**BACKGROUND**

Wisconsin Registry for Alzheimer’s Prevention (WRAP) is a longitudinal cohort study of asymptomatic adult children of persons with Alzheimer’s disease (AD). The overall goal of WRAP is to determine if risk factors affect brain function or structure in this asymptomatic population. We have targeted the posterior cingulate and mesial temporal lobe for our fMRI studies.

**METHODS**

Subjects included:
- 736 asymptomatic middle-aged individuals with a parent with AD (median age = 52 years).
- 250 control participants with a negative family history of AD.
All participants undergo an extensive baseline battery of neuropsychological tests, laboratory evaluations and APOE genotyping. Serum, plasma and DNA are stored for future analyses. Subgroups of WRAP volunteers participate in cerebrospinal fluid and neuroimaging studies which are highlighted in this poster.

**BASELINE CHARACTERISTICS**

Baseline characteristics of WRAP participants are shown below. A second wave of testing is currently underway after a 4-year interval.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>AD Children (n = 736)</th>
<th>Controls (n = 250)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>52.4 (6.6)</td>
<td>55.7 (6.1)</td>
<td>&lt;.000</td>
</tr>
<tr>
<td>Education</td>
<td>15.9 (2.7)</td>
<td>16.8 (3.1)</td>
<td>&lt;.000</td>
</tr>
<tr>
<td>Female gender</td>
<td>72</td>
<td>66</td>
<td>.05</td>
</tr>
<tr>
<td>White/Caucasian</td>
<td>98</td>
<td>98</td>
<td></td>
</tr>
<tr>
<td>APOE ε4 allele, %</td>
<td>0</td>
<td>55</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>40</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Subjective memory complaint, %</td>
<td>27</td>
<td>14</td>
<td>&lt;.000</td>
</tr>
</tbody>
</table>

**FINDINGS TO DATE**

Analyses of baseline variables show no difference in traditional neuropsychological test comparisons while CSF and imaging studies suggest underlying preclinical disease. Importantly, the imaging studies and analyses of serial position effects on a list learning task (not shown) suggest evidence of preclinical AD in the family history cohort that either is independent of or interacts with APOE genotype. This suggests that family history may be an important consideration in biomarker studies of preclinical disease.

**CONTACT & ACKNOWLEDGEMENTS**

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Imaging Studies: Research was supported by a Merit Review Grant from the Department of Veterans Affairs and NIH grant AG21155.

CSF Studies: Research was supported by a Beeson Career Development Award (K23 AG026752, a grant jointly funded by NIA, the John A. Hartford Foundation, Atlantic Philanthropies, and the Starr Foundation) and the University of Wisconsin General Clinical Research Center (NCRR M01 RR03186).

Merck and Co., Inc. provided study medication for this investigator-initiated trial.

**OBJECTIVE**

To describe the relationship of CSF β-amyloid-42 (Aβ42), a biomarker of AD risk, with cognitive function in asymptomatic middle-aged adults at risk for AD.

**DESIGN: 2X2 FACTORIAL**

Parental history status (present/absent) and APOE ε4 status.

**BRAIN IMAGING PROTOCOL**

3.0 Tesla GE scanner with T1-weighted 3D volume and field mapping.

**STUDY 1: ENCODING**

Johnson, et al. (2006), J. Neurosci. N=132 subjects. Figure 1 indicates that -FH show a stronger response than +FH. Figure 2 indicates a weak interaction with ε4 in some voxels.

**STUDY 2: METACOGNITION**

N=110. This study used a metacognitive appraisal task which activates the anterior mesial temporal lobe and cortical midline structures including the posterior cingulate. On this task, +FH was associated with decreased activity in the hippocampus and medial parietal lobe. There were no main effects of APOE. Johnson et al. (in press), Archives of General Psychiatry.

**STUDY 3: FACE RECOGNITION**

Face recognition strongly activates the posterior cingulate, a region that is vulnerable to AD. In this preliminary analysis in Figure 4 (which is restricted to the PC and precuneus) we show that 14 asymptomatic subjects at high risk (+FH, +APOE) activate less than 27 matched subjects at low risk (+FH, -APOE) on an event-related face recognition task.

**IMAGING STUDIES SUMMARY**

These imaging studies suggest that an as yet undefined FH factor(s) is influencing brain function in areas of the brain affected by AD. Studies are planned to investigate the mechanism of these changes including molecular and metabolic imaging and genetic investigations.

**CSF STUDIES**

In persons with mild cognitive impairment, cerebrospinal fluid (CSF) biomarkers predict risk of progressing to Alzheimer’s disease (AD), but it is unclear if they are associated with cognitive function in asymptomatic adults at risk for AD.

**RESULTS**

Participants (n=27, mean ± SD age 53.4 ± 8.5 yrs, 17 women) had a mean MMSE score of 29.5 ± 0.8 points and 16.9 ± 3.1 yrs education. Lower CSF Aβ42 levels, suggestive of preclinical disease progression, were associated with worse function on two measures of working memory (mental control and spatial span; see Figure 5). Regression models including age, education (yrs), APOE ε4, sex, and CSF Aβ42 predicted 48% of the variance in mental control, a measure of working memory. Other cognitive measures were not associated with CSF Aβ42.

**FIGURE 5. RELATIONSHIP OF CSF Aβ42 WITH WORKING MEMORY TASKS**

- **Mental Control (Time, Sec)**
  - r = -0.420
  - p = 0.029

- **Spatial Span, Backwards (Score)**
  - r = 0.378
  - p = 0.052

**SUMMARY**

In asymptomatic middle-aged adults at risk for AD, lower CSF Aβ42 levels, suggestive of possible preclinical disease progression, were associated with worse working memory function. Larger studies are needed to confirm these findings.