# Serum uric acid is a GFR-independent long-term predictor of renal insufficiency: The Jerusalem Lipid Research Clinic cohort study

## Supplementary Methods

*Study participants*

All Jewish citizens and permanent residents of Israel are obligated to undergo a medical examination at the age of 17 to determine their fitness for military service. Inductees who were Jerusalem residents were invited to participate in the Jerusalem LRC (by 6-month birth cohorts) to 2 screening cycles per year, with 5 cycles being included between 1976 to 1978. A sample of parent pairs of the visit 1 youngsters was invited to visit 1 as follows: a 25% random sample of each of the first 2 cycles, a 50% random sample of the 3rd cycle, and in the last 2 cycles, all the parents were invited[1]. At visit 2 of the Jerusalem LRC, a 20% random sample of fathers from the 1st two screening cycles, and a 50% random sample from the last 3 screening cycles was invited. The 30% enrichment sample of the third cycle began late, response was low, and many fathers may have received their visit 1 lipid results before coming to visit 2. Therefore these 32 men are excluded[1]. In addition a 20% random enrichment sample of North African and Asian origin was invited for cycles 4 and 5 (i.e. between 50-70%). For all 5 cycles, a 20% random sample of mothers who participated at visit 1 was invited. Information was gathered on 2544 middle-aged Jewish individuals (that include the additional 82 North African and Asian men, and who form our current study population), of whom 69.2% were randomly sampled from visit 1 participants. The additional 30.8% of visit 2 participants was sampled from the entire visit 1 population with high lipid levels based on the age-specific cut-off points for total cholesterol and triglyceride levels employed by the North American LRCs[1].

*Statistical analysis*

In this study, we explored the value of data clustering and reduction tools, in addition to conventional statistical analyses. The hierarchical clustering procedure and results are described in the main text. Principal component analysis (PCA) is a multivariate analysis involving transformation of a number of correlated variables into a smaller number of uncorrelated variables: the principal components. Each principal component is calculated to account for as much of the remaining variability as possible. PCA can potentially reveal a fundamental structure of the data. In this study, principal components were extracted from baseline variables to probe for factors driving serum uric acid (SUA) levels. Varimax method was applied for factor rotation (an orthogonal rotation method that minimizes the number of variables with high loadings on each component and thus simplifies the interpretation), to search for variables influenced by SUA-shared forces. Also, we introduced principal components as independent variables in Cox models to search for an added value in outcome analysis.

## Supplementary Results

*Baseline associations of serum uric acid*

Principal components were extracted by gender from baseline demographic, anthropometric and laboratory variables: age, secular education, smoking level, alcohol consumption, protein consumption, hypoglycemic medications (yes/no), BP-lowering medications, lipid-lowering medications, height, weight, BMI, triceps skinfold thickness, systolic and diastolic BP, heart rate, total cholesterol, LDL-cholesterol, HDL-cholesterol, VLDL-cholesterol, triglycerides (ln), hematocrit, glucose, creatinine, $eGFR_{MDRD}$, SUA, thyroxin, globulins, bilirubin, alanine aminotransferase and stick proteinuria. In women, SUA was mostly represented by the first principal component, which was also strongly loaded with measures of adiposity and negatively with protein intake. On the other hand, in men only the fifth principal component was notably associated with SUA, along with creatinine, education level and non-smoking. In both men and women, the first 5 components captured ~50% of the original data variance. Aside of the above-mentioned factors ($1^{st}$ in women and $5^{th}$ in men), no component had a substantial correlation (either positive or negative) with SUA.

*All-cause mortality*

In mortality analyses (including those reported in the main text) one participant that has died during the study period was excluded, because her date of death could not be ascertained.

A Cox model was constructed that included the first 5 principal components (which are orthogonal by definition). Age was also introduced as a separate term notwithstanding its presence in the component analysis. The results differed between genders. In men, the principal component with the highest weight for SUA (r=0.53) had an inverse association with mortality. This might be explained by other strong determinants of this component, mainly serum creatinine (an indicator of muscle mass, once CKD patients have been excluded), education level, and non-smoking. In women, the principal component that was best associated with SUA (r=0.57) was positively associated with mortality. This component was also linked strongly with weight, BMI and skinfold thickness, and was inversely associated with dietary protein consumption. Interestingly, in men the strongest predicting component was that associated with age and blood pressure, while in women a metabolic syndrome-like component encompassing high triglycerides, VLDL cholesterol, glucose and low HDL cholesterol levels was the strongest predictor.

*Hospital diagnosis of chronic renal failure*

Introducing principal components from the PCA procedure to a Cox model for CRF yielded significant predictive associations for 4 of the 5 factors. In men, the factor most strongly associated with SUA (the “educated, non-smoking, SUA” factor) was protective (HR=0.73 per 1SD, p=0.003). Another principal factor, capturing a lesser portion of SUA (an “adiposity-SUA” factor), was linked with increased incidence of CRF (HR=1.63 per 1SD, p<0.001). In women the predominant SUA-associated principal component (the “adiposity-SUA” factor) was predictive of CRF (HR 1.97 per 1SD, p=0.001). Another factor, capturing almost as much of the SUA variability (the “creatinine-SUA” factor) did not predict CRF (p=0.3).

*Acute renal failure*

In sex-specific models, only age and SUA were significant in men, while in women smoking and DBP were significant (triglycerides and education were of borderline significance).

**Supplementary Discussion**

We applied data mining tools, often used in bioinformatics, to interrogate the relationship of SUA with other measured variables by a different approach. Based on Pearson correlation, SUA hierarchically clustered next to indices of adiposity and alanine aminotransferase, and also near creatinine and education in men, and stick proteinuria in women. Data reduction using principal component analysis showed that in women the first component (that which captures the greatest portion of variability and reflected measures of adiposity and protein intake) was in strong inverse association with SUA, while in men only the fifth component was strongly related to SUA, as it was with education level, smoking (negative) and creatinine. Collectively, these auxiliary analyses are in agreement with the traditional calculations, but emphasize different aspects and add new perspectives (for example, that in women but not in men SUA might be governed by a chief variability factor yet to be identified).

Complementary outcome analyses based on primary components that were extracted from baseline variables better defined the differences between men and women in relation to SUA levels and their prognostic impact. In women, SUA was highly represented by the chief primary component, which was predictive of both mortality and

CRF. In contrast, in men only the 5$^{th}$ primary component had a considerable weight for SUA, and this component was independently protective for both mortality and CRF. Obviously, in both men and women the extracted components represent only a part (albeit a large part) of the variation in SUA. Nonetheless, this helps to understand the stronger link between SUA and outcome often reported in women. It may be interpreted as pointing to a fundamental factor, present in women but not in men, that incorporates information on both SUA levels and on outcome, but these are not necessarily related directly.

## Supplementary References

1. Slater PE, Friedlander Y, Baras M, et al. The Jerusalem Lipid Research Clinic: sampling, response and selected methodological issues. *Isr J Med Sci* 1982; **18**: 1106-1112.

**Table S1**: Baseline characteristics according to sex-specific serum uric acid quintiles, as calculated from raw data (top panel) or data weighed by sampling probabilities (bottom panel)

| | weighing by sampling probability: OFF | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | men | | | | | | | women | | | | | | |
| | quintile 1 | quintile 2 | quintile 3 | quintile 4 | quintile 5 | linear p-value | quadratic p-value | quintile 1 | quintile 2 | quintile 3 | quintile 4 | quintile 5 | linear p-value | quadratic p-value |
| SUA (mg/dl) | 4.3±0.6 | 5.2±0.2 | 5.7±0.1 | 6.2±0.2 | 7.3±0.7 | 0.000 | 0.002 | 3.1±0.4 | 3.9±0.1 | 4.4±0.1 | 5±0.2 | 6.1±0.6 | 0.000 | 0.000 |
| Age (yr) | 50±6 | 51±7 | 50±6 | 50±6 | 50±6 | 0.815 | 0.665 | 45±5 | 45±5 | 46±6 | 46±5 | 47±5 | 0.000 | 0.350 |
| Education (yr) | 8.3±5.2 | 9.3±5.5 | 9.5±5.8 | 10.2±5.4 | 10.3±5.7 | 0.000 | 0.298 | 10±5.9 | 10±5.1 | 9.7±5.2 | 9.6±5.3 | 8.4±5.5 | 0.003 | 0.104 |
| Origin: Asia | 33.8% | 30.4% | 27.2% | 25.3% | 22.4% | 0.001 | | 25.5% | 22.3% | 25.6% | 24.7% | 29.0% | 0.379 | |
| Origin: N. Africa | 21.7% | 20.5% | 17.4% | 18.8% | 14.7% | 0.030 | | 16.8% | 21.1% | 20.0% | 17.7% | 19.1% | 0.857 | |
| Origin: Europe | 14.6% | 23.5% | 25.9% | 26.0% | 30.1% | 0.000 | | 22.1% | 20.6% | 21.9% | 25.8% | 24.0% | 0.353 | |
| Origin: Israel | 29.9% | 25.6% | 29.5% | 29.9% | 32.8% | | | 35.6% | 36.0% | 32.5% | 31.8% | 27.9% | | |
| Smoking (Y) | 52.3% | 48.1% | 34.8% | 36.3% | 34.1% | 0.000 | | 30.3% | 20.0% | 26.5% | 23.2% | 19.1% | 0.041 | |
| Smoking (level) | 1.1±1.2 | 1±1.2 | 0.7±1.1 | 0.7±1.1 | 0.7±1.1 | 0.000 | 0.036 | 0.4±0.8 | 0.3±0.7 | 0.4±0.8 | 0.4±0.8 | 0.3±0.6 | 0.078 | 0.460 |
| Alcohol (g/week) | 33±30 | 32±20 | 31±21 | 34±28 | 29±22 | 0.205 | 0.583 | 15±13 | 14±14 | 15±14 | 12±12 | 14±16 | 0.242 | 0.572 |
| Protein (g/d) | 76±31 | 82±34 | 77±29 | 76±29 | 76±32 | 0.339 | 0.306 | 56±19 | 55±24 | 57±24 | 52±19 | 50±21 | 0.003 | 0.113 |
| Protein (% of cal) | 15.4±4.2 | 15.8±4.1 | 15±3.6 | 15.3±4.5 | 15.8±4.2 | 0.749 | 0.148 | 15.1±3.9 | 15.4±4.4 | 15.7±4.7 | 15.6±4.6 | 16.4±5.1 | 0.007 | 0.639 |
| Protein (g/kg) | 1.07±0.43 | 1.13±0.5 | 1.03±0.41 | 1.01±0.39 | 0.96±0.39 | 0.000 | 0.149 | 0.91±0.34 | 0.87±0.4 | 0.88±0.41 | 0.77±0.29 | 0.7±0.32 | 0.000 | 0.058 |
| DM med (Y) | 5.7% | 2.4% | 2.6% | 0.7% | 0.3% | 0.000 | | 2.4% | 1.7% | 1.4% | 0.0% | 1.6% | 0.206 | |
| Height (cm) | 167±7 | 168±7 | 169±7 | 169±7 | 169±7 | 0.000 | 0.670 | 157±6 | 157±7 | 157±6 | 156±6 | 157±6 | 0.343 | 0.974 |
| weight (kg) | 72±11 | 73±10 | 76±11 | 76±12 | 80±12 | 0.000 | 0.359 | 63±8 | 65±10 | 66±12 | 70±12 | 73±12 | 0.000 | 0.165 |
| BMI (kg/m$^2$) | 25.6±3.3 | 26±3 | 26.7±3.5 | 26.8±3.5 | 28±3.5 | 0.000 | 0.186 | 25.5±3.5 | 26.3±4 | 27.1±4.9 | 28.6±4.9 | 29.9±5 | 0.000 | 0.159 |
| Triceps skinfold (mm) | 22±10 | 21±9 | 23±9 | 23±10 | 24±10 | 0.002 | 0.906 | 27±8 | 30±8 | 29±9 | 32±9 | 33±9 | 0.000 | 0.719 |
| Heart rate (1/min) | 75±10 | 76±11 | 75±11 | 75±11 | 75±10 | 0.508 | 0.971 | 76±10 | 78±12 | 78±11 | 77±11 | 77±10 | 0.612 | 0.118 |
| Systolic BP (mmHg) | 119±16 | 120±17 | 121±17 | 121±16 | 124±18 | 0.001 | 0.158 | 115±17 | 116±16 | 118±20 | 120±19 | 125±20 | 0.000 | 0.154 |
| Diastolic BP (mmHg) | 80±11 | 79±10 | 80±11 | 80±11 | 82±11 | 0.001 | 0.164 | 75±10 | 75±10 | 77±13 | 78±11 | 81±12 | 0.000 | 0.240 |
| Hematocrit (%) | 46±5 | 46±4 | 46±4 | 46±4 | 45±4 | 0.255 | 0.251 | 41±5 | 41±5 | 41±4 | 42±4 | 42±4 | 0.043 | 0.439 |
| Glucose (mg/dl) | 116±51 | 105±25 | 103±18 | 104±15 | 106±16 | 0.019 | 0.000 | 102±42 | 99±24 | 99±23 | 102±23 | 104±18 | 0.004 | 0.076 |
| Cholesterol (mg/dl) | 209±43 | 209±40 | 207±39 | 210±40 | 213±41 | 0.287 | 0.230 | 207±41 | 216±44 | 211±43 | 219±39 | 225±45 | 0.000 | 0.498 |
| LDL-C (mg/dl) | 135±36 | 135±34 | 133±36 | 135±36 | 132±36 | 0.268 | 0.730 | 130±37 | 136±40 | 135±37 | 139±35 | 143±39 | 0.000 | 0.890 |
| HDL-C (mg/dl) | 41±10 | 41±10 | 42±12 | 40±11 | 39±9 | 0.001 | 0.014 | 54±13 | 52±14 | 51±13 | 50±13 | 46±12 | 0.000 | 0.383 |
| VLDL-C (mg/dl) | 33±28 | 34±25 | 32±17 | 35±24 | 43±26 | 0.000 | 0.000 | 23±15 | 28±16 | 26±14 | 30±17 | 36±25 | 0.000 | 0.043 |
| Triglycerides (mg/dl) | 160±130 | 165±118 | 161±85 | 182±121 | 216±121 | 0.000 | 0.005 | 110±59 | 128±81 | 125±69 | 141±64 | 178±108 | 0.000 | 0.050 |
| AST (U/L) | 30±17 | 31±8 | 32±10 | 32±14 | 33±12 | 0.012 | 0.343 | 25±6 | 26±7 | 26±7 | 27±13 | 30±11 | 0.000 | 0.488 |
| Globulins (g/l) | 31±4 | 31±3 | 31±3 | 32±5 | 32±4 | 0.000 | 0.185 | 33±3 | 33±4 | 33±4 | 33±4 | 33±3 | 0.033 | 0.995 |
| Bilirubin (micromol/l) | 5.6±2.4 | 6±2.2 | 6.2±2 | 6.4±2.4 | 6.5±2.7 | 0.000 | 0.235 | 4.6±1.8 | 4.8±2.1 | 4.8±1.9 | 4.8±2.1 | 5.5±2.8 | 0.001 | 0.095 |
| Thyroixin (mcg/l) | 44±7 | 45±7 | 44±7 | 44±8 | 44±8 | 0.685 | 0.419 | 46±8 | 45±9 | 47±10 | 45±9 | 45±8 | 0.142 | 0.287 |
| Creatinine (mg/dl) | 0.83±0.13 | 0.88±0.14 | 0.9±0.13 | 0.92±0.13 | 0.94±0.14 | 0.000 | 0.109 | 0.64±0.12 | 0.66±0.11 | 0.69±0.12 | 0.71±0.11 | 0.74±0.12 | 0.000 | 0.931 |
| CCr (ml/min) | 111±25 | 106±24 | 109±27 | 106±25 | 110±27 | 0.693 | 0.085 | 115±29 | 114±31 | 110±29 | 113±29 | 112±28 | 0.276 | 0.428 |
| $MDRD_{GFR}$ (ml/min/1.73m$^2$) | 108±20 | 100±19 | 99±18 | 95±16 | 93±18 | 0.000 | 0.028 | 113±26 | 107±23 | 101±21 | 98±19 | 93±18 | 0.000 | 0.460 |
| $CKD\text{-}EPI_{GFR}$ (ml/min/1.73m$^2$) | 102±10 | 98±12 | 97±12 | 95±12 | 93±13 | 0.000 | 0.130 | 107±12 | 105±11 | 101±13 | 100±13 | 96±14 | 0.000 | 0.528 |
| MDRD < 90 ml/min/1.73m | 13.2% | 29.7% | 35.1% | 41.1% | 46.2% | 0.000 | | 17.8% | 20.6% | 29.3% | 33.3% | 41.0% | 0.000 | |
| CKD-EPI < 90 ml/min/1.73m$^2$ | 12.5% | 26.6% | 29.5% | 33.9% | 42.5% | 0.000 | | 12.0% | 12.0% | 22.8% | 25.8% | 32.8% | 0.000 | |
| Stick proteinuria (mg/dl) | 16.5±43.8 | 8.4±19.9 | 11.5±29.5 | 13.6±31.8 | 16.8±48.1 | 0.392 | 0.007 | 5.3±10.9 | 9.4±20.2 | 12.4±32.6 | 13.9±46.2 | 12.4±33.6 | 0.011 | 0.145 |

**Table S1** (cont)

| | weighing by sampling probability: ON | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | men | | | | | | | women | | | | | | |
| | quintile 1 | quintile 2 | quintile 3 | quintile 4 | quintile 5 | linear p-value | quadratic p-value | quintile 1 | quintile 2 | quintile 3 | quintile 4 | quintile 5 | linear p-value | quadratic p-value |
| SUA (mg/dl) | 4.3±0.6 | 5.2±0.2 | 5.7±0.1 | 6.2±0.2 | 7.2±0.7 | 0.000 | 0.005 | 3.1±0.4 | 3.9±0.1 | 4.4±0.1 | 5±0.2 | 6±0.6 | 0.000 | 0.000 |
| Age (yr) | 50±6 | 51±7 | 50±7 | 50±7 | 50±6 | 0.587 | 0.502 | 44±5 | 45±5 | 46±6 | 45±5 | 47±6 | 0.000 | 0.350 |
| Education (yr) | 8.1±5.2 | 9.1±5.5 | 9.4±5.7 | 10.1±5.5 | 10.3±5.8 | 0.000 | 0.495 | 10.1±6 | 9.9±5.1 | 9.8±5.3 | 9±5 | 8.4±5.6 | 0.003 | 0.104 |
| Origin: Asia | 36.5% | 32.6% | 27.2% | 26.7% | 23.6% | 0.001 | | 26.1% | 25.7% | 26.3% | 24.5% | 26.6% | 0.973 | |
| Origin: N. Africa | 22.4% | 21.6% | 20.0% | 20.4% | 14.9% | 0.066 | | 18.8% | 22.9% | 20.3% | 17.9% | 23.7% | 0.697 | |
| Origin: Europe | 14.8% | 23.8% | 25.8% | 24.9% | 29.8% | 0.001 | | 20.3% | 19.0% | 18.9% | 19.8% | 22.3% | 0.743 | |
| Origin: Israel | 26.3% | 22.0% | 27.0% | 28.0% | 31.7% | | | 34.8% | 32.4% | 34.5% | 37.8% | 27.4% | | |
| Smoking (Y) | 50.5% | 47.4% | 32.8% | 35.1% | 34.1% | 0.000 | | 27.5% | 20.0% | 24.1% | 26.4% | 19.4% | 0.409 | |
| Smoking (level) | 1±1.2 | 1±1.2 | 0.6±1 | 0.7±1.1 | 0.7±1.1 | 0.000 | 0.066 | 0.4±0.7 | 0.3±0.7 | 0.4±0.8 | 0.4±0.8 | 0.3±0.6 | 0.078 | 0.460 |
| Alcohol (g/week) | 33±30 | 33±19 | 30±20 | 32±27 | 30±22 | 0.167 | 0.917 | 15±13 | 14±14 | 15±14 | 12±13 | 16±19 | 0.242 | 0.572 |
| Protein (g/d) | 75±29 | 81±34 | 76±29 | 76±29 | 76±32 | 0.660 | 0.344 | 55±19 | 53±23 | 58±26 | 53±19 | 51±21 | 0.003 | 0.113 |
| Protein (% of cal) | 15.4±4.2 | 15.4±3.8 | 14.9±3.6 | 15.1±4.4 | 15.7±4.4 | 0.709 | 0.084 | 15±3.6 | 15.6±4.6 | 15.7±5.1 | 15.6±4.6 | 16.5±5 | 0.007 | 0.639 |
| Protein (g/kg) | 1.06±0.41 | 1.13±0.48 | 1.03±0.42 | 1.01±0.4 | 0.96±0.4 | 0.001 | 0.130 | 0.91±0.35 | 0.84±0.38 | 0.89±0.42 | 0.76±0.28 | 0.71±0.33 | 0.000 | 0.058 |
| DM med (Y) | 5.2% | 2.6% | 2.1% | 0.9% | 0.5% | 0.001 | | 1.4% | 1.0% | 0.8% | 0.0% | 1.1% | 0.472 | |
| Height (cm) | 167±7 | 167±7 | 169±7 | 169±6 | 169±7 | 0.000 | 0.559 | 157±6 | 158±7 | 157±6 | 157±6 | 157±6 | 0.343 | 0.974 |
| weight (kg) | 71±11 | 73±10 | 75±11 | 75±11 | 80±12 | 0.000 | 0.170 | 62±8 | 66±11 | 67±11 | 71±13 | 73±13 | 0.000 | 0.165 |
| BMI (kg/m$^2$) | 25.6±3.5 | 25.9±3.1 | 26.4±3.5 | 26.5±3.4 | 27.8±3.4 | 0.000 | 0.053 | 25.3±3.5 | 26.4±4.1 | 27.2±4.6 | 28.7±5.3 | 29.9±5.4 | 0.000 | 0.159 |
| Triceps skinfold (mm) | 22±10 | 21±9 | 23±9 | 23±10 | 23±10 | 0.014 | 0.930 | 28±8 | 30±8 | 29±9 | 33±10 | 34±10 | 0.000 | 0.719 |
| Heart rate (1/min) | 75±10 | 76±12 | 75±11 | 74±11 | 75±10 | 0.464 | 0.445 | 76±10 | 77±11 | 78±11 | 76±10 | 76±10 | 0.612 | 0.118 |
| Systolic BP (mmHg) | 119±17 | 119±17 | 120±18 | 120±16 | 123±18 | 0.014 | 0.192 | 114±16 | 115±16 | 117±19 | 118±16 | 122±18 | 0.000 | 0.154 |
| Diastolic BP (mmHg) | 79±11 | 78±10 | 81±11 | 79±11 | 82±11 | 0.009 | 0.133 | 74±10 | 75±10 | 76±12 | 77±10 | 79±12 | 0.000 | 0.240 |
| Hematocrit (%) | 45±5 | 46±4 | 46±4 | 45±4 | 45±4 | 0.746 | 0.146 | 41±5 | 41±5 | 41±4 | 42±4 | 42±4 | 0.043 | 0.439 |
| Glucose (mg/dl) | 114±46 | 104±24 | 102±16 | 103±14 | 105±16 | 0.047 | 0.000 | 96±26 | 96±16 | 97±17 | 100±20 | 103±18 | 0.004 | 0.076 |
| Cholesterol (mg/dl) | 198±38 | 201±37 | 199±36 | 201±38 | 205±39 | 0.090 | 0.459 | 191±34 | 199±39 | 192±37 | 201±36 | 206±39 | 0.000 | 0.498 |
| LDL-C (mg/dl) | 128±33 | 129±31 | 127±33 | 130±33 | 127±33 | 0.933 | 0.970 | 115±30 | 123±36 | 119±33 | 124±31 | 131±35 | 0.000 | 0.890 |
| HDL-C (mg/dl) | 41±10 | 41±10 | 43±12 | 40±10 | 39±9 | 0.014 | 0.038 | 54±13 | 51±13 | 51±13 | 50±13 | 46±13 | 0.000 | 0.383 |
| VLDL-C (mg/dl) | 29±20 | 31±22 | 29±16 | 31±21 | 38±23 | 0.000 | 0.015 | 21±12 | 24±13 | 22±11 | 26±14 | 28±18 | 0.000 | 0.043 |
| Triglycerides (mg/dl) | 145±97 | 154±104 | 150±78 | 165±105 | 195±109 | 0.000 | 0.057 | 100±49 | 110±62 | 107±52 | 128±55 | 145±81 | 0.000 | 0.050 |
| AST (U/L) | 30±15 | 32±9 | 32±10 | 33±15 | 33±12 | 0.017 | 0.440 | 25±7 | 26±7 | 26±8 | 28±17 | 29±13 | 0.000 | 0.488 |
| Globulins (g/l) | 31±4 | 31±3 | 31±3 | 32±5 | 32±4 | 0.001 | 0.390 | 33±3 | 33±4 | 33±4 | 33±4 | 33±3 | 0.033 | 0.995 |
| Bilirubin (micromol/l) | 5.8±2.4 | 6.2±2.1 | 6.4±2.1 | 6.5±2.4 | 6.7±2.9 | 0.000 | 0.362 | 4.7±1.8 | 4.9±2.1 | 5±2.1 | 4.9±1.9 | 5.6±3.4 | 0.001 | 0.095 |
| Thyroixin (mcg/l) | 44±7 | 44±7 | 44±7 | 44±8 | 45±8 | 0.905 | 0.203 | 46±8 | 45±10 | 47±10 | 46±10 | 45±9 | 0.142 | 0.287 |
| Creatinine (mg/dl) | 0.83±0.13 | 0.89±0.13 | 0.9±0.13 | 0.92±0.13 | 0.94±0.14 | 0.000 | 0.057 | 0.63±0.12 | 0.66±0.1 | 0.69±0.12 | 0.7±0.11 | 0.74±0.12 | 0.000 | 0.931 |
| CCr (ml/min) | 110±25 | 104±23 | 107±26 | 105±24 | 109±27 | 0.782 | 0.016 | 115±29 | 116±31 | 112±27 | 117±31 | 111±28 | 0.276 | 0.428 |
| $MDRD_{GFR}$ (ml/min/1.73m$^2$) | 107±21 | 99±19 | 98±18 | 95±16 | 93±17 | 0.000 | 0.013 | 113±26 | 107±22 | 102±21 | 100±18 | 92±16 | 0.000 | 0.460 |
| $CKD\text{-}EPI_{GFR}$ (ml/min/1.73m$^2$) | 102±11 | 97±12 | 96±12 | 95±12 | 93±13 | 0.000 | 0.054 | 107±12 | 106±10 | 102±13 | 102±12 | 96±13 | 0.000 | 0.528 |
| MDRD < 90 ml/min/1.73m | 13.7% | 31.7% | 36.6% | 41.3% | 45.2% | 0.000 | | 18.8% | 18.1% | 29.3% | 28.6% | 40.9% | 0.000 | |
| CKD-EPI < 90 ml/min/1.73m$^2$ | 12.9% | 28.5% | 31.9% | 34.2% | 41.6% | 0.000 | | 11.6% | 8.6% | 20.5% | 19.8% | 29.0% | 0.000 | |
| Stick proteinuria (mg/dl) | 16.4±45.5 | 8.5±19.5 | 11.4±29.7 | 13.6±31.1 | 17.7±50 | 0.326 | 0.013 | 6±12.9 | 10.8±22.8 | 11.8±28 | 14.5±43.2 | 9.6±26.6 | 0.011 | 0.145 |

P-values represent the ANOVA linear and quadratic trends for interval variables and chi-squared linear trends for dichotomized variables. Glucose and triglycerides were tested after logarithmic (ln) transformation. N. Africa, North Africa; DM med, diabetes medication status; BMI, body-mass-index; LDL, low density lipoprotein; HDL, high density lipoprotein; VLDL, very low density lipoprotein; AST, aspartate aminotransferase; CCr, estimated creatinine clearance

**Table S2:** Outcome-related comorbidities according to hospital discharge summaries or death notifications

| Comorbidity | Outcome | |
|---|---|---|
| | Acute renal failure | Chronic renal failure |
| Ischemic heart disease (ICD9: 410-414) | 52% | 49% |
| Congestive heart failure (ICD9: 428) | 22% | 25% |
| Gout (ICD9: 274) | 0% | 0% |
| Diabetes mellitus (ICD9: 250) | 41% | 38% |
| Cirrhosis / chronic liver disease (ICD9: 571) | 4% | 1% |
| Glomerulonephritis (ICD9: 580-583) | 15% | 3% |
| Kidney transplant (ICD9: V42.0) | 0% | 0% |
| Chronic renal failure (ICD9: 585) | 56% | - |
| Acute renal failure (ICD9: 584) | - | 8% |

**Table S3:** Logistic regression models predicting chronic renal failure

| | 12 years | | | | 16 years | | | | 20 years | | | | 24 years | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | weighing off | | weighing on | | weighing off | | weighing on | | weighing off | | weighing on | | weighing off | | weighing on | |
| | OR (95% CI) | p-value | OR (95% CI) | p-value | OR (95% CI) | p-value | OR (95% CI) | p-value | OR (95% CI) | p-value | OR (95% CI) | p-value | OR (95% CI) | p-value | OR (95% CI) | p-value |
| **Age, yr** | 1.10 (1.02-1.19) | 1.5E-02 | 1.10 (1.00-1.2) | 5.5E-02 | 1.02 (0.97-1.08) | 4.4E-01 | 1.03 (0.96-1.11) | 4.5E-01 | 1.12 (1.07-1.17) | 5.0E-07 | 1.12 (1.07-1.18) | 5.8E-06 | 1.13 (1.08-1.18) | 3.7E-08 | 1.13 (1.07-1.20) | 1.1E-05 |
| **Sex, F vs. M** | nd | nd | nd | nd | 0.22 (0.06-0.85) | 2.8E-02 | 0.08 (0.01-1.00) | 5.0E-02 | 0.48 (0.20-1.13) | 9.3E-02 | 0.20 (0.04-0.89) | 3.5E-02 | 0.48 (0.22-1.01) | 5.3E-02 | 0.24 (0.09-0.69) | 8.2E-03 |
| **Education, yr.** | 0.91 (0.82-1.02) | 1.0E-01 | 0.89 (0.77-1.02) | 9.0E-02 | 0.90 (0.84-0.97) | 3.7E-03 | 0.91 (0.82-1.00) | 4.3E-02 | 0.95 (0.91-1.00) | 6.0E-02 | - | - | 0.93 (0.88-0.98) | 4.4E-03 | 0.93 (0.87-1.00) | 4.3E-02 |
| **Smoking, Y vs. N** | 3.74 (1.07-13.1) | 3.9E-02 | 4.02 (0.91-17.8) | 6.7E-02 | 3.90 (1.71-8.87) | 1.2E-03 | 4.37 (1.50-12.7) | 6.8E-03 | 2.66 (1.50-4.71) | 7.9E-04 | 2.32 (1.18-4.57) | 1.5E-02 | 2.37 (1.34-4.19) | 3.0E-03 | - | - |
| **DM med, Y vs. N** | - | - | - | - | - | - | - | - | 4.13 (1.15-14.8) | 2.9E-02 | - | - | - | - | - | - |
| **Systolic BP, mmHg** | - | - | - | - | - | - | - | - | - | - | - | - | - | - | 1.02 (1.00-1.05) | 2.8E-02 |
| **Diastolic BP, mmHg** | - | - | - | - | - | - | - | - | - | - | - | - | 1.03 (1.00-1.05) | 2.6E-02 | - | - |
| **Hyperuricemia, Q5** | **3.09 (0.88-10.9)** | **7.9E-02** | **4.6 (1.06-19.9)** | **4.1E-02** | **2.81 (1.23-6.46)** | **1.5E-02** | **3.21 (1.09-9.44)** | **3.4E-02** | **2.05 (1.12-3.75)** | **1.9E-02** | **1.80 (0.85-3.84)** | **1.3E-01** | **3.72 (2.02-6.85)** | **2.4E-05** | **3.19 (1.43-7.16)** | **4.8E-03** |
| **Glucose, per 2.7-fold** | 65.0 (13.1-322) | 3.2E-07 | 94.5 (12.5-716) | 1.1E-05 | 16.9 (4.16-68.6) | 7.8E-05 | 80.1 (17.9-358) | 9.5E-09 | 6.32 (2.00-20.0) | 1.7E-03 | 18.3 (5.59-59.9) | 1.5E-06 | 19.0 (6.32-57.0) | 1.5E-07 | 19.2 (4.18-87.8) | 1.4E-04 |
| **Cholesterol, mg/dl** | - | - | - | - | - | - | - | - | 1.01 (1.00-1.02) | 1.1E-03 | - | - | - | - | - | - |
| **LDL-C, mg/dl** | - | - | - | - | - | - | - | - | - | - | - | - | 1.01 (1.00-1.02) | 1.8E-03 | 1.01 (1.00-1.03) | 6.0E-03 |
| **Globulins, g/l** | - | - | - | - | 1.14 (1.02-1.27) | 1.8E-02 | 1.15 (1.00-1.33) | 5.5E-02 | 1.10 (1.01-1.19) | 2.1E-02 | 1.12 (1.01-1.24) | 2.7E-02 | 1.07 (0.99-1.15) | 9.2E-02 | - | - |
| **Bilirubin, mg/l** | - | - | - | - | 0.72 (0.57-0.92) | 7.2E-03 | 0.69 (0.50-0.94) | 2.0E-02 | - | - | - | - | - | - | - | - |
| **Creatinine, mg/dl** | 21.3 (0.4-1261) | 1.4E-01 | 18.3 (0.15-2194) | 2.3E-01 | 7.0 (0.46-106) | 1.6E-01 | 2.77 (0.08-92.1) | 5.7E-01 | 2.15 (0.29-15.9) | 4.5E-01 | 1.14 (0.11-11.9) | 9.1E-01 | 5.56 (0.71-43.5) | 1.0E-01 | 7.80 (0.51-119) | 1.4E-01 |
| **Stick protein, mg/dl** | - | - | - | - | 1.01 (1.00-1.01) | 1.2E-02 | - | - | 1.01 (1.00-1.01) | 6.1E-03 | - | - | 1.01 (1.01-1.02) | 9.2E-05 | 1.01 (1.01-1.02) | 8.4E-04 |

Age, sex, serum uric acid (sex-specific quintile 5 vs. quintiles 1-4) and creatinine were forced into the logistic regression models. Dark-shaded columns correspond to models in which subjects' data were weighed according to the sampling probability (see Supplementary Methods). OR, odds ratio; DM med, diabetes medication status; BP, blood pressure; LDL-C, low density lipoprotein cholesterol; nd, not defined. By 12 years there were 15 event (n=2299); 16 years – 38 events (n=2223); 20 years – 70 events (n=2124); and 24 years – 108 events (n=730).

**Figure S1**

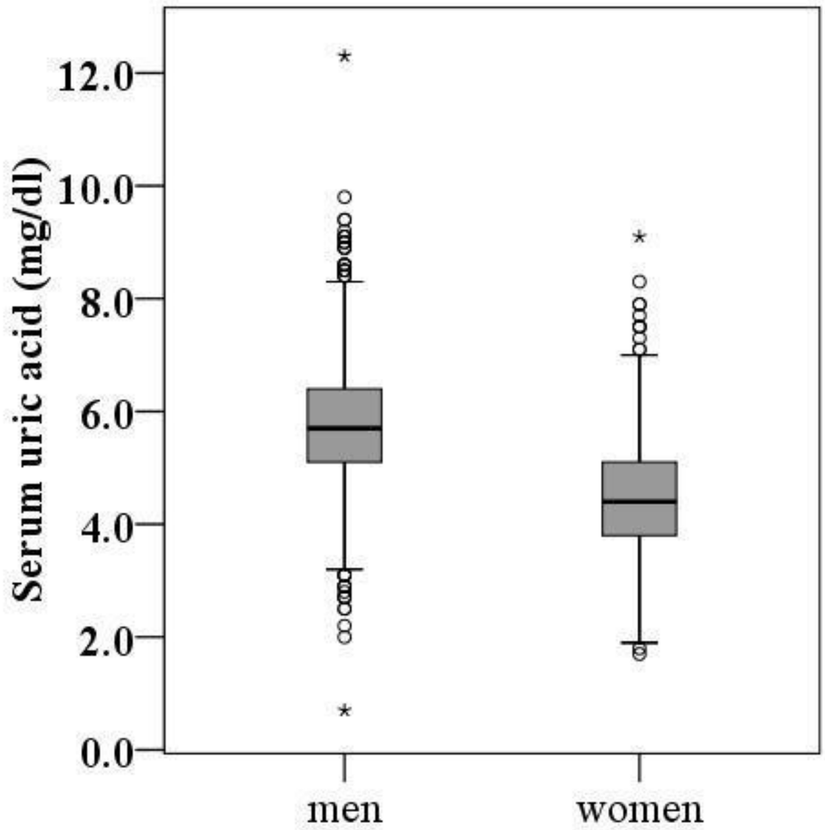


**Figure S1:** Distribution box plots for serum uric acid levels in men (n=1470) and women (n=979). Thick horizontal lines represent medians; boxes – interquartile range (IQR); whiskers are 1.5 IQR from box ends; circles – outliers (1.5-3.0 IQR); asterisks; extreme cases (>3.0 IQR). P-value for the comparison between men and women (t-test) = 9E-158.

**Figure S2**

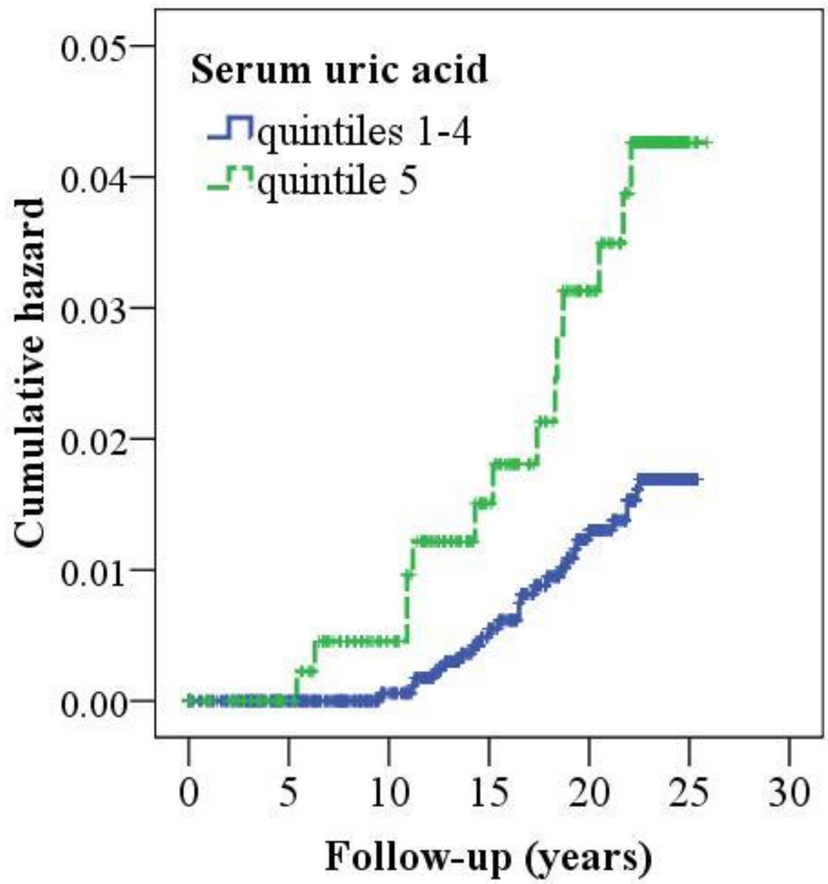


**Figure S2**: Kaplan-Meier curves plotting coronary heart disease-censored hazards of chronic renal failure by serum uric acid quintiles, log-rank p-value = 0.003 (n=2449; 39 events).

**Figure S3**

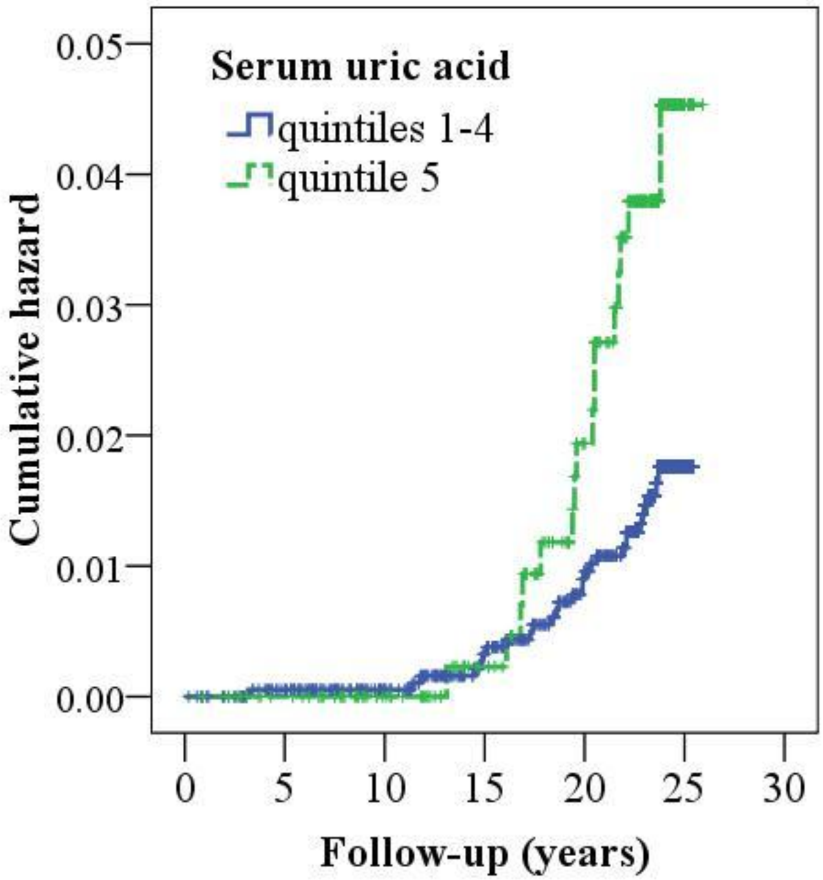


**Figure S3**: Kaplan-Meier curves plotting hazards of acute renal failure by serum uric acid quintiles, log-rank p-value = 0.003 (n=2449; 44 events).

**Figure S4**

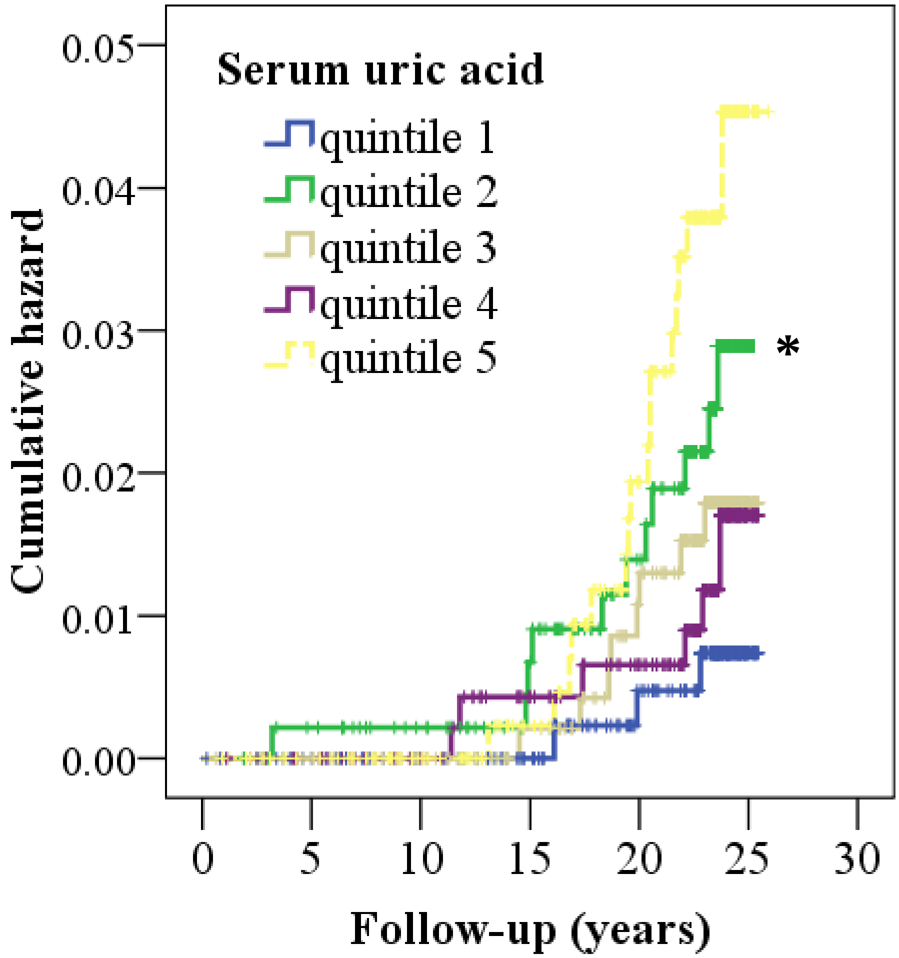


**Figure S4**: Kaplan-Meier curves plotting hazards of acute renal failure by individual serum uric acid quintiles, log-rank p-value = 0.01 (n=2449; 44 events). The asterisk (*) marks an inconsistent quintile that may be expected with small numbers of events.