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BRIEF COMMUNICATION

Brain White Matter Structure and Amyloid Deposition in Black and White Older Adults: The ARIC-PET Study

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BACKGROUND: White matter abnormalities are a common feature of aging and Alzheimer disease, and tend to be more severe among Black individuals. However, the extent to which white matter abnormalities relate to amyloid deposition, a marker of Alzheimer pathology, remains unclear. This cross-sectional study examined the association of white matter abnormalities with cortical amyloid in a community sample of older adults without dementia and examined the moderating effect of race.

METHODS AND RESULTS: Participants from the ARIC-PET (Atherosclerosis Risk in Communities-Positron Emission Tomography) study underwent brain magnetic resonance imaging, which quantified white matter hyperintensity volume and microstructural integrity using diffusion tensor imaging. Participants received florbetapir positron emission tomography imaging to measure brain amyloid. Associations between measures of white matter structure and elevated amyloid status were examined using multivariable logistic regression. Among 322 participants (43% Black), each SD increase in white matter hyperintensity volume was associated with a greater odds of elevated amyloid (odds ratio [OR], 1.37; 95% CI, 1.03–1.83) after adjusting for demographic and cardiovascular risk factors. In race-stratified analyses, a greater white matter hyperintensity volume was more strongly associated with elevated amyloid among Black participants (OR, 2.00; 95% CI, 1.15–3.50), compared with White participants (OR, 1.29; 95% CI, 0.89–1.89). However, the race interaction was not statistically significant (*P* interaction=0.09). We found no association between white matter microstructure and elevated amyloid.

CONCLUSIONS: The results suggest a modest positive relationship between white matter hyperintensity and elevated amyloid in older adults without dementia. Although the results indicate that this association is nonsignificantly stronger among Black participants, these findings will need to be confirmed or refuted using larger multiracial cohorts.

Key Words: Alzheimer disease ■ amyloid ■ cerebral microbleeds ■ dementia ■ white matter disease

White matter dysfunction is a pervasive feature of Alzheimer disease (AD) that has been consistently associated with cognitive decline and symptomatic progression.[1] Magnetic resonance imaging (MRI)–defined white matter hyperintensities (WMHs) and white matter microstructural abnormalities often emerge one or more decades before the onset of clinically defined dementia, even in relatively younger individuals with autosomal dominant AD and minimal vascular disease.[2,3] Cerebral small vessel disease is believed to be a primary cause of white matter abnormalities, and there is accumulating support for a bidirectional relationship between cerebral small vessel disease and AD pathology, including amyloid-ß.[4]

A 2017 systematic review examining the relationship between WMHs and cortical amyloid[5] concluded that the association between positron emission tomography (PET)–defined amyloid and WMH volume was not consistently supported. However, several recent studies with larger sample sizes (compared with

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most previous studies) have found a modest positive association between WMH volume and cortical amyloid levels in individuals without dementia.[2,6] While these findings hint at a connection between cerebral small vessel disease and cortical amyloid in the preclinical and/or prodromal phase of AD, it remains unknown whether these results translate to non-White/European populations with differing vascular risk profiles, lifetime environmental exposures, and AD genetic architecture. Thus, there is a clear need to understand the relationship between white matter abnormalities and amyloid accumulation, particularly among Black older adults given that: (1) the prevalence of cerebrovascular disease, vascular risk factors, and dementia is higher in this group, and (2) white matter abnormalities tend to be more severe in Black, compared with White, older adults.[7] To begin to understand whether white matter structural abnormalities and amyloid cooccur similarly among these race groups, the current study examined the association of WMH volume and WM microstructural integrity with cortical amyloid in a community sample of Black and White older adults without dementia in the ARIC (Atherosclerosis Risk in Communities) study.

METHODS

The data, analytic methods, and study materials will be made available to other researchers for purposes of reproducing the results or replicating the procedure in accordance with ARIC study policies. Data from the ARIC study can be accessed, with appropriate approvals, through the National Heart, Lung, and Blood Institute's Biospecimen and Data Repository Information Coordinating Center (https://biolincc.nhlbi.nih.gov/home/) or by contacting the ARIC Coordinating Center.

Study Design and Participants

The ARIC study is a community-based cohort study that enrolled 15 792 participants from 4 US communities upon its initiation (1987–1989).[8] Of the 6538 participants who attended ARIC visit 5 (2011–2013), 1978 were selected to undergo brain MRI (Data S1). We used available data from 346 of participants with MRI scans who underwent florbetapir PET imaging as part of the ARIC-PET study.[9] Study inclusion/exclusion criteria are outlined in Figure 1A. ARIC study protocols were approved by the institutional review boards at each participating center. All participants gave written informed consent at each study visit.

Brain MRI and PET Imaging

Brain MRI scans were conducted using a 3T scanner. Images were analyzed at the ARIC MRI Reading Center (Mayo Clinic). Magnetization-prepared rapid acquisition gradient echo (MP-RAGE), axial T2*gradient echo, axial T2 fluid-attenuated inversion recovery (FLAIR), and axial diffusion tensor imaging (DTI) sequences were obtained from all participants. WMH volumes were derived from FLAIR images using a quantitative computer-aided segmentation program to measure the volumetric burden of leukoaraiosis, defined as increased signal intensity within white matter.[10] The computer-aided segmentation program is an update of the in-house semi-automated method previously described by Raz et al.[10] WMHs were segmented on native 2-dimensional FLAIR images using an automated seed initialization

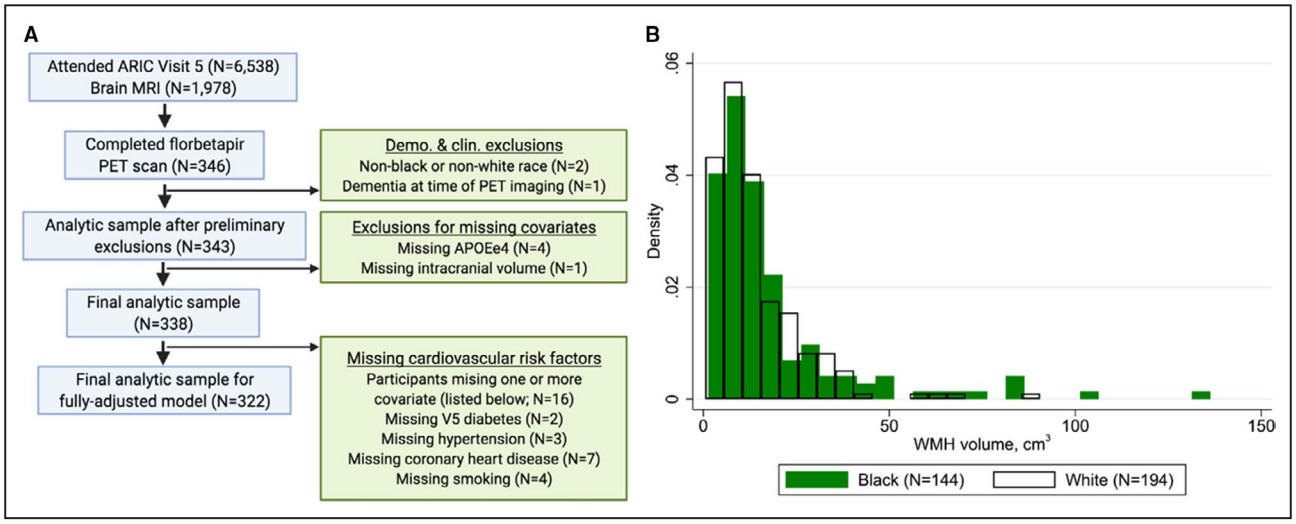

Figure 1. Study inclusion and exclusion criteria and white matter hyperintensity (WMH) volume by race.
ARIC indicates Atherosclerosis Risk in Communities; MRI, magnetic resonance imaging; and PET, positron emission tomography. Figure created with BioRender.com.

based on location (spatial priors), intensity relative to the distribution of grey matter intensity values, and the intensity relative to its local neighborhood. To reduce the number of false-positive segmentations of WMHs from FLAIR images, the MP-RAGE image was resampled in FLAIR space and the MP-RAGE segmentation was used to generate a white matter mask.[10] Using this method, a continuous measure of WMH volume was derived. T2*gradient echo scans were used to identify lobar and subcortical cerebral microbleeds (CMBs). DTI measures of fractional anisotropy (FA) and mean diffusivity (MD) were used to assess white matter microstructural integrity. Lower FA and higher MD are accepted as measures of reduced white matter integrity. Our primary analysis examined composite FA and MD measures derived using 4 white matter tracts known to be affected early in AD: the cingulate gyrus cingulum, hippocampal cingulum, superior longitudinal fasciculus, and splenium of the corpus callosum.[11–13] Using these tracts, we derived a general factor for FA and MD from the first unrotated principal component of the standardized FA and MD values (Table S1).

Florbetapir PET neuroimaging was used to identify participants with elevated cortical amyloid. PET scans were conducted within 1 year of brain MRIs and were coregistered with MRI MP-RAGE sequences at 3 ARIC-PET sites. We used a 20-minute (4×5 minute) uptake scan that was obtained starting 50 minutes after intravenous injection of the florbetapir isotope. The Wong laboratory (D.F.W. and Y.Z.) at Johns Hopkins University reviewed images for quality and calculated standardized uptake value ratios using a cerebellar gray matter reference region. The current analyses used a global measure of cortical florbetapir uptake defined as the volume-dependent weighted averages of 9 regions. Elevated cortical amyloid (standardized uptake value ratio >1.2) was defined a priori based on the ARIC-PET sample median, consistent with previous ARIC-PET studies.[9] See Data S1 for further description of the PET protocol.

Covariate and Clinical Assessment

Age at index visit (visit 5) and participant demographic data (race [Black/White], education, sex) reported by participants at ARIC visit 1 were used as covariates. The TaqMan assay (Applied Biosystems) was used to define *APOE* genotype (0 versus ≥1 *APOE*ε4 alleles). Annual combined family income was assessed at visit 4 (1996–1998) based on self-report. All other covariates were defined at visit 5. Body mass index was defined based on participant height and measured weight. Hypertension was defined based on measured systolic and diastolic blood pressure >140/90 mm/Hg or use of antihypertensive medication. Diabetes mellitus was defined based on self-report of physician diagnosis, diabetes mellitus medication use, or glycated hemoglobin level ≥6.5%. History of coronary heart disease was defined by self-report at visit 1 and adjudicated between visits 1 and 5. Current smoking status was defined based on self-report. Participants' cognitive status (normal/mild cognitive impairment) was defined based on National Institute on Aging (NIA) and the Alzheimer's Association (AA)/*Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (*DSM*-5) criteria (Data S1). Participants who met criteria for dementia were not included in the ARIC-PET study.

Statistical Analysis

We used multivariable logistic regression to examine the association of WMH volume and DTI FA/MD (independent variables) with elevated cortical amyloid (dependent variable). We examined 2 models. The first model included demographic risk factors (age, study center, race, sex, education, and *APOE* genotype). The second model additionally adjusted for cardiovascular risk factors (CRFs), ie, body mass index, diabetes mellitus, hypertension, coronary heart disease, and current smoking status. Based on recent findings suggesting that CMBs may account for the relationship between WMHs and amyloid,[2] we repeated the primary analyses after excluding participants with any/lobar CMBs. To examine the modifying effect of race on the white matter-amyloid relationship, we also examined race-by-WMH and race-by-FA/MD interaction terms and conducted stratified analyses. WMH volume and DTI FA/MD were modeled as continuous variables and divided into quartiles to examine nonlinear associations. WMH quartiles were defined after WMH volume was normalized for intracranial volume. Analyses examining WMH volume as a continuous variable were adjusted for intracranial volume. Additionally, WMH volumes were log-transformed because of skewness. A 2-sided P value <0.05 was used to designate statistical significance. Analyses were conducted using Stata version 14 (StataCorp).

RESULTS

A total of 338 participants were included in the final analytic sample (age 76 years [SD, 5 years]; 43% [N=144] were of Black race and 57% [N=191] were women). A total of 51% (N=173) of the sample was amyloid-positive; 64% (N=92) of Black participants and 42% (N=81) of White participants were amyloid-positive (Figure S1). Sixteen participants were missing

≥1 CRF covariates and were not included in the CRF-adjusted model. Full sample characteristics are displayed in Table S2. WMH volume did not significantly differ between Black and White participants (Mann-Whitney *U* test, *z*=1.50; *P*=0.13), although there were more Black participants at the highest end of the distribution (Figure 1B).

In a model adjusted for demographic characteristics, participants with greater WMH volume had a higher odds of elevated cortical amyloid (OR, 1.36 per SD increase WMH volume; 95% CI, 1.03–1.79; Table). The results were similar after adjustment for CRFs, after excluding participants with ≥1 CMB or lobar CMB (Table S3), and after additionally adjusting for the presence of cerebral infarcts (Table S4). In race-stratified analyses, each SD increase in WMH volume doubled the odds of elevated cortical amyloid among Black participants (Table). The association between WMH volume and amyloid did not extend to White participants, however. A formal assessment of effect modification by race did not yield statistical significance (*P* interaction=0.09). Overall, the results were similar when WMH volume was examined by quartile (Table; Figure S2). Use of race-specific WMH quartiles did not change these results (Figure 2A and 2B; Table S5). Results were similar using a common alternative threshold for elevated amyloid (standardized uptake value ratio >1.11; Table S6).

In post hoc sensitivity analyses that examined the effect of adjusting for midlife vascular risk factors (which have been previously linked to late-life WMH and amyloid levels), the association between WMH and elevated amyloid persisted in the full sample (Table S7). However, the magnitude of the association was attenuated among Black participants, suggesting that midlife vascular risk factors account, in part, for the WMH-amyloid relationship in this group. Adding combined annual family income (a proxy of socioeconomic status) to the primary model did not meaningfully change the results (Table; Table S8). The relationship between greater WMH volume and elevated amyloid among Black participants was maintained when 7 participants with outlier WMH volumes (>3 SD above the total sample mean) were excluded (odds ratio [OR], 1.94 [95% CI, 1.06–3.55] *P*=0.03; N=132) and when only cognitively normal Black participants were examined (OR, 2.07 [95% CI, 1.11–3.86] *P*=0.02; N=102). An examination of region-specific amyloid found the WMH volume-amyloid association was strongest in the precuneus region (Figure 2C). Results were similar among race groups.

General and tract-specific DTI measures of white matter microstructural integrity were unrelated to elevated cortical amyloid in demographically adjusted and CRF-adjusted models, and in race-stratified analyses (Tables S9–S12).

DISCUSSION

The current study provides evidence for a positive relationship between brain WMH volume and cortical amyloid in older adults without dementia. This association occurred independent of CMBs, a marker of cerebral amyloid angiopathy, and tended to be stronger among Black participants, although not significantly. In contrast to WMH volume, general and tract-specific measures of DTI white matter microstructure were unrelated to amyloid status.

Previous studies of the relationship between WMH volume and cortical amyloid have been conducted in European, US White, or Korean populations and have yielded mixed results.[5] Among studies showing positive results, modest effect sizes were typically observed,[6] comparable with that found in the current analysis of White participants. By comparison, our analysis revealed a strong association between WMH volume and cortical amyloid in Black participants, even among the subset of Black participants without cognitive impairment. This finding is of particular relevance to understanding of the role that race, perhaps a proxy for lifelong social experiences and physiological and environmental exposures, may play in the development of AD. Black adults are disproportionately affected by Alzheimer dementia compared with their age-adjusted White counterparts.[14] Although the causes of this disparity are not yet fully understood, there likely exist a multitude of factors, social, environmental, and possibly biologic.

While causal inferences cannot be derived from this cross-sectional analysis, the findings do suggest a connection between cerebrovascular processes underlying WMHs and amyloid accumulation that is independent of cardiovascular risk factors (late-life and midlife), cerebral infarcts, and cerebral amyloid angiopathy. If there is a causal relationship between cerebrovascular dysfunction and amyloid accumulation, as has been suggested elsewhere,[4] the strong association between WMHs and amyloid deposition in Black older adults may be relevant to understanding the pattern of increased dementia risk in this population. Regarding predictors of amyloid status, we found that demographic factors accounted for the bulk of the variance in amyloid status in the full sample, and in race-stratified analyses. In contrast, prevalent (late-life) CRFs did not account for much additional variance in amyloid status and do not appear to account for the association between WMH volume and amyloid. However, the presence of midlife vascular risk factors did account in part for the stronger association between WMH volume and elevated amyloid among Black participants, suggesting that distal health factors, rather than race itself, may contribute to group differences in the magnitude of the WMH-amyloid association. Similar to distal health factors, social

Table. Association of WMH Volume With Elevated Cortical Amyloid

WMH volume*	Model 0 N=338 Elevated amyloid OR (95% CI)	*P* value	Model 1 N=338 Elevated amyloid OR (95% CI)	*P* value	Model 2 N=322 Elevated amyloid OR (95% CI)	*P* value	Model 3 N=309 Elevated amyloid OR (95% CI)	*P* value
Quartile 1, 0.5–7.5, cm^3 (reference)	1 (reference)	…	1 (reference)	…	1 (reference)	…	1 (reference)	…
Quartile 2, 6.1–13.0, cm^3	1.57 (0.86–2.89)	0.15	1.37 (0.69–2.71)	0.37	1.34 (0.65–2.75)	0.42	1.47 (0.70–3.09)	0.31
Quartile 3, 9.5–21.8, cm^3	1.40 (0.76–2.57)	0.28	1.08 (0.54–2.16)	0.82	1.05 (0.50–2.18)	0.90	1.07 (0.51–2.27)	0.86
Quartile 4, 15.8–133.5, cm^3	2.84 (1.52–5.31)	0.001	2.16 (1.04–4.47)	0.04	2.19 (1.03–4.69)	0.04	2.45 (1.12–5.39)	0.03
WMH (log), Per 1 SD (continuous)	1.51 (1.19–1.90)	0.001	1.36 (1.03–1.79)	0.03	1.37 (1.03–1.83)	0.03	1.40 (1.04–1.88)	0.03
WMH Volume*	**Black (Model 0) N=144** **Elevated amyloid OR (95% CI)**	***P* value**	**White (Model 0) N=194** **Elevated amyloid OR (95% CI)**	***P* value**	**Black (Model 2) N=139** **Elevated amyloid OR (95% CI)**	***P* value**	**White (Model 2) N=183** **Elevated amyloid OR (95% CI)**	***P* value**
Quartile 1, 0.5–7.5, cm^3 (reference)	1 (reference)	…	1 (reference)	…	1 (reference)	…	1 (reference)	…
Quartile 2, 6.1–13.0, cm^3	2.62 (0.96–7.12)	0.06	1.05 (0.48–2.31)	0.91	3.05 (0.88–10.61)	0.08	0.98 (0.38–2.52)	0.96
Quartile 3, 9.5–21.8, cm^3	2.33 (0.86–6.29)	0.10	0.93 (0.42–2.05)	0.85	2.23 (0.62–8.04)	0.22	0.70 (0.26–1.83)	0.46
Quartile 4, 15.8–133.5, cm^3	5.84 (2.01–17.02)	0.001	1.62 (0.73–3.61)	0.24	8.06 (1.85–35.16)	0.006	1.67 (0.63–4.46)	0.30
WMH (log), Per 1 SD (continuous)	1.97 (1.30–2.98)	0.001	1.21 (0.89–1.65)	0.21	2.00 (1.15–3.50)	0.02	1.29 (0.89–1.89)	0.18

Model 0 is unadjusted (model includes only intracranial volume). Model 1 is adjusted for intracranial volume, age, center, race, sex, education, and *APOE* ε4 status. Model 2 is additionally adjusted for late-life (visit 5) body mass index, diabetes mellitus, hypertension, coronary heart disease, and current smoking status. Sixteen participants included in model 1 were excluded from model 2 for missing ≥1 model 2 covariates. Model 3 is additionally adjusted for total combined annual family income. Thirteen participants included in model 2 were excluded from model 3 for missing household family income data. *P* values for the white matter hyperintensity (WMH) volume by race interaction term derived from model 2 were 0.13 for the quartiled analysis and 0.09 for the continuous analysis. OR indicates odds ratio.

*WMH volumes were quartiled after normalization for intracranial volume. As a result, there is some overlap among quartiles for the provided non-normalized WMH volumes.

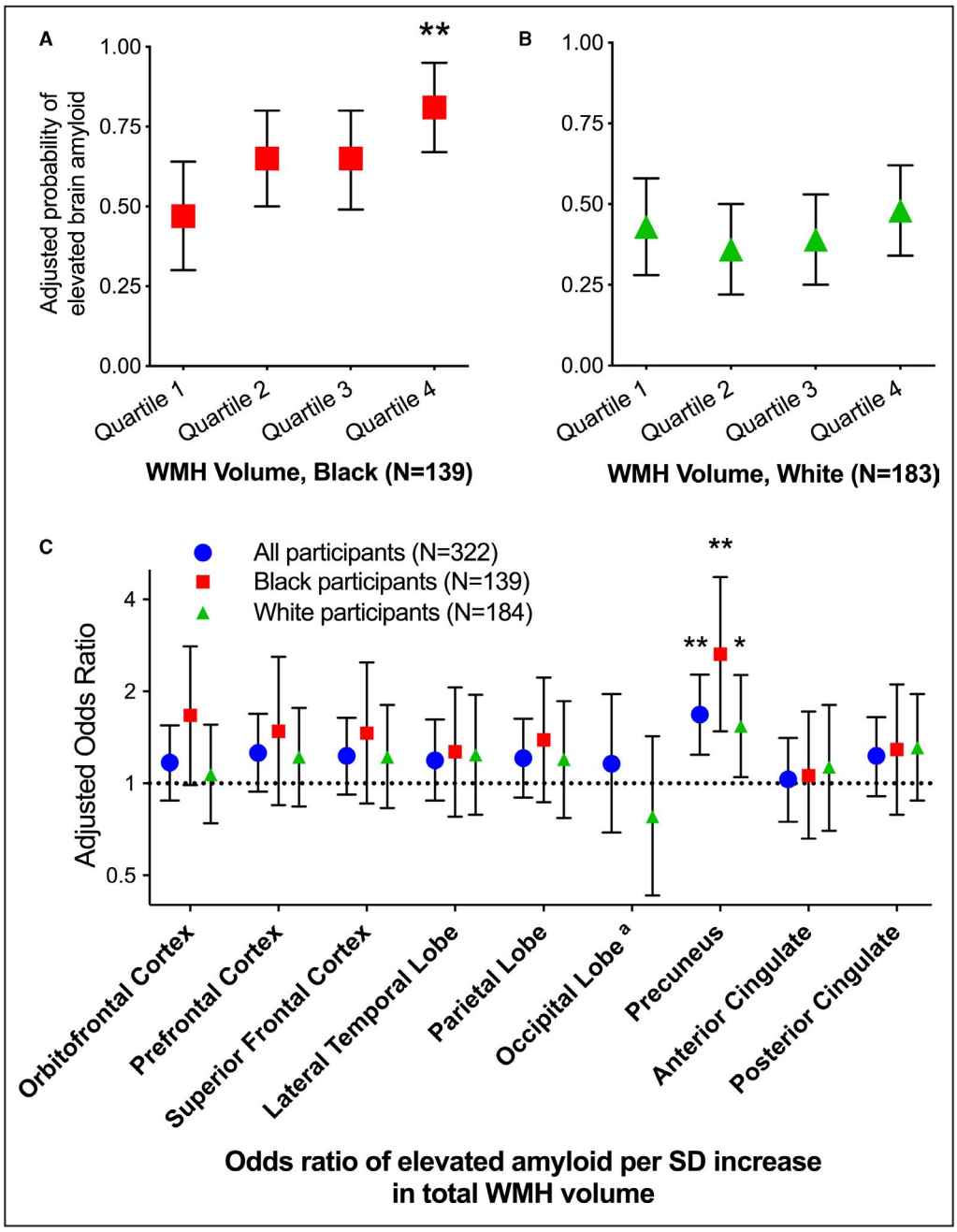

Figure 2. Race- and brain region–specific associations between white matter hyperintensity (WMH) volume and elevated cortical amyloid.
All models were adjusted for intracranial volume, age, center, race, sex, education, *APOE* ε4 status, and late-life (visit 5) body mass index, diabetes mellitus, hypertension, coronary heart disease, and current smoking status (ie, model 2). **A**, **B**, The adjusted probability and standard error of elevated cortical amyloid for each quartile of WMH volume, calculated using logistic regression. Race-specific WMH quartiles were used for analyses. **C**, The adjusted odds ratio (OR) of regional elevated cortical amyloid per SD increase in WMH volume, calculated using logistic regression. The adjusted OR for Black participants was imprecise: OR, 25.2 (95% CI, 1.9–339.8); coronary heart disease and smoking status covariates were excluded because they predicted the outcome perfectly.*P<0.05; **P<0.01.

determinants of health (eg, socioeconomic status/position, stress/discrimination, access to health care, and neighborhood and environmental exposures), which tend to differ between Black and White individuals living within the United States, may account for the stronger link between WMH and amyloid observed in Black

participants. Although the current study attempted to account for socioeconomic status using a crude proxy measure (family income level), future work that more carefully accounts for social health determinants will be needed to identify drivers of disparities in AD.

The lack of association between white matter microstructural integrity and amyloid-positive status also deserves some consideration. While studies examining the association of PET- and cerebrospinal fluid-defined amyloid levels with DTI measures of FA and MD have yielded mixed results, a more consistent association has emerged between DTI white matter microstructure and tau pathology, particularly for white matter tracts in areas that experience early tau pathology.[15] If the associations between amyloid levels and white matter microstructural integrity are indeed driven by tau pathology, it is possible that the amyloid-positive participants in the present study are not advanced enough in their disease, ie, do not have enough tau neurofibrillary tangle pathology, to show amyloid-DTI associations.

The current results should be interpreted within the context of several limitations. First, the study is limited by its cross-sectional design. Understanding the time course of the amyloid-WMH relationship with respect to the clinical manifestations of symptoms will be essential in advancing the understanding of AD pathophysiology. Second, because the majority of Black participants who underwent amyloid PET neuroimaging were from a single study site (Jackson, Mississippi), it is possible that the demonstrated race-specific findings are attributable to a nondescribed phenomenon specific to the geographic region. Thus, additional multiethnic community-based studies in other geographic regions are required to confirm the generalizability of our findings. Third, the lack of region-specific WMH information limited the ability to look at how WMH occurring in specific brain regions related to amyloid levels. Finally, selection into the ARIC-PET substudy, which excluded participants with dementia and participants with MRI and PET contraindications, may have introduced a positive selection bias for those participants who have generally better cardiovascular health compared with the population in totum. This selection may also affect the generalizability of the findings.

Within the context of these limitations, the current study provides support for a relationship between WMHs and elevated cortical amyloid in older adults without dementia. This relationship was particularly strong among Black participants. However, there was no relationship between DTI-defined white matter microstructural integrity and cortical amyloid. These findings will need to be confirmed or refuted using larger multiracial cohorts.

ARTICLE INFORMATION

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Supplementary Material

Data S1
Tables S1–S12
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Supplemental Material

Data S1.

Supplemental Methods

Participant selection for ARIC visit 5 brain MRI
Of the 6,528 participants who attended ARIC visit 5, 1,978 underwent a brain MRI. Participants were selected based on the criteria listed below, as previously outlined in Knopman et al. (2015).[16] Participants with MRI contraindications were excluded from this selection. Participants were selected to receive a visit 5 brain MRI if they (1) received a brain MRI as part of the 2004-06 ARIC Brain MRI Ancillary Study, or (2) demonstrated cognitive impairment, defined as a low Mini-Mental State Exam (MMSE) score (<21 for White and <19 for Black participants), two or more low cognitive domain scores at visit 5 (<-1.5 standard deviations) and cognitive decline on the Delayed Word Recall test, the Digit Symbol Substitution test, or the Word Fluency test (<10th percentile of decline on serial testing on 1 or more tests or <20th percentile on 2 or more tests). Additionally, we selected an age-stratified random sample of cognitively intact participants with an age distribution that approximated that of cognitively impaired participants.

ARIC-PET florbetapir PET methods
Florbetapir PET imaging was conducted at the Washington County, MD, Jackson, MS, and Forsyth County, NC study sites with Philips TruFlight, GE Discovery 690, and GE Discovery ST scanners, respectively. Phantom scan with ~1mCi of F-18 were conducted throughout the course of the study to ensure spatial uniformity and quantitative accuracy across study sites. To arrive at an effectively equivalent spatial resolution of 8.30 mm for the three sites, PET images at the Washington County and Forsyth County study sites were spatially smoothed. Images were analyzed at Reading center of the Wong Lab located in the Johns Hopkins University Section of High-Resolution Brain PET Imaging, Department of Radiology although no PET scans for ARIC were performed there. Consistent with the typical static florbetapir PET imaging protocol as employed in ADNI 2, 4-frame dynamic images were used to derive the mean of the 20-minute image acquisition. These mean PET images were then coregistered with corresponding structural MRI images. Using SPM8 and VBM8 toolbox, MRI images were normalized to the standard Montreal Neurologic Institute (MNI) space; the transformation parameters determined by MRI spatial normalization were then applied to coregistered PET images for PET spatial normalization. Thirty-four regions of interest were manually drawn on the MRI template in standard MNI space using PMOD software (PMOD Technologies Ltd., Zurich, Switzerland). Standard uptake value ratio (SUVR) images were calculated using the cerebellar gray as the reference region, and ROIs were applied to SUVR images.[9] The current analyses used a global measure of cortical florbetapir uptake defined as the volume-dependent weighted averages of the orbitofrontal, prefrontal, and superior frontal lobes; the lateral temporal, parietal, and occipital lobes; the precuneus, and the anterior cingulate, and the posterior cingulate regions.

Cognitive classification
Dementia and mild cognitive impairment (MCI) at ARIC visit 5 were defined based on National Institute on Aging-Alzheimer's Association (NIA-AA) workgroup and Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5) criteria [17–19] based on a comprehensive battery provided at visit 5, data from repeated cognitive testing administered at ARIC visits 2, 4, and 5, and an informant interview conducted at ARIC visit 5, which incorporated the Clinical Dementia Rating Scale (CDR) and Functional Activities Questionnaire (FAQ). An algorithm used this information to classify participants as either being cognitively normal, as meeting criteria for MCI, or as meeting criteria for dementia. An expert panel of physicians and neuropsychologists then confirmed each of these classifications. An algorithmic diagnosis of *Dementia* was defined as >1 cognitive domain worse than -1.5 Z, a CDR sum of boxes >3, and a decline from the previous cognitive assessment that was below the 10th percentile on one or more

test, or below the 20th percentile on two or more tests in the repeated ARIC cognitive battery. *Mild cognitive impairment (MCI)* was defined as at least one domain score worse than -1.5 Z, a CDR sum of boxes between >0.5 and ≤3, an FAQ ≤5, and a decline on the repeated ARIC cognitive battery below the 10th percentile on one test or below the 20th percentile on two or more tests [20]. Participants who did not meet criteria for dementia or MCI were classified as cognitively normal.

Table S1. **Principal component analysis (PCA) for white matter tracts included in general FA (gFA) and MD (gMD) composite scores.**

White matter tract	PC1 (FA)	PC1 (MD)
Cingulate Gyrus Cingulum, Left	0.43	0.40
Cingulate Gyrus Cingulum, Right	0.42	0.41
Hippocampal Cingulate Gyrus, Left	0.38	0.34
Hippocampal Cingulate Gyrus, Right	0.38	0.36
Superior Longitudinal Fasciculus, Left	0.37	0.38
Superior Longitudinal Fasciculus, Right	0.34	0.39
Splenium of the Corpus Callosum	0.32	0.36
Eigenvalue	3.06	5.03
Proportion of variance	44%	72%

The factor scores for FA and MD derived from an unrotated principal component analysis of standardized FA and MD values. The factor score captures the shared variance in white matter integrity across multiple white matter tracts known to be affected in Alzheimer's disease. N=336 (all participants with available DTI data).

Abbreviations: FA, fractional anisotropy; MD, mean diffusivity; PC1, first principal component

Table S2. Baseline (Visit 5; 2011-13) participant characteristics.

Characteristic	Total Sample (N = 338)	Black Participants (N = 144)	White Participants (N = 194)
Demographic Variables			
Age	75.9 (5.4)	75.6 (5.1)	76.2 (5.6)
Female (%)	191 (57%)	88 (61%)	103 (53%)
Black (%)	144 (43%)	--	--
Center			
Washington County, Maryland	128 (38%)	3 (2%)	125 (64%)
Forsyth County, North Carolina	72 (21%)	3 (2%)	69 (36%)
Jackson, Mississippi	138 (41%)	138 (96%)	0 (0%)
Education (%)			
Less than high school	56 (17%)	30 (21%)	26 (13%)
High school/GED/vocational	145 (43%)	53 (37%)	92 (47%)
College/graduate/professional	137 (41%)	61 (42%)	76 (39%)
APOEε4 alleles			
0 (%)	235 (70%)	91 (63%)	144 (74%)
1 (%)	95 (28%)	48 (33%)	47 (24%)
2 (%)	8 (2%)	5 (3%)	3 (2%)
Clinical & Physiological Variables			
Body mass index, kg/m^{2*}	29.1 (5.4)	29.9 (5.3)	28.5 (5.4)
Total cholesterol, mg/dl	180.8 (39.2)	185.5 (41.6)	177.4 (37.0)
Hypertension*	241 (72%)	119 (83%)	122 (64%)
Diabetes mellitus	116 (35%)	54 (38%)	62 (32%)
Coronary heart disease*	26 (8%)	6 (4%)	20 (11%)
Current smoker	17 (5%)	9 (6%)	8 (4%)
Cognitively normal	247 (73%)	106 (73%)	141 (73%)
Mild cognitive impairment	91 (27%)	53 (27%)	91 (27%)

Values are displayed as means (standard deviation) and frequencies (percentages). Black and white participant characteristics were compared using independent-samples t-tests and chi-square tests.
*Difference between black and white participants statistically significant ($p < .05$)

Table S3. The association of WMH volume with elevated cortical amyloid after excluding participants with cerebral microbleeds (CMBs).

White Matter Hyperintensity (WMH) Volume [*]	Excluding participants with any CMBs (Model 2)[†] N=241		Excluding participants with lobar CMBs (Model 2)[†] N=287	
	Elevated Amyloid OR (95% CI)	*P*	Elevated Amyloid OR (95% CI)	*P*
WMH Quartile 1, (reference)	1 (ref)	--	1 (ref)	--
WMH Quartile 2	1.43 (0.60, 3.39)	0.42	1.46 (0.68, 3.15)	0.34
WMH Quartile 3	0.88 (0.36, 2.15)	0.78	1.00 (0.46, 2.20)	0.99
WMH Quartile 4	2.95 (1.10, 7.92)	0.03	2.67 (1.15, 6.22)	0.02
WMH (log), Per 1 SD (continuous)	1.50 (1.04, 2.16)	0.03	1.49 (1.08, 2.05)	0.02

Among the 322 participants eligible for this analysis: N=78 had one or more CMB; N=30 had one or more lobar CMB; N=3 had missing data for any CMB; N=5 had missing data for lobar CMB.
[*]WMH volumes were quartiled after normalization for intracranial volume.
[†]Model 2 is adjusted for intracranial volume, age, center, race, sex, education, *APOE* ε4 status, and late-life (visit 5) BMI, diabetes, hypertension, coronary heart disease, and current smoking status.
Abbreviations: CMB, cerebral microbleed; OR, odds ratio; SD, standard deviation.

Table S4. The association of WMH volume with elevated cortical amyloid after adjusting for presence of cerebral infarct.

White Matter Hyperintensity (WMH) Volume*	Full Sample (Model 2 + cerebral infarct) N=322		Black (Model 2 + cerebral infarct) N=139		White (Model 2 + cerebral infarct) N=183	
	Elevated Amyloid OR (95% CI)	*P*	Elevated Amyloid OR (95% CI)	*P*	Elevated Amyloid OR (95% CI)	*P*
Q1, 0.5 to 7.5 cm^3 (reference)	1 (ref)	--	1 (ref)	--	1 (ref)	--
Q2, 6.1 to 13.0 cm^3	1.32 (0.64, 2.71)	0.45	3.04 (0.87, 10.64)	0.08	0.97 (0.37, 2.49)	0.94
Q3, 9.5 to 21.8 cm^3	1.02 (0.49, 2.15)	0.95	2.21 (0.60, 8.16)	0.23	0.68 (0.26, 1.81)	0.44
Q4, 15.8 to 133.5 cm^3	2.12 (0.98, 4.61)	0.06	7.94 (1.72, 36.62)	0.008	1.63 (0.60, 4.40)	0.33
WMH (log), Per 1 SD (continuous)	1.36 (1.01, 1.82)	0.04	2.00 (1.11, 3.60)	0.02	1.29 (0.88, 1.88)	0.20

All models were adjusted for intracranial volume, age, center, race, sex, education, *APOE* ε4 status, and late-life (visit 5) BMI, diabetes, hypertension, coronary heart disease, and current smoking status (i.e., Model 2) in addition to cerebral infarct (present/absent).
A total of 70 of the 322 participants (22%) included in this analysis had one or more infarct, including 31 (22%) infarcts among Black participants and 39 (21%) infarcts among White participants.
Abbreviations: OR, odds ratio; Q1, quartile 1; Q2, quartile 2; Q3, quartile 3; Q4, quartile 4; SD, standard deviation.
*WMH volumes were quartiled after normalization for intracranial volume. As a result, there is some overlap among quartiles for the provided non-normalized WMH volumes

Table S5. **The association of WMH volume with elevated cortical amyloid, stratified by race using race-specific quartiles to define WMH burden.**

White Matter Hyperintensity (WMH) Volume*	Black N=139	
	Elevated Amyloid OR (95% CI)	*P*
Q1, 1.3 to 8.0 cm^3 (reference)	1 (ref)	--
Q2, 6.6 to 12.8 cm^3	2.52 (0.77, 8.26)	0.13
Q3, 9.9 to 20.3 cm^3	2.47 (0.73, 8.31)	0.14
Q4, 19.2 to 133.5 cm^3	6.67 (1.61, 27.68)	0.009
White Matter Hyperintensity (WMH) Volume*	White N=183	
	Elevated Amyloid OR (95% CI)	*P*
Q1, 0.5 to 7.3 cm^3 (reference)	1 (ref)	--
Q2, 5.9 to 11.4 cm^3	0.71 (0.27, 1.92)	0.50
Q3, 9.4 to 21.6 cm^3	0.81 (0.30, 2.19)	0.68
Q4, 15.8 to 89.4 cm^3	1.24 (0.46, 3.35)	0.67

All models were adjusted for age, center, race, sex, education, *APOE* ε4 status, and late-life (visit 5) BMI, diabetes, hypertension, coronary heart disease, and current smoking status (i.e., Model 2). Race-specific WMH quartiles were used for analyses.

*WMH volumes were quartiled after normalization for intracranial volume. As a result, there is some overlap among quartiles for the provided non-normalized WMH volumes.

Abbreviations: OR, odds ratio; Q1, quartile 1; Q2, quartile 2; Q3, quartile 3; Q4, quartile 4.

Table S6. **The association of WMH volume with elevated cortical amyloid using an alternative threshold for elevated amyloid (SUVR>1.11).**

White Matter Hyperintensity (WMH) Volume*	Model 1 N=338		Model 2 N=322	
	Elevated Amyloid OR (95% CI)	*P*	Elevated Amyloid OR (95% CI)	*P*
Q1, 0.5 to 7.5 cm^3 (reference)	1 (ref)	--	1 (ref)	--
Q2, 6.1 to 13.0 cm^3	1.60 (0.71, 3.60)	0.25	1.88 (0.79, 4.47)	0.15
Q3, 9.5 to 21.8 cm^3	1.25 (0.56, 2.78)	0.58	1.24 (0.53, 2.88)	0.62
Q4, 15.8 to 133.5 cm^3	2.61 (1.07, 6.41)	0.04	2.62 (1.04, 6.61)	0.04
WMH (log), Per 1 SD (continuous)	1.36 (0.97, 1.91)	0.07	1.35 (0.95, 1.93)	0.10

White Matter Hyperintensity (WMH) Volume*	Black (Model 2) N=139		White (Model 2) N=183	
	Elevated Amyloid OR (95% CI)	*P*	Elevated Amyloid OR (95% CI)	*P*
Q1, 0.5 to 7.5 cm^3 (reference)	1 (ref)	--	1 (ref)	--
Q2, 6.1 to 13.0 cm^3	34.26 (2.60, 451.93)	0.007	1.26 (0.46, 3.43)	0.66
Q3, 9.5 to 21.8 cm^3	11.84 (1.25, 112.22)	0.03	0.86 (0.32, 2.30)	0.76
Q4, 15.8 to 133.5 cm^3	5.78E03 (18.41, 1.82E06)	0.003	1.39 (0.49, 3.89)	0.54
WMH (log), Per 1 SD (continuous)	3.60 (1.26, 10.24)	0.02	1.20 (0.80, 1.79)	0.38

Model 1 is adjusted for intracranial volume, age, center, race, sex, education, and *APOE* ε4 status. Model 2 is additionally adjusted for late-life (visit 5) BMI, diabetes, hypertension, coronary heart disease, and current smoking status. Sixteen participants included in model 1 were excluded from model 2 due to missing one or more model 2 covariate. *P*-values for the WMH volume by race interaction term were 0.07 for the quartiled analysis and 0.13 for the continuous analysis. The current smoking covariate was omitted from the analysis of Black participants because it predicted the outcome exactly.

Abbreviations: OR, odds ratio; Q1, quartile 1; Q2, quartile 2; Q3, quartile 3; Q4, quartile 4; SD, standard deviation.

*WMH volumes were quartiled after normalization for intracranial volume. As a result, there is some overlap among quartiles for the provided non-normalized WMH volumes.

Table S7. The association of WMH volume with elevated cortical amyloid after adjusting for midlife vascular risk factors.

White Matter Hyperintensity (WMH) Volume*	Full Sample (Model 2 + midlife vascular risk factors) N=328		Black (Model 2 + midlife vascular risk factors) N= 140		White (Model 2 + midlife vascular risk factors) N= 185	
	Elevated Amyloid OR (95% CI)	*P*	Elevated Amyloid OR (95% CI)	*P*	Elevated Amyloid OR (95% CI)	*P*
Q1, 0.5 to 7.5 cm^3 (reference)	1 (ref)	--	1 (ref)	--	1 (ref)	--
Q2, 6.1 to 13.0 cm^3	1.14 (0.56, 2.33)	0.72	2.70 (0.81, 8.95)	0.11	0.79 (0.31, 2.01)	0.62
Q3, 9.5 to 21.8 cm^3	1.02 (0.49, 2.10)	0.97	2.05 (0.60, 7.02)	0.25	0.65 (0.25, 1.71)	0.38
Q4, 15.8 to 133.5 cm^3	2.03 (0.96, 4.31)	0.06	4.76 (1.26, 17.91)	0.02	1.54 (0.58, 4.06)	0.38
WMH (log), Per 1 SD (continuous)	1.35 (1.01, 1.79)	0.04	1.66 (1.00, 2.76)	0.05	1.28 (0.88, 1.86)	0.20

All models were adjusted for intracranial volume, age, center, race, sex, education, and *APOE* ε4 status, and midlife (visit 1; 1987-89) BMI, diabetes, hypertension, coronary heart disease, and current smoking status. Ten participants included in model 1 were excluded from this analysis due to missing one or more covariate.

Abbreviations: OR, odds ratio; Q1, quartile 1; Q2, quartile 2; Q3, quartile 3; Q4, quartile 4; SD, standard deviation.

*WMH volumes were quartiled after normalization for intracranial volume. As a result, there is some overlap among quartiles for the provided non-normalized WMH volumes

Table S8. The association of WMH volume with elevated cortical amyloid, stratified by race and additionally adjusted for family income.

White Matter Hyperintensity (WMH) Volume*	Black (Model 3) N=133		White (Model 3) N=176	
	Elevated Amyloid OR (95% CI)	*P*	Elevated Amyloid OR (95% CI)	*P*
Q1, 0.5 to 7.5 cm^3 (reference)	1 (ref)	--	1 (ref)	--
Q2, 6.1 to 13.0 cm^3	2.95 (0.83, 10.46)	0.09	1.15 (0.43, 3.07)	0.78
Q3, 9.5 to 21.8 cm^3	1.90 (0.52, 7.00)	0.33	0.72 (0.27, 1.94)	0.51
Q4, 15.8 to 133.5 cm^3	9.66 (2.07, 45.02)	0.004	1.79 (0.65, 4.98)	0.26
WMH (log), Per 1 SD (continuous)	1.99 (1.13, 3.51)	0.02	1.30 (0.88, 1.91)	0.19

All models were adjusted for age, center, race, sex, education, *APOE* ε4 status, and late-life (visit 5) BMI, diabetes, hypertension, coronary heart disease, current smoking status, and total combined annual family income (i.e., Model 3). Thirteen participants included in model 2 were excluded from model 3 due to missing household family income data.

Abbreviations: OR, odds ratio; Q1, quartile 1; Q2, quartile 2; Q3, quartile 3; Q4, quartile 4; SD, standard deviation.

*WMH volumes were quartiled after normalization for intracranial volume. As a result, there is some overlap among quartiles for the provided non-normalized WMH volumes.

Table S9. The association of white matter DTI gFA with elevated cortical amyloid.

General Fractional Anisotropy (gFA)	Model 0 N=336		Model 1 N=336		Model 2 N=320		Model 3 N=307	
	Elevated Amyloid OR (95% CI)	*P*	Elevated Amyloid OR (95% CI)	*P*	Elevated Amyloid OR (95% CI)	*P*	Elevated Amyloid OR (95% CI)	*P*
Q1, -3.57, -0.66 Z (reference)	1 (ref)	--	1 (ref)	--	1 (ref)	--	1 (ref)	--
Q2, -0.63, 0.03 Z	1.97 (1.06, 3.64)	0.03	1.80 (0.93, 3.49)	0.08	1.59 (0.79, 3.20)	0.19	1.71 (0.83, 3.53)	0.15
Q3, 0.06, 0.66 Z	1.21 (0.66, 2.22)	0.54	1.31 (0.65, 2.61)	0.45	1.08 (0.51, 2.29)	0.83	1.12 (0.52, 2.39)	0.77
Q4, 0.66, 2.48 Z	1.05 (0.57, 1.93)	0.88	1.15 (0.56, 2.36)	0.71	1.00 (0.47, 2.13)	0.99	1.06 (0.49, 2.29)	0.89
gFA, Per 1 SD (continuous)	0.99 (0.80, 1.23)	0.95	1.03 (0.80, 1.33)	0.82	1.02 (0.78, 1.33)	0.90	1.03 (0.78, 1.36)	0.84

General Fractional Anisotropy (gFA)	Black (Model 0) N=143		White (Model 0) N=193		Black (Model 2) N=138		White (Model 2) N=182	
	Elevated Amyloid OR (95% CI)		Elevated Amyloid OR (95% CI)	*P*	Elevated Amyloid OR (95% CI)	*P*	Elevated Amyloid OR (95% CI)	*P*
Q1, -3.57, -0.66 Z (reference)	1 (ref)	--	1 (ref)	--	1 (ref)	--	1 (ref)	--
Q2, -0.63, 0.03 Z	2.41 (0.77, 7.59)	0.13	1.64 (0.76, 3.52)	0.21	2.09 (0.56, 7.78)	0.27	1.30 (0.54, 3.15)	0.56
Q3, 0.06, 0.66 Z	1.12 (0.40, 3.11)	0.83	0.99 (0.45, 2.22)	0.99	1.02 (0.29, 3.56)	0.97	1.01 (0.37, 2.73)	0.99
Q4, 0.66, 2.48 Z	0.68 (0.26, 1.84)	0.45	1.09 (0.48, 2.49)	0.84	0.98 (0.27, 3.56)	0.97	1.18 (0.41, 3.36)	0.76
gFA, Per 1 SD (continuous)	0.78 (0.54, 1.12)	0.18	1.02 (0.77, 1.36)	0.89	0.91 (0.56, 1.46)	0.68	1.15 (0.79, 1.67)	0.46

Model 0 is unadjusted. Model 1 is adjusted for age, center, race, sex, education, and *APOE* ε4 status. Model 2 is additionally adjusted for late-life (visit 5) BMI, diabetes, hypertension, coronary heart disease, and current smoking status. Sixteen participants included in model 1 were excluded from model 2 due to missing one or more model 2 covariate. Model 3 is additionally adjusted for total combined annual family income. Thirteen participants included in model 2 were excluded from model 3 due to missing household family income data. *P*-values for the gFA by race interaction term derived from model 2 were 0.42 for the quartiled analysis and 0.13 for the continuous analysis.
Abbreviations: OR, odds ratio; Q1, quartile 1; Q2, quartile 2; Q3, quartile 3; Q4, quartile 4; SD, standard deviation.

Table S10. **The association of white matter DTI gMD with elevated cortical amyloid.**

General Mean Diffusivity (gMD)	Model 0 N=336		Model 1 N=336		Model 2 N=320		Model 3 N=307	
	Elevated Amyloid OR (95% CI)	*P*	Elevated Amyloid OR (95% CI)	*P*	Elevated Amyloid OR (95% CI)	*P*	Elevated Amyloid OR (95% CI)	*P*
Q1, -1.95, -0.73 Z (reference)	1 (ref)	--	1 (ref)	--	1 (ref)	--	1 (ref)	--
Q2, -0.71, -0.15 Z	0.62 (0.34, 1.14)	0.12	0.53 (0.27, 1.05)	0.07	0.49 (0.24, 1.00)	0.05	0.51 (0.24, 1.05)	0.07
Q3, -0.13, 0.58 Z	1.10 (0.60, 2.03)	0.76	0.78 (0.38, 1.62)	0.51	0.82 (0.38, 1.76)	0.61	0.80 (0.37, 1.73)	0.57
Q4, 0.62, 3.22 Z	0.79 (0.43, 1.44)	0.44	0.75 (0.30, 1.88)	0.54	0.80 (0.30, 2.13)	0.66	0.72 (0.27, 1.95)	0.52
gMD, Per 1 SD (continuous)	0.99 (0.80, 1.23)	0.94	0.91 (0.65, 1.28)	0.59	0.94 (0.66, 1.34)	0.73	0.92 (0.64, 1.32)	0.66

General Mean Diffusivity (gMD)	Black (Model 0) N=143		White (Model 0) N=193		Black (Model 2) N=138		White (Model 2) N=182	
	Elevated Amyloid OR (95% CI)	*P*	Elevated Amyloid OR (95% CI)	*P*	Elevated Amyloid OR (95% CI)	*P*	Elevated Amyloid OR (95% CI)	*P*
Q1, -1.95, -0.73 Z (reference)	1 (ref)	--	1 (ref)	--	1 (ref)	--	1 (ref)	--
Q2, -0.71, -0.15 Z	0.73 (0.31, 1.70)	0.47	0.53 (0.22, 1.29)	0.16	0.49 (0.17, 1.44)	0.20	0.37 (0.13, 1.06)	0.06
Q3, -0.13, 0.58 Z	3.65 (1.27, 10.52)	0.02	0.57 (0.24, 1.34)	0.20	2.71 (0.70, 10.55)	0.15	0.34 (0.11, 0.98)	0.05
Q4, 0.62, 3.22 Z	1.71 (0.55, 5.25)	0.35	0.69 (0.31, 1.54)	0.37	1.22 (0.22, 6.78)	0.82	0.46 (0.12, 1.78)	0.26
gMD, Per 1 SD (continuous)	1.49 (0.98, 2.27)	0.06	0.96 (0.72, 1.26)	0.75	1.28 (0.69, 2.35)	0.44	0.72 (0.43, 1.22)	0.22

Model 0 is unadjusted. Model 1 is adjusted for age, center, race, sex, education, and *APOE* ε4 status. Model 2 is additionally adjusted for late-life (visit 5) BMI, diabetes, hypertension, coronary heart disease, and current smoking status. Sixteen participants included in model 1 were excluded from model 2 due to missing one or more model 2 covariate. Model 3 is additionally adjusted for total combined annual family income. Thirteen participants included in model 2 were excluded from model 3 due to missing household family income data. *P*-values for the gMD by race interaction term derived from model 2 were 0.02 for the quartiled analysis and 0.02 for the continuous analysis.
Abbreviations: OR, odds ratio; Q1, quartile 1; Q2, quartile 2; Q3, quartile 3; Q4, quartile 4; SD, standard deviation.

Table S11. **The association of tract-specific white matter DTI measures (FA and MD) with elevated cortical amyloid.**

Diffusion Tensor Imaging (DTI) White Matter Tract	FA N=320		MD N=320	
	Elevated Amyloid OR (95% CI)*	*P*	Elevated Amyloid OR (95% CI)*	*P*
Cingulate Gyrus Cingulum, Left	0.89 (0.69, 1.15)	0.38	0.75 (0.52, 1.08)	0.12
Cingulate Gyrus Cingulum, Right	1.00 (0.78, 1.29)	0.97	0.89 (0.64, 1.24)	0.51
Hippocampal Cingulate Gyrus, Left	0.92 (0.70, 1.22)	0.57	1.03 (0.76 1.41)	0.84
Hippocampal Cingulate Gyrus, Right	0.99 (0.75, 1.30)	0.94	1.00 (0.73, 1.36)	0.98
Superior Longitudinal Fasciculus, Left	1.12 (0.86, 1.45)	0.40	1.02 (0.75, 1.39)	0.89
Superior Longitudinal Fasciculus, Right	1.33 (1.02, 1.74)	0.03	0.92 (0.68, 1.25)	0.60
Splenium of the Corpus Callosum	0.91 (0.70, 1.19)	0.49	1.10 (0.81, 1.48)	0.55

Values represent odds of elevated cortical amyloid per SD increase in fractional anisotropy (FA) and mean diffusivity (MD).

*Logistic regression models were adjusted for age, center, race, sex, education, *APOE* ε4 status, and late-life (visit 5) BMI, diabetes, hypertension, coronary heart disease, and current smoking status (model 2).

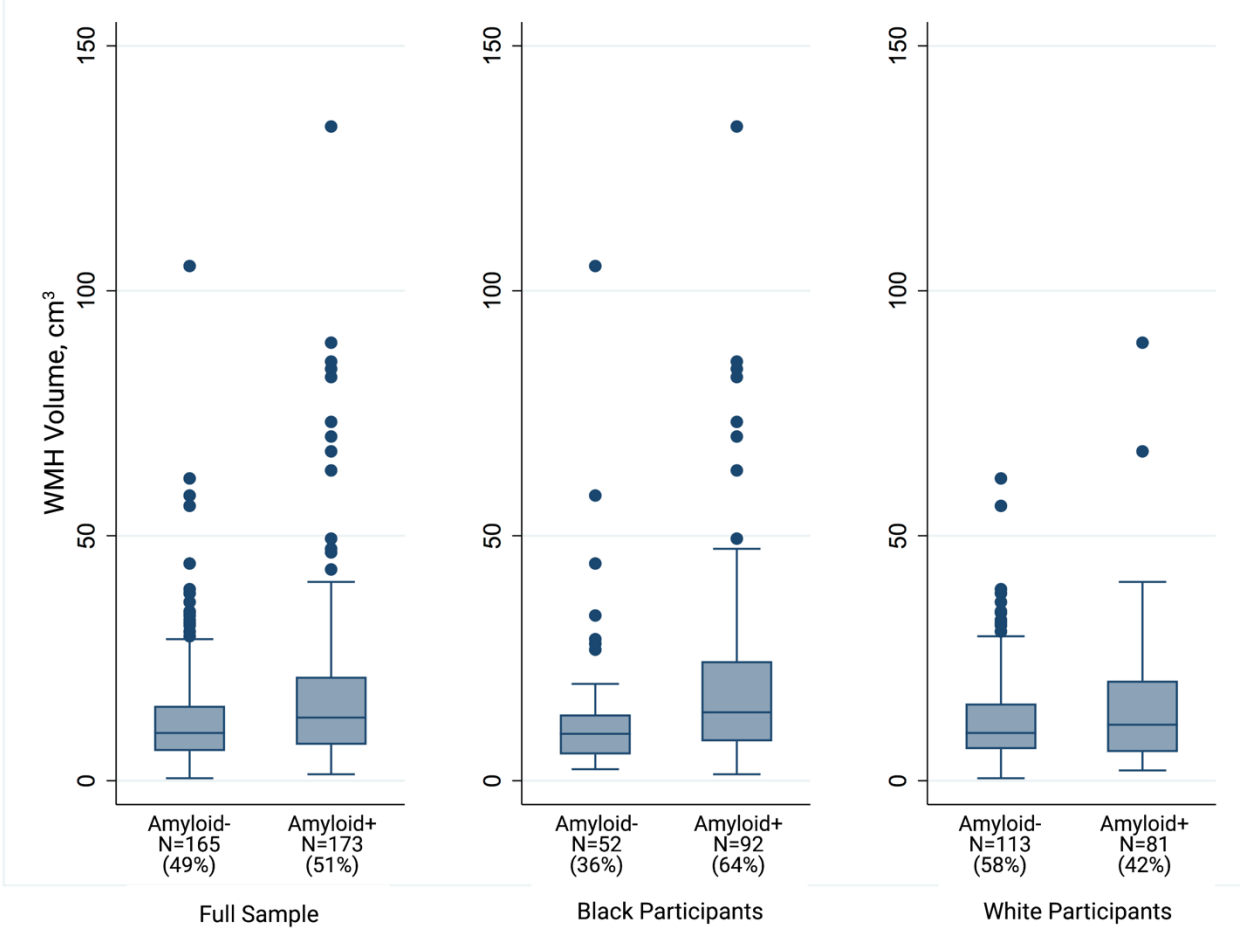
Abbreviations: FA, fractional anisotropy; MD, mean diffusivity.

Table S12. The association of tract-specific white matter DTI measures (FA and MD) with elevated cortical amyloid, stratified by race.

Diffusion Tensor Imaging (DTI) White Matter Tract	Black				White			
	FA N=138		MD N=138		FA N=182		MD N=182	
	Elevated Amyloid OR (95% CI)*	*P*	Elevated Amyloid OR (95% CI)*	*P*	Elevated Amyloid OR (95% CI)*	*P*	Elevated Amyloid OR (95% CI)*	*P*
Cingulate Gyrus Cingulum, Left	0.67 (0.43, 1.05)	0.08	0.99 (0.53, 1.85)	0.97	1.02 (0.73, 1.44)	0.90	0.62 (0.38, 1.02)	0.06
Cingulate Gyrus Cingulum, Right	0.82 (0.52, 1.30)	0.40	1.01 (0.59, 1.74)	0.97	1.17 (0.83, 1.63)	0.36	0.82 (0.51, 1.31)	0.40
Hippocampal Cingulate Gyrus, Left	0.95 (0.60, 1.50)	0.84	1.33 (0.82, 2.16)	0.25	0.91 (0.63, 1.31)	0.61	0.80 (0.51, 1.26)	0.34
Hippocampal Cingulate Gyrus, Right	1.14 (0.74, 1.75)	0.56	1.09 (0.66, 1.82)	0.74	0.93 (0.62, 1.40)	0.74	0.83 (0.52, 1.33)	0.44
Superior Longitudinal Fasciculus, Left	1.02 (0.64, 1.61)	0.94	1.33 (0.77, 2.29)	0.30	1.23 (0.88, 1.72)	0.23	0.92 (0.60, 1.41)	0.70
Superior Longitudinal Fasciculus, Right	1.62 (1.02, 2.58)	0.04	0.96 (0.58, 1.58)	0.87	1.31 (0.92, 1.86)	0.14	0.85 (0.55, 1.31)	0.45
Splenium of the Corpus Callosum	0.77 (0.50, 1.19)	0.24	1.52 (0.91, 2.54)	0.11	1.07 (0.72, 1.61)	0.73	0.82 (0.52, 1.29)	0.40

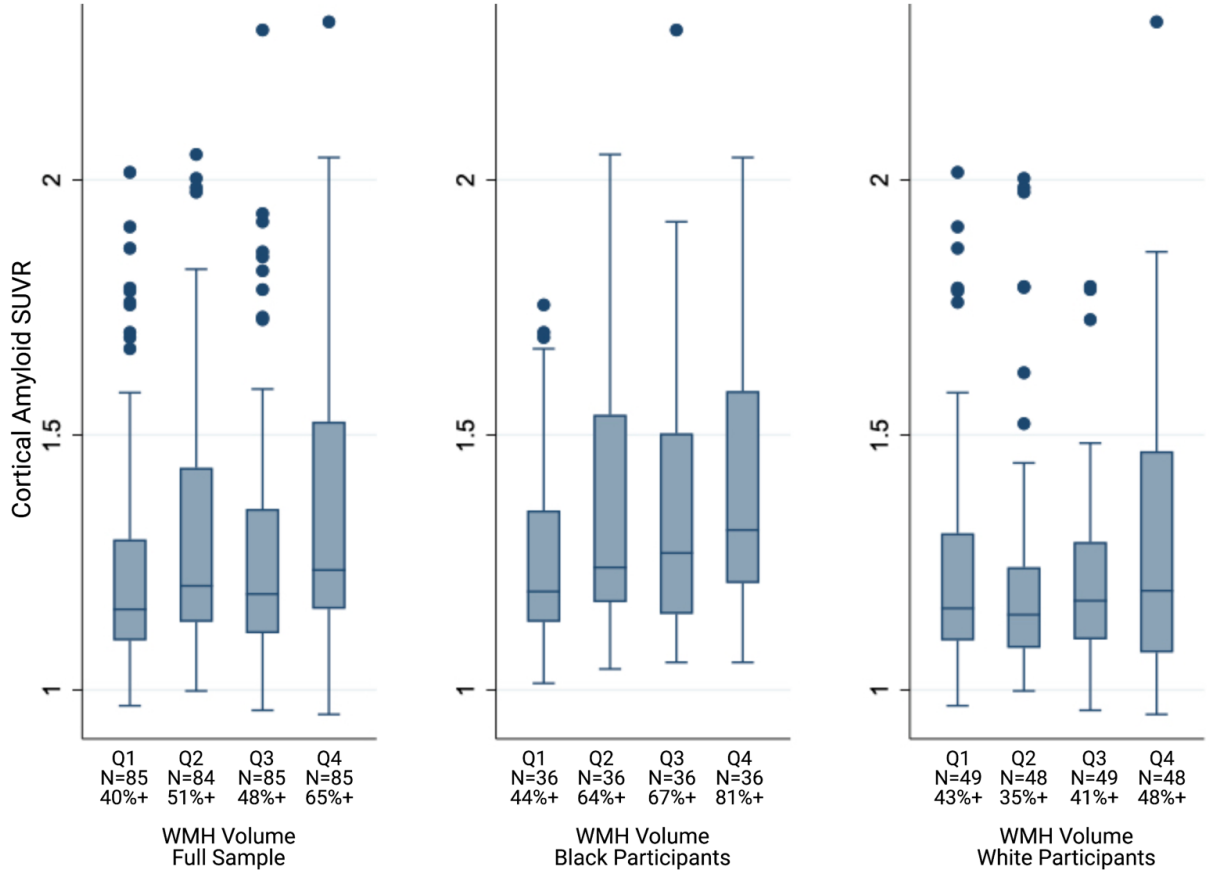
Values represent odds of elevated cortical amyloid per SD increase in fractional anisotropy (FA) and mean diffusivity (MD).
*Logistic regression models are adjusted for age, center, race, sex, education, *APOE* ε4 status, and late-life (visit 5) BMI, diabetes, hypertension, coronary heart disease, and current smoking status (model 2).
Abbreviations: FA, fractional anisotropy; MD, mean diffusivity.

Figure S1. WMH volume among amyloid-negative and amyloid-positive participants.



A standardized uptake value ratio (SUVR) >1.2 was considered amyloid positive (Amyloid+).

Figure S2. Cortical amyloid standardized uptake value ratio by WMH volume.



A standardized uptake value ratio (SUVR) >1.2 was considered amyloid positive (+)
Abbreviations: Q1, quartile 1; Q2, quartile 2; Q3, quartile 3; Q4, quartile 4; Standardized Uptake Value Ratio (SUVR)