Supplementary Materials

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1. Supplementary Notes

1.1 Study Design

In the first stage, we utilized a large-scale hospital-based prospective registry to assess this correlation.(1) In the second stage, we conducted a meta-analysis incorporated the results obtained from the registry study, along with relevant findings from other studies in the field, enhancing the overall understanding of the correlation. Finally, in the third stage, we performed a MR analysis utilizing summary data from the CKDGen and the Genetics of Ischemic Stroke Functional Outcome Network (GISCOME). Mendelian randomization allowed us to assess whether genetically determined UA was causally linked to stroke functional outcomes. This approach provided a unique perspective and added robustness to our investigation.

1.2 Nanjing Stroke Registry Program (NSRP)

1.2.1 Details of NSRP

Nanjing Stroke Registry program is the first hospital-based stroke registry program, started in July 2002, collects demographic, clinical, neuroimaging, and laboratory data from consecutively enrolled patients with stroke in mainland China.(1–3). Stroke severity was evaluated utilizing the National Institute of Health Stroke Scale (NIHSS),(4) while stroke subtypes were classified based on the Trial of ORG 10172 in Acute Stroke Treatment (TOAST) classification.(5) Laboratory data, including serum UA levels in blood samples collected within 24 hours of hospital admission, using standard laboratory procedures with urate oxidase reagent on a Dax analyzer. The interassay coefficient of variation was <3-5%.

The follow-up protocol was previously published elsewhere.(1) In brief, enrolled patients were prospectively followed up through clinical visits or telephone interviews by two certified investigators who were blinded to the baseline data. The research received approval from the Ethics Committee of Jingling Hospital, and informed consent was obtained from all participating patients.

1.2.2 Statistical Analyses in NSRP

The multivariable model was built in several steps: (1) inclusion of covariates with $P<0.1$ from univariable analyses; (2) inclusion of universal confounders (age, sex and recruitment year); (3) forward elimination of covariates with $P<0.1$; (4) removal of collinear covariates with a variance inflation factor greater than 5. To assess linear trends, the median value of each UA category was included as a continuous variable in the models. Restricted cubic spline (RCS) regression with four knots was used to explore potential nonlinear relationships. These models were adjusted for the covariates included in the multivariable model.

Subgroup analyses were performed to explore potential effect modification by factors associated with stroke prognosis. The likelihood ratio test assessed interactions between serum UA and subgroup variables for the primary outcome. Adjustment for covariates was conducted, except when the variable

was used as a subgroup variable. Propensity scores were calculated based on covariates in the multivariable logistic regression model, and cases with poor and good outcomes were matched in a 1:1 ratio using the nearest-neighbor method. Conditional logistic regression models were then fitted.

1.3 Meta-analysis

1.3.1 Data Extraction and Quality Evaluation

We extracted data on the first author, publication year, country, study design, sample size, follow-up duration, age, number of cases, the median or mean UA level, outcome assessment, adjusted covariates, effect value, and 95% CI. In studies where multiple multivariable-adjusted ORs were reported, we selected the effect estimate that incorporated the maximum adjustment for potential confounding factors. To evaluate the quality of the included studies, we employed the Newcastle-Ottawa Scale (NOS), which evaluates studies based on three areas: the selection of study subgroups, the comparability between subgroups, and the assessment of study endpoints.(6) In the selection of study subgroups category, we evaluated whether the group, characterized by UA levels, was truly representative of the study population. We also considered the methods used for ascertaining UA. In the comparability between subgroups category, we scrutinized whether the studies adequately accounted for potential confounders, including baseline characteristics, in the statistical analyses. The effect of UA on 90-day mRS outcomes in patients with ischemic stroke can be more accurately assessed. Lastly, the assessment of study endpoints category examines how each study assessed the outcome, considering factors such as the methodology used for assessment, the duration of the follow-up period, and the sufficiency of the follow-up data. The total score is calculated from the scores of each answer. Studies with a total score exceeding 6 (out of a total of 9) are considered to be of high quality.

1.3.2 Dose-response Meta-analysis

We further collected the number of cases and participants and OR estimates with 95% CIs for each category of UA levels (excluding studies with fewer than 3 quantitative categories). We extracted the OR (95% CI) that reflected the greatest degree of control for potential confounders. The group with the lowest number of UA levels was considered the reference category in most studies. When the reference category was not the lowest, we used the methodology proposed by Hamling and his collaborators to convert the risk estimates.(7) For each category, the corresponding OR in each study was assigned the median or mean UA level. In instances where median or mean UA levels were not available per category, the midpoint between the upper and lower bounds was considered as the dose. In cases where the highest category was open-ended, the midpoint of the category was set at 1.5 times the lower limit.(8,9) A two-stage random-effects dose-response meta-analysis was conducted, considering the heterogeneity between studies, to calculate the trend based on the correlated log OR estimates across different categories of uric acid (UA) levels.(10) Additionally, a non-linearity test was performed using restricted cubic spline analysis with three knots to assess the association between UA levels and stroke prognosis.(10)

1.4 Mendelian Randomization (MR)

1.4.1 Selection of Instrumental Variables (IVs)

To ensure robust causal inference, the MR design depends on three crucial assumptions: (1) single-nucleotide polymorphisms (SNPs) are strongly associated with the exposure of interest; (2) the genetic variant is not related to the outcome through a confounding factor; and (3) the genetic variant affects the outcome indirectly, rather than directly, primarily through the exposure of interest.(11) To fulfill the first MR assumption, SNPs that were associated with exposure at a genome-wide significance level ($P < 5\times10^{-8}$) and without linkage disequilibrium ($r^2 < 0.01$ and clump window >10000 kb) were employed as IVs. To further ascertain the first assumption, we computed the proportion of the variance of UA explained by whole SNPs and the F-statistic. Instrument strength is decided on the precision and magnitude of association of the IVs with the risk factor. When the F statistic is >10, it is considered to be sufficient.(12)

1.4.2 Positive Control Study

To validate the genetic instruments of UA, we conducted positive control analyses. As gout is a well-established effect of high serum UA, we investigated the association of the exposures of interest with gout as a positive control study. In the positive control study, we utilized the same set of instrumental variables as the univariable MR analysis.

1.4.3 Sensitivity analysis

To fulfill the third MR assumption, we assessed heterogeneity across estimates of SNPs for the association using Cochran's Q value.(13) We also conducted the MR-Egger intercept method and MRPRESSO global tests to detect potential pleiotropy ($P<0.05$ means potential pleiotropy exiting).(14,15) Furthermore, we performed Radial-MR analysis to identify outliers. Once outliers were identified, they were removed and the results were reanalyzed.(16) Finally, we conducted leave-one-out analysis and provided scatter plots depicting the associations of genetically determined serum UA levels with functional outcomes. In the reverse MR, the threshold P-value was relaxed to 5×10^{-6} to identify the SNPs associated with the functional outcome of ischemic stroke. Details of the instrument SNPs for the functional outcome of ischemic stroke are shown in Table S11. To discuss whether there was a collision bias in our MR results, we performed an MR study of uric acid and ischemic stroke risk.

1.4.4 Multivariable MR Analysis

To fulfill the second MR assumption, we examined associations between instrument SNPs and potential confounding factors in the PhenoScanner database. If the traits associated with SNP were potential confounders, we conducted multivariable MR analysis to account for correlated pleiotropy. PhenoScanner search revealed significant associations between instruments and BMI, CAD, CKD, and T2D. Hence, we performed multivariable MR analysis to assess the impact of confounding factors (CKD, BMI, CAD, and T2D) on the association between UA and stroke outcomes. (17)

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3. Supplemental Tables

Table S1 Baseline characteristics between the serum urate assayed and unassayed groups.

	Overall	Assayed	Unassayed	P value
Patients, n	5909	5631	278	
Demographics				
Female, n (%)	1720 (29.1)	1628 (28.9)	92 (33.1)	0.152
Age, y	62.00 (54.00, 70.00)	63.00 (54.00, 70.50)	60.00 (51.00, 68.00)	0.004
Physical examination				
BMI, kg/m^2	24.61 (22.84, 26.57)	24.62 (22.86, 26.61)	24.48 (22.60, 26.55)	0.591
SBP, mmHg	143.00 (130.00, 158.00)	143.00 (130.00, 158.00)	142.00 (130.00, 157.75)	0.439
DBP, mmHg	80.00 (75.00, 90.00)	80.00 (75.00, 90.00)	80.00 (73.25, 89.75)	0.317
NIHSS score at admission	4.00 (2.00, 9.00)	4.00 (2.00, 9.00)	4.00 (1.00, 8.00)	0.093
NIHSS at discharge	2.00 (0.00, 6.00)	2.00 (0.00, 6.00)	2.00 (0.00, 5.00)	0.385
Laboratory test				
FBG, mmol/L	5.50 (4.80, 7.30)	5.50 (4.80, 7.20)	5.80 (4.90, 8.50)	0.01
HbA1C	5.90 (5.50, 7.10)	5.90 (5.50, 7.00)	5.90 (5.40, 7.90)	0.458
TG, mmol/L	1.36 (1.00, 1.91)	1.35 (1.00, 1.89)	1.54 (1.05, 2.32)	0.001
TC, mmol/L	4.20 (3.51, 4.95)	4.20 (3.50, 4.93)	4.36 (3.59, 5.33)	0.005
HDL, mmol/L	1.00 (0.85, 1.19)	1.00 (0.86, 1.19)	1.07 (0.82, 1.33)	0.017
LDL, mmol/L	2.51 (1.91, 3.10)	2.50 (1.91, 3.08)	2.80 (1.99, 3.43)	0.002
Hb, g/L	139.00 (127.00, 150.00)	139.00 (127.00, 150.00)	139.00 (128.00, 147.00)	0.957
WBC, $10^9/L$	7.10 (5.80, 8.73)	7.10 (5.80, 8.73)	7.00 (5.53, 8.70)	0.613
PLT, $10^9/L$	200.00 (165.00, 243.00)	200.00 (164.00, 243.00)	208.50 (169.25, 248.50)	0.025

Scr, mmol/L	65.00 (55.00, 78.00)	65.00 (55.00, 77.90)	69.00 (51.10, 87.00)	0.135
Fib, g/L	3.10 (2.52, 4.10)	3.10 (2.52, 4.10)	3.10 (2.46, 4.30)	0.731
INR	1.01 (0.96, 1.06)	1.01 (0.96, 1.06)	1.02 (0.96, 1.08)	0.294
Medical history, n (%)				
Hypertension	3816 (64.6)	3646 (64.7)	170 (61.2)	0.246
Diabetes	1577 (26.7)	1513 (26.9)	64 (23.0)	0.178
Hyperlipidemia	211 (3.6)	200 (3.6)	11 (4.0)	0.85
TIA	20 (0.3)	20 (0.4)	0 (0.0)	0.687
AF	407 (6.9)	393 (7.0)	14 (5.0)	0.259
Coronary heart disease	374 (6.3)	354 (6.3)	20 (7.2)	0.631
MI	50 (0.8)	46 (0.8)	4 (1.4)	0.441
Hyperbilirubinemia	1199 (20.3)	1119 (19.9)	80 (28.8)	<0.001
Behavioral history, n (%)				
Smoking	2294 (38.8)	2191 (38.9)	103 (37.1)	0.577
Drinking	1388 (23.5)	1334 (23.7)	54 (19.4)	0.118
Family history of stroke	191 (3.2)	181 (3.2)	10 (3.6)	0.858
TOAST Types, n(%)				0.803
Large-artery atherosclerosis				0.393
Cardioembolism	4495 (76.1)	4276 (75.9)	219 (78.8)	
Small-vessel occlusion	556 (9.4)	538 (9.6)	18 (6.5)	
Others	513 (8.7)	489 (8.7)	24 (8.6)	
Medication of history, n(%)	345 (5.8)	328 (5.8)	17 (6.1)	
Antiplatelet	5800 (98.2)	5527 (98.2)	273 (98.2)	>0.999
Anticoagulation	900 (15.2)	866 (15.4)	34 (12.2)	0.18

90d mRS, n(%)				0.444
0 (no symptoms)	1267 (21.4)	1209 (21.5)	58 (20.9)	
1 (no significant disability)	2409 (40.8)	2287 (40.6)	122 (43.9)	
2 (slight disability)	773 (13.1)	737 (13.1)	36 (12.9)	
3 (moderate disability)	650 (11.0)	617 (11.0)	33 (11.9)	
4 (moderately severe disability)	460 (7.8)	446 (7.9)	14 (5.0)	
5 (severe disability)	309 (5.2)	294 (5.2)	15 (5.4)	
6 (dead)	41 (0.7)	41 (0.7)	0 (0.0)	

Continuous variables are described as mean ± SD for those with normal distribution and median (IQR) for those with nonnormal distribution.

Abbreviations: Q, quintile; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; NIHSS, National Institutes of Health Stroke Scale; FBG, fasting blood glucose; HbA1C, glycolated hemoglobin; TG, higher levels of triglyceride; TC, total cholesterol; HDL, high-density lipoprotein; LDL, low-density lipoprotein; Hb, hemoglobin; WBC, white blood cell; PLT, platelet; Scr, serum creatinine; Fib, fibrinogen; INR, international standard ratio; UA, uric acid; TIA, transient ischemic attack; AF, atrial fibrillation; MI, myocardial infarction; TOAST, trial of ORG 10172 in acute stroke treatment; mRS, modified Rankin Scale.

Table S2 Specific search strategies in Meta-analysis.

Search number	Query	Results
11	#3 and #6 and #9 and #10	63
10	"cohort studies"[mesh] OR "comparative study"[pt] OR "risk factors"[mesh] OR "cohort"[tw] OR "compared"[tw] OR "groups"[tw] OR "multivariate"[tw]	9,221,676
9	#7 or #8	1,940,319
8	Prognoses[Title/Abstract] OR Prognostic Factors[Title/Abstract] OR Prognostic Factor[Title/Abstract] OR Factor, Prognostic[Title/Abstract] OR Factors, Prognostic[Title/Abstract]	135,922
7	"Prognosis"[Mesh]	1,893,487
6	#4 or #5	182,390

5	Strokes[Title/Abstract] OR Cerebrovascular Accident[Title/Abstract] OR Cerebrovascular Accidents[Title/Abstract] OR CVA (Cerebrovascular Accident[Title/Abstract]) OR CVAs (Cerebrovascular Accident[Title/Abstract]) OR Cerebrovascular Apoplexy[Title/Abstract] OR Apoplexy, Cerebrovascular[Title/Abstract] OR Vascular Accident, Brain[Title/Abstract] OR Brain Vascular Accident[Title/Abstract] OR Brain Vascular Accidents[Title/Abstract] OR Vascular Accidents, Brain[Title/Abstract] OR Cerebrovascular Stroke[Title/Abstract] OR Cerebrovascular Strokes[Title/Abstract] OR Stroke, Cerebrovascular[Title/Abstract] OR Strokes, Cerebrovascular[Title/Abstract] OR Apoplexy[Title/Abstract] OR Cerebral Stroke[Title/Abstract] OR Cerebral Strokes[Title/Abstract] OR Stroke, Cerebral[Title/Abstract] OR Strokes, Cerebral[Title/Abstract] OR Stroke, Acute[Title/Abstract] OR Acute Stroke[Title/Abstract] OR Acute Strokes[Title/Abstract] OR Strokes, Acute[Title/Abstract] OR Cerebrovascular Accident, Acute[Title/Abstract] OR Acute Cerebrovascular Accident[Title/Abstract] OR Acute Cerebrovascular Accidents[Title/Abstract] OR Cerebrovascular Accidents, Acute[Title/Abstract]	30,953
4	"Stroke"[Mesh]	168,220
3	#1 or #2	32,263

2	Acid, Uric[Title/Abstract] OR 2,6,8-Trihydroxypurine[Title/Abstract] OR Trioxopurine[Title/Abstract] OR Potassium Urate[Title/Abstract] OR Urate, Potassium[Title/Abstract] OR Urate[Title/Abstract] OR Ammonium Acid Urate[Title/Abstract] OR Acid Urate, Ammonium[Title/Abstract] OR Urate, Ammonium Acid[Title/Abstract] OR Sodium Urate Monohydrate[Title/Abstract] OR Monohydrate, Sodium Urate[Title/Abstract] OR Urate Monohydrate, Sodium[Title/Abstract] OR Monosodium Urate Monohydrate[Title/Abstract] OR Monohydrate, Monosodium Urate[Title/Abstract] OR Urate Monohydrate, Monosodium[Title/Abstract] OR Sodium Acid Urate Monohydrate[Title/Abstract] OR Sodium Urate[Title/Abstract] OR Urate, Sodium[Title/Abstract] OR Monosodium Urate[Title/Abstract] OR Urate, Monosodium[Title/Abstract] OR Sodium Acid Urate[Title/Abstract] OR Acid Urate, Sodium[Title/Abstract] OR Urate, Sodium Acid[Title/Abstract]	9,763
1	"Uric Acid"[Mesh]	27,748

Table S3. Details of the GWASes included in the Mendelian randomization.

Traits	Consortium	Sample size	Ancestry	PubMed ID
Uric acid	CKDGen	288649	European	31578528
Functional outcome	GISCOME	6021	European	30796134
CKD	CKDGen	118147	European	26831199
BMI	GIANT	322154	European	25673413
CAD	CARDIoGRAMplusC4D	184305	Predominantly European	26343387
T2D	DIAGRAM	898130	European	30297969
Gout	GUGC	69374	European	23263486
Ischemic stroke	GIGASTROKE	1308460	European	36180795

Abbreviations: GISCOME, Genetics of Ischemic Stroke Functional Outcome network. DIAGRAM, Diabetes Genetics Replication And Meta-analysis. GIANT, The Genetic Investigation of Anthropometric Traits. CARDIoGRAMplusC4D, Coronary Artery Disease Genome wide Replication and Meta-analysis plus The Coronary Artery Disease Genetics. GUGC, Global Urate Genetics Consortium. CKD, chronic kidney disease. BMI, body mass index. CAD, coronary artery disease. T2D, type 2 diabetes.

Table S4. Baseline characteristics and clinical information of participants.

	Overall	Q1(≤234 μmol/L)	Q2(≤297 μmol/L)	Q3(≤366 μmol/L)	Q4(>366 μmol/L)	P value
Patients, n	5631	1423	1398	1421	1389	
Demographics						
Female, n (%)	1628 (28.9)	668 (46.9)	446 (31.9)	314 (22.1)	200 (14.4)	<0.001
Age, y	63.0 (54.0, 70.5)	64.0 (56.0, 72.0)	63.0 (54.0, 70.0)	62.0 (54.0, 70.0)	61.0 (51.0, 70.0)	<0.001
Recruitment year, y	2017 (2015, 2020)	2017 (2015, 2019)	2017 (2015, 2020)	2017 (2015, 2020)	2018 (2016, 2021)	0.001
Physical examination						
BMI, kg/m^2	24.6 (22.9, 26.6)	24.0 (22.0, 25.3)	24.5 (22.9, 26.4)	24.7 (22.9, 26.6)	25.4 (23.7, 27.3)	<0.001
SBP, mmHg	143.0 (130.0, 158.0)	142.0 (130.0, 157.0)	143.0 (130.0, 158.0)	143.0 (130.0, 158.0)	143.0 (130.0, 159.0)	0.673
DBP, mmHg	80.0 (75.0, 90.0)	80.0 (74.0, 89.0)	80.0 (75.0, 90.0)	80.0 (75.0, 90.0)	82.0 (75.0, 92.0)	<0.001
NIHSS score at admission	4.0 (2.0, 9.0)	6.0 (3.0, 13.0)	4.0 (2.0, 9.0)	3.0 (1.0, 7.0)	3.0 (1.0, 7.0)	<0.001
NIHSS at discharge	2.0 (0.0, 6.0)	4.0 (1.0, 10.0)	2.0 (0.0, 6.0)	1.0 (0.0, 4.0)	1.0 (0.0, 4.0)	<0.001
Laboratory test						
FBG, mmol/L	5.5 (4.8, 7.2)	6.2 (5.0, 8.5)	5.5 (4.8, 7.1)	5.4 (4.7, 6.7)	5.3 (4.6, 6.6)	<0.001
HbA1C	5.9 (5.5, 7.0)	6.1 (5.5, 7.8)	5.9 (5.5, 7.1)	5.9 (5.5, 6.9)	5.8 (5.5, 6.6)	<0.001
TG, mmol/L	1.4 (1.0, 1.9)	1.2 (0.9 1.6)	1.3 (1.0, 1.8)	1.4 (1.0, 1.9)	1.6 (1.2, 2.3)	<0.001
TC, mmol/L	4.2 (3.5, 4.9)	4.1 (3.4, 4.8)	4.1 (3.4, 4.8)	4.2 (3.5, 5.0)	4.3 (3.6, 5.1)	<0.001
HDL, mmol/L	1.0 (0.9, 1.2)	1.1 (0.9, 1.3)	1.0 (0.9, 1.2)	1.0 (0.9, 1.2)	0.9 (0.8, 1.1)	<0.001
LDL, mmol/L	2.5 (1.9, 3.1)	2.4 (1.9, 3.0)	2.5 (1.9, 3.0)	2.5 (1.9, 3.1)	2.6(2.0, 3.2)	<0.001
Hb, g/L	139.0 (127.0, 150.0)	132.0 (121.5, 143.0)	139.0 (127.0, 149.0)	141.0 (131.0, 152.0)	143.0 (131.0, 154.0)	<0.001
WBC, $10^9/L$	7.1 (5.8, 8.7)	7.4 (5.8, 9.3)	6.9 (5.7, 8.6)	6.9 (5.8, 8.4)	7.2 (6.0, 8.9)	<0.001
PLT, $10^9/L$	200.0 (164.0, 243.0)	201.0 (163.5, 247.0)	199.0 (165.0, 242.0)	198.0 (162.0, 238.0)	202.0 (165.0, 245.0)	0.225
Scr, mmol/L	65.0 (55.0, 77.9)	56.0 (47.0, 65.0)	62.0 (54.0, 72.0)	68.6 (58.1, 79.0)	77.0 (66.0, 95.0)	<0.001
Fib, g/L	3.1 (2.5, 4.1)	3.3 (2.6, 4.2)	3.1 (2.5, 4.0)	3.0 (2.5, 3.9)	3.1 (2.5, 4.0)	<0.001
INR	1.0 (1.0, 1.1)	1.0 (1.0, 1.1)	1.0 (1.0, 1.1)	1.0 (1.0 1.1)	1.0 (1.0, 1.1)	0.028

UA, μmol/L	296.0 (234.0, 366.0)	194.0 (167.0, 217.0)	266.0 (252.0, 281.0)	328.0 (313.0, 345.0)	419.0 (388.0, 465.0)	<0.001
Medical history, n (%)						
Hypertension	3646 (64.7)	858 (60.3)	888 (63.5)	924 (65.0)	976 (70.3)	<0.001
Diabetes	1513 (26.9)	453 (31.8)	385 (27.5)	368 (25.9)	307 (22.1)	<0.001
Hyperlipidemia	200 (3.6)	44 (3.1)	49 (3.5)	43 (3.0)	64 (4.6)	0.088
TIA	20 (0.4)	10 (0.7)	4 (0.3)	5 (0.4)	1 (0.1)	0.042
AF	393 (7.0)	114 (8.0)	90 (6.4)	80 (5.6)	109 (7.8)	0.036
Coronary heart disease	354 (6.3)	94 (6.6)	86 (6.2)	73 (5.1)	101 (7.3)	0.124
MI	46 (0.8)	8 (0.6)	15 (1.1)	6 (0.4)	17 (1.2)	0.049
Hyperbilirubinemia	1119 (19.9)	248 (17.4)	292 (20.9)	287 (20.2)	292 (21.0)	0.058
Behavioral history, n (%)						
Smoking	2191 (38.9)	398 (28.0)	509 (36.4)	617 (43.4)	667 (48.0)	<0.001
Drinking	1334 (23.7)	232 (16.3)	329 (23.5)	377 (26.5)	396 (28.5)	<0.001
Family history of stroke	181 (3.2)	37 (2.6)	50 (3.6)	52 (3.7)	42 (3.0)	0.336
TOAST Types, n (%)						0.002
Large-artery atherosclerosis	4276 (75.9)	1085 (76.2)	1092 (78.1)	1088 (76.6)	1011 (72.8)	
Cardioembolism	538 (9.6)	143 (10.0)	124 (8.9)	129 (9.1)	142 (10.2)	
Small-vessel occlusion	489 (8.7)	102 (7.2)	118 (8.4)	137 (9.6)	132 (9.5)	
Others	328 (5.8)	93 (6.5)	64 (4.6)	67 (4.7)	104 (7.5)	
Medication of history, n (%)						
Antiplatelet	5527 (98.2)	1397 (98.2)	1374 (98.3)	1397 (98.3)	1359 (97.8)	0.782
Anticoagulation	866 (15.4)	250 (17.6)	227 (16.2)	190 (13.4)	199 (14.3)	0.009
90d mRS, n (%)						<0.001
0 (no symptoms)	1209 (21.5)	206 (14.5)	293 (21.0)	327 (23.0)	383 (27.6)	
1 (no significant disability)	2287 (40.6)	485 (34.1)	598 (42.8)	632 (44.5)	572 (41.2)	
2 (slight disability)	737 (13.1)	202 (14.2)	189 (13.5)	180 (12.7)	166 (12.0)	

3 (moderate disability)	617 (11.0)	222 (15.6)	144 (10.3)	140 (9.9)	111 (8.0)
4 (moderately severe disability)	446 (7.9)	170 (11.9)	112 (8.0)	79 (5.6)	85 (6.1)
5 (severe disability)	294 (5.2)	123 (8.6)	54 (3.9)	52 (3.7)	65 (4.7)
6 (dead)	41 (0.7)	15 (1.1)	8 (0.6)	11 (0.8)	7 (0.5)

Continuous variables are described as mean ± SD for those with normal distribution and median (IQR) for those with nonnormal distribution.

Abbreviations: Q, quintile; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; NIHSS, National Institutes of Health Stroke Scale; FBG, fasting blood glucose; HbA1C, glycolated hemoglobin; TG, higher levels of triglyceride; TC, total cholesterol; HDL, high-density lipoprotein; LDL, low-density lipoprotein; Hb, hemoglobin; WBC, white blood cell; PLT, platelet; Scr, serum creatinine; Fib, fibrinogen; INR, international standard ratio; UA, uric acid; TIA, transient ischemic attack; AF, atrial fibrillation; MI, myocardial infarction; TOAST, trial of ORG 10172 in acute stroke treatment; mRS, modified Rankin Scale.

Table S5. Subgroup analysis of odds ratio (95%CI) of primary outcome according to UA quintile.

Subgroup	Outcomes/patients	Q1	Q2	P value	Q3	P value	Q4	P value	$P_{interaction}$
Age, y									0.894
≤60	441/2468	1.00 (reference)	0.78 (0.52-1.15)	0.211	0.90 (0.6-1.34)	0.594	0.69 (0.44-1.08)	0.101	
>60	957/3163	1.00 (reference)	0.84 (0.64-1.09)	0.191	0.92 (0.69-1.22)	0.564	0.93 (0.68-1.28)	0.667	
Sex									0.776
Men	894/4003	1.00 (reference)	0.82 (0.62-1.09)	0.168	0.90 (0.68-1.20)	0.486	0.78 (0.57-1.07)	0.127	
Women	504/1628	1.00 (reference)	0.80 (0.56-1.14)	0.223	0.86 (0.56-1.29)	0.459	0.99 (0.61-1.61)	0.975	
BMI, kg/m2									0.198
≤24	596/2238	1.00 (reference)	0.73 (0.53-1.00)	0.052	0.90 (0.64-1.27)	0.540	0.84 (0.56-1.26)	0.407	
>24	802/3393	1.00 (reference)	0.90 (0.66-1.22)	0.507	0.89 (0.65-1.22)	0.470	0.83 (0.59-1.16)	0.275	
NIHSS score at admission									0.007
≤4	1234/3050	1.00 (reference)	0.83 (0.53-1.28)	0.394	0.92 (0.59-1.45)	0.728	0.83 (0.50-1.35)	0.446	
>4	1172/2633	1.00 (reference)	0.83 (0.64-1.06)	0.138	0.92 (0.70-1.21)	0.550	0.86 (0.64-1.17)	0.343	
History of hypertension									0.240
No	442/1985	1.00 (reference)	0.73 (0.49-1.07)	0.112	0.72 (0.47-1.10)	0.133	0.85 (0.52-1.38)	0.518	
Yes	956/3646	1.00 (reference)	0.88 (0.67-1.15)	0.333	1.01 (0.76-1.34)	0.943	0.84 (0.62-1.14)	0.258	
History of diabetes									0.333
No	985/4118	1.00 (reference)	0.73 (0.56-0.96)	0.022	0.81 (0.61-1.07)	0.130	0.77 (0.56-1.05)	0.093	
Yes	413/1513	1.00 (reference)	1.09 (0.73-1.62)	0.672	1.13 (0.74-1.73)	0.565	0.99 (0.6-1.61)	0.954	
Smoking									0.600
No	930/3440	1.00 (reference)	0.83 (0.64-1.08)	0.165	0.99 (0.74-1.32)	0.956	1.00 (0.72-1.38)	0.998	
Yes	468/2191	1.00 (reference)	0.77 (0.52-1.16)	0.211	0.76 (0.51-1.15)	0.195	0.59 (0.38-0.91)	0.018	
Drinking									0.570
No	1120/4297	1.00 (reference)	0.86 (0.67-1.09)	0.214	0.95 (0.73-1.23)	0.711	0.92 (0.69-1.23)	0.577	
Yes	278/1334	1.00 (reference)	0.62 (0.37-1.05)	0.076	0.68 (0.40-1.16)	0.158	0.55 (0.30-0.99)	0.046	

ORs and 95% CIs was calculated with the use of the logistic regression model. Q1 level (≤234 μmol/L) of uric acid was set as the reference.
Abbreviations: Q, quintile; OR, odd ratio; CI, confidence interval; BMI, body mass index; NIHSS, National Institutes of Health Stroke Scale.
Analyses were adjusted for adjusted for sex, age, recruitment year, BMI, NIHSS Score at admission, hypertension, systolic blood pressure, diastolic blood pressure, diabetes, fasting blood glucose, glycolated hemoglobin, hyperlipidemia, higher levels of triglyceride, high-density lipoprotein, history of transient ischemic attack, smoking, drinking, family history of stroke, history of atrial fibrillation, history of coronary heart disease, history of myocardial infarction, hemoglobin, white blood cell, platelet, hyperbilirubinemia, serum creatinine, fibrinogen, international standard ratio, TOAST type, antiplatelet treatment, anti-coagulation treatment and NIHSS at discharge when they were not the strata variables.
$P_{interaction}$: Test for interaction between UA quintile and prespecified factors on primary outcome.

Table S6 Baseline characteristics and clinical information of participants after performing PSM (Propensity Score Matching).

	Overall	Good outcome	Poor outcome	P value
Patients, n	1616	808	808	
Demographics				
Female, n (%)	559 (34.6)	286 (35.4)	273 (33.8)	0.530
Age, y	66.00 (57.00, 73.00)	66.00 (57.75, 74.00)	65.00 (56.00, 73.00)	0.122
Recruitment year, y	2017 (2015, 2020)	2017.00 (2015, 2020)	2017 (2015, 2020)	0.957
Physical examination				
BMI, kg/m^2	24.27 (22.60, 26.30)	24.36 (22.49, 26.35)	24.22 (22.71, 26.24)	0.886
SBP, mmHg	144.00 (132.00, 160.00)	144.00 (131.00, 160.00)	144.00 (132.00, 159.25)	0.627
DBP, mmHg	80.00 (75.00, 90.00)	80.00 (75.00, 90.00)	80.00 (74.75, 90.00)	0.565
NIHSS score at admission	8.00 (4.00, 12.00)	8.00 (4.00, 12.00)	8.00 (4.00, 12.00)	0.275
NIHSS at discharge	5.00 (2.00, 9.00)	5.00 (2.00, 8.00)	6.00 (3.00, 9.00)	0.019
Laboratory test				
FBG, mmol/L	5.80 (4.90, 7.80)	5.80 (4.90, 7.60)	5.90 (4.90, 7.93)	0.252
HbA1C	6.00 (5.50, 7.30)	6.00 (5.50, 7.20)	6.00 (5.50, 7.43)	0.837
TG, mmol/L	1.29 (0.95, 1.75)	1.29 (0.92, 1.74)	1.29 (0.97, 1.75)	0.395
TC, mmol/L	4.14 (3.45, 4.90)	4.14 (3.44, 4.90)	4.13 (3.47, 4.92)	0.901
HDL, mmol/L	1.01 (0.85, 1.19)	1.01 (0.85, 1.18)	1.01 (0.85, 1.20)	0.857
LDL, mmol/L	2.50 (1.91, 3.12)	2.52 (1.92, 3.13)	2.45 (1.91, 3.08)	0.214
Hb, g/L	136.00 (124.00, 146.00)	135.00 (123.00, 147.00)	137.00 (125.00, 146.00)	0.174
WBC, $10^9/L$	7.40 (6.00, 9.27)	7.40 (6.00, 9.40)	7.40 (6.03, 9.10)	0.995
PLT, $10^9/L$	200.00 (161.00, 245.00)	200.00 (159.00, 243.00)	200.00 (165.00, 247.00)	0.237

Scr, mmol/L	63.00 (53.00, 76.00)	63.00 (53.00, 77.00)	63.00 (52.40, 76.00)	0.667
Fib, g/L	3.29 (2.62, 4.34)	3.26 (2.64, 4.36)	3.30 (2.61, 4.33)	0.908
INR	1.02 (0.97, 1.07)	1.02 (0.97, 1.08)	1.02 (0.97, 1.07)	0.753
UA, μmol/L	276.50 (218.00, 344.00)	279.50 (221.00, 349.00)	273.50 (214.00, 339.00)	0.221
Medical history, n (%)				
Hypertension	1106 (68.4)	561 (69.4)	545 (67.5)	0.422
Diabetes	495 (30.6)	249 (30.8)	246 (30.4)	0.914
Hyperlipidemia	48 (3.0)	22 (2.7)	26 (3.2)	0.660
TIA	6 (0.4)	3 (0.4)	3 (0.4)	>0.999
AF	142 (8.8)	66 (8.2)	76 (9.4)	0.429
Coronary heart disease	118 (7.3)	56 (6.9)	62 (7.7)	0.633
MI	25 (1.5)	13 (1.6)	12 (1.5)	>0.999
Hyperbilirubinemia	350 (21.7)	177 (21.9)	173 (21.4)	0.856
Behavioral history, n (%)				
Smoking	549 (34.0)	258 (31.9)	291 (36.0)	0.093
Drinking	347 (21.5)	171 (21.2)	176 (21.8)	0.809
Family history of stroke	32 (2.0)	14 (1.7)	18 (2.2)	0.592
TOAST Types, n(%)				0.796
Large-artery atherosclerosis	1233 (76.3)	623 (77.1)	610 (75.5)	
Cardioembolism	194 (12.0)	92 (11.4)	102 (12.6)	
Small-vessel occlusion	114 (7.1)	58 (7.2)	56 (6.9)	
Others	75 (4.6)	35 (4.3)	40 (5.0)	
Medication of history, n(%)				
Antiplatelet	1579 (97.7)	788 (97.5)	791 (97.9)	0.739

Anticoagulation	310 (19.2)	160 (19.8)	150 (18.6)	0.570

Continuous variables are described as mean ± SD for those with normal distribution and median (IQR) for those with nonnormal distribution.

Abbreviations: Q, quintile; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; NIHSS, National Institutes of Health Stroke Scale; FBG, fasting blood glucose; HbA1C, glycolated hemoglobin; TG, higher levels of triglyceride; TC, total cholesterol; HDL, high-density lipoprotein; LDL, low-density lipoprotein; Hb, hemoglobin; WBC, white blood cell; PLT, platelet; Scr, serum creatinine; Fib, fibrinogen; INR, international standard ratio; UA, uric acid; TIA, transient ischemic attack; AF, atrial fibrillation; MI, myocardial infarction; TOAST, trial of ORG 10172 in acute stroke treatment; mRS, modified Rankin Scale.

Table S7. Characteristics of included cohort studies in meta-analysis.

Author	Year	Study design	Country	Sample	Male (%)	Age	Basline urate (μmol/L)	UA measurement time	Follow Up Duration
Dawson	2009	cohort	Britain	852	61.5	68	350	within 6 h of stroke onset	3m
Miedema	2012	cohort	Holland	226	54.4	71	320	within 6 h of stroke onset	3m
Wu	2014	cohort	China	1452	64.7	63	303	on the morning after admission	12m
Chen	2016	cohort	China	3284	63.6	62.6	≥365	within 24 hours of hospital admission	3m
Zhang	2016	cohort	China	303	66.3	64.6	>402	within 24 hours of hospital admission	3m
Mapoure	2018	cohort	Afirca	480	53.1	62.8	423	on the morning after admission	3m
Yang	2018	cohort	China	752	52.8	59	255	within 24 hours of hospital admission	3m
Wang	2019	cohort	China	1041	64.8	63.93	341.70	on the morning after admission	12m
Liu	2022	cohort	China	636	57.1	70.6	>368.9	at the time of admission	3m
Zhong	2023	cohort	China	5631	71.1	63	>366	within 24 hours of hospital admission	3m

Continued.

Author	Year	Definition of Good Outcome	Definition of Bad Outcome	Covariance	Quality Assessment[a]
Dawson	2009	90 d mRS ≤ 2	90 d mRS ≥ 3	Age, Male, BSSS, Creatinine, SBP, Glucose, Hypertension, AF, CHF.	8
Miedema	2012	90 d mRS ≤ 2	90 d mRS ≥ 3	age, baseline NIHSS, serum glucose level, sex, history of coronary artery disease, history of previous stroke and large vessel disease as stroke aetiology.	8
Wu	2014	90 d mRS ≤ 2	90 d mRS ≥ 3	age, NIHSS at admission, hemoglobin at admission, fasting glucose, HbA1C, SBP, DBP, triglyceride, HDL, LDL, creatinine, CHOL, BMI, ASPECT, homocysteine, hs-CRP	8

Chen	2016	90 d mRS ≤ 2	90 d mRS ≥ 3	adjusted for age, time from onset to hospitalization, current smoking, alcohol consumption, glucose, SBP, WBC, dyslipidemia, history of hypertension, history of coronary heart disease, history of diabetes mellitus, family history of stroke, and current use of antihypertensive medications, basline NIHSS	7
Zhang	2016	90 d mRS ≤ 1	90 d mRS≥2	Age, AF, hypertension, smokers, CAD, previous stroke, hyperlipidemia, ASCO, baseline NIHSS scores, thrombolysis treatment, drugs, GFR	8
Mapoure	2018	90 d mRS ≤ 2	90 d mRS ≥ 3	Age, hyperyension, smoking, previous stroke, NIHSS, hyperglycemia, hyperuremia, hypercreatinemia, HDL, complications	6
Yang	2018	90 d mRS ≤ 2	90 d mRS ≥ 3	age, NIHSS, lesion volumes, AF, smoking history, hypertension, stroke syndrome, stroke etiology, Hs-CRP, FBG, HCY.	9
Wang	2019	90 d mRS ≤ 2	90 d mRS ≥ 3	age, sex, tobacco use, alcohol abuse, hypertension, hyperlipidaemia, hyperuricemia, atrial fibrillation, coronary heart disease, heart failure, myocardial infarction, other heart diseases, previous stroke, serum TC, TG, LDL, HDL, stroke subtypes and NIHSS at admission.	7
Liu	2022	90 d mRS ≤ 1	90 d mRS ≥ 2	Age, sex, BMI, SBP, DBP, OSAS, smoking, drinking, TG, TC, HDL-C, LDL-C, Hcy, eGFR, and ESR, and NIHSS score on admission.	5
Zhong	2023	90 d mRS ≤ 2	90 d mRS ≥ 3	Sex, Age, BMI, NIHSS Score, Hypertension, SBP, DBP, Diabetes, FBG, HbA1C, Hyperlipidemia, TG, HDL, History of TIA, Smoking, Drinking, Family history of stroke, History of AF, History of CHD, History of MI, History of stroke, Hb, WBC, PLT, HBI, Scr, FIB, INR, TOAST, Anti platelet treatment, Anti coagulation treatment, NIHSS at discharge	9

[a] The quality assessment score was determined according to the Newcastle-Ottawa Scale for cohort studies (0-9 points).

Abbreviations: mRS, modified Rankin Scale; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; NIHSS, National Institutes of Health Stroke Scale; FBG, fasting blood glucose; HbA1C, glycolated hemoglobin; TG, higher levels of triglyceride; TC, total cholesterol; HDL, high-density lipoprotein; LDL, low-density lipoprotein; Hb, hemoglobin; WBC, white blood cell; PLT, platelet; Scr, serum creatinine; Fib, fibrinogen; INR, international standard ratio; UA, uric acid; TIA, transient ischemic attack; AF, atrial fibrillation; MI, myocardial infarction; TOAST, trial of ORG 10172 in acute stroke treatment; CHF, chronic heart failure; CHOL, cholesterol; ASPECT, Alberta Stroke Programme early CT score; ASCO, A means atherosclerosis, S means small vessel disease, C means cardiac sources, O means other causes; GFR, glomerular filtration rate; hs-CRP, high sensitivity C-reactive protein; HCY, homocysteine.

Table S8 Genome-wide significant (p<5x10-8) single nucleotide polymorphisms that were used as instruments for serum urate level.

SNP	Chr	Pos	Effect Allele	Other Allele	EAF	Nearest gene	Beta	Se	P-value	F-statistics
rs2480712	1	2156999	C	G	0.66	*SKI*	0.024	0.004	6.25E-09	33.76
rs4646068	1	15828704	T	C	0.69	*CASP9*	0.024	0.004	7.71E-09	33.35
rs79598313	1	27284913	T	C	0.03	*KDF1*	0.100	0.013	9.22E-15	60.06
rs141990161	1	119943525	T	C	0.98	*HAO2*	0.133	0.023	1.59E-08	31.94
rs10910845	1	145723120	A	C	0.47	*NBPF20*	0.058	0.004	1.50E-51	228.16
rs11204701	1	150662179	A	T	0.78	*GOLPH3L*	-0.036	0.005	1.04E-14	59.81
rs2070803	1	155157715	A	G	0.58	*TRIM46*	0.053	0.004	4.09E-41	180.34
rs2760215	1	163675883	T	C	0.50	*LOC100422212*	-0.025	0.004	5.81E-11	42.88
rs12037861	1	221038177	A	T	0.70	*HLX-AS1*	0.023	0.004	3.39E-08	30.47
rs2867112	2	651349	T	G	0.83	*TMEM18*	0.035	0.005	9.84E-12	46.36
rs72782806	2	15788511	A	G	0.26	*DDX1*	0.025	0.004	8.12E-09	33.24
rs1260326	2	27730940	T	C	0.40	*GCKR*	0.070	0.004	4.61E-69	308.52
rs12472381	2	59321225	A	G	0.39	*LINC01122*	0.022	0.004	1.80E-08	31.70
rs12987661	2	69813458	T	C	0.87	*AAK1*	0.041	0.006	1.44E-12	50.13
rs17050272	2	121306440	A	G	0.42	*LINC01101*	0.032	0.004	1.57E-15	63.54
rs11683692	2	145509615	T	C	0.94	*TEX41*	-0.048	0.008	1.32E-08	32.30
rs1234413	2	148844369	T	C	0.44	*MBD5*	-0.022	0.004	7.08E-09	33.51
rs9287911	2	170037294	A	T	0.25	*LRP2*	0.038	0.004	1.13E-17	73.28
rs187355703	2	176993583	C	G	0.97	*HOXD8*	-0.086	0.013	2.70E-11	44.38
rs1047891	2	211540507	A	C	0.31	*CPS1*	-0.024	0.004	2.09E-08	31.41
rs9288447	2	213083638	T	C	0.55	*ERBB4*	-0.023	0.004	3.27E-09	35.02

rs2581817	3	53071797	C	G	0.42	*SFMBT1*	0.048	0.004	4.87E-35	152.52
rs11128111	3	69145632	T	C	0.48	*ARL6IP5*	-0.021	0.004	4.64E-08	29.86
rs7640441	3	125118082	A	C	0.25	*ZNF148*	-0.028	0.005	1.26E-09	36.88
rs80120242	3	132235344	A	T	0.95	*DNAJC13*	-0.062	0.010	1.87E-09	36.11
rs4447862	4	9931645	C	G	0.73	*SLC2A9*	0.330	0.004	0.00E+00	6136.85
rs98270	4	48019323	A	G	0.36	*NIPAL1*	0.022	0.004	4.21E-08	30.05
rs10857147	4	81181072	A	T	0.71	*FGF5*	0.024	0.004	2.21E-08	31.30
rs74904971	4	89050026	A	C	0.11	*ABCG2*	0.254	0.006	0.00E+00	1763.06
rs1440411	4	144158285	T	C	0.57	*USP38*	-0.028	0.004	1.08E-12	50.69
rs455213	5	34660235	T	C	0.54	*RAI14*	-0.027	0.004	6.05E-12	47.31
rs10942549	5	72426137	C	G	0.31	*TMEM171*	-0.042	0.004	1.64E-22	95.29
rs76004499	5	176705865	C	G	0.97	*NSD1*	-0.074	0.013	3.26E-08	30.54
rs12530084	6	7214676	T	C	0.22	*RREB1*	0.066	0.005	9.55E-48	210.73
rs1359232	6	25809716	A	C	0.47	*SLC17A1*	-0.091	0.004	4.12E-126	570.61
rs1574430	6	43269029	A	C	0.41	*SLC22A7*	0.029	0.004	2.77E-14	57.89
rs10223666	6	43805502	C	G	0.70	*VEGFA*	0.046	0.004	6.62E-28	119.91
rs4897160	6	126223944	A	G	0.48	*NCOA7*	0.030	0.004	1.96E-14	58.57
rs62435145	7	1286567	T	G	0.69	*UNCX*	0.042	0.005	2.36E-16	67.28
rs13226650	7	73017005	A	G	0.81	*MLXIPL*	0.049	0.005	1.34E-23	100.25
rs11551890	7	97845713	A	G	0.51	*TECPR1*	0.023	0.004	2.40E-08	31.14
rs10480300	7	151406005	T	C	0.28	*PRKAG2*	0.030	0.004	4.26E-12	48.00
rs34861762	8	23748420	T	C	0.42	*STC1*	0.034	0.004	3.50E-19	80.13
rs2466077	8	32432753	T	G	0.53	*NRG1*	-0.022	0.004	1.78E-08	31.72
rs2943539	8	76479839	T	C	0.48	*HNF4G*	0.041	0.004	6.42E-28	119.97

rs10956924	8	95678312	T	C	0.28	*ESRP1*	-0.024	0.004	1.79E-08	31.72
rs10971420	9	33125000	T	C	0.69	*B4GALT1*	0.031	0.004	4.14E-14	57.10
rs56106601	9	130770484	A	C	0.95	*FAM102A*	0.061	0.009	2.67E-11	44.40
rs74440730	10	16920892	A	C	0.89	*CUBN*	-0.037	0.006	2.22E-09	35.77
rs10994860	10	52645424	T	C	0.18	*A1CF*	0.064	0.005	1.31E-36	159.71
rs1649078	10	60293320	A	C	0.48	*BICC1*	-0.039	0.004	4.08E-19	79.83
rs1171617	10	61467182	T	G	0.77	*SLC16A9*	0.079	0.005	1.81E-66	296.61
rs9420446	10	88880689	T	C	0.14	*FAM35A*	-0.038	0.006	1.13E-11	46.09
rs35198068	10	114754784	T	C	0.71	*TCF7L2*	0.025	0.004	5.85E-09	33.88
rs35506085	11	2165576	A	G	0.19	*IGF2*	-0.029	0.005	1.50E-08	32.06
rs3925584	11	30760335	T	C	0.55	*DCDC1*	0.030	0.004	1.66E-15	63.43
rs71456318	11	64332862	A	C	0.48	*SLC22A11*	0.079	0.004	4.41E-92	414.23
rs10896028	11	65432187	A	T	0.65	*RELA*	-0.048	0.004	4.10E-33	143.72
rs10892354	11	119238381	T	C	0.38	*USP2*	0.030	0.004	2.60E-13	53.49
rs7303595	12	15359063	A	T	0.34	*RERG*	0.025	0.004	7.05E-10	38.01
rs7315236	12	52251933	T	C	0.36	*LOC105369971*	0.029	0.004	1.91E-13	54.10
rs12313306	12	57751854	T	C	0.25	*R3HDM2*	-0.076	0.004	6.74E-65	289.40
rs10774625	12	111910219	A	G	0.48	*ATXN2*	0.032	0.004	5.54E-17	70.14
rs1800574	12	121416864	T	C	0.03	*HNF1A*	-0.081	0.012	2.84E-12	48.80
rs28530689	12	122500748	A	C	0.51	*LOC100506691*	0.032	0.004	1.27E-16	68.50
rs12423664	12	133069894	A	G	0.15	*FBRSL1*	0.042	0.006	1.75E-13	54.27
rs7986094	13	31029931	A	C	0.30	*HMGB1*	-0.024	0.004	1.74E-08	31.77
rs626277	13	72347696	A	C	0.59	*DACH1*	0.026	0.004	2.69E-11	44.39
rs861536	14	104167564	A	G	0.62	*KLC1*	0.024	0.004	2.16E-09	35.82

rs1478604	15	39873321	T	C	0.71	*THBS1*	-0.026	0.004	4.49E-10	38.89
rs2929508	15	72246964	A	T	0.26	*MYO9A*	-0.029	0.005	3.65E-09	34.80
rs8040109	15	73334225	A	C	0.71	*NEO1*	0.025	0.004	5.85E-09	33.88
rs10851885	15	76304503	A	G	0.76	*NRG4*	-0.054	0.005	4.16E-32	139.11
rs55781567	15	78857986	C	G	0.65	*CHRNA5*	0.023	0.004	1.10E-08	32.65
rs12908437	15	99287375	T	C	0.38	*IGF1R*	0.046	0.004	1.56E-30	131.92
rs4997081	16	20365234	C	G	0.20	*UMOD*	-0.030	0.005	4.18E-10	39.03
rs8050136	16	53816275	A	C	0.40	*FTO*	0.025	0.004	2.34E-10	40.16
rs62052820	16	69575238	A	G	0.21	*MIR1538*	0.041	0.005	2.81E-18	76.02
rs4788815	16	71634811	A	T	0.36	*TAT*	-0.026	0.004	7.44E-11	42.40
rs57652769	16	79753976	T	C	0.31	*MAFTRR*	-0.036	0.004	8.56E-18	73.82
rs11644696	16	81572093	A	G	0.48	*CMIP*	0.022	0.004	1.41E-08	32.17
rs2453580	17	19438321	T	C	0.60	*SLC47A1*	0.025	0.004	7.01E-10	38.02
rs3794748	17	53365172	A	G	0.41	*HLF*	0.038	0.004	1.38E-21	91.08
rs9895661	17	59456589	T	C	0.82	*BCAS3*	0.050	0.005	7.23E-23	96.92
rs11663816	18	57876227	T	C	0.73	*MC4R*	-0.030	0.004	1.40E-12	50.18
rs57070985	19	4969053	A	G	0.65	*KDM4B*	0.029	0.004	2.04E-12	49.44
rs10405423	19	7211311	A	C	0.66	*INSR*	0.039	0.004	1.07E-20	87.03
rs4808762	19	18326222	T	C	0.72	*PDE4C*	-0.024	0.004	1.36E-08	32.25
rs2868194	19	33350060	T	C	0.41	*SLC7A9*	-0.027	0.004	8.90E-12	46.56
rs35396326	19	45357003	C	G	0.70	*NECTIN2*	0.025	0.004	2.30E-08	31.22
rs62128132	19	50217955	T	C	0.97	*CPT1C*	-0.118	0.015	1.32E-15	63.88
rs7267595	20	10643850	A	C	0.51	*JAG1*	0.023	0.004	3.15E-09	35.09
rs6119510	20	33287782	T	G	0.60	*TP53INP2*	-0.023	0.004	3.20E-09	35.06

rs1800961	20	43042364	T	C	0.03	*HNF4A*	-0.076	0.012	1.63E-10	40.87
rs219781	21	37832621	T	G	0.25	*CLDN14*	-0.025	0.004	1.56E-08	31.97
rs12485100	22	44325516	T	G	0.17	*PNPLA3*	-0.033	0.005	2.44E-10	40.08

Abbreviations: SNP, single-nucleotide polymorphisms; Chr, chromosome; Pos, position; EAF, effect allele frequency; SE, standard error.

Table S9 Genetic association for serum UA and functional outcomes of stroke in GISCOME.

SNP	beta.exposure	se.exposure	beta.outcome	se.outcome
rs10223666	0.046	0.004	-0.0478	0.0537
rs10405423	0.039	0.004	4.00E-04	0.0531
rs1047891	-0.024	0.004	-0.0297	0.0548
rs10480300	0.03	0.004	0.1478	0.0547
rs10774625	0.032	0.004	0.0549	0.049
rs10851885	-0.054	0.005	-0.0432	0.0579
rs10857147	0.024	0.004	-0.0301	0.0533
rs10892354	0.03	0.004	-0.0345	0.0503
rs10896028	-0.048	0.004	-0.0111	0.0515
rs10942549	-0.042	0.004	-0.0574	0.0542
rs10956924	-0.024	0.004	0.0695	0.0542
rs10971420	0.031	0.004	-0.0581	0.0532
rs10994860	0.064	0.005	-0.0212	0.0636
rs11128111	-0.021	0.004	-0.0758	0.0494
rs11204701	-0.036	0.005	-0.0658	0.0592
rs11551890	0.023	0.004	0.0309	0.0517
rs11644696	0.022	0.004	-0.037	0.0495
rs11663816	-0.03	0.004	-0.0151	0.0553
rs11683692	-0.048	0.008	-0.0926	0.1162
rs1171617	0.079	0.005	0.0132	0.0585
rs12037861	0.023	0.004	0.0238	0.0533
rs12313306	-0.076	0.004	0.069	0.0572

rs1234413	-0.022	0.004	0.0613	0.0491
rs12423664	0.042	0.006	0.0295	0.0701
rs12472381	0.022	0.004	0.0251	0.0505
rs12485100	-0.033	0.005	-0.0353	0.0663
rs12530084	0.066	0.005	-0.0568	0.0589
rs1260326	0.07	0.004	-0.1244	0.0504
rs12908437	0.046	0.004	-0.0216	0.0497
rs12987661	0.041	0.006	-0.0273	0.0748
rs1359232	-0.091	0.004	-0.0639	0.0498
rs141990161	0.133	0.023	-0.6016	0.2822
rs1440411	-0.028	0.004	0.0726	0.0497
rs1478604	-0.026	0.004	-0.0279	0.0537
rs1574430	0.029	0.004	0.0436	0.0501
rs1649078	-0.039	0.004	0.0473	0.05
rs17050272	0.032	0.004	0.0597	0.0501
rs1800574	-0.081	0.012	-0.1703	0.16
rs1800961	-0.076	0.012	-0.1494	0.1366
rs187355703	-0.086	0.013	0.2088	0.1713
rs2070803	0.053	0.004	0.0392	0.0494
rs219781	-0.025	0.004	-0.0911	0.0576
rs2453580	0.025	0.004	0.0037	0.0516
rs2466077	-0.022	0.004	0.0483	0.0496
rs2480712	0.024	0.004	-0.0157	0.0521
rs2581817	0.048	0.004	-0.1508	0.0498

rs2760215	-0.025	0.004	0.0206	0.0487
rs28530689	0.032	0.004	-0.0708	0.0492
rs2867112	0.035	0.005	0.1156	0.068
rs2868194	-0.027	0.004	0.0685	0.0499
rs2929508	-0.029	0.005	-0.0062	0.0564
rs2943539	0.041	0.004	0.1324	0.0488
rs34861762	0.034	0.004	0.0094	0.0488
rs35198068	0.025	0.004	-0.1267	0.0538
rs35396326	0.025	0.004	0.013	0.0561
rs35506085	-0.029	0.005	-0.0362	0.0622
rs3794748	0.038	0.004	0.0537	0.0505
rs3925584	0.03	0.004	-0.0873	0.049
rs4447862	0.33	0.004	0.0546	0.0548
rs455213	-0.027	0.004	0.0787	0.05
rs4646068	0.024	0.004	0.0941	0.0535
rs4788815	-0.026	0.004	0.0065	0.0513
rs4808762	-0.024	0.004	0.0414	0.0547
rs4897160	0.03	0.004	0.0319	0.049
rs4997081	-0.03	0.005	0.1027	0.0634
rs55781567	0.023	0.004	0.0714	0.0513
rs56106601	0.061	0.009	-0.0061	0.1217
rs57070985	0.029	0.004	0.0017	0.0524
rs57652769	-0.036	0.004	0.0688	0.0524
rs6119510	-0.023	0.004	-0.0615	0.0495

rs62052820	0.041	0.005	0.0136	0.0584
rs62128132	-0.118	0.015	0.0889	0.1622
rs62435145	0.042	0.005	-0.0174	0.053
rs626277	0.026	0.004	0.0366	0.05
rs71456318	0.079	0.004	0.0435	0.0492
rs7267595	0.023	0.004	0.0507	0.0488
rs72782806	0.025	0.004	-0.0141	0.0575
rs7303595	0.025	0.004	0.0556	0.0532
rs7315236	0.029	0.004	-0.0833	0.0514
rs74440730	-0.037	0.006	0.0051	0.0783
rs74904971	0.254	0.006	-0.0698	0.0874
rs76004499	-0.074	0.013	0.0809	0.1718
rs7640441	-0.028	0.005	-0.0591	0.0572
rs79598313	0.1	0.013	0.0546	0.165
rs7986094	-0.024	0.004	-0.0491	0.054
rs80120242	-0.062	0.01	0.1814	0.1222
rs8040109	0.025	0.004	0.0298	0.0536
rs8050136	0.025	0.004	0.0309	0.0495
rs861536	0.024	0.004	0.0133	0.0506
rs9287911	0.038	0.004	-0.0019	0.0562
rs9288447	-0.023	0.004	-0.0598	0.05
rs9420446	-0.038	0.006	0.047	0.071
rs98270	0.022	0.004	0.0272	0.0515

Abbreviations: GISCOME, Genetics of Ischemic Stroke Functional Outcome network; SNP, single nucleotide polymorphism; Se, standard error.

Table S10. Mendelian randomization association of genetically predicted serum urate level with functional outcomes using different statistical models.

Outcome	Method	nsnp	P for Cochran's Q	$P_{intercept}$	OR	95%CI	P value
Functional outcome	Inverse variance weighted	93	0.294	0.610	1.07	(0.89-1.30)	0.461
	MR Egger	93			1.02	(0.78-1.34)	0.881
	Weighted median	93			1.07	(0.82-1.40)	0.597
	Simple mode	93			1.33	(0.62-2.87)	0.467
	Weighted mode	93			1.10	(0.86-1.40)	0.446
Functional outcome_NIHSS[a]	Inverse variance weighted	93	0.052	0.785	1.03	(0.82-1.31)	0.741
	MR Egger	93			1.00	(0.71-1.40)	0.862
	Weighted median	93			1.18	(0.85-1.62)	0.947
	Simple mode	93			1.86	(0.76-4.59)	0.796
	Weighted mode	93			1.14	(0.86-1.51)	0.844

[a]: Mendelian randomization utilized the summary data of 3-month functional outcomes of ischemic stroke from the Genetics of Ischemic Stroke Functional Outcome Network adjusted for age, sex, ancestry and baseline NIHSS.

$P_{intercept}$: P for MR-Egger intercept test to quantify the effect of directional pleiotropy. Values that significantly differ from zero indicated potential pleiotropy, which suggested exposure-associated genetic variables may influence the outcome through other pathways rather than through exposure.

Abbreviations: OR odds ratio; CI, confidence interval.

Table S11 6SNPs and effect sizes for functional outcome.

SNP	Effect Allele	Other Allele	EAF	Beta	Se	P-value	F-statistics
rs1842681	A	G	0.2341	0.3395	0.0582	5.272E-09	34.03
rs73712229	A	C	0.0662	0.4683	0.0965	0.000001224	23.55
rs59665378	T	C	0.4676	-0.2346	0.0499	0.000002565	22.10
rs2236406	T	C	0.6446	-0.2401	0.0517	0.000003427	21.57
rs80078009	T	C	0.036	0.7189	0.1556	0.000003829	21.35
rs76926687	T	C	0.0174	1.0006	0.2184	0.000004603	20.99

Abbreviations: SNP, single-nucleotide polymorphisms; EAF, effect allele frequency; SE, standard error.

Table S12 The reverse causal effect of functional outcome of stroke on serum urate levels using different statistical models.

Outcome	Method	nsnp	P for Cochran's Q	$P_{intercept}$	Beta	95%CI	P value
Uric Acid	Inverse variance weighted	4	0.962	0.901	-0.012	(-0.027,0.004)	0.143
	MR Egger	4			-0.013	(-0.055,0.030)	0.619
	Weighted median	4			-0.009	(-0.027,0.008)	0.307
	Simple mode	4			-0.008	(-0.033,0.018)	0.599
	Weighted mode	4			-0.007	(-0.029,0.015)	0.568

$P_{intercept}$: P for MR-Egger intercept test to quantify the effect of directional pleiotropy. Values that significantly differ from zero indicated potential pleiotropy, which suggested exposure-associated genetic variables may influence the outcome through other pathways rather than through exposure.

Abbreviations: OR odds ratio; CI, confidence interval.

Table S13 Genetic association for serum UA and Ischemic stroke.

Outcome	Method	nsnp	P for Cochran's Q	$P_{intercept}$	OR	95%CI	P value
Ischemic stroke	Inverse variance weighted	71	0.002	0.022	0.94	(0.89-0.99)	0.025
	MR Egger	71			1.03	(0.94-1.13)	0.521
	Weighted median	71			0.99	(0.93-1.06)	0.854
	Simple mode	71			0.99	(0.86-1.13)	0.864
	Weighted mode	71			1.01	(0.95-1.09)	0.672

$P_{intercept}$: P for MR-Egger intercept test to quantify the effect of directional pleiotropy. Values that significantly differ from zero indicated potential pleiotropy, which suggested exposure-associated genetic variables may influence the outcome through other pathways rather than through exposure.

Abbreviations: OR odds ratio; CI, confidence interval.

4. Supplemental Figures

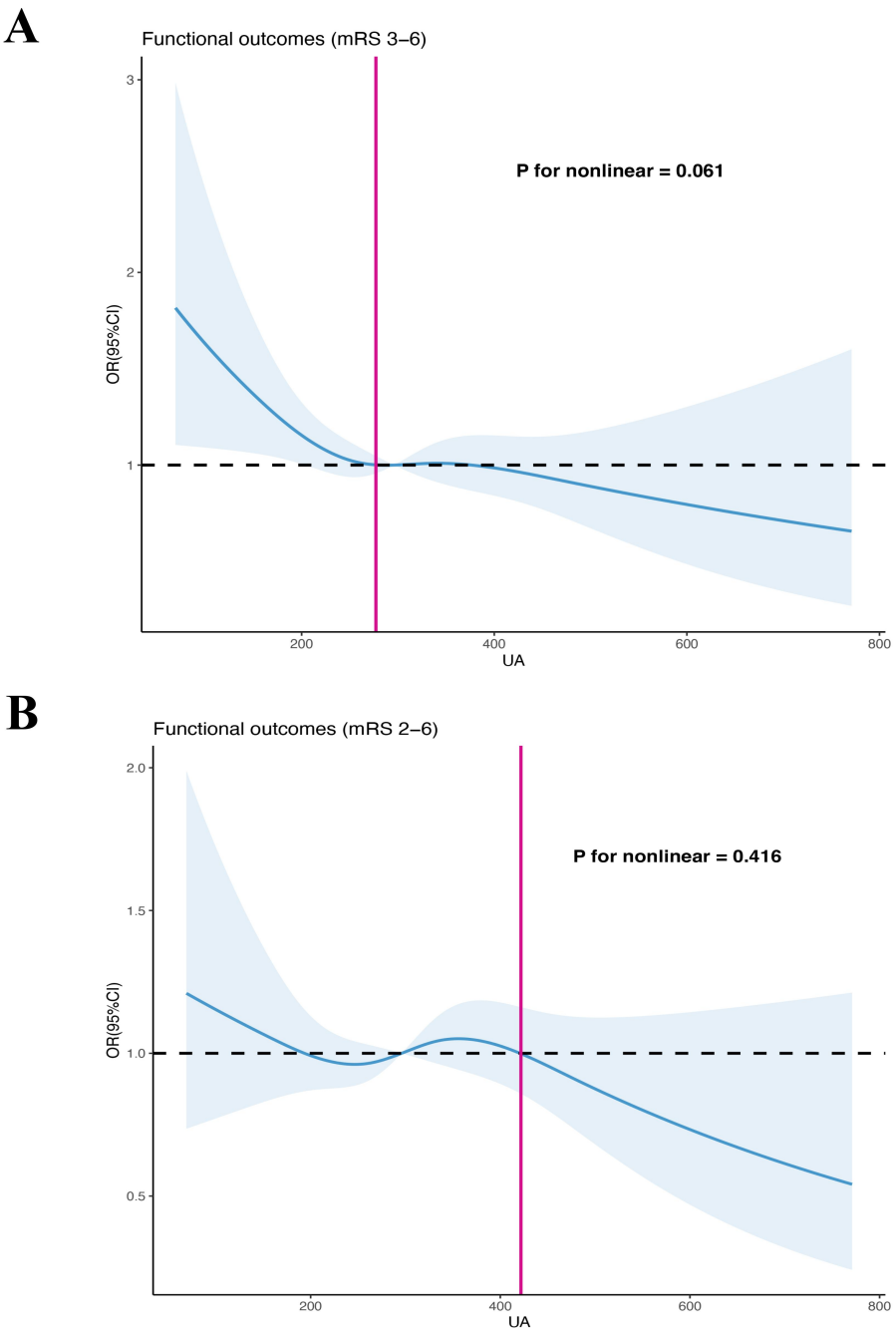

Figure S1 Analysis of restricted cubic spline regression with functional outcome (mRS 3-6 and mRS 2-6).

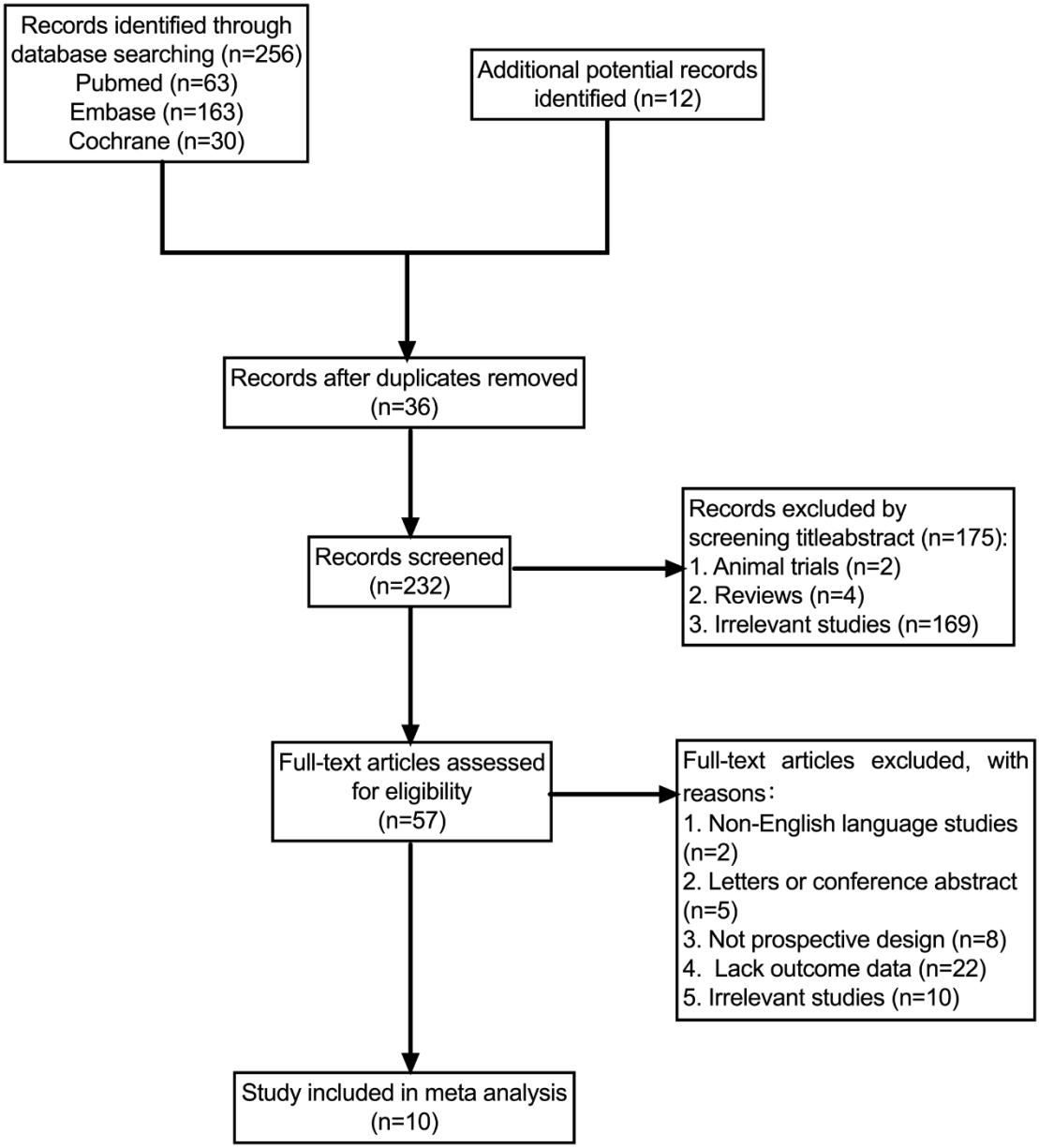

Figure S2 Study identification and selection in the Meta-analysis.

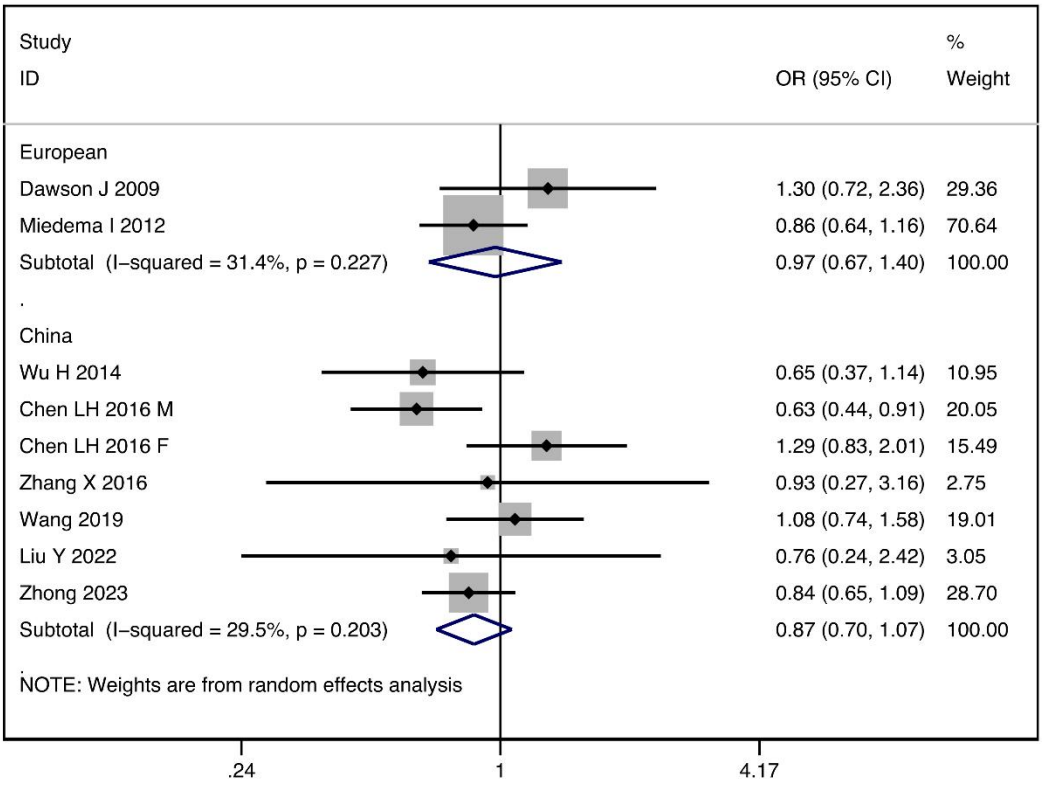

Figure S3 Forest plots of the subgroup analyses on race in relation to serum UA levels between prognosis of stroke.

Note: The size of gray box is positively proportional to the weight assigned to each study, and horizontal lines represent the 95% confidence intervals

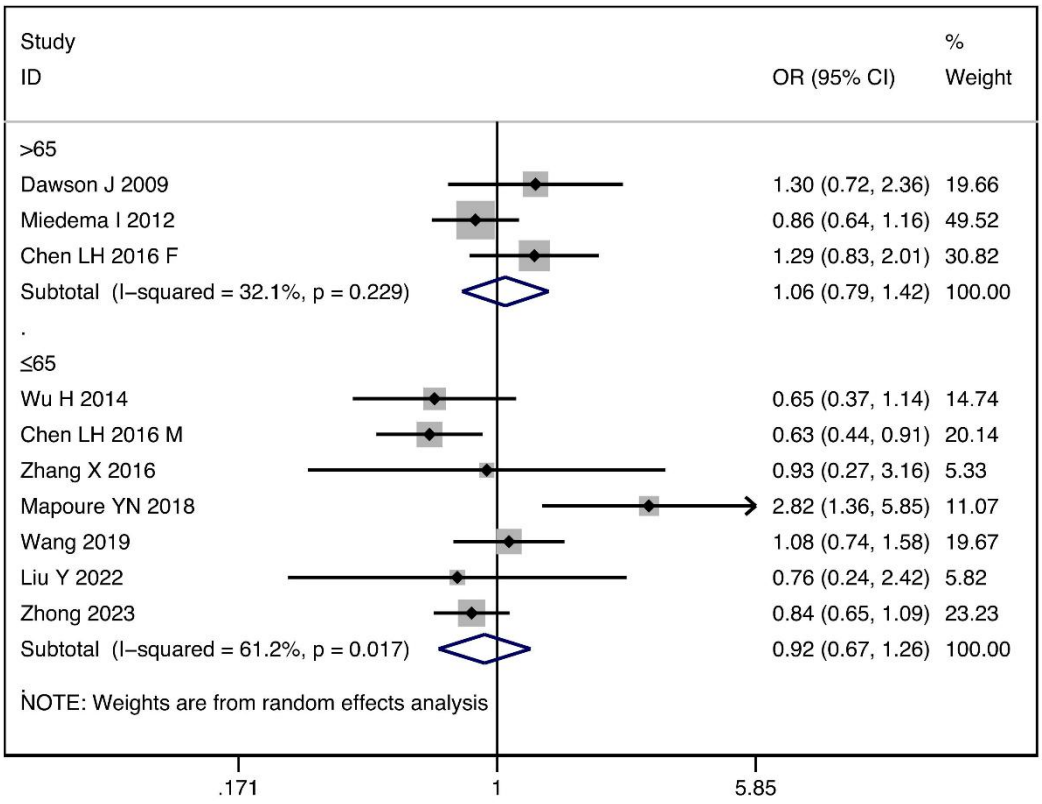

Figure S4 Forest plots of the subgroup analyses on age in relation to serum UA levels between prognosis of stroke.

Note: The size of gray box is positively proportional to the weight assigned to each study, and horizontal lines represent the 95% confidence intervals.

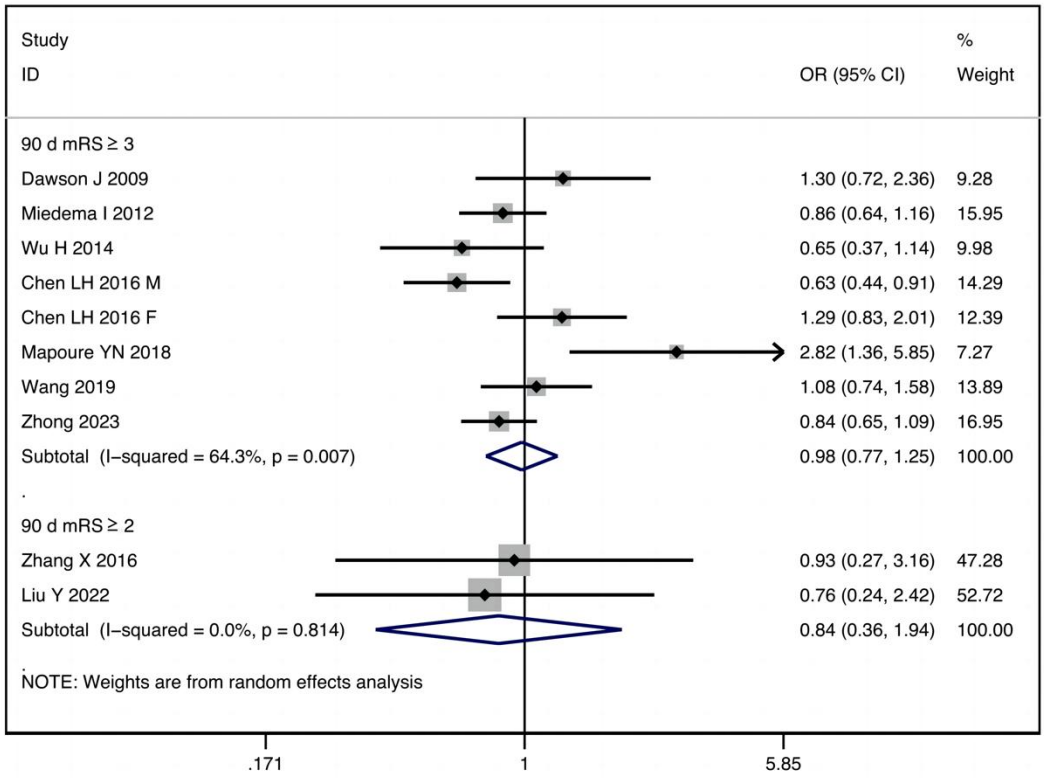

Figure S5 Forest plots of the subgroup analyses on different outcome definition in relation to serum UA levels between prognosis of stroke.

Note: The size of gray box is positively proportional to the weight assigned to each study, and horizontal lines represent the 95% confidence intervals.

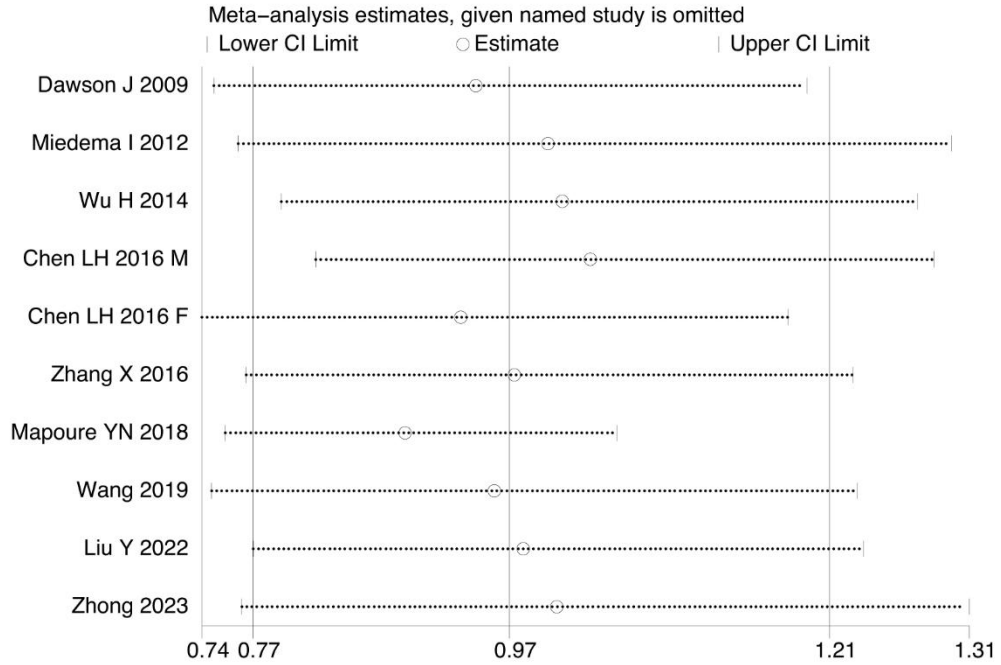

Figure S6 The sensitive plot on the association of uric acid levels and stroke prognosis with the exclusion of lower-quality studies.

Abbreviations: CI, confidence interval.

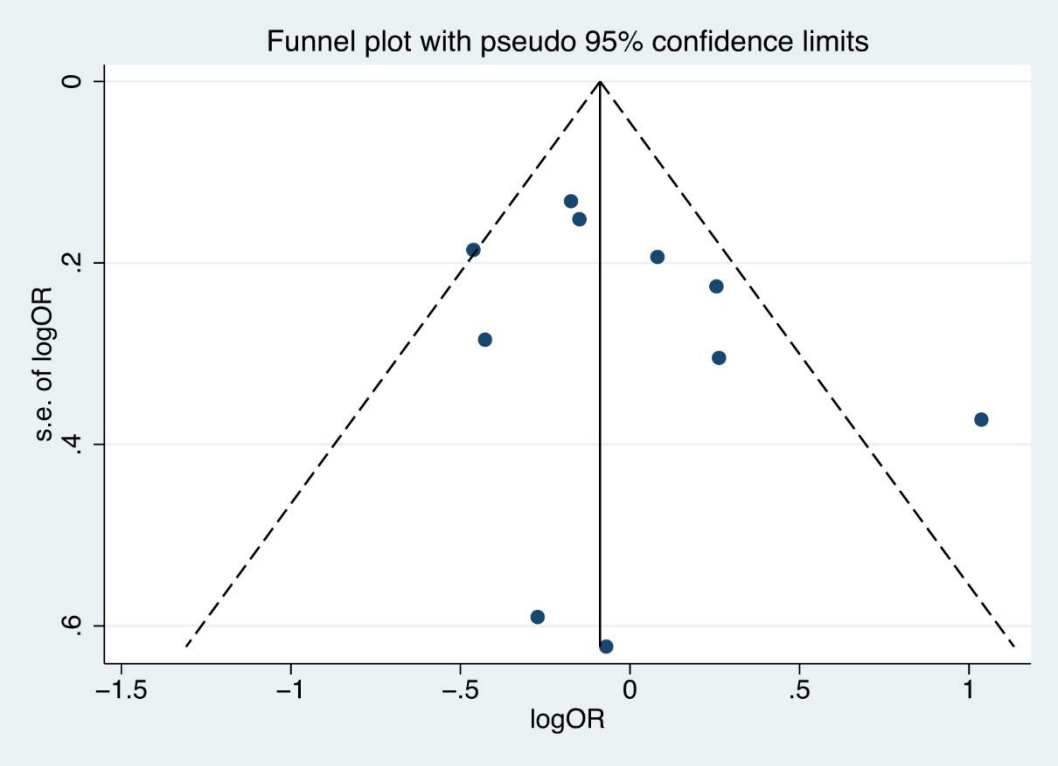

Figure S7 Funnel plots on the association of uric acid levels and poor outcomes of strokes.

Note: Egger test showed no evidence of publication bias (p for publication bias was 0.324)

Abbreviations: rr, risk ratio; s.e., standard error.

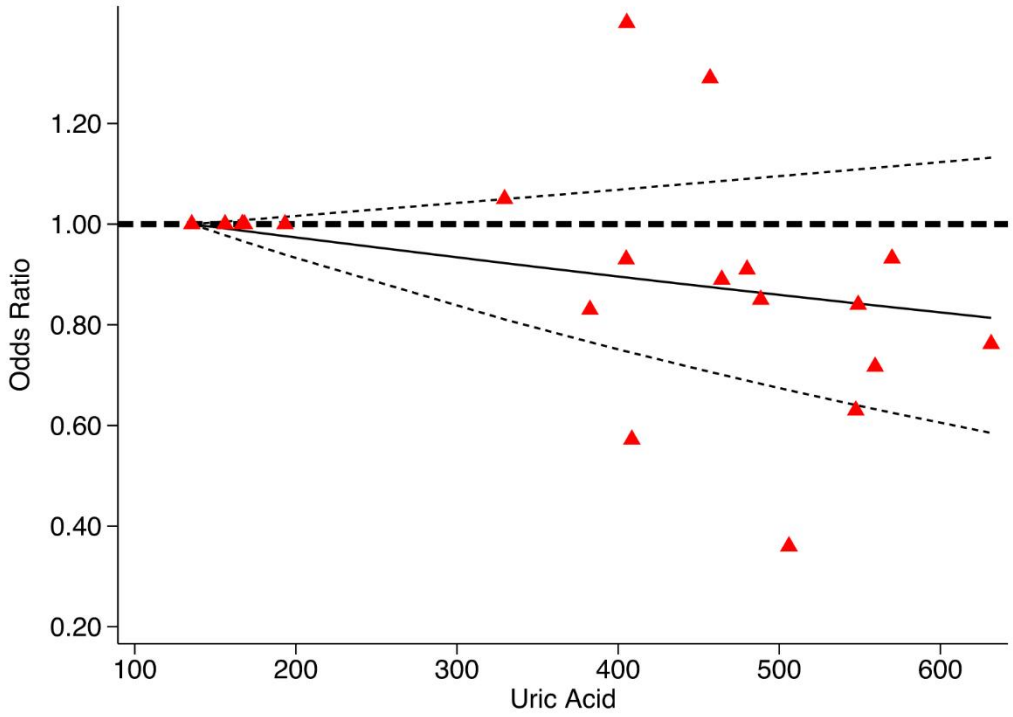

Figure S8 Linear does-response analyses of UA and stroke prognosis.

Note: The red triangle represents the OR of each study, the dashed line is the 95% confidence interval, and the solid line in the middle is the OR of the estimated nonlinear curve.

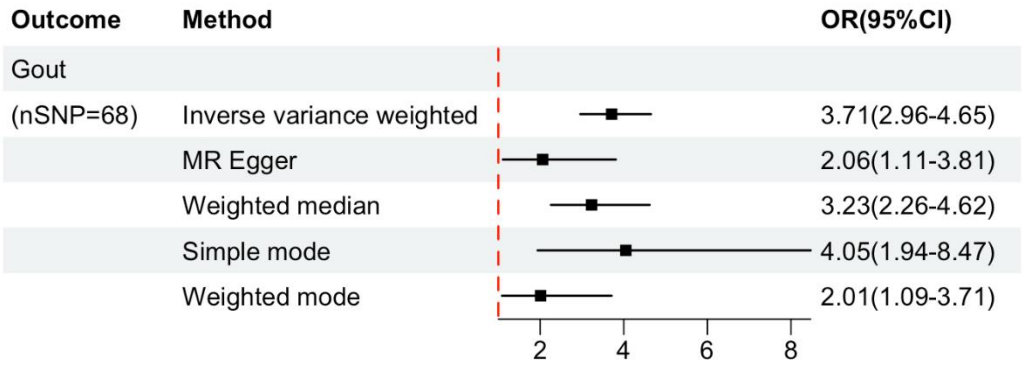

Figure S9 Mendelian randomization association of genetically predicted serum uric acid level with gout using different statistical models.

Abbreviations: OR, odd ratio; CI, confidence interval.

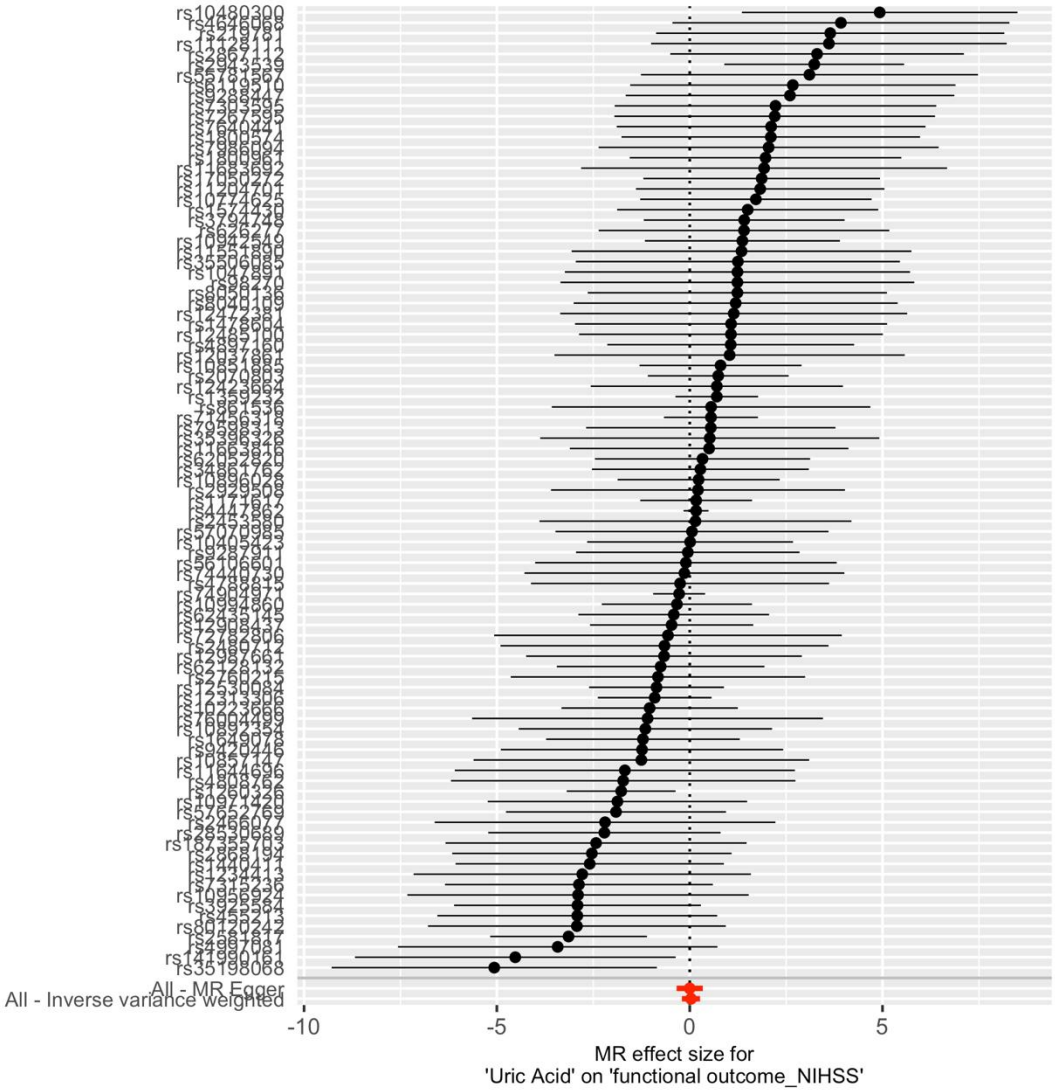

Figure S10 The forest plot for the association between serum uric acid and functional outcome of stroke.

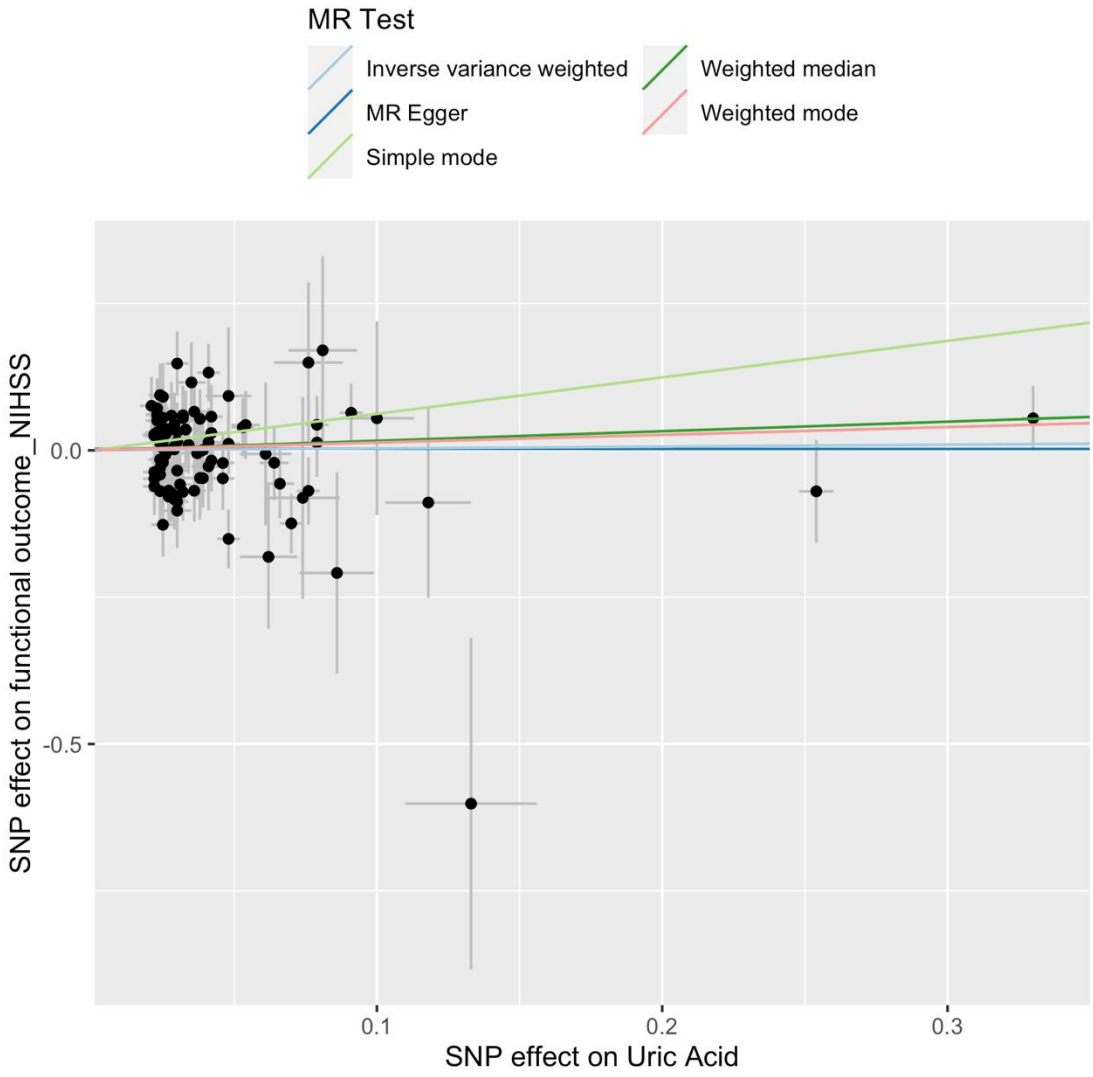

Figure S11 The scatter plot for the association between serum uric acid and functional outcome of stroke.

Note:The plot presents the effect size and confidence intervals for each SNP presented in the model on serum uric acid (exposure) and functional outcome of stroke (outcome). The slope of the plotted lines represents the Mendelian randomization associations with different approaches.

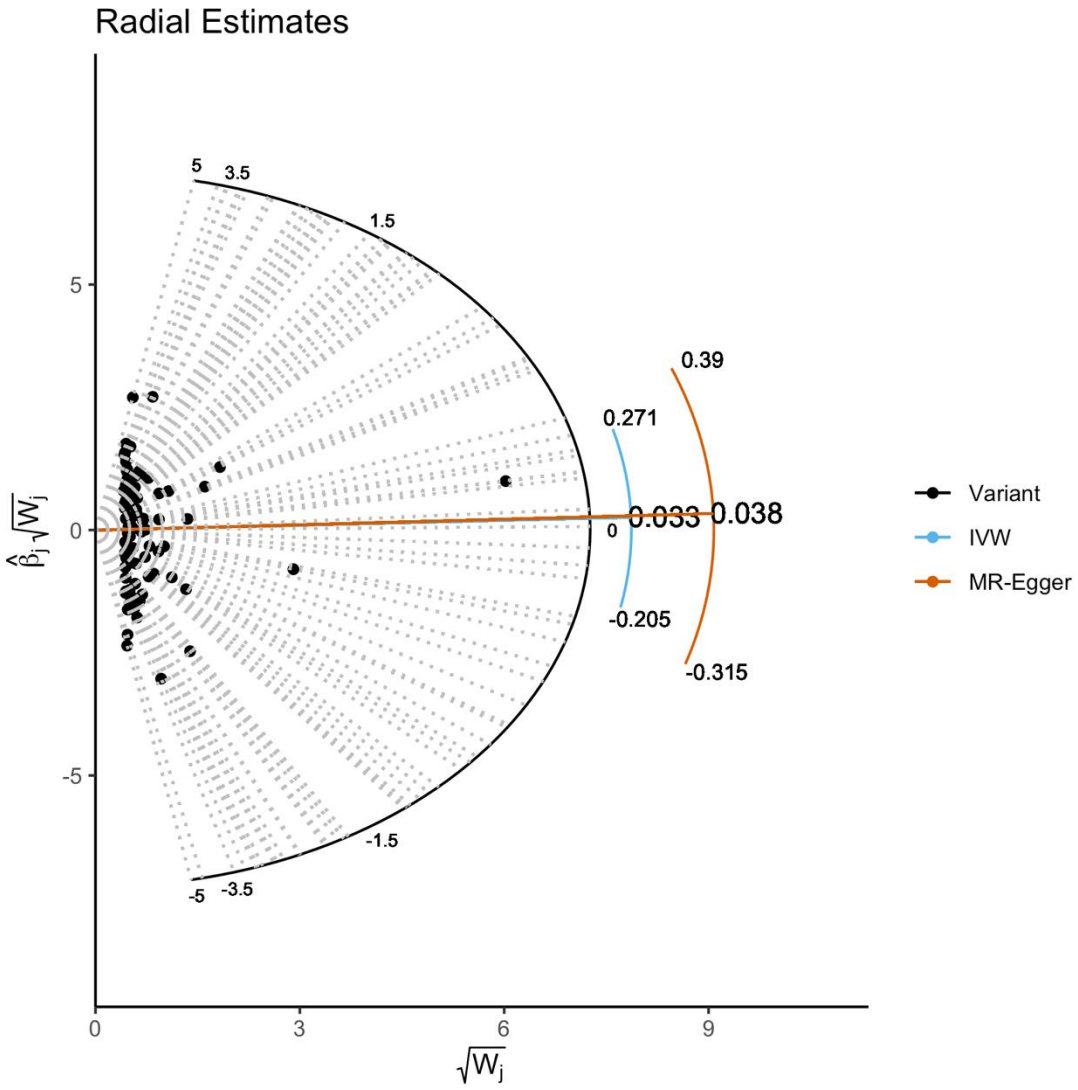

Figure S12 The Radial MR plot for the association between serum uric acid and functional outcome of stroke.

Note: The radial curve means the ratio estimate for each SNP, no outlier is identified.

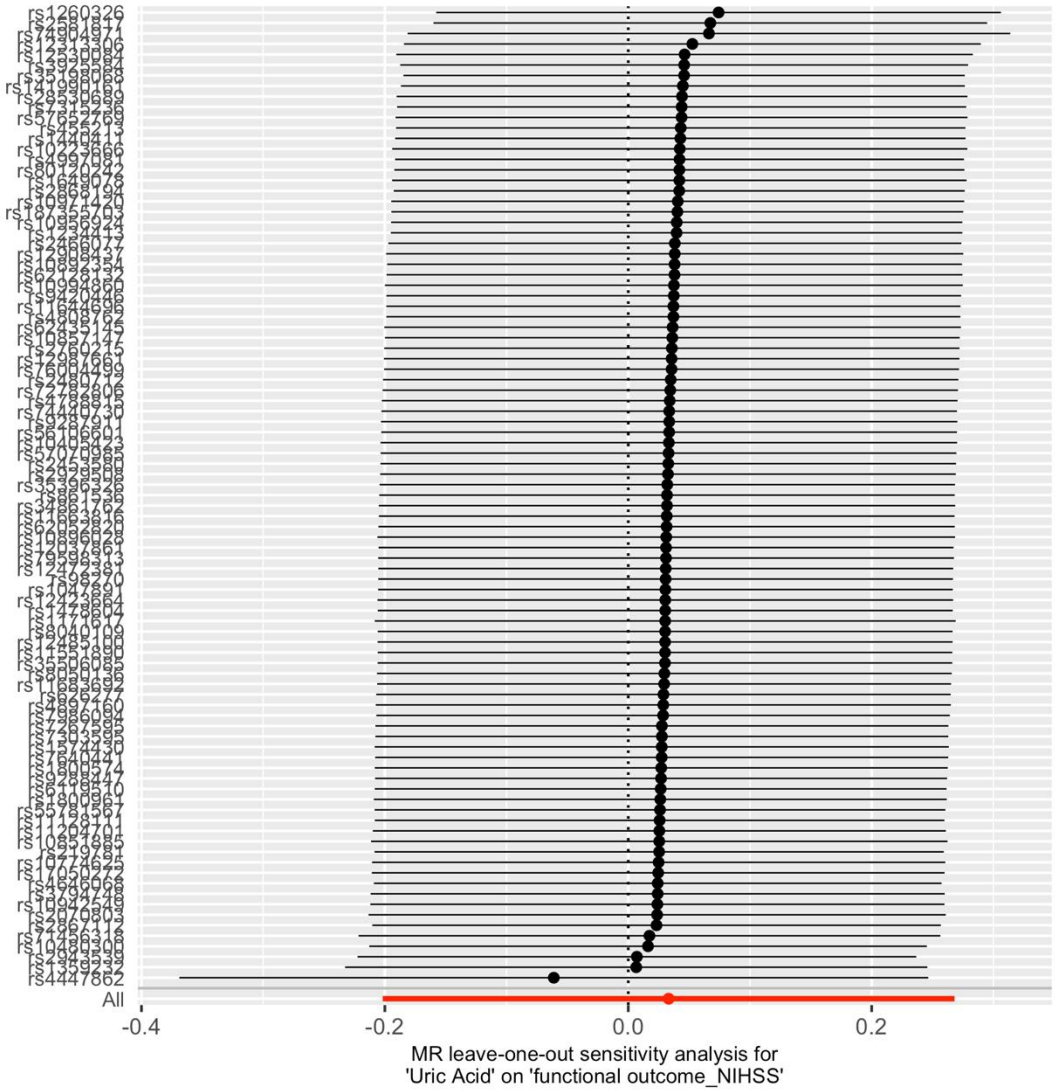

Figure S13 The leave-one-out analysis for the association between serum uric acid and functional outcome of stroke.

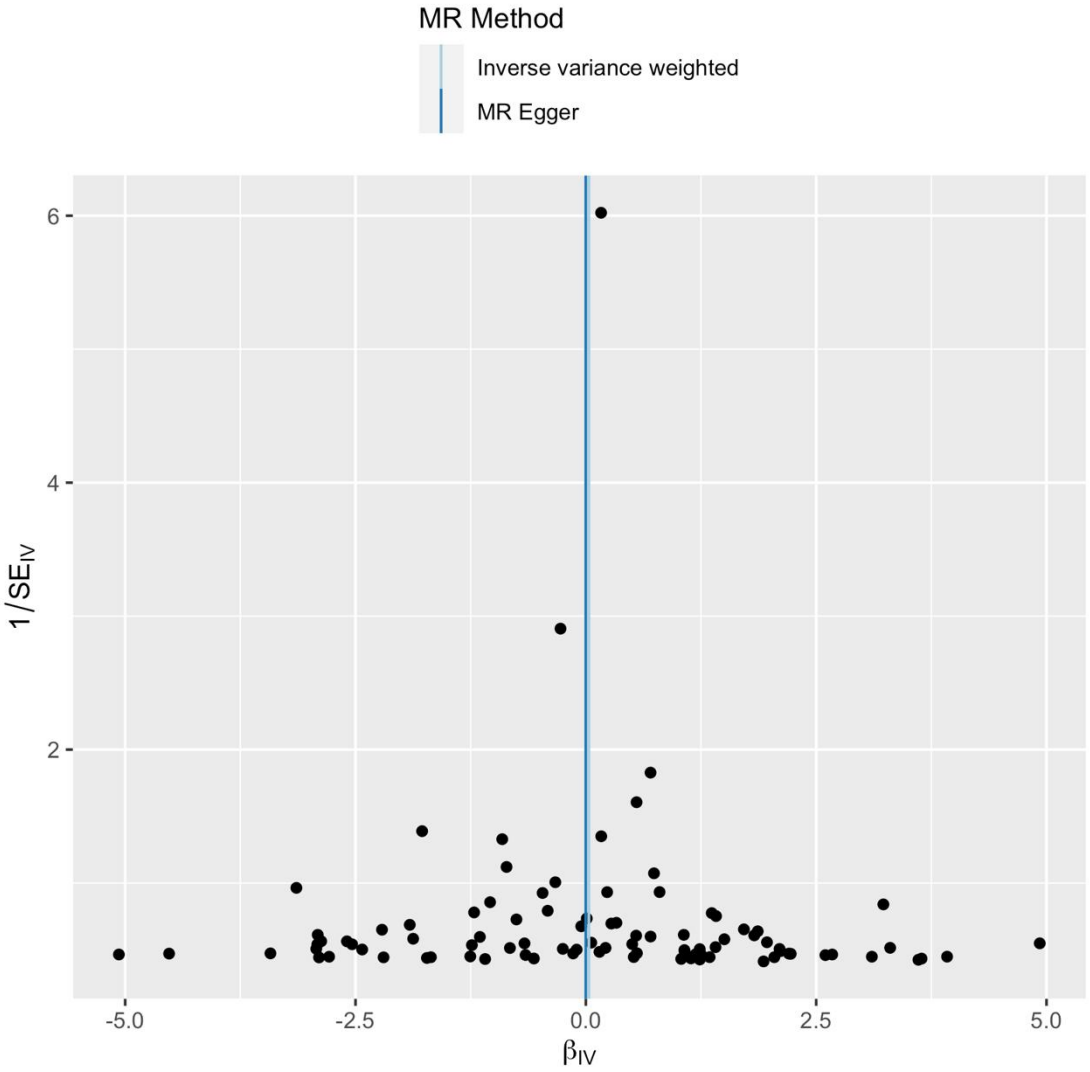

Figure S14 The funnel plot for the association between serum uric acid and functional outcome of stroke.

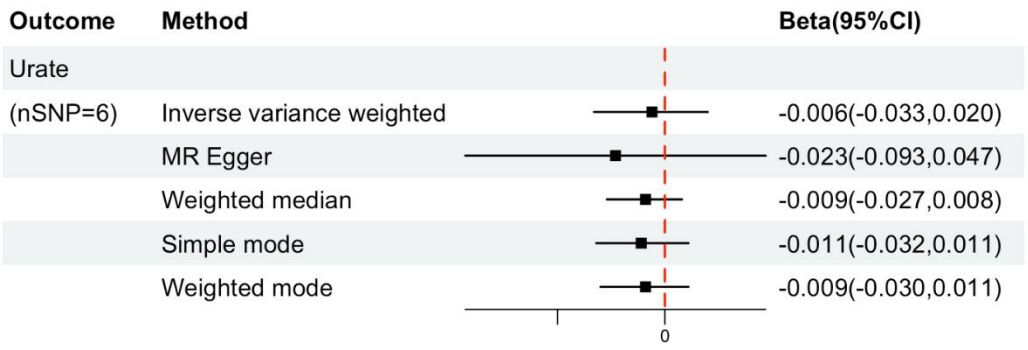

Figure S15 The reverse causal effect of functional outcome of stroke on serum uric acid levels using different statistical models.

Abbreviations: CI, confidence interval.