Baseline Characteristics of the Wisconsin Registry for Alzheimer's Prevention (WRAP)

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INTRODUCTION

With the aging of the American population, the prevalence of Alzheimer's disease (AD) in the US is expected to triple over the next forty years.[1] Research efforts are increasingly focused on prevention of the disease in pre-symptomatic at-risk populations. These efforts require the careful characterization of risk factors for AD. There has been much interest in genetic risk factors, such as APOE **ε4** genotype. Less attention, however, has been given to another risk factor for the disease, an individual's family history of AD. Projects examining this risk factor have often included a mix of family members (siblings and children of the patient),[2-5] perhaps obscuring the relationship between family history and risk for AD.

The Wisconsin Registry for Alzheimer's Prevention (WRAP) is enrolling adult children of patients with AD. Unique aspects of this registry include the age of the participants and the verification of parents' diagnosis. All registry participants were between the ages of 40 and 65 at baseline. Furthermore, the diagnosis of parents of enrollees was confirmed with a clinical evaluation or a review of records from a comprehensive clinical evaluation.

METHODS

At present, 593 individuals with a parental history of AD and 136 control participants are enrolled in WRAP. A comprehensive neuropsychology battery and detailed questionnaire of health and lifestyle history are administered at baseline. Additionally, APOE genotype is determined and limited laboratory tests are completed.

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RESULTS

Table 1. Distribution of APOE Genotypes in WRAP Participants with a Family History of AD and Controls

APOE Genotype	Family History n (%)	Controls n (%)	Totals
2,2	0 (0)	0 (0)	0
2,3	51 (8.6)	20 (14.8)	71
2,4	22 (3.7)	2 (1.5)	24
3,3	276 (46.5)	96 (71.1)	372
3,4	216 (36.4)	17 (12.6)	233
4,4	28 (4.7)	0 (0)	28
Totals	593	135	728

Family History total reflects 1 less participant who chose not to have genotype determined.

The distribution of APOE genotype depicted in Table 1 indicates that the Family History cohort is at increased risk for AD resulting from an over-representation of the APOE 4 allele (41.1%) compared to the Control group (12.6%). The difference in APOE distribution between the two groups is significantly different ($p<0.001$).

Table 2. Demographic, Lifestyle Variables, and Vitals for WRAP Participants

Measure	WRAP ε4+ (N=266)	WRAP ε4- (N=327)	Controls (N=136)
Demographics			
Age in years (SD)	52.02 (6.25)	52.59 (6.66)	55.71 (6.10)[Ŧ]
Education in years (SD)	16.21 (2.65)	15.94 (2.64)	16.74 (2.79)[ŦŦ]
Female gender, n (%)	186 (71.6)	234 (69.9)	78 (57.4)[ŦŦ]
White/Caucasian, n (%)	265 (99.6)	318 (97.2)	133 (97.8)
Lifestyle Variables			
Exercise, n exercising ≥ 3x/wk (%)	177 (66.5)	244 (75.3)	110 (80.9)
Alcohol, n consuming > 4 drinks/wk (%)	34 (14.4)	47 (16.9)	20 (16.7)
Smoke tobacco in past month, n (%)	20 (19.6)	27 (20.5)	11 (22.0)
Depression rating, CESD Total Score (SD)	6.23 (6.65)	6.77 (6.67)	4.24 (4.67)
Vitals			
Body Mass Index kg/m^2 (SD)	28.25 (6.12)	28.26 (5.70)	27.67 (5.50)[Ŧ]
Systolic blood pressure mm/Hg (SD)	131.42 (16.94)	133.48 (16.74)	126.34 (17.99)
Diastolic blood pressure mm/Hg (SD)	76.06 (9.72)	76.85 (10.05)	73.43 (10.75)

[Ŧ] Significant difference between WRAP and Controls, $p<0.00$
[ŦŦ] Significant difference between WRAP and Controls, $p<0.01$
*Significant difference between three groups in frequency of individuals exercising for 30+ minutes more than 3x/week, $p=0.03$

Among the WRAP participants, those with and those without an APOE 4 allele are well-matched on demographic and lifestyle variables. The only significant difference between the ε4+ and ε4- groups is the frequency of exercise. This bodes well for future comparisons of genetic and lifestyle risk predictors of cognitive change. A number of initial differences emerged when WRAP partipants are compared to their controls. These included small but significant differences in age, education, percent female gender, and frequency of exercise. Steps have been taken to recruit additional well-matched controls, such as expanded recruitment outside of the Madison area.

Table 3. Baseline Neuropsychological Performance of WRAP Participants and Controls

Measure	WRAP ε4+ (N=266)	WRAP ε4- (N=327)	Controls (N=136)
Intellectual Performance (WASI)			
Verbal IQ estimate	111.34 (8.89)	111.25 (9.88)	115.88 (8.79)
Performance IQ estimate	111.80 (9.84)	112.09 (10.21)	111.67 (10.02)
Full-Scale IQ estimate	113.05 (8.66)	113.22 (9.59)	114.88 (9.68)
Learning and Memory			
AVLT learning total (sum of 5 trials)	51.50 (8.05)	51.39 (7.92)	52.34 (7.95)*
AVLT delayed recall	10.78 (2.81)	10.50 (3.00)	10.49 (2.70)
Face Recognition - immediate	38.18 (4.31)	37.53 (4.50)	38.53 (4.00)**
Face Recognition - delayed	39.14 (4.22)	39.31 (3.92)	39.02 (3.67)
Verbal Ability and Language			
Vocabulary (WASI)	65.38 (5.81)	65.25 (6.02)	67.13 (6.29)
Similarities (WASI)	38.46 (3.98)	38.40 (4.21)	39.26 (3.98)
WRAT3 Reading	50.48 (4.46)	51.03 (4.40)	51.60 (4.42)
Boston Naming Test (# spontaneously correct)	56.13 (2.74)	56.24 (3.14)	56.62 (2.69)
Verbal Fluency (COWA)	43.24 (10.64)	42.50 (11.00)	44.81 (11.65)
Visual Spatial Ability			
Block Design (WASI)	45.08 (11.14)	46.36 (11.91)	44.07(13.33)
Matrix Reasoning (WASI)	25.80 (3.67)	25.46 (3.43)	24.89 (31.90)
Judgment of Line Orientation	25.87 (3.73)	25.67 (3.76)	25.21 (4.19)
Clock Draw Test	9.62 (0.78)	9.43 (1.03)	9.44 (0.81)
Working Memory and Executive Function			
Working Memory Index Score (WAIS-III)	105.42 (13.01)	104.76 (12.99)	106.32 (10.51)
Stroop Color-Word (# items named)	111.34 (20.01)	110.98 (21.01)	106.74 (21.41)
Trail Making Test-B (seconds to complete)	62.16 (22.38)	61.41 (25.99)	64.41 (25.38)
Wisconsin Card Sort (total errors)	13.69 (7.07)	14.16 (7.64)	14.11 (7.51)

*Family history (WRAP) group vs. Controls significantly different, $p=0.006$
**Family history (WRAP) group vs. Controls significantly different, $p=0.009$

Analysis of neuropsychological data revealed generally similar findings in WRAP participants and their age-matched controls. The sole cognitive domain in which significant differences are detected was memory, specifically immediate memory for words and faces. However, the effect sizes of these differences are small. There were no differences between the WRAP ε4+ and ε4- groups on any cognitive outcome. Overall, testing indicates that WRAP APOE ε4 carriers are generally asymptomatic compared to APOE ε4 non-carriers and the control group. These data suggest that the baseline testing has occurred prior to the development of significant cognitive differences among groups.

SUB-STUDY RESULTS

Table 4. Cerebrospinal Fluid (CSF) Aß42 and Tau in APOE **ε**4 Carrier and Non-Carrier WRAP Participants

Characteristic	APOE ε4 Carrier (n=19)	APOE ε4 Non-Carrier (n=31)	P value
Genotypes	2,4 (n=1) 3,4 (n=17) 4,4 (n=1)	2,2 (n=1) 2,3 (n=4) 3,3 (n=26)	- - -
Women (n, %)	15 (79)	22 (71)	0.255
Age (years)	52.6 ± 6.9	54.0 ± 6.6	0.461
Education (years)	16.2 ± 2.2	16.8 ± 3.0	0.524
CSF AB42 (pg/mL)	713.9 ± 179.2	946.6 ± 251.0	0.001
CSF Tau (pg/mL)	431.2 ± 253.4	616.4 ± 284.9	0.024

These data indicate that WRAP ε4 carriers are already experiencing abnormal changes in CSF $Aß_{42}$ which may affect the pathobiology of the disease in the pre-clinical state. Additional analyses suggested that the effects may differ according to gender and vascular risk factors. Thus, understanding the influence and interaction of APOE allele, gender, and vascular risk factors in this cohort at increased risk of AD is critical in identifying potential targets for preventive therapies.

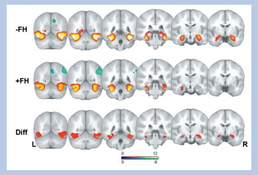

Figure 1. Statistical Parametric maps of the signal change to novel versus previously learned items in (TOP) the negative family history (-FH) group (n=64), and (MIDDLE) the positive family history (+FH) group (n=68). The BOTTOM row is the difference between –FH and +FH groups indicated greater activity in the mesial and ventral temporal lobe in the –FH group. The statistical maps are overlaid on the same atlas brain. Images are in radiological orientation; left is on right.

Individuals from WRAP were recruited for investigations; findings from two of these studies are presented here.

These results demonstrate a robust main effect of family history of AD on brain function. Further, by stratifying by risk groups as we have done, the findings help resolve the issue of whether ε4 carriers will exhibit compensatory activation. We show that only ε4 carriers without family history of AD exhibit greater activation, suggesting that some as yet unknown risk factor embodied by family history of AD is influencing the expression of ε4 on brain function. There were no significant gray matter differences in the medial temporal lobes that could account for the result. The results suggest that pre-clinical functional brain changes may be occurring in advance of frank structural or cognitive decline in the family history group. It remains to be determined whether baseline or rate of change in volume or activation can predict cognitive decline.

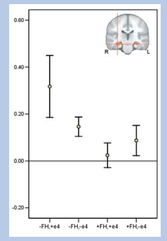

Figure 2. Plot of signal change in the right hippocampal region (at the crosshairs in the inlay) for each group. Error bars denote the 95% confidence interval. The signal in the hippocampal region is defined as the principle eigenvariate of a 2mm radius sphere at submaxima location 34, -22, -18.

CONCLUSIONS

The WRAP cohort is unique in that it represents a study population that is homogeneous for an important and rarely studied risk factor, *family history*. Indeed our data demonstrate that adult children with a confirmed parental history of AD are a high-risk group given the significantly elevated prevalence of APOE ε4, compared to Control subjects. Among our Family History participants, we find minimal baseline differences between adult children APOE ε4 carriers and non-carriers in demographic characteristics, lifestyle and cognitive function. The comparability of the groups suggests that the interpretation of any future cognitive changes observed between WRAP APOE ε4 carriers and non-carriers will not be confounded by baseline differences in these variables. Furthermore, baseline neuropsychological data reveal only minimal differences between WRAP participants and their controls, suggesting that WRAP subjects are asymptomatic. However, the preliminary data also suggest that this is an important at-risk cohort to study. Significant differences in underlying neurobiology, reflected in fMRI activation patterns and CSF $Aß_{42}$ and tau levels, may already be present in WRAP APOE ε4 carriers in the absence of identifiable cognitive differences.

Family history may prove to be an important confounder in studies of biomarkers in pre-clinical AD. The importance of family history is illustrated by findings from our fMRI sub-study. As reported in other studies, greater activation in the hippocampus is detected in ε4 carriers. However, this effect was present only among persons without a family history of AD. An interaction was detected in the hippocampus with the no family history ε4 carriers exhibiting the greatest signal changes and the family history ε4 carriers the least. These findings raise the possibility that an as yet unspecified factor embodied in family history is influencing the expression of ε4 on brain function and emphasize the importance of the proposed study.

The collection of stored plasma and serum samples as well as cerebrospinal fluid (CSF) will provide WRAP investigators with the opportunity to test hypotheses about the diagnostic or prognostic value of new and existing biological markers. The current inability to identify a specific etiology for AD suggests that the disease processes are complex and multi-factoral and that a single diagnostic or prognostic AD biomarker is unlikely to exist. It is much more likely that a combination of two or more biomarkers will prove to be a better predictor of risk than one alone and that the predictive power of any biomarker will be influenced by genetic, environmental and health factors. The WRAP study design and analyses are designed to evaluate this possibility.

Finally, these preliminary findings also demonstrate our ability to recruit and investigate a unique and highly motivated cohort of research participants. This is the largest existing cohort of adult children of persons with AD who has already undergone extensive baseline testing. The ongoing study will overcome the recognized limitations of cross-sectional findings by tracking changes over time in cognition and biomarkers for the disease.