

Regional White Matter Hyperintensity Volume, Not Hippocampal Atrophy, Predicts Incident Alzheimer Disease in the Community

Adam M. Brickman, PhD; Frank A. Provenzano, BS; Jordan Muraskin, BS; Jennifer J. Manly, PhD; Sonja Blum, MD, PhD; Zoltan Apa, BA; Yaakov Stern, PhD; Truman R. Brown, PhD; José A. Luchsinger, MD; Richard Mayeux, MD

Background: New-onset Alzheimer disease (AD) is often attributed to degenerative changes in the hippocampus. However, the contribution of regionally distributed small vessel cerebrovascular disease, visualized as white matter hyperintensities (WMHs) on magnetic resonance imaging, remains unclear.

Objective: To determine whether regional WMHs and hippocampal volume predict incident AD in an epidemiological study.

Design: A longitudinal community-based epidemiological study of older adults from northern Manhattan, New York.

Setting: The Washington Heights/Inwood Columbia Aging Project.

Participants: Between 2005 and 2007, 717 participants without dementia received magnetic resonance imaging scans. A mean (SD) of 40.28 (9.77) months later, 503 returned for follow-up clinical examination and 46 met criteria for incident dementia (45 with AD). Regional WMHs and relative hippocampal volumes were derived. Three Cox proportional hazards models were run to predict incident dementia, controlling for rel-

evant variables. The first included all WMH measurements; the second included relative hippocampal volume; and the third combined the 2 measurements.

Main Outcome Measure: Incident AD.

Results: White matter hyperintensity volume in the parietal lobe predicted time to incident dementia (hazard ratio [HR]=1.194; $P=.03$). Relative hippocampal volume did not predict incident dementia when considered alone (HR=0.419; $P=.77$) or with the WMH measures included in the model (HR=0.302; $P=.70$). Including hippocampal volume in the model did not notably alter the predictive utility of parietal lobe WMHs (HR=1.197; $P=.049$).

Conclusions: The findings highlight the regional specificity of the association of WMHs with AD. It is not clear whether parietal WMHs solely represent a marker for cerebrovascular burden or point to distinct injury compared with other regions. Future work should elucidate pathogenic mechanisms linking WMHs and AD pathology.

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AMONG THE MOST SIGNIFICANT advances in Alzheimer disease (AD) research over the past 20 years has been the integration of biologically relevant data with well-defined clinical information. High-resolution neuroimaging techniques have been at the forefront, allowing for the appreciation of structural and functional changes in the aging brain that might provide insights into the pathogenic mechanisms of the disease, operationally defined biological markers of disease state, and clues about strategies for disease prevention. In recent years, data from structural magnetic

resonance imaging (MRI) and positron emission tomography (PET) coupled with cognitive data and clinical diagnosis have suggested a cascade of biological events that ultimately lead to the neuropsychological syndrome attributed to AD. These

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data were synthesized in an influential report by Jack and colleagues¹ that offered a hypothetical model of dynamic AD-related biomarkers. According to the model, abnormal β -amyloid processing

Author Affiliations are listed at the end of this article.

leads to brain amyloidosis, precipitating tau-related neuronal and synaptic dysfunction, and neurodegeneration, which manifest ultimately as cognitive decline and dementia. The putative biological changes are ostensibly reflected in neuroimaging-derived markers, including amyloid “positivity” in cortical regions on PET; regional hypometabolism on fluorodeoxyglucose PET; and medial temporal lobe atrophy on MRI. The model provides a framework to test hypotheses regarding the temporal ordering of biological changes and influence of other relevant factors in prospective research studies.

However, despite fairly consistent observations showing a relationship between vascular disease and AD,² vascular factors have not been incorporated formally into the proposed theoretical model of AD pathogenesis¹ or newly proposed research criteria for AD and its antecedent conditions,³⁻⁵ although most of the major identified risk factors for later development of AD have been vascular in nature.⁶ The gradual accumulation of these vascular risk factors manifests in the brain as small vessel cerebrovascular disease, visualized as hyperintense signal, or white matter hyperintensities (WMHs), on T2-weighted MRI.⁷ Because peripheral vascular disease is often treated successfully and ascertainment of vascular disease history via medical interview may be unreliable, MRI assessment of WMHs may provide the most direct measurement of cerebrovascular damage. White matter hyperintensity burden, particularly in posterior brain regions, is elevated in individuals at risk for AD and with prevalent AD⁸ and predicts the rate of cognitive decline among individuals with AD.⁹ Although some population-based reports suggest that WMH burden is associated with future development of AD,¹⁰ it is unclear whether this association is independent of hypothesized biological etiological markers (eg, hippocampus atrophy), which would suggest a role of small vessel cerebrovascular disease in the pathogenesis of the disease.

Herein, we sought to determine whether regionally distributed WMH volume and hippocampal atrophy independently predict incident AD in a community-based cohort of older adults without dementia. Consistent with the prevailing hypothesized pathogenic model of AD,¹ we hypothesized that degree of hippocampal atrophy would be associated with incident AD. We also hypothesized that WMH volume, particularly in posterior regions, would be associated with incident AD, reflecting the contributing role of cerebrovascular disease.

METHODS

PARTICIPANTS

Subjects were participants in the Washington Heights/Inwood Columbia Aging Project (WHICAP), an ongoing longitudinal community-based study of aging and dementia in northern Manhattan, New York. They were recruited at 2 points beginning in 1992 and 1999.¹¹ Members of the study cohort received a full medical, neurological, and neuropsychological examination at each of the follow-up visits, which occurred every 18 to 24 months. Beginning in 2004, active participants (n=2776) who did not meet criteria for dementia at their preceding follow-up visit were invited to participate in an MRI study.¹² Briefly,

769 underwent MRI. Compared with the 407 cohort members who were eligible for MRI but refused participation, those who received MRI scans were 1 year older, more likely to be female, and more likely to be African American. Among the 769 individuals with MRI scanning, 52 met diagnostic criteria for dementia at the clinical visit that was closest to the MRI scan and were thus excluded from analyses. This study was approved by an institutional ethics committee and all participants gave written informed consent to participate.

For the purposes of this report, we refer to “baseline” as the visit that was contemporaneous with the MRI scan and “follow-up” as the subsequent visit. Of the 717 participants without dementia with MRI seen at baseline, 503 (70.2%) were seen at follow-up. Reasons for lack of follow-up assessment include refusal (n=37) and participant moved out of the area (n=19), was confirmed deceased (n=46), or was lost to follow-up (n=131). Additionally, data from 34 participants were excluded from analyses because scan artifact or image quality precluded the quantification of WMHs (n=11), hippocampal volume (n=17), or both (n=6).

DIAGNOSTIC PROCEDURES

Participants underwent in-person evaluation at each follow-up visit, which included medical history, physical and neurological examination, and neuropsychological testing. The neuropsychological battery comprises measures of memory, orientation, language, abstract reasoning, and visuospatial¹³ and has been shown to measure equivalent traits across the 2 language groups represented in the study population.¹⁴ The diagnosis of dementia was established using all available clinical information (apart from neuroimaging data) and was based on standard research criteria.¹⁵ Following each clinical evaluation, a consensus conference that included physicians and neuropsychologists reviewed all available data. First, a diagnosis of dementia was made¹⁵ and then the etiology was determined based on research criteria for probable or possible AD,¹⁶ Lewy body dementia,¹⁷ vascular dementia,¹⁸ and other dementias.

Additionally, history of diabetes mellitus, hypertension, heart disease, and clinical stroke was ascertained by self-report.^{12,19} These 4 dichotomous variables were summed to create a vascular history score (score range, 0-4).¹²

MAGNETIC RESONANCE IMAGING

Procedures regarding MRI scanning have been described previously.¹² Magnetic resonance imaging scan acquisition was performed on a 1.5-T Philips Intera scanner at Columbia University. For quantification of hippocampal, total cranial, and WMH volume, T1-weighted (repetition time=20 milliseconds, echo time=2.1 milliseconds, field of view=240 cm, 256×160 matrix, and 1.3 mm slice thickness) and T2-weighted fluid-attenuated inversion recovery (FLAIR) (repetition time=11 000 milliseconds, echo time=144.0 milliseconds, inversion time=2800 milliseconds, field of view=25 cm, number of excitations=2, and 256×192 matrix with 3 mm slice thickness) images were acquired in the axial orientation. Regional WMH volumes were derived following procedures developed in our laboratory.^{20,21} Briefly, FLAIR images were skull stripped. A Gaussian curve was fit to map the voxel intensity values and WMHs were seeded by labeling voxels that were more than 3 SD of the image mean. Each seed was passed through an iterative mean intensity-based seed growing algorithm using a 10-point connectivity scheme. This approach labels adjacent voxels that fall within 5% of the mean intensity value of the seed, continuing iteratively, such that labeled voxels are added to the image and a new seed mean is created. To derive WMH vol-

umes in the frontal, temporal, parietal, and occipital lobes, a standard “lobar” atlas²² was spatially normalized to each subject’s labeled FLAIR image. Regional volumes were defined by the intersection of each atlas lobe with the labeled WMH voxels in that region; labeled voxel values were multiplied by voxel dimensions and summed to yield volumes in cm³.

Hippocampal volume and total cranial volumes were derived manually at University of California, Davis.¹² The T1-weighted images were reoriented in the coronal plane. Boundaries were placed along the borders of the hippocampus as previously described.¹² Intrarater reliabilities for the left and right hippocampus were good (intraclass correlation coefficients: 0.98 and 0.96).

Total cranial volume was determined manually¹² by tracing the dura mater within the cranial vault on the FLAIR MRI. The number of voxels contained within the traced space was multiplied by the voxel dimensions to yield a single volume value. We derived the relative hippocampal volume, a measure of hippocampal atrophy, by dividing the sum of the left and right hippocampal volume by total cranial volume and multiplying that value by 100.

STATISTICAL ANALYSES

We used *t* tests, χ^2 analysis, and the Mann-Whitney *U* test to compare demographic features, including age, years of education, sex distribution, ethnic/race distribution, presence of the APOE $\epsilon 4$ allele, individual vascular risk factors, and vascular history scores at baseline between participants who were included in the analyses (*n*=503) and those who were not included based on loss to follow-up (*n*=214). Descriptive statistics were generated for the same demographic features at baseline in the total sample and compared between participants who met criteria for incident dementia at follow-up and those who remained without dementia. We examined the average time between the MRI scan and the baseline clinical evaluation and the average time between the MRI scan and the follow-up visit. Participants with incident dementia and those who remained without dementia throughout follow-up were compared for baseline differences in hippocampal and regional WMH volume with general linear models controlling for age at baseline, sex, education, presence of the APOE $\epsilon 4$ allele, and ethnicity.

Three Cox proportional hazards models were constructed to address the primary aims of the study. The first determined whether the regional distribution of WMHs predicted the time to incident dementia, or cumulative “survival.” The incident dementia date was defined as the halfway point between the date of the MRI scan and the follow-up visit in which the diagnosis of dementia was made. However, all primary analyses were also run with the incident dementia date corresponding to the date of follow-up evaluation in which the diagnosis of dementia was made, and the findings were not notably altered. White matter hyperintensity volumes in all regions were entered simultaneously in the model as continuous predictors. Additional covariates included age (at baseline), sex, education (in years), presence of the APOE $\epsilon 4$ allele, and race/ethnicity. For race/ethnicity, Hispanic and black were entered as individual dichotomous variables, with non-Hispanic white as the reference. In the second model, relative hippocampal volume was entered rather than the regional WMH volume measurements. The third model contained both WMH and relative hippocampal volume entered simultaneously, along with the other covariates noted earlier, to examine the independent contributions of each predictive factor. The third model was also rerun with the vascular history score as an additional covariate.

Compared with those who were excluded from analyses, participants who were included were about a year younger (mean [SD] age, 79.66 [5.20] years vs 80.99 [6.18] years; $t_{715}=2.970$; $P=.003$) and comprised a greater proportion of women (69.7% vs 62.2%; $\chi^2_1=3.986$; $P=.046$) but were similar in number of years of education (mean [SD], 10.58 [4.37] years vs 10.80 [4.97] years; $t_{713}=0.569$; $P=.57$), race/ethnicity distribution (32.1% African American, 38.3% Hispanic vs 40.5% African American, 31.9% Hispanic; $\chi^2_2=4.901$; $P=.09$), and presence of the APOE $\epsilon 4$ allele (24.3% vs 30.3%, $\chi^2_1=2.779$; $P=.10$). Those included in the analyses had higher rates of hypertension (68.8% vs 61.2%; $\chi^2_1=3.87$; $P=.049$) but similar rates of diabetes ($\chi^2_1=0.80$; $P=.37$), heart disease ($\chi^2_1=0.029$; $P=.87$), and stroke ($\chi^2_1=3.71$; $P=.054$) than those who were not.

Forty-six participants met criteria for dementia at the follow-up visit; 45 of these individuals met criteria for probable AD (*n*=27 probable AD; *n*=6 probable AD with stroke; *n*=2 probable AD with Parkinson disease; and *n*=9 probable AD with other concomitant disease) and 1 met criteria for dementia with Lewy bodies. **Table 1** displays demographic differences between incident dementia cases and those who remained without dementia. Patients with incident dementia were older, had fewer years of education, and were more likely to be Hispanic but had similar APOE $\epsilon 4$ frequency and interval between baseline MRI and baseline clinical evaluation and between follow-up clinical evaluation and baseline MRI. Hippocampal volume did not differ between the 2 groups at baseline ($F_{1,435}=0.339$; $P=.56$). Overall WMH volume (main effect of diagnostic group: $F_{1,441}=0.258$; $P=.61$) and regional WMH volume (diagnostic group \times region interaction: $F_{3,1323}=0.534$; $P=.66$) at baseline did not vary as a function of diagnostic group.

Table 2 displays the results from the Cox proportional hazards models. White matter hyperintensity volume in the parietal lobe predicted the time to incident dementia, whereas distribution of WMHs in other regions did not (omnibus model $\chi^2_{10}=27.870$; $P=.002$). Interpretation of the hazards ratio suggests that for every 1-cm³ increase in WMH volume in the parietal lobe there is an associated 19% increase in the risk of incident dementia. Of the other covariates in the model, only increased age and decreased education were associated with incident dementia. It is notable that the hazard ratio for parietal lobe WMHs was larger than the one for age (Table 2). In the second model, in which relative hippocampus volume was entered instead of the regional WMH measurements, only age and education emerged as reliable predictors of incident dementia (omnibus model $\chi^2_7=20.101$; $P=.005$). While greater hippocampus atrophy was associated with a greater risk for incident dementia, the observation was not significant. The third model, in which regional WMH volumes and relative hippocampal volume were entered simultaneously, showed that only increased WMH volume in the parietal lobes, age, and education were associated with an increased

Table 1. Descriptive Statistics at Baseline Evaluation for Incident Dementia Cases, Participants Who Remained Without Dementia, and Total Sample

	Remained Without Dementia (n = 457)	Incident Dementia (n = 46)	Total Sample (n = 503)	Statistics	P Value
Age at baseline, y, mean (SD)	79.41 (5.12)	82.15 (5.55)	79.66 (5.20)	$t_{501} = 3.434$.001
Education, y, mean (SD)	11.12 (4.86)	7.70 (5.01)	10.58 (4.37)	$t_{499} = 4.537$	<.001
Race/ethnicity, %					
White/other	30.2	21.7	29.6] $\chi^2 = 7.083$.03
African American	33.2	21.7	32.1		
Hispanic	36.5	56.5	38.3		
APOE ϵ 4 frequency, %	24.4	22.7	24.3	$\chi^2 = 0.062$.80
Vascular risk factors, %					
Diabetes mellitus	21.0	23.9	21.3	$\chi^2 = 0.211$.65
Hypertension	69.1	65.2	68.8	$\chi^2 = 0.301$.58
Heart disease	22.5	17.4	22.1	$\chi^2 = 0.644$.42
Stroke	9.8	15.2	10.3	$\chi^2 = 1.300$.25
Vascular history score, median	1	1	1	Mann-Whitney $U = 10\,242.50$.76
Time between MRI scan and baseline evaluation, mo, mean (SD)	0.96 (5.27)	1.61 (7.05)	0.79 (6.25)	$t_{499} = 0.766$.44
Time between MRI scan and follow-up visit, mo, mean (SD)	40.18 (9.68)	41.63 (10.69)	40.28 (9.77)	$t_{474} = 0.911$.36
Regional WMH volume, cm ³ , mean (SD)					
Frontal	1.69 (3.19)	2.04 (2.84)	1.70 (3.16)] Diagnostic group: $F_{1,441} = 0.258$; group \times region: $F_{3,1323} = 0.534$.61; .66
Temporal	0.12 (0.28)	0.13 (0.23)	0.12 (0.27)		
Parietal	1.24 (2.48)	1.77 (2.55)	1.29 (2.49)		
Occipital	0.16 (0.38)	0.13 (0.17)	0.15 (0.37)		
Relative hippocampus volume, mean (SD)	0.29 (0.06)	0.28 (0.07)	0.29 (0.06)	$F_{1,435} = 0.339$.56

Abbreviations: MRI, magnetic resonance imaging; WMH, white matter hyperintensity.

risk of incident dementia. For illustration purposes, the **Figure** displays cumulative survival curves for individuals with high WMH volumes in the parietal lobe as compared with the rest of the sample. The models were rerun with a parietal lobe WMH \times hippocampus volume interaction term, which did not emerge as a significant predictor. When the vascular history score was entered as an additional covariate, it was not associated with incident dementia nor did it notably alter the hazard ratio for parietal lobe WMH (ie, 1.19 vs 1.17).

COMMENT

In this community-based, multiethnic group cohort of older adults, we found that WMH volume in the parietal lobes predicted incident AD, while WMH volume in other areas and hippocampal volume did not. The findings suggest, perhaps, a primary pathogenic role of small vessel cerebrovascular disease in AD, which is independent of the neurodegenerative changes ostensibly reflected in measures of hippocampal atrophy. Surprisingly, hippocampal atrophy at baseline did not predict incident dementia in this cohort either when considered alone or in the context of WMHs.

Although previously thought to be of little clinical relevance, WMHs have emerged in recent years as particularly salient radiological correlates of cognitive aging. Our

observation that WMHs predict future AD is in line with other recent studies that have shown increased WMHs in prevalent AD and mild cognitive impairment,⁸ as well as recent observations that WMHs predict rate of cognitive decline among individuals with prevalent AD.⁹ White matter hyperintensities are thought to reflect small vessel cerebrovascular disease that is primarily ischemic in nature,²³ but relatively few clinic-pathological correlates studies have been conducted, and although appearing as relatively homogenous signal on MRI scans, the regional distribution might reflect varying pathological features.^{20,24}

That our findings were restricted to the parietal lobes raises questions about the unique role parietal lobe pathology may play in the clinical expression of AD. The parietal lobes have been differentially implicated in the disease since Alois Alzheimer's second case study (Johann F.) in 1911, in which plaques were described to be ". . . present in enormous numbers in the parietal" lobe.^{25(p116)} White matter hyperintensities distributed in parietal lobe networks have been shown to be related to cognitive decline among individuals with mild cognitive impairment²⁶ and cross-sectionally to AD diagnosis.⁸ Positron emission tomography-derived glucose hypometabolism and lobar microbleeds, which reflect cerebral amyloid angiopathy, tend to colocalize in posterior brain regions, particularly the parietal lobes, in the context of AD or risk of AD.²⁷⁻³¹ It is unclear why the pa-

Table 2. Results From the 3 Cox Proportional Hazard Models

Predictors	Model 1: WMH Only		Model 2: Hippocampus Only		Model 3: WMH + Hippocampus	
	HR	P Value (95% CI)	HR	P Value (95% CI)	HR	P Value (95% CI)
Age	1.078	.02 (1.01-1.15)	1.072	.03 (1.01-1.14)	1.075	.03 (1.01-1.15)
Frontal WMH	0.959	.47 (0.86-1.07)			0.949	.42 (0.84-1.08)
Temporal WMH	0.887	.90 (0.15-5.23)			1.116	.90 (0.19-6.55)
Parietal WMH	1.194	.03 (1.02-1.40)			1.197	.049 (1.01-1.43)
Occipital WMH	0.298	.19 (0.05-1.81)			0.221	.16 (0.03-1.78)
Relative hippocampal volume			0.419	.77 (0.01-134.67)	0.302	.70 (0.01-136.48)
APOE ε4	1.224	.59 (0.58-2.57)	1.054	.90 (0.47-2.35)	1.129	.77 (0.50-2.53)
Sex (1 = female)	1.536	.32 (0.66-3.58)	1.567	.30 (0.67-3.63)	1.378	.46 (0.58-3.25)
Education	0.881	.008 (0.80-0.97)	0.871	.006 (0.79-0.96)	0.870	.006 (0.79-0.96)
Hispanic	0.613	.37 (0.21-1.79)	0.574	.31 (0.20-1.68)	0.543	.28 (0.18-1.65)
Black	0.762	.57 (0.30-1.96)	0.753	.56 (0.29-1.97)	0.657	.41 (0.24-1.78)

Abbreviations: HR, hazard ratio; WMH, white matter hyperintensities.

rietal lobes per se appear to have a particular vulnerability, but this converging evidence across modalities and pathological markers highlights the importance of further study on the regional distribution of WMHs. It is possible that WMHs distributed in parietal regions comprise mixed pathology, which may interact mechanistically with other neurodegenerative processes. Further work examining pathogenic links between white matter pathology and primary AD pathology is clearly warranted.

We hypothesized that detectable hippocampal atrophy would precede cognitive and functional decline attributable to AD and would thus predict future incident AD diagnosis.¹ Indeed, there are myriad examples of hippocampal volume reduction among patients with AD and those at risk for AD,³² although these studies have generally focused on clinic-based samples, and the extent to which hippocampal degeneration has prognostic utility in population studies remains somewhat unclear. There are several notable potential explanations for the negative predictive utility of hippocampal atrophy for incident AD seen in our community-based study. First, the sample is older than typical aging and dementia cohorts and it is possible that within this age group the neurobiological underpinnings of the AD phenotype are mediated primarily by vascular factors rather than neurodegenerative or atrophic changes in the hippocampus. This idea is supported by autopsy studies that show that brain pathology related to dementia varies in younger and older elderly individuals.³³ Second and similarly, clinic-based samples often explicitly exclude participants with significant vascular disease history; thus, other samples may be restricted to a subset of participants in whom hippocampal atrophy is more relevant. Third, cross-sectional calculations of relative hippocampal volume may underestimate or overestimate atrophy particularly among older adults from diverse backgrounds in whom variance in brain morphology may reflect a combination of developmental and degenerative processes. Follow-up work will measure longitudinal rates of hippocampal volume change to better characterize rates of atrophic changes in the hippocampus.

This work has implications for both pathogenic models of AD as well as current diagnostic criteria. In terms of AD pathogenesis, it is clear that vascular fac-

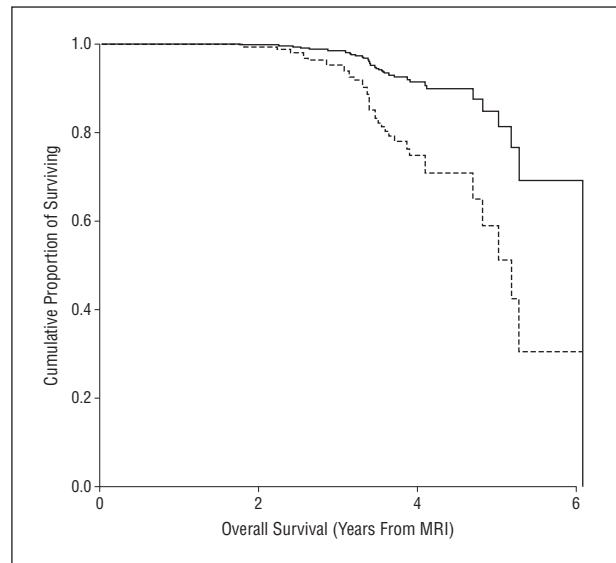


Figure. For illustration, cumulative survival curves were generated that compared individuals with high white matter hyperintensity volumes in the parietal lobes, defined here as the top quartile (dotted line), with all other participants, defined as the bottom 3 quartiles (solid line). MRI indicates magnetic resonance imaging.

tors may play a primary role in the clinical presentation of AD. Whether vascular factors should be incorporated formally into pathogenic models of the disease¹ is a matter of some debate, but what is consistent across studies is their contributing role to syndrome presentation. These observations have obvious implications for treatment and prevention strategies as AD becomes an increasingly salient public health problem and as prevalence of vascular disease increases throughout the life span.³⁴ In terms of diagnosis, newly proposed research criteria for AD explicitly note that the diagnostic label of AD “should not be applied when there is evidence of substantial concomitant cerebrovascular disease.”^{4(p265)} In addition to a lack of consensus regarding operational definitions of “substantial concomitant cerebrovascular disease,” excluding individuals with evidence of cerebrovascular disease may result in rarified samples comprising only a subset of individuals who are not representative

of the overall population with the syndrome. There is therefore a risk of “diagnostic prophecy” in which the etiology of the syndrome is defined by the proposed inclusion and exclusion criteria of the disease, as opposed to the opposite scenario in which known etiological factors are incorporated into more comprehensive criteria.

There are several unique aspects of this study that strengthen the confidence in the results. The WHICAP cohort is a large, community-based sample that represents the increasing ethnic and racial diversity that defines the population of older adults in this country. Quantitative analysis of high-resolution neuroimaging data is relatively rare in large community-based studies, particularly those comprising older adults from diverse backgrounds.^{35,36} The cohort is neuropsychologically well characterized and attrition rates are in line with comparable large-scale community-based studies. Future work will incorporate longitudinal neuroimaging data and other biological markers of disease.

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Author Affiliations: Taub Institute for Research on Alzheimer’s Disease and the Aging Brain (Drs Brickman, Manly, Stern, and Mayeux and Messrs Provenzano, Muraskin, and Apa), Gertrude H. Sergievsky Center (Drs Brickman, Manly, Blum, Stern, and Mayeux), and Departments of Neurology (Drs Brickman, Manly, Blum, Stern, and Mayeux), Psychiatry (Drs Stern and Mayeux), and Medicine (Dr Luchsinger), College of Physicians and Surgeons, and Department of Epidemiology, Mailman School of Public Health (Drs Luchsinger and Mayeux), Columbia University, New York, New York; and Department of Radiology and Radiological Science, Medical University of South Carolina, Charleston (Dr Brown).

Correspondence: Adam M. Brickman, PhD, Taub Institute for Research on Alzheimer’s Disease and the Aging Brain, Department of Neurology, College of Physicians and Surgeons, Columbia University, 630 W 168th St, P&S Box 16, New York, NY 10032 (amb2139@columbia.edu).

Author Contributions: *Study concept and design:* Brickman, Blum, Stern, and Luchsinger. *Acquisition of data:* Provenzano, Manly, Stern, Brown, Luchsinger, and Mayeux. *Analysis and interpretation of data:* Brickman, Provenzano, Muraskin, Blum, Apa, and Luchsinger. *Drafting of the manuscript:* Brickman, Provenzano, Muraskin, Brown, Luchsinger, and Mayeux. *Critical revision of the manuscript for important intellectual content:* Brickman, Provenzano, Muraskin, Manly, Blum, Apa, Stern, and Mayeux. *Statistical analysis:* Brickman and Muraskin. *Obtained funding:* Brickman, Manly, Stern, Luchsinger, and Mayeux. *Administrative, technical, and material support:* Manly, Brown, and Mayeux. *Study supervision:* Brickman. **Financial Disclosure:** None reported.

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