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Effect of vitamin D supplementation on blood pressure – a systematic review and meta-analysis incorporating individual patient data

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Abstract

Importance

Low vitamin D levels are associated with elevated blood pressure and future cardiovascular events. It is unclear if vitamin D supplementation reduces blood pressure, or which patient characteristics predict response.

Objective

To systematically review whether treatment with vitamin D or its analogs reduce blood pressure

Data sources

Medline, CINAHL, EMBASE, Cochrane Central Register of Controlled Trials and clinical trials.com, augmented by handsearching references from included articles and previous reviews. Google was searched for grey literature. No language restrictions were applied. The search period spanned 1966 to end March 2014

Study selection

Randomised placebo controlled trials, using vitamin D supplementation for a minimum of 4 weeks for any indication, which reported blood pressure data. Studies were included if they used active or inactive forms of vitamin D or vitamin D analogs. Cointerventions were permitted if identical in all treatment arms.

Data extraction and synthesis

Data were extracted on baseline demographics, 25-hydroxyvitamin D levels, systolic and diastolic blood pressures and change in blood pressure between baseline and final follow up

timepoint. Individual patient data on age, sex, medication use, diabetes, baseline and follow up blood pressures and 25-hydroxyvitamin D levels were requested from authors of included studies. For trial level data, between-group differences in blood pressure change were combined in a random-effects model. For individual patient level data, between-group differences in blood pressure at final follow up, adjusted for baseline blood pressure levels, were calculated before combining in a random-effects model.

Main outcomes and measures

Difference in office systolic and diastolic blood pressure

Results

46 trials (n=4541) were included in the trial-level meta-analysis. Individual patient data were successfully obtained for 27 trials (n=3092). At trial level, no effect of vitamin D supplementation was seen on systolic blood pressure (0.0mmHg, 95%CI -0.8, 0.8; I^2=21%) or diastolic blood pressure (-0.1mmHg; 95%CI -0.6, 0.5; I^2=20%). Similar results were found analysing individual patient data (systolic -0.5mmHg; 95%CI -1.3, 0.4; I^2=0%; diastolic 0.2mmHg; 95%CI -0.3, 0.7; I^2=0%). Subgroup analysis did not reveal any baseline factor predicting better response to therapy.

Conclusions and relevance

Vitamin D supplementation is ineffective as an agent for lowering blood pressure.

Introduction

A wealth of observational data have demonstrated relationships between circulating vitamin D metabolite levels and blood pressure. Lower 25-hydroxyvitamin D (25OHD) levels are associated with higher blood pressure in cross-sectional studies[1,2], and 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], reduces the production of pro-inflammatory cytokines[7], reduces parathyroid hormone levels (which is itself vasculotoxic) and reduces activity of the renin-angiotension-aldosterone system[8]. Any or all of these mechanisms could therefore potentially mediate an effect of vitamin D on blood pressure.

Intervention studies to date have thus far produced conflicting evidence on the blood pressure lowering effect of vitamin D. One previous meta-analysis[9], based on a number of small trials, demonstrated a modest but significant decrease in blood pressure in studies where mean blood pressure was raised at baseline; another meta-analysis conducted at a similar time did not demonstrate a significant effect of vitamin D supplementation on blood pressure[10] and a more recent meta-analysis[11] showed a small decrease in diastolic, but not systolic blood pressure. Although effects of vitamin D on blood pressure appear small in previous meta-analyses, even a modest improvement in blood pressure would be of public health importance, as widespread supplementation with vitamin D would be an inexpensive intervention. Furthermore, it is possible that selected subgroups (for example non-white populations, those with very low 25-hydroxyvitamin D levels) could benefit to a greater extent, potentially making vitamin D part of the therapeutic armamentarium in treating individuals with hypertension.

In the five years since the first meta-analyses were published, there has been a proliferation in randomised controlled trials studying vitamin D and cardiovascular health. We therefore sought to update our systematic review of randomised controlled trials to evaluate whether vitamin D supplementation reduces blood pressure when compared to placebo across a range of study populations and vitamin D analogs. We also sought to perform an individual patient data meta-analysis to further explore which subgroups of patients might potentially derive 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). We included randomised controlled trials which reported blood pressure or other measures of vascular function including arterial stiffness, endothelial function and left ventricular mass index within their outcomes. Medline, CINAHL, EMBASE, Cochrane Central Register of Controlled Trials and clinicaltrials.com were searched using our search strategy. We also searched for grey literature using Google, and hand searched references of included articles and references from previous reviews of vitamin D therapy. No language restrictions were applied to eligible reports. The search period spanned from 1966 to end March 2014 and was conducted by two of the authors (LAB and MDW).

Search Strategy

Search terms used were 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 given in the eAppendix.

Study Selection

We considered studies with participants with any baseline 25OHD level. Studies with blood pressure reduction or changes in surrogate markers of cardiovascular risk were included; a minimum of 4 weeks 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-alpha-vitamin D, paricalcitol and doxerocalciferol. Control groups receiving placebo were used and those receiving placebo plus co-intervention were included provided both arms of the study received the cointervention. Studies from both 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 less than 16 years old or studying patients on dialysis.

The primary outcome of the meta-analysis was change in office systolic and diastolic blood pressure between baseline and follow up.

Data extraction

Two researchers (MDW, LAB) independently extracted data from all trial reports using 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 colour, functional status/dwelling place, diabetes status and glycosylated haemoglobin, kidney function, history of cardiovascular events, history of hypertension, baseline blood pressure, baseline use of angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers, statins and aspirin. The following outcome measures were recorded for use in this analysis: change in office blood pressure (systolic and diastolic), change in 24 hour blood pressure. Study authors were contacted to provide missing data or to clarify data unclear from primary reports.

Individual patient data (IPD) collection:

For all eligible studies, authors were approached to provide individual patient data in order to conduct subgroup analyses by baseline characteristics at patient level, in particular by baseline 25OHD level, baseline medication use, baseline blood pressure and presence of diabetes mellitus. Data requested for each patient were: age, sex, body mass index (BMI), ethnicity, month of recruitment, systolic blood pressure at baseline and follow up, diastolic blood pressure at baseline and follow up, dose of vitamin D given (type, dose, frequency, duration), baseline 25OHD level (and follow up 25OHD level if available), baseline and post-treatment parathyroid hormone (PTH) and serum calcium/albumin, total cholesterol, high density lipoprotein (HDL) cholesterol, diagnosis of diabetes mellitus at baseline, diagnosis of previous stroke, myocardial infarction at baseline and whether patients were on ACE inhibitor, statin, angiotensin receptor antagonist at baseline.

Risk of bias assessment

Each included study was assessed for risk of bias using fields from the Delphi risk of bias checklist[12] to assess the following parameters: quality of random allocation concealment,

intention to treat analysis, blinding of outcome assessors, treatment and control group comparability, inclusion and exclusion criteria clearly defined, participant blinding to allocation and description of withdrawals and dropouts. Funnel plots were generated to examine possible publication bias, supplemented by formal statistical testing using Egger's test. Study quality was assessed by two reviewers (MDW and LAB) independently, and discrepancies were resolved by consensus.

Strategy for data synthesis

Meta-analysis at trial level was performed using Comprehensive Meta-Analysis Software (Biostat, NJ, USA). Weighted squares method was used, using random effects models in all cases. For all treatment effects, a negative value denotes a reduction in blood pressure with intervention compared to placebo. For each analysis at trial level, mean change between baseline and the last follow-up timepoint reported was compared between groups as these data were most commonly supplied in trial-level reports. For studies with more than one vitamin D group, the highest dose of vitamin D or analog was compared with the control group; intermediate dose groups were not analysed. Heterogeneity was assessed using the I^2 test. Pre-planned subgroup analyses were performed to examine effects of different preparations of vitamin D, dose ranges and baseline blood pressure. Degree of change in blood pressure was regressed against baseline blood pressure, trial duration, daily dose equivalent of vitamin D given and mean baseline 25OHD level.

For individual patient data analysis, a two-stage analysis was performed, as recommended by Riley *et al* [13]. For each study, the mean blood pressure values for each group at the final follow up timepoint were calculated, adjusted for baseline values using ANCOVA (SPSS v21, IBM, New York, USA). These values were then combined using weighted least-squares, random-

effects models using RevMan 5.3 software (Cochrane Collaboration). For studies with more than one vitamin D dose, patients taking the highest dose were compared to placebo; patients taking the lower dose were excluded from analysis. A series of prespecified patient-level subgroup analyses were performed using these methods – diabetes mellitus vs no diabetes mellitus; ACE inhibitor vs no ACE inhibitor; baseline SBP above and below 140mmHg; DBP above and below 90mmHg, baseline PTH above and below the median level for the IPD dataset, and baseline 25OHD levels <25, 25-50 and >50nmol/L. For analyses of ACE inhibitor use, patients taking angiotensin receptor blockers were excluded from analysis 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 blood pressure, low 25OHD levels and higher PTH levels), non-white participants, and summer versus winter enrolment; northern hemisphere summer was defined as June to August, and winter defined as December to February, with 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; of these, 46 yielded data that could be combined in the trial-level meta-analysis. Six studies used mean arterial pressure, or reported median blood pressure readings and we were unable to obtain mean readings from the authors. We successfully obtained 27 datasets for individual patient data analysis. For the trials where we did not succeed in obtaining individual patient data, two author groups felt unable to share their data; one 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. Six trials used 1-alpha hydroxylated vitamin D or calcitriol, four used paricalcitol, and the others used ergocalciferol or cholecalciferol.

Quality assessment and publication bias

Quality assessments, performed by assessing the risk of bias across a range of domains, are shown in eTable 2. Allocation concealment was deemed adequate in 51/52 trials, and most trials had adequate blinding for participants (49/52), other healthcare staff (49/52) and outcomes assessment (46/52). Only 22/52 trials clearly described analysis on intention to treat. Of the 30 trials where intention to treat was not well described, 19 trials clearly did not perform analyses on an intention to treat basis. Visual inspection of the funnel plot for systolic blood pressure treatment effect (see eFigure 1) revealed no obvious asymmetry to suggest publication bias; Egger's test was not significant (p=0.62).

Main outcome measures – trial level data

Meta-analysis of change in blood pressure between baseline and final follow-up for each trial revealed no clinically or statistically significant effect on either systolic blood pressure (treatment effect 0.0mmHg, 95% CI -0.8 to 0.8; p=;0.97 I^2=21%) or diastolic blood pressure (treatment effect -0.1mmHg, 95%CI -0.6 to 0.5; p=0.84; I^2=20%). Forest plots for the overall effect of treatment on systolic and diastolic blood pressure are presented in Figure 2. Prespecified subgroup analyses are shown in Table 1; analysis by baseline blood pressure category, type of intervention, dose interval or baseline 25OHD category did not affect the results significantly.

Trial-level metaregression

No significant relationship was found at trial level between systolic blood pressure treatment effect and mean baseline systolic blood pressure (slope 0.016mmHg per mmHg baseline SBP, 95% CI -0.037 to 0.069; p=0.55, see eFigure 2), baseline 25OHD level (slope 0.003mmHg per

nmol/L baseline 25OHD, 95% CI -0.014 to 0.021; p=0.70), baseline PTH level (slope -0.009mmHg per pmol/L baseline PTH, 95% CI -0.036 to 0.053; p=0.53) or trial duration (slope 0.007mmHg per month of trial, 95% CI -0.005 to 0.019; p=0.27). Similarly, for trials using vitamin D3, no significant relationship was found on metaregression between systolic blood pressure treatment effect and the daily dose equivalent used as treatment (slope -0.001mmHg per unit of vitamin D3, 95% CI -0.018 to 0.018; p=0.93). Small numbers of trials precluded metaregression of D2, paricalcitol or 1-alphacalcidol daily dose effects.

Metaregression of diastolic treatment effect against baseline variables similarly showed no significant relationships: mean baseline diastolic blood pressure slope 0.001mmHg per mmHg baseline DBP (95% CI -0.003 to 0.006; p=0.54), baseline 25OHD level slope -0.001mmHg per nmol/L baseline 25OHD (95% CI -0.005 to 0.003; p=0.67), baseline PTH level slope -0.020mmHg per pmol/L baseline PTH (95% CI -0.051 to 0.011; p=0.21), trial duration slope 0.007mmHg per month of trial, 95% CI -0.005 to 0.020; p=0.23) and daily dose equivalent slope 0.000mmHg per unit of vitamin D3 (95% CI 0.000 to 0.001; p=0.34).

IPD analyses

Analyses of the individual patient datasets are shown in Figure 3, with subgroup analyses shown in Table 2. The overall treatment effect derived from the IPD datasets was similar to that derived from the trial level data despite the use of a small number of trials (systolic blood pressure treatment effect -0.5mmHg, 95% CI -1.3 to 0.4, p=0.27, I^2=0%; diastolic blood pressure treatment effect -0.2mmHg, 95%CI -0.7 to 0.3, p=0.38, I^2=0%). In subgroup analyses, no significant differences were seen between patients with or without diabetes, taking or not taking ACE inhibitors, or by subgroups of baseline blood pressure, PTH or 25OHD (Table 2).

Analysis of the small group of patients with a combination of baseline factors potentially most likely to benefit (SBP>140mmHg, 25OHD<25nmol/L and PTH>4.8pmol) showed no evidence of benefit (n=60; treatment effect on systolic blood pressure 2.7mmHg, 95%CI -5.0 to 10.4, p=0.49; I^2=0%). Similarly, analysis of participants of non-white ethnicity (n=214) showed no evidence of benefit (systolic BP treatment effect: 2.2mmHg, 95%CI -1.1 to 5.4; p=0.19; I^2=28%; diastolic BP treatment effect: 0.4mmHg, 95%CI -1.7 to 2.6; p=0.70; I^2=11%). Comparison of patients recruited during summer and winter months did not reveal any significant differences (systolic BP treatment effect for summer: -1.1mmHg, 95%CI -4.1 to 2.0, p=0.50, I^2=37; for winter: 1.3mmHg, 95%CI -1.4 to 4.0, p=0.35, I^2=60%. Diastolic treatment effect for summer: 1.4mmHg, 95%CI -0.4 to 3.2, p=0.11, I^2=38%; for winter 0.8mmHg, 95%CI -0.1 to 1.6, p=0.07, I^2=0%)

Discussion

Our analysis found no evidence of blood pressure reduction by vitamin D or vitamin D analogs, a result that was consistent between the trial-level and individual patient analyses. Subgroup analyses found no evidence of blood pressure reduction in patients with elevated baseline blood pressure or patients with diabetes mellitus; there was no relationship between the effect of supplementation on blood pressure and use of ACE inhibitors, baseline 25OHD levels, baseline blood pressure or baseline PTH level. The narrow confidence intervals around the main result suggest that a clinically significant reduction in blood pressure 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 either as a treatment for blood pressure control in individual patients, or as a population-based intervention to reduce blood pressure. These results are broadly consistent with previous meta-analyses[9-11], although they contrast with the small reduction in blood pressure in trials with high baseline blood pressure found in our previous meta-analysis. Our

analysis however includes a much larger number of studies than previous analyses, and hence a larger number of patients and 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 have allowed analysis of subgroups, there remain limitations to this systematic review. Included studies are almost all single centre trials, and most are of modest size; none recruited >1000 patients. As a result, baseline imbalances between trials were common, and such imbalances are difficult to fully correct for, even with individual patient data analysis[13]. Not all studies were of high quality; deficiencies in intention-to-treat, reporting of masking and allocation concealment were noted. It is possible that not all eligible studies have been included, although our wide search strategy, contact with leading authors in the field, lack of language restriction and grey literature search would be expected to mitigate against this. Nevertheless, it is possible that other blood pressure data exists (e.g. from osteoporosis trials) that has not as yet been published and that we have been unable to locate[63]. A further limitation is the small number of trials which have specifically targeted patients with hypertension at baseline; such patients would perhaps 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 (e.g. 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 such levels. Levels of >75nmol/L have

been postulated as necessary for optimum health[64], but such levels are based on observational data and do not necessarily 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 from 1600 IU per day to over 5000 IU per day have been advocated as necessary[65,66]. 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 effects[67] when compared to smaller, regular doses; intermittent doses appeared less effective at reducing the incidence of respiratory infection in a recent systematic review[68], although no such effect was evident for blood pressure reduction in our analysis. Although it is possible that larger, frequent doses of vitamin D might still have effects on reducing blood pressure, we found no evidence of a dose-response relationship in our analyses. Further, most studies were in participants with European ancestry, and beneficial effects cannot be excluded in other ethnic groups although our subgroup analysis did not find evidence to support this.

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 infection and all-cause mortality[68,69]. Recent analyses have shown that although observational data suggests an association between low 25OHD levels and cardiovascular events, diabetes and many cancers, intervention data do not support an effect across most of these diseases[70]. This may be in part because of the difficulty in fully disentangling low 25OHD levels from other, closely associated factors (e.g. ageing, obesity, smoking, inactivity) that affect both 25OHD levels and promote disease, but also in part that not all studies have targeted patients with the lowest circulating 25OHD levels. A further 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[71], although whether chronic inflammation caused by subclinical disease can have the same effect is not known. It is also possible that vitamin D has beneficial actions on cardiovascular health that are not captured by office brachial artery blood pressure measurement, which has been argued to be less reliable than other measures, e.g. ambulatory blood pressure measurement or central aortic blood pressure measurement – although previous work suggests that central effects of antihypertensives may be smaller than effects on peripherally-measured blood pressure[72]. Alternative mechanisms of action of vitamin D such as alteration of endothelial function or markers of thrombogenicity have been postulated[5,55], and trials examining vascular events as the primary outcome are still required to examine these possibilities. Such trials of vitamin D supplementation are now underway in Finland, New Zealand and USA, 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 randomisation study[73] suggests that alleles linked to higher circulating 25OHD levels are associated with slightly lower systolic and diastolic blood pressure, and with a lower risk of hypertension. These findings are not inconsistent with our results however; Mendelian randomisation studies are predicated on the alleles in question having no effects on the vascular system other than their effect on 25OHD levels, which may not be the case for the alleles tested (cytochrome *CYP21R* and *DHCR7*, a cholesterol metabolising gene). Furthermore, differences in 25OHD levels seen in Mendelian randomisation studies are likely to have been present since birth given the genetic influences under test, and it is possible that exposure of the vascular tree to higher levels of 25OHD during development and in subsequent decades has small beneficial effects that cannot be replicated in shorter-term intervention studies.

In conclusion, the results from this analysis do not support the use of vitamin D analogs as an individual patient treatment for hypertension or as a population-level intervention to lower blood pressure.

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Table 1. Trial level meta-analysis results

Parameter	N for trials	N for participants	Effect size (95% CI)	p	I^2(%)	P between groups
Systolic BP (mmHg)						
Overall	46	4541	0.0 (-0.8, 0.8)	0.97	21	-
Mean baseline systolic >140mmHg	16	1361	-0.7 (-3.2, 1.7)	0.55	38	0.54
Mean baseline systolic <=140mmHg	30	3180	0.1 (-0.6, 0.9)	0.77	11	
D2 and D3	38	4058	0.0 (-0.9, 0.9)	0.97	26	-
1-alpha OHD	5	191	-1.6 (-6.3, 7.1)	0.50	4	0.64
Paricalcitol	3	292	1.4 (-3.3, 6.1)	0.56	0	0.57
Mean baseline 25OHD <=50nmol/L	27	2555	-0.7 (-2.2, 0.7)	0.31	38	0.31
Mean baseline 25OHD >50nmol/L	13	1723	0.1 (-0.4, 0.6)	0.75	0	
Daily dosing	16	1522	-0.7 (-2.5, 1.0)	0.41	24	-
Weekly / fortnightly dosing	8	1303	1.3 (-0.1, 2.6)	0.07	0	0.07
>=Monthly dosing	14	1216	-0.2 (-1.6, 1.2)	0.76	28	0.66
Diastolic BP (mmHg)						

Overall	45	4434	-0.1 (-0.6, 0.5)	0.84	20	-
Mean baseline systolic >140mmHg	14	1074	-0.4 (-2.1, 1.3)	0.61	55	0.65
Mean baseline systolic <=140 mmHg	30	3180	0.0 (-0.4, 0.3)	0.85	0	
D2 and D3	37	3951	0.1 (-0.3, 0.5)	0.65	4	-
1-alpha OHD	5	191	-3.5 (-6.8, -0.1)	0.04	54	0.04
Paricalcitol	2	112	-1.0 (-3.9, 1.9)	0.50	0	0.46
Mean baseline 25OHD 25-50nmol/L	26	2375	0.2 (-0.5, 1.0)	0.54	17	0.50
Mean baseline 25OHD >50nmol/L	12	1616	-0.1 (-0.5, 0.4)	0.69	0	
Daily dosing	16	1466	-0.5 (-1.5, 0.4)	0.26	23	-
Weekly / fortnightly dosing	8	1303	0.6 (-0.4, 1.5)	0.23	0	0.11
>=Monthly dosing	14	1213	0.0 (-0.4, 0.5)	0.84	0	0.35

25OHD: 25-hydroxyvitamin D

Table 2. Individual Patient Data meta-analysis results

Systolic blood pressure	n	Effect size (95% CI) (mmHg)	P	I^2 (%)	P between groups
Overall	3092	-0.5 (-1.3, 0.4)	0.27	0	-
Baseline systolic BP >140mmHg	926	0.1 (-2.5, 2.6)	0.97	33	0.84
Baseline systolic BP <=140mmHg	2148	-0.6 (-1.5, 0.3)	0.18	0	
Baseline 25OHD<25nmol/L	427	-0.4 (-3.0, 2.3)	0.80	14	-
Baseline 25OHD 25-50nmol/L	1289	-0.7 (-2.0, 0.6)	0.31	0	0.83
Baseline 25OHD >50nmol/L	1331	-0.2 (-1.8, 1.3)	0.77	26	0.95
Diabetes mellitus	353	1.1 (-2.9, 5.1)	0.58	50	0.46
No diabetes mellitus	2728	-0.4 (-1.3, 0.4)	0.35	0	
On ACEi	475	-1.4 (-3.7, 1.0)	0.24	1	0.31
Not on ACEi	1485	0.1 (-1.4, 1.6)	0.94	29	
Baseline PTH>4.8pmol/L	1318	-0.8 (-2.1, 0.5)	0.23	0	0.76
Baseline PTH<=4.8pmol/L	1364	-0.5 (-2.1, 1.2)	0.58	37	
Baseline adjusted serum calcium >2.31mmol/L	1267	-1.0 (-2.3, 0.4)	0.17	0	0.39
Baseline adjusted serum calcium <=2.31mmol/L	1340	0.2 (-2.2, 2.6)	0.86	64	

Diastolic blood pressure	n	Effect size (95% CI) (mmHg)	P	I^2 (%)	P for interaction
Overall	3075	0.2 (-0.3, 0.7)	0.38	0	-
Baseline diastolic BP >90mmHg	315	-0.2 (-3.3, 2.9)	0.90	52	0.83
Baseline diastolic BP <=90mmHg	2736	0.1 (-0.4, 0.7)	0.60	0	
Baseline 25OHD<25mmol/L	427	-1.2 (-2.4, 0.0)	0.05	46	-
Baseline 25OHD 25-50nmol/L	1289	-0.2 (-1.0, 0.6)	0.66	0	0.11
Baseline 25OHD >50nmol/L	1328	0.2 (-0.5, 0.9)	0.50	23	0.03
Diabetes mellitus	342	1.2 (-0.1, 3.4)	0.28	36	0.32
No diabetes mellitus	2722	0.1 (-0.4, 0.6)	0.81	0	
On ACEi	475	0.1 (-1.3, 1.5)	0.92	0	0.64
Not on ACEi	1482	0.4 (-0.2, 1.1)	0.19	43	
Baseline PTH>4.8pmol/L	1324	0.0 (-0.8, 0.8)	0.99	0	0.80
Baseline PTH<=4.8pmol/L	1362	0.2 (-0.7, 1.0)	0.70	10	
Baseline adjusted serum calcium >2.31mmol/L	1266	0.1 (-0.7, 0.9)	0.73	0	0.22
Baseline adjusted serum calcium <=2.31mmol/L	1340	1.1 (-0.3, 2.4)	0.12	54	

ACEi: Angiotensin converting enzyme inhibitor. 25OHD: 25-hydroxyvitamin D. PTH: Parathyroid hormone

Figure legends:

Figure 1. PRISMA diagram of study selection

Fig 2. Results of trial-level meta-analysis (panel a = systolic, panel b = diastolic)

Fig 3. Results of Individual Patient Data analysis (using final BP adjusted for baseline BP) (panel a = systolic, panel b = diastolic)

Effect of vitamin D supplementation on blood pressure – a systematic review and meta-analysis incorporating individual patient data

On-line only supplementary material

eTable 1. Characteristics of included studies

Study	*N*	*Latitude*	*Study Population*	*Outcomes*	*Mean Age*	*% Male*	*Mean baseline 25OHD* (nmol/l)	*Mean baseline SBP* (mmHg)	*Control*	*Intervention*	*Duration*
Lind et al[1], Sweden, 1987	29	60° N	Healthy volunteers with intermittent hypercalcaemia	Blood pressure	63	40	Not known	149	Placebo	Alphacalcidol 1 µg/day	6 months
Lind et al[2], Sweden, 1988a	36	61° N	Patients with primary hyperparathyroidism	Blood pressure	65	19	Not known	149	Placebo	Alphacalcidol (0.25 µg/day up-titrated to 1 µg/day after 8 weeks)	6 months
Lind et al[3], Sweden, 1988b	65	60° N	Patients with impaired glucose tolerance	Blood pressure and glucose tolerance	Not stated	100	Not known	152	Placebo	Alphacalcidol 0.75µg/day	12 weeks
Lind et al[4], Sweden, 1989	42	61° N	Patients with mild to moderate hypertension	Blood pressure and plasma renin activity	51	80	Not known	157	Placebo	Alphacalcidol 1µg/day	18 weeks
Myrup et al[5], Denmark, 1992	113	56° N	Elderly female patients	Blood pressure, cholesterol, weight	70	0	Not known	101 (MAP)	Placebo	Calcitriol 0.5µg/day	12 months
Pan et al[6], Taiwan, 1993	58	25° N	Institutionalised adults	Blood pressure	74	78	61	133	Placebo	Cholecalciferol 200IU/day + placebo	11 weeks
Scragg et al[7], England, 1995	191	52° N	Elderly patients	Blood pressure, cholesterol	70	54	35	148	Placebo	Cholecalciferol 100,000IU once-off	5 weeks

Pfeifer et al[8], Germany, 2001	148	52° N	Elderly female patients	Blood pressure, cholesterol	75	0	25	142	Calcium 1200mg/daily +Placebo	Calcium 1200mg/ daily + Cholecalciferol 800IU/day	8 weeks
Schleithoff et al[9], Germany, 2006	123	51° N	Heart failure patients	Blood pressure, cytokine levels, survival	55	83	38 (median)	123	Calcium 500mg once/daily + placebo	Calcium 500mg/ once daily + Cholecalciferol 2000IU/day	9 months
Alborzi et al[10], USA, 2008	24	40° N	Patients with chronic kidney disease and on ACE-I or ARB	Endothelial function, 24 hour ambulatory BP, GFR, CRP	70	83	34	125.4 (24hr BP)	Placebo	Paricalcitol 1µg daily Paricalcitol 2µg daily	1 month
Sugden et al[11], Scotland, 2008	34	56 ° N	Type 2 Diabetes patients	Endothelial function, blood pressure, insulin sensitivity	64	53	38	141	Placebo	Ergocalciferol 100,000IU single dose	8 weeks
Nagpal et al[12], India, 2009	100	28° N	Centrally obese, non-diabetic, healthy males	Insulin sensitivity, insulin secretion, lipid concentration, blood pressure	44	100	33	124	Placebo	Cholecalciferol 120,000IU /2 weekly	6 weeks
Zittermann et al[13], Germany, 2009	200	52° N	Healthy overweight subjects participating in weight reduction program	Weight loss, cardiovascular disease risk markers including blood pressure	48	33	30	128	Placebo	Cholecalciferol 3332 IU/day	12 months
Jorde et al[14], Norway, 2010	438	69° N	Overweight or obese subjects	Cardiovascular risk factors	48	36	58	124	Placebo + 500mg calcium/day	Cholecalciferol 20,000 IU weekly + 500mg calcium/day	12 months

			without diabetes or IHD							Cholecalciferol 40,000 IU weekly + 500mg calcium/day	
Witham et al[15], Scotland, 2010a	61	56° N	Type II Diabetes and baseline Vitamin D <100nmol/l	Endothelial function, blood pressure, markers of glycaemic control	65	67	45	146	Placebo	100,000 IU Cholecalciferol 200,000 IU cholecalciferol single dose	16 weeks
Witham et al[16], Scotland, 2010b	105	56° N	Older adults with heart failure	Walk test, physical activity, cardiovascular and inflammatory markers, blood pressure	80	66	22	141	Placebo	Ergocalciferol 100,000 IU 10 weekly.	20 weeks
de Zeeuw et al[17], Multinational, 2010	281	Multinational	Patients with Type II diabetes and albuminuria receiving ACEi/ARBs	Albuminuria, eGFR, blood pressure	64	65	41	142	Placebo	Paricalcitol 1µg daily Paricalcitol 2µg daily	24 weeks
Harris et al[18], USA, 2011	45	33° N	African-American Adults with no overt cardiovascular, pulmonary or metabolic disease	Endothelial function, anthropometric assessments, blood pressure	30	47	36	124	Placebo	Cholecalciferol 60,000IU/ 4 weekly	16 weeks

Shab-Bidar et al[19], Iran 2011	100	36° N	Non-insulin requiring Type II Diabetes Mellitus	Glycaemic status, lipid profile and endothelial biomarkers	53	43	38	127	Plain Yoghurt Drink with 170mg/ calcium twice a day	Cholecalciferol fortified yoghurt drink 170mg/calcium and 500IU/250ml twice daily	12 weeks
Alvarez et al[20], USA, 2012	48	34° N	Early chronic kidney disease	Vitamin D status, circulating PTH concentrations	62	95	74	129	Placebo	Cholecalciferol 50,000 IU/ week for 12 weeks then 50,000 IU every other week for 40 weeks.	12 months
Bonakdaran et al[21], Iran, 2012	51	35° N	Untreated Polycystic Ovarian syndrome Patients	Improvement in ovulation, insulin resistance, blood pressure	25	0	51	110	Placebo	Metformin 1g/day; Calcitriol 0.5µg/day	3 months
Gepner et al[22], USA, 2012	114	43° N	Healthy community dwelling postmenopausal females with serum vitamin D >10 and <60ng/ml	Endothelial function (pulse wave velocity, flow mediated dilatation, augmentation index)	64	0	78	119.4	Placebo	Cholecalciferol 2500 IU/day	4 months
Heshmat et al[23], Iran, 2012	42	36° N	Type II Diabetes Mellitus	Insulin resistance and anthropometric factors	56	36	103	119	Placebo	Cholecalciferol 300,000IU once-off	3 months
Kjaergaard et al[24], Norway, 2012	243	69° N	Adults aged 30-75 years	Depressive symptoms,	53	44	48	129	Placebo	Cholecalciferol 40,000 IU once weekly	6 months

Larsen et al[25], Denmark,2012	130	56° N	Caucasian hypertensive patients	Blood pressure, arterial stiffness	61	31	58	143	Placebo	Cholecalciferol 3000 IU/day	20 weeks
Longenecker et al[26], 2012, USA	45	42° N	Vitamin D deficient HIV infected adults	Endothelial function	45	78	21	118	Placebo	Cholecalciferol 4000 IU daily	12 weeks
Muldowney et al[27], Ireland 2012a	209	51-55° N	Older adults aged >64 years during winter	Biomarkers of cardiovascular disease risk	71	40	54	146	Placebo	Cholecalciferol 200 IU per day or 400 IU per day or 600 IU per day	22 weeks
Muldowney et al[27], Ireland 2012b	233	51-55° N	Young adults aged 20-40 years during winter	Biomarkers of cardiovascular disease risk	30	51	70	124	Placebo	Cholecalciferol 200 IU per day or 400 IU per day or 600 IU per day	22 weeks
Salehpour et a [28], Iran, 2012	85	36° N	Healthy premenopausal overweight and obese women	Blood pressure, lipid profile, anthropometric parameters	38	0	42	113.5	Placebo	Cholecalciferol 1000 IU/day	90 days
Stricker et al[29], Switzerland, 2012	62	46° N	Chronic peripheral vascular disease and vitamin D deficiency	Endothelial function and arterial stiffness, coagulation and inflammation parameters.	74	61	42	137	Placebo	Cholecalciferol (Vitamin D3) 100,000 IU single dose	1 month
Witham et al[30], Scotland, 2012	58	56° N	Older adults with previous stroke	Blood pressure, endothelial function	67	72	38	128	Placebo	100,000 IU Ergocalciferol	16 weeks
Wood et al[31], Scotland, 2012	305	57° N	Healthy Postmenopausal women aged 60-70 years	Lipid profile, insulin resistance, inflammatory	64	0	34	128.5	Placebo	400 IU/day Cholecalciferol 1000 IU/day Cholecalciferol	1 year

				biomarkers, blood pressure							
Asemi et al[32], Iran, 2013	54	34° N	Pregnant women in Iran	C-Reactive Protein, Insulin resistance and biomarkers of oxidative stress	25	0	40	112	Placebo + 400µg/day folic acid + 60 µg/day iron	Cholecalciferol 400 IU/day + 400µg/day folic acid + 60 µg/day iron	9 weeks
Boxer et al[33], USA, 2013	64	41° N	Over 50 year olds with heart failure and vitamin D deficiency	Cardiopulmonary stress testing	66	52	46	116	Placebo once weekly + Calcium Citrate 400mg twice daily	Cholecalciferol 50,000 IU weekly + Calcium Citrate 400mg twice daily	6 months
Breslavsky et al[34], Israel, 2013	47	32° N	Type II Diabetics with cardiovascular risk factors	Arterial properties, adiponectin, leptin and glucose homeostasis	66	47	30	153	Placebo	Cholecalciferol 1000 IU/day	12 months
Chai et al[35], USA, 2013	92	21° N	30 – 75 year olds with adenomatous colorectal polys	Blood pressure, serum lipids and carotenoids	61	70	Not known	126	Placebo	Calcium carbonate 2g/day OR Cholecalciferol 800 IU/day OR Calcium carbonate 2g/day + Cholecalciferol 800 IU/day	6 months
Forman et al[36], USA, 2013	283	42° N	Healthy Black Population	Systolic and diastolic blood pressure	51	35	39	122	Placebo +200mg calcium daily	Cholecalciferol 1000 IU/day or 2000 IU/day or 4000 IU/day all + 200mg calcium daily	3 months
Larsen et al[37] 2013, Denmark	30	56° N	Non-diabetic, albuminuric stage II-IV chronic kidney disease	Plasma renin concentration, albuminuria	61	73	56	136	Placebo	Paricalcitol 2 µg daily	6 weeks

Petchey et al[38], Australia, 2013	28	28° S	Chronic Kidney Disease Stage 3-4	Insulin resistance	66	71	91	135	Placebo	Cholecalciferol 2000IU daily	6 months
Roth et al[39], Bangladesh, 2013	160	24° N	Third trimester of pregnancy	Vitamin D status	22	0	45	104	Placebo	Cholecalciferol 35,000 IU weekly	Mean 10 weeks
Toxqui et al[40], Spain, 2013	129	40° N	Healthy 18-35 year old Caucasian women	Iron and bone metabolism biomarkers, blood pressure, glucose and lipid levels	25	0	63	109	15mg Iron-fortified dairy product	15mg iron fortified dairy product and 200 IU cholecalciferol daily	16 weeks
Wamberg et al[41], Denmark, 2013	55	56° N	Obese subjects aged 18-50years with low vitamin D levels	Obesity related complications such as chronic low grade inflammation, insulin resistance, hypertension and hyperlipidaemia	40	29	35	133	Placebo	Cholecalciferol 7000 IU/day	26 weeks
Witham 2013 et al[42], Scotland, 2013a	159	56° N	Isolated systolic hypertension in over 70 year olds	Blood pressure, Endothelial function	77	52	45	163	Placebo	Cholecalciferol 100,000 IU three monthly	12 months
Witham et al[43], Scotland, 2013b	75	56 ° N	Recent myocardial infarction patients	Endothelial function, blood pressure, cholesterol	66	69	47	127.5	Placebo	Cholecalciferol 100,000IU/ 2 monthly	6 moths

Witham et al[44], Scotland, 2013c	50	56° N	South-east Asian women living in UK for 10 years	Macrovascular and microvascular endothelial function	41	0	27	120	Placebo	Cholecalciferol 100,000 IU once off	8 weeks
Yiu et al[45], Hong Kong 2013	100	22° N	Type II diabetes mellitus with suboptimal vitamin D status	Endothelial function, endothelial progenitor cells, CRP	65	50	54	146	Placebo	Cholecalciferol 5000 IU daily	12 weeks
Dalbeni et al[46], Italy, 2014`	36	45° N	Chronic heart failue aged >40 years	Ejection fraction and echocardiography parameters	72	74	44	133	Placebo	Cholecalciferol 600,000 IU at baseline, 100,000 IU at 10 weeks and 20 weeks	6 months
Scragg et al[47], New Zealand, 2014	322	44° S	Healthy adults	Number and severity of upper respiratory tract infections	48	25	71	123	Placebo	Cholecalciferol 200000 IU first month, 200000 IU second month then 100000 IU monthly	18 months
Sollid et al[48], Norway, 2014	511	70° N	Prediabetes	Glucose metabolism and cardiovascular risk factors	62	61	61	135	Placebo	Cholecalciferol 20000 IU weekly	12 months
Strobel et al[49], Germany 2014	86	50° N	Non-insulin requiring Type II Diabetes Mellitus	Insulin resistance and blood glucose levels	60	56	36	141	Placebo	Cholecalciferol 1904IU/day Once Weekly	6 months
Wang et al[50], Hong Kong, 2014	60	23° N	Stage 3-5 non-dialysis CKD with left	Change in Left Ventricular mass index	61	53	Not known	133	Placebo	Paricalcitol – if iPTH<500pg/ml Paricalcitol 1µg If iPTH >500pg/ml Paricalcitol 2µg	12 months

			ventricular hypertrophy								
Witham et al[51], Scotland, 2014	68	56° N	Resistant hypertension	Blood pressure, glucose, cholesterol and Left ventricular mass index	63	65	42	154	Placebo	Cholecalciferol 100,000 IU every 2 months	6 months

eTable 2: Risk of bias table for all included studies

Study	Quality of allocation concealment	Analysis on intention to treat	Number and description of dropouts	Blinding – patients	Blinding – health care providers	Blinding – outcome assessors	Comparable treatment and placebo groups
Lind 1987 [1]	+	U	+	U	U	U	-
Lind 1988a [2]	+	+	+	+	+	U	+
Lind 1988b [3]	+	U	_	+	+	+	-
Lind 1989 [4]	+	+	+	+	+	U	+
Myrup 1992 [5]	+	U	-	+	+	+	+
Pan 1993 [6]	+	-	+	+	+	+	-
Scragg 1995 [7]	+	+	+	+	+	+	+
Pfeifer 2001 [8]	+	+	+	+	+	+	+
Schleithoff 2006 [9]	+	-	+	+	+	+	+
Alborzi 2008 [10]	+	+	+	+	+	+	-
Sugden 2008 [11]	+	-	+	+	+	+	+

Nagpal 2009 [12]	+	+	+	+	+	+	+
Zittermann 2009 [13]	+	U	+	+	+	+	+
Jorde 2010 [14]	+	-	+	+	+	+	+
Witham 2010a [15]	+	U	+	+	+	+	+
Witham 2010b [16]	+	+	+	+	+	+	+
de Zeeuw 2010 [17]	+	+	+	+	+	+	+
Harris 2011 [18]	+	U	+	+	+	+	+
Shab-Bidar 2011 [19]	+	-	+	+	+	+	+
Alvarez 2012 [20]	+	+	+	+	+	+	+
Bonakdaran 2012 [21]	-	-	+	U	U	U	-
Gepner 2012 [22]	+	+	+	+	+	+	+
Heshmat 2012 [23]	+	U	+	+	+	+	-
Kjærgaard 2012 [24]	+	-	+	+	+	+	+
Larsen 2012 [25]	+	-	+	+	+	+	+
Longenecker 2012 [26]	+	U	+	+	+	+	+
Muldowney 2012a [27]	+	-	+	+	+	+	+

Muldowney 2012b [27]	+	-	+	+	+	+	+
Salehpour 2012 [28]	+	U	+	+	+	+	-
Stricker 2012 [29]	+	+	+	+	+	+	-
Witham 2012 [30]	+	U	+	+	+	+	+
Wood 2012 [31]	+	+	+	+	+	+	+
Asemi 2013 [32]	+	-	+	+	+	-	+
Boxer 2013 [33]	+	+	+	+	+	+	+
Breslavsky 2013 [34]	+	-	+	U	U	U	+
Chai 2013 [35]	+	U	+	+	+	+	-
Forman 2013 [36]	+	+	+	+	+	+	-
Larsen 2013 [37]	+	-	+	+	+	+	U
Petchey 2013 [38]	+	-	+	+	+	+	-
Roth 2013 [39]	+	+	+	+	+	+	+
Toxqui 2013 [40]	+	-	+	+	+	+	+
Wamberg 2013 [41]	+	+	+	+	+	+	+
Witham 2013a [42]	+	-	+	+	+	+	+

Witham 2013b [43]	+	+	+	+	+	+	+
Witham 2013c [44]	+	+	+	+	+	+	+
Yiu 2013 [45]	+	+	+	+	+	+	+
Dalbeni 2014 [46]	+	-	-	+	+	+	-
Scragg 2014 [47]	+	+	+	+	+	+	+
Sollid 2014 [48]	+	-	+	+	+	+	+
Strobel 2014 [49]	+	-	+	+	+	+	+
Wang 2014 [50]	+	+	+	+	+	+	+
Witham 2014 [51]	+	+	+	+	+	+	+

+ Adequate / yes, - Inadequate / no, U: Unclear

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eAppendix: Search strategy for D-PRESSURE systematic review

[vitamin D OR vitamin D2 OR vitamin D3 OR cholecalciferol OR ergocalciferol OR alphacalcidol OR alfacalcidol OR calcitriol OR paricalcitol OR doxerocalciferol]

AND

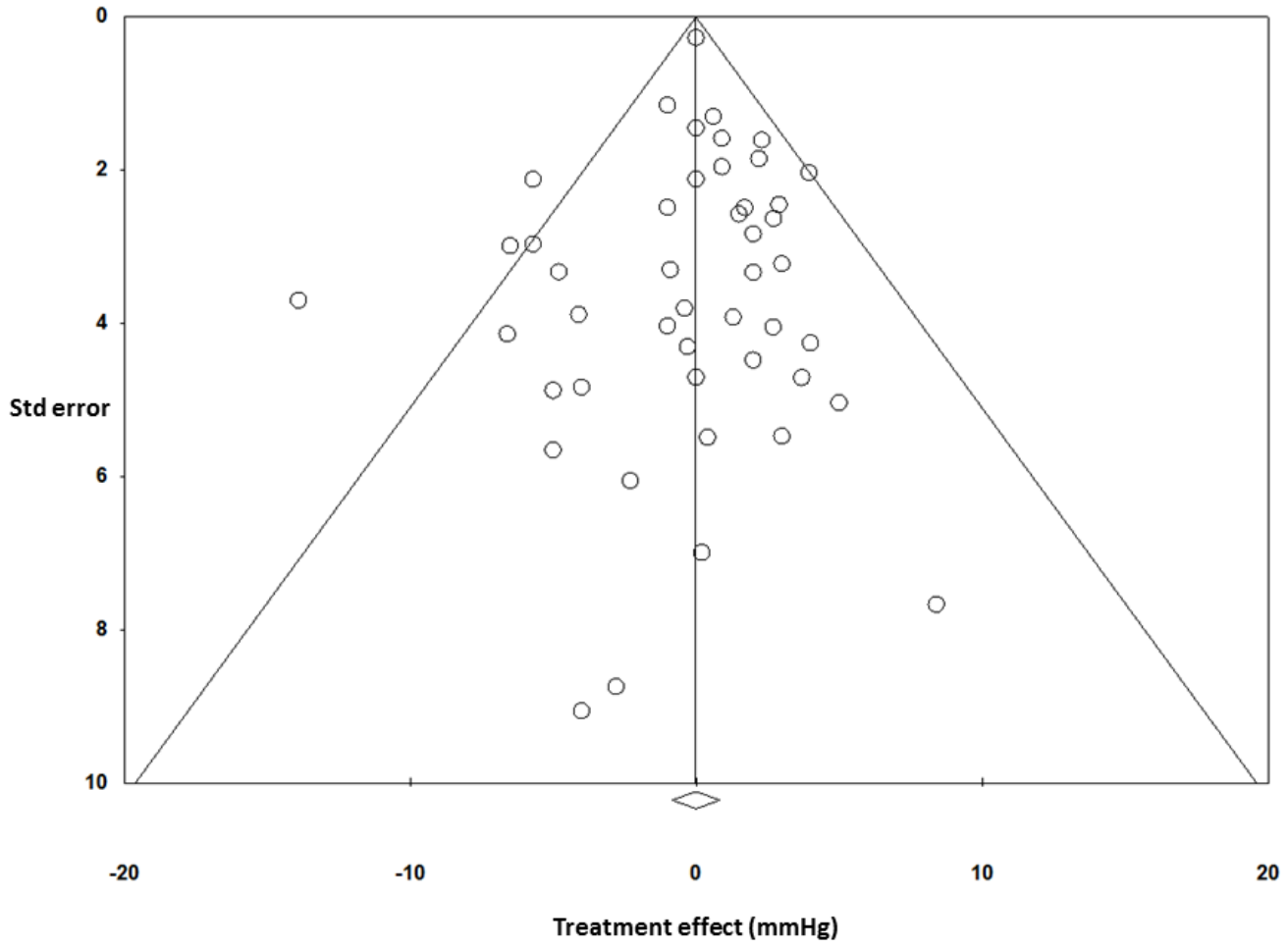
[randomised controlled trial OR placebo]

AND

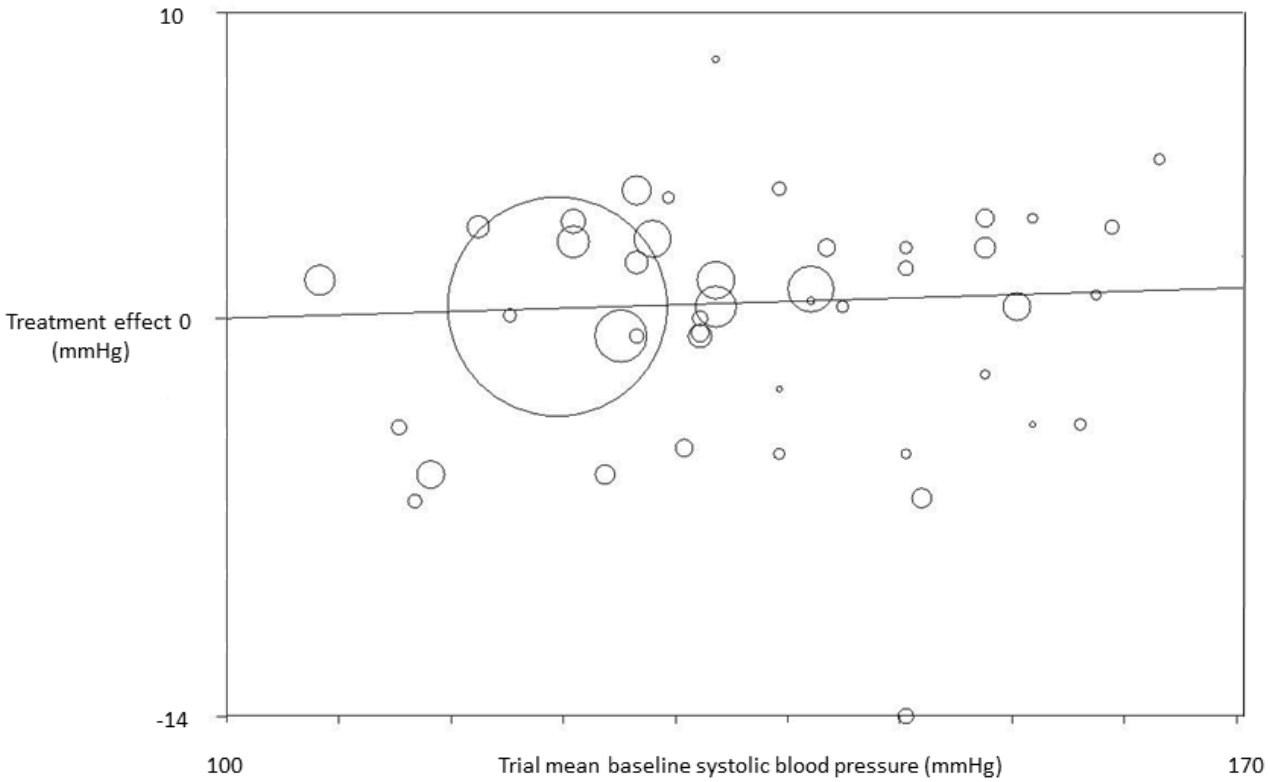
[blood pressure OR hypertension OR vascular OR cardiovascular OR mortality]

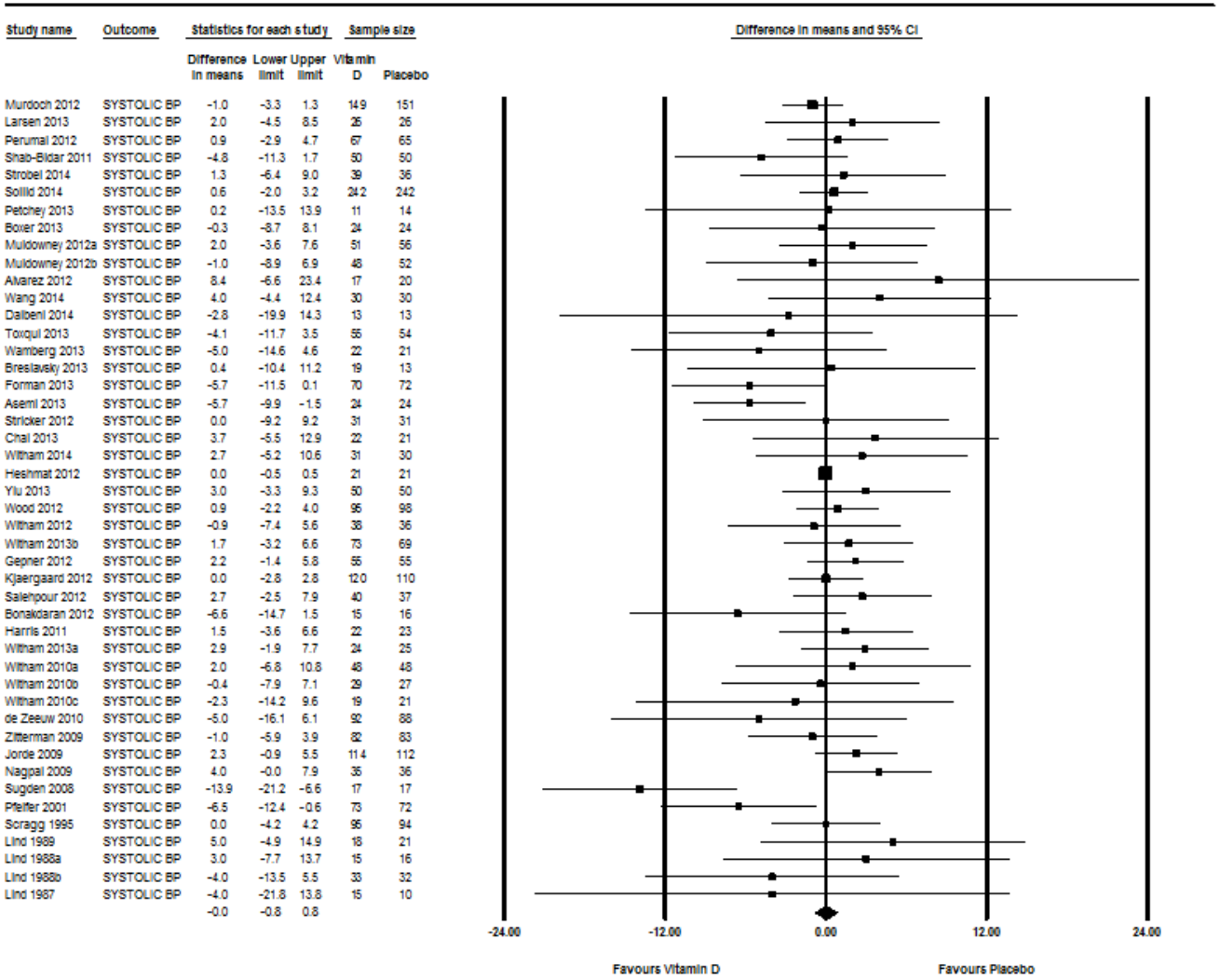
Applied to all fields within database; not restricted to MeSH headings

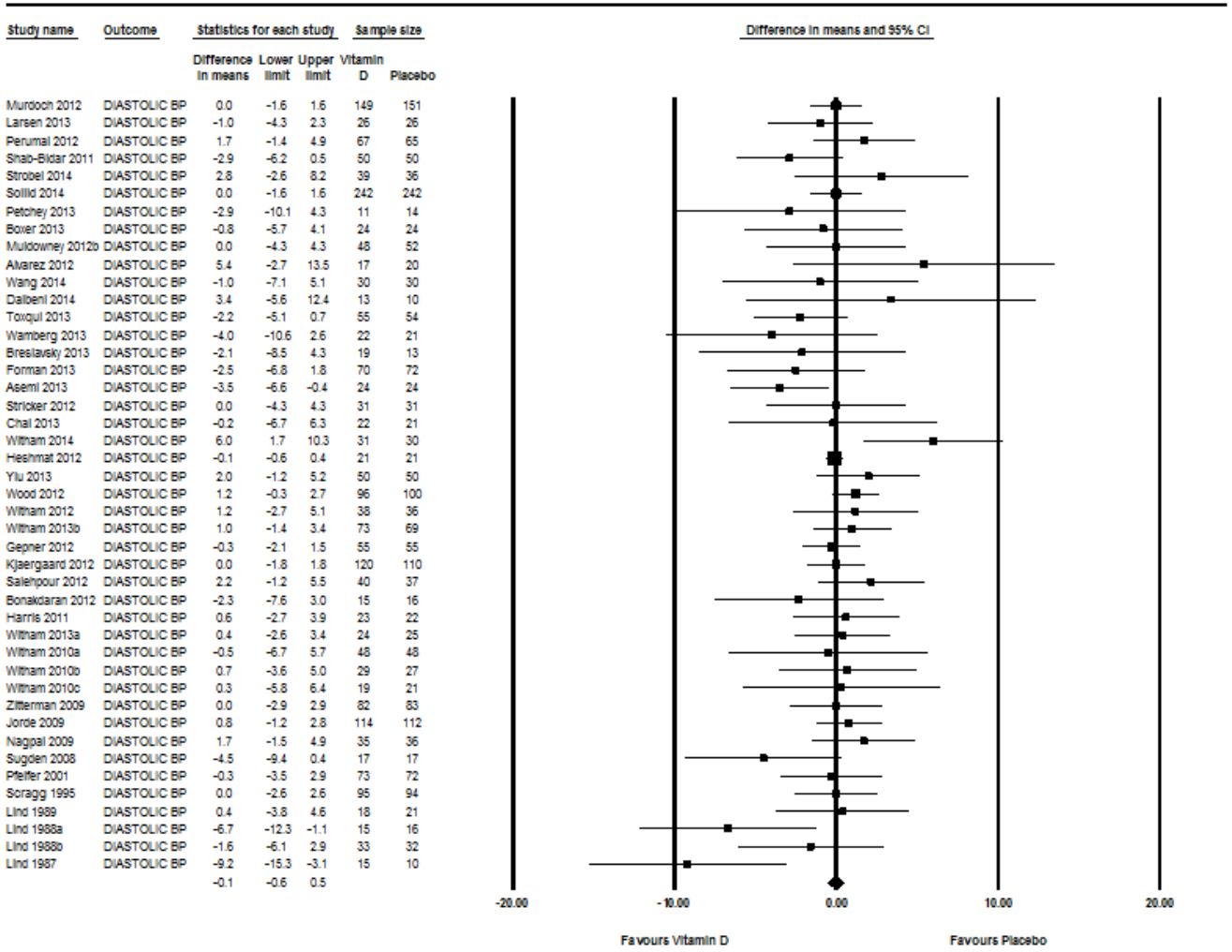
eFigure 1. Funnel plot for trial-level systolic blood pressure treatment effects

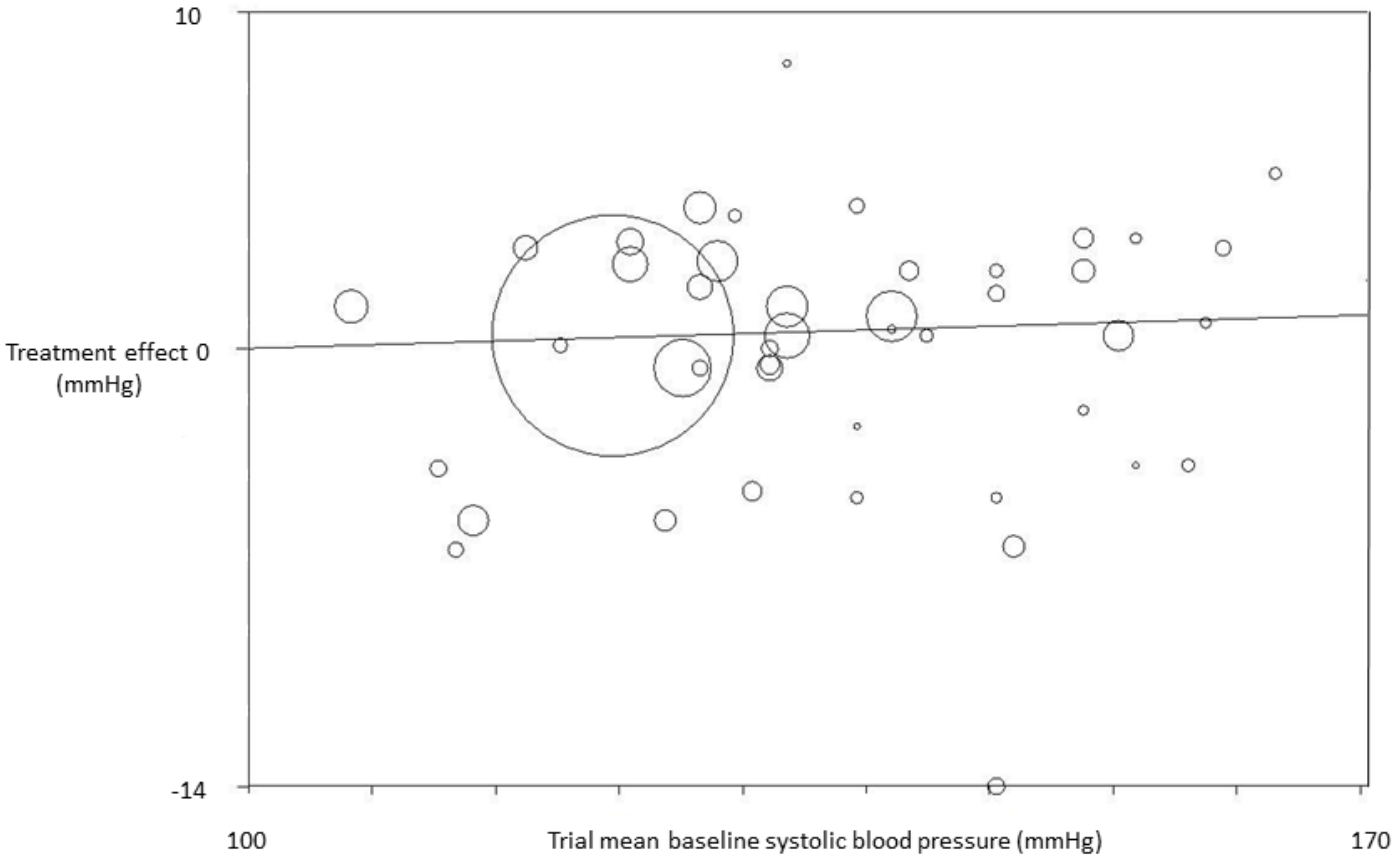


eFigure 2: Meta-regression of treatment effect vs mean trial-level baseline systolic blood pressure




Study name
Outcome
Statistics for each study
Sample size
Difference in means
Lower limit
Upper limit
Vitamin D
Placebo
Difference in means and 95% CI
Murdoch 2012 SYSTOLIC BP -1.0 -3.3 1.3 149 151
Larsen 2013 SYSTOLIC BP 2.0 -4.5 8.5 26 26
Perumal 2012 SYSTOLIC BP 0.9 -2.9 4.7 67 65
Shab-Bidar 2011 SYSTOLIC BP -4.8 -11.3 1.7 50 50
Strobel 2014 SYSTOLIC BP 1.3 -6.4 9.0 39 36
Solilid 2014 SYSTOLIC BP 0.6 -2.0 3.2 242 242
Petchey 2013 SYSTOLIC BP 0.2 -13.5 13.9 11 14
Boxer 2013 SYSTOLIC BP -0.3 -8.7 8.1 24 24
Muldowney 2012a SYSTOLIC BP 2.0 -3.6 7.6 51 56
Muldowney 2012b SYSTOLIC BP -1.0 -8.9 6.9 48 52
Alvarez 2012 SYSTOLIC BP 8.4 -6.6 23.4 17 20
Wang 2014 SYSTOLIC BP 4.0 -4.4 12.4 30 30
Dalbeni 2014 SYSTOLIC BP -2.8 -19.9 14.3 13 13
Toxqui 2013 SYSTOLIC BP -4.1 -11.7 3.5 55 54
Wamberg 2013 SYSTOLIC BP -5.0 -14.6 4.6 22 21
Breslavsky 2013 SYSTOLIC BP 0.4 -10.4 11.2 19 13
Forman 2013 SYSTOLIC BP -5.7 -11.5 0.1 70 72
Asemi 2013 SYSTOLIC BP -5.7 -9.9 -1.5 24 24
Stricker 2012 SYSTOLIC BP 0.0 -9.2 9.2 31 31
Chai 2013 SYSTOLIC BP 3.7 -5.5 12.9 22 21
Witham 2014 SYSTOLIC BP 2.7 -5.2 10.6 31 30
Heshmat 2012 SYSTOLIC BP 0.0 -0.5 0.5 21 21
Yiu 2013 SYSTOLIC BP 3.0 -3.3 9.3 50 50
Wood 2012 SYSTOLIC BP 0.9 -2.2 4.0 95 98
Witham 2012 SYSTOLIC BP -0.9 -7.4 5.6 38 36
Witham 2013b SYSTOLIC BP 1.7 -3.2 6.6 73 69
Gepner 2012 SYSTOLIC BP 2.2 -1.4 5.8 55 55
Kjaergaard 2012 SYSTOLIC BP 0.0 -2.8 2.8 120 110
Salehpour 2012 SYSTOLIC BP 2.7 -2.5 7.9 40 37
Bonakdaran 2012 SYSTOLIC BP -6.6 -14.7 1.5 15 16
Harris 2011 SYSTOLIC BP 1.5 -3.6 6.6 22 23
Witham 2013a SYSTOLIC BP 2.9 -1.9 7.7 24 25
Witham 2010a SYSTOLIC BP 2.0 -6.8 10.8 48 48
Witham 2010b SYSTOLIC BP -0.4 -7.9 7.1 29 27
Witham 2010c SYSTOLIC BP -2.3 -14.2 9.6 19 21
de Zeeuw 2010 SYSTOLIC BP -5.0 -16.1 6.1 92 88
Zitterman 2009 SYSTOLIC BP -1.0 -5.9 3.9 82 83
Jorde 2009 SYSTOLIC BP 2.3 -0.9 5.5 114 112
Nagpal 2009 SYSTOLIC BP 4.0 -0.0 7.9 35 36
Sugden 2008 SYSTOLIC BP -13.9 -21.2 -6.6 17 17
Pfeifer 2001 SYSTOLIC BP -6.5 -12.4 -0.6 73 72
Scragg 1995 SYSTOLIC BP 0.0 -4.2 4.2 95 94
Lind 1989 SYSTOLIC BP 5.0 -4.9 14.9 18 21
Lind 1988a SYSTOLIC BP 3.0 -7.7 13.7 15 16
Lind 1988b SYSTOLIC BP -4.0 -13.5 5.5 33 32
Lind 1987 SYSTOLIC BP -4.0 -21.8 13.8 15 10
-0.0 -0.8 0.8
-24.00
-12.00
0.00
12.00
24.00
Favours Vitamin D
Favours Placebo

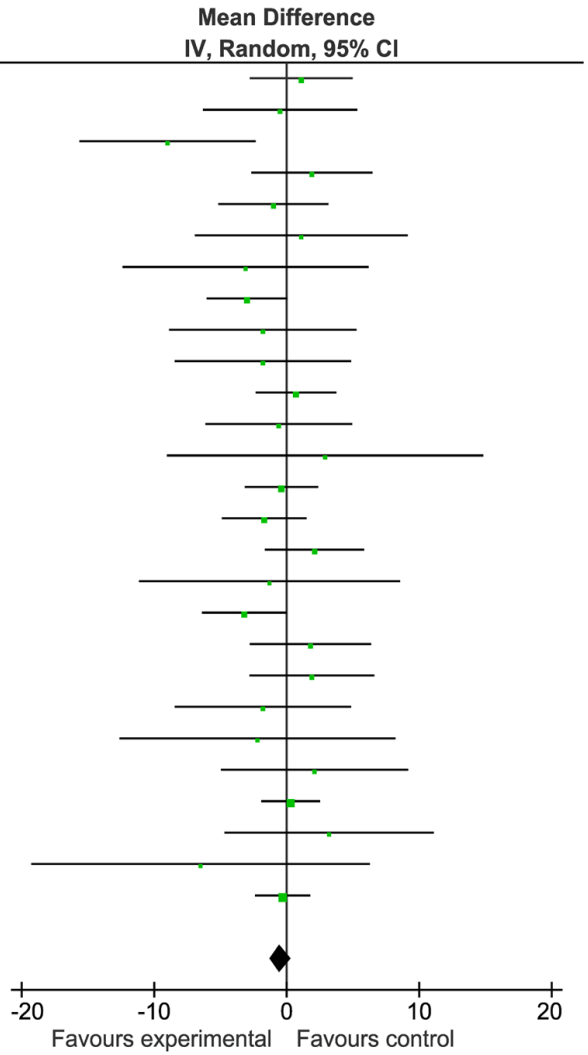

Study name
Outcome
Statistics for each study
Sample size
Difference in means
Lower limit
Upper limit
Vitamin D
Placebo
Murdoch 2012 DIASTOLIC BP 0.0 -1.6 1.6 149 151
Larsen 2013 DIASTOLIC BP -1.0 -4.3 2.3 26 26
Perumal 2012 DIASTOLIC BP 1.7 -1.4 4.9 67 65
Shab-Bidar 2011 DIASTOLIC BP -2.9 -6.2 0.5 50 50
Strobel 2014 DIASTOLIC BP 2.8 -2.6 8.2 39 36
Solilid 2014 DIASTOLIC BP 0.0 -1.6 1.6 242 242
Petchey 2013 DIASTOLIC BP -2.9 -10.1 4.3 11 14
Boxer 2013 DIASTOLIC BP -0.8 -5.7 4.1 24 24
Muldowney 2012b DIASTOLIC BP 0.0 -4.3 4.3 48 52
Alvarez 2012 DIASTOLIC BP 5.4 -2.7 13.5 17 20
Wang 2014 DIASTOLIC BP -1.0 -7.1 5.1 30 30
Dalbeni 2014 DIASTOLIC BP 3.4 -5.6 12.4 13 10
Toxqui 2013 DIASTOLIC BP -2.2 -5.1 0.7 55 54
Wamberg 2013 DIASTOLIC BP -4.0 -10.6 2.6 22 21
Breslavsky 2013 DIASTOLIC BP -2.1 -8.5 4.3 19 13
Forman 2013 DIASTOLIC BP -2.5 -6.8 1.8 70 72
Asemi 2013 DIASTOLIC BP -3.5 -6.6 -0.4 24 24
Stricker 2012 DIASTOLIC BP 0.0 -4.3 4.3 31 31
Chai 2013 DIASTOLIC BP -0.2 -6.7 6.3 22 21
Witham 2014 DIASTOLIC BP 6.0 1.7 10.3 31 30
Heshmat 2012 DIASTOLIC BP -0.1 -0.6 0.4 21 21
Yiu 2013 DIASTOLIC BP 2.0 -1.2 5.2 50 50
Wood 2012 DIASTOLIC BP 1.2 -0.3 2.7 96 100
Witham 2012 DIASTOLIC BP 1.2 -2.7 5.1 38 36
Witham 2013b DIASTOLIC BP 1.0 -1.4 3.4 73 69
Gepner 2012 DIASTOLIC BP -0.3 -2.1 1.5 55 55
Kjaergaard 2012 DIASTOLIC BP 0.0 -1.8 1.8 120 110
Salehpour 2012 DIASTOLIC BP 2.2 -1.2 5.5 40 37
Bonakdaran 2012 DIASTOLIC BP -2.3 -7.6 3.0 15 16
Harris 2011 DIASTOLIC BP 0.6 -2.7 3.9 23 22
Witham 2013a DIASTOLIC BP 0.4 -2.6 3.4 24 25
Witham 2010a DIASTOLIC BP -0.5 -6.7 5.7 48 48
Witham 2010b DIASTOLIC BP 0.7 -3.6 5.0 29 27
Witham 2010c DIASTOLIC BP 0.3 -5.8 6.4 19 21
Zittermann 2009 DIASTOLIC BP 0.0 -2.9 2.9 82 83
Jorde 2009 DIASTOLIC BP 0.8 -1.2 2.8 114 112
Nagpal 2009 DIASTOLIC BP 1.7 -1.5 4.9 35 36
Sugden 2008 DIASTOLIC BP -4.5 -9.4 0.4 17 17
Pfeifer 2001 DIASTOLIC BP -0.3 -3.5 2.9 73 72
Scragg 1995 DIASTOLIC BP 0.0 -2.6 2.6 95 94
Lind 1989 DIASTOLIC BP 0.4 -3.8 4.6 18 21
Lind 1988a DIASTOLIC BP -6.7 -12.3 -1.1 15 16
Lind 1988b DIASTOLIC BP -1.6 -6.1 2.9 33 32
Lind 1987 DIASTOLIC BP -9.2 -15.3 -3.1 15 10
-0.1 -0.6 0.5
Difference in means and 95% CI
-20.00
-10.00
0.00
10.00
20.00
Favours Vitamin D
Favours Placebo


10
Treatment effect 0 (mmHg)
-14
100
Trial mean baseline systolic blood pressure (mmHg)
170

Study or Subgroup	Vitamin D Mean	Vitamin D SD	Vitamin D Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean Difference IV, Random, 95% CI	Year
Scragg 1995	143.4	13.6455	95	142.3	13.5735	94	4.3%	1.10 [-2.78, 4.98]	1995
Schleithoff 2006	122.6	14.0869	41	123.1	13.8564	48	1.9%	-0.50 [-6.33, 5.33]	2006
Sugden 2008	135.8	10.7331	20	144.8	10.7331	20	1.5%	-9.00 [-15.65, -2.35]	2008
Nagpal 2009	122	10.0573	35	120.1	9.6	36	3.1%	1.90 [-2.68, 6.48]	2008
Zittermann 2009	123.7	13.5	81	124.7	13.5	81	3.7%	-1.00 [-5.16, 3.16]	2009
Witham 2010b	136	19.6688	46	134.9	19.6688	46	1.0%	1.10 [-6.94, 9.14]	2010
Witham 2010a	140.5	14.8492	18	143.6	14.6642	21	0.7%	-3.10 [-12.39, 6.19]	2010
Jorde 2010	124.5	11.6413	112	127.5	11.2716	105	6.9%	-3.00 [-6.05, 0.05]	2010
Witham 2012	126.6	13.2288	28	128.4	13.2575	26	1.3%	-1.80 [-8.87, 5.27]	2012
Stricker 2012	138.7	13.3626	31	140.5	13.3626	31	1.5%	-1.80 [-8.45, 4.85]	2012
Wood 2012	127.4	10.4355	90	126.7	10.608	93	6.9%	0.70 [-2.35, 3.75]	2012
Witham 2013b	129.1	12.49	39	129.7	12	36	2.1%	-0.60 [-6.14, 4.94]	2012
Alvarez 2012	131.8	18.554	17	128.9	16.9047	17	0.5%	2.90 [-9.03, 14.83]	2012
Kjaergaard 2012	127.1	10.9545	120	127.5	10.4881	110	8.4%	-0.40 [-3.17, 2.37]	2012
Larsen 2012	130.2	8.8994	55	131.9	8.3048	57	6.3%	-1.70 [-4.89, 1.49]	2012
Gepner 2012	121.4	8.5159	37	119.3	8.1185	39	4.6%	2.10 [-1.64, 5.84]	2012
Wamberg 2013	129.4	14.8	16	130.7	14.8203	19	0.7%	-1.30 [-11.15, 8.55]	2013
Toxqui 2013	105.5	8.2316	56	108.7	8.7361	53	6.3%	-3.20 [-6.39, -0.01]	2013
Witham 2013c	115.8	8.3283	24	114	8	25	3.1%	1.80 [-2.78, 6.38]	2013
Witham 2013a	162.7	14.5248	73	160.8	14.1213	69	2.9%	1.90 [-2.81, 6.61]	2013
Boxer 2013	138.7	13.3626	31	140.5	13.3626	31	1.5%	-1.80 [-8.45, 4.85]	2013
Petchey 2013	124.2	13.2665	11	126.4	13.0958	14	0.6%	-2.20 [-12.62, 8.22]	2013
Strobel 2014	142.9	15.6125	39	140.8	15.6	36	1.3%	2.10 [-4.97, 9.17]	2014
Sollid 2014	132.3	12.4451	242	132	12.4451	242	13.1%	0.30 [-1.92, 2.52]	2014
Witham 2014	150	15.5897	31	146.8	15.617	29	1.0%	3.20 [-4.70, 11.10]	2014
Dalbeni 2014	125	15.5039	13	131.5	17.6672	13	0.4%	-6.50 [-19.28, 6.28]	2014
Scragg 2014	125.3	9.7652	149	125.6	8.6017	151	14.8%	-0.30 [-2.38, 1.78]	2014
Total (95% CI)			**1550**			**1542**	**100.0%**	**-0.45 [-1.25, 0.35]**	

Heterogeneity: Tau² = 0.00; Chi² = 22.38, df = 26 (P = 0.67); I² = 0%

Test for overall effect: Z = 1.09 (P = 0.27)



Study or Subgroup	Vitamin D Mean	Vitamin D SD	Vitamin D Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean Difference IV, Random, 95% CI	Year
Scragg 1995	80.7	7.7974	95	81	8.7258	94	4.2%	-0.30 [-2.66, 2.06]	1995
Schleithoff 2006	74.5	9.6047	41	76.3	9.6995	48	1.5%	-1.80 [-5.82, 2.22]	2006
Sugden 2008	78.7	6.7082	20	81.5	6.7082	20	1.4%	-2.80 [-6.96, 1.36]	2008
Nagpal 2009	76.7	8.8741	35	76.9	9	36	1.4%	-0.20 [-4.36, 3.96]	2008
Zittermann 2009	83.1	8.1	81	82.8	8.1	81	3.8%	0.30 [-2.19, 2.79]	2009
Witham 2010a	78.8	8.9095	18	78.2	8.7069	21	0.8%	0.60 [-4.95, 6.15]	2010
Witham 2010b	73	13.5647	46	72.6	13.5647	46	0.8%	0.40 [-5.14, 5.94]	2010
Jorde 2010	75.9	7.4081	112	76.5	7.1729	105	6.2%	-0.60 [-2.54, 1.34]	2010
Wood 2012	76.5	4.7434	90	75.5	4.8218	93	12.2%	1.00 [-0.39, 2.39]	2012
Witham 2012	72.5	7.9373	28	72.7	8.1584	26	1.3%	-0.20 [-4.50, 4.10]	2012
Witham 2013b	73.9	8.1185	39	72.5	8.4	36	1.7%	1.40 [-2.34, 5.14]	2012
Stricker 2012	74.5	6.1245	31	74.5	6.1245	31	2.5%	0.00 [-3.05, 3.05]	2012
Larsen 2012	75.8	5.1913	55	77	5.331	58	6.2%	-1.20 [-3.14, 0.74]	2012
Gepner 2012	71.6	4.2579	37	72	4.3715	39	6.2%	-0.40 [-2.34, 1.54]	2012
Kjaergaard 2012	78.9	6.5727	120	79.1	6.2929	110	8.5%	-0.20 [-1.86, 1.46]	2012
Alvarez 2012	75.4	11.957	17	72.2	12.2049	19	0.4%	3.20 [-4.70, 11.10]	2012
Witham 2013a	77.7	6.8352	73	76.4	6.6453	69	4.8%	1.30 [-0.92, 3.52]	2013
Witham 2013c	73.6	5.3889	24	73.2	5.5	25	2.5%	0.40 [-2.65, 3.45]	2013
Toxqui 2013	66.4	6.735	56	67.4	6.4273	51	3.8%	-1.00 [-3.49, 1.49]	2013
Wamberg 2013	83	9.6825	15	85	9.5896	19	0.6%	-2.00 [-8.53, 4.53]	2013
Petchey 2013	76.9	9.2865	11	78.3	9.3541	14	0.4%	-1.40 [-8.76, 5.96]	2013
Boxer 2013	67.4	7.3485	24	66.7	7.3485	24	1.4%	0.70 [-3.46, 4.86]	2013
Witham 2014	83	8.3516	31	79	8.0777	29	1.4%	4.00 [-0.16, 8.16]	2014
Strobel 2014	86.5	9.992	39	83.6	9.6	36	1.2%	2.90 [-1.53, 7.33]	2014
Scragg 2014	78.6	6.1033	149	77.7	6.1441	151	12.2%	0.90 [-0.49, 2.29]	2014
Sollid 2014	78.9	7.7782	242	78.5	7.7782	242	12.2%	0.40 [-0.99, 1.79]	2014
Dalbeni 2014	73.5	9.0139	13	73	8.8544	10	0.4%	0.50 [-6.86, 7.86]	2014
Total (95% CI)			**1542**			**1533**	**100.0%**	**0.22 [-0.27, 0.70]**	

Heterogeneity: Tau² = 0.00; Chi² = 16.93, df = 26 (P = 0.91); I² = 0%

Test for overall effect: Z = 0.88 (P = 0.38)