# Interrelations Between Serum Uric Acid, Silent Myocardial Infarction, and Mortality in the General Population

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**Whether elevated uric acid (UA) is associated with silent myocardial infarction (SMI) or whether their joint association predicts an increased risk of mortality has not been explored. This analysis included 6,323 participants (58.4 ± 13.1 years, 53.9% women, and 49.7% Non-Hispanic whites) without clinical cardiovascular disease (CVD) from third National Health and Nutrition Examination Survey. SMI was defined as electrocardiographic evidence of myocardial infarction (MI) without a history of MI. Multivariable logistic regression model was used to examine the cross-sectional association between baseline UA and SMI. Cox-proportional hazard analysis was used to calculate hazard ratio (HR) with 95% confidence interval (CI) for the risk of all-cause and CVD mortality with UA in the absence and presence of SMI. The higher baseline level of UA was associated with higher odds of baseline SMI. The prevalence of SMI was 0.79%, 1.18%, 1.59%, and 2.27% across the UA quartiles respectively; multivariable-adjusted odds ratio (95% CI): 2.37 (1.11 to 5.08) comparing the upper with lower quartile. During a median follow up of 14 years, there were 1916 all-cause death of whom 774 were CVD deaths. Compared with participants with the lowest UA quartile values and without SMI, those with highest UA had a 29% increased the risk of all-cause mortality (multivariable-adjusted HR: [95% CI]: 1.29 [1.10 to 1.51]). This risk increased by 107% in the presence of SMI (multivariable-adjusted HR (95% CI): 2.07 (1.38 to 3.10)). Similar results were observed for CVD mortality. SMI carried an increased risk of all-cause and CVD mortality only in higher quartiles of UA. In conclusion, the strong association of UA with SMI and the additive effect of UA and SMI on mortality further support the potential role of UA as a marker of poor outcomes.**  **(Am J Cardiol 2019;123:882−888)**

The association of uric acid (UA) with cardiovascular disease (CVD) and mortality remains controversial. Elevated UA is associated with CVD and mortality in some studies[1,2] whereas other studies failed to find such an association.[3,4] Elevated UA, however, has shown to predict the poor outcomes in participants with coronary heart disease (CHD).[5,6] Silent myocardial infarction (SMI) determined by electrocardiogram (ECG) has been associated with CHD, all-cause and CVD mortality.[7,8] Whether elevated UA is associated with SMI or modify the risk of mortality associated with SMI and vice versa has also not been explored previously. As the debate continues whether elevated UA has any causal link with CVD or not, exploring its association with SMI, a marker of poor future outcome will further facilitate in establishing the potential role of UA in CVD. Therefore, we proposed to explore this relationship in a sample from the third National Health and Nutrition Examination Survey (NHANES-III) free of clinical CVD. We hypothesized that elevated UA would be associated with prevalent SMI and risk of mortality would increase with increasing UA quartiles and the risk would be greater when UA quartile and SMI are present together than in isolation.

## Methods

NHANES is a periodic survey of a representative sample of the civilian noninstitutionalized US population aimed to determine estimates of disease prevalence and health status of the US population. The National Center for Health Statistics of the Center for Disease Control and Prevention institutional review board approved the protocol for NHANES III. All participants gave written informed consent. Between 1988 and 1994, initial home interviews were conducted to collect baseline information, including demographics (age, sex, race/ethnicity), medication data (e.g., use of antihypertensive), past medical history (e.g., history of CVD), and behavioral data (e.g., smoking). Subsequently, participants visited mobile examination centers and gave blood samples to record basic laboratory values for each participant.

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Of the 8561 NHANES III participants who underwent a 12-lead screening ECG, we excluded participants with a history of CVD (coronary heart disease, heart failure, or stroke), those with QRS ≥120 msec or missing key covariates. After all exclusions, 6323 participants were included in the final analysis.

Age (continuous in years), sex (male and female), race/ethnicity (non-Hispanic white, non-Hispanic black, Mexican American and other), income (<$20,000/year, > $20,000/year), smoking status (never, current, and former), history of gout, leisure time physical activity (number of times engaged in physical activity in past month), were self-reported. Alcohol intake (<12 drinks in the lifetime or lifetime abstainers and ≥12 drinks over the lifetime including both current and former drinkers) was also self-reported. Among current drinkers, alcohol use was classified by the number of drinks per week using the following criteria: moderate (1 to 2 drinks/day for men and 1 drink/day for women), and heavy (>2 drinks/day for men and >1 drink/day for women). Body mass index (BMI) was calculated from height and weight measurements. Blood pressure (mm Hg) was measured using a mercury sphygmomanometer according to the American Heart Association recommendations. Blood pressure was taken whereas seated, using a standard mercury sphygmomanometer and up to three measurements were averaged. Blood samples were collected via venipuncture by a phlebotomist. Samples were analyzed for total cholesterol (TC), triglycerides (TG), glucose, serum creatinine, etc., using laboratory procedures as reported by NCHS.[9] Serum UA levels were measured by uricase-mediated oxidation to form allantoin and hydrogen peroxide (Hitachi 737 Analyzer; Boehringer Mannheim Diagnostics, Indianapolis, IN).[10] Diabetes mellitus (DM) was defined as fasting blood sugar ≥126 mg/dl or self-reported history of DM or use of anti-diabetic medications. Hyperlipidemia (HLD) was defined as total serum cholesterol ≥200 mg/dl or TG ≥150 mg/dl or use of lipid-lowering agents. Estimated glomerular filtration rate (GFR) was calculated using a Modification of Diet in Renal Disease (MDRD) method.[11]

Resting 12-lead electrocardiograms were obtained with a Marquette MAC 12 system (Marquette Medical Systems, Milwaukee, Wisconsin) during the mobile examination visits by trained technicians. Analysis of electrocardiograms was achieved through a computerized automated process and visual inspection by a trained technician located in a centralized core laboratory. Participants were considered to have SMI if they reported no history of myocardial infarction (MI) but had evidence of MI on ECG. ECG diagnosis of previous MI was defined using the Minnesota code (MC) as the presence of a major Q wave abnormality (MC 1-1-X or 1-2-X) or minor Q/QS waves with major ST-T abnormalities (MC 1-3-X with 4-1-X, or 4-2, or 5-1, or 5-2).[12]

NHANES III participants have been followed up for mortality through December 31, 2006. All-cause mortality and CVD mortality served as outcomes for this study. The method of probabilistic matching was used to link NHANES III participants with the National Death Index. Matching was based on 12 identifiers for each participant, including Social Security number, gender, and date of birth. The follow-up period for each study participant was calculated as the interval between their NHANES III examination and the date of death or December 31, 2006, whichever occurred first.

Baseline characteristics were compared across UA quartiles. Continuous variables were reported as mean ± standard deviation (SD) whereas categorical variables were reported as frequency and percentage. Analysis of variance (ANOVA) was used to compare the continuous variables whereas chi-square was used to compare the categorical variables. To report a cross-sectional association, a multivariable logistic regression analysis was performed to compute odds ratios (ORs) and 95% confidence interval (CI) for SMI across UA quartiles. We also computed ORs and 95% CI for SMI per 1 standard deviation (SD) increase in UA. In both approaches, model 1 was adjusted for age, sex, race and total annual family income. Model 2 adjusted for model 1 plus smoking, physical activity, systolic blood pressure (SBP), diastolic blood pressure (DBP), antihypertensive medications, diuretics, DM, BMI, HLD, alcohol intake, history of gout and eGFR.

To assess for the consistency of association among subgroups, we also examined the association between per SD increase in UA and SMI among subgroups stratified by age (≤60 years vs >60 years), sex, race (white vs non-white).

To examine whether there is an additive risk of mortality associated with UA quartiles when SMI is present, we used Cox-proportional hazard analysis to report hazard ratio (HR) and 95% CI of association of all-cause and CVD mortality among UA quartiles in the absence and presence of SMI. In the models, we used different combinations of SMI and UA quartiles as follows: "1st UA quartile + no SMI (reference)"; "2nd UA quartile + no SMI"; "2nd UA quartile + SMI"; "3rd UA quartile + no SMI"; "3rd UA quartile + SMI"; "4th UA quartile+ no SMI"; "4th quartile + SMI".

To examine how the mortality risk associated with SMI is modified by UA quartiles, we used cox-proportional hazard analysis and calculated HR and 95% CI of association of SMI with all-cause and CVD mortality across UA quartiles. In both approaches, Model 1 was adjusted for age, sex, race and total family income, and model 2 adjusted for model 1 plus smoking, physical activity, SBP, DBP, antihypertensive medications, diuretics, DM, BMI, HLD, alcohol intake, history of gout and eGFR.

All statistical analyses were performed using with SAS version 9.4 (SAS Institute Inc, Cary, NC) and p values were considered significant if less than 0.05.

## Results

A total of 6323 were included in the final analysis (58.4 ± 13.1 years, 53.9% women, and 49.7% Non-Hispanic whites, mean UA level 5.42 ± 1.46). **Table 1** shows the baseline characteristics by UA quartiles. Participants with higher UA quartile were more likely to be old, men, non-white, smokers, heavy alcohol drinkers and had prevalent CVD risk factors such as elevated SBP, DBP, high BMI, high cholesterol, triglycerides, and low eGFR. The prevalence of SMI was 0.79%, 1.18%, 1.59% and 2.27% among 1st, 2nd, 3rd, and 4th UA quartiles, respectively.

In a model adjusted for demographics, and other potential confounders participants with highest UA quartile were

Table 1
Baseline characteristics of study participants stratified by uric acid quartiles

| Characteristics Mean ± SD or n (%) | Uric acid quartiles First (n = 1515) | Second (n = 1695) | Third (n = 1568) | 4th (n = 1545) | p *value*† |
|---|---|---|---|---|---|
| **Uric acid (mg/dl)** | 3.63 ± 0.54 | 4.85 ± 0.28 | 5.82 ± 0.28 | 7.38 ± 0.91 | <.0001 |
| **Age (years)** | 56.3 ± 12.9 | 58.5 ± 13.1 | 59.4 ± 13.1 | 59.5 ± 13.0 | <.0001 |
| **Men** | 258(17.0%) | 655(38.6%) | 887(56.5%) | 1115(72.1%) | <.0001 |
| **Race** | | | | | <.0001 |
| **White** | 742(48.9%) | 847(49.9%) | 814(51.9%) | 740(47.9%) | |
| **Blacks** | 282(18.6%) | 360(21.2%) | 363(23.1%) | 422(27.3%) | |
| **Mexican American** | 421(27.7%) | 412(24.3%) | 332(21.1%) | 328(21.2%) | |
| **Others** | 70(4.6%) | 76(4.4%) | 59(3.7%) | 55(3.5%) | |
| **Total annual income <$ 20,000** | 654(43.7%) | 743(44.5%) | 690(44.6%) | 653(42.9%) | 0.76 |
| **Systolic blood pressure (mm Hg)** | 127.3 ± 20.0 | 130.7 ± 19.6 | 133.5 ± 18.1 | 135.3 ± 18.7 | <.0001 |
| **Diastolic blood pressure (mm Hg)** | 73.6 ± 9.4 | 75.1 ± 9.5 | 77.6 ± 10.1 | 79.2 ± 10.7 | <.0001 |
| **Antihypertensive** | 198(13.0%) | 289(17.0%) | 320(20.4%) | 480(31.0%) | <.0001 |
| **Diuretics** | 45(2.9%) | 67(3.9%) | 87(5.5%) | 176(11.3%) | <.0001 |
| **Diabetes mellitus** | 270(17.8%) | 219(12.9%) | 195(12.4%) | 221(14.3%) | <.0001 |
| **Total cholesterol (mg/dl)** | 212.6 ± 42.9 | 216.6 ± 42.2 | 219.6 ± 43.3 | 221.7 ± 45.4 | <.0001 |
| **Triglycerides (mg/dl)** | 128.7 ± 102.5 | 146.4 ± 105.1 | 162.6 ± 116.0 | 199.2 ± 169.4 | <.0001 |
| **Antihyperlipidemic edications** | 34(2.2%) | 37(2.1%) | 53(3.3%) | 59(3.8%) | 0.01 |
| **Body mass index (kg/m$^2$)** | 25.9 ± 5.0 | 27.1 ± 5.3 | 28.3 ± 5.4 | 29.2 ± 5.5 | <.0001 |
| ***Estimated glomerular filtration rate** | 79.4 ± 20.5 | 74.0 ± 17.3 | 70.4 ± 17.0 | 66.4 ± 16.8 | <.0001 |
| **Gout** | 28(1.8%) | 33(1.9%) | 46(2.9%) | 122(7.9%) | <.0001 |
| **Gout medications** | | | | | |
| ***Allopurinol*** | 12 (0.7%) | 10 (0.5%) | 12 (0.7%) | 26 (1.6%) | 0.006 |
| ***Colchicine*** | 2 (0.1%) | 5 (0.2%) | 2 (0.1%) | 6 (0.3%) | 0.35 |
| **Alcohol intake** | | | | | |
| ***Moderate*** | 217(14.3%) | 300(17.7%) | 335(21.3%) | 330(21.3%) | <.0001 |
| ***High*** | 278(18.3%) | 328(19.3%) | 346(22.0%) | 432(27.9%) | <.0001 |
| **Smoker** | | | | | |
| ***Current*** | 334(22.0%) | 395(23.3%) | 350(22.3%) | 347(22.4%) | 0.84 |
| ***Former*** | 352(23.2%) | 493(29.0%) | 537(34.2%) | 607(39.2%) | <.0001 |
| ***Never*** | 829(54.7%) | 807(47.6%) | 681(43.4%) | 591(38.2%) | <.0001 |
| **Physical activity** ** **(*METs per week*)** | 8.8(1.1-30.3) | 10.5(1.6-33.2) | 10.1(1.1-33.0) | 11.5(2.0-31.3) | 0.02 |
| **Silent myocardial infarction** | 12(0.79%) | 20(1.18%) | 25(1.59%) | 35(2.27%) | 0.005 |

METs: metabolic equivalents.
† p value by ANOVA for continuous variables and $\chi^2$ for categorical variables.
** METs per week reported as median and IQR.
* Estimated GFR calculated by Modification of Diet in Renal Disease method.

associated with higher odds of SMI (p = 0.02) (**Table 2**). Each SD increase in UA level was associated with a 42% higher prevalence of SMI (p = 0.003) (**Table 2**).

The association between UA levels and SMI was consistent across groups stratified by age, sex, and race in a fully adjusted model (**Table 3**).

During a median follow-up of 14 years, there were 1916 all-cause death of whom 774 were CVD deaths. **Figures 1** and **2** show the incidence rate of all-cause and CVD mortality associated with UA quartiles in the absence and presence of SMI. Incidence rate increased with increasing quartile of UA and rate was higher for participants with SMI than without it. Mortality rate was highest among participants with the highest quartile of UA and SMI for both all-cause and CVD mortality and was lowest among those with 1st quartile of UA and without SMI for both all-cause and CVD mortality.

Compared with the referent category; participants with the lowest UA quartile and no SMI, the HR increased with

Table 2
Association of uric acid quartiles with silent myocardial infarction

| Uric acid quartiles | Model 1* OR (95% CI) | p *value* | Model 2† OR (95% CI) | p *value* |
|---|---|---|---|---|
| **Q1** | *Reference* | – | *Reference* | – |
| **Q2** | 1.32 (0.63-2.73) | 0.45 | 1.36 (0.65-2.85) | 0.40 |
| **Q3** | 1.71 (0.84-3.49) | 0.13 | 1.76 (0.84-3.68) | 0.13 |
| **Q4** | 2.43 (1.21-4.86) | 0.01 | 2.37 (1.11-5.08) | 0.02 |
| ****Per 1 SD increase in uric acid** | 1.41 (1.15-1.73) | 0.0007 | 1.42 (1.12-1.81) | 0.003 |

* Model 1 adjusted for age, sex, race and total annual income.
† Model 2 adjusted for model 1 plus smoking, physical activity, systolic blood pressure, diastolic blood pressure, antihypertensive medications, diuretics, diabetes, body mass index, hyperlipidemia, alcohol intake, history of gout and estimated glomerular filtration rate.
** SD (1.46 mg/dl) increase in uric acid.

Table 3
Association of uric acid with silent myocardial infarction across subgroups

| Subgroups | Uric acid | OR (95% CI) * | *Interaction* p *value* |
|---|---|---|---|
| **Male** | Per 1SD Increase | 1.60 (1.17-2.19) | 0.38 |
| **Female** | Per 1SD Increase | 1.24 (0.85-1.80) | |
| **White** | Per 1SD Increase | 1.42 (0.99-2.02) | 0.68 |
| **Non-white** | Per 1SD Increase | 1.43 (1.03-1.99) | |
| **Age ≤60 years** | Per 1SD Increase | 1.35 (0.89-2.04) | 0.88 |
| **Age >60 years** | Per 1SD Increase | 1.45 (1.08-1.95) | |

* Model adjusted for age, sex, race, total annual income, smoking, physical activity, systolic blood pressure, diastolic blood pressure, antihypertensive medications, diuretics, diabetes, body mass index, hyperlipidemia, alcohol intake, history of gout and estimated glomerular filtration rate.

increasing quartile of UA. In a model adjusted for all potential confounders, highest UA quartile was associated with 29% increased risk of all-cause mortality (p = 0.001) and this risk increased to 107% in the presence of SMI (p = 0.0004). There was no significant association between 2nd and 3rd quartile of UA with all-cause mortality; however, in the presence of SMI, these UA quartiles were significantly predictive of increased risk of mortality with 3rd quartile of UA (p = 0.04) (**Table 4**). A similar pattern of association of quartiles of UA with CVD mortality was observed, with the highest risk in participants with the highest quartile of UA and concomitant SMI (p = 0.02) (**Table 4**).

**Table 5** shows the HR and 95% CI of association of SMI with all-cause and CVD mortality across UA quartiles. In a fully-adjusted model, SMI was associated with increased risk of all-cause and CVD mortality only in 3rd and 4th quartile of UA. There was no significant association of SMI with mortality across 1st and 2nd quartile of UA. Overall, the interaction between SMI and UA quartiles was not significant for both all-cause (interaction p = 0.34) and CVD mortality (interaction p = 0.57).

## Discussion

In this analysis from NHANES-III, we examined the association between UA quartiles, SMI, and their interrelationship in terms of all-cause and CVD mortality. The findings of the study are followings: (1) UA is strongly associated with prevalent SMI, with high odds in participants with the highest UA quartile; (2) This association is consistent across subgroups stratified by age, sex, and race; (3) high UA quartile is associated with all-cause and CVD mortality independent of CVD risk factors and other potential confounders and this association is stronger in the presence of SMI than without it; (4) SMI carries increased risk of all-cause and CVD mortality only in participants with higher UA quartiles.

The association between UA and CHD or mortality remained controversial with some studies supporting this association,[1,2] whereas others refuted such association.[3,4] Although, an association of UA with CVD is conflicting, high UA levels consistently exhibited poor prognosis in participants with stable CHD and acute coronary syndromes (ACS).[1,5,6,13,14] In a study by Bickel et al. patients with angiographically proven CAD, the risk of mortality increased from 3.4% to 17.1% in those with highest UA quartile (7.1 mg/dl) compared with the lowest quartile (5.1 mg/dl).[5] Similarly, Okura et al. examined association of

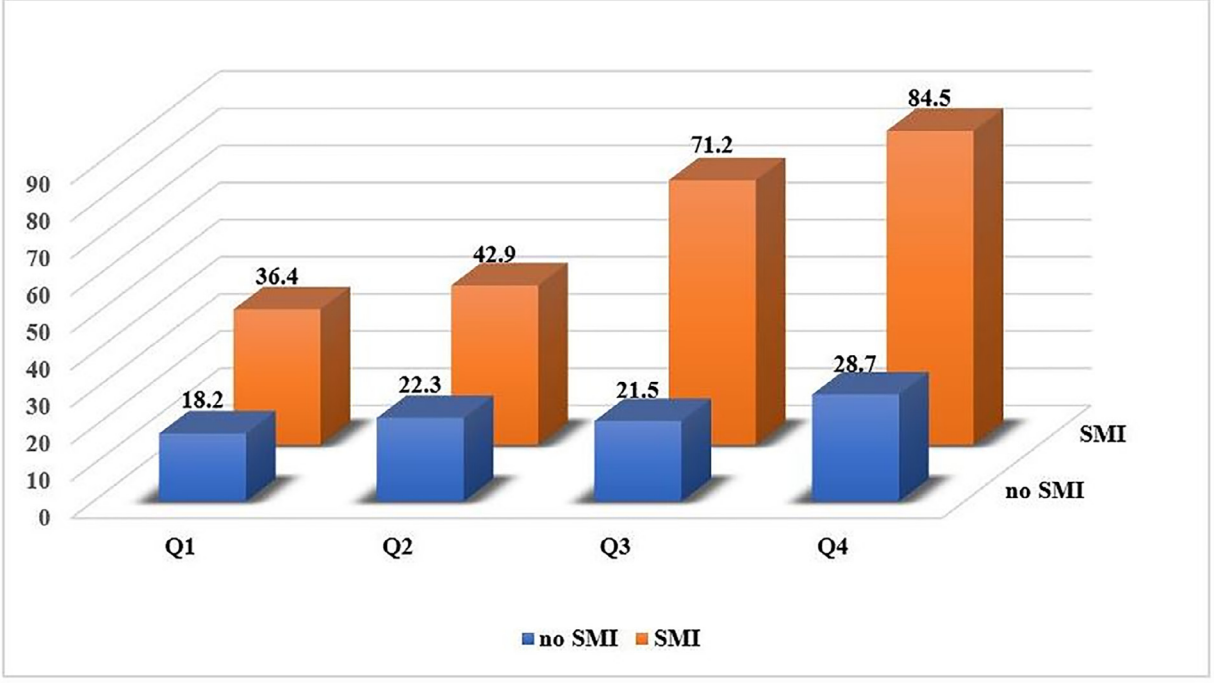


Figure 1. Incidence rates* of all-cause mortality stratified by UA quartiles and SMI status
*Incidence rate per 1000 person-years
SMI = silent myocardial infarction; UA = uric acid.

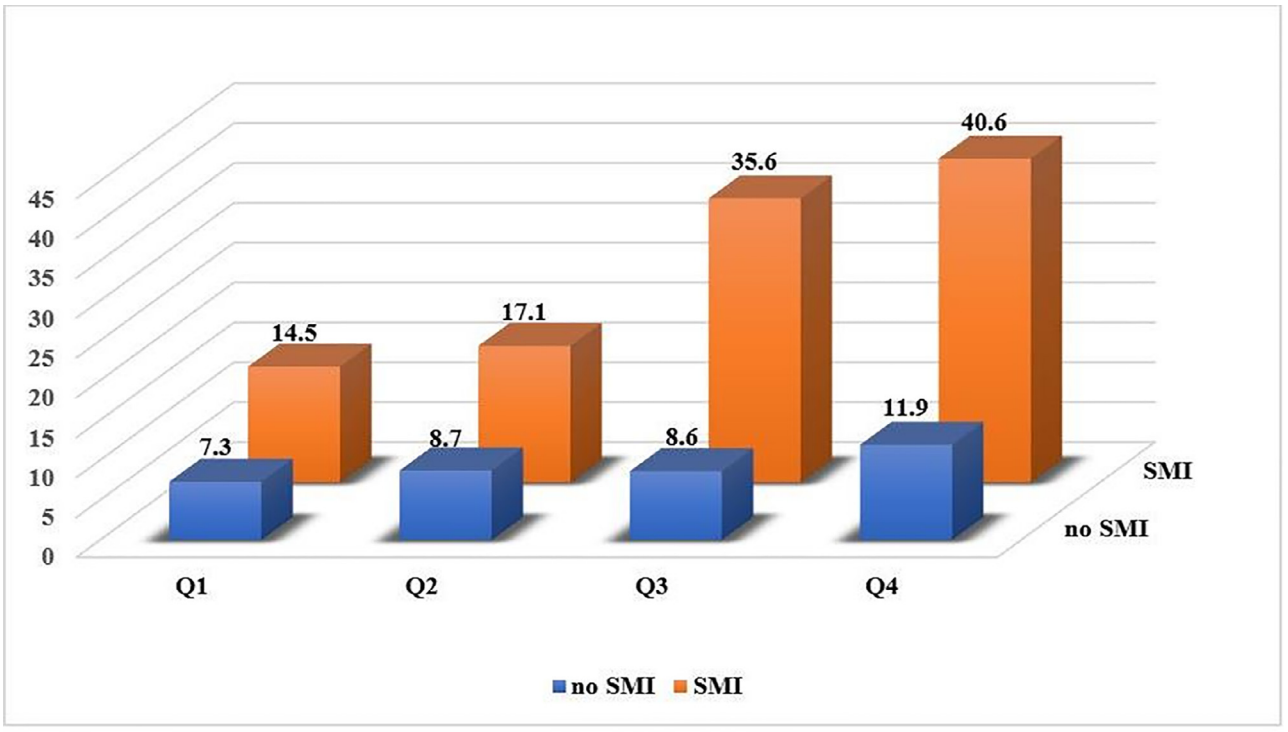


Figure 2. Incidence rates* of CVD mortality stratified by UA quartiles and SMI status
*Incidence rate per 1000 person-years
CVD = cardiovascular disease; SMI = silent myocardial infarction; UA = uric acid.

Table 4
Association between uric acid quartiles and mortality stratified by SMI status

| Association between uric acid and all-cause mortality | | | | | |
|---|---|---|---|---|---|
| **Uric acid quartiles** | **SMI** | **Model 1*** HR (95% CI) | p *value* | **Model 2†** HR (95% CI) | p *value* |
| **Q1** | **Absent** | *Reference* | | *Reference* | |
| | **Present** | 0.96 (0.39-2.32) | 0.92 | 0.93 (0.38-2.27) | 0.88 |
| **Q2** | **Absent** | 0.98 (0.85-1.13) | 0.83 | 1.09 (0.94-1.25) | 0.21 |
| | **Present** | 1.31 (0.70-2.48) | 0.39 | 1.21 (0.64-2.27) | 0.55 |
| **Q3** | **Absent** | 0.86 (0.74-1.00) | 0.06 | 0.94 (0.80-1.09) | 0.42 |
| | **Present** | 1.82 (1.10-3.01) | 0.01 | 1.69 (1.02-2.80) | 0.04 |
| **Q4** | **Absent** | 1.18 (1.02-1.35) | 0.02 | 1.29 (1.10-1.51) | 0.001 |
| | **Present** | 2.03 (1.37-3.02) | 0.0004 | 2.07 (1.38-3.10) | 0.0004 |
| **Association between uric acid and CVD mortality** | | | | | |
| **Uric acid quartiles** | **SMI** | **Model 1*** HR (95%CI) | p *value* | **Model 2†** HR (95% CI) | p *value* |
| **Q1** | **Absent** | *Reference* | | *Reference* | |
| | **Present** | 0.85 (0.21-3.44) | 0.82 | 0.90 (0.22-3.64) | 0.88 |
| **Q2** | **Absent** | 0.95 (0.76-1.18) | 0.66 | 1.03 (0.82-1.28) | 0.77 |
| | **Present** | 1.21 (0.44-3.30) | 0.70 | 1.00 (0.37-2.73) | 0.98 |
| **Q3** | **Absent** | 0.90 (0.72-1.13) | 0.37 | 0.90 (0.71-1.14) | 0.39 |
| | **Present** | 2.11 (1.03-4.32) | 0.03 | 1.81 (0.88-3.73) | 0.09 |
| **Q4** | **Absent** | 1.26 (1.01-1.57) | 0.03 | 1.24 (0.92-1.50) | 0.10 |
| | **Present** | 2.38 (1.34-4.23) | 0.003 | 1.96 (1.09-3.53) | 0.02 |

CVD: cardiovascular disease; SMI: silent myocardial infarction.
* Model 1 adjusted for age, sex, race and total annual income.
† Model 2 adjusted for model 1 plus smoking, physical activity, systolic blood pressure, diastolic blood pressure, antihypertensive medications, diuretics, diabetes, body mass index, hyperlipidemia, alcohol intake, history of gout and estimated glomerular filtration rate.

Table 5
Association between SMI and mortality across uric acid quartiles

| Association between SMI and all-cause mortality | | | | | |
|---|---|---|---|---|---|
| **Uric acid quartiles** | **SMI status** | **Model 1*** HR (95% CI) | p *value* | **Model 2†** HR (95% CI) | p *value* |
| **Q1** | **Absent** | *Reference* | – | *Reference* | – |
| | **Present** | 1.01 (0.41-2.47) | 0.96 | 0.86 (0.35-2.11) | 0.75 |
| **Q2** | **Absent** | *Reference* | – | *Reference* | – |
| | **Present** | 1.39 (0.74-2.61) | 0.30 | 1.09 (0.57-2.07) | 0.77 |
| **Q3** | **Absent** | *Reference* | – | *Reference* | – |
| | **Present** | 2.06 (1.24-3.42) | 0.005 | 1.81 (1.08-3.03) | 0.02 |
| **Q4** | **Absent** | *Reference* | – | *Reference* | – |
| | **Present** | 1.79 (1.21-2.65) | 0.003 | 1.72 (1.16-2.56) | 0.007 |
| **Association between SMI and CVD mortality** | | | | | |
| **Uric acid quartiles** | **SMI status** | **Model 1*** HR (95% CI) | p *value* | **Model 2†** HR (95% CI) | p *value* |
| **Q1** | **Absent** | *Reference* | – | *Reference* | – |
| | **Present** | 0.88 (0.21-3.61) | 0.86 | 0.80 (0.19-3.30) | 0.75 |
| **Q2** | **Absent** | *Reference* | – | *Reference* | – |
| | **Present** | 1.24 (0.45-3.38) | 0.67 | 0.85 (0.31-2.34) | 0.75 |
| **Q3** | **Absent** | *Reference* | – | *Reference* | – |
| | **Present** | 2.43 (1.18-5.01) | 0.01 | 2.22 (1.06-4.64) | 0.03 |
| **Q4** | **Absent** | *Reference* | – | *Reference* | – |
| | **Present** | 2.11 (1.20-3.72) | 0.009 | 1.94 (1.09-3.45) | 0.02 |

CVD = cardiovascular disease; SMI = silent myocardial infarction.
* Model 1 adjusted for age, sex, race and total annual income.
† Model 2 adjusted for model 1 plus smoking, physical activity, systolic blood pressure, diastolic blood pressure, antihypertensive medications, diuretics, diabetes, body mass index, hyperlipidemia, alcohol intake, history of gout, and estimated glomerular filtration rate.

UA with CVD events in participants with severe CAD and observed that an increase in UA of ≥1 mg/dl had a significantly higher rate of CVD events compared with those in which UA level did not change.[6] A recent meta-analysis demonstrated that hyperuricemia is associated with a significantly increased risk of CHD morbidity and mortality in participants with suspected or definite CHD. The risk of CHD mortality increased by 15% for each increase of 1 mg/dl of UA, especially in females.[1] These studies suggest that UA may improve risk prediction in participants with CHD. In our study, a stronger association of higher UA quartiles with mortality in the presence of SMI supports this notion.

Several mechanisms may have been involved in the pathogenesis of increased risk of CVD with UA. UA has been closely correlated with metabolic syndrome (MetS).[15] UA is a marker of oxidative stress, reduces nitric oxide (NO) level, promote inflammation, endothelial dysfunction and potentiate vasoconstrictor and proliferative vascular stimuli.[16,17] In addition to that excessive amounts of UA are known to be present in atherosclerotic plaques where it promotes thrombus formation.[18] All these mechanisms make it plausible that UA is associated with CVD and mortality.

The prognostic significance of SMI is well-established in population studies. The prognosis of SMI has been shown to be similar or worse than clinically recognized MI.[7,19] SMI has been associated with increased risk of CHD, all-cause, CVD mortality, and incident HF.[8,20,21] In clinical trials, SMI is used as a clinical endpoint, thus increasing the statistical power of the study, reducing sample size, and cost of the trial.[22] We found a strong association of highest UA quartile with prevalent SMI, a marker of poor outcomes. Although the association of UA with mortality has been investigated previously using data from NHANES-III.[10,23] To the best of our knowledge, no population studies have examined the association between UA and SMI and their additive effect on mortality. UA quartiles especially higher quartiles carried a higher risk of mortality in the presence of SMI and SMI carried a higher risk of mortality among those with high UA quartiles.

Whether UA can be used a biomarker for identification of high-risk group remains debatable given conflicting reports of association of UA with CVD. Also, the effect of UA-lowering therapy in patients with gout on reducing CVD death and non-fatal MI is not evident.[24] Whether UA is a risk factor for CVD or simply a risk marker, risk prediction by using simple, inexpensive and widely available tools like ECG is a cost-effective way to screen those at high risk for CVD and mortality.

Our study has certain limitations. First, we used the only single measurement of UA. Thus, intrapatient variability and possible changes in UA levels with the passage of time are unaccounted for. ECG has low sensitivity in detecting SMI, and its detection can be enhanced by imaging modalities such as an echocardiogram or cardiac MRI.[25] Therefore, our estimates of SMI are conservative, another limitation of the study. Some of the measurements like alcohol intake, smoking, and physical activity are self-reported and thus subject to recall bias. Finally, we adjusted for several confounders, but residual confounding remains a possibility. Strengths of the study include a large sample size and a community-living multiracial population with generalizability to the US population.

## Conflict of Interest

The investigators have no conflicts of interest to disclose.


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