Kidney Function Is Related to Cerebral Small Vessel Disease

M. Arfan Ikram, MD; Meike W. Vernooij, MD; Albert Hofman, MD, PhD; Wiro J. Niessen, PhD; Aad van der Lugt, MD, PhD; Monique M.B. Breteler, MD, PhD

Background and Purpose—Poor kidney function, as measured by glomerular filtration rate (GFR), is closely associated with presence of glomerular small vessel disease. Given the hemodynamic similarities between the vascular beds of the kidney and the brain, we hypothesized an association between kidney function and markers of cerebral small vessel disease on MRI. We investigated this association in a population-based study of elderly persons.

Methods—We measured GFR using the Cockcroft-Gault equation in 484 participants (60 to 90 years of age) from the Rotterdam Scan Study. Using automated MRI-analysis we measured global as well as lobar and deep volumes of gray matter and white matter, and volume of WML. Lacunar infarcts were rated visually. Volumes of deep white matter and WML and presence of lacunar infarcts reflected cerebral small vessel disease. We used linear and logistic regression models to investigate the association between GFR and brain imaging parameters. Analyses were adjusted for age, sex, and additionally for cardiovascular risk factors.

Results—Persons with lower GFR had less deep white matter volume (difference in standardized volume per SD decrease in GFR: \(-0.15\) [95% CI \(-0.26\) to \(-0.04\)], more WML (difference per SD decrease in GFR: \(0.14\) [95% CI \(0.03\) to \(0.25\)], and more often lacunar infarcts, although the latter was not significant. GFR was not associated with gray matter volume or lobar white matter volume. Additional adjustment for cardiovascular risk factors yielded similar results.

Conclusions—Impaired kidney function is associated with markers of cerebral small vessel disease as assessed on MRI. (Stroke. 2008;39:55-61.)

Key Words: brain ■ epidemiology ■ glomerular filtration rate ■ magnetic resonance imaging ■ small vessel disease

Poor kidney function is highly prevalent in the general elderly population.1,2 It often remains subclinical and is then only identified by measuring a decreased glomerular filtration rate (GFR).3 Poor kidney function is associated with features of large vessel disease, such as hypertension, arterial stiffness, and ischemic heart disease.4–6 Moreover, kidney dysfunction is also characterized by glomerular endothelium dysfunction and lipohyalinosis, both of which are features of small vessel disease in the kidney.7

In the elderly, small vessel disease is also abundantly present in the brain.8,9 White matter lesions (WML), lacunar infarcts, and subcortical atrophy are markers of cerebral small vessel disease that are visible on MRI10 and that increase the risk of stroke, cognitive decline, and dementia.11–13 Given the hemodynamic similarities between the vascular beds of the kidney and the brain, the small vessel disease in the kidney may be indicative of presence of small vessel disease in the brain. However, data on the relationship between kidney function and MRI-markers of cerebral small vessel disease are scarce. Two studies showed that decreased kidney function was associated with an increased prevalence of subclinical brain infarcts on MRI,15,16 which are mostly lacunar infarcts.9 However, they did not investigate WML or subcortical atrophy. Recently, the Northern Manhattan Study presented data that showed an association between kidney function and WML.17

We hypothesized an association between kidney function, as measured by GFR, and MRI-markers of cerebral small vessel disease and investigated this association in the population-based Rotterdam Scan Study.

Materials and Methods

Study Population

The Rotterdam Study is a large population-base cohort study in the Netherlands that started in 1990 and investigates the prevalence, incidence, and determinants of chronic diseases in the elderly.18 In 1995 to 1996 we randomly selected 965 living members (60 to 90 years of age) of the cohort in strata of sex and age (5 years) to participate in the Rotterdam Scan Study, designed to investigate age-related brain abnormalities on MRI.19 After excluding persons who were demented or had MRI contraindications, 832 persons were...
eligible and invited. Among these, 563 persons gave their written informed consent and participated in the study, which included physical examination, blood sampling, and an MRI scan of the brain (response 68%). Participants were in general healthier than nonparticipants.20 Of the 563 participants, 52 developed claustrophobia during MRI acquisition. Twenty-one datasets were unusable because of excessive ghosting artifacts (n = 5), scanning outside the range of coil sensitivity (n = 10), or other reasons (n = 6), leaving a total of 490 participants with complete and usable MRI data.21 The study protocol was approved by the medical ethics committee of the Erasmus MC, Rotterdam, the Netherlands. The large majority of participants (>97%) were of Caucasian ethnicity.

Measurement of Glomerular Filtration Rate
Nonfasting blood was collected and centrifuged within 30 minutes at 3000 rotations per minute for 10 minutes. Subsequently the serum was stored at −20°C for 1 week, until serum creatinine level was assessed by a nonkinetic alkaline picrate (Jaffe) method1 (Kone Autoanalyzer, Kone Corporation, Espoo, Finland and Elan, Merck, Darmstadt, Germany). The method was standardized against high performance liquid chromatography. The within-run precision was >98.5% and the day-by-day precision was >95.0%. Creatinine clearance was computed with the Cockcroft-Gault equation,22 corrected with a factor 0.9, and standardized for 1.73 m² body surface area using the Dubois23 formula: GFR=(140−age[years])(weight[kg]×1.23) (0.85 if female) (serum creatinine [μmol/L])−1 (0.9) (1.73) (weight[kg])−0.425 (height[cm])−0.127 (0.007184)−1. Creatinine clearance generally exceeds GFR by 10% to 15% because of additional urinary creatinine excretion attributable to tubular secretion.24 The Cockcroft Gault estimate of GFR was therefore additionally corrected with a factor of 0.9. Serum creatinine could not be assessed in 6 of the 490 persons because of technical difficulties, leaving 484 persons in our analysis.

MRI Acquisition
MRI scans of the brain were performed on a 1.5-Tesla MRI System (VISION MR, Siemens AG). The protocol included T1-weighted, proton-density weighted, and T2-weighted scans.20 Furthermore, a high-resolution, inversion-recovery double contrast, 3-D HASTE sequence was acquired.21 We used the proton-density, T2-weighted, and the first HASTE module (HASTE-Odd) for our multispectral volumetry.

Multi-Spectral Brain Tissue Volumetry
Data were stored onto a Linux Workstation. Preprocessing steps and the classification algorithm have been described.21,25 In summary, preprocessing included coregistration, nonuniformity correction, and variance scaling. Afterward, we used the k-nearest-neighbor (kNN) classifier to classify voxels into cerebrospinal fluid (CSF), gray matter (GM), normal white matter (WM), and WML.26 To minimize any misclassification of partial volume voxels as WML around cortical GM, we registered a manually created mask, within which voxels could be classified as WML. Using the kNN-classifier infarcts are classified as CSF and are not included in the volume of WML.

Using nonlinear transformation, noncerebral tissues (eg, eyes, skull, dura) were stripped.27,28 Volumes were calculated by summing all voxels of a single tissue class and multiplying by the voxel volume.

Validation methods and results have been described and showed very good to excellent agreement between automated classification and manual classification used as reference.21,25

For differentiation between lobar and deep brain tissue volumes, we first created a template scan, in which the lobar and deep regions were labeled according to the protocol as described by Bokde et al.29,30 Figure 1 shows an example of this segmentation, which uses anatomical landmarks and cerebral fissures as boundaries and distinguishes the lobar regions from a deep central region (ie, the area around the ventricles, which comprises the basal ganglia, insular cortex, corpus callosum, and the white matter in this region). The volume of the deep region reflects subcortical atrophy. Subsequently, we used validated nonrigid transformation to transform this template to each brain.27,28

Rating of Lacunar Infarcts
Lacunar infaracts were rated visually as focal hyperintensities on T2-weighted images, 3 mm in size or larger, and with a corresponding prominent hypointensity on T1-weighted images. We used the linear aspect of dilated perivascular spaces and their characteristic location around the anterior commissure to distinguish these from lacunar infaracts. Intrarater agreement for detection of infaracts was good (κ=0.80).31

Cardiovascular Determinants
Blood pressure was measured twice in sitting position on the right arm with a random-zero sphygmomanometer. We used the average of these 2 measurements in the analyses. Diabetes mellitus was defined as a random or postload glucose level of 11.1 mmol/L or higher, or use of oral blood glucose lowering drugs or insulin. Total cholesterol, high-density lipoprotein cholesterol, and C-reactive protein were measured in nonfasting serum with an automated enzymatic procedure. Plasma homocysteine was determined by fluorescence polarization immunosassay in IMX analyzer (Abbott Laboratories). History of myocardial infarction was positive if a participant had reported a myocardial infarction that was confirmed...
Table 1. Characteristics of the Study Population

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total Cohort, n=484</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, year</td>
<td>73.4 (7.8)</td>
</tr>
<tr>
<td>Women, n</td>
<td>245 (51%)</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>145.7 (20.5)</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>76.5 (11.5)</td>
</tr>
<tr>
<td>Blood pressure-lowering medication use, n</td>
<td>185 (38%)</td>
</tr>
<tr>
<td>Diabetes mellitus, n</td>
<td>24 (5%)</td>
</tr>
<tr>
<td>Smoking, pack years</td>
<td>20.4 (24.7)</td>
</tr>
<tr>
<td>History of myocardial infarction, n</td>
<td>37 (8%)</td>
</tr>
<tr>
<td>C-reactive protein, mg/l</td>
<td>3.71 (6.22)</td>
</tr>
<tr>
<td>Homocysteine, μmol/l</td>
<td>11.96 (4.47)</td>
</tr>
<tr>
<td>Total cholesterol, mmol/l</td>
<td>5.88 (1.05)</td>
</tr>
<tr>
<td>High-density lipoprotein cholesterol, mmol/l</td>
<td>1.28 (0.36)</td>
</tr>
<tr>
<td>Serum creatinine, μmol/l</td>
<td>89.9 (20.6)</td>
</tr>
<tr>
<td>Glomerular filtration rate, ml/min/1.73m²</td>
<td>54.8 (13.0)</td>
</tr>
</tbody>
</table>

Values are means (SD) or numbers (percentages).

by ECG or medical records. Use of blood pressure-lowering medication and smoking history were assessed during a home interview. The number of pack years of smoking was calculated by multiplying the number of cigarette packs smoked per day by the number of years smoked.

Statistical Analysis
All volumes were expressed as percentage of intracranial volume (=CSF+GM+normal WM+WML) to correct for individual head-size differences. Whole brain volume was defined as intracranial volume minus CSF volume. Total WM was defined as the sum of normal WM and WML. WML were natural log transformed because of skewness of the untransformed measure.

Apart from global brain tissue volumes, we also assessed lobar and deep brain tissue volumes. To enable better comparison between the effects of kidney function on different tissue types we calculated z-scores for each participant for each tissue type separately (z-score=individual tissue volume minus mean tissue volume divided by the standard deviation).

With multiple linear regression we first investigated the association of quartiles of GFR with brain tissue volumes and WML volume. Persons in the highest quartile of GFR (indicating best kidney function) were taken as reference category. We then investigated the association of GFR continuously per standard deviation (SD) decrease with brain tissue volumes and WML volume. We first examined global brain tissue volumes and subsequently lobar and deep tissue volumes separately. With logistic regression we investigated the association of GFR with lacunar infarcts.

All analyses were adjusted for age and sex and additionally for systolic blood pressure, diastolic blood pressure, blood pressure-lowering medication, diabetes mellitus, pack years of smoking, previous myocardial infarction, homocysteine, total cholesterol, high-density lipoprotein cholesterol, and C-reactive protein.

Finally, we repeated the analyses after adjusting for or excluding persons with a cortical infarct on MRI (n=25).

Results
Table 1 shows the characteristics of the study population. Figure 2 shows the associations between quartiles of kidney function and z-scores of global brain tissue volumes. Table 2 shows these associations using GFR continuously per SD decrease. Persons with low GFR had a smaller brain volume (difference in brain volume, expressed as percentage of intracranial volume, per SD decrease in GFR: −0.35% [95% confidence interval (CI) −0.68% to −0.03%]). This smaller brain volume was not attributable to smaller GM volume, but rather attributable to smaller total and normal WM volume (Figure 2 and Table 2). Also, persons with low GFR had a larger volume of WML (difference in WML volume, expressed as percentage of intracranial volume, between lowest and upper quartile of GFR 0.47% [95% CI 0.02% to 0.92%]; difference per SD decrease 0.19% [95% CI 0.03% to 0.36%]; see also Figure 2 and Table 2).

Investigating lobar and deep tissue volumes separately showed that decreased GFR was associated with both smaller lobar and deep WM volume. However, this association was weak for lobar WM, whereas it was very strong for deep WM (Table 3 and Figure 3). GFR was also related to lobar WML, and to a somewhat lesser extent deep WML (Table 3). We did not find any association between GFR and either lobar or deep GM volume.

When additionally adjusting for cardiovascular risk factors, the associations attenuated marginally, but GFR was still related to volume of WML, to deep WM volume, and (borderline) to brain volume (Tables 2 and 3).

Finally, persons with lower GFR had a higher prevalence of lacunar infarcts, although this was not statistically significant (age and sex adjusted prevalence odds-ratio of lacunar infarcts per SD decrease in GFR: 1.11 [95% CI 0.81 to 1.51]).

Repeating the analyses after adjusting for or excluding persons with a cortical infarct on MRI did not change any of the associations. Finally, separate analyses for men and women yielded no consistent results different from the overall analyses.

Discussion
In this population-based study we found that persons with a decreased kidney function, as measured by low GFR, had smaller brain volume, smaller deep WM volume and more WML. GFR was not associated with GM volume or lobar WM volume. These associations were independent of cardiovascular risk factors.

Strengths of our study include the population-based setting, the large sample size of elderly persons aged 60 years and older, and our focus on various subclinical manifestations of cerebral small vessel disease. Moreover, the automated MR-analysis not only allowed us to accurately quantify GM and WM atrophy, but also to investigate lobar and subcortical brain atrophy separately.

Before interpreting our data some methodological issues need to be considered. The study is based on a cross-sectional study design, which limits the interpretation of our results with respect to cause and effect. Another consideration is that we used the Cockcroft Gault equation to estimate GFR and not the abbreviated Modification of Diet in Renal Disease (MDRD). However, the MDRD equation has been developed in a population for which a large part of our participants would not meet inclusion criteria. Therefore, using the MDRD in our population would yield misclassified measures of kidney function and would lead to dilution of the associations. For this reason and because participants were predominantly of only one ethnicity, we chose to use the Cockcroft-Gault equation in our present study. We measured serum
creatinine only once, ignoring possible intraindividual fluctuations in serum creatinine levels. This may have caused our estimates to be slightly underestimated. Furthermore, serum creatinine is influenced by nonrenal factors and additional measurement of urinary albumin might have improved the sensitivity and specificity of our assessment of kidney function. Also, cystatin C is considered a superior measure of kidney function to serum creatinine. However, neither urinary albumin nor cystatin C were measured in our study.

We cannot exclude that in some cases lacunar infarcts may have been misclassified as dilated perivascular spaces and vice versa. However, given that no association has been reported yet between kidney function and dilated perivascular spaces we feel that any misclassification would probably be random and would lead to an underestimation of the true effect.

We defined subcortical (deep) brain regions according to the protocol by Bokde et al., which could be criticized for using arbitrarily defined borders between lobar and deep regions. Insular cortex for example is included in the deep brain region, whereas white matter adjacent to occipital horns for example is not. We are aware that this division may not fully correspond to the “true” position of the borders, and might not completely disentangle the separate effects of kidney function on lobar and deep brain regions. However, because the “true” position of the borders itself is still largely unknown, we chose to apply a protocol that was designed for its practical use in population-based studies.

Table 2. Relationship Between Kidney Function and z-Scores of Brain Tissue Volumes

<table>
<thead>
<tr>
<th>Glomerular Filtration Rate</th>
<th>Brain Volume</th>
<th>Grey Matter</th>
<th>Normal White Matter</th>
<th>Total White Matter</th>
<th>White Matter Lesions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Per SD decrease, Model I</td>
<td>-0.10 (-0.18; -0.01)</td>
<td>0.02 (-0.10;0.14)</td>
<td>-0.10 (-0.20;0.01)</td>
<td>-0.08 (-0.18;0.03)</td>
<td>0.14 (0.03;0.25)</td>
</tr>
<tr>
<td>Per SD decrease, Model II</td>
<td>-0.09 (-0.19;0.01)</td>
<td>0.02 (-0.12;0.16)</td>
<td>-0.08 (-0.20;0.04)</td>
<td>-0.04 (-0.17;0.08)</td>
<td>0.16 (0.04;0.29)</td>
</tr>
</tbody>
</table>

Values represent difference in z-scores of brain tissue volumes per standard deviation decrease in kidney function. Total white matter is the sum of normal white matter and white matter lesions. White matter lesions are further natural log transformed. SD standard deviation.

Model I: adjusted for age, sex. Model II: adjusted for age, sex, systolic and diastolic blood pressure, blood pressure-lowering medication use, diabetes mellitus, smoking, C-reactive protein, homocysteine, total cholesterol, high-density lipoprotein cholesterol, and previous myocardial infarction.

Figure 2. The association between quartiles of kidney function and z-scores of global brain tissue volumes. A, Brain volume. B, Gray matter. C, Normal white matter. D, Total white matter. E, White matter lesions. Total white matter is the sum of normal white matter and white matter lesions. White matter lesions are further natural log transformed. The range of glomerular filtration rate for each quartile was as follows: quartile 1, 18.23 to 45.57 mL/min/1.73 m²; quartile 2, 45.58 to 54.37 mL/min/1.73 m²; quartile 3, 54.38 to 64.26 mL/min/1.73 m²; quartile 4, 64.27 to 98.25 mL/min/1.73 m². Dots represent the age- and sex-adjusted means. Lines represent standard errors. *Significantly different from persons in the highest quartile (P<0.05).
Several studies have shown that poor kidney function is associated with cardiovascular complications attributable to large-vessel disease, such as arterial calcification, heart failure, myocardial infarction, and cardiac mortality.\textsuperscript{4,14,34,35} Only a few studies investigated kidney function specifically in relation to cerebrovascular disease and found that poor kidney function indicated an increased risk of clinical and subclinical stroke.\textsuperscript{15,16,36,37}

We found that decreased GFR was related to WML, subcortical atrophy, and to a lesser extent lacunar infarcts. We hypothesize that small vessel disease may underlie this association. The vascular beds of both the kidney and the brain have very low resistance and are passively perfused at high flow throughout systole and diastole.\textsuperscript{14} Because of these unique features, which are not present in other organs, the blood vessels in the kidney and brain are highly susceptible to fluctuations in blood pressure and flow. Indeed, high blood pressure and other vascular risk factors have been shown to lead to glomerular lipohyalinosis and endothelium dysfunction, both of which are characteristics of small vessel disease in the kidney.\textsuperscript{7,38} Lipohyalinosis and endothelium dysfunction are also underlying features of WML and lacunar infarcts in the brain.\textsuperscript{39} Moreover, because cerebral small vessel disease affects deep perforating arterioles, it is also characterized by atrophy in this deep subcortical region.\textsuperscript{40} This is reflected in our dataset by the relationship between GFR and deep WM atrophy.

We did not find any association between GFR and GM volume. This observation is in line with our previous report showing that cardiovascular risk factors, such as diastolic blood pressure and smoking, were more related to WM atrophy than to GM atrophy.\textsuperscript{21}

Previously, we have reported that several cardiovascular risk factors are associated with cerebral small vessel disease, including blood pressure,\textsuperscript{20} CRP,\textsuperscript{41} and homocysteine.\textsuperscript{42} We found that adjustment for such cardiovascular risk factors only marginally changed the associations of GFR with cerebral small vessel disease. This could mean that these

### Table 3. Relationship Between Kidney Function and z-Scores of Lobar and Deep White Matter Volume

<table>
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<tbody>
<tr>
<td>Per SD decrease, Model I</td>
<td>−0.08 (−0.19;0.02)</td>
<td>−0.06 (−0.17;0.04)</td>
<td>0.15 (0.04;0.26)</td>
<td>−0.17 (−0.28;−0.07)</td>
<td>−0.15 (−0.26;−0.04)</td>
<td>0.10 (−0.01;0.21)</td>
</tr>
<tr>
<td>Per SD decrease, Model II</td>
<td>−0.07 (−0.19;0.05)</td>
<td>−0.03 (−0.16;0.09)</td>
<td>0.18 (0.05;0.30)</td>
<td>−0.17 (−0.29;−0.04)</td>
<td>−0.13 (−0.26;0.00)</td>
<td>0.11 (−0.01;0.24)</td>
</tr>
</tbody>
</table>

Values represent difference in z-scores of brain tissue volumes per standard deviation decrease in kidney function. Total white matter is the sum of normal white matter and white matter lesions. White matter lesions are further natural log transformed.

Model I: adjusted for age, sex. Model II: adjusted for age, sex, systolic and diastolic blood pressure, blood pressure-lowering medication use, diabetes mellitus, smoking, C-reactive protein, homocysteine, total cholesterol, high-density lipoprotein cholesterol, and previous myocardial infarction.

### Figure 3.

The association between quartiles of kidney function and z-scores of lobar and deep white matter volumes. A, Normal white matter, lobar. B, Total white matter, lobar. C, White matter lesions, lobar. D, Normal white matter, deep. E, Total white matter, deep. F, White matter lesions, deep. Total white matter is the sum of normal white matter and white matter lesions. White matter lesions are further natural log transformed. The range of glomerular filtration rate for each quartile was as follows: quartile 1, 18.23 to 45.57 mL/min/1.73 mm\textsuperscript{2}; quartile 2, 45.58 to 54.37 mL/min/1.73 mm\textsuperscript{2}; quartile 3, 54.38 to 64.26 mL/min/1.73 mm\textsuperscript{2}; quartile 4, 64.27 to 98.25 mL/min/1.73 mm\textsuperscript{2}. Dots represent the age and sex adjusted means. Lines represent standard errors. *Significantly different from persons in the highest quartile (P<0.05).
associations are not mediated by these risk factors, but by a different mechanism. A possibility is that GFR reflects risk factors for cerebral small vessel disease that we did not measure in our study, eg, genetic factors. Another explanation could be that GFR is a better marker of small vessel disease than these concomitantly measured cardiovascular risk factors. However, more studies are needed to elucidate the exact mechanism underlying the association of GFR with cerebral small vessel disease.

In conclusion, our study shows that impaired kidney function, as measured by decreased GFR, is related to subclinical markers of cerebral small vessel disease, independent of cardiovascular risk factors. Therefore, GFR might be used as an easily measurable indicator of cerebral small vessel disease. Moreover, given that cerebral small vessel disease is related to an increased risk of stroke, cognitive decline, and dementia, our data provide important information in addition to the known risk of adverse cardiac outcomes in persons with poor kidney function. Thus, our study further emphasizes the importance of identifying those with subclinical kidney disease. These persons might then benefit from installment of proper therapy. However, more studies are needed to investigate the extent to which any intervention can be beneficial.

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Disclosures

None.

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