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Effects of menopause and hormone replacement therapy on the associations of hyperuricemia with mortality

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Abstract

Objective—Serum uric acid (SUA) levels have been associated with cardiovascular and all-cause mortality. It remains unclear whether these associations differ by gender, menopausal status and hormone replacement therapy (HRT) and whether they persist after adjustment for known cardiovascular risk factors.

Methods—We determined the associations between fasting SUA level and death certificate-based mortality among 5856 participants of the third US National Health and Nutrition Examination Survey aged ≥20 years recruited between 1988–1994 and followed for mortality until December 2006 (mean follow-up: 13.5 years; maximum follow-up: 18 years). Cox proportional hazards regression analysis was used to adjust for demographic characteristics, cardiovascular risk factors and other variables potentially associated with SUA levels.

Results—Among women, SUA level was associated with all-cause and cardiovascular mortality (adjusted hazard ratio [AHR] 1.17, 95% CI 1.03–1.32 and AHR 1.23 (1.01–1.51) respectively per unit increase in SUA. These associations persisted among postmenopausal but not premenopausal women. Furthermore, among postmenopausal women, significant associations were identified between SUA and all-cause (AHR 1.30 [1.11–1.51]) or cardiovascular (AHR 1.61 [1.33–1.94]) mortality only among women not taking HRT, but not among women on HRT.

We did not identify associations between SUA levels and all-cause or cardiovascular mortality in men, either under or over 51 years of age, in unadjusted or adjusted analyses.

Conclusions—SUA level predicts cardiovascular and all-cause mortality independently of major predictors and risk factors in postmenopausal women not taking HRT but not in premenopausal women, postmenopausal women on HRT, or men.

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Keywords

serum uric acid; mortality; cardiovascular mortality; cohort study; population-based

INTRODUCTION

Elevated serum uric acid (SUA) levels have been associated with many established risk factors for cardiovascular disease, cardiovascular mortality and all-cause mortality including insulin resistance, systemic inflammation, oxidative stress, gender, race, obesity, chronic kidney disease, the metabolic syndrome and each of its 5 components individually (hypertension, waist circumference, plasma glucose, triglyceride and HDL cholesterol levels) -(reviewed in[1–2]). Therefore, it might be expected that in unadjusted analyses, SUA level would be associated with cardiovascular and all-cause mortality. However, whether SUA levels significantly predict cardiovascular or all-cause mortality after simultaneous adjustment for currently accepted cardiovascular risk factors and other potential confounding factors remains uncertain despite multiple studies. Many studies reported significant independent associations[3–9], but others did not[10–13]. Many studies have been unable to adjust for important potential confounding variables, because these variables were not ascertained. Two prospective population[4] or community-based[10] US cohort studies reported conflicting results regarding the association between SUA level and mortality while also being unable to adjust for some important, potential confounding variables, such as glomerular filtration rate, insulin resistance, C-reactive protein level and fasting plasma triglyceride and HDL-cholesterol levels. Consequently, hyperuricemia is not yet considered an independent cardiovascular risk factor by major professional societies.

Another controversy is whether the association between SUA and all-cause or cardiovascular mortality differs by gender. Investigating such gender differences is reasonable because SUA levels are much higher in men than in women[14]. A previous US population-based study[4] showed a much weaker association in men than in women and another American study showed no association between SUA level and cardiovascular death among men at high risk of coronary heart disease[15]. However, community-based studies from Germany[7] and Finland[3] suggested that SUA levels were associated with all-cause and cardiovascular mortality in men. A recent meta-analysis of 9 cohort studies reported that hyperuricemia was only associated with cardiovascular mortality in women and not men and suggested that this difference by gender should be investigated in future studies[16].

SUA level rises substantially in women after menopause almost approaching the level in men. Use of hormone replacement therapy (HRT) in postmenopausal women causes a reduction in SUA level. High levels of endogenous estrogen in premenopausal women or exogenous administration of estrogen in postmenopausal women are thought to promote more efficient renal clearance of urate leading to lower SUA levels[17]. However, we are not aware of studies that determined the association between SUA level and mortality separately in premenopausal women and postmenopausal women on or off HRT.

Our aim was to determine whether SUA level predicts cardiovascular and all-cause mortality in the United States population independently of known, established risk factors

and other potential confounders which were not available in previous studies. Additionally, we wanted to investigate whether the association between SUA and cardiovascular or all-cause mortality is different in women versus men and in premenopausal versus postmenopausal women, on or off HRT.

METHODS

Study Design

We investigated the associations between baseline SUA level, measured in 1988–1994, and cardiovascular or all-cause mortality ascertained until December 31, 2006.

Baseline data were derived from the Third National Health and Nutrition Examination Survey (NHANES III), a cross-sectional study conducted by the National Center for Health Statistics (NCHS) between 1988–1994 in order to assess the health and nutritional status of the non-institutionalized US population[18]. NHANES datasets, related documentation and analytical guidelines are made available by the NCHS and were downloaded from http://www.cdc.gov/nchs/nhanes.htm in February 2010. Participants completed personal, structured interviews at home and then attended a mobile examination center at 89 locations throughout the US to undergo various examinations and provide a blood sample.

Follow-up mortality data were obtained from the 2006 NHANES III-Linked Mortality File. This file was created by the NCHS by linking NHANES III with the National Death Index[19], a computerized database of all certified deaths in the United States since 1979. National Death Index records provided data on date and underlying causes of death. Linkage of NHANES III and National Death Index records was performed by a validated method of probabilistic matching[20].

Study Population

We limited our analyses to NHANES participants assigned to the morning (10am) examination session, who constituted a nationally-representative sample, because SUA levels as well as the levels of important potential confounders such as plasma lipids, glucose and serum insulin, vary according to duration of fast and time of day. Out of 7959 participants aged ≥20 years assigned to the morning session, we excluded 492 participants who fasted for less than 8 hours, 120 pregnant women and 469 participants who did not have SUA level measured. Additionally, we excluded participants with missing data on potential confounders including serum insulin or plasma glucose levels (n=148), waist circumference or body mass index (n=235), educational attainment (n=27), systolic or diastolic blood pressure (n=200), alcohol consumption (n=204), and serum cholesterol, HDL-cholesterol, or triglyceride levels (n=47). We excluded 155 participants who had self-reported gout or were taking allopurinol, or uricosuric agents. Only 6 additional participants did not have data linked to the NHANES III mortality file leaving 5856 participants in the current analyses, including 2719 men, 1274 postmenopausal women and 1863 premenopausal women.

Measurement of SUA Level

SUA level was measured by oxidation with the specific enzyme uricase to form allantoin and H_2O_2 (Hitachi Model 737 Multichannel Analyzer, Boehringer Manheim Diagnostics, Indianapolis, Ind).

Definition of Cardiovascular and All-Cause Mortality

Cardiovascular mortality was defined by the presence of any of the following underlying causes of death on a death certificate:

a. Coronary heart disease, defined as “acute myocardial infarction” (ICD-10 codes I21–I22), “other acute ischemic heart diseases” (I24), “atherosclerotic cardiovascular disease” (I25.0), and “all other forms of chronic ischemic heart disease” (I20, I25.1–I25.9).

b. Heart failure, defined by ICD-10 code I50.

c. Cerebrovascular disease, defined by ICD-10 codes I60–I69.

d. Atherosclerosis (I70) and arterial embolism (I74), excluding the coronary and cerebral vasculature.

All-cause mortality was defined as death from any cause.

Determination of Menopausal Status and Hormone Replacement Therapy

Menopause was defined by absence of menstruation in the preceding 12 months, consistent with World Health Organization criteria[21]. Women who underwent a hysterectomy without ovariectomy that coincided with their last menstrual period were reassigned to premenopausal status if they were under 51 years of age[21]. Postmenopausal hormone replacement therapy was defined by use of “estrogen or female hormone pills by mouth other than oral contraceptive pills” or “estrogen patches, injections or suppositories”. These variables were self-reported as part of a dedicated Reproductive Health questionnaire.

Risk Variables and Potential Confounders

We considered *a priori* variables that may be associated with SUA level and mortality as potential confounders in multivariate models, including: age; menopausal status and hormone replacement therapy; alcohol consumption (categorized as none or less than 12 drinks in any year, >0 to 1 drink/day, >1 to 2 drinks/day, and >2 drinks/day on average over the preceding 12 months); race-ethnicity (categorized as non-Hispanic white, non-Hispanic black, Mexican-American and “other”); body mass index (calculated as the measured weight in kilograms divided by the square of the height in meters) ; waist-to-hip ratio; educational attainment (years of school and university completed); smoking status (never, former, < 1 pack/day, ≥1 pack/day); physical activity (calculated by multiplying each recreational and non-recreational activity by its intensity value and adding up the products for all activity types); homeostasis model assessment insulin resistance (HOMA-IR) calculated as [(fasting serum insulin (μU/mL) fasting plasma glucose (mmol/L))/22.5]; self-reported diabetes mellitus; fasting plasma glucose; systolic and diastolic blood pressure (calculated as the average of the last 2 of 3 blood pressure measurements); C-reactive protein; plasma total and

HDL cholesterol and triglycerides; glomerular filtration rate (GFR), estimated by using the simplified Modification of Diet in Renal Disease (MDRD) study equation: GFR (ml/min/$1.73m^2$) = 186 × (serum creatinine level [mg/dl])$^{-1.154}$ × (age)$^{-0.203}$× [0.742, if female] × [1.212, if black][22]. (Serum creatinine was calibrated for measurement variance between NHANES III and MDRD clinical laboratories[23]); urine albumin-creatinine ratio (mg/g), a measure of albuminuria; use of diuretics, β-blockers, other anti-hypertensives, aspirin, and nonsteroidal anti-inflammatory drugs; consumption of meat, seafood, dairy foods, coffee and sugar-sweetened soft drinks, estimated using a validated food frequency questionnaire[24].

Statistical Analyses

Men and women were analyzed separately given differences in SUA levels by gender[4] and the different associations between SUA and mortality previously reported in women versus men. SUA level was either analyzed as a continuous variable or divided into sex and menopause specific quartiles as follows: for men, 0–5.2, >5.2–6, >6–6.9, and >6.9 mg/dL; all women 0–3.8, >3.8–4.5, >4.5–5.4, and >5.4 mg/dL; postmenopausal women, 0–4.3, >4.3–5.0, >5.0–5.9, and >5.9 mg/dL; and premenopausal women 0–3.7, >3.7–4.4, >4.4–5.1, and >5.1 mg/dL.

We used Kaplan-Meier curves to compare graphically mortality by SUA category. The associations between SUA level and cardiovascular or all-cause mortality after adjustment for potential confounders were evaluated using the Cox proportional hazards model[25]. We confirmed the proportional hazards assumption using −log (−log) plots. The date of the NHANES III baseline examination was used as time zero for the proportional hazards models. Person-years of follow-up were calculated from the examination date to the date of death or to December 31st, 2006, for participants who were still alive as of that date. For analyses of cardiovascular mortality, participants were censored if they died of non-cardiovascular causes.

It has been suggested that certain important risk factors for death or cardiovascular disease such as diabetes, insulin resistance, hypertension or impaired renal function are actually caused by hyperuricemia. If so, these factors are not true confounders but rather “in the causative path” between hyperuricemia and excess mortality and adjusting for them eliminates that portion of the association between hyperuricemia and mortality that is mediated by these factors. To enable the most informative interpretation of our results we used the following levels of adjustment, in addition to unadjusted and age-adjusted models:

Model A Age, race/ethnicity, menopausal status and hormone replacement therapy (in women only), smoking, alcohol consumption, educational attainment, physical activity, body mass index, waist-to-hip ratio, serum C-reactive protein, plasma triglyceride, total cholesterol, and HDL cholesterol, use of aspirin, NSAIDs, and diuretics and coffee, meat, fish, dairy, and sugar-sweetened beverage consumption.

Model B Variables of Model A, plus diabetes and insulin resistance.

Model C Variables of Model B, plus systolic and diastolic blood pressure, and use of antihypertensives.

Model D Variables of Model C, plus glomerular filtration rate and urine albumin-creatinine ratio.

Age-adjusted and the fully-adjusted Model D are presented in Tables 3 and 4 while the additional models are presented online as Supplementary tables.

Interaction terms for (gender*uric acid) or (menopausal status*uric acid) or (hormone replacement therapy*uric acid) were included in appropriate models to investigate for interaction by gender, menopausal status or HRT. A p-value <0.05 in the coefficient of each of these interaction terms was considered evidence of statistically significant linear, first-order interaction.

NHANES III involved a complex sampling design. This induces a correlation structure among the observations, which means they cannot be treated as a simple random sample. In addition, because NHANES III involved increased rates of sampling for certain age, gender, and racial groups, sample weights are provided to reflect this and also to attempt to adjust for non-response bias (due to people refusing to participate) and non-coverage bias (due to people who do not live in households and, therefore, could not participate). We accounted for the sampling and weighting processes using the survey commands of STATA version 11 statistical software and the appropriate weight, strata, and primary sampling unit variables such that our results are representative of the US population.

RESULTS

Among both women (Table 1) and men (Table 2), increasing quartiles of SUA were associated with increasing BMI, waist circumference, waist-to-hip ratio, total cholesterol, triglycerides, HOMA-IR, C-reactive protein, albuminuria, and blood pressure, increasing prevalence of hypertension and diuretic medication use and decreasing HDL-cholesterol, GFR, and physical activity. Diagnosed diabetes or a plasma glucose value ≥ 126 mg/dL were more common in the highest SUA quartile in women but not in men. Mean age increased with increasing SUA quartile in women but not in men. Menopausal status in women was also strongly associated with increasing SUA quartile. In these unadjusted analyses, we found little association between SUA level and educational attainment, race/ethnicity, aspirin or NSAID use, and intake of meat, seafood, dairy food, or sugar-sweetened soft drinks in either men or women.

During 13.5 years of mean follow-up, 1284 persons died, including 455 of cardiovascular causes. Among 2719 men in our study population, there were 696 deaths, including 244 cardiovascular deaths. Among 3137 women, there were 588 deaths, including 211 cardiovascular deaths.

Among women, both all-cause and cardiovascular mortality appeared to increase with increasing SUA level, in unadjusted and adjusted analyses (Table 3 and Supplemental Figure 1). Adjustment for age and then for the group of variables included in each model A–D, attenuated somewhat the hazard ratios associated with SUA. However, even in the fully-

adjusted Model D, increasing SUA level modeled as a continuous variable was significantly associated with all-cause and cardiovascular mortality (adjusted HRs 1.17, 95% CI 1.03–1.32 and 1.23, 95% CI 1.01–1.51, respectively). The associations were stronger for cardiovascular than for all-cause mortality as reflected by greater hazard ratios.

We confirmed statistically significant linear interaction between gender and SUA level ($p<0.001$), supporting our *a priori* decision to present results separately for men and women. Among women, we did not find statistically significant interaction between menopausal status and SUA. However, there were only 70 deaths, including only 15 cardiovascular deaths, among 1863 premenopausal women thus limiting our power to detect interaction. Among postmenopausal women, there was significant interaction between hormone replacement therapy and SUA ($p=0.01$). Given these findings, we presented results separately for premenopausal and postmenopausal women and for postmenopausal women on or off HRT(Table 3). Among postmenopausal women, all-cause and cardiovascular mortality increased with increasing SUA and these associations remained statistically significant even in the fully adjusted model D, when SUA was modeled as a continuous variable. However, among premenopausal women, all-cause mortality did not increase with increasing SUA. Instead, the highest risk was observed among premenopausal women in the second SUA quartile (>3.7–4.4 mg/dL). Consequently, when modeled as a continuous linear variable, SUA was not associated with all-cause mortality among premenopausal women. There were too few cardiovascular deaths among premenopausal women for meaningful analyses.

The most robust associations between SUA and mortality were observed among postmenopausal women who were not taking HRT (Table 3): the risk of all-cause and cardiovascular mortality significantly increased with increasing SUA and women in the top SUA quartile (>5.9 mg/dL) had ~2 times the risk of all-cause mortality and ~3 times the risk of cardiovascular mortality compared to those in the lowest SUA quartile (SUA 0–4.3 mg/dL). However, among postmenopausal women who received HRT, the associations between SUA and mortality were blunted, were not statistically significant and did not appear to be monotonic. Instead, the highest risk of all-cause or cardiovascular mortality was observed among postmenopausal women on HRT who were in the second quartile of SUA (4.3–5.0 mg/dL)

Among men, there was no association between SUA level and all-cause or cardiovascular mortality in unadjusted or multivariate adjusted analyses (Table 4 and Supplemental Figure 1). When SUA category >5.2–6 mg/dL was used as the reference category, rather than 0–5.2 mg/dL, (because of recent reports suggesting a J-shaped association between SUA level and mortality in men with the lowest risk being in the ~5–6 mg/dL range[8]), the higher quartiles (>6–6.9 and >6.9) were not associated with increased all-cause or cardiovascular mortality relative to SUA category >5.2–6 mg/dL. Given the observed effect on the SUA associations by menopausal status in women, we subdivided men by age into <51 and ≥51 year olds. There was no association between SUA and mortality in either age group.

Supplemental Figure 1. SUA level (in quartiles) and all-cause (a–f) or cardiovascular (g–k) mortality presented according to gender, menopausal status and use of hormone replacement therapy.

DISCUSSION

Our results suggest that SUA level most strongly predicts all-cause and cardiovascular mortality among postmenopausal women who are not using HRT. Among these women we identified a significant, monotonic association between SUA level and all-cause, or cardiovascular mortality. In contrast, we did not identify significant associations between SUA and mortality among postmenopausal women who received HRT, premenopausal women and men.

Despite multiple publications, controversy still exists as to whether SUA predicts mortality in both women and men, particularly in US populations, and whether these associations persist after adjustment for appropriate confounders. Many previous studies were unable to adjust for important potential confounders leading to uncertainty as to whether SUA was truly an independent predictor. Our aim was to ascertain accurately important, known confounders in a nationally representative sample. Thus, we limited our analyses to the NHANES participants who were assigned to the 10am phlebotomy and examination session and who fasted for ≥8 hours such that reliable, consistent laboratory values for tests such as plasma glucose, serum insulin and plasma lipids would be available. In our fully adjusted model, we included 28 covariates that captured all important factors known to be associated with SUA level and mortality.

Whether hyperuricemia plays any direct role in causing cardiovascular disease and death or whether it is just a marker for an adverse metabolic profile, remains an unanswered question, debated in recent reviews[1–2]. Although hyperuricemia has been clearly associated with alcohol consumption, obesity, insulin resistance, systemic inflammation and the metabolic syndrome[1, 26], the associations that we describe with mortality persisted after adjustment for these conditions. However, we cannot exclude the possibility of residual confounding by conditions such as insulin resistance and systemic inflammation, which are likely not captured completely even after adjustment for HOMA-IR, CRP and a host of related metabolic parameters that we included in our regression models. It has been proposed recently that hyperuricemia might contribute to the cause of insulin resistance, oxidative stress, systemic inflammation and the metabolic syndrome, rather than being simply their marker[1–2]. Hyperuricemia can induce endothelial dysfunction and reduce bioavailability of endothelial nitric oxide in rats[27] while treatment with allopurinol can improve endothelial function in patients with hyperuricemia[28]. Glucose uptake in skeletal muscle depends in part on increases in blood flow mediated by the insulin-stimulated release of nitric oxide from endothelial cells[29]. Therefore, hyperuricemia-induced endothelial dysfunction can potentially promote insulin resistance by impairing insulin-stimulated release of nitric oxide. Furthermore, hyperuricemia induces inflammatory and oxidative changes in adipocytes, a process that is crucial in causing the metabolic syndrome in obese mice[30]. Whether hyperuricemia is a cause or a consequence of conditions that promote cardiovascular disease is of considerable significance since pharmacological reduction of serum UA levels is possible but would only be useful if hyperuricemia was a cause rather than a consequence of these conditions. In humans, this question can ultimately only be resolved by randomized controlled trials aimed at lowering SUA level, as has been

recommended by Feig *et al*[1]. Our results suggest that if such studies are undertaken, they should initially involve postmenopausal women not using HRT.

It is tempting to speculate why there is an association between SUA level and mortality in postmenopausal women off HRT, but not in men, premenopausal women or postmenopausal women on HRT. This finding is at first sight counterintuitive since men have higher SUA levels than women and might have been expected to have stronger associations between SUA level and mortality. Our findings could be explained by hypothesizing that women are more susceptible to hyperuricemia than men but are protected by estrogen before menopause, either due to the effect of estrogen on renal urate excretion causing a reduction in SUA levels or due to putative anti-oxidant and anti-inflammatory effects of estrogen antagonizing putative pro-oxidant, pro-inflammatory effects of hyperuricemia. Another potential explanation might be that it is the *increase* in SUA level that occurs in women after menopause that causes the association with mortality, rather than the absolute SUA level. Although men have higher SUA levels that women, their levels remain largely stable in adulthood. Unfortunately, our epidemiological study cannot provide further insight into these mechanistic hypotheses.

Our study is limited by a relatively small number of deaths (n=70) among 1863 premenopausal women in our analysis which may have been underpowered to detect a weak association between SUA and mortality. Only 15 cardiovascular deaths occurred among premenopausal women; therefore the association with cardiovascular death in premenopausal women could not be investigated. Our results are based on a single baseline measurement of SUA level. If there is substantial variability in SUA level over time, then this would contribute to regression dilution[31] and tend to bias the associations towards the null (i.e. the “true” association between SUA level and mortality among postmenopausal women would, if anything, be even greater than what we described, if there is substantial variability in SUA level over time). However, the most important changes in SUA level that occur over time are the result of aging and menopause in women leading to a dramatic elevation in SUA level. We have already accounted for these factors both by adjusting and by subgroup analyses by gender, menopausal status and HRT status.

Our study also has important strengths that overcome some of the limitations of previous studies. Our results are representative of the US population. All laboratory tests were performed on samples obtained around 10am after an overnight fast of at least 8 hours. Our multivariate models included a more complete adjustment for potential confounders than was afforded by previous studies of which we are aware.

Our results suggest that SUA level is associated with cardiovascular and all-cause mortality among women but not among men, as had been reported by some previous studies[16]. A novel finding of our study is that this association exists primarily among postmenopausal women not taking HRT and persists after adjustment for factors associated with SUA level and mortality. Thus, SUA level may be used as an independent predictor of cardiovascular and all-cause mortality in postmenopausal women not taking HRT.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Baseline characteristics of women by serum uric acid quartile.

Characteristic	Serum Uric Acid Level (mg/dL)				P-value
	0–3.8	>3.8–4.5	>4.5–5.4	>5.4	
Age (y)	41.7 (1)	42.0 (0.9)	44.9 (0.8)	52.1 (1)	<0.001
Post-menopausal (%)	28.1 (3)	31.8 (3)	39.3 (3)	59.9 (3)	<0.001
Postmenopausal hormone use (%)[e]					
Never	52 (5)	61 (5)	55 (4)	60 (3)	
Past	27 (4)	15 (3)	20 (3)	24 (2)	
Current	21 (4)	24 (4)	24 (3)	16 (3)	
Years of school completed, mean	12.6 (0.2)	12.6 (0.2)	12.5 (0.2)	11.9 (0.2)	0.001
Ethnicity (%)					0.2
Non-Hispanic White	80 (2)	79 (2)	74 (2)	79 (2)	
Non-Hispanic Black	11 (1)	10 (1)	10 (1)	12 (1)	
Mexican American	5 (0.7)	4 (0.4)	4 (0.6)	4 (0.5)	
Other	4 (1)	6 (1)	12 (2)	6 (2)	
Cigarette smoking (%)					0.2
Never	57 (3)	53 (3)	58 (3)	50 (2)	
Former	16 (2)	20 (2)	21 (2)	31 (2)	
<1 pack per day	13 (2)	13 (2)	10 (2)	10 (1)	
≥1 pack per day	15 (2)	13 (2)	12 (2)	10 (2)	
BMI (kg/m^2)	23.6 (0.2)	24.8 (0.2)	26.4 (0.3)	30.0 (0.3)	<0.001
Waist circumference (cm)	81 (0.7)	84 (0.7)	88 (0.8)	99 (0.7)	<0.001
Waist-to-hip ratio	0.83 (0.005)	0.85 (0.005)	0.86 (0.004)	0.91 (0.004)	<0.001
Serum total cholesterol (mg/dL)	192 (2)	198 (2)	204 (2)	220 (2)	<0.001
Serum HDL cholesterol (mg/dL)	57 (1)	56 (0.8)	56 (1)	51 (0.9)	<0.001
Serum triglycerides (mg/dL)	93 (3)	111 (4)	122 (5)	165 (5)	<0.001
C-reactive protein >0.3 mg/dL, %	21 (3)	24 (2)	32 (2)	49 (3)	<0.001
Glomerular Filtration Rate (ml/min^{-1}/1.73m^{-2})	109 (1)	105 (1)	99 (2)	89 (2)	<0.001

Characteristic	Serum Uric Acid Level (mg/dL)				P-value
	0–3.8	>3.8–4.5	>4.5–5.4	>5.4	
Urine albumin-creatinine ratio (mg/g)	15 (2)	13 (1)	14 (2)	40 (12)	0.04
HOMA-IR[a]	1.8 (0.06)	2.2 (0.1)	2.4 (0.1)	3.8 (0.2)	<0.001
Diabetes (diagnosed)[b]**, %**	2.0 (0.6)	2.4 (0.6)	1.6 (0.4)	5.6 (0.9)	0.002
Fasting plasma glucose (mg/dL), %					<0.001
100–125	10 (1)	17 (2)	18(2)	30 (2)	
≥126	1.9 (0.6)	2.9 (0.8)	1.9 (0.4)	9.6 (1.5)	
Systolic blood pressure (mm Hg), mean	110 (1)	112 (0.9)	115 (0.5)	124 (1)	<0.001
Diastolic blood pressure (mm Hg), mean	68 (0.5)	69 (0.5)	70 (0.5)	73 (0.6)	<0.001
Hypertension[c]**, %**	14 (2)	20 (2)	23 (2)	47 (3)	<0.001
Diuretic medications, %	3.2 (0.7)	3.7 (0.9)	6.8 (1)	19 (2)	<0.001
Aspirin or NSAIDs, %	40 (3)	39 (2)	35 (3)	35 (2)	0.09
Physical activity intensity (METs) [d]**, mean**	109 (9)	97 (7)	102 (7)	90 (6)	0.07
Meat intake (servings/day)	1 (0.02)	1 (0.03)	0.9 (0.03)	1 (0.02)	0.5
Seafood intake (servings/day)	0.2 (0.01)	0.2 (0.02)	0.2 (0.02)	0.2 (0.009)	0.7
Dairy food intake (servings/day)	1.7 (0.05)	1.4 (0.07)	1.5 (0.08)	1.3 (0.05)	0.002
Sugar-sweetened soft drinks (drinks/day)	0.3 (0.03)	0.3 (0.03)	0.5 (0.05)	0.4 (0.03)	0.006
Alcohol consumption (%)					0.03
None to <12 drinks per year	53 (3)	50 (3)	53 (3)	60 (3)	
>0 to 1 drink per day	43 (3)	42 (3)	40 (3)	32 (3)	
>1 to 2 drinks per day	3 (1)	5 (1)	6 (2)	5 (1)	
>2 drinks per day	0.5 (0.2)	2 (0.7)	1 (0.4)	2 (0.7)	
Coffee intake (cups/day)	1.1 (0.1)	1.1 (0.09)	1.1 (0.09)	1.0 (0.09)	0.5

NOTE: Values are means or percentages ± standard error. Results were adjusted for sampling and weighting processes of NHANES III to reflect estimates for the US population

[a] HOMA-IR is the Homeostasis Model Assessment Insulin Resistance

[b] Diagnosed diabetes refers to persons who reported a physician diagnosis of diabetes or taking diabetic medications (the proportions are lower than in the entire NHANES population because patients on insulin were instructed not to fast and were hence excluded from our study sample)

[c] Hypertension was defined as a systolic blood pressure >130 mmHg or diastolic blood pressure >85 mmHg or use of antihypertensive medications

[d] Physical activity was calculated as the sum of the products of activity frequency in the previous month and an intensity rating for nine common activities.

[e] Among postmenopausal women only

Table 2

Baseline characteristics of men by serum uric acid quartile.

Characteristic	Serum Uric Acid Level (mg/dL)				P-value
	0–5.2	>5.2–6	>6–6.9	>6.9	
Age (y), mean	44 (0.9)	42 (0.7)	42 (1)	44 (1)	0.9
Years of school completed, mean	12 (0.2)	13 (0.2)	13 (0.2)	13 (0.2)	0.2
Race/Ethnicity, %					0.3
Non-Hispanic White	76 (2)	82 (2)	79 (2)	74 (4)	
Non-Hispanic Black	9 (0.9)	8 (0.9)	8 (1)	11 (1.1)	
Mexican American	6 (0.8)	5 (0.7)	6 (1)	6 (0.7)	
Other	9 (2)	5 (1)	7 (1)	10 (3)	
Cigarette smoking, %					0.5
Never	33 (3)	37 (3)	41 (3)	35 (3)	
Former	29 (3)	28 (3)	30 (4)	41 (3)	
<1 pack per day	13 (2)	14 (2)	12 (2)	9 (2)	
≥1 pack per day	24 (3)	21 (2)	16 (2)	16 (3)	
BMI (kg/m^2), mean	25 (0.3)	26 (0.3)	27 (0.3)	29 (0.3)	<0.001
Waist circumference (cm), mean	91 (0.7)	94 (0.8)	95 (0.8)	101 (0.8)	<0.001
Waist-to-hip ratio, mean	0.93 (0.03)	0.95 (0.005)	0.95 (0.004)	0.97 (0.003)	<0.001
Serum total cholesterol (mg/dL), mean	198 (3)	203 (2)	202 (3)	208 (3)	0.02
Serum HDL cholesterol (mg/dL), mean	48 (0.6)	45 (1)	45 (0.8)	43 (0.9)	<0.001
Serum triglycerides (mg/dL), mean	115 (4)	132 (6)	148 (6)	185 (13)	<0.001
C-reactive protein >0.3 mg/dL, %	15 (2)	19 (3)	20 (3)	29 (3)	<0.001
Glomerular Filtration Rate ($ml/min^{-1}/1.73m^{-2}$), mean	105 (1)	100 (1)	100 (1)	94 (2)	<0.001
Urine albumin-creatinine ratio (mg/g)	14 (2)	10 (1)	10 (2)	25 (6)	0.04
HOMA-IR [a]	2.3 (0.1)	2.6 (0.2)	2.7 (0.1)	3.6 (0.2)	<0.001
Diabetes (diagnosed)[b], **%**	4.0 (1)	2.6 (1)	3.7 (1)	4.2 (1)	0.7
Fasting plasma glucose (mg/dL), %					0.2
100–125	29 (6)	30 (4)	36 (2)	33 (3)	

Characteristic	Serum Uric Acid Level (mg/dL)				P-value
	0–5.2	>5.2–6	>6–6.9	>6.9	
≥126	6.2 (1)	4.7 (1)	5.2 (1)	5.8 (0.9)	
Systolic blood pressure (mm Hg), mean	119 (0.9)	120 (0.9)	121 (0.9)	123 (1)	<0.001
Diastolic blood pressure (mm Hg), mean	74 (0.6)	74 (0.7)	76 (0.7)	78 (0.6)	<0.001
Hypertension[c], %	25 (3)	26 (3)	36 (3)	44 (3)	<0.001
Diuretic medications, %	2.1 (0.9)	1.4 (0.5)	3.6 (0.7)	9.3 (1)	<0.001
Aspirin or NSAIDs, %	38 (2)	38 (3)	43 (3)	42 (3)	0.2
Physical activity intensity (METs) [d], mean	148 (14)	132 (8)	135 (11)	119 (7)	0.09
Meat intake (servings/day), mean	1.1 (0.04)	1.2 (0.04)	1.1 (0.04)	1.2 (0.04)	0.5
Seafood intake (servings/day), mean	0.2 (0.02)	0.2 (0.01)	0.2 (0.02)	0.2 (0.009)	0.2
Dairy food intake (servings/day), mean	1.6 (0.09)	1.6 (0.07)	1.5 (0.07)	1.6 (0.07)	0.5
Sugar-sweetened soft drinks (drinks/day), mean	0.7 (0.1)	0.6 (0.09)	0.7 (0.05)	0.6 (0.04)	0.8
Alcohol consumption, %					0.1
None to <12 drinks per year	35 (4)	34 (4)	30 (3)	30 (4)	
>0 to 1 drink per day	45 (3)	45 (4)	44 (2)	40 (3)	
>1 to 2 drinks per day	9 (2)	12 (2)	15 (3)	15 (2)	
>2 drinks per day	11 (2)	8 (2)	12 (2)	15 (2)	
Coffee intake (cups/day), mean	1.8 (0.2)	1.6 (0.1)	1.4 (0.1)	1.3 (0.1)	0.03

NOTE: Values are means or percentages ± standard error. Results were adjusted for sampling and weighting processes of NHANES III to reflect estimates for the US population

[a] HOMA-IR is the Homeostasis Model Assessment Insulin Resistance

[b] Diagnosed diabetes refers to persons who reported a physician diagnosis of diabetes or taking diabetic medications (the proportions are lower than in the entire NHANES population because patients on insulin were instructed not to fast and were hence excluded from our study sample)

[c] Hypertension was defined as a systolic blood pressure >130 mmHg or diastolic blood pressure >85 mmHg or use of antihypertensive medications

[d] Physical activity was calculated as the sum of the products of activity frequency in the previous month and an intensity rating for nine common activities.

Table 3

The association between serum uric acid level and all-cause or cardiovascular mortality in women.

Seum uric acid, mg/dL	Number Of Subjects	Person-years	Deaths	Mortality per 1000 person-years	Age-Adjusted hazard ratio (95% CI)	Multivariate-adjusted* hazard ratio (95% CI)
ALL WOMEN (N=3137)						
All cause mortality						
0–3.8	758	10,998	78	7.1	1	1
>3.8–4.5	740	10,413	104	10.0	1.26 (0.85–1.86)	1.25 (0.84–1.88)
>4.5–5.4	756	10,238	148	14.5	1.41 (1.07–1.86)	1.39 (0.98–1.98)
>5.4	883	11,286	258	22.9	1.69 (1.23–2.32)	1.39 (0.90–2.15)
SUA per mg/dL	N/A	N/A	N/A	N/A	1.22 (1.12–1.32)	1.17 (1.03–1.32)
Cardiovascular mortality						
0–3.9	758	10,998	24	2.2	1	1
>3.9–4.5	740	10,413	31	3.0	1.18 (0.48–2.89)	1.51 (0.58–3.91)
>4.5–5.4	756	10,238	54	5.3	1.61 (0.74–3.51)	2.16 (0.80–5.85)
>5.4	883	11,286	102	9.0	2.25 (1.01–5.0)	2.64 (0.90–7.76)
SUA per mg/dL	N/A	N/A	N/A	N/A	1.28 (1.13–1.46)	1.23 (1.01–1.51)
POSTMENOPAUSAL WOMEN (N=1274)						
All-cause mortality						
0–4.3	316	4084	106	26	1	1
>4.3–5.0	311	3893	124	32	1.14 (0.74–1.76)	1.33 (0.83–2.14)
>5.0–5.9	303	3754	121	32	1.26 (0.88–1.79)	1.25 (0.79–1.99)
>5.9	344	3940	167	42	1.71 (1.21	1.58 (0.90–2.77)
SUA per mg/dL	N/A	N/A	N/A	N/A	1.24 (1.11–1.39)	1.22 (1.06–1.40)
Cardiovascular mortality						
0–4.3	316	4084	42	10	1	1
>4.3–5.0	311	3893	40	10	0.96 (0.53–1.74)	1.21 (0.55–2.64)
>5.0–5.9	303	3754	48	13	1.41 (0.70–2.84)	1.50 (0.62–3.62)
>5.9	344	3940	66	17	1.97 (1.09–3.56)	1.94 (0.71–5.27)

Seum uric acid, mg/dL	Number Of Subjects	Person-years	Deaths	Mortality per 1000 person-years	Age-Adjusted hazard ratio (95% CI)	Multivariate-adjusted* hazard ratio (95% CI)
SUA per mg/dL	N/A	N/A	N/A	N/A	1.31 (1.14–1.51)	1.31 (1.03–1.66)
PREMENOPAUSAL WOMEN (N=1863)						
All-cause mortality						
0–3.7	442	6647	13	2.0	1	1
>3.7–4.4	486	7156	20	2.8	1.72 (0.73–4.1)	1.71 (0.62–4.73)
>4.4–5.1	486	7087	15	2.1	1.16 (0.46–2.93)	1.01 (0.32–3.16)
>5.1	449	6375	22	3.5	1.53 (0.54–4.27)	0.80 (0.26–2.47)
SUA per mg/dL	N/A	N/A	N/A	N/A	1.30 (0.91–1.84)	1.13 (0.84–1.53)
POSTMENOPAUSAL WOMEN ON HRT (N=480)						
All-cause mortality						
0–4.3	120	1572	35	22	1	1
>4.3–5.0	132	1736	43	25	1.19 (0.67–2.12)	1.76 (0.94–3.28)
>5.0–5.9	111	1453	34	23	0.89 (0.48–1.64)	0.81 (0.32–2.09)
>5.9	117	1444	38	26	1.30 (0.75–2.24)	0.95 (0.31–2.90)
SUA per mg/dL	N/A	N/A	N/A	N/A	1.11 (0.98–1.25)	1.12 (0.86–1.46)
Cardiovascular mortality						
0–4.3	120	1572	15	9.5	1	1
>4.3–5.0	132	1736	17	9.8	1.38 (0.56–3.39)	1.75 (0.50–6.03)
>5.0–5.9	111	1453	14	9.6	1.19 (0.40–3.55)	0.65 (0.13–3.20)
>5.9	117	1444	13	9.0	1.42 (0.56–3.59)	0.60 (0.15–2.39)
SUA per mg/dL	N/A	N/A	N/A	N/A	1.13 (0.92–1.39)	0.99 (0.77–1.28)
POSTMENOPAUSAL WOMEN NOT ON HRT (N=794)						
All-cause mortality						
0–4.3	196	2512	71	28	1	1
>4.3–5.0	179	2157	81	38	1.14 (0.65–2.01)	1.18 (0.64–2.18)
>5.0–5.9	192	2300	87	38	1.52 (0.99–2.34)	1.35 (0.69–2.62)
>5.9	227	2496	129	52	1.97 (1.32–2.96)	1.89 (0.99–3.62)
SUA per mg/dL	N/A	N/A	N/A	N/A	1.29 (1.18–1.41)	1.30 (1.11–1.51)

Seum uric acid, mg/dL	Number Of Subjects	Person-years	Deaths	Mortality per 1000 person-years	Age-Adjusted hazard ratio (95% CI)	Multivariate-adjusted* hazard ratio (95% CI)
Cardiovascular mortality						
0–4.3	196	2512	27	11	1	1
>4.3–5.0	179	2157	23	11	0.71 (0.31–1.65)	1.05 (0.40–2.76)
>5.0–5.9	192	2300	34	15	1.61 (0.74–3.52)	1.66 (0.76–3.59)
>5.9	227	2496	53	21	2.43 (1.36–4.37)	3.15 (1.21–8.23)
SUA per mg/dL	N/A	N/A	N/A	N/A	1.48 (1.28–1.71)	1.61 (1.33–1.94)

*Adjusted forage, race/ethnicity, menopausal status, smoking, alcohol consumption, educational attainment, physical activity, body mass index, waist-to-hip ratio, serum C-reactive protein, plasma triglyceride, total cholesterol, and HDL cholesterol, use of aspirin, NSAIDs, and diuretics, consumption of coffee, meat, fish, dairy, and sugar-sweetened beverage consumption, use of hormone replacement therapy (except in premenopausal women), diabetes, insulin resistance, systolic blood pressure, diastolic blood pressure, use of antihypertensives, glomerular filtration rate and urine albumin-creatinine ratio.

Table 4

The association between serum uric acid level and all-cause or cardiovascular mortality in men.

Seum uric acid, mg/dL	Number Of Subjects	Person-years	Deaths	Mortality per 1000 person-years	Age-Adjusted hazard ratio (95% CI)	Model D multivariate hazard ratio (95% CI)
All cause mortality						
0–5.2	708	9404	194	20.6	1	1
>5.2–6.0	710	9602	165	17.2	0.88 (0.62–1.23)	0.93 (0.64–1.36)
>6.0–6.9	626	8456	148	17.5	0.80 (0.59–1.07)	0.79 (0.56–1.11)
>6.9	675	8731	189	21.6	1.01 (0.68–1.48)	0.97 (0.60–1.57)
Serum uric acid: comparing persons with a serum UA difference of 1	N/A	N/A	N/A	N/A	0.99 (0.88–1.11)	0.97 (0.85–1.10)
Cardiovascular mortality						
0–5.2	708	9404	63	6.7	1	1
>5.2–6.0	710	9602	65	6.8	1.24 (0.68–2.25)	1.63 (0.94–2.82)
>6.0–6.9	626	8456	49	5.8	0.68 (0.44–1.08)	0.72 (0.42–1.24)
>6.9	675	8731	67	7.7	0.98 (0.50–1.92)	0.92 (0.49–1.71)
Serum uric acid: comparing persons with a serum UA difference of 1	N/A	N/A	N/A	N/A	0.95 (0.77–1.17)	0.94 (0.80–1.10)

*Adjusted for age, race/ethnicity, smoking, alcohol consumption, educational attainment, physical activity, body mass index, waist-to-hip ratio, serum C-reactive protein, plasma triglyceride, total cholesterol, and HDL cholesterol, use of aspirin, NSAIDs, and diuretics and coffee, meat, fish, dairy, and sugar-sweetened beverage consumption, diabetes, insulin resistance, systolic blood pressure, diastolic blood pressure, use of antihypertensives, glomerular filtration rate and urine albumin-creatinine ratio.