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ORIGINAL ARTICLE

Effect of Oral Vitamin C Supplementation on Serum Uric Acid: A Meta-Analysis of Randomized Controlled Trials

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Objective. **To assess the effect of vitamin C supplementation on serum uric acid (SUA) by pooling the findings from published randomized controlled trials (RCTs).**

Methods. **A total of 2,082 publications identified through systematic search were subjected to the following inclusion criteria: 1) RCTs conducted on human subjects, 2) reported end-trial SUA means and variance, 3) study design with oral vitamin C supplementation and concurrent control groups, and 4) trial duration of at least 1 week. Trials that enrolled children or patients receiving dialysis were excluded. Two investigators independently abstracted trial and participant characteristics. SUA effects were pooled by random-effects models and weighted by inverse variance.**

Results. **Thirteen RCTs were identified in the Medline, EMBase, and Cochrane Central Register of Controlled Trials databases. The total number of participants was 556, the median dosage of vitamin C was 500 mg/day, trial size ranged from 8–184 participants, and the median study duration was 30 days. Pretreatment SUA values ranged from 2.9–7.0 mg/dl (Système International d'Unités [SI units]: 172.5–416.4 μmoles/liter). The combined effect of these trials was a significant reduction in SUA of −0.35 mg/dl (95% confidence interval −0.66, −0.03 [$P = 0.032$]; SI units: −20.8 μmoles/liter). Trial heterogeneity was significant ($I^2 = 77\%$, $P < 0.01$). Subgroup analyses based on trial characteristics indicated larger reductions in uric acid in trials that were placebo controlled.**

Conclusions. **In aggregate, vitamin C supplementation significantly lowered SUA. Future trials are needed to determine whether vitamin C supplementation can reduce hyperuricemia or prevent incident and recurrent gout.**

INTRODUCTION

Hyperuricemia is a well-established risk factor for gout (1). In population-based studies, the risk of gout steadily increases at successively higher levels of serum uric acid (SUA) (2), with a 10-fold increase in risk reported among those with serum urate levels of >9 mg/dl (3). Medications to prevent gout recurrence either act by reducing uric acid synthesis (e.g., xanthine oxidase inhibition) or via enhanced uric acid excretion (e.g., probenecid) (1). Although medical therapy is effective at preventing gout flares (4), both classes of drugs carry significant side-effect profiles (5–7). Dietary approaches to lower uric acid therefore provide an alternative and attractive approach to gout management (8). Recommendations to reduce consumption of high-protein foods such as meat or seafood (to reduce purine intake), consume vegetable-based proteins, and lower alcohol consumption continue to play a critical role in disease management (9). Supplementation with vitamin C has also been examined as an alternative dietary approach (10).

In vitro and animal models have demonstrated that vitamin C has uricosuric properties, inhibits uric acid synthesis (11), and lowers SUA (12,13). Furthermore, in small laboratory-based, clinical studies in humans, ascorbic acid has been shown to lower SUA (14–20). Human observational studies have also reported an inverse association between plasma ascorbic acid (21) or vitamin C intake (22) and SUA concentrations. A prospective cohort study reported that vitamin C intake from diet sources was associated with a lower risk of developing gout (23). Moreover, a recent randomized trial of a daily intravenous infusion of 500 mg of vitamin C for 10 days in patients with acute

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Significance & Innovations

- Combining the results of 13 randomized controlled trials resulted in a significant reduction in serum uric acid (SUA) of −0.35 mg/dl (95% confidence interval −0.66, −0.03 [$P = 0.032$]; Système International d'Unités: −20.8 μmoles/liter).
- The 13 trials were very heterogeneous ($I^2 = 77\%$).
- Reductions in SUA were larger among trials administering 500 mg/day or greater of vitamin C, trials administering vitamin C without other interventions, and trials that used a placebo group.

ischemic stroke resulted in a significant reduction in SUA compared to placebo infusion (24).

Over the past 30 years, at least 13 randomized controlled clinical trials have examined the effect of oral vitamin C supplementation on SUA measurements (10,25–36). However, these trials have yielded inconclusive results. To date, to our knowledge there have been no published systematic reviews that have pooled the results of these individual studies together. To provide more stable estimates of the efficacy of vitamin C supplementation on SUA and to examine trial characteristics that predict stronger effects, we performed a meta-analysis of these published trials.

MATERIALS AND METHODS

We searched the Medline, EMBase, and Cochrane Central Register of Controlled Trials databases from January 1966 through September 2010 using the following terms: kidney, kidney disease(s), nephropathy, glomerulonephritis, renal insufficiency, gout, uricosuria, hyperuricosuria, hypouricosuria, hyperuricemia, hypouricemia, nephrolithiasis, uric acid, ascorbic acid, antioxidant(s), vitamin(s), randomized controlled trials, and clinical trials. The search was limited to human studies without language restrictions. Search details are shown in Supplementary Appendix A (available in the online version of this article at http://onlinelibrary.wiley.com/journal/10.1002/(ISSN)2151-4658). Search results were complemented with trials found in bibliographies of original research studies and previous reviews.

For inclusion in the primary analysis, studies were required to meet the following prespecified criteria: 1) randomized controlled trials on human subjects, 2) intervention and control groups reported end-trial SUA means and variance, 3) the intervention included oral vitamin C supplementation and a concurrent control group, 4) constituent differences between treatment and control groups did not include agents with known antihyperuricemic activity, and 5) trial was of a duration of at least 7 days. Trials that included children or patients with end-stage renal disease were excluded. Each included trial was required to explicitly state the word "random" in the description of treatment assignment. Further details regarding randomization methods used (blocking, random-number generation, etc.) were not required.

Two investigators (SPJ, ERM) independently abstracted the articles. Discrepancies were resolved by adjudication. The following information was retrieved from each article: 1) study population, mean age, and percent male; 2) mean pretreatment SUA and ascorbic acid concentrations; 3) mean trial-end SUA and ascorbic acid concentrations; and 4) characteristics affecting trial quality: design (parallel, crossover, factorial), blinding (open, single, double, triple), intervention dose, type of control, trial duration, mechanism of SUA measurement, mention of concealment, description of randomization, intent-to-treat analysis, evaluation of losses to followup, and subject compliance. We recorded blinding as reported by trial authors; however, when it was not explicitly mentioned, we examined the trials' Methods sections for blinding of participants, providers, and outcome assessors. An attempt was made to contact authors of publications where SUA was measured but not fully reported (37–41).

For each trial following a parallel design, effect was calculated as the difference in baseline and end-trial SUA between the intervention and placebo groups (25–27,30,32–35). This is demonstrated by the equation: $(E_T - B_T) - (E_C - B_C)$, where E = an end-trial SUA value and B = a baseline SUA value for treatment (T) and control (C) groups (42,43). The variance in SUA baseline change, i.e., E − B, was calculated with the equation: variance (E − B) = variance (E) + variance (B) − 2 × covariance. The correlation coefficient was assumed to be 0.7, and a sensitivity analysis was conducted using a correlation coefficient of 0.5. The standard error of the difference in baseline change, i.e., $(E_T - B_T) - (E_C - B_C)$, was calculated using the equation: standard error = $\sqrt{(SD_T^2/n_T + SD_C^2/n_C)}$ (44). For the 3 crossover trials in this meta-analysis (28,33,36), we utilized the following equation: $E_T - E_C$, where E = an end-trial SUA value for treatment (T) and control (C) groups (44). Standard error was calculated as above using: standard error = $\sqrt{(SD_T^2/n_T + SD_C^2/n_C)}$ (44). A sensitivity analysis for crossover trials using the equation, variance (E − B) = variance (E) + variance (B) − 2 × covariance, with the correlation coefficient assumed to be 0.7, yielded virtually the same results (data not shown).

Three of the 13 trials did not conform to the algorithms described above. Huang et al directly provided the difference in baseline change and its variance (10), which was utilized in place of the abovementioned calculation. Furthermore, 1 parallel trial did not report baseline SUA values, instead providing only end-trial SUA measurements (31). This trial was treated as a crossover trial in our meta-analysis. In another trial, Vrca et al reported only median SUA values in the form of a figure (29). These values were estimated from the figure and assumed to be equal to mean SUA values. Variance was estimated from P values given in the text using the most conservative estimate when a range was reported (e.g., $P < 0.01$ was estimated to be $P = 0.01$).

Other abstraction nuances are as follows. One trial examined 2 distinct vitamin C interventions and was treated as 2 separate trials in our analysis (36). Another trial seemed to mislabel SD as "SEM" (34). Close review of its

Table 1. Clinical trials examining the effect of vitamin C supplementation upon serum uric acid, ordered by year of study*

Author (ref.), year	Country	Population	Size	Age, mean ± SD or mean (range) years	Men, %	Study design	Study duration, days†	Intervention, per day	Control	Baseline uric acid, mean ± SD mg/dl‡	Pretreatment plasma ascorbic acid, mean ± SD μmoles/liter§	Uric acid measurement	Completing trial, %
Naziroglu and Simsek (25), 2009¶	Turkey	Postmenopausal and diabetic women	40	51 (45–65)	0	P, O	42	Vitamin C 1,000 mg, vitamin E 600 mg, estradiol 0.625 mg, medrox. 5 mg	Estradiol 0.625 mg, medrox. 5 mg	3.6 ± 1.1	–	Routine kits, autoanalyzer	100
Teixeira et al (26), 2009	Portugal	Athletes	20	19.7 ± 3.6	70	P, D	28	Vitamin C 400 mg, vitamin E 272 mg, β-carotene 30 mg, lutein 2 mg, selenium 400 μg, zinc 30 mg, magnesium 600 mg	Placebo	4.9 ± 1.0	56.2 ± 24.0	Enzymatic method at 550 nm using commercial kit (Horiba ABX A11A01670)	100
Huang et al (10), 2005¶	US	Adult nonsmokers	184	58.2 ± 13.7	45	F, P, T	60	Vitamin C 500 mg	Placebo	5.2 ± 1.5	62.2 ± 15.5	Hitachi 917 autoanalyzer (Roche Diagnostics); uricase–peroxidase method with ascorbate oxidase incubation	92
Polidori et al (27), 2005	Italy	Acute ischemic stroke	59	77.0 ± 7.2	53	P, O	90	Vitamin C 200 mg, aspirin 300 mg	Aspirin 300 mg	2.9 ± 0.9	27.0 ± 4.5	High-performance liquid chromatography with Supelco columns	100
Van Hoydonck et al (28), 2004	Belgium	Healthy male smokers	42	52 ± 12	100	X, D	28	Vitamin C 500 mg	Placebo	–	45 ± 20	Enzyme-linked calorimetric assay (Roche)	81
Vrca et al (29), 2004¶	Croatia	Patients with Graves' disease	57	–	9	P, O	28	Vitamin C 200 mg, β-carotene 6 mg, vitamin E 36 mg, selenium 60 μg, methimazole at varying doses	Methimazole at varying doses	3.5#	–	Olympus AU500 analyzer	100
Yanai and Morimoto (30), 2004	Japan	Healthy, nonsmoking male athletes	8	20.4 ± 1.6	100	P, S	21	Vitamin C 1,000 mg	Placebo	5.2 ± 0.8	–	Uricase calorimetric method	100
Nieman et al (31), 2002¶	US	Ultramarathon runners	29	47.7 ± 12.1	–	P, D	7	Vitamin C 1,500 mg	Placebo	–	–	Hematology laboratory	97
Martinez-Abundis et al (32), 2001	Mexico	Obese male volunteers	16	26.5 ± 6.3	100	P, D	28	Vitamin C 1,000 mg	Placebo	7.0 ± 1.2	–	Enzymatic methods	100
Hamilton et al (33), 2000¶	UK	Healthy adults	32	35 ± 9	50	X, D	42	Vitamin C 500 mg	Vitamin E 73.5 mg as placebo	4.4 ± 0.9	63.6 ± 12.5	Commercial kits on a Cobas Fara (Roche Diagnostic Systems)	94

(continued)

Table 1. *(Cont'd)*

Author (ref.), year	Country	Population	Size	Age, mean ± SD or mean (range) years	Men, %	Study design	Study duration, days†	Intervention, per day	Control	Baseline uric acid, mean ± SD mg/dl‡	Pretreatment plasma ascorbic acid, mean ± SD μmoles/liter§	Uric acid measurement	Completing trial, %
Rokitzki et al (34), 1994	Germany	Male athletes	24	38.5 ± 8.5	100	P, D	31.5	Vitamin C 200 mg, vitamin E 400 IU	Placebo	5.9 ± 1.0	46.3 ± 12.8	Enzymatic test	92
Maxwell et al (35), 1993	UK	Healthy students	16	19.6 ± 1.5	67	P, O	21	Vitamin C 400 mg	Vitamin E 400 mg	4.8 ± 1.0	77.7 ± 19.3	Automated uricase–peroxidase system	100
Kyllastinen et al (36), 1990 (a)	Finland	Long-stay hospital patients	29	81 (68–93)#	0	X, D	42	Vitamin C 200 mg	Placebo	–	–	Routine laboratory methods	93
Kyllastinen et al (36), 1990 (b)¶	Finland	Long-stay hospital patients	29	81 (68–93)#	0	X, D	42	Vitamin C 2,000 mg	Placebo	–	–	Routine laboratory methods	93

* P = parallel; O = open; medrox. = medroxyprogesterone; D = double blind; F = factorial; T = triple blind; X = crossover; S = single blind.
† 1 month = 30 days.
‡ Uric acid converted from μmoles/liter to mg/dl by dividing by 59.48.
§ Vitamin C converted from mg/dl to μmoles/liter by multiplying by 56.776.
¶ Trials reporting significant baseline reductions in uric acid.
# Median value.

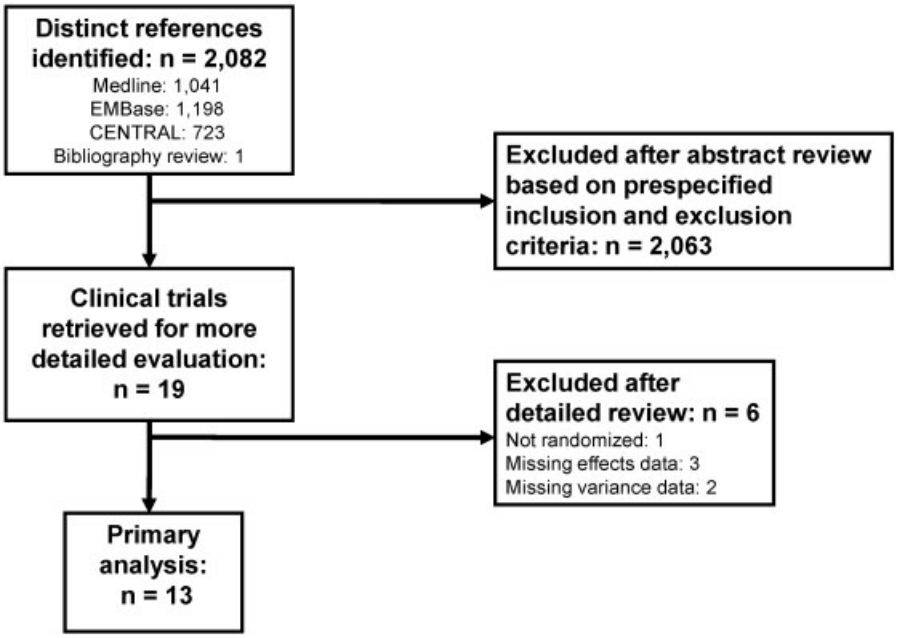

Figure 1. Flow diagram of the search results of the trial selection process.

Methods section supported interpretation of these data as the mean ± SD rather than the SEM. Moreover, several trials examined the effect of vitamin C supplementation on SUA in the context of exercise (26,30,31,34,35). In general, we attempted to minimize this variable by examining SUA values measured prior to physical exertion, with the exception of Yanai and Morimoto, who only reported post-training values (30). In similar fashion, whenever possible we attempted to avoid inclusion of other supplements and pharmaceuticals in our results by comparing vitamin C supplementation to placebo rather than to other treatment arms. In 1 trial, however, baseline SUA was provided for a vitamin E intervention, rather than placebo (35). In this case, we compared vitamin C to vitamin E since its baseline SUA values made it possible to calculate baseline change. Other circumstances in which vitamin C was administered with other supplements and pharmaceuticals are described in Table 1 and the Results.

The pooled estimate and 95% confidence interval (95% CI) were calculated with a random-effects model; trial effects were weighted by inverse variance. Heterogeneity between studies was assessed by the Q statistic and by the I^2 statistic (45). Individual trial influence was determined by removing each trial from the overall analysis. Publication bias was examined by a funnel plot of the standard error versus SUA effect, Begg's rank correlation test, and Egger's linear regression test. Statistical analyses were performed using Stata, version 8.2. All SUA units were reported as the mg/dl with Système International d'Unités (SI units) reported in parentheses, converting to μmoles/liter by multiplying by 59.48.

Subgroup analyses were performed on select trial characteristics. Trial characteristics included: vitamin C dosage (median value <500 or ≥500 mg/day); trial duration (median value <30 or ≥30 days); administration of vitamin C alone or with other vitamins, minerals, or pharmacologic agents (yes or no); trial design (parallel or crossover); double-blind design (yes or no); trial mention of participant compliance (yes or no); allocation concealment (yes or not reported); trial target population (healthy, yes or no); placebo use (yes or no); and trial size (median <29 or ≥29 participants). Subject characteristics examined in subgroup analyses, according to the median value for the characteristic, were baseline serum ascorbic acid (median value <56.2 or ≥56.2 μmoles/liter), mean age (median value <47.7 or ≥47.7 years), percentage of male subjects (median value <53% or ≥53%), and baseline SUA (median value <4.85 or ≥4.85 mg/dl; SI units: 288.5 μmoles/liter).

RESULTS

Search results are displayed in Figure 1. Among the trials abstracted, the principal exclusion factors were: 1) lack of randomization (46), 2) missing SUA variance (37,38), and 3) incomplete SUA effects (39–41). Characteristics of the 13 clinical trials satisfying our inclusion criteria are summarized in Table 1. These 13 trials were conducted between 1990 and 2009, comprising 556 participants. Trial size ranged from 8–184 participants; mean age ranged from 20–81 years. With regard to trial design, 3 of the 13 trials were crossover, 10 were parallel, 9 were double-blind trials, 1 was single blind, and 3 reported no blinding. Trials were conducted over the course of 7–90 days with a median duration of 30 days. Among crossover trials, washout periods ranged from 1 week to 2 months. Pretreatment SUA values ranged from 2.9–7.0 mg/dl (SI units: 172.5–416.4 μmoles/liter); pretreatment plasma ascorbic acid ranged from 27.0–77.7 μmoles/liter. Eight trials administered vitamin C as the only intervention, while 5 trials administered vitamin C in combination with other vita-

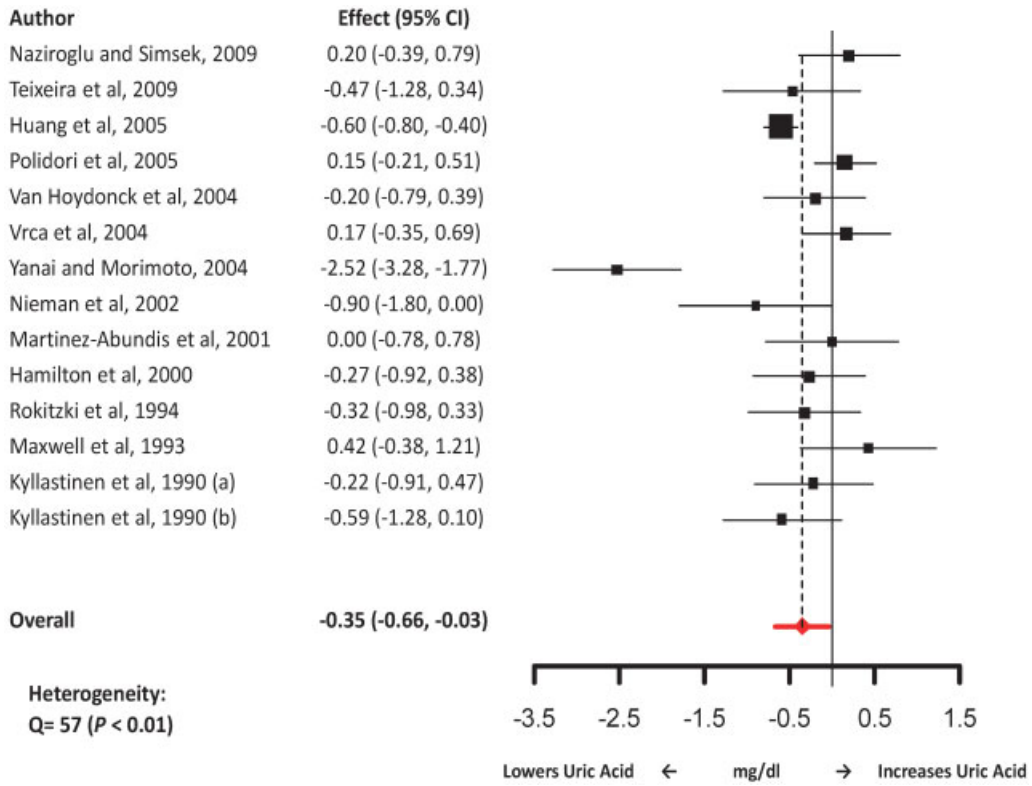

Figure 2. Forest plot of the pooled effect of vitamin C supplementation on serum uric acid. The net change in each individual study for serum uric acid in randomized controlled trials of vitamin C supplementation and overall pooled result is shown. The area of each square is proportional to the study weight in the analysis. Horizontal lines show the 95% confidence interval (95% CI). The **red diamond** shows the pooled estimate and the 95% CI obtained from inverse variance–weighted random-effects models.

mins, minerals, or pharmacologic agents. The median dosage of vitamin C was 500 mg/day, ranging from 200 mg/day to 2,000 mg/day. Trial subjects were quite heterogeneous, ranging from healthy adults, the most common subject description, to several inpatient populations diagnosed with stroke, Graves' disease, or in long-term care.

Vitamin C supplementation was associated with reductions in SUA in 8 of the 13 trials included in this meta-analysis (10,26,28,30,31,33,34,36). Six of the 13 trials reported significant baseline reductions in SUA (10,25,29,31,33,36). The overall pooled effect of vitamin C supplementation on SUA was −0.35 mg/dl (95% CI −0.66, −0.03 [$P = 0.032$]; SI units: −20.8 μmoles/liter) (Figure 2). Notably, the pooled effect was significant for heterogeneity with Q = 57 ($I^2 = 77\%$, $P < 0.01$). Using a covariance correlation value of 0.5 rather than 0.7 (see Methods) yielded a similar magnitude SUA effect at −0.34 ($P = 0.027$).

Subgroup analyses are summarized in Table 2. SUA reduction was −0.78 mg/dl (95% CI −1.46, −0.09; SI units: −46.4 μmoles/liter) in trials with subjects possessing baseline SUA values ≥4.85 mg/dl (SI units: 288.5 μmoles/liter). There was a significant difference between trials with participants possessing baseline SUA values below 4.85 mg/dl (SI units: 288.5 μmoles/liter) versus those above 4.85 mg/dl ($P = 0.030$). Furthermore, stratifying trials by reported use of placebo showed significant SUA reductions in trials utilizing placebo at −0.59 mg/dl (95% CI −0.95, −0.24; SI units: −35.1 μmoles/liter), while trials that did not use a placebo had no effect (0.19 mg/dl; 95% CI −0.07, 0.45; SI units: 11.3 μmoles/liter). The pooled effects of these groups were significantly different ($P = 0.01$). Also, trials utilizing at least a 500 mg daily dose of vitamin C, and trials where vitamin C was the only intervention, reduced vitamin C at −0.59 mg/dl (95% CI −1.05, −0.13; SI units: −35.1 μmoles/liter) and −0.54 mg/dl (95% CI −0.96, −0.11; SI units: −32.1 μmoles/liter), respectively. These effect sizes were not significantly different, however, when compared to trials utilizing smaller doses ($P = 0.10$) and trials that administered vitamin C in combination with other vitamins, minerals, or pharmacologic agents ($P = 0.16$).

Trial quality features are shown in Table 3. The majority of trials did not report details regarding allocation concealment (3 of 13) or randomization method (0 of 13). Only 1 trial clearly reported intent-to-treat (10), and only 1 trial reported blinding of the assessor in addition to subjects and care provider (10). Five of 13 trials mentioned the trial subjects' compliance with treatment protocol, and only 1 trial (10) discussed losses to followup.

In a plot of SUA effect versus standard error, trials appeared to follow the shape of a funnel (Figure 3). Publication bias was also examined by performing Begg's rank correlation test, which yielded a nonsignificant Kendall score of −22 ($P = 0.23$). Egger's linear regression test confirmed these findings with a nonsignificant SUA bias

Table 2. Subgroup analyses consisting of the pooled effect sizes of vitamin C supplementation on serum uric acid level, stratified by trial and subject characteristics

	Change in serum uric acid (mg/dl)				
	N*	Effect	95% confidence interval	I^2, %	*P*†
Dosage, mg/day					
<500	6	0.02	−0.21, 0.26	0.0	0.10
≥500	8	−0.59	−1.05, −0.13	79.9	
Duration, days					
<30	7	−0.49	−1.20, 0.22	85.2	0.52
≥30	7	−0.25	−0.56, 0.06	63.0	
Baseline serum ascorbic acid, μmoles/liter					
<56.2	3	−0.02	−0.30, 0.27	0.0	0.20
≥56.2	4	−0.33	−0.75, 0.09	53.7	
Mean age, years					
<47.7	6	−0.53	−1.32, 0.27	85.3	0.55
≥47.7	7	−0.29	−0.61, 0.04	66.1	
Men, %					
<53	6	−0.26	−0.59, 0.07	58.5	0.66
≥53	7	−0.41	−1.06, 0.24	85.6	
Baseline serum uric acid, mg/dl					
<4.85	5	0.13	−0.12, 0.37	0.0	0.03
≥4.85	5	−0.78	−1.46, −0.09	85.0	
Trial design					
Parallel	10	−0.37	−0.80, 0.07	83.8	0.91
Crossover	4	−0.31	−0.63, 0.02	0.0	
Vitamin C–only intervention					
Yes	9	−0.54	−0.96, −0.11	78.1	0.16
No	5	0.04	−0.20, 0.29	0.0	
Placebo use					
Yes	10	−0.59	−0.95, −0.24	71.2	0.01
No	4	0.19	−0.07, 0.45	0.0	
Allocation concealment					
Yes	4	−0.31	−0.75, 0.13	76.5	0.89
Not reported	10	−0.37	−0.86, 0.11	79.1	
Double-blind design					
Yes	9	−0.50	−0.66, −0.35	0.0	0.75
No	5	−0.30	−1.17, 0.58	90.8	
Trial reported compliance					
Yes	5	−0.35	−0.75, 0.05	71.1	0.92
No	9	−0.34	−0.87, 0.18	0.0	
Healthy trial population					
Yes	7	−0.60	−1.26, 0.06	82.5	0.20
No	7	−0.15	−0.49, 0.20	71.1	
Trial size					
<29	5	−0.58	−1.58, 0.41	87.9	0.37
≥29	9	−0.23	−0.51, 0.05	63.4	

* N represents the number of trials. The number of trials may not always add to 13 due to the treatment of 1 trial as 2 groups (Kyllastinen et al, 1990) (36) and due to the varying availability of subgroup data in each trial.
† *P* values represent comparison of effects between subgroups. Category bounds were determined by the median of abstracted values.

coefficient at $P = 0.67$ (44), suggesting that publication bias was not a significant factor in this meta-analysis. Furthermore, a random-effects analysis was conducted after the omission of each trial to examine the influence of the omitted study on the pooled effect. As such, the overall effects ranged from −0.20 mg/dl ($P = 0.09$; SI units: −11.9 μmoles/liter) to −0.40 mg/dl ($P = 0.019$; SI units: −23.8 μmoles/liter), following omission of trials with greatest weight for (30) and against (27) an overall reduction in SUA.

DISCUSSION

To our knowledge, this study is the first quantitative review of published randomized clinical trials examining the effect of oral vitamin C supplementation on SUA. Overall, vitamin C supplementation reduced SUA with a mean aggregate effect of −0.35 mg/dl ($P = 0.032$; SI units: −20.8 μmoles/liter). Although only 6 of the 13 trials reported significant reductions in SUA, pooling these small trials made it possible to estimate an overall effect, a key

Table 3. Trial quality design features*

Author (ref.), year	Allocation concealment	Randomization method	Intent-to-treat analysis	Blinding of participants	Blinding of providers	Blinding of outcome assessor	Description of subject compliance	Evaluation of treatment-specific losses to followup
Naziroglu and Simsek (25), 2009	NR	NR	NR	No	No	No	No	–
Teixeira et al (26), 2009	NR	NR	NR	Yes	Yes	No	Yes	–
Huang et al (10), 2005	Yes	NR	Yes	Yes	Yes	Yes	Yes	Yes
Polidori et al (27), 2005	Yes	NR	NR	No	No	No	Yes	–
Van Hoydonck et al (28), 2004	NR	NR	No	Yes	Yes	No	Yes	No
Vrca et al (29), 2004	NR	NR	NR	No	No	No	No	–
Yanai and Morimoto (30), 2004	NR	NR	No	Yes	No	No	No	–
Nieman et al (31), 2002	NR	NR	NR	Yes	Yes	No	Yes	No
Martinez-Abundis et al (32), 2001	NR	NR	No	Yes	Yes	No	No	–
Hamilton et al (33), 2000	NR	NR	No	Yes	Yes	No	No	No
Rokitzki et al (34), 1994	NR	NR	NR	Yes	Yes	No	No	No
Maxwell et al (35), 1993	NR	NR	No	No	No	No	No	–
Kyllastinen et al (36), 1990	Yes	NR	No	Yes	Yes	No	No	No

* Summary of design characteristics reported by trials included in our meta-analysis. Trials that reported no loss to followup did not receive a "yes" or "no" designation. NR = not reported.

advantage of the meta-analysis method. These findings support the observed inverse associations between intake of dietary and supplemental vitamin C and SUA levels.

Vitamin C is an essential micronutrient in a number of physiologic processes. When plasma ascorbate levels fall below 11 μmoles/liter, clinical features of scurvy may develop (47). The median dosage of vitamin C used in the trials was 500 mg/day, which is well above the recommended dietary allowances for vitamin C, 90 mg/day in men and 75 mg/day in women. Surpassing the tolerable upper intake level of 2 gm/day (48) may cause osmotic diarrhea, gastrointestinal disturbance (49), and calcium oxalate nephrolithiasis (50). Most studies report few side effects, however, when doses are below the tolerable upper intake level (49). None of the trials included in this meta-analysis reported adverse effects from vitamin C supplementation.

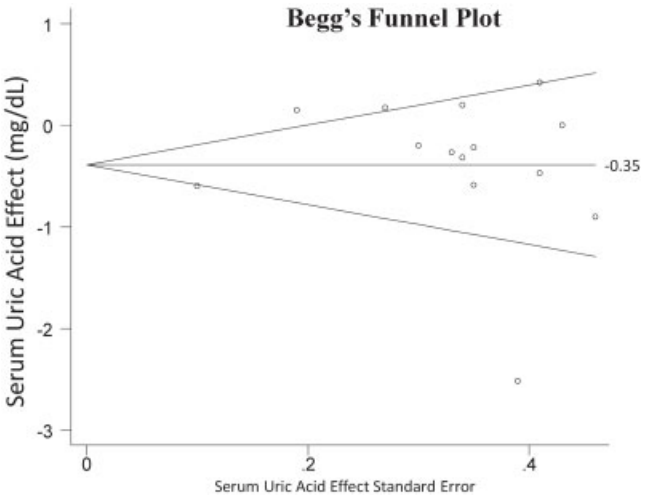

Figure 3. Begg's funnel plot with pseudo 95% confidence limits (sloped lines). Serum uric acid effect (mg/dl) is plotted on the y-axis, and the standard error is plotted on the x-axis. The vertical line shows the overall pooled effect (−0.35 mg/dl). **Circles** show the serum uric acid effect and standard error of each trial.

Several studies have described biologic mechanisms by which vitamin C reduces SUA. In vivo studies suggest that vitamin C has uricosuric properties, increasing renal fractional clearance of uric acid, thereby reducing SUA (14). This is likely due to competitive inhibition of an anion exchange transport system at the proximal tubule in the nephron (16). Vitamin C may act specifically at uric acid reabsorption sites in the apical brush border of the proximal tubule, such as URAT1, and a sodium-dependent anion cotransporter, SLC5A8/A12 (22,51–53). It is also possible that vitamin C increases the glomerular filtration rate by reducing glomerular microvascular ischemia and increasing dilatation of afferent arterioles (10,54–56). Furthermore, as an effective antioxidant, vitamin C decreases free radical–induced damage to body cells (57), thereby reducing production and ultimately serum concentration of uric acid (22).

There are a number of limitations to this meta-analysis that warrant consideration. Heterogeneity between trials was found to be significant ($I^2 = 77\%$, $P < 0.01$). An attempt to address heterogeneity by performing subgroup analyses based on trial characteristics did not fully explain differences in effect as demonstrated by elevated I^2 values

within strata. Significance observed among some subgroup strata may indicate that baseline SUA, dose of vitamin C, use of vitamin C alone without any other supplement(s), and placebo use play a greater role in heterogeneity than other subject and trial characteristics. However, strata based on the comparison of patient characteristics across trials, specifically mean age, percent male sex, baseline serum ascorbate, and baseline serum uric acid, are prone to ecological bias and should be interpreted with additional caution (58).

Another important consideration is publication bias. Although our funnel plot (Figure 3) and other analyses did not support the presence of publication bias (Egger's test: $P = 0.70$), during the search we identified 1 trial whose authors decided not to report SUA findings because of nonsignificant results (41). It is possible that other trials lacking significant results were never published, skewing the overall results toward an effect. Another interpretation of the asymmetrical funnel plot is "small study effects." Smaller studies often lack methodologic rigor in design and analysis, contributing to inflated treatment effects (44). This is particularly evidenced by trials' rare mention of design quality features in this meta-analysis (Table 3). Further, even when optimally designed, small trials experience the inherent limitation of low statistical power. Indeed, small trial size and the paucity of reported assurances regarding trial quality constitute an important limitation of this meta-analysis.

Another important consideration affecting interpretation of our results is the method by which SUA is measured. Of the 13 trials included in this study, there are considerable differences in the manner by which SUA was determined and in the detail provided to describe this critical aspect of trial methodology (Table 1). Prior research describes the ability of vitamin C to interfere with SUA measurements (19,59–64). Moreover, depending on the biochemical assay, vitamin C has been demonstrated to artificially increase (15,65,66) or decrease measured SUA (67). Artificial reduction in SUA is particularly related to the use of a biochemical assay employing the oxidase–peroxidase system, i.e., the Trinder method (68). In 1 study, Martinello and da Silva (2006) administered vitamin C to 18 volunteers and measured SUA via the Trinder method and ultraviolent light (67). The Trinder method found a significant baseline decrease in SUA, while ultraviolent light showed no change in SUA (67). Although the exact mechanism of interference is not understood, it is believed that vitamin C as an antioxidant depletes the H_2O_2 utilized by the Trinder method to produce chromophore and detect SUA (69). Contrary to expectations in this meta-analysis, however, the one trial that explicitly describes use of the oxidase–peroxidase system without addressing vitamin C interference (35) did not observe a reduction in SUA after vitamin C supplementation. A number of researchers note that the addition of ascorbate oxidase, which oxidizes ascorbic acid to dehydroascorbic acid, does not interfere with the chromogen system responsible for SUA detection (69–71). Of all the trials included in this meta-analysis, this method was only explicitly mentioned by Huang and colleagues (10). Despite potential interference in serum measurements, prior small clinical studies have documented a concurrent increase in uric acid excretion after introduction of vitamin C (14,16). Mitch et al (1980) note, however, that urine uric acid measures are also susceptible to interference, depending on the measurement assay used (62). As SUA measurement integrally affects conclusions, future trials should employ methods that minimize vitamin C interference in serum measurements and also quantify urinary excretion of uric acid.

One trial in this meta-analysis that reported null effects of vitamin C on SUA included 300 mg/day of aspirin in its combination therapy (27). Aspirin has a mixed effect on the uric acid excretion with dosages of >3 gm/day causing uricosuria, while doses between 1 and 2 gm promote uric acid retention (72). Recent studies suggest that even small doses of aspirin, i.e., dosages between 75 and 325 mg/day, also decrease uric acid clearance, causing uric acid retention (73–75). It is hypothesized that aspirin competes with uric acid at tubular secretion and reabsorption receptors and more globally suppresses glomerular filtration rate (72,75–77). Consistent with this hypothesis, the trial utilizing aspirin in this meta-analysis (27) contributed the largest weight against vitamin C reduction of SUA. It is possible that aspirin inhibits the uricosuric action of vitamin C, nullifying its effect. Exclusion of this trial increased the magnitude and significance of our pooled effect to −0.40 mg/dl ($P = 0.019$; SI units: −23.8 μmoles/liter).

Five of the 13 trials in this study (26,30,31,34,35) evaluated SUA in the context of exercise. As acute exercise is known to increase oxidative stress and levels of serum and salivary uric acid (39,40,78–82), we attempted to avoid inclusion of this variable in our pooled analysis. This was not possible in 1 of the trials because the authors did not measure preexercise SUA values (30). Conducting the meta-analysis using the SUA values measured closest to the conclusion of exercise rather than preexercise SUA values revealed an overall SUA reduction of −0.42 ($P = 0.012$), which is greater and more significant than the pooled effect reported in our analysis. This may suggest that the role of vitamin C is more pronounced in contexts of oxidative stressors and that greater protection against acute hyperuricemia could be achieved. Additional trials are necessary to evaluate this hypothesis.

Hyperuricemia has been associated with a wide range of diseases, including hypertension, obesity, renal disease, metabolic syndrome, obstructive sleep apnea, stroke, vascular dementia, and preeclampsia (83). However, large trials of vitamin C on cardiovascular events (84,85) as well as a recent meta-analysis on mortality have failed to demonstrate significant protective effects (86). These studies did not examine gout among their outcomes. Among all of the aforementioned clinical outcomes, the strongest support for a casual relationship exists between elevated SUA and gout (1). Importantly, none of the trials included in this meta-analysis examined vitamin C in a population of patients with gout, although an exploratory subgroup analysis suggests that greater SUA reduction could be achieved in individuals with SUA greater than 4.85 mg/dl (Table 2). If vitamin C with its low cost and relatively innocuous side-effect profile was administered to patients with gout as an adjunctive therapy, it is possible that a

greater number would achieve target SUA levels, reducing the likelihood of flares. It has yet to be determined, however, whether vitamin C would enhance or add to the SUA reduction of standard antihyperuricemic agents.

In summary, this meta-analysis suggests that oral vitamin C supplementation results in modest SUA reduction. Future trials of adequate size and duration should address issues of vitamin C assay interference and should measure both SUA and renal excretion of uric acid. Furthermore, future trials should be adequately powered to evaluate whether or not the urate-lowering effects of vitamin C are enhanced in patients with elevated SUA as found in our exploratory subgroup analysis and described in a previous trial (10). Ultimately, whether vitamin C supplementation lowers the risk of gout or hyperuricemia needs to be determined.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Gelber had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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