20 YEARS
Cerebrovascular Diseases

Level of Albuminuria and Risk of Stroke: Systematic Review and Meta-Analysis

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Abstract

Background: Gross albuminuria is associated with increased stroke risk, but it is unclear whether stroke incidence varies by level of albuminuria. We meta-analyzed prospective cohort studies to investigate the impact of various albuminuria levels and continuous urinary albumin excretion (UAE) change on stroke risk. *Methods:* Systematic search for studies reporting quantitative estimates of the multivariate-adjusted relative risk (RR) and 95% CI for stroke risk associated with microalbuminuria (UAE 30–300 mg/day or nearest equivalent interval) and macroalbuminuria (UAE >300 mg/day) and studies that analyzed the relation of stroke with UAE continuously. Estimates were combined using a random-effect model. *Results:* We identified seven studies comprising 46,638 participants with 1,479 stroke events. Incident stroke risk was greater for macroalbuminuria (RR 2.65, 95% CI 2.25–3.14) than microalbuminuria (RR 1.58, 95% CI 1.39–1.80), a difference that was significant (p for heterogeneity < 0.001, I^2 = 96%). In addition, risk of stroke increased proportionally with rising UAE (p < 0.001), even for UAE within normal range (beginning from levels as low as 2–4 mg/g). *Conclusions:* Higher albuminuria level confers greater stroke risk. These findings provide additional weight to evidence that albuminuria is strongly linked to stroke risk, and suggest that persons with elevated UAE levels may especially benefit from more intensive vascular risk reduction.

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Introduction

Presence of overt proteinuria has been independently linked to greater stroke risk [1]. Furthermore, emerging data suggest that microalbuminuria may boost stroke risk [2], but the full extent of the relationship between urinary albumin excretion (UAE) and stroke has not been established. Specifically, it is not clear whether there is a greater risk of stroke with progressively higher levels of albuminuria. In this study, we utilized a systematic review and meta-analysis to assess: (1) the impact of various levels of albuminuria and macroalbuminuria on incident stroke risk, and (2) the influence of continuous change in level of UAE on risk of stroke.
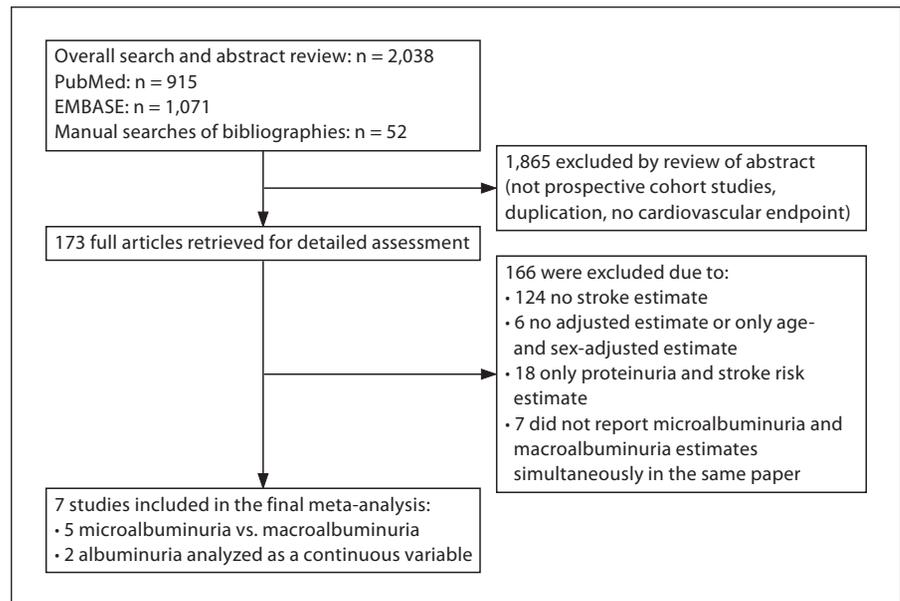
Fig. 1. Study selection flow.

The flowchart contains the following text:

Overall search and abstract review: n = 2,038
PubMed: n = 915
EMBASE: n = 1,071
Manual searches of bibliographies: n = 52

1,865 excluded by review of abstract (not prospective cohort studies, duplication, no cardiovascular endpoint)

173 full articles retrieved for detailed assessment

166 were excluded due to:
• 124 no stroke estimate
• 6 no adjusted estimate or only age- and sex-adjusted estimate
• 18 only proteinuria and stroke risk estimate
• 7 did not report microalbuminuria and macroalbuminuria estimates simultaneously in the same paper

7 studies included in the final meta-analysis:
• 5 microalbuminuria vs. macroalbuminuria
• 2 albuminuria analyzed as a continuous variable

Methods

The search strategy was conducted according to the recommendations of the Meta-analysis of Observational Studies in Epidemiology [3]. We performed a systematic search of Pubmed (1966 to October 2009) and Embase (1947 to October 2009) using the following search strategy: 'proteinuria' or 'albuminuria' or 'microalbuminuria' or 'macroalbuminuria' or 'normoalbuminuria' or 'low grade albuminuria' crossed with 'stroke' or 'cerebrovascular disease' or 'cerebral ischemia' or 'brain ischemia' or 'intracranial hemorrhage'. Additionally, we identified potentially relevant studies using a manual search of references from all eligible studies and review articles. Studies were selected if they met the following entry criteria: (1) prospective cohort design; (2) reported quantitative estimates of multivariate-adjusted relative risk (RR) and 95% CI for stroke risk associated with microalbuminuria and macroalbuminuria, separately, or provided relationship of stroke risk and albuminuria by analyzing albuminuria as continuous variables, and (3) follow-up duration was at least one year. Studies were excluded if (1) they were of cross-sectional, case-control, or retrospective cohort design; (2) a majority of the participants had chronic kidney disease, and (3) only reported unadjusted or age- and sex-adjusted RR.

Data analysis used multivariate-adjusted outcome data (expressed as RR and 95% CI). We converted these values by using their natural logarithms, and standard errors were calculated from these logarithmic numbers and their corresponding 95% CI. The inverse variance approach was used to combine log RR and standard errors and data pooled across trials using the random-effects model [using Cochrane Collaboration's Review Manager Software Package (RevMan 5)]. All reported p values were two-sided with significance <0.05. Heterogeneity was assessed by p value of χ^2 statistics and I^2. A funnel plot was conducted to evaluate potential systematic bias in studies, including publication bias.

Results

Our final analysis (fig. 1) included five studies that compared stroke risk among subjects with baseline normoalbuminuria (UAE <30 mg/day or nearest equivalent interval), microalbuminuria (UAE 30–300 mg/day or nearest equivalent interval), and macroalbuminuria (UAE >300 mg/day) [4–8], generating six independent adjusted stroke risk estimates. Only two studies analyzed albuminuria level versus stroke risk as a continuous variable [9, 10]. There were 46,638 participants with 1,479 stroke events included in the meta-analysis. Study characteristics can be found in table 1.

Stroke risk was greater for macroalbuminuria (RR 2.65, 95% CI 2.25–3.14) than microalbuminuria (RR 1.58, 95% CI 1.39–1.80) and the test for difference between these two groups by level of albuminuria was highly significant (p for heterogeneity <0.001, I^2 = 96%; fig. 2a). When albuminuria levels were analyzed as a continuous variable, risk of stroke increased proportionally with rising albuminuria even starting within the normal range of albuminuria from levels as low as about 2–4 mg/g (fig. 2b). There was no major asymmetric appearance on the funnel plot (fig. 3).

Table 1. Study characteristics

Study	Study design and population	Country	n/N	Age mean ± SD years	Follow-up years	End point	Definition of albuminuria	Adjusted variables (number of adjusted variables)
Miettinen 1996a [4]	Non-diabetic cohort, stroke history at entry was 1%	Finland	30/1,375	58 ± 0.2	7	All stroke	Microalbuminuria: 150–300 mg/l Macroalbuminuria: >300 mg/l	Age, sex, smoking, hypertension, total cholesterol, HDL cholesterol, TG, area, history of stroke (9)
Miettinen 1996b [4]	Type 2 diabetic cohort, stroke history at entry was 6%	Finland	125/1,056	58 ± 0.2	7	All stroke	Microalbuminuria: 150–300 mg/l Macroalbuminuria: >300 mg/l	Age, sex, smoking, hypertension, total cholesterol, HDL cholesterol, TG, area, history of stroke (9)
Valmadrid 2000 [5]	Population-based older-onset diabetic cohort	USA	85/840	67 ± 11	12	Fatal stroke	Microalbuminuria: 30–299 mg/l Macroalbuminuria: ≥300 mg/l	Age, sex, glycemic control, insulin use, alcohol intake, physical activity, history of CVD, intake of anti-hypertensive agents, presence and severity of diabetic retinopathy (10)
Yang 2008 [6]	Type 2 diabetic clinic-based cohort, no stroke history at entry	China	287/6,445	57 (IQR 46–67)	5.4	Ischemic stroke	Microalbuminuria: 2.5–25 mg/mmol in men and 3.5–25 mg/mmol in women Macroalbuminuria: ≥25 mg/mmol	Age, sex, smoking status (current and former), hypertension, duration of DM, HDL cholesterol, BMI, eGFR, use of drugs at baseline (lipid-lowering drugs, oral anti-diabetic drugs, and insulin) (11)
Yuyun 2004 [7]	Population-based cohort, no stroke history at entry	UK	246/23,630	58 ± 9	7.2	All stroke	Microalbuminuria: 2.5–25 mg/mmol Macroalbuminuria: ≥25 mg/mmol	Age, sex, smoking, systolic BP, DM, total cholesterol, BMI, physical activity, family history of stroke, baseline CHD, hypertension treatment (11)
Zhang 2008 [8]	Population-based cohort, stroke history at entry was 1%	USA (American Indians)	306/4,549	57 ± 9	13.4	All stroke	Microalbuminuria: 30–299 mg/g Macroalbuminuria: ≥300 mg/g	Age, sex, smoking, systolic and diastolic BP, fasting glucose, LDL and HDL cholesterol, triglycerides, BMI, waist circumference, physical activity, alcohol use (13)
Kistorp 2005 [9]	Population-based cohort without CVD history at entry	Denmark	21/537	68 ± 11	5	Ischemic stroke	Lower limit of albuminuria start from 1 mg/l, analyzed as per SD increased	Age, sex, current smoking, hypertension, DM, total cholesterol, AF, LVEF <50%, LVH, serum creatinine (10)
Wachtell 2003 [10]	HTN cohort from a clinical trial	International	379/8,206	66 ± 7	4.8	All stroke	Lower limit of albuminuria start from 0.25 mg/mmol, analyzed as every 10-fold increase in UACR	Age, sex, smoking, left ventricular mass by ECG, serum creatinine level, race, study treatment allocation (7)

AF = Atrial fibrillation; BP = blood pressure; CHD = coronary heart disease; CVD = cardiovascular disease; DM = diabetes mellitus; ECG = electro-cardiography; HF = heart failure; LVEF = left ventricular ejection fraction; LVH = left ventricular hypertrophy; MI = myocardial infarct; N = number of participants; n = number of strokes; UACR = urine albumin creatinine ratio.
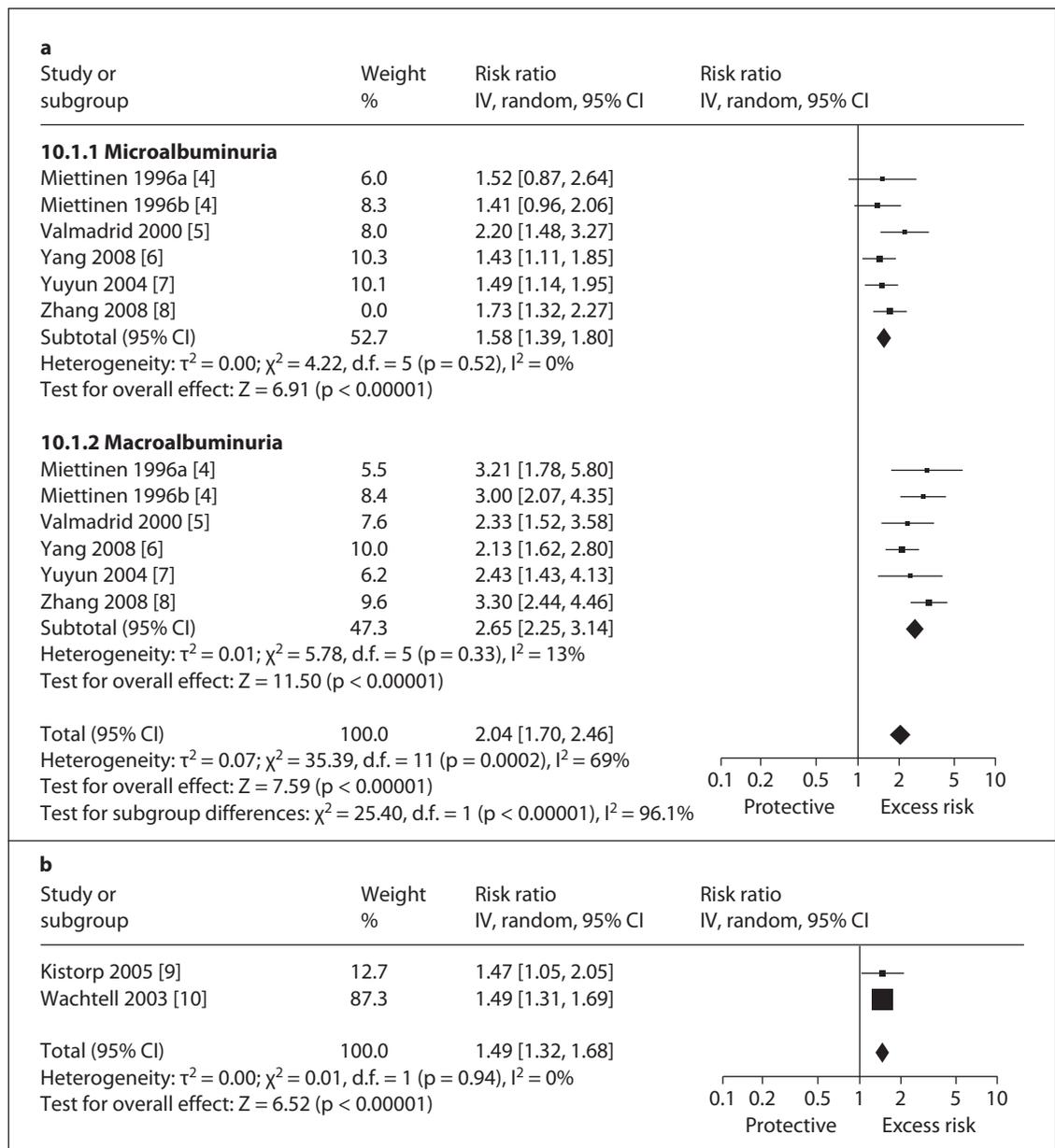
Fig. 2. Impact of albuminuria level on stroke risk. **a** Macroalbuminuria and microalbuminuria. **b** Albuminuria analyzed as a continuous variable (starting from normal albuminuria range).

Discussion

We found a significant and strong independent dose-response relationship between albuminuria and incident stroke. Whether examined as two differing levels of albuminuria or continuously, greater degree of baseline albuminuria was linked to higher stroke risk. Our results are strengthened by several factors. Microalbuminuria and macroalbuminuria were reported separately in each study, and so we had the same reference (normoalbuminuria) across studies for comparison. Also, the inclusion of only prospective data lessened effects of selection and recall bias. Finally, the relatively large number of subjects enhances generalizability and incorporation of only multivariate-adjusted RR reduced influence of known confounders.
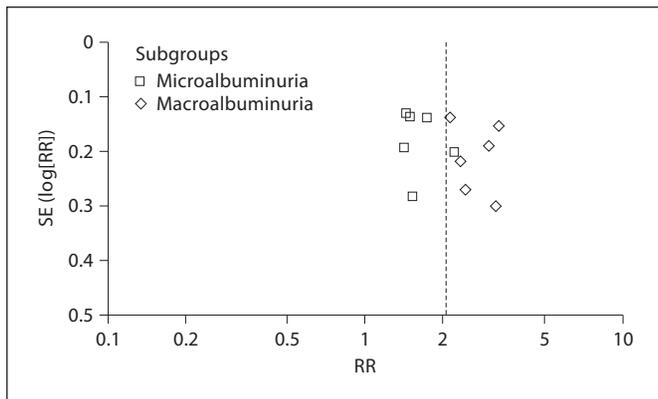
Fig. 3. Funnel plot evaluating potential systematic bias in studies included in the meta-analysis.

Interestingly, the studies in this review met several of the Hill criteria [11] for causation. First, an appropriate temporal relationship: albuminuria preceded stroke in all studies. Second, the findings were consistent with a dose-response relationship, with stronger associations for macroalbuminuria relative to microalbuminuria and a positive relationship in continuous analysis. Third, there was consistency across all studies (fig. 2). Fourth, biological plausibility also existed, since albuminuria is commonly found among patients with diabetes who have symptomatic large vessel atherosclerosis (41%), and this appears to be a strong independent predictor of future death from vascular causes [12, 13]. Still, observational studies cannot prove causality and mechanistically it is unclear how albuminuria would directly cause stroke. It is more likely that both albuminuria and stroke closely share similar underlying pathophysiologic processes (e.g. generalized endothelial dysfunction) [14, 15], and albuminuria can serve as useful risk marker for future stroke risk, especially since obtaining urine samples is relatively cheap and simple. Persons with higher levels of albuminuria may be candidates for more intensive global vascular risk reduction, particularly using agents like statins and modulators of the renin angiotensin system, which have been shown to reduce albuminuria and prevent vascular events [14].

There are some limitations to our study. First, the statistical methods of population studies founded in probability theory may not necessarily reflect the unique causal pattern in a given patient. Second, since this was a study-level meta-analysis (not an individual-level meta-analysis), we were unable to apply a uniform adjustment for confounding variables to all studies. As such, our summary result could be an overestimation of the true magnitude of the link between albuminuria and stroke. However, the number of variables adjusted in the included studies ranged from 5 to 11 and comprised several factors such as hypertension [16], diabetes [17], and left ventricular dysfunction [18], which are well known to be associated with both stroke and albuminuria level, so we believe that any potential summary result overestimation by our study is likely modest. Third, although we found no major asymmetric appearance on the funnel plot, it is conceivable that a publication bias may exist such that only studies showing a relation between urine albumin levels and stroke risk have been published. Fourth, two studies which analyzed albuminuria as a continuous variable used different units of UAE increment, thus making a precise quantification of the overall magnitude of impact difficult. However, qualitatively the association was positive, and in both studies the stroke risk rose proportionally with rising UAE from very low levels within the normal range of albuminuria. Together with results from the microalbuminuria versus macroalbuminuria analysis, we believe that the evidence points in the direction of a dose-response relationship between baseline albuminuria and stroke risk.

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