Neurobiology of Aging 139 (2024) 11–19

Contents lists available at ScienceDirect

Neurobiology of Aging

journal homepage: www.elsevier.com/locate/neuaging.org

Apolipoprotein E and Alzheimer's disease pathology in African American older adults

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ARTICLE INFO

Keywords:
racialization
apolipoprotein-E
β-amyloid
tau
PET

ABSTRACT

The apolipoprotein-E4 (*APOE*4*) and apolipoprotein-E2 (*APOE*2*) alleles are more common in African American versus non-Hispanic white populations, but relationships of both alleles with Alzheimer's disease (AD) pathology among African American individuals are unclear. We measured *APOE* allele and β-amyloid (Aβ) and tau using blood samples and positron emission tomography (PET) images, respectively. Individual regression models tested associations of each *APOE* allele with Aβ or tau PET overall, stratified by racialized group, and with a racialized group interaction. We included 358 older adults (42% African American) with Aβ PET, 134 (29% African American) of whom had tau PET. *APOE*4* was associated with higher Aβ in non-Hispanic white ($P < 0.0001$), but not African American ($P = 0.64$) participants; racialized group modified the association between *APOE*4* and Aβ ($P < 0.0001$). There were no other racialized group differences. These results suggest that the association of *APOE*4* and Aβ differs between African American and non-Hispanic white populations. Other drivers of AD pathology in African American populations should be identified as potential therapeutic targets.

1. Background

The apolipoprotein-E4 (*APOE*4*) and E2 (*APOE*2*) alleles are the strongest genetic risk and protective factors, respectively, of sporadic Alzheimer's disease (AD) (Serrano-Pozo et al., 2021). Compared to the most common E3 (*APOE*3*) allele, *APOE*4* is associated with earlier onset of clinical symptoms, earlier β-amyloid (Aβ) positivity, and higher Aβ burden throughout the natural history of disease (Hampeletal.,2021). Conversely, the *APOE*2* allele is related to delayed symptom onset and lesser Aβ burden compared to *APOE*3*. Emerging evidence additionally suggests that both alleles may directly influence pathological tau, such that *APOE*4* carriers show greater tau deposition (Therriaultetal.,2020) and *APOE*2* carriers show less tau deposition (Youngetal.,2023) relative to *APOE*3* carriers.

Most work surrounding respective risk and protective effects of *APOE*4* and *APOE*2* on AD has been collected in non-Hispanic white populations. However, a greater proportion of African American individuals carry at least one copy of the *APOE*4* allele compared to those

Abbreviations: A4, Anti-Amyloid Treatment in Asymptomatic Alzheimer's disease; Aβ, beta-amyloid; AD, Alzheimer's disease; ADRC, Alzheimer's Disease Research Center; APOE, apolipoprotein; ARIC, Atherosclerosis Risk in Communities; Arg, Arginine; CIC, Imperial College London Clinical Imaging Centre; CoBRA, Connectomics in Brain Aging; Cys, Cysteine; FTP, flortaucipir; Heart SCORE, Heart Strategies Concentrating on Risk Evaluation; MCI, Mild Cognitive Impairment; MMSE, Mini Mental State Examination; MoCA, Montreal Cognitive Assessment; MPRAGE, magnetization-prepared rapid gradient echo; MRI, magnetic resonance imaging; MTL, medial temporal lobe; PART, primary age-related tauopathy; PET, positron emission tomography; PiB, Pittsburgh Compound-B; ROI, region of interest; SDOH, social determinants of health; SNP, single nucleotide polymorphism; SUVR, standardized uptake value ratio.

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https://doi.org/10.1016/j.neurobiolaging.2024.03.005
Received 8 December 2023; Received in revised form 7 March 2024; Accepted 22 March 2024
Available online 30 March 2024

who are non-Hispanic white (Beydounetal.,2021;Rajanetal.,2019). While early work suggested that *APOE*2* is less common African American, versus non-Hispanic white, individuals (Kambohetal.,1989), recent studies from large, population-based samples have challenged this, indicating that *APOE*2* is also relatively more prevalent in those who are African American (Beydounetal.,2021;Rajanetal.,2019). Interestingly, despite being more likely to carry either an *APOE*4* or *APOE*2* allele, a small body of evidence suggests that the influence of both alleles on AD may differ among African American versus non-Hispanic white individuals. Specifically, studies have reported that the associations of *APOE*4* and *APOE*2* with clinical AD are comparatively weaker in African American populations (Evansetal.,2003;Farreretal.,1997;Sahotaetal.,1997;Tangetal.,1998).

Whether or not relationships between *APOE* allele and AD pathology differ between African American and non-Hispanic white populations is more unclear. Of the few studies that have examined this, results have been inconsistent. Some have found a comparatively attenuated association between *APOE* and brain Aβ burden in African American, versus non-Hispanic white, participants (Ali et al., 2023;Detersetal.,2021), while others report no differences (Gottesmanetal.,2016). One study found that the association between *APOE*4* and cerebrospinal fluid (CSF)-derived total- and phosphorylated-tau was weaker in African American individuals compared to those who were non-Hispanic white (Morrisetal.,2019). We are unaware of any neuroimaging studies that have examined differences in *APOE* allele-and-tau associations. This gap in knowledge ultimately holds important public health consequences, as African American populations are disproportionately burdened by AD (Alzheimer's Association, 2022), making characterization of disease risk and protective factors necessary for both treatment development and disparity reduction efforts.

In this study, we interrogated if being African American modifies associations between *APOE* allele and indices AD pathologic burden. To emphasize that race is a social construct, herein, we refer to African American and non-Hispanic white populations as "racialized," rather than "race," groups, where racialization is the historical process of individuals being assigned to different social groups based on real or imagined phenotypes (Kalewold,2020). Using genotyping and neuroimaging data from two large cohorts of African American and non-Hispanic white older adults, we tested racialized group differences in relationships of *APOE*4* and *APOE*2* with indices of cerebral in vivo Aβ and tau burden. We hypothesized that such associations would be comparatively attenuated among African American, versus non-Hispanic white, participants.

2. METHODS

2.1. Study population

This work was conducted using a combined analytic sample of data from two ongoing studies of brain structure and function in community-dwelling older adults: The Connectomics in Brain Aging and Dementia (CoBRA) project and the Heart Strategies Concentrating on Risk Evaluation (SCORE)-500 study (Cohenetal.,2021).

Since 2017, CoBRA recruits older adults from the Pittsburgh, Pennsylvania area via word-of-mouth, the University of Pittsburgh's Alzheimer's Disease Research Center (ADRC), the community-based Pitt + Me research recruitment web portal, and active links with other studies of aging, including the Heart SCORE study (Bambsetal.,2011) and Long Life Family study (Newmanetal.,2011). Individuals aged 50–89 years are eligible for study participation; those with contraindications for magnetic resonance imaging (MRI), history of stroke, or presence of psychiatric, neurologic, or medical conditions with potential to affect neuropsychologic assessment or brain structure or function are excluded. Further detail on inclusion and exclusion criteria for this study have been published previously (Cohenetal.,2021).

Heart SCORE-500 participants are recruited from the parent Heart SCORE study, which began in 2003 as a longitudinal investigation of racialized group differences in cardiovascular risk factors among adults residing in Allegheny County, Pennsylvania (Bambsetal.,2011). Participants who were active in the parent study as of May 30, 2017, aged between 45 and 59 years at baseline, and exhibit no cognitive impairment or Mild Cognitive Impairment (MCI) are eligible for Heart SCORE-500 participation. Those with contraindications for MRI or dementia diagnosis are excluded.

2.2. Image acquisition and analysis

Each participant acquired a magnetization-prepared rapid gradient echo (MPRAGE) structural T1 MRI (repetition time (TR)=2400 msec; echo time (TE)=2.22 msec; field of view (FOV)=256×256 mm; voxel size=0.8 mm x 0.8 mm) on a Siemens 3 T PRISMA scanner. With MRIs, we defined regions-of-interest (ROIs) using FreeSurfer version 7.1 and the Imperial College London Clinical Imaging Centre (CIC) atlas (for functional subdivisions of the striatum) (Fischl,2012;Tziortzietal., 2011). For quality control, all parcellations were visually inspected prior to further analysis.

Brain Aβ and tau indices were measured using [^{11}C]Pittsburgh Compound B (PiB) and [^{18}F]Flortaucipir (FTP), respectively (Klunketal., 2004;Schwarzetal.,2016). In all CoBRA and Heart SCORE-500 participants, [^{11}C]PiB scans were acquired over 50–70 min. Heart SCORE-500 participants additionally underwent [^{18}F]FTP imaging over the 80–100-minute interval. PET images were acquired using a Siemens ECAT Exact HR+ scanner ([^{11}C]PiB) or a Siemens Biograph mCT PET/CT scanner ([^{11}C]PiB and [^{18}F]FTP), binned into 5-minute frames.

PET images were inspected for inter-frame motion and corrected as necessary. We then averaged frames over tracer-appropriate post-injection intervals ([^{11}C]PiB: 50–70 min; [^{18}F]FTP: 80–100 min). We used SPM version 12 (Fristonetal.,2011) to co-register each PET image to its corresponding native space MRI with a rigid body registration. Finally, PET images were sampled in FSL using FreeSurfer and CIC ROIs (Jenkinsonetal.,2012).

2.3. Predictors

Our primary predictors were *APOE*4* and *APOE*2* alleles. For each participant, we used Taqman assays to determine two-site *APOE* genotyping for the single nucleotide polymorphisms (SNPs) rs429358 and rs7412 (Kambohetal.,1995). The rs429358 SNP corresponds to the *APOE*4* variation at codon 112, where a missense mutation changes Cysteine (Cys) to Arginine (Arg); the rs7412 SNP corresponds to the *APOE*2* variation at codon 158, where a missense mutation changes Arg to Cys (Kamboh,2022). We analyzed data separately for each SNP, where the most common genotype was compared with mutation carriers as follows: for *APOE*4* SNP, Cys112/Cys112 versus Cys112/Arg112 + Arg112/Arg112; for *APOE*2* SNP, Arg158/Arg158 versus Arg158/-Cys112 + Cys158/Cys158.

2.4. Outcomes

Our primary outcomes were indices of brain Aβ and tau burden. Because we did not have a priori knowledge of which regions may be susceptible to racialized group differences, we quantified composite indices of both [^{11}C]PiB and [^{18}F]FTP tracer retention, as is consistent with previous work from our group (Gogolaetal.,2023;Snitzetal.,2020).

For each participant, we derived global [^{11}C]PiB standardized uptake value ratio (SUVR) as a measure of Aβ deposition. This was calculated as the volume-weighted average of tracer retention in the anterior cingulate, anterior ventral striatum, superior frontal gyrus, orbitofrontal gyrus, insula, lateral temporal gyrus, parietal lobe, posterior cingulate, and precuneus, normalized to cerebellar grey matter (Snitzetal.,2020). We created two indices of tau burden: (1) medial temporal lobe (MTL) [^{18}F]FTP SUVR (calculated as volume-weighted average of radioactivity

in the entorhinal cortex, parahippocampal gyrus, fusiform gyrus, and amygdala, normalized to cerebellar grey matter (Gogolaetal.,2023)) and (2) meta-temporal lobe [^{18}F]FTP SUVR (calculated as the volume weighted average of radioactivity in MTL regions, inferior temporal gyrus, and middle temporal gyrus, normalized to cerebellar grey matter (Jacketal.,2017)). We opted to compute both tau indices considering trade-offs between the two in the context of our study. [^{18}F]FTP MTL SUVR captures early tau accumulation in AD. Because many of our participants were cognitively unimpaired (see Section 3.0; and as such, likely exhibited low tau burden (Jacketal.,2012)), we deemed this smaller region to be suitable for detecting subtle racialized group differences. However, individuals with non-AD processes, including primary age-related tauopathy (PART), can exhibit tau in the MTL (Craryetal.,2014). Thus, we additionally calculated meta-temporal lobe [^{18}F]FTP SUVR, as others have suggested that this is a more specific index of AD-related tau deposition (Jacketal.,2017).

2.5. Effect modifier

Our effect modifier of interest was racialized group. Participants self-reported being African American or non-Hispanic white at their study visits.

2.6. Other descriptive variables

We collected several variables to describe our study sample. Cognitive diagnosis (cognitively unimpaired, MCI, or AD) was assigned via multi-disciplinary consensus procedures, either in the ADRC or in the CoBRA study, following published diagnostic criteria (Albertetal.,2011; McKhannetal.,2011); the procedures and acting neuropsychologist (B.E. S.) were the same for both studies.

We assessed global cognition using either the Mini Mental State Examination (MMSE; Heart SCORE-500) or the Montreal Cognitive Assessment (MoCA; CoBRA) (Folsteinetal.,1975;Nasreddineetal.,2005). We converted MMSE scores to MoCA following published crosswalk methods (Bergeronetal.,2017).

Using FreeSurfer ROIs, we calculated MTL cortical thickness (mm) for an AD-signature composite region as the surface area-weighted average of cortical thickness in the entorhinal, inferior temporal gyrus, middle temporal gyrus (Jacketal.,2017).

Any participant with a [^{11}C]PiB SUVR $\geq$ 1.35 was classified as Aβ positive. This cut-off was determined for our FreeSurfer-based analysis pipeline using a sparse k-means clustering and resampling method in a cognitively unimpaired participant sample, as described previously (Cohenetal.,2013).

2.7. Statistical analysis

We used Mann Whitney-U and Chi square tests to examine differences in participant characteristics between: (1) racialized groups; (2) the most common genotype with mutation carriers at each of the two *APOE* polymorphic sites, as described above; and (3) study cohorts. To improve normality of outcome variables, we log-transformed PET SUVRs prior to entry into linear models.

We used individual linear regressions to test the relationships of *APOE*4*/Arg112 with PET SUVRs in the full sample, then stratified by racialized group. If an association was significant in one racialized group, but not the other, we tested an *APOE*4*/Arg112-by-racialized group interaction term in the entire sample (Wardetal.,2019). We ran separate models with [^{11}C]PiB SUVR, meta-temporal [^{18}F]FTP SUVR, and MTL [^{18}F]FTP SUVR as the outcome. We repeated analyses using these models twice: First, we re-ran [^{11}C]PiB models excluding participants aged < 65 years to determine if age explained any racialized group differences in associations; age is the strongest risk factor for AD (Jacketal.,2015) and in our sample, African American participants were younger than those who were non-Hispanic white. Second, we repeated all models substituting mutation presence with number of mutations (e.g. *APOE*4* SNP: Cys112/Cys112=0; Cys112/Arg112=1; Arg112/Arg112=2). To make African American and non-Hispanic white groups more comparable, we adjusted for age, sex, and education in all models; in those with [^{18}F]FTP SUVR as the outcome, we additionally adjusted for global [^{11}C]PiB SUVR. We repeated the above analyses substituting *APOE*4*/Arg112 for *APOE*2*/Cys158. All tests were two-sided with alpha set to 5%.

We conducted statistical analyses using SAS Software version 9.4 (SAS Institute, Cary, NC).

3. RESULTS

In the combined sample (N = 379), we excluded anyone who identified as belonging to a racialized group other than African American or non-Hispanic white (N = 2) or who had not yet received genotyping (N = 19). Our final analytic sample comprised of 358 participants with [^{11}C]PiB data and 134 participants with both [^{11}C]PiB and [^{18}F]FTP data.

Our full sample included 42% African American participants, 29% *APOE*4*/Arg112 carriers, and 18% *APOE*2*/Cys158 carriers (Table 1). Relative to non-Hispanic white participants, those who were African American were more likely to be *APOE*4*/Arg112 carriers (36% vs. 24%; $P = 0.02$) and *APOE*2*/Cys158 carriers (24% vs. 14%; $P = 0.02$). Non-Hispanic white participants who carried *APOE*4*/Arg112 exhibited higher [^{11}C]PiB SUVRs relative to non-*APOE*4*/Arg 112 carriers (median [IQR] 1.33 [0.51] vs. 1.14 [0.12]; $P < 0.0001$), but this was not true among African American participants (median [IQR] 1.11 [0.11] vs. 1.10 [0.10]; $P = 0.99$; Supplementary Figure 1).

In the subset of participants with [^{18}F]FTP data, 29% self-reported being African American, 25% were *APOE*4*/Arg112 carriers, and 15% were *APOE*2*/Cys158 carriers (Table 2). Racialized groups did not differ in their distribution of either being *APOE*4*/Arg112 carriers (33% vs. 22%; $P = 0.19$) or *APOE*2*/Cys158 carriers (21% vs. 13%; $P = 0.24$). Compared to non-carriers, those who carried *APOE*4*/Arg112 exhibited higher [^{11}C]PiB SUVRs (median (IQR) 1.40 [0.47] vs. 1.16 [0.09]; $P = 0.003$) and MTL [^{18}F]FTP SUVRs (median (IQR) 1.19 [0.10] vs. 1.14 [0.12]; $P = 0.03$) among non-Hispanic white participants, but not among those who were African American ([^{11}C]PiB SUVR: median (IQR) 1.16 [0.16] vs. 1.15 [0.10]; $P = 0.26$; [^{18}F]FTP MTL SUVR: median (IQR) 1.12 [0.14] vs. 1.15 [0.09]; $P = 0.30$).

Distributions of participant characteristics by racialized groups and *APOE*4*/Arg112 and *APOE*2*/Cys158 carriers were similar among participants $\geq$ 65 (Supplementary Table 1; Supplementary Figure 2).

Compared to participants in the Heart SCORE-500 study, those enrolled in CoBRA were more likely to be African American (51% vs. 28%; $P < 0.0001$), were younger (median [IQR] 62 [13] vs. 73 [7]; $P < 0.0001$), had fewer years of education (median [IQR] 14 [4] vs. 16 [6]; $P = 0.001$), and exhibited lower [^{11}C]PiB SUVRs (median [IQR] 1.10 [0.12] vs. 1.17 [0.04]; $P < 0.0001$; Supplementary Table 2).

3.1. Associations of APOE*4/Arg112 with Aβ and tau

In the full sample, exhibiting *APOE*4*/Arg112 was associated with 3% higher global [^{11}C]PiB SUVR relative to not carrying it ($P = 0.0008$; Table 3). When stratified by racialized group, *APOE*4*/Arg112 was associated with 7% higher [^{11}C]PiB SUVR among those who were non-Hispanic white ($P < 0.0001$), but was not significantly related to [^{11}C]PiB SUVR in African American participants ($P = 0.64$). Racialization significantly modified the relationship between *APOE*4*/Arg112 and [^{11}C]PiB SUVR in the full sample (t value = −4.16; $P < 0.0001$ for overall interaction). Results did not change when participants aged <65 were excluded (Supplementary Table 3) or when *APOE*4*/Arg112 mutation carriership was replaced with mutation dosage (Supplementary Table 5).

*APOE*4*/Arg112 was not significantly associated with meta-

Table 1
Sample characteristics.

Characteristics[a]	Overall N=358	African American participants N = 152				Non-Hispanic white participants N = 206			
		APOE4/rs429348		*APOE2*/rs7412		*APOE4*/rs429348		*APOE2*/rs7412	
		Cys112/Cys112 N = 98	Arg112 carriers N = 54 36%	Arg158/Arg158 N = 116	Cys158 carriers N = 36 24%	Cys112/Cys112 N = 156	Arg112 carriers N = 50 24%	Arg158/Arg158 N = 177	Cys158 carriersN = 29 14%
Demographics									
Age, y	69 (13)	63 (14)	63 (13)	63 (14)	64 (12)	71 (11)	71 (10)	70 (9)[d]	73 (11)[d]
Female, No. (%)	232 (65%)	70 (71%)	39 (72%)	84 (72%)	25 (69%)	97 (62%)	26 (52%)	107 (60%)	16 (55%)
Education, y	15 (6)	14 (4)	14 (4)	14 (4)	14 (3)	16 (6)	16 (6)	16 (6)	18 (4)
Cognition									
MoCA score[b]	24 (4)	24 (5)	24 (4)	23 (5)	24 (4)	26 (6)	26 (6)	26 (4)	25 (7)
Diagnosis, No. (%)[c]									
AD	6 (2%)	3 (3%)	0 (0%)	3 (3%)	0 (0%)	1 (1%)	2 (4%)	3 (2%)	0 (0%)
MCI	79 (23%)	27 (28%)	13 (27%)	34 (30%)	6 (17%)	27 (17%)	12 (24%)	34 (19%)	5 (17%)
Unimpaired	271 (76%)	66 (69%)	41 (76%)	78 (68%)	29 (83%)	128 (82%)	36 (72%)	140 (79%)	24 (83%)
Imaging									
[^{11}C]PiB SUVR	1.13 (0.14)	1.10 (0.10)	1.11 (0.11)	1.10 (0.10)	1.10 (0.10)	1.14 (0.12)[e]	1.33 (0.51)[e]	1.16 (0.18)	1.18 (0.23)
[^{11}C]PiB positive, No.(%)	61 (17%)	8 (8%)	3 (6%)	10 (9%)	1 (3%)	26 (17%)[e]	24 (48%)[e]	42 (24%)	7 (24%)
MTL cortical thickness	2.73 (0.14)	2.72 (0.15)	2.70 (0.10)	2.72 (0.13)[d]	2.67 (0.12)[d]	2.77 (0.14)	2.73 (0.15)	2.76 (0.14)	2.73 (0.13)
***APOE4*/rs429348**									
Cys112/Cys112	254 (71%)	98 (100%)	NA	-	-	156 (100%)	NA	-	-
Cys112/Arg112	95 (27%)	NA	49 (91%)	-	-	NA	46 (92%)	-	-
Arg112/Arg112	9 (3%)	NA	5 (9%)	-	-	NA	4 (8%)	-	-
***APOE2*/rs7412**									
Arg158/Arg158	293 (82%)	-	-	116 (100%)	NA	-	-	177 (100%)	NA
Arg158/Cys158	59 (16%)	-	-	NA	33 (92%)	-	-	NA	26 (90%)
Cys158/Cys158	6 (2%)	-	-	NA	3 (8%)	-	-	NA	3 (10%)

Abbreviations: AD = Alzheimer's disease; Arg = Arginine; APOE = apolipoprotein-E; Cys = Cysteine; MCI = Mild Cognitive Impairment; PiB = Pittsburgh Compound-B; SUVR = standardized uptake value ratio

[a] All values are median [IQR] unless otherwise noted
[b] N=345
[c] N = 356
[d] P < 0.05
[e] P < 0.01

temporal [^{18}F]FTP SUVR in overall (P = 0.49) or racialized group-stratified (African American: P = 0.10; non-Hispanic white: P = 0.42) analyses (Table 3). *APOE*4*/Arg112 was also not related to MTL [^{18}F]FTP SUVR in the combined sample (P = 0.75) or in either racialized group (African American: P = 0.16; non-Hispanic white: P = 0.31). In unadjusted analyses of non-Hispanic white participants, each additional mutation of *APOE*4*/Arg112 was associated with a 2% higher [^{18}F]FTP SUVR in both the meta-temporal (P = 0.03) and MTL (P = 0.04) regions (Supplementary Table 4). No such associations were detected in African American participants (meta-temporal [^{18}F]FTP SUVR: P = 0.15; MTL [^{18}F]FTP SUVR: P = 0.21). Interaction terms between number of *APOE*4*/Arg112 mutations and racialization were significant for both meta-temporal [^{18}F]FTP SUVR (t value = −2.58; P = 0.01 for overall interaction) and MTL [^{18}F]FTP SUVR (t value = −2.58; P = 0.01 for overall interaction). However, all associations disappeared after potential confounders were added to the models.

3.2. Associations of APOE*2/Cys158 with Aβ and tau

Compared to Arg158/Arg158, carrying *APOE*2*/Cys158 was associated with 2% lower [^{11}C]PiB SUVR within the entire sample (P = 0.04) (Table 4). However, in racialized group-stratified analyses, *APOE*2*/Cys158 carrier status was not significantly related to [^{11}C]PiB SUVR for either African American (P = 0.13) or non-Hispanic white (P = 0.26) participants. Results were similar when *APOE*2*/Cys158 carriership was replaced with number of *APOE*2*/Cys158 mutations (Supplementary Table 5). When excluding participants aged <65, the association in the full sample disappeared (Supplementary Table 3).

Neither *APOE*2*/Cys158 presence nor *APOE*2*/Cys158 dosage were associated with meta-temporal [^{18}F]FTP SUVR or MTL [^{18}F]FTP SUVR in the combined sample or stratified groups (Table 4; Supplementary Table 5).

4. DISCUSSION

In this study, we used data from two large, community-based cohorts of older adults ranging from cognitively unimpaired to AD to determine if African American racialization modifies the relationships of (1) *APOE*4* (operationalized as a missense mutation for Arg at codon 112) and (2) *APOE*2* (operationalized as a missense mutation for Cys at codon 158) with in vivo measures of Aβ and tau burden. We found that the association of *APOE*4* and brain Aβ burden differed between African American and non-Hispanic white individuals. Specifically, carrying an *APOE*4* allele was associated with greater Aβ burden in non-Hispanic white participants, but not among those racialized as African American, in whom we did not detect a relationship. We did not find any other racialized group differences.

Similar to our results, Deters et al. (2021) reported that among cognitively unimpaired participants in the Anti-Amyloid Treatment in Asymptomatic Alzheimer's disease (A4) study, being African American modified the association between number of *APOE*4* allele copies and global Aβ deposition such that African American *APOE*4* carriers exhibited lower brain Aβ burden than non-Hispanic white carriers (Detersetal.,2021). While no formal interaction analysis was conducted, a recent large meta-analysis of clinic- and population-based cohorts similarly found that the strength of the association between *APOE*4* and

Table 2
Sample characteristics in the subset of participants with [18 F]flortaucipir imaging.

Characteristic[a]	Overall N=134	African American participants N = 39				Non-Hispanic white participants N = 95			
		APOE4/rs429348		*APOE2*/rs7412		*APOE4*/rs429348		*APOE2*/rs7412	
		Cys112/Cys112 N = 26	Arg112 carriers N = 13	Arg158/Arg158 N = 31	Cys158 carriersN = 8	Cys112/Cys112 N = 74	Arg112 carriersN = 21	Arg158/Arg158 N = 83	Cys158 carriersN = 12
Demographics									
Age, y	73 (7)	73 (4)	75 (5)	74 (5)	74 (5)	73 (8)	71 (7)	72 (7)[d]	76 (7)[d]
Female, No. (%)	88 (66%)	20 (77%)	11 (85%)	26 (84%)	5 (63%)	45 (61%)	12 (57%)	51 (61%)	6 (50%)
Education, y	16 (6)	14 (6)	12 (4)	14 (4)	15 (3)	16 (4)	18 (4)	16 (4)	18 (4)
Cognition									
MoCA score[b]	23 (5)	23 (2)	23 (8)	23 (5)	21 (4)	26 (5)	23 (5)	26 (3)	22 (10)
Diagnosis, No.(%)[c]									
AD	1 (1%)	1 (4%)	0 (0%)	1 (3%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
MCI	22 (17%)	7 (28%)	3 (23%)	7 (23%)	3 (38%)	7 (9%)	5 (24%)	10 (12%)	2 (17%)
Unimpaired	110 (83%)	17 (68%)	10 (77%)	22 (73%)	5 (63%)	67 (91%)	16 (76%)	73 (88%)	8 (89%)
Imaging									
[^{11}C]PiB SUVR	1.17 (0.13)	1.15 (0.10)	1.16 (0.16)	1.15 (0.19)	1.14 (0.06)	1.16 (0.09)[d]	1.40 (0.47)[d]	1.17 (0.12)	1.28 (0.43)
[^{11}C]PiB positive, No.(%)	27 (20%)	2 (8%)	3 (23%)	5 (16%)	0 (0%)	12 (16%)[d]	10 (48%)[d]	16 (19%)[d]	6 (50%)[d]
MTL cortical thickness	2.73 (0.15)	2.67 (0.22)	2.69 (0.06)	2.70 (0.19)	2.66 (0.07)	2.77 (0.15)	2.74 (0.13)	2.77 (0.15)	2.71 (0.13)
[^{18}F]FTP meta temporal SUVR	1.15 (0.10)	1.15 (0.16)	1.15 (0.10)	1.16 (0.11)	1.14 (0.09)	1.14 (0.10)	1.19 (0.07)	1.15 (0.10)	1.19 (0.07)
[^{18}F]FTP MTL SUVR	1.15 (0.11)	1.15 (0.09)	1.12 (0.14)	1.17 (0.12)	1.11 (0.04)	1.14 (0.12)[d]	1.19 (0.10)[d]	1.14 (0.11)	1.19 (0.11)
***APOE4*/rs429348**									
Cys112/Cys112	100 (75%)	26 (100%)	NA	-	-	74 (100%)	NA	-	-
Cys112/Arg112	31 (23%)	NA	12 (92%)	-	-	NA	19 (90%)	-	-
Arg112/Arg112	3 (2%)	NA	1 (8%)	-	-	NA	2 (10%)	-	-
***APOE2*/rs7412**									
Arg158/Arg158	114 (85%)	-	-	31 (100%)	NA	-	-	83 (100%)	NA
Arg158/Cys158	18 (13%)	-	-	NA	7 (88%)	-	-	NA	11 (92%)
Cys158/Cys158	2 (1%)	-	-	NA	1 (13%)	-	-	NA	1 (8%)

Abbreviations: AD = Alzheimer's disease; Arg = Arginine; APOE = apolipoprotein-E; Cys = Cysteine; FTP = flortaucipir; MCI = Mild Cognitive Impairment; MTL = medial temporal lobe; PiB = Pittsburgh Compound-B; SUVR = standardized uptake value ratio

[a] All values are median [IQR] unless otherwise noted

[b] N=126

[c] N = 133

[d] $P < 0.05$

Table 3
Associations of APOE4/Arg112 with global ß-amyloid and temporal tau burden.

Outcome		Racialized group								
		Overall			African American			Non-Hispanic white		
		Beta	95% CI	*P* value	Beta	95% CI	*P* value	Beta	95% CI	*P* value
[^{11}C]PiB SUVR	Model 1[a]	0.03	0.01, 0.04	0.005	-0.004	-0.02, 0.01	0.68	0.07	0.04, 0.09	<0.0001
	Model 2[b]	0.03	0.01, 0.05	0.0008	-0.004	-0.02, 0.01	0.64	0.07	0.04, 0.09	<0.0001
[^{18}F]FTP Meta-temporal SUVR	Model 1[a]	0.003	-0.01, 0.02	0.73	-0.02	-0.05, 0.01	0.12	0.02	-0.001, 0.03	0.06
	Model 2[c]	-0.005	-0.02, 0.01	0.49	-0.02	-0.05, 0.004	0.10	0.01	-0.01, 0.02	0.42
[^{18}F]FTP MTL SUVR	Model 1[a]	0.005	-0.01, 0.02	0.52	-0.02	-0.05, 0.01	0.20	0.02	0.003, 0.04	0.046
	Model 2[c]	-0.002	-0.02, 0.01	0.75	-0.02	-0.05, 0.01	0.16	0.01	-0.01, 0.03	0.31

Abbreviations: FTP = flortaucipir; MTL = medial temporal lobe; PiB = Pittsburgh Compound-B; SUVR = standardized uptake value ratio

[a] Unadjusted

[b] Adusted for age, sex, education

[c] Adjusted for age, sex, education, global PiB SUVR

Aβ PET outcomes was comparatively weaker in African American, versus non-Hispanic white, participants (Ali et al., 2023). Conversely, in one study conducted within a dementia-free subset of the Atherosclerosis Risk in Communities (ARIC) cohort, investigators did not find an interaction between racialized group and *APOE*4* on Aβ positivity (Gottesmanetal.,2016). However, this group also reported greater Aβ deposition in African American participants relative to those who were non-Hispanic white, which may have rendered them unable to detect effect modification; neither our study nor that by Deters et al. (2021) observed that Aβ burden was greater in African American versus non-Hispanic white participants, which is consistent with other work to date (Royseetal.,2021). It is also worth noting that, more broadly, recent work has found that relationships of *APOE*4 and Aβ burden are also attenuated in Hispanic, versus non-Hispanic white, populations (Duaraetal.,2019;O'Bryant et al., 2022), similar to previously observed differences in *APOE*4 and clinical AD associations (Farreretal.,1997). Altogether, findings from our community-based cohort build on previous studies by providing further evidence that the differential

Table 4
Associations of *APOE2*/Cys158 with global ß-amyloid and temporal tau burden.

		Racialized group								
		Overall			African American			Non-Hispanic white		
Outcome		Beta	95% CI	*P* value	Beta	95% CI	*P* value	Beta	95% CI	*P* value
[^{11}C]PiB SUVR	Model 1[a]	-0.02	-0.04, 0.004	0.10	-0.01	-0.04, 0.01	0.18	-0.01	-0.04, 0.03	0.70
	Model 2[b]	-0.02	-0.04, −0.001	0.04	-0.01	-0.03, 0.004	0.13	-0.02	-0.05, 0.01	0.26
[^{18}F]FTP Meta-temporal SUVR	Model 1[a]	-0.0001	-0.02, 0.02	0.99	-0.004	-0.04, 0.04	0.80	0.004	-0.02, 0.03	0.74
	Model 2[c]	0.002	-0.01, 0.02	0.85	0.004	-0.03, 0.04	0.26	-0.0005	-0.02, 0.02	0.96
[^{18}F]FTP MTL SUVR	Model 1[a]	-0.001	-0.02, 0.01	0.91	-0.01	-0.04, 0.02	0.41	0.01	-0.01, 0.03	0.50
	Model 2[c]	-0.001	-0.02, 0.02	0.90	-0.01	-0.04, 0.03	0.65	0.002	-0.02, 0.02	0.87

Abbreviations: FTP = flortaucipir; MTL = medial temporal lobe; PiB = Pittsburgh Compound-B; SUVR = standardized uptake value ratio
[a] Unadjusted
[b] Adusted for age, sex, education
[c] Adjusted for age, sex, education, global PiB SUVR

relationship of *APOE*4* and clinical AD between racialized groups may be driven by pathology.

While our effect modifier of interest was racialization, it has been postulated that African ancestry may be the more relevant moderator. Previous studies have found that more African ancestry in the *APOE* region is related to increasingly weaker associations of *APOE*4* with clinical AD (Blueetal.,2019;Naslavskyetal.,2022;Rajablietal.,2018) and Aβ deposition (Detersetal.,2021). This is potentially due to differential gene expression, such that *APOE*4* carriers with European ancestry in this region demonstrate higher expression than those with African ancestry (Griswoldetal.,2021). We mention this work on ancestry to note one hypothesized mechanism which may drive the results of our study, but we do so with caution. As stated previously, racialization is a social construct that is based on phenotypes. Ancestry, on the other hand, is the genetic origin of one's ancestors and is considered to be a separate concept from racialization (Borrelletal.,2021). However, as others have noted, racialization and ancestry are inextricably linked through historical racist practices, including the Transatlantic Slave Trade and forced procreation of individuals inhabiting Africa and the Americas by colonial settlers (Adkins-Jackson et al., 2023). Current measurements of continental ancestry and its admixture may therefore be insufficient to distinguish ancestry from the generational trauma and epigenetic change that are likely resultant of such events (Adkins--Jackson et al., 2023). Investigators who wish to further interrogate the *APOE*4*-and-AD association in African American populations should be mindful of this moving forward.

Potential mechanisms notwithstanding, there are at least two major implications to our finding that *APOE*4* was not associated with brain Aβ among African American individuals. First, ongoing treatment development efforts, particularly those that target the deleterious effects of *APOE*4*, may be less effective among African American, versus non-Hispanic white, populations. Indeed, many such treatments have proven successful in mouse models and as such, some have begun to be translated to clinical trials (Serrano-Pozo et al., 2021). However, in light of our findings, it is unclear whether this therapeutic approach would be equally beneficial to both non-Hispanic white and African American individuals. Second, other exposures outside the *APOE*4* allele likely confer the observed disproportionate risk of AD in African American populations. Importantly, these risk factors remain to be comprehensively defined and understood. One likely relevant group of exposures are social determinants of health (SDOH), which emerging evidence suggests are related to clinical and pathological AD (MajokaandSchimming,2021). Due to their unique historical position in the United States, African American individuals are more likely than those who are non-Hispanic white to experience adverse SDOH across the life course, which likely increases risk for AD (Baileyetal.,2021).

While we detected a significant relationship between *APOE*2* and Aβ in the entire sample, this association disappeared in racialized group-stratified analyses. The lack of an association between *APOE*2* and brain Aβ deposition in those racialized as African American is consistent with results from Deters et al. (2021) (Detersetal.,2021). These results are also in agreement with a previous study that found that *APOE*2* was not significantly protective against clinical AD in African American populations (Farreretal.,1997). However, the inverse relationship between *APOE*2* and Aβ burden is robust among non-Hispanic white individuals (Serrano-Pozo et al., 2021). Our inability to detect this association may have been due to lack of power; only 12% of non-Hispanic white participants in our sample were *APOE*2* carriers.

To our knowledge, this study is among the first to measure the relationship between *APOE* and brain tau deposition in African American individuals. After controlling for confounders, we did not detect associations of either *APOE*4* or *APOE*2* with tau in overall or racialized group-stratified analyses. These findings within non-Hispanic white participants are in contrast to previous studies, which have reported that both alleles are associated with tau burden (Serrano-Pozo et al., 2021). In African American participant samples, at least one study has reported significant associations between *APOE*4* and CSF-derived total- and phosphorylated-tau (Groecheletal.,2023). Another reported that relationships of *APOE*4* and both CSF-derived total- and phosphorylated-tau measurements were comparatively weaker in African American, versus non-Hispanic white, participants (Morrisetal., 2019). It is possible that we did not observe such relationships as our participants exhibited fairly low levels of tau pathology. Future work should aim to test the relationship between *APOE* genotype and tau deposition in a sample that includes more participants with AD, in whom tau pathology should be more advanced, making any potential racialized group differences more likely to be detected (JackandHoltzman,2013).

Our study has limitations. First, our African American participants were younger than those who were non-Hispanic white. We addressed this by (1) including age as a covariate in all linear models and (2) performing sensitivity analyses wherein we excluded participants aged <65. While we believe that these approaches were adequate to answer our research questions, we cannot completely rule out the possibility of residual confounding by age. Second, each of our comparator groups included participants whose genotypes were not E3/E3, which may bias results toward the null. However, given the fairly small sample size and the relatively few *APOE*4* and *APOE*2* carriers in our study, we believe that this approach is appropriate for our analysis. Investigators with larger data sets should aim to replicate our findings using only individuals with the E3/E3 genotype as the comparator. Third, the cross-sectional design of our study rendered us unable to measure racialized group differences in associations over time. Notably, one recent study found that among *APOE*4* carriers, African American individuals exhibited slower brain and CSF-derived Aβ accumulation relative to those who were non-Hispanic white (Xiongetal.,2022). However, the interaction term between *APOE* genotype and racialization was non-significant, potentially due to lack of power. Future studies with

more longitudinal outcomes from African American participants should seek to interrogate this further. Finally, our findings may be subject to selection bias. That is, individuals who enroll in neuroimaging research studies tend to be healthier than other older adults and most participants, especially those racialized as African American, were women. Further, both *APOE*2* and *APOE*4* are also associated with cardiovascular disease (Mahley,2016). Because cardiovascular disease disproportionately burdens African American populations, leading to excess risk of death in mid-life (Kyalwazietal.,2022;Tsaoetal.,2022), it is possible that by surviving into late-life, the African American participants in this sample are healthier than both African American and non-Hispanic white populations, ultimately attenuating the magnitude of our results. Studies that employ more sophisticated epidemiological methods for characterizing and correcting for these types of selection biases are necessary.

5. Conclusions

We found that *APOE*4* was associated with brain Aβ burden among non-Hispanic white, but not African American, participants, which is consistent with previous reports of a comparatively attenuated association between *APOE*4* and clinical AD in African American individuals. In light of ongoing treatment development efforts, including some that target *APOE*, it is of great public health importance to identify AD drivers and their mechanisms in African American populations; doing so is necessary to effectively reduce AD incidence and prevalence both overall and with respect to racialized group disparities.

CRediT authorship contribution statement

Ann D. Cohen: Writing – review & editing, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Data curation, Conceptualization. **Ashley V. Hill:** Writing – review & editing, Supervision, Methodology, Conceptualization. **Alexandria C. Reese:** Writing – review & editing, Methodology, Formal analysis, Data curation. **Steven E. Reis:** Writing – review & editing, Resources, Project administration, Methodology, Investigation, Funding acquisition, Conceptualization. **James T. Becker:** Writing – review & editing, Resources, Project administration, Methodology, Investigation, Funding acquisition, Data curation, Conceptualization. **Beth E. Snitz:** Writing – review & editing, Supervision, Resources, Project administration, Methodology, Funding acquisition, Data curation, Conceptualization. **Oscar L. Lopez:** Writing – review & editing, Supervision, Resources, Project administration, Investigation, Funding acquisition, Data curation, Conceptualization. **Sarah K Royse:** Writing – review & editing, Writing – original draft, Visualization, Methodology, Investigation, Formal analysis, Conceptualization. **Brian J. Lopresti:** Writing – review & editing, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Data curation, Conceptualization. **Victor L. Villemagne:** Writing – review & editing, Supervision, Project administration, Methodology, Investigation, Funding acquisition. **Marnie Bertolet:** Writing – review & editing, Visualization, Supervision, Investigation, Formal analysis, Conceptualization. **Anum Saeed:** Writing – review & editing, Investigation, Formal analysis. **Rebecca E. Roush:** Writing – review & editing, Resources, Project administration, Methodology, Data curation, Conceptualization. **M. Ilyas Kamboh:** Writing – review & editing, Supervision, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation.

Declaration of Competing Interest

None.

Acknowledgements

Funding: This work was supported by the National Institute on Aging (R01-AG072641, R01-AG052446 and R01-AG064877). The funding source had no involvement in the design, collection, analysis, interpretation, writing, or submission of the current study.

Verification

Apolipoprotein E and Alzheimer's disease pathology in African American older adults

We have carefully adhered to the submission guidelines and have included all necessary materials, such as the manuscript, figures, and supplementary data. We confirm that all authors approved the manuscript for submission and have no conflicts of interest. In addition, we confirm that the manuscript has not been published or submitted for publication elsewhere.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.neurobiolaging.2024.03.005.

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