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Review

Baseline serum uric acid level as a predictor of cardiovascular disease related mortality and all-cause mortality: A meta-analysis of prospective studies

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ABSTRACT

Objective: Serum uric acid (SUA) levels have been used to predict cardiovascular and all-cause mortality event, but the data have yielded conflicting results. We investigated whether SUA was an independent predictor for cardiovascular or all-cause mortality with prospective studies by meta-analysis.
Methods: Pubmed and Embase were searched without language restrictions for publications available till April 2013. Only prospective studies on cardiovascular or all-cause mortality related to SUA levels were included. Pooled adjust relative risk (RR) and corresponding 95% confidence intervals (CI) were calculated separately for the highest vs. lowest category or the lowest vs. middle category.
Results: For the highest SUA, eleven studies with 172,123 participants were identified and analyzed. Elevated SUA increased risk of all-cause mortality (RR 1.24; 95% CI 1.09–1.42) and cardiovascular mortality (RR 1.37; 95% CI 1.19–1.57). Subgroup analyses showed that elevated SUA significantly increase the risk of all-cause mortality among men (RR 1.23; 95% CI 1.08–1.42), but not in women (RR 1.05; 95% CI 0.79–1.39). Risk of cardiovascular mortality appeared to be more pronounced among women (RR 1.35; 95% CI 1.06–1.72). The association between extremely low SUA and mortality was reported in three studies; we did not perform a pooled analysis because of high degree of heterogeneity in these studies.
Conclusions: Baseline SUA level is an independent predictor for future cardiovascular mortality. Elevated SUA appears to significantly increase the risk of all-cause mortality in men, but not in women. Whether low SUA levels are predictors of mortality is still inconclusive.

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1. Introduction

Cardiovascular disease (CVD) is the leading cause of mortality worldwide. Many traditional risk factors have been for CVD, such as hyperlipidemia, hypertension, diabetes, uric acid levels, smoking,

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etc. Early detection of high-risk subjects is likely to aid in the prevention of CVD and further lower CVD mortality.

Uric acid is the end product of purine metabolism in humans. The available evidence indicates that elevated serum uric acid (SUA) is related to the development and progression of hypertension [1], coronary heart disease (CHD) [2], myocardial infarction [3], stroke [4], and cardiovascular disease (CVD) [5]. Furthermore, elevated SUA are also predictors of all-cause mortality among heart failure patients [6]. Many studies have indicated [7–12] that higher SUA is a predictor of cardiovascular or all-cause mortality in the general population. A gender specific association with mortality was found only for women in one study [13], whereas other studies [14–17] showed that higher SUA could not predict the development of cardiovascular or all-cause mortality. In addition, there is some evidence that suggests that lower SUA levels are also associated with an accelerated rate of mortality [18–20]. Therefore, studies that evaluated the role of SUA levels as an independent risk factor for cardiovascular or all-cause mortality produced conflicting results. These inconsistent results are possibly related to the differences in the populations that were studied, duration of follow-up, outcomes studied and the statistical adjustments.

To the best of our knowledge, no meta-analysis has been conducted to evaluate the association between baseline SUA and the risk of cardiovascular or all-cause mortality. The aim of this study was to systematically evaluate the association between baseline SUA levels and cardiovascular or all-cause mortality risk in the general population through a meta-analysis.

2. Methods

The meta-analysis was conducted according to the checklist of the Meta-Analysis of Observational Studies in Epidemiology [21]. Electronic literature databases (Pubmed and Embase) were searched for relevant prospective observational studies published prior to April 2013. Studies assessed baseline SUA levels and subsequent cardiovascular or all-cause mortality events in the general population without language restrictions. Potentially relevant studies were identified by various combinations of the following search terms: uric acid, hyperuricemia, urate, cardiovascular mortality, mortality, death, heart death, cohort studies, observational studies, and prospective studies (Supplementary text-S1). In addition, the reference list of the selected relevant publications was manually searched to identify possible additional studies.

Studies that satisfied the following criteria were included in the meta-analysis: 1) prospective observational studies with follow-up time of >4 years; 2) description of risk estimates for the association between SUA levels and subsequent cardiovascular or all-cause mortality in the general population; and 3) providing multiple adjusted relative risk (RR) or hazard ratio (HR) with 95% confidence interval (CI) for SUA comparing the highest SUA levels to the lowest SUA levels or the lowest vs. middle SUA levels. Studies were excluded if 1) the study design was a review, a case–controlled study, a retrospective cohort, or an animal study; 2) unadjusted RR or HR was reported.

Outcome measures that were included in our study were cardiovascular or all-cause mortality. Mortality outcomes were based on the death certificate with an underlying cause of death coded according to the International Classification of Diseases Ninth Revision (ICD-9). Cardiovascular mortality included the following subgroups according to ICD-9: 390–459 or ICD-10 I0–I15, I30–I41, I44–I49, I51.0, I51.4, I51.8, I51.9, I70–I74.

Two reviewers (G Zhao and L Huang) independently extracted the data from each trial using a standardized form with predefined criteria that had been developed specifically for this meta-analysis. The data with the most fully adjusted RR or HR and 95% CI were extracted for all the included studies. We also extracted the following items from every study: authors, year of publication, the region where the study was conducted, the follow-up period, sample size, gender of the patients, the mean age or age range of subjects, number of deaths, and statistical adjustments for confounding factors. The reviewers resolved any discrepancies that were identified through discussions.

The quality of the studies obtained from the literature search was assessed by two reviewers according to the meta-analysis of Observational Studies in Epidemiology (MOOSE) reporting guidelines [21]. Quality assessment was performed with consideration of the following aspects: 1) clear inclusion and exclusion criteria; 2) documentation of the loss to follow-up rate; 3) clear definition of outcome and outcome assessment; 4) sufficient duration of follow-up; 5) appropriate statistical analysis; and 6) identification of important confounding and prognostic factors. All items had the following answer options: yes/no/unclear information to answer the question. When a criterion was fulfilled, a score of 1 was given, 0 if a criterion was unclear, and −1 if a criterion was not achieved.

Data analyses were performed using multivariate-adjusted RR or HR and 95% CI. If the publications reported separate RR for gender, we pooled the separate RR for the different items and compared the highest SUA to the lowest SUA category from the individual study. Before pooling the data, adjusted RR from each study was converted to logRR to stabilize the variances and to normalize the distributions. The standard errors (SEs) for logRR were calculated from reported 95% CI.

Heterogeneity due to effect sizes across studies was assessed with Cochrane Q test and the I^2 statistic. A $p > 0.10$ or $I^2 < 50\%$ were taken as indicators of the same scale of outcomes using a fixed-effect model. The $p \leq 0.10$ or $I^2 > 50\%$ were taken as indicators of different scales of outcomes using a random effect model, based on the suggestion of the Cochrane Handbook for Systematic Review of Interventions [22]. The pooled RR was computed using either fixed-effects models or random-effects models in the presence of

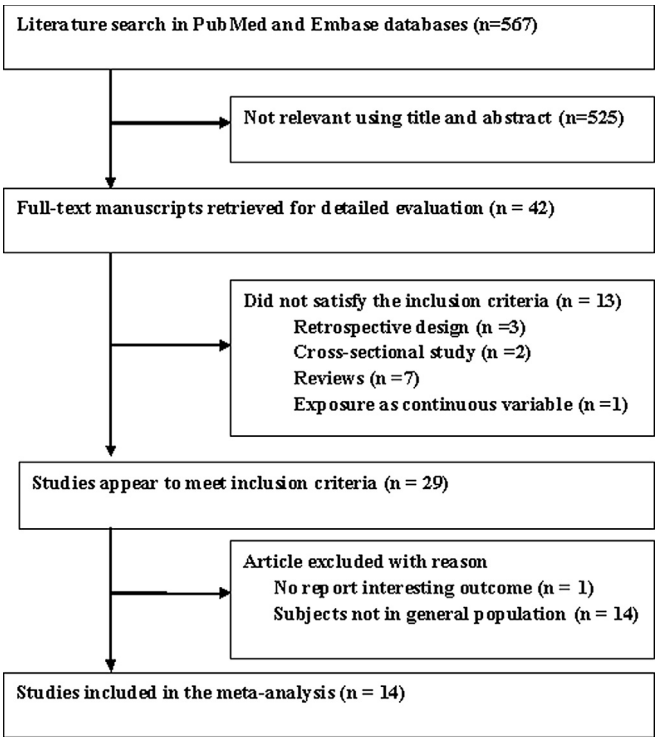

Fig. 1. Flow chart of study selection process for meta-analysis.