

Vitamin C Intake and Serum Uric Acid Concentration in Men

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ABSTRACT. *Objective.* We examined associations between vitamin C intake and serum uric acid in men in a population-based study.

Methods. We included 1387 men without hypertension and with body mass index (BMI) < 30 kg/m² in the Health Professional Follow-up Study. Dietary intake was assessed with a semiquantitative food frequency questionnaire validated for use in this population. Serum uric acid concentrations were measured.

Results. Greater intakes of total vitamin C were significantly associated with lower serum uric acid concentrations, after adjustment for smoking, BMI, ethnicity, blood pressure, presence of gout, use of aspirin, and intake of energy, alcohol, dairy protein, fructose, meat, seafood and coffee. An inverse dose-response association was observed through vitamin C intake of 400–500 mg/day, and then reached a plateau. Adjusted mean uric acid concentrations across total vitamin C intake categories (< 90, 90–249, 250–499, 500–999, or ≥ 1000 mg/day) were 6.4, 6.1, 6.0, 5.7, and 5.7 mg/dl, respectively (p for trend < 0.001). Greater vitamin C intake was associated with lower prevalence of hyperuricemia (serum uric acid > 6 mg/dl). Multivariate odds ratios for hyperuricemia across total vitamin C intake categories were 1 (reference), 0.58, 0.57, 0.38, and 0.34 (95% CI 0.20–0.58; P for trend < 0.001). When we used dietary data, which were assessed 4–8 years before blood collection, as predictors, we observed similar inverse associations between vitamin C intake and uric acid.

Conclusion. These population-based data indicate that vitamin C intake in men is inversely associated with serum uric acid concentrations. These findings support a potential role of vitamin C in the prevention of hyperuricemia and gout. (First Release May 1 2008; J Rheumatol 2008;35:1853–8)

Key Indexing Terms:

GOUT

DIET

EPIDEMIOLOGY

Hyperuricemia is considered a precursor of gout, which is the most common inflammatory arthritis in adult men¹. Among the potentially useful protective factors against

hyperuricemia and gout, vitamin C is an essential micronutrient for humans. Metabolic experiments have shown that high-dose vitamin C supplementation (3+ g/day) lowers serum uric acid (UA) via a uricosuric effect^{2–4}. This effect may be due to competition for renal reabsorption via an anion-exchange transport system in the proximal tubules^{4,5}. Recently, a double-blinded placebo-controlled randomized trial (n = 184) showed that supplementation with vitamin C as low as 500 mg daily for 2 months reduced serum UA by 0.5 mg/dl, compared to no change in the placebo group⁶. However, no population-based study has investigated whether vitamin C intake is associated with serum UA concentrations. Further, most trials used a single large dose of vitamin C, therefore it is unclear whether there is a dose-response relationship between vitamin C intake and UA concentrations. We examined associations between vitamin C intake, assessed with a semiquantitative food frequency questionnaire, and serum UA in a subsample population of the Health Professional Follow-up Study (HPFS), a large ongoing cohort study of US men.

MATERIALS AND METHODS

Study population. The HPFS is a large, well characterized prospective cohort designed to study association between diet and chronic diseases. The HPFS was established in 1986, when 51,529 male US health professionals

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(dentists, optometrists, osteopaths, podiatrists, pharmacists, and veterinarians) aged 40–75 years completed a mailed questionnaire about their medical history and lifestyle. Dietary intake data have been collected since 1986 and updated every 4 years. Followup questionnaires have been mailed to participants every 2 years to update information on potential risk factors and to ascertain newly diagnosed diseases. Blood samples were collected in 1993 and 1994⁷, and 18,025 men contributed blood samples that were stored in liquid nitrogen (–130°C). We used data from a subsample of 1387 HPFS participants previously selected for a prospective nested case-control study of serum UA and hypertension among men with available blood samples and without prevalent hypertension in 1994 (roughly 1 year after blood samples were collected)⁸. Criteria for inclusion in the case-control study were: (1) blood sample drawn after fasting ≥ 8 hours; (2) body mass index (BMI) < 30 kg/m² in 1994; and (3) no history of hypertension in 1994. The BMI restriction was imposed because obesity is a strong predictor of UA level and is a powerful predictor of hypertension and because the association between UA and hypertension may be modified by obesity⁸.

Assessment of dietary and nondietary exposures. Dietary intakes were assessed with a semiquantitative food frequency questionnaire validated for use in this population^{9,10}. In brief, participants were asked how often on average over the previous year they had consumed a specific amount of each food item, with 9 possible responses ranging from “never” to “six or more times per day.” Food composition values for nutrients were obtained from the Harvard University Food Composition Database derived from US Department of Agriculture sources¹¹. 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. The correlations between the intakes measured by a food frequency questionnaire and diet records were 0.86 for total vitamin C and 0.68 for dietary vitamin C intake^{9,10}. Information on age, ethnicity, weight, height, smoking status, presence of gout, blood pressure, and use of aspirin was collected through questionnaires. BMI was calculated as weight (kg)/height (m²).

Assessment of serum UA. UA concentrations were determined by oxidation with the specific enzyme uricase to form allantoin and H₂O₂ (Roche Diagnostics, Indianapolis, IN, USA) at Boston Children’s Hospital Laboratory. The coefficient of variation using blind quality control specimens was 2.7%. Hyperuricemia was defined as > 6 mg/dl (360 μ mol/l)¹².

Statistical analyses. All statistical analyses were completed with SAS 9.1 (SAS Institute, Cary, NC, USA). We categorized vitamin C intake into 5 groups, as we did previously, for total vitamin C, i.e., vitamin C from both food and supplements: < 90 , 90–249, 250–499, 500–999, or ≥ 1000 mg/day; for dietary vitamin C, i.e., vitamin C from food alone: < 50 , 50–99, 100–199, 200–299, or ≥ 300 mg/day; and for vitamin C supplement: 0, 1–249, 250–499, 500–999, or ≥ 1000 mg/day¹³. We used the general linear models procedure to compare mean differences in levels of serum UA across vitamin C intake categories, with Duncan adjustment for multiple comparisons (lowest category as reference)¹⁴. Logistic regression was used to test differences in prevalence of hyperuricemia across vitamin C intake categories and to calculate odds ratios and 95% confidence intervals. We adjusted for age (< 60 , 60–64, 65–69, 70–74, ≥ 75 yrs), smoking (never, past, current: 1–14, or ≥ 15 cigarettes/day), BMI (< 23 , 23–24.9, 25–26.9, 27–28.9, or ≥ 29 kg/m²), ethnicity (Caucasian vs others), systolic blood pressure (< 105 , 105–114, 115–124, or ≥ 125 mm Hg), presence of gout (yes/no), use of aspirin (yes/no), and intake of total energy (kcal/day), alcohol (0, < 5 , 5–9, 10–14, 15–29, 30–49, or ≥ 50 g/day), fructose (g/day), dairy protein (g/day), meat (servings/day), seafood (servings/day), and coffee (0, < 1 , 1–3, 4–5, or ≥ 6 cups/day). We also examined potential interactions of vitamin C intake with age (< 60 vs ≥ 60 yrs in 1994), alcohol (none vs > 0 g/day), smoking status (never vs ever), and BMI (< 25 vs ≥ 25 kg/m²). To test significance for interaction, we included multiplicative terms in the linear regression models, with adjustment for other potential confounders. The continuous measure of vitamin C intake was used to fit a

restricted cubic spline model and to obtain a smooth representation of the OR as a function of vitamin C intake with adjustment for the effects of potential confounders¹⁵. We used 4 knots to divide continuous vitamin C intake into 5 intervals.

In primary analyses, we used dietary intakes recorded in 1994 as exposures to examine the cross-sectional relationship between vitamin C intake and serum UA concentrations. In secondary analyses, we used average of diets collected in 1986 and 1990 as exposures to reflect longterm dietary intake patterns. All *p* values are 2-sided.

RESULTS

Participants with higher total vitamin C intake were more likely to have had lower BMI and lower intake of total meat and coffee, had higher intake of fructose, alcohol and seafood, and were more likely to use aspirin, and less likely to be current smokers, and Caucasian, relative to those in the lowest intake quartile (Table 1). No clear relationship was observed between vitamin C intake and other characteristics.

A higher intake of total vitamin C was significantly associated with lower serum UA concentrations, after adjustment for smoking, BMI, intake of total energy, dairy protein, and alcohol, and other potential confounders (Table 2). We observed 2 plateaus for the inverse associations: the first was seen at 90–499 mg/day and then 500 mg/day and higher. Adjusted mean UA concentrations across total vitamin C intake categories were 6.4, 6.1, 6.0, 5.7, and 5.7 mg/dl (*p* for trend < 0.001). Greater vitamin C supplement intake was significantly associated with a lower serum UA (*p* for trend < 0.001). Although higher dietary vitamin C intake categories tended to have lower serum UA levels than the lowest category, the linear trend was not significant (*p* for trend = 0.10; Table 2). Of note, the range of dietary vitamin C exposure was substantially smaller than that of total or supplemental vitamin C intake. After excluding subjects with vitamin C supplement intake, we observed a similar nonlinear pattern with dietary vitamin C intake. Further adjustment for beer intake did not materially change the associations between vitamin C intake and UA concentrations.

The results of logistic regression with hyperuricemia (serum UA > 6 mg/dl) as a dichotomous outcome were similar (Figure 1A). Multivariate OR for hyperuricemia across total vitamin C intake categories were 1 (reference), 0.58, 0.57, 0.38, and 0.34 (95% CI 0.20–0.58; *p* for trend < 0.001). The cubic spline curve (Figure 1B) showed a similar pattern for the association between total vitamin C and hyperuricemia. A similar inverse association persisted with supplementary vitamin C intake (*p* for trend < 0.001), but not with dietary vitamin C intake (*p* for trend = 0.15). An alternative definition of hyperuricemia (serum UA > 7 mg/dl)¹⁶ resulted in similar significant results. The multivariate OR for the highest versus lowest categories of total vitamin C intake was 0.31 (95% CI 0.17–0.56, *p* for trend = 0.009).

Significant associations between vitamin C intake and UA concentrations did not change materially after excluding subjects with gout or those not Caucasian. When we used

Table 1. Characteristics according to vitamin C intake in a subsample of the Health Professionals Followup Study in 1994 (n = 1387). Data are mean unless indicated otherwise.

| Characteristic | Total Vitamin C Intake, mg/day | | | | |
|----------------------------------|--------------------------------|--------|---------|---------|--------|
| | < 90 | 90–249 | 250–499 | 500–999 | ≥ 1000 |
| No. | 96 | 605 | 245 | 214 | 227 |
| Dietary vitamin C intake, mg/day | 72.0 | 145 | 204 | 180 | 181 |
| Use of vitamin C supplement, % | 8.5 | 38.1 | 81.2 | 99.4 | 100 |
| Vitamin C supplement, mg/day | 1.2 | 20.8 | 131 | 513 | 1263 |
| Age, yrs | 59.3 | 61.2 | 61.7 | 61.6 | 60.7 |
| Current smokers, % | 12.5 | 5.1 | 3.7 | 4.2 | 5.8 |
| Past smokers, % | 50.0 | 45.7 | 40.5 | 47.8 | 51.6 |
| BMI, kg/m ² | 25.4 | 25.0 | 24.9 | 25.0 | 24.8 |
| Caucasian, % | 95.1 | 90.9 | 91.0 | 92.0 | 90.9 |
| Systolic blood pressure, mm Hg | 125 | 124 | 123 | 123 | 122 |
| Presence of gout, % | 4.1 | 2.8 | 4.3 | 2.7 | 3.6 |
| Use of aspirin, % | 24.1 | 35.2 | 40.9 | 55.9 | 46.6 |
| Total energy intake, kcal/day | 1839 | 2053 | 2106 | 2104 | 1954 |
| Alcohol intake, g/day | 11.3 | 13.0 | 11.0 | 12.1 | 12.0 |
| Fructose intake, g/day | 17.7 | 24.5 | 28.6 | 27.0 | 28.2 |
| Dairy protein intake, g/day | 15.2 | 15.4 | 14.6 | 15.7 | 13.5 |
| Total meat intake, servings/day | 1.4 | 1.3 | 1.2 | 1.1 | 1.1 |
| Seafood intake, servings/day | 0.26 | 0.30 | 0.31 | 0.33 | 0.36 |
| Coffee intake, cups/day | 2.6 | 2.0 | 1.8 | 2.1 | 2.0 |

Table 2. Serum uric acid concentration according to total, dietary, and supplement vitamin C intake (1994) in a subsample of the Health Professional Followup study (n = 1387). Data are mean ± SD.

| | Serum Uric Acid Concentration, mg/dl | | | | | P _{trend} |
|---|--------------------------------------|-------------|--------------|---------------|---------------|--------------------|
| | < 90 | 90–249 | 250–499 | 500–999 | ≥ 1000 | |
| Total vitamin C intake, mg/day | < 90 | 90–249 | 250–499 | 500–999 | ≥ 1000 | |
| n | 96 | 605 | 245 | 214 | 227 | |
| Age-and BMI-adjusted | 6.3 ± 0.1 | 6.1 ± 0.05 | 6.1 ± 0.08 | 5.7 ± 0.08*** | 5.8 ± 0.08** | < 0.001 |
| Multivariate [†] | 6.4 ± 0.1 | 6.1 ± 0.05* | 6.0 ± 0.08* | 5.7 ± 0.08*** | 5.7 ± 0.08*** | < 0.001 |
| Vitamin C supplement, mg/day | 0 | 1–249 | 250–499 | 500–999 | ≥ 1000 | |
| n | 509 | 405 | 105 | 165 | 203 | |
| Age-and BMI-adjusted | 6.2 ± 0.05 | 6.0 ± 0.06 | 5.8 ± 0.12* | 5.8 ± 0.09** | 5.8 ± 0.08*** | < 0.001 |
| Multivariate [†] | 6.2 ± 0.05 | 6.0 ± 0.06 | 5.8 ± 0.12** | 5.8 ± 0.09*** | 5.7 ± 0.08*** | < 0.001 |
| Dietary vitamin C, mg/day | < 50 | 50–99 | 100–199 | 200–299 | ≥ 300 | |
| n | 26 | 241 | 791 | 271 | 58 | |
| Age-and BMI-adjusted | 6.6 ± 0.24 | 6.0 ± 0.07* | 6.0 ± 0.04* | 6.0 ± 0.07* | 6.1 ± 0.16 | 0.49 |
| Multivariate [†] | 6.6 ± 0.24 | 6.1 ± 0.08 | 6.0 ± 0.04* | 6.0 ± 0.08* | 5.9 ± 0.17 | 0.10 |
| Excluding vitamin C supplement users [†] | 6.9 ± 0.36 | 6.3 ± 0.13 | 6.2 ± 0.07 | 6.0 ± 0.13 | 6.2 ± 0.29 | 0.12 |

[†] Adjusted for age (years), smoking status (never smoker, past smoker, or current smoker: 1–14 or ≥ 15 cigarettes/day), BMI (< 23, 23–24.9, 25–26.9, 27–28.9, or ≥ 29 kg/m²), ethnicity (Caucasian vs others), systolic blood pressure (< 105, 105–114, 115–124, or ≥ 125 mm Hg), presence of gout (yes/no), use of aspirin (yes/no), total energy (kcal/day), meat (servings/day), seafood (servings/day), dairy protein (g/day), fructose (g/day), alcohol (0, < 5, 5–9, 10–14, 15–29, 30–49, or ≥ 50 g/day), and coffee (0, < 1, 1–3, 4–5, or ≥ 6 cups/day). * p < 0.05, ** p < 0.01, *** p < 0.001.

the average of diets in 1986 and 1990, we found similar results. Total vitamin C data were inversely associated with serum UA concentrations (p for trend = 0.002) and hyperuricemia (p for trend = 0.02).

We found no significant interactions between vitamin C and age, alcohol intake, smoking status, and BMI (p for interaction > 0.1 for all). The inverse association between vitamin C intake and serum UA concentration persisted in

subgroup analysis according to age, smoking, overweight, and alcohol intakes (Table 3).

DISCUSSION

In men without hypertension and BMI < 30 kg/m², we found intakes of vitamin C to be inversely related to serum UA concentrations, independent of dietary and other risk factors for gout such as BMI, age, and alcohol intake. The associa-

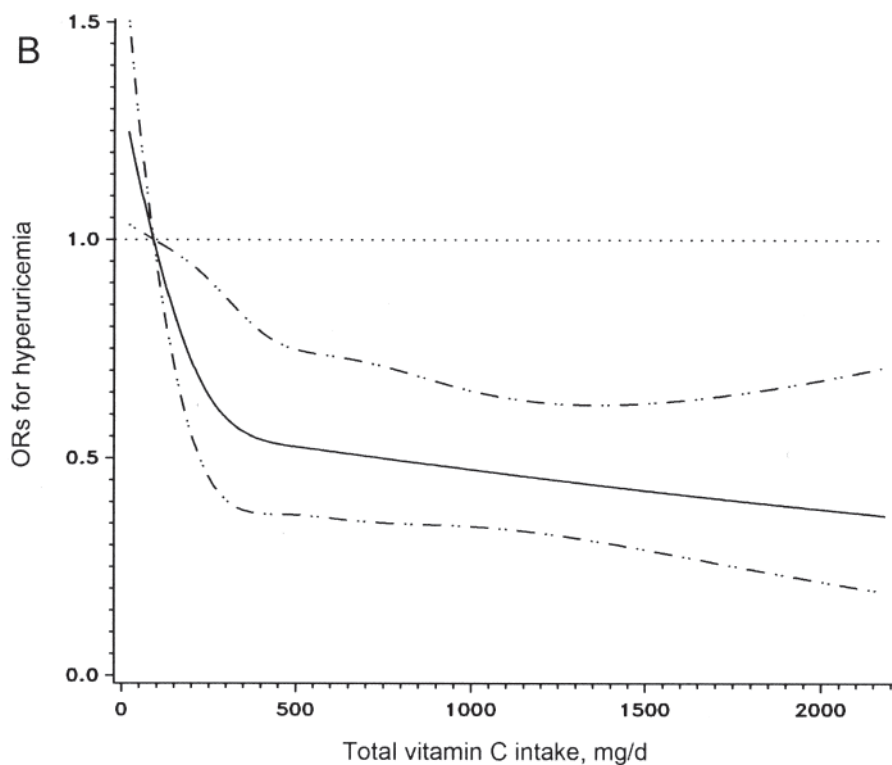
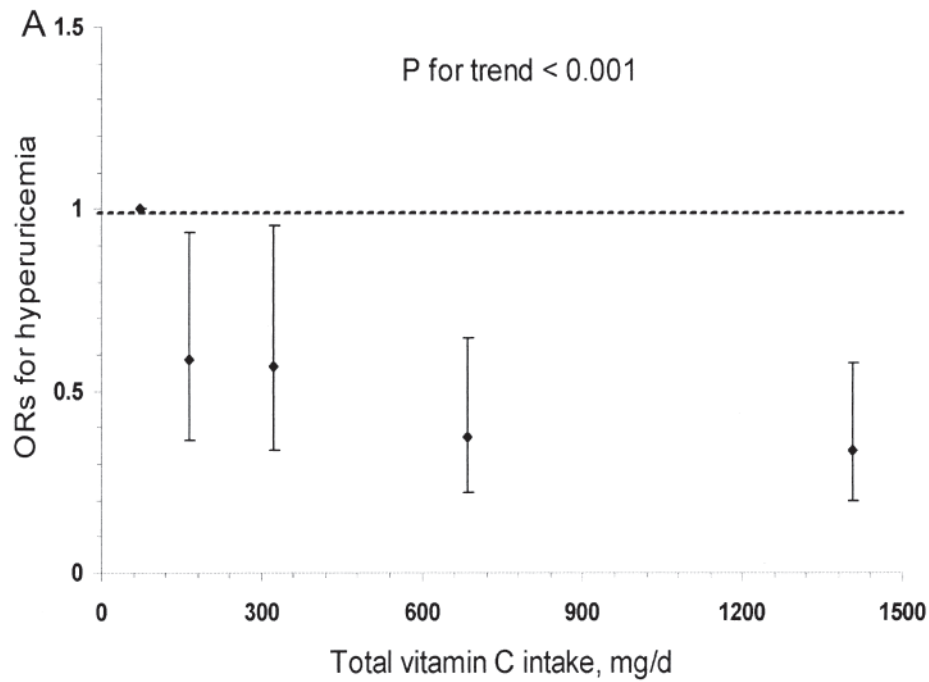


Figure 1. Odds ratio and 95% CI of hyperuricemia (serum uric acid > 6 mg/dl) according to total vitamin C intake category. A. Logistic regression model with the lowest intake category (< 90 mg/day) as the reference group. B. Cubic spline logistic model with 90 mg/day as the reference group (95% CI indicated by broken lines). Both models were adjusted for age (years), smoking status (never smoker, past smoker, or current smoker: 1–14 or ≥ 15 cigarettes/day), BMI (< 23, 23–24.9, 25–26.9, 27–28.9, ≥ 29 kg/m²), ethnicity (Caucasian vs others), systolic blood pressure (< 105, 105–114, 115–124, ≥ 125 mm Hg), presence of gout (yes/no), use of aspirin (yes/no), total energy (kcal/day), dairy protein (g/day), fructose (g/day), alcohol (0, < 5, 5–9, 10–14, 15–29, 30–49, ≥ 50 g/day), and coffee (0, < 1, 1–3, 4–5, ≥ 6 cups/day).

Table 3. Serum uric acid concentration according to total vitamin C intake (1994) in a subsample of the Health Professional Followup study (n = 1387), stratified by age, smoking status, BMI, and alcohol intake[†].

| | Serum Uric Acid Concentration, mg/dl, mean ± SE | | | | | P _{trend} |
|--------------------------------|---|------------|-------------|---------------|---------------|--------------------|
| | < 90 | 90–249 | 250–499 | 500–999 | ≥ 1000 | |
| Total vitamin C intake, mg/day | | | | | | |
| Age, yrs | | | | | | |
| < 60 | 6.3 ± 0.17 | 6.1 ± 0.07 | 6.1 ± 0.12 | 5.8 ± 0.13 | 5.8 ± 0.12 | 0.02 |
| ≥ 60 | 6.5 ± 0.18 | 6.2 ± 0.07 | 6.0 ± 0.10* | 5.7 ± 0.11*** | 5.7 ± 0.11*** | < 0.001 |
| Smoking | | | | | | |
| Never | 6.2 ± 0.20 | 6.0 ± 0.07 | 6.0 ± 0.10 | 5.6 ± 0.12 | 5.8 ± 0.12 | 0.05 |
| Ever | 6.6 ± 0.16 | 6.2 ± 0.07 | 6.1 ± 0.12 | 5.8 ± 0.11*** | 5.7 ± 0.11*** | < 0.001 |
| BMI, kg/m ² | | | | | | |
| < 25 | 6.1 ± 0.20 | 5.9 ± 0.07 | 5.8 ± 0.10 | 5.6 ± 0.11* | 5.5 ± 0.11* | 0.05 |
| ≥ 25 | 6.6 ± 0.17 | 6.3 ± 0.07 | 6.3 ± 0.12 | 5.9 ± 0.12** | 6.0 ± 0.12** | 0.01 |
| Alcohol intake, g/day | | | | | | |
| None | 6.0 ± 0.22 | 5.9 ± 0.10 | 5.6 ± 0.17 | 5.4 ± 0.18 | 5.6 ± 0.17 | 0.12 |
| > 0 | 6.5 ± 0.16 | 6.2 ± 0.06 | 6.2 ± 0.09 | 5.8 ± 0.09*** | 5.8 ± 0.09*** | 0.002 |

[†] Adjusted for age (years), smoking status (never smoker, past smoker, or current smoker: 1–14 or ≥ 15 cigarettes/day), BMI (< 23, 23–24.9, 25–26.9, 27–28.9, or ≥ 29 kg/m²), ethnicity (Caucasian vs others), systolic blood pressure (< 105, 105–114, 115–124, or ≥ 125 mm Hg), presence of gout (yes/no), use of aspirin (yes/no), total energy (kcal/day), meat (servings/day), seafood (servings/day), dairy protein (g/day), fructose (g/day), alcohol (0, < 5, 5–9, 10–14, 15–29, 30–49, or ≥ 50 g/day), and coffee (0, < 1, 1–3, 4–5, or ≥ 6 cups/day). * p < 0.05, ** p < 0.01, *** p < 0.001, relative to the lowest intake category.

tions were largely derived by vitamin C supplement use. Further, we observed similar significant associations when we used dietary exposure data, which were assessed 4–8 years before blood collection, as predictors.

Our results showed that total vitamin C intake ≥ 500 mg/day is associated with a ~0.6–0.7 mg/dl lower level of serum UA relative to those with intake < 90 mg/day. The magnitude of difference of serum UA associated with total vitamin C intake of 500 mg/day was closely in agreement with that from a recent trial⁶. That randomized trial showed that supplementation with vitamin C as low as 500 mg/day for 2 months reduced serum UA by 0.5 mg/dl, compared to no change in the placebo group⁶. This level of population mean difference of serum UA levels^{17,18} can be translated into a clinically relevant difference in the risk for incident gout, as we have reported^{19,20}. For example, one daily serving increase in beer intake was associated with a mean serum UA level increase of 0.4 mg/dl in the cross-sectional analysis of the National Health and Nutrition Examination Survey III¹⁷, and with a 50% increased risk of incident gout in our prospective analysis of the HPFS¹⁹. This potentially significant effect on the eventual risk of gout is also supported by our results, using hyperuricemia as a dichotomous outcome. Nevertheless, prospective studies with outcome of incident gout would be valuable.

Vitamin C likely modulates serum UA concentration through its uricosuric effect. Vitamin C and UA are reabsorbed through anion-exchange transport in the proximal tubule⁶. Increased vitamin C concentration in the filtrate may competitively inhibit UA reabsorption⁵. Recent advances in understanding of the molecular mechanisms of renal UA transport suggest that the uricosuric effect may be

through cis-inhibition of URAT1 (uric acid transporter 1, the key target of typical uricosurics)²¹, Na⁺-dependent anion cotransporter (e.g., SLC5A8/A12)²², or both in the proximal tubules²³. Further, greater vitamin C intake may possibly improve renal function and increase the glomerular filtration rate^{6,24,25}, providing another potential mechanism for the uricosuric effect of vitamin C. Human and animal studies have shown that administration of vitamin C increases renal plasma flow and glomerular filtration rate and attenuates increases in arterial pressure^{24,26}. The antioxidant property of vitamin C could reduce oxidative stress and inflammation and could, therefore, be related to lower UA synthesis¹⁶.

Strengths of our study include use of a validated food frequency questionnaire to assess dietary intake and multiple measurements of dietary exposure. Besides assessment of dietary intake in 1994 as the predictor of serum UA, we conducted a sensitivity analysis using average dietary intake recorded in 1986 and 1990. In this way we may reduce random errors introduced by a single dietary measurement, and, because of both dietary assessments prior to blood collection, minimize misclassification of exposure (vitamin C intake) due to change of diet related to high serum UA. We observed similar results with the main analyses, suggesting robustness of our findings. Our study population consisted of participants without hypertension and with BMI < 30 kg/m², limiting the generalizability of our findings. Our study is also limited by including only men; thus the effect of gender could not be studied. Another limitation is that our cohort did not represent random samples of US men, therefore the dietary patterns cannot be taken to reflect the general population. Nevertheless, the biological effects of diet in this cohort should be the same as those among men in

general. Although validation studies suggested a high level of validity in vitamin C intake measured by the food frequency questionnaire used in our study^{9,10}, measurement of plasma vitamin C concentration could provide a more accurate estimate of vitamin C status. Further, because of the observational design of our study, we cannot exclude a possibility of residual confounding due to unmeasured confounders. For example, lack of information on use of gout-specific medicines may confound the association between vitamin C and UA concentration. However, we obtained similar results after excluding patients with gout.

We found that that intake of vitamin C is inversely associated with serum uric acid concentrations in a population-based study. These findings support a potential role for vitamin C in the prevention of hyperuricemia and gout. Our findings are most directly generalizable to men aged 50 years or older without hypertension and obesity. Corresponding studies of men with these conditions and of women would be valuable.

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