Effect of High-Dose Oral Vitamin C on 24-Hour Urinary Oxalate Excretion: A Systematic Review and Meta-analysis of Intervention Trials

Nutthavuth Arjinpathana, Phawit Norchai

Department of Antiaging and Regenerative Science, College of Integrative Medicine, Dhurakij Pundit University, Bangkok, Thailand.

Abstract

Background: High-dose oral vitamin C (≥ 1,000 mg/day) is widely consumed, yet its impact on 24-hour urinary oxalate—a primary driver of calcium oxalate supersaturation—remains a critical clinical concern, particularly for patients with nephrolithiasis. This study evaluated the effect of high-dose vitamin C on changes in 24-hour urinary oxalate concentration, with specific subgroup analyses comparing stone formers (SF) to non-stone formers (NSF).

Methods: We conducted a systematic review and random-effects meta-analysis of human intervention trials published between January 2000 and December 2025. Eligible studies included adults receiving oral vitamin C (≥1,000 mg/day) for >2 days, with documented 24-hour urinary oxalate measurements.

Results: Three short-term trials (n=141$; SF=59, NSF=82) were included. In the primary analysis (r=0.50), high-dose vitamin C significantly increased 24-hour urinary oxalate concentration by a pooled mean difference (MD) of 9.57 mg/day (95% CI: 0.56 to 18.57; I^2=96.4 %). Subgroup analysis revealed a significantly larger increase in SF (MD 15.86 mg/day; 95% CI: 5.01 to 26.70) compared to NSF (MD 6.76 mg/day; 95% CI: 0.28 to 13.24; $p < 0.001$). While the magnitude of statistical significance for the overall and NSF effects was sensitive to the correlation coefficient, the direction of the effect remained consistently positive.

Conclusion: High-dose oral vitamin C is associated with increased 24-hour urinary oxalate excretion, with a more pronounced effect observed in the SF group. Given the high heterogeneity and the sensitivity of the results, supplementation in high-risk individuals should be managed with caution.

Keywords: ascorbic acid; ascorbate; kidney stone; renal stone

Corresponding author: *Nutthavuth Arjinpathana*
Email: *68130657@dpu.ac.th*

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Introduction

Vitamin C (ascorbic acid) is widely consumed at gram-level doses for its perceived health benefits. However, a proportion of ingested ascorbate is metabolized to oxalate, an important determinant of calcium oxalate supersaturation and kidney stone risk. This question is clinically relevant because calcium oxalate stones are the most common form of nephrolithiasis, recurrence is common, and even modest increases in urinary oxalate may be important in susceptible individuals, particularly stone formers.

The importance of this topic extends beyond stone-forming populations. High-dose vitamin C is commonly used in the general population and is often perceived as harmless, yet its potential lithogenic effect may be underrecognized in routine clinical practice. Clarifying its effect on 24-hour urinary oxalate may therefore improve patient counseling, risk stratification, and decisions regarding urinary monitoring in both stone formers and non-stone formers.

Interpretation of the literature is complicated by methodological issues. In addition to true in vivo conversion of ascorbate to oxalate, ascorbic acid can undergo non-enzymatic conversion to oxalate in vitro during urine collection or processing if pre-analytical handling is inadequate. Accordingly, preservative-aware methods are essential for obtaining reliable urinary oxalate measurements and minimizing measurement bias.

Although prior human intervention studies have examined the relationship between vitamin C supplementation and urinary oxalate, the available evidence remains limited by small sample sizes, short study duration, heterogeneous designs, and variable methodological rigor. Some studies have reported increases in urinary oxalate and calcium oxalate supersaturation, whereas others have shown smaller or inconsistent effects.

The novelty of the present study lies in its preservative-aware quantitative synthesis of human intervention trials specifically evaluating high-dose oral vitamin C (≥1,000 mg/day) and 24-hour urinary oxalate excretion. Unlike prior narrative discussions or broader reviews of kidney stone risk, this study focuses on a common biochemical outcome, integrates evidence across intervention designs, and prespecifies a comparison between stone formers and non-stone formers.

Accordingly, this systematic review and meta-analysis aimed to quantify the effect of high-dose oral vitamin C supplementation on 24-hour urinary oxalate excretion and to compare its magnitude between stone formers and non-stone formers.

Methods

Protocol and reporting

The review followed PRISMA 2020 guidance and Cochrane methods. No prospective registration was performed **(Figure 1)**.[1-2]

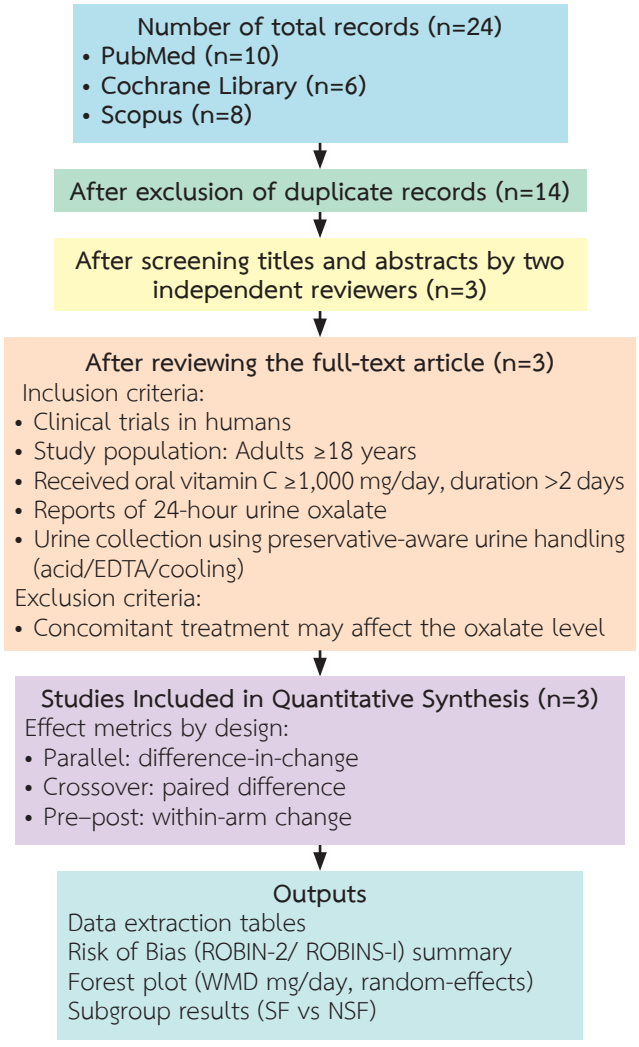


Figure 1 PRISMA flow diagram showing the study selection process from identification through screening to final inclusion

Eligibility criteria

We included human intervention trials (randomized controlled trials [parallel or crossover], nonrandomized controlled trials, and pre–post trials) enrolling adults (≥18 years) who received oral vitamin C ≥1,000 mg/day for >2 days. Studies had to report 24-hour urinary oxalate or provide data that could be converted. To minimize measurement artifact, studies were required to use preservative-aware handling (acidification/EDTA and/or refrigeration) or demonstrate equivalence of collection methods.[3]

Information sources and search

PubMed, CENTRAL, and Scopus were searched from January 2000 through December 2025 using terms for vitamin C/ascorbate and oxalate/stone/nephrolithiasis, and the results were filtered to clinical trials. Two reviewers independently screened and extracted data.

Outcome and effect measures

The primary outcome was the change in 24-hour urinary oxalate (mg/24 h). Values reported in μmol/day were converted using mg = μmol × 0.08802. For parallel trials, the effect was the between-group difference. For crossover trials, the preferred effect was the within-participant paired difference (vitamin C vs. control), with the paired difference standard deviation (SD). If this information was not available or no true placebo comparator existed, the within-period pre–post change was used. For pre–post trials, within-arm change was used.[4]

Risk of bias and certainty of evidence

These tools were used to evaluate the quality of the trials included. RoB 2 (Risk of Bias 2) was used for randomized trials and ROBINS-I (Risk of Bias in Non-randomized Studies) for nonrandomized pre–post studies. Certainty was assessed using GRADE (Grading of Recommendations, Assessment, Development, and Evaluations).[5-7]

Synthesis

We pooled mean differences (MD) using a random-effects model (generic inverse variance), reporting 95% confidence intervals (CI) and measures of heterogeneity, including I^2 and τ^2 values. When the SD of change was not reported, it was imputed using the Cochrane correlation approach and tested with r=0.25/0.50/0.75. Prespecified subgroup analyses compared SF vs NSF.[8-9]

Results

Study selection and characteristics

From 24 records, 3 trials met the inclusion criteria (n=141): one pre–post study (Baxmann 2003) including SF and healthy controls; one placebo-controlled double-blind crossover trial (Traxer 2003) including SF and normal subjects; and one double-blind crossover trial in healthy subjects comparing two vitamin C formulations (Moyad 2009). All studies used acidification and refrigeration during 24-hour urine collection.[10-12] **(Table 1)**

Risk of bias

The pre–post study was at high risk of bias primarily because of its nonrandomized design, while the crossover RCTs raised concerns due to limited reporting of sequence generation and selective reporting. Outcome measurement risk was low because urinary oxalate was objectively quantified under preservative-aware handling.

Meta-analysis

Overall, high-dose vitamin C increased 24-hour urinary oxalate. In the primary analysis (r=0.50), pooled MD was 9.57 mg/24 h (95% CI 0.56 to 18.57) with considerable heterogeneity (I^2=96.4%; $\tau^2$60.91). Sensitivity analyses showed stable point estimates across r values (9.61–9.52 mg/24 h), while p-values varied (0.029–0.056).[9] **(Table 2 and Figure 2)**

Table 1 Characteristics of all studies

Study	Design	Population	N	Intervention	Duration	Comparator	Urine collection & preservative
Baxmann 2003	Pre–post	SF	23 (1g) 24 (2g)	AA 1 g/day (500 mg BID) or 2 g/day (1,000 mg BID)	6 days	Baseline	Baseline, day3, and day 6
		NSF	20 (1g)	AA 1 g/day (500 mg BID)			Acidified with 20 mL of 6N HCl); Refrigerated
Traxer 2003	Randomized double-blind crossover RCT	NSF	12	AA 2 g/day (500 mg × 2 BID)	6 days / period washout ≥1 week*	Placebo	Day 5 to 6 for each period Acidified (~pH2); refrigerated.
		SF	12	AA 2 g/day (500 mg × 2 BID)			
Moyad 2009	Randomized double-blind crossover RCT	NSF	50	AA 1 g/day × 5 days → 2 g/day × 5 days	10 days / period washout 1 week	Ester-C®	Baseline and day 10; Container acidified with HCl; Refrigerated

AA, ascorbic acid; SF, stone formers; NSF, non-stone formers; BID, twice daily; RCT, randomized controlled trial; HCl, hydrochloric acid. *washout ≥1 week (≥3 weeks for women)

Table 2 Meta-analysis results of all studies and sensitivity by correlation

Correlation (r)	Number of Studies	Number of Patients	Pooled MD (mg/24h)	95% CI	Z-score	p-value	I^2 (%)	τ^2
0.25	3	141	9.52	0.96 to 18.08	2.18	0.029	94.8	53.98
0.50	3	141	9.57	0.56 to 18.57	2.08	0.037	96.4	60.91
0.75	3	141	9.61	-0.23 to 19.44	1.91	0.056	97.9	73.92

MD, mean difference; CI, confidence interval

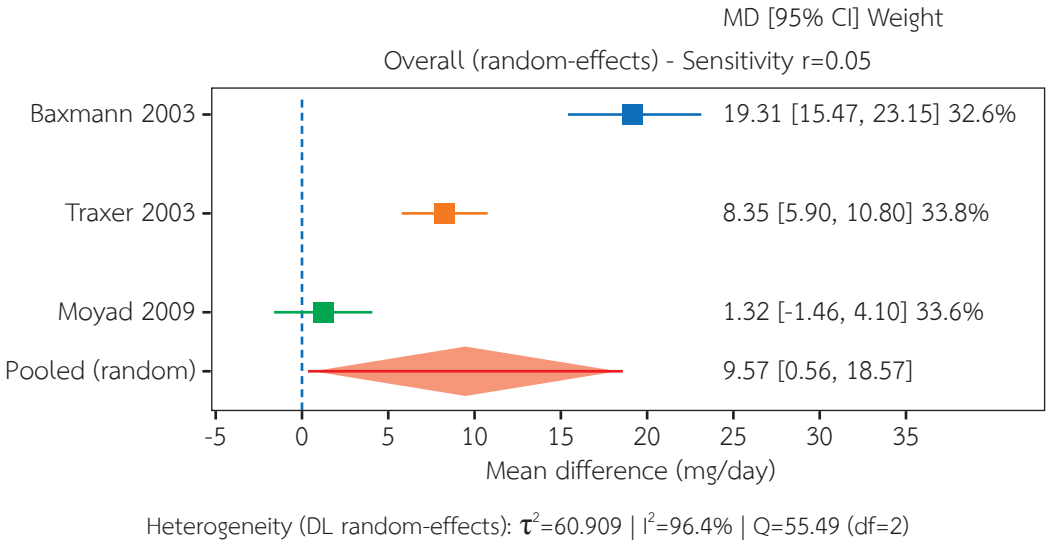


Figure 2 Forest plot showing meta-analysis results of all studies

In subgroup analyses (r=0.50), SF (2 studies, n=59) had a pooled MD of 15.86 mg/24 h (95% CI 5.01 to 26.70; I^2=93.4%), and NSF (3 studies, n=82) had a pooled MD of 6.76 mg/24 h (95% CI 0.28 to 13.24; I^2=87.9%). The test for subgroup differences was significant (p<0.001), but interpretation is limited by the small number of studies and residual heterogeneity.[9] **(Table 3, 4, and Figure 3)**

Table 3 Meta-analysis of the subgroup of stone formers and non-stone formers

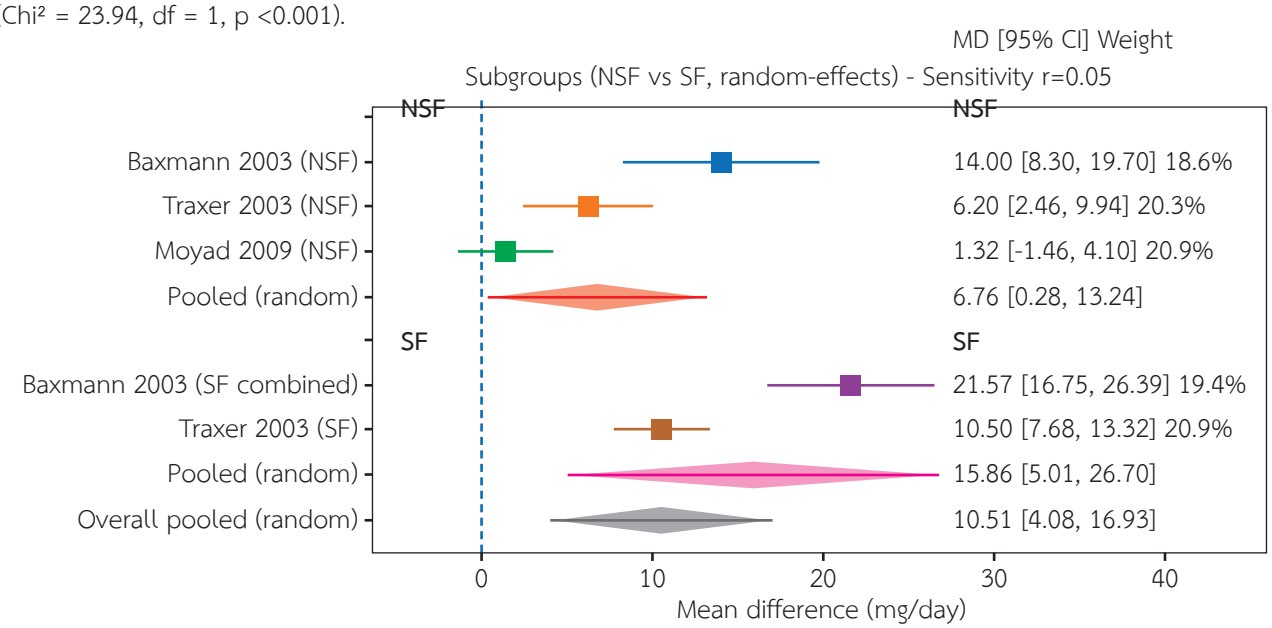
Group	Correlation (r)*	Number of Studies	Number of Patients	Pooled MD (mg/24h)	95% CI	p-value	I^2 (%)
Stone Formers	0.25	2	59	15.75	4.91 to 26.58	0.004	91.4
	0.50	2	59	15.86	5.01 to 26.70	0.004	93.4
	0.75	2	59	15.96	5.12 to 26.81	0.004	95.3
Non-Stone Formers	0.25	3	82	6.49	0.44 to 12.55	0.036	82.2
	0.50	3	82	6.76	0.28 to 13.24	0.041	87.9
	0.75	3	82	7.02	-0.34 to 14.38	0.062	93.7

*Correlation in Stone Former (Baxmann 2003); Non-Stone Former (Baxmann 2003 and Moyad 2009); Standard deviation (Traxer 2003). MD, mean difference; CI, confidence interval

Table 4 Comparison between subgroups of stone formers and non-stone formers

Subgroup	Number of Studies	Number of Patients	Pooled MD (mg/24h)	95% CI	p-value	I^2 (%)
Stone formers	2	59	15.86	5.01 to 26.70	0.004	93.4
Non-stone formers	3	82	6.76	0.28 to 13.24	0.041	87.9

Test for subgroup difference (interaction, primary analysis r = 0.50): statistically significant (Chi^2 = 23.94, df = 1, p <0.001).



Heterogeneity (DL random-effects): NSF I^2=87.9% τ^2=28.312; SF I^2=93.4% τ^2=57.210; All I^2=93.4% τ^2=49.321

Figure 3 Forest plot for subgroup analysis between stone formers vs. non-stone formers
SF, stone formers; NSF, non-stone formers

Discussion

This study demonstrates a clear association between high-dose oral vitamin C (1–2 g/day) and increased 24-hour urinary oxalate excretion. While the absolute increase was modest, oxalate is a critical driver of calcium oxalate supersaturation; even small elevations may push susceptible individuals, particularly stone formers, toward lithogenic thresholds.[13]

The pooled increase was more pronounced in stone formers, which is biologically plausible given their higher baseline risk. However, this subgroup finding remains exploratory. The substantial heterogeneity observed likely stems from variations in study design (pre–post vs. crossover), dietary control (metabolic diets vs. advice-based restriction), vitamin C formulations (ascorbic acid vs. buffered), and baseline urinary chemistry.

The analysis is limited by the inclusion of only three small, short-duration trials focused on biochemical surrogates rather than actual stone events. Furthermore, the high heterogeneity and the need to impute standard deviations for certain estimates weaken the overall certainty. One study's industry involvement raises concerns about generalizability.

For patients with a history of calcium oxalate stones, routine gram-dose vitamin C supplementation should be approached with caution. If clinically necessary, clinicians should emphasize adequate hydration and consider monitoring 24-hour urine profiles in high-risk individuals. For those without a history of stones, the absolute risk is lower, yet high-dose supplementation offers uncertain benefits while potentially adding avoidable lithogenic risk.[14]

To provide definitive evidence, future trials must be larger and longer, focusing on clinical endpoints like stone recurrence. Research designs should standardize dosages, formulations, and dietary controls while measuring comprehensive 24-hour urine panels, including citrate and supersaturation indices.

In conclusion, high-dose vitamin C increases urinary oxalate, particularly in stone formers. Given the limited and heterogeneous nature of current evidence, supplementation should be individualized until long-term trials with clinical outcomes are available.

Author's contributions:

Nutthavuth Arjinpathana: Conceptualization, Methodology, Literature search, Study selection, Data extraction, Risk of bias assessment, Formal analysis, Interpretation of findings, Writing—original draft, Writing—review & editing, and Final approval of the manuscript.

Phawit Norchai: Second reviewer for study selection and risk of bias assessment, Writing—critical revision, and Final approval of the manuscript.

Ethical approval: Not applicable (systematic review and meta-analysis of published studies).

Generative AI Use Declaration: Generative AI and AI-assisted technologies were used only to improve readability and language. The authors take full responsibility for the content of this manuscript.

Data availability: Extracted data and analytic code are available from the corresponding author upon reasonable request.

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