

Original Investigation

Effect of Vitamin D Supplementation on Blood Pressure

A Systematic Review and Meta-analysis

Incorporating Individual Patient Data

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IMPORTANCE Low levels of vitamin D are associated with elevated blood pressure (BP) and future cardiovascular events. Whether vitamin D supplementation reduces BP and which patient characteristics predict a response remain unclear.

OBJECTIVE To systematically review whether supplementation with vitamin D or its analogues reduce BP.

DATA SOURCES We searched MEDLINE, CINAHL, EMBASE, Cochrane Central Register of Controlled Trials, and <http://www.ClinicalTrials.com> augmented by a hand search of references from the included articles and previous reviews. Google was searched for gray literature (ie, material not published in recognized scientific journals). No language restrictions were applied. The search period spanned January 1, 1966, through March 31, 2014.

STUDY SELECTION We included randomized placebo-controlled clinical trials that used vitamin D supplementation for a minimum of 4 weeks for any indication and reported BP data. Studies were included if they used active or inactive forms of vitamin D or vitamin D analogues. Cointerventions were permitted if identical in all treatment arms.


DATA EXTRACTION AND SYNTHESIS We extracted data on baseline demographics, 25-hydroxyvitamin D levels, systolic and diastolic BP (SBP and DBP), and change in BP from baseline to the final follow-up. Individual patient data on age, sex, medication use, diabetes mellitus, baseline and follow-up BP, and 25-hydroxyvitamin D levels were requested from the authors of the included studies. For trial-level data, between-group differences in BP change were combined in a random-effects model. For individual patient data, between-group differences in BP at the final follow up, adjusted for baseline BP, were calculated before combining in a random-effects model.

MAIN OUTCOMES AND MEASURES Difference in SBP and DBP measured in an office setting.

RESULTS We included 46 trials (4541 participants) in the trial-level meta-analysis. Individual patient data were obtained for 27 trials (3092 participants). At the trial level, no effect of vitamin D supplementation was seen on SBP (effect size, 0.0 [95% CI, -0.8 to 0.8] mm Hg; $P = .97$; $I^2 = 21\%$) or DBP (effect size, -0.1 [95% CI, -0.6 to 0.5] mm Hg; $P = .84$; $I^2 = 20\%$). Similar results were found analyzing individual patient data for SBP (effect size, -0.5 [95% CI, -1.3 to 0.4] mm Hg; $P = .27$; $I^2 = 0\%$) and DBP (effect size, 0.2 [95% CI, -0.3 to 0.7] mm Hg; $P = .38$; $I^2 = 0\%$). Subgroup analysis did not reveal any baseline factor predictive of a better response to therapy.

CONCLUSIONS AND RELEVANCE Vitamin D supplementation is ineffective as an agent for lowering BP and thus should not be used as an antihypertensive agent.

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A wealth of observational data has demonstrated relationships between circulating vitamin D metabolite levels and blood pressure (BP). Lower 25-hydroxyvitamin D (25OHD) levels are associated with higher BP levels in cross-sectional studies^{1,2} and with increased rates of incident hypertension.³ Such observations are underpinned by a number of biologically plausible mechanisms and the fact that vitamin D receptors are found on endothelial cells, smooth muscle cells, and myocytes.⁴ Vitamin D has been shown to improve endothelial function in some studies,^{5,6} reduce the production of proinflammatory cytokines,⁷ reduce activity of the renin-angiotension-aldosterone system, and reduce parathyroid hormone (PTH) levels.⁸ Parathyroid hormone has been posited as vasculotoxic in its own right. Any or all of these mechanisms therefore potentially mediate an effect of vitamin D on BP levels.

Intervention studies to date have produced conflicting evidence on the BP-lowering effect of vitamin D. One previous meta-analysis⁹ based on a number of small trials demonstrated a modest but significant decrease in BP in studies in which the mean BP reading was elevated at baseline; another meta-analysis¹⁰ conducted at a similar time did not demonstrate a significant effect of vitamin D supplementation on BP; and a more recent meta-analysis¹¹ showed a small decrease in diastolic BP (DBP) but not systolic BP (SBP). Although the effects of vitamin D on BP appeared to be small in previous meta-analyses, even a modest improvement in BP would be of public health importance because widespread supplementation with vitamin D would be an inexpensive intervention. Furthermore, selected subgroups (eg, nonwhite populations and those with very low 25OHD levels) could benefit to a greater extent, potentially making vitamin D part of the therapeutic armamentarium in treating individuals with hypertension.

In the 5 years since the first meta-analyses were published, a proliferation of randomized clinical trials has studied vitamin D and cardiovascular health. We therefore sought to update a systematic review of randomized clinical trials⁹ to evaluate whether vitamin D supplementation reduces BP when compared with placebo across a range of study populations and vitamin D analogues. We also sought to perform an individual patient data meta-analysis to explore further which subgroups of patients might derive the greatest benefit.

Methods

Review Design

We conducted a systematic review based on a predefined protocol. The protocol was registered with the PROSPERO International Prospective Register of Systematic Reviews (http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42012002816). Institutional review board approval was not required, and data were deidentified at the source before transfer. We included randomized clinical trials that reported BP or other measures of vascular function, including arterial stiffness, endothelial function, and left ventricular mass index, as outcomes. We searched MEDLINE, CINAHL, EMBASE, the Cochrane Central Register of Controlled Trials, and <http://www.ClinicalTrials.com> using our strategy. We also searched for gray

literature (ie, material not published in recognized scientific journals) using Google and hand searched the references of included articles and previous reviews of vitamin D therapy. No language restrictions were applied to eligible reports. The search period spanned January 1, 1966, through March 31, 2014. Two of us (L.A.B. and M.D.W.) conducted the search.

Search Strategy

Search terms included *vitamin D*, *vitamin D₃*, *vitamin D₂*, *cholecalciferol*, *ergocalciferol*, *alphacalcidol*, *alfacalcidol*, *paricalcitol*, and *doxercalciferol* combined with *blood pressure*, *hypertension*, *cardiovascular*, *mortality*, *randomized controlled trials*, or *placebo*. The electronic search strategy used for MEDLINE is described in the eAppendix in the Supplement.

Study Selection

We considered studies with participants with any reported baseline 25OHD level. Studies with BP reduction or changes in surrogate markers of cardiovascular risk were included; a minimum of 4 weeks of therapy was necessary for inclusion in the review to ensure that the intervention had sufficient time to produce an effect. We included the following interventions: vitamin D₂ (ergocalciferol), vitamin D₃ (cholecalciferol), calcitriol (1,25-hydroxyvitamin D₃), 1- α -hydroxylated versions of vitamin D, paricalcitol, and doxercalciferol. Control groups receiving placebo were used, and those receiving placebo plus a cointervention were included if both arms of the study received the cointervention. Studies from primary and secondary care or population settings were included. We placed no restrictions on sex or ethnicity. We did not include any studies recruiting participants younger than 16 years or studying patients who were receiving dialysis. The primary outcome of the meta-analysis was the change in office-measured SBP and DBP readings from baseline through follow-up.

Data Extraction

Two researchers (L.A.B. and M.D.W.) independently extracted data from all trial reports with data collection forms used in a previous systematic review.⁹ Differences were resolved by consensus. The following data were recorded for all eligible studies: sex, age, smoking status, social class, ethnic group/skin color, functional status/dwelling place, diabetes mellitus status and glycated hemoglobin level, kidney function, history of cardiovascular events, history of hypertension, baseline BP reading, and baseline use of angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers, statins, and aspirin. For use in this analysis, we recorded change in office-measured SBP and DBP readings and change in 24-hour BP as outcome measures. We contacted the study authors to provide missing data or to clarify data that were unclear from primary reports.

IPD Collection

For all eligible studies, the authors were approached to provide individual patient data to conduct subgroup analyses by baseline characteristics at the patient level, in particular by baseline 25OHD level, baseline medication use, baseline BP level, and the presence of diabetes mellitus. The following data

were requested for each patient: age; sex; body mass index; ethnicity; month of recruitment; SBP and DBP readings at baseline and follow-up; vitamin D supplement given (type, dose, frequency, and duration); baseline 25OHD level (and follow-up 25OHD level if available); baseline and posttreatment levels of PTH, serum calcium/albumin, total cholesterol, and high-density lipoprotein cholesterol levels; diagnosis of diabetes mellitus, previous stroke, or myocardial infarction at baseline; and whether patients were receiving an ACE inhibitor, statin, or angiotensin receptor antagonist at baseline.

Risk for Bias Assessment

We assessed each included study for risk for bias using fields from the Delphi checklist¹² to assess the following variables: 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. We generated funnel plots to examine possible publication bias; these were supplemented by formal statistical testing using the Egger test.¹³ Study quality was assessed independently by 2 of us (L.A.B. and M.D.W.), and discrepancies were resolved by consensus.

Strategy for Data Synthesis

We performed the meta-analysis at the trial level using commercially available software (Comprehensive Meta-analysis; Biostat). We used the weighted squares method with random-effects models in all cases. For all treatment effects, a negative value denotes a reduction in BP with the intervention compared with placebo. For each analysis at the trial level, the mean change from baseline to the last follow-up reported was compared between groups because these data were most commonly supplied in trial-level reports. For studies with more than 1 vitamin D group, the highest dose of vitamin D or an analogue was compared with the control group; intermediate dose groups did not undergo analysis. Heterogeneity was assessed using the I^2 test. Preplanned subgroup analyses were performed to examine the effects of different preparations of vitamin D, dose ranges, and baseline BP. Degree of change in BP was regressed against baseline BP, trial duration, daily dose equivalent of vitamin D given, and mean baseline 25OHD level.

For the individual patient data analysis, a 2-stage analysis was performed, as recommended by Riley et al.¹⁴ For each study, the mean BP values for each group at the final follow-up were calculated and adjusted for baseline values using analysis of covariance (SPSS, version 21; IBM). These values were then combined using weighted least-squares random-effects models with commercially available software (RevMan 5.3; Cochrane Collaboration). For studies with more than 1 vitamin D dose, patients taking the highest dose were compared with those taking a placebo; patients taking the lower dose were excluded from the analysis. We performed the following prespecified patient-level subgroup analyses using these methods: diabetes mellitus vs no diabetes mellitus; ACE inhibitor vs no ACE inhibitor; baseline SBP of no greater than 140 mm Hg vs greater than 140 mm Hg; DBP of no greater than 90 mm Hg vs greater than 90 mm Hg; baseline PTH level of no

greater than vs greater than the median level for the individual patient data set; and baseline 25OHD level of less than 10, 10 to 20, and greater than 20 ng/mL (to convert to nanomoles per liter, multiply by 2.496). For analyses of ACE inhibitor use, patients taking angiotensin receptor blockers were excluded given the similar but not identical biological effect of these agents. Exploratory post hoc analyses were undertaken for subgroups with combinations of risk factors (high BP, low 25OHD levels, and higher PTH levels), nonwhite participants, and summer vs winter enrollment. The northern hemisphere summer was defined as June through August and winter as December through February, with the definitions inverted for southern hemisphere studies.

Results

Details of the search process are given in **Figure 1**. We included 52 studies in the systematic review^{5,7,15-63}; 46 of these studies* yielded data that could be combined in the trial-level meta-analysis. Six studies used mean arterial pressure or reported median BP readings, and we were unable to obtain mean readings from the authors. We successfully obtained 27 data sets for the individual patient data analysis. For the trials from which we did not succeed in obtaining individual patient data, 2 author groups felt unable to share their data, 1 author group agreed but did not supply data, and in all other cases, authors did not respond to requests or could not be contacted. Details of all included studies are given in eTable 1 in the Supplement. Six trials^{15-19,33} used 1- α -hydroxylated vitamin D derivatives or calcitriol; 4 trials,^{23,29,49,62} paricalcitol; and the other trials, ergocalciferol or cholecalciferol.

Quality Assessment and Publication Bias

Results of the quality assessments performed by assessing the risk for bias across a range of domains are shown in eTable 2 in the Supplement. Allocation concealment was deemed adequate in 51 of 52 trials,^{5,7,15-32,34-63} and most trials had adequate blinding for participants (49 of 52),^{5,7,16-32,34-45,47-63} other health care staff (49 of 52),^{5,7,16-32,34-45,47-63} and outcomes assessment (46 of 52).† Only 22 of 52 trials‡ clearly described analysis on intention to treat. Of the 30 trials in which intention to treat was not well described, 19 trials did not perform analyses on an intention-to-treat basis. Visual inspection of the funnel plot for SBP treatment effect (eFigure 1 in the Supplement) revealed no obvious asymmetry to suggest publication bias; results of the Egger test were not significant ($P = .62$).

Main Outcome Measures for Trial-Level Data

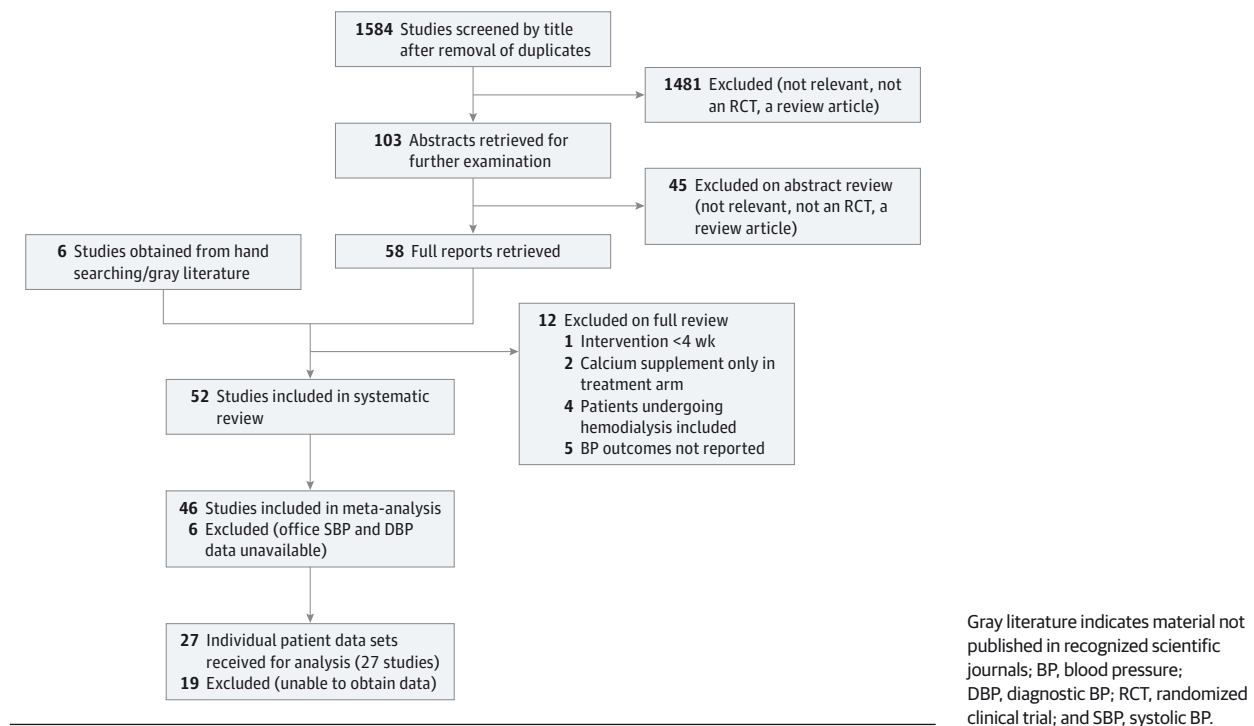
Meta-analysis of the change in BP between baseline and the final follow-up for each trial revealed no clinically or statistically significant effect on SBP (treatment effect, 0.0 [95% CI, -0.8 to 0.8] mm Hg; $P = .97$; $I^2 = 21\%$) or DBP (treatment effect, -0.1 [95% CI, -0.6 to 0.5] mm Hg; $P = .84$; $I^2 = 20\%$). Forest plots for the overall effect of treatment on SBP and DBP are

*References 5, 15-18, 21, 22, 24-36, 39-63

†References 5, 7, 17, 19-32, 34-43, 45, 47-63

‡References 16, 18, 21-24, 28, 29, 32, 34, 41, 43, 45, 48, 51, 53, 55-57, 59, 62, 63

Figure 1. PRISMA Diagram of Study Selection



presented in **Figure 2** and eFigure 2 in the Supplement, respectively. Prespecified subgroup analyses are shown in **Table 1**; analysis by baseline BP category, type of intervention, dose interval, or baseline 25OHD category did not affect the results significantly.

Trial-Level Meta-regression

No significant relationship was found at the trial level between SBP treatment effect and mean baseline SBP (slope, 0.016 [95% CI, -0.037 to 0.069] mm Hg per 1-mm Hg increase of baseline SBP measurement; $P = .55$) (eFigure 3 in the Supplement), baseline 25OHD level (slope, 0.003 [95% CI, -0.014 to 0.021] mm Hg per 1-ng/mL increase of baseline 25OHD level; $P = .70$), baseline PTH level (slope, -0.009 [95% CI -0.036 to 0.053] mm Hg per 1-pg/mL increase of baseline PTH level; $P = .53$) (to convert to micromoles per liter, divide by 9.43), or trial duration (slope, 0.007 [95% CI, -0.005 to 0.019] mm Hg per month of the trial; $P = .27$). Similarly, for trials using vitamin D₃, no significant relationship was found on meta-regression between SBP treatment effect and the daily dose equivalent used as treatment (slope, -0.001 [95% CI, -0.018 to 0.018] mm Hg per 1-U dose of vitamin D₃; $P = .93$). Small numbers of trials precluded meta-regression of the daily dose effects of vitamin D₂, paricalcitol, or 1- α -hydroxylated vitamin D derivatives. Meta-regression of the DBP treatment effect against baseline variables similarly showed no significant relationships for mean baseline DBP (slope, 0.001 [95% CI, -0.003 to 0.006] mm Hg per 1-mm Hg increase in baseline DBP; $P = .54$), baseline 25OHD level (slope, -0.001 [95% CI, -0.005 to 0.003] mm Hg per 1-ng/mL increase of baseline 25OHD level; $P = .67$), baseline PTH level (slope, -0.020 [95%

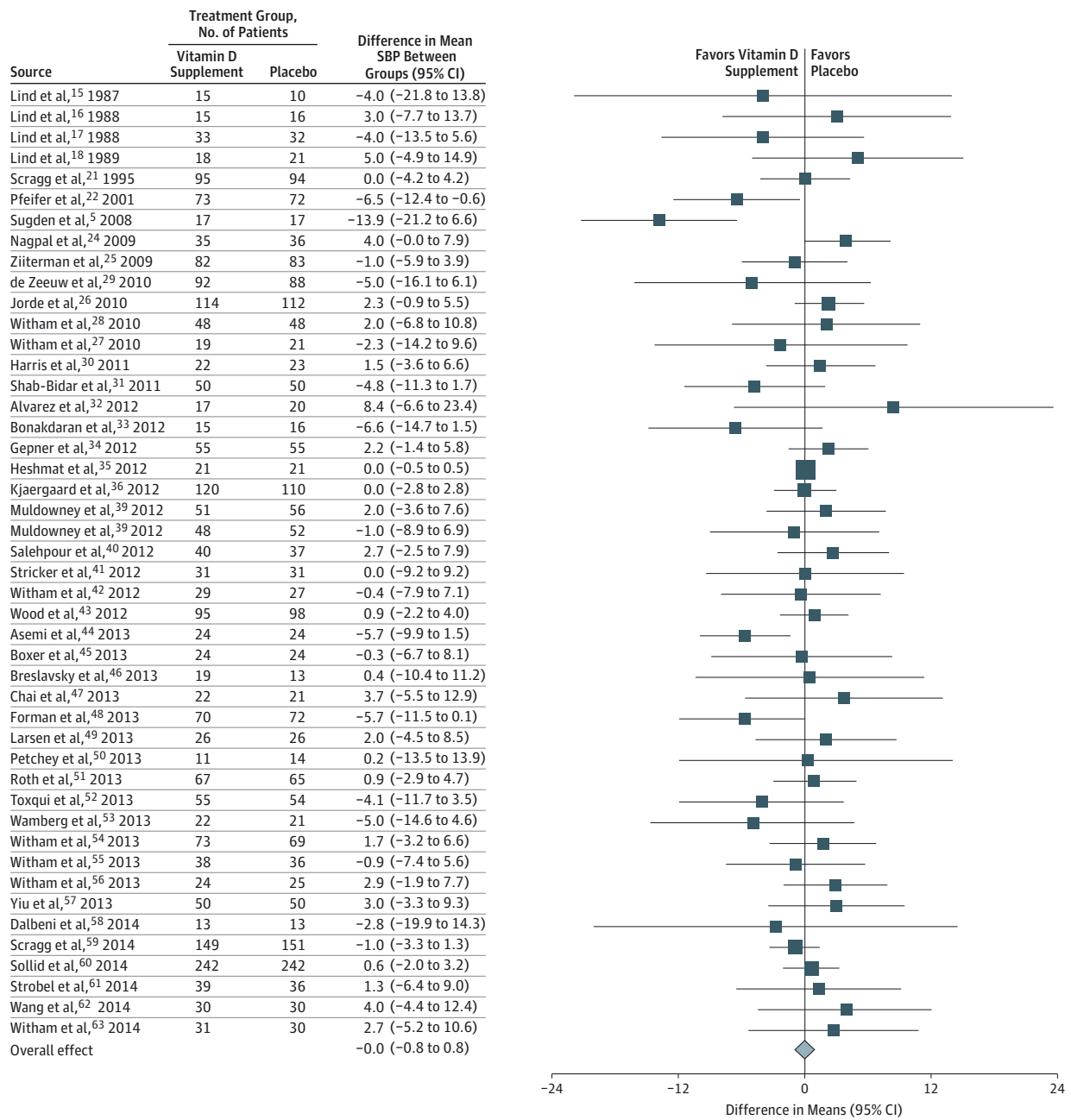
CI, -0.051 to 0.011] mm Hg per 1-pg/mL increase of baseline PTH level; $P = .21$), trial duration (slope, 0.007 [95% CI, -0.005 to 0.020] mm Hg per month of trial; $P = .23$), and daily dose equivalent (slope, 0.000 [95% CI, 0.000 to 0.001] mm Hg per 1-U dose of vitamin D₃; $P = .34$).

Individual Patient Data Analyses

Analyses of the individual patient data sets for SBP and DBP are shown in **Figure 3** and eFigure 4 in the Supplement, respectively, with subgroup analyses shown in **Table 2**. The overall treatment effect derived from the individual patient data sets was similar to that derived from the trial-level data, despite the use of a smaller number of trials, for SBP (treatment effect, -0.4 [95% CI, -1.2 to 0.4] mm Hg; $P = .27$; $I^2 = 0\%$) and DBP (treatment effect, -0.2 [95% CI, -0.7 to 0.3] mm Hg; $P = .38$; $I^2 = 0\%$). In subgroup analyses, no significant differences were seen between patients with or without diabetes mellitus, between those taking or not taking ACE inhibitors or by subgroups of baseline BP, PTH level, or 25OHD level (Table 2).

Analysis of the small group of patients with a combination of baseline factors potentially most likely to benefit (SBP >140 mm Hg; 25OHD level <10 ng/mL; and PTH level >217 pg/mL) showed no evidence of benefit (60 patients; treatment effect on SBP, 2.7 [95% CI, -5.0 to 10.4] mm Hg, $P = .49$; $I^2 = 0\%$). Similarly, analysis of participants of nonwhite ethnicity ($n = 214$) showed no evidence of benefit for SBP (treatment effect, 2.2 [95% CI, -1.1 to 5.4] mm Hg; $P = .19$; $I^2 = 28\%$) and DBP (treatment effect, 0.4 [95% CI, -1.7 to 2.6] mm Hg; $P = .70$; $I^2 = 11\%$). Comparison of patients recruited during the summer and winter months did not reveal any significant differences between the SBP treatment effect for the summer (-1.1

Figure 2. Results of Trial-Level Meta-analysis for Systolic Blood Pressure Outcomes



Different sizes of data markers correspond to the relative weight assigned in the pooled analysis. Diamond marker indicates the overall result.

[95% CI, -4.1 to 2.0] mm Hg; $P = .50$; $I^2 = 37$) or for the winter (1.3 [95% CI, -1.4 to 4.0] mm Hg; $P = .35$, $I^2 = 60$ %) or between the DBP treatment effect for the summer (1.4 [95% CI, -0.4 to 3.2] mm Hg; $P = .11$; $I^2 = 38$ %) or for the winter (0.8 [95% CI, -0.1 to 1.6] mm Hg; $P = .07$; $I^2 = 0$ %).

Discussion

Our analysis found no evidence of BP reduction by supplementation with vitamin D or vitamin D analogues, a result that

was consistent between the trial-level and individual patient data analyses. Subgroup analyses found no evidence of BP reduction in patients with elevated baseline BP or in patients with diabetes mellitus; in addition, we found no relationship between the effect of supplementation on BP and the use of ACE inhibitors, baseline 25OHD level, baseline BP, or baseline PTH level. The narrow CIs around the main result suggest that a clinically significant reduction in BP is unlikely based on the doses of vitamin D studied in this analysis; the lack of effect argues against a role for vitamin D supplementation as a means of BP control in individual patients or as a population-based

Table 1. Trial Level Results of Meta-analysis

Variable	No. of Trials	No. of Patients	Effect Size (95% CI), mm Hg	P Value	I ² , %	Between-Group P Value
Systolic Blood Pressure						
Overall	46	4541	0.0 (-0.8 to 0.8)	.97	21	NA
Mean baseline SBP >140 mm Hg	16	1361	-0.7 (-3.2 to 1.7)	.55	38	.54
Mean baseline SBP ≤140 mm Hg	30	3180	0.1 (-0.6 to 0.9)	.77	11	
Vitamin D ₂ and D ₃ supplements	38	4058	0.0 (-0.9 to 0.9)	.97	26	NA
1- α -Hydroxylated vitamin D derivatives	5	191	-1.6 (-6.3 to 7.1)	.50	4	.64
Paricalcitol	3	292	1.4 (-3.3 to 6.1)	.56	0	.57
Mean baseline 25OHD level ≤20 ng/mL	27	2555	-0.7 (-2.2 to 0.7)	.31	38	.31
Mean baseline 25OHD level >20 ng/mL	13	1723	0.1 (-0.4 to 0.6)	.75	0	
Daily dosing	16	1522	-0.7 (-2.5 to 1.0)	.41	24	NA
Weekly/fortnightly dosing	8	1303	1.3 (-0.1 to 2.6)	.07	0	.07
Monthly or less frequent dosing	14	1216	-0.2 (-1.6 to 1.2)	.76	28	.66
Diastolic Blood Pressure						
Overall	45	4434	-0.1 (-0.6 to 0.5)	.84	20	NA
Mean baseline SBP >140 mm Hg	14	1074	-0.4 (-2.1 to 1.3)	.61	55	.65
Mean baseline SBP ≤140 mm Hg	30	3180	0.0 (-0.4 to 0.3)	.85	0	
Vitamins D ₂ and D ₃ supplements	37	3951	0.1 (-0.3 to 0.5)	.65	4	NA
1- α -Hydroxylated vitamin D derivatives	5	191	-3.5 (-6.8 to -0.1)	.04	54	.04
Paricalcitol	2	112	-1.0 (-3.9 to 1.9)	.50	0	.46
Mean baseline 25OHD level ≤20 ng/mL	26	2375	0.2 (-0.5 to 1.0)	.54	17	.50
Mean baseline 25OHD level >20 ng/mL	12	1616	-0.1 (-0.5 to 0.4)	.69	0	
Daily dosing	16	1466	-0.5 (-1.5 to 0.4)	.26	23	NA
Weekly/fortnightly dosing	8	1303	0.6 (-0.4 to 1.5)	.23	0	.11
Monthly or less frequent dosing	14	1213	0.0 (-0.4 to 0.5)	.84	0	.35

Abbreviations: SBP, systolic blood pressure; NA, not applicable; 25OHD, 25-hydroxyvitamin D.

SI conversion factor: To convert 25OHD to nanomoles per liter, multiply by 2.496.

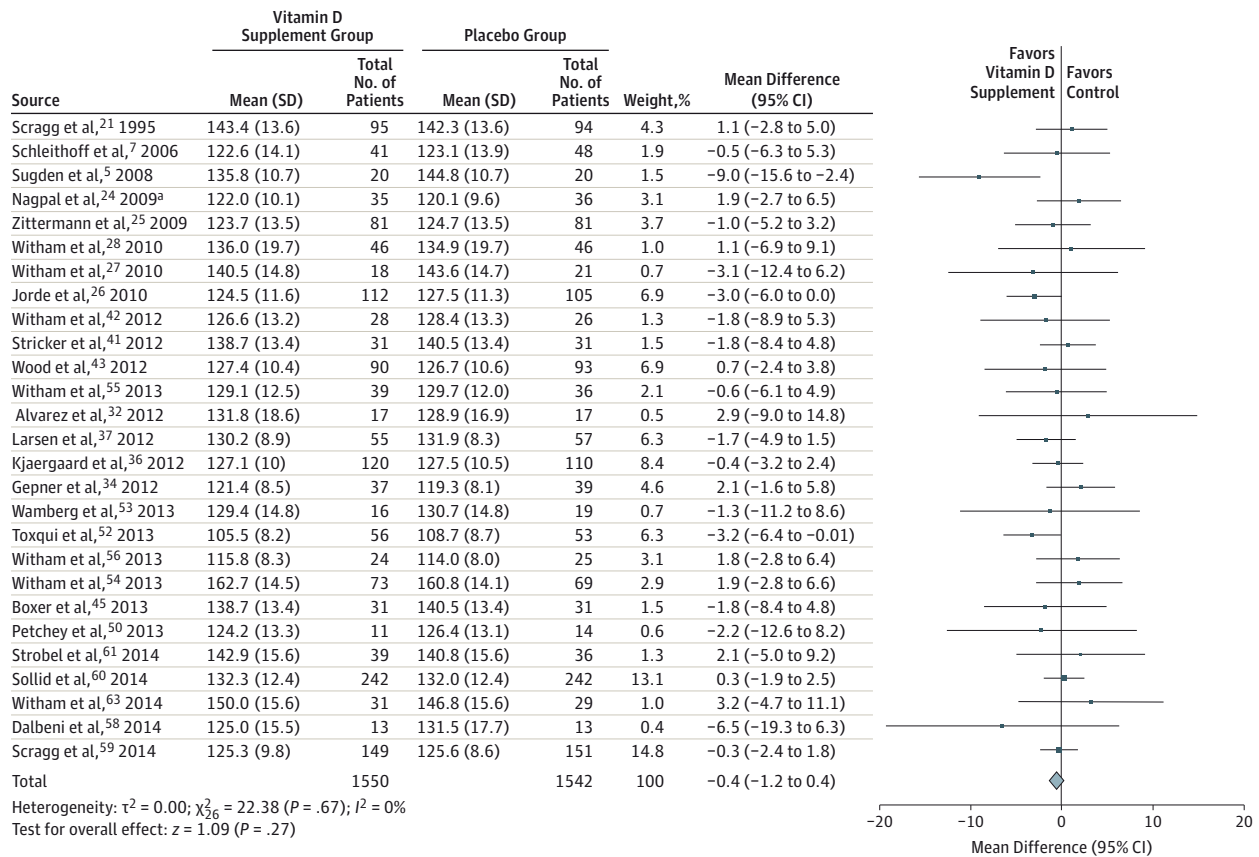
intervention to reduce BP. These results are broadly consistent with those of previous meta-analyses,⁹⁻¹¹ although they contrast with the small reduction in BP in trials with high baseline BP found in a previous meta-analysis.⁹ However, our analysis includes a much larger number of studies than previous analyses and therefore a larger number of patients and a larger range of doses. Our use of individual patient data allowed us to examine whether particular subgroups might still benefit from vitamin D supplementation, which previous analyses have not been able to address.

Although the number of included patients is greater than in previous meta-analyses and the use of individual patient data has allowed analysis of subgroups, limitations to this systematic review remain. The included studies are almost all single-center trials, and most are of modest size; none recruited more than 1000 patients. As a result, baseline imbalances between trials were common, and such imbalances are difficult to correct for fully, even with individual patient data analysis.¹⁴ Not all studies were of high quality; we noted deficiencies in intention to treat and in reporting of masking and allocation concealment. All eligible studies may not have been included, although our wide search strategy, contact with leading authors in the field, lack of a language restriction, and search of the gray literature minimized this issue. Nevertheless, other BP data may exist (eg, from osteoporosis trials) that have not been published yet and that we have been unable to locate.⁶⁴ An additional limi-

tation is the small number of trials that have specifically targeted patients with hypertension at baseline; such patients perhaps would be more likely to respond to antihypertensive interventions. We did not see an effect of vitamin D supplementation even in this subgroup, although the high level of background treatment with antihypertensives and other cardiovascular medications known to interact with vitamin D (eg, statins) may again obscure detection of small treatment effects.

Debate continues as to what level of 25OHD constitutes a biological optimum and what level of vitamin D supplementation is necessary to achieve that optimum. Levels of more than 30 ng/mL have been postulated as necessary for optimum health,⁶⁵ but such levels are based on observational data and do not indicate the level required for maximal antihypertensive effects. Levels of vitamin D supplementation required to reach such levels vary widely depending on age, sex, obesity, and baseline 25OHD levels; doses ranging from 1600 to more than 5000 IU/d have been advocated as necessary.^{66,67} Most doses studied in this review were at or below the lower end of this range, and several studies used intermittent dosing (weekly, monthly, or less frequent). Intermittent doses may have different biological effects⁶⁸ when compared with smaller regular doses; intermittent doses appeared to be less effective at reducing the incidence of respiratory tract infection in a recent systematic review,⁶⁹ although no such effect was evident for BP reduction in our analysis. Although larger, more

Figure 3. Results of Individual Patient Data Analysis Using Final Systolic Blood Pressure (BP) Adjusted for Baseline BP



Different sizes of data markers correspond to the relative weight assigned in the pooled analysis. Diamond marker indicates the overall result.

^a Study was completed in the year before publication.

frequent doses of vitamin D might still have effects on reducing BP, we found no evidence of a dose-response relationship in our analyses. Furthermore, most studies included participants of European ancestry, and beneficial effects cannot be excluded in other ethnic groups, although our subgroup analysis did not find evidence to support such exclusion.

The results of this analysis add to the growing body of literature casting doubt on the ability of vitamin D supplementation to influence health outcomes beyond falls, fractures, and possibly respiratory tract infection and all-cause mortality.^{69,70} Recent analyses have shown that although observational data suggest an association between low 25OHD levels and cardiovascular events, diabetes mellitus, and many cancers, intervention data do not support an effect across most of these diseases.⁷¹ This lack of effect may exist in part because of the difficulty in fully disentangling low 25OHD levels from other closely associated factors (eg, aging, obesity, smoking, inactivity) that affect 25OHD levels and promote disease, but also in part because not all studies have targeted patients with the lowest circulating 25OHD levels. Another possibility is that 25OHD is a consequence, rather than a cause, of disease or disease precursor states; inflammatory responses have been shown to acutely reduce 25OHD levels,⁷² although whether

chronic inflammation caused by subclinical disease can have the same effect is not known. Vitamin D may have beneficial actions on cardiovascular health that are not captured by office brachial artery BP measurement, which has been argued to be less reliable than other measures, such as ambulatory BP measurement or central aortic BP measurement, although previous work suggests that the central effects of antihypertensives may be smaller than effects on peripherally measured BP.⁷³ Alternative mechanisms of action of vitamin D, such as alteration of endothelial function or markers of thrombogenicity, have been postulated,^{5,56} and trials examining vascular events as the primary outcome are still required to examine these possibilities. Such trials of vitamin D supplementation are now under way in Finland, New Zealand, and the United States, and the results of these trials should further clarify the position of vitamin D in the cardiovascular therapeutic armamentarium. Recent data from a large mendelian randomization study⁷⁴ suggest that alleles linked to higher circulating 25OHD levels are associated with slightly lower SBP and DBP and a lower risk for hypertension. These findings are not inconsistent with our results, however; mendelian randomization studies are predicated on the alleles in question having no effects on the vascular system other than their effect on

Table 2. Results of Individual Patient Data Meta-analysis

Variable	No. of Patients	Effect Size (95% CI), mm Hg	P Value	I ² , %	P Value ^a
Systolic Blood Pressure					
Overall	3092	-0.5 (-1.3 to 0.4)	.27	0	NA
Baseline SBP >140 mm Hg	926	0.1 (-2.5 to 2.6)	.97	33	.84
Baseline SBP ≤140 mm Hg	2148	-0.6 (-1.5 to 0.3)	.18	0	
Baseline 25OHD level <10 ng/mL	427	-0.4 (-3.0 to 2.3)	.80	14	NA
Baseline 25OHD level 10-20 ng/mL	1289	-0.7 (-2.0 to 0.6)	.31	0	.83
Baseline 25OHD level >20 ng/mL	1331	-0.2 (-1.8 to 1.3)	.77	26	.95
Diabetes mellitus	353	1.1 (-2.9 to 5.1)	.58	50	.46
No diabetes mellitus	2728	-0.4 (-1.3 to 0.4)	.35	0	
Using ACE inhibitors	475	-1.4 (-3.7 to 1.0)	.24	1	.31
Not using ACE inhibitors	1485	0.1 (-1.4 to 1.6)	.94	29	
Baseline PTH level >217 pg/mL	1318	-0.8 (-2.1 to 0.5)	.23	0	.76
Baseline PTH level ≤217 pg/mL	1364	-0.5 (-2.1 to 1.2)	.58	37	
Baseline adjusted serum calcium level >9.2 mg/dL	1267	-1.0 (-2.3 to 0.4)	.17	0	.39
Baseline adjusted serum calcium level ≤9.2 mg/dL	1340	0.2 (-2.2 to 2.6)	.86	64	
Diastolic Blood Pressure					
Overall	3075	0.2 (-0.3 to 0.7)	.38	0	NA
Baseline DBP >90 mm Hg	315	-0.2 (-3.3 to 2.9)	.90	52	.83
Baseline DBP ≤90 mm Hg	2736	0.1 (-0.4 to 0.7)	.60	0	
Baseline 25OHD level <10 ng/mL	427	-1.2 (-2.4 to 0.0)	.05	46	NA
Baseline 25OHD level 10-20 ng/mL	1289	-0.2 (-1.0 to 0.6)	.66	0	.11
Baseline 25OHD level >20 ng/mL	1328	0.2 (-0.5 to 0.9)	.50	23	.03
Diabetes mellitus	342	1.2 (-0.1 to 3.4)	.28	36	.32
No diabetes mellitus	2722	0.1 (-0.4 to 0.6)	.81	0	
Using ACE inhibitors	475	0.1 (-1.3 to 1.5)	.92	0	.64
Not using ACE inhibitors	1482	0.4 (-0.2 to 1.1)	.19	43	
Baseline PTH level >217 pg/mL	1324	0.0 (-0.8 to 0.8)	.99	0	.80
Baseline PTH level ≤217 pg/mL	1362	0.2 (-0.7 to 1.0)	.70	10	
Baseline adjusted serum calcium level >9.2 mg/dL	1266	0.1 (-0.7 to 0.9)	.73	0	.22
Baseline adjusted serum calcium level ≤9.2 mg/dL	1340	1.1 (-0.3 to 2.4)	.12	54	

Abbreviations: ACE, angiotensin converting enzyme; DBP, diastolic blood pressure; NA, not applicable; PTH, parathyroid hormone; SBP, systolic blood pressure; 25OHD, 25-hydroxyvitamin D.

SI conversion factors: To convert calcium to millimoles per liter, multiply by 0.25; PTH to picomoles per liter, divide by 9.43; and 25OHD to millimoles per liter, multiply by 2.496.

^a P values for SBP are calculated for between-group interaction; for DBP, for interaction.

25OHD levels, which may not be the case for the alleles tested (cytochrome *CYP21R* and *DHCR7*, a cholesterol-metabolizing gene). Furthermore, differences in 25OHD levels seen in mendelian randomization studies are likely to have been present since birth given the genetic influences being tested, and exposure of the vascular tree to higher levels of 25OHD during development and in subsequent decades may have small beneficial effects that cannot be replicated in shorter-term intervention studies.

Conclusions

The results of this analysis do not support the use of vitamin D or its analogues as an individual patient treatment for hypertension or as a population-level intervention to lower BP. The lack of efficacy of vitamin D treatment on blood pressure also argues against routine measurement of 25OHD levels in patients with hypertension.

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REFERENCES

- Scragg R, Sowers M, Bell C. Serum 25-hydroxyvitamin D, ethnicity, and blood pressure in the Third National Health and Nutrition Examination Survey. *Am J Hypertens*. 2007;20(7):713-719.
- Fraser A, Williams D, Lawlor DA. Associations of serum 25-hydroxyvitamin D, parathyroid hormone and calcium with cardiovascular risk factors: analysis of 3 NHANES cycles (2001-2006). *PLoS One*. 2010;5(11):e13882.
- Kunutsor SK, Apekey TA, Steur M. Vitamin D and risk of future hypertension: meta-analysis of 283 537 participants. *Eur J Epidemiol*. 2013;28(3):205-221.
- Norman AW. From vitamin D to hormone D: fundamentals of the vitamin D endocrine system essential for good health. *Am J Clin Nutr*. 2008;88(2):491S-499S.
- Sugden JA, Davies JI, Witham MD, Morris AD, Struthers AD. Vitamin D improves endothelial function in patients with type 2 diabetes mellitus and low vitamin D levels. *Diabet Med*. 2008;25(3):320-325.
- Tarcin O, Yavuz DG, Ozben B, et al. Effect of vitamin D deficiency and replacement on endothelial function in asymptomatic subjects. *J Clin Endocrinol Metab*. 2009;94(10):4023-4030.
- Schleithoff SS, Zittermann A, Tenderich G, Berthold HK, Stehle P, Koerfer R. Vitamin D supplementation improves cytokine profiles in patients with congestive heart failure: a double-blind, randomized, placebo-controlled trial. *Am J Clin Nutr*. 2006;83(4):754-759.
- Forman JP, Williams JS, Fisher ND. Plasma 25-hydroxyvitamin D and regulation of the renin-angiotensin system in humans. *Hypertension*. 2010;55(5):1283-1288.
- Witham MD, Nadir MA, Struthers AD. Effect of vitamin D on blood pressure: a systematic review and meta-analysis. *J Hypertens*. 2009;27(10):1948-1954.
- Wu SH, Ho SC, Zhong L. Effects of vitamin D supplementation on blood pressure. *South Med J*. 2010;103(8):729-737.
- Kunutsor SK, Burgess S, Munroe PB, Khan H. Vitamin D and high blood pressure: causal association or epiphenomenon? *Eur J Epidemiol*. 2014;29(1):1-14.
- Verhagen AP, de Vet HC, de Bie RA, et al. The Delphi list: a criteria list for quality assessment of randomized clinical trials for conducting systematic reviews developed by Delphi consensus. *J Clin Epidemiol*. 1998;51(12):1235-1241.
- Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ*. 1997;315(7109):629-634.
- Riley RD, Kauler I, Bland M, et al. Meta-analysis of randomised trials with a continuous outcome according to baseline imbalance and availability of individual participant data. *Stat Med*. 2013;32(16):2747-2766.
- Lind L, Wengle B, Ljunghall S. Blood pressure is lowered by vitamin D (alphacalcidol) during long-term treatment of patients with intermittent hypercalcaemia: a double-blind, placebo-controlled study. *Acta Med Scand*. 1987;222(5):423-427.
- Lind L, Wengle B, Wide L, Sörensen OH, Ljunghall S. Hypertension in primary hyperparathyroidism—reduction of blood pressure by long-term treatment with vitamin D (alphacalcidol): a double-blind, placebo-controlled study. *Am J Hypertens*. 1988;1(4, pt 1):397-402.
- Lind L, Lithell H, Skarfors E, Wide L, Ljunghall S. Reduction of blood pressure by treatment with alphacalcidol: a double-blind, placebo-controlled study in subjects with impaired glucose tolerance. *Acta Med Scand*. 1988;223(3):211-217.
- Lind L, Wengle B, Wide L, Ljunghall S. Reduction of blood pressure during long-term treatment with active vitamin D (alphacalcidol) is dependent on plasma renin activity and calcium status: a double-blind, placebo-controlled study. *Am J Hypertens*. 1989;2(1):20-25.
- Myrup B, Jensen GF, McNair P. Cardiovascular risk factors during estrogen-norethindrone and cholecalciferol treatment. *Arch Intern Med*. 1992;152(11):2265-2268.
- Pan WH, Wang CY, Li LA, Kao LS, Yeh SH. No significant effect of calcium and vitamin D supplementation on blood pressure and calcium metabolism in elderly Chinese. *Chin J Physiol*. 1993;36(2):85-94.
- Scragg R, Khaw KT, Murphy S. Effect of winter oral vitamin D₃ supplementation on cardiovascular risk factors in elderly adults. *Eur J Clin Nutr*. 1995;49(9):640-646.
- Pfeifer M, Begerow B, Minne HW, Nachtigall D, Hansen C. Effects of a short-term vitamin D₃ and calcium supplementation on blood pressure and parathyroid hormone levels in elderly women. *J Clin Endocrinol Metab*. 2001;86(4):1633-1637.
- Alborzi P, Patel NA, Peterson C, et al. Paricalcitol reduces albuminuria and inflammation in chronic kidney disease: a randomized double-blind pilot trial. *Hypertension*. 2008;52(2):249-255.
- Nagpal J, Pande JN, Bhartia A. A double-blind, randomized, placebo-controlled trial of the short-term effect of vitamin D₃ supplementation on insulin sensitivity in apparently healthy, middle-aged, centrally obese men. *Diabet Med*. 2009;26(1):19-27.
- Zittermann A, Frisch S, Berthold HK, et al. Vitamin D supplementation enhances the beneficial effects of weight loss on cardiovascular disease risk markers. *Am J Clin Nutr*. 2009;89(5):1321-1327.
- Jorde R, Sneve M, Torjesen P, Figenschau Y. No improvement in cardiovascular risk factors in overweight and obese subjects after supplementation with vitamin D₃ for 1 year. *J Intern Med*. 2010;267(5):462-472.
- Witham MD, Dove FJ, Dryburgh M, Sugden JA, Morris AD, Struthers AD. The effect of different doses of vitamin D₃ on markers of vascular health in patients with type 2 diabetes: a randomised controlled trial. *Diabetologia*. 2010;53(10):2112-2119.
- Witham MD, Crighton LJ, Gillespie ND, Struthers AD, McMurdo ME. The effects of vitamin D supplementation on physical function and quality of life in older patients with heart failure: a randomized controlled trial. *Circ Heart Fail*. 2010;3(2):195-201.
- de Zeeuw D, Agarwal R, Amdahl M, et al. Selective vitamin D receptor activation with paricalcitol for reduction of albuminuria in patients with type 2 diabetes (VITAL study): a randomised controlled trial. *Lancet*. 2010;376(9752):1543-1551.
- Harris RA, Pedersen-White J, Guo DH, et al. Vitamin D₃ supplementation for 16 weeks improves flow-mediated dilation in overweight African-American adults. *Am J Hypertens*. 2011;24(5):557-562.
- Shab-Bidar S, Neyestani TR, Djazayeri A, et al. Regular consumption of vitamin D-fortified yogurt drink (Doogh) improved endothelial biomarkers in subjects with type 2 diabetes: a randomized double-blind clinical trial. *BMC Med*. 2011;9:125. doi:10.1186/1741-7015-9-125.
- Alvarez JA, Law J, Coakley KE, et al. High-dose cholecalciferol reduces parathyroid hormone in patients with early chronic kidney disease: a pilot, randomized, double-blind, placebo-controlled trial. *Am J Clin Nutr*. 2012;96(3):672-679.
- Bonakdaran S, Hami M, Hatefi A. The effects of calcitriol on albuminuria in patients with type-2 diabetes mellitus. *Saudi J Kidney Dis Transpl*. 2012;23(6):1215-1220.
- Gepner AD, Ramamurthy R, Krueger DC, Korcarz CE, Binkley N, Stein JH. A prospective randomized controlled trial of the effects of vitamin D supplementation on cardiovascular disease risk. *PLoS One*. 2012;7(5):e36617.
- Heshmat R, Tabatabaei-Malazy O, Abbaszadeh-Ahranjani S, et al. Effect of vitamin D on insulin resistance and anthropometric parameters in type 2 diabetes: a randomized

- double-blind clinical trial. *Daru*. 2012;20(1):10. doi:10.1186/2008-2231-20-10.
36. Kjærgaard M, Waterloo K, Wang CE, et al. Effect of vitamin D supplement on depression scores in people with low levels of serum 25-hydroxyvitamin D: nested case-control study and randomised clinical trial. *Br J Psychiatry*. 2012; 201(5):360-368.
37. Larsen T, Mose FH, Bech JN, Hansen AB, Pedersen EB. Effect of cholecalciferol supplementation during winter months in patients with hypertension: a randomized, placebo-controlled trial. *Am J Hypertens*. 2012;25(11):1215-1222.
38. Longenecker CT, Hileman CO, Carman TL, et al. Vitamin D supplementation and endothelial function in vitamin D deficient HIV-infected patients: a randomized placebo-controlled trial. *Antivir Ther*. 2012;17(4):613-621.
39. Muldowney S, Lucey AJ, Hill TR, et al. Incremental cholecalciferol supplementation up to 15 µg/d throughout winter at 51-55° N has no effect on biomarkers of cardiovascular risk in healthy young and older adults. *J Nutr*. 2012;142(8): 1519-1525.
40. Salehpour A, Shidfar F, Hosseini F, et al. Vitamin D₃ and the risk of CVD in overweight and obese women: a randomised controlled trial. *Br J Nutr*. 2012;108(10):1866-1873.
41. Stricker H, Tosi Bianda F, Guidicelli-Nicolosi S, Limoni C, Colucci G. Effect of a single, oral, high-dose vitamin D supplementation on endothelial function in patients with peripheral arterial disease: a randomised controlled pilot study. *Eur J Vasc Endovasc Surg*. 2012;44(3): 307-312.
42. Witham MD, Dove FJ, Sugden JA, Doney AS, Struthers AD. The effect of vitamin D replacement on markers of vascular health in stroke patients: a randomised controlled trial. *Nutr Metab Cardiovasc Dis*. 2012;22(10):864-870.
43. Wood AD, Secombes KR, Thies F, et al. Vitamin D₃ supplementation has no effect on conventional cardiovascular risk factors: a parallel-group, double-blind, placebo-controlled RCT. *J Clin Endocrinol Metab*. 2012;97(10):3557-3568.
44. Asemi Z, Hashemi T, Karamali M, Samimi M, Esmailzadeh A. Effects of vitamin D supplementation on glucose metabolism, lipid concentrations, inflammation, and oxidative stress in gestational diabetes: a double-blind randomized controlled clinical trial. *Am J Clin Nutr*. 2013;98(6): 1425-1432.
45. Boxer RS, Kenny AM, Schmotzer BJ, Vest M, Fiutem JJ, Piña IL. A randomized controlled trial of high dose vitamin D₃ in patients with heart failure. *JACC Heart Fail*. 2013;1(1):84-90.
46. Breslavsky A, Frand J, Matas Z, Boaz M, Barnea Z, Shargorodsky M. Effect of high doses of vitamin D on arterial properties, adiponectin, leptin and glucose homeostasis in type 2 diabetic patients. *Clin Nutr*. 2013;32(6):970-975.
47. Chai W, Cooney RV, Franke AA, Bostick RM. Effects of calcium and vitamin D supplementation on blood pressure and serum lipids and carotenoids: a randomized, double-blind, placebo-controlled, clinical trial. *Ann Epidemiol*. 2013;23(9):564-570.
48. Forman JP, Scott JB, Ng K, et al. Effect of vitamin D supplementation on blood pressure in blacks. *Hypertension*. 2013;61(4):779-785.
49. Larsen T, Mose FH, Bech JN, Pedersen EB. Effect of paricalcitol on renin and albuminuria in non-diabetic stage III-IV chronic kidney disease: a randomized placebo-controlled trial. *BMC Nephrol*. 2013;14(1):163. doi:10.1186/1471-2369-14-163.
50. Petchey WG, Hickman JJ, Prins JB, et al. Vitamin D does not improve the metabolic health of patients with chronic kidney disease stage 3-4: a randomized controlled trial [published correction appears in *Nephrology (Carlton)*. 2013;18(6):481]. *Nephrology (Carlton)*. 2013;18(1):26-35.
51. Roth DE, Al Mahmud A, Raqib R, et al. Randomized placebo-controlled trial of high-dose prenatal third-trimester vitamin D₃ supplementation in Bangladesh: the AVID trial. *Nutr J*. 2013;12(1):47. doi:10.1186/1475-2891-12-47.
52. Toxqui L, Blanco-Rojo R, Wright I, Pérez-Granados AM, Vaquero MP. Changes in blood pressure and lipid levels in young women consuming a vitamin D-fortified skimmed milk: a randomised controlled trial. *Nutrients*. 2013;5(12): 4966-4977.
53. Wamberg L, Kampmann U, Stødkilde-Jørgensen H, Rejnmark L, Pedersen SB, Richelsen B. Effects of vitamin D supplementation on body fat accumulation, inflammation, and metabolic risk factors in obese adults with low vitamin D levels: results from a randomized trial. *Eur J Intern Med*. 2013;24(7):644-649.
54. Witham MD, Price RJ, Struthers AD, et al. Cholecalciferol treatment to reduce blood pressure in older patients with isolated systolic hypertension: the VitDISH randomized controlled trial. *JAMA Intern Med*. 2013;173(18):1672-1679.
55. Witham MD, Dove FJ, Khan F, Lang CC, Belch JJ, Struthers AD. Effects of vitamin D supplementation on markers of vascular function after myocardial infarction: a randomised controlled trial. *Int J Cardiol*. 2013;167(3):745-749.
56. Witham MD, Adams F, Kabir G, Kennedy G, Belch JJ, Khan F. Effect of short-term vitamin D supplementation on markers of vascular health in South Asian women living in the UK: a randomised controlled trial. *Atherosclerosis*. 2013;230(2): 293-299.
57. Yiu YF, Yiu KH, Siu CW, et al. Randomized controlled trial of vitamin D supplement on endothelial function in patients with type 2 diabetes. *Atherosclerosis*. 2013;227(1):140-146.
58. Dalbeni A, Scaturro G, Degan M, Minuz P, Delva P. Effects of six months of vitamin D supplementation in patients with heart failure: a randomized double-blind controlled trial. *Nutr Metab Cardiovasc Dis*. 2014;24(8):861-868.
59. Scragg R, Slow S, Stewart AW, et al. Long-term high-dose vitamin D₃ supplementation and blood pressure in healthy adults: a randomized controlled trial. *Hypertension*. 2014;64(4):725-730.
60. Sollid ST, Hutchinson MY, Fuskevåg OM, et al. No effect of high-dose vitamin D supplementation on glycemic status or cardiovascular risk factors in subjects with prediabetes. *Diabetes Care*. 2014; 37(8):2123-2131.
61. Strobel F, Reusch J, Penna-Martinez M, et al. Effect of a randomised controlled vitamin D trial on insulin resistance and glucose metabolism in patients with type 2 diabetes mellitus. *Horm Metab Res*. 2014;46(1):54-58.
62. Wang AY, Fang F, Chan J, et al. Effect of paricalcitol on left ventricular mass and function in CKD: the OPERA trial. *J Am Soc Nephrol*. 2014;25(1): 175-186.
63. Witham MD, Ireland S, Houston JG, et al. Vitamin D therapy to reduce blood pressure and left ventricular hypertrophy in resistant hypertension: randomized, controlled trial. *Hypertension*. 2014;63(4):706-712.
64. Thadhani R, Appelbaum E, Pritchett Y, et al. Vitamin D therapy and cardiac structure and function in patients with chronic kidney disease: the PRIMO randomized controlled trial. *JAMA*. 2012;307(7):674-684.
65. Bischoff-Ferrari HA, Giovannucci E, Willett WC, Dietrich T, Dawson-Hughes B. Estimation of optimal serum concentrations of 25-hydroxyvitamin D for multiple health outcomes [published correction appears in *Am J Clin Nutr*. 2006;84(5):1253]. *Am J Clin Nutr*. 2006;84(1):18-28.
66. Gallagher JC, Sai A, Templin T II, Smith L. Dose response to vitamin D supplementation in postmenopausal women: a randomized trial. *Ann Intern Med*. 2012;156(6):425-437.
67. Aloia JF, Patel M, Dimaano R, et al. Vitamin D intake to attain a desired serum 25-hydroxyvitamin D concentration. *Am J Clin Nutr*. 2008;87(6): 1952-1958.
68. Rossini M, Gatti D, Viapiana O, et al. Short-term effects on bone turnover markers of a single high dose of oral vitamin D₃. *J Clin Endocrinol Metab*. 2012;97(4):622-626.
69. Bergman P, Lindh AU, Björkhem-Bergman L, Lindh JD. Vitamin D and respiratory tract infections: a systematic review and meta-analysis of randomized controlled trials. *PLoS One*. 2013;8(6): e65835. doi:10.1371/journal.pone.0065835.
70. Bjelakovic G, Gluud LL, Nikolova D, et al. Vitamin D supplementation for prevention of mortality in adults. *Cochrane Database Syst Rev*. 2014;1:CD007470.
71. Autier P, Boniol M, Pizot C, Mullie P. Vitamin D status and ill health: a systematic review. *Lancet Diabetes Endocrinol*. 2014;2(1):76-89.
72. Reid D, Toole BJ, Knox S, et al. The relation between acute changes in the systemic inflammatory response and plasma 25-hydroxyvitamin D concentrations after elective knee arthroplasty. *Am J Clin Nutr*. 2011;93(5): 1006-1011.
73. Manisty CH, Hughes AD. Meta-analysis of the comparative effects of different classes of antihypertensive agents on brachial and central systolic blood pressure, and augmentation index. *Br J Clin Pharmacol*. 2013;75(1):79-92.
74. Vimalaswaran KS, Cavadino A, Berry DJ, et al; LifeLines Cohort Study investigators; International Consortium for Blood Pressure (ICBP); Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) consortium; Global Blood Pressure Genetics (Global BPGen) consortium; Caroline Hayward. Association of vitamin D status with arterial blood pressure and hypertension risk: a mendelian randomisation study. *Lancet Diabetes Endocrinol*. 2014;2(9):719-729.