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Effects of vitamin C supplementation on blood pressure: a meta-analysis of randomized controlled trials[1–3]

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ABSTRACT

Background: In observational studies, increased vitamin C intake, vitamin C supplementation, and higher blood concentrations of vitamin C are associated with lower blood pressure (BP). However, evidence for blood pressure–lowering effects of vitamin C in clinical trials is inconsistent.

Objective: The objective was to conduct a systematic review and meta-analysis of clinical trials that examined the effects of vitamin C supplementation on BP.

Design: We searched Medline, EMBASE, and Central databases from 1966 to 2011. Prespecified inclusion criteria were as follows: *1*) use of a randomized controlled trial design; *2*) trial reported effects on systolic BP (SBP) or diastolic BP (DBP) or both; *3*) trial used oral vitamin C and concurrent control groups; and *4*) trial had a minimum duration of 2 wk. BP effects were pooled by random-effects models, with trials weighted by inverse variance.

Results: Twenty-nine trials met eligibility criteria for the primary analysis. The median dose was 500 mg/d, the median duration was 8 wk, and trial sizes ranged from 10 to 120 participants. The pooled changes in SBP and DBP were −3.84 mm Hg (95% CI: −5.29, −2.38 mm Hg; $P < 0.01$) and −1.48 mm Hg (95% CI: −2.86, −0.10 mm Hg; $P = 0.04$), respectively. In trials in hypertensive participants, corresponding reductions in SBP and DBP were −4.85 mm Hg ($P < 0.01$) and −1.67 mm Hg ($P = 0.17$). After the inclusion of 9 trials with imputed BP effects, BP effects were attenuated but remained significant.

Conclusions: In short-term trials, vitamin C supplementation reduced SBP and DBP. Long-term trials on the effects of vitamin C supplementation on BP and clinical events are needed. *Am J Clin Nutr* 2012;95:1079–88.

INTRODUCTION

Vitamin C (ascorbic acid) is an essential micronutrient that is acquired primarily through the consumption of fruit, vegetables, supplements, fortified beverages, and fortified breakfast or "ready-to-eat" cereals (1). Vitamin C is a powerful aqueous-phase antioxidant that reduces oxidative stress (2) and enhances endothelial function through effects on nitric oxide production (3). Antihypertensive effects of vitamin C were hypothesized as early as 1946 (4), and many laboratory (5, 6) and human studies (7, 8) have established biological plausibility. Population-based observational studies have shown an inverse association between plasma vitamin C concentrations (9) and vitamin C intake with blood pressure (BP)[4] (10), providing justification for trials evaluating vitamin C supplementation and BP reduction.

A large number of small randomized controlled trials have evaluated the effect of vitamin C supplementation on BP (11–48), but the results were inconsistent, possibly because of heterogeneous methods and the small sample size of individual trials (49, 50). Our objective was to conduct a systematic review and meta-analysis of randomized controlled trials to determine the effects of vitamin C supplementation on BP in adults.

METHODS

Search strategy and eligibility criteria

We performed a search of Medline, EMBASE, and the Cochrane Central Register of Controlled Trials (Central) databases from January 1966 through December 2010 using the following terms: *blood pressure*, *hypertension*, *hypertensive*, *hypotension*, *hypotensive*, *endothelial dysfunction*, *endothelial function*, *ascorbic acid*, *antioxidant(s)*, *vitamin(s)*, *randomized controlled trials*, and *clinical trials.* The search was confined to human studies without language restrictions. *See* the online supplemental material under "Supplemental data" in the online issue for details. We reviewed bibliographies of original research and previous reviews to complement the search.

Prespecified inclusion criteria were as follows: *1*) use of a randomized controlled trial design, *2*) trial reported effects on systolic BP (SBP) or diastolic BP (DBP) or both, *3*) trial used oral vitamin C supplementation and concurrent control groups, and *4*) trial had a minimum duration of 2 wk. Exclusion criteria were as follows: *1*) trials that enrolled pregnant women, children, or patients with end-stage renal disease; *2*) trials in which vitamin C was included as part of a calorie-containing beverage, eg, milk or fruit juice; or *3*) trials lasted >1 y (because of

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[4] Abbreviations used: ABPM, ambulatory blood pressure monitoring; BP, blood pressure; DBP, diastolic blood pressure; SBP, systolic blood pressure.

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concerns related to differential antihypertensive medication use and/or noninformative censoring).

Two investigators (SPJ and ERM) independently abstracted the articles. Discrepancies were adjudicated by consensus. The following information was abstracted: *1*) participant characteristics, including preexistent disease or condition, mean age, sex, treatment with antihypertensive medications; *2*) characteristics of trial design (parallel, crossover, factorial, blinding, intervention dose, type of control, trial duration); *3*) details of BP measurement, such as position (eg, seated or standing), location, device [eg, oscillometric monitor, sphygmomanometric cuff, 24-h ambulatory device, ambulatory blood pressure monitoring (ABPM)], number of measurements; *4*) mean pretreatment SBP and DBP; *5*) pretreatment plasma ascorbic acid concentrations; and *6*) mean trial-end SBP, DBP, and plasma ascorbic acid concentrations. In trials in which methods were described in previous publications (51–53), these articles were abstracted for relevant information. We contacted authors of publications in which BP was recorded but results were not adequately reported or not available in English. Data provided by these authors were also included in the primary analysis (12, 18, 23).

Statistical analysis

For the primary analysis we determined the between-group differences in BP change for vitamin C and placebo groups and then pooled these results. In parallel trials (12–15, 17, 18, 21, 24–27, 29, 32, 33, 35, 37), to account for imbalances in baseline BP (54), we used the reported between-arm difference in end minus baseline BP or calculated it by using the information reported in the trial. If not provided, the variance for the end minus baseline difference in BP was calculated assuming a correlation coefficient of 0.7. A sensitivity analysis was conducted by using a correlation coefficient of 0.5, with virtually identical results (not shown). In 2 parallel trials that did not report baseline values, we used the difference between treatment and control end-BP (11, 28). In factorial studies (17, 19, 20), results were based on marginal (2-way) analyses, except in one trial that provided a 4-way comparison without sufficient data to calculate the marginal comparison (20). In crossover trials (16, 19, 30, 36), because the baseline was shared by all participants, we used the given or calculated difference between the end-period treatment and control BP values (55). Some crossover trials provided mean end-baseline differences (31, 34, 39), and the difference between treatment and control groups was calculated for the overall effect.

In cases in which the intervention included vitamin C and another agent or agents, we used the agent or agents as the control group when available (11, 13, 32). In trials that reported more than one BP measure—for example, night and daytime ambulatory BP (ABPM)—we used the mean BP resulting from the greatest number of measurements (31). When data were reported as subgroups without an overall effect, subgroups were used in the analysis (34, 36). In a sensitivity analysis, we included trials with incomplete reporting of BP or BP variance after an assumption of no effect of supplementation on BP (36, 40–48). *See* Supplemental Tables 2 and 3 under "Supplemental data" in the online issue for characteristics of these trials and details of our imputation methodology.

Exploratory subgroup analyses focused on participant and trial characteristics including hypertension status of study population or average participant BP values (baseline SBP $>$140 mm Hg, baseline DBP $>$90 mm Hg), diabetes status (prespecified population, yes or no), baseline plasma ascorbic acid (median value), and mean age ($<$50, 50–60, $>$60 y). Trial characteristics included trial duration (median value), vitamin C dose (median value), study design (parallel or crossover), vitamin C only as the intervention (yes or no), use of stable doses of antihypertensive agents by participants during the trial (yes or no), number of BP measurements [1–2, 3–4, 60–66 (ABPM)], and the trial size (median value). We also conducted a sensitivity analysis after exclusion of trials with missing baseline ascorbic acid measurements and trials with serum ascorbic acid $>$60 μmol/L at baseline. This cutoff was chosen because it represents the lower range of the vitamin C urinary excretion threshold, which might suggest that, on average, participants in these trials had baseline vitamin C concentrations that had reached saturation (56).

Finally, we assessed individual trial quality based on adherence to conventional trial standards, including a description of allocation concealment (yes or no), description of randomization methods (yes or no), blinding of participants (yes or no), blinding of investigators or trial staff (yes or no), description of methods for assessing participant compliance (yes or no), and description of adverse events. We also report whether or not trials included a statement regarding the exclusion of supplement users or restriction of supplement use throughout the trial. With regard to crossover trials, we abstracted the duration of the washout period.

Pooled estimates and 95% CIs of effect sizes were calculated by using a random-effects model with each effect weighted by the inverse variance. Heterogeneity between studies was assessed by Q statistics and by the I^2 statistic (55), which provides the proportion of total variation in study estimates due to heterogeneity. Individual trial influence was evaluated by removing each trial from the pooled effect. Statistical analyses were performed by using STATA 8.2 (Stata Corp).

RESULTS

The trial selection process of our systematic review is shown in **Figure 1**. We excluded 3 trials in which vitamin C was administered in a calorie-containing beverage (57–59), 5 trials that lacked a concurrent control group (60–64), and 3 trials lasting $>$1 y (65–67). Two frequently cited vitamin C trials were also excluded from our analysis, one due to concurrent administration of a vitamin C–containing multivitamin to both intervention and control groups, the other due to vitamin C contained in both the placebo and intervention pills (high and low dose) (68, 69). Fifteen trials reported baseline BP but did not report end-BP values or effect variance, CIs, or P values. Nine trials reported incomplete SBP data, and 10 reported incomplete DBP data (36, 40–48). These trials were excluded from the primary analysis but added for a sensitivity analysis after data imputations were performed.

Twenty-nine clinical trials were pooled in our primary analysis. Trial characteristics are summarized in **Table 1**. These trials, conducted from 1982 through 2010, included 1407 participants. Trial size ranged from 10 to 120 participants. The mean age of trial participants ranged from 22 to 74 y. Seven trials used a crossover design, 22 used a parallel design, and 3 used a factorial design. Trial duration ranged from 2 to 26 wk (median: 8 wk). Average pretreatment SBP ranged from 117 to

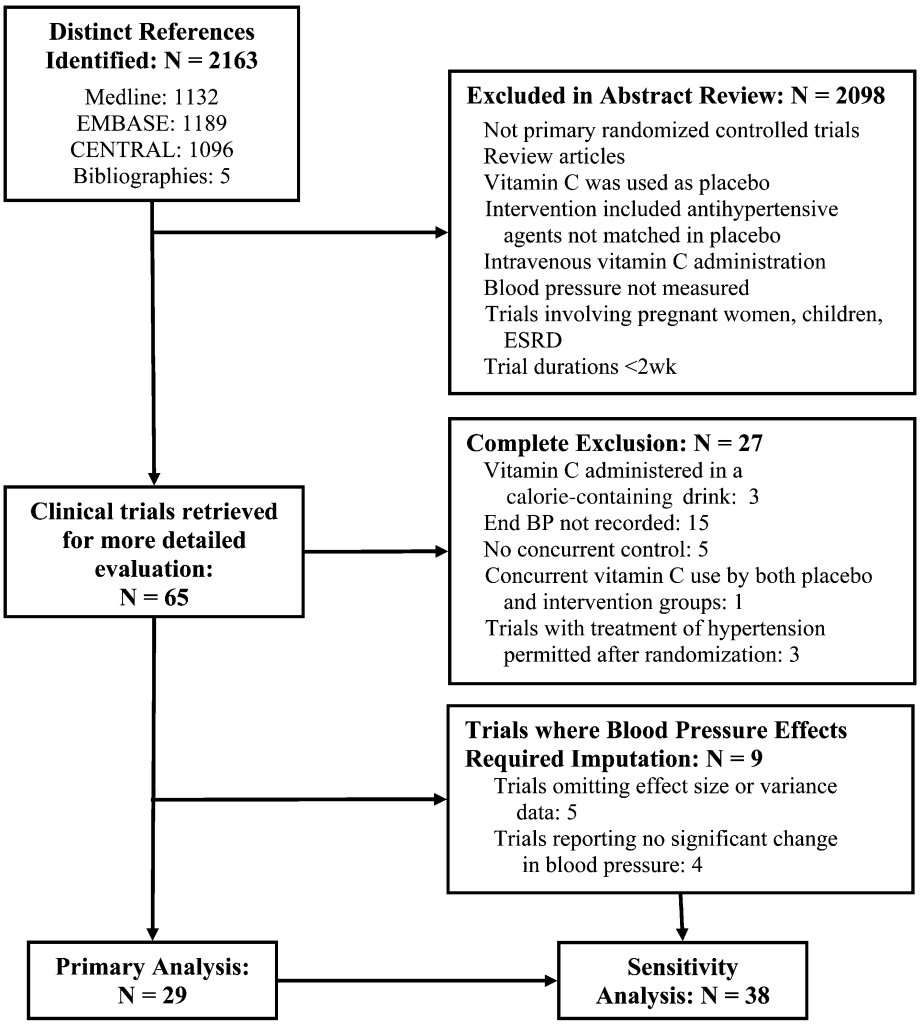

FIGURE 1. Flow diagram of the trial selection process. Medline (www.pubmed.org); EMBASE (http://www.embase.com/home); Central (http://onlinelibrary.wiley.com/o/cochrane/cochrane_clcentral_articles_fs.html). BP, blood pressure; ESRD, end-stage renal disease.

175 mm Hg and average DBP from 73 to 97 mm Hg. Fifteen trials permitted concurrent use of antihypertensive agents, and 14 did not. In 2 trials, an antihypertensive agent was used in the vitamin C and placebo groups. Twenty-five trials were double-blind, 3 were single-blind, and 1 did not report blinding. Vitamin C supplementation dose ranged from 60 to 4000 mg/d. Fifteen trials used vitamin C alone in their intervention arms, whereas 13 trials used a combination of vitamins and minerals that included vitamin C. Pretreatment plasma ascorbic acid ranged from 38 to 83 μmol/L.

Trial quality features can be found in Supplemental Table 1 under "Supplemental data" in the online issue. Most trials did not report details regarding allocation concealment (5 of 29) or randomization method (7 of 29). Most trials included blinding of investigators or staff in addition to study participants (25 of 29), whereas 16 described some method for evaluating participant compliance. The majority of trials stated that they either excluded supplement users or did not permit supplement use beyond the trial protocol (23 of 29). Few trials reported adverse events (6 of 29). All crossover trials had a washout period, ranging from 1 to 4 wk.

In pooled analyses, vitamin C supplementation reduced SBP by an average of −3.84 mm Hg (95% CI: −5.29, −2.38 mm Hg; $P < 0.001$) and DBP by −1.48 mm Hg (95% CI: −2.86, −0.10 mm Hg; $P = 0.036$) (**Figure 2**). Both SBP and DBP pooled effects were heterogeneous (I^2 of 69% and 81% for SBP, and DBP respectively; both $P < 0.001$). BP effects did not differ by hypertensive status for either SBP ($P = 0.28$) or DBP ($P = 0.85$). Greater SBP reductions were observed in trials with younger participants; in trials that administered vitamin C with other vitamins, minerals, or pharmacologic agents; and in trials with fewer BP measurements (*see* **Table 2**). Greater DBP reductions were noted in trials with fewer BP measurements and in trials that included 38 or greater participants.

Plotting inverse SEs against BP effects for each trial showed an inverted, funnel-shaped pattern for both SBP and DBP with no evidence of publication or related biases. In addition, Begg's rank correlation tests yielded an SBP Kendall score of −57 ($P = 0.33$) for SBP and of −28 ($P = 0.60$) for DBP, and Egger's linear regression test yielded −0.051 ($P = 0.93$) for SBP and −0.64 ($P = 0.47$) for DBP. The omission of trials with greatest influence did not alter overall effects. The pooled random effects for SBP

TABLE 1
Trial characteristics[1]

Trials included in the primary analysis (n = 29)	Population	Size	Age	Male	BP medication	Trial design	Trial length[2]	Intervention (per day)	Control	Baseline SBP	Baseline DBP	Baseline ascorbic acid[3]	BP measurement: position, location, device, no. of measurements
		n	*y*	%			*wk*			*mm Hg*	*mm Hg*	*μmol/L*	
Farvid, 2010 (18)[4]	T2D	75	52.5 ± 8.5[5]	52	No	P, D	16	Vit C 400 mg, vit E 200 mg, Mg 500 mg, zinc 40 mg, thiamine 20 mg, riboflavin 20 mg, vit B-6 20 mg, vit B-12 20 μg, folic acid 2 mg	Placebo	130.3 ± 15.59	82.8 ± 10.00	48.8 ± 14.8	Seated, arm, Powerlab sphygmomanometer, 2
Shargorodsky, 2010 (27)[4]	Patients with cardiovascular risk factors	70	62.6 ± 5.7	51	Yes	P, S	24	Vit C 1000 mg, vit E 400 IU, coenzyme Q10 120 mg, selenium 200 μg	Placebo	141.7 ± 23.3	77.2 ± 10.0	—	Supine, NA, NA, NA
Wang, 2009 (33)[4]	Obese women	64	42.0 ± 6.9	0	Yes	P, D	26	Vit C 60 mg, multiple vitamins and minerals	Maize starch	128.0 ± 22.9	85.0 ± 14.2	—	NA, arm, standard mercury sphygmomanometer, 2
Farah, 2008 (11)[4]	Essential hypertension	16	26–57[6]	56	Yes	P, O	24	Vit C 500 mg, vit E 600 IU, lercanidipine 10 mg	Lercanidipine 10 mg	159.6	96.2	—	—
Rodrigo, 2008 (12)[4]	Essential hypertension	110	45.6 ± 11.5	100	No	P, D	8	Vit C 1000 mg, vit E 400 IU	Placebo	138.7 ± 5.9	97.0 ± 6.3	37.5 ± 18.9	NA, arm, oscillometric monitor (Spacelabs 90207), NA
Mahajan, 2007 (13)[4]	Essential hypertension	40	37.3 ± 7.7	100	Yes	P, O	12	Vit C 1000 mg, amlodipine 5 mg	Amlodipine 5 mg	159.1 ± 8.6	96.1 ± 3.9	—	NA, NA, NA, 1
Nightingale, 2007 (15)	CHF and left ventricular systolic dysfunction	37	63.5 ± 8.6	84	Yes	P, D	4	Vit C 4000 mg	Placebo	130 ± 34	75 ± 15	39.05 ± 28.19	NA, thigh and ankle, peripheral pulse waveform recorder (QYLP84), NA
Plantinga, 2007 (16)	Essential hypertension	30	50 (42–60)[7]	100	No	X, D	8	Vit C 1000 mg, vit E 400 IU	Placebo	135 ± 10	87 ± 7	39.12 ± 22.43	Supine, arm, automatic device (OMRON-950), 3
Farvid, 2005 (17)	T2D	76	51 ± 9	46	No	F, P, D	12	Vit C 200 mg, vit E 100 IU, zinc 15 mg, Mg 100 mg	Placebo, zinc 15 mg, Mg 100 mg	126 ± 16	84 ± 10	62.28 ± 18.58	Seated, NA, NA, 2
Hutchins, 2005 (19)	Healthy postmenopausal women	10	56 ± 8	0	No	F, X, D	2	Vit C 500 mg, soy isoflavones 5 mg (per kg/body weight)	Placebo, soy isoflavones 5 mg	—	—	49.4 ± 11.4	Seated, arm, sphymomanometer (Sprague Rappaport), 1
Ward, 2005 (20)[4]	Hypertension	38	62 ± 7	70	Yes	F, P, D	6	Vit C 500 mg	Placebo	133.8 ± 9.1	79.5 ± 7.5	40.5 ± 13.5	Ambulatory, arm, oscillometric ABPM monitor (Spacelabs 90207), 64[8]
Magen, 2004 (21)	Hyperlipidemic subjects with resistant hypertension	36[9]	52.0 ± 12.5	52	Yes	P, S	8	Vit C 500 mg	Placebo	150.8 ± 6.4	86.4 ± 4.7	—	Ambulatory, arm, ABPM monitor (Profilomat), 66
Schutte, 2004 (22)[4]	Healthy normotensive white men	38	22.0 ± 2.1	100	No	P, D	12	Vit C 1000 mg, vit E 800 mg, folate 10 mg	Placebo	128.9 ± 9.0	79.1 ± 6.2	—	Fowler's position, finger, Finometer, NA
Nightingale, 2003 (14)	CHF and left ventricular systolic dysfunction	45	59.0 ± 8.7	74	Yes	P, D	4	Vit C 2000 mg	Placebo	126 ± 24	73 ± 11	44.4 ± 18.2	NA, arm, Finapres (Ohmeda)/Portapres (TNO), NA
Block, 2002 (23)[4]	Smokers	111[9]	43.7 ± 13.4	38	No	P, D	8	Vit C 515 mg	Placebo	117.0 ± 11.8	75.9 ± 9.5	51.7	Seated, arm, mercury sphygmomanometer, 2
Brody, 2002 (28)	Healthy young recruits	120	25.0 ± 4.2	39	No	P, D	2	Sustained-release vit C 3000 mg	Placebo	—	—	82.6	NA, arm, self-inflating sphygmomanometer, 1
Darko, 2002 (24)	Uncomplicated T2D	35	56.0 ± 6.5	66	Yes	P, D	3	Vit C 1500 mg	Placebo	140 ± 19	78 ± 11	55 ± 23	Supine, arm, automated measuring device (Dynamap), 3
Mullan, 2002 (25)[4]	T2D	30	59.5 ± 6.6	73	Yes	P, D	4	Vit C 500 mg	Placebo	141.6 ± 12.6	83.9 ± 5.1	43.3 ± 19.3	Supine, arm, oscillometric sphygmomanometer (OMRON HEM 705CP), 3
Singh, 2002 (26)	Healthy older subjects	36	67 ± 7	50	No	P, D	6	Vit C 1000 mg	Placebo	135 ± 19	79 ± 11	83 ± 19	Seated, arm, oscillometric sphygmomanometer (OMRON HEM 705CP), 3
Duffy, 2001 (29)[4]	Healthy patients with hypertension	45	33.9 ± 12.1	49	Yes	P, D	4	Vit C 500 mg	Placebo	156 ± 21	88 ± 12	48.9 ± 17.7	Semirecumbent, arm, automated monitor (Dinamap), 3
Gaede, 2001 (30)	T2D	30	58.7 ± 7.3	69	Yes	X, D	4	Vit C 1250 mg, vit E 680 IU	Placebo	155 ± 18	91 ± 10	41.9 ± 18.4	Supine, arm, Hawksley Random Zero Sphygmomanometer, 4
Fotherby, 2000 (31)[4]	Normotensive and hypertensive older adults	40	72 ± 4	50	No	X, D	12	Vit C 500 mg	Placebo	135 ± 15	79 ± 9	49 ± 14	Ambulatory, arm, oscillometric ABPM monitor (Spacelabs 90207), 60
Title, 2000 (32)	Coronary artery disease	50	58.0 ± 10.7	76	Yes	P, D	16	Vit C 2000 mg, vit E 800 IU, folic acid 5 mg	Folic acid 5 mg	133 ± 18	81 ± 11	—	—
Gokce, 1999 (35)	Coronary artery disease	55	55 ± 10	91	Yes	P, D	4	Vit C 500 mg	Placebo	138 ± 22	77 ± 9	42 ± 17	—
Galley, 1997 (36)[4]	Normotensive and hypertensive outpatients	40	25–73	—	Yes	X, D	8	Vit C 500 mg, α-tocopherol 600 mg, β-carotene 30 mg, zinc sulfate 200 mg	Placebo	107–207	67.0–110.0[10]	—	Supine, arm, mercury sphygmomanometer, 3
Ghosh, 1994 (37)[4]	Elderly patients with hypertension	48	73.8 ± 5.1	38	No	P, D	6	Vit C 500 mg	Placebo	175.3 ± 16.0	90.7 ± 11.6	51.7 ± 17.5	Seated, arm, Hawksley Random Zero Sphygmomanometer, 3
Salonen, 1994 (38)[4]	Normotensive male smokers	40	30–58	100	No	P, D	12	Vit C 400 mg, selenium 100 μg, *d*-α-tocopheryl acetate 200 mg, β-carotene 30 mg	Placebo	140.9 ± 15.5	84.5 ± 9.9	49.0 ± 20.7	Seated, arm, mercury sphygmomanometer, 2

(Continued)

TABLE 1 (*Continued*)

Trials included in the primary analysis (n = 29)	Population	Size	Age	Male	BP medication	Trial design	Trial length[2]	Intervention (per day)	Control	Baseline SBP	Baseline DBP	Baseline ascorbic acid[3]	BP measurement: position, location, device, no. of measurements
Osilesi, 1991 (39)[4]	Hypertensive and normotensive outpatients	20	57.8 ± 14.3	25	No	X, D	6	Vit C 1000 mg	Placebo	139 ± 18	81 ± 12	74[11]	Supine and seated, arm, mercury sphygmomanometer, 4
Keith, 1982 (34)	Smoking and nonsmoking men	22	29.2 ± 4.2	100	No	X, D	3	Vit C 300 mg	Citric acid	125 ± 10	73 ± 7	44.08 ± 15.02	Supine, arm, 1[12]

[1] ABPM, ambulatory blood pressure monitoring; BP, blood pressure; CHF, congestive heart failure; D, double-blind; DBP, diastolic blood pressure; F, factorial trial; NA, not available; O, no blinding; P, parallel trial; S, single blind; SBP, systolic blood pressure; T2D, type 2 diabetes; Vit/vit, vitamin; X, crossover trial.

[2] Months were converted to weeks by using 1 mo = 4 wk; years were converted by using 1 y = 52 wk.

[3] Values were multiplied by 56.78 to convert mg/dL to μmol/L.

[4] Trial reported a significant end-baseline reduction in SBP or DBP.

[5] Mean ± SD (all such values).

[6] Range (all such values).

[7] Mean; range in parentheses.

[8] Estimated assuming an 8-h night, 16-h day.

[9] Size approximated because of unknown randomization of dropouts.

[10] Range of normotensive subjects only.

[11] Based on end-placebo values.

[12] Obtained from a previously published trial design article (52).

ranged from −3.3 mm Hg [$P < 0.01$, after the omission of Rodrigo et al (12)] to −4.1 mm Hg [$P < 0.01$, after the omission of Title et al (32)]. The omission of DBP trials with greatest influence yielded effects ranging from −1.2 mm Hg [$P = 0.06$, after the omission of Rodrigo et al (12)] to −1.8 mm Hg [$P = 0.01$, after the omission of Magen et al (21)].

A sensitivity analysis was performed by conservatively imputing SBP effects for 9 trials and DBP effects for 10 trials without complete reporting of BP and/or variance (36, 40–48). Characteristics of these trials and imputed data are available in the online supplement (*see* Supplemental Tables 2–3 under "Supplemental data" in the online issue). After adding these trials, the pooled reductions in SPB and DBP were −3.13 mm Hg (95% CI: −4.39, −1.87 mm Hg; $P < 0.01$) and −1.14 mm Hg (95% CI: −2.18, −0.10 mm Hg; $P = 0.03$), respectively. In a sensitivity analysis, the exclusion of trials with missing baseline ascorbic acid measurements and trials with serum ascorbic acid >60 μmol/L at baseline resulted in greater reductions in SBP and DBP of −4.16 mm Hg (95% CI: −6.11, −2.21 mm Hg; $P < 0.01$) and −2.14 mm Hg (95% CI: −3.92, −0.36 mm Hg; $P = 0.02$), respectively.

DISCUSSION

This meta-analysis is the first quantitative review of randomized trials evaluating the effect of vitamin C supplementation on BP. We found that vitamin C supplementation significantly reduced SBP (−3.84 mm Hg) and DBP (−1.48 mm Hg). The trials included in the meta-analysis, however, were small, and there was significant heterogeneity of effects across studies.

Recent mechanistic studies examining the effects of vitamin C on vascular function provide evidence for the biological plausibility of these findings (70, 71). For example, ascorbate increases intracellular concentrations of tetrahydrobiopterin, a cofactor of endothelial nitric oxide synthase, which enhances production of nitric oxide—a potent vasodilator (72). Furthermore, there is evidence that vitamin C improves nitric oxide bioactivity (72, 73). Moreover, in short-term human trials, vitamin C supplementation has been shown to improve endothelial function of both brachial (74, 75) and coronary (76) arteries.

Our meta-analysis included a number of trials that varied in vitamin C dose, participant characteristics, trial duration, and quality of BP reporting, which resulted in significant trial heterogeneity (I^2 of 69% and 81% for SBP and DBP, respectively). Many of the design features and quality measures are informative for future trials on vitamin C supplementation and BP. Although the majority of design and population features did not significantly alter the pooled effects of vitamin C on BP (crossover design, trial duration, vitamin C dose, and concurrent hypertension medication use), several subgroups did significantly alter effects (Table 2). We found that trials that assessed BP by ABPM (20, 21, 31) were associated with a smaller magnitude of BP reduction. We also found that larger trials had greater reductions in BP [SBP: −4.68 mm Hg ($P = 0.12$); DBP: −2.69 ($P = 0.01$)]. Finally, we observed greater BP reduction in a sensitivity analysis, which excluded trials with elevated baseline ascorbic acid concentrations (>60 μmol/L). It is possible that trial populations with high preexisting vitamin C intakes would minimize the effectiveness of a vitamin C intervention due to renal excretion (56). Future trials of vitamin C supplementation and BP would

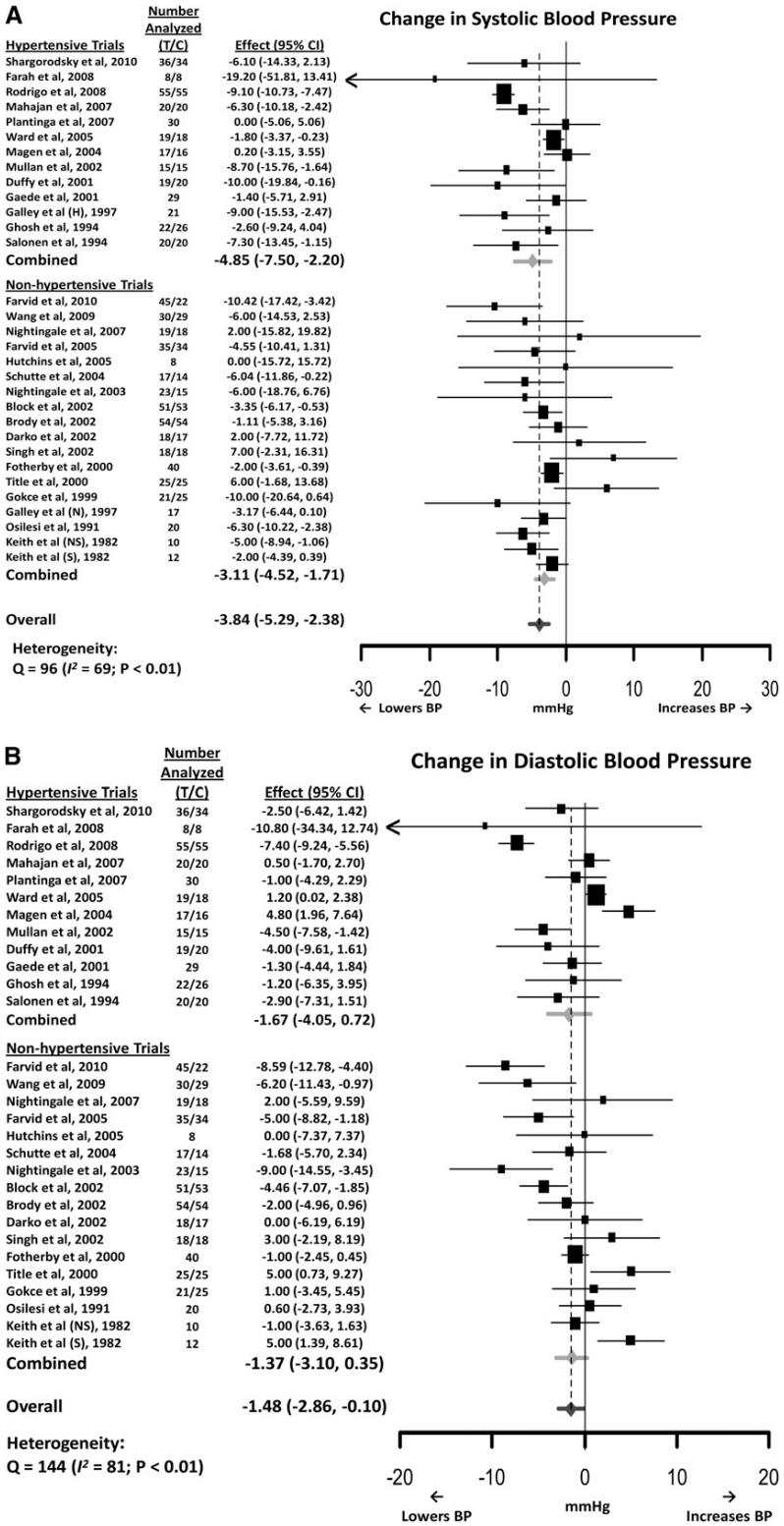

FIGURE 2. Net changes in systolic BP (A) and diastolic BP (B) in randomized trials of vitamin C supplementation. The area of each square is proportional to the study weight in the analysis. Horizontal lines represent 95% CIs. Diamonds represent pooled estimates. Galley et al (36) included 2 distinct trial populations: hypertensives (H) and normotensives (N). Keith included 2 distinct trial populations: smoking (S) and nonsmoking (NS). BP, blood pressure; T/C, treatment group/control group.

TABLE 2
Subgroup analyses of mean change in BP[1]

	Change in SBP				Change in DBP			
Subgroup	No. of trials	Effect	95% CI	*P*	No. of trials	Effect	95% CI	*P*
		mm Hg	*mm Hg*			*mm Hg*	*mm Hg*	
Hypertension								
Yes	13	−4.85	−7.50, −2.20	0.28	12	−1.67	−4.05, 0.72	0.85
No	18	−3.11	−4.52, −1.71		17	−1.37	−3.10, 0.35	
Diabetes								
Yes	5	−4.71	−8.73, −0.68	0.63	5	−4.06	−6.72, −1.40	0.08
No	26	−3.70	−5.28, −2.11		24	−0.94	−2.45, 0.57	
Baseline ascorbic acid								
<49.0 μmol/L	11	−4.95	−7.96, −1.93	0.28	11	−2.43	−5.30, 0.44	0.53
≥49.0 μmol/L	11	−3.09	−4.66, −1.52		11	−1.61	−2.82, −0.40	
Mean age								
<50 y	12	−5.07	−7.22, −2.92	0.04	11	−2.44	−4.87, −0.01	0.19
50–60 y	13	−3.59	−6.23, −0.94		12	−1.43	−3.99, 1.13	
>60 y	6	−1.85	−2.94, −0.77		6	0.03	−1.49, 1.55	
Duration								
<8 wk	15	−2.89	−4.43, −1.36	0.43	15	−0.60	−2.15, 0.94	0.37
≥8 wk	16	−4.45	−6.63, −2.27		14	−2.34	−4.55, −0.14	
Vitamin C dose								
<500 mg/d	6	−4.79	−7.25, −2.33	0.26	6	−2.96	−6.76, 0.85	0.72
500 mg/d	11	−2.89	−4.50, −1.29		9	−0.27	−2.24, 1.71	
>500 mg/d	14	−2.96	−5.58, −0.34		14	−1.50	−3.56, 0.56	
Study design								
Crossover	9	−2.96	−4.34, −1.57	0.51	7	−0.10	−1.59, 1.39	0.17
Parallel	22	−4.17	−6.27, −2.07		22	−2.07	−3.91, −0.23	
Vitamin C administered as the only intervention								
Yes	16	−2.59	−3.81, −1.38	0.06	16	−0.52	−2.07, 1.04	0.12
No	15	−4.98	−7.30, −2.65		13	−2.73	−5.03, −0.42	
Antihypertensive medication use								
Yes	15	−3.58	−5.78, −1.37	0.79	14	−0.78	−2.68, 1.12	0.41
No	16	−3.93	−5.86, −2.00		15	−2.01	−3.84, −0.18	
No. of BP measurements								
1–2	10	−4.02	−5.57, −2.47	0.01	10	−2.37	−4.64, −0.10	0.05
3–4	10	−3.46	−6.01, −0.90		8	−1.28	−2.90, 0.35	
60–66 (ABPM)	3	−1.69	−2.75, −0.62		3	1.38	−1.17, 3.93	
Trial size								
<38 participants	14	−2.76	−4.60, −0.91	0.12	12	0.49	−1.48, 2.47	0.01
≥38 participants	17	−4.68	−6.74, −2.63		17	−2.69	−4.49, −0.88	

[1] If a trial reported effects in 2 distinct subgroups, it was counted twice. As a result, the total number may exceed the 29 trials included in the primary analysis. *P* represents whether or not the groups were different and was determined by meta-regression of the subgroups. ABPM, ambulatory blood pressure monitoring; BP, blood pressure; DBP, diastolic blood pressure; SBP, systolic blood pressure.

benefit from addressing the limitations noted in our article. Specifically, trials should be longer term and assess the time course of change in BP to assess sustained effects. Furthermore, BP as a primary outcome should be measured with blinded, repeated measures by using instruments and procedures that reduce imprecision and observer biases. Finally, participants in trials should ideally not take antihypertensive medications or remain on stable doses of daily medications to avoid the confounding effects of medication changes on BP outcomes.

In our search, we encountered 3 large, long-term clinical trials of vitamin C supplementation that were designed to detect clinical events. These trials were excluded from this meta-analysis because they permitted the use of antihypertensive medications after randomization. We excluded them because of the risk of differential medication use after randomization and/or noninformative censoring, both of which can bias effects toward the null when BP is the outcome (65–67). Still, in each of these trials, there was some evidence of BP lowering. The Linxian Nutrition Intervention Trial reported significant reductions in the prevalence of hypertension and lower rates of mortality from stroke in those assigned to the multivitamin/mineral supplement, which included vitamin C. Similarly, the supplement arm of the Lianxian Population Trial had lower BP and end-trial prevalence of hypertension at 5 y. Both of these trials were conducted in populations with micronutrient-poor diets, which limits generalizability to Western populations. In the third trial, SU.VI.MAX, there was a nonsignificant trend toward fewer participants being diagnosed with hypertension in the group randomly assigned to a multivitamin/mineral supplement, which included vitamin C, compared with the placebo group at the end of follow-up (17.4% compared with 21.0%; $P = 0.11$), with a tendency for lower pulse wave velocity, a marker of vascular stiffness, in the vitamin group ($P = 0.13$). Overall, the pattern of results in these long-term trials is consistent with the BP effects we observed in our meta-analysis.

The expected result of a therapy that lowers BP would be reductions in clinical events such as stroke or cardiovascular disease outcomes. Although our meta-analysis reported significant BP-lowering effects with vitamin C supplementation, several long-term trials powered for clinical endpoints have not shown benefit. A recent meta-analysis of antioxidant trials found 34 trials in which vitamin C was administered, usually with another antioxidant, and found no significant effect on total mortality (77). Similarly, large trials of vitamin C on cardiovascular endpoints, including the Physicians Health Study II and the Women's Antioxidant Cardiovascular Study, showed no benefit on nonfatal myocardial infarction, nonfatal stroke, coronary revascularization, or cardiovascular disease death (78, 79). It is possible that these trials suffered from similar limitations described above: physician intervention and medical management of BP during trials, which results in equivalent BP between groups after randomization. Long-term trials with clinical endpoints are difficult and costly but are still needed to determine whether vitamin C supplementation reduces the risk of cardiovascular events.

Our analyses did have limitations. First, the sample size of each trial was relatively small, and there was considerable evidence of trial heterogeneity, as reported previously (50, 80). Differences in trial duration, vitamin C dose, control of antihypertensive medications during trials, and subject characteristics (eg, age, background diet given the large number of countries) may all contribute to variation in trial effects. Second, there was some evidence that with stronger methods—ie, greater number of measurements—BP effects were attenuated. Third, combining vitamin C with other agents, as performed by 13 trials, may also affect results. Although the commonly used supplements, vitamin A and vitamin E, are not known to cause reductions in BP, it is possible that interactions might occur. Fourth, there is the potential for publication bias, a major concern of most meta-analyses. In fact, we found 4 trials that specifically stated their decision not to report BP results because of a lack of significant results (40, 43, 44, 48). The inclusion of these trials with imputed BP data still showed antihypertensive effects of vitamin C. The challenge in abstracting high-quality BP effects highlights the need for additional well-designed trials. Finally, our subgroup analyses of patient-aggregated data, in particular, hypertensive status, mean age, and baseline ascorbic acid, are prone to ecological bias (*see* Table 2). We included these subgroup analyses to explore potential population characteristics that should be considered in the design and powering of future vitamin C trials. Caution should be observed in the interpretation of these subgroup analyses, however.

In summary, our meta-analysis suggests that vitamin C supplementation may have a useful role in lowering BP. However, before vitamin C supplementation can be recommended for the prevention of hypertension or as adjuvant antihypertensive therapy, additional trials are needed, designed with large sample sizes, and with attention to quality of BP assessment.

The authors' responsibilities were as follows—SPJ and ERM: conceived and designed the study, conducted the literature review, and drafted the manuscript; SPJ and EG: conducted the statistical analysis; and LJA: provided critical revision and important intellectual content. All of the authors made significant contributions to this manuscript. None of the authors had a conflict of interest to report.

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