

REVIEW

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

Haiyan Jiang^{1,2,*}, Yunyi Su^{1,†}, Ruixue Liu¹, Xinyi Xu¹, Qi Xu¹, Jie Yang³, Yapeng Lin^{1,4}

¹School of Clinical Medicine, Chengdu Medical College, Chengdu, Sichuan Province, China

²Department of Rheumatology and Immunology, The First Affiliated Hospital of Chengdu Medical College, Chengdu, Sichuan Province, China ³Department of Neurology, Sichuan Academy of Medical Sciences, Sichuan Provincial People's Hospital, Chengdu, Sichuan Province, China ⁴Department of Neurology, The First Affiliated Hospital of Chengdu Medical College, Chengdu, Sichuan Province, China

Correspondence: Yapeng Lin, MD. **E-mail:** linyapengsjnk@163.com

Received: June 02, 2024 Accepted: August 05, 2024 Published online: March 17, 2025

* These authors contributed equally to this work.

Citation: Jiang H, Su Y, Liu R, Xu X, Xu Q, Yang J, et al. Hyperuricemia and the risk of stroke incidence and mortality: A systematic review and meta-analysis. Arch Rheumatol 2025;40(1):128-143. doi: 10.46497/ ArchRheumatol.2025.10808.

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes (http://creativecommons.org/ licenses/by-nc/4.0/).

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% Cl, 1.31-1.53) and stroke mortality (pooled RR, 1.53; 95% Cl, 1.18-1.99) in our meta-analyses. Relative risk of stroke incidence was as follows: females (pooled RR, 1.67; 95% Cl, 1.44-1.92) and males (pooled RR, 1.13; 95% Cl, 1.20-1.25). Relative risk of mortality was as follows: female (pooled RR, 1.41; 95% Cl, 1.31-1.52) and males (pooled RR, 1.27; 95% Cl, 1.20-1.34). For the risk of stroke mortality, the association between HUA and ischemic stroke (pooled RR, 1.3; 95% Cl, 1.31-1.47) was more significant than that of hemorrhagic stroke (pooled RR, 1.13; 95% Cl, 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 μ mol/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

| Participation Autor: Participation Autor: Var County Var Spani-6 Monts/6 Monts/6 </th <th>Tab</th> <th>Table 1. Characteristics of included cohort studies</th> <th>or include</th> <th>a conort stud</th> <th>les</th> <th></th> <th></th> <th></th> <th></th> <th></th> <th></th> <th></th> <th></th> | Tab | Table 1. Characteristics of included cohort studies | or include | a conort stud | les | | | | | | | | | | | | | | | | | | | | | | | | | | |
|---|-----------------------------|---|---------------------------|--------------------------|-------------------------|------------------------|-----------------------|----------------------|---------------------|--------------------|--|---|------------------------------|--|---|------|-----|--|-----|--------------------------|------|-------------|-------|-------|--|--|------|-----------|-----|--|-------------|
| dthota lt county lt county lt lt< lt lt< lt lt< lt< lt< lt< | | | | | Participar | nts (Male) | | | | | | | | | | | | | | | | | | | | | | | | | |
| Chene tal. ¹¹ 2005 Chua 3.02 7.28 N 11 1 Tutal. ¹¹ 2015 Chua 3.243 55 7.08±0 ¹ 1 1 3.55±3.0 m Tutal. ¹¹ 2021 Chua 3.243 55 7.08±0 ¹ 1 1 3.55±3.0 m Hutal. ¹¹ 2021 Chua 11,841 6.16 2.95±1.4 1 1 3.55±3.0 m Hutal. ¹¹ 2021 Chua 11,841 6.17 2.95±1.4 1 1 1 1 Hutal. ¹¹ 2010 Nether 13.1 6.29±1.4 1 </td <td></td> <td>Author</td> <td>Year</td> <td>Country</td> <td>с</td> <td>%</td> <td>Mean±SD</td> <td>Range</td> <td>Median</td> <td>Min-Max</td> <td>Follow-up (year)</td> <td>Mean±SD</td> <td>Hyperuricemia definition</td> | | Author | Year | Country | с | % | Mean±SD | Range | Median | Min-Max | Follow-up (year) | Mean±SD | Hyperuricemia definition | | | | | | | | | | | | | | | | | | |
| | | Chien et al. ²¹ | 2005 | China | 3,602 | 47.28 | | NA | | | 11 | | M≥7.7 mg/dL F≥6.6 mg/dL | | | | | | | | | | | | | | | | | | |
| Chemeteral ² Cuta Space Space Space Space Hottal ² Cuta Luta Space Space Space Space Space Hottal ² Cuta Luta Space Space Space Space Space Space Bostal ³ Cuta Luta Space Space Space Space Space Space Hottal ³ Cuta Space Space <td< td=""><td></td><td>Tu et al.¹²</td><td>2019</td><td>China</td><td>3,243</td><td>55</td><td>70.8±6.0</td><td></td><td></td><td></td><td></td><td>35.5±3.0 m</td><td>M>7.0 mg/dL F≥6.0 mg/dL</td></td<> | | 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 | | | | | | | | | | | | | | | | | | |
| Hotela 2021 China 11341 5535 5535 5535 5537 5143 51433212 day Bsetal ¹⁴ 2006 Nethends 4385 5337 5337 5337 534 534 Tehmeretal ³⁶ 2016 Ush 1215 664 629±134 5 55259 yar Tehmeretal ³⁶ 2016 Ush 1215 647 5397 5 5529 yar Tehmeretal ³⁶ 2016 Ush 1316 643 5 5 5 5 5 Utetal ³¹⁰ 2026 1342 301 643 5 | | Cheng et al. ²² | 2021 | China | 29,974 | 61.49 | 47.2±13.9 | | | | | 5.78±0.83 year | ≥6 mg/dL | | | | | | | | | | | | | | | | | | |
| Bosetal ^{3e} 2006 Nethendands 4.385 5.37 5.37 6.00 6.5.762 8.4 5.5.29 year Techner et al ^{3e} 2016 Netri 1.115 6.04 6.29.134 7 5.5.29 year 5.5.29 year Jubriber et al ^{3e} 2016 USA 57.92 51.4 7 6.0 6.5.76 8.4 5.5.29 year Jubriber et al ^{3e} 2016 USA 55.79 51.4 7 7 7 7 Let al ^{3e} 2016 USA 57.92 51.4 7 55.05 7 7 7 7 Let al ^{3e} 2020 USA 54.1 54.1 55.05 7 7 7 7 Let al ^{3e} 2031 1017 54.15 7 7 7 7 7 Let al ^{3e} 2016 Abrit 54.15 7 7 7 7 Let al ^{3e} 2017 USA 2018 2018 2018 7 | 90 | 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 | | | | | | | | | | | | | | | | | | |
| Ticken et al.** 2018 Austrial 1,215 6.64 6.29±13.4 $ 5.5±2.9 term Ticken et al.** 2016 USA 920 0 <<<<<<<<<<< < < < < < <<$ | $<<<<<<<<<< < < < < < <<$ | $<<<<<<<<< < < < < < <<$ | $<<<<<<<< < < < < < <<$ | $<<<<<<< < < < < < <<$ | $<<<<<< < < < < < <<$ | $<<<<< < < < < < <<$ | $<<<< < < < < < <<$ | $<<< < < < < < <<$ | $<< < < < < < <<$ | $< < < < < < <<$ | < <th> < <th><math><<th> < <th> < <th <="" <th=""><math><<th <="" <th=""><math><<th <="" <t="" <th="" math=""></th></math></th></math></th></th></th></math></th></th> | < <th><math><<th> < <th> < <th <="" <th=""><math><<th <="" <th=""><math><<th <="" <t="" <th="" math=""></th></math></th></math></th></th></th></math></th> | $< < < <<$ | < <th> < <th <="" <th=""><math><<th <="" <th=""><math><<th <="" <t="" <th="" math=""></th></math></th></math></th></th> | < <th <="" <th=""><math><<th <="" <th=""><math><<th <="" <t="" <th="" math=""></th></math></th></math></th> | $<<$ | $<$ | | uəp | Bos et al. ²⁴ | 2006 | Netherlands | 4,385 | 35.37 | | | 69.0 | 62.5-76.2 | 8.4 | | ≥381 mmol/L |
| Immere et al.32016USA20200111Hozawe et al.32006USA15,79251,451,412,612,612,6Hozawe et al.32006USA13,420390154,18 $55,0323,123,1Liet al.32026Handa10,1754,1856,0323,123,1Liet al.32036Katha28,013054,1856,037Stasak et al.42008Anstra28,013054,1851,577Stasak et al.42009Japan8,17346,3346,3315,2Stasak et al.42001Japan8,17346,3346,3316,3Comta et al.82001Japan8,17325,6077Unde et al.92002Japan49,41310055,607Unde et al.82003Japan49,41310055,607Unde et al.82003Japan49,1310055,607Unde et al.82003Japan49,2348,15477Unde et al.82003Japan49,2348,15477Unde et al.82003Natria83,63310077Unde et al.82003Japan23,16310077Unde et al.82003Natria83,63310077Unde et al.82003Natria83,633100<$ | isni 9Å | 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 | | | | | | | | | | | | | | | | | | |
| Hozawa et al. ⁴ Cubber of al. and the advance of a | Stro | Jiménez et al. ²⁸ | 2016 | NSA | 920 | 0 | | | 61 | | 17 | | >6.8 mg/dL | | | | | | | | | | | | | | | | | | |
| ltetal ³ 2020 Japan [3,420] 301 5.503 2.31 2.31 Lehto etal ¹⁷ 198 Fnland 1,017 5.418 5.03 7 7 7 Strasket al ¹⁴ 2008 Auxtha 28613 0 7 7 7 Strasket al ¹⁴ 2008 Auxtha 28613 0 62.3 7 7 7 Chen etal ¹⁷ 2008 Auxtha 8.173 44 481±13.06 55.60 7 7 7 State atal ¹⁸ 2009 Japan 8.173 48.15±11.76 7 7 14 Unite atal ¹⁹ 2009 Usabe 49.15 52.60 7 7 14 Unite atal ¹⁹ 2009 Usabe 417.34 52.95 48.15±11.76 7 14 Vou etal ²⁸ 2009 Usabe 9.126 100 74 14 Vou etal ²⁹ 2006 Isabe 15.60 7 74 116 | ; | Hozawa et al. ³¹ | 2006 | NSA | 15,792 | 51.4 | | | 53.97 | | 12.6 | | ≥6.9 mg/dL | | | | | | | | | | | | | | | | | | |
| left of et al. ⁷ 199 Finand 1017 54.18 54.05 54.18 7 7 Frask et al. ³ 2008 Astria 28,613 0 62.3 62.3 15.2 Chen et al. ³ 2009 Astria 28,613 0 9 51.5 15.2 Stata et al. ³ 2001 Japan 8,172 44 49.81±13.06 15.6 15 | | Li et al. ³³ | 2020 | Japan | 13,420 | 39.01 | | | 55.03 | | 23.1 | | M>6.7 mg/dL F>5.2 mg/dL | | | | | | | | | | | | | | | | | | |
| Brask et al. ¹⁴ 2008 Metria 26613 0 51.5 15.2 15.2 Chen et al. ²⁴ 2009 Uhan 8,172 46.3 4.5.3 15.5 15.5 15.5 Sakate et al. ⁴⁶ 2001 Japan 8,172 44 49.81±130 14 14 Tomia et al. ³⁶ 2003 Japan 8,172 44 49.81±130 14 14 Tomia et al. ³⁶ 2000 Japan 8,173 100 25.60 14 14 Holme et al. ³⁶ 2003 Sweden 17/73 52.60 16 14 Vot et al. ³⁶ 2003 Sweden 17/73 55.60 7 14 Vot et al. ³⁶ 2003 Vot et al. ³⁶ 17/73 16 11.8 11.8 Vot et al. ³⁶ 2003 1903 15/53 18/54 17/6 11.8 11.8 Vot et al. ³⁶ 2003 1903 1903 1903 1904 11.8 11.8 11.8 | | Lehto et al. ¹⁷ | 1998 | Finland | 1,017 | 54.18 | | | 58.05 | | 7 | | >295 µmol/L | | | | | | | | | | | | | | | | | | |
| Chene tai. ² 2009 China 90,393 46.33 51.5 7 7 Sakate tai. ¹⁰ 201 Japan 8,172 44 49.81±130 7 14 14 Tomita et ai. ¹⁰ 2010 Japan 8,173 100 25-60 7 14 11.8 Tomita et ai. ¹⁰ 2009 Ushen 41,734 52.95 48.15±1176 25-60 11.8 11. | | Strasak et al. ¹⁴ | 2008 | Austria | 28,613 | 0 | | | 62.3 | | 15.2 | | ≥5.41 mg/dL | | | | | | | | | | | | | | | | | | |
| Sakata et al. ¹⁶ 2001 Japan 8.172 44 49.81±13.06 14 14 14 Tomia et al. ¹⁹ 2000 Japan 49,413 100 25-60 5.4 7.4 7.9 7.4 Holme et al. ¹⁹ 2009 Usada 49,17,34 52.95 48.15±11.76 26.40 5.4 11.8 7.4 27.4 <td< td=""><td></td><td>Chen et al.²³</td><td>2009</td><td>China</td><td>90,393</td><td>46.33</td><td></td><td></td><td>51.5</td><td></td><td>7</td><td></td><td>>7 mg/dL</td></td<> | | Chen et al. ²³ | 2009 | China | 90,393 | 46.33 | | | 51.5 | | 7 | | >7 mg/dL | | | | | | | | | | | | | | | | | | |
| Sakata et al. ¹⁶ 2001 Japan 8.172 44 4981 ± 306 7 14 14 Tomita et al. ¹⁹ 2000 Japan 49413 100 $25-60$ 5.4 5.4 5.4 Holme et al. ¹⁹ 2009 Swelen 417734 52.95 48.15 ± 11.76 5.6 5.4 5.6 5.4 5.6 5 | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Tomita et al. ³ 2000Japan49,413100 $25-60$ $< $ 5.4 $< $ Holme et al. ³ 2009Sweden417,73452.9548.15±11.7611.811.8You et al. ² 2009USA15,58348.2848.28747474Vou et al. ² 2006Israel9,125100 $< $ 747474Gerber et al. ² 2008Israel9,125100 $< $ 492374Greber et al. ² 2008Austria83,683100 $< $ 44.62323Vasak et al. ¹⁵ 2008Austria83,683100 $< $ 44.699Joe et al. ²⁹ 2004Jopan2,63316.2 $< $ 44.699Sakata et al. ¹⁶ 2020Japan2,63316.2 $< $ 44.699Kuo et al. ¹⁸ 2013Joban2,63316.2 $< $ 44.699Kuo et al. ¹⁸ 2013China36,11054.71 $< $ 49.619Kuo et al. ¹⁸ 2013China36,31343.04 $< $ 49.810Kuo et al. ¹⁹ 2015China36,31343.04 $< $ 49.810Kuo et al. ¹⁹ 2015China36,31343.04 $< $ 49.810Kuo et al. ¹⁹ 2015China36,31343.04 $< $ 49.810Kuo et al. ¹⁹ 201520152015 </td <td></td> <td>Sakata et al.¹⁶</td> <td>2001</td> <td>Japan</td> <td>8,172</td> <td>44</td> <td>49.81±13.06</td> <td></td> <td></td> <td></td> <td>14</td> <td></td> <td>M≥386 mmol/L F≥291 mmol/L</td> | | Sakata et al. ¹⁶ | 2001 | Japan | 8,172 | 44 | 49.81±13.06 | | | | 14 | | M≥386 mmol/L F≥291 mmol/L | | | | | | | | | | | | | | | | | | |
| Holme et al. ¹⁹ 2009Sweden $417,734$ 52.95 48.15 ± 11.76 T11.811.8You et al. ²⁵ 2009USA $15,83$ 48.28 48.28 48.28 74 74 74 Gerber et al. ²⁰ 2006Israel $9,125$ 100 81.63 49.2 23 23 Gerber et al. ²⁰ 2006Israel $9,125$ 100 81.63 100 49.6 23 Gerber et al. ²⁰ 2004Kreea $22,698$ 100 44.6 91.6 91.6 Joe et al. ²⁰ 2004Kreea $26,33$ 16.2 44.6 91.6 91.6 Shata et al. ¹⁶ 2020Japan $2,633$ 16.2 94.6 91.6 91.6 Kuo et al. ⁸ 2013China $354,110$ 54.71 59.23 91.6 91.6 Kuo et al. ⁸ 2013China $354,110$ 54.71 91.6 91.6 91.6 Kuo et al. ⁸ 2013China $354,100$ 34.04 91.6 91.6 91.6 | | Tomita et al. ¹³ | 2000 | Japan | 49,413 | 100 | | 25-60 | | | 5.4 | | ≥6.5 mg/dL | | | | | | | | | | | | | | | | | | |
| You et al. ²⁵ 2009USA15,58348.2848.2865.874 \sim Gerber et al. ²⁰ 2006Israel9,125100492323Strasak et al. ¹⁵ 2008Austria83,68310041.62323Jee et al. ²⁹ 2004Korea22,69810044.699Jee et al. ²⁹ 2004Korea26,3316.244.699Sakat et al. ¹⁶ 2020Japan2,63316.259.23199Kuo et al. ¹⁸ 2013China354,11054.71949.819Kuo et al. ¹⁹ 2013China36,31343.0453.541010Zhang et al. ¹¹ 2015China36,31343.0453.541010 | l | Holme et al. ¹⁹ | 2009 | Sweden | 417,734 | 52.95 | 48.15±11.76 | | | | 11.8 | | M>362 mmol/L F>327 mmol/L | | | | | | | | | | | | | | | | | | |
| Gerber et al. ²⁰ 2006 Israel 9,125 100 49 23 203 Strask et al. ¹⁵ 2008 Austria 83,683 100 41.6 13.6 73.6 Jee et al. ²⁹ 2004 Korea 22,698 100 41.6 9 9 7 Jee et al. ²⁹ 2004 Korea 22,698 100 44.6 9 9 7 Sakata et al. ¹⁶ 2020 Japan 2,633 16.2 59.23 19 7 7 Kuo et al. ¹⁸ 2013 China 354,110 54.71 59.23 19 7 7 Xuo et al. ¹⁸ 2013 China 354,110 54.71 7 7 7 7 Zhang et al. ¹¹ 2015 China 36,313 43.04 7 | tile: | You et al. ²⁵ | 2009 | NSA | 15,583 | 48.28 | | | 55.8 | | 7.4 | | >7.5 mg/dL | | | | | | | | | | | | | | | | | | |
| Strask et al. ¹⁵ 2008 Austria 83,683 100 41.6 13.6 13.6 Jee et al. ²⁹ 2004 Korea 22,698 100 44.6 9 9 7 Jee et al. ²⁹ 2003 Japan 2,633 16.2 29.23 19 7 Kuo et al. ¹⁸ 2013 China 364,110 54.71 29.23 19 7 Kuo et al. ¹⁸ 2013 China 36,313 43.04 23 23.2 10 20 20 19 20 | nort | Gerber et al. ²⁰ | 2006 | Israel | 9,125 | 100 | | | 49 | | 23 | | >5.6 mg/dL | | | | | | | | | | | | | | | | | | |
| Jee et al. ²⁹ 2004 Korea 22,698 100 44.6 9 9 Sakata et al. ¹⁶ 2020 Japan 2,633 16.2 59.23 19 19 Kuo et al. ¹⁸ 2013 China 354,110 54.71 29.2 19 19 Kuo et al. ¹⁸ 2013 China 354,110 54.71 29.2 19 19 Kuo et al. ¹⁸ 2013 China 354,110 54.71 10 49.8 4.65 10 Zhang et al. ¹¹ 2015 China 36,313 43.04 53.54 10 10 | у әу | Strasak et al. ¹⁵ | 2008 | Austria | 83,683 | 100 | | | 41.6 | | 13.6 | | >398.81 mmol/L | | | | | | | | | | | | | | | | | | |
| Sakata et al. ¹⁶ 2020 Japan 2.633 16.2 59.23 19 19 Kuo et al. ¹⁸ 2013 China 354.110 54.71 49.8 4.65 16 1 Zhang et al. ¹¹ 2015 China 36.313 43.04 53.54 10 10 | Stro | Jee et al. ²⁹ | 2004 | Korea | 22,698 | 100 | | | 44.6 | | 6 | | >414 mmol/L | | | | | | | | | | | | | | | | | | |
| 2013 China 354,110 54.71 49.8 4.65 .1 2015 China 36,313 43.04 53.54 10 | | Sakata et al. ¹⁶ | 2020 | Japan | 2,633 | 16.2 | | | 59.23 | | 19 | | M>412 mmol/l F>311 mmol/L | | | | | | | | | | | | | | | | | | |
| 2015 China 36,313 43.04 53.54 10 | | 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 | | | | | | | | | | | | | | | | | | |

Arch Rheumatol

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 22 prospective cohort studies from (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 year³⁰ 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 RR. individuals (pooled 1.42: 95% 1.31-1.53).^{12,14,21-23,26,28,30,31,33} CI. 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}

| 5 | troke Incidence | | % |
|--|-----------------|-------------------|--------|
| author (year) | | RR (95% CI) | Weight |
| Lehto et al. (1998) | | 1.91 (1.24, 2.94) | 3.18 |
| Chien et al. (2005) | | 1.58 (1.05, 2.37) | 3.58 |
| Hozawa et al. (2005) | | 1.25 (0.91, 1.73) | 5.75 |
| Bos et al. (2006) | | 1.50 (1.05, 2.14) | 4.68 |
| Strasak et al. (2008) | | 1.37 (1.09, 1.74) | 10.84 |
| Chen et al. (2009) | | 1.26 (1.02, 1.55) | 13.55 |
| Jiménez et al. (2016) | | 1.98 (1.11, 3.51) | 1.79 |
| Tscharre et al. (2018) | | 1.10 (0.49, 2.06) | 1.15 |
| Tu et al. (2019) | | 2.27 (1.52, 3.37) | 3.74 |
| Li et al. (2020) | | 1.39 (1.22, 1.59) | 33.81 |
| Cheng et al. (2021) | - | 1.42 (1.16, 1.73) | 14.85 |
| Hu et al. (2021) | | 1.22 (0.79, 1.90) | 3.08 |
| Overall, IV (l ² = 6.6%, p = 0.381) | \diamond | 1.42 (1.31, 1.53) | 100.00 |

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 followup. 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).

| Stroke Mortali | ty | % |
|---|----------------------------|-------|
| author (year) | RR (95% CI) We | eight |
| Tomita et al. (2000) | 1.69 (1.18, 2.42) 1 | 0.54 |
| Sakata et al. (2001) | 1.49 (0.90, 2.48) | 8.80 |
| Jee et al. (2004) | 1.10 (0.71, 1.72) | 9.56 |
| Gerber et al. (2006) | 1.20 (0.81, 1.78) 1 | 0.14 |
| Strasak et al. (2008) | 1.59 (1.23, 2.04) 1 | 1.72 |
| Holme et al. (2009) | 1.90 (1.85, 1.96) 1 | 3.16 |
| Kuo et al. (2012) 🛨 | 1.01 (0.93, 1.10) 1 | 3.00 |
| Zhang et al. (2015) | 2.02 (1.71, 2.39) 1 | 2.50 |
| Sakata et al. (2020) | * 3.77 (1.54, 9.24) | 5.16 |
| You et al. (2021) | 1.27 (0.54, 3.01) | 5.42 |
| Overall, DL (l ² = 95.7%, p = 0.000) | 1.53 (1.18, 1.99) 10 | 0.00 |

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

| Sex and author (year) | Stroke Incidence RR (95% CI) | ہ Weigh |
|--|--|--|
| Female | | |
| Chien et al. (2005) | 1.68 (0.91, 3.10 |)) 1.8 |
| Bos et al. (2006) | 1.45 (1.05, 2.0 | |
| Chen et al. (2009) | 1.49 (1.04, 2.14 | |
| Jiménez et al. (2006) | 1.98 (1.11, 3.5 | |
| Tu et al. (2019) | 2.16 (1.25, 3.7) | |
| Li et al. (2020) | 1.45 (1.07, 1.9 | |
| Cheng et al. (2021) | 2.13 (1.53, 2.9 | |
| Hu et al. (2021) | | |
| Subgroup, IV ($I^2 = 0.0\%$, p = 0.637) | | |
| Subgroup, $1V(1^{2} = 0.0\%, p = 0.057)$ | 1.67 (1.44, 1.9) | 2) 33.8 |
| Male | | |
| Chien et al. (2005) | 1.51 (0.88, 2.60 |)) 2.3 |
| Bos et al. (2006) | 1.41 (0.90, 2.2 | - |
| Chen et al. (2009) | 1.15 (0.89, 1.49 | |
| Tu et al. (2019) | 2.34 (1.31, 4.10 | |
| Li et al. (2020) | 1.02 (0.74, 1.3 | |
| Cheng et al. (2021) | 1.06 (0.93, 1.2 | |
| Hu et al. (2021) | 1.06 (0.58, 1.9 | |
| Subgroup, IV (I ² = 36.3%, p = 0.151) | 1.13 (1.02, 1.2 | - |
| Subgroup, IV (I = 50.5 %, p = 0.151) | | , 00.1 |
| Heterogeneity between groups: $p = 0.0$ Overall, IV ($l^2 = 58.1\%$, $p = 0.003$) | |) 100.0 |
| Overall, IV (I = 58.1%, p = 0.005) | 1.29 (1.18, 1.40 | /) 100.0 |
| .25 Normourio | cemia 1 Hyperuricemia 4 | |
| | Cemia 1 Hyperuricemia 4 Stroke Incidence RR (95% CI) | Weigl |
| ype and author (year) | Stroke Incidence | |
| lype and author (year) Ischemic stroke | Stroke Incidence RR (95% CI) | Weig |
| ype and author (year) schemic stroke Hozawa et al. (2005) | Stroke Incidence RR (95% CI) | Weigl 3) 10.9 |
| ype and author (year) schemic stroke Hozawa et al. (2005) Bos et al. (2006) | Stroke Incidence RR (95% Cl) | Weigl 3) 10.9 1) 4.8 |
| ype and author (year) schemic stroke Hozawa et al. (2005) Bos et al. (2006) Strasak et al. (2008) | Stroke Incidence RR (95% Cl) | Weigl 3) 10.9 1) 4.8 9) 5.8 |
| ype and author (year) schemic stroke Hozawa et al. (2005) Bos et al. (2006) Strasak et al. (2008) Chen et al. (2009) | Stroke Incidence RR (95% Cl) | Weigl 3) 10.9 1) 4.8 9) 5.8 6) 16.3 |
| ype and author (year) schemic stroke Hozawa et al. (2005) Bos et al. (2006) Strasak et al. (2008) Chen et al. (2009) Jiménez et al. (2016) | Stroke Incidence RR (95% Cl) | Weigl 3) 10.9 1) 4.8 9) 5.8 6) 16.3 1) 3.4 |
| ype and author (year) schemic stroke Hozawa et al. (2005) Bos et al. (2006) Strasak et al. (2008) Chen et al. (2009) Jiménez et al. (2016) Tscharre et al. (2018) – | Stroke Incidence RR (95% Cl) | Weigl 3) 10.9 1) 4.8 9) 5.8 6) 16.3 1) 3.4 6) 2.2 |
| ype and author (year) schemic stroke Hozawa et al. (2005) Bos et al. (2006) Strasak et al. (2008) Chen et al. (2009) Jiménez et al. (2016) Fscharre et al. (2018) – Fu et al. (2019) | Stroke Incidence RR (95% Cl) 125 (0.91, 1.7 1.49 (0.92, 2.4 1.15 (0.74, 1.7 1.35 (1.04, 1.7 1.98 (1.11, 3.5 1.10 (0.49, 2.0 1.75 (1.18, 2.5 | Weigl 3) 10.9 1) 4.8 9) 5.8 6) 16.3 1) 3.4 6) 2.2 9) 7.3 |
| ype and author (year) schemic stroke Hozawa et al. (2005) Bos et al. (2006) Strasak et al. (2008) Chen et al. (2009) Jiménez et al. (2016) Fscharre et al. (2018) – Fu et al. (2019) Li et al. (2020) | Stroke Incidence RR (95% Cl) 125 (0.91, 1.7 1.49 (0.92, 2.4 1.15 (0.74, 1.7 1.35 (1.04, 1.7 1.98 (1.11, 3.5 1.10 (0.49, 2.0 1.75 (1.18, 2.5 1.23 (0.94, 1.6 | Weigl 3) 10.9 1) 4.8 9) 5.8 6) 16.3 1) 3.4 6) 2.2 9) 7.3 0) 16.0 |
| ype and author (year) schemic stroke łozawa et al. (2005) 3os et al. (2006) Strasak et al. (2008) Chen et al. (2009) liménez et al. (2016) Fscharre et al. (2018) Fu et al. (2019) Li et al. (2020) fu et al. (2021) | Stroke Incidence RR (95% Cl) 125 (0.91, 1.7 1.49 (0.92, 2.4 1.15 (0.74, 1.7 1.35 (1.04, 1.7 1.35 (1.04, 1.7 1.98 (1.11, 3.5 1.10 (0.49, 2.0 1.75 (1.18, 2.5 1.23 (0.94, 1.6 1.28 (0.69, 2.3 | Weigl 3) 10.9 1) 4.8 9) 5.8 6) 16.3 1) 3.4 6) 2.2 9) 7.3 0) 16.0 9) 2.9 |
| ype and author (year) schemic stroke łozawa et al. (2005) 3os et al. (2006) Strasak et al. (2008) Chen et al. (2009) liménez et al. (2016) Fscharre et al. (2018) Fu et al. (2019) di et al. (2020) fu et al. (2021) | Stroke Incidence RR (95% Cl) 125 (0.91, 1.7 1.49 (0.92, 2.4 1.15 (0.74, 1.7 1.35 (1.04, 1.7 1.98 (1.11, 3.5 1.10 (0.49, 2.0 1.75 (1.18, 2.5 1.23 (0.94, 1.6 | Weigl 3) 10.9 1) 4.8 9) 5.8 6) 16.3 1) 3.4 6) 2.2 9) 7.3 0) 16.0 9) 2.9 |
| ype and author (year) schemic stroke Hozawa et al. (2005) Bos et al. (2006) Strasak et al. (2008) Chen et al. (2009) liménez et al. (2016) Fscharre et al. (2016) Fu et al. (2019) Li et al. (2020) Hu et al. (2021) Subgroup, IV (I ² = 0.0%, p = 0.750) | Stroke Incidence RR (95% Cl) 125 (0.91, 1.7 1.49 (0.92, 2.4 1.15 (0.74, 1.7 1.35 (1.04, 1.7 1.35 (1.04, 1.7 1.98 (1.11, 3.5 1.10 (0.49, 2.0 1.75 (1.18, 2.5 1.23 (0.94, 1.6 1.28 (0.69, 2.3 | Weigl 3) 10.9 1) 4.8 9) 5.8 6) 16.3 1) 3.4 6) 2.2 9) 7.3 0) 16.0 9) 2.9 |
| ype and author (year) schemic stroke Hozawa et al. (2005) Bos et al. (2006) Strasak et al. (2008) Chen et al. (2009) Jiménez et al. (2016) Fscharre et al. (2016) Fu et al. (2019) Li et al. (2020) Hu et al. (2021) Subgroup, IV (I ² = 0.0%, p = 0.750) Hemorrhagic stroke | Stroke Incidence RR (95% Cl) 125 (0.91, 1.7 1.49 (0.92, 2.4 1.15 (0.74, 1.7 1.35 (1.04, 1.7 1.35 (1.04, 1.7 1.98 (1.11, 3.5 1.10 (0.49, 2.0 1.75 (1.18, 2.5 1.23 (0.94, 1.6 1.28 (0.69, 2.3 1.35 (1.19, 1.5 | Weigl 3) 10.9 1) 4.8 9) 5.8 6) 16.3 1) 3.4 6) 2.2 9) 7.3 0) 16.0 9) 2.9 3) 69.9 |
| ype and author (year) schemic stroke Hozawa et al. (2005) Bos et al. (2006) Strasak et al. (2008) Chen et al. (2009) Jiménez et al. (2016) Tscharre et al. (2016) Tu et al. (2019) Li et al. (2020) Hu et al. (2021) Subgroup, IV (I ² = 0.0%, p = 0.750) Hemorrhagic stroke Bos et al. (2006) | Stroke Incidence RR (95% Cl) 125 (0.91, 1.7 1.49 (0.92, 2.4 1.15 (0.74, 1.7 1.35 (1.04, 1.7 1.35 (1.04, 1.7 1.35 (1.04, 1.7 1.98 (1.11, 3.5 1.10 (0.49, 2.0 1.75 (1.18, 2.5 1.23 (0.94, 1.6 1.28 (0.69, 2.3 1.35 (1.19, 1.5 2.06 (0.81, 5.2 | Weigl 3) 10.9 1) 4.8 9) 5.8 6) 16.3 1) 3.4 6) 2.2 9) 7.3 0) 16.0 9) 2.9 3) 69.9 5) 1.3 |
| ype and author (year) schemic stroke Hozawa et al. (2005) Bos et al. (2006) Strasak et al. (2008) Chen et al. (2009) Jiménez et al. (2016) Fscharre et al. (2016) Fu et al. (2019) Li et al. (2020) Hu et al. (2021) Subgroup, IV (I ² = 0.0%, p = 0.750) Hemorrhagic stroke Bos et al. (2006) Strasak et al. (2008) | Stroke Incidence RR (95% Cl) 125 (0.91, 1.7 1.49 (0.92, 2.4 1.15 (0.74, 1.7 1.35 (1.04, 1.7 1.35 (1.04, 1.7 1.35 (1.04, 1.7 1.98 (1.11, 3.5 1.10 (0.49, 2.0 1.75 (1.18, 2.5 1.23 (0.94, 1.6 1.28 (0.69, 2.3 1.35 (1.19, 1.5 2.06 (0.81, 5.2 1.29 (0.71, 2.4 | Weigl 3) 10.9 1) 4.8 9) 5.8 6) 16.3 1) 3.4 6) 2.2 9) 7.3 0) 16.0 9) 2.9 3) 69.9 5) 1.3 0) 3.0 |
| ype and author (year) schemic stroke Hozawa et al. (2005) Bos et al. (2006) Strasak et al. (2008) Chen et al. (2009) Jiménez et al. (2016) Fischarre et al. (2016) Fi et al. (2020) Hu et al. (2020) Hu et al. (2021) Subgroup, IV ($I^2 = 0.0\%$, p = 0.750) Hemorrhagic stroke Bos et al. (2006) Strasak et al. (2008) Chen et al. (2009) | Stroke Incidence RR (95% Cl) 125 (0.91, 1.7 1.49 (0.92, 2.4 1.15 (0.74, 1.7 1.35 (1.04, 1.7 1.35 (1.04, 1.7 1.98 (1.11, 3.5 1.10 (0.49, 2.0 1.75 (1.18, 2.5 1.23 (0.94, 1.6 1.28 (0.69, 2.3 1.35 (1.19, 1.5 2.06 (0.81, 5.2 1.29 (0.71, 2.4 1.18 (0.83, 1.6 | Weigl 3) 10.9 1) 4.8 9) 5.8 6) 16.3 1) 3.4 6) 2.2 9) 7.3 0) 16.0 9) 2.9 3) 69.9 5) 1.3 0) 3.0 7) 9.2 |
| ype and author (year) schemic stroke Hozawa et al. (2005) Bos et al. (2006) Strasak et al. (2008) Chen et al. (2009) Jiménez et al. (2016) Fischarre et al. (2016) Fischarre et al. (2018) | Stroke Incidence RR (95% Cl) 125 (0.91, 1.7 1.49 (0.92, 2.4 1.15 (0.74, 1.7 1.35 (1.04, 1.7 1.35 (1.04, 1.7 1.35 (1.04, 1.7 1.98 (1.11, 3.5 1.10 (0.49, 2.0 1.75 (1.18, 2.5 1.23 (0.94, 1.6 1.28 (0.69, 2.3 1.35 (1.19, 1.5) 2.06 (0.81, 5.2 1.29 (0.71, 2.4 1.18 (0.83, 1.6 1.63 (1.10, 2.4) | Weigl 3) 10.9 1) 4.8 9) 5.8 6) 16.3 1) 3.4 6) 2.2 9) 7.3 0) 16.0 9) 2.9 3) 69.9 5) 1.3 0) 3.0 7) 9.2 1) 7.3 |
| ype and author (year) schemic stroke Hozawa et al. (2005) Bos et al. (2006) Strasak et al. (2008) Chen et al. (2009) Jiménez et al. (2016) Fischarre et al. (2016) Fischarre et al. (2018) | Stroke Incidence RR (95% Cl) 125 (0.91, 1.7 1.49 (0.92, 2.4 1.15 (0.74, 1.7 1.35 (1.04, 1.7 1.35 (1.04, 1.7 1.35 (1.04, 1.7 1.98 (1.11, 3.5 1.10 (0.49, 2.0 1.75 (1.18, 2.5 1.23 (0.94, 1.6 1.28 (0.69, 2.3 1.35 (1.19, 1.5) 2.06 (0.81, 5.2 1.29 (0.71, 2.4 1.18 (0.83, 1.6 1.63 (1.10, 2.4 1.14 (0.79, 1.6 | Weigl 3) 10.9 1) 4.8 9) 5.8 6) 16.3 1) 3.4 6) 2.2 9) 7.3 0) 16.0 9) 2.9 3) 69.9 5) 1.3 0) 3.0 7) 9.2 1) 7.3 6) 8.2 |
| ype and author (year) schemic stroke Hozawa et al. (2005) Bos et al. (2006) Strasak et al. (2008) Chen et al. (2009) liménez et al. (2016) Fischarre et al. (2018) Fi et al. (2020) Hu et al. (2021) Subgroup, IV (I ² = 0.0%, p = 0.750) Hemorrhagic stroke Bos et al. (2006) Strasak et al. (2008) Chen et al. (2009) Fu et al. (2019) Li et al. (2019) Li et al. (2020) Hu et al. (2020) Hu et al. (2020) Hu et al. (2021) | Stroke Incidence RR (95% Cl) 125 (0.91, 1.7 1.49 (0.92, 2.4 1.15 (0.74, 1.7 1.35 (1.04, 1.7 1.35 (1.04, 1.7 1.35 (1.04, 1.7 1.98 (1.11, 3.5 1.10 (0.49, 2.0 1.75 (1.18, 2.5 1.23 (0.94, 1.6 1.28 (0.69, 2.3 1.35 (1.19, 1.5 2.06 (0.81, 5.2 1.29 (0.71, 2.4 1.18 (0.83, 1.6 1.63 (1.10, 2.4 1.14 (0.79, 1.6 1.48 (0.45, 4.8 | Weigl 3) 10.9 1) 4.8 9) 5.8 6) 16.3 1) 3.4 6) 2.2 9) 7.3 0) 16.0 9) 2.9 3) 69.9 5) 1.3 0) 3.0 7) 9.2 1) 7.3 6) 8.2 5) 0.8 |
| ype and author (year) schemic stroke łozawa et al. (2005) 3os et al. (2006) Strasak et al. (2008) Chen et al. (2009) liménez et al. (2016) Fscharre et al. (2016) Fu et al. (2020) łu et al. (2020) łu et al. (2021) Subgroup, IV (I ² = 0.0%, p = 0.750) Hemorrhagic stroke Bos et al. (2006) Strasak et al. (2008) Chen et al. (2009) Fu et al. (2019) Li et al. (2019) Li et al. (2020) | Stroke Incidence RR (95% Cl) 125 (0.91, 1.7 1.49 (0.92, 2.4 1.15 (0.74, 1.7 1.35 (1.04, 1.7 1.35 (1.04, 1.7 1.35 (1.04, 1.7 1.98 (1.11, 3.5 1.10 (0.49, 2.0 1.75 (1.18, 2.5 1.23 (0.94, 1.6 1.28 (0.69, 2.3 1.35 (1.19, 1.5) 2.06 (0.81, 5.2 1.29 (0.71, 2.4 1.18 (0.83, 1.6 1.63 (1.10, 2.4 1.14 (0.79, 1.6 | Weigl 3) 10.9 1) 4.8 9) 5.8 6) 16.3 1) 3.4 6) 2.2 9) 7.3 0) 16.0 9) 2.9 3) 69.9 5) 1.3 0) 3.0 7) 9.2 1) 7.3 6) 8.2 5) 0.8 |
| ype and author (year) schemic stroke Hozawa et al. (2005) Bos et al. (2006) Strasak et al. (2008) Chen et al. (2009) liménez et al. (2016) Fischarre et al. (2018) Fi et al. (2020) Hu et al. (2021) Subgroup, IV (I ² = 0.0%, p = 0.750) Hemorrhagic stroke Bos et al. (2006) Strasak et al. (2008) Chen et al. (2009) Fu et al. (2019) Li et al. (2019) Li et al. (2020) Hu et al. (2020) Hu et al. (2020) Hu et al. (2021) | Stroke Incidence RR (95% Cl) 1.25 (0.91, 1.7 1.49 (0.92, 2.4 1.15 (0.74, 1.7 1.35 (1.04, 1.7 1.35 (1.19, 1.5 1.23 (0.94, 1.6 1.28 (0.69, 2.3 1.35 (1.19, 1.5 1.18 (0.83, 1.6 1.63 (1.10, 2.4 1.14 (0.79, 1.6 1.48 (0.45, 4.8 1.32 (1.08, 1.6) | Weigl 3) 10.9 1) 4.8 9) 5.8 6) 16.3 1) 3.4 6) 2.2 9) 7.3 0) 16.0 9) 2.9 3) 69.9 5) 1.3 0) 3.0 7) 9.2 1) 7.3 6) 8.2 5) 0.8 |
| ype and author (year) schemic stroke łozawa et al. (2005) Bos et al. (2006) Strasak et al. (2008) Chen et al. (2009) timénez et al. (2016) Fscharre et al. (2018) Tu et al. (2020) du et al. (2021) Subgroup, IV ($f^2 = 0.0\%$, p = 0.750) Hemorrhagic stroke Bos et al. (2006) Strasak et al. (2008) Chen et al. (2009) Tu et al. (2019) Li et al. (2020) Hu et al. (2020) Hu et al. (2020) Hu et al. (2021) Subgroup, IV ($f^2 = 0.0\%$, p = 0.697) | Stroke Incidence RR (95% Cl) 1.25 (0.91, 1.7 1.49 (0.92, 2.4 1.15 (0.74, 1.7 1.35 (1.04, 1.7 1.35 (1.19, 1.5 1.23 (0.94, 1.6 1.28 (0.69, 2.3 1.35 (1.19, 1.5 1.18 (0.83, 1.6 1.63 (1.10, 2.4 1.14 (0.79, 1.6 1.48 (0.45, 4.8 1.32 (1.08, 1.6) | Weigl 3) 10.9 1) 4.8 9) 5.8 6) 16.3 1) 3.4 6) 2.2 9) 7.3 0) 16.0 9) 2.9 3) 69.9 5) 1.3 0) 3.0 7) 9.2 1) 7.3 6) 8.2 5) 0.8 0) 30.0 |

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

| | Stroke Mortality | 9 |
|---|---|---|
| Sex and author (year) | RR (95% CI) | Weigh |
| Female | | |
| Sakata et al. (2001) | 1.12 (0.46, 2.74) | 0.25 |
| Holme et al. (2009) | + 1.41 (1.31, 1.53) | 33.24 |
| Zhang et al. (2015) | 1.46 (0.98, 2.19) | 1.24 |
| You et al. (2021) | 1.36 (0.79, 2.34) | 0.68 |
| Subgroup, IV (l ² = 0.0%, p = 0.960) | 1.41 (1.31, 1.52) | 35.41 |
| Male | | |
| Sakata et al. (2001) | 1.71 (0.92, 3.17) | 0.52 |
| Jee et al. (2004) | 1.10 (0.71, 1.72) | |
| Gerber et al. (2006) | 1.20 (0.81, 1.78) | 1.29 |
| Strasak et al. (2008) | 1.59 (1.23, 2.04) | 3.13 |
| Holme et al. (2009) | + 1.26 (1.19, 1.34) | 56.84 |
| Zhang et al. (2015) | 1.19 (0.84, 1.68) | 1.67 |
| You et al. (2021) | 1.26 (0.35, 4.60) | 0.12 |
| Subgroup, IV (l ² = 0.0%, p = 0.595) | 1.27 (1.20, 1.34) | 64.59 |
| Heterogeneity between groups: p = 0.0 | 032 | |
| | | |
| Overall, IV (I ² = 0.0%, p = 0.486) | icemia 1 Hyperuricemia 4 | 100.00 |
| 1 .25 Normouri | icemia 1 Hyperuricemia 4 | 100.00 |
| 1 .25 Normouri | icemia 1 Hyperuricemia 4 Stroke Mortality | 9 |
| 1 _25 Normouri | icemia 1 Hyperuricemia 4 | |
| 1 _25 Normouri | icemia 1 Hyperuricemia 4 Stroke Mortality | 9 |
| 1 25 Normouri ype and author (year) schemic stroke | icemia 1 Hyperuricemia 4 Stroke Mortality | e Weigh |
| 1 Normouri 25 Normouri ype and author (year) schemic stroke Serber et al. (2006) | icemia 1 Hyperuricemia 4 Stroke Mortality RR (95% CI) | 9 Weigh) 1.3 |
| 1 25 Normouri ype and author (year) schemic stroke Serber et al. (2006) Strasak et al. (2008) | Stroke Mortality RR (95% Cl) | 9 Weigh) 1.3) 0.9 |
| I Normouri 25 Normouri 25 Schemic stroke Serber et al. (2006) Strasak et al. (2008) Itolme et al. (2009) | Cemia 1 Hyperuricemia 4 Stroke Mortality RR (95% Cl) 1.15 (0.75, 1.74) 1.81 (1.07, 3.04) | 9 Weigh) 1.3) 0.9) 74.2 |
| I Normouri //pe and author (year) schemic stroke Serber et al. (2006) itrasak et al. (2008) Iolme et al. (2009) hang et al. (2015) | Cemia 1 Hyperuricemia 4 Stroke Mortality RR (95% Cl) 1.15 (0.75, 1.74) 1.81 (1.07, 3.04) 1.39 (1.31, 1.47) | 9 Weigh) 1.3) 0.9) 74.2) 1.8 |
| 1 25 Normouri 25 Normouri schemic stroke Serber et al. (2006) strasak et al. (2008) Iolme et al. (2009) Iolme et al. (2015) Subgroup, IV (I² = 0.0%, p = 0.556) | Incernia 1 Hyperuricernia 4 Stroke Mortality RR (95% Cl) 1.15 (0.75, 1.74) 1.81 (1.07, 3.04) 1.39 (1.31, 1.47) 1.25 (0.87, 1.80) | 9 Weigh) 1.3) 0.9) 74.2) 1.8 |
| 1 25 Normouri 25 Normouri schemic stroke Serber et al. (2006) Strasak et al. (2008) Holme et al. (2009) Hong et al. (2015) Subgroup, IV (I ² = 0.0%, p = 0.556) Hemorrhagic stroke Strasak | Incernia 1 Hyperuricernia 4 Stroke Mortality RR (95% Cl) 1.15 (0.75, 1.74) 1.81 (1.07, 3.04) 1.39 (1.31, 1.47) 1.25 (0.87, 1.80) | 9 Weigh) 1.3) 0.9) 74.2) 1.8) 78.3 |
| I Normouri 25 Normouri 25 Normouri 25 Schemic stroke 26 Serber et al. (2006) 27 Strasak et al. (2008) 28 Solme et al. (2009) 29 Subgroup, IV (I ² = 0.0%, p = 0.556) 29 Serber et al. (2006) | Cemia 1 Hyperuricemia 4 Stroke Mortality RR (95% Cl) 1.15 (0.75, 1.74) 1.81 (1.07, 3.04) 1.39 (1.31, 1.47) 1.39 (1.31, 1.47) | 9 Weigh) 1.3) 0.9) 74.2) 78.3) 78.3 |
| 1 .25 Normouri .25 Normouri schemic stroke Serber et al. (2006) Strasak et al. (2008) Holme et al. (2009) Hong et al. (2015) Subgroup, IV (I² = 0.0%, p = 0.556) Hemorrhagic stroke Serber et al. (2006) Serber et al. (2006) - | Incernia 1 Hyperuricemia 4 Stroke Mortality RR (95% Cl) 1.15 (0.75, 1.74) 1.81 (1.07, 3.04) 1.39 (1.31, 1.47) 1.39 (1.31, 1.47) 1.62 (0.51, 5.18) | 9 Weigh) 1.3) 0.9) 74.2) 78.3) 78.3 |
| 1 25 Normouri 25 Normouri schemic stroke Serber et al. (2006) Strasak et al. (2009) Stang et al. (2015) Holgroup, IV (I² = 0.0%, p = 0.556) Serber et al. (2006) Strasak et al. (2008) Serber et al. (2008) Hemorrhagic stroke Serber et al. (2008) Strasak et al. (2008) Serber et al. (2008) Holme et al. (2009) Serber et al. (2009) | Image: Stroke Mortality RR (95% Cl) Image: Stroke Mortality 1.15 (0.75, 1.74) 1.81 (1.07, 3.04) 1.39 (1.31, 1.47) 1.25 (0.87, 1.80) 1.39 (1.31, 1.47) Image: Stroke Mortality 1.62 (0.51, 5.18) Image: Stroke Mortality 1.81 (0.70, 2.01) | () 1.3 () 0.9 () 74.2 () 1.8 () 78.3 () 0.1 () 0.8 () 0.8 () 19.4 |
| $\frac{1}{25}$ Normouri schemic stroke Serber et al. (2006) strasak et al. (2008) tolme et al. (2015) subgroup, IV (I ² = 0.0%, p = 0.556) temorrhagic stroke Serber et al. (2006) strasak et al. (2008) tolme et al. (2009) thang et al. (2015) | Cemia 1 Hyperuricemia 4 Stroke Mortality RR (95% Cl) 1.15 (0.75, 1.74) 1.81 (1.07, 3.04) 1.39 (1.31, 1.47) 1.25 (0.87, 1.80) 1.39 (1.31, 1.47) 1.62 (0.51, 5.18) 1.18 (0.70, 2.01) 1.11 (0.99, 1.24) | Weigh 1.3 0.9 74.2 1.8 78.3 0.1 0.8 19.4 1.1 |
| 1 .25 Normouri | Image: Stroke Mortality RR (95% Cl) Image: Stroke Mortality 1.15 (0.75, 1.74) Image: Stroke Mortality 1.39 (1.31, 1.47) Image: Stroke Mortality 1.62 (0.51, 5.18) Image: Stroke Mortality 1.16 (0.70, 2.01) Image: Stroke Mortality 1.11 (0.99, 1.24) Image: Stroke Mortality 1.13 (1.02, 1.26) | 9 Weigh) 1.3) 0.9) 74.2) 78.3) 78.3) 0.1 ;) 0.1 ;) 0.8 ;) 19.4 ;) 1.1 |

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. $^{\rm 59\text{-}61}$

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 observational studies. causal any а 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, doubleblind, 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.

Conflict of Interest: The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

Funding: The authors received no financial support for the research and/or authorship of this article.

REFERENCES

- GBD 2019 Stroke Collaborators. Global, regional, and national burden of stroke and its risk factors, 1990-2019: A systematic analysis for the Global Burden of Disease Study 2019. Lancet Neurol.2021;20:795-820. doi: 10.1016/S1474-4422(21)00252-0.
- Strong K, Mathers C, Bonita R. Preventing stroke: Saving lives around the world. Lancet Neurol 2007;6:182-7. doi: 10.1016/S1474-4422(07)70031-5.
- O'Donnell MJ, Chin SL, Rangarajan S, Xavier D, Liu L, Zhang H, et al. Global and regional effects of potentially modifiable risk factors associated with acute stroke in 32 countries (INTERSTROKE): A case-control study. Lancet 2016;388:761-75. doi: 10.1016/S0140-6736(16)30506-2.
- 4. Ndrepepa G. Uric acid and cardiovascular disease. Clin Chim Acta 2018;484:150-63. doi: 10.1016/j. cca.2018.05.046.
- 5. Hamburger M, Baraf HS, Adamson TC 3rd, Basile J, Bass L, Cole B, et al. 2011 Recommendations for the diagnosis and management of gout and hyperuricemia. Postgrad Med 2011;123(6 Suppl 1):3-36. doi: 10.3810/pgm.2011.11.2511.
- Brinjikji W, Rabinstein AA, Kallmes DF, Cloft HJ. Patient outcomes with endovascular embolectomy therapy for acute ischemic stroke: A study of the national inpatient sample: 2006 to 2008. Stroke 2011;42:1648-52. doi: 10.1161/STROKEAHA.110.607952.
- 7. Ponticelli C, Podestà MA, Moroni G. Hyperuricemia as a trigger of immune response in hypertension and chronic kidney disease. Kidney Int 2020;98:1149-59. doi: 10.1016/j.kint.2020.05.056.
- 8. Kang DH, Nakagawa T, Feng L, Watanabe S, Han L, Mazzali M, et al. A role for uric acid in the progression

of renal disease. J Am Soc Nephrol 2002;13:2888-97. doi: 10.1097/01.asn.0000034910.58454.fd.

- Johnson RJ, Kang DH, Feig D, Kivlighn S, Kanellis J, Watanabe S, et al. Is there a pathogenetic role for uric acid in hypertension and cardiovascular and renal disease? Hypertension 2003;41:1183-90. doi: 10.1161/01.HYP.0000069700.62727. C5.
- Butler R, Morris AD, Belch JJ, Hill A, Struthers AD. Allopurinol normalizes endothelial dysfunction in type 2 diabetics with mild hypertension. Hypertension 2000;35:746-51. doi: 10.1161/01.hyp.35.3.746.
- Zhang W, Iso H, Murakami Y, Miura K, Nagai M, Sugiyama D, et al. Serum uric acid and mortality form cardiovascular disease: EPOCH-JAPAN study. J Atheroscler Thromb 2016;23:692-703. doi: 10.5551/jat.31591.
- Tu W, Wu J, Jian G, Lori J, Tang Y, Cheng H, et al. Asymptomatic hyperuricemia and incident stroke in elderly Chinese patients without comorbidities. Eur J Clin Nutr 2019;73:1392-402. doi: 10.1038/s41430-019-0405-1.
- Tomita M, Mizuno S, Yamanaka H, Hosoda Y, Sakuma K, Matuoka Y, et al. Does hyperuricemia affect mortality? A prospective cohort study of Japanese male workers. J Epidemiol 2000;10:403-9. doi: 10.2188/jea.10.403.
- Strasak AM, Kelleher CC, Brant LJ, Rapp K, Ruttmann E, Concin H, et al. Serum uric acid is an independent predictor for all major forms of cardiovascular death in 28,613 elderly women: A prospective 21-year follow-up study. Int J Cardiol 2008;125:232-9. doi: 10.1016/j.ijcard.2007.11.094.
- Strasak A, Ruttmann E, Brant L, Kelleher C, Klenk J, Concin H, et al. Serum uric acid and risk of cardiovascular mortality: A prospective long-term study of 83,683 Austrian men. Clin Chem 2008;54:273-84. doi: 10.1373/clinchem.2007.094425.
- Sakata S, Hata J, Honda T, Hirakawa Y, Oishi E, Shibata M, et al. Serum uric acid levels and cardiovascular mortality in a general Japanese population: The Hisayama Study. Hypertens Res 2020;43:560-8. doi: 10.1038/s41440-019-0390-8.
- Lehto S, Niskanen L, Rönnemaa T, Laakso M. Serum uric acid is a strong predictor of stroke in patients with non-insulin-dependent diabetes mellitus. Stroke 1998;29:635-9. doi: 10.1161/01.str.29.3.635.
- Kuo CF, See LC, Yu KH, Chou IJ, Chiou MJ, Luo SF. Significance of serum uric acid levels on the risk of all-cause and cardiovascular mortality. Rheumatology (Oxford) 2013;52:127-34. doi: 10.1093/rheumatology/kes223.
- Holme I, Aastveit AH, Hammar N, Jungner I, Walldius G. Uric acid and risk of myocardial infarction, stroke and congestive heart failure in 417,734 men and women in the Apolipoprotein MOrtality RISk study (AMORIS). J Intern Med 2009;266:558-70. doi: 10.1111/j.1365-2796.2009.02133.x.

- Gerber Y, Tanne D, Medalie JH, Goldbourt U. Serum uric acid and long-term mortality from stroke, coronary heart disease and all causes. Eur J Cardiovasc Prev Rehabil 2006;13:193-8. doi: 10.1097/01.hjr.0000192745.26973.00.
- Chien KL, Hsu HC, Sung FC, Su TC, Chen MF, Lee YT. Hyperuricemia as a risk factor on cardiovascular events in Taiwan: The Chin-Shan Community Cardiovascular Cohort Study. Atherosclerosis 2005;183:147-55. doi: 10.1016/j.atherosclerosis.2005.01.018.
- 22. Cheng Z, Zheng T, Zhang D, Yang J, Hu X, Yin C, et al. High-level uric acid in asymptomatic hyperuricemia could be an isolated risk factor of cardio-cerebrovascular diseases: A prospective cohort study. Nutr Metab Cardiovasc Dis 2021;31:3415-25. doi: 10.1016/j.numecd.2021.08.043.
- Chen JH, Chuang SY, Chen HJ, Yeh WT, Pan WH. Serum uric acid level as an independent risk factor for all-cause, cardiovascular, and ischemic stroke mortality: A Chinese cohort study. Arthritis Rheum 2009;61:225-32. doi: 10.1002/art.24164.
- Bos MJ, Koudstaal PJ, Hofman A, Witteman JC, Breteler MM. Uric acid is a risk factor for myocardial infarction and stroke: The Rotterdam study. Stroke 2006;37:1503-7. doi: 10.1161/01. STR.0000221716.55088.d4.
- 25. You H, Chen K, Han P, Yue C, Zhao X. U-shaped relationship between cardiovascular mortality and serum uric acid may be attributed to stroke- and heart-specific mortality, respectively, among hypertensive patients: A nationally representative cohort study. Med Sci Monit 2021;27:e928937. doi: 10.12659/MSM.928937.
- Tscharre M, Herman R, Rohla M, Hauser C, Farhan S, Freynhofer MK, et al. Uric acid is associated with longterm adverse cardiovascular outcomes in patients with acute coronary syndrome undergoing percutaneous coronary intervention. Atherosclerosis 2018;270:173-9. doi: 10.1016/j.atherosclerosis.2018.02.003.
- 27. Sakata K, Hashimoto T, Ueshima H, Okayama A. Absence of an association between serum uric acid and mortality from cardiovascular disease: NIPPON DATA 80, 1980-1994. National integrated projects for prospective observation of non-communicable diseases and its trend in the aged. Eur J Epidemiol 2001;17:461-8. doi: 10.1023/a:1013735717961.
- Jiménez MC, Curhan GC, Choi HK, Forman JP, Rexrode KM. Plasma uric acid concentrations and risk of ischaemic stroke in women. Eur J Neurol 2016;23:1158-64. doi: 10.1111/ene.12998.
- Jee SH, Lee SY, Kim MT. Serum uric acid and risk of death from cancer, cardiovascular disease or all causes in men. Eur J Cardiovasc Prev Rehabil 2004;11:185-91. doi: 10.1097/01.hjr.0000130222.50258.22.
- Hu F, Hu L, Yu R, Han F, Zhou W, Wang T, et al. Prospective study of serum uric acid levels and first stroke events in Chinese adults with hypertension. Front Physiol 2021;12:807420. doi: 10.3389/ fphys.2021.807420.

- 31. Hozawa A, Folsom AR, Ibrahim H, Nieto FJ, Rosamond WD, Shahar E. Serum uric acid and risk of ischemic stroke: The ARIC Study. Atherosclerosis 2006;187:401-7. doi: 10.1016/j. atherosclerosis.2005.09.020.
- 32. Peterson J, Welch V, Losos M, Tugwell P. The Newcastle-Ottawa scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. 2011. Available at: https://www.ohri.ca/programs/ clinical_epidemiology/oxford.asp
- 33. Li J, Muraki I, Imano H, Cui R, Yamagishi K, Umesawa M, et al. Serum uric acid and risk of stroke and its types: The Circulatory Risk in Communities Study (CIRCS). Hypertens Res 2020;43:313-21. doi: 10.1038/s41440-019-0385-5.
- 34. Suarna C, Dean RT, May J, Stocker R. Human atherosclerotic plaque contains both oxidized lipids and relatively large amounts of alpha-tocopherol and ascorbate. Arterioscler Thromb Vasc Biol 1995;15:1616-24. doi: 10.1161/01.atv.15.10.1616.
- 35. Miedema I, Uyttenboogaart M, Koch M, Kremer B, de Keyser J, Luijckx GJ. Lack of association between serum uric acid levels and outcome in acute ischemic stroke. J Neurol Sci 2012;319:51-5. doi: 10.1016/j. jns.2012.05.019.
- 36. Grayson PC, Kim SY, LaValley M, Choi HK. Hyperuricemia and incident hypertension: A systematic review and meta-analysis. Arthritis Care Res (Hoboken) 2011;63:102-10. doi: 10.1002/ acr.20344.
- Kang DH, Han L, Ouyang X, Kahn AM, Kanellis J, Li P, et al. Uric acid causes vascular smooth muscle cell proliferation by entering cells via a functional urate transporter. Am J Nephrol 2005;25:425-33. doi: 10.1159/000087713.
- Alerhand S, Lay C. Spontaneous intracerebral hemorrhage. Emerg Med Clin North Am 2017;35:825-45. doi: 10.1016/j.emc.2017.07.002.
- O'Carroll CB, Brown BL, Freeman WD. Intracerebral hemorrhage: A common yet disproportionately deadly stroke subtype. Mayo Clin Proc 2021;96:1639-54. doi: 10.1016/j.mayocp.2020.10.034.
- Jin M, Yang F, Yang I, Yin Y, Luo JJ, Wang H, et al. Uric acid, hyperuricemia and vascular diseases. Front Biosci (Landmark Ed) 2012;17:656-69. doi: 10.2741/3950.
- 41. Tariq MA, Shamim SA, Rana KF, Saeed A, Malik BH. Serum uric acid risk factor for acute ischemic stroke and poor outcomes. Cureus 2019;11:e6007. doi: 10.7759/cureus.6007.
- 42. Nieto FJ, Iribarren C, Gross MD, Comstock GW, Cutler RG. Uric acid and serum antioxidant capacity: A reaction to atherosclerosis? Atherosclerosis 2000;148:131-9. doi: 10.1016/s0021-9150(99)00214-2.
- 43. Mazzali M, Kanbay M, Segal MS, Shafiu M, Jalal D, Feig DI, et al. Uric acid and hypertension: Cause or effect? Curr Rheumatol Rep 2010;12:108-17. doi: 10.1007/s11926-010-0094-1.

- 44. Borghi C, Agnoletti D, Cicero AFG, Lurbe E, Virdis A. Uric acid and hypertension: A review of evidence and future perspectives for the management of cardiovascular risk. Hypertension 2022;79:1927-36. doi: 10.1161/HYPERTENSIONAHA.122.17956.
- 45. Shah A, Keenan RT. Gout, hyperuricemia, and the risk of cardiovascular disease: Cause and effect? Curr Rheumatol Rep 2010;12:118-24. doi: 10.1007/s11926-010-0084-3.
- 46. Maruhashi T, Hisatome I, Kihara Y, Higashi Y. Hyperuricemia and endothelial function: From molecular background to clinical perspectives. Atherosclerosis 2018;278:226-31. doi: 10.1016/j. atherosclerosis.2018.10.007.
- Becker BF. Towards the physiological function of uric acid. Free Radic Biol Med 1993;14:615-31. doi: 10.1016/0891-5849(93)90143-i.
- 48. Steinberg HO, Brechtel G, Johnson A, Fineberg N, Baron AD. Insulin-mediated skeletal muscle vasodilation is nitric oxide dependent. A novel action of insulin to increase nitric oxide release. J Clin Invest 1994;94:1172-9. doi: 10.1172/JCl117433.
- 49. Baynes JW. Role of oxidative stress in development of complications in diabetes. Diabetes 1991;40:405-12. doi: 10.2337/diab.40.4.405.
- 50. Cortese F, Scicchitano P, Cortese AM, Meliota G, Andriani A, Truncellito L, et al. Uric acid in metabolic and cerebrovascular disorders: A review. Curr Vasc Pharmacol 2020;18:610-8. doi: 10.2174/157016111 8666191217123930.
- 51. Verdoia M, Barbieri L, Schaffer A, Cassetti E, Nardin M, Bellomo G, et al. Impact of diabetes on uric acid and its relationship with the extent of coronary artery disease and platelet aggregation: A single-centre cohort study. Metabolism 2014;63:640-6. doi: 10.1016/j.metabol.2014.01.010.
- 52. Li T, Yuan D, Yuan J. Antithrombotic drugspharmacology and perspectives. Adv Exp Med Biol 2020;1177:101-31. doi: 10.1007/978-981-15-2517-9_4.
- 53. Sumino H, Ichikawa S, Kanda T, Nakamura T, Sakamaki T. Reduction of serum uric acid by hormone replacement therapy in postmenopausal women with hyperuricaemia. Lancet 1999;354:650. doi: 10.1016/ S0140-6736(99)92381-4.
- 54. Naseem R, Al-Fareed Zafar SM, Jawed S, Mukhtar S, Ijaz F, Aftab RK. Influence of serum estradiol on serum uric acid level in pre and postmenopausal women. TPMJ 2019;26:1587-1591.
- 55. Yahyaoui R, Esteva I, Haro-Mora JJ, Almaraz MC, Morcillo S, Rojo-Martínez G, et al. Effect of longterm administration of cross-sex hormone therapy on serum and urinary uric acid in transsexual persons. J Clin Endocrinol Metab 2008;93:2230-3. doi: 10.1210/jc.2007-2467.
- 56. Adams HP Jr, Bendixen BH, Kappelle LJ, Biller J, Love BB, Gordon DL, et al. Classification of subtype of acute ischemic stroke. Definitions for use in a

multicenter clinical trial. TOAST. Trial of Org 10172 in Acute Stroke Treatment. Stroke 1993;24:35-41. doi: 10.1161/01.str.24.1.35.

- 57. GBD 2017 Disease and Injury Incidence and Prevalence Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990-2017: A systematic analysis for the Global Burden of Disease Study 2017. Lancet 2018;392:1789-858. doi: 10.1016/S0140-6736(18)32279-7.
- 58. Chao TF, Liu CJ, Chen SJ, Wang KL, Lin YJ, Chang SL, et al. Hyperuricemia and the risk of ischemic stroke in patients with atrial fibrillationcould it refine clinical risk stratification in AF? Int J Cardiol 2014;170:344-9. doi: 10.1016/j. ijcard.2013.11.011.
- 59. Berry C, Hamilton CA, Brosnan MJ, Magill FG, Berg GA, McMurray JJ, et al. Investigation into the sources of superoxide in human blood vessels: Angiotensin II increases superoxide production in human internal

mammary arteries. Circulation 2000;101:2206-12. doi: 10.1161/01.cir.101.18.2206.

- Kang DH, Park SK, Lee IK, Johnson RJ. Uric acidinduced C-reactive protein expression: Implication on cell proliferation and nitric oxide production of human vascular cells. J Am Soc Nephrol 2005;16:3553-62. doi: 10.1681/ASN.2005050572.
- Vannorsdall TD, Jinnah HA, Gordon B, Kraut M, Schretlen DJ. Cerebral ischemia mediates the effect of serum uric acid on cognitive function. Stroke 2008;39:3418-20. doi: 10.1161/ STROKEAHA.108.521591.
- Niu JW, Yuan J, Gao S, Xu WH. Low awareness of stroke guidelines and preference for Chinese herbs in community physicians: A national survey in China. Ann Transl Med 2014;2:76. doi: 10.3978/j.issn.2305-5839.2014.08.06.
- 63. Giordano C, Karasik O, King-Morris K, Asmar A. Uric acid as a marker of kidney disease: Review of the current literature. Dis Markers 2015;2015:382918. doi: 10.1155/2015/382918.



Supplementary Figure 1. PRISMA inclusion flow chart.

| 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 |

Supplementary Table 1. Quality assessment of included studies based on



Supplementary Figure 2. Egger's funnel plot for publication bias in studies for stroke incidence and mortality. SE: Standard error; Inrr: Natural logarithm of the risk ratio.

| Stroke | Incidence | % |
|--|----------------------|--------|
| ime and author (year) | RR (95% CI) | Weight |
| ess than ten years | | |
| ehto et al. (1998) | 1.91 (1.24, 2.94) | 3.57 |
| Bos et al. (2006) | 1.50 (1.05, 2.14) | 5.18 |
| Chen et al. (2009) | 1.26 (1.02, 1.55) | 13.89 |
| Tscharre et al. (2018) | 1.10 (0.49, 2.06) | 1.31 |
| Гu et al. (2019) | 2.27 (1.52, 3.37) | 4.18 |
| Cheng et al. (2021) | 1.42 (1.16, 1.73) | 15.06 |
| Hu et al. (2021) | 1.22 (0.79, 1.90) | 3.46 |
| Subgroup, DL (I ² = 36.1%, p = 0.153) | 1.47 (1.26, 1.73) | 46.64 |
| nore than ten years | | |
| Chien et al. (2005) | 1.58 (1.05, 2.37) | 4.00 |
| Hozawa et al. (2005) - | 1.25 (0.91, 1.73) | 6.30 |
| Strasak et al. (2008) | 1.37 (1.09, 1.74) | 11.37 |
| liménez et al. (2016) | 1.98 (1.11, 3.51) | 2.03 |
| .i et al. (2020) | 1.39 (1.22, 1.59) | 29.65 |
| Subgroup, DL (1 ² = 0.0%, p = 0.689) | 1.40 (1.26, 1.55) | 53.36 |
| Heterogeneity between groups: p = 0.589 | | |
| Overall, DL (l ² = 6.6%, p = 0.381) | \$ 1.42 (1.31, 1.54) | 100.00 |

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

| Stro | oke Mortality | | % |
|--|---------------|----------------|--------|
| time and author (year) | RR | (95% CI) | Weight |
| Less than ten years | | | |
| Tomita et al. (2000) | 1.6 | 9 (1.18, 2.42) | 10.54 |
| Sun et al. (2004) | . 1.1 | 0 (0.71, 1.72) | 9.56 |
| Kuo et al. (2012) | 1.0 | 1 (0.93, 1.10) | 13.00 |
| You et al. (2021) | 1.2 | 7 (0.54, 3.01) | 5.42 |
| Subgroup, DL (l ² = 61.3%, p = 0.051) | 1.2 | 0 (0.90, 1.60) | 38.52 |
| More than ten years | | | |
| Sakata et al. (2001) | 1.4 | 9 (0.90, 2.48) | 8.80 |
| Yariv et al. (2006) | 1.2 | 0 (0.81, 1.78) | 10.14 |
| Alexander et al. (2008) | 1.5 | 9 (1.23, 2.04) | 11.72 |
| Holme et al. (2009) | • 1.9 | 0 (1.85, 1.96) | 13.16 |
| Zhang et al. (2015) | 2.0 | 2 (1.71, 2.39) | 12.50 |
| Sakata et al. (2020) | 3.7 | 7 (1.54, 9.24) | 5.16 |
| Subgroup, DL (1 ² = 53.5%, p = 0.057) | ♦ 1.7 | 9 (1.56, 2.06) | 61.48 |
| Heterogeneity between groups: p = 0.013 | | | |
| Overall, DL (l ² = 95.7%, p = 0.000) | 1.5 | 3 (1.18, 1.99) | 100.00 |

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