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Effect of Vitamin D Supplementation on Markers of Vascular Function: A Systematic Review and Individual Participant Meta-Analysis

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***Background*—**Low 25-hydroxyvitamin D levels are associated with an increased risk of cardiovascular events, but the effect of vitamin D supplementation on markers of vascular function associated with major adverse cardiovascular events is unclear.

***Methods and Results*—**We conducted a systematic review and individual participant meta-analysis to examine the effect of vitamin D supplementation on flow-mediated dilatation of the brachial artery, pulse wave velocity, augmentation index, central blood pressure, microvascular function, and reactive hyperemia index. MEDLINE, CINAHL, EMBASE, Cochrane Central Register of Controlled Trials, and http://www.ClinicalTrials.gov were searched until the end of 2016 without language restrictions. Placebo-controlled randomized trials of at least 4 weeks duration were included. Individual participant data were sought from investigators on included trials. Trial-level meta-analysis was performed using random-effects models; individual participant meta-analyses used a 2-stage analytic strategy, examining effects in prespecified subgroups. 31 trials (2751 participants) were included; 29 trials (2641 participants) contributed data to trial-level meta-analysis, and 24 trials (2051 participants) contributed to individual-participant analyses. Vitamin D3 daily dose equivalents ranged from 900 to 5000 IU; duration was 4 weeks to 12 months. Trial-level meta-analysis showed no significant effect of supplementation on macrovascular measures (flow-mediated dilatation, 0.37% [95% confidence interval, −0.23 to 0.97]; carotid-femoral pulse wave velocity, 0.00 m/s [95% confidence interval, −0.36 to 0.37]); similar results were obtained from individual participant data. Microvascular function showed a modest improvement in trial-level data only. No consistent benefit was observed in subgroup analyses or between different vitamin D analogues.

***Conclusions*—**Vitamin D supplementation had no significant effect on most markers of vascular function in this analysis. **(*J Am Heart Assoc*. 2018;7:e008273. DOI: 10.1161/JAHA.117.008273.)**

Key Words: endothelial function • paricalcitol • systematic review • vascular function • vitamin D

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Clinical Perspective

What Is New?

- This is the first individual participant data meta-analysis examining the effect of vitamin D analogues on markers of vascular function that are surrogates for cardiovascular events.
- No consistent effect was found at trial level or on analysis of individual participant-level data of supplementation on measures of endothelial function, arterial stiffness, or central blood pressure.
- No subgroup benefited consistently on analysis of individual participant data.

What Are the Clinical Implications?

- This analysis did not find convincing evidence of benefit from Vitamin D supplementation on a range of markers of vascular function.

Low circulating levels of 25-hydroxyvitamin D (25(OH)D) have been associated with a wide range of illness states and physiological derangements. Within the field of cardiometabolic medicine, low 25(OH)D levels have been associated with higher levels of blood pressure (BP), with diabetes mellitus, stroke, myocardial infarction, and heart failure[1,2] in observational studies. Vitamin D affects hundreds of gene targets and has effects on a wide variety of cell types and organ systems, including the heart and vascular system.[3,4] Several pathophysiological pathways have been postulated to explain the observed associations between low 25(OH)D levels and cardiovascular disease, including effects on arterial stiffness, endothelial function, cytokine secretion, vascular endothelial growth factor, and cellular calcium influx.[4]

Despite a sound rationale for improved cardiovascular health with vitamin D supplementation, results from intervention trials have been less encouraging. A recent individual participant data (IPD) meta-analysis reported that vitamin D supplementation had no significant effect on BP,[5] even in those participants with low baseline 25(OH)D levels or with high baseline BP. Similarly, only marginal effects were observed on glycemic control in a meta-analysis of vitamin D supplementation in participants with diabetes mellitus.[6] Meta-analyses of cardiovascular outcomes show no effect of vitamin D supplementation on myocardial infarction or stroke, but suggest a possible effect in reducing new diagnoses of heart failure.[7] It is important to note that these meta-analyses include mostly trials performed in participants at risk for falls or with osteoporosis and may therefore not be generalizable. Several large trials of vitamin D supplementation with adequate power to detect reductions in cardiovascular events are due to report over the next few years, but the first of these trials did not report any reduction in cardiovascular event rates in a population of older people in New Zealand.[8]

These results call into question the causal link between vitamin D status and vascular health. Results from trials investigating the effect of vitamin D supplementation on aspects of vascular health other than BP have shown mixed results. Arterial stiffness and endothelial function measures are validated markers of cardiovascular disease risk and major adverse cardiac events, but the beneficial impact of vitamin D supplementation on these markers is unclear. We therefore performed a systematic review with meta-analysis of trial-level and individual participant-level data to ascertain whether (1) vitamin D supplementation improves measures of arterial stiffness and endothelial function and (2) certain subgroups of individuals are more likely to benefit.

Methods

Data Sharing Statement

To preserve the rights of data owners, and as agreed with those who contributed data sets for this analysis, the data, analytical methods, and study materials will not be made available to other researchers for the purposes of reproducing the results or replicating the procedure.

Review Design and Search Strategy

We conducted a systematic review according to a prespecified protocol, which was registered on the PROSPERO database of systematic reviews. The protocol is accessible at: (http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42012002816). Ethics committee approval was not required because no new data were collected as part of this review. We included randomized controlled trials, which compared vitamin D or analogues with placebo, with a minimum exposure period of 4 weeks. The following databases were searched from inception to end of December 2016: Medline, EMBASE, CINAHL, ClinicalTrials.gov, and the Cochrane central register of controlled trials. Gray literature was sought using Google, and references of included studies were hand-searched for further candidate trials. Only trials where a full published trial report was available were included; trials published in abstract form only were excluded.

Trial Selection

Trials with changes in the following vascular markers were included: brachial artery flow-mediated dilatation; reactive hyperemia index measures using finger plethysmography;

pulse wave velocity (PWV) and pulse wave analysis; central aortic BP derived from peripheral artery tonometry; microvascular function measured using acetylcholine iontophoresis; and laser Doppler perfusion imaging. Studies with any baseline 25(OH)D level were eligible for inclusion. The following interventions were eligible for inclusion: vitamin D2 (ergocalciferol), vitamin D3 (cholecalciferol), calcitriol (1,25 hydroxyvitamin D3), 1-alpha-vitamin D, paricalcitol, and doxerocalciferol. Control groups receiving placebo were used and those receiving placebo plus cointervention were included, provided both arms of the study received the cointervention. A minimum of 4 weeks of therapy was necessary for inclusion to ensure sufficient time for vascular markers to change. Studies from both primary and secondary care or population settings were included; no restrictions were placed on sex or ethnicity. Studies recruiting participants less than 16 years old were not included, but in contrast to our previous review,[5] we did include studies of participants on renal replacement therapy (hemodialysis or peritoneal dialysis) given their very high cardiovascular risk and the current interest in using vitamin D supplementation therapy in this group.

Data Extraction

Data were extracted independently by 2 researchers (L.A.B. and M.D.W.) and differences resolved by consensus. Baseline trial population data were identified, including age, sex, ethnicity, diabetes mellitus, kidney function, history of cardiovascular events, history of hypertension, baseline BP, and baseline use of angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers, and statins. For each measure of vascular function, we recorded change in the outcome in each group between baseline and the last follow-up visit. Study authors were contacted if data were incomplete or ambiguous in primary reports.

IPD Collection

Lead authors for each included trial were contacted and invited to contribute individual-level participant data. Data were anonymized and transferred using a standard template before cleaning and incorporation in the final data set. Individual-level participant data were sought for age, sex, body mass index, baseline and follow-up 25(OH)D level, baseline medication use including ACE inhibitors and angiotensin receptor blockers, baseline estimated glomerular filtration rate (eGFR), total cholesterol, serum calcium and parathyroid hormone (PTH), presence of diabetes mellitus and previous vascular events, baseline and follow up BP and cholesterol, and baseline and follow-up measures of vascular function.

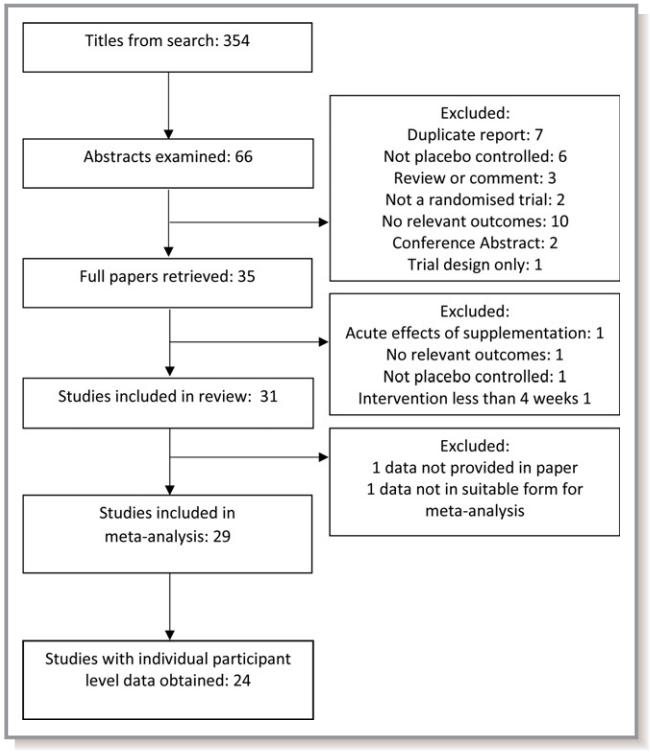

Figure. PRISMA diagram showing trial selection.

Risk of Bias Assessment

Risk of bias was evaluated by 2 authors independently, with discrepancies resolved by consensus. We assessed each included study for risk for bias using the following fields from a risk of bias checklist[9]: quality of random allocation concealment, intention-to-treat analysis, blinding of outcome assessors, treatment and control group comparability, clear definition of inclusion and exclusion criteria, participant blinding to allocation, and description of withdrawals and dropouts. Funnel plots were generated and inspected for evidence of publication bias, supplemented by Egger's test for funnel plot asymmetry.

Statistical Analysis

Meta-analysis at the trial level was performed using RevMan 5.3 software (Cochrane Collaboration). For all analyses, random-effects and fixed-effects meta-analyses using a weighted least-squares approach were performed. For outcomes measured with the same technique and same units (most brachial-artery flow-mediated dilatation [FMD] measures, reactive hyperemia index, augmentation index [AIx], central BP, and subgroups of PWV), results were expressed as mean difference between groups. For comparisons where dissimilar units were combined, results were expressed as standardized mean difference (SMD). Heterogeneity was assessed using the I^2 statistic. Trial-level meta-regression

Table 1. Measurements From Included Studies

Title and Year	Preparation Tested	FMD	PWV	AIx	RHI	Central BP	Microvascular Function	Included in IPD Analysis?
Alborzi 2008[11]	Paricalcitol	X						No
Sugden 2008[12]	Vitamin D2	X						Yes
Witham 2010[13]	Vitamin D3	X						Yes
Harris 2011[14]	Vitamin D3	X						Yes
Gepner 2012[15]	Vitamin D3	X	X	X		X		Yes
Larsen 2012[16]	Vitamin D3		X	X		X		Yes
Marckmann 2012[17]	Vitamin D3		X	X		X		Yes
Sokol 2012[18]	Vitamin D2				X			Yes
Stricker 2012[19]	Vitamin D3			X		X	X	Yes
Witham 2012[20]	Vitamin D2	X						Yes
Breslavsky 2013[21]	Vitamin D3			X				Yes
Hewitt 2013[22]	Vitamin D3		X					No
Witham 2013[23]	Vitamin D3	X	X					Yes
Witham 2013[24]	Vitamin D3				X			Yes
Witham 2013[25]	Vitamin D3	X	X	X		X	X	Yes
Yiu 2013[26]	Vitamin D3	X	X					No
Dreyer 2014[27]	Vitamin D2		X				X	Yes
Martins 2014[28]	Vitamin D3			X				No
Mose 2014[29]	Vitamin D3		X	X		X		Yes
Ryu 2014[30]	Vitamin D3		X	X				No
Zoccali 2014[31]	Paricalcitol	X						Yes
Garg 2015[32]	Vitamin D3		X	X				Yes
Pilz 2015[33]	Vitamin D3		X					Yes
Thethi 2015[34]	Paricalcitol	X						No
Witham 2015[35]	Vitamin D3	X	X	X				Yes
Barchetta 2016[36]	Vitamin D3	X						Yes
Borgi 2017[37]	Vitamin D2	X						No
Bressendorff 2016[38]	Vitamin D3		X	X		X		Yes
Dalan 2016[39]	Vitamin D3			X	X			Yes
Forouhi 2016[40]	Vitamin D2 Vitamin D3		X					Yes
Hin 2017[41]	Vitamin D3		X	X				Yes

AIx indicates augmentation index; BP, blood pressure; FMD, flow-mediated dilatation of the brachial artery; IPD, individual participant data; PWV, pulse wave velocity; RHI, reactive hyperemia index.

was undertaken for FMD, PWV, and augmentation index outcomes, regressing treatment effect on daily dose equivalent (for trials using vitamin D3) and trial duration in months. Metaregression was not used for other outcomes because there were too few to produce reliable results. Metaregression was undertaken using Comprehensive Meta Analysis tools software (version 3; Biostat, Englewood, NJ).

A 2-stage analysis was used for IPD.[10] For each trial, or subgroup within each trial, mean outcome values at follow-up in each group were calculated and adjusted for baseline outcome values using ANCOVA (SPSS version 24; IBM, Armonk, NY). These values were then combined using RevMan software as described above. For those trials using more than 1 type or dose of vitamin D, the vitamin D arms were analyzed as a single arm. The following prespecified subgroup analyses were performed: diabetes mellitus versus no diabetes mellitus; baseline systolic BP of no greater than 140 mm Hg versus greater than 140 mm Hg; diastolic BP of no greater

Table 2. Details of Included Studies

Study	N	Latitude	Study Population	Mean Age, y	% Male	25(OH)D Range for Inclusion (nmol/L)	Mean Baseline 25(OH)D (nmol/L)	Mean Baseline SBP (mm Hg)	Control	Intervention	Duration
Alborzi,[11] USA, 2008	24	40°N	CKD and on ACE-I or ARB	70	83	No restriction	34	125.4 (24 hours BP)	Placebo	Paricalcitol 1 μg daily Paricalcitol 2 μg daily	1 mo
Sugden,[12] Scotland, 2008	34	56°N	Type 2 diabetes mellitus	64	53	<50	38	141	Placebo	Ergocalciferol 100 000 IU single dose	8 wks
Witham,[13] Scotland, 2010	61	56°N	Type 2 diabetes mellitus	65	67	<100	45	146	Placebo	100 000 IU Cholecalciferol 200 000 IU cholecalciferol single dose	16 wks
Harris,[14] USA, 2011	45	33°N	Black adults with no overt cardiovascular, pulmonary or metabolic disease	30	47	No restriction	36	124	Placebo	Cholecalciferol 60 000 IU/4 weekly	16 wks
Gepner,[15] USA, 2012	114	43°N	Healthy community dwelling postmenopausal females	64	0	>25 and <150	78	119.4	Placebo	Cholecalciferol 2500 IU/day	4 mo
Larsen,[16] Denmark, 2012	130	56°N	Hypertension	61	31	No restriction	58	143	Placebo	Cholecalciferol 3000 IU/day	20 wks
Marckmann,[17] Denmark, 2012	52	55°N	CKD	67	75	<50	33	138	Placebo	Cholecalciferol 40 000 IU weekly	8 wks
Sokol,[18] USA, 2012	90	41°N	Angiographically confirmed coronary artery disease	56	73	<50	?	133	Placebo	Ergocalciferol 50 000 IU weekly	12 wks
Stricker,[19] Switzerland, 2012	62	46°N	Chronic peripheral vascular disease and vitamin D deficiency	74	61	<75	42	137	Placebo	Cholecalciferol (vitamin D3) 100 000 IU single dose	1 mo
Witham,[20] Scotland, 2012	58	56°N	Older adults with previous stroke	67	72	<75	38	128	Placebo	100 000 IU Ergocalciferol single dose	16 wks
Breslavsky,[21] Israel, 2013	47	32°N	Type 2 diabetes mellitus with cardiovascular risk factors	66	47	No restriction	30	153	Placebo	Cholecalciferol 1000 IU daily	12 mo
Hewitt,[22] Australia, 2013	60	34°S	Adults on hemodialysis	?	48	<60	43	152	Placebo	Cholecalciferol 50 000 IU weekly for 8 wks, then monthly for 4 mo	6 mo
Witham,[23] Scotland, 2013	159	56°N	Isolated systolic hypertension in over 70 year olds	77	52	<75	45	163	Placebo	Cholecalciferol 100 000 IU 3 monthly	12 mo
Witham,[24] Scotland, 2013	75	56°N	Recent myocardial infarction	66	69	No restriction	47	127.5	Placebo	Cholecalciferol 100 000 IU/ 2 monthly	6 mo
Witham,[25] Scotland, 2013	50	56°N	South-East Asian women living in UK for 10 y	41	0	<75	27	120	Placebo	Cholecalciferol 100 000 IU single dose	8 wks

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Table 2. Continued

Study	N	Latitude	Study Population	Mean Age, y	% Male	25(OH)D Range for Inclusion (nmol/L)	Mean Baseline 25(OH)D (nmol/L)	Mean Baseline SBP (mm Hg)	Control	Intervention	Duration
Yiu,[26] Hong Kong, 2013	100	22°N	Type 2 diabetes mellitus with suboptimal vitamin D status	65	50	<75	54	146	Placebo	Cholecalciferol 5000 IU daily	12 wks
Dreyer,[27] England, 2014	38	51°N	CKD stage 3 to 4	47	74	<40	25	116	Placebo	Ergocalciferol 50 000 IU weekly for 1 mo, then monthly for 5 mo	6 mo
Martins,[28] USA, 2014	130	34°N	Overweight blacks with hypertension	18 to 70	61	25 to 63	43	127	Placebo	Cholecalciferol 100 000 IU monthly	3 mo
Mose,[29] Denmark, 2014	50	56°N	Hemodialysis or peritoneal dialysis	68	64	No restriction	39	136	Placebo	Cholecalciferol 3000 IU daily	6 mo
Ryu,[30] Korea, 2014	62	38°N	Type 2 diabetes mellitus aged 30 to 69 y	56	?	<50	29	130	Placebo+200 mg calcium daily	Cholecalciferol 2000 IU daily+200 mg calcium daily	24 wks
Zoccali,[31] Italy, 2014	88	39°N	CKD stage 3 to 4 and PTH >65 pg/mL	63	65	No restriction	36	126	Placebo	Paricalcitol 2 μg daily	12 wks
Garg,[32] India, 2015	32	29°N	Women aged 18 to 35 y with polycystic ovary syndrome	22	0	No restriction	36	Not known	Placebo+1.5 g metformin daily	120 000 IU Cholecalciferol monthly+1.5 g metformin daily	6 mo
Pilz,[33] Austria, 2015	188	47°N	Hypertension	60	53	<75	53	143	Placebo	Cholecalciferol 2800 IU daily	8 wks
Thethi,[34] USA, 2015	55	30°N	CKD 3 to 4 and type 2 diabetes mellitus	63	67	No restriction	NA	136	Placebo	Paricalcitol 1 μg daily	12 wks
Witham,[35] Scotland, 2015	50	56°N	Chronic fatigue syndrome	49	24	<75	46	128.5	Placebo	Cholecalciferol 100 000 IU/2 monthly	6 mo
Barchetta.[36] Italy. 2016	55	42°N	Type 2 diabetes mellitus with nonalcoholic fatty liver disease	58	70	No restriction	NA	131	Placebo	Cholecalciferol 2000 IU daily	24 wks
Borgi,[37] USA, 2017	93	42°N	Overweight or obese nonhypertensives with vitamin D deficiency	37	?	<50	NA	118	Placebo	Ergocalciferol 50 000 IU weekly	8 wks
Bressendorff,[38] Denmark, 2016	40	56°N	Normotensive adults with vitamin D deficiency	43	58	<50	32	118	Placebo	Cholecalciferol 3000 IU daily	16 wks
Dalan,[39] Singapore, 2016	64	1°N	Multiethnic group with type 2 diabetes mellitus	54	52	No restriction	45	139	Placebo	Cholecalciferol 2000 to 4000 IU daily depending on baseline 25(OH)D and response	16 wks

Continued

DOI: 10.1161/JAHA.117.008273

Table 2. Continued

Study	N	Latitude	Study Population	Mean Age, y	% Male	25(OH)D Range for Inclusion (nmol/L)	Mean Baseline 25(OH)D (nmol/L)	Mean Baseline SBP (mm Hg)	Control	Intervention	Duration
Forouhi,[40] England, 2016*	160	52°N	Adults with elevated risk of type 2 diabetes mellitus	53	57	No restriction	52	128	Placebo	Ergocalciferol 100 000 IU monthly Cholecalciferol 100 000 IU monthly	4 mo
Hin,[41] England, 2017	305	52°N	Aged ≥65 y	72	51	No restriction	50	131	Placebo	Cholecalciferol 2000 IU daily Cholecalciferol 4000 IU daily	12 mo

25(OH)D indicates 25-hydroxyvitamin D; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BP, blood pressure; CKD, chronic kidney disease; NA, not available; SBP, systolic blood pressure.
*Data from 1 of 2 centers included as vascular function measured only at 1 center.

than 90 mm Hg versus greater than 90 mm Hg; baseline PTH level of above versus below median level for the IPD set; baseline adjusted serum calcium level and baseline total cholesterol above versus below median level for the individual participant data set; estimated glomerular filtration rate (eGFR) 60 mL/min per 1.73 m^2 or above versus subgroups of eGFR below 60 mL/min per 1.73 m^2; baseline 25(OH)D level of less than 25, 25 to 50, and greater than 50 nmol/L; and baseline ACE inhibitor versus no ACE inhibitor use. For analyses of ACE inhibitor use, participants taking angiotensin receptor blockers were excluded given their similar, but not identical, biological effects. Subgroups for analysis were selected on the basis of possible mechanisms by which vitamin D might act (eg, through effects on the renin-angiotensin system or by suppressing PTH),[4] to explore groups thought to be most likely to benefit (eg, high BP, low 25(OH)D levels), and to identify disease populations that might be targeted by future studies (diabetes mellitus, chronic kidney disease [CKD]). For CKD, subgroups of eGFR 45 to 59, 30 to 44, 15 to 29, and <15 mL/min per 1.73 m^2 were used where sufficient numbers of participants were available for the outcome; for outcomes with small numbers of participants, these subgroups were collapsed into a category eGFR <60 mL/min per 1.73 m^2. Participants on dialysis were included in the <15 mL/min per 1.73 m^2 subgroup.

Results

A total of 31 trials, involving 2751 participants, were eligible for inclusion in the review.[11–41] Of these, 29 trials (2641 participants) had data suitable for inclusion in the trial-level meta-analyses; IPD were obtained from 24 trials (2051 participants). The PRISMA flowchart is shown in Figure. One study that did not include data in the published article suitable for trial-level meta-analysis[36] provided IPD data and was included in the IPD analyses. Study size ranged from 24 to 305 participants; vitamin D3 was the most common intervention, being used in 23 of 31 (74%) of trials. The daily dose equivalent given in trials of vitamin D3 ranged from 900 to 5000 IU, and the duration of administration ranged from 4 weeks to 12 months. Paricalcitol was the only activated vitamin D analogue used in studies included in this review. Table 1 shows which vascular outcomes were measured in each included trial, and baseline trial characteristics are shown in Table 2.

Risk of Bias Assessment

Overall risk of bias was low. Most trials (27 of 31) reported clear evidence of effective allocation concealment, and most trials reported clear evidence for masking of participants (30 of 31), healthcare professionals (30 of 31), and outcomes

Table 3. Risk of Bias Assessment of Included Studies

Title and Year	Quality of Allocation Concealment	Analysis on Intention to Treat	No. and Description of Dropouts	Blinding—Participants	Blinding—Health Care Providers	Blinding—Outcome Assessors	Comparable Treatment and Placebo Groups
Alborzi 2008[11]	+	+	+	+	+	+	–
Sugden 2008[12]	+	–	+	+	+	+	+
Witham 2010[13]	+	U	+	+	+	+	+
Harris 2011[14]	+	U	+	+	+	+	+
Gepner 2012[15]	+	+	+	+	+	+	+
Larsen 2012[16]	+	–	+	+	+	+	+
Marckmann 2012[17]	+	–	+	+	+	+	+
Sokol 2012[18]	+	+	U	+	+	+	+
Stricker 2012[19]	+	+	+	+	+	+	–
Witham 2012[20]	+	U	+	+	+	+	+
Breslavsky 2013[21]	+	–	+	U	U	U	+
Hewitt 2013[22]	+	U	+	+	+	+	+
Witham 2013[23]	+	–	+	+	+	+	+
Witham 2013[24]	+	+	+	+	+	+	+
Witham 2013[25]	+	+	+	+	+	+	+
Yiu 2013[26]	+	+	+	+	+	+	+
Dreyer 2014[27]	+	+	+	+	+	+	+
Martins 2014[28]	U	+	+	+	+	+	+
Mose 2014[29]	+	U	+	+	+	+	+
Ryu 2014[30]	U	–	+	+	+	+	+
Zoccali 2014[31]	+	+	+	+	+	+	+
Garg 2015[32]	U	–	+	+	+	+	+
Pilz 2015[33]	+	+	+	+	+	+	+
Thethi 2015[34]	U	U	U	+	+	U	+
Witham 2015[35]	+	+	+	+	+	+	+
Barchetta 2016[36]	+	–	+	+	+	+	+
Borgi 2017[37]	+	+	–	+	+	+	+
Bressendorff 2016[38]	+	U	+	+	+	+	+
Dalan 2016[39]	+	+	U	+	+	+	–
Forouhi 2016[40]	+	+	+	+	+	+	+
Hin 2017[41]	+	+	+	+	+	+	+

– indicates high risk of bias; +, low risk of bias; U, unclear risk of bias.

assessors (29 of 31). Groups were comparable at baseline in 27 of 31 trials, dropouts were clearly described in 27 of 31 trials, but analysis was clearly by intention to treat in only 16 of 31 trials. A full description of the quality assessment for each trial is shown in Table 3. Funnel plots showed no asymmetry for any of the vascular outcomes; Egger's test was calculated only for those outcomes with at least 10 trials to ensure reliability; this was nonsignificant for FMD (P=0.18), AIx (P=0.32), and PVW (P=0.70).

Trial-Level Data

Meta-analysis of trial-level data showed no significant treatment effect of vitamin D analogues on FMD (mean difference, 0.5%; 95% confidence interval [CI], −0.1 to 1.1; P=0.12), PVW (SMD, 0.02; 95% CI, −0.13 to 0.17; P=0.81), AIx (mean difference, 0.0%; 95% CI, −1.3 to 1.3; P=0.98), reactive hyperemia index (mean difference, 0.02 units; 95% CI, −0.11 to 0.14; P=0.79), or central BP. Microvascular

Table 4. Trial-Level Analysis of Effect Size: Vitamin D Supplementation and Markers of Vascular Function

Outcome	Intervention	No. of Studies	n	Random-Effects		Fixed-Effects		I^2
				Treatment Effect (95% CI)	*P* Value	Treatment Effect (95% CI)	*P* Value	
FMD (%)	All	12	785	0.49 (−0.13 to 1.11)	0.12	0.48 (0.06–0.90)	0.02	46%
	D3	7	495	0.17 (−0.49 to 0.84)	0.61	0.19 (−0.30 to 0.67)	0.45	38%
	D2	3	163	0.79 (−1.04 to 2.62)	0.40	0.91 (−0.39 to 2.21)	0.17	45%
	Paricalcitol	2	103	1.72 (0.63–2.82)	0.002	1.72 (0.63–2.82)	0.002	0%
AIx (%)	All	14	1030	0.0 (−1.3 to 1.3)	0.98	0.0 (−1.1 to 1.1)	0.98	25%
	D3	14	1030	0.0 (−1.3 to 1.3)	0.98	0.0 (−1.1 to 1.1)	0.98	25%
	D2	0	…	…	…	…	…	…
	Paricalcitol	0	…	…	…	…	…	…
RHI, units	All	3	217	0.02 (−0.11 to 0.14)	0.79	0.02 (−0.11 to 0.14)	0.79	0%
	D3	2	130	0.02 (−0.18 to 0.21)	0.86	0.04 (−0.10 to 0.18)	0.61	37%
	D2	1	87	−0.05 (−0.30 to 0.20)	0.70	−0.05 (−0.30 to 0.20)	0.70	…
	Paricalcitol	0	…	…	…			…
PWV (all; SMD)	All	16	1333	0.04 (−0.11 to 0.20)	0.60	0.04 (−0.07 to 0.15)	0.50	44%
	D3	15	1304	0.05 (−0.11 to 0.21)	0.52	0.04 (−0.07 to 0.15)	0.45	47%
	D2	2*	138	−0.24 (−0.57 to 0.10)	0.17	−0.24 (−0.57 to 0.10)	0.17	0%
	Paricalcitol	0	…	…	…	…	…	…
PWV (carotid-femoral only; m/s)*	All	10	674	0.04 (−0.32 to 0.41)	0.81	−0.01 (−0.20 to 0.21)	0.94	58%
	D3	10	674	0.00 (−0.32 to 0.41)	0.81	−0.01 (−0.20 to 0.21)	0.94	58%
	D2	1	107	−0.53 (−1.34 to 0.28)	0.20	−0.53 (−1.34 to 0.28)	0.20	…
	Paricalcitol	0	…	…	…	…	…	…
PWV (others; SMD)	All	6	659	0.11 (−0.06 to 0.28)	0.22	0.11 (−0.04 to 0.27)	0.15	8%
	D3	5	630	0.12 (−0.06 to 0.30)	0.19	0.13 (−0.03 to 0.29)	0.11	14%
	D2	1	29	−0.20 (−0.93 to 0.53)	0.59	−0.20 (−0.93 to 0.53)	0.59	…
	Paricalcitol	0	…	…	…	…	…	…
Microvascular function (SMD)	All	3	140	0.43 (0.09–0.76)	0.01	0.43 (0.09–0.76)	0.01	0%
	D3	2	111	0.37 (−0.01 to 0.75)	0.05	0.37 (−0.01 to 0.75)	0.05	0%
	D2	1	29	0.65 (−0.10 to 1.41)	0.09	0.65 (−0.10 to 1.41)	0.09	…
	Paricalcitol	0	…	…	…	…	…	…
Central SBP, mm Hg	All	5	324	−1.5 (−5.6 to 2.6)	0.46	−1.2 (−3.8 to 1.4)	0.36	47%
	D3	5	324	−1.5 (−5.6 to 2.6)	0.46	−1.2 (−3.8 to 1.4)	0.36	47%
	D2	0	…	…	…	…	…	…
	Paricalcitol	0	…	…	…	…	…	…
Central DBP, mm Hg	All	5	324	−0.8 (−2.2 to 0.6)	0.28	−0.8 (−2.2 to 0.6)	0.28	0%
	D3	5	324	−0.8 (−2.2 to 0.6)	0.28	−0.8 (−2.2 to 0.6)	0.28	0%
	D2	0	…	…	…	…	…	…
	Paricalcitol	0	…	…	…	…	…	…

AIx indicates augmentation index; CI, confidence interval; D2, vitamin D2 (ergocalciferol); D3, vitamin D3 (cholecalciferol); DBP, diastolic blood pressure; FMD, flow-mediated dilatation of the brachial artery; PWV, pulse wave velocity; RHI, reactive hyperemia index; SBP, systolic blood pressure; SMD, standardized mean difference.
*Data from Forouhi et al[40] contain comparisons of D3 vs placebo and D2 vs placebo. Only D3 analysis was included in "All" category for PWV analyses.

function measured by laser Doppler iontophoresis (SMD, 0.43; 95% CI, 0.09–0.76; *P*=0.01) showed a modest improvement with vitamin D supplementation. Results are shown in Table 4. Fixed-effects analyses showed similar point estimates, but narrower CIs, leading to a significant treatment effect for all vitamin D analogues on FMD (mean

Table 5. Results of Trial-Level Metaregression

Outcome	Moderator Variable	No. of Trials	Random-Effects		Fixed-Effects		Regression Coefficient Units
			Regression Coefficient (95% CI)	*P* Value	Regression Coefficient (95% CI)	*P* Value	
FMD (%)	Trial duration	11	−0.06 (−0.11 to −0.01)	0.03	−0.06 (−0.10 to −0.01)	0.009	% per mo
	Daily dose equivalent	6	0.14 (0.01–0.27)	0.03	0.14 (0.01–0.27)	0.03	% per 1000 units D3
PWV (SMD)	Trial duration	16	0.01 (−0.04 to 0.06)	0.77	0.02 (−0.01 to 0.05)	0.18	SD per mo
	Daily dose equivalent	15	0.07 (−0.08 to 0.23)	0.35	0.06 (−0.05 to 0.17)	0.29	SD per 1000 units D3
AIx (%)	Trial duration	14	−0.01 (−0.05 to 0.04)	0.73	−0.00 (−0.04 to 0.03)	0.84	% per mo
	Daily dose equivalent	14	0.10 (−0.06 to 0.25)	0.22	0.09 (−0.04 to 0.23)	0.18	% per 1000 units D3

AIx indicates augmentation index; CI, confidence interval; FMD, flow-mediated dilatation of the brachial artery; PWV, pulse wave velocity; SMD, standardized mean difference.

difference, 0.5%; 95% CI, 0.1–0.9; *P*=0.02). On subgroup analysis by treatment type, only paricalcitol showed a significant treatment benefit on FMD (mean difference, 1.7%; 95% CI, 0.6–2.8; *P*=0.002); analysis for interaction showed no significant difference between the paricalcitol treatment effect and that for vitamin D3 (*P*=0.62) or vitamin D2 (*P*=0.17). No significant difference was evident in the effects of daily dosing versus intermittent dosing either for FMD (mean difference, 0.85% [95% CI, 0.01–1.69] for daily dosing versus 0.26% [95% CI, −0.58 to 1.11] for intermittent dosing; *P*=0.06) or for PWV (SMD, 0.10 [95% CI, −0.04 to 0.23] for daily dosing versus −0.04 [95% CI, −0.34 to 0.26] for intermittent dosing; *P*=0.40). Metaregression results for daily dose equivalent and for trial duration are shown in Table 5. No association between these factors and treatment effect for PWV or AIx was found, but higher dose and shorter trial length were associated with a slightly greater treatment effect for FMD.

Individual Participant Data

Similarly, meta-analysis of IPD showed no significant treatment effect on any of the vascular outcomes studied; no effect was evident when PWV analyses were confined to studies using carotid-femoral PWV. The main results for IPD analysis are shown in Table 6. For most analyses, heterogeneity as shown by the I^2 statistic was low to moderate. Prespecified subgroup analysis of IPD data for each vascular outcome (Tables 7 through 13) did not show any subgroup consistently deriving significant benefit from vitamin D or analogues; treatment/subgroup interaction analyses suggested that participants with eGFR <60 mL/min per 1.73 m^2 may be less likely to show improvements in FMD or aortic diastolic BP with treatment, and those with 25(OH)D levels <25 nmol/L may be more likely to show improvements in reactive hyperemia index and AIx with treatment. Participants with diabetes mellitus appeared to have a significantly

Table 6. IPD Analysis of Effect Size: Vitamin D Supplementation and Markers of Vascular Function

Outcome	No. of Studies	n	Mean Baseline Value Across All Groups (SD)	Random Effects		Fixed Effects		I^2
				Treatment Effect (95% CI)	*P* Value	Treatment Effect (95% CI)	*P* Value	
FMD (%)	10	655	5.6 (3.6)	−0.03 (−0.78 to 0.71)	0.93	−0.17 (−0.58 to 0.25)	0.44	63%
AIx (%)	11	832	27 (16)	0.1 (−1.4 to 1.6)	0.91	0.0 (−1.0 to 1.1)	0.96	39%
RHI, units	3	220	1.65 (0.81)	−0.02 (−0.12 to 0.08)	0.68	−0.02 (−0.12 to 0.08)	0.68	0%
PWV (all; SMD)	13	1154	ND	−0.01 (−0.16 to 0.13)	0.85	−0.04 (−0.15 to 0.08)	0.56	25%
PWV (carotid-femoral only; m/s)	9	652	7.9 (2.8)	−0.01 (−0.31 to 0.30)	0.96	−0.04 (−0.25 to 0.17)	0.70	44%
PWV (others; SMD)	4	502	ND	−0.02 (−0.20 to 0.16)	0.83	−0.05 (−0.36 to 0.26)	0.75	0%
Microvascular function (SMD)	3	129	ND	0.36 (0.01–0.71)	0.05	0.36 (0.01–0.71)	0.13	0%
Central SBP, mm Hg	7	400	120.7 (23.9)	−0.6 (−3.2 to 1.9)	0.63	−0.4 (−2.4 to 1.6)	0.67	31%
Central DBP, mm Hg	7	400	76.5 (9.9)	−0.4 (−1.5 to 0.7)	0.48	−0.4 (−1.5 to 0.7)	0.48	0%

AIx indicates augmentation index; CI, confidence interval; DBP, diastolic blood pressure; FMD, flow-mediated dilatation of the brachial artery; IPD, individual participant data; ND, not done because of heterogeneity of measurement methods; PWV, pulse wave velocity; RHI, reactive hyperemia index; SBP, systolic blood pressure; SMD, standardized mean difference.

Table 7. IPD Subgroup Analyses for FMD

Subgroup	No. of Studies	n	Mean Baseline Value (%) (SD)	Random Effects			Fixed Effects			I^2
				Treatment Effect (%) (95% CI)	*P* Value	*P* for Interaction	Treatment Effect (%) (95% CI)	*P* Value	*P* for Interaction	
SBP >140 mm Hg	9	242	5.2 (3.2)	0.0 (−1.1 to 1.0)	0.94	0.88	−0.1 (−0.6 to 0.5)	0.82	1.0	56%
SBP ≤140 mm Hg	9	376	5.9 (3.8)	0.1 (−0.9 to 1.0)	0.90		−0.1 (−0.6 to 0.5)	0.79		58%
Baseline 25(OH)D <25 nmol/L	6	89	5.7 (4.0)	−0.3 (−1.8 to 1.2)	0.65	…	−0.1 (−1.0 to 0.9)	0.92	…	43%
Baseline 25(OH)D 25 to 50 nmol/L	9	292	5.3 (3.3)	−0.1 (−1.2 to 1.0)	0.87	0.83	−0.1 (−0.7 to 0.5)	0.66	1.0	66%
Baseline 25(OH)D >50 nmol/L	8	222	5.4 (3.4)	−0.2 (−1.1 to 0.7)	0.66	0.91	−0.2 (−0.9 to 0.4)	0.47	0.87	41%
DM	6	198	5.2 (3.5)	0.1 (−1.1 to 1.4)	0.82	0.47	0.4 (−0.5 to 1.2)	0.40	0.27	37%
No DM	7	454	5.7 (3.5)	−0.4 (−0.9 to 0.1)	0.14		−0.3 (−1.2 to 0.6)	0.55		63%
No ACEi or ARB	9	254	6.5 (3.6)	0.1 (−2.0 to 2.2)	0.92	…	−0.6 (−1.3 to 0.1)	0.09	…	88%
ACEi, no ARB	7	171	5.4 (3.5)	−0.4 (−1.7 to 1.0)	0.58	0.69	−0.2 (−1.0 to 0.6)	0.64	0.46	47%
ACEi or ARB	7	297	5.0 (3.4)	−0.7 (−1.9 to 0.5)	0.28	0.52	−0.7 (−1.4 to −0.1)	0.03	0.84	60%
PTH >5.0 pmol/L	8	254	5.4 (3.6)	−0.3 (−1.5 to 0.9)	0.61	0.39	−0.8 (−1.5 to −0.2)	0.02	0.02	62%
PTH ≤5.0 pmol/L	7	230	5.7 (3.1)	0.3 (−0.3 to 1.0)	0.30		0.3 (−0.3 to 1.0)	0.30		0%
Ca >2.30 mmol/L	7	226	6.0 (3.4)	0.3 (−0.3 to 1.0)	0.30	0.19	0.3 (−0.3 to 1.0)	0.30	0.08	0%
Ca ≤2.30 mmol/L	7	371	5.2 (3.4)	−0.5 (−1.5 to 0.5)	0.30		−0.5 (−1.1 to 0.1)	0.09		56%
eGFR ≥60 mL/min per 1.73 m^2	6	382	5.6 (3.4)	0.5 (−0.2 to 1.2)	0.18	…	0.6 (0.0–1.2)	0.04	…	27%
eGFR 45 to 59 mL/min per 1.73 m^2	5	59	5.3 (3.1)	−0.1 (−2.2 to 2.1)	0.94	0.60	0.3 (−1.0 to 1.5)	0.66	0.67	55%
eGFR 30 to 44 mL/min per 1.73 m^2	3	38	4.5 (2.9)	−1.0 (−2.7 to 0.7)	0.27	0.11	−1.0 (−2.7 to 0.7)	0.27	0.08	0%
eGFR 15 to 29 mL/min per 1.73 m^2	1	24	3.4 (3.0)	−3.1 (−5.7 to −0.5)	0.02	0.009	−3.1 (−5.7 to −0.5)	0.02	0.007	…
eGFR <15 mL/min per 1.73 m^{2*}	0	…	…	…	…	…	…	…	…	…
Total cholesterol ≥4.60 mmol/L	8	223	5.4 (3.4)	−0.9 (−1.9 to 0.1)	0.07	0.23	−1.0 (−1.6 to −0.4)	0.002	0.06	51%
Total cholesterol <4.60 mmol/L	8	283	5.6 (3.7)	0.1 (−1.1 to 1.4)	0.83		−0.2 (−0.8 to 0.4)	0.60		69%

25(OH)D indicates 25-hydroxyvitamin D; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; Ca, calcium; CI, confidence interval; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; FMD, flow-mediated dilatation of the brachial artery; IPD, individual participant data; PTH, parathyroid hormone; SBP, systolic blood pressure.
*Or on dialysis.

greater rise in aortic BP than those without diabetes mellitus. For outcomes in both trial-level and IPD analysis that were performed using SMD, standardizing SDs are given in Table 14 to facilitate interpretation at the individual trial level.

Discussion

The present meta-analysis found little evidence to support the hypothesis that supplementation of vitamin D or use of vitamin D analogues can improve markers of cardiovascular health. Our results were broadly consistent across a range of vascular markers and interventions, and subgroup analyses using IPD did not identify a subgroup that was more likely to benefit from treatment—this remained true even for those participants with the lowest 25(OH)D levels, with high baseline BP, and with higher baseline PTH levels. Random-effects and fixed-effects analyses gave very similar results in the majority of analyses. Our results are consistent with our

Table 8. IPD Subgroup Analyses for PWV

Subgroup	No. of Studies	N	Mean Baseline Value (m/s) (SD)*	Random Effects			Fixed Effects			I^2
				Treatment Effect (95% CI) (SMD)	*P* Value	*P* for Interaction	Treatment Effect (95% CI) (SMD)	*P* Value	*P* for Interaction	
SBP >140 mm Hg	9	396	8.9 (3.2)	−0.1 (−0.3 to 0.1)	0.21	0.49	−0.1 (−0.3 to 0.1)	0.21	0.43	0%
SBP ≤140 mm Hg	11	728	7.5 (2.6)	0.0 (−0.2 to 0.2)	1.00		−0.0 (−0.2 to 0.1)	0.62		40%
Baseline 25(OH)D <25 nmol/L	11	157	7.6 (2.8)	0.2 (−0.2 to 0.5)	0.36	…	0.2 (−0.2 to 0.5)	0.36	…	0%
Baseline 25(OH)D 25 to 50 nmol/L	12	508	8.0 (3.2)	−0.1 (−0.3 to 0.2)	0.67	0.17	−0.1 (−0.3 to 0.1)	0.38	0.15	39%
Baseline 25(OH)D >50 nmol/L	10	482	7.8 (2.6)	0.0 (−0.2 to 0.2)	0.81	0.33	0.0 (−0.2 to 0.2)	0.76	0.33	12%
DM	6	130	8.5 (4.5)	0.1 (−0.3 to 0.4)	0.65	0.30	0.1 (−0.3 to 0.4)	0.65	0.30	0%
No DM	13	1021	7.8 (2.5)	−0.1 (−0.2 to 0.1)	0.32		−0.1 (−0.2 to 0.1)	0.32		0%
No ACEi or ARB	9	399	7.7 (3.1)	−0.1 (−0.3 to 0.2)	0.70	…	−0.1 (−0.3 to 0.1)	0.44	…	21%
ACEi, no ARB	7	203	8.5 (3.3)	−0.2 (−0.5 to 0.1)	0.17	0.62	−0.2 (−0.5 to 0.1)	0.17	0.62	0%
ACEi or ARB	8	364	8.1 (3.2)	0.0 (−0.3 to 0.2)	0.68	0.58	0.0 (−0.3 to 0.2)	0.68	0.58	0%
PTH >5.0 pmol/L	12	482	7.9 (2.9)	−0.1 (−0.3 to 0.1)	0.16	0.49	−0.1 (−0.3 to 0.1)	0.16	0.49	0%
PTH ≤5.0 pmol/L	12	594	7.9 (3.2)	0.0 (−0.2 to 0.2)	0.97		0.0 (−0.2 to 0.2)	0.95		12%
Ca >2.30 mmol/L	9	456	7.8 (3.5)	0.0 (−0.2 to 0.2)	0.91	0.12	0.0 (−0.2 to 0.2)	0.91	0.12	0%
Ca ≤2.30 mmol/L	10	496	8.0 (2.6)	−0.2 (−0.3 to 0.0)	0.11		−0.2 (−0.3 to 0.0)	0.10		2%
eGFR ≥60 mL/min per 1.73 m^2	10	897	7.8 (2.3)	0.0 (−0.2 to 0.1)	0.57	…	0.0 (−0.2 to 0.1)	0.55	…	5%
eGFR 45 to 59 mL/min per 1.73 m^2	6	76	7.2 (4.8)	0.3 (−0.3 to 0.9)	0.35	0.34	0.2 (−0.3 to 0.7)	0.41	0.45	12%
eGFR 30 to 44 mL/min per 1.73 m^2	3	27	8.8 (2.0)	−0.8 (−1.6 to 0.1)	0.07	0.07	−0.8 (−1.6 to 0.1)	0.07	0.07	0%
eGFR 15 to 29 mL/min per 1.73 m^2	2	8	13.7 (1.1)	0.1 (−2.0 to 2.2)	0.95	0.93	0.1 (−2.0 to 2.2)	0.95	0.93	0%
eGFR <15 mL/min per 1.73 $m^{2\dagger}$	2	54	9.0 (4.9)	0.4 (−0.1 to 1.0)	0.12	0.17	0.4 (−0.1 to 1.0)	0.12	0.17	0%
Total cholesterol ≥4.60 mmol/L	11	651	7.8 (2.3)	−0.1 (−0.3 to 0.1)	0.24	0.54	−0.1 (−0.3 to 0.1)	0.24	0.49	0%
Total cholesterol <4.60 mmol/L	11	398	7.7 (3.0)	0.0 (−0.2 to 0.3)	0.83		0.0 (−0.2 to 0.2)	0.87		23%

25(OH)D indicates 25-hydroxyvitamin D; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; Ca, calcium; CI, confidence interval; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; IPD, individual participant data; PTH, parathyroid hormone; PWV, pulse wave velocity; SBP, systolic blood pressure; SMD, standardized mean difference.

*Data only from studies measuring baseline carotid-femoral PWV.

†Or on dialysis.

previous work that failed to find a beneficial effect of vitamin D therapy on BP[5] and are also in accord with 2 recent, smaller meta-analyses examining arterial stiffness and endothelial function.[42,43] One further recent meta-analysis, examining only FMD, showed a slightly greater benefit (treatment effect of vitamin D was 1.27% for FMD),[44] perhaps attributable to differences in both study selection and the data used; our analysis had the benefit of access to IPD, which allowed us to verify the accuracy of published data and data used in previous meta-analyses. The results are also consistent with recent data suggesting no effect of vitamin D supplementation on plasma N-terminal pro-B-type natriuretic peptide levels or echocardiographic indices in older people after 12 months of therapy.[45]

Table 9. IPD Subgroup Analyses for AIx

Subgroup	No. of Studies	n	Mean Baseline Value (%) (SD)	Random Effects			Fixed Effects			I^2
				Treatment Effect (%) (95% CI)	*P* Value	*P* for Interaction	Treatment Effect (%) (95% CI)	*P* Value	*P* for Interaction	
SBP >140 mm Hg	9	214	33.3 (16.6)	0.8 (−1.1 to 2.7)	0.39	0.31	0.8 (−1.1 to 2.7)	0.39	0.26	0%
SBP ≤140 mm Hg	11	615	24.9 (14.6)	−0.6 (−2.5 to 1.4)	0.57		−0.5 (−1.7 to 0.7)	0.44		52%
Baseline 25(OH)D <25 nmol/L	8	93	24.9 (14.9)	−4.3 (−11.0 to 2.4)	0.20	…	−4.8 (−7.8 to −1.7)	0.002	…	76%
Baseline 25(OH)D 25 to 50 nmol/L	10	357	25.8 (16.7)	0.1 (−1.9 to 2.1)	0.92	0.22	0.0 (−1.5 to 1.5)	0.99	0.006	30%
Baseline 25(OH)D >50 nmol/L	8	342	28.6 (15.2)	0.5 (−1.1 to 2.0)	0.58	0.17	0.5 (−1.1 to 2.0)	0.58	0.002	0%
DM	7	163	26.1 (15.6)	2.0 (−2.6 to 6.6)	0.40	0.37	0.4 (−2.2 to 3.1)	0.75	0.68	61%
No DM	9	666	27.3 (15.7)	−0.2 (−1.4 to 1.1)	0.80		−0.2 (−1.3 to 0.9)	0.73		11%
No ACEi or ARB	9	209	23.1 (14.3)	−0.2 (−2.0 to 1.7)	0.86	…	−0.2 (−2.0 to 1.6)	0.85	…	4%
ACEi, no ARB	7	137	25.4 (12.6)	0.3 (−1.6 to 2.2)	0.79	0.71	0.3 (−1.6 to 2.2)	0.79	0.71	0%
ACEi or ARB	7	243	26.4 (12.7)	−0.1 (−2.1 to 1.9)	0.94	0.94	−0.4 (−1.9 to 1.2)	0.63	0.87	27%
PTH >5.0 pmol/L	9	282	25.3 (15.9)	0.1 (−2.4 to 2.5)	0.96	0.89	−0.3 (−2.1 to 1.5)	0.73	0.62	43%
PTH ≤5.0 pmol/L	9	441	27.9 (16.9)	0.3 (−1.3 to 1.8)	0.72		0.3 (−1.3 to 1.8)	0.72		0%
Ca >2.30 mmol/L	5	286	28.3 (18.7)	0.0 (−3.6 to 3.6)	1.00	0.45	−0.1 (−3.4 to 3.2)	0.96	0.39	11%
Ca ≤2.30 mmol/L	6	265	26.2 (13.3)	1.6 (−0.4 to 3.6)	0.12		1.6 (−0.4 to 3.6)	0.12		0%
eGFR ≥60 mL/min per 1.73 m^2	9	678	27.3 (15.7)	−0.3 (−1.7 to 1.2)	0.34	…	−0.2 (−1.4 to 0.9)	0.72	…	25%
eGFR 45 to 59 mL/min per 1.73 m^2	6	64	28.3 (16.7)	−5.4 (−11.7 to 0.9)	0.09	0.36	−11.7 (−12.2 to −11.3)	<0.001	<0.001	86%
eGFR 30 to 44 mL/min per 1.73 m^2	2	17	29.7 (18.2)	−0.8 (−8.8 to 7.2)	0.85	0.43	−0.8 (−8.8 to 7.2)	0.85	0.88	0%
eGFR 15 to 29 mL/min per 1.73 m^2	0	…	…	…	…	…	…	…	…	…
eGFR <15 mL/min per 1.73 m^2*	2	51	22.9 (12.8)	6.6 (2.1–11.2)	0.005	0.40	6.6 (2.1–11.2)	0.005	0.005	0%
Total cholesterol ≥4.60 mmol/L	9	434	27.8 (15.6)	−0.5 (−2.7 to 1.7)	0.66	0.95	0.0 (−1.4 to 1.5)	1.00	0.61	39%
Total cholesterol <4.60 mmol/L	9	298	26.4 (16.2)	−0.4 (−2.5 to 1.7)	0.73		−0.6 (−2.4 to 1.2)	0.52		20%

25(OH)D indicates 25-hydroxyvitamin D; ACEi, angiotensin-converting enzyme inhibitor; Aix, augmentation index; ARB, angiotensin receptor blocker; Ca, calcium; CI, confidence interval; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; IPD, individual participant data; PTH, parathyroid hormone; SBP, systolic blood pressure.
*Or on dialysis.

Despite the large number of participants included in this analysis, it is not possible to completely refute the possibility that vitamin D or its analogues could still have a modest benefit on vascular health. The markers measured in studies included in this meta-analysis are subject to changes attributed to differences in environment, diet, smoking, medications, and operator skill; such factors require careful use of protocols to standardize measurement and reduce variability.[46,47] The upper limit of the 95% CIs in our analyses encompasses a 1% improvement in FMD, a 1% improvement in AIx, a 0.3-m/s improvement in PWV, and a 5.6 mm Hg improvement in aortic systolic BP. A 5 mm Hg reduction in aortic systolic BP would be consistent with significant clinical benefit, and a 1% improvement in FMD would be consistent with an 8% to 13% reduction in cardiovascular event rates.[48,49] A trial published too recently to be included in

Table 10. IPD Subgroup Analyses for RHI

Subgroup	No. of Studies	n	Mean Baseline Value (Units) (SD)	Random Effects			Fixed Effects			I^2
				Treatment Effect (Units) (95% CI)	*P* Value	*P* for Interaction	Treatment Effect (Units) (95% CI)	*P* Value	*P* for Interaction	
SBP >140 mm Hg	3	73	1.71 (0.94)	−0.21 (−0.52 to 0.10)	0.18	0.21	−0.14 (−0.33 to 0.05)	0.16	0.20	49%
SBP ≤140 mm Hg	3	147	1.62 (0.74)	0.01 (0.11–0.14)	0.85		0.01 (0.11–0.14)	0.85		0%
Baseline 25(OH)D <25 nmol/L	1	21	1.82 (0.68)	0.23 (−0.10 to 0.56)	0.18	…	0.23 (−0.10 to 0.56)	0.18	…	…
Baseline 25(OH)D 25 to 50 nmol/L	3	153	1.71 (0.83)	−0.02 (−0.19 to 0.16)	0.86	0.19	0.02 (−0.09 to 0.14)	0.67	0.24	46%
Baseline 25(OH)D >50 nmol/L	2	40	1.33 (0.76)	−0.21 (−0.42 to 0.00)	0.05	0.03	−0.21 (−0.42 to 0.00)	0.05	0.03	0%
DM	3	110	1.23 (0.74)	0.01 (−0.10 to 0.11)	0.91	0.17	0.01 (−0.10 to 0.11)	0.91	0.17	0%
No DM	2	101	2.07 (0.63)	−0.15 (−0.35 to 0.06)	0.16		−0.15 (−0.35 to 0.06)	0.16		0%
No ACEi or ARB	3	49	1.57 (0.79)	0.42 (−0.72 to 1.57)	0.47	…	0.47 (0.29 to 0.66)	<0.001	…	97%
ACEi, no ARB	3	128	1.75 (0.82)	−0.00 (−0.16 to 0.15)	0.96	0.48	−0.00 (−0.14 to 0.13)	0.96	<0.001	27%
ACEi or ARB	3	171	1.67 (0.81)	−0.05 (−0.21 to 0.11)	0.54	0.43	−0.04 (−0.15 to 0.07)	0.50	<0.001	46%
PTH >5.0 pmol/L	3	117	1.77 (0.77)	−0.02 (−0.17 to 0.13)	0.80	0.85	−0.02 (−0.17 to 0.13)	0.80	0.85	0%
PTH ≤5.0 pmol/L	3	102	1.52 (0.84)	0.00 (−0.14 to 0.14)	1.00		0.00 (−0.14 to 0.14)	1.00		0%
Ca >2.30 mmol/L	3	127	1.50 (0.81)	−0.08 (−0.21 to 0.05)	0.21	0.22	−0.08 (−0.21 to 0.05)	0.21	0.22	0%
Ca ≤2.30 mmol/L	3	93	1.86 (0.76)	0.05 (−0.11 to 0.21)	0.55		0.05 (−0.11 to 0.21)	0.55		0%
eGFR ≥60 mL/min per 1.73 m^2	3	192	1.69 (0.80)	−0.04 (−0.14 to 0.07)	0.48	0.81	−0.04 (−0.14 to 0.07)	0.48	0.77	0%
eGFR <60 mL/min per 1.73 m^2	2	27	1.41 (0.84)	−0.10 (−0.58 to 0.39)	0.69		0.00 (−0.25 to 0.25)	1.00		54%
Total cholesterol ≥4.60 mmol/L	3	60	1.44 (0.85)	−0.04 (−0.38 to 0.30)	0.81	1.00	0.00 (−0.19 to 0.18)	0.98	0.73	43%
Total cholesterol <4.60 mmol/L	3	141	1.72 (0.81)	−0.04 (−0.16 to 0.09)	0.57		−0.04 (−0.16 to 0.09)	0.57		0%

25(OH)D indicates 25-hydroxyvitamin D; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; Ca, calcium; CI, confidence interval; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; IPD, individual participant data; PTH, parathyroid hormone; RHI, reactive hyperemia index; SBP, systolic blood pressure.

this systematic review suggested a large improvement in FMD in participants with nondialyzed CKD,[50] and it therefore remains possible that individuals with nondialyzed CKD, particularly with baseline low 25(OH)D levels, might benefit, although results from trials enrolling nondialyzed CKD participants that we included in this review showed improvement in FMD in only 1 of 3 trials.[11,31,34] Similarly, a recently published substudy using monthly high-dose vitamin D3 showed an improvement in aortic BP and arterial stiffness measures in those with baseline 25(OH)D levels <50 nmol/L; effect sizes were consistent with our IPD analysis findings for this subgroup. No significant improvements were observed in the overall trial group, however.[51]

Pooled observational data show that a $\log_e$ difference in PWV (≈2.7 m/s) corresponds to a 35% to 45% increase in the risk of a cardiovascular event. A 0.3-m/s improvement in PWV is therefore unlikely to be associated with a clinically important reduction in cardiovascular events.[52] Furthermore, it is still possible that agents such as paricalcitol might provide a greater magnitude of benefit to selected markers such as FMD. Paricalcitol is an active analogue of vitamin D (ie, it does not require further hydroxylation before binding to and activating the vitamin D receptor), and it is possible that this pharmacological difference from vitamin D2 or D3 might account for the observed result. It is, however, more likely that this result is attributed to the play of chance given the large number of comparisons contained in our analysis.

A modest improvement in microvascular function with vitamin D was noted in the trial-level analysis, although this was of smaller magnitude in the IPD analyses and did not reach significance. The clinical significance of such an improvement in microvascular function is less clear than for changes in macrovascular markers, given that there are few long-term prognostic studies evaluating microvascular

Table 11. IPD Subgroup Analyses for Microvascular Function

Subgroup	No. of Studies	n	Random Effects			Fixed Effects			I^2
			Treatment Effect (SMD) (95% CI)	*P* Value	*P* for Interaction	Treatment Effect (SMD) (95% CI)	*P* Value	*P* for Interaction	
SBP >140 mm Hg	1	21	0.08 (−0.80 to 0.96)	0.86	0.47	0.08 (−0.80 to 0.96)	0.86	0.47	…
SBP ≤140 mm Hg	3	106	0.44 (0.05–0.82)	0.03		0.44 (0.05–0.82)	0.03		0%
Baseline 25(OH)D <25 nmol/L	3	46	0.05 (−0.54 to 0.64)	0.86	…	0.05 (−0.54 to 0.64)	0.86	…	0%
Baseline 25(OH)D 25 to 50 nmol/L	3	56	0.20 (−0.39 to 0.79)	0.51	0.72	0.20 (−0.34 to 0.74)	0.47	0.71	11%
Baseline 25(OH)D >50 nmol/L	2	26	1.04 (0.14–1.93)	0.02	0.04	1.04 (0.14–1.93)	0.02	0.04	0%
DM	1	18	0.41 (−0.54 to 1.35)	0.40	0.91	0.41 (−0.54 to 1.35)	0.40	0.91	…
No DM	3	111	0.35 (−0.03 to 0.73)	0.07		0.35 (−0.03 to 0.73)	0.07		0%
No ACEi or ARB	2	70	0.19 (−0.28 to 0.66)	0.44	…	0.19 (−0.28 to 0.66)	0.44	…	0%
ACEi, no ARB	2	29	0.37 (−0.38 to 1.13)	0.33	0.69	0.37 (−0.38 to 1.13)	0.33	0.69	0%
ACEi or ARB	2	57	0.65 (0.11–1.18)	0.02	0.21	0.65 (0.11–1.18)	0.02	0.21	0%
PTH >5.0 pmol/L	3	70	0.24 (−0.24 to 0.72)	0.33	0.54	0.24 (−0.24 to 0.72)	0.33	0.54	0%
PTH ≤5.0 pmol/L	2	54	0.47 (−0.08 to 1.02)	0.09		0.47 (−0.08 to 1.02)	0.09		0%
Ca >2.30 mmol/L	2	25	−0.45 (−1.25 to 0.35)	0.27	0.10	−0.45 (−1.25 to 0.35)	0.27	0.10	0%
Ca ≤2.30 mmol/L	2	37	0.43 (−0.23 to 1.09)	0.20		0.43 (−0.23 to 1.09)	0.20		0%
eGFR ≥60 mL/min per 1.73 m^2	2	86	0.22 (−0.21 to 0.64)	0.32	0.46	0.22 (−0.21 to 0.64)	0.32	0.46	0%
eGFR <60 mL/min per 1.73 m^2	2	43	0.50 (−0.11 to 1.11)	0.11		0.50 (−0.11 to 1.11)	0.11		0%
Total cholesterol ≥4.60 mmol/L	3	66	0.05 (−0.47 to 0.57)	0.85	0.32	0.05 (−0.45 to 0.54)	0.85	0.31	7%
Total cholesterol <4.60 mmol/L	3	61	0.42 (−0.10 to 0.94)	0.11		0.42 (−0.10 to 0.94)	0.11		0%

25(OH)D indicates 25-hydroxyvitamin D; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; Ca, calcium; CI, confidence interval; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; IPD, individual participant data; PTH, parathyroid hormone; SBP, systolic blood pressure; SMD, standardized mean difference.

markers. Differences in the physiological control of small and large blood vessels, particularly the role of local metabolic factors in determining microvascular tone, may underpin the difference in response to vitamin D observed here.

A number of limitations of our analysis require discussion. Despite the large number of participants, power for subgroup analyses was limited by the available data; most trials measured only 1 or 2 vascular outcomes, and some baseline variables were not collected in all trials. Caution is warranted in overinterpreting the results of positive associations in the IPD subgroup analyses; the large number of comparisons poses a risk of type I statistical error. Conversely, our decision to combine results from active treatment arms in trials with more than 1 active treatment arm risks diluting the apparent size of any treatment effect, although the impact of this is likely to be minimal given the small number of trials with more than 1 active treatment arm. For some outcomes, heterogeneity of measurement techniques required use of SMDs. Use of SMD limits the clinical utility of the results, and the heterogeneity of measurements means that translating SMD results to clinically meaningful values is challenging. However, use of SMD does at least allow some inferences about possible effect direction and magnitude to be obtained. Despite an extensive series of hypothesis-driven subgroup analyses and metaregressions to examine potential causes for heterogeneity, we were unable to identify subgroups of patients more likely to benefit from intervention, and heterogeneity in our IPD subgroup analyses remained high. Some of this heterogeneity may be attributable to the small number of trials in each analysis, but other, unmeasured sources of real difference between trials may still exist.

Although the risk of bias in most trials was low, only half of the included trials analyzed data by intention to treat, and the inclusion of trials with non-intention-to-treat analyses will tend

Table 12. IPD Subgroup Analyses for Aortic SBP

Subgroup	No. of Studies	n	Mean Baseline Value (mm Hg) (SD)	Random Effects			Fixed Effects			I^2
				Treatment Effect (95% CI) (mm Hg)	*P* Value	*P* for Interaction	Treatment Effect (95% CI) (mm Hg)	*P* Value	*P* for Interaction	
SBP >140 mm Hg	5	79	141.4 (26.3)	0.4 (−8.8 to 9.6)	0.93	0.95	0.4 (−5.5 to 6.3)	0.90	0.82	57%
SBP ≤140 mm Hg	7	319	115.8 (19.1)	0.1 (−3.3 to 3.5)	0.96		−0.3 (−2.4 to 1.9)	0.82		51%
Baseline 25(OH)D <25 nmol/L	6	77	114.2 (28.7)	−2.7 (−9.8 to 4.4)	0.46	…	−1.7 (−5.9 to 2.5)	0.42	…	50%
Baseline 25(OH)D 25 to 50 nmol/L	7	148	121.9 (24.7)	−2.9 (−6.0 to 0.3)	0.08	0.96	−2.9 (−6.0 to 0.3)	0.08	0.65	0%
Baseline 25(OH)D >50 nmol/L	6	171	123.0 (20.1)	0.7 (−3.8 to 5.1)	0.76	0.43	1.2 (−1.9 to 4.2)	0.45	0.27	24%
DM	4	45	119.3 (35.3)	9.4 (−0.2 to 19.1)	0.06	0.17	7.9 (0.3 to 15.4)	0.04	0.006	26%
No DM	7	355	120.9 (22.0)	−1.6 (−13.8 to 10.6)	0.80		−3.0 (−5.1 to −1.0)	0.004		97%
No ACEi or ARB	5	138	111.8 (24.1)	−6.1 (−11.8 to −0.4)	0.04	…	−5.8 (−9.1 to −2.1)	<0.001	…	51%
ACEi, no ARB	3	78	130.4 (22.1)	−5.4 (−10.8 to 0.1)	0.05	0.87	−5.4 (−10.8 to 0.1)	0.05	0.9	0%
ACEi or ARB	4	173	132.6 (23.7)	−3.1 (−7.1 to 0.8)	0.12	0.40	−3.1 (−7.1 to 0.8)	0.12	0.32	0%
PTH >5.0 pmol/L	6	168	121.0 (27.5)	−1.0 (−4.3 to 2.3)	0.55	0.52	−1.0 (−4.3 to 2.3)	0.55	0.67	0%
PTH ≤5.0 pmol/L	6	154	123.1 (24.0)	2.8 (−8.2 to 13.8)	0.62		−1.9 (−5.6 to 1.8)	0.31		85%
Ca >2.30 mmol/L	2	30	118.4 (20.0)	0.3 (−5.5 to 6.0)	0.93	0.61	0.3 (−5.5 to 6.0)	0.93	0.61	0%
Ca ≤2.30 mmol/L	3	120	121.9 (25.9)	2.0 (−0.9 to 5.0)	0.18		2.0 (−0.9 to 5.0)	0.18		0%
eGFR ≥60 mL/min per 1.73 m^2	5	300	120.0 (17.7)	−1.3 (−4.8 to 2.2)	0.47	0.70	−0.6 (−2.8 to 1.5)	0.56	0.92	59%
eGFR <60 mL/min per 1.73 m^2	4	44	130.9 (20.2)	0.8 (−9.2 to 10.9)	0.87		−0.9 (−6.3 to 4.6)	0.76		69%
Total cholesterol ≥4.60 mmol/L	5	158	122.2 (21.6)	−2.3 (−5.8 to 1.2)	0.20	0.68	−2.3 (−5.8 to 1.2)	0.20	0.76	0%
Total cholesterol <4.60 mmol/L	5	138	122.5 (27.5)	−0.7 (−7.5 to 6.1)	0.83		−1.5 (−5.3 to 2.4)	0.45		66%

25(OH)D indicates 25-hydroxyvitamin D; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; Ca, calcium; CI, confidence interval; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; IPD, individual participant data; PTH, parathyroid hormone; SBP, systolic blood pressure.

to inflate observed effect sizes. It is also possible that not all eligible trials were found or included; for some trials, published trial reports had not been produced or could not be obtained from the authors. New trials continue to be published in this area, but most continue to use small numbers of participants and are likely to have limited impact on our conclusions. Not all authors were willing to share their IPD, and not all trial reports contained sufficient information to allow data to be extracted for meta-analysis. A further limitation is inherent in the populations studied; most populations contained only a minority of participants with 25(OH)D levels below 25 nmol/L, a group that would be thought to be most likely to benefit. Similarly, some trials were conducted in groups without overt vascular disease, where again the possibilities for improving vascular function might have been limited. Most trials were conducted in white populations, which potentially limits the generalizability of the findings. In particular, few blacks were enrolled in the included studies; this group have particularly low 25(OH)D levels when living at high latitudes and may be more likely to show a reduction in BP with vitamin D supplementation.[53]

A range of vitamin D doses were used in the included trials; debate continues as to what dose of vitamin D is optimum or indeed what the target level of 25(OH)D should be. If a level of 75 nmol/L is regarded as optimum as has been suggested from observational studies,[54] doses at the upper end of the range included in this analysis are required to reach this level.[40,55,56] Metaregression of vitamin D dose versus treatment effect suggested that higher doses of vitamin D were associated with a slightly greater treatment effect for FMD, but not for PWV or AIx. We found no evidence that daily dosing was more efficacious than intermittent dosing, despite previous work that has suggested that daily dosing provides more-consistent tissue exposure to the parent compound,

Table 13. IPD Subgroup Analyses for Aortic DBP

Subgroup	No. of Studies	n	Mean Baseline Value (mm Hg) (SD)	Random Effects			Fixed Effects			I^2
				Treatment Effect (95% CI)	*P* Value	*P* for Interaction	Treatment Effect (95% CI)	*P* Value	*P* for Interaction	
SBP >140 mm Hg	5	79	79.8 (11.1)	−0.7 (−3.3 to 2.0)	0.62	0.95	−0.7 (−3.3 to 2.0)	0.62	0.95	0%
SBP ≤140 mm Hg	7	320	75.7 (9.3)	−0.6 (−1.9 to 0.6)	0.33		−0.6 (−1.9 to 0.6)	0.33		0%
Baseline 25(OH)D <25 nmol/L	6	77	75.8 (9.5)	1.0 (−2.4 to 4.5)	0.56	…	1.0 (−2.4 to 4.5)	0.56	…	0%
Baseline 25(OH)D 25 to 50 nmol/L	7	151	77.2 (10.0)	−0.7 (−2.8 to 1.3)	0.48	0.41	−0.7 (−2.8 to 1.3)	0.48	0.41	0%
Baseline 25(OH)D >50 nmol/L	6	171	76.3 (10.0)	−0.5 (−2.0 to 1.0)	0.52	0.43	−0.5 (−2.0 to 1.0)	0.52	0.43	0%
DM	4	45	74.0 (11.5)	3.8 (−1.6 to 9.1)	0.17	0.12	2.8 (0.1 to 5.4)	0.04	0.02	68%
No DM	7	355	76.9 (9.6)	−0.6 (−1.9 to 0.6)	0.29		−0.6 (−1.9 to 0.6)	0.29		0%
No ACEi or ARB	6	152	75.4 (9.8)	−0.5 (−2.6 to 1.5)	0.61	…	−0.5 (−2.6 to 1.5)	0.61	…	0%
ACEi, no ARB	4	92	79.3 (11.4)	0.6 (−1.9 to 3.1)	0.62	0.50	0.6 (−1.9 to 3.1)	0.62	0.50	0%
ACEi or ARB	4	173	78.4 (10.5)	−0.4 (−2.2 to 1.4)	0.69	0.94	−0.4 (−2.2 to 1.4)	0.69	0.94	0%
PTH >5.0 pmol/L	6	169	77.3 (10.2)	0.1 (−2.3 to 2.5)	0.93	0.62	0.1 (−2.3 to 2.5)	0.93	0.59	0%
PTH ≤5.0 pmol/L	6	154	77.2 (10.4)	−0.7 (−2.7 to 1.3)	0.52		−0.7 (−2.4 to 1.0)	0.39		17%
Ca >2.30 mmol/L	2	31	79.3 (9.8)	0.4 (−4.7 to 5.5)	0.88	0.94	0.4 (−4.7 to 5.5)	0.88	0.94	0%
Ca ≤2.30 mmol/L	3	120	77.0 (10.2)	0.2 (−1.6 to 1.9)	0.86		0.2 (−1.6 to 1.9)	0.86		0%
eGFR ≥60 mL/min per 1.73 m^2	5	300	77.3 (9.2)	−0.6 (−1.8 to 0.7)	0.35	0.07	−0.6 (−1.8 to 0.7)	0.35	0.03	0%
eGFR <60 mL/min per 1.73 m^2	4	45	75.5 (9.2)	4.6 (−0.9 to 10.1)	0.10		2.9 (−0.1 to 5.9)	0.06		46%
Total cholesterol ≥4.60 mmol/L	5	158	77.3 (9.5)	−0.6 (−2.6 to 1.3)	0.52	0.76	−0.6 (−2.6 to 1.3)	0.52	0.89	0%
Total cholesterol <4.60 mmol/L	5	138	74.5 (9.8)	0.0 (−3.3 to 3.4)	0.98		−0.8 (−3.0 to 1.3)	0.45		49%

25(OH)D indicates 25-hydroxyvitamin D; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; Ca, calcium; CI, confidence interval; DBP, diastolic blood pressure; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; IPD, individual participant data; PTH, parathyroid hormone; SBP, systolic blood pressure.

facilitating uptake and autocrine activation,[57] and evidence that daily dosing may be more efficacious in some conditions (eg, respiratory disease).[58] Our results are consistent with our previous analysis that did not find a difference between daily and intermittent dosing on BP.[5] A final explanation that requires consideration is that the duration of therapy in most trials may simply have been too short to produce biological effects—particularly those trials intervening for only a few weeks. This explanation is plausible for outcomes such as arterial stiffness if biological effects are mediated by changes in vascular calcification, but seems less so for outcomes such as FMD and reactive hyperemia index, where other interventions are known to alter these parameters within days or weeks. Further evidence against this hypothesis is provided by the metaregression results, which suggest that longer trial duration was associated with a smaller treatment effect for FMD.

The results of these analyses add to the growing body of evidence suggesting that vitamin D supplementation may not have any beneficial effects on cardiovascular health. The lack of effect on vitamin D supplementation on BP in most studies to date[5,53] and the lack of effect on vascular markers observed in the current analysis suggests that associations between 25(OH)D levels and cardiovascular events observed in observational studies may not be causal. Not all observational studies have been prospective in nature, and the degree of adjustment for confounders has been variable. There are several reasons why assumptions about causality may be incorrect, including reverse causality (where overt or preclinical illness leads to lower 25(OH)D levels through mechanisms such as immobility, obesity, or inflammation[59,60]), and confounding by shared risk factors for both cardiovascular disease and low 25(OH)D levels; obesity, inactivity, smoking, and advanced age are all known to be associated with lower

Table 14. Standardizing SDs Pertaining to Trials Combined Using SMD Method

Study	Trial Level		IPD (Pooled SD)	
	PWV (m/s) (Vitamin D, Placebo)	Microvascular Function (Units) (Vitamin D, Placebo)	PWV (m/s)	Microvascular Function (Units)
Gepner 2012[15]	0.9, 1.1	…	1.0	…
Larsen 2012[16]	0.9, 1.4	…	1.2	…
Marckmann 2012[17]	2.6, 2.6	…	3.1	…
Stricker 2012[19]	…	16.4, 12.4	…	13.4
Hewitt 2013[22]	5.3, 4.8	…	…	…
Witham 2013[23]	1.4, 1.3	…	1.2	…
Witham 2013[25]	1.2, 1.6	1.1, 3.3	1.2	1.8
Yiu 2013[26]	3.4, 4.1	…	…	…
Dreyer 2014[27]	1.1, 0.8	727, 391	1.0	591
Mose 2014[29]	2.1, 2.4	…	2.3	…
Ryu 2014[30]	1.4, 1.8	…	…	…
Garg 2015[32]	1.3, 1.2	…	1.1	…
Pilz 2015[33]	1.6, 1.6	…	1.9	…
Witham 2015[35]	2.5, 1.6	…	0.9	…
Bressendorff 2016[38]	0.9, 0.4	…	1.1	…
Forouhi 2016[40]	2.1, 1.7	…	1.7	…
Hin 2017[41]	1.4, 1.4	…	3.7	…

IPD indicates individual participant data; PWV, pulse wave velocity; SMD, standardized mean difference.

25(OH)D levels, and such confounding is notoriously difficult to fully adjust for. Existing evidence from meta-analyses of vascular events in osteoporosis trials using vitamin D does not support an effect of vitamin D in lowering cardiovascular event rates,[1,7] with the possible exception of heart failure, and the first of a new wave of large, population-based vitamin D trials has recently reported, again showing no effect of vitamin D supplementation on cardiovascular event rates.[8] Randomized trials of relatively short duration cannot exclude a benefit of vitamin D supplementation over the span of a lifetime; observational designs including Mendelian randomization studies[61] may still be the only way to shed light on very long exposures to vitamin D, although even these designs are subject to bias and confounding.

A number of other large vitamin D trials are due to report over the next 3 to 4 years,[62] and most of these include cardiovascular events as key outcomes—outcomes which our analysis did not focus on. Existing evidence does not support the use of vitamin D to reduce cardiovascular risk, and the results of our analysis do not suggest a specific target group that is particularly likely to benefit from vitamin D supplementation, although we found no evidence of a deleterious effect on cardiovascular function. The relative lack of representation of some groups, particularly nonwhite groups, tempers the generalizability of this conclusion. In the absence of a subgroup with clear benefit, and with large trial reports expected soon, further small-scale trials examining surrogate vascular end points are unlikely to advance this field of research significantly.

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Disclosures

None.

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