Examining AT(N) – Defined Biomarkers Among Diverse Populations – Data from the HABS-HD Study

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Health & Aging Brain Study
Health Disparities

Disclosures

- Funding:
  - U19AG078109, R01AG058533, R01AG058537, R01AG054073, R01AG051848, R01AG058252
  - Alzheimer's Association, Michael J Fox Foundation
- Biotechnology
  - Multiple Commercial Methods developed
  - Cx Precision Medicine, Inc., founding scientist

Thank You!!!

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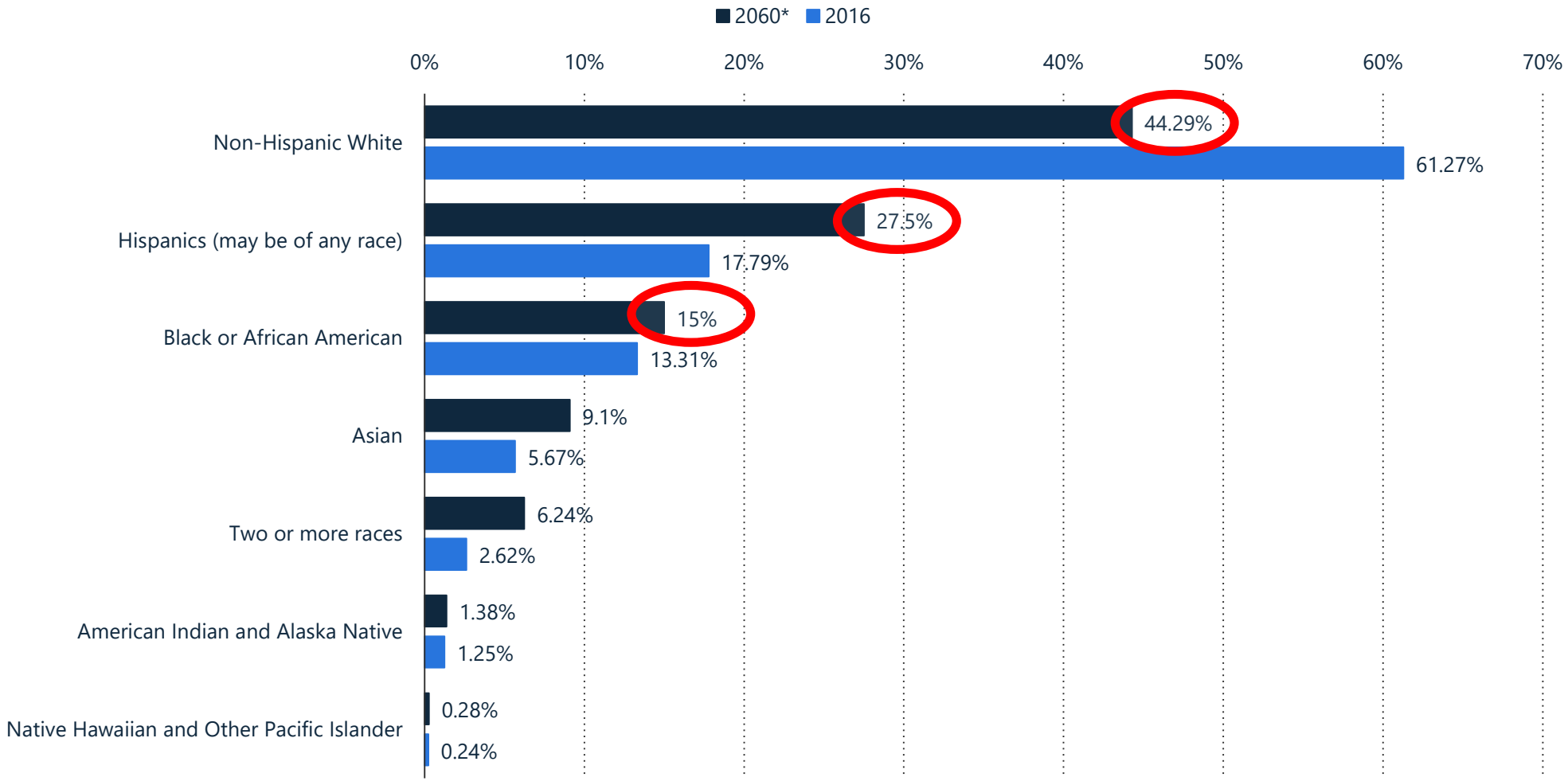
- *HABS-HD Team*
- *ABC-DS Consortium*
- *ADPC Team*
- *ATRI/ACTC*

Alzheimer's Disease among African Americans and Hispanics

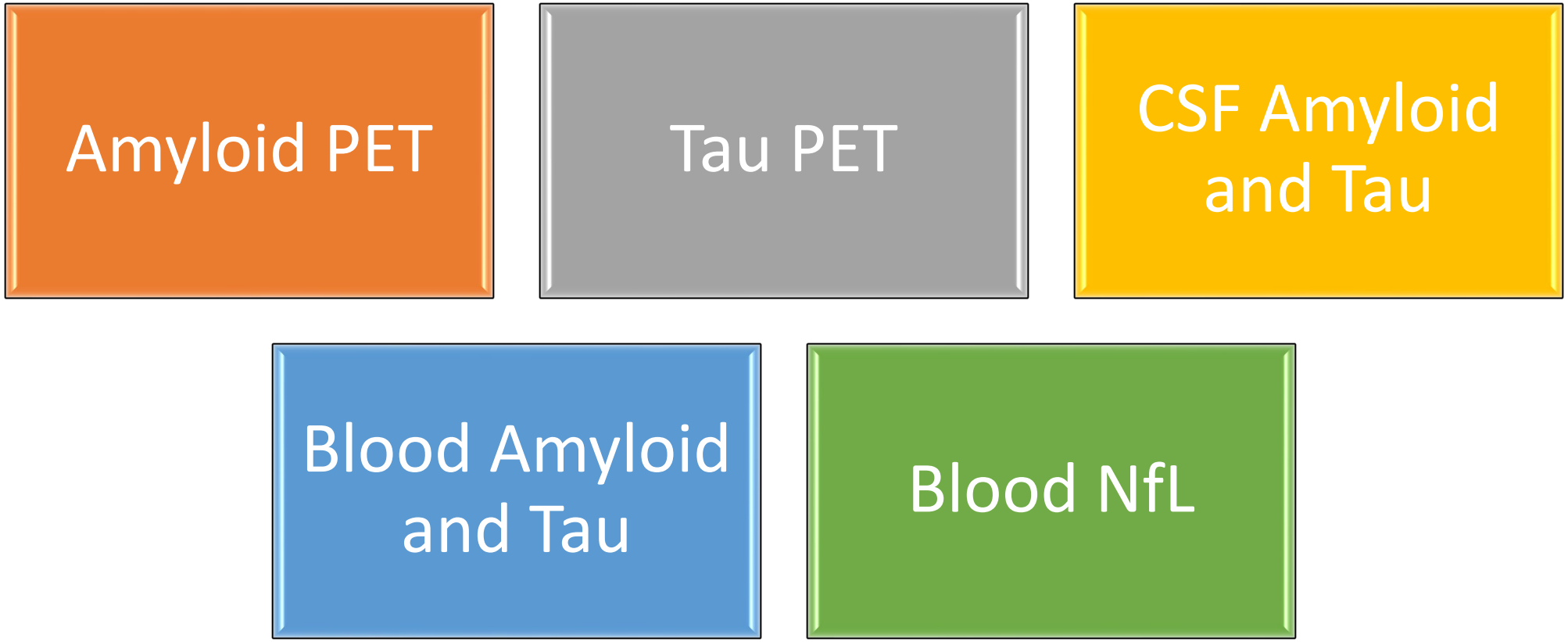
- African Americans currently suffer the greatest burden of Alzheimer's disease (AD) and AD Related Dementias (ADRDs)
- Hispanics will experience the largest increase in AD/ADRDs by 2060
- Diverse groups experience delays in diagnosis, are diagnosed with more severe pathology, more likely to be diagnosed with affective/psychiatric conditions, live longer with disease and incur greater increased healthcare costs
- **Over 90% of individuals in the research that led to the AT(N) framework were non-Hispanic whites**
- Less than 5% of individuals in AD clinical trials have been African American or Hispanic

Imperative to evaluate amyloid, tau and neurodegeneration [AT(N)] in these diverse populations

U.S. Population By Race and Hispanic Ethnicity
2016 vs 2060



Imaging, CSF and Blood Alzheimer's Biomarkers are in clinical practice



1. AT(N) – defined biomarkers vary by race/ethnicity

2. AT(N) – defined BBB vary by race/ethnicity

3. The link between AT(N) biomarkers and clinical outcomes vary by race/ethnicity

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The Health & Aging Brain Study – Health Disparities (HABS-HD)

A comprehensive study of the biomarkers of Alzheimer's disease across diverse populations all within a health disparities framework

Health & Aging Brain Study – Health Disparities (HABS-HD)

Enrollment Numbers & Targets:

- 1,500 Mexican Americans (>1,000 enrolled)
- 1,500 Blacks/African Americans (>800 enrolled)
- 1,500 non-Hispanic whites (>1,000 enrolled)
- Three Visits with/ 24-month follow-up intervals (>1,000 V2 completed)
- Ages 30+

Data Accessibility:

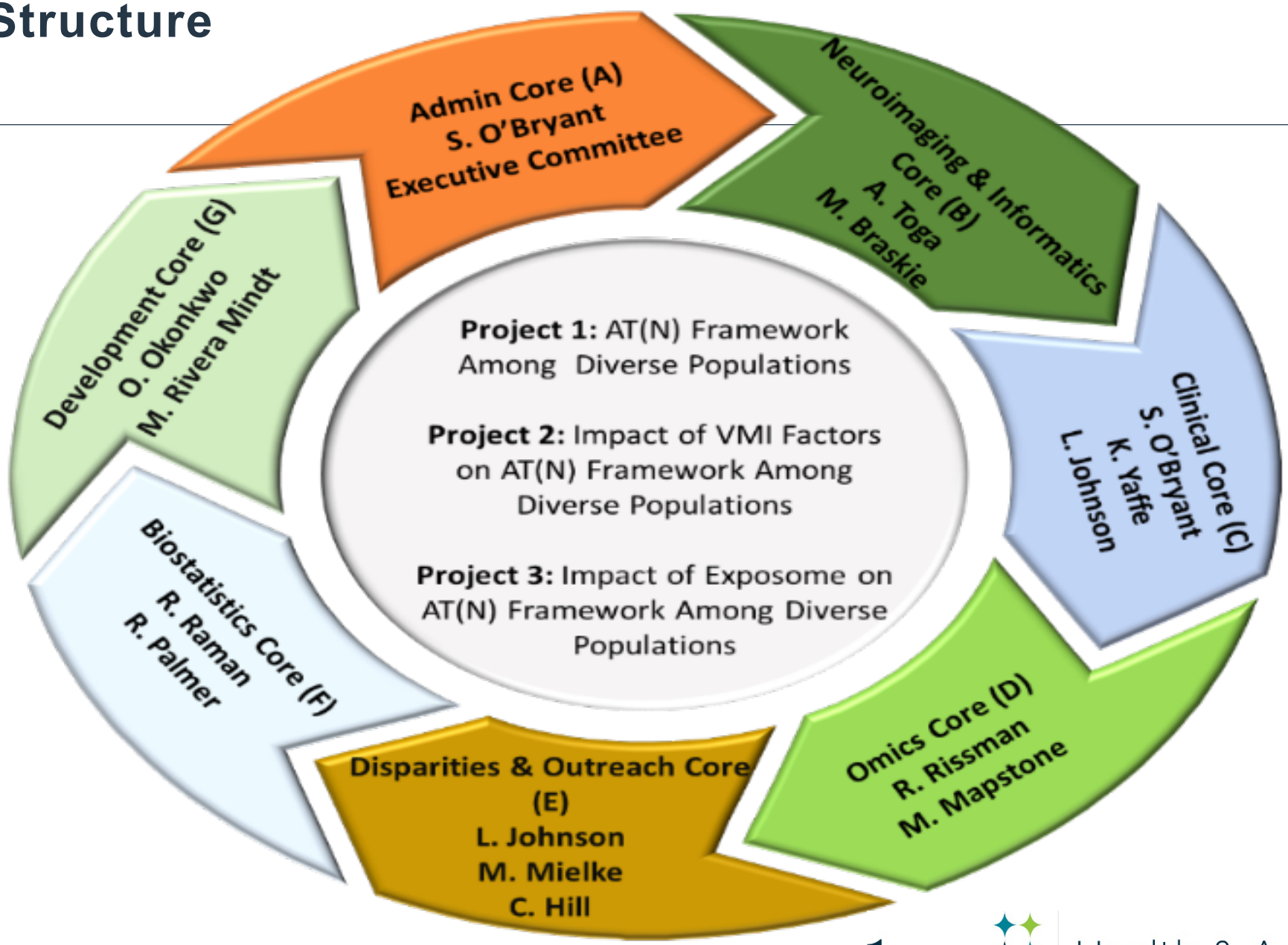
- HABS-HD data currently readily available at: https://apps.unthsc.edu/itr/request/hd

Data Details:

- Functional exam
- Clinical labs
- Sociocultural, environmental & behavioral Factors
- Cognitive Data
- Biorepository (n>500,000 aliquots available)
- 3T MRI, Amyloid and Tau PET Scans
- Omics – WGS, GWAS, methylation, targeted/untargeted proteomics, targeted/untargeted metabolomics, exosome, transcriptomics

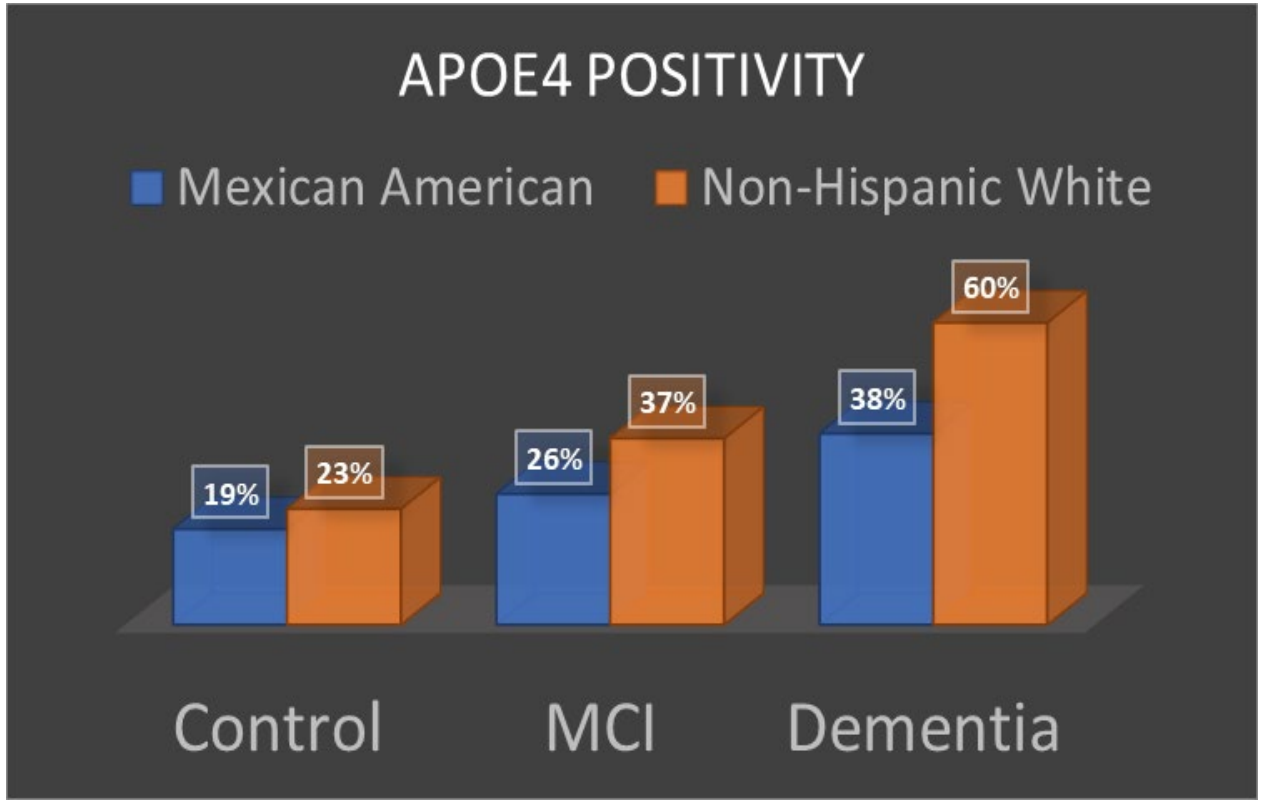
U19AG078109 , R01AG054073, AG058533

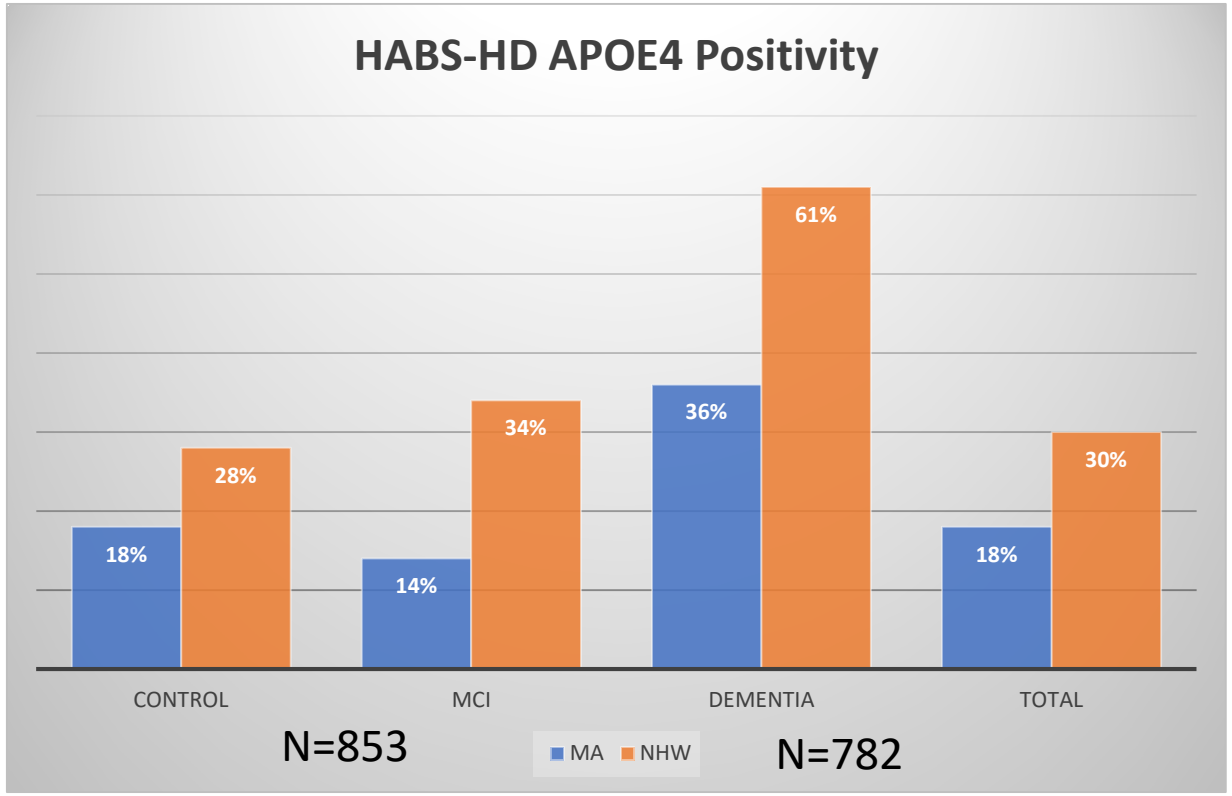
HABS-HD Structure



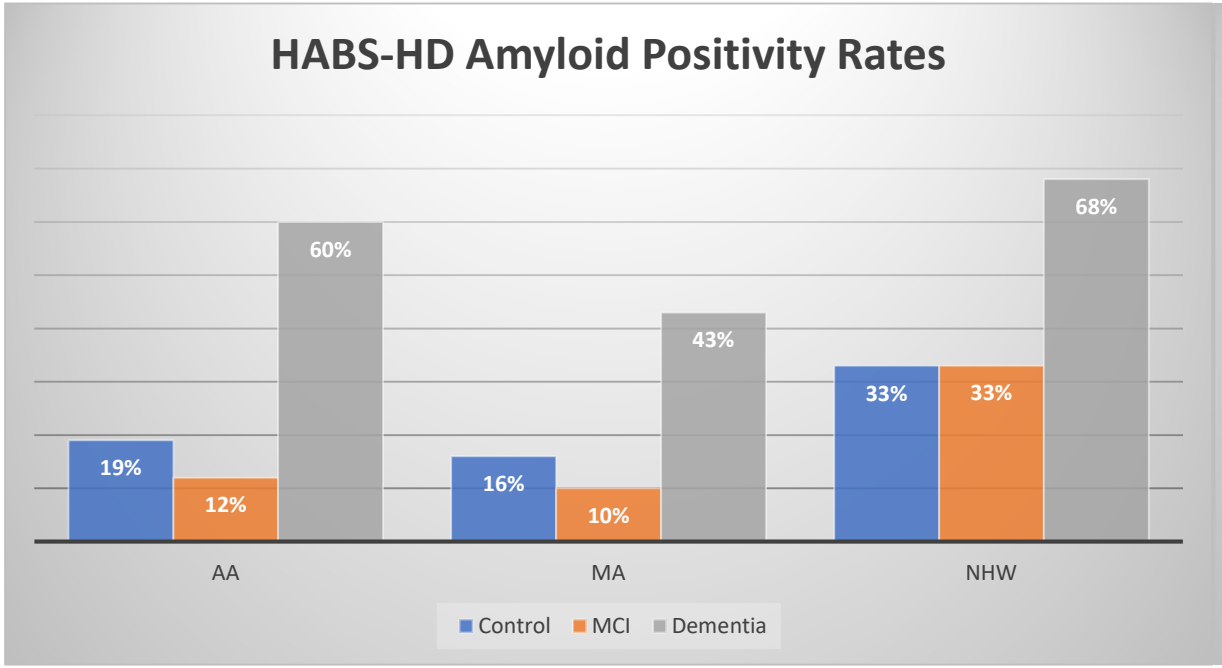
AT(N) – defined biomarkers vary by race/ethnicity

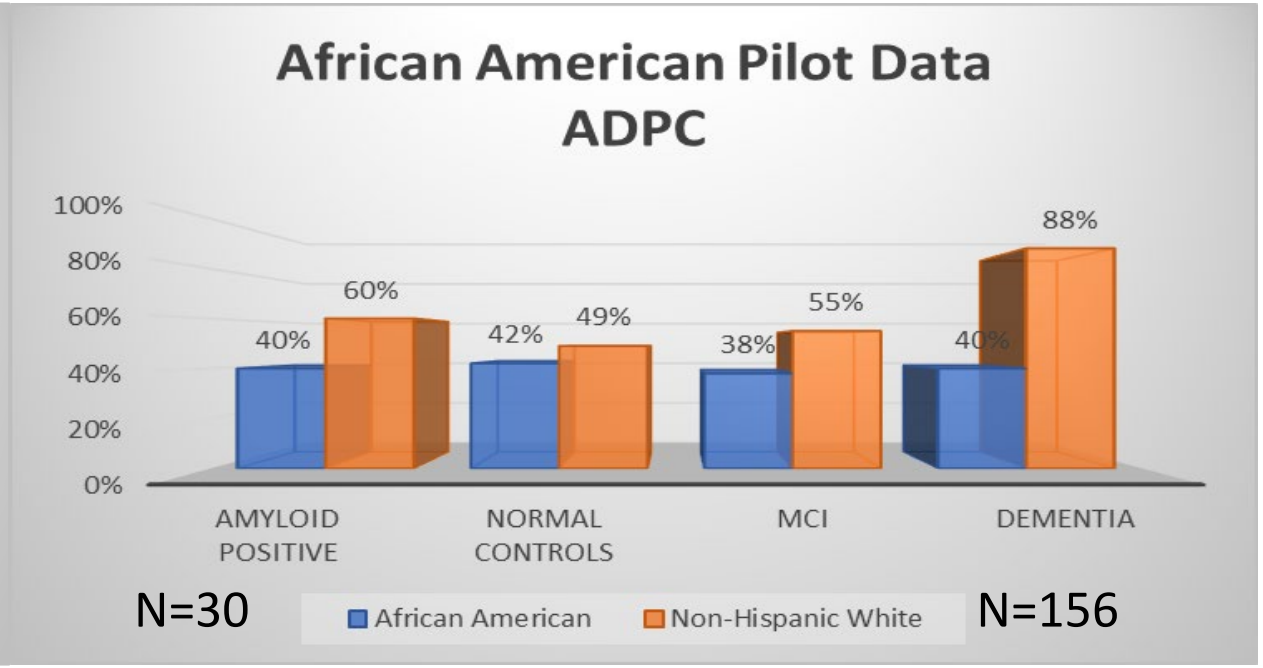
Lower Apoe4 Positivity Rates among Mexican Americans

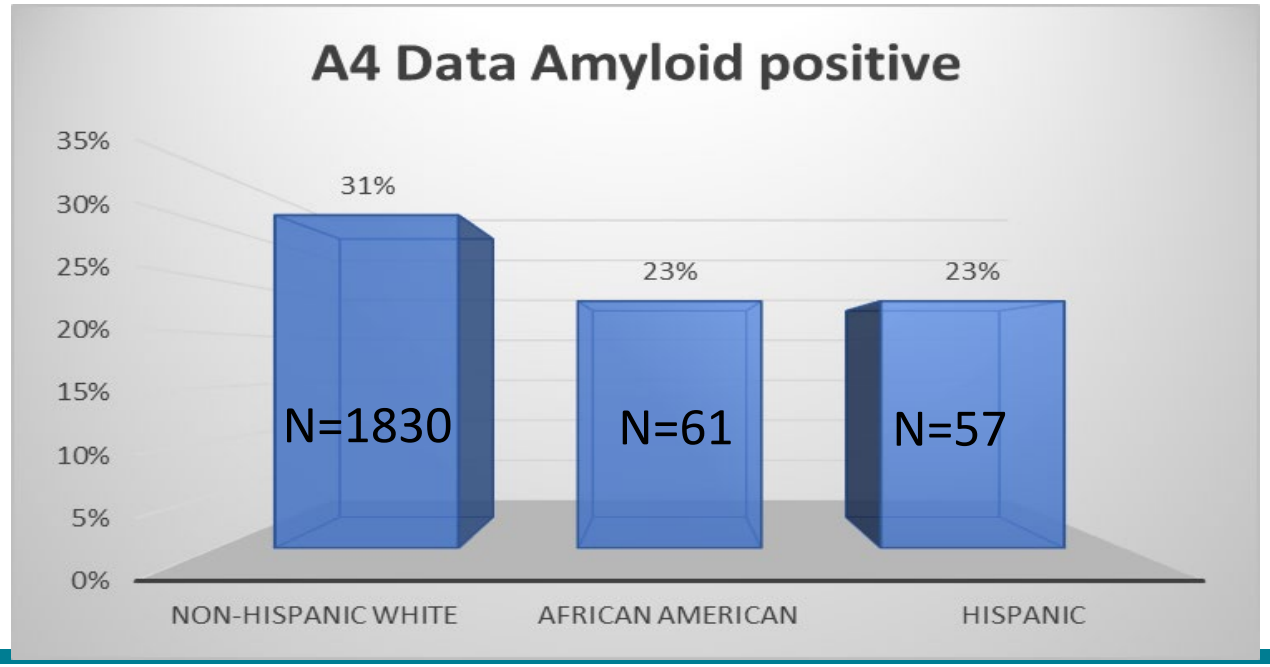




O'Bryant et al 2013, unpublished data







- All $p<0.05$
- HABS-HD currently scheduling approximately 45 new amyloid PET scans weekly
- N>600 participants already awaiting consent process
- O'Bryant et al 2021 DADM

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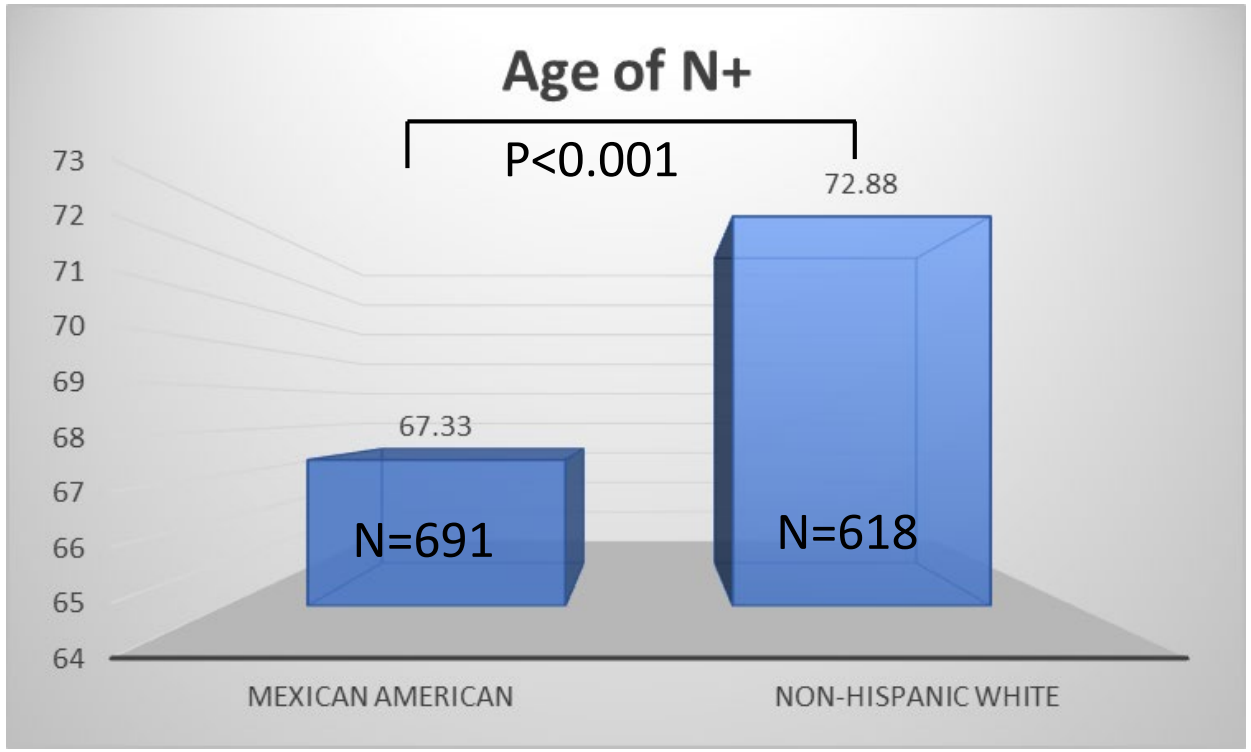
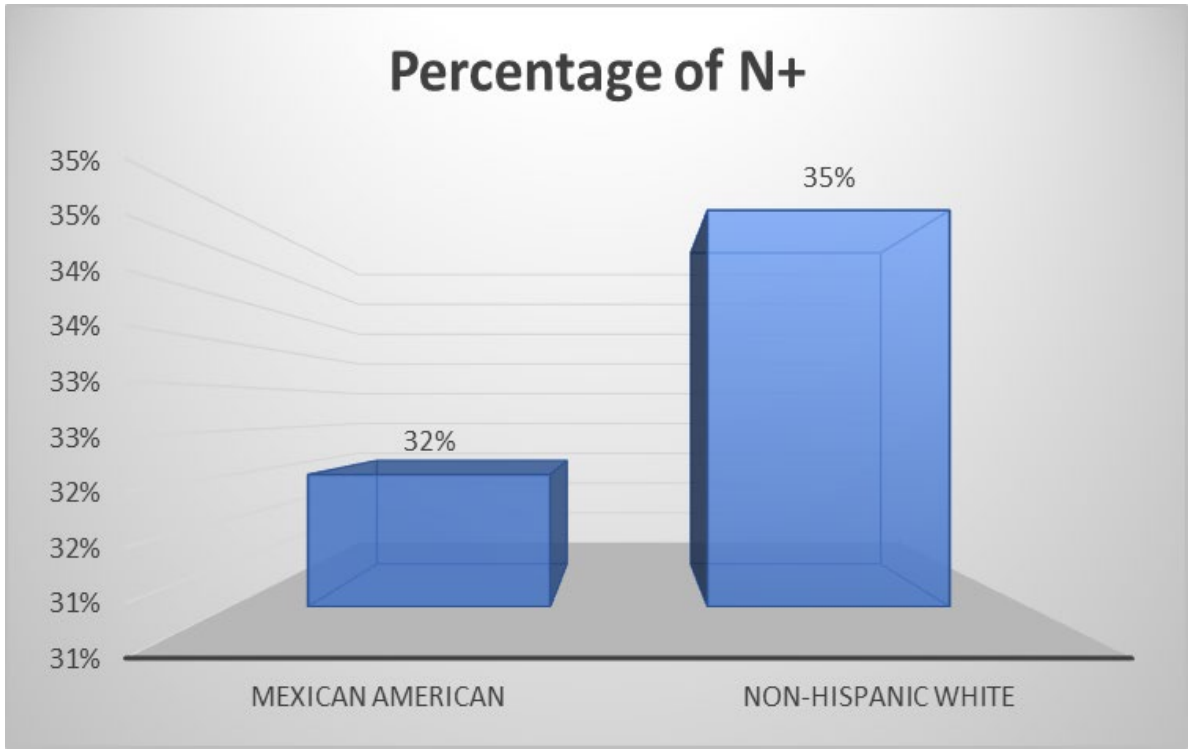
Younger age of onset of MRI Neurodegeneration Positivity (Jack 'meta ROI') among Mexican Americans





O'Bryant et al in press DADM

BBB Alzheimer's Biomarkers Across Diverse Populations in HABS-HD

hsc Health & Aging Brain Study Health Disparities

Characterizing Plasma Biomarkers of Alzheimer's in a Diverse Community-Based Cohort: A Cross-Sectional Study of the HAB-HD Cohort

James R. Hall [1], Melissa Petersen [1,2], Leigh Johnson [1] and Sid E. O'Bryant [1] on behalf of the Health and Aging Brain Study (HABS-HD) Study Team*

[1] Institute for Translational Research, University of North Texas Health Science Center, Fort Worth, TX, United States,
[2] Department of Family Medicine, University of North Texas Health Science Center, Fort Worth, TX, United States

TABLE 2 | Normal cognition.

	Non-Hispanic Whites *N* = 644	Mexican Americans *N* = 642	African Americans *N* = 142	*F* Statistic
$A\beta_{40}$	M = 266.014 SD = 62.656 95% CI [261.167, 270.861]	M = 237.727 SD = 66.410 95% CI [232.581, 242.872]	M = 163.380 SD = 41.831 95% CI [156.463, 170.297]	*F* (2.1425) = 160.258 *P* = 0.0000*
$A\beta_{42}$	M = 12.238 SD = 3.121 95% CI [11.996, 12.480]	M = 11.855 SD = 3.350 95% CI [11.595, 12.115]	M = 8.871 SD = 3.027 95% CI [8.370, 9.371]	*F* (2.1425) = 64.585 *p* = 0.0000*
Tau	M = 2.311 SD = 1.066 95% CI [2.229, 2.392]	M = 2.555 SD = 1.065 95% CI [2.472, 2.639]	M = 1.710 SD = 0.644 95% CI [1.604, 1.816]	*F* (2.1425) = 40.3912 *p* = 0.0000*
NfL	M = 20.100 SD = 12.689 95% CI [19.119, 21.080]	M = 16.747 SD = 12.968 95% CI [15.744, 17.749]	M = 12.579 SD = 10.451 95% CI [10.850, 14.307]	F (2.1425) = 25.098 *p* = 0.0000*
$A\beta_{42}/A\beta_{40}$	M = 0.0473 SD = 0.0133 95% CI [0.046, 0.048]	M = 0.0514 SD = 0.0217 95% CI [0.050, 0.053]	M = 0.0651 SD = 0.0289 95% CI [0.063, 0.067]	*F* (2.1425) = 49.168 *P* = 0.0000*

*$p \leq 0.05$.

Characterization of Mild Cognitive Impairment and Dementia among Community-Dwelling Mexican Americans and Non-Hispanic Whites

Sid E. O'Bryant[a,*], Melissa Petersen[a,b], James Hall[a], Leigh A. Johnson[a,c], Robert Barber[c], Nicole Phillips[c], Meredith N. Braskie[d], Kristine Yaffe[e,f], Robert Rissman[g,h], Arthur Toga[i] and for the HABS-HD Study Team

Table 1
(*Continued*)

	Mexican American			Non-Hispanic White					
	CU $N = 659$ Mean (SD)	MCI $N = 164$ Mean (SD)	Dementia $N = 67$ Mean (SD)	CU $N = 669$ Mean (SD)	MCI $N = 97$ Mean (SD)	Dementia $N = 49$ Mean (SD)	CU F-value χ^2 p	MCI F-value χ^2 p	Dementia F-value χ^2 p
Clinical									
CDR SB	0.00 (0.00)	1.08 (0.58)	4.48 (3.23)	0.00 (0.2)	0.99 (0.53)	3.94 (1.87)	$F = 0.98$ $p = 0.321$	$F = 1.49$ $p = 0.223$	$F = 1.096$ $p = 0.297$
MMSE	26.94 (2.66)	25.01 (3.38)	19.85 (6.52)	29.19 (1.02)	28.09 (1.51)	24.04 (4.47)	$F = 419.06$ $p < 0.001$	$F = 72.40$ $p < 0.001$	$F = 15.02$ $p < 0.001$
GDS	5.90 (5.97)	7.82 (6.43)	10.27	4.22 (4.69)	6.77 (6.18)	7.04 (7.36)	$F = 32.87$	$F = 1.66$	$F = 5.17$
Biomarker									
APOE ε4 positive	17%	15%	36%	28%	33%	61%	$\chi^2 = 19.52$ $p < 0.001$	$\chi^2 = 10.57$ $p = 0.002$	$\chi^2 = 6.69$ $p = 0.012$
MetaROI thickness (mm)	2.75 (0.13)	2.73 (0.13)	2.58 (0.22)	2.74 (0.13)	2.65 (0.16)	2.48 (0.27)	$F = 1.07$ $p = 0.299$	$F = 13.44$ $p < 0.001$	$F = 2.82$ $p = 0.097$
N Positive	29%	34%	66%	30%	56%	68%	$\chi^2 = 0.24$	$\chi^2 = 8.71$	$\chi^2 = 0.02$
Plasma NfL	16.46 (11.48)	18.38 (13.69)	28.49 (25.63)	19.87 (11.01)	26.57 (23.63)	28.03 (16.42)	$F = 29.23$ $p < 0.001$	$F = 11.91$ $p = 0.001$	$F = 0.011$ $p = 0.916$
Plasma $A\beta_{40}$	236.42 (64.42)	245.21 (71.89)	255.81 (92.88)	264.98 (64.37)	282.56 (69.73)	267.57 (67.52)	$F = 62.63$ $p < 0.001$	$F = 15.90$ $p < 0.001$	$F = 0.533$ $p = 0.467$
Plasma $A\beta_{42}$	11.77 (3.36)	12.29 (3.65)	11.90 (4.17)	12.22 (3.12)	12.75 (3.44)	12.09 (3.80)	$F = 6.03$ $p = 0.014$	$F = 0.98$ $p = 0.323$	$F = 0.062$ $p = 0.803$
Plasma total tau	2.55 (0.92)	2.64 (1.57)	2.82 (1.31)	2.33 (0.93)	2.47 (1.78)	2.58 (1.14)	$F = 17.86$	$F = 0.634$	$F = 0.980$
$A\beta_{42}/A\beta_{40}$ Ratio, Mean (SD)	0.051 (0.015)	0.051 (0.013)	0.049 (0.013)	0.047 (0.013)	0.046 (0.011)	0.046 (0.012)	$F = 24.16$ $p < 0.001$	$F = 11.12$ $p = 0.001$	$F = 1.76$ $p = 0.186$

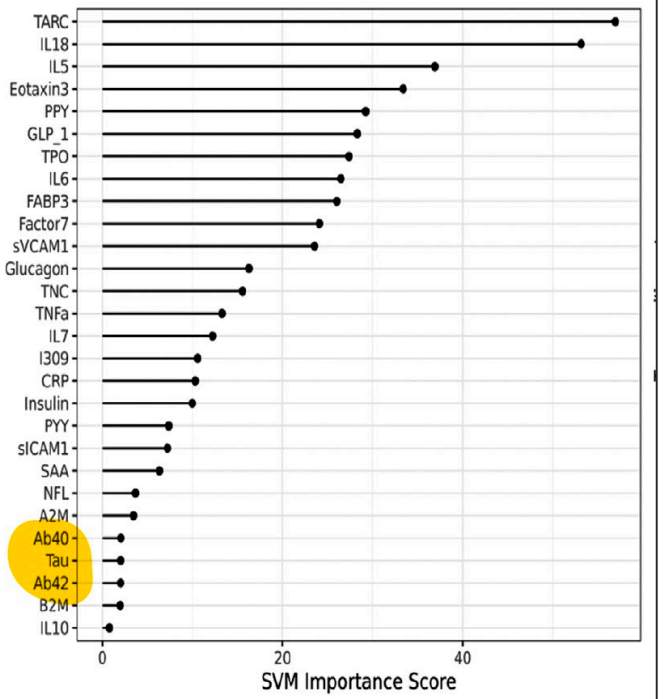
MCI, mild cognitive impairment; CU, cognitively unimpaired; ADI, area deprivation index; Meta ROI, Jack et al. meta ROI of neurodegeneration; N positive, neurodegeneration positive based on Meta ROI; CDR SB, Clinical Dementia Rating Scale Sum of Boxes score; MMSE, Mini-Mental State Exam; GDS, Geriatric Depression Scale (30-item).

Proteomic profiles of MCI and AD are different among Mexican Americans as compared to non-Hispanic whites

A

	Actual	
Predicted	MCI	NC
MCI	83	4
NC	26	498
Sensitivity	76.15%	
Specificity	99.20%	
NPV	95.04%	
AUC	91.41%	

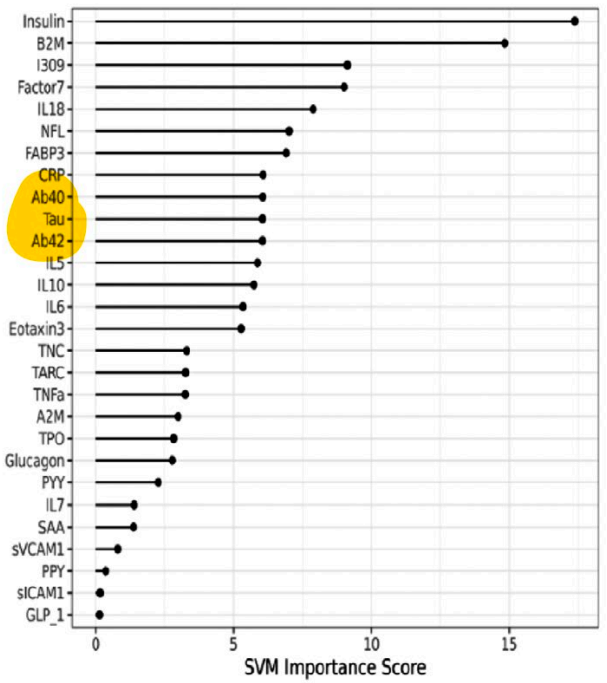
MCI Classification in Mexican Americans



B

	Actual	
Predicted	MCI	NC
MCI	62	7
NC	9	539
Sensitivity	87.32%	
Specificity	98.72%	
NPV	98.36%	
AUC	93.96%	

MCI Classification in Non-Hispanic Whites



- O'Bryant 2013 demonstrated the impact of race/ethnicity on proteomics of AD
- Findings are cross-validated in HABS-HD (**O'Bryant et al 2021**)
- Note that plasma markers of amyloid and tau do not rank among top half of Mexican Americans (**O'Bryant et al 2021)**

Medical comorbidities and ethnicity impact plasma Alzheimer's disease biomarkers: Important considerations for clinical trials and practice

Sid E. O'Bryant[1] | Melissa Petersen[1,2] | James Hall[1] | Leigh A. Johnson[1,3] | for the HABS-HD Study Team

Volume 6 • Issue 2 | 23

fortune Journals

Research Article

ARCHIVES OF NEPHROLOGY AND UROLOGY

ISSN: 2644-2833

Kidney Function Impacts Plasma Alzheimer's Biomarkers In A Cognitively Normal Multi-Ethnic Cohort

James R. Hall[a,b*], Melissa Petersen[a,b], Leigh A Johnson[a,c] & Sid O'Bryant[a,b] for the HABS-HD Study Team

TABLE 2 Partial correlation coefficients of link between plasma biomarkers and comorbidity measures

	$A\beta_{40}$ pg/ml	$A\beta_{42}$ pg/ml	$A\beta_{42}/A\beta_{40}$ ratio	Tau pg/ml	NfL pg/ml
Total cholesterol	−0.14 $P > .05$	−0.02 $P > .05$	0.003 $P > .05$	−0.14 $P < .001$	−0.03 $P > .05$
HDL	-0.14 $P < .001$	-0.12 $P < .001$	0.05 $P > .05$	-0.10 $P = .002$	0.02 $P > .05$
Triglycerides	0.22 $P < .001$	0.25 $P < .001$	0.007 $P > .05$	0.01 $P > .05$	0.07 $P = .05$
Glucose	0.09 $P = .007$	0.08 $P = .01$	−0.03 $P > .05$	0.05 $P > .05$	0.20 $P < .001$
HbA1c	0.09 $P = .009$	0.09 $P = .005$	−0.016 $P > .05$	0.09 $P = .01$	0.22 $P < .001$
eGFR	−0.46 $P < .001$	−0.46 $P < .001$	0.027 $P > .05$	−0.23 $P < .001$	−0.35 $P < .001$
Systolic BP	0.03 $P > .05$	0.01 $P > .05$	-0.03 $P > .05$	0.06 $P = .06$	0.01 $P > .05$
Diastolic BP	−0.03 $P > .05$	0.01 $P > .05$	−0.015 $P > .05$	0.02 $P > .05$	−0.07 $P = .04$

Abbreviations: Aβ, amyloid beta; ANCOVA, analyses of covariance; BP, blood pressure; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; HbA1c, hemoglobin A1c; HDL, high-density lipoproteins; NfL, plasma neurofilament light chain; tau, plasma total tau.

Notes: Covariates in ANCOVA include age, sex, and education.

The link between AT(N) biomarkers and clinical outcomes vary by race/ethnicity

APOEε4 Genotype Is Related to Brain Amyloid Among Mexican Americans in the HABS-HD Study

Sid E. O'Bryant[1,2], Melissa Petersen[1,2], James Hall[1,2] and Leigh Johnson[1,3] for the HABS-HD Study Team*

[1] *Institute for Translational Research, University of North Texas Health Science Center, Fort Worth, TX, United States,*
[2] *Department of Family Medicine, University of North Texas Health Science Center, Fort Worth, TX, United States,*
[3] *Department of Pharmacology and Neuroscience, University of North Texas Health Science Center, Fort Worth, TX, United States*

- While **less frequent** among Mexican Americans, the *APOE*-ε4 genotype appears to be a significant **risk factor for AD pathological burden** among this group.

TABLE 2 | APOEε4genotype and cerebral amyloid.

	Mexican American *n* = 105	**Non-Hispanic white participants *n* = 150**
Global SUVR	$F = 3.03$, $p = 0.003$ 8% variance	$F = 4.62$, $p < 0.001$ 13% variance
Frontal SUVR	$F = 3.19$, $p < 0.001$ 8% variance	$F = 4.72$, $p < 0.001$ 13% variance
Cingulate SUVR	$F = 2.85$, $p = 0.005$ 7% variance	$F = 4.94$, $p < 0.001$ 14% variance
Lateral/parietal SUVR	$F = 3.06$, $p = 0.003$ 8% variance	$F = 4.22$, $p < 0.001$ 11% variance
Lateral temporal	$F = 2.73$, $p = 0.008$ 6% variance	$F = 4.09$, $p < 0.001$ 10% variance

The Link between APOE4 Presence and Neuropsychological Test Performance among Mexican Americans and Non-Hispanic Whites of the Multiethnic Health & Aging Brain Study – Health Disparities Cohort

Sid E. O'Bryant[a], Robert C. Barber[b], Nicole Philips[b], Leigh A. Johnson[a,b], James R. Hall[a], Kumudu Subasinghe[b], Melissa Petersen[a,c], Arthur W. Toga[d], Kristine Yaffe[e,f], Robert A. Rissman[g,h], HABS-HD Study Team

	APOE4 +	APOE2+
Mexican American	18.4%	6.6%
Non-Hispanic White	30.3%	15.9%

	Total cohort	MA	NHW
WMS-III LM1	$t = -3.29, p < 0.001$	$t = -3.44, p < 0.001$	$t = -2.63, p = 0.009$
WMS-III LM2	$t = -3.73, p < 0.001$	$t = -2.91, p = 0.004$	$t = -3.34, p < 0.001$
SEVLT 1–5	$t = -3.38, p < 0.001$	$t = -2.29, p = 0.02$	$t = -3.20, p = 0.001$
SEVLT Delayed	$t = -3.49, p < 0.001$	$t = -2.40, p = 0.02$	$t = -3.19, p = 0.001$
Trials A	$t = 1.65, p = 0.10$	$t = 1.15, p > 0.05$	$t = 1.76, p = 0.08$
Trails B	$t = 1.53, p > 0.05$	$t = 0.40, p > 0.05$	$t = 3.07, p = 0.002$
WMS-III DS	$t = -0.57, p > 0.05$	$t = -0.52, p > 0.05$	$t = -2.06, p = 0.04$
FAS	$t = -0.16, p > 0.05$	$t = -0.64, p > 0.05$	$t = -0.38, p > 0.05$
Animals	$t = -2.18, p = 0.03$	$t = -0.95, p > 0.05$	$t = -2.41, p = 0.02$

Metabolic Factors Are Related to Brain Amyloid Among Mexican Americans: A HABS-HD Study

Sid E. O'Bryant, Melissa Petersen, James Hall, Leigh Johnson

Family Medicine and Osteopathic Manipulative Medicine, Institute for Healthy Aging, Institute for Translational Research, Texas College of Osteopathic Medicine, Pharmacology & Neuroscience, School of Biomedical Sciences

Background: Despite the tremendous amount of research on Alzheimer's disease (AD) biomarkers, very little data is available regarding the fundamental biomarkers of AD among Mexican Americans. Objective: Here we sought to examine the link between metabolic markers and brain amyloid among Mexican Americans as compared to non-Hispanic whites from the Health Aging Brain Study -Health Disparities (HABS-HD) cohort. Methods: PET amyloid (florbetaben) data was analyzed from 34 Mexican American and 22 non-Hispanic white participants. Results: Glucagon ($t = 3.84$, $p < 0.001$) and insulin ($t = -2.56$, $p = 0.02$) were both significantly related to global SUVR levels among Mexican Americans. Glucagon and insulin were both related to most ROIs. No metabolic markers were significantly related to brain amyloid levels among non-Hispanic whites. Conclusion: Metabolic markers are related to brain amyloid burden among Mexican Americans. Given the increased risk for diabetes, additional research is needed to determine the impact of diabetes on core AD biomarkers among this underserved population.

Metabolic Markers and PET Amyloid (O'Bryant et al 2022)

	Global	Frontal	Cingulate	Lateral Parietal	Lateral Temporal
Mexican American (n=34)					
Glucagon	t=3.84, p<0.001	t=2.93, p=0.008	t=3.06, p=0.006	t=3.99, p<0.001	t=5.34, p<0.001
Insulin	t=-2.56, p=0.02	t=-2.56, p=0.02	t=-1.92, p=0.07	t=-2.18, p=0.04	t=-3.52, p=0.002
Non-Hispanic White (n=22)	ns	ns	ns	ns	ns

THE GERONTOLOGICAL SOCIETY OF AMERICA®

Journals of Gerontology: Biological Sciences
cite as: *J Gerontol A Biol Sci Med Sci*, 2022, Vol. XX, No. XX, 1–7
https://doi.org/10.1093/gerona/glac169
Advance Access publication August 18, 2022

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Original Article

Plasma Biomarkers of Alzheimer's Disease Are Associated with Physical Functioning Outcomes Among Cognitively Normal Adults in the Multiethnic HABS-HD Cohort

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Table 4. Link Between Plasma Alzheimer's Disease Biomarkers and Physical Function by Ethnicity

	$A\beta_{40}$	$A\beta_{42}$	Total Tau	NfL
NHW				
TUG	(0.003, **<0.001**)	(0.039, 0.116)	(0.182, **0.028**)	(0.006, 0.466)
	[0.001, 0.006]	[−0.010, 0.088]	[0.020, 0.345]	[−0.009, 0.021]
SPPB	(−0.002, 0.055)	(−0.028, 0.054)	(−0.134, **0.044**)	(−0.007, 0.232)
	[−0.004, 0.000]	[−0.078, 0.001]	[−0.265, −0.003]	[−0.020, 0.005]
MA				
TUG	(0.006, **<0.001**)	(0.068, **0.020**)	(0.180, 0.095)	(0.037, **<0.001**)
	[0.003, 0.009]	[0.011, 0.126]	[−0.032, 0.391]	[0.020, 0.054]
SPPB	(−0.003, **0.004**)	(−0.065, **0.005**)	(−0.191, **0.023**)	(−0.033, **<0.001**)
	[−0.006, −0.001]	[−0.110, −0.020]	[−0.355, −0.026]	[−0.046, −0.020]

Notes: $A\beta_{40}$ = plasma beta amyloid 40; $A\beta_{42}$ = plasma beta amyloid 42; MA = Mexican American; NfL = plasma neurofilament light chain; NHW = non-Hispanic White; total tau = plasma total tau. All models are adjusted for age, gender, and education: (β, *p*-value) [95% confidence interval]. All *p* values < .05 are bolded.

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Conclusions

- ATN-defined biomarkers are differentially prevalent among diverse populations
- ATN-defined biomarkers are differentially related to clinical outcomes among diverse populations
- Clinical, demographic and sociocultural factors are differentially related to ATN-defined and cognitive outcomes among diverse populations
- We cannot advance true precision medicine without inclusion of diverse communities

Data Sharing

- Item-level data currently available through data portal
- **All** HABS-HD data is available
- **All** raw imaging files are available
- Investigators review Data Access and Publications Committee Proposal and Publication Policy, sign the DUA, create an account and submit a proposal.
- Proposals are administratively reviewed with decisions provided within 2 weeks with DAPC members given 36-hours for review before the proposal is defaulted to another member

https://apps.unthsc.edu/itr/request/hd

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Questions?