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The role of urinary albumin-to-creatinine ratio as a biomarker to predict stroke: A meta-analysis and systemic review

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Abstract:

Albuminuria excretion rate, calculated as urinary albumin-to-creatinine ratio (UACR), is used clinically to evaluate albuminuria. There are different attitudes to whether high UACR predicts higher risk of stroke. The aim of this study was to evaluate the relationship between UACR and stroke. Two investigators independently searched MEDLINE, EMBASE, Cochrane Controlled Trials Register Database, Scopus and Google Scholar from January 1966 through June 2021 were screened. In addition, a manual search was conducted using the bibliographies of original papers and review articles on this topic. Two blinded reviewers abstracted the data independently to a predefined form. Among the 10,939 initially identified studies, 7 studies with 159,302 subjects were finally included. It is demonstrated that UACR predicted an increased risk of stroke using cutoff value of either 0.43 (HR, 2.39; 95% CI: 1.24 - 4.61; P <0.01), 10 mg/g (HR, 1.60; 95% CI: 1.30 - 1.97; P < 0.01) or 30 mg/g (HR, 1.84; 95% CI: 1.49 - 2.28; P < 0.01). The overall analysis confirmed that high UACR was associated with an increased rate of stroke (HR, 1.81; 95% CI: 1.52 - 2.17; P < 0.01). Furthermore, High UACR predicted higher risk of stroke in local inhabitants (HR, 1.67; 95% CI: 1.17 – 2.37; P = 0.04), adults (HR, 2.21; 95% CI: 2.07 – 2.36; P < 0.01) or elderly adults (HR, 1.96; 95% CI: 1.56 – 2.46; P < 0.01). Whereas, high UACR was unable to predict stroke in patients with either T2DM (HR, 2.25; 95% CI: 0.55 – 9.17; P = 0.26) or hypertension (HR, 0.95; 95% CI: 0.28 – 3.22; P = 0.93). Another subgroup analysis revealed that high UACR was associated with increased risk of ischemic stroke (HR, 1.60; 95% CI: 1.43 - 1.80; P < 0.01), as well as hemorrhagic stroke (HR, 1.76; 95% CI: 1.22 - 1.45; P < 0.01). In conclusion, UACR is associated with an increased risk of hemorrhagic and ischemic stroke. UACR may be used as an indicator to predict stroke in non-diabetic and non-hypertensive subjects.

Keywords:

Biomarker, meta-analysis, stroke, systemic review, urinary albumin-to-creatinine ratio

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Introduction

Ischemic stroke is a reduction in blood flow in a specific area of the brain or spinal cord caused by various causes, resulting in nerve damage accompanied by transient or permanent loss of nerve function.[1,2] In 2010, the survey showed that the incidence of stroke had an increase of nearly 68% compared to 1990.[3] Stroke is the second leading cause in the 2010 global disease mortality, causing approximately 5.9 million deaths in a year and bringing a heavy and sustained economic burden to every country.[3,4] Therefore, identifying the risk factors for stroke is in urgent need.

It is reported that chronic kidney disease (CKD), accompanied by a decline in glomerular filtration rate (eGFR) or the presence of albuminuria, has been identified as an important contributor

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to the development of stroke.[5-8] Recent studies have indicated that albuminuria is an independent risk factor for ischemic stroke.[8,9] In addition, Aguilar *et al*. pointed out that albuminuria has a certain impact on any type of stroke and other vascular diseases.[7] Studies have shown that short-term reduction of albuminuria reduced the risk of future stroke.[10] Furthermore, a meta-analysis conducted by Savarese *et al*.[11] indicated that reduction in urinary albumin excretion implies reduced risk of stroke in diabetic and/or hypertensive patients.

Albuminuria excretion rate was estimated as the urinary albumin-to-creatinine ratio (UACR) by using either spot urine sample or 24-h sample.[12] UACR is not affected by urine volume and is more sensitive to proteinuria with low protein concentration compared to urinary albumin concentration.[12,13] Therefore, UACR is currently recommended clinically as a more reliable indicator to evaluate albuminuria.[13] Many studies have demonstrated that high UACR predicts higher risk of stroke, while others argued that UACR is irrelevant to stroke.[7,8,10,14-18] In this meta-analysis and systemic review, we aimed to summarize all the current results regarding the relationship between UACR and stroke, and investigate whether high UACR predicts higher risk of stroke.

Methods

This systematic review was organized based on the guidelines of the Meta-analysis of Observational Studies in Epidemiology Group and the Quality of Reports of Meta-Analyses of Randomized Controlled Trials recommendations.[19,20]

Search strategy

We carefully searched MEDLINE, EMBASE, Cochrane Controlled Trials Register Database, Scopus and Google Scholar from January 1966 to June 2021 by using the following keywords: "albuminuria" or "microalbuminuria" or "macroalbuminuria" or "proteinuria" or "UACR" "or "ACR" in combination with "stroke" or "cerebrovascular disease" or "cerebral haemorrhage" or "cerebral ischemia" or "cerebral infarction." Two investigators (Min Li and Aichun Cheng) independently conducted a systematic search of all relevant references. There are no restrictions in language. In addition, a manual search was conducted using the bibliographies of original papers and review articles on this topic.

Study selection

The inclusion criteria of this study included: (1) Retrospective/prospective cohort study or clinical trial study; (2) human subjects; (3) hazard ratio (HR) or adjusted HR of high UACR is either available or can be calculated from the data provided in the article; (4) follow-up time exceeded 1 Year; (5) The sample size is large enough ($n > 100$);

Data extraction

Two blinded reviewers (Jingkun Sun and Chunqiu Fan) abstracted the data independently to a predefined form. The following data were extracted and tabulated: (1) Publication details, including the first author's surname, study population, inclusion criteria, study period, publication year, total number of patients, definition of high UACR, follow-up period, risk estimate and study quality [Table 1]. (2) Basic clinical characteristics of the studies including age, gender, smoking, ischemic stroke, hemorrhagic stroke, diabetes mellitus (DM), atrial fibrillation,[1] chronic heart failure, body mass index, systolic blood pressure, diastolic blood pressure, serum cholesterol, serum triglycerides, serum high density lipoprotein-cholesterol, serum low density lipoprotein-cholesterol [Table 2]. Study quality was assessed based on Newcastle-Ottawa Scale.[21]

Statistical analysis

The HR or adjusted HR[17] with 95% confidence intervals (CI) were used to describe the strength of the association between UACR and stroke. The values of I^2 exceeding 75% was considered as an indicator of significant heterogeneity.[22] The random effect model and the fixed effect model combined with inverse variance method was both used to evaluate the overall effect of multiple independent studies. However, If $I^2 > 75\%$, the random effect model is the primary analysis; otherwise, the fixed effect model is the primary analysis. A $P = 0.05$ in test for overall effect was considered statistically significant. We also performed a series of subgroup analysis based on definitions of high UACR, study population and the type of stroke to explore the probable influencing factors. The publication bias is assessed by plotting the funnel plots. Selection bias, performing bias, detection bias, attrition bias and reporting bias were evaluated by Cochrane Risk of Bias Tool.[23] All analyses were performed using Review Manager (RevMan, version 5.2, Copenhagen, Denmark: The Nordic Cochrane Centre and the Cochrane Collaboration, 2012).

Results

Overall analysis

A total of 10,939 articles were found by searching in MEDLINE, EMBASE, Cochrane Clinical Trials Database, Scopus and Google Scholar. 10,556 studies were excluded due to duplication and irrelevant topics. Of the remaining 383 studies, only 18 studies were reviewed for full publication. 365 studies were excluded due to absence of UACR value, animal studies and review articles. Others were discarded due to absence of

Table 1: Characteristics of studies included in this meta-analysis

Investigator	Study population	Inclusion criteria	Study period	Publication year	Total number of participants	Definition of high UACR	Follow-up period	Study design	Study quality
bMahmoodi	Inhabitants	NA	1996-2002	2014	29595	UACR >30 mg/g	Average follow-up of 9.5 years	Prospective	7
Scirica	Patients with T2DM	NA	2010-2013	2017	15760	UACR >10 mg/g	Median follow-up of 2.1 years	Prospective	8
Tebbe	Hypertensive Patients	SBP ≥140 mmHg or DBP ≥90 mmHg; age >18 years	2005-2007	2010	2173	UACR >30 mg/g	12 months	Prospective	5
Solbu	Inhabitants	Born before 1970	1994-1995	2008	5215	UACR >0.43 mg/mmol	Average follow-up of 9.7 years	Prospective	5
Yamamoto	Patients with T2DM	NA	2004-2006	2009	653	UACR >30 mg/g	3 years	Retrospective	5
Aguilar	Elderly adults	Age ≥65 years	1996-1997	2010	3205	UACR >30 mg/g	Average follow-up of 8.7 years	Prospective	6
Bello	Adults	Age ≥18 years	2002-2006	2011	102701	UACR>30 mg/g	Median follow-up of 35 months	Prospective and retrospective	6

T2DM: Type 2 diabetes mellitus, NA: Not available, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, UACR: Urinary albumin creatinine ratio

Table 2: Risk estimate and adjusted variables of included studies

Investigator	Risk estimate	Adjusted variables
Mahmoodi	HR	NA
Scirica	aHR	Treatment, age, sex, race, history of heart failure, duration of diabetes, hemoglobin A1C, systolic blood pressure, prior myocardial infarction, history of hypertension, history of dyslipidemia, current smoker, and estimated glomerular filtration rates, and for the models with biomarkers, high-sensitivity troponin T quartiles, pro B-type natriuretic peptide quartiles and C-reactive protein
Tebbe	HR	Age
Solbu	HR	NA
Yamamoto	HR	NA
Aguilar	aHR	Age, sex, race, body mass index, current smoking, hypertension, diabetes, left ventricular hypertrophy and atrial fibrillation
Bello	HR	NA

HR: Hazard ratio, aHR: Adjusted HR, NA: Not available

UACR, animal studies or review articles. After intensive reading of the remaining 18 studies, 5 studies which only enrolled patients with stroke were excluded. 6 studies were excluded due to lack of HR or aHR. 7 articles were finally retained [Figure 1].[7,8,14-18] The characteristics of the included studies are shown in Table 1. A total of 159,302 subjects were enrolled in the included studies. The follow-up period ranged from 1 to 9.7 years. The risk estimates and adjusted variables in the included studies were summarized in Table 2. The baseline data for each study are presented in Table 3. The overall analysis confirmed that high UACR was associated with an increased rate of stroke [Figure 2, Random model: HR, 1.83; 95% CI: 1.49–2.25; $P < 0.01$, Fixed model: HR, 2.04; 95% CI: 1.93–2.15; $P < 0.01$].

Subgroup analysis for distinctive standard of high urinary albumin-to-creatinine ratio

The definitions of high UACR differed in each study. When using UACR > 0.43 mg/mmol as a cutoff value, and the results showed that high UACR indicated an increased risk of stroke [Figure 3, Random model: HR, 2.39; 95% CI: 1.24–4.61; $P = 0.009$, Fixed model: HR, 2.39; 95% CI: 1.24–4.61; $P = 0.009$]. Furthermore, it is demonstrated that UACR > 10 mg/g also predicted an increased risk of stroke [Figure 3, Random model: HR, 1.60; 95% CI: 1.30–1.97; $P < 0.01$, Fixed model: HR, 1.60; 95% CI: 1.30–1.97; $P < 0.01$]. Notably, UACR > 30 mg/g was used as a cutoff value of high UACR in most studies. Results from these studies supported the previous findings [Figure 3, Random model: HR, 1.84; 95% CI: 1.49–2.28; $P < 0.01$, Fixed model: HR, 2.05; 95% CI: 1.94–2.17; $P < 0.01$]. However, based on the studies where high UACR was defined as >20 mg/g, no correlation was identified between high UACR and stroke [Figure 3, Random model: HR, 2.12; 95% CI: 0.24–18.95; $P = 0.50$, Fixed model: HR, 1.36; 95% CI: 0.44–4.19; $P = 0.59$].

Table 3: The demographic characteristics of included studies

Investigator	Mahmoodi	Scirica	Tebbe	Solbu	Yamamoto	Aguilar	Bello
Age (years)	60.54	NA	61.4±11.3	59.5±10.3	67.12	78.45	56.9
Gender (% women)	54.2	NA	42.6	49.3	35.4	60.6	45.5
BMI	27.72	NA	29.7±5	NA	23.66	26.93	NA
SBP (mmHg)	128.67	NA	159.8±20.1	156.9±21.6	129.93	137.15	NA
DBP (mmHg)	71.95	NA	93.4±11.9	89.7±12.2	73.25	69.89	NA
Smoking (%)	19.06	NA	12.1	32.2	NA	7.72	NA
Ischemic strokes (%)	3.73	NA	2.5	NA	13.01	NA	NA
Hemorrhagic strokes (%)	0.53	NA	NA	NA	NA	NA	NA
DM (%)	12.36	100	22.6	NA	100	14.4	53.8
AF (%)	NA	NA	6.8	NA	NA	3.9	NA
CHF (%)	NA	NA	4.7	NA	NA	NA	5.29

Continuous variables are expressed as mean±SD. DM: Diabetes mellitus, AF: Atrial fibrillation, CHF: Chronic heart failure, BMI: Body mass index, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, NA: Not available

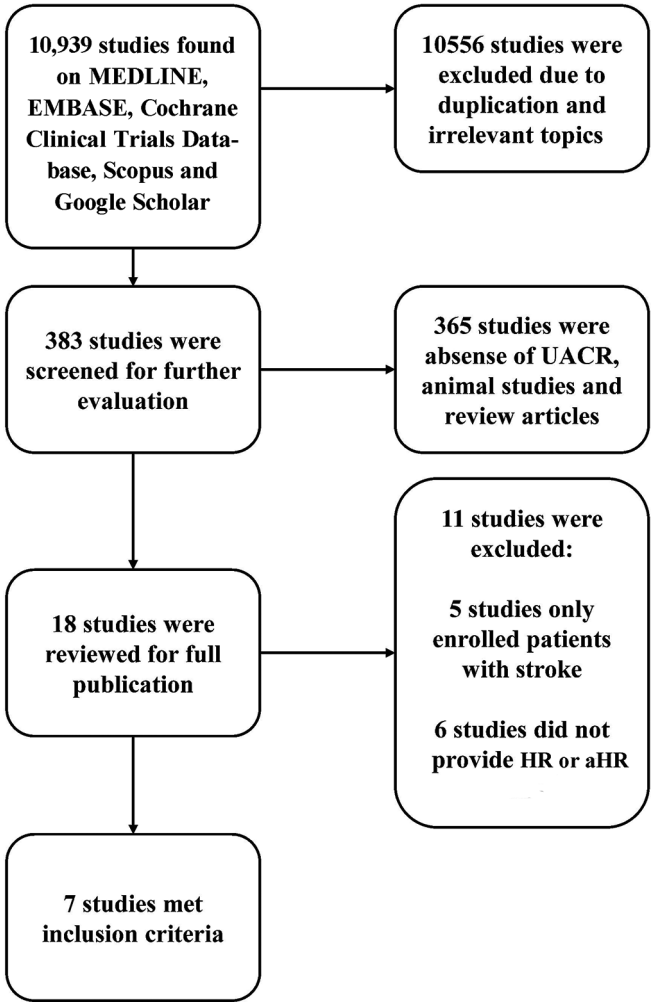

Figure 1: Flow diagram of study selection process. Urinary albumin-to-creatinine ratio, urinary albumin-to-creatinine ratio; hazard ratio, hazard ratio; a hazard ratio, adjusted hazard ratio

Subgroup analysis for distinctive study population

The populations enrolled in the four studies were local inhabitants, included adults and elderly adults.[7,8,14,16] Results from the 4 studies revealed that high UACR predicted higher risk of stroke in local inhabitants [Figure 4, Random model: HR, 1.67; 95% CI: 1.17–2.37; P = 0.004, Fixed model: HR, 1.55; 95% CI: 1.34–2.79; P < 0.01], adults [Figure 4, Random model: HR, 2.21; 95% CI: 2.07–2.36; P < 0.01, Fixed model: HR, 2.21; % CI: 2.07–2.36; P < 0.01] or elderly adults [Figure 4, Random model: HR, 1.96; 95% CI: 1.56–2.46; P < 0.01, Fixed model: HR, 1.96; 95% CI: 1.56–2.46; P < 0.01]. Whereas, other studies recruited patients with Type 2 DM (T2DM)[15,17] and patients with hypertension.[18] A subgroup analysis using random effect model revealed that high UACR was unable to predict stroke in patients with T2DM [Figure 4a, Random model: HR, 2.25; 95% CI: 0.55–9.17; P = 0.26]. However, analysis using fixed effect model showed that high UACR predicted higher risk of stroke in T2DM patients [Figure 4b, Fixed model: HR, 1.62; 95% CI: 1.31–1.99; P < 0.01]. High UACR lost the predictive power for stroke using either random or fixed effect model in patients with hypertension [Figure 4, Random model: HR, 0.95; 95% CI: 0.28–3.22; P = 0.93, Fixed model: HR, 0.95; 95% CI: 0.28–3.22; P = 0.93].

Subgroup analysis for ischemic stroke and hemorrhagic stroke

Another subgroup analysis was performed to evaluate the role of high UACR on ischemic stroke and hemorrhagic stroke. It is suggested that high UACR was associated with increased risk of both ischemic [Figure 5, Random model: HR, 1.63; 95% CI: 1.42–1.87; P < 0.01, Fixed model: HR, 1.60; 95% CI: 1.43–1.80; P < 0.01] and hemorrhagic strokes [Figure 5, Random model: HR, 1.76; 95% CI: 1.22–2.54; P = 0.003, Fixed model: HR, 1.76; 95% CI: 1.22–2.54; P = 0.003].

Bias analysis

The funnel plot was used to evaluate the publication bias [Figure 6a], the roughly symmetrical distribution pattern showed little publication bias. There was no significant interaction between log HR and the quality score [Figure 6b]. It is suggested that the quality score had no impact on HR in each study. The risk of bias summary of enrolled studies was presented in Figure 7.

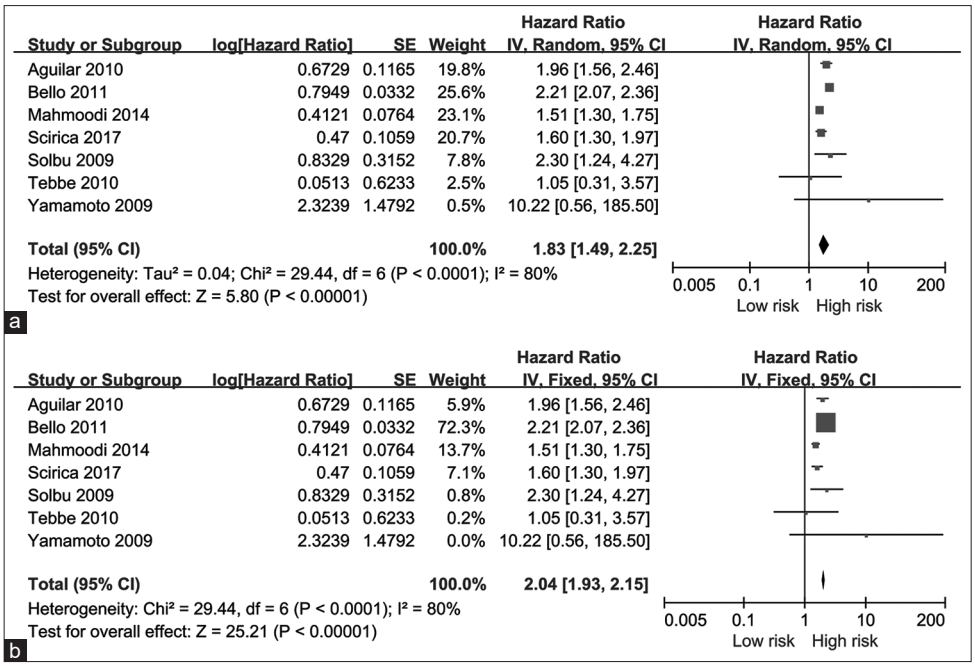

Figure 2: High urinary albumin-to-creatinine ratio predicted an increased risk of stroke in random effect model (a) and fixed effect model (b). Urinary albumin-to-creatinine ratio, urinary albumin-to-creatinine ratio

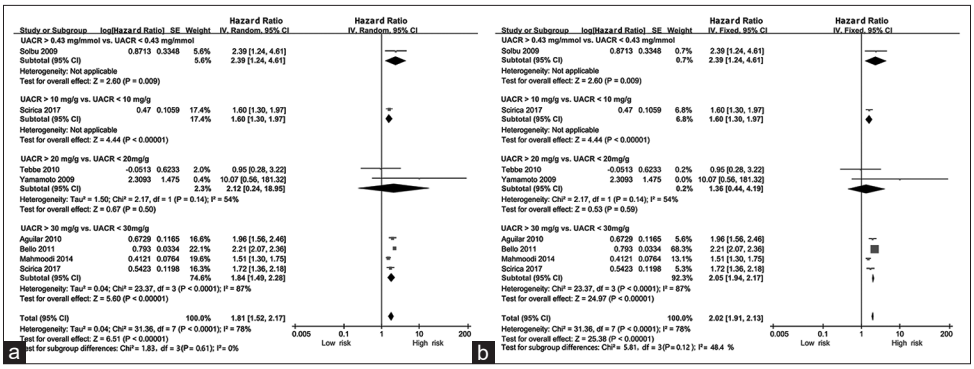

Figure 3: High urinary albumin-to-creatinine ratio predicted an increased risk of stroke using cutoff value of 0.43 mg/mmol, 10 mg/g or 30 mg/g in random effect model (a) and fixed effect model (b). Confidence interval; standard error; urinary albumin-to-creatinine ratio, urinary albumin-to-creatinine ratio

All the seven included studies were double-blinded trials. Five experiments did not describe in detail about the random sequence generation and the concealment of the allocation scheme. Four of the seven included studies had attrition bias.

Discussions

UACR, independent of other renal biomarkers such as eGFR and cystatin C, is linked with the risk of stroke.[7] This study also showed that UACR played a crucial role in predicting stroke. It is demonstrated that albuminuria was correlated with hypercysteinemia, coagulopathy, endothelial dysfunction, elevation of inflammatory factors and enhancement of oxidative stress.[24-26] Gaede *et al*.[27] hypothesized that albuminuria may be a biomarker of generalized vascular wall disease involving small and large blood vessels. Knopman also supported this view.[28] This generalized vascular wall disease may lead to either hemorrhagic or ischemic stroke. It is reported that albuminuria is associated with increased risk of deep or under-the-fold microbleeding.[8,29] It is also demonstrated that UACR was independently associated with neurological deterioration after cerebral infarctions and white matter lesions.[30-32] The present study also revealed that UACR served as a predictor of either hemorrhagic or ischemic stroke.

However, the definitions of high UACR were not the same in 7 included studies. The well-accepted normal range of UACR is between 2 and 20 mg/g.[33] The 0.43 mg/mmol, 10 mg/g, 20 mg/g, 30 mg/g of UACR were used as the cutoff values in the included studies. Subgroup analysis showed that high UACR was unable to predict stroke when using 20 mg/g of UACR as cutoff value [Figure 3].

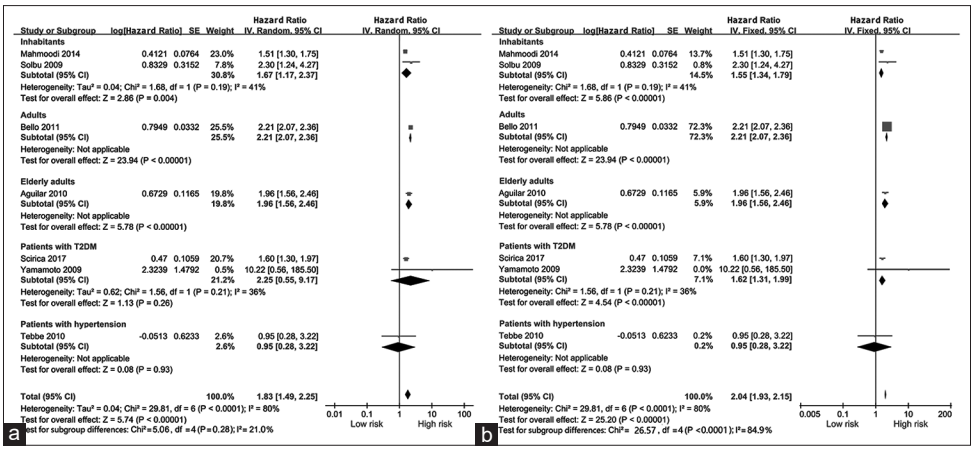

Figure 4: High urinary albumin-to-creatinine ratio predicted an increased risk of stroke in local inhabitants, adults or elderly adults, but not patients with hypertension using random effect model (a) and fixed effect model (b). However, high urinary albumin-to-creatinine ratio was uncapable of predicting high risks of stroke in patients with Type 2 diabetes mellitus using random effect model (a). Confidence interval; standard error; urinary albumin-to-creatinine ratio, urinary albumin-to-creatinine ratio

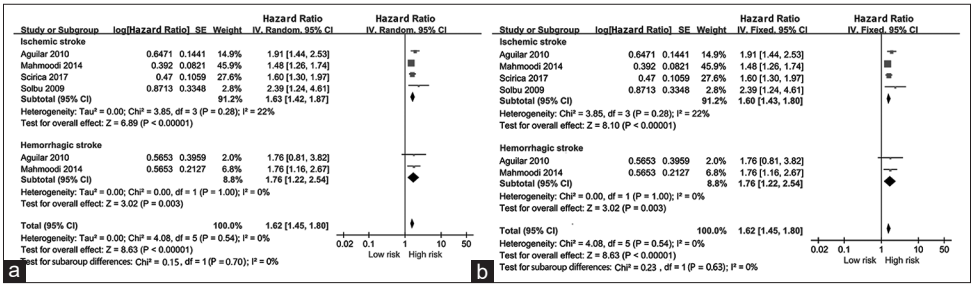

Figure 5: High urinary albumin-to-creatinine ratio was associated with an increased risk of ischemic stroke, as well as hemorrhagic stroke in random effect model (a) and fixed effect model (b). Confidence interval; standard error; urinary albumin-to-creatinine ratio, urinary albumin-to-creatinine ratio

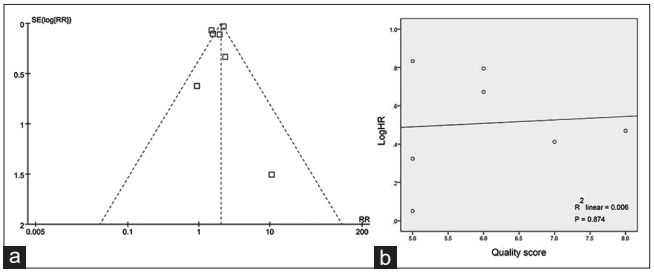

Figure 6: The funnel plot of included studies (a). Linear regression of log hazard ratio and quality score (b). Standard error; hazard ratio, hazard ratio

The 20 mg/g of UACR as cutoff value was used in two studies which recruited the patients with hypertension and T2DM, respectively. Further analysis was performed to identify whether UACR lost its predictive power for stoke due to the cutoff value of 20 mg/g or the study population of patients with T2DM and hypertension.

Subgroup analysis showed that high UACR was unable to predict stroke in patients with hypertension [Figure 4]. Subsequently, we analyzed the effect of UACR on stroke in patients with T2DM. The overall effect of UACR on stroke assessed by random effect model is inconsistent with that assessed by fixed effect model. It seems that results by random effect model are more convincing due to great heterogeneity ($I^2 > 75\%$). Results from the present study suggested that high UACR lost its predictive power for stroke in T2DM patients. As known, hypertension and T2DM are recognized risk factors for stroke.[34] The predictive power of UACR may be interfered by the severity of hypertension and T2DM.

Currently, a study revealed that aspirin combined with clopidogrel was effective on reducing stroke recurrence in patients with none or mild CKD, but not better than aspirin alone in patients with moderate or severe CKD.[35] Aspirin was also recommended for primary prevention of stroke in patients with CKD.[36] Clinical trials have demonstrated that statins are safe and efficacious in the prevention of stroke in preend stage CKD.[37] However, CKD is diagnosed based on eGFR. Further studies on medication adjustment in primary and secondary stroke prevention based on UACR level are required.

Limitations

The limitations of this meta-analysis and systemic review were as follows: First, the number of included studies was not large enough. Second, there was only one randomized controlled trial among seven included studies. Third,

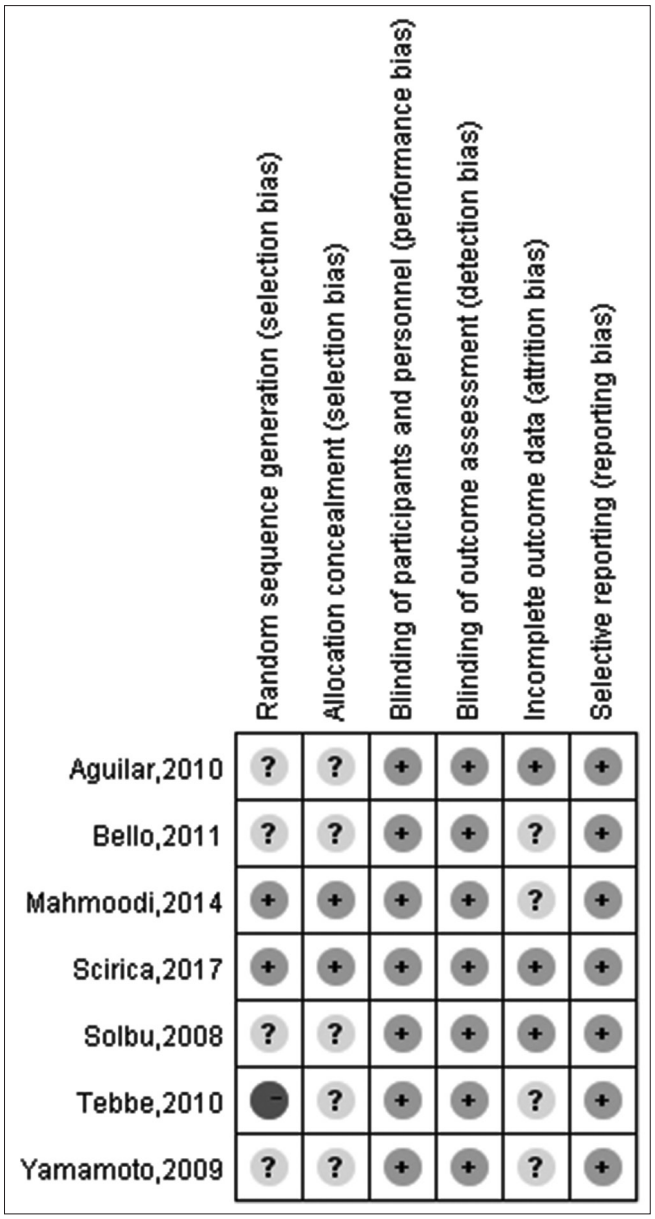

Figure 7: The risk of bias summary of enrolled studies

the definition of end point event differed in each study. In studies by Bello *et al*.[16] and Tebbe *et al*.,[18] end point events were defined as transient ischemic attack[38] and stroke. However, other studies defined only stroke as the end point event. The last but not least, merging adjusted HR and unadjusted HR is a limitation to this study.

Conclusions

Subjects with high UACR is associated with an increased risk of both ischemic and hemorrhagic stroke. UACR can be used as an indicator to predict stroke in nondiabetic and nonhypertensive population.

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Conflicts of interest

Dr. Ran Meng is an Editorial Board member of *Brain Circulation*. The article was subject to the journal's standard procedures, with peer review handled independently of this Editorial Board member and their research groups.

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