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SYSTEMATIC REVIEWS AND META-ANALYSES

Effect of regulated vitamin D increase on vascular markers in patients with chronic kidney disease: A systematic review and meta-analysis of randomized controlled trials

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Meta-analysis

Abstract *Aim:* The effect of increased vitamin D levels on vascular function in patients with chronic kidney disease (CKD) is controversial. This meta-analysis aimed to assess the effect of regulated vitamin D increase on vascular markers in patients with CKD.
Data synthesis: We searched PubMed, Web of Science, Embase and ClinicalTrials.gov from database inception up until July 21, 2023. We included randomized controlled trials assessing the effects of using vitamin D and its analogues on vascular function in patients with CKD. Fixed-effects and random-effects model analyses were performed using weighted mean difference effects for each trial by heterogeneity (I2) assessment. Primary outcomes encompassed blood flow-mediated dilation (FMD)、pulse wave velocity (PWV) and augmentation index (AIx).
Findings: From 1964 records we selected 12 trials, 5 (n = 331) on FMD, 8 (n = 626) on PWV and 4 (n = 393) on AIx. Vitamin D and VDRA supplementation failed to significantly improve FMD (WMD 1.68%; 95% CI -0.18 to 3.53; P = 0.08; I^2 = 88%)、PWV (WMD -0.41 m/s; 95%CI -0.95 to 0.13; P = 0.14; I^2 = 57%)and AIx (WMD -0.53%; 95%CI -1.69 to 0.63; P = 0.37; I^2 = 0%). Subgroup analysis revealed that 2 μg paricalcitol significantly improved FMD (WMD 2.09%; 95%CI 1.28 to 2.90; P < 0.00001); I^2 = 0%), as did cholecalciferol (WMD 5.49%; 95% CI 4.35 to 6.63; P < 0.00001).
Conclusion: Supplementation vitamin D and VDRA are associated with improved vascular function as measured by FMD, but not arterial stiffness as measured by PWV and AIx, tentatively suggesting that regulating the increase of vitamin D could not potentially reduce the incidence of cardiovascular disease.

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1. Introduction

An estimated 8%–16% of the world's population suffers from chronic kidney disease (CKD) [1], which imposes a heavy burden on individuals and the society. Impaired renal function is associated with increased risk of disease in multiple organ systems, especially the cardiovascular system. Cardiovascular complications (for example, coronary disease, stroke, peripheral artery disease, arrhythmias and heart failure) being a major cause of mortality in end-stage renal disease [2]. Therefore, it is very important for CKD patients to reduce the risk of cardiovascular disease (CVD). Pathologic factors in CKD, such as proteinuria [3], disorders of mineral metabolism, inflammation [4], oxidative stress and accumulation of uremic toxins [5] are associated with cardiac decompensation, vascular sclerosis and calcification. Many studies [6,7] have found that the earliest manifestations of cardiovascular disease occur at the level of the microcirculation and are mainly characterised by endothelial dysfunction, whereas endothelial dysfunction due to CKD is extremely complex and involves multiple mechanisms. Vascular endothelial cell stiffness appears to be associated with cortical actin polymerisation, which leads to an impaired ability to release NO, triggering a cascade of events that lead to arterial wall stiffness [8]. The two biggest concerns for CVD risk are the development of endothelial dysfunction in the vasculature, often assessed as brachial artery flow-mediated dilation (FMD) [9,10] and the stiffening of large elastic arteries, often measured in terms of pulse wave velocity (PWV) and augmentation index (AIx) [11]. Non-invasive indices of arterial stiffness and endothelial function predict cardiovascular disease and major adverse cardiac events [12,13] and are independent predictors of future cardiovascular events and mortality [14,15].

Vitamin D is a steroid hormone whose complex effects on the immune and cardiovascular systems remain poorly understood [16]. Many epidemiological observational studies have reported that vitamin D deficiency is associated with an increased risk of cardiovascular disease [17,18]. Animal studies [19] have shown that calcitriol and related analogues including paricalcitol reduce the frequency of heart failure. Observational studies [20,21] have long demonstrated that calcitriol and vitamin D receptor activators (VDRA) have reduced the risk of death from cardiovascular causes in dialysis populations. Li et al. [22] conducted a meta-analysis and showed that calcitriol/VDRA treatment reduced cardiovascular events compared to placebo or no treatment, but randomized controlled trials have failed to conclude [23,24].

Although Vitamin D therapy is considered essential in CKD treatment, the KDIGO clinical practice guidelines [25] pointed out that recent randomized controlled trials and meta-analyses of patients with CKD have not shown that vitamin D analog supplementation improves clinically relevant outcomes. In contrast, a study by Nihil Chitalia et al. showed that increasing vitamin D levels improved endothelial vasomotor and secretory function in patients with CKD without significant adverse effects on arterial stiffness [26]. This meta-analysis was conducted to dispel the controversy surrounding the effect of regulated vitamin D increase on vascular function in patients with CKD.

2. Method

This systematic review and meta-analysis adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) [27] 2020 guidelines (Supplementary Table 1). The study protocol was registered with the International Prospective Register of Systematic Reviews Database (PROSPERO) under the registration number CRD42022323761.

2.1. Inclusion and exclusion criteria

Studies meeting the following criteria were included: 1. The participants were patients with CKD (defined as an abnormality in the structure or function of the kidneys, present for >3 months with health implications [28]) of stage1∼4; 2. The study was designed as a randomized controlled trial or clinical trial; 3. The intervention evaluated was vitamin D or VDRA (defined as vitamin D3 and its derivatives, it has a high affinity for the vitamin D receptor and is significant in regulating calcium and phosphorus metabolism, modulating immunity, inhibiting tumour cell proliferation, inducing tumour cell differentiation and promoting tumour cell apoptosis) supplementation compared with placebo; and 4. Primary outcomes reported included the vascular markers FMD, PWV, and AIx.

Studies evaluating combination therapy with vitamin D or VDRA and a calcimimetic were excluded.

2.2. Data sources and searches

Two independent reviewers conducted a thorough screening of all records identified in the initial search. The screening process involved evaluating the relevance of the records based on their titles, abstracts, and full texts. Conflicts between the two reviewers were resolved by discussion among all the authors. We searched PubMed, Web of Science, Embase and ClinicalTrials.gov from database inception up until July 21, 2023. The search strategy used a combination of MeSH subject terms and free words. The complete search strategy is available in Supplementary Table 2.

Two independent researchers eliminated duplicates from all studies that met the inclusion and exclusion criteria and then reviewed the titles of the remaining studies. Subsequently, irrelevant articles were further excluded based on the abstract review. The remaining studies underwent full-text assessment to determine their eligibility for inclusion. Any discrepancies were resolved through consensus. The same authors conducted the full-text screening process to ensure the final selection of studies.

2.3. Data extraction

Two independent researchers summarised the data extracted from the study into tables. The extracted data

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were as follows: (1) name of the first author; (2) year of publication; (3) CKD stage of the patients; (4) intervention; (5) study sample size; (6) duration of follow-up; (7) primary outcomes including FMD, PWV, and AIx; (8) demographic characteristics of the patients and clinical profile. Any discrepancies and disagreements about data extraction were arbitrarily resolved by discussion and inspection of the original data by a third researcher.

2.4. Quality assessment

Two evaluators independently used the Cochrane Manual of Reviews for quality assessment, including quality of randomization, allocation concealment, blinding (single-blind, double-blind, triple-blind), attrition, selective reporting and other biases. Using RevMan Manager (version 5.4.1, The Cochrane Collaboration), the included studies were divided into three quality grades according to the above evaluation criteria: green (low bias), red (high bias), and yellow (unclear).

2.5. Data synthesis and analysis

Two authors independently performed a meta-analysis using RevMan Manager 5.4.1. Measurement data were expressed as means±standard deviations, and the weighted mean difference (WMD) was used as an effect analysis statistic. Each effect size was expressed as a 95% confidence interval (CI).

We used the WMD between the vitamin D or VDRA-treated intervention group and the placebo-treated control group to assess the effect of regulated vitamin D increase on the vascular markers FMD, PWV, and AIX. Data provided in the study were converted to means ± standard deviations when they were the median and upper and lower poles or the mean and 95% CI.

To assess heterogeneity, we calculated the I2, and where I2 $<$ 50%, the heterogeneity was considered to be small; 50%–75%, moderate and $>$75%, significant. We used a random-effects model where the heterogeneity was high, or a fixed-effects model where the heterogeneity was low. The mean difference of all included studies was assessed and studies were weighted using an inverse variance weighting technique. In addition, subgroup analyses were performed to assess potential sources of heterogeneity. Publication bias was assessed quantitatively by calculation using Egger's test. A P-value that was less than 0.05 represented the possibility of small-study effects.

3. Results

3.1. Literature selection

A total of 1964 articles were found, and EndNote 20 (Clarivate, Philadelphia, PA, USA) was used to filter out 378 duplicate articles, leaving 1586 articles. After the initial screening, 103 papers remained. After the full texts of these 103 articles were read, 12 studies [29–40] were finally included, comprising a total of 811 participants (Table 1). Among them, the experimental groups in the studies by Alborzi et al. [29] and Lundwall et al. [33] received paricalcitol at doses of 1 μg and 2 μg. We included the two different dose groups in the forest plot as the results of two studies. In the study by Levin et al. [36], calcidiol and calcitriol were administered to the intervention group, and we also included these two different types of vitamin D or VDRA as the results of two studies into the forest plot. The specific retrieval process is shown in Fig. 1.

3.2. Quality assessment and risk of bias

Quality assessment showed that all 12 studies [29–40] had a low risk of bias in both randomization method and selection reporting. Five studies [33,36,38–40] did not report specific allocation concealment. Sinha et a [39] had an unclear risk of bias in both participant and investigator blinding. Seven studies [30,31,35,36,38–40] had an unclear risk of bias in the blinding of outcome assessors. Thethi et al. [34] had a high risk of bias in the completeness of the data results. In addition, among other biases, all 12 studies [29–40] had unclear risk of bias.

Notably, 27 participants in the paricalcitol group and 28 participants in the placebo group in the study by Thethi et al. [34] completed the study, but the paired FMD analysis of the two time points was limited to 23 participants in each group. Of the 25 participants in the placebo group, only 19 had analyzable PWV data and 22 had analyzable AIx data. In the study by Marckmann et al. [30] we selected only data from non-dialysis patients for analysis. Four studies [29,31,33,38] explicitly used an intention-to-treat protocol, and in the remaining studies this was not explicitly stated. Supplementary Fig. 1 show the detailed assessment of study quality and risk of bias.

Results from Egger's test (FMD: P = 0.455; PWV: P = 0.510; AIx: P = 0.593; Ca: P = 0.902; P: P = 0.727; PTH: P = 0.126; FGF-23: P = 0.271) showed no significant publication bias.

3.3. Study and participant characteristics

The included studies were randomized controlled trials. Nine of the studies [30–36,40] had participants with CKD stages 3–4, two had participants with CKD stages 1–3, and only one study [29] did not differentiate between CKD stages. The 12 trials ranged in size from 15 to 130 participants, and all trial groups were treated with oral vitamin D or VDRA, with follow-up ranging from one to twelve months. Table 1 shows the general characteristics of the included studies. Table 2 shows the mean general characteristics of the participants and the study results.

3.4. Brachial artery-mediated flow dilation, PWV, and AIx results

A total of five studies measuring FMD were included in this meta-analysis [29,32–35] comprising a total of 311 participants. The forest plot of the random effects model analysis shown in Fig. 2a indicates that vitamin D

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Table 1 Baseline characteristics of participants and treatment protocols in included studies.

Author (Reference)	Baseline kidney disease	Intervention		Duration of follow-up	Primary outcome	No. of participants (Intervention/ Control)	ITT
		Treatment group (Vitamin D or VDRA)	Control group				
Alborzi 2008	CKD[a] 1-3	Paricalcitol (1 or 2 μg)	Placebo	1 month	FMD[b]	8/8/8	✓
Marckmann2012	CKD	Cholecalciferol (40 000 IU weekly)	Placebo	8 weeks	PWV[c]、AIx[d]	26/26	
Larsen 2013	CKD 3–4、non-diabetic	paricalcitol (2 μg/day)	Placebo	6 weeks	PWV、AIx	13/13	
Dreyer 2014	CKD 3–4、non-diabetic	Ergocalciferol (50 000 IU weekly for 1 month and then 5000 IU monthly for 5 months)	Placebo	6 month	PWV	14/15	✓
Zoccali 2014	CKD 3–4、non-diabetic	Paricalcitol (2 μg daily)	Placebo	12 weeks	FMD	44/44	
Lundwall 2015	CKD 3–4、non-diabetic	Paricalcitol (1 or 2 μg)	Placebo	3 month	FMD	12/12/12	✓
Thethi 2015	CKD 3–4、T2DM	Paricalcitol (1 mcg daily)	Placebo	3 month	FMD	23/23	
Kumar 2017	CKD 3–4、non-diabetic	Cholecalciferol (300 000 IU at baseline and 8 weeks)	Placebo	16 weeks	FMD、PWV	58/59	
Levin 2017	CKD 3b-4	Calcitriol (0.5 μg thrice weekly) Calcifediol (5000 IU thrice weekly)	Placebo	6 month	PWV	28/29/30	
Das 2021	CKD 3、T2DM	Cholecalciferol (60 000 IU weekly for 8 weeks)	Placebo	8 weeks	PWV、AIx	42/44	
Karalliedde 2022	CKD 3、T2DM	Calcitriol (0.25 mcg daily)	Placebo	48 weeks	PWV、AIx	64/63	
Sinha 2022	CKD 1-3a、non-diabetic	Cholecalciferol (100 000 IU every month for 3 months)	Placebo	12 weeks	PWV、AIx	65/65	

ITT: intention-to-treat.
[a] Chronic kidney disease.
[b] Flow-mediated dilation.
[c] pulse wave velocity.
[d] augmentation index.

treatment did not significantly improve FMD (WMD 1.68%; 95% CI -0.18 to 3.53; P = 0.08; I2 = 88%). Because of significant heterogeneity, we performed a subgroup analysis. The results showed that paricalcitol 2 μg (WMD 2.09%; 95%CI 1.28 to 2.90; P < 0.00001); I2 = 0%) and cholecalciferol (WMD 5.49%; 95% CI 4.35 to 6.63; P < 0.00001) significantly improved FMD. However, paricalcitol 1 μg failed to significantly improve FMD (WMD -0.22%; 95%CI -1.34 to 0.89; P = 0.70; I2 = 0%). Eight studies [30,31,35–40] with a total of 626 participants evaluated PWV. As shown in Fig. 2b, a random-effects model analysis revealed that compared to placebo, vitamin D and VDRA treatment did not significantly reduced PWV (WMD -0.41 m/s; 95%CI -0.95 to 0.13; P = 0.14; I2 = 57%). Five studies [30,37–40] totaling 393 participants that evaluated AIx reported no significant effect (WMD -0.53%; 95%CI -1.69 to 0.63; P = 0.37; I2 = 0%) of vitamin D on AIx in Fig. 2c.

To explore the effects of vitamin D and VDRA on vascular markers in diabetic and non-diabetic patients with CKD, we screened the included literature, and nine of them were ultimately further analyzed. As shown in Fig. 3a, 3b and 3c, we found that vitamin D and VDRA did not improve vascular markers in diabetic (FMD: WMD -0.30%; 95%CI -4.12 to 3.52; P = 0.88 PWV: WMD -0.25 m/s; 95%CI -1.02 to 0.52; P = 0.53; I2 = 0% AIx: WMD -0.81%; 95%CI 0.02 to 4.72; P = 0.05; I2 = 94%) and non-diabetic patients with CKD (FMD: WMD 2.37%; 95%CI -4.12 to 3.52; P = 0.88 PWV: WMD -0.41 m/s; 95%CI -1.13 to 0.32; P = 0.28; I2 = 77% AIx: WMD 0.76%; 95%CI -1.86 to 3.39; P = 0.57; I2 = 0%), and there was a large heterogeneity among studies.

3.5. Ca (mg/dL), P (mg/dL), PTH (pg/mL) and FGF-23 (pg/mL) results

Our results showed that vitamin D and VDRA supplementation significantly increased serum calcium (WMD 0.22 mg/dl; 95% CI 0.1 to 0.33; P = 0.0002; I2 = 74%) (Fig. 4a) and serum FGF-23 (WMD 9.41 pg/ml; 95% CI 5.71 to 13.11, P < 0.00001; I2 = 99%) (Fig. 4d) and decreased serum PTH (WMD -0.51 pg/ml; 95% CI -0.69 to −0.34, P < 0.00001; I2 = 90%) (Fig. 4c), but did not reduce serum phosphorus (WMD 0.07 mg/dl; 95% CI -0.02 to 0.15; P = 0.13; I2 = 33%) (Fig. 4b).

4. Discussion

We conducted a comprehensive search of randomized controlled trials evaluating the effect of vitamin D and VDRA on markers of vascular function in patients with CKD. Our meta-analysis included 12 studies comprising 820 participants and found that vitamin D and VDRA improved endothelial function as measured by FMD, but did not improve arterial stiffness as measured by PWV and AIx. As stated in the introduction, there is currently a lack of hard indicators to assess cardiovascular risk, and surrogate indicators of cardiovascular risk such as FMD, PWV and AIx are well used.

Because of the large heterogeneity in studies evaluating FMD, we chose a random-effects model and performed a subgroup analysis. No heterogeneity was observed in subgroups according to vitamin D or VDRA type and dose. We infer that the heterogeneity largely stemmed from the

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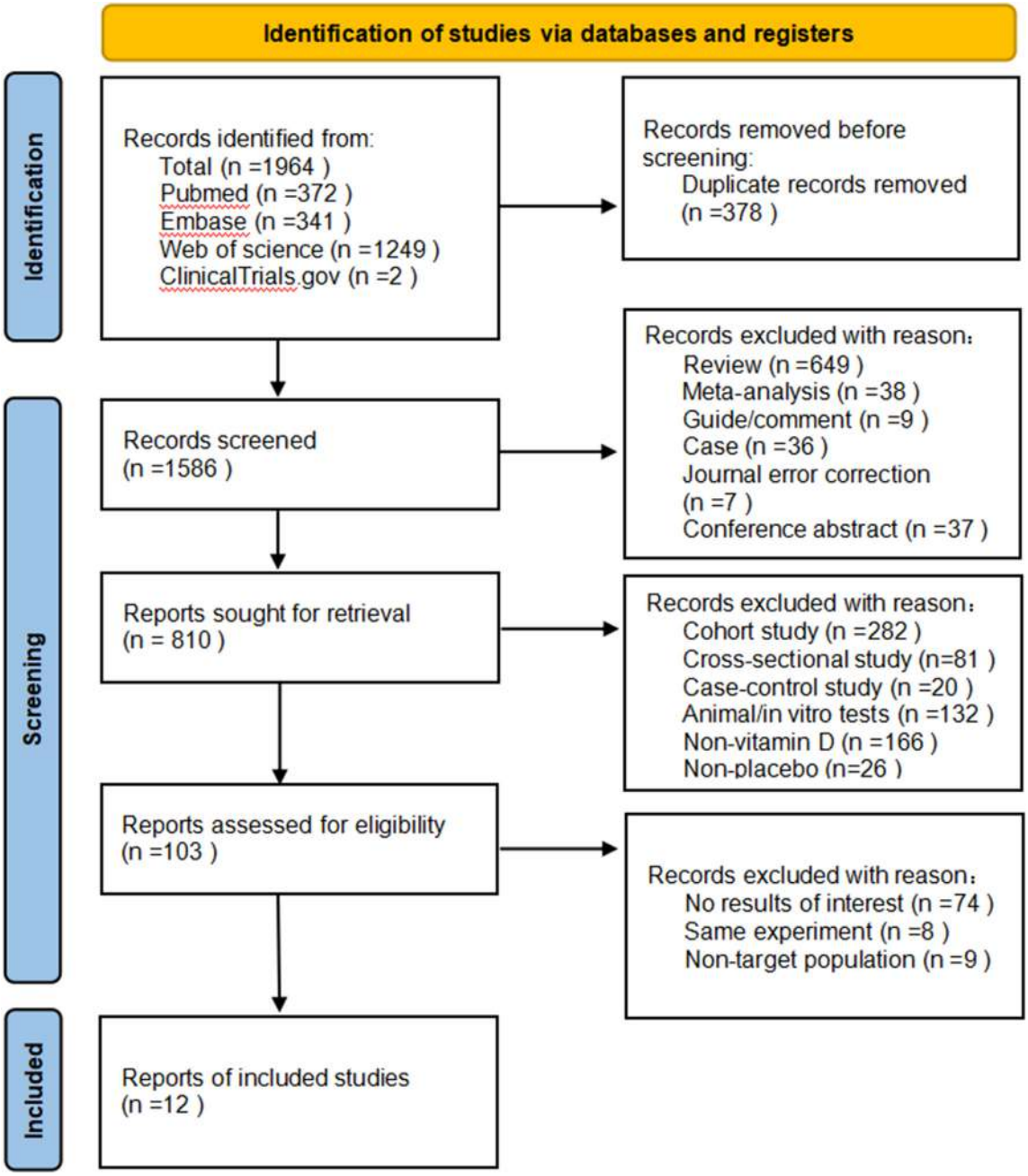

Figure 1 Retrieval flowchart.

different dosages of VDRA administered. Our study showed that supplementation with 2 μg paricalcitol and cholecalciferol significantly improved FMD, while the 1 μg paricalcitol group failed to show improvement. Increased oxidative stress in CKD inhibits NO synthesis, which reduces NO bioavailability causing endothelial dysfunction and ultimately cardiovascular complications. FMD is a measure of the ability of endothelial cells to produce nitric oxide [41]. A 1% increase in FMD is associated with a reduction in cardiovascular events by 8%–13% [42,43]. Vitamin D has anti-inflammatory activity and modulates NO bioavailability by mediating endothelial NO synthase (eNOS) activity and influencing antioxidant enzyme activity to increase antioxidant capacity [44]. Some in vitro studies [45] have shown that administration of high concentrations of paricalcitol after H2O2-induced cellular injury enhances antioxidant capacity and then increases cell viability. Wu-Wong JR et al. [46] and Marc Vila Cuenca et al. [47] also found that paricalcitol improved endothelial function in 5/6 NX rats or vitro cells with CKD in a dose-dependent manner. It is not known whether all vitamin D analogues exhibit similar effects on endothelial function, but early in vitro studies have demonstrated that 1,25 hydroxyvitamin D reduces hydrogen peroxide-induced

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Table 2 Mean baseline participant characteristics and outcomes of included studies.

Author (Reference)	Groups	No.	Male (%)	Age (years)	Systolic BP[d] (mmHg)	Diastolic BP[d] (mmHg)	FMD[a] (%)	PWV[b] (m/s)	Alx[c] (%)	25 (OH) D (nmol/l)	Ca (mg/dl)	P (mg/dl)	PTH (pg/mL)	FGF-23 (pg/mL)
Alborzi 2008	treatment	8	6 (75%)	72.6 ± 9.1	121.5 ± 9.15	64.2 ± 3.23	5.8 ± 1.55	/	/	36.9 ± 17.7	9.5 ± 0.2	3.2 ± 0.6	/	/
	treatment	8	6 (75%)	67.5 ± 9.1	124 ± 12.86	65.5 ± 6.40	6.2 ± 2.21	/	/	28.7 ± 17.7	9.5 ± 0.3	3.3 ± 0.6	/	/
	control	8	8 (100%)	68.4 ± 12.4	130.0 ± 8.13	74.4 ± 8.49	5.9 ± 1.79	/	/	35.2 ± 18.7	9.3 ± 0.4	3.4 ± 0.7	/	/
Marckmann2012	treatment	13	/	70.33 ± 12.55	139 ± 25.88	72.67 ± 9.41	/	11.97 ± 5.27	25 ± 13.78	39.3 ± 24.2	9.08 ± 0.52	3.38 ± 0.81	89.91 ± 87.74	76.33 ± 93.85
	control	11	/	67.67 ± 13.33	139 ± 29.80	74.67 ± 12.55	/	9.4 ± 5.18	25.67 ± 6.25	28.6 ± 13.6	9.16 ± 0.56	3.41 ± 0.74	129.91 ± 113.68	132.33 ± 194.25
Larsen 2013	total	13	19 (73%)	61 ± 9	136 ± 13	83 ± 9	/	/	/	56 ± 21	4.88 ± 0.2	3.69 ± 0.84	/	/
	treatment	13	/	/	/	/	/	/	/	/	/	/	/	/
	control	14	/	/	/	/	/	/	/	/	/	/	/	/
Dreyer 2014	treatment	141	/	45.8 ± 10.0	114 ± 10	70 ± 8	/	8.5 ± 1.1	/	< 39.94	8.8 ± 0.8	3.8 ± 0.6	102.8 ± 76.4	/
	control	5	/	48.8 ± 12.2	119 ± 10	71 ± 7	/	8.5 ± 1.5	/	< 39.94	8.8 ± 0.8	3.5 ± 0.6	102.8 ± 76.4	/
Zoccali 2014	treatment	44	22 (50%)	63 ± 11	123 ± 16	73 ± 9	3.6 ± 2.9	/	/	33 ± 16	9 ± 0.48	3.72 ± 0.59	102 ± 48.15	64.7 ± 21.11
	control	44	31 (70%)	62 ± 12	129 ± 21	73 ± 11	3.6 ± 2.9	/	/	38 ± 16	8.84 ± 0.4	3.81 ± 0.50	102 ± 51.11	78 ± 36.59
Lundwall 2015	Treatment	12	11 (92%)	66.1 ± 7.9	147 ± 21.1	/	/	/	/	71.7 ± 34.2	9.04 ± 0.32	3.41 ± 0.62	68.87 ± 33.96	/
	treatment	12	8 (67%)	70.8 ± 10.0	130 ± 14.7	/	/	/	/	69.3 ± 22.4	9.12 ± 0.28	3.41 ± 0.62	66.04 ± 24.53	/
	control	12	9 (75%)	59.1 ± 11.6	134 ± 12.8	/	/	/	/	64.6 ± 27.9	9.04 ± 0.28	3.10 ± 0.62	87.74 ± 33.02	/
Thethi 2015	treatment	23	18 (78%)	63 ± 4.74	136.75 ± 20.88	75.75 ± 11.43	3.65 ± 7.26	/	/	/	/	/	70.25 ± 32.55	/
	control	23	19 (83%)	61 ± 5.01	135.25 ± 17.28	75.75 ± 13.77	−1±13.32	/	/	/	/	/	96.75 ± 52.94	/
Kumar 2017	treatment	58	41 (70.7%)	43.17 ± 11.79	128.48 ± 14.43	83.38 ± 10.09	7.65 ± 2.25	7.98 ± 1.63	/	33.4 ± 11	9.01 ± 0.73	3.65 ± 0.91	139 ± 94.82	57.88 ± 20.46
	control	59	40 (67.8%)	45.20 ± 11.61	127.88 ± 15.67	82.33 ± 10.21	7.85 ± 2.35	7.98 ± 1.74	/	33 ± 11.9	9.09 ± 0.94	4.03 ± 1.39	146 ± 107.41	57.66 ± 32.9
Levin 2017	Treatment	28	/	66.9 ± 11.7	134.9 ± 12.5	70.4 ± 9.7	11.6 ± 3.8	12.2 ± 3.6	25.4 ± 8.8	26.6 ± 10.7	9.3 ± 0.6	3.5 ± 0.6	84 ± 70.52	89.2 ± 57.11
	treatment	29	/	65.9 ± 15.3	140.0 ± 20.3	72.1 ± 12.5	12.1 ± 4.2	12.4 ± 4.4	23.7 ± 11.6	25.2 ± 9.3	9.2 ± 0.5	3.5 ± 0.7	90.1 ± 69.48	101.6 ± 69.56
	control	30	/	64.5 ± 12.2	140.5 ± 17.2	74.2 ± 12.3	10.7 ± 3.7	10.6 ± 3.6	24.0 ± 11.0	29.4 ± 12.7	9.3 ± 0.4	3.5 ± 0.7	150 ± 116	142.3 ± 152
Das 2021	treatment	42	/	54.18 ± 8.10	135.84 ± 21.29	75.71 ± 9.60	/	17.35 ± 9.10	25.76 ± 8.24	38.3 ± 8	22.1 ± 1.5	3.84 ± 0.75	/	/
	control	44	/	54.68 ± 7.08	133.38 ± 19.40	76.73 ± 8.34	/	16.92 ± 2.81	25.46 ± 6.52	39.9 ± 7.1	22.4 ± 1.5	3.79 ± 0.64	/	/
Karalliedde 2022	treatment	63	41 (65.1%)	67 ± 6.67	149.72 ± 21.9	77.3 ± 11	/	11.8 ± 2.5	23.4 ± 9.1	42.4 ± 18.37	9.44 ± 0.4	3.38 ± 0.43	91.3 ± 47.4	81.1 ± 33.8
	control	64	48 (75.0%)	67 ± 6.81	143.1 ± 17	76 ± 11	/	10.9 ± 2.5	21.7 ± 7.8	39.9 ± 16.07	9.36 ± 0.4	3.38 ± 0.56	81.9 ± 37.3	82.6 ± 38.2
Sinha 2022	treatment	65	24 (37%)	50.4 ± 10.1	125.4 ± 16.1	81.1 ± 11.4	/	9.1 ± 2.4	28.1 ± 11.2	42.43 ± 12.98	9.35 ± 0.3	/	43.0 ± 20	/
	control	65	27 (42%)	49.5 ± 8.8	128.5 ± 15.2	84.5 ± 10.5	/	9.1 ± 1.8	31.0 ± 12	41.18 ± 12.48	9.30 ± 0.4	/	50 ± 34	/

ITT: intention-to-treat.
[a] Chronic kidney disease.
[b] Flow-mediated dilation.
[c] pulse wave velocity.
[d] augmentation index.

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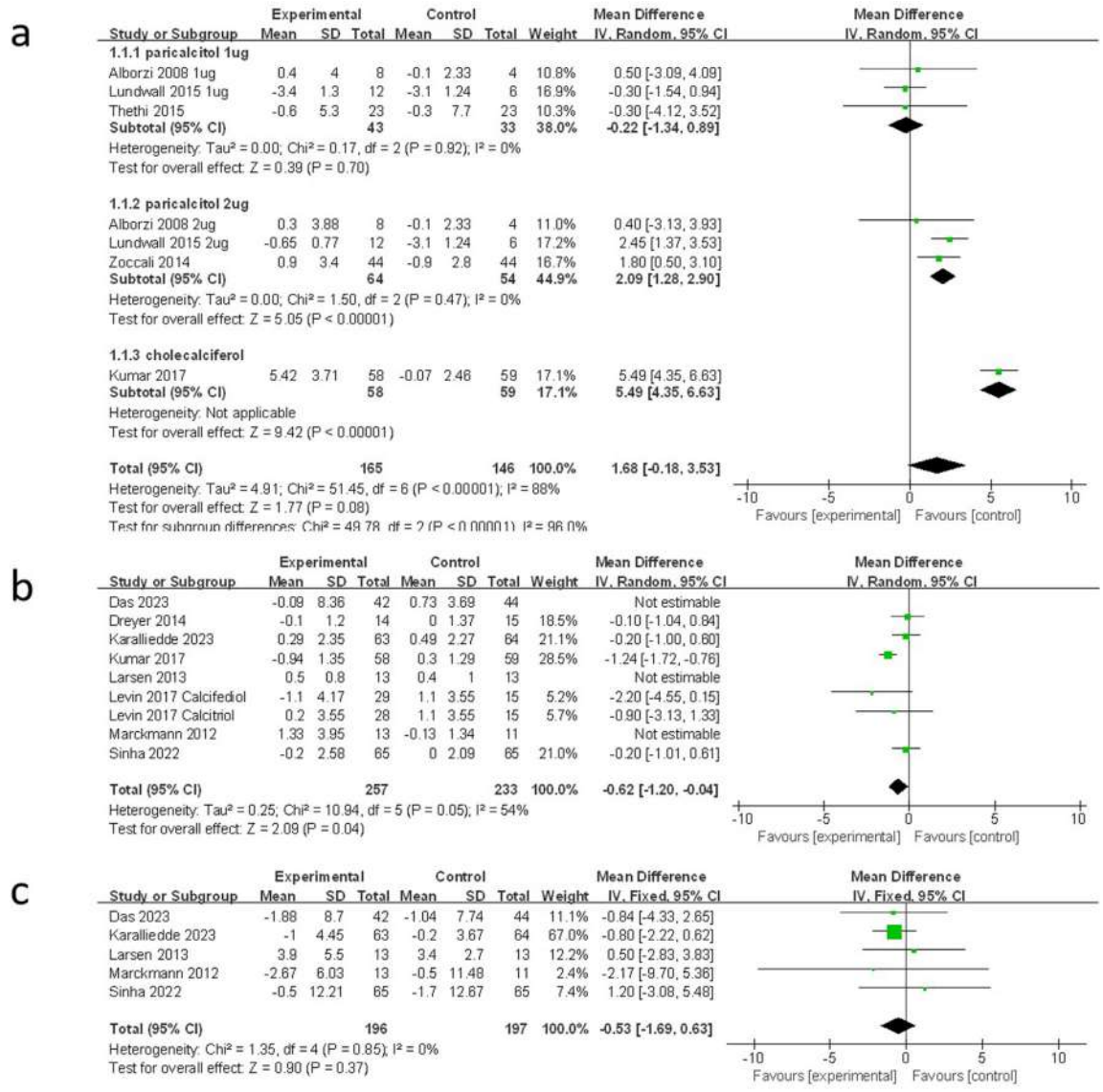

Figure 2 a. Forest plots of blood flow-mediated dilation in patients with chronic kidney disease. b. Forest plots of pulse wave velocity in patients with chronic kidney disease. c. Forest plots of augmentation index in patients with chronic kidney disease.

oxidative stress and apoptosis in endothelial cells in a dose-dependent manner [48], as well as improves the number, migration, and proliferative activity of endothelial progenitor cells in patients with systemic lupus erythematosus [49].

We used a random-effects model to assess PWV and a fixed-effects model analysis to assess AIx, and our results showed that vitamin D and VDRA did not improve both. However, this is inconsistent with the findings of Dou D et al. [50]. In contrast, we included a larger number of study results and a larger number of patients with CKD, so the results are also relatively more reliable.

The high heterogeneity of results in our study may be due to the type [51] and dose [52] of vitamin D, baseline concentrations [53], duration of the intervention, study power, and possible confounders including sunlight exposure, diet, and medications. Unfortunately, we performed relevant subgroup analyses but were still unable to identify the source of heterogeneity. PWV is the gold standard for measuring arterial stiffness and independently predicts cardiovascular outcomes or all-cause and cardiovascular mortality in patients with diabetes, hypertension, the general adult population, and end-stage renal disease [54–56]. For each 1 m/s increase in PWV in patients with CKD, the combined estimated relative risk for all-cause mortality is 1.25 (95% CI 1.17–1.34) [57]. Although PWV is a gravimetric measure of arterial stiffness, it is susceptible to age and blood pressure [58]. Moreover, different tests are measured in different vascular beds, areas with different characteristics, different determinants of stiffness and different atherosclerotic influences [59], so methodological heterogeneity is inevitable. This article is the first meta-analysis to use AIx to assess arterial stiffness in patients with CKD, but the results show that vitamin D supplementation has no positive effect on AIx. However, in this case, the results may have

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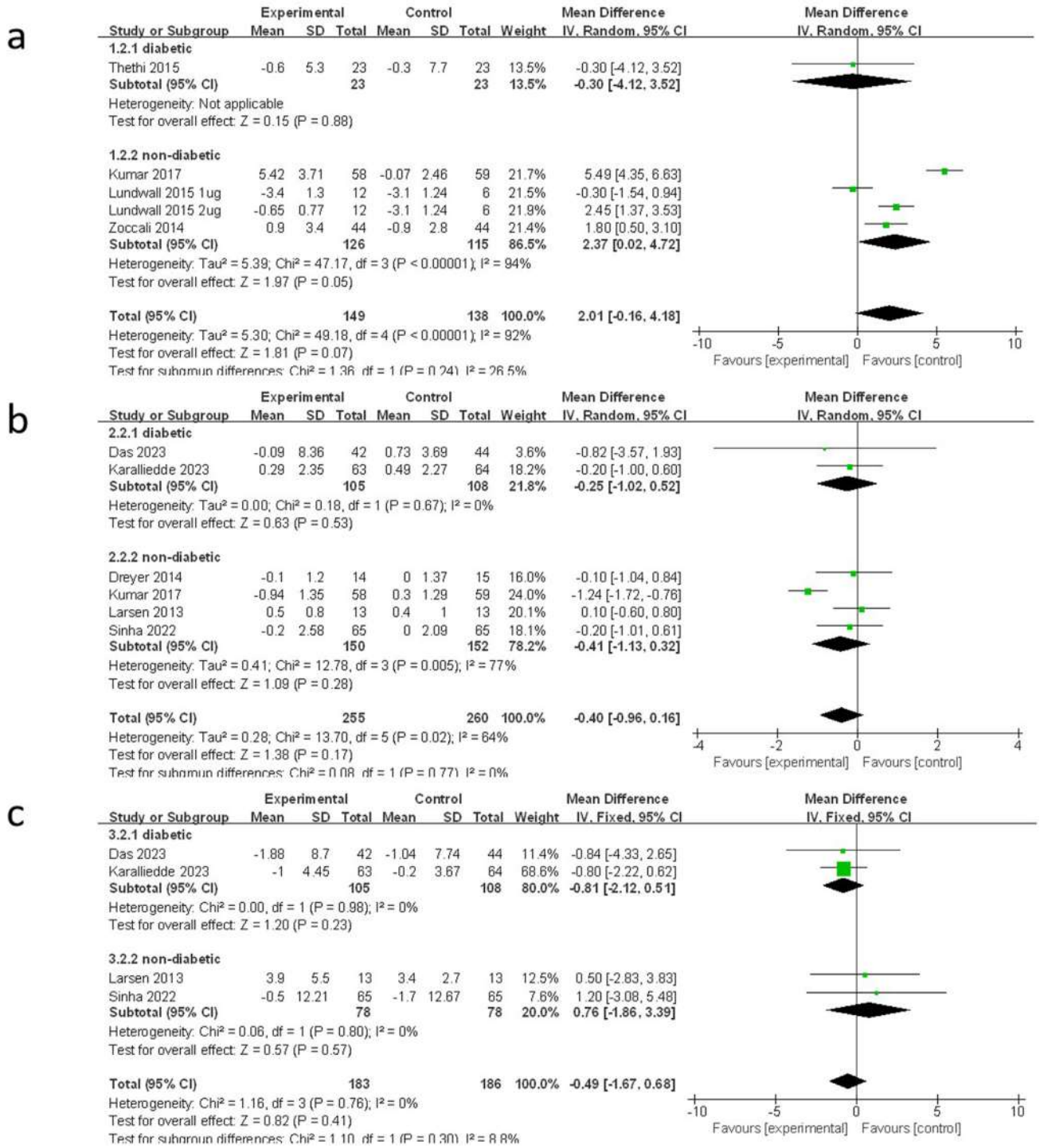

Figure 3 a. Forest plots of blood flow-mediated dilation in diabetic and non-diabetic patients with CKD. b. Forest plots of pulse wave velocity in diabetic and non-diabetic patients with CKD. c. Forest plots of augmentation index in diabetic and non-diabetic patients with CKD.

been masked by the small sample size. AIx is more sensitive in assessing arterial aging in young adults and may underestimate arterial stiffness and cardiovascular risk in older adults [60]. Patients with chronic kidney disease are generally older, and AIx loses its sensitivity to a certain extent.

Our meta-analysis specifically performed subgroup analyses of diabetes and showed no significant effect of vitamin D and VDRA on vascular markers in both diabetic and non-diabetic patients. Diabetes is a significant risk factor for cardiovascular disease, and the resulting metabolic disturbances double the risk of coronary heart disease, ischaemic stroke and vascular death [61]. High levels of glucose lead to increased oxidative stress and inflammation, which can lead to endothelial dysfunction and atherosclerosis [62]. Vitamin D supplementation has been

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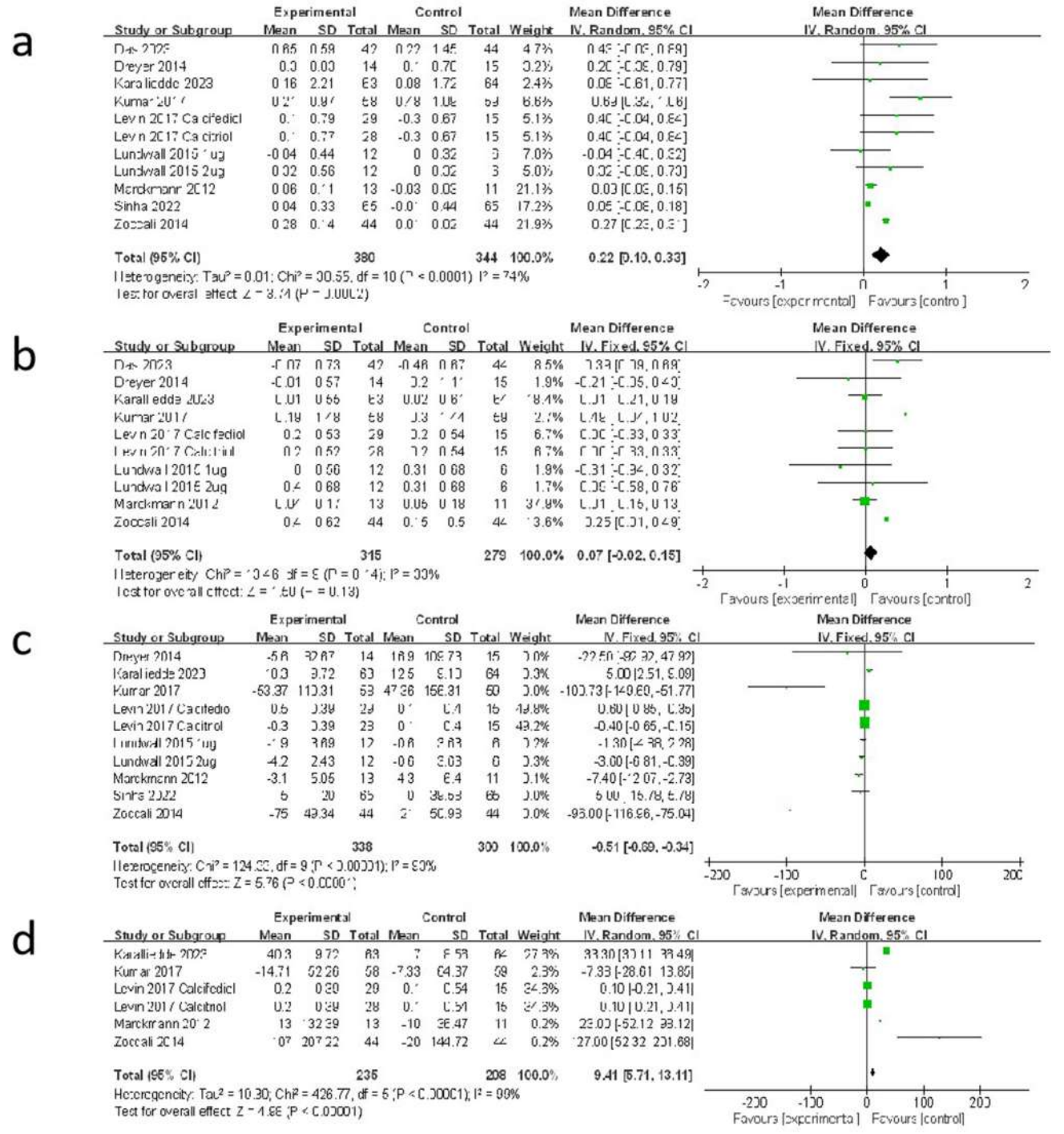

Figure 4 a. Serum calcium in patients with chronic kidney disease. b. Serum phosphorus in patients with chronic kidney disease.c. Serum PTH in patients with chronic kidney disease. d. Serum FGF-23 in patients with chronic kidney disease.

found to improve glycemic control in patients with T2DM [63], but this benefit is controversial [64]. A recent study [65] found that vitamin D supplementation improved endothelial function in diabetic hypertensive patients, but our study failed to produce beneficial results.

Decreased levels of serum calcium, and increased levels of phosphorus, fibroblast factor 23(FGF-23) and parathyroid hormone have already appeared by the middle stage of CKD. Hyperphosphatemia is considered a decisive determinant of vascular calcification in CKD, and both it and increased level of PTH are associated with vascular calcification as well as increased risk for cardiovascular events [66]. FGF-23 was found to play a key role in regulating phosphate homeostasis and was associated with cardiovascular and all-cause mortality [67]. The results of our meta-analysis showed that vitamin D and VDRA

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significantly increased serum calcium and decreased serum parathyroid hormone, but did not decrease serum FGF-23 and instead elevated it.

The current meta-analysis had some limitations. First, the number of included study participants was relatively small. Second, the follow-up time of the included studies was not long enough to potentially observe a facilitating effect of vitamin D on surrogate indices of endothelial function and arterial stiffness.

In conclusion, we speculate that supplementation with vitamin D and VRDA, in particular forms and dosages, contributes to the improvement of vascular endothelial function and abnormal mineral metabolism, but not arterial stiffness. And it is not yet possible to conclude that vitamin D supplementation reduces the risk of cardiovascular events in patients with CKD. Trials with larger populations and longer durations are needed to provide more reliable evidence.

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Author contribution

Shujun Pan, Kaibi Yang: study idea and design; Shujun Pan, Kaibi Yang: literature search and data extraction; Yiwei Shang, Lin Liu: quality evaluation and data analysis; Shujun Pan: first draft; all Authors: study critical revision and manuscript draft. All authors provided final approval of the version to publish. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Data access and sharing

Databases and statistical codes are available on request from the corresponding author (Rizhen Yu, Juan Jin, Qiang He).

Ethics

This article does not contain any study with human participants performed by any of the authors.

Declaration of competing interest

All authors disclosed no relevant relationships.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.numecd.2023.09.015.

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