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REVIEW

Hyperuricemia and the risk of stroke incidence and mortality: A systematic review and meta-analysis

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ABSTRACT

Objectives: The relationship between hyperuricemia (HUA) and stroke remains controversial. In this systematic review, we discuss the association between HUA and stroke.

Materials and methods: The PubMed, Embase, Web of Science, and Cochrane Library were searched from their earliest records to March 13th, 2024, and additional papers were identified through a manual search. Prospective studies that provided a multivariate-adjusted estimate of the association between HUA and risk of stroke incidence and mortality, represented as relative risks (RRs) with 95% confidence intervals (CIs), were eligible.

Results: A total of 22 studies including 770,532 adults were eligible and included. Hyperuricemia was associated with a significantly increasing risk of both stroke incidence (pooled RR, 1.42; 95% CI, 1.31-1.53) and stroke mortality (pooled RR, 1.53; 95% CI, 1.18-1.99) in our meta-analyses. Relative risk of stroke incidence was as follows: females (pooled RR, 1.67; 95% CI, 1.44-1.92) and males (pooled RR, 1.13; 95% CI, 1.02-1.25). Relative risk of mortality was as follows: female (pooled RR, 1.41; 95% CI, 1.31-1.52) and males (pooled RR, 1.27; 95% CI, 1.20-1.34). For the risk of stroke mortality, the association between HUA and ischemic stroke (pooled RR, 1.39; 95% CI, 1.31-1.47) was more significant than that of hemorrhagic stroke (pooled RR, 1.13; 95% CI, 1.02-1.26).

Conclusion: Our study confirms an association between HUA and risk of stroke, which is more pronounced in females.

Keywords: Cohort study, hyperuricemia, meta-analysis, stroke.

Stroke is the leading cause of disability and the second most common cause of death worldwide. In 2019, stroke caused 6.6 million deaths and 143 million disabilities worldwide.[1] According to the World Health Organization (WHO), strokes would cause 7.8 million deaths by 2030.[2] Therefore, primary prevention of stroke has been a major public health priority. Hypertension, hyperlipidemia, diabetes mellitus, obesity, and smoking are the main risk factors for stroke.[2,3]

Serum uric acid (SUA) is an organic substance. It is the final product of purine metabolism in the body.[4] The hyperuricemia (HUA) is usually defined as SUA concentration in excess than 6.8 mg/dL,[5] although different studies have different definitions of HUA. The prevalence of HUA was high in mainland Chinese. The incidence of HUA in male was 21.6% (95% confidence interval [CI], 18.9 to 24.6%), and that in female was 8.6% (95% CI, 8.2 to 10.2%).[6] Hyperuricemia is the key to gout,[5] and a growing number of evidence indicates that HUA may be involved in the development of hypertension and chronic kidney disease.[7]

There have been several proposed pathophysiological mechanisms linking HUA to cardiovascular disease, including endothelial dysfunction, oxidative metabolism, platelet adhesiveness, and aggregation.[8-10] Current studies have shown an association between HUA and stroke incidence and mortality.[11-24] However, the results are still controversial,

probably due to a small sample size or different study designs.[25-31] Moreover, it is unclear whether the association between HUA and the risk of stroke differs between males and females, whether the association between HUA and the risk of stroke differs between stroke subtype.

In this meta-analysis, we reviewed prospective studies to investigate the association between HUA and stroke incidence and mortality, and whether sex and stroke subtype modifies the association. Clarifying this potential sex-specific and subtype-specific association is of great importance for precise and effective prevention of stroke.

MATERIALS AND METHODS

Search strategy

We complied data in accordance with the PRISMA guidelines. We ran a search on the search platform PubMed, EMBASE, Web of Science, and the Cochrane library (including CENTRAL) up to March 13th, 2024. The terms in PubMed searched were as follows: ("uric acid" OR "hyperuricemia" OR "urate" OR "hyperuric") AND ("stroke" OR "brain ischemic" OR "transient brain ischemia" OR "cerebra arterial disease"). We restricted the search to human studies. There were no language restrictions. The grey literature was also searched. In addition, we identified additional articles by manually searching the references of included articles.

Study selection

Two authors independently screened the titles, abstracts and/or full text of articles for potential inclusion. Any disagreements were resolved through consulting the third author.

Studies were considered eligible if they met the following inclusion criteria: *(i)* Prospective cohort study of the population; *(ii)* exposure to HUA; *(iii)* the literature reported stroke incidence or mortality, multivariate-adjusted relative risk (RR) values, and 95% CIs; *(iv)* having at least one year of follow-up; *(v)* participants without renal disease, stroke or other serious diseases, such as a tumor at the beginning of the study. Studies with the following conditions were excluded: *(i)* The study design was a non-prospective cohort study; *(ii)* unadjusted RRs and 95% CIs were reported; *(iii)* follow-up was less than one year; *(iv)* study populations had previous stroke or kidney disease. No uncertainty was found in included studies.

Main outcome variables

The following data were extracted from each included study: first author's surname, year of publication, study country, follow-up data, sample size, mean age, definition of outcome, and percentage of males, number of outcome events, and adjusted (included age, comorbidity, using of diuretics) RR.

Based on the adjusted RRs and 95% CIs published in each study, we examined the relationship between HUA levels and stroke risk. Odds ratios (ORs) and HRs were regarded as equivalent to RRs. Natural logarithms were used in every study to convert these values. When some studies included in our meta-analysis reported SUA levels using the International System of Units, we converted those measurements to conventional units by using a conversion rate of 16.81 (1 mg/dL= 59.48 μmol/L).

Risk of bias assessment

Study methodological quality was evaluated using the Newcastle-Ottawa Scale (NOS).[32] Cohort studies were scored according to three major aspects: selection of study groups (0-4 points), comparability of study groups (0-2 points), and measurement of the outcome (0-3 points). Better methodological quality is reflected in a higher score.

Analysis

We used the I^2 test to measure statistical heterogeneity between the studies. In effect estimates, the I^2 statistic describes the percentage of variance that is attributable to heterogeneity rather than chance. An I^2 statistic above 50% may indicate significant heterogeneity, and pooled analysis with random-effects model was done. There is considered to be less heterogeneous if I^2 is less than or equal to 50%, and pooled analysis with fixed-effects model was done.

To further investigate potential causes of heterogeneity, we carried out meta-regression and subgroup analysis, which were performed

Table 1. Characteristics of included cohort studies

				Participants (Male)								
	Author	Year	Country	n	%	Mean±SD	Range	Median	Min-Max	Follow-up (year)	Mean±SD	Hyperuricemia definition
Stroke incidence	Chien et al.[21]	2005	China	3,602	47.28		NA			11		M≥7.7 mg/dL F≥6.6 mg/dL
	Tu et al.[12]	2019	China	3,243	55	70.8±6.0					35.5±3.0 m	M>7.0 mg/dL F≥6.0 mg/dL
	Cheng et al.[22]	2021	China	29,974	61.49	47.2±13.9					5.78±0.83 year	≥6 mg/dL
	Hu et al.[30]	2021	China	11,841	45.67	62.95±9.14					612.14±32.12 day	M>420 μmol/L F>360 μmol/L
	Bos et al.[24]	2006	Netherlands	4,385	35.37			69.0	62.5-76.2	8.4		≥381 mmol/L
	Tscharre et al.[26]	2018	Austria	1,215	66.4	62.9±13.4					5.5±2.9 year	M>7.0 mg/dL F>6.0 mg/dL
	Jiménez et al.[28]	2016	USA	920	0			61		17		>6.8 mg/dL
	Hozawa et al.[31]	2006	USA	15,792	51.4			53.97		12.6		≥6.9 mg/dL
	Li et al.[33]	2020	Japan	13,420	39.01			55.03		23.1		M>6.7 mg/dL F>5.2 mg/dL
	Lehto et al.[17]	1998	Finland	1,017	54.18			58.05		7		>295 μmol/L
	Strasak et al.[14]	2008	Austria	28,613	0			62.3		15.2		≥5.41 mg/dL
	Chen et al.[23]	2009	China	90,393	46.33			51.5		7		>7 mg/dL
Stroke mortality	Sakata et al.[16]	2001	Japan	8,172	44	49.81±13.06				14		M≥386 mmol/L F≥291 mmol/L
	Tomita et al.[13]	2000	Japan	49,413	100		25-60			5.4		≥6.5 mg/dL
	Holme et al.[19]	2009	Sweden	417,734	52.95	48.15±11.76				11.8		M>362 mmol/L F>327 mmol/L
	You et al.[25]	2009	USA	15,583	48.28			55.8		7.4		>7.5 mg/dL
	Gerber et al.[20]	2006	Israel	9,125	100			49		23		>5.6 mg/dL
	Strasak et al.[15]	2008	Austria	83,683	100			41.6		13.6		>398.81 mmol/L
	Jee et al.[29]	2004	Korea	22,698	100			44.6		9		>414 mmol/L
	Sakata et al.[16]	2020	Japan	2,633	16.2			59.23		19		M>412 mmol/l F>311 mmol/L
	Kuo et al.[18]	2013	China	354,110	54.71			49.8		4.65		>7 mg/dL
	Zhang et al.[11]	2015	China	36,313	43.04			53.54		10		M>6.7 mg/dL F>5.1 mg/dL

SD: Standard deviation.

by sex and stroke type. As we identified sources of heterogeneity by meta-regression, no further sensitivity analyses were performed. Funnel plots and Egger's test were used to detect publication bias. Statistical analysis was performed using the STATA version 16.0 software (STATA Corp., College Station, TX, USA).

RESULTS

In total, 5,037 articles were identified from the initial the search platform search. The final analysis included 770,532 participants from 22 prospective cohort studies (Supplementary Figure 1).[11-23] The characteristics of the studies and their participants are presented in Table 1. Among the 22 included studies, three were performed in the United States,[25,28,31] seven from Europe,[14,15,17,19,20,24,26] and 12 from Asian countries.[11-13,16,18,21-23,27,29,30,33] The number of participants ranged from 920 in the study by Jiménez et al.[28] to 417,734 in the Apolipoprotein MOrtality RISk study (AMORIS) by Holme et al.[19] The duration of follow-up ranged from one year[30] to 23 years.[20,33] Of the 22 articles included, 15 covered sex. Eleven studies[11,12,19,21-25,27,30,33] included both males and females, three studies[15,20,29] only males, and one study only females.[28] Among these studies, 13 studies.[11,12,14,15,19,20,23,24,26,28,30,31,33] distinguished between ischemia and hemorrhagic strokes, while nine studies[13,16-18,21,22,25,27,29] mentioned either ischemia or hemorrhagic strokes. The definition of HUA varied among studies. The quality score of studies ranged from 6 to 9, overall quality of included studies was good.

The multivariate-adjusted RRs of stroke incidence in relation to HUA are presented in Figure 1. The HUA group had a higher stroke incidence than normouricemic individuals (pooled RR, 1.42; 95% CI, 1.31-1.53).[12,14,21-23,26,28,30,31,33] The multivariate-adjusted RRs of stroke mortality in relation to HUA are presented in Figure 2. The HUA group had a higher stroke mortality than normouricemic individuals (pooled RR, 1.53; 95% CI, 1.18-1.99).[11,13,15,16,18-20,25,27,29]

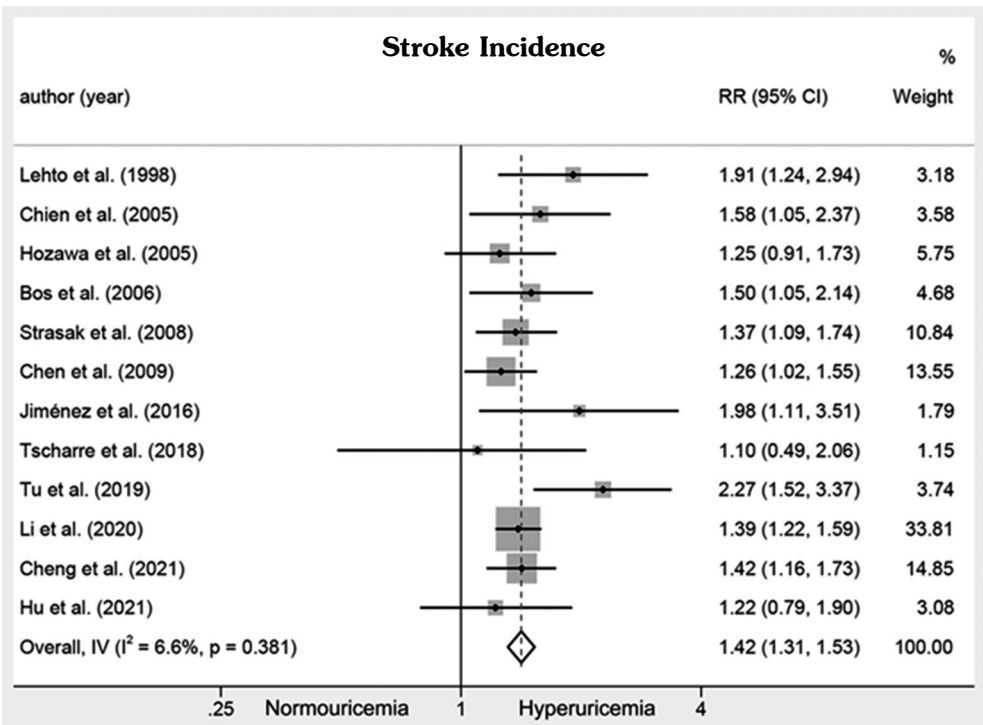

Figure 1. Fixed effects analysis of fully adjusted studies for the association between hyperuricemia and stroke incidence.

In the subgroup analysis of HUA and stroke incidence, there was no significant difference in sex between the groups. Female patients (pooled RR, 1.67; 95% CI, 1.44-1.92) were at a higher risk of stroke than male patients (pooled RR, 1.13; 95% CI, 1.02-1.25).[12,21-24,28,30,33] For a subgroup analysis for different types in stroke, there was no significant difference between ischemic and hemorrhagic stroke (p=0.846), (Figure 3).[12,14,23,24,26,28,30,31,33]

For a subgroup analysis of HUA and stroke mortality for different sexes, we found that the association also held for both sexes, and female patients (pooled RR, 1.41; 95% CI, 1.31-1.52) were at a higher risk of stroke mortality than male patients (pooled RR, 1.27; 95% CI, 1.20-1.34).[11,15,19,20,25,27,29] For a subgroup analysis for different stroke types, we found that the association also held for both stroke types. And the association between HUA and ischemic stroke (pooled RR, 1.39; 95% CI, 1.31-1.47) was higher than that of hemorrhagic stroke (pooled RR, 1.13; 95% CI, 1.02-1.26), (Figure 4).[11,15,19,20]

For stroke incidence, there was no statistically significant evidence of publication bias among the included studies by using the Egger's test (p=0.264). For stroke mortality, there was no publication bias either (p=0.371) (Supplementary Figure 2).

A meta-regression was carried out to investigate the predefined potential source of heterogeneity, as significant heterogeneity was found among the individual studies. The results of regression suggested that sex, ethnicity were not significant sources of heterogeneity of the mortality, while the follow-up time was a significant source of heterogeneity (p=0.039). We analyzed the duration of follow-up into two subgroups: those with more than 10 years of follow-up and those with less than 10 years of follow-up. The results showed that there was no statistically significant difference in the stroke incidence and follow-up time (p=0.589), there was a statistically significant difference between stroke mortality and follow-up time (p=0.013). After excluding the heterogeneous interference of follow-up time, the risk of stroke death in the HUA group was significantly increased compared with the normal uric acid group (pooled RR,1.79; 95% CI, 1.56-2.06), (Supplementary Figures 3, 4).

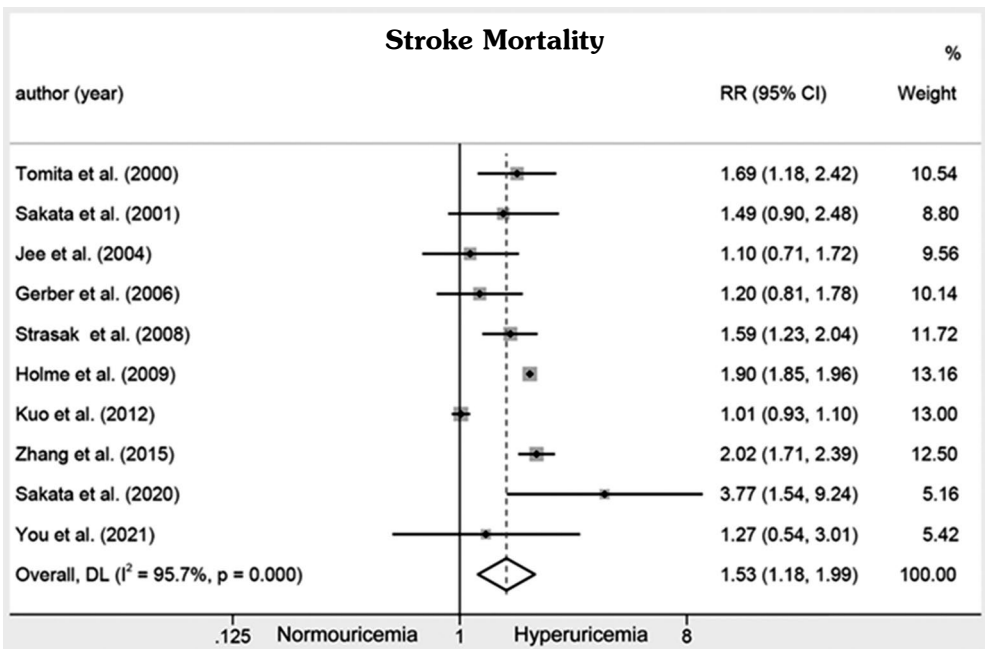

Figure 2. Random effects analysis of fully adjusted studies for the association between hyperuricemia and stroke mortality.

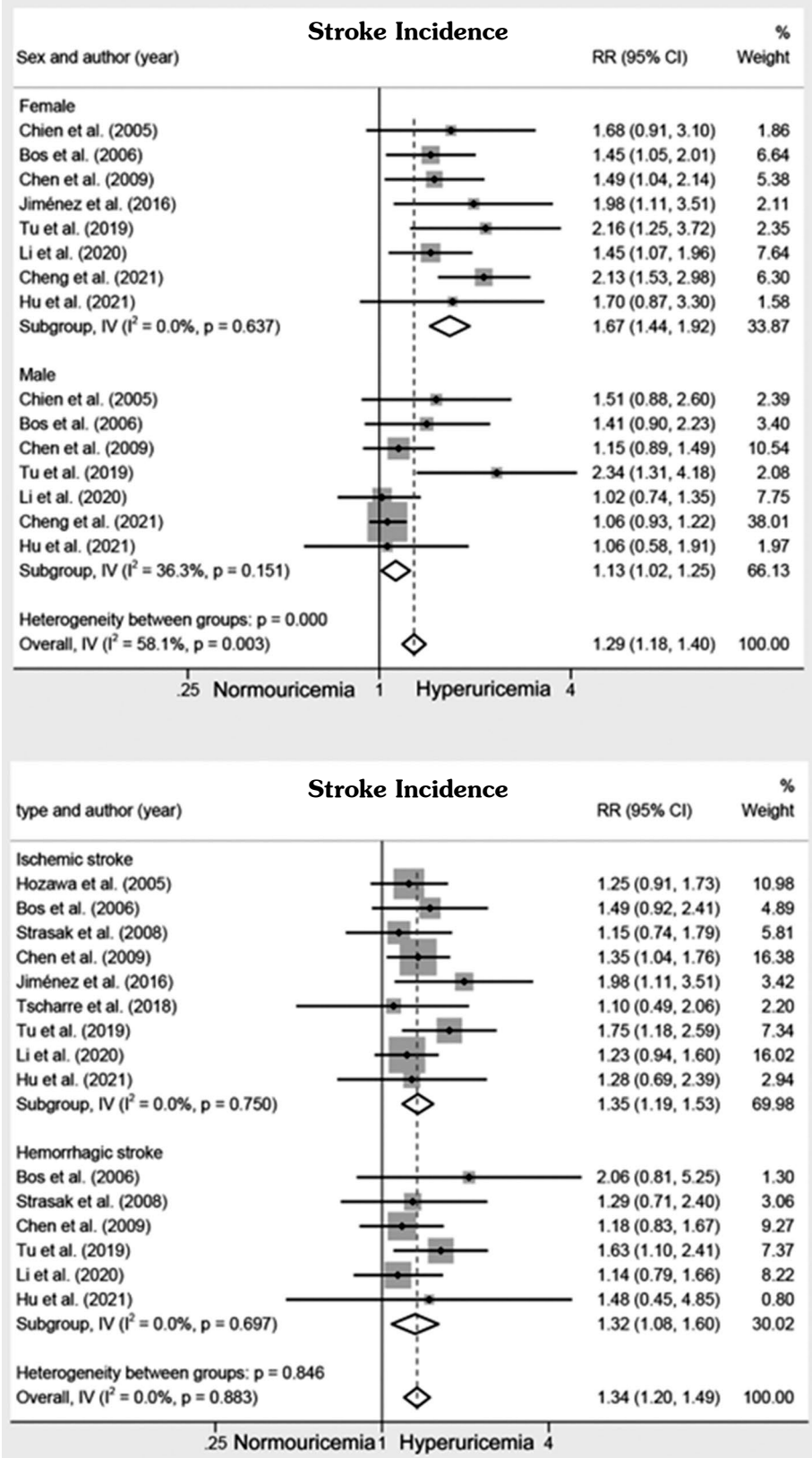

Figure 3. Fixed effects subgroup analysis of fully adjusted studies for the association between hyperuricemia and stroke incidence.

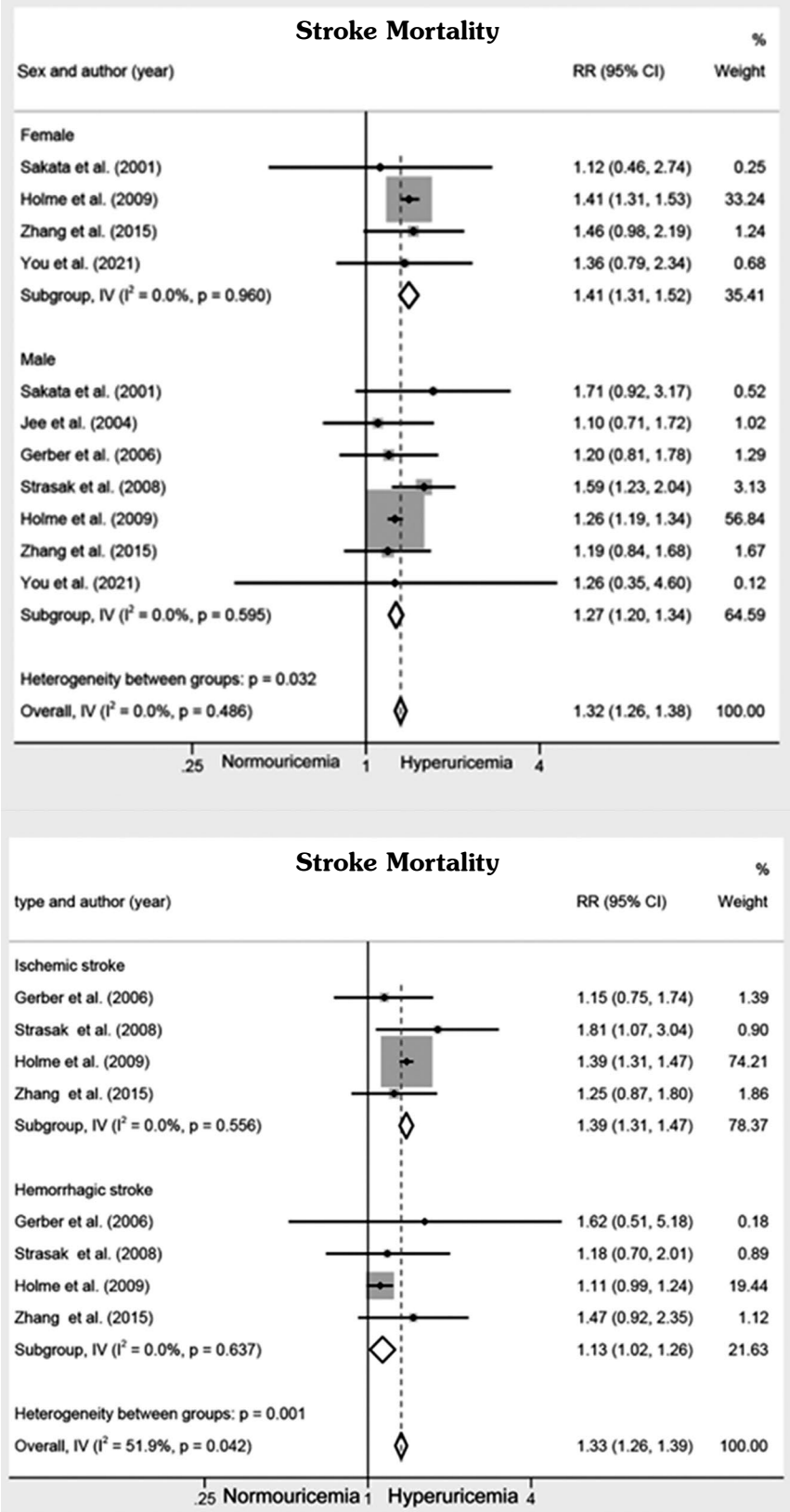

Figure 4. Fixed effects subgroup analysis of fully adjusted studies for the association between hyperuricemia and stroke mortality.

DISCUSSION

In this systematic review and meta-analysis, we summarized the relationship between HUA and stroke incidence and mortality including 22 studies with 770,532 participants. Pooled data showed that HUA had a significant risk of stroke incidence and mortality, and the risk was higher in females than males. In terms of stroke types, patients with HUA had a higher mortality risk of ischemic stroke than hemorrhagic stroke.

Stroke is regarded as a heterogeneous, multifactorial disease caused by atrial fibrillation, obesity, smoking, diabetes, high blood pressure, and other risk factors. Hyperuricemia plays a direct and indirect role in increasing the risk of stroke. The positive association of HUA with stroke incidence and mortality may be due to: firstly, uric acid may play a direct role in the development of atherosclerosis and indirectly lead to the occurrence of stroke.[34] Hyperuricemia can further promote the oxidation of low-density lipoprotein (LDL) cholesterol and lipid peroxidation. Lipid peroxidation leads to an increase in the generation of oxygen free radicals and their involvement in inflammatory reactions, thus affecting the function of vascular intimal smooth muscle. Fibrosis and thickening of the inner lining of the arteries occur, which promote the formation and progression of atherosclerosis.[35-37] Secondly, hypertension is a major risk factor for hemorrhagic stroke.[38,39] Some studies have suggested that hypertension may mediate the effect of HUA on stroke risk.[40-42] The mechanism may be due to that uric acid first activates the renin-angiotensin system (RAS) and inhibits nitric oxide (NO), leading to increased vascular resistance in the system, and then uric acid reduces renal blood flow by constricting the renal afferent arteriole and leads to sodium-sensitive hypertension.[43,44] Besides, uric acid can induce the production of vascular endothelial inflammatory factors and directly participate in the occurrence of stroke.[40,45,46] In all, numerous pathophysiological mechanisms, such as endothelial dysfunction,[45,46] oxidative metabolism, platelet adhesiveness, and aggregation, elevated circulating levels of systemic inflammatory mediators have been proposed to link HUA to cardiovascular disease.[40,42,44-52] The detailed mechanisms associated with HUA and stroke need to be further explored.

The prevalence of HUA in males is higher than that in females,[6] and the definition of HUA in males and females is not completely uniform, internationally. Therefore, we conducted a subgroup analysis to investigate the sex differences in the risk of stroke in patients with HUA. We found that the relationship between HUA and incidence and mortality of stroke were higher in females than in males. Undoubtedly, we believe that this may be due to the fact that estrogen may play a diminished heart-protective role in older women.[23,53] Estrogen has a protective effect on cardiovascular and cerebrovascular diseases, but this protective factor is lost with age. The decrease of estrogen level in postmenopausal women was accompanied by the increase of SUA level.[54] Yahyaoui et al.[55] demonstrated that the lower levels of uric acid in women were due to estrogen-induced increases in fractional excretion of uric acid. Therefore, elevated uric acid may be a sign of escaping hormonal protection.[23]

In this review, we assessed the differences between HUA and the risk of different types of stroke. There are two main types of stroke: ischemic stroke and hemorrhagic stroke, of which 79% of patients are ischemic stroke.[56,57] Our results showed that the association between HUA and the mortality of IS was stronger than that of hemorrhagic stroke. This finding is consistent with the findings of Strasak et al.[15] However, the specific mechanism is not clear, and some studies suggest that it may be because each of the above factors leading to stroke may potentially stimulate the cascade of clotting, leading to thrombosis and arterial occlusion, and eventually to the development of intracranial atherosclerosis.[58] There is also evidence that HUA may be an important predictor of atrial fibrillation. Elevated SUA also associated with impaired cerebrovascular tone and endothelial dysfunction may contribute to the occurrence of some ischemic changes, as they allow cerebrospinal fluid to cross the blood-brain barrier and allow interstitial water to accumulate, leading to the occurrence of

brain edema areas, leading to the occurrence of ischemic changes.[59-61]

Heterogeneity analysis of the included studies involving stroke mortality showed that the length of follow-up was responsible for the high heterogeneity. Therefore, the length of follow-up of the included references may indirectly affect the results of this meta-analysis. As it is a lengthy process from high-risk population to stroke onset or death, we recommend that studies should be followed as long as possible. We found that patients with longer follow-up were at a higher risk of death with longer follow-up, probably as longer follow-up was associated with more deaths.

Our study has some strengths. This meta-analysis included 22 studies with 770,532 participants. We excluded studies including patients with kidney disease and prior stroke, as stroke patients are at high risk of recurrent stroke,[62] and in patients with chronic kidney disease, SUA levels increase due to reduced clearance.[63] Besides, all RR values from the studies we extracted were adjusted, every study was high quality after assessing the quality of individual studies by using the NOS. Based on the above advantages, our results should be reliable.

Nonetheless, there are some limitations. First, the studies included in this meta-analysis were prospective cohort studies, including any observational studies, a causal relationship between HUA and stroke risk cannot fully be established. Second, the data extracted were limited, particularly the data that could be used for subgroup analysis was less. Third, there is a bias caused by English language restrictions. By conducting a non-language-restricted search of four significant electronic the search platforms, we attempted to reduce this bias. However, some non-English articles that have not been published in international journals may be overlooked.

In conclusion, our study confirms to some extent the association between HUA and stroke risk and mortality, showing differences between sex and stroke subtypes. In the future, more basic studies are needed to explain the possible physiological mechanism of HUA and stroke incidence. Furthermore, multi-center, double-blind, randomized-controlled trials are needed to explore the role of lowering HUA for stroke prevention.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions: Idea, data collection: H.J., Y.S.; Design: Y.L.; Control: H.J., R.L.; Analysis: Q.X.; Literature review: X.X.; Writing the article: Y.S.; Critical review: H.J., Y.L.; References and fundings: H.J., J.Y.; Materials: X.X.

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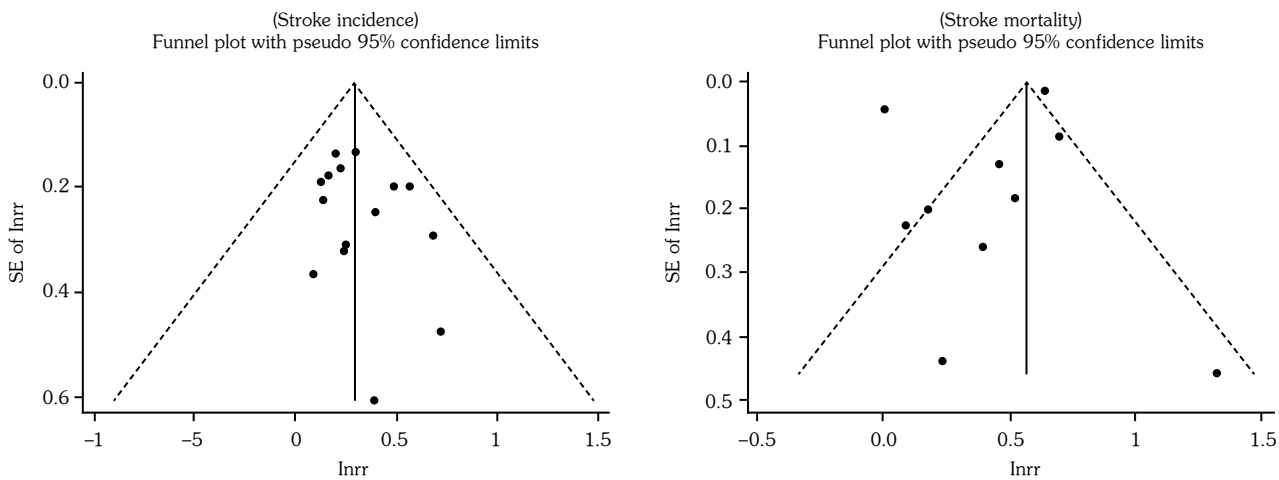
Supplementary Figure 1. PRISMA inclusion flow chart.

Supplementary Table 1. Quality assessment of included studies based on Newcastle-Ottawa Scale

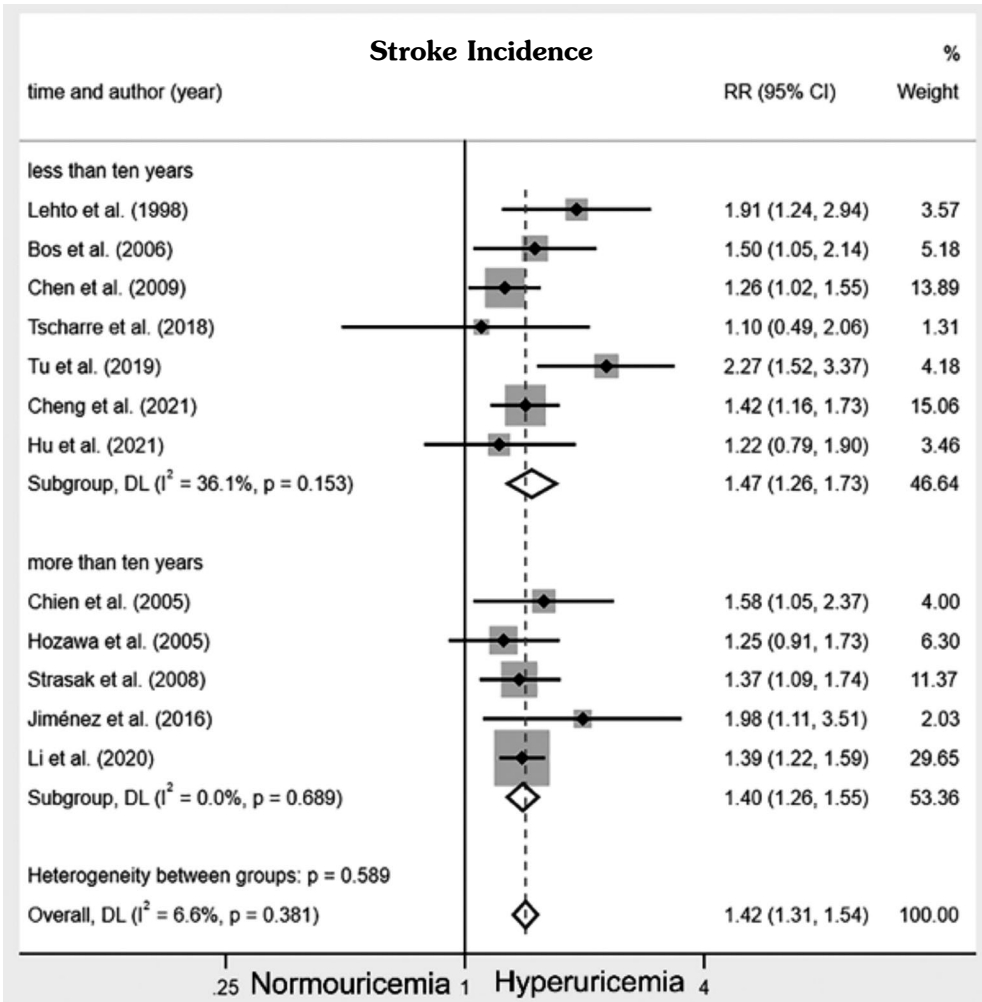
Author	Selection	Comparability	Outcome	NOS overall score
Chien et al.[21]	4	2	3	9
Sakata et al.[16]	4	2	3	9
Tu et al.[12]	4	2	2	8
Tomita et al.[13]	4	1	3	8
Cheng et al.[22]	4	2	2	8
Hu et al.[30]	4	2	2	8
Holme et al.[19]	4	1	2	7
Bos et al.[24]	4	2	2	8
Tscharre et al.[26]	3	2	1	6
You et al.[25]	4	2	2	8
Jiménez et al.[28]	3	2	2	7
Gerber et al.[20]	2	2	3	7
Zhang et al.[11]	3	2	3	8
Strasak et al.[14]	4	2	3	9
Jee et al.[29]	2	2	2	6
Hozawa et al.[31]	3	2	3	8
Li et al.[33]	2	2	3	7
Lehto et al.[17]	3	2	2	7
Strasak et al.[15]	4	2	3	9
Chen et al.[23]	3	2	2	7
Sakata et al.[27]	4	2	3	9
Kuo et al.[18]	2	2	2	6

NOS: Newcastle-Ottawa Scale.

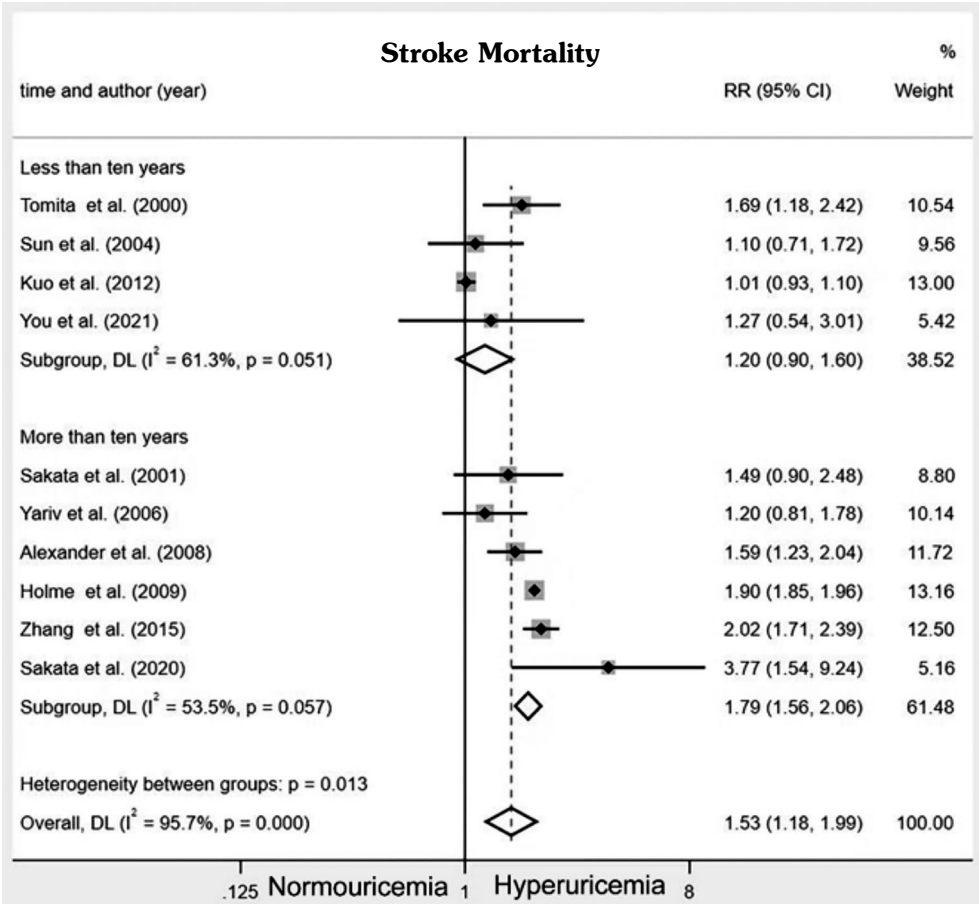


Supplementary Figure 2. Egger's funnel plot for publication bias in studies for stroke incidence and mortality.

SE: Standard error; lnrr: Natural logarithm of the risk ratio.



Supplementary Figure 3. Fixed effects subgroup analysis of fully adjusted studies for the association between hyperuricemia and stroke incidence (duration of follow-up).



Supplementary Figure 4. Fixed effects subgroup analysis of fully adjusted studies for the association between hyperuricemia and stroke mortality (duration of follow-up).