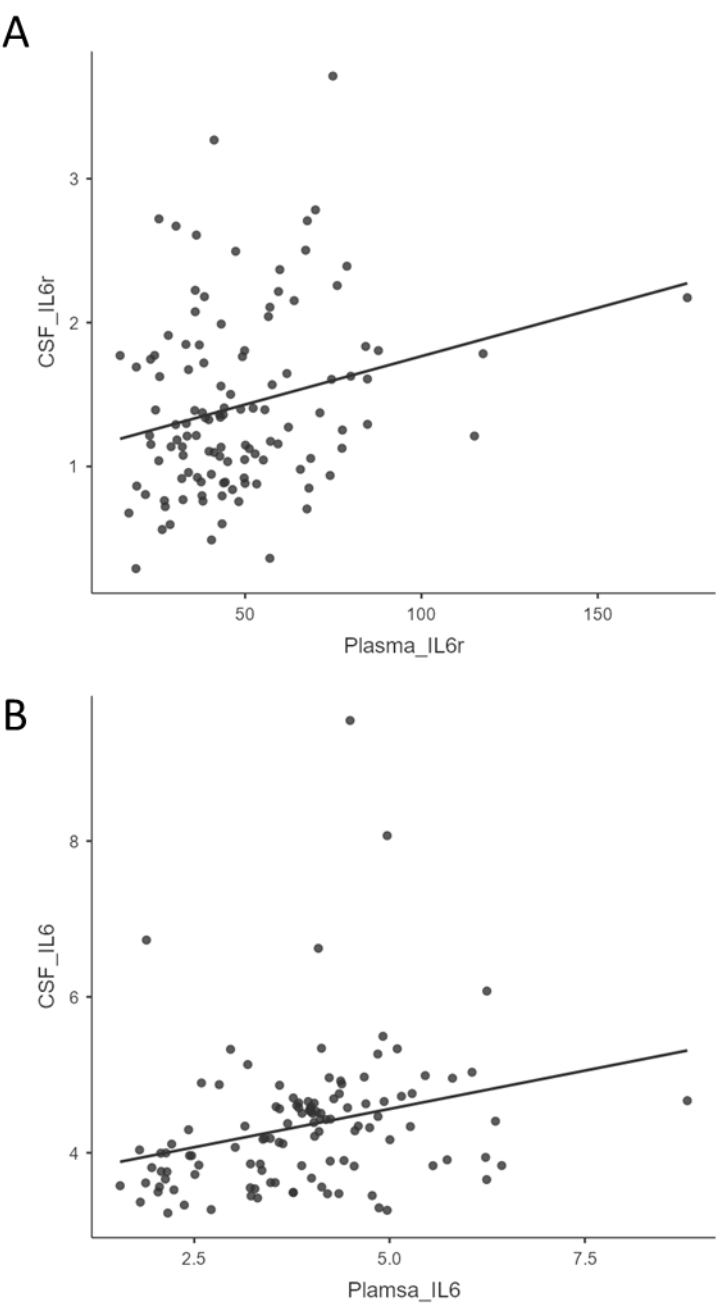


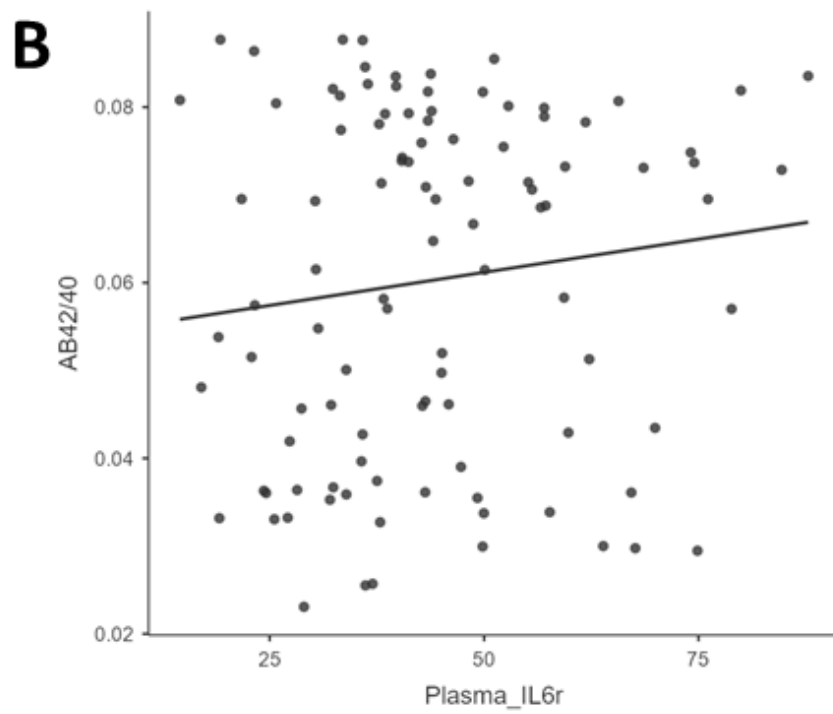
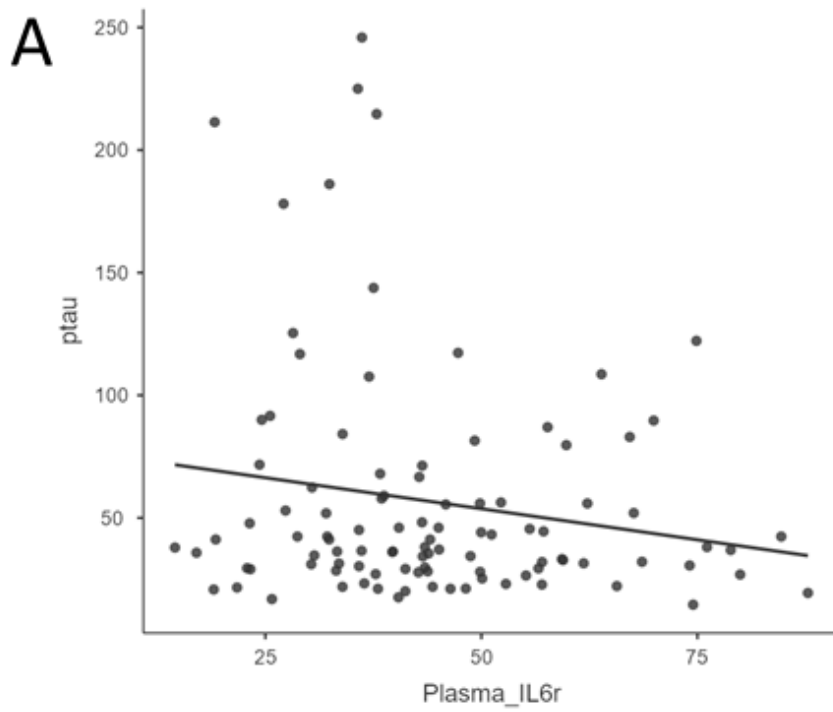
eFigure 1:



eFigure 1: CSF and Plasma IL6 and IL6r are significantly correlated

(A) Plasma sIL6R and CSF sIL6R are significantly positively correlated (n=118, R=.206, unadj p=.008). (B) Plasma IL6 and CSF IL6 are significantly correlated (n=118, R=.295, unadj p=.003). R and p values were determined via linear regression analysis.

eFigure 2



eFigure 2: There is no Significant Relationship Between Plasma sIL6R and AD Biomarkers.

(A) There is no significant relationship between plasma sIL6R and CSF pTau concentrations. (B)

There is no significant relationship between plasma sIL6R and CSF A β 42/40 concentration ratio.

eTable 1: ADRC Participant Demographics

	Participants donating plasma and CSF	Participants donating plasma only	p-value
Number of participants (% female)	118 (64%)	569 (76%)	0.645
Race			
African-American (number; %F)	11 (9%)	132 (76%)	0.002
Caucasian (number; %F)	107 (91%)	434 (23%)	
Age (years) mean $\pm$ SD (min-max; 95% confidence interval)	69.4 $\pm$ 7.7 (55-88; 68.0-70.8)	70.3 $\pm$ 8.3 (49-95; 69.6-71.0)	0.274
Education (years) mean $\pm$ SD (min-max; 95% confidence interval)	16.1 $\pm$ 2.3 (12-20; 15.6-16.5)	15.6 $\pm$ 2.5 (6-20; 15.4-15.8)	0.075
BMI mean $\pm$ SD (min-max; 95% confidence interval)	27.5 $\pm$ 5.0 (18.3-41.6; 26.6-28.4)	28.1 $\pm$ 5.9 (14.9-56.3; 27.6-28.6)	0.313
Cognitive Status (number of participants; % Total)			0.315
Normal	66 (44%)	267 (49%)	
impaired	52 (56%)	276 (51%)	
MOCA Z mean $\pm$ SD (min-max; 95% confidence interval)	0.3 $\pm$ 0.8 (-2.1-1.4; 0.2-0.5)	-0.1 $\pm$ 1.0 (-4.0-1.5; -0.2-0.0)	<0.001
Mpaac5 mean $\pm$ SD (min-max; 95% confidence interval)	-0.5 $\pm$ 1.3 (-4.8-1.7; -0.8,-0.3)	-0.9 $\pm$ 1.3 (-7.2-1.3; -1.0,-0.8)	0.009
Memory Domain mean $\pm$ SD (min-max; 95% confidence interval)	-0.3 $\pm$ -1.1 (-3.4-1.6; -0.5,-0.1)	-0.5 $\pm$ 1.1 (-4.5-2.1; -0.6,-0.4)	0.173

eTable 2: Biological Factors and Behavioral Scores

	total	AA	C* genotype group	p-value adj p- value
Plasma IL-6R (ug/ml) mean $\pm$ SD (number of samples) (min-max; 95% confidence interval)	48.3 $\pm$ 22.7 (n=116) (14.5- 175.4; 43.7- 52.0)	35.1 $\pm$ 11.5 (n=42) (17.0- 74.1; 31.6, 38.6)	55.6 $\pm$ 24.2 (n=74) (14.5- 175.4; 49.5,61.3)	<0.001 < 0.001
CSF IL-6R (ug/ml) mean $\pm$ SD (number of samples) (min-max; 95% confidence interval)	1.4 $\pm$ 0.6 (n=116) (0.3- 3.7; 1.3-1.5)	1.2 $\pm$ 0.5 (n=42) (0.3- 2.7; 1.0-1.4)	1.6 $\pm$ 0.6 (n=74) (0.5-3.7; 1.4- 1.7)	0.002 0.019
Plasma IL-6 (ug/ml) mean $\pm$ SD (number of samples) (min-max; 95% confidence interval)	3.9 $\pm$ 1.2 (n=118) (1.6- 8.8; 3.7-4.1)	3.9 $\pm$ 1.5 (n=44) (1.6- 8.8; 3.5-4.3)	3.9 $\pm$ 1.1 (n=74) (1.8-6.4; 3.6- 4.1)	0.988 0.372
CSF IL-6 (ug/ml) mean $\pm$ SD (number of samples) (min-max; 95% confidence interval)	4.3 $\pm$ 0.9 (n=113) (3.2- 9.5; 4.2-4.5)	4.3 $\pm$ 0.9 (n=46) (3.2- 8.1; 4.0-4.6)	4.4 $\pm$ 0.9 (n=69) (3.3-9.5;4.1- 4.6)	0.687 0.535
CSF Ab42/40 ratio mean $\pm$ SD (number of samples) (min-max; 95% confidence interval)	0.06 $\pm$ 0.02 (n=102) (0.023-0.088; 0.056-0.064)	0.06 $\pm$ 0.02 (n=41) (0.023- 0.088; 0.052- 0.065)	0.06 $\pm$ 0.02 (n=61) (0.026- 0.088; 0.056- 0.065)	0.608 0.568
CSF phospho-Tau ^{T181} mean $\pm$ SD (number of samples) (min-max; 95% confidence interval)	56.8 $\pm$ 47.1 (n=102) (14.6- 245.9; (47.7- 66.0)	56.8 $\pm$ 46.0 (n=41) (16.9- 211.4; 42.5- 71.2)	56.8 $\pm$ 48.1 (n=61) (14.6- 245.9; 44.6- 69.1)	0.997 0.474
MOCA Z mean $\pm$ SD (number of samples) (min-max; 95% confidence interval)	0.3 $\pm$ 0.8 (n=116) (-2.1- 1.4;0.2-0.5)	0.4 $\pm$ 0.8 (n= 44) (-2.1-1.4; 0.2-0.7)	0.3 $\pm$ 0.7 (n=72) (-1.9-1.4; 0.1- 0.5)	0.490 0.215
Mpacc5 mean $\pm$ SD (number of samples) (min-max; 95% confidence interval)	-0.5 $\pm$ 1.3 (n= 114) (-4.8-1.7; -0.8,-0.3)	-0.3 $\pm$ 1.3 (n=44) (-4.8- 1.7; 1.7, -0.7)	-0.7 $\pm$ 1.3 (n=70) (-4.5- 1.3; -1.0, -0.4	0.144 0.098
Memory Domain mean $\pm$ SD (number of samples) (min-max; 95% confidence interval)	-0.3 $\pm$ 1.1 (n=116) (-3.4- 1.6; -0.5, -0.1)	0.1 $\pm$ 1.0 (n=44) (-3.0- 1.5; -0.2, 0.4)	-0.6 $\pm$ 1.1 (n=72) (-3.4- 1.6; -0.8, -0.3	0.001 0.013

Adjusted: adjusted for sex, race, age, education, BMI, tobacco use, and alcohol use.

eTable 3: Regression Analysis

eTable 3. Predictors of Plasma sIL6r and CSF sIL6r							
	Plasma sIL6r						
		Model 1		Model 2		Model 3	
	N	B (SE)	P-value	B (SE)	P-value	B (SE)	P-value
MOCA Z	114	-0.0048 (0.0031)	0.126	-0.0042 (0.0026)	0.114	-0.0040 (0.0026)	0.123
Mpacc5	112	-0.0096 (0.0053)	0.072	-0.0072 (0.0045)	0.113	-0.0071 (0.0044)	0.114
Memory domain	114	-0.0104 (0.0044)	0.022	-0.0089 (0.0041)	0.034	-0.0094 (0.0040)	0.02
pTau	102	-0.5061 (0.2886)	0.083	-0.4190 (0.2786)	0.136	-0.3340 (0.2804)	0.237
AB42/40	102	0.0002 (0.0001)	0.211	0.0001 (0.0001)	0.597	0.0000 (0.0001)	0.787
Executive domain	115	-0.0009 (0.0034)	0.789	-0.0010 (0.0034)	0.761	-0.0011 (0.0033)	0.741
Language and phonemic domain	114	-0.0035 (0.0027)	0.199	-0.0033 (0.0028)	0.241	-0.0032 (0.0029)	0.271
Attention domain	115	-0.0015 (0.0032)	0.646	-0.0022 (0.0033)	0.499	-0.0026 (0.0033)	0.435
Visuospatial domain	115	-0.0008 (0.0042)	0.84	0.0007 (0.0042)	0.868	-0.0006 (0.0041)	0.892
	CSF sIL6r						
		Model 1		Model 2		Model 3	
	N	B (SE)	P-value	B (SE)	P-value	B (SE)	P-value
MOCA Z	114	-0.2572 (0.1162)	0.029	-0.2472 (0.0999)	0.015	-0.2294 (0.1002)	0.024
Mpacc5	112	-0.3900 (0.2112)	0.067	-0.2301 (0.1882)	0.224	-0.2088 (0.1860)	0.264
Memory domain	114	-0.4687 (0.1610)	0.004	-0.3601 (0.1570)	0.024	-0.3205 (0.1522)	0.038
pTau	103	19.4787 (7.1137)	0.007	13.4493 (7.0333)	0.059	12.2920 (7.0358)	0.084
AB42/40	103	-0.0081 (0.0030)	0.007	-0.0060 (0.0026)	0.026	-0.0052 (0.0026)	0.05
Executive domain	115	0.0044 (0.1257)	0.972	0.0316 (0.1310)	0.81	0.0299 (0.1295)	0.818
Language and phonemic domain	114	-0.0934 (0.1025)	0.364	-0.0656 (0.1106)	0.555	-0.0739 (0.1121)	0.511
Attention domain	115	-0.0787 (0.1165)	0.501	-0.0831 (0.1247)	0.506	-0.0770 (0.1246)	0.538
Visuospatial domain	115	-0.0908 (0.1523)	0.552	-0.0722 (0.1616)	0.656	-0.0773 (0.1572)	0.624

Model 1: unadjusted

Model 2: adjusted for sex, race, age, education.

Model 3: adjusted for sex, race, age, education, BMI, tobacco use, and alcohol use.

eTable 4: APOE Interaction Analysis

eTable 4. IL6 and Cognitive Score - Interaction P-values										
		Genotype X Cognitive Status			Genotype X APOE			Cognitive Status X APOE		
IL6	N	Model 1	Model 2	Model 3	Model 1	Model 4	Model 5	Model 1	Model 4	Model 5
Plasma sIL6r ug/ul	115	0.125	0.095	0.069	0.320	0.159	0.118	0.925	0.882	0.988
CSF sIL6r ug/ul	115	0.896	0.825	0.817	0.558	0.482	0.517	0.856	0.647	0.543
Plasma IL6 pg/ul	117	0.132	0.138	0.129	0.146	0.335	0.286	0.487	0.397	0.670
CSF IL6 pg/ul	112	0.594	0.401	0.330	0.586	0.807	0.810	0.159	0.138	0.116
MOCA Z	115	0.975	0.462	0.505	0.095	0.505	0.488	0.737	0.816	0.996
Mpacc5	113	0.730	0.822	0.749	0.385	0.989	0.852	0.074	0.083	0.101
Memory domain	116	0.354	0.575	0.724	0.910	0.821	0.791	0.035	0.021	0.061

Model 1: unadjusted

Model 2: adjusted for sex, race, age, education, and APOE.

Model 3: adjusted for sex, race, age, education, APOE, BMI, tobacco use, and alcohol use.

Model 4: adjusted for sex, race, age, and education.

Model 5: adjusted for sex, race, age, education, BMI, tobacco use, and alcohol use.