

## *Supplementary Material*

### **1 Supplementary Figures and Tables**

#### **1.1 Supplemental Tables**

**Table S1. Ethics committees approving clinical study.**

Ethics committees approving clinical study

Principal Investigator	IRB/Ethic Committee	Reference number
Dr Albert Ludolph	Ethikkommission der Universität Ulm	412/16
Dr Siegfried Muhlack	Ethik-Kommission der Ruhr-Universität Bochum	16-5929
Dr Catherine Mummery	London-Central Research Ethics Committee Manchester HRA Centre	17/LO/0440
Dr Simon Ducharme	MUHC Neurosciences Research Ethics Board	2017-3206
Dr Juha Rinne	National Committee on Medical Research Ethics	73/06.00.01/2017
Dr Ralf Bodenschatz	Ethikkommission der Sächsischen Landesärztekammer	EK-AMG-MCB-155/16-1
Dr Peter Paul de Deyn	Central Committee on Research Involving Human Subjects	NL60032.000.16
Dr Anne Borjesson Hansen	Regionala etikprövningsnämnden i Stockholm Karolinska Institutet i Solna	2017/300-31
Dr Michael Jonsson	Regionala etikprövningsnämnden i Stockholm Karolinska Institutet i Solna	2017/300-31
Dr Daniel Blackburn	London-Central Research Ethics Committee Manchester HRA Centre	17/LO/0440
Dr Anja Schneider	Ethikkommission an der Medizinischen Fakultät der Rheinischen Friedrich-Wilhelms-Universität Bonn	035/18-AMG
Dr Phillipus Scheltens	Central Committee on Research Involving Human Subjects	NL60032.000.16

**Table S2. Description of CSF biomarkers of AD pathology, glial activation, neuroaxonal damage, and synaptic injury.**

<b>CSF analyte</b>	<b>Biology indexed</b>
<b>A<math>\beta</math><sub>42</sub></b> ( $\beta$ -amyloid 1-42) Elecsys $\beta$ -amyloid 1-42 CSF performed at Roche Diagnostics, Indianapolis, IN	Parenchymal amyloid accumulation
<b>p-tau<sub>181</sub></b> (tau phosphorylated at threonine 181) Elecsys Phospho-Tau (181P) CSF performed at Roche Diagnostics, Indianapolis, IN	Tau pathophysiology. CSF p-tau <sub>181</sub> may reflect a mix of amyloid and tau pathological changes in the brain and is, therefore, not a “pure” marker of tau tangle load in the brain.
<b>NfL*</b> (neurofilament light chain) Uman, performed at Immunologix, Tampa, FL	Neuroaxonal degeneration
<b>Ng*</b> (neurogranin) Euroimmune, performed at Immunologix, Tampa, FL)	Postsynaptic injury
<b>YKL-40*</b> (chitinase-3-like protein 1) ELLA (Protein Simple), performed at Immunologix, Tampa, FL)	Putative master regulator of microglial and astrocyte activation. YKL-40 is a context-dependent modulator of glial phagocytic activity in both mice and humans. The associations of this biomarker with transcriptional, morphological, and functional states of glia are not clear and clarity may require large multi-omic datasets and machine learning.

\*All CSF samples for NfL, Ng, and YKL-40 were tested using a single batch of reagents.

**Table S3. Mild AD phenotype across APOE4 allele frequency groups.**

Variable			2 APOEε4 (N = 10)	1 APOEε4 (N = 23)	No APOEε4 (N = 12)	1 or 2 APOEε4 (N = 33)	Overall (N=45)
Sex	Female	N	6	12	4	18	22
		(%)	(60.0%)	(52.2%)	(33.3%)	(54.5%)	(48.9%)
	Male	N	4	11	8	15	23
		(%)	(40.0%)	(47.8%)	(66.7%)	(45.5%)	(51.1%)
Onset of AD	Age-at-diagnosis (yrs)	Mean	64.2	65.2	63.3	64.9	64.5
		(SD, SEM)	(5.4, 1.7)	(5.8, 1.2)	(7.4, 2.1)	(5.6, 1.0)	(6.1, 0.9)
		Median	63.0	66.3	62.7	65.8	65.4
		(P25, P75)	(61.0, 67.8)	(63.1, 69.1)	(58.5, 69.3)	(62.7, 68.4)	(61.3, 69.1)
		(Min, Max)	(54.8, 72.8)	(49.04, 72.4)	(47.99, 74.1)	(49.04, 72.8)	(48.0, 74.1)
	Age-at-baseline (yrs)	Mean	65.4	66.6	64.6	66.2	65.8
		(SD, SEM)	(5.4, 1.7)	(5.6, 1.2)	(6.5, 1.9)	(5.5, 1.0)	(5.8, 0.9)
		Median	65.0	67.0	66.0	67.0	67.0
		(P25, P75)	(63.0, 68.0)	(63.0, 71.0)	(59.5, 70.0)	(63.0, 70.0)	(63.0, 70.0)
		(Min, Max)	(55.0, 73.0)	(50.0, 74.0)	(52.0, 74.0)	(50.0, 74.0)	(50.0, 74.0)
Concomitant Medications	AChE-I	N	7	13	8	20	28
		(%)	(70%)	(56.5%)	(66.7%)	(60.6%)	(62.2%)
Neuroimaging	Hippocampal vol., % of ICV	Mean	0.24	0.25	0.28	0.25	0.26
		(SD, SEM)	(0.04, 0.01)	(0.04, 0.01)	(0.03, 0.01)	(0.04, 0.01)	(0.04, 0.01)
		Median	0.24	0.25	0.29	0.24	0.26
		(P25, P75)	(0.23, 0.27)	(0.21, 0.27)	(0.27, 0.30)	(0.22, 0.27)	(0.23, 0.28)
		(Min, Max)	(0.18, 0.29)	(0.17, 0.34)	(0.22, 0.32)	(0.17, 0.34)	(0.17, 0.34)
	Ventricular vol., % of ICV	Mean	1.84	3.26	2.66	2.83	2.78
		(SD, SEM)	(0.53, 0.17)	(1.32, 0.28)	(1.08, 0.31)	(1.31, 0.23)	(1.25, 0.19)
		Median	1.81	2.98	2.49	2.65	2.65
		(P25, P75)	(1.36, 2.23)	(2.07, 4.34)	(1.92, 3.29)	(1.94, 3.86)	(1.93, 3.49)

Variable		2 <i>APOEε4</i> (N = 10)	1 <i>APOEε4</i> (N = 23)	No <i>APOEε4</i> (N = 12)	1 or 2 <i>APOEε4</i> (N = 33)	Overall (N=45)
		(Min, Max)	(1.12, 2.65)	(1.02, 6.20)	(1.07, 5.11)	(1.02, 6.20)
CSF Markers	Aβ <sub>42</sub> , pg/mL	Mean	580.7	700.2	799.2	700.0
		(SD, SEM)	(109.6, 34.7)	(188.0, 39.2)	(179.6, 51.9)	(184.7, 27.5)
		Median	587.5	687.1	823.3	664.7
		(P25, P75)	(479.8, 661.5)	(582.7, 849.7)	(638.0, 900.1)	(582.7, 845.8)
		(Min, Max)	(428.5, 767.3)	(340.4, 1059.5)	(568.3, 1126.0)	(340.4, 1126.0)
	p-tau <sub>181</sub> , pg/mL	Mean	35.18	41.05	41.27	39.80
		(SD, SEM)	(9.31, 2.94)	(15.24, 3.18)	(13.79, 3.98)	(13.70, 2.04)
		Median	32.96	39.36	38.45	36.07
		(P25, P75)	(31.04, 36.07)	(28.28, 53.22)	(30.01, 51.29)	(30.87, 48.31)
		(Min, Max)	(19.71, 52.59)	(20.55, 81.28)	(23.03, 69.12)	(19.71, 81.28)
	NfL, pg/mL	Mean	1038.51	1383.13	1398.91	1278.70
		(SD, SEM)	(319.07, 100.90)	(438.08, 91.35)	(296.26, 85.52)	(431.79, 75.17)
		Median	1074.33	1395.08	1358.55	1296.26
		(P25, P75)	(737.72, 1167.61)	(1091.94, 1572.58)	(1178.45, 1615.49)	(1042.67, 1540.23)
		(Min, Max)	(630.83, 1718.68)	(580.97, 2391.81)	(999.92, 1992.84)	(580.97, 2391.81)
	Ng, pg/mL	Mean	481.62	546.25	525.67	526.66
		(SD, SEM)	(119.604, 37.82)	(270.94, 56.50)	(235.10, 67.87)	(235.38, 40.97)
		Median	472.20	479.52	460.33	474.23
		(P25, P75)	(369.62, 538.99)	(307.056, 684.49)	(338.81, 696.19)	(369.62, 582.30)
		(Min, Max)	(332.57, 738.87)	(194.62, 1306.92)	(237.78, 1013.23)	(194.62, 1306.92)
	YKL-40, ng/mL	Mean	201.54	267.09	317.58	247.23
		(SD, SEM)	(63.83, 201.86)	(114.89, 239.57)	(161.89, 467.34)	(105.63, 18.39)
		Median	223.08	252.31	256.48	235.44
		(P25, P75)	(145.79, 242.01)	(197.20, 321.40)	(204.27, 433.66)	(189.72, 294.80)
		(Min, Max)	(98.75, 294.80)	(125.21, 598.33)	(131.16, 662.67)	(98.75, 598.33)

Variable			2 <i>APOEε4</i>	1 <i>APOEε4</i>	No <i>APOEε4</i>	1 or 2 <i>APOEε4</i>	Overall
			(N = 10)	(N = 23)	(N = 12)	(N = 33)	(N=45)
Cognition	MMSE Total (0-30)	Mean	24.4	23.3	23.7	23.6	23.6
		(SD, SEM)	(2.1, 0.7)	(2.3, 0.5)	(2.2, 0.6)	(2.3, 0.4)	(2.3, 0.3)
		Median	24.5	23.0	23.5	24.0	24.0
		(P25, P75)	(23.0, 26.0)	(21.0, 25.0)	(21.5, 26.0)	(22.0, 26.0)	(22.0, 26.0)
		(Min, Max)	(21.0, 27.0)	(20.0, 27.0)	(21.0, 26.0)	(20.0, 27.0)	(20.0, 27.0)
	MMSE Memory (0-6)	Mean	4.1	4.0	4.6	4.1	4.2
		(SD, SEM)	(1.0, 0.3)	(1.1, 0.2)	(1.2, 0.4)	(1.1, 0.2)	(1.1, 0.2)
		Median	4.0	4.0	4.5	4.0	4.0
		(P25, P75)	(3.0, 5.0)	(3.0, 4.0)	(3.5, 6.0)	(3.0, 4.0)	(3.0, 5.0)
		(Min, Max)	(3.0, 6.0)	(2.0, 6.0)	(3.0, 6.0)	(2.0, 6.0)	(2.0, 6.0)
	MMSE Visual Construction (0-1)	Mean	0.8	0.7	0.5	0.7	0.6
		(SD, SEM)	(0.4, 0.1)	(0.5, 0.1)	(0.5, 0.2)	(0.5, 0.1)	(0.5, 0.1)
		Median	1.0	1.0	0.5	1.0	1.0
		(P25, P75)	(1.0, 1.0)	(0.0, 1.0)	(0.0, 1.0)	(0.0, 1.0)	(0.0, 1.0)
		(Min, Max)	(0.0, 1.0)	(0.0, 1.0)	(0.0, 1.0)	(0.0, 1.0)	(0.0, 1.0)
	RBANS Total (40-160)	Mean	73.4	64.0	68.5	66.8	67.3
		(SD, SEM)	(10.5, 3.3)	(11.2, 2.3)	(12.3, 3.5)	(11.7, 2.0)	(11.7, 1.7)
		Median	78.0	61.0	67.5	66.0	67.0
		(P25, P75)	(61.0, 80.0)	(54.0, 73.0)	(61.5, 78.5)	(57.0, 77.0)	(57.0, 77.0)
		(Min, Max)	(57.0, 85.0)	(49.0, 88.0)	(49.0, 90.0)	(49.0, 88.0)	(49.0, 90.0)
	RBANS Delayed Memory (40-154)	Mean	52.8	48.0	66.3	49.5	53.9
		(SD, SEM)	(12.5, 3.9)	(7.4, 1.6)	(22.5, 6.5)	(9.3, 1.6)	(15.7, 2.3)
		Median	50.0	48.0	60.0	48.0	48.0
		(P25, P75)	(44.0, 56.0)	(44.0, 48.0)	(48.0, 91.5)	(44.0, 52.0)	(44.0, 56.0)
		(Min, Max)	(40.0, 84.0)	(40.0, 68.0)	(40.0, 102.0)	(40.0, 84.0)	(40.0, 102.0)
		Mean	100.8	81.1	79.9	87.1	85.2

Variable		2 <i>APOEε4</i> (N = 10)	1 <i>APOEε4</i> (N = 23)	No <i>APOEε4</i> (N = 12)	1 or 2 <i>APOEε4</i> (N = 33)	Overall (N=45)
RBANS Visuospatial/ Constructional (40-154)	(SD, SEM)	(20.0, 6.3)	(19.8, 4.1)	(21.7, 6.3)	(21.6, 3.8)	(21.6, 3.2)
	Median	102.5	78.0	79.5	84.0	81.0
	(P25, P75)	(84.0, 121.0)	(64.0, 105.0)	(61.0, 99.0)	(69.0, 105.0)	(64.0, 105.0)
	(Min, Max)	(60.0, 121.0)	(50.0, 126.0)	(50.0, 116.0)	(50.0, 126.0)	(50.0, 126.0)

ICV, intracranial volume; MMSE, Mini-Mental Status Examination; RBANS, Repeatable Battery for the Assessment of Neuropsychological Status; SD, standard deviation; SEM, standard error of the mean.

**Table S4. Mild AD phenotype in APOE4 carriers by APOE4 allele frequency and sex.**

			Male			Female		
			2 APOEε4	1 APOEε4	No APOEε4	2 APOEε4	1 APOEε4	No APOEε4
			(n = 4)	(n = 11)	(n = 8)	(n = 6)	(n = 12)	(n = 4)
Onset of AD	Age-at-diagnosis (yrs)	Mean	64.4	65.5	59.7	64.0	65.0	70.4
		(SD, SEM)	(5.7, 2.9)	(5.1, 1.5)	(6.1, 2.2)	(5.7, 2.3)	(6.6, 1.90)	(3.2, 1.6)
		Median	62.2	66.3	60.2	64.0	66.1	70.4
		(P25, P75)	(60.7, 68.1)	(63.1, 67.9)	(57.3, 62.7)	(61.9, 67.8)	(63.4, 69.7)	(68.0, 72.8)
		(Min, Max)	(60.5, 72.8)	(54.6, 72.4)	(48.0, 69.2)	(54.8, 71.4)	(49.0, 72.1)	(66.6, 74.1)
	Age-at-baseline (yrs)	Mean	66.5	67.4	61.5	64.7	65.9	70.8
		(SD, SEM)	(4.8, 2.4)	(4.7, 1.4)	(5.5, 1.9)	(6.0, 2.5)	(6.5, 1.9)	(3.4, 1.7)
		Median	65.5	67.0	61.0	64.5	67.5	71.5
		(P25, P75)	(63.0, 70.0)	(63.0, 71.0)	(58.5, 66.0)	(63.0, 68.0)	(63.0, 70.5)	(68.5, 73.0)
		(Min, Max)	(62.0, 73.0)	(59.0, 74.0)	(52.0, 69.0)	(55.0, 73.0)	(50.0, 73.0)	(66.0, 74.0)
Concomitant Medications	AChE-I	N	3	6	4	4	7	4
		(%)	(75.0%)	(54.5%)	(50.0%)	(66.7%)	(58.3%)	(100.0%)
Neuroimaging	Hippocampal vol., % of ICV	Mean	0.22	0.24	0.27	0.26	0.25	0.30
		(SD, SEM)	(0.03, 0.01)	(0.05, 0.01)	(0.03, 0.01)	(0.03, 0.01)	(0.03, 0.01)	(0.02, 0.01)
		Median	0.23	0.24	0.28	0.27	0.26	0.30
		(P25, P75)	(0.21, 0.23)	(0.19, 0.27)	(0.26, 0.29)	(0.24, 0.29)	(0.23, 0.27)	(0.29, 0.32)
		(Min, Max)	(0.18, 0.23)	(0.17, 0.34)	(0.22, 0.30)	(0.21, 0.29)	(0.20, 0.33)	(0.28, 0.32)
	Ventricular vol., % of ICV	Mean	1.97	3.53	2.97	1.75	3.01	2.05
		(SD, SEM)	(0.28, 0.14)	(1.48, 0.45)	(1.11, 0.39)	(0.66, 0.27)	(1.17, 0.34)	(0.82, 0.41)
		Median	2.04	3.45	3.07	1.49	2.89	2.02
		(P25, P75)	(1.78, 2.16)	(2.09, 4.90)	(1.96, 3.40)	(1.23, 2.50)	(2.00, 3.86)	(1.50, 2.59)
		(Min, Max)	(1.57, 2.23)	(1.47, 6.20)	(1.75, 5.11)	(1.12, 2.65)	(1.02, 5.02)	(1.07, 3.06)
CSF Markers	Aβ42, pg/mL	Mean	582.1	699.5	775.7	579.7	700.8	846.3

		Male			Female		
		2 APOEε4 (n = 4)	1 APOEε4 (n = 11)	No APOEε4 (n = 8)	2 APOEε4 (n = 6)	1 APOEε4 (n = 12)	No APOEε4 (n = 4)
p-tau <sub>181</sub> , pg/mL	(SD, SEM)	(139.2, 69.6)	(209.6, 63.2)	(188.9, 66.8)	(100.0, 40.8)	(175.3, 50.6)	(174.9, 87.4)
	Median	545.4	661.6	757.5	606.1	688.0	859.0
	(P25, P75)	(475.0, 689.2)	(491.4, 890.4)	(622.9, 875.3)	(500.4, 661.5)	(612.5, 789.5)	(714.5, 978.1)
	(Min, Max)	(470.3, 767.3)	(372.2, 1012.0)	(568.3, 1126.0)	(428.5, 675.8)	(340.4, 1059.5)	(628.3, 1039.0)
	Mean	36.41	40.05	35.27	34.37	41.96	53.26
	(SD, SEM)	(8.33, 4.16)	(14.62, 4.41)	(10.58, 3.74)	(10.60, 4.33)	(16.39, 4.73)	(12.20, 6.10)
	Median	33.53	39.36	33.22	32.96	38.96	51.29
	(P25, P75)	(30.66, 42.17)	(26.50, 54.61)	(28.97, 38.45)	(31.91, 36.07)	(29.70, 52.08)	(43.94, 62.58)
	(Min, Max)	(30.29, 48.31)	(20.55, 63.98)	(23.03, 57.86)	(19.71, 52.59)	(23.19, 81.28)	(41.36, 69.12)
	Mean	984.23	1431.56	1389.31	1074.70	1338.73	1418.09
NfL, pg/mL	(SD, SEM)	(215.96, 107.98)	(346.40, 104.44)	(346.27, 122.42)	(389.02, 158.82)	(519.86, 150.07)	(203.24, 101.62)
	Median	1015.80	1420.15	1368.45	1074.33	1181.24	1358.55
	(P25, P75)	(803.00, 1165.46)	(1348.61, 1622.87)	(1076.94, 1615.49)	(736.10, 1213.90)	(1064.39, 1514.50)	(1285.74, 1550.44)
	(Min, Max)	(737.72, 1167.61)	(807.05, 1903.66)	(999.92, 1992.84)	(630.83, 1718.68)	(580.97, 2391.81)	(1245.68, 1709.57)
	Mean	513.22	557.146	419.85	460.54	536.26	737.32
Ng, pg/mL	(SD, SEM)	(158.02, 79.01)	(329.39, 99.32)	(175.80, 62.15)	(97.13, 39.65)	(218.98, 63.22)	(202.38, 101.19)
	Median	472.203	463.83	387.17	483.59	510.607	696.19 (
	(P25, P75)	(419.90, 606.55)	(271.13, 707.49)	(308.79, 460.33)	(361.91, 538.99)	(366.248, 633.395)	592.87, 881.77)
	(Min, Max)	(369.62, 738.87)	(194.62, 1306.92)	(237.78, 808.44)	(332.57, 562.59)	(280.045, 1017.305)	(543.66, 1013.23)
YKL-40, ng/mL	Mean	221.97	260.34	259.76	187.93	273.28	433.23
	(SD, SEM)	(23.27, 11.64)	(81.03, 24.43)	(117.50, 41.54)	(80.33, 32.80)	(142.64, 41.18)	(192.70, 96.35)
	Median	228075.3	284.33	237.35	185.62	234.48	433.66
	(P25, P75)	(205.21, 238.72)	(197.20, 321.40)	(189.91, 286.86)	(112.02, 250.77)	(175.04, 312.17)	(291.56, 574.90)



		Male			Female		
		<i>2 APOEε4</i> (n = 4)	<i>1 APOEε4</i> (n = 11)	<i>No APOEε4</i> (n = 8)	<i>2 APOEε4</i> (n = 6)	<i>1 APOEε4</i> (n = 12)	<i>No APOEε4</i> (n = 4)
		(Min, Max)	(189.72, 242.01)	(134.47, 385.38)	(131.16, 518.66)	(98.75, 294.80)	(125.21, 598.33)
Cognition	MMSE Total (0-30)	Mean	25.0	22.6	23.4	24.0	23.8
		(SD, SEM)	(2.2, 1.1)	(2.5, 0.8)	(2.3, 0.8)	(2.2, 0.9)	(2.1, 0.6)
		Median	25.5	22.0	22.5	23.5	24.5
		(P25, P75)	(23.5, 26.5)	(20.0, 26.0)	(21.5, 26.0)	(23.0, 26.0)	(22.5, 25.0)
		(Min, Max)	(22.0, 27.0)	(20.0, 26.0)	(21.0, 26.0)	(21.0, 27.0)	(20.0, 27.0)
	MMSE Memory (0-6)	Mean	4.0	3.8	4.6	4.2	4.3
		(SD, SEM)	(0.8, 0.4)	(0.9, 0.3)	(1.3, 0.5)	(1.2, 0.5)	(1.3, 0.4)
		Median	4.0	4.0	4.5	4.0	4.0
		(P25, P75)	(3.5, 4.5)	(3.0, 4.0)	(3.5, 6.0)	(3.0, 5.0)	(3.5, 5.5)
		(Min, Max)	(3.0, 5.0)	(3.0, 6.0)	(3.0, 6.0)	(3.0, 6.0)	(2.0, 6.0)
	MMSE Visual Construction (0-1)	Mean	1.0	0.5	0.3	0.7	0.8
		(SD, SEM)	(0.0, 0.0)	(0.5, 0.2)	(0.5, 0.2)	(0.5, 0.2)	(0.4, 0.1)
		Median	1.0	0.0	0.0	1.0	1.0
		(P25, P75)	(1.0, 1.0)	(0.0, 1.0)	(0.0, 0.5)	(0.0, 1.0)	(1.0, 1.0)
		(Min, Max)	(1.0, 1.0)	(0.0, 1.0)	(0.0, 1.0)	(0.0, 1.0)	(0.0, 1.0)
	MMSE Attention/Calculation (0-5)	Mean	3.5	3.5	2.8	3.5	3.8
		(SD, SEM)	(1.9, 1.0)	(1.3, 0.4)	(1.7, 0.6)	(1.5, 0.6)	(1.5, 0.4)
		Median	4.0	4.0	3.0	3.5	4.0
		(P25, P75)	(2.0, 5.0)	(3.0, 5.0)	(1.0, 4.0)	(3.0, 5.0)	(3.5, 5.0)
		(Min, Max)	(1.0, 5.0)	(1.0, 5.0)	(1.0, 5.0)	(1.0, 5.0)	(1.0, 5.0)
	RBANS Total (40-160)	Mean	74.0	61.6	67.9	73.0	66.1
		(SD, SEM)	(11.6, 5.8)	(9.2, 2.8)	(14.8, 5.2)	(10.8, 4.4)	(12.7, 3.7)
		Median	78.0	60.0	64.5	76.5	65.0

		Male			Female		
		<i>2 APOEε4</i>	<i>1 APOEε4</i>	<i>No APOEε4</i>	<i>2 APOEε4</i>	<i>1 APOEε4</i>	<i>No APOEε4</i>
		(n = 4)	(n = 11)	(n = 8)	(n = 6)	(n = 12)	(n = 4)
	(P25, P75)	(67.0, 81.0)	(54.0, 71.0)	(56.5, 81.0)	(61.0, 80.0)	(54.0, 76.5)	(65.0, 74.5)
	(Min, Max)	(57.0, 83.0)	(49.0, 76.0)	(49.0, 90.0)	(59.0, 85.0)	(49.0, 88.0)	(62.0, 77.0)
	<b>Mean</b>	<b>48.0</b>	<b>46.9</b>	<b>67.9</b>	<b>56.0</b>	<b>49.0</b>	<b>63.0</b>
	<b>(SD, SEM)</b>	<b>(7.3, 3.7)</b>	<b>(6.9, 2.1)</b>	<b>(25.0, 8.8)</b>	<b>(14.8, 6.0)</b>	<b>(8.0, 2.3)</b>	<b>(19.7, 9.8)</b>
	Median	48.0	48.0	64.0	50.0	48.0	56.0
RBANS Delayed Memory (40-154)	(P25, P75)	(42.0, 54.0)	(40.0, 48.0)	(44.0, 92.5)	(48.0, 60.0)	(44.0, 50.0)	(52.0, 74.0)
	(Min, Max)	(40.0, 56.0)	(40.0, 64.0)	(40.0, 102.0)	(44.0, 84.0)	(40.0, 68.0)	(48.0, 92.0)
	<b>Mean</b>	<b>104.3</b>	<b>78.2</b>	<b>70.9</b>	<b>98.5</b>	<b>83.8</b>	<b>98.0</b>
	<b>(SD, SEM)</b>	<b>(16.0, 8.0)</b>	<b>(23.7, 7.1)</b>	<b>(21.0, 7.4)</b>	<b>(23.4, 9.6)</b>	<b>(16.2, 4.7)</b>	<b>(7.1, 3.5)</b>
	Median	106.0	64.0	63.0	102.5	78.0	99.0
RBANS Visuospatial/ Constructional (40-154)	(P25, P75)	(92.0, 116.5)	(64.0, 105.0)	(58.0, 79.5)	(84.0, 121.0)	(72.0, 94.5)	(92.5, 103.5)
	(Min, Max)	(84.0, 121.0)	(50.0, 126.0)	(50.0, 116.0)	(60.0, 121.0)	(64.0, 112.0)	(89.0, 105.0)
	<b>Mean</b>	<b>82.8</b>	<b>73.7</b>	<b>71.4</b>	<b>74.8</b>	<b>79.8</b>	<b>81.0</b>
	<b>(SD, SEM)</b>	<b>(13.0, 6.5)</b>	<b>(12.9, 3.9)</b>	<b>(9.4, 3.3)</b>	<b>(24.8, 10.1)</b>	<b>(15.2, 4.4)</b>	<b>(14.2, 7.1)</b>
	Median	86.5	72.0	73.5	73.5	83.5	86.5
RBANS Attention (40-154)	(P25, P75)	(74.5, 91.0)	(64.0, 79.0)	(68.0, 75.0)	(53.0, 82.0)	(68.0, 91.0)	(72.5, 89.5)
	(Min, Max)	(64.0, 94.0)	(56.0, 106.0)	(53.0, 85.0)	(49.0, 118.0)	(53.0, 100.0)	(60.0, 91.0)

ICV, intracranial volume; MMSE, Mini-Mental Status Examination; RBANS, Repeatable Battery for the Assessment of Neuropsychological Status; SD, standard deviation; SEM, standard error of the mean.

## 1.2 Supplementary Figures

**Figure S1: R squared linear regression results across all comparisons.**

Comparison of all CSF biomarker linear regression results for the overall population (a), *APOE4* genotypes (b), sex (c), and combined *APOE4* genotypes and sex (d). Correlation coefficients were defined as:  $0.81 \leq R^2 < 1$  as strong;  $0.49 \leq R^2 < 0.81$  as moderately strong;  $0.25 \leq R^2 < 0.49$  as moderate;  $0.09 \leq R^2 < 0.25$  as weak; and  $R^2 < 0.09$  as negligible. R-squared values are shown for each comparison. °  $p < 0.1$ ; •  $p < 0.05$ , ••  $p < 0.01$ , •••  $p < 0.001$ . Linear regressions with a positive slope are shown in red and negative slopes are shown in blue. CSF amyloid  $\beta$  levels are inversely correlated with A $\beta$  pathology.

