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Hypouricemia and Mortality Risk in the United States General Population

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Abstract

Objective: The most recent European League Against Rheumatism (EULAR) recommendations for gout advise against maintaining serum urate (SU) < 3 mg/dL for prolonged periods. While several Asian cohort studies reported higher mortality in individuals with extremely low SU, non-Asian data are scarce, and the relationship between hypouricemia, cardiovascular risk, and mortality remains unclear.

Methods: Using the National Health and Nutrition Examination Survey (NHANES) from 1988-1994 and 1999-2008, we examined the relations between SU and overall and cause-specific mortality among 41,807 adults in the United States (US). We calculated multivariable hazard ratios (HR) compared to a referent SU level of 5-6 mg/dL for SU categories <4, 4-5, 6-7, 7-8, and >8 mg/dL in men and <3, 3-4, 4-5, 6-7, >7 mg/dL in women.

Results: Among women, there was no higher mortality risk at SU <3 mg/dL (HR 1.09, 95% confidence interval [CI] 0.92 to 1.28). Among men, there was a 28% higher mortality risk at SU<4 mg/dL (HR 1.28, 95% CI 1.13 to 1.45), with nearly three-times higher mortality from diabetes (HR 2.89, 95% CI 1.59 to 5.23), but no increase in mortality from any other specific cause.

Conclusion: We found no long-term excess mortality risk among US women with SU as low as <3 mg/dL, which is incompatible with causality between hypouricemia and premature mortality in women. We found excess all-cause and diabetes-related mortality among hypouricemic US men, which may, in part, be attributable to the uricosuric effect of hyperglycemia in fatal uncontrolled diabetes (analogous to reverse causality).

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INTRODUCTION

The potential causal role of hyperuricemia on the risk of cardiovascular disease and premature mortality has long been a topic of clinical and research interest;[1] however, that of hypouricemia has also been recently raised.[2-6] Although several studies from Japan, Korea, and Taiwan have reported an association between very low serum urate (SU) levels (e.g., <3.5 mg/dL in men and <2.5 mg/dL in women) and higher all-cause and cardiovascular sex-specific mortality, the overall relationship between hypouricemia, cardiovascular risk, and mortality remains unclear.[2-7] Furthermore, the association of hypouricemia with premature mortality in non-Asian cohorts remains poorly understood.

The potential harm of extreme hypouricemia has been speculated to originate from SU's antioxidant properties, potentially contributing to lowering the risk of neurodegenerative conditions. To that end, general population studies (not limited to gout) have reported an inverse association with SU levels and the risk of Alzheimer's dementia[8-10] and Parkinson's disease.[11, 12] Prompted by these data, the latest EULAR recommendations for gout care advise against maintaining SU <3 mg/dL for prolonged periods.[13]

To examine the evidence gap in non-Asian populations and to further clarify the potential risk associated with hypouricemia, we examined all-cause and cause-specific mortality in the United States (US) combining follow-up data from multiple cycles of the National Health and Nutrition Examination Survey (NHANES III [1988-1994] and 1999-2008).

PATIENTS AND METHODS

Study Population

The National Health and Nutrition Examination Survey (NHANES) is a nationwide survey in the US that assesses the health and nutritional status of adults and children using interviews, physical examinations, and laboratory data.[14, 15] The survey utilizes a complex, multistage probability design to provide a nationally representative sample of the noninstitutionalized US civilian population.[16] NHANES was conducted on a periodic basis until 1999, after which they became continuous surveys. For the present study, we analyzed data from subjects aged ≥18 in NHANES III (1988-1994) and 1999-2008 with a SU level measured at enrollment. All procedures in each NHANES were approved by the National Center for Health Statistics Ethics Review Board, and written informed consent was obtained from all subjects at time of enrollment in NHANES.[14, 15]

Serum Urate Level Measurement

SU levels were measured at the time of subject enrollment in NHANES using a colorimetric method where uric acid is oxidized to allantoin and hydrogen peroxide by uricase (Hitachi Model 737 Multichannel Analyzer, Boehringer Mannheim Diagnostics, Indianapolis, IN, USA); the details of quality-control procedures have been published elsewhere.[15] Values are reported in mg/dl and can be converted to μmol/L by multiplying by 59.48.

Assessment of Outcome

Deaths and their underlying causes were obtained from data linkage to the National Death Index until December 31, 2015, which reflects data from death certificate documentation. Death certificates document the immediate cause of death as well as the underlying cause of death, which is the initiating event in the causal sequence leading to the death.[17] For example, if a patient with severe uncontrolled diabetes died from myocardial infarction, the immediate cause may be listed as myocardial infarction and the underlying cause may be listed as diabetes, at the discretion of the certifying physician.[17, 18] Specific underlying causes of death included cardiovascular, malignancy, chronic lower respiratory disease, Alzheimer's disease, and diabetes mellitus. Contributory causes of death were not included in this analysis.

Statistical Analysis

Baseline covariates obtained from NHANES included age, race (White, Black, Other), education (some high school or lower, high school, college, graduate school or higher), body mass index (BMI), hypertension (yes/no), diabetes mellitus (defined by the American Diabetes Association [ADA] criteria[19], self-reported diabetes, or use of an anti-diabetic drug), alcohol consumption (drinks/month), smoking status (current, former, or never), estimated glomerular filtration rate (GFR), serum albumin, and total cholesterol level.

Our analysis was stratified by sex, given the higher SU level in men than women.[20] SU levels were categorized into six groups among men (<4, 4-5, 5-6, 6-7, 7-8, and >8 mg/dL) and women (<3, 3-4, 4-5, 5-6, 6-7, >7 mg/dL). More extreme categories (e.g., <3 mg/dL and 3-4 mg/dL in men and 7-8 mg/dL and >8 mg/dL in women) did not provide sufficient sample sizes for analyses. We used a common reference of SU 5-6 mg/dL in both sexes, analogous to having the same therapeutic target for urate-lowering therapy for gout between sexes. Age was used as a time-scale for survival analyses.

We calculated multivariable hazard ratios using three different models with increasing adjustments for covariates. Our *age-race adjusted model* adjusted for age, race, NHANES cycle, and competing risk (for cause-specific mortality, using a cause-specific model).[21] Our *primary multivariable model* additionally adjusted for BMI, education, smoking status, alcohol consumption, and total cholesterol. The *extended multivariable model* additionally adjusted for hypertension and estimated GFR, which remain potential causal intermediates in the relation between SU and all-cause and cardiovascular-renal mortality. However, as diabetes-specific mortality was an outcome of interest in our study, our multivariable models did not include diabetes mellitus, an obvious causal intermediate.

We performed several sensitivity analyses to assess the robustness of our findings. First, to account for the known positive correlation between SU level and BMI, the study population was matched to subjects with BMI within the same range (± 1 kg/m^2).[22] We also performed an analysis according to race, as classified in NHANES (White, Black, Other). To account for variable follow-up time, a sensitivity analysis was performed in which follow-up time was truncated at 10 years. Given the variation in SU level based on menopausal status in women, a subgroup analysis of post-menopausal women was performed. We did not

perform analyses in pre-menopausal women owing to small numbers. Lastly, we performed an additional analysis excluding subjects with diabetes, defined by the ADA criteria [19], self-reported diagnosis, or use of an anti-diabetic drug. For all measures, we calculated 95% confidence intervals (95% CI). All p-values were two-sided, and a significance level was set at 0.05. All statistical analyses were performed using SAS version 9.4.

RESULTS

Baseline Characteristics

Among 19,954 men and 21,853 women, there were 5,714 male deaths and 4,901 female deaths over mean follow-up times of 13.7 years in men and 14.6 years in women. Age-adjusted baseline characteristics of the study population are shown for men (Table 1) and women (Table 2). Among men, as SU increased, age-adjusted BMI, hypertension, alcohol use, and total cholesterol tended to increase, while diabetes and estimated GFR tended to decrease. Among women, as SU increased, age and age-adjusted BMI, hypertension, alcohol use, and total cholesterol tended to increase, as did diabetes, while estimated GFR tended to decrease. Serum albumin levels were generally similar across all SU levels in men and women. In men, mean hemoglobin A1c levels were highest at the lowest SU range (mean hemoglobin A1c 6.3% at SU 0-4 mg/dl), while in women, the mean hemoglobin A1c was highest at the highest SU range (mean hemoglobin A1c 6.0% at SU >7 mg/dL).

Mortality in Men

At low SU (<4 mg/dL), the age-race adjusted model showed a 33% higher risk of all-cause mortality (HR 1.33, 95% CI 1.18 to 1.50) compared to those with SU 5-6 mg/dL (Table 3). The primary multivariable HR attenuated slightly but remained significant (HR 1.28, 95% CI 1.13 to 1.45), and the extended multivariable model showed a similar effect to the age-race adjusted model (HR 1.33, 95% CI 1.17 to 1.51). At high SU (>8 mg/dL), there was a 59% higher risk of all-cause mortality in the primary multivariable model (HR 1.59, 95% CI 1.44 to 1.75) (Table 3).

For cause-specific deaths at low SU, only diabetes-specific mortality was elevated, with a primary multivariable HR of 2.89 (95% CI 1.59 to 5.23) and extended multivariable HR of 3.39 (95% CI 1.89 to 6.09) among men with SU <4 mg/dL compared to 5-6 mg/dL. In contrast, higher SU levels (>8 mg/dL) were associated with higher mortality from cardiovascular disease (primary multivariable HR 1.39, 95% CI 1.16 to 1.67) and chronic lower respiratory disease (primary multivariable HR 1.70, 95% CI 1.10 to 2.61) compared to SU 5-6 mg/dL. Higher SU levels were also associated with higher diabetes-specific mortality (primary multivariable HR 1.77, 95% CI 1.01 to 3.10), although the association became not significant after further adjusting for hypertension and GFR (extended multivariable HR 1.60, 95% CI 0.87 to 2.95).

Mortality in Women

In women, lower SU levels were not associated with higher all-cause mortality risk. At SU <3 mg/dL, the age-race adjusted HR was 1.13 (95% CI 0.96 to 1.32), and the primary multivariable HR was 1.09 (95% CI 0.92 to 1.28) compared to SU 5-6 mg/dL (Table 4).

However, higher SU levels were associated with higher risk of all-cause mortality. At SU levels >7 mg/dL, the age-race adjusted HR was 1.60 (95% CI 1.46 to 1.76), and the primary multivariable HR was 1.58 (95% CI 1.43 to 1.74) compared to SU 5-6 mg/dL. Compared to the age-adjusted and primary multivariable HRs, the extended multivariable HR was of slightly lower magnitude but still significant (HR 1.45, 95% CI 1.31 to 1.61).

Lower SU levels were not associated with cause-specific deaths in women. However, higher SU levels were associated with a higher risk of cardiovascular deaths (primary multivariable HR 1.38, 95% CI 1.15 to 1.65) (Table 4). Similarly, high SU levels were associated with higher risk of diabetes-related mortality (primary multivariable HR 1.91, 95% CI 1.23 to 2.98).

Sensitivity Analyses

To finely adjust for BMI across SU levels given their close association, we conducted a sensitivity analysis matched on BMI's within ± 1 kg/m^2, where our results persisted with higher overall and diabetes-related mortality at low SU among men (Supplemental Table 1) and no such effect among women (Supplemental Table 2). A subgroup sensitivity analysis by race also showed a similar relation between low SU and higher all-cause mortality in White men but not White women, although analyses were limited among Blacks and Others due to small sample sizes at extremes of SU (Supplemental Table 3). Another analysis with follow-up time truncated at 10 years yielded similar results to the primary analysis (Supplemental Table 4-5). An analysis of women limited to postmenopausal status also revealed similar results compared to the full cohort of women, with no significantly higher risk of all-cause or cause-specific mortality at the lowest SU range versus the referent range (Supplemental Table 6). Lastly, after excluding patients with diabetes, the risk of death in men at the lowest SU range was largely attenuated (multivariable HR 1.18, 95% CI: 1.00 to 1.38 and extended multivariable HR 1.17, 95% CI: 0.99 to 1.38), and the risk of diabetes-related death was no longer significantly higher (multivariable HR 1.34, 95% CI: 0.16 to 11.31 and extended multivariable HR 1.27, 95% CI: 0.15 to 10.75) in the lowest SU range versus the referent range (Supplemental Table 7).

DISCUSSION

In this multi-period US national survey follow-up cohort, we found no long-term excess mortality risk among US women with SU as low as <3 mg/dL. Among men, we found an approximately 30% higher all-cause mortality risk among those with SU <4 mg/dL, which was also associated with a nearly three-fold higher risk of diabetes-related mortality. As hyperglycemia leads to uricosuria and thus hypouricemia in diabetes patients, uncontrolled hyperglycemia in fatally severe diabetes could have led to extreme hypouricemia (analogous to reverse causality).[23] Overall, these findings appear to differ from recent Asian data[2-6] and do not support a causal relation between extreme hypouricemia and mortality. To that end, familial hypouricemia, a rare genetic disorder of urate handling in the renal tubules due to mutations in the human urate transporter 1 (hURAT1) gene, is associated with chronic severe hypouricemia generally <2 mg/dL, providing a natural model of extreme hypouricemia. Although the condition is associated with exercise-induced acute renal

failure,[24] it is not known to be associated with premature mortality,[24, 25] which is congruent with our findings.

Several previous studies from Asian countries including Japan, Korea, and Taiwan have reported higher mortality among those with extreme hypouricemia.[2, 3, 5, 6] Previous Japanese[5] and Korean[6] studies independently reported a higher mortality in hypouricemic men but not women, similar to our findings. In these studies, the association among Japanese men was driven by cardiovascular mortality,[5] and the association among Korean men was driven by cardiovascular and malignancy-related mortality.[6] However, neither study examined diabetes-specific mortality. Another Korean cohort study found higher all-cause, cardiovascular, and malignancy-related mortality in both hypouricemic men and women.[2] Our study found no such associations with all-cause or cardiovascular-related mortality among women or with malignancy-related mortality in either sex. A Taiwanese geriatric (age ≥ 65) cohort study concluded that a higher risk of mortality among hypouricemic men and women was explained by malnutrition (reflected by body mass index and serum albumin),[3] whereas our findings in the US general adult population (reflective of all age ranges) were not influenced by body mass index or serum albumin. Lastly, a recent Japanese single center cohort study reported that women with SU levels <2 mg/dl and without cardiometabolic disease at baseline (n = 14) may be at higher odds of incident CKD and hypertension [7], while not addressing mortality risk. In contrast, our study examined mortality in the US general population without excluding those with prevalent cardiometabolic comorbidities.

In our study, a notable portion of the excess mortality risk in men with low SU was driven by diabetes. Diabetes mellitus was recorded as the primary underlying cause of death in approximately 13% of decedents with diabetes in the National Death Index from January 1, 2000, through December 31, 2007, in the United States.[18] Over time, there has been a trend of increased reporting of diabetes as the primary underlying cause of death, which correlates with decreased reporting of cardiovascular death as the underlying cause.[18] Furthermore, previous studies have found a positive association between blood glucose and serum urate levels up to serum glucose of 180 mg/dL, after which SU had a negative association with higher levels of glucose (a bell-shaped relation).[23, 26-29] An underlying biologic mechanism behind this relation is explained by the uricosuric effect of glycosuria, which occurs when the blood glucose level is > 180 mg/dL,[27] whereas the positive relation before that level is thought to be dominated by the physiologic effects of insulin resistance, which raise SU.[23, 26-29] While pre-diabetes and obesity are associated with rising SU levels due to insulin resistance, chronic diabetes is associated with lower SU levels due to uricosuria, possibly due to impaired reabsorption of uric acid in the proximal tubules of the kidney in the setting of glycosuria.[23] Interestingly, the relation between hypouricemia and hyperglycemia has been shown to be stronger in men than in women.[26, 28, 29] This is consistent with our sex-specific results, which showed higher diabetes-specific mortality at low SU in men but not women. The mechanism underlying these sex-specific differences remains unclear, although the role of sex hormones in uric acid metabolism has been speculated.[30, 31]

Our study also found that high SU levels in men were associated with higher mortality from chronic lower respiratory diseases. As such, up to 50% of sleep apnea patients have been found to have hyperuricemia (thought to be due to hypoxia-induced nucleotide turnover), which increases the risk of incident nocturnal gout attacks.[32, 33] Additionally, prior studies have demonstrated higher SU levels in patients with more severe chronic obstructive pulmonary disease (COPD), with an association between high SU and higher risk of acute COPD exacerbation, hospitalization, and need for non-invasive ventilation.[34, 35] Furthermore, high SU levels have been associated with higher 30-day mortality in patients admitted with COPD exacerbations.[35]

The strengths and limitations of our study deserve comment. Given that NHANES data are collected from community-based samples of men and women and weighted to be representative of the US population, our findings are likely generalizable. While evaluating chronic inherent risk factors such as SU (as opposed to incident exposure) is always methodologically challenging, our stratification by sex, several levels of adjustments, and multiple sensitivity analyses have found consistent results. Nevertheless, similar to other observational studies, our findings cannot rule out residual or unmeasured confounding. Causes of death recorded according to the National Death Index are subject to misclassification bias, similar to other studies using the same database. Some of the subgroups had small numbers of deaths, especially at the extremes of SU levels, and further studies would be helpful to confirm our findings. As all covariates and SU measurements were at baseline, we cannot comment on the trajectory of SU over time and its relationship to mortality risk. Although we were able to provide findings for SU <3 mg/dL in women, we had to perform analyses at SU <4 mg/dl in men due to the low number of male subjects with SU <3 mg/dL. Lastly, due to the small numbers of patients with gout in NHANES, we were unable to examine the relationship between serum urate levels and mortality in gout patients, and further studies are needed, especially among gout patients treated with urate-lowering therapy.

In conclusion, in a large cohort representative of the US general population, there was no significant long-term excess mortality among women with SU levels as low as <3 mg/dL, which does not support causality between hypouricemia and premature mortality. In men, higher mortality risk associated with hypouricemia was considerably driven by diabetes-related mortality, which may reflect the uricosuric effect of hyperglycemia rather than a deleterious causal effect of low SU itself (analogous to reverse causality). Overall, these findings reduce prior concerns that prolonged extreme hypouricemia increases mortality risk in the general population.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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SIGNIFICANCE & INNOVATIONS

- Extreme hypouricemia is suspected to be deleterious, although the nature of the relationship remains unclear.
- In large cohorts representative of the US general population, low serum urate (SU) was associated with higher mortality in men but not women.
- In men, diabetes contributed to higher mortality at low SU, which may be explained by the uricosuric effect of hyperglycemia in uncontrolled diabetes.
- These findings reduce prior concerns that extreme hypouricemia increases the risk of mortality.

Table 1.

Age-adjusted baseline characteristics of **men** aged ≥18 with serum urate measurement at enrollment in NHANES III (1988-1994) and 1999-2008 (n=19,954).

Serum urate range (mg/dL)	**< 4**	**4-5**	**5-6**	**6-7**	**7-8**	**> 8**
Number of subjects	781	3114	6083	5444	2931	1601
Age, years	53.9 ± 19.9	47.9 ± 19.9	45.8 ± 20.0	46.4 ± 19.7	48.7 ± 20.0	51.9 ± 19.9
Race[1]						
White	341 (43.7%)	1330 (42.7%)	2737 (45.0%)	2586 (47.5%)	1413 (48.2%)	728 (45.5%)
Black	162 (20.7%)	688 (22.1%)	1320 (21.7%)	1160 (21.3%)	703 (24.0%)	463 (28.9%)
Other	278 (35.6%)	1096 (35.2%)	2026 (33.3%)	1698 (31.2%)	815 (27.8%)	410 (25.6%)
Education						
Some high school or lower	264 (33.8%)	959 (30.8%)	1703 (28.0%)	1448 (26.6%)	777 (26.5%)	456 (28.5%)
High school	220 (28.2%)	856 (27.5%)	1728 (28.4%)	1492 (27.4%)	783 (26.7%)	437 (27.3%)
College	172 (22.0%)	707 (22.7%)	1411 (23.2%)	1366 (25.1%)	771 (26.3%)	380 (23.7%)
Graduate school or higher	125 (16.0%)	592 (19.0%)	1241 (20.4%)	1138 (20.9%)	600 (20.5%)	328 (20.5%)
BMI, kg/m^2	25.1 ± 0.2	25.5 ± 0.1	26.7 ± 0.1	28.1 ± 0.1	29.5 ± 0.1	30.7 ± 0.2
Hypertension	158 (20.2%)	607 (19.5%)	1338 (22.0%)	1399 (25.7%)	929 (31.7%)	677 (42.3%)
Diabetes mellitus	200 (25.6%)	478 (15.4%)	664 (10.9%)	569 (10.4%)	327 (11.2%)	251 (15.7%)
Alcohol use, times/month	3.9 ± 0.4	3.9 ± 0.1	4.4 ± 0.1	5.1 ± 0.1	5.3 ± 0.2	5.9 ± 0.3
Smoking						
Current	266 (34.1%)	984 (31.6%)	1898 (31.2%)	1584 (29.1%)	765 (26.1%)	413 (25.8%)
Former	206 (26.4%)	831 (26.7%)	1691 (27.8%)	1557 (28.6%)	941 (32.1%)	508 (31.7%)
Never	309 (39.5%)	1299 (41.7%)	2494 (41.0%)	2303 (42.3%)	1225 (41.8%)	680 (42.5%)
Estimated GFR, ml/min	100.6 ± 1.3	96.3 ± 0.5	91.8 ± 0.4	88.6 ± 0.3	86.3 ± 0.5	80.8 ± 0.6
Albumin, mg/dL	4.2 ± 0.02	4.2 ± 0.01	4.3 ± 0.01	4.3 ± 0.01	4.3 ± 0.01	4.2 ± 0.02
Hemoglobin A1c, %	6.3 ± 2.0	5.7 ± 1.4	5.5 ± 1.0	5.5 ± 0.9	5.6 ± 0.9	5.7 ± 1.0
Total cholesterol, mg/dL	191.3 ± 1.9	193.5 ± 0.7	198.5 ± 0.5	202.9 ± 0.6	206.2 ± 0.8	210.5 ± 1.3

Data are represented as mean ± standard deviation for continuous variables and number (percentage) for categorical variables. BMI = body mass index. GFR = glomerular filtration rate.

[1]Race is not age-adjusted.

Table 2.

Age-adjusted baseline characteristics of **women** aged ≥18 with serum urate measurement at enrollment in NHANES III (1988-1994) and 1999-2008 (n=21,853).

Serum urate range (mg/dL)	**< 3**	**3-4**	**4-5**	**5-6**	**6-7**	**> 7**
Number of subjects	1156	5273	7226	4666	2212	1320
Age, years	39.2 ± 17.2	40.0 ± 17.8	44.5 ± 19.3	50.5 ± 19.9	55.7 ± 19.9	62.9 ± 17.3
Race[1]						
White	468 (40.5%)	2193 (41.6%)	3237 (44.8%)	2174 (46.6%)	1104 (49.9%)	663 (50.2%)
Black	442 (38.2%)	1946 (36.9%)	2385 (33.0%)	1395 (29.9%)	509 (23.0%)	227 (17.2%)
Other	246 (21.3%)	1134 (21.5%)	1604 (22.2%)	1097 (23.5%)	599 (27.1%)	430 (32.6%)
Education						
Some high school or lower	343 (29.7%)	1392 (26.4%)	1807 (25.0%)	1241 (26.6%)	580 (26.2%)	366 (27.7%)
High school	327 (28.3%)	1440 (27.3%)	2153 (29.8%)	1386 (29.7%)	679 (30.7%)	411 (31.1%)
College	251 (21.7%)	1339 (25.4%)	1828 (25.3%)	1134 (24.3%)	544 (24.6%)	381 (28.9%)
Graduate school or higher	235 (20.3%)	1102 (20.9%)	1438 (19.9%)	905 (19.4%)	409 (18.5%)	162 (12.3%)
BMI, kg/m^2	24.7 ± 0.2	26.0 ± 0.1	27.7 ± 0.1	30.4 ± 0.1	33.0 ± 0.2	34.4 ± 0.4
Hypertension	195 (16.9%)	1039 (19.7%)	1770 (24.5%)	1488 (31.9%)	927 (41.9%)	725 (54.9%)
Diabetes mellitus	143 (12.3%)	606 (11.5%)	769 (10.6%)	583 (12.5%)	364 (16.4%)	279 (21.1%)
Alcohol use, times/month	1.4 ± 0.1	1.6 ± 0.1	2.0 ± 0.1	2.0 ± 0.1	2.0 ± 0.1	2.4 ± 0.4
Smoking						
Current	243 (21.0%)	1002 (19.0%)	1467 (20.3%)	1041 (22.3%)	549 (24.8%)	317 (24.0%)
Former	169 (14.6%)	891 (16.9%)	1279 (17.7%)	854 (18.3%)	438 (19.8%)	269 (20.4%)
Never	744 (64.4%)	3380 (64.1%)	4480 (62.0%)	2771 (59.4%)	1225 (55.4%)	734 (55.6%)
Estimated GFR, ml/min	109.6 ± 1.5	98.4 ± 0.5	93.0 ± 0.4	87.9 ± 0.5	85.0 ± 0.7	76.9 ± 1.4
Albumin, mg/dL	4.0 ± 0.02	4.1 ± 0.01	4.1 ± 0.01	4.0 ± 0.01	4.0 ± 0.01	4.0 ± 0.02
Hemoglobin A1c, %	5.4 ± 1.3	5.4 ± 1.1	5.5 ± 1.0	5.6 ± 1.0	5.8 ± 1.0	6.0 ± 1.1
Total cholesterol, mg/dL	201.5 ± 1.2	201.7 ± 0.6	205.0 ± 0.5	208.2 ± 0.7	209.0 ± 1.0	214.8 ± 1.8

Data are represented as mean ± standard deviation for continuous variables and number (percentage) for categorical variables. BMI = body mass index. GFR = glomerular filtration rate.

[1]Race is not age-adjusted.

Table 3.

All-cause and cause-specific mortality in **men** with baseline serum urate measurement in NHANES III (1988-1994) and 1999-2008 (n=19,954).

	Serum urate range (mg/dL)	**< 4**	**4-5**	**5-6**	**6-7**	**7-8**	**> 8**
All-cause mortality	Deaths (n)	325	934	1513	1412	872	658
	Mortality rate/1000 PY	2.75 (2.46, 306)	1.83 (1.71, 1.95)	1.48 (1.41, 1.56)	1.53 (1.45, 1.61)	1.84 (1.72, 1.97)	2.75 (2.55, 2.97)
	Age-race adjusted HR[1]	**1.33 (1.18, 1.50)**	**1.20 (1.10, 1.30)**	1.00	1.00 (0.93, 1.08)	**1.11 (1.02, 1.20)**	**1.56 (1.43, 1.72)**
	Multivariable HR[2]	**1.28 (1.13, 1.45)**	**1.15 (1.05, 1.25)**	1.00	1.03 (0.96, 1.11)	**1.14 (1.05, 1.25)**	**1.59 (1.44, 1.75)**
	Extended multivariable HR[3]	**1.33 (1.17, 1.51)**	**1.17 (1.07, 1.28)**	1.00	1.04 (0.96, 1.13)	**1.13 (1.04, 1.24)**	**1.52 (1.37, 1.69)**
Cardiovascular mortality	Deaths (N)	75	257	408	377	270	194
	Mortality rate/1000 PY	0.63 (0.50, 0.80)	0.50 (0.44, 0.57)	0.40 (0.36, 0.44)	0.41 (0.37, 0.45)	0.57 (0.51, 0.64)	0.81 (0.70, 0.93)
	Age-race adjusted HR[1]	0.97 (0.76, 1.24)	1.12 (0.96, 1.31)	1.00	0.98 (0.86, 1.13)	**1.24 (1.06, 1.44)**	**1.44 (1.21, 1.72)**
	Multivariable HR[2]	0.94 (0.73, 1.21)	1.08 (0.92, 1.27)	1.00	0.96 (0.84, 1.11)	**1.21 (1.04, 1.42)**	**1.39 (1.16, 1.67)**
	Extended multivariable HR[3]	0.97 (0.75, 1.27)	1.10 (0.93, 1.30)	1.00	0.93 (0.80, 1.08)	1.13 (0.96, 1.34)	1.22 (1.00, 1.49)
Malignancy-related mortality	Deaths (N)	71	219	355	316	182	112
	Mortality rate/1000 PY	0.60 (0.47, 0.76)	0.43 (0.37, 0.49)	0.35 (0.31, 0.39)	0.34 (0.30, 0.38)	0.39 (0.33, 0.45)	0.47 (0.39, 0.56)
	Age-race adjusted HR[1]	1.12 (0.86, 1.44)	1.10 (0.93, 1.30)	1.00	0.95 (0.82, 1.10)	0.91 (0.76, 1.09)	0.85 (0.69, 1.06)
	Multivariable HR[2]	1.05 (0.81, 1.37)	1.06 (0.90, 1.26)	1.00	0.97 (0.83, 1.13)	0.94 (0.78, 1.13)	0.88 (0.70, 1.09)
	Extended multivariable HR[3]	1.08 (0.82, 1.42)	1.12 (0.93, 1.34)	1.00	1.03 (0.87, 1.21)	1.04 (0.85, 1.26)	0.90 (0.71, 1.15)
Chronic lower respiratory disease mortality	Deaths (N)	14	49	70	63	27	34
	Mortality rate/1000 PY	0.12 (0.06, 0.20)	0.10 (0.07, 0.13)	0.07 (0.05, 0.09)	0.07 (0.05, 0.09)	0.06 (0.04, 0.08)	0.14 (0.10, 0.20)
	Age-race adjusted HR[1]	1.09 (0.61, 1.94)	1.24 (0.86, 1.79)	1.00	0.96 (0.68, 1.35)	0.69 (0.45, 1.08)	1.42 (0.94, 2.14)
	Multivariable HR[2]	0.97 (0.54, 1.73)	1.12 (0.77, 1.62)	1.00	1.05 (0.74, 1.50)	0.81 (0.52, 1.28)	**1.70 (1.10, 2.61)**
	Extended multivariable HR[3]	0.92 (0.51, 1.68)	0.96 (0.64, 1.43)	1.00	1.01 (0.69, 1.47)	0.86 (0.53, 1.38)	**1.91 (1.18, 3.10)**
Alzheimer's disease mortality	Deaths (N)	<10	23	36	35	15	<10
	Mortality rate/1000 PY	0.07 (0.03, 0.13)	0.05 (0.03, 0.07)	0.04 (0.02, 0.05)	0.04 (0.03, 0.05)	0.03 (0.02, 0.05)	0.02 (0.00, 0.04)
	Age-race adjusted HR[1]	1.07 (0.49, 2.33)	1.11 (0.66, 1.87)	1.00	1.04 (0.65, 1.65)	0.73 (0.40, 1.33)	**0.31 (0.11, 0.87)**
	Multivariable HR[2]	1.05 (0.48, 2.30)	1.05 (0.61, 1.82)	1.00	1.10 (0.68, 1.78)	0.83 (0.45, 1.53)	**0.29 (0.09, 0.93)**

	Serum urate range (mg/dL)	< 4	4-5	5-6	6-7	7-8	> 8
	Extended multivariable HR[3]	1.13 (0.50, 2.55)	0.88 (0.48, 1.61)	1.00	1.14 (0.69, 1.91)	0.87 (0.45, 1.69)	**0.23 (0.05, 0.99)**
Diabetes mellitus mortality	Deaths (N)	18	38	37	29	19	22
	Mortality rate/1000 PY	0.15 (0.09, 0.24)	0.07 (0.05, 0.10)	0.04 (0.03, 0.05)	0.03 (0.02, 0.05)	0.04 (0.02, 0.06)	0.09 (0.06, 0.14)
	Age-race adjusted HR[1]	**2.62 (1.47, 4.66)**	**1.78 (1.13, 2.80)**	1.00	0.85 (0.52, 1.37)	0.98 (0.56, 1.71)	**1.78 (1.04, 3.03)**
	Multivariable HR[2]	**2.89 (1.59, 5.23)**	**1.80 (1.12, 2.91)**	1.00	0.90 (0.55, 1.46)	1.01 (0.57, 1.78)	**1.77 (1.01, 3.10)**
	Extended multivariable HR[3]	**3.39 (1.89, 6.09)**	**1.81 (1.10, 3.00)**	1.00	0.86 (0.51, 1.44)	0.93 (0.51, 1.69)	1.60 (0.87, 2.95)

All values are rate or risk (95% CI). Cox proportional hazards models using age as a time scale were used to estimate HR and CI. PY = person years. HR = hazard ratio. CI = 95% confidence interval. Counts below 10 recorded as "<10" per NHANES analysis guidelines. Numbers in bold indicate statistical significance.

[1]Age-race adjusted model was adjusted for age (time scale), race, NHANES cycle, and competing risk (for cause-specific mortality).

[2]Multivariable adjusted model was further adjusted for body mass index (BMI), education (some high school or lower, high school, college, graduate school or higher), smoking (former, current, never), alcohol consumption (drinks/month), and total cholesterol.

[3]Extended multivariable model was further adjusted for hypertension (yes/no) and estimated glomerular filtration rate (GFR).

Table 4.

All-cause and cause-specific mortality in **women** with baseline serum urate measurement in NHANES III (1988-1994) and 1999-2008 (n=21,853).

	Serum urate range (mg/dL)	**< 3**	**3-4**	**4-5**	**5-6**	**6-7**	**> 7**
All-cause mortality	Deaths (N)	181	750	1321	1170	776	703
	Mortality rate/1000 PY	0.82 (0.70, 0.95)	0.75 (0.70, 0.81)	1.02 (0.97, 1.08)	1.47 (1.39, 1.56)	2.25 (2.09, 2.41)	3.94 (3.65, 4.24)
	Age-race adjusted HR[1]	1.13 (0.96, 1.32)	0.99 (0.90, 1.08)	0.96 (0.89, 1.04)	1.00	**1.17 (1.07, 1.29)**	**1.60 (1.46, 1.76)**
	Multivariable HR[2]	1.09 (0.92, 1.28)	0.99 (0.90, 1.09)	0.98 (0.91, 1.07)	1.00	**1.15 (1.05, 1.27)**	**1.58 (1.43, 1.74)**
	Extended multivariable HR[3]	1.11 (0.93, 1.31)	1.03 (0.93, 1.14)	1.00 (0.92, 1.09)	1.00	1.11 (1.00, 1.22)	**1.45 (1.31, 1.61)**
Cardiovascular mortality	Deaths (N)	51	196	316	318	221	217
	Mortality rate/1000 PY	0.23 (0.17, 0.30)	0.20 (0.17, 0.23)	0.24 (0.22, 0.27)	0.40 (0.36, 0.45)	0.64 (0.56, 0.73)	1.22 (1.06, 1.39)
	Age-race adjusted HR[1]	1.20 (0.89, 1.63)	1.06 (0.89, 1.26)	0.90 (0.77, 1.05)	1.00	1.10 (0.93, 1.31)	**1.41 (1.19, 1.68)**
	Multivariable HR[2]	1.20 (0.88, 1.64)	1.07 (0.89, 1.29)	0.92 (0.79, 1.08)	1.00	1.10 (0.92, 1.31)	**1.38 (1.15, 1.65)**
	Extended multivariable HR[3]	1.23 (0.88, 1.71)	1.11 (0.92, 1.34)	0.94 (0.80, 1.11)	1.00	1.06 (0.89, 1.28)	1.16 (0.95, 1.41)
Malignancy-related mortality	Deaths (N)	31	163	289	229	122	112
	Mortality rate/1000 PY	0.14 (0.10, 0.20)	0.16 (0.14, 0.19)	0.22 (0.20, 0.25)	0.29 (0.25, 0.33)	0.35 (0.29, 0.42)	0.63 (0.52, 0.76)
	Age-race adjusted HR[1]	0.82 (0.56, 1.19)	0.95 (0.77, 1.16)	1.03 (0.87, 1.23)	1.00	0.97 (0.78, 1.21)	1.24 (0.99, 1.56)
	Multivariable HR[2]	0.85 (0.58, 1.24)	0.98 (0.80, 1.21)	1.05 (0.88, 1.26)	1.00	0.95 (0.76, 1.19)	1.22 (0.97, 1.54)
	Extended multivariable HR[3]	0.75 (0.50, 1.12)	0.91 (0.73, 1.13)	1.01 (0.84, 1.22)	1.00	0.98 (0.78, 1.24)	1.26 (0.98, 1.61)
Chronic lower respiratory disease mortality	Deaths (N)	<10	38	52	53	24	24
	Mortality rate/1000 PY	0.04 (0.02, 0.08)	0.04 (0.03, 0.05)	0.04 (0.03, 0.05)	0.07 (0.05, 0.09)	0.07 (0.04, 0.10)	0.13 (0.09, 0.20)
	Age-race adjusted HR[1]	1.32 (0.65, 2.66)	1.17 (0.77, 1.77)	0.86 (0.59, 1.26)	1.00	0.74 (0.46, 1.20)	0.95 (0.58, 1.55)
	Multivariable HR[2]	1.18 (0.58, 2.39)	1.11 (0.73, 1.69)	0.88 (0.59, 1.29)	1.00	0.76 (0.47, 1.24)	0.95 (0.57, 1.57)
	Extended multivariable HR[3]	1.26 (0.62, 2.57)	1.11 (0.72, 1.72)	0.87 (0.58, 1.30)	1.00	0.66 (0.39, 1.12)	0.85 (0.49, 1.45)
Alzheimer's disease mortality	Deaths (N)	<10	22	53	40	24	11
	Mortality rate/1000 PY	0.04 (0.02, 0.07)	0.02 (0.01, 0.03)	0.04 (0.03, 0.05)	0.05 (0.04, 0.07)	0.07 (0.04, 0.10)	0.06 (0.03, 0.11)
	Age-race adjusted HR[1]	1.82 (0.85, 3.92)	1.03 (0.62, 1.73)	1.26 (0.84, 1.90)	1.00	0.90 (0.54, 1.50)	0.51 (0.26, 1.00)
	Multivariable HR[2]	1.46 (0.65, 3.26)	0.98 (0.59, 1.63)	1.17 (0.77, 1.77)	1.00	0.87 (0.51, 1.47)	0.50 (0.25, 1.02)

	Serum urate range (mg/dL)	< 3	3-4	4-5	5-6	6-7	> 7
	Extended multivariable HR[3]	1.38 (0.57, 3.36)	0.97 (0.54, 1.73)	1.15 (0.73, 1.81)	1.00	0.79 (0.44, 1.41)	0.54 (0.25, 1.15)
Diabetes mellitus mortality	Deaths (N)	<10	28	39	45	32	43
	Mortality rate/1000 PY	0.03 (0.01, 0.06)	0.03 (0.02, 0.04)	0.03 (0.02, 0.04)	0.06 (0.04, 0.08)	0.09 (0.06, 0.13)	0.24 (0.17, 0.32)
	Age-race adjusted HR[1]	0.95 (0.41, 2.21)	0.99 (0.62, 1.58)	0.77 (0.50, 1.18)	1.00	1.22 (0.78, 1.93)	**2.14 (1.41, 3.25)**
	Multivariable HR[2]	1.22 (0.52, 2.87)	1.23 (0.76, 2.01)	0.89 (0.57, 1.38)	1.00	1.14 (0.72, 1.82)	**1.91 (1.23, 2.98)**
	Extended multivariable HR[3]	1.69 (0.71, 4.02)	1.50 (0.89, 2.53)	0.91 (0.56, 1.46)	1.00	1.11 (0.68, 1.82)	**1.66 (1.02, 2.71)**

All values are rate or risk (95% CI). Cox proportional hazards models using age as a time scale were used to estimate HR and CI. PY = person years. HR = hazard ratio. CI = 95% confidence interval. Counts below 10 recorded as "<10" per NHANES analysis guidelines. Numbers in bold indicate statistical significance.

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[3]Extended multivariable model was further adjusted for hypertension (yes/no) and estimated glomerular filtration rate (GFR).