TITLE

Genetic Risk and Cognitive Performance in the Wisconsin Registry for Alzheimer's Prevention (WRAP)

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BACKGROUND

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

Participants (N=771)	
Baseline age (SD)	54 (6.5)
Sex (female)	70%
College degree	63%
Race (white)	99%
IQ (SD)	114 (9.0)
APOE-ε4+	39%
Family history	75%

METHODS

Participants: 771 WRAP volunteers who have had 2 visits (Table 1)

Protocol: 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.

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)

METHODS

Hypothesis 1. FH and ε4 will predict worse cognitive performance.

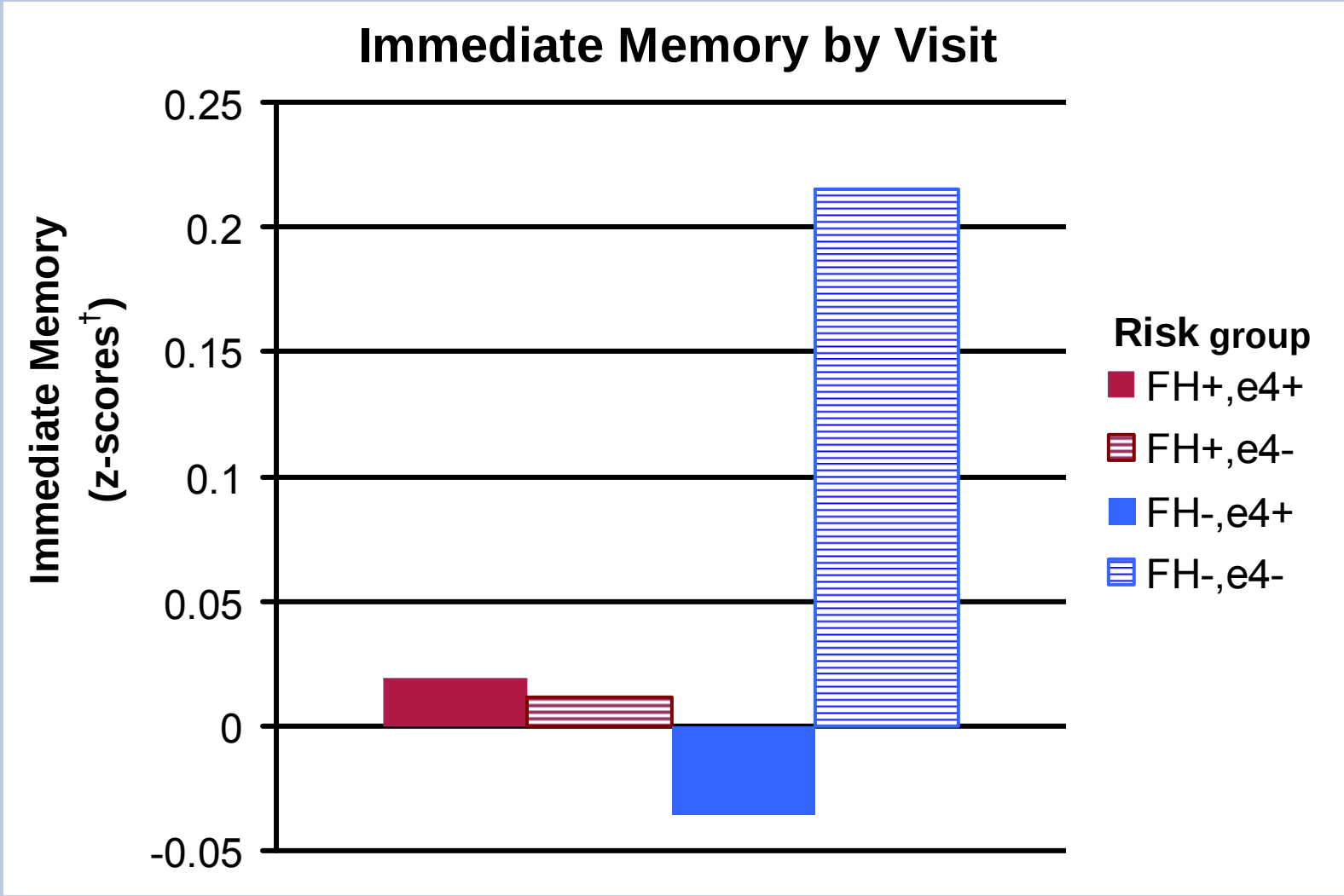
Hypothesis 2. FH and ε4 will predict faster cognitive decline.

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

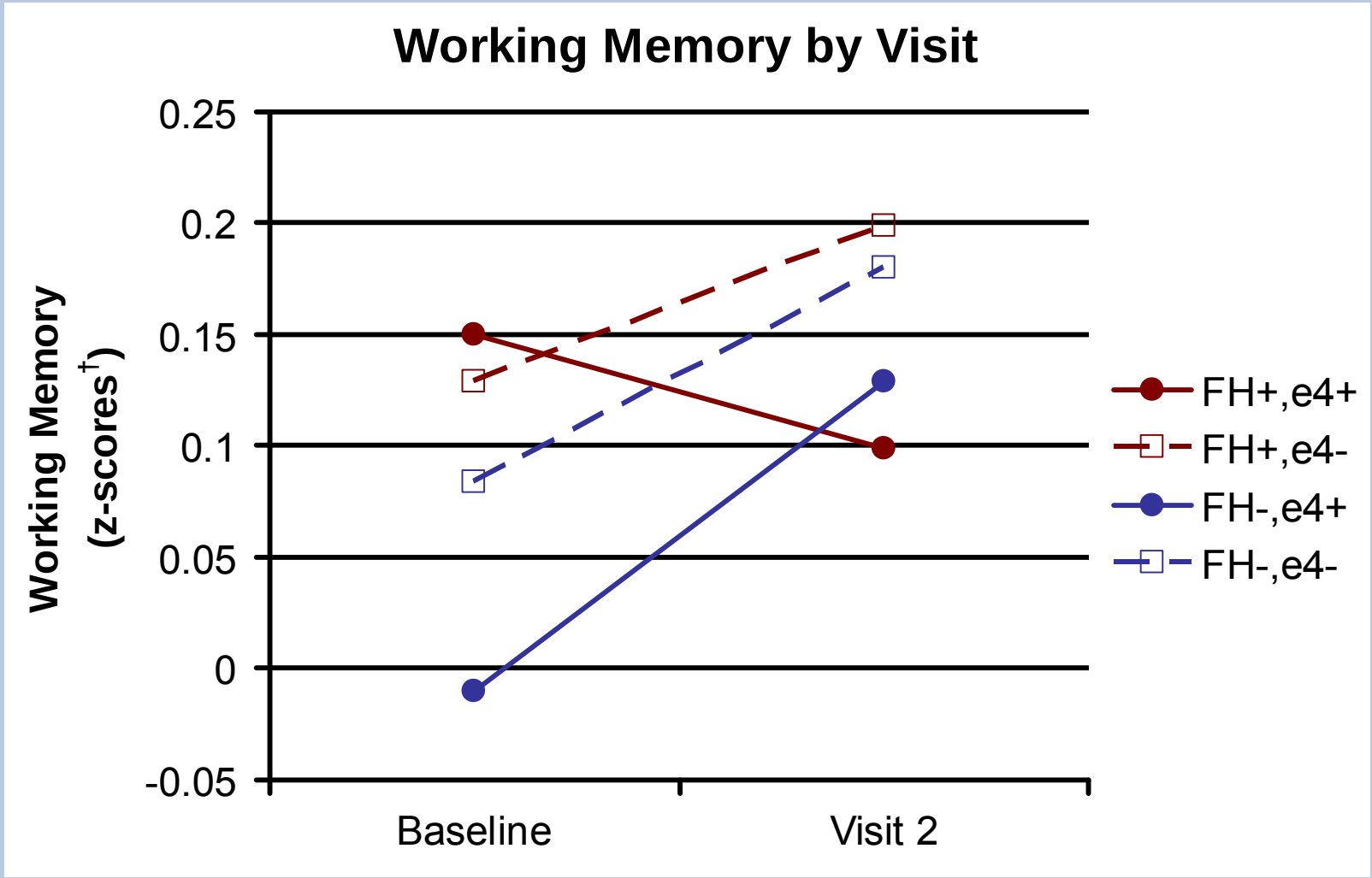
- Risk groups differed on Immediate Memory, ($p=.006$; Fig. 1), with FH-, ε4- scoring best (0.22 ± 0.07).
- Risk groups' trajectories on Working Memory also differed ($p=.02$; Figure 2). Scores of FH+, ε4+ participants declined over time (slope = -0.13/decade), while others' scores increased.
- No effects were observed for Verbal Learning or Speed & Flexibility ($p > .05$).

FIGURE 1



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

FIGURE 2



†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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