Vitamin C Intake and the Risk of Gout in Men

A Prospective Study

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Background: Several metabolic studies and a recent double-blind, placebo-controlled, randomized trial have shown that higher vitamin C intake significantly reduces serum uric acid levels. Yet the relation with risk of gout is unknown.

Methods: We prospectively examined, from1986 through 2006, the relation between vitamin C intake and risk of incident gout in 46 994 male participants with no history of gout at baseline. We used a supplementary questionnaire to ascertain the American College of Rheumatology criteria for gout. Vitamin C intake was assessed every 4 years through validated questionnaires.

Results: During the 20 years of follow-up, we documented 1317 confirmed incident cases of gout. Compared with men with vitamin C intake less than 250 mg/d, the multivariate relative risk (RR) of gout was 0.83 (95% confidence interval [CI], 0.71-0.97) for total vitamin C intake of 500 to 999 mg/d, 0.66 (0.52-0.86) for 1000 to 1499 mg/d, and 0.55 (0.38-0.80) for 1500 mg/d or greater ($P<.001$ for trend). The multivariate RR per 500-mg increase in total daily vitamin C intake was 0.83 (95% CI, 0.77-0.90). Compared with men who did not use supplemental vitamin C, the multivariate RR of gout was 0.66 (95% CI, 0.49-0.88) for supplemental vitamin C intake of 1000 to 1499 mg/d and 0.55 (0.36-0.86) for 1500 mg/d or greater ($P<.001$ for trend).

Conclusions: Higher vitamin C intake is independently associated with a lower risk of gout. Supplemental vitamin C intake may be beneficial in the prevention of gout.

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GOUT IS THE MOST COMMON type of inflammatory arthritis in men.[1] Epidemiologic studies[2] suggest that the overall disease burden of gout is substantial and growing. The identification of the risk factors for gout that are modifiable with available measures is an important first step in the prevention and management of this common and excruciatingly painful condition.[3-5] In this context, to identify protective factors is equally as important as to identify hazardous factors for gout. Among the potentially useful protective factors against hyperuricemia and gout is vitamin C, an essential micronutrient for humans.

Previous studies have suggested that vitamin C supplementation lowers serum uric acid levels via a uricosuric effect.[6-9] These studies, however, were small, of short duration, and used exceptionally high doses of vitamin C (1-time ingestion of 3-12 g for several days).[10] The uricosuric effect of vitamin C may be due to competition for renal reabsorption via an anion exchange transport system at the proximal tubules.[7,9] Recently, a randomized trial[10] found that supplementation with vitamin C, 500 mg/d, for 2 months reduced serum uric acid levels. Yet, the relation with the risk of gout (the clinical outcome of hyperuricemia) remains unknown. This effect, if confirmed, may have implications for the prevention and management of gout. To examine these issues, we prospectively evaluated the relation between vitamin C intake and risk of incident gout in a cohort of 46 994 men with no history of gout.

METHODS

STUDY POPULATION

The Health Professionals Follow-up Study[3] is an ongoing longitudinal study of 51 529 male dentists, optometrists, osteopaths, pharmacists, podiatrists, and veterinarians who are predominantly white (91%) and were aged 40 to 75 years in 1986. The participants returned a mailed questionnaire in 1986 concerning diet, medical history, and medications. Of the 49 776 men who provided complete information on vitamin C intake, 2782 (5.6%) reported a his-

Table 1. Baseline Characteristics According to Total Vitamin C Intake (1986)

Variable	Total Vitamin C Intake, mg/d					All Participants (N=46 994)
	<250 (n=25 430)	250-499 (n=9476)	500-999 (n=6349)	1000-1499 (n=3369)	≥1500 (n=2370)	
Age, mean (SD), y	54	55	56	55	54	55 (10)
Body mass index,[a] mean (SD)	25.0	24.8	24.6	24.6	24.5	24.8 (5)
Diuretic use, %	10	10	10	10	9	10
History of hypertension, %	21	21	22	21	21	21
History of renal failure, %	0.1	0.1	0.2	0.2	0.1	0.1
Alcohol intake, mean (SD), g/d	11	11	11	11	12	11 (15)
Total meat intake, mean (SD), servings/d	1.4	1.4	1.3	1.2	1.2	1.4 (0.7)
Seafood intake, mean (SD), servings/d	0.3	0.4	0.4	0.5	0.5	0.4 (0.3)
Dairy intake, mean (SD), servings/d	1.9	2.1	2.0	1.8	1.8	1.9 (1.4)
Coffee intake, mean (SD), servings/d	1.5	1.2	1.2	1.1	1.0	1.3 (1.6)
Fructose intake of energy, mean (SD), %	4.6	5.7	5.6	5.4	5.7	5.1 (2.3)
Sweetened soft drink intake, mean (SD), servings/d	0.3	0.3	0.2	0.2	0.2	0.3 (0.5)
Dietary vitamin C intake, mean (SD), mg	131	215	202	182	196	164 (92)
Supplemental vitamin C intake, mean (SD), mg	14	127	493	1037	1599	255 (433)
Supplemental vitamin C use, %	24	74	97	99	100	53

[a] Calculated as weight in kilograms divided by height in meters squared.

tory of gout on the baseline questionnaire. These prevalent cases at baseline were excluded from this analysis. The rate of follow-up for this cohort exceeded 90% during the study period.

ASSESSMENT OF VITAMIN C, DIET, AND NONDIETARY FACTORS

To assess dietary intake, including vitamin C intake, we used a semiquantitative food frequency questionnaire that inquired about the average use of more than 130 foods and beverages during the previous year.[3,11,12] In addition, respondents provided information on the use of supplemental vitamins, taken either alone or in multivitamin form. The baseline dietary questionnaire was completed in 1986, and it was updated every 4 years. Nutrient intake (including dietary vitamin C intake) was computed from the reported frequency of consumption of each specified unit of food or beverage and from published data on the nutrient content of the specified portions.[12] For supplemental vitamin C, respondents chose from the following categories: 0, 1 to 399, 400 to 700, 750 to 1250, and 1300 mg or more daily. The amount of vitamin C in multivitamin preparations was determined by the brand, type, and frequency of reported use. Food and nutrient intake assessed by this dietary questionnaire have been validated previously against two 1-week diet records in this cohort.[11,13] Specifically, the Pearson correlation coefficient for energy-adjusted total vitamin C intake between the dietary records and the questionnaire was 0.86.[14] After adjustment for the week-to-week variation in vitamin C intake, the correlation coefficient was 0.92. After excluding supplemental vitamin use, the correlation coefficient for vitamin C was 0.77.

At baseline, and every 2 years thereafter, the participants provided information on weight, regular use of medications (including diuretics), and medical conditions (including hypertension and chronic renal failure).[5] Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared.

ASCERTAINMENT OF INCIDENT CASES OF GOUT

We ascertained incident cases of gout by using the American College of Rheumatology gout criteria survey, as previously described.[3] Briefly, on each biennial questionnaire, participants indicated whether they had received a physician diagnosis of gout. We mailed to those individuals with self-reported incident cases of gout from 1986 onward a supplementary questionnaire to confirm the report and to ascertain the American College of Rheumatology gout criteria survey.[3,15] The primary end point in this study was an incident case of gout that met 6 or more of the 11 gout criteria.[3,15] To confirm the validity of the gout criteria survey in this cohort, we reviewed the relevant medical records from a sample of 50 men who had reported having gout.[3] The concordance rate of confirmation of the report of gout between the gout survey criteria and the medical record review was 94.0% (47/50).[3]

STATISTICAL ANALYSIS

We computed person-time of follow-up for each participant from the return date of the 1986 questionnaire to the date of diagnosis of gout, death from any cause, or February 1, 2006, whichever came first. Men who died or who had reported having gout on previous questionnaires were excluded from subsequent follow-up.

To represent individuals' long-term vitamin C (and other dietary) intake patterns, we used cumulative mean intakes based on information from the 1986, 1990, 1994, 1998, and 2002 dietary questionnaires.[3-5,16,17] For example, the incidence of gout in 1986 through 1990 was related to the vitamin C intake reported on the 1986 questionnaire, and the incidence in 1990 through 1994 was related to the average intake reported on the 1986 and 1990 questionnaires. We repeated the analyses using baseline vitamin C (and other dietary) intake (in 1986) or updated vitamin C (and other dietary) intake every 4 years without cumulative averaging. When we aggregated items to compute the composite dietary items (**Table 1**), we assumed that individual foods for the values that were missing implied no intake.[18,19] Participants who did not respond to a questionnaire during 1 follow-up cycle were not removed from the study; they were included in the next mailing of the questionnaire (they could skip answering a questionnaire but then answer the next one).

We used Cox proportional hazards modeling to estimate the relative risk (RR) of incident gout in all multivariate analyses (SAS Institute Inc, Cary, North Carolina). We categorized total daily vitamin C intake into 5 categories: less than 250, 250 to 499, 500 to 999, 1000 to 1499, and 1500 mg or more.[20,21] In

Table 2. Relative Risk (RR) of Incident Gout According to Total Vitamin C Intake

	Total Vitamin C Intake, mg/d					*P* Value for Trend
	<250	250-499	500-999	1000-1499	≥1500	
Cases, No.	693	326	202	67	29	. . .
Person-years	436 888	212 384	153 002	62 415	32 412	. . .
Age-adjusted RR (95% CI)[a]	1 [Reference]	1.00 (0.88-1.15)	0.85 (0.73-1.00)	0.68 (0.53-0.88)	0.55 (0.38-0.80)	<.001
Multivariate RR (95% CI)[b]	1 [Reference]	0.97 (0.85-1.12)	0.83 (0.71-0.97)	0.66 (0.52-0.86)	0.55 (0.38-0.80)	<.001

Abbreviation: CI, confidence interval.
[a] Age-adjusted models were adjusted for total energy intake and age.
[b] Multivariate models were adjusted for age, total energy intake, body mass index, diuretic use, history of hypertension, history of renal failure, and intake of alcohol, total meats, seafood, dairy foods, fructose, and coffee (regular and decaffeinated).

Table 3. Relative Risk (RR) of Incident Gout According to Supplemental Vitamin C Intake

	Supplemental Vitamin C Intake, mg/d						*P* Value for Trend
	0	1-249	250-499	500-999	1000-1499	≥1500	
Cases, No.	374	583	129	157	53	21	. . .
Person-years	243 731	361 396	103 744	111 577	51 476	24 682	. . .
Age-adjusted RR (95% CI)[a]	1 [Reference]	1.14 (0.99-1.30)	0.88 (0.72-1.08)	0.96 (0.79-1.16)	0.69 (0.51-0.92)	0.55 (0.36-0.86)	<.001
Multivariate RR (95% CI)[b]	1 [Reference]	1.10 (0.96-1.26)	0.86 (0.70-1.06)	0.92 (0.76-1.11)	0.66 (0.49-0.88)	0.55 (0.36-0.86)	<.001

Abbreviation: CI, confidence interval.
[a] Age-adjusted models were adjusted for total energy intake and age.
[b] Multivariate models were adjusted for age, total energy intake, body mass index, diuretic use, history of hypertension, history of renal failure, and intake of alcohol, total meats, seafood, dairy foods, fructose, coffee (regular and decaffeinated), and dietary vitamin C.

addition, we categorized daily supplemental vitamin C intake into 6 categories: none, 1 to 249, 250 to 499, 500 to 999, 1000 to 1499, and 1500 mg or more and daily dietary vitamin C intake into 6 categories: less than 50, 50 to 99, 100 to 199, 200 to 299, and 300 mg or more. Multivariate models were adjusted for age (continuous), total energy intake (continuous), alcohol use (7 categories), BMI (5 categories), use of diuretics (thiazide or furosemide; yes or no), history of hypertension (yes or no), history of chronic renal failure (yes or no), and daily average intake of total meats (quintiles), seafood (quintiles), dairy foods (quintiles), fructose (quintiles), and coffee (regular and decaffeinated in 4 and 3 categories, respectively).[3-5] Trends in gout risk across categories of vitamin C intake were assessed in Cox proportional hazards models by using the median values of intake for each category to minimize the effect of outliers. The RRs for the continuous measures for vitamin C intake indicate the increase in risk associated with an average increment of 500 mg/d. We conducted analyses stratified by BMI (<25 vs ≥25), alcohol use (median: ≤5.5 vs >5.5 g/d), and daily dairy intake (median: ≤1.6 vs >1.6 servings) to assess possible effect modification. We tested the significance of the interaction using a likelihood ratio test by comparing a model with the main effects of vitamin C intake and the stratifying variable and the interaction terms with a reduced model with only the main effects. For all RRs, we calculated 95% confidence intervals (CIs). All *P* values are 2-sided.

RESULTS

BASELINE CHARACTERISTICS

During 20-year follow-up, we documented 1317 new cases of gout that met the American College of Rheumatology criteria.[15] The characteristics of the cohort according to total daily vitamin C intake at baseline are given in Table 1. With increasing vitamin C consumption, total meat and coffee intake tended to decrease but total seafood intake tended to increase slightly. Fructose intake was lower in the lowest category of vitamin C intake. Other variables were similar across the levels of vitamin C intake (Table 1).

VITAMIN C INTAKE AND INCIDENT GOUT

The incidence of gout decreased with increasing total vitamin C intake (**Table 2**). Compared with men with vitamin C intake less than 250 mg/d, the multivariate RR of gout was 0.83 (95% CI, 0.71-0.97) for total vitamin C intake of 500 to 999 mg/d, 0.66 (0.52-0.86) for 1000 to 1499 mg/d, and 0.55 (0.38-0.80) for 1500 mg/d or more ($P<.001$ for trend) (Table 2). Absolute risk reductions associated with total vitamin C intake categories of 500 to 999, 1000 to 1499, and 1500 mg/d or more were 27, 51, and 69 cases per 100 000 person-years, respectively. The multivariate RR per 500-mg increase in total daily vitamin C intake was 0.83 (95% CI, 0.77-0.90). When we repeated the analyses using updated vitamin C intake without cumulative averaging and baseline vitamin C intake, multivariate RRs of gout between extreme categories of total daily vitamin C intake were 0.64 (95% CI, 0.48-0.86) and 0.69 (0.51-0.92) ($P<.001$ for trend for both), respectively.

The incidence of gout also decreased with increasing supplemental vitamin C intake (**Table 3**). Compared with men who did not use supplemental vitamin C, the multivariate RR of gout was 0.66 (95% CI, 0.49-0.88) for supplemental vitamin C intake of 1000 to 1499 mg/d and 0.55 (0.36-0.86) for 1500 mg/d or more ($P<.001$ for trend) (Table 3). The multivariate RR per 500-mg increase in supplemental daily vitamin C intake was 0.85 (95% CI,

0.77-0.93). The risk of gout did not significantly differ between the extreme categories of dietary vitamin C intake (multivariate RR <50 to >300 mg/d: 1.13; 95% CI, 0.69-1.83), but the range of intake was substantially smaller than for total or supplemental vitamin C intake.

We conducted stratified analyses to evaluate whether the association between vitamin C intake and the risk of gout varied according to BMI, alcohol use (median: ≤5.5 vs >5.5 g/d), and daily dairy intake (median: ≤1.6 vs >1.6 servings). The RRs from these stratified analyses consistently suggested inverse associations similar to those from the main analyses, and no significant interaction was found with these variables ($P > .73$ for interaction for all) (**Figure**).

COMMENT

The objective of this study was to evaluate prospectively in a large cohort of men the suspected protective effect of vitamin C intake against the risk of gout. Using the American College of Rheumatology criteria for gout,[15] we found that the risk of gout decreased with increasing vitamin C intake, resulting in up to a 45% lower risk at the top vitamin C intake category of 1500 mg or more. These associations were independent of dietary and other risk factors for gout, such as BMI, age, hypertension, diuretic use, alcohol use, and chronic renal failure. The decreasing risk persisted across subgroups stratified by BMI, alcohol use, and dairy intake. The present study, to our knowledge, provides the first prospective evidence about the inverse association between vitamin C intake and risk of gout.

The suggestion of a potential protective effect of vitamin C intake against gout originally stemmed from metabolic experiments that examined the impact of short-term loading of high-dose vitamin C on serum uric acid levels. For example, ingestion of a single dose of 4 g of vitamin C doubled the fractional excretion of uric acid, and daily ingestion of 8 g of vitamin C for 3 to 7 days reduced serum uric acid levels by 2.0 to 3.1 mg/dL (to convert uric acid to micromoles per liter, multiply by 59.485) as a result of uricosuria.[9] Recently, a double-blinded placebo-controlled randomized trial[10] (n = 184) showed that supplementation with vitamin C as low as 500 mg/d for 2 months reduced serum uric acid levels by 0.5 mg/dL compared with no change in the placebo group. Furthermore, a retrospective Taiwanese case-control study[22] (91 gout cases and 91 controls) reported an inverse association between vitamin C intake and the presence of gout (unadjusted odds ratios between the extreme tertiles, 0.31; 95% CI, 0.15-0.35), although no multivariate adjustment for the link was reported.

The uricosuric effect of vitamin C is likely due to a competition for renal reabsorption of uric acid via an anion exchange transport system at the proximal tubule.[7,9] Recent advances in molecular mechanisms of renal urate transport suggest that the uricosuric effect may be through *cis*-inhibition of *URAT1* (urate transporter 1, the key target of typical uricosurics),[23] sodium-dependent anion cotransporter (eg, *SLC5A8/A12*), or both in the proximal tubules.[2] Furthermore, a recent randomized trial[10] showed that vitamin C supplements (500 mg/d) significantly increased the glomerular filtration rate, providing another potential mechanism for the uricosuric effect of vitamin C intake. It remains speculative whether the antioxidant action of vitamin C may have a protective effect against gouty inflammation, as was suggested for reducing the risk of inflammatory polyarthritis according to a recent prospective study.[24]

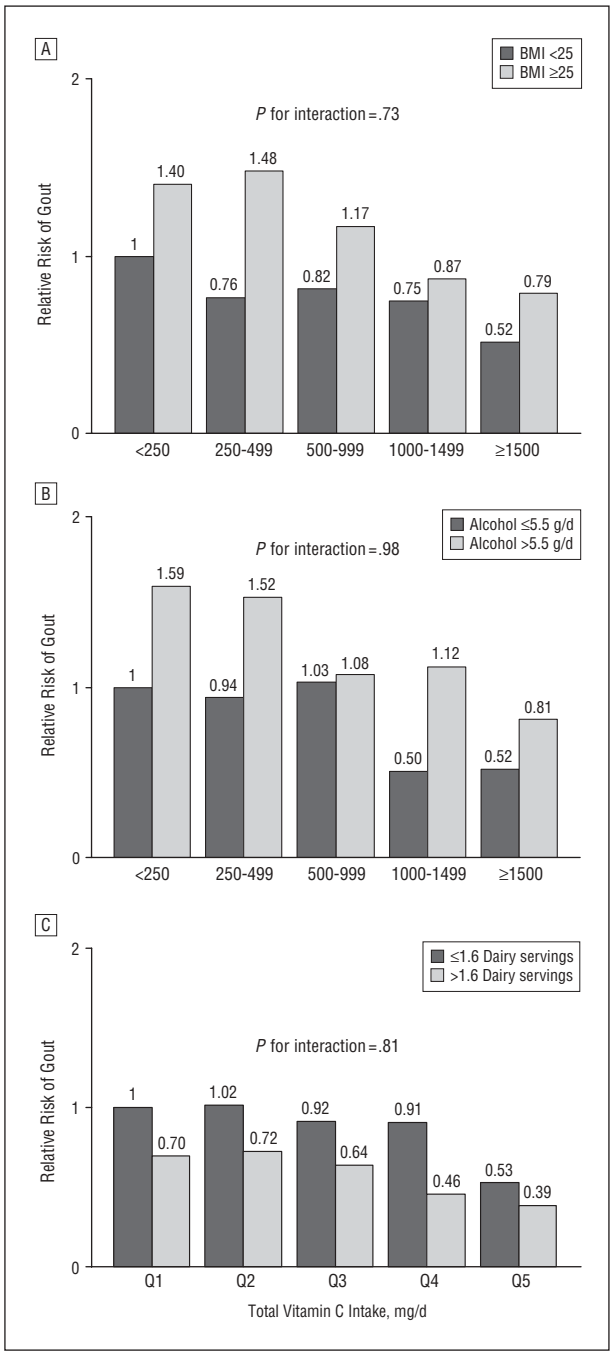

Figure. Multivariate relative risk of incident gout according to total vitamin C intake and body mass index (BMI) (calculated as weight in kilograms divided by height in meters squared) (A), alcohol use (B), and dairy intake (C). The reference groups for the comparisons were men who had total daily vitamin C intake less than 250 mg and a BMI less than 25 (A), men who had total daily vitamin C intake less than 250 mg and alcohol intake of 5.5 g/d or less (B), and men who had total daily vitamin C intake less than 250 mg and total daily dairy intake of 1.6 servings or less (C). The relative risks were adjusted for the same covariates included in the multivariate models in Table 2. Q1 indicates lowest quintile; Q5, highest quintile.

Although the present data suggest that total vitamin C intake of 500 mg/d or more is associated with reduced risk, the potential benefit of lower intake is not clear. According to a recent analysis[25] of 9 prospective studies, compared with individuals who did not take supplemental vitamin C, those who took more than 700 mg/d had a 25% lower risk of coronary heart disease (95% CI, 7%-40%; $P<.001$ for trend). The same study found that supplemental vitamin E intake was not significantly related to reduced coronary heart disease risk.[25] This potential cardiovascular benefit of vitamin C may be particularly relevant in patients with gout given their increased risk of cardiovascular morbidity and mortality.[26,27] Given the general safety profile associated with vitamin C intake, particularly in the generally consumed ranges as in the present study (eg, tolerable upper intake level of vitamin C <2000 mg in adults according to the Food and Nutrition Board, Institute of Medicine),[28] vitamin C intake may provide a useful option in the prevention of gout.

Several strengths and potential limitations of this study deserve comment. This study was substantially larger than previous studies concerning gout.[1,29-34] Also, dietary data, including vitamin C information, were prospectively collected and validated. Potential biased recall of diet was avoided in this study because the intake data were collected before the diagnosis of gout. Because dietary consumption was self-reported by questionnaire, some misclassification of exposure is inevitable. However, the food frequency questionnaire has been extensively validated in a subsample of this cohort, and any remaining misclassification would have likely biased the results toward the null. The use of repeated dietary assessments in the analyses not only accounts for changes in dietary consumption across time but also decreases measurement error.[11,13] However, this study was observational; thus, we cannot rule out the possibility that unmeasured factors might contribute to the observed associations. As in other epidemiologic studies of gout,[1,29-32] our primary definition of gout did not require observation of urate crystals in joint fluid examination. Although the presence of a tophus or urate crystal in joint fluid would be diagnostic of gout,[15] the sensitivity of these findings is too low, especially in a population study such as this one, because arthrocentesis is performed infrequently. Thus, its application would likely miss most genuine gout cases. The reliable information provided by health professionals in this cohort, the obvious nature of the clinical presentation of gout, and the ready access to medical care for these men would have helped ensure a high level of sensitivity in the detection of gout. In this study, fulfillment of 6 of the 11 American College of Rheumatology survey criteria[15] showed a high degree of concordance with medical record review, and the incidence rate of gout that fulfilled the criteria in this cohort closely agreed with that estimated in male physicians in the Johns Hopkins Precursor Study[1] (1.5 vs 1.7 per 1000 person-years).

The restriction to health professionals in this cohort is a strength and a limitation. The cohort of well-educated men minimizes the potential for confounding associated with socioeconomic status, and we obtained high-quality data with minimal loss to follow-up. Although the absolute rates of gout and distribution of vitamin C intake may not be representative of a random sample of US men, the biological effects of vitamin C on gout should be similar. Of note, other dietary and lifestyle risk factors of gout observed in this cohort[3,4,35,36] have all been found to be significant in studies based on the Third National Health and Nutrition Examination Survey.[37-40] The present findings are most directly generalizable to men aged 40 years and older (the most gout-prevalent population[29]) with no history of gout. Given the potential effect of female hormones on the risk of gout in women[41] and an increased role of dietary effect on uric acid levels in patients with existing gout,[42] prospective studies of these populations would be valuable.

In conclusion, these prospective data indicate that vitamin C intake is strongly associated with a lower risk of gout. Increasing vitamin C intake may be beneficial in the prevention of gout.

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