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RESEARCH ARTICLE

Characterization of plasma AT(N) biomarkers among a racial and ethnically diverse community-based cohort: an HABS-HD study

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Abstract

INTRODUCTION: Alzheimer's disease (AD) biomarkers of Amyloid(A), Tau(T), and Neurodegeneration(N) have been increasingly studied to fill the gap in our understanding of racial and ethnic differences. This study aimed to examine the relationship between plasma AT(N) biomarkers and (1) AT(N) neuroimaging biomarkers, (2) demographics, (3) medical comorbidities, and (4) cognitive diagnosis.

METHODS: Data were analyzed from $n = 764$ non-Hispanic Black (NHB), $n = 1230$ Hispanic, and $n = 1232$ non-Hispanic White (NHW) participants. Plasma AT(N) biomarkers were derived using single molecule array (SIMOA) technology on an HD-X imager and included amyloid beta (Aβ)42/40, total tau, ptau181, and neurofilament light chain (NfL). Clinical reads of positron emission tomography (PET) amyloid and tau positivity were used to examine the link between AT(N) plasma and neuroimaging

biomarkers. Generalized linear models were conducted to examine the relationship between plasma AT(N) biomarkers and select demographic, diagnostic, and medical comorbidities (hypertension, diabetes, dyslipidemia, chronic kidney disease).

RESULTS: Differences in the AT(N) biomarkers were found across racial/ethnic groups. Plasma Aβ42/40 was found to be associated with PET amyloid positivity only among NHW participants, while plasma NfL was found to correlate with Meta-ROI among NHB and Hispanic participants. Ptau181 was associated with PET amyloid positivity among NHB and NHW participants and well as PET tau positivity among the latter group and Hispanic participants. Diabetes was related to increased plasma AT(N) biomarkers among NHB and Hispanic participants. CKD was associated with increased AT(N) biomarkers for all race/ethnic groups with the exception of Aβ42/40. While Aβ42/40, total tau, ptau181, and NfL were found to be related to a dementia diagnosis among NHW participants, only ptau181 and NfL were found to be related to this same diagnostic category among NHB and Hispanic participants.

DISCUSSION: Our findings indicate differential relationships between comorbidities (demographic, medical, diagnostic) across NHB, Hispanic, and NHW participants. This work expands our knowledge regarding the associations of plasma biomarkers to AD pathology in diverse populations.

KEYWORDS
AT(N), Black participants, biomarkers, community-based, Hispanic participants, plasma

Highlights

- Differences in AT(N) plasma biomarkers were found in a diverse community cohort.
- While plasma Aβ42/40 was associated with PET amyloid positivity among non-Hispanic white participants, this did not apply to non-Hispanic Black or Hispanic participants.
- Medical comorbidity of diabetes and chronic kidney disease was related to increased plasma AT(N) biomarkers among the ethnically diverse segment of the cohort.
- Plasma AT(N) biomarkers were more so related to a diagnosis of dementia for non-Hispanic white as compared to Hispanic or non-Hispanic Black participants.
- Across racial/ethnic groups, the plasma biomarkers of neurodegeneration (NfL) and ptau181 were related to a diagnosis of dementia.

1 | BACKGROUND

Application of plasma biomarkers for the detection of neurodegenerative diseases such as Alzheimer's disease (AD) have continued to gain interest. Plasma AD biomarkers such as amyloid beta (Aβ) 42/40 and total tau have historically been the most studied for their utility; however, emerging plasma phosphorylated tau isotopes have been increasingly looked at. The AT(N) framework for AD utilizes such biomarkers to assist with the study of AD and, ultimately, diagnosis and treatment.[1] Research leveraged to support the development of this framework, however, has been broadly representative of non-Hispanic White (NHW) participants, as has historically been the case in AD research that employs a clinic-based approach to recruitment. The lack of diverse representation in developing such a framework led the authors to acknowledge the considerable need to examine the application among other racial/ethnic groups.[1]

Several studies have been conducted to examine AD biomarkers among select racial/ethnic groups, such as Hispanic participants and NHB participants with varying results. One study conducted through the Alzheimer's Disease Neuroimaging Initiative consisting of $n = 47$ NHB and $n = 43$ Latino participants with matched NHW participants found no significant difference in either plasma or cerebrospinal fluid (CSF) AD biomarkers between racial/ethnic groups once adjusting for covariates, despite initial differences found in CSF levels of total tau

and ptau181.[1] Additional work conducted through the Washington Heights/Inwood Columbia Aging Project similarly found no difference in plasma AD biomarkers in their multi-ethnic cohort comprised of n = 99 NHW, n = 98 NHB, and n = 100 Hispanic participants.[2]

In contrast, other work conducted by Fischer and colleagues[3] found that among their cohort of NHB participants, cognitive performance over time was related to a lower baseline plasma Aβ42/40 ratio, despite baseline cognition itself not being significantly associated with the plasma AD biomarkers. In our own prior work, racial/ethnic differences were shown with findings to suggest Mexican American individuals experience lower levels of plasma Aβ40 coupled with higher levels of total tau as compared to NHW individuals, following adjustments for demographic and medical comorbidities.[4] In a recent large cross-sectional study of plasma AD biomarkers conducted among a more diverse sample (n = 235 NHB, n = 852 Mexican American, and n = 775 NHW participants), NHB participants, as compared to NHW and Mexican American participants with dementia, were shown to have lower plasma levels of Aβ40, total tau, and NfL.[5]

Work conducted through the Mayo Clinic Alzheimer's Disease Research Center leveraging n = 267 NHB and n = 268 NHW participants showed that despite an overall nonsignificant finding in AD biomarker levels across racial/ethnic groups, specific medical comorbidities such as chronic kidney disease (CKD) were found to be associated with higher ptau181 and NfL levels.[6] Other work examining the link between medical comorbidities and plasma AD biomarkers among a combined sample of n = 520 NHW and n = 445 Hispanic individuals revealed a similar link between CKD and AD biomarkers; specifically, this study found elevations in amyloid-specific biomarkers (Aβ40 and 42) to be associated with this medical comorbidity.[4] These same plasma amyloid-specific biomarkers were also found to be related to other medical conditions such as dyslipidemia, hypertension, and diabetes.[4] Interestingly, biomarkers related to neurodegeneration (total tau, NfL) were only found to be related to conditions such as diabetes and CKD.[4]

Taken together, increased work conducted through large cohort studies reveal differences in plasma AT(N) biomarkers across multiple racial/ethnic groups, and the link between such biomarkers has shown to differ by particular factors, including medical comorbidities.[4] As was called for in the AT(N) framework, additional work is needed to fully characterize and understand such plasma AD biomarkers among the largest segments of the US population, which includes NHB, Hispanic, and NHW participants. This study sought to address this by characterizing select plasma AT(N) biomarkers among an ethnically diverse community-dwelling cohort.

RESEARCH IN CONTEXT

1. **Systematic review**: A review of the literature was conducted through PubMed utilizing key phrases to capture previously published work examining plasma biomarkers related to Alzheimer's disease (AD) particularly among diverse populations. While several studies have been conducted, the findings have been varied.
2. **Interpretation**: Findings revealed age, diabetes, and chronic kidney disease were related to increased AT(N) biomarkers across all groups. The association or correlation between AT(N) plasma and neuroimaging biomarkers varied with the only significant association between amyloid biomarkers found for non-Hispanic White participants. Plasma biomarkers of neurodegeneration and ptau181 were related to a diagnosis of Dementia across groups.
3. **Future direction**: Racial/ethnic differences were shown with AT(N) plasma biomarkers. Future work will need to focus on more emerging AD biomarkers and specific factors related to how comorbidities (or duration of such) further impact the link with AT(N) plasma biomarkers among diverse populations.

2 | METHODS

2.1 | Participants

Participants included in this study were derived from the Health and Aging Brain Study-Health Disparities (HABS-HD), an ongoing, community-based study of aging. The HABS-HD protocol includes follow-up visits every 24 months with data captured across multiple days for one study visit. All components of HABS-HD are completed within a 3-month span, with up to 6 months allowed. See Table 1 for participant demographic characteristics. A total of 3226 participants were included in this study (n = 764 NHB, n = 1230 Hispanic, n = 1232 NHW participants) with data derived from their baseline visit. Of those who self-identified as Hispanic, n = 1184 (96%) self-identified as Mexican American, n = 10 (<1%) as Puerto Rican, n = 2 (<1%) as Cuban, and n = 34 (2%) as Other. HABS-HD data from Release 5 were included in this study. Each participant visit consists of a clinical interview, fasting blood draw, neuropsychological testing, medical examination, and functional assessment. Participants also consent and undergo neuroimaging, which includes both magnetic resonance imaging (MRI) and positron emission tomography (PET). As part of the HABS-HD protocol, participants also agree to provide an informant to address questions specific to the participant's daily functioning. Informant interviews include the administration of the Clinical Dementia Rating (CDR) scale. Demographic information is collected during the clinical interview. Medical comorbidities are determined by a medical professional associated with the study and are based on participants' self-report and data derived from the medical examination, clinical labs, current medications, and objective measures. The neuropsychological battery and reference to normative data has been previously published.[7] Participants self-report their race/ethnicity. The HABS-HD study protocol is conducted under institutional review board (IRB) approval, and each participant (and/or legal guardian) provides signed written informed consent to participate in the study.

TABLE 1 Demographic characteristics.

Parameter	Overall N = 3226	Non-Hispanic Black participants N = 764	Hispanic participants N = 1230	Non-Hispanic White participants N = 1232	p-value
Age, mean (SD)	65.17 (8.68)	63.08 (7.96)[b]	63.13 (8.03)[c]	68.52 (8.71)[b,c]	<0.001
Range		50–90	50–91	50–92	
Education, mean (SD)	13.24(4.38)	14.82 (2.63)[a,b]	9.98 (4.66)[a,c]	15.52 (2.63)[b,c]	<0.001
Sex, F *N* (%)	2016 (62%)	490 (64%)[b]	825 (67%)[c]	701 (57%)[b,c]	<0.001
Cognitive diagnosis		[a,b]	[a,c]	[b,c]	<0.001
Cognitively unimpaired	2399 (74%)	502 (66%)	905 (74%)	992 (81%)	
Mild cognitive impairment	607 (19%)	198 (26%)	243 (20%)	166 (13%)	
Dementia	220 (6.8%)	64 (8.4%)	82 (6.7%)	74 (6.0%)	
Diabetes mellitus, *N* (%)	786 (24%)	195 (26%)[a,b]	423 (34%)[a,c]	168 (14%)[b,c]	<0.001
Hypertension, *N* (%)	2117 (66%)	610 (80%)[a,b]	783 (64%)[a,c]	724 (59%)[b,c]	<0.001
Dyslipidemia, *N* (%)	2110 (66%)	480 (63%)[a]	832 (68%)[a]	798 (65%)	0.078
Chronic kidney disease, *N* (%)	370 (12%)	89 (13%)[a]	94 (7.9%)[a,c]	187 (16%)[c]	<0.001
Aβ42/40 ratio pg/mL, mean (SD)	0.05 (0.01)	0.04 (0.01)[a,b]	0.05 (0.01)[a]	0.05 (0.01)[b]	<0.001
Total Tau pg/mL, mean (SD)	2.47 (1.18)	2.79 (1.43)[a,b]	2.42 (1.06)[a,c]	2.32 (1.06)[b,c]	<0.001
Ptau-181 pg/mL, mean (SD)	2.13 (1.40)	1.94 (1.16)[b]	1.92 (1.24)[c]	2.40 (1.56)[b,c]	<0.001
NfL pg/mL, mean (SD)	17.27 (19.27)	14.97 (13.75)[a,b]	16.91 (20.75)[a,c]	19.05 (20.50)[b,c]	<0.001

Abbreviations: Aβ, amyloid beta; NfL, neurofilament light chain.
Note: Significant group differences between racial/ethnic groups: [a] = non-Hispanic Black versus Hispanic participants; [b] = non-Hispanic Black versus non-Hispanic White participants, [c] = Hispanic versus non-Hispanic White participants. Significance $p < 0.01$ was for multiple comparisons and $p < 0.05$ for pairwise comparison of [a], [b], and [c].

2.2 | Cognitive diagnosis

Cognitive diagnosis is determined through a consensus review process and has been previously published.[8] Briefly, data, including self- and informant reports of daily functioning and neuropsychological test results, were considered in the diagnostic process, while neuroimaging data was not considered. Cognitively unimpaired (CU): no complaints by self or other of cognitive changes, CDR scale sum of boxes (SOB) of 0, and neuropsychological test scores within normative ranges. Participants with a subjective cognitive complaint or a single neuropsychological test score ≤1.5 standard deviations (SD) below the adjusted norms who otherwise meet criteria for CU were included into the CU category. Mild cognitive impairment (MCI): complaint by self or other of cognitive changes, CDR scale SOB of 0.5–2.0, and at least one neuropsychological test score falling at or below 1.5 standard deviations from the adjusted norms. Dementia: complaint by self or other of cognitive changes, CDR scale SOB ≥2.5, and performance on two or more neuropsychological tests at or below two standard deviations from the normative mean.

2.3 | Neuroimaging

Neuroimaging for HABS-HD includes an MRI using ADNI3 protocols (available at https://adni.loni.usc.edu/methods/mri-tool/mri-analysis/) on a 3T Siemens Magnetom SKYRA whole-body scanner (Erlangen, Germany). Scan sequences include the following: T1-weighted whole brain volumetric spoiled magnetization-prepared rapid gradient (MPRAGE), whole brain volumetric fluid-attenuated inversion recovery (FLAIR), susceptibility-weighted imaging (SWI), diffusion tensor, 3D arterial spin labeling, resting-state functional and T2-weighted hippocampal high-resolution scan. The Meta-ROI is generated to determine MRI-derived neurodegeneration (see O'Bryant et al.[9] and Table S1 for methodology). PET scans were also completed as part of the study for both amyloid and tau using Siemens Biograph Vision 450 whole-body PET/computed tomography (CT) scanners that again follow ADNI3 protocols (available at https://adni.loni.usc.edu/methods/pet-analysis-method/pet-analysis/). The amyloid tracer was florbetaben (FBB; 8.1 mCi, 4×5 min frames, 90 min post-injection), while the tau tracer was 18F-PI-2620 (PI-2620; 10.0 mCi, 6×5 min frames, 45–75 min post-injection). A clinical read of positivity (Amyloid and Tau) was determined by a neuroradiologist (see Table S1 for methodology).

2.4 | Assays

Non-fasting plasma samples were collected as part of the HABS-HD protocol[7] and processed per international guidelines for sample preparation and storage, which includes a 2-h processing from stick to freezer.[10] See Supplementary File Material 1 for detailed methods regarding sample preparation and processing. All plasma biomarkers

TABLE 2 Association and/or correlation between plasma AT(N) and neuroimaging biomarkers by race and ethnicity.

Parameter	PET amyloid clinical read (Yes/No)- amyloid positivity β	PET Tau clinical read (Yes/No)- Tau positivity β	Meta-ROI r
Aβ42/40			
Non-Hispanic Black participants	−30.57		
Hispanic participants	−26.12		
Non-Hispanic White participants	−157.06**		
Ptau181			
Non-Hispanic Black participants	0.05***	0.03	
Hispanic participants	0.02	−0.60*	
Non-Hispanic White participants	0.07**	0.06*	
Total Tau			
Non-Hispanic Black participants			−0.09**
Hispanic participants			−0.04
Non-Hispanic White participants			−0.06*
NfL			
Non-Hispanic Black participants			−0.12**
Hispanic participants			−0.12***
Non-Hispanic White participants			−0.03

Abbreviations: Aβ, amyloid beta; β, logistic regression coefficient; NfL, neurofilament light chain; r = Pearson correlation coefficient.
*$p < 0.05$.
**$p < 0.01$.
***$p < 0.001$.

were assayed using single molecule array (Simoa) technology (Simoa; Quanterix, Lexington, Massachusetts, USA) and run on the HD-X Automated Immunoassay Analyzer (HD-X), which automates the assay and quantifies target proteins in unknown samples by using a two-step immunoassay to generate a fluorescent signal. The HD-X Automated Immunoassay Analyzer generates a four-parameter logistic curve with $1/y^2$ weighting from which unknown and control sample concentrations were calculated. For assay-specific parameters, see Table S2.

2.5 | Statistical analysis

Analyses were conducted utilized R (V4.3.3). Normality was assessed using the Shapiro-Wilk test supported by visual inspection through Q-Q plots. Outliers were identified as data points with z-scores greater than ± 3 standard deviations from the mean. Demographic characteristics were generated utilizing analyses of variance (ANOVAs) stratified by race/ethnic group (see Table 1) and further by cognitive diagnosis in Table S3. In order to examine the link between AT(N) plasma and neuroimaging biomarkers, a Pearson correlation was conducted between the plasma biomarkers and the continuous measure of neurodegeneration (Meta-ROI). For the binary neuroimaging measures (clinical read of PET positivity), a logistic regression was conducted (see Table 2). Models were adjusted for age, sex, education, and scanner type and stratified by race/ethnicity.

Generalized linear models were also conducted with plasma AT(N) biomarkers as the dependent variables, medical comorbidities and cognitive diagnosis as independent variables, and demographic variables as covariates (see Table 3). We conducted sensitivity analyses for all generalized linear models using the Sobol method R Package Sensitivity (V1.30.1). The results revealed significant differences in the sensitivity indices, for each independent variable and covariate, highlighting their varying effects on neuroimaging biomarkers across the three groups ($p < 0.05$) (see Table S3). The impact of select demographic factors (age and sex) on other demographic, medical, and cognitive diagnostic factors is presented in Table S4. Violin and Boxplots were also derived from univariate one-way analyses of covariance (ANCOVAs) with post-hoc testing (adjusting for age, sex, and education) to examine the difference by racial/ethnic group in Aβ42/40 ratio levels by PET amyloid positivity status (Figure 1) and select plasma AT(N) biomarkers by cognitive diagnosis (Figure 2). Given the large sample size and the multiple analyses performed, a more stringent alpha level of $p < 0.01$ was applied for multiple comparisons, while a $p < 0.05$ was retained for post-hoc pairwise comparisons.

3 | RESULTS

Table 1 presents the demographic characteristics. NHW participants, on average, were older with higher mean levels of education.

TABLE 3 Relationship between select plasma AT(N) biomarkers and demographic and medical comorbidities as well as cognitive diagnosis stratified by race and ethnic group.

Parameter	Amyloid beta (Aβ) 42/40 ratio β	Total Tau β	pTau181 β	NfL β
Demographic factors				
Age				
Non-Hispanic Black participants	−0.00	−0.00	0.03***	0.26***
Hispanic participants	−0.00**	0.00	0.02***	0.51***
Non-Hispanic White participants	−0.00***	−0.00	0.04***	0.37***
Sex (male)				
Non-Hispanic Black participants	−0.00	−0.51***	0.26	−0.13
Hispanic participants	0.00*	−0.36***	0.19*	−0.11
Non-Hispanic White	0.00	−0.44***	0.18**	−0.60
Education				
Non-Hispanic Black participants	0.00*	−0.03*	−0.02	−0.38*
Hispanic participants	0.00*	0.00	0.01	−0.10
Non-Hispanic White participants	0.00	−0.01	0.00	0.23
Medical comorbidities				
Hypertension				
Non-Hispanic Black participants	−0.00	0.05	−0.04	1.00
Hispanic participants	−0.00	0.15*	0.04	0.18
Non-Hispanic White participants	0.00	0.03	−0.05	−0.19
Diabetes				
Non-Hispanic Black participants	−0.00*	0.24**	−0.19	4.13***
Hispanic participants	−0.00**	0.08	0.20**	4.72***
Non-Hispanic White participants	−0.00	0.18*	−0.11	1.72
Dyslipidemia				
Non-Hispanic Black participants	0.00**	−0.00	−0.06	−1.59
Hispanic participants	−0.00	−0.12*	−0.08	−0.09
Non-Hispanic White participants	−0.00	0.13*	−0.08	−0.03
Chronic kidney disease (CKD)				
Non-Hispanic Black participants	0.00	0.52***	0.92***	11.03***
Hispanic participants	−0.00	0.88***	1.16***	10.44***
Non-Hispanic White participants	0.00	0.38***	0.63**	10.57***
Cognitive diagnosis				
Mild cognitive impairment				
Non-Hispanic Black participants	0.00	−0.01	0.10	1.55
Hispanic participants	0.00	0.13	0.33***	4.60**
Non-Hispanic White participants	−0.00	0.04	0.29*	3.17
Dementia				
Non-Hispanic Black participants	0.00	0.30	1.06***	6.48***
Hispanic participants	−0.00	0.17	0.76***	6.22*
Non-Hispanic White participants	−0.00**	0.31**	1.45***	13.04***

Abbreviations: Aβ, amyloid beta; NfL, neurofilament light chain.
*$p < 0.05$.
**$p < 0.01$.
***$p < 0.001$.

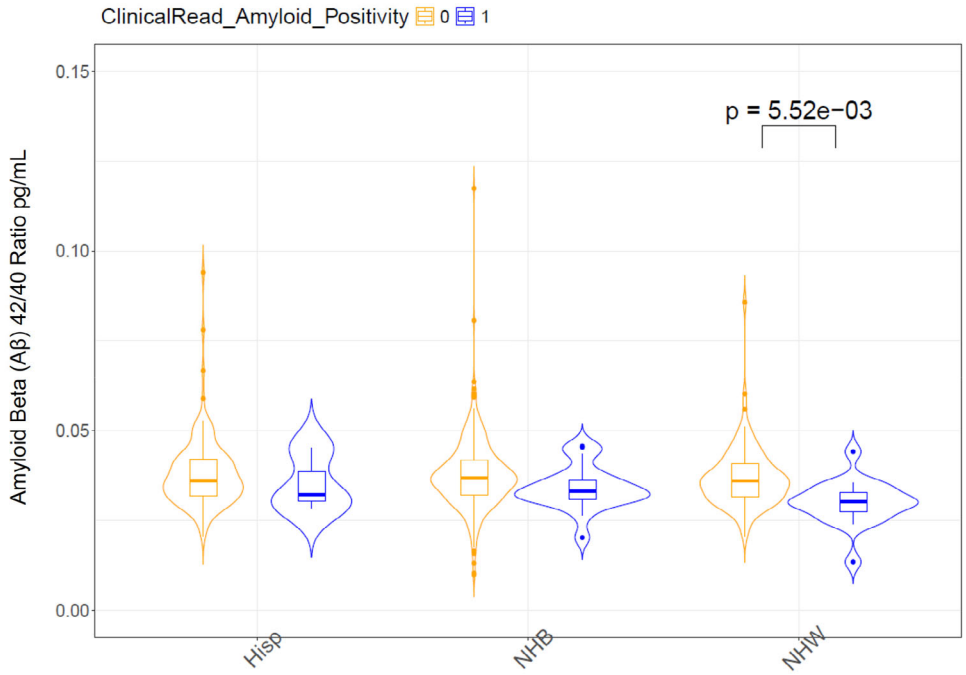

FIGURE 1 Violin plot for amyloid beta (Aβ) 42/40 ratio levels by race/ethnic group based on a positron emission tomography amyloid positivity status.

Differences in level of education were also found between Hispanic and NHB participants, with the latter presenting with a higher mean level. Mean plasma Aβ42/40 ratio and NfL levels were further identified to be different across groups, with lower mean levels found for NHB compared to Hispanic participants, with both groups being significantly lower than NHW participants for NfL. In addition, NHB participants were found to have higher levels of total tau compared to NHW and Hispanic participants with the latter also having higher mean total tau levels as compared to NHW participants. The p-tau181 levels were shown to be highest among NHW as compared to NHB or Hispanic participants.

The prevalence of select medical comorbidities were also shown to differ. NHW participants were shown to experience lower rates of diabetes (14%) as compared to NHB (26%) or Hispanic (34%) participants, with a similar pattern shown for hypertension (59% NHW, 80%NHB, 64%Hispanic participants). Interestingly, rates of dyslipidemia were only shown to be significantly different between NHB and Hispanic participants, with the latter showing a higher rate (68% vs. 63%). Rates of CKD were also shown to be different with Hispanic participants showing lower rates (7.9%) as compared to NHB (13%) and NHW (16%) participants. Rates of cognitive diagnosis were further shown to be significantly different across race and ethnic groups ($p < 0.001$).

3.1 | Correlation and/or association between AT(N) plasma and neuroimaging biomarkers

The link between AT(N) plasma and neuroimaging biomarkers was explored and presented in Table 2. Among NHB participants, ptau181 was found to be associated with PET amyloid positivity. Both total tau and NfL were found to be significantly correlated with Meta-ROI. Among Hispanic participants, ptau181 was found to be significantly associated with PET tau positivity. In addition, NfL was found to be significantly correlated with Meta-ROI. Among NHW participants, both the plasma Aβ42/40 ratio and ptau181 levels were found to be significantly associated with PET amyloid positivity, while ptau181 was associated with PET tau positivity. Total tau was further found to be significantly correlated with Meta-ROI. A violin plot of Aβ42/40 ratio levels stratified by race/ethnic group revealed that the only significance difference between those identified as PET amyloid positive or negative was for NHW participants, while no significant difference in ratio levels were found among Hispanic or NHB participants (see Figure 1).

3.2 | Demographic factors

In examining the relationship between plasma AT(N) biomarkers and demographic factors, the results revealed that, among NHB participants, increased age was associated with higher levels of NfL and ptau181. Additionally, lower levels of education were found to be associated with higher levels of the Aβ42/40 ratio and markers of neurodegeneration (total tau and NfL). Among Hispanic participants, increased age was associated with a lower Aβ42/40 ratio and higher levels of NfL and ptau181. The only significant relationship between education was with the Aβ42/40 ratio. Among NHW participants, again, increased age was associated with a lower Aβ42/40 ratio as well as increased levels of NfL and ptau181. Across all race/ethnic groups,

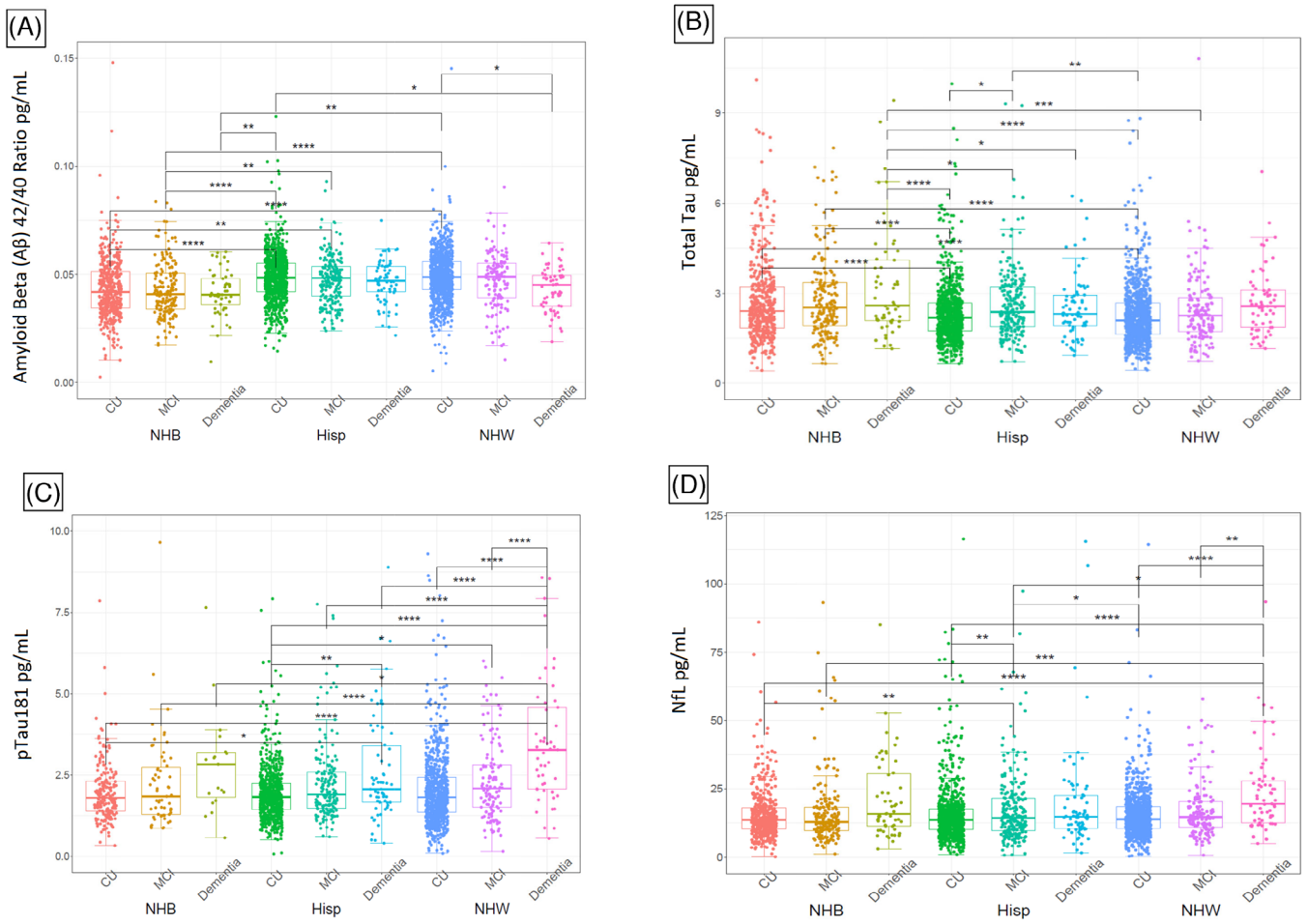

FIGURE 2 Boxplots for plasma AT(N) biomarker levels (adjusted by age, gender, and education) stratified by (A) amyloid beta (Aβ) 42/40 ratio, (B) total Tau, (C) pTau181, and (D) neurofilament light chain (NfL) as well as by race/ethnic group and cognitive diagnosis. Significance $p < 0.05^{*}$, $p < 0.01^{**}$, $p < 0.001^{***}$, $p < 0.0001^{****}$. CU, cognitively unimpaired; MCI, mild cognitive impairment.

being male was significantly associated with lower levels of total tau while higher levels of ptau181 were also found for this sex for Hispanic and NHW participants. See Table 3.

3.3 | Medical comorbidities

Commonly co-occurring medical conditions were also examined in relation to the select plasma AT(N) biomarkers. Among NHB participants, a decreased Aβ42/40 ratio along with increased levels of total tau and NfL were all significantly related to a diagnosis of diabetes. Similarly, higher levels of total tau, ptau181, and NfL were also found to be related to a diagnosis of CKD. Among Hispanic participants, a diagnosis of hypertension was found to be significantly related to higher levels of total tau while lower levels were found to be related to a diagnosis of dyslipidemia. Diabetes was also found to be related to a decreased Aβ42/40 ratio and elevated NfL and ptau181 levels. CKD was found to be significantly associated with elevations across multiple AT(N) plasma biomarkers, including ptau181, total tau, and NfL. Among NHW participants, increased levels of total tau were found to be related to a diagnosis of diabetes, dyslipidemia, and CKD, while increased ptau181 and NfL were also both found to be significantly related to the latter comorbidity. See Table 3.

3.4 | Cognitive diagnosis

In examining the relationship between cognitive diagnosis and select plasma AT(N) biomarkers, the results revealed that among NHB participants, increased ptau181 and NfL levels were found to be related to a diagnosis of dementia. Among Hispanic participants, higher levels of ptau181 and NfL were found to be related to both a diagnosis of MCI and dementia. Among NHW participants, decreased levels of the Aβ42/40 ratio along with increased levels of total tau, ptau181, and NfL were all found to be significantly related to a diagnosis of dementia. See Table 3.

3.5 | Racial/ethnic group by cognitive diagnosis

Additional analyses examining the differences in select plasma AT(N) biomarkers across the racial/ethnic groups stratified by cognitive diagnosis (adjusting for age, sex, and education) (see Figure 2 and Table S5 for all significant findings) revealed differences in Aβ42/40 levels between CU NHB and Hispanic participants diagnosed as CU or MCI and NHW participants diagnosed as CU, with lower levels found for NHB participants. This also extended into NHB participants diagnosed as MCI with similar findings shown, and for NHB participants diagnosed as dementia again showing lower levels relative to CU Hispanic or NHW participants. Hispanic or NHW participants diagnosed as CU were also found to have a significant difference in levels as compared to NHW participants with dementia. For ptau181, specific race/ethnicity findings revealed lower levels among NHB and Hispanic participants regardless of cognitive diagnosis when compared to NHW participants with dementia. A further difference in levels was found between CU NHB and Hispanic participants with dementia. In addition, NHW participants with either a CU or MCI diagnosis were shown to have lower levels as compared to those with dementia. Differences in levels were also shown for Hispanic participants with higher levels found among those with MCI versus CU. In examining total tau, a significant difference was shown between CU Hispanic participants or NHW and NHB participants across multiple diagnostic states (CU, MCI). An additional significant difference was found between NHB participants with dementia and NHW or Hispanic participants diagnosed as CU or MCI as well as dementia for the latter group, with higher levels found among NHB participants. Finally, differences were also shown in NfL levels between NHB participants with CU or MCI compared to NHW participants with dementia. NfL levels were also shown to be different between Hispanic participants with CU versus MCI and Hispanic participants with MCI as compared to NHW participants with either CU or dementia, the latter showing higher levels. NfL increases were also shown with disease severity for NHW participants with higher levels found for those with dementia as compared to CU or MCI. See Figure 2.

4 | DISCUSSION

The results of this study reveal race and ethnic-specific findings across the select plasma AT(N) biomarkers. Among NHB and Hispanic participants, the Aβ42/40 ratio was not found to be associated with corresponding neuroimaging measures (after adjusting for covariates), while ptau181 was shown to be associated across several racial/ethnic groups with both PET amyloid and tau positivity. Among NHW participants, findings are consistent with other work with a significant association found between plasma (Aβ42/40 ratio) and neuroimaging measures of amyloid.[11,12] This work expands on prior findings to examine the link between plasma and neuroimaging AT(N) biomarkers across the three largest racial/ethnic groups in the United States, thereby providing a broader examination of group differences.

This study also sought to expand on prior work by examining the relationship between select plasma AT(N) biomarkers and medical comorbidities (hypertension, diabetes, dyslipidemia, CKD). This was in an effort to address growing work in the field that looks at potentially expanding the AT(N) framework to capture additional biological components such as inflammation and vascular factors. Our findings suggest that medical comorbidities such as diabetes is significantly related across all racial/ethnic groups with certain plasma AT(N) biomarkers such as the Aβ42/40 ratio, total tau, ptau181, and NfL. The utility of understanding how such plasma AT(N) biomarkers are differentially related among certain racial/ethnic groups to common comorbid conditions will be important to explore further as this holds potential therapeutic avenues.

Findings from this work also expands on prior work conducted by Hall et al.[5] that examined select biomarkers across different diagnostic groups, which found that NHB individuals with a diagnosis of dementia had lower levels of Aβ40, total tau, and NfL as compared to Hispanic individuals. Our study found similar results and also expanded to find a significant relationship between NfL and ptau181 for Hispanic participants with a diagnosis of MCI. Corresponding to this prior work, which indicated lower levels of amyloid biomarkers among select racial/ethnic groups,[5] our findings supported that the Aβ42/40 ratio was not significantly related to either a diagnosis of MCI or dementia for Hispanic or NHB participants once adjusting for covariates.

In placing this work into the context of prior findings in plasma, Grewal et al. found that NHB females diagnosed as CU as compared to NHW individuals (with the same diagnosis) had lower levels of Aβ42 along with higher levels of total tau and ptau.[13] A similar finding was shown by Deniz et al., with total tau being higher among NHB individuals with AD, while amyloid-specific markers were not shown to have an association.[14] Gonzales et al. found that, when examining serum AD biomarkers within a matched subset of their larger sample, a relationship between higher levels of total tau, glial fibrillary acidic protein (GFAP), and NfL was found with risk of dementia.[15] These findings have not, however, always been consistent with work from WHICAP, seeing in their community-based study that although specific AD biomarkers, including ptau181 and ptau217, were elevated among those with AD, no differences were found in biomarker concentrations across the racial/ethnic groups examined, including Hispanic, NHB, and NHW individuals.[2]

Several studies are now utilizing the AT(N) framework to assist with clinical diagnosis or enrollment into clinical trials; however, much of the sample population used to make such informative decisions has largely been exclusive of diverse populations. Work examining differences in plasma AT(N) biomarkers within the context of health disparities remains a critical gap area. Important take homes from this study include that differences in the AT(N) plasma biomarkers exist with lower levels in a number of biomarkers including the Aβ42/40 ratio and NfL being found among NHB relative to NHW individuals as well as Hispanic individuals. Additionally, the link between plasma and neuroimaging markers of similar pathology was found to be more strongly related for NHW individuals (consistent with prior literature including work conducted utilizing the Quanterix assay[11,12]), with significant links found for the Aβ42/40 ratio and ptau181 with PET amyloid positivity.

Application of plasma AT(N) biomarkers will likely need to take into consideration medical comorbid conditions such as diabetes and CKD, as a number of the biomarkers in this study were found to be significantly related across multiple race/ethnic groups. CKD, in particular, was shown to impact ptau181, total tau, and NfL across all groups, while it was not shown to be related to the Aβ42/40 ratio. Additional work will be needed to understand the extent that comorbid conditions have on the progression of plasma AD biomarkers including AT(N) biomarkers and if such biomarkers should be considered within the context of such comorbid conditions. As diverse populations, such as Hispanic populations, face higher rates of comorbid conditions such as diabetes,[16,17] it will be critical to focus on the understanding and application of AD biomarkers among these groups. This is important given the enrollment into clinical trials or proposed models for disease detection utilizing plasma AT(N) biomarkers to determine disease pathology as their application may be limited among diverse populations.

The binary approach for neuroimaging and medical comorbidities was selected, as it reflects the current healthcare system and clinical decision-making process that relies on clinical reads and test determinations. As cutoffs are still being determined for different populations and tracers, understanding the relationship between more continuous neuroimaging biomarkers will be important to understand particularly in the translation of these biomarkers into clinical application. Additionally, the duration of medical comorbidities has been shown to impact select biomarkers and was not explicitly explored in this work; however, future work is planned. Novel AD biomarkers (GFAP, ptau217) are now being run in HABS-HD and will be looked at in relation to this work and others once data become available. The ability for plasma AT(N) biomarkers to detect amyloid and tau PET positivity is of incredible importance and was not examined in this study; however, future work is ongoing to address this.

Due to the lack of racial/ethnic representation in the original construction and support of the AT(N) framework, determining how closely biomarkers align with AD pathology and diagnosis in diverse groups and expanding the AT(N) framework to reflect those racial/ethnic alignments remains a critical need. The data herein have characterized the relationship of plasma AT(N) biomarkers with neuroimaging markers, comorbidities, and cognitive diagnoses across the largest populations within the United States, identifying and highlighting specific racial/ethnic differences, thereby narrowing the gap with respect to the applicability of the AT(N) framework to diverse groups.

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CONFLICT OF INTEREST STATEMENT

Sid E. O'Bryant has multiple patents pending related to precision medicine technologies for neurodegenerative diseases. He is the founding scientist of Cx Precision Medicine and has served on an Advisory Board for Roche Diagnostics. All other authors have nothing to disclose. Author disclosures are available in the Supporting information.

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SUPPORTING INFORMATION

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

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