2023FALL ADRC MEETING

SOUTH TEXAS ALZHEIMER'S DISEASE RESEACH CENTER

NIA-AA Revised Criteria for Diagnosis and Staging of Alzheimer's Disease: Impact on Diagnosis and Treatment of Underrepresented Groups

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San Diego, CA Oct 19th, 2023

DISCLOSURES

None

FUNDING

1P30AG059305-01, 1P30AG066546-01A1,
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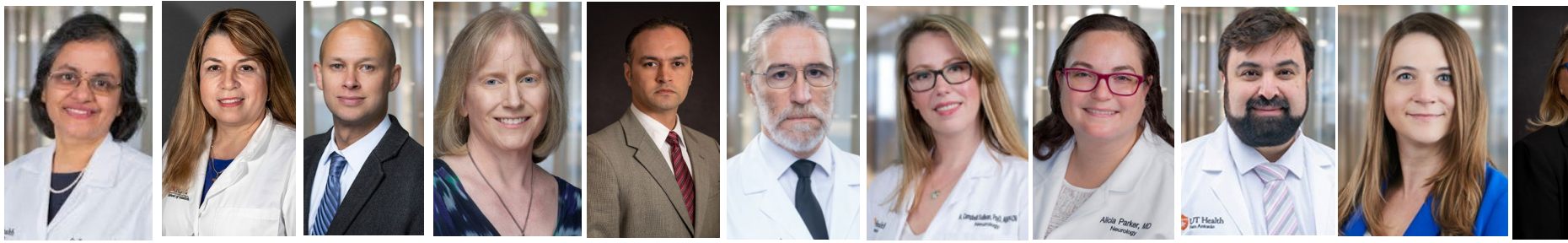
Texas Alzheimer’s Disease Research and Consortium

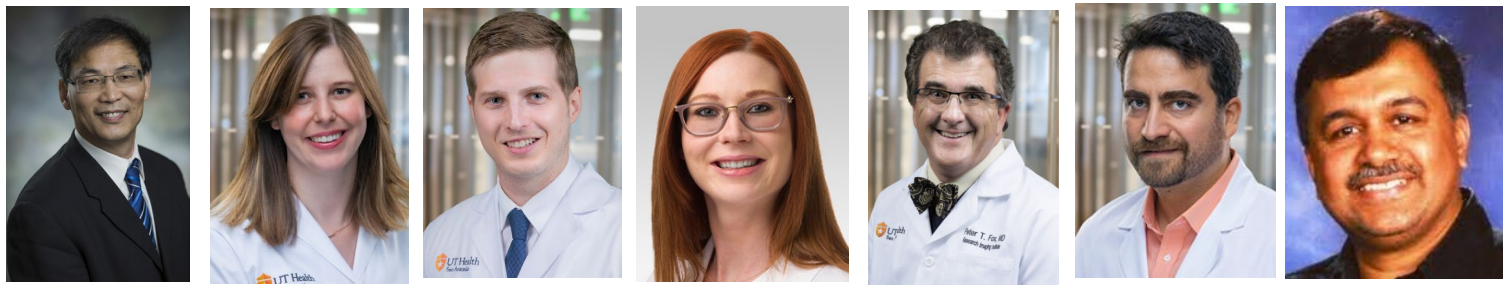


Administrative

Clinical

Population Neuroscience

Genomics



Biomarker

Neuropathology

Imaging

OREC

Data Management

REC

SOUTH TEXAS ALZHEIMER'S DISEASE RESEACH CENTER

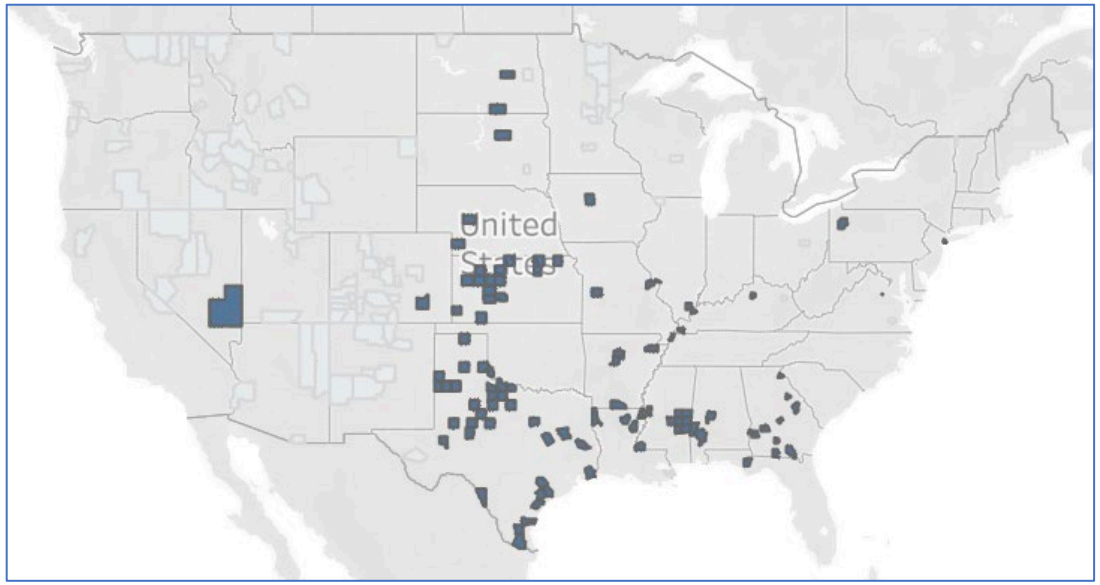
UT Health San Antonio
Glenn Biggs Institute for Alzheimer's & Neurodegenerative Diseases

UTRGV
UT Health Rio Grande Valley

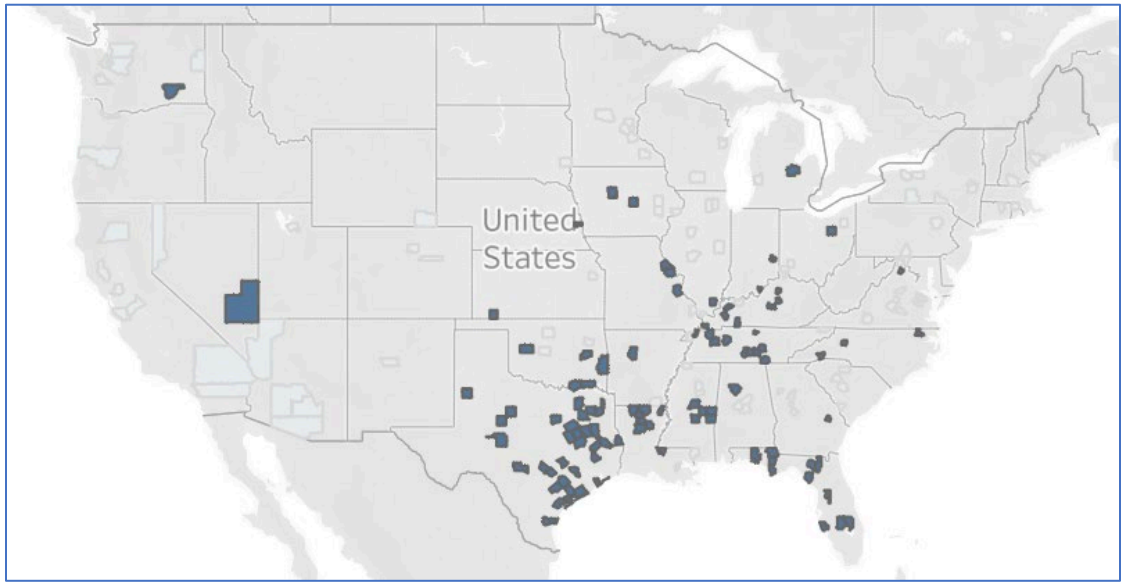
REC Scholars

Core Concepts

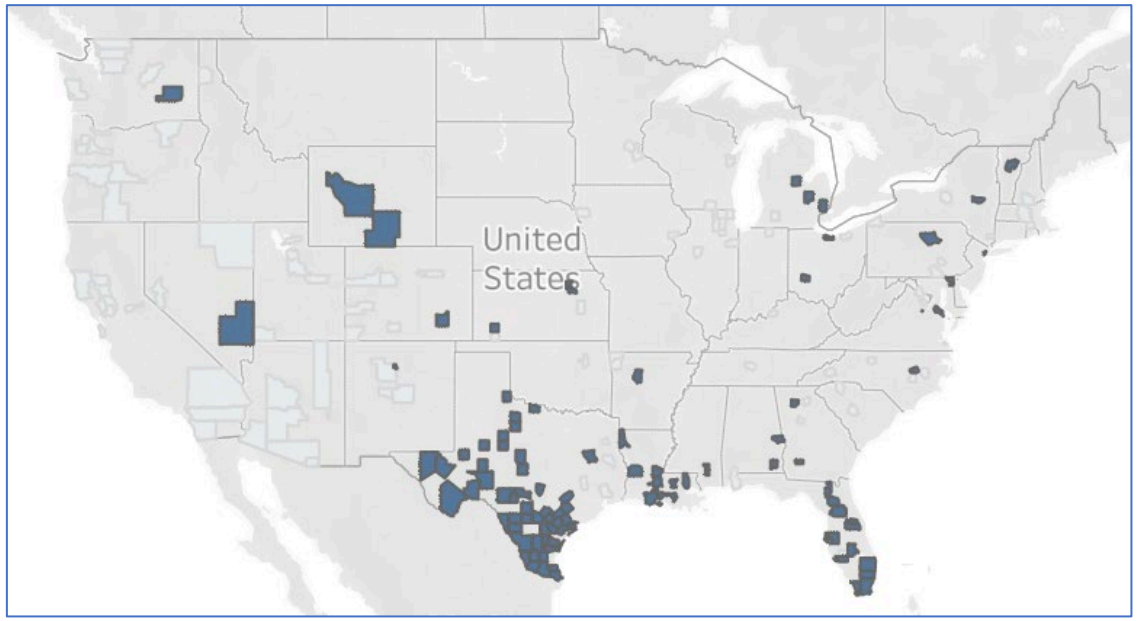
- **Impact:** Change.
- **Diagnostic Process:**
  - Is a complex, patient-centered, collaborative activity involving information gathering and clinical reasoning to determine a person's health situation. National Academies Press (US); 2015 https://www.ncbi.nlm.nih.gov/books/NBK338593/
  - cyclical process of information gathering, integration and interpretation, and forming a working diagnosis Parasuraman et al. (2000) PMID: 11760769.
- **Treatment:** provision, coordination or management of health care and related services by one or more providers.



Non-Hispanic Whites



Blacks

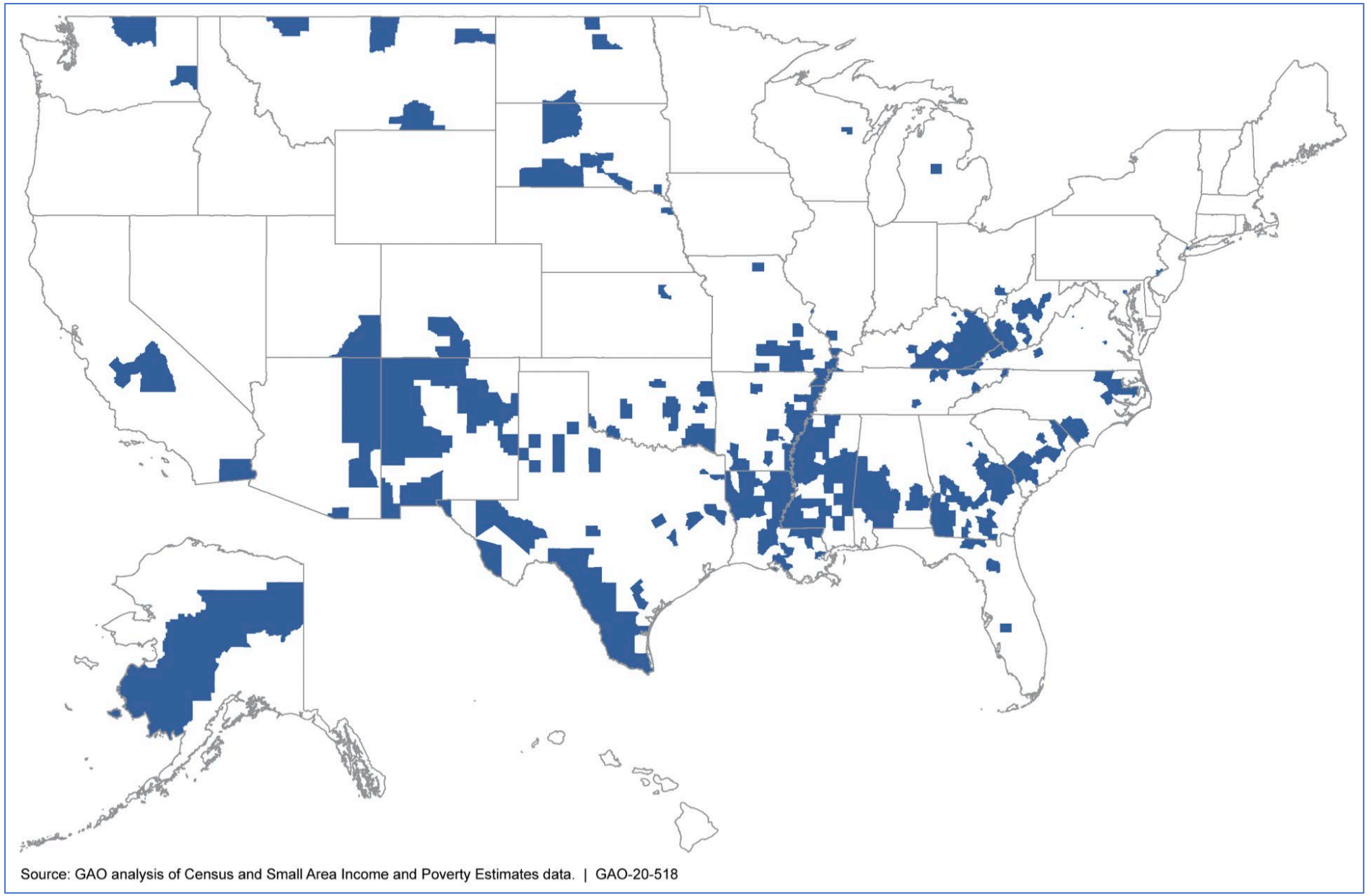


Hispanic/LatinX

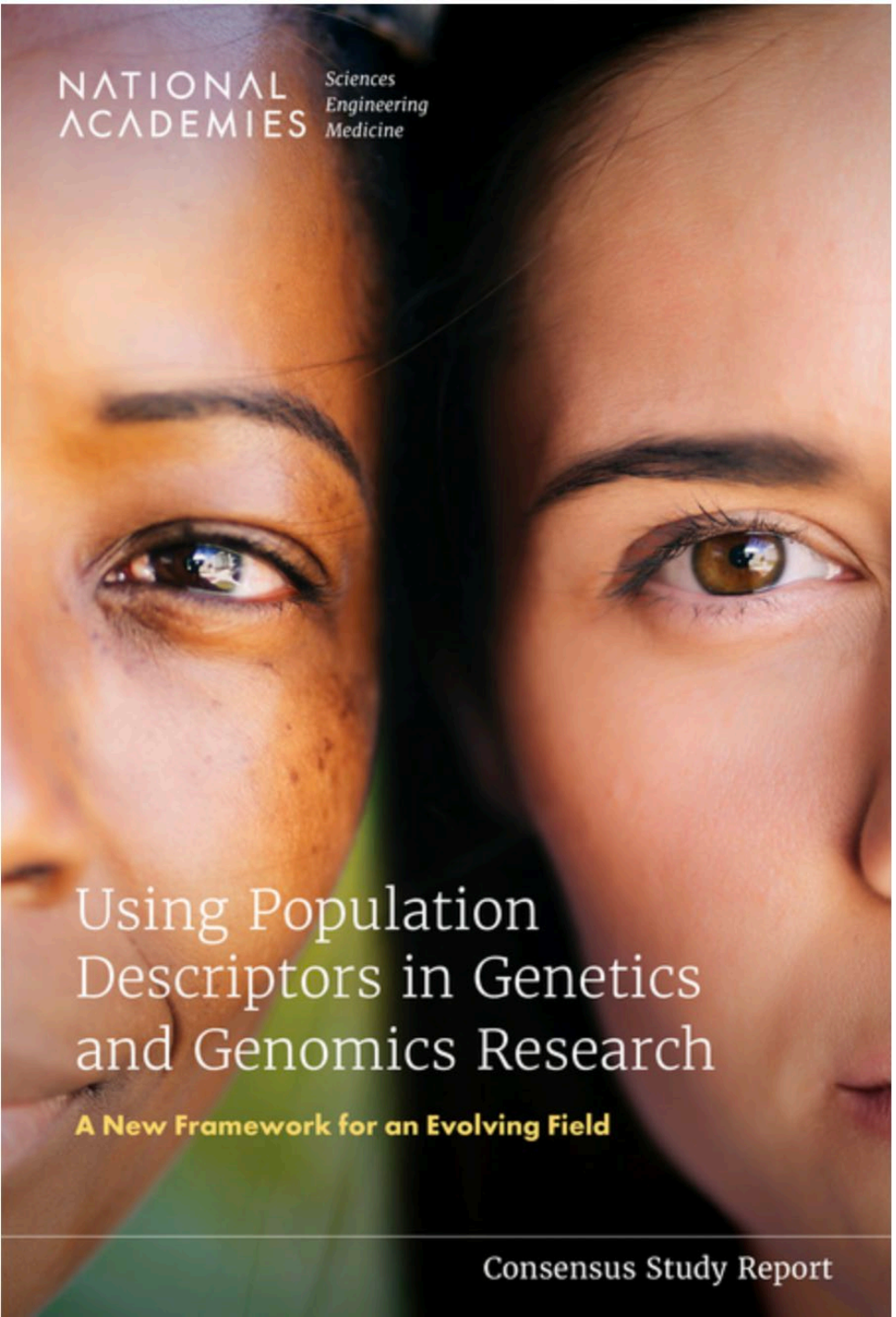
100 counties in the US with **highest** AD/ADRD prevalence by race/ethnicity

Race represents a social rather than a biological construct.

Persistent-Poverty Counties, as of 2017



Source: GAO analysis of Census and Small Area Income and Poverty Estimates data. | GAO-20-518



Conclusion 4-1. Race is neither useful nor scientifically valid as a measure of the structure of human genetic variation.

Conclusion 4-2. Using socially constructed groupings indiscriminately in human genetics research can be harmful.

Conclusion 4-3. Current practices often reinforce typological views of human genetic ancestry (e.g., the use of continental ancestry groups). Therefore, new models that reflect a more complex and realistic portrait of genetic ancestry are needed (e.g., genetic similarity).

Conclusion 4-4. The requirement to report participant demographics using OMB categories has perpetuated misconceptions or exacerbated typological thinking and can undermine the selection of variables that are most appropriate for a given study.

Are ATN-defined biomarkers equally prevalent among diverse populations?

Table 2. Amyloid Positivity Differences Between 1:1 Matched Participants

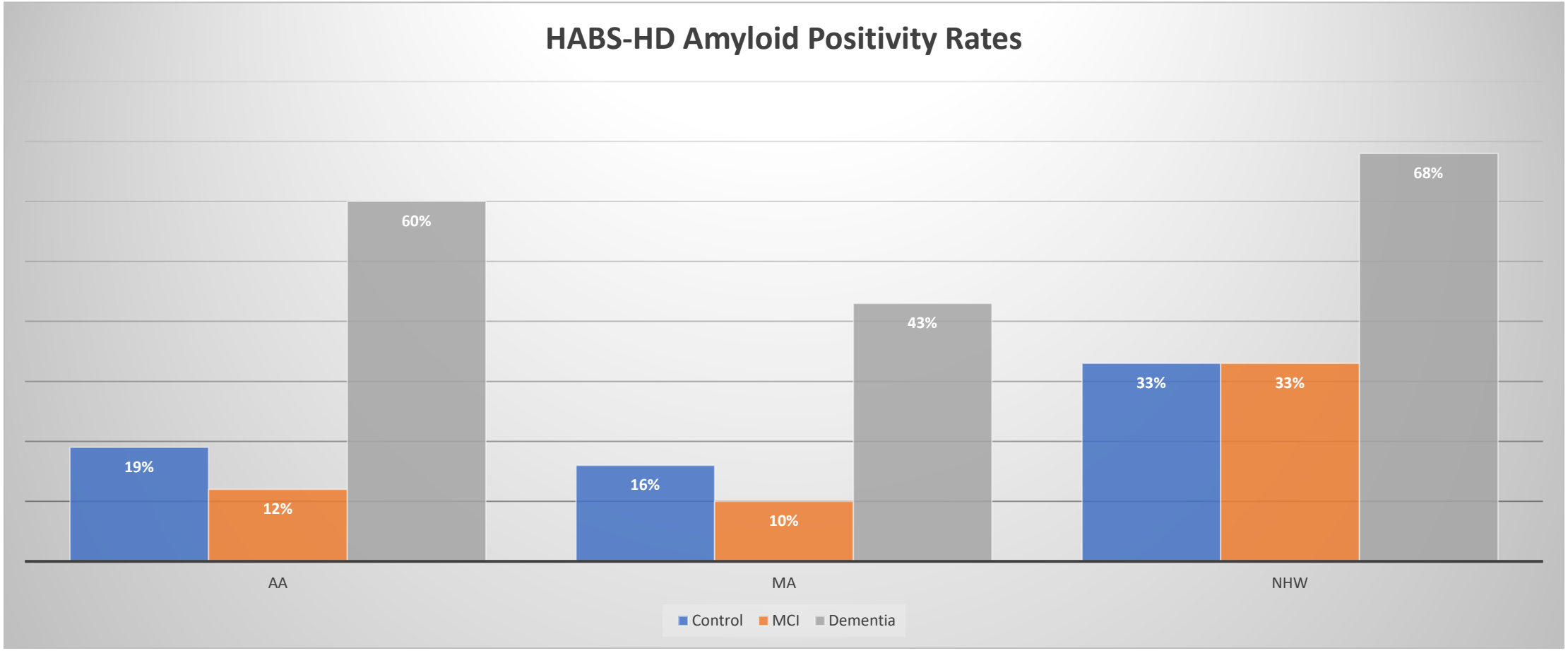
Amyloid PET scan result	Matched participants, No. (%)					
	Asian	White	Black	White	Hispanic	White
No.	313	313	615	615	780	780
MCI and dementia						
Positive, No. (%) [95% CI]	142 (45.4) [39.9-50.9]	181 (57.8) [52.3-63.2]	333 (54.1) [50.2-58.0]	359 (58.4) [54.4-62.2]	425 (54.5) [51.0-58.0]	482 (61.8) [58.3-65.1]
Negative	171 (54.6)	132 (42.2)	282 (45.9)	256 (41.6)	355 (45.5)	298 (38.2)

Wilkins et al., Racial and Ethnic Differences in Amyloid PET Positivity in Individuals With Mild Cognitive Impairment or DementiaJAMA Neurol. 2022;79(11):1139-1147. doi:10.1001/jamaneurol.2022.3157

Biomarker	Study by	NHB vs NHW
Amyloid-PET	Gottesman et al, 2016 Morris et al., 2019 Meeker et al., 2020 Deters et al., 2021	NHB Higher No difference No difference NHB Lower
CSF AB42 & AB40	Howell et al., 2017 Garrett et al 2019 Morris et al., 2019 Deters et al., 2021	No difference NHB higher if HC NHB higher if MCI
PET-tau	Meeker et al., 2020	No difference
CSF-tau	Howell et al., 2017 Garrett et al 2019 Morris et al., 2019 Deters et al., 2021	NHB Lower

Gleason, CE, Zuelsdorff, M, Gooding, DC, et al. Alzheimer's disease biomarkers in Black and non-hispanic White cohorts: A contextualized review of the evidence. Alzheimer's Dement. 2022; 18: 1545–1564. https://doi.org/10.1002/alz.12511

HABS-HD (formally the Health & Aging Brain study among Latino Elders, HABLE study)

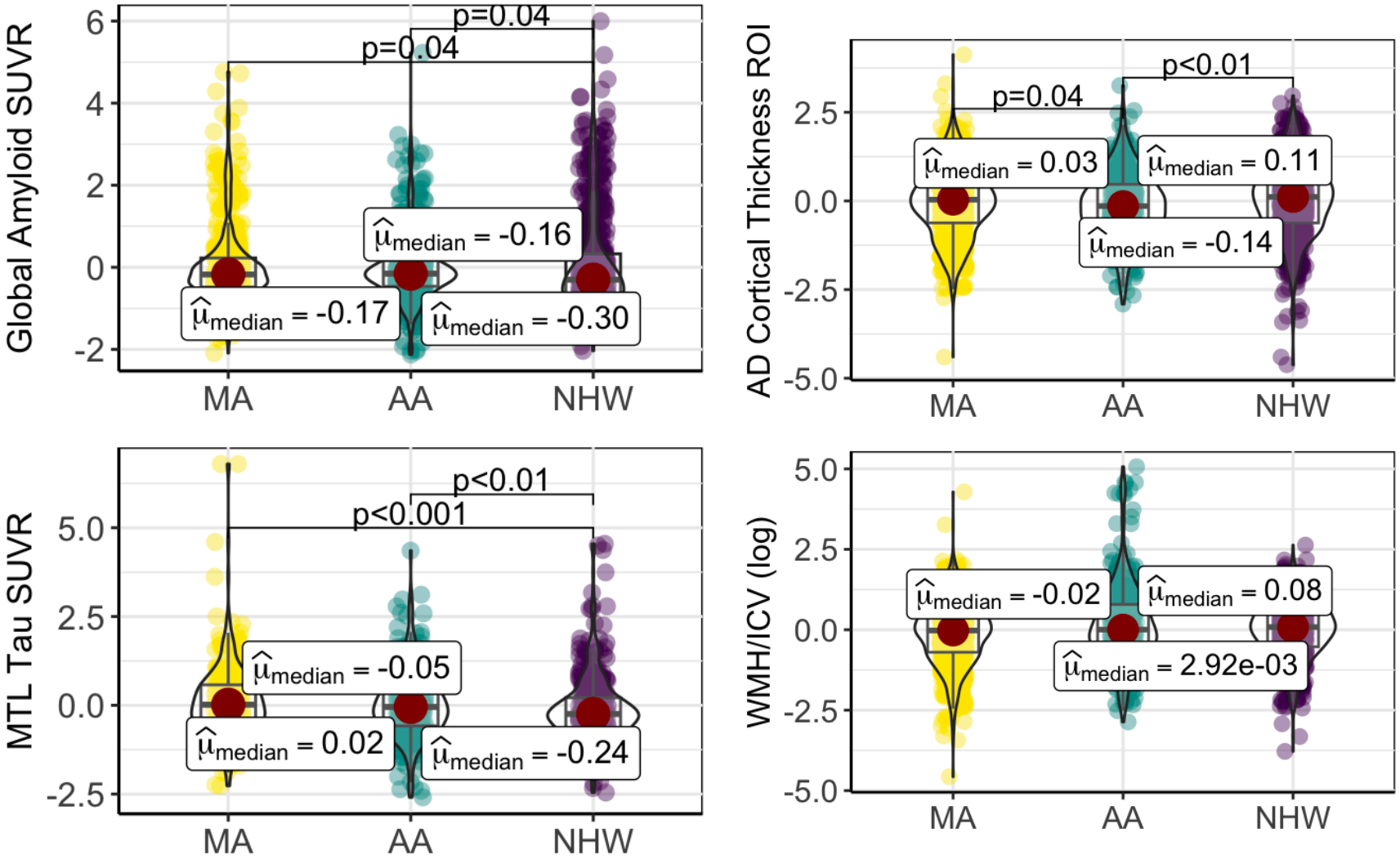


Mexican American participants had significantly lower Aβ40 ($P < .001$) and higher total tau ($P = .005$) and Aβ42/Aβ40 ratio ($P < .001$) levels.

A, T and N, but not V differ by group (With CDR)

Health & Aging Brain Study
Health Disparities

MA = 1171
AA. = 700
NHW= 1164

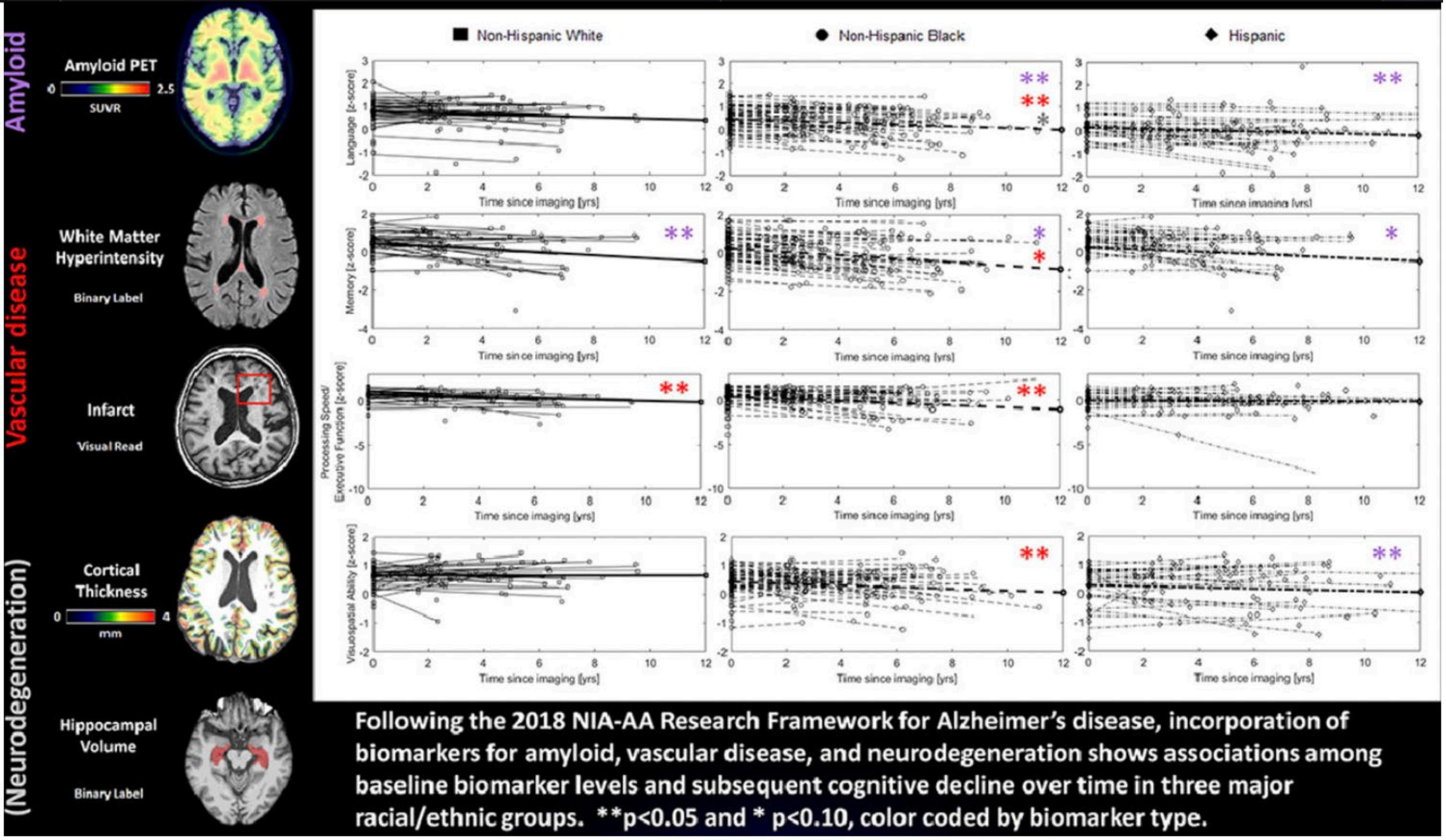


*Values = residuals after accounting for age, gender, education, and time difference between MRI and PET

Modified from Slide from Dr. Karim Meeker

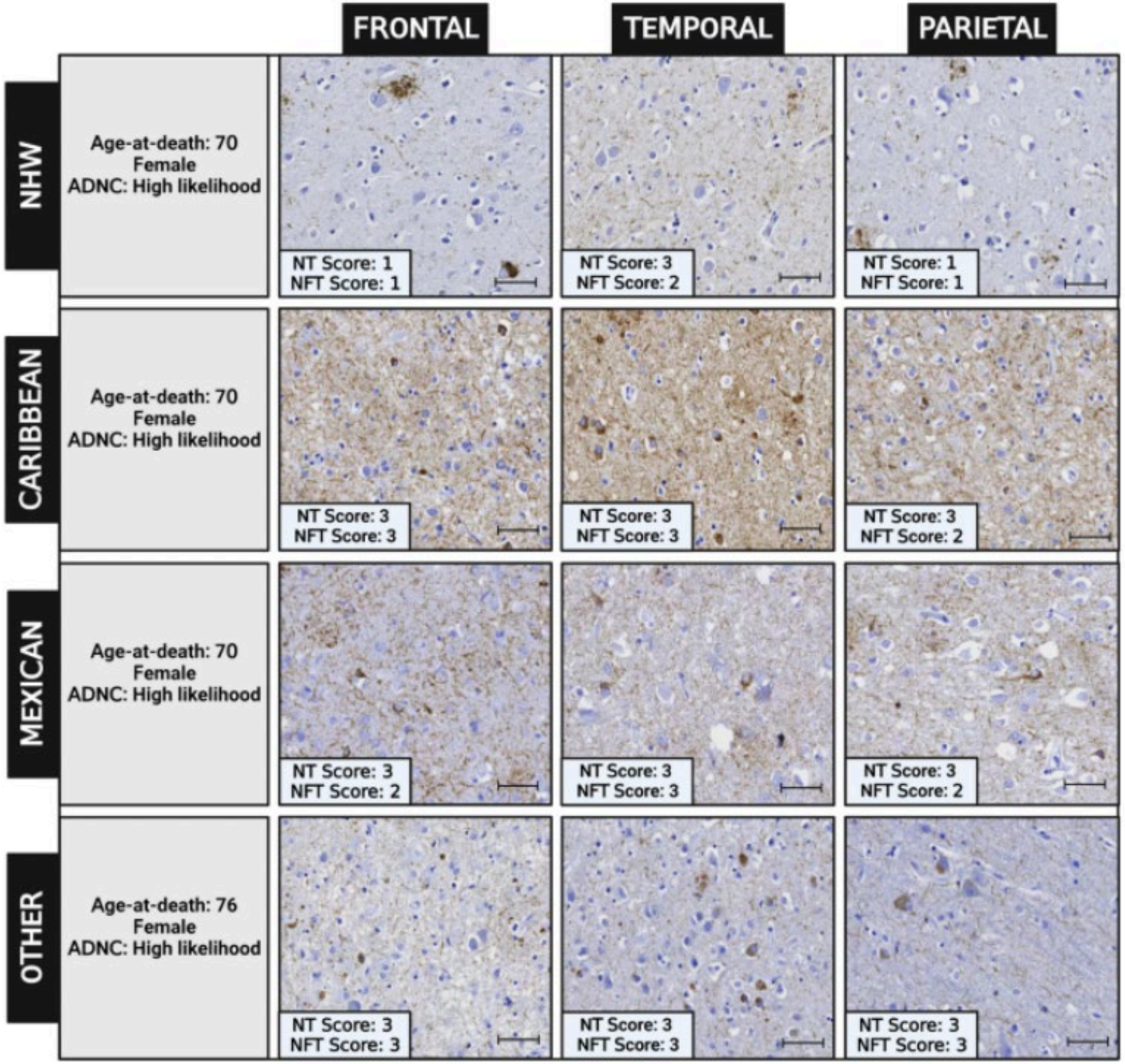
Are ATN-defined biomarkers equally prevalent among diverse populations? No

Are ATN-defined biomarkers equally related to clinical outcomes among diverse populations?



Following the 2018 NIA-AA Research Framework for Alzheimer's disease, incorporation of biomarkers for amyloid, vascular disease, and neurodegeneration shows associations among baseline biomarker levels and subsequent cognitive decline over time in three major racial/ethnic groups. **p<0.05 and * p<0.10, color coded by biomarker type.

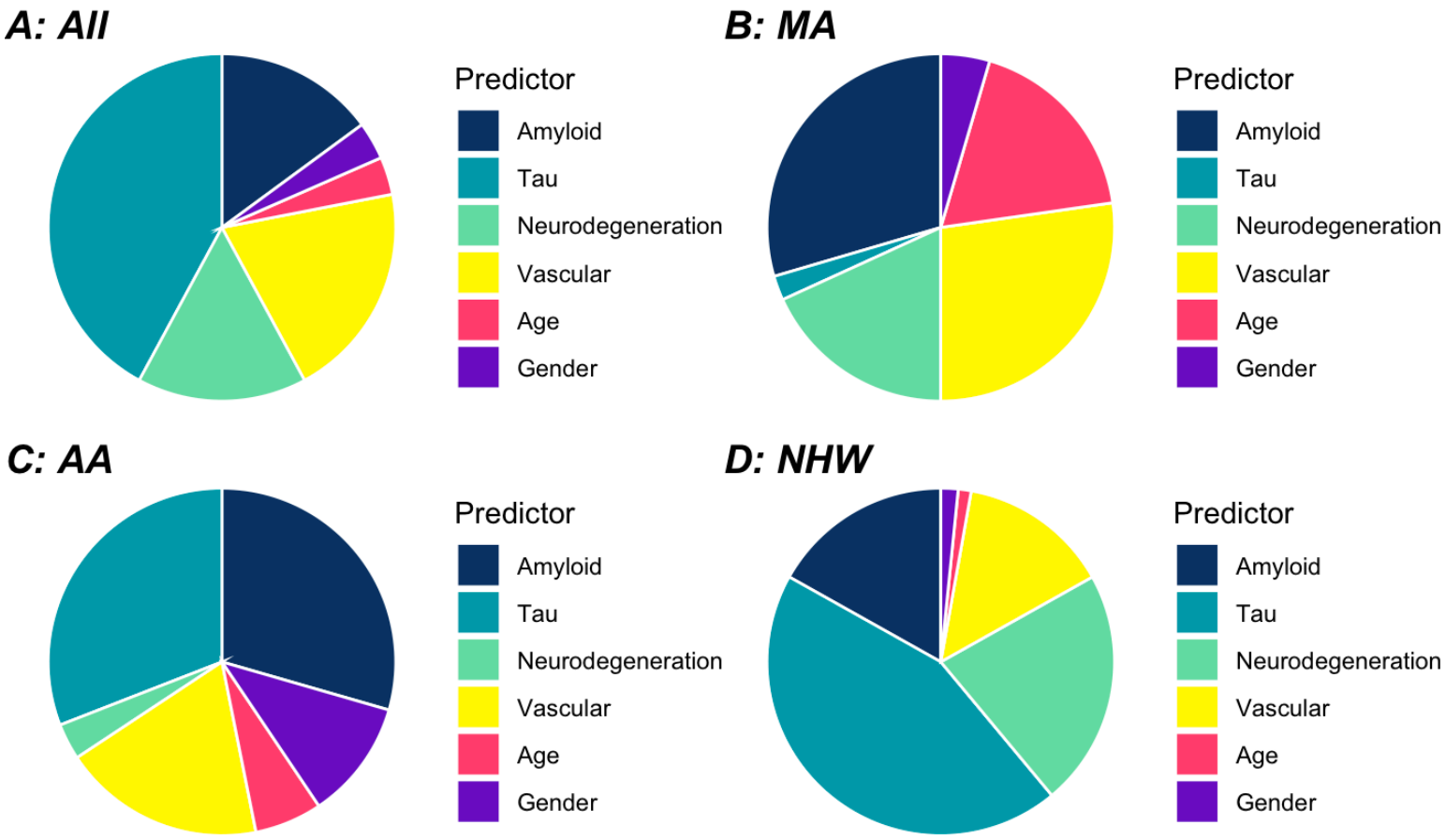
Examples of the histopathologic densities of tau-deposits and corresponding overall regional density scores (for neuropil threads: NTs, and neurofibrillary tangles: NFTs- lower left corner in each image) in three brain regions (frontal, temporal, and parietal cortices).



Scalco, R., Saito, N., Beckett, L. *et al.* The neuropathological landscape of Hispanic and non-Hispanic White decedents with Alzheimer disease. *acta neuropathol commun* **11**, 105 (2023). https://doi.org/10.1186/s40478-023-01574-1

hsc
Health & Aging Brain Study
Health Disparities

Importance of AT(N)-V imaging markers differs by group when predicting cognitive impairment



Slide from Dr. Karim Meeker

Are ATN-defined biomarkers equally prevalent among diverse populations? No

Are ATN-defined biomarkers equally related to clinical outcomes among diverse populations? No

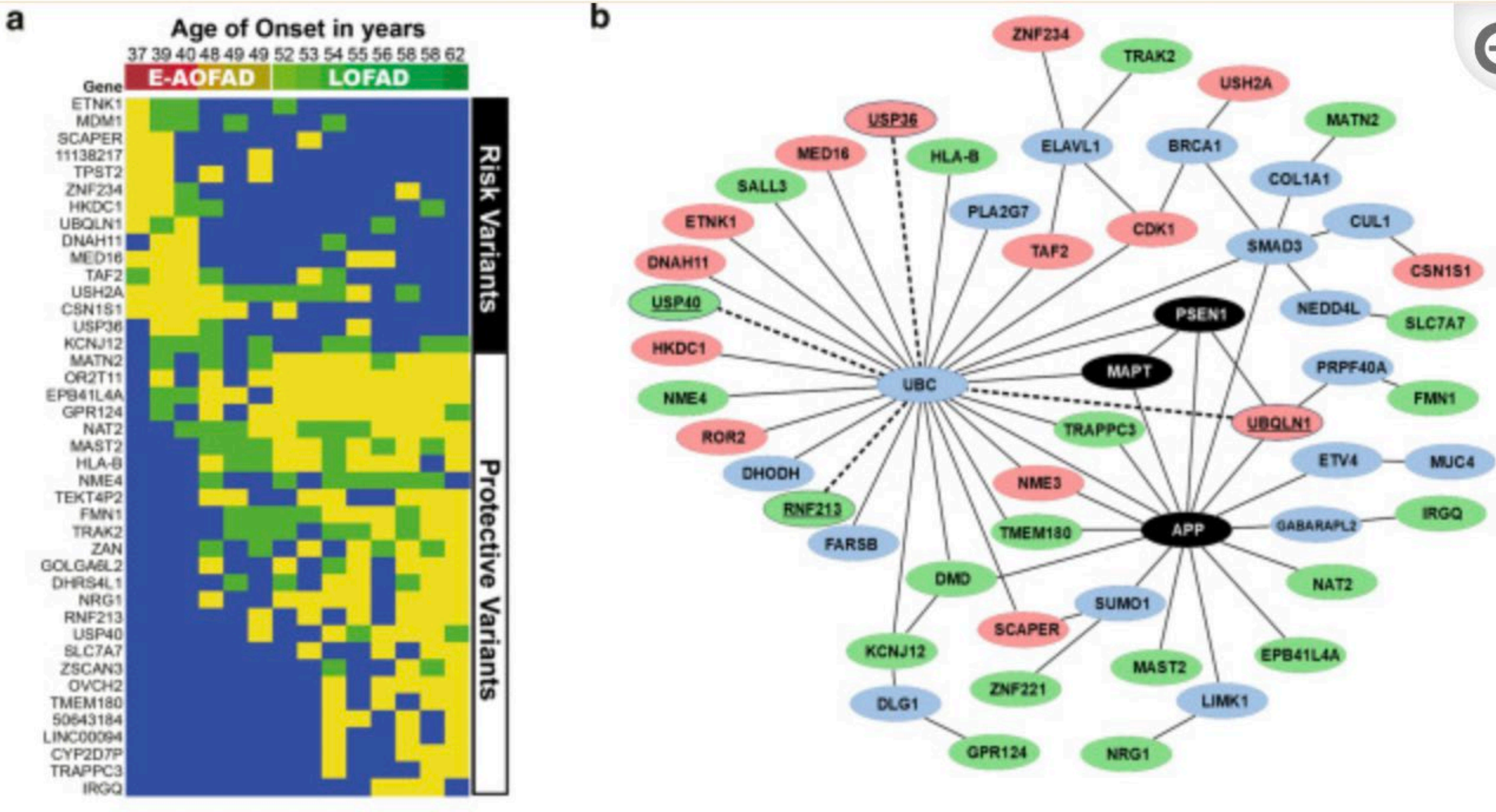
Are modifiers of ATN-defined biomarkers the same across diverse populations?

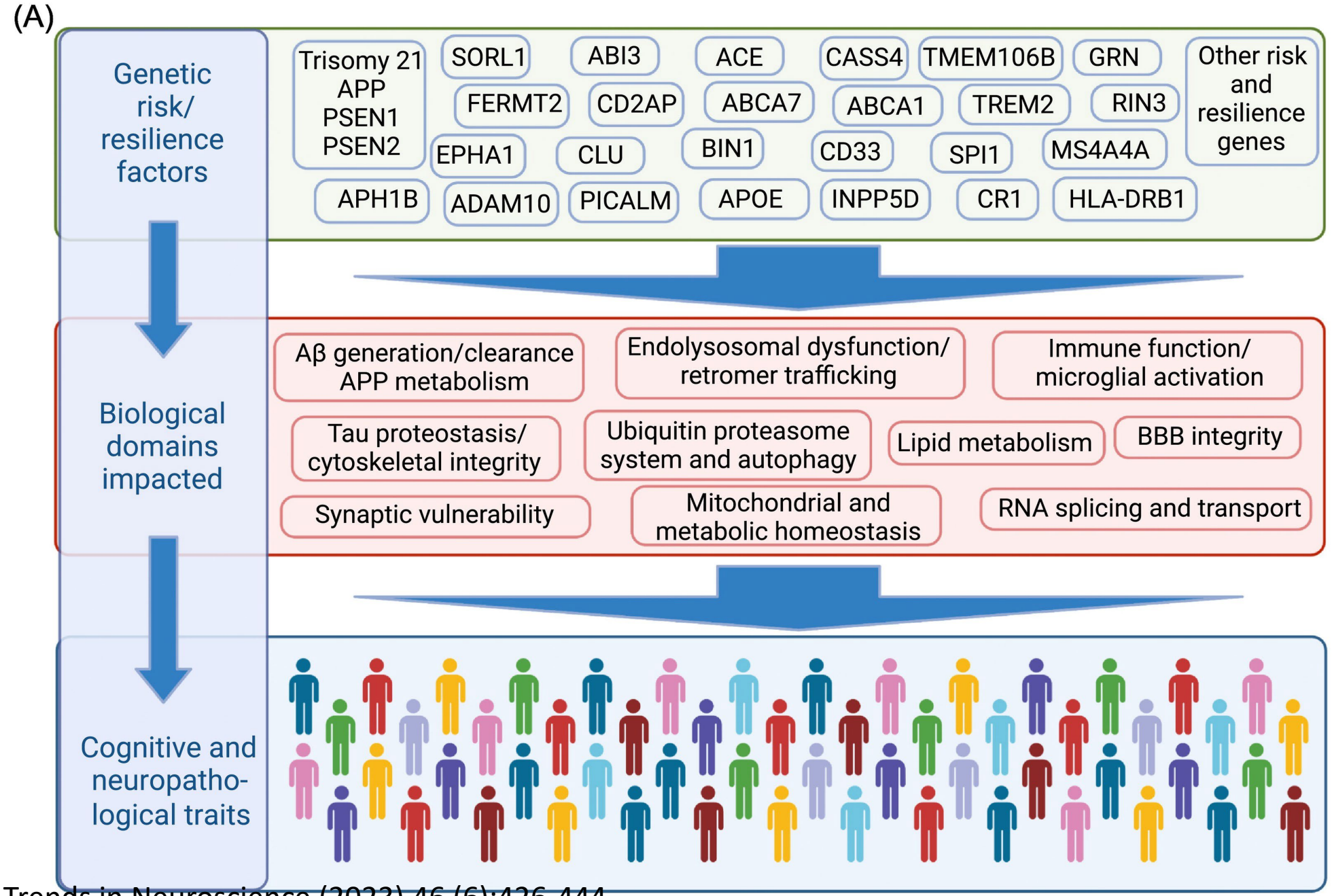
Standardized Beta Results From Regression Models Examining Associations Between Demographic and Cardiovascular Risk Factors With Serum GFAP Stratified by Ethnicity

Variables	Overall			Cognitively unimpaired			MCI			Dementia	
	MA	NHW		MA	NHW		MA	NHW		MA	NHW
Age	0.604‡	0.392‡		0.483‡	0.469‡		0.639‡	0.479‡		0.306‡	0.298‡
Women	-0.184‡	-0.132‡		-0.198‡	-0.133		-0.164‡	-0.116		-0.172*	-0.113*
BMI	-0.184‡	-0.132‡		-0.198‡	-0.133		-0.164‡	-0.116		-0.172*	-0.036*
SBP	0.037	-0.028		0.079*	-0.029		-0.038	-0.157*		0.134	-0.017
Diabetes	-0.023	-0.160‡		-0.085*	-0.134*		-0.124†	-0.211†		-0.075	-0.190‡
Tabaco use	-0.064†	-0.029		-0.124‡	0.027		-0.003	-0.085		-0.032	-0.039
APOE e-4	0.108‡	0.151‡		0.037	0.146*		0.156‡	0.173*		0.186*	0.024
Cognitive impairment	0-0.88‡	0.237‡									

APOE = apolipoprotein E; MA = Mexican American; NHW = non-Hispanic White.
Standardized beta values derived from regression models examining associations with serum GFAP in the whole sample and by the diagnostic group with stratification for ethnicity.
*P<0.05; †P<0.01; ‡P<0.001

Gonzales, M et al., Neurology, 101(15):e1531-e1541, October 10, 2023.
DOI: 10.1212/WNL.0000000000207706


a
Age of Onset in years
37 39 40 48 49 49 52 53 54 55 56 58 58 62
E-AOFAD
LOFAD
Gene
ETNK1
MDM1
SCAPER
11138217
TPST2
ZNF234
HKDC1
UBQLN1
DNAH11
MED16
TAF2
USH2A
CSN1S1
USP36
KCNJ12
MATN2
OR2T11
EPB41L4A
GPR124
NAT2
MAST2
HLA-B
NME4
TEKT4P2
FMN1
TRAK2
ZAN
GOLGA6L2
DHRS4L1
NRG1
RNF213
USP40
SLC7A7
ZSCAN3
OVCH2
TMEM180
50643184
LINC00094
CYP2D7P
TRAPPC3
IRGQ
Risk Variants
Protective Variants
b
ZNF234
TRAK2
USH2A
USP36
MATN2
MED16
HLA-B
ELAVL1
BRCA1
COL1A1
SALL3
PLA2G7
CUL1
ETNK1
CDK1
TAF2
SMAD3
CSN1S1
DNAH11
USP40
PSEN1
NEDD4L
SLC7A7
HKDC1
MAPT
PRPF40A
UBC
NME4
FMN1
UBQLN1
ROR2
TRAPPC3
ETV4
MUC4
DHODH
NME3
RNF213
IRGQ
TMEM180
APP
GABARAPL2
FARSB
DMD
NAT2
SUMO1
SCAPER
KCNJ12
EPB41L4A
MAST2
ZNF221
LIMK1
DLG1
GPR124
NRG1



Selkoe et al., Trends in Neuroscience (2023) 46 (6):426-444

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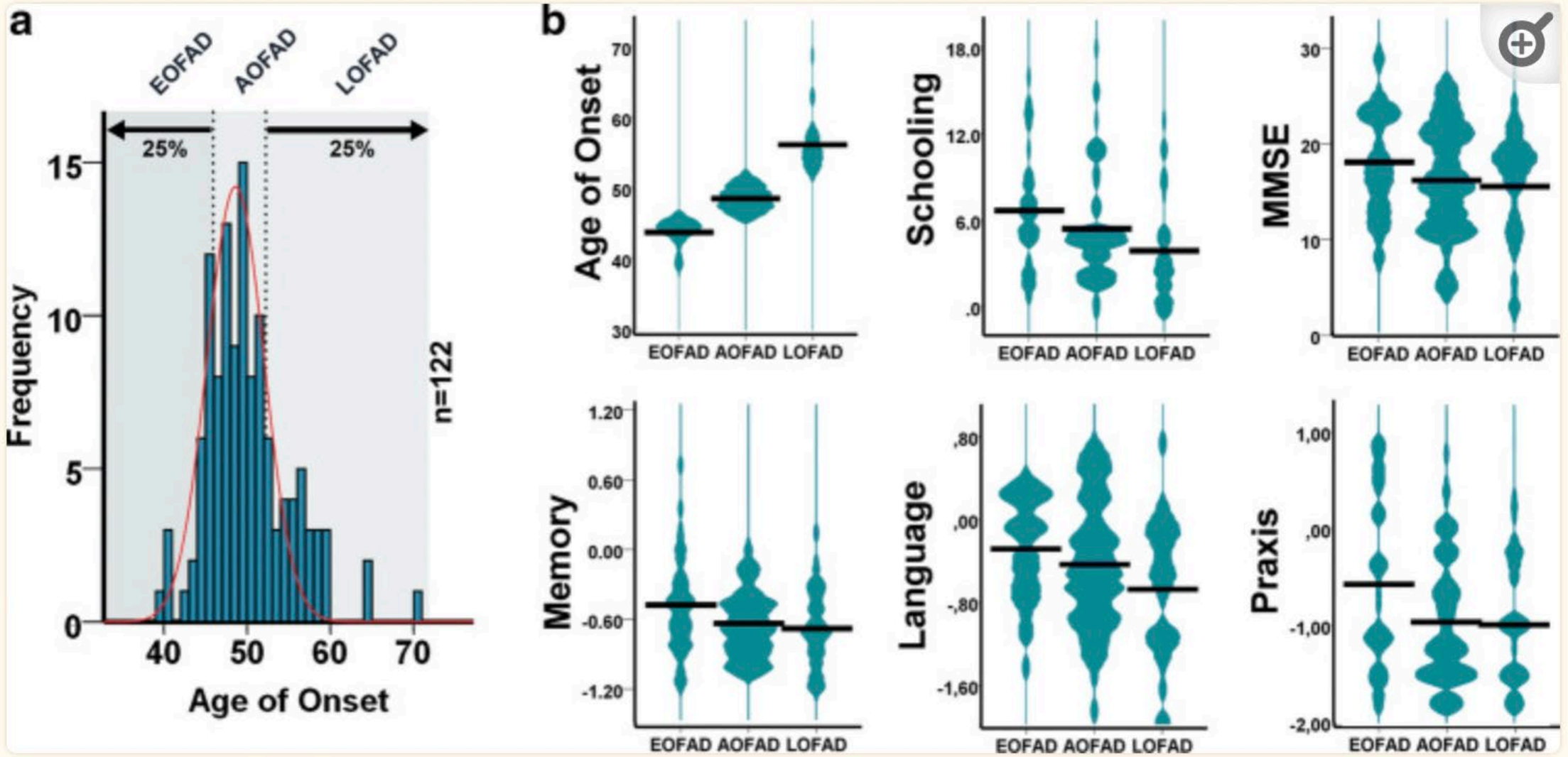
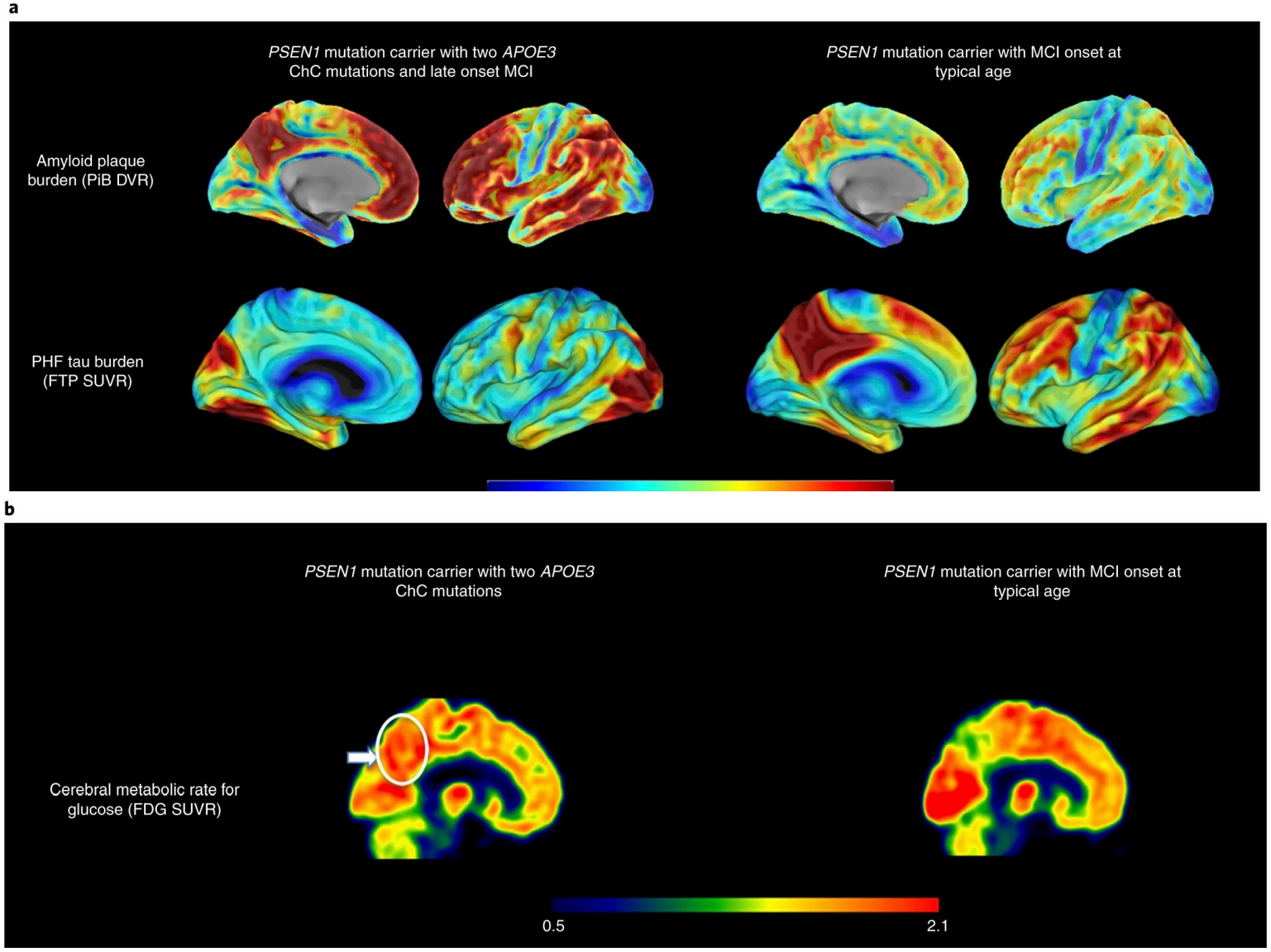
Age of onset in PSEN 1 E280A dementia patients in Colombia

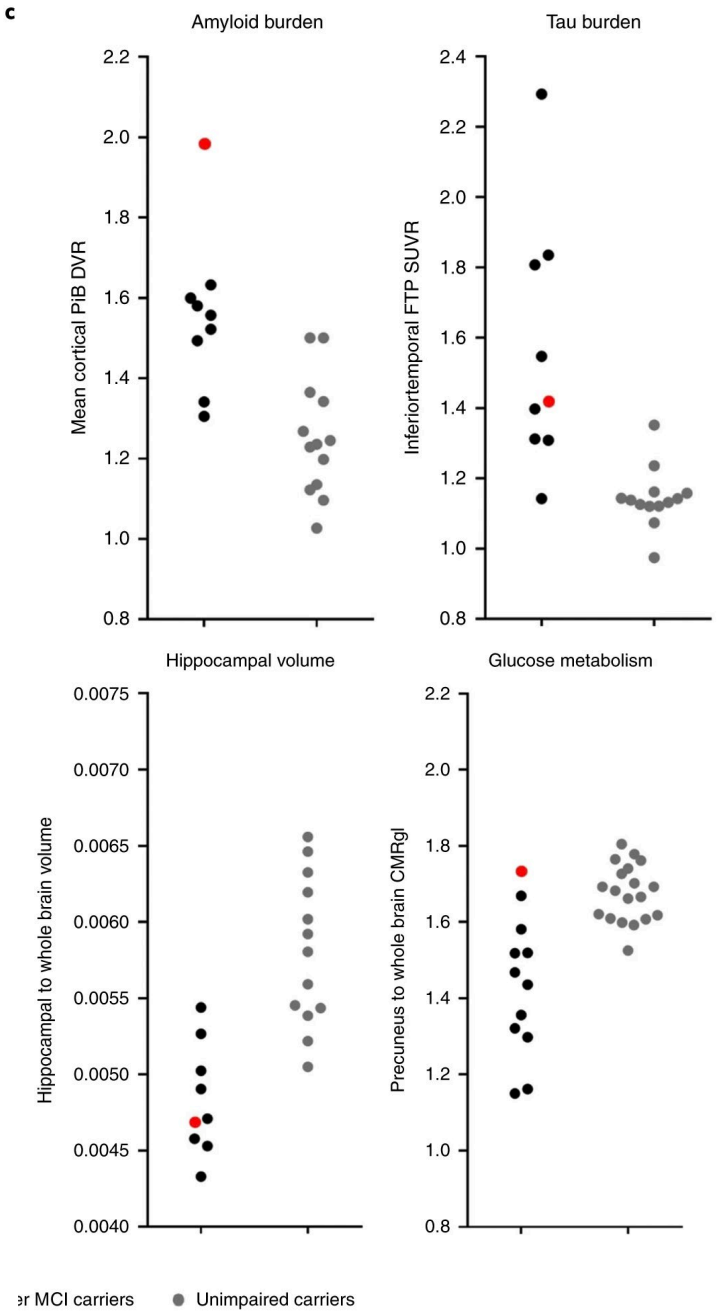


Falla-Sepulveda D, et al, A multifactorial model of pathology for age of onset heterogeneity in familial Alzheimer's disease. Acta Neuropathol. 2021

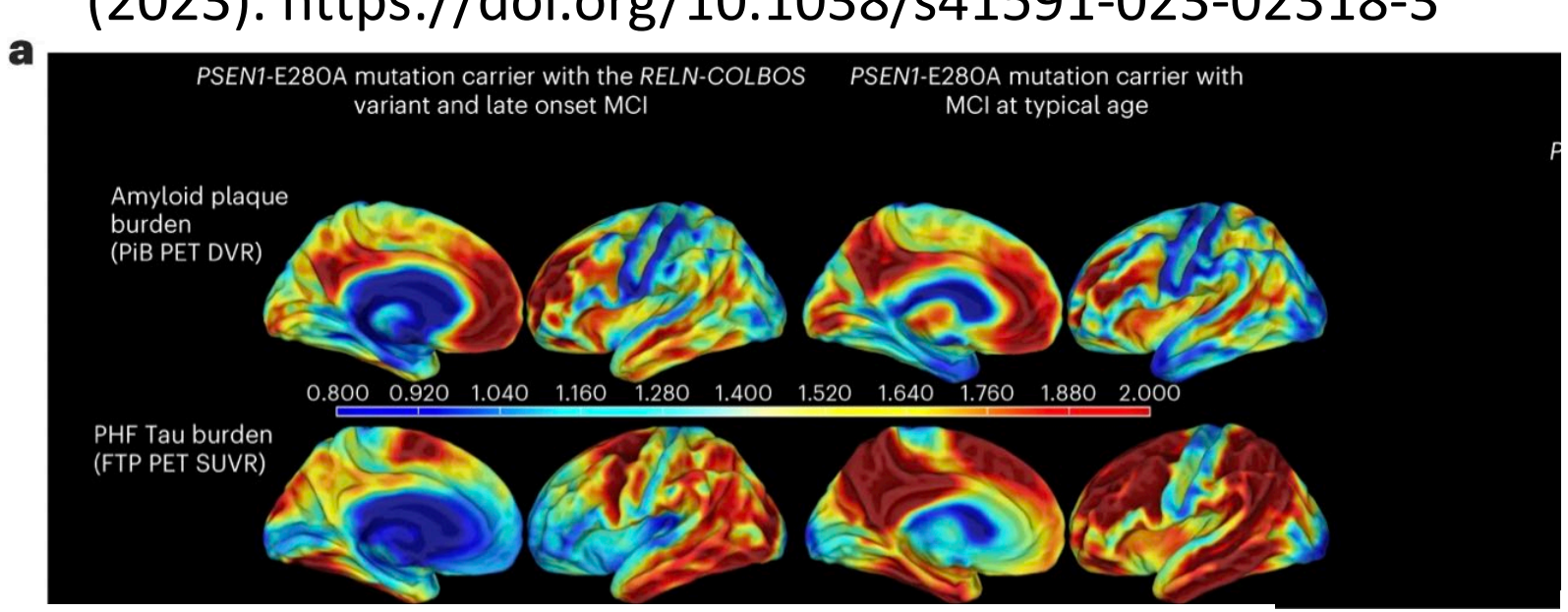
Colombian woman with PS1 E280A mutation without cognitive impairment for 73 years. She died with MCI from melanoma at 78y.

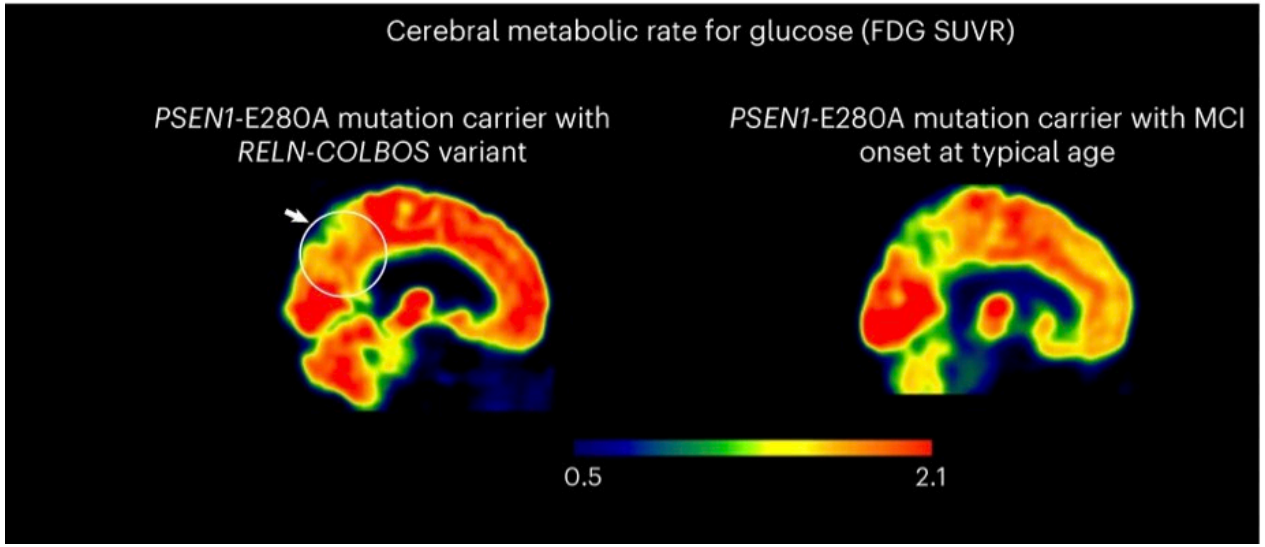
Arboleda-Velasquez, J.F., Lopera, F., O'Hare, M. et al. Resistance to autosomal dominant Alzheimer's disease in an APOE3 Christchurch hon
Nat Med 25, 1680–1683 (2019). https://doi.org/10.1038/s4

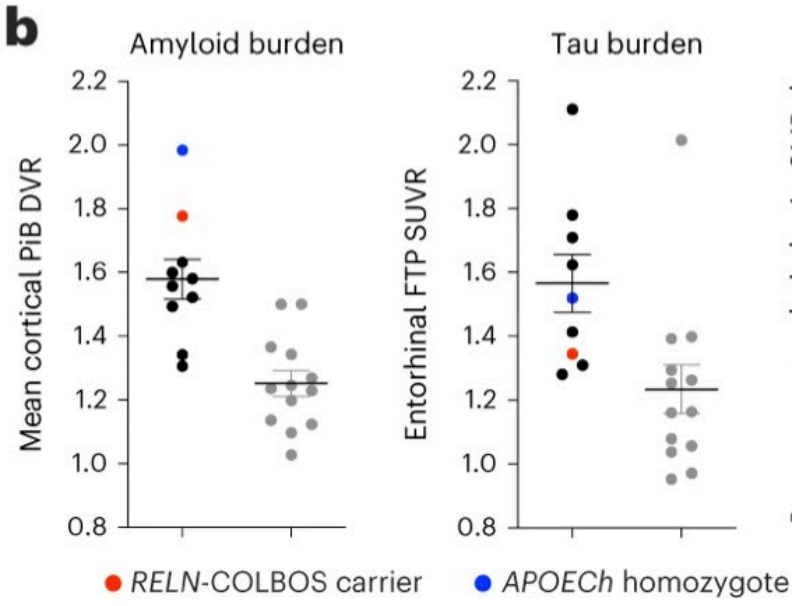


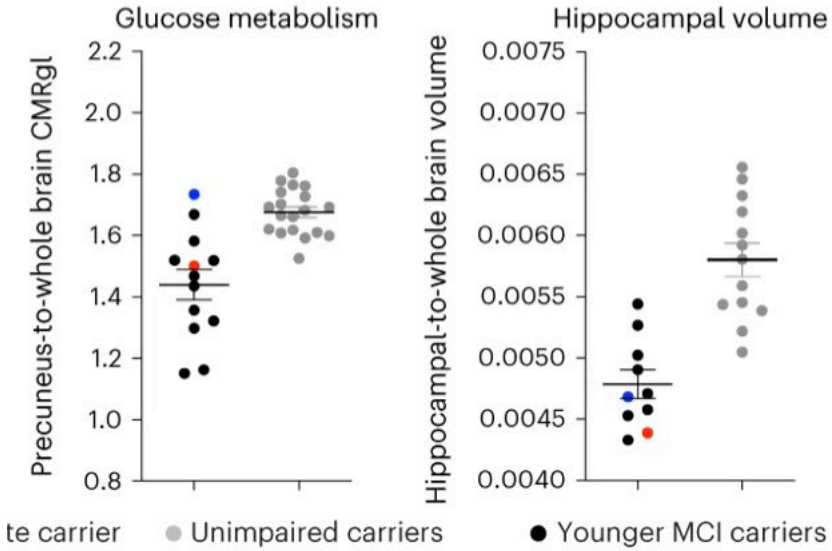


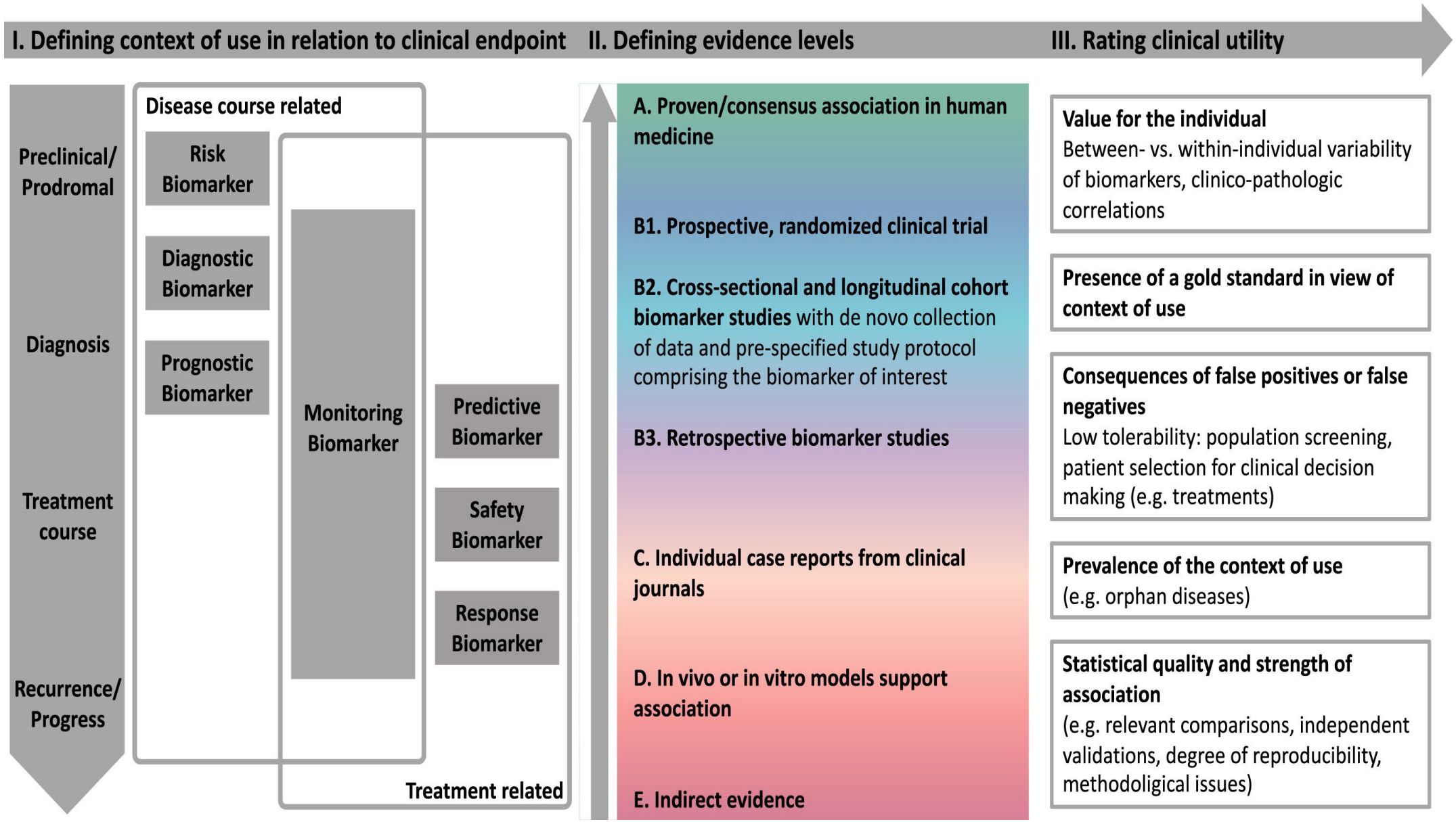
Lopera, F., Marino, C., Chandrahas, A.S. et al. Resilience to autosomal dominant Alzheimer's disease in a Reelin-COLBOS heterozygous man. Nat Med 29, 1243–1252 (2023). https://doi.org/10.1038/s41591-023-02318-3



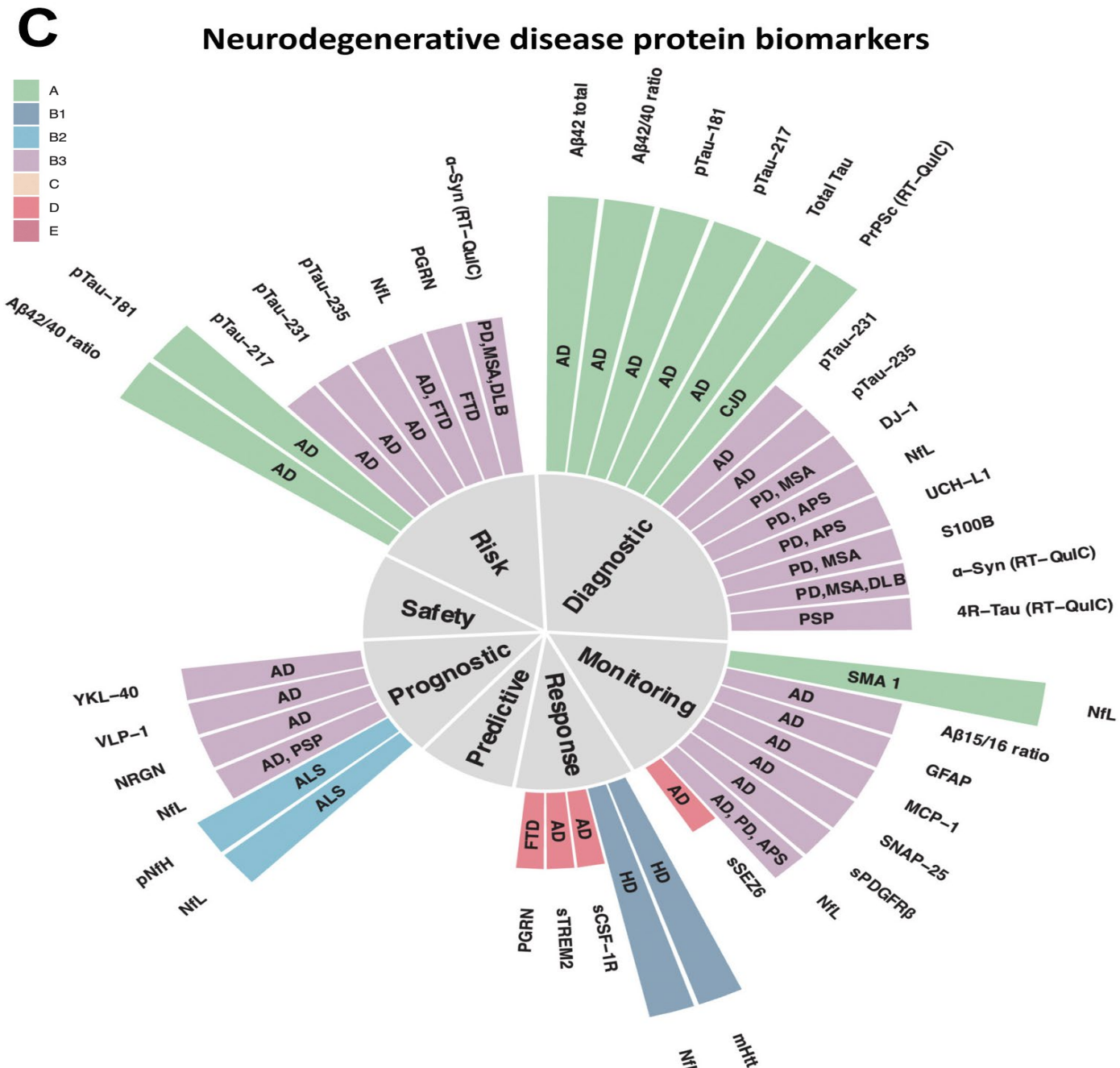








eBioMedicine Volume 89 (March 2023) DOI: 10.1016/j.ebiom.2023.104456



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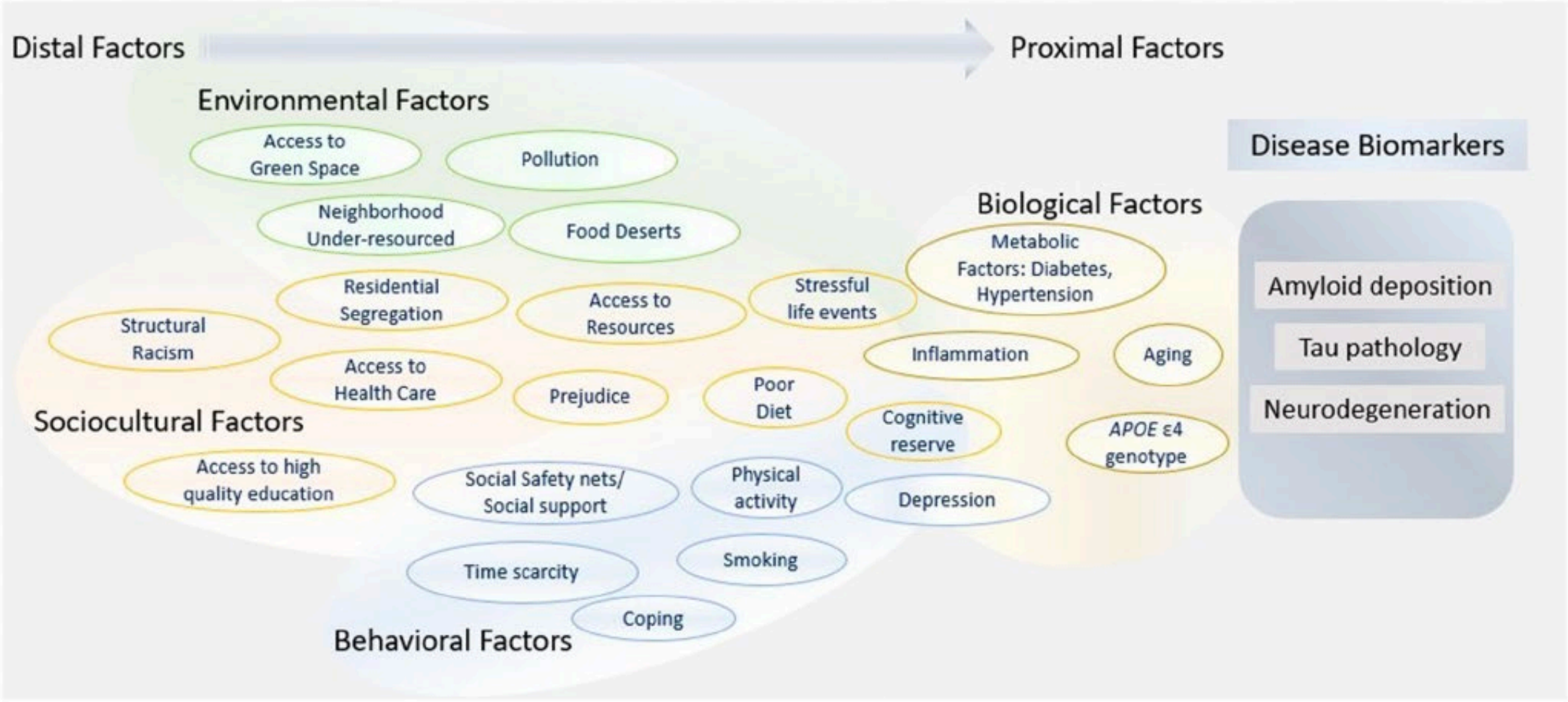
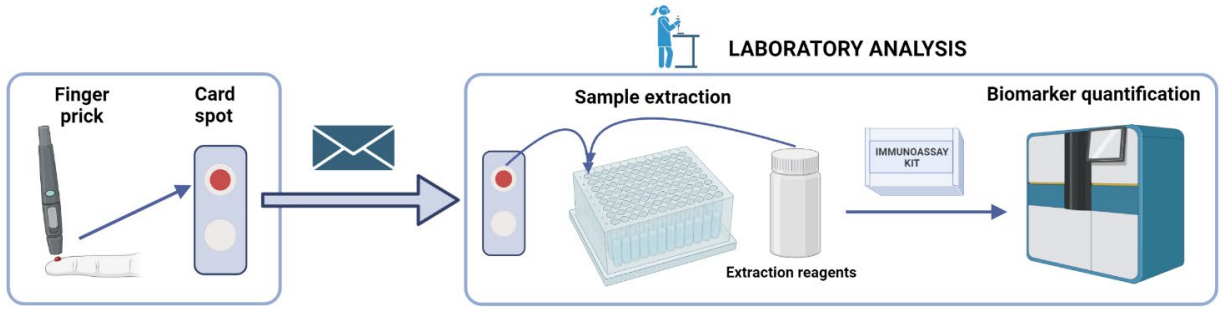
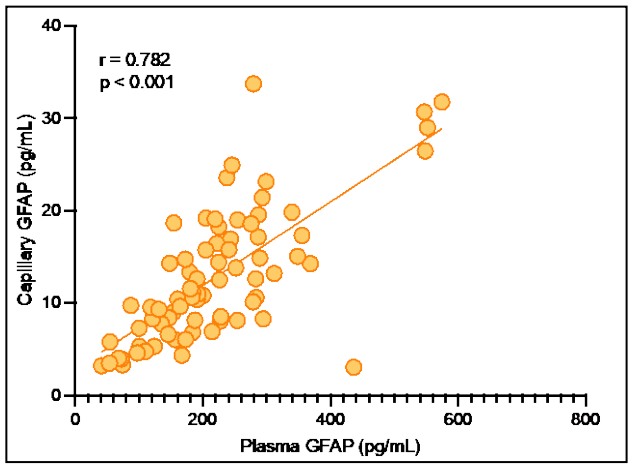


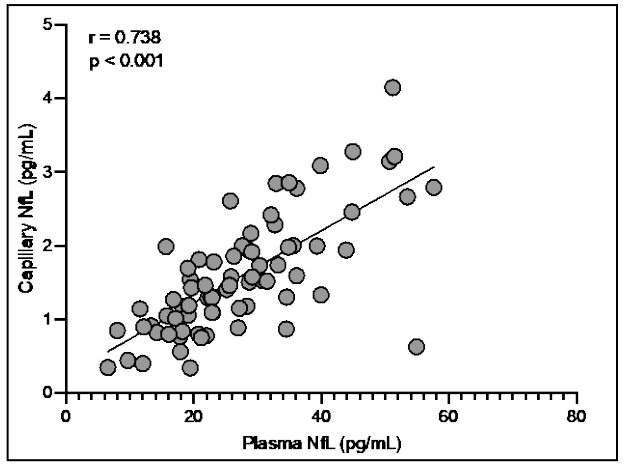
FIGURE 1 Hypothetical model integrating the National Institute on Aging (NIA) Health Disparities Research Framework with the amyloid/tau/neurodegeneration (AT[N]) criteria from the NIA–Alzheimer's Assocation Research Framework. Evidence supporting individual examples association with Alzheimer's disease biomarkers is hypothetical in some instances. Examples are generally categorized as environmental, sociocultural, behavioral, or biological factors. However, we acknowledge that many examples can belong in multiple categories

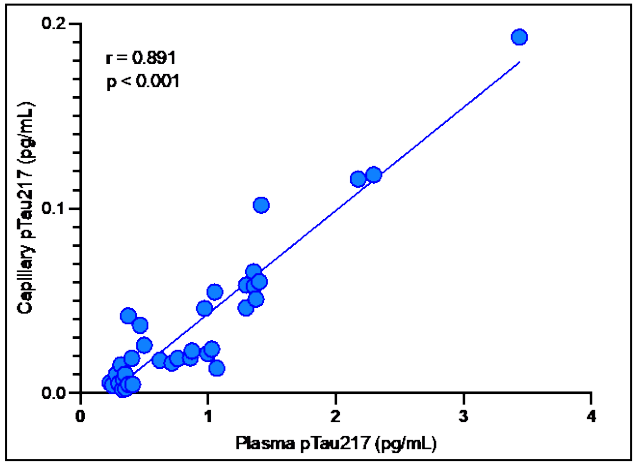
DROP-AD: detecting AD blood biomarkers using a finger-prick

- Current blood processing protocol require a strict procedures – useful in primary care?
- How do we monitor people overtime (including those on DMT) for personalised management?
- Detecting pre-clinical changes – if/when that it is required?









Ashton, Zetterberg et al. 2023

1.- Align communication to meet the education and support needs that may be unique to each patient and family

2.- Clarify context of use before testing

3.-Pretest-counseling and post-disclosure support

4.-Cautios selection and usage of lay language

5.-Comprehension checks

6.-Avoid positive/negative qualifiers

https://www.agreedementia.org

Thank you!

¡Gracias!