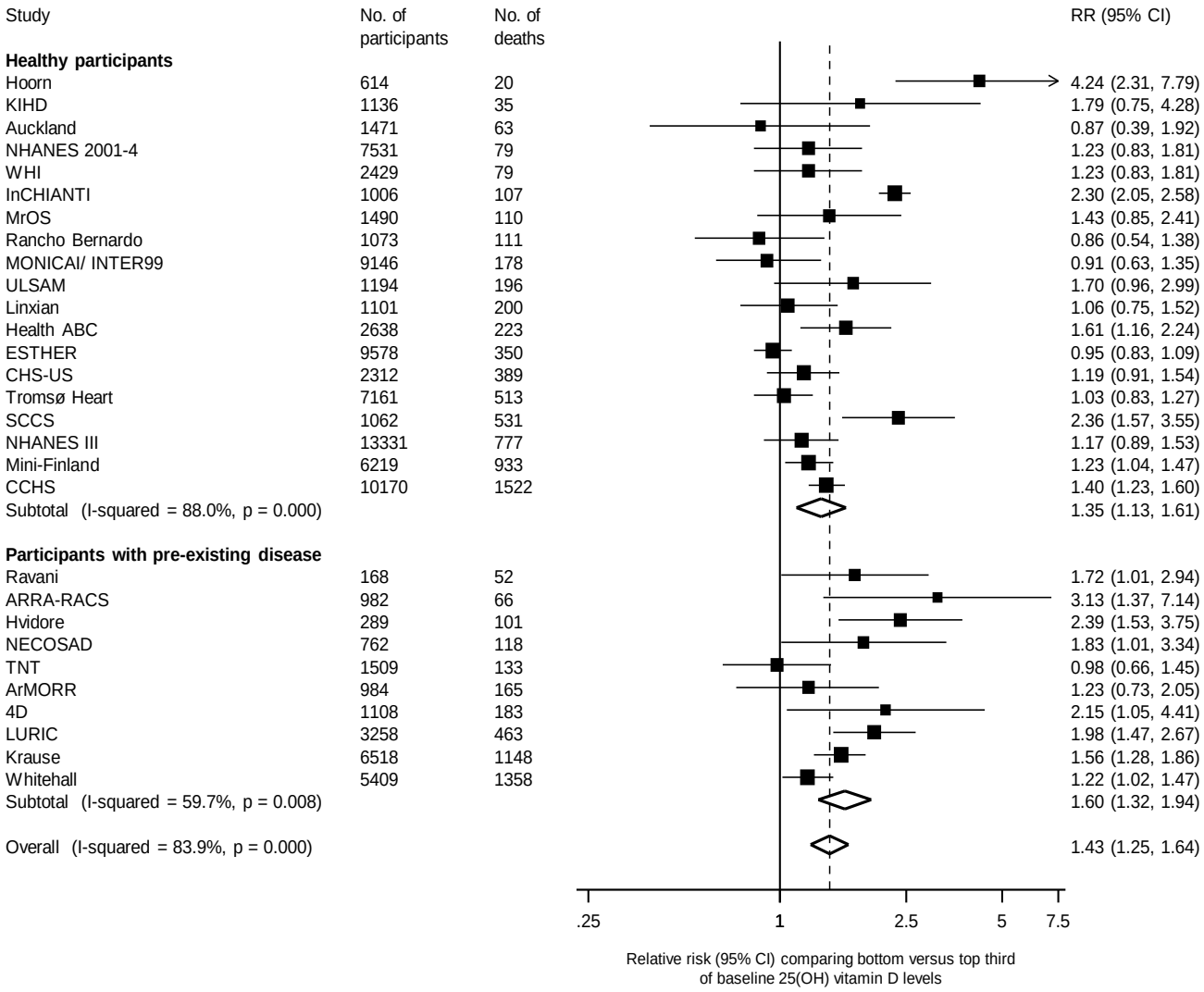
Lead Author (Study name), publication year	Location	Baseline population	Age group, years	Sex	Allocation concealment	Blinding to subjects	Blinding to carers	Intervention form	Intervention Type	Dose per day, IU‡	Intervention period (yrs)	Control	No of total participants†	Average Follow up, yrs	No of all cause mortality events
Lehouck, 2012	Belgium	Hospitalized COPD patients	> 50	Both	Yes	Yes	Yes	Tablet	D3	3,288	1	Placebo	182	1	15
Schleithoff, 2006	Germany	CHF patients	56*	Both	Yes	Yes	Yes	NR	D3	1,500	0.75	Placebo	123	1.25	13
TIDE Trial Investigators, 2012	Canada	T2D patients	≥ 50	Both	Yes	Yes	Yes	NR	D3	440	0.44	No treatment	1,221	0.44	2
Total†											*1.67*		*30,716*	*2.09*	*5,114*

*, mean age; ‡, Calculated in IU based on reported individual study dose units; † total participants in the vitamin D supplement and the control groups combined. NR, not reported;
ASCENT, AIPC Study of Calcitriol Enhancing Taxotere; CHF, Congestive heart failure; COPD, Chronic Obstructive Pulmonary Disease; FITNESS, Frailty Interventions Trial in Elderly Subjects; GP, General Practitioner; NoNOF, Nottingham Neck of Femur; RECORD, Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycaemia in Diabetes; T2D, Type 2 Diabetes; TIDE, Thiazolidinedione Intervention with vitamin D Evaluation

eFigure 1. Search strategy for studies included in current review

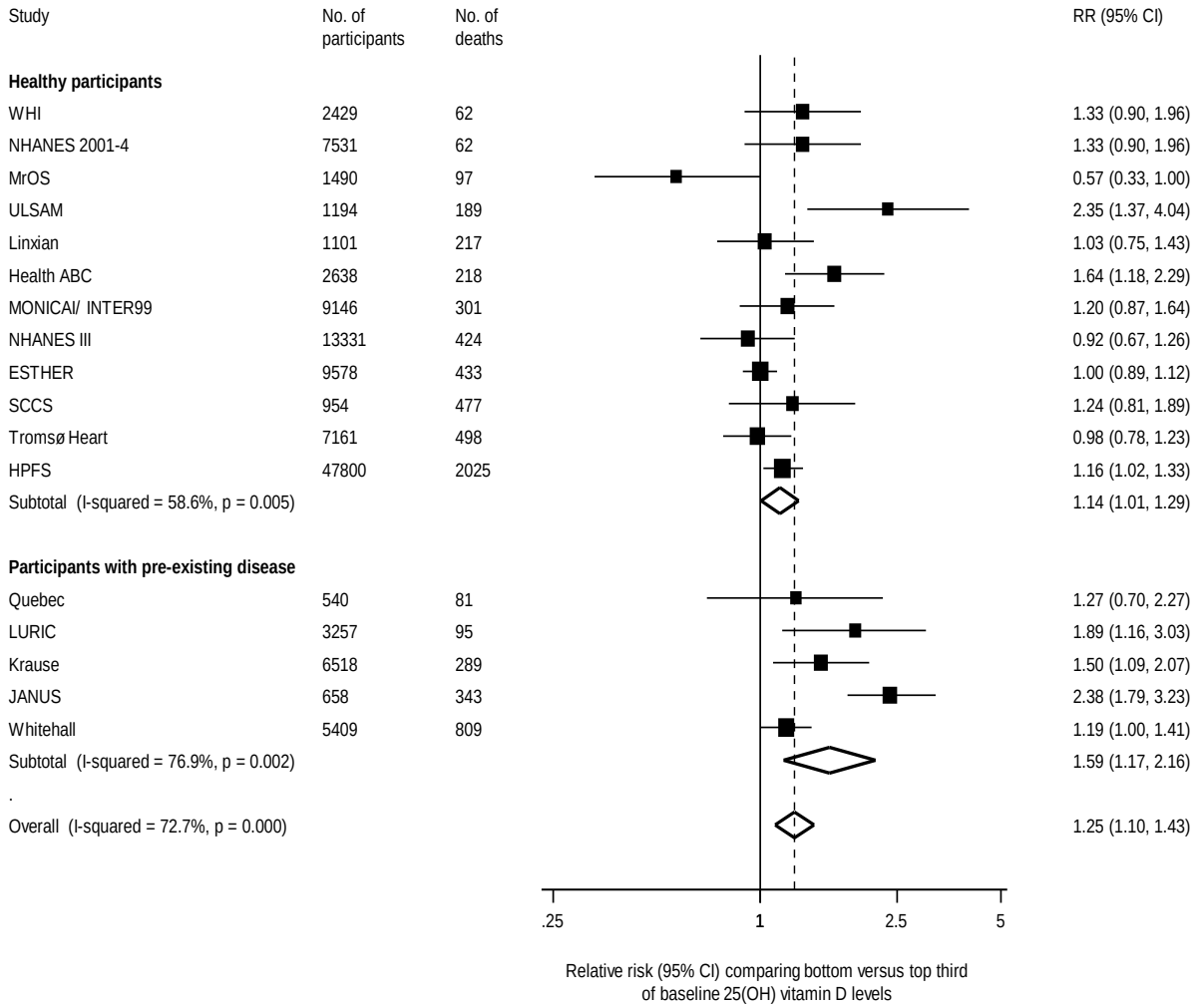


eFigure 2a. Relative risks of cardiovascular mortality for baseline 25(OH) vitamin D levels in observational cohort studies*



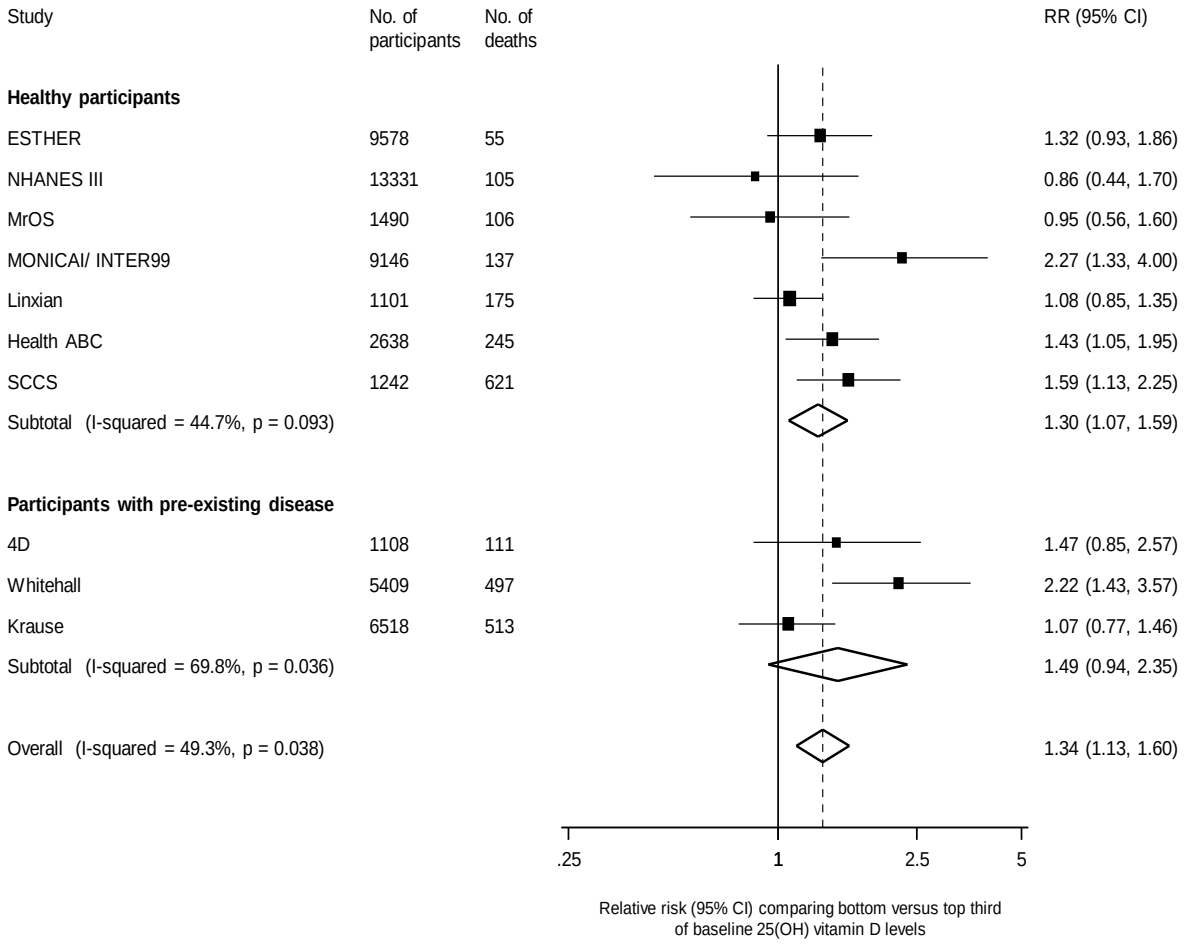
*Based on observational cohort studies that measured (that is, not predicted) levels of circulating 25-hydroxyvitamin D in bloodstream.

eFigure 2b. Relative risks of cancer mortality for baseline 25(OH) vitamin D levels in observational cohort studies*



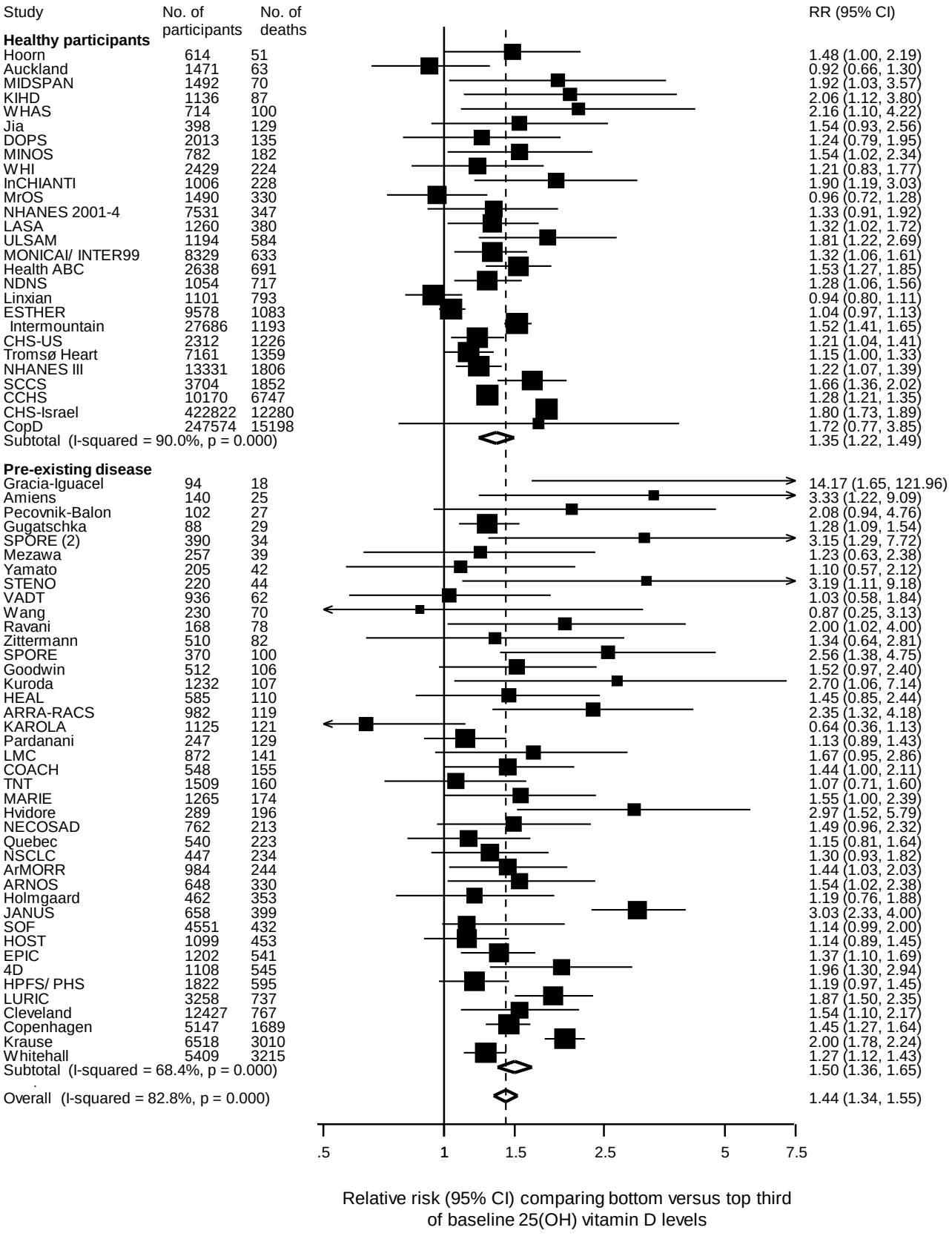
*Based on observational cohort studies that measured (that is, not predicted) levels of circulating 25-hydroxyvitamin D in bloodstream.

eFigure 2c. Relative risks of nonvascular, noncancer mortality for baseline 25(OH) vitamin D levels in observational cohort studies*



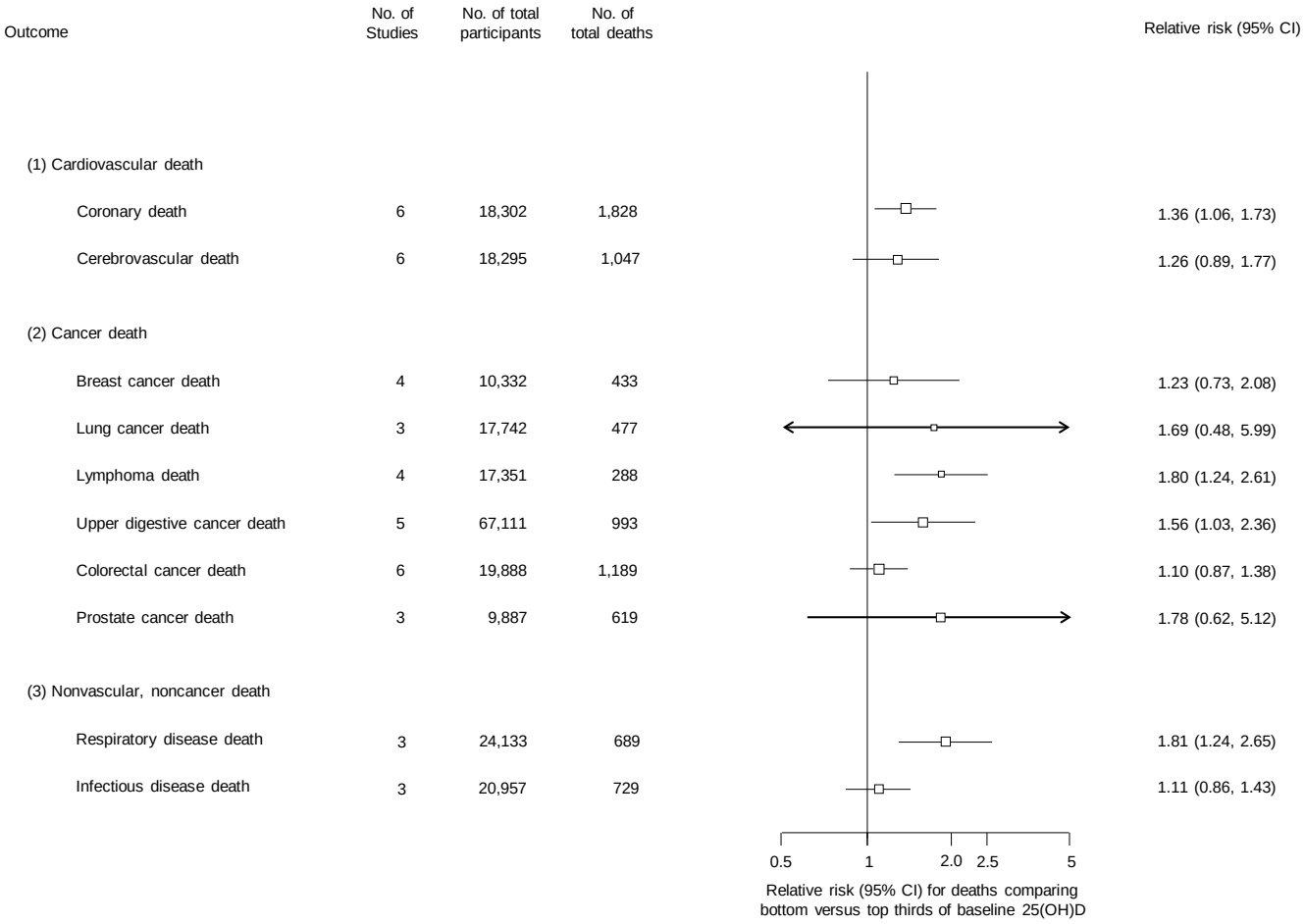
*Based on observational cohort studies that measured (that is, not predicted) levels of circulating 25-hydroxyvitamin D in bloodstream.

eFigure 2d. Relative risks of all-cause mortality for baseline 25(OH) vitamin D levels in observational cohort studies*



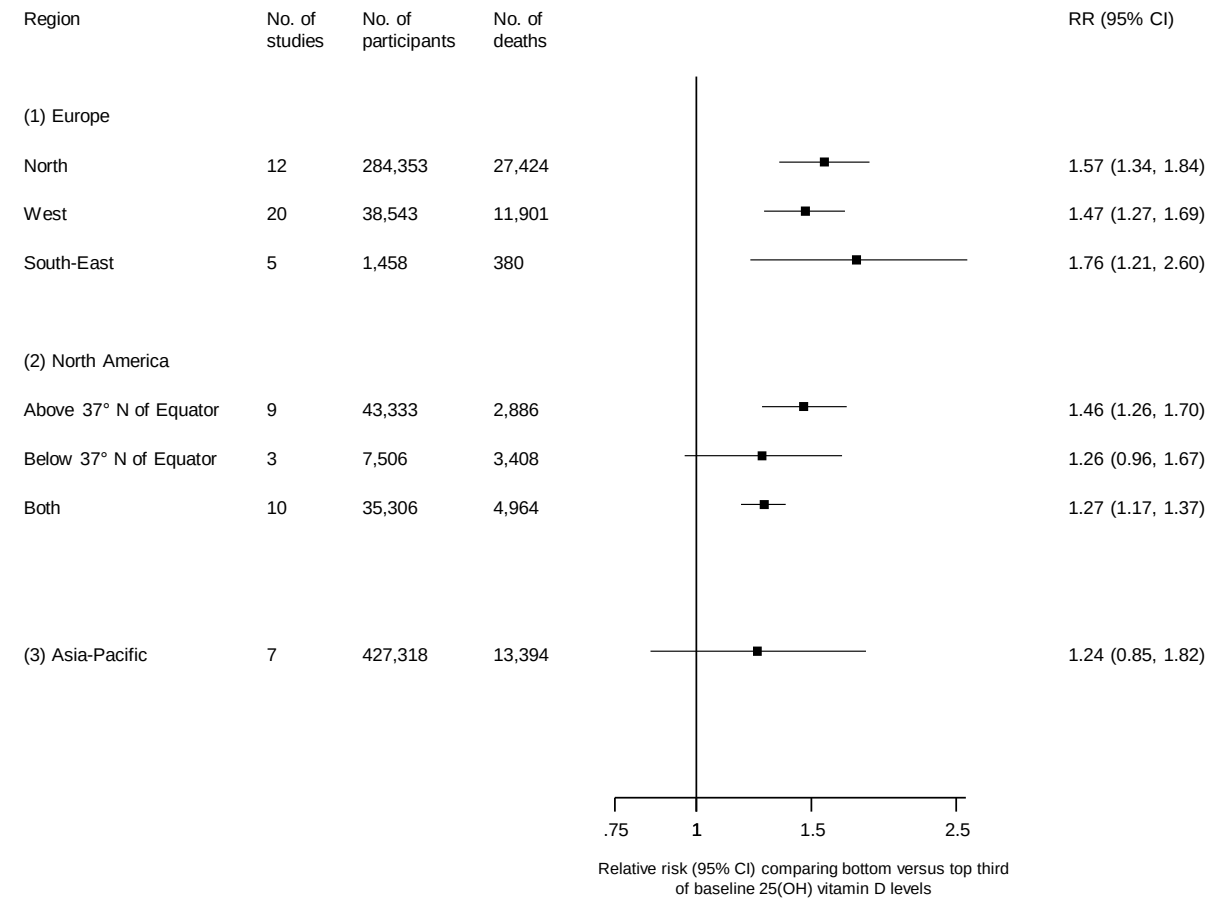
*Based on observational cohort studies that measured (that is, not predicted) levels of circulating 25-hydroxyvitamin D in bloodstream.

eFigure 3. Relative risks of various mortality outcomes for baseline circulating 25(OH) vitamin D levels, based on a subset of observational cohort studies with available relevant data



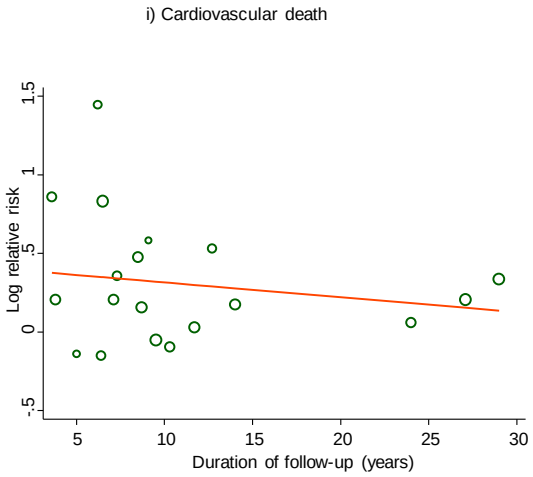
Based on observational cohort studies that measured (that is, not predicted) levels of circulating 25-hydroxyvitamin D in bloodstream.

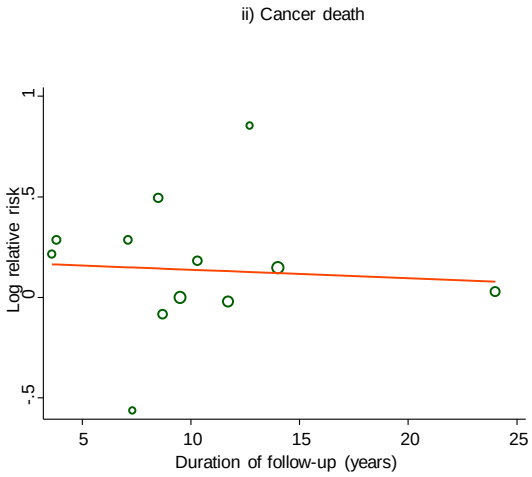
eFigure 4. Relative risks of all cause mortality for baseline 25(OH) vitamin D levels in observational cohort studies, based on geographical locations*

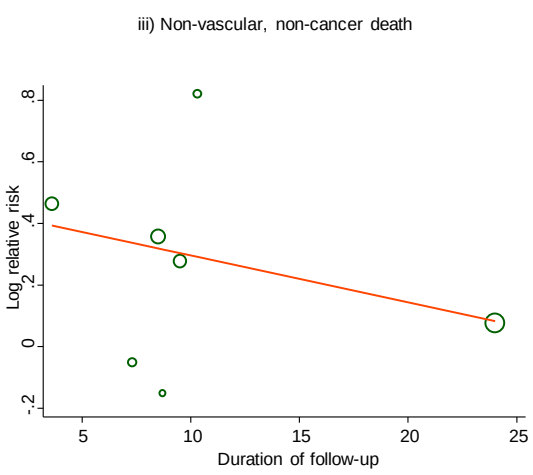


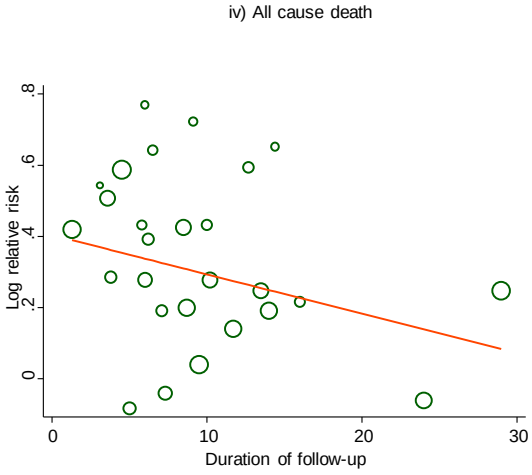
Based on subset of studies with available data. *(1) http://en.wikipedia.org/wiki/Western_Europe; (2) http://en.wikipedia.org/wiki/List_of_countries_by_latitude

eFigure 5. Relationships of relative risk with duration of follow-up in the primary prevention observational cohort studies



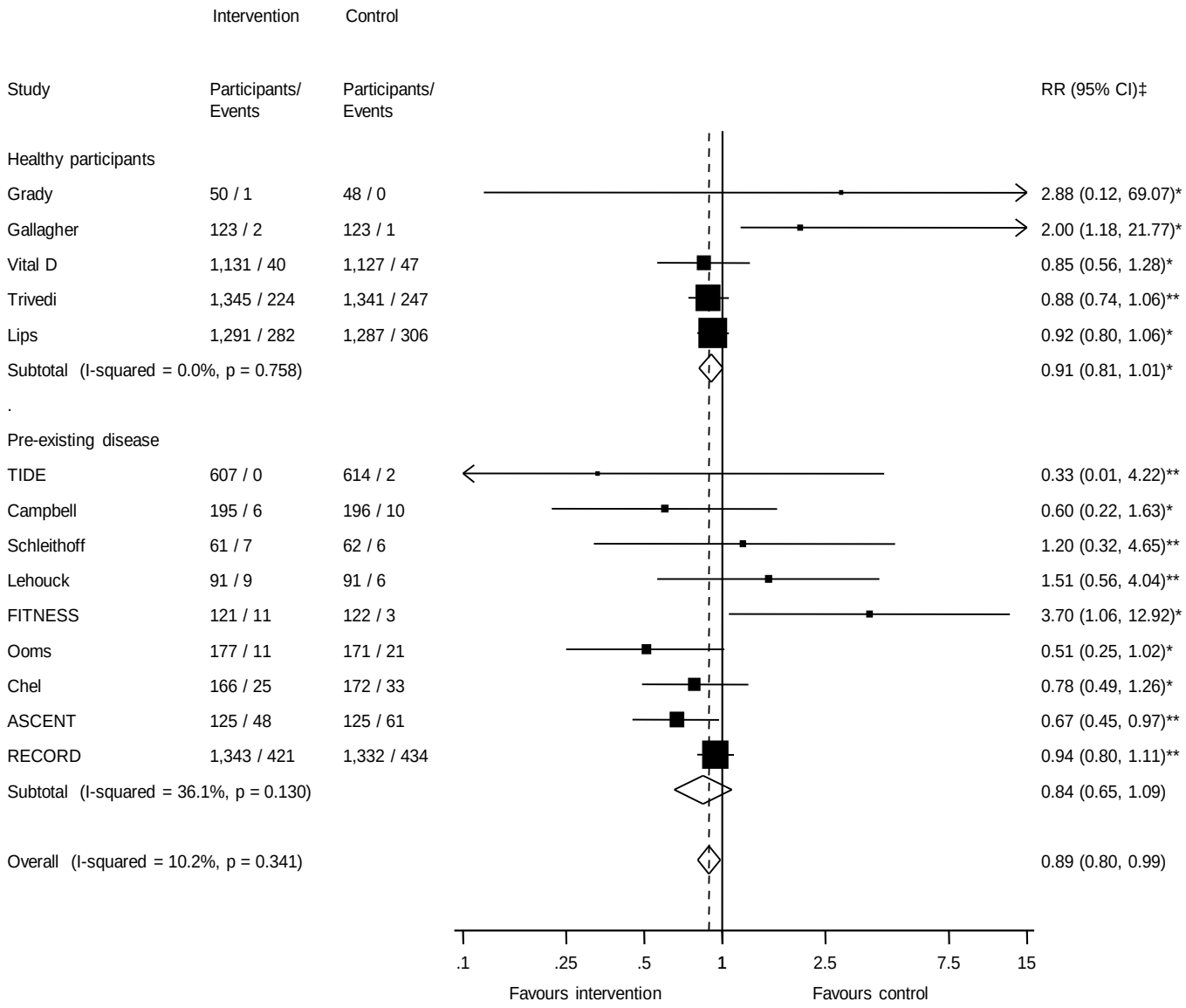






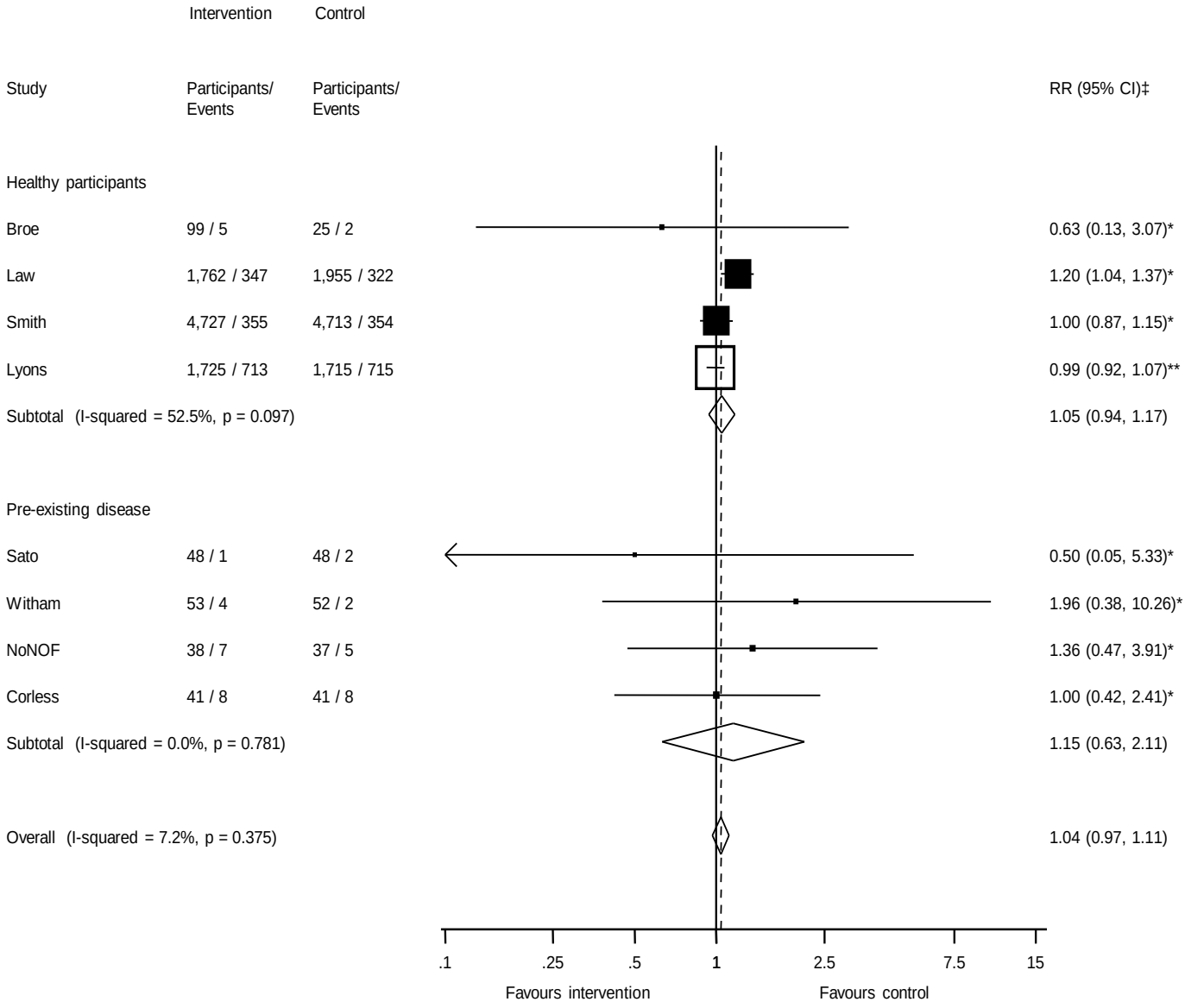
All *p*-values are > 0.05

eFigure 6a. Relative risks of all cause mortality in vitamin D3 supplementation trials†



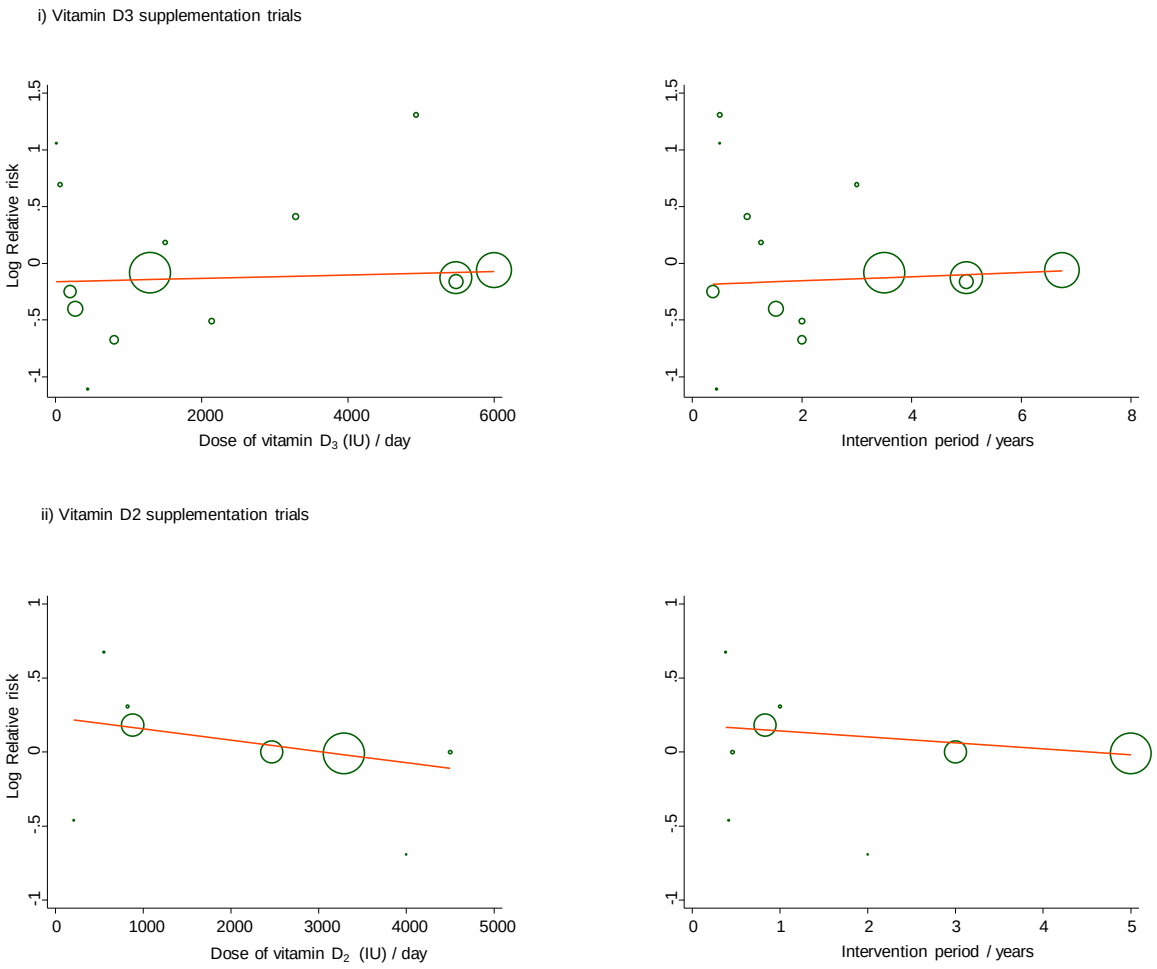
†Includes randomised controlled trials that assessed effects of vitamin D supplements on mortality when given singly (i.e. trials with a "vitamin D alone" intervention group) in adults compared with a placebo or no treatment.
‡Includes both reported effect estimates that were typically adjusted for various study-level factors, and the unadjusted effect estimates that were calculated based on event rates alone if the former was unavailable.
Source of RR estimates: *, extracted from Cochrane Reviews; **, extracted from published report.

eFigure 6b. Relative risks of all cause mortality in vitamin D2 supplementation trials†



†Includes randomised controlled trials that assessed effects of vitamin D supplements on mortality when given singly (i.e. trials with a "vitamin D alone" intervention group) in adults compared with a placebo or no treatment.
‡Includes both reported effect estimates that were typically adjusted for various study-level factors, and the unadjusted effect estimates that were calculated based on event rates alone if the former was unavailable.
Source of RR estimates: *, extracted from Cochrane Reviews; **, extracted from published report.

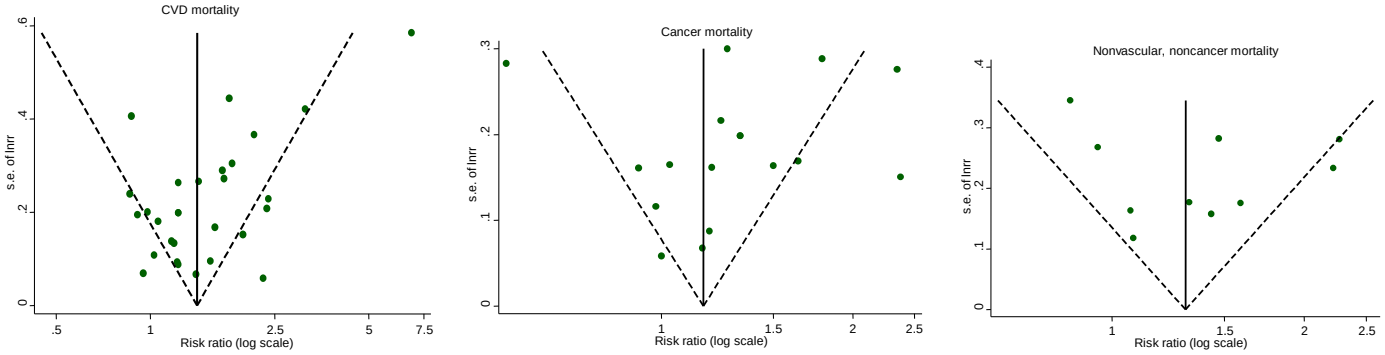
eFigure 7. Relationships of relative risk with daily intervention dose of vitamin D supplement and average intervention period in trials of vitamins D3 and D2 supplementation



All *p*-values are > 0.05

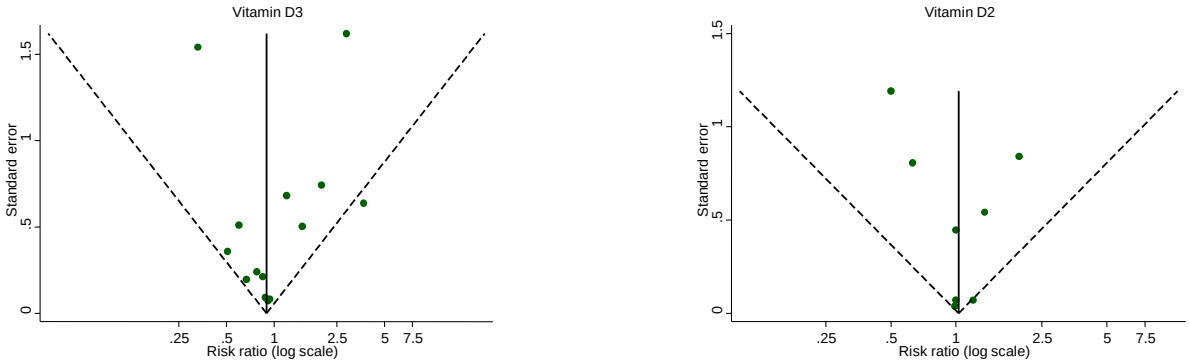
eFigure 8. Funnel plots showing associations of vitamin D with cause-specific mortality in both observational cohort studies and supplementation trials

(i) Observational studies



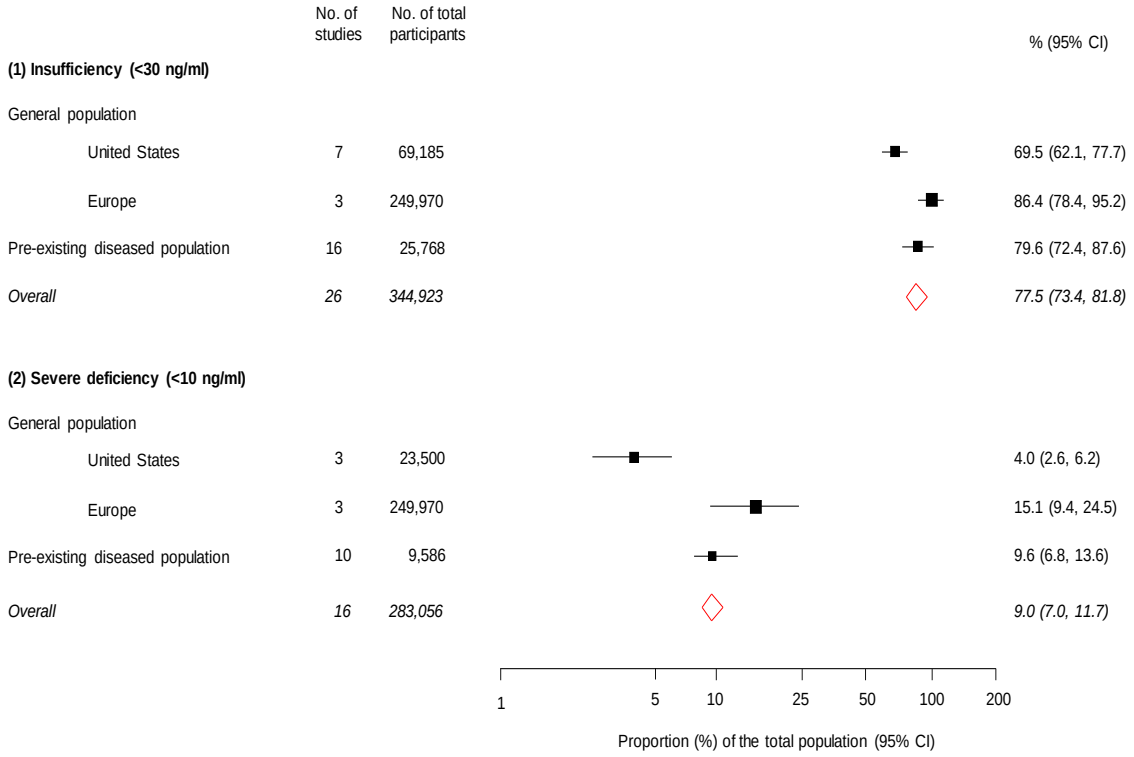
The dotted lines show 95% confidence intervals around the overall summary estimate.
Egger's asymmetry test of associations for CVD mortality, *P*=0.96; associations for cancer mortality, *P*=0.12; associations for non-vascular, non-cancer mortality, *P*=0.39

(ii) Clinical trials



The dotted lines show 95% confidence intervals around the overall summary estimate.
Egger's asymmetry test of associations for vitamin D3, *P*=0.76; associations for vitamin D2, *P*=0.75

eFigure 9. Prevalence of vitamin D deficiency, derived from subset of observational cohort studies with available information



eAppendix 1. PRISMA 2009 check-list

Section / topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	3
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	4
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	4
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	4
Search	8	Present full electronic search strategy for at least one database, including any limits used.	eAppendix 3
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	4
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	4

Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	4
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	5, eAppendix 4
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	5
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	5
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	5
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	5
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	7 and eFigure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	7, Table 1, eTables 1-3
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	7-9
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	7-9
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	7-9
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	7-9
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	7-9
DISCUSSION			

Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	10-12
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	13
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	12-13
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	15

eAppendix 2. MOOSE Checklist

Criteria		Brief description of how the criteria were handled in the meta-analysis
Reporting of background should include		
√	Problem definition	Low levels of vitamin D have been implicated as a potential determinant of mortality because of its wide-ranging anti-inflammatory and immune-modulating effects. However, a supposed role on overall and cause-specific death in observational and intervention studies remains uncertain.
√	Hypothesis statement	Vitamin D is associated with risk of cause-specific deaths
√	Description of study outcomes	Overall mortality and deaths due to cardiovascular, cancer and other nonvascular-noncancer causes
√	Type of exposure or intervention used	Circulating vitamin D levels (25-hydroxyvitamin D) and vitamin D supplementations (given alone and not in combination with other supplements such as calcium)
√	Type of study designs used	Observational cohort studies (prospective and retrospective cohorts) and randomized clinical trials
√	Study population	Primarily general populations and other secondary populations (eg, people with pre-existing chronic diseases at baseline).
Reporting of search strategy should include		
√	Qualifications of searchers	The credentials of the investigators are indicated in the authors list.
√	Search strategy, including time period included in the synthesis and keywords	Search strategy and time periods are detailed in page 4 of the manuscript and in eAppendix 3.
√	Databases and registries searched	MEDLINE, EMBASE, and the Cochrane databases.
√	Search software used, name and version, including special features	We did not employ a search software. Reference Manager was used to merge retrieved citations and eliminate duplications.
√	Use of hand searching	We hand-searched bibliographies of retrieved papers and relevant reviews for additional references.
√	List of citations located and those excluded, including justifications	Details of the literature search process are outlined in the flow chart. Citations for the included studies are enclosed with the supplementary material. The citation list for excluded studies is available upon request.
√	Method of addressing articles published in languages other than English	We placed no restrictions on language. Local scientists fluent in the original language of the article were contacted for translation.
√	Method of handling abstracts and unpublished studies	We had contacted several authors for unpublished studies on the association.
√	Description of any contact with authors	We contacted authors who had conducted multivariate analysis with vitamin D as a covariate, but had not reported relative risk for cause-specific mortality.
Reporting of methods should include		
√	Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested	Detailed inclusion and exclusion criteria are described in the Methods section.

Criteria		Brief description of how the criteria were handled in the meta-analysis
√	Rationale for the selection and coding of data	Data extracted from each of the studies were relevant to the population characteristics, study design, exposure, outcome, and possible effect modifiers of the association.
√	Assessment of confounding	We assessed confounding by ranking individual studies on the basis of different adjustment levels, and performed sub-group analyses to evaluate differences in the overall estimates according to levels of adjustment.
√	Assessment of study quality, including blinding of quality assessors; stratification or regression on possible predictors of study results	Sensitivity analyses by several quality indicators such as study size, duration of follow-up, laboratory measurements, allocation concealment, and method of blinding and adjustment factors (eTable 1 and eAppendix 4).
√	Assessment of heterogeneity	Heterogeneity of the studies were explored using Cochrane's Q test of heterogeneity and I^2 statistic that provides the relative amount of variance of the summary effect due to the between-study heterogeneity.
√	Description of statistical methods in sufficient detail to be replicated	Description of methods of meta-analyses, sensitivity analyses, meta-regression and assessment of publication bias are detailed in the methods.
√	Provision of appropriate tables and graphics	We included 7 main figures, 1 main table, and 16 supplementary figures and tables
Reporting of results should include		
√	Graph summarizing individual study estimates and overall estimate	Figures 1,2, and 6; eFigures 2,3, and 5
√	Table giving descriptive information for each study included	eTables 1-3
√	Results of sensitivity testing	Figures 3-5,and 7, eFigures 4,6, and 7
√	Indication of statistical uncertainty of findings	95% confidence intervals were presented with all summary estimates, I^2 values and results of sensitivity analyses
Reporting of discussion should include		
√	Quantitative assessment of bias	Sensitivity analyses indicate heterogeneity in strengths of the association due to most common biases in observational studies.
√	Justification for exclusion	We excluded studies that used different exposure or outcome assessment for the comparison groups.
√	Assessment of quality of included studies	We discussed the results of the sensitivity analyses, and potential reasons for the observed heterogeneity.
Reporting of conclusions should include		
√	Consideration of alternative explanations for observed results	We discussed that potential unmeasured confounders may have caused residual confounding. Additionally, our findings could have been over-estimated somewhat due to preferential publication of extreme findings. The variations in the strengths of association may also be due to true population differences, or to

Criteria		Brief description of how the criteria were handled in the meta-analysis
		differences in quality of studies.
√	Generalization of the conclusions	The generalisability of our findings has been enhanced by the involvement of data from over 883 435 participants from 24 countries. However, we noted the lack of studies from the African continent.
√	Guidelines for future research	We recommend future studies that would include larger studies with serial vitamin D measurements. Additionally, carefully designed long-term trials based on general population are needed.
√	Disclosure of funding source	No separate funding was necessary for the undertaking of this systematic review.

eAppendix 3. Search strategy

Relevant studies, published before August 1, 2013 (date last searched), were identified through electronic searches not limited to the English language using MEDLINE, EMBASE, and Cochrane databases. Electronic searches were supplemented by scanning reference lists of articles identified for all relevant studies (including review articles), by hand searching of relevant journals and by correspondence with study investigators. The computer-based searches combined search terms related to vitamin D and mortality without language restriction.

(i) MEDLINE strategy to identify relevant exposures:
("Vitamin D"[Mesh] OR "vitamin d"[All Fields] OR “25-hydroxyvitamin D”[All Fields] OR “25(OH)D”[All Fields] OR “calcidiol”[All Fields] OR "ergocalciferols"[Mesh] OR "ergocalciferols"[All Fields] OR "Vitamin D Deficiency"[Mesh])

(ii) MEDLINE strategy to identify relevant outcomes:
("Mortality"[Mesh] OR "mortality"[All Fields] OR "all cause mortality"[All Fields] OR "death"[All Fields] OR "survival"[All Fields] OR ("Neoplasms"[Mesh] AND (“death” OR “mortality”)) OR ("Cardiovascular Diseases"[Mesh] AND (“death” OR “mortality”)) OR ("Communicable Diseases"[Mesh] AND (“death” OR “mortality”)) OR ("Respiratory Tract Diseases"[Mesh] AND (“death” OR “mortality”)))

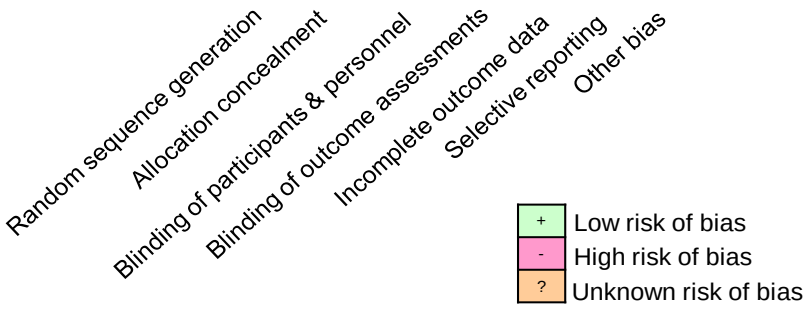
(iii) MEDLINE strategy to identify relevant population:
("humans"[MeSH Terms])

Parts I, ii and iii were combined using ‘AND’ to search the MEDLINE. Additionally, each part was specifically translated for searching alternative databases.

eAppendix 4. Assessment of risk of bias in the randomised controlled trials included in this review

. .

Broe KE et al.	2007	+	+	+	+	+	+	+
Corless D et al.	1985	+	+	+	?	-	+	?
Harwood RH et al.	2004	+	+	-	-	-	+	-
Law M et al.	2006	+	-	-	+	?	+	?
Lyons RA et al.	2007	+	+	+	-	+	+	-
Smith H et al.	2007	+	+	+	-	+	+	+
Witham MD et al.	2010	+	+	+	-	-	+	+
Sato Y et al.	2005	+	+	+	-	-	+	+
Avenell A et al.	2012	+	+	+	?	-	+	?
Campbell AJ et al.	2005	+	+	-	+	+	+	-
Chel V et al.	2008	+	+	?	?	+	+	?
Gallagher JC et al.	2004	+	+	+	-	-	+	?
Grady D et al.	1991	+	?	+	?	?	+	?
Latham NK et al.	2003	+	+	+	+	+	+	+
Lips P et al.	1996	+	+	+	?	+	+	+
Ooms ME et al.	1995	+	+	+	?	-	+	?
Sanders KM et al.	2010	+	+	+	+	+	+	+
Trivedi DP et al.	2003	+	+	+	+	+	+	+
Beer TM et al.	2007	+	+	+	-	+	+	?
Lehouck A et al.	2012	+	+	+	+	+	+	+
Schleithoff SS et al.	2006	+	+	+	?	-	+	?
TIDE Trial Investigators	2012	+	+	+	+	+	+	+



eAppendix 5. Calculation of the absolute risk

The corresponding absolute risk differences associated with Vitamin D deficiency are based on the most recent statistics for the United States (US) and Europe.

Absolute risk difference = background incidence in the general US/Europe population*(estimated RR−1).

(1) Background Incidence rates per 100,000 US and European populations

(a) Age standardized death rate of Mortality (US), 2008 = 460 per 100,000
Ref: http://www.who.int/gho/countries/en/

(b) Age standardized death rate of Mortality (Europe), 2008 = 628.2 per 100,000
http://epp.eurostat.ec.europa.eu/portal/page/portal/health/public_health/data_public_health/main_tables)

(2) RR (95% CI) of all cause mortality comparing approximately healthy individuals with baseline vitamin D level of <30 versus. ≥30 ng/mL, based on the current meta-analysis

(a) US: 1.21 (1.09-1.35)

(b) Europe: 1.12 (1.10-1.15)

Absolute risk difference for All Cause Mortality

Absolute risk difference associated with Vitamin D Deficiency in the US = 460*(0.21)
= 96.6 per 100,000 deaths

Absolute risk difference associated with Vitamin D Deficiency in the Europe = 628.2*(0.12)
= 75.4 per 100,000 deaths

Population Attributable Risk

PAR = P_e (RR_e-1) **/** [1 + P_e (RR_e-1)], for which Pe is the prevalence of the exposure

PAR for Vit D deficiency in US = 100*0.70*0.21/ [(0.70*0.21)+1] = **12.8%**

PAR for Vit D deficiency in Europe = 100*0.86*0.12/ [(0.86*0.12)+1] = **9.4%**

Notes on PAR calculation:

*(i) RR_e were based on pooled estimates from the corresponding primary prevention cohort studies that were included in this current review, and based in the US and Europe, respectively (**see point (2) above**);*

*(ii) P_e for the US and Europe were based on the updated prevalence estimates calculated in the current review (**see eFigure 9**).*

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