Vascular Imaging Abnormalities and Cognition

Mediation by Cortical Volume in Nondemented Individuals: Atherosclerosis Risk in Communities-Neurocognitive Study

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

Methods—Total of 1906 nondemented 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 MRI for white matter hyperintensities (WMH) and infarcts. The Freesurfer imaging analysis pipeline was used to determine regional cerebral volumes. We examined the associations of cognitive domain outcomes with cerebral volumes (hippocampus and separate groups of posterior and frontal cortical regions of interest) 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 the associations between cerebrovascular imaging features and cognition.

Results—In unmediated analyses, WMH and infarcts were both associated with worse psychomotor speed/executive function. In mediation analyses, WMH and infarct associations on psychomotor speed/executive function were significantly attenuated, but not abolished, by the inclusion of the posterior cortical regions of interest volume in the models, and the infarcts on psychomotor speed/executive function association were attenuated, but not abolished, by inclusion of the frontal cortical regions of interest 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 1 candidate for such a clinically covert process. (Stroke. 2015;46:433-440. DOI: 10.1161/STROKEAHA.114.007847.)

Key Words: cerebral infarction ■ cerebral small vessel diseases ■ cognition ■ magnetic resonance imaging

The mechanisms by which cerebrovascular disease (CVD) causes cognitive impairment have been elusive. Although the volume of infarcted tissue was an obvious initial candidate as a quantitative marker of pathology,1 individuals with clinically overt, large infarcts account for only a small fraction of cognitively impaired individuals with CVD.2-5 The presence of even 1 visible lacunar infarct is associated with cognitive impairment or cognitive decline,6-10 and the associations of white matter hyperintensities (WMH) with cognition do not occur only with severe disease.11-15 Because 1 or 2 lacunar infarcts or moderate WMH burden is itself 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 nondemented 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 to 1989 baseline examination of cardiovascular risk factors in men and women aged 45 to 64 years who were representative of 4 US communities, Washington County MD, Forsyth County NC, Jackson MS, and suburban Minneapolis MN (ARIC study flow is given in Figure 1 and Materials in the online-only Data Supplement).

ARIC conducted a fifth examination between June 2011 and August 2013: Institutional Review Boards of each ARIC center approved the protocol. Of 10749 original ARIC cohort members alive at the start of fifth examination recruitment, 713 (6.6%) died before an examination, leaving 10036 alive through August 2013. Of these, 6538 (age, 66–90 years) took part (5918 full clinic examination, 228 abbreviated clinic examination, and 392 home- or care-facility examination). The overall fifth examination response rate was 65% (6538/10 036).

A subset of ARIC fifth examination participants without contraindications were selected for a brain MRI: (1) all people who had previous scans in 2004 to 2006, (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) took part (5918 full clinic examination, 228 abbreviated clinic examination, and 392 home- or care-facility examination). The overall fifth examination response rate was 65% (6538/10 036).

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1987-89 ARIC visit 1 initial recruitment of ARIC cohort 15,792 aged 45-64 years

1990-92 ARIC visit 2 All ARIC participants (n=14,348) receive 3 test cognitive battery

1993-95 ARIC visit 3 All ARIC participants (n= 12873) receive 3 test cognitive battery

1993-95 Jackson, Forsyth County Subset (n=2891) aged ≥55 years undergoes cognitive assessment, MR imaging (n=1920 with usable scans)

1996-98 ARIC visit 4 All eligible ARIC participants (n=10,963) receive 3 test cognitive battery

2004-06 All eligible (n=1602) from 1993-94 imaging cohort invited to undergo 2nd MR (n=1130 scanned successfully)

2011-2013 ARIC Visit 5 All surviving ARIC cohort reexaminet (n = 6538), receive cognitive assessment, screening for dementia

ARIC Visit 5 cohort who underwent MR imaging and were non-demented (n=1906)

Figure 1. Time line of the Atherosclerosis Risk in Communities (ARIC) study relevant to current analysis.

1980 (4%) were excluded because of cognitive impairment sufficient to suspect dementia (Mini-Mental Status Examination 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. 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 digit 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 SD. A global composite Z-score was also derived from the 3 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 of 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 Materials in the online-only Data Supplement for details).

Imaging

MRI scans were performed at each site on 3 Tesla Siemens (various models) scanners using a common set of sequences that included 3-dimensional volumetric magnetization prepared gradient echo and fluid-attenuated inversion recovery sequences. WMH burden was measured quantitatively using an algorithm developed at Mayo Clinic, Rochester,22,23 and reported in cubic centimeters. 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 cubic centimeters.

Brain infarcts were identified, counted, and measured by a trained imaging technician and confirmed by radiologists (K.K. and C.R.J.) as previously described.26 Cortical infarctions were characterized on fluid-attenuated inversion recovery sequences as hyperintense lesions ≥10 mm (large) or 5 to 10 mm (small) in the 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 (≥3 mm 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 ≥1 infarct of any type, size, or location, referred to as infarcts.

Using the Freesurfer atlas,27 we prespecified 3 regions of interest (ROIs) based on relevance to CVD 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 or default mode network28 and are associated with Alzheimer disease29 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 midfrontal, 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 cubic centimeter, 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 locally weighted scatterplot smoothing smooth curves and modeled using fractional polynomial and linear-spline formulations. Potential outlier effects were assessed with DFFITS for influential points, Cook 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 examination to account for dropout/misgiving. All models incorporated these probability sampling weights 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 because of cognitive impairment were assigned a Z-score of \(-2\) for that test.

WMH burden was positively skewed, and therefore, we log2-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 \(\pm 60\) mm\(^3\) for hippocampal ROIs, \(\leq 60\) mm\(^3\) for posterior cortical ROIs, and \(\leq 150\) 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 to examine whether relationships between CVD imaging features (WMH and infarcts) and cognition (global, memory, and PS/EF) potentially operated through regional volumetric paths (hippocampal, posterior, and frontal ROIs; 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 (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 (ie, a 1 unit increase in log2[WMH cm\(^3\)] volume) was associated with a decrease in hippocampal ROI volume of 0.095 cm\(^3\) or 0.102 standard units. Similarly, posterior cortical volumes decreased by 0.348 cm\(^3\) with doubling WMH burden, relationally \(\approx \frac{1}{2}\) the effect size of the hippocampal effect (0.050 standard units); note that posterior volumes were \(\approx 10\times\) 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 versus larger volumes (Table 3). For example, each 1 cm\(^3\) increase from 4 to 6 cm\(^3\) in hippocampal ROI was associated with a 0.44 increase in the (standardized) global cognition measure, whereas increases from 6 to 10 cm\(^3\) showed little to no association. The posterior cortical ROI was associated with all 3 cognitive composites. The hippocampal ROI was associated with all 3 but only marginally for PS/EF. The frontal ROI was associated with PS/EF and global cognition marginally. Marginal and nonsignificant 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 \(\approx 0.061\) PS/EF with each doubling of WMH burden), as well as a marginal association between the global composite and WMH. Marginal and nonsignificant relationships were excluded from mediation analyses.

We also considered the relationship between WMH and infarcts and conducted mediation analyses of their individual relationships with PS/EF by the other features. Although there was a slight attenuation of the association between infarcts and PS/EF (Table 4, standardized \(\beta=0.141\) by the inclusion of WMH in the model, the association of infarcts with PS/EF remained significant (standardized \(\beta=-0.117\) \([-0.218\) to \(-0.015\); \(P=0.025\)]. There was no evidence for mediation of the WMH and PS/EF association by infarcts. Therefore, it was justifiable to consider the 2 cerebrovascular features as being largely independent.

![Figure 2](http://stroke.ahajournals.org/)

Figure 2. Analysis model for mediation in Atherosclerosis Risk in Communities 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). PS/EF indicates psychomotor speed/executive function; ROI, region of interest; and WMH, white matter hyperintensities.
We considered mediation models (Figure 2, path 4), when all 3 bivariate associations were supported (paths 1–3). There were 3, all related to PS/EF performance: (1) WMH association mediated by posterior cortical ROI; (2) WMH association mediated by frontal ROI; and (3) infarct association mediated by frontal cortical ROI. We found evidence of...
some mediation effects for each of these (Table 4, mediation columns). For example, ±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 infarct features remained.

### Discussion

In a biracial group of nondemented elderly individuals, cross-sectional mediation analyses showed that 2 cortical ROIs, one representing posterior cortical regions that are part of the default mode network and another, a group of frontal regions, moderately mediated the associations between WMH burden and a cognitive composite representing 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 effects of WMH or infarct burden on cognitive function may have been the result of mechanisms that these lesions share with pathological processes that affect the 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 CVD 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 pathophysiological mechanisms, with mediation analyses substantially strengthening the argument by showing that the associations affected the cognition. Several previous reports have shown associations between the brain volume and burden of CVD lesions longitudinally and cross-sectionally. The conceptual model that motivated our analyses required some important predicates that were supported both by previous 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. Second, for all 3 of our ROIs, cortical volume was associated with cognition, which has also been frequently observed. Each ROI showed associations with cognition corresponding to expected cognitive–anatomic relationships: hippocampal volume was strongly associated

### Table 2. Associations of ROI Volumes With Cardiovascular Imaging Features* (Atherosclerosis Risk in Communities Neurocognitive Study)

<table>
<thead>
<tr>
<th>Cerebrovascular Imaging Feature (Predictor)</th>
<th>Volumetric ROI (Outcome)</th>
<th>Raw Scale Outcomes (cm³)</th>
<th>Standardized Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>WMH (log₂(WMH))</td>
<td>Hippocampal</td>
<td>−0.095; 0.001; −0.133 to −0.058</td>
<td>−0.102; &lt;0.001; −0.143 to −0.062</td>
</tr>
<tr>
<td></td>
<td>Posterior</td>
<td>−0.348; 0.001; −0.561 to −0.135</td>
<td>−0.050; 0.001; −0.081 to −0.020</td>
</tr>
<tr>
<td></td>
<td>Frontal</td>
<td>−0.953; 0.001; −1.443 to −0.464</td>
<td>−0.060; &lt;0.001; −0.090 to −0.029</td>
</tr>
<tr>
<td>Any infarct (large cortical, small cortical, or subcortical)</td>
<td>Hippocampal</td>
<td>−0.135; 0.005; −0.230 to −0.040</td>
<td>−0.145; 0.005; −0.248 to −0.043</td>
</tr>
<tr>
<td></td>
<td>Posterior</td>
<td>−0.684; 0.010; −1.202 to −0.165</td>
<td>−0.099; 0.010; −0.174 to −0.024</td>
</tr>
<tr>
<td></td>
<td>Frontal</td>
<td>−0.528; 0.408; −1.778 to 0.723</td>
<td>−0.033; 0.408; −0.111 to 0.045</td>
</tr>
</tbody>
</table>

*Example interpretation: each 1 U increase in log₂(WMH), a doubling of WMH burden, was associated with a decrease in a hippocampal ROI volume of 0.095 cm³ or 0.102 standard volume units (standard volumes constructed by subtracting the mean and dividing by the SD). Similarly, posterior cortical volumes decreased by 0.348 cm³ with doubling WMH burden, relationally ≈½ the effect size of the hippocampal effect (0.050 standard volume units), given that posterior volumes were ≈10 times larger.

### Table 3. Associations of Cognitive Composite Scores With ROI Volumes, Stratified by ROI Size (Atherosclerosis Risk in Communities Neurocognitive Study)

<table>
<thead>
<tr>
<th>Cognitive Composite Outcome</th>
<th>Hippocampal ROI</th>
<th>Posterior ROI</th>
<th>Frontal ROI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smaller volumes*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Global cognition</td>
<td>0.44; 0.001; 0.18 to 0.70</td>
<td>0.04; &lt;0.001; 0.02 to 0.05</td>
<td>0.01; 0.049; 0.00 to 0.02</td>
</tr>
<tr>
<td>Memory</td>
<td>0.45; &lt;0.001; 0.20 to 0.70</td>
<td>0.03; 0.002; 0.01 to 0.05</td>
<td>0.00; 0.276; −0.00 to 0.01</td>
</tr>
<tr>
<td>PS/EF</td>
<td>0.23; 0.088; −0.03 to 0.50</td>
<td>0.05; &lt;0.001; 0.03 to 0.07</td>
<td>0.02; &lt;0.001; 0.01 to 0.02</td>
</tr>
<tr>
<td>Larger volumes*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Global cognition</td>
<td>0.05; 0.149; −0.02 to 0.12</td>
<td>0.02; 0.059; −0.00 to 0.04</td>
<td>0.00; 0.946; −0.01 to 0.01</td>
</tr>
<tr>
<td>Memory</td>
<td>0.03; 0.369; −0.04 to 0.11</td>
<td>0.01; 0.193; −0.01 to 0.03</td>
<td>−0.00; 0.914; −0.01 to 0.01</td>
</tr>
<tr>
<td>PS/EF</td>
<td>0.09; 0.024; 0.01 to 0.17</td>
<td>0.02; 0.038; 0.00 to 0.03</td>
<td>−0.01; 0.158; −0.01 to 0.00</td>
</tr>
</tbody>
</table>

CI indicates confidence interval; PS/EF, psychomotor speed/executive function; and ROI, region of interest.

*See Statistical Analyses and Methods sections for definition of size. Example interpretation: each 1 cm³ increase from 4–6 cm³ (the smaller volume) in the hippocampal ROI was associated with a 0.44 increase in the (standardized) global cognition measure.
Cerebrovascular imaging feature

Cognitive composite outcome \( \text{With clinical and demographic adjustment} \)

\( \text{Base model+posterior ROI Mediation estimate Base model+frontal ROI Mediation estimate} \)

\( \text{WMH (log WMH)} \)

Global cognition
\(-0.046; 0.037; -0.090 \text{ to } -0.003 \)
\( \text{Not estimated; path 3 unsupported} \)
\( \text{Not estimated; path 3 unsupported} \)

Memory
\(-0.027; 0.274; -0.076 \text{ to } 0.021 \)
\( \text{Not estimated; path 3 unsupported} \)
\( \text{Not estimated; path 3 unsupported} \)

PS/EF
\(-0.061; 0.001; -0.098 \text{ to } -0.023; -0.050; 0.008; -0.088 \text{ to } -0.010; 0.003; -0.017 \)
\(-0.013 \text{ to } -0.003 \)
\(-0.055; 0.004; -0.006; 0.032; -0.092 \text{ to } -0.017 \)
\(-0.011 \text{ to } 0.000 \)

Any infarct (large cortical, small cortical, or subcortical)

Global cognition
\(-0.074; 0.125; -0.168 \text{ to } 0.020 \)
\( \text{Not estimated; path 3 unsupported} \)
\( \text{Not estimated; path 3 unsupported} \)

Memory
\(-0.050; 0.358; -0.156 \text{ to } 0.056 \)
\( \text{Not estimated; path 3 unsupported} \)
\( \text{Not estimated; path 3 unsupported} \)

PS/EF
\(-0.141; 0.066; -0.241 \text{ to } -0.042; -0.119; 0.020; -0.022 \text{ to } -0.019; -0.017; 0.011; -0.030 \text{ to } -0.004 \)
\( \text{Not estimated; path 3 unsupported} \)

Values for the mediation analyses are shown for relationships for which all bivariate associations were significant at \( P<0.01 \). Example interpretation: each 1 U increase in \( \text{log WMH} \), a doubling of WMH burden, was associated with a decrease in the global cognition \( Z \)-score measure of 0.046SD. CI indicates confidence interval; PS/EF, psychomotor speed/executive function; ROI, region of interest; and WMH, white matter hyperintensities.

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, infarcts, 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. Clinical–pathological studies 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 CVD. Microinfarcts are typically found in cortical regions at boundaries of major vascular territories. Both our posterior and frontal ROIs included not only watershed territory but also nonwatershed regions. That both our posterior and frontal cortical ROIs mediated WMH→PS/EF associations suggests that the underlying process affecting isocortex was not highly localized. Other important methodological factors include the following: (1) ours was a cross-sectional study, (2) our nondemented cohort represented robust survivors of the original sample, and (3) we imaged only a subset of ARIC visit 5 participants (though we used 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 the consideration of alternative mechanisms or explanations for the influence of WMH and infarcts directly on cognition. One obvious mechanism would be the disconnection by white matter disease or subcortical infarcts of cortical–cortical or cortical–subcortical pathways. There is evidence from cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy that disconnection could occur as a result CVD. Perhaps, alterations in connectivity and structural changes in white matter pathways that are observed with diffusion tensor imaging but cannot be detected by fluid-attenuated inversion recovery imaging are the critical underlying mechanisms that link observable WMH, visible infarcts, and cognitive impairment. Not all studies detect unique contributions from diffusion tensor imaging. However, just as the diffusion tensor imaging changes are dissociable from the WMH changes, perhaps the connectivity changes may be dissociable from diffusion tensor imaging changes.

To the best of our knowledge, no previous study has sought to explore how measures of brain volume mediate relationships between cerebrovascular lesions and cognition. One previous study found that WMH burden and brain atrophy measures displayed a synergistic interactive effect on declines in EF. Another study that recruited patients with active large vessel vascular disease in brain, heart, or peripheral
vascularity\textsuperscript{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 CVD 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 CVD and cognition.

Appendix

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Disclosures

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References


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the ARIC Neurocognitive Investigators

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SUPPLEMENTAL MATERIAL

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

Additional Methodology Issues

ARIC Background. ARIC's first visit occurred in 1987-89. The second ARIC visit occurred in 1990-92 and a cognitive assessment was included that has subsequently been repeated on all subsequent visits. In 1993-5, all ARIC participants were reexamined, and a subset of individuals older than age 55 years from the Jackson MS and Forsyth Co NC sites were invited to undergo MR imaging. A fourth ARIC visit occurred in 1996-98 that included all eligible ARIC participants. In 2004-06, participants at the Jackson MS and Forsyth Co NC were again offered brain imaging, as well as a more detailed neuropsychological battery, similar to the one performed for the current ARIC visit 5, described in the main text.

MRI exclusions: Participants with contraindications to MRI were excluded; these included: cardiac pacemaker, defibrillator or valvular prosthesis, histories of meningioma, arachnoid cyst, craniotomy with resection or radiation therapy involving the skull or brain, normal pressure hydrocephalus, metal fragments in the eyes, brain or spinal cord, cochlear implant, spinal cord stimulator, or other internal electrical device, permanent eyeliner, or weight > 350 pounds. 1554 ARIC NCS participants underwent imaging.

Vascular Risk Factors and APOE genotype: As reported in prior ARIC publications (Knopman DS, Penman AD, Catellier DJ et al. Vascular risk factors and longitudinal changes on brain MRI: The ARIC study. Neurology 2011; 76: 1879-85), prevalent diabetes mellitus was diagnosed if there was a fasting glucose of > 126 mg/dl, non-fasting glucose of > 200mg/dl, a self-reported history of diabetes, or treatment for diabetes in the past 2 weeks. Serum glucose was assessed by the hexokinase method. Hypertension was diagnosed if there was a systolic blood pressure > 140 mm Hg, diastolic BP > 90 mm Hg, or use of antihypertensive medications in the past 2 weeks. Prevalent stroke was identified at ARIC visit 1. Incident stroke was defined as stroke occurring after baseline validated by an ARIC clinician through review of medical records occurring after baseline. The identification and validation of incident strokes is complete to December 31, 2011. Approximately 90% of incident strokes were characterized as ischemic (embolic or thrombotic strokes), the remainder as hemorrhagic. For the current analyses, prevalent and incident strokes were combined.

APOE genotype determinations were available on most subjects. Genotyping of the APOE polymorphisms was performed using the TaqMan assay (Applied Biosystems, Foster City, CA).

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