Cerebral amyloid angiopathy and cognitive outcomes in community-based older persons

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ABSTRACT

Objective: We tested the hypothesis that cerebral amyloid angiopathy (CAA) is related to Alzheimer disease (AD) dementia and decline in multiple cognitive systems in old age, independent of AD plaque and tangle pathology and other common age-related neuropathologies.

Methods: Participants (n = 1,113) came from 2 longitudinal clinical-pathologic studies of aging, the Rush Memory and Aging Project and the Religious Orders Study. All underwent annual clinical evaluations including detailed cognitive testing for a mean of 7.1 years before death. Clinical diagnoses of AD were established after reviewing all clinical data, blinded to neuropathologic information. Neuropathologic examinations provided measures of CAA, AD pathology, macroscopic infarcts, microinfarcts, and neocortical Lewy bodies. The association of CAA with AD dementia was examined using logistic regression models, and its association with cognitive decline was examined using linear mixed models.

Results: CAA was common, present in 78.9% of participants, and moderately related to AD pathology ($\rho = 0.401$, $p < 0.0001$). In analyses adjusted for plaques, tangles, and other common age-related neuropathologies, CAA was associated with an increased odds of AD dementia (odds ratio = 1.237, 95% confidence interval 1.082–1.414) and an increased rate of decline in global cognition, perceptual speed, episodic memory, and semantic memory. The associations of CAA with cognitive outcomes were not driven by the presence of capillary involvement.

Conclusions: CAA is an important determinant of AD dementia and decline in multiple cognitive systems in old age. *Neurology*® 2015;85:1930–1936

GLOSSARY

AD = Alzheimer disease; **CAA** = cerebral amyloid angiopathy.

Cerebral amyloid angiopathy (CAA) is frequently observed in the brains of older persons and co-occurs with Alzheimer disease (AD) pathology.[1,2] However, the independent relation of CAA with late-life cognitive outcomes is unclear. Although several studies suggest a link between CAA and dementia,[3–7] findings come mainly from highly selected samples, and AD and other common age-related neuropathologies have infrequently been considered.[8–11] Furthermore, little is known about the relation of CAA with cognitive decline. We previously reported associations between CAA, perceptual speed, and episodic memory proximate to death in a sample a third the size of that in this study,[12] but studies examining the relation of CAA with the rate of change in multiple cognitive systems over time are rare.

We tested the hypothesis that CAA is related to cognitive outcomes over and above other common age-related neuropathologies, particularly AD. Participants and data came from 2 longitudinal clinical-pathologic studies of aging.[13] We first examined the independent relation of CAA with likelihood of AD dementia, and then examined the association of CAA with cognitive decline using data collected annually for up to 19 years before death.

METHODS

Standard protocol approvals, registrations, and patient consents. Data for this study came from 2 ongoing longitudinal cohort studies of aging.[13,14] These studies were approved by the institutional review board of Rush University Medical Center.

Supplemental data at Neurology.org

From the Rush Alzheimer's Disease Center (P.A.B., L.Y., S.N., S.L., R.S.W., D.A.B., J.A.S.) and Departments of Behavioral Sciences (P.A.B., R.S.W.), Neurological Sciences (L.Y., S.N., S.L., R.S.W., D.A.B., J.A.S.), and Pathology (S.N., J.A.S.), Rush University Medical Center, Chicago, IL.

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All participants signed informed consent and anatomical gift acts and agreed to annual clinical evaluations and brain donation. The follow-up rate in these studies is more than 95% among survivors and the autopsy rate exceeds 85%.

Participants. This study used data from autopsied persons. Of 3,069 participants enrolled at the time of analyses, 1,429 had died and 1,232 (86.2%) had autopsies. The postmortem evaluation was complete for 1,188 cases. We excluded 43 with missing CAA data and 32 with missing/non-AD dementia diagnosis, leaving a total of 1,113 cases for analyses. The mean age at death was 88.5 years (SD = 6.6 years, range = 65.9–108.3 years). The mean education was 16.3 years (SD = 3.7 years, range = 3–30 years). Seven hundred twenty-one participants (64.8%) were women.

Clinical/cognitive evaluation. All participants underwent a baseline structured evaluation including neuropsychological testing and neurologic examination.[13,14] Annual follow-up examinations were nearly identical to baseline and conducted by clinicians blinded to prior assessments. Cognitive function was evaluated using a standardized battery of 19 tests from which composite measures of global cognitive function and 5 specific domains were computed: episodic, semantic, and working memory, perceptual speed, and visuospatial ability, as described previously.[13–17] Composite measures were derived by standardization of the raw scores of individual tests to z scores using the baseline mean and SD of the pooled cohorts.

Following death, a board-certified neurologist blinded to pathologic data reviewed all available clinical information to determine whether clinical dementia was present proximate to death and, if so, its likely etiology. The diagnosis of AD dementia (probable or possible) was made in accordance with standard criteria,[13,14,18] and the term AD dementia refers to the presence of the clinical syndrome of AD.[19,20]

Neuropathologic assessment. Brain autopsy procedures have been previously described in detail.[13–15,17] CAA pathology was assessed in 4 neocortical regions: midfrontal, midtemporal, angular, and calcarine cortices. Paraffin-embedded sections were immunostained for β-amyloid using 1 of 3 monoclonal anti-human antibodies: 4G8 (1:9000; Covance Labs, Madison, WI), 6F/3D (1:50; Dako North America Inc., Carpinteria, CA), and 10D5 (1:600; Elan Pharmaceuticals, San Francisco, CA).

For CAA assessment, we expanded on a previously published methodology[21] similar to a recently proposed protocol.[22] For each region, meningeal and parenchymal vessels were assessed for amyloid deposition and scored from 0 to 4, where 0 = no deposition, 1 = scattered segmental but no circumferential deposition, 2 = circumferential deposition up to 10 vessels, 3 = circumferential deposition up to 75% of the region, and 4 = circumferential deposition over 75% of the total region (figure e-1 on the *Neurology*® Web site at Neurology.org). The CAA score for each region was the maximum of the meningeal and parenchymal CAA scores. Scores were averaged across regions and summarized as a continuous measure of CAA pathology for analyses. In addition, for illustration of findings and supporting analyses, we classified CAA scores into a 4-level severity rating including none, mild, moderate, and severe using cutoffs determined by the neuropathologist. Finally, capillary CAA was rated as present or absent.

To quantify global AD pathology, tissue blocks from the midfrontal, superior temporal, inferior parietal and entorhinal cortices, and hippocampus (CA1/subiculum) were sectioned at 6 μm and stained with a modified Bielschowsky silver stain. Counts of silver-stained neuritic plaques, diffuse plaques, and neurofibrillary tangles were used to create a composite measure of AD pathology, as described.[15,17] For secondary analyses, pathologic AD was defined using the National Institute on Aging–Reagan criteria with intermediate and high likelihood cases indicating a pathologic diagnosis.[23]

Lewy bodies were examined in 7 brain regions (inferior parietal, superior or middle temporal, midfrontal, entorhinal, anterior cingulate cortices, amygdala, and substantia nigra) with 1 of 2 monoclonal antibodies to α-synuclein (LB 509 1:150 or 1:100; Zymed Labs, Invitrogen Corp., Carlsbad, CA) or pSyn#64 (1:20,000; Wako Chemicals Inc., Richmond, VA) and rated as present or absent. Chronic gross and microscopic infarcts were rated as present or absent.[15,17]

Statistical analysis. Spearman correlations and Wilcoxon tests were used to examine bivariate associations of CAA with demographics and covariates. We used multivariable logistic regression models to examine the association of CAA with odds of AD dementia diagnosis, with dementia as the binary outcome and CAA the primary predictor. The coefficient for CAA estimates the log odds of AD dementia associated with CAA. Our first model adjusted for age, sex, and education. In order to further test that the association was independent of other neuropathologies, we then added terms for AD pathology, chronic gross and microinfarcts, and Lewy bodies.

Next, we used linear mixed models to examine the association of CAA with rate of change in global cognition. Here, repeated cognitive measures collected over multiple years were the longitudinal outcome. The slope, estimated by a term for time in years since baseline, represents the average annual rate of change in global cognition. The interaction term of time and CAA estimates the association of CAA with the cognitive slope. A significant and negative coefficient for the interaction suggests that a greater burden of CAA is associated with faster decline. We first adjusted for age, sex, and education, and then in a separate model, we further adjusted for AD, Lewy bodies, and infarcts. We then repeated the fully adjusted analysis to examine the associations of CAA with decline in 5 specific cognitive systems.[15,17]

Analyses were done using SAS/STAT software, version 9.3 (SAS Institute Inc., Cary, NC) and statistical packages in R version 3.1.2 (www.r-project.org). A nominal threshold of $p < 0.05$ was applied for statistical significance.

RESULTS

Burden of CAA. Demographic, clinical, and neuropathologic characteristics of the participants are shown in table 1. At autopsy, CAA pathology was present in 878 cases (78.9%, median 0.75, interquartile range 0.25–1.75), about a third of whom had moderate or severe CAA. A greater burden of CAA pathology was weakly associated with older age (Spearman correlation $\rho = 0.146$, $p < 0.0001$) and lower Mini-Mental State Examination scores proximate to death (Spearman correlation $\rho = -0.262$, $p < 0.0001$), and CAA pathology was greater among persons with AD dementia (Wilcoxon test, $z = 7.912$, $p < 0.0001$) compared to persons without dementia. CAA was moderately associated with AD pathology ($\rho = 0.401$, $p < 0.0001$) and marginally associated with microinfarcts (Wilcoxon test, $z = 1.873$, $p = 0.061$). CAA was not associated with macroscopic infarcts or Lewy bodies.

Table 1 Participant characteristics	
Age at death, y, mean (SD)	88.5 (6.6)
Sex, male, n (%)	392 (35.2)
Education, y, mean (SD)	16.3 (3.7)
MMSE score before death, mean (SD)	21.2 (9.1)
MCI, n (%)	285 (25.6)
Clinical AD dementia, n (%)	463 (41.6)
Global AD pathology, mean (SD)	0.74 (0.63)
Macroscopic infarcts, n (%)	386 (34.7)
Microinfarcts, n (%)	314 (28.2)
Lewy bodies, n (%)	247 (22.2)
CAA, median (interquartile range)	0.75 (0.25–1.75)

Abbreviations: AD = Alzheimer disease; CAA = cerebral amyloid angiopathy; MCI = mild cognitive impairment; MMSE = Mini-Mental State Examination.

CAA and AD dementia. Four hundred sixty-three (41.6%) of the cases had a clinical diagnosis of AD dementia. In a logistic regression model adjusted for demographics, persons with more severe CAA pathology had a substantially increased odds of AD dementia ($p < 0.0001$; table 2). Next, to test the hypothesis that the association of CAA with AD dementia is over and above other common neuropathologies, we further adjusted for AD, macro- and microscopic infarcts, and Lewy bodies. In the fully adjusted model, AD, macroscopic infarcts, Lewy bodies, and CAA were all associated with increased odds of AD dementia (table 2). Figure 1 illustrates the additive burden of these pathologies on the probability of AD dementia. On average, for a woman 89 years of age and with 16 years of education, the estimated probability of AD dementia was 0.22 if she had the median level of AD pathology. This probability increased to 0.49 if she had comorbid macroscopic infarcts and Lewy bodies, and further increased to 0.56 if she had the median level of CAA.

Table 2 Association of CAA with AD dementia[a]		
Model terms	OR (95% CI)	OR (95% CI)
Age at death	1.074 (1.052–1.096)	1.070 (1.046–1.095)
Male sex	0.892 (0.679–1.170)	0.970 (0.719–1.307)
Education	1.018 (0.983–1.054)	1.033 (0.994–1.074)
AD	—	3.868 (3.005–4.981)
Macroscopic infarcts	—	1.510 (1.257–1.815)
Microinfarcts	—	1.180 (0.958–1.453)
Lewy bodies	—	2.176 (1.567–3.023)
CAA	1.523 (1.352–1.715)	1.237 (1.082–1.414)

Abbreviations: AD = Alzheimer disease; CAA = cerebral amyloid angiopathy; CI = confidence interval; OR = odds ratio.
[a] Derived from separate logistic regression models.

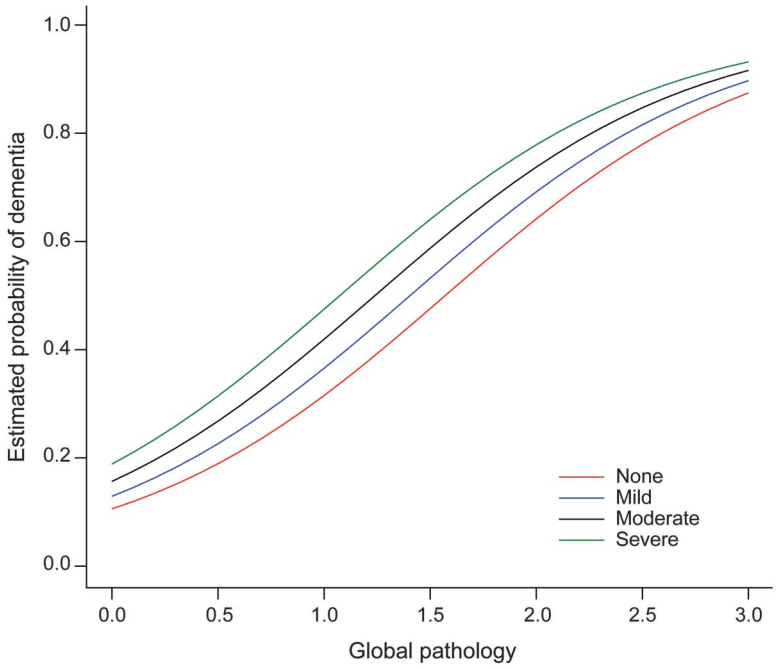
CAA and cognitive decline. It is now widely recognized that considerable cognitive decline occurs over years or even decades before the diagnosis of AD dementia, and prevention of age-related cognitive decline is a top public health priority. Using data from cognitive assessments administered over multiple years before death (mean = 7.1, SD = 4.2, range 0.6–19.1), we examined the association of CAA with cognitive decline in a series of linear mixed models (table 3). In the initial analysis adjusted for age, sex, and education, CAA pathology was associated with a lower level of global cognition and a faster rate of decline (p values <0.0001). Next, we augmented the previous model by adjusting for other common neuropathologies. In analysis, AD, macroscopic infarcts, and Lewy body pathology were all independently associated with faster global cognitive decline. Further, after adjusting for these neuropathologies, CAA pathology was associated with faster global cognitive decline ($p = 0.0001$). Figure 2 shows the rates of decline in global cognition for persons with mild, moderate, and severe CAA pathology compared to the rate of decline for those without CAA.

Next, to examine the cognitive profile associated with CAA, we examined the relation of CAA with rates of decline in 5 specific cognitive systems (table e-1). In separate analyses adjusted for demographics and other common neuropathologies, CAA pathology was associated with faster rates of decline in perceptual speed ($p = 0.032$), episodic memory ($p = 0.006$), and semantic memory ($p < 0.0001$). The associations of CAA with working memory ($p = 0.114$) and visuospatial abilities ($p = 0.148$) did not meet the threshold for statistical significance.

CAA with and without capillary involvement and cognitive outcomes. Two forms of CAA have been described, with and without capillary involvement, and some prior work suggests that these subtypes may have differential pathologic and clinical correlates.[24] To examine this issue, we repeated the fully adjusted logistic regression and mixed-effects models described above after including a term for capillary CAA. Of note, the associations of CAA with AD dementia and cognitive decline were essentially unchanged and the terms for capillary CAA were not significant in these models (data not shown), suggesting that the relation of CAA with cognitive outcomes is not driven by the presence of capillary CAA.

Supporting analyses. First, because CAA may be preferentially related to cortical microinfarcts (as opposed to the general measure of microinfarcts used in primary analyses, which included cortical and subcortical infarcts), we examined the role of cortical microinfarcts specifically. In bivariate analyses, CAA was associated with cortical microinfarcts

Figure 1 Association of CAA pathology with AD dementia for persons with no, mild, moderate, and severe CAA



Derived from a logistic regression model adjusted for age, sex, education, AD pathology, macro- and microscopic infarcts, and Lewy bodies. AD = Alzheimer disease; CAA = cerebral amyloid angiopathy.

(Wilcoxon test, $z = 2.410$, $p = 0.016$). However, in logistic regression and mixed-effects models adjusted for demographics, cortical microinfarcts, global AD pathology, and Lewy bodies, the associations of CAA with AD dementia (odds ratio 1.243, 95% confidence interval 1.089–1.416) and cognitive decline (estimate for global cognition = −0.013, standard error = 0.004, $p < 0.001$) were essentially unchanged, suggesting that cortical microinfarcts do not account for the association of CAA with cognitive outcomes.

Second, because the associations of CAA with AD dementia and cognitive decline may vary depending on CAA severity, we repeated the fully adjusted models after replacing the continuous measure of CAA with a categorical measure (i.e., no, mild, moderate, and severe CAA). In these analyses, moderate and severe CAA were associated with AD dementia and cognitive decline; there was essentially no effect of mild CAA on cognitive outcomes (data not shown).

Third, because CAA may interact with AD pathology to influence cognition, we examined whether the presence of pathologic AD modified the relation of CAA with AD dementia and cognitive decline. Moderate to severe CAA was present in 20% of persons without pathologic AD compared to 44% with pathologic AD. However, fully adjusted models revealed no significant interactions, suggesting that the effect of CAA pathology on the likelihood of AD dementia or the rate of cognitive decline did not differ among persons with and without pathologic AD (data not shown).

Table 3 Association of CAA with decline in global cognition[a]

Model terms	β (SE), *p* value	β (SE), *p* value
Age at death	−0.0009 (0.0007), 0.183	−0.000007 (0.0006), 0.9061
Male sex	0.013 (0.009), 0.165	0.005 (0.008), 0.533
Education	0.002 (0.001), 0.118	0.001 (0.001), 0.230
AD	—	−0.087 (0.007), <0.0001
Macroscopic infarcts	—	−0.022 (0.005), <0.0001
Microinfarcts	—	−0.002 (0.006), 0.703
Lewy bodies	—	−0.046 (0.009), <0.0001
CAA	−0.029 (0.004), <0.0001	−0.012 (0.004), 0.0001

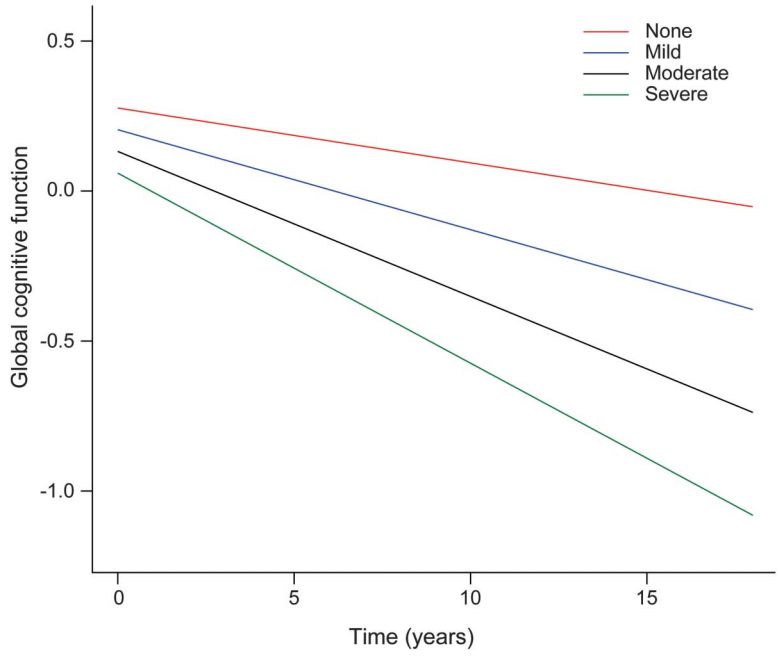
Abbreviations: AD = Alzheimer disease; CAA = cerebral amyloid angiopathy; SE = standard error.
[a] Derived from separate mixed-effects models.

DISCUSSION Using data from more than 1,100 well-characterized older persons, we found that CAA pathology is an independent contributor to AD dementia, over and above AD pathology and other common age-related neuropathologies. Furthermore, in analyses based on annual cognitive data collected over a period of 19 years, CAA pathology was associated with faster rates of decline in global cognition, perceptual speed, episodic memory, and semantic memory. These findings suggest that CAA pathology makes an important and relatively independent contribution to late-life cognitive outcomes.

The association of CAA with cognition has been a topic of debate. Although several prior studies suggest a link between CAA and dementia,[4–7] most used data from highly selected groups and other common age-related neuropathologies typically were not considered. Furthermore, the limited findings available from community-based studies that incorporated other neuropathologies are inconclusive. Whereas severe CAA pathology was associated with an increased likelihood of dementia in the Medical Research Council study,[11] CAA was not associated with dementia in the Honolulu Asia Aging Study.[10] In addition, in Honolulu, CAA was associated with cognition only in the presence of AD, leaving open the question as to the degree to which CAA makes a separate contribution to dementia.

This study extends prior work in 4 important ways. First, the association of CAA with AD dementia after controlling for AD and other common pathologies suggests that CAA affects cognitive outcomes over and above the main causes of dementia. The clinical symptoms of AD were long thought to reflect a singular disease process of plaques and tangles, and

Figure 2 Association of cerebral amyloid angiopathy pathology with decline in global cognition



Derived from a mixed-effects model adjusted for age, sex, education, Alzheimer disease pathology, macro- and microscopic infarcts, and Lewy bodies.

AD drug development efforts continue to focus largely on mechanisms to reduce these intraparenchymal pathologies. However, increasing evidence suggests that multiple pathologies (e.g., infarcts, Lewy bodies) contribute to the clinical deficits that characterize AD dementia.[19,20] Herein, we provide evidence that CAA pathology, often implicated in vascular cognitive syndromes, makes an independent contribution to AD dementia; thus, these findings add to evidence showing that considerable pathologic heterogeneity underlies AD dementia. Efforts to treat and prevent AD dementia ultimately will be optimized by taking a multipronged approach to combat several neuropathologic processes simultaneously.

Second, this study extends our understanding of the functional consequences and cognitive profile of CAA. Despite widespread awareness that cognitive decline is the leading cause of disability and mortality in old age, we are not aware of prior studies examining the association of CAA with decline in multiple cognitive systems. The finding that CAA is associated with decline independent of other common neuropathologies suggests that interventions to prevent or treat CAA may reduce the public health burden posed by cognitive decline. Furthermore, while we previously reported relations of CAA with episodic memory and perceptual speed proximate to death,[12] in this study, CAA was associated with a faster rate of decline in perceptual speed, episodic memory, and semantic memory. Thus, the effect of CAA is relatively general, impairing multiple cognitive abilities over time including episodic memory, the hallmark of AD. Targeted therapies to prevent or treat CAA may benefit multiple cognitive systems in old age, even in the presence of other common age-related diseases.

Third, this study suggests that the association of CAA with cognitive outcomes is not driven by capillary involvement. Prior studies have suggested that subtypes of CAA (i.e., capillary CAA present vs absent) may have differing associations with AD-related risk factors and neuropathology[24]; however, we are not aware of studies examining whether capillary involvement differentially affects dementia risk or cognitive decline. This study suggests that CAA pathology is an important determinant of cognitive outcomes regardless of capillary involvement.

Fourth, this study suggests that CAA pathology is present among persons with and without pathologic AD and that the effect of CAA on cognitive outcomes does not differ across groups. Whereas prior work suggested that the effect of CAA may depend on dementia status, our finding suggests that CAA has significant consequences among persons with pathologic AD as well as milder degrees of AD-related pathologic burden. Therefore, it is likely that CAA pathology is not merely a surrogate for more severe AD pathology, but rather a relatively distinct pathologic process associated with adverse cognitive outcomes in old age.

CAA may work via multiple pathways to affect cognition. CAA typically affects leptomeningeal medium/small arteries and cortical arterioles, and CAA-related damage can result in microinfarcts, intracerebral hemorrhage, and white matter abnormalities. Here, CAA was related to cortical microinfarcts, but they did not account for the relation of CAA with AD dementia or cognitive decline. In imaging studies, persons with CAA exhibit diverse markers of small vessel disease, including cerebral microbleeds, white matter hyperintensities,[25] microstructural tissue changes, and associated cognitive impairment.[26–28] Of note, CAA evident via neuroimaging likely represents moderate to severe pathology, and our findings also suggest that more severe levels of CAA most potently affect cognitive outcomes. In addition, other factors may be important, including inflammation and oxidative stress. Future studies examining the mechanisms that link CAA with late-life cognitive outcomes are warranted.

Strengths of this study include the use of detailed, uniform diagnostic procedures to classify AD dementia, annual cognitive testing using psychometrically sound measures, and uniform neuropathologic evaluations by examiners blinded to clinical data. Limitations include the lack of potentially relevant data on

other CAA-related changes, including hemorrhage, inflammation, and ischemic white matter changes. Furthermore, our pathologic data collection does not include a detailed investigation of the vascular/perivascular processes (e.g., smooth muscle degeneration and complement deposition) that may be important in the pathogenesis of CAA-related cognitive decline. Indeed, in the absence of a relation with cognition, it remains unclear whether mild CAA is pathologic or physiologic. Finally, sufficient data are not yet available to examine whether CAA is related to the specific distribution of neuropathology (e.g., amyloid). Future work is needed to clarify the role of mild CAA and investigate the impact of additional CAA-related pathologies.

AUTHOR CONTRIBUTIONS

Drafting/revising manuscript for content: Boyle, Yu, Nag, Leurgans, Wilson, Bennett, Schneider. Study concept or design: Boyle, Wilson, Yu, Bennett, Schneider. Analyses or interpretation of the data: Boyle, Yu, Wilson, Leurgans, Bennett, Schneider. Acquisition of data: Nag, Bennett, Schneider. Statistical analysis: Yu. Study supervision or coordination: Boyle, Wilson, Nag, Bennett, Schneider. Obtaining funding: Boyle, Bennett, Schneider.

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