Influence of Race and Ethnicity on AD Biomarkers

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• Senior Editor: *Alzheimer’s and Dementia – A Journal of the Alzheimer’s Association, Alzheimer’s Research and Therapy*

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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>
<thead>
<tr>
<th>Study</th>
<th>Biomarker(s)</th>
<th>Number of Black or African American participants</th>
<th>Number of white participants</th>
<th>Biomarker levels in Black or African American participants compared with white participants</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gottesman et al. (2016)</td>
<td>Aβ PET</td>
<td>141</td>
<td>188</td>
<td>Higher</td>
</tr>
<tr>
<td>Howell et al. (2017)</td>
<td>CSF p-tau, t-tau</td>
<td>65</td>
<td>70</td>
<td>Lower</td>
</tr>
<tr>
<td>Garrett et al. (2019)</td>
<td>CSF p-tau, t-tau</td>
<td>152</td>
<td>210</td>
<td>Lower</td>
</tr>
<tr>
<td>Morris et al. (2019)</td>
<td>CSF p-tau, t-tau</td>
<td>97</td>
<td>816</td>
<td>Lower</td>
</tr>
<tr>
<td>Kumar et al. (2020)</td>
<td>CSF p-tau, t-tau</td>
<td>30</td>
<td>50</td>
<td>Lower</td>
</tr>
<tr>
<td>Meeker et al. (2020)</td>
<td>Aβ PET, tau PET and structural and functional MRI</td>
<td>70</td>
<td>434</td>
<td>No difference in tau PET, Aβ PET, or functional MRI; lower brain volume</td>
</tr>
</tbody>
</table>

Table 2: Studies of Alzheimer disease biomarkers in Black or African American individuals and white individuals.
Racial and ethnic differences in Amyloid PET - IDEAS

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

<table>
<thead>
<tr>
<th>Amyloid PET scan result</th>
<th>Matched participants, No. (%)</th>
<th>No.</th>
<th>White</th>
<th>Black</th>
<th>Hispanic</th>
<th>White</th>
</tr>
</thead>
<tbody>
<tr>
<td>No.</td>
<td>Asian</td>
<td>313</td>
<td>313</td>
<td>615</td>
<td>780</td>
<td>780</td>
</tr>
<tr>
<td>MCI and dementia</td>
<td>Positive, No. (%) [95% CI]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>142 (45.4) [39.9-50.9]</td>
<td>181 (57.8) [52.3-63.2]</td>
<td>333 (54.1) [50.2-58.0]</td>
<td>359 (58.4) [54.4-62.2]</td>
<td>425 (54.5) [51.0-58.0]</td>
<td>482 (61.8) [58.3-65.1]</td>
</tr>
<tr>
<td>Negative</td>
<td>171 (54.6)</td>
<td>132 (42.2)</td>
<td>282 (45.9)</td>
<td>256 (41.6)</td>
<td>355 (45.5)</td>
<td>298 (38.2)</td>
</tr>
<tr>
<td>MCI</td>
<td>Positive</td>
<td>61 (36.3)</td>
<td>89 (53.0)</td>
<td>128 (42.4)</td>
<td>149 (49.3)</td>
<td>164 (46.1)</td>
</tr>
<tr>
<td></td>
<td>Negative</td>
<td>107 (63.7)</td>
<td>79 (47.0)</td>
<td>174 (57.6)</td>
<td>153 (50.7)</td>
<td>192 (53.9)</td>
</tr>
<tr>
<td>Dementia</td>
<td>Positive</td>
<td>81 (55.9)</td>
<td>92 (63.4)</td>
<td>205 (65.5)</td>
<td>210 (67.1)</td>
<td>261 (61.6)</td>
</tr>
<tr>
<td></td>
<td>Negative</td>
<td>64 (44.1)</td>
<td>53 (36.6)</td>
<td>108 (34.5)</td>
<td>103 (32.9)</td>
<td>163 (38.4)</td>
</tr>
</tbody>
</table>

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**
CSF & Plasma – African Americans and Whites

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
### 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

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>African American participants</th>
<th>White participants</th>
<th>P value</th>
<th>Adjusted LSM (SE)*</th>
<th>African American participants</th>
<th>White participants</th>
<th>P value</th>
<th>Adjusted mean difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aβ42 pg/mL</td>
<td>10.35 (3.43)</td>
<td>9.12 (3.47)</td>
<td>.02</td>
<td>8.43 (0.47)</td>
<td>9.62 (0.39)</td>
<td>.04</td>
<td>-1.20 (&lt;-2.33 to -0.07)</td>
<td></td>
</tr>
<tr>
<td>Aβ40 pg/mL</td>
<td>160.68 (50.74)</td>
<td>186.79 (59.75)</td>
<td>.002</td>
<td>147.30 (9.28)</td>
<td>185.88 (7.67)</td>
<td>.001</td>
<td>-37.78 (&lt;-60.16 to -15.39)</td>
<td></td>
</tr>
<tr>
<td>p-tau217, pg/mL</td>
<td>17.95 (7.54)</td>
<td>21.78 (9.59)</td>
<td>.002</td>
<td>18.05 (1.05)</td>
<td>22.79 (1.20)</td>
<td>.004</td>
<td>-4.66 (&lt;-7.05 to -1.90)</td>
<td></td>
</tr>
<tr>
<td>Aβ42/Aβ40</td>
<td>0.07 (0.03)</td>
<td>0.05 (0.02)</td>
<td>&lt;.001</td>
<td>0.06 (0.00)</td>
<td>0.05 (0.00)</td>
<td>.08</td>
<td>0.01 (0.01 to 0.01)</td>
<td></td>
</tr>
<tr>
<td>NFL, pg/mL</td>
<td>11.15 (6.38)</td>
<td>13.41 (6.18)</td>
<td>&lt;.001</td>
<td>12.06 (0.52)</td>
<td>13.64 (0.57)</td>
<td>.03</td>
<td>-1.58 (&lt;-2.83 to -0.19)</td>
<td></td>
</tr>
</tbody>
</table>

#### AlzBle Immuno

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Unadjusted mean (SD)</th>
<th>Adjusted LSM (SE)*</th>
<th>P value</th>
<th>Adjusted mean difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aβ42 pg/mL</td>
<td>278.71 (99.26)</td>
<td>255.13 (9.24)</td>
<td>.15</td>
<td>16.97 (&lt;-6.26 to 40.21)</td>
</tr>
<tr>
<td>Total tau, pg/ml</td>
<td>42.61 (20.24)</td>
<td>61.27 (3.11)</td>
<td>&lt;.001</td>
<td>-16.46 (-21.82 to 10.37)</td>
</tr>
<tr>
<td>p-tau217, pg/ml</td>
<td>14.05 (6.86)</td>
<td>18.19 (0.93)</td>
<td>&lt;.001</td>
<td>-3.81 (&lt;-5.56 to -1.83)</td>
</tr>
</tbody>
</table>

#### Lumipulse

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Unadjusted mean (SD)</th>
<th>Adjusted LSM (SE)*</th>
<th>P value</th>
<th>Adjusted mean difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aβ42 pg/mL</td>
<td>740.70 (370.23)</td>
<td>680.46 (138.9)</td>
<td>.11</td>
<td>128.41 (-31.07 to 287.89)</td>
</tr>
<tr>
<td>Aβ40 pg/mL</td>
<td>95854.33 (585.18)</td>
<td>10231 (2068)</td>
<td>.20</td>
<td>1541.64 (-3916.31 to 833.04)</td>
</tr>
<tr>
<td>Total tau, pg/ml</td>
<td>267.21 (143.52)</td>
<td>436.82 (134.6)</td>
<td>.003</td>
<td>-186.57 (-261.17 to -80.29)</td>
</tr>
<tr>
<td>p-tau217, pg/ml</td>
<td>37.67 (21.77)</td>
<td>55.84 (17.89)</td>
<td>.002</td>
<td>-24.87 (-34.41 to -11.09)</td>
</tr>
<tr>
<td>Aβ42/Aβ40</td>
<td>0.08 (0.03)</td>
<td>0.07 (0.01)</td>
<td>.002</td>
<td>0.02 (0.01 to 0.03)</td>
</tr>
<tr>
<td>NFL, pg/mL</td>
<td>740.11 (342.20)</td>
<td>918.64 (35.80)</td>
<td>.034</td>
<td>-94 (-174.14 to -5.23)</td>
</tr>
</tbody>
</table>

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

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

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
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
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 Amyloid 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
Factors associated with plasma P-tau181 and P-tau217

Further investigation of mediators

Mediator
- ADI or Education
- WMH Volume
- Systolic BP
- BMI

Measured Outcome
- Amyloid Accumulation OR
- Tau Accumulation OR
- AD Signature Volume OR
- Intranetwork rsFC Signature

Covariates
- Age AND/OR
- APOE ε4 Status AND/OR
- PRS AND/OR
- Sex
**Further investigation of mediators**

**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

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