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Plasma Uric Acid Concentrations and Risk of Ischemic Stroke in Women

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Abstract

Background—Elevated plasma uric acid has been inconsistently associated with a increased risk of total stroke; however, data are sparse among women. We examined the association between plasma uric acid concentrations and ischemic stroke among women and evaluate effect modification by key cardiovascular risk factors.

Methods—A nested case-control design with matching by age, race/ethnicity, smoking status, menopausal status, postmenopausal hormone therapy use, date of blood draw and fasting status was utilized among female participants of the Nurses' Health Study who provided blood samples between 1989-1990. Plasma uric acid was measured on stored blood samples. The National Survey of Stroke criteria were utilized to confirm 460 incident cases of ischemic stroke by medical records from 1990-2006. Multivariable conditional logistic regression models were estimated.

Results—In matched analysis, risk of ischemic stroke increased by 15% for each 1 mg/dL increase in plasma uric acid (95% CI: 3%-28%), but was no longer significant after adjustment for cardiovascular risk factors, particularly history of hypertension. The highest quartile of uric acid was significantly associated with greater risk of ischemic stroke (OR=1.56; 95% CI: 1.06-2.29, extreme quartiles) in matched analysis, but estimates were no longer significant after adjustment for cardiovascular risk factors (OR=1.43; 95% CI: 0.93-2.18). Significant effect modification by key cardiovascular risk factors was not observed.

Conclusions—Plasma uric acid levels were not independently associated with increased risk of ischemic stroke in this cohort of women. While plasma uric acid was associated with stroke risk factors, it was not independently associated with stroke risk.

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Keywords

Ischemic stroke; uric acid; women; hyperuricemia

Introduction

Uric acid, a product of purine metabolism in humans, may be higher either due to decreased secretion (e.g. diuretic medication) and/or increased production (e.g. high animal protein intake, fructose consumption, increased cell turnover).[1, 2] Although there is no predefined clinical threshold for hyperuricemia, higher plasma uric acid concentrations (5-7.7 mg/dL) without gout have been associated with a wide range of cardiovascular outcomes, including: incidence and mortality of total cardiovascular disease (CVD), coronary heart disease (CHD), total and ischemic stroke, congestive heart failure and hypertension.[3-5] Excess plasma uric acid may contribute to atherosclerotic mechanisms by inducing inflammation and endothelial dysfunction.[1] Moreover, plasma uric acid is a potentially modifiable risk factor and may be easily assessed during routine clinical visits. However, the role of plasma uric acid as an independent risk factor versus a risk marker of CVD remains controversial. In a meta-analysis, Kim et al.[4] reported that among women, hyperuricemia (>6.8mg/dL) was associated with a modestly higher risk of total stroke incidence (RR=1.42, 95% CI: 1.03-1.80) and mortality (RR=1.35, 95% CI: 1.04-1.66). However, the data among women are sparse and inconsistent;[5-8] subsequent studies have failed to provide consensus.[9-11]

We examined the association between plasma uric acid concentrations and ischemic stroke among women while adjusting for important cardiovascular risk factors. Furthermore, we evaluated whether the association varied by key cardiovascular risk factors including age, history of hypertension, diuretic use, body mass index (BMI), smoking, postmenopausal hormone use and high sensitivity C-reactive protein (hsCRP).

Methods

Nurses' Health Study Cohort

The Nurses' Health Study (NHS) enrolled 121,700 primarily white female registered nurses living in 11 US states, aged 30-55 years who completed a mailed questionnaire in 1976. Follow-up questionnaires have been mailed biennially, with a semi-quantitative food frequency questionnaire (FFQ) mailed approximately every 4 years since 1980. Detailed descriptions of the NHS have been previously published.[12] Over 90% of the baseline population has responded to follow-up questionnaires and mortality follow-up is greater than 98% complete.[13] Between 1989 and 1990, 32,826 participants, aged 43-69 years, provided blood samples. Women who provided blood samples were similar to those in the complete NHS cohort with respect to age, lifestyle factors and history of chronic disease, except for current smoking which was lower among those who provided blood (Supplemental Information Table I). Of these, 18,743 participants provided a second blood sample, approximately 10 years later (2000-2001), and an equal number of cases and controls had a second sample prior to stroke date. Women had their blood drawn and shipped to our

laboratory via overnight courier for processing. Samples were processed and archived and have been continuously stored in monitored liquid nitrogen freezers.[14]

A nested case-control study of ischemic stroke was conducted among those women with blood samples available. Among those, stroke cases were defined as women free of known prior stroke or cancer at the time of the blood collection, but with incident ischemic stroke confirmed by medical records during follow-up. For each stroke case, one control participant was selected from those women who were free of known prior stroke or cancer at the time of the blood collection and who did not have a stroke by the time of the index case. Controls were randomly selected eligible participants and matched to the index case by age (±2 years), race/ethnicity (White/African-American/ Asian/ Hispanic/ Other/ Unknown), smoking status (current/past/never at blood sample collection), menopausal status, postmenopausal hormone use at time of blood draw (yes/no), date of blood draw and fasting status (yes/no).

Blood Sample Assay

Case-control pair samples were handled identically and together, shipped to the laboratory in the same batch and assayed in the same run. Each batch included replicate, blinded plasma samples to assess laboratory precision. Plasma uric acid was measured on 460 complete case-control pairs by colorimetric enzyme assay (R&D Systems, Indianapolis, MN) in the Clinical and Epidemiological Research Laboratory at Children's Hospital (Boston, MA) for all cases and controls, with a mean intra-assay coefficient of variation (CV) of 3%. Time to blood lab processing did not affect reproducibility, with correlation coefficients >95%. An intra-class correlation (ICC) was estimated among the 102 pairs with 2 measurements approximately 10 years apart and indicated moderate reproducibility, ICC=0.50 (95% CI: 0.40-0.60). Total cholesterol, low density lipoprotein (LDL-C) and high density lipoprotein (HDL-C) cholesterol, hsCRP, creatinine and erythrocyte hemoglobin A1c (HbA_{1C}) were measured in the Clinical and Epidemiological Research Laboratory at Children's Hospital (Boston, MA) for all cases and controls using standard lab assays and with CVs<5%, except for creatinine (CV=10.6%; Supplemental Information).

Cerebrovascular Disease Assessment

We restricted to confirmed ischemic strokes that occurred from the return of the blood sample (1989-1990) through June 2006, resulting in up to 17 years of follow-up. Nonfatal stroke was reported on biennial questionnaires and confirmed by medical records. Deaths were detected through information provided by the next of kin, postal authorities or by systematic searches of the National Death Index. In addition to death certificates, fatal stroke was also confirmed by review of hospital records or autopsy. Women (or next-of-kin for decedents) reporting stroke on follow-up questionnaires were asked for permission to review medical records, which were reviewed by a physician blinded to exposure status. Stroke was classified according to criteria established by the National Survey of Stroke[15] requiring evidence of a neurologic deficit with sudden or rapid onset that persisted for >24 hours or until death. Stroke type and subtype classification has been previously published in detail with high reproducibility.[16] Ischemic stroke was classified as an event due to thrombotic or embolic occlusion of a cerebral artery with imaging data from CT or MRI or data on

autopsy available for >94% of events. Embolic strokes were defined as cerebral infarction caused by emboli from extracranial sources and thrombotic strokes were defined as lacunar or large artery infarction from in situ thrombosis. The primary outcome was ischemic stroke with secondary analyses conducted for embolic and thrombotic events.

Statistical Analysis

Descriptive analyses for baseline characteristics were conducted comparing cases and controls. Age adjusted Spearman correlation coefficients among the controls were calculated between plasma uric acid concentrations, age, BMI and CVD biomarkers. Plasma uric acid was modeled as continuous, as quartiles and as a dichotomous variable (based on the saturation point of plasma uric acid, >6.8 mg/dL) using multivariable conditional logistic regression models to estimate the association with ischemic stroke. The odds ratio (OR) and 95% confidence intervals (CI) were used to approximate the relative risk (RR).

We estimated 5 nested multivariable models, each sequentially adjusted for additional confounders and stroke risk factors (Supplemental Information). A missing indicator variable was used to model missing values for smoking and postmenopausal hormone use. Alcohol intake was missing in 24 cases and 18 controls and the median value was imputed by case control status. We examined the potentially non-linear relationship between plasma uric acid and ischemic stroke non-parametrically with restricted cubic and linear splines based on 4 knots located at: 2.9, 4.2, 5.2, 7.3 mg/dL.[17] Tests for non-linearity used the likelihood ratio test, comparing a model with a linear term to a model with a linear and cubic spline terms.

A priori we proposed to evaluate effect modification, using a likelihood ratio test, of the association between selected risk factors, including age, BMI, smoking, history of hypertension, use of diuretic medication, postmenopausal hormone use, hsCRP and time period of event occurrence. Additionally, we restricted analyses to those with eGFR≥60 mL/min/1.73 m^2. All p-values were two-sided. Analyses were conducted with SAS for UNIX statistical software (version 9.1.3; SAS Institute, Cary, NC). This study was approved by the Institutional Review Board of Brigham and Women's Hospital and all procedures followed were in accordance with institutional guidelines. Informed consent was implied by receipt of completed self-administered questionnaires and blood samples.

Results

The mean age among both cases and controls at baseline was 61 years (Table 1) with a mean age at stroke onset of 71 years. As expected, women who later developed ischemic stroke were more likely to be diabetic and hypertensive at baseline (p=<0.001). Mean plasma uric acid concentrations (mg/dL) were not significantly higher among cases compared with controls (p=0.06), but differed significantly by hypertension status, BMI and hsCRP (p<0.001; Supplemental Information Table II). Age adjusted Spearman rank correlations among controls indicated a significant positive correlation between plasma uric acid and BMI, HbA1c, triglycerides, hsCRP, and total cholesterol to HDL ratio (p<0.001; Supplemental Information Table III). In contrast, plasma uric acid was significantly inversely correlated with eGFR and HDL concentrations (p<0.001).

Each 1 mg/dL increase in uric acid concentration was associated with a 15% greater risk of ischemic stroke (RR=1.15; 95% CI: 1.03-1.28) in analyses conditional on matching factors. Estimates were only marginally attenuated but no longer statistically significant when adjusted for potential confounders in model 2 and chronic disease risk factors in model 3 (RR=1.13; 95% CI: 1.00-1.28; results not shown). Estimates were further attenuated towards the null after adjustment for history of hypertension (model 4, RR=1.09; 95% CI: 0.96-1.24) and biomarkers of cardiovascular risk (total cholesterol/HDL-C ratio and ln[hsCRP], model 5: RR=1.05; 95% CI: 0.92-1.19). In quartile analysis, women in the highest quartile of plasma uric acid had a 56% significantly greater risk of ischemic stroke compared with those in the lowest quartile when adjusted for matching factors (RR=1.56; 95% CI: 1.06-2.29; Table 2), but the association was no longer significant after adjustment for potential confounders and chronic disease factors. Adjustment for history of hypertension and CVD biomarkers attenuated results toward the null more substantially than other covariates. There was no evidence of a deviation from linearity for the association between plasma uric acid and ischemic stroke based on spline analysis (p=0.36). Hyperuricemia (>6.8 vs. ≤6.8 mg/dL) was significantly associated with an approximately twofold greater risk of ischemic stroke when adjusted for potential confounders (model 2: RR=1.98; 95% CI: 1.11-3.51; Figure 1). However, results were attenuated and no longer statistically significant after adjustment for history of hypertension (model 4) and biomarkers of cardiovascular risk (model 5).

The association between plasma uric acid and ischemic stroke did not vary significantly by age, history of hypertension, use of diuretic medication, BMI, smoking status, postmenopausal hormone use, hsCRP or time period of event occurrence (all $P_{\text{interaction}}>0.05$, Supplemental Information Table IV). Results were virtually unchanged after adjusting for thiazide or lasix use (results not shown).Analyses restricted to those with normal kidney function (eGFR≥60) were consistent with those from the overall sample. Additionally, estimates for thrombotic and embolic ischemic stroke subtype were not materially different from total ischemic stroke analyses (Supplemental Information Table V).

Discussion

In this cohort of generally healthy women, free of CVD at the time of blood collection with up to 17 years of follow-up, plasma uric acid levels were associated with stroke risk factors but not independently associated with stroke risk. Although an association was observed in matched analyses, it was modestly attenuated and no longer statistically significant after adjustment for potential confounders and cardiovascular risk factors.

Higher uric acid levels have been associated with a modestly greater risk of ischemic stroke compared to lower concentrations; however, the data among women are sparse and inconsistent.[4, 6, 8] A clinical definition of hyperuricemia has not been well defined and the biologically relevant threshold may be lower for women than men. To date, 8 studies have provided estimates of uric acid and stroke risk specifically among women,[5-11] although two present data only for total stroke[7] (Supplemental Information Table VI). Of the five which reported age-adjusted analyses, [5-7, 10, 11] only one[5] failed to observe a significant association between plasma uric acid and ischemic stroke. However, similar to our results, among those with significant age-adjusted analyses, estimates were attenuated

towards the null and no longer statistically significant after adjustment for key cardiovascular risk factors including hypertension or systolic blood pressure in all[5, 7, 8, 11] except one of the studies. There was no clear difference between studies which reported a significant association and those which did not according to follow-up time, population characteristics or potential confounders, except for the study by Holme et al.,[10] which was substantially larger than others with over 6952 strokes among women. Authors reported a 41% increased risk of total stroke (95% CI: 31%-53%) and 56% increased risk of ischemic stroke (95% CI: 42%-72%) among women in the highest compared with the lowest quartile in analyses adjusted for hypertension and other stroke risk factors.

It is unclear, whether hypertension acts as a confounder, an intermediate in the causal pathway or simply as part of a broader common syndrome of adverse cardiovascular risk. Hypertension may lead to kidney dysfunction with concomitant impairment in uric acid excretion.[1] Uric acid has also consistently been associated with incident hypertension in men and women, although the association may be limited to younger individuals (<60 years).[3, 18, 19] Our estimates were substantially attenuated and no longer significant when adjusted for history of hypertension. Moreover, we observed the association between uric acid and ischemic stroke was further attenuated by adjusting for total cholesterol-to-HDL ratio and hsCRP, potentially supporting the role of other CVD pathways. However, in this study we could not identify the mechanistic role of hypertension.

Some studies have reported potential variation of the association between uric acid concentrations and ischemic stroke by cardiovascular risk factors[7, 8] However, effect modification by cardiovascular risk factors has not been examined among female populations nor has the role of menopausal hormone use been assessed, which has been shown to be associated with elevated uric acid concentrations.[20] In one study in men and women, higher uric acid concentrations were associated with a greater risk of ischemic stroke among those with hypertension[7] (HR=1.27, 95% CI: 1.05-1.55), metabolic syndrome[7] (HR=1.30, 95% CI: 1.03-1.65) and non-users of diuretics (HR=1.49, 95% CI: 1.00-2.23).[8] In contrast, we did not observe significant effect modification by key cardiovascular risk factors, including history of hypertension, use of diuretic medication, postmenopausal hormone use or time to stroke in our cohort of women; however, these analyses were likely underpowered.

Uric acid is known to exhibit anti- and pro-oxidative properties, depending upon the local cellular environment. For example, anti-oxidative functions may be impaired when concentrations are very low[1] or under local conditions of oxidation, uric acid may exhibit pro-oxidant properties (e.g. impairing nitric oxide production) by inducing vascular smooth muscle cell proliferation and endothelial dysfunction.[21, 22] It is unclear how other factors such as diet, circadian rhythm and medication use may influence underlying mechanisms.[23, 24]

We had limited power to conduct exploratory sub-group analyses by key cardiovascular risk factors and stroke subtypes; however, this study is the first to our knowledge to explore these associations among women. Additionally, plasma uric acid concentrations are known to be lower among women, therefore generalizability to men or ethnically diverse populations

may be limited. While primary analyses were restricted to one sample taken up to 17 years prior to case ascertainment, any influence of sample degradation would be non-differential across case and control status and potentially lead to attenuated estimates. Furthermore, the association between uric acid and risk of ischemic stroke did not vary by follow-up time ($P_{interaction}>0.05$). We did observe a moderate correlation between measures of plasma uric acid collected 10 years apart (ICC=0.50, 95% CI: 0.40-0.60). Notable strengths of this study include the nested case control design with up to 17 years of follow-up prior to stroke events and a moderate number of events which allowed for adjustment of potential confounders.

We observed an association between plasma uric acid and ischemic stroke that was not independent of traditional cardiovascular risk factors. Estimates from analyses adjusted for matching factors were no longer statistically significant after adjustment for potential confounders and cardiovascular risk factors. Uric acid may be a risk marker of underlying cardiovascular risk rather than an independent determinant of stroke risk. Further research is needed, in particular randomized controlled trials, to explore these associations in other populations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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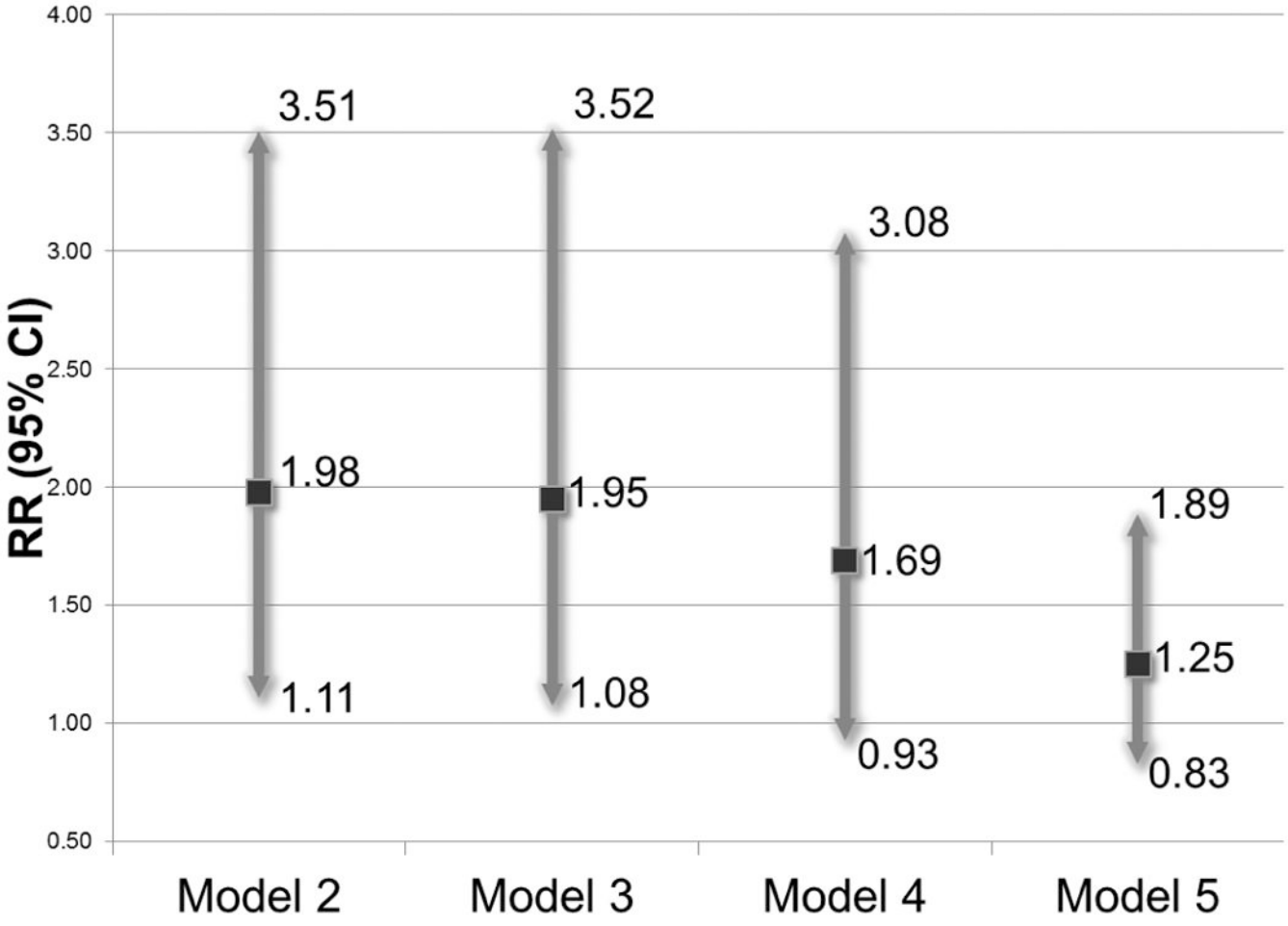

Figure 1. The multivariable association between hyperuricemia (≤6.8 vs. >6.8 mg/dL) and ischemic stroke

Model 2 adjusted for matching factors (age, menopausal status, postmenopausal hormone use, smoking, race/ethnicity, date of blood draw and fasting status)), BMI, physical activity, alcohol intake and aspirin use. Model 3 additionally adjusted for eGFR, history of diabetes and heart disease. Model 4 further includes history of hypertension. Model 5 additionally adjusted for total cholesterol/HDL-C ratio and ln(hsCRP). RR= relative risk; 95% CI=95% Confidence Interval

Table 1
Baseline characteristics by case-control status in 1990

Characteristic	Cases	Controls	p-value
N,%	460	460	
Age, years	60.8 ± 6.0	60.7 ± 6.0	0.93 *
Uric Acid (mg/dL)	4.9 ± 1.4	4.7 ± 1.2	0.06
Current Smokers, %	18	17%	0.84 *
High Cholesterol, %	48	46	0.60
Hypertension, %	47	34	<0.0001
History of Coronary Heart Disease, %	5	6	0.55
Diabetic, %	13	6	<0.001
HbA1c, %	5.8 ± 1.0	5.7 ± 0.7	0.13
hsCRP≥ 3 (mg/L), %	40	34	0.09
Physical Activity (METs/wk)	9.0 ± 19.6	10.2 ± 18.5	0.13
Alcohol (gm/day)	5.7 (0-6.6)	0.9 (0-6.0)	0.46
BMI (kg/m^2)	25.1 (22.3-28.3)	25.4 (22.1-28.1)	0.11
Postmenopausal Status, %	48	47	0.92 *

Means ± SD, medians (IQR) or percentages and are standardized to the age distribution of the study

population (except for age)

Normally distributed continuous variables compared using t-test, skewed variables compared using Wilcoxon rank-sum test and categorical variables compared with Chi-squared test

* Case-control matching factors

Table 2

Multivariable adjusted relative risk (95% CI) of ischemic stroke by uric acid quartiles

		Quartiles* of Uric Acid (mg/dL)				
		Q1	**Q2**	**Q3**	**Q4**	P_{trend}
Range (mg/dL)		<3.9	3.9-4.5	4.6-5.4	≥5.5	
Cases/Controls	460/460	102/125	103/96	117/125	138/114	
Model 1	Matching factors	1.00	1.34 (0.91-1.97)	1.19 (0.80-1.75)	1.56 (1.06-2.29)	0.04
Model 2	+ BMI, physical activity, alcohol and aspirin use	1.00	1.31 (0.88-1.94)	1.13 (0.76-1.68)	1.42 (0.94-2.14)	0.16
Model 3	+ eGFR, history of diabetes, CHD	1.00	1.31 (0.87-1.95)	1.19 (0.79-1.78)	1.43 (0.93-2.18)	0.16
Model 4	+ history of hypertension	1.00	1.32 (0.88-1.97)	1.19 (0.79-1.80)	1.28 (0.83-1.98)	0.38
Model 5	+ total/HDL-C, ln(hsCRP)	1.00	1.26 (0.83-1.89)	1.11 (0.73-1.68)	1.13 (0.72-1.76)	0.77

*Quartiles of uric acid based on distribution in controls

Model 1: Conditional on matching factors (age, menopausal status, postmenopausal hormone use, smoking, race/ethnicity, date of blood draw and fasting status)

All models are sequentially nested models.