Influence of Race and Ethnicity on AD Biomarkers

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Outline

- Examination of AD biomarkers by race/ethnicity
  - Autopsy
  - PET
  - Fluid (CSF and blood)

- Putting differences into context
  - APOE
  - Effects of chronic conditions
  - Mediators
  - Racialization

Studies examining biomarker differences by race/ethnicity

Background

- Several advantages to applying biomarkers in conjunction with clinical examination across race/ethnicities in the population (Gleason CE et al, 2022)
  - Biomarkers can help in clinical diagnosis, especially in light of neuropsych test limitations
  - Better diagnosis can help better target individuals to best therapies, trials, or inventions
  - Blood biomarkers are advantageous in leveling the playing field for research and clinically
    - Lower participation rates for under-represented minorities for amyloid and tau PET and CSF collection
    - Less access for under-represented minorities

Autopsy studies

- Autopsy is the gold standard, for which we compare fluid and PET biomarkers
- Nguyen M et al. 2022 – highlighted all peer-reviewed autopsy studies including non-White individuals: 10 with African Americans, 6 Hispanic, 6 Japanese American Men (all HAAS), 0 Native American/other groups
- Many studies do not report differences in AD pathology (e.g., Sandberg G et al. 2001; Miller FD et al. 1984; Bonner GJ et al. 2000; Wilkins CH et al. 2006; Riudavets MA et al. 2006)
- Several limited by sample sizes of racial/ethnic groups and limited pre-morbid cognitive information (i.e. medical examiner autopsy)
- Mixed pathologies more common in African Americans compared to whites, including atherosclerosis, arteriolosclerosis, infarcts and Lewy Bodies (Barnes LL et al. 2015; Graff-Radford NR et al. 2016)
- Hispanics 2x as likely to have higher Braak NFT stage vs. NHW (Santos OA et al. 2019)

PET and CSF biomarkers – African Americans vs. Whites

Table 2 | Studies of Alzheimer disease biomarkers in Black or African American individuals and white individuals

Study	Biomarker(s)	Number of Black or African American participants	Number of white participants	Biomarker levels in Black or African American participants compared with white participants
Gottesman et al. (2016)[69]	Aβ PET	141	188	Higher
Howell et al. (2017)[62]	CSF p-tau$_{181}$ and t-tau	65	70	Lower
Garrett et al. (2019)[63]	CSF p-tau$_{181}$ and t-tau	152	210	Lower
Morris et al. (2019)[64]	CSF p-tau$_{181}$ and t-tau	97	816	Lower
Kumar et al. (2020)[65]	CSF p-tau$_{181}$ and t-tau	30	50	Lower
Meeker et al. (2020)[66]	Aβ PET, tau PET and structural and functional MRI	70	434	No difference in tau PET, Aβ PET, or functional MRI; lower brain volume

Barnes LL. Nature Reviews Neurology 2022

Racial and ethnic differences in Amyloid PET - IDEAS

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

	Matched participants, No. (%)					
Amyloid PET scan result	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)
MCI						
Positive	61 (36.3)	89 (53.0)	128 (42.4)	149 (49.3)	164 (46.1)	190 (53.4)
Negative	107 (63.7)	79 (47.0)	174 (57.6)	153 (50.7)	192 (53.9)	166 (46.6)
Dementia						
Positive	81 (55.9)	92 (63.4)	205 (65.5)	210 (67.1)	261 (61.6)	292 (68.9)
Negative	64 (44.1)	53 (36.6)	108 (34.5)	103 (32.9)	163 (38.4)	132 (31.1)

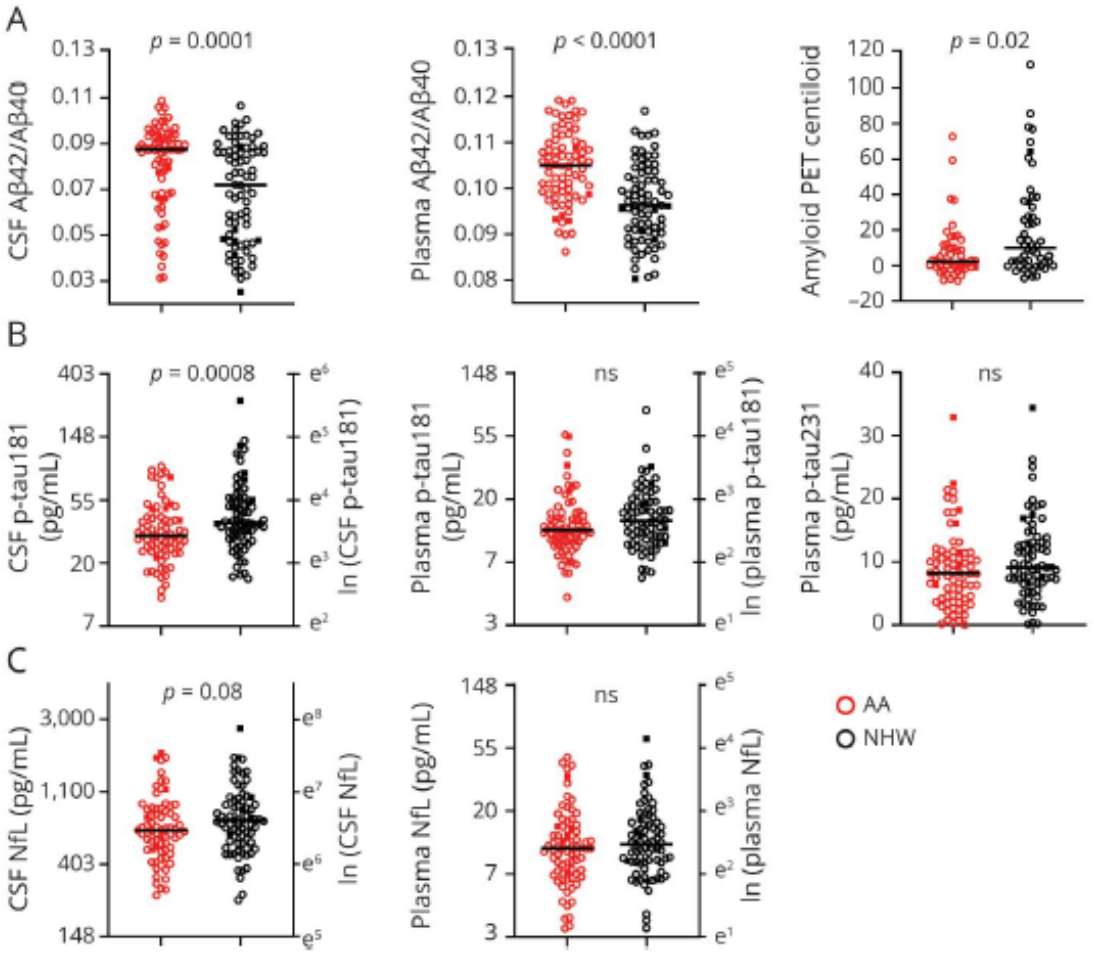
Abbreviations: MCI, mild cognitive impairment; PET, positron emission tomography.

**In unmatched analysis with whole sample, all race/ethnic groups had lower odds of Amyloid positivity vs. Whites

Wilkins CH et al. JAMA Neurology 2022

CSF & Plasma – African Americans and Whites

Figure 1 Biomarkers by Race



Predicting CSF AB42/40 or amyloid PET

- In models with p-tau191, p-tau231 or NfL, African Americans had lower probability
- In models with all plasma biomarkers and covariates, race was not a predictor

Schindler SE et al. Neurology 2022

CSF and Plasma – African Americans and Whites

Brain, Stress, Hypertension, and Aging Research Program (B-SHAPE)
- 300 AA
- 303 White

Table 2. Unadjusted Mean and Covariate-Adjusted LSM Concentrations of Plasma and CSF Alzheimer Dementia Biomarkers and Ratios by Race

Biomarker	Unadjusted mean (SD)			Adjusted LSM (SE)[a]			Adjusted mean difference (95% CI)
	African American participants	White participants	*P* value	African American participants	White participants	*P* value	
Plasma							
Aβ42, pg/mL	10.35 (3.43)	9.12 (3.47)	.02	8.43 (0.47)	9.62 (0.39)	.04	−1.20 (−2.33 to −0.07)
Aβ40, pg/mL	160.68 (50.74)	186.79 (59.75)	.002	147.30 (9.28)	185.08 (7.67)	.001	−37.78 (−60.16 to −15.39)
p-tau$_{181}$, pg/mL[b]	17.99 (7.54)	21.78 (9.59)	.002	18.05 (1.05)	22.70 (1.20)	.004	−4.66 (−7.05 to −1.90)
Aβ42/Aβ40	0.07 (0.02)	0.05 (0.02)	<.001	0.06 (0.00)	0.05 (0.00)	.08	0.01 (0 to 0.01)
NFL, pg/mL[b]	11.19 (6.38)	13.41 (6.18)	<.001	12.06 (0.52)	13.64 (0.57)	.03	−1.58 (−2.83 to −0.19)
CSF							
AlzBio Innotest							
Aβ42, pg/mL	278.71 (99.26)	260.46 (95.91)	.08	272.51 (10.26)	255.53 (9.24)	.15	16.97 (−6.26 to 40.21)
Total tau, pg/mL[b]	42.61 (20.24)	60.67 (31.49)	<.001	44.80 (2.52)	61.27 (3.11)	<.001	−16.46 (−21.82 to −10.37)
p-tau$_{181}$, pg/mL[b]	14.05 (6.86)	18.46 (10.40)	<.001	14.38 (0.82)	18.19 (0.93)	<.001	−3.81 (−5.56 to −1.83)
Lumipulse							
Aβ42, pg/mL	740.70 (370.23)	634.98 (262.92)	.21	808.87 (138.3)	680.46 (138.9)	.11	128.41 (−31.07 to 287.89)
Aβ40, pg/mL	9584.5 (3358.1)	11439 (3382.9)	.02	8688.9 (2059)	10231 (2068)	.20	−1541.64 (−3916.31 to 833.04)
Total tau, pg/mL[b]	267.21 (143.52)	454.55 (269.61)	<.001	250.25 (76.79)	436.82 (134.6)	.003	−186.57 (−261.17 to −80.29)
p-tau$_{181}$, pg/mL[b]	37.67 (21.77)	64.81 (44.15)	<.001	30.97 (9.88)	55.84 (17.89)	.002	−24.87 (−34.41 to −11.09)
Aβ42/Aβ40	0.08 (0.03)	0.06 (0.02)	<.001	0.09 (0.01)	0.07 (0.01)	.002	0.02 (0.01 to 0.03)
Simoa							
NFL, pg/mL[b]	740.11 (342.20)	902.23 (374.76)	<.001	824.64 (35.97)	918.64 (35.80)	.034	−94 (−174.14 to −5.23)

Hajjar et al. JAMA Network Open 2022

Comparison of biomarkers in Health & Aging Brain among Latino Elders (HABLE)

TABLE 5 HABLE Characteristics – Blood Biomarker Biomarkers

	Total Cohort N = 1705	Mexican American N = 890	Non-Hispanic White N = 813
Plasma AT(N) Markers			
Plasma A			
Aβ40	252.55 (67.69)	239.25 (67.31)	267.30 (65.06)***
Aβ42	12.06 (3.31)	11.86 (3.41)	12.26 (3.18)
Plasma T (total tau)	2.47 (0.96)	2.57 (0.98)	2.35 (0.92)***
Plasma N (NfL)	18.97 (11.36)	17.31 (11.47)	20.81 (10.98)

Amyloid PET positivity:

Mexican American (mean age 64): 30% CU, 8% CMI, 45% AD

Non-Hispanic White (mean age 69): 44% CU, 33% MCI, 67% AD

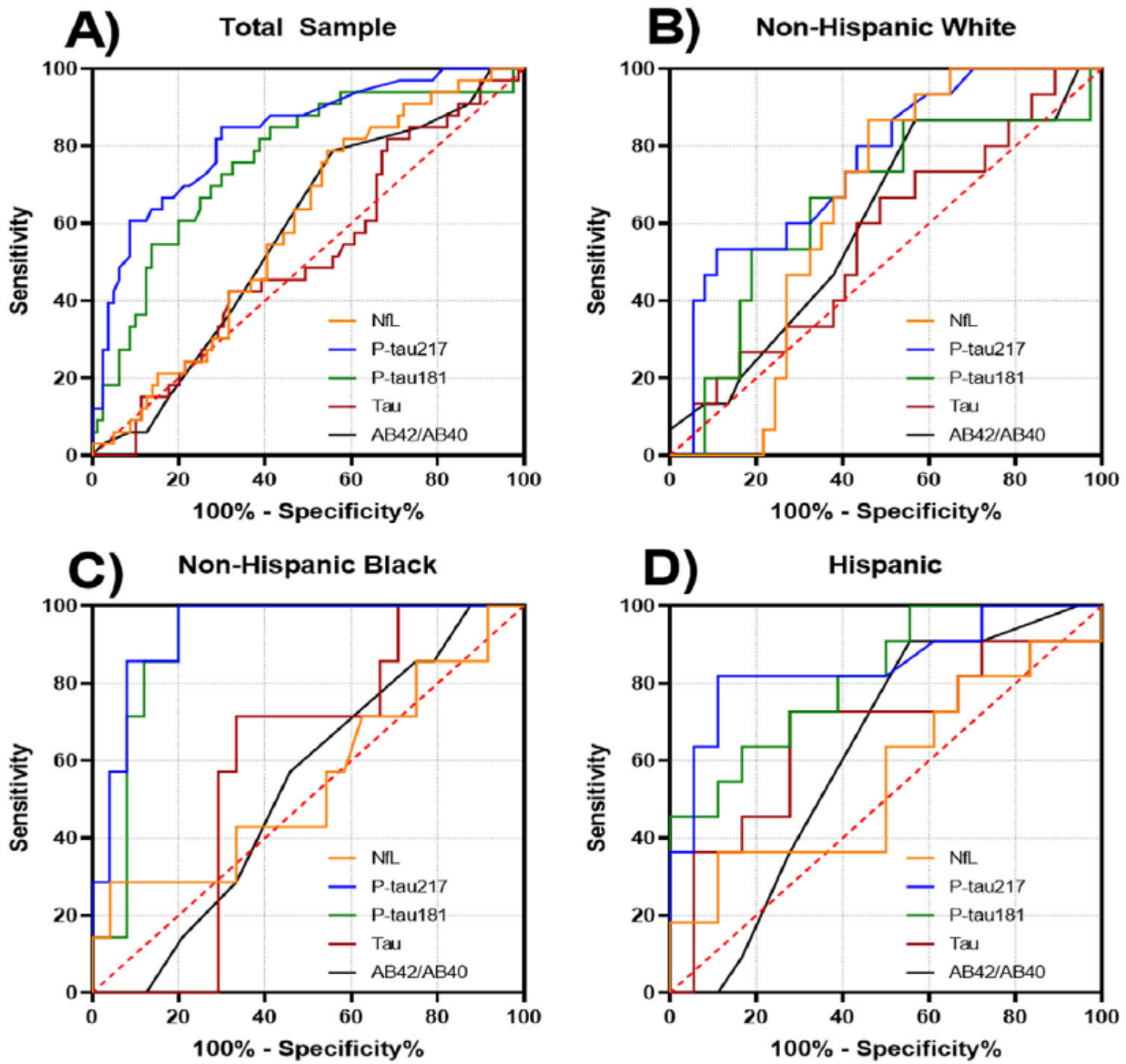
O'Bryant SE et al. DADM 2022

ROC for postmortem diagnosis of AD, by race/ethnicity

52 white, 31 non-Hispanic black, 29 Hispanic

No difference in blood biomarker levels

P-tau numerically better for black and Hispanic vs white. NfL notably worse



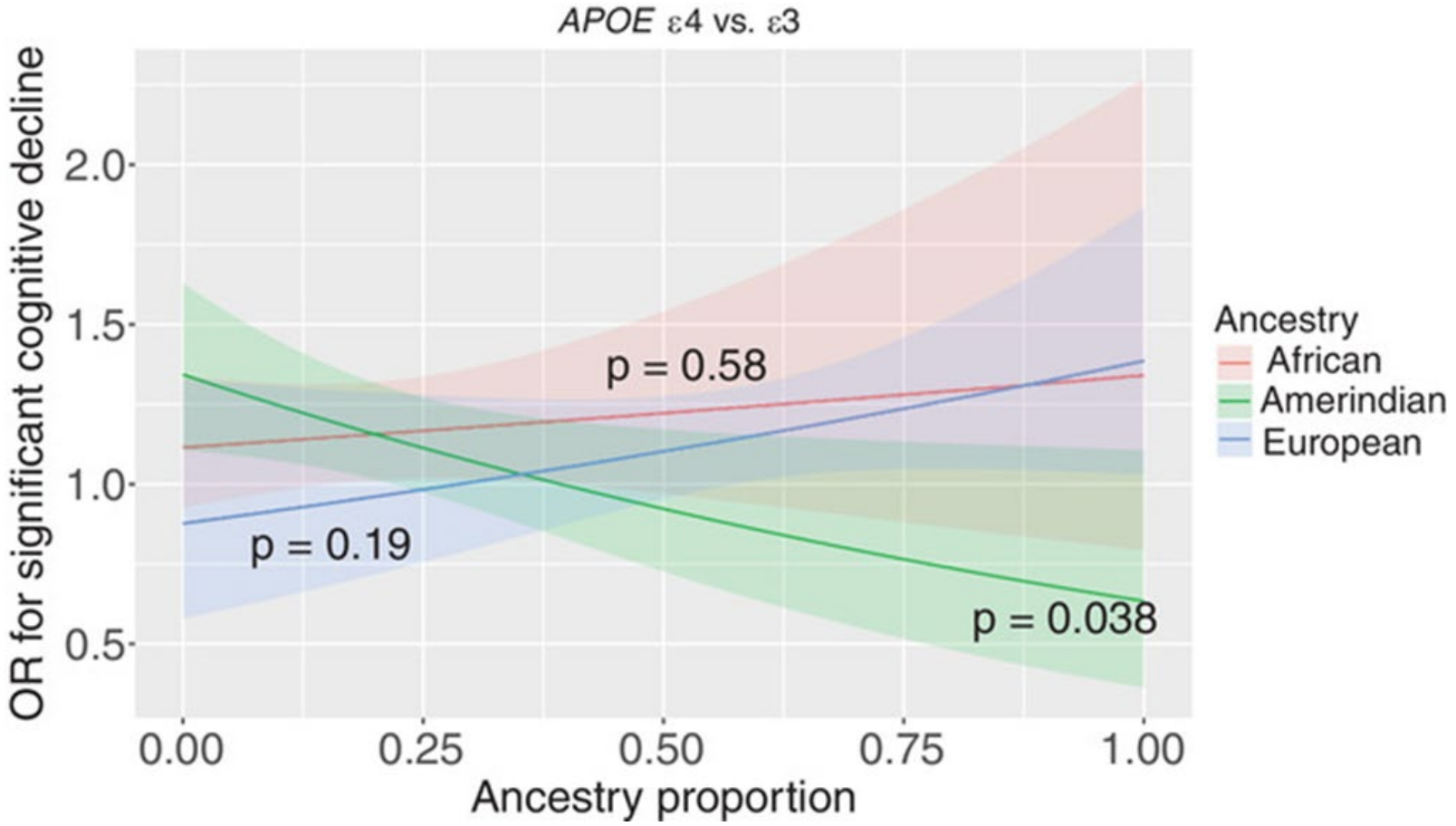
Brinkman AM et al. Alz Dem 2021

Potential Explanations

APOE effects

- APOE E4 had a significant, but weaker effect on incident AD and cognitive decline in Yoruba than in African Americans (Hendrie H et al., 2014)
- Association of E4 allele with risk of AD much lower among African Americans than Whites (Evans DA et al, 2003)
- Association of APOE and AD also weaker among Latinos relative to non-Latino whites (Campos M et al., 2013)
- In the Strong Heart Study of American Indians, the E4 allele was not associated with hippocampal volume or most cognitive tests (Cholerton B et al., 2017)

Differential effects of APOE on cognition by ancestry in Latinos

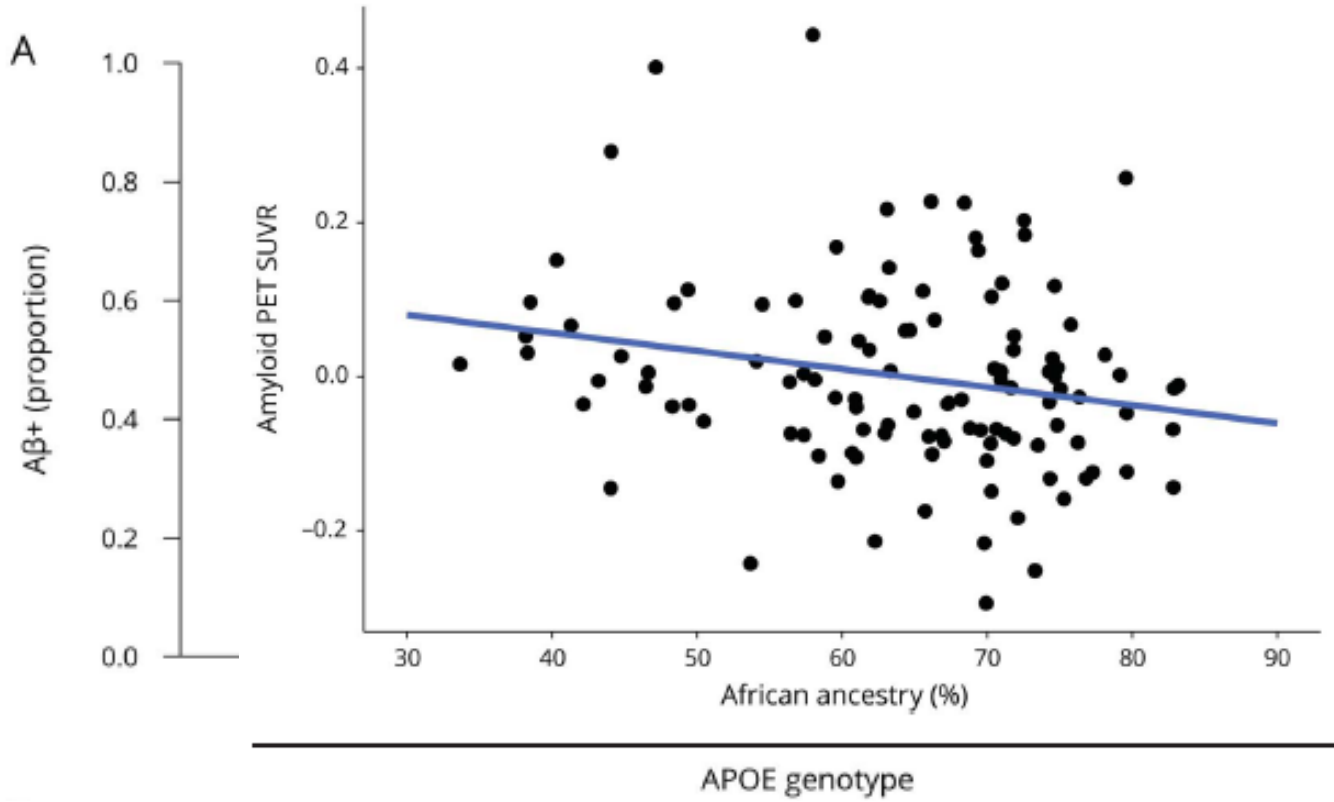


Granot-Hershkovitz E et al. Alz Dem 2021

Non-Hispanic Black differences in A4

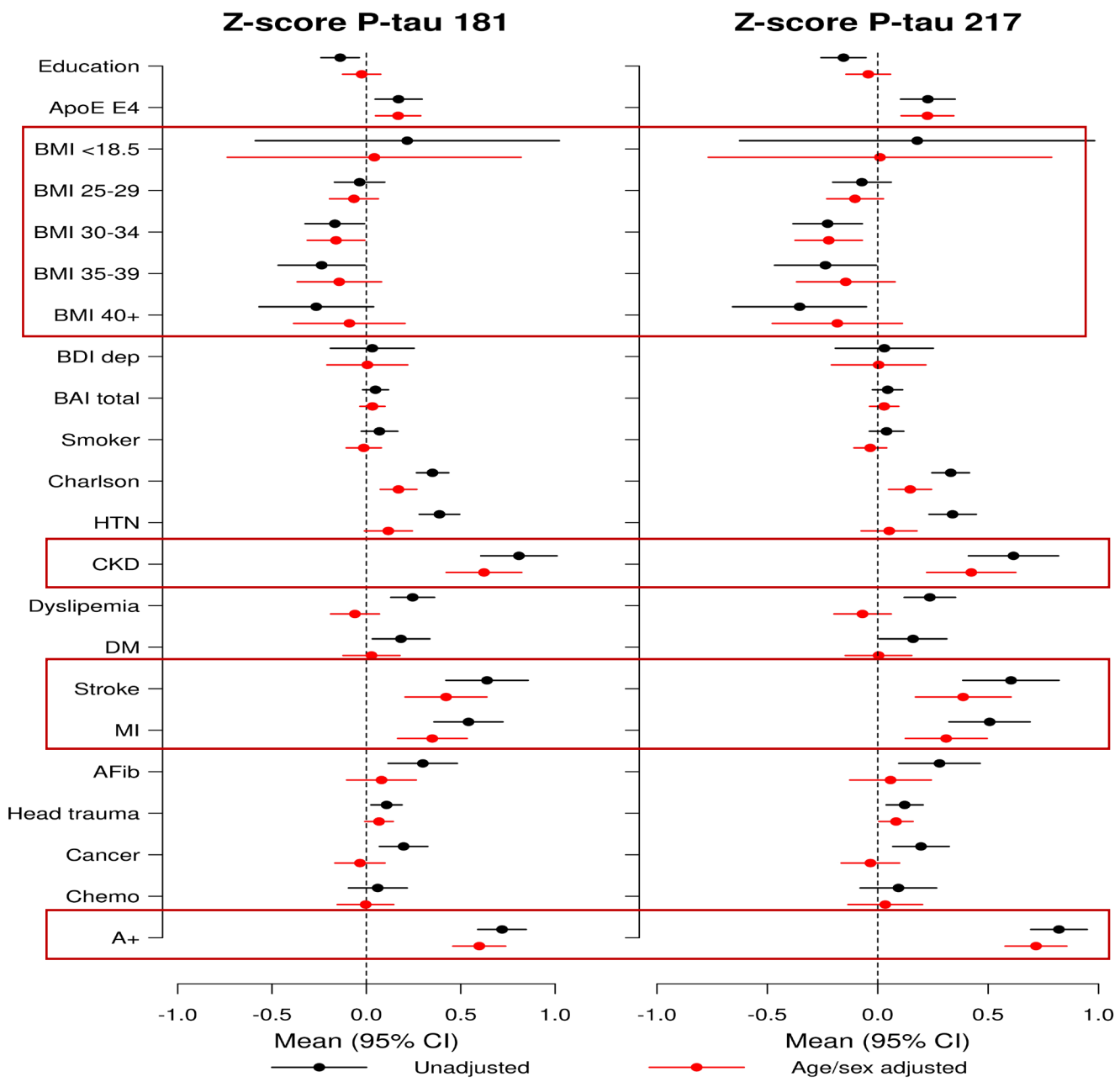
Figure 1 Proportion of Amyl
Genotypes for the

Figure 3 Plot of Continuous Amyloid PET Standardized Uptake Value Ratios (SUVRs) Compared to Percent African Ancestry, With Amyloid Residualized by Age, Sex, Number of *APOE4* Alleles, and Number of *APOE2* Alleles

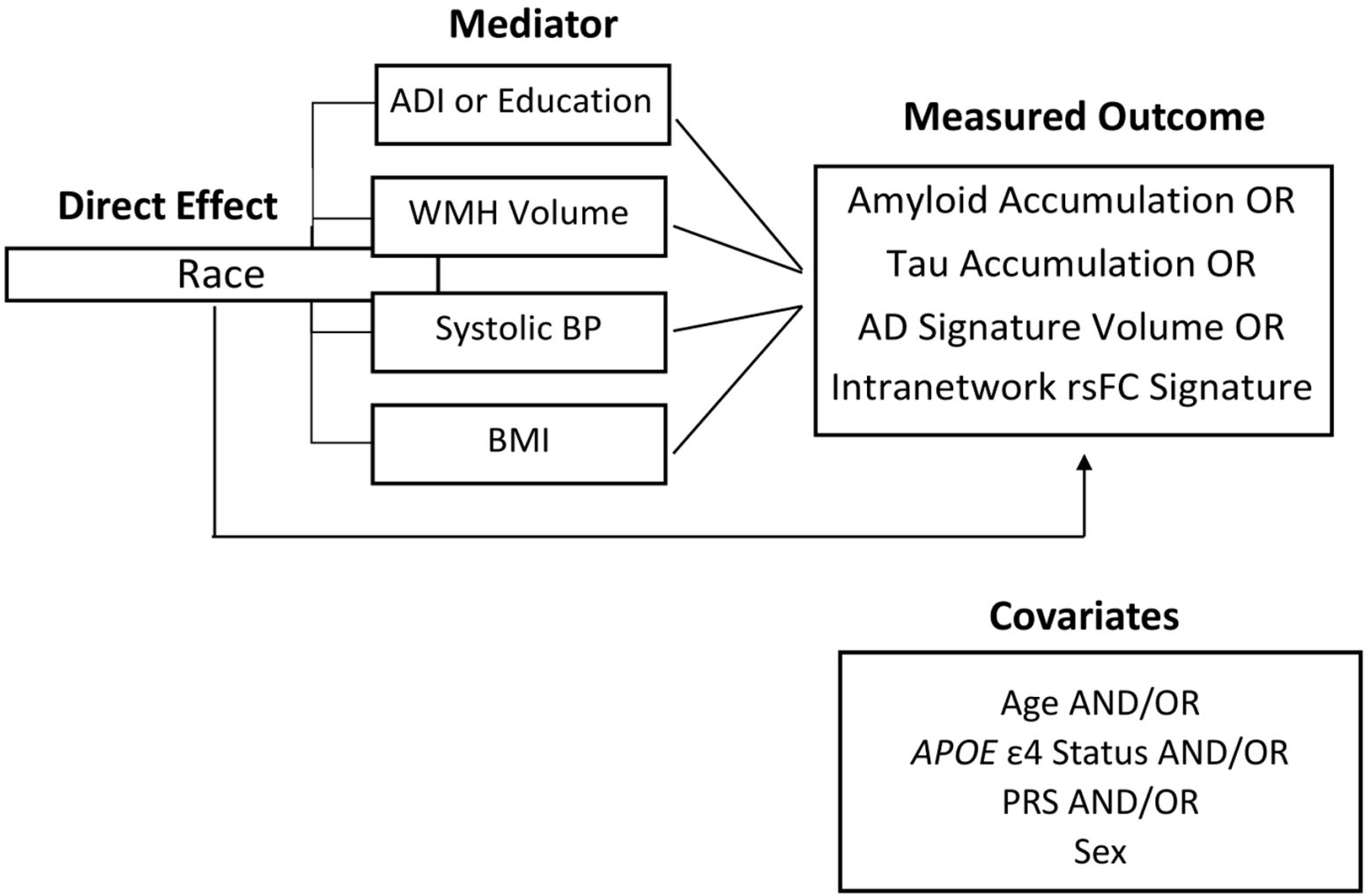


Deters KD et al. Neurology 2021

Factors associated with plasma P-tau181 and P-tau217



Further investigation of mediators



Meeker et al. Ann Neurol 2021

Further investigation of mediators

eTable. Mediation Effect Summary (P Values)

Mediation		M1/CRP			M1/Mean SBP Siting			M1/BMI		
Source	Variables	Total Effect	Direct Effect	Indirect Effect	Total Effect	Direct Effect	Indirect Effect	Total Effect	Direct Effect	Indirect Effect
CSF AlzBio Innotest	Aβ42	0.10	0.13	0.71	0.033	0.063	0.46	0.13	0.25	0.30
	Tau	<.0001	<.0001	0.70	<.0001	<.0001	0.67	<.0001	<.0001	0.41
	$pTau_{181}$	0.0052	0.0033	0.67	0.0036	0.0017	0.25	0.0023	0.0003	0.040
CSF LUMIPULSE	Aβ42	0.34	0.40	0.97	0.25	0.25	0.96	0.27	0.29	0.81
	Aβ40	0.14	0.22	0.77	0.14	0.15	0.96	0.19	0.12	0.81
	Tau	0.060	0.017	0.69	0.011	0.011	0.99	0.034	0.016	0.81
	$pTau_{181}$	0.041	0.031	0.74	0.024	0.024	0.97	0.028	0.017	0.82
	Aβ42/Aβ40	0.018	0.019	0.78	0.011	0.010	0.96	0.046	0.014	0.81
CSF, SIMOA	NFL	0.15	0.16	0.82	0.20	0.13	0.36	0.20	0.32	0.27
Plasma	Aβ42	0.14	0.15	0.89	0.16	0.24	0.29	0.14	0.45	0.11
	Aβ40	0.060	0.041	0.65	0.0064	0.0061	0.79	0.0050	0.0028	0.30
	$pTau_{181}$	0.019	0.022	0.98	0.019	0.075	0.15	0.023	0.057	0.26
	Aβ42/Aβ40	0.42	0.32	0.64	<.0001	<.0001	0.33	<.0001	0.0001	0.27
	NFL	0.24	0.24	0.88	0.35	0.26	0.38	0.29	0.79	0.016

Mediation		M1/ ADI			M1/APOE4		
Source	Variables	Total Effect	Direct Effect	Indirect Effect	Total Effect	Direct Effect	Indirect Effect
CSF AlzBio Innotest	Aβ42	0.11	0.74	0.10	0.15	0.17	0.50
	Tau	<.0001	0.0004	0.70	<.0001	<.0001	0.48
	$pTau_{181}$	0.0099	0.036	0.99	0.0017	0.0018	0.58
CSF LUMIPULSE	Aβ42	0.43	0.92	0.50	0.47	0.37	0.77
	Aβ40	0.11	0.064	0.30	0.089	0.072	0.78
	Tau	0.016	0.046	0.66	0.024	0.0075	0.77
	$pTau_{181}$	0.034	0.061	0.57	0.037	0.013	0.77
	Aβ42/Aβ40	0.017	0.10	0.95	0.050	0.0023	0.77
CSF, SIMOA	NFL	0.27	0.080	0.14	0.19	0.18	0.91
Plasma	Aβ42	0.25	0.48	0.87	0.16	0.12	0.54
	Aβ40	0.014	0.030	0.53	0.0062	0.0055	0.67
	$pTau_{181}$	0.023	0.021	0.43	0.020	0.019	0.70
	Aβ42/Aβ40	0.0001	0.0021	0.59	<.0001	<.0001	0.52
	NFL	0.28	0.052	0.050	0.31	0.33	0.59

Hajjar et al. JAMA Network Open 2022 (B-SHARP)

Meeker KL et al. 2021

- ADI mediated racial differences in AD signature volume

Timing of assessment of mediators important

- African Americans have earlier CV pathology – longer duration and likely more cerebrovascular pathology in later life

Discussion

- Some studies suggest that AD fluid and imaging biomarker levels differ by race/ethnicity but many others do not
  - Limited by small sample size and type of study as well as differential access
  - Need to move beyond just comparing levels (to whites) and start thinking in more of a sociocultural context
  - Factors can similarly be associated with AD pathology/biomarkers across racial/ethnic groups, but some groups may be overburdened due to a greater frequency (e.g., Htn, Diabetes, education)
- Most studies including racial ethnic groups are not representative – higher education or eligibility exclusion criteria (e.g., cerebrovascular disease, etc)
  - Many groups not examined
- Limited examination of racialization, including environmental and sociocultural exposures, on AD biomarkers

Thank You!

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