Genetic Risk and Cognitive Performance in the Wisconsin Registry for Alzheimer’s Prevention (WRAP)
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APOE ε4 and family history of Alzheimer’s disease (AD) are associated with higher risk of developing AD. Little is known about when pre-clinical cognitive symptoms develop and whether differences can be detected in mid-life. The purpose of this study is to compare cognitive performance across family history (FH) and APOE (ε4) risk groups in a middle-aged healthy sample.
# TABLE 1

<table>
<thead>
<tr>
<th>Participants (N=771)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline age (SD)</td>
<td>54 (6.5)</td>
</tr>
<tr>
<td>Sex (female)</td>
<td>70%</td>
</tr>
<tr>
<td>College degree</td>
<td>63%</td>
</tr>
<tr>
<td>Race (white)</td>
<td>99%</td>
</tr>
<tr>
<td>IQ (SD)</td>
<td>114 (9.0)</td>
</tr>
<tr>
<td>APOE-ε4+</td>
<td>39%</td>
</tr>
<tr>
<td>Family history</td>
<td>75%</td>
</tr>
<tr>
<td><strong>Participans:</strong></td>
<td>771 WRAP volunteers who have had 2 visits (Table 1)</td>
</tr>
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<td>------------------</td>
<td>-----------------------------------------------</td>
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<td><strong>Protocol:</strong></td>
<td>Volunteers return for Wave 2 after 4 years, and at 2-year intervals thereafter. At each visit, they complete a battery of neuropsychological tests. The battery comprises six factors, four of which may be sensitive to early change.</td>
</tr>
</tbody>
</table>
METHODS

Cognitive summary z-scores:

- *Immediate memory* (Rey AVLT: Trials 1&2)
- *Verbal Learning* (Rey AVLT: Trials 3-5 & Delayed Recall)
- *Working memory* (WAIS-III: Digit Span, Arithmetic, Letter-Number Sequencing)
- *Speed & flexibility* (Stroop Test, Trail-Making Test)
Hypothesis 1. FH and ε4 will predict worse cognitive performance.

Hypothesis 2. FH and ε4 will predict faster cognitive decline.

We tested these using mixed models, modeling Hypothesis 1 as a main effect of FH/ ε4 and Hypothesis 2 as an FH/ ε4 x time interaction. We covaried age, sex, education, and test site, and included random effects for person, family, and time.
RESULTS

• Risk groups differed on Immediate Memory, (p=.006; Fig. 1), with FH-, ε4- scoring best (0.22 ± 0.07).

• Risk groups’ trajectories on Working Memory also differed (p=.02; Figure 2). Scores of FH+, ε4+ participants declined over time (slope = -0.13/decade), while others’ scores increased.

• No effects were observed for Verbal Learning or Speed & Flexibility (p > .05).
Immediate Memory by Visit

†Scores adjusted for age, sex, education, and test site.
FIGURE 2

Working Memory by Visit

Working Memory (z-scores†)

Baseline  Visit 2

FH+,e4+
FH+,e4-
FH-,e4+
FH-,e4-

†Scores adjusted for age, sex, education, and test site.
CONCLUSIONS

- Cognitive differences may be emerging already in middle age -- long before clinical symptoms appear.
- Individuals who are FH+ and ε4+ may be at highest risk of early declines.
- Follow-up will determine whether group differences become clinical with age.
- Finding illustrates importance of family history to studying preclinical AD.
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