

APOE ε4, Plasma pTau217, and Vascular Comorbidities in Hispanics and Non-Hispanic Whites from the South Texas ADRC

Amaya Seidl, Chen-Pin Wang, Roman A. Fernandez, Juan Garcia, Jennifer Del Bosque, Luis Gutierrez, Rajeswar Kumar, Anika Thomson, Hector Trevino, Monica Goss, Sarah Dean, Jake Pap, Yelitza Ramirez, Avery Zuniga, Xianlin Han, Jeremy Tanner, Silvia Mejia-Arango, Bruce LeForce, Amy Werry, Gabrielle Hromas, Stephanie Santiago-Meijas, Robin C. Hilsabeck, Alicia Parker, Arash Salardini, Gabriel de Erausquin, Julia Castro, Claudia Satizabal, Gladys Maestre, Sudha Seshadri, Joanne Curran, Agustin Ruiz, Vanessa M. Young, A. Campbell Sullivan, Tiffany Kautz, Ashley LaRoche

Background

AD Discrepancy: Hispanics are 1.5 times more likely to develop Alzheimer’s disease (AD) than non-Hispanic whites (NHWs), but they remain understudied.

APOE ε4 Genetic Risk: While the APOE ε4 allele is the strongest genetic risk factor for AD (increasing risk 2–12 times in NHWs), it is less common in Hispanics—especially Mexican Americans. Its exact impact on Hispanic AD risk remains unclear and conflicting.

ptau217 Biomarker: Phosphorylated tau (ptau217) is a highly effective blood biomarker for diagnosing AD. However, because current studies heavily focus on NHWs, biomarker interpretation for Hispanics may be skewed by higher rates of comorbidities and elevated BMIs, which can alter raw plasma ptau levels.

Study Aims:

- 1) Examine APOE ε4 prevalence and associated risk of dementia by ethnicity
- 2) Compare plasma ptau217 measures across diagnostic groups and between ethnic groups
- 3) Evaluate the impact pf APOE ε4 and vascular comorbidities on ptau217 measures

Methods

Participants: 488 STAC participants (264 Hispanic [90% Mexican heritage], 224 NHW) completed UDSv3 visits (Feb 2023–Feb 2025). Clinical diagnoses were established via case consensus, blinded to APOE and ptau217 data.

Genotyping & Biomarkers: Genomic DNA was isolated from blood and APOE genotyped via TaqMan Real-Time PCR. Plasma ptau217 was quantified by NCRAD using the Quanterix Simoa HD-X platform and AlzPath assay.

Statistical Analysis: Multivariable multinomial logistic regression evaluated ethnicity-specific associations between APOE ε4 and clinical diagnosis. Multivariable regression assessed links between log-transformed ptau217 and clinical diagnosis, APOE ε4 and comorbidities (BMI, HTN, HCL, T2DM). All R-based models adjusted for age, sex, education, and comorbidities.

Table 1: Descriptive statistics of STAC Sample

Characteristic	Overall N= 488 ¹	NHW N = 224 ¹	Hispanic N = 264 ¹
Age	72 (9)	73 (9)	71 (9)
Years of education	15.0 (3.3)	16.4 (2.4)	13.8 (3.4)
Female	296 (61%)	117 (52%)	179 (68%)
Normal Cognition	257 (53%)	100 (45%)	157 (60%)
MCI	108 (22%)	43 (19%)	65 (25%)
Dementia	118 (24%)	79 (35%)	39 (15%)
Hypertension	287 (59%)	117 (52%)	170 (64%)
Hypercholesterolemia	312 (64%)	139 (62%)	173 (66%)
Type II Diabetes	102 (21%)	28 (13%)	74 (28%)
ε2ε2	2 (0.4%)	2 (0.9%)	0 (0%)
ε3ε2	25 (5.1%)	12 (5.4%)	13 (4.9%)
ε3ε3	310 (64%)	111 (50%)	199 (75%)
ε3ε4	125 (26%)	76 (34%)	49 (19%)
ε4ε2	9 (1.8%)	7 (3.1%)	2 (0.8%)
ε4ε4	17 (3.5%)	16 (7.1%)	1 (0.4%)
ε4 carriers	151 (31%)	99 (44%)**	52 (20%)**

¹Mean (SD); n (% of N)
*p<0.05
**p<0.001

Results

Aim 1: Examine APOE ε4 prevalence and associated risk of dementia by ethnicity

In our sample, the ε4 risk allele was more common among NHWs than Hispanics (p <0.001), with 44% of NHW participants carrying at least one copy of ε4, compared to only 20% of Hispanics.

Table 2. Odds Ratios of Dementia and MCI diagnoses based on APOE ε4 allele presence

Factor-Outcome	Total Cohort ¹	Hispanic ¹	NHW ¹
ε4-Dementia	3.39** (2.01-5.17)	2.27 (0.93-5.57)	4.42** (2.25-8.69)
ε4-MCI	1.72* (1.01-2.93)	1.55 (0.73-3.27)	2.02 (0.94-4.37)

Abbreviations: NHW = Non-Hispanic White, MCI = Mild Cognitive Impairment

¹Odds ratio (95% Confidence Interval)

*p<0.05

**p<0.001

ε4 was significantly associated with dementia in the combined sample and among NHWs, but below significance threshold among Hispanics. An ε4-MCI association was only significant in the combined sample.

Aim 2: Compare plasma ptau217 measures across diagnostic groups and between ethnic groups

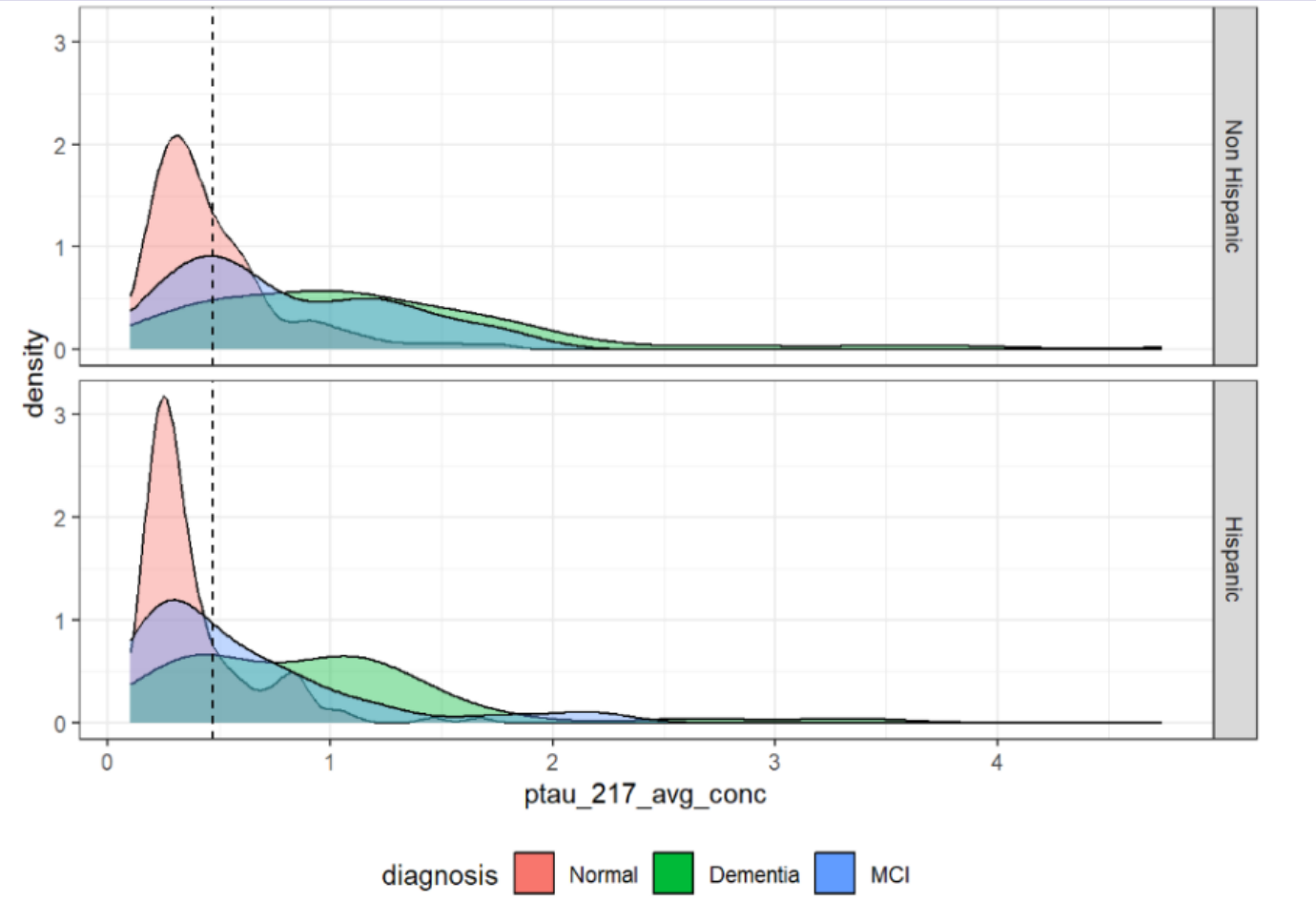
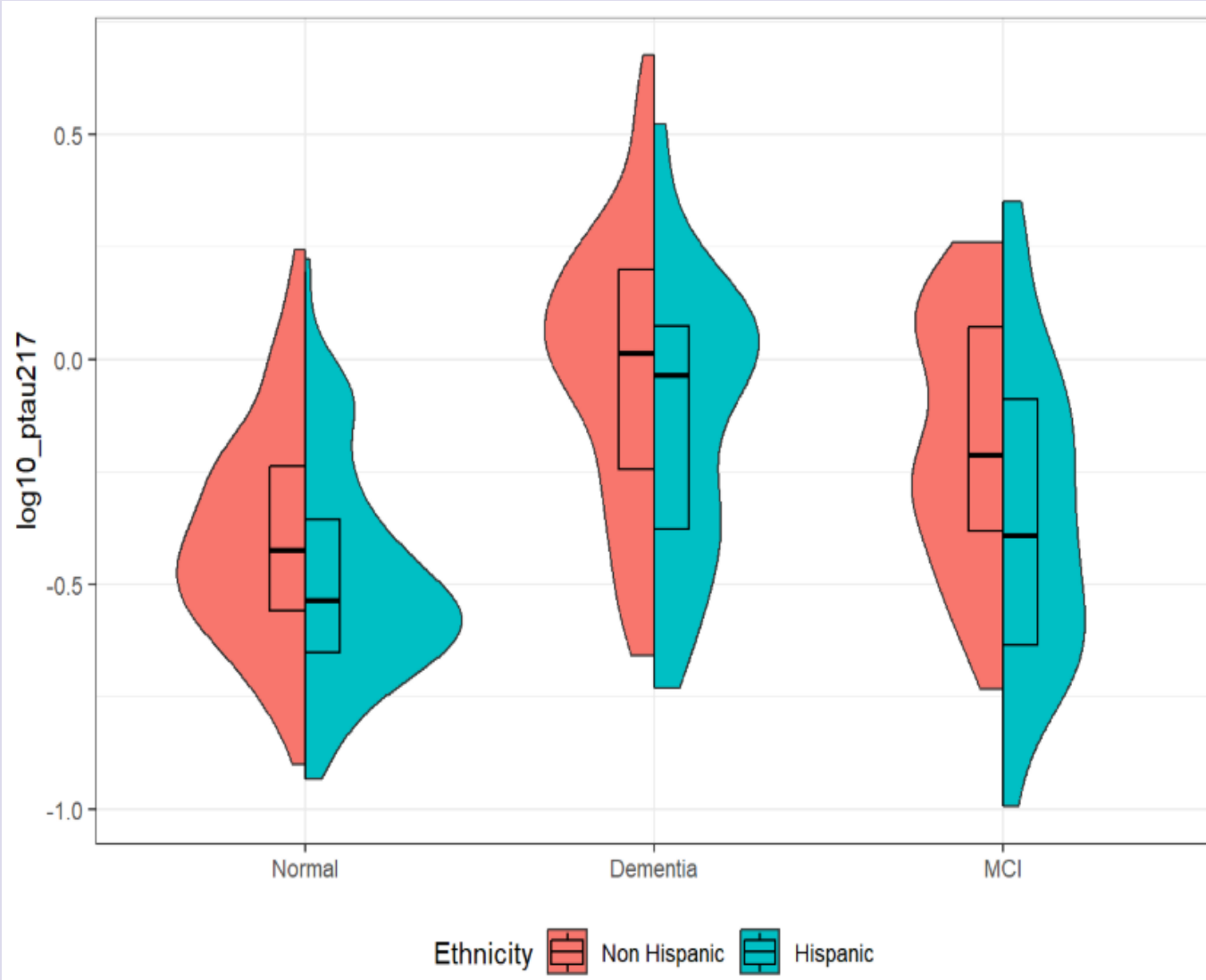


Figure 1. Density plot of plasma ptau217 concentrations (pg/mL) across ethnic and diagnostic groups in the STAC Cohort. Dotted line marks the Alzpath ptau217 cut point of 0.47 pg/mL.



In the overall sample, participants with dementia diagnoses had higher plasma ptau217 levels than cognitively normal participants (β = 0.27, 95% CI: 0.21; 0.33, p < 0.001). This difference was also significant within both the NHW (β = 0.32, 95% CI: 0.24; 0.40, p < 0.001) and Hispanic (β = 0.23, 95% CI: 0.14; 0.33, p < 0.001) groups. Participants with MCI diagnoses also had higher plasma ptau217 levels compared to cognitively normal counterparts in the overall sample (β = 0.11, 95% CI: 0.06; 0.17, p < 0.001), as well as within NHW (β = 0.16, 95% CI: 0.07; 0.25, p < 0.001) and Hispanic (β = 0.08, 95% CI: 0.01; 0.15, p = 0.029) subsets. Hispanic participants had lower ptau217 measures compared to NHW counterparts (p = 0.011).

Aim 3: Evaluate the impact of APOE ε4 and comorbidities on ptau217 measures

Table 3. Associations between APOE ε4, cognitive and comorbid diagnoses, and Hispanic ethnicity with ptau217

Characteristic	Beta	95% CI	p-value
ε4 allele	0.15	0.10, 0.20	<0.001
BMI	-0.01	-0.01, 0.00	0.017
HTN	0.05	0.00, 0.10	0.034
HCL	-0.05	-0.10, 0.00	0.048
T2DM	0.07	0.01, 0.12	0.023
Dementia	0.27	0.21, 0.33	<0.001
MCI	0.11	0.06, 0.17	<0.001
Hispanic ethnicity	-0.07	-0.12, -0.02	0.011

Abbreviation: CI = Confidence Interval, BMI = Body Mass Index, HTN = Hypertension, HCL = Hypercholesterolemia, T2DM = Type II Diabetes

Vascular/Metabolic Comorbidities:

Higher BMI and HCL correlated with lower ptau217, while HTN and T2DM correlated with higher ptau217.

Ethnicity: No significant interactions were found between ethnicity and any comorbidity on ptau217 levels (all *p* > 0.09).

Conclusions

In our STAC sample, APOE ε4 is less common and confers less risk for dementia among Hispanics compared to NHW

ptau217 signals clinical diagnoses similarly among NHWs and Hispanics

APOE ε4 and common comorbidities impact plasma ptau217 and may require consideration in interpretations of this biomarker

Discussion & Future Directions

The South Texas Hispanic population faces elevated risk for AD yet is underrepresented in research. In our sample, the APOE ε4 risk allele is less common among Hispanics and confers less risk for dementia compared to NHW counterparts, which aligns with several previous studies.

Our findings demonstrate that elevated plasma ptau217 is associated with abnormal cognitive profiles, both dementia and MCI, in Hispanic and NHW groups alike. We also found that common vascular and metabolic factors influence plasma ptau217 values. There is a strong need for individualized biomarker cut-offs for specific groups, especially those at higher risk. Our findings also support the association between APOE ε4 carriership and higher ptau217 measures among both Hispanics and NHWs.

Multifactorial assessments of genetic risk and biomarkers may provide additional insight into overall risk of cognitive decline and dementia.

Limitations of this study include small sample size and potential sampling bias by ethnicity and disease spectrum. Further, it is important to consider potential interpretation biases, considering the limited inclusion of Hispanic participants in existing research.

Future work should incorporate gold-standard amyloid PET to confirm AD pathology in relation to ptau217. Longitudinal analyses will be essential to evaluate APOE-associated changes in clinical diagnoses, including risk ratios and differences in age of onset, as well as trajectories of plasma ptau217 over time. Integrating vascular risk scores will help disentangle neurodegenerative and vascular contributions to biomarker and clinical outcomes.

Affiliations, References & Acknowledgements

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