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# Serum Uric Acid Predicts Incident Hypertension in a Biethnic Cohort

## The Atherosclerosis Risk in Communities Study

Philip B. Mellen, Anthony J. Bleyer, Thomas P. Erlinger, Gregory W. Evans, F. Javier Nieto, Lynne E. Wagenknecht, Marion R. Wofford, David M. Herrington

**Abstract**—Serum uric acid has been positively associated with incident hypertension, but previous studies have had limited ability to explore this relationship across sex and ethnic strata. We sought to evaluate this association in a biethnic cohort of middle-aged men and women. Participants in the Atherosclerosis Risk in Communities (ARIC) study who were free of hypertension at baseline (N=9104) were evaluated for hypertension at 3-year intervals over 4 examinations. Adjusted Cox proportional hazards models evaluated risk of incident hypertension or progression of blood category for each SD higher baseline serum uric acid. At baseline, the mean age was 53.3 years (range: 45 to 64 years), with a mean (SD) systolic blood pressure of 113.8 (12.2) mm Hg, mean diastolic blood pressure of 70.2 (8.6) mm Hg, and mean serum uric acid of 5.7 (1.4). Higher serum uric acid was associated with greater risk of hypertension in the overall cohort (hazard ratio for each SD of higher uric acid [95% CI]: 1.10 [1.04 to 1.15]) and in subgroup analyses (black men: 1.32 [1.14 to 1.54]; black women: 1.16 [1.03 to 1.31]; white men: 1.01 [0.94 to 1.09]; white women: 1.04 [0.96 to 1.11]), after adjustment for age, baseline blood pressure, body mass index, renal function, diabetes, and smoking. The pattern was similar when modeling blood pressure progression (overall: 1.10 [1.05 to 1.14]; black men: 1.26 [1.11 to 1.42]; black women: 1.18 [1.06 to 1.31]; white men: 1.05 [0.99 to 1.11]; white women: 1.05 [1.00 to 1.12]). In conclusion, serum uric acid was positively associated with incident hypertension over 9 years of follow-up, and this relationship was stronger in blacks than in whites. More research is warranted concerning the physiological and clinical consequences of hyperuricemia, especially in blacks. (*Hypertension*. 2006;48:1-6.)

**Key Words:** hypertension ■ uric acid ■ epidemiology ■ middle aged ■ ethnic groups

The positive association between serum uric acid (SUA) and hypertension was observed over a century ago,<sup>1</sup> but in the past it has been unclear whether hyperuricemia played a causal role in arterial hypertension or if it was merely a marker of an underlying pathophysiological process. Although elevated SUA levels have been predictive of hypertension in longitudinal studies,<sup>2-9</sup> the relationship between uric acid and blood pressure is confounded by numerous factors, including age, diabetes, obesity, alcohol use, and sodium intake or volume status. These factors have rendered it difficult to establish a causal role for SUA in the development of hypertension on the basis of epidemiological investigations.

Recent findings in animal models have helped elucidate possible mechanisms whereby SUA may lead to hypertension. In animal models, experimental hyperuricemia causes hypertension through multiple mechanisms, including decreased NO synthesis, upregulated renin production, renal

tubular injury,<sup>10</sup> and an afferent arteriopathy.<sup>11</sup> Moreover, a causal role for hyperuricemia has been demonstrated in rat models for the metabolic syndrome.<sup>12</sup> These results from basic science investigations have spurred a renewed interest in discerning a causal role for elevated SUA in primary hypertension.

One limitation of the epidemiological studies of SUA and hypertension has been an underrepresentation of blacks in prospective studies. Although blacks have a higher prevalence of hypertension<sup>13</sup> and experience more associated target organ damage than do whites,<sup>14,15</sup> data on the relationship between SUA and hypertension in this group is limited. One prospective study in a large, biethnic cohort of young adults suggested that the relationship was stronger in blacks.<sup>16</sup> Our goal was to evaluate the longitudinal relationship between SUA and incident hypertension in a large, biethnic cohort of middle-aged adults.

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## Methods

### Study Population

The Atherosclerosis Risk in Communities (ARIC) study is a prospective epidemiological cohort study of clinical and subclinical cardiovascular risk in 4 US communities (Washington County, Md, Minneapolis, Minn, Jackson, Miss, and Forsyth County, NC). The cohort is composed of 15 792 participants, ages 45 to 64 years at baseline, selected by probability sampling at the 4 field centers. Of note, the Jackson field center recruited blacks exclusively, whereas the sample from Forsyth County was biethnic, and samples from the other centers were predominantly white. Response rates were 65% in Washington County, 67% in Minneapolis, 46% in Jackson, and 45% (blacks) and 71% (whites) in Forsyth County. The protocol was approved by the institutional review board of each field center, and all of the participants signed written informed consent. The baseline examination (visit 1) took place in 1987–1989, with 3 follow-up exams at  $\approx$ 3-year intervals thereafter (visit 2: 1990–1992; visit 3: 1993–1995; visit 4: 1996–1998).

Participants were excluded from the current analyses for the following reasons: baseline hypertension (systolic blood pressure [SBP] $\geq$ 140 mm Hg, diastolic blood pressure [DBP] $\geq$ 90 mm Hg, or current use of antihypertensive medications for any reason, N=5495; blacks: N=2374 [56%]; whites: N=3121 [20%]), prevalent coronary heart disease (by history or ECG criteria, N=766; blacks: N=171 [4%]; whites: N=594 [5%]), history of stroke (N=286; blacks: N=91 [2%]; whites: N=195 [2%]), stage 4 or 5 chronic kidney disease (estimated glomerular filtration rate [GFR] <30 mL/min/1.73 m<sup>2</sup>,<sup>17</sup> N=247; blacks: N=169 [4%]; whites: N=23 [ $<$ 1%]), current use of uricosuric medications (N=78; blacks: N=20 [0.5%]; whites: N=58 [0.5%]), self-identified ethnicity other than black or white (N=48), or missing values for important predictor variables (uric acid, N=204; SBP and DBP, N=68; body mass index [BMI], N=78). A total of 9104 participants were included in the primary analyses (black N=1687; white N=7417). Secondary analyses evaluating the baseline association between SUA and blood pressure included additional individuals not taking antihypertensive medications at baseline (N=10 430).

### Examination

The baseline and follow-up examinations included standardized medical history, physical examination with anthropometric measures, and laboratory testing. SUA was measured using the uricase method, and the reliability coefficient of SUA was 0.91 assessed by repeated measurements taken  $\geq$ 1 week apart in 40 subjects.<sup>18</sup> Blood pressure was measured by certified technicians with a random-0 sphygmomanometer. Following a standardized protocol, the second and third of 3 measurements were averaged to estimate SBP and DBP. Based on repeated measurements of 190 ARIC participants 1 to 2 weeks apart during the second follow-up examination period, the reliability coefficients were 0.75 for SBP and 0.62 for DBP.<sup>19</sup> Trained technicians measured height, weight, and waist circumference following a standardized protocol. Diabetes was defined as history of diabetes, current use of glucose-lowering medications, fasting glucose  $\geq$ 126 mg/dL, or nonfasting glucose  $\geq$ 200 mg/dL.<sup>20</sup> GFR was estimated with baseline serum creatinine using the Modification of Diet in Renal Disease Study equation.<sup>17</sup> Current smoking and ethanol intake were ascertained from a standardized questionnaire, and daily sodium intake was estimated from a semiquantitative food frequency questionnaire adapted from the instrument validated previously by Willett et al.<sup>21</sup> Leisure-time physical activity was measured at visits 1 and 3 using a modification of the Baecke Physical Activity questionnaire.<sup>22</sup>

### Outcome

Hypertension status was ascertained at each examination. Hypertension was defined as SBP  $\geq$ 140 mm Hg, DBP  $\geq$ 90 mm Hg, or use of antihypertensive medications. In addition, individuals with SBP  $\geq$ 120 mm Hg or DBP  $\geq$ 80 mm Hg who did not meet criteria for hypertension were considered “prehypertensive,” as defined by the Joint National Committee on Prevention, Detection, Evaluation, and

Treatment of High Blood Pressure (JNC 7).<sup>23</sup> Hypertension onset was estimated at the midpoint between the last examination when the participant was free of hypertension and the first examination at which hypertension was documented.<sup>24</sup> Additional analyses modeled the time to blood pressure progression of blood pressure defined as an increase of  $\geq$ 1 JNC 7 category.

### Statistical Analysis

For descriptive analyses across groups, we used  $\chi^2$  analyses for categorical variables and ANOVA for continuous traits. Cross-sectional analyses evaluated the relationship between SUA and SBP or DBP in all of the individuals not taking antihypertensive medications at the baseline examination, using general linear models adjusted for age, BMI, GFR, diabetes status, smoking status, and field center.

The primary analyses used Cox proportional hazards models to estimate hazard ratios for incident hypertension for each SD higher baseline SUA. Because there was marginal evidence of an ethnicity/sex/uric acid interaction ( $P=0.1$ ), race–sex subgroups were analyzed in addition to the overall cohort analyses. The proportional hazards assumption was evaluated by examining log–log survival plots. The base model adjusted for age and field center (model 1). A second model adjusted for covariates in the base model, as well as baseline SBP and DBP (model 2). A third model included the covariates in model 2, as well as diabetes status, current smoking, and BMI (model 3). Because weight gain is associated with an increase in blood pressure, BMI was used as a time-dependent covariate using updated measures. Because renal function could represent a confounder or an intermediary in the association between uric acid and hypertension, Model 4 included the covariates in model 3 with the addition of estimated GFR. A fifth model, evaluated in a subsample (N=7603), included model 4 covariates plus baseline log-transformed sodium intake (log normal [sodium milligrams per day]), log-transformed alcohol intake (log normal [1+ethanol grams per week]), and leisure time physical activity. For this model, the lifestyle variables were included as time-dependent covariates when updated measures were available. All of the models evaluating the overall cohort also include race and sex as covariates. All of the analyses in race–sex subgroups used the subgroup-specific SDs for calculating standardized hazard ratios.

A secondary outcome was time-to-progression of JNC 7 category,<sup>23</sup> adjusted for the covariates in model 4. For comparison with other studies, we performed analyses using the race–sex-specific median or 7 mg/dL as the cutoff, as well as modeling that compared with the fourth and first race–sex-specific quartile and that evaluated at the hazard ratio for each 1-mg/dL increment of SUA. Additional models included visit 2 measures of SUA, with SUA modeled as a time-dependent predictor. The primary analyses were also repeated after restricting the cohort to individuals with an estimated GFR of  $>$ 60 mL/min/1.73 m<sup>2</sup> (N=7353).

To further account for measurement error in SBP and DBP at baseline, we performed sensitivity analyses using a 2-stage linear mixed-effects/Cox model.<sup>25</sup> In the first stage, general linear mixed models<sup>26</sup> used repeated measures of SBP and DBP from the baseline and follow-up visits to generate new estimates for baseline blood pressure. These new estimates were then used as the baseline measures for fully adjusted (model 4 covariates) Cox proportional hazards models of incident hypertension and blood pressure progression. All of the analyses were performed using SAS version 9.1 (SAS Institute), and all of the statistical tests were 2-tailed with an  $\alpha$  level of 0.05.

## Results

At the baseline examination, the mean age of the cohort was 53.3 years (range: 44 to 65 years), with a mean (SD) SBP of 113.8 (12.2) mm Hg and DBP of 70.2 (8.6) mm Hg. There were significant differences among the race–sex subgroups for all of the covariates evaluated (Table 1). When comparing covariates by uric acid levels (above or below the median)

**TABLE 1. Characteristics of ARIC Participants Free of Hypertension at Baseline Exam (N=9104)**

Baseline Characteristics	Total Cohort	Black Men	Black Women	White Men	White Women	P*
No. (% of cohort)	9104	677 (7.4)	1010 (11.1)	3465 (38.1)	3952 (43.4)	
Age	53.3 (5.6)	52.6 (5.8)	51.9 (5.5)	53.9 (5.6)	53.2 (5.6)	<0.0001
BMI, kg/m <sup>2</sup>	26.6 (4.7)	26.6 (4.3)	29.5 (6.0)	26.9 (3.7)	25.6 (4.8)	<0.0001
Smoking, %	27.0	38.3	25.5	26.2	26.0	<0.0001
Diabetes, %	6.6	11.1	11.7	6.5	4.6	<0.0001
Estimated GFR (mL/min/1.73 m <sup>2</sup> )	68.8 (11.3)	80.1 (12.7)	76.6 (12.7)	69.0 (9.8)	64.6 (9.3)	<0.0001
Alcohol intake median [25th to 75th percentile], g/wk	0 [0–47.5]	0 [0–69.8]	0 [0–0]	15.1 [0–92.4]	0 [0–25.9]	<0.0001
Sodium intake median [25th to 75th percentile], mg/d	1407 [1059–1839]	1513 [1114–1963]	1272 [952–1734]	1520 [1122–1973]	1339 [1023–1725]	<0.0001
SBP, mm Hg	113.8 (12.2)	117.4 (10.9)	116.7 (11.6)	115.1 (11.4)	111.2 (12.8)	<0.0001
DBP, mm Hg	70.2 (8.6)	75.4 (7.9)	76.6 (7.9)	71.3 (8.2)	67.6 (8.5)	<0.0001
Uric acid, mg/dL	5.7 (1.4)	6.5 (1.4)	5.3 (1.3)	6.5 (1.2)	5.0 (1.1)	<0.0001

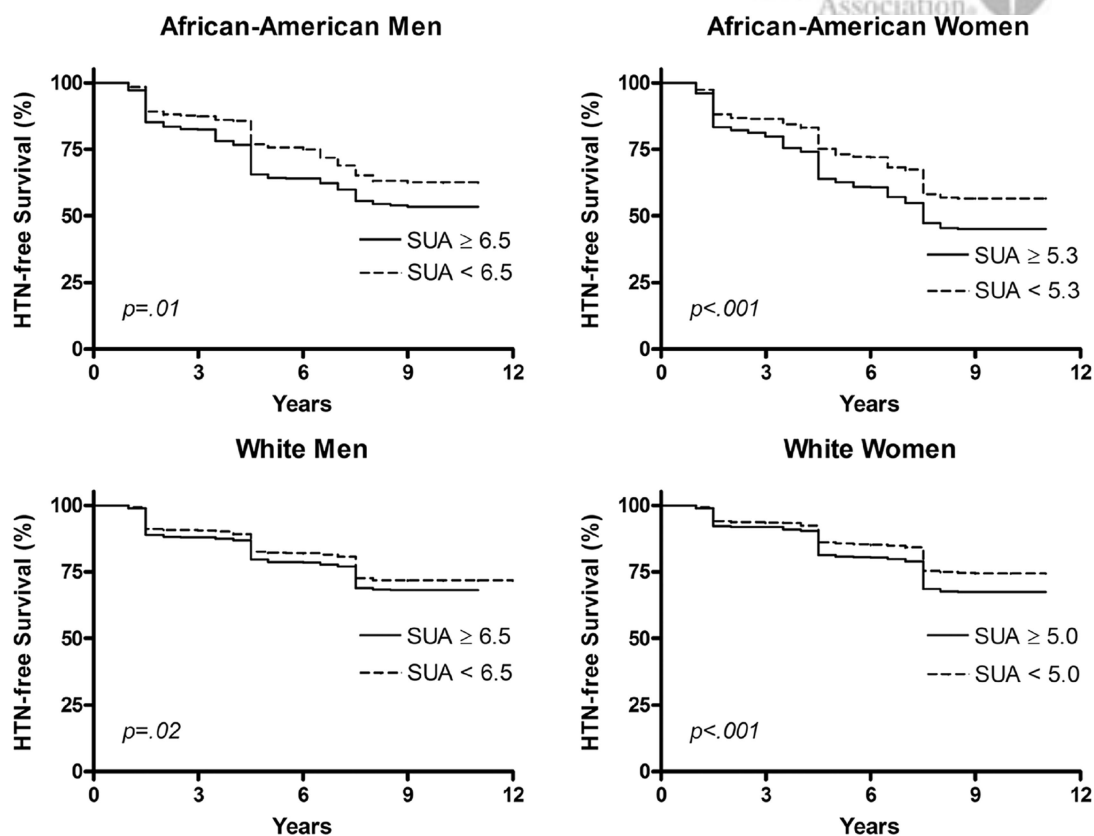
Values for continuous characteristics are mean (SD) or median [25th to 75th percentile].

\*P for ANOVA or  $\chi^2$  comparisons across race–sex groups.

within race–sex subgroups, BMI, SBP, and DBP were consistently higher in those with higher uric acid, and estimated GFR was consistently lower (Supplementary Tables I to IV available online at <http://hyper.ahajournals.org>). In cross-sectional analyses of individuals not taking antihypertensive medications at baseline (N=10 430), SUA was positively associated with both SBP and DBP in the overall sample and in all of the race–gender subgroups except black women (Figure 1, available online). This pattern was attenuated but

essentially unchanged when the analyses were restricted to individuals with SBP <140 mm Hg and DBP <90 mm Hg (data not shown).

In unadjusted analyses, SUA above the median was associated with incident hypertension in all of the race–sex subgroups (Figure 1). However, in multivariable modeling, the association between SUA and incident hypertension was largely attenuated by adjusting for baseline SBP and DBP (Model 2) in white men and women (Table 2). In models



**Figure 1.** Kaplan–Meier plots of incident hypertension by race–sex subgroups, stratified by median serum uric acid. P value from log-rank test.

**TABLE 2. Hazard Ratios of Incident Hypertension per SD Increment of Baseline Serum Uric Acid**

Analytic Model	Overall*		Black Men		Black Women		White Men		White Women	
	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
Model 1†	1.24 (1.18 to 1.30)	<0.0001	1.35 (1.18 to 1.55)	<0.0001	1.27 (1.14 to 1.41)	<0.0001	1.12 (1.05 to 1.20)	0.0006	1.21 (1.13 to 1.29)	<0.0001
Model 2‡	1.11 (1.05 to 1.16)	<0.0001	1.27 (1.10 to 1.46)	0.0006	1.23 (1.10 to 1.38)	0.0002	1.02 (0.96 to 1.09)	0.49	1.07 (1.00 to 1.14)	0.06
Model 3§	1.06 (1.01 to 1.12)	0.02	1.32 (1.13 to 1.53)	0.0003	1.16 (1.03 to 1.31)	0.02	1.01 (0.94 to 1.08)	0.88	1.02 (0.95 to 1.10)	0.57
Model 4	1.07 (1.02 to 1.13)	0.007	1.32 (1.14 to 1.54)	0.0003	1.16 (1.03 to 1.31)	0.01	1.01 (0.94 to 1.09)	0.73	1.04 (0.96 to 1.11)	0.34
Model 5¶	1.08 (1.02 to 1.14)	0.007	1.31 (1.10 to 1.54)	0.002	1.16 (1.01 to 1.33)	0.04	1.02 (0.95 to 1.10)	0.58	1.04 (0.97 to 1.12)	0.30
Hypertension cases/total (%)	2561/9104 (28.1)		226/677 (33.4)		400/1010 (39.6)		922/3465 (26.6)		1013/3952 (25.6)	

HR indicates hazard ratio.

\*Race and sex included as covariates in all models of the overall cohort.

†Model 1: adjusted for age and field center.

‡Model 2: adjusted for covariates in model 1+baseline SBP and DBP.

§Model 3: adjusted for covariates in model 2+BMI, diabetes status, smoking status.

||Model 4: adjusted for covariates in model 3+estimated GFR.

¶Model 5: adjusted for covariates in model 4+alcohol intake, sodium intake, physical activity (N=7603).

adjusting for baseline age, clinical center, SBP, DBP, BMI, diabetes status, smoking status, and estimated GFR, each SD higher baseline SUA was associated with an increased hazard of incident hypertension for the overall cohort (hazard ratio: 1.07 [95% CI: 1.02 to 1.13]), black men (hazard ratio: 1.32 [95% CI: 1.14 to 1.54]), and black women (hazard ratio: 1.16 [95% CI: 1.03 to 1.31]). This trend was not significant for white men (hazard ratio: 1.01 [95% CI: 0.94 to 1.09]) or white women (hazard ratio: 1.04 [95% CI: 0.96 to 1.11]). These findings did not change after accounting for alcohol intake, sodium intake, and leisure time physical activity (model 5). The patterns were similar in analyses using different SUA thresholds (race–sex-specific median, fourth versus first quartile, or 7 mg/dL), modeling a 1-mg/dL increment of baseline SUA, using follow-up measures of SUA, or restricted to individuals with estimated GFR  $\geq 60$  mL/min/1.73 m<sup>2</sup> (Table V, available online). Additional models that included other medications (hormone replacement therapy, salicylates, and nonsteroidal anti-inflammatory medications), dietary factors (animal protein intake and vitamin C intake), alternative measures of renal function (serum creatinine or GFR estimated by Cockcroft–Gault), or alternative measures of obesity (waist circumference) did not alter these findings (data not shown).

Similarly, each SD greater than baseline SUA was associated with a significantly increased risk for blood pressure progression (increase in JNC 7 category  $\geq 1$ ) in the overall sample (hazard ratio: 1.12 [95% CI: 1.07 to 1.19];  $P < 0.0001$ ). The ethnic difference in event rates was less pronounced with this outcome (black men: 51%; black women: 55%; white men: 49%; white women: 50%), but the differences in the relationship between SUA and blood pressure among race–sex subgroups were similar (Figure 2).

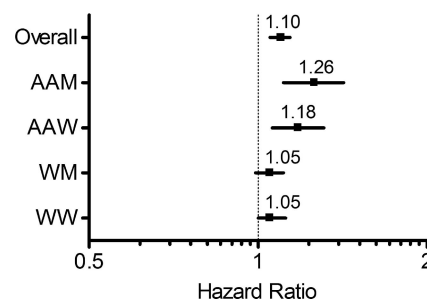
Finally, sensitivity analyses evaluated incident hypertension or blood pressure progression using baseline SBP and DBP estimated from repeated blood pressure measures over follow-up. In these models, greater SUA remained predictive of the primary and secondary outcomes, although statistical significance of this relationship was attenuated (Table 3). The pattern among race–sex groups was similar.

## Discussion

In this biethnic cohort of middle-aged men and women, each SD increment of baseline SUA was associated with a 7%

greater risk of incident hypertension over 9 years of follow-up, independent of age, baseline blood pressure, body mass, diabetes status, smoking status, and renal function. This study extends findings from previous studies on the longitudinal association between SUA and hypertension to middle-aged blacks, because the ARIC cohort had nearly twice as many cases of incident hypertension among blacks (N=626) as any previous prospective study.<sup>2,8,16</sup>

The positive association between SUA and incident hypertension was stronger in blacks and most pronounced among black men. This observation is significant considering the fact that blacks suffer disproportionately from hypertension and its associated target-organ damage.<sup>13,14</sup> Hypertension control rates are lower among blacks, despite the fact that hypertension awareness and treatment is equal or higher in blacks compared with non-Hispanic whites.<sup>13,27</sup> Our results are consistent with findings from the Coronary Artery Risk Development in (Young) Adults study (CARDIA), in which the association between SUA and incident hypertension was stronger in blacks than in whites.<sup>16</sup> This is also consistent with earlier reports from the ARIC cohort with respect to SUA and cardiovascular events. A previous study found an association between SUA and incident heart disease in black women but not in other women.<sup>28</sup> Similarly, SUA in the highest quartile was associated with a 79% increased risk of



**Figure 2.** Hazard ratio for incident blood pressure progression for each SD increase in baseline serum uric acid. Blood pressure progression increase of  $\geq 1$  JNC 7 category; Cox models adjusted for age, field center, SBP, DBP, BMI, diabetes status, smoking status, and estimated GFR (overall model also adjusted for race and sex). Note that x axis scale is log<sub>2</sub>. AAM indicates black men; AAW, black women; WM, white men; WW, white women.

**TABLE 3. Hazard Ratios of Incident Hypertension or Blood Pressure Category Increase ( $\geq 1$ ) per SD Higher Than Baseline Serum Uric Acid in Sensitivity Analyses**

Analytic Model	Overall*		Black Men		Black Women		White Men		White Women	
	HR (95% CI)	<i>P</i>	HR (95% CI)	<i>P</i>	HR (95% CI)	<i>P</i>	HR (95% CI)	<i>P</i>	HR (95% CI)	<i>P</i>
Sensitivity analysis 1† (incident HTN)	1.05 (1.00 to 1.12)	0.05	1.26 (1.08 to 1.47)	0.003	1.14 (1.01 to 1.28)	0.04	0.99 (0.92 to 1.07)	0.78	1.03 (0.96 to 1.11)	0.38
Sensitivity analysis 2‡ (BP progression)	1.05 (1.01 to 1.10)	0.01	1.20 (1.06 to 1.35)	0.004	1.16 (1.04 to 1.29)	0.006	1.02 (0.96 to 1.09)	0.50	1.04 (0.96 to 1.11)	0.26

Sensitivity analyses used baseline and follow-up blood pressure measures in general linear mixed models to estimate baseline SBP and DBP; all models adjusted for age, field center, SBP, DBP, BMI, diabetes, smoking, and estimated GFR. HTN indicates hypertension; BP, blood pressure; HR, hazard ratio.

\*Race and sex included as covariates in all models of the overall cohort.

†Modeling incident hypertension (SBP  $\geq 140$  mm Hg, DBP  $\geq 90$  mm Hg, or antihypertensive medication use).

‡Modeling incident increase in JNC 7 blood pressure category  $\geq 1$  (normal  $\rightarrow$  prehypertension; prehypertension  $\rightarrow$  hypertension; normal  $\rightarrow$  hypertension).

ischemic stroke in blacks compared with a 27% increased risk among whites, although this interaction was not statistically significant.<sup>29</sup> Thus, the prognostic significance of SUA with respect to both hypertension and its cardiovascular end points may vary by ethnicity.

The association we observed was weaker in black females than in black men. This could be because of the overall high rate of incident hypertension and a diminution of a true association because of competing risks for hypertension. Black women had the highest mean baseline BMI of the groups examined, and models accounting for BMI resulted in the greatest attenuation of the association. This is consistent with an earlier study that found that the association between SUA and incident hypertension was diluted in obese individuals.<sup>5</sup> The relationship between SUA and incident hypertension was less pronounced in whites, but this is not inconsistent with earlier reports. As Sundstrom et al noted,<sup>9</sup> the observed strength of the association between SUA and hypertension has been less pronounced in older cohorts, and the ARIC study is the oldest cohort in which this association has been explored. One potential explanation, consistent with the model proposed by Johnson et al,<sup>30</sup> is that the pathogenic role for uric acid is greater early in the natural history of hypertension. In the ARIC study, 35% of the cohort was hypertensive at baseline, and this study did not assess the predictive role of SUA for those individuals. This study was unable to assess the relative strength of the association across subgroups as they approach middle age. However, taken in conjunction with the earlier CARDIA findings, the strength of the association in blacks compared with whites seems to be consistent in different age groups.

Exploring ethnic variation in disease pathogenesis is challenging, because self-identified race is a complex construct reflecting biological, psychosocial, economic, and environmental factors.<sup>31</sup> Thus, we are reluctant to ascribe the differences we observed to underlying “genetic” factors, because self-identified race is a poor proxy for genetic ancestry,<sup>32</sup> and other factors correlated to this construct may be equally or more important in disease pathogenesis,<sup>33</sup> albeit challenging to measure. Nonetheless, our study complements other investigations that have not been able to prospectively address the question of SUA and incident hypertension in a large number of blacks.

In addition to the biethnic cohort, this study has several significant strengths. ARIC is the largest epidemiological

cohort in which the longitudinal relationship between SUA and hypertension has been addressed with fully adjusted models. As noted previously, this middle-aged cohort complements earlier investigations in younger populations, potentially reflecting a different stage in the pathogenesis of hypertension. Furthermore, the serial examinations at which to detect hypertension offer greater power to evaluate hypertension incidence over time.

Although our analyses adjusted for important potential confounders, there remains the possibility that the observed relationship was secondary to residual confounding. The black participants had higher body mass indices, diabetes prevalence, and baseline blood pressure, and it is possible that models accounting for these differences failed to capture important associated confounders. Similarly, adjustment for estimated GFR may fail to fully account for underlying preclinical renal impairment, which would be reflected by baseline SUA elevations and could precede elevated blood pressure. Of note, SUA has been strongly correlated with urinary microalbumin, a marker of early vascular damage and renal dysfunction, in prehypertensive subjects.<sup>34</sup> In the absence of baseline measures of urinary albumin, we are unable to assess the potential mediating or confounding role of preclinical proteinuria in the associations we observed.

There are several limitations to this study. The exclusion of individuals who were hypertensive at baseline selected out individuals with hypertension onset at a younger age, and, thus, our findings may not be reflective of earlier-onset hypertension. This is of particular concern given the fact that the majority of blacks (56%) in ARIC were hypertensive at baseline, which could introduce selection bias. Similarly, the prevalence of baseline renal insufficiency, an exclusion criterion, was higher in blacks. Thus, the differences among ethnic groups should be viewed with caution. However, as noted above, a similar pattern was observed in the younger CARDIA cohort. Another potential limitation is misclassification of hypertensive individuals as normotensive at baseline. However, the pattern of our results was consistent when modeling the alternative outcome of blood pressure progression. Furthermore, variability in measures of blood pressure, SUA, or their covariance is a source of measurement error that could bias results.<sup>35</sup> Although the data required to fully account for this were not available, the observed measurement variability was more pronounced for blood pressure,<sup>19</sup> and our findings were consistent in sensitivity analyses designed to minimize baseline measurement error in SBP and DBP.

An additional consideration is the fact that most of the black participants came from 1 field center (Jackson: 86%), limiting our ability to distinguish the effect of ethnicity from field center effects. The exclusion of the field center covariate from these analyses did not alter our findings, suggesting that field center did not completely account for the observed heterogenous associations across race–sex subgroups.

### Perspectives

SUA was positively associated with incident hypertension over 9 years of follow-up, and this relationship was stronger in blacks. More research is warranted concerning the physiological and clinical consequences of hyperuricemia, especially in blacks.

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### Disclosures

None.

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