WISCONSIN REGISTRY FOR ALZHEIMER'S PREVENTION: BIOMARKERS OF PRECLINICAL ALZHEIMER'S DISEASE

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WRAP STUDY

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 define the biological and neurocognitive course of preclinical AD. A person is eligible for WRAP if they are between the ages of 40 and 65, have a parent with AD verified by autopsy or review of medical records, and are willing to participate in genetic, epidemiologic and clinical studies that focus on early identification of neurobiological markers of incipient AD.

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.

Characteristic	AD Children (n = 736)	Controls (n = 250)	p value
Age (years)	52.4 (6.6)	55.7 (6.1)	< .000
Education (years)	15.9 (2.7)	16.8 (3.1)	< .000
Female gender, %	72	66	.05
White/Caucasian, %	98	98	
APOE ε4 allele, %			
0	55	83	
1	40	16	
2	5	1	
Subjective memory complaint, %	27	14	< .000

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.

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IMAGING STUDIES

BACKGROUND

WRAP subjects are asked to participate in imaging studies 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 presented here.

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 echoplanar fMRI with HOS and field mapping.

STUDY 1: ENCODING

Figure 1

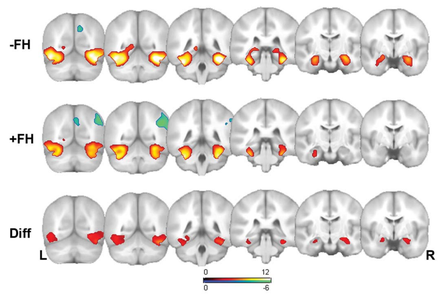
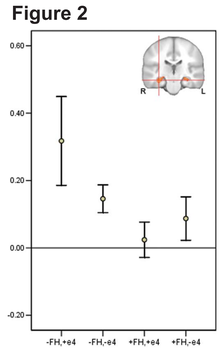


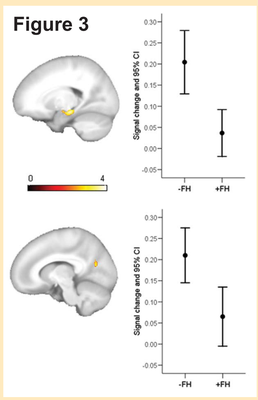
Figure 2



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

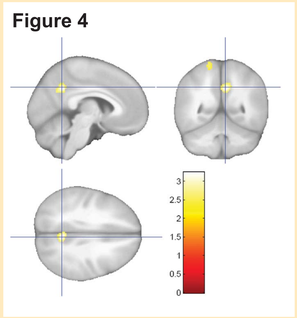
Figure 3



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

Figure 4



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

BACKGROUND

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.

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.

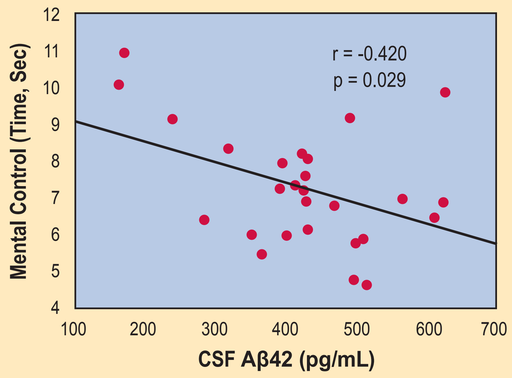
METHODS

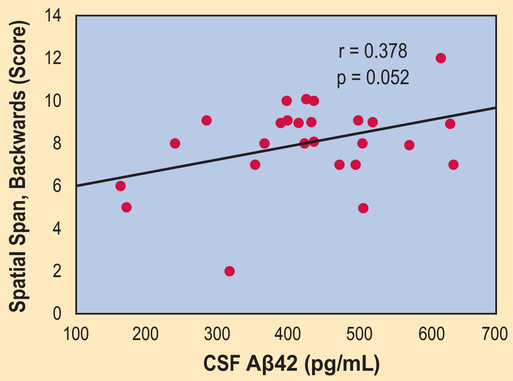
Cross-sectional baseline data were used in this interim analysis of an ongoing trial evaluating CSF biomarkers and cognition in adult children (ages 37-66 yrs) of persons with AD. Pearson correlations and backwards stepwise linear regression models were used to evaluate relationships of CSF Aβ42 levels with cognitive tests.

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





CSF STUDIES 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.