Risk and Resilience of Alzheimer's Disease in African Americans

CSF and imaging biomarkers of Alzheimer's disease in African Americans

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- WTH has patent on CSF-based diagnosis of FTLD-TDP; prognosis of MCI due to AD; prognosis of SMA on gene replacement therapy; licensed SARS-CoV-2 serological assays to Millipore-Sigma

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Clinical diagnostic accuracy for AD remains poor

	Community sample of 134 patients with dementia, 1987-1996		National Alzheimer's Disease Coordinating Center, 2005-2010	
	Clinical AD (probable or possible)	Not clinically AD	Clinical AD (probable or possible)	Not clinically AD
AD pathology	80	14	511	107
No AD pathology	20	20	137	164
	Sensitivity=85% Specificity=**50%** Accuracy=74%		Sensitivity=83% Specificity=**54%** Accuracy=73%	

Lim, 1999; Beach, 2012

"5.8 million with AD"

Clinical AD (probable or possible)	Not clinically AD
4.6 m	0.9 m
1.2 m	1.5 m

Default accuracy is ~70% if you assume everyone walking through the door has AD; thus diagnostic algorithm improves PPV by 5-10%

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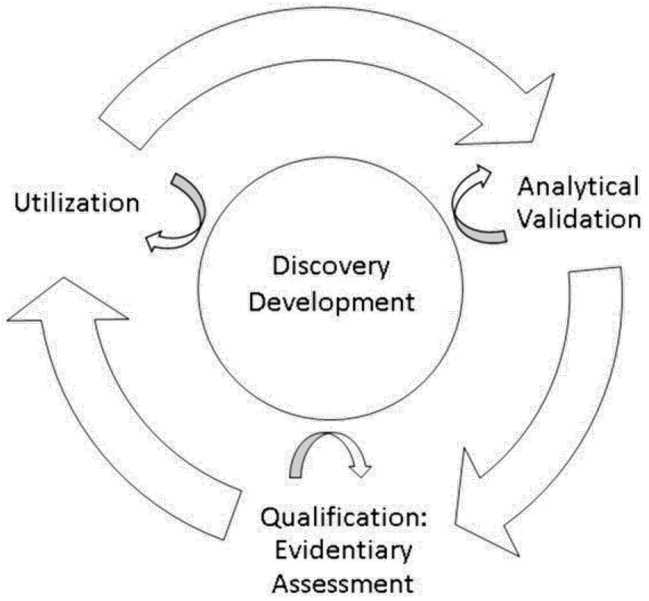
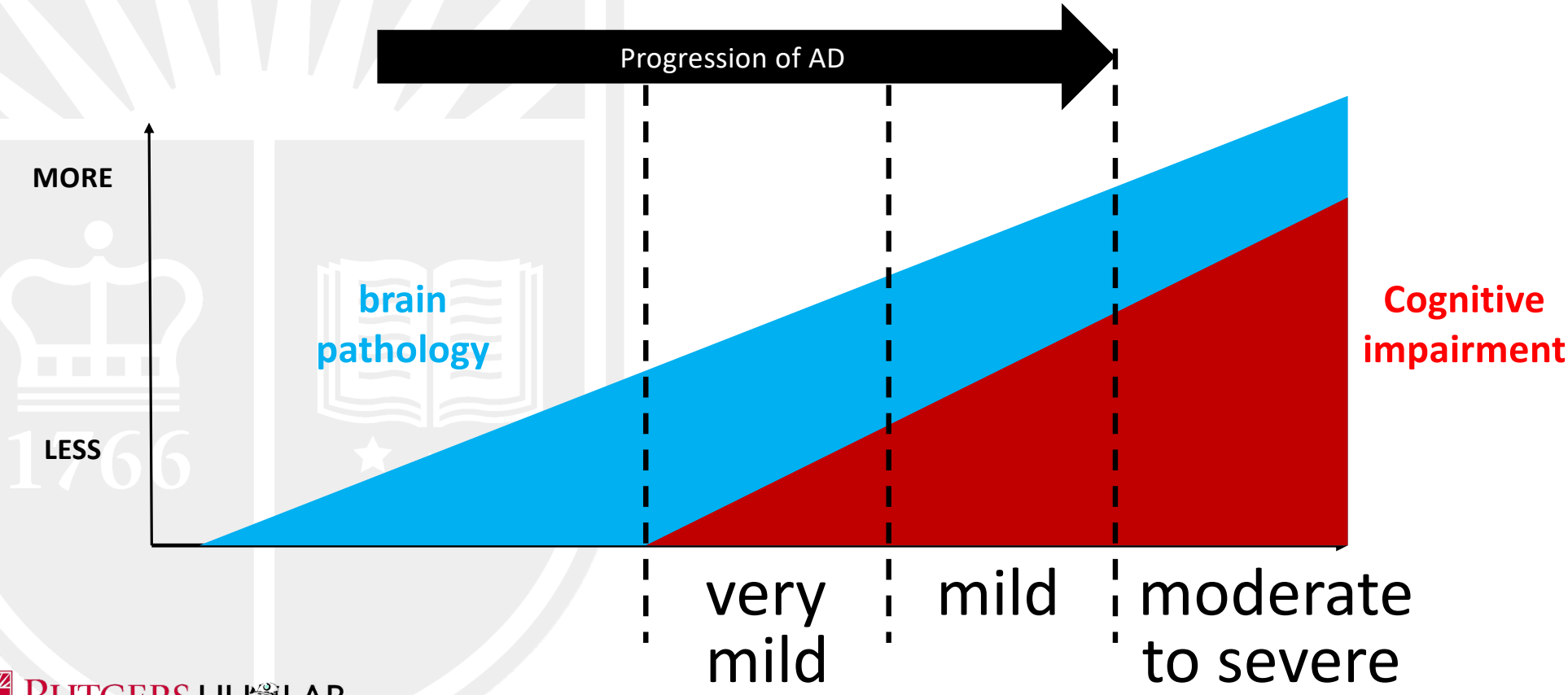
Biomarkers can lead to early & accurate diagnosis

1. **Reflects underlying biology** (normal, pathogenic process, response to intervention)
   - Distinct from how a person feels, functions, or survives (clinical outcome assessments or COA)
2. **Can be objectively measured**
3. **Associated with COA** – *"mark"*
4. **Different classes**
   - Diagnostic
   - Monitoring
   - Pharmacodynamic/response
   - Predictive
   - Prognostic
   - Safety
   - Susceptibility/risk



Califf, *Exp Biol Med*, 2018.

A role of diagnostic biomarkers



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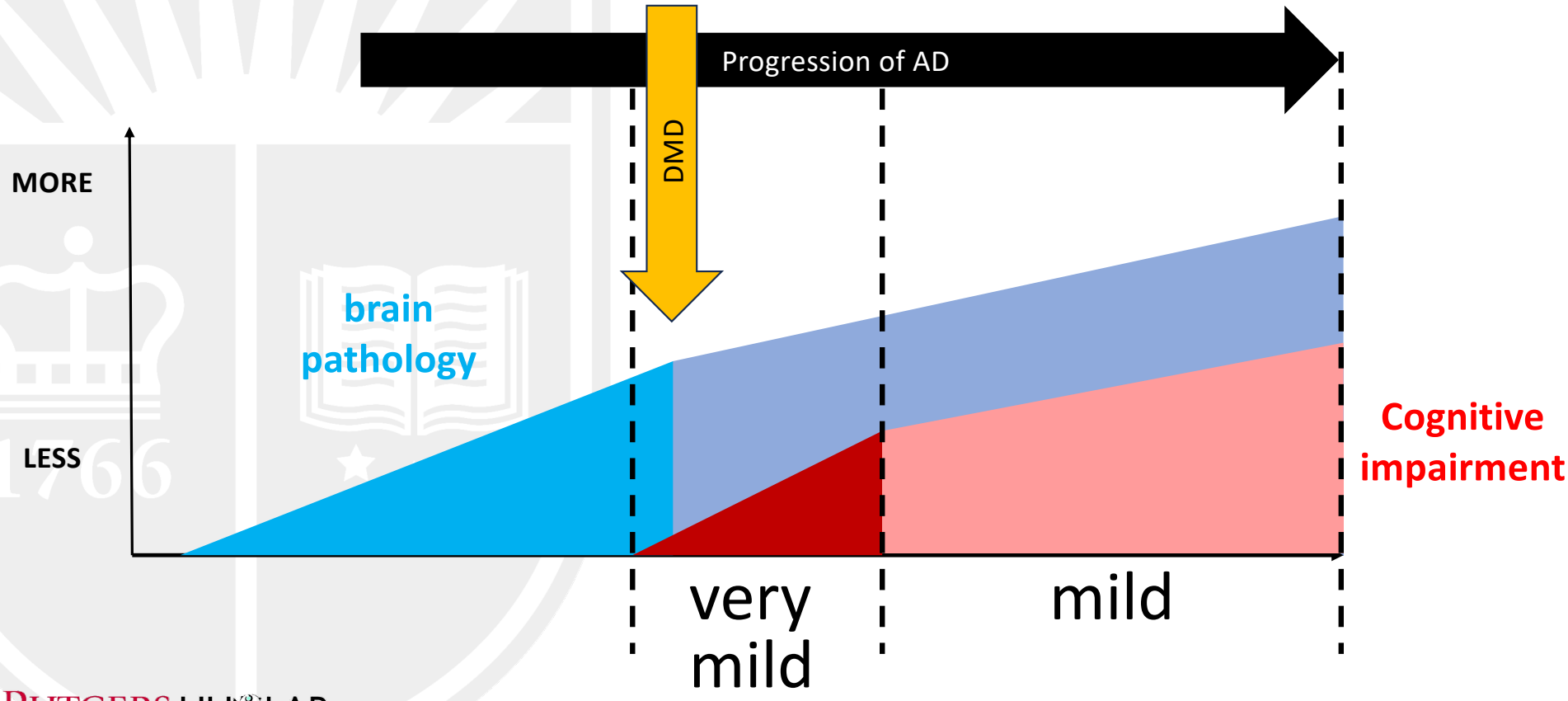
A role of diagnostic biomarkers



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Clinical observation & ADNI led to the study of CSF AD biomarkers in African Americans

Table 1
Baseline characterization of ADNI 1 cohorts

Characteristic	Controls (n = 229)	MCI (n = 398)	Mild AD (n = 192)
Age, mean ± SD, yr	75.8 ± 5.0	74.7 ± 7.4	75.3 ± 7.5
Education, mean ± SD, yr	16.0 ± 2.9	15.7 ± 3.0	14.7 ± 3.1
Sex (% Female)	48.0	35.4	47.4
Apolipoprotein E ε4, % carriers	26.6	53.3	66.1
MMSE Score	29.1 ± 1.0	27.0 ± 1.8	23.3 ± 2.1
CDR Global Score	0.0 ± 0.0	0.5 ± 0.0	0.7 ± 0.3
CDR Sum of Boxes	0.0 ± 0.1	1.6 ± 0.9	4.3 ± 1.6
GDS Score	0.8 ± 1.1	1.6 ± 1.4	1.7 ± 1.4
ADCS MCI-ADL (FAQ) Score	0.1 ± 0.6	3.9 ± 4.5	13.0 ± 6.9
ADAS-cog total	6.2 ± 2.9	11.5 ± 4.4	18.6 ± 6.3
ADAS word list delayed recall	2.9 ± 1.7	6.2 ± 2.3	8.6 ± 1.6
AVLT Trials 1–5	43.3 ± 9.1	30.7 ± 9.0	23.2 ± 7.7
AVLT delayed recall	7.4 ± 3.7	2.8 ± 3.3	0.7 ± 1.6
AVLT DR/Trial 5%	65.8 ± 27.6	32.1 ± 31.3	11.2 ± 22.0
Trails A (s)	36.5 ± 13.2	44.9 ± 22.8	68.0 ± 36.9
Trails B (s)	89.2 ± 44.3	130.7 ± 73.5	198.9 ± 87.2

Table 1. Demographic and CSF profiles of AA in ADNI (n=9) and Emory (n=16), compared with Caucasians in ADNI. Low Aβ42 is less than 192 pg/mL. * p < 0.05 and ** p = 0.065 compared with NHW.

	AA (Emory + ADNI)			NHW (ADNI)		
	Normal	MCI	AD	Normal	MCI	AD
N (% men)	6 (50%)	9 (44%)	10 (40%)	51 (53%)	179 (66%)	98 (57%)
Age	64.7 (14.6)	65.8 (9.3)*	59.6 (7.3)*	75.6 (5.8)	74.6 (7.4)	75.0 (7.8)
EDU	13.7 (2.6)	14.8 (2.3)	14.8 (2.2)	16.0 (2.7)	15.8 (3.0)	15.3 (3.1)
Low CSF Aβ42	0%	44%**	80%	0%	70%	89%

~2% of ADNI-1 participants were African American

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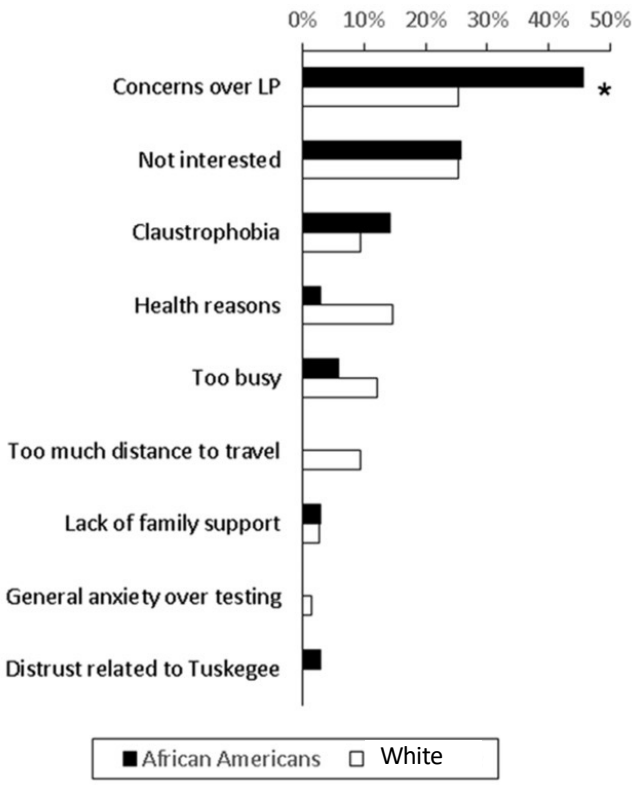
Aisen, *Alzheimers Dement*, 2010; Hu, R21 AG043885, 2012.

What made African Americans say no to our research?



	Black (n=48)	White (n=38)
Atraumatic needle was used	40 (83%)	34 (89%)
Views LP as a frightening invasive procedure	3 (6%)	3 (8%)
Reluctant or somewhat reluctant	5 (10%)	8 (21%)
Needle injection site pain	7 (15%)	6 (16%)
Back pain/stiffness	3 (6%)	1 (3%)
Any headache	7 (15%)	4 (10%)
Post-LP headache Mild Moderate or more	4 (8%)	3 (8%)

Howell, *Alz Res Ther*, 2016.

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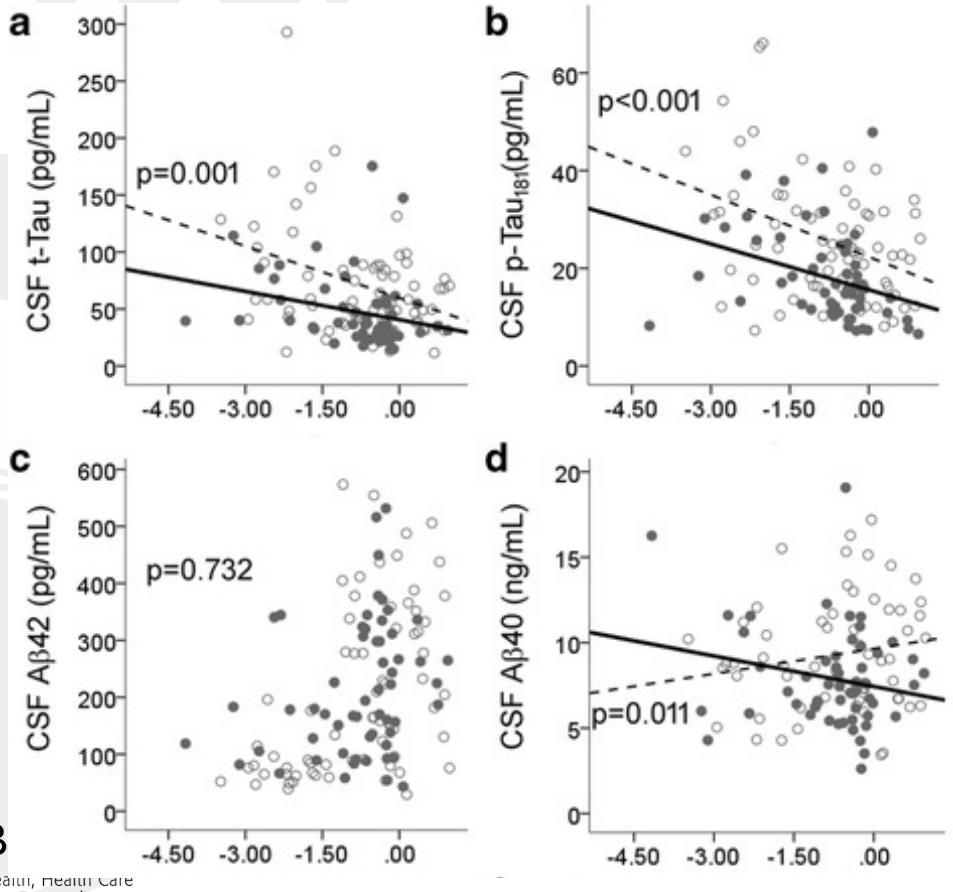
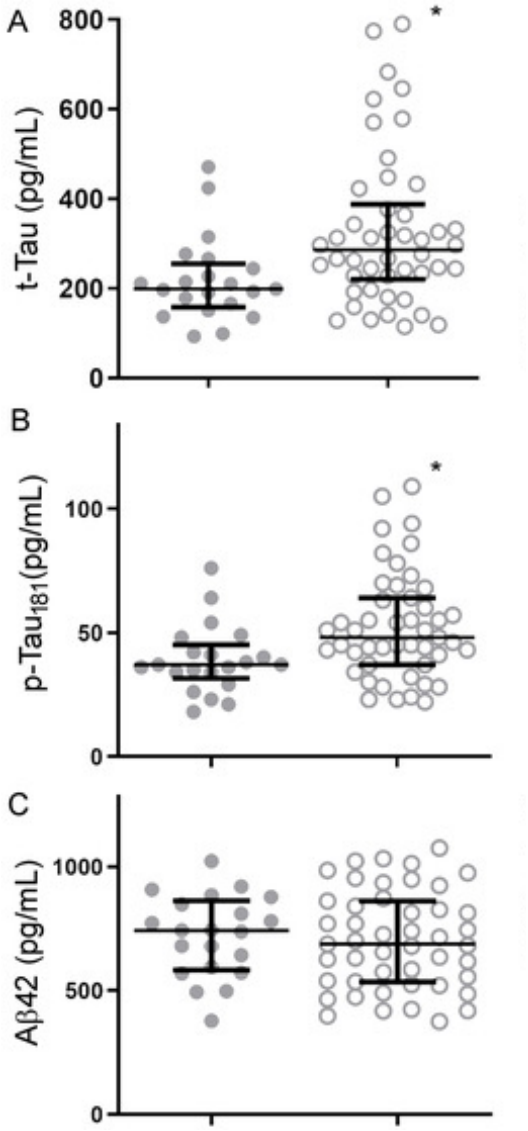
CSF t-Tau and p-Tau$_{181}$ levels differed between Black and White Americans



Howell, *Alz Res Ther*, 2017.

This observation extends to people with normal cognition in mid-life & early life…



Wharton, *Ann Neurol*, 2019;
Ozturk, *Sci Rep*, 2019.

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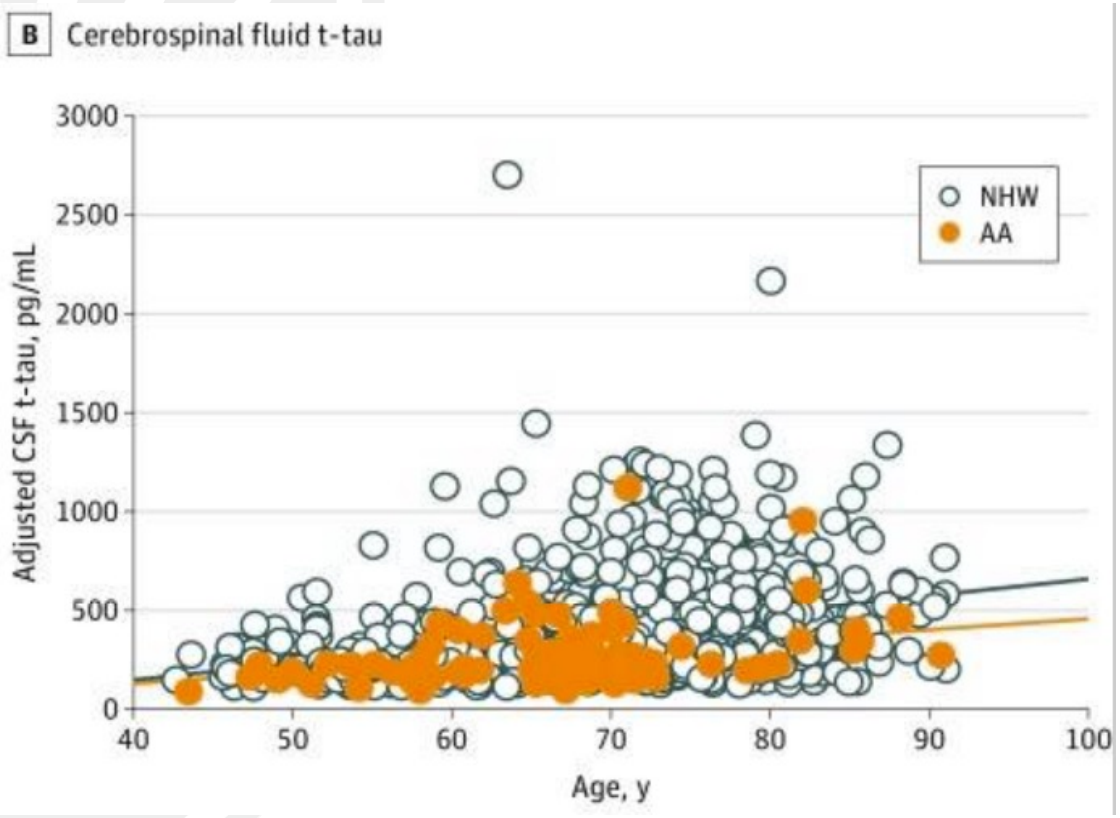
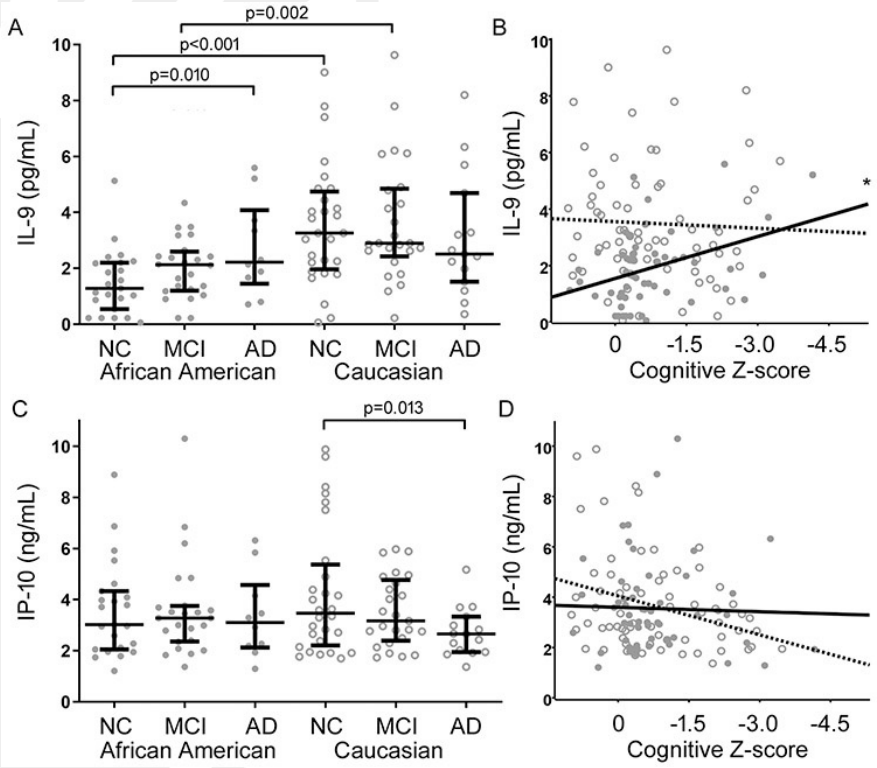
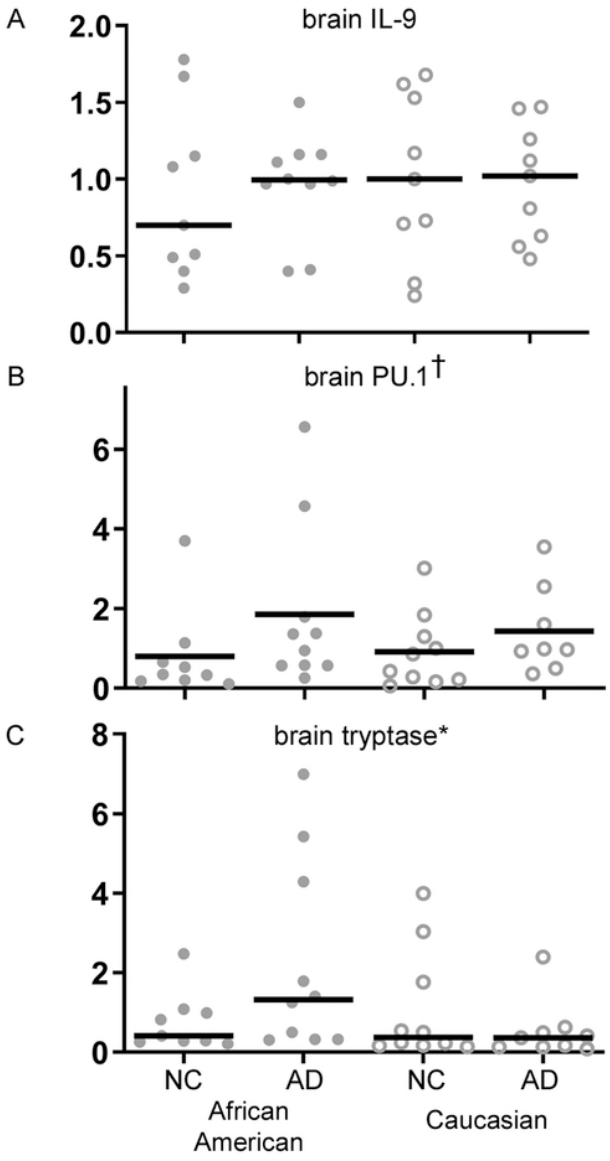
from Atlanta to St. Louis…



Morris, *JAMA Neurol*, 2019.

is associated with different inflammatory cascades in CSF & brain…





Wharton, *Ann Neurol*, 2019.

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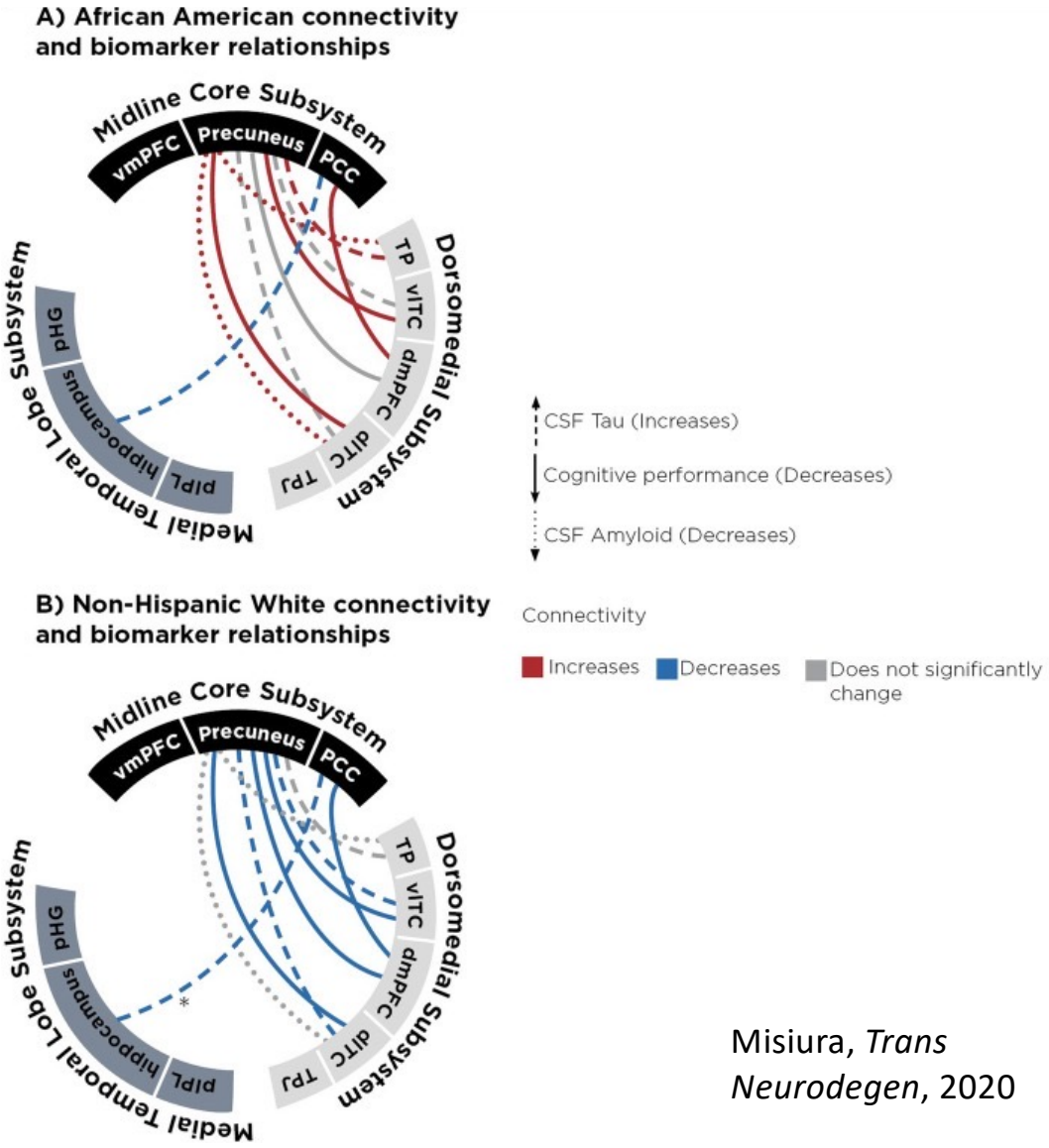
and may be associated with different ***aging-associated patterns*** *of brain functional network connectivity*



Misiura, *Trans Neurodegen*, 2020

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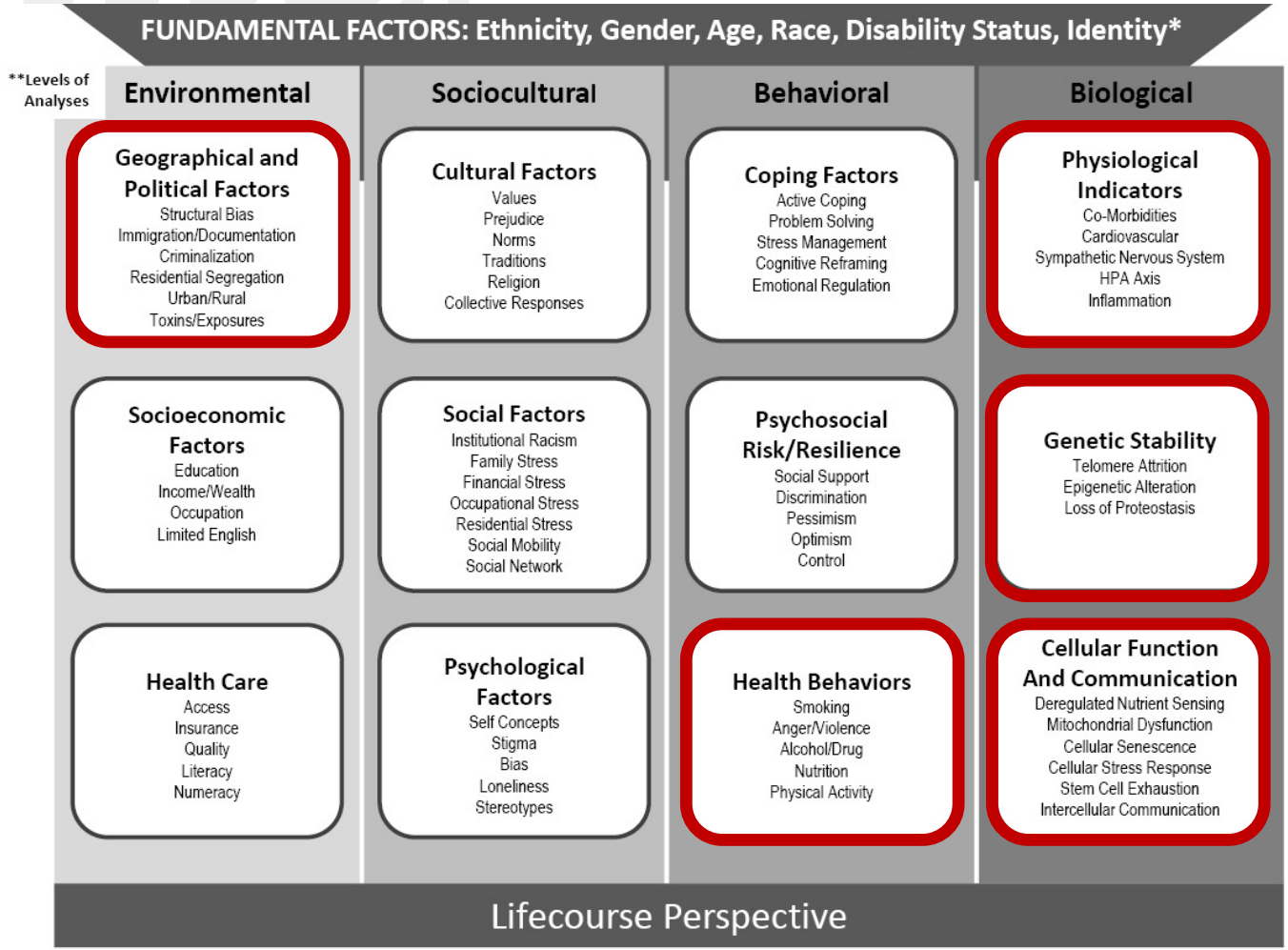
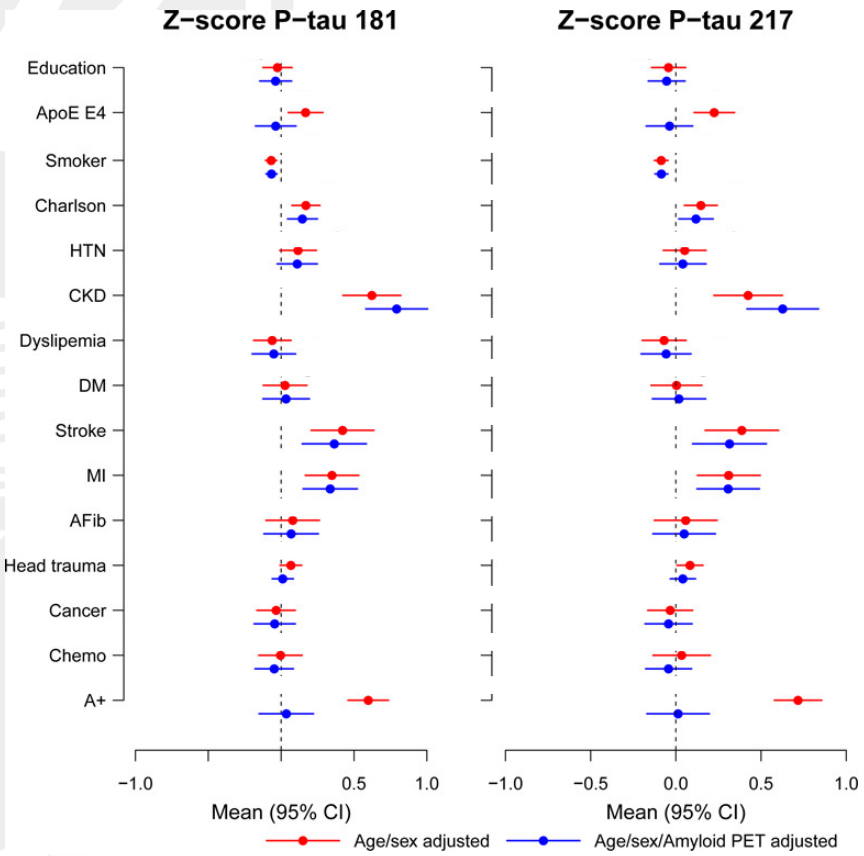
Where does this variability come from?



Hill, *Ethn Dis*, 2015.

and this likely can't be resolved by blood biomarkers



no effect

plaque dependent ☑

plaque independent ☒

plaque independent ☒

no effect

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plaque dependent ☑

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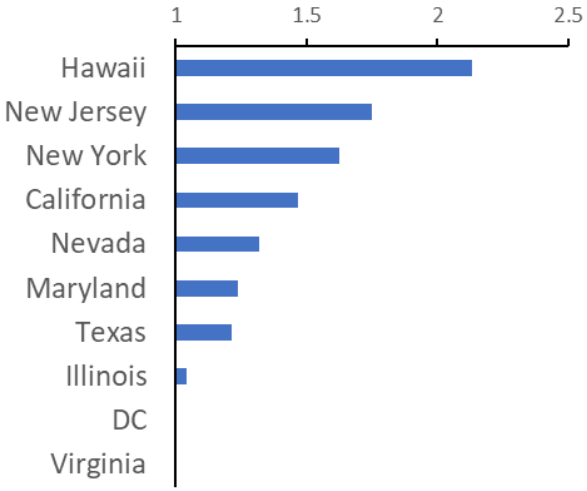
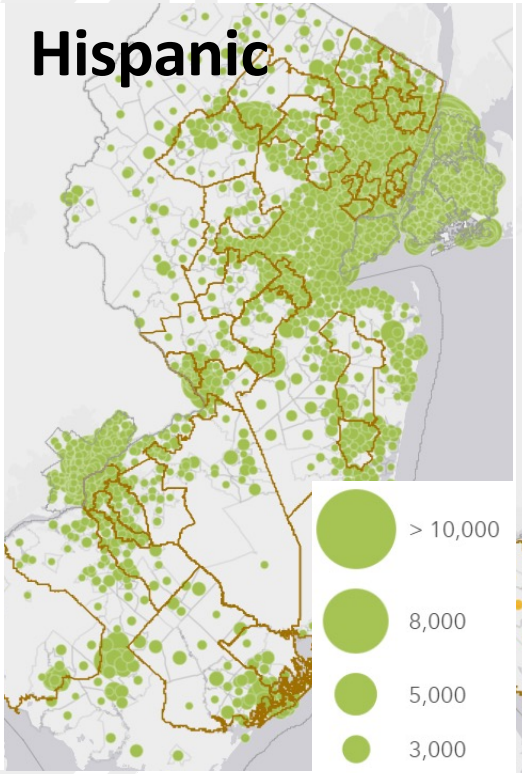
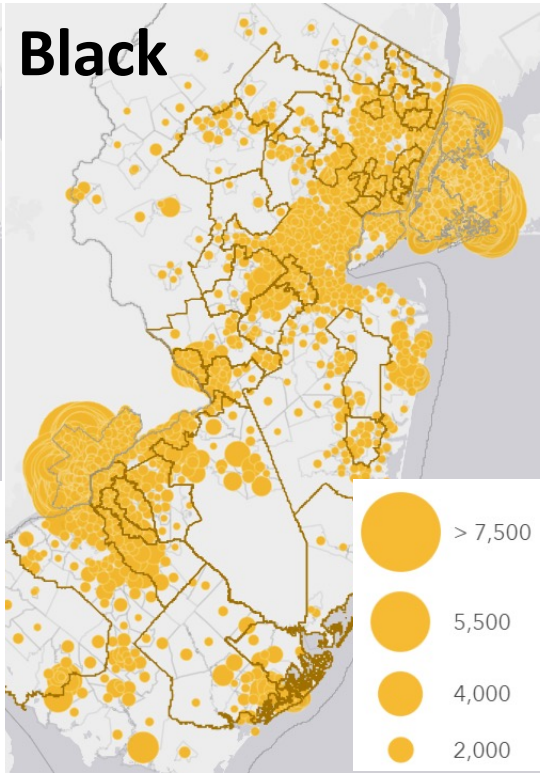
Modified from Mielke, *Nat Med*, 2022.

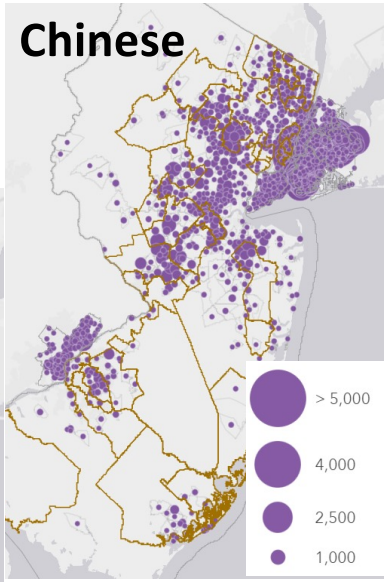
New Jersey: *2nd most diverse US state*

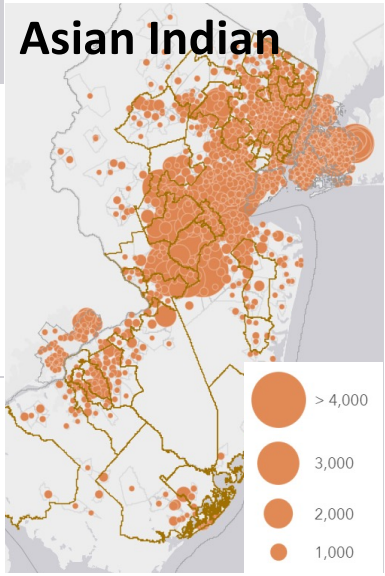
Odds of 4 randomly selected residents belonging to 4 different racial/ethnic groups
relative to national odds











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