*Systematic Review*

# Vitamins and Minerals for Blood Pressure Reduction in the General, Normotensive Population: A Systematic Review and Meta-Analysis of Six Supplements

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**Abstract:** Hypertension is the leading preventable risk factor for cardiovascular disease and all-cause mortality worldwide. However, studies have shown increased risk of mortality from heart disease and stroke even within the normal blood pressure (BP) range, starting at BPs above 110–115/70–75 mm Hg. Nutraceuticals, such as vitamins and minerals, have been studied extensively for their efficacy in lowering BP and may be of benefit to the general, normotensive population in achieving optimal BP. Our study investigated the effects of six nutraceuticals (Vitamins: C, D, E; Minerals: Calcium, Magnesium, Potassium) on both systolic blood pressure (SBP) and diastolic blood pressure (DBP) in this population. We performed a systematic review and pairwise meta-analysis for all six supplements versus placebo. Calcium and magnesium achieved significant reductions in both SBP and DBP of $-1.37/-1.63$ mm Hg and $-2.79/-1.56$ mm Hg, respectively. Vitamin E and potassium only yielded significant reductions in SBP with values of $-1.76$ mm Hg and $-2.10$ mm Hg, respectively. Vitamins C and D were not found to significantly lower either SBP or DBP. Future studies should determine optimal dosage and treatment length for these supplements in the general, normotensive population.

**Keywords:** vitamins; minerals; nutraceuticals; blood pressure reduction; normotensive; general population

## 1. Introduction

Approximately 1.39 billion people in the world have hypertension, the leading preventable risk factor for cardiovascular disease and all-cause mortality worldwide [1]. Hypertension can contribute to and cause both heart disease and stroke, the first and fifth leading causes of death in the United States as of 2017 [2]. Given these statistics, the importance of blood pressure (BP) control is evident. Currently, the American College of Cardiology/American Heart Association (ACC/AHA) defines normal BP as systolic < 120 mm Hg and diastolic < 80 mm Hg, with stage 1 hypertension starting at systolic BP of 130–139 mm Hg or diastolic BP of 80–89 mm Hg [3]. However, prior literature suggests that adverse effects on health can be seen even within the normal BP range. In a meta-analysis of nearly one million people without known vascular disease, a positive correlation was seen between vascular mortality and BPs above 115/75 [4]. This study also

suggested that, for the general normotensive population, even consistent reductions of 2 mm Hg in systolic BP could result in large reductions of disabling strokes and premature deaths from vascular causes [4]. Another meta-analysis of 147 randomized controlled trials (RCTs) found that BPs above 110/70 were correlated with increased deaths from coronary heart disease (CHD) and stroke [5]. The authors suggested that some patients, although considered normotensive by conventional definitions, may benefit from treatment with antihypertensives to reduce this increased mortality risk [5].

Aside from prescription antihypertensives, there is ample literature regarding the BP-lowering ability of various nutraceuticals [6,7]. These nutraceuticals include vitamins (C, D, and E) and minerals (calcium, magnesium, and potassium). Studies have addressed both the mechanisms of action and efficacy of these nutraceuticals for BP reduction. Vitamins C and E are thought to mediate BP through antioxidant effects and enhancement of nitric oxide pathways that prevent endothelial dysfunction [8–10]. Vitamin D is a regulator of the renin-angiotensin-aldosterone system (RAAS) [11]. The mechanism underlying calcium is not well-understood but is suspected to be regulated by the parathyroid hormone, vitamin D, and RAAS systems [12]. Magnesium can affect BP by inducing vascular changes through the production of nitric oxide, by indirectly affecting intracellular calcium concentrations, and through the alteration of smooth muscle tone [13]. Finally, potassium exhibits a direct effect on BP via two mechanisms: by downregulation of the sodium-chloride cotransporter within the distal tubule of the kidneys leading to reduced reabsorption of sodium and chloride, as well as increasing activation of RAAS in response to high serum potassium levels [14].

The effectiveness of these six nutraceuticals in lowering BP, when taken as dietary supplements, has been the focus of numerous randomized controlled trials (RCTs) and meta-analyses. In fact, the most recently published meta-analyses suggest that all but vitamin D and calcium are capable of achieving a 2 mm Hg systolic BP reduction [15–20]. However, the majority of these meta-analyses have included RCTs where the supplements were used as first-line treatments among patients with uncontrolled hypertension. This limits the generalizability of BP reductions for normotensive patients and likely overestimates their true effect.

This study aims to investigate the effects of the above six nutraceuticals (Vitamins: C, D, E; Minerals: Calcium, Magnesium, Potassium) on systolic and diastolic BP in the general, normotensive population using a pairwise meta-analysis for each supplemental compared to placebo. We chose these six based on our prior knowledge of the literature. The overlap of supplements mentioned in the two aforementioned review articles on nutraceuticals with a blood pressure-lowering effect was also used in this decision [6,7]. Further, we used these review articles to confirm the presence of RCTs examining the effect of supplementation on BP to perform our analysis. We hypothesize finding similar efficacy of these nutraceuticals to what is seen in the most recent published meta-analyses of them. However, we also hypothesize our reductions will be lower than what they obtained because of our controlling for this population, thus excluding studies in which these supplements were used in solely hypertensive patients. To our knowledge, this will be the first study to investigate the effect of all six of these nutraceuticals amongst normotensive subjects in the general population within a single paper. We hope the availability of this data will aid clinicians and patients in determining the efficacy of these nutraceuticals and deciding whether any may be of benefit. Furthermore, it seeks to lay the foundation for future studies that may determine the optimal dosages, treatment length, and long-term safety profiles of these nutraceuticals in this population.

## 2. Methods

This study adhered to the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) statement [21]. The protocol was not registered.

### 2.1. Eligibility Criteria

Studies were included if they were (1) published in English; (2) randomized controlled trials (RCTs) of one, or more if not used solely in combination, of the six supplements with dosing versus placebo; (3) focused on a general, adult participant population with <50% having a common medical condition; (4) trials that reported the mean effect with variance of these supplements on systolic, diastolic, or mean arterial pressure (or provided data that allowed for calculation of this data, such as *p*-values and 95% confidence intervals); and (5) at least two weeks in duration. It should be noted that our study did not consider the following as medical conditions: being elderly, postmenopausal, obese, at-risk of a medical condition (such as being prediabetic) or having baseline deficiency of a supplement. Aside from these, all other medical conditions were cause for exclusion if they affected more than 50% of the study population, including hyperlipidemia, alcoholism, smoking, and psychiatric conditions.

Trials were excluded if (1) they were not published in English; (2) they did not follow a RCT study design; (3) the supplement dosing was not given, was administered via fortified foods or through dietary changes, or was calculated by urinary excretion or other indirect measures; (4) they focused solely on patients with specific medical conditions or had ≥50% of participants sharing a common medical condition; (5) participants were less than 18 years old or pregnant; (6) the average baseline systolic BP was ≥140 or baseline diastolic BP was ≥90; (7) they did not provide data on pre- and post-intervention BP, or sufficient data to calculate this; (8) additional interventions were administered alongside the supplement, such as an exercise program or sodium restriction; and/or (9) the studies were less than two weeks in duration.

### 2.2. Information Sources and Search Strategy

A systematic search of literature was conducted on Cochrane, Embase, MEDLINE (PubMed), and Web of Science for placebo-controlled RCTs of the six supplements examining their effects on BP. The dates searched were inception to 22 July 2022. The search strings were constructed by a medical librarian using a combination of keywords and Medical Subject Headings (MeSH terms). The keywords and MeSH terms used in this search are listed in Table S1 of the Supplementary Data file. Additional studies were retrieved by handsearching the references of all included studies. It should be noted that Vitamin B was included in the literature search but was not used in this study due to the number of different types of B vitamins and their variable mechanisms and effects.

### 2.3. Selection Process

The RCTs obtained through this search were imported into Covidence, which automatically screened for duplicates [22]. Two independent researchers (BJB and JM) screened the title and abstracts of studies, excluding irrelevant ones. The full-text articles were obtained for studies that made it through this initial screening. The same two authors then independently screened these, examining their adherence to eligibility criteria. Disagreements during the screening process were settled through discussion, with a third author (MJS) available to decide any that could not be resolved.

### 2.4. Data Collection Process and Data Items

Two independent researchers (JLD and CJG) completed extraction of the basic characteristics of included studies, with subsequent review by the first author (BJB). This included the last name of the first author, year of publication, type of trial, baseline BP of participants and their past medical history, length of the trial, supplement dosing, sample size for intervention and placebo groups, and whether there were any adverse outcomes. Disagreements were settled through discussion.

The first author (BJB) extracted all data in relation to systolic blood pressure (SBP) and diastolic blood pressure (DBP) for all arms of the trials. This included mean baseline and final BP values for each group, effect sizes for each arm of the trial, and overall treatment

effect sizes (supplement minus placebo). The corresponding variances, 95% Confidence Intervals (CIs), and sample sizes for each arm of the trial were also extracted. This was subsequently verified by at least two other authors (BMB, SMA, JLD, or CJG) for accuracy.

### 2.5. Study Risk of Bias Assessment

Quality assessment was performed using the Risk of Bias 2 tool from the Cochrane Handbook for Systematic Reviews of Interventions [23]. This tool examined risk of bias across five domains: (1) Arising from the randomization process; (2) Arising from deviations from the intended interventions; (3) Due to missing outcome data; (4) From the method of measuring the outcome; and (5) In selection of the reported result [23]. Two authors (BJB and RSS) independently performed this, assigning each domain either "Low", "Some Concerns", or "High". Studies with one or more domains receiving "High" grades or more than two domains with "Some Concerns" were considered at overall high risk of bias. Further, studies with two domains with "Some Concerns" were deemed to have some concerns for bias overall. Disagreements were resolved through discussion.

### 2.6. Effect Measures and Statistical Analysis

The primary endpoints were the effect size between the intervention (supplement) and placebo groups in regard to change in systolic blood pressure (SBP) and diastolic blood pressure (DBP). This was represented by the mean BP changes from baseline in the intervention group minus the changes in the placebo group. Its standard error (SE) was either reported or calculated from 95% CIs, *p*-values, and/or t-statistics. When the effect size and its SE were not provided, the effect size was calculated by subtracting the mean changes between the two groups. The SE was then estimated by multiplying the pooled standard deviations of the two groups by the square root of the sum of the reciprocals of their sample sizes. Our effect sizes are the overall effect size of the supplement versus placebo across all dosages and treatment lengths, with the intention of providing insight into whether these nutraceuticals have any effect on BP in this population.

In parallel trials that did not provide mean change from baseline data for each arm of the trial, this was calculated by subtracting the baseline mean BP values from the final mean BP values. The standard deviations of these changes were then imputed according to Chapter 6 of the Cochrane Handbook for Systematic Reviews of Interventions (Cochrane Handbook), assuming a correlation coefficient of 0.7 [24]. A sensitivity analysis adopting a correlation coefficient of 0.5 was also conducted. For studies with multiple treatment arms with different dosages of the supplement or with different subtypes of the same supplement, these arms were combined into one intervention group using the methodology outlined in the Cochrane Handbook. This combined treatment group was then compared against the placebo group in a pairwise analysis. When trials had participants separated into subgroups with both treatment and placebo arms, we treated the subgroups as if they were separate trials.

For cross-over studies, the final mean BP values of the two groups were used to calculate the mean differences, as all participants shared the same baseline values. Our methodology followed Chapter 23 of the Cochrane Handbook [25]. The SEs were obtained by dividing the standard deviations of the differences by the square root of the sample sizes with an imputed correlation coefficient of 0.7. Sensitivity analyses adopting correlation coefficients of 0.5 and 0.9 were also conducted.

The overall effect sizes and the 95% CIs for each intervention were estimated and reported under both common- and random-effects settings. Heterogeneity was assessed by *Q* statistic at the significance level of 0.1 [26]. A significant *Q* statistic would indicate use of the random-effects model results. The $I^2$ statistic was also reported to explain the percentage of variability accounted for by the between-study variation [27]. This between-study variance was estimated using the restricted maximum likelihood (REML) method [28]. The publication bias was assessed using Egger's regression, at a significance level of 0.1 [29]. Contour-enhanced funnel plots of the six supplements with respect to SBP

and DBP were also constructed to visualize potential publication bias [30,31]. Statistical analyses were conducted by using R 4.3.0 and the R package 'meta' [32].

## 3. Results

### 3.1. Study Selection

The literature search yielded 16,198 total articles from the four databases: Cochrane (*n* = 4497), Embase (*n* = 6585), MEDLINE (PubMed) (*n* = 4579), and Web of Science (*n* = 537). Covidence automatically removed 7352 duplicates, leaving 8846 articles for screening. After title/abstract screening removed 8439 articles, full texts were obtained for the remaining 407 articles. Analysis for their adherence to the inclusion criteria resulted in 82 eligible studies [33–114]. However, five of these were later deemed ineligible due to insufficient data for analysis [68,77,78,80,84]. The full list of reasons for excluded full-text articles and explanations for these five studies can be found in Tables S2 and S3, respectively. Ten additional eligible studies were identified by scanning the reference lists of included studies [115–124], for a total of 87 RCTs included in the analysis. The study selection process is summarized with a PRISMA flowchart in Figure 1.
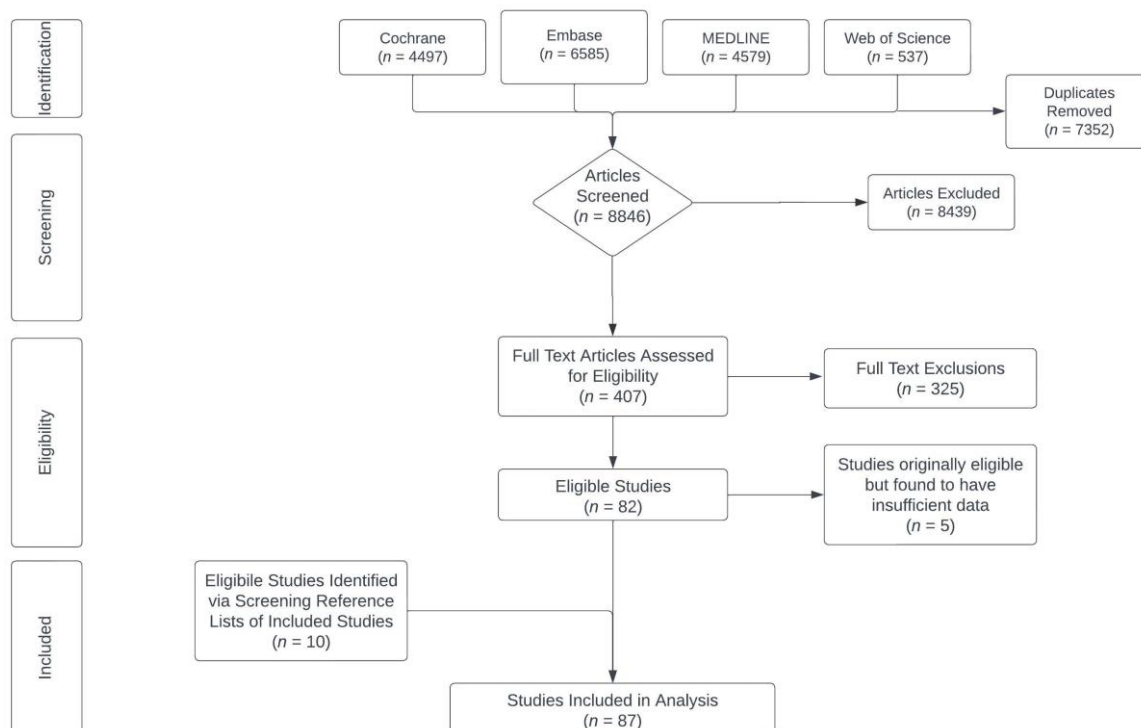


**Figure 1.** PRISMA flowchart documenting the literature search and screening process.

### 3.2. Study Characteristics

The 87 RCTs were published from 1982 to 2022 [33–67,69–76,79,81–83,85–124]. The basic characteristics of each included study can be found in Table S4. These 87 RCTs resulted in 95 pairwise comparisons for SBP and 91 for DBP, as some trials had treatment arms for multiple supplements or distinct subgroups with both treatment and placebo groups. Overall, these trials enrolled 12,526 participants. Forty-four of the trials (50.6%) consisted of an entirely healthy population. The remaining trials were broken down into 20 (23.0%) with a general population, 15 trials (17.2%) with healthy but obese participants, and 8 (9.2%) focused on postmenopausal women. There were 71 parallel trials and 16 cross-over. Trial lengths varied from 2 weeks to 208 weeks (4 years).

All six supplements consisted of a mixture of parallel and cross-over studies, except for vitamin D which consisted of only parallel trials. Additionally, all 87 trials (100%) included data on SBP, while DBP was also measured in all but four (95.4%). Of these

four trials, two were of vitamin E and one for both vitamin C and vitamin D. A healthy population was predominant for all six supplements. Vitamin C, vitamin D, and vitamin E were represented in 5, 29, and 7 trials, respectively, with sample sizes of 122, 4897, and 302. Calcium, magnesium, and potassium were represented in 21, 18, and 12 trials, respectively, with sample sizes of 4534, 1575, and 1096. As noted, not all studies measured DBP, resulting in slight decreases in the sample size used in its analysis. There was a wide range of dosages and treatment lengths for all six supplements. A comprehensive summary of the basic characteristics of included studies broken down by supplement is depicted in Table 1.

**Table 1.** Summary of the basic characteristics of included studies broken down by supplement.

| Supplement (Total Number of Studies) | Type of Studies | Data | Sample Size | Population | Dose Range | Treatment Length Range |
|---|---|---|---|---|---|---|
| Vitamin C (*n* = 5) | P: 1 (20%) CO: 4 (80%) | Sys: 5 (100%) Dia: 4 (80%) | Sys: 122 Dia: 114 | Healthy: 4 (80%) General: 1 (20%) | 200–1000 mg/day | 2–52 weeks |
| Vitamin D (*n* = 29) | P: 29 (100%) CO: 0 (0%) | Sys: 29 (100%) Dia: 28 (96.6%) | Sys: 4897 Dia: 4578 | Healthy: 9 (31.0%) General: 8 (27.6%) Obese: 8 (27.6%) Postmenopausal: 4 (13.8%) | 200–8000 IU/day | 2–208 weeks |
| Vitamin E (*n* = 7) | P: 5 (71.4%) CO: 2 (28.6%) | Sys: 7 (100%) Dia: 5 (71.4%) | Sys: 302 Dia: 240 | Healthy: 6 (85.7%) Postmenopausal: 1 (14.3%) | 50–320 mg/day | 3–26 weeks |
| Calcium (*n* = 21) | P: 20 (95.2%) CO: 1 (4.8%) | Sys: 21 (100%) Dia: 21 (100%) | Sys: 4534 Dia: 4525 | Healthy: 12 (57.1%) General: 3 (14.3%) Obese: 3 (14.3%) Postmenopausal: 3 (14.3%) | 162–2000 mg/day | 4–208 weeks |
| Magnesium (*n* = 18) | P: 14 (77.8%) CO: 4 (22.2%) | Sys: 18 (100%) Dia: 18 (100%) | Sys: 1575 Dia: 1575 | Healthy: 11 (61.1%) Obese: 4 (22.2%) General: 3 (16.7%) | 212–636 mg/day | 4–26 weeks |
| Potassium (*n* = 12) | P: 7 (58.3%) CO: 5 (41.7%) | Sys: 12 (100%) Dia: 12 (100%) | Sys: 1096 Dia: 1096 | Healthy: 7 (58.3%) General: 5 (41.7%) | 24–100 mmol/day (938.4–3910 mg/day) | 3–26 weeks |
| Total (*n* = 87) | P: 71 (81.6%) CO: 16 (18.4%) | Sys: 87 (100%) Dia: 83 (95.4%) | Sys: 12,526 Dia: 12,128 | Healthy: 44 (50.6%) General: 20 (23.0%) Obese: 15 (17.2%) Postmenopausal: 8 (9.2%) | | |

The number of parallel versus cross-over studies, number of studies reporting systolic and diastolic data, and number of each type of population is given in *n* (%), representing the frequency of findings. The denominator for this frequency is noted in the first column. Dosage and treatment length are given as ranges. P represents parallel trials, CO represents cross-over trials, Sys represents systolic blood pressure data, and Dia represents diastolic blood pressure data.

### 3.3. Risk of Bias in Studies

The complete results of the Cochrane Risk of Bias screening by study can be found in Table S5. Overall, five studies (5.7%) were determined to have high risk of bias, while nine (10.3%) were determined to have some concerns. Domain 2, bias arising from deviations from the intended interventions, was the most implicated of the five, with one (1.1%) study having high risk of bias and 22 (25.3%) having some concerns. Domain 1, bias arising from the randomization process, was second with 17 (19.5%) studies having some concerns, but none exhibiting high risk of bias. The Risk of Bias results across the five domains, as well as the overall judgment, for all included studies can be seen in Figure 2.

A summary of the risk of bias judgments by supplement can be found in Table 2. Calcium had the most studies at high risk of bias with 2 (9.5% of its total studies), while vitamin D (3.4% of its total studies), vitamin E (14.3%), and potassium (8.3%) each had one.
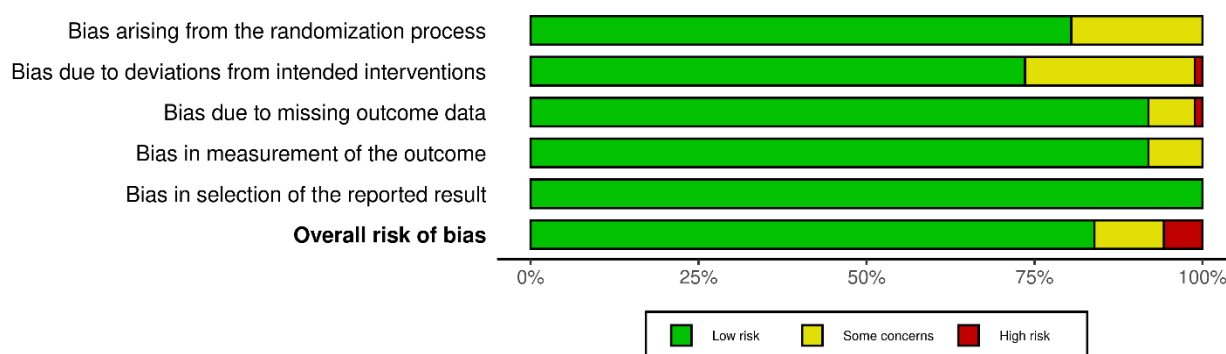
**Figure 2.** Graphical representation of the risk of bias across all five domains, as well as the overall judgment, for all included studies.

**Table 2.** Overall risk of bias by supplement. N represents the total number of studies for each supplement.

| Supplement | Overall Risk of Bias |
|---|---|
| Vitamin C (*n* = 5) | Low: 4 (80%) Some concerns: 1 (20%) High: 0 (0%) |
| Vitamin D (*n* = 29) | Low: 25 (86.2%) Some concerns: 3 (10.3%) High: 1 (3.4%) |
| Vitamin E (*n* = 7) | Low: 6 (85.7%) Some concerns: 0 (0%) High: 1 (14.3%) |
| Calcium (*n* = 21) | Low: 17 (81.0%) Some concerns: 2 (9.5%) High: 2 (9.5%) |
| Magnesium (*n* = 18) | Low: 17 (94.4%) Some concerns: 1 (5.6%) High: 0 (0%) |
| Potassium (*n* = 12) | Low: 9 (75%) Some concerns: 2 (16.7%) High: 1 (8.3%) |

The number of studies obtaining each of the three grades is noted in Column 2, with the percentages reflecting the frequency of each assignment for each supplement.

*3.4. Results of Syntheses/Statistical Analyses*

3.4.1. Systolic Blood Pressure

The pooled results for the difference in the change of SBP for the vitamins versus placebo are shown in Figure 3. Overall, out of the three vitamins (C, D, E), only vitamin E was found to significantly reduce SBP versus placebo by a mean difference of $-1.76$ mm Hg (95% CI: $-3.05$, $-0.47$) using the common effects model due to low heterogeneity ($I^2 = 16\%$; *p*-value for *Q* statistic: 0.30). Vitamins C and D did not show a significant reduction in SBP versus placebo with values of $-1.45$ mm Hg (95% CI: $-4.26$, 1.35) and $-0.47$ mm Hg (95% CI: $-2.29$, 1.34), respectively. Both of these vitamins also had low heterogeneity ($I^2 = 1\%$; *p*-value: 0.40 and $I^2 = 15\%$; *p*-value: 0.23, respectively), so a common effects model was used for them.

The pooled results for the difference in the change of SBP for the minerals versus placebo are shown in Figure 4. All three minerals (calcium, magnesium, and potassium) showed a significant reduction of SBP versus placebo. Calcium reduced SBP by an average of $-1.37$ mm Hg (95% CI: $-2.03$, $-0.71$) using a common effects model due to low heterogeneity ($I^2 = 25\%$; *p*-value: 0.13). Magnesium had an average reduction in SBP of

−2.79 mm Hg (95% CI: −5.25, −0.34) using the random effects model due to high heterogeneity ($I^2$ = 95%; *p*-value: < 0.001). Potassium also used the random effects model due to high heterogeneity ($I^2$ = 83%; *p*-value: < 0.001) and was found to reduce SBP by an average of −2.10 mm Hg (95% CI: −3.81, −0.38).

| Study | Number Analyzed (T/C) | MD | 95% CI |
|---|---|---|---|
| **Vitamin C** | | | |
| Fotherby 2000 | 23/23 | 0.00 | [−3.94; 3.94] |
| Hutchins 2005 | 8 | 2.00 | [−5.81; 9.81] |
| Keith 1982 | 10/10 | −3.00 | [−11.54; 5.54] |
| Osilesi 1991 | 8 | −7.60 | [−15.24; 0.04] |
| Woo 2021 | 19/21 | −3.00 | [−11.01; 5.01] |
| COMMON−EFFECT | | −1.45 | [−4.26; 1.35] |
| RANDOM−EFFECTS | | −1.53 | [−4.46; 1.40] |
| Heterogeneity: $c_4^2$ = 4.03 (*P* = .40), $I^2$ = 1% | | | |
| **Vitamin D** | | | |
| Agbalalah 2021 | 24/24 | −5.20 | [−10.46; 0.06] |
| Al−Dujaili 2016 | 9/6 | −7.60 | [−18.43; 3.23] |
| Aringazina 2021 | 186/150 | 0.01 | [−1.70; 1.72] |
| Bressendorff 2016 | 22/18 | 1.90 | [−0.84; 4.64] |
| Chai 2013 | 23/22 | 3.70 | [−4.73; 12.13] |
| Cheung 2022 | 34/23 | −1.20 | [−6.63; 4.23] |
| Forman 2013 | 211/72 | −4.42 | [−9.08; 0.25] |
| Forouhi 2016 | 226/114 | −0.87 | [−3.37; 1.64] |
| Gariballa 2022 | 68/75 | −2.00 | [−4.15; 0.15] |
| Indhavivadhana 2022 | 39/37 | 0.21 | [−5.59; 6.01] |
| Khosravi 2018 | 26/27 | 0.10 | [−3.18; 3.38] |
| Kubiak 2018 | 208/203 | 1.10 | [−0.35; 2.55] |
| McMullan 2017 | 29/27 | 0.20 | [−3.55; 3.95] |
| Mitchell 2015 | 40/50 | 0.00 | [−3.92; 3.92] |
| Moghassemi 2014 | 38/36 | −1.89 | [−8.69; 4.91] |
| Muldowney 2012 | 146/56 | 2.30 | [−1.09; 5.70] |
| Nagpal 2009 | 35/36 | 3.95 | [−0.05; 7.95] |
| Nimitphong 2015 | 29/18 | −1.70 | [−7.47; 4.07] |
| Ramly 2014 | 93/99 | −0.80 | [−4.20; 2.60] |
| Salehpour 2011 | 39/38 | 2.71 | [−2.44; 7.86] |
| Scragg 2014 | 149/151 | −0.30 | [−2.69; 2.09] |
| Seibert 2017 | 54/51 | −0.47 | [−1.60; 0.67] |
| Sluyter 2017 | 256/261 | −2.10 | [−4.47; 0.27] |
| Sollid 2014 | 242/242 | 0.60 | [−1.96; 3.16] |
| Tomson 2017 | 195/95 | −2.40 | [−5.75; 0.95] |
| Wamberg 2013 | 22/21 | −5.00 | [−12.46; 2.46] |
| Witham 2013 | 25/23 | 1.30 | [−3.56; 6.16] |
| Wood 2012 | 191/98 | 0.55 | [−1.79; 2.89] |
| Zittermann 2009 | 82/83 | −1.00 | [−5.88; 3.88] |
| COMMON−EFFECT | | −0.19 | [−0.71; 0.33] |
| RANDOM−EFFECTS | | −0.21 | [−0.80; 0.38] |
| Heterogeneity: $c_{28}^2$ = 33.05 (*P* = .23), $I^2$ = 15% | | | |
| **Vitamin E** | | | |
| Chin 2011 (a) | 16/15 | 2.00 | [−4.82; 8.82] |
| Chin 2011 (b) | 16/15 | 3.00 | [−5.53; 11.53] |
| Goon 2017 | 48/23 | −1.40 | [−6.89; 4.09] |
| McSorley 2005 | 13/13 | −3.00 | [−4.79; −1.21] |
| Patil 2009 | 19/18 | 1.56 | [−1.89; 5.01] |
| Rasool 2003 | 17/17 | −2.00 | [−7.90; 3.90] |
| Rasool 2006 | 27/9 | −2.80 | [−6.35; 0.75] |
| Rasool 2008 | 27/9 | −0.40 | [−6.35; 5.55] |
| COMMON−EFFECT | | −1.76 | [−3.05; −0.47] |
| RANDOM−EFFECTS | | −1.21 | [−3.02; 0.60] |
| Heterogeneity: $c_7^2$ = 8.34 (*P* = .30), $I^2$ = 16% | | | |

X-axis: −20　−10　0　10　20

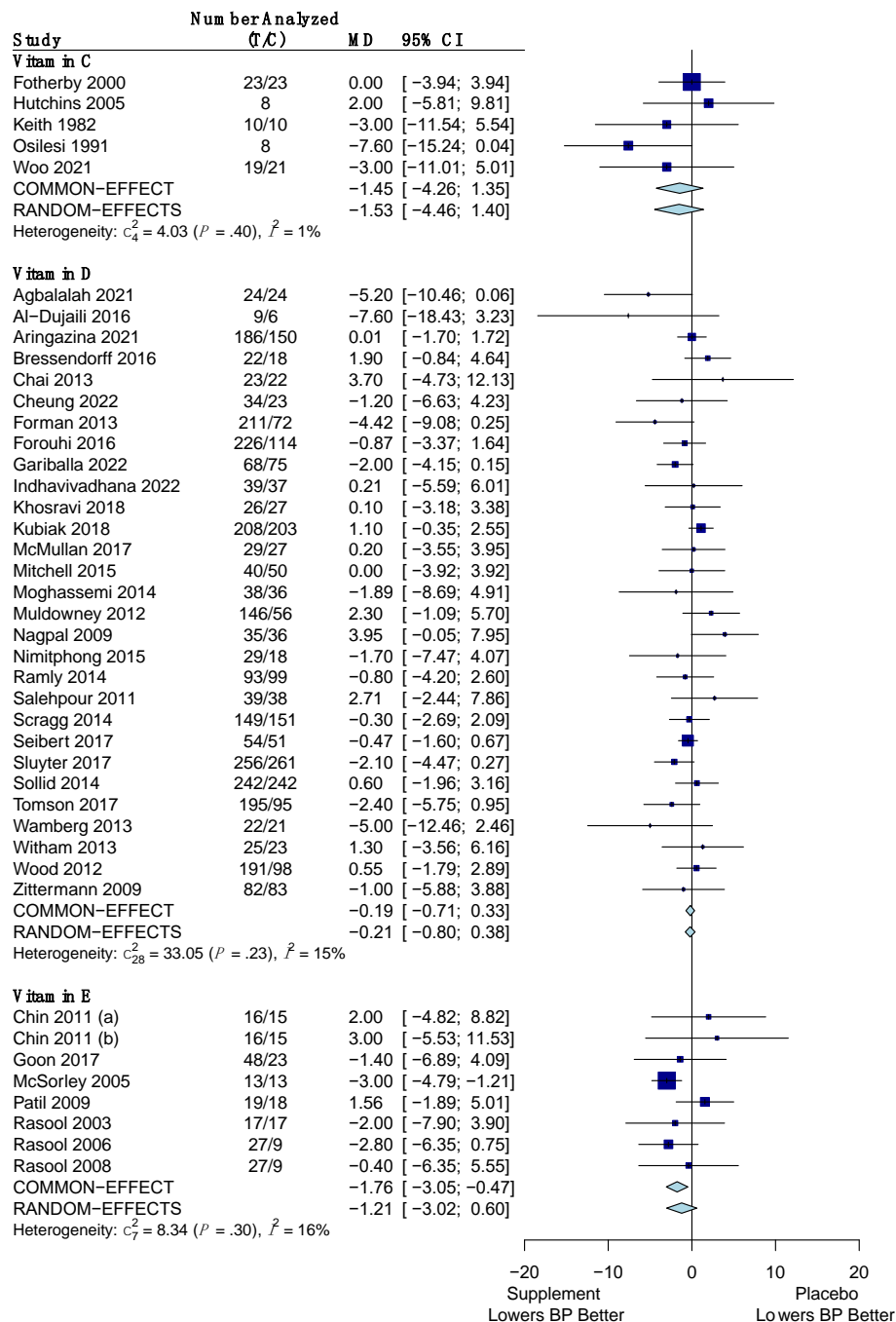Supplement Lowers BP Better　　　　Placebo Lowers BP Better

**Figure 3.** Forest plot showing the mean difference of change in systolic blood pressure between vitamins (C, D, E) and placebo. T represents the sample size of the treatment (supplement/vitamin) group and C represents the sample size of the control (placebo) group. The pooled mean difference is given in mm Hg with its 95% CI. The weighted mean difference in mm Hg and its 95% CI is given for each study. A graphical representation with the weighted mean difference and its SE is also given for each study. References: Vitamin C ([51,56,61,85,112]); Vitamin D ([33–35,42–44,49,50,52,57,63,64,74,75,79,81,83,87,97,99,100,104,105,107,108,111,113,122,124]); Vitamin E ([86,88–90,115,117,120]).
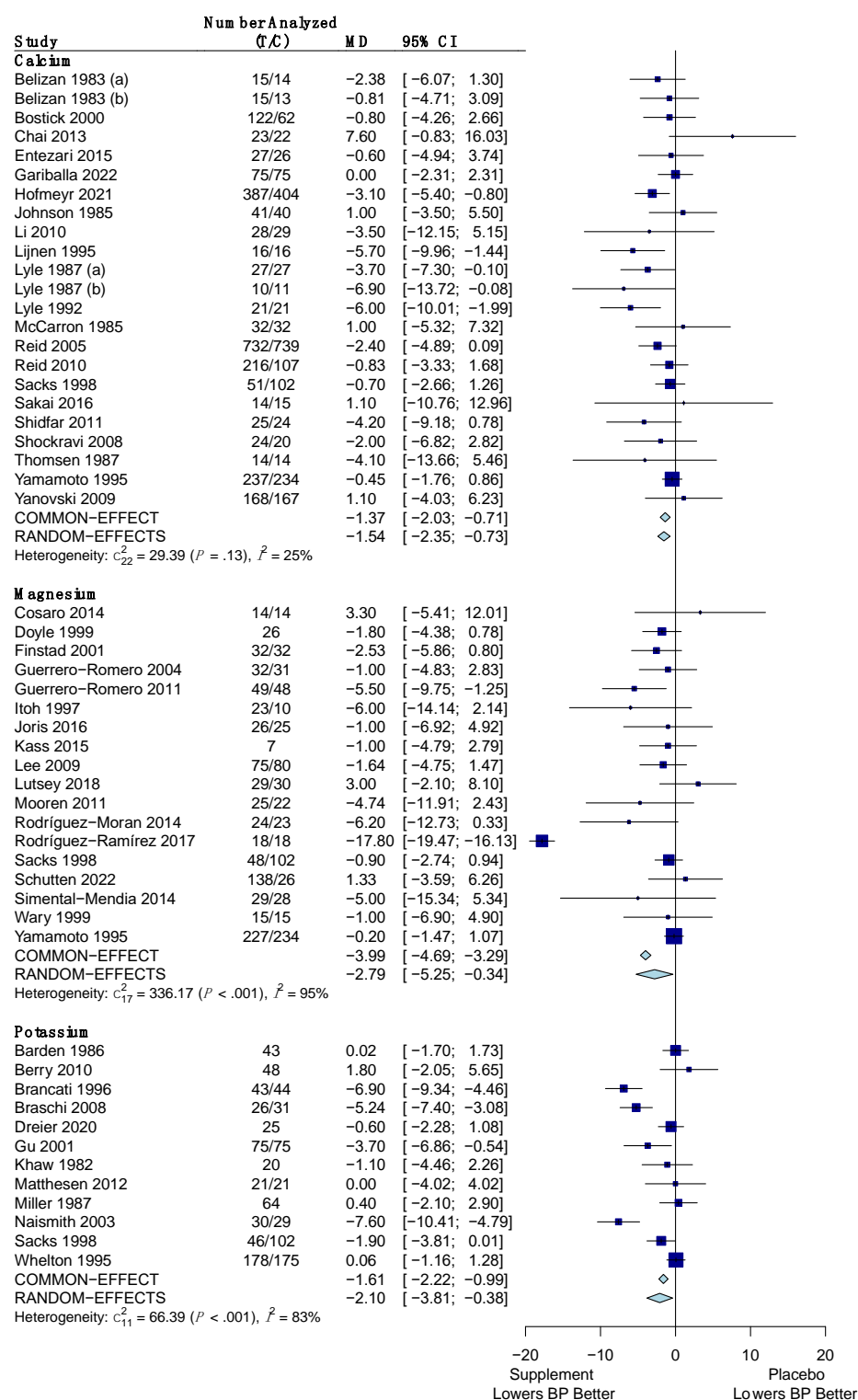
|  | Number Analyzed |  |  |
|---|---|---|---|
| Study | (T/C) | MD | 95% CI |
| **Calcium** |  |  |  |
| Belizan 1983 (a) | 15/14 | −2.38 | [−6.07; 1.30] |
| Belizan 1983 (b) | 15/13 | −0.81 | [−4.71; 3.09] |
| Bostick 2000 | 122/62 | −0.80 | [−4.26; 2.66] |
| Chai 2013 | 23/22 | 7.60 | [−0.83; 16.03] |
| Entezari 2015 | 27/26 | −0.60 | [−4.94; 3.74] |
| Gariballa 2022 | 75/75 | 0.00 | [−2.31; 2.31] |
| Hofmeyr 2021 | 387/404 | −3.10 | [−5.40; −0.80] |
| Johnson 1985 | 41/40 | 1.00 | [−3.50; 5.50] |
| Li 2010 | 28/29 | −3.50 | [−12.15; 5.15] |
| Lijnen 1995 | 16/16 | −5.70 | [−9.96; −1.44] |
| Lyle 1987 (a) | 27/27 | −3.70 | [−7.30; −0.10] |
| Lyle 1987 (b) | 10/11 | −6.90 | [−13.72; −0.08] |
| Lyle 1992 | 21/21 | −6.00 | [−10.01; −1.99] |
| McCarron 1985 | 32/32 | 1.00 | [−5.32; 7.32] |
| Reid 2005 | 732/739 | −2.40 | [−4.89; 0.09] |
| Reid 2010 | 216/107 | −0.83 | [−3.33; 1.68] |
| Sacks 1998 | 51/102 | −0.70 | [−2.66; 1.26] |
| Sakai 2016 | 14/15 | 1.10 | [−10.76; 12.96] |
| Shidfar 2011 | 25/24 | −4.20 | [−9.18; 0.78] |
| Shockravi 2008 | 24/20 | −2.00 | [−6.82; 2.82] |
| Thomsen 1987 | 14/14 | −4.10 | [−13.66; 5.46] |
| Yamamoto 1995 | 237/234 | −0.45 | [−1.76; 0.86] |
| Yanovski 2009 | 168/167 | 1.10 | [−4.03; 6.23] |
| COMMON-EFFECT |  | −1.37 | [−2.03; −0.71] |
| RANDOM-EFFECTS |  | −1.54 | [−2.35; −0.73] |
| Heterogeneity: $c_{22}^2 = 29.39$ ($P = .13$), $I^2 = 25\%$ |  |  |  |
| **Magnesium** |  |  |  |
| Cosaro 2014 | 14/14 | 3.30 | [−5.41; 12.01] |
| Doyle 1999 | 26 | −1.80 | [−4.38; 0.78] |
| Finstad 2001 | 32/32 | −2.53 | [−5.86; 0.80] |
| Guerrero-Romero 2004 | 32/31 | −1.00 | [−4.83; 2.83] |
| Guerrero-Romero 2011 | 49/48 | −5.50 | [−9.75; −1.25] |
| Itoh 1997 | 23/10 | −6.00 | [−14.14; 2.14] |
| Joris 2016 | 26/25 | −1.00 | [−6.92; 4.92] |
| Kass 2015 | 7 | −1.00 | [−4.79; 2.79] |
| Lee 2009 | 75/80 | −1.64 | [−4.75; 1.47] |
| Lutsey 2018 | 29/30 | 3.00 | [−2.10; 8.10] |
| Mooren 2011 | 25/22 | −4.74 | [−11.91; 2.43] |
| Rodríguez-Moran 2014 | 24/23 | −6.20 | [−12.73; 0.33] |
| Rodríguez-Ramírez 2017 | 18/18 | −17.80 | [−19.47; −16.13] |
| Sacks 1998 | 48/102 | −0.90 | [−2.74; 0.94] |
| Schutten 2022 | 138/26 | 1.33 | [−3.59; 6.26] |
| Simental-Mendia 2014 | 29/28 | −5.00 | [−15.34; 5.34] |
| Wary 1999 | 15/15 | −1.00 | [−6.90; 4.90] |
| Yamamoto 1995 | 227/234 | −0.20 | [−1.47; 1.07] |
| COMMON-EFFECT |  | −3.99 | [−4.69; −3.29] |
| RANDOM-EFFECTS |  | −2.79 | [−5.25; −0.34] |
| Heterogeneity: $c_{17}^2 = 336.17$ ($P < .001$), $I^2 = 95\%$ |  |  |  |
| **Potassium** |  |  |  |
| Barden 1986 | 43 | 0.02 | [−1.70; 1.73] |
| Berry 2010 | 48 | 1.80 | [−2.05; 5.65] |
| Brancati 1996 | 43/44 | −6.90 | [−9.34; −4.46] |
| Braschi 2008 | 26/31 | −5.24 | [−7.40; −3.08] |
| Dreier 2020 | 25 | −0.60 | [−2.28; 1.08] |
| Gu 2001 | 75/75 | −3.70 | [−6.86; −0.54] |
| Khaw 1982 | 20 | −1.10 | [−4.46; 2.26] |
| Matthesen 2012 | 21/21 | 0.00 | [−4.02; 4.02] |
| Miller 1987 | 64 | 0.40 | [−2.10; 2.90] |
| Naismith 2003 | 30/29 | −7.60 | [−10.41; −4.79] |
| Sacks 1998 | 46/102 | −1.90 | [−3.81; 0.01] |
| Whelton 1995 | 178/175 | 0.06 | [−1.16; 1.28] |
| COMMON-EFFECT |  | −1.61 | [−2.22; −0.99] |
| RANDOM-EFFECTS |  | −2.10 | [−3.81; −0.38] |
| Heterogeneity: $c_{11}^2 = 66.39$ ($P < .001$), $I^2 = 83\%$ |  |  |  |

−20  −10  0  10  20
Supplement  Placebo
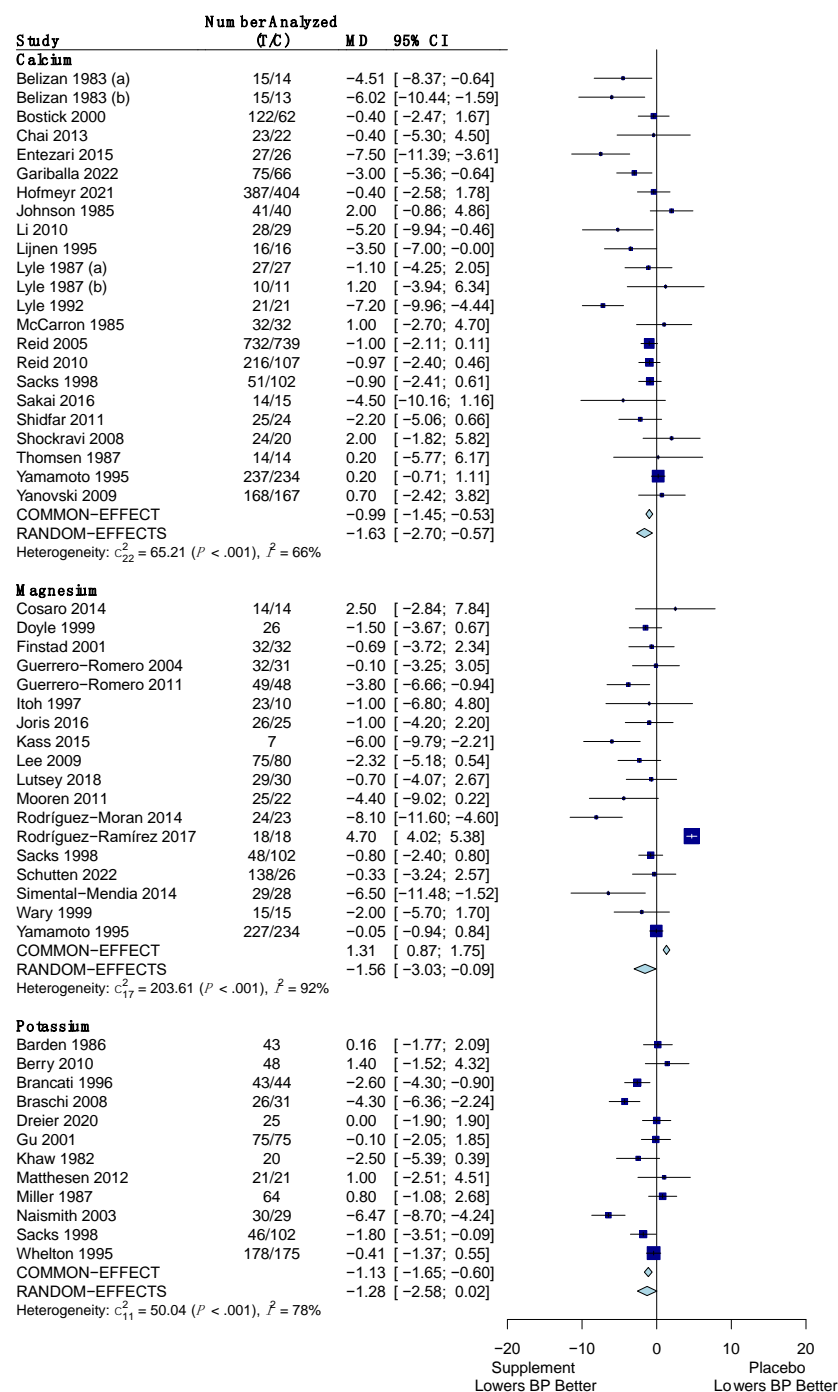Lowers BP Better  Lowers BP Better

**Figure 4.** Forest plot showing the mean difference of change in systolic blood pressure between minerals (calcium, magnesium, potassium) and placebo. T represents the sample size of the treatment (supplement/mineral) group and C represents the sample size of the control (placebo) group. The pooled mean difference is given in mm Hg with its 95% CI. The weighted mean difference in mm Hg and its 95% CI is given for each study. A graphical representation with the weighted mean difference and its SE is also given for each study. References: Calcium ([37,39,43,52,55,66,67,70,71,73,91,92,95, 96,101,102,106,114,116,119,123]); Magnesium ([45,46,48,54,58–60,65,69,76,93–95,98,103,109,114,118]); Potassium ([36,38,40,41,47,53,62,72,82,95,110,121]).

### 3.4.2. Diastolic Blood Pressure

The pooled results for the difference in the change of DBP for the vitamins versus placebo are shown in Figure 5. None of the three vitamins (C, D, E) were able to reduce DBP versus placebo. Vitamin C and E were deemed to have low heterogeneity ($I^2 = 0\%$; *p*-value: 0.96 and $I^2 = 0\%$; *p*-value: 0.51, respectively) and thus their effects on DBP were determined using the common effects model. These effects were −0.47 mm Hg (95% CI: −2.29, 1.34) and +1.17 mm Hg (95% CI: −0.51, 2.84), respectively. Vitamin D resulted in an increase in DBP versus placebo of +0.11 mm Hg (95% CI: −0.47, 0.69) using the random effects model due to high heterogeneity ($I^2 = 53\%$; *p*-value: < 0.001).
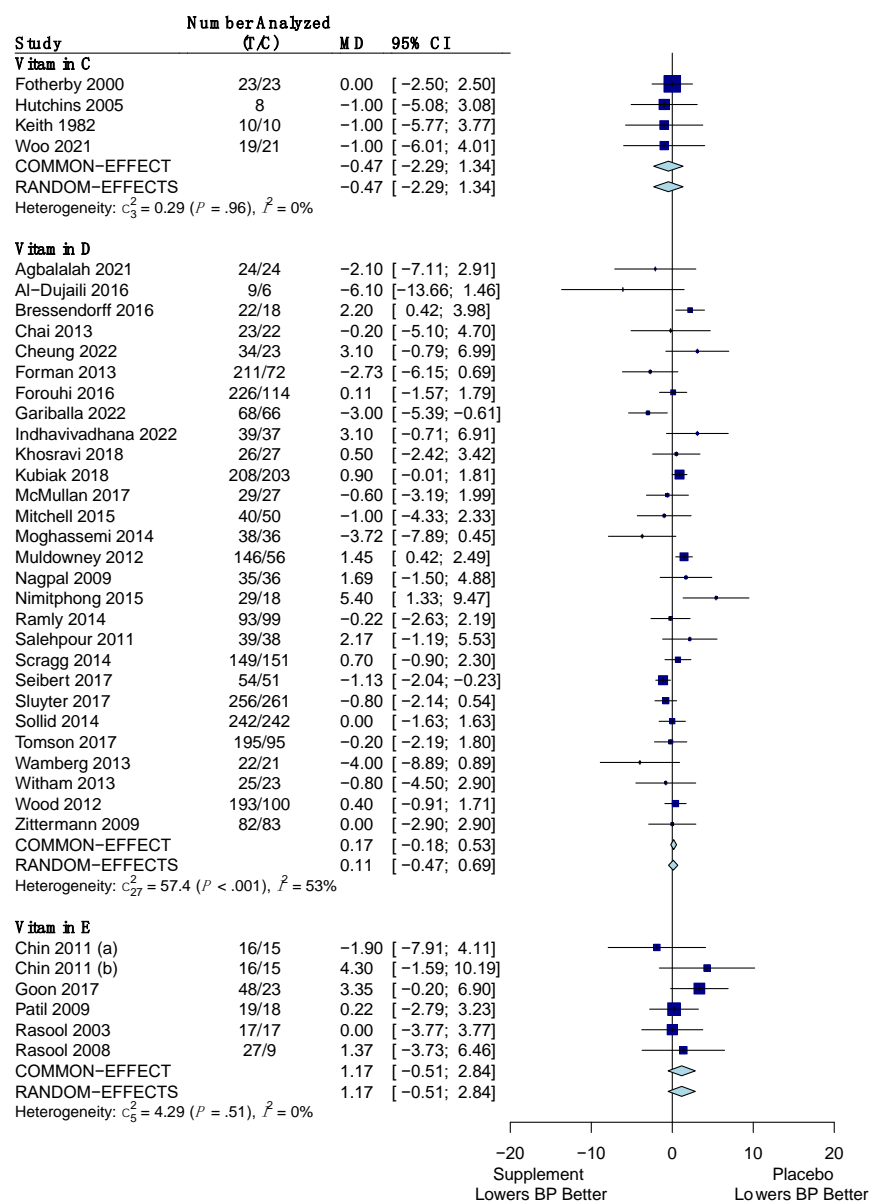


**Figure 5.** Forest plot showing the mean difference of change in diastolic blood pressure between vitamins (C, D, E) and placebo. T represents the sample size of the treatment (supplement/vitamin) group and C represents the sample size of the control (placebo) group. The pooled mean difference is given in mm Hg with its 95% CI. The weighted mean difference in mm Hg and its 95% CI is given for each study. A graphical representation with the weighted mean difference and its SE is also given for each study. References: Vitamin C ([51,56,61,112]); Vitamin D ([33,34,42–44,49,50,52,57,63,64,74,75,79, 81,83,87,97,99,100,104,105,107,108,111,113,122,124]); Vitamin E ([86,88,90,115,117]).

　　　The pooled results for the difference in the change of DBP for the minerals versus placebo are shown in Figure 6. These effects were calculated using the random effects model for all three minerals (calcium, magnesium, and potassium) due to high heterogeneity. Potassium was the only one of the three to have a statistically insignificant reduction in DBP, with a mean difference of −1.28 mm Hg (95% CI: −2.58, 0.02) and high heterogeneity ($I^2 = 78\%$; *p*-value: < 0.001). Calcium reduced DBP by a mean difference of −1.63 mm Hg (95% CI: −2.70, −0.57) with high heterogeneity amongst the studies ($I^2 = 66\%$; *p*-value: < 0.001). Magnesium had a mean difference in DBP of −1.56 mm Hg (95% CI: −3.03, −0.09), again with high heterogeneity ($I^2 = 92\%$; *p*-value: < 0.001).



| Study | Number Analyzed (T/C) | MD | 95% CI |
|---|---|---|---|
| **Calcium** | | | |
| Belizan 1983 (a) | 15/14 | −4.51 | [−8.37; −0.64] |
| Belizan 1983 (b) | 15/13 | −6.02 | [−10.44; −1.59] |
| Bostick 2000 | 122/62 | −0.40 | [−2.47; 1.67] |
| Chai 2013 | 23/22 | −0.40 | [−5.30; 4.50] |
| Entezari 2015 | 27/26 | −7.50 | [−11.39; −3.61] |
| Gariballa 2022 | 75/66 | −3.00 | [−5.36; −0.64] |
| Hofmeyr 2021 | 387/404 | −0.40 | [−2.58; 1.78] |
| Johnson 1985 | 41/40 | 2.00 | [−0.86; 4.86] |
| Li 2010 | 28/29 | −5.20 | [−9.94; −0.46] |
| Lijnen 1995 | 16/16 | −3.50 | [−7.00; −0.00] |
| Lyle 1987 (a) | 27/27 | −1.10 | [−4.25; 2.05] |
| Lyle 1987 (b) | 10/11 | 1.20 | [−3.94; 6.34] |
| Lyle 1992 | 21/21 | −7.20 | [−9.96; −4.44] |
| McCarron 1985 | 32/32 | 1.00 | [−2.70; 4.70] |
| Reid 2005 | 732/739 | −1.00 | [−2.11; 0.11] |
| Reid 2010 | 216/107 | −0.97 | [−2.40; 0.46] |
| Sacks 1998 | 51/102 | −0.90 | [−2.41; 0.61] |
| Sakai 2016 | 14/15 | −4.50 | [−10.16; 1.16] |
| Shidfar 2011 | 25/24 | −2.20 | [−5.06; 0.66] |
| Shockravi 2008 | 24/20 | 2.00 | [−1.82; 5.82] |
| Thomsen 1987 | 14/14 | 0.20 | [−5.77; 6.17] |
| Yamamoto 1995 | 237/234 | 0.20 | [−0.71; 1.11] |
| Yanovski 2009 | 168/167 | 0.70 | [−2.42; 3.82] |
| COMMON−EFFECT | | −0.99 | [−1.45; −0.53] |
| RANDOM−EFFECTS | | −1.63 | [−2.70; −0.57] |
| Heterogeneity: $c^2_{22} = 65.21$ (*P* < .001), $I^2 = 66\%$ | | | |
| **Magnesium** | | | |
| Cosaro 2014 | 14/14 | 2.50 | [−2.84; 7.84] |
| Doyle 1999 | 26 | −1.50 | [−3.67; 0.67] |
| Finstad 2001 | 32/32 | −0.69 | [−3.72; 2.34] |
| Guerrero−Romero 2004 | 32/31 | −0.10 | [−3.25; 3.05] |
| Guerrero−Romero 2011 | 49/48 | −3.80 | [−6.66; −0.94] |
| Itoh 1997 | 23/10 | −1.00 | [−6.80; 4.80] |
| Joris 2016 | 26/25 | −1.00 | [−4.20; 2.20] |
| Kass 2015 | 7 | −6.00 | [−9.79; −2.21] |
| Lee 2009 | 75/80 | −2.32 | [−5.18; 0.54] |
| Lutsey 2018 | 29/30 | −0.70 | [−4.07; 2.67] |
| Mooren 2011 | 25/22 | −4.40 | [−9.02; 0.22] |
| Rodríguez−Moran 2014 | 24/23 | −8.10 | [−11.60; −4.60] |
| Rodríguez−Ramírez 2017 | 18/18 | 4.70 | [4.02; 5.38] |
| Sacks 1998 | 48/102 | −0.80 | [−2.40; 0.80] |
| Schutten 2022 | 138/26 | −0.33 | [−3.24; 2.57] |
| Simental−Mendia 2014 | 29/28 | −6.50 | [−11.48; −1.52] |
| Wary 1999 | 15/15 | −2.00 | [−5.70; 1.70] |
| Yamamoto 1995 | 227/234 | −0.05 | [−0.94; 0.84] |
| COMMON−EFFECT | | 1.31 | [0.87; 1.75] |
| RANDOM−EFFECTS | | −1.56 | [−3.03; −0.09] |
| Heterogeneity: $c^2_{17} = 203.61$ (*P* < .001), $I^2 = 92\%$ | | | |
| **Potassium** | | | |
| Barden 1986 | 43 | 0.16 | [−1.77; 2.09] |
| Berry 2010 | 48 | 1.40 | [−1.52; 4.32] |
| Brancati 1996 | 43/44 | −2.60 | [−4.30; −0.90] |
| Braschi 2008 | 26/31 | −4.30 | [−6.36; −2.24] |
| Dreier 2020 | 25 | 0.00 | [−1.90; 1.90] |
| Gu 2001 | 75/75 | −0.10 | [−2.05; 1.85] |
| Khaw 1982 | 20 | −2.50 | [−5.39; 0.39] |
| Matthesen 2012 | 21/21 | 1.00 | [−2.51; 4.51] |
| Miller 1987 | 64 | 0.80 | [−1.08; 2.68] |
| Naismith 2003 | 30/29 | −6.47 | [−8.70; −4.24] |
| Sacks 1998 | 46/102 | −1.80 | [−3.51; −0.09] |
| Whelton 1995 | 178/175 | −0.41 | [−1.37; 0.55] |
| COMMON−EFFECT | | −1.13 | [−1.65; −0.60] |
| RANDOM−EFFECTS | | −1.28 | [−2.58; 0.02] |
| Heterogeneity: $c^2_{11} = 50.04$ (*P* < .001), $I^2 = 78\%$ | | | |

**Figure 6.** Forest plot showing the mean difference of change in diastolic blood pressure between minerals (calcium, magnesium, potassium) and placebo. T represents the sample size of the treatment

(supplement/mineral) group and C represents the sample size of the control (placebo) group. The pooled mean difference is given in mm Hg with its 95% CI. The weighted mean difference in mm Hg and its 95% CI is given for each study. A graphical representation with the weighted mean difference and its SE is also given for each study. References: Calcium ([37,39,43,52,55,66,67,70,71,73,91,92,95, 96,101,102,106,114,116,119,123]); Magnesium ([45,46,48,54,58–60,65,69,76,93–95,98,103,109,114,118]); Potassium ([36,38,40,41,47,53,62,72,82,95,110,121]).

### 3.4.3. Summary

A summary of the effects of the vitamins and minerals versus placebo is provided in Table 3. All three minerals (calcium, magnesium, and potassium), as well as vitamin E, had a statistically significant mean reduction in SBP, whereas only calcium and magnesium had a statistically significant reduction in DBP. However, potassium was close to having a statistically significant mean reduction in DBP with the upper limit of its 95% CI being just above 0.

**Table 3.** Summary of the effects of vitamins (C, D, E) and minerals (calcium, magnesium, potassium) versus placebo on systolic and diastolic blood pressure.

| Supplement | Systolic | Diastolic |
| --- | --- | --- |
| Vitamin C | −1.45 mm Hg (−4.26, 1.35) | −0.47 mm Hg (−2.29, 1.34) |
| Vitamin D | −0.19 mm Hg (−0.71, 0.33) | +0.11 mm Hg (−0.47, 0.69) |
| Vitamin E | −1.76 mm Hg (−3.05, −0.47) * | +1.17 mm Hg (−0.51, 2.84) |
| Calcium | −1.37 mm Hg (−2.03, −0.71) * | −1.63 mm Hg (−2.70, −0.57) * |
| Magnesium | −2.79 mm Hg (−5.25, −0.34) * | −1.56 mm Hg (−3.03, −0.09) * |
| Potassium | −2.10 mm Hg (−3.81, −0.38) * | −1.28 mm Hg (−2.58, 0.02) |

Values are mean systolic and diastolic blood pressure reductions for each supplement versus placebo with their corresponding 95% Confidence Intervals. Asterisks (*) denote statistical significance.

### 3.4.4. Sensitivity Analysis

A sensitivity analysis was performed by imputing the missing standard deviations of change-from-baseline scores for parallel comparisons assuming a correlation coefficient of 0.5. For cross-over studies, the standard errors of effect sizes were calculated assuming correlation coefficients of 0.5 and 0.9. The results are summarized in Table S6. Overall, only the effect of magnesium on DBP reduction became nonsignificant when a smaller correlation coefficient was used to impute standard deviations of change-from-baseline scores.

### 3.4.5. Publication Bias

Contour-enhanced funnel plots of the six supplements with their effect sizes on the horizontal axis and SEs on the vertical axis were constructed to visualize potential publication bias. These plots can be found by supplement for systolic and diastolic BP in Figures S1 and S2, respectively. The asymmetric patterns seen in the SBP analysis for vitamin E and the DBP analyses for calcium and magnesium indicate potential publication bias associated with these analyses. This was confirmed by Egger's regression, yielding significant results for these three analyses (*p*-values of 0.075, 0.069, and 0.001, respectively). The DBP analysis for vitamin C was also noted to have publication bias with Egger's regression (*p*-value: 0.036).

## 4. Discussion

Our results provide evidence that vitamin E, calcium, magnesium, and potassium are effective in lowering SBP in the general, normotensive population. Both magnesium and potassium achieved a greater than −2 mm Hg reduction in SBP, with reductions of −2.79 mm Hg and −2.10 mm Hg, respectively. These reductions can be considered clinically significant, as prior studies have found that a −2 mm Hg reduction in SBP could reduce mortality from heart disease and stroke by as much as 7% and 10%,

respectively [4,125]. Our results also show that both calcium and magnesium are effective in lowering DBP in this population. Furthermore, although the DBP reduction of −1.28 mm Hg by potassium was not significant, the upper limit of its confidence interval was just above zero at 0.02. Overall, this study and its findings are important as no previous study has conducted meta-analyses on the effectiveness of multiple nutraceuticals in reducing BP amongst this population. We hope that our significant findings and accessibility of data will be of help to those interested in the BP-lowering capabilities of these nutraceuticals.

Our reductions in blood pressure were generally lower than the values in previously published meta-analyses of these nutraceuticals. This supports our hypothesis that these studies, which included subjects with uncontrolled hypertension who were receiving these nutraceuticals as an initial treatment, likely saw greater reductions in BP as a result. This discrepancy was largest for vitamin C, vitamin E, and potassium. For example, the most recent published meta-analysis on vitamin C yielded statistically significant reductions of both systolic and diastolic blood pressure of −4.09 mm Hg and −2.30 mm Hg [15]. This is a drastic contrast to our values of −1.45 mm Hg and −0.47 mm Hg, with neither being significant. While vitamin E provided a statistically significant reduction in SBP of −1.76 mm Hg in our study, this was lower than a 2019 meta-analysis of 18 RCTs that achieved a value of −3.4 mm Hg [17]. We also obtained an increase in DBP of 1.17 mm Hg compared to their reduction of −1.19 mm Hg, although neither result was deemed significant [17]. Similar differences existed with potassium. The most recent publication on potassium obtained reductions of −3.9 mm Hg and −2.4 mm Hg [20], nearly twice our values of −2.10 mm Hg and −1.28 mm Hg, the latter of which did not reach significance, as mentioned earlier. However, it is worth noting that we do not know whether the differences between our values and the most recent published meta-analyses are statistically significant since no analysis was performed to assess.

Our results for vitamin D and calcium were similar to those found in the most recent publications [16,18]. Upon further examination of these studies, we found that they targeted a similar normotensive population, which could explain the similarity in our findings. However, even outside of this controlled population, vitamin D has not shown to be effective at lowering systolic or diastolic BP [126,127]. This holds true even in individuals with vitamin D deficiency [128]. On the other hand, calcium has been consistently shown to reduce BP. Another meta-analysis of 40 trials with an average daily calcium dose of 1200 mg showed similar reductions to what we obtained in regard to SBP and DBP [129]. Although, they further noted that these reductions were more pronounced in people with lower baseline calcium intake [129]. Interestingly, a meta-analysis of 8 trials with vitamin D and calcium co-supplementation showed no significant reduction in SBP and only −0.23 mm Hg in DBP [130]. Further studies with larger sample sizes should be conducted before passing judgement on the efficacy of this combination.

Aside from calcium, magnesium was the only other nutraceutical to produce a significant reduction in both SBP and DBP. Notably, the −2.79 mm Hg reduction in SBP was greater than the −2.00 mm Hg seen in a meta-analysis of 34 trials that did not control for our general, normotensive population [19]. However, another study obtained vastly different results, concluding that magnesium supplementation does not lower BP in normotensives or controlled hypertensives, even at high doses [131]. Due to this discrepancy in the literature, future research is warranted, especially given the promising results that our study obtained. Aside from having larger sample sizes to ensure power, these studies should investigate a variety of dosages, given the large ranges noted in the trials we included. Additionally, longer treatment periods should be utilized, as the longest trial in our study was just six months.

Potassium was the only other nutraceutical to produce a reduction in SBP of at least −2 mm Hg. As noted, however, this reduction was only half of what has been seen in studies that were not controlling for a general, normotensive population [20]. This previous study also performed a dose-response meta-analysis that yielded a U-shaped graph,

suggesting that while potassium can lower BP, higher dosages might increase it [20]. It is important to note that not only did the normotensive group experience smaller reductions in BP but they were also more sensitive to higher dosages of potassium, experiencing an increased BP at a dosage of 60 mmol/day versus 90 mmol/day in the hypertensive group [20]. Another study examining the effect of potassium on primary essential hypertension obtained similarly sized reductions in SBP and DBP to the previously mentioned one, but showed that higher dosages of potassium, specifically ≥100 mmol/day, achieved the greatest reductions [132]. Given the conflicting results between these studies, future studies should focus on the optimal dosage for various populations, as well as the long-term safety of potassium supplementation.

Although vitamin C and vitamin E yielded uninspiring results for BP reduction in this population, our study may have been limited by low power due to the relatively low number of eligible trials and their small sample sizes. Future studies with larger power should evaluate the efficacy of these two vitamins amongst this general, normotensive population, especially with their promising results in previous studies. If conducted, these studies should focus on vitamin C at a dosage of ≥500 mg/day and a duration of ≥6 weeks, as subgroup analysis in the prior meta-analysis found these to yield the greatest reductions in BP [15]. Vitamin E was found to achieve the greatest reduction at dosages ≤ 400 mg/day and their results were independent of treatment duration [17]. This data on vitamin E may be of interest since we did obtain a significant reduction in SBP in our study.

While we did not investigate ideal dosage and treatment length in our study, prior studies provide insight into these. A systematic review provided the recommended daily intake for the supplements used in our study [133]. These are 70–90 mg, 10–20 μg (400–800 IU), and 10–15 mg for vitamins C, D, and E, respectively [133]. Calcium, magnesium, and potassium have recommended daily values of 1000–1300 mg, 350–420 mg, and 4700–4800 mg, respectively [133]. The published meta-analyses with subgroup analyses can be used to further speculate on optimal dosage and treatment length in our population for those nutraceuticals that showed efficacy in our study. Calcium, which had a significant reduction in both SBP and DBP in our study, showed greatest efficacy at dosages > 1500 mg/day and treatment durations < 6 months [18]. Magnesium achieved greatest reductions in BP at dosages < 300 mg/day and with a duration of 30–89 days (1–3 months) [19]. The effects of potassium on BP have been shown to be independent of treatment duration, but the optimal dosage is still to be determined, as we mentioned above [20,132]. We intend to investigate ideal dosage and treatment length for this population in future studies to build upon our findings. Further subgroup analyses will also be considered at that time, such as into variations by age, gender, ethnicity, and past medical history to further refine recommendations into the use of these nutraceuticals. However, for the purposes of this study, we felt in-depth subgroup analyses across all six nutraceuticals in a single paper would complicate the reporting of our results and take away from the clear overview that we sought to provide.

Our results are important because they shed light onto what the general, normotensive population can take to achieve optimal BP. We are the first study to provide data on multiple vitamins and minerals for this purpose, allowing access for easy comparison of efficacy versus placebo in this population. We achieved high power with large sample sizes for vitamin D, calcium, magnesium, and potassium that we hope adds credibility to our results and promise for its generalizability. Furthermore, while proving to be effective in lowering BP, these six supplements are considered natural and part of a balanced diet. This may help appeal to individuals who are hesitant to take pharmaceuticals for controlling BP, although these supplements should not be viewed as alternatives in those requiring antihypertensives. Current clinical practice guidelines recommend initiating antihypertensives when SBP is ≥140 and/or DBP is ≥90 in patients with primary hypertension without other co-morbidities warranting sooner intervention [134,135]. Therefore, we hope our results aid in the decision-making for those who have BPs outside of this range but still above optimal. Specifically, our data should be used for individuals with BPs above the optimal range of

110–115/70–75 mm Hg that don't qualify for initiation of prescription antihypertensives based on clinical practice guidelines. The goal of initiation of these vitamins and minerals would be to lower BP closer to this level, potentially reducing the increased mortality seen from vascular events and coronary heart disease at higher BPs in the process.

Additionally, no adverse events were reported in any of our 87 included trials, while mild side effects were seen with the supplement group in only six, with magnesium and vitamin D accounting for three each. These side effects included mild diarrhea in the three magnesium trials and a range of symptoms in the vitamin D trials from headache to abdominal pain to constipation/diarrhea. Overall, these supplements appear to be an inexpensive and safe option for better BP control when patients don't qualify for antihypertensives. While all six would be eligible options for the general, normotensive population, particular attention should be given to the four (vitamin E, calcium, magnesium, and potassium) that showed efficacy in lowering BP. This is especially true for magnesium and potassium because of their clinically significant reduction in SBP, with magnesium exhibiting efficacy in lowering DBP also. Due to this efficacy, magnesium appears to be the most promising of our six supplements in this population.

Our study is not without limitations, the most glaring of which is that we did not control for subgroups, including differences in patient populations, dosages of supplements, and treatment length. While we had strict inclusion and exclusion criteria, differences in efficacy likely exist amongst patient population subgroups, as well as the various dosages and/or treatment lengths. Ultimately, we were willing to accept this limitation going into the study, as we hoped this paper could serve mainly as a preliminary, foundational analysis of how these six nutraceuticals could be used amongst a general, normotensive population. The interpretation of our results is thereby limited, as we can only state the mean reductions in SBP and DBP for the supplements against placebo across a range of patient populations, dosages, and treatment lengths. However, we hope that our compiled references, data points, and findings will be used to guide more specific analyses in the future. As mentioned, future studies should investigate optimal dosage and treatment length, as well as the long-term efficacy and safety of these supplements. Priority should be given to those that showed significant reductions in this population: vitamin E, calcium, magnesium, and potassium. Combinations of supplements could also be explored to explore for additive and/or synergistic effects, as we excluded these studies in our study to determine the individual efficacy of each nutraceutical versus placebo.

Additionally, publication bias was noted in some of our analyses, as evidenced by the asymmetry in their funnel plots. This occurred in the meta-analyses of SBP with vitamin E and DBP for calcium and magnesium, with confirmation for all three provided by Egger's regression. The Egger's regression also highlighted potential publication bias in the meta-analysis of DBP for vitamin C. Given these risks of bias, the pooled results of these analyses should be considered with caution. On the same token, significant heterogeneity was seen in certain analyses, thus its effect on the analyses cannot be ignored when considering the validity of the results.

## 5. Conclusions

In conclusion, to our knowledge, this is the first study to run pairwise meta-analyses on the BP lowering capacity of all six of these nutraceuticals versus placebo in the general, normotensive population. Our results displayed evidence for vitamin E, calcium, magnesium, and potassium being effective at lowering SBP in this population, with both magnesium and potassium achieving a greater than 2 mm Hg reduction. Additionally, calcium and magnesium were determined to be effective at lowering DBP in this population. Given these findings, magnesium seems to be the most effective of the six nutraceuticals studied in lowering BP in this population. Future studies should look further into the use of these nutraceuticals to determine optimal dosage and treatment length, long-term safety and efficacy, and potential additive and/or synergistic effects.

**Supplementary Materials:** The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/nu15194223/s1, Figure S1: Contour-enhanced funnel plots of the six meta-analyses in systolic blood pressure reduction; Figure S2: Contour-enhanced funnel plots of the six meta-analyses in diastolic blood pressure reduction; Table S1: Search terms for each of the four databases; Table S2: Reasons for exclusion of full-text articles (*n* = 325); Table S3: Reasons for exclusion of the five studies that met eligibility; Table S4: Basic characteristics of included studies; Table S5: Risk of bias results by individual study; Table S6: Results of sensitivity analyses for each supplement.

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