Review Article

Increased Spot Urine Albumin-to-Creatinine Ratio and Stroke Incidence: A Systematic Review and Meta-Analysis

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Objective: This study aimed to clarify the association between an increased spot urine albumin-to-creatinine ratio (UACR) and the risk of stroke. *Methods:* We performed a systematic review and meta-analysis of cohort studies, case-control studies, and ancillary data randomized controlled trials (RCTs), which were treated as cohorts in this study, and estimated the association between albuminuria, as measured with the UACR, and the risk of stroke. We performed a comprehensive search of PubMed, Embase, and the Cochrane Library and conducted a systematic review and cumulative meta-analysis of cohort studies with a cross-sectional with prospective design in which stroke incidence was reported and the baseline UACR was measured. Ancillary data from RCTs were also included as part of the cohort study. We studied the characteristics of the participants, quality scores and risk ratios (RR, with confidence intervals, CI) of stroke associated with normal and high UACRs, and we synthesized the data via a meta-analysis. *Results:* Twelve eligible studies including a total of 32,888 participants and 3,944 cases of stroke were identified. A high UACR (>30 mg/mmol) increased the risk of stroke by 1.67 times (RR: 1.67, 95% CI: 1.49-1.86, P<0.001 $I^2 = 26\%$). The results were not different between Asian and non-Asian patients (RR: 1.64, 95% CI: 1.41-1.91, P<0.001, $I^2 = 23\%$ compared with RR: 1.67, 95% CI: 1.50-1.85, *P*<0. 00, $I^2 = 39\%$) or between subgroups classified by old age (RR: 1.61, 95% CI: 1.39-1.88, *P*<0.001, $I^2 = 34\%$ compared with RR: 1.68, 95% CI: 1.52-1.87, *P*<0.001, $I^2 = 13\%$). A sensitivity analysis did not significantly change the results. *Conclusion:* The incidence of stroke increased significantly in the high UACR group compared with the normal UACR group. The UACR could be a clinical addition for the early indication of high-risk stroke patients.

Key Words: Urine albumin-to-creatinine ratio (UACR)—stroke—albuminuria—systemic review.

Stroke is the second leading cause of death and the primary cause of chronic neurological disability worldwide,[1] and a high prevalence has been reported in China in the past 10 years. Based on a survey conducted in 2015 by the National Health and Family Planning Commission, cardiocerebrovascular disease has become the leading cause of death in China (44.2%); over half of the population dies of a chronic disease (51%). Moreover, it has been shown

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that the incidence of stroke is still increasing rapidly, and this trend may last until 2030.[2] Similarly, chronic kidney disease (CKD) is a considerable public health challenge worldwide. In 2012, a national survey reported that the prevalence of CKD was 10.8%, encompassing approximately 119.5 million adults aged 18 years or older in China.[2] Growing evidence indicates that the presence of protein in the urine, which represents an early sign of kidney disease, may be related to the risk of stroke. There are different data regarding whether proteinuria, which is often measured via the urine albumin-to-creatinine ratio (UACR), could be a risk factor for stroke and its subtypes.[3,4] Renal insufficiency could be one considerable risk for worse clinical outcome of cerebral vascular disease. High albumin urea, better interpreted by UACR, predicts higher risk of renal insufficiency, latent glomerular damage, and systemic change of small arteries. Further studies are needed.

Stroke and CKD share common cardiovascular risk factors, including high blood pressure, smoking status, high cholesterol, and diabetes.[5] The UACR is associated with diabetes and increased cardiovascular risk.[6] Morning urine albumin and creatinine are measured to calculate the UACR. Numerous studies have shown that proteinuria and CKD can be risk factors for worse clinical outcomes,[3,7] but few studies have evaluated whether proteinuria is a risk factor for predicting stroke. Albuminuria may not only reflect glomerular damage but also systemic damage to small arteries and capillaries. Marios K has reported that albuminuria is independently associated with cerebral small vessel disease, common microvascular pathology in the kidneys and brain are the main contributing mechanism.[8] However, insufficient literature has implied an association between the UACR and stroke incidents, which requires further study.

We conducted a systematic review and meta-analysis to examine the most recent evidence for the association between an elevated UACR and stroke.

Materials and Methods

We performed a systematic review and meta-analysis of cohort studies, case-control studies, and ancillary data from randomized controlled trials (RCTs), which were treated as cohorts in this study, to estimate the association between albuminuria and the risk of stroke. Our main variable of interest was albuminuria, as assessed by the UACR. Participants with a UACR less than equal to 30 mg/mmol were grouped into the normal UACR group, and those with a UACR more than 30 mg/mmol were grouped into the high UACR group. For each group of studies, we recorded the number of patients with stroke, the method of measurement and the units of quantification used.

Data Source and Searches

A literature search was performed using electronic databases, including PubMed, Embase, and Cochrane Library, for articles published prior to June 2018 without restriction to particular regions, publication types or languages. The authors followed a standardized search protocol to identify eligible studies. The related article function was also used to broaden the search, and the computer search was supplemented with manual searches of the reference lists of all retrieved studies, review articles, and conference abstracts. All RCTs and retrospective comparative studies (cohort or case-control studies) that compared the incidence of stroke between high and normal UACR groups were included. Editorials, letters to the editor, review articles, case reports, and animal studies were excluded.

Data from the included studies were extracted and evaluated independently by 2 of the authors (Huang and Chen). Any disagreement was discussed and resolved by consulting with the senior author (Chen). The main outcome of interest was the difference in stroke rates between the normal UACR group and the high UACR group. Specifically, we obtained effect estimates from the most fully adjusted model presented, noting for which variables the model had been adjusted. The standard error of the estimate was also extracted or estimated from the reported 95% confidence interval (CI) or *P* value.

Quality Assessment and Statistical Analysis

Retrospective studies were assessed with the modified Newcastle-Ottawa Scale, which consists of 3 parts including patient selection, comparability, and outcome. A score with a range of 0-9 was allocated to each study, and those with a score of 6 or more were considered to be high-quality studies.

The meta-analysis was performed using Review Manager 5.3 (Cochrane Collaboration, Oxford, UK). The risk ratio (RR) and weighted mean difference were used to compare continuous and dichotomous variables, respectively. All results were reported with 95% CIs.

Statistical heterogeneity between studies was assessed using the Cochran Q test with the significance set at $P < .10$, and heterogeneity was quantified using the I^2 statistic. A random-effects model was used if there was heterogeneity between studies; otherwise, a fixed-effects model was used.[9] According to the original studies, subgroup analyses were performed to compare the impact of the UACR on stroke in participants from Asia and outside Asia. In addition, subgroup analyses were also performed to test the differences between aged and young patients. Sensitivity analyses were performed for high-quality studies. Funnel plots were used to screen for potential publication bias.

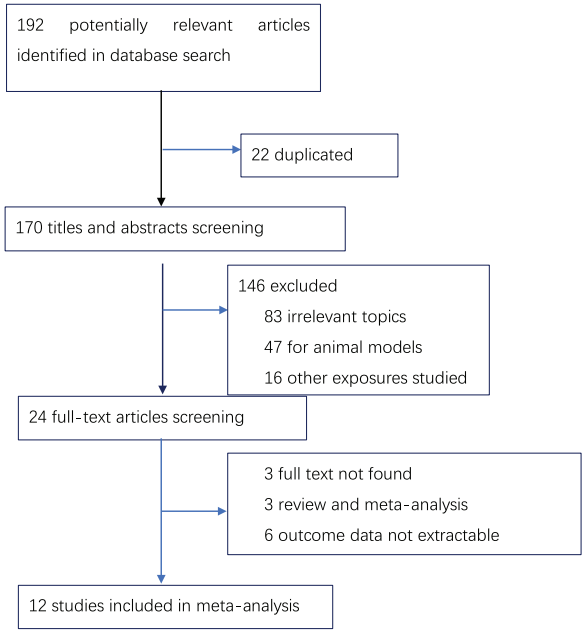

Figure 1. *Showed the selection of studier for meta-analysis.*

Results

Of the 192 identified studies, 12 were eligible for inclusion (Fig 1). In total, 32,888 participants with 3944 all-cause causes of stroke were analyzed. The follow-up time ranged from 90 days to 8.7 years. Of these studies, 1 (8.33%) were ancillary RCTs,[2] which we analyzed as cohorts; 4 (33.3%) were cross-sectional studies[7,10-12]; 6 (50%) were cohort studies[4,13-17]; and one (8.3%) was a case-control study.[18] These studies were conducted in 8 countries and more than 10 districts, and all were published in English (Table 1).

Six out of 12 (50%) studies included were classified as high-quality studies, although most of the studies were observational, and only one of the studies was an ancillary analysis of an RCT (Table 2). No studies provided information about allocation concealment or blinding methods. Matching criteria between the groups were available, and 6 studies mentioned the length of follow-up. Methods for handling missing data and intention-to-treat analyses were described inadequately in most of the studies.

UACR and Stroke

Participants were allocated into 2 different groups based on the degree of albuminuria, as measured by the UACR. The participants with a UACR more than equal to 30 mg/mmol were assigned to the high UACR group, whereas those with a UACR less than 30 mg/mmol were assigned to the normal UACR group (Fig 2). The risk of all-cause stroke in the high UACR group was greater than that in the normal UACR group (RR 1.67, 95% CI 1.49-1.86, $P < .001$ $I^2 = 26\%$). The magnitudes of risk estimates were not available for stroke subtype, severity or incident versus recurrent stroke. The risk did not vary by the method used to quantify albuminuria.

In the subgroup analysis, first, demographic information was taken into consideration, and there were no significant differences between participants from Asia or outside Asia (RR 1.64, 95% CI 1.41-1.91, $P < .001$, $I^2 = 23\%$ compared with RR 1.67, 95% CI 1.50-1.85, $P < .00$, $I^2 = 39\%$; Fig 3). Second, subgroups of elderly participants (>65 years old) and young participants (no more than 65 years old) also showed little difference (RR 1.61, 95% CI 1.39-1.88, $P < .001$, $I^2 = 34\%$ compared with RR 1.68, 95% CI 1.52-1.87, $P < .001$, $I^2 = 13\%$; Fig 4). A pooled analysis indicated that an elevated UACR could be an important factor for predicting stroke, but this parameter could be affected by the glomerular filtration rate (GFR). This

Table 1. *Characteristics of the included studies*

	Evidence	Design	Patient no.	Method of UACR testing	Follow-up period	Country/district
A. Vilar-Bergua 2016	2B	cohort	976	Single spot†	NA‡	Spain
Aguilar 2010	2B	cohort+P*	3287	Single spot	8.7 y	US
C. Zhang 2015	2A	cohort (RCT)	19,599	Single spot	4.5 y	China
E.B. Cho 2016	3B	cross-sec	1215	Single spot	NA	Korea
F. Anan 2008	3B	cross-sec	90	24 h for 3 days	NA	Japan
N.B. Beamer 1999	3B	case-control+P	186	Single spot	2 y	Poland
O.M. Guierrez 2012	2B	Cohort	25,310	Single spot	4.7 y	US
P. Vemuri 2017	2B	Cohort	240	Single spot	NA	US
P.M. Costa 2018	2B	cohort+P	1048	24-h urine	7.5 y	Brazil
S. Elyas 2016	2B	cohort	150	Single spot	3 m	US
Watanabe 2009	3B	cross-sec	288	Once/twice	NA	Japan
M. Wada 2007	3B	cross-sec	651	Single spot	NA	Japan

*+P represent prospective study.
†Single spot = the UACR was calculated by single spot albuminuria and creatinine testing; 24 h = the UACR was calculated by evaluating for albuminuria on a 24-h urine sample and by measuring creatinine.
‡NA represents no follow-up.

Table 2. *Assessment of the quality of included studies*

	Selection	Comparability	Outcome	Quality score
A. Vilar-Bergua 2016	★★★	★	★★	6
Aguilar 2010	★★★	★★	★	6
C. Zhang 2015	★★★★	★	★★★	8
E.B. Cho 2016	★★★	★★	–	5
F. Anan 2008	★★★	★	–	4
N.B. Beamer 1999	★★	★	★★	5
O.M. Guierrez 2012	★★★	★★	★★★	8
P. Vemuri 2017	★★★	★	★★	6
P.M. Costa 2018	★★★★	★	★★★	8
S. Elyas 2016	★★	–	★★	4
Watanabe 2009	★★★	–	★	4
M. Wada 2007	★★★	–	★	4

The retrospective studies were assessed with the modified Newcastle-Ottawa Scale, which consists of 3 parts including patient selection, comparability, and outcome. The Newcastle-Ottawa Scale is attached. A score with a range of 0-9 was allocated to each study, and those with a score of 6 or more were considered to be high-quality studies.

analysis suggests that an elevated UACR predicted an increased possibility of developing stroke regardless of ethnicity or age.

Sensitivity Analysis and Publication Bias

The studies with scores of 6 or higher on the modified Newcastle-Ottawa Scale were included in the sensitivity analysis. No obvious changes in the significance of any of the outcomes were detected. Figures 5 and 6 depict a funnel plot of the studies included in this meta-analysis. All studies lie inside the 95% CIs, with mostly even distribution in the vertical dimension (Figs 5 and 6), indicating that no obvious publication bias might exist in the analysis.

Discussion

In 1974, the first evidence of an association between the UACR and hypertension in nondiabetic patients was described, and to date, this association has been exhaustively confirmed.[4] Despite the extensive surveys conducted in population-based studies of diabetes mellitus and hypertension, the prognostic value of UACR in diabetes-related complications, such as stroke and small vessel disease of the brain, still have not been thoroughly discussed.

In this meta-analysis of 12 studies, which included data from more than 3000 strokes in 32,888 participants, we included the most recently published evidence that increasing albuminuria, mainly estimated by evaluation of the UACR from a single spot test, were related to an increased risk of stroke. This finding was consistent with the results of previous research showing that an average 10% increase in the RR of stroke was associated with every 25 mg/mmol increase in the UACR.[5] In addition, this finding was also consistent when subgroup analyses considering ethnicity and age was performed. No obvious change was observed between elderly and young participants, nor was there a difference between ethnicities. In a word, patients in the elevated UACR group had a higher likelihood of developing stroke regardless of their ethnicity or age.

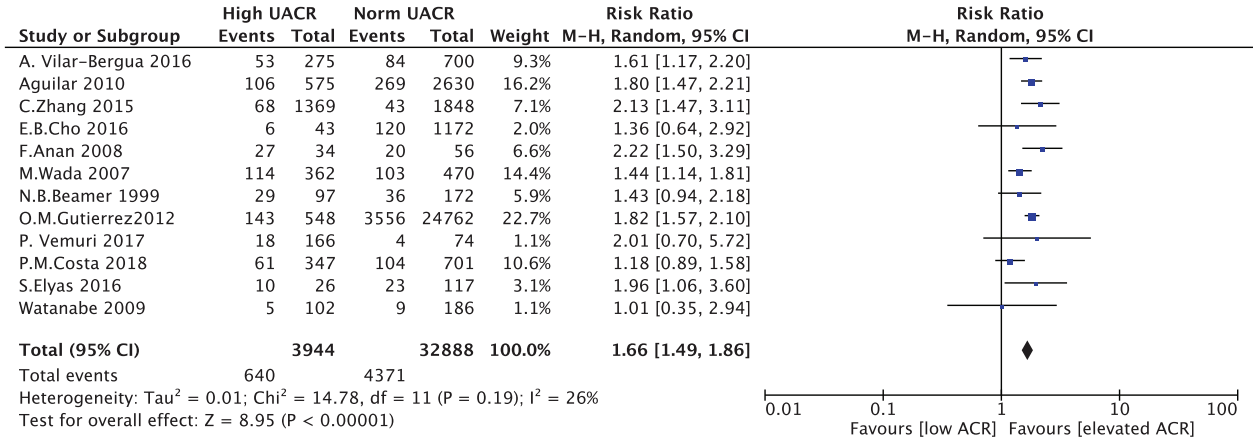

Figure 2. *Forest plot showed that the risk of all-cause stroke in the high UACR group was greater than that in the normal UACR group. (RR, 1.67, 95% CI 1.49-1.86, P < .001 I^2 = 26%). Abbreviation: UACR, urine albumin-to-creatinine ratio.*

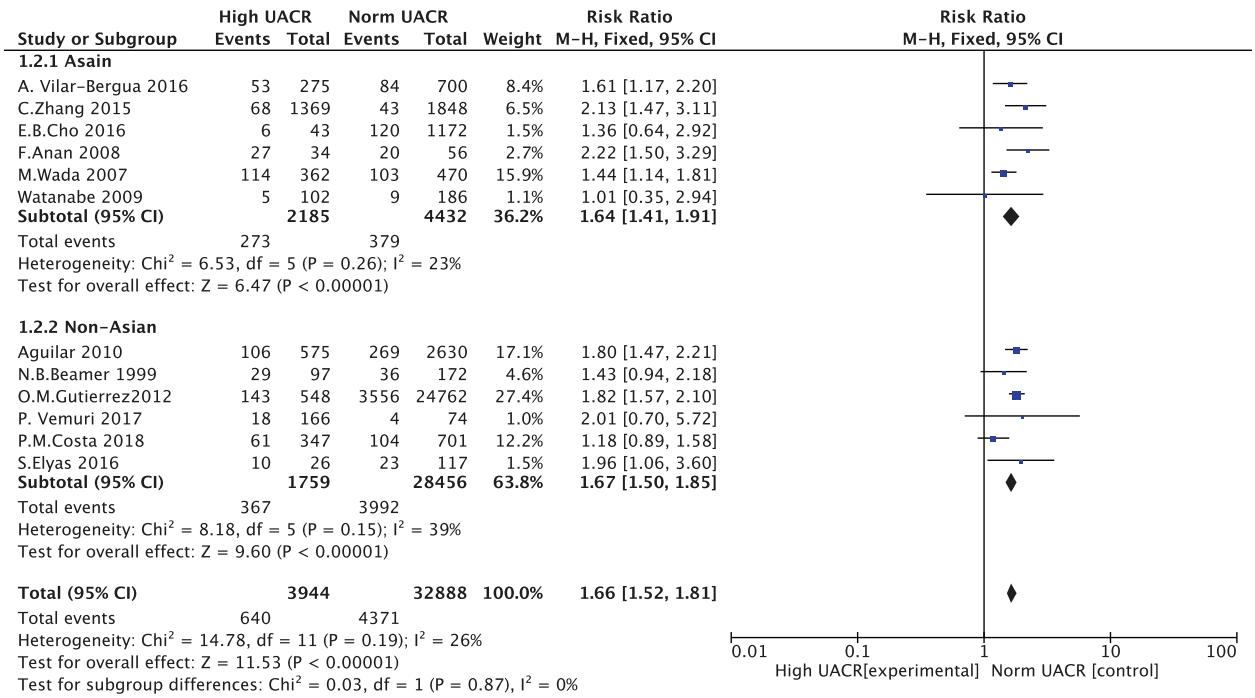

Figure 3. *Subgroup analysis indicated that there were no significant differences between participants from Asia or outside Asia (RR 1.64, 95% CI 1.41-1.91, P < .001, I^2 = 23% compared with RR 1.67, 95% CI 1.50-1.85, P < . 00, I^2 = 39%).*

Although rare in clinically healthy population-based samples, microalbuminuria may be present in up to one-fourth of patients with cardiovascular risk factors, most notably those with diabetes, hypertension, coronary artery disease, and/or a smoking habit. From a patho-physiological point of view, it has been speculated that diffuse arteriopathy of the cerebral small vessels results in hypoperfusion, impaired autoregulation, and subsequent

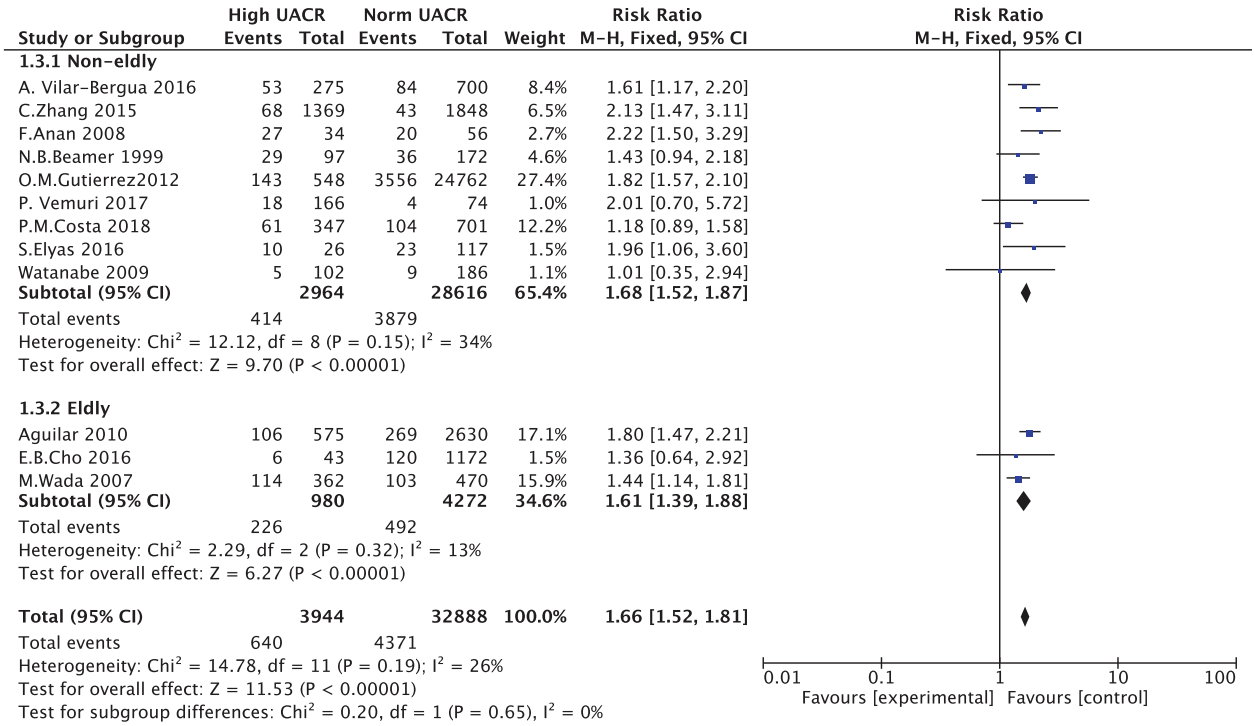

Figure 4. *Subgroups of elderly participants (>65 years old) and young (no more than 65 years old) also showed little difference (RR 1.61, 95% CI 1.39-1.88, P < .001, I^2 = 34% compared with RR 1.68, 95% CI 1.52-1.87, P < .001, I^2 = 13%).*

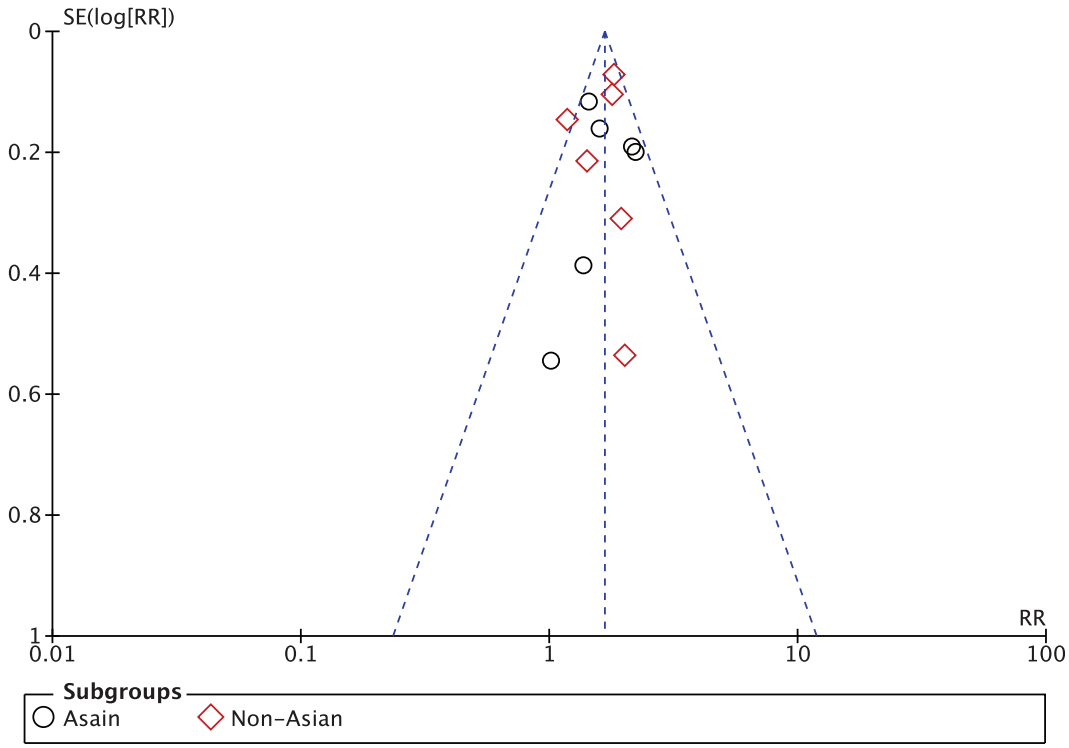

Figure 5. *Funnel plot of the subgroup studies of demographic. All studies lie inside the 95% CIs, with mostly even distribution in the vertical dimension.*

ischemia. Notably, increased albuminuria has a well-established prognostic value in patients with diabetes and hypertension, in the elderly and in population-based cohorts. The association between albuminuria and a decreased GFR seems to be close, and the most likely common link is endothelial dysfunction.[4]

To assess any impact of study quality, we performed a sensitivity analysis including only high-quality studies.

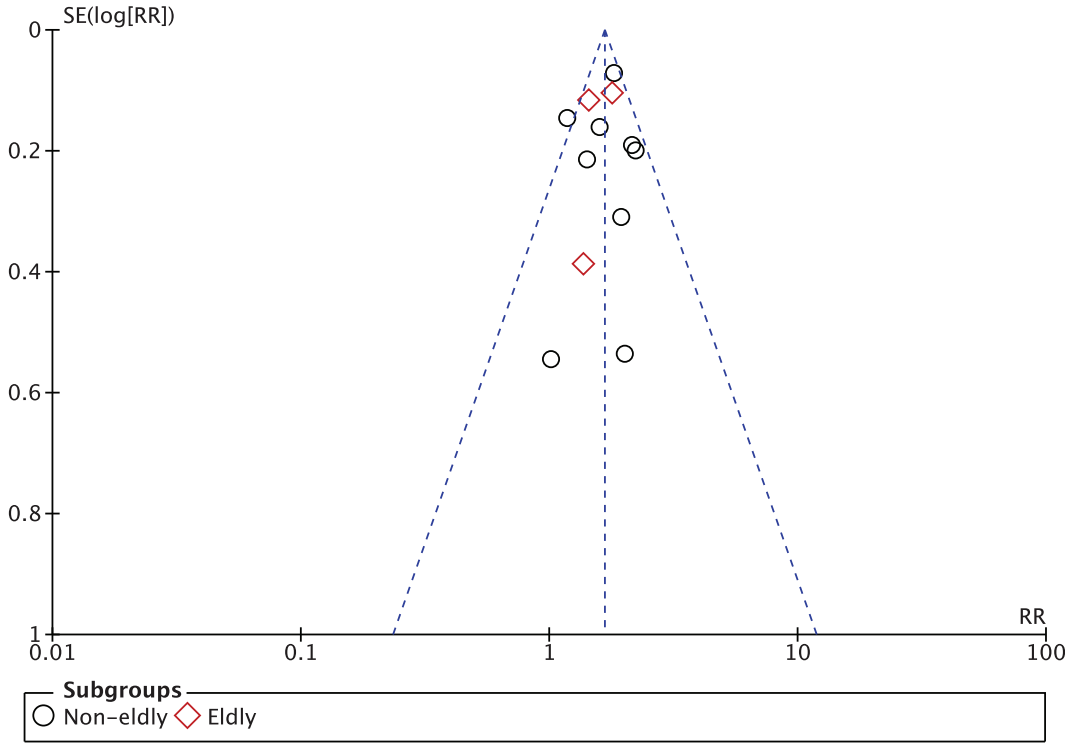

Figure 6. *Funnel plot of the subgroup studies of age. All studies lie inside the 95% CIs, with mostly even distribution in the vertical dimension.*

The results were similar to those of the primary analysis. Although a meta-analysis of only RCTs would be ideal, the limited number of RCTs prevented us from reaching any definitive conclusions based on sensitivity analyses alone.

The present meta-analysis has the following limitations that must be taken into consideration. As most of the included studies were observational and retrospective, many studies did not report data for known confounders of stroke risk, particularly the use of treatments for complications of CKD (including erythropoietin for anemia and angiotensin II enzyme inhibitors for people with albuminuria) or treatment to reduce cardiovascular risk (including aspirin and statins), which may have affected the risks of ischemic and hemorrhagic stroke differently. Second, the eGFR was not analyzed synchronously. With the exception of the UACR, the eGFR was mostly included to estimate the stage of CKD and clinical outcomes. In most of the included studies and those studies screened in the first step, the UACR was a more sensitive index and an earlier indicator of kidney dysfunction, though less specificity. In this meta-analysis, we did not account for the eGFR in the model because of the limited number of studies that reported this parameter. In most of the studies, the UACR was tested at a single point in time, which might have limited the accuracy and consistency of the calculated UACR. On the other hand, the UACR increased much earlier than small blood vessel injury could be detected, indicated that elevated UACR may appear earlier that eGFR.

In this meta-analysis, we included 11 observational studies and 1 ancillary RCT. The lack of RCTs was mainly due to the criteria that the UACR be recorded as a baseline variable. There would have been few studies included if the inclusion criteria only allowed RCTs. Taken together, the findings support the hypothesis that elevated albuminuria shown in the high UACR group conferring an increased risk of incident stroke independent of age or ethnicity.

Conflict of Interest

The authors have no conflict of interest related to this article to disclose.

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