SUPPLEMENTAL MATERIAL

Table S1. Search Strategy.

Search Terms
1. (“stroke” OR “cerebrovascular disease” OR “intracranial hemorrhage” OR “cerebrovascular disorder” OR “cerebral hemorrhage” OR “brain infarction”)
2. ("UA" OR "uric acid" OR "urate" OR "hyperuricemia" OR "hyperuric")
3. 1 AND 2

Table S2. Quality scores of prospective studies using Newcastle-Ottawa Scale.

	Selection				Comparability	Outcome			NOS
	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of anthropometric indexes	Demonstration that outcomes was not present at start of study	Comparability on the basis of the design or analysis	Assessment of outcome	Adequate follow-up duration	Adequate follow-up rate	Overall score
Kamei et al.[1]	1	1	1	1	2	0	0	0	6
Jiménez et al.[2]	0	1	1	1	2	1	1	0	7
Zhang et al.[3]	1	1	1	1	1	1	1	1	8
Storhaug et al.[4]	0	1	1	1	2	1	1	0	7
Holme et al.[5]	1	1	1	1	1	1	1	0	7
Strasak et al.[6]	1	1	1	1	2	1	1	1	9
Strasak et al.[7]	1	1	1	1	2	1	1	1	9
Hozawa et al.[8]	0	1	1	1	2	1	1	1	8
Bos et al.[9]	0	1	1	1	0	1	1	1	6
Chien et al.[10]	0	1	1	1	1	1	1	1	7
Gerber et al.[11]	0	1	1	1	1	1	1	0	6
Jee et al.[12]	1	1	0	1	1	1	1	1	7
Sakata et al.[13]	1	1	1	1	2	1	1	1	9

Table S3. Relative risks of stroke among men and women in the included prospective studies.

Study, year	Uric acid Assessment	Sex	Uric acid levels, mg/dl	Effect size (95% CI)			Variables adjusted for
Kamei et al., 2016[1]	Enzymatic method	Men		Total stroke			Age, obesity, hypertension, diabetes, dyslipidemia, smoking, alcohol consumption, eGFR, and proteinuria.
			Q1: ≤4.9	1.12 (0.92-1.37)			
			Q2: 5.0-5.6	1.07 (0.88-1.30)			
			Q3: 5.7-6.2	1.00 (reference)			
			Q4: 6.3-7.0	1.00 (0.81-1.21)			
			Q5: ≥7.1	1.26 (1.04-1.54)			
		Women		Total stroke			
			Q1: ≤3.7	1.12 (0.90-1.38)			
			Q2: 3.8-4.3	1.09 (0.89-1.33)			
			Q3: 4.4-4.8	1.00 (reference)			
			Q4: 4.9-5.4	1.04 (0.85-1.29)			
			Q5: ≥5.5	1.21 (1.00-1.48)			
Jiménez et al., 2016[2]	Colorimetric enzyme assay	Women		IS			Conditional on matching factors (age, menopausal status, smoking, postmenopausal hormone use, race/ethnicity, date of blood draw and fasting status); Adjusted BMI, physical activity, alcohol and aspirin use, eGFR, history of diabetes, CHD, history of hypertension, total/HDL-C and ln(hsCRP).
			Q1: <3.9	1.00 (reference)			
			Q2: 3.9-4.5	1.26 (0.83-1.89)			
			Q3: 4.6-5.4	1.11 (0.73-1.68)			
			Q4: ≥5.5	1.13 (0.72-1.76)			
Zhang et al., 2016[3]	Colorimetric phosphotungstic acid	Men		Total stroke	IS	HS	Age, body mass index, smoking status, ethanol intake, systolic blood pressure and total cholesterol.
			Q1: 0.6-4.6	1.00 (reference)	1.00 (reference)	1.00 (reference)	
			Q2: 4.7-5.2	0.83 (0.58-1.18)	0.87 (0.54-1.40)	0.90 (0.46-1.77)	
			Q3: 5.3-5.8	0.77 (0.52-1.13)	0.75 (0.45-1.26)	1.07 (0.54-2.14)	
			Q4: 5.9-6.6	0.77 (0.52-1.13)	0.91 (0.55-1.50)	0.83 (0.41-1.68)	

			Q5: 6.7-16.0	1.19 (0.84-1.68)	1.19 (0.75-1.90)	1.41 (0.75-2.65)	
		Women		Total stroke	IS	HS	
			Q1: 0.4-3.3	1.00 (reference)	1.00 (reference)	1.00 (reference)	
			Q2: 3.4-3.8	1.27 (0.90-2.01)	1.42 (0.74-2.74)	1.41 (0.64-3.13)	
			Q3: 3.9-4.3	0.98 (0.62-1.54)	0.80 (0.40-1.61)	1.33 (0.63-2.80)	
			Q4: 4.4-5.0	1.05 (0.67-1.64)	1.22 (0.65-2.30)	1.09 (0.48-2.43)	
			Q5: 5.1-10.8	1.46 (0.98-2.19)	1.35 (0.75-2.44)	1.54 (0.76-3.10)	
Storhaug et al., 2013[4]	Enzymatic colorimetric test	Men		IS			Age, BMI, SBP, DBP, HDL-C, TC, renal factors, use of diuretics and antihypertensive medication, current smoking and physical activity.
			per SD (87 µmol/L)	1.31 (1.14-1.50)			
		Women		IS			
			per SD (87 µmol/L)	1.13 (0.94-1.36)			
Holme et al., 2009[5]	Enzymatic uricase method	Men		Total stroke	IS	HS	Age, TC, TG, hypertension and DM.
			Q1: <4.7	1.00 (reference)	1.00 (reference)	1.00 (reference)	
			Q2: 4.7-5.4	1.03 (0.97-1.09)	1.08 (1.00-1.16)	0.83 (0.71-0.96)	
			Q3: 5.4-6.1	1.09 (1.02-1.15)	1.10 (1.02-1.18)	0.92 (0.80-1.07)	
			Q4: >6.1	1.26 (1.19-1.34)	1.30 (1.22-1.40)	1.10 (0.96-1.27)	
		Women		Total stroke	IS	HS	
			Q1: <3.5	1.00 (reference)	1.00 (reference)	1.00 (reference)	
			Q2: 3.5-4.1	1.05 (0.97-1.15)	1.12 (1.00-1.24)	0.81 (0.64-1.01)	
			Q3: 4.1-5.5	1.16 (1.07-1.26)	1.27 (1.15-1.40)	1.01 (0.82-1.24)	
			Q4: >5.5	1.41 (1.31-1.53)	1.56 (1.42-1.72)	1.13 (0.92-1.37)	
Strasak et al., 2008[6]	Enzymatic method	Women		Total stroke	IS	HS	Age, body mass index, systolic and diastolic blood pressure, total cholesterol, triglycerides, gamma-glutamyltransferase, glucose, smoking status, occupational status and year of examination.
			Q1: ≤3.70	1.00 (reference)	1.00 (reference)	1.00 (reference)	
			Q2: 3.71-4.50	1.25 (0.99-1.57)	1.17 (0.76-1.79)	1.14 (0.65-2.01)	
			Q3: 4.51-5.40	1.48 (1.18-1.86)	1.19 (0.76-1.84)	1.47 (0.83-2.52)	
			Q4: ≥5.41	1.37 (1.09-1.74)	1.15 (0.74-1.79)	1.29 (0.71-1.79)	

			Per unit increase	1.07 (1.01-1.13)	1.02 (0.91-1.14)	1.06 (0.91-1.23)	
Strasak et al., 2008[7]	Enzymatic method	Men		Total stroke	IS	HS	Age, body mass index, systolic and diastolic blood pressure, total cholesterol, triglycerides, GGT, glucose, smoking status, and year of examination (triglyceride and GGT data were log-transformed).
			Q1: ≤4.60	1.00 (reference)	1.00 (reference)	1.00 (reference)	
			Q2: 4.60-5.30	1.00 (0.76-1.30)	0.92 (0.52-1.63)	1.02 (0.60-1.72)	
			Q3: 5.30-5.90	1.05 (0.80-1.38)	1.19 (0.68-2.07)	0.89 (0.51-1.57)	
			Q4: 5.90-6.70	1.02 (0.78-1.34)	1.01 (0.57-1.80)	0.92 (0.53-1.60)	
			Q5: >6.70	1.59 (1.23-2.04)	1.81 (1.07-3.04)	1.18 (0.70-2.01)	
			Per unit increase	1.11 (1.05-1.18)	1.13 (1.00-1.27)	1.06 (0.93-1.20)	
Hozawa et al., 2006[8]	Uricase method	Men		IS			Age, race, education, systolic blood pressure, diabetes mellitus, anti-hypertensive medication, cigarette smoking status, ethanol intake, serum albumin, von Willebrand factor, BMI, WHR, and low HDL cholesterol.
			Q1: ≤4.8	1.00 (reference)			
			Q2: 4.9-5.8	1.01 (0.48-2.13)			
			Q3: 5.9-6.8	1.30 (0.67-2.53)			
			Q4: ≥6.9	1.63 (0.83-3.19)			
		Women		IS			
			Q1: ≤4.8	1.00 (reference)			
			Q2: 4.9-5.8	0.85 (0.51-1.41)			
			Q3: 5.9-6.8	1.22 (0.75-1.99)			
			Q4: ≥6.9	1.27 (0.70-2.30)			
Bos et al., 2006[9]	Kone Diagnostica reagent kit	Men		Total stroke	IS	HS	Age
			T1: <5.21	1.00 (reference)	1.00 (reference)	1.00 (reference)	
			T2: 5.21-6.30	1.78 (1.16-2.74)	1.57 (0.88-2.79)	1.23 (0.38-4.04)	
			T3: ≥6.30	1.41 (0.90-2.23)	1.36 (0.74-2.48)	1.11 (0.32-3.83)	
			Per SD	1.15 (0.95-1.38)	1.18 (0.92-1.51)	0.97 (0.55-1.70)	
		Women		Total stroke	IS	HS	
			T1: <4.42	1.00 (reference)	1.00 (reference)	1.00 (reference)	
			T2: 4.42-5.39	1.45 (1.05-2.02)	1.44 (0.91-2.27)	1.22 (0.48-3.10)	

			T3: ≥5.39 Per SD	1.45 (1.05-2.01) 1.18 (1.05-1.34)	1.68 (1.08-2.62) 1.26 (1.07-1.49)	1.32 (0.53-3.26) 1.23 (0.87-1.74)	
Chien et al., 2005[10]	Enzymatic with commercial kits	Men Women	 Per unit Per unit	Total stroke 1.13 (0.88-1.46) Total stroke 1.32 (1.00-1.73)			Age, SBP, BMI, diabetes, LDL-C, HDL-C, smoking, drinking, electrocardiographic left ventricular hypertrophy and AF history.
Gerber et al., 2006[11]	Fister's adaptation of colorimetric method	Men	 Q1: ≤3.9 Q2: 4.0-4.4 Q3: 4.5-4.9 Q4: 5.0-5.5 Q5: ≥5.6	Total stroke 1.52 (1.04-2.23) 1.46 (1.00-2.12) 1.00 (reference) 1.25 (0.85-1.84) 1.20 (0.81-1.78)	IS 1.34 (0.87-2.05) 1.33 (0.89-2.00) 1.00 (reference) 1.21 (0.81-1.82) 1.15 (0.75-1.74)	HS 3.27 (1.14-9.33) 2.52 (0.87-7.29) 1.00 (reference) 1.55 (0.49-4.89) 1.62 (0.51-5.18)	Age, body mass index, systolic blood pressure, diabetes, serum cholesterol, smoking, and left ventricular hypertrophy on electrocardiogram.
Jee et al., 2004[12]	NR	Men	 Q1: <4.45 Q2: 4.45-5.14 Q3: 5.14-5.97 Q4: 5.97-6.96 Q5: >6.96	Total stroke 1.00 (reference) 0.97 (0.60-1.58) 1.03 (0.64-1.65) 1.35 (0.88-2.08) 1.10 (0.71-1.72)			Age, diabetes, hypertension, hypercholesterolaemia and smoking status.
Sakata et al., 2001[13]	Colorimetric phosphotungstic acid	Men Women	 Q1: <4.99 Q2: 4.99-5.68 Q3: 5.68-6.47 Q4: ≥6.47 Q1: <3.60 Q2: 3.60-4.17	Total stroke 1.00 (reference) 0.84 (0.45-1.59) 0.66 (0.33-1.33) 1.71 (0.92-3.17) Total stroke 1.00 (reference) 1.40 (0.54-3.63)			Age, body mass index, systolic blood pressure, use of antihypertensive agents, serum total cholesterol level, serum creatinine level, serum glucose level, smoking status, alcohol intake, and left ventricular hypertrophy.

			Q3: 4.17-4.87 Q4: ≥4.87	0.95 (0.37-2.45) 1.12 (0.46-2.74)	

Table S4. Uric acid levels and stroke in men and women, nonlinear dose-response.

Men			Women		
Uric acid levels, mg/dl	RR	95% CI	Uric acid levels, mg/dl	RR	95% CI
3.5	1.00	-	3.0	1.00	-
4.0	1.00	0.98-1.00	3.5	1.10	1.00-1.10
4.5	1.00	0.95-1.10	4.0	1.10	1.10-1.20
5.0	1.00	0.94-1.10	4.5	1.20	1.10-1.30
5.5	1.00	0.95-1.10	5.0	1.20	1.10-1.30
6.0	1.10	1.02-1.20	5.5	1.30	1.20-1.40
6.5	1.20	1.12-1.30	6.0	1.40	1.30-1.50
7.0	1.30	1.24-1.50	6.5	1.50	1.40-1.60
7.5	1.50	1.36-1.60	7.0	1.60	1.40-1.70

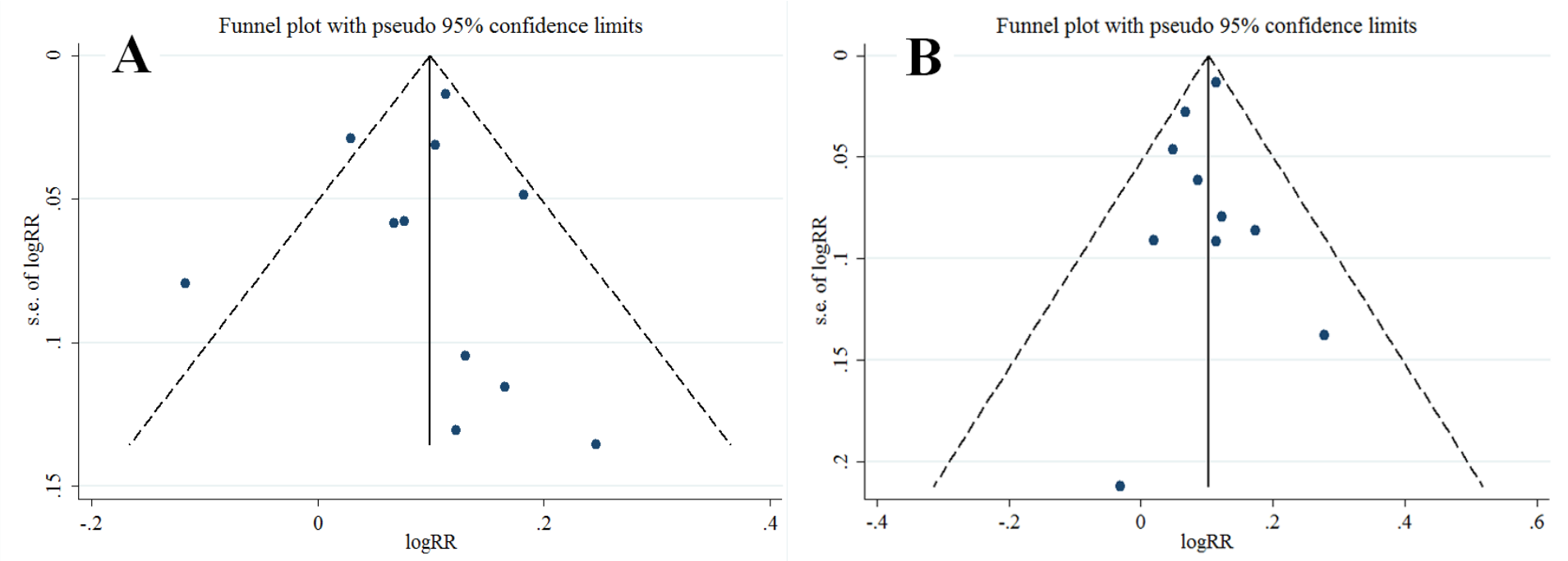

Figure S1. Funnel plots of uric acid and risk of stroke among men (**A**) and women (**B**).

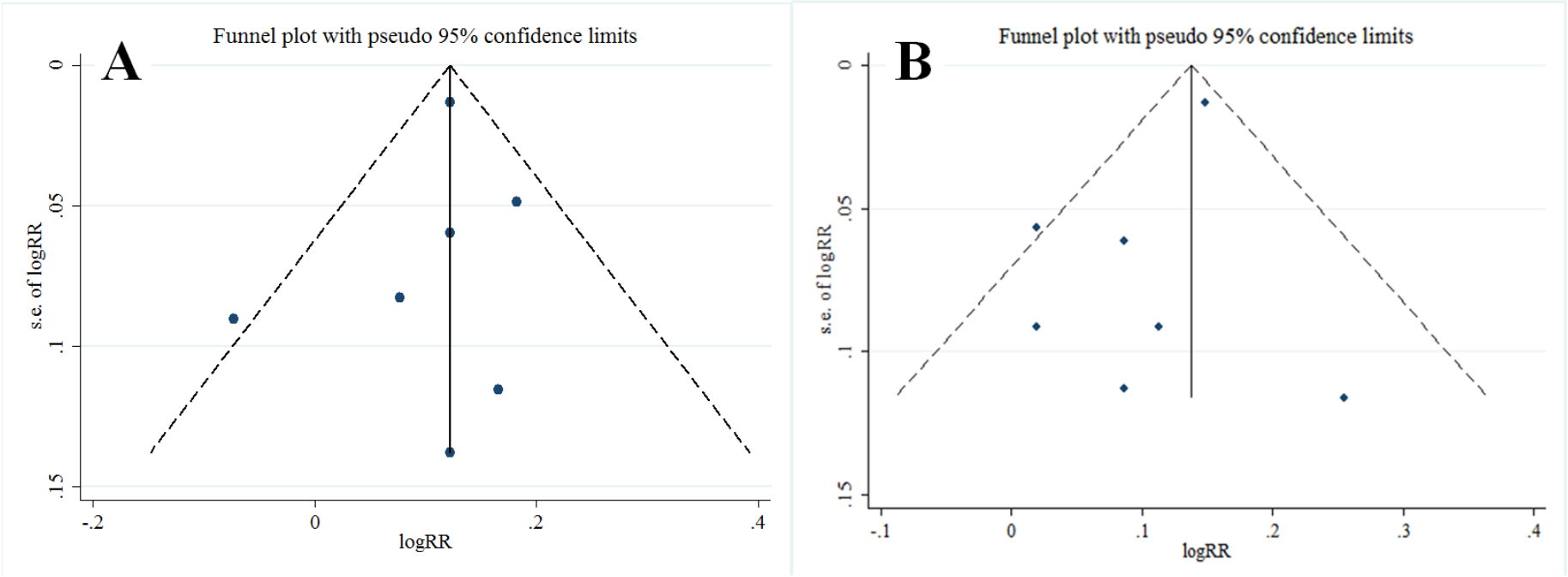

Figure S2. Funnel plots of uric acid and risk of ischemic stroke among men (**A**) and women (**B**).

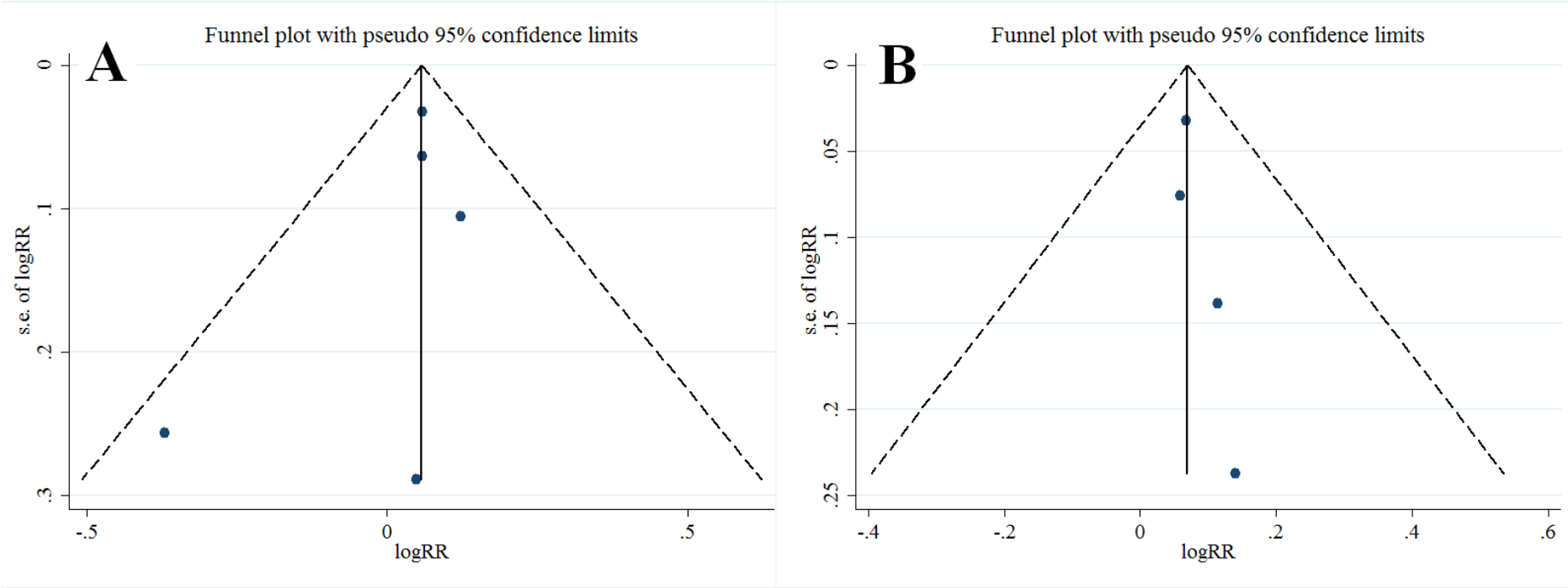

Figure S3. Funnel plots of uric acid and risk of hemorrhagic stroke among men (**A**) and women (**B**).

Supplemental References:

1. Kamei K, Konta T, Hirayama A, Ichikawa K, Kubota I, Fujimoto S, Iseki K, Moriyama T, Yamagata K, Tsuruya K, Narita I, Kondo M, Shibagaki Y, Kasahara M, Asahi K, Watanabe T. Associations between serum uric acid levels and the incidence of nonfatal stroke: a nationwide community-based cohort study. *Clin Exp Nephrol.* 2016 Jul 12. [Epub ahead of print].

2. Jimenez MC, Curhan GC, Choi HK, Forman JP, Rexrode KM. Plasma uric acid concentrations and risk of ischaemic stroke in women. *Eur J Neurol.* 2016;23:1158-1164.

3. Zhang W, Iso H, Murakami Y, Miura K, Nagai M, Sugiyama D, Ueshima H, Okamura T. Serum Uric Acid and Mortality Form Cardiovascular Disease: EPOCH-JAPAN Study. *J Atheroscler Thromb*. 2016;23:692-703.

4. Storhaug HM, Norvik JV, Toft I, Eriksen BO, Lochen ML, Zykova S, Solbu M, White S, Chadban S, Jenssen T. Uric acid is a risk factor for ischemic stroke and all-cause mortality in the general population: a gender specific analysis from The Tromso Study. *BMC Cardiovasc Disord.* 2013;13:115.

5. 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;266:558-570.

6. Strasak AM, Kelleher CC, Brant LJ, Rapp K, Ruttmann E, Concin H, Diem G, Pfeiffer KP, Ulmer H. 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;125:232-239.

7. Strasak A, Ruttmann E, Brant L, Kelleher C, Klenk J, Concin H, Diem G, Pfeiffer K, Ulmer H. Serum uric acid and risk of cardiovascular mortality: a prospective long-term study of 83,683 Austrian men. *Clin Chem*. 2008;54:273-284.

8. 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;187:401-407.

9. 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;37:1503-1507.

10. 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;183:147-155.

11. 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;13:193-198.

12. 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;11:185-191.

13. 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;17:461-468.