Associations of serum uric acid with cardiovascular events and mortality in moderate chronic kidney disease

Clinical assessment of high users from a case-control study [1]*

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Abstract

Background. It is unclear whether the presence of kidney disease modifies the associations of uric acid with cardiovascular events and death.

Methods. In the limited access, public use Atherosclerosis Risk In Communities (ARIC) database, associations of serum uric acid levels with cardiovascular events and death were analysed using a parametric proportional hazards model and the modification of these associations by the presence of CKD was assessed using a likelihood ratio test.

Results. Of the 15 366 ARIC participants included in this analysis, 461 had CKD (eGFR <60 ml/min/1.73 m^2). In both non-CKD and CKD sub-groups, participants with hyperuricaemia ($\geq$ 7 mg/dl in men and $\geq$ 6 mg/dl in women) compared to those with normal serum uric acid levels had higher waist circumference and fasting serum insulin levels. In the entire cohort, in a multivariate parametric proportional hazards model, each mg/dl increase in serum uric acid was associated with an increased hazard of cardiovascular events (HR 1.09, 95% CI 1.05–1.12) and death. A multiplicative interaction term of serum uric acid and CKD when added to the above models was significant ($P < 0.001$). The likelihood ratio test of the models with and without the interaction term was also significant ($P < 0.001$). In the non-CKD population, a multivariate analysis after adjusting for comorbidities and metabolic syndrome showed a significant association between hyperuricaemia and mortality (HR 1.18, 95% CI 1.04–1.33) but not for cardiovascular events (HR 1.07, 95% CI 0.96–1.19). In the CKD population, the association was not significant for both mortality and cardiovascular events.

Conclusion. We conclude that hyperuricaemia is associated with insulin resistance and mortality in the non-CKD population. The presence of CKD attenuates the associations of uric acid with mortality. Interventional studies are warranted to establish the biological role of hyperuricaemia in mortality in non-CKD and CKD populations.

Introduction

Hyperuricaemia is associated with metabolic syndrome and predicts the development of obesity and diabetes in the general population [1–3]. Many but not all observational studies suggest that hyperuricaemia is an independent risk factor for cardiovascular mortality and/or all-cause mortality in the general population [4–12]. It remains controversial whether elevated serum uric acid levels in metabolic syndrome represent an epiphenomenon or whether uric acid has a pathogenic role in insulin resistance. Thus, most national guidelines have not made recommendations on whether serum uric acid is a risk factor for cardiovascular disease [13,14].

About two-thirds of uric acid that is generated daily is excreted through kidneys, and patients with chronic kidney disease (CKD) develop hyperuricaemia as the glomerular filtration rate (GFR) declines. Further, renal clearance of uric acid is inversely related to the degree of insulin resistance, i.e. the higher the insulin resistance, lower the urate clearance [15–17]. Thus, in CKD patients with insulin resistance, the prevalence of hyperuricaemia will still be higher.

An increase in serum uric acid levels resulting from decreased urinary excretion might have different consequences than an increase in serum uric acid levels resulting from overproduction as increased purine catabolism *per se* rather than uric acid might play a causative role in oxidative stress, inflammation, insulin resistance and atherosclerosis [18]. Probenecid that reduces uric acid concentrations by increased urinary excretion had no effects on endothelial function and oxidative stress whereas allopurinol that decreases the uric acid level by inhibiting xanthine oxidase resulted in lower oxidative stress and improved endothelial function [19]. Thus, higher uric acid concentrations in those with CKD might have different clinical implications than in those without CKD. More importantly, to our knowledge, no previous studies have analysed whether the presence of CKD modifies the associations of uric acid with

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cardiovascular events and death. This is especially important with the growing CKD epidemic around the globe.

Thus, we aimed to analyse whether the presence of moderate CKD modifies the associations of serum uric acid concentrations with cardiovascular events or all-cause mortality in the limited access, public use Atherosclerosis Risk In Communities (ARIC) database.

Methods

Study population

The ARIC Study is a large-scale, National Heart Lung Blood Institute (NHLBI) sponsored, long-term prospective study that measured the associations of established and suspected coronary heart disease (CHD) risk factors with atherosclerosis in a cohort of men and women aged 45–64 years in four US communities.

Assessment of baseline characteristics in the ARIC Study

Information on age, sex and race was based on self-report. Prevalent CHD was defined as a reported history of physician-diagnosed heart attack, cardiovascular surgery, coronary angioplasty or evidence of previous myocardial infarction (MI) on electrocardiogram. Congestive heart failure was defined as a history of leg swelling associated with either orthopnoea or paroxysmal nocturnal dyspnoea. Peripheral vascular disease was defined as the presence of intermittant claudication or the absence of posterior tibialis pulse. History of physician-diagnosed stroke, chronic lung disease or malignancy was defined as prevalent stroke, chronic lung disease and malignancy, respectively. Diabetes was defined as fasting blood sugar > 125 mg/dl or a history of physician-diagnosed diabetes or use of insulin or oral anti-diabetic medications. Smoking was categorized as never, past and current. Trained technicians measured blood pressure in the sitting position three times and the average of last two readings were used.

Anthropometry measures

Waist circumference was measured at the umbilical level with a cloth tape placed horizontally at the end of relaxed expiration with the participant in the standing position. Height was measured to the nearest centimetre using a metal rule attached to a wall and a standard triangular headboard. Weight was measured in pounds using a beam balance with the subject standing in a scrub suit and no shoes. BMI was calculated as weight in kilograms divided by height in metres squared.

Laboratory data

Participants were asked to fast for 12 h before the clinical examination. Fasting blood samples were drawn into vacuum tubes containing sodium citrate (for haemostatic factors), EDTA (for lipids) or a serum separator gel (for glucose and chemistries). The former two tubes were centrifuged immediately; in the latter tube, the contents were allowed to clot for 30 to 45 min and the tube was centrifuged at 3000 g for 10 min at 4°C. The sample aliquots

were quickly frozen at -70°C until analysis, which was performed within a few weeks.

The ARIC Central Laboratories measured serum glucose by using the hexokinase method, serum uric acid by using the method of Haeckel (Beckman Instruments, Inc., Carlsbad, CA, USA), serum creatinine by an alkaline picrate colorimetric assay (Coulter Diagnostics, Hialeah, FL, USA), serum insulin by a radio-immuno assay (Cambridge ^{125}I Insulin Kit, Cambridge Medical Diagnostics, Inc., Billerica, MA, USA), serum von Williebrand factor (vWF) by an ELISA (American Bioproducts Co., Diagnostica Stago, NJ, USA) and plasma fibrinogen by the thrombin-time titration method. Enzymatic methods were used to measure plasma total cholesterol and triglycerides as well as high-density, measure high-density lipoprotein (HDL) cholesterol after dextran–magnesium precipitation of non-HDL lipoproteins and calculate low-density lipoprotein (LDL) cholesterol values. The percent of coefficients of variation ranged from 1.3 to 6% for these assays. Laboratories in each study community performed leukocyte cell counts (WBC) by using cell counters. The homeostatic model of assessment of insulin resistance (HOMA) was calculated from fasting serum glucose and insulin levels.

Definition of CKD

GFR was estimated from the four-variable Modification of Diet in Renal Disease (MDRD) equation (GFR = 186.3 × serum creatinine$^{-1.154}$ × age$^{-0.203}$ × 0.742 if female × 1.21 if black) [20]. Serum creatinine concentration was calibrated with Cleveland Clinic measurement standards by subtraction of 0.24 mg/dl [21]. Those with calculated GFR >150 ml/min/1.73 m^2 were excluded [21]. CKD was defined as GFR <60 ml/min/1.73 m^2 and non-CKD was defined as GFR ≥60 ml/min/1.73 m^2.

Definition of metabolic syndrome

The National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATP III) considered metabolic syndrome present if any three of the following five conditions were present [22]: abdominal obesity (waist circumference ≥102 cm in men and 88 cm in women), elevated serum triglycerides (≥150 mg/dl after 12-h fasting), reduced levels of serum HDL cholesterol (<40 mg/dl in men and <50 mg/dl in women), hypertension (systolic blood pressure ≥130 mmHg or diastolic blood pressure ≥85 mmHg, or use of antihypertensive medications or a self-reported history of hypertension) and insulin resistance (fasting glucose ≥110 mg/dl or use of anti-diabetic agents or self-reported history of diabetes).

Follow-up of cardiovascular events and mortality

Participants underwent a baseline examination during 1987–1989. Follow-up included annual telephone interviews (to identify hospitalizations and deaths), examinations every 3 years in 1990–1992, 1993–1995 and 1996–1998 and survey of death certificates and discharge lists from local hospitals. Out-of-hospital deaths were traced by using death certificate data and, in most cases, an

interview with next of kin and questionnaires completed by the patients' physicians. Coroner reports and autopsy reports were obtained, when available, for use in validation. The follow-up data until 1998 are used in the current analyses.

ARIC Study definition of coronary events

An ARIC Morbidity and Mortality Classification Committee reviewed and adjudicated all potential clinical CHD events that occurred during the follow-up [23]. Hospitalized definite/probable MI was defined by the ARIC Morbidity and Mortality Classification Committee based upon the presence or absence of cardiac pain, ECG findings and enzymes using published criteria. Further, this committee defined a definite fatal CHD event as lack of evidence to diagnose definite fatal MI and the absence of another lethal non-atherosclerotic or non-cardiac atherosclerotic process with either one or both of the following: history of chest pain within 72 h of death or history of ever having had chronic ischaemic heart disease in the absence of valvular heart disease or non-ischaemic cardiomyopathy. Coronary revascularization procedures were identified from hospital admissions.

ARIC Study definitions of ischaemic stroke

Using symptoms, diagnostic procedures performed and autopsy evidence, cases were classified as definite stroke, probable stroke, possible stroke of undetermined type or no stroke by computer algorithm and by a physician reviewer [24]. Differences between the computer and physician diagnoses were adjudicated by another physician.

Definition of composite cardiovascular event

Based on the ARIC Study classification of events, we defined a composite cardiovascular event as the first occurrence of any one of the following events: definite/probable MI, definite/probable fatal CHD event, definite/probable incident stroke or performance of a coronary revascularization procedure.

Statistical methods

Participants with and without CKD were divided into normal uric acid (male: ≤ 7 mg/dl and female: ≤ 6 mg/dl) and hyperuricaemia (>7 mg/dl in males and >6 mg/dl in females) groups. Baseline characteristics across the uric acid groups within CKD and non-CKD participants were examined using the chi-squared test for categorical variables and the Kruskal–Wallis test for continuous variables.

Examination of cardiovascular events

The analyses focused on (1) whether the associations of serum uric acid with the composite cardiovascular outcome and mortality were modified by the presence or absence of CKD and (2) whether the associations of serum uric acid with cardiovascular events and death were atten-

uated/abolished by adjusting for metabolic syndrome or its components in non-CKD and CKD sub-groups.

Effect modification of the associations of uric acid with outcomes by the presence or absence of CKD

First, the association of serum uric acid as a continuous variable with time to the composite cardiovascular outcome was examined in the entire cohort adjusted for age, gender, race, coronary artery disease, cerebrovascular disease, peripheral vascular disease, congestive heart failure, malignancy, smoking, alcohol use and estimated GFR. If CKD modifies the associations of serum uric acid with cardiovascular events, a multiplicative interaction term of serum uric acid and CKD will be statistically significant and hence that interactive term was added to the above model. The likelihood ratio test of models that included the interaction term of serum uric acid and CKD adjusted for the above covariates versus those that excluded the interaction term adjusted for the above covariates was examined as a formal test of interaction.

Effects of adjusting for metabolic syndrome or its components

Using the normal uric acid group as the reference, the unadjusted association of the hyperuricaemic group with time to the composite cardiovascular outcome was examined in each of the non-CKD and CKD groups (Model A). Then, the above model was adjusted for age, gender and race (Model B). Next, coronary artery disease, cerebrovascular disease, peripheral vascular disease, congestive heart failure, malignancy, smoking, alcohol use and estimated GFR were added to the above model (Model C). Finally, metabolic syndrome or its component conditions (hypertension, insulin resistance, abdominal obesity, hypertriglyceridaemia and low-HDL cholesterol) were added individually to Model C to examine the effects of adjusting for these conditions on the associations of uric acid groups with cardiovascular events in the CKD and non-CKD groups.

In the above analyses, as serum uric acid violated the proportionality assumption of Cox models, the parametric proportional hazards model was used to examine the associations of body size with mortality [23]. The proportional hazards multivariable model with one internal knot was the most parsimonious model and was used in these analyses.

Examination of all-cause mortality

The above analyses were repeated with time to death as the outcome variable.

Results

Data on 15 732 of the 15 792 ARIC participants were available in the public use, limited access ARIC database. Of these, GFR data were available in 15 582 participants. Two hundred and sixteen participants with GFR >150 ml /min/1.73 m^2 were excluded as these values could be

Table 1. Baseline clinical characteristics by uric acid levels in non-CKD and CKD populations in the ARIC cohort

Characteristic	Non-CKD (GFR ≥ 60 ml/min/1.73 m²)		CKD (GFR < 60 ml/min/1.73 m²)	
	Normal serum uric acid (N = 9745)	High serum uric acid[a] (N = 5160)	Normal serum uric acid (N = 139)	High serum uric acid[a] (N = 322)
GFR (ml/min/1.73 m²)	95 ± 17	90 ± 17	52 ± 10	49 ± 12
Serum uric acid (mg/dl)	5.2 ± 0.9	7.6 ± 1.1	5.3 ± 0.9	8.3 ± 1.6
Demographics				
Age (years)	54 ± 5	55 ± 5	56 ± 6	57 ± 5
Gender (% women)[b]	57	49	69	60
Race (%African Americans)	22	33	11	31
Clinical characteristics				
Diabetes (%)	9	14	16	29
Metabolic syndrome[c] (%)	20	48	29	59
Coronary artery disease (%)	4	7	10	18
Cerebrovascular disease (%)[b,d]	4	5	9	10
Congestive heart failure (%)[b]	7	11	16	21
Peripheral vascular disease (%)	2	3	2	7
Cancer (%)[b,d]	5	5	8	6
Past or current smoking (%)[b]	56	60	62	56
Past or current alcohol intake (%)	74	74	77	65

[a]High serum acid was defined as >7 mg/dl in men and >6 mg/dl in women. [b]P-value not significant for the comparison of the low and high uric acid groups in CKD.
[c]Metabolic syndrome was defined as the presence of three out of five following components—abdominal obesity, hypertriglyceridaemia, decreased HDL cholesterol, hypertension and insulin resistance.
[d]P-value not significant for the comparison of the low and high uric acid groups in non-CKD.
All other P-value <0.05.

Table 2. Baseline nutritional and metabolic characteristics by uric acid levels in non-CKD and CKD populations in the ARIC cohort

Variable	Non-CKD (GFR ≥ 60 ml/min/1.73 m²)		CKD (GFR < 60 ml/min/1.73 m²)	
	Normal serum uric acid (n = 9745)	High serum uric acid[a] (n = 5160)	Normal serum uric acid (n = 139)	High serum uric acid[a] (n = 322)
Body mass index (kg/m²)	26 ± 4	29 ± 5	26 ± 4	29 ± 5
Waist circumference (cm)	93 ± 12	102 ± 13	95 ± 12	102 ± 14
Insulin level (U/ml)	11 ± 26	18 ± 28	12 ± 12	32 ± 72
Blood glucose (mg/dl)	106 ± 39	111 ± 37	114 ± 54	130 ± 75
Log HOMA	0.6 ± 0.8	1.2 ± 0.7	0.8 ± 0.8	1.4 ± 1.0
WBC count (10⁹/l)	6.0 ± 1.9	6.3 ± 1.9	6.7 ± 5.8	6.6 ± 2.1
Plasma fibrinogen (mg/dl)	297 ± 62	311 ± 67	321 ± 78	343 ± 84
VonWillebrand factor (U/dl)	114 ± 45	123 ± 50	136 ± 53	152 ± 68
Serum LDL-cholesterol (mg/dl)[b]	135 ± 38	142 ± 40	143 ± 37	146 ± 46
Serum triglycerides (mg/dl)	116 ± 72	157 ± 107	127 ± 83	176 ± 121
Serum HDL-cholesterol (mg/dl)	53 ± 17	47 ± 15	54 ± 18	46 ± 16

[a]High serum acid was defined as >7 mg/dl in men and >6 mg/dl in women.
[b]P-value not significant for the comparison of the low and high uric acid groups in CKD.
All other P-value <0.05.

erroneous [21]. Of the remaining 15 366 ARIC participants, 461 had CKD (defined as GFR <60 ml/min/1.73 m²). Most of the participants had stage 3 CKD (n = 429) and only few were in stage 4 CKD (n = 32).

Baseline participant characteristics

Participants with hyperuricaemia compared to those with normal serum uric acid in both non-CKD and CKD subgroups were older and more likely to be men and African American (Table 1). Overall, they had a higher prevalence of diabetes and coronary artery disease (Table 1). Furthermore, they had higher BMI and waist circumference as well as higher levels of serum insulin, plasma fibrinogen, serum

von Williebrand factor, WBC count and serum triglycerides (Table 2).

Effect modification of the associations of uric acid with outcomes by the presence of CKD

In the entire cohort, there were a total of 1724 cardiovascular events over 146 617 years of follow-up and 9.3 deaths over 1000 years of follow-up (1421 deaths over 152 715 years). Adjusted for demographics (age, gender and race), comorbid conditions (coronary artery disease, cerebrovascular disease, heart failure, peripheral vascular disease, cancer, smoking and alcohol) and estimated GFR, each mg/dl increase in uric acid was associated with an

Table 3. Associations of the high uric acid group (with the normal uric acid group as the reference) with cardiovascular events or mortality in the non-CKD and CKD sub-groups in the ARIC cohort

	Non-CKD cohort [HR (95% CI)]		CKD cohort [HR (95% CI)]	
	CV events	Death	CV events	Death
Model A	1.55 (1.40–1.71)	1.54 (1.38–1.72)	1.56 (1.00–2.41)	2.27 (1.43–3.60)
Model B	1.38 (1.25–1.52)	1.30 (1.16–1.45)	1.12 (0.71–1.76)	1.61 (1.00–2.59)
Model C	1.26 (1.14–1.40)	1.27 (1.13–1.43)	0.91 (0.57–1.46)	1.37 (0.84–2.23)

Model A—unadjusted.
Model B—adjusted age for age, race and sex.
Model C—adjusted for above, coronary artery disease, cerebrovascular disease, heart failure, peripheral vascular disease, cancer, smoking, alcohol and GFR.

Table 4. Associations of the high uric acid group (with the normal uric acid group as the reference) with cardiovascular events or mortality adjusted for metabolic syndrome or its components in the non-CKD and CKD sub-groups in the ARIC cohort

	Non-CKD cohort [HR (95% CI)]		CKD cohort [HR (95% CI)]	
	CV events	Death	CV events	Death
Model C	1.27 (1.13–1.43)	1.27 (1.13–1.43)	0.91 (0.57–1.46)	1.37 (0.84–2.23)
Model C + metabolic syndrome	1.07 (0.96–1.19)	1.18 (1.04–1.33)	0.82 (0.50–1.33)	1.28 (0.79–2.09)
Model C + hypertension	1.12 (1.01–1.24)	1.19 (1.06–1.34)	0.85 (0.53–1.37)	1.31 (0.81–2.14)
Model C + insulin resistance	1.19 (1.07–1.32)	1.22 (1.08–1.37)	0.84 (0.52–1.35)	1.31 (0.80–2.13)
Model C + abdominal obesity	1.21 (1.09–1.34)	1.26 (1.12–1.42)	1.21 (1.09–1.34)	1.37 (0.84–2.23)
Model C + hypertriglyceridaemia	1.16 (1.05–1.29)	1.23 (1.09–1.38)	0.85 (0.53–1.37)	1.31 (0.80–2.14)
Model C + low HDL cholesterol	1.16 (1.05–1.29)	1.23 (1.09–1.38)	0.93 (0.57–1.50)	1.33 (0.81–2.18)

Model C—same as in Table 3, i.e. adjusted for age, race, sex, coronary artery disease, cerebrovascular disease, heart failure, peripheral vascular disease, cancer, smoking, alcohol and GFR.

increased hazard of cardiovascular events (HR 1.09, 95% CI 1.05–1.12). A multiplicative interaction term of serum uric acid and CKD when added to the above model was significant ($P < 0.001$). The likelihood ratio test of the models with and without the interaction term was also significant ($P < 0.001$). Similarly, a multiplicative interaction term of serum uric acid and CKD was significant ($P < 0.001$) in a multivariate proportional hazards model of death in the entire cohort adjusted for demographics, comorbidity and estimated GFR. The likelihood ratio test of the models with and without the interaction term was also significant ($P < 0.001$) for death.

These data suggest that the associations of serum uric acid with cardiovascular events or death differ on the basis of the presence or absence of CKD.

Effects of adjusting for metabolic syndrome or its components

There were 11.3 cardiovascular events per 1000 years of follow-up in the non-CKD sub-group (1614 events over 142 816 years of follow-up) and 28.9 events per 1000 years of follow-up in the CKD sub-group (110 events over 3801 years). In both non-CKD and CKD sub-groups, hyperuricaemia was associated with increased cardiovascular events in unadjusted analyses (Table 3). However, adjusting for age, race and sex abolished the associations of uric acid with cardiovascular events in the CKD sub-group (Table 3) but not in the non-CKD sub-group. Even after further adjustment for coronary artery disease, cerebrovascular disease, heart failure, peripheral vascular disease, cancer, smoking,

alcohol and estimated GFR, the associations of uric acid with cardiovascular events remained significant in the non-CKD sub-group (Table 3) but not in the CKD sub-group.

In the non-CKD sub-group, when adjusted separately for each component of metabolic syndrome, hyperuricaemia was still associated with an increased risk of cardiovascular events (Table 4), but this was abolished when adjusted for metabolic syndrome (Table 4).

There were 8.7 deaths over 1000 years of follow-up (1294 deaths over 148 678 years) in the non-CKD sub-group, and 31.4 deaths over 1000 years of follow-up (127 deaths over 4037 years) in the CKD sub-group. The associations of hyperuricaemia with death paralleled that of cardiovascular events except that the association of hyperuricaemia with an increased risk of death in the non-CKD sub-group persisted even after adjustment for metabolic syndrome (Table 4).

Discussion

It remains controversial whether uric acid plays a pathogenic role in insulin resistance and atherosclerosis. As discussed below, experimental studies in animals and small interventional studies in humans strongly suggest a pathogenic role for uric acid whereas epidemiological studies are discrepant.

Compared to controls, fructose-fed rats developed hyperuricosaemia, hyperinsulinaemia, hypertriglyceridaemia and hypertension and treatment of these animals with allopurinol reduced serum uric acid, insulin and triglyceride levels as well as systolic blood pressure [25]. In another study

of the carotid artery ligation model using spontaneously hypertensive rats, treatment with allopurinol induced a reduction in the neointima/media ratio by 27% at 3 weeks after ligation when compared to the control [26]. In an *in vitro* study, uric acid at concentrations of 2–4 mg/dl but not at 1 mg/dl stimulated vascular smooth muscle cell growth [25]. In different small randomized controlled trials, allopurinol treatment resulted in improvement of oxidative stress, endothelial function [27–29] and progression of kidney disease [30].

In contrast to the above data, epidemiological studies have produced conflicting results. Data from National Health And Nutrition Examination Survey (NHANES) [4] and other studies [4–9] suggest an increased risk of cardiovascular events or death with higher uric acid concentrations. On the other hand, analyses of the Framingham Study and the ARIC Study did not support such an association [10–12]. Several non-traditional risk factors such as low albumin and haemoglobin levels, increased triglyceride and fibrinogen levels have been linked to the adverse outcomes (a composite of stroke, MI and all-cause mortality) in patients with stage 3 and 4 CKD in the combined analysis of the ARIC Study and Cardiovascular Health Study database [31]. Uric acid was not associated with these adverse events in the multivariate analysis of this study. But this analysis did not analyse whether the presence of CKD modifies the association between uric acid and CKD.

In the current study, we noted the associations of serum uric acid with adiposity and metabolic milieu, i.e. insulin resistance, dyslipidaemia, higher WBC count and higher concentrations of serum vonWillebrand factor and plasma fibrinogen in both non-CKD and CKD populations. While epidemiological studies such as the current study cannot establish causality, experimental animal studies and interventional human trials can establish causality. As noted above, experimental studies support a causal role for uric acid in insulin resistance, dyslipidaemia, hypertension and atherosclerosis [25,26].

Our analysis suggests that in the non-CKD population, serum uric acid is associated with cardiovascular events and mortality and the presence of moderate CKD modifies the associations of uric acid with cardiovascular events and mortality. In this moderate CKD population, hyperuricaemia was associated with a 56% increase in cardiovascular events and a 2.3-fold increase in mortality in unadjusted analyses (Tables 3 and 4), but once adjusted for age, gender and race, these associations were abolished. As demographics are likely confounding variables rather than intermediate variables (i.e. variables that are in the causal pathway between uric acid and outcomes), these data suggest that uric acid might not be an independent predictor of outcomes in the CKD population. This is in contrast to the finding of J-shaped associations of uric acid with mortality noted in two earlier studies of stage 5 CKD [32,33]. The reasons for these discrepant results are not evident.

Furthermore, the finding of an increased risk of death (even after adjusting for metabolic syndrome and its components individually) in the non-CKD population in this study supports the data from several earlier studies [10–12] but contradicts the earlier conclusion from the Framingham and ARIC studies that uric acid is not an independent

predictor [10–12]. Of note, these studies [10–12] adjusted for diabetes, hypertension and dyslipidaemia to examine the associations of uric acid with outcomes. If uric acid causes insulin resistance as suggested by experimental data [26], then insulin resistance might be an intermediate variable that mediates the effects of uric acid on cardiovascular events and death and adjusting for these effects of uric acid will underestimate/nullify the possible true effects of uric acid on outcomes. Furthermore, the previous analysis of ARIC data [12] only examined the associations of uric acid with cardiovascular events whereas we examined both cardiovascular events and mortality.

While epidemiological studies could provide valuable insights into pathogenic mechanisms, causality cannot be proven by such studies. But unlike other risk factors for cardiovascular disease, no randomized controlled trial has examined whether lowering serum uric acid levels could impact on cardiovascular events in the general population. Such studies are particularly relevant in CKD population because nearly 13% of US adult population have CKD and hyperuricaemia, insulin resistance and atherosclerotic events are common in this population [34].

The strengths of this study include (a) careful data collection in the ARIC cohort and (b) the study population includes a large sample of moderate CKD participants. However, there are several limitations to this study. We did not have data on C-reactive protein (CRP). The current analysis is based on a single measurement of uric acid and the impact of the change in uric acid levels on these outcomes over time is unknown. Also data on albuminuria and haematuria are unavailable, and hence ARIC participants with GFR $\geq$ 60 ml/min/1.73 m^2 and kidney damage evidenced by haematuria and proteinuria are classified in the non-CKD group in this analysis. Thus, inferences on whether stage 1 and 2 CKD modifies the effects of serum uric acid on outcomes could not be drawn from the results of this study, but nonetheless, these results indicate that such effect modification occurs in stages 3 and 4 of CKD.

In summary, higher concentrations of serum uric acid is associated with mortality in the non-CKD population even after adjustment for metabolic syndrome but the presence of CKD appears to modify this association. Interventional studies of surrogate end-points (insulin resistance, inflammation and oxidative stress) and hard outcomes (cardiovascular events and mortality) are warranted to establish the clinical relevance of serum uric acid in the CKD population.

Conflict of interest statement. None declared.

References

1. Nakagawa T, Kang DH, Feig D *et al*. Unearthing uric acid: an ancient factor with recently found significance in renal and cardiovascular disease. *Kidney Int* 2006; 69: 1722–1755

2. Masuo K, Kawaguchi H, Mikami H *et al*. Serum uric acid and plasma norepinephrine concentrations predict subsequent weight gain and blood pressure elevation. *Hypertension* 2003; 42: 474–480

3. Nakanishi N, Okamoto M, Yoshida H *et al*. Serum uric acid and risk for development of hypertension and impaired fasting glucose or Type II diabetes in Japanese male office workers. *Eur J Epidemiol* 2003; 18: 523–530

4. Fang J, Alderman MH. Serum uric acid and cardiovascular mortality the NHANES I epidemiologic follow-up study, 1971–1992. National Health And Nutrition Examination Survey. *JAMA* 2000; 283: 2404–2410

5. Liese AD, Hense HW, Lowel H *et al*. Association of serum uric acid with all-cause and cardiovascular disease mortality and incident myocardial infarction in the MONICA Augsburg cohort. World Health Organization Monitoring Trends and Determinants in Cardiovascular Diseases. *Epidemiology* 1999; 10: 391–397

6. Niskanen LK, Laaksonen DE, Nyyssonen K *et al*. Uric acid level as a risk factor for cardiovascular and all-cause mortality in middle-aged men: a prospective cohort study. *Arch Intern Med* 2004; 164: 1546–1551

7. Franse LV, Pahor M, Di Bari M *et al*. Serum uric acid, diuretic treatment and risk of cardiovascular events in the Systolic Hypertension in the Elderly Program (SHEP). *J Hypertens* 2000; 18: 1149–1154

8. Hoieggen A, Alderman MH, Kjeldsen SE *et al*. The impact of serum uric acid on cardiovascular outcomes in the LIFE study. *Kidney Int* 2004; 65: 1041–1049

9. Bickel C, Rupprecht HJ, Blankenberg S *et al*. Serum uric acid as an independent predictor of mortality in patients with angiographically proven coronary artery disease. *Am J Cardiol* 2002; 89: 12–17

10. Culleton BF, Larson MG, Kannel WB *et al*. Serum uric acid and risk for cardiovascular disease and death: the Framingham Heart Study. *Ann Intern Med* 1999; 131: 7–13

11. Hozawa A, Folsom AR, Ibrahim H *et al*. Serum uric acid and risk of ischemic stroke: the ARIC Study. *Atherosclerosis* 2006; 187: 401–407

12. Moriarity JT, Folsom AR, Iribarren C *et al*. Serum uric acid and risk of coronary heart disease: Atherosclerosis Risk in Communities (ARIC) Study. *Ann Epidemiol* 2000; 10: 136–143

13 Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) Express. Available at http://www.nhlbi.nih.gov/guidelines/hypertension/express.pdf

14. K/DOQI Clinical Practice Guidelines for Cardiovascular Disease in Dialysis Patients. Available at http://www.kidney.org/professionals/kdoqi/guidelines_cvd/index.htm

15. Ter Maaten JC, Voorburg A, Heine RJ *et al*. Renal handling of urate and sodium during acute physiological hyperinsulinaemia in healthy subjects. *Clin Sci (Lond)* 1997; 92: 51–58

16. Muscelli E, Natali A, Bianchi S *et al*. Effect of insulin on renal sodium and uric acid handling in essential hypertension. *Am J Hypertens* 1996; 9: 746–752

17. Quinones Galvan A, Natali A, Baldi S *et al*. Effect of insulin on uric acid excretion in humans. *Am J Physiol* 1995; 268: E1–E5

18. Erdei N, Toth A, Pasztor ET *et al*. High-fat diet-induced reduction in nitric oxide-dependent arteriolar dilation in rats: role of xanthine oxidase-derived superoxide anion. *Am J Physiol Heart Circ Physiol* 2006; 291: H2107–H2115

19. George J, Carr E, Davies J *et al*. High-dose allopurinol improves endothelial function by profoundly reducing vascular oxidative stress and not by lowering uric acid. *Circulation* 2006; 114: 2508–2516

20. Levey AS, Bosch JP, Lewis JB *et al*. Modification of Diet in Renal Disease Study Group. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. *Ann Intern Med* 1999; 130: 461–470

21. Manjunath G, Tighiouart H, Ibrahim H *et al*. Level of kidney function as a risk factor for atherosclerotic cardiovascular outcomes in the community. *J Am Coll Cardiol* 2003; 41: 47–55

22. Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults. Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *JAMA* 2001; 285: 2486–2497

23. Royston P, Parmar MK. Flexible parametric proportional-hazards and proportional-odds models for censored survival data, with application to prognostic modelling and estimation of treatment effects. *Stat Med* 2002; 21: 2175–2197

24. National Heart Lung and Blood Institute. Atherosclerosis Risk in Communities (ARIC) Study. *Operations Manual*. Chapel Hill, NC: ARIC Coordinating Center, School of Public Health, University of North Carolina, 1987

25. Nakagawa T, Hu H, Zharikov S *et al*. A causal role for uric acid in fructose-induced metabolic syndrome. *Am J Physiol* 2006; 290: F625–F631

26. Yamamoto Y, Ogino K, Igawa G *et al*. Allopurinol reduces neointimal hyperplasia in the carotid artery ligation model in spontaneously hypertensive rats. *Hypertens Res* 2006; 29: 915–921

27. Farquharson CA, Butler R, Hill A *et al*. Allopurinol improves endothelial dysfunction in chronic heart failure. *Circulation* 2002; 106: 221–226

28. George J, Carr E, Davies J *et al*. High-dose allopurinol improves endothelial function by profoundly reducing vascular oxidative stress and not by lowering uric acid. *Circulation* 2006; 114: 2508–2516

29. El Solh AA, Saliba R, Bosinski T *et al*. Allopurinol improves endothelial function in sleep apnoea: a randomised controlled study. *Eur Respir J* 2006; 27: 997–1002

30. Siu YP, Leung KT, Tong MK *et al*. Use of allopurinol in slowing the progression of renal disease through its ability to lower serum uric acid level. *Am J Kidney Dis* 2006; 47: 51–59

31. Weiner D, Tighiouart H, Elsayed EF *et al*. The relationship between nontraditional risk factors and outcomes in individuals with stage 3 to 4 CKD. *Am J Kidney Dis* 2008; 51: 212–223

32. Hsu SP, Pai MF, Peng YS *et al*. Serum uric acid levels show a 'J-shaped' association with all-cause mortality in haemodialysis patients. *Nephrol Dial Transplant* 2004; 19: 457–462

33. Suliman ME, Johnson RJ, Garcia-Lopez E *et al*. J-shaped mortality relationship for uric acid in CKD. *Am J Kidney Dis* 2006; 48: 761–771

34. Coresh J, Selvin E, Stevens LA *et al*. Prevalence of chronic kidney disease in the United States. *JAMA* 2007; 298: 2038–2047