ORIGINAL CONTRIBUTION

Measuring Cerebral Atrophy and White Matter Hyperintensity Burden to Predict the Rate of Cognitive Decline in Alzheimer Disease

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Objective: To determine if baseline measurements of cerebral atrophy and severity of white matter hyperintensity (WMH) predict the rate of future cognitive decline in patients with Alzheimer disease (AD).

Design: Data were drawn from the Predictors Study, a longitudinal study that enrolls patients with mild AD and reassesses them every 6 months with use of the Columbia modified Mini-Mental State (mMMS) examination (score range, 0-57). Magnetic resonance images were analyzed to determine the severity of WMH, using the Scheltens scale, and the degree of atrophy, using the bicaudate ratio. Generalized estimating equations were used to determine whether severity of baseline magnetic resonance image measurements and their interaction predicted the rate of mMMS score decline at subsequent visits.

Setting: Three university-based AD centers in the United States.

Participants: At baseline, 84 patients with AD from the Predictors Study received structural magnetic resonance imaging and were selected for analysis. They had a mean of 6 follow-up evaluations.

Main Outcome Measure: The mMMS score.

Results: Generalized estimating equation models demonstrated that the degree of baseline atrophy ($\beta = -0.316$; $P = .04$), the severity of WMH ($\beta = -0.173$; $P = .03$), and their interaction ($\beta = -6.061$; $P = .02$) predicted the rate of decline in mMMS scores.

Conclusions: Both degree of cerebral atrophy and severity of WMH are associated with the rapidity of cognitive decline in AD. Atrophy and WMH may have a synergistic effect on future decline in AD, such that patients with a high degree of both have a particularly precipitous cognitive course. These findings lend further support to the hypothesis that cerebrovascular pathological abnormalities contribute to the clinical syndrome of AD.

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In the absence of definitive diagnostic instruments for Alzheimer disease (AD), structural magnetic resonance imaging (MRI) has emerged as an important tool for the characterization of morphological changes associated with the disease.[1] Increased atrophy, for example, is a consistent structural neuroimaging finding that is a hallmark of AD.[2,3] Longitudinal analyses revealed greater rates of brain atrophy among patients with AD than among healthy adults[4-6] and a correlation between the severity of atrophic change and severity of cognitive deficits.[2,7] These findings suggest that measures of cerebral atrophy provide a reasonable marker for disease staging in AD.

Areas of increased intensity on T2-weighted MRI sequences, including fluid-attenuated inversion recovery (FLAIR) sequences, called white matter hyperintensities (WMHs), are thought to reflect small vessel cerebrovascular disease[8-12] and may contribute to age-associated cognitive decline.[13] Similar to the degree of cerebral atrophy, WMHs are prevalent in patients with AD,[14] and the absence of neuroradiological markers of cerebrovascular disease among individuals with dementia is rare.[13]

Whether evaluation of neuroimaging data at one point has prognostic value to determine future cognitive decline remains an important question. Data from the Cardiovascular Health Study[15] showed that baseline ventricular volumes were larger among individuals who progressed from neurological health to dementia during a 4-year period. In one study,[16] ven-

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tricular volume and severity of WMH predicted the rate of future decline among healthy older adults, but only ventricular volume predicted the rate of decline among those with mild cognitive impairment and AD. However, only 39 patients with AD were included in the study, and the investigators did not examine the interaction between ventricular volume and WMH severity. Examining the 2 imaging markers together may help determine the relative importance of cerebrovascular disease in the course of AD and whether it synergistically interacts with disease state.

In the current study, we used data from the Predictors Study cohort[17-19] to examine the prognostic utility of baseline measurements of atrophy and cerebrovascular disease on rates of cognitive decline among individuals in the early stages of AD. An overarching goal of the Predictors Study is to elucidate the determinants of the cognitive and functional course of AD. A subset of participants received standard MRI studies as part of their diagnostic workup. We used these data and rated the severity of cerebral atrophy and WMH to predict future decline in cognitive abilities. We hypothesized that baseline atrophy and WMH ratings would predict future decline in cognition and that the 2 measures would interact.

METHODS

SAMPLE CHARACTERISTICS

The sample was drawn from the Predictors Study cohort and included individuals with AD.[20,21] Complete inclusion criteria and other details of the study are described elsewhere.[17,18] Briefly, participants met diagnostic criteria for dementia of the Alzheimer type[21] and probable AD.[20] Exclusion criteria included parkinsonism, stroke, alcoholism, schizophrenia, schizoaffective disorder, and history of electroconvulsive treatments. Participants were recruited from Columbia University, Johns Hopkins School of Medicine, and Massachusetts General Hospital between April 1989 and September 2005. The study was approved by local ethics committees. Neuroimaging was acquired for clinical diagnostic purposes, and images were available for 84 individuals in the study cohort. These subjects constitute the current study sample. Mean (SD) age at the time of the neuroimaging study was 73.2 (8.0) years; 40 subjects (48%) were male, and 76 (90%) were white. Mean (SD) number of years of education was 14.8 (3.7). Participants were relatively mildly impaired at the time of their neuroimaging studies, as indicated by a mean (SD) Columbia modified Mini-Mental State (mMMS) examination score of 41.3 (7.1), which is comparable to a Mini-Mental State Examination (MMSE)[22] score of approximately 22. The mean (SD) number of follow-up visits, at approximate 6-month intervals, was 5.8 (3.0). Of 62 subjects for whom data were available, 31 (50%) had the apolipoprotein E ε4 (*APOE ε4*) allele. At baseline, 8 of 84 (10%) had a self-reported history of diabetes mellitus, 14 (17%) had dyslipidemia, 14 (17%) had coronary artery disease, and 30 (36%) had hypertension. Compared with the participants without available neuroimages (n=456) in the Predictors Study, the current study participants were similar in age, sex, number of evaluations, and proportion with the *APOE ε4* allele, diabetes mellitus, dyslipidemia, coronary artery disease, and hypertension. Those without available neuroimages had fewer years of education than those with available neuroimages (mean [SD], 13.4 [3.5] vs 14.8 [3.7]; $t_{537}=3.192$; $P=.001$).

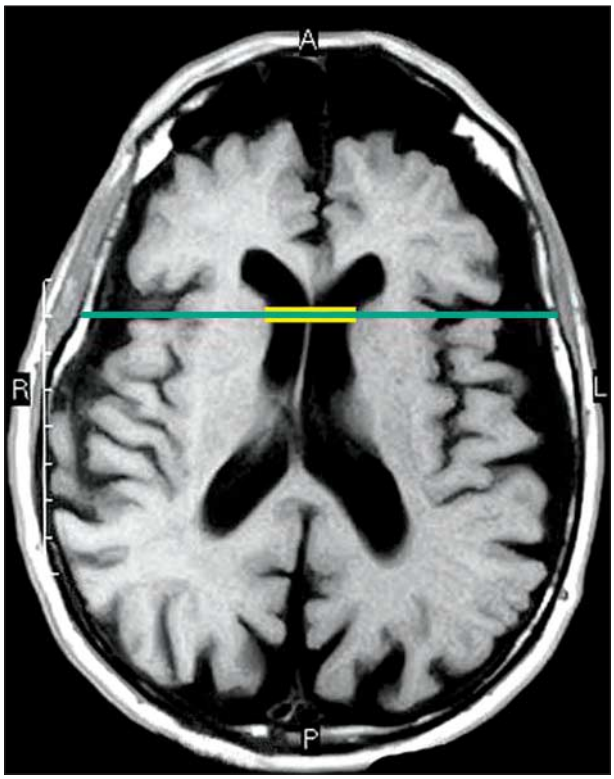

Figure 1. The bicaudate ratio is calculated by dividing the ventricular dimension (the distance between the 2 apices of the caudate nuclei; yellow bar) by the inner skull dimension (turquoise line). A higher ratio indicates greater atrophy. A indicates anterior; L, left; P, posterior; R, right.

NEUROIMAGING

Estimates of total brain atrophy were computed primarily from T1-weighted images, which were available for 53 (63%) of 84 participants with neuroimaging data; atrophy measurements were computed for the remaining participants on FLAIR–, proton-, or T2-weighted images. Findings did not change when we included image sequence as a dummy-coded covariate. Bicaudate ratios were derived from axially acquired images as an estimate of total brain atrophy following established protocols.[23-25] To derive the bicaudate ratio, the axial slice on which the caudate nuclei produced the greatest amount of indentation on the lateral ventricles was identified, and the distance between the 2 caudate apices was measured in millimeters. This value was divided by the maximum width of the skull at the same level as the caudate measurement (**Figure 1**). Using this approach, enlarged ventricles increase the distance between the 2 caudate nuclei, resulting in a higher bicaudate ratio. Therefore, a larger value indicates a greater degree of atrophy. Bicaudate ratio measurements were made by 2 experienced raters (A.M.B. and L.S.H.). Interrater reliability, computed for 12 images, was good for bicaudate distance (intraclass correlation coefficient, 0.861), skull width (0.991), and bicaudate ratio (0.740). Furthermore, in an independent sample of digital T1-weighted MRIs from 17 patients with dementia, we calculated bicaudate ratios and compared them with manually derived full relative brain volumes and found a strong relationship between the 2 measures (Spearman ρ, –0.814; $P<.001$). These findings suggest that the bicaudate ratio is a reliable and valid index of cerebral atrophy.

The WMH severity ratings were attained from FLAIR– and T2-weighted images using the Scheltens scale.[26] The Scheltens scale is a visual rating scale that includes anchored 7-point severity ratings in periventricular (ie, frontal horn, occipital horn, and lateral bands), cortical (ie, frontal, temporal, parietal, and

Table. GEE Analyses to Test the Effects of Cerebral Atrophy and GEE on Rate of Cognitive Decline

Variable	Model 1[a] β	Model 1[a] *P* Value	Model 2[b] β	Model 2[b] *P* Value
		Atrophy		
Time[c]	1.619	.49	2.964	.12
Bicaudate ratio	–0.786	.02	–0.497	.09
Time[c] × bicaudate ratio	–0.316	.04	–0.415	<.001
		WMH		
Time[c]	–2.706	<.001	–3.160	<.001
Scheltens scale score	–0.082	.68	–0.106	.56
Time[c] × Scheltens scale score	–0.173	.03	–0.122	.71
		Atrophy and WMH		
Time[c]	–1.988	.30	0.977	.50
Bicaudate ratio	–0.445	.15	–0.427	.12
Scheltens scale score	–0.224	.25	–0.145	.36
Time[c] × bicaudate ratio	–6.277	.62	–0.278	.003
Time[c] × Scheltens scale score	0.968	.05	0.512	.09
Time[c] × bicaudate ratio × Scheltens scale score	–6.061	.02	–3.250	.05

Abbreviations: GEE, generalized estimating equation; WHM, white matter hyperintensity.
[a] Adjusted for age, sex, educational level, apolipoprotein E ε4 allele, diabetes mellitus, dyslipidemia, coronary artery disease, and hypertension.
[b] Adjusted for age, sex, and educational level.
[c] The main effect of "time" shows the rate of change in modified Mini-Mental State (mMMS) score per 1-year interval as a function of each unit of the independent variable. For example, the "time × bicaudate ratio" interaction shows the effect of baseline atrophy measures on the annual rate of change in mMMS score (ie, for every 1% increase in baseline bicaudate ratio, there is an associated 0.316-point decrease in mMMS score per year).

occipital lobes), subcortical (ie, caudate, putamen, globus pallidus, internal capsule, and thalamus), and infratentorial (ie, mesencephalon, pons, medulla, and cerebellum) regions. The WMH severity measure for the current study was the sum of ratings for the 4 regions. All WMH ratings were performed by one rater (L.S.H.). Intrarater reliability, computed for 12 images, was high (intraclass correlation coefficient, 0.912).

CLINICAL EVALUATION

Performance on the mMMS[27] was the primary outcome measure. The mMMS is an expanded version of the MMSE[22] and consists of attention/calculation, general knowledge, language, and construction tasks. The scale has a maximum score of 57. All participants in the Predictors Study were required to score 30 or higher for inclusion, which is equivalent to a score of about 16 on the MMSE. The mMMS was administered at each semiannual visit and served as the indicator of cognitive change.

Additional risk factor clinical data included presence or absence of the following variables: *APOE-ε4* allele,[28] diabetes mellitus, dyslipidemia, coronary artery disease, and hypertension, which were coded as present based on reported history of treatment or diagnosis.

STATISTICAL ANALYSIS

Baseline associations between MRI-derived measurements and cognition were evaluated with multiple linear regression analyses. First, baseline bicaudate ratio, age, sex, educational level, and risk factor variables were entered as independent variables, and total score on the mMMS was the dependent variable. The model was conducted again without the risk factors. Next, the same 2 regression analyses were conducted substituting Scheltens scale WMH severity ratings for the bicaudate ratio. Finally, the same 2 regression analyses were conducted with WMH ratings, atrophy ratings, and their interaction term.

A similar approach was taken to evaluate the effect of baseline atrophy and WMH severity on longitudinal change in cognition. A series of generalized estimating equations (GEEs)[29] tested associations between baseline bicaudate ratio or WMH severity and change in mMMS score with and without risk factor covariates. This approach takes into account multiple visits per subject and the likelihood that characteristics of the same individuals over time are correlated. To establish the rate of cognitive decline, the first GEE model was run with mMMS score as the dependent variable and time (in years from baseline) as the independent variable. In all subsequent GEE models, mMMS score was the dependent variable, and the MRI measurement (ie, Scheltens scale score or bicaudate ratio), time, and an MRI measurement × time interaction term were included as predictors. All models included age, sex, and educational level as additional covariates. In a final GEE model, we included WMH severity ratings and bicaudate ratios, their interaction terms with time, and their 3-way interaction (ie, bicaudate ratio × Scheltens scale score × time) to evaluate their combined effects on cognitive decline. The 3 models were run with and without risk factor variables as additional covariates. Significant main effects of MRI measurements would indicate a difference in cognitive performance for each unit of measurement. A significant time effect would indicate a change in test scores over time. A significant interaction term with time would indicate differential rates of change in cognition over time as a function of the MRI measurement. Finally, a significant 3-way interaction would suggest an interaction of the 2 MRI measurements with time.

RESULTS

BASELINE ASSOCIATIONS WITH COGNITION

Mean (SD) bicaudate ratio and WMH ratings were 0.16 (0.02) and 3.79 (4.55), respectively. The overall multiple regression model testing the baseline association of atrophy with cognition was significant ($F_{9,55}$ = 2.357; P = .03), although only increased number of years of education entered into the model as a predictor of higher mMMS scores (β = 1.161; SE, 0.307; P < .001).

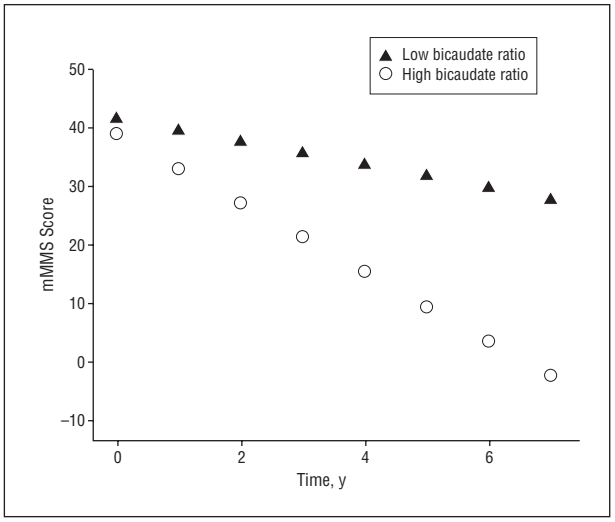

Figure 2. Predicted rates of cognitive change based on baseline characterization of bicaudate ratio. Baseline bicaudate ratio is presented as a dichotomous variable based on the median split of the entire sample (median, 0.1567). Note that a higher bicaudate ratio indicates greater amount of atrophy. The results from the generalized estimating equation analysis suggest that the greater the amount of atrophy at baseline, the greater the rate of cognitive decline. mMMS indicates modified Mini-Mental State.

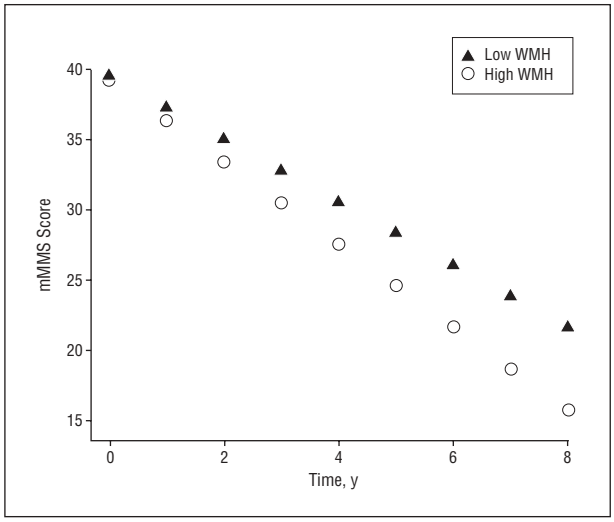

Figure 3. Predicted rates of cognitive change based on baseline characterization of white matter hyperintensity (WMH) severity. Baseline Scheltens scale score is presented as a dichotomous variable based on the median split of the entire sample (median, 3.0). The results from the generalized estimating equation analysis suggest that the higher and more severe the baseline WMH, the greater the rate of cognitive decline. mMMS indicates modified Mini-Mental State.

The regression model testing the association of WMH severity with baseline cognition was not significant with ($F_{9,53}$ = 1.981; P = .07) or without ($F_{4,76}$ = 2.302; P = .07) risk factor variables included. Similarly, when the 2 MRI measurements and their interaction terms were included, the model was not significant whether risk factor variables were ($F_{11,53}$ = 1.898; P = .07) or were not ($F_{6,76}$ = 1.960; P = .08) included.

In a separate bivariate correlational analysis, controlling for age, severity of WMH was not significantly associated with atrophy ratings (r_{74} = 0.103; P = .38).

LONGITUDINAL ANALYSIS

The mMMS scores declined a mean of 3.5 points per year (estimated β = −3.455; P < .001). The **Table** displays the primary results of the 3 GEE analyses. For every 1% increase in baseline bicaudate ratio, there was an additional associated 0.316-point decrease in mMMS score per year (significant time × bicaudate interaction). Increased age (β = 0.452; P = .04), being male (β = 5.263; P = .04), and lower educational level (β = 1.239; P < .001) were associated with poorer mMMS scores. The effect of bicaudate ratio on mMMS score decline was similar when the vascular risk factors were excluded. **Figure 2** displays the estimated rate of decline in mMMS scores in participants with low and high bicaudate ratio values, which were defined on the basis of a median split (median ratio, 0.1567).

A similar pattern emerged when examining the effect of baseline WMH severity on future decline. For each Scheltens scale point (ie, increase in WMH severity), there was an additional 0.173-point loss in mMMS score per visit (significant WMH × time interaction) (**Figure 3**). Being male (β = 4.801; P = .04) and lower educational level (β = 1.018; P = .002) were associated with lower mMMS scores. None of the risk factor variables reached significance for this model. When they were removed from the analysis, the findings remained essentially unchanged, although the significance of the time × WMH interaction was reduced to a trend-level effect.

When we examined the combined effect of baseline atrophy and WMH severity on future decline, a significant 3-way interaction indicated that individuals with the highest severity of WMH and greatest atrophy had the most precipitous rate of cognitive decline (Table and **Figure 4**). Excluding the vascular risk factors, the 3-way interaction remained statistically significant, and baseline atrophy ratings significantly predicted rate of decline.

COMMENT

The current study sought to determine whether measures of cerebral atrophy and WMH were associated with cognitive function and the rate of future cognitive decline in AD. Several important findings emerged. First, when examined cross-sectionally, increased atrophy was modestly associated with poorer cognitive performance, but the relationship between severity of WMH and cognition was unremarkable. When examined longitudinally, severity of baseline atrophy and severity of baseline WMH were associated with a faster rate of future cognitive decline. When both severity measures were considered in the same statistical model, they interacted and had an effect on future decline. Taken together, the findings suggest a synergistic interaction of AD pathology and small vessel vascular disease on the course of cognitive symptoms in AD.

The results add to a growing corpus of work examining the associations among measures of AD pathology, vascular disease, and their clinical expression. In most studies, atrophy is more prominent among patients with AD than controls[1-3,30] and is associated with more severe cognitive symptoms.[31,32] Others have reported that increased

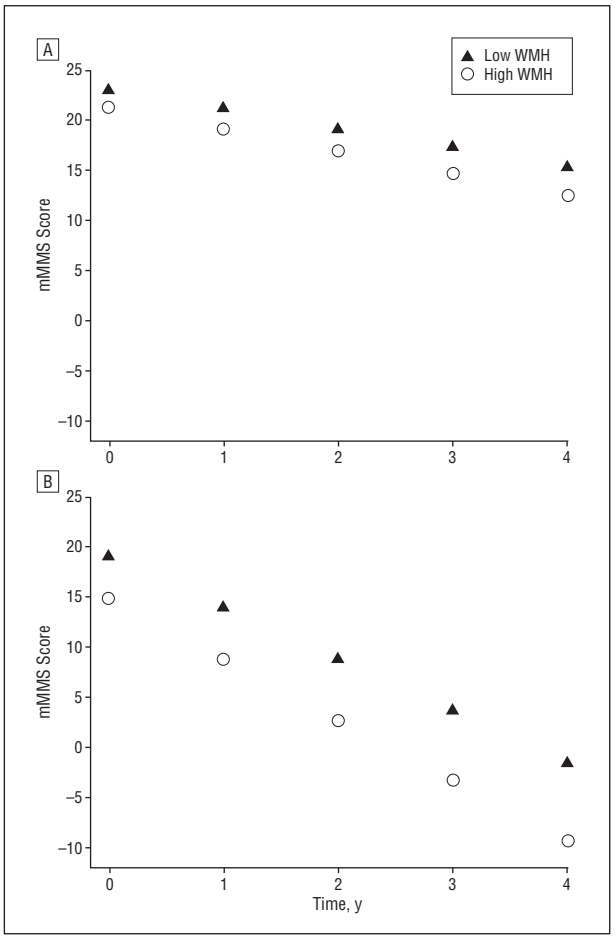

Figure 4. Graphical representation of the significant time × baseline white matter hyperintensity (WMH) × baseline atrophy interaction. The WMH severity and low (A) and high (B) degree of atrophy groups are based on the median severity. The predicted modified Mini-Mental State (mMMS) scores declined most precipitously among individuals with greater levels of atrophy and greater baseline WMH burden (B).

atrophy is associated with future risk of developing AD[15,33,34] and that the rate of regional atrophy predicts decline among patients with mild cognitive impairment and AD.[35,36] The current study extends these findings. Although cross-sectional associations with cognitive abilities were weak, global atrophy was robustly associated with a more precipitous cognitive decline. The findings suggest that, among individuals with mild AD, the severity of pathology-associated atrophy at one point in time has prognostic utility. Whole brain atrophy is not specific to the diagnosis of AD; however, within a sample of well-defined patients with AD, it is a good marker of disease severity. Thus, the current study supports previous cognitive studies showing an accelerated rate of future decline among more severely affected patients with AD.[37]

White matter hyperintensity burden has been reported to be more severe among patients with AD than nondemented elderly persons,[3,14,38] although not all studies have shown this association.[39,40] Furthermore, some studies have shown that increased burden is associated with poorer cognitive abilities in AD,[41,42] whereas others have not,[40,43,44] but the relationship between severity of WMH and cognitive abilities among older adults without dementia has been more consistently demonstrated.[42,45-47] It is possible that small vessel vascular disease, reflected in the severity of WMH, significantly affects cognitive abilities among individuals with no or very little AD pathology. Among those with more severe manifestations of disease, AD pathology may play a more salient role in cognitive abilities, effectively concealing the effect of small vessel vascular disease. Our results partially support this idea: on a cross-sectional basis, the severity of WMH was not associated with severity of cognitive impairment

Our findings are consistent with the idea that cerebrovascular pathology interacts with AD pathology. Whereas severity of baseline atrophy and severity of baseline WMH were associated with the rate of cognitive decline, when the 2 measures were included in the same model, the interaction effect was significant and the individual main effects were not. The observation is reminiscent of autopsy studies that have shown that individuals with vascular disease and AD pathology were more likely to have clinical dementia compared with those without vascular disease[48] or findings that less AD pathology is required to produce the same degree of cognitive impairment when vascular disease is present.[49] Our findings are most consistent with a report[50] that demonstrated a significant interaction of WMH and medial temporal lobe atrophy in the classification of older adults as AD or being normal; the risk associated with having a high degree of atrophy and a high degree of WMH was greater than the risk incurred by the product of the 2 factors. Although we did not observe an interaction between degree of atrophy and WMH cross-sectionally, the significant effect on future decline suggests a synergistic interaction of the 2 pathologies on the course of AD.

From a mechanistic perspective, the interaction of cerebrovascular and AD pathology may be a reflection of β-amyloid (Aβ) peptide deposition, which comprises the senile plaques characteristic of AD pathology, in the Aβ42 species, and cerebrovascular amyloid, in its Aβ40 form. Indeed, plasma concentrations of Aβ40 peptide were associated with increased WMH volume among patients with AD and cerebral amyloid angiopathy in a clinic-based sample[51] and among participants in the population-based Rotterdam Study.[52] In the current study, WMH severity predicted rate of cognitive decline among patients with AD only after statistical adjustment for common vascular risk factors (Table), suggesting that the variance in WMH related to cognitive course in AD is not owing to these risk factors. Rather, it is possible that WMH-associated cerebrovascular Aβ deposition specifically accounts for this association. Future work should examine the association among concentrations of plasma Aβ, WMH, and longitudinal changes in cognition.

Although inconsistencies exist in the literature regarding the exact relationship among AD pathological characteristics, vascular abnormalities, and cognition, findings do converge in demonstrating that increased cerebrovascular disease burden is not beneficial and is most likely harmful. At present, there are no available disease-modifying treatments for AD. However, there are a number of potentially modifiable risk factors and behaviors for cerebrovascular disease.[53-55] The reduction of these conditions could have therapeutic effects for the treat-

ment of the cognitive symptoms associated with AD, and further study of the determinants of WMH among patients with AD may highlight newer treatment targets.

This study has several limitations. First, neuroimaging was available for only a subset of participants in the Predictors Study, although participants with and without neuroimaging were similar. Second, analyses were conducted on ratings of clinical MRI scans, as opposed to digital scans that were acquired uniformly and analyzed automatically. Because clinical scans were acquired in the axial orientation, our analyses focused on global atrophy as opposed to atrophy in areas more specific to AD, such as the medial temporal lobe, which would require scans oriented in the coronal plane. Newer protocols exist that are able to quantify regional atrophy and WMH signal with higher precision and accuracy. It should be noted, however, that rater reliability for the bicaudate ratio and Scheltens scale was high and that estimates of atrophy from the bicaudate ratio were highly correlated with whole-brain atrophy measures derived in an independent sample. Third, although the study included well-characterized longitudinal cognitive data, neuroimaging data were only available at one point in time, thus limiting inference about the emergence and evolution of the imaging markers themselves. Future studies should incorporate prospectively collected longitudinal clinical and neuroradiological data.

This study also has a number of particular strengths. To our knowledge, this is among the largest studies that have examined prognostic utility of baseline neuroimaging characteristics on future cognitive decline in AD. Patients were carefully diagnosed at academic medical centers with specific expertise in aging and dementia, and diagnoses were based on uniform application of widely accepted criteria via consensus diagnosis procedures. Diagnoses from the Predictors Study are accurate. For example, 93% of patients that came to autopsy had pathologically confirmed AD at postmortem evaluation.[56] Patients were evaluated prospectively and relatively frequently (ie, biannually). Because participants were generally mildly demented at their baseline evaluation, we were able to capture a large range of progression over time.

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Author Contributions: Drs Brickman, Scarmeas, and Stern and Mss Tatarina and Sanders had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. *Study concept and design:* Brickman, Honig, Scarmeas, and Stern. *Acquisition of data*: Brickman, Honig, Scarmeas, Tatarina, Sanders, Albert, Brandt, Blacker, and Stern. *Analysis and interpretation of data*: Brickman, Honig, Scarmeas, and Stern. *Drafting of the manuscript*: Brickman and Scarmeas. *Critical revision of the manuscript for important intellectual content:* Honig, Scarmeas, Brandt, Blacker, and Stern. *Statistical analysis:* Brickman and Scarmeas. *Obtained funding*: Brickman and Stern. *Administrative, technical, and material support*: Honig, Tatarina, Sanders, Brandt, Blacker, and Stern. *Study supervision:* Scarmeas, Albert, Brandt, Blacker, and Stern.
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