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Associations of microalbuminuria with brain atrophy and white matter hyperintensities in hypertensive sibships

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Abstract

Background—Because of similarities between brain and kidney microvascular disease, there may be a relationship between measures of renal microvascular disease and brain structural changes in middle aged or elderly individuals

Objective—To determine whether the urine albumin/creatinine ratio (UACR), a measure of renal microvascular disease, is associated with brain atrophy and white matter hyperintensities.

Methods—As part of a larger study of the genetics of hypertension, we performed brain imaging and assessed microalbuminuria and other vascular risk factors including diabetes, hypertension, hyperlipidemia and hyperhomocysteinemia in 1253 individuals from hypertensive sibships (age mean 63.8 years, range 50 to 91; 65% women; 49% African-American; 78% hypertensive). Semi-automated quantitative measurements of brain atrophy (BA) and white matter hyperintensities (WMH) were carried out on the brain MR scans.

Results—In logistic regression models, elevated UACR was associated with greater BA (odds ratio (OR)=1.70 (95% CI 1.14, 2.54) and burden of WMH (OR=2.06 (95% CI 1.37, 3.10) after controlling for demographic factors, blood glucose, hypertension severity, duration of smoking and serum homocysteine. In contrast to elevated UACR, the associations with elevated creatinine or reduced glomerular filtration rate and WMH were not significant in the fully adjusted models.

Conclusions—In this cohort with an overrepresentation of hypertensives, elevated UACR was independently associated with both brain atrophy and white matter hyperintensities. Brain volume

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loss and WMH burden might represent expressions of microvascular disease that share common mechanisms with nephrosclerosis.

Keywords

brain; magnetic resonance imaging; microalbuminuria; vascular risk factors; diabetes; hypertension

Introduction

Brain microvascular disease is a strong candidate mechanism to account for associations between vascular risk factors and brain structural changes such as white matter hyperintensities and brain atrophy[1–6]. Neuropathological evidence of micro-infarcts and lacunar infarcts in dementing illness[7–12] supports the clinical relevance of brain microvascular disease.

Hypertensive nephrosclerosis is the second most common cause of chronic kidney disease in the United States. Typically, nephrosclerosis develops gradually over decades[13]. Histologically, nephrosclerosis is characterized by vascular, glomerular, and interstitial involvement. Vascular involvement includes intimal thickening and luminal narrowing of small renal arteries and glomerular arterioles[14]. Glomerular and interstitial changes are largely the consequence of ischemic injury. In hypertensives, microalbuminuria indicates endothelial dysfunction and may be an early sign of renal microvascular disease leading to nephrosclerosis. It can be measured non-invasively using a ratio of albumin to creatinine in the urine[15–17]. Renal microvascular disease has been associated with stroke[18]. However, there has been only scant examination of relationships between renal microvascular disease and brain structural changes[19] in persons without stroke.

In the setting of a large cross-sectional study of the genetics of microangiopathic complications of hypertension[20, 21], we examined the urine albumin/creatinine ratio (UACR) for its associations with white matter hyperintensities and brain atrophy. Based on prior studies, we expected that diabetes, hypertension, and hyperhomocysteinemia[1, 22] would show associations with the MR measures of brain injury. We were interested in learning whether the UACR would also show associations with brain volume and white matter hyperintensities, independent of the established risk factors. This is important because while the brain and the kidney are known to be affected by hypertension and other vascular risk factors, the mechanisms of brain injury by microvascular disease – separate from frank infarction – remain controversial. To the extent that cross sectional associations imply some commonality in pathogenesis, the consequences of endothelial damage in the kidney imply that associated brain structural changes might also be due to endothelial damage.

Methods

Subjects

The subjects in the present study, the Genetics of Microangiopathic Brain Injury (GMBI) Study, were a subset of the 3434 subjects who were members of sibships that were initially enrolled in Rochester, MN and Jackson MS between June 1996 and August 2000 in the Genetic Epidemiology Network of Arteriopathy (GENOA) of the Family Blood Pressure Program[23], a study designed to identify and characterize genetic determinants of hypertension and its associated cardiac, renal and cerebral complications. Subjects were enrolled if two or more members of their sibship had hypertension. The only exclusionary criterion at enrollment into the GENOA study was the presence of a secondary cause of hypertension (such as documented renal artery stenosis or advanced renal insufficiency) in the index sibs.

The sampling frame of the GENOA Rochester cohort was the Mayo Clinic diagnostic index and medical record linkage system of the Rochester Epidemiology Project. It was used to identify non-Hispanic white residents of Olmsted County, MN with a diagnosis of essential hypertension made before age 60. The Jackson MS cohort of the Atherosclerosis Risk in Communities study [24], which had originally been a probability sample of persons with driver's licenses, was used to ascertain African-American sibships. If the eligible proband had at least one sibling with hypertension, all available full biologic siblings of the index hypertensive including normotensive siblings were invited to participate in interviews, physical examinations, and phlebotomy.

Between December 2000 and May 2006, the subjects returned for a second study visit that included assessment of cardiovascular risk factors, followed by an ancillary study visit that included a cognitive assessment and a brain MR scan. The only exclusions to participation in the brain MR were a history of stroke, neurologic disease or implanted metal devices. For the current analysis, we included only subjects who participated in the MR scan and were 50 years or older. Of the 1525 MR-eligible subjects, 64 were excluded due to technically unsuitable MR scans, 78 were excluded because they had Mini-Mental State examination scores <24, 71 were excluded because their risk factor assessments predated the MR scan by more than 36 months, and 59 were excluded due to missing risk factor data, leaving 1253 subjects for the current analysis.

Study protocols were approved by the human studies review board of the Mayo Clinic and the University of Mississippi Medical Center, and written informed consent was obtained from all participants.

Imaging

All scans were performed on identically equipped Signa 1.5 Tesla MRI scanners (GE Medical Systems, Waukesha, WI) under the supervision of Mayo Clinic and University of Mississippi Medical Center neuroradiologists.

The methodology for the semi-automated MR measurements has been previously described [25]. Total intracranial volume was measured from T1-weighted sagittal images with each set consisting of contiguous 5-mm-thick slices; matrix 256 × 192; no interslice gap: repetition time=500 milliseconds, echo time=minimum full (14) milliseconds, repetitions=2, time=2.5 minutes, field of view=24 cm.

Brain volume, ventricular volume (VV) and white matter hyperintensity (WMH) volumes were determined from axial fluid-attenuated inversion recovery images with each set consisting of contiguous 3-mm interleaved slices with no interslice gap obtained with the following sequence: echo time=144.8 ms, inversion time=2600 ms, repetition time=16,000 ms, bandwidth=±32 kHz, echo train length=22, one signal average, time=8 minutes, field of view=22 cm, matrix=256 × 160. The difference between total intracranial volume and brain volume provided a measure of brain atrophy (BA).

Interactive image processing steps were performed by a research associate who had no knowledge of the subjects' personal or medical histories. A fully automated algorithm was used to segment each slice of the edited multislice fluid-attenuated inversion recovery sequence based on image intensity into voxels assigned to 1 of 3 categories: brain, cerebrospinal fluid, or WMH. The mean absolute error of this method is 1.4% for brain volume and 6.6% for WMH volume, and the mean test–retest coefficient of variation is 0.3% for brain volume and 1.4% for WMH volume.

Subjects with cortical infarcts (n=31) were excluded from these analyses because of the distortion that would be introduced in the automated segmentation algorithm. Lacunar infarcts were included in the WMH image intensity category and therefore in the WMH estimates. Both subcortical and periventricular WMH are included in the WMH estimate.

Measurement of urine albumin and other risk factors

For all included subjects, the assessment of urine albumin and creatinine, as well as all other risk factors, was performed once within 36 months of the MR scan. Interviews regarding risk factors were conducted by trained and certified interviewers.

Blood was drawn after an overnight fast, and urine was collected on the morning of the study visit. Serum creatinine, glucose, homocysteine, total cholesterol, HDL cholesterol, and triglyceride concentrations and urine albumin, total protein and creatinine concentrations were measured by standard methods on a Hitachi 911 Chemistry analyzer (Roche Diagnostics, Indianapolis, IN)[26]. Urinary albumin was measured by immunoturbidimetry utilizing antibody to human albumin in an automated immunoprecipitin analysis system (Diasorin Inc, Stillwater, MN) and urinary creatinine was measured by a colorometric dye-binding technique in the Roche Hitachi 911 system as previously described[27]. Plasma lipids and lipoproteins were determined by enzymatic methods. LDL cholesterol was estimated by the Friedewald equation as previously described for this study[28].

A subject was considered to have an elevated UACR if the value was > 20 for men and > 30 for women. These values for a spot urine sample correspond to microalbuminuria as measured by a 24 hour urine collection of ≥ 30 mg albumin/24 h[29].

Estimated glomerular filtration rate was calculated using National Kidney Foundation practice guidelines MDRD equation[30]. The equation used was: eGFR = 186.3 × (serum creatinine$^{-1.154}$) × (age$^{-0.203}$) × (0.742 for women) × (1.21 for blacks). Reduced estimated glomerular filtration rate was defined as having a value of <45 ml/min per 1.73 m^2.

To calibrate our measurements of creatinine with the Cleveland Clinic assay used in the MDRD equation, 0.22 mg/dL was added to the raw serum creatinine values[26]. Elevated serum creatinine was defined using the cutpoints of 1.51 mg/dL for men and 1.26 mg/dL for women[31].

In order to have a measure of hypertension that accounted for medication use, we defined severity of hypertension based on the number of anti-hypertensive medications and the level of blood pressure: number of hypertension medication categories a patient was taking + (DBP-70)/30 + (SBP-120)/60.

Analyses

SAS (Carey, NC) were used for all analyses. Descriptive statistics were generated for demographic, risk factor and imaging data. We defined increased BA, VV and WMH as the upper quartile of the residual values from models of each imaging feature adjusting for age at MR scan, race, sex, and TIV (for BA and VV) or brain volume (for WMH). The other 3 quartiles served as the reference group. We used multivariable logistic regression models to estimate the odds ratios (OR) and 95% confidence intervals (95% CI) of increased BA, VV and WMH for persons with elevated UACR, elevated serum creatinine and reduced glomerular filtration rate. Analyses were performed separately for each of the 3 imaging features.

Results

The 1253 individuals (643 whites and 610 African-Americans; 812 women and 441 men) had a mean age of 63.8 years (standard deviation = 7.5; range 50 to 91 years). There were 994 (79%) individuals aged 50–70 years and 259 (21%) over 70 years. By virtue of the design of the parent study, 78% were hypertensive. A large fraction (90%) of the 265 (21% of entire study) diabetics in the study were also hypertensive. The lag between measurement of the vascular risk factors and the MR scan was <12 months for 727 (58%) subjects, between 12–24 months for 444 (35.5%) subjects and between 24 and 36 months for 82 (6.5%) subjects.

The median and intra-quartile values of imaging features, stratified by race and sex, are given in Table 1. Because WMH and VV had skewed distributions, the values were log-transformed for analyses. Initial models (Table 2A) found that age, gender, race, and total intracranial volume (for BA and VV) or brain volume (for WMH) were each significant predictors ($p \leq .01$) of one or more imaging feature. Consequently, this set of covariates was forced into all models.

Levels of UACR, other kidney functions and other vascular risk factors across race and gender groups are shown in Table 3. Only 5.8% of subjects had an eGFR <45 ml/min per 1.73 m^2. In univariate analyses, measures of hypertension, hyperglycemia, hyperhomocysteinemia and smoking history showed significant associations in the expected direction ($p<.01$) with one or more imaging feature (Table 2B). Higher levels of total cholesterol and calculated low density lipoproteins showed associations with lower levels of WMH.

In models controlling for age at the time of the MR scan, gender, race, and either total intracranial volume (in the BA and VV models) or brain volume (in the WMH models), elevated UACR was associated with increased OR's for having increased BA, VV and WMH (Table 4). A second set of models was constructed in which measures of hyperglycemia and hypertension severity were included, and a third set in which smoking history (log(pack years) and serum homocysteine were also added. In the third set of models, OR's for both BA (OR=1.70, 95% CI 1.14, 2.54) and WMH (2.06, 95% CI 1.37, 3.10) indicated that elevated UACR was significantly and independently associated with increased BA and WMH burden. Associations of elevated UACR with VV were not significant models with other risk factors. Table E-1 shows the parameter estimates for all predictor variables in the fully adjusted models for BA and WMH. Addition of total cholesterol or calculated low-density lipoproteins resulted in no change in the models. Addition of an indicator variable for antihypertensive drugs and anti-diabetic had little to no impact on the models for either BA (OR=1.61, 95% CI 1.08, 2.42) or WMH (2.08, 95% CI 1.37, 3.16).

We also constructed similar logistic regression models using elevated creatinine and reduced glomerular filtration rate (Table 4). The cut-points for elevated creatinine and reduced glomerular filtration rate yielded similar numbers of subjects with impairment to that of elevated UACR (see Table 3). Reduced estimated glomerular filtration rate was also associated increased BA in all models, but not associated with WMH changes in any model. In models without other risk factors, elevated creatinine was associated with increased risks for brain imaging changes. However, in contrast to elevated UACR, there were no significant associations with elevated creatinine and imaging features in the fully adjusted models including hyperglycemia, hypertension severity, smoking history and serum homocysteine levels.

We also performed a number of additional analyses to assess the robustness of the UACR associations. When UACR was analyzed as a continuous variable using (log(UACR), significant odds ratios were also seen in the fully adjusted model for WMH (OR=1.19 (95%

CI 1.06, 1.33). For each doubling in the amount of UACR, there was a 4.0% increase in WMH. However, the association was not significant for BA (OR=1.07 (95% CI 0.95, 1.20) or VV.

Analyses using elevated UACR were repeated after stratifying the cohort based on the presence or absence of hypertension. The point estimates of the OR's for WMH and BA were all in the same direction and approximately the same magnitude, but because of wider confidence intervals in the small non-hypertensive subsample (n= 270), significant associations were seen only in the hypertensive (n=983) subsample. For example, among hypertensives, there was a significant association in model 3 between WMH and elevated UACR (OR=2.08 (95%CI 1.34, 3.25) which is very similar to the group as a whole (Table 4). We also stratified by the presence or absence of diabetes. The point estimates were larger for the diabetics than the non-diabetics. For example, among diabetics, there was a significant association in model 3 between WMH and elevated UACR (OR=2.74 (95%CI 1.43, 5.25) which was larger than in the group as a whole but with a wider confidence interval (Table 4).

We examined models of elevated UACR stratified by gender (Table 5). OR's for associations with BA and WMH were significant for women in all 3 models. A similar pattern was seen for men although the associations were not as strong. However, even in the fully adjusted models for men, trends for increased risk were present for BA and WMH.

Models stratified by race suggested differences between African-Americans and whites (Table 5). While elevated UACR was associated with increased WMH in both race groups, the OR's were nearly doubled in whites compared to African-Americans. In contrast, elevated UACR was associated with an increased risk of BA only in African-Americans.

Discussion

In the normal state, the renal glomerular filtration apparatus effectively prevents leakage of serum albumin into the urine. A consequence of endothelial dysfunction in the renal microvasculature is glomerular leakage of small amounts of albumin into the urinary space. Consistent with its role as a marker of generalized microvascular dysfunction, microalbuminuria is an established risk factor for cardiovascular disease[15–18]. Although it often occurs in the setting of diabetes or hypertension, prior studies have indicated that the association of microalbuminuria with cardiovascular disease endpoints is independent of diabetes and hypertension[16, 18]. Microalbuminuria is a more specific measure of kidney microvascular disease than either elevated serum creatinine or reduced glomerular filtration rate. Serum creatinine elevations and reduced glomerular filtration may occur for reasons other than microvascular disease.

We found that elevated UACR was associated with increased risk of WMH and BA. The association with WMH was previously reported recently[19], while the associations with BA are novel, to the best of our knowledge. African-Americans showed stronger associations between UACR and BA, while whites showed stronger associations between UACR and WMH. The associations with WMH were stronger for UACR than for either elevated serum creatinine or reduced estimated glomerular filtration rate, consistent with the greater specificity of microvascular pathology to both microalbuminuria and white matter lesions. The magnitude of the associations of elevated UACR with BA or WMH were modest, roughly a 2-fold increased risk, but the associations persisted even when other risk factors[1–6] known to affect brain structural integrity including homocysteine, diabetes, hypertension, lipoprotein levels and cigarette smoking were included in models, or when the group was stratified by diabetes or hypertension.

That the presence of WMH can be linked to microvascular disease is not a new observation. However, the mechanisms through which microvascular disease produces changes in WMH

as well as BA are unclear. WMH[3, 32, 33] and covert lacunar infarcts[34, 35], accumulate gradually with advancing age. Loss of brain volume with advancing age occurs gradually. How might these processes occur insidiously?

The intimal fibromuscular hyperplasia and lipohyalinosis observed in cerebral arterioles of the elderly[8–10] are similar to the vascular changes in nephrosclerosis. In the kidney, it is not infarction but rather endothelial dysfunction that occurs as a result of microvascular disease. Endothelial damage in the kidney in the setting of hypertension and other diseases occurs gradually and cumulatively. Thus, considering the parallels between brain and kidney, gradual endothelial damage and leakage of serum proteins into the brain's interstitial spaces could also be part of the pathophysiology of brain microvascular disease[36]. The pathology of WMH has been considered to be due to "incomplete infarction"[37], but an equally plausible mechanism would be chronic micro-extravasation of blood proteins into perivascular spaces in white matter. Dysfunction in cerebral endothelium has also been hypothesized to contribute to Alzheimer's disease[38, 39]. The manner in which microvascular changes occur in the kidney illuminates how a "vascular" disease might produce gradual anatomic changes in the brain *without* stroke-like clinical events. While association studies such as ours cannot prove how microvascular disease contributes to loss of brain structural integrity, they support the hypothesis. The magnitude of the impact of microvascular disease on brain volume or white matter hyperintensities may be small on a yearly basis, but its cumulative consequences over decades could be clinically important.

We found no compelling evidence for gender specificity to the association of UACR and WMH or BA. However, the pattern of associations with WMH and BA differed between African-Americans and whites. These differences should be replicated by others, but in the meantime, they suggest that the expression of brain microvascular disease might differ based on racial background.

Microvascular disease in the retina measured in late middle age has also been shown to be associated with cognitive impairment and brain structural changes[40–42]. The link between retinal microvascular changes and brain structural changes represents additional support for the systemic involvement of microvascular mechanisms.

The strengths of the study include the large number of African-Americans and whites. Imaging studies utilized quantitative techniques to measure brain volume, ventricular volume and burden of white matter hyperintensities rather than more subjective rating scales. However, there are limitations of the study. All measurements of risk factors were performed at one point in time. Although the measurement of UACR and other risk factors preceded the MR scanning by up to 3 years, the study should be considered cross-sectional. The study cohort was selected on the basis of hypertension in at least 2 family members. Thus, the results may not be generalizable to normotensive cohorts. In addition, most hypertensive subjects were being treated with blood pressure lowering medications. Although we screened out large infarcts, our automated image analysis combined lacunar infarcts and WMH. We also did not differentiate between subcortical and periventricular locations of WMH.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. Knopman DS, Mosley TH, Catellier DJ, Sharrett AR. Cardiovascular risk factors and cerebral atrophy in a middle-aged cohort. Neurology 2005;65:876–81. [PubMed: 16186527]
2. Longstreth WT Jr, Arnold AM, Manolio TA, et al. Clinical correlates of ventricular and sulcal size on cranial magnetic resonance imaging of 3,301 elderly people. The Cardiovascular Health Study. Collaborative Research Group. Neuroepidemiology 2000;19:30–42. [PubMed: 10654286]
3. Longstreth WT Jr, Manolio TA, Arnold A, et al. Clinical correlates of white matter findings on cranial magnetic resonance imaging of 3301 elderly people. The Cardiovascular Health Study Stroke 1996;27:1274–82.
4. Carmelli D, Swan GE, Reed T, et al. Midlife cardiovascular risk factors and brain morphology in identical older male twins. Neurology 1999;52:1119–24. [PubMed: 10214731]
5. den Heijer T, Vermeer SE, Clarke R, et al. Homocysteine and brain atrophy on MRI of non-demented elderly. Brain 2003;126:170–5. [PubMed: 12477704]
6. den Heijer T, Vermeer SE, van Dijk EJ, et al. Type 2 diabetes and atrophy of medial temporal lobe structures on brain MRI. Diabetologia 2003;46:1604–10. [PubMed: 14595538]
7. White L, Petrovitch H, Hardman J, et al. Cerebrovascular pathology and dementia in autopsied Honolulu-Asia Aging Study participants. Ann N Y Acad Sci 2002;977:9–23. [PubMed: 12480729]
8. Esiri MM, Wilcock GK, Morris JH. Neuropathological assessment of the lesions of significance in vascular dementia. J Neurol Neurosurg Psychiatry 1997;63:749–53. [PubMed: 9416809]
9. Thal DR, Ghebremedhin E, Orantes M, Wiestler OD. Vascular pathology in Alzheimer disease: correlation of cerebral amyloid angiopathy and arteriosclerosis/lipohyalinosis with cognitive decline. J Neuropathol Exp Neurol 2003;62:1287–301. [PubMed: 14692704]
10. Vinters HV, Ellis WG, Zarow C, et al. Neuropathologic substrates of ischemic vascular dementia. J Neuropathol Exp Neurol 2000;59:931–45. [PubMed: 11089571]
11. Chui HC, Zarow C, Mack WJ, et al. Cognitive impact of subcortical vascular and Alzheimer's disease pathology. Ann Neurol 2006;60:677–87. [PubMed: 17192928]
12. Kovari E, Gold G, Herrmann FR, et al. Cortical microinfarcts and demyelination significantly affect cognition in brain aging. Stroke 2004;35:410–4. [PubMed: 14707236]
13. Cohen, EP. Chronic Renal Failure and Dialysis. In: Dale, DC.; Federman, DD., editors. ACP Medicine, 2006 Edition. American College of Physicians; New York: 2006. p. 2031-2042.
14. Kashgarian, M. Hypertensive Disease and Kidney Structure. In: Laragh, JH.; Brenner, BM., editors. Hypertension: Pathophysiology, Diagnosis and Management. 2. Raven Press, Ltd; New York: 1995. p. 433-43.
15. Govindarajan G, Whaley-Connell A, Mugo M, Stump C, Sowers JR. The cardiometabolic syndrome as a cardiovascular risk factor. Am J Med Sci 2005;330:311–8. [PubMed: 16355016]
16. Donnelly R, Yeung JM, Manning G. Microalbuminuria: a common, independent cardiovascular risk factor, especially but not exclusively in type 2 diabetes. J Hypertens Suppl 2003;21:S7–12. [PubMed: 12769161]
17. Gerstein HC, Mann JF, Yi Q, et al. Albuminuria and risk of cardiovascular events, death, and heart failure in diabetic and nondiabetic individuals. JAMA 2001;286:421–6. [PubMed: 11466120]
18. Cao JJ, Barzilay JI, Peterson D, et al. The association of microalbuminuria with clinical cardiovascular disease and subclinical atherosclerosis in the elderly: the Cardiovascular Health Study. Atherosclerosis 2006;187:372–7. [PubMed: 16242696]
19. Wada M, Nagasawa H, Kurita K, et al. Microalbuminuria is a risk factor for cerebral small vessel disease in community-based elderly subjects. J Neurol Sci 2007;255:27–34. [PubMed: 17320908] Epub 2007 Feb 23
20. Turner ST, Fornage M, Jack CR Jr, et al. Genomic susceptibility loci for brain atrophy in hypertensive sibships from the GENOA study. Hypertension 2005;45:793–8. [PubMed: 15699467]
21. Turner ST, Jack CR, Fornage M, et al. Heritability of leukoaraiosis in hypertensive sibships. Hypertension 2004;43:483–7. [PubMed: 14718359]

22. Vermeer SE, van Dijk EJ, Koudstaal PJ, et al. Homocysteine, silent brain infarcts, and white matter lesions: The Rotterdam Scan Study. Ann Neurol 2002;51:285–9. [PubMed: 11891822]
23. Daniels PR, Kardia SL, Hanis CL, et al. Familial aggregation of hypertension treatment and control in the Genetic Epidemiology Network of Arteriopathy (GENOA) study. Am J Med 2004;116:676–81. [PubMed: 15121494]
24. ARIC Investigators. The Atherosclerosis Risk in Communities (ARIC) Study: design and objectives. Am J Epidemiol 1989;129:687–702. [PubMed: 2646917]
25. Jack CR Jr, O'Brien PC, Rettman DW, et al. FLAIR histogram segmentation for measurement of leukoaraiosis volume. J Magn Reson Imaging 2001;14:668–76. [PubMed: 11747022]
26. Turner ST, Kardia SL, Mosley TH, et al. Influence of genomic loci on measures of chronic kidney disease in hypertensive sibships. J Am Soc Nephrol 2006;17:2048–55. [PubMed: 16775034]Epub 2006 Jun 14
27. Freedman BI, Beck SR, Rich SS, et al. A genome-wide scan for urinary albumin excretion in hypertensive families. Hypertension 2003;42:291–6. [PubMed: 12925555]Epub 2003 Aug 18
28. O'Meara JG, Kardia SL, Armon JJ, et al. Ethnic and sex differences in the prevalence, treatment, and control of dyslipidemia among hypertensive adults in the GENOA study. Arch Intern Med 2004;164:1313–8. [PubMed: 15226165]
29. de Jong PE, Curhan GC. Screening, monitoring, and treatment of albuminuria: Public health perspectives. J Am Soc Nephrol 2006;17:2120–6. [PubMed: 16825331]
30. Levey AS, Coresh J, Balk E, et al. National Kidney Foundation practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Ann Intern Med 2003;139:137–47. [PubMed: 12859163]
31. Rule AD, Jacobsen SJ, Schwartz GL, et al. A comparison of serum creatinine-based methods for identifying chronic kidney disease in hypertensive individuals and their siblings. Am J Hypertens 2006;19:608–14. [PubMed: 16733233]
32. Longstreth WT Jr, Arnold AM, Beauchamp NJ Jr, et al. Incidence, manifestations, and predictors of worsening white matter on serial cranial magnetic resonance imaging in the elderly: the Cardiovascular Health Study. Stroke 2005;36:56–61. [PubMed: 15569873]
33. Liao D, Cooper L, Cai J, et al. The prevalence and severity of white matter lesions, their relationship with age, ethnicity, gender, and cardiovascular disease risk factors: the ARIC Study. Neuroepidemiology 1997;16:149–62. [PubMed: 9159770]
34. Longstreth WT Jr, Bernick C, Manolio TA, et al. Lacunar infarcts defined by magnetic resonance imaging of 3660 elderly people: the Cardiovascular Health Study. Arch Neurol 1998;55:1217–25. [PubMed: 9740116]
35. Vermeer SE, Den Heijer T, Koudstaal PJ, et al. Incidence and risk factors of silent brain infarcts in the population-based Rotterdam Scan Study. Stroke 2003;34:392–6. [PubMed: 12574548]
36. Wardlaw JM, Sandercock PA, Dennis MS, Starr J. Is breakdown of the blood-brain barrier responsible for lacunar stroke, leukoaraiosis, and dementia? Stroke 2003;34:806–12. [PubMed: 12624314]
37. Englund E. Neuropathology of white matter lesions in vascular cognitive impairment. Cerebrovasc Dis 2002;13(Suppl 2):11–5. [PubMed: 11901237]
38. Roher AE, Kuo YM, Esh C, et al. Cortical and leptomeningeal cerebrovascular amyloid and white matter pathology in Alzheimer's disease. Mol Med 2003;9:112–22. [PubMed: 12865947]
39. Iadecola C. Neurovascular regulation in the normal brain and in Alzheimer's disease. Nat Rev Neurosci 2004;5:347–60. [PubMed: 15100718]
40. Wong TY, Mosley TH Jr, Klein R, et al. Retinal microvascular changes and MRI signs of cerebral atrophy in healthy, middle-aged people. Neurology 2003;61:806–11. [PubMed: 14504325]
41. Wong TY, Klein R, Sharrett AR, et al. Retinal microvascular abnormalities and cognitive impairment in middle-aged persons: the Atherosclerosis Risk in Communities Study. Stroke 2002;33:1487–92. [PubMed: 12052979]
42. Ikram MK, De Jong FJ, Van Dijk EJ, et al. Retinal vessel diameters and cerebral small vessel disease: the Rotterdam Scan Study. Brain 2006;129:182–8. [PubMed: 16317022]

Table 1

Imaging Features in Study Cohort

Variable	African American Women (N=428)		African American Men (N=182)		White Women (N=384)		White Men (N=259)	
	Median	(Q1, Q3)*	Median	(Q1, Q3)*	Median	(Q1, Q3)*	Median	(Q1, Q3)*
Brain volume (cc)	1030.2	(972.5, 1087.8)	1136.9	(1073.2, 1226.4)	1098.0	(1036.4, 1164.7)	1226.9	(1137.2, 1285.7)
Brain atrophy (BA) (Total intracranial volume – brain volume, cc)	286.7	(245.41, 326.1)	342.9	(293.3, 390.5)	281.1	(244.2, 322.3)	343.4	(290.4, 389.4)
Ventricle volume (VV) (cc)	17.2	(12.87, 25.5)	23.0	(17.1, 31.8)	19.3	(13.7, 27.4)	27.8	(19.2, 41.6)
White matter hyperintensity (WMH) volume (cc)	6.8	(4.87, 10.2)	8.2	(5.8, 13.8)	5.8	(4.3, 9.3)	6.6	(5.2, 9.5)

* Interquartile range

Table 2

Linear Regression Models of demographic variables for (A) imaging features and (B) vascular risk factors.

	Brain Atrophy			Log (Ventricular Volume)			Log (Volume of White Matter Hyperintensity)		
	Estimate	**SE**	***p***	**Estimate**	**SE**	***p***	**Estimate**	**SE**	***p***
A. Imaging Features									
Intercept	−326.506	28.146	<0.001	−10.1139	1.2609	<0.001	−7.7731	1.4610	<0.001
Age	3.397	0.215	<0.001	0.0310	0.0018	<0.001	0.0381	0.0022	<0.001
Male Gender	6.176	4.368	0.157	0.1163	0.0335	<0.001	0.0448	0.0381	0.239
African-American Race	17.569	3.567	<0.001	−0.0811	0.0306	0.008	0.2058	0.0351	<0.001
Log (Brain Volume)/Log (TIV)/TIV*	0.289	0.017	<0.001	1.5416	0.1721	<0.001	1.0318	0.1992	<0.001
B. Vascular Risk Factors†									
Hypertension severity	4.909	1.372	<0.001	0.0251	0.0099	0.011	0.0690	0.0125	<0.001
Log(serum glucose)	29.03	6.487	<0.001	0.1875	0.0558	<0.001	0.1350	0.0676	0.046
Serum homocysteine	2.573	0.557	<0.001	0.0107	0.0039	0.007	0.0167	0.0063	0.008
Log(pack-years smoking)	0.999	1.035	0.334	0.0143	0.0079	0.071	0.0282	0.0100	0.005
Total Cholesterol	−0.030	0.042	0.478	0.0003	0.0003	0.314	−0.0011	0.0004	0.007
High-density Lipoproteins	0.147	0.093	0.114	0.0006	0.0007	0.405	−0.0014	0.0009	0.111
Calculated Low-density Lipoproteins	−0.064	0.044	0.143	0.0000	0.0003	0.927	−0.0011	0.0004	0.014
Log(triglycerides)	3.449	3.194	0.280	0.0749	0.0257	0.004	0.0547	0.0287	0.056

*TIV: Total Intracranial Volume

†Risk factor models control for age at time of MR exam, gender, race, and total intracranial volume (for BA and VV) or brain volume (for WMH)

Table 3

Distribution of vascular risk factors across race and sex groups.

Variable†	African American Women (N=428)		African American Men (N=182)		White Women (N=384)		White Men (N=259)	
	Median or N	(Q1, Q3)* or %	Median or N	(Q1, Q3)* or %	Median or N	(Q1, Q3)* or %	Media n or N	(Q1, Q3)* or %
Urine Albumin/ Creatinine Ratio	5.4	(2.8, 13.0)	4.8	(2.8, 15.1)	2.9	(1.5, 5.3)	3.5	(2.0, 6.4)
Elevated Urine Albumin/ Creatinine Ratio (N, %)	61	(14%)	37	(20%)	10	(3%)	21	(8%)
Serum Creatinine (mg/dL)	1.0	(0.8, 1.1)	1.2	(1.1, 1.4)	1.0	(0.9, 1.1)	1.2	(1.1, 1.4)
Elevated Creatinine (N, %)	42	(10%)	38	(21%)	32	(8%)	42	(16%)
Estimated GFR	75.7	(63.5, 89.0)	75.7	(64.4, 85.9)	63.5	(52.9, 71.6)	62.6	(55.1, 72.0)
Reduced GFR (N, %)	17	(4%)	6	(3%)	29	(7.5%)	21	(8%)
Diabetes (N, %)	119	(28%)	47	(26%)	50	(13%)	49	(19%)
Taking Anti-diabetic Medication (N, %)	103	(24%)	39	(21%)	33	(8.6%)	33	(13%)
Ever smoke (N, %)	123	(29%)	112	(62%)	150	(39%)	155	(60%)
Pack-years (for smokers)	15.0	(5.9, 31.5)	23.0	(9.4, 38.0)	18.1	(5.0, 34.6)	24.0	(10.0, 42.0)
Hypertension (N, %)	341	(80%)	129	(71%)	304	(79%)	209	(81%)
Severity of Hypertension	1.9	(0.9, 2.8)	1.7	(0.7, 2.8)	1.6	(0.8, 2.4)	1.8	(1.0, 2.6)
Taking Anti-hypertensive Medication (N, %) ††	312	(73%)	110	(60%)	293	(76%)	197	(76%)
Homocysteine (μM/L)	9.1	(7.6, 10.8)	10.3	(8.7, 12.1)	9.0	(7.8, 10.5)	10.3	(9.0, 12.0)
Total Cholesterol	202.5	(179.3, 231.5)	190.0	(163.0, 214.0)	203.8	(182.0, 228.0)	185.0	(164.5, 212.0)
High-density Lipoproteins	59.3	(49.5, 73.4)	47.3	(39.6, 57.2)	55.1	(46.9, 64.5)	42.0	(37.5, 49.7)
Calculated Low-density Lipoproteins	120.0	(95.5, 146.8)	116.3	(92.9, 144.2)	122.2	(99.1, 143.9)	115.8	(97.7, 137.9)
Triglycerides	101.0	(75.5, 140.5)	95.8	(72.5, 144.5)	146.5	(98.5, 206.8)	127.5	(97.5, 175.0)
Taking Lipid-lowering Medication (N, %)	78	(18%)	38	(21%)	101	(26%)	114	(44%)

* Interquartile Range

† See Methods section for description of risk factors

†† Use of antihypertensive medication regimens: There were 353 (28.2%) of subjects on monotherapy (beta-blocker (7% of total cohort), calcium channel blocker (5%), diuretic (7%), renin-angiotensin-aldosterone system (RAAS) inhibitors (8%), others (1%). There were 559 (44.6%) of subjects on combination therapy: beta blockers plus others (no RAAS) (8%), beta blockers and RAAS (9%), RAAS and others (no beta blockers) 20%, neither beta blockers nor RAAS (7%).

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Table 4

Logistic Regression Models for upper quartile of BA, WMH and VV for elevated UACR, elevated serum creatinine and reduced glomerular filtration rate.[†]

	Model 1[a]			Model 2[b]			Model 3[c]		
	OR	95% CI		OR	95% CI		OR	95% CI	
Elevated UACR									
Brain atrophy	2.117*	1.447	3.097	1.824*	1.222	2.721	1.701*	1.139	2.540
White matter hyperintensities	2.380*	1.639	3.457	2.106*	1.409	3.148	2.058*	1.366	3.102
Ventricular Volume	1.718*	1.155	2.557	1.473	0.957	2.267	1.422	0.924	2.189
Elevated serum creatinine									
Brain atrophy	1.804*	1.232	2.641	1.666*	1.132	2.453	1.448	0.970	2.161
White matter hyperintensities	1.693*	1.166	2.458	1.533+	1.042	2.255	1.474	0.980	2.219
Ventricular Volume	1.158	0.786	1.706	1.090	0.732	1.624	0.995	0.662	1.496
Reduced glomerular filtration rate									
Brain atrophy	2.926*	1.780	4.811	2.657*	1.610	4.383	2.226*	1.294	3.829
White matter hyperintensities	1.117	0.676	1.845	0.986	0.592	1.643	0.864	0.502	1.486
Ventricular Volume	1.439	0.869	2.382	1.325	0.794	2.221	1.178	0.698	1.987

[a] Model 1: Adjusts for age, race, sex, and TIV/Brain.

[b] Model 2: Included variables in model 1 plus log(glucose) and hypertension severity.

[c] Model 3: Included variables in model 2 plus log(pack-years) and serum homocysteine.

[+] p-value < 0.05

[*] p-value < 0.01

[†] Brain Atrophy, White Matter Hyperintensities, and ventricle classified using the upper quartile of the residual values from models adjusting for age, race, sex, and brain size (TIV for BA, log(TIV) for VV, and log(brain volume) for WMH).

UACR classified using clinical definition of > 20 for men and > 30 for women.

Elevated serum creatinine defined using the cutpoints of 1.51 mg/dL for men and 1.26 mg/dL for women.

Reduced estimated GFR defined as < 45 ml/min per 1.73 m^2.

Table 5

Race and Sex stratified logistic regression models of elevated UACR

	Model 1[a]			Model 2[b]			Model 3[c]		
	OR	95% CI		OR	95% CI		OR	95% CI	
Race									
Brain Atrophy									
White	1.381	0.662	2.882	1.268	0.616	2.610	1.201	0.583	2.472
Black	2.432*	1.549	3.818	2.286*	1.396	3.745	2.106*	1.281	3.461
White Matter Hyperintensities									
White	3.290*	1.524	7.105	3.388*	1.563	7.346	3.314*	1.499	7.325
Black	2.110*	1.371	3.245	1.650+	1.009	2.698	1.605	0.973	2.648
Ventricular Volume									
White	2.142+	1.045	4.391	1.970	0.935	4.150	1.845	0.880	3.868
Black	1.557	0.968	2.502	1.358	0.805	2.293	1.359	0.805	2.297
Sex									
Brain Atrophy									
Women	2.138*	1.276	3.582	1.902+	1.093	3.312	1.760+	1.001	3.096
Men	1.925+	1.080	3.431	1.545	0.832	2.872	1.441	0.776	2.674
White Matter Hyperintensities									
Women	2.171*	1.308	3.603	2.054*	1.198	3.522	2.096*	1.215	3.614
Men	2.776*	1.509	5.104	2.019+	1.016	4.012	1.950	0.965	3.941
Ventricular Volume									
Women	1.581	0.928	2.693	1.226	0.695	2.164	1.168	0.668	2.041
Men	1.795	0.986	3.268	1.720	0.900	3.288	1.684	0.875	3.239

[a] Model 1: Adjusted for age, race, sex, and TIV/logTIV/LogBrain.

[b] Model 2: Included variables in model 1 plus log(glucose) and hypertension severity.

[c] Model 3: Included variables in model 2 plus log(pack-years) and homocysteine.

+ p-value < 0.05

* p-value < 0.01

BA, VV and WMH classified using the upper quartile of the residual values from models adjusting for age, race (not in models stratified by race), sex (not in models stratified by sex), and brain size (TIV for BA, log(TIV) for VV, and log(brain volume) for WMH).

UACR classified using clinical definition of > 20 for men and > 30 for women.