ARTHRITIS & RHEUMATISM
Vol. 52, No. 6, June 2005, pp 1843–1847
DOI 10.1002/art.21105


# The Effects of Vitamin C Supplementation on Serum Concentrations of Uric Acid

## Results of a Randomized Controlled Trial

Han-Yao Huang,[1] Lawrence J. Appel,[1] Michael J. Choi,[1] Allan C. Gelber,[1] Jeanne Charleston,[1] Edward P. Norkus,[2] and Edgar R. Miller, III[1]

***Objective.*** **Reductions in serum uric acid levels are clinically relevant. Previous studies have suggested a uricosuric effect of vitamin C. Whether vitamin C reduces serum uric acid is unknown. We undertook this study to determine the effects of vitamin C supplementation on serum uric acid concentrations.**

***Methods.*** **The study was a double-blinded placebo-controlled randomized trial conducted in research units affiliated with an academic institution. Study participants were 184 nonsmokers, randomized to take either placebo or vitamin C supplements (500 mg/day) for 2 months.**

***Results.*** **At the end of the study period, serum uric acid levels were significantly reduced in the vitamin C group (mean change −0.5 mg/dl [95% confidence interval −0.6, −0.3]), but not in the placebo group (mean change 0.09 mg/dl [95% confidence interval −0.05, 0.2]) ($P < 0.0001$). The same pattern of results was evident in subgroups defined by age, sex, race, body mass index, chronic illness, diuretic use, and quartiles of baseline serum ascorbic acid levels. In the subgroups, from the lowest to the highest quartile of baseline serum uric acid, net mean changes (95% confidence intervals) in serum uric acid with vitamin C supplementation were −0.4 (−0.8, 0.01), −0.5 (−0.9, −0.2), −0.5 (−0.8, −0.2), and −1.0 (−1.6, −0.4) mg/dl ($P = 0.06$, 0.005, 0.003, and 0.002, respectively). Compared with placebo, vitamin C increased the estimated glomerular filtration rate.**

***Conclusion.*** **Supplementation with 500 mg/day of vitamin C for 2 months reduces serum uric acid, suggesting that vitamin C might be beneficial in the prevention and management of gout and other urate-related diseases.**

Vitamin C is an essential micronutrient that participates in a number of important enzymatic reactions. It also acts as a nonenzymatic, water-soluble antioxidant to prevent oxidative damage by free radicals and reactive oxygen and nitrogen species. The purported but largely unproven health benefits of vitamin C include reduced susceptibility to and duration of the common cold, and reduced risk of cardiovascular disease, cancer, and other degenerative diseases.

Previous studies (1–4) suggest that vitamin C exerts a uricosuric effect that may be beneficial. By increasing urinary excretion of uric acid, vitamin C may reduce serum concentrations of uric acid that at high levels could become crystallized in the joint and kidney and lead to gout and kidney stones. However, these studies were small, of short duration, and used exceptionally high doses of vitamin C (1-time ingestion of 3–12 gm for some days). If confirmed, the uricosuric effect of vitamin C may have important implications for the prevention and management of gout and other urate-related diseases. However, the effect of vitamin C supplementation on serum uric acid levels has not been well documented.

We performed secondary analyses in a 2 × 2 factorial trial of vitamin C and vitamin E supplementa-

Supported by the NIH (grant RR-00722 from the National Center for Research Resources).

[1]Han-Yao Huang, PhD, Lawrence J. Appel, MD, Michael J. Choi, MD, Allan C. Gelber, MD, PhD, Jeanne Charleston, RN, Edgar R. Miller, III, MD, PhD: Johns Hopkins University, Baltimore, Maryland; [2]Edward P. Norkus, PhD: Our Lady of Mercy Medical Center, Bronx, New York.

Address correspondence and reprint requests to Han-Yao Huang, PhD, Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, 615 N. Wolfe Street, E-6144, Baltimore, MD 21205-2223. E-mail: hyhuang@jhsph.edu.

Submitted for publication October 4, 2004; accepted in revised form March 14, 2005.

tion designed to test for the effects of these vitamins on in vivo lipid peroxidation (5). Since there was no previously assumed biologic rationale to support a potential effect of vitamin E on serum uric acid, and because vitamin E had neither a main effect nor an interactive effect with vitamin C on serum uric acid levels in this trial, we report findings on the effects of vitamin C across the vitamin E and corresponding placebo groups.

## SUBJECTS AND METHODS

The Institutional Review Boards of the Johns Hopkins Medical Institutions approved the trial protocol. All participants provided written informed consent prior to study enrollment.

**Study population.** A total of 184 adult nonsmokers were recruited from the metropolitan area of Baltimore, Maryland. Inclusion criteria were willingness to provide written informed consent and to take study pills, but no other vitamin supplements, for 2 months. Exclusion criteria were regular exposure to passive tobacco smoke for ≥1 hour per day or consumption of ≥14 servings of alcoholic beverages per week. Persons who regularly consumed vitamin supplements were eligible after a 2-month period of supplement abstinence.

**Conduct of the trial.** Participants had 2 in-person visits to ascertain eligibility and to provide baseline data, including a 12-hour fasting blood sample and a food frequency questionnaire. Eligible persons were randomly assigned to 1 of the 4 supplementation groups: 1) placebo (dicalcium phosphate 380 mg/day and soybean oil 500 mg/day), 2) vitamin C and placebo (500 mg ascorbate/day and soybean oil 500 mg/day), 3) vitamin E and placebo (400 IU RRR-$\alpha$-tocopheryl acetate/day and dicalcium phosphate 380 mg/day), and 4) vitamin C and vitamin E (500 mg ascorbate/day and 400 IU RRR-$\alpha$-tocopheryl acetate/day). Participants, data collectors, and laboratory technicians were blinded with regard to group assignment. The vitamin C supplements and corresponding placebo tablets were purchased from Consolidated Midland (Brewster, NY). The vitamin E capsules and corresponding placebo capsules were donated by Henkel (LaGrange, IL). Participants were instructed to take 2 types of supplements (vitamin C or placebo, and vitamin E or placebo) each day, and to avoid taking any other supplements during the trial period. Adherence to pill-taking was assessed by pill counts (observed/expected number of pills taken × 100%).

Two months after randomization, 12-hour fasting blood samples were collected again. The blood samples were allowed to clot for no more than 15 minutes after collection, and were then centrifuged at 2,000*g* for 15 minutes at room temperature. Serum uric acid and creatinine were analyzed on the day of blood collection. Serum specimens were portioned and stored at −70°C until assayed for ascorbic acid. Estimated glomerular filtration rate (GFR) was calculated according to the modified Modification of Diet in Renal Disease equation: $186 \times (\text{serum creatinine in mg/dl})^{-1.154} \times \text{age}^{-0.203} \times 0.742$ (if female) × 1.21 (if African American) (6).

**Laboratory assays.** A Hitachi 917 autoanalyzer obtained from Roche Diagnostics (Mannheim, Germany) was used to measure uric acid and creatinine. Ascorbic acid is known to interfere with the measurement of uric acid by redox reaction–based colorimetric methods (4) or by uricase/peroxidase-based methods (7). In our analysis, serum samples were initially incubated with a reagent mixture that contained ascorbate oxidase to remove ascorbic acid (≤1,703 $\mu$moles/liter). Uric acid in serum was oxidized by uricase to form allantoin and $H_2O_2$. In the presence of peroxidase, $H_2O_2$ reacts with *N*-ethyl-*N*-(2-hydroxy-3-sulfopropyl)-3-methylaniline and 4-aminophenazone to form quinonelmine dye. Creatinine in serum was digested in order by creatininase, creatinase, and sarcosine oxidase to form $H_2O_2$, which, in the presence of peroxidase, reacted with 3-hydroxy-2,4,6-triiodobenzoic acid and 4-aminophenazone to produce red dye. Serum ascorbic acid was measured based on the reduction of $Fe^{3+}$ to $Fe^{2+}$ by ascorbic acid, followed by chromogenic chelation of $Fe^{2+}$ with ferrozine (8).

**Statistical analysis.** The differences in characteristics between the participants in the placebo and active vitamin C groups were analyzed by *t*-test or Wilcoxon rank sum test for continuous variables and by chi-square test for categorical variables. For each outcome variable, linear regression was used to estimate the effects of vitamin C supplementation. Subgroup analyses with linear regression were performed according to age (above versus below the median age of 62 years), sex, race (white versus African American), body mass index (BMI) (≤25 versus >25 kg/m$^2$), chronic illness (presence versus absence of hypertension, diabetes mellitus, and/or hypercholesterolemia), diuretic use (yes versus no), quartiles of baseline uric acid concentrations (cutoff points at 4.2, 5.0, and 6.4 mg/dl), quartiles of baseline ascorbic acid concentrations (cutoff points at 52.8, 61.9, and 72.7 $\mu$moles/liter), and hyperuricemia (baseline serum uric acid >7 versus ≤7 mg/dl). Two-sided *P* values less than 0.05 were considered significant.

## RESULTS

Of the 318 individuals screened, 184 were randomized for inclusion in the study. Loss of interest was the main reason for nonenrollment. Baseline characteristics and dietary intake of protein, purine-rich food, and dairy products were similar in the placebo and active vitamin C groups, except for a higher proportion of African Americans in the placebo group (Table 1). Men had higher serum uric acid levels than women (mean ± SD 5.9 ± 1.2 versus 4.6 ± 1.4 mg/dl; $P < 0.0001$). Persons with chronic illnesses had higher uric acid levels than persons with no chronic illnesses (mean ± SD 5.4 ± 1.3 versus 4.7 ± 1.4 mg/dl; $P = 0.003$).

Followup rates and adherence to pill-taking were high, and did not differ by supplement group. Ninety-two percent of the subjects completed 2 months of supplementation, and 93% took ≥90% of study pills assigned. Compared with the placebo group, serum concentrations of ascorbic acid were significantly in-

**Table 1.** Baseline characteristics of the study participants, by supplementation group

| Characteristic | Supplementation group | |
|---|---|---|
| | Placebo (n = 92) | Vitamin C (n = 92) |
| Age, mean ± SD years | 56.8 ± 14.1 | 59.5 ± 13.2 |
| Women, % | 56.5 | 54.4 |
| Race, %* | | |
| African American | 59.8 | 40.2 |
| White | 35.9 | 55.4 |
| Other | 4.3 | 4.4 |
| Education beyond high school, % | 72.1 | 82.6 |
| Body mass index, mean ± SD kg/m$^2$ | 28.8 ± 5.0 | 28.8 ± 5.7 |
| Diuretic use, % | 12 | 7 |
| Hypertension, % | 53 | 47 |
| Chronic illness, %† | 63.0 | 66.3 |
| Alcohol consumption, % | | |
| None | 56.5 | 54.4 |
| <2 drinks/day | 43.5 | 45.6 |
| Prior vitamin C supplement use, % | 7.5 | 15.0 |
| Dietary intake, median (interquartile range)‡ | | |
| Vitamin C, mg/day | 139.5 (77.0, 178.0) | 132.0 (90.0, 169.0) |
| Vitamin E, α-TE/day | 6.6 (5.3, 10.5) | 7.1 (4.8, 12.0) |
| Protein, gm/day | 48.7 (37.5, 70.3) | 53.6 (38.0, 75.3) |
| Fruits/vegetables, servings/day | 3.4 (2.2, 5.5) | 3.8 (2.5, 5.2) |
| High-purine food, servings/day§ | 1.0 (0.7, 1.7) | 1.0 (0.7, 1.6) |
| Moderate-purine food, servings/day¶ | 1.2 (0.7, 1.7) | 1.2 (0.8, 1.7) |
| Dairy products, servings/day | 0.7 (0.3, 1.3) | 0.9 (0.5, 1.5) |
| Serum creatinine, mean ± SD mg/dl | 1.0 ± 0.2 | 1.0 ± 0.3 |

* $P = 0.02$ for the difference in distribution between groups, by chi-square test.
† Hypertension, diabetes mellitus, and/or hypercholesterolemia.
‡ Measured by food frequency questionnaire; α-TE = α-tocopherol equivalents.
§ Intake of beef, pork, chicken, liver, seafood, and turkey, calculated as frequency (none or <1/month, 1/month, 2–3/month, 1/week, 2/week, 3–4/week, 5–6/week, 1/day, and 2+/day were coded as 0, 0.0357, 0.0893, 0.143, 0.286, 0.5, 0.786, 1, and 2, respectively) multiplied by serving size (large, medium, and small size were coded as 1.5, 1, and 0.5, respectively, as instructed on the food frequency questionnaire).
¶ Intake of peas, beans, chili, broccoli, cauliflower, spinach, cole slaw, coffee, and tea, calculated as frequency (none or <1/month, 1/month, 2–3/month, 1/week, 2/week, 3–4/week, 5–6/week, 1/day, and 2+/day were coded as 0, 0.0357, 0.0893, 0.143, 0.286, 0.5, 0.786, 1, and 2, respectively) multiplied by serving size (large, medium, and small size were coded as 1.5, 1, and 0.5, respectively, as instructed on the food frequency questionnaire).

creased at the end of the supplementation period in the active vitamin C group ($P < 0.0001$) (Table 2).

As anticipated, there was neither a main effect of vitamin E on serum uric acid (main effect −0.08 [95% confidence interval −0.28, 0.11]; $P = 0.40$) nor an interactive effect of vitamin E and vitamin C ($P$ for interaction = 0.94). At the end of the supplementation period, the serum uric acid concentration was significantly reduced in the active vitamin C group, but not in the placebo group ($P < 0.0001$) (Table 2). This result persisted after adjustment for age, sex, and baseline serum concentrations of ascorbic acid and uric acid. Changes in serum uric acid were inversely correlated with changes in serum ascorbic acid (Pearson's correlation coefficient −0.29 [$P < 0.0001$] and −0.32 [$P = 0.0002$] in the total group and in the vitamin C group, respectively). Estimated GFR was increased in the vitamin C group (Table 2).

Reductions in serum uric acid with vitamin C supplementation were statistically significant in the subgroups defined by age, sex, race, BMI, chronic illnesses, diuretic use, quartiles of baseline serum uric acid levels, and quartiles of baseline serum ascorbic acid levels (Table 3). Among persons who were hyperuricemic at baseline (baseline serum uric acid >7 mg/dl; n = 21), vitamin C supplementation reduced serum uric acid by a mean of 1.5 mg/dl ($P = 0.0008$, adjusted for age, sex, and baseline serum uric acid and ascorbic acid concentrations).

## DISCUSSION

In this randomized controlled trial, supplementation with vitamin C at 500 mg/day for 2 months reduced serum concentrations of uric acid. This finding was remarkably consistent across subgroups defined by age, sex, race, BMI, chronic illnesses, diuretic use, quartiles of baseline serum uric acid, and quartiles of baseline serum ascorbic acid. Changes in serum uric acid were inversely correlated with changes in serum ascorbic acid.

Strengths of this trial include the randomized, placebo-controlled study design. High rates of followup and of participant adherence to pill-taking enhance the internal validity of the study. The extent and internal consistency of the trial findings reduce the chance of a Type I error (false-positive results). Also, a demographically heterogeneous sample (55% women, 50% African American) was enrolled; therefore, results should be applicable to the general adult population. We did not determine the impact of long-term vitamin C supplement use on clinical end points that are associated with uric acid. In addition, the trial only tested vitamin C at one dosage level. These limitations warrant further investigation.

The mechanisms by which vitamin C reduced

**Table 2.** Mean baseline levels and mean change from baseline to the end of supplementation in serum concentrations of ascorbic acid and uric acid levels, and estimated GFR by supplementation group*

| Measure | Supplementation group | | Unadjusted difference in mean change | Adjusted difference in mean change† |
|---|---|---|---|---|
| | Placebo | Vitamin C | | |
| Serum ascorbic acid, μmoles/liter | | | | |
| Baseline, mean ± SD | 60.0 ± 16.7 | 64.4 ± 14.1 | | |
| Mean change (95% CI) | 1.2 (−2.1, 4.5) | 21.3 (14.7, 27.9) | 20.2 (13.0, 27.4)‡ | 21.5 (14.8, 28.2)‡ |
| Serum uric acid, mg/dl | | | | |
| Baseline, mean ± SD | 5.1 ± 1.5 | 5.2 ± 1.4 | | |
| Mean change (95% CI) | 0.09 (−0.05, 0.2) | −0.5 (−0.6, −0.3) | −0.6 (−0.8, −0.4)‡ | −0.5 (−0.7, −0.3)‡ |
| GFR, ml/min/1.73 $m^2$§ | | | | |
| Baseline, mean ± SD | 78.1 ± 17.1 | 74.7 ± 15.0 | | |
| Mean change (95% CI) | 0.4 (−2.6, 3.5) | 4.8 (1.5, 8.0) | 4.0 (0.5, 7.4)¶ | 3.5 (0.3, 6.8)# |

* GFR = glomerular filtration rate; 95% CI = 95% confidence interval.
† Mean change in serum ascorbic acid was adjusted for age, sex, and baseline ascorbic acid levels. Mean change in serum uric acid was adjusted for age, sex, baseline ascorbic acid levels, and baseline uric acid levels. Mean change in GFR was adjusted for age, sex, race, baseline ascorbic acid, and estimated GFR.
‡ $P < 0.0001$.
§ Estimated according to the modified Modification of Diet in Renal Disease equation.
¶ $P = 0.02$.
# $P = 0.03$.

**Table 3.** Effects of vitamin C supplementation on serum uric acid by subgroup*

| Subgroup | Placebo | | | Vitamin C | | | Net change, mean (95% CI)† | *P*† |
|---|---|---|---|---|---|---|---|---|
| | n | Baseline mean ± SD | Within-group change, mean (95% CI) | n | Baseline mean ± SD | Within-group change, mean (95% CI) | | |
| Age, years | | | | | | | | |
| <62 | 51 | 4.8 ± 1.5 | 0.09 (−0.1, 0.3) | 38 | 5.2 ± 1.5 | −0.5 (−0.7, −0.3) | −0.6 (−0.9, −0.3) | 0.0003 |
| ≥62 | 41 | 5.4 ± 1.4 | 0.07 (−0.1, 0.3) | 54 | 5.3 ± 1.4 | −0.4 (−0.6, −0.3) | −0.6 (−0.9, −0.3) | <0.0001 |
| Sex | | | | | | | | |
| Women | 52 | 4.7 ± 1.6 | −0.08 (−0.2, 0.07) | 50 | 4.5 ± 1.1 | −0.4 (−0.5, −0.2) | −0.4 (−0.6, −0.1) | 0.002 |
| Men | 40 | 5.7 ± 1.1 | 0.3 (0.05, 0.6) | 42 | 6.1 ± 1.3 | −0.6 (−0.8, −0.3) | −0.8 (−1.2, −0.5) | <0.0001 |
| Race | | | | | | | | |
| White | 33 | 5.4 ± 1.6 | 0.2 (−0.03, 0.5) | 51 | 5.4 ± 1.4 | −0.6 (−0.8, −0.3) | −0.8 (−1.2, −0.4) | <0.0001 |
| African American | 55 | 5.0 ± 1.4 | −0.01 (−0.2, 0.2) | 37 | 5.2 ± 1.5 | −0.3 (−0.6, −0.1) | −0.3 (−0.6, −0.1) | 0.01 |
| BMI, $kg/m^2$ | | | | | | | | |
| ≤25 | 22 | 4.3 ± 1.2 | −0.04 (−0.3, 0.3) | 22 | 4.9 ± 1.4 | −0.5 (−0.8, −0.2) | −0.4 (−0.9, 0.02) | 0.06 |
| >25 | 70 | 5.4 ± 1.5 | 0.1 (−0.01, 0.3) | 70 | 5.4 ± 1.4 | −0.5 (−0.6, −0.3) | −0.6 (−0.9, −0.4) | <0.0001 |
| Chronic illness‡ | | | | | | | | |
| No | 29 | 4.6 ± 1.6 | 0.08 (−0.2, 0.4) | 30 | 4.8 ± 1.3 | −0.4 (−0.6, −0.2) | −0.5 (−0.8, −0.2) | 0.005 |
| Yes | 63 | 5.3 ± 1.4 | 0.09 (−0.08, 0.3) | 62 | 5.5 ± 1.5 | −0.5 (−0.7, −0.3) | −0.6 (−0.9, −0.4) | <0.0001 |
| Diuretic use | | | | | | | | |
| No | 80 | 5.0 ± 1.5 | 0.09 (−0.1, 0.2) | 85 | 5.1 ± 1.4 | −0.5 (−0.6, −0.3) | −0.6 (−0.8, −0.3) | <0.0001 |
| Yes | 12 | 5.9 ± 1.4 | 0.09 (−0.4, 0.6) | 7 | 6.8 ± 0.9 | −0.6 (−1.2, −0.1) | −0.8 (−1.7, −0.03) | 0.04 |
| Uric acid§ | | | | | | | | |
| First | 24 | 3.3 ± 0.5 | 0.1 (−0.1, 0.4) | 21 | 3.6 ± 0.4 | −0.3 (−0.5, −0.06) | −0.4 (−0.8, 0.01) | 0.06 |
| Second | 17 | 4.6 ± 0.2 | 0.1 (−0.2, 0.4) | 26 | 4.6 ± 0.2 | −0.4 (−0.7, −0.2) | −0.5 (−0.9, −0.2) | 0.005 |
| Third | 29 | 5.5 ± 0.4 | −0.005 (−0.2, 0.2) | 20 | 5.5 ± 0.4 | −0.4 (−0.7, −0.2) | −0.5 (−0.8, −0.2) | 0.003 |
| Fourth | 22 | 7.2 ± 0.8 | 0.2 (−0.3, 0.6) | 25 | 7.2 ± 0.8 | −0.7 (−1.0, −0.3) | −1.0 (−1.6, −0.4) | 0.002 |
| Ascorbic acid¶ | | | | | | | | |
| First | 32 | 42.4 ± 7.9 | 0.1 (−0.1, 0.3) | 12 | 40.9 ± 5.6 | −0.4 (−0.8, −0.1) | −0.6 (−1.0, −0.2) | 0.008 |
| Second | 20 | 57.8 ± 2.8 | 0.1 (−0.1, 0.4) | 29 | 57.5 ± 3.0 | −0.4 (−0.6, −0.1) | −0.5 (−0.8, −0.2) | 0.006 |
| Third | 19 | 65.9 ± 3.0 | 0.2 (−0.1, 0.4) | 31 | 67.6 ± 3.5 | −0.6 (−0.8, −0.4) | −0.7 (−1.1, −0.4) | 0.0001 |
| Fourth | 21 | 80.0 ± 7.0 | 0.2 (−0.2, 0.6) | 20 | 83.6 ± 8.7 | −0.5 (−0.9, −0.04) | −0.6 (−1.2, −0.03) | 0.04 |

* 95% CI = 95% confidence interval; BMI = body mass index.
† Obtained from a linear regression model with adjustment for age, sex (not included in the sex subgroups), and baseline serum uric acid and ascorbic acid concentrations.
‡ Hypertension, diabetes mellitus, and/or hypercholesterolemia.
§ Quartiles of serum uric acid concentrations at baseline (cutoff points 4.2, 5.0, and 6.4 mg/dl).
¶ Quartiles of serum ascorbic acid concentrations at baseline (cutoff points 52.8, 61.9, and 72.7 μmoles/liter).

serum uric acid might include increased glomerular filtration and/or competition for renal reabsorption, i.e., vitamin C and uric acid are both reabsorbed via anion-exchange transport at proximal tubules (1,3). Possible reasons for an increase in glomerular filtration include an antioxidant effect that reduces microvascular ischemia in glomeruli and leads to increased blood flow at the site, dilation of afferent arterioles, and competition for reabsorption with ions such as sodium and potassium that exert osmotic effects.

Several lines of evidence suggest that changes in serum uric acid levels are clinically relevant. Although hyperuricemia alone is not sufficient to cause gout, a dose-response relationship between serum uric acid and the risk of developing gout is well documented (9). Preventive strategies against recurrent gout attacks include use of uricosuric drugs which increase renal excretion of uric acid, or use of allopurinol which inhibits xanthine oxidase and uric acid production.

Hyperuricemia may initiate or promote the progression of renal disease. Evidence for a possible causal link between hyperuricemia and renal disease comes from a remnant kidney model in rats, in which hyperuricemia induced systemic high blood pressure, proteinuria, renal dysfunction, and progressive glomerulosclerosis and interstitial fibrosis (10). In other studies, allopurinol administered to rats prevented hyperuricemia, systemic and glomerular hypertension, and arteriolopathy (11,12). Hyperuricemia was found to be associated with a significantly increased risk of renal insufficiency (13) and progression of IgA nephropathy (14,15) in humans.

In conclusion, supplementation with vitamin C at 500 mg/day for 2 months reduced serum uric acid concentration. This finding suggests that vitamin C might be beneficial in the prevention or management of gout and other urate-related diseases.

## ACKNOWLEDGMENTS

We would like to thank the trial participants for their sustained commitment and effort. We also thank the staff of the ProHealth Clinical Research Unit and of the Johns Hopkins Outpatient General Clinical Research Center for their assistance in conducting the trial.

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