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The AGES-Reykjavik Study suggests that change in kidney measures is associated with subclinical brain pathology in older community-dwelling persons

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Abstract

Decreased glomerular filtration rate (GFR) and albuminuria may be accompanied by brain pathology. Here we investigated whether changes in these kidney measures are linked to development of new MRI-detected infarcts and microbleeds, and progression of white matter hyperintensity volume. The study included 2671 participants from the population-based AGES-Reykjavik Study (mean age 75, 58.7% women). GFR was estimated from serum creatinine, and albuminuria was assessed by urinary albumin-to-creatinine ratio. Brain MRI was acquired at baseline (2002-2006) and 5 years later (2007-2011). New MRI-detected infarcts and microbleeds were counted on the follow-up scans. White matter hyperintensity progression was estimated as percent change in white matter hyperintensity volumes between the two exams. Participants with a large eGFR decline (over 3 ml/min/1.73m^2 per year) had more incident subcortical infarcts (odds ratio 1.53; 95% confidence interval 1.05, 2.22), and more marked progression of white matter hyperintensity volume (difference: 8%; 95% confidence interval: 4%, 12%), compared to participants without a large decline. Participants with incident albuminuria (over 30 mg/g) had 21% more white matter hyperintensity volume progression (95% confidence interval: 14%, 29%) and 1.86 higher odds of developing new deep microbleeds (95% confidence interval 1.16, 2.98), compared to participants without incident albuminuria. The findings were independent of cardiovascular risk factors. Changes in kidney measures were not associated with occurrence of

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DISCLOSURE

All the authors declared no competing interests.

SUPPLEMENTARY MATERIAL

Supplementary material is linked to the online version of the paper at www.kidney-international.org.

cortical infarcts. Thus, larger changes in eGFR and albuminuria are associated with increased risk for developing manifestations of cerebral small vessel disease. Individuals with larger changes in these kidney measures should be considered as a high risk population for accelerated brain pathology.

Keywords

albuminuria; cortical infarcts; glomerular filtration rate; microbleeds; subcortical infarcts; white matter hyperintensity

Patients with kidney disease commonly have cerebrovascular comorbidities.[1,2] Prevalence of stroke is 5-fold higher in chronic kidney disease (CKD) patients as compared with their age- and sex-matched controls.[1] Current evidence indicates that this excess number of cerebrovascular comorbidities is not only limited to CKD patients but also to individuals with abnormalities in kidney measures that are not at the level for a diagnosis of CKD.[3,4] Previous studies in the general populations have shown that even a mild decrease in glomerular filtration rate or mild increase in albuminuria is associated with higher risk of stroke.[1,5,6]

Apart from clinically overt brain pathology, cross-sectional studies have shown concomitant presence of decreased glomerular filtration rate (GFR) or increased albuminuria and subclinical cerebrovascular disease.[7–9] However, there is no evidence whether changes in kidney measures are also associated with higher risk of developing subclinical cerebrovascular small vessel diseases. Subclinical cerebrovascular small vessel disease, such as magnetic resonance imaging (MRI)-detected infarcts, white matter hyperintensities, and cerebral microbleeds, are reported to increase the risk of stroke and dementia,[10,11] and hence their relation with kidney measures can reflect an earlier phase of the association of kidney impairment with an excess number of neurologic outcomes.[12,13]

The kidneys and brain are low-resistance end-organs exposed to high-volume blood flow and are susceptible to vascular damage.[12] Moreover, alterations in kidney measures are associated with high blood pressure, which has been implicated as a risk factor for cerebrovascular pathology.[2]

Determining whether there are concurrent changes in both the kidney and the brain has implications for the screening and treatment of patients seeking medical care from both nephrologists and neurologists.

In this prospective population-based study, we aimed to investigate whether changes in kidney measures are associated with a concurrent higher risk of developing MRI-detected infarcts, microbleeds, and progression of white matter hyperintensity volume. In addition, we investigated whether changes in kidney measures are related to higher risk of microbleeds, specifically in lobar or deep cerebral regions.

RESULTS

Participants had an average (± SD) age of 74.7 ± 4.8 years, and 58.7% were women. The mean estimated GFR (eGFR) was 77.6 ± 15.5 ml/min per 1.73 m^2, and the median albumin-to-creatinine ratio (ACR) was 2.3 (range, 1.1–5.1) (Table 1). Participants with a subsequent large decline in eGFR (>3 ml/min per 1.73 m^2 per year) were more likely to be female, diabetic, and hypertensive. They had higher systolic blood pressure and lower cholesterol values. Participants with incident albuminuria (urine albumin to creatinine ratio >30 mg/g) were older and had higher loads of cardiovascular risk factors and diseases (Table 1). During an average 5.2 years elapsed between the baseline and follow-up examination, 202 new subcortical infarcts, 300 new cortical infarcts, and 456 new microbleeds were identified.

Association between baseline kidney measures and occurrence of new subclinical cerebrovascular small vessel disease

In age- and sex-adjusted models (Table 2, model 1), each SD higher baseline eGFR was associated with a 5.5% higher more diffusely distributed white matter hyperintensity volume progression, which did not change after adjustment for cardiovascular risk factors (model 2).

A higher log-transformed baseline ACR was associated with a higher incidence of more focally distributed subcortical infarcts and microbleeds (Table 2, model 1); further adjustment for cardiovascular risk factors did not change the findings (model 2).

Association between change in kidney measures and occurrence of subclinical cerebrovascular small vessel disease

Each 1 ml/min per 1.73 m^2 per year decline in eGFR was associated with a risk for 1.11 higher odds of occurrence of subcortical infarct and a tendency toward a higher risk for cortical infarcts; there was a 2% higher progression of white matter hyperintensity (Table 3, model 1). These results did not substantially change after adjustment for cardiovascular risk factors (model 2). The magnitude of the associations in progression of white matter lesions and infarcts was attenuated with the addition of baseline levels of eGFR and white matter lesions (Table 3, model 3). When eGFR decline was dichotomized, compared with participants without large eGFR decline, those with large eGFR decline had a significantly higher occurrence of subcortical infarcts and a higher percent of white matter hyperintensity volume progression (Table 3, model 1). Control for cardiovascular risk factors did not change these conclusions (model 2). Addition of baseline eGFR and MRI values (Table 3, model 3) attenuated the associations but did not substantially change the conclusions. There was no association between eGFR decline and occurrence of cortical infarcts or microbleeds. Removal of persons with prevalent dementia and stroke and adjustment for C-reactive protein did not change the associations (data not shown).

Individuals who developed incident albuminuria had 21% significantly higher white matter hyperintensity volume progression compared with other participants (Table 3, model 1). Incident albuminuria was also associated with a higher occurrence of microbleeds (odds ratio [OR] 1.42, 95% confidence interval [CI] 1.02, 1.96), which was mainly driven by deeply located microbleeds (OR 1.96, 95% CI 1.24, 3.09) (Supplementary Table S1). There

was no association between incident albuminuria and occurrence of new cortical infarcts (Table 3, model 1). Adjusting for baseline ACR and MRI values did not change the association with white matter hyperintensity progression but attenuated the associations with infarcts and microbleeds (Table 3, model 3). Excluding participants with prevalent dementia or clinical stroke in the sensitivity analyses attenuated the associations minimally but did not change the findings (data not shown). Similarly, adjusting for C-reactive protein did not change our findings (data not shown).

Stratified analyses by baseline blood pressure

In the stratified analyses we observed that participants with higher systolic and diastolic blood pressure had higher occurrence of new MRI-detected infarcts per units of eGFR decline (*P* for interaction for decline in eGFR × systolic or diastolic blood pressure: 0.001 and 0.009, respectively) (Figure 1; Supplementary Table S2). There was no interaction between blood pressure levels and incident albuminuria in relation to subclinical brain pathology (data not shown).

DISCUSSION

In this population-based study, we observed that participants with larger eGFR decline have a higher occurrence of new MRI-detected infarcts, in particular subcortical infarcts, and greater progression of white matter hyperintensity volumes. Participants who developed incident albuminuria had greater white matter hyperintensity volume progression and higher occurrence of deeply located microbleeds. There was no association between kidney measures and occurrence of cortical infarcts. Participants with higher baseline blood pressure had higher occurrence of new MRI-detected infarcts related to eGFR decline.

We observed that larger decline in eGFR is associated with subcortical infarcts and not with cortical infarcts. Cortical infarcts are usually the result of an embolus from the heart or large arteries (i.e., the aortic arch or carotid artery), whereas subcortical infarcts are caused by blockage of small penetrating arteries, and thus they are categorized as manifestations of cerebral small vessel diseases.[14] This is in line with the literature considering brain–kidney interactions to be based on small vessel disease in both organs.[15] In the present study we showed that larger decline in eGFR was associated with greater progression in white matter hyperintensity volume. Similar to subcortical infarcts, white matter lesions are also regarded as manifestations of cerebral small vessel disease.[15] We did not find a link between decline in eGFR and microbleeds; however, the incidence of albuminuria was associated with the development of deeply located microbleeds, which is in line with the existing literature.[7,9,16] GFR and albuminuria are different measures of glomerular function, and abnormalities associate differently with the ischemic and hemorrhagic subtypes of brain pathology.[7] Previous reports hypothesized that albuminuria is an early sign of vascular damage in strain vessels, such as perforating and juxtame-dullary afferent arterioles. Perforating arterioles in the brain have a similar structure, which might explain the association between albuminuria and development of microbleeds located in the deep regions of the brain.[17]

Kidney and brain share hemodynamic and anatomic features.[2,18] Both organs' vascular beds are exposed to a high blood flow through each cardiac cycle. Such a high-volume blood flow

renders both the kidney and brain susceptible to vascular abnormalities.[18] Shared vascular risk factors, in particular high arterial blood pressure, can lead to simultaneous damage to the vascular beds and endothelium of both organs.[12] Endothelial damage in the kidney can manifest as decline in glomerular filtration rate and in the brain as defects in blood–brain barrier integrity and development of cerebral infarcts, microbleeds, and white matter changes.[12] Furthermore, the kidney is a key organ in blood pressure regulation, and thus high arterial blood pressure can act as a risk modifier and moderate the association between abnormalities in kidney measures and adverse brain outcomes. In this study, adjusting for blood pressure did not change the findings regarding the association between eGFR decline and risk of MRI-detected infarcts, but the association was stronger in participants with higher baseline blood pressure, suggesting that high blood pressure could accentuate the link between GFR decline and brain damage. Nevertheless, it is not clear whether the concurrent action of high blood pressure and GFR decline leads to the brain lesions of presumed vascular origin or one follows the other. Longitudinal studies with multiple time points are needed to further investigate the role of hypertension in the link between kidney measures and brain lesions of presumed vascular origin. In particular, studies directed toward finding additional markers that could be an indicator of concurrent damage would be of value. In this study, we showed that changes in kidney measures are associated with structural changes in the brain. Future studies are needed to address whether decline in kidney function is also related to alterations in brain function.

Another underlying mechanism that has been proposed to explain the observed associations is the direct effect of kidney disease. Kidney disease, even in earlier stages, is associated with increases in inflammation, high oxidative stress, and homocysteinaemia.[8,12,13] Thus, abnormalities in kidney measures can be associated with a proinflammatory state, which may accelerate microvascular damage by endothelial dysfunction and atherosclerosis.[19] Furthermore, it has been shown that high levels of systemic inflammation result in blood–brain barrier dysfunction and microglial activation with subsequent neuronal injuries.[20] Uremia-induced oxidative stress can result in higher nitric oxide synthesis and peroxynitrite and protein nitration formation and contribute to both biochemical and structural cerebral changes.[13] All these factors have been implicated in the development and progression of brain disorders such as stroke and dementia.[2,13] In our study, adjusting the analyses for C-reactive protein, a nonspecific marker of inflammation, did not change our finding. Future studies are required to address the mechanisms behind the association between changes in kidney measures and brain pathology.

Previous studies showed that abnormalities in kidney measures that are not sufficient for the diagnosis of CKD are related to considerably higher risk of cardiovascular disorders and mortality.[21,22] Changes in kidney measures may reflect a longer-term impact compared with a single measurement. In this study, change in kidney measures was associated with a wider range of brain pathology compared with baseline kidney measures. However, given that in our study changes in kidney measures and occurrence of brain pathology happened in the same time interval, it is not possible to assign a given time point within this interval.

Strengths of our study include the relatively large sample size, long follow-up time, and repeated assessment of brain MRI. In addition, extensive phenotyping regarding

cardiovascular risk factors enabled us to correct for several potential confounders. We also acknowledge the limitations of our study. We used eGFR-based creatinine measurements; however, changes in creatinine may be due to GFR as well as non-GFR determinants, such as loss of muscle mass. In particular, participants who are older and/or sicker may have lost muscle mass, leading to overestimates of GFR and underestimates of eGFR decline. This would have biased our results toward the null.[23] Second, our study population consists of Caucasians with relatively high eGFR values and no albuminuria at baseline. Therefore, our finding might not be generalizable to other populations, such as other ethnicities and patient populations. Another factor that should be taken into account when interpreting the data is that 2053 participants (n = 1039 due to death, including 538 due to cardiovascular causes) were not included in this follow-up analysis. Individuals who participated only at baseline compared with those who participated in both examinations had lower baseline eGFR and more cardiovascular risk factors. Individuals with lower eGFR and more cardiovascular risk factors tend to decline more in eGFR; therefore, we may have underestimated the associations of interest. Finally, results of the analyses using eGFR decline may have been affected by regression to the mean. Regression to the mean may result in an underestimation of the association.

In conclusion, we showed that changes in kidney measures over time are associated with risk of subclinical brain pathology in an elderly population. Our findings indicate that subjects who experience larger change in kidney measures can be regarded as a high-risk population for brain pathologic changes and may need additional intervention to mitigate the burden of brain pathology.

METHOD

Participants

This study was performed in the framework of the Age, Gene/Environment Susceptibility (AGES)-Reykjavik Study, which originates from the Reykjavik Study, as described fully elsewhere.[24] In summary, 5764 individuals (born January 1, 1907 to December 31, 1935) participated in the baseline examinations of the AGES-Reykjavik Study (2002–2006). Follow-up examinations of 3316 individual were conducted from April 1, 2007 through September 30, 2011. The mean ± SD time elapsed between the baseline and follow-up examination was 5.2 ± 0.2 years.

The study was approved by the Icelandic National Bioethics Committee (VSN 00-063) and the intramural institutional review board of the National Institute on Aging, National Institutes of Health, USA. All participants gave written informed consent.

Kidney measures

Serum creatinine was measured both at baseline and follow-up examinations. Baseline measurements were done using the Jaffe method and follow-up measurements using the Roche Hitachi P-Module instrument with the Roche Creatinine Plus assay (Roche Diagnostics, Mannheim, Germany) (coefficient of variation was 2.3% for creatinine assay).[24] To calibrate the baseline creatinine values to the enzymatic method, we remeasured 180

baseline samples with the enzymatic method and compared them using a weighted Deming regression model. We then calibrated baseline creatinine values to follow-up measurements on the basis of the following correction values: creatinine at follow-up (mg/dl) = creatinine at baseline/0.947 – 0.209. eGFR was estimated according to the Chronic Kidney Disease Epidemiology Collaboration equation.[25] To calculate the annual eGFR decline, we first subtracted the eGFR estimates of the follow-up examination from the eGFR estimates at baseline and then divided by the time between the 2 visits. We defined large eGFR decline as >3 ml/min per 1.73 m^2/year.[26] Urine albumin and creatinine were measured from first morning urine samples. Urine albumin was measured on a fresh sample on a Hitachi 912 using the Tina-quant immunoturbimetric assay (intra-assay CV 7.2%) (Roche Diagnostics, Mannheim, Germany). ACR (milligrams per gram) was estimated by dividing albumin by creatinine. Because urine ACR values were not normally distributed, we used log base 2 transformed values to obtain values per 2-fold higher urine ACR. We added 1 to all the untransformed values to account for those who did not have albuminuria (n = 177). Incident albuminuria was defined as urine ACR >30 mg/g at follow-up among individuals with urine ACR <30 mg/g at baseline.[27]

MRI-detected infarcts, cerebral microbleeds, and white matter hyperintensity

High-resolution MRI of the brain using a study-dedicated 1.5-T scanner (Signa Twinspeed; General Electric Medical Systems, Waukesha, WI) was performed, at baseline and follow-up, with a similar MRI protocol described elsewhere.[28] Briefly, we used the T1-weighted 3-dimensional spoiled-gradient recalled echo (for brain volumes), proton density/T2-weighted fast spin-echo, fluid-attenuated inversion recovery (for vascular changes), and T2*-weighted gradient-echo type echo sequences (for microbleeds). All images were acquired to give full brain coverage with slices angled parallel to the anterior commissure–posterior commissure line to yield reproducible image views in the oblique-axial plane.

We have previously described the radiologic features of the 4 lesions we investigated.[28–31] Briefly, white matter hyperintensity volume was quantified automatically by postprocessing pipelines.[30] Number of cortical infarct–like lesions and number and location of subcortical infarcts were assessed using standardized radiologic features.[31] Cerebral microbleeds were defined as focal areas of signal void within the brain parenchyma visible on T2*-weighted gradient-echo type echo planar scans.[29] Cerebral microbleeds, also visually assessed by number and location, were categorized as lobar (frontal, parietal, temporal, and occipital) and deep or infratentorial (basal ganglia and thalamus, corpus callosum, and infratentorium, including the brainstem and cerebellum) regions. Deeply located cerebral microbleeds are thought to be largely reflective of hypertensive damage to the microvessels in this area. As a measure of head size, intracranial volume was estimated by summing grey and white matter and cerebrospinal fluid volumes.[28] Information on reproducibility of the process, including the image acquisition and the automatic pipeline, is provided in detail elsewhere.[28] In brief, reproducibility was performed in 32 subjects, yielding in interclass correlations of >0.98.[28]

New lesions were defined as appearance of MRI-detected infarcts or microbleeds in the follow-up scans that were not present in the baseline images.[29] White matter hyperintensity volume progression was defined as percentage change in the volume of white matter

hyperintensity between 2 visits (white matter hyperintensity at follow-up minus white matter hyperintensity volume at baseline, divided by the white matter hyperintensity volume at baseline, multiplied by 100).

Other covariates

On the basis of previous studies, we included covariates measured at baseline examination to control for confounding.[4,6–8] Body mass index was calculated as weight in kilograms divided by height in meters squared. Blood pressure was measured twice in a supine position using a wall model mercury sphygmomanometer (Erkameter, Erka, Copiague, NY) after a 5-minute rest. Hypertension was defined as systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg or by the use of antihypertensive medications. Total cholesterol and high-density lipoprotein cholesterol were determined on a chemistry analyzer using comparable enzymatic procedures (Hitachi 912; Roche Diagnostics). Diabetes was defined as fasting glucose level >126 mg/dl, random glucose level >200 mg/dl, or self-reports of having a diagnosis of diabetes or maintaining a diabetic diet or medication use. Smoking was categorized as current, never, and former smoker. History of cardiovascular disease was defined as baseline coronary heart disease or stroke according to adjudicated Icelandic Heart Association registry or hospital records. Diagnosis of dementia (all subtypes) was made according to *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition criteria by a panel that included a geriatrician, a neurologist, a neuropsychologist, and a neuroradiologist.

Analytical sample

Among 3316 individuals who had a second examination, brain MRI data were missing for 272 participants owing to contraindications, 337 owing to refusal or nonattendance, and for 35 individuals because of technical reasons. This resulted in 2672 people with complete baseline and follow-up MRI data. We further excluded 1 participant without follow-up creatinine values, which resulted in 2671 participants for analyses of baseline and decline in eGFR. Among them, 2656 participants with ACR at baseline were included for analyses of baseline ACR. In incident albuminuria analyses, we further excluded participants with ACR >30 mg/g at baseline, which resulted in 2459 participants (Supplementary Figure S1). Participants included in this study, as compared with the original population, were younger and had higher eGFR and lower ACR levels and better profiles of cardiovascular risk factors and diseases, but they did not differ in terms of mean systolic and diastolic blood pressure levels (Supplementary Table S3).

Statistical analysis

Associations of baseline and change in kidney measures markers (eGFR or ACR) with MRI-detected infarcts and microbleeds were assessed using logistic regression models. We used multinomial logistic regression to study the association between change in kidney measures and different types of microbleeds (lobar and deeply located). Associations of baseline and change in kidney measure markers with white matter hyperintensity volume progression were assessed using linear regression models.

We examined 3 models. In the first model we adjusted the analyses for age and sex. In the second model we additionally adjusted for baseline cardiovascular risk factors (systolic and

diastolic blood pressure, body mass index, smoking, history of cardiovascular disease, history of diabetes mellitus, history of hypertension, and total cholesterol) and intracranial volume. In the third model we additionally adjusted for baseline kidney measures and subclinical brain pathology to take into account the baseline differences between the participants. In sensitivity analyses we repeated the model 1 analyses, excluding participants with history of stroke (n = 75) or dementia (n = 37). Additionally, to explore whether inflammation has a role in the association between kidney measures and subclinical brain pathologies, we adjusted all analyses for C-reactive protein, a nonspecific marker of inflammation.

Because elevated blood pressure is a known risk factor for cerebrovascular pathology and a major component of CKD,[18,32] we investigated whether the associations between decline in eGFR or incident albuminuria and the outcomes differ according to baseline blood pressure. To test for interaction we included the cross-product of systolic or diastolic blood pressure and eGFR decline or incident albuminuria. To better understand the interaction, we also stratified analyses by studying the association between change in kidney measures and brain outcomes (with statistically significant interactions, $P < 0.10$) at different levels of blood pressure (systolic blood pressure: <120, 120–140, 140–160, >160 mm Hg; diastolic blood pressure: <80, 80–90, >90 mm Hg).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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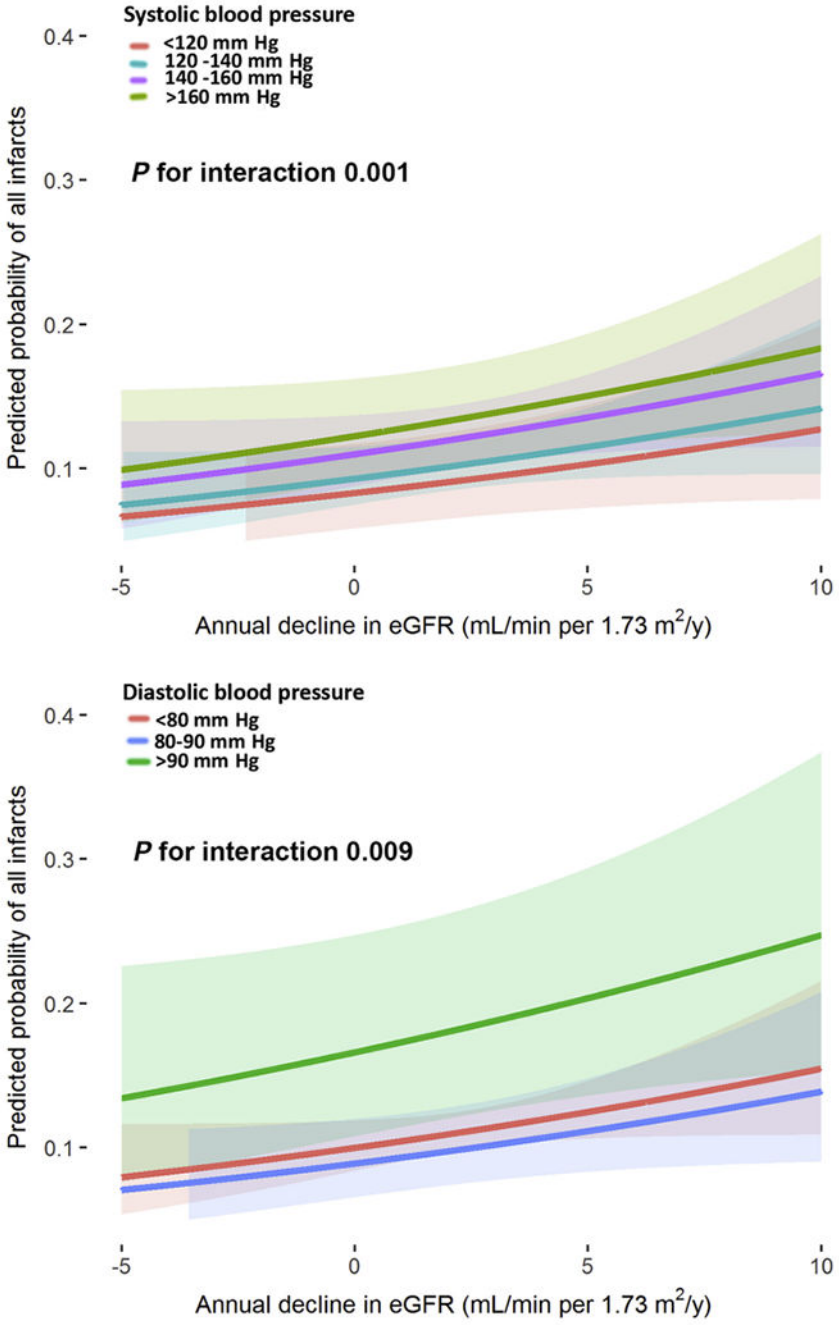

Figure 1 |.

Predicted probability of all magnetic resonance imaging–detected infarcts in different categories of systolic and diastolic blood pressure across annual estimated glomerular filtration rate (eGFR) decline in Age, Gene/Environment Susceptibility–Reykjavik Study participants.

Table 1 |

Baseline characteristics of the AGES-Reykjavik Study participants according to eGFR decline and incident albuminuria during follow-up

	Decline in eGFR			Incident albuminuria		
Characteristic	**Total population (n = 2671)**	**<3 ml/min per 1.73 m^2 per year (n = 1679)**	**>3 ml/min per 1.73 m^2 per year (n = 992)**	**Total population (n = 2459)**	**No (n = 2231)**	**Yes (n = 228)**
Age, yr	74.7 (4.8)	74.6 (4.9)	74.8 (4.6)	74.6 (4.8)	74.4 (4.6)	77.0 (5.5)
Women	1568 (58.7)	955 (56.8)	613 (61.7)	1477 (60.1)	1362 (61.0)	115 (50.4)
eGFR, ml/min per 1.73 m^2	77.60 (15.5)	74.8 (16.3)	82.2 (12.9)	78.1 (15.3)	78.7 (14.7)	72.6 (19.1)
Urine ACR, median (range), mg/g	2.3 (1.1–5.1)	2.1 (1.0–4.6)	2.6 (1.3–5.8)	2.1 (1.1–4.2)	1.9 (1.0–3.8)	5.6 (2.6–13.1)
Body mass index	27.2 (4.1)	27.2 (4.0)	27.3 (4.3)	27.2 (4.1)	27.2 (4.1)	27.2 (4.2)
Systolic blood pressure, mm Hg	141.1 (19.8)	139.8 (19.1)	143.5 (20.7)	140.7 (19.7)	140.4 (19.5)	144.2 (21.7)
Diastolic blood pressure, mm Hg	74.1 (9.3)	74.1 (9.0)	74.2 (9.9)	74.0 (9.3)	73.9 (9.3)	74.4 (9.3)
Total cholesterol, mg/dl	218.4 (43.7)	219.9 (44.0)	216.2 (43.3)	218.8 (43.5)	219.5 (43.4)	212.3 (43.6)
HDL cholesterol, mg/dl	61.6 (16.8)	61.9 (17.1)	61.3 (16.4)	62.0 (16.9)	62.3 (16.9)	59.2 (16.7)
History of cardiovascular disorders	607 (22.7)	388 (23.3)	219 (22.2)	547 (22.5)	484 (21.7)	63 (27.6)
Smoking						
Current	286 (10.7)	180 (10.7)	106 (10.7)	260 (10.6)	226 (10.1)	34 (14.9)
Former	1214 (45.6)	746 (44.5)	468 (47.4)	1118 (45.5)	1016 (45.5)	102 (44.7)
Diabetes mellitus	251 (9.4)	138 (8.2)	113 (11.4)	205 (8.3)	167 (7.5)	38 (16.7)
Hypertension	2078 (77.8)	1285 (76.5)	793 (79.9)	1894 (77.0)	1692 (75.8)	202 (88.6)
Subcortical infarcts	202 (7.6)	117 (6.9)	85 (8.5)	175 (7.1)	149 (6.7)	26 (11.4)
Cortical infarcts	300 (11.2)	186 (11.0)	114 (11.5)	264 (10.7)	239 (10.7)	25 (11.0)
Microbleeds	456 (17.1)	297 (17.7)	159 (16.0)	413 (16.8)	360 (16.1)	53 (23.2)
White matter hyperintensity, median (range)	11.6 (6.6–21.8)	11.8 (6.7–21.9)	11.3 (6.4–21.9)	11.3 (6.4–20.9)	11.2 (6.3–20.5)	14.8 (7.4–26.4)

AGES, Age, Gene/Environment Susceptibility; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein.

Continuous variables are presented as mean (SD) and categorical variables as number (%). The following variables had missing values: body mass index (n = 1), smoking (n = 8), and cardiovascular disorders (n = 26).

Table 2 |

Association of baseline kidney measures with incident MRI-detected infarcts, microbleeds and white matter hyperintensity volume progression in AGES-Reykjavik Study participants

Regression models	Infarcts,[a] OR (95% CI)	Subcortical infarcts, OR (95% CI)	Cortical infarcts, OR (95% CI)	Microbleeds, OR (95% CI)	White matter hyperintensity, percentage difference (95% CI)
Baseline eGFR, per SD	n/case = 2671/303	n/case = 2671/119	n/case = 2671/210	n/case = 2671/495	n = 2606
Model 1	1.02 (0.90, 1.16)	1.16 (0.95, 1.42)	0.96 (0.83, 1.12)	0.98 (0.89, 1.09)	**5.49 (3.36, 7.62)**
Model 2	1.04 (0.91, 1.19)	1.14 (0.93, 1.42)	1.01 (0.86, 1.18)	0.97 (0.87, 1.08)	**5.32 (3.14, 7.52)**
Baseline ACR, 2-fold higher	n/case = 2656/300	n/case = 2656/119	n/case = 2656/207	n/case = 2656/491	n = 2597
Model 1	**1.08 (1.01, 1.16)**	**1.18 (1.07, 1.29)**	1.01 (0.93, 1.10)	**1.06 (1.01, 1.13)**	0.59 (−0.75, 1.94)
Model 2	1.06 (0.98, 1.14)	**1.14 (1.03, 1.27)**	1.01 (0.92, 1.10)	1.06 (0.99, 1.12)	0.75 (−0.63, 2.12)

ACR, albumin-to-creatinine ratio; AGES, Age, Gene/Environment Susceptibility; CI, confidence interval; MRI, magnetic resonance imaging; OR, odds ratio.

Model 1: Adjusted for age, and sex. Model 2: Additionally adjusted for intracranial volume, systolic and diastolic blood pressure, body mass index, smoking, history of cardiovascular disease, history of diabetes mellitus, history of hypertension, and total cholesterol. Each SD eGFR is 15.5 ml/min per 1.73 m^2 per year. Bold indicates $P < 0.05$.

[a]Combination of cortical and subcortical infarcts.

Table 3 |

Association of change in kidney measures with incident MRI-detected infarcts, microbleeds and with progression of white matter hyperintensity volume in AGES-Reykjavik Study participants

Regression models	Infarcts,[a] OR (95% CI)	Subcortical infarcts, OR (95% CI)	Cortical infarcts, OR (95% CI)	Microbleeds, OR (95% CI)	White matter hyperintensity, Percentage difference (95% CI)
eGFR decline	n/case = 2671/303	n/case = 2671/119	n/case = 2671/210	n/case = 2671/495	n = 2606
Model 1					
Decline in eGFR, ml/min per 1.73 m^2 per year	**1.06 (1.01,1.12)**	**1.11 (1.02,1.20**)	1.05 (0.99,1.12)	0.98 (0.94,1.02)	**1.79 (0.89, 2.69)**
Large eGFR decline >3 ml/min per 1.73 m^2 per year	1.17 (0.91,1.49)	**1.53 (1.05,2.22)**	1.11 (0.82,1.49)	0.96 (0.78,1.18)	**8.31 (4.04, 12.57)**
Model 2					
Decline in eGFR, ml/min per 1.73 m^2 per year	**1.06 (1.00,1.12)**	**1.09 (1.00,1.18)**	**1.06 (1.00,1.13)**	0.97 (0.93,1.01)	**1.89 (0.79, 2.81)**
Large eGFR decline >3 ml/min per 1.73 m^2 per year	1.15 (0.88,1.48)	**1.47 (1.00,2.16)**	1.11 (0.82,1.50)	0.93 (0.75,1.15)	**8.64 (4.32, 12.97)**
Model 3					
Decline in eGFR, ml/min per 1.73 m^2 per year	**1.05 (1.00, 1.11)**	1.07 (0.97, 1.17)	1.06 (0.99, 1.14)	.097 (0.93, 1.02)	**1.29 (0.32, 2.27)**
Large eGFR decline >3 ml/min per 1.73 m^2 per year	1.08 (0.0.82, 1.41)	1.34 (0.89, 2.01)	1.07 (0.77, 1.46)	0.95 (0.77, 1.19)	**6.59 (2.15, 11.04)**
Albuminuria	n/case = 2459/266	n/case = 2459/104	n/case = 2459/186	n/case = 2459/444	n = 2409
Model 1					
Incident albuminuria (>30 mg/g)	0.88 (0.57, 1.35)	1.35 (0.74, 2.44)	0.74 (0.43, 1.24)	**1.42 (1.02, 1.96)**	**21.78 (14.25, 29.32)**
Model 2					
Incident albuminuria (>30 mg/g)	0.90 (0.58, 1.40)	1.34 (0.73, 2.46)	0.75 (0.44, 1.28)	1.34 (0.96, 1.88)	**21.06 (13.41, 28.72)**
Model 3					
Incident albuminuria (>30 mg/g)	0.80 (0.49, 1.29)	1.01 (0.52, 1.98)	0.72 (0.40, 1.29)	1.27 (0.88, 1.81)	**22.28 (14.27, 30.29)**

ACR, albumin-to-creatinine ratio; AGES, Age, Gene/Environment Susceptibility; CI, confidence interval; MRI, magnetic resonance imaging; OR, odds ratio.

Model 1: Adjusted for age, and sex. Model 2: Additionally adjusted for intracranial volume, systolic and diastolic blood pressure, body mass index, smoking, history of cardiovascular disease, history of diabetes mellitus, history of hypertension, and total cholesterol. Model 3: Additionally adjusted for baseline kidney measures (eGFR for eGFR decline or baseline ACR for incident albuminuria) and corresponding baseline subclinical brain pathology. Bold indicates $P < 0.05$.

[a]Combination of cortical and subcortical infarct.