Title

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Journal

Alzheimers & Dementia: The Journal of the Alzheimers Association, 20(6)

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Publication Date

2024-06-01

DOI

10.1002/alz.13803

Peer reviewed

Received: 26 December 2023 | Revised: 27 February 2024 | Accepted: 28 February 2024

DOI: 10.1002/alz.13803

Alzheimer's & Dementia®
THE JOURNAL OF THE ALZHEIMER'S ASSOCIATION

RESEARCH ARTICLE

Racial and ethnic differences in plasma biomarker eligibility for a preclinical Alzheimer's disease trial

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Funding information
NIH/NIA, Grant/Award Numbers: U24AG057437, R01AG054029, R01AG061848; Eisai Inc.; Gerald and Henrietta Rauenhorst (GHR) Foundation; Alzheimer's Association, Grant/Award Number: SG-22-877415-AHEAD

Abstract

INTRODUCTION: In trials of amyloid-lowering drugs for Alzheimer's disease (AD), differential eligibility may contribute to under-inclusion of racial and ethnic under-represented groups. We examined plasma amyloid beta 42/40 and positron emission tomography (PET) amyloid eligibility for the ongoing AHEAD Study preclinical AD program (NCT04468659).

METHODS: Univariate logistic regression models were used to examine group differences in plasma and PET amyloid screening eligibility.

RESULTS: Of 4905 participants screened at time of analysis, 1724 were plasma eligible to continue in screening: 13.3% Hispanic Black, 24.7% Hispanic White, 20.8% non-Hispanic (NH) Asian, 24.7% NH Black, and 38.9% NH White. Plasma eligibility differed across groups in models controlling for covariates (odds ratio from 1.9 to 4.0 compared to the NH White reference group, $P < 0.001$). Among plasma eligible participants, PET eligibility did not differ by group.

DISCUSSION: These results suggest that prevalence of brain amyloid pathology differed, but that eligibility based on plasma was equally effective across racial and ethnic group members.

KEYWORDS
amyloid, biomarker, ethnicity, plasma, positron emission tomography, race

Highlights

- Plasma amyloid eligibility is lower in underrepresented racial and ethnic groups.
- In plasma eligible adults, positron emission tomography eligibility rates are similar across race and ethnicity.
- Plasma biomarker tests may be similarly effective across racial and ethnic groups.

1 | INTRODUCTION

Alzheimer's disease (AD) is a neurodegenerative disorder characterized by progressive cognitive and functional decline. Intervening at early stages of the disease is key to maximizing treatment benefit; thus, the development and testing of AD therapeutics targeted at the asymptomatic or "preclinical" stage of the disease holds much promise.[1–4] Preclinical AD refers to the disease stage in which individuals exhibit biomarker evidence of AD pathology but have not yet developed clinical impairment.[5] Preclinical AD and early AD trials are becoming increasingly common, particularly aimed at targeting amyloid removal or preventing brain amyloid accumulation.[6–10] Recent and compelling preliminary data from amyloid-lowering therapeutics such as lecanemab and donanemab suggest a stronger treatment effect at earlier stages of the disease.[10–12]

Despite the recognized increased risk for dementia among some racial and ethnic groups, individuals belonging to racial and ethnic minoritized populations groups continue to be underrepresented in AD clinical trials, including preclinical AD trials, and constitute racial and ethnic underrepresented groups (RE-URGs).[13–16] Underrepresentation of these groups in trials can limit the external validity of study findings and limit confidence in the ability of interventions to benefit all populations at risk.[17] A recent systematic review by Franzen et al.[18] analyzed 101 AD trials and found the median percentage of non-Hispanic (NH) Black participants was 1.2% (interquartile range [IQR]: 0.4%–1.7%). NH Asian participants had a median percentage of 4.4% (IQR: 0.3%–177.3%). Hispanic participants had a median of 5.6% (IQR: 4.2%–11.4%) based on a subset of seven studies in which Hispanic ethnicity was reported.[18]

Challenges such as lack of access, limited trial awareness, and mistrust may be important contributors to underrepresentation in trials. Inadequate adjustment for education and other predictors of cognitive tests scores, English language and study partner requirements, and exclusion due to the presence of comorbidities may lead to differential exclusion of demographically diverse subgroups.[16,18] Amyloid-biomarker eligibility, however, has also proven to be an important contributor to the disproportionate exclusion of certain RE-URGs.[16,19] Biomarkers of amyloid and tau pathology measured by positron emission tomography (PET) imaging or in cerebrospinal fluid (CSF) are key assessments used to identify individuals with preclinical AD. Amyloid biomarkers are particularly critical in trials of amyloid-lowering treatments, due to the need to ensure presence of the treatment target.

Plasma-based biomarkers have recently emerged as a tool to increase screening efficiency in preclinical AD trials. Plasma biomarkers are more accessible, less costly, and more convenient than amyloid PET imaging but appear to provide high predictive accuracy for PET outcomes.[20–22] Incorporating plasma enrichment early in the screening process, therefore, can reduce the number of PET scans needed, reducing cost and accelerating enrollment.[22–25] In an ongoing preclinical AD study, the AHEAD 3-45 Study, we incorporated plasma amyloid beta (Aβ)42, Aβ40, Aβ42/40 ratio, and Apolipoprotein E (ApoE) proteotyping assessments (PrecivityAD, C_2N Diagnostics) adjusted for age and ApoE to identify participants with higher likelihood of meeting the amyloid PET eligibility criteria for the study, effectively reducing burden for research sites and participants. We selected a plasma amyloid threshold favoring sensitivity over specificity to minimize the loss of potentially eligible participants, particularly those belonging to RE-URGs, for whom there are limited data.

In the current analyses, we explored whether there were differences in eligibility rates among participants from diverse RE-URGs based on their plasma Aβ42/40 ratio and subsequently on amyloid PET status in plasma biomarker–eligible participants screening for the AHEAD 3-45 Study in North America.

2 | METHODS

2.1 | The AHEAD 3-45 Study

The AHEAD 3-45 Study is conducted as a public–private partnership of the Alzheimer's Clinical Trials Consortium (ACTC), funded by

RESEARCH IN CONTEXT

1. **Systematic review**: We reviewed the literature using traditional sources (e.g., PubMed), meeting abstracts, and presentations. Racial and ethnic minorities are underrepresented in Alzheimer's disease (AD) clinical trials. Differential eligibility related to biomarker requirements may contribute to this underrepresentation. Plasma amyloid biomarkers are promising screening tools that may enrich for participants likely to qualify for preclinical AD trials based on amyloid positron emission tomography (PET) eligibility criteria. We evaluated eligibility rates across racial and ethnic groups in a preclinical AD trial incorporating plasma amyloid biomarker testing prior to any other screening assessment.
2. **Interpretation**: Our findings indicate that plasma amyloid eligibility rates differ by race and ethnicity based on the use of a single liberal cutpoint applied across groups to favor sensitivity over specificity. Among plasma-eligible participants, however, the proportions of PET-eligible individuals were no different across race and ethnic groups. Our findings suggest differential prevalence of amyloid pathology by race and ethnicity.
3. **Future directions**: Differential prevalence of plasma amyloid biomarkers by race and ethnicity is consistent with previous reports in autopsy, cerebrospinal fluid, and PET studies. Whether this reflects a true differential prevalence in disease risk or other biases (i.e., selection bias, information or misclassification bias, or competing risks from other causes) is unknown. Addressing these questions in future research will be critical.

the National Institute on Aging (NIA), Eisai Inc., GHR Foundation, the Alzheimer's Association, and philanthropic donors. It is an ongoing multi-center, double-blind, placebo-controlled clinical trial program designed to assess the safety and efficacy of lecanemab in preclinical AD.[26] The study consists of two sister trials with a single screening process that enroll participants without AD dementia but with biomarker evidence of AD. A3 enrolls participants with intermediate brain amyloid levels; A45 enrolls participants with elevated amyloid. The screening process for the study, as pictured in Figure 1, includes two main stages. Stage 1 includes plasma amyloid screening at screening visit 1a (ScV1a) and subsequent cognitive and functional evaluation at screening visit 1b (ScV1b). During Stage 2, Stage 1–eligible participants undergo amyloid PET scan at screening visits 2 and 3. PET–eligible participants are randomized to either A3 or A45 consonant with PET amyloid levels.

2.2 | Sample

Interested and cognitively unimpaired participants aged 55 to 80 with an available study partner and absence of cognitive impairment or dementia diagnosis were screened at any of 75 North American clinical study sites. Since its inception the study has used a variety of methods to facilitate the recruitment of traditionally underrepresented groups into the study, including referrals from national and site-level registries such as the Trial-Ready Cohort for the Prevention of Alzheimer's Dementia (TRC-PAD); a central catchment website (www.aheadstudy.org) with a robust site referral system; social media campaigns using Facebook, Google, and YouTube; earned and paid national and local media in print, radio, and television across a variety of outlets and cities to reach and engage members of demographically diverse groups.[27,28]

Participants' self-reported race was captured as "American Indian or Alaskan Native," "Asian," "Black" or "African American," "Hawaiian or other Pacific Islander," "White," "Other," and "More than One Race," "Unknown," or "Not Reported." Ethnicity was captured as "Hispanic or Latino," "non-Hispanic or Latino," "Unknown," or "Not Reported" (Figure 2).

The participants included in this analysis underwent initial plasma screening, between February 2022 and May 2023, using the age and ApoE-adjusted Aβ42/40 ratio. The AHEAD Study has since transitioned to, and currently also uses plasma phosphorylated tau (p-tau)217 to determine likelihood of amyloid PET eligibility.

2.3 | Biomarker eligibility

At the outset of the screening process plasma assays were used to measure Aβ42/40 ratio and ApoE proteotype using the C_2N Diagnostics PrecivityAD test, which uses mass spectrometry.[22,23,29] A pre-specified algorithm based on age, ApoE and Aβ42/40 ratio using a liberal cutpoint of > 11 Centiloids (CL) on amyloid PET (eligibility for the trial requires at least 20 CL on amyloid PET) was used to determine eligibility to proceed to cognitive and clinical testing at the second screening visit (ScV1b).[23] We deliberately established a threshold to prevent the exclusion of potentially eligible participants from RE-URGs, given the paucity of data in the plasma biomarker literature on these groups.

Clinical and cognitive eligibility criteria at ScV1b were as follows: Global Clinical Dementia Rating (CDR) score of 0, Mini-Mental State Examination (MMSE) of ≥ 27 (with adequate educational adjustments,[30,31] specifically, ≤12 years of education, MMSE ≥ 25; 13—15 years of education, MMSE ≥ 26; ≥ 16 years of education, MMSE ≥ 27), and Wechsler Memory Scale-Revised Logical Memory Subscale II (WMSR-LMS II) score of ≥ 6 at the time of screening as described by Rafii et al.[6] Participants eligible at ScV1b underwent PET imaging with [^{18}F] NAV4694 for detecting cerebral amyloid (ScV2/3) during Stage 2. Those within 20 to 40 CL were eligible for randomization to A3 and those > 40 CL were eligible for randomization to A45.

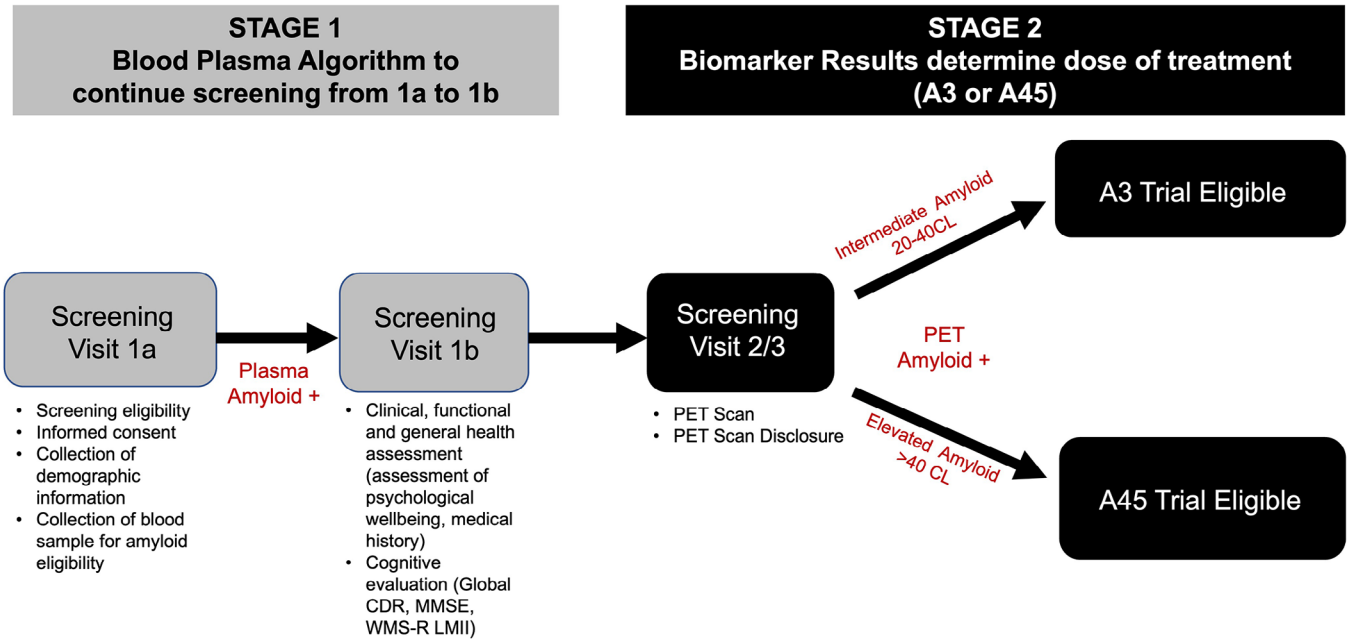


FIGURE 1 AHEAD A3-45 Study sister trials with a common screening process. Randomization to A3-A45 after Stage 2 is dependent on levels of PET amyloid. CDR, Clinical Dementia Rating; CL, Centiloids; MMSE, Mini-Mental State Examination; PET, positron emission tomography; WMSR-LMS II, Wechsler Memory Scale-Revised Logical Memory Subscale II

2.4 | Statistical analysis

For these analyses, all participants enrolled in North America with plasma results at ScV1a determined based on age and ApoE-adjusted Aβ42/40 ratios were included (Figure 1). Race and ethnicity were combined to derive a single variable (Race and Ethnicity) that included five mutually exclusive racial and ethnic categories: Hispanic Black, Hispanic White, NH Asian, NH Black, NH White. Participants who identified as "More than one Race," "Other Race," "American Indian or Alaskan Native," "Native Hawaiian or other Pacific Islander," and unknown race and ethnicity were not included in the analysis given the small numbers of those participants. All groups except NH White participants were considered members of RE-URGs. Participants who were approved to move forward from ScV1a to SCV1b through manual overrides by the Coordinating Center due to prior knowledge of amyloid status from results acquired outside the AHEAD screening process were not included in the analysis as detailed in Figure 2.

We summarized participant characteristics across the groups using means and standard deviations for continuous variables and using counts and percentages for categorical variables. To compare the effect of race and ethnicity on plasma and PET eligibility rates, we used univariate logistic regression analysis in which models were fit on ineligibility rates. We used a Kruskal–Wallis *H* test to examine continuous PET levels across groups, given the non-normal distribution of the data. Given previous reports of differential *APOE* ε4 carrier risk of AD across RE-URGs, we evaluated Aβ42/A40 ratios across groups by ε4 allele carrier status (ApoE4). All statistical analyses were performed in R version 4.2.0. Results are reported using odds ratios (ORs) and corresponding 95% confidence intervals (CIs).

3 | RESULTS

Out of 7145 participants enrolled at the time of the analysis, 2240 participants were not included in the analysis based on not having a plasma result ($N = 1878$), belonging to self-reported racial categories that had small numbers of participants ($N = 214$), or being screened into the study as a manual override based on prior knowledge of elevated amyloid ($N = 152$; Figure 2). Among the 4905 participants included in this analysis, the proportion of participants across self-reported race and ethnicity groups were: 60 (1.22%) Hispanic Black, 671 (13.7%) Hispanic White, 101 (2.06%) NH Asians, 381 (7.8%) NH Black, and 3692 (75.3%) NH White. Demographic characteristics of participants are displayed in Table 1. Age was similar across groups, with an overall mean of 67.2 $\pm$ 6.4. NH Asian, NH Black, and NH White participants had higher mean years of education, compared to Hispanic Black and Hispanic White participants. Most of the participants were female, though the NH Black group had the largest proportion of females (76.6%). Overall, 40% of participants were ApoE4 carriers, with the lowest ApoE4 prevalence observed in the Hispanic Black and Hispanic White groups, and highest in the NH Black and NH White groups. Most participants across all groups were married and reported independent residential status (Table 1).

Out of the 4905 participants who underwent plasma amyloid testing, 1724 (35.1%) were determined plasma Aβ42/40 eligible. Plasma Aβ42/40 ratios by group are reported in the supplement (Table S1 in supporting information). The proportions of plasma Aβ42/40–eligible participants by group are shown in Figure 3. Overall, the NH White group had the highest proportion of plasma Aβ42/40–eligible participants (38.9%). The Hispanic Black group had the lowest proportion

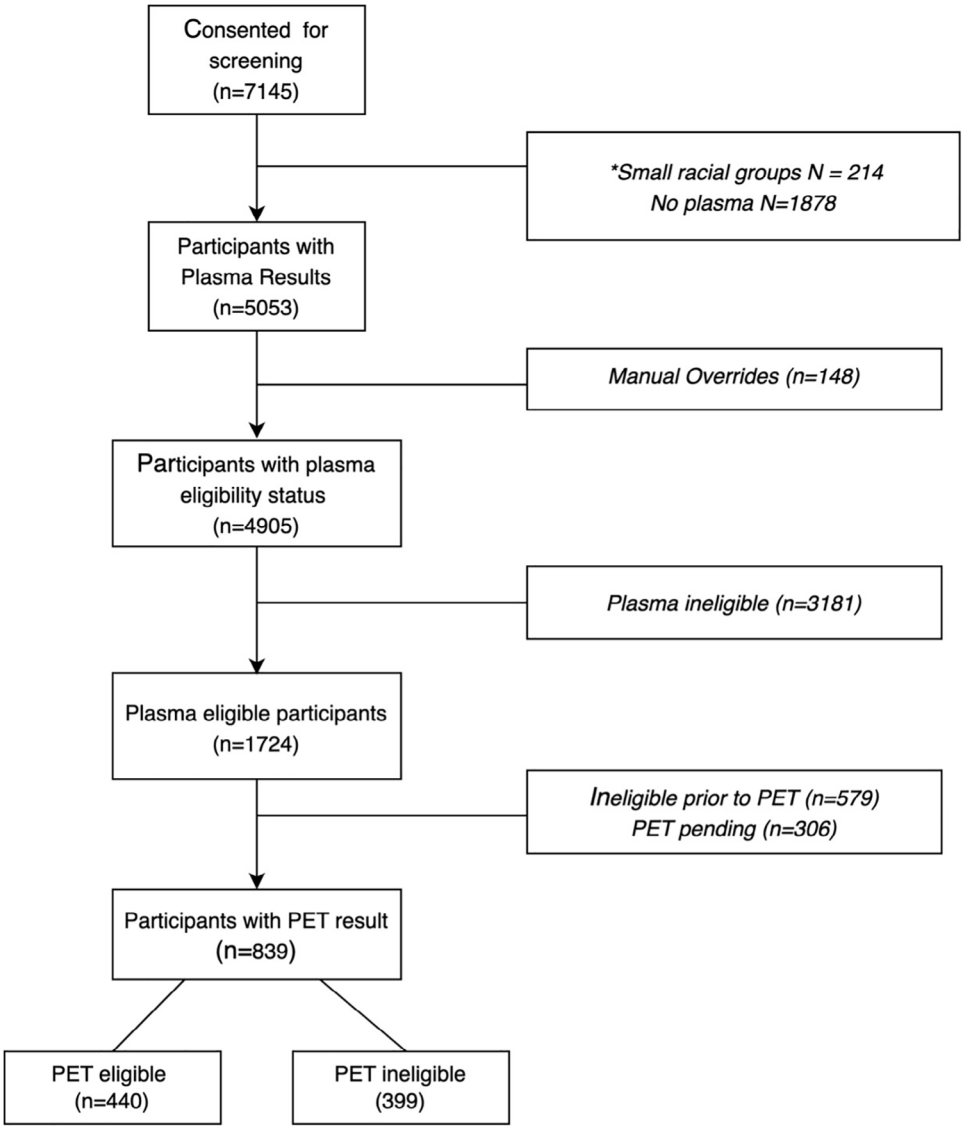


FIGURE 2 Consort diagram of consented participants included in the analysis. *Participants in small racial groups not included in the analysis: Missing *N = 31;* More than One Race *N = 34*; Other Race *N = 63*; American Indian or Alaskan Native *N = 33*; Native Hawaiian or other Pacific Islander *N = 9*; Unknown *N = 44*. PET, positron emission tomography

of participants eligible based on plasma Aβ42/40 (13.3%); however, all RE-URGs showed lower rates of plasma Aβ42/40 eligibility (Hispanic White 24.7%; NH Asian 20.8%; NH Black 24.7%) compared to NH White participants. Overall, compared to NH White participants, all RE-URG participants had significantly higher odds of being ineligible based on plasma criteria. Participants self-identifying as NH Black (OR = 1.830 [1.46, 2.31] $P < 0.001$), NH Asian (OR = 2.6 [1.69, 4.16] $P < 0.001$), Hispanic White (OR = 1.831 [1.53, 2.2] $P < 0.001$) Hispanic Black (OR = 3.5 [1.81, 7.61] $P = 0.001$) were at significantly increased odds of being ineligible to proceed in screening based on plasma Aβ42/40 result compared to those self-identifying as NH White (Figure 4). Unadjusted Aβ42/A40 ratios by ApoE4 carriership were not different across groups (Figure S1 and Table S2 in supporting information).

Among plasma-eligible participants included in our analyses 34% were ineligible prior to amyloid PET based on cognitive and functional criteria. Global CDR, MMSE, and WMSR-LMS II cognitive assessment scores were the most frequent sources of ineligibility (Figure 2, Table 2, Tables S3 and S4 in supporting information). Because the AHEAD Study is an ongoing program, 18% of plasma and clinically eligible participants were pending PET at the time of data freeze (Figure 2). The remaining plasma- and ScV1b-eligible participants (49%) underwent PET scans. Figure 5 depicts amyloid PET eligibility by RE-URG. The eligibility rates across groups were nearly identical, with 52% of participants demonstrating amyloid PET CL values that met the > 20 CL threshold for randomization. Amyloid PET levels by group are reported in the supplement (Figure S2 and Table S5 in supporting information). We observed no difference in

TABLE 1 Demographics characteristics of participants with plasma result across race and ethnic groups.

Characteristics	Race and ethnicity no. (%)						
	H Black (*N* = 60)	H White (*N* = 671)	NH Asian (*N* = 101)	NH Black (*N* = 381)	NH White (*N* = 3692)	Total (*N* = 4905)	*P* value
Age, mean ± SD	66.4 ± 6.3	66.5 ± 6.7	66.9 ± 6.7	67.5 ± 5.9	67.2 ± 6.4	67.1 ± 6.4	0.056
Education, mean ± SD*	11.5 ± 3.4	12.8 ± 4.0	16.8 ± 2.5	16.1 ± 2.6	16.5 ± 2.7	15.9 ± 3.2)	
Female sex	30 (50.8)	418 (62.3)	70 (69.3)	285 (74.8)	2444 (66.2)	3247 (66.2)	
ApoE	13 (21.7)	156 (23.2)	36 (35.6)	160 (42.9)	1584 (42.9)	1949 (39.7)	<0.001
Marital status							
Married	18 (30.0)	261 (38.9)	80 (79.2)	185 (48.7)	2571 (69.7)	3115 (63.5)	
Divorced	18 (30.0)	245 (36.5)	11 (10.9)	100 (26.3)	592 (16.0)	966 (19.7)	
Single	15 (25.0)	88 (13.1)	4 (4.0%)	51 (13.4%)	191 (5.2%)	349 (7.1%)	
Widowed	8 (13.3)	75 (11.2%)	6 (5.9%)	38 (10.0%)	276 (7.5%)	403 (8.2%)	
Other	1 (1.7%)	2 (0.3%)	0 (0.0%)	6 (1.6%)	61 (1.7%)	70 (1.4%)	
Residence							
Assisted (%)	0 (0.0%)	1 (0.2%)	0 (0.0%)	0 (0.0%)	3 (0.1%)	4 (0.1%)	
Independent (%)	37 (97.4%)	446 (98.9%)	93 (98.9%)	366 (99.2%)	3565 (99.2%)	4507 (99.2%)	
With family (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Senior facility (%)	0 (0.0%)	2 (0.4%)	1 (1.1%)	2 (0.5%)	7 (0.2%)	12 (0.3%)	
Other (%)	1 (2.6%)	2 (0.4%)	0 (0.0%)	1 (0.3%)	18 (0.5%)	22 (0.5%)	
Hollingshead							
Upper (%)	3 (5.1%)	60 (9.2%)	31 (31.0%)	50 (13.3%)	846 (23.2%)	990 (20.5%)	
Upper-middle (%)	7 (11.9%)	128 (19.6%)	49 (49.0%)	182 (48.5%)	1777 (48.6%)	2143 (44.3%)	
Middle (%)	8 (13.6%)	114 (17.5%)	12 (12.0%)	85 (22.7%)	706 (19.3%)	925 (19.1%)	
Lower-middle (%)	12 (20.3%)	131 (20.1%)	8 (8.0%)	44 (11.7%)	228 (6.2%)	423 (8.7%)	
Lower (%)	29 (49.2%)	220 (33.7%)	0 (0.0%)	14 (3.7%)	96 (2.6%)	359 (7.4%)	

Note: Discrepancies in number may be attributed to missing data.
Abbreviations: ApoE, apolipoprotein E; H, Hispanic; NH, non-Hispanic; SD, standard deviation.

TABLE 2 Summary of ineligibility based on cognitive and clinical criteria of plasma eligible participants prior to PET evaluation.

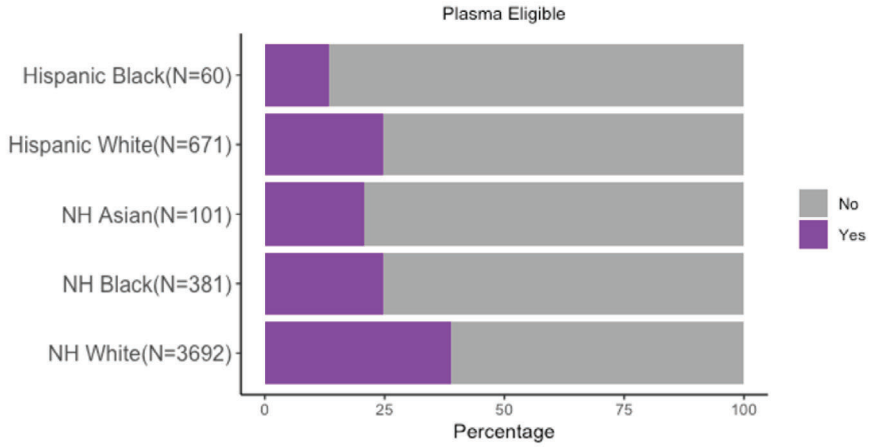
Ineligibility reason	Race and ethnicity no. (%)					
	Hispanic Black (*N* = 8)	Hispanic White (*N* = 166)	NH Asian (*N* = 21)	NH Black (*N* = 94)	NH White (*N* = 1435)	Total (*N* = 1724)
ScV1b cognitive or functional inclusion or exclusion criteria	2 (25)	48 (29)	10 (48)	44 (46)	481 (34)	585 (34)
Pending	2 (25)	42 (25)	4 (19)	26 (28)	215 (15)	289 (17)
Eligible for PET evaluation	4 (50)	76 (46)	7 (33.3)	24 (26)	739 (51)	850 (49)

Note: Discrepancies in data may be attributed to data missingness, ineligibility based on exclusion criteria, or pending disposition.
Abbreviations: NH, non-Hispanic; PET, positron emission tomography; ScV1b, screening visit 1b.

continuous amyloid PET CL across groups in those who were plasma eligible ($P = 0.78$).

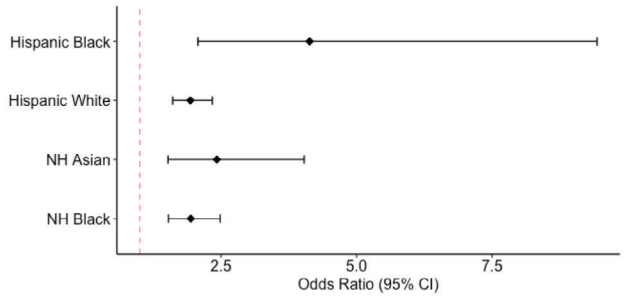
4 | DISCUSSION

Participants from RE-URGs are severely underrepresented overall in AD clinical trials despite their higher risk of cognitive impairment and dementia.[14–16,32] In the ongoing AHEAD Study, composed of two linked preclinical AD trials with a single screening process, we aimed to improve the diversity and representation of individuals RE-URGs through a series of outreach and recruitment initiatives. Despite success in those efforts (≈ 25% screens have been from RE-URGs), the diversity of the randomized cohort has been limited due to disproportionate ineligibility rates based on amyloid plasma Aβ42/40 measures. These findings are consistent with prior observations[18,33]



Plasma Eligibility	Race and Ethnicity No. (%)						P-value
	Hispanic Black (N=60)	Hispanic White (N=671)	NH Asian (N=101)	NH Black (N=381)	NH White (N=3692)	Total (N=4905)	
Yes	8 (13.3)	166 (24.7)	21 (20.8)	94 (24.7)	1435 (38.9)	1724 (35.1)	<0.001
No	52 (86.7)	505 (75.3)	80 (79.2)	287 (75.3)	2257 (61.1)	3181 (64.9)	

FIGURE 3 Proportion of plasma-eligible participants by race and ethnic groups. NH, non-Hispanic

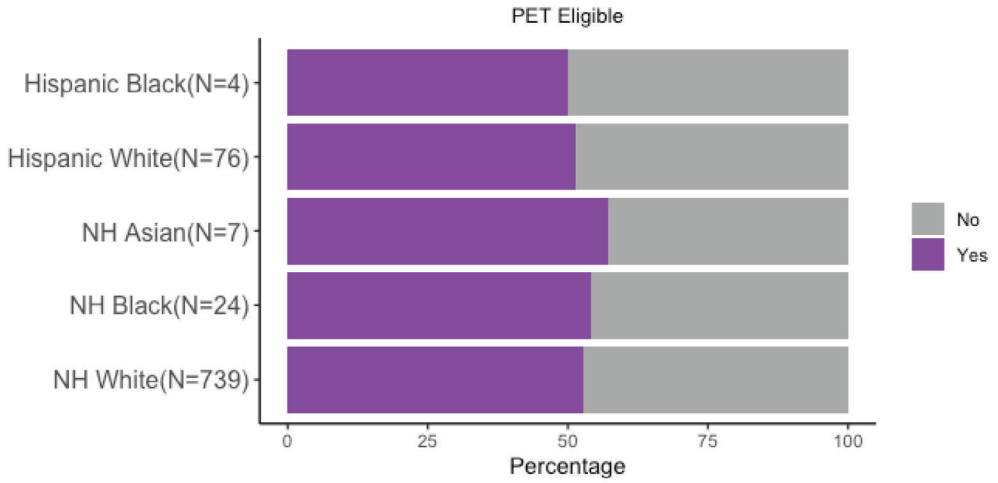


	Race and Ethnic Group			
	Hispanic Black	Hispanic White	NH Asian	NH Black
OR	4.1	1.9	2.4	1.9
95% CI	[2.1, 9.4]	[1.6, 2.3]	[1.5, 4.0]	[1.5, 2.5]
P-value	<0.001	<0.001	<0.001	<0.001

FIGURE 4 Odds of plasma ineligibility across groups compared to NH White participants as reference group. CI, confidence interval; NH, non-Hispanic; OR, odds ratio

despite removing potential sources of bias in assessment of group differences by conducting the plasma biomarker screening prior to cognitive, functional, and medical screening assessments. In our plasma Aβ42/40 screening algorithm, we also applied a liberal cutpoint for eligibility determination, intended to favor sensitivity over specificity to perhaps reduce concerns that differential thresholds are needed for specific groups. While the adoption of different cutoffs by race and ethnicity has been proposed,[34] in light of differential amyloid eligibility rates, a more adequate approach is to use a standard cutpoint for plasma AD biomarkers that perform consistently and accurately across groups.[34–37] Our results posit the consistent performance of the plasma Aβ42/A40 ratio adjusted by age and ApoE as suggested by the equal proportions of plasma-eligible individuals who were subsequently PET eligible across RE-URGs.

Results from previous amyloid CSF and PET studies are consistent with our findings and suggest differential prevalence of amyloidosis rather than differential performance of the plasma biomarker test, among RE-URGs.[16,30,34,37–40] The Phase III Clarity AD trial of lecanemab, which enrolled participants aged 50 to 90 years with early symptomatic AD and evidence of amyloid positivity by PET, observed lower rates of eligibility in NH Black participants.[41] In the IDEAS Study, a cohort study of 17,107 Medicare beneficiaries with mild cognitive impairment or dementia, lower rates of amyloid-positive scans were observed in Asian and Black adults compared to White adults.[38] These findings extended to CSF, plasma, and autopsy studies. Schindler et al. reported lower likelihood of amyloidosis by CSF and plasma Aβ42/A40 in one-to-one matched self-identified NH Black adults compared to Non-Hispanic White adults.[37] Earlier autopsy studies have reported that compared to NH White decedents, NH Black decedents were less likely to have AD amyloid pathology as a single dementia pathology, but not less likely to have evidence of mixed AD co-pathology.[40,42] Similar findings were also observed at earlier stages of the disease as reported in two analyses of the preclinical AD A4 Study in which screening of PET data similarly showed lower likelihood of amyloid eligibility among RE-URGs.[16,30] Altogether, these studies point to the lower prevalence of brain amyloid pathology in some RE-URGs, which likely contributes to lower eligibility rates in amyloid-lowering clinical trials.



PET Eligibility	Race and ethnicity No. (%)						P-value
	Hispanic Black N=4	Hispanic White N=76	NH Asian N=7	NH Black N=24	NH White N=739	Total N=839	
Yes N (%)	2 (50)	37 (48.7)	3 (42.9)	11 (45.8)	350 (47.4)	403 (47.4)	0.998
No N (%)	2 (50)	39 (51.3)	4 (57.1)	13 (54.2)	389 (52.6)	447 (52.6)	

FIGURE 5 Proportion of PET eligible participants, among those who were plasma eligible, across race, and ethnic groups. NH, non-Hispanic; PET, positron emission tomography

Intriguingly, the reported lower prevalence of amyloid in RE-URGs conflicts with the higher risk of all-cause dementia and cognitive impairment reported in the literature for some populations such as Hispanic and NH Black adults.[43–48] One plausible explanation is that in groups with lower amyloid prevalence other factors, including differences in AD pathophysiology, genetic influence, differences in medical comorbidities, and structural and psychosocial determinants of health and their intersections, may contribute to increased prevalence of cognitive impairment.[49] In an analysis of the effect of race on amyloid PET using screening data for the Anti-Amyloid Treatment in Asymptomatic Alzheimer's Disease (A4) Study, Deters et al.[30] reported that self-identified NH Black participants had lower rates of amyloid compared to NH White participants. Among self-identified NH Black participants, those with lower proportions of genetically determined African ancestry had higher amyloid PET CL values. Notably, the strongest effect of race was observed in ApoE4 carriers. The *APOE ε4* allele has been widely known for increasing the risk of developing dementia and is associated with higher prevalence of amyloid abnormality.[50–52] However, studies suggest that the degree of risk conferred may vary by age, sex, race, and ethnicity.[53–56] In our studied preclinical AD population differential ApoE4 carrier rates didn't explain the observed amyloid biomarker differences. The smaller number of participants across each of the RE-URGs limits the conclusions than can be made related to the role of ApoE4 carrier status in amyloid prevalence across these groups. Further investigation of interactions between ApoE and amyloid by race and ethnicity and other demographic characteristics may help reconcile previous reports and our current findings. Moreover, examination of medical conditions in the A4 Study suggested that total number of endorsed medical conditions was associated with greater PET amyloid levels; however, despite this association the impact of racial identification on amyloid eligibility remained significant.[30,57,58] Future studies will evaluate specific medical conditions, including vascular and inflammatory contributions to biomarkers of amyloid pathology.

Another unexplored explanation is that in groups that have higher prevalence of cognitive impairment and lower prevalence of amyloid, cognitive impairment is driven by the presence of other co-pathologies which potentially increase vulnerability to amyloid neurodegeneration. Cardiovascular disease, which is prevalent at higher rates in the NH Black and Hispanic populations largely due to structural and psychosocial determinants of health,[59–62] may be a potential contributor to differential levels of amyloid. Recent work also suggests that greater vascular risk, especially hypertension, and higher body mass index increases the rate of tau accumulation and cognitive decline even at relatively lower levels of amyloid pathology.[63–66] Moreover, some reports suggest that there may be a higher susceptibility to inflammatory diseases and systemic inflammation in Black and Hispanic or Latino populations.[67–70] One possibility is that heightened inflammatory responses in the central nervous system, as observed in some RE-URGs, could result in more effective amyloid clearance,[71,72] but might also trigger adverse downstream effects, such as synaptic pruning and neuronal damage.[73–76] The extent of these consequences requires further study with peripheral and central nervous system markers of immune function.[49] Further examination of vascular and inflammatory biomarkers, as well as other comorbidities, will serve to

elucidate their contributions to trajectories of amyloid accumulation and cognitive dysfunction. These findings provide important insights that can inform future AD trial design, in particular, the design of combination trials to address multiple processes contributing to cognitive decline among RE-URGs.

Importantly, while our analyses did not include examination of social determinants of health including socioeconomic factors, limited access to health care, psychosocial and cultural factors, psychological risk, and resilience, the likely contribution of these factors to aging disparities cannot be ignored.[77] The role of environmental, sociocultural, behavioral, and biological factors and their varying impact across the life course may help explain differences in advantage versus disadvantage experienced across social groups. We speculate that these factors could influence either resistance to developing late life brain pathology and/or to resilience to cognitive decline in the setting of these pathologies; however, their direct impact must be further elucidated.

Although we sought to decrease bias due to cognitive testing, exclusionary cutpoints on neuropsychological tests that are not well culturally normed in diverse communities prevented some participants from eligibility for PET imaging. Exclusionary medical conditions may contribute to systematic differences in eligibility, and there are likely still many inherent factors that can create bias in the subset of racially and ethnically diverse individuals who volunteer for AD clinical trial research. Although we included plasma Aβ42/40 screening prior to cognitive screening we were not able to eliminate the inherent bias of cognitive exclusionary factors. We are now in the process of launching a new observational study, the Alzheimer's Plasma EXtension (APEX) Study, to obtain longitudinal plasma measures, cognitive assessments, and PET imaging on individuals who screen failed for the AHEAD Study, with a focus on enrolling participants from underrepresented racial and ethnic communities. Evaluation of intra-individual longitudinal biomarker trajectories across decades may be the best opportunity to understand potential racial and ethnic differences in the early evolution of AD pathology.

Our findings highlight the potential importance of plasma biomarker screening tests (Aβ42/40, p-tau species, etc.) in assembling a more inclusive and diverse cohort for AD clinical trials. Considering the comparatively lower rates of amyloid positivity observed within RE-URGs, the imperative to screen broader populations becomes paramount to identify a representative sample of amyloid-positive individuals. Using a streamlined amyloid blood test enables the efficient screening of extensive groups within registries[78] and in community settings, significantly enhancing the feasibility of this endeavor. This approach is crucial for bolstering the timely inclusion of underrepresented groups in AD studies, ultimately driving toward more equitable representation in AD clinical trials.

5 | LIMITATIONS

Although this study presents a relatively large and unique population of cognitively unimpaired older individuals screening for an AD prevention trial, there are several limitations. First, the current analysis suggests that the plasma Aβ42/40 values reflect brain amyloid consistently across RE-URGs. This is an important question that will require further research, including longitudinal cohort studies. The APEX Study, which will oversample for racial and ethnic underrepresented populations with lower levels of amyloid, is anticipated to be one such study.

Second, while our ongoing efforts to increase diversity in the screening population have had some success, to date this subset of the AHEAD Study screening population remains predominantly NH White with high levels of education and possibly easier access to clinical trial centers. Overall, limited numbers of participants have been from underrepresented groups across the full range of key characteristics, including race, ethnicity, education, and socioeconomic status.

Notably, several aspects of AD clinical trials can contribute to selection bias, due to study-specific requirements, and the way in which participants may be enrolled in the study. This can contribute to lack of cultural, geographic, and socioeconomic representation, which in turn may limit the applicability of our findings across the broader spectrum of the population. Our future work in the longitudinal APEX cohort, which will enroll larger numbers of members from RE-URGs, will allow us to replicate and further explore explanations for differential amyloid levels in these groups.

Early adoption of plasma biomarker screening in the AHEAD Study used a plasma Aβ42/40 ratio for eligibility, whereas subsequent studies have shown that plasma phosphorylated tau species, in particular the variant p-tau217 and the p-tau217 ratio (p-tau217/np-tau217), have greater accuracy in predicting amyloid PET status.[79,80] We have recently added p-tau217/np-tau217 to the AHEAD Study screening algorithm and will evaluate race and ethnic group differences when screening is completed.

6 | CONCLUSIONS AND IMPLICATIONS

Altogether, our results and previous data suggest that there are differences in prevalence of amyloid pathology among individuals from some RE-URGs that appropriately preclude them from participating in amyloid-lowering drug trials. These findings do not imply that individuals from underrepresented groups who show elevated amyloid would not benefit from anti-amyloid treatment. To the contrary, the limited data in RE-URGs with abnormal amyloid levels in the recent Phase 3 trials suggest similar treatment effects.[81,82] Our analyses also support that a single plasma Aβ42/40 cutpoint may work equally well across RE-URGs in predicting brain amyloid pathology on PET. Given the higher risk of cognitive decline and dementia experienced by some RE-URGs, it is critical to further elucidate potential differences in disease mechanisms and the likely multiple factors that contribute to cognitive decline and continue to improve our efforts to screen and enroll higher numbers of individuals from diverse racial and ethnic backgrounds to improve the inclusivity of trials. Future trials might include combination therapies that would target multiple mechanisms,

including vascular, metabolic, or inflammatory pathways, in addition to treating lower levels of amyloid pathology. Promoting participation and engaging individuals from different communities will be critical to improve our understanding of disease mechanisms and how to best address them.

ACKNOWLEDGMENTS

The authors would like to thank the site principal investigators, staff, and participants and their study partners for their involvement in this study. The AHEAD 3-45 Study is conducted as a public–private partnership of the Alzheimer's Clinical Trial Consortium (ACTC), funded by the National Institute on Aging, National Institutes of Health (NIH), Eisai Inc., the GHR Foundation, and other philanthropists.

CONFLICT OF INTEREST STATEMENT

DPMH has received funding from the American Heart Association. AL, OL, and LS are employees of the Keck School of Medicine of USC. JBB, KEY, VV, TW, and PBV and are paid employees of C2N Diagnostics, and collectively have research grants from the NIH, BrightFocus Foundation, GHR Foundation, and Alzheimer's Drug Discovery Foundation. SD and MI are paid employees of Eisai. RAR and RR have grants from the NIH. RR has received grants from Eisai, Eli Lilly, the Alzheimer's Association, and the American Heart Association. KAJ has grants from the NIH and GHR Foundation, and has consulted for Novartis, Janssen, and Merck. CG has nothing to disclose. GJ-M has received support from C2N Diagnostics, Eisai Co, Ltd, and the NIH. PSA has research grants from Eisai, NIH, Lilly, the Alzheimer's Association, and Janssen and serves as a consultant for Merck, Bristol Myers Squibb, Switch Therapeutics, Roche, Arrowhead, ImmunoBrain, Checkpoint, Biogen, Abbvie, Genetech, and NewAmsterdam Pharma. JDG has received consultancy fees from SiteRx, outside the submitted work. RAS has grants from the NIH, the Alzheimer's Association, the GHR Foundation, Eli Lilly, and Eisai, and has consulted for Abbvie, AC Immune, Acumen, Alector, Alnylam, Genentech, Janssen, JOMDD, Nervgen, Neuraly, Neurocentria, Oligomerix, Prothena, Shionogi, Vigil Neuroscience, Ionis, Vaxxinity, and Bristol Myers Squibb. Author disclosures are available in the supporting information.

CONSENT STATEMENT

Informed consent was obtained from all participants and their study partners.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Molina-Henry DP, Raman R, Liu A, et al. Racial and ethnic differences in plasma biomarker eligibility for a preclinical Alzheimer's disease trial. *Alzheimer's Dement*. 2024;20:3827–3838.
https://doi.org/10.1002/alz.13803