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Vascular imaging abnormalities and cognition: Mediation by Cortical Volume in non-demented persons: ARIC-NCS Study

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Abstract

Background and Purpose—The relationships between cerebrovascular lesions visible on imaging and cognition are complex. We explored the possibility that cerebral cortical volume mediated the relationship.

Methods—1906 non-demented participants (59% women; 25% African-American; mean age 76.6 years) in the Atherosclerosis Risk in Communities (ARIC) study underwent cognitive assessments, risk factor assessments, and quantitative MR imaging for white matter hyperintensities (WMH) and infarcts. The Freesurfer imaging analysis pipeline was used to determine regional cerebral volumes. We examined associations of cognitive domain outcomes with cerebral volumes (hippocampus, and separate groups of posterior and frontal cortical regions

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of interest (ROI)) and cerebrovascular imaging features (presence of large or small cortical/subcortical infarcts and WMH volume). We performed mediation pathway analyses to assess the hypothesis that hippocampal and cortical volumes mediated associations between cerebrovascular imaging features and cognition.

Results—In unmediated analyses, WMH and infarcts were both associated with worse psychomotor speed/executive function (PS/EF). In mediation analyses, WMH and infarcts associations on PS/EF were significantly attenuated, but not abolished, by the inclusion of the posterior cortical ROI volume in the models, and the infarcts on PS/EF association was attenuated, but not abolished, by inclusion of the frontal cortical ROI volume.

Conclusions—Both WMH and infarcts were associated with cortical volume, and both lesions were also associated with cognitive performance, implying shared pathophysiological mechanisms. Although cross-sectional, our findings suggest that WMH and infarcts could be proxies for clinically covert processes that directly damage cortical regions. Microinfarcts are one candidate for such a clinically covert process.

Keywords

Magnetic resonance imaging; cerebral small vessel disease; white matter hyperintensities; cerebral infarction; cognition

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The mechanisms by which cerebrovascular disease (CVD) causes cognitive impairment have been elusive. While the volume of infarcted tissue was an obvious initial candidate as a quantitative marker of pathology[1], persons with clinically overt, large infarcts account for only a small fraction of cognitively impaired individuals with CVD[2–5]. The presence of even one visible lacunar infarct is associated with cognitive impairment or cognitive decline[6–10], and the associations of white matter hyperintensities with cognition do not occur only with severe disease[11–14]. Because one or two lacunar infarcts or moderate WMH burden are themselves unlikely to be sufficient to damage enough cognitively eloquent grey matter or pathways, the associations of WMH and smaller infarcts with cognitive impairment imply that WMH or visible lacunes must be proxies for a more broadly distributed pathological process.

We had the opportunity to conduct a large-scale clinical and imaging cross-sectional analysis of non-demented individuals in the Atherosclerosis Risk in Communities (ARIC) Neurocognitive Study cohort. We tested the hypothesis that the cognitive consequences of WMH and smaller infarcts are mediated by another pathophysiological process, specifically variations in regional cerebral cortical volume. Regional cortical volumes are a measure of neuronal and synaptic structural integrity. Our analyses do not require us to specify how visible subcortical cerebrovascular lesions cause loss of cortical volume, but microinfarcts are the most plausible candidate mechanism[5, 15–18].

METHODS

Participants

The ARIC study began with a 1987–89 baseline examination of cardiovascular risk factors in men and women aged 45–64 years who were representative of four US communities, Washington County MD, Forsyth County NC, Jackson MS, and suburban Minneapolis MN. See Figure 1 and Appendix for ARIC study flow.

ARIC conducted a fifth examination (V5) between June, 2011 and August, 2013; institutional review boards of each ARIC center approved the protocol. Of 10,749 original ARIC cohort members alive at the start of V5 recruitment, 713 (6.6%) died prior to an examination, leaving 10,036 alive through August 2013. Of these, 6,538 (age 66–90) took part (5,918 full clinic exams, 228 abbreviated clinic exams, 392 home or care-facility exams). The overall V5 response rate was 65% (6,538/10,036).

A subset of ARIC V5 participants without contraindications were selected for a brain MRI: 1) all persons who had previous scans in 2004–6, 2) those with low cognitive test scores \declines on longitudinally-administered tests, and 3) an age-stratified random sample of the remaining individuals. Sampling fractions for the random sample were set for participants <80 and ≥80 years of age to approximate the age distribution of those selected from the cognitively suspect group and were modified slightly over the course of the study to achieve a goal of approximately 2000 total MRI scans. 74/1980 (4%) were excluded due to cognitive impairment sufficient to suspect dementia (Mini-Mental Status Examination (MMSE) scores, <21 if white and <19 if African-American).

Cognitive Assessments

Participants were administered a battery of neuropsychological tests. Standardized administration and scoring have been described previously with normative data from the ARIC cohort[19]. Cognitive domains included: Memory (Delayed Word Recall Test, Logical Memory immediate and delayed recall, and incidental Learning from the Wechsler Memory Scale-III), Psychomotor Speed/Executive Function (PS/EF) (Digit Symbol Substitution Test, Trail Making Test parts A and B and WAIS-R Digits Span Backwards), and Language (Letter fluency, Boston Naming Test, and Animal Naming). As previously reported, we constructed Z-scores for each domain by averaging the test scores within a domain, subtracting the domain mean and dividing by the domain standard deviation. A global composite Z-score was also derived from the three domain scores. The language domain Z-score lacked associations with imaging features in preliminary analyses and was not further examined in mediation analyses.

Vascular Risk Factors and APOE genotype

All participants also underwent an extensive evaluation of vascular risk factors at each ARIC visit[20, 21] Medical histories for diabetes mellitus, hypertension, smoking and a history of stroke (through December 31, 2011) were used in the current analyses. APOE genotyping was performed using standard methods. (see Appendix for details.)

Imaging

MR scans were performed at each site on 3 Tesla Siemens (various models) scanners using a common set of sequences that included a 3D volumetric Magnetization Prepared Gradient Echo (MPRAGE) and a Fluid Attenuated Inversion Recovery (FLAIR) sequences. WMH burden was measured quantitatively using an algorithm developed at Mayo Clinic Rochester[22, 23] and reported in cm^3. WMH were defined as has been codified in recent guidelines[24]. All analyses involving WMH include total intracranial volume as a covariate. Freesurfer (version 5.1)[25] was used to calculate regional cortical volumes, reported in cm^3.

Brain infarcts were identified, counted and measured by a trained imaging technician and confirmed by radiologists (KK, CRJ) as previously described[26]. Cortical infarctions were characterized on FLAIR sequences as hyperintense lesions ≥ 10 mm (large) or 5–10 mm (small) in greatest dimension, extending to the cortical surface, that includes cortical grey matter and may include underlying white matter. Subcortical infarctions were characterized as hyperintense lesions with a dark center (≥ 3mm in diameter) seen in the white matter, infratentorial, and central gray/capsular regions, and distinguishable from perivascular spaces. Because the number of participants with multiple infarcts was low, we collapsed all infarct ratings into a new variable representing the presence of at least one infarct of any type, size or location, referred to as “infarcts.”

Using the Freesurfer atlas[27], we prespecified 3 regions of interest (ROI’s) based on relevance to cerebrovascular disease or cognition. They were (1) the combined right and left hippocampal formations; (2) Posterior ROI: mean cortical volume of a group of regions that are part of the posterior default mode network[28] and are associated with Alzheimer’s disease (AD)[29] from both right and left hemispheres: hippocampus, parahippocampal gyrus, entorhinal cortex, inferior parietal lobule, precuneus and cuneus; and (3) Frontal ROI: mean cortical volume of regions in the frontal lobe from both right and left hemispheres: rostral/caudal anterior cingulate, rostral/caudal mid-frontal, lateral orbital frontal, medial orbital frontal, paracentral, pars opercularis, pars triangularis, precentral, superior frontal, and frontal pole. Frontal dysfunction has been specifically implicated in CVD[30]. All ROI volumes are expressed in cm^3, and all models adjusted for total intracranial volume to account for differences in head size across participants.

Statistical Analyses

Primary analyses were conducted using general linear models. Potential nonlinear relationships were examined with lowess smooth curves and modeled using fractional polynomial and linear-spline formulations. Potential outlier effects were assessed with DFFITS for influential points, Cook’s D statistic, and graphical displays such as residual and added-variable plots.

ARIC participants were selected to receive an MRI under the probabilistic sampling plan described above. Sampling weights were derived as the product of inverse sampling fractions and the inverse probability of completing the exam to account for dropout/missingness. All models incorporated these probability sampling weights in order to represent the full ARIC visit 5 clinic cohort.

Scores from the Trail Making tests were first log-transformed and multiplied by −1 so that low scores across all tests indicated worse performance. For the Logical Memory tests, a single Z score was created as the average Z score for the immediate and delayed recall sections. Participants who were unable to complete any test due to cognitive impairment were assigned a Z score of −2 for that test.

White matter hyperintensity burden was positively skewed, therefore and we $\log_2$-transformed WMH volumes.

Nonlinearity diagnostics showed that associations between cognitive composites and volumetric measures were substantially stronger for participants with smaller versus larger volumes. We expressed this analytically using fully stratified models for structural association estimates, with cut-points of ≤6 mm^3 for hippocampal ROIs, ≤60 mm^3 for posterior cortical ROI's and ≤150 mm^3 for frontal cortical ROIs, and using fractional polynomial formulations for mediation estimates. Cut-point knots were found using maximum likelihood type approaches.

We used standard mediation pathway approaches[31] to examine whether relationships between CVD imaging features (WMH and infarcts) and cognition (global, memory, PS/EF) potentially operated through regional volumetric paths (hippocampal, posterior and frontal ROI's); see Figure 2. *First*, we examined relationships between CVD imaging features and ROI volumes. *Second*, we examined relationships between ROI volumes and cognition. *Third*, we examined relationships between CVD imaging features and cognition. *Fourth*, we assessed whether relationships between CVD imaging features and cognition were attenuated when additionally adjusting for ROI volumes. Formal mediation estimates were calculated from indirect effects (i.e. the difference between path #3: total effect and path #4: direct effect) using structural equation models[32] with pathways specified as in Figure 2.

All models were adjusted for clinical and demographic variables including age, sex, race, education, history of diabetes, history of hypertension, history of alcohol use, history of smoking, *APOE* 4 genotype and total intracranial volume. Interaction terms were examined to assess potential modifying effects of sex and/or race; none were supported. Sensitivity analyses to examine stability of estimates were conducted examining adjustment model, nonlinearity threshold and sampling weight incorporation; similar results were found throughout.

RESULTS

Table 1 shows that the 1906 non-demented ARIC participants who underwent MR (mean age 75 (range 67–90) years, 60% women, 22% black) and the 4558 who did not were fairly similar. Vascular risk factors were common in the cohort, with 29% diabetic and 68% hypertensive. The *APOE* 4 allele frequency of 28% was in line with a typical non-demented population.

We first determined total adjusted associations between sets of cognitive composites, volumetric composites and the two CV imaging features (WMH and infarcts). For path #1 in Figure 2, we found associations between the volumetric measures, and both WMH and

infarcts after adjusting for demographics, vascular risk factors and *APOE* genotype (Table 2). For example, each doubling of WMH burden (i.e. a one unit increase in $\log_2$(WMH cm^3) volume was associated with a decrease in hippocampal ROI volume of 0.095 cm^3, or 0.102 std units. Similarly, posterior cortical volumes decreased by 0.348 cm^3 with doubling WMH burden, relationally about ½ the effect size of the hippocampal effect (0.050 std units); note that posterior volumes were around 10 times as large. All path #1 associations were significant, except for infarcts on frontal ROI volume, which was therefore excluded from mediation analyses.

For path #2 in Figure 2, adjusted models revealed nonlinear associations between volumetric and cognitive measures with threshold effects indicating larger associations for smaller vs larger volumes (Table 3). For example, each 1 cm^3 increase from 4–6 cm^3 in hippocampal ROI was associated with a 0.44 increase in the (standardized) global cognition measure, while increases from 6–10 cm^3 showed little to no association. The posterior cortical ROI was associated with all three cognitive composites. The hippocampal ROI was associated with all three but only marginally for PS/EF. The frontal ROI was associated with PS/EF and global cognition marginally. Marginal and non-significant relationships were excluded from mediation analyses.

For path #3 in Figure 2, adjusted total associations between cerebrovascular imaging features and cognition were evaluated (Table 4: first column). Associations of PS/EF with both WMH and infarcts were supported (expected decrease of −0.061 PS/EF with each doubling of WMH burden), as well as a marginal association between the global composite and WMH. Marginal and non-significant relationships were excluded from mediation analyses.

We also considered the relationship between WMH and infarcts and conducted mediation analyses of their individual relationships to PS/EF by the other feature. Although there was a slight attenuation of the association between infarcts and PS/EF (Table 4: standardized −.141) by the inclusion of WMH in the model, the association of infarcts and PS/EF remained significant (standardized = −.117 (−.218, −.015) p=0.025). There was no evidence for mediation of the WMH and PS/EF association by infarcts. Therefore, it was justifiable to consider the two features as being largely independent.

We considered mediation models (Figure 2, path #4), when all three bivariate associations were supported (paths #1–3). There were three, all related to PS/EF performance: (i) WMH association mediated by posterior cortical ROI; (ii) WMH association mediated by frontal ROI; and (iii) infarcts association mediated by frontal cortical ROI. We found evidence of some mediation effects for each of these (Table 4: mediation columns). For example, approximately 16% (−0.010/−0.061) of the association between WMH and PS/EF might be explained by a mediation pathway via effects of WMH on posterior cortical ROI volumes. Even after inclusion of the volumetric mediators, significant associations between PS/EF and the WMH and infarcts features remained.

DISCUSSION

In a biracial group of non-demented elderly individuals, cross-sectional mediation analyses showed that two cortical ROI's – one representing posterior cortical regions that are part of the default mode network and another, a group of frontal regions – moderately mediated associations between WMH burden and a cognitive composite representing psychomotor speed and executive function (PS/EF). The association between infarcts, the variable representing the presence of any infarct, and the PS/EF composite was also moderately mediated by the posterior cortical ROI. These findings imply that some of the impact of WMH or infarcts burden on cognitive function may have been the result of mechanisms that these lesions share with pathological processes that affect cortical volume. Although the magnitude of the mediation effect was modest, our findings support the hypothesis that a widely distributed process beyond the visible lesions leads to cognitive impairment. Our results do not specifically implicate cortical microinfarcts as the lesion that links visible cerebrovascular disease and cognitive function, but microinfarcts are the prime prospect, in the absence of stronger candidates, for a diffuse microvascular process that affects isocortex.

In bivariate analyses, both CVD imaging features – WMH and infarcts – were associated with posterior cortical ROI volume. Only WMH were associated with frontal ROI volume. These associations themselves suggest shared pathophysiologic mechanisms, with mediation analyses substantially strengthening the argument by showing that the associations impacted cognition. Several prior reports have shown associations between brain volume and burden of CVD lesions longitudinally[33, 34] and cross-sectionally[35].

The conceptual model that motivated our analyses required some important predicates that were supported both by prior literature and our own findings. Paths #1, #2 and #3 in Figure 2 were required to show significant associations. WMH and infarcts were associated with cognition, specifically PS/EF, as observed by others[7, 13, 36]. Second, for all 3 of our ROI's, cortical volume was associated with cognition, which has also been frequently observed[37–42]. Each ROI showed associations with cognition corresponding to expected cognitive-anatomic relationships: hippocampal volume was strongly associated with the memory composite, the posterior ROI showed similar associations with all 3 cognitive measures, and frontal ROI was associated with PS/EF. Third, there were associations, as observed by others, between WMH[13, 43–45], infarcts[6, 8, 46, 47] and cognition.

The motivation for conducting these analyses was based on the view that neither a small number of visible lacunar infarcts in various locations nor a modest amount of WMH seem sufficiently destructive to cause cognitive dysfunction. We sought evidence for another covert process that was linked pathophysiologically to the visible cerebrovascular lesions. Microinfarcts are the most attractive candidate lesion fitting that description[48–52]. Clinical-pathological studies[17, 49] support an association between microinfarcts and brain volume loss, justifying our use of cortical volume as the indicator of the covert microscopic process.

There are methodological considerations that might have reduced our ability to demonstrate more robust mediation of the relationship between vascular imaging features and cognition by regional cortical volume. Many other regions, beyond the 3 we chose, were not explored,

and our choice of cortical regions might have failed to include other salient regions for cerebrovascular disease. Microinfarcts are typically found in cortical regions at boundaries of major vascular territories[49, 53]. Both our posterior and frontal ROI's include watershed territory, but also included non-watershed regions as well. That both our posterior and frontal cortical ROI's mediated WMHPS/EF associations suggests that the underlying process affecting isocortex was not highly localized. Other important methodological factors include: 1) ours was a cross-sectional study; 2) our non-demented cohort represented robust survivors of the original sample, and 3) we imaged only a subset of ARIC visit 5 participants (though we utilized an inverse proportional weighting approach for representing the ARIC visit 5 clinic visit cohort as a whole).

Our findings support our hypothesis that cognitive function in the setting of imaging-visible cerebrovascular lesions is at least in part mediated by a process that affects cerebral cortical volume. However, the modest magnitude of the mediation effect should also prompt consideration of alternative mechanisms or explanations for the influence of WMH and infarcts directly on cognition. One obvious mechanism would be disconnection by white matter disease or subcortical infarcts of cortical-cortical or cortical-subcortical pathways. There is evidence from CADASIL that disconnection could occur as a result cerebrovascular disease[54]. Perhaps alterations in connectivity[55] and structural changes in white matter pathways that are observed with diffusion tensor imaging but cannot be detected by FLAIR imaging[56] are the critical underlying mechanisms that link observable WMH, visible infarcts and cognitive impairment. Not all studies detect unique contributions from diffusion tensor imaging[57]. However, just as the diffusion tensor imaging changes are dissociable from the white matter hyperintensity changes, perhaps the connectivity changes may be dissociable from diffusion tensor imaging changes.

To the best of our knowledge, no prior study has sought to explore how measures of brain volume mediate relationships between cerebrovascular lesions and cognition. One prior study[58] found that WMH burden and brain atrophy measures displayed a synergistic interactive effect on declines in executive function. Another study that recruited patients with active large vessel vascular disease in brain, heart, or peripheral vasculature[59] found an interaction between brain volume, infarcts and severe WMH for executive dysfunction. In the current analyses, we asked a different question: whether relationships between overt cerebrovascular disease and cognition were mediated by cortical volume. In finding such a relationship, it strengthens the argument that there is a link between overt and covert cerebrovascular disease and cognition.

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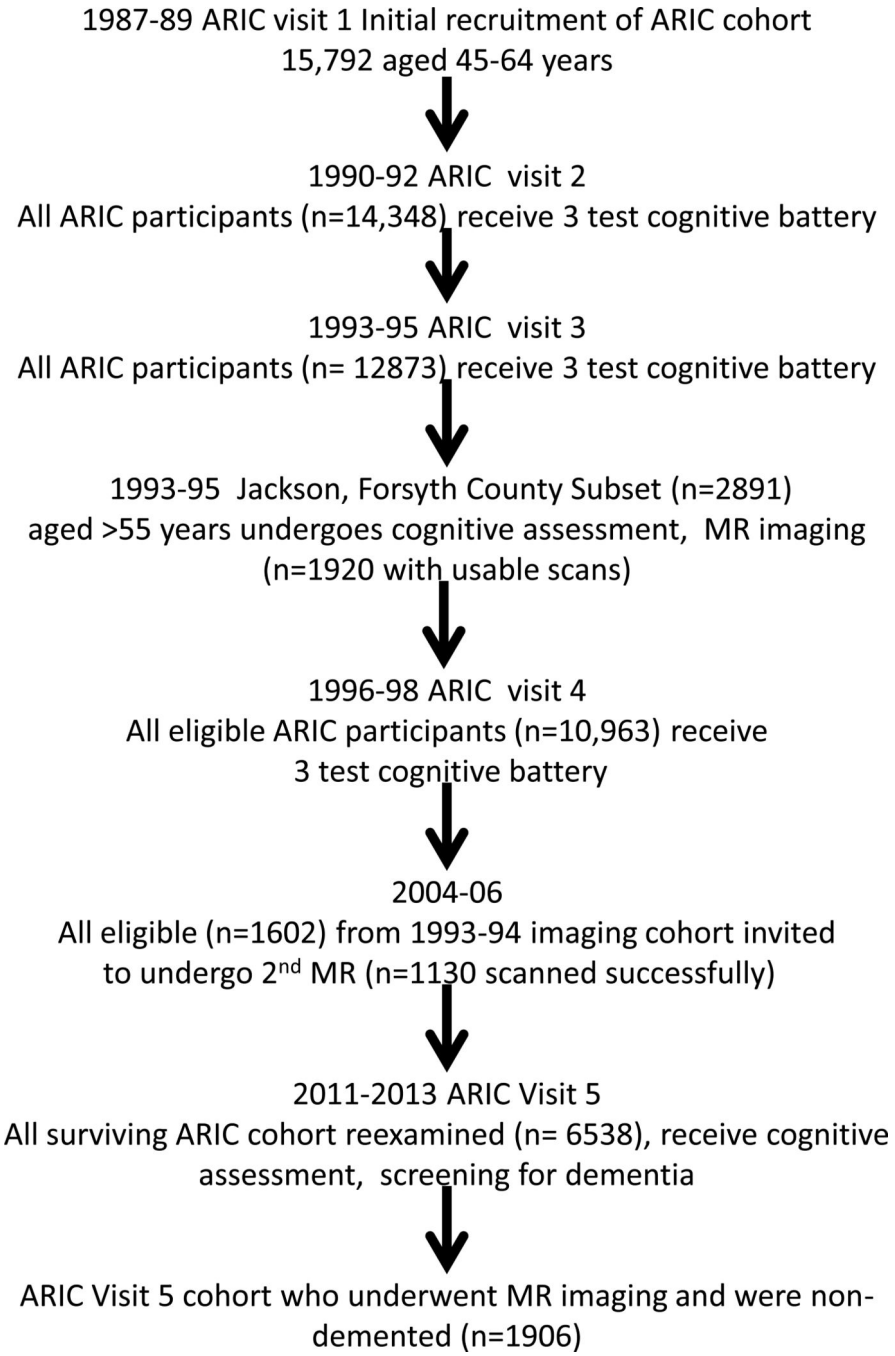

Figure 1.
Time line of the ARIC study relevant to current analysis.

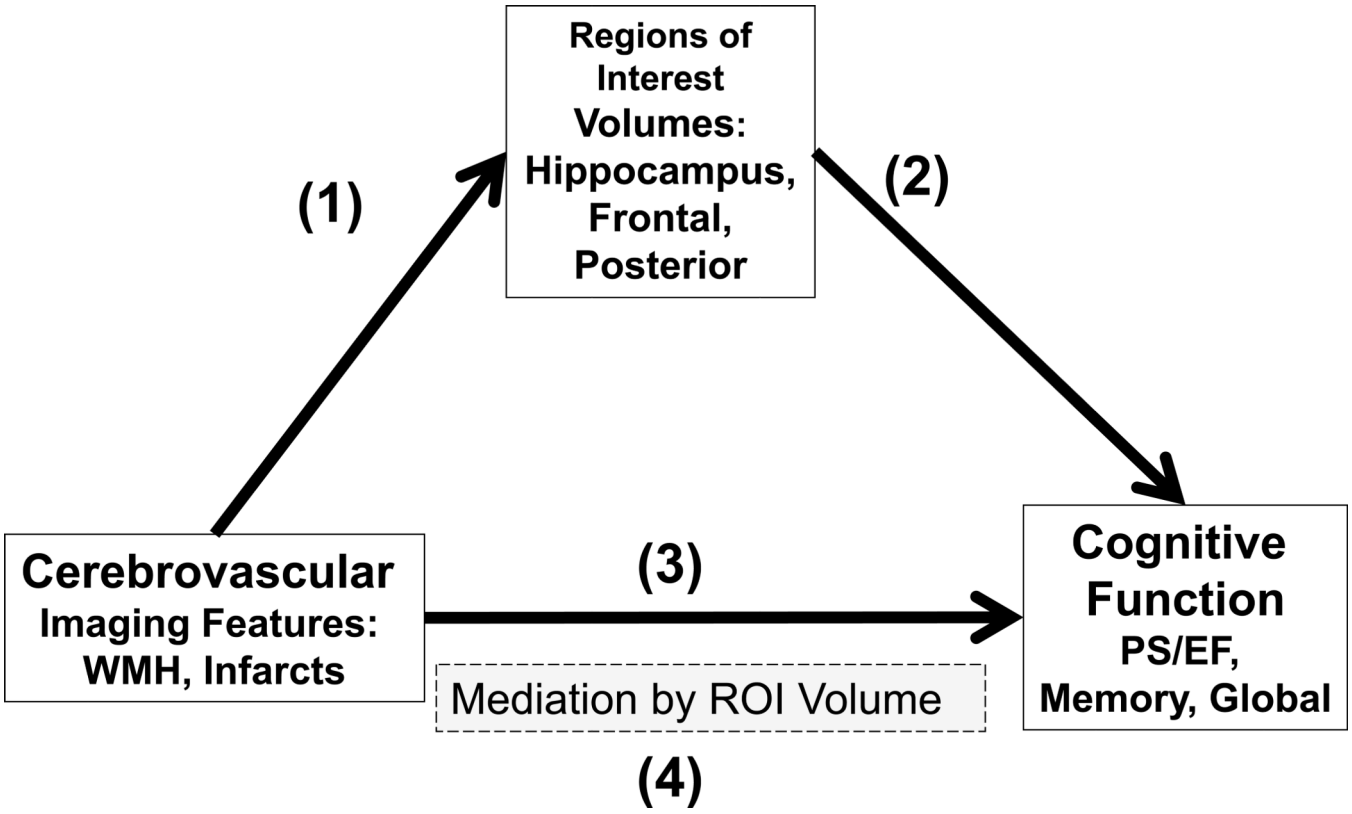

Figure 2.

Analysis model for mediation in ARIC Neurocognitive Study. With strong mediating influences, pathways (1) and (2) should be present, and the apparent pathway (3) should be attenuated when additionally adjusting for the potential mediator, as in pathway (4). Abbreviations: ROI=Brain regions of interest; WMH=white matter hyperintensities; INF= any subcortical or cortical infarction; ROI= Region of Interest; PS/EF = Psychomotor speed/ executive function.

Table 1

Participant Characteristics. ARIC Neurocognitive Study

			Participants with MR	Participants without MR
Type	**Characteristic**		**N=1906**	**N=4558**
Demographic	**Sex**	Female	2662 (58%)	3580 (61%)
	Race	Black	986 (22%)	1258 (21%)
	Age (yrs)		75.55 (5.21)	75.21 (5.21)
	Education Level	< 11 years	705 (15%)	639 (11%)
		High School/Vocational	1902 (42%)	2408 (41%)
		College +	1942 (43%)	2793 (48%)
	Center	Forsyth	947 (21%)	1345 (23%)
		Jackson	903 (20%)	1131 (19%)
		Minneapolis	1458 (32%)	1801 (31%)
		Washington	1250 (27%)	1578 (27%)
Clinical	**Diabetic**	Yes	1258 (29%)	1576 (27%)
	Hypertension	Yes	3055 (68%)	3883 (66%)
	Drinking	Current	2097 (50%)	3078 (53%)
		Former	1249 (30%)	1470 (25%)
		Never	843 (20%)	1193 (20%)
	Smoking	Current	262 (7%)	299 (5%)
		Former	2025 (52%)	2842 (49%)
		Never	1583 (41%)	2409 (41%)
MRI Cerebrovascular Imaging Features	**WMH Volume (cm^3)**		17.29 (16.86)	
	WMH % of total WM volume		3.88 (3.45)	
	Large Cortical Infarct Frequency	0	1820 (96%)	
		1	55 (3%)	
		2+	25 (1%)	
	Small Cortical Infarct Frequency	0	1770 (93%)	
		1	108 (6%)	
		2+	22 (1%)	
	Subcortical Infarct Frequency	0	1543 (81%)	
		1	260 (14%)	
		2+	97 (5%)	
Cognitive Measures	**Delayed Word Recall**		5.00 (1.87)	5.31 (1.87)

		Participants with MR	Participants without MR
Type	**Characteristic**	**N=1906**	**N=4558**
	WAIS-r Digit Symbol Substitution	36.37 (11.41)	38.53 (12.19)
	Letter Fluency	33.01 (12.48)	34.17 (11.73)
	Mini-Mental State Examination	27.39 (2.22)	27.28 (3.35)
ROI Volumes	**Hippocampal (cm^3)**	6.89 (0.93)	
	Posterior ROI (cm^3)	59.07 (6.90)	
	Frontal ROI (cm^3)	150.21 (16.00)	

Cells contain N (%) for categorical and mean (sd) for continuous / semi-continuous variables

Table 2

Associations of Regions of Interest Volumes with Cardiovascular Imaging Features*. ARIC Neurocognitive Study.

Cerebrovascular Imaging Feature (Predictor)	Volumetric Region of Interest (Outcome)	Association β p-value, (95% CI)	
		Raw Scale Outcomes (cm^3)	Standardized Outcomes
White Matter Hyperintensities {log_2(WMH)}	Hippocampal	−0.095 p<0.001 (−0.133,−0.058)	−0.102 p<0.001 (−0.143,−0.062)
	Posterior	−0.348 p=0.001 (−0.561,−0.135)	−0.050 p=0.001 (−0.081,−0.020)
	Frontal	−0.953 p<0.001 (−1.443,−0.464)	−0.060 p<0.001 (−0.090,−0.029)
Any Infarct {Large Cortical, Small Cortical or Subcortical}	Hippocampal	−0.135 p=0.005 (−0.230,−0.040)	−0.145 p=0.005 (−0.248,−0.043)
	Posterior	−0.684 p=0.010 (−1.202,−0.165)	−0.099 p=0.010 (−0.174,−0.024)
	Frontal	−0.528 p=0.408 (−1.778,0.723)	−0.033 p=0.408 (−0.111,0.045)

*Example interpretation: Each 1 unit increase in log_2(WMH), (a doubling of WMH burden), was associated with a decrease in hippocampal ROI volume of 0.095 cm^3, or 0.102 std volume units (std volumes constructed by subtracting the mean and dividing by the SD). Similarly, posterior cortical volumes decreased by 0.348 cm^3 with doubling WMH burden, relationally about ½ the effect size of the hippocampal effect (0.050 std volume units), given that posterior volumes were around 10 times larger.

CI: Confidence Interval

Table 3

Associations of Cognitive Composite Scores with Region of Interest Volumes, stratified by ROI size. ARIC Neurocognitive Study.

		Volumetric Measures Standardized with p value, 95% Confidence Interval		
	Cognitive Composite Outcome	**Hippocampal ROI**	**Posterior ROI**	**Frontal ROI**
Smaller Volumes*	**Global Cognition**	**0.44 p=0.001 (0.18,0.70)**	**0.04 p<0.001 (0.02,0.05)**	**0.01 p=0.049 (0.00,0.02)**
	Memory	**0.45 p<0.001 (0.20,0.70)**	**0.03 p=0.002 (0.01,0.05)**	0.00 p=0.276 (−0.00,0.01)
	PS/EF	0.23 p=0.088 (−0.03,0.50)	**0.05 p<0.001 (0.03,0.07)**	**0.02 p<0.001 (0.01,0.02)**
Larger Volumes*	**Global Cognition**	0.05 p=0.149 (−0.02,0.12)	0.02 p=0.059 (−0.00,0.04)	0.00 p=0.946 (−0.01,0.01)
	Memory	0.03 p=0.369 (−0.04,0.11)	0.01 p=0.193 (−0.01,0.03)	−0.00 p=0.914 (−0.01,0.01)
	PS/EF	**0.09 p=0.024 (0.01,0.17)**	**0.02 p=0.038 (0.00,0.03)**	−0.01 p=0.158 (−0.01,0.00)

*See Statistical Analysis, Methods for definition of size.

Example interpretation: Each 1 cm^3 increase from 4–6 cm^3 (the smaller volume) in the hippocampal ROI was associated with a 0.44 increase in the (standardized) global cognition measure

Table 4

Mediation Models of Associations of Cognition with Cerebrovascular Imaging Features: Effects of Region of Interest Volumes. Values for the mediations analyses are shown for relationships for which all bivariate associations were significant at p<0.01. ARIC Neurocognitive Study.

		Unmediated Associations Base Model (β) p-value 95% CI	With Mediation by inclusion of Volumetric Measures Standardized β, p-value 95% Confidence Intervals			
Cerebro-vascular Imaging Feature	**Cognitive Composite Outcome**	**With Clinical & Demographic Adjustment**	**Base Model + Posterior ROI**	**Mediation estimate**	**Base Model + Frontal ROI**	**Mediation estimate**
White Matter Hyper-intensities {$\log_2$(WMH)}	**Global Cognition**	−0.046 p=0.037 (−0.090,−0.003)	*Not estimated; Path 3 unsupported*		*Not estimated; Path 3 unsupported*	
	Memory	−0.027 p=0.274 (−0.076,0.021)	*Not estimated; Path 3 unsupported*		*Not estimated; Path 3 unsupported*	
	PS/EF	**−0.061 p=0.001 (−0.098,−0.023)**	**−0.050 p=0.008 (−0.088,−0.013)**	**−0.010 p=0.003 (−0.017, −0.003)**	**−0.055 p=0.004 (−0.092,−0.017)**	**−0.006 p=0.032 (−0.011, 0.000)**
Any Infarct {Large Cortical, Small Cortical or Subcortical}	**Global Cognition**	−0.074 p=0.125 (−0.168,0.020)	*Not estimated; Path 3 unsupported*		*Not estimated; Path 3 unsupported*	
	Memory	−0.050 p=0.358 (−0.156,0.056)	*Not estimated; Path 3 unsupported*		*Not estimated; Path 3 unsupported*	
	PS/EF	**−0.141 p=0.006 (−0.241,−0.042)**	**−0.119 p=0.020 (−0.220,−0.019)**	**−0.017 p=0.011 (−0.030, −0.004)**	*Not estimated; Path 3 unsupported*	

Example Interpretation: Each 1 unit increase in log2(WMH), (a doubling of WMH burden) was associated with a decrease in the global cognition Z-score measure of 0.046 standard deviations