Serum Uric Acid and Cardiovascular Mortality
The NHANES I Epidemiologic Follow-up Study, 1971-1992

Jing Fang, MD

Michael H. Alderman, MD

MANY, BUT NOT ALL, EPIDE-miological studies have suggested that serum uric acid is a risk factor for cardiovascular disease.[1-9] Increased serum uric acid levels are linked to obesity, dyslipidemia, and hypertension (insulin resistance or syndrome X), all of which are also associated with increased risk for cardiovascular disease.[3] However, the specific role of serum uric acid in this constellation remains uncertain.[10]

An earlier report, based on the First National Health and Nutrition Examination Survey (NHANES I) Epidemiologic Follow-up Study (NHEFS), 1971-1987,[8] indicated that baseline serum uric acid level was an independent predictor of mortality and, particularly, of ischemic heart disease death but only for women. Recently, a study generated from Framingham Heart Study data reported that by controlling for other risk factors, the apparent relationship of uric acid to cardiovascular or all-cause mortality was not sustained.[9] The authors concluded that use of diuretics was the covariate most responsible for reducing the statistical significance of serum uric acid to cardiovascular outcome.[9]

To further explore the now unresolved relationship of serum uric acid to cardiovascular disease, we report on an extension of the NHEFS from 1987 to 1992. The additional 5 years of follow-up has nearly doubled the number of deaths (892 to 1593) available for analysis.[8] This updated report extends the earlier study of the association of serum uric acid levels with car-

Context Although many epidemiological studies have suggested that increased serum uric acid levels are a risk factor for cardiovascular mortality, this relationship remains uncertain.

Objective To determine the association of serum uric acid levels with cardiovascular mortality.

Design and Setting Cross-sectional population-based study of epidemiological follow-up data from the First National Health and Nutrition Examination Survey (NHANES I) from 1971-1975 (baseline) and data from NHANES I Epidemiologic Follow-up Study (NHEFS).

Participants A total of 5926 subjects who were aged 25 to 74 years and had serum uric acid level measurements at baseline.

Main Outcome Measures Ischemic heart disease mortality, total cardiovascular mortality, and all-cause mortality, compared by quartiles of serum uric acid level.

Results In an average of 16.4 years of follow-up, 1593 deaths occurred, of which 731 (45.9%) were ascribed to cardiovascular disease. Increased serum uric acid levels had a positive relationship to cardiovascular mortality in men and women and in black and white persons. Deaths due to ischemic heart disease in both men and women increased when serum uric acid levels were in the highest quartile compared with the lowest quartile (men, >416 vs <321 µmol/L; risk ratio, 1.77 [95% confidence interval {CI}, 1.08-3.98]; women, >333 vs <238 µmol/L; risk ratio, 3.00 [95% CI, 1.45-6.28]). Cox regression analysis showed that for each 59.48-µmol/L increase in uric acid level, cardiovascular mortality and ischemic heart disease mortality increased. Hazard ratios for men were 1.09 (95% CI, 1.02-1.18) and 1.17 (95% CI, 1.06-1.28), and for women were 1.26 (95% CI, 1.16-1.36) and 1.30 (95% CI, 1.17-1.45), respectively, after adjustment for age, race, body mass index, smoking status, alcohol consumption, cholesterol level, history of hypertension and diabetes, and diuretic use. Further analysis, stratifying by cardiovascular risk status, diuretic use, and menopausal status, confirmed a significant association of uric acid and cardiovascular mortality in all subgroups except among men using diuretics (n=79) and men with 1 or more cardiovascular risk factors (n=1140).

Conclusion Our data suggest that increased serum uric acid levels are independently and significantly associated with risk of cardiovascular mortality.

JAMA. 2000;283:2404-2410   www.jama.com

diovascular mortality and ischemic heart disease mortality in men and women and, for the first time, examines this relationship separately for blacks and whites, accounting for diuretic use, cardiovascular risk profile, and menopausal status among women.

METHODS
Study Design

The NHANES I, sponsored by the National Center for Health Statistics, was conducted from 1971 to 1975 on a nationwide probability sample of the US civilian noninstitutionalized population. The survey included a standardized medical examination and question-

Author Affiliations: Department of Epidemiology and Social Medicine, Albert Einstein College of Medicine, Bronx, NY.

Corresponding Author and Reprints: Michael H. Alderman, MD, Department of Epidemiology and Social Medicine, Albert Einstein College of Medicine, 1300 Morris Park Ave, Bronx, NY 10461 (e-mail: alderman@aecom.yu.edu).

naires that addressed a variety of health-related topics. Low-income persons, the elderly, and women of childbearing age were oversampled. The total NHANES I sample included 20 729 persons aged 25 to 74 years, of whom 14 407 (70%) were medically examined. A subsample of 6913, the "detailed sample," were examined in greater depth, which rendered additional data including serum uric acid levels.[11]

NHEFS is a longitudinal follow-up of participants in NHANES I who were aged 25 to 74 years at the time of survey. The personal interviews and physical and laboratory examinations of NHANES I provided the baseline data for NHEFS.

Among 6913 subjects in the detailed sample, information on serum uric acid was available in 6651. Of these, subjects were excluded if they reported myocardial infarction, stroke, and gout or were pregnant at baseline (439); if their racial or ethnic background was other than non-Hispanic white or non-Hispanic black (63); and if their vital status was missing in the 1992 follow-up (223). The remaining 5926 are the subjects of this analysis.

Baseline Measurements

Blood samples were obtained from non-fasting persons, and frozen serum was sent to the Centers for Disease Control and Prevention for analysis. Serum uric acid was measured using an automated colorimetric phosphotungstic acid procedure, which had been validated against a uricase assay, on a Technicon SMA 12-60 (Technicon Instruments, Tarrytown, NY). The baseline medical history questionnaire provided information about history of selected conditions, eg, diabetes, heart disease, hypertension, and gout, as well as history of using any medicine. At the beginning of the baseline physical examination, blood pressure was measured by a physician once while the examinee was seated. Smoking status and the number of cigarettes smoked for current smokers were obtained at baseline for 50% of the detailed subsample of 6913. For the remaining persons, smoking status at baseline was deter-

mined by questionnaire in the 1982 to 1984 follow-up interview on lifetime smoking history, which applied to both subject and surrogate interview. The validity of this approach has been documented.[12,13] The smoking status information used in this analysis therefore combines the 2 interviews, which increased the available information on smoking to more than 95% of the study population. Current smoking was defined as answering yes to both questions, "Did you ever smoke at least 100 cigarettes or more in your lifetime?" and, "Do you smoke cigarettes now?" For women, pregnancy and menstrual cycle status also were obtained from the medical history. Menopause was defined by the answer "yes" for the question, "Have the cycles entirely stopped?" Of note is the missing data for some important baseline characteristics. For example, serum creatinine concentration was absent in about 60% of records, and menopause status information was missing for about 60% of women.

Outcome Measures

Follow-up data, based on interviews, health care facility medical records, and death certificates, were collected in 4 waves of follow-up: 1982 to 1984, 1986, 1987, and 1992.[14] Death was ascertained by either death certificate, a proxy interview, or both. In the former case, the underlying cause of death was coded according to the *International Classification of Diseases, Ninth Revision (ICD-9)*. Deaths were analyzed for all causes, total cardiovascular disease (*ICD-9* codes 390-459), and ischemic heart disease (*ICD-9* codes 410-414). Years of follow-up for each individual were calculated from baseline to the date of death for decedents and to the date of follow-up for those still alive.

Statistical Analysis

Subjects were then stratified into quartiles of baseline serum uric acid level by sex. The baseline characteristics of continuous variables were measured by quartiles of serum uric acid level, and the differences across quartiles were tested with analysis of variance for men

and women separately. For dichotomous variables, such as history of disease, diuretic use, and substance abuse, the mean levels of uric acid were measured for each group ("yes" vs "no"). Statistical significance was tested using the *t* test, specifying by sex and race.

Age- and race-adjusted ischemic heart disease mortality rates, expressed as per 1000 person-years, were calculated for each quartile of serum uric acid for both sexes, using the direct method of standardization with the total sample serving as the standard population. The mortality ratio, using the lowest quartile as reference for each other quartile of serum uric acid, was calculated with Mantel-Haenszel method. Cox proportional hazard regression models were used separately to examine the relationship of serum uric acid levels to all-cause, total cardiovascular, and ischemic heart disease mortality, adjusting for baseline characteristics. Separate models for sex- and race-specific analysis were also produced. These analyses were adjusted for age, race, body mass index, cholesterol level, smoking status, alcohol consumption, and history of hypertension and diabetes. The adjusted hazard ratios were for each 59.48-μmol/L difference in serum uric acid level. The interaction term of uric acid level and diuretic use was tested in the Cox regression models.

The association of mortality to serum uric acid level was also estimated after stratifying by age into 3 groups (<45, 45-54, and ≥55 years), as well as by cardiovascular risk status (those with any 1 of the risk factors: hypertension [with history of hypertension, blood pressure ≥160/95 mm Hg, or taking antihypertensive medication], cholesterol level ≥6.35 mmol/L [≥245 mg/dL]; with history of diabetes; and those with any 2 of these conditions; as well as those without any of these conditions). The interaction term of uric acid level and diuretic use was tested in Cox regression model. In addition, as diuretic use is related to both serum uric acid level and cardiovascular events, the subjects were stratified into 2 groups by diuretic use. Women, due to substan-

tially increased uric acid level after menopause,[4,8] were stratified into 2 groups by menopausal status for those (n=1092) in whom menopausal information was available. Cox regression models were used to determine the relationship of serum uric acid levels to cardiovascular mortality in each stratified group. Other cardiovascular risk factors adjusted for in these models were age, race, body mass index, smoking status, and alcohol consumption.

RESULTS

Serum Uric Acid Levels

The mean age of the study population was 48.1 years. The mean (SD) serum uric acid level was 327 (86) µmol/L (range, 42-744 µmol/L). Men had significantly higher uric acid levels than women (370 vs 291 µmol/L, P<.001), and black persons had significantly higher levels than white persons (340 vs 325 µmol/L, P<.001). The mean levels of serum uric acid increased with age, from 316 µmol/L among those younger than 45 years to 340 µmol/L among those older than 65 years (P<.001).

In general, among both men and women, the higher quartiles of serum uric acid levels were associated with increasing blood pressure, cholesterol levels, and body mass index (TABLE 1). Of particular note is the different age distribution by quartile for men and women. For men, age was similar throughout the quartiles, but for women, age increased from the lower to higher quartiles. Serum creatinine levels, which were measured in 2267 of the total of 5926 subjects, were associated with serum uric acid. Creatinine levels by uric acid quartile were 95.5 (1.08), 97.2 (1.10), 97.2 (1.10), and 104.3 µmol/L (1.18 mg/dL) for men (P<.001), and 79.6 (0.90), 83.1 (0.94), 84.9 (0.96), 96.4 µmol/L (1.09 mg/dL) for women (P<.001).

Serum uric acid levels were substantially higher among persons reporting diuretic use within the past 30 days, or alcohol use (at least twice a week) for the 4 race and sex groups (TABLE 2).

Table 1. Characteristics by Quartiles of Baseline Level of Uric Acid*

| | Quartiles of Serum Uric Acid, µmol/L | | | | | | | | | |
| | Men | | | | | Women | | | | |
Characteristics	1 (<321)	2 (321-363)	3 (364-416)	4 (>416)	P Value	1 (<238)	2 (238-280)	3 (281-333)	4 (>333)	P Value
No. of subjects	666	674	700	662		859	798	800	767	
Age, y	49.6 (13.9)	46.9 (14.3)	47.8 (13.9)	48.6 (13.8)	<.03	44.6 (13.1)	45.6 (13.5)	48.5 (14.0)	53.7 (13.6)	<.001
Body mass index, kg/m²	24.0 (3.6)	25.3 (4.5)	26.1 (4.0)	27.6 (4.2)	<.001	23.5 (4.4)	24.4 (4.3)	26.0 (5.4)	29.2 (7.0)	<.001
Blood pressure, mmHg										
Systolic	131.4 (21.1)	132.9 (20.3)	132.5 (19.0)	138.2 (21.7)	<.001	124.7 (21.8)	126.7 (21.9)	131.9 (23.6)	143.4 (26.4)	<.001
Diastolic	83.5 (11.6)	84.7 (11.8)	85.3 (11.6)	89.7 (13.5)	<.001	78.8 (11.4)	80.3 (11.4)	83.3 (12.1)	88.5 (14.6)	<.001
Cholesterol, mmol/L	5.55 (1.11)	5.64 (1.11)	5.66 (1.17)	5.83 (1.19)	<.001	5.51 (1.18)	5.73 (1.21)	5.84 (1.23)	6.23 (1.30)	<.001

*Data are presented as mean (SD). To convert from µmol/L per liter to mg/dL divide by 59.48.

Table 2. Baseline Serum Uric Acid by Medical History, Behavior, Race, and Sex

| | White | | | | | Black | | | | |
| | Variable Present | | Variable Not Present | | | Variable Present | | Variable Not Present | | |
Variables	No. of Subjects	Serum Uric Acid Level, µmol/L	No. of Subjects	Serum Uric Acid Level, µmol/L	P Value	No. of Subjects	Serum Uric Acid Level, µmol/L	No. of Subjects	Serum Uric Acid Level, µmol/L	P Value
				Men						
Hypertension	208	393	2178	368	<.001	61	401	255	374	.05
Diabetes	43	357	2343	366	.27	9	343	307	382	.13
Diuretics use	66	415	2276	369	<.001	13	447	292	378	<.001
Alcohol use ≥2 times weekly	1001	384	1385	359	<.001	120	394	196	371	.04
Kidney disease	209	358	2177	367	.09	22	389	294	379	.19
Current smoking	809	363	1522	373	.10	158	378	135	380	.90
				Women						
Hypertension	345	319	2466	284	<.001	116	321	297	307	.21
Diabetes	58	307	2753	288	.05	24	343	389	309	.04
Diuretics use	307	333	2441	282	<.001	58	364	344	301	<.001
Alcohol use ≥2 times weekly	529	297	2282	286	.04	61	321	352	309	.05
Kidney disease	279	298	2532	287	.10	26	312	387	311	.97
Current smoking	742	280	1896	290	.31	148	312	231	309	.10

Table 3. Relationship of Serum Uric Acid Level and Ischemic Heart Disease Mortality by Sex

	Quartiles of Serum Uric Acid, µmol/L							
	Men				Women			
Variables	1 (<321)	2 (321-363)	3 (364-416)	4 (>416)	1 (<238)	2 (238-280)	3 (281-333)	4 (>333)
No. of deaths	50	51	63	85	25	26	42	79
Person-years	10 245	11 204	11 235	10 177	15 035	13 906	13 484	11 998
Ischemic heart disease death rate*	4.59	4.58	5.80	8.14	2.02	2.31	3.02	6.05
Risk ratio (95% confidence interval)	1.0	1.00 (0.13-3.34)	1.26 (0.45-3.76)	1.77 (1.08-3.98)	1.0	1.15 (0.51-3.89)	1.50 (0.89-4.01)	3.00 (1.45-6.28)

*Per 1000 person-years. Adjusted by age and race.

Subjects with a history of hypertension had a significantly higher serum uric acid level than those who did not, except for black women ($P = .21$), among whom this difference did not reach statistical significance. Women with diabetes, but not men, had higher serum uric acid levels than those without it (307 vs 288 µmol/L, white women; 343 vs 309 µmol/L for black women). Neither those currently smoking nor those who ever smoked more than 100 cigarettes were associated with increased serum uric acid levels. History of kidney disease was not associated with serum uric acid level.

Mortality

During an average of 16.4 years of follow-up (18.5 years, survivors; 10.9 years, decedents), 1593 persons (26.9%) in the study group died. Of the total deaths, 731 (45.9%) were ascribed to cardiovascular disease (ischemic heart disease, 421; stroke, 111; and other cardiovascular deaths, 199), and 429 deaths (26.9%) were cancer related.

Overall, crude all-cause and cardiovascular mortality rates were 16.4 (1593/97288) and 7.5 (731/97288) per 1000 person-years, respectively. Black persons had substantially higher crude mortality rates than did white persons (25.6 [282/11009] vs 15.2 [1311/86279], all-cause; and 11.5 [127/11009] vs 7.0 [604/86279], cardiovascular mortality, respectively).

Compared with the lowest quartile of uric acid level, age- and race-adjusted death rates for ischemic heart disease were significantly higher in quartile 4 for both men and women. In fact, the is-

Figure 1. Age-Adjusted Cardiovascular Mortality Rates by Quartile of Serum Uric Acid Level
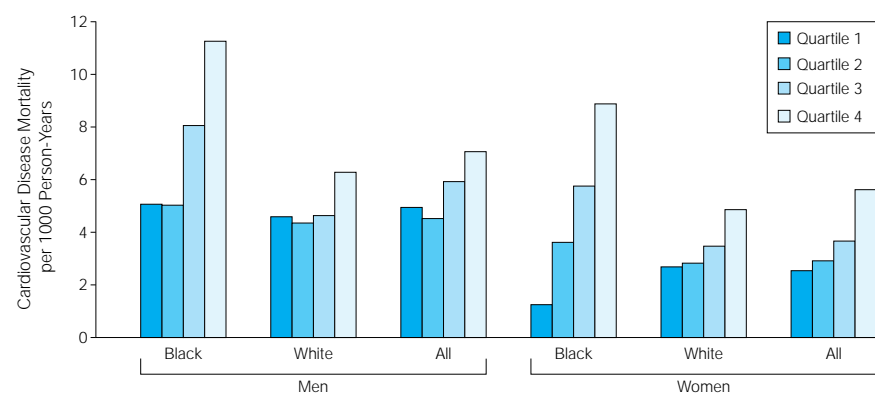
In each quartile, the serum uric acid levels for men are quartile 1, less than 321; quartile 2, from 321 through 263; quartile 3, from 364 through 416; and quartile 4, higher than 416 µmol/L, and for women are quartile 1, less than 238; quartile 2, from 238 through 280; quartile 3, 281 through 333; and quartile 4, higher than 333 µmol/L. $P < .01$ for all groups.

chemic heart disease mortality rate increased 77% for men (from 4.59 to 8.14 per 1000 person-years, $P = .01$), and 3-fold for women (from 2.02 to 6.05, $P < .001$) for serum uric acid level from quartile 1 to quartile 4 (**TABLE 3**). Although the mortality rate increased by 50% among women in quartile 3, it did not reach statistical significance ($P = .35$).

Age-adjusted cause-specific death rates for all races, as well as between races separately, revealed that total cardiovascular mortality was highest in the highest serum uric acid level quartile for all subjects, with the steepest rise in rates for black women (**FIGURE 1**). This was also true for ischemic heart disease (data not provided).

In separate multivariate Cox regression analyses, the association of serum uric acid level and all-cause, total cardiovascular, and ischemic heart dis-

ease mortality rates were estimated, controlling for age, race, body mass index, cholesterol level, smoking status, alcohol consumption, history of hypertension and diabetes, and diuretic use. For example, with each 59.48-µmol/L increase in serum uric acid level, the hazard ratio of cardiovascular disease and ischemic heart disease mortality were 1.09 (95% confidence interval [CI], 1.02-1.18) and 1.17 (95% CI, 1.06-1.28) for men, and 1.26 (95% CI, 1.16-1.36) and 1.30 (95% CI, 1.17-1.45) for women, respectively (**FIGURE 2**). This association was also found for all-cause mortality. Further stratification of subjects by race showed the above associations were observed for both white and black persons. For each 59.48-µmol/L increase in serum uric acid, hazard ratios and 95% CIs of cardiovascular disease mortality for

Figure 2. Hazard Ratios of All-Cause, Cardiovascular Disease, and Ischemic Heart Disease Mortality for Each 59.48-μmol/L Increase in Serum Uric Acid Levels
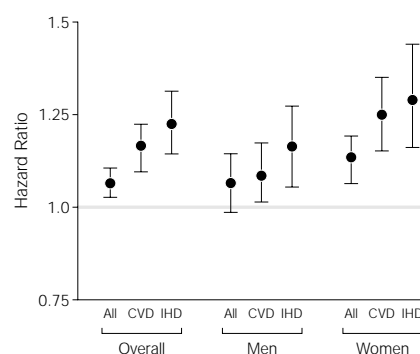
Cox regression analysis was adjusted for age, cholesterol level, race, body mass index, smoking status, alcohol consumption, and history of hypertension and diabetes for overall population and by sex. Error bars indicate 95% confidence intervals; gray line, no increase in uric acid level; All, all-cause; CVD, cardiovascular disease; and IHD, ischemic heart disease.

Figure 3. Hazard Ratios of Cardiovascular Mortality for Each 59.48-μmol/L Increase in Serum Acid Levels
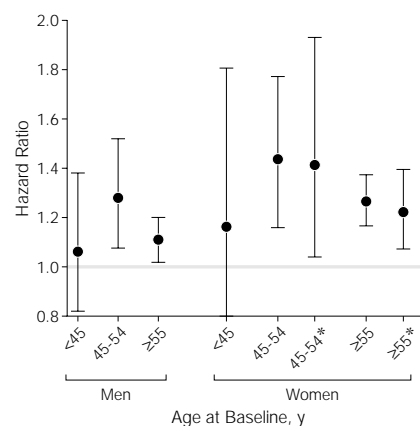
Analyses by Cox regression by sex and age, and adjusted for race, cholesterol level, body mass index, smoking status, alcohol consumption, history of hypertension and diabetes. Gray line indicates no increase in serum uric acid level. Models were adjusted for cholesterol levels, body mass index, race, smoking status, alcohol consumption, history of diabetes or hypertension, and use of diuretic. Asterisk indicates menopause status was included in the model. Error bars indicate 95% confidence intervals.

black men and women were 1.19 (95% CI, 1.00-1.42) and 1.38 (95% CI, 1.14-1.68) and for white men and women were 1.10 (95% CI, 1.02-1.18) and 1.26 (95% CI, 1.16-1.38), respectively.

Cox regression models were also constructed for those 2267 subjects with serum creatinine levels available (cardiovascular disease deaths, n=192). Controlling for risk factors cited above, plus serum creatinine, the hazard ratio for cardiovascular disease mortality for each 59.48- μmol/L increasing level in serum uric acid was 1.21 (95% CI, 1.11-1.34).

Stratification by age (<45, 45-54, and ≥55 years) influenced the predictive value of serum uric acid level for cardiovascular mortality (**FIGURE 3**). In multivariate analysis, increased serum uric acid levels were not associated with cardiovascular mortality in men and women younger than 45 years. However, for those aged 45 years and older, increased serum uric acid levels were related to higher cardiovascular mortality. For both men and women, the risk of increased serum uric acid levels for cardiovascular mortality was highest for those aged 45 to 54 years. For example, among that age group, an increase of 59.48 μmol/L in serum uric acid level predicted an increase in cardiovascular mortality rate of 28% (95% CI, 1.08-1.52) in men and 43% (95% CI, 1.16-1.77) in women. For those aged 55 years and older, the predictive value of increasing serum uric acid level fell to 11% (95% CI, 1.02-1.20) for men and 26% (95% CI, 1.16-1.37) for women. Among women aged 45 years and older whose menopausal status was available, adjusting with menopausal status did not change the predictive value of serum uric acid level (Figure 3).

The interaction of uric acid levels and diuretic use was not significantly associated with cardiovascular mortality. Nevertheless, the study population was further stratified by cardiovascular risk profile, by diuretic use, and by women with known menopausal status (**TABLE 4**). For women, in all subgroups, uric acid was a significant predictor of total cardiovascular mortality. Of note is that among women using diuretics, the risk of cardiovascular mortality for a 59.48-μmol/L increase in serum uric acid levels was higher than for those not using diuretics (1.47 vs 1.30).

The risk of a high uric acid level for cardiovascular mortality was substantially higher among menstruating women than postmenopausal women (hazard ratio, 1.51 vs 1.29). For men, hazard ratios were lower than for women in all subgroups. In addition, among men with increasing cardiovascular risk (2 and more risk factors, n=384; 1 risk factor, n=756), as well as those small number of persons using diuretics (n=79), there was no association between serum uric acid level and cardiovascular mortality.

COMMENT

In this representative general population, serum uric acid level bore a continuous, independent, specific, and significant positive relationship to cardiovascular mortality. This association was true for men and women and for blacks and whites. The impact of serum uric acid level on cardiovascular mortality in different age groups varied by sex. In neither men nor women, however, was the association manifest in persons younger than 45 years old. For both men and women, the highest risk of an increased serum uric acid level was between the ages of 45 and 54 years. Among women, this association was more robust than in men and persisted through all levels of cardiovascular risk, regardless of diuretic use or menopausal status. Among men at high cardiovascular risk and the rather small group taking diuretics, there was no association of serum uric acid to cardiovascular mortality.

These results are consistent with and extend an earlier, shorter follow-up of the NHANES I population. That study, based on 1987 NHANES I Epidemiologic Follow-up Study data, showed that an increased serum uric acid level was an independent predictor of all-cause and ischemic heart disease mortality for women only.[8] The ischemic heart disease mortality rate among women with a serum uric acid level of 416 μmol/L or more was almost 5-fold greater than for those with a level less than 238 μmol/L. This study, using the same baseline cohort, with nearly twice the

number of events (1593 vs 892) over a longer follow-up period (18.5 years vs 13.5 years for survivors), shows that the association of increased serum uric acid levels and cardiovascular mortality exists in most men as well. These data are consistent with a variety of other studies suggesting that an elevated serum uric acid level is an independent risk factor for cardiovascular mortality in the general population.[1,2,4,8]

These data have also provided the first opportunity to explore the relationship between serum uric acid level and cardiovascular disease separately in black and white populations. The 729 black subjects (12.3%) had serum uric acid levels that were higher than in white subjects, and the relative risk of an elevated serum uric acid level was greater in black persons than in white persons.

After controlling for potential risk factors, the association of serum uric acid levels with cardiovascular mortality persisted. Even among subjects with low cardiovascular risk (ie, those without an increased cholesterol level, hypertension, or diabetes), we found that increased serum uric acid levels were a predictor of cardiovascular mortality. This association is unlikely to be confounded by other factors in these low-risk subjects.

Recently, Culleton et al,[9] using Framingham Heart Study data, reported that an elevated serum uric acid level at baseline was not independently associated with increased risk of cardiovascular mortality. They concluded that the apparent association of serum uric acid to cardiovascular events was probably due to confounding by other cardiovascular risk factors, particularly by diuretic use. In our study, however, both after stratification and multivariate analysis, diuretic use only affected the association of serum uric acid level with mortality in the 84 men taking diuretics.

The different results seen in these 2 studies may be due to differences in the populations studied. The homogeneous Framingham population is almost exclusively white, while NHANES is a vastly more heterogeneous representation of the US population; 12.3% of the study subjects were black. Although follow-up was similar (17.3 vs 16.4 years), the mortality rates between the 2 studies differed. Most notably, NHANES participants had a substantially higher all-cause mortality rate (16.4 vs 12.4 per 1000 person-years), and they had a higher cardiovascular mortality rate (7.5 vs 3.7 per 1000 person-years) than did Framingham residents. Even among whites only, the NHANES population had substantially higher crude all-cause mortality rate (15.2 vs 12.4 per 1000 person-years), as well as a crude cardiovascular disease mortality rate (7.0 vs 3.7 per 1000 person-years) than did Framingham residents. That cardiovascular mortality was twice as frequent in the NHANES population than in the Framingham study provides strong evidence that the 2 populations are not the same. These population differences may have substantially influenced the different results observed. Besides differences in survival rates, the 2 groups differed in mean age, with NHANES participants being slightly older than Framingham residents (48.3 vs 47 years), and age influenced the relationship of uric acid levels to cardiovascular disease mortality.

The question then is how to interpret these conflicting results. Both studies have strong internal validity. The real issue therefore may be which of the 2 studies has greater general applicability. We would argue that NHANES, which represents the total US population, may have broader relevance. In any event, no single observational study can, by itself, finally settle the issue. However, the findings in this large national sample, together with that of other studies with similar findings,[1-8,10] suggests that perhaps failure to identify an association in Framingham may be an exception, rather than the rule.

Uric acid is the major product of purine metabolism and is formed from xanthine by the action of xanthine oxidase. The normal limits of serum uric acid are between 387 and 416 µmol/L in men and lower than 327 µmol/L in women.[15] Hyperuricemia is usually defined as a serum uric acid level of 416 µmol/L or higher in men, and 357 µmol/L or higher in women.[16,17] After menopause, values for women increase. In adults, serum uric acid levels vary with height, body weight, blood pressure, renal function, and alcohol in-

Table 4. Hazard Ratio of Serum Uric Acid Level to Cardiovascular Disease Mortality*

Variables	No. of Cardiovascular Disease Risks†			Diuretic Use‡		Menopausal Status	
	≥2	1	None	Yes	No	Before	After
Men							
No. of subjects§	384 (139)	756 (115)	1562 (151)	79 (24)	2568 (370)	. . .	. . .
Hazard ratio (95% confidence interval)	1.08 (0.92-1.27)	1.07 (0.92-1.24)	1.15 (1.02-1.37)	1.18 (0.88-1.73)	1.15 (1.03-1.30)	. . .	. . .
Women							
No. of subjects§	465 (119)	940 (122)	1819 (85)	365 (59)	2785 (257)	466 (17)	626 (138)
Hazard ratio (95% confidence interval)	1.56 (1.28-1.90)	1.28 (1.07-1.54)	1.49 (1.23-1.81)	1.47 (1.16-1.85)	1.30 (1.16-1.47)	1.51 (1.03-2.23)	1.29 (1.13-1.47)

*All the models were also adjusted by age, race, body mass index, smoking status, and alcohol consumption. The hazard ratios were calculated for an increase of 59.48 µmol/L (1 µg/dL) of serum uric acid level. Ellipses indicate not applicable.
†Risk factors included blood pressure of 160/95 mm Hg or higher; cholesterol level of 6.34 mmol/L (244.88 mg/dL) or higher, or a history of diabetes.
‡Using diuretics in the past 30 days (at least twice a week).
§Number of subjects at risk for cardiovascular disease (number of deaths).

take.[18] Serum uric acid concentration is influenced by the rate of production on the one hand,[19] and the rate of elimination on the other.[20] The changing level of serum uric acid concentration in women at menopause suggests an interaction with sex hormones.[4]

Besides gout, hyperuricemia is related to a variety of other conditions including increased alcohol consumption, obesity, diabetes, hyperlipidemia, hypertension, renal disease, ischemic heart disease, and diuretic use.[3,18-26] More recently, it has been noted that the main associates of hyperuricemia are identical to the components of insulin resistance syndrome. Perhaps the increase in serum uric acid levels may be an expression of an insulin-resistant state.[23] This is supported by evidence that increased serum uric acid levels correlate with decreased insulin-stimulated glucose uptake and increased plasma insulin response to oral glucose loading.[27-29]

Among women, we found a strong association between increased uric acid levels and cardiovascular mortality, even after stratifying by diuretic use and menopausal status. The mechanism of higher risk of increasing uric acid level among menstruating women compared with postmenopausal women cannot be explained by the available data. Perhaps increasing uric acid level after menopause influences outcome.

The vital question is whether increased serum uric acid is a causal factor for cardiovascular disease. Observational data alone cannot answer that question. However, serum uric acid may be involved in platelet adhesiveness, aggregation, or inflammation[30-32] and may be implicated in the genesis of hypertension.[33]

The limitations of this study included loss to follow-up, missing baseline data, and the lack of information on potentially important characteristics such as fasting plasma glucose and insulin concentration. It is also likely that there have been errors in measurement of baseline variables and misclassification of mortality due to inaccuracy of diagnoses coded on death certificates. The study is strengthened by carefully standardized methods, long follow-up, a large number of events, and mortality as end point.

In summary, we believe that these data add to the large body of literature supporting a strong, significant, specific, and independent association of serum uric acid to cardiovascular mortality. This association is stronger among women than men and among blacks than whites, and it is independent of diuretic use, cardiovascular risk status, or menopausal status. The mechanisms by which hyperuricemia might be linked to heart disease are unknown. Nevertheless, we believe the available data, when considered in total, favor the view that serum uric acid is a useful contributor to the determination of cardiovascular risk.

REFERENCES

1. Klein R, Klein BE, Cornoni J, Maready J, Cassel JC, Tyroler HA. Serum uric acid, Georgia. *Arch Intern Med*. 1973;132:401-410.
2. Bengtsson C, Lapidus L, Stendahal C, Waldenstrom J. Hyperuricemia and risk of cardiovascular disease and overall death. *Acta Med Scand*. 1988;224: 549-555.
3. Burack RC, Keller JB, Higgins MW. Cardiovascular risk factors and obesity. *J Chronic Dis*. 1985;38:865-872.
4. Levine W, Dyer AR, Shekelle RB, Schoenberger JA, Stamler J. Serum uric acid and 11.5-year mortality of middle-aged women. *J Clin Epidemiol*. 1989;42:257-267.
5. Fessel WJ. High uric acid as an indicator of cardiovascular disease. *Am J Med*. 1980;68:401-404.
6. Staessen J. The determinants and prognostic significance of serum uric acid in elderly patients of the European Working Party on High Blood Pressure in the Elderly Trial. *Am J Med*. 1991;90(suppl 3A):50S.
7. Woo J, Swaminathan R, Cockram C, Lau E, Chan A. Association between serum uric acid and some cardiovascular risk factors in a Chinese population. *Postgrad Med J*. 1994;70:486-491.
8. Freedman DS, Williamson DF, Gunter EW, Byers T. Relation of serum uric acid to mortality and ischemic heart disease. *Am J Epidemiol*. 1995;141:637-644.
9. Culleton BF, Larson MG, Kannel WB, Levy D. Se-rum uric acid and risk for cardiovascular disease and death. *Ann Intern Med*. 1999;131:7-13.
10. Dzielak DJ, Kivlighn SD. Emerging concepts in cardiovascular disease. *Exp Opin Invest Drugs*. 1998;7: 85-89.
11. National Center for Health Statistics. *Plan and Operation of the Health and Nutrition Examination Survey, United States, 1971-1973*. Washington, DC: National Center for Health Statistics; Reprinted 1979. Publication HSM73-1310.
12. McLaughlin JK, Dietz MS, Mehl ES, Blot WJ. Reliability of surrogate information on cigarette smoking by type informant. *Am J Epidemiol*. 1987;126: 144-146.
13. Machlin SR, Kleinman JC, Madans JH. Validity of mortality analysis based on retrospective smoking information. *Stat Med*. 1989;8:997-1009.
14. Cox CS, Mussolino ME, Rothwell ST. Plan and operation of the NHANES I Epidemiologic Follow-Up Study 1992. *Vital Health Stat 1*. December 1997:1-231.
15. Low RK, Stoller ML. Uric acid-related nephrolithiasis. *Urol Clin North Am*. 1997;24:135-148.
16. Roubenoff R. Gout and hyperuricemia. *Rheum Dis Clin North Am*. 1990;16:539-550.
17. Grantham JJ, Chonko AM. Renal handling of organic anions and cations; excretion of uric acid. In: Brenner BM, Rector FC, eds. *The Kidney*. Philadelphia, Pa: WB Saunders Co; 1991:483-509.
18. Nishioka K, Mikanagi K. Hereditary and environmental factors influencing on the serum uric acid throughout ten years population study in Japan. *Adv Exp Med Biol*. 1980;122A:155-159.
19. Gutman AB, Yu TF. Gout: a derangement of purine metabolism. *Adv Intern Med*. 1952;5:227-302.
20. Steele TH. Control of uric acid excretion. *N Engl J Med*. 1971;284:1193-1196.
21. Maclachlan MJ, Rodman GP. Effects of food, fast and alcohol on serum uric acid and acute attacks of gout. *Am J Med*. 1967;42:38-57.
22. Lellouch J, Schwartz D, Tran MH. The relationship between smoking and levels of serum urea and uric acid. *J Chronic Dis*. 1969;22:9-15.
23. Bonora E, Targher G, Zenere MB, et al. Relationship of uric acid concentration to cardiovascular risk factors in young men: role of obesity and central fat distribution. *Int J Obes Relat Metab Disord*. 1996;20: 975-980.
24. Benedek TG. Correlations of serum uric acid and lipid concentrations in normal, gouty, and atherosclerotic men. *Ann Intern Med*. 1967;66:851-861.
25. Tweeddale MG, Fodor JG. Elevated serum uric acid. *Nephron*. 1979;23(suppl 1):3-6.
26. Steele TH, Oppenheimer S. Factors affecting urate excretion following diuretic administration in man. *Am J Med*. 1969;47:564-574.
27. Zavaroni I, Mazza S, Fantuzzi M, et al. Changes in insulin and lipid metabolism in males with asymptomatic hyperuricemia. *J Intern Med*. 1993;234: 25-30.
28. Facchini F, Chen YDI, Hollenbeck CB, Reaven GM. Relationship between resistance to insulin-mediated glucose uptake, urinary uric acid clearance, and plasma uric acid concentration. *JAMA*. 1991;266:3008-3011.
29. Vuorinen-Markkola H, Yki-Jarinen H. Hyperuricemia and insulin resistance. *J Clin Endocrinol Metab*. 1994;78:25-29.
30. Mustard JF, Murphy EA, Ogryzlo MA. Blood coagulation and platelet economy in subjects with primary gout. *CMAJ*. 1963;89:1207-1211.
31. Newland H. Hyperuricemia in coronary, cerebral, and peripheral arterial disease: an explanation. *Med Hypotheses*. 1975;1:152-155.
32. Selby JV, Friedman GD, Quesenberry CP Jr. Precursors of essential hypertension. *Am J Epidemiol*. 1990;131:1017-1027.
33. Nicholls A, Snaith ML, Scott JT. Effect of estrogen therapy on plasma and urinary levels of uric acid. *BMJ*. 1973;1:449-451.