Effect of vitamin D supplementation for major adverse **cardiovascular events: A meta-analysis based on randomized controlled trials**

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Abstract

This meta-analysis assesses the relationship between vitamin D supplementation and incidence of major adverse cardiovascular events (MACEs). Pubmed, Web of science, Ovid, Cochrane Library and Clinical Trials were used to systematically search from their inception until July 2024. Hazard ratios (HR) and 95% confidence intervals (95%CI) were employed to assess the association between vitamin D supplementation and MACEs. This analysis included 5 randomized controlled trials (RCTs). Pooled results showed no significant difference in the incidence of MACEs (HR: 0.96; p=0.77), expanded MACEs (HR: 0.96; p=0.77) between the vitamin D intervention group and the control group. Further, the vitamin D intervention group had a lower incidence of myocardial infarction (MI), but the difference was not statistically significant (HR: 0.88, 95%CI: 0.77-1.01; p=0.061); nevertheless, vitamin D supplementation had no effect on the reduced incidence of stroke (p=0.675) or cardiovascular death (p=0.422). Among males (p=0.109) and females (p=0.468), vitamin D supplementation had no effect on the reduced incidence of MACEs. For participants with a body mass index (BMI)<25 kg/m^2, the difference was not statistically significant (p=0.782); notably, the vitamin D intervention group had a lower incidence of MACEs for those with BMI≥25 kg/m^2 (HR: 0.91, 95%CI: 0.83-1.00; p=0.055). Vitamin D supplementation did not significantly contribute to the risk reduction of MACEs, stroke and cardiovascular death in the general population, but may be helpful for MI. Notably, effect of vitamin D supplementation for MACEs was influenced by BMI. Overweight/obese people should be advised to take vitamin D to reduce the incidence of MACEs.

Keywords: vitamin D supplementation, MACEs, sex, BMI, risk, meta-analysis

Abbreviations

CVD: cardiovascular disease; WHO: World Health Organization; MI: myocardial infarction; AF: atrial fibrillation; MACEs: major adverse cardiovascular events; RCTs: randomized controlled trials; AMI: acute myocardial infarction; BMI: body mass index; HR: hazard Ratio; 95%CI: 95% confidence interval; VDR: vitamin D receptor; IL: inhibited interleukin; MMP: matrix metalloproteinase.

Introduction

Cardiovascular disease (CVD) is already the leading cause of death worldwide, claiming an estimated 17.9 million lives each year according to the World Health Organization (WHO). In 2019 alone, 18.6 million people died and 34.4 million were disabled[1]. Moreover, its prevalence is increasing, with the prevalence of high blood pressure estimated to increase from 51.2% of U.S. adults in 2020 to 61.0% in 2050. The prevalence of coronary artery disease (7.8% to 9.2%), heart failure (2.7% to 3.8%), stroke (3.9% to 6.4%), atrial fibrillation (AF) (1.7% to 2.4%) and total CVD (11.3% to 15.0%) will also increase[2].

Therefore, the prevention of CVD is particularly important, and the current measures are from the perspectives of nutrition & diet, exercise & physical activity[3]. Among them, vitamin D regulates blood pressure, heart function, endothelial and smooth muscle cell function and therefore plays a role in cardiovascular health[4]. A cross-sectional study showed that the prevalence of CVD in vitamin D deficiency was 74%[5]. Meanwhile, the D-Health trial concluded that vitamin D supplementation may reduce the incidence of MACEs[6]. Also in a prospective cohort study, vitamin D supplementation in adults with hypertension reduced the risk of cardiovascular mortality[7].

On the contrary, two recently published meta-analyses[8, 9] showed no association between vitamin D supplementation and cardiovascular mortality, stroke, myocardial infarction (MI), arrhythmia, or overall cardiovascular event risk. However, the effect sizes in these two articles were calculated using risk ratios, which are missing the time variable relative to the hazard ratio (HR). And they also had limitations included the relatively short follow-up time of the included literature (mostly less than 3 years), the fact that cardiovascular events were secondary outcomes in most trials, and the absence of more detailed subgroup analyses. Incidentally, due to the long duration of the onset and progression of cardiovascular disease itself and the fact that vitamin D supplements are primarily intended to improve the microenvironment and thus promote health, a longer follow-up is required to achieve this. Meanwhile, in the article by Rossello, X.[10], which summarises a number of studies on prophylactic medication in patients after MI, it is pointed out that most of the long-term follow-up considered in these articles is less than 3 years. By analogy, this study considers a follow-up of at least 3 years. According to the above reasons, the purpose of this study is to explore the relationship between vitamin D supplementation and incidence of major adverse cardiovascular events (MACEs), based on high-quality randomized controlled trials (RCTs).

Methods

Protocol and guidance

This study was conducted according to the guidelines of Preferred Reporting Items for Systematic Reviews and Meta-Analyse (PRISMA)[11]. In addition, this research protocol has been registered in the International Registry of Prospective Systems Reviews (PROSPERO identifier: CRD42024566447).

Literature retrieval

Pubmed, Web of science, Ovid, Cochrane Library and Clinical Trials were used to systematically search RCTs on the topic of vitamin D intervention and the occurrence of cardiovascular events from the beginning of the database until July 2024, using the following headings and free words: "vitamin D" AND ("cardiovascular diseases" OR "cardiovascular events" OR "adverse cardiovascular" OR "cardiovascular system" OR "cardiac events"). Meanwhile, the references included in the literature are also searched. Grey literature was searched through Clinical Trials. Detailed strategies can be found in Supplemental Search Strategies. Finally, duplicate articles were removed by EndNote. Two authors (F. Y. Y. and Z. Q. F.) then independently screened all titles and abstracts of the remaining papers to identify potentially relevant articles. Subsequently, two authors assessed the full text of potentially relevant studies. Discrepancies were resolved by consensus or arbitrated by a third author (C. B. S.).

Inclusion and exclusion criteria

Inclusion criteria were as follows: (1) including participants >18 years old, (2) the intervention group received any dose of vitamin D, (3) the control group received placebo treatment, (4) studies reported MACEs or related outcomes, (5) the study belongs to RCT.

Exclusion criteria were: (1) the follow-up time of trials was less than 2 years, (2) the published literature was not written in English, (3) updated articles were published and only the most recent or comprehensive data were included, (4) the full text or the data were not available.

Primary outcome and secondary outcomes definition

The primary outcome of this study was MACEs. The definition of adverse cardiovascular events is complicated. According to previous review, 15.5% of the literatures considered MACEs to include acute myocardial infarction (AMI) and stroke; 13.8% of the literatures

included AMI, stroke, and all-cause death; 8.6% of the literatures considered to include AMI, stroke, and cardiovascular death[12]. This study combines these ideas by defining MACEs as studies that were included as long as they included MI and stroke. At the same time, the expanded MACEs refers to the addition to the original MACEs that was not previously considered (including but not limited to cardiovascular death or coronary revascularization).

The secondary outcome of this study were MACEs for specific diseases such as MI, stroke, all-cause death, etc.

Data extraction and quality evaluation

Full-text assessment was performed independently by two authors (C. Z. H. and C. X. Q.) and data were extracted from the full text by two authors (F. Y. Y. and Z. Q. F.). Discrepancies were resolved by consensus or arbitrated by a third author (X.W.).

Data were extracted from the included articles using pre-set tables, including the basic information of the articles (authors, publication year, region, medication regimen, follow-up time, MACEs evaluation criteria) and the patient's basic characteristics (underlying disease history, age, sex, body mass index (BMI), primary outcome).

The Cochrane Code assessment was carried out on a line-by-line basis in the following seven areas: (1) random sequence generation (selection bias), (2) allocation concealment (selection bias), (3) blinding of participants and personnel (performance bias), (4) blinding of outcome assessment (detection bias), (5) incomplete outcome data (attrition bias), (6) selective reporting (reporting bias), (7) other bias. The appeals items were compared with the included studies one by one, and the corresponding basis was given. The evaluation results were high risk, unknown risk and low risk.

Statistical analysis

Review Manager (RevMan, version 5.3) and Stata (version 12.0) were used for statistical analysis. HR and 95% confidence interval (95%CI) were used to evaluate the association of vitamin D interventions with cardiovascular events. Note that when the study had multiple groups of vitamin D supplementation, they were all experimental groups and were combined. When HR<1, the results support the experimental group; when HR>1, support the control group. Chi-square tests are used to assess heterogeneity, using I^2 to indicate that I^2<25% is low heterogeneity, 25%≤I^2<50% is moderate heterogeneity, and I^2>50% is high heterogeneity. When I^2≤50%, the fixed effects model was employed, and when I^2>50%, the random effects model was employed.

Subgroup analyses were performed based on sex and BMI. All tests were two sides, and $p<0.05$ was considered statistically significant. When more than 10 studies were included, sensitivity analysis was carried out and Egger's test was used to test for publication bias.

Results

Basic characteristics of the study and quality assessment

A total of 26,278 studies were retrieved from Pubmed, Web of science, Ovid, Cochrane Library databases and Clinical Trials. After removing duplications and no additional channel supplementation, 22,365 studies were remained. By reading the titles and abstracts, 22,302 studies were excluded. Then, after reading 63 full texts, 58 studies were removed, of which 5 were excluded because they were not RCTs, 21 were excluded because the data were not available, 32 were excluded because they had no interesting outcomes (its outcome measure is not the HR, or results do not include incidence of MACEs). Finally, 5 RCTs[6, 13-16] were included, as shown in Figure 1.

The five studies[6, 13-16] involved a total of 57,201 participants, including 29,019 in the intervention group and 28,182 in the control group, published between 2017 and 2023. The studies were conducted in two in the United States, one in New England, one in Australia and one in Finland. The intervention group received vitamin D supplementation (oral), while the control group received a placebo. The average follow-up period was 3-5.3 years. Additional baseline information for participants can be viewed in Table 1 and Supplemental Table 1.

For quality evaluation, among all RCTs, 1 is at unclear risk of attrition bias, while others are low risk, as shown in Supplemental Figure 1 and Supplemental Figure 2.

Primary outcome

Pooled results including all RCTs[6, 13-16] showed no significant difference in the incidence of MACEs between the vitamin D intervention group and the control group (HR: 0.96, 95%CI: 0.89-1.03; p=0.77; I^2=13.6%; fixed-effect model), as shown in Figure 2a.

In addition, the pooled results from three RCTs[13, 15, 16], involving 30,789 participants, showed no significant difference between the vitamin D intervention group and the control group for expanded MACEs incidence (HR: 0.96, 95%CI: 0.86-1.06; p=0.77; I^2=0%; fixed-effect model), as shown in Figure 2b.

Secondary outcomes

For MI and stroke, four RCTs[6, 13-15] were included, involving 54,778 participants. Subgroup analysis showed that the vitamin D intervention group had a lower incidence of MI than the control group, but the difference was not statistically significant (HR: 0.88, 95%CI: 0.77-1.01; p=0.061; I^2=0%; fixed-effect model), as shown in Figure 5a. In addition, there was no significant difference in the incidence of stroke between the both groups (HR: 0.97, 95%CI: 0.84-1.12; p=0.675; I^2=0%; fixed-effect model), as shown in Figure 5b.

For cardiovascular death, two RCTs[13, 15] were included, involving 28,366 participants. Subgroup analyses showed no significant difference in cardiovascular death rates in the vitamin D intervention group compared with the control group (HR: 1.10, 95%CI: 0.87-1.38; p=0.422; I^2=0%; fixed-effect model), as shown in Figure 5c.

Subgroup analysis

For sex, three RCTs[6, 13, 15] were included, involving 49,668 participants. Subgroup analysis showed that among male participants, there was no significant difference in the incidence of MACEs between the both groups (HR: 0.92, 95%CI: 0.84-1.02; p=0.109; I^2=14.1%; fixed-effect model), as shown in Figure 3a. Also, among female participants, there was no significant difference in the incidence of MACEs between the both groups (HR: 0.95, 95%CI: 0.82-1.10; p=0.468; I^2=24.3%; fixed-effect model), as shown in Figure 3b.

For BMI, three RCTs[6, 13, 15] were included, involving 49,668 participants. Subgroup analysis showed no significant difference in the incidence of MACEs between the both groups among participants with BMI<25 kg/m^2 (HR: 1.04, 95%CI: 0.80-1.35; p=0.782; I^2=51.7%; random-effect model), as shown in Figure 4a. However, among participants with BMI≥25 kg/m^2, the vitamin D intervention group had a lower incidence of MACEs than the control group (HR: 0.91, 95%CI: 0.83-1.00; p=0.055; I^2=0%; fixed-effect model), reduced MACE risk by 9% but the difference was not statistically significant, as shown in Figure 4b.

Discussion

This meta-analysis was based on five high-quality RCTs that assessed the effect of vitamin D supplementation on the incidence of MACE for primary prevention. Some results of this study were consistent with previous meta-analyses, which showed that vitamin D supplementation had no significant effect on MACEs incidence, extended MACEs incidence, cardiovascular mortality, or stroke incidence. However, subgroup analysis found that the effect of vitamin D supplementation on the incidence of MACEs was influenced by BMI. Overweight/obese participants (BMI≥25 kg/m^2) benefit, while men, women and

non-overweight/obese participants (BMI<25 kg/m^2) do not. In addition, the study also found a possible association between vitamin D supplementation and a reduction in the incidence of MI.

Previous studies have shown that vitamin D plays an important protective role in cardiovascular effects. The mechanism may be as follows: 1. in the renin-angiotensin system, angiotensin II causes significant constriction of small arteries throughout the body and increases blood pressure, which can lead to hypertension and increased cardiac workload. Vitamin D promotes the expression of angiotensin converting enzyme-2, which breaks down angiotensin II into angiotensin 1-7. Vitamin D also counteracts excess angiotensin II, thereby enhancing the antihypertensive, antifibrotic and anti-inflammatory properties of angiotensin 1-7[17]. In one experiment, renin expression and plasma angiotensin II production were increased several-fold in vitamin D receptor (VDR)-deficient mice, while 1,25$(OH)_2D_3$ injections resulted in renin inhibition[18]. 2. In the immune system, 1,25$(OH)_2D_3$ inhibited interleukin (IL)-12 production by dendritic cell while inducing IL-10 production. 1,25$(OH)_2D_3$ was also observed to act in T cells, which inhibits the production of IL-2, IL-17 and interferon-ϒ and attenuates the cytotoxic activity and proliferation of cluster of differentiation 4 and cluster of differentiation 8 T cells[19]. Thereby maintaining the stability of endothelial and vascular smooth muscle cells. 3. In the fibrinolytic system, it has also been shown that plasminogen activator inhibitor-1 is a major mediator involved in CVD, and 1,25$(OH)_2D_3$ reduces CVD by blocking NF-κB activation to downregulate plasminogen activator inhibitor-1[20].

Meanwhile, vitamin D deficiency may be a risk factor for CVD. A meta-analyse involving up to 180,000 individuals have shown that low vitamin D levels are associated with a significantly increased risk of hypertension, cardiovascular events, and cardiovascular mortality[21]. And observational studies have shown associations between serum 25(OH)D levels and general health, CVD risk factors, and CVD mortality[22, 23]. In several mouse studies, matrix metalloproteinase (MMP), a protein responsible for abnormal remodelling of cardiomyocytes after injury and atherosclerosis, was found to be upregulated in VDR knockout mice[24], and cardiac diastolic and systolic forces were impaired and left ventricular hypertrophy developed in VDR knockout mice[25]. Finally, it has also been shown that dietary vitamin D is insufficient to accelerate calcification in the vascular system of low density lipoprotein receptor knockout and wild-type mice, and that vascular calcification is reduced after increased vitamin D supplementation[26]. It was also found that in patients with chronic kidney disease, active vitamin D may have a beneficial effect on vascular calcification by increasing the secretion of the anti-aging factor Klotho and arterial medial bone bridging protein[27].

However, the present study found that vitamin D supplementation was not helpful for the incidence of MACEs in the general population or for the extended MACEs incidence. Previous meta-analysis[21, 28] of dose-response analyses of circulating 25(OH)D concentrations found that a non-linear relationship was observed between 25(OH)D and CVD, with a plateau between 20 and 30 ng/ml (50 and 75 nmol/l), and that in populations below 30 ng/ml, the lower the vitamin D level, the greater the risk of CVD and the greater the benefit of vitamin D supplementation. However, vitamin D supplementation had little effect in people with levels above 30 ng/ml. This may be because oversupplementation does not convert all the vitamin D into active vitamin D. Experiments have shown that $1,25(OH)_2D_3$ inhibits the hepatic synthesis of its precursor 25-OHD, preventing further conversion of vitamin D into $1,25(OH)_2D_3$[29]. It is also possible that because there is a limited amount of VDR in the body, in people who are not vitamin D deficient, the excess vitamin D does not have receptors to bind to efficiently and is converted to $24,25(OH)_2D_3$, which has little binding to the VDR[30]. It is also possible that when the concentration of $1,25(OH)_2D_3$ in the body is high, the level of vitamin D-24-hydroxylase[31], the enzyme that breaks down and metabolises it, increases and converts it to inactive vitamin D, thus maintaining the dynamic balance of active vitamin D in the body. In our study, mean baseline 25(OH)D levels ranged from 24.4 to 30.9 ng/ml (non-vitamin D-deficient population), suggesting that additional supplements in the non-vitamin D-deficient population may not reduce the risk of MACEs.

MACEs include a wide range of cardiovascular outcomes, mainly MI, stroke and cardiovascular death. Subgroup analyses have been performed that show a protective effect of vitamin D against MI. Higher serum 25(OH)D levels were associated with a lower prevalence of MI than lower levels in both case-control studies and showed that the optimal 25(OH)D level should be at least 30 ng/ml to reduce the risk of MI[32]. This phenomenon may be mediated by vasodilatory effects, improved endothelial and vascular smooth muscle cell function[33, 34]. Also, through a number of pathways vitamin D inhibits MMP, the enzymes that are important in plaque destabilisation, especially MMP-9 and MMP-2 which are increased in MI[35]. However, vitamin D does not reduce cardiovascular death or stroke. A meta-analysis of all-cause mortality found no further reduction in cardiovascular mortality when vitamin D levels exceeded 36 ng/ml[36]. This may be due to the existence of competition for death, with MI accounting for only about 10% of all-cause deaths[37], and the difference was not statistically significant due to the limited sample size. Stroke is divided into ischaemic and haemorrhagic strokes, with haemorrhagic strokes mainly associated with cerebral haemorrhage and subarachnoid haemorrhage and ischaemic strokes mainly associated with AF and carotid plaque. No significant association has been found between vitamin D supplementation and cerebral and subarachnoid haemorrhage, so vitamin D supplementation is not associated with haemorrhagic stroke. There are conflicting conclusions regarding the association of vitamin and others suggesting that there is no

correlation[38, 39]. Studies have also reported a non-linear positive association between serum 25OHD levels and carotid intima-media thickness in participants with adequate serum 25(OH)D (≥50 nmol/l)[40]. Similarly, the effect of vitamin D supplementation on AF is inconclusive, with some studies finding no association between low levels of 25(OH)D (<20 ng/ml) and the incidence of AF[41]. Therefore, the effect of vitamin D supplementation on ischaemic stroke is not clear.

Similarly, since vitamin D supplementation has no significance for the total population, there is no point in distinguishing between the sexes. However, it is worth exploring the fact that the included studies did not differentiate between female subjects with menopause. Then again, it is well known that oestrogen has a protective effect on lipids[42] and blood pressure[43, 44]. This could then interfere with the experimental results and lead to some bias. Secondly, the studies included different races, which may also affect the role of vitamin D.

Although vitamin D supplementation had no effect on the overall population or by sex, BMI subgroup analyses showed some significant results. It is well known that obesity is one of the cardiovascular risk factors[45]. Our study analysed BMI in subgroups and it is noteworthy that vitamin D supplementation reduced the risk of MACEs in overweight/obese people. The reasons for this are: 1. obesity itself is an independent cardiovascular risk factor[46], and obese patients often have comorbid metabolic diseases such as hypertension, type 2 diabetes mellitus[47], hyperuricaemia[48], fatty liver disease[49]. In this high-risk group, vitamin D supplementation has helped to reduce the risk of MACEs. 2. Obesity is associated with vitamin D deficiency[50], which may be related to four aspects: first, obese people have short exercise time, short sunshine, limited synthesis of vitamin D[51]; second, volume dilution[52], obese people need more vitamin D, vitamin D is relatively insufficient; and then it may be associated with people living with obesity throughout. The decrease in vitamin D intake is due to a decrease in their intake of oily fish and dairy products[53]; finally, the bioavailability of vitamin D is lower in obese people than in normal-weight people because they have more deposits in fat tissue that they cannot use[54]. It has also been shown experimentally that the expression levels of vitamin D 25-hydroxylase CYP2J2 and vitamin D 1α-hydroxylase CYP27B1 in the subcutaneous adipose tissue of obese women are 71% and 49% lower[55], respectively, than in lean women. Therefore, vitamin D deficiency is more common in the obese population.

For the 5 RCTs[6, 13-16] included in the study, some of the research designs and research results can still be thought about for their impact on this study. First, adherence was high in all five studies, with most adherence around 80%. However, there were still some trial patients who did not participate in the surveys or had poor adherence, which could have biased the results. Second, the D2d trial[16] included patients with pre-diabetes, which may have affected the

results. Finally, the D-Health trial[6] did not measure baseline vitamin D levels, but rather created a model to predict them, which could also have biased the results. Based on these analyses, it is possible that these confounding factors and the effect of adherence contributed to the fact that the primary outcome of this study was not statistically significant.

However, when in the BMI subgroup, the presence of the weight factor modifies the degree of association between vitamin D supplementation and MACEs, making it present a benefit of supplementation in the overweight/obese population and vice versa no benefit. This may be related to the previously stated idea that obesity itself is one of the cardiovascular disease risks, volume dilution, poor diet, limited vitamin D synthesis and low vitamin D utilisation in these populations. In contrast, in the sex subgroup, the sex factor relatively did not change the association between vitamin D supplementation and MACEs, so the results were still not statistically signific. So more and larger, multicentre RCTs are needed to troubleshoot these confounding factors and further explore and validate ideas.

For all we know, this is the first meta-analysis to comprehensively and systematically explore the relationship between vitamin D supplementation and the incidence of MACEs using HR and 95%CI as an indicator for evaluating the relationship, which could be informative about the value of vitamin D supplementation in the prevention of MACEs. Importantly, meta-analysis were based on recent (2017-2023), high-quality RCTs. However, there are some limitations to this meta-analysis. First, the limited number of studies did not allow for further subgroup analyses. Meanwhile, the statistical efficacy of the study may also be weak due to the small number of included literature, which makes it difficult to perform publication bias assessment and sensitivity analysis. Second, this meta-analysis did not have the means to examine the dose-effect relationship and the effect of supplementation duration on the incidence of MACEs. Finally, a small number of unavailable articles and non-English articles were excluded, which may have an increased risk of publication bias and selection bias.

Conclusion

The meta-analysis showed that vitamin D supplementation did not significantly contribute to the risk reduction of MACEs and expanded MACEs in the general population, as well as to the reduction of stroke risk, and cardiovascular death. Notably, vitamin D supplementation was found to reduce the incidence of MACEs in overweight/obese populations (BMI≥25 kg/m^2), but not in non-overweight/obese populations (BMI<25 kg/m^2). Vitamin D should be recommended for overweight/obese people. Vitamin D supplementation was also found to be potentially helpful in reducing the incidence of MI in the general population. Unfortunately, vitamin D supplementation did not have a significant protective effect for the entire population, but it is still worth continuing to study the effects for different populations.

Finally, due to the limited number of RCTs included and the restricted experimental population, the findings may not be fully applicable to the entire population, more multicenter RCTs with larger-scale were needed to further confirm the conclusion.

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Disclosures

Ethics Approval and Consent to Participate

Not applicable, as this paper is based on research from global databases.

Consent to Publish

Not applicable.

Availability of Data and Materials

The datasets supporting the conclusions of this article are included within the article. For further details, please contact the corresponding author.

Competing Interests

The authors declare no conflict of interest.

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Authors' Contributions

Each author contributed significantly to the conception and development of the present paper. Xiaoqing Cheng and Zhenghao Chen designed the research process. Yingying Fang and Qiufeng Zhang searched the database for corresponding articles and extracted useful information from the articles above. Bangsheng Chen and Wang Xi used statistical software for analysis. Ziqiao Pan and Luyong Guo drafted the meta-analysis. All authors have read and approved the final manuscript.

Clinical trial number

Not applicable

Reference

1. Roth GA, Mensah GA, Johnson CO, Addolorato G, Ammirati E, Baddour LM, et al. Global Burden of Cardiovascular Diseases and Risk Factors, 1990-2019: Update From the GBD 2019 Study. Journal of the American College of Cardiology. 2020;76(25):2982-3021.

2. Joynt Maddox KE, Elkind MSV, Aparicio HJ, Commodore-Mensah Y, de Ferranti SD, Dowd WN, et al. Forecasting the Burden of Cardiovascular Disease and Stroke in the United States Through 2050-Prevalence of Risk Factors and Disease: A Presidential Advisory From the American Heart Association. Circulation. 2024;150(4):e65-e88.

3. Arnett DK, Blumenthal RS, Albert MA, Buroker AB, Goldberger ZD, Hahn EJ, et al. 2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation. 2019;140(11):e596-e646.

4. Wimalawansa SJ. Vitamin D and cardiovascular diseases: Causality. The Journal of steroid biochemistry and molecular biology. 2018;175:29-43.

5. Kim DH, Sabour S, Sagar UN, Adams S, Whellan DJ. Prevalence of hypovitaminosis D in cardiovascular diseases (from the National Health and Nutrition Examination Survey 2001 to 2004). The American journal of cardiology. 2008;102(11):1540-4.

6. Thompson B, Waterhouse M, English DR, McLeod DS, Armstrong BK, Baxter C, et al. Vitamin D supplementation and major cardiovascular events: D-Health randomised controlled trial. BMJ (Clinical research ed). 2023;381:e075230.

7. Ye H, Li Y, Liu S, Zhang X, Liang H, Wang Y, et al. Association between serum 25-hydroxyvitamin D and vitamin D dietary supplementation and risk of all-cause and cardiovascular mortality among adults with hypertension. Nutrition journal. 2024;23(1):33.

8. Mattumpuram J, Maniya MT, Faruqui SK, Ahmed A, Jaiswal V, Harshakumar SP. Cardiovascular and Cerebrovascular Outcomes With Vitamin D Supplementation: A Systematic Review and Meta-Analysis. Current problems in cardiology. 2024;49(1 Pt

C):102119.

9. Pei YY, Zhang Y, Peng XC, Liu ZR, Xu P, Fang F. Association of Vitamin D Supplementation with Cardiovascular Events: A Systematic Review and Meta-Analysis. Nutrients. 2022;14(15).

10. Rossello X, Pocock SJ, Julian DG. Long-Term Use of Cardiovascular Drugs: Challenges for Research and for Patient Care. Journal of the American College of Cardiology. 2015;66(11):1273-85.

11. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ (Clinical research ed). 2021;372:n71.

12. Bosco E, Hsueh L, McConeghy KW, Gravenstein S, Saade E. Major adverse cardiovascular event definitions used in observational analysis of administrative databases: a systematic review. BMC medical research methodology. 2021;21(1):241.

13. Virtanen JK, Nurmi T, Aro A, Bertone-Johnson ER, Hyppönen E, Kröger H, et al. Vitamin D supplementation and prevention of cardiovascular disease and cancer in the Finnish Vitamin D Trial: a randomized controlled trial. The American journal of clinical nutrition. 2022;115(5):1300-10.

14. Scragg R, Stewart AW, Waayer D, Lawes CMM, Toop L, Sluyter J, et al. Effect of Monthly High-Dose Vitamin D Supplementation on Cardiovascular Disease in the Vitamin D Assessment Study : A Randomized Clinical Trial. JAMA cardiology. 2017;2(6):608-16.

15. Manson JE, Bassuk SS, Buring JE. Principal results of the VITamin D and OmegA-3 TriaL (VITAL) and updated meta-analyses of relevant vitamin D trials. The Journal of steroid biochemistry and molecular biology. 2020;198:105522.

16. Desouza C, Chatterjee R, Vickery EM, Nelson J, Johnson KC, Kashyap SR, et al. The effect of vitamin D supplementation on cardiovascular risk in patients with prediabetes: A secondary analysis of the D2d study. Journal of diabetes and its complications. 2022;36(8):108230.

17. Cui C, Xu P, Li G, Qiao Y, Han W, Geng C, et al. Vitamin D receptor activation regulates microglia polarization and oxidative stress in spontaneously hypertensive rats and

angiotensin II-exposed microglial cells: Role of renin-angiotensin system. Redox biology. 2019;26:101295.

18. Li YC, Kong J, Wei M, Chen ZF, Liu SQ, Cao LP. 1,25-Dihydroxyvitamin D(3) is a negative endocrine regulator of the renin-angiotensin system. The Journal of clinical investigation. 2002;110(2):229-38.

19. Mora JR, Iwata M, von Andrian UH. Vitamin effects on the immune system: vitamins A and D take centre stage. Nature reviews Immunology. 2008;8(9):685-98.

20. Chen Y, Kong J, Sun T, Li G, Szeto FL, Liu W, et al. 1,25-Dihydroxyvitamin D_3 suppresses inflammation-induced expression of plasminogen activator inhibitor-1 by blocking nuclear factor-κB activation. Archives of biochemistry and biophysics. 2011;507(2):241-7.

21. Zhang R, Li B, Gao X, Tian R, Pan Y, Jiang Y, et al. Serum 25-hydroxyvitamin D and the risk of cardiovascular disease: dose-response meta-analysis of prospective studies. The American journal of clinical nutrition. 2017;105(4):810-9.

22. Mandarino NR, Júnior F, Salgado JV, Lages JS, Filho NS. Is vitamin d deficiency a new risk factor for cardiovascular disease? The open cardiovascular medicine journal. 2015;9:40-9.

23. Park S, Lee BK. Vitamin D deficiency is an independent risk factor for cardiovascular disease in Koreans aged ≥ 50 years: results from the Korean National Health and Nutrition Examination Survey. Nutrition research and practice. 2012;6(2):162-8.

24. Rahman A, Hershey S, Ahmed S, Nibbelink K, Simpson RU. Heart extracellular matrix gene expression profile in the vitamin D receptor knockout mice. The Journal of steroid biochemistry and molecular biology. 2007;103(3-5):416-9.

25. Tishkoff DX, Nibbelink KA, Holmberg KH, Dandu L, Simpson RU. Functional vitamin D receptor (VDR) in the t-tubules of cardiac myocytes: VDR knockout cardiomyocyte contractility. Endocrinology. 2008;149(2):558-64.

26. Schmidt N, Brandsch C, Schutkowski A, Hirche F, Stangl GI. Dietary vitamin D inadequacy accelerates calcification and osteoblast-like cell formation in the vascular system of LDL receptor knockout and wild-type mice. The Journal of nutrition. 2014;144(5):638-46.

27. Lau WL, Leaf EM, Hu MC, Takeno MM, Kuro-o M, Moe OW, et al. Vitamin D receptor agonists increase klotho and osteopontin while decreasing aortic calcification in mice with chronic kidney disease fed a high phosphate diet. Kidney international. 2012;82(12):1261-70.

28. Wang L, Song Y, Manson JE, Pilz S, März W, Michaëlsson K, et al. Circulating 25-hydroxy-vitamin D and risk of cardiovascular disease: a meta-analysis of prospective studies. Circulation Cardiovascular quality and outcomes. 2012;5(6):819-29.

29. Bell NH, Shaw S, Turner RT. Evidence that 1,25-dihydroxyvitamin D3 inhibits the hepatic production of 25-hydroxyvitamin D in man. The Journal of clinical investigation. 1984;74(4):1540-4.

30. Tebben PJ, Milliner DS, Horst RL, Harris PC, Singh RJ, Wu Y, et al. Hypercalcemia, hypercalciuria, and elevated calcitriol concentrations with autosomal dominant transmission due to CYP24A1 mutations: effects of ketoconazole therapy. The Journal of clinical endocrinology and metabolism. 2012;97(3):E423-7.

31. Hahn CN, Baker E, Laslo P, May BK, Omdahl JL, Sutherland GR. Localization of the human vitamin D 24-hydroxylase gene (CYP24) to chromosome 20q13.2-->q13.3. Cytogenetics and cell genetics. 1993;62(4):192-3.

32. Scragg R, Jackson R, Holdaway IM, Lim T, Beaglehole R. Myocardial infarction is inversely associated with plasma 25-hydroxyvitamin D3 levels: a community-based study. International journal of epidemiology. 1990;19(3):559-63.

33. Wakasugi M, Noguchi T, Inoue M, Kazama Y, Tawata M, Kanemaru Y, et al. Vitamin D3 stimulates the production of prostacyclin by vascular smooth muscle cells. Prostaglandins. 1991;42(2):127-36.

34. Artaza JN, Norris KC. Vitamin D reduces the expression of collagen and key profibrotic factors by inducing an antifibrotic phenotype in mesenchymal multipotent cells. The Journal of endocrinology. 2009;200(2):207-21.

35. Timms PM, Mannan N, Hitman GA, Noonan K, Mills PG, Syndercombe-Court D, et al. Circulating MMP9, vitamin D and variation in the TIMP-1 response with VDR genotype: mechanisms for inflammatory damage in chronic disorders? QJM : monthly journal of the Association of Physicians. 2002;95(12):787-96.

36. Garland CF, Kim JJ, Mohr SB, Gorham ED, Grant WB, Giovannucci EL, et al. Meta-analysis of all-cause mortality according to serum 25-hydroxyvitamin D. American journal of public health. 2014;104(8):e43-50.

37. Benjamin EJ, Virani SS, Callaway CW, Chamberlain AM, Chang AR, Cheng S, et al. Heart Disease and Stroke Statistics—2018 Update: A Report From the American Heart Association. 2018;137(12):e67-e492.

38. Chen FH, Liu T, Xu L, Zhang L, Zhou XB. Association of Serum Vitamin D Level and Carotid Atherosclerosis: A Systematic Review and Meta-analysis. Journal of ultrasound in medicine : official journal of the American Institute of Ultrasound in Medicine. 2018;37(6):1293-303.

39. Blondon M, Sachs M, Hoofnagle AN, Ix JH, Michos ED, Korcarz C, et al. 25-Hydroxyvitamin D and parathyroid hormone are not associated with carotid intima-media thickness or plaque in the multi-ethnic study of atherosclerosis. Arteriosclerosis, thrombosis, and vascular biology. 2013;33(11):2639-45.

40. van Dijk SC, Sohl E, Oudshoorn C, Enneman AW, Ham AC, Swart KM, et al. Non-linear associations between serum 25-OH vitamin D and indices of arterial stiffness and arteriosclerosis in an older population. Age and ageing. 2015;44(1):136-42.

41. Vitezova A, Cartolano NS, Heeringa J, Zillikens MC, Hofman A, Franco OH, et al. Vitamin D and the risk of atrial fibrillation--the Rotterdam Study. PloS one. 2015;10(5):e0125161.

42. Haffner SM, Valdez RA. Endogenous sex hormones: impact on lipids, lipoproteins, and insulin. The American journal of medicine. 1995;98(1a):40s-7s.

43. Xue B, Pamidimukkala J, Lubahn DB, Hay M. Estrogen receptor-alpha mediates estrogen protection from angiotensin II-induced hypertension in conscious female mice. American journal of physiology Heart and circulatory physiology. 2007;292(4):H1770-6.

44. Vlachovsky SG, Di Ciano LA, Oddo EM, Azurmendi PJ, Silberstein C, Ibarra FR. Role of Female Sex Hormones and Immune Response in Salt-Sensitive Hypertension Development: Evidence from Experimental Models. Current hypertension reports. 2023;25(11):405-19.

45. Ng M, Fleming T, Robinson M, Thomson B, Graetz N, Margono C, et al. Global, regional, and national prevalence of overweight and obesity in children and adults during 1980-2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet (London, England). 2014;384(9945):766-81.

46. Afshin A, Forouzanfar MH, Reitsma MB, Sur P, Estep K, Lee A, et al. Health Effects of Overweight and Obesity in 195 Countries over 25 Years. The New England journal of medicine. 2017;377(1):13-27.

47. Martos-Moreno G, Martínez-Villanueva J, González-Leal R, Chowen JA, Argente J. Sex, puberty, and ethnicity have a strong influence on growth and metabolic comorbidities in children and adolescents with obesity: Report on 1300 patients (the Madrid Cohort). Pediatric obesity. 2019;14(12):e12565.

48. Kubota M. Hyperuricemia in Children and Adolescents: Present Knowledge and Future Directions. Journal of nutrition and metabolism. 2019;2019:3480718.

49. Anderson EL, Howe LD, Jones HE, Higgins JP, Lawlor DA, Fraser A. The Prevalence of Non-Alcoholic Fatty Liver Disease in Children and Adolescents: A Systematic Review and Meta-Analysis. PloS one. 2015;10(10):e0140908.

50. López-Galisteo JP, Gavela-Pérez T, Mejorado-Molano FJ, Pérez-Segura P, Aragón-Gómez I, Garcés C, et al. Prevalence and risk factors associated with different comorbidities in obese children and adolescents. Endocrinologia, diabetes y nutricion. 2022;69(8):566-75.

51. Gutiérrez Medina S, Gavela-Pérez T, Domínguez-Garrido MN, Gutiérrez-Moreno E, Rovira A, Garcés C, et al. The influence of puberty on vitamin D status in obese children and the possible relation between vitamin D deficiency and insulin resistance. Journal of pediatric endocrinology & metabolism : JPEM. 2015;28(1-2):105-10.

52. Drincic AT, Armas LA, Van Diest EE, Heaney RP. Volumetric dilution, rather than sequestration best explains the low vitamin D status of obesity. Obesity (Silver Spring, Md). 2012;20(7):1444-8.

53. Benedik E. Sources of vitamin D for humans. International journal for vitamin and nutrition research Internationale Zeitschrift fur Vitamin- und Ernahrungsforschung Journal international de vitaminologie et de nutrition. 2022;92(2):118-25.

54. Wortsman J, Matsuoka LY, Chen TC, Lu Z, Holick MF. Decreased bioavailability of vitamin D in obesity. The American journal of clinical nutrition. 2000;72(3):690-3.

55. Wamberg L, Christiansen T, Paulsen SK, Fisker S, Rask P, Rejnmark L, et al. Expression of vitamin D-metabolizing enzymes in human adipose tissue -- the effect of obesity and diet-induced weight loss. International journal of obesity (2005). 2013;37(5):651-7.

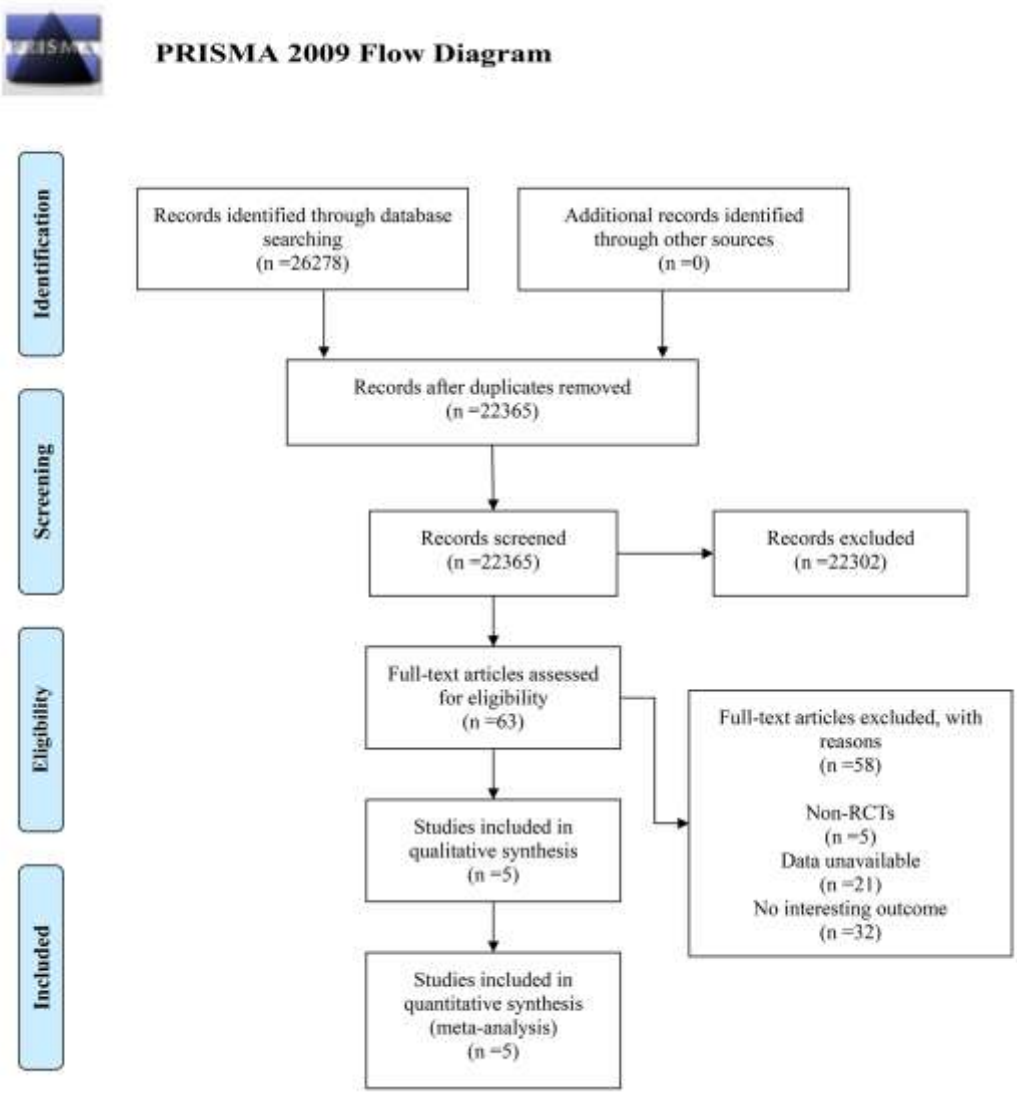

Fig. 1: Flow diagram of the selection process.

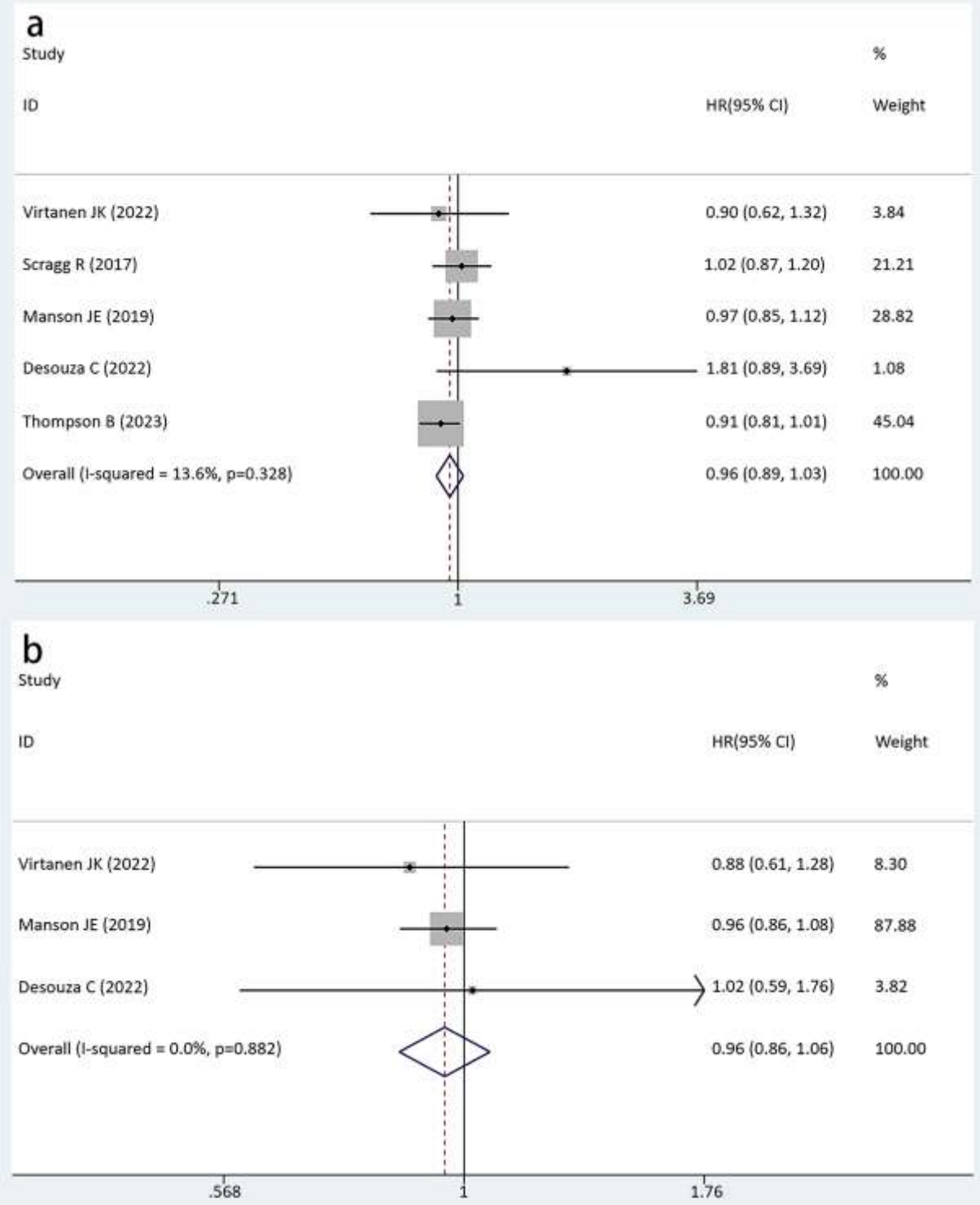

Fig. 2: Forest plot of the association between vitamin D supplementation and incidence of MACEs (a: MACEs, p=0.77, fixed-effect model; b: expand MACEs, p=0.77, fixed-effect model).

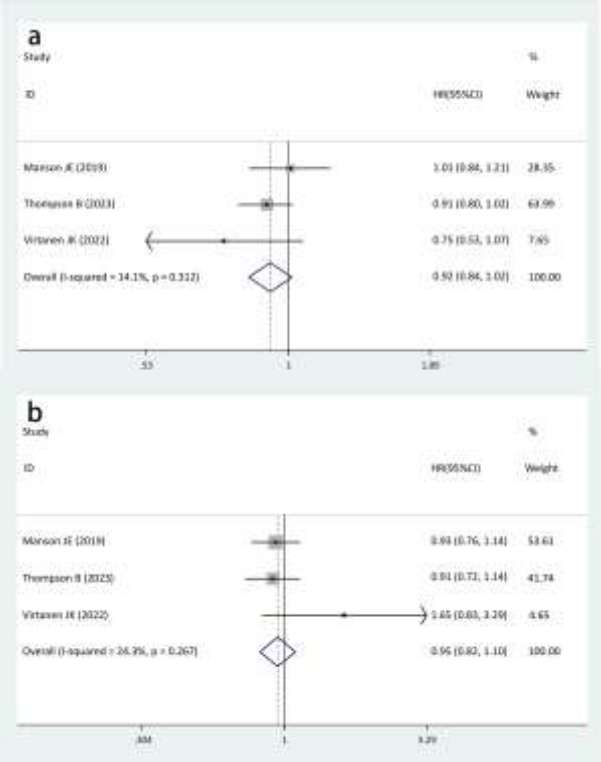

Fig. 3: Forest plots of the association between vitamin D supplementation and incidence of MACEs in sex-specific subgroups (a: male, p=0.109, fixed-effect model; b: female, p=0.468, fixed-effect model).

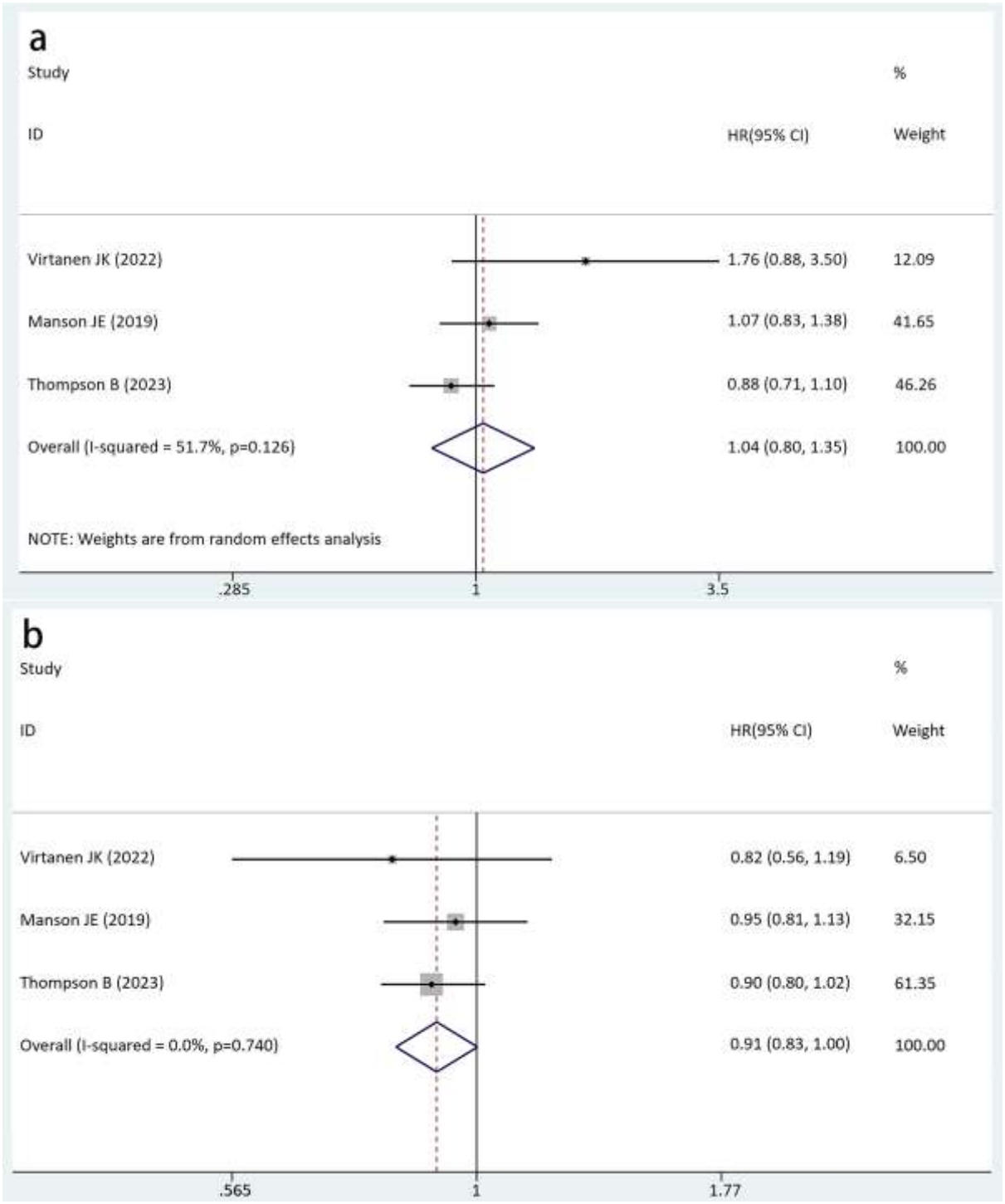

Fig. 4: Forest plots of the association between vitamin D supplementation and incidence of MACEs in BMI subgroups (a: BMI<25 kg/m^2, p=0.782, random-effect model; b: BMI≥25 kg/m^2, p=0.055, fixed-effect model).

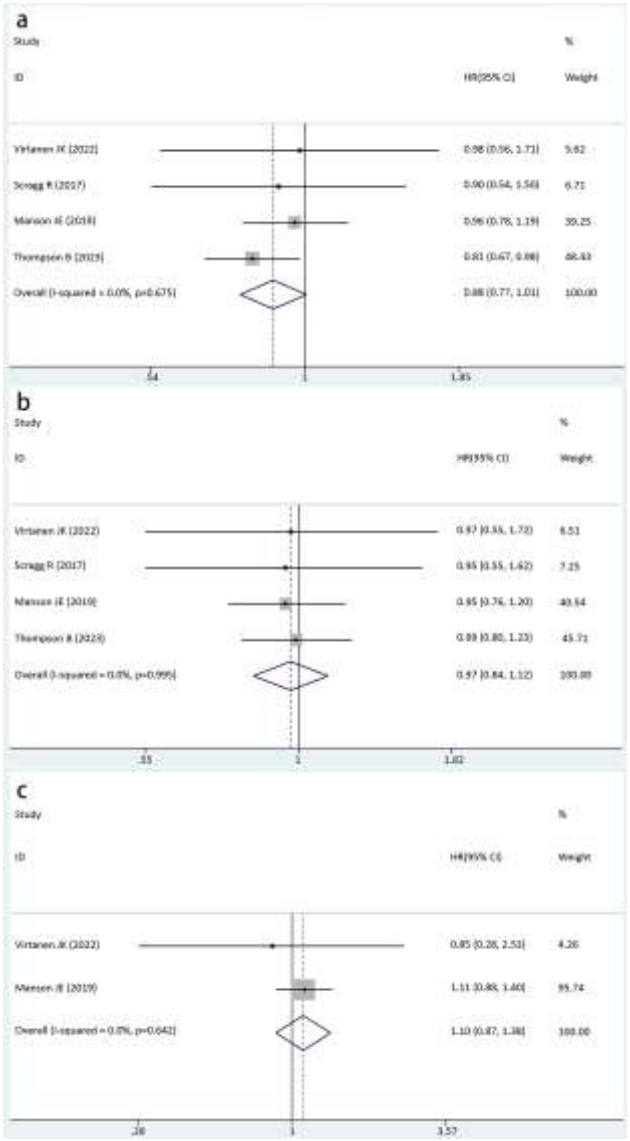

Fig. 5: Forest plots of the association between vitamin D supplementation and incidence of different cardiovascular outcome in cardiovascular event subgroups (a: MI, p=0.061, fixed-effect model; b: stroke, p=0.675, fixed-effect model; c: cardiovascular death, p=0.422, fixed-effect model).

Table 1. Characteristics of all the studies included in the meta-analysis.

Author	Year	RCTs	Country	Age restriction		Intervention group treatment	Number		Primary outcome	Median follow-up (years)
				Man	Woman		Experimental	Control		
Virtanen JK	2022	FIND	Finnish	≥60	≥65	vitamin D3 (1600 IU/d) vitamin D3 (3200 IU/d)	832 833	830	MACEs	4.3
Scragg R	2017	VidA	New Zealand	50-84		vitamin D3 (first month 200000 IU, after 100000 IU/month)	2558	2552	CVD	3.3
Manson JE	2019	VITAL	U.S.	≥50	≥55	vitamin D3 (2000 IU/d) + marine omega-3 fatty acids	12927	12944	MACEs	5.3
Desouza C	2022	D2d	U.S.	≥30		vitamin D3 (4000 IU/d)	1211	1212	MACEs	3
Thompson B	2023	D-Health	Australian	60-84		vitamin D3 (60000 IU/month)	10658	10644	MACEs	5

RCTs, randomized control trials; MACEs, major adverse cardiovascular events; CVD, cardiovascular disease.