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Chronic kidney disease and the risk of stroke: a systematic review and meta-analysis

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ABSTRACT

Background. People with chronic kidney disease (CKD) have an increased risk of stroke but the magnitude of increased risk and the independent effects of glomerular filtration rate (GFR) and albuminuria are unclear. We aimed to quantify the association between the independent and combined effects of GFR and albuminuria on stroke risk.

Methods. We searched MEDLINE and EMBASE (February 2014) for cohort studies or randomized controlled trials (RCTs) which reported stroke incidence in adults with a baseline measurement of GFR and/or albuminuria. We extracted study and participant characteristics, risk of bias and relative risks (RR, with confidence interval; CI) of stroke associated with GFR and/or quantity of albuminuria, synthesized data using random effects meta-analysis and explored heterogeneity using meta-regression.

Results. We identified 83 studies; 63 cohort studies (2 085 225 participants) and 20 RCTs (168 516 participants) reporting 30 392 strokes. There was an inverse linear relationship between GFR and risk of stroke, with risk of stroke increasing 7% (RR: 1.07, CI: 1.04–1.09) for every 10 mL/min/1.73 m^2 decrease in GFR. A 25 mg/mmol increase in albumin–creatinine ratio was associated with a 10% increased risk of stroke (RR: 1.10, 95% CI: 1.01–1.20). The effect of albuminuria was independent of GFR. Results were not different across subtypes of stroke, sex and varying prevalence of cardiovascular risk factors.

Conclusions. Stroke risk increases linearly and additively with declining GFR and increasing albuminuria. CKD staging may also be a useful clinical tool for identifying people who may benefit most from interventions to reduce cardiovascular risk.

Keywords: albuminuria, chronic kidney disease, glomerular filtration rate, stroke, systematic review

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BACKGROUND

Stroke and chronic kidney disease (CKD) are major health problems worldwide but are usually considered separately. One in every four men and one in every five women will suffer a stroke by 85 years of age. Stroke is the second biggest cause of death and the primary cause of chronic neurological disability worldwide [1, 2]. In the USA, stroke accounted for 5.2% of all deaths and 6–8% (US$66.5 billion) of federal health care spending in direct and indirect medical costs in 2010 [3, 4]. CKD is a similarly large public health challenge which affects around 8% of the population (though >50% of the population aged over 70 years) and accounted for 22% of Medicare expenditure in 2006 [5, 6]. In addition to consuming resources, both stroke and CKD are associated with premature death, falls, dementia and decreased quality of life [1, 7].

Stroke and CKD share common cardiovascular risk factors including high blood pressure, smoking, high cholesterol and diabetes [8]. CKD has also been identified as a risk factor for stroke, with a glomerular filtration rate (GFR) of <60 mL/min/1.73 m^2 and albuminuria independently associated with stroke [9, 10]. It remains uncertain how the magnitude of this increased risk changes as CKD progresses and whether GFR and albuminuria act alone or in combination to modify stroke risk.

The primary aim of our study was to establish how stroke risk varied by stage of CKD. Specifically, we aimed to quantify the associations between GFR and/or albuminuria and stroke risk by CKD stage. We also aimed to explore how the association between GFR, albuminuria and stroke risk varied by stroke subtype and severity.

MATERIALS AND METHODS

We performed a systematic review and meta-analysis of randomized controlled trials (RCTs) and cohort studies that had estimated the association between GFR and/or albuminuria and the risk of stroke.

Data sources and searches

We searched MEDLINE (1948 to February 2014) and EMBASE (1947 to February 2014) databases using a search strategy developed by a specialized librarian that combined text word and medical subject headings without language restrictions (Supplementary Data, Appendix Table S1). The authors followed a standardized study protocol for identification of eligible studies.

Study selection

We included all RCTs and cohort studies which measured GFR and/or albuminuria and reported quantitative estimates and a measure of precision (or original data which allowed their calculation) of the risk of subsequent stroke. GFR had to be either estimated using a validated algorithm [Cockcroft-Gault, modification of diet in renal disease (MDRD), CKD epidemiology collaboration (CKD-EPI)], measured directly, approximated from urinary creatinine clearance or estimable from serum creatinine. We required that albuminuria was quantified by 24-h urine collection, urine aliquot albumin–creatinine or protein–creatinine ratio, urine dipstick or agglutination assay. Our outcome of interest was symptomatic stroke confirmed by physician examination, hospital record review or identified from data-linkage of administrative records. We excluded cross-sectional and case–control studies, studies where GFR or albuminuria were measured using non-validated methods or algorithms, studies where outcomes were measured by self-reports or proxy reports and studies where stroke was diagnosed by radiological imaging but not confirmed clinically.

Data extraction

Using a standardized electronic data abstraction spreadsheet, two reviewers independently recorded key descriptive and quantitative data for study characteristics, participants, exposures and outcomes. We collected details of the year of study publication, location, size and duration. Abstracted participant characteristics included age, gender, race and the prevalence of diabetes, known vascular diseases, smoking and hypertension. We also noted if participants were recruited at a time of high stroke risk including around an acute coronary event, coronary revascularization procedure or carotid arterial intervention. Our main exposures of interest were GFR and quantity of albuminuria, and for each group of study participants we recorded the GFR and/or the quantity of albuminuria (mean or category range reported), the method of measurement and units of quantification used. We then extracted data for the relative risk (RR), odds, rate or hazard ratio of stroke associated with each specified GFR and/or quantity of albuminuria and noted whether reported strokes were fatal or non-fatal, incident or recurrent, as well as the subtype of stroke (all-cause, haemorrhagic, ischaemic or unspecified). Specifically, we obtained effect estimates from the most fully adjusted model presented noting which variables the model had adjusted for. The standard error of the estimate was also extracted or estimated from the reported 95% CI or P-value. Finally, we assessed the risk of bias in RCTs using the Cochrane risk of bias tool and cohort study quality using the Newcastle–Ottawa Scale [11, 12].

Data synthesis and analysis

The main outcomes of interest were the risks of stroke in patients with different GFR and/or categories of albuminuria (microalbuminuria, macroalbuminuria). We converted RRs associated with averaged GFR or categories of albuminuria to their natural logarithms and synthesized log RRs and standard errors using the generic-invariance method in a random effects model. Heterogeneity among included studies was assessed using the Cochran Q test and the I^2 test, with an alpha of 0.05 used for statistical significance. We used subgroup analyses and meta-regression to explore heterogeneity. Subgroups were pre-specified and included study characteristics (study design, size, location, duration of follow-up, level of adjustment of the effect estimate), participant characteristics (age, gender, race, prevalence of diabetes, hypertension, smoking, atrial fibrillation, undergoing cardiac or carotid intervention, quantity of albuminuria, GFR defined by CKD stage) and characteristics of stroke

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recorded (subtype, severity and whether incident or recurrent). To investigate the simultaneous effect of multiple potential study-level confounders, we then fitted a multivariate-adjusted random-effects meta-regression model for each stroke subtype and for each exposure (GFR and albuminuria). Studies used varying reference ranges of GFR and so risks may not have quantified the same sized difference in GFR between comparison and reference groups. To adjust for this, we included the difference in GFR between comparison and reference groups in our adjusted model and estimated the average risk per 10 mL/min/1.73 m^2 decrease in GFR. For studies reporting albuminuria, we converted measurements from their original units to their equivalent ACR (mg/mmol) using a validated conversion table and then estimated the average adjusted risk per 25 mg/mmol increase in ACR in each comparison group relative to the reference group [13]. All models were adjusted for study and participant characteristics specified a priori including the duration of the study, age and sex of participants and proportion of diabetics, people with hypertension and smokers in the study. We then used backward step-wise elimination of any characteristic associated with risk of stroke ($P < 0.2$) before testing for interaction between GFR and albuminuria in our final models. Finally, we conducted sensitivity analyses to assess the effect of varying study quality on estimates of effect. Specifically, we examined the effect of excluding randomized controlled trials where intention-to-treat analysis was not performed and cohort studies where adjustment for at least age, sex and smoking was not performed. For all analyses, we used STATA software version 11.2 (StataCorp, College Station, TX, USA).

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RESULTS

We identified 83 eligible studies (63 cohort studies and 20 RCTs) including 2 253 741 participants with follow-up ranging from 0.25 months to 21 years (Figure 1 and Supplementary Data, Appendix Table S2). In total, there were 30 392 all-cause stroke events including 21 633 which were not classified by pathological subtype (unspecified), 7498 ischaemic and 1625 haemorrhagic strokes. Characteristics of the included studies and randomized trials are described in Table 1 and Supplementary Data, Appendix Table S2. Seventy-two studies (87%) reported unspecified stroke types, 23 studies (28%) reported ischaemic strokes and 18 studies (22%) reported haemorrhagic strokes (Table 1 and Figure 1). Twenty-seven (33%) of all studies were conducted in North America but studies which reported subtypes of stroke were more often conducted in Asia: 13 (57%) studies reporting ischaemic and 11 (61%) studies reporting haemorrhagic strokes. GFR was most commonly estimated using the MDRD formula (30 studies, 54% of studies reporting GFR) and albuminuria most commonly measured by ACR (17 studies, 46% of studies reporting ACR).

GFR and stroke

Fifty-six (67%) studies (2 156 147 participants) assessed the association between GFR and stroke. We first analyzed data by stage of CKD. A GFR of <90 mL/min/1.73 m^2 was associated with an increased risk of all-cause stroke by 39% (RR: 1.39, 95% CI: 1.31–1.47). The risk of all-cause stroke increased further with declining renal function. In participants with a GFR of 60–90 mL/min/1.73 m^2 the risk of stroke was increased by 10% (RR: 1.10, 95% CI: 1.03–1.19), by 43% in participants with a GFR of 30–60 mL/min/1.73 m^2 (RR: 1.43, 95% CI: 1.33–1.54) and by 70% in participants with an GFR of <30 mL/min/1.73 m^2 (RR: 1.70, 95% CI: 1.47–1.96, test for difference, $P < 0.001$) (Figure 2). For every 10 mL/min/1.73 m^2 decrease in GFR (relative to the reference group), the risk of having a stroke increased by 7% (RR: 1.07, 95% CI: 1.04–1.09) (Figure 3). In our multivariate-adjusted model, we observed 29% smaller risk estimates for stroke in larger studies (>20 000 participants) compared with smaller studies (<2500) (RR: 0.71, 95% CI: 0.55–0.91) and 27% smaller risk estimates for stroke in studies where effect estimates were adjusted compared with studies where estimates were unadjusted (RR: 0.73, 95% CI: 0.60–0.90) (Figure 1). Studies where participants underwent a heart procedure reported a 91% higher risk of stroke (RR: 1.91, 95% CI: 1.36–2.69). Risk of stroke did not vary among studies by any stroke characteristic including subtype, severity and whether incident or recurrent. Similarly, risk did not vary by the formula used to estimate GFR (Supplementary Data, Appendix Table S3).

Albuminuria and stroke

Thirty-seven (45%) studies (1 262 952 participants) assessed the association of albuminuria with stroke. Any degree of albuminuria increased the risk of all-cause stroke by 68% (RR: 1.68, 95% CI: 1.54–1.84). There was some evidence that the risk of all-cause strokes rose with increasing quantity of albuminuria, from 53% with microalbuminuria (RR: 1.53, 95% CI: 1.40–1.67) to 94% with macroalbuminuria (RR: 1.94, 95% CI 1.64–2.29, test for difference $P = 0.06$) (Figure 2). The risk of having a stroke increased by 10% (RR: 1.10, 95% CI: 1.01–1.20) for every 25 mg/mmol increase in ACR (Figure 3). In our multivariate-adjusted model, studies with a higher proportion of Asian participants reported a 75% increased risk of stroke (RR: 1.75; 95% CI: 1.07–2.86) compared with studies recruiting mainly white participants (Supplementary Data, Appendix Figure 2). Albuminuria impacted risk of stroke differently according to age, with people aged 60–65 years experiencing a 45% smaller increased stroke risk than people aged <60 years (RR: 0.45, 95% CI: 0.28–0.71). The stroke subtype, severity and whether incident or recurrent had no effect on magnitude of risk estimates. Risk did not vary by the method used to quantify albuminuria (Supplementary Data, Appendix Table S3).

GFR with albuminuria and stroke

Eight studies (12%) examined the association between GFR with albuminuria and stroke, but we could use data from only six studies because two studies used a reference range of GFR other than >60 mL/min/1.73 m^2 or a reference range of albuminuria other than none. Risk of stroke in participants with a GFR <60 mL/min/1.73 m^2 and any albuminuria (RR: 2.18, 95% CI: 1.68–2.84) was additive, approximately equal to the sum of the risk of stroke in participants with GFR <60 mL/min/1.73 m^2 (RR: 1.51, 95% CI: 1.41–1.61) and the risk of stroke among participants with any albuminuria (RR: 1.68, 95% CI:

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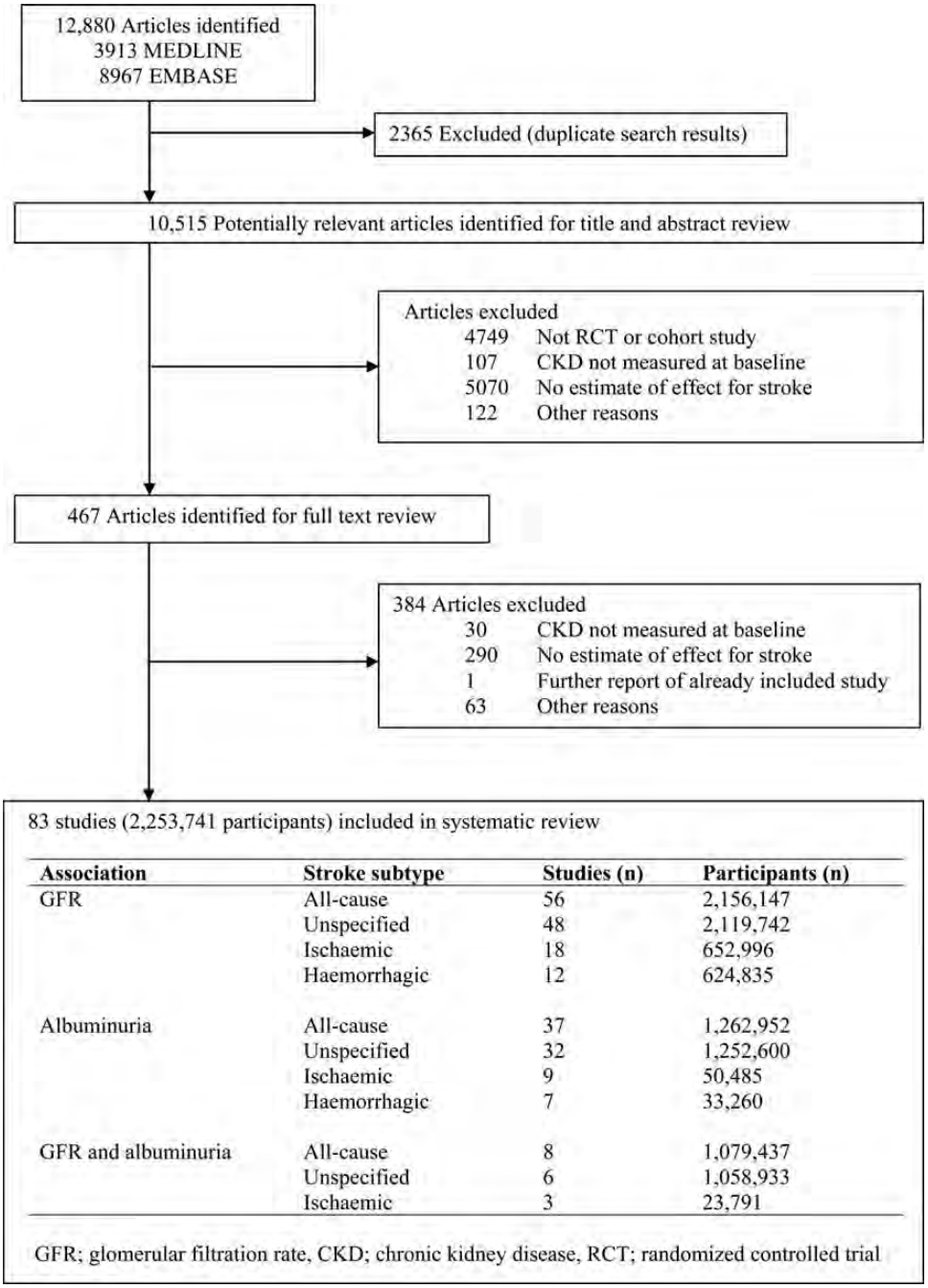

Association	Stroke subtype	Studies (n)	Participants (n)
GFR	All-cause	56	2,156,147
	Unspecified	48	2,119,742
	Ischaemic	18	652,996
	Haemorrhagic	12	624,835
Albuminuria	All-cause	37	1,262,952
	Unspecified	32	1,252,600
	Ischaemic	9	50,485
	Haemorrhagic	7	33,260
GFR and albuminuria	All-cause	8	1,079,437
	Unspecified	6	1,058,933
	Ischaemic	3	23,791

GFR; glomerular filtration rate, CKD; chronic kidney disease, RCT; randomized controlled trial

FIGURE 1: Identification and inclusion of study reports of CKD and stroke risk.

1.54–1.84). In our multivariate-adjusted regression models, we tested for interaction between GFR and albuminuria and found none detectable.

Sensitivity analyses

Excluding randomized controlled trials where attrition bias was judged unclear (seven studies) and cohort studies where estimates of effect were unadjusted for at least age, gender and smoking (47 studies) did not alter the association we observed for the association between either GFR or albuminuria and the risk of all, unspecified, ischaemic or haemorrhagic stroke (Supplementary Data, Appendix Table S4).

DISCUSSION

In this meta-analysis of 83 studies, which included data for >30 000 strokes in 2 253 741 participants, we have demonstrated a linear relationship between decreasing GFR and the risk of stroke, and between increasing albuminuria and the risk of stroke. Specifically, we observed an average 7% increase in the RR of stroke associated with every 10 mL/min/1.73 m^2 reduction in GFR, and an average 10% increase in the RR of stroke associated with every 25 mg/mmol increase in ACR. Findings were consistent when GFR was analyzed by stage of CKD and albuminuria

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Table 1. Characteristics of included studies

Characteristics	Number of studies, total = 83	
	N	%
Study		
Design		
Randomized controlled trial	20	24
Cohort study	63	76
Location		
North America	27	33
Europe	16	19
South-East Asia	23	28
Multinational	17	20
Number of participants		
0 to <2500	31	37
≥2500 to <5000	18	22
≥5000 to <20 000	23	28
≥20 000	11	13
Duration of follow-up (months)		
0 < 24	16	19
≥24 to <60	25	30
≥60 to <96	15	18
≥96	27	33
Decade of publication		
1970s	1	1
1980s	2	3
1990s	5	6
2000s	51	61
2010s	24	29
Association investigated[a]		
GFR	56	67
Albuminuria	37	45
Combined GFR and albuminuria	8	9
Participant		
Mean age (years)		
<60	33	40
≥60 to <65	14	17
≥65 to <70	24	29
≥70	12	14
Comparison subgroup GFR (mL/min/1.73 m^2)[a]		
≥90 to <100	1	1
≥60 to <90	15	18
≥30 to <60	52	63
<30	15	18
Comparison subgroup albuminuria[a]		
Macroalbuminuria	24	29
Microalbuminuria	24	29
Stroke		
Subtype		
Unspecified	72	87
Ischaemic	23	28
Haemorrhagic	18	22

GFR, glomerular filtration rate.
[a]Some studies investigated more than one association and/or had more than one comparison subgroup.

analyzed by category of albuminuria. Our analyses also provide compelling evidence about the thresholds of GFR and albuminuria at which the risk of having a stroke starts to increase with a GFR below 90 mL/min/1.73 m^2 and microalbuminuria each independently associated with an increased stroke risk.

Our observations were consistent across different subtypes of stroke, in men and women, and among studies where participants had varying levels of risk factors for vascular disease (diabetes, hypertension and smoking). Study size, adjustment for potential confounders, the clinical setting of the study and the race of study participants all affected the size of the estimated risk of stroke. In particular, we observed a 91% increased risk of stroke in studies where participants with reduced GFR were undergoing a heart procedure. For albuminuria, risk of stroke was 75% greater in studies which recruited mainly South-East Asian participants compared with studies where most participants were white, an observation which has major public health implications. Data were lacking for patients with end stage kidney disease requiring renal replacement therapy.

Based on our data, we propose that the revised Kidney Disease: Improving Global Outcomes (KDIGO) classification of CKD may be a useful tool for stratifying the risk of stroke in the general population though estimates of absolute risk of stroke require adjustment for race and clinical setting [14] (Figure 4).

To our knowledge, this study forms the largest and most comprehensive review of stroke in relation to kidney function and is the first meta-analysis to consider CKD in terms of both GFR and albuminuria. In identifying potential studies for inclusion, we performed a comprehensive literature search and included a large number of studies, so that estimates of effect were generally precise. We included only RCTs and cohort studies and consequently, selection bias, recall bias and reverse causality are unlikely to have affected our results. We also used validated tools to assess the quality of included studies and undertook sensitivity analyses to determine how robust our effect estimates were to varying levels of quality of discreet study methodology. Our analyses also present the most comprehensive exploration of heterogeneity among studies examining the associations of GFR and albuminuria with the risk of stroke.

Our study does have some potential limitations. First, most included studies were observational and we were limited to examining heterogeneity based on data published for known cardiovascular risk factors. Many studies did not report data for known confounders of stroke risk, particularly the use of treatments for complications of CKD (including erythropoietin for anaemia and angiotensin II enzyme inhibitors for people with albuminuria) or the reduction of cardiovascular risk (including aspirin and statins) which may affect the risk of ischaemic and haemorrhagic stroke differently. Residual confounding may exist within our results and explain why we observed no difference in the associations between CKD and the risk of ischaemic or haemorrhagic strokes. Second, the diagnosis of CKD requires the presence of kidney damage for ≥3 months. GFR or albuminuria was frequently only measured once meaning that some patients with acute kidney injury or non-persistent albuminuria may have been misclassified as having CKD and that our estimates of effect may be subject to regression dilution bias. Estimates of GFR may be subject to misclassification bias. The MDRD equation underestimates GFR and the Cockcroft-Gault equation overestimates GFR at >60 mL/min/1.73 m^2 in healthy individuals, and both equations overestimate GFR at >60 mL/min/1.73 m^2 in people with reduced muscle mass (who are more likely to be unwell and may be at higher risk of stroke) [15]. We also estimated average levels of GFR and albuminuria within category ranges based on previously

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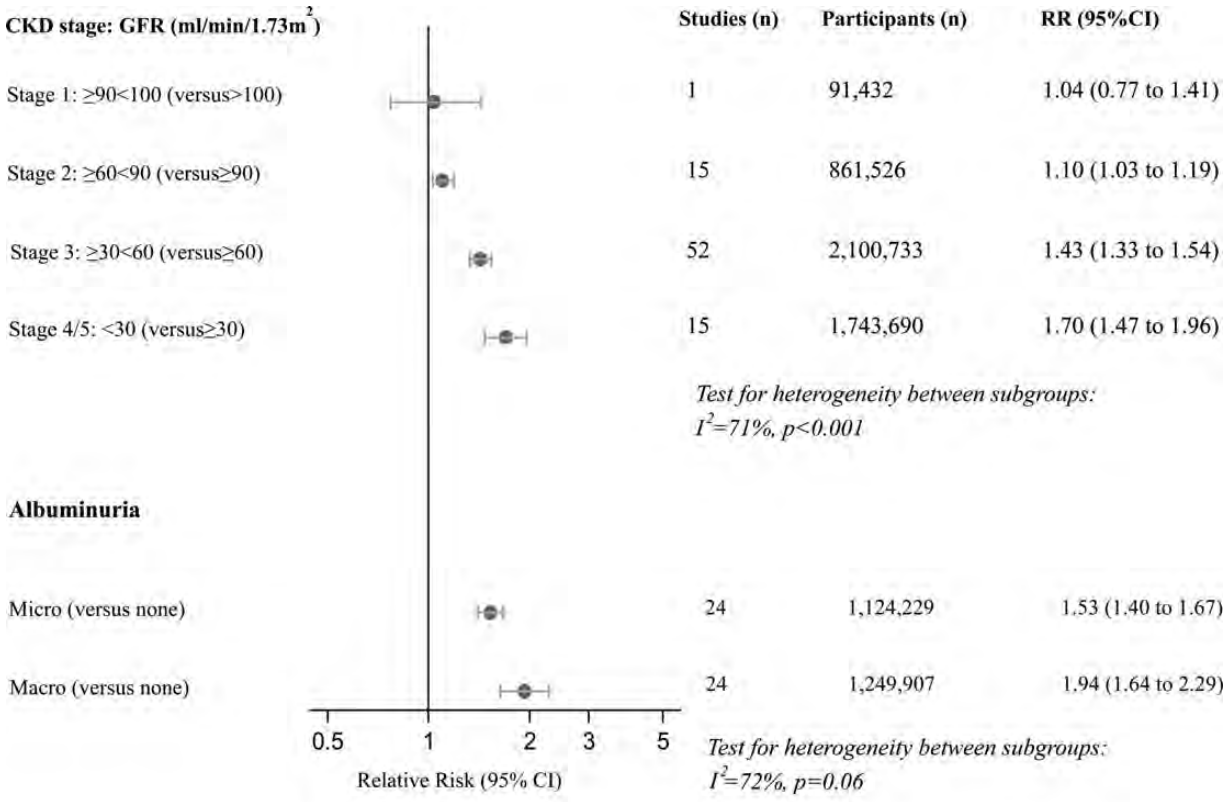

RR: Relative risk; GFR: glomerular filtration rate; CI: confidence interval

FIGURE 2: Risk of all-cause stroke by GFR and albuminuria thresholds.

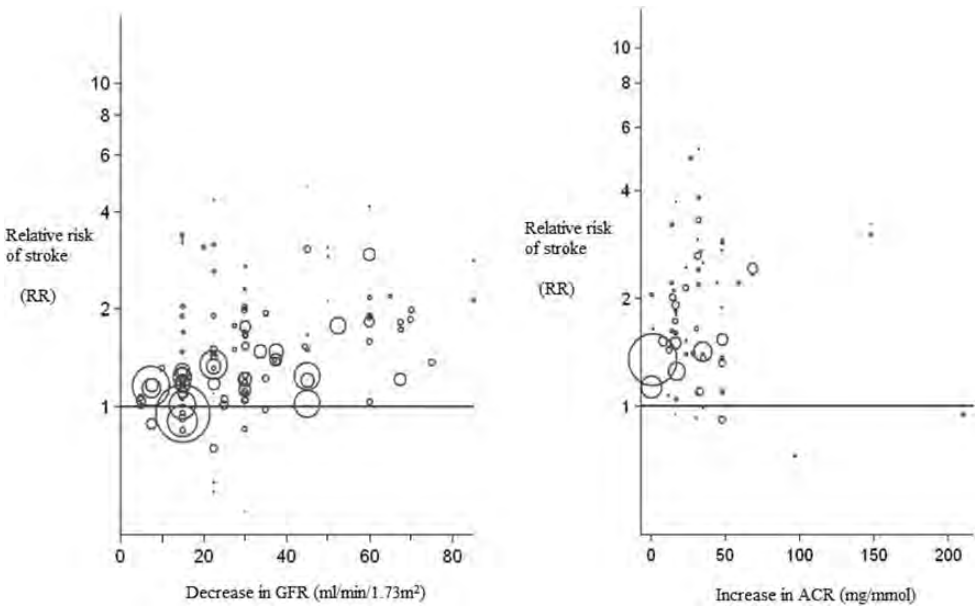

FIGURE 3: RR of all-cause stroke by (i) decrease in GFR and (ii) increase in ACR from reference to comparison groups. Circles represent study-specific effect estimates and are proportional in size to the precision of effect estimates. GFR explains 67% and proteinuria 55% of total variation in risk of stroke after adjusting for other study/participant characteristics significantly associated with risk of stroke.

described methods which assume a near-normal distribution of GFR or albuminuria within each defined CKD stage or category of albuminuria, an assumption we could not test without individual patient data [16]. Finally, the lack of confirmation of type of stroke (ischaemic versus haemorrhagic) in many studies limited our ability to explore stroke subtype in detail.

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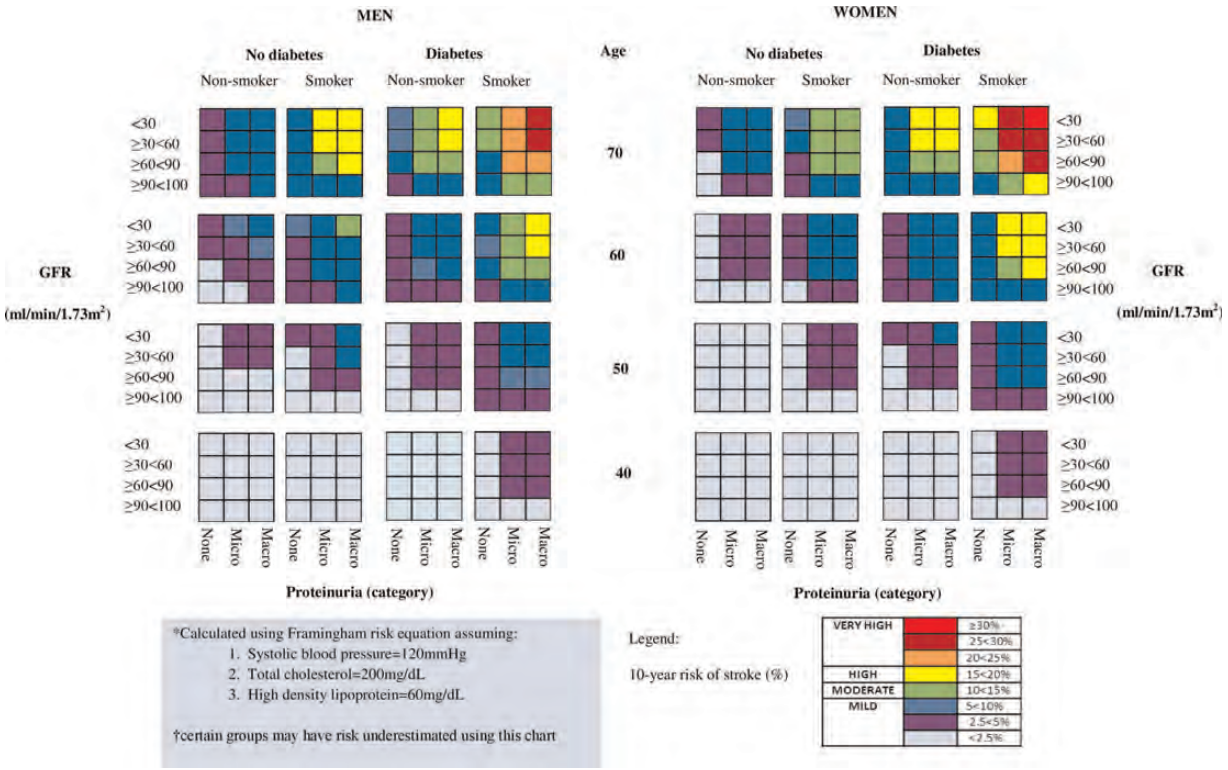

FIGURE 4: Ten year absolute risk of all-cause stroke (fatal and non-fatal).

The magnitude of increased risk of stroke we observed in study participants with a GFR < 60 mL/min/1.73 m^2 is similar to that seen in a previous meta-analysis of 21 prospective studies, but the GFR threshold at which we began to see risk of stroke increase (<90 mL/min/1.73 m^2) suggests an earlier stage of CKD than previously thought [9]. A previous review that included 10 studies identified albuminuria as being associated with an increased risk of stroke but did not observe an increasing risk with increasing quantities of albuminuria or any variation in the effect of albuminuria by race [10].

Our findings for stroke are also broadly consistent with the effects of GFR and albuminuria on the risk of other cardiovascular events. The magnitudes of risk of stroke associated with GFR and albuminuria are similar to size of risk of myocardial infarction and cardiovascular mortality, which are increased by 33 and 57% when GFR is <60 mL/min/1.73 m^2 and by 48 and 63% with microalbuminuria [17, 18]. The threshold GFR at which risk begins to increase is <60 mL/min/1.73 m^2 for myocardial infarction and <75 mL/min/1.73 m^2 for cardiovascular death [17, 19, 20]. For albuminuria, increased risk of myocardial infarction and cardiovascular death are also seen with micro albuminuria [18]. Linear dose–response relationships exist between GFR, quantity of albuminuria and risk of myocardial infarction and cardiovascular death [18, 20, 21]. GFR and albuminuria independently increase the risk of myocardial infarction and cardiovascular mortality without interaction [20, 22]. Considering effect modifiers of GFR, although age and ethnicity modify the effect of GFR on cardiovascular death, we did not observe this for stroke [20]. Patients with lower GFRs undergoing heart procedures are at increased risk of myocardial infarction, heart failure and death compared with patients with higher GFRs, and our observation of increased stroke risk is consistent with these established associations [23]. For albuminuria, no good data on factors that modify the effect of albuminuria on cardiovascular events exist.

There are several possible explanations for finding a near-doubled risk of stroke in studies with mainly Asian participants who had albuminuria, most of which assume that increased exposure to albuminuria increases the risk of stroke. Hypertension occurs at a younger age and may cause more profound end-organ damage in Asians than in whites, and no study that we included adjusted for the duration of hypertension [24]. Diabetes occurs a decade earlier, at lower body mass index and is more frequently associated with albuminuria and worse glycaemic control in Asians than whites [25]. Although we adjusted for differences in the prevalence of diabetes, we could not adjust for either the duration of diabetes or glycaemic control. Asians with albuminuria are also more likely to have a lower GFR than whites with albuminuria and not all studies adjusted for the effect of GFR on the association between albuminuria and stroke [26].

Plausible pathological mechanisms provide further support for GFR and/or albuminuria having a role in causing stroke in addition to the strength, consistency and biological gradient of effect that we have demonstrated. Endothelial dysfunction is common in CKD in which uraemic toxins, insulin resistance, vascular calcification, dyslipidaemia, anaemia and renin–angiotensin activation are proposed to cause chronic inflammation, oxidative stress and promote atherogenesis and arteriosclerosis [27, 28]. To date, data from RCTs demonstrating a reduction in the risk of stroke coincident with slowing the rate of GFR decline or reducing albuminuria is lacking with only a few

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conflicting reports for other cardiovascular endpoints. Synthesis of eight RCTs failed to show any reduction in the risk of cardiovascular mortality amongst participants randomized to treatments known to slow decline in GFR [29]. For albuminuria, one RCT reported that reducing albuminuria by 50% reduced the risk of a cardiovascular event [30].

For researchers, the challenge is to generate further evidence that preventing progressive CKD reduces the risk of having a stroke. Specifically, the effects of reducing albuminuria in South-East Asians, slowing the rate of change in GFR and how dynamic changes in the quantity of albuminuria affect stroke risk should be examined. The public health implications of our data are also considerable and the potential for stroke prevention is substantial. Our data suggest that each year up to 4% of all strokes (31 800 in the USA) may be attributable to having a GFR <90 mL/min/1.73 m^2, having any degree of albuminuria may account for 6% (47 770) of all strokes, and that as many as 10 000 (1.2%) strokes could be prevented if people with microalbuminuria received an angiotensin-converting enzyme inhibitor [31].

SUPPLEMENTARY DATA

Supplementary data are available online at http://ndt.oxfordjournals.org.

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CONFLICT OF INTEREST STATEMENT

None declared.

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