ARTICLE

Amyloid PET Imaging in Self-Identified Non-Hispanic Black Participants of the Anti-Amyloid in Asymptomatic Alzheimer's Disease (A4) Study

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Abstract

Objective

To examine whether amyloid PET in cognitively normal (CN) individuals screened for the Anti-Amyloid in Asymptomatic Alzheimer's Disease (A4) study differed across self-identified non-Hispanic White and Black (NHW and NHB) groups.

Methods

We examined 3,689 NHW and 144 NHB participants who passed initial screening for the A4 study and underwent amyloid PET. The effect of race on amyloid PET was examined using logistic (dichotomous groups) and linear (continuous values) regression controlling for age, sex, and number of *APOE* ε4 and *APOE* ε2 alleles. Associations between amyloid and genetically determined ancestry (reflecting African, South Asian, East Asian, American, and European populations) were tested within the NHB group. Potential interactions with *APOE* were assessed.

Results

NHB participants had lower rates of amyloid positivity and lower continuous amyloid levels compared to NHW participants. This race effect on amyloid was strongest in the *APOE* ε4 group. Within NHB participants, those with a lower percentage of African ancestry had higher amyloid. A greater proportion of NHB participants did not pass initial screening compared to NHW participants, suggesting potential sources of bias related to race in the A4 PET data.

Conclusion

Reduced amyloid was observed in self-identified NHB participants who passed initial eligibility criteria for the A4 study. This work stresses the importance of investigating AD biomarkers in ancestrally diverse samples as well as the need for careful consideration regarding study eligibility criteria in AD prevention trials.

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Glossary

A4 = Anti-Amyloid in Asymptomatic Alzheimer's Disease; **AD** = Alzheimer disease; **CDR** = Clinical Dementia Rating; **CN** = clinically normal; **LONI** = Laboratory of NeuroImaging; **MCI** = mild cognitive impairment; **MMSE** = Mini-Mental State Examination; **NHB** = non-Hispanic Black; **NHW** = non-Hispanic White; **SNP** = single nucleotide polymorphism; **SUVR** = standardized uptake value ratio.

The ability to measure Alzheimer disease (AD) biomarker abnormalities among older clinically normal (CN) individuals has accelerated attempts to identify at-risk individuals and implement clinical trials that focus on prevention.[1] Large cohort studies consistently report that amyloid+ CN individuals are at elevated risk of cognitive decline[2] and dementia.[3,4] Studies have shown that approximately 30% of CN individuals in their 70s are amyloid-positive,[5] highlighting that a large proportion of CN individuals may be good candidates for intervention.

Despite progress understanding the impact of AD pathology among CN individuals, cohort-based studies largely comprise non-Hispanic White (NHW) individuals and little is known regarding how AD biomarker findings translate to other populations. Greater representation of minority populations is needed, especially considering that self-identified non-Hispanic Black (NHB) individuals are at greater risk of clinical AD.[6,7] The mechanisms underlying this heightened risk of clinical AD in NHB people remain unknown, but may be related to several risk factors that differ between NHW and NHB people (genetics, vascular disease, social determinants of health).[8–11] Interestingly, the effect of *APOE4*, the most established genetic risk factor for AD[12,13] as well as a robust predictor of abnormal amyloid in the preclinical stage of the disease,[14,15] has been shown to have a weaker effect on AD risk[13,16–19] and cognitive decline[8] in NHB individuals relative to NHW individuals. Thus, despite an overall greater risk of dementia in NHB individuals, it is possible that established risk factors of AD in NHW individuals (such as *APOE4*) do not have a similar impact in non-European populations and require further investigation.

To this end, we examined the effect of NHW and NHB race on amyloid in CN individuals who were screened for the Anti-Amyloid in Asymptomatic Alzheimer's Disease (A4) study[20] and whether these effects were influenced by *APOE* or African ancestry.

Methods

Participants

The A4 study is a phase III clinical trial that enrolled CN older adults with evidence of brain amyloid as measured by ^{18}F-florbetapir PET.[20] The overall goal of this clinical trial is to understand whether intervention with an anti–amyloid antibody treatment (solanezumab) in amyloid+ CN individuals will slow cognitive decline.[21] Participants age 65–85 were assessed to be CN and had scores of 25–30 on the Mini-Mental State Examination (MMSE), 0 on the global Clinical Dementia Rating (CDR) scale, and 6–18 on the Logical Memory II test. In addition, enrollment into the clinical trial (into either the treatment or placebo arm) required amyloid positivity using a hybrid qualitative/quantitative algorithm. Thus, a number of individuals were screened for the A4 clinical trial to determine eligibility for enrollment into treatment or placebo arms. The first round of screening was performed on 6,763 individuals and involved neuropsychological testing to determine clinical status and medical assessment to exclude individuals with comorbid conditions,[20] with 4,371 passing all initial screening and completing an amyloid PET scan. After the amyloid PET scan, amyloid+ CN individuals were then randomized into treatment or placebo arms. The data presented herein incorporate all available screening data for individuals who self-identify as either NHW or NHB, enabling the examination of the full range of amyloid PET values among CN individuals as well as potential selection biases introduced after the initial screening based on neuropsychological testing and medical assessment that precluded individuals from obtaining an amyloid PET scan (data available from Dryad, figure S1, doi.org/10.5061/dryad.7h44j0zsh).

Race self-identification was collected across the following categories: American Indian/Alaskan Native, Asian, Native Hawaiian/Other Pacific Islander, Black/African American, White, or Unknown. For this study, we examined all participants who self-identified as NHB or NHW. Participants who identified as more than one category were excluded (resulting in 325 NHB and 5,753 NHW individuals). Those who continued to meet study criteria after completing all initial screening visits then underwent amyloid PET (153 NHB and 3,818 NHW). We excluded individuals missing *APOE* or who had the *APOE2/4* genotype, resulting in a final sample of 144 NHB and 3,689 NHW participants with amyloid PET data (data available from Dryad, figure S1, doi.org/10.5061/dryad.7h44j0zsh).

Amyloid PET

Amyloid PET data were acquired 50–70 minutes post-injection of 10 mCi of ^{18}F-florbetapir. We examined mean global cortical standardized uptake value ratio (SUVR, whole cerebellar reference region). We used a data-driven gaussian mixture modeling approach[22] to classify participants into amyloid groups using a cutoff of ≥1.17 (because amyloid group assignment using the A4 criteria is not publicly available[20]). We examined global amyloid levels continuously.

Genotyping and Ancestry Determination

All participants were genotyped on the Illumina Global Screening Array at Columbia University. No participants had autosome missingness exceeding 5%. Single nucleotide polymorphisms (SNPs) reporting a call rate >95% and a minor allele frequency >1% were considered for ancestry determination. Approximately 18,000 ancestry informative markers from the 1000 Genomes Consortium were used to determine individual ancestry using SNPweights v2.1.[23,24] This resulted in percentages for each participant that reflect ancestry across 5 superpopulations (Africans, Europeans, Americans, South Asians, and East Asians) with these 5 percentages summing to 100% for each participant. Twenty-eight NHB participants were missing genotyping data, resulting in a subset of 116 NHB participants for the analysis with ancestry. A total of 2,915 of the 3,689 NHW participants had genotyping data available for ancestry calculations.

Lifestyle Risk Factors and Medical Conditions

Lifestyle factors and medical conditions were available for the majority of individuals who received an amyloid PET scan, as well as a smaller subset of individuals who screen failed (data available from Dryad, figure S1 and table S1, doi.org/10.5061/dryad.7h44j0zsh). Notably, these data are missing for the majority of individuals who screen failed due to low neuropsychological testing scores (data available from Dryad, figure S1, doi.org/10.5061/dryad.7h44j0zsh). Thus, examination of these variables was restricted to the subset of individuals who met initial study criteria (neuropsychological and medical assessment) and completed the amyloid PET scan.

Statistical Analysis

Analyses were performed using R v3.4.1. Differences in demographics across race were examined with an analysis of variance for continuous variables and Fisher exact tests for categorical variables. The effect of *APOE* in all analyses was examined by modeling the number of *APOE4* and *APOE2* alleles (0, 1, or 2). Given demographic differences across race, propensity score matching was used for causal inference with racial group (NHB vs NHW) on age, sex, and education using the nearest neighbor matching method in the MatchIt package in R v4.9-3[25] (using a ratio of 2:1 for NHW to NHB). This method calculates a propensity score (i.e., the probability that a NHW participant will have the same characteristics as a NHB participant, thus reducing the effects of confounding variables) estimated using logistic regression to create the matched NHW group.

Raw continuous amyloid SUVR was examined using linear models, whereas the dichotomous amyloid positivity group was examined with logistic regression. All models investigated the effect of self-identified race (NHB vs NHW), number of *APOE2* and *APOE4* alleles, age, and sex on amyloid outcomes. The interaction between race and *APOE4* and *APOE2* was also examined in separate regression models. To determine the impact of African ancestry on amyloid within the NHB group, we investigated the association between percentage of African ancestry and amyloid with linear regression. Post hoc contrasts were run to further demonstrate potential interactions between race and *APOE* genotypes (i.e., to demonstrate the effect of race across genotype, we contrasted NHB ε4+ with NHW ε4+, NHB ε3/3 with NHW ε3/3, and NHB ε2+ with NHW ε2+; to further understand the effect of *APOE2* within race, we contrasted NHB ε2+ with NHB ε3/3, and NHW ε2+ with NHW ε3/3). Finally, additional sensitivity analyses were run to examine potential effects between amyloid and lifestyle as well as self-reported medical conditions that differed by race (these lifestyle and medical conditions were included in models predicting amyloid to determine whether effects of race on amyloid remained significant).

Standard Protocol Approvals, Registrations, and Patient Consents

All analyses were performed on data collected as part of the A4 study (NCT02008357). This study was approved by the institutional review boards of all of the participating institutions. Informed written consent was obtained from all participants at each site.

Data Availability

Data used in this article are available for download from the Laboratory of NeuroImaging (LONI; loni.usc.edu). All variables were extracted from spreadsheets posted on LONI, with the exception of ancestry measures, which were processed from genotyping data posted on LONI.

Results

Participant Characteristics

The full NHW group had higher education and more men compared to the NHB group (table 1). The distribution of *APOE* genotype by race was also significantly different (χ^2 = 19.69, $p < 0.0001$), such that there was a higher proportion of the *APOE2*/3 genotype in the NHB group (21.5% in NHB participants compared to 10.3% in NHW participants). Given demographic differences, we in addition examined patterns of amyloid PET in a demographically matched group of 288 NHW individuals (table 1).

Effect of Amyloid Across Race

NHW participants were more likely to be amyloid+ relative to NHB participants (figure 1A and table 2), as well as to have greater continuous levels of amyloid (figure 1B and table 2). NHW participants were ~2 times more likely to be amyloid-positive than NHB participants, and had ~0.05 SUVR units more on average than NHB participants. Similar results were observed when examining regional rather than global amyloid (data available from Dryad, table S2, doi.org/10.5061/dryad.7h44j0zsh) and after controlling for MMSE (data available from Dryad, table S3, doi.org/10.5061/dryad.7h44j0zsh).

Race Effect Strongest in *APOE4* Carriers

Linear models predicting continuous amyloid levels were repeated with an *APOE4* allele number × race interaction

term, as well as an *APOE2* allele number × race term (in separate models). The interaction between *APOE4* and race was significant ($p = 0.01$), whereas the *APOE2* and race term was near significant ($p = 0.06$). Although *APOE3/4* and *APOE4/4* genotypes were associated with higher amyloid across both races (figure 1), the difference between NHB and NHW groups on continuous amyloid was greatest within the *APOE4+* group (*APOE3/4* and *APOE4/4* combined). This was confirmed with a significant post hoc contrast between NHB participants and NHW *APOE4+* groups, revealing that *APOE4+* NHB participants had 0.094 SUVR units less than *APOE4+* NHW participants (table 3). There was a marginal difference, although not significant, between NHB and NHW among the *APOE3/3* genotype (0.034 SUVR less in *APOE3/3* NHB participants), while no significant race effect was found among the *APOE2* group (*APOE2/2* and *APOE2/3* combined, table 3).

Interestingly, *APOE2* did not appear to be protective within NHB participants (figure 1), such that levels of amyloid were not significantly different between *APOE2/3* NHB participants compared to *APOE3/3* NHB participants (table 3). In fact, values were qualitatively higher in *APOE2/3* NHB participants compared to *APOE3/3* NHB participants, though this increase was not significant. As expected, the *APOE2/3* group had significantly lower levels of amyloid than the *APOE3/3* group within NHW participants (table 3).

Ancestry Estimation and Effect on Amyloid

Genome-wide SNP array data to compute continuous ancestry was available for 2,915/3,689 NHW participants and 116/144 NHB participants. This subset analysis revealed that those who self-identified as NHW largely had European ancestry above 89% (mean 91%, SD 0.07; figure 2A) whereas those who self-identified as NHB had a wide range of African ancestry that was largely admixed with European ancestry (mean 0.63, SD 0.14; figure 2B). There were 2 NHB outliers with African ancestry at 2.1% and 4.2% that were excluded from further analysis (resulting in 114 NHB for this analysis).

Within NHB, higher African ancestry was associated with less amyloid and this effect was independent of number of *APOE4* alleles (% African ancestry: $\beta = -0.239$, SE = 0.103, $p = 0.023$; *APOE4* allele count: $\beta = 0.083$, SE = 0.021, $p = 0.0002$) (figure 3). The interaction between ancestry and *APOE4* ($p = 0.99$) or *APOE2* allele count ($p = 0.45$) was not significant.

Higher Exclusion Rate in NHB

In order to undergo amyloid PET for the A4 study, participants first underwent an initial screening visit to determine eligibility based on having a clinical diagnosis of CN, CDR = 0, within cutoff values for the MMSE (25 or above), Logical Memory delayed recall (between 18 and 6; thus both low and high scoring participants were excluded based on this test), as well as lack of comorbid health conditions. Of all the participants who underwent initial screening (data available from Dryad, figure S1, doi.org/10.5061/dryad.7h44j0zsh), NHB participants were more likely to screen fail at this stage relative to NHW participants (53% vs 33%; $\chi^2 = 54.9$, $df = 1$, $p < 0.0001$). We then compared the proportions across 3 categories of screen failure criteria: (1) exclusion due to low testing scores, (2) high Logical Memory scores, or (3) other reasons (data available from Dryad, figure S1, doi.org/10.5061/dryad.7h44j0zsh). Among those who screen failed during this initial stage, the reasons for exclusion across these 3 categories significantly differed by race ($\chi^2 = 31.5$, $df = 2$, $p < 0.0001$). Specifically, NHB participants were more likely to screen fail due to low testing scores compared to NHW participants (51.1% vs 34.6%) and less likely to screen fail due to high Logical Memory scores (1.1% vs 10.5%). Exclusion for other reasons was similar across race (47.7% vs 49.0%). Other possible exclusion criteria such as self-reported medical conditions were not collected on the majority of screen fail participants, precluding further assessment of whether ineligibility due to medical reasons differed by race during initial screening (data available from Dryad, figure S1, doi.org/10.5061/dryad.7h44j0zsh).

Impact of Lifestyle Factors and Self-Reported Medical Conditions on Amyloid

Among individuals who underwent amyloid PET, we examined whether there were differences between lifestyle factors and/or self-reported medical conditions by race (data available from Dryad, table S1, figure S2, doi.org/10.5061/dryad.7h44j0zsh). Overall, NHB participants had lower self-reported alcohol consumption (data available from Dryad, figure S2A, doi.org/10.5061/dryad.7h44j0zsh), greater cardiovascular risk factors (higher blood pressure, higher body mass index, and higher self-reported cardiovascular conditions) (data available from Dryad, figure S2B–E, doi.org/10.5061/dryad.7h44j0zsh), and lower self-report of multiple medical conditions (specifically, psychiatric, dermatologic–connective tissue, gastrointestinal, and head, eyes, nose, and throat) (data available from Dryad; figure S2F–I, doi.org/10.5061/dryad.7h44j0zsh). Further, summation across total self-reported medical conditions revealed that NHW participants had a greater total burden of self-reported conditions than NHB participants (data available from Dryad, figure S2J–K, doi.org/10.5061/dryad.7h44j0zsh).

Given these differences in cardiovascular risk factors (higher in NHB) and self-reported medical conditions (lower in NHB), we performed additional analyses to explore whether these factors may be associated with amyloid. There were no significant associations between these vascular and medical factors with amyloid, and the effect of race on amyloid remained significant (data available from Dryad, table S4–5, doi.org/10.5061/dryad.7h44j0zsh). Finally, we explored whether the total number of endorsed medical conditions was associated with amyloid, given that the total burden was less in NHB participants (and may account for reduced amyloid in NHB participants). Interestingly, we did find that a higher number of medical conditions was associated with greater amyloid levels, but the effect of race on amyloid remained

significant (data available from Dryad, table S6, doi.org/10.5061/dryad.7h44j0zsh).

Discussion

In a large sample of older CN participants screened for a secondary prevention trial, we found that self-identified NHB individuals had reduced levels of amyloid measured with PET compared to self-identified NHW individuals, an effect that was strongest within *APOE4* carriers. Within the NHB group, higher levels of continuous African ancestry were associated with lower amyloid. Finally, rates of screen failure were higher in NHB participants, and this was at least partially related to eligibility criteria for neuropsychological testing scores, suggesting potential selection bias (more NHB participants were excluded from receiving a PET scan). Overall, our results highlight the importance of understanding race-specific factors and selection bias in studies of preclinical AD.

Our main result was that NHB CN participants had less amyloid as measured with PET than NHW CN participants. This effect was consistent regardless of whether amyloid was treated as a dichotomous or continuous variable, as well as whether the entire sample of NHW participants was used or a demographically matched NHW group. This effect also remained significant after inclusion of potential confounds related to vascular risk factors and medical conditions. Given that abnormal levels of amyloid in CN are associated with future memory decline and progression to clinical impairment,[26] our finding of reduced amyloid in NHB suggests other risk factors may contribute to AD dementia in NHB. These other risk factors in NHB may include comorbid vascular risk factors, TDP43 pathology, and other age-related pathologic accumulations that are known to influence the clinical expression of dementia.[9,27] Along these lines, we found evidence of greater vascular risk factors in the NHB sample, consistent with an increased role of vascular disease in NHB participants. Further, social determinants of health, including increased exposure to stressful events throughout the lifespan, is increased in NHB participants and associated with cognitive decline in aging.[28] However, given the severe paucity of AD biomarker studies specifically within NHB CN samples, it is simply unknown whether PET measures of AD pathology hold a similar predictive value regarding future progression to dementia in NHB compared to NHW CN cohorts. This represents a critical gap in knowledge, especially as the field of AD research shifts towards preventative strategies in hopes of targeting CN individuals with initial evidence of AD pathology.

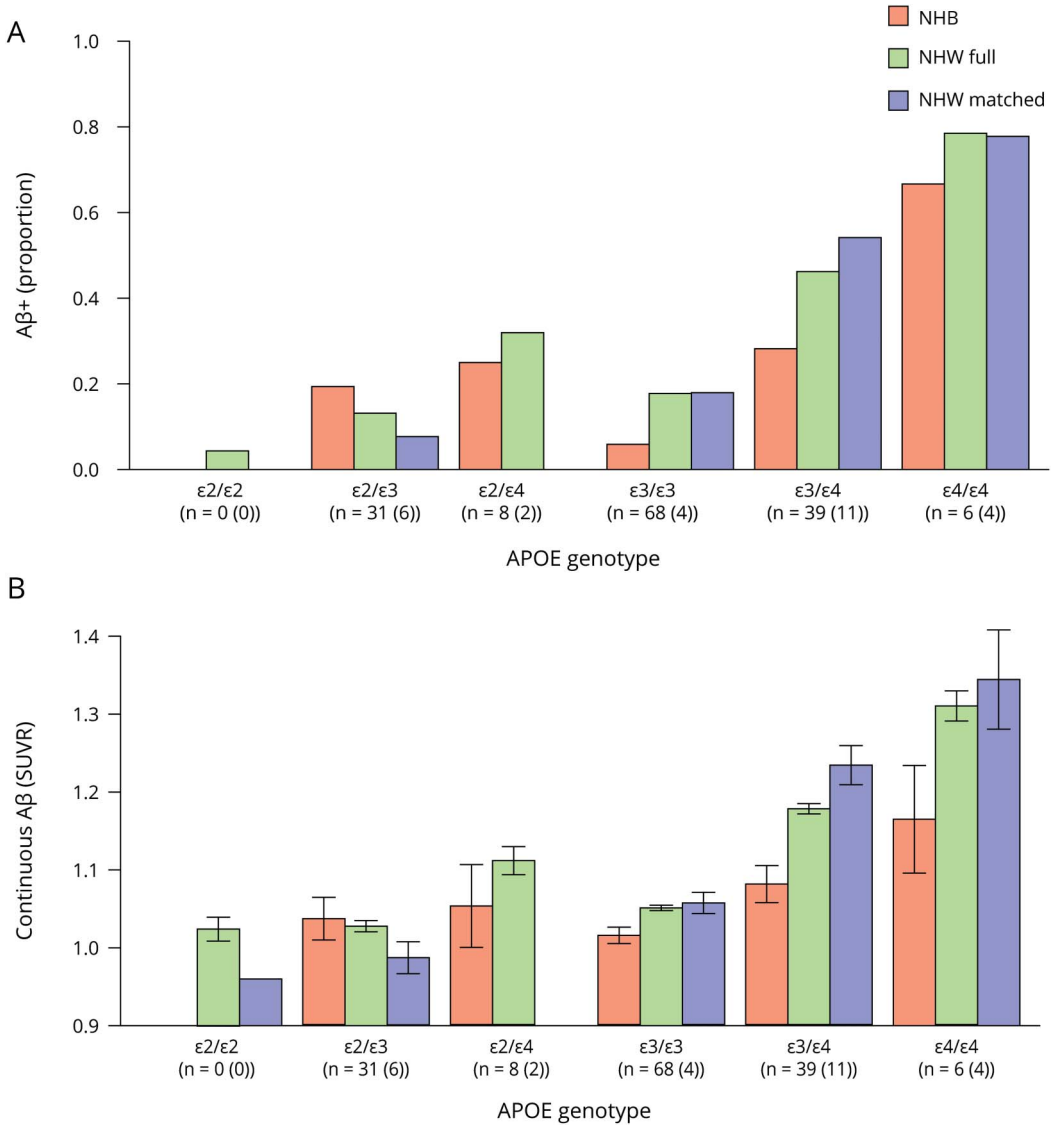
To our knowledge, one study has compared amyloid PET across NHB and NHW cohorts within a CN sample from the Atherosclerosis Risk in Communities (ARIC) study.[29] In contrast to our study, Gottesman et al.[29] found that NHB individuals had greater amyloid positivity and continuous levels of amyloid than NHW individuals in a sample of CN combined with patients with mild cognitive impairment (MCI). When divided by diagnosis, the effect remained significant within their sample of 37 NHB individuals with MCI compared to 52 NHW individuals with MCI, such that the NHB MCI group had elevated amyloid compared to the NHW MCI group. However, when examining the group of 104 CN NHB individuals compared to 136 CN NHW individuals, there was no significant difference across race. A few recent studies have examined CSF levels of amyloid and tau proteins across race, but these have focused on the spectrum

Table 1 Demographics

	NHB	NHW	NHW-m
N	144	3,689	288
Age, y	70.77 (4.87)	71.24 (4.67)	70.72 (4.44)
Education, y	16.10 (2.76)	16.65 (2.83)	16.27 (2.63)
MMSE	28.54 (1.34)	28.84 (1.19)	28.99 (1.11)
% Female	105 (72.9)	2,199 (59.6)	215 (74.7)
Amyloid SUVR	1.04 (0.13)	1.10 (0.19)	1.12 (0.22)
% Amyloid+	25 (17.4)	1,030 (27.9)	89 (30.9)
% *APOE*[a]	—	—	—
APOE2/3, APOE2/2	31 (21.5)	403 (10.9)	27 (9.4)
APOE3/3	68 (47.2)	2,036 (55.2)	156 (54.2)
APOE3/4, APOE4/4	45 (31.2)	1,250 (33.9)	40.5

Abbreviations: MMSE = Mini-Mental State Examination; NHB = non-Hispanic Black; NHW = non-Hispanic White; SUVR = standardized uptake value ratio. Mean (SD) listed for continuous values. NHW-m matched to NHB on age, sex, and education using 2:1 propensity matching to the NHB group.
[a] *APOE2/4* excluded.

Figure 1 Proportion of Amyloid Positivity and Continuous Amyloid Standardized Uptake Value Ratios (SUVRs) Across *APOE* Genotypes for the Non-Hispanic Black (NHB) Group



(A) Amyloid positivity. (B) Continuous amyloid SUVRs. The ε2/4 group is shown in this plot but was excluded from statistical analyses. Sample sizes for each NHB genotype are listed, with the subset of individuals classified as amyloid+ in parentheses. Bars are missing for NHB *APOE2*/2 because there were no NHB individuals with this genotype. Likewise, bars are missing for the non-Hispanic White (NHW) matched *APOE2*/4 because there were no NHW matched individuals with this genotype. Given that there was just one ε2/2 participant in the NHW matched group, there is no error bar drawn.

of AD (CN, MCI, and AD dementia) and have not specifically examined the pattern of these AD biomarkers specifically within the CN group.[30–32] These studies generally report no difference in CSF amyloid levels by race, but have converged to reveal less CSF tau in NHB individuals compared to NHW individuals. It is possible that differences in CSF vs PET measures of amyloid may be relevant for understanding these different patterns across studies (e.g., soluble vs fibrillar amyloid), and to our knowledge have not been fully investigated with respect to race. Taken together, these studies highlight that race-specific differences may exist in profiles of AD biomarkers; however, the inconsistencies underscore the importance of examining these effects in larger cohorts, and the need to explore factors that may drive these patterns, such as study selection criteria, disease stage, and biomarker measurement differences.

The *APOE* genotype is the strongest genetic risk factor for late-onset AD and has consistently been associated with elevated AD risk in NHW populations. *APOE4* has been related to abnormal accumulation of the β-amyloid protein, as well as to influence the rate of cognitive decline in early stages of dementia.[14,15,33–35] Interestingly, although the *APOE4* allele has been shown to have a higher frequency in NHB relative to NHW individuals, this genetic risk variant has a weaker effect on clinical AD dementia risk[13,16–18,36] and cognitive decline[8]

Table 2 Regression Models Summarizing Effect of Race on Amyloid

	Full NHW sample vs NHB	Matched NHW sample vs NHB
Logistic regression predicting amyloid group, OR (95% CI); *p* value		
Race (NHW v NHB)	1.94 (1.22–3.19); 0.007	2.33 (1.35–4.13); 0.003
Sex (female v male)	1.18 (1–1.39); 0.044	1.37 (0.78–2.47); 0.284
Age, y	1.11 (1.09–1.12); <0.0001	1.09 (1.04–1.15); 0.0007
***APOE2* (0, 1, 2)**	0.69 (0.51–0.91); 0.012	1.12 (0.45–2.49); 0.791
***APOE4* (0, 1, 2)**	4.74 (4.09–5.5); <0.0001	5.66 (3.62–9.13); <0.0001
Linear regression predicting continuous amyloid SUVR, β estimate (standard error); *p* value		
Race (NHW v NHB)	0.046 (0.015); 0.002	0.066 (0.018); 0.0003
Sex (female v male)	0.015 (0.006); 0.008	0.036 (0.019); <0.0001
Age, y	0.007 (0.001); <0.0001	0.005 (0.002); 0.006
***APOE2* (0, 1, 2)**	−0.020 (0.008); 0.016	−0.016 (0.026); 0.523
***APOE4* (0, 1, 2)**	0.133 (0.005); <0.0001	0.137 (0.016); <0.0001

Abbreviations: NHB = non-Hispanic Black; NHW = non-Hispanic White; SUVR = standardized uptake value ratio.

in NHB relative to NHW individuals. Our analysis revealed that the reduced effect of amyloid in NHB individuals was strongest among *APOE4* carriers. This suggests that the lower effect of *APOE4* on AD risk in NHB individuals may be mediated by pathways related to amyloid accumulation. Interestingly, we also found that *APOE2* had a reduced protective effect in NHB individuals, such that amyloid levels in the *APOE2* group were nonsignificantly higher than the *APOE3* group within NHB individuals (as opposed to the expected reduction in amyloid levels in *APOE2* compared to *APOE3* in NHW individuals). Our finding is consistent with work by Farrer et al.[13] that showed a lack of protective effect of *APOE2* on risk of clinical AD dementia in NHB individuals. Other genetic risk factors, such as *ABCA7*[16] and *RBFOX1*,[37] have been identified as having a larger effect on AD phenotypes in NHB compared to NHW individuals. Overall, our findings are consistent with a broader literature suggesting that genetic risk factors of AD have varying effects across race.

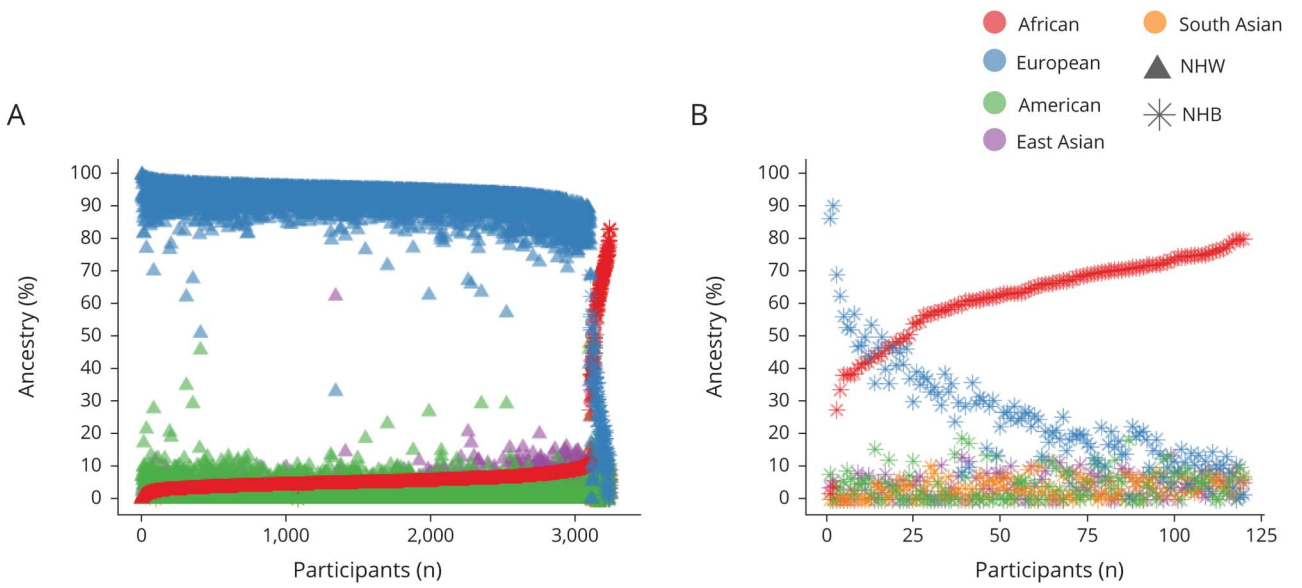
Although we identified an association between higher African ancestry and reduced levels of amyloid, it is important to emphasize that race is a social construct that is typically based on visible characteristics and predominantly used in the United States.[38] The current dataset is ill-equipped to examine how the social construct of race influences risk of AD and amyloid burden. Recent studies suggest that coming from a disadvantaged neighborhood is associated with increased odds for postmortem AD neuropathology[39] and having more life stressors has been associated with cognitive decline in NHB individuals.[28] It is becoming increasingly recognized that other pervasive factors are important to consider when examining race and dementia risk. Nevertheless, examination of genetic ancestry is an approach that allows quantification of genetic loci that have specific allele frequencies based on geographical origin.[40] Previous studies have shown that NHB individuals in the United States have admixed genetic African and European ancestry.[41,42] This is in stark contrast to those Americans of European descent, who have very little genetic contribution from non-European ancestral backgrounds. Thus, the continuum of African ancestry may be relevant when understanding differences in AD risk factors in NHB individuals, given that multiple genetic factors related to AD vary across race.[13,16–19,36] Along these lines, Nigerian Yoruban individuals have been shown to have a lower incidence rate of AD dementia than NHB individuals who

Table 3 Post Hoc Contrasts Showing Effect of Race on Amyloid SUVR for *APOE4* and *APOE3/3* Genotypes as well as Effect of *APOE2* Within Race

Effects of race by genotype	β estimate (standard error); *p* value
NHB ε4+ vs NHW ε4+	−0.094 (0.033); 0.004
NHB ε3/3 vs NHW ε3/3	−0.034 (0.019); 0.070
NHB ε2+ vs NHW ε2+	0.009 (0.026); 0.723
Effect of ε2 within race	
NHB ε2+ vs NHB ε3/3	0.024 (0.024); 0.315
NHW ε2+ vs NHW ε3/3	−0.025 (0.008); 0.002

Abbreviations: NHB = non-Hispanic Black; NHW = non-Hispanic White; SUVR = standardized uptake value ratio.
All contrasts were performed with the full NHW group, controlling for age and sex.

Figure 2 Genetic Ancestry Measures for All Anti-Amyloid in Asymptomatic Alzheimer's Disease (A4) Participants and Non-Hispanic Black (NHB) Individuals

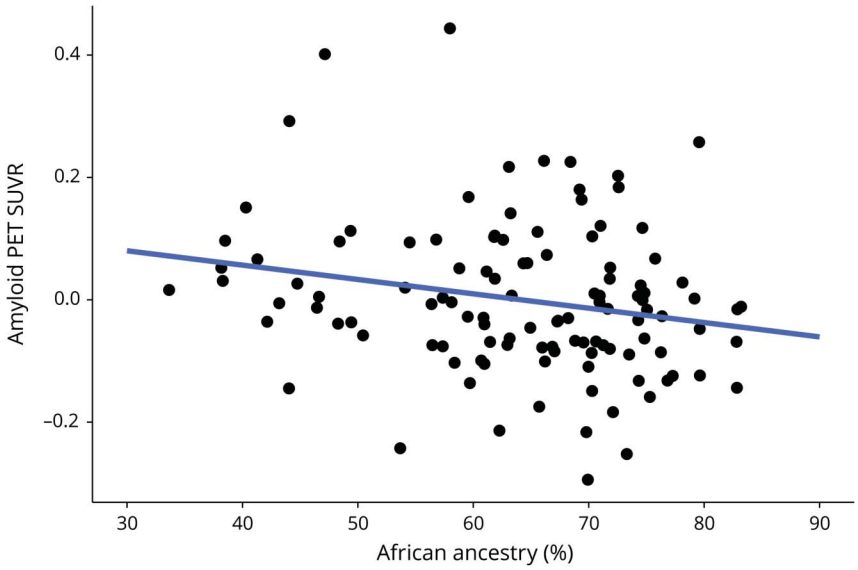


(A) All A4 participants. (B) NHB individuals. Data are ranked by African ancestry, with each row representing the ancestry composition of a single individual participant. The non-Hispanic White (NHW) group showed little variance beyond the European ancestry (A), whereas examination of the NHB group revealed a continuum of African ancestry (B).

live in the United States.[43,44] Our results are consistent with this, and suggest that within the NHB group prominently from the United States, higher levels of African ancestry were associated with lower levels of amyloid. Thus, it is possible that genetic differences, such as ancestral origin of *APOE4*,[45] captured by ancestry measures, may influence amyloid accumulation, and in turn are protective against AD dementia. It is also possible that discrepant findings across studies of NHB individuals on AD risk more broadly reflect different amounts of African ancestry between study populations.

In addition to finding overall lower levels of amyloid PET in NHB individuals, we also found significant differences in

Figure 3 Plot of Continuous Amyloid PET Standardized Uptake Value Ratios (SUVRs) Compared to Percent African Ancestry, With Amyloid Residualized by Age, Sex, Number of *APOE4* Alleles, and Number of *APOE2* Alleles



screen failure rates by race that precluded more NHB individuals from receiving an amyloid PET scan. Specifically, NHB individuals were more likely to screen fail than NHW individuals before the stage of receiving an amyloid PET scan, and one reason for this exclusion was due to worse scores during neuropsychological testing (NHB individuals were more likely to perform under the predefined cutoffs for these tests). NHB individuals often perform lower at baseline on many standardized neuropsychological tests used in clinical trials of AD, but this intercept effect does not translate to greater decline over time.[46] The lower performance on neuropsychological tests is thought to represent socioeconomic and demographic issues such as limited educational opportunities.[47] This pattern implies that baseline neuropsychological tests may not accurately capture true cognitive performance in NHB individuals, and instead reflect biases in these tests and inadequate norming procedures.[48] Such a selection bias related to neuropsychological screening within the A4 study could drive the apparent reductions in amyloid PET in NHB compared to NHW individuals by excluding NHB participants who are more likely to be amyloid+ and creating a more "resilient" NHB group that was included in the PET dataset. Consistent with this interpretation, we did find that among those who underwent a PET scan, NHB individuals had fewer self-reported medical conditions than NHW individuals. Interestingly, we found that a greater burden of self-reported medical conditions was related to higher levels of amyloid. However, this effect did not account for the association between race and amyloid (both aggregated medical conditions and race significantly predicted amyloid levels independently). Nevertheless, we were restricted to self-reported medical conditions, so it remains possible that selection bias present in the A4 dataset may have resulted in a more resilient and healthier NHB group relative to NHW individuals who underwent PET, and that factors associated with this resilience are directly related to reduced amyloid levels. We were unable to assess whether there was a higher degree of medical conditions in the screen failure group because these variables were not collected across all excluded participants (in particular, the majority of individuals who screen failed based on cognitive testing scores did not have these data available). Along these lines, factors related to survival bias have been shown to influence race differences in stroke,[49] and it is possible that similar confounds are present in the A4 screening dataset. However, even if the observed effect of reduced amyloid in NHB individuals is driven by a selection bias, the pattern of results remains highly relevant for clinical trial design and recruitment. As a field, it is critical to be cognizant of the biases introduced in the recruitment of individuals into clinical trials and the degree to which resulting cohorts accurately reflect our target populations.

In addition to differential rates of screen failure by race during the initial screening phase, there are also known biases related to general participation in clinical trials, and it is possible that these biases systematically vary by race. For instance, recent work from the cancer field has shown specific bias in the actions of health care professionals when recruiting minority participants into clinical trials (including negative perceptions held by health care professionals related to minorities as unsuitable participants, ultimately leading to reduced recruitment of minority participants).[50] Implicit biases present during the recruitment stages may further contribute to a selection bias within the NHB group that does enroll. Furthermore, older CN individuals who volunteer for AD prevention trials likely represent a biased group of educated individuals who are aware of these opportunities and have greater health care access. It is unclear how these motivations vary by race and result in different degrees of selection bias. Overall, as the field aims to reduce health disparities in AD, it will be critical to address confounds that influence the recruitment of NHB individuals into AD clinical trials.

Our study has limitations. First, the current study lacks data on social health determinants such as socioeconomic status and lifetime stress exposures. Likewise, our examination of vascular factors was limited to a small list of variables, and there are undoubtedly additional vascular measures that may affect amyloid in CN cohorts. Next, longitudinal measures of clinical progression would allow us to estimate whether the effect of amyloid on future clinical progression varies by race. Finally, replication of our findings in a larger CN NHB population is warranted, especially given the mixed findings across preexisting literature.[29]

Taken together, we found that CN NHB individuals who were screened for an AD prevention trial had lower levels of fibrillar amyloid as measured with PET compared to CN NHW individuals. Higher levels of African ancestry within the NHB group were associated with reduced amyloid levels, which may partially explain the group level effect of lower levels of amyloid in NHB individuals. Finally, significant differences in eligibility and screen failure rates existed across race that may influence our findings. Overall, the presence of a race effect on a central AD phenotype (amyloid PET) highlights the need to understand disease mechanisms and potential selection bias in diverse populations.

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Appendix Authors

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Valerio Napolioni, PhD	Stanford University, CA	Data analysis, revised manuscript, data interpretation
Reisa A. Sperling, MD	Brigham and Women's Hospital, Boston, MA	Acquisition of data, revised manuscript
Michael D. Greicius, MD	Stanford University, CA	Data interpretation, manuscript revision, interpretation of data
Richard Mayeux, MD	Columbia University Medical Center, New York	Data interpretation, revised manuscript
Timothy Hohman, PhD	Vanderbilt Genetics Institute, Nashville, TN	Data interpretation, revised manuscript
Elizabeth C. Mormino, PhD	Stanford University, CA	Drafted manuscript, data interpretation, data analysis, revised manuscript

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