Mapping Associations between Creatinine, Cystatin C and Brain Atrophy in the Elderly: An N=716 ADNI Study

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INTRODUCTION

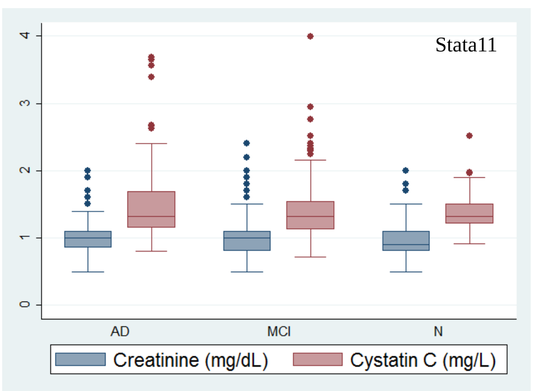
Chronic kidney disease impairs glomerular filtration rate (GFR) which is detected as elevated serum levels of kidney biomarkers such as creatinine and cystatin C. Prior studies have related poor kidney function to cognitive decline and generalized brain atrophy. However, so far, there have been no 3D maps showing the anatomical pattern of brain volumes associated with these kidney biomarkers.

HYPOTHESIS

We hypothesized that higher baseline serum creatinine & cystatin C would be associated with changes in brain volumes.

METHODS

To do this, we conducted a voxelwise regression using tensor based morphometry in a large cohort of 716 elderly Caucasian subjects scanned at baseline, as part of the Alzheimer's Disease Neuroimaging Initiative (ADNI). At each voxel within the brain, multiple regression was carried out to analyze statistical associations between brain volumes and inverse of serum creatinine levels. We used a standard false discovery rate (FDR) correction for multiple statistical comparisons across voxels of the brain, at the conventionally accepted level of q = 0.05.

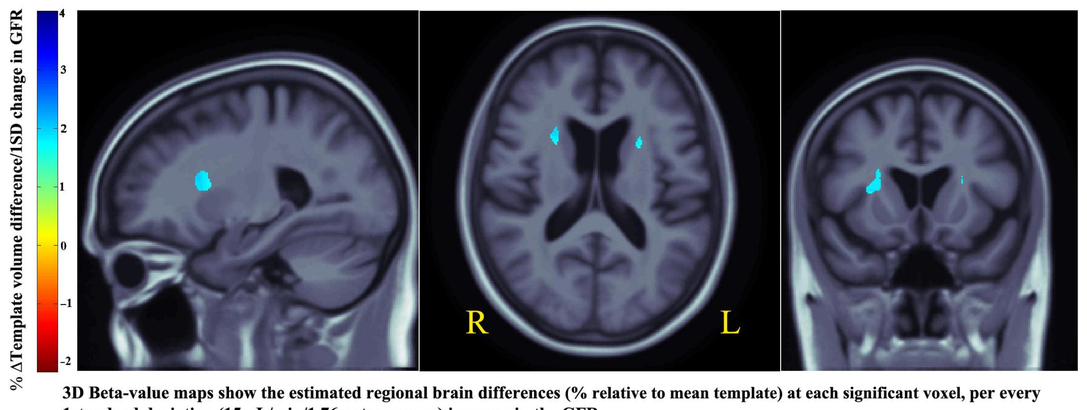


Box plots depicting the mean total plasma creatinine and cystatin C levels for AD, MCI and control groups respectively.

Mean±SD	AD	MCI	Controls
Age	75.6±7.6	75.1±7.2	76.2±5.0
Sex (M/F)	95/78	231/128	112/94
MMSE	23.4±2.0	27.1±1.8	29.2±1.0
Creatinine (mg/dL)	1.02±0.26 (n=164)	1.01±0.26 (n=348)	0.96±0.25 (n=204)
eGFR (ml/min/1.73m^2)	58.70±15.95	62.28±15.1	61.67±12.06
Systolic blood pressure (mm Hg)	137.0±16.97	135.2±17.8	134.4±17.0
White matter hyperintensity (cc)	1.34±2.7	0.87±2.5	0.72±2.2

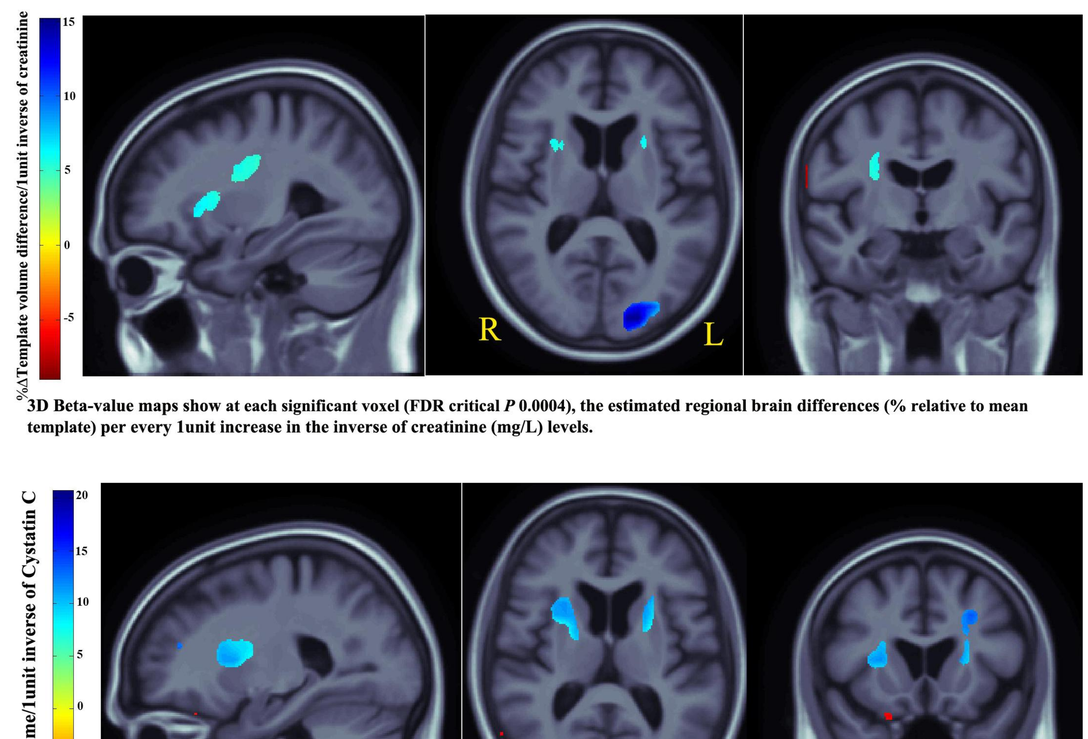
RESULTS

Linear regression analysis showed significant brain associations with inverse of creatinine and cystatin C levels in ADNI subjects. After correcting for multiple statistical comparisons, every 1SD (15 ml/min/1.76m^2) increase in GFR showed brain volume expansion of up to 4% , relative to the MDT. These correlations are partially independent of risk factors that affect brain atrophy such as age, sex and cardiovascular risk factors including systolic blood pressure.



3D Beta-value maps show the estimated regional brain differences (% relative to mean template) at each significant voxel, per every 1standard deviation (15mL/min/1.76metre square) increase in the GFR.

1/Creatinine and 1/CystatinC were significantly associated with brain volumes and also MMSE scores. There were no associations with white matter hyperintensity volumes, CSF beta amyloid or tau proteins respectively.



3D Beta-value maps show at each significant voxel (FDR critical *P* 0.0004), the estimated regional brain differences (% relative to mean template) per every 1unit increase in the inverse of creatinine (mg/L) levels.

3D Beta-value maps show at each significant voxel (<FDR critical *P*-value 0.0007), the estimated regional brain differences (% relative to mean template), per every 1unit increase in inverse of serum Cystatin C levels (1/(mg/L)).

CONCLUSION

Automated whole brain volumetric analysis of brain MRI revealed a three-dimensional pattern of creatinine and cystatin C associated brain atrophy, specifically in the white matter region. Early diagnosis of worsening renal function could permit early intervention to reduce the risks of cardiovascular events and cerebro-vascular events with kidney dysfunction.

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