Aortic Stiffness and its Relationship to Kidney Disease, Brain Structure, and Cognition

A thesis

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Abstract

Among the aging population, chronic kidney disease and cognitive impairment are highly prevalent and account for a significant portion of medical problems and health care costs. Unfortunately, the disease mechanisms are not well understood. Aortic stiffness increases with age and results in transmittance of increased pressures to the microvasculature of both organs. Aortic stiffness has been linked to both diseases, but prior studies have shown mixed results or were performed in select populations. We hypothesized that higher aortic stiffness would be associated with lower kidney function, lower kidney function would be associated with changes in brain structure and impaired cognition, and these latter associations would be attenuated by adjustment for aortic stiffness. We conducted a cross sectional study utilizing data from a subset of the Age, Gene/Environment, Susceptibility-Reykjavik Study, a large community-based prospective cohort study of cardiovascular disease in Iceland. We used linear or logistic regression as appropriate to assess the associations between aortic stiffness [carotid femoral pulse wave velocity (CFPWV) and carotid pulse pressure (CPP)] and kidney function and damage [estimated glomerular filtration rate (eGFR) and urine albumin to creatinine ratio (ACR)] as well as eGFR and ACR and brain structure and cognition. Sequential sets of multivariable models were performed adjusting for demographics and cardiovascular risk factors. We included 940 patients (mean age 75.8 years, mean eGFR 68 ml/min/1.73m^2, median UACR 3 mg/g). Age was strongly related to eGFR, ACR, CFPWV, and CPP. Although CFPWV was associated with eGFR [β (SE)=0.08 (0.02), p-value<0.001] and ACR [β (SE)=-0.009 (0.002), p-value<0.001], the association was

attenuated after adjusting for age and blood pressure. In those patients with CPP greater than 80 mmHg, CPP was associated with eGFR [β (SE)=-0.22 (0.09), p-value=0.011], but the relationship became nonsignificant after adjustment for cardiovascular disease risk factors. CPP was significantly related to ACR in fully adjusted models [β (SE)=0.006 (0.003), p-value=0.013]. ACR was significantly associated with all measures of brain structure; effect was minimally attenuated after adjustment for aortic stiffness. In summary, aortic stiffness was not strongly related to eGFR but higher CPP was related to albuminuria. Albuminuria was more strongly associated than eGFR with brain structure but neither were related to cognition. There was no consistent change in effect size after adjustment for aortic stiffness. Adjustment for age attenuated all relationships.

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List of Abbreviations

CKD: Chronic kidney disease

AGES-RS: Age, Gene, Environment, Susceptibility-Reykjavik Study

CFPWV: Carotid femoral pulse wave velocity

iCFPWV: Inverse carotid femoral pulse wave velocity

CPP: Carotid pulse pressure

GFR: Glomerular filtration rate

eGFR: Estimated glomerular filtration rate

ACR: Urine albumin to creatinine ratio

WMH: White matter hyperintensity

Introduction

Chronic kidney disease (CKD) and neurocognitive impairment, manifested by changes in structure and function of the kidney and brain, both account for a significant portion of the medical problems and health care costs in the growing older population of the United States (1-8). Despite the high prevalence of both of these diseases, the causes are not clearly understood, and there are limited therapies for treatment or prevention.

The high prevalence of both CKD and neurocognitive impairment suggests a common underlying cause or that complications of CKD may cause neurocognitive impairment. Vascular disease is often hypothesized as a cause of both conditions because they are both associated with its risk factors and the kidney and brain have similar vascular properties (1, 9-12). There are significant age-related changes in kidney structure and function, which may be partly related to vascular disease (13-16). Aortic stiffness, a structural and functional change in the central vasculature, has been shown to increase with age and results in transmittance of increased pressures and flow to the peripheral microvasculature (17-20). The kidney and brain are high flow and low impedance organs, making them particularly vulnerable to hemodynamic changes in the central vasculature (21). Increased aortic stiffness was associated with changes in brain structure, subclinical infarcts, and cognitive scores in the Age, Gene/Environment, Susceptibility Reykjavik Study (AGES-RS) (22). Aortic stiffness may offer a possible explanation of the pathophysiology of kidney disease and cognitive impairment in older populations and a potential target for interventions.

Increased aortic stiffness has been associated with kidney impairment and progression of chronic kidney disease in prior studies. However, these studies have been carried out in relatively small and highly selected patient populations, are not representative of the general elderly population, or did not use state of the art measures of aortic stiffness and kidney function (23-37). CKD has been associated with changes in brain structure and cognitive function (38-48). However, various measures of brain structure and cognition have been used and the role of aortic stiffness in this relationship has not been explored.

The Age, Gene/Environment, Susceptibility-Reykjavik Study (AGES-RS) is a population-based prospective cohort study in Iceland initially designed to explore cardiovascular disease risk factors. We utilized a subset of the AGES-RS Study that included a large sample of older adults. Our first objective was to examine the associations between kidney function and aortic stiffness. We hypothesized that increased aortic stiffness would be associated with measures of kidney disease. Our second objective was to determine the strength of the associations between kidney disease and neurocognitive function and brain structure as well as examine the effect of aortic stiffness on those relationships. We hypothesized kidney disease would be associated with abnormal brain structure and cognitive function.

Methods

Study Population

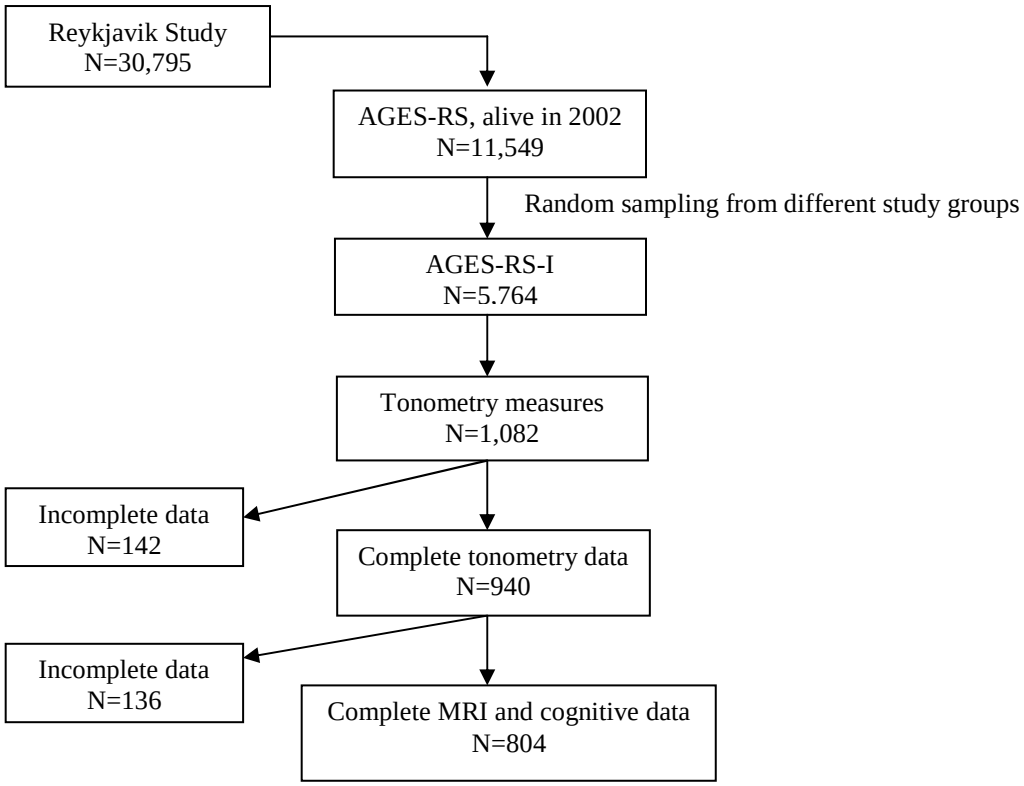
We utilized data from a substudy of the Age, Gene/Environment, Susceptibility-Reykjavik Study (AGES-RS). Details of study population are provided elsewhere (49).

The Reykjavik Study was started in 1967 as a population-based prospective cohort study to examine cardiovascular risk factors and outcomes. People born between 1907-1935 and living in Reykjavik in 1967 were eligible for inclusion in the Reykjavik Study and a random sampling of the population yielded 30,795 participants. The AGES-RS began in 2002 as a follow-up to the Reykjavik Study to examine risk factors, genetic components, and gene-environment interactions for disease in older adults. The 5,764 participants in AGES-RS were randomly selected from the 11,549 survivors from the original Reykjavik Study participants. Aortic tonometry was added to the study protocol for all patients who presented for examination during a specified time period. Of the participants in AGES-RS, 1,082 had aortic tonometry performed and were eligible for this study. Of those with tonometry performed, 940 had complete tonometry data obtained and were included in analyses of aortic stiffness and kidney disease. Of those with complete tonometry, 804 had complete cognitive testing and MRI data obtained and were included in analyses of kidney disease and brain disease (Figure 1).

Study Design

For our first aim, we conducted a cross-sectional study at the AGES-RS-I visit in 2002 utilizing the data from the study population as described above with aortic measures as the independent variable and the kidney measures as the dependent variable. For our second aim, we conducted a cross-sectional study at the AGES-RS-I visit in 2002 with kidney function and damage as the independent variables and the brain structure and cognitive measures as the dependent variables.

Figure 1. Flowchart of participants of the AGES-RS Study



Aortic Stiffness Measures

Aortic tonometry was performed with a standardized protocol is described in detail elsewhere (17, 50-52). Aortic tonometry with electrocardiogram was obtained from the brachial, radial, femoral, and carotid arteries using a custom transducer (Cardiovascular Engineering, Inc.). Images and flows were assessed with an Acuson Sequoia ultrasound system using a duplex linear array probe with an 8.0 MHz imaging frequency and a 4.0 MHz Doppler carrier frequency. Transit distances were assessed by body surface measurements from the suprasternal notch to each pulse-recording site. Carotid-femoral pulse wave velocity (CFPWV) and carotid pulse pressure (CPP) were used as the primary metrics because they are the most robust and reproducible measurements and have been associated with increased risk of cardiovascular events (50, 53-56).

Kidney Measures

Glomerular filtration rate (GFR) is accepted as a general measure of kidney function. Estimated GFR (eGFR) was calculated with the CKD-EPI 2012 equation based on the combination of creatinine and cystatin C (57). We used the equation based on both markers rather than equations based on creatinine or cystatin C alone because the combination has been shown to provide a more accurate and precise estimate (57-60). Serum creatinine assays were performed at Icelandic Heart Association using the Roche-Hitachi P-module instrument with Creatininase Plus assay (CV 2.3%) and calibrated to isotope dilution mass spectrometry reference materials at the University of Minnesota. Serum cystatin C assays were performed at University of Minnesota using a particle-

enhanced immune-nephelometric assay (PENIA) assay (CV 2.7%) and standardized to International Federation for Clinical Chemists reference materials (61).

Albuminuria is considered a measure of kidney damage, more specific for glomerular damage, which may occur before the decline in GFR. Albuminuria was assessed from a spot urine albumin to creatinine ratio (ACR) (62-63). Urine albumin and creatinine assays were performed at Icelandic Heart Association using Tina-quant immunoturbimetric assay and HiCo Creatinine Jaffe method assay, respectively (CVs 7.2% and 4.2 %, respectively), and calibrated to reference materials at the University of Minnesota.

CKD was defined as eGFR < 60 ml/min/1.73 m^2 or ACR > 30 mg/g. GFR < 30 ml/min/1.73 m^2 and ACR >300 mg/g are considered severe abnormalities.

Brain Structure Measures

High-resolution brain MRIs were obtained with four sequences (FLAIR, T1-, PD-, and T2-weighted) using a well established protocol (49). Total brain, white and grey matter, and white matter hyperintensity volumes were computed automatically with an algorithm based on the Montreal Neurological Institute pipeline (64). White matter hyperintensity (WMH) volume was used as the primary metric of brain volume because it is a marker of microvascular disease, which has been more closely related to aortic stiffness. Infarcts were defined as a brain parenchyma defect with signal intensity equal to cerebrospinal fluid (65). Cortical infarcts were defined as parenchymal defects greater than 4 mm

involving or limited to the cortical ribbon and surrounded by an area of high signal intensity on FLAIR images. Subcortical infarcts were defined as lesions in the subcortical area greater than 4 mm in the subcortical area with a rim of high signal intensity on FLAIR (22). Subcortical infarcts were used as the primary metric because they are a marker of microvascular disease.

Cognition Measures

Dementia assessment was done in all participants with a Mini-Mental State Examination and the Digit Symbol Substitution Test (66-67). If participants screened positive on these tests, a diagnosis of dementia was confirmed with a second battery of tests and a consensus diagnosis by a panel of experts. Depression was screened with an initial geriatric depression scale at the first visit and participants with positive screens were given a Mini-International Neuropsychiatric Interview (68). All participants were then given a battery of 9 neurocognitive tests. Raw scores on the different components of neurocognitive tests were converted to composite scores for executive function, memory, and speed with mean equal to zero and standard deviation equal to 1. The composite scores have been previously evaluated by confirmatory factor analysis and found to be a good fit (69). The composite score for executive function included the following tests: Digits Backward, the Cambridge Neuropsychological Test Automated Battery Spatial Working Memory Test, and the Stroop Test, Part II (word-color interference) (66-67, 70). The composite score for memory included the following tests: California Verbal Learning Test immediate and delayed recall (71-72). The composite score for speed included the following tests: Digit Symbol Substitution Test, Figure Comparison and the

Stroop Test, Parts I (word naming) and II (color naming) (67, 70, 73). Executive function was used as the primary metric because it is thought to be a reflection of microvascular disease.

Statistical Analysis

Data was summarized with descriptive statistics including means, standard deviations, ranges, p-values, and 95% confidence intervals. Albuminuria was described with median and interquartile ranges. Due to skewed nature of the data, ACR and CFPWV were transformed using log and inverse methods, respectively. Natural logarithm of ACR and inverse CPWV (iCFPWV) were used in all analyses unless otherwise specified.

Scatter plots were used to assess crude associations. The association between aortic stiffness (CFPWV and CPP) and kidney measures (eGFR and ACR) was assessed using linear regression, with assessment for non-linear relationships. The associations between kidney measures (eGFR and ACR) and brain structure and cognition were assessed using linear regression, with assessment for non-linear relationships. The association between kidney measures and infarcts was assessed using logistic regression. Based on scatterplot data, the relationship between eGFR and CPP was found to be non-linear. A piecewise model with cut point of CPP of 80 mm Hg was found to be a better fit by ANOVA test when compared to linear or spline models and, therefore, was used for subsequent models for aim 1 (Table 1). CPP in all other relationships was linear and was analyzed as such. Bivariate models were performed and covariates with p-value of less than 0.2 were eligible for a multivariable model in addition to the covariates stated a priori. Sequential

Table 1. Comparison of model type for relationship of CPP and eGFR in full cohort

Model	β (SE)	p-value
Linear	-0.08 (0.02)	0.001
Spline:CPP*	0.17 (0.13)	0.193
Spline:CPP^2	-0.002 (0.001)	0.051
Piecewise: CPP≤80§	0.01 (0.04)	0.878
Piecewise: CPP>80	-0.22 (0.09)	0.011

*ANOVA and likelihood ratio tests for linear vs. spline models yielded p-value of 0.05.

§ANOVA and likelihood ratio tests for linear vs. piecewise models yielded a p-value of 0.01.

Abbreviations: CPP, carotid pulse pressure; eGFR, estimated glomerular filtration rate.

sets of multivariable models were created to explore the impact of demographic (age, sex, heart rate, height), cardiovascular disease risk factors (hemoglobin A1c, C-reactive protein, cholesterol, mean arterial blood pressure), and education on the associations. Heart rate and height are included in these models as they affect the measurement of CPP and CFPWV, respectively, with aortic tonometry (36). Various blood pressure measurements were explored, including systolic blood pressure (SBP), diastolic blood pressure (DBP), peripheral pulse pressure (PPP), and mean arterial pressure (MAP). MAP was used in the final models to reduce issues of colinearity. We then examined the effect on the associations of kidney measures and brain structure and cognition after the addition of measures of aortic stiffness to multivariable models. Both CFPWV and CPP were used in multivariable models as they capture different properties of aortic stiffness (53). We evaluated the impact of aortic stiffness with statistical significance of multivariable models, magnitude of the attenuation of the beta coefficient, and the change in R^2 of the multivariable models after inclusion of CPP and CFPWV. A p-value <0.05 was considered statistically significant. Statistical analyses were done in R version 2.15.1 (74).

Ethics

AGES-RS was approved by the National Bioethics Committee in Iceland, which acts as the institutional review board for the Icelandic Heart Association (approval number VSN-00-063), and by the National Institute on Aging Intramural Institutional Review Board. Our investigation of aortic stiffness, kidney function, and aging in the AGES-RS cohort

was approved by the Institutional Review Board of Tufts Medical Center (IRB # 9222). All participants gave written informed consent.

Results

Aim 1

Description of the population

Characteristics of the overall study population and by age are described in Table 2. This older population [mean (SD) age 75.8 (4.7) years, range 69-96 years] had a high prevalence of hypertension (57%) and diabetes (22%). At the time of visit, mean blood pressure was 139/67 mm Hg and mean HgbA1c was 5.6%. Mean (SD) eGFR was 68 (16) ml/min/1.73 m^2 and was lower in older participants. Median (IQR) ACR was 3 (2-6) mg/g and higher in older participants. 28.3% had eGFR < 60 ml/min/1.73 m^2, 8.0% had ACR > 30 mg/g, and 32.0% had CKD. Prevalence of CKD increased significantly in older age categories. Only 1.8% of participants had eGFR < 30 ml/min/1.73m2 and less than 1% had ACR > 300 mg/g.

Mean CFPWV was 12.9 m/s and mean CPP was 69 mmHg (Table 2, distributions shown in Figure 2). Both measures of arterial stiffness were higher in older participants (Table 2 and Figure 3, left panels). CPP was highly correlated with SBP and PPP (r=0.83 and r=0.93, respectively), but had a lower correlation with DBP and MAP (r=0.21 and r=0.36, respectively) (Table 3). CFPWV was more weakly correlated with peripheral blood pressure measurements, including SBP and MAP (r=0.40 and r=0.36, respectively). CFPWV and CPP were not strongly correlated with each other (r=0.29).

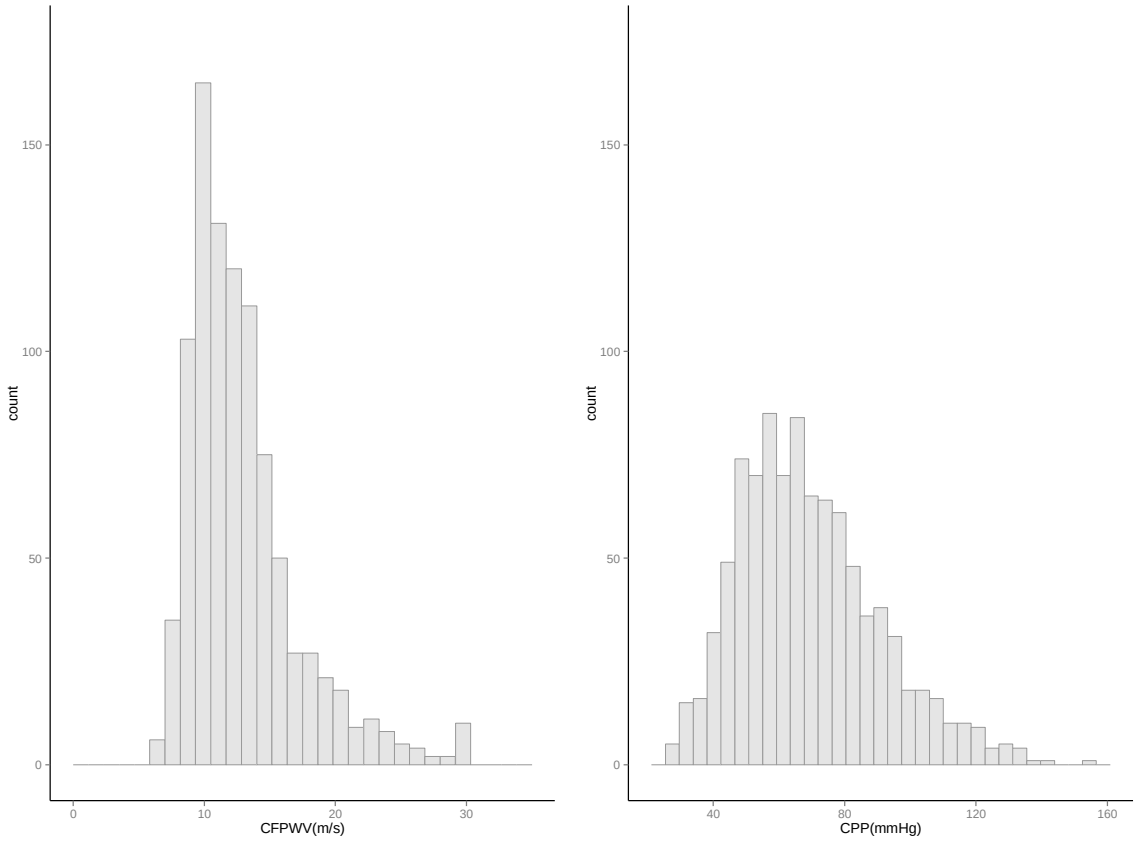
Table 2. Clinical characteristics by age

Age Range	Overall N=940	69-73 N=339	74-78 N=367	79-83 N=165	84-96 N=69	p-value for trend
Age (yrs)	75.8 (4.7)	71.4 (1.2)	75.7 (1.4)	80.5 (1.3)	86.9 (3.1)	<0.001
Male, N (%)	421 (44.8)	149(44)	164 (45)	74 (45)	34 (49)	0.511
Hypertension, N (%)	535 (57)	182 (54)	208 (57)	107 (65)	38 (55)	0.120
SBP (mmHg)	139 (19)	136 (18)	140 (19)	141 (21)	142 (23)	0.006
DBP (mm Hg)	67 (10)	68 (9)	67 (9)	66 (11)	62 (10)	<0.001
MAP (mm Hg)	94 (12)	94 (11)	95 (12)	94 (13)	91 (14)	0. 221
PPP (mm Hg)	72 (18)	68 (17)	74 (17)	75 (19)	80 (20)	<0.001
Diabetes, N (%)	203 (22)	76 22)	89 (24)	27 (16)	11 (16)	0.094
Hemoglobin A1c (%)	5.6 (0.50)	5.6 (0.5)	5.7 (0.5)	5.6 (0.4)	5.6 (0.4)	0.971
Hyperlipidemia, N (%)	246 (26)	76 (22)	117 (32)	42 (26)	11 (16)	0.834
Total cholesterol (mg/dL)	209 (43)	212 (42)	206 (44)	205 (42)	214 (49)	0.424
LDL (mg/dL)	126 (39)	128 (37)	123 (40)	123 (38)	132 (45)	0.680
HDL (mg/dL)	63 (17)	63 (18)	62 (16)	63 (17)	64 (17)	0.973
History of CAD, N (%)	177 (19)	50 (15)	77 (21)	36 (22)	14 (20)	0.057
Current smoker, N (%)	118 (13)	50 (15)	49 (13)	17 (10)	2 (3)	0.008
Height (cm)	168.0 (9.1)	169.6 (8.9)	168.2 (8.8)	166.1 (9.0)	163.7 (9.2)	<0.001
Weight (kg)	76.0 (13.9)	78.5 (13.9)	76.9 (13.6)	72.4 (13.0)	67.8 (12.5)	<0.001
Heart rate (bpm)	63 (11)	63 (10)	62 (11)	63 (11)	64 (12)	0.861
Hemoglobin (g/dL)	13.5 (1.2)	13.7 (1.1)	13.5 (1.2)	13.2 (1.3)	13.1 (1.0)	<0.001
CRP (mg/dL)	3.3 (5.7)	3.2 (4.7)	3.4 (6.8)	3.3 (4.9)	3.6 (5.9)	0.593
Serum albumin (g/dL)	4.1 (0.3)	4.1 (0.2)	4.1 (0.3)	4.0 (0.3)	4.0 (0.3)	<0.001
CFPWV (m/s)	12.9 (4.2)	11.5 (3.3)	13.0 (4.1)	14.3 (4.8)	15.1 (4.8)	<0.001
iCFPWV (ms/m)	84.4 (22.5)	92.6 (22.2)	82.7 (20.6)	76.7 (22.7)	71.7 (19.0)	<0.001
Carotid pulse pressure (mm Hg)	69 (21)	65 (19)	71 (20)	73 (24)	75 (23)	<0.001
CKD, N (%)	299 (32)	70 (21)	114 (31)	72 (44)	43 (64)	<0.001
Serum creatinine (mg/dL)	0.97 (0.36)	0.94 (0.28)	0.97 (0.34)	1.01 (0.34)	1.14 (0.66)	<0.001
Serum cystatin C (mg/L)	1.09 (0.33)	0.91 (0.20)	0.96 (0.26)	1.04 (0.30)	1.21 (0.58)	<0.001
eGFRcr-cys (ml/min/1.73 m^2)	68 (16)	73 (15)	69 (15)	63 (16)	57 (18)	<0.001
ACR (mg/g), median (IQR)	3 (2-6)	2 (2-5)	3 (2-6)	5 (2-9)	5 (3-20)	<0.001

Values are means (SD) unless otherwise noted.

Abbreviations: CAD, coronary artery disease; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; PPP, peripheral pulse pressure; LDL, low-density lipoprotein; HDL, high-density lipoprotein; CRP, C-reactive protein; CFPWV, carotid femoral pulse wave velocity; iCFPWV; inverse carotid femoral pulse wave velocity; CPP, carotid pulse pressure; eGFRcr-cys, estimated glomerular filtration rate; ACR, urine albumin to creatinine ratio; CKD, chronic kidney disease.

Figure 2. Distribution of aortic stiffness



Abbreviations: CFPWV, carotid femoral pulse wave velocity; CPP, carotid pulse pressure.

Table 3. Correlation matrix of measures of aortic stiffness and measures of peripheral blood pressure

	CPP (mm Hg)	CFPWV (m/s)	SBP (mm Hg)	DBP (mm Hg)	MAP (mm Hg)	PPP (mm Hg)
CPP (mm Hg)	1.00	0.29	0.83	-0.07	0.53	0.93
CFPWV (m/s)	0.29	1.00	0.40	0.21	0.36	0.32
SBP (mm Hg)	0.83	0.40	1.00	0.39	0.84	0.87
DBP (mm Hg)	-0.07	0.21	0.39	1.00	0.79	-0.12
MAP (mm Hg)	0.53	0.36	0.84	0.79	1.00	0.48
PPP (mm Hg)	0.93	0.32	0.87	-0.12	0.48	1.00

Abbreviations: CPP, carotid pulse pressure; CFPWV, carotid femoral pulse wave velocity; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; PPP, peripheral pulse pressure.

Association of aortic stiffness with eGFR.

The associations of all covariates with kidney measures and aortic stiffness are shown in Table 4 and 5, respectively. Although higher CFPWV was associated with lower eGFR in unadjusted model (Model 1: β=0.08, SE=0.02, p-value<0.001), this association was attenuated once age was included in multivariable models (Model 3: β=0.03, SE=0.02, p-value=0.196) (Figure 3 and Table 6). When CPP was less than 80 mmHg, there was no association of CPP and eGFR in both unadjusted and adjusted models. Conversely, when CPP was greater than 80 mmHg, higher CPP was associated with lower eGFR in the unadjusted model (Model 1: β=-0.22, SE=0.09, p-value=0.011) and after adjustment for age and blood pressure (Model 4: β=-0.16, SE=0.08, p-value=0.044). The association was no longer significant once adjusted for cardiovascular risk factors (Model 5: β=-0.12, SE=0.08, p-value=0.120).

Association of aortic stiffness with urine ACR

Higher CFPWV was associated with higher levels of albuminuria in the unadjusted model (Model 1: β=-0.009, SE=0.002, p-value<0.001), but the association was attenuated with the addition of age and cardiovascular risk factors into the model (Model 5: β=-0.001, SE=0.002, p-value=0.832) (Figure 3, Table 7). Higher CPP was associated with higher levels of albuminuria in the unadjusted model (Model 1: β=0.008, SE=0.002, p-value<0.001) and the association remained significant even in the fully adjusted model (Model 6: β=0.006, SE=0.003, p-value=0.013).

Table 4. Univariate associations of covariates with kidney measures in full cohort

	eGFR (ml/min/1.73 m^2)			ln ACR (mg/g)		
	β (SE)	p-value	R^2	β (SE)	p-value	R^2
Age (years)	-1.07 (0.11)	<0.001	0.099	0.06 (0.01)	<0.001	0.050
Gender	-0.58 (1.05)	0.583	0.0003	-0.37 (0.09)	<0.001	0.020
Height (cm)	0.12 (0.06)	0.037	0.005	0.01 (0.01)	0.123	0.003
Weight (kg)	-0.004 (0.04)	0.916	<0.001	-0.0002 (0.003)	0.946	<0.001
HR (bpm)	0.11 (0.05)	0.024	0.005	0.01 (0.004)	0.083	0.003
SBP (mm Hg)	-0.02 (0.03)	0.379	0.001	0.01 (0.002)	<0.001	0.018
DBP (mm Hg)	0.20 (0.05)	<0.001	0.014	0.001 (0.01)	0.788	<0.001
MAP (mm Hg)	0.07 (0.04)	0.107	0.003	0.01 (0.004)	0.017	0.006
PPP (mm Hg)	-0.08 (0.03)	0.004	0.009	0.01 (0.002)	<0.001	0.020
Total Cholesterol (mg/dL)	0.02 (0.01)	0.117	0.003	-0.003 (0.001)	<0.001	0.012
HDL (mg/dL)	0.17 (0.03)	<0.001	0.031	-0.005 (0.003)	0.055	0.004
LDL (mg/dL)	0.02 (0.01)	0.208	0.002	-0.003 (0.001)	0.002	0.010
HgbA1c (%)	-2.29 (1.06)	0.030	0.005	0.36 (0.09)	<0.001	0.018
CRP (mg/dL)	-0.33 (0.09)	<0.001	0.014	-0.002 (0.01)	0.815	<0.001

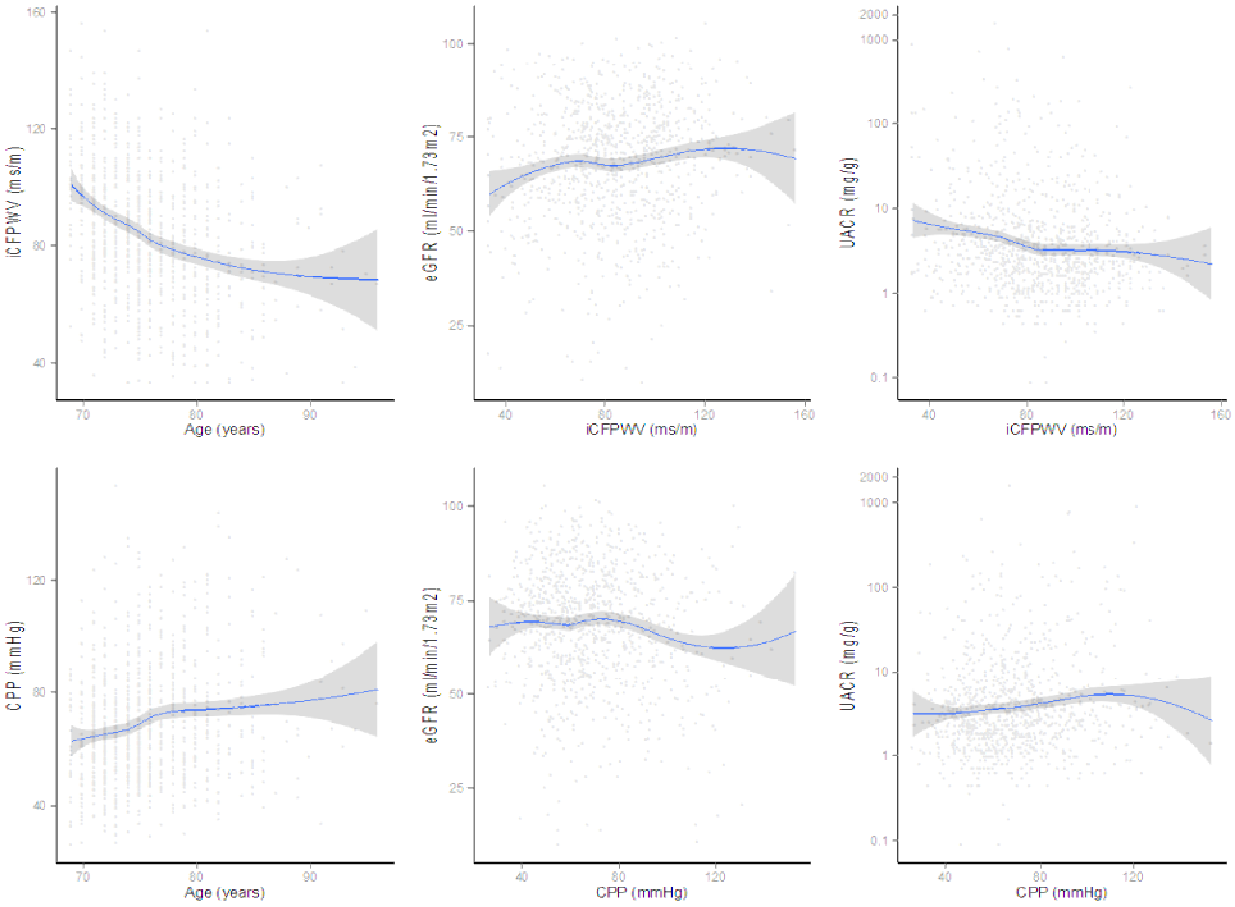
Abbreviations: eGFR, estimated glomerular filtration rate; ln ACR, natural logarithm of urine albumin to creatinine ratio; HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; PPP, peripheral pulse pressure; HDL, high-density lipoprotein; LDL, low-density lipoprotein; HgbA1c, hemoglobin A1c; CRP, C-reactive protein.

Table 5. Univariate associations of covariates with aortic stiffness in full cohort

	CFPWV			CPP		
	β (SE)	p-value	R^2	β (SE)	p-value	R^2
Age (years)	0.27 (0.27)	<0.001	0.090	0.77 (0.15)	<0.001	0.029
Gender	-1.27 (0.27)	<0.001	0.023	6.19 (1.38)	<0.001	0.021
Height (cm)	0.04 (0.02)	0.007	0.008	-0.45 (0.08)	<0.001	0.036
Weight (kg)	0.03 (0.01)	0.005	0.009	-0.21 (0.05)	<0.001	0.019
HR (bpm)	0.08 (0.01)	<0.001	0.037	-0.51 (0.06)	<0.001	0.064
SBP (mm Hg)	0.09 (0.01)	<0.001	0.159	0.91 (0.02)	<0.001	0.689
DBP (mm Hg)	0.09 (0.01)	<0.001	0.043	-0.15 (0.07)	0.040	0.005
MAP (mm Hg)	0.12 (0.01)	<0.001	0.130	0.92 (0.05)	<0.001	0.280
PPP (mm Hg)	0.07 (0.01)	<0.001	0.102	1.10 (0.01)	<0.001	0.863
Total Cholesterol (mg/dL)	-0.008 (0.003)	0.008	0.008	-0.03 (0.02)	0.072	0.004
HDL (mg/dL)	-0.03 (0.01)	<0.001	0.016	0.08 (0.04)	0.063	0.004
LDL (mg/dL)	-0.007 (0.004)	0.046	0.004	-0.04 (0.02)	0.008	0.008
HgbA1c (%)	1.18 (0.27)	<0.001	0.019	3.77 (1.40)	0.007	0.008
CRP (mg/dL)	0.08 (0.02)	<0.001	0.012	0.15 (0.12)	0.213	0.002

Abbreviations: HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; PPP, peripheral pulse pressure; HDL, high-density lipoprotein; LDL, low-density lipoprotein; HgbA1c, hemoglobin A1c; CRP, C-reactive protein.

Figure 3. Relationship of age, aortic stiffness, and kidney, measures



Top left: relationship of age on iCFPWV. Top center: relationship of iCFPWV on eGFR. Top right: relationship of iCFPWV on UACR. Bottom left: relationship of age on CPP. Bottom center: relationship of CPP on eGFR. Bottom right: relationship of CPP on UACR.
Abbreviations: iCFPWV, inverse carotid femoral pulse wave velocity; eGFR, estimated glomerular filtration rate; UACR, urine albumin to creatinine ratio; CPP, carotid pulse pressure.

Table 6. Multivariable linear regression of aortic stiffness measures and eGFR (ml/min/1.73m2)

	iCFPWV (ms/m)			CPP ≤80 (mmHg) N=686			CPP >80 (mmHg) N=254		
	β (SE)	p-value	R^2	β (SE)	p-value	R^2	β (SE)	p-value	R^2
Model 1	0.08 (0.02)	<0.001	0.014	0.01 (0.04)	0.878	0.018	-0.22 (0.09)	0.011	0.018
Model 2	0.10 (0.02)	<0.001	0.032	0.03 (0.04)	0.506	0.027	-0.22 (0.09)	0.008	0.027
Model 3	0.03 (0.02)	0.196	0.110	0.05 (0.04)	0.253	0.113	-0.17 (0.08)	0.033	0.113
Model 4	0.05 (0.03)	0.042	0.114	0.003 (0.05)	0.940	0.118	-0.16 (0.08)	0.044	0.118
Model 5	0.02 (0.03)	0.580	0.161	-0.01 (0.04)	0.887	0.166	-0.12 (0.08)	0.120	0.166
Model 6	0.01 (0.03)	0.623	0.174	0.01 (0.05)	0.826	0.178	-0.13 (0.08)	0.102	0.178

Model 1: Unadjusted
Model 2: Sex, heart rate, height
Model 3: Sex, heart rate, height, age
Model 4: Sex, heart rate, height, age, MAP
Model 5: Sex, heart rate, height, age, MAP, HDL, HgbA1c, CRP
Model 6: Sex, heart rate, height, age, MAP, HDL, HgbA1c, CRP, ln ACR

Abbreviations: eGFR, estimated glomerular filtration rate based on creatinine and cystatin C; iCFPWV, inverse carotid femoral pulse wave velocity; CPP, carotid pulse pressure; MAP, mean arterial pressure; HDL, high-density lipoprotein; HgbA1c, hemoglobin A1c; CRP, C-reactive protein; ln ACR, natural logarithm of urine albumin to creatinine ratio.

Table 7. Multivariable linear regression of aortic stiffness measures and albuminuria (ln ACR, mg/g)

	iCFPWV (ms/m)			CPP (mmHg)		
	β (SE)	p-value	R^2	β (SE)	p-value	R^2
Model 1	-0.009 (0.002)	<0.001	0.025	0.008 (0.002)	<0.001	0.015
Model 2	-0.007 (0.002)	<0.001	0.049	0.011 (0.002)	<0.001	0.061
Model 3	-0.004 (0.002)	0.047	0.075	0.009 (0.002)	<0.001	0.089
Model 4	-0.002 (0.002)	0.365	0.080	0.008 (0.003)	0.002	0.089
Model 5	-0.001 (0.002)	0.832	0.098	0.007 (0.003)	0.007	0.105
Model 6	-0.0003 (0.002)	0.882	0.112	0.006 (0.003)	0.013	0.119

Model 1: Unadjusted
Model 2: Sex, heart rate, height
Model 3: Sex, heart rate, height, age
Model 4: Sex, heart rate, height, age, MAP
Model 5: Sex, heart rate, height, age, MAP, HDL, HgbA1c, CRP
Model 6: Sex, heart rate, height, age, MAP, HDL, HgbA1c, CRP, eGFR

Abbreviations: ln ACR, natural logarithm of urine albumin to creatinine ratio; iCFPWV, inverse carotid femoral pulse wave velocity; CPP, carotid pulse pressure; MAP, mean arterial pressure; HDL, high-density lipoprotein; HgbA1c, hemoglobin A1c; CRP, C-reactive protein; eGFR estimated glomerular filtration rate based on creatinine and cystatin C.

Aim 2

Description of the population

Table 8 shows the characteristics of the study population included in Aim 2 as well as those excluded due to missing data. There were no significant differences in baseline characteristics of the populations that excluded missing MRI data, missing cognitive data, both missing MRI and cognitive data, and the full tonometry cohort. The population was older with a mean age 75.8 years, range 69-96 years, and had high rates of hypertension (57%), diabetes (20%), and hyperlipidemia (26%). Mean (SD) eGFR was 69 (15) ml/min/1.73m^2 and median (IQR) ACR was 3 (2-6) mg/g. A total of 210 (26.1%) had eGFR < 60 ml/min/1.73 m^2, 59 (7.4%) had ACR > 30 mg/g, and 235 (29.3%) had CKD. Only 1.2% of participants had eGFR < 30 ml/min/1.73m^2 and less than 1% had ACR > 300. Mean CFPWV was 13.0 m/s and mean CPP was 69 mmHg; both measures of arterial stiffness were higher in older participants. Brain MRI data is summarized in Table 9. Composite scores for cognition resulted in means (SD) of 0.08 (0.66) for executive function, 0.08 (0.89) for memory, and 0.13 (0.76) for speed.

Association of eGFR and brain measures

The univariate analyses of all covariates with the four measures of brain structures, infarcts, and cognition are shown in Table 10, 11, and 12, respectively. Table 13 shows the results of multivariable linear regression examining the relationship between eGFR and brain volumes calculated from brain MRIs. eGFR was associated with total brain parenchyma and white matter volumes in unadjusted models [Model 1: β (SE)=0.0004

Table 8. Clinical characteristics of brain cohort and those with missing data		
	Complete cognitive and MRI data N=804	**Incomplete data N=136**
Age (years)	75.7 (4.5)	76.5 (5.7)
Male, N (%)	359 (45)	62 (46)
Current smoker, N (%)	92 (11)	26 (19)
Hypertension, N (%)	454 (57)	81 (60)
SBP (mmHg)	139 (20)	137 (19)
DBP (mmHg)	67 (9)	65 (11)
MAP (mmHg)	95 (12)	92 (13)
PPP (mmHg)	72 (18)	73 (19)
Diabetes, N (%)	160 (20)	43 (32)
Hemoglobin A1c (%)	5.6 (0.5)	5.7 (0.4)
Hyperlipidemia, N (%)	212 (26)	34 (25)
Total cholesterol (mg/dL)	208 (43)	209 (46)
LDL (mg/dL)	126 (39)	126 (40)
HDL (mg/dL)	63 (17)	61 (18)
History of CAD, N (%)	151 (19)	26 (19)
History of TIA, N (%)	26 (3)	6 (4)
History of Stroke, N (%)	41 (5)	12 (9)
Cognitive Status, N (%)		
Dementia	17 (2)	3 (2)
Mild impairment	85 (11)	20 (15)
Normal	700 (87)	109 (83)
Education, N (%)		
Primary School	177 (22)	30 (23)
Secondary School	421 (52)	73 (55)
College	119 (15)	14 (11)
University	87 (11)	16 (12)
MMSE	27 (3)	26 (5)
Height (cm)	168 (9)	168 (9)
Weight (kg)	75.8 (13.8)	77.5 (14.3)
Heart rate (bpm)	62 (11)	65 (10)
Hemoglobin (g/dL)	13.5 (1.2)	13.6 (1.1)
CRP (mg/dL)	3.2 (5.7)	3.6 (5.8)
Serum albumin (g/dL)	4.1 (0.3)	4.1 (0.2)
CFPWV (m/s)	13.0 (4.2)	12.4 (3.9)
iCFPWV (ms/m)	83.9 (22.3)	87.3 (23.4)
CPP (mmHg)	69 (21)	68 (21)
CKD, N (%)	235 (29)	64 (47)
Serum creatinine (mg/dL)	0.96 (0.32)	1.08 (0.51)
Serum cystatin C (mg/L)	0.96 (0.26)	1.08 (0.44)
eGFR (ml/min/1.73 m2)	69 (15)	64 (19)
ACR (mg/g), median (IQR)	3 (2-6)	3 (2-8)

Values are means (SD) unless otherwise noted.
Abbreviations: CAD, coronary artery disease; TIA, transient ischemic attack; MMSE, mini-mental status examination; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; PPP, peripheral pulse pressure; LDL, low-density lipoprotein; HDL, high-density lipoprotein; CRP, C-reactive protein; CFPWV, carotid femoral pulse wave velocity; CPP, carotid pulse pressure; eGFR-crcys, estimated glomerular filtration rate; ACR, urine albumin to creatinine ratio; CKD, chronic kidney disease.

Table 9. Brain MRI measures

Variable	Mean (SD)	Range
Total brain parenchyma, % ICV	72 (4)	57,83
Grey matter volume, % ICV	46 (3)	29,55
White matter volume, % ICV	26 (2)	18,32
White matter hyperintensity volume, ln % ICV	-4.8 (0.9)	-7.3,-2.5)
White matter hyperintensity volume, median (IQR) ml	11.7 (6.3-24.7)	1.0,114.2
Infarcts, N (%)		
Subcortical	122 (15)	
Cortical	88 (11)	
Cerebellar	111 (14)	

Abbreviations: MRI, magnetic resonance imaging; ICV, intracranial volume; ln, natural logarithm.

Table 10. Univariate associations of covariates with brain structure

	ln WMH	TBP	WM	GM
	β (SE)	β (SE)	β (SE)	β (SE)
Age (years)	0.06 (0.01)	-0.003 (0.0003)	-0.002 (0.0001)	-0.003 (0.0002)
Male	-0.06 (0.06)	0.02 (0.003)	0.003 (0.001)	0.02 (0.002)
Height (cm)	-0.002 (0.004)	-0.001 (0.0002)	0.0001 (0.001)	-0.001 (0.0001)
Weight (kg)	-0.003 (0.002)	0.0001 (0.0001)	-0.0001 (0.0001)	0.0002 (0.0001)
HR (bpm)	0.006 (0.003)	0.00004 (0.0001)	-0.00001 (0.0001)	-0.00003 (0.0001)
SBP (mm Hg)	0.005 (0.002)	-0.00003 (0.0001)	-0.0001 (0.00003)	-0.000002 (0.0001)
DBP (mm Hg)	0.004 (0.003)	0.0003 (0.0001)	0.0001 (0.0001)	0.0002 (0.0001)
MAP (mm Hg)	0.005 (0.003)	0.0001 (0.0001)	-0.0001 (0.0001)	0.0001 (0.0001)
PPP (mm Hg)	0.004 (0.002)	-0.0001 (0.0001)	-0.0001 (0.00004)	-0.0001 (0.0001)
Total Cholesterol (mg/dL)	-0.001 (0.001)	0.0001 (0.00003)	0.00002 (0.00002)	0.0001 (0.00003)
HDL (mg/dL)	0.003 (0.002)	0.0002 (0.0001)	0.0001 (0.00004)	0.0001 (0.0001)
LDL (mg/dL)	-0.002 (0.001)	0.0001 (0.00003)	0.00002 (0.00002)	0.0001 (0.00003)
HgbA1c (%)	0.04 (0.06)	-0.003 (0.003)	-0.003 (0.001)	-0.001 (0.002)
Hemoglobin (mg/dL)	-0.05 (0.03)	0.001 (0.001)	0.001 (0.001)	0.0004 (0.001)
iCFPWV (ms/m)	-0.008 (0.001)	0.0004 (0.0001)	0.0002 (0.00003)	0.0003 (0.0001)
CPP (mm Hg)	0.002 (0.002)	-0.0001 (0.0001)	-0.0001 (0.00003)	-0.00004 (0.0001)

Shaded boxes represent associations that are statistically significant, p-value< 0.05.
Abbreviations: ln WMH, natural logarithm of white matter hyperintensities; TBP, total brain parenchyma; WM, white matter; GM, grey matter; HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; PPP, peripheral pulse pressure; HDL, high-density lipoprotein; LDL, low-density lipoprotein; HgbA1c, hemoglobin A1c,; iCFPWV, inverse carotid femoral pulse wave velocity; CPP, carotid pulse pressure.

Table 11. Univariate associations of covariates with infarcts

	Subcortical infarcts OR (95% CI)	Cortical infarcts OR (95% CI)	Cerebellar infarcts OR (95% CI)
Age (years)	1.05 (1.01-1.09)	1.02 (0.98-1.07)	1.06 (1.01-1.10)
Male	0.45 (0.30-0.66)	0.38 (0.24-0.60)	0.68 (0.46-1.01)
Height (cm)	1.04 (1.02-1.06)	1.03 (1.00-1.05)	1.01 (0.99-1.03)
Weight (kg)	1.02 (1.00-1.03)	1.01 (1.00-1.03)	0.99 (0.98-1.01)
HR (bpm)	1.01(0.99-1.02)	0.99 (0.96-1.01)	0.98 (0.96-1.00)
SBP (mm Hg)	1.01 (1.01-1.02)	0.99 (0.98-1.00)	1.00 (0.99-1.01)
DBP (mm Hg)	1.00 (0.98-1.02)	0.98 (0.96-1.00)	0.98 (0.96-1.00)
MAP (mm Hg)	1.01 (1.00-1.03)	0.98 (0.96-1.00)	0.99 (0.98-1.01)
PPP (mm Hg)	1.02 (1.01-1.03)	1.00 (0.98-1.01)	1.01 (1.00-1.02)
Total Cholesterol (mg/dL)	1.00 (0.99-1.00)	0.99 (0.99-1.00)	1.00 (0.99-1.00)
HDL (mg/dL)	0.99 (0.98-1.00)	0.98 (0.97-0.99)	0.99 (0.98-1.00)
LDL (mg/dL)	1.00 (0.99-1.00)	0.99 (0.99-1.00)	1.00 (0.99-1.00)
HgbA1c (%)	1.17 (0.81-1.62)	1.28 (0.87-1.80)	1.11 (0.75-1.56)
CRP (mg/dL)	0.99 (0.94-1.02)	1.01 (0.97-1.04)	0.98 (0.93-1.02)
Hemoglobin (mg/dL)	1.12 (0.96-1.32)	1.16 (0.97-1.40)	1.17 (0.99-1.38)
iCFPWV (ms/m)	0.98 (0.97-0.99)	1.00 (0.99-1.01)	0.99 (0.98-1.00)
CPP (mm Hg)	1.01 (1.00-1.02)	1.00 (0.99-1.01)	1.01 (0.99-1.02)

Shaded boxes represent statistically significant associations.

Abbreviations: HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; PPP, peripheral pulse pressure; HDL, high-density lipoprotein; LDL, low-density lipoprotein; HgbA1c, hemoglobin A1c,; CRP, C-reactive protein; iCFPWV, inverse carotid femoral pulse wave velocity; CPP, carotid pulse pressure.

Table 12. Univariate associations of covariates with cognition

	Executive Function		**Memory**		**Speed**	
Covariate	β (SE)	p-value	β (SE)	p-value	β (SE)	p-value
Age (years)	-0.05 (0.01)	<0.001	-0.07 (0.01)	<0.001	-0.07 (0.01)	<0.001
Male	-0.07 (0.04)	0.090	0.38 (0.06)	<0.001	0.1 (0.1)	0.060
Height (cm)	0.01 (0.002)	<0.001	-0.002 (0.003)	0.530	0.01 (0.003)	<0.001
Weight (kg)	0.001 (0.002)	<0.001	0.002 (0.002)	0.466	0.01 (0.002)	0.010
HR (bpm)	-0.002 (0.002)	0.267	-0.003 (0.003)	0.371	-0.002 (0.003)	0.435
SBP (mm Hg)	-0.003 (0.001)	0.014	-0.003 (0.002)	0.060	0.001 (0.001)	0.422
DBP (mm Hg)	0.004 (0.002)	0.058	0.01 (0.003)	0.044	0.01 (0.003)	0.001
MAP (mm Hg)	-0.001 (0.002)	0.615	-0.001 (0.003)	0.847	0.01 (0.002)	0.020
PPP (mm Hg)	-0.004 (0.001)	<0.001	-0.01 (0.002)	0.002	-0.001 (0.002)	0.363
Total Cholesterol (mg/dL)	0.001 (0.001)	0.225	0.002 (0.001)	0.016	0.002 (0.001)	<0.001
HDL (mg/dL)	0.001 (0.001)	0.309	0.01 (0.002)	<0.001	0.004 (0.002)	0.026
LDL (mg/dL)	0.0004 (0.001)	0.437	0.001 (0.001)	0.507	0.002 (0.001)	0.009
HgbA1c (%)	-0.07 (0.04)	0.140	0.04 (0.06)	0.484	-0.1 (0.1)	0.159
CRP (mg/dL)	-0.01 (0.004)	0.132	-0.0003 (0.01)	0.950	-0.003 (0.01)	0.559
Hemoglobin (mg/dL)	0.06 (0.02)	0.001	-0.004 (0.03)	0.879	0.07 (0.02)	0.002
iCFPWV (ms/m)	0.01 (0.001)	<0.001	0.01 (0.001)	<0.001	0.004 (0.001)	0.002
CPP (mm Hg)	-0.004 (0.001)	<0.001	-0.004 (0.001)	0.005	-0.002 (0.001)	0.189

Abbreviations: HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; PPP, peripheral pulse pressure; HDL, high-density lipoprotein; LDL, low-density lipoprotein; HgbA1c, hemoglobin A1c,; CRP, C-reactive protein; iCFPWV, inverse carotid femoral pulse wave velocity; CPP, carotid pulse pressure.

Table 13. Multivariable linear regression of kidney measures and brain structure

	eGFR (ml/min/1.73m^2)			ln ACR (mg/g)		
	β (SE)	p-value	R^2	β (SE)	p-value	R^2
Total brain parenchyma						
Model 1	0.0004 (0.0001)	<0.001	0.027	-0.005 (0.001)	<0.001	0.032
Model 2	0.0002 (0.0001)	0.011	0.224	-0.003 (0.001)	0.002	0.226
Model 3	0.0002 (0.0001)	0.011	0.224	-0.003 (0.001)	0.002	0.226
Model 4	0.0002 (0.0001)	0.006	0.233	-0.003 (0.001)	0.003	0.232
Model 5	0.0002 (0.0001)	0.008	0.239	-0.003 (0.001)	0.005	0.239
Model 6	0.0002 (0.0001)	0.007	0.242	-0.003 (0.001)	0.006	0.242
Grey matter volume						
Model 1	0.0002 (0.0001)	0.001	0.014	-0.004 (0.001)	<0.001	0.035
Model 2	0.0001 (0.0001)	0.228	0.209	-0.002 (0.001)	0.001	0.218
Model 3	0.0001 (0.0001)	0.229	0.209	-0.003 (0.001)	0.001	0.218
Model 4	0.0001 (0.0001)	0.086	0.221	-0.002 (0.001)	0.001	0.228
Model 5	0.0001 (0.0001)	0.086	0.228	-0.002 (0.001)	0.001	0.235
Model 6	0.0001 (0.0001)	0.062	0.233	-0.002 (0.001)	0.002	0.239
White matter volumes						
Model 1	0.0002 (0.00004)	<0.001	0.032	-0.002 (0.001)	<0.001	0.026
Model 2	0.0001 (0.00004)	0.003	0.134	-0.002 (0.001)	0.001	0.136
Model 3	0.001 (0.00004)	0.003	0.138	-0.002 (0.001)	0.001	0.138
Model 4	0.0001 (0.00004)	0.010	0.148	-0.001 (0.001)	0.004	0.149
Model 5	0.0001 (0.00004)	0.015	0.155	-0.001 (0.001)	0.007	0.156
Model 6	0.0001 (0.00004)	0.013	0.155	-0.001 (0.001)	0.007	0.156
White matter hyperintensities						
Model 1	-0.002 (0.002)	0.309	0.001	0.10 (0.02)	<0.001	0.022
Model 2	0.002 (0.002)	0.316	0.079	0.08 (0.02)	0.001	0.095
Model 3	0.002 (0.002)	0.343	0.083	0.07 (0.02)	0.001	0.099
Model 4	0.002 (0.002)	0.476	0.091	0.07 (0.02)	0.002	0.106
Model 5	0.001 (0.002)	0.605	0.135	0.07 (0.02)	0.002	0.117
Model 6	0.001 (0.002)	0.647	0.198	0.07 (0.02)	0.002	0.117

Model 1: Unadjusted
Model 2: Sex, age
Model 3: Sex, age, MAP
Model 4: Sex, age, MAP, HDL, HgbA1c, CRP
Model 5: Sex, age, MAP, HDL, HgbA1c, CRP, iCFPWV, CPP
Model 6: Sex, age, MAP, HDL, HgbA1c, CRP, iCFPWV, CPP, heart rate, height

Abbreviations: eGFR, estimated glomerular filtration rate; ln ACR, natural logarithm of urine albumin to creatinine ratio; SE, standard error; MAP, mean arterial pressure; HDL, high-density lipoprotein; HgbA1c, hemoglobin A1c; CRP, c-reactive protein; iCFPWV, inverse carotid femoral pulse wave velocity; CPP, carotid pulse pressure.

(0.0001), p-value<0.001 and β (SE)=0.0002 (0.00004), p-value<0.001, respectively], but not white matter hyperintensities [Model 1: β (SE)=-0.002 (0.002), p-value=0.309]. The associations for total brain parenchyma and white matter volumes remained statically significant after adjustment for age, sex, cardiovascular disease risk factors, and aortic stiffness [Model 6: β (SE)=0.0002 (0.0001), p-value=0.007 and β (SE)=0.0001 (0.00004), p-value=0.013, respectively].

The addition of iCFPWV and CPP to multivariable models for total brain parenchyma and white matter volumes did not attenuate the effect size of eGFR. In contrast, there was a 50% reduction in effect size for eGFR in its association with WMH (β=0.001 vs. 0.002), although the effect was not statistically significant overall (Table 13). The addition of the two measures of aortic stiffness did increase the amount of variability in brain structure that was explained (R^2=0.091 vs. 0.135 for WMH, R^2=0.233 vs. 0.239 for total brain parenchyma, R^2=0.148 vs. 0.155 for white matter volume, and R^2=0.221 vs. 0.228 for grey matter volume).

Table 14 shows the results of multivariable logistic regression examining the relationship between eGFR and brain infarcts. There was no evidence for an association between eGFR and subcortical infarcts in unadjusted or fully adjusted models [Model 1: OR (95% CI)=1.00 (0.99-1.02) and Model 6: OR (95% CI)=1.01 (1.00-1.03)]. eGFR was associated with cerebellar infarcts in unadjusted models [Model 1: OR (95% CI)=0.99 (0.99-1.00)], but the association became non- significant after adjustment for age and sex

Table 14. Multivariable logistic regression of kidney measures and infarcts

	eGFR (ml/min/1.73m^2)	ln ACR (mg/g)
	OR (95% CI)	OR (95% CI)
Subcortical infarcts		
Model 1	1.00 (0.99-1.02)	1.20 (1.04-1.37)
Model 2	1.01 (1.00-1.02)	1.11 (0.97-1.28)
Model 3	1.01 (1.00-1.02)	1.10 (0.96-1.33)
Model 4	1.01 (1.00-1.02)	1.09 (0.95-1.26)
Model 5	1.01 (1.00-1.03)	1.08 (0.93-1.24)
Model 6	1.01 (1.00-1.03)	1.08 (0.93-1.25)
Cortical infarcts		
Model 1	0.99 (0.98-1.01)	1.14 (0.97-1.33)
Model 2	0.99 (0.98-1.01)	1.08 (0.91-1.27)
Model 3	0.99 (0.98-1.01)	1.10 (0.93-1.29)
Model 4	0.99 (0.98-1.01)	1.08 (0.91-1.28)
Model 5	0.99 (0.98-1.01)	1.07 (0.91-1.27)
Model 6	0.99 (0.98-1.01)	1.06 (0.90-1.27)
Cerebellar infarcts		
Model 1	0.99 (0.97-1.00)	1.10 (0.95-1.27)
Model 2	0.99 (0.98-1.00)	1.05 (0.91-1.21)
Model 3	0.99 (0.98-1.00)	1.05 (0.91-1.22)
Model 4	0.99 (0.98-1.00)	1.04 (0.91-1.21)
Model 5	0.99 (0.98-1.00)	1.04 (0.90-1.20)
Model 6	0.99 (0.98-1.00)	1.04 (0.90-1.21)

Model 1: Unadjusted
Model 2: Sex, age
Model 3: Sex, age, MAP
Model 4: Sex, age, MAP, HDL, HgbA1c, CRP
Model 5: Sex, age, MAP, HDL, HgbA1c, CRP, iCFPWV, CPP
Model 6: Sex, age, MAP, HDL, HgbA1c, CRP, iCFPWV, CPP, heart rate, height

Abbreviations: eGFR, estimated glomerular filtration rate; ln ACR, natural logarithm urine albumin to creatinine ratio; MAP, mean arterial pressure; HDL, high-density lipoprotein; HgbA1c, hemoglobin A1c.

[Model 2: OR (95% CI)=0.99 (0.98-1.00)]. In multivariable models, there was minimal change in effect size after adjustment for iCFPWV and CPP with any of the infarcts.

Table 15 shows the results of multivariable linear regression examining the associations between eGFR and cognition. Higher eGFR was associated with higher scores of executive function, memory, and speed in unadjusted models [Model 1: β (SE)=0.0005 (0.002), p-value=0.002; β (SE)=0.006 (0.002), p-value=0.002; and β (SE)=0.005 (0.002), p-value=0.003, respectively]. However, these relationships became non-significant after adjustment for age [Model 2: β (SE)=0.001 (0.002), p-value=0.389; β (SE)=0.002 (0.002), p-value=0.337; and β (SE)=0.001 (0.002), p-value=0.687, respectively]. There were no meaningful changes in effect sizes with adjustment for aortic stiffness and only a small increase in the amount of variability explained (R^2=0.185 vs. 0.189 for executive function, R^2=0.206 vs. 0.214 for memory, and R^2=0.255 vs. 0.255 for speed).

Association of urine ACR and brain measures

Table 13 shows multivariable linear regression examining the relationship between ACR and brain volumes calculated from brain MRIs. ACR was associated with total brain parenchyma, grey matter volume, white matter volume, and white matter hyperintensities, even after adjustment for age, sex, cardiovascular risk factors, and aortic stiffness [Model 6: β (SE)=-0.003 (0.001), p-value=0.006; β (SE)=-0.002 (0.001), p-value=0.002; β (SE)=-0.001 (0.001), p-value=0.007; β (SE)=0.07 (0.02), p-value=0.002, respectively]. When adjusted for demographics and cardiovascular risk factors, iCFPWV remained statistically significantly associated with all brain structure measures but CPP was not. However, inclusion in multivariable models did not change the effect size. The

Table 15. Multivariable linear regression of kidney measures and cognition

	eGFR (ml/min/1.73m^2)			ln ACR (mg/g)		
	β (SE)	p-value	R^2	β (SE)	p-value	R^2
Executive Function						
Model 1	0.005 (0.002)	0.002	0.012	-0.02 (0.02)	0.389	0.001
Model 2	0.001 (0.002)	0.389	0.104	-0.001 (0.02)	0.977	0.100
Model 3	0.001 (0.002)	0.378	0.105	0.0004 (0.02)	0.981	0.101
Model 4	0.0004 (0.002)	0.773	0.112	0.003 (0.02)	0.877	0.108
Model 5	0.0004 (0.002)	0.773	0.185	0.001 (0.02)	0.932	0.181
Model 6	0.0003 (0.002)	0.861	0.189	0.003 (0.02)	0.838	0.185
Model 7	0.001 (0.002)	0.718	0.202	0.01 (0.02)	0.700	0.198
Memory						
Model 1	0.006 (0.002)	0.002	0.011	-0.08 (0.02)	0.001	0.014
Model 2	0.002 (0.002)	0.337	0.139	-0.04 (0.02)	0.108	0.139
Model 3	0.002 (0.002)	0.314	0.142	-0.03 (0.02)	0.138	0.141
Model 4	0.001 (0.002)	0.584	0.149	-0.04 (0.02)	0.101	0.149
Model 5	0.001 (0.002)	0.548	0.206	-0.04 (0.02)	0.065	0.210
Model 6	0.001 (0.002)	0.627	0.214	-0.04 (0.02)	0.089	0.219
Model 7	0.002 (0.002)	0.441	0.234	-0.03 (0.02)	0.154	0.236
Speed						
Model 1	0.005 (0.002)	0.003	0.011	-0.03 (0.02)	0.168	0.002
Model 2	0.001 (0.002)	0.687	0.143	0.002 (0.02)	0.906	0.144
Model 3	0.001 (0.002)	0.707	0.144	0.0002 (0.02)	0.992	0.146
Model 4	-0.001 (0.002)	0.786	0.153	0.002 (0.02)	0.915	0.154
Model 5	-0.001 (0.002)	0.752	0.255	-0.002 (0.02)	0.934	0.254
Model 6	-0.001 (0.002)	0.727	0.255	-0.001 (0.02)	0.955	0.255
Model 7	-0.0001 (0.002)	0.936	0.279	0.003 (0.02)	0.846	0.280

Model 1: Unadjusted
Model 2: Sex, age
Model 3: Sex, age, MAP
Model 4: Sex, age, MAP, HDL, HgbA1c, CRP
Model 5: Sex, age, MAP, HDL, HgbA1c, CRP, education
Model 6: Sex, age, MAP, HDL, HgbA1c, CRP, education, iCFPWV, CPP
Model 7: Sex, age, MAP, HDL, HgbA1c, CRP, education, iCFPWV, CPP, heart rate, height

Abbreviations: eGFR, estimated glomerular filtration rate; ln ACR, natural logarithm urine albumin to creatinine ratio; MAP, mean arterial pressure; HDL, high-density lipoprotein; HgbA1c, hemoglobin A1c.

addition of measures of aortic stiffness to multivariable models did increase the amount of variability in brain structure that was explained (R^2=0.106 vs. 0.117 for WMH, R^2=0.232 vs. 0.239 for total brain parenchyma, R^2=0.149 vs. 0.156 for white matter volume, and R^2=0.228 vs. 0.235 for grey matter volume).

Table 14 shows multivariable logistic regression examining the relationship between ACR and brain infarcts. ACR was associated with subcortical infarcts in unadjusted models [Model 1: OR (95% CI)=1.20 (1.04-1.37)], but not after adjustment for age and sex [Model 1: OR (95% CI)=1.11 (0.97-1.28)]. ACR was not related to either cortical or cerebellar infarcts. Addition of iCFPWV and CPP to multivariable models resulted in minimal change to effect sizes.

Table 15 shows the results of multivariable linear regression examining the associations between ACR and cognition. In unadjusted models, higher ACR was associated with lower scores of memory [Model 1: β (SE)=-0.08 (0.02), p-value=0.001] but not with executive function or speed [Model 1: β (SE)=-0.02 (0.02), p-value=0.389 and β (SE)=-0.03 (0.02), p-value=0.168, respectively]. Adjustment for age and sex attenuated the association with memory [Model 2: β (SE)=-0.04 (0.02), p-value=0.108). The inclusion of aortic stiffness measures in multivariable models resulted in a larger increase in executive function scores with higher level of albuminuria, but remained non-significant. When aortic stiffness measures were included in the models we observed an increase in the amount of variability explained (R^2=0.108 vs. 0.181 for executive function, R^2=0.149 vs. 0.210 for memory, and R^2=0.154 vs. 0.254 for speed).

Discussion

Aim 1

CKD affects a large segment of the aging population, yet the cause has not been clearly defined. In a population-based study of 940 older adults, we found a prevalence of CKD of 32.0% and a broad range of values of both measures of aortic stiffness, CFPWV and CPP. We found that CPP was more strongly related to kidney disease measures than CFPWV, but that both measures were attenuated after adjustments for age and cardiovascular disease risk factors. In particular, higher levels of CPP were significantly associated with higher levels of albuminuria after adjustments, suggesting that aortic stiffness may play a role in the development of kidney disease. Additionally, age was strongly related to measures of kidney disease and aortic stiffness, making it a challenge to interpret our results.

The ranges of CFPWV and CPP seen in our study were similar to those seen in other older populations (29, 75). The average aortic stiffness measures were higher than those seen in younger cohorts from both the general population, such as the Framingham Study, as well as CKD populations, such as the Chronic Renal Insufficiency Cohort Study (30, 27). The observed aortic stiffness in our population included values that have previously been associated with increased risk of cardiovascular events (50).

Although CFPWV and CPP are both used as measures of aortic stiffness, we found them to have different relationships to kidney disease measures, especially ACR. CFPWV is computed from the distance from the carotid to femoral sites over transit time between

the end of diastole at the two sites; it is primarily affected by the blood vessel wall properties, such as thickness and elasticity (53). These changes in wall properties can lead to loss of impedance mismatch between the central and peripheral vasculature, resulting in increased transmittance of pressures into the peripheral arterial beds, such as the kidneys. The higher pressures in the kidney are hypothesized to lead to vasoconstriction and reduced GFR, although we did not observe this relationship in our study. On the other hand, CPP is primarily affected by pulsatility of blood flow, which is related to aortic stiffness as well as cardiac function and aortic diameter (76). The increased pulsatility with increased CPP may, in particular, damage the endothelium of the glomerulus, potentially resulting in albuminuria (17). The majority of previous studies examining aortic stiffness and albuminuria have used CFPWV or PWV at other sites as the measure of aortic stiffness.

We found no evidence for a relationship between eGFR and either measure of aortic stiffness. The narrow confidence intervals for the relationship of eGFR to iCFPWV (-0.04 to +0.07 ml/min/1.73 m^2 per 1.0 ms/m) and CPP (-0.29 to +0.03 ml/min/1.73 m^2 per 1.0 mm Hg) make it extremely unlikely that there is a clinically meaningful association in our study population. However, our study population might not have been optimal to detect the associations. Due to the age of our participants, those who had died prior to the AGES-RS-I visit or declined participation may have been more likely to have higher aortic stiffness or lower kidney function, resulting in underestimation of the true relationship. This type of informative censoring would bias our findings towards the null hypothesis. Our measures of aortic stiffness and kidney disease, although state of-the-art,

may be imprecise, presenting another possible source of bias towards the null hypothesis. For example, eGFR is known to be an imprecise estimate of measurement of measured GFR, due to non-GFR determinants of both creatinine and cystatin C.

The lack of a strong relationship between eGFR and aortic stiffness that we observed here is consistent with findings from two other population-based studies with both cross-sectional and longitudinal components, the Health ABC and Framingham Heart Studies, which both noted attenuation of the relationship after adjustment for age, sex, blood pressure, and other cardiovascular disease risk factors (29-30). However, other studies in the general population as well as CKD cohorts found significant associations between aortic stiffness and lower eGFR in cross-sectional and longitudinal studies (27, 29, 31-32, 35), even after adjustment for age, blood pressure, and cardiovascular disease risk factors. These associations were often seen in younger populations, minimizing the effect of survivor bias seen in our population.

We found a significant association between aortic stiffness measured with CPP, but not CFPWV, and ACR even after adjustment for age, sex, MAP, and other cardiovascular disease risk factors. Since albuminuria is an early manifestation of kidney disease, pulsatility associated with CPP may lead to changes in albuminuria prior to any decline in eGFR. We may have been able to observe a relationship with CPP and albuminuria but not eGFR due to the relatively high eGFR in our population. The narrow confidence intervals for the relationship of ACR to iCFPWV (-0.005 to +0.004 ml/min/1.73 m^2 per 1.0 ms/m) suggest that it is unlikely that there is a clinically meaningful association in our

study population. Similar issues of survivor bias and imprecise measurements would bias our findings towards the null hypothesis.

Our findings of the association of CPP and albuminuria are consistent with the Framingham Heart Study. In that study, CPP and CFPWV at baseline were associated with baseline albuminuria in cross-sectional analyses and incident albuminuria during longitudinal follow-up in age and gender adjusted models. However, the longitudinal association was attenuated and became non-significant after adjustment for blood pressure and other cardiovascular disease risk factors, suggesting confounding by other conditions already present at baseline (30). In contrast to our findings, other studies have also shown significant relationships between CFPWV and albuminuria (77-83). The largest of the prior studies were cross-sectional analyses of patients with CKD based on eGFR and may represent changes already present in those with reduced kidney function.

The results of this study were significantly confounded by age with strong relationships observed between age and both measures of aortic stiffness as well as with both measures of kidney disease. However, there was no evidence of interaction with age in our multivariable models. Aging is associated with an increase in vascular disease through decreased elasticity, decreased compliance, and increased wall thickness, potentially resulting in both aortic stiffness and changes in kidney measures found in CKD (13-20). Because there are numerous changes with age, many of which may be unmeasured, and age precedes our outcomes of interest, age introduces considerable confounding by baseline conditions as well as potential mechanisms along the causal pathway.

Unfortunately, these complicated relationships are unable to be clarified with the cross-sectional design of our study.

The findings from our study have several implications. Aortic stiffness has previously been shown to be associated with increased risk of cardiovascular events and decreased survival in ESRD (50, 55-56, 84-87). With the findings of our studies, CPP may offer the additional benefit of risk stratification for development of albuminuria as well as a potentially modifiable risk factor. Since peripheral pulse pressure was highly correlated with CPP (Table 3), peripheral pulse pressure could be used as a surrogate marker for aortic stiffness and potentially to determine patient's risk of albuminuria. Medications that could reduce aortic stiffness should be evaluated in their potential role in reducing risk for development of albuminuria. Furthermore, because the prevalence of low eGFR is higher than the prevalence of albuminuria, there may be additional mechanisms leading to lower eGFR aside from aortic stiffness or microvascular disease resulting in albuminuria. Therefore, there should be further investigation in to possible mechanisms as well as other markers of kidney damage.

There are several strengths of our study. First, the study design is a population-based cohort that is representative of the Icelandic population at large. Second, the relatively large sample size is likely to give sufficient power to determine associations. Most importantly, we used high quality measurements in these analyses. The aortic tonometry protocol, including CFPWV and CPP, is highly standardized and has high correlation coefficients for reproducibility (16). Additionally, the ascertainment of kidney disease

included both ACR, a measure of kidney damage, as well as eGFR based on the combination of creatinine and cystatin C which has been shown to be more accurate and precise compared to either alone as a measure of kidney function.

There are also several limitations of our study. First, the population of Iceland is relatively homogenous. The large majority of Caucasians may limit the generalizability to the population of the United States. However, the homogeneity of the population may allow a more accurate assessment of the true relationship. Survivor bias and regression dilution are introduced with the older age of the study population. Additionally, we have used estimated GFR instead of measured GFR as the primary metric for kidney function. Although measured GFR would provide the true quantification of kidney function, the estimated GFR is used more often clinically and is more practical. Lastly, this is a cross-sectional study and the direction of causality cannot be determined. Previous studies have suggested that baseline aortic stiffness leads to changes in kidney function instead of baseline kidney function leading to changes in aortic stiffness (32). The longitudinal nature of these associations should be more thoroughly explored to make any causal inferences.

In conclusion, aortic stiffness measured with CPP was related to albuminuria in a representative elderly Icelandic population; higher CPP was associated with higher levels of albuminuria. CPP did not provide additional information above other cardiovascular disease risk factor to risk stratify those with lower eGFR. In contrast to previous literature, CFPWV was not associated with kidney disease. Lower eGFR in older adults

may be related to other mechanisms besides damage from albuminuria or aortic stiffness. Future studies are needed to explore the mechanism underlying kidney disease as well as better markers of vascular disease and kidney damage.

Aim 2

Changes in kidney and neurocognitive function are extremely common in older people, but the etiology of these changes is unclear. We hypothesized that there were similarities in the pathophysiology underlying both of these changes due to the specific vascular properties of the kidney and the brain and, therefore, kidney measures would be associated with brain structure and cognitive function. Lower eGFR was associated with lower volumes of total brain parenchyma and white matter, but not WMH or number of infarcts, and higher ACR was associated with lower volumes of total brain parenchyma, white matter, grey matter, and increased WMH, but not number of infarcts. Lower eGFR was associated with lower executive function, memory, and speed scores and higher ACR was associated with lower memory scores, but not executive function or speed scores, in unadjusted analyses. However, we found no evidence for an association of either eGFR or ACR to measures of cognition after adjustment for age and sex. There was no consistent attenuation of effect size after adjustment for aortic stiffness measures.

We found an association between lower eGFR and lower total brain parenchyma and white matter volume. It has been proposed that small vessel disease will affect the deep arterioles of the brain, leading to loss of white matter (88). Total brain parenchyma and

white matter volume have been shown to significantly decrease with age (89-90). Thus, our findings may be related to the large impact of age in our population. We found no evidence for a relationship between eGFR and WMH, infarcts, or cognition. Differences in these observations may be related to our study population and design.

Our findings regarding the association of eGFR to total brain parenchyma and white matter volume are consistent with the Rotterdam Scan Study, which showed that people with lower eGFR had smaller total brain and white matter volumes (38). However, they and others found additional results that conflicted with ours. Lower eGFR has been shown to be associated with greater WMH and lacunar or subclinical infarcts (8, 38-40, 91). In terms of our cognitive findings, we found results consistent with the Reasons for Geographic and Racial Disparities in Stroke (REGARDS) Study, a prospective community-based study of greater than 19,000 people who found no association of eGFR with incident cognitive impairment after adjustment for multiple risk factors (41). Conversely, lower eGFR or presence of CKD has been associated with worse cognitive test scores in both younger and older general population as well as CKD cohorts (42-43, 45). There are multiple potential reasons for some of these discordant results including differences in study populations, different sample sizes leading to differences in power, and differences in ascertainment of measures of kidney function, brain structure, and cognitive testing.

We found an association between higher ACR and all measures of brain structure including lower total brain parenchyma, grey matter, white matter volume and increased

WMH. Since albuminuria is an early manifestation of kidney disease, this relationship between albuminuria and brain structure may be significant in our population before other changes occur that affect both eGFR and brain structure. However, there was no evidence of relationship between albuminuria and infarcts or cognition.

There are no examinations of the relationship of albuminuria to total brain parenchyma, white matter, and grey matter but the association of higher albuminuria and higher WMH, evidence of small vessel cerebrovascular disease, was consistent with a cross-sectional study in the homebound elderly (44). The previous literature regarding albuminuria and cognition has yielded discrepant results. Our results are consistent with NHANES III and The Rancho Bernardo Study, which both showed no association between microalbuminriua and cognitive tests in cross-sectional analyses after adjustment for other risk factors (43, 47). However, the Rancho Bernardo Study did find evidence for cognitive decline in men in longitudinal follow-up. Our results were inconsistent with cross-sectional findings from the Cardiovascular Health Study and the study of homebound elders, which both showed more cognitive impairment or dementia at higher levels of albuminuria (44, 46). Issues surrounding variable measurement can potentially explain some of these discrepancies. These studies used different cognitive tests, making their comparisons difficult. Different measures may be better at capturing those domains of cognition associated with microvascular disease, such as executive function.

Two studies of cognition attempted to clarify interactions of ACR and eGFR. Our findings were consistent with the Chronic Renal Insufficiency Cohort Study which provided no evidence of a longitudinal relationship of albuminuria to cognition in patients with CKD, suggesting that albuminuria is not as influential at lower levels of eGFR (45). However, the REGARDS study showed a significant increase in cognitive impairment with higher albuminuria and that ACR was more strongly related to incident cognitive impairment at higher GFR compared to lower GFR (41). Our cross-sectional study design was unable to contribute to the understanding of causal inference in these relationships because of poor control for baseline confounding conditions.

We hypothesized that aortic stiffness would attenuate the relationship between kidney and brain disease. However, we showed no strong evidence for attenuation of the relationship after adjustment for aortic stiffness measures. Aortic stiffness has been associated with kidney impairment and progression of CKD in prior studies (27-35). There have been discrepant relationships on the association between arterial stiffness and brain disease with several studies showing an association between arterial stiffness and a decline in cognitive function scores or increased structural abnormalities, while others showing limited or no association (35, 92-95). There are several possible explanations for our lack of evidence for attenuation. Vascular disease may not be the common underlying mechanism of disease. Other complications of CKD such as inflammation, uremic toxins, hyperhomocysteinemia, and anemia may contribute more to the pathophysiology of brain disease (45-46, 12, 96-100). On the other hand, we may not

have the most precise or accurate measure of vascular disease and are, therefore, not seeing this relationship.

Several limitations of our study design may have influenced our results and interpretation. Our sample size, smaller than most of the larger, population-based cohorts, may have been insufficient to detect a true association. Survivor bias poses a threat to the interpretation of our study. Subjects with worse kidney and brain disease were potentially less likely to be included in our cohort at the AGES-RS-I visit because of death, loss to follow-up, or non-participation. This would lead to informative censoring, and, therefore, bias our findings to the null hypothesis. Although we attempted to use state-of-the-art measures of kidney and brain disease, various measures of our different outcomes may have introduced imprecision. For example, kidney disease was measured with eGFR and ACR. eGFR is known to be an imprecise estimate of measurement of measured GFR, due to non-GFR determinants of both creatinine and cystatin C. ACR was obtained at only one visit and may not capture variability in albuminuria. Our composite scores for cognition were based on different components of different cognitive tests and potentially may have resulted in some misclassification. Lastly, this is a cross-sectional study and causal inferences cannot be made based on our results.

There are several strengths of our study. First, the study design is a population-based cohort that is representative of the Icelandic population at large. State-of-the-art measurement of kidney function based on creatinine and cystatin C were used in this

analysis. The neurological evaluation was comprehensive with multiple measures of brain structure and cognitive tests obtained.

In summary, we found that a higher level of albuminuria was associated with decreased brain structure volumes and increased white matter hyperintensities. Neither eGFR nor ACR was associated with subclinical infarcts or cognition after adjustment for other risk factors. Adjustment for aortic stiffness did not consistently attenuate the relationships between kidney and brain disease, suggesting other disease mechanisms or need for more precise markers of vascular disease. Further longitudinal studies are needed to clarify these relationships and investigate additional pathways.

Future Directions

Future studies are needed to examine the longitudinal relationships between aortic stiffness and kidney function as well as kidney disease and brain disease. Some of our negative findings suggest other mechanism may be involved in the pathophysiology of these diseases, which should be explored further. Additionally, more work is needed to clarify the accuracy of our current markers of vascular disease and kidney damage and investigate new markers.

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