RESEARCH ARTICLE OPEN ACCESS

Effect of Race on Prediction of Brain Amyloidosis by Plasma Aβ42/Aβ40, Phosphorylated Tau, and Neurofilament Light

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Neurology® 2022;99:e245-e257. doi:10.1212/WNL.0000000000200358

Abstract

Background and Objectives

To evaluate whether plasma biomarkers of amyloid (Aβ42/Aβ40), tau (p-tau181 and p-tau231), and neuroaxonal injury (neurofilament light chain [NfL]) detect brain amyloidosis consistently across racial groups.

Methods

Individuals enrolled in studies of memory and aging who self-identified as African American (AA) were matched 1:1 to self-identified non-Hispanic White (NHW) individuals by age, *APOE* ε4 carrier status, and cognitive status. Each participant underwent blood and CSF collection, and amyloid PET was performed in 103 participants (68%). Plasma Aβ42/Aβ40 was measured by a high-performance immunoprecipitation–mass spectrometry assay. Plasma p-tau181, p-tau231, and NfL were measured by Simoa immunoassays. CSF Aβ42/Aβ40 and amyloid PET status were used as primary and secondary reference standards of brain amyloidosis, respectively.

Results

There were 76 matched pairs of AA and NHW participants (n = 152 total). For both AA and NHW groups, the median age was 68.4 years, 42% were *APOE* ε4 carriers, and 91% were cognitively normal. AA were less likely than NHW participants to have brain amyloidosis by CSF Aβ42/Aβ40 (22% vs 43% positive; $p = 0.003$). The receiver operating characteristic area under the curve of CSF Aβ42/Aβ40 status with the plasma biomarkers was as follows: Aβ42/Aβ40, 0.86 (95% CI 0.79–0.92); p-tau181, 0.76 (0.68–0.84); p-tau231, 0.69 (0.60–0.78); and NfL, 0.64 (0.55–0.73). In models predicting CSF Aβ42/Aβ40 status with plasma Aβ42/Aβ40 that included covariates (age, sex, *APOE* ε4 carrier status, race, and cognitive status), race did not affect the probability of CSF Aβ42/Aβ40 positivity. In similar models based on plasma p-tau181, p-tau231, or NfL, AA participants had a lower probability of CSF Aβ42/Aβ40 positivity (odds ratio 0.31 [95% CI 0.13–0.73], 0.30 [0.13–0.71], and 0.27 [0.12–0.64], respectively). Models of amyloid PET status yielded similar findings.

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Go to Neurology.org/N for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

The Article Processing Charge was funded by NIH.

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Glossary

AA = African American; **Aβ** = β-amyloid; **AD** = Alzheimer disease; **ADRC** = Alzheimer Disease Research Center; **AUC** = area under the curve; **CDR** = Clinical Dementia Rating; **IQR** = interquartile range; **LP** = lumbar puncture; **NfL** = neurofilament light chain; **NHW** = non-Hispanic White; **OR** = odds ratio; **p-tau181** = tau phosphorylated at position 181; **PiB** = Pittsburgh compound B; **ROC** = receiver operating characteristic; **SUVR** = standardized uptake value ratio; **t-tau** = total tau; **UDS** = Uniform Data Set.

Discussion

Models predicting brain amyloidosis using a high-performance plasma Aβ42/Aβ40 assay may provide an accurate and consistent measure of brain amyloidosis across AA and NHW groups, but models based on plasma p-tau181, p-tau231, and NfL may perform inconsistently and could result in disproportionate misdiagnosis of AA individuals.

Biomarkers of Alzheimer disease (AD) brain pathology are used by research studies, clinical trials, and memory clinics for a variety of indications, including to determine whether the etiology of cognitive impairment is likely to be related to AD or another cause. Amyloid PET is a well-established technique to determine whether an individual has significant brain amyloidosis that could be causing or contributing to cognitive impairment; however, amyloid PET is expensive and has limited availability.[1] CSF biomarkers are also highly accurate predictors of brain amyloidosis and are less expensive, but skilled clinicians are required to perform lumbar puncture (LP) procedures, and some individuals perceive LPs as invasive.[2] Several commercial assays can be used to measure concentrations of CSF β-amyloid (Aβ) peptide 42 (Aβ42), Aβ40, total tau (t-tau), and tau phosphorylated at position 181 (p-tau181), and cutoffs consistent with brain amyloidosis have been established.[3-5]

Biomarker cutoffs for brain amyloidosis have been defined in cohorts largely comprised of non-Hispanic White (NHW) individuals and then applied to all individuals. However, several studies have found lower levels of CSF t-tau and p-tau181 in African American (AA) individuals as compared with NHW individuals, even after adjusting for factors such as age, sex, *APOE* ε4 carrier status, and cognitive impairment.[6-9] Why AA individuals have lower levels of CSF t-tau and p-tau181 is unknown and could be due to differences in medical comorbidities, biological factors, or social determinants of health.[8,10,11] Regardless of the underlying reasons, these differences have important implications for the utility of CSF biomarkers. Applying biomarker cutoffs defined in NHW to groups in which the biomarker has not been studied could potentially subject the other groups to additional testing, incorrect medical management, missed opportunities for treatment with AD-specific therapies, and lower enrollment in AD clinical trials.[9,12] However, it is also highly problematic to adjust the interpretation of medical tests based on race, especially given the heterogeneity represented within racial groups and the dynamic nature of race because it is a social rather than a biological construct.[9,13,14] It would be preferable to use AD biomarkers that perform accurately and consistently across racial and ethnic groups. Alternatively, adjusting for the factors that underlie racial differences in AD biomarkers (e.g., medical comorbidities) may be more valid and generalizable across groups.

Over the past 3 years, there has been rapid development of blood-based biomarkers for AD.[15] The PrecivityAD test offered by C2N Diagnostics, which includes highly precise measurement of plasma Aβ42/Aβ40 and *APOE* proteotype by mass spectrometry, is now available for clinical use.[16,17] Multiple plasma p-tau isoforms can also be used as biomarkers of brain amyloidosis, including p-tau181,[18,19] p-tau217,[20-22] and p-tau231.[23] Plasma neurofilament light chain (NfL) may also be useful as a nonspecific marker of neuroaxonal injury.[24] It is critical to evaluate whether these assays accurately and consistently predict brain amyloidosis across various racial and ethnic groups. In this study, one of the largest cohorts of AA individuals with CSF biomarker and amyloid PET information was used to examine the relationship of these reference measures of brain amyloidosis with the C2N Diagnostics PrecivityAD assay for plasma Aβ42/Aβ40 as well as Simoa immunoassays for p-tau181, p-tau231, and NfL.

Methods

Participants

This study analyzed samples and data from the Charles F. and Joanne Knight Alzheimer Disease Research Center (ADRC), which includes one of the largest groups of AA individuals in AD research who have undergone CSF collection or amyloid PET. The cohort consists of community-dwelling older adults recruited from the St. Louis area, including participants with and without cognitive impairment, who enrolled in research studies of memory and aging at Washington University in St. Louis. Participants underwent clinical and cognitive assessments using the Uniform Data Set (UDS)[25] that includes the Clinical Dementia Rating (CDR)[26] and Mini-Mental State Examination.[27] The UDS includes the Hollingshead 2 factor index of social position,[28] which assigns a social class based on the participant's educational level and the occupation of the head of the participant's household. Presence or absence of

Table 1 Characteristics of the Knight Alzheimer Disease Research Center Matched Cohort

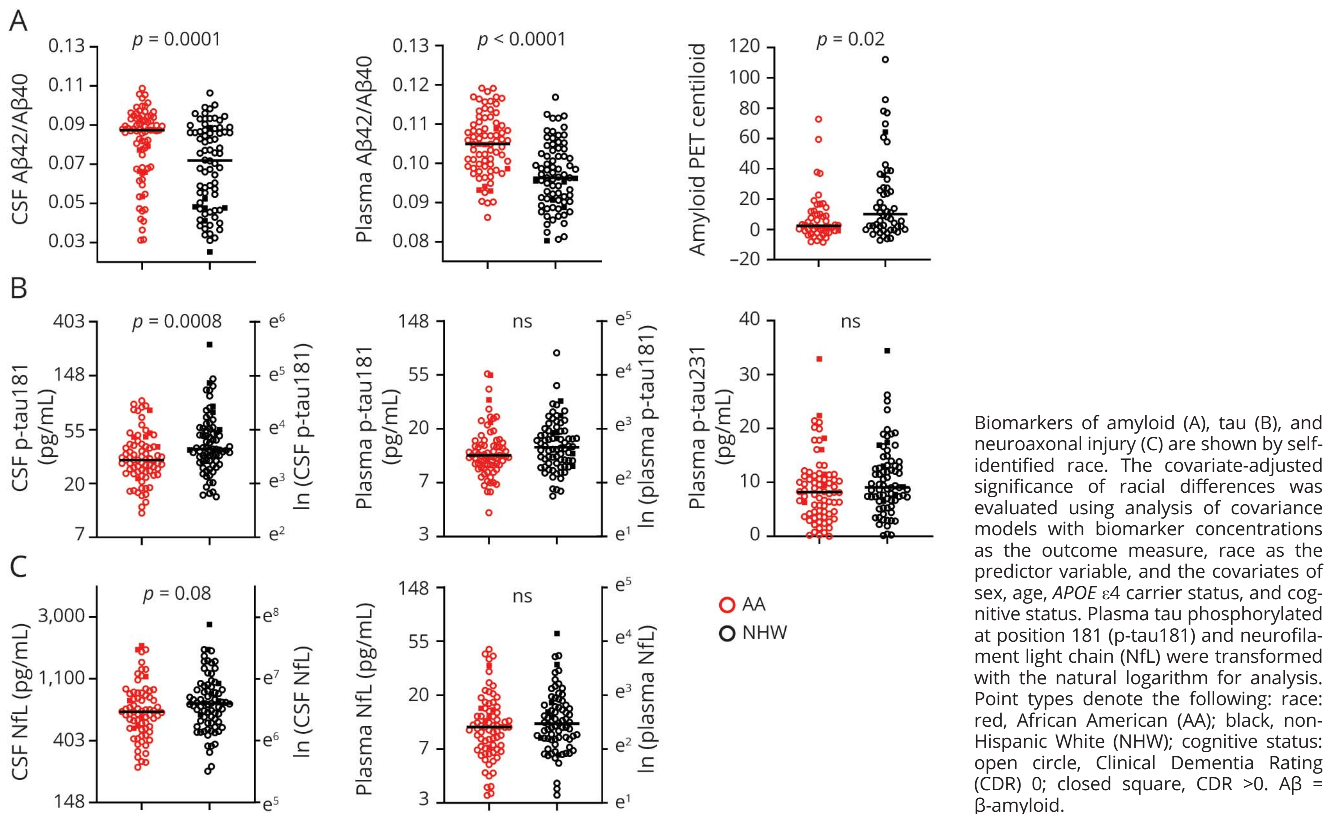
Characteristics	African American participants (n = 76)	Non-Hispanic White participants (n = 76)	*p*	Adjusted *p*
Demographics				
Age at CSF collection, y	68.4 (64.9–73.2)	68.4 (64.1–73.1)	NS	
Sex, n (% Female)	44 (58)	39 (51)	NS	
APOE ε4 status, n (% carrier)	32 (42)	32 (42)	NS	
CDR 0/0.5/1 (% >0)	69/4/3 (9)	69/5/2 (9)	NS	
Years of education	16 (12–18)	16 (14–18)	NS	
Hollingshead index	2.0 (2.0–3.5)	2.0 (1.0–3.0)	0.002	
Hypertension, yes/no/not reported (% yes of reported)	51/25/0 (67)	33/40/3 (45)	0.006	
Diabetes, yes/no/not reported (% yes of reported)	21/55/0 (28)	4/69/3 (5)	0.0003	
CSF/plasma to LP interval, y	0.11 (0.05–0.21)	0.08 (0.04–0.23)	NS	
CSF biomarker concentrations				
CSF Aβ42, pg/mL	735 (544–971)	682 (516–883)	NS	NS
CSF Aβ40, pg/mL	9,490 (7,150–11,600)	10,100 (8,880–12,300)	0.07	NS
CSF Aβ42/Aβ40	0.0874 (0.0681–0.0935)	0.0719 (0.0477–0.0870)	0.0003	0.0001
CSF Aβ42/Aβ40 < 0.0673, n (%)	17 (22)	33 (43)	0.006	0.003
CSF total tau, pg/mL	212 (165–287)	290 (217–482)	0.0002	0.002
CSF p-tau181, pg/mL	31 (24.6–41.1)	38.0 (30.4–55.7)	0.002	0.0008
CSF NfL, pg/mL	644 (493–868)[a]	736 (542–973)	0.09	0.08
Plasma biomarker concentrations				
Plasma Aβ42, pg/mL	41.9 (39.3–49.6)	40.9 (37.8–46.3)	0.06	0.03
Plasma Aβ40, pg/mL	409 (380–470)	425 (390–482)	NS	NS
Plasma Aβ42/Aβ40	0.1047 (0.0990–0.1101)	0.0963 (0.0904–0.1028)	<0.0001	<0.0001
Plasma p-tau181, pg/mL	12.3 (10.2–16.2)	14.2 (10.6–19.3)	NS	NS
Plasma p-tau231, pg/mL	8.2 (4.4–11.3)	9.1 (6.6–13.1)	0.09	NS
Plasma NfL, pg/mL	11.1 (7.6–15.5)	11.8 (8.9–16.7)	NS	NS
Amyloid PET				
Amyloid PET Centiloid	2.3 (−1.0–10.1)[b]	10.1 (0.0–33.0)[c]	0.01	0.02
Amyloid PET positive, n (%)	5 (10)[b]	21 (39)[c]	0.0008	0.003

Abbreviations: Aβ = β-amyloid; CDR = Clinical Dementia Rating; LP = lumbar puncture; NfL = neurofilament light; p-tau181 = tau phosphorylated at position 181; p-tau231 = tau phosphorylated at position 231.
Continuous values are presented as median (interquartile range). The significance of differences by self-identified race was evaluated with Wilcoxon rank sum tests for continuous variables and χ^2 or Fisher exact tests for categorical variables. The covariate-adjusted significance of racial differences was evaluated using analysis of covariance models with biomarker concentrations as the outcome measure, race as the predictor variable, and the covariates of age, sex, *APOE* ε4 carrier status, and cognitive status. Plasma p-tau181 and NfL were transformed with the natural logarithm in covariate-adjusted models.
[a] n = 72.
[b] n = 49.
[c] n = 54.

hypertension or diabetes was noted by the clinician. Race and sex were self-identified.

Participants with CSF biomarker information and adequate aliquots of plasma available for analysis were considered for inclusion. Each self-identified AA participant was matched 1:1 to a self-identified NHW participant by a computer algorithm. Participants were matched by age at the time of plasma collection (within 2 years), *APOE* ε4 status (carrier or non-carrier), and cognitive status at the time of plasma collection

Figure 1 Biomarkers by Race



Biomarkers of amyloid (A), tau (B), and neuroaxonal injury (C) are shown by self-identified race. The covariate-adjusted significance of racial differences was evaluated using analysis of covariance models with biomarker concentrations as the outcome measure, race as the predictor variable, and the covariates of sex, age, *APOE* ε4 carrier status, and cognitive status. Plasma tau phosphorylated at position 181 (p-tau181) and neurofilament light chain (NfL) were transformed with the natural logarithm for analysis. Point types denote the following: race: red, African American (AA); black, non-Hispanic White (NHW); cognitive status: open circle, Clinical Dementia Rating (CDR) 0; closed square, CDR >0. Aβ = β-amyloid.

(cognitively normal [CDR 0] or cognitively impaired [CDR >0]). If >1 NHW participant matched an AA participant, the participant with the closest age was selected.

Standard Protocol Approvals, Registrations, and Patient Consents

Written informed consent was obtained from all participants and their study partners. All procedures were approved by Washington University's Human Research Protection Office.

Genotyping

The *APOE* genotype was determined by genotyping rs7412 and rs429358 with TaqMan genotyping technology.[29] Genetic sex determined by sex chromosome–specific analysis was concordant with gender in all individuals in this cohort.

CSF and Plasma Collection and Analysis

CSF and blood samples from each participant were collected at a single session at approximately 8 AM following overnight fasting as previously described.[5,30] Concentrations of CSF Aβ40, Aβ42, t-tau, and p-tau181 were measured by chemiluminescent enzyme immunoassay using a fully automated platform (LUMIPULSE G1200; Fujirebio). CSF NfL was measured via commercial ELISA kit (UMAN Diagnostics). Plasma Aβ42 and Aβ40 were measured in the C2N Diagnostics commercial laboratory with the PrecivityAD immunoprecipitation–mass spectrometry assay.[16] Plasma p-tau181 and p-tau231 were measured in the Clinical Neurochemistry Laboratory, University of Gothenburg, using in-house Single molecule array (Simoa) assays on an HD-X analyzer (Quanterix), as previously described.[19,23] Plasma NfL was measured with Quanterix NfLight assay kits at Washington University on a HD-X analyzer. All assays were performed by personnel who were blind to participant information.

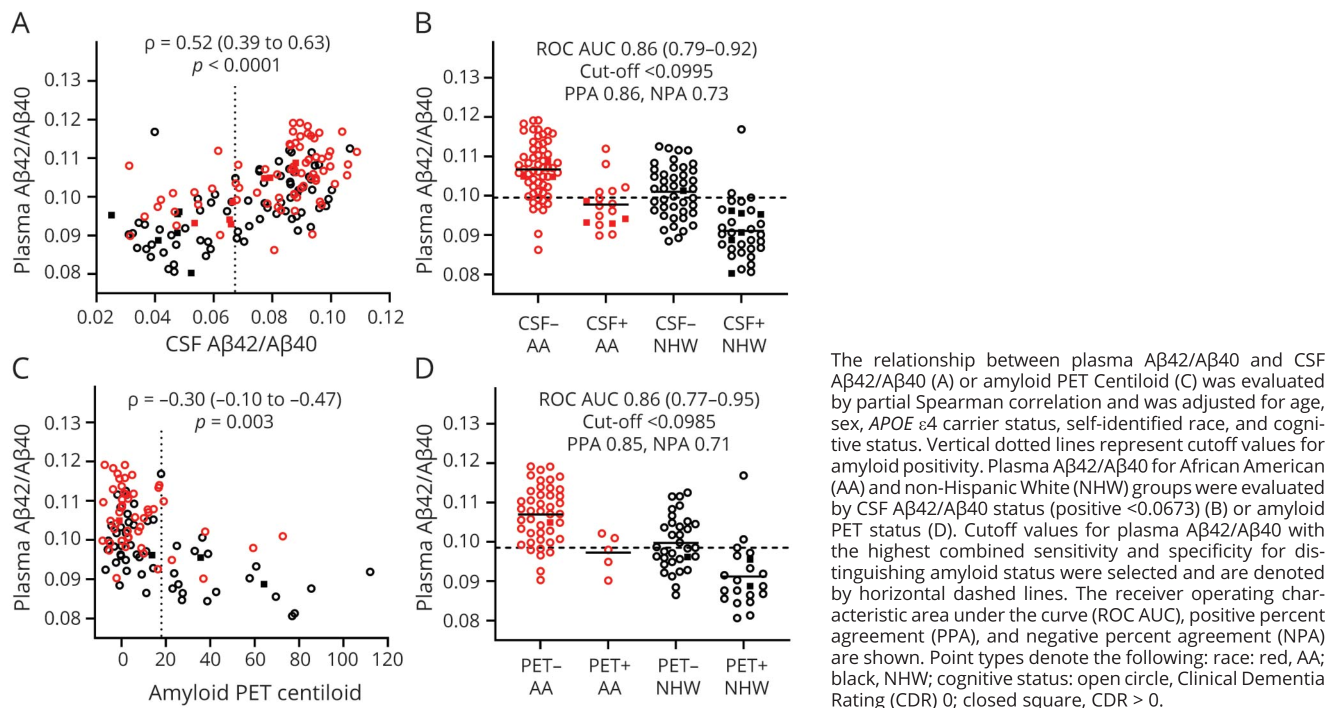
Amyloid PET

Participants underwent a dynamic scan with either florbetapir (n = 48) or Pittsburgh compound B (PiB; n = 55) in coordination with a structural MRI scan. Regional data from the 30–60 minutes postinjection window for PiB and the 50–70 minutes window for florbetapir were converted to standardized uptake value ratios (SUVRs) using cerebellar gray as a reference and partial volume corrected using a geometric transfer matrix approach based upon the Freesurfer parcellation.[31] Values from regions where amyloid deposition occurs early in AD were averaged together to represent mean cortical SUVR, which was converted to Centiloid using previously published equations.[32,33]

Statistical Analysis

The significance of differences by self-identified race were evaluated with Wilcoxon rank sum tests for continuous variables and χ^2 or Fisher exact tests for categorical variables. The covariate-adjusted significance of racial differences were

Figure 2 Relationship of Plasma Aβ42/Aβ40 With CSF Aβ42/Aβ40 and Amyloid PET



The relationship between plasma Aβ42/Aβ40 and CSF Aβ42/Aβ40 (A) or amyloid PET Centiloid (C) was evaluated by partial Spearman correlation and was adjusted for age, sex, *APOE* ε4 carrier status, self-identified race, and cognitive status. Vertical dotted lines represent cutoff values for amyloid positivity. Plasma Aβ42/Aβ40 for African American (AA) and non-Hispanic White (NHW) groups were evaluated by CSF Aβ42/Aβ40 status (positive <0.0673) (B) or amyloid PET status (D). Cutoff values for plasma Aβ42/Aβ40 with the highest combined sensitivity and specificity for distinguishing amyloid status were selected and are denoted by horizontal dashed lines. The receiver operating characteristic area under the curve (ROC AUC), positive percent agreement (PPA), and negative percent agreement (NPA) are shown. Point types denote the following: race: red, AA; black, NHW; cognitive status: open circle, Clinical Dementia Rating (CDR) 0; closed square, CDR > 0.

evaluated using analysis of covariance models with biomarker concentrations as the outcome measure, self-identified race as the predictor variable, and including the covariates of age, sex, *APOE* ε4 carrier status, and cognitive status (cognitively normal [CDR = 0] or cognitively impaired [CDR > 0]). Models used natural logarithm transformed values for CSF and plasma p-tau181 and NfL, which were positively skewed. Models including the interaction between race and *APOE* ε4 carrier status were also evaluated.

CSF Aβ42/Aβ40 status was chosen as the primary reference standard for brain amyloidosis because all individuals in the study had both CSF and blood collected at the same session, whereas only a subcohort had an amyloid PET scan performed within 2 years of CSF/blood collection. Positive CSF Aβ42/Aβ40 was defined by a CSF Aβ42/Aβ40 <0.0673, a cutoff that maximally distinguished amyloid PET status in an overlapping cohort with a receiver operating characteristic area under the curve (ROC AUC) of 0.97.[34] Amyloid PET positivity was previously defined as a mean cortical SUVR >1.42 for PiB and >1.19 for florbetapir.[32,35] Logistic regression models were implemented with CSF Aβ42/Aβ40 or amyloid PET status as the outcome measure and each plasma biomarker as the predictor variable. Covariate adjusted models included self-identified race, sex, age, *APOE* ε4 carrier status, and cognitive status. Models that in addition included either the interaction between race and *APOE* ε4 carrier status or race and plasma biomarker levels were evaluated. Differences between ROC AUCs were evaluated using the DeLong test.[36]

Statistical analyses were implemented using SAS 9.4 (SAS Institute Inc.). Plots were created with GraphPad Prism version 9.2.0 (GraphPad Software). All p values were from 2-sided tests, and results were deemed statistically significant at $p < 0.05$.

Data Availability

Data are available to qualified investigators upon request to the Knight ADRC (knightadrc.wustl.edu/Research/ResourceRequest.htm).

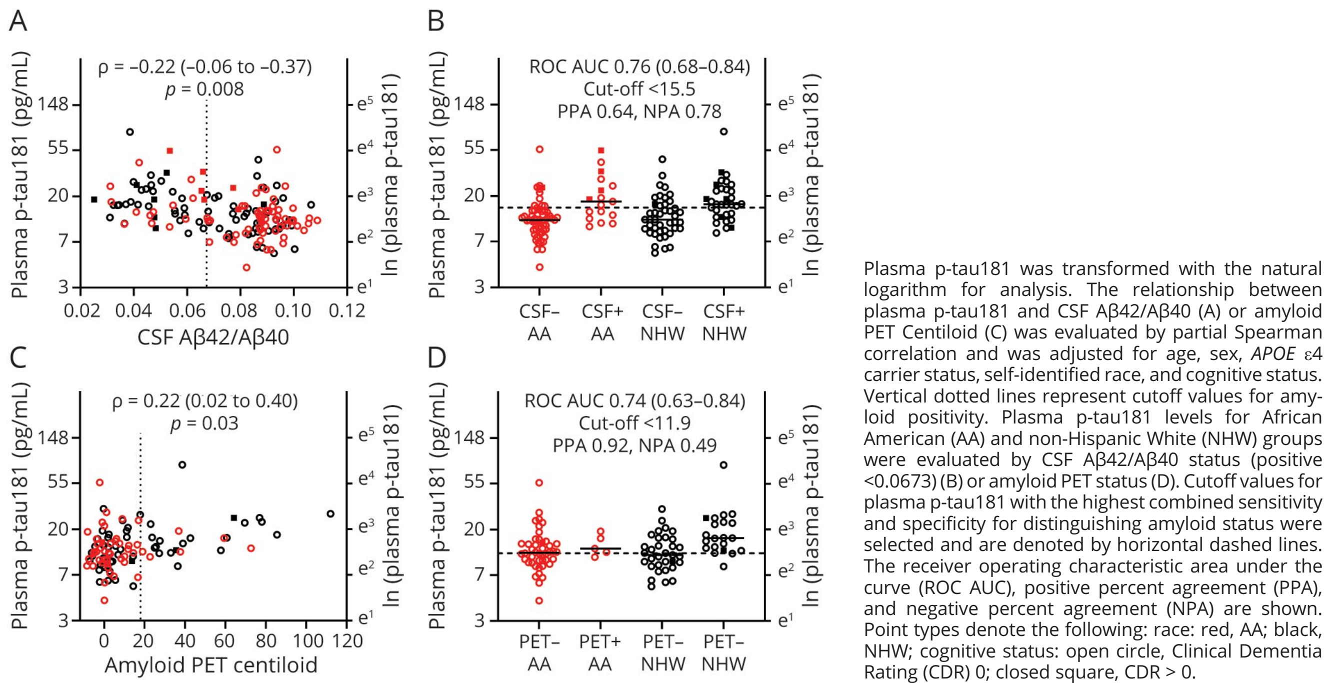
Results

Participant Characteristics

Based on the inclusion criteria of CSF biomarker information and adequate aliquots of plasma available for analysis, 79 AA and 775 NHW participants were potentially eligible for the study. Each AA participant was matched 1:1 to a NHW participant by age, *APOE* ε4 carrier status and cognitive status. Three AA participants who could not be matched to a NHW participant were not included in the study. The final study cohort included a total of 152 participants (76 AA and 76 matching NHW) who contributed samples that underwent measurement of plasma biomarkers (see Table 1 for cohort characteristics). An amyloid PET scan was performed within 2 years of plasma collection in 49 AA (64%) and 54 NHW (71%) participants (eTable 1, links.lww.com/WNL/B978). All AA participants identified their ethnicity as non-Hispanic.

For both the AA and NHW groups, the median age was 68.4 years, 42% carried at least 1 *APOE* ε4 allele (8% were ε4

Figure 3 Relationship of Plasma p-tau181 With CSF Aβ42/Aβ40 and Amyloid PET



Plasma p-tau181 was transformed with the natural logarithm for analysis. The relationship between plasma p-tau181 and CSF Aβ42/Aβ40 (A) or amyloid PET Centiloid (C) was evaluated by partial Spearman correlation and was adjusted for age, sex, *APOE* ε4 carrier status, self-identified race, and cognitive status. Vertical dotted lines represent cutoff values for amyloid positivity. Plasma p-tau181 levels for African American (AA) and non-Hispanic White (NHW) groups were evaluated by CSF Aβ42/Aβ40 status (positive <0.0673) (B) or amyloid PET status (D). Cutoff values for plasma p-tau181 with the highest combined sensitivity and specificity for distinguishing amyloid status were selected and are denoted by horizontal dashed lines. The receiver operating characteristic area under the curve (ROC AUC), positive percent agreement (PPA), and negative percent agreement (NPA) are shown. Point types denote the following: race: red, AA; black, NHW; cognitive status: open circle, Clinical Dementia Rating (CDR) 0; closed square, CDR > 0.

homozygotes), and 9% were cognitively impaired as defined by a CDR >0. There was no difference in dementia severity by race as measured by the CDR. Both the AA and NHW groups were well-educated (median of 16 years of education), but the AA group had a slightly lower social position than the NHW group as measured by the Hollingshead 2-factor index of social position (median 2.0 [interquartile range (IQR) 2.0–3.5] vs 2.0 [IQR 1.0–3.0], respectively; $p < 0.002$). Because the AA and NHW participants had no significant differences in years of education, this suggests that the median occupational level of the head of household in the AA group was lower (e.g., fewer of the AA participants lived in households headed by executives/major professionals). Compared with NHW individuals, AA individuals were more likely to have hypertension (67% vs 45%; $p = 0.006$) or diabetes (28% vs 5%; $p = 0.0003$).

CSF and Plasma Biomarkers by Race

CSF Aβ42 and Aβ40 concentrations were not significantly different between the AA and NHW groups (Table 1). However, AA individuals had higher CSF Aβ42/Aβ40 (median 0.0874 [IQR 0.0681 to 0.0935] vs 0.0719 [0.0477 to 0.0870]; $p < 0.0001$) and lower amyloid PET Centiloid (median 2.3 [IQR −1.0 to 10.1] vs 10.1 [0.0–33.0]; $p = 0.02$), consistent with the AA group having lower average levels of brain amyloidosis compared with the NHW group (Figure 1). In the overall cohort, 22% of the AA and 43% of the NHW groups had brain amyloidosis by CSF Aβ42/Aβ40 status ($p = 0.003$); in the subcohort with amyloid PET, 10% of AA and 39% of the NHW groups had brain amyloidosis by amyloid PET status ($p = 0.003$). Plasma Aβ42 was only slightly higher in the AA group ($p = 0.03$) and plasma Aβ40 did not vary by racial group, but plasma Aβ42/Aβ40 was markedly higher in the AA group (median 0.1047 [IQR 0.0990–0.1101] vs 0.0963 [0.0904–0.1028]; $p < 0.0001$), again consistent with the AA group having lower average levels of brain amyloidosis compared with the NHW group. CSF total tau and p-tau181 were lower in the AA group than the NHW group ($p = 0.002$ and $p = 0.0008$, respectively), but there were no statistically significant differences in plasma p-tau181 and p-tau231 between racial groups. There was a trend towards lower CSF NfL in AA compared with NHW individuals ($p = 0.08$), but there was no difference in plasma NfL by racial group.

Plasma Biomarkers, CSF Aβ42/Aβ40 or Amyloid PET Centiloid, and Race

Nonlinear associations between plasma biomarkers and CSF Aβ42/Aβ40 or amyloid PET Centiloid were examined by Spearman correlations, as depicted in Figures 2 and 3 and eFigures 1–2, links.lww.com/WNL/B978 and summarized in eTable 2. Of the plasma biomarkers, Aβ42/Aβ40 had the strongest correlations with CSF Aβ42/Aβ40 (ρ = 0.52 [0.39 to 0.63]) and amyloid PET Centiloid (−0.30 [-0.10 to −0.47]) after adjustment for covariates. To examine the relationships between the plasma biomarkers, brain amyloid, and race, biomarker concentrations were modeled as a function of CSF Aβ42/Aβ40 status and included race, age, sex, *APOE* ε4 carrier status, and cognitive status as covariates (Table 2). More abnormal (lower) plasma Aβ42/Aβ40 was associated with NHW race ($p < 0.0001$), male sex ($p < 0.0001$), and positive CSF Aβ42/Aβ40 status ($p < 0.0001$). In contrast, more abnormal (higher) plasma p-tau181 levels were associated with older age ($p < 0.0001$), positive CSF Aβ42/Aβ40 status ($p = 0.003$), male

Table 2 Relationship Between Plasma Biomarkers, CSF Aβ42/Aβ40 Status, and Covariates

Parameter	Estimate	SE	*p*
Plasma Aβ42/Aβ40			
Intercept	0.1052	0.0051	<0.0001
CSF Aβ42/Aβ40 status (positive)	−0.008	0.0013	<0.0001
Race (African American)	0.0060	0.0011	<0.0001
Sex (female)	0.0044	0.0011	<0.0001
Age (y)	−0.00010	0.00007	NS
APOE ε4 status (carrier)	−0.0009	0.0011	NS
Cognitive status (CDR >0)	−0.0010	0.0019	NS
Ln (plasma p-tau181)			
Intercept	1.267	0.311	<0.0001
CSF Aβ42/Aβ40 status (positive)	0.239	0.079	0.003
Race (African American)	−0.044	0.066	NS
Sex (female)	−0.164	0.065	0.01
Age (y)	0.020	0.004	<0.0001
APOE ε4 status (carrier)	0.017	0.068	NS
Cognitive status (CDR >0)	0.278	0.115	0.02
Plasma p-tau231			
Intercept	−1.655	4.474	NS
CSF Aβ42/Aβ40 status (positive)	2.525	1.140	0.03
Race (African American)	−0.970	0.946	NS
Sex (female)	−0.985	0.940	NS
Age (y)	0.160	0.063	0.01
APOE ε4 status (carrier)	−0.190	0.985	NS
Cognitive status (CDR >0)	5.585	1.651	0.0009
Ln (plasma NfL)			
Intercept	−0.710	0.357	0.05
CSF Aβ42/Aβ40 status (positive)	−0.015	0.091	NS
Race (African American)	−0.091	0.075	NS
Sex (female)	−0.052	0.075	NS
Age (y)	0.046	0.005	<0.0001
APOE ε4 status (carrier)	0.092	0.079	NS
Cognitive status (CDR >0)	0.297	0.132	0.03

Abbreviations: Aβ = β-amyloid; CDR = Clinical Dementia Rating; NfL = neurofilament light; p-tau181 = tau phosphorylated at position 181; p-tau231 = tau phosphorylated at position 231.
Analysis of covariance models evaluated the effects of CSF Aβ42/Aβ40 status (positive <0.0673), self-identified race, sex, age, *APOE* ε4 carrier status, and cognitive status on levels of each plasma biomarker. Plasma p-tau181 and NfL were transformed with the natural logarithm for analysis.

sex ($p = 0.01$), and impaired cognitive status ($p = 0.02$). More abnormal (higher) p-tau231 levels were associated with impaired cognitive status ($p = 0.0009$), older age ($p = 0.01$), and positive CSF Aβ42/Aβ40 status ($p = 0.03$). More abnormal (higher) plasma NfL levels were associated with older age ($p < 0.0001$) and impaired cognitive status ($p = 0.03$). Similar models of plasma biomarker levels including amyloid PET status rather than CSF Aβ42/Aβ40 status yielded similar results except that cognitive status was not a significant predictor in any model (eTables 3–6); few participants with cognitive impairment had amyloid PET data (4 of 103), limiting power to detect differences by cognitive status in these models. Models that included the interaction between race and *APOE* ε4 carrier status were evaluated, but the interaction was not significant for any model and therefore it was not included in the final analyses.

Correspondence of Plasma Biomarkers With CSF Aβ42/Aβ40 and Amyloid PET Status

Prediction of CSF Aβ42/Aβ40 or amyloid PET status by plasma biomarkers was evaluated by logistic regression analyses, as depicted in Figures 2 and 3 and eFigures 1 and 2, links.lww.com/WNL/B978, shown in eTables 7–11, and summarized in Tables 3 and 4. Models predicting CSF Aβ42/Aβ40 status based on plasma biomarker levels had ROC AUCs as follows: Aβ42/Aβ40, 0.86 (95% CI 0.79–0.92); p-tau181, 0.76 (0.68–0.84); p-tau231, 0.69 (0.60–0.78); and NfL, 0.64 (0.55–0.73). The amyloid probability score, a proprietary modeled value provided by C2N Diagnostics that is based on plasma Aβ42/Aβ40, *APOE* proteotype and age,[17] had an ROC AUC of 0.89 (0.84–0.95) with CSF Aβ42/Aβ40 status. Comparisons of ROC AUCs showed that plasma Aβ42/Aβ40 had significantly better prediction of CSF Aβ42/Aβ40 status compared with p-tau181, p-tau231, and NfL ($p < 0.05$, 0.004, and <0.0001, respectively; Table 3).

Covariate adjusted models of CSF Aβ42/Aβ40 status incorporating each plasma biomarker and covariates (age, sex, *APOE* ε4 carrier status, race, and cognitive status) are summarized in Table 4. The model based on plasma Aβ42/Aβ40 had an ROC AUC of 0.90 (0.85–0.96) (eTable 7, links.lww.com/WNL/B978), which was superior to a model of covariates alone (0.82 [0.74–0.89] (eTable 12); $p = 0.006$ for difference in ROC AUCs). In the model of CSF Aβ42/Aβ40 status incorporating plasma Aβ42/Aβ40 and covariates, a higher probability of CSF Aβ42/Aβ40 positivity was associated with *APOE* ε4 carriers (odds ratio [OR] 5.6 [95% CI 2.0–16]; $p = 0.001$), older age in years (OR 1.12 [1.03–1.21]; $p = 0.007$), and cognitive impairment (OR 9.2 [1.9–46]; $p = 0.007$). Notably, in models incorporating plasma Aβ42/Aβ40 and covariates, race did not significantly affect correspondence with CSF Aβ42/Aβ40 or amyloid PET status.

The covariate-adjusted model for CSF Aβ42/Aβ40 status based on p-tau181 had an ROC AUC of 0.85 (0.79–0.92) (Table 4 and eTable 9, links.lww.com/WNL/B978). In this model, a higher probability of CSF Aβ42/Aβ40 positivity was associated with *APOE* ε4 carriers (OR 5.7 [2.3–14]; $p = 0.0002$), cognitive

Table 3 CSF Aβ42/Aβ40 or Amyloid PET Status as Predicted by Plasma Aβ42/Aβ40 and Covariates

	Unadjusted model			**Covariate adjusted model**		
	ROC AUC	**Biomarker *p***	**Versus plasma Aβ42/Aβ40 *p***	**ROC AUC**	**Biomarker *p***	**Versus plasma Aβ42/Aβ40 *p***
Prediction of CSF Aβ42/Aβ40 status (n = 152)						
Plasma Aβ42/Aβ40	0.86 (0.79–0.92)	<0.0001	reference	0.90 (0.85–0.96)	<0.0001	reference
Amyloid probability score	0.89 (0.84–0.95)	<0.0001	0.05	0.91 (0.87–0.96)	<0.0001	NS
Ln (plasma p-tau181)	0.76 (0.68–0.84)	<0.0001	<0.05	0.85 (0.79–0.92)	0.007	NS
Plasma p-tau231 (pg/mL)	0.69 (0.60–0.78)	0.0002	0.004	0.85 (0.78–0.91)	0.01	0.07
Ln (plasma NfL)	0.64 (0.55–0.73)	0.008	<0.0001	0.81 (0.74–0.89)	NS	0.005
Covariates alone	NA	NA	NA	0.82 (0.74–0.89)	NA	0.006
Prediction of amyloid PET status (n = 103)						
Plasma Aβ42/Aβ40	0.86 (0.77–0.95)	<0.0001	reference	0.89 (0.82–0.97)	0.0004	reference
Amyloid probability score	0.90 (0.82–0.97)	<0.0001	NS	0.90 (0.84–0.96)	0.0006	NS
Ln (plasma p-tau181)	0.74 (0.63–0.84)	0.002	0.05	0.84 (0.75–0.92)	0.02	NS
Plasma p-tau231 (pg/mL)	0.69 (0.58–0.81)	0.004	0.02	0.84 (0.75–0.92)	0.01	NS
Ln (plasma NfL)	0.55 (0.43–0.67)	NS	<0.0001	0.82 (0.73–0.91)	NS	NS
Covariates alone	NA	NA	NA	0.81 (0.72–0.90)	NA	0.08

Abbreviations: Aβ = β-amyloid; AUC = area under the receiver operating characteristic curve; CDR = Clinical Dementia Rating; NfL = neurofilament light; p-tau181 = tau phosphorylated at position 181; p-tau231 = tau phosphorylated at position 231; ROC = receiver operating characteristic.
Logistic regression models evaluated prediction of CSF Aβ42/Aβ40 (positive <0.0673) or amyloid PET status by each plasma biomarker alone (unadjusted models) or plasma biomarkers and the covariates of self-identified race, sex, age, *APOE* ε4 carrier status, and cognitive status (adjusted models). The amyloid probability score is a proprietary modeled value that incorporates plasma Aβ42/Aβ40, age, and *APOE* proteotype. Plasma p-tau181 and NfL were transformed with the natural logarithm for analysis. For each model, the ROC AUC with 95% CIs is shown. The significance of each biomarker as a predictor in the model (biomarker *p*) and the difference between the ROC AUC for the plasma Aβ42/Aβ40 model and other models (versus plasma Aβ42/Aβ40 *p*) is shown.

Table 4 CSF Aβ42/Aβ40 Status as Predicted by Plasma Biomarkers and Covariates

Parameter	Estimate	SE	*p*
Plasma Aβ42/Aβ40, ROC AUC 0.90 (0.85–0.96)			
Intercept	13.0	4.7	0.005
Plasma Aβ42/Aβ40 (pg/mL)	−220	46	<0.0001
Race (African American)	0.058	0.274	NS
Sex (female)	0.843	0.568	NS
Age, y	0.109	0.04	0.007
***APOE* ε4 status (carrier)**	0.865	0.269	0.001
Cognitive status (CDR>0)	1.11	0.41	0.007
Plasma p-tau181, ROC AUC 0.85 (0.79-0.92)			
Intercept	−8.69	2.71	0.001
Ln (plasma p-tau181)	1.53	0.57	0.007
Race (African American)	−0.59	0.22	0.007
Sex (female)	−0.21	0.44	NS
Age, y	0.072	0.035	0.04
***APOE* ε4 status (carrier)**	0.87	0.23	0.0002
Cognitive status (CDR>0)	1.02	0.39	0.009
Plasma p-tau231, ROC AUC 0.85 (0.78-0.91)			
Intercept	−6.95	2.50	0.006
Plasma p-tau231 (pg/mL)	0.098	0.040	0.01
Race (African American)	−0.60	0.22	0.006
Sex (female)	−0.37	0.43	NS
Age, y	0.096	0.034	0.004
***APOE* ε4 status (carrier)**	0.94	0.23	<0.0001
Cognitive status (CDR >0)	1.07	0.38	0.006
Plasma NfL, ROC AUC 0.81 (0.74-0.89)			
Intercept	−6.20	2.41	0.01
Ln (plasma NfL)	−0.097	0.476	NS
Race (African American)	−0.65	0.22	0.003
Sex (female)	−0.50	0.42	NS
Age, y	0.109	0.040	0.007
***APOE* ε4 status (carrier)**	0.89	0.23	<0.0001
Cognitive status (CDR>0)	1.27	0.39	0.001

Abbreviations: Aβ = β-amyloid; AUC = area under the receiver operating characteristic curve; CDR = Clinical Dementia Rating; NfL = neurofilament light; p-tau181 = tau phosphorylated at position 181; ROC = receiver operating characteristic.
Logistic regression models evaluated prediction of CSF Aβ42/Aβ40 status (positive <0.0673) by each plasma biomarker and the covariates of self-identified race, sex, age, *APOE* ε4 carrier status, and cognitive status. Plasma p-tau181 and NfL were transformed with the natural logarithm for analysis. For each model, the ROC AUC with 95% CI is shown.

impairment (OR 7.7 [1.7–36]; $p = 0.009$), and older age in years (OR 1.08 [1.00–1.15]; $p = 0.04$); AA race was associated with a lower probability of positivity (OR 0.31 [0.13–0.73]; $p = 0.007$). Models of CSF Aβ42/Aβ40 or amyloid PET status based on p-tau231 (eTable 10) or NfL (eTable 11) were also evaluated and are summarized in Table 4.

A model of CSF Aβ42/Aβ40 status based only on covariates demonstrated that AA race was associated with a lower probability of CSF Aβ42/Aβ40 positivity (OR 0.27 [0.12–0.64]; $p = 0.003$) (eTable 12, links.lww.com/WNL/B978). AA race significantly decreased the probability of CSF Aβ42/Aβ40 positivity in models based on plasma p-tau181 (OR 0.31 [0.13–0.73]; $p = 0.007$), p-tau231 (OR 0.30 [0.13–0.71]; $p = 0.006$), or NfL (OR 0.27 [0.12–0.64]; $p = 0.003$) levels. Consistent with these results, AA race decreased the probability of amyloid PET positivity in models including plasma p-tau181 (OR 0.19 [0.06–0.63]; $p = 0.007$), p-tau231 (OR 0.17 [0.05–0.59]; $p = 0.005$), or NfL (OR 0.17 [0.05–0.55]; $p = 0.003$) levels (eTables 9–11, respectively). In contrast, race did not affect the probability of CSF Aβ42/Aβ40 or amyloid PET positivity associated with plasma Aβ42/Aβ40 (eTable 7). Models of CSF Aβ42/Aβ40 status including only cognitively normal individuals (91% of cohort) showed the same major findings as models that included the entire cohort (eTable 13). Models of CSF Aβ42/Aβ40 status were also evaluated that incorporated either the interaction between race and *APOE* ε4 carrier status or race and plasma biomarker levels, but neither interaction was significant for any model and therefore the interactions were not included in the final analyses.

Combining Plasma Biomarkers

A model of CSF Aβ42/Aβ40 status including levels of all plasma biomarkers and covariates had an ROC AUC of 0.92 (0.88–0.96), which was not significantly different from the ROC AUC of the model including Aβ42/Aβ40 as the only plasma biomarker (eTable 14, links.lww.com/WNL/B978). In the model with all plasma biomarkers, plasma Aβ42/Aβ40 was the only biomarker that was a significant predictor ($p < 0.0001$): plasma p-tau181, p-tau231, and NfL were not significant predictors of CSF Aβ42/Aβ40 after adjusting for the effects of plasma Aβ42/Aβ40 and covariates. In a similar model of amyloid PET status, plasma Aβ42/Aβ40 and plasma NfL levels were both significant predictors ($p = 0.0004$ and $p = 0.007$, respectively). In models of CSF Aβ42/Aβ40 or amyloid PET status with all plasma biomarkers and covariates (including plasma Aβ42/Aβ40), race was not a significant predictor.

Discussion

This study found that the C2N Diagnostics PrecivityAD plasma Aβ42/Aβ40 assay more accurately classified CSF Aβ42/Aβ40 or amyloid PET status compared with Simoa-based assays for plasma p-tau181, p-tau231, and NfL in a mostly cognitively normal cohort of matched AA and NHW

research participants. Self-identified race did not affect prediction of CSF Aβ42/Aβ40 or amyloid PET status by plasma Aβ42/Aβ40. However, AA individuals had a significantly lower probability of CSF or amyloid PET positivity compared with NHW in models incorporating plasma p-tau181, p-tau231, or NfL levels, suggesting that predictive algorithms for these assays would perform inconsistently across racial groups and that applying cutoffs established in NHW individuals to AA individuals could lead to disproportionate misdiagnosis of AA.

Plasma biomarkers have been almost exclusively studied in non-Hispanic White cohorts, with little data available on the performance of these biomarkers in other groups. A recent study of a multiracial cohort found good performance of plasma p-tau217 in distinguishing clinical, pathologic, and amyloid PET status, but performance of the assay in predicting amyloid PET status across racial groups could not be ascertained because only 40 individuals had amyloid PET data.[37] Another study found that plasma p-tau181 and plasma p-tau181/Aβ42 were associated with brain amyloidosis and hippocampal atrophy in a Singaporean AD cohort with high burden of cerebrovascular disease, but it did not investigate potential plasma biomarker differences across racial groups.[38] Plasma NfL has been studied in a large Latino cohort, but amyloid PET data were only available in a relatively small subset of participants.[39] To reduce racial disparities in research and clinical care, it is important to confirm that plasma biomarker assays have accurate and consistent performance in identifying amyloid status across racial and ethnic groups.

Comparing the absolute values of biomarkers corrected for covariates may be misleading in evaluating which biomarkers perform consistently across racial groups. For example, in this study AA individuals had higher average plasma Aβ42/Aβ40 compared with NHW individuals, but this reflected lower levels of brain amyloidosis in AA individuals and did not affect the probability of CSF Aβ42/Aβ40 positivity associated with a given plasma Aβ42/Aβ40 value. In contrast, plasma p-tau181 levels did not vary by race, but AA individuals were less likely to be amyloid positive at a given plasma p-tau181 value. Without a comparison to reference standards, investigators might have concluded that plasma Aβ42/Aβ40 was more variable across racial groups and that p-tau isoforms were more consistent, when in fact plasma Aβ42/Aβ40 was accurately detecting differences in brain amyloidosis by racial group. Confirming that plasma biomarker assays have accurate and consistent performance in identifying amyloid status across racial and ethnic groups requires comparison with a reference standard, and not just covariate-adjusted models of absolute levels.

Previous studies have found an inconsistent relationship between amyloid biomarkers and race. One study found that AA individuals had higher measures of amyloid PET[40]; another recent study found the opposite result.[12] Some studies have found no differences in CSF Aβ42 levels by racial group,[6-8] but the current findings demonstrate that CSF Aβ42 alone may not reveal significant racial differences that are apparent when CSF Aβ42/Aβ40 is evaluated. The inconsistent relationship between race and amyloid biomarkers could reflect variation in recruitment methods: NHW and AA individuals are often recruited differently (e.g., NHW are more often referred by health care providers and AA individuals are more often referred by community contacts).[41,42] Recruitment differences could result in racial groups having significantly different comorbidities, social determinants of health, or frequencies of brain amyloidosis. Potential differences in brain amyloidosis by racial group again suggest that comparison of plasma biomarkers with a reference standard, rather than comparison of absolute values, may be more helpful in establishing which plasma biomarker assays are accurate and consistent across racial groups.

One important issue in the fluid biomarker field is that different assays for plasma analytes have widely varying performance. A recent head-to-head comparison of 8 different plasma Aβ42/Aβ40 assays found ROC AUCs with CSF Aβ42/Aβ40 status ranging from a maximum of 0.86 for the Washington University assay that is the basis for the C2N assay used in this study down to a minimum of 0.69 for some immunoassays (0.50 is chance alone).[43] In another head-to-head comparison study, different p-tau assays yielded somewhat different findings, even for the same p-tau isoform.[44] The differences in assay performance complicate comparisons of the relationship of different biomarker analytes to factors such as race. For example, it is unclear whether the probability of CSF Aβ42/Aβ40 or amyloid PET positivity would be affected by race in models incorporating plasma p-tau181, p-tau231, or p-tau217 measured with higher performing assays (e.g., ROC AUC of >0.85 with CSF Aβ42/Aβ40 or amyloid PET status). Performance of plasma assays may vary markedly in prediction of brain amyloidosis depending on the study cohort. For example, the p-tau181 assay used in the current study performed very well in predicting amyloid PET status in a cohort including both cognitively normal and cognitively impaired individuals (ROC AUC 0.88),[19] but the performance was lower when predicting amyloid PET status in cognitively normal individuals (ROC AUC 0.82).[45] Overall, use of consistently high-performing assays is needed to make accurate conclusions about comparative associations of biomarkers.

Although this study made use of one of the largest AD research cohorts with CSF and amyloid PET data, there are major limitations in the conclusions. Individuals enrolled in this study were primarily from the greater St. Louis metropolitan area and individuals from other geographic regions may vary in key characteristics such as medical comorbidities or social determinants of health. The very small number of individuals with cognitive impairment (7 of 76 in each group) was not sufficient to allow analysis of the relationships between cognitive impairment, race, and biomarker levels. This study of 76 matched pairs of individuals, in which 6 variables had significant effects, was also not sufficiently powered to evaluate the underlying reasons for the racial differences. The

Hollingshead index of social position demonstrated that AA individuals had a slightly lower social position compared with NHW individuals. However, this measure does not capture the complex social factors that may underlie biomarker differences between the groups. AA individuals had a higher rate of hypertension and diabetes compared with NHW individuals, but the relatively small cohort did not permit a detailed investigation of these effects. For example, only 4 NHW individuals had diabetes, which does not permit analysis of race by diabetes interactions. Although this study is insufficiently powered or does not have the data available to answer many important questions, it does document racial differences in plasma biomarkers that could potentially lead to clinical misdiagnosis, bias clinical trials that use a biomarker cutoff for inclusion,[12,46] and affect interpretation of biomarkers as a secondary end point. These findings should encourage investigators to evaluate the performance of plasma biomarker assays in diverse cohorts. This report strengthens the justification for the creation of large, diverse cohorts that are adequately powered to evaluate the underlying reasons for racial differences.

It is critical to understand that biomarker differences associated with race likely reflect differences in medical comorbidities, social determinants of health, or the effects of systemic racism rather than inherent biological differences.[10] For example, in this study cohort there were differences in the rates of hypertension and diabetes by racial group, and recent work has demonstrated that major medical comorbidities such as heart and kidney disease may affect plasma biomarker levels.[47] AD research cohorts have traditionally not collected detailed information about social determinants of health such as economic stability, access to healthy foods, neighborhood safety, and quality of education that may be associated with dementia; the importance of these factors is now gaining greater recognition.[48] The greater accessibility and acceptance of blood-based AD biomarkers may enable creation of larger cohorts and increased inclusion of groups, such as AA individuals, that have been underrepresented in AD biomarker studies.[49] Much larger longitudinal studies of diverse cohorts are needed to evaluate the intersection of race, AD biomarkers, cognitive impairment, medical comorbidities, and social determinants of health.[50] Improved understanding of these complex factors will enable more accurate AD diagnosis and improve patient care for all groups.

Acknowledgment

The authors thank the research volunteers who participated in the studies from which these data were obtained and their families and the Clinical, Fluid Biomarker and Imaging Cores at the Knight Alzheimer Disease Research Center for sample and data collection.

Study Funding

This study was supported by National Institute on Aging grants R01AG070941 (S.E.S.), K23AG053426 (S.E.S.), P30AG066444 (J.C.M.), P01AG003991 (J.C.M.), P01AG026276 (J.C.M.), R01AG067505 (C.X.), and RF1R01AG053550 (C.X.) and the Cure Alzheimer's Fund (K.L.M.). C2N Diagnostics provided the plasma Aβ42/Aβ40 assays for this study. T.K.K. was funded by the Alzheimer's Association Research Fellowship (850325), the BrightFocus Foundation (A2020812F), the International Society for Neurochemistry's Career Development Grant, the Swedish Alzheimer Foundation (Alzheimerfonden; AF-930627), the Swedish Brain Foundation (Hjärnfonden; FO2020-0240), the Swedish Dementia Foundation (Demensförbundet), the Swedish Parkinson Foundation (Parkinsonfonden), the Gamla Tjänarinnor Foundation, the Aina (Ann) Wallströms and Mary-Ann Sjöbloms Foundation, the Agneta Prytz-Folkes & Gösta Folkes Foundation (2020-00124), the Gun and Bertil Stohnes Foundation, and the Anna Lisa and Brother Björnsson's Foundation. H.Z. is a Wallenberg Scholar supported by grants from the Swedish Research Council (2018–02532), the European Research Council (681712), Swedish State Support for Clinical Research (ALFGBG-720931), the Alzheimer Drug Discovery Foundation (ADDF) USA (201809–2016862), the AD Strategic Fund and the Alzheimer's Association (ADSF-21-831376-C, ADSF-21-831381-C, and ADSF-21-831377-C), the Olav Thon Foundation, the Erling-Persson Family Foundation, Stiftelsen för Gamla Tjänarinnor, Hjärnfonden, Sweden (FO2019-0228), the European Union's Horizon 2020 research and innovation programme under the Marie Skłodowska-Curie grant agreement 860197 (MIRIADE), and the UK Dementia Research Institute at UCL. K.B. is supported by the Swedish Research Council (2017-00915), the Swedish Alzheimer Foundation (AF-742881), Hjärnfonden, Sweden (FO2017-0243), the Swedish state under the agreement between the Swedish government and the County Councils, the ALF-agreement (ALFGBG-715986), and the Alzheimer's Association 2021 Zenith Award (ZEN-21-848,495).

Disclosure

S.E. Schindler has received data on behalf of Washington University from C2N Diagnostics at no cost. T.K. Karikari, N.J. Ashton, and R.L. Henson report no disclosures relevant to the manuscript. K.E. Yarasheski, T. West, M.R. Meyer, and K.M. Kirmess are employees of C2N Diagnostics, which offers the PrecivityAD test described in this article. Y. Li, B. Saef, K.L. Moulder, and D. Bradford report no disclosures relevant to the manuscript. A.M. Fagan has received research funding from Biogen, Centene, Fujirebio, and Roche Diagnostics; is a member of the scientific advisory boards for Roche Diagnostics, Genentech, and Diadem; and consults for DiamiR and Siemens Healthcare Diagnostics Inc. B.A. Gordon reports no disclosures relevant to the manuscript. T.L.S. Benzinger has investigator-initiated research funding from the NIH, the Alzheimer's Association, the Barnes-Jewish Hospital Foundation, and Avid Radiopharmaceuticals (a wholly owned subsidiary of Eli Lilly); participates as a site investigator in clinical trials sponsored by Avid Radiopharmaceuticals, Eli Lilly, Biogen, Eisai, Janssen, and Roche; serves as an unpaid consultant to Eisai and Siemens; and is on the speaker's bureau for Biogen. J. Balls-Berry is a member of the patient advisory board and receives financial support for the Dartmouth University project Implementation of Uterine Fibroid

Option Grid Patient Decision Aids Across Five Organizational Settings (UPFRONT; NCT03985449). R.J. Bateman co-founded C2N Diagnostics, receives income from C2N Diagnostics for serving on the scientific advisory board, and consults for Roche, Genentech, AbbVie, Pfizer, Boehringer-Ingelheim, and Merck. Dr. Bateman and Washington University have equity ownership interest in C2N Diagnostics and receive royalty income based on technology (stable isotope labeling kinetics and blood plasma assay) licensed by Washington University to C2N Diagnostics. Washington University, with Dr. Bateman as coinventor, has submitted the US provisional patent application "Plasma Based Methods for Detecting CNS Amyloid Deposition." C. Xiong consults for Diadem. H. Zetterberg has served on scientific advisory boards and/or as a consultant for Alector, Eisai, Denali, Roche Diagnostics, Wave, Samumed, Siemens Healthineers, Pinteon Therapeutics, Nervgen, AZTherapies, CogRx, and Red Abbey Labs; has given lectures in symposia sponsored by Cellectricon, Fujirebio, Alzecure, and Biogen; and is a co-founder of Brain Biomarker Solutions in Gothenburg AB (BBS), which is a part of the GU Ventures Incubator Program. K. Blennow has served as a consultant, on advisory boards, or on data monitoring committees for Abcam, Axon, Biogen, JOMDD/Shimadzu, Julius Clinical, Lilly, MagQu, Novartis, Prothena, Roche Diagnostics, and Siemens Healthineers, and is a co-founder of Brain Biomarker Solutions in Gothenburg AB (BBS), which is a part of the GU Ventures Incubator Program. J.C. Morris is Chair of the Research Strategy Council of the Cure Alzheimer's Fund. Go to Neurology.org/N for full disclosures.

Publication History

Received by *Neurology* September 24, 2021. Accepted in final form February 22, 2022. Submitted and externally peer reviewed. The handling editor was Linda Hershey, MD, PhD.

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