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Association of vascular brain injury, neurodegeneration, amyloid, and cognitive trajectory

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Abstract

Objective

To determine whether vascular and neurodegenerative factors influence cognition before clinically relevant Alzheimer disease pathology, we analyzed MRI measures and amyloid imaging in an ethnographically diverse cohort of cognitively normal individuals older than 60 years.

Methods

Participants (n = 154; mean age 74.15 ± 6.94; 50% female; 54% Caucasian, 22.1% Hispanic, 14.9% African American) were recruited from the University of California, Davis Alzheimer's Disease Research Center, who were cognitively normal at baseline, time of PET, and MRI, and received yearly cognitive assessment for 6.23 ± 4.16 years. Mixed model regression with random slope and intercept was calculated for episodic memory and executive function, adjusting for age, sex, education, and ethnicity.

Results

Vascular burden score was associated with total white matter hyperintensity (WMH) volume (β , 0.171; 95% confidence interval [CI], 0.024–0.318). WMH volume was associated with low baseline executive function (–0.115; –0.226 to –0.003) and rate of change in memory (–0.029; –0.045 to –0.012). Hippocampal volume was associated with the rate of change in memory (0.040; 0.021–0.059) and executive function (0.024; 0.008–0.039). Continuous measures of amyloid status influenced change in memory (–0.026; –0.044 to –0.008) and executive function (–0.033; –0.046 to –0.021) independently of MRI measures.

Conclusion

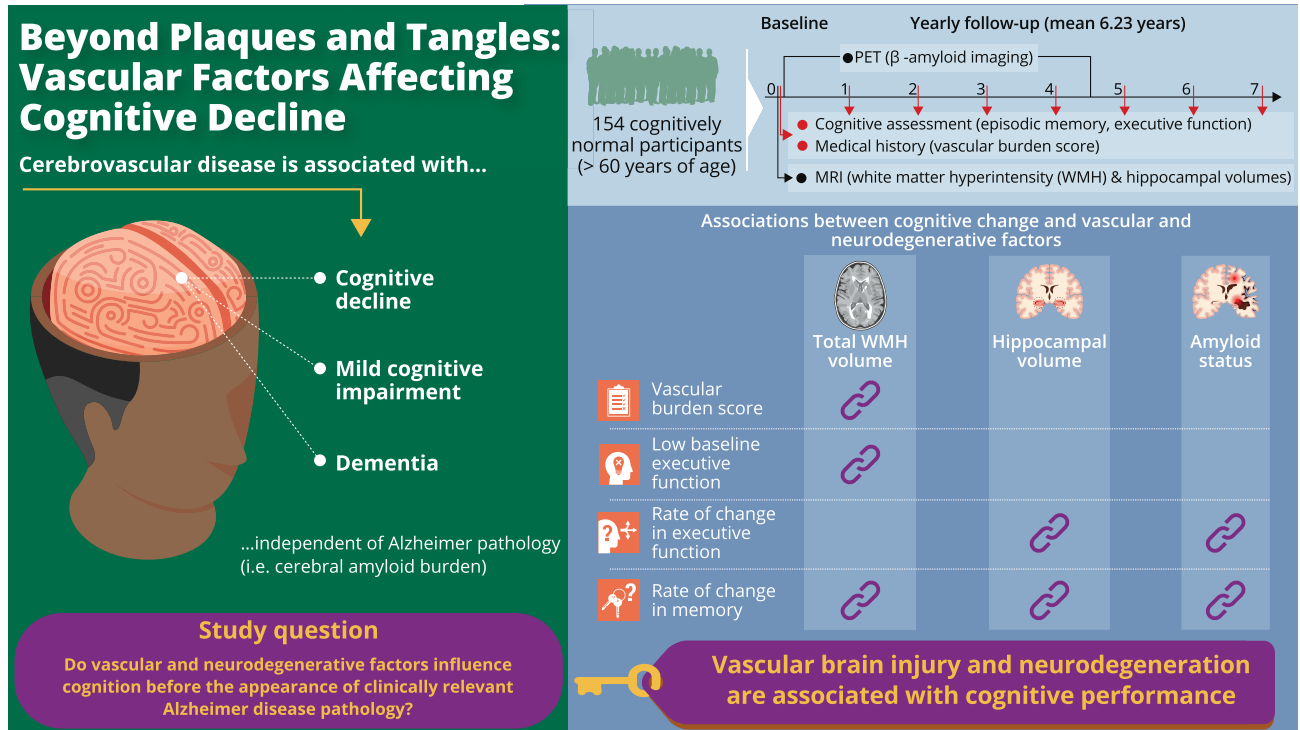
Vascular brain injury and neurodegeneration are associated with baseline cognitive performance and the rate of longitudinal change independent of amyloid status among community-dwelling, ethnographically diverse cognitively normal individuals, supporting the role of vascular diseases as risk factors for later-life dementia.

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Glossary

$A\beta$ = β -amyloid; AD = Alzheimer disease; ADNI = Alzheimer's Disease Neuroimaging Initiative; CI = confidence interval; CVD = cerebrovascular disease; DVR = distribution volume ratio; FLAIR = fluid-attenuated inversion recovery; IVD = ischemic vascular contributions to cognitive decline and dementia; MCI = mild cognitive impairment; PiB = Pittsburgh compound B; SENAS = Spanish and English Neuropsychological Assessment Scale; SUVR = standard uptake value ratio; TE = echo time; TI = inversion time; TR = repetition time; UCD ADRC = University of California, Davis Alzheimer's Disease Research Center; VBS = vascular burden score; WMH = white matter hyperintensities.



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Neurology®

Advancing age is associated with changes in brain structure¹ and varying trajectories of cognitive performance.² Cerebral amyloid burden accumulates with age³ and is associated with poorer memory performance,⁴ incident cognitive impairment, and dementia.⁵ Nearly 75% of cognitively normal individuals aged 70–79⁵ and about one-third of individuals with mild cognitive impairment (MCI), however, are free of significant amyloid on PET imaging,⁶ suggesting that factors other than amyloidosis are associated with declining cognitive performance.

Cerebrovascular disease (CVD) is common and associated with cognitive decline,⁷ incident MCI, and dementia,⁸ independent of Alzheimer pathology,⁹ particularly among Blacks and Hispanics.¹⁰ While the effect of CVD is generally assumed to be associated with MRI measures of white matter hyperintensities (WMH), and infarcts on MRI,⁸ additional evidence shows that CVD also can cause cerebral and hippocampal atrophy.¹¹

Previous studies show that MRI measures of vascular brain injury (WMH and infarcts) have an early and independent

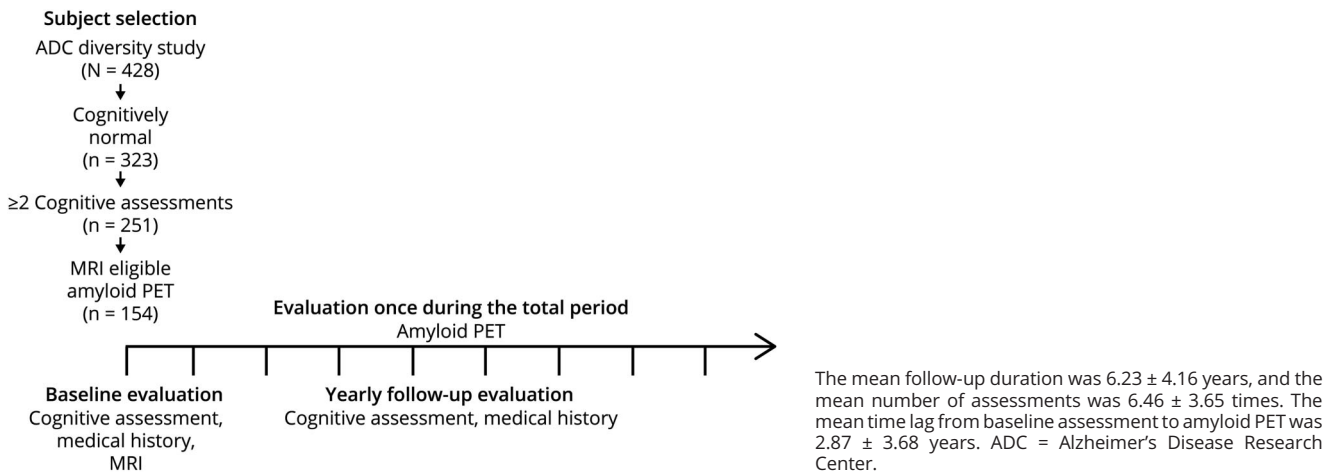
effect on cognition, even among those who have substantial co-occurring amyloid burden.^{7,12,13} However, given evidence that the population burden of age-related cognitive decline may be considerably lessened through prevention and treatment of vascular risk factors,¹⁴ it is important to identify the extent and consequences of vascular brain injury in the absence of clinically relevant amyloid pathology. This study aimed to examine the individual and combined effect of MRI measures of WMH, global and regional atrophy, and cerebral amyloid burden on the trajectory of cognitive performance comprehensively among an ethnically diverse, cognitively normal population over an extended period of observation.

Methods

Study population

A total of 154 participants were recruited for this study from the University of California, Davis Alzheimer's Disease Research Center (UCD ADRC) diversity cohort.¹⁵ All participants were

Figure 1 Timeline of study measurements



cognitively normal at baseline and time of PET and MRI and received yearly cognitive assessment at least 2 or more times (figure 1). Inclusion criteria required the participant to be over 60 years of age at enrollment. Exclusion criteria included unstable major medical illness, major primary psychiatric disorder (history of schizophrenia, bipolar disorder, or recurrent major depression), or substance abuse or dependence in the last 5 years. The presence of vascular risk factors or stroke that did not render the participant incapable of cognitive testing and longitudinal assessment were not exclusionary.¹⁵

Participants received a thorough multidisciplinary clinical evaluation, which included detailed medical history, neurologic examination, laboratory tests, and neuropsychological testing using the Uniform Data Set battery.^{16,17} Diagnosis of cognitive status (normal, MCI, or dementia) was made according to standard criteria and methods.¹⁷ Each participant was initially diagnosed as cognitively normal at a multidisciplinary consensus conference.

Neuropsychological measures

We used measures of episodic memory and executive function to assess cognition. Individuals in this sample were originally recruited and evaluated by 2 different batteries of neuropsychological tests, although the majority of participants in this study came from the UCD ADRC diversity cohort that used the Spanish and English Neuropsychological Assessment Scale (SENAS).¹⁸ The second group was enrolled in a program project grant on ischemic vascular contributions to cognitive decline and dementia (IVD) that ran from 1996 to 2012 using a different neuropsychological test battery. Individuals from the IVD cohort were transitioned to follow-up with the UCD ADRC neuropsychological battery at the close of the IVD study. A total of 95 individuals received neuropsychological test batteries for both protocols.

Conceptually similar measures of episodic memory and executive function were derived from the different tests that

composed the ADRC and IVD neuropsychological test batteries. Item response theory methods were used to create equated episodic memory and executive function scores from these 2 batteries that are on the same measurement metric and can be combined in analyses using data from both projects. The general approach followed methods described in previous publications¹⁹ and a detailed description of methods and results are available for review in the supplementary files.

Vascular burden score

The presence and number of vascular risk factors for each participant was based on a thorough review of the participant's medical history, medical records, and medications brought into the study site at the time of evaluation. The vascular burden score (VBS) for each individual was the sum of 5 vascular risk factors and vascular diseases (presence, 1; absence, 0; per each) and could vary from 0 to 5: (1) hypertension, (2) diabetes, (3) hyperlipidemia, (4) cardiovascular disease (1 or more among heart attack, atrial fibrillation, angioplasty, coronary artery bypass surgery, pacemaker, and congestive heart failure), and (5) CVD (1 or more among stroke and TIA) as previously described.⁷

MRI

Image acquisition

Structural MRI scans for 85 participants were obtained at the UCD MRI research center on a 3T Siemens (Munich, Germany) Magnetom Trio Syngo System with an 8-channel head coil. Acquired images included a T1-weighted volumetric magnetization-prepared rapid gradient echo (repetition time [TR] 2,500, echo time [TE] 2.94 or 2.98, inversion time [TI] 1,100, with 1 mm³ isotropic resolution) and a fluid-attenuated inversion recovery (FLAIR) scan (TR 5,000, TE 403, TI 1700, with 1.00 × 1.00 mm² in-plane resolution and 2.00 mm slice thickness). Sixty-nine participants received scans using a 1.5T GE (Cleveland, OH) Signa Genesis system at the UCD

research center. Each session included a T1-weighted 3D spoiled gradient recalled echo scan (TR 9, TE 1.9, with $0.98 \times 0.98 \text{ mm}^2$ in-plane resolution and 1.5 mm slice thickness) and a FLAIR scan (TR 11,002, TE 147, TI 2,250, with $0.98 \times 0.98 \text{ mm}^2$ in-plane resolution and 3.00 mm slice thickness). The mean time lag from initial assessment to MRI was 0.13 ± 0.14 years.

MRI tissue classification

MRI measurements were made as part of our in-house processing pipeline as previously described.²⁰ Structural MRIs were processed to remove the skull using an atlas-based method.²¹ Gray, white, and CSF tissues segmentation was performed using an algorithm designed to enhance accuracy at likely tissue boundaries.²² Segmentation of WMHs utilized a Bayesian approach where the likelihood of WMH was estimated from FLAIR signal characteristics, the prior probability of WMH occurrence was calculated from previous supervised segmentations of independent FLAIR images, and additional posterior probability constraints were applied at each image voxel.⁷ Hippocampal volume was computed by a multiatlas hippocampal segmentation algorithm.²¹

PET

Image acquisition

Pittsburgh compound B (PiB) PET images were acquired for 65 individuals at the Lawrence Berkeley National Laboratory on a Siemens ECAT EXACT HR PET scanner in 3D acquisition model. PiB radiotracer was synthesized at this facility using a standard protocol²³ where 10–15 mCi of [¹¹C] PiB was injected into an antecubital vein. Dynamic acquisition frames (34–35 frames total) were obtained over 90 minutes.

Florbetapir-PET scans were acquired on a Siemens Biograph mCT 40 PET machine for 89 individuals during a 50- to 70-minute interval following a 10 mCi (370 MBq) bolus injection of florbetapir (¹⁸F).

PET analysis

PET analysis was performed in 2 ways. PiB data were pre-processed with procedures described previously using a gray matter cerebellar reference region to calculate distribution volume ratio (DVR) images.¹³ The Global PiB Index was generated from the mean DVRs from regions of interest vulnerable to early β -amyloid (A β) deposition, which include the frontal cortex (anterior to the precentral gyrus), lateral parietal cortex, lateral temporal cortex, posterior cingulate, and precuneus.¹³ The occipital cortex was also examined because of its susceptibility to cerebral amyloid angiopathy.

Florbetapir data were analyzed using standard uptake value ratio (SUVR) measures.²⁴ Four 5-minute frames 50–70 minutes after injection were averaged and the image data were spatially normalized to a standard anatomical atlas in our laboratory. Mean tracer retention was calculated from 6

predefined target cortical regions of interest (medial orbital frontal, temporal, parietal, anterior cingulate, posterior cingulate, and precuneus) and whole cerebellar gray matter reference region, based on T1-weighted high-resolution MRI.

Participants were determined to be amyloid-positive using published DVR¹³ or SUVR²⁴ thresholds according to each radiotracer. Secondary analyses included scaled DVR or SUVR values from the PiB and florbetapir images as additional predictor variables to assess the effect of amyloid retention as a continuous effect on cognitive change. The scaled DVR or SUVR values were calculated based on a Gaussian 2 mixture model. The fitted parameters for the normal distributions of SUVR or DVR of each tracer were then used to create *z* score variance from the mean for each individual and each tracer.

Statistical analysis

Because of our hypothesis related to vascular brain injury and cognition, initial linear regression models evaluated the association of VBS with WMH and hippocampal volumes and the scaled DVR or SUVR values. Demographic differences between amyloid-positive and -negative groups were tested using Pearson χ^2 tests for dichotomous variables and independent sample *t* tests for continuous variables.

Association of demographics and baseline MRI measures with baseline and change in cognitive scores

To assess cross-sectional associations, we used linear models including baseline cognitive performance (episodic memory or executive function) as the dependent variable, and baseline demographic variables (age, sex, education, ethnicity, cognitive test form) and baseline MRI variables as independent variables. Longitudinal associations were assessed using linear mixed effect models with repeated measures of cognition as the dependent variable. Time since initial assessment, demographic variables, and baseline MRI variables were included as predictors, as well as the interaction with time. Random effects for the intercept and time were also included.

Additional effect of amyloid burden on baseline and change in cognitive scores

We used an analytical approach similar to that described in the previous study⁷ based on serial regression analyses to investigate the additional effect of amyloid burden, as reflected by PiB and florbetapir imaging, on cognition. This goal was assessed by adding in the linear mixed models amyloid positivity (yes/no, model A) or continuous measures of scaled DVR or SUVR values (model B) as a predictor. Tracer type and a time-lag variable computed as the difference in years between the date of PET imaging and the date of the first neuropsychological testing were added as covariates. All continuous independent variables, except time, were transformed into *z* scores to facilitate regression coefficient comparisons.

Table 1 Demographic information, brain measures, and neuropsychological test scores in the baseline evaluation, compared by binary classification group for amyloid positivity

	Total (n = 154)	Amyloid-negative (n = 91)	Amyloid-positive ^f (n = 63)	p Value ^g
Age, y	74.15 ± 6.94	73.39 ± 7.01	75.26 ± 6.74	0.101
Female	77 (50)	57 (62.6)	20 (31.7)	<0.001
Education, y	14.92 ± 3.83 (0–20)	15.01 ± 3.84 (0–20)	14.78 ± 3.84 (2–20)	0.712
Ethnicity: African American/Hispanic/Caucasian/others	23/34/83/14 (14.9/22.1/53.9/9.1)	16/17/46/12 (17.6/18.7/50.5/13.2)	7/37/17/2 (11.1/27.0/58.7/3.2)	0.079
Follow-up duration, y	6.23 ± 4.16	6.82 ± 4.37	5.38 ± 3.70	0.033
No. of assessments	6.46 ± 3.65	6.99 ± 3.93	5.70 ± 3.07	0.024
Current/prior smoker ^a	2 (1.3)/8 (56.5)	1 (1.1)/50 (54.9)	1 (1.6)/37 (58.7)	1.000/0.756
Cardiovascular disorder ^b	34 (22.1)	20 (22)	14 (22.2)	1.000
Stroke/TIA	20 (13)/9 (5.8)	11 (12.1)/4 (4.4)	9 (14.3)/5 (7.9)	0.877/0.568
Diabetes/hypertension	49 (31.8)/109 (70.8)	25 (27.5)/64 (70.3)	24 (38.1)/45 (71.4)	0.224/1.000
Hypercholesterolemia	87 (56.5)	48 (52.7)	39 (61.9)	0.336
Gray matter volume/TCV	0.41 ± 0.02	0.41 ± 0.02	0.41 ± 0.02	0.405
HC volume/TCV	0.006 ± 0.001	0.006 ± 0.001	0.005 ± 0.001	0.081
WMH volume/TCV ^c	−5.76 ± 1.32	−5.90 ± 1.34	−5.55 ± 1.28	0.106
PiB DVR	1.17 ± 0.23 (0.88–1.78)	1.02 ± 0.04 (0.88–1.10)	1.41 ± 0.07 (1.12–1.78)	<0.001
Florbetapir SUVR	1.14 ± 0.18 (0.85–1.73)	1.02 ± 0.07 (0.85–1.13)	1.31 ± 0.16 (1.13–1.73)	<0.001
Scaled DVR or SUVR ^d	1.50 ± 3.50	−0.45 ± 0.71	4.31 ± 3.98	<0.001
PET tracer: PiB/florbetapir	65/89 (42.2/57.8)	39/52 (42.9/57.1)	26/37 (41.3/58.7)	0.976
PET image time lag, y	2.87 ± 3.68	3.15 ± 3.90	2.47 ± 3.33	0.258
Episodic memory ^e	1.00 ± 0.90	1.10 ± 0.86	0.88 ± 0.93	0.113
Executive function ^e	0.76 ± 0.71	0.83 ± 0.76	0.65 ± 0.63	0.110

Abbreviations: DVR = distribution volume ratio; HC = hippocampus; PiB = Pittsburgh compound B; SUVR = standard uptake value ratio; TCV = total cerebrum cranial volume; WMH = white matter hyperintensities.

Values are mean ± SD (range) or n (%).

^a History and chart review at each visit.

^b Including heart attack/cardiac arrest, atrial fibrillation, angioplasty/endarterectomy/stent, cardiac bypass surgery, congestive heart failure.

^c Natural log-transformed to normalize variance.

^d z Score variance from the mean for each individual and each trace based on a Gaussian 2 mixture model.

^e Scaled unit; SDs adjusted for age, sex, and educational achievement.

^f According to the published criterion for amyloid positivity (for DVR¹³; for SUVR²⁴).

^g Derived from Student t test for continuous variables, from a χ^2 test for categorical variables.

All tests used were 2-tailed, with $\alpha = 0.05$. All statistical analyses were performed using R version 3.6.1 (R Foundation for Statistical Computing, Vienna, Austria).

Standard protocol approvals, registrations, and patient consents

This study was approved by the institutional review board at UC Davis and all study participants provided written informed consent.

Data availability

The data that support the findings of this study are available from the corresponding author on reasonable request. Supplementary file is available from Dryad (doi.org/10.25338/B8P60R).

Results

Sample characteristics

Participants were 74.15 ± 6.94 years of age on average, 50% female, and had an average of 14.92 ± 3.83 years of educational achievement (table 1) at baseline evaluation. The overall sample consisted of 23 African Americans, 34 Hispanics, 83 Caucasians, and 14 persons from other racial or ethnic groups. A total of 42 participants had the IVD cognitive testing paradigm at baseline enrollment whereas the remaining received SENAS testing throughout. The mean follow-up duration was 6.23 ± 4.16 years, and the mean number of assessments was 6.46 ± 3.65. The ranges of hippocampal and WMH volume were 4.68–8.16 and 0.10–59.94 mL. The mean

Table 2 Effects of demographic and brain MRI measures on baseline cognition and cognitive trajectories

Variables ^a	Episodic memory		Executive function	
	Estimate (95% CI)	p Value	Estimate (95% CI)	p Value
Time	-0.043 (-0.069 to -0.017)	0.003	-0.035 (-0.059 to -0.012)	0.005
Gray matter volume/TCV	-0.081 (-0.224 to 0.061)	0.267	-0.067 (-0.182 to 0.050)	0.250
Gray matter/TCV × time	-0.003 (-0.018 to 0.011)	0.657	0.005 (-0.008 to 0.018)	0.485
HC volume/TCV	0.027 (-0.116 to 0.171)	0.710	0.021 (-0.094 to 0.137)	0.717
HC volume/TCV × time	0.035 (0.017 to 0.052)	<0.001	0.026 (0.011 to 0.041)	0.001
WMH volume/TCV ^b	-0.056 (-0.187 to 0.076)	0.410	-0.130 (-0.236 to -0.025)	0.017
WMH volume/TCV ^b × time	-0.033 (-0.049 to -0.018)	<0.001	-0.007 (-0.021 to 0.007)	0.319
Age, y	-0.070 (-0.218 to 0.077)	0.351	-0.032 (-0.150 to 0.086)	0.599
Age × time	-0.011 (-0.028 to 0.007)	0.237	-0.002 (-0.017 to 0.013)	0.844
Male	-0.667 (-0.937 to -0.396)	<0.001	-0.267 (-0.484 to -0.050)	0.017
Male × time	0.006 (-0.027 to 0.038)	0.739	-0.012 (-0.041 to 0.016)	0.402
Education, y	0.308 (0.168 to 0.449)	<0.001	0.274 (0.162 to 0.386)	<0.001
Education × time	-0.001 (-0.017 to 0.015)	0.911	0.003 (-0.011 to 0.017)	0.698
Ethnicity (ref Caucasian)				
African American	-0.257 (-0.622 to 0.107)	0.169	-0.332 (-0.624 to -0.040)	0.027
Hispanic	-0.217 (-0.561 to 0.128)	0.220	-0.301 (-0.575 to -0.026)	0.034
Others	0.017 (-0.412 to 0.446)	0.938	0.054 (-0.291 to 0.398)	0.761
Ethnicity (ref Caucasian) × time				
African American	0.026 (-0.015 to 0.068)	0.222	0.009 (-0.028 to 0.046)	0.635
Hispanic	-0.026 (-0.066 to 0.015)	0.222	-0.003 (-0.038 to 0.031)	0.846
Others	0.014 (-0.040 to 0.068)	0.612	-0.023 (-0.070 to 0.025)	0.354

Abbreviations: CI = confidence interval; HC = hippocampus; TCV = total cerebrum cranial volume; WMH = white matter hyperintensities.

^a All continuous variables, except time, were transformed into z scores.

^b Natural log transformation of absolute value for normal distribution.

time lag from initial assessment to PET was 2.87 ± 3.68 years. Secondary analysis of bias due to death or dropout did not indicate bias due to incomplete follow-up or subject representation (data not shown).

The frequency of cardiovascular disease history was 22.1% (heart attack 9.1%, atrial fibrillation 5.9%, angioplasty 10.5%, coronary artery bypass surgery 5.8%, congestive heart failure 2.6%), and that of CVD was 16.9% (stroke 13.0%, TIA 5.8%). Hypertension, hypercholesterolemia, and diabetes had frequencies of 70.8%, 56.5%, and 31.8% (table 1), respectively. There were no significant differences in prevalence of vascular risk factors or disease by race/ethnicity.

VBS was positively associated with WMH volume (β , 0.171; 95% confidence interval [CI], 0.024–0.318) but not with cerebral gray matter volume (-0.027 ; -0.179 to 0.124), hippocampal volume (0.044 ; -0.092 to 0.179), or the scaled DVR or

SUVR values (0.034 ; -0.118 to 0.186), after adjusting age, sex, and ethnicity, indicating that vascular risk and disease were associated with WMH, but not atrophy or PET measures. WMH volumes were associated with scaled DVR or SUVR values (0.188 ; 0.025 – 0.351) whereas hippocampal volume was not associated with WMH (0.098 ; -0.049 to 0.245).

Binary classification of participants according to amyloid positivity produced no significant differences between the 2 groups except for sex, follow-up duration, and the number of assessments (table 1).

Association of demographics and baseline MRI measures with baseline and change in cognitive scores

Over the course of observation, the estimated slopes of episodic memory (β , -0.043 SD/year; 95% CI, -0.069 to -0.017) and executive function (β , -0.035 SD/year; 95% CI,

Table 3 Effect of MRI and amyloid PET measures on cognitive trajectories

Variables ^a	Episodic memory				Executive function			
	Model 1A		Model 1B		Model 2A		Model 2B	
	Estimate	95% CI	Estimate	95% CI	Estimate	95% CI	Estimate	95% CI
Time	-0.041 ^d	-0.076 to -0.007	-0.040 ^d	-0.074 to -0.006	-0.043 ^e	-0.071 to -0.014	-0.036 ^d	-0.062 to -0.009
Gray matter volume/TCV	-0.104	-0.253 to 0.045	-0.108	-0.256 to 0.041	-0.040	-0.159 to 0.079	-0.042	-0.161 to 0.077
Gray matter/TCV × time	0.000	-0.016 to 0.016	-0.001	-0.017 to 0.014	0.012	-0.002 to 0.025	0.009	-0.003 to 0.021
HC volume/TCV	0.054	-0.097 to 0.204	0.057	-0.093 to 0.207	-0.003	-0.123 to 0.117	0.001	-0.119 to 0.122
HC volume/TCV × Time	0.040 ^f	0.021 to 0.059	0.038 ^f	0.020 to 0.057	0.024 ^e	0.008 to 0.039	0.022 ^e	0.008 to 0.037
WMH volume/TCV^b	-0.034	-0.174 to 0.105	-0.029	-0.168 to 0.109	-0.115 ^d	-0.226 to -0.003	-0.114 ^d	-0.225 to -0.003
WMH volume/TCV^b × time	-0.029 ^e	-0.045 to -0.012	-0.028 ^e	-0.044 to -0.011	-0.002	-0.016 to 0.011	-0.001	-0.013 to 0.012
AV45 tracer (ref PiB)	-0.110	-0.133 to 0.392	0.077	-0.195 to 0.350	0.102	-0.106 to 0.311	0.073	-0.144 to 0.291
AV45 tracer × time	0.019	-0.015 to 0.054	0.002	-0.033 to 0.038	0.019	-0.009 to 0.047	-0.005	-0.032 to 0.021
PET image time lag, y	-0.028	-0.267 to 0.046	-0.116	-0.272 to 0.040	0.091	-0.033 to 0.215	0.087	-0.037 to 0.211
PET image time lag × time	-0.011	-0.034 to 0.012	-0.007	-0.029 to 0.016	0.011	-0.007 to 0.029	0.014	-0.003 to 0.031
Amyloid positivity	-0.009	-0.273 to 0.254			-0.034	-0.245 to 0.177		
Amyloid positivity × time	-0.033	-0.066 to 0.001			-0.036 ^d	-0.063 to -0.009		
Scaled DVR or SUVR^c			-0.065	-0.194 to 0.063			-0.036	-0.139 to 0.067
Scaled DVR or SUVR^c × time			-0.026 ^e	-0.044 to -0.008			-0.033 ^f	-0.046 to -0.021

Abbreviations: AV45 = florbetapir (F18-AV-45); CI = confidence interval; DVR = distribution volume ratio; HC = hippocampus; PiB = Pittsburgh compound B; SUVR = standard uptake value ratio; TCV = total cerebrum cranial volume; WMH = white matter hyperintensities.

Model A: amyloid positivity as a dichotomous variable. Model B: amyloid SUVR index as a continuous variable.

^a All continuous variables, except time, were transformed into z scores. Demographic variables and their time interaction were included in all models (table 4).

^b Natural log transformation of absolute value for normal distribution.

^c z Score variance from the mean for each individual and each trace based on a Gaussian 2 mixture model.

^d $p < 0.05$.

^e $p < 0.01$.

^f $p < 0.001$.

Table 4 Effect of the demographic variables on cognitive trajectories in the models of table 3

Variables ^a	Episodic memory				Executive function			
	Model 1A		Model 1B		Model 2A		Model 2B	
	Estimate	95% CI	Estimate	95% CI	Estimate	95% CI	Estimate	95% CI
Age	-0.080	-0.229 to 0.070	-0.070	-0.219 to 0.080	-0.018	-0.137 to 0.102	-0.012	-0.131 to 0.108
Age × time	-0.012	-0.030 to 0.006	-0.012	-0.030 to 0.006	-0.001	-0.016 to 0.014	-0.001	-0.015 to 0.013
Male	-0.689 ^b	-0.984 to -0.393	-0.667 ^b	-0.952 to -0.382	-0.206	-0.442 to 0.030	-0.199	-0.428 to 0.029
Male × time	0.015	-0.022 to 0.052	0.010	-0.026 to 0.045	0.012	-0.019 to 0.042	0.007	-0.021 to 0.034
Education	0.302 ^b	0.160 to 0.444	0.304 ^b	0.162 to 0.445	0.282 ^b	0.168 to 0.395	0.285 ^b	0.171 to 0.398
Education × time	-0.002	-0.018 to 0.015	-0.002	-0.019 to 0.015	0.000	-0.013 to 0.014	-0.000	-0.013 to 0.012
Ethnicity (ref Caucasian)								
African American	-0.256	-0.624 to 0.112	-0.286	-0.658 to 0.086	-0.366 ^c	-0.660 to -0.072	-0.377 ^c	-0.675 to -0.078
Hispanic	-0.167	-0.518 to 0.184	-0.168	-0.518 to 0.182	-0.340 ^c	-0.620 to -0.060	-0.337 ^c	-0.617 to -0.057
Others	-0.001	-0.438 to 0.436	-0.056	-0.498 to 0.386	0.046	-0.305 to 0.398	0.017	-0.339 to 0.373
Ethnicity × time								
African American	0.028	-0.013 to 0.064	0.013	-0.030 to 0.056	0.007	-0.029 to 0.042	-0.012	-0.046 to 0.021
Hispanic	-0.025	-0.061 to 0.013	-0.032	-0.073 to 0.010	-0.009	-0.043 to 0.024	-0.018	-0.049 to 0.014
Others	0.013	-0.038 to 0.061	0.006	-0.050 to 0.061	-0.027	-0.072 to 0.019	-0.036	-0.079 to 0.007

Abbreviation: CI = confidence interval.

^aAll continuous variables, except time, were transformed into z scores.^b $p < 0.001$.^c $p < 0.05$.

-0.059 to -0.012; table 2) showed small declines in both cognitive domains. None of the brain measures was associated with baseline episodic memory. Normalized WMH volume, however, had a significant negative effect on baseline executive function. For longitudinal differences in cognition, WMH and hippocampal volumes were associated with trajectories of episodic memory, but only the hippocampus was associated with executive change. Female sex and higher educational attainment were associated with higher memory and higher executive performance. None of the demographic variables, however, showed significant interactions with time.

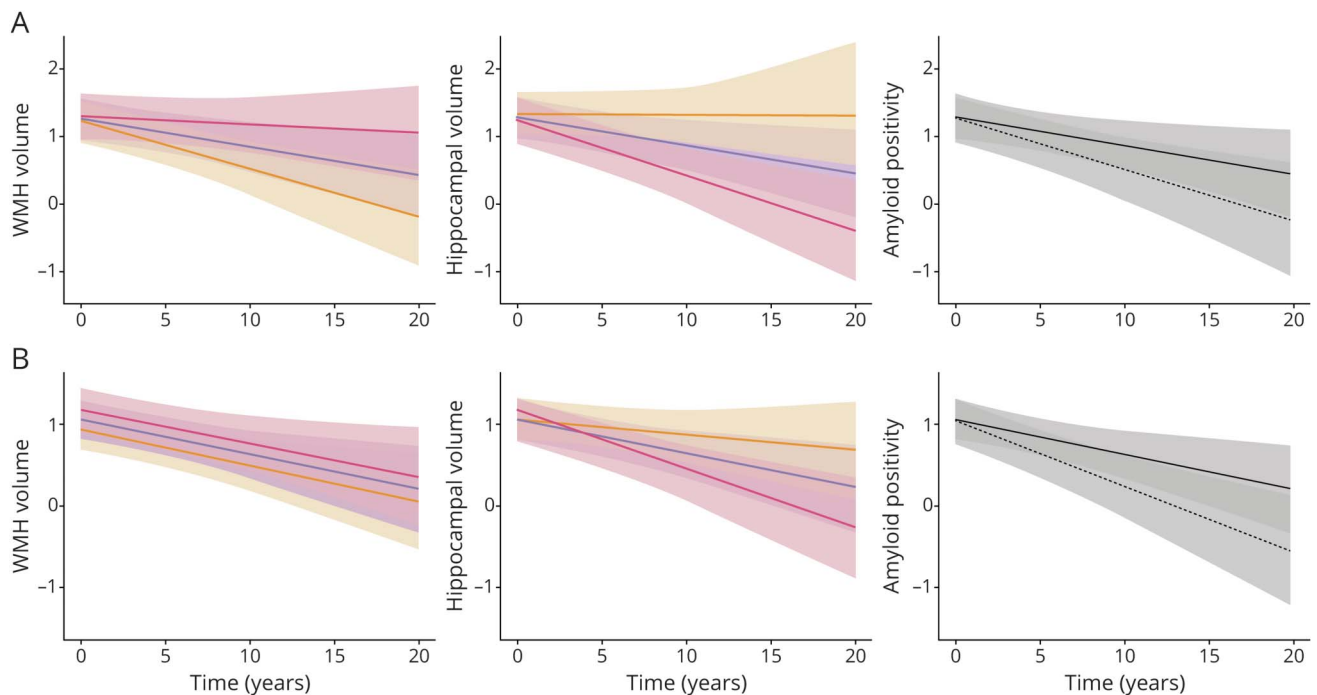
Additional effect of amyloid burden on baseline and change in cognitive scores

Sequential modeling that added amyloid retention is summarized in tables 3 and 4. Models 1A and 2A revealed that amyloid positivity was not independently associated with baseline performance (β , -0.009; 95% CI, -0.273 to 0.254) or the rate of change (β , -0.033; 95% CI, -0.066 to 0.001) for episodic memory, whereas the effect of hippocampal volume and WMH volume on the rate of change was maintained (table 3). The statistical significance of each demographic variable including

interaction with time was not changed compared to the model that did not include PET information (table 4). For executive function, amyloid positivity was associated with the rate of change/decline (β , -0.036; 95% CI, -0.063 to -0.009). Hippocampal volume also maintained its effect on the rate of change in executive function, and WMH volume maintained a significant association with baseline executive performance (table 3). Sex was not associated with executive performance, and other demographic variables (including interactions with time) were not changed in statistical significance compared to the model that did not include PET information (table 4).

When continuous amyloid retention was entered into the sequential model (models 1B and 2B in table 3), amyloid retention was associated with the rate of change in both cognitive functions (β , -0.026; 95% CI, -0.044 to -0.008 for episodic memory; β , -0.033; 95% CI, -0.046 to -0.021 for executive function). The significant effects of the MRI measures on both memory and executive function were not changed when compared to models 1A and 2A. The kind of PET tracer and PET image time lag were not associated with cognitive performance or the rate of changes in any model.

Figure 2 Plots of marginal effects of mixed regression models



Each graph shows cognitive trajectories for various levels of a single brain measure. (A) Predictive values of episodic memory performance. (B) Predictive values of executive function performance. Y axes represent cognitive performance. X axes are time. Red line, 1.0 SD below the mean; blue line, mean; yellow line, 1.0 SD above the mean for white matter hyperintensities (WMH) and hippocampal volumes; solid black line, amyloid-negative; dotted black line, amyloid-positive.

Figure 2 summarizes the marginal effects of MRI measures and amyloid positivity from model A in table 3 according to SDs of MRI measures and amyloid positivity for PET measures. Individuals with -1 SD of WMH and 1 SD of hippocampal volume both showed little change in memory performance over time. Executive function declined for all groups, but performance remained overall better for those with the -1 SD of WMH and the 1 SD of hippocampal volume. Conversely, those individuals with $+1$ SD of WMH or -1 SD of hippocampal volume performed significantly worse on baseline executive function and trajectories of memory and executive function. Modest but significant divergence over time as an effect of amyloid positivity is seen with executive function performance, but there are no overlapping CIs of the estimate in trajectories of memory performance.

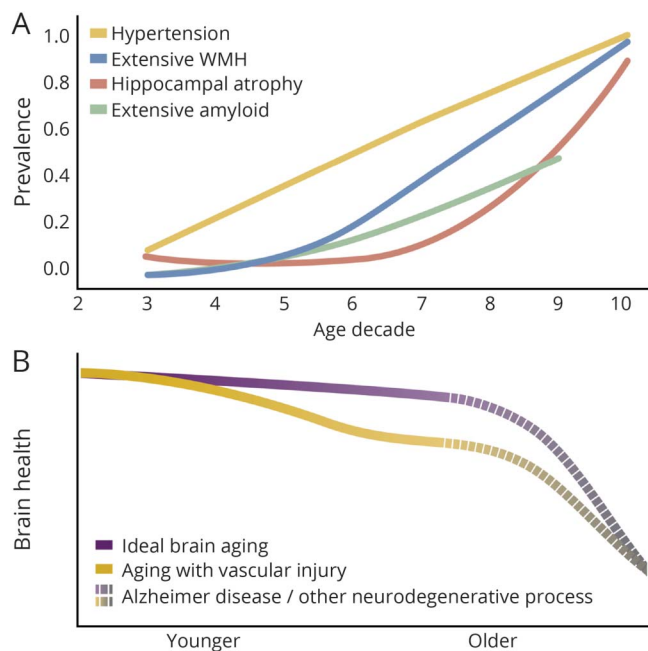
Discussion

This study found a consistent effect of WMH and hippocampal volumes on cognitive function independent of amyloid status in a community-based, ethnically diverse cohort of cognitively normal individuals. WMH volume, which was significantly associated with VBS in this study, had the strongest effect on level of baseline executive function among various brain measures, and showed an effect similar to hippocampal volume and continuous amyloid status on the rate of change in episodic memory. Hippocampal volume also had

a consistent effect on the rate of change in both episodic memory and executive function. Amyloid burden, when treated as a dichotomous variable, did not affect the level or the rate of change in memory performance, though there was a modest effect on the rate of change in executive function. Amyloid burden, when considered as a continuous measure, however, had a significant association with change in both memory and executive function, but this influence remained independent of structural brain measures. We further show that individuals with WMH volume 1 SD below average (nonvascular path) had limited change in memory performance over the period of observation, whereas those having 1 SD above average (vascular path) had significant decline. While similar to the previous study,²⁵ we further extend the findings by showing that hippocampal volumes 1 SD above average showed limited change in memory and executive performance over the period of observation (figure 2), whereas those with volumes 1 SD below average resulted in significant decline in cognition. In sum, cognitively normal individuals with low WMH burden or high hippocampal volume underwent modest changes in memory performance, independently of amyloid status.

These results emphasize the important role of nonamyloid processes as early risk factors for cognitive decline and future dementia in the general population and challenge current concepts regarding the role of Alzheimer disease (AD) pathologies in cognitive aging.²⁶ The fact that WMH volume

Figure 3 Proposed models of timing of amyloid and non-amyloid processes in the general population



Vascular and degenerative factors influence cognition before clinically relevant Alzheimer disease pathology and likely create susceptibility to later life dementia. (A) Age-specific prevalence of hypertension, abnormal white matter hyperintensities (WMH), hippocampus, and amyloid status modified from references 1, 29, and 50. (B) Hypothetical model by which vascular risk factors cause subtle brain injury increasing risk for later-life dementia when neurodegeneration is more prevalent.

was associated with degree of amyloid retention when considered as a continuous variable is consistent with previous studies examining the effect of vascular risk and disease on cerebral amyloid retention²⁷ and indicates an association among vascular risk, amyloid, and WMH.²⁸

Figure 3A summarizes currently available data regarding population prevalence of hypertension (the most common vascular risk factor), extensive WMH, hippocampal atrophy, and excessive amyloid burden. Given that vascular risk factors and vascular disease become prevalent at a relatively early age²⁹ and the findings that vascular risk factors have an early and cumulative effect on brain injury,³⁰ we confirmed the association of vascular risk factors with WMH volume in our population and hypothesized that vascular risk factors throughout the lifespan increase susceptibility to late-life dementia.³⁰ Figure 3B summarizes this hypotheses.

The combined effects of cerebrovascular pathology on dementia appear even more prominent for African Americans and Hispanics than non-Hispanic Whites.¹⁰ Given that vascular risk factors such as systolic blood pressure and obesity are associated with increased likelihood of dementia¹¹ and recent evidence that lifestyle modification³¹ or ideal control of systolic blood pressure³² are associated with lower risk for incident cognitive impairment or decline, the increasingly

recognized role of risk modification for dementia prevention supports the relevance of these findings.

Increased volumes of WMH are considered a common consequence of the aging process,¹ but are exacerbated by vascular risk factors that influence brain and cognitive health, even during middle life.¹¹ In later life, evolution of WMH is associated with declines in both memory and executive function³³ and extensive WMH predict incident MCI and dementia.⁸ While WMH also accompany AD^{20,34} and mediate cognitive effect,³⁴ previous cross-sectional studies examining individuals with normal cognition or MCI find that WMH and infarction have a negative effect on cognition independent of concurrent amyloid status.^{12,13}

WMH, which was associated with VBS, had the greatest effect on the level of baseline executive function (nearly 3 times that of any other measures) in our study. Previous studies from our group show that WMH was associated with executive function by reducing the functional connectivity of the prefrontal cortex with other cortical or subcortical regions³⁵ independent of location.³⁶ We also found that WMHs affect memory trajectory, which might be also likely via frontal systems impairment.³⁵ The lack of association between WMH volume and decline in executive function could indicate that change in executive function is more sensitive to the progression of WMH than to baseline WMH.³³ We conclude from previous data and the results of this study that WMH have early and consistent effects on cognition not influenced by amyloid burden, consistent with data indicating an increased risk of WMH for future MCI and dementia⁸ likely through increased susceptibility to later life neurodegeneration as depicted in figure 3B.

Age-related differences in global and regional brain volumes, including hippocampal volume, are well described.¹ Vascular risk factors increase these age-related differences and are associated with declines in cognitive function³⁷ even when the diseases are mild³⁸ or well controlled.³⁹ Similarly, even pure vascular disease is known to cause both generalized⁴⁰ and hippocampal atrophy⁴¹ and associated decline in cognition. Although neurodegeneration markers are commonly used in AD research,²⁶ they are not specific to AD, but rather are indicators of damage that may be derived from a variety of etiologies including vascular brain injury.²⁶ Given that CVD is associated with cerebral and hippocampal atrophy,^{11,37,39} we investigated the effect of hippocampal volume and gray matter volume as markers of neurodegeneration on cognition along with WMH volume. While hippocampal volume was associated with both memory and executive function trajectories, amyloid burden and WMH volume were not associated with hippocampal volume in the present study. Further studies are needed to understand potential causes of hippocampal atrophy among diverse, cognitively normal individuals.

Lack of effect of gray matter atrophy on cognition most likely reflects the intact cognitive status of this study group. Conversely, the effect of hippocampal atrophy is more specific to

cognition and therefore had greater influence, suggesting that gray matter volume atrophy may be related to cognitive decline at a later pathophysiologic stage⁴² in our population. Longitudinal imaging of this group would further elucidate the relationship between generalized atrophy measures and cognition.

Individuals of this study were diverse, not only in relation to race or ethnicity, but also along demographic variables such as social economic status and education. In addition, we enrolled individuals irrespective of medical history, resulting in an increased prevalence of vascular risk factors more in line with the US population.²⁹

Including a more representative older population in our study likely accounts for some of the differences found. First, as expected,⁴³ there was a significant decline in performance across both memory and executive function among this group of cognitively normal individuals, which differs from cognitive trajectories for normal individuals from other studies such as the Alzheimer's Disease Neuroimaging Initiative (ADNI). While there were some baseline differences in cognitive performance in relation to race or ethnicity, sex, and level of education in our group (tables 2 and 4), these demographic variables did not influence longitudinal cognitive performance in this cohort, similar to findings previously reported by our group.⁴⁴ This lack of longitudinal effect of demographic variables may support generalizability of our findings, despite the demographic diversity of the cohort.

The findings that VBS was associated with WMH and WMH was associated with continuous amyloid burden are also likely influenced by population characteristics. The prevalence of vascular risk factors and vascular diseases among the participants of our study was higher than in other biomarker studies such as ADNI. In our study, the prevalence of these diseases did not vary significantly by race/ethnicity and, therefore, it is more likely that it was the result of our efforts to recruit participants directly from the community without regard to risk factors or concurrent vascular disease that led to this difference.

In clinically normal study populations, the effects of amyloid deposition on cognition have been mixed. Studies that find no definite effect on cognition^{12,13} note that A β is an initiating factor in the progression toward AD that may not influence cognition early in the course of disease. In cognitively intact older adults, therefore, it may be the delayed sequelae of A β deposition, such as tau aggregation and subsequent tau-mediated neurodegeneration, that produce cognitive deficits.⁴⁵ Given that the effect of amyloidosis on cognitive impairment is most strongly associated with the combined effects of tauopathy and neurodegeneration,^{26,46} the degree of amyloid burden, which was relatively mild (maximum values of DVR or SUVR were under 2.0) in our cognitively normal population, might explain the lack of effect on cognition in this study. Our lower values of amyloid burden likely reflect that individuals were determined to be cognitively normal at enrollment and time of

PET imaging. Although the relative effect sizes of amyloid, hippocampal, and WMH volumes on cognitive trajectory were similar in this study as well as previous studies,^{25,47} the distinguishing finding of this study is the large effect size of WMH volume on the level of executive function. This effect was about 3–3.5 fold compared to the effect of amyloid status (whether categorical or continuous) on cognitive trajectory. Our finding that WMH volume was associated with increased amyloid retention may support the possibility of an interaction between vascular brain injury and amyloid deposition, but there was no interaction between WMH volume and amyloid status (or 3-way interaction with time) in the linear mixed model (data not shown); therefore, further research is needed to test potential hypotheses.

Our study has a number of limitations. First, while our study emphasized community-based recruitment, the number of participants is relatively small and likely does not represent the entire local population. Second, amyloid PET was obtained later in the course of follow-up, thereby reducing the ability of PET to estimate the level of cognitive performance at baseline. Amyloid accumulation, however, is likely to be relatively modest during the period of follow-up in this cognitively normal cohort.⁴⁸ Moreover, model adjustment by the variable for the time lag of PET acquisition showed no effect on cognitive function or trajectory in every model. Third, participants in this study are a select cohort designed to examine a specific hypothesis from an ongoing longitudinal cohort limiting generalizability.

This study found that vascular brain injury measured by WMH volume and neurodegeneration measured by hippocampal volume were associated with decreased level of baseline cognitive performance and increased rate of cognitive decline independent of amyloid status among community-dwelling, ethnicity diverse (53.9% non-Hispanic White) cognitively normal individuals. The first strength of this study is the sample characteristics including diverse race/ethnicity, which better represents the representativeness of the community in the United States, and the second is the comprehensive examination of WMH, global/regional atrophy, and cerebral amyloid burden. The study that has been conducted on the effect of these 4 comprehensive brain variables in ethnically diverse, cognitively normal community populations is rare. Finally, we proposed the model indicating that vascular and degenerative factors influence cognition before clinically relevant AD pathology and likely play a role in later life dementia risk (figure 3B). Given evidence that vascular risk can be mitigated with positive effects on cognition,³² aggressive treatment of vascular risk factors may substantially reduce dementia incidence. This is particularly true for African Americans and Hispanics, where dementia prevalence is estimated to be nearly twice that of non-Hispanic Whites⁴⁹ and who have a higher prevalence of vascular risk factors and vascular disease.²⁹

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Disclosure

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Pauline Maillard, PhD	University of California at Davis	Performed the statistical analyses, participated in study concept and design, revised the manuscript
Danielle Harvey, PhD	University of California at Davis	Participated in study concept and design
Evan Fletcher, PhD	University of California at Davis	Participated in study concept and design, revised the manuscript
Oliver Martinez, BS	University of California at Davis	Analyzed the data
David K. Johnson, PhD	University of California at Davis	Participated in study concept and design
John M. Olichney, MD	University of California at Davis	Participated in study concept and design, revised the manuscript
Sarah T. Farias, PhD	University of California at Davis	Participated in study concept and design, revised the manuscript
Sylvia Villeneuve, PhD	McGill University, Canada	Participated in study concept and design, revised the manuscript
William Jagust, MD	University of California, Berkeley	Participated in study concept and design, revised the manuscript
Dan Mungas, PhD	University of California at Davis	Participated in study concept and design, revised the manuscript
Charles DeCarli, MD	University of California at Davis	Conceived the study concept and design, analyzed and interpreted the data, revised and finalized the manuscript

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