Plasma biomarkers associate with amyloid and tau PET binding in cognitively unimpaired older adults with a parental history of AD


for the Presymptomatic Evaluation of Experimental or Novel Treatments for Alzheimer Disease (PREVENT-AD) Research Group
No disclosures
Objective and methods

Objectives:

1. To test whether high sensitivity ELISA (SiMoA) or mass spectrometry plasma Aβ biomarkers are best suited for the detection of cerebral amyloid deposition

2. To test whether plasma-derived tau biomarkers associate with AV1451 tracer retention.

3. To test whether a combination of plasma biomarkers detects cerebral Aβ load

Methods:

• 129 healthy older adults from the PREVENT-AD study of healthy older adults with family history of AD dementia

• Cerebral amyloid and tau pathologies assessed using NAV4694 (Aβ) in a global cortical ROI and AV1451 in a temporal metaROI

• Plasma Aβ_{40} and Aβ_{42} measured using LC-MS and SiMoA, t-tau, a novel $^{181}$P-tau assay developed in Göteborg.
The PREVENT-AD cohort (cognitively normal older adults)

<table>
<thead>
<tr>
<th></th>
<th>Aβ-negative YA</th>
<th>All OA</th>
<th>Aβ-negative OA</th>
<th>Aβ-positive OA</th>
<th>P for difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sample size</td>
<td>8</td>
<td>129</td>
<td>103</td>
<td>26</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>26.95 (3.00)</td>
<td>68.50 (5.49)</td>
<td>67.13 (4.72)</td>
<td>68.50 (5.49)</td>
<td>0.21</td>
</tr>
<tr>
<td>Sex %F (N)</td>
<td>6 (75)</td>
<td>74 (85)</td>
<td>75 (77)</td>
<td>73 (19)</td>
<td>1</td>
</tr>
<tr>
<td>APOE ε4 carriers % (N)</td>
<td>1 (13)</td>
<td>41 (53)</td>
<td>35 (36)</td>
<td>65 (17)</td>
<td>0.007</td>
</tr>
<tr>
<td>Education years</td>
<td>19.38 (1.85)</td>
<td>15.15 (3.28)</td>
<td>15.47 (3.40)</td>
<td>13.88 (2.41)</td>
<td>0.03</td>
</tr>
<tr>
<td>Global Aβ SUVR</td>
<td>1.16 (0.04)</td>
<td>1.34 (0.34)</td>
<td>1.20 (0.08)</td>
<td>1.90 (0.39)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>metaROI AV1451 SUVR</td>
<td>1.15 (0.09)</td>
<td>1.18 (0.12)</td>
<td>1.16 (0.08)</td>
<td>1.28 (0.18)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Plasma-PET Delay (days)</td>
<td>151.5 [34.5-505.5]</td>
<td>236.5 [6-1612.5]</td>
<td>247.5 [7.5-1612.5]</td>
<td>190 [6.5-569.5]</td>
<td>0.05</td>
</tr>
</tbody>
</table>
Aβ and tau deposition in the PREVENT-AD group

NAV4694 binding

Flortaucipir binding

L | R
---|---

0.5 NAV SUVR | 2.2

0.5 FTP SUVR | 1.8
Plasma $\text{A\beta}_{42}$: Mass spectrometry and SiMoA biomarkers associate cortical $\text{A\beta}$ deposition

![Plasma vs PET graph](image)

**LC-MS $\text{A\beta}_{42}$ vs PET $\text{A\beta}$ load (SUVR)**

- $R^2 = 0.07^{***}$

**SiMoA $\text{A\beta}_{42}$ vs PET $\text{A\beta}$ load (SUVR)**

- $R^2 = 0.06^{***}$
Plasma Aβ$_{42/40}$: Mass spectrometry and SiMoA biomarkers associate cortical Aβ deposition

Plasma vs PET

R$^2 = 0.17^{***}$

R$^2 = 0.08^{***}$
Plasma $A\beta_{42/40}$: Mass spectrometry and SiMoA biomarkers associate cortical Aβ deposition

Plasma vs PET

$R^2 = 0.17^{***}$

PET Aβ load (SUVR)

Plasma vs CSF

$R^2 = 0.25^{***}$

CSF $A\beta_{42/40}$

Green YA, Orange Aβ- OA, Red Aβ+ OA
Mass spectrometry measures of plasma $\text{A} \beta_{42/40}$ are widely associated with cortical $\text{A} \beta$ deposition

Voxelwise associations of NAV4694 binding and plasma LC-MS $\text{A} \beta_{42/40}$

$P < 0.001 \text{ unc., } k > 200 \text{ voxels}$
T-tau does not associate with PET and CSF measures of tau pathology
Plasma $^{181}$P-tau associates with AV1451 binding in ‘early’ tau regions

Plasma vs PET

Plasma vs CSF

$R^2 = 0.11^{***}$

$R^2 = 0.20^{***}$
Plasma $^{181}$P-tau associates with AV1451 binding in ‘early’ tau regions

P < 0.001 unc., k > 200 voxels

R² = 0.10***
R² = 0.11***
R² = 0.13**

YA  Aβ- OA  Aβ+ OA
Plasma biomarkers distinguish Aβ-PET positivity and negativity
Take Home

• Plasma LC-MS Aβ$_{42/40}$ more accurately detects brain Aβ pathology

• Plasma $^{181}$P-tau associates with FTP binding in regions of early tau accumulation

• ... but plasma biomarkers are general indicators of presence of AD pathology

• Take this home with you
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