

Mini-Review

Effectiveness of Vitamin D Supplementation for Cardiovascular Health Outcomes

Panagiota Veloudi Graeme Jones James E. Sharman

Menzies Institute for Medical Research, University of Tasmania, Hobart, TAS, Australia

Keywords

Vitamin D supplementation · Cardiovascular health · Randomized controlled trials · Blood pressure · Large artery stiffness

Abstract

There is a plausible physiological theory, supported by many observational studies, that vitamin D supplementation should be effective for improving cardiovascular end points, such as blood pressure (BP), large artery stiffness, atherosclerosis, endothelial function and clinical events. However, results from randomised controlled trials (RCTs) have been inconsistent. In this review, we evaluated the evidence regarding the effectiveness of vitamin D supplementation for cardiovascular surrogate and hard clinical end points. RCTs were assessed in terms of sample size, duration of supplementation, baseline vitamin D level inclusion criteria (i.e., absence of vitamin D deficiency), dosage of vitamin D and population under investigation. Forty-five RCTs were identified. Eight RCTs with BP and 6 RCTs with large artery stiffness as the end points were found to comply with guidelines for the optimal design of clinical trials evaluating nutrient effects. Only 2 of the RCTs with an optimal design were effective in decreasing BP with vitamin D supplementation, although these were of moderate sample size (<150) and very short duration (8 weeks for both), whilst no RCT was effective in reducing large artery stiffness. Similar results were observed for atherosclerotic and endothelial function markers as end points. Only 1 RCT reported cardiovascular events as an end point and found neither increased nor decreased incident cardiovascular events over 7 years of follow-up. In conclusion, results from published RCTs indicate that vitamin D supplementation is ineffective in improving cardiovascular health among various patient populations, including in the presence or absence of vitamin D deficiency.

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Assoc. Prof. James E. Sharman
Menzies Institute for Medical Research, University of Tasmania
Medical Science 1 Building, Liverpool Street
Hobart, TAS 7000 (Australia)
E-Mail James.Sharman@utas.edu.au

Introduction

Vitamin D (VitD), a lipid-soluble vitamin, plays a well-recognised role in musculoskeletal health [1, 2], but evidence also suggests a critical role in blood pressure (BP) regulation and vascular health [3]. In vivo and in vitro studies have suggested a number of pathways by which VitD could directly benefit the vasculature [4–6] in addition to acting as a negative regulator of the renin-angiotensin system to influence BP control [7, 8] and modify large artery stiffness [9]. Observational data during the last decade suggest a relationship of low VitD levels with cardiovascular end points, including coronary artery disease, myocardial infarction (MI), heart failure (HF), stroke and cardiovascular death. Additionally, more than 4 decades of cross-sectional research generally show a consistent inverse association between VitD levels and surrogate cardiovascular markers of BP, large artery stiffness, atherosclerotic burden and endothelial function. Nevertheless, the highest level of evidence, derived from well-designed randomised controlled trials (RCTs), has been inconsistent as to whether VitD exerts cardioprotective effects. In this short narrative review, we sought to summarise the observational data and critique evidence from published RCTs on the effect of VitD supplementation on cardiovascular surrogate and hard clinical end points, with particular consideration of study design (i.e., sample size, duration of supplementation, selection of VitD-deficient subjects, VitD dose and population under investigation).

Summary of Observational Data on the Relationship between Serum VitD and Cardiovascular Outcomes

Cardiovascular Events and Cardiovascular Death

Studies examining whether VitD is associated with cardiovascular events or cardiovascular death are seen in Figure 1. VitD deficiency has been associated with an increased risk of death, HF, MI or stroke in healthy postmenopausal women [10], as well as with an increased risk of sudden cardiac death or fatal or non-fatal stroke, non-fatal MI and death related to other heart diseases among diabetic patients with chronic kidney disease (CKD) [11]. In a small study of patients with acute coronary syndrome, VitD deficiency was also independently associated with in-hospital cardiovascular death [12]. In general population studies, low VitD levels were associated with an increased incidence of coronary artery disease, MI, HF, stroke and all-cause death [13], as well as increased cardiovascular death [14]. Several other studies have demonstrated an increased risk of cardiovascular death associated with low VitD levels among different patient groups including HF outpatients (in a small study) [15], patients with metabolic syndrome and cardiovascular symptoms [16], and patients with chronic obstructive pulmonary disease [17]. Furthermore, data extracted from medical records of 126 men with moderate CKD and VitD deficiency showed that VitD treatment was associated with decreased cardiovascular events [18]. In this study, the treatment group was defined based on an increase in serum VitD levels by 25% from baseline within 6 months, whilst the remaining patients were considered as controls. The risk of cardiovascular death was also lower among haemodialysis patients regularly using VitD supplements in a Japanese hospital (the VitD dose varied according to prescription) [19]. Overall, these data suggest fairly consistently that low VitD levels are associated with an increased risk of cardiovascular events, including death; in addition, the data hint towards the potential for VitD supplementation possibly reversing the adverse cardiovascular effects of low VitD.

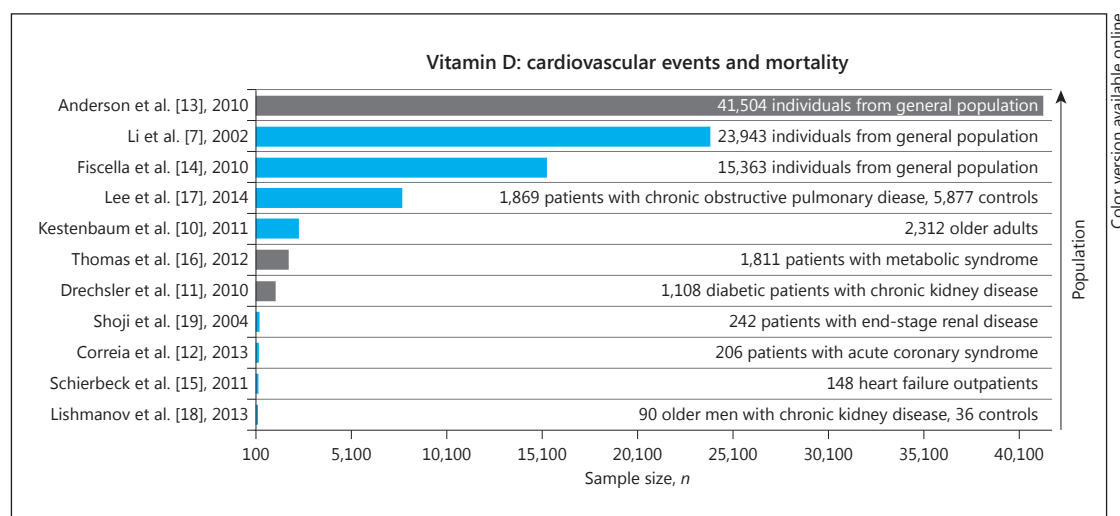


Fig. 1. Longitudinal cohort and case-control studies on the association between vitamin D and incidence of cardiovascular events or cardiovascular mortality according to sample size and population characteristics. Blue bars indicate studies that reported significant associations between vitamin D and cardiovascular end points, and grey bars indicate studies that reported no significant associations. (Colours refer to the online version only.)

BP and Large Artery Stiffness

Brachial BP, large artery stiffness (as measured by carotid-to-femoral pulse wave velocity [cfPWV], an estimate of aortic pulse wave velocity and the current “gold standard” measure of large artery stiffness) [20] and central hemodynamic parameters (such as augmentation index [AIx], a marker of central systolic loading) are independent predictors of cardiovascular risk [21, 22]. Many observational studies have reported an inverse association between low VitD levels and brachial BP in large samples from the general population [23–25], but also among Peruvian adolescents [26], middle-aged individuals [27], people aged >60 years and the elderly [28, 29], pregnant women and women aged 20–80 years [30, 31]. Similarly, the evidence from medium to large observational studies shows strong and independent inverse associations between serum VitD and cfPWV among diverse study populations [32–38]. Other markers of regional arterial stiffness, including increased carotid-radial pulse wave velocity and brachial-ankle pulse wave velocity, have been associated with lower VitD levels among people with type 2 diabetes mellitus (T2DM) [39, 40]. An inverse association between VitD levels and AIx has also been shown in pre-diabetic individuals and cardiac or kidney clinic outpatients [41, 42]. In summary, observational evidence is consistently and strongly supportive of an association between VitD, BP and vascular health.

Markers of Atherosclerotic Burden and Endothelial Function

Strong relationships have also been observed between VitD level, atherosclerotic burden and endothelial function markers. Carotid intima medial thickness (CIMT), a marker of large artery atherosclerosis, known to be predictive of cardiovascular events [43], was found to be inversely associated with low VitD levels among different populations, including apparently healthy, predominantly white older individuals [44], relatively healthy Chinese women [45] and patients with peripheral arterial disease [46]. Additionally, endothelial flow-mediated dilation (FMD; the change in vessel diameter during reactive hyperaemia after cuff release), a marker of nitric oxide-mediated endothelial function, has been shown to be decreased in

the presence of low serum VitD levels in patients with T2DM [47], end-stage renal disease [48] and CKD [49]. Altogether, the above observational evidence points to the need for intervention trials to determine if there is a causative link between low VitD and poor cardiovascular health.

Summary of RCT Data on the Effect of VitD Supplementation on Cardiovascular Diseases Outcomes

Cardiovascular Events and Cardiovascular Death, BP and Large Artery Stiffness

A total of 45 RCTs on the effect of VitD supplementation on cardiovascular surrogate and hard clinical end points were identified through an English language search of PubMed and Google. To our knowledge, only 1 RCT has investigated the effects of VitD supplementation on hard clinical end points, which included incident MI, stroke and death related to coronary heart disease. This study randomised 36,282 postmenopausal women to 200 IU VitD plus calcium carbonate twice daily or placebo for 7 years and found that VitD supplementation did not improve cardiovascular risk [50]. Importantly, this study was criticised for using a low VitD dose and not measuring serum VitD levels [51, 52]. In terms of effects on BP, some RCTs have reported significant improvements in brachial BP after short-term supplementation of VitD among participants encompassing a variety of clinical characteristics, including patients with hypercalcaemia [53] or impaired glucose tolerance [54], patients with primary hyperparathyroidism [55], patients with T2DM [56–58], patients with elevated BP and VitD deficiency [59] and women with VitD deficiency [60]. However, the majority of RCTs have been ineffective in improving brachial BP in a range of populations as shown in Table 1 [61–79]. Indeed, a recent individual-level meta-analysis of RCTs concluded that VitD was ineffective in lowering BP [80].

Organ damage is more closely associated with central BP (cBP) than brachial BP [81] and, whilst individuals could have similar brachial systolic BP levels, central systolic BP may significantly differ [82]. Only 1 study has shown VitD supplementation to be effective in decreasing cBP (Table 1) [83], whereas others have shown no improvement in older individuals with osteoarthritis [77] or among postmenopausal women [61, 62]. VitD supplementation was also ineffective in changing visit-to-visit BP variability [77]. Central arterial stiffness is strongly associated with BP [9], and there is a need for interventions aimed at improving central arterial stiffness independent of BP changes. Virtually all RCTs investigating the effect of VitD supplementation on cPWV reported no improvement [61, 64, 70, 71, 77, 83–85] apart from 1 study in black youths [74]. The results from RCTs on AIx are more contradicting; no improvement was reported in the majority of studies [61, 62, 64, 71, 72, 77, 83]. Alternatively, decreases in AIx were observed among patients with T2DM [66], overweight people with elevated BP [75], people with VitD deficiency [84] and those with prehypertension and VitD deficiency [85]. Conversely, 1 study reported significant increases in AIx in patients with T2DM and hypovitaminosis [63]. No improvements were reported in a small number of RCTs for carotid-radial PWV and brachial-ankle PWV [64, 65, 74, 75]. In summary, the majority of evidence from RCTs is not supportive of VitD treatment for improving BP control or large artery stiffness.

Markers of Atherosclerotic Burden and Endothelial Function

RCTs examining markers related to atherosclerotic burden as measured by CIMT are limited. No improvement in CIMT was reported among postmenopausal women; however, in this trial the supplementation regimen contained both VitD and vitamin K [86]. In terms of brachial FMD, improvements were reported among African Americans [87] and patients with

Table 1. Effect of vitamin D supplementation on cardiovascular outcomes in randomised controlled trials in various populations

Study [ref.], year	Population (group n)	Vitamin D level; inclusion criteria, ng/mL	Effect on brachial BP†	Effect on cBP†	Effect on cfPWV†	Effect on AIx†
Dalan et al. [63], 2016	Individuals with T2DM and hypovitaminosis D (treatment = 33, control = 31)	<30	Null	–	–	Increase
Zaleski et al. [85], 2015	Individuals with pre-hypertension and vitamin D deficiency (low dose = 22, high dose = 19)	≤25*	Null	–	Null	Decrease
Veloudi et al. [77], 2015	Older individuals with osteoarthritis and vitamin D deficiency (intervention = 118, control = 123)	<24*	Null	Null	Null	Null
Pilz et al. [92], 2015	Individuals with hypertension (intervention = 100, control = 100)	<30	Null	–		
McGreevey et al. [84], 2015	Individuals with vitamin D deficiency (low dose = 60, high dose = 50)	<20*	–		Null	Decrease
Gepner et al. [62], 2015	Healthy postmenopausal Native American women (low dose = 49, high dose = 49)	<60	Null	Null	–	Null
Thethi et al. [90], 2015	Individuals with T2DM and stage 3 or 4 CKD (treatment = 30, control = 30)	No restrictions	Null	–	–	–
Arora et al. [94], 2015	Individuals with pre-hypertension or stage 1 hypertension and low vitamin status (low dose = 188, high dose = 175)	≤25*	Null	–	–	–
Witham et al. [95], 2014	Patients aged >70 years with orthostatic hypotension (intervention = 38, control = 37)	<30	Null	–	–	–
Witham et al. [116], 2014	Patients with resistant hypertension (intervention = 31, control = 30)	<30	Null	–	–	–
Scragg et al. [68], 2014	Healthy adults (intervention = 161, control = 161)	No restrictions	Null	–	–	–
Ryu et al. [64], 2014	Individuals with T2DM (intervention = 40, control = 41)	<20*	Null	–	Null	Null
Nasri et al. [58], 2014	Individuals with T2DM (intervention = 30, control = 30)	No restrictions	Decrease		–	–
Mozaffari-Khosravi et al. [59], 2015	Patients with elevated BP and vitamin D deficiency (intervention = 19, control = 20)	<30	Decrease	–	–	–
Martins et al. [75], 2014	Overweight and obese African Americans with elevated BP (intervention = 65, control = 65)	10–25*	–	–	–	Decrease
Dreyer et al. [70], 2014	Patients with CKD (intervention = 20, control = 18)	<16*	Null	–	Null	–
Yiu et al. [65], 2013	Individuals with T2DM (intervention = 50, control = 50)	<30	Null	–	–	–
Witham et al. [96], 2013	Older patients with isolated hypertension (intervention = 80, control = 79)	<30	Null	–	–	–
Witham et al. [73], 2013	Patients with a history of myocardial infarction (intervention = 39, control = 36)	No restrictions	Null	–	–	–
Forman et al. [79], 2013	Black individuals (intervention 1,000 IU/day = 68, intervention 2,000 IU/day = 73, intervention 4,000 IU/day = 70, control = 72)	No restrictions	Decrease‡	–	–	–
Breslavsky et al. [66], 2013	Individuals with T2DM (intervention = 24, control = 23)	No restrictions	Null	–	–	Decrease
Marckmann et al. [71], 2012	CKD patients with hypovitaminosis D (intervention = 25, control = 24)	<20*	Null	–	Null	Null
Stricker et al. [72], 2012	Patients with peripheral arterial disease (intervention = 31, control = 31)	<30	–	–	–	Null
Witham et al. [69], 2012	Stroke patients with well-controlled BP (intervention = 30, control = 28)	<30	Null	–	–	–
Gepner et al. [61], 2012	Postmenopausal women (intervention = 55, control = 54)	<60	Null	Null	Null	Null
Larsen et al. [83], 2012	Individuals with hypertension (intervention = 55, control = 57)	No restrictions	Null	Decrease	Null	Null
Witham et al. [57], 2010	Individuals with T2DM (intervention 100,000 IU = 19, intervention 200,000 IU = 20, control = 22)	<40	Decrease	–	–	–
Jorde et al. [76], 2010	Overweight and obese subjects (intervention 40,000 IU = 150, intervention 10,000 IU = 139, control = 149)	No restrictions	Increase	–	–	–
Dong et al. [74], 2010	Black youth (intervention = 23, control = 21)	No restrictions	Null	–	Decrease	–
Daly et al. [78], 2009	Men aged >50 years (intervention = 73, control = 67)	No restrictions	Null	–	–	–
Zittermann et al. [97], 2009	Healthy overweight subjects with inadequate vitamin D status (intervention = 82, control = 83)	No restrictions	Null	–	–	–
Sugden et al. [56], 2008	Individuals with T2DM and low vitamin D levels (intervention = 17, control = 17)	<20*	Decrease	–	–	–
Margolis et al. [93], 2008	Postmenopausal women (intervention = 15,176, control = 18,106)	No restrictions	Null	–	–	–
Pfeifer et al. [60], 2001	Women with vitamin D deficiency (intervention = 74, control = 74)	<20*	Decrease	–	–	–
Scragg et al. [67], 1995	Healthy adults (intervention = 95, control = 94)	No restrictions	Null	–	–	–

Table 1 (continued)

Study [ref.], year	Population (group <i>n</i>)	Vitamin D level; inclusion criteria, ng/mL	Effect on brachial BP [†]	Effect on cBP [†]	Effect on cfPWV [†]	Effect on AIx [†]
Pan et al. [117], 1993	Elderly individuals (intervention Ca = 14, intervention vitamin D = 14, intervention Ca + vitamin D = 15, control = 15)	No restrictions	Null	–	–	–
Orwoll et al. [98], 1990	Normotensive men (intervention = 35, control = 30)	No restrictions	Null	–	–	–
Lind et al. [118], 1989	Patients with essential hypertension (<i>n</i> = 39, allocation not reported)	No restrictions	Null	–	–	–
Lind et al. [55], 1988	Patients with primary hyperparathyroidism (intervention = 15, control = 16)	No restrictions	Decrease	–	–	–
Lind et al. [54], 1988	Men with impaired glucose tolerance (intervention = 33, control = 32)	No restrictions	Decrease	–	–	–
Lind et al. [53], 1987	Patients with marginal, intermittent hypercalcaemia (intervention = 29, control = 57)	No restrictions	Decrease	–	–	–

AIx, augmentation index; BP, blood pressure; cBP, central blood pressure; cfPWV, carotid-to-femoral pulse wave velocity; CKD, chronic kidney disease; T2DM, type 2 diabetes mellitus. * Vitamin D deficiency (<25 ng/mL). [†] Statistically significant increase or decrease or no change (null) with vitamin D supplementation. [‡] No longer statistically significant after adjustment for BP differences at baseline.

T2DM [56], whilst brachial FMD was improved after 8 weeks in stroke patients, but this did not persist at 16 weeks [69]. No improvements in brachial FMD were observed among patients with coronary artery disease [88], patients with T2DM [57, 65], HIV-infected individuals [89] and postmenopausal women [61, 90]. Lastly, VitD was found to have no effect on the reactive hyperaemia index in patients with T2DM or after MI [63, 73]. Based on current evidence, VitD supplementation appears to be ineffective in improving CIMT or FMD.

Critical Factors to Consider Regarding the Interpretation of RCT Data

Adequate Sample Size

Sample size should be adequate to determine a clinically relevant change from intervention, and this will vary depending on outcomes. With respect to BP, we have calculated that at least 100 participants in each randomisation arm are needed to detect at least 4.5 mm Hg between-group change in brachial BP or cBP [91]. Figure 2 depicts RCTs in relation to their sample size and effectiveness of VitD treatment for cardiovascular end points. Generally, most of the effective trials were of a smaller sample size. Seven RCTs with an apparently appropriate sample size have investigated the effects of VitD on brachial BP, and from these, 6 reported no significant improvement [68, 76, 77, 92–94]. Only 1 trial reported significant BP lowering, and this was in a population of black individuals [79]; importantly though, this effect was no longer significant after correcting for between-group differences in BP at baseline. We recently published the largest RCT investigating changes in cBP, cfPWV and AIx, which found no significant effects of VitD (Fig. 2) [77]. Overall, Figure 2 shows that in the larger RCTs with a sample size >200, VitD has been ineffective in improving cardiovascular surrogate markers.

Adequate Length of Intervention Period

The generalizability of RCT findings must be interpreted in the context of the duration of intervention, given that a short-term RCT may produce results discordant with long-term effects. Although there is no consensus as to the minimum duration of VitD intervention for maximum improvements in BP, interventions of <6 months may not be adequate to modify the structural characteristics of the large arteries (i.e., improving arterial stiffness independent of BP). The majority of the RCTs included in this review had a duration of ≤6 months

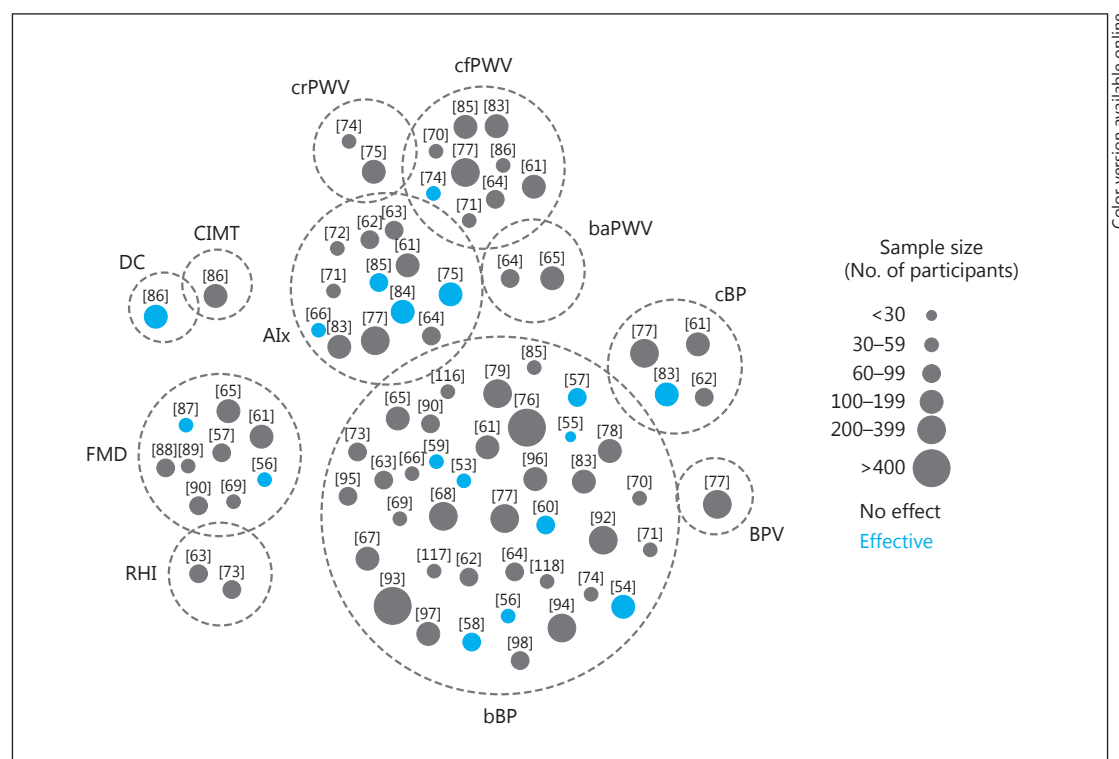


Fig. 2. Randomised controlled trials (RCTs) with vitamin D supplementation as the intervention according to sample size and the outcome in terms of effective or no effect on cardiovascular end points (reported either as primary or secondary outcomes). Each grey dotted circle represents a different cardiovascular end point, and the size of the circle is proportional to the number of RCTs for each end point. Blue circles indicate a significant improvement with vitamin D supplementation (effective RCTs), and grey circles indicate that RCTs had no significant effect on respective end points. Numbers above the circles represent the corresponding RCT reference number. bBP, brachial blood pressure; RHI, reactive hyperaemia index; FMD, flow-mediated dilation; DC, distensibility coefficient of the carotid artery; CIMT, carotid intimal medial thickness; AIX, augmentation index; crPWV, carotid-radial pulse wave velocity; cfPWV, carotid-femoral pulse wave velocity; baPWV, brachial-ankle pulse wave velocity; cBP, central blood pressure; BPV, visit-to-visit blood pressure variability. (Colours refer to the online version only.)

(76%), whilst approximately half of these short-term RCTs had a duration of ≤ 3 months. Figure 3 shows RCTs according to trial duration and effect of estimated monthly dose on brachial BP and cfPWV. Only 10 RCTs examining the effects of treatment on brachial BP had a duration ≥ 12 months. Importantly, none of these longer-term RCTs observed an improvement in brachial BP with VitD supplementation [66, 68, 76–78, 93, 95–98]. Additionally, the only longer-term (1 year) RCT investigating the effects of VitD on cfPWV was ineffectual [77]. Although Breslavsky et al. [66] showed an improvement in AIX after 1 year of supplementation among patients with T2DM, this was a small study ($n = 47$). Lastly, a long-term RCT (3 years) among postmenopausal women, with CIMT as the outcome, found no significant effects [86]. When RCT duration is taken into account, it is clear that intervention durations >6 months have been ineffective in improving cardiovascular outcomes.

Baseline VitD Level

A series of rules regarding optimal design of RCTs examining nutrient effects has recently been introduced [99]. Rule 1 states that individuals with low baseline nutrient levels should

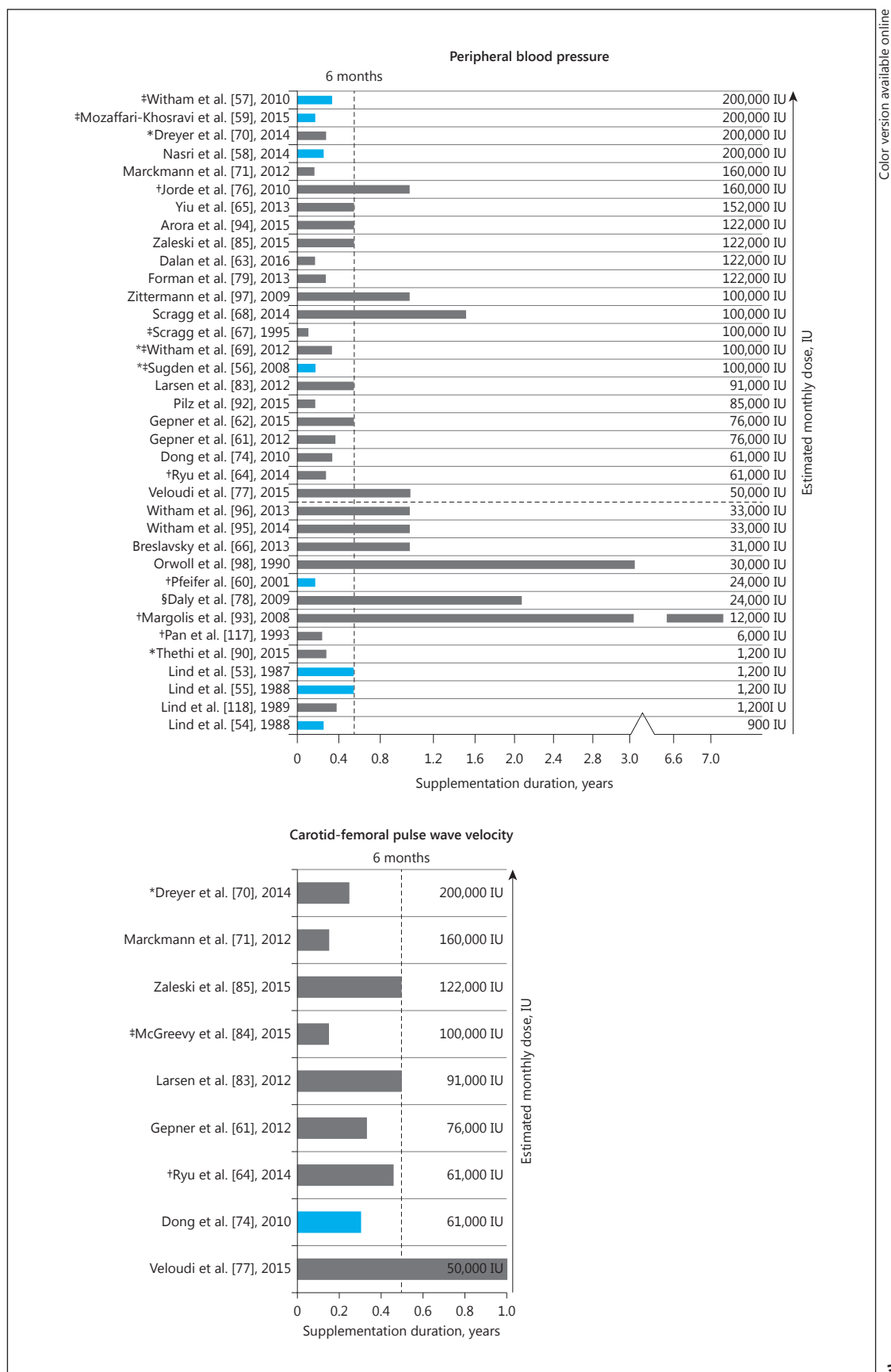
be recruited. This is based on the pharmacological dose-response curve of nutrient intake; if baseline nutrient levels are deficient, then an increase in these levels is expected to produce a clinically meaningful and measurable effect on outcomes, whereas if baseline levels are within optimal ranges, then a further increase will produce no significant effects. Conversely, if baseline levels are high, then intervention could cause adverse effects due to toxicity. Overall, among the 45 RCTs included in this review, only 27% ($n = 12$) included patients with VitD deficiency (defined as <25 ng/ml; according to Mayo Medical Laboratories reference ranges) [100]. The remaining 73% of studies placed no restrictions on baseline serum VitD levels or included a combination of deficient and non-deficient participants (i.e., <30 , <40 or <60 ng/ml), which could confound the results. Among the RCTs that included VitD-deficient participants and investigated the effects on brachial BP ($n = 8$), 6 had no significant effects [64, 70, 71, 77, 85, 94] and 2 (very short-term; ≤ 3 months) trials reported an improvement in brachial BP [56, 60] (Table 1). None of the RCTs appropriately addressing rule 1 found a significant effect on cfPWV [64, 70, 71, 77, 84, 85], carotid-radial PWV [75] or brachial-ankle PWV [64]. With respect to A1x, among the trials that have recruited VitD-deficient participants, 2 short-term RCTs showed an improvement [75, 84], 2 RCTs with longer duration failed to find significant effects [64, 77] and 1 RCT reported a paradoxical increase in A1x among individuals with T2DM [63]. FMD was improved in 1 RCT, 8 weeks after a single oral VitD dose [56], but was not improved in 2 RCTs meeting rule 1 [88, 89]. In brief, VitD interventions that have recruited VitD-deficient participants generally failed to show significant treatment effects.

Adequate VitD Dose

Rules 2 and 3 of Heaney [99] require that the intervention dosage should be sufficient to change nutrient status (from deficient levels at baseline to sufficient levels at follow-up) and that the change in nutrient status must be reported. All ($n = 12$) but 1 RCT [85] that recruited VitD-deficient subjects were effective in increasing average VitD levels above deficiency, and all these RCTs reported the changes in serum VitD levels. In order to change baseline VitD levels from being deficient at baseline to being sufficient at follow-up, the dose of VitD should be adequate to raise serum VitD. Supplementation of 1,000–2,000 IU or lower, taken once or twice weekly (which translates to approximately 8,000–16,000 IU/month), has been shown to be insufficient for raising plasma 25-hydroxyvitamin D levels (the most objective biomarker for VitD nutritional adequacy [101]) higher than those of individuals who are not taking VitD supplements [102]. It is recommended that the VitD dose should be at least 50,000 IU/month in order to successfully raise baseline (deficient) serum VitD levels above 30 ng/mL (75 nmol/L; the lowest sufficient threshold) [103]. Importantly, these recommendations are based on expectations for improving skeletal health outcomes and may not be relevant to cardiovascular related outcomes. Nonetheless, Figure 3 shows clearly that irrespective of the dose, the majority of RCTs failed to improve brachial BP or cfPWV.

Fig. 3. Randomised controlled trials (RCTs) on the effect of vitamin D supplementation according to trial duration and estimated monthly dose on brachial blood pressure and carotid-femoral pulse wave velocity. Blue bars indicate effective RCTs (significant reduction in end points), and grey bars indicate RCTs that had no effect on end points. Black dotted horizontal lines indicate adequate dose to raise serum vitamin D levels above deficiency levels. Black dotted vertical line indicates RCT duration of 6 months. Monthly dose was calculated using the highest dose if there was more than 1 vitamin D supplementation group. IU, international units. * Vitamin D₂ supplementation. † Vitamin D plus calcium. ‡ Single dose. § Vitamin D/calcium-fortified milk. (Colours refer to the online version only.)

(For figure see next page.)



Rule 4 aims to ensure that the effect of a trial is a result of the change in the nutrient from the study intervention rather than a change in the diet. Although all 12 RCTs that met rules 1–3 reported changes in serum VitD levels, they did not state whether other steps were employed in order to monitor and adjust for issues related to adherence, such as variations in individual VitD absorption, changes in diet or other conditions that may have affected the change in serum VitD levels (i.e., physical activity, obesity or amount of exposure to sunlight [104, 105]). Rule 5 considers confounding effects induced by changes in co-nutrient levels known to affect the outcomes (i.e., changes in serum calcium levels are monitored so that results are not biased by confounding effects). Among RCTs meeting rule 1–3, 7 studies monitored calcium and phosphorous levels but did not adjust the final results for the changes in calcium levels. None of the RCTs meeting rules 1–3 adjusted the final outcomes for changes in these factors. Thus, it cannot be excluded that the results from RCTs that met rules 1–3 may have been confounded by significant uncontrolled factors influencing nutrient status.

High-Risk Populations

The interpretation of RCTs may also be complicated by the selection of individuals without a high-risk profile in terms of cardiovascular disease or VitD deficiency. Table 1 shows the effect of VitD interventions on brachial and cBP, cfPWV and AIx in various populations. It can be seen that VitD is ineffective in improving cardiovascular health, irrespective of the population risk profile. Further examination among those RCTs meeting rules 1–3 as per Heaney [99] shows that VitD supplementation is ineffective in VitD-deficient individuals with pre-hypertension, hypertension, T2DM or CKD. Our own work found that VitD supplementation was not beneficial among older individuals with VitD deficiency and osteoarthritis, a condition associated with increased cardiovascular risk [106] and a population enriched with vascular risk factors that should be most amenable to benefit from treatment.

Systematic Reviews and Meta-Analyses

Several systematic reviews concluded that VitD supplementation does not have a significant effect on systolic BP (included RCTs: $n = 46$ [80]; $n = 8$ [107]; $n = 10$ [108]; $n = 16$ [109]), whilst a small meta-analysis of 4 RCTs showed evidence of a statistically significant effect on systolic BP [110], and others showed a statistically significant effect on diastolic BP (included RCTs: $n = 8$ [107]; $n = 15$ [111]; $n = 16$ [112]). At the same time, recent systematic reviews and meta-analyses concluded that VitD has no effect on markers of arterial stiffness (included RCTs: $n = 7$ [113]; $n = 13$ [114]) or markers of endothelial function (included RCTs: $n = 16$ [112]). In alignment with this narrative review, almost all of the published systematic reviews highlight the significant methodological heterogeneity in terms of dose and duration of treatment, which limits the interpretation of the findings and raises the need for a critical appraisal, over and beyond the reported results. Although some systematic reviews have used criteria to establish the quality of study design (i.e., allocation concealment, blinding, baseline comparability of groups, description of dropouts and intention-to-treat analysis), none of them have pooled the data according to the guidelines by Heaney [99]. Nevertheless, sensitivity analyses among the above analyses looking separately at either the effect of dose or duration of supplementation or baseline VitD status did not alter the null-effect findings [80, 112, 114].

Conclusions

In summary, after consideration of the discrepancies in the study design of RCTs (i.e., sample size, duration of supplementation, selection of VitD-deficient subjects, VitD dose and population under investigation), VitD supplementation appears to be ineffective in improving brachial BP, large artery stiffness or central haemodynamics. This conclusion, though, cannot be generalised to other forms of contributions to endogenous VitD. The lack of evidence from large-scale RCTs with a priori primary measures of cardiovascular disease does not exclude the possibility of small but yet clinically meaningful VitD effects. Several large-scale RCTs in general populations ($n > 18,000$; duration of 5 years) are underway and should provide a more definite answer to this question [115]. Despite a lack of large and long-term studies investigating atherosclerotic burden and endothelial function markers, evidence from RCTs also contradicts observational data that support a role of VitD in improving these markers. Thus, this review supports the notion that the inverse associations seen in observational studies between low VitD levels and cardiovascular end points are likely to be epiphenomena rather than true cause-and-effect relationships.

Disclosure Statement

The authors declare that they have no conflicts of interest.

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