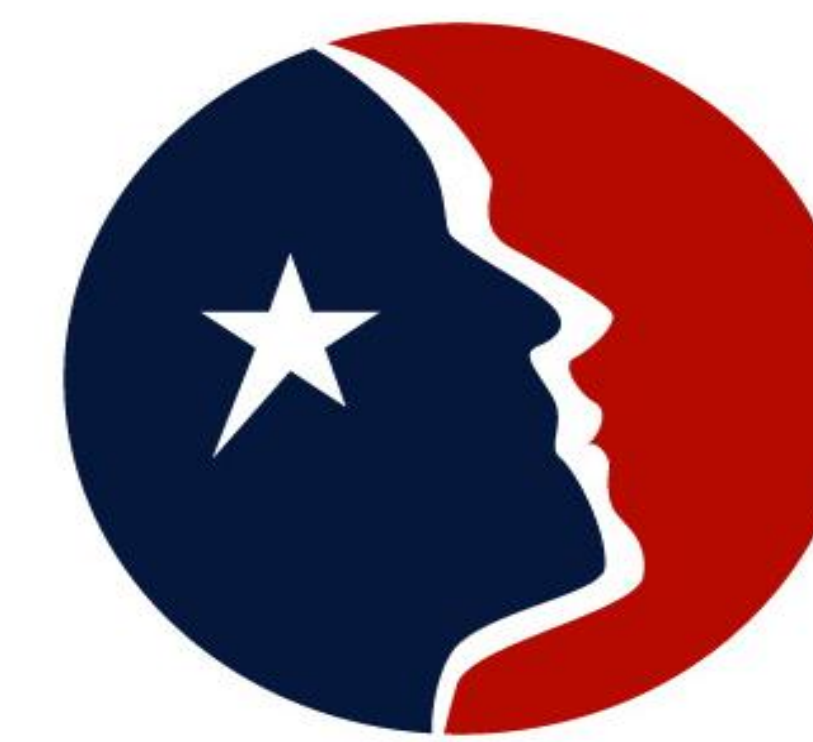




TEXAS ALZHEIMER'S  
RESEARCH CONSORTIUM

# AN INFLAMMATORY ENDOPHENOTYPE OF ALZHEIMER'S DISEASE

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## Background

Numerous reports have linked inflammation to cognitive dysfunction and/or decline as well as with the development of Alzheimer's disease.

The Honolulu-Aging Study & Honolulu-heart study found that CRP levels at midlife were associated with increased risk for the development of Alzheimer's disease, as well as Vascular Dementia 25-years later.

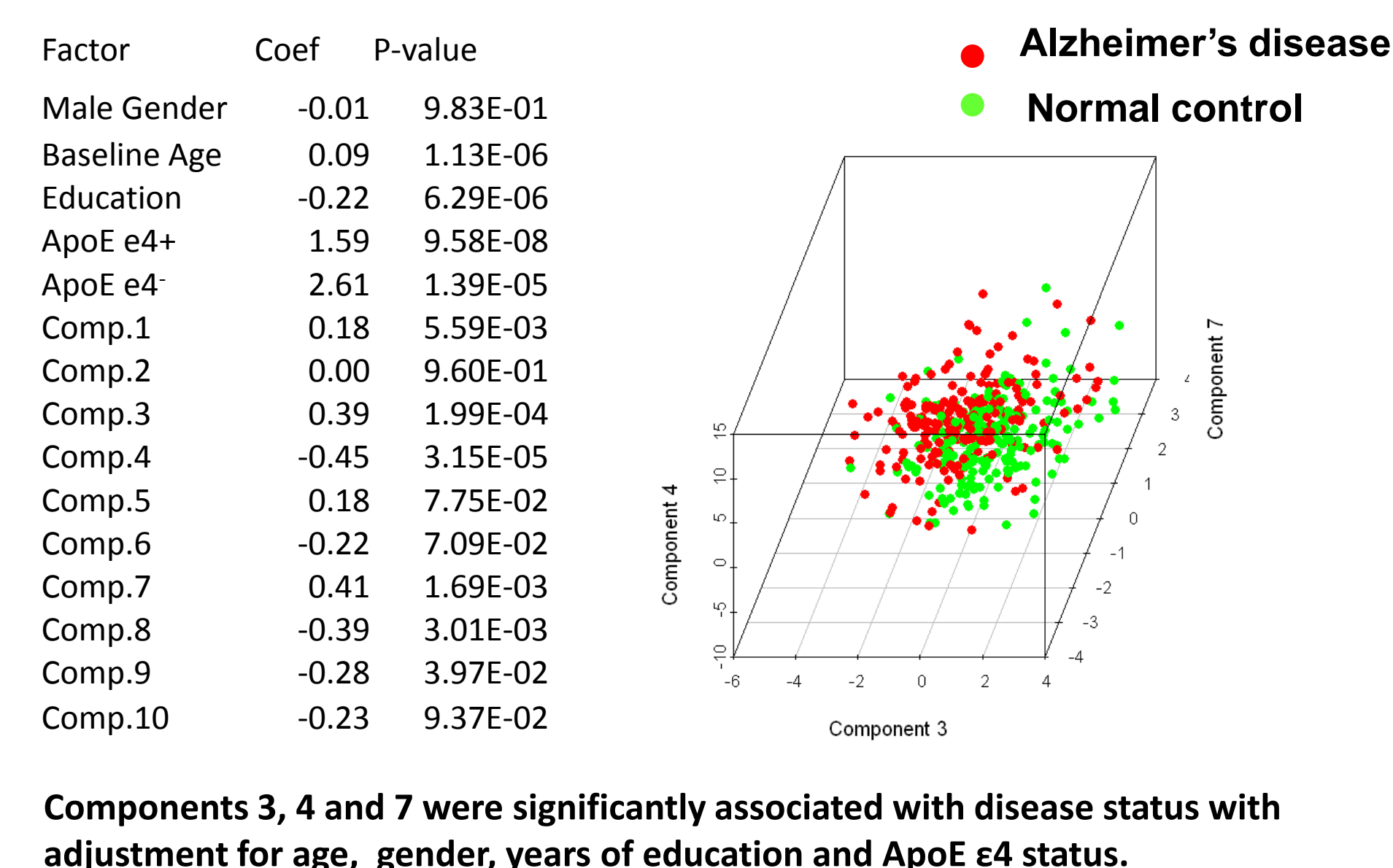
The Health, Aging, and Body Composition Study (Health ABC) found that serum IL-6 and CRP levels were associated with cognitive decline in a multi-ethnic sample of well-functioning elders.

There is evidence that inflammation is the mediator between cardiovascular risk factors (eg; metabolic syndrome, hypertension) and cognitive functioning.

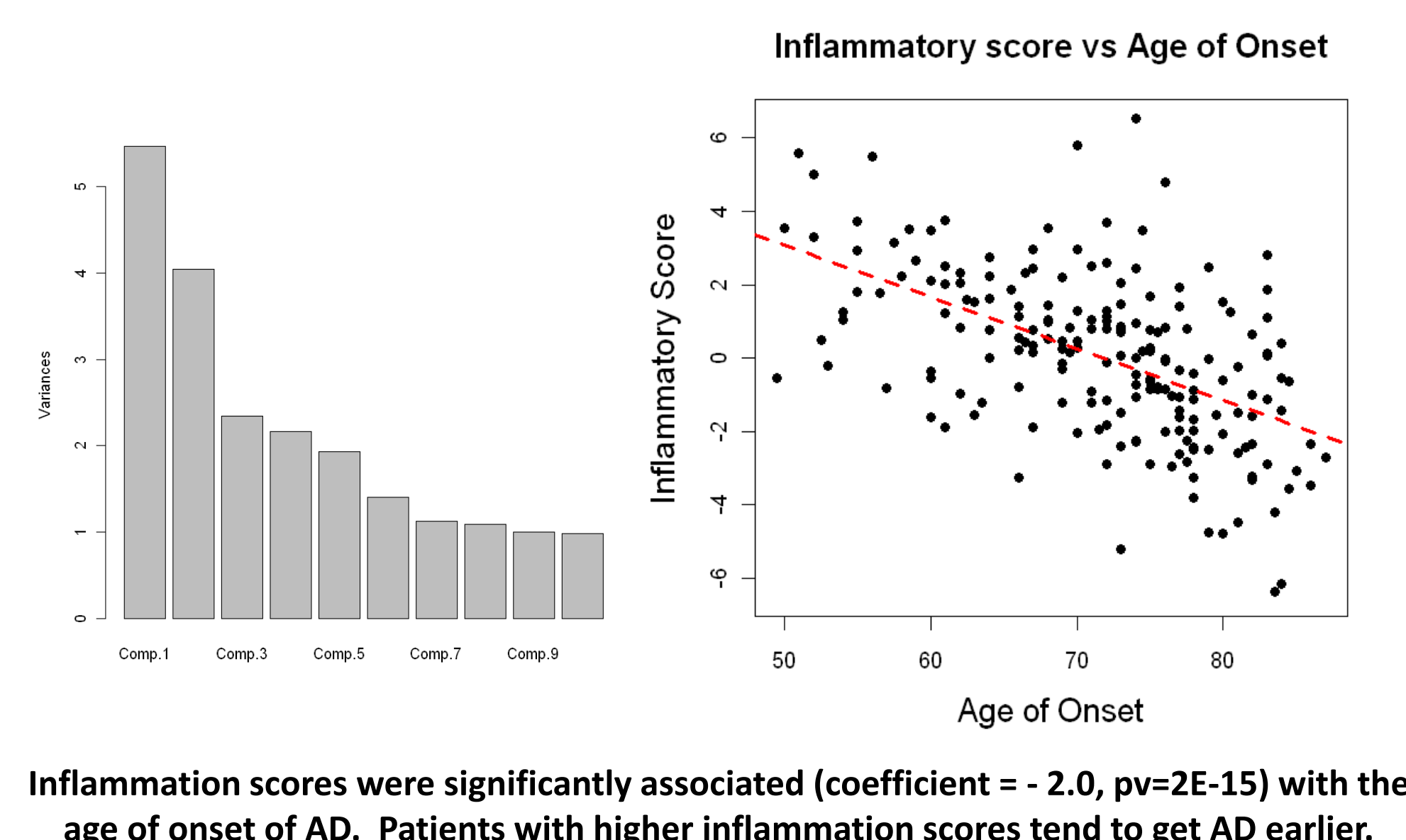
## Patient Demographics

	AD (N=197)	Control (N=203)	P-value
<b>Site</b>			
11	72 (73%)	27	<0.0001
25	34 (69%)	15	
51	58 (45%)	70	
61	33 (27%)	91	
<b>Gender (male)</b>	34.5%	32.0%	0.67
<b>Age (year)</b>			
Range	57.0 - 94.0	52.0 - 90.0	<0.0001
Median	79.0	70.0	
<b>Education (year)</b>			
Range	0-22	10-25	<0.0001
Median	14	16	
<b>APOE</b>			
Ex/Ex	71	147	<0.0001
Ex/E4	83	48	
E4/E4	27	5	
Unknown	16	3	
<b>Hispanic Ethnicity</b>	3.6%	5.4%	0.47
<b>Race</b>			
White	187	190	0.67
Non-White	10	13	

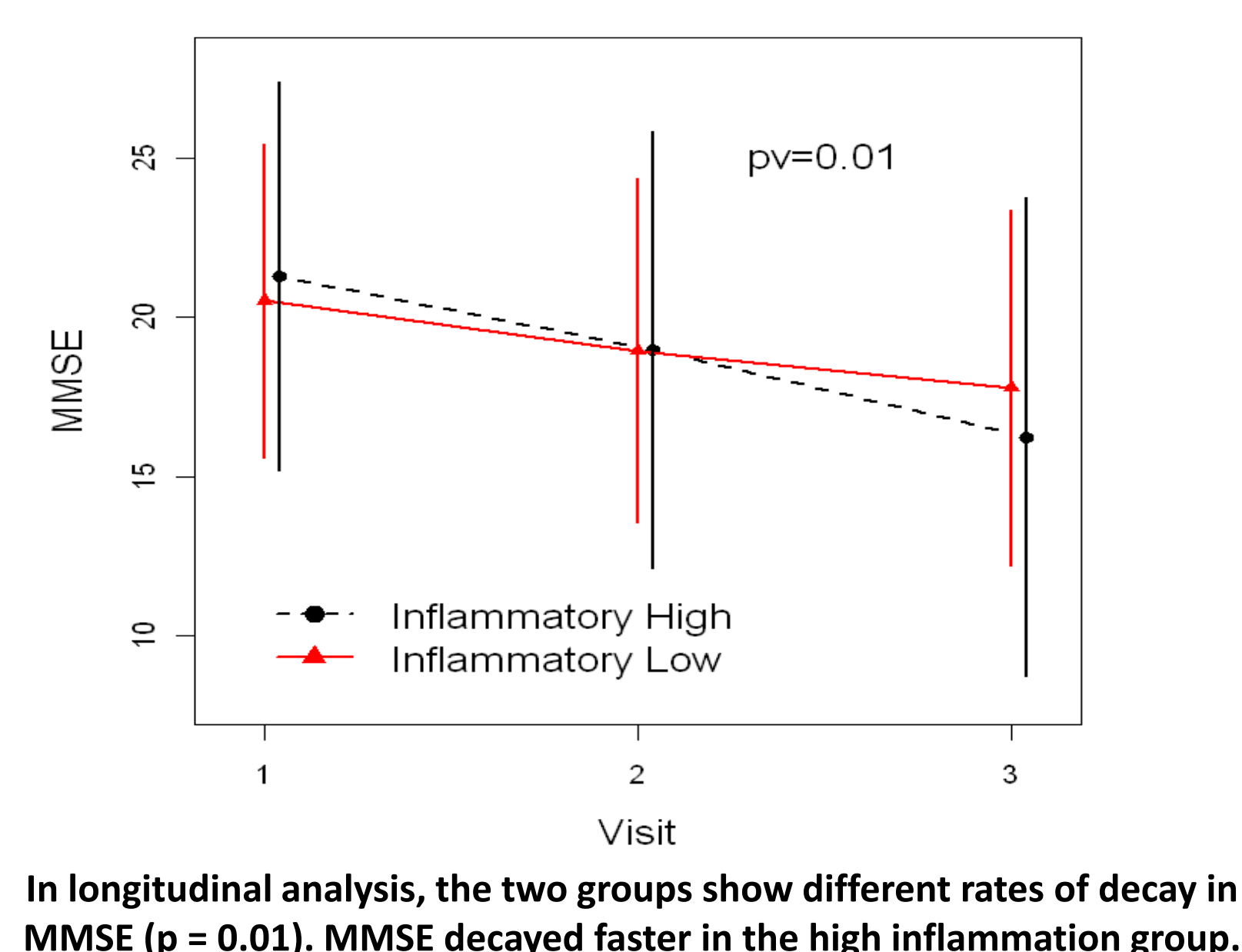
## Association between Inflammatory Endophenotype and Disease Status



## Association between Inflammatory Endophenotype and Age at Onset



## Association between Inflammatory Endophenotype and MMSE Decline



## Inflammatory Biomarker Panel

Alpha-1 Antitrypsin	ICAM1	RANTES
Alpha-2 Macroglobulin	IFN gamma	Stem Cell Factor
Beta-2 Microglobulin	IL 10	TIMP 1
BDNF	IL 12p40	TNF RII
C Reactive Protein	IL 15,	TNF-alpha
Complement 3	IL 1ra	TNF-beta
Eotaxin	IL 3	VCAM1
Factor VII	IL 5	VDBP
Ferritin	IL 7	VEGF
Fibrinogen	IL 8	von Willebrand Factor
GCSF	MCP-1	
Haptoglobin	MMP3	

## Methods

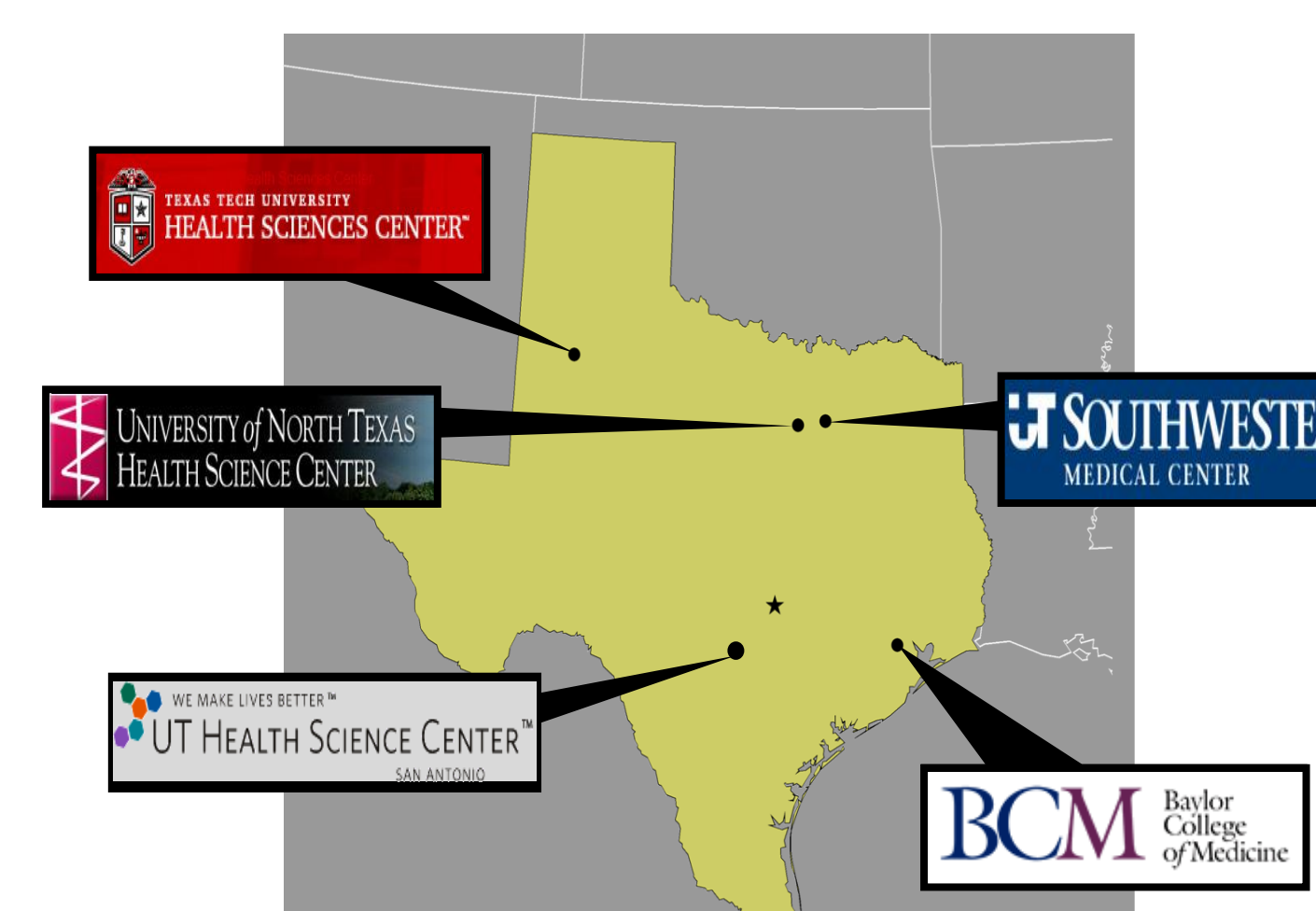
Subjects were enrolled through the Texas Alzheimer's Research Consortium, a longitudinal, multi-institutional study of Alzheimer's disease funded by the state of Texas. Details of the study have been published. Demographic data are presented in the Patient Demographics panel. Serum samples were isolated by standard protocols and submitted to Rules Based Medicine, Austin, Texas for multiplexed assessment of 34 inflammatory protein concentrations on a Luminex platform.

**ASSOCIATION WITH AGE AT ONSET:**  
Principal component analysis (PCA) of variation within the serum protein data was conducted. The association between principal component one (PCA1) among Alzheimer's patients and Age at Onset was tested using Pearson's Correlation Coefficient.

**ASSOCIATION WITH MINI MENTAL STATUS EXAM (MMSE):**  
Alzheimer's patients with an PCA1 score higher than the median for the group were defined as 'High Inflammation' all patients with inflammatory scores below the median were defined as 'Low Inflammation'. A mixed effects model was used to test for significant difference in MMSE decline between the two groups.

**ASSOCIATION WITH DISEASE STATUS:**  
Association between Alzheimer's disease status and each principal component was determined by the Mann Whitney U test and with adjustment using multivariate Logistic regression.

## The Texas Alzheimer's Research Consortium



## Results

Several inflammatory components were identified by PCA among Alzheimer's disease cases.

Components three, four, and seven were significantly associated with case status.

Component one was associated with significantly younger age of onset as well as accelerated decline of MMSE scores.

Component one was also significantly associated with poorer delayed visual and verbal memory.

## Discussion

These findings suggest that a pro-inflammatory endophenotype exists and is a powerful mediator of cognitive impairment.

This endophenotype offers preliminary evidence of one possible biological pathway for cognitive and functional decline among a subgroup of individuals with direct therapeutic implications.

Further research is needed to validate this endophenotype in other populations and to examine the biomarker composition and prevalence rates of the endophenotype across various ethnic groups.

Additional studies are underway with TARC data to identify other AD endophenotypes covering multiple biological pathways

## Acknowledgment<sup>§</sup>

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