Proteinuria and Stroke: A Meta-analysis of Cohort Studies

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Background: The associations between decreased kidney function and cardiovascular disease recently have been established. However, there is uncertainty about the consistency between the independent associations of proteinuria as a risk factor across all cardiovascular end points. We undertook a meta-analysis of published cohort studies to provide a reliable estimate of the strength of association between proteinuria and risk of stroke.

Study Design: Meta-analysis of observational cohort studies.

Setting & Population: General population of participants with diabetes. Studies were excluded if participants had known glomerular disease or had undergone dialysis or transplantation.

Selection Criteria for Studies: MEDLINE, EMBASE, and CINAHL databases were searched for studies that reported age- or multivariate-adjusted risk ratio with some estimate of the variance of the association between proteinuria and risk of stroke, without language restriction.

Factor: Proteinuria or albuminuria.

Outcomes: Fatal or nonfatal stroke.

Results: Data from 10 published studies involving 140,231 participants and 3,266 strokes were eligible for inclusion. Participants with proteinuria had a 71% greater risk of stroke compared with those without proteinuria (95% confidence interval, 1.39 to 2.10). There was evidence of significant quantitative heterogeneity in the magnitude of the association across studies (I^2 = 60%; P for heterogeneity = 0.008), which was partially explained by differences in methods for measuring proteinuria. The risk of stroke remained significant after adjustment for other vascular risk factors.

Limitations: Because individual patient data were unavailable, we were unable to fully examine the impact of adjustment for known cardiovascular risk factors on the strength of the association between proteinuria and stroke risk. It is possible that the pooled estimate was affected by regression dilution bias.

Conclusions: These findings support the independent relationship between proteinuria and stroke. Additional studies are warranted to determine whether interventions to reduce proteinuria are effective at reducing rates of stroke.

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INDEX WORDS: Stroke; epidemiology; risk factors; proteinuria; meta-analysis.

Stroke is a leading cause of death and disability worldwide.[1] Substantial progress has been made in our understanding of the role of traditional cardiovascular risk factors, namely blood pressure, smoking, diabetes, and cholesterol level, in the cause of stroke.[2-4] However, uncertainty remains regarding the significance of more novel risk factors in contributing to the burden of stroke. In particular, several prospective studies have suggested that the presence of protein in urine (albuminuria or proteinuria) is associated directly with cardiovascular events, including stroke.[5-11] Given that population-based studies have suggested that approximately 1 in 10 adults in the United States[12] and 1 in 20 adults in Australia[13] have proteinuria, the significance of this disorder as a risk marker and/or risk factor is potentially large. Thus, better understanding of the precise nature of the relationship between proteinuria and stroke is important from both a clinical and public health perspective. Here, we report results of a systematic review with meta-analysis of published cohort studies undertaken to obtain a reliable and precise estimate of the association between proteinuria and risk of stroke.

Table 1. Prespecified Definitions of Albuminuria and Overt Proteinuria

Measurement Method	Microalbuminuria	Macroalbuminuria	Overt Proteinuria
24-h urine collection (mg/d)	30-300	>300	>300
Spot urine albumin (mg/dL)	3-30	>30	>30
Spot urine dipstick	Specific microalbuminuria dipstick positive	NA	≥1+
Spot urine albumin-creatinine ratio (mg/g, g/mmol)	30-300, 3.4-34	>300, >34	>200, >23

Abbreviation: NA, not available.
Based on Sarnak et al.[15]

METHODS

Search Strategy and Selection Criteria

The Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines for the conduct of meta-analyses of observational cohort studies[14] were followed. Relevant studies published between 1966 and November 2006 were identified from MEDLINE, EMBASE, and CINAHL by using relevant text words and medical subject headings that included all spellings of "proteinuria," "albuminuria," "microalbuminuria," and "macroalbuminuria" and combined these with all spellings of "stroke," "apoplexy," "cerebrovascular accident," "brain infarction," "cerebral infarction," "intracranial hemorrhage," "cerebral hemorrhage," "cardiovascular disease," and "mortality." The search was limited to cohort or case-control studies, without language restriction. References from identified studies were manually scanned to identify other relevant studies.

Studies were included if they reported quantitative estimates and SEs (or 95% confidence intervals [CI]) of the risk ratio (RR) for fatal or nonfatal stroke associated with some measure of proteinuria. The prespecified definitions of proteinuria are listed in Table 1[1]; however, studies that used somewhat different definitions were included if they were comparable. Fatal stroke was defined as death attributed to *International Classification of Diseases, Ninth Revision* codes 430 to 438 or *International Statistical Classification of Diseases, 10th Revision* codes I60 to I69. Nonfatal stroke was defined as clinical symptoms consisting of neurological deficit persisting for 24 hours or longer. Studies were excluded if they met the following criteria: (1) a hospital-based study, (2) a study population that included pathological subgroups (eg, participants with a preexisting stroke, known glomerular disease, dialysis, or transplantation), (3) a study reporting the estimate of the effect without an ability to derive the SE, and (4) a study not reporting an estimate that was at least adjusted by age. The literature search and data extraction were conducted by 2 authors (C.V. and T.N.). Disagreement over eligibility was resolved by consensus after paper review by 3 additional authors (R.H., V.P., F.B.).

Statistical Analysis

Summary estimates of the RR and 95% CI were obtained by using a random-effects model. When studies published more than 1 estimate of the association between proteinuria and risk of stroke[,6,8,9,11,16] according to subgroups (eg, by sex or diabetes status), a within-study summary estimate

was obtained. These single-study estimates were then combined with the other study estimates, which were combined for subgroup before combining them with these estimates. Heterogeneity across included studies was analyzed formally by using Cochran Q test and the I^2 statistic, which approximates the proportion of total variation in the estimates caused by between-study heterogeneity.[17] We investigated possible sources of heterogeneity by comparing summary results obtained from subsets of studies grouped by duration of follow-up or by differences in the method of measurement. We performed additional subgroup analyses by pooling estimates for subgroups within the cohort, defined by sex, diabetes status, level of albuminuria, and level of adjustment when these were reported. Tests of heterogeneity between subgroups were estimated by using univariate meta-regression analysis. We also performed univariate and multivariate meta-regression analysis to assess possible sources of heterogeneity affecting the relationship between proteinuria and risk of stroke across studies.[18] Results were presented with the exponentiated regression coefficients and their 95% CIs, showing the proportional change in RR for the first listed factor compared with that of that second listed factor or for every 1-scale increment in each factor. All analyses were performed using Stata (release 9.2; Stata Corp, College Station, TX). A standard level ($P < 0.05$) of statistical significance was used in all analyses.

RESULTS

Literature Search

The literature search yielded 3,028 articles, of which 220 were reviewed in full. Ten published studies[5-11,16,19,20] including information for 140,231 participants and 3,266 stroke events (37.0% fatal) were eligible for inclusion in the analysis. A flow chart detailing the process of study identification and selection is shown in Fig 1, and characteristics of the included studies are listed in Table 2. Two studies[5,19] reported the effects of macroalbuminuria compared with normal levels of albuminuria, whereas the remaining 8 studies reported an estimate of risk associated with overt proteinuria compared with no overt proteinuria. Eight studies[5-11,19] provided an estimate of the effect of the association be-
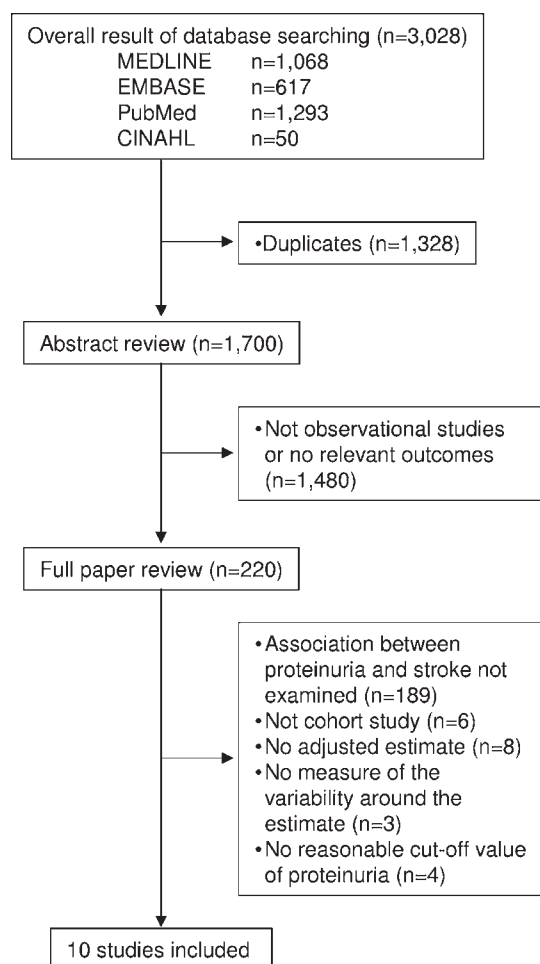
Figure 1. Identification process for eligible studies.

minuria or overt proteinuria by using laboratory methods (n = 26,901) was approximately 80% higher compared with the 7 studies[7-11,16,20] that measured overt proteinuria by using a dipstick method (n = 113,330) (RR, 2.71 [95% CI, 1.95 to 3.77] versus RR, 1.50 [95% CI, 1.28 to 1.75]; *P* for heterogeneity = 0.003). There was also some suggestion that the association was weaker in Asian compared with non-Asian populations (RR, 1.43 [95% CI, 1.14 to 1.79] versus RR, 2.02 [95% CI, 1.54 to 2.65]; *P* for heterogeneity = 0.07; Fig 3). However, after adjusting for method of protein measurement, there was no evidence to support an ethnic difference in the magnitude of the association (Table 3). There was also no evidence to suggest a difference according to type of study population, type of outcome (fatal versus nonfatal stroke), duration of study follow-up, and number of participants (all *P* > 0.1; Fig 3). Furthermore, there was no difference in the summary estimate between studies[9,16,20] that adjusted for only age and sex compared with studies[5-11,19] that adjusted for other cardiovascular risk factors (Fig 3). However, comparison of summary estimates from the 6 studies[5,6,8,9,11,19] that reported both age-adjusted and fully-adjusted estimates (n = 125,701) showed that the relationship between proteinuria and stroke attenuated by 30% after adjusting for known cardiovascular risk factors (RR, 2.81 [95% CI, 1.78 to 4.42] versus RR, 1.94 [95% CI, 1.37 to 2.75]; *P* = 0.2).

Association of Proteinuria With Risk of Stroke by Sex and Diabetes Status

Five studies with information for 127,173 participants[8,9,11,16,19] had reported sex-specific outcomes of the association between proteinuria and stroke. The pooled summary estimates indicated there was no evidence to suggest a sex difference in the magnitude of the association (RR, 1.62 [95% CI, 1.21 to 2.19] in men versus RR, 1.38 [95% CI, 1.02 to 1.87] in women; *P* for heterogeneity = 0.5). In the 3 studies (n = 32,313 participants)[6-8] that reported separate risk estimates for subgroups of participants with and without diabetes, the association was unaffected by diabetes status (RR, 2.10 [95% CI, 1.18 to 3.72] versus RR, 2.07 [95% CI, 1.46 to 2.93], respectively; *P* for heterogeneity = 0.9).

tween proteinuria and stroke that was adjusted for major cardiovascular risk factors, including blood pressure, smoking, diabetes, and total cholesterol level, whereas the remaining 2 studies provided estimates that were adjusted for only age and sex (Table 2).

Association of Proteinuria With Risk of Stroke

Overall, proteinuria was associated with a 71% (95% CI, 1.39 to 2.10) greater risk of stroke (Fig 2), with evidence of significant heterogeneity in the magnitude of the association across studies (I^2 = 60%; *P* for heterogeneity = 0.008). Subgroup analysis indicated that the significant source of between-study heterogeneity identified was caused by differences in the method of measuring proteinuria (Fig 3); the risk of stroke from the 3 studies[5,6,19] that measured macroalbu-

Table 2. Characteristics of Studies Reporting on the Association Between Proteinuria and Subsequent Stroke Risk†
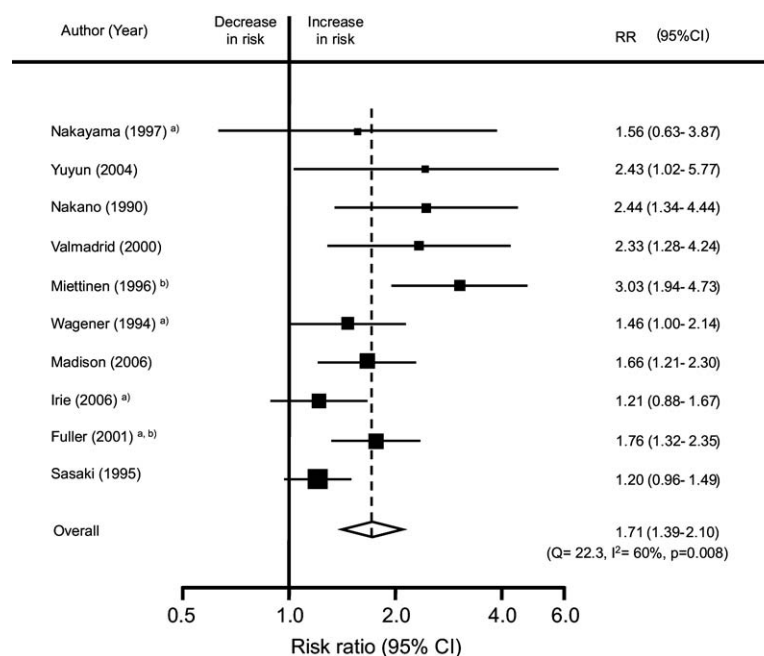
Reference	Country	Study Size (% men)	No. of Strokes	Follow-up (y)	Lost to Follow-up (%)	Age Range (y)	Population	End Point	Criteria for End Point	Definition of Proteinuria (measuring method)	Level of Adjustment
Irie et al,[8] 2006	Japan	90,363 (34)	952	10	3	40-79	General	Fatal stroke	ICD-9 430-438, ICD-10 I60-I69	Overt proteinuria (dipstick)	Age, HT, DM, CHOL, HDLC, BMI, SCr, smoking, alcohol
Madison et al,[7] 2006	United States (Japanese American)	6,252 (100)	457	27	ND	45-68	General (DM, NDM)	Fatal + nonfatal stroke	Standard criteria*	Overt proteinuria (dipstick)	Age, HT, DM, CHOL, BMI, PA, smoking, alcohol
Yuyun et al,[19] 2004	United Kingdom	23,630 (47)	246	7.2	ND	40-79	General (DM, NDM)	Fatal + nonfatal stroke, subtype of stroke	ICD-9 430-438, ICD-10 I60-I69	Microalbuminuria, macroalbuminuria (urinary albumin-creatine ratio)	Age, sex, SBP, HT treatment, DM, CHOL, BMI, PA, family Hx stroke, Hx CHD, smoking
Fuller et al,[16] 2001	Multicountries, 10 centers (Europe, Asia, United States)	4,743 (49)	287	12	7	46 (mean)	T1DM, T2DM	Fatal + nonfatal stroke	ICD-9 430-438	Overt proteinuria (dipstick)	Age
Valmadrid et al,[5] 2000	United States	840 (45)	85	12	0.4	68 (mean)	DM	Fatal stroke	ICD-9 430-438	Microalbuminuria, macroalbuminuria† (urinary albumin concentration)	Age, sex, HT treatment, glycemic control, insulin use, PA, Hx CVD, diabetic retinopathy, alcohol
Nakayama et al,[9] 1997	Japan	2,302 (42)	142	15.5	6	≥40	General	Fatal + nonfatal stroke, subtype of stroke	WHO and other criteria	Overt proteinuria (dipstick)	Age, mean BP, urinary glucose, CHOL, hematocrit, ECG Ab, AF, BMI, PA, Hx CHD, optic fundus
Miettinen et al,[6] 1996	Finland	2,431 (50)	155	7	ND	45-64	General (DM, NDM)	Fatal + nonfatal stroke	WHO criteria	Overt proteinuria (Coomassie brilliant blue)	Age, sex, area, HT, DM duration, glycosylated HbA1, CHOL, HDLC, TG, Hx CVD, smoking
Sasaki et al,[10] 1995	Japan	1,939 (62)	84	9.4	ND	53 (mean)	T2DM	Fatal stroke	ICD-8	Overt proteinuria (dipstick)	Age, sex, HT, BG, DM duration, CHOL, ECG Ab, obesity, retinopathy
Wagner et al,[11] 1994	United States	6,135 (47)	771	16	4	45-74	General	Fatal + nonfatal stroke	ICD-9 430-438	Overt proteinuria (dipstick)	Age, SBP, history DM, education level, Hx CVD, smoking
Nakano et al,[20] 1990	Japan	1,596 (38)	87	20	<1	30-69	General	Fatal stroke	ICD-9	Overt proteinuria (dipstick)	Age, sex

Abbreviations: AF, atrial fibrillation; BG, blood glucose; BP, blood pressure; BMI, body mass index; CHD, coronary heart disease; CHOL, total cholesterol; CVD, cardiovascular disease; DBP, diastolic blood pressure; DM, diabetes mellitus; ECG Ab, electrocardiogram abnormalities; HbA1, hemoglobin A1; HDLC, high-density lipoprotein cholesterol; HT, hypertension; Hx, history; ICD-9, *International Classification of Diseases, Ninth Revision*; ICD-10, *International Statistical Classification of Diseases, 10th Revision*; ND, not described; NDM, no diabetes mellitus; LVH, left ventricular hypertrophy, PA, physical activity; SCr, serum creatinine; SBP, systolic blood pressure; T1DM, type1 diabetes mellitus; T2DM, type 2 diabetes mellitus; TG, triglycerides; WHO, World Health Organization.

*Stroke defined as "a new neurologic deficit developed without prolonged loss of consciousness, when there was evidence of nuchal rigidity or bloody cerebrospinal fluid identified by an atraumatic lumber puncture and when there was absence of fever or pronounced leukocytosis."

†Macroalbuminuria defined as urinary protein concentration of 300 mg/L.

Figure 2. Overall risk ratio (RR) for the association of proteinuria with risk of stroke in population-based cohort studies for 5 studies[6,8,9,11,16] reporting separate estimates according to subgroups of [a]sex or [b]diabetic status. Separate estimates were pooled so that 1 study contributed 1 estimate to summary estimates. Abbreviation: CI, confidence interval.

Association Between Levels of Albuminuria With Risk of Stroke

Two studies with information for 24,470 participants[5,19] reported separate estimates of the association between microalbuminuria (n = 62 events) or macroalbuminuria (n = 12 events) with risk of stroke. Based on this limited amount of data, there was some evidence to indicate a greater risk in individuals with macroalbuminuria (compared with those with normoalbuminuria) than in individuals with evidence of microalbuminuria (compared with controls; RR, 1.70 [95% CI, 1.19 to 2.45] versus RR, 2.36 [95% CI, 1.44 to 3.86]; *P* for heterogeneity = 0.2).

Association of Proteinuria With Stroke Subtype

Two studies with information for 25,932 participants[9,19] reported on the association of proteinuria with risk of different stroke subtypes (188 ischemic strokes and 76 hemorrhagic strokes). There was no evidence of a difference in the magnitude of association between subtypes of stroke (RR, 2.06 [95% CI, 1.02 to 4.17] versus RR, 1.66 [95% CI, 0.78 to 3.54]; *P* for heterogeneity = 0.7).

DISCUSSION

The key finding from this systematic overview, which included data for more than 3,000 stroke events in 140,000 participants, is that the presence of proteinuria confers a 50% to 70% greater risk of stroke. This association was uniformly consistent across important subgroups characterized by sex, ethnicity, and diabetes status and was apparent in studies that had adjusted for known cardiovascular risk factors, most notably blood pressure. Although the potential for residual confounding remains, we consider that the findings indicate proteinuria is an important risk factor for stroke.

The exact mechanism that might mediate the link between proteinuria and stroke is not known, but it may be governed by blood pressure, which is accepted to be causally associated with proteinuria, as well as being the major risk factor for stroke.[21] Unfortunately, it was not possible to further tease out the relationships among blood pressure, proteinuria, and stroke risk in the present analyses. To do so would require individual participant data. Similarly, because proteinuria is strongly associated with other cardiovascular risk factors,[22-25] it might be serving as a surrogate marker of subclinical vascular disease and atherosclerosis,[21,26-29] rather than as a specific indicator of kidney pathological state.

There was evidence of a relatively small amount of heterogeneity in the magnitude of the association between proteinuria and risk of stroke across studies. Some of this was attributable to
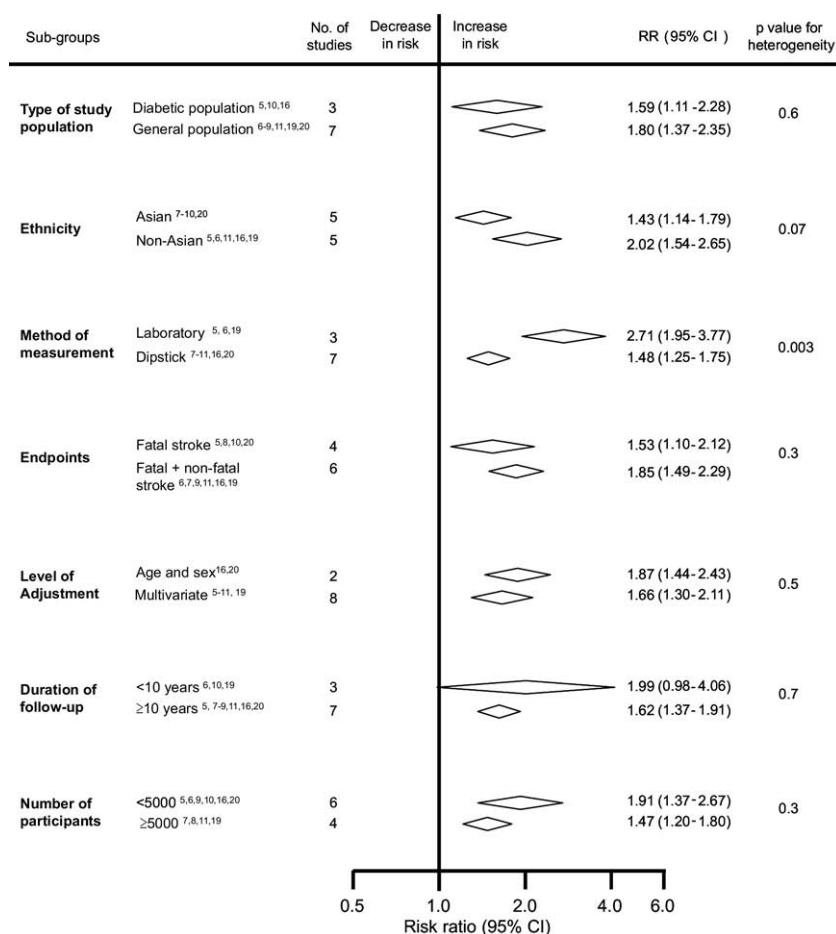
Figure 3. Subgroup analysis for the comparison between studies reporting associations of proteinuria with stroke risk. Abbreviations: CI, confidence interval; RR, risk ratio.

differences in methods of measuring proteinuria, with studies using laboratory methods more likely to give a stronger association compared with studies using only urinary dipstick. Urinary dipstick testing[30,31] has poor sensitivity and specificity for detecting proteinuria and hence would be more likely to give false-positive and false-negative results compared with more specific laboratory methods of measurement.[31,32] Typically, when imprecise methods of measurement are used, the measure of effect is attenuated,[17] such that the use of dipstick testing in some studies may have underestimated the strength of the association between proteinuria and stroke.

Data in support of a causal role for proteinuria in patients with stroke are derived from post hoc analyses of large-scale clinical trials that suggest that reducing the level of albuminuria is associated with a concurrent decrease in cardiovascular risk. For example, in the RENAAL (Reduction in Endpoints in Non-insulin-dependent Diabetes Mellitus With the Angiotensin II Antagonist Losartan) Study involving 1,500 patients with type 2 diabetes mellitus and nephropathy, a 50% decrease in albuminuria was associated with a significant 18% decrease in risk of cardiovascular disease.[33] Similarly, in the LIFE (Losartan Intervention for Endpoint Reduction in Hypertension) Study, of 8,200 patients with hypertension and left ventricular hypertrophy, participants who achieved a lower level of albuminuria using losartan- or atenolol-based regimens had a significantly lower risk of subsequent fatal or nonfatal stroke than those with persistent albuminuria.[34] Although these associations do not necessarily imply causality and potentially are confounded by parallel changes in blood pressure, they suggest that decreases in urinary protein excretion may result in a decrease in risk of subsequent cardiovascular events.

Well-established risk factors for stroke include hypertension and diabetes.[3,4] In this study, the pooled risk estimate was of a magnitude similar

Table 3. Univariate or Multivariate Meta-Regression Analysis of Possible Sources of Heterogeneity Across Studies

Possible Source of Heterogeneity	Scale	Univariate			Multivariate*		
		Proportional Change in Risk Ratio†	95% Confidence Interval	P	Proportional Change in Risk Ratio†	95% Confidence Interval	P
Type of study population	Diabetic (*v* general)	0.89	0.57-1.39	0.6			
Ethnicity	Asian (*v* non-Asian)	0.72	0.50-1.02	0.07	0.85	0.62-1.16	0.3
Method of measurement	Laboratory (*v* dipstick)	1.82	1.22-2.71	0.003	1.65	1.07-2.54	0.02
Type of end point	Fatal and nonfatal stoke (*v* fatal stroke)	1.25	0.85-1.84	0.3			
Level of adjustment	Multivariate adjusted (*v* age and sex adjusted)	0.84	0.50-1.41	0.5			
Duration of follow-up	Every 1-y increase	1.00	0.96-1.03	0.9			
No. of participants	Every 1,000-participant increase	1.00	0.99-1.00	0.2			

*Multivariate meta-regression was performed by using the model including the variables Asian population and method of measurement as covariates.

†Results presented with exponentiated regression coefficients and their 95% confidence intervals, showing the proportional change in risk ratio for the first listed factor compared with that of that second listed factor or for every scale increase in each factor.

to the stroke risk associated with hypertension and diabetes. Because the summary estimate was derived from studies that were largely adjusted for diabetes and/or hypertension, this would suggest that the effects of proteinuria on risk of stroke are largely independent of these 2 risk factors. Further investigation into the relationship between proteinuria and stroke risk is warranted and, if confirmed, would support the inclusion of proteinuria into risk prediction models for stroke.

There are several potential limitations of this meta-analysis. First, we were unable to assess the influence of decreased kidney function on the relationship between proteinuria and risk of stroke. Of studies included in this meta-analysis, only 1 study[8] provided the risk estimate adjusted for serum creatinine levels. Importantly, several observational cohort studies[8,35-37] have shown that proteinuria and impaired kidney function are significant and independent risk factors for cardiovascular disease, and furthermore, the coexistence of proteinuria and decreased kidney function more than doubled the risk of cardiovascular disease compared with participants with neither condition. Second, because we relied on published data, we were unable to fully examine the impact of adjustment for known cardiovascular risk factors, such as

hypertension or dyslipidemia, on the strength of the association between proteinuria and stroke risk, which may have overestimated the magnitude of the relationship. Although there was no evidence to suggest a difference in the strength of the association between studies that had adjusted for only age compared with those that had attempted to adjust for multiple risk factors, subsequent restriction of the analysis to the 6 studies that had reported both unadjusted and adjusted estimates showed that the strength of the association was attenuated (but remained significant), indicating the potential for residual confounding by known and unknown risk factors. Conversely, it is possible that the impact of regression dilution bias[17] might have underestimated the strength of the association between proteinuria and stroke risk. For example, data from the Honolulu Heart Program indicated that participants with proteinuria measured on at least 2 separate occasions had an approximately 70% greater risk of incident stroke than those with positive results at only 1 examination.[7] Finally, all studies included in this meta-analysis were conducted in higher income countries; therefore, the applicability of our results to populations in lower and middle-income countries is uncertain. Further assessment using individual participant data is needed to resolve these limitations.

In conclusion, data from this meta-analysis support the hypothesis that proteinuria is an independent risk factor for stroke. Routine measurement of urinary protein therefore may improve current tools for the assessment and modification of stroke risk. Further studies are warranted to determine whether interventions to reduce proteinuria are effective at reducing rates of stroke.

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