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Association of kidney disease measures with ischemic versus hemorrhagic strokes: Pooled analyses of 4 prospective community-based cohorts

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Abstract

Background and purpose—Although low glomerular filtration rate (GFR) and albuminuria are associated with increased risk of stroke, few studies compared their contribution to risk of ischemic versus hemorrhagic stroke separately. We contrasted the association of these kidney measures with ischemic versus hemorrhagic stroke.

Methods—We pooled individual participant data from four community-based cohorts: three from the United States and one from The Netherlands. GFR was estimated by using both creatinine and cystatin C, and albuminuria was quantified by urinary albumin-to-creatinine ratio (ACR). Associations of eGFR and ACR were compared for each stroke type (ischemic vs. intraparenchymal hemorrhagic) using study-stratified Cox-regression.

Results—Amongst 29,595 participants (mean age 61 [SD 12.5] years, 46% males, 17% black), 1,261 developed stroke (12% hemorrhagic) during 280,549 person-years. Low eGFR was significantly associated with increased risk of ischemic, but not hemorrhagic, stroke risk, while

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high ACR was associated with both stroke types. Adjusted HRs for ischemic and hemorrhagic stroke at eGFR of 45 (vs. 95) ml/min/1.73m^2 were 1.30 (95% CI, 1.01–1.68) and 0.92 (0.47–1.81), respectively. In contrast, the corresponding HR for ACR 300 (vs. 5) mg/g were 1.62 (1.27–2.07) for ischemic and 2.57 (1.37–4.83) for hemorrhagic stroke, with significantly stronger association with hemorrhagic stroke (P =0.04). For hemorrhagic stroke, the association of elevated ACR was of similar magnitude as that of elevated systolic blood pressure.

Conclusions—Whereas albuminuria showed significant association with both stroke types, the association of decreased eGFR was only significant for ischemic stroke. The strong association of albuminuria with both stroke types warrants clinical attention and further investigations.

INTRODUCTION

Stroke is a leading cause of mortality and morbidity and requires substantial health-care expenditures.[1] Excluding subarachnoid hemorrhages from consideration, strokes are broadly classified as ischemic and intraparenchymal hemorrhagic.[1] Whereas the incidence rate of ischemic versus hemorrhagic strokes and their treatment are distinct, some risk factors such as blood pressure have similar effects in both stroke types while others such as cholesterol do not.[1, 2] However, head-to-head comparison of the strength of associations between traditional cardiovascular risk factors and ischemic versus hemorrhagic is lacking, perhaps due to the generally low incidence of hemorrhagic stroke in Western populations.

Chronic kidney disease (CKD), defined by reduced kidney function (estimated glomerular filtration rate [eGFR], <60 m/min/1.73m^2), elevated albuminuria (albumin-creatinine ratio [ACR] ≥30 mg/g), or both is common (10–16% in general adult population) and confers high cardiovascular risk.[3–6] Studies on stroke in CKD subjects generally have reported a composite endpoint for stroke types or limited their analyses to ischemic strokes.[7, 8] Studies addressing the association of CKD with hemorrhagic stroke had limited numbers of hemorrhagic strokes or did not fully take albuminuria into account.[7–12] Moreover, a few new equations for eGFR with higher precision have recently been published and may allow better quantification of the GFR-stroke association.[13, 14]

To overcome the issues above, we pooled four population-based prospective cohorts to assess the association of eGFR and albuminuria with incident ischemic and hemorrhagic stroke. Our primary objective was to assess whether the associations of eGFR and albuminuria with ischemic versus hemorrhagic stroke are similar or not. In secondary analyses we compared the associations observed for these kidney measures to those for traditional cardiovascular risk factors.

METHODS

Study characteristics

Analyses were based on individual level data from four community-based prospective cohorts that ascertained stroke types, serum creatinine and cystatin C as well as quantitative albuminuria assessed by ACR. These cohorts were the Atherosclerosis Risk in Communities Study (ARIC), the Cardiovascular Heart Study (CHS), the Multi-Ethnic Study of Atherosclerosis (MESA) and the Prevention of REnal and Vascular ENd-stage Disease

(PREVEND) Study. Details of the study protocols have been published elsewhere[15–18] and briefly summarized in the supplemental material. Review committees of each participating cohort approved sharing of the de-identified individual-level data and the conducted analyses presented in this paper.

Chronic kidney disease measures

GFR was estimated using the latest CKD Epidemiology Collaboration (CKD-EPI) equations.[13, 14] In the primary analysis the cystatin C and creatinine combined eGFR equation was used, since this is the best available equation to estimate GFR.[13] In a sensitivity analysis, we also examined the equations using single filtration markers, i.e., creatinine or cystatin C.[13, 14] In all studies cystatin C and creatinine were calibrated to standardized serum cystatin C and isotope dilution mass spectrometry, respectively (supplemental material). Albuminuria was quantified as ACR in a spot or 24-hour (PREVEND) urine sample, which is the recommended method of albuminuria measurement.[19] CKD was defined as eGFR <60 mL/min/1.73 m^2, ACR ≥30 mg/g, or both according to prevailing guidelines.[19]

Traditional cardiovascular risk factors

History of cardiovascular disease was defined as previous myocardial infarction, coronary revascularization or heart failure at the baseline exams in which kidney markers were measured. Participants with prevalent stroke cases were excluded from the analyses. Hypertension was defined as systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, or use of antihypertensive medication. Diabetes mellitus was defined as fasting glucose concentration ≥7.0 mmol/L (≥126 mg/dL), non-fasting glucose concentration ≥11.1 mmol/L (≥200 mg/dL), use of glucose lowering drugs, or self-reported diabetes. Smoking was dichotomized to current smokers versus former or nonsmokers. Hypercholesterolemia was defined as total cholesterol concentration 5.0 mmol/L (193 mg/dL) or more in patients with a history of cardiovascular disease and as 6.0 mmol/L (232 mg/dL) or more in patients without a history of cardiovascular disease. Body mass index (BMI) was calculated as measured body weight in kilograms divided by height in meters squared.

Stroke types

Incident stroke types were divided into ischemic stroke and hemorrhagic stroke and were verified by computed tomography, magnetic resonance imaging or at autopsy (Supplemental material). Participants with hemorrhagic stroke included those with intraparenchymal hemorrhages but excluded those with subarachnoid hemorrhages. Ischemic stroke subtypes were not determined in a similar fashion in all cohorts and thus were not considered in these analyses.

Statistical analysis

Individual participant data from the four cohorts were pooled. Participants were excluded if demographics or measurements of all three kidney measures (i.e., cystatin C, creatinine and albuminuria) were missing. For all other participants, missing values of the kidney measures and potential confounders were imputed using stochastic multiple imputations using the

chained-equation method (supplemental material).[20] Except for 12% missing ACR in the CHS study, all other variables had less than 5% of missing values.

Stratified Cox proportional hazards models, allowing for cohort-specific baseline hazard, were used to estimate hazard ratios (HRs) for stroke types. Fully adjusted models included eGFR, log ACR, sex, black ethnicity, age (continuous), diabetes, current smoking, systolic blood pressure (continuous), total cholesterol (continuous), history of cardiovascular disease, BMI (continuous), statins and antihypertensive drug use. To assess non-linear associations of eGFR and ACR with risk of stroke types, we modeled eGFR and ACR using restricted cubic splines with knots at 45, 60, 75, 90 and 105 mL/min/1.73m^2 for eGFR, and 10, 30 and 300 mg/g (to convert to mg/mmol multiply by 0.113) for ACR. eGFR of 95 mL/min/1.73m^2 and ACR of 5 mg/g were selected as reference points, based on previous literature.[5, 21, 22] HRs of stroke types for eGFR were estimated at each 1 mL/min/1.73 m^2 from 15 to 120 mL/min/1.73m^2. HRs for ACR were estimated at every 8% increment of ACR from 2.5 to 1000 mg/g. Overall P-values for eGFR and ACR splines were obtained from the inverse-variance average of the six linear spline coefficients for eGFR and the four linear spline coefficients for log ACR, respectively.

When assessing differences in the strength of eGFR- and ACR-risk association between ischemic and hemorrhagic stroke, eGFR and log ACR were modeled linearly. Differences in log HRs were obtained by subtracting log HRs for hemorrhagic strokes from the log HRs for ischemic strokes. Standard errors for the differences in log HRs were estimated by 1,000 bootstraps of the difference of log HRs.

We also evaluated the association of combined categories of eGFR and ACR according to the Kidney Disease: Improving Global Outcomes (KDIGO) classification[19] with both stroke types. Interaction between eGFR and ACR was assessed by likelihood ratio tests between the models with and without product terms of eGFR and ACR in the complete dataset. P values for the differences were obtained using a Wald-test. Statistical significance was considered as a 2-tailed P <0.05. All statistical analyses were performed using Stata software version 11.2 (StataCorp LP, College Station, Texas) and R software version 2.14.1.

RESULTS

Table 1 depicts the characteristics of the four cohorts. Overall, 29,595 participants (mean age 61 [SD 12.5] years, 46% males, 17% black) contributed to a total follow-up of 280,549 person-years. During average follow-up of 9.5 years, 1,261 strokes occurred of which 156 (12%) were classified as hemorrhagic. Participants of the Dutch (PREVEND) cohort, almost exclusively whites, were on average younger, less often hypertensive and diabetic, and had lower BMI and higher eGFR compared to the other three cohorts. However, prevalence of current smoking and hyperlipidemia were higher in the PREVEND cohort.

Independent and combined associations of the kidney measures with stroke types

When the kidney measures were modeled continuously with spline-terms, low eGFR was significantly associated with increased risk of ischemic stroke, but not with hemorrhagic stroke (Figure 1). The association of low eGFR and hemorrhagic stroke started to increase

only at eGFR 45 and below but did not reach statistical significance even at eGFR 15. Relative to eGFR of 95 mL/min/1.73m^2, adjusted HRs for ischemic and hemorrhagic stroke at eGFR of 45 mL/min/1.73m^2 were 1.30 (1.01–1.68) and 0.92 (0.47–1.81), respectively. Nonetheless, difference in the association of continuous eGFR with ischemic vs. hemorrhagic stroke was not significant (P difference = 0.69). Similarly, when GFR was estimated with equations using either cystatin C or creatinine as filtration marker, differences in the association of eGFR between stroke types were not significant (Supplemental Figure I). The associations of eGFR remained similar, even when systolic blood pressure and antihypertensive drug use were dropped from the fully adjusted model (Supplemental Figure II).

In contrast, ACR was significantly positively associated with both types of stroke without any threshold effects (Figure 1). The risk gradient was steeper for hemorrhagic stroke than for ischemic stroke. For example, the HRs for ischemic and hemorrhagic stroke at ACR 300 mg/g compared to ACR 5 mg/g were 1.62 (1.27–2.07) and 2.57 (1.37–4.83), respectively. The associations of ACR with both stroke types became even stronger when systolic blood pressure and antihypertensive drug use were dropped from the fully adjusted model (Supplemental Figure II). Moreover, overall linear log-ACR was more strongly associated with hemorrhagic stroke than with ischemic stroke (P for difference = 0.04).

When combined categories of eGFR and ACR were assessed,[19] higher risk was generally observed for both ischemic and hemorrhagic stroke as eGFR decreased and ACR increased (Figure 2). The risk increase was not clearly multiplicative with lower eGFR and higher ACR categories. Nevertheless, no significant interaction between eGFR and ACR categories was observed (ischemic stroke: overall P for interaction =0.06; hemorrhagic stroke: overall P for interaction =0.70). Also, there was no significant interaction between continuous eGFR and log ACR (ischemic stroke: overall P for interaction =0.66; hemorrhagic stroke: overall P for interaction =0.50).

Traditional cardiovascular risk factors versus kidney measures

Generally traditional cardiovascular risk factors showed significantly positive associations with ischemic stroke, but not necessarily with hemorrhagic stroke (Figure 3A). Male gender, diabetes, history of CVD, BMI and cholesterol were inversely associated with hemorrhagic stroke, although only cholesterol reached significance (HR of 0.77 per 1 SD increase [95% CI, 0.64–0.92; P=0.003]). The HR differences between ischemic and hemorrhagic stroke were significant for cholesterol (P = 0.001), sex (P = 0.01), and BMI (P = 0.04).

To facilitate comparison between kidney measures and cardiovascular risk factors, kidney measures were modeled per SD difference and as binary variables (eGFR of <60 [vs. ≥60 mL/min/1.73m^2], ACR ≥30 [vs. <30] mg/g, and their combination [CKD] [vs. non-CKD]) (Figure 3B). Among the continuous traditional predictors, age was most strongly associated with both stroke types, followed by systolic blood pressure. As compared to systolic blood pressure, log-ACR was slightly less strongly associated with ischemic stroke (HR per 1 SD increment, 1.30 [95% CI, 1.23–1.38] vs. 1.17 [1.11–1.24]) but was more strongly associated with hemorrhagic stroke (1.25 [1.07–1.14] vs. 1.39 [1.19–1.62]), when both were modeled together along with other confounders. HR per 1 SD lower eGFR (1.09 [95%CI, 1.02–1.18])

was only significant for ischemic stroke in a magnitude similar to total cholesterol (HR per 1 SD decrement, 1.07 [95%CI, 1.01–1.14]). The HR for elevated ACR (i.e., ≥30 mg/g vs. <30) was comparable with that for diabetes and history of cardiovascular disease for ischemic stroke but was higher for hemorrhagic stroke. This association of ACR, with stroke types was largely consistent across the cohorts (Supplemental Figure III).

DISCUSSION

In this pooled analysis of four population-based prospective cohorts with 29,595 participants experiencing 1,261 strokes over 280,549 person-years of follow-up, both lower eGFR and higher albuminuria were associated with higher risk of ischemic stroke independently of each other and traditional stroke risk factors. In contrast, only higher albuminuria, but not lower eGFR, was significantly associated with increased risk of hemorrhagic stroke. Of note, at a given level of elevated albuminuria, HRs were significantly greater for hemorrhagic stroke as compared to ischemic stroke. The association of albuminuria with increased risk of hemorrhagic stroke was independent of potential confounders including blood pressure.

Several studies have documented a positive association of albuminuria with ischemic stroke.[8, 9, 11] In a recent meta-analysis of 13 studies, risk of ischemic stroke was about 2-fold in subjects with microalbuminuria as compared to subjects with normoalbuminuria.[8] In contrast, data on hemorrhagic stroke are limited, as only one prospective study was identified in the aforementioned systematic review.[8] In that study with a total of 49 hemorrhagic strokes, ascertained from hospital discharge registries of Norfolk (United Kingdom), the association of categorical albuminuria with hemorrhagic stroke did not reach statistical significance;[11] however, a positive dose-response risk was observed for micro- and macro-albuminuria. Similarly, a more recent paper reporting results of the CHS study,[9] which is included in this paper, also found a positive but non-significant association of albuminuria categories with hemorrhagic stroke. In the CHS analysis, the association of albuminuria was highly significant when ACR was modeled continuously, implicating limited power for categorical ACR analysis.

In our pooled analysis, notably the association of albuminuria with hemorrhagic stroke was stronger than with ischemic stroke. This association was independent of blood pressure, and the strength of association was comparable with systolic blood pressure.[23] A plausible explanation for this observation may include a suggestion from recent work that albuminuria might be particularly reflecting damage of “strain vessels” that are abundantly present not only in the kidneys but also in the brain.[24] In fact, an association of albuminuria with increased risk of deep or infratentorial microbleeds, which anatomically correspond with the brain “strain vessels,” has been reported.[25, 26] It could be argued that blood pressure may be in the causal pathway for the association of kidney measures with stroke, and therefore adjustment for blood pressure may have resulted in conservative estimates. Indeed the relative risks of both stroke types for albuminuria became higher when systolic blood pressure and antihypertensive drug use were dropped from the model (Supplemental Figure II).

Regarding the association with stroke, kidney function has been more intensively assessed compared to albuminuria. In a meta-analysis of 21 studies addressing the association of eGFR (based on the MDRD Study or Cockcroft-Gault equations) with stroke, eGFR of <60 ml/min/1.73m^2 was associated with a 43% risk increase of overall unspecified stroke as compared to the reference eGFR (generally ≥60 or ≥90 ml/min/1.73m^2).[7] No differences in the strength of associations with ischemic versus hemorrhagic stroke were observed in a subgroup analysis of studies that reported separate estimates for ischemic (6 studies) and hemorrhagic (3 studies) stroke.[7] However, none of these studies conducted head-to-head comparisons of the two stroke types, and the pooled estimate for the association of eGFR with hemorrhagic stroke did not reach statistical significance in this meta-analysis.[7] Similarly, our pooled analysis showed no significant difference in the hazard ratios associating eGFR with hemorrhagic versus ischemic stroke, although only the association with ischemic stroke was statistically significant. The lack of a significant association of eGFR with hemorrhagic stroke needs to be interpreted with caution in light of relatively limited statistical power for hemorrhagic stroke.

The association of decreased eGFR with increased stroke risk may be explained by its association with atherosclerosis,[27] atrial fibrillation,[28] and cerebral small-vessel disease.[29] Although we used the best available equation incorporating creatinine and cystatin C for our primary analysis,[13] the association of eGFR with ischemic stroke was weaker for eGFR based on creatinine compared with eGFR based on cystatin C (Supplemental Figure I), suggesting the involvement of non-GFR determinants surrounding creatinine and cystatin C. In fact, stronger relationships to other cardiovascular endpoints has been previously reported for eGFR based on cystatin C levels compared to creatinine-based eGFR.[15]

Our study extended previous literature in various aspects.[7, 9–11] First, we used state-of-the-art equations for eGFR,[13, 14] which improves estimation of measured GFR and risk prediction of clinical outcomes. Second, our analysis fully accounted for traditional cardiovascular risk factors and both key kidney measures,[7, 8] whereas only two previous studies investigated both kidney measures simultaneously.[9, 11] Third, stroke was verified by an independent committee in three of the four cohorts. Fourth, we explored the eGFR and albuminuria association with both types of stroke in various categorical and continuous analyses. Fifth, unlike the previous meta-analysis of eGFR and albuminuria associations with stroke,[7, 8] our analyses used the same adjustment variables and the same reference range across the four studies.

Several limitations of this study warrant acknowledgement. First, some studies measured albumin in fresh urine samples whereas other studies used frozen samples, and single centralized laboratory was not utilized by all studies. Care was taken, however, to use the same definitions for exposure variables. Regardless, any misclassification due to non-standardization is likely to result in underestimation of the exposure-risk relationship. Second, information was not available on anticoagulant and antiplatelet medication use, which may be associated with higher risk of hemorrhagic stroke. However, the association of albuminuria with hemorrhagic stroke was independent of conditions predisposing to use of these drugs, such as history of cardiovascular disease and diabetes. Third, even though we adjusted for various cardiovascular risk factors, residual confounding cannot be completely

ruled out. Fourth, the comparison of kidney measure versus traditional cardiovascular risk may be hampered by the differences in distributions and prevalence of the risk factors. Despite theses limitations, this report is the most comprehensive analysis on the association of kidney disease measures with stroke types.

In conclusion, decreased eGFR showed comparable risk gradients for both stroke types, although statistical significance was only observed for ischemic stroke. In contrast, elevated albuminuria was significantly associated with increased risk of both ischemic and hemorrhagic strokes, with quantitatively stronger relationship with hemorrhagic stroke. Notably, the association of albuminuria with hemorrhagic stroke was independent of and at least as strong as for systolic blood pressure, one of the most potent risk factors for this stroke type, suggesting that kidney damage, systemic vessel strain or both play an important role in the pathophysiology of hemorrhagic stroke. The strong association of albuminuria with both stroke types warrants clinical attention and further investigations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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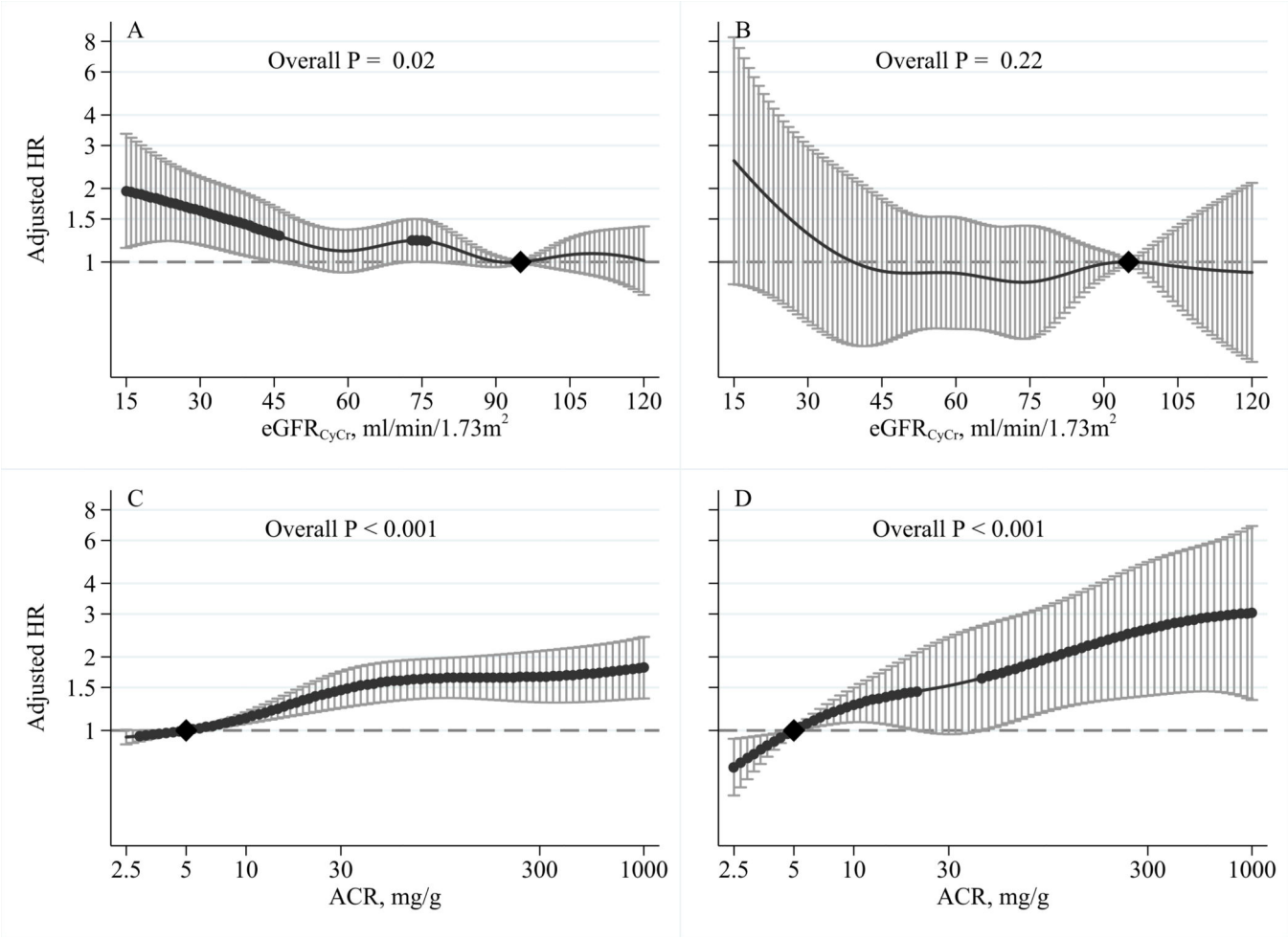


Figure 1. Adjusted associations of continuous eGFR and ACR with ischemic and hemorrhagic strokes

Top panels show the association of the creatinine and cystatin C combined equation based eGFR with ischemic (A) and hemorrhagic (B) strokes. Bottom panels display the association of ACR with ischemic (C) and hemorrhagic (D) stroke. Diamonds represent the reference points (eGFR=95 mL/min/1.73m^2, ACR=5 mg/g). Error bars denote 95%CIs of the adjusted hazard ratios, and the black circles denote P <0.05 compared to the reference. Hazard ratios were adjusted for sex, age, black ethnicity, diabetes, current smoking, systolic blood pressure, total cholesterol, history of cardiovascular disease, BMI, statins and antihypertensive drug use. eGFR$_{CyCr}$ = cystatin C and creatinine combined equation based estimated glomerular filtration rate; ACR= albumin-to-creatinine ratio.

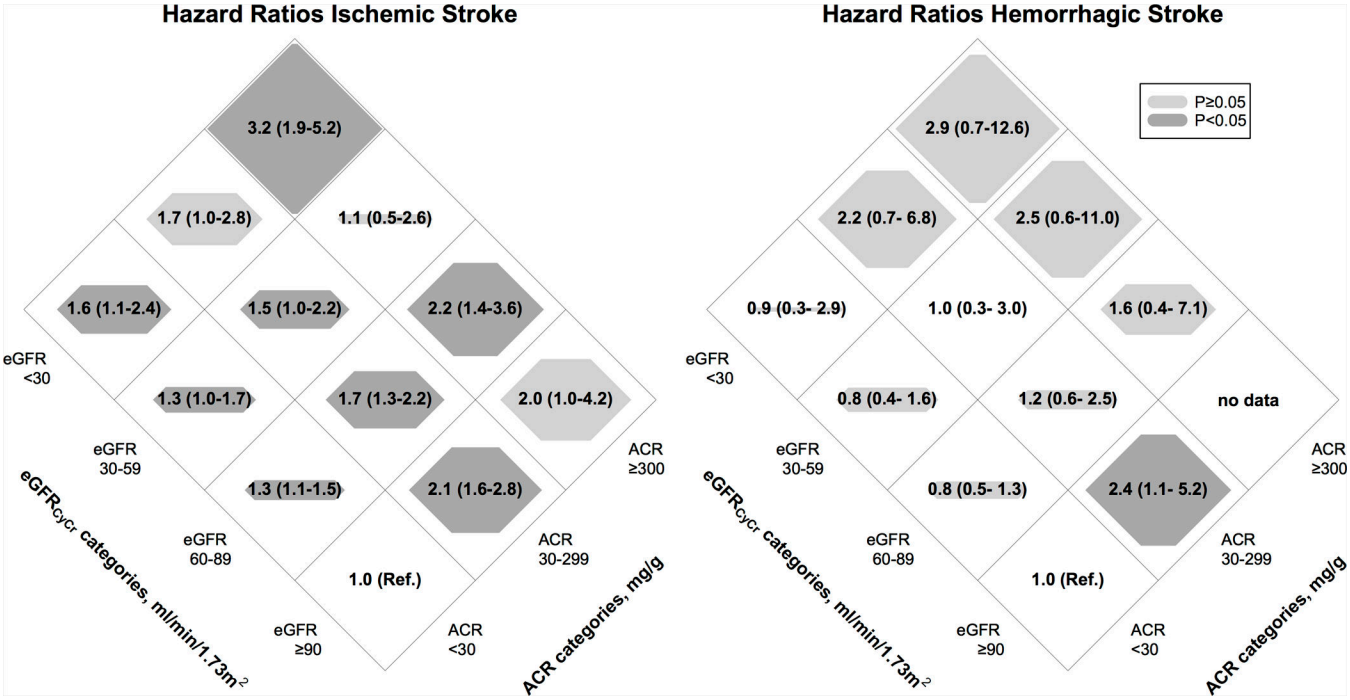
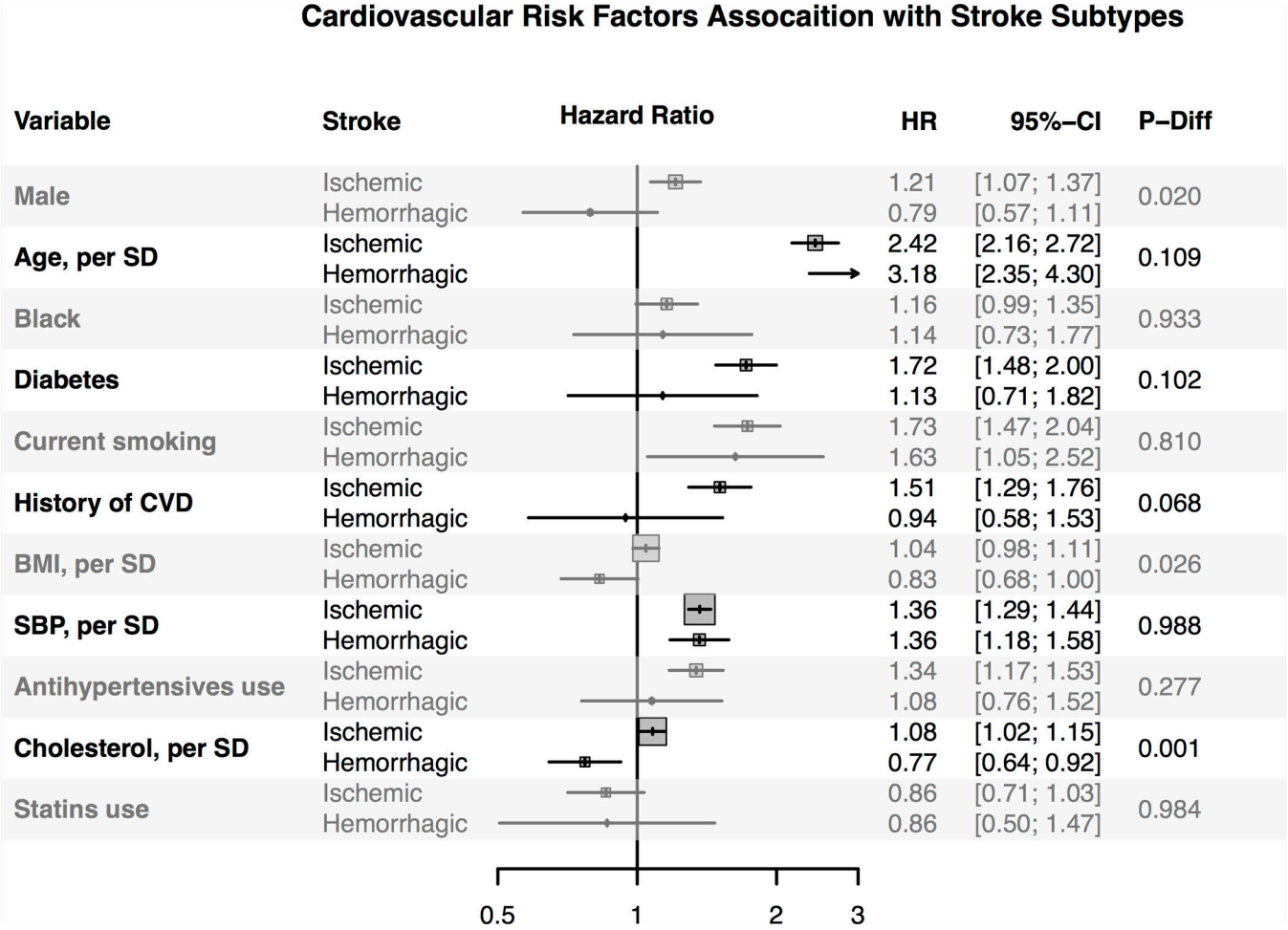


Figure 2. Adjusted risk of ischemic (left) and hemorrhagic (right) stroke according to clinical eGFR and ACR categories

The diamond sizes are proportional to the HRs estimate with full cells corresponding to the highest HRs (i.e. HR=3.2) and empty cells corresponding to HR=1.0 or no data. Hazard ratios were adjusted for sex, age, black ethnicity, diabetes, current smoking, systolic blood pressure, total cholesterol, history of cardiovascular disease, BMI, statins and antihypertensive drug use. The dark-gray diamond color corresponds to P<0.05. $eGFR_{CyCr}$ = combined cystatin C and creatinine based equation estimated glomerular filtration rate; ACR= albumin-to-creatinine ratio.



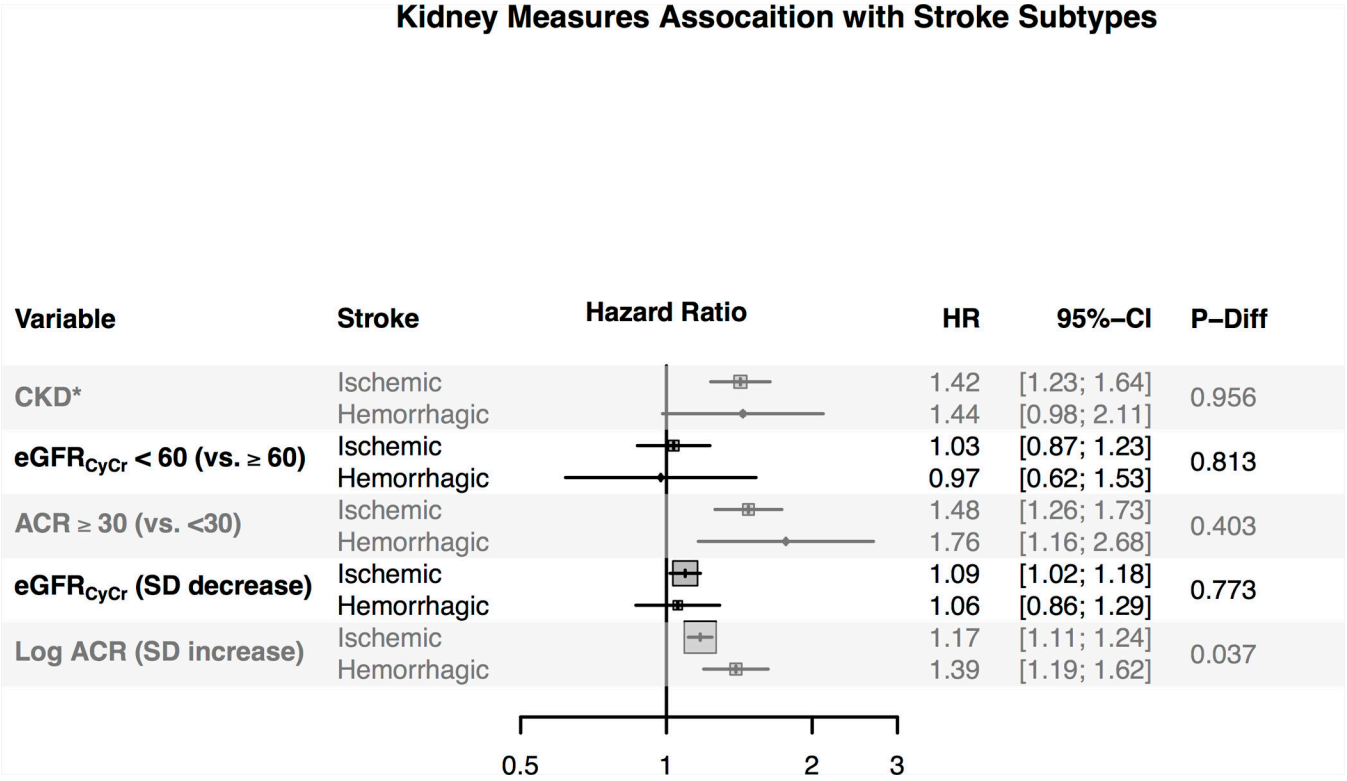


Figure 3. Adjusted association of traditional cardiovascular risk factors (panel A) versus kidney measures (panel B) with ischemic and hemorrhagic strokes

*CKD was defined as $eGFR_{CyCr}$ <60 mL/min/1.73m^2 and/or ACR ≥30 mg/g; $eGFR_{CyCr}$= Cystatin C and creatinine combined estimated glomerular filtration rate. 1 SD of age = 12.5 years; 1SD of BMI = 5.3 kg/m^2; 1 SD of systolic blood pressure = 20.3 mmHg; and 1SD of cholesterol = 1.0 mmol/L.

$eGFR_{CysC}$ = cystatin C based estimated glomerular filtration rate; $eGFR_{Creat}$ = creatinine based estimated glomerular filtration rate; ACR = albumin-to-creatinine ratio; CVD = cardiovascular disease; BMI = body mass index; SBP = systolic blood pressure. Estimates in panel A were obtained from a single multivariable model with additional adjustment for $eGFR_{CyCr}$ and ACR. Estimates in panel B were adjusted for traditional cardiovascular risk factors shown in panel A and either $eGFR_{CyCr}$ or ACR as appropriate. P-diff = P for difference between ischemic and hemorrhagic stroke. The size of the box around the hazard ratio estimates is proportional to the inverse of the hazard ratio variance.

Table 1

Characteristics by cohort.

	Cohorts (Baseline years)			
	ARIC* (1996–1998)	**CHS* (1996–1997)**	**MESA (2000–2002)**	**PREVEND (1997–1998)**
Participants, n	11,306	3,283	6,767	8,239
Baseline characteristics				
Mean age, years	63 (6)	78 (5)	62 (10)	49 (13)
Male	44%	39%	47%	50%
Black	22%	16%	28%	1%
Hypertension	47%	58%	45%	33%
Diabetes	17%	16%	13%	4%
Hypercholesterolemia	33%	37%	28%	40%
Current smoking	15%	8%	13%	34%
History of CVD	13%	26%	0%	4%
Mean body mass index, kg/m^2	28.8 (5.6)	26.9 (4.7)	28.3 (5.5)	26.1 (4.2)
Mean systolic BP, mm Hg	127 (19)	137 (21)	127 (21)	129 (20)
Mean diastolic BP, mm Hg	71 (10)	70 (11)	72 (10)	74 (10)
Mean total cholesterol, mmol/L	5.2 (1.0)	5.3 (1.0)	5.0 (0.9)	5.6 (1.1)
Antihypertensive drug use	43%	57%	37%	15%
Statins use	11%	9%	15%	6%
Mean $eGFR_{CyCr}$, $ml/min/1.73m^2$	91 (17)	66 (17)	85 (17)	95 (17)
Median ACR, mg/g	3.7 (1.8–7.7)	9.9 (5.4–22)	5.3 (3.3–11.0)	7.0 (4.7 – 13.2)
Mean follow-up, years	11.3 (2.8)	8.1 (3.7)	7.1 (1.5)	9.6 (2.4)
Ischemic strokes, n	465	351	111	178
Hemorrhagic strokes, n	50	57	16	33

ARIC denotes the Atherosclerosis Risk in Communities Study; CHS, the Cardiovascular Heart Study; MESA, the Multi-Ethnic Study of Atherosclerosis; PREVEND, the Prevention of REnal and Vascular ENd-stage Disease study; CVD, cardiovascular disease; BP, blood pressure; $eGFR_{CyCr}$, Cystatin C and creatinine based estimated glomerular filtration rate and ACR, albumin-to-creatinine ratio. Values in parenthesis are SDs, except for ACR, which is interquartile range.

*Since serum cystatin C and albuminuria were only measured at visit four (1996–1998) in ARIC and visit nine (1996–1997) in CHS, these visits were considered as the baseline for ARIC and CHS.