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Letter to the Editor

Serum uric acid as a predictor for cardiovascular and all-cause mortality in women versus men

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Uric acid is the end product of purine metabolism in humans. Higher levels of serum uric acid (SUA) are confirmed in men than in women at all ages [1]. Many studies [2–5] indicated excess mortality in women than men, but others [6,7] did not confirm these findings. Most studies on SUA levels and mortality risk were conducted in single sex populations [8–11] or not conducted gender specific analyses [12]. Therefore, whether SUA conferring the same risk of mortality between women and men is conflicting. A meta-analysis [13] suggested that elevated SUA increased all-cause mortality risk among men but not in women, and the risk of cardiovascular mortality was more pronounced in women. However, these conclusions were based on the indirect comparisons. Direct comparisons of the relation between SUA levels and mortality risk in men and women through within-study comparisons could reduce the impact of extraneous between-study factors. Therefore, we conducted this meta-analysis to investigate SUA levels and risk of cardiovascular or all-cause mortality comparing women with men using the female-to-male ratio of relative risks (RRR).

We searched from PubMed, Embase, and Cochrane Library databases for studies published prior to May 2014. Potentially articles were identified by the following words: hyperuricemia, uric acid, mortality, death, prospective, and follow-up. Studies were included if: 1) prospective design; 2) participants in the general population; and 3) providing multiple adjusted risk ratio (RR) with 95% confidence interval (CI) of cardiovascular or all-cause mortality for the highest versus lowest SUA levels in males and females, respectively. Studies were excluded if they were conducted in single gender populations. Quality assessment was done using the Newcastle–Ottawa Scale (NOS) [14]. We pooled the sex-specific RR for the highest versus lowest SUA category from each study, and then used the sex-specific multivariate-adjusted RR and 95% CI in the individual study to estimate the female-to-male ratio of RRR. All analyses were carried out with STATA statistical software (version 12.0; Stata Corporation).

Our initial search identified 629 articles, six studies [2–7] finally included in this meta-analysis. Characteristics of the individual studies are shown in Table 1. Overall quality of the included studies was good (range from 6 to 8) based on a 9-star NOS scales. Six studies [2–7] reported data on all-cause mortality according to the gender. Compared the highest to lowest SUA category, pooled RR of all-cause mortality was 1.15 (95% CI 0.89–1.49) for women and 1.13 (95% CI 1.05–1.20) for men (Fig. 1). Three studies [3,4,6] reported data on cardiovascular mortality according to gender. Pooled RR of cardiovascular mortality compared the highest SUA with lowest SUA category was 1.27 (95% CI 0.78–2.07) for women and 1.20 (95% CI 1.00–1.43) for men (Fig. 2).

Six studies [2–7] reported data on gender-stratified RR of all-cause mortality. Pooled female-to-male RRR of all-cause mortality was 1 · 06 (95% CI 0.81–1.38) compared the highest with the lowest SUA category (Fig. 3). Publication bias was not observed according to Begg's rank correlation test ($P = 0.707$) or Egger's linear regression test ($P = 0.429$). Three studies [3,4,6] reported data on gender-stratified RR of cardiovascular mortality. Pooled female-to-male RRR of cardiovascular mortality was 1.08 (95% CI 0.6–1.96) compared the highest with the lowest SUA category (Fig. 3). Sensitivity analyses indicated that there was little influence in the pooled estimate of RRR and 95% CI when any one study was omitted from the analysis.

To our knowledge, this is the first meta-analysis focusing on sex-specific differences on SUA levels and excess mortality risk. Our study suggests that there is no significant gender difference in the relationship between SUA levels and mortality risk. However, elevated SUA levels show some trend to confer excessive risk of cardiovascular or all-cause mortality in women than those in men. The possible mechanisms for gender differences of mortality risk might be explained by different SUA levels between men and women. Many factors contribute to higher SUA levels with excess risk of mortality in women. SUA levels are influenced by sex, age, alcohol consumption, obesity, use of diuretics, glucose intolerance, hypertension, and dyslipidemia [15]. Higher SUA levels in men than in women might attribute to the gender-related steroids involved in uric acid regulation [16]. Moreover, inflammatory process appeared to have a strong impact on the relationship between SUA

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Table 1
Summary of clinical studies included in meta-analysis.

Study/year	Region	Design	Subjects (% women)	Age/range Mean (SD)	Comparison	Outcome assessment	Events number/RR (95% CI)	Follow-up (year)	Adjustment for covariates
Freedman et al. [9] 1995	USA	Prospective study	5421 (54)	≥25	Highest vs. lowest ≥7 mg/dl vs. <4 mg/dl	Death certificate or proxy respondent.	Total (892) 0.9 (0.56–1.43) M 1.6 (1. 04–2. 45) F	13.5	Age, race, quetelet index, TC, DBP, smoking, antihypertensive treatment, alcohol, education, and use of diuretics.
Culleton et al. [10] 1999	USA	Prospective study	6763 (54.5)	45 ± 15 M 48 ± 16 F	Highest quintile vs. lowest quintile ≥400 μmol/l vs. <280 μmol/l in men and ≥311 vs. <196 in women	Medical records. CVD death (CHD, congestive heart failure, stroke, or other CVD).	Total (1460); CVD (429) 0.98 (0.78–1.24) Total M 1.16 (0.89–1.51) Total F 0.92 (0.61–1.40) CVD M 1.46 (0.84–2.53) CVD F	9.6	Age, BMI, SBP, use of antihypertensive agents, use of diuretics, DM, TC, smoking status, alcohol intake, LVH, and menopausal status.
Hu et al. [14] 2001	USA	Prospective cohort study	870 (53.2)	70-79	Highest vs. lowest >6.8 mg/dl vs. <5.7 mg/dl in men and >5.9 mg/dl vs. <4.9 mg/dl in women.	Contact with proxies or linkage with National Death Index	Total (147) 1.24 (0.70–2.20) Total M 0.47 (0.22–0.99) Total F	7	Age, race, CAD, hypertension, DM, number of chronic conditions, diuretic use, smoking, alcohol, BMI, TC, HDL, CRP, interleukin-6, and serum creatinine.
Sakata et al. [13] 2001	Japan	Prospective study	8172 (56.0)	≥30	Highest quintile vs. lowest quintile ≥ 386 μmol/l vs. <297 μmol/l in men and ≥291 vs. <214 in women	Local public health centers; ICD9:390–459.	Total (960); CVD (249) 1.20 (0.91–1.59) Total M 0.73 (0.53–1.02) Total F 1.45 (0.91–2.30) CVD M 0.74 (0.43–1.27) CVD F	14	Age, BMI, SBP, use of antihypertensive agents, TC, serum creatinine, glucose, smoking, alcohol, and LVH.
Chen et al. [11] 2009	Taiwan	Prospective cohort study	90393 (53.7)	51.5 ± 11.5	High vs. low ≥7 mg/dl vs. <7 mg/dl	National Mortality Registry Office. ICD 9: 390–459.	Total (5424); CVD (1151) 1.10 (1.02–1.20) Total M 1.27 (1.12–1.43) Total F 1.23 (1.03–1.46) CVD M 1.69 (1.33–2.16) CVD F	8.2	Age, sex, BMI, TC, triglycerides, DM, hypertension, heavy cigarette smoking, and frequent alcohol consumption.
Juraschek et al. [12] 2014	Scotland	Prospective cohort study	15,083 (49.9)	48.7 ± 9.3	High vs. low ≥416.36 μmol/l vs. <416.36 μmol/l in men and ≥356.88 vs. <356.88 in women	Death registrations and the national record. cardiovascular death ICD9 codes 390–459, ICD10 codes I00–I99	Total (3980) 1.23 (1.07–1.46) Total M 1.68 (1.41–2.00) Total F	23	Age, sex, SBP, DBP, blood pressure medication use, SBP & medication use interaction, smoking, number of cigarettes per day among smokers, TC, HDL, BMI, baseline DB status, daily alcohol use, and the Scottish Index of Multiple Deprivation.

Abbreviations: M, male; F, female; NR,not report; BMI, body mass index; RR, risk ratio; LVH, left ventricular hypertrophy; SBP, systolic blood pressure; DBP, diastolic blood pressure; DM, diabetes mellitus; TC, total cholesterol; LDL, low-density lipoprotein; HDL, High-density lipoprotein; CVD, cardiovascular disease; CRP, C-Reactive protein; ICD, International Classification of Diseases.