Hyperuricemia and the Prognosis of Hypertensive Patients: A Systematic Review and Meta-Analysis

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The aim of this study was to assess the prognostic value of hyperuricemia in patients with established hypertension by systematic review and meta-analysis of cohort studies. MEDLINE, Embase, and the Chinese Biomedical Literature Database were searched through January 2015. Seventeen cohort studies were included and their methodological quality was moderate to high, with Newcastle-Ottawa Scale scores ranging from 6 to 9. Random-effects model meta-analyses showed that in terms of adjusted categorical data, hyperuricemia significantly correlated with cardiovascular diseases in hypertensive patients (hazard ratio [HR], 1.51; 95% confidence interval [CI], 1.13–2.03), all-cause mortality (HR, 1.12; 95%CI, 1.02–1.23), and diabetes (HR, 1.84; 95% CI, 1.02–3.30) but not with stroke (HR, 0.85; 95%CI, 0.57–1.27); while, in terms of adjusted continuous data, the corresponding pooled HRs were 1.17 (95% CI, 1.07–1.27), 1.05 (95% CI, 0.98–1.13), 1.28 (95% CI, 1.18–1.38), and 1.06 (95% CI, 0.98–1.16), respectively. The findings of our meta-analysis suggest that hyperuricemia could slightly increase the risk of cardiovascular diseases and diabetes in patients with hypertension. *J Clin Hypertens (Greenwich).* 2016;18: 1268–1278. © 2016 Wiley Periodicals, Inc.

Uric acid (UA) is the end product of purine metabolism. Humans are more susceptible to hyperuricemia than other mammals because of the loss of urate oxidase activity during human evolution.[1] As an increasingly common metabolic disorder, with the exception of the association with metabolic syndrome and chronic kidney disease, the relationship of hyperuricemia with cardiovascular diseases (CVDs) has received more and more attention for many years.[2,3]

Hypertension is an established important risk factor for CVDs and has been observed to be a leading contributor to the burdens of mortality and morbidity both in developed and developing countries. The World Health Organization reported that approximately 40% of adults aged 25 and older had been diagnosed with hypertension worldwide in 2008.[4] Confronted with these complications of hypertension, apart from various antihypertension drugs, we should pay more attention to the contributing factors that may worsen the prognosis of hypertensive patients, such as serum UA (SUA).[5]

A number of studies and several meta-analyses[6,7] have assessed the relationship between hyperuricemia and subsequent risk of hypertension development, demonstrating that elevated SUA could be a risk factor for incident hypertension. Studies have investigated the impact of SUA on the prognosis of hypertension; however, the findings are inconsistent and vary considerably as a result of the differences in study participants, sample sizes, ethnicity, follow-up duration, and study quality. If UA is associated with the complications of established hypertensive patients, appropriate control of UA level could improve prognosis. Therefore, this systematic review aims to clarify whether UA is an independent prognostic factor for hypertensive patients.

MATERIALS AND METHODS

This systematic review and meta-analysis was performed fundamentally according to the checklist of the Meta-Analysis of Observational Studies in Epidemiology (MOOSE)[8] and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[9]

Data Sources and Searches

We conducted a comprehensive literature search of MEDLINE, Embase, and the Chinese Biomedical Literature Database (CBM) through January 2015 using the terms urate, UA, hyperuricemia, hypertension, and high blood pressure (BP). The following search strategy was used for MEDLINE: (exp Uric Acid/OR exp Hyperuricemia/OR urate.ab,ti. OR uric acid.ab,ti. OR Hyperuricemia.ab,ti. OR Hyperuric$.ab,ti.) AND (exp Hypertension/OR hypertension.ab,ti. OR high blood pressure.ab,ti.). Similar search strategies were used for Embase and CBM. In addition, we searched the reference lists of all identified relevant studies.

Study Selection

All studies identified from the electronic databases were imported to EndNote. Two reviewers (TQ, XZ)

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independently screened the records based on titles and abstracts to select the potentially eligible studies. We only considered studies that investigating the prognostic effect of SUA on hypertensive patients with a mean or median follow-up duration of more than 1 year and a sample size larger than 100, including both cohort studies and nested case-control studies and randomized controlled trials (RCTs) with appropriate cohorts. Included studies must have reported the hazards ratios (HRs) or risk ratios (RRs) and their corresponding 95% confidence intervals (CIs) or data available to calculate these measurements. The following studies were excluded: studies on gout patients; nonhuman studies; editorial, conference proceedings, or literature reviews; and studies investigating only the relationship of various biochemical variables. When two or more studies were conducted based on the same cohort participants, only the study with the most recently updated data was included. Any disagreements were resolved by consensus.

Data Extraction and Quality Assessment

Data extraction was performed independently by two authors (JW, XZ) with a standardized data extraction form. For each included study, we extracted the details regarding study and patient characteristics, publication year, study location, study design, sample size, definition of hyperuricemia, follow-up duration, number of adverse events, effect sizes (unadjusted or adjusted RRs, HRs and corresponding 95% CIs based on categorical or continuous variables), and adjusted potential confounding factors when multivariable model was available. For studies that reported several multivariable models, we extracted the most fully adjusted trial. If effect sizes were not available, we used the original data reported in the studies to impute an unadjusted RR. All data was cross-checked and any discrepancies were resolved by discussion with JL.

Two reviewers (TQ, XZ) independently assessed the methodological quality of each study using the Newcastle-Ottawa Scale (NOS)[10] for cohort study and cohorts derived from RCTs, with disagreements resolved by consensus and consultation with a third reviewer (JL). An overall quality score was calculated on three broad perspectives: (1) the selection of the study groups (0–4 points), (2) the comparability of the groups (0–2 points), and (3) the ascertainment of the outcome of interest (0–3 points). The score for each item was added up, with a range from the minimum 0 to the maximum 9, and a higher score representing better methodological quality.

Data Synthesis and Analysis

The unadjusted and multivariable-adjusted risk estimates (HRs or RRs) for categorical (highest vs lower categories) or continuous data (1 standard deviation [SD] or 1 mg increase in SUA, or other specific increments) were both used to explore the relationship between SUA level and the prognosis of hypertension. For studies that only provided the data of men and women separately, the overall risk estimates were calculated using the data of each subgroup. All of these calculations were performed by Stata/SE (version 12.0, Stata Corp, College Station, TX).

We used the *metan* command in Stata to pool the effect sizes (RR or HR) across the included studies using the random-effects models described by DerSimonian and Laird,[11] which takes both within-study and between-study variability into account. Heterogeneity was assessed by the Cochran Q test with a significance level set at P=.10 and quantified by I^2 statistics with a rough cutoff of 50%. Subgroup analysis and meta-regression were used to explore sources of heterogeneity.[12] A dose-response association between SUA and outcome events was assessed based on the studies that distributed SUA levels into at least three categories. A two-sided P value <.05 was considered statistically significant for pooled effect sizes.

RESULTS

Characteristics of the Included Studies

The results of the literature search are shown in Figure 1. We identified 17 eligible studies, including 15 prospective cohort studies[13–27] and two retrospective cohort studies.[28,29] Among the 15 prospective cohort studies, five pairs of comparative cohorts were derived from four RCTs[14,16,19,23] and one simple controlled clinical trial.[18]

Table I summarizes the characteristics and details of the included 17 studies. Three studies were conducted in the United States,[14–16] three in China/Taiwan,[18,20,22] three in Japan,[13,21,25] three in Italy,[17,24,26] two in the United Kingdom,[28,29] one in Norway,[23] one in Turkey,[27] and one in several countries in Europe.[19] There

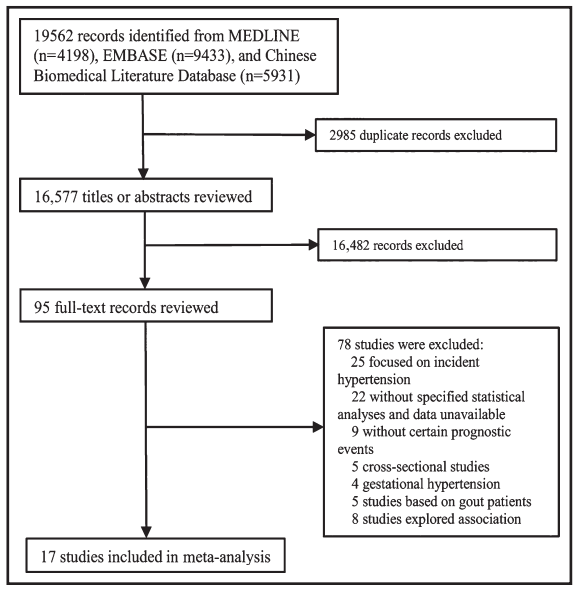

FIGURE 1. Flowchart of study selection.

TABLE I. Characteristics of the 17 Included Studies

Author, Year, Country	Study Design	Study Population (M/F)	Uric Acid Cutoff/Upper Quartile[a]	Mean Age (range), y	Follow-Up, y	Prognostic Events	Model	Variables Adjusted	Risk Estimates[f] (95% CI)	Study Quality[k]
Tofuku 1978 Japan[13]	PC	117 (88/29) hypertensive patients (153 original patients)	7.0 mg/dL	M: 52.5 (16–77) F: 52.7 (24–72)	3.7 (mean)	Six cerebrovascular disease events (4 deaths) and 9 myocardial infarctions and heart failures (7 deaths)	Crude	NA	CVD: 3.09 (1.13–8.45)[e,g] stroke: 1.54 (0.33–7.32),[e,g] mortality: 4.12 (1.15–14.71)[e,g]	6 (3/1/2)
HDFP 1985 USA[14]	PC in RCT	10,785 hypertensive patients with DBP ≥90/95 mm Hg	7.0 mg/dL	50.8 (30–69)	≥5	754 deaths	Crude	NA	Mortality: 1.70 (1.47–1.95)[e,g]	7 (3/1/3)
Alderman 1999 USA[15]	PC	7978 (4883/3095) mild to moderate treated hypertension with BP ≥160/95 mm Hg (140/90 mm Hg after 1993)	Per 1 SD (0.086 mmol/L or 1.45 mg/dL); upper quartile: M: ≥0.447 mmol/L, F: ≥0.370 mmol/L	53.2 (M), 53.9 (F); (20–85)	6.6 (mean)	548 cardiovascular events (183 deaths), 116 non-CVDs	Multivariable[d]	Age, sex, race, history of CVD, history of diabetes, prior treatment, smoking status, LVH by ECG, blood sugar, cholesterol, serum creatinine, BMI, and initial SBP	CVD: 1.22 (1.11–1.35)[h]	8 (3/2/3)
Franse 2000 USA[16]	PC in RCT	4327 (1859/2468) patients with isolated systolic hypertension without recent MI or stroke	Upper quartile, M: 0.40–0.67 mmol/L (6.72–11.26 mg/dL) F: 0.34–0.61 mmol/L (5.71–10.25 mg/dL)	71.6 (≥60)	5.0	638 any cardiovascular event, 290 coronary heart disease, 243 stroke, 403 deaths	Multivariable[d]	Age, sex, race, BMI, history of heart attack, stroke, or diabetes, serum creatinine, glucose, cholesterol, TG, and HDL cholesterol	CVD: 1.32 (1.03–1.69)[g] stroke: 0.85 (0.57–1.28)[g] mortality: 1.05 (0.77–1.44)[g]	8 (3/2/3)
Lip 2000 UK[28]	RC	153 (98/55) MHT on the Birmingham MHT register	0.41 mmol/L (6.89 mg/dL)	50.3, SD: 13.5	5.5 (mean)	34 deaths	Crude	NA	Mortality: 1.47 (0.8–2.73)[e,g]	7 (3/1/3)
Verdecchia 2000 Italy[17]	PC	1720 (920/800) hypertensive patients	Upper quartile: M >6.2 mg/dL, F: >4.6 mg/dL	51, SD: 12	≤12, 4.0 (mean)	184 cardiovascular events, (42 cardiovascular deaths), 80 deaths	Multivariable[d]	Age, sex, diabetes, total cholesterol/HDL cholesterol ratio, serum creatinine, LVH, ambulatory BP, and use of diuretics during follow-up	CVD: 1.73 (1.01–3.00)[g] mortality from CVD: 1.96 (1.02–3.79)[g] mortality: 1.63 (1.02–2.57)[g]	9 (4/2/3)

TABLE I. Characteristics of the 17 Included Studies (Continued)

Author, Year, Country	Study Design	Study Population (M/F)	Uric Acid Cutoff/Upper Quartile[a]	Mean Age (range), y	Follow-Up, y	Prognostic Events	Model	Variables Adjusted	Risk Estimates[f] (95% CI)	Study Quality[k]
Wang 2001 China[18]	PC in trial	1873 (1207/666) isolated systolic hypertension with SBP 160–219 mm Hg and DBP <95 mm Hg	Per 50 μmol/L (0.84 mg/dL); M: 7.0 mg/dL, F: 6.0 mg/dL	67 (≥60)	3.0 (median)	Mortality: 114 total, 62 cardiovascular, 26 stroke; fatal and nonfatal: 138 total, 43 cardiac, 87 stroke	Multivariable[d]	Age, sex, active treatment, SBP, DBP, BMI, serum total cholesterol, smoking and drinking habits, previous cardiovascular complications, and diabetes mellitus	Mortality: 1.04 (0.96–1.14)[,g] mortality from CVD: 1.14 (1.02–1.27)[,g] mortality from stroke: 1.34 (1.14–1.57)[,g] CVD: 1.06 (0.98–1.15), stroke: 1.04 (0.94–1.16)	8 (3/2/3)
De Leeuw 2002 Europe[b19]	PC in RCT	4552 (1600/2952) isolated systolic hypertension with SBP 160–219 mm Hg and DBP <95 mm Hg	Per 50 μmol/L (0.84 mg/dL); upper quartile: 370 μmol/L (6.22 mg/dL)	70.2 (≥60)	2.0 (median)	Mortality: 261 total, 136 cardiovascular, 36 stroke; fatal and nonfatal: 324 total, 202 cardiac, 125 stroke	Multivariable[d]	Age, sex, active treatment, SBP, smoking status, previous cardiovascular complications, and diabetes mellitus	Mortality: 1.03 (0.96–1.11)[,g] mortality from CVD: 1.03 (0.93–1.14)[,g] mortality from stroke: 1.06 (0.88–1.29)[,g] CVD: 1.06 (0.99–1.13), stroke: 1.00 (0.90–1.12)	8 (3/2/3)
Chien 2005 Taiwan[20]	PC	3553[c] (1673/1880) patients	Per 1 SD; M: ≥7.7 mg/dL, F: ≥6.6 mg/dL	≥35	8.5 (mean), 9.0 (median)	86 incident coronary heart disease and 155 incident stroke events	Multivariable[d]	Age, CHD, SBP, BMI, diabetes status, HDL cholesterol, LDL cholesterol, smoking and drinking history. Stroke: added LVH and AF history	CHD: 1.26 (0.95–1.68)[,g] stroke: 1.27 (1.05–1.55)[g]	8 (3/2/3)
Iwashima 2006 Japan[21]	PC	619 (296/323) hypertensive patients free of CVD	M: 374.7 μmol/L (6.30 mg/dL), F: 303.3 μmol/L (5.10 mg/dL)	61, SD: 0.7; M: 60.2, F: 62.5	2.8 (mean)	28 patients developed cardiovascular disease	Multivariable[d]	Age, sex, duration of hypertension, BMI, DBP and SBP, heart rate, cholesterol, TG, HDL, Ccr, CRP, smoking, HOMA index, pulse pressure, and diabetes	CVD: 1.14 (0.48–2.47)[h]	9 (4/2/3)
Chen 2009 Taiwan[22]	PC	29,421 (13,475/15,946) hypertensive patients of 90,393 (41,897/48,514)	7.0 mg/dL; upper quartile: >9 mg/dL	51.5 (≥35), SD: 11.5 for all, 58 for hypertensive patients	8.2 (mean), SD: 1.3	3272 total deaths, 882 cardiovascular deaths	Multivariable[d]	Age, sex, BMI, cholesterol, TG, diabetes, hypertension, heavy cigarette smoking, and frequent alcohol consumption	Mortality: 1.15 (1.10–1.28)[,h] mortality from CVD: 1.44 (1.20–1.70)[h]	8 (3/2/3)
Wiik 2010 Norway[23]	PC in RCT	7489 (3437/4052) patients with hypertension and ECGc LVH	Per 1.3 mg/dL; upper quartile: 6.35–11.93 mg/dL	66.9 (55–80)	4.9 (mean), SD: 0.8	522 new-onset diabetes	Multivariable[d]	Treatment with losartan vs atenolol, baseline serum glucose, urinary albumin/creatinine ratio, eGFR and Framingham risk score, BMI, HDL, maximum dose hydrochlorothiazide, time-varying SBP, DBP, and LVH	Diabetes: 1.29 (1.18–1.42)[,g] 1.48 (1.22–1.80)[h]	8 (3/2/3)

TABLE I. Characteristics of the 17 Included Studies (Continued)

Author, Year, Country	Study Design	Study Population (M/F)	Uric Acid Cutoff/Upper Quartile[a]	Mean Age (range), y	Follow-Up, y	Prognostic Events	Model	Variables Adjusted	Risk Estimates[f] (95% CI)	Study Quality[k]
Viazzi 2011 Italy[24]	PC	758 (56% men) untreated hypertensive patients	M: 420 μmol/L (7.06 mg/dL), F: 318 μmol/L (5.34 mg/dL)	49, SD: 10	11.0 (median)	42 new-onset diabetes	Multivariable[d]	Age, sex, eGFR, components of MS and MS as a whole	Diabetes: 2.78 (1.35–5.70)[h]	9 (4/2/3)
Kawai 2012 Japan[25]	PC	669 (369/300) patients with essential hypertension	Per 1 mg/dL; upper quartile: >8.0 mg/dL	61.9, SD: 0.5	7.1 (mean)	71 strokes, 58 cardiovascular disease events, 64 deaths	Multivariable[di]	Age, sex, diabetes mellitus, dyslipidemia, systolic BP	CVD: 1.30 (1.07–1.58)[·g] stroke: 1.08 (0.90–1.30),[g] mortality: 1.23 (1.01–1.50)[g]	8 (4/2/2)
Perticone 2013 Italy[26]	PC	500 (189/311) uncomplicated hypertensive patients	Per 1 mg/dL	47.3	7.3 (median)	54 new cases of diabetes	Multivariable[d]	Age, HOMA index, ACh-stimulated FBF, CRP, CRP and ACh-stimulated FBF interaction	Diabetes: 1.23 (1.04–1.46)[g]	9 (4/2/3)
Dawson 2013 UK[29]	RC	6984 (3307/3677) patients with treated hypertension	Upper quartile: M: ≥0.45 mmol/L (7.56 mg/dL), F: ≥0.37 mmol/L (6.22 mg/dL)	50.3; 46.69 (M), 50.86 (F)	≥5	2243 all-cause mortality (1285, 958 cardiovascular and noncardiovascular mortality, respectively)	Multivariable[d]	Age, epochs, SBP, DBP, BMI, smoking, alcohol use, eGFR, chronic kidney disease status, baseline CVD, and stratified for diuretics use	Mortality: 1.05 (0.92–1.19)[·h,j] mortality from CVD: 1.03 (0.85–1.21)[h,j] mortality from stroke: 0.72 (0.45–1.10)[h,j]	8 (3/2/3)
Turak 2014 Turkey[27]	PC	921 (501/420) essential hypertensive patients	Per 1 mg/dL; upper quartile: M: >6.4 mg/dL, F: >6.0 mg/dL	57.9	3.3 (median)	103 cardiovascular events	Multivariable[d]	Age, sex, diabetes, hypertension status, smoking status, history of aortic aneurysm, CHD or PAD, TG, MBPS, SBP, eGFR	CVD: 1.38 (1.15–1.67)[·g] 2.75 (1.29–5.88)[h]	9 (4/2/3)

Abbreviations: Ach, acetylcholine; AF, atrial fibrillation; BMI, body mass index; Ccr, creatinine clearance; CHD, coronary heart disease; CRP, C-reactive protein; CVD, cardiovascular disease; ECG, electrocardiogram; eGFR, estimated glomerular filtration rate; FBF, forearm blood flow; HDL/LDL, high-/low-density lipoprotein; HDFP, Hypertension Detection and Follow-up Program Cooperative Research Group; HOMA, homeostasis Model Assessment; LVH, left ventricular hypertrophy; MBPS, early morning blood pressure surge; M/F, male/female; MHT, malignant-phase hypertension; MI, myocardial infarction; MS, metabolic syndrome; NA, not adjusted; PAD, peripheral artery disease; PC/RC, prospective/retrospective cohort; RCT, randomized controlled trial; SBP/DBP, systolic/diastolic blood pressure; SD, standard deviation; TG, triglyceride. [a]1 mg/dL=0.05948 mmol/L=59.48 μmol/L. [b]A multicenter randomized, placebo-controlled, double-blind intervention trial in Europe. [c]Total number of patients in the study, without specific number of hypertensive patients. [d]Cox proportional hazards regression model. [e]Risk ratio (RR) imputed with primary data reported in original article using the calculator in RevMan (Review Manager version 5.2, London, England). [f]Risk estimates show only the RRs for these crude models and adjusted hazard ratios (HRs) for multivariable models. [g]Uric acid was treated as a continuous variable. [h]Uric acid was treated as a categorical or binary variable. [i]Two Cox regression models existed and we chose one that adjusted these traditional factors for cardiovascular and mortality rather than the other that adjusted factors related to uric acid. [j]Estimates reported were stratified by sex, therefore we used fixed effects to pool them before meta-analysis. [k]The methodological scores of study quality were based on the Newcastle-Ottawa Scale.

were a total of 82,419 participants (117–29,421 participants), aged 16 to 85 years, with a mean or median follow-up duration of 2.0 to 11.0 years. Conditions of hypertension varied among included studies with isolated systolic hypertension in three studies,[16,18,19] diastolic hypertension in one study,[14] malignant hypertension in one study,[28] a limited range of systolic BP (160–200 mm Hg) and diastolic BP (95–115 mm Hg) in one study,[23] and no restrictions in 11 studies in which six studies[15,17,20–22,26] defined hypertension as systolic BP ≥140 mm Hg and diastolic BP≥90 mm Hg and the other five studies did not report their criteria.[13,24,25,27,29] Table II shows the unadjusted risk estimates from studies that reported both adjusted and unadjusted data.

The methodological quality of the 17 included studies was moderate to high, with NOS scores varying from 6 to 9 and a median of 8.

Hyperuricemia and Prognoses of Hypertension

Among the 17 eligible studies, UA was presented as categorical data (binary or quartiles) in 10 studies,[13,14,16,17,20–22,24,28,29] continuous data in four studies,[18,19,25,26] and both in three studies.[15,23,27] The adverse outcomes in our meta-analysis included CVDs, stroke, all-cause mortality (including studies that reported mortality from CVDs and/or stroke), and diabetes.

Hyperuricemia and CVDs. Ten studies (26,329 patients) assessed the effects of hyperuricemia on the development of CVDs in hypertensive patients. Of them, six provided categorical data[13,15–17,21,27] and 6 provided continuous data.[15,18–20,25,27] Pooled HRs from unadjusted data were 1.51 (95% CI, 1.28–1.79; I^2=37.2%) for categorical data and 1.10 (95% CI, 1.04–1.18; I^2=31.4%) for continuous data. Four of six sets with categorical data and all sets with continuous data provided adjusted effect size. There was significant heterogeneity among the adjusted continuous data (I^2=66.9%, P=.010) and nonsignificant heterogeneity among the categorical data (I^2=25.3%, P=.259). Random-effects model meta-analysis suggested that hyperuricemia in terms of both adjusted categorical and continuous data could significantly increase the risk of CVD development in patients with hypertension (HR=1.17, 95% CI, 1.07–1.27; HR=1.51, 95% CI, 1.13–2.03, respectively) (Figure 2).

Hyperuricemia and Stroke. Six cohort studies (15,091 patients) evaluated the effects of hyperuricemia on the risk of stroke in hypertensive patients.[13,16,18–20,25] Among the six studies, four provided adjusted continuous data,[18–20,25] one provided adjusted categorical data (HR=0.85; 95% CI 0.57–1.28),[16] and five provided unadjusted data (two categorical and three continuous).[13,18–20,25] Pooled results showed that

TABLE II. Unadjusted Risk Estimates for Studies With Both Adjusted and Unadjusted Data

Author, Year, Country	Variable Type	Prognostic Events	Effect Size	Risk Estimates (95%CI)	Model
Alderman 1999 USA[15]	Categorical[a]	CVD	RR	1.48 (1.18–1.86)	Age and sex adjusted
Franse 2000 USA[16]	Categorical[a]	CVD	HR	1.32 (1.06–1.64)	Age, sex, and race adjusted
		Stroke		0.92 (0.65–1.31)	
		Mortality		1.05 (0.79–1.40)	
Wang 2001 China[18]	Continuous, 50 μmol/L increase	CVD	HR	1.10 (1.02–1.19)	Univariate Cox model
		Stroke		1.07 (0.97–1.18)	
		Mortality		1.08 (1.00–1.18)	
		CVD mortality		1.17 (1.06–1.30)	
		Stroke mortality		1.29 (1.12–1.50)	
De Leeuw 2002 Europe[19]	Continuous, 50 μmol/L increase	CVD	HR	1.08 (1.02–1.15)	Univariate Cox model
		Stroke		1.02 (0.92–1.13)	
		Mortality		1.04 (0.97–1.11)	
		CVD mortality		1.05 (0.96–1.16)	
		Stroke mortality		1.08 (0.90–1.29)	
Chien 2005 Taiwan[20]	Continuous, 1 SD increase	CVD	HR	1.34 (1.05–1.70)	Age adjusted
		Stroke		1.33 (1.12–1.59)	
Iwashima 2006 Japan[21]	Binary (male: 6.30 mg/dL, female: 5.10 mg/dL)	CVD	HR	1.01 (0.43–2.17)	Univariate Cox model
Wiik 2010 Norway[23]	Continuous, 1.3 mg/dL	Diabetes	HR	1.43 (1.32–1.55)	Univariate Cox model
	Categorical[a]			3.65 (2.73–4.89)	
Viazi 2011 Italy[24]	Binary (male: 7.06 mg/dL, female: 5.34 mg/dL)	Diabetes	HR	3.65 (1.99–6.69)	Univariate Cox model
Turak 2014 Turkey[27]	Continuous	CVD	HR	1.72 (1.44–2.06)	Unadjusted Cox model

Abbreviations: CVD, cardiovascular disease; HR, hazards ratio; RR, risk ratio; SD, standard deviation. [a]The highest quartile compared with the lowest quartile of uric acid level.

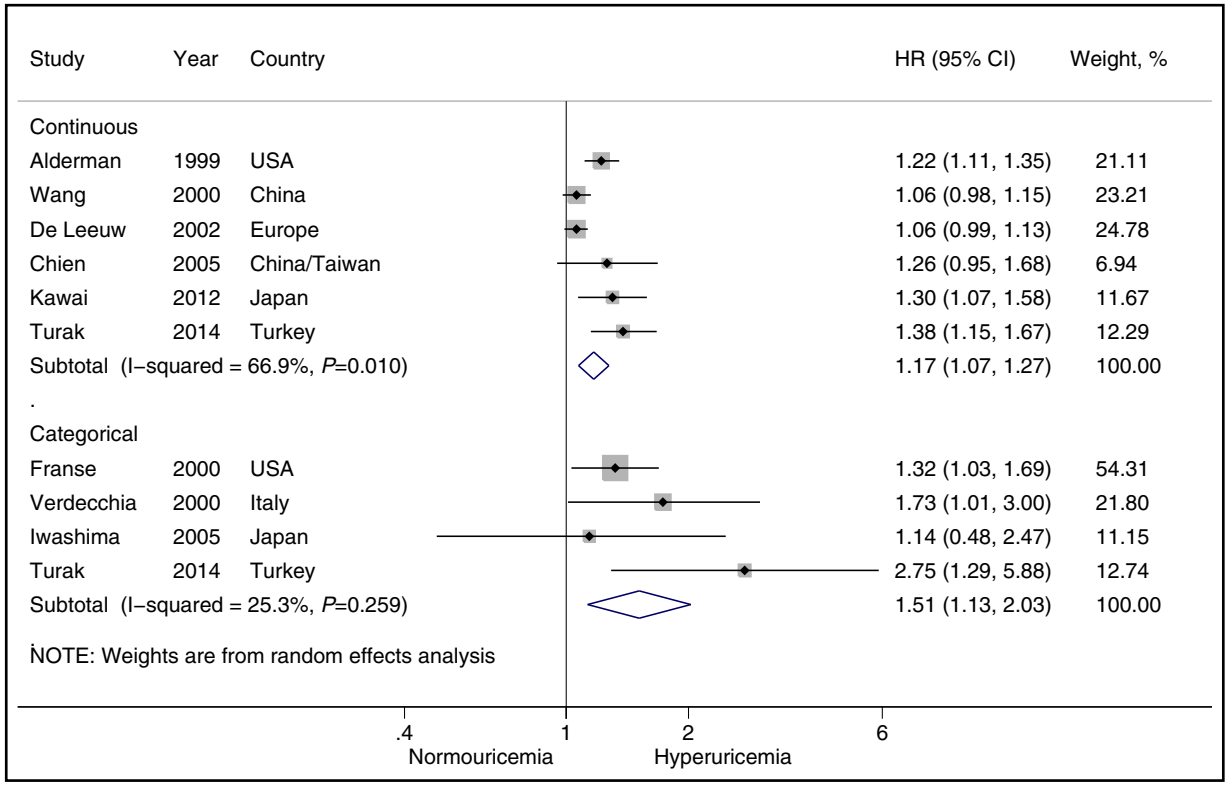

FIGURE 2. Hyperuricemia and risk of cardiovascular disease in hypertensive patients from adjusted data. HR indicates hazard ratio; CI, confidence interval.

hyperuricemia in terms of either unadjusted categorical data (HR=0.94; 95% CI, 0.67–1.33; I^2=0.0%) or continuous data (adjusted HR=1.06; 95% CI, 0.96–1.16; I^2=33.9%; unadjusted HR=1.11; 95% CI, 0.98–1.16) did not increase the risk of stroke in hypertensive patients (Figure S1).

Hyperuricemia and Mortality. The impact of hyperuricemia on mortality could be presented in three ways: all-cause mortality (10 studies, 60,601 patients), mortality from CVDs (five studies, 44,667 patients), and stroke (three studies, 13,409 patients).

For all-cause mortality, seven studies provided categorical data[13,14,16,17,22,28,29] and three provided continuous data.[18,19,25] Meta-analysis with random-effects model suggested that hyperuricemia was associated with an increased risk of all-cause mortality (categorical data: unadjusted HR=1.49; 95% CI, 1.03–2.16; I^2=72.8%; adjusted HR=1.12; 95% CI, 1.02–1.23; I^2=26.5%; unadjusted continuous data: HR=1.06; 95% CI, 1.00–1.11; I^2=0.0%) except the pooled result from adjusted continuous data (HR=1.05; 95% CI, 0.98–1.13; I^2=27.7%) (Figure 3).

For mortality from CVDs, three studies provided only adjusted categorical data[17,22,29] and two provided continuous data.[18,19] The pooled result suggested a consistent relationship from both categorical and continuous data (adjusted categorical data: HR=1.31; 95% CI, 0.96–1.78; I^2=77.6%; continuous data: unadjusted HR=1.11, 95% CI, 1.00–1.23; I^2=56.9%; adjusted HR=1.08; 95% CI, 0.98–1.19; I^2=43.4%) (Figure S2).

For mortality from stroke, two studies provided both adjusted and unadjusted continuous data[18,19] and one provided only adjusted categorical data[29] (HR=0.72; 95% CI, 0.48–1.07). Except for a borderline effect from unadjusted continuous data (HR=1.19; 95% CI, 1.00–1.42; I^2=55.7%), results from adjusted continuous data showed a nonsignificant association between hyperuricemia and mortality from stroke (HR=1.20; 95% CI, 0.95–1.51; I^2=70.5%) (Figure S3).

Hyperuricemia and Incident Diabetes. Three cohort studies with 8747 hypertensive patients assessed the effects of hyperuricemia on the development of new-onset diabetes (NOD),[23,24,26] among which two studies provided categorical data[23,24] and two provided continuous data.[23,26] Meta-analysis with random-effects model revealed that both categorical and continuous data could significantly increase the risk of NOD in hypertensive patients (categorical data: unadjusted HR=3.65, 95% CI, 2.81–4.75; adjusted HR=1.84; 95% CI, 1.02–3.30; I^2=63.5%; continuous data: unadjusted HR=1.43; 95% CI, 1.32–1.55; adjusted HR, 1.28; 95% CI, 1.18–1.38; I^2=0.0%) (Figure 4).

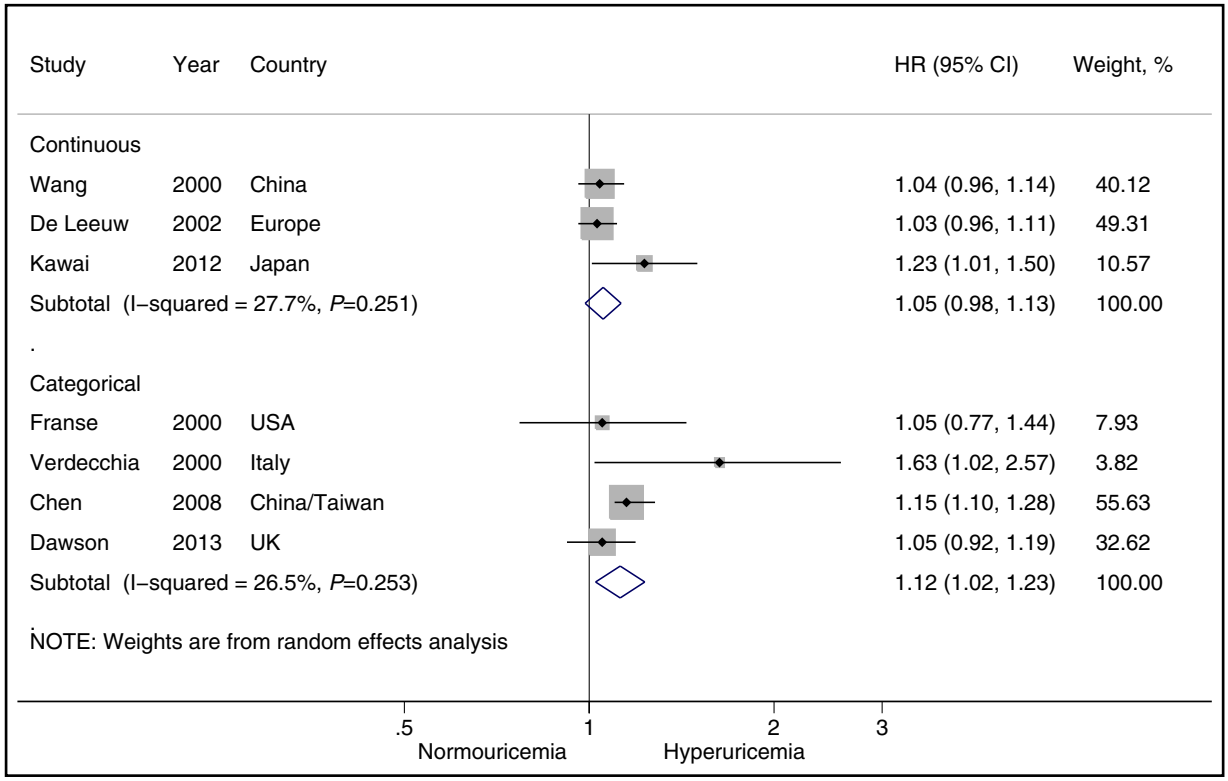

FIGURE 3. Hyperuricemia and all-cause mortality in hypertensive patients from adjusted data. HR indicates hazard ratio; CI, confidence interval.

Dose-Response Relationship

Ten studies that divided SUA levels into at least three groups were identified to explore the relationship between SUA and outcomes,[15–19,22,23,25,27,29] among which four studies provided numerical results[16,25,27,29] and six reported only graphic results.[15,17–19,22,23] Because of limited data and great differences among the cutoff points of SUA levels, we did not pool the data with meta-analysis. Almost all the results suggested that a higher category of SUA level was associated with a higher risk of complications in hypertensive patients except one study that did not find this relationship in male participants.[29]

Heterogeneity Among Included Studies

Unfortunately, because of the differences in the characteristics of participants, definitions of either hypertension or hyperuricemia and the small number of studies under each prognostic outcome, we could not explore the sources of heterogeneity with subgroup analysis or meta-regression according to our prespecified procedures.

Publication Bias and Funnel Plots

Owing to the small number of included studies under each outcome, with a maximum of seven studies investigating CVDs and all-cause mortality, the graphical or statistical assessment of publication bias was not sensitive.[30]

DISCUSSION

In the present systematic review of 17 studies, pooled results from random-effects model indicated that hyperuricemia could increase the risk of CVDs and incident diabetes in hypertensive patients. Whereas, except the result of all-cause mortality from categorical data (HR=1.12; 95% CI, 1.02–1.23), although not statistically significant, there was an increased tendency of risk in terms of stroke (continuous data: HR=1.06; 95% CI, 0.98–1.16) and all-cause mortality from continuous data (HR=1.05; 95% CI, 0.98–1.13).

To our knowledge, our systematic review and meta-analyses is the first to explore the prognostic values of hyperuricemia on the development of complications in hypertensive patients. Our findings are supported by previous interventional and observational studies relevant to the effects of urate-lowering drugs on both surrogate and hard cardiovascular endpoints in hypertensive patients with hyperuricemia. In a 10-week randomized placebo-controlled crossover trial conducted in patients with newly diagnosed stage 1 primary hypertension with hyperuricemia (SUA ≥6 mg/dL), allopurinol showed a greater mean decrease of 5 mm Hg in systolic BP and a 2.5 mm Hg decrease in

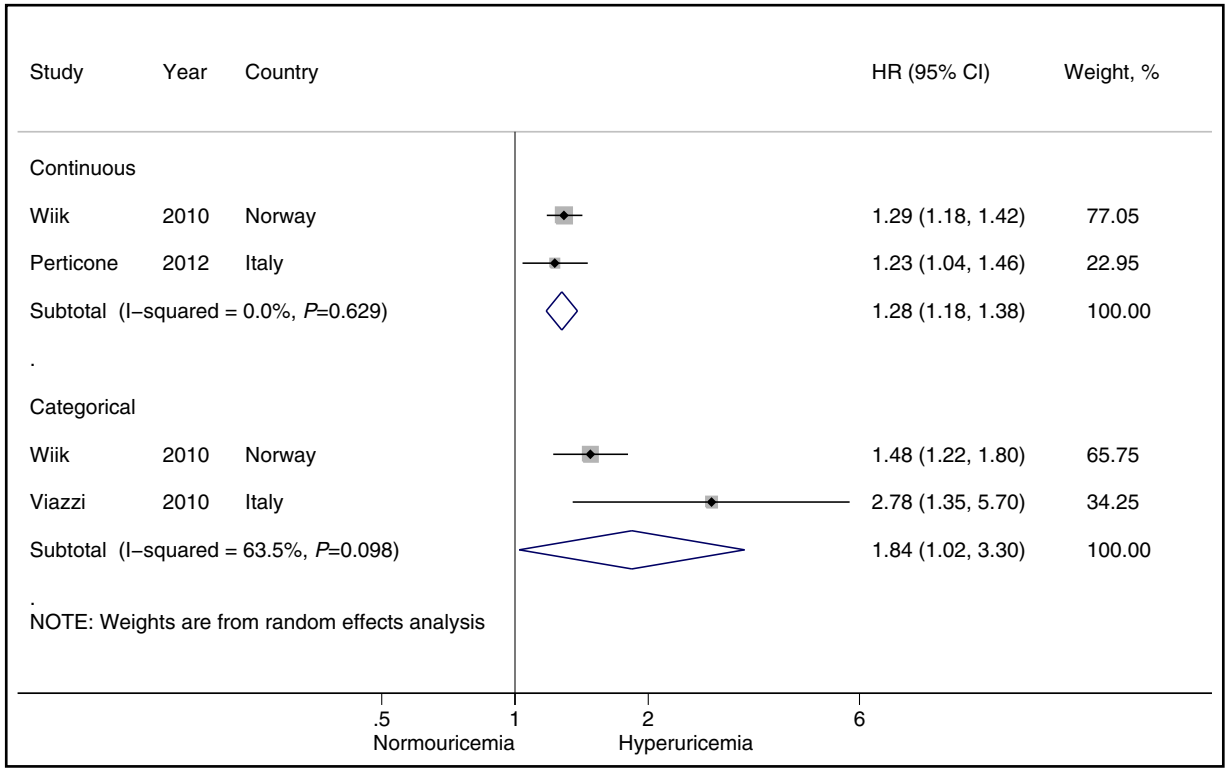

FIGURE 4. Hyperuricemia and risk of diabetes in hypertensive patients from adjusted data. HR indicates hazard ratio; CI, confidence interval.

diastolic BP over placebo. the differences were even greater according to ambulatory BP, with a 7 mm Hg greater decline in systolic BP and a 4 mm Hg greater decline in diastolic BP.[31] A subsequent meta-analysis of 10 clinical studies (nine RCTs and one prospective study) concluded that allopurinol could modestly but significantly decrease diastolic BP by 3.3 mm Hg and diastolic BP by 1.3 mm Hg.[32] A recently published retrospective observational study based on a registered database found that allopurinol use was associated with a significantly lower risk of both stroke (HR=0.50; 95% CI, 0.32–0.80) and cardiac events (HR=0.61; 95% CI, 0.43–0.87) in older adults with hypertension, particularly at higher doses. The findings of this study highlight the potential of a urate-lowering strategy in protecting against cardiovascular events and support the conduct of prospective clinical endpoint studies in hypertensive patients.[33] Furthermore, several meta-analyses have also suggested beneficial effects of UA-lowering therapy in slowing the progression of chronic kidney disease[34,35] and reducing left ventricular mass in patients with ischemic heart disease,[36] type 2 diabetes mellitus, and left ventricular hypertrophy.[37] However, there is no evidence from RCTs to support treatment of asymptomatic hyperuricemia even though xanthine oxidase (XO) inhibitors are indicated in some countries.[38] Since the available literature suggest that the best therapeutic approach to obtaining cardiovascular and renal benefits through UA lowering is through XO inhibition when hyperuricemia accompanies other cardiovascular risk factors, allopurinol and febuxostat are considered the most appropriate choices.

Although it is not fully understood what role serum UA plays in the prognosis of hypertension, it has been found that hyperuricemia is associated with a number of effects on the vascular endothelium, vessel walls, and kidney parenchyma. UA can functionally upregulate XO, which is a key enzyme in purine metabolism.[39] XO-derived reactive oxygen species and oxidative stress may play an important role in the negative effect of UA on the cardiovascular system.[40] UA can exert, along with extracellular antioxidant activity, an intracellular pro-oxidant effect. As a consequence, hyperuricemia has a detrimental effect on the vascular endothelium and may cause endothelial dysfunction that plays a key pathophysiologic role in the development and progression of atherosclerosis since it loses the ability to protect the vascular system by reducing its antiatherosclerotic and antithrombotic actions. UA also stimulates proliferation of the smooth muscle cells of the vascular system through activating the renin-angiotensin system and inhibiting the synthesis of nitric oxide, and finally can impair arterial function and cause arterial stiffening, a risk factor for hypertension and cardiovascular and cerebrovascular events.[41] Meanwhile, either animal models or epidemiological studies support high SUA as

a precursor of type 2 diabetes, in which SUA increases insulin resistance via inhibiting the synthesis and bioavailability of nitric oxide,[26,42] promoting oxidative stress and production of tumor necrosis factor α,[43] or via a direct cytotoxic effect on the pancreatic β-cell.[23]

STRENGTHS AND LIMITATIONS

Our review has several strengths. First, temporality: All of the 17 included studies were cohort studies or cohorts from RCTs, which denotes that an elevated UA precedes the development of complications in hypertensive patients. Second, dose-response relationship: In addition to the conventional unidirectional relationship, a U- or J-shaped distribution was revealed in three studies[15,17,19] that divided SUA into quartiles and showed a nadir in the second quartile ranged from 4.5 mg/dL to 6.5 mg/dL in men and 3.2 mg/dL to 5.2 mg/dL in women. Third, time-to-event effect: Instead of using the general measure RRs for estimating the effect size of the cohort studies, most of our included studies used time-to-event data analysis with HRs from Cox regression model,[44] which could take into consideration both event and time-to-event occurrence simultaneously.

Some limitations should also be noted. First, factors adjusted: Although the majority of our included studies used a multivariable analysis model to adjust demographic, baseline BP, medications, renal function, BMI, and some other factors, the number and factors adjusted were different among studies. There may be residual confounding factors that have effects on the findings. Second, heterogeneity: There was significant heterogeneity among the included studies. However, as a result of the limited number of included studies for each outcome, we could not identify the sources of heterogeneity Third, our meta-analysis only included cohort studies indexed in databases of MEDLINE, Embase, and CBM, and we did not search for unpublished studies, which might cause some extent publication bias and limit the generalizability to other settings.

CONCLUSIONS

Our systematic review reveals that elevated SUA or hyperuricemia could increase the risk of subsequent CVDs, all-cause mortality, and new-onset diabetes in hypertensive patients. However, it is a meta-analysis of observational studies and the results should be interpreted with caution because of the vulnerability of observational studies to the risk of biases. As most UA-lowering drugs are not benign drugs and the official definition of hyperuricemia is still disputed, additional large, high-quality interventional trials are needed to clarify whether urate-lowering therapy can improve the prognoses of hypertensive patients with hyperuricemia and to identify a clinically meaningful cutoff above which there is a substantial increase in cardiovascular and renal risk.

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Supporting Information

Additional Supporting Information may be found online in the supporting information tab for this article:

Figure S1. Hyperuricemia and risk of stroke in hypertensive patients from adjusted data.

Figure S2. Hyperuricemia and mortality from CVDs in hypertensive patients from adjusted data.

Figure S3. Hyperuricemia and mortality from stroke in hypertensive patients from adjusted data.