Uric Acid Levels, Kidney Function, and Cardiovascular Mortality in US Adults: National Health and Nutrition Examination Survey (NHANES) 1988-1994 and 1999-2002

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Uric Acid Levels, Kidney Function, and Cardiovascular Mortality in US Adults: NHANES 1988-1994 and 1999-2002

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ABSTRACT:

Background: Chronic kidney disease (CKD) and hyperuricemia often coexist and both conditions are increasing in prevalence in the U.S., although their shared role on cardiovascular risk remains highly debated.

Study Design: Cross-sectional and longitudinal

Setting and Participants: Participants in the National Health and Nutrition Examination Survey (NHANES) from 1988 to 2002 (n = 10,956); data were linked to mortality data from the National Death Index through December 31st, 2006.

Predictors: Serum uric acid concentration, categorized as the sex-specific lowest 25th percentile, 25th-75th, and 75th percentile and higher; and kidney function measured by estimated glomerular filtration rate (eGFR) based on the combined creatinine and cystatin C estimating equation developed by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI), and urinary albumin to creatinine ratio (ACR)

Outcomes: Cardiovascular death and all-cause mortality

Results: Uric acid levels were correlated with eGFRCr-Cys ($r = -0.29$, $p<0.001$), and were only slightly correlated with ACR ($r = 0.04$, $p<0.001$). There were 2,203 deaths up until December 31st, 2006, of which 981 were due to cardiovascular causes. Overall, there was a U-shaped association between uric acid levels and cardiovascular mortality in both women and men, although the lowest risk of cardiovascular mortality occurred at a lower level of uric acid for women compared with men. There was an association between the highest quartile of uric acid and cardiovascular mortality even after adjustment for potential confounders (1.48, 95% CI: 1.13, 1.96), although this association was attenuated after adjustment for ACR and eGFRCr-Cys (HR = 1.25, 95% CI: 0.89, 1.75). The pattern of association between uric acid levels and all-cause mortality was similar.

Limitations: GFR not measured; mediating events were not observed.

Conclusions: High uric acid is associated with cardiovascular and all-cause mortality, although this relationship was no longer statistically significant after accounting for kidney function.

Chronic kidney disease (CKD) and hyperuricemia often coexist and both conditions are increasing in prevalence in the United States (U.S.) [1,2] The importance of hyperuricemia in CKD remains an issue of active debate. For example, some studies have shown that hyperuricemia may contribute to CKD progression and that use of allopurinol to lower uric acid may slow down CKD progression.[3,4] In addition, several studies have reported an association of hyperuricemia with cardiovascular and all-cause mortality in persons with CKD. [5-7] In contrast, there is some evidence that the presence of CKD attenuates the strength of association between hyperuricemia and mortality compared to that observed among persons without CKD. [8] Other research reported no association of hyperuricemia with cardiovascular mortality after adjustment for other cardiovascular risk factors. [9,10]

CKD is strongly and consistently associated with cardiovascular disease and mortality.[11] The mechanism through which uric acid is regulated by the kidney, and the relationship between uric acid, kidney function, and cardiovascular disease are not fully understood. [12] Describing the association of hyperuricemia and CKD, and the interaction between uric acid levels and CKD is important to increase our understanding of these associated conditions. The majority of prior literature on uric acid levels and CKD has used creatinine-based measures of kidney function; creatinine may be less accurate in older adults, the population primarily affected by hyperuricemia.[13,14] In the present study, we use a nationally representative population to further explore the distribution and role of uric acid levels in the presence of reduced kidney function, measured by three renal markers: creatinine, cystatin C, and urinary albumin to creatinine ratio (ACR).

The purpose of this study is twofold. First, we assess the mean uric acid levels in persons with reduced kidney function based on the new CKD staging system, using data from the National Health and Nutrition Examination Survey (NHANES). These stages are based on the new classification system proposed by the Kidney Disease Improving Global

Outcomes (KDIGO) group, which considers both level of estimated glomerular filtration rate (eGFR) and albuminuria.[15,16] In the present study, we use eGFR based on the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equations for combined creatinine-cystatin C, which was demonstrated to be more accurate compared with equations that used creatinine or cystatin C alone. [17] The second goal of this study is to examine the association of high uric acid levels with cardiovascular mortality and to examine potential effect modification by reduced kidney function. These results will help to elucidate the role of uric acid and reduced kidney function on cardiovascular mortality in U.S. adults.

METHODS

Study Population

The present study includes data from NHANES participants aged 20 years and older surveyed in NHANES III (1988-1994) and continuous NHANES (1999 - 2002). Participants were excluded if they were pregnant, did not complete both the interview and exam; 16,429 participants in NHANES III and 8,909 in NHANES 1999-2002 met these criteria. In NHANES III, creatinine and uric acid levels were measured in 15,394 participants and cystatin C was measured in 6,842 participants; 6,630 participants had all three measures. In NHANES 1999-2002, creatinine and uric acid levels were measured in 8,294 participants and cystatin C was measured in 4,440 participants; 4,326 participants had all three measures. The primary analyses were conducted in the population with all three measures available (n = 10,956), although sensitivity analyses were conducted in those with only uric acid and creatinine measures (n = 23,688).

Kidney Function

Creatinine was measured by the Jaffe reaction and standardized by methods described previously.[18] Cystatin-C levels were measured in all participants 60 years and older with stored serum samples; a random 25% of participants aged 12 - 59 years was sampled and supplemented with participants with creatinine levels greater than 1.2mg/dL for men and greater than 1 mg/dL for women. Cystatin C levels were measured with an automated particle-enhanced nephelometric assay run on the Dade Behring Nephelometer II (BNII). [19] A random urine specimen was collected from participants, and urinary creatinine was measured by the Jaffé rate reaction, and urinary albumin was measured by solid-phase fluorescent immunoassay.[20] Albuminuria was measured by urinary albumin to creatinine ratio (ACR).

Estimated glomerular filtration rate ($eGFR_{Cr-Cys}$) was calculated based on the CKD-EPI equations for combined creatinine-cystatin C, which was demonstrated to be more accurate compared with equations that used creatinine or cystatin C alone [17]. The combined equation may reduce the influence of the non-GFR determinants of the markers. We also calculated $eGFR_{Cys}$ and $eGFR_{Cr}$, also based on the CKD-EPI equations, for comparison.

We used the kidney disease classification system recommended by the KDIGO conference report [16], which accounts for both level of eGFR and albuminuria. As a simplified classification scheme, we defined dysfunction for $eGFR_{Cr-Cys}$ as a level <60mL/min/1.73m^2 (low) and for ACR as a level ≥30mg/g (high).

Hyperuricemia

Serum uric acid was measured using a colorimetric method, and we created a 3-level variable corresponding to the lowest 25th percentile, 25th-75^{th,} and 75th percentile and higher. This corresponds to <4.0, 4.0 to <6.0, and ≥6.0 mg/dL in women and <5.0, 5.0 to <7.0, and ≥7.0 mg/dL in men. We use the term "low uric acid" to refer to <4.0 in women and <5.0 mg/dL in men, the term "normal uric acid" to refer to 4.0 to <6.0 in women and 5.0 to <7.0 mg/dL in men, and the term "high uric acid" to refer to ≥6.0 in women ≥7.0 mg/dL in men.

Mortality

The National Center for Health Statistics has linked mortality data from NHANES to death certificate data in the National Death Index (NDI). Mortality data were available from the date of the survey participation through December 31st, 2006, based on a probabilistic match between NHANES and NDI death certificate records. Cause of death was determined using the *International Classification of Disease, Tenth Revision (ICD-10).* Cardiovascular

death was classified using ICD-10 codes I00-I78. We censored participants after 10 years to minimize the differences in follow-up between NHANES III and NHANES 1999-2002.

Other covariates

Demographic data and history of chronic health conditions (diabetes, hypertension, myocardial infarction, stroke, and heart failure) were based on self-report. Systolic and diastolic blood pressure and body mass index (BMI) were measured by standard protocol. Smoking status categorized as current smoker, former smoker and never smoked was based on self-report. Alcohol consumption was assessed by self-report and classified as non-drinker, less than 1 drink per week, 1-3 drinks per week, and 4 or more drinks per week. Daily aspirin use was assessed by self-report and this question was asked differently across the two surveys. In NHANES III, aspirin use was defined as answering "yes" to the question, "In the past month, have you taken any aspirin…?"; and subsequently responding that they take aspirin 28 or more times per month. In 1999-2002, participants were asked about the use of analgesic products and were coded as a daily aspirin user if they reported they were currently taking 1 or more aspirin pill per day. Other prescription medication use was assessed by self-report, and verified by interviewers through examination of medication containers.

Statistical Analysis

We pooled data across NHANES III and NHANES 1999-2002 cycles. Demographic and baseline characteristics of all subjects were stratified by the level of uric acid, and presented as weighted percentages for categorical data and as mean and standard error for continuous data, while accounting for the specific cystatin C weights. Differences were tested across groups based on a chi-squared test for categorical variables, and a Wald test for

continuous variables. We ln-transformed ACR because of the right-skewed distribution. We calculated age-adjusted sex-specific mean uric acid levels across multi-level categories of eGFR and albuminuria, based on the classification system recommended by KDIGO. We noted small cell sizes; we used 50 as a threshold as it was the average design effect in this analysis (1.7) multiplied by 30.[21] We calculated Pearson's correlation coefficients for the relationships between uric acid, $eGFR_{Cr\text{-}Cys}$, and ln(ACR).

Next, we plotted the sex-specific age-adjusted association of uric acid levels and risk of cardiovascular mortality, based on fractional polynomial regression models with inclusion of the survey weights. This data-adaptive method allows for the visualization of non-linear associations). We describe the incidence rate of CVD mortality overall, and in persons with low $eGFR_{Cr\text{-}Cys}$ and high ACR. We explored the association between uric acid levels and risk of cardiovascular mortality, adjusted for NHANES cycle, age, sex, and race, based on Cox proportional hazards models. We tested the proportional hazards assumption by the examination of the Kaplan Meier curves and Schoenfeld residuals. We tested for an interaction between uric acid level and sex, and because no significant interactions were observed we pooled models across sex. We included the following potential confounders in fully adjusted models: survey year, age, sex, race, education, smoking status, alcohol consumption, systolic blood pressure, diastolic blood pressure, total cholesterol, HDL-cholesterol, obesity, obesity x NHANES cycle, hypertension, diabetes, myocardial infarction, stroke, heart failure, gout medications, gout medications x NHANES cycle, aspirin use, aspirin use x NHANES cycle, diuretic use, diuretic use x NHANES cycle. The interaction terms between NHANES cycle and obesity and medication use were included to account for any temporal differences in these variables. We also explored the addition of ACR, $eGFR_{Cr\text{-}Cys}$, $eGFR_{Cys}$, and $eGFR_{Cr}$ to the fully adjusted models. Additionally, we examined this same series of models in the larger sample without restricting to those with cystatin C

measurements (n=23,688). We next evaluated the interaction between uric acid level and low $eGFR_{Cr-Cys}$, $eGFR_{Cys}$, and $eGFR_{Cr}$, or abnormal ACR by inclusion of interaction terms into the fully adjusted models. Finally, we repeated all adjusted models for the outcome of all-cause mortality.

All analyses were conducted using Stata 12.0 (College Station, TX) using the survey commands to account for the complex sampling design and non-response in the survey.

RESULTS

Over a maximum of 10 years of follow-up (median = 7.7; range = 0.1-10 years), there were 2,203 deaths, of which 981 were due to cardiovascular causes. In the pooled sample of NHANES III and NHANES 1999-2002, women with higher uric acid levels were older and were more likely to be age 65 and older (Table 1). Women were more likely to have never smoked compared with men ($p<0.001$), although the differences across level of uric acid were minimal within women or men. On average, women and men with higher uric acid levels had higher, systolic and diastolic blood pressure, BMI, and ACR, and lower $eGFR_{Cr-Cys}$, $eGFR_{Cys}$, and $eGFR_{Cr}$. In women and men with higher uric acid levels, there was a higher prevalence of obesity, hypertension, diabetes, and heart failure; and women with higher uric acid levels were also more likely to have a history of myocardial infarction and stroke. Participants with higher uric acid were more likely to take diuretics, and women were more likely to take medications for gout.

Uric acid levels were correlated with $eGFR_{Cr-Cys}$ ($r = -0.29$, $p<0.001$), and slightly with ACR ($r = 0.04$, $p=0.007$). The measures of kidney function, $eGFR_{Cr-Cys}$ and ACR were modestly correlated ($r = -0.26$, $p<0.001$). The correlations of $eGFR_{Cr-Cys}$ and ACR with uric acid were slightly stronger in women ($r =- 0.46$, $p<0.001$; $r = 0.14$, $p<0.001$) compared with men ($r = -0.24$, $p<0.001$; $r = 0.09$, $p<0.001$). The correlations of $eGFR_{Cr-Cys}$ and ACR were -0.22 and -0.29 (both $p<0.001$) in women and men, respectively. The correlation of uric acid levels and $eGFR_{Cr}$ and $eGFR_{Cys}$ ($r = -0.31$, $p<0.001$ and $r = -0.27$, $p<0.001$, respectively). Based on the full sample of 23,688 participants with uric acid levels and creatinine, the correlation of uric acid and $eGFR_{Cr}$ was -0.27, $p<0.001$.

There was a pattern of higher age-adjusted uric acid levels in women and men with lower $eGFR_{Cr-Cys}$, although the sample sizes were small for participants with the lowest eGFR and highest ACR categories. (Tables 2 and 3) On average, women had about a 1 mg/dL lower

age-adjusted uric acid level for any given level of kidney function, although there was substantial variability across groups. The age-adjusted mean uric acid level was greater than 6.0 in women and 7.0 mg/dL in men with moderate-severe reduction in $eGFR_{Cr\text{-}Cys}$. The age-adjusted levels of uric acid appeared slightly higher among persons with higher ACR. Overall, there was a U-shaped association between uric acid levels and cardiovascular mortality in both women and men, although the lowest risk of cardiovascular mortality occurred at a lower level of uric acid for women compared with men. (Figure 1)

The CVD mortality rate in persons with high uric acid was over double that in persons without high uric acid (Table 4). There was evidence of an association of high uric acid levels and cardiovascular mortality, and this persisted after adjustment for potential confounders (hazard ratio [HR] = 1.48, 95% CI: 1.13, 1.93). (Table 4) The estimate for the association of low uric acid levels and cardiovascular mortality was in the harmful direction, but was not statistically significant. There was no evidence for an interaction between sex and uric acid level; p-values for interaction were 0.64 and 0.69 in demographic-adjusted and confounder-adjusted models, respectively. The association between high uric acid level and cardiovascular mortality was modestly changed by adjustment for ACR, and was additionally attenuated after adjustment for $eGFR_{Cys\text{-}Cr}$ (HR = 1.25, 95% CI: 0.89, 1.75). A similar pattern was observed when we adjusted for $eGFR_{Cys}$ and $eGFR_{Cr.}$ The results were also similar when we examined the associations in the larger sample where creatinine was available (N = 23,688). The demographic-adjusted association of low and high uric acid levels with cardiovascular mortality were 1.18 (95% CI: 0.97, 1.44) and 1.66 (95% CI: 1.44, 1.91). After adjustment for confounders, ACR, and $eGFR_{Cr}$, the association of high uric acid level and cardiovascular mortality was attenuated to 1.17 (95% CI: 0.90, 1.52).

The elevated risk of CVD mortality in persons with low uric acid levels appeared stronger when we restricted to the population with low $eGFR_{Cr\text{-}Cys}$; the incidence rates in

persons with low, normal, and high uric acid levels and low $eGFR_{Cr-Cys}$ were 531, 257, and 348 per 10,000 person-years. The incidence rates of CVD mortality in persons with elevated ACR appeared J-shaped across category of uric acid level; the rates in persons with low, normal, and high uric acid levels and high ACR were 156, 118, and 271 per 10,000 person-years. There was no evidence of a statistical interaction between uric acid level and kidney function. The p-value for the interaction term between uric acid and low $eGFR_{Cr-Cys}$ was 0.6 in a demographic-adjusted model and 0.5 in a confounder-adjusted model. The p-value for the interaction term between uric acid and high ACR was 0.6 in a demographic-adjusted model and 0.9 in a confounder-adjusted model.

The pattern of association between uric acid levels and all-cause mortality was similar to that for cardiovascular mortality, although the effect sizes were slightly smaller. (Table 5) The demographic-adjusted association of high uric acid level and mortality was 1.44 (95% CI: 1.36, 1.65) and was attenuated to 1.11 (95% CI: 0.93, 1.33) after adjustment for potential confounders, ACR, and $eGFR_{Cys-Cr.}$

DISCUSSION

This is the first study to examine uric acid levels in the U.S. population, based on the new KDIGO recommended classification system, and based on three renal markers. We found uric acid levels were associated with eGFR, and were highest among persons with the lowest levels eGFR. There was a U-shaped association between uric acid levels and cardiovascular morality; although the association of low uric acid levels and mortality was attenuated in adjusted models. The associations of high uric acid levels and cardiovascular and all-cause mortality were strong and consistent, even after adjustment for potential confounders. Adjustment for ACR had a modest impact on this association, and it was further attenuated after accounting for eGFR. These findings suggest uric acid and eGFR may be either in the same causal pathway or are capturing a similar dimension of cardiovascular risk.

Our findings on the U-shape association of uric acid and cardiovascular mortality are consistent with prior literature. Suliman *et al*. reported a J-shaped relationship for uric acid and mortality in 294 persons with stage 5 CKD.[7] The authors reported that uric acid levels ≥9.0 mg/dL and ≤5.2 mg/dL had an increased risk of mortality. This J-shaped association has also been observed in the general population and dialysis patients.[22,23] A recent publication based on NHANES III data demonstrated modest evidence of a J-shaped relationship between uric acid level and CVD mortality in a population limited to those without a history of diabetes or CVD.[24] Investigators have suggested that this inverted association may be due to the protective role of uric acid as an antioxidant. [21,23] It has also been suggested that low uric acid levels may reflect persons with poor nutritional status or wasting, although in the present study persons with lower uric acid have more optimal levels of measured health characteristics compared with persons with higher uric acid levels. An additional explanation is that low uric acid could be due to altered dietary consumption in persons concerned about cardiovascular risk.

In our study, the association of high uric acid levels and cardiovascular mortality was modestly attenuated after the inclusion of kidney function. Although we did not find evidence for a statistical interaction between uric acid level and eGFR or ACR, prior studies that have reported an attenuation of the association between uric acid levels and cardiovascular events in persons with CKD. Navaneethan *et al*. conducted an analysis of 15,366 participants in the Atherosclerosis Risk in Communities Study (ARIC).[8] The authors examined the association between uric acid and cardiovascular events in persons with and without CKD, and found the presence of CKD attenuated the association between uric acid and cardiovascular events. The association of uric acid and cardiovascular events was 1.26 (1.14, 1.40) and 0.91 (0.57, 1.46) in the non-CKD and CKD groups, respectively. This attenuation in the presence of CKD could also demonstrate that uric acid level and CKD capture a similar dimension of cardiovascular risk.

There are two main explanations as to why the association of high uric acid and cardiovascular mortality may be attenuated after adjustment for eGFR. First, high uric acid may be a marker of filtration capacity, as uric acid levels are normally excreted by the kidney. Uric acid levels were correlated with eGFR, so it is possible that these markers measure overlapping dimensions of kidney health. Second, it is possible that uric acid levels and eGFR are in the same causal pathway. Hyperuricemia is a risk factor for end stage kidney disease, and has been demonstrated to be associated with the progression of eGFR decline. [25,26] Additionally, lowering levels of uric acid by allopurinol appears to slow the progression of decline in filtration ability, but not protein excretion. [3,4,27] These findings are consistent with the theory that eGFR may be in the causal pathway between high uric acid levels and cardiovascular risk.

The strengths of this study include the use of a national representative sample, the longitudinal evaluation of mortality, and the use of the new KDIGO CKD classification

which captures more dimensions of kidney function. However this study has some limitations which should be considered in the interpretation of results. Primarily, due to the cross-sectional nature of the kidney function and uric acid data, temporality cannot be determined. Because uric acid levels and kidney function were measured concurrently, we cannot infer the direction of a potentially causal relationship. Furthermore, other mediating events, such as non-fatal cardiovascular events, were not captured. Finally, we did not directly measure GFR.

The present study demonstrates that different domains of kidney function may interact differently with uric acid levels. This highlights the importance of capturing these two domains with the adoption of the new KDIGO classification system. Future studies of uric acid and risk of events should evaluate both domains of kidney function.

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Table 1: Weighted U.S. population characteristics

	Uric Acid Level*							
	Women				Men			
	<25% n = 1,321	25 to <75% n = 3,000	≥75% n = 1,226	p-value	<25% n = 1,130	25 to <75% n = 2,978	≥75% n = 1,301	p-value
	Mean ± SE or %*				Mean ± SE or %*			
Mean Age (years)	42.2 ± 0.6	46.8 ± 0.5	56.3 ± 1.0	<0.001	45.7 ± 0.8	43.7 ± 0.7	45.8 ± 0.8	<0.001
≥ 65 Years	10.3%	18.8%	38.8%	<0.001	16.4%	13.9%	16.3%	0.10
Race								
White	77.6%	78.7%	77.4%	0.5	75.8%	78.1%	78.5%	0.3
Black	11.5%	11.4%	13.8%		11.6%	9.3%	11.6%	
Other	11.0%	9.9%	8.8%		12.6%	12.6%	9.9%	
Education								
< High School	18.0%	23.5%	22.8%	<0.001	26.7%	22.7%	20.7%	0.01
High School	27.1%	31.5%	30.4%		25.8%	30.7%	23.2%	
> High School	54.9%	45.0%	46.8%		47.5%	46.6%	56.2%	
Smoking Status								
Never	54.8%	53.0%	55.5%	0.04	34.9%	35.0%	32.9%	0.04
Former	19.1%	24.4%	25.5%		28.5%	32.5%	39.2%	
Current	26.0%	22.7%	19.0%		36.7%	32.5%	32.3%	
Alcohol Consumption								
None	38.9%	39.5%	53.8%	0.01	22.9%	20.6%	22.3%	0.5
< 1 drinks per week	28.9%	30.4%	23.9%		30.8%	27.6%	27.0%	
1-3 drinks per week	24.8%	23.0%	15.4%		32.1%	31.7%	32.0%	
4+ drinks per week	7.4%	7.1%	6.9%		14.2%	20.1%	18.7%	
Physiologic Variables								
Systolic BP (mmHg)	115 ± 0.3	122.1 ± 0.6	131.7 ± 1.1	<0.001	123.4 ± 1.2	123.5 ± 0.5	127.4 ± 0.8	<0.001
Diastolic BP (mmHg)	69.7 ± 0.4	71.9 ± 0.3	73.4 ± 0.6	<0.001	74.3 ± 0.7	75.3 ± 0.4	78.4 ± 0.5	<0.001

BMI (kg/m2)	24.4 ± 0.3	27.7 ± 0.2	32.5 ± 0.5	<0.001	25.4 ± 0.3	27.0 ± 0.2	29.8 ± 0.4	<0.001
$eGFR_{Cr-Cys}$ (ml/min/1.73m^2)	105.1 ± 0.7	95.0 ± 0.7	75.9 ± 1.1	<0.001	101.6 ± 1.0	98.7 ± 0.6	89.9 ± 1.0	<0.001
$eGFR_{Cys}$ (ml/min/1.73m^2)	101.0 ± 1.2	99.0 ± 0.7	89.3 ± 1.2	<0.001	103.0 ± 0.7	93.5 ± 0.8	72.7 ± 1.2	<0.001
$eGFR_{Cr}$ (ml/min/1.73m^2)	104.0 ± 0.8	95.7 ± 0.6	80.9 ± 1.1	<0.001	99.9 ± 0.9	97.3 ± 0.7	90.3 ± 0.9	<0.001
ACR (μg/mg)	13.8 ± 1.2	28.6 ± 3.9	77.3 ± 12.3	<0.001	24.0 ± 4.1	22.9 ± 3.6	69.4 ± 13.2	0.001
Chronic conditions								
Obese	13.1%	31.0%	57.5%	<0.001	13.6%	20.3%	39.4%	<0.001
Hypertension	12.5%	24.5%	50.1%	<0.001	16.2%	19.4%	31.6%	<0.001
Diabetes	4.2%	4.8%	11.2%	<0.001	10.8%	5.3%	5.1%	<0.001
Myocardial Infraction	1.0%	1.8%	5.8%	<0.001	4.6%	3.8%	5.6%	0.23
Stroke	1.0%	2.0%	2.3%	<0.001	2.4%	1.6%	2.7%	0.19
Heart Failure	0.3%	1.8%	6.0%	<0.001	1.5%	1.4%	4.8%	<0.001
Medication Use								
Aspirin	3.9%	3.5%	7.7%	0.002	3.3%	4.0%	6.5%	0.03
Diuretic	6.4%	11.6%	39.9%	<0.001	5.2%	6.3%	16.8%	<0.001
Any Gout Medication	0.3%	0.3%	2.0%	<0.001	2.4%	1.9%	3.4%	0.2

* Lowest 25%, middle 25-75%, and highest 25% were <4.0, 4.0 to <6.0, and ≥6.0 mg/dL for women; and <5.0, 5.0 to <7.0, and ≥7. 0 mg/dL for men

BMI = body mass index, eGFR = estimated glomerular filtration rate, ACR = albumin/creatinine ratio

Table 2: Age-adjusted mean (standard error) of uric acid levels (mg/dL) by level of kidney function in women

				ACR (μg/mg)			
				A1		A2	A3
				Optimum	High-normal	High	Very High
				< 10	10 to <30	30 to <300	300+
$eGFR_{Cr\text{-}Cys}$ (ml/min/1.72m^2)	G1	High & optimum	>105	4.1 (0.09) (n=917)	4.0 (0.11) (n=244)	4.2 (0.18) (n=113)	4.9 (0.50) (n=16*)
			90-104	4.4 (0.06) (n=594)	4.5 (0.12) (n=265)	4.8 (0.21) (n=100)	5.4 (0.59) (n=13*)
	G2	Mild	75-89	4.9 (0.07) (n=699)	4.8 (0.13) (n=339)	5.2 (0.22) (n=149)	6.1 (0.57) (n=18*)
			60-74	5.4 (0.10) (n=526)	5.3 (0.10) (n=330)	5.4 (0.24) (n=182)	6.2 (0.58) (n=18*)
	G3a	Mild-moderate	45-59	5.9 (0.15) (n=262)	5.8 (0.10) (n=220)	5.7 (0.18) (n=128)	6.7 (0.18) (n=44*)
	G3b	Moderate-severe	30-44	7.0 (0.20) (n=82)	7.2 (0.25) (n=73)	6.4 (0.18) (n=97)	7.1 (0.50) (n=26*)
	G4/G5	Severe-Failure	0-29	9.3 (0.57) (n=13*)	8.4 (0.51) (n=16*)	7.8 (0.33) (n=34*)	6.8 (0.49) (n=29*)

* Small cell size

Table 3: Age-adjusted mean (standard error) of uric acid levels (mg/dL) by level of kidney function in men

				ACR (μg/mg)			
				A1		A2	A3
				Optimum	High-normal	High	Very High
				< 10	10 to <30	30 to <300	300+
$eGFR_{Cr-Cys}$ (ml/min/1.72m^2)	G1	High & optimum	>105	5.3 (0.09) (n=966)	5.4 (0.18) (n=136)	6.0 (0.36) (n=53*)	5.5 (0.38) (n=9*)
			90-104	5.7 (0.08) (n=824)	5.9 (0.20) (n=189)	5.6 (0.21) (n=122)	6.9 (0.43) (n=15*)
	G2	Mild	75-89	6.2 (0.11) (n=810)	6.1 (0.19) (n=273)	6.4 (0.28) (n=132)	6.4 (0.37) (n=29*)
			60-74	6.5 (0.08) (n=556)	6.6 (0.14) (n=237)	6.6 (0.24) (n=150)	6.3 (0.27) (n=37)
	G3a	Mild-moderate	45-59	7.2 (0.10) (n=215)	6.9 (0.17) (n=162)	7.0 (0.18) (n=114)	7.3 (0.24) (n=53)
	G3b	Moderate-severe	30-44	7.6 (0.26) (n=63)	7.7 (0.28) (n=54)	8.0 (0.30) (n=78)	7.1 (0.38) (n=43)
	G4/G5	Severe-Failure	0-29	11.3 (1.18) (n=6*)	8.6 (0.97) (n=7*)	8.2 (0.58) (n=25*)	7.9 (0.34) (n=51)

* Small cell size

Table 4: Association of uric acid and 10 year cardiovascular mortality

	<25% Uric Acid*	25 to <75% Uric Acid*	≥75% Uric Acid*
N	1,349	5,824	3,783
Cardiovascular Deaths	132	404	445
Incidence Rate	30.3 per 10,000 py	27.6 per 10,000 py	79.8 per 10,000 py

	HR (95% CI)	p value	HR (95% CI)	p value	HR (95% CI)	p value
Demographic Adjusted †	1.18 (0.89, 1.59)	0.3	1.00	Ref	1.77 (1.41, 2.22)	<0.001
Adjusted ‡	1.22 (0.82, 1.81)	0.3	1.00	Ref	1.48 (1.13, 1.93)	0.005
Adjusted + ACR	1.14 (0.77, 1.68)	0.5	1.00	Ref	1.34 (1.04, 1.73)	0.03
Adjusted + $eGFR_{Cr\text{-}Cys}$	1.33 (0.91, 1.95)	0.1	1.00	Ref	1.28 (0.91, 1.79)	0.2
Adjusted + ACR + $eGFR_{Cr\text{-}Cys}$	1.20 (0.83, 1.75)	0.3	1.00	Ref	1.25 (0.89, 1.75)	0.2
Adjusted + ACR + $eGFR_{Cys}$	1.28 (0.89, 1.85)	0.2	1.00	Ref	1.21 (0.87, 1.68)	0.3
Adjusted + ACR + $eGFR_{Cr}$	1.20 (0.83, 1.75)	0.3	1.00	Ref	1.29 (0.93, 1.78)	0.1

* Lowest 25%, middle 25-75%, and highest 25% were <4.0, 4.0 to <6.0, and ≥6.0 mg/dL for women; and <5.0, 5.0 to <7.0, and ≥7. 0 mg/dL for men

†Included NHANES cycle, age, sex, race

‡Included demographics and education, smoking status, alcohol consumption, systolic blood pressure, diastolic blood pressure, total cholesterol, HDL-cholesterol, obesity, obesity x NHANES cycle, hypertension, diabetes, myocardial infarction, stroke, heart failure, gout medications, gout medications x NHANES cycle, aspirin use, aspirin use x NHANES cycle, diuretic use, diuretic use x NHANES cycle

Table 5: Association of uric acid and 10 year all-cause mortality

	<25% Uric Acid*		25 to <75% Uric Acid*		≥75% Uric Acid*	
n	1,349		5,824		3,783	
Deaths	315		971		917	
Incidence Rate	84.7 per 10,000 py		72.9 per 10,000 py		176.4 per 10,000 py	
	HR (95% CI)	p value	HR (95% CI)	p value	HR (95% CI)	p value
Demographic Adjusted †	1.08 (0.90, 1.30)	0.4	1.00	Ref	1.44 (1.26, 1.65)	<0.001
Adjusted ‡	1.05 (0.83, 1.35)	0.7	1.00	Ref	1.33 (1.14, 1.56)	0.001
Adjusted + ACR	1.02 (0.80, 1.29)	0.9	1.00	Ref	1.23 (1.04, 1.45)	0.02
Adjusted + $eGFR_{Cr\text{-}Cys}$	1.18 (0.92, 1.50)	0.2	1.00	Ref	1.14 (0.96, 1.37)	0.1
Adjusted + ACR + $eGFR_{Cr\text{-}Cys}$	1.11 (0.87, 1.41)	0.4	1.00	Ref	1.11 (0.93, 1.33)	0.2
Adjusted + ACR + $eGFR_{Cys}$	1.17 (0.91, 1.49)	0.2	1.00	Ref	1.07 (0.89, 1.30)	0.5
Adjusted + ACR + $eGFR_{Cr}$	1.06 (0.84, 1.35)	0.6	1.00	Ref	1.18 (1.00, 1.41)	0.05

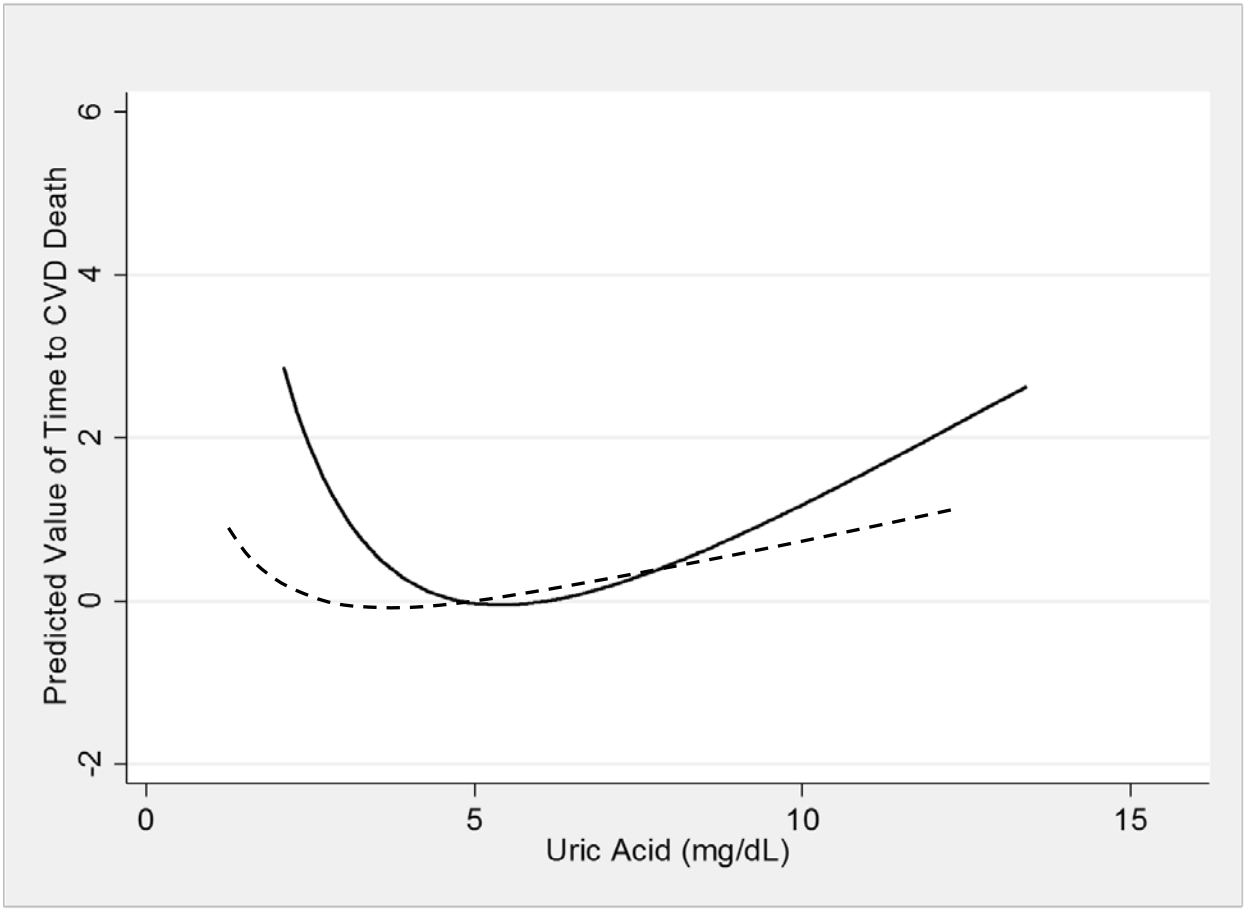
* Lowest 25%, middle 25-75%, and highest 25% were <4.0, 4.0 to <6.0, and ≥6.0 mg/dL for women; and <5.0, 5.0 to <7.0, and ≥7. 0 mg/dL for men

†Included NHANES cycle, age, sex, race

‡Included demographics and education, smoking status, alcohol consumption, systolic blood pressure, diastolic blood pressure, total cholesterol, HDL-cholesterol, obesity, obesity x NHANES cycle, hypertension, diabetes, myocardial infarction, stroke, heart failure, gout medications, gout medications x NHANES cycle, aspirin use, aspirin use x NHANES cycle, diuretic use, diuretic use x NHANES cycle

Figure 1 Legend: There is a U-shaped association of uric acid level and cardiovascular mortality in women (solid line) and men (dotted line), based on weighted fractional polynomials regression adjusted for age.

Figure 1:


Predicted Value of Time to CVD Death
-2
0
2
4
6
0
5
10
15
Uric Acid (mg/dL)