Kidney function and microstructural integrity of brain white matter

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ABSTRACT

Objective To investigate the association of kidney function with white matter microstructural integrity.

Methods We included 2726 participants with a mean age of 56.6 years (45% men) from the population-based Rotterdam Study. Albumin-to-creatinine ratio, and glomerular filtration rate (eGFR), using serum cystatin C (eGFRcys) and creatinine (eGFRcr), were measured to evaluate kidney function. Diffusion-MRI was used to assess microstructural integrity of the normal-appearing white matter. Multiple linear regression models, adjusted for macrostructural MRI-markers and cardiovascular risk factors were used to model the association of kidney function with white matter microstructure.

Results Participants had average eGFRcr of 86.1 mL/min/1.73 m^2, average eGFRcys of 86.2 mL/min/1.73 m^2, and median albumin-to-creatinine ratio of 3.4 mg/g. Lower eGFRcys was associated with worse global white matter microstructural integrity, reflected as lower fractional anisotropy (FA) (standardized difference per SD: -0.053, 95%CI: -0.092, -0.014) and higher mean diffusivity (MD) (0.036, 95%CI: 0.001, 0.070). Similarly, higher albumin-to-creatinine ratio was associated with lower FA (-0.044, 95%CI: -0.078, -0.011). There was no linear association between eGFRcr and white matter integrity. Subgroup analyses showed attenuation of the associations after excluding subjects with hypertension. The associations with global DTI-measures didn't seem to be driven by particular tracts, but rather spread across multiple tracts in various brain regions.

Conclusions Reduced kidney function is associated with worse white matter microstructural integrity. Our findings highlight the importance for clinicians to consider concomitant macro- and microstructural changes of brain in subjects with impaired kidney function.

INTRODUCTION

The brain and the kidney are both vulnerable to vascular and hemodynamic alterations due to similar high flow and low resistance circulation.[1] Therefore, vascular damage in the kidney could mirror cerebrovascular changes in the brain.[1] Accordingly, a higher prevalence of cerebrovascular diseases such as stroke and vascular dementia among patients with chronic kidney disease (CKD) has been reported.[2, 3] Beyond clinically evident cerebrovascular diseases, previous studies showed an association between kidney function and subclinical cerebrovascular diseases including brain atrophy and white matter lesions.[2, 4, 5] However, subclinical cerebrovascular diseases have a wide spectrum and conventional MRI sequences are not capable of capturing this entire spectrum. Diffusion tensor imaging (DTI) is an advanced MRI technique that provides quantitative information of microscopic changes of the cerebral white matter. Recognition of early changes in white matter structural integrity is of importance as it might help to prevent further progression of brain pathologies before reaching an irreversible stage.[6] Despite the current evidence indicating that advanced impairments in kidney function are associated with brain pathologies,[2, 3] it is unknown whether changes in kidney function and glomerular integrity are linked to more subtle, microstructural changes in the brain. In this study, we hypothesized that loss of kidney function is associated with microstructural changes of the white matter.

METHODS

Study population

The present study is embedded within the second extension of the population-based Rotterdam Study (2005-2009), including participants of 45 years and older. For the current study, we included 2825 individuals with DTI data, of whom 2680 had urine albumin and urine creatinine measurements, 2717 had serum creatinine measurements, and 2726 had available data on serum cystatin C measurements (**Figure e-1**).

Standard Protocol Approvals, Registrations, and Patient Consents

The Rotterdam Study has been approved by the medical ethics committee according to the Population Study Act Rotterdam Study, executed by the Ministry of Health, Welfare and Sports of the Netherlands. Written informed consent was obtained from all participants.[7]

Kidney function

Estimated glomerular filtration rate (eGFR) was calculated for creatinine (eGFRcr) and cystatin C (eGFRcys) measurements separately as well as for both measurements

combined (eGFRcrcys), according to the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula.[8] Albumin-to-creatinine ratio was estimated by dividing albumin by creatinine (mg/g).[9] Since measures of albumin-to-creatinine ratio were not normally distributed, albumin-to-creatinine ratio values were natural log transformed (further details about kidney function measurements in supplemental material). We defined three categories of kidney function using information from both eGFR and albumin-to-creatinine ratio. This categorization is based on the cutoffs of the Kidney Disease: Improving Global Outcomes (KDIGO) 2013,[10] and has been applied in the research setting before.[11] Categories were defined on the basis of two criteria: eGFR-crcys > 60 mL/min/1.73 m^2 and albumin-to-creatinine ratio < 30 mg/g. First category included participants that met both criteria. Second category included participants that met only one criterion. Participants that met none of the criteria were classified as the third category.[11]

Brain DTI-MRI

Brain MRI scanning was performed on a 1.5 tesla MRI scanner (GE Signa Excite). Scan protocol and sequence details are described extensively elsewhere.[12] For DTI, we performed a single shot, diffusion-weighted spin echo echo-planar imaging sequence. Maximum b-value was 1000 s/mm^2 in 25 non-collinear directions; three volumes were acquired without diffusion weighting (b-value = 0 s/mm^2).[12] All diffusion data were pre-processed using a standardized pipeline, including correction for motion and eddy currents, estimation of the diffusion tensor, and registration to tissue segmentation to obtain global mean DTI-measures in the normal-appearing white matter. These measures includes fractional anisotropy (FA), mean diffusivity (MD), and axial and radial diffusivities.[13] In general, lower values of FA and higher values of MD are indicative of worse microstructural integrity of the white matter. Next, white matter tracts were segmented using a diffusion tractography approach described previously.[14] We identified 14 different white matter tracts (11 tracts were defined for left and right hemispheres) in subject native space. Tracts were categorized into brainstem tracts, projection fibers association fibers, limbic system fibers and callosal fibers.[15] Tract-specific measurements of microstructure were obtained by taking median measures inside each white matter tract, with subsequent combination of left and right measures.[14] DTI values, both global and tract-specific, were measured using fully automated methods (no readers involved). Since these measures are not observer dependent, no observer bias was introduced. However, there might be some random measurement noise in the scan protocol. The average tract-specific reproducibility of our multi-step method was 87%. More details about the reproducibility of tract-specific DTI-parameters are provided elsewhere.[14]

Cardiovascular risk factors

Information related to smoking and alcohol consumption was acquired using questionnaires. Alcohol consumers were categorized into non, moderate and heavy drinkers. Smoking was categorized in never, former and current smoking. Information on medication use was based on home interviews. Hypertension was defined as a systolic blood pressure ≥140 mmHg or a diastolic blood pressure ≥ 90 mmHg or the use of antihypertensive medication. Cardiovascular disease was considered as a history of myocardial infarction, stroke or coronary revascularization procedures.[16] Diabetes mellitus was defined by use of blood glucose lowering medication and/or a fasting serum glucose level equal to or greater than 7.0 mmol/l.

Statistical analysis

Associations between kidney function markers and DTI-parameters were evaluated using multiple linear regression models. Subject-specific global and tract-specific DTI-parameters were standardized to z scores. Betas and 95% confidence intervals (CI) for difference in DTI parameters were estimated per standard deviation increase of measures of the kidney function. We performed the analyses in four steps. The first model was performed unadjusted. In the second model analyses were adjusted for age, sex, and macrostructural MRI-markers including white matter volume, intracranial volume, and WML (also known as white matter hyperintensities) volume. In the third model we additionally adjusted the analyses for cardiovascular risk factors (systolic blood pressure, diastolic blood pressure, alcohol intake, smoking, total cholesterol, high density lipoprotein cholesterol, diabetes mellitus, history of cardiovascular disease, and body mass index) and antihypertensive and lipid-lowering medication. In the fourth model, analyses with eGFR as determinants were adjusted for albumin-to-creatinine ratio, and analyses with albumin-to-creatinine ratio as determinant were further adjusted for eGFRcrcys. Based on previous literature[17] suggesting a U-shaped association between serum creatinine and brain outcomes, we further checked the non-linear association of eGFRcr with DTI-parameters of white matter integrity by including the quadratic term in the model. We performed an analysis of covariance where mean values of FA and MD were compared across three categories of kidney function. Moreover, we performed a series of sensitivity analyses, excluding subjects with chronic kidney disease (defined as eGFRcrcys < 60 mL/min/1.73 m^2), diabetes mellitus, hypertension, and with a history of cardiovascular disease. To investigate whether the association between kidney function and white matter integrity differs in participants with and without hypertension, we assessed the interactions between kidney function markers and hypertension in relation to DTI-parameters. In exploratory analyses, we evaluated if the associations between kidney function and white matter integrity is independent of C-reactive protein levels. Furthermore, to compare the magnitude of the association

with age, as an established risk factor for impairments in white matter integrity, we calculated the effect estimates for the association of age with FA and MD. Then, we divided the betas (per standard deviation) of kidney function markers by the betas of age in relation to DTI-parameters and reported the corresponding ratios.
In all analyses, we treated the phase encoding direction of the diffusion scan as a potential confounder. In tract specific analyses of the medial lemniscus, we additionally corrected for its varying coverage inside the field of view of the diffusion acquisition across participants. All analyses were carried out using SPSS 20.0.2 for windows or R version 2.15.0.

RESULTS

Table 1 presents the characteristics of the 2726 study participants. Average age of the participants was 56 ±6.4 years and 45 % were male. **Table 2** presents baseline characteristics of participants in different categories based on participants' kidney function.

The association between kidney function markers and global DTI-parameters of white matter microstructural integrity are presented in **Table 3**. In the unadjusted model, higher albumin-to-creatinine ratio was associated with lower FA and higher MD (standardized difference FA: -0.102, 95% confidence interval (CI): -0.139, -0.066; standardized difference MD: 0.096, 95%CI: 0.061, 0.132). Higher albumin-to-creatinine ratio was also associated with higher radial diffusivity (0.063, 95%CI: 0.027, 0.100) and higher axial diffusivity (0.103, 95%CI: 0.067, 0.139). Adjustments for age, sex, and macrostructural MRI-markers (white matter volume, intracranial volume, and WML volume) attenuated the association of albumin-to-creatinine ratio with FA, MD, and radial diffusivity (**Table 3**).There was no association between albumin-to-creatinine ratio and axial diffusivity in the second model. After further adjustments for cardiovascular risk factors, in the third model, associations of albumin-to-creatinine ratio with FA and radial diffusivity did not change, but the association with MD became non-significant (p: 0.09). Adjustment for eGFRcrcys in the fourth model didn't change the results (**Table 3**).

Table 1. Population Characteristics

Characteristics	**n= 2726**
Age, years	56.6 (6.4)
Men	1225 (44.9)
Systolic blood pressure, mmHg	131.9 (18.5)
Diastolic blood pressure, mmHg	82.3 (10.8)
Antihypertensive medication	595 (21.8)
Alcohol	
Moderate drinker	1640 (60.4)
Heavy drinker	806 (29.6)
Smoking	
Current	715 (26.2)
Former	1190 (43.7)
Total cholesterol, mmol/l	5.6 (1.0)
HDL cholesterol, mmol/l	1.4 (0.4)
Lipid-lowering medication	570 (20.9)
Diabetes mellitus	214 (7.9)
History of cardiovascular disease	128 (4.7)
Hypertension	1191 (43.7)
Body mass index, kg/m^2	27.5 (4.3)
Albumin-to-creatinine ratio, mg/g	3.4 (2.2, 6.2)
eGFRcr, mL/min/1.73 m^2	86.1 (13.5)
eGFRcys, mL/min/1.73 m^2	86.2 (16.0)
eGFRcrcys, mL/min/1.73 m^2	86.3 (13.4)
Intracranial volume, mL	1128.6 (122.0)
White matter volume, mL	416.8 (59.9)
White matter lesion volume, mL	2.0 (1.3, 3.5)
Fractional anisotropy	0.33 (0.01)
Mean diffusivity, 10^{-3} mm^2/s	0.74 (0.02)
Axial diffusivity, 10^{-3} mm^2/s	1.01 (0.03)
Radial diffusivity, 10^{-3} mm^2/s	0.60 (0.02)

Categorical variables are presented as numbers (percentages), continuous variables as means (standard deviations) and white matter lesions and albumin-to-creatinine ratio are presented as medians (interquartile ranges). The following variables had missing data: blood pressure (n=9), smoking (n=5), alcohol (n=12), lipid-lowering medication (n= 24), antihypertensive medication (n=24), HDL: high density lipoprotein cholesterol (n=7), Total cholesterol (n= 5), albumin-to-creatinine ratio (n=141), history of cardiovascular disease (n=28), body mass index (n=2), hypertension (n=24).

Abbreviations: eGFRcys: cystatin C based estimated glomerular filtration rate, eGFRcr: creatinine based estimated glomerular filtration rate, eGFRcrcys: creatinine and cystatin C based estimated glomerular filtration rate

Table 2. Population characteristics in categories of kidney function

Characteristics*	First category	Second category	Third category
	eGFR>60 and ACR<30 N=2320	eGFR<60 or ACR>30 N=179	eGFR<60 and ACR >30 N=14
Age, years	56.4 (5.9)	60.5 (9.6)	65.4 (9.2)
Men	1040 (44.8)	76 (42.5)	7 (50.0)
SBP, mmHg	131.4 (18.1)	139.6 (21.1)	145.5 (23.5)
DBP, mmHg	82.1 (10.7)	85.1 (12.0)	85.1 (11.2)
Anti-HTN Med	476 (20.5)	68 (38.0)	11 (78.6)
Alcohol			
Moderate drinker	1393 (60.0)	111 (62.0)	6 (42.9)
Heavy drinker	694 (29.0)	45 (25.1)	4 (28.6)
Smoking			
Current	590 (25.4)	49 (27.4)	4 (28.6)
Former	1014 (43.7)	80 (44.7)	7 (50.0)
Total chol, mmol/l	5.6 (1.0)	5.4 (1.1)	5.8 (1.3)
HDL chol, mmol/l	1.4 (0.4)	1.3 (0.4)	1.4 (0.5)
Lipid lowering Med	469 (20.2)	53 (29.6)	6 (42.9)
DM	155 (6.7)	34 (19.0)	2 (14.3)
CVD	99 (4.3)	19 (10.6)	2 (14.3)
HTN	982 (42.3)	116 (64.8)	14 (100)
BMI, kg/m^2	27.4 (4.2)	29.0 (5.1)	28.4 (4.6)
ACR, mg/g	3.3 (2.1, 5.5)	39.0 (8.4, 74.4)	130.1 (73.4, 229.1)
eGFRcr, mL/min/1.73 m^2	87.0 (11.9)	77.3 (18.9)	44.8 (16.7)
eGFRcys, mL/min/1.73 m^2	87.4 (14.3)	74.2 (21.4)	38.1 (13.3)
eGFRcrcys, mL/min/1.73 m^2	87.4 (11.7)	75.6 (20.0)	40.2 (13.9)
ICV, mL	1127.6 (121.1)	1125.3 (136.9)	1103.7 (133.5)
WMV, mL	417.3 (58.7)	408.7 (68.5)	385.9 (93.1)
WMLV, mL	2.0 (1.3, 3.4)	2.9 (1.6, 5.5)	8.9 (3.1, 13.0)
FA	0.33 (0.01)	0.33(0.01)	0.32 (0.02)
MD, 10^{-3} mm^2/s	0.74 (0.02)	0.75 (0.03)	0.76 (0.03)
Axial diffusivity, 10^{-3} mm^2/s	1.01 (0.03)	1.02 (0.03)	1.03 (0.03)
Radial diffusivity, 10^{-3} mm^2/s	0.60 (0.02)	0.61 (0.03)	0.63 (0.04)

*Sample size in this table is based on participants with available data for both eGFRcrcys and ACR (n=2513).
Categorical variables are presented as numbers (percentages), continuous variables as means (standard deviations) and white matter lesions and albumin-to-creatinine ratio are presented as medians (interquartile ranges).
Abbreviations: SBP: systolic blood pressure, DBP: diastolic blood pressure, Anti-HTN Med: antihypertensive medication, Total chol: total cholesterol, HDL chol: high density lipoprotein cholesterol, DM: diabetes mellitus, CVD: cardiovascular disease, HTN: hypertension, BMI: body mass index, ACR: Albumin-to-creatinine ratio, eGFRcys: cystatin C based estimated glomerular filtration rate, eGFRcr: creatinine based estimated glomerular filtration rate, eGFRcrcys: creatinine and cystatin C based estimated glomerular filtration rate, ICV: intracranial volume, WMV: white matter volume, WMLV: white matter lesion volume. FA: fractional anisotropy, MD: mean diffusivity.

Table 3. The association of kidney function parameters with DTI-parameters of white matter microstructural integrity

	Fractional anisotropy	Mean diffusivity	Axial diffusivity	Radial diffusivity
	Difference*(95% CI)	Difference*(95% CI)	Difference*(95% CI)	Difference*(95% CI)
Albumin-to-creatinine ratio N= 2680				
Model I	**-0.102 (-0.139, -0.066)**	**0.096 (0.061, 0.132)**	**0.063 (0.027, 0.100)**	**0.103 (0.067, 0.139)**
Model II	**-0.049 (-0.081, -0.016)**	**0.033(0.004, 0.062)**	0.018 (-0.015, 0.050)	**0.037 (0.008, 0.066)**
Model III	**-0.044 (-0.078, -0.011)**	0.026(-0.004, 0.056)	0.010 (-0.024, 0.044)	**0.031 (0.001, 0.061)**
Model IV	**-0.043 (-0.078, -0.008)**	0.027 (-0.004, 0.058)	0.013 (-0.022, 0.049)	**0.031 (0.001, 0.062)**
eGFRcys N=2726				
Model I	**0.204 (0.168, 0.240)**	**-0.248 (-0.283, -0.213)**	**-0.157 (-0.194, -0.120)**	**-0.268 (-0.303, -0.233)**
Model II	**0.053(0.016, 0.090)**	**-0.040 (-0.073, -0.007)**	-0.001 (-0.038, 0.036)	**-0.057 (-0.091, -0.024)**
Model III	**0.053(0.014, 0.092)**	**-0.036 (-0.070, -0.001)**	0.006 (-0.033, 0.045)	**-0.056 (-0.090, -0.021)**
Model IV	0.039 (-0.002, 0.079)	-0.033 (-0.069, 0.003)	0.003 (-0.038, 0.044)	**-0.050 (-0.087, -0.014)**
eGFRcr N= 2717				
Model I	**0.100 (0.063, 0.136)**	**-0.136 (-0.171, -0.100)**	**-0.092 (-0.129, -0.055)**	**-0.143 (-0.179, -0.107)**
Model II	-0.007 (-0.041, 0.027)	0.011 (-0.020, 0.041)	0.015 (-0.020, 0.049)	0.007 (-0.024, 0.038)
Model III	0.002 (-0.033, 0.036)	0.003 (-0.028, 0.034)	0.008 (-0.027, 0.043)	-0.001 (-0.032, 0.031)
Model IV	-0.013 (-0.049, 0.023)	0.009 (-0.023, 0.041)	0.008 (-0.029, 0.044)	0.009 (-0.024, 0.041)

*Differences (betas), and 95% CI are calculated using the per standard deviation increase in log-transformed albumin-to-creatinine ratio/ eGFRcys/ eGFRcr and subject-specific mean standardized z scores for fractional anisotropy, mean diffusivity, and axial and radial diffusivity. Model I: crude model. Model II: adjusted for age, sex, intracranial volume, white matter volume, and log transformed white matter lesion volume. Model III: additionally adjusted for systolic blood pressure, diastolic blood pressure, antihypertensive medication, alcohol intake, smoking, total cholesterol, high density lipoprotein cholesterol, lipid-lowering medication, diabetes mellitus, history of cardiovascular disease, and body mass index. Model IV: additionally adjusted for eGFRcrcys in analyses with albumin-to-creatinine ratio as determinant, and additionally adjusted for albumin-to-creatinine-ratio in analyses with eGFRcr or eGFRcys. *Abbreviations: CI: confidence interval, eGFRcys: cystatin C based estimated glomerular filtration rate, eGFRcr: creatinine based estimated glomerular filtration rate, eGFRcrcys: creatinine and cystatin C based estimated glomerular filtration rate.*

In the unadjusted model, each standard deviation higher eGFRcys was associated with higher FA and lower MD (FA: 0.204, 95% CI: 0.168, 0.240; MD: -0.248, 95%CI: -0.283, -0.213). Likewise, each standard deviation higher eGFRcys was associated with lower radial diffusivity (-0.268, 95%CI: -0.303, -0.233) and lower axial diffusivity (-0.157, 95%CI: -0.194, -0.120). The association of eGFRcys with FA, MD, and radial diffusivity attenuated after adjustment for age, sex, and macrostructural MRI-markers. There was no association between eGFRcys and axial diffusivity in the second model. Further adjustments for cardiovascular risk factors, in the third model, did not change the associations of eGFRcys with DTI-parameters of white matter integrity. After adjustment for albumin-to-creatinine ratio in the fourth model, the association of eGFRcys with FA and MD attenuated and became non-significant (p: 0.061 and 0.068, respectively) (**Table 3**). Each standard deviation higher eGFRcr was associated with higher FA, lower MD, and lower radial and axial diffusivity (all $p < 0.05$). There was no linear association be-

tween eGFRcr and DTI-parameters of white matter integrity after adjustment for age, sex, and macrostructural MRI-markers (all p>0.05) (**Table 3**). Including the quadratic term of eGFRcr in the model suggested a U-shaped association between eGFRcr and markers of white matter integrity (all P-values <0.05 for test of quadratic term) (**Table e-1**). After excluding the participants with 4 standard deviation lower/higher eGFRcr (n=9) the U-shaped association was not present anymore. Performing the analyses with eGFRcrcys as the determinant, the effect estimates were intermediate between two separate equations of eGFRcr and eGFRcys and resulted in borderline significant findings (**Table e-2**).

Figure 1 shows age and sex adjusted means of FA and MD in three categories of kidney function. We observed a linear trend between different categories of kidney function and white matter microstructural DTI-parameters, reflecting worse white matter microstructure in persons with worse kidney function (p for trend 0.001 for FA and 0.002 for MD).

Excluding individuals with chronic kidney disease, diabetes mellitus, or history of cardiovascular disease yielded similar findings. Excluding individuals with hypertension attenuated the association of kidney function with DTI parameters (**Figure e-2**). In the stratified analyses, the association between eGFRcys and MD was stronger in hypertensive participants (P for interaction, 0.001). A similar, borderline significant trend was observed for the interaction between albumin-to-creatinine ratio and hypertension in relation to FA (P for interaction 0.059) (**Table e-3**). Adjusting the association between markers of kidney function and DTI-parameters of white matter integrity for C-reactive protein didn't substantially change the associations (data not shown).
In an extra analysis, we observed that each year increase in age was associated with lower FA and higher MD (**Table e-4**). Comparing the effect estimates of age with eGFRcys in relation to FA, we showed that each standard deviation lower eGFRcys had the magnitude equal to 4.1 years of increase in age. Similarly, each standard deviation lower eGFRcys in relation to MD had the magnitude equal to 1.5 years increase in age.

Associations between kidney function and tract-specific diffusion measures are presented in **Figure 2** and **Table e-5**. Higher albumin-to-creatinine ratio was associated with higher MD in all tracts (projection fibers, association fibers, limbic system fibers, and callosal fibers). Likewise, higher eGFRcys was related to MD in all tracts, except for brain stem tracts. We did not observe any linear association between eGFRcr and tract-specific DTI-measures.

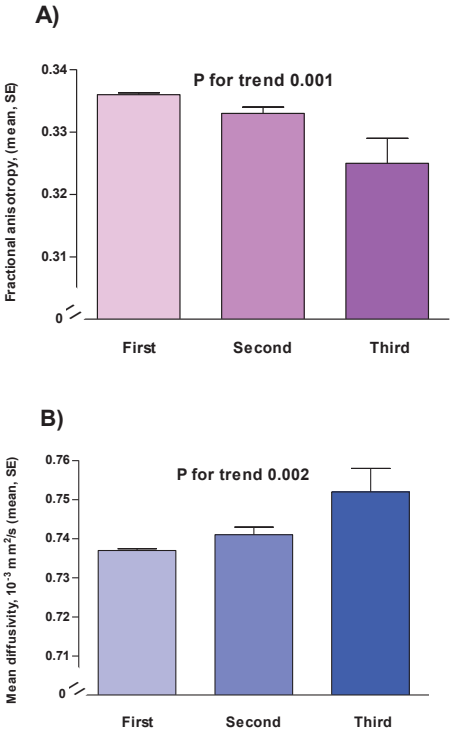

Figure 1. Means of **A)** fractional anisotropy **B)** and mean diffusivity in different categories of kidney function
First category: indicates eGFRcrcys > 60 mL/min/1.73 m^2 AND albumin-to-creatinine ratio < 30 mg/g (N=2320)
Second category: indicates eGFRcrcys > 60 mL/min/1.73 m^2 AND albumin-to-creatinine ratio > 30 mg/g OR eGFRcrcys < 60 mL/min/1.73 m^2 AND albumin-to-creatinine ratio < 30 mg/g (N=179)
Third category: indicates eGFRcrcys < 60 mL/min/1.73 m^2 AND albumin-to-creatinine ratio > 30 mg/g (N= 14)
Means are adjusted for age and sex.
Abbreviations: eGFRcrcys: creatinine and cystatin C based estimated glomerular filtration rate

DISCUSSION

In this cross-sectional study, we demonstrated that reduced kidney function was independently associated with worse microstructural integrity of cerebral white matter. The associations did not seem to be confined to specific white matter tracts.
Most of previous studies that investigated the association of kidney function with brain outcomes have focused either on cerebrovascular accidents, conventional macrostructural MRI-markers such as brain atrophy, or manifestations of cerebral small vessel disease.[2, 4, 5] In this study we show that reduced kidney function is related to loss of white matter microstructural integrity, which may be considered a more sensitive or subtle measure of white matter disease compared to macrostructural MRI-markers.

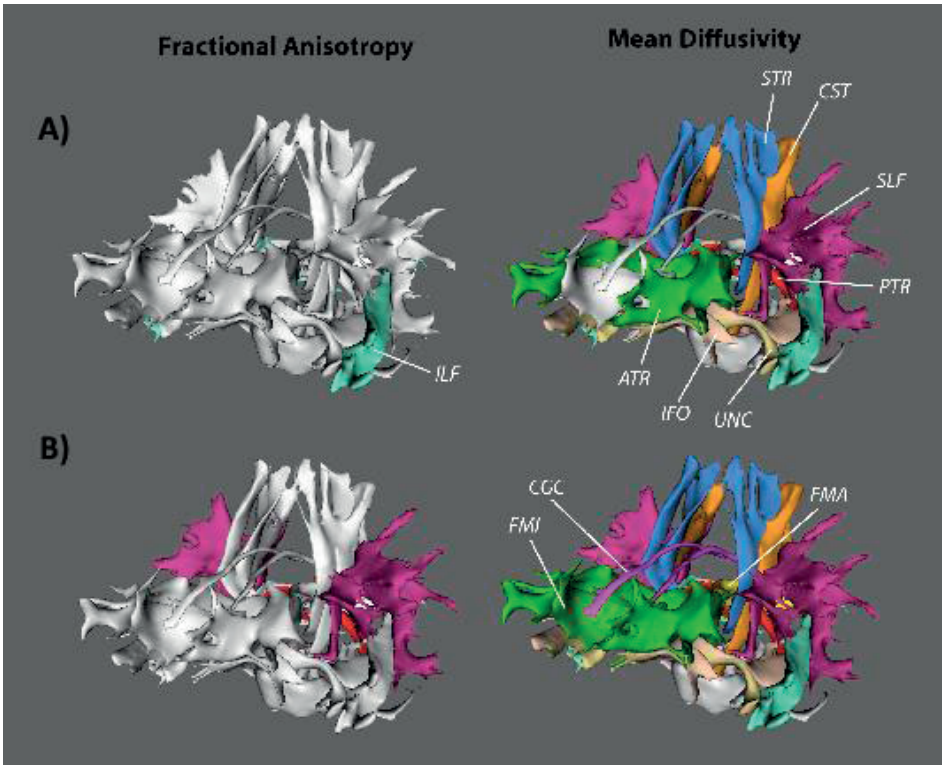

Figure 2. Association of **A)** ACR and **B)** eGFRcys with FA and MD in specific tracts. Adjusted for age, sex, white matter volume, intracranial volume, and log transformed white matter lesion volume.
Tracts with significant associations (after Bonferroni correction: $p<3.6\times10^{-3}$) are labelled and coloured.
Abbreviations: ACR: albumin-to-creatinine ratio, eGFRcys: cystatin C based estimated glomerular filtration rate, FA: fractional anisotropy, MD: mean diffusivity, ATR: anterior thalamic radiation, IFO: inferior fronto-occipital fasciculus, ILF: inferior longitudinal fasciculus, PTR: posterior thalamic radiation, SLF: superior longitudinal fasciculus, UNC: uncinate fasciculus, FMA: forceps major, FMI: forceps minor, CGC: cingulate gyrus part of cingulum, CGH: parahippocampal part of cingulum, CST: corticospinal tract, MCP: middle cerebellar peduncle, ML: medial lemniscus, STR: superior thalamic radiation.

The associations persisted after adjusting for history of stroke and conventional MRI-markers, indicating that decrease in kidney function might reflect early brain microstructural changes independent of co-existing comorbidities and pathologies.
A linear association between eGFRcys and white matter microstructure was present; however, we observed a U-shaped association between eGFRcr and DTI-parameters of white matter integrity. This discrepancy could be explained by the fact that subjects with very low creatinine are also at increased risk because of malnutrition and loss of muscle mass.[18] In line with this explanation, Seliger et al. reported a linear association between higher levels of serum cystatin C and prevalence of subclinical brain infarcts.[17] In contrast, they found that the prevalence of subclinical brain infarcts was higher in

both subjects with low and high serum creatinine suggesting a U-shaped association.[17] Levels of serum cystatin C are reported to be independent of muscle mass; nevertheless, some cardiovascular risk factors such as obesity and diabetes can be non-GFR determinants of serum cystatin C levels.[19] In addition, previous reports proposed that underlying inflammation can influence levels of cystatin C.[19] Since inflammation itself is a vascular risk factor, cystatin C may reflect inflammatory status independent of eGFR. However, in this study adjusting for cardiovascular risk factors as well as an inflammatory marker (C-reactive protein) did not change the associations.

Several explanations can be proposed for the association of kidney function with degeneration of white matter. First, kidney and the brain share several cardiovascular risk factors. Therefore, existence of these risk factors can simultaneously damage the vasculature of both kidney and brain.[1] While in this study adjusting for conventional cardiovascular risk factors such as blood pressure and excluding participants with diabetes, and cardiovascular disease did not change our findings, excluding participants with hypertension attenuated the associations. This might indicate that history of hypertension plays a role as an effect modifier and not as a confounder in the association between kidney function and white matter integrity. Future studies are needed to explore whether subjects with hypertension are more vulnerable to detrimental influences of impaired kidney function on white matter microstructural integrity. Second, it has been suggested that vascular damage is a diffuse phenomenon.[20] Given that the brain and kidney have similar circulation systems, and endothelial cells play a crucial role in both blood brain barrier and glomerular integrity,[1] it is possible that this association can originate from a systemic process affecting vascular beds in both organs.[20] Third, it is possible that impaired kidney function can lead to brain vascular injury via increase in pro-inflammatory factors and decrease in serum nitric oxide.[5] Nitric oxide regulates the function of the cerebral microcirculation and the blood brain barrier, which can contribute to cerebral hypoperfusion and subsequently white matter damage.[1]

In the tract-specific analyses, MD seemed to be a more sensitive marker for loss of white matter microstructural integrity in relation to kidney function. This might be explained by the prevailing theory that less uniform changes in FA are seen in deterioration of crossing fibers regions,[21] in contrast to MD that may show more consistent changes in areas of white matter loss. This is further supported by the considerable estimates for the prevalence of crossing fiber regions in the brain.[21]

The integrity of white matter is of great importance in normal functioning of the brain. Complex cognitive tasks are coordinated by interactions between different regions of the brain and intact white matter integrity plays an essential role in these interactions.[14, 22] In line with this notion, we previously showed that early changes in the white matter microstructure, as reflected in DTI-measures of the white matter, are associated with impaired cognitive function.[22] These associations were independent of

macrostructural brain abnormalities such as white matter lesions. Our findings might suggest that impairments in white matter integrity can be an underlying mechanism behind the association between impaired kidney function and cognitive dysfunction.
Strengths of our study include the large sample size and availability of extensive data on various cardiovascular risk factors, and macrostructural MRI-markers that enabled us to control for several potential confounders. Nevertheless, a number of limitations should be acknowledged. First, due to the cross-sectional design of the study, we cannot draw conclusions about the directionality and causality. Second, the cerebellum was not being fully incorporated in the field of view of the diffusion scan, making conclusion on brain stem tracts less reliable. In addition, our findings are based on a population-based study including relatively young and healthy individuals. Prevalence of kidney disease in this population is low and hence the associations are based on minor degrees of kidney dysfunction. Therefore, it is possible that the associations would be more prominent in older populations and in patients with kidney disease. In this study we did not have enough power to perform the analyses in participants with eGFR<60 mL/min/1.73 m^2.Further patient-based studies are needed to investigate this link in high risk individuals with lower eGFR levels.
In this study we showed that kidney function is related to impaired white matter microstructural integrity, suggesting that both kidney biomarkers and microstructural changes of white matter are biologically related. Our findings suggest that clinicians need to consider concomitant macro- and microstructural changes in the brain among subjects with impaired kidney function.

CHAPTER REFERENCES

1. Mogi M, Horiuchi M. Clinical Interaction between Brain and Kidney in Small Vessel Disease. Cardiol Res Pract 2011;2011:306189.
2. Bugnicourt JM, Godefroy O, Chillon JM, Choukroun G, Massy ZA. Cognitive disorders and dementia in CKD: the neglected kidney-brain axis. J Am Soc Nephrol 2013;24:353-363.
3. Krishnan AV, Kiernan MC. Neurological complications of chronic kidney disease. Nat Rev Neurol 2009;5:542-551.
4. Fabbian F, Casetta I, De Giorgi A, et al. Stroke and renal dysfunction: are we always conscious of this relationship? Clin Appl Thromb Hemost 2012;18:305-311.
5. Ikram MA, Vernooij MW, Hofman A, Niessen WJ, van der Lugt A, Breteler MM. Kidney function is related to cerebral small vessel disease. Stroke 2008;39:55-61.
6. Vermeer SE, Hollander M, van Dijk EJ, et al. Silent brain infarcts and white matter lesions increase stroke risk in the general population: the Rotterdam Scan Study. Stroke 2003;34:1126-1129.
7. Hofman A, Darwish Murad S, van Duijn CM, et al. The Rotterdam Study: 2014 objectives and design update. Eur J Epidemiol 2013;28:889-926.
8. Inker LA, Schmid CH, Tighiouart H, et al. Estimating glomerular filtration rate from serum creatinine and cystatin C. N Engl J Med 2012;367:20-29.
9. Rietveld I, Hofman A, Pols HA, van Duijn CM, Lamberts SW, Janssen JA. An insulin-like growth factor-I gene polymorphism modifies the risk of microalbuminuria in subjects with an abnormal glucose tolerance. Eur J Endocrinol 2006;154:715-721.
10. Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. Kidney inter, Suppl 2013;3:1-150.
11. Mahmoodi BK, Yatsuya H, Matsushita K, et al. Association of kidney disease measures with ischemic versus hemorrhagic strokes: pooled analyses of 4 prospective community-based cohorts. Stroke 2014;45:1925-1931.
12. Ikram MA, van der Lugt A, Niessen WJ, et al. The Rotterdam Scan Study: design and update up to 2012. Eur J Epidemiol 2011;26:811-824.
13. Koppelmans V, de Groot M, de Ruiter MB, et al. Global and focal white matter integrity in breast cancer survivors 20 years after adjuvant chemotherapy. Hum Brain Mapp 2014;35:889-899.
14. de Groot M, Ikram MA, Akoudad S, et al. Tract-specific white matter degeneration in aging. The Rotterdam Study. Alzheimers Dement 2014.
15. de Groot M, Vernooij MW, Klein S, et al. Improving alignment in Tract-based spatial statistics: evaluation and optimization of image registration. Neuroimage 2013;76:400-411.
16. Leening MJ, Kavousi M, Heeringa J, et al. Methods of data collection and definitions of cardiac outcomes in the Rotterdam Study. Eur J Epidemiol 2012;27:173-185.
17. Seliger SL, Longstreth WT, Jr., Katz R, et al. Cystatin C and subclinical brain infarction. J Am Soc Nephrol 2005;16:3721-3727.
18. Seronie-Vivien S, Delanaye P, Pieroni L, et al. Cystatin C: current position and future prospects. Clin Chem Lab Med 2008;46:1664-1686.
19. Stevens LA, Schmid CH, Greene T, et al. Factors other than glomerular filtration rate affect serum cystatin C levels. Kidney Int 2009;75:652-660.
20. Thompson CS, Hakim AM. Living beyond our physiological means: small vessel disease of the brain is an expression of a systemic failure in arteriolar function: a unifying hypothesis. Stroke 2009;40:e322-330.

21. Jeurissen B, Leemans A, Tournier JD, Jones DK, Sijbers J. Investigating the prevalence of complex fiber configurations in white matter tissue with diffusion magnetic resonance imaging. Hum Brain Mapp 2013;34:2747-2766.
22. Vernooij MW, Ikram MA, Vrooman HA, et al. White matter microstructural integrity and cognitive function in a general elderly population. Arch Gen Psychiatry 2009;66:545-553.

SUPPLEMENTAL MATERIAL