Oxidative stress contributes to dopaminergic neuron degeneration in Parkinson’s disease. Urate, a potent antioxidant, could be neuroprotective. To determine whether higher plasma concentrations of urate predict a reduced risk of Parkinson’s disease, the authors conducted a nested case-control study among participants in the Health Professionals Follow-up Study, a cohort comprising over 18,000 men who provided blood samples in 1993–1995. Eighty-four incident cases of Parkinson’s disease were diagnosed through 2000, and each was randomly matched to two controls by year of birth, race, and time of blood collection. Rate ratios of Parkinson’s disease according to quartile of uricemia were estimated by use of conditional logistic regression. The mean urate concentration was 5.7 mg/dl among cases and 6.1 mg/dl among controls ($p = 0.01$). After adjustment for age, smoking, and caffeine, the rate ratio of Parkinson’s disease for the highest quartile of uricemia compared with the lowest was 0.43 (95% confidence interval: 0.18, 1.02; $p_{\text{trend}} = 0.017$). This association was stronger in analyses excluding cases diagnosed within 4 years (median) from blood collection (rate ratio = 0.17, 95% confidence interval: 0.04, 0.69; $p_{\text{trend}} = 0.010$). These results suggest that high plasma urate concentrations may decrease the risk of Parkinson’s disease, and they raise the possibility that interventions to increase plasma urate may reduce the risk and delay the progression of Parkinson’s disease.

Abbreviation: CI, confidence interval.

Plasma urate concentrations are low in most mammals, because of urate’s degradation by uricase. Several mutations in the gene encoding uricase during evolution, however, have resulted in the complete loss of a functional enzyme in apes and humans and a severalfold increase in uricemia. It has been proposed that this loss may reflect a beneficial effect of urate against aging, related to its ability to prevent the oxidative damage caused by reactive nitrogen and oxygen species (1). Because oxidative stress appears to play a key role in the progressive loss of dopaminergic neurons in the substantia nigra that characterizes Parkinson’s disease (2), urate could be an important determinant of disease susceptibility. The association between urate and risk of Parkinson’s disease has been investigated in only two previous prospective studies; in both, there was a trend suggesting that individuals with high serum urate have a lower risk of Parkinson’s disease, but these associations were either not significant or only marginally significant (3, 4), and whether urate predicts Parkinson’s disease risk remains uncertain. We have therefore conducted a nested case-control study among participants in the Health Professionals Follow-up Study to examine the a priori hypothesis that high plasma urate concentrations are associated with a reduced risk of Parkinson’s disease.
levels of urate predict a reduced risk of developing Parkinson’s disease.

**MATERIALS AND METHODS**

**Study population**

The Health Professionals Follow-up Study was established in 1986, when 51,529 male health professionals (dentists, optometrists, pharmacists, osteopaths, podiatrists, and veterinarians), aged 40–75 years, responded to a mailed questionnaire that included a comprehensive diet survey, in addition to questions on disease history and lifestyle (5). Participants are mostly White and of European ancestry. Follow-up questionnaires are mailed to participants every 2 years to update information on potential risk factors for chronic diseases and to ascertain whether major medical events have occurred. From April 1993 through August 1995, blood samples were collected from 18,018 participants in the Health Professionals Follow-up Study cohort. Participants were followed for incidence of Parkinson’s disease until the return of the 2002 questionnaire. Those with history of cancer or Parkinson’s disease before blood collection were excluded from the study. For each confirmed case of Parkinson’s disease, we randomly selected two controls among men who had no report of Parkinson’s disease and were alive at the time of the Parkinson’s disease diagnosis of their matched case. The controls were matched on year of birth, race (White/other), fasting status at blood draw (>8 hours vs. less or unknown), time of day of the blood draw in 2-hour intervals, and month and year of blood draw. The research herein was approved by the human subjects committees of the Brigham and Women’s Hospital and the Harvard School of Public Health.

**Case ascertainment**

Ascertainment of the Parkinson’s disease cases in this cohort has been described previously (6). In brief, after obtaining permission, we asked the treating neurologist of cohort participants who reported a new diagnosis of Parkinson’s disease (or internist if the neurologist did not respond) to complete a questionnaire to confirm the diagnosis of Parkinson’s disease and the certainty of the diagnosis or to send a copy of the medical record. A case was confirmed if a diagnosis of Parkinson’s disease was considered definite or probable by the treating neurologist or internist, or if the medical record included either a final diagnosis of Parkinson’s disease made by a neurologist or evidence at a neurologic assessment of at least two of the four cardinal signs of Parkinson’s disease (with one being rest tremor or bradykinesia), a progressive course, and the absence of unresponsiveness to levodopa (L-dopa) or other features suggesting an alternative diagnosis. The review of medical records was conducted by the investigators, blind to the exposure status. Overall, the diagnosis was confirmed by the treating neurologist in 82 percent of the cases, by review of the medical records in 6 percent, and the rest by the treating internist without further support. Because the diagnosis of idiopathic Parkinson’s disease remains essentially clinical, the certainty of diagnosis was left to the judgment of the clinician, which has been found to be highly reliable (7). Deaths in the cohort were reported by family members, coworkers, or postal authorities, or they were identified by searching the National Death Index. If Parkinson’s disease was listed as a cause of death on the death certificate, we requested permission from the family to contact the treating neurologist or physician and followed the same procedure as for the nonfatal cases.

**Assessment of exposure**

The blood samples were returned to our laboratory via overnight courier; over 95 percent of the samples arrived within 24 hours of being drawn. Upon arrival in our laboratory, the blood samples were centrifuged, and blood components were aliquoted into cryotubes and stored in the vapor phase of liquid nitrogen freezers. The concentration of urate was determined by a colorimetric enzyme assay on a Hitachi 911 analyzer (Roche Diagnostics, Indianapolis, Indiana). The day-to-day variabilities of the assay at concentrations of 4.86, 7.20, and 9.39 mg/dl are 1.3, 1.7, and 1.6 percent, respectively. Because the determination of urate was conducted specifically for this study and not as part of a blood chemistry panel, results of other routine chemistry tests are not available in these samples.

**Statistical analyses**

To account for the matched design of the study, we used conditional logistic regression to estimate odds ratios of Parkinson’s disease according to plasma levels of urate, and their 95 percent confidence intervals. Under the design of this study, the odds ratios from conditional logistic regression estimate the corresponding rate ratios. For this reason, we have used the latter term throughout the paper. In the main analyses, we categorized plasma levels of urate into quartiles defined according to the distribution of urate among controls. Tests for trend were conducted by including urate as a continuous variable in the conditional logistic regression models. Comparison of means between cases and controls was done by use of random effects models to account for correlation within matched sets. Data on additional covariates considered in analyses were taken from responses to the 1992 questionnaire—the most recent survey prior to the period of blood donation—except for dietary data (including vitamin use), which were derived from a semiquantitative food frequency questionnaire administered in 1990 (6) because dietary data were not collected in 1992, and data on physical activity, which were from the 1986 questionnaire. These covariates included pack-years of smoking; caffeine intake (mg/day); alcohol intake (g/day); body mass index (kg/m²); physical activity (metabolic equivalents/week); dairy, meat, and fish consumption (servings/day); regular use of aspirin or other nonsteroidal anti-inflammatory drug use (≥2 per week vs. less); use of thiazide or other diuretics; and history of hypertension or gout. Indicator variables were created for covariates with missing data. In regression models, alcohol was split into categories based on grams per day (0, 1–9, 10–19, 20–29, 30+).
while quartiles or quintiles of other covariates were determined with respect to the distribution among the controls. Interactions between the urate concentration and the other covariates were explored by including in the conditional logistic regression models the product of urate and the covariate of interest, both as continuous variables. Finally, we estimated a summary rate ratio for 1-standard deviation increase in urate concentration by combining our results with those of the two previous prospective studies (3, 4). For this purpose, we estimated the rate ratio corresponding to a 1.32-mg/dl increase in urate concentration (corresponding to 1 standard deviation in our cohort) for each study and obtained pooled estimates by averaging the natural logarithms of the rate ratios from individual studies, weighted by the inverses of their variances. Because there was no heterogeneity among the risk estimates from three cohorts, the pooled rate ratio estimate and confidence interval were estimated by use of a fixed-effect model. The meta-analysis was performed with STATA software, version 9 (StataCorp LP, College Station, Texas). All other analyses were conducted with the SAS software, version 9 (SAS Institute, Inc., Cary, North Carolina). All p values are two sided.

### RESULTS

We identified 84 incident cases of Parkinson’s disease diagnosed after the time of blood collection. The mean age at Parkinson’s disease diagnosis was 71.5 years (range: 55–85 years). The mean plasma urate concentration was 5.7 mg/dl (339 μmol/liter) among cases and 6.1 mg/dl (363 μmol/liter) among the 165 matched controls ($p = 0.0097$). Table 1 shows the distribution of covariates among controls by quartile of urate concentration. As expected, body mass index and pack-years of smoking increased somewhat with increasing urate concentration, as did the prevalence of thiazide use and reported history of high blood pressure or gout. Alcohol consumption increased with each quartile of urate concentration up to the third quartile but then declined, suggesting that men with a high plasma urate level refrained from alcohol consumption.

In analyses adjusted for age, pack-years of smoking, and quintiles of caffeine intake, the rate ratio for Parkinson’s disease decreased with increasing urate quartile (figure 1A). The rate ratio for the highest quartile compared with the lowest was 0.43 (95 percent confidence interval (CI): 0.18,

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**TABLE 1. Baseline characteristics* of controls by urate concentration quartiles, Health Professionals Follow-up Study, 1992**

<table>
<thead>
<tr>
<th>Urate concentration (mg/dl)</th>
<th>No.</th>
<th>Age (years) at blood collection in 1993–1995</th>
<th>Body mass index (kg/m²)</th>
<th>Pack-years of smoking</th>
<th>Caffeine intake (mg/day)</th>
<th>Total alcohol intake (g/day)</th>
<th>Alcohol from</th>
<th>Meat as main dish (servings/day)</th>
<th>Fish (servings/day)</th>
<th>Physical activity (METs‡/week)</th>
<th>Thiazide users (%)</th>
<th>Other diuretics (%)</th>
<th>Aspirin users (≥2 times/week) (%)</th>
<th>Other NSAIDs‡ (%)</th>
<th>Total NSAIDs (%)</th>
<th>History of high blood pressure (%)</th>
<th>History of self-reported gout (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;5.3 (≤309)†</td>
<td>41</td>
<td>67.8</td>
<td>24.7</td>
<td>12.0</td>
<td>227.6</td>
<td>9.3</td>
<td>4.3</td>
<td>1.14</td>
<td>0.38</td>
<td>23.4</td>
<td>0</td>
<td>0</td>
<td>43.9</td>
<td>13.5</td>
<td>45.9</td>
<td>15.6</td>
<td>0</td>
</tr>
<tr>
<td>5.3–6.0 (310–352)</td>
<td>42</td>
<td>66.2</td>
<td>23.3</td>
<td>10.6</td>
<td>202.8</td>
<td>11.7</td>
<td>4.9</td>
<td>1.07</td>
<td>0.40</td>
<td>21.0</td>
<td>4.2</td>
<td>0</td>
<td>38.2</td>
<td>6.0</td>
<td>38.2</td>
<td>26.7</td>
<td>6.7</td>
</tr>
<tr>
<td>6.1–6.9 (353–410)</td>
<td>39</td>
<td>65.8</td>
<td>26.3</td>
<td>12.7</td>
<td>227.7</td>
<td>15.3</td>
<td>2.9</td>
<td>1.29</td>
<td>0.32</td>
<td>19.1</td>
<td>4.1</td>
<td>3.8</td>
<td>38.2</td>
<td>7.0</td>
<td>48.3</td>
<td>32.0</td>
<td>12.8</td>
</tr>
<tr>
<td>7.0–9.7 (411–577)</td>
<td>43</td>
<td>68.7</td>
<td>26.9</td>
<td>15.9</td>
<td>231.7</td>
<td>7.6</td>
<td>1.7</td>
<td>3.1</td>
<td>0.46</td>
<td>18.5</td>
<td>7.6</td>
<td>0</td>
<td>45.8</td>
<td>4.0</td>
<td>37.7</td>
<td>40.3</td>
<td>18.5</td>
</tr>
</tbody>
</table>

* All variables except age are age adjusted by direct standardization to all controls. Dietary data (including vitamin use) are from 1990.
† Numbers in parentheses, μmol/liter.
‡ METs, metabolic equivalents; NSAIDs, nonsteroidal antiinflammatory drugs.
The difference in plasma urate concentration between cases and controls in our study is unlikely to be artifactual, because both groups were drawn from the same population and because their plasma samples were collected at the same time, processed and stored in the same manner, and sent in random order and without disease status identification for laboratory analyses. A limitation of the present study is that we could not physically examine the participants, and there-
Urate and Parkinson’s Disease

A meta-analysis of cohort studies of Parkinson’s disease. Rectangles indicate the rate ratio (RR) of Parkinson’s disease corresponding to a 1.32-mg/dl (1-standard deviation in the Health Professionals Follow-up Study (HPFS)) increase in the plasma concentration of urate in each study. The size of the rectangle is proportional to the percent weight of the corresponding rate ratio in the meta-analysis; horizontal lines, representing the 95% confidence interval, are plotted on a log scale. The pooled (combined) rate ratio and 95% confidence interval (CI) are indicated by the diamond. Urate in the Honolulu Heart Program (HHP) was determined twice, at the time of the first examination—about 30 years before the end of the follow-up—and at the third examination, 6 years after the first. Results in the figure are based on the third examination, because results from the first examination are more likely to be attenuated by unaccounted changes in plasma urate during the follow-up. The pooled rate ratio using results from the first examination would be 0.82 (95% confidence interval: 0.71, 0.95; p = 0.0059).

Medical records. Although some diagnostic misclassification may have occurred, error from this source is probably modest because, according to recent clinicopathologic studies, the accuracy of the clinical diagnosis of Parkinson’s disease made by neurologists is approximately 90 percent (7). Most importantly, diagnostic errors are probably unrelated to plasma urate concentration and would thus tend to attenuate any true association. An additional limitation is that we relied on a single measurement of plasma urate. Repeated blood samples over time would allow a more accurate determination of the long-term average urate concentration, which would be expected a priori to be the strongest predictor of Parkinson’s disease. Because the error in assessing average urate concentration is most likely independent from the rate of Parkinson’s disease, it would also tend to attenuate the association between urate and the rate of Parkinson’s disease.

Direct evidence from studies in humans of a role for urate in the development of Parkinson’s disease has so far been modest. Urate was found to be reduced in serum (8), cerebrospinal fluid (9), and postmortem substantia nigra (10) of patients with Parkinson’s disease as compared with controls, but these findings could have been consequences rather than causes of the disease process. In the Honolulu Heart Program, which included about 8,000 men of Japanese ancestry followed for 30 years, the age- and smoking-adjusted rates of Parkinson’s disease were 40 percent lower among men with serum urate above the median as compared with those with urate below the median (3). The overall trend suggests a 20–30 percent decrease in the rate of Parkinson’s disease for each standard deviation increase in urate concentration, but the statistical significance for an association was marginal. A similar association was observed in the Rotterdam Study, comprising 4,695 men and women and 68 incident cases of Parkinson’s disease during an average of 9 years of follow-up (4). The consistency between the rate ratio estimates in these previous studies and that presented here is impressive, and the pooled results provide compelling evidence of a decreasing rate of Parkinson’s disease for higher levels of urate.

Because of its observational design, the results of the present and previous investigations cannot establish whether high levels of urate are causally related to the rate of Parkinson’s disease, or whether uricemia and a low rate of Parkinson’s disease share an unknown common cause. A preventive effect of uricemia, however, would be consistent with the strong evidence for a role of oxidative stress in the progressive degeneration of dopaminergic neurons in individuals with Parkinson’s disease (2, 11). The oxidative metabolism of dopamine can produce hydrogen peroxide and other reactive oxygen species, as well as conditions favorable to oxidative stress, including increased iron (12, 13) and decreased glutathione, and signs of oxidative damage to lipids, proteins, and DNA have been observed in postmortem Parkinson’s disease brains (11). Urate is present in plasma as the sodium salt, at high concentrations maintained by active kidney reabsorption (1, 14). Urate in physiologic concentrations is as effective as ascorbate in preventing lipid peroxidation initiated in vitro by hydrogen peroxide (1); stabilizes ascorbate (15), possibly by forming complexes with iron ions (16); and scavenges nitrogen radicals (17, 18), which have a critical role in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-induced dopaminergic neurotoxicity, an animal model of Parkinson’s disease (19, 20). Further, administration of urate reduced the homocysteine-induced exacerbation of the oxidative stress and mitochondrial dysfunction in human dopaminergic cells exposed to the pesticides rotenone or to iron ions (21).

Although the cerebrospinal fluid urate concentration is only about 7 percent that of plasma, there is a strong correlation between plasma and cerebrospinal fluid urate (22), and, in spite of being present at low concentrations, urate could still be important in the brain because of its distinct antioxidant effects (23) or its ability to stabilize ascorbate. It is also possible that a localized increase in the blood-brain barrier permeability precedes the clinical onset of Parkinson’s disease. Changes in blood vessels in the substantia nigra of Parkinson’s disease patients have been described (24), and the results of a recent study provide preliminary evidence of a blood-brain barrier dysfunction (25). Urate seems to prevent the increase in permeability of the blood-brain barrier observed in inflammatory diseases of the central nervous system, such as Borna disease virus encephalitis (26) or experimental allergic encephalomyelitis, an animal model of multiple sclerosis (27–30). Consistently with the results in experimental allergic encephalomyelitis, low urate has been associated with optic neuritis (31) and multiple sclerosis (32–34).

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The hypothesis that uricemia could effectively reduce the susceptibility to Parkinson’s disease has potentially important therapeutic implications, because plasma levels of urate can be increased by inosine, a urate precursor sold over the counter as a nutritional supplement and athletic performance enhancer (35), which is now being tested in a randomized trial for multiple sclerosis treatment (36). A primary prevention trial for Parkinson’s disease would be unfeasible, because elevated levels of urate are an important risk factor for cardiovascular diseases and overall mortality. In the Honolulu Heart Program cohort itself, men in the top quartile of serum urate concentration had a reduced rate of Parkinson’s disease but a 20 percent increased total mortality rate. Whether uricemia itself is harmful or whether it is a marker of an underlying systemic stress remains to be established, but, if the harm is real, any putative beneficial effect of increasing plasma urate concentration on risk of Parkinson’s disease would be offset by increased cardiovascular morbidity and mortality. A more cogent question, therefore, is whether increasing the plasma urate concentration could decelerate the progression of neurodegeneration among individuals with Parkinson’s disease, for whom the benefits of neuroprotection could possibly outweigh the potential adverse effects. The recent findings of a slower rate of Parkinson’s disease progression among individuals with higher serum urate (37) or cerebrospinal fluid urate (38) concentrations support this possibility.

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Conflict of interest: none declared.

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