Uric Acid Is a Risk Factor for Myocardial Infarction and Stroke
The Rotterdam Study

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Background and Purpose—The role of uric acid as a risk factor for myocardial infarction is controversial, and little is known about its role as a risk factor for stroke. Recent evidence suggests that uric acid may be an important causal agent in cardiovascular disease, for example, by inducing renal disease and hence hypertension. We investigated the association between serum uric acid and coronary heart disease and stroke in a large prospective population-based study.

Methods—The study was based on 4385 participants of the Rotterdam Study who, at baseline (1990 to 1993), were ≥55 years of age, free from stroke and coronary heart disease, and had blood taken. Follow-up for incident stroke and myocardial infarction was complete until January 1, 2002. Data were analyzed with Cox proportional hazards models with adjustment for relevant confounders.

Results—Average follow-up was 8.4 years. High serum uric acid levels were associated with risk of myocardial infarction and stroke; age- and sex-adjusted hazard ratios (95% CIs) for highest versus lowest quintile of uric acid were 1.68 (1.24 to 2.27) for cardiovascular disease (515 cases), 1.87 (1.12 to 3.13) for myocardial infarction (194 cases), 1.57 (1.11 to 2.22) for stroke (381 cases), 1.77 (1.10 to 2.83) for ischemic stroke (205 cases), and 1.68 (0.68 to 4.15) for hemorrhagic stroke (46 cases). Adjustment for other vascular risk factors only slightly attenuated these associations. Associations were stronger in persons without hypertension than in those with hypertension.

Conclusions—Uric acid is a strong risk factor for myocardial infarction and stroke. (Stroke. 2006;37:1503-1507.)

Key Words: cerebrovascular disorders ■ epidemiology ■ risk factors ■ stroke ■ myocardial infarction

As early as the 19th century, it was known that high uric acid levels are associated with hypertension. Despite the lack of experimental studies, increased uric acid levels were commonly considered a consequence rather than a cause of cardiovascular disease. However, both animal and human studies have recently shown that high uric acid levels may impair kidney function by causing glomerular damage and preglomerular arteriolosclerosis, 2 effects that ultimately result in arterial hypertension.1–7 Large cohort studies have shown that uric acid is an important independent risk factor for cardiovascular mortality.8,9 The role of uric acid in coronary heart disease is less clear. Some studies reported an independent association between uric acid and coronary heart disease,10–14 but others only found an association in women,15–17 and in yet others, the associations disappeared after adjustment for confounders,15,17–19 Little is known on the association between uric acid and stroke risk: an association was found between uric acid and stroke risk in diabetics20 and between uric acid and fatal stroke in the general population.21 Recently, a population-based study in elderly persons also found an association between uric acid and stroke.22

We investigated the association between serum uric acid and coronary heart disease and stroke in a large prospective population-based cohort study in subjects ≥55 years of age who were free from stroke and coronary heart disease at baseline. We studied the associations between uric acid and cardiovascular disease in persons with and without hypertension separately because of the assumed importance of hypertension in the pathogenesis of uric acid–induced cardiovascular disease.5,6

Materials and Methods

Population
The present study is part of the Rotterdam Study, a population-based cohort study on chronic and disabling diseases. All inhabitants of Ommoord, a district of the city of Rotterdam in the Netherlands, ≥55 years of age were invited. People living in homes for the elderly were included. At baseline, participants were invited in random order from the source population. Participation rate of those invited for the study was 78%; in total, 7983 subjects participated. The medical ethics committee of Erasmus University Rotterdam approved the study. Written informed consent to retrieve information from treating
physicians was obtained from all participants. Baseline measure-
ments were obtained from 1990 through 1993 and consisted of a home
interview and 2 visits to the research center for physical examination. At
the baseline visit to the research center, we sampled blood and
performed carotid duplex ultrasonography and electrocardiography.

Assessment of Stroke and Myocardial Infarction
History of stroke at baseline was assessed and verified as described
previously. A medical history of coronary heart disease was
positive if a myocardial infarction, coronary artery bypass graft, or
percutaneous transluminal angioplasty was reported in the baseline
interview and confirmed by baseline ECG or medical records. Once
subjects enter the Rotterdam Study, they are monitored continuously
for major events through automated linkage of the study database
with files from general practitioners and the municipality. Also,
nursery home physicians’ files are scrutinized. For reported events,
additional information (including brain imaging) is obtained from
hospital records. Research physicians reviewed information on all
possible strokes and transient ischemic attacks; an experienced
stroke neurologist (P.J.K.) verified all diagnoses blinded for uric acid
status. Subarachnoid hemorrhages and retinal strokes were excluded.
Ischemic strokes were diagnosed when a patient had typical symp-
toms and a computed tomography (CT) or MRI that was made within
4 weeks after the stroke occurred, ruled out other diagnoses, or when
indirect evidence (deficit limited to one limb or completely resolved
within 72 hours, atrial fibrillation in absence of anticoagulants)
pointed at an ischemic nature of the stroke. Hemorrhagic strokes
were diagnosed when a relevant hemorrhage was shown on CT or
MRI scan or the subject lost consciousness permanently or died
within hours after onset of focal signs. If a stroke did not match any
of these criteria, it was called unspecified.

For coronary heart disease, 2 research physicians independently
coded all reported events according to the International Classifica-
tion of Diseases, 10th edition (ICD-10). Codes on which the research
physicians disagreed were discussed to reach consensus. Finally, a
medical expert in cardiovascular disease, whose judgment was
considered final, reviewed all events. Incident coronary heart disease
was defined as the occurrence of a fatal or nonfatal myocardial
infarction (ICD-10 code I21), a revascularization procedure (percu-
taneous transluminal coronary angioplasty or coronary artery bypass
graft), other forms of acute (I24) or chronic ischemic (I25) heart
disease, sudden (cardiac) death (I46 and R96), and death attributable
to ventricular fibrillation (I49) and congestive heart failure (I50)
during follow-up. Follow-up was completed until January 1, 2002,
for 97.1% of all potential person years.

Population for Analysis
Participants who had coronary heart disease (n=869), stroke
(n=213), or both (n=48) before baseline were excluded. Uric acid
assessments were only performed until December 31, 1992, when
they were stopped because of financial constraints. Therefore, for
the present analyses, we excluded participants who visited the research
center after this date (n=1539). After exclusion of participants who
died before the first center visit, of participants who did not visit the
research center because of refusal or physical inability (n=750),
and of participants of whom we did not have blood available for the
uric acid essays (n=204), 4385 participants were included in the
analyses.

Uric Acid
Nonfasting blood was collected and centrifuged. Within 30 minutes,
the blood was centrifuged for 10 minutes at 3000 rotations per
minute. Subsequently, the serum was stored at −20°C for 1 week,
until uric acid activity was determined with a Kone Diagnostica
reagent kit and a Kone autoanalyzer. To check calibration, after
every 10 samples, 3 control samples were included; if the average
values of the control samples of each run (100 samples) were not
within 2.5% of the true value, the run was repeated. Day-by-day
variation had to be within 5%.

Confounders and Effect Modifiers
Blood pressure was measured twice in sitting position on the right
arm with a random-zero sphygmomanometer. We used the average
of these 2 measurements. Hypertension was defined as a diastolic
blood pressure of ≥100 mm Hg or a systolic blood pressure of
≥160 mm Hg or use of antihypertensive medication indicated to

treat high blood pressure. Total cholesterol and high-density lipopro-
tein cholesterol were measured in nonfasting baseline blood with an
automated enzymatic procedure. We considered diabetes mellitus to
be present if a random or postload glucose level was ≥11.1 mmol/L
or if a person used antidiabetic medication. During the home
interview, smoking status (classified as current, former, or never)
and medication use were assessed. The waist/hip ratio was calculated
by dividing the waist circumference by the hip circumference.

Statistical Analysis
We used Cox proportional hazards models to calculate hazard ratios
with 95% CIs for the associations between uric acid and cardiovas-
ducular disease after inspection of log(-log) survival curves. Hazard
ratios were calculated for uric acid quintiles (relative to the lowest
quintile) and per SD increase in uric acid level. We adjusted for
confounding by age and sex and additionally for confounding by
other putative confounders. We also did analyses in subgroups
(participants not using serum uric acid influencing medication at
baseline [diuretics, lipid-lowering medication, antigout preparations,
analgesics], men, women, hypertensives, and nonhypertensives).
Missing values in confounders and effect modifiers were imputed
using a linear regression model based on age and sex. Interaction, if
appropriate, was examined by studying the statistical significance of
interaction terms entered into the models. Analyses were performed
using SPSS 12.0.1 for Windows.

Results
The total follow-up was 36 794 person years (on average 8.4
years). During follow-up, 515 participants experienced coro-

TABLE 1. Baseline Characteristics of the Study

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Median (interquartile range) or Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>69.0 (62.5–76.2)</td>
</tr>
<tr>
<td>Female sex</td>
<td>64.6 %</td>
</tr>
<tr>
<td>Uric acid (µmol/L)</td>
<td>309 (263–364)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>33.2 %</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>138 (124–153)</td>
</tr>
<tr>
<td>Cholesterol (mmol/L)</td>
<td>6.6 (5.8–7.4)</td>
</tr>
<tr>
<td>High-density lipoprotein (mmol/L)</td>
<td>1.3 (1.1–1.6)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>10.2 %</td>
</tr>
<tr>
<td>Ever smoking</td>
<td>63.4 %</td>
</tr>
<tr>
<td>Diuretic use</td>
<td>14.8 %</td>
</tr>
<tr>
<td>Lipid-lowering medication use</td>
<td>1.7 %</td>
</tr>
<tr>
<td>Analgesic use</td>
<td>23.1 %</td>
</tr>
<tr>
<td>Antigout medication use</td>
<td>0.5 %</td>
</tr>
<tr>
<td>Waist/hip ratio</td>
<td>0.90 (0.83–0.97)</td>
</tr>
</tbody>
</table>
High serum uric acid levels were associated with the risk of coronary heart disease; the age- and sex-adjusted hazard ratio (95% CI) for the highest versus the lowest quintile of uric acid was 1.68 (1.24 to 2.27) for coronary heart disease and 1.87 (1.12 to 3.13) for myocardial infarction alone (Table 2; Figure). High serum uric acid levels were also associated with the risk of stroke; age- and sex-adjusted hazard ratios (95% CIs) for the highest versus the lowest quintile of uric acid were 1.57 (1.11 to 2.22) for all strokes, 1.77 (1.10 to 2.83) for ischemic strokes, and 1.68 (0.68 to 4.15) for hemorrhagic strokes (Table 3; Figure). Adjustment for potential confounding (model 2; Tables 2 and 3) only slightly attenuated these associations. Also, exclusion of subjects receiving serum uric acid influencing medication at baseline (diuretics, analgesics, and lipid-lowering and antigout preparations; n=1155) slightly changed the estimated hazard ratios; age- and sex-adjusted hazard ratios for the highest versus the lowest quintile of uric acid were 1.37 (0.92 to 2.03) for coronary heart disease (n=298) and 2.06 (1.25 to 3.40) for strokes (n=216). In both instances, P for trend <0.01.

### TABLE 2. Hazard Ratios for the Associations Between Serum Uric Acid and Coronary Heart Disease (n=4385)

<table>
<thead>
<tr>
<th>Event</th>
<th>Uric Acid*</th>
<th>Hazard Ratio (95% CI)</th>
<th>Model 1†</th>
<th>Model 2†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coronary heart disease (n=515)</td>
<td>Quintile 1</td>
<td>1 (ref)</td>
<td>1 (ref)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Quintile 2</td>
<td>1.01 (0.73–1.40)</td>
<td>0.97 (0.70–1.34)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Quintile 3</td>
<td>1.40 (1.03–1.90)</td>
<td>1.28 (0.94–1.75)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Quintile 4</td>
<td>1.32 (0.97–1.79)</td>
<td>1.14 (0.83–1.56)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Quintile 5</td>
<td>1.68 (1.24–2.27)</td>
<td>1.30 (0.96–1.78)</td>
<td></td>
</tr>
<tr>
<td>Per SD</td>
<td></td>
<td>1.27 (1.17–1.39)</td>
<td>1.17 (1.07–1.28)</td>
<td></td>
</tr>
<tr>
<td>Myocardial infarction (n=194)</td>
<td>Quintile 1</td>
<td>1 (ref)</td>
<td>1 (ref)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Quintile 2</td>
<td>1.01 (0.57–1.79)</td>
<td>0.95 (0.54–1.68)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Quintile 3</td>
<td>1.91 (1.15–3.19)</td>
<td>1.69 (1.01–2.82)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Quintile 4</td>
<td>1.72 (1.03–2.87)</td>
<td>1.40 (0.83–2.36)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Quintile 5</td>
<td>1.87 (1.12–3.13)</td>
<td>1.38 (0.82–2.35)</td>
<td></td>
</tr>
<tr>
<td>Per SD</td>
<td></td>
<td>1.21 (1.05–1.40)</td>
<td>1.10 (0.95–1.27)</td>
<td></td>
</tr>
</tbody>
</table>

*Cut points for quintiles are 251, 292, 327, and 381 μmol/L.
†Model 1: uric acid, age, and sex; model 2: model 1 + systolic blood pressure, total cholesterol, high-density lipoprotein, diabetes mellitus, ever smoking, diuretic use, and waist/hip ratio.

### Table 3. Hazard Ratios for the Associations Between Serum Uric Acid and Cerebrovascular Disease (n=4385)

<table>
<thead>
<tr>
<th>Event</th>
<th>Uric Acid*</th>
<th>Hazard Ratio (95% CI)</th>
<th>Model 1†</th>
<th>Model 2†</th>
</tr>
</thead>
<tbody>
<tr>
<td>All stroke (n=381)</td>
<td>Quintile 1</td>
<td>1 (ref)</td>
<td>1 (ref)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Quintile 2</td>
<td>1.04 (0.72–1.50)</td>
<td>1.08 (0.75–1.56)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Quintile 3</td>
<td>1.53 (1.09–2.15)</td>
<td>1.57 (1.11–2.22)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Quintile 4</td>
<td>1.44 (1.02–2.03)</td>
<td>1.46 (1.03–2.07)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Quintile 5</td>
<td>1.57 (1.11–2.22)</td>
<td>1.50 (1.05–2.14)</td>
<td></td>
</tr>
<tr>
<td>Per SD</td>
<td></td>
<td>1.18 (1.06–1.30)</td>
<td>1.15 (1.03–1.27)</td>
<td></td>
</tr>
<tr>
<td>Ischemic stroke (n=205)</td>
<td>Quintile 1</td>
<td>1 (ref)</td>
<td>1 (ref)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Quintile 2</td>
<td>1.08 (0.66–1.78)</td>
<td>1.07 (0.65–1.76)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Quintile 3</td>
<td>1.41 (0.88–2.27)</td>
<td>1.33 (0.82–2.14)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Quintile 4</td>
<td>1.68 (1.06–2.67)</td>
<td>1.53 (0.95–2.44)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Quintile 5</td>
<td>1.77 (1.10–2.83)</td>
<td>1.49 (0.92–2.41)</td>
<td></td>
</tr>
<tr>
<td>Per SD</td>
<td></td>
<td>1.24 (1.08–1.42)</td>
<td>1.16 (1.00–1.34)</td>
<td></td>
</tr>
<tr>
<td>Hemorrhagic stroke (n=46)</td>
<td>Quintile 1</td>
<td>1 (ref)</td>
<td>1 (ref)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Quintile 2</td>
<td>0.71 (0.25–2.06)</td>
<td>0.80 (0.27–3.21)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Quintile 3</td>
<td>1.47 (0.59–3.63)</td>
<td>1.75 (0.70–4.38)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Quintile 4</td>
<td>0.70 (0.24–2.05)</td>
<td>0.86 (0.29–2.57)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Quintile 5</td>
<td>1.68 (0.68–4.15)</td>
<td>2.06 (0.81–5.25)</td>
<td></td>
</tr>
<tr>
<td>Per SD</td>
<td></td>
<td>1.15 (0.86–1.55)</td>
<td>1.23 (0.91–1.66)</td>
<td></td>
</tr>
</tbody>
</table>

*Cut points for quintiles are 251, 292, 327, and 381 μmol/L.
†Model 1: uric acid, age and sex; model 2: model 1 + systolic blood pressure, total cholesterol, high-density lipoprotein, diabetes mellitus, ever smoking, diuretic use, and waist/hip ratio.

The associations between uric acid and various kinds of cardiovascular disease were not significantly different for men and women (P interaction >0.3 for all events; Table 4). The associations between uric acid and cardiovascular disease seemed stronger in persons without than in persons with hypertension, although this effect was more pronounced for cerebrovascular disease than for coronary heart disease (Table 5).

### Discussion

In this community-based study in subjects ≥55 years of age who were free from stroke and coronary heart disease at baseline, we found a strong and significant association
between baseline serum uric acid levels and risk of both coronary heart disease and stroke. These associations were attenuated only slightly by adjustment for other cardiovascular risk factors and were stronger in persons without than in those with hypertension. Before these results can be interpreted, some methodological issues need to be discussed.

Strengths of our study are the large study population (n=4385), the intense stroke case finding, and the nearly complete follow-up (loss of potential person years 2.9%). Our stringent stroke monitoring procedures allowed us to also include stroke patients who were not referred to a hospital. A disadvantage is that in these cases, neuroimaging was often lacking (60% of our cases had neuroimaging) and examinations not thorough enough to subclassify 34% of strokes into ischemic or hemorrhagic. Uric acid examinations were performed not thorough enough to subclassify 34% of strokes into ischemic or hemorrhagic. Uric acid examinations were stopped before all participants had visited the research center. Because participants were invited in random order, we do not think that this affected our results.

Our finding that uric acid increases risk of coronary heart disease is in line with previous studies on the association between uric acid and coronary heart disease. Some of these studies found the association only in women. In our study, too, associations seemed to be stronger in women than in men, although the differences were not statistically significant. In some previous studies, the association between uric acid and coronary heart disease disappeared after adjustment for potential confounders, which led to the opinion that uric acid has no role in the etiology of cardiovascular disease. This was legitimate because at the time that these studies were published, uric acid was regarded as a biologically inert molecule. However, recent insights in the biological effects of uric acid have falsified this view, and many epidemiological studies, including our present study, found that uric acid plays a clear and independent role in cardiovascular disease. Although we can never be sure that no residual confounding remains, we do think that the role of uric acid in cardiovascular disease has been underestimated for a long time and should be reconsidered.

There is relatively little information on the role of uric acid as a risk factor for stroke. An association between uric acid and coronary heart disease, was seen in most studies. However, some studies have shown a non-significant association. In our study, the association between uric acid and coronary heart disease was significant in both men and women. The association was stronger in women than in men, although the differences were not statistically significant. In some previous studies, the association between uric acid and coronary heart disease disappeared after adjustment for potential confounders, which led to the opinion that uric acid has no role in the etiology of cardiovascular disease. This was legitimate because at the time that these studies were published, uric acid was regarded as a biologically inert molecule. However, recent insights in the biological effects of uric acid have falsified this view, and many epidemiological studies, including our present study, found that uric acid plays a clear and independent role in cardiovascular disease. Although we can never be sure that no residual confounding remains, we do think that the role of uric acid in cardiovascular disease has been underestimated for a long time and should be reconsidered.

TABLE 4. Hazard Ratios for the Associations Between Serum Uric Acid and Subtypes of Cardiovascular Disease for Men and Women Separately (adjusted for age)

<table>
<thead>
<tr>
<th>Stratum</th>
<th>Uric Acid*</th>
<th>Coronary Heart Disease</th>
<th>Myocardial Infarctions</th>
<th>All Strokes</th>
<th>Ischemic Strokes</th>
<th>Hemorrhagic Strokes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Tertile 1</td>
<td>1 (ref)</td>
<td>1 (ref)</td>
<td>1 (ref)</td>
<td>1 (ref)</td>
<td>1 (ref)</td>
</tr>
<tr>
<td>Men</td>
<td>Tertile 2</td>
<td>1.11 (0.82–1.51)</td>
<td>1.23 (0.77–1.96)</td>
<td>1.78 (1.64–2.74)</td>
<td>1.57 (0.88–2.79)</td>
<td>1.23 (0.38–4.04)</td>
</tr>
<tr>
<td></td>
<td>Tertile 3</td>
<td>1.37 (1.01–1.84)</td>
<td>1.33 (0.83–2.12)</td>
<td>1.41 (0.90–2.23)</td>
<td>1.36 (0.74–2.48)</td>
<td>1.11 (0.32–3.83)</td>
</tr>
<tr>
<td></td>
<td>Per SD</td>
<td>1.21 (1.06–1.38)</td>
<td>1.15 (0.94–1.41)</td>
<td>1.15 (0.95–1.38)</td>
<td>1.18 (0.92–1.51)</td>
<td>0.97 (0.55–1.70)</td>
</tr>
<tr>
<td>Women</td>
<td>Tertile 1</td>
<td>1 (ref)</td>
<td>1 (ref)</td>
<td>1 (ref)</td>
<td>1 (ref)</td>
<td>1 (ref)</td>
</tr>
<tr>
<td></td>
<td>Tertile 2</td>
<td>1.20 (0.85–1.67)</td>
<td>1.40 (0.78–2.54)</td>
<td>1.45 (1.05–2.02)</td>
<td>1.44 (0.91–2.27)</td>
<td>1.22 (0.48–3.10)</td>
</tr>
<tr>
<td></td>
<td>Tertile 3</td>
<td>1.73 (1.27–2.36)</td>
<td>2.03 (1.17–3.54)</td>
<td>1.45 (1.05–2.01)</td>
<td>1.68 (1.08–2.62)</td>
<td>1.32 (0.53–3.26)</td>
</tr>
<tr>
<td></td>
<td>Per SD</td>
<td>1.30 (1.16–1.46)</td>
<td>1.27 (1.03–1.56)</td>
<td>1.18 (1.05–1.34)</td>
<td>1.26 (1.07–1.49)</td>
<td>1.23 (0.87–1.74)</td>
</tr>
</tbody>
</table>

*Cut points for tertiles are 310 μmol/L and 325 μmol/L for men and 263 μmol/L and 321 μmol/L for women.

between baseline serum uric acid levels and risk of both coronary heart disease and stroke. These associations were attenuated only slightly by adjustment for other cardiovascular risk factors and were stronger in persons without than in those with hypertension. Before these results can be interpreted, some methodological issues need to be discussed.

TABLE 5. Hazard Ratios for the Associations Between Serum Uric Acid and Subtypes of Cardiovascular Disease for Nonhypertensives and Hypertensives Separately

<table>
<thead>
<tr>
<th>Stratum</th>
<th>Uric Acid*</th>
<th>Coronary Heart Disease</th>
<th>Myocardial Infarctions</th>
<th>All Strokes</th>
<th>Ischemic Strokes</th>
<th>Hemorrhagic Strokes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Tertile 1</td>
<td>1 (ref)</td>
<td>1 (ref)</td>
<td>1 (ref)</td>
<td>1 (ref)</td>
<td>1 (ref)</td>
</tr>
<tr>
<td>Nonhypertensives</td>
<td>n=2881</td>
<td>Tertile 2</td>
<td>1.23 (0.89–1.70)</td>
<td>1.56 (0.89–2.72)</td>
<td>2.03 (1.36–3.04)</td>
<td>1.98 (1.16–3.39)</td>
</tr>
<tr>
<td></td>
<td>Tertile 3</td>
<td>1.51 (1.10–2.09)</td>
<td>2.01 (1.16–3.50)</td>
<td>2.15 (1.41–3.26)</td>
<td>2.16 (1.24–3.77)</td>
<td>2.27 (0.65–7.95)</td>
</tr>
<tr>
<td></td>
<td>Per SD</td>
<td>1.25 (1.09–1.43)</td>
<td>1.33 (1.08–1.64)</td>
<td>1.30 (1.10–1.53)</td>
<td>1.33 (1.07–1.66)</td>
<td>1.08 (0.63–1.85)</td>
</tr>
<tr>
<td>Hypertensives</td>
<td>n=1433</td>
<td>Tertile 1</td>
<td>1 (ref)</td>
<td>1 (ref)</td>
<td>1 (ref)</td>
<td>1 (ref)</td>
</tr>
<tr>
<td></td>
<td>Tertile 2</td>
<td>1.34 (0.95–1.90)</td>
<td>2.33 (1.27–4.27)</td>
<td>0.91 (0.64–1.30)</td>
<td>0.81 (0.49–1.34)</td>
<td>0.99 (0.36–2.76)</td>
</tr>
<tr>
<td></td>
<td>Tertile 3</td>
<td>1.37 (0.97–1.94)</td>
<td>1.64 (0.86–3.13)</td>
<td>0.93 (0.65–1.33)</td>
<td>0.91 (0.55–1.49)</td>
<td>1.37 (0.53–3.52)</td>
</tr>
<tr>
<td></td>
<td>Per SD</td>
<td>1.20 (1.06–1.35)</td>
<td>1.03 (0.83–1.27)</td>
<td>1.01 (0.88–1.16)</td>
<td>1.05 (0.86–1.27)</td>
<td>1.04 (0.73–1.48)</td>
</tr>
</tbody>
</table>

P interaction Hypertension yes/no

Reported for tertiles of uric acid and per SD increase in uric acid level. Adjusted for age and sex.

*Cut points for tertiles are 269 μmol/L and 328 μmol/L for nonhypertensives and 298 μmol/L and 374 μmol/L for hypertensives; †nonhypertensives and hypertensives, respectively.
and stroke risk has been found in diabetics.20 In the general population, an association was found between uric acid and fatal stroke.21 We know of one published report on the relationship between uric acid and (fatal and nonfatal) stroke in the general population; in this study, an independent relationship between uric acid and stroke was found only in subjects not using diuretics. Because we may presume that nearly all subjects who use diuretics experience hypertension, these findings are compatible with our view that the association between uric acid and stroke is most pronounced in normotensive subjects.22 In our study, too, this association seemed to be strongest in participants not using uric acid— influencing medication (which seemed opposite for the association between uric acid and coronary heart disease). We found that the effect of uric acid on stroke risk was lower in persons with hypertension. This fits the observation in rats that once renal disease has been established, the hypertension is driven by renal mechanisms independent of uric acid status.5,6

Our data suggest that uric acid is an important cardiovascular risk factor. Additional studies are required to assess whether lowering of uric acid levels can actually reduce the risk of coronary heart disease and stroke.

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References
Uric Acid Is a Risk Factor for Myocardial Infarction and Stroke: The Rotterdam Study
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