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# Effect of vitamin $B_2$, vitamin C, vitamin D, vitamin E and folic acid in adults with essential hypertension: a systematic review and network meta-analysis

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## ABSTRACT

**Objectives** The objective of the current study is to compare the treatment effects of different vitamins on essential hypertension to provide an initial basis for developing evidence-based practices.

**Design** Systematic review and network meta-analysis.

**Data sources** Five electronic databases (PubMed, Embase, Web of Science, Cochrane Central Register of Controlled Trials and ClinicalTrials.gov) were searched from their inception to 25 September 2023.

**Outcomes** The primary outcomes were the difference between the intervention group and the control group in changes in office systolic blood pressure (SBP) and office diastolic blood pressure (DBP) from baseline. The secondary outcomes were the difference between the intervention group and the control group in changes in 24-hour mean ambulatory systolic blood pressure (24 hours SBP), 24-hour mean ambulatory diastolic blood pressure (24 hours DBP) and heart rate (HR) from baseline.

**Results** A total of 23 studies comparing five vitamins (vitamin $B_2$, vitamin C, vitamin D, vitamin E, folic acid) and involving 2218 participants were included. The included trials were all vitamin versus placebo, so the network was star-shaped. Among the five vitamins, only vitamin E was significantly more effective at reducing SBP (mean difference: −14.14 mm Hg, 95% credible intervals: −27.62 to −0.88) than placebo. In addition, no evidence was found that any of the five vitamins influenced DBP, 24 hours SBP, 24 hours DBP, or HR. The dose of vitamins, geographical region and percentage of males (only SBP) might be sources of heterogeneity. Sensitivity and subgroup analysis revealed that the effect of vitamin intervention on blood pressure varies according to different doses of vitamins.

**Conclusions** According to the results, vitamin E might be an effective measure to reduce SBP, but more research is needed to validate this finding.

**PROSPERO registration number** CRD42022352332.

## STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The systematic review and network meta-analysis included the most recent randomised controlled trials and directly compared the treatment effects of different vitamins on essential hypertension.
⇒ Vitamin E might be an effective measure to reduce office systolic blood pressure.
⇒ The sample sizes of the included studies were small, thus affecting the interpretation of the results.
⇒ Heterogeneity was observed in some comparisons.

## INTRODUCTION

The prevalence of hypertension gradually increased worldwide from 1990 to 2019. In low-income and middle-income regions (eg, central and eastern Europe, Central Asia, Oceania, Southern Africa and some countries in Latin America and the Caribbean), the prevalence of hypertension is as high as 50%.[1] The major pathophysiological mechanism of hypertension includes renin-angiotensin-aldosterone system activation, oxidative stress, innate and adaptive immunity, genetics, sodium homeostasis, sympathetic activation, renal mechanisms and endothelial dysfunction.[2] In addition to standard pharmacological treatments (eg, diuretics, ACE inhibitors, angiotensin receptor blockers and calcium channel blockers), there has been an increase in the use of non-pharmacological management (eg, weight loss, dietary modifications and exercise) to improve blood pressure control.[3]

In hypertension treatment, intensive lifestyle interventions are critical. According to the most recent study, this type of treatment is primarily based on physical exercise, body weight management, healthy dietary patterns, circadian synchrony and stress management.[4] Intensive lifestyle intervention improves vascular function and, as a result, decreases central blood pressure. Furthermore, intensive lifestyle treatment may increase anti-inflammatory nutrient levels in patients.[5] A balanced and adequate intake of nutrients is an important part of a healthy eating pattern,

but there is insufficient evidence regarding the pros and cons of vitamin supplementation for the prevention of cardiovascular disease.[6] Many subsequent studies have confirmed that vitamin deficiency is strongly associated with hypertension, especially vitamin C and vitamin D deficiencies.[7 8] However, the efficacy of vitamin supplementation for reducing blood pressure in patients with hypertension remains unclear. Differences in the populations tested, doses of intervention and duration of intervention could result in different trial outcomes.[9 10] Meta-analysis could provide strong evidence to inform clinical decision-making by integrating and analysing existing trial data. Some traditional pairwise meta-analyses have examined the effects of vitamin treatment.

When multiple interventions are available for comparison, head-to-head trial evidence may be limited and it may be impossible to make comparisons between specific interventions. In such cases, network meta-analysis can help guide clinical decision-making by estimating direct and indirect treatment effects, comparing multiple treatment approaches and providing a ranking of interventions. This systematic review and network meta-analysis aims to summarise existing data from randomised trials and to provide evidence to guide clinical decision-making regarding the effects of different vitamin supplements on blood pressure in patients with hypertension.

## METHODS

This network meta-analysis was conducted in strict accordance with the latest version of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses reporting guidelines[11] and the extension statement for reporting network meta-analyses.[12]

### Patient and public involvement

No patient was involved in this systematic review and network meta-analysis.

### Data sources

We searched PubMed, Embase, Web of Science (Web of Science Core Collection) and Cochrane Central Register of Controlled Trials from the date of their inception to 25 September 2023. ClinicalTrials.gov was also searched to identify any published, unpublished and ongoing randomised controlled trials (RCTs). We also contacted the authors of articles with incomplete data to retrieve missing information. Moreover, we manually searched the reference lists of relevant systematic reviews and meta-analyses. Only English-language papers were considered for inclusion. The search strategy used the terms 'hypertens*' or 'blood pressure' combined with various vitamin names (online supplemental table S1).

### Trial selection criteria and trial identification

We included RCTs comparing vitamins with placebo or other vitamins as oral therapy for hypertension. The participants were adults (≥18 years old and of both sexes) with essential hypertension. The diagnostic criteria for hypertension were based on the WHO/International Society of Hypertension standard. We excluded quasi-randomised trials and participants with secondary hypertension. The inclusion and exclusion criteria were developed in accordance with the PICOS (Participants, Intervention, Comparison, Outcomes and Study design) principle and are shown in online supplemental table S2. Two investigators independently screened the literature, reviewed the full texts and extracted the relevant data. Any discrepancies between the two investigators were resolved by consulting a third investigator.

### Outcomes and data extraction

The primary outcomes were the difference between the intervention group and the control group in changes in office systolic blood pressure (SBP) and office diastolic blood pressure (DBP) from baseline. The secondary outcomes were the difference between the intervention group and the control group in changes in 24-hour mean ambulatory systolic blood pressure (24 hours SBP), 24-hour mean ambulatory diastolic blood pressure (24 hours DBP) and heart rate (HR) from baseline. If the article did not provide detailed blood pressure data, we performed data conversion according to the Cochrane Handbook for Systematic Reviews of Interventions V.6.3.

### Quality and risk of bias assessment

We independently assessed the risk of bias in RCTs following the Cochrane Handbook for Systematic Reviews of Interventions and used the Cochrane Risk of Bias tool V.2.0,[13] which includes assessment bias of the randomisation process, deviations from intended interventions, missing outcome data, measurement of the outcome and selection of the reported result. The overall risk of bias was divided into three categories: low risk of bias, some concern or high risk of bias.

### Data synthesis and analysis

We performed a network meta-analysis by combining all available comparisons in a hierarchical Bayesian model. We estimated the mean difference (MD) for efficacy-related continuous outcomes. The pooled analyses were conducted using random effects models. Network meta-analyses for all outcomes were performed using the Markov chain Monte Carlo method in R software (V. 4.1.2) using the package 'gemtc' (V.1.0–1).[14] Publication bias was assessed using Stata V.17.0 MP software. The surface under the cumulative ranking curves (SUCRAs) were calculated using the Bayesian model, these values are used to rank treatments for each outcome. We assessed publication bias using a comparison-adjusted funnel plot. Moreover, Egger's and Begg's tests were also used to evaluate publication bias.

In network meta-analysis, heterogeneity is assessed across three aspects: clinical heterogeneity, methodological heterogeneity and statistical heterogeneity. We examined the characteristics and design of the

included trials to assess clinical and methodological heterogeneity. Diverse study objects, study designs and the risk of bias can all contribute to heterogeneity. Studies of statistical heterogeneity were evaluated using the Cochran Q total statistic and the inconsistency index ($I^2$ statistic). P value<0.1 (Q test) or $I^2$>50% indicated significant heterogeneity. We assessed the transitivity assumption in the network by comparing the distribution of potential effect covariates as possible confounders: publication year, mean age, percentage of males and intervention duration time, to check whether these covariates were balanced across comparisons. If the network diagram shows a closed loop, it is necessary to assess network heterogeneity between direct and indirect comparisons within loops. We assessed the statistical inconsistency of direct and indirect comparisons using node-splitting models.

Meta-regression analysis was performed to explore the influence of potential effect modifiers, such as publication year, mean age, percentage of males, sample size, intervention duration time, sponsorship (whether the sponsor was the manufacturer of the vitamins or placebo) and geographical region (the region in which the participants lived), on the outcome. The sensitivity was evaluated by analysing the following restrictions: publication year (including only studies published after 2000), risks of bias (including only studies with some concern and low risk of bias), race of participants (including only studies with the white race), dose of vitamin (including only studies without the high dose of vitamin supplements) and intervention duration time (including only studies intervention duration time longer than 4 weeks). Subgroup analyses were performed using the dose of vitamin (high dose vitamins vs low dose vitamins), and intervention duration time (longer than 4 weeks vs less than 4 weeks).

We assessed the overall credibility of the evidence using the Grading of Recommendations Assessment, Development and Evaluation framework, which was developed by Salanti and colleagues.[15] We also used the Confidence in Network Meta-Analysis (CINeMA)[16] web application, which evaluates six domains (within-study bias, publication bias, indirectness, imprecision, heterogeneity and incoherence) and classifies the credibility of evidence into four grades: high, moderate, low and very low.

## RESULTS

### Search results

A total of 23861 studies were retrieved from four systematic databases and one clinical trial register platform (figure 1). After removing duplicate records and screening titles and abstracts, 122 full-text articles were considered to be potentially relevant. Ninety-nine studies were excluded because they were meeting abstracts, not RCTs, did not examine patients with essential hypertension, or were unavailable for detailed blood pressure results. Overall, 23 RCTs[17–39] were included in our analysis after the inclusion and exclusion criteria were applied. These RCTs included 2218 participants and compared five vitamins (including vitamin $B_2$, vitamin C, vitamin D, vitamin E and folic acid) with placebo.

### Study characteristics

The characteristics of the included trials are summarised in online supplemental tables S3 and S4. In total, the study sample mean size was 48±38 (SD) participants. A total of 1182 participants were randomly assigned to the vitamin group, and 1036 were randomly assigned to the placebo group. The mean age was 59.29±12.48 (SD) years for both men and women. The size of the study's male sample population was 808 (36%). In the classification of geographical region, 839 (38%) participants in eight trials recruited patients from Europe and 573 (26%) and 506 (23%) participants recruited patients from East Asia and West Asia, respectively. The remaining participants recruited patients from North America and South America. In addition, 608 (27%) participants in four studies Larsen 2012, Palumbo 2000, Pilz 2015 and, Sheikh 2020 were funded by pharmaceutical companies. The boxplot presents the change in the possible confounders: publication year, mean age, percentage of males and intervention duration time (online supplemental figures S1–S4). Most of the comparisons had similar confounders about transitivity, but a few comparisons differed considerably about confounders.

### Risk of bias in included studies

All 23 included trials were assessed for risk of bias using the Risk of Bias tool V.2.0 described in the Cochrane Handbook for Systematic Reviews of Interventions. The percentages of studies with a low risk of bias, some concern and a high risk of bias, respectively, for each domain, were as follows: 47.8%, 52.2% and 0%, for the randomisation process; 91.3%, 0% and 8.7% for deviation from intended interventions; 95.7%, 0% and 4.3% for missing outcome data; 100%, 0% and 0% for measurement of the outcome; 60.9%, 39.1% and 0% for the selection of the reported result; and 40%, 45% and 15% for overall bias (online supplemental figure S5). The risk of bias assessment for both primary and secondary outcomes is summarised in online supplemental table S5.

### Network graphic

A graphical network structure presented the network of trials for each outcome (figure 2, online supplemental figures S6–S8). Because all vitamin trials compared with the placebo cause the network to not have a closed loop, this is a 'star-shaped' network. Each node (circle) represents a special treatment. A solid black line connects different treatments. The width of the line edges indicates the number of studies. The size of the nodes indicates the total sample size of each comparison.

### Primary outcome

Of all 23 trials, the primary outcomes of SBP and DBP were pooled in 18 trials representing 1668 participants,

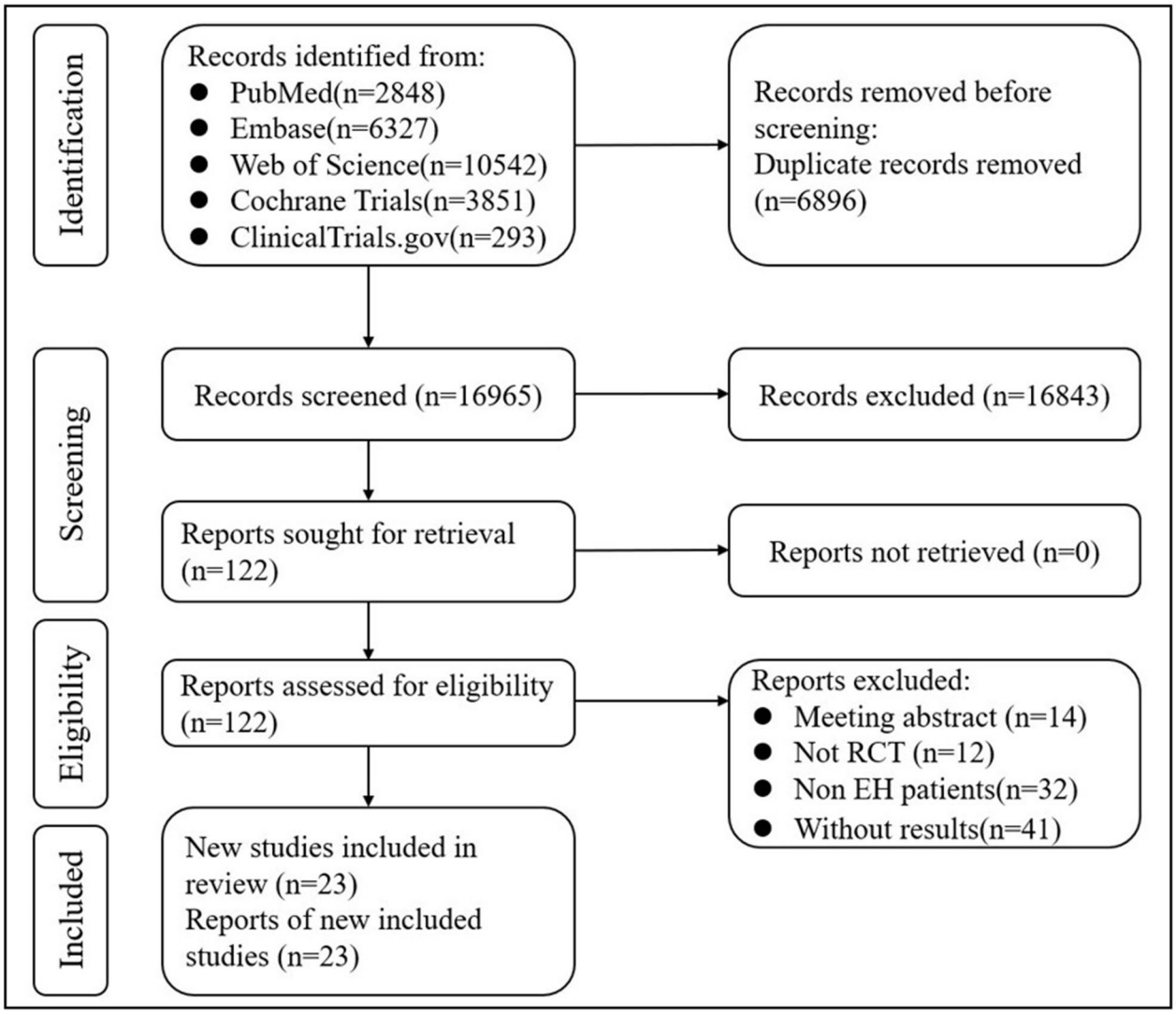


**Figure 1** Flow diagram of the study selection process for this network meta-analysis.EH, essential hypertension; RCT, randomised controlled trial.

comparing vitamin $B_2$, vitamin C, vitamin D, vitamin E, folic acid and placebo. The network meta-analysis indicated that vitamin E was significantly more effective in reducing SBP (MD: −14.14 mm Hg, 95% credible intervals (CrIs): −27.62 to −0.88) than placebo. Vitamin $B_2$, vitamin C, vitamin D and folic acid were not significantly different compared with placebo. DBP did not significantly differ between the five vitamins and placebo. We also combined individual head-to-head studies to assess the differences between vitamins. There was no evidence that any vitamin intervention treatment effect was superior to another. The league table presents these data for the primary outcomes (table 1).

Regarding SBP, the treatments were ranked based on the SUCRA values as follows: placebo (82%), vitamin D (60%), vitamin $B_2$ (51%), vitamin C (49%), folic acid (42%) and vitamin E (16%). Regarding DBP, the treatments were ranked based on the SUCRA values as follows: folic acid (66%), placebo (64%), vitamin D (58%), vitamin $B_2$ (43%), vitamin E (38%) and vitamin C (32%). We found significant overall heterogeneity in SBP (heterogeneity test results, $I^2$=98%) and DBP (heterogeneity test results, $I^2$=96%). The pairwise meta-analysis also showed significant heterogeneity (online supplemental table S6). Because of the star-shaped network, we could not statistically detect inconsistency in the network.

### Secondary outcome

Nine RCTs reported 24 hours SBP and 24 hours DBP, including 980 patients. Five RCTs reported HR, including 357 patients. For all secondary outcomes, there was no evidence that any vitamin treatment was superior to another (tables 2 and 3). The rankings of the interventions for the secondary outcomes are summarised in online supplemental tables S7 and S8. We also found significant overall heterogeneity in 24 hours SBP (heterogeneity test results, $I^2$=99%) and 24 hours DBP (heterogeneity test results, $I^2$=99%) (online supplemental table S9). No heterogeneity was observed in HR (online supplemental

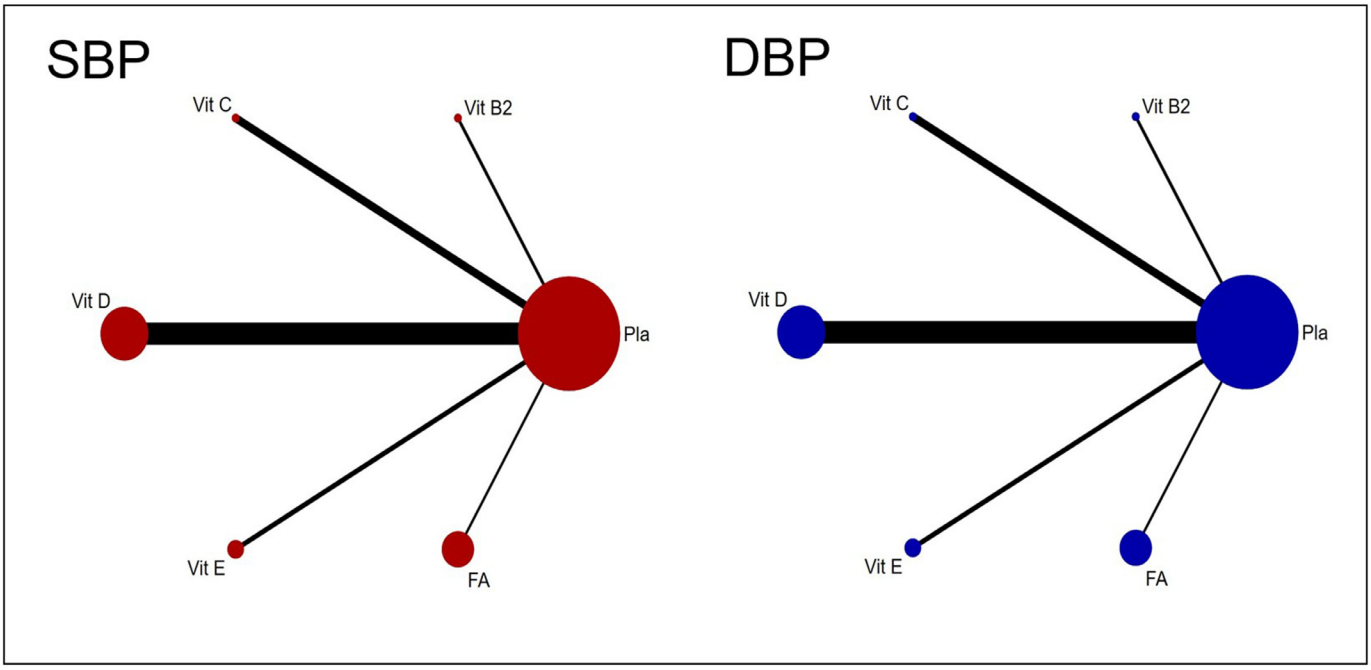


**Figure 2** Evidence network of SBP and DBP in the meta-analysis. DBP, office diastolic blood pressure; FA, folic acid; Pla, placebo; SBP, office systolic blood pressure; Vit $B_2$, vitamin $B_2$; Vit C, vitamin C; Vit D, vitamin D; Vit E, vitamin E.

table S9). Because of the star-shaped network, we could not statistically detect inconsistency in the network.

### Meta-regression, sensitivity and subgroup analyses

Meta-regression revealed that geographical region and percentage of males (only SBP) might be sources of heterogeneity in the primary outcome. However, other covariates, such as publication year, mean age, sample size, intervention duration time and sponsorship, did not lead to significant changes (online supplemental table S10). The results of the sensitivity analysis varied only slightly from our findings in the primary analysis when we adjusted for possible effect moderators (publication year, risks of bias, race of participants and intervention duration time) one by one. However, after the exclusion of high doses of vitamins, the effect of vitamin E on reducing SBP was overall superior to that of other vitamins (vitamin $B_2$, vitamin C, vitamin D, vitamin E and folic acid) and placebo. In the secondary outcome analysis, vitamin C+vitamin E reduced 24 hours DBP across the board compared with vitamin C, vitamin D and placebo after excluding high-dose vitamins (online supplemental tables S11–S15). Subgroup analysis showed that the effect

**Table 1** League table of SBP and DBP

| DBP (mm Hg) | | | | | |
|---|---|---|---|---|---|
| Pla | −1.61 (−10.29 to 7.21) | −2.53 (−9.72 to 4.69) | −0.25 (−3.16 to 2.72) | −1.62 (−6.34 to 3.01) | 0.31 (−4.17 to 4.77) |
| −5.43 (−29.18 to 18.63) | Vit B2 | −0.92 (−12.14 to 10.47) | 1.36 (−7.93 to 10.48) | 0.01 (−9.99 to 9.79) | 1.94 (−7.97 to 11.68) |
| −5.93 (−23.82 to 11.39) | −0.66 (−30.09 to 28.67) | Vit C | 2.31 (−5.51 to 10.03) | 0.90 (−7.65 to 9.43) | 2.80 (−5.61 to 11.30) |
| −3.28 (−10.99 to 4.43) | 2.09 (−23.15 to 27.08) | 2.80 (−16.23 to 22.19) | Vit D | −1.38 (−6.86 to 4.07) | 0.55 (−4.77 to 5.90) |
| **−14.14 (−27.62 to −0.88)** | −8.74 (−36.41 to 18.38) | −8.11 (−30.19 to 13.82) | −10.87 (−26.44 to 4.43) | Vit E | 1.92 (−4.50 to 8.51) |
| −7.31 (−20.78 to 6.04) | −1.86 (−29.23 to 25.43) | −1.37 (−23.04 to 20.70) | −4.02 (−19.50 to 11.52) | 6.79 (−11.61 to 25.79) | FA |
| SBP (mm Hg) | | | | | |

Data are MD (95% CrI) in the column-defining treatment compared with the row-defining treatment. Results of the SBP are presented in the left lower half and results from DBP are in the upper right half. Significant results are in bold.
CrI, credible interval.; DBP, office diastolic blood pressure; FA, folic acid; MD, mean differences; Pla, placebo; SBP, office systolic blood pressure; Vit $B_2$, vitamin $B_2$; Vit C, vitamin C; Vit D, vitamin D; Vit E, vitamin E.

**Table 2** League table of 24 hours SBP and 24 hours DBP

| | | | | |
|---|---|---|---|---|
| 24 hours DBP (mm Hg) | | | | |
| Pla | 2.82 (–6.62 to 11.94) | 2.27 (–5.89 to 1.57) | –1.80 (–10.81 to 7.10) | –7.35 (–16.96 to 2.30) |
| 0.31 (–15.18 to 15.87) | Vit C | –5.04 (–15.01 to 4.97) | –4.66 (–17.73 to 8.24) | –10.14 (–23.53 to 3.08) |
| –2.82 (–9.15 to 3.69) | –3.19 (–19.78 to 13.74) | Vit D | 0.46 (–9.21 to 9.92) | –5.06 (–15.50 to 5.12) |
| –2.18 (–17.43 to 13.21) | –2.45 (–24.32 to 19.36) | 0.57 (–15.93 to 17.22) | Vit E | –5.51 (–18.43 to 7.57) |
| –8.53 (–24.71 to 7.60) | –8.82 (–31.06 to 13.45) | –5.73 (–23.41 to 11.75) | –6.33 (–28.47 to 15.85) | Vit C+E |
| 24 hours SBP (mm Hg) | | | | |

Data are MD (95% CrI) in the column-defining treatment compared with the row-defining treatment. Results of the 24 hours SBP are presented in the left lower half and results from 24 hours DBP are in the upper right half.
CrI, credible interval; 24 hours DBP, 24-hour mean ambulatory diastolic blood pressure; 24 hours SBP, 24-hour mean ambulatory systolic blood pressure; MD, mean differences; Pla, placebo; Vit C, vitamin C; Vit C+E, vitamin C+ vitamin E; Vit D, vitamin D; Vit E, vitamin E.

of different vitamins on blood pressure changed with dose differentiation and the heterogeneity was significantly reduced (online supplemental table S16).

### Publication biases and credibility of evidence

The comparison-adjusted funnel plot was not visually asymmetric, and some studies' comparisons fell outside the funnel plot 95% CI sloped lines (online supplemental figures S9 and S10). Egger's (p=0.2981) and Begg's (p=0.2889) tests revealed no publication bias among the included studies for SBP. Additionally, Egger's (p=0.7541) and Begg's (p=0.2255) tests revealed that there was no publication bias in DBP. We only assessed publication biases of the primary outcomes. Publication bias for the secondary outcomes was not assessed due to the insufficient number of studies. The credibility of the evidence was low or very low for the primary and secondary outcomes according to the CINeMA web application (online supplemental table S17). Among all included trials at the outcome level, the 'imprecision' and 'incoherence' were major concerns for at least one domain. Moreover, there were major concerns or some concerns in terms of 'within-study bias'.

**Table 3** League table of HR

| | | | |
|---|---|---|---|
| Pla | | | |
| 4.06 (–3.62 to 11.59) | Vit C | | |
| 0.19 (–4.38 to 4.86) | –3.88 (–12.59 to 5.12) | Vit D | |
| 0.46 (–3.32 to 4.31) | –3.60 (–12.04 to 4.91) | 0.26 (–5.79 to 6.20) | Vit E |

Data are MD (95% CrI) in the column-defining treatment compared with the row-defining treatment. Results of the HR are presented in the left lower half.
CrI, credible interval; HR, heart rate; MD, mean differences; Pla, placebo; Vit C, vitamin C; Vit D, vitamin D; Vit E, vitamin E;

## DISCUSSION

This network meta-analysis included 23 RCTs involving 2218 patients randomly assigned to five individual vitamin interventions. To our knowledge, this study is the first comprehensive comparison of RCTs assessing the treatment effect of various vitamins on essential hypertension. Our network meta-analysis revealed that among the five vitamins, only vitamin E was significantly more effective at reducing SBP (MD: −14.14 mm Hg, 95% CrIs: −27.62 to −0.88) than placebo. We found no evidence that any of the five vitamins influenced DBP, 24 hours SBP, 24 hours DBP and HR. Sensitivity analysis revealed that vitamin dose was an important effect moderator that could influence the analysis results. After the exclusion of high doses of vitamins, the effect of vitamin E on reducing SBP was overall superior to that of other vitamins (vitamin B2, vitamin C, vitamin D, vitamin E and folic acid) and placebo. In the secondary outcome analysis, vitamin C+vitamin E reduced 24 hours DBP across the board compared with vitamin C, vitamin D and placebo after excluding high-dose vitamins. Subgroup analysis also supported this result, different vitamin doses have different effects on blood pressure and might be a source of heterogeneity. In this network meta-analysis, we included a total of three vitamin E-related RCTs studies. In the sensitivity and subgroup analysis, only one vitamin E study was included after excluding studies of high doses of vitamins. Small-sample studies are prone to yield exaggerated treatment effects.[40] Furthermore, there was significant heterogeneity, and the credibility of the evidence was very low due to within-study bias, imprecision and inconsistency. Therefore, this result should be interpreted with caution, and the effects of different vitamin doses on hypertension should be further investigated.

Our network meta-analysis revealed that vitamin E significantly reduced SBP, which is consistent with the findings of Emami *et al*. Emami *et al*[41] pooled data from 839 participants from 18 studies and discovered that

vitamin E supplements reduced SBP but had no effect on DBP or mean arterial pressure. Zhang *et al*[42] found an inverse J-shaped curve association between dietary vitamin E intake and new-onset hypertension, with the lowest risk of new-onset hypertension when dietary vitamin E intake was 18.75~40.53 mg/day. The mechanisms by which vitamin E lowers blood pressure are varied, and vitamin E is similar to vitamin C in that its main biological function is antioxidant.[43] Jabeen *et al*[44] showed that vitamin E can reduce the inflammatory response induced by aluminium chloride in rats and reduce serum interleukin-6 levels to exert anti-inflammatory effects. In addition, vitamin E can also inhibit smooth muscle cell proliferation and prevent aortic damage.[45] Controversially, gamma-tocopherol serum concentration (GTSC) was linearly positively associated with systolic, diastolic and hypertension prevalence. The higher the concentration of GTSC, the higher the prevalence of hypertension and blood pressure.[46] This is similar to the results of Zhang *et al*[42] who found that when dietary vitamin E intake was greater than 40.53 mg/day, the risk of new hypertension was higher. The specific mechanism needs further study.

According to the meta-regression, the geographical region and percentage of males (only SBP) could be a source of heterogeneity and have an impact on effect estimates. The geographical region of our study was divided into Europe, North America, South America, West Asia and East Asia. In the primary outcome analysis, eight studies were from Europe, five from West Asia, three from North America and two from East Asia alone. Seven European studies found no treatment effect of vitamin intervention on blood pressure. Interestingly, all five of the studies in West Asia found that vitamin interventions had a significant effect on blood pressure. There were significant regional differences. In addition, the percentage of males may also be the source of heterogeneity in the SBP results. The effect of vitamin intervention on different gender groups might be quite different.

Currently, related research on hypertension and vitamins is gradually becoming a focus area, but the research results are inconsistent and contentious.[47] Ran *et al*[7] discovered that serum levels of vitamin C were relatively low in patients with hypertension, and vitamin C was negatively correlated with SBP and DBP. Ried *et al*[48] found that intravenous high doses of vitamin C reduced blood pressure by 8~9 mm Hg in patients with prehypertension. However, some studies have vastly different perspectives and opinions. Vitamin C supplementation had no additional blood pressure-lowering effect, according to Mihalj *et al*.[49] Guan *et al*[50] used traditional meta-analysis to synthesise data from 614 participants in eight RCTs. Vitamin C supplementation was found to significantly reduce SBP and DBP in patients with essential hypertension. The Juraschek *et al* study[51] yielded similar results. According to a recent nonlinear Mendelian randomisation analysis study, vitamin D deficiency may cause higher blood pressure.[52] Studies from both Zhang *et al*[53] and Mokhtari *et al*[54] have shown that circulating 25-hydroxyvitamin D levels were inversely associated with the incidence of adult hypertension. However, there is some uncertainty about vitamin D supplementation's antihypertensive properties.[55] According to He *et al*,[56] vitamin D3 could lower SBP and DBP in patients with hypertension, individuals older than 50 years old, or obese patients with vitamin D deficiency. However, in the non-hypertensive population, vitamin D3 had no treatment effect. The pooled data from the RCTs in the Zhang *et al* study[53] also did not confirm that vitamin D supplementation lowers blood pressure in the general population. Folic acid and vitamin $B_2$ are B vitamins. Despite their very different biological functions, the effects on blood pressure are largely related to the methylenetetrahydrofolate reductase (MTHFR) 677CT genotype. MTHFR 677CT has been linked to hypertension in numerous genome and clinical studies.[57] Blood pressure control is especially difficult for the MTHFR 677 TT genotype. MTHFR requires vitamin $B_2$ as a cofactor. Vitamin $B_2$ levels associated with hypertension risk. Therefore, not only was a higher dietary intake of vitamin $B_2$ associated with a lower risk of new-onset hypertension,[58] but vitamin $B_2$ supplementation also significantly reduced blood pressure levels.[59] Folic acid is commonly used as a prenatal supplement, which may reduce the risk associated with maternal MTHFR 677CT genotype polymorphisms. A recent study discovered that taking a high-dose folic acid supplement (5 mg/day) could lower SBP and DBP.[60] On the other hand, McRae MP[61] examined the effect of folic acid supplementation in patients with hypertension in a previous study. However, no effect of folic acid on hypertension SBP and DBP was found.

Our network meta-analysis differs from previous traditional meta-analyses in several important ways. First, we comprehensively compared the antihypertensive effects of five different vitamins on hypertension. Second, our study, similar to previous traditional meta-analyses, had significant heterogeneity. However, we discovered the significance of the dose of vitamins, geographical region and percentage of males (only SBP). This has significant implications for future research. Third, our study also includes a more comprehensive evidence credibility assessment. Fourth, aside from the differences in study results, our study used a stricter inclusion criterion for essential hypertension. The current research on vitamins and hypertension is still insufficient. Many studies have confirmed the link between vitamin deficiency and high blood pressure. Paradoxically, vitamin supplements have little effect on hypertension. First, the human body's vitamin metabolism is affected by many factors, such as the living environment, dietary intake, sunlight exposure and outdoor exercise. These factors may affect the body's metabolism after vitamin supplementation, making it difficult to achieve the expected therapeutic purpose. Second, the current study did not conduct an in-depth analysis of participants' smoking,[62] alcohol consumption[63] and other related conditions. Smoking and drinking are important factors affecting vitamin metabolism. Third, hypertension is a disease caused by multiple pathogenic

factors. Further research is needed to determine whether vitamin supplementation can affect key hypertensive pathophysiological mechanisms (eg, renin-angiotensin-aldosterone system activation, sympathetic activation, water and sodium retention).

This study has several limitations that should be acknowledged. First, the sample sizes of the included studies were small, thus affecting the accuracy of the results. Therefore, the findings should be interpreted with caution, and global multicentre RCTs with large sample sizes are necessary in the future. Second, heterogeneity was noticeable in some comparisons. We found no evidence of heterogeneity based on study publication year, participants' mean age, study sample size, intervention duration time or sponsorship in the exploratory analysis. However, the possibility of another source of heterogeneity cannot be ruled out. Because these variables were examined at the study level rather than the patient level, the findings must be interpreted with caution. Third, the primary outcome analysis included only a small number of low-risk studies. In the primary outcome, seven low-risk studies, nine concern studies and two high-risk studies were included. As a result, the included studies may have flaws in design, implementation or analysis that could lead to lower credibility evidence. Fourth, the evidence has a low or very low level of credibility. We reduced the level of incoherence by two because all of the included trial comparisons lacked closed loops in the network.[16] Although imprecision was rated as a major concern, it was associated with inconsistency and was not repeatedly downgraded.[64 65] Furthermore, there were major or some concerns about within-study bias. Overall, the credibility of the evidence was reduced by two or three grades. Therefore, more rigorous experimental design and implementation are needed for future RCTs studies. In addition, head-to-head studies of different vitamin interventions in hypertension are also needed to obtain direct comparative evidence. Fifth, only those studies published in English were included, which may have contributed to language bias. Sixth, factors such as the participants' diet and how long they were exposed to the sun were closely related to vitamin levels. However, these conditions were not documented in the included studies, and we cannot answer whether these factors can affect the effect of the intervention. Finally, trial participants in network meta-analysis cannot be directly randomised in each group. As a result, there should be no direct evidence linking treatments and outcomes. In summary, we found that vitamin E can reduce SBP, different vitamin doses can significantly affect the antihypertensive effect and the dose of vitamins, geographical region and percentage of males (only SBP) might be sources of heterogeneity. However, due to the high heterogeneity, low credibility of evidence and few included studies, the results should be interpreted with caution.

## CONCLUSION

Our study found that vitamin E can reduce SBP, and vitamin $B_2$, vitamin C, vitamin D and folic acid have no antihypertensive effects. Although many animal experiments have confirmed the effect of vitamins on blood pressure regulation, the results of clinical trials are controversial. The results of this network meta-analysis can serve as a reference for clinicians and researchers. Our findings highlight the necessity for further research on the effect of vitamins on hypertension.

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