Does vitamin D supplementation modulate metabolic risk factors of cardiovascular disease? A systematic review and meta-analysis of clinical trials

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ABSTRACT

Background and Objectives: Vitamin D has been proposed to influence several cardiometabolic risk factors; however, evidence from randomized controlled trials (RCTs) and recent meta-analyses remains inconsistent regarding the magnitude of these effects. This meta-analysis evaluated the effects of vitamin D supplementation on lipid profile, blood pressure, and glycaemic parameters, and explored whether age and baseline serum vitamin D concentrations modified these associations. **Methods and Study Design:** A systematic review and meta-analysis of RCTs was conducted to compare oral vitamin D supplementation with placebo in adults. PubMed, the Cochrane Library, and ClinicalTrials.gov were searched systematically. Risk of bias was assessed using the Cochrane risk-of-bias tool. Pooled effect sizes with 95% confidence intervals (CIs) were estimated using random-effects models. **Results:** A total of 14,051 abstracts were identified, and 45 RCTs were included in the final analysis. Vitamin D supplementation significantly reduced low-density lipoprotein cholesterol (LDL-C) by 0.136 mmol/L (95% CI: -0.215, -0.056), systolic blood pressure (SBP) by 2.79 mm Hg (95% CI: -4.65, -0.94), fasting blood glucose (FBG) by 0.11 mmol/L (95% CI: -0.19, -0.04), and hemoglobin A1c (HbA1c) by 0.164% (95% CI: -0.32, -0.01) compared with placebo. Subgroup analyses showed reductions in SBP and LDL-C among participants aged ≥55 years, whereas FBG was reduced in those aged <55 years. **Conclusions:** Vitamin D supplementation may modestly improve selected cardiometabolic risk factors. Age and baseline vitamin D status may influence these effects, although their clinical significance remains uncertain. Further well-designed RCTs are needed.

Key Words: Vitamin D, cardiovascular disease, cardiometabolic risk factors, systolic blood pressure, low-density lipoprotein cholesterol

INTRODUCTION

Cardiovascular disease (CVD) remains the leading cause of death in developed and developing countries.[1-3] Consequently, there is growing interest in dietary supplements that may favourably influence both traditional and emerging risk factors for (CVD).

Several prospective human studies have demonstrated an association between vitamin D status and CVD mortality risk. For instance, Ginned et al.[4] followed 3,408 participants for about 7.3 years and found that subjects with vitamin D levels less than 25.0 nmol/L were at higher risk for CVD mortality (hazard ratio = 2.36, 95% CI:1.17-4.75) than those with levels of 100 nmol/L or higher. Similarly, Doping et al.[5] reported higher cardiovascular mortality

among participants in the lowest two quartiles of vitamin D status (median concentrations of 7.6 and 13.3 ng/mL), with hazard ratios of 2.22 and 1.82, respectively, compared with participants in the highest quartile (median 28.4 ng/mL).

Vitamin D receptors are expressed in almost all human cells, supporting a potential role for vitamin D in multiple physiological processes relevant to cardiovascular health. Evidence suggests that vitamin D may influence several risk factors associated with CVD including hypertension, hyperlipidemia, diabetes mellitus, inflammation, and endothelial dysfunction. Proposed mechanisms include modulation of renin-angiotensin-aldosterone systems (RASS), decrease in parathyroid hormones, enhancement in insulin secretion and insulin sensitivity, downregulation of inflammatory cytokines, and increase arterial intimae thickness.[6] On the basis of these proposed biological mechanisms, numerous randomized clinical trials have been undertaken to evaluate the effect of vitamin D supplementation on metabolic risk factors associated with cardiovascular disease, however, mixed results have been reported. Recent systematic reviews and meta-analyses have reported mixed findings regarding the effects of vitamin D supplementation on cardiometabolic outcomes. While some reviews have demonstrated beneficial effects on selected cardiovascular risk factors, others have reported limited or no significant effects, highlighting the need for continued evaluation of the available evidence.[7-8] Therefore, Pooling the results of these trials may help clarify the relationship between vitamin D supplementation and cardiometabolic risk factors associated with cardiovascular disease. Moreover, utilizing sub-group techniques to study multiple potential effect modifiers—such as age and baseline vitamin D levels—may help clarify the relationship between vitamin D supplements and metabolic risk factors for CVD, and explain observed heterogeneity, as suggested by previous meta-analyses.[9-10]

Accordingly, the objectives of this systematic review and meta-analysis were to (1) quantify the effects of vitamin D supplementation on cardiometabolic risk factors associated with cardiovascular disease (CVD), including blood lipids [total cholesterol, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and triglycerides], blood pressure [systolic blood pressure (SBP) and diastolic blood pressure (DBP)], inflammatory markers [C-reactive protein (CRP) and interleukin-6 (IL-6)], parameters of glucose metabolism [fasting blood glucose (FBG) and hemoglobin A1c (HbA1c)], and body mass index (BMI); and (2) examine whether age and baseline serum vitamin D concentrations modify the effects of vitamin D supplementation on these outcomes.

MATERIALS AND METHODS

Registration and reporting

This systematic review and meta-analysis were registered with PROSPERO (CRD42020165293) and is reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

Ethics approval and consent to participate

Ethical approval and informed consent were not required because this study was a systematic review and meta-analysis based exclusively on data from previously published studies.

Literature search

Clinical trials were identified by searching the following databases: PubMed, the Cochrane Library, and ClinicalTrials.gov from the commencement until March 2020. An updated search was carried out in PubMed from March 2020 to July 2024. The updated search resulted in inclusion of the 14 clinical trials in the final analysis.

For non-English language literature, studies were included if an English abstract provided sufficient data for extraction; otherwise, the study was excluded. A comprehensive search strategy was employed using the following terms and their combinations: vitamin D, 25-hydroxyvitamin D3, calcidiol, 1,25-dihydroxyvitamin D, cholecalciferol (D3), and ergocalciferol (D2).

Eligibility criteria and study selection

Trials were included in the analysis if they met the following criteria: 1) randomised control trials of parallel or crossover design, 2) participants were adults, 3) they provided the intervention as vitamin D compared to a placebo, and 4) reported at least one outcome of interest, including lipid profile, blood pressure, inflammatory cytokines, and parameters of glucose metabolism. One reviewer conducted the initial screening of titles and abstracts, while a second reviewer independently verified the included and excluded studies.

Risk of bias assessment

Randomised controlled studies were assessed for methodological quality with the Cochrane risk of bias tool,[11] evaluating sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessors, incomplete outcome data, selective

reporting, and other potential sources of bias. For each category, the risk of bias was then categorized as "low," "high," or "unclear".[9]

Data extraction

For eligible studies, data were extracted on mean values and standard deviations of outcomes, as well as study characteristics including trial design, intervention type, vitamin D dose (IU/day), duration of supplementation, and participant characteristics. Two reviewers independently extracted data, and a third reviewer cross-checked the extracted data. Disagreements were resolved through discussion.

The effect size for continuous outcomes was calculated as the difference in means, and its standard error was calculated for every study using a specialized program (Comprehensive Meta-Analysis V2 (Biostat, Englewood, NJ, USA)) for calculating pooled effect size and 95% confidence interval (CI), and performing subgroup analysis by age group, and baseline blood vitamin D concentrations.

Statistical analysis and management of heterogeneity

The effect size for continuous outcomes was calculated as the mean difference with corresponding standard errors. Meta-analyses were conducted using Comprehensive Meta-Analysis software (version 2; Biostat, Englewood, NJ, USA).

Given the anticipated clinical and methodological heterogeneity among studies—including wide variation in vitamin D dose, supplementation duration, baseline vitamin D status, and participant health status—a random-effects model was applied initially for all pooled analyses. This approach accounts for both within-study and between-study variability and provides more conservative effect estimates when heterogeneity is present.

The heterogeneity or variation of the results across the trials was evaluated using the I^2 statistic, which assesses the percentage of between-study variance due to study heterogeneity versus sampling error, ranging from 0.0% (no heterogeneity) to 100% (high heterogeneity). A guide to I^2 interpretation is as follows: 0% to 40% might not be important; 30% to 60% may represent moderate heterogeneity; 50% to 90% may represent substantial heterogeneity; and 75% to 100%: considerable heterogeneity.[12]

In addition, sensitivity analysis was carried out for all outcomes to explore the influence of each individual study on the estimated pooled effects and thus to check the robustness of findings in the presence of high heterogeneity.

The presence of publication bias was examined using a funnel plot. Subgroup analysis was used to explore the effects of potential modifiers on the outcomes of interest, and data were presented as forest plots.

RESULTS

A total of 14,051 records were identified through database searching. After removal of duplicates and screening, 45 RCTs met the inclusion criteria and were used for data analysis (Figure 1). Studies were excluded for reasons including: methodological papers, did not measure any of the outcomes of interest, presented the results of the screening procedure, reported outcome after treatment cessation, intravenous infusion, a re-analysis of a previous report or results reported previously, assessed treatment efficacy and not effectiveness, no placebo or not appropriate control, could not find the full article, i.e., only abstract available or no access, participants were children or adolescents, and in vitro study.

Table 1 summarizes the characteristics of the included studies. All the studies were randomised, double-blinded with parallel design. Study duration ranged from 1 to 36 months. Vitamin D dose ranged from 20 to 100,000 IU administered as daily, weekly, or bolus regimens. Most studies included both male and female participants. The majority of the studies supplied vitamin D in the form of cholecalciferol. Participants ranged in age from 18 to 88 years and included healthy individuals as well as populations with cardiovascular disease, diabetes, hypertension, overweight, obesity, coronary artery disease, polycystic ovary syndrome, chronic kidney disease, chronic heart failure, gestational diabetes mellitus, hypercholesterolemia, left ventricular hypertrophy, secondary hyperparathyroidism, ischemic heart disease, chronic fatigue, heart failure, metabolic syndrome, myocardial infarction, and high waist circumference. Blood vitamin D concentration was assessed by using different laboratory methods such as enzyme-linked immunosorbent assay and liquid chromatography–tandem mass spectrometry. Studies evaluated mostly the efficacy of vitamin D3 supplement as a modulator of risk factors associated with cardiovascular disease.

Table 2 summarizes the pooled effect sizes and corresponding 95% confidence intervals. The primary analysis showed that vitamin D supplementation did not significantly improve lipid profile, inflammatory markers, glucose parameters, or BMI compared with placebo. That compared with placebo supplementation, vitamin D did not improve lipid profile,

inflammatory markers, glucose parameters, or BMI. Compared to the placebo, vitamin D supplementation was associated with a modest but statistically significant reduction in SPB (−2.80 mm Hg; 95% CI: −4.65 to −0.94), whereas no significant effect was observed for DBP. Considerable statistical heterogeneity was observed for most outcomes (I^2 >75%), indicating substantial between-study variability.

Sensitivity analysis

To address the considerable heterogeneity identified in the primary analysis, we conducted a series of sensitivity analyses by excluding influential trials that their effect size deviated substantially from the common distribution of the other included trials, disproportionately inflating the I^2 values (Supplementary Figures 1 and 2).

For LDL-C, exclusion of three influential trials (Kubiak et al; Rashad et al; Imanparast et al), all assessed as having a high-risk trial, reduced heterogeneity substantially (I^2 from 56.1% to 23.4%). The revised pooled estimate showed an overall significant reduction in LDL-C (−0.136 mmol/L; 95% CI: −0.215 to −0.056).

For glycemic outcomes, removal of the Kubiak et al trial significantly improved the findings for FBG and HbA1c. The analysis for FBG yielded a significant reduction (−0.110 mmol/L; 95% CI: −0.185 to −0.036) and a moderated heterogeneity (I^2 = 50.9%). Vitamin D supplementation reduced HbA1c by 0.164 (95% CI: −0.322, −0.006) compared with placebo, with no heterogeneity observed.

For other outcomes, sensitivity analyses did not identify influential studies, and pooled estimates remained consistent with the primary analysis.

Subgroup analysis

Subgroup analysis by age showed that reductions of LDL-C (−0.142 mmol/L; 95% CI: −0.180 to −0.105) (Figure 2a), and SBP (−3.150 mm Hg; 95% CI: −3.982 to −2.318) (Figure 2b), were significant among participants aged ⩾55 years. In contrast, FBG reduction was significant (−0.142 mmol/L; 95% CI: −0.254 to −0.030) in participants who aged less than 55 years (Figure 2c).

Subgroup analyses by baseline vitamin D status showed a favourable effect on FBG (−0.127 mmol/L; 95% CI: −0.204 to −0.050) (Figure 3a) and HbA1c (−0.252%; 95% CI:

−0.464 to −0.039) (Figure 3b). Subgroup analyses showed no significant differences in effects for the remaining outcomes across age groups or baseline vitamin D status.

Risk of bias and publication bias

A summary of each risk of bias item presented as percentages across all included studies is provided in Supplementary Figure 3. The authors' judgment of each risk of bias item for individual studies is summarized in Supplementary Figure S4. The method of random sequence generation was performed in about 70% of the trials, while allocation concealment was reported in about 30%. Around 70% of studies were judged to have an unclear risk of detection bias due to insufficient reporting of outcome assessor blinding. Approximately 25% of the trials did not report whether or how blinding was achieved, and 50% of the trials were at high risk of performance bias. About 25% of the trials did not provide enough information on withdrawals or loss to follow-up to permit an evaluation of this. For about half of the trials, there was insufficient information to judge selective reporting.

Funnel plots for LDL-C, SBP, fasting blood glucose, and HbA1c are shown in Supplementary Figures 4–8. Visual examination of the funnel plots shows a symmetrical appearance suggesting no evidence of publication bias for LDL-C, SBP, and fasting blood glucose, whereas asymmetry was observed for HbA1c.

DISCUSSION

Based on the available evidence, the present meta-analysis shows that vitamin D supplementation reduces LDL-C, SBP, FBG and HbA1c. Moreover, this analysis provides evidence that age and baseline vitamin D blood concentration may influence the efficacy of vitamin D supplementation as a modulator for some CVD metabolic risk factors. However, these results should be interpreted cautiously given the substantial heterogeneity and variable methodological quality of the included trials.

Previous meta-analyses have reported inconsistent effects of vitamin D supplementation on lipid parameters. A 2012 on 12 randomized clinical trials reported that vitamin D supplementation increased LDL-C concentration and did not significantly affect total cholesterol, HDL-C, or triglycerides.[13] In the meta-analysis by Wang et al.,[13] seven RCTs using cholecalciferol were included, with daily vitamin D supplementation doses ranging from 300 to 3,332 IU and intervention durations between 42 days and 3 years. The Wang et al.,[13] primarily included non-Hispanic white, elderly participants and trials not specifically designed to assess lipid outcomes, thereby limiting generalizability. In contrast, a larger meta-

analysis by Dibaba et al. in 2019,[14] including 41 trials, showed that vitamin D supplementation exerted beneficial effects on total cholesterol, LDL-C, and triglycerides concentrations but not HDL-C concentrations.[12] particularly among individuals with hypercholesterolemia and vitamin D insufficiency who are at high risk of cardiovascular disease.[14] Conversely, a more recent meta-analysis of seven trials of vitamin D supplementation in adults with metabolic syndrome reported no significant effects on any blood lipid parameter.[15] These discrepancies likely reflect differences in inclusion criteria, baseline vitamin D status, participant health profiles, and supplementation regimens.

Regarding blood pressure, prior evidence has also been mixed. Witham et al reported DBP lowering, but no effects on SBP, due to vitamin D supplementation. [16] whereas Elamin et al., analyzing 11 trials, found no reduction in SBP or DBP due to vitamin D supplementation.[17] Similarly, Shu et al reported that vitamin D supplementation did not affect blood pressure parameters in vitamin D-deficient participants from seven trials.[18]

In contrast to some previous findings, this meta-analysis using of randomised clinical trials showed an overall LDL-C and SBP reduction effect of vitamin D and this effect was particularly among participants aged 55 years and older. and that the lowering effect of vitamin D on FBG was in participants less than 55 years of age. These findings are consistent with observations by Farapti et al, who found that age was a modulator for the hypotensive effect of vitamin D supplementation.[19] Nonetheless, additional well-designed randomized trials are required to establish the cause-effect of vitamin D supplementation on blood pressure, LDL-C, and glycemic control indicators and determine whether these reductions translate into clinically meaningful cardiovascular benefits. A plausible mechanism by which vitamin D can affect CVD risk factors is through its action on RASS, parathyroid hormones, and insulin secretion and sensitivity.[6]

Evidence regarding glucose metabolism remains inconclusive. While some previous meta-analyses combining previous trials failed to detect an overall favorable effect on glucose metabolism linked to vitamin D supplementation.[20] Tang et al. found that vitamin D supplementation decreased FBG levels[21] consistent with our findings. In the present analysis, improvements in FBG were mainly observed among participants younger than 55 years and those with baseline serum vitamin D concentrations below 50 nmol/L. Although a reduction in HbA1c was also observed, this finding should be interpreted cautiously due to evidence of publication bias. Proposed mechanisms linking vitamin D deficiency to insulin resistance include inflammation-mediated pathways,[21] however, this analysis showed that vitamin D does not affect inflammatory markers including CRP and IL-6.

More recently, Aquino et al. (2023) reported that vitamin D supplementation may improve selected cardiometabolic parameters in individuals with metabolic syndrome, although the certainty of evidence varied across outcomes8. Similarly, An et al. (2024) found favourable effects of vitamin D supplementation on blood pressure, lipid profile, and glycemic parameters, while highlighting the influence of participant characteristics on treatment response.[7] Consistent with these findings, the present meta-analysis demonstrated a beneficial effect of vitamin D supplementation on selected cardiometabolic outcomes, particularly SBP. However, unlike previous reviews, no overall improvements were observed in lipid profile, glucose metabolism, inflammatory markers, or BMI in the current analysis. In agreement with An et al. (2024),[7] our subgroup analyses suggest that treatment response may vary according to participant characteristics, with greater benefits observed among older adults and individuals with higher baseline vitamin D concentrations. Furthermore, the present review included RCTs published up to July 2024 and evaluated inflammatory markers, including CRP and IL-6, in addition to traditional cardiometabolic risk factors.

Most included studies in this analysis reported a baseline 25-hydroxyvitamin D [25(OH)D] of less than 50 nmol/L. suggesting widespread insufficiency among participants. It is possible that serum vitamin D levels must reach a threshold before measurable improvements improvement in cardiovascular risk factors could be detected. Previous meta-analysis suggests that a daily supplemental intake of vitamin D of 797 to 2519 IU for European adults, and 729, 2026, and 1229 IU for adults in North America, Asia, and the Middle East and Africa, respectively, are needed to achieve a 25(OH) vitamin D concentration of 75 nmol/L.[22] Further research is needed to investigate the optimal dose of vitamin D needed to achieve a vitamin D blood concentration that is needed to modify the metabolic risk factors associated with cardiovascular disease. Importantly, whether the modest reductions reported in this analysis in SBP, LDL-C, fasting blood glucose, and HbA1c by vitamin D supplementation can be translated to a reduction in cardiovascular events in the general population remains uncertain and should be evaluated in trials specifically designed with clinical endpoints.

Limitations

This analysis is not without limitations. First, limitations of our analysis arise from the characteristics of the included studies. Despite the use of random-effects models and rigorous sensitivity analyses and the exclusion of outliers, considerable statistical heterogeneity persisted for some outcomes. This residual heterogeneity is likely stemming from the broad diversity in study protocols. Specifically, the included trials utilized a wide range of dosages

and durations, across healthy participants and populations with distinct pathophysiologies. Given that vitamin D metabolism is highly dependent on baseline status and adiposity, these clinical variations naturally hindered a uniform effect size. Future studies should recruit participants based on pre-determined baseline blood vitamin D concentrations, as well as obesity status based on other measurements and not solely on BMI.

Additionally, the methodological quality of the included studies was variable. A considerable proportion of the trials included were identified as having an unclear or high risk of bias, particularly regarding performance and detection bias. Consequently, the overall certainty of the evidence is limited. Finally, subgroup analyses for certain metabolic markers—although useful for hypothesis generation—were not powered to establish definitive effect modification and should be interpreted with caution until confirmed by large-scale, prospective trials specifically designed to compare the effect of age and baseline blood vitamin D concentration as potential modulators to vitamin D supplementation for risk factors associated with CVD.

Conclusion

Based on the findings of this meta-analysis, vitamin D supplementation may be associated with modest modifications in selected cardiometabolic risk factors, including SBP, low-density lipoprotein cholesterol, fasting blood glucose, and HbA1c. Although the primary analyses exhibited substantial statistical heterogeneity, the application of robust sensitivity analyses—excluding influential outliers and studies with a high risk of bias—confirmed significant reductions in LDL-C, SBP, fasting blood glucose, and HbA1c. Consequently, the certainty and clinical relevance of these findings remain limited. Future clinical trials employing standardized protocol for vitamin D dosing, intervention durations, and conducted on participants with defined health/disease status are necessary to determine whether vitamin D supplementation confers meaningful cardiometabolic or cardiovascular benefits.

SUPPLEMENTARY MATERIALS

All supplementary tables and figures are available upon request from the editorial office, and are also accessible on the journal's webpage (apjcn.qdu.edu.cn).

CONFLICT OF INTEREST AND FUNDING DISCLOSURE

The authors declare no conflict of interest.

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Table 1. Characteristics of randomized controlled trials included in the meta-analysis

Author	Design	Blinding	Status	Age group†	BMI	Gender	Baseline 25(OH)D categories‡
Nasri et al. [24]	Parallel	DB	O, DM2	2	O	MF	2
Andersen et al.[25]	Parallel	DB	N, O		O	MF	1
Javed et al. [26]	Parallel	DB	PCOS	1	Ob	F	1
Mose et al.[27]	Parallel	DB	CKD (on dialysis), T1DM, T2DM	2	N	MF	1
Larsen et al.[28]	Parallel	DB	HT	2	O	MF	2
Khosravi et al.[29]	Parallel	DB	O, Ob	1	O,Ob	F	1
Yeow et al. [30]	Parallel	DB	former GDM	1	O	F	1
Chandler et al.[31]	Parallel	DB	O	1	N, O, Ob	MF	1
Scragg et al.[32,33]	Parallel	DB	N	1	O	MF	2
Barnes et al.[34]	Parallel	DB	N	1	O	MF	2
Akbarzadeh et al.[35]	Parallel	DB	T2DM		O	MF	2
Bressendorf et al.[36]	Parallel	DB	N	1	N	MF	1
Jastrzebski et al.[37]	Parallel	DB	N	1	N	NR	1

Author	25(OH)D assay method	Type of vitamin D	Dose of vitamin D IU	Duration of supplementation in months	The frequency of vit D intake	Control
Nasri et al. [24]	ELISA	D3	50000	3	W	P
Andersen et al.[25]	NR	D3	800	12	D	P
Javed et al. [26]	Isotope-dilution liquid chromatography tandem mass spectrometry	NR	3200	3	D	P
Mose et al.[27]	Commercial chemiluminescence immunoassays	D3	3000	6	D	P
Larsen et al.[28]	Immunoassays	D3	3000	5	D	P
Khosravi et al.[29]	ELISA	NR	50000	1.5	W	P
Yeow et al. [30]	Elecsys Vitamin D Total assay	D3	4000	6	D	P
Chandler et al.[31]	Diasorin (Radioimmunoassay)	D3	4000	6	D	P
Scragg et al.[32,33]	Liquid chromatography–tandem mass spectrometry	D3	100 000	18	M	P
Barnes et al.[34]	ELISA	D3	600	5.5	D	P
Akbarzadeh et al.[35]	ELISA	D3	20	3	D	P
Bressendorf et al.[36]	Direct competitive chemiluminescence immunoassay	D3	3000	4	D	P
Jastrzebski et al.[37]	Architect method (Abbott)	D3	5000	1	D	P

CAD, coronary artery disease; CFS, chronic fatigue syndrome; CKD, chronic kidney disease; DB, double blind; DM, diabetes mellitus; ELISA, enzyme-linked immunosorbent assay; GDM, gestational diabetes mellitus; HC, hypercholesterolemia; HF, heart failure; HT, hypertension; LC-MS/MS, liquid chromatography-tandem mass spectrometry; MS, metabolic syndrome; NR, not reported; O, overweight; Ob, obesity; PCOS, polycystic ovary syndrome.

†Age group categories: 1, <55 years; 2, ≥55 years.

‡Baseline serum 25(OH)D categories: 1, <50 nmol/L; 2, ≥50 nmol/L.

Table 1. Characteristics of randomized controlled trials included in the meta-analysis (cont.)

Author	Design	Blinding	Status	Age group†	BMI	Gender	Baseline 25(OH)D categories‡
Kubiak et al.[38]	Parallel	DB	N,O	1	O	MF	1
Witham et al.[16]	Parallel	DB	CFS	1	O	MF	1
Mozaffari-Khosravi et al.[39]	Parallel	DB	HT, O	1	O	MF	1
Qin et al.[40]	Parallel	DB	HC,DM,HT	2	N	MF	2
Rashad et al. [41]	Parallel	DB	PCOS	1	O	F	1
Abootorabi et al.[42]	Parallel	SB	PCOS	1	NR	F	1
Muldowney et al.[43]	Parallel	DB	N, O, Ob	1	O, Ob	MF	2
Elkassaby et al.[44]	Parallel	DB	T2DM, Ob	2	Ob	MF	2
Munoz-Aguirre et al.[45]	Parallel	DB	T2DM, Ob	2	Ob	F	2
Salekzamani et al.[46]	Parallel	DB	O, MS	1	Ob	MF	1
Zittermann et al.[47,48]	Parallel	DB	Advanced HF, DM , arterial HTN, O	2	O	MF	1
Angellotti et al.[49]	Parallel	DB	T2DM, Ob	2	Ob	MF	2
Eric Seibert et al.[50]	Parallel	DB	N	1	N	MF	1

Author	25(OH)D assay method	Type of vitamin D	Dose of vitamin D IU	Duration of supplementation in months	The frequency of vit D intake	Control
Kubiak et al.[38]	In-house liquid chromatography–tandem mass spectrometry	D3	20000	4	W	P
Witham et al.[16]	Radioimmunoassay	D3	100000	6	Q2M	P
Mozaffari-Khosravi et al.[39]	Chemiluminescence method	D3	50000	2	W	P
Qin et al.[40]	BioSource 25-OH-Vit.D3-Ria-CT Kit	D3	2000	6	D	P
Rashad et al. [41]	Enzyme-linked immunosorbent assay	NR	42000	3	W	calcium carbonate 500mg + P
Abootorabi et al.[42]	ELISA	D3	50000	2	W	P
Muldowney et al.[43]	ELISA	D3	600	5.5	D	P
Elkassaby et al.[44]	Duasorin radioimmunoassay	D3	6000	6	D	P
Munoz-Aguirre et al.[45]	High performace liquid chromatoghraphy	D3	4000	6	D	P
Salekzamani et al.[46]	Quantitative chemiluminescent immunoassay	D3	50000	4	W	P
Zittermann et al.[47,48]	Diasorin radioimmunoassay	D3	4000	36	D	P
Angellotti et al.[49]	LCMS	D3	4000	12	D	P
Eric Seibert et al.[50]	Liquid chromatography with tandemmass spectrometry	D3	800	3	D	P

CAD, coronary artery disease; CFS, chronic fatigue syndrome; CKD, chronic kidney disease; DB, double blind; DM, diabetes mellitus; ELISA, enzyme-linked immunosorbent assay; GDM, gestational diabetes mellitus; HC, hypercholesterolemia; HF, heart failure; HT, hypertension; LC-MS/MS, liquid chromatography-tandem mass spectrometry; MS, metabolic syndrome; NR, not reported; O, overweight; Ob, obesity; PCOS, polycystic ovary syndrome.

†Age group categories: 1, <55 years; 2, ≥55 years.

‡Baseline serum 25(OH)D categories: 1, <50 nmol/L; 2, ≥50 nmol/L.

Table 1. Characteristics of randomized controlled trials included in the meta-analysis (cont.)

Author	Design	Blinding	Status	Age group†	BMI	Gender	Baseline 25(OH)D categories‡
Jorde et al.[51]	Parallel	DB	T2DM, Ob	2	Ob	MF	2
Chen et al.[52]	Parallel	DB	HT	2	N	MF	1
Jamilian et al.[53]	Parallel	DB	GDM, O	1	O	F	1
Wamberg et al.[54]	Parallel	DB	N, Ob	1	Ob	MF	1
Ghaderi et al.[55]	Parallel	DB	Maintenance methadone treatment patients	1	N, O	NR	1
Ebadi et al.[56]	Parallel	DB	O,Ob	1	O, Ob	MF	1
Bayyari et al.[57]	Parallel	DB	O	1	O	MF	1
Safarpour et al.[58]	Parallel	DB	DM,O	1	Ob	MF	1
Ghorbani et al. [59]	Parallel	DB	Migraine patients	1	O	MF	2
Limonte et al. [60]	Parallel	DB	DM	2	Ob	MF	2
Gariballa et al. [61]	Parallel	DB	N	1	O	MF	2
Trummer et al. [62]	Parallel	NR	N	1	O	F	2

Author	25(OH)D assay method	Type of vitamin D	Dose of vitamin D IU	Duration of supplementation in months	The frequency of vit D intake	Control
Jorde et al.[51]	Immunometry (electrochemiluminescence: ECLIA)	D3	4000	6	W	P
Chen et al.[52]	BioSource 25-OHVit.D3-Ria-CT Kit	D3	2000	6	D	P
Jamilian et al.[53]	Commercial enzyme-linked immunosorbent assay kit	D3		1.5	Q2W	vit D P + omega 3 P
Wamberg et al.[54]	Isotope dilution liquid chromatography–tandem mass spectrometry (LC–MS/MS)	D3	7000	6.5	D	P
Ghaderi et al.[55]	ELISA	NR	50000	3	every 2 weeks	p
Ebadi et al.[56]	NR	D3	50,000	2	W	P
Bayyari et al.[57]	endocrine automated analyzer	D3	50,000	2	W	P
Safarpour et al.[58]	Enzyme Immunoassay kit	NR	50,000	2	W	P
Ghorbani et al. [59]	CLIA	D3	2000	3	D	P
Limonte et al. [60]	LCMS/MS	D3	2000	60	D	P
Gariballa et al. [61]	COBAS e411 analyzer	D3	2000	6	D	P
Trummer et al. [62]	ID-LC-MS/MS	D3	24000	P	W	P

CAD, coronary artery disease; CFS, chronic fatigue syndrome; CKD, chronic kidney disease; DB, double blind; DM, diabetes mellitus; ELISA, enzyme-linked immunosorbent assay; GDM, gestational diabetes mellitus; HC, hypercholesterolemia; HF, heart failure; HT, hypertension; LC-MS/MS, liquid chromatography-tandem mass spectrometry; MS, metabolic syndrome; NR, not reported; O, overweight; Ob, obesity; PCOS, polycystic ovary syndrome.

†Age group categories: 1, <55 years; 2, ≥55 years.

‡Baseline serum 25(OH)D categories: 1, <50 nmol/L; 2, ≥50 nmol/L.

Table 1. Characteristics of randomized controlled trials included in the meta-analysis (cont.)

Author	Design	Blinding	Status	Age group†	BMI	Gender	Baseline 25(OH)D categories‡
Imanparast et al. [63]	Parallel	NR	DM	1	O	MF	1,2
Sheikh et al. [64]	Parallel	DB	HTN	2	O	MF	1
Grübler et al. [65]	Parallel	DB	HTN	2	NR	MF	2
El Hajj et al. [66]	Parallel	DB	DM	2	N	MF	1
Gaughran et al. [67]	Parallel	DB	N	1	N	MF	1
Bhatt et al. [68]	Parallel	Open label	Pre-DM	1,2	O,Ob	F	1
Mehdizadehkashi et al. [69]	Parallel	DB	Endometriosis	1	N,O	F	1

Author	25(OH)D assay method	Type of vitamin D	Dose of vitamin D IU	Duration of supplementation in months	The frequency of vit D intake	Control
Imanparast et al. [63]	Immunoassay analyzer	D3	50,000	4	W	P
Sheikh et al. [64]	NR	D3	50,000	2	W	P
Grübler et al. [65]	ChemiLuminescence	D3	2800	2	D	P
El Hajj et al. [66]	Radioimmunoassay	D3	30000	6	3D/W	P
Gaughran et al. [67]	NR	D3	120000	6	M	P
Bhatt et al. [68]	chemiluminescence	D3+Calcium	60000	20	W	Pca
Mehdizadehkashi et al. [69]	NR	D3	50000	3	Q3W	P

CAD, coronary artery disease; CFS, chronic fatigue syndrome; CKD, chronic kidney disease; DB, double blind; DM, diabetes mellitus; ELISA, enzyme-linked immunosorbent assay; GDM, gestational diabetes mellitus; HC, hypercholesterolemia; HF, heart failure; HT, hypertension; LC-MS/MS, liquid chromatography-tandem mass spectrometry; MS, metabolic syndrome; NR, not reported; O, overweight; Ob, obesity; PCOS, polycystic ovary syndrome.

†Age group categories: 1, <55 years; 2, ≥55 years.

‡Baseline serum 25(OH)D categories: 1, <50 nmol/L; 2, ≥50 nmol/L

Table 2. Effects of vitamin D supplementation on cardiometabolic risk factors: primary and sensitivity analyses†

Risk factor and analysis type	No. of studies	Effect size		Heterogeneity	
		Point Estimate (95% CI)	p-value	I^2‡	p-value
Total cholesterol mmol/L					
Primary	26	-0.058 (-0.149, 0.032)	0.205	51.1	0.002
Sensitivity					
LDL-C mmol/L					
Primary	24	-0.078 (-0.167, 0.012)	0.089	56.1	<0.0001
Sensitivity	21	-0.136(-0.215,-0.056)	0.001	23.4	0.162
HDL-C mmol/L					
Primary	25	0.018 (-0.021, 0.058)	0.364	82.7	<0.0001
Sensitivity					
Triglycerides mmol/L					
Primary	24	-0.045 (-0.178, 0.089)	0.513	88.9	<0.0001
Sensitivity					
SBP mm Hg					
Primary	23	-2.8 (-4.648, -0.938)	0.003	82.6	<0.0001
Sensitivity					
DBP mm Hg					
Primary	23	-0.76 (-1.84,0.312)	0.164	72.1	<0.0001
Sensitivity					
CRP nmol/L					
Primary	15	-4.753 (-20.432, 10.926)	0.552	99.9	<0.0001
Sensitivity					
IL 6 pg/mL					
Primary	6	0.375 (-0.394, 1.144)	0.339	85.7	<0.0001
Sensitivity					
FBG mmol/L					
Primary	20	-0.078 (-0.171, 0.015)	0.099	78.4	<0.0001
Sensitivity	19	-0.110 (-0.185, -0.036)	0.004	50.7	0.006
HbA1c (%)					
Primary	10	0.007 (-0.053, 0.035)	0.816	0.0	0.425
Sensitivity	9	-0.164 (-0.322, -0.006)	0.42	0.0	0.797
BMI kg/m^2					
Primary	19	-0.056 (-0.446, 0.335)	0.779	15.0	0.264
Sensitivity					

LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; SBP, systolic blood pressure; DBP, diastolic blood pressure; CRP, C-reactive protein; IL-6, interleukin-6; HbA1c, hemoglobin A1c.
†Data are presented as mean differences with 95% confidence intervals (CI).
‡I^2 represents the percentage of variability attributable to between-study heterogeneity.

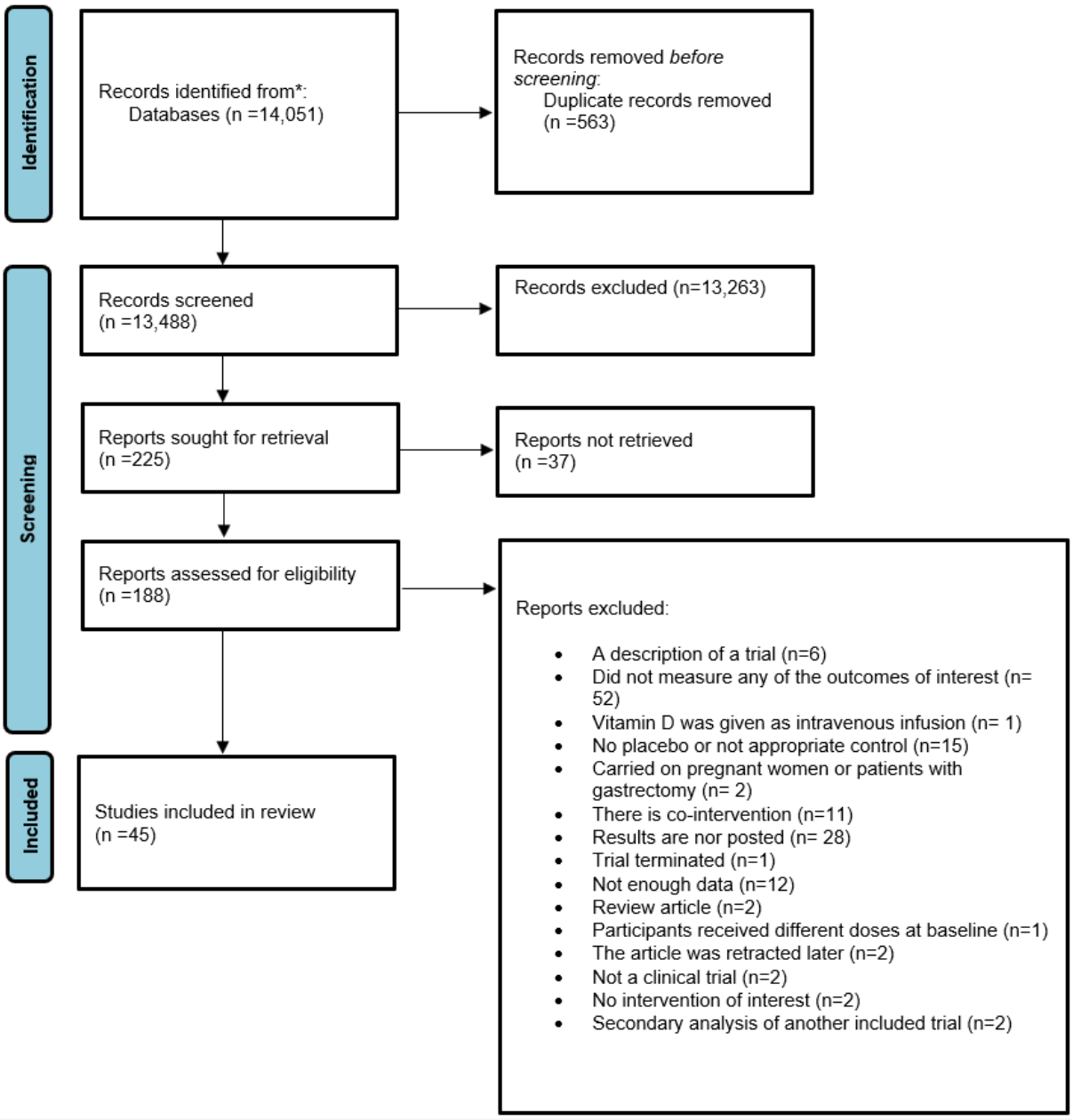
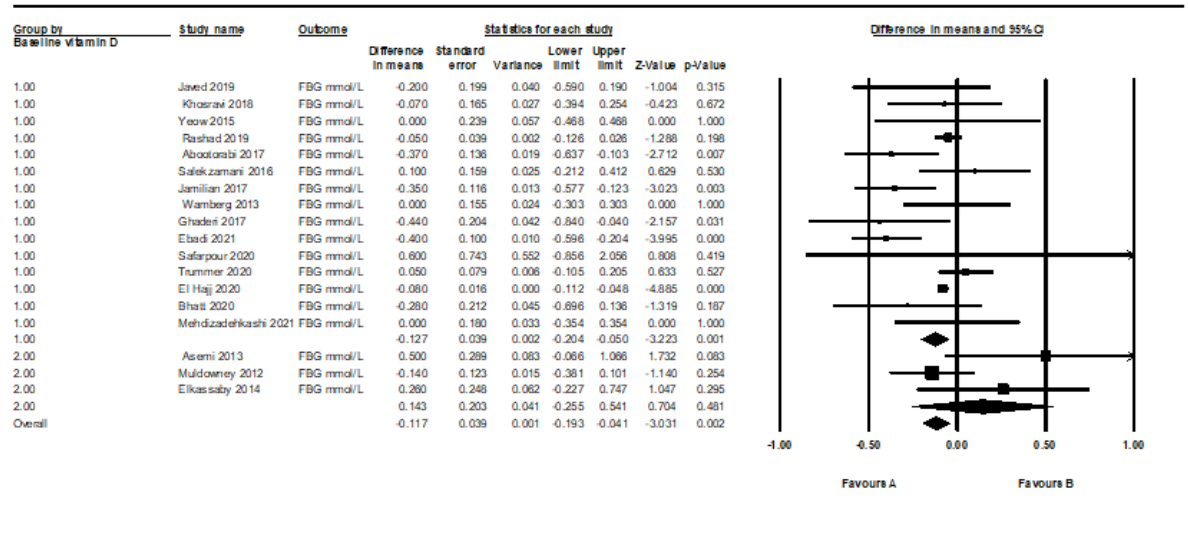


Figure 1. Flowchart of literature search for vitamin D supplementation and cardiovascular disease risk factors.

(A)



(B)

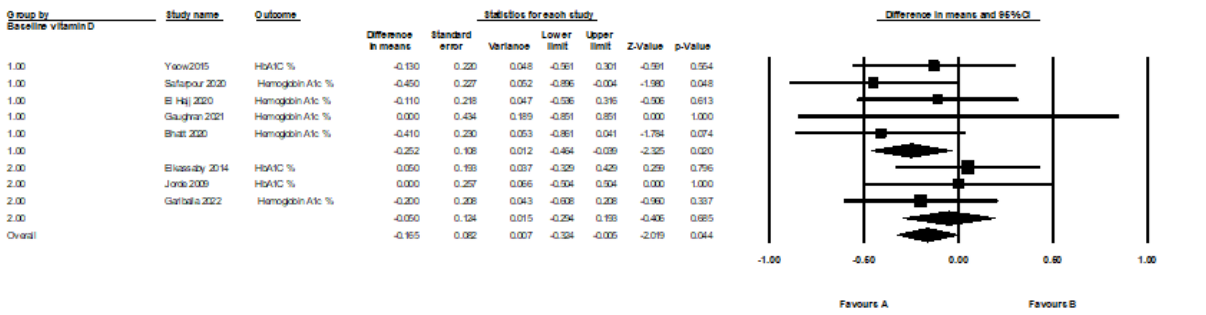
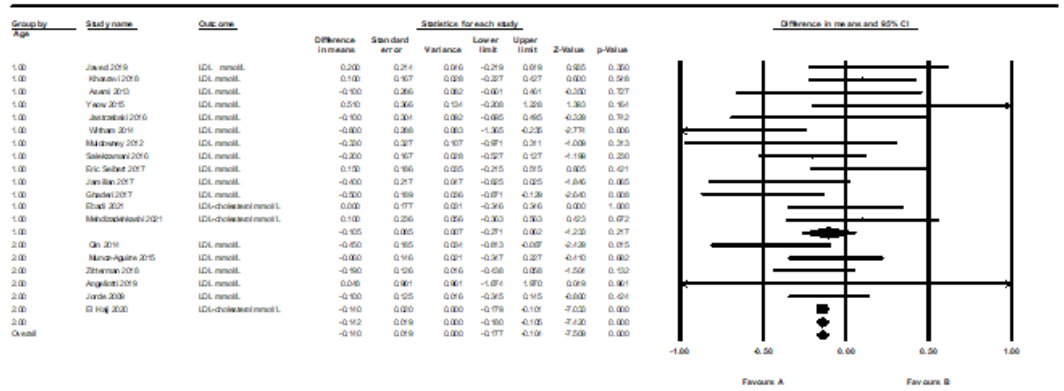
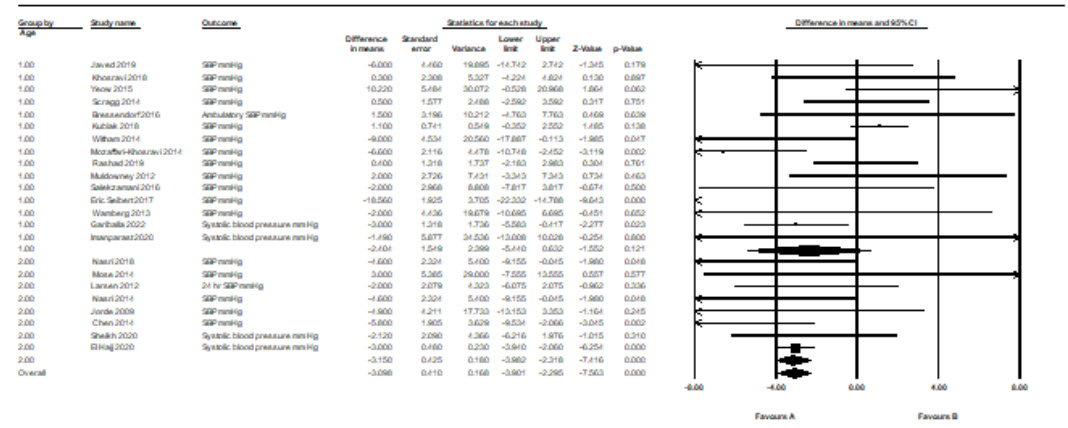


Figure 2. Forest plot of subgroup analysis by age of (A) low-density-lipoprotein cholesterol, (B) systolic blood pressure, (C) fasting blood glucose

(A)



(B)



(C)

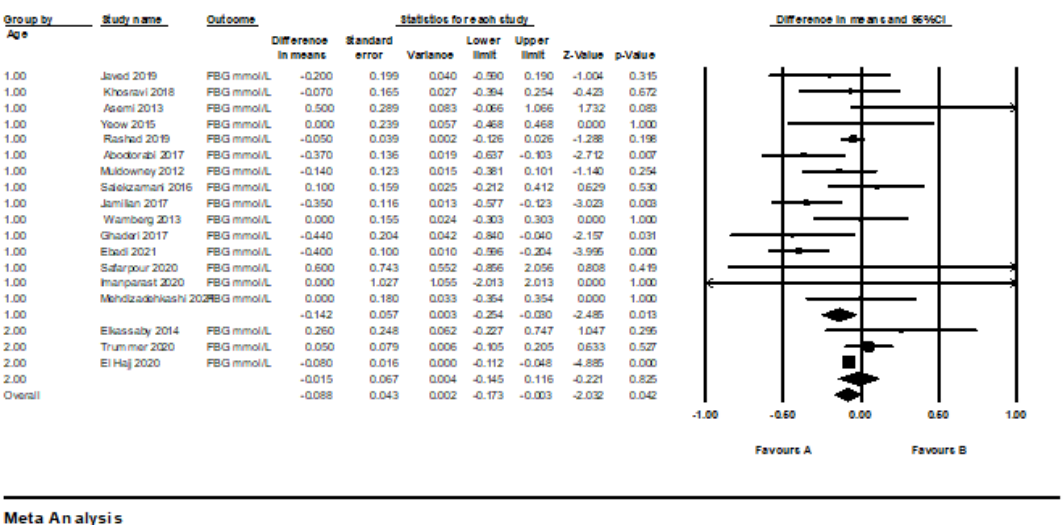


Figure 3. Forest plot of subgroup analysis by baseline blood vitamin D concentrations of: (A) fasting blood glucose and (B) HbA1c