

# The ARIC-PET amyloid imaging study

## Brain amyloid differences by age, race, sex, and *APOE*



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### ABSTRACT

**Objective:** To evaluate differences in amyloid deposition in a community-based cohort without dementia by age, sex, race, education, and *APOE*  $\epsilon$ 4 allele status.

**Methods:** Recruited from the longitudinal Atherosclerosis Risk in Communities study, 329 participants without dementia, ages 67–88 years, were imaged using florbetapir PET at 3 US community sites (Washington County, Maryland; Forsyth County, North Carolina; and Jackson, Mississippi). Standardized uptake value ratios (SUVRs) were calculated; global cortical SUVR  $>1.2$  was evaluated as the primary outcome. Age, race, sex, education level, and number of *APOE*  $\epsilon$ 4 alleles were evaluated in multivariable models including vascular risk factors, brain white matter hyperintensity and total intracranial volume, and cognitive status.

**Results:** A total of 141 of the participants (43%) were black. In multivariable models, odds of elevated SUVR was increased in participants with increasing age (odds ratio [OR] 1.63, 95% confidence interval [CI] 1.01–2.65 per 10 years of age) and black race (OR 2.08, 95% CI 1.23–3.51) but did not differ by educational level. Each  $\epsilon$ 4 allele was associated with increased odds of elevated SUVR (OR 2.65, 95% CI 1.61–4.39).

**Conclusions:** In this community-based cohort without dementia, florbetapir uptake is associated with older age and *APOE* genotype. Black race was associated with higher SUVR, after adjusting for demographics, vascular risk factors, cognitive status, white matter hyperintensity volume, and *APOE* genotype, with effect sizes nearing those seen for *APOE*  $\epsilon$ 4. Replication of these findings is needed in other cohorts, and reasons for and consequences of these observed differences by race warrant further study. **Neurology® 2016;87:473–480**

### GLOSSARY

**A $\beta$**  =  $\beta$ -amyloid; **AD** = Alzheimer disease; **ARIC** = Atherosclerosis Risk in Communities; **ARIC-NCS** = Atherosclerosis Risk in Communities-Neurocognitive Study; **CDR** = Clinical Dementia Rating; **CI** = confidence interval; **FAQ** = Functional Activities Questionnaire; **FLAIR** = fluid-attenuated inversion recovery; **HS** = high school; **IQR** = interquartile range; **MCI** = mild cognitive impairment; **MMSE** = Mini-Mental State Examination; **MPRAGE** = magnetization-prepared rapid gradient echo; **OR** = odds ratio; **ROI** = region of interest; **SUVR** = standardized uptake value ratio; **TIV** = total intracranial volume; **WMH** = white matter hyperintensity.

The prevailing hypothesis behind the pathophysiology of Alzheimer disease (AD) focuses on the accumulation of brain amyloid in  $\beta$ -amyloid (A $\beta$ ) plaques as a critical mechanism. Use of PET ligands that bind to A $\beta$  allows for the evaluation of A $\beta$  in persons with or without clinical symptoms. Although a recent meta-analysis reported positive amyloid scans in 10% of healthy 50- to 90-year-old participants, and in 27% of similarly aged adults with mild cognitive impairment (MCI),<sup>1</sup> few studies in persons of European extraction<sup>2,3</sup> have evaluated patterns of A $\beta$  deposition using PET, and none in black participants, to our knowledge. Using A $\beta$  imaging in a biracial cohort would allow further exploration of racial disparities in dementia etiology.

Dementia is more prevalent in blacks than in whites,<sup>4–6</sup> although AD-type neuropathologic findings are found on autopsy with equal prevalence in both groups.<sup>7,8</sup> Thus, a larger component

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of dementia in blacks may be due to vascular disease, supported by recent data showing that black decedents with clinical AD more frequently have mixed pathologies on autopsy,<sup>9</sup> or that some autopsy series select racial groups differentially. Further, typical AD risk factors may have different associations with clinical AD in blacks than in whites. Carrying an *APOE*  $\epsilon 4$  gene has stronger associations with AD in whites than in blacks,<sup>10</sup> with some studies even suggesting that, in black patients, AD is independent of *APOE* genotype.<sup>11</sup>

In this study of participants without dementia from the Atherosclerosis Risk in Communities (ARIC) study, we evaluated differences in amyloid deposition, using florbetapir PET, by race, age, sex, education, and *APOE* status. We hypothesized that racial differences, if observed, would be modified by *APOE* status, with the specific hypothesis that *APOE*'s effect would be less in black compared to white participants.

**METHODS Participant inclusion.** Participants were recruited for this ancillary study (ARIC-PET) from the ARIC–Neurocognitive Study (ARIC–NCS), a major ancillary to the ARIC study. The ARIC study included, at its onset in 1987–1989, 15,792 individuals from 4 US communities<sup>12</sup>; participants completed 5 in-person visits. The fifth visit, ARIC–NCS (2011–2013), was attended by 6,538 surviving participants, and included an extensive neuropsychological battery,<sup>13</sup> with informant interview in a subset, and expert classification of cognitive status (normal/MCI/dementia<sup>14</sup>). A subset of ARIC–NCS participants without a contraindication to MRI and meeting one of the following criteria was selected for a brain MRI: (1) prior brain MRI during the ARIC brain MRI ancillary visit<sup>15</sup>; (2) low cognitive scores on a thorough neuropsychological battery from ARIC–NCS or decline on scores on tests repeated at ARIC visits 2, 4, and ARIC–NCS; or (3) an age-stratified random sample of participants with normal cognition.<sup>13</sup>

Among the participants with a brain MRI during the 2011–2013 visit, participants from 3 ARIC sites (Jackson, Mississippi; Washington County, Maryland; and Forsyth County, North Carolina) were recruited into the ARIC–PET study. Only participants without dementia were included (dementia defined as [1] expert committee diagnosis of dementia when adjudication was complete; but, if not complete, when [2] Clinical Dementia Rating [CDR] sum-of-boxes score<sup>16</sup> was  $>3$ , [3] Functional Activities Questionnaire [FAQ] was  $>5$ , or [4] Mini-Mental State Examination [MMSE] score was  $<19$  [blacks] or  $<21$  [whites]). Additional exclusion criteria included heavy current alcohol use, renal dysfunction (creatinine  $>2$  mg/dL), or prolonged QT-c interval ( $>450$  ms).

**Standard protocol approvals, registrations, and patient consents.** This study was approved by each institution's institutional review board. All participants provided written informed consent.

**Brain MRI and PET.** MRI scans were performed on 3T MRI scanners at each site; magnetization-prepared rapid gradient echo (MPRAGE) was used for coregistration of PET images. Other details about MRI analysis, completed at the ARIC MRI Reading Center (Mayo Clinic), are reported elsewhere.<sup>13</sup> Briefly, white matter hyperintensity (WMH) volume was measured quantitatively from fluid-attenuated inversion recovery (FLAIR) sequences, using an in-house algorithm,<sup>17</sup> and total intracranial volume (TIV) was measured on MPRAGE, using Freesurfer version 5.1.

Florbetapir PET scans were performed at each site, within 1 year of the brain MRI. Isotope was injected through a butterfly needle, with images acquired from 50 to 70 minutes for a 20-minute ( $4 \times 5$  minutes) uptake scan. Images were transferred to the PET image analysis center (Johns Hopkins), where they were reviewed qualitatively for incidental findings, image quality, and quantified for standardized uptake value ratios (SUVRs). Images were coregistered to the MRI, spatially normalized, and 34 total regions of interest (ROIs) were manually drawn and applied to the SUVR images. Further details about image acquisition and processing are provided in the e-Methods on the *Neurology*<sup>®</sup> Web site at Neurology.org.

Although SUVR values were available for each ROI,<sup>18</sup> the primary analysis uses a global cortical measure of  $\beta$ -amyloid ( $A\beta$ ), calculated as a weighted average of the following regions: orbitofrontal, prefrontal, and superior frontal cortices, lateral temporal, parietal, and occipital lobes, precuneus, and anterior and posterior cingulates. The SUVR value was dichotomized at the sample median of SUVR  $>1.2$ , due to the highly skewed distribution of the data. The Wilcoxon rank-sum test was used to evaluate differences in non-normally distributed, continuous, global cortical SUVR by race for univariate analyses.

**Demographic and covariate information.** Primary variables included age at the time of the scan (in years), sex, education level (less than high school [HS]; HS/general educational development/vocational school; any college, graduate, or professional school), race (both self-reported at ARIC visit 1), and *APOE* genotype (TaqMan assay; Applied Biosystems, Foster City, CA). Status of hypertension (systolic blood pressure  $>140$  mm Hg, diastolic blood pressure  $>90$  mm Hg, or use of antihypertensive medications) and diabetes (fasting glucose  $\geq 126$  mg/dL, nonfasting glucose  $\geq 200$  mg/dL, HbA1c  $\geq 6.5$ , self-report of physician-diagnosed diabetes, or use of oral diabetes medications or insulin) at the time of ARIC–NCS was included in multivariable models, as were WMH and TIV, by brain MRI.

Cognitive status was defined according to expert-adjudicated cognitive outcomes, available at analysis although not complete at the time of ARIC–PET recruitment. A panel of experts classified all cases determined to be not normal and a subset of cases determined to be normal by computerized algorithm, by current standard criteria,<sup>19,20</sup> as normal, MCI, or dementia. Detailed methods are described elsewhere.<sup>14</sup> The algorithm and expert review included neuropsychological battery test Z scores, MMSE score, CDR sum-of-boxes, change in neuropsychological scores for the 3 repeated tests, and FAQ. MMSE at ARIC–NCS was included as a covariate in sensitivity analyses. For participants who did not complete the full MMSE (e.g., due to a physical impairment), a prorated score was derived from the total number of items actually completed.

**Statistical analysis.** Stata SE version 13 for Macintosh (College Station, TX) was used for all analyses. Descriptive analyses were conducted including box plots for visualization of group comparisons. Florbetapir uptake was evaluated as a dichotomous (SUVR  $>1.2$ ) measure in logistic regression models. Initial

models included age, sex, race, educational level, and *APOE* status; subsequent models added hypertension and diabetes, and finally, MCI status, WMH volume, and TIV.

Secondary analyses evaluated the specific ROIs contained within the global measure and that were identified as frequent locations for amyloid deposition. We also evaluated effect modification of the *APOE* genotype on the amyloid outcome by race and by sex.

Sensitivity analyses included restricting the sample to individuals with (1) normal cognition (excluding MCI); (2) no *APOE*  $\epsilon 4$  alleles; and (3) using other published florbetapir thresholds (1.11<sup>21</sup> and 1.10<sup>22</sup>).

**RESULTS** Of the 346 participants in ARIC-PET, 2 were excluded for nonwhite or nonblack race, 14 for missing covariates (5: *APOE*, 3: hypertension status, 5: diabetes status; 1: TIV), and 1 who was eventually classified as having dementia, leaving 329 participants without dementia, representing 95% of the ARIC-PET sample.

More participants were female than male, with a mean age of 75.9 years (table 1). Fewer white participants had <HS education than black participants, and fewer had MCI. Black and white participants had similar proportions of MCI by expert review. Median

florbetapir uptake for the entire sample was 1.20 (interquartile range [IQR] 1.12–1.40; range 0.95–2.31). Of the 89 participants with MCI, 68.5% had positive florbetapir scans (SUVR >1.2), with higher rates by age: 67.2% of participants aged 67 to <80, vs 72.0% of participants aged 80–89 years. In cognitively normal adults, 45.0% had positive florbetapir uptake, with similar rates by age group.

**Analysis of florbetapir uptake by demographic variables.** Florbetapir uptake was higher in participants who were older, female, carried 1 or 2 *APOE*  $\epsilon 4$  alleles, and who were black (table 2). There was no association with education level. This pattern persisted despite adjustment for hypertension, diabetes, cognitive status (MCI yes/no), and markers of brain microvascular disease in the models (table 2). Black participants had a >2-fold increased odds of elevated SUVR in the fully adjusted model. Global cortical SUVR, analyzed continuously, was higher in blacks ( $p < 0.0001$ ).

**Secondary and sensitivity analyses.** Secondary analysis of separate ROIs showed similar associations between

**Table 1** Participant characteristics overall and by race: Atherosclerosis Risk in Communities-PET study (2011–2013) (n = 329)

	Overall (n = 329)	Blacks (n = 141)	Whites (n = 188)	p Value <sup>a</sup>
Age, y, mean (SD)	75.9 (5.4)	75.5 (5.1)	76.1 (5.6)	0.331
Female, %	56.8	61.7	53.2	0.123
Center, %				<0.001
Washington County, MD	37.4	2.1	63.8	
Forsyth County, NC	21.6	2.1	36.2	
Jackson, MS	41.0	95.7	0.0	
Education level, %				0.056
College, graduate, or professional school	40.4	42.6	38.8	
High school, GED, or vocational school	43.5	36.9	48.4	
< High school	16.1	20.6	12.8	
<i>APOE</i> $\epsilon 4$ genotype, %				0.108
2/2, 2/3, or 3/3	69.0	63.1	73.4	
2/4 or 3/4	28.6	33.3	25.0	
4/4	2.4	3.6	1.6	
Hypertension, %	71.4	82.3	63.3	<0.001
Diabetes, %	37.4	38.3	36.7	0.767
Mild cognitive impairment, %	27.1	26.3	27.7	0.774
Prorated MMSE score, points, mean (SD)	27.2 (2.2)	26.3 (2.3)	27.8 (1.8)	<0.001
White matter hyperintensity volume, cm <sup>3</sup> , median (IQR)	11.1 (6.6–18.3)	11.7 (6.9–19.2)	10.6 (6.2–17.5)	0.445
Estimated total intracranial volume, cm <sup>3</sup> , mean (SD)	1,372.1 (155.4)	1,331.3 (141.1)	1,402.7 (159.0)	<0.001

Abbreviations: GED = general educational development; IQR = interquartile range; MMSE = Mini-Mental State Examination.  
<sup>a</sup>p Values determined using t tests (continuous data) or  $\chi^2$  tests (proportions). For white matter hyperintensity volume, which was highly skewed, medians are presented and quantile regression was used to compare means in the 2 groups.

**Table 2** Adjusted odds ratios (ORs) (95% confidence intervals [CIs]) for global cortex SUVR >1.2 (median) (n = 329)

	Model 1, OR (95% CI)	Model 2, OR (95% CI)	Model 3, OR (95% CI)
Age (per 10 y)	1.97 (1.26-3.08)	1.91 (1.22-2.99)	1.63 (1.01-2.65)
Female vs male	1.70 (1.05-2.75)	1.72 (1.06-2.79)	1.53 (0.78-2.98)
Black race vs white race	2.29 (1.42-3.70)	2.18 (1.34-3.56)	2.08 (1.23-3.51)
<b>Education level</b>			
College, graduate, or professional school	1 (reference)	1 (reference)	1 (reference)
High school, GED, or vocational school	0.88 (0.52-1.48)	0.87 (0.52-1.46)	0.88 (0.52-1.49)
< High school	1.04 (0.52-2.07)	0.99 (0.49-1.98)	0.88 (0.43-1.80)
<i>APOE</i> ε4 genotype (per 1 additional ε4 allele)	2.62 (1.61-4.24)	2.70 (1.66-4.41)	2.65 (1.61-4.39)

Abbreviations: GED = general educational development; SUVR = standardized uptake value ratio.

Model 1: Adjusted for age, sex, race, education, and *APOE* ε4 genotype. Model 2: Model 1 + hypertension and diabetes.

Model 3: Model 2 + mild cognitive impairment status, white matter hyperintensity volume, and total intracranial volume.

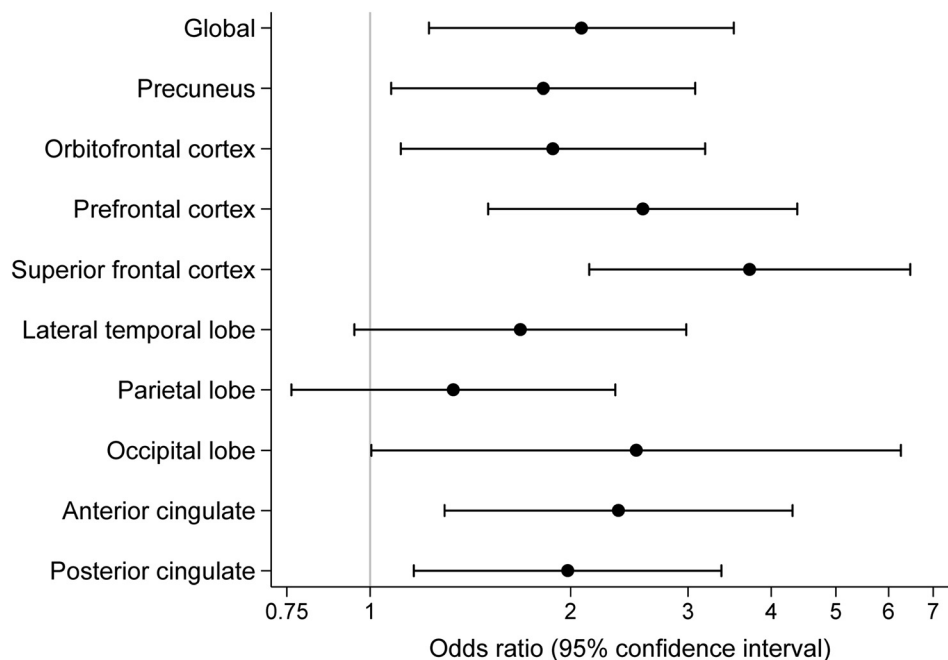
race and elevated SUVR as for the global cortical SUVR measure, although race associations in the lateral temporal lobe and parietal lobe did not reach statistical significance (figure 1).

We found no statistical evidence of an interaction of sex × *APOE* ( $p = 0.22$ ) or race × *APOE* ( $p = 0.85$ ). Global cortical SUVR increased in persons with race and increasing *APOE* ε4 alleles (figure 2).

When racial differences in global cortical SUVR were analyzed in separate cognitive groups (figure 3), differences by race were no longer statistically significant ( $p = 0.07$ ) in the fully adjusted model among the group of individuals with normal cognition (n = 240;

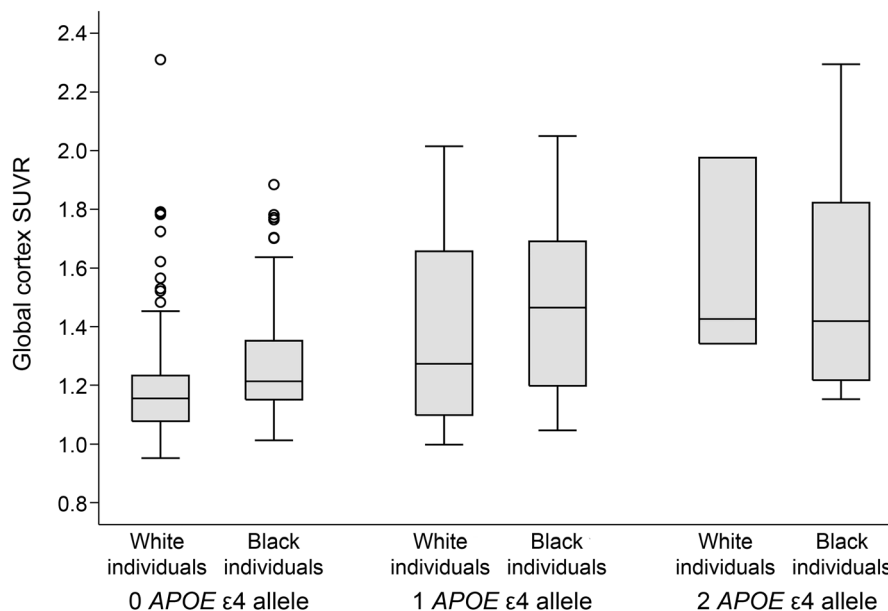
table e-1), although differences by race remained in the MCI group (n = 89; table e-2). When MMSE was included instead of MCI, race differences were not statistically significant in the fully adjusted model (odds ratio [OR] 1.53, 95% confidence interval [CI] 0.88–2.66).

When the primary analysis was repeated only among participants without any ε4 alleles (n = 227), black race remained significantly associated in the fully adjusted model (OR 1.96, 95% CI 1.06–3.62), with loss of statistical significance for sex ( $p = 0.23$ ) and age ( $p = 0.26$ ). Within each *APOE* genotype, blacks had higher median SUVR values than whites (figure e-1).

**Figure 1** Adjusted odds ratios for elevated florbetapir associated with black race

The odds ratios and their 95% confidence intervals are displayed for black race for a standardized uptake value ratio >1.2. A weighted cortical average ("global") as well as specific regions of interest are shown. Adjusted for age, sex, education, *APOE* ε4 genotype, hypertension, diabetes, white matter hyperintensities, total intracranial volume, and mild cognitive impairment status.

**Figure 2** Unadjusted box plots of global cortex standardized uptake value ratio (SUVR) by race and *APOE*  $\epsilon 4$  genotype

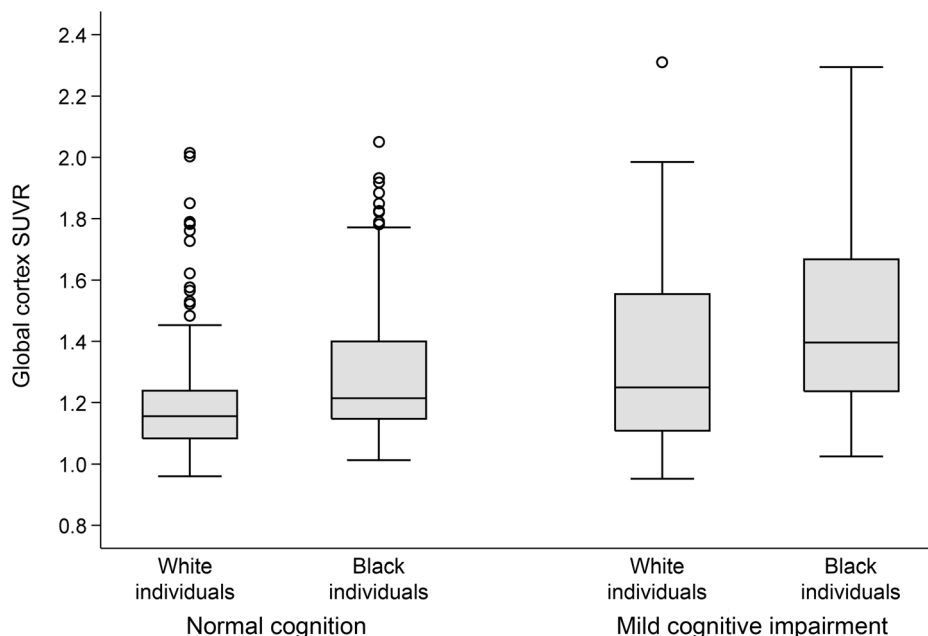


Evaluation of other SUVR cutpoints as previously used in the literature demonstrated similar associations for race (for SUVR >1.11: model 3 OR 3.22, 95% CI 1.64–6.30) and female sex (OR 2.22, 95% CI 1.03–4.79), although *APOE* genotype and age were no longer statistically significant (table e-3).

**DISCUSSION** This population-based biracial study of 329 adults without dementia aged 67–88 years

supports prior work in whites,<sup>1</sup> demonstrating higher amyloid deposition, measured by florbetapir PET, in persons with older age, and with a dose response for *APOE*  $\epsilon 4$ . We also found that blacks (representing nearly half of our cohort) had a 2-fold increase in rates of elevated A $\beta$  compared to whites. This represents an important extension of prior studies, with clear implications for a possible mechanism underlying observed disparities<sup>23</sup> in dementia risk.

**Figure 3** Unadjusted box plots of global cortex standardized uptake value ratio (SUVR) by race and mild cognitive impairment status





We have previously postulated that differences in rates of cognitive decline and dementia by race are due to differences in prevalence of vascular risk factors.<sup>24</sup> The present results do not support significant confounding by current levels of vascular risk factors (including brain microvascular disease) as an explanation for race disparities in amyloid, although we acknowledge that vascular effects are more likely related to decades of exposure than just current levels; the higher brain amyloid levels we find may still be due to longstanding uncontrolled vascular risk factors that are disproportionately present in black compared to white participants, or vascular brain changes not reflected by our markers. To argue that disproportionate vascular disease explains the current findings, vascular risk factors would need to have contributed to elevated brain amyloid, despite lack of evidence for this association.<sup>25,26</sup> If vascular and AD processes are simply additive, one would have predicted, in this study of individuals without dementia, less brain amyloid in blacks compared to whites (since more vascular disease is found in blacks, and, to have relatively normal cognition, high amounts of both amyloid and vascular disease would be unlikely). Thus, the vascular mechanism story does not fit the current observations. The failure to see a race  $\times$  *APOE*  $\epsilon$ 4 interaction argues against differences in *APOE*  $\epsilon$ 4 carriage as an explanation, as do our findings demonstrating the race differences to be unchanged in the sample without any  $\epsilon$ 4 alleles.

*APOE*  $\epsilon$ 4 is the strongest genetic risk factor for AD,<sup>27</sup> and our data support its importance as a risk factor for amyloid deposition, even in cognitively normal persons. Our results are consistent with prior reports of a 2- to 3.5-fold increased odds of amyloid positivity in cognitively normal carriers with one  $\epsilon$ 4 allele.<sup>1</sup> We see similar increased risk, however, in both races, without effect modification by *APOE*; further, results remain similar in participants without any  $\epsilon$ 4 alleles. Other studies have suggested that *APOE* is a less important risk factor for dementia in blacks than in whites,<sup>28</sup> although  $\epsilon$ 4 carriage is more common in blacks than in whites.<sup>29</sup> Age's effect on amyloid levels is slightly lower than what has been described elsewhere,<sup>1,30</sup> but our overall levels of amyloid positivity are higher than those in other reports.<sup>1</sup>

Studies of clinical dementia are potentially biased by errors in diagnosis by race, not always fully corrected by use of available racially appropriate normative cognitive data. This potential for diagnostic error, however, cannot explain our observed differences in amyloid deposition, particularly since MCI in this study was defined using our own robust ARIC-derived race-based norms.<sup>31</sup> Social factors such as access to medical care and socioeconomic status may play an important role in management of vascular risk factors

or identification of cognitive decline, but unless absence of these factors directly acts to reduce amyloid deposition, differences in social factors are not likely to directly cause differences in amyloid deposition by race. Other potential explanations for racial disparities in dementia rates, and in this study, amyloid deposition rates, include genetic or metabolomic differences by race. The fact that our results no longer show significantly elevated levels in blacks when MMSE scores are included as a covariate, or among persons with normal cognition, is likely a result of the restricted range of cognitive ability resulting from adjusting the comparison for the MMSE or limiting it to those with normal cognition. Since brain amyloid affects cognition, comparing blacks with whites at the same or similar levels of cognition necessarily reduces the black-white difference in amyloid. But such a finding does not affect the interpretation or our primary result, which suggests that blacks, at least in our sample, have more amyloid than whites, providing a partial explanation of their higher dementia prevalence. However, it is also possible that the relationship of amyloid to cognition is subtly different by race. This difference might require a larger study to demonstrate accurately, and would require demonstration of a similar racial difference in other cohorts, which would improve the generalizability of the current findings.

We also found sex differences in florbetapir uptake, in contrast to prior studies,<sup>3</sup> with more amyloid positivity in women. Some epidemiologic data have suggested that age-adjusted incidence of AD is higher in women,<sup>32</sup> and our data suggest that this may be through more amyloid deposition. Estrogen may reduce aggregation of  $A\beta$ , so the decrease in estrogen during menopause might contribute to a rise in  $A\beta$ .<sup>33</sup> Interestingly, although others have reported higher amyloid in persons with higher educational attainment,<sup>1</sup> we did not confirm this association in our study. Further, our own work in ARIC has suggested that level of educational attainment does not influence rate of cognitive decline itself, but rather raises the absolute level of scores, a manifestation of cognitive reserve, and might delay the age at which an individual passes below a threshold and is diagnosed with dementia.<sup>34</sup> These florbetapir data support that hypothesis, suggesting that the effect of education on healthy brain aging may be via cognitive reserve rather than through direct changes in amyloid deposition. Our education-adjusted data do not suggest that the race differences observed are the effects of differences in education.

Although we observe a pattern of higher florbetapir uptake in black participants in our study, most of these participants were from a single site (Jackson, Mississippi), which may lead to concern that the effect could be geographic rather than specific to race.

Although numbers are small at the other 2 sites (Forsyth County, North Carolina, and Washington County, Maryland), each recruited 3 black participants, and florbetapir values were not significantly elevated in those 6 participants compared to white participants at those field centers. Black participants from these other 2 sites had a median florbetapir SUVR of 1.20 (IQR 1.11–1.64), compared to 1.25 (IQR 1.16–1.51) among black participants from Jackson (and 1.17 [IQR 1.10–1.31] in white participants). Given these small numbers, we cannot rule out the possibility that the effect we are seeing is due to some highly influential exposures unique to the Jackson site. Further studies will need to evaluate diverse populations from other communities.

In addition, we acknowledge a concern that our community-based cohort may not be fully representative: participants recruited into the ARIC-PET study represent those who are able to tolerate MRI and PET scans, who also might be more health-aware. However, we anticipate that, if anything, this might bias our population towards the null of any observed associations. It is clear, however, that individuals in our study who are black differ from those who are white with regards to underlying comorbidities and cognitive performance. Although we have attempted to account for this potential confounding by adjusting for vascular risk factors and markers, as well as cognitive status, we acknowledge that these are observational data so confounding may remain. Finally, we chose an SUVR cutpoint of 1.2 based on our sample median, whereas varying numbers have been used in the literature<sup>1</sup>; however, our primary findings for race and sex persist despite evaluation of lower cutpoints.

Our study supports prior work demonstrating higher amyloid uptake in persons of older age without dementia who carry 1 or 2 *APOE*  $\epsilon$ 4 alleles, and, importantly, suggests higher amyloid in blacks. The mechanism and consequences of this observed difference in amyloid by race requires further study, since, if repeated in additional cohorts, this may reflect differences in risk factor prevalence or control, or may be due to some unsuspected exposures or a genetic predisposition to amyloid deposition. It will be important to further investigate in future studies if the relationship between amyloid and cognition differs by race. Given the existing disparities noted in dementia rates, these data may ultimately help reduce these disparities through analysis of mechanism.

#### AUTHOR CONTRIBUTIONS

Dr. Gottesman: drafting the manuscript, study concept, analysis or interpretation of data, study supervision, obtaining funding. Dr. Schneider: revising the manuscript for content, analysis or interpretation of data, statistical analysis. Dr. Zhou: revising the manuscript for content, analysis or interpretation of data. X. Chen: revising the manuscript for content, analysis or interpretation of data. Dr. Green: revising the manuscript for content, acquisition of data. Dr. Gupta: revising the manuscript for content,

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#### DISCLOSURE

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