

**Supplementary Table 1.** Results of Cox proportional hazards models when forcing the variables of biomarker, age, education, and gender into each model and then using the stepwise selection method.

	<u>Pittsburgh Compound B (N=286)</u>				<u>Adjusted CSF A<math>\beta</math><sub>42</sub> (N=302)</u>				
	P-value	HR	Lower 95%CI	Higher 95%CI	P-value	HR	Lower 95%CI	Higher 95%CI	
Biomarker	0.008	1.34	1.08	1.65	0.017	0.66	0.46	0.93	
Age, y	0.004	1.94	1.23	3.05	0.087	1.05	0.99	1.11	
Education, y	0.940	1.01	0.72	1.43	0.627	1.03	0.91	1.18	
Women	0.307	0.71	0.36	1.38	0.286	0.68	0.34	1.38	
Selective Reminding Test	<.001	0.51	0.35	0.74	0.026	0.93	0.87	0.99	
Normalized hippocampal volume, ml	---	---	---	---	<.001	0.475	0.32	0.71	
Trailmaking B	0.031	1.38	1.03	1.86	---	---	---	---	
		<u>CSF tau (N=302)</u>				<u>CSF ptau<sub>181</sub> (N=302)</u>			
	P-value	HR	Lower 95%CI	Higher 95%CI	P-value	HR	Lower 95%CI	Higher 95%CI	
Biomarker	0.067	1.00	1.00	1.00	0.180	1.01	1.00	1.02	
Age, y	0.195	1.04	0.98	1.10	0.117	1.05	0.99	1.11	
Education, y	0.674	1.03	0.90	1.18	0.734	1.02	0.89	1.17	
Women	0.431	0.77	0.38	1.54	0.398	0.74	0.37	1.48	
Reminding Test	0.016	0.93	0.88	0.99	0.022	0.93	0.88	0.99	
Normalized hippocampal volume, ml	<.001	0.46	0.30	0.69	<.001	0.46	0.30	0.69	
Trailmaking B	---	---	---	---	---	---	---	---	
		<u>Adjusted CSF tau/A<math>\beta</math><sub>42</sub> (N=302)</u>				<u>Adjusted CSF ptau<sub>181</sub>/A<math>\beta</math><sub>42</sub> (N=302)</u>			
	P-value	HR	Lower 95%CI	Higher 95%CI	P-value	HR	Lower 95%CI	Higher 95%CI	
Biomarker	0.003	1.46	1.14	1.89	0.012	1.38	1.07	1.77	
Age, y	0.289	1.03	0.97	1.10	0.194	1.04	0.98	1.10	
Education, y	0.618	1.04	0.90	1.19	0.689	1.03	0.90	1.18	
Women	0.397	0.74	0.38	1.47	0.314	0.71	0.36	1.39	
Reminding Test	0.029	0.94	0.88	0.99	0.035	0.94	0.88	1.00	
Normalized hippocampal volume, ml	<.001	0.44	0.29	0.67	<.001	0.44	0.29	0.66	
Trailmaking B	---	---	---	---	---	---	---	---	

Abbreviations: HR=hazard ratio; 95%CI=95% confidence interval.

**Supplementary Table 2.** Demographics and baseline cognitive test scores for biomarker-positive persons followed at least 10 years who did and did not develop CDR>0.

	<u>A<math>\beta</math><sub>42</sub> positive</u>					<u>tau positive</u>				
	<u>CDR 0 (N=15)</u>		<u>CDR&gt;0 (N=3)</u>		<u>P-value</u>	<u>CDR 0 (N=16)</u>		<u>CDR&gt;0 (N=7)</u>		<u>P-value</u>
	<u>Mean/N</u>	<u>SD/%</u>	<u>Mean/N</u>	<u>SD/%</u>		<u>Mean/N</u>	<u>SD/%</u>	<u>Mean/N</u>	<u>SD/%</u>	
Age, y	63.7	10.2	72.8	6.9	0.160	62.6	7.5	74.2	6.1	0.002
Education, y	16.1	3.1	18.3	0.6	0.236	15.8	2.8	14.4	4.0	0.370
Women, N	8	53.3%	2	66.7%	0.671	15	93.8%	5	71.4%	0.144
<i>APOE4+</i> , N	5	33.3%	2	66.7%	0.280	6	37.5%	3	42.9%	0.809
Animal Naming	24.1	6.1	22.0	2.7	0.569	22.6	5.5	22.1	3.4	0.834
Selective Reminding										
Test Free Recall	30.1	4.7	35.0*	N/A*	N/A*	31.8	6.9	31.7	3.1	0.977
Trailmaking A	31.7	7.3	36.3	8.5	0.342	39.1	38.2	39.5	11.6	0.973
Trailmaking B	72.9	21.2	109.3	63.0	0.423	59.9	16.0	103.1	45.1	0.044

	<u>ptau<sub>181</sub> positive</u>					<u>tau/A<math>\beta</math><sub>42</sub> positive</u>				
	<u>CDR 0 (N=11)</u>		<u>CDR&gt;0 (N=5)</u>		<u>P-value</u>	<u>CDR 0 (N=12)</u>		<u>CDR&gt;0 (N=5)</u>		<u>P-value</u>
	<u>Mean/N</u>	<u>SD/%</u>	<u>Mean/N</u>	<u>SD/%</u>		<u>Mean/N</u>	<u>SD/%</u>	<u>Mean/N</u>	<u>SD/%</u>	
Age, y	63.3	7.0	74.9	6.2	0.007	65.4	8.1	71.5	5.2	0.145
Education, y	15.6	3.2	15.4	4.3	0.941	15.9	3.3	15.4	4.3	0.789
Women, N	11	100.0%	3	60.0%	0.025	10	83.3%	3	60.0%	0.301
<i>APOE4+</i> , N	5	45.5%	1	20.0%	0.330	5	41.7%	2	40.0%	0.949
Animal Naming	22.9	5.3	22.0	4.0	0.740	24.0	6.8	20.8	3.8	0.343
Selective Reminding										
Test Free Recall	47.7	0.7	47.5	0.7	0.711	30.5	6.3	32.0	4.2	0.758
Trailmaking A	29.0	6.5	42.2	11.0	0.009	29.8	7.2	41.4	12.0	0.025
Trailmaking B	54.6	12.0	106.5	48.7	0.075	58.5	14.2	103.6	51.6	0.122

	<u>ptau<sub>181</sub>/A<math>\beta</math><sub>42</sub> positive</u>				
	<u>CDR 0 (N=13)</u>		<u>CDR&gt;0 (N=4)</u>		<u>P-value</u>
	<u>Mean/N</u>	<u>SD/%</u>	<u>Mean/N</u>	<u>SD/%</u>	
Age, y	65.0	8.1	72.8	4.9	0.092
Education, y	16.4	2.8	14.8	4.7	0.389
Women, N	10	76.9%	2	50.0%	0.301
<i>APOE4+</i> , N	7	53.9%	1	25.0%	0.312
Animal Naming	25.2	6.7	21.3	4.2	0.295
Selective Reminding					
Test Free Recall	32.3	6.0	29.0*	N/A*	N/A*
Trailmaking A	29.3	7.6	44.8	10.9	0.006
Trailmaking B	60.3	17.5	114.8	52.1	0.126

\* Only one person in the CDR>0 group had a score on the Selective Reminding Task Free Recall subtest

Footnote. Abbreviations: CDR=Clinical Dementia Rating; *APOE4+*=at least one *APOE*  $\epsilon$ 4 allele.

**Supplementary Table 3.** Data available for each of the biomarkers.

Biomarker	Earliest biomarker availability date	# participants with biomarker	# of biomarker assessments per person		Range of biomarker measurements	
			Mean	SD	Minimum	Maximum
Pittsburgh Compound B	November 3, 2004	462	1.8	0.9	1	5
CSF A $\beta$ <sub>42</sub>	June 18, 1998	599	1.8	1.1	1	5
CSF tau	June 18, 1998	598	1.8	1.1	1	5
CSF ptau <sub>181</sub>	June 18, 1998	599	1.8	1.1	1	5
Selective Reminding Task - Free Recall	August 8, 2002	656	5.3	2.9	1	14
Trailmaking A	October 2, 1985	661	5.6	3.6	1	29
Trailmaking B	September 24, 1991	661	5.5	3.4	1	24
Animal Naming	March 20, 1997	661	5.5	3.3	1	19
Mini Mental State Exam	October 21, 1996	664	5.9	3.5	1	20
Clinical Dementia Rating						
Sum of Boxes	May 6, 1985	664	6.2	4	2	29
Normalized hippocampal and whole brain volume	November 22, 2006	569	2.2	1.2	1	7

**Supplementary Table 4.** Baseline values on biomarkers and demographics for Pittsburgh Compound B accumulators and non-accumulators.

	Non-accumulators (N=53)		Accumulators (N=38)		P-value
	N/Mean	%/SD	N/Mean	%/SD	
Adjusted A $\beta$ <sub>42</sub> , pg/mL	0.22	0.74	-1.14	-1.12	<0.0001
tau, pg/mL	352.0	432.6	487.9	203.1	0.084
ptau <sub>181</sub> , pg/mL	53.1	24.7	79.87	29.83	<0.001
Age, y	67.4	8.1	73.7	7.5	<0.0001
Women, N	145	55.1%	17	43.6%	0.177
Minority race, N	32	12.2%	4	10.3%	0.731
<i>APOE</i> $\epsilon$ 4, N	84	31.9%	11	28.2%	0.639
Education, y	15.9	2.6	16.0	3.0	0.990
Follow-up time, y	4.9	2.6	5.7	2.1	0.022
Animal Naming	17.4	5.8	16.0	5.7	0.255
Selective Reminding Task - Free Recall	24.5	8.2	23.8	6.4	0.698
Trailmaking A	39.3	13.0	38.9	20.1	0.904
Trailmaking B	78.8	30.9	93.5	38.8	0.029
Normalized whole brain volume, mm <sup>3</sup>	1027410.0	66569.8	972905.0	10015.8	<0.0001
Normalized hippocampal volume, mm <sup>3</sup>	6735.7	1105.4	6537.9	641.7	0.352

Footnote: Abbreviations: *APOE*  $\epsilon$ 4=at least one *APOE*  $\epsilon$ 4 allele.

### **Supplementary Figure 1. Bubble plots.**

Bubble plots showing the relationship between the molecular biomarkers, normalized hippocampal volume, follow-up time and incident CDR>0 for Pittsburgh Compound B (A), and CSF A $\beta$ <sub>42</sub> (B), tau (C), ptau<sub>181</sub> (D), tau/A $\beta$ <sub>42</sub> (E), and ptau<sub>181</sub>/A $\beta$ <sub>42</sub> (F). Bubble size reflects time to dementia onset or length of follow-up for those who did not develop dementia. Filled bubbles indicate persons who developed dementia, clear bubbles indicate those who did not develop dementia.

Footnote. Abbreviations: CDR=Clinical Dementia Rating, PIB=Pittsburgh Compound B, SUVR= standardized uptake value ratio.

### **Supplementary Figure 2. Spaghetti plots for CSF tau.**

Spaghetti plots for CSF tau showing the relationship between having at least one *APOE*  $\epsilon$ 4 allele (in red), having at least one *APOE*  $\epsilon$ 2 allele (in green), and magnitude and changes in CSF tau values with time for participants who did (A, B) and did not (C, D) develop CDR>0. Data points are labeled with the specific *APOE*  $\epsilon$  genotype for that individual.

Footnote. Data for one participant with extreme values of CSF tau are not shown to enable closer inspection of the remaining data. Abbreviations: CDR=Clinical Dementia Rating; ACA=arbitrary clinical assessment.

### **Supplementary Figure 3. Spaghetti plots for CSF ptau<sub>181</sub>.**

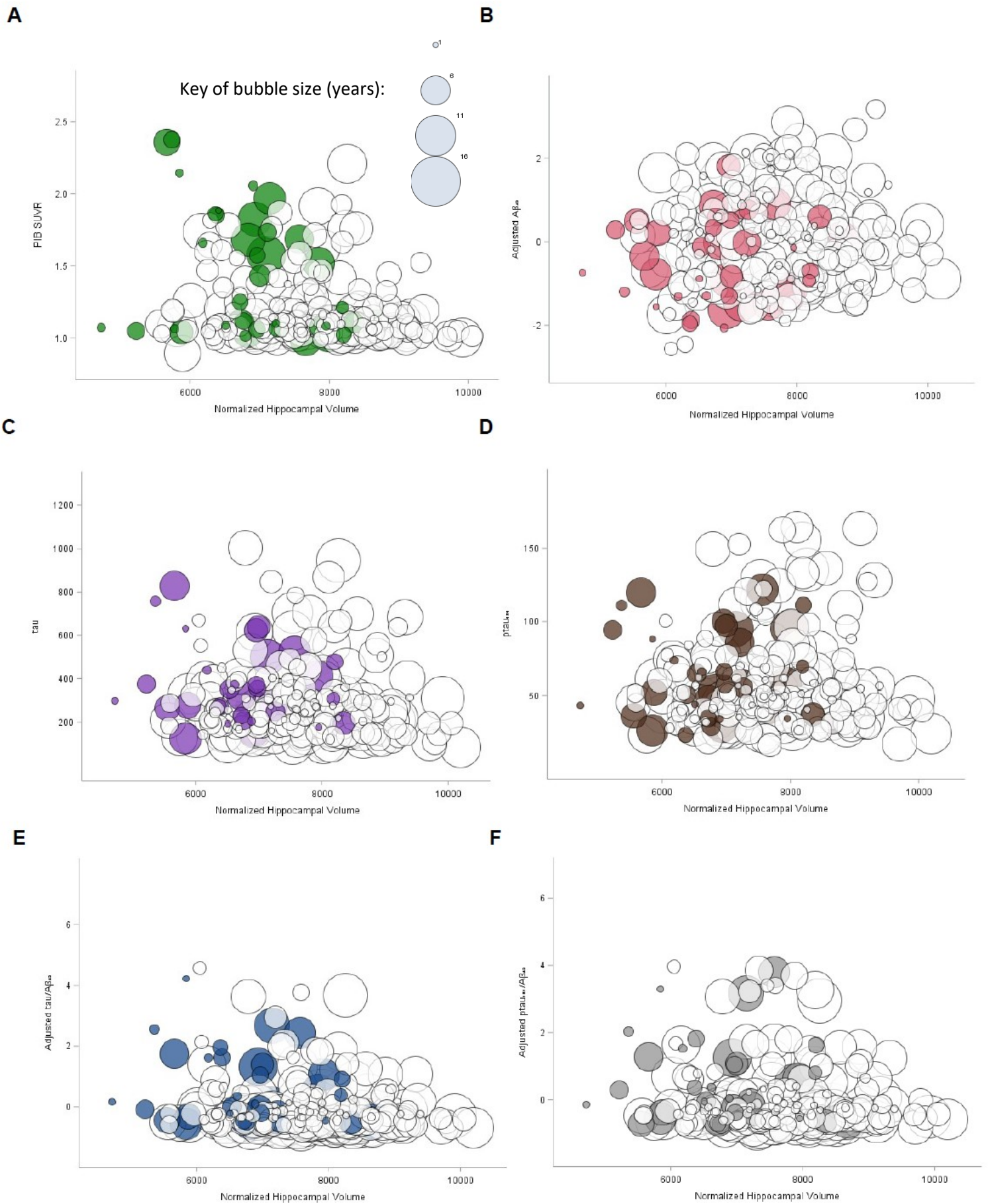
Spaghetti plots for CSF ptau<sub>181</sub> showing the relationship between having at least one *APOE*  $\epsilon$ 4 allele (in red), having at least one *APOE*  $\epsilon$ 2 allele (in green), and magnitude and changes in CSF ptau<sub>181</sub> values with time for participants who did (A, B) and did not (C, D) develop CDR>0. Data points are labeled with the specific *APOE*  $\epsilon$  genotype for that individual.

Footnote. Abbreviations: CDR=Clinical Dementia Rating; ACA=arbitrary clinical assessment.

**Supplementary Figure 4.** Copy of Figure 3 from the main manuscript including estimates of linear fits (black lines). As can be seen, the linear fits tend to underestimate the drop in Pittsburgh Compound B (which is suspected to be due to smaller sample size) and overestimates the drop in hippocampal and brain volume.

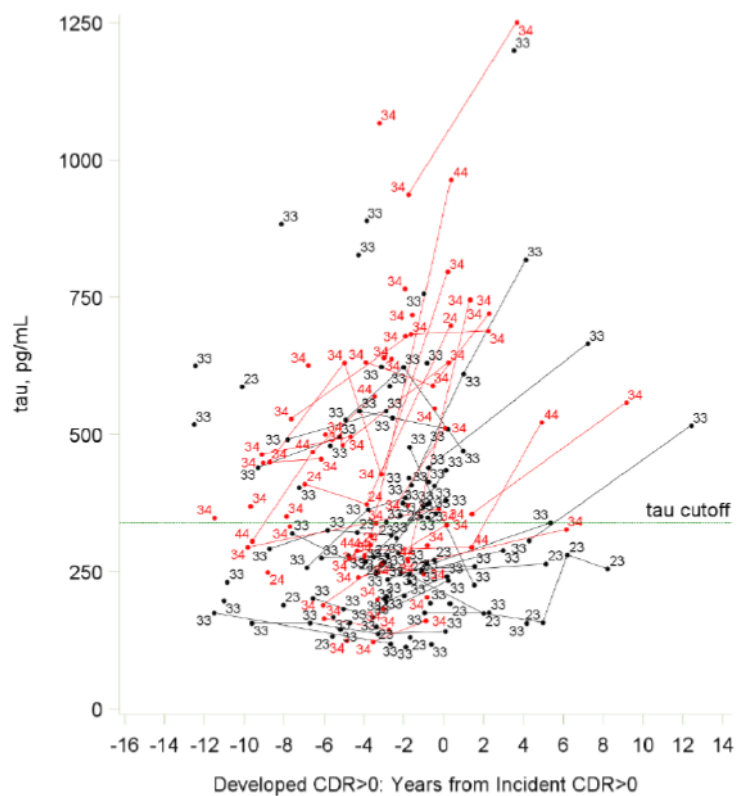
**Supplementary Figure 5.** Copy of Figure 3 from the main manuscript, but now including tables below each x-axis indicating the number of participants who contributed data within each of the three-year bins. In the tables, shaded cells represent those who developed a Clinical Dementia Rating > 0, and clear cells represent the group who remained cognitively normal across the follow-up period.

Supplementary Figure 1

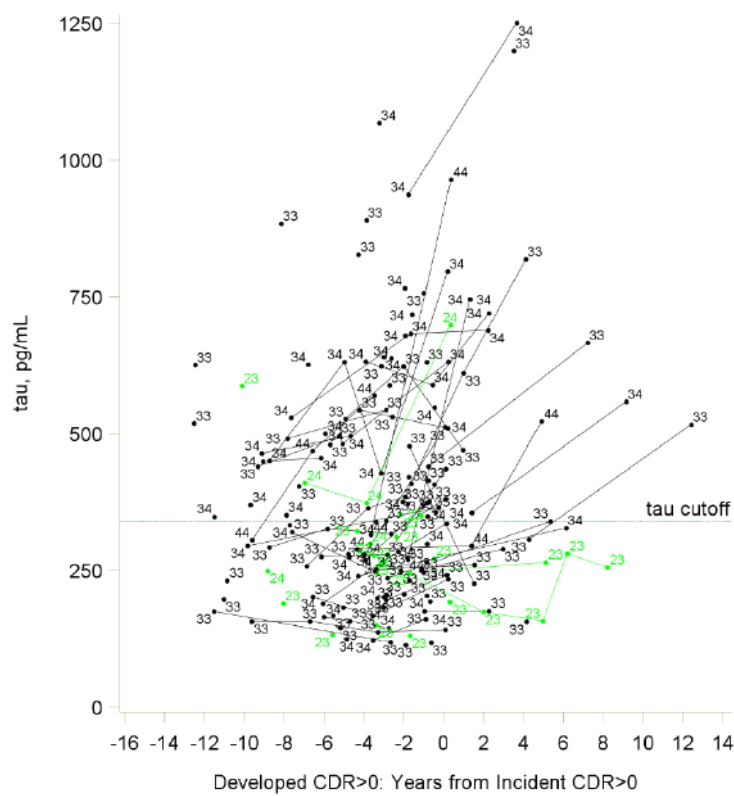


Supplementary Figure 2

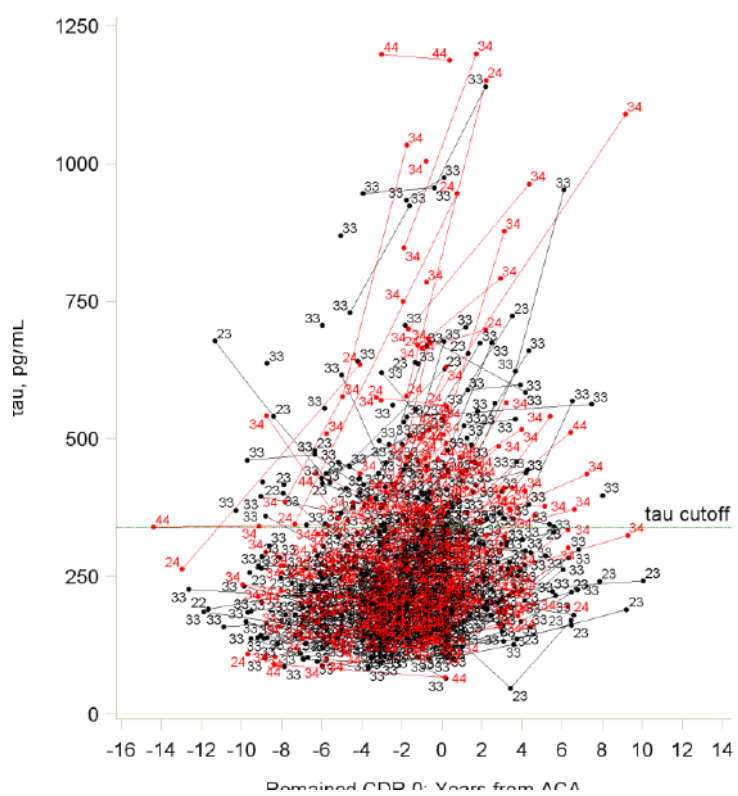
**A**



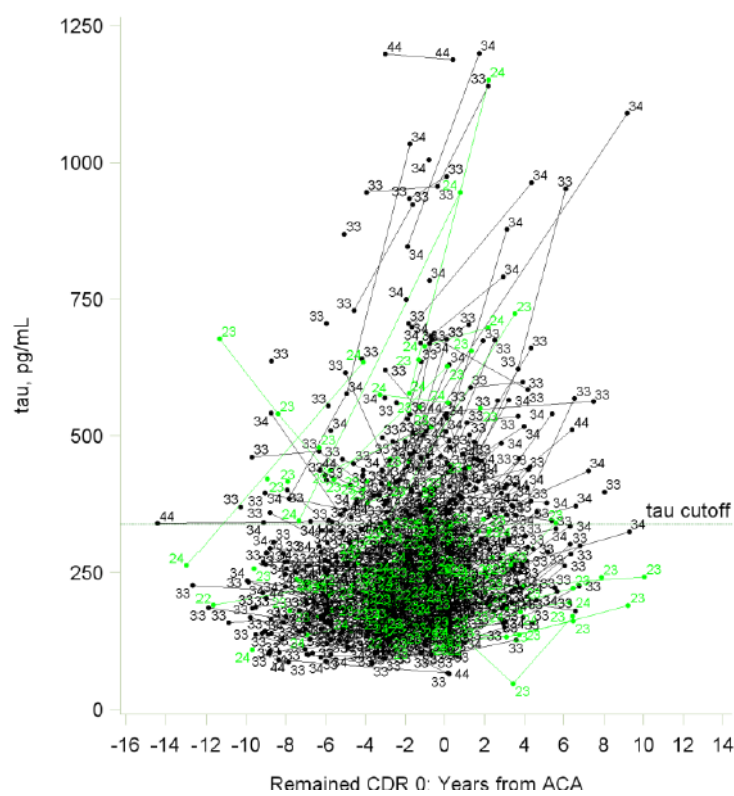
**B**



**C**

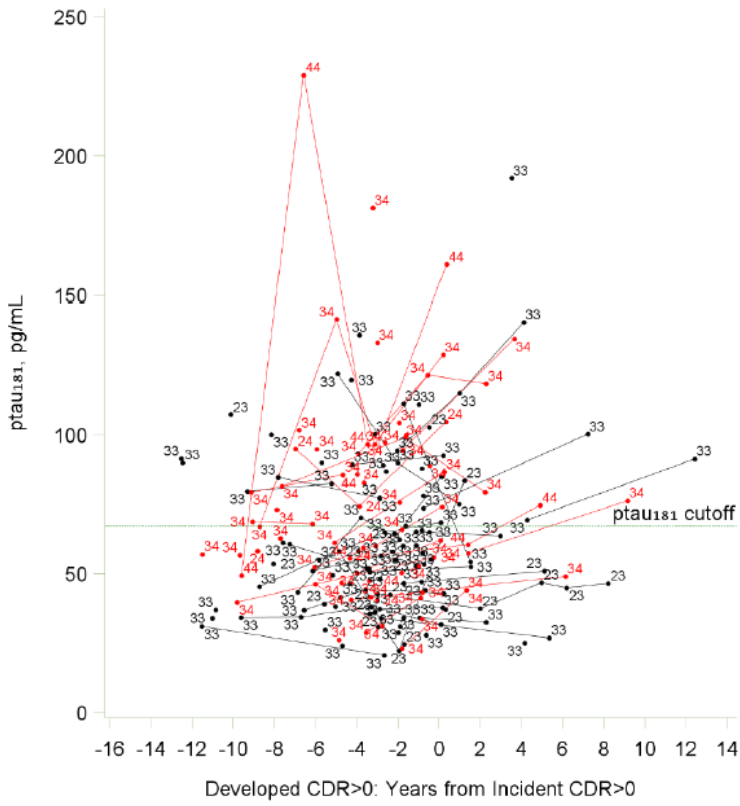


**D**

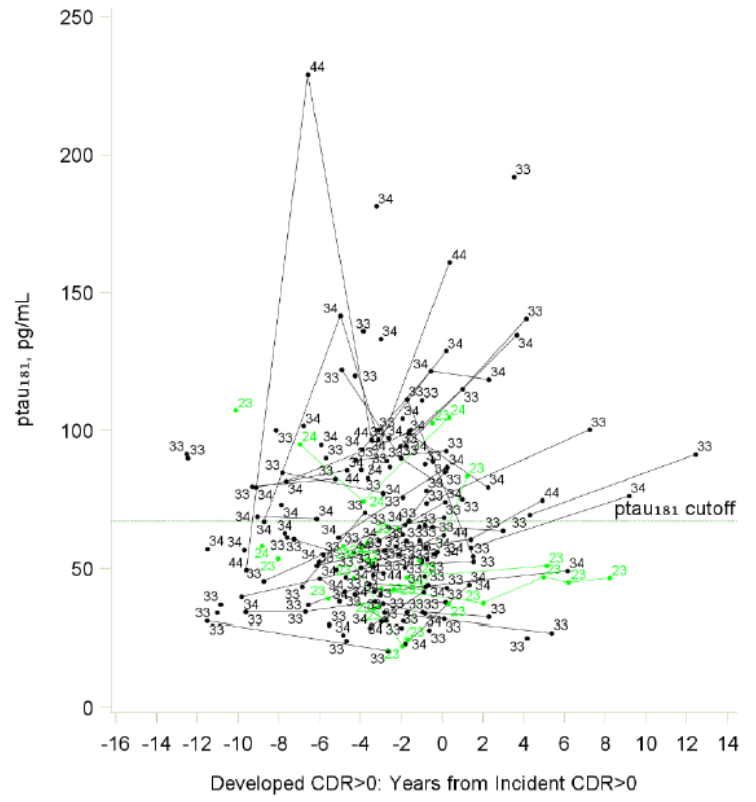


Supplementary Figure 3

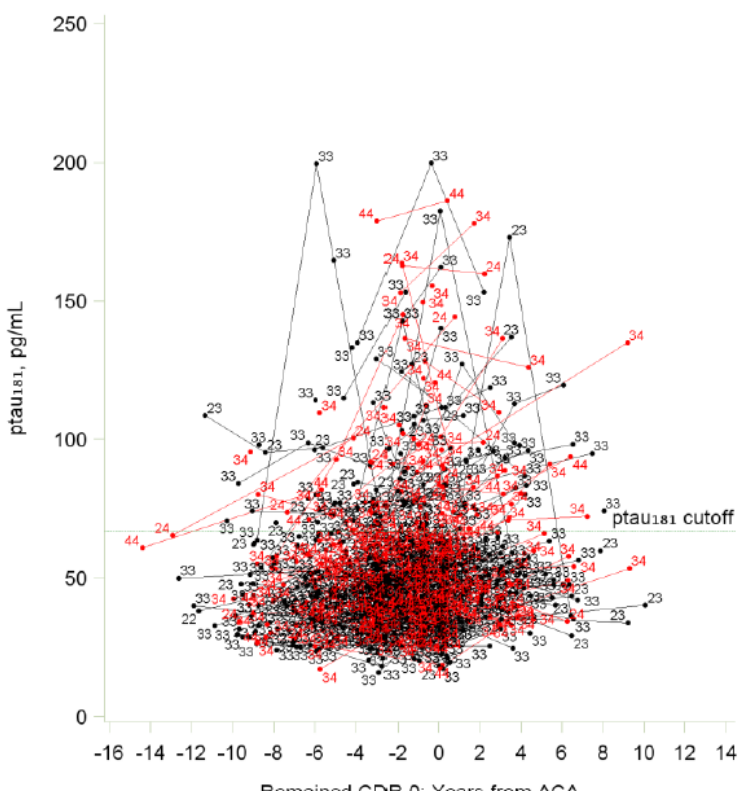
**A**



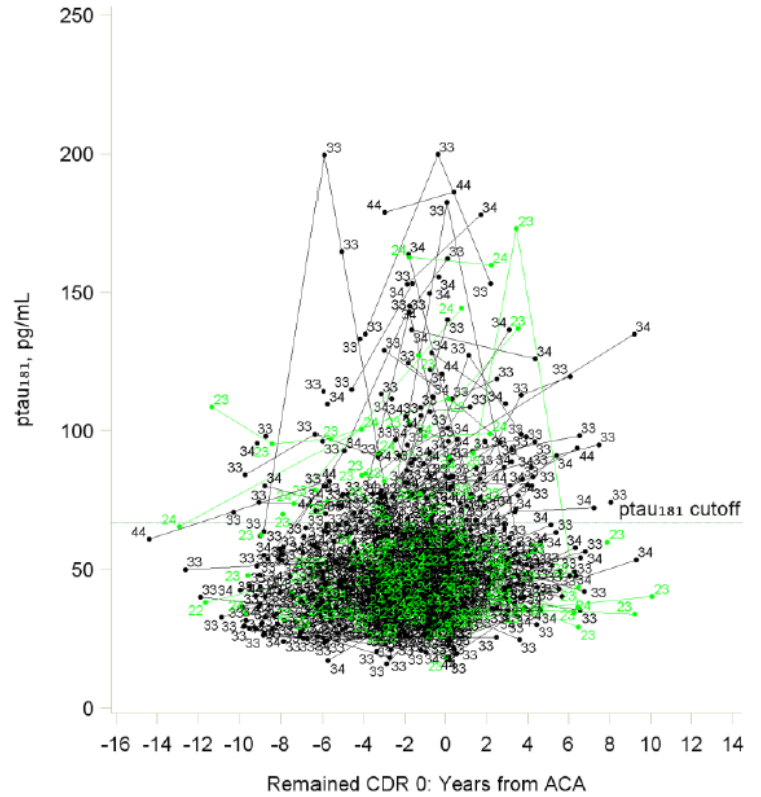
**B**



**C**



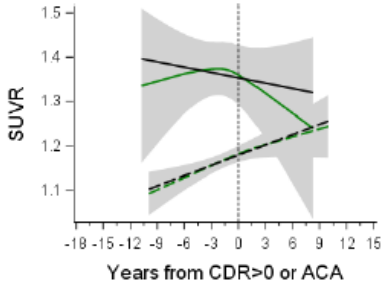
**D**



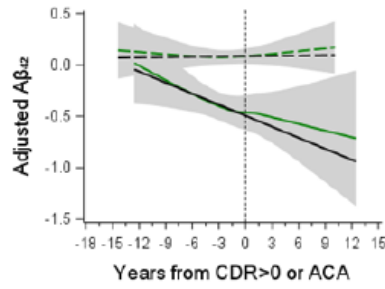


Supplementary Figure 4.

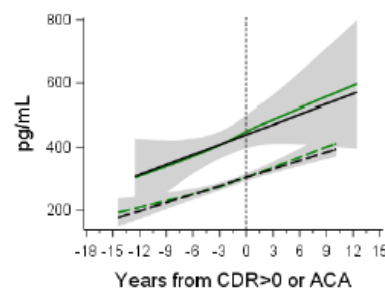
A. PIB,  $p=.735$



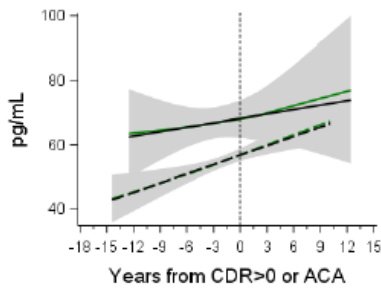
B. Adjusted CSF  $A\beta_{42}$ ,  $p=.034$



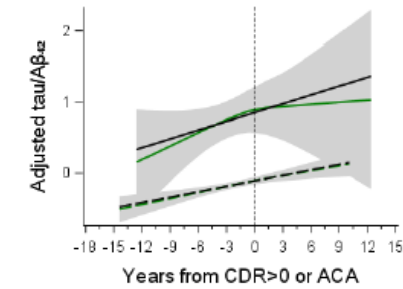
C. CSF tau,  $p=.105$



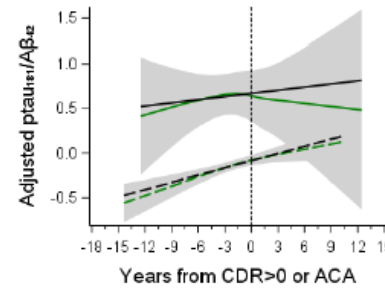
D. CSF ptau<sub>181</sub>,  $p=.857$



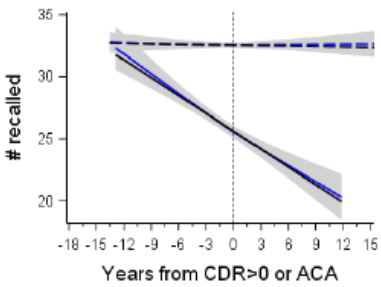
E. Adjusted CSF tau/ $A\beta_{42}$ ,  $p=.094$



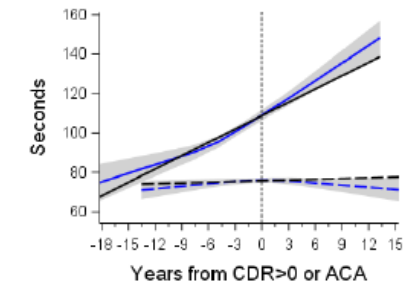
F. Adjusted CSF ptau<sub>181</sub>/ $A\beta_{42}$ ,  $p=.884$



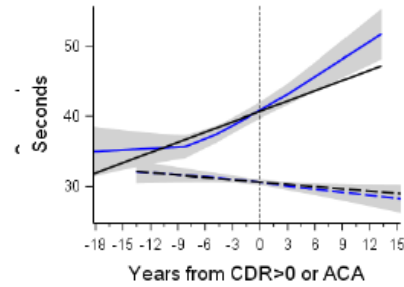
G. SRTFREE,  $p<.0001$



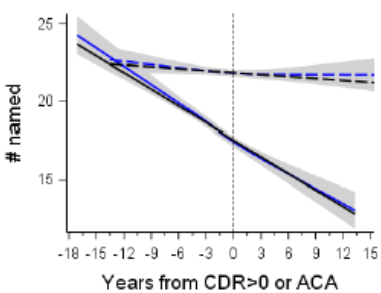
H. Trailmaking A,  $p<.0001$



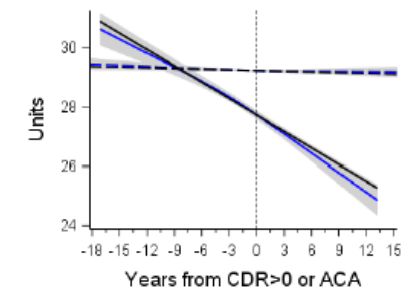
I. Trailmaking B,  $p<.0001$



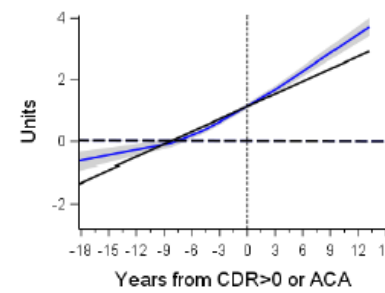
J. Animal Naming,  $p<.0001$



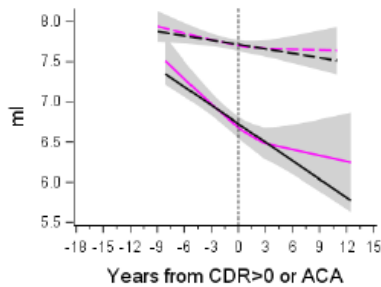
K. MMSE\*,  $p<.0001$



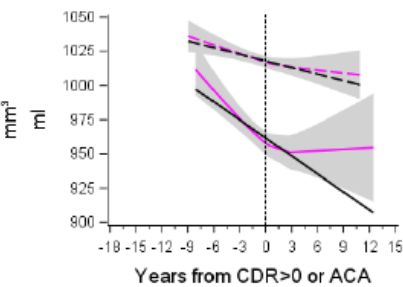
L. CDR Sum of Boxes\*,  $p<.0001$



M. nHV,  $p<.0001$

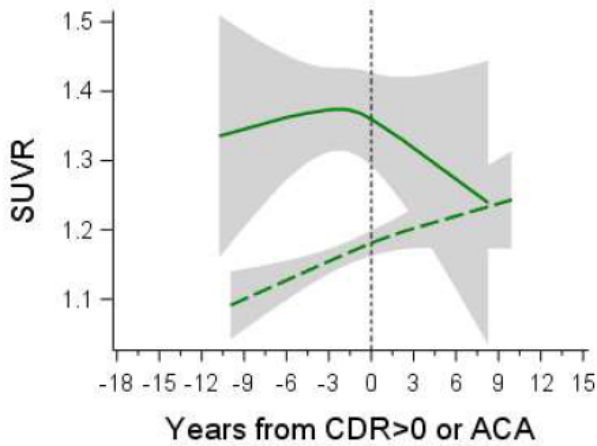


N. nWBV,  $p=.0536$



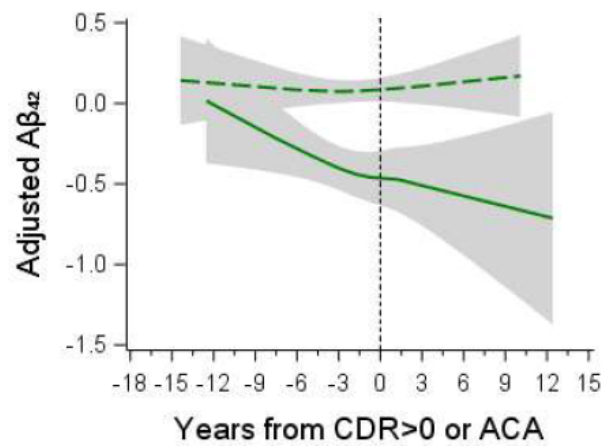
Supplementary Figure 5.

A. PIB,  $p=.735$



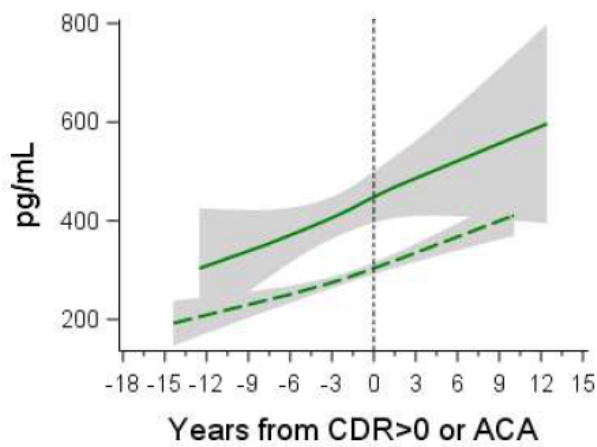
0	0	5	47	117	370	202	116	43	10	1	0
0	0	3	13	34	73	31	16	9	1	0	0

B. Adjusted CSF  $A\beta_{42}$ ,  $p=.034$



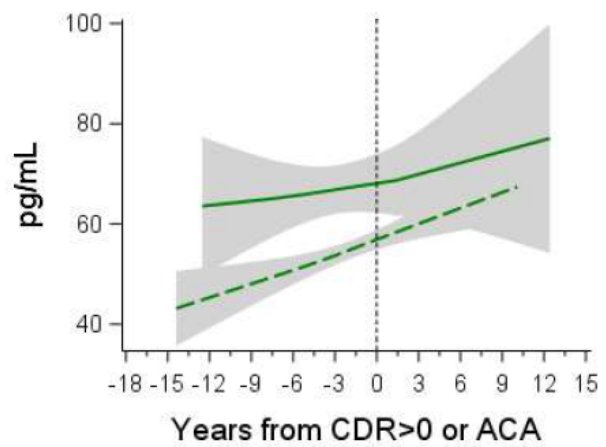
0	3	17	72	153	468	241	132	58	13	1	0
0	1	10	22	45	97	33	16	12	4	1	0

C. CSF tau,  $p=.105$



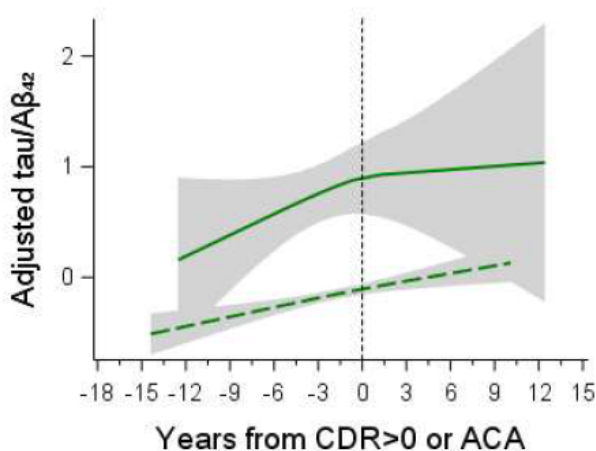
0	3	17	72	153	499	247	134	58	13	1	0
0	1	10	22	45	99	35	18	12	4	1	0

D. CSF ptau<sub>181</sub>,  $p=.857$



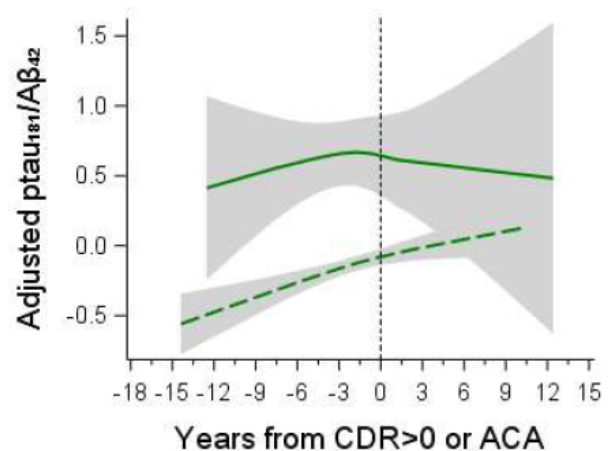
0	3	17	72	153	499	247	134	58	13	1	0
0	1	10	22	45	99	35	18	12	4	1	0

E. Adjusted CSF tau/ $A\beta_{42}$ ,  $p=.094$



0	3	17	72	153	499	247	134	58	13	1	0
0	1	10	22	45	99	35	18	12	4	1	0

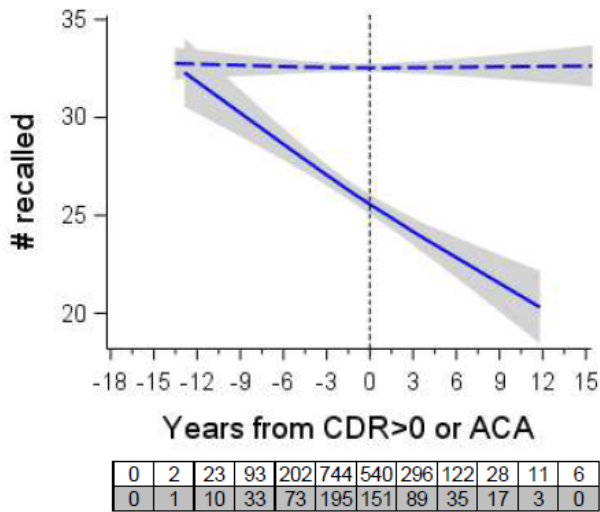
F. Adjusted CSF ptau<sub>181</sub>/ $A\beta_{42}$ ,  $p=.884$



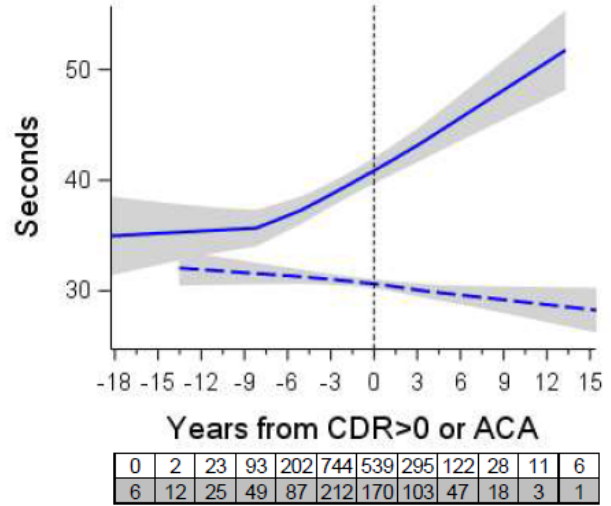
0	3	17	72	153	499	247	134	58	13	1	0
0	1	10	22	45	99	35	18	12	4	1	0

Supplementary Figure 5 (continued).

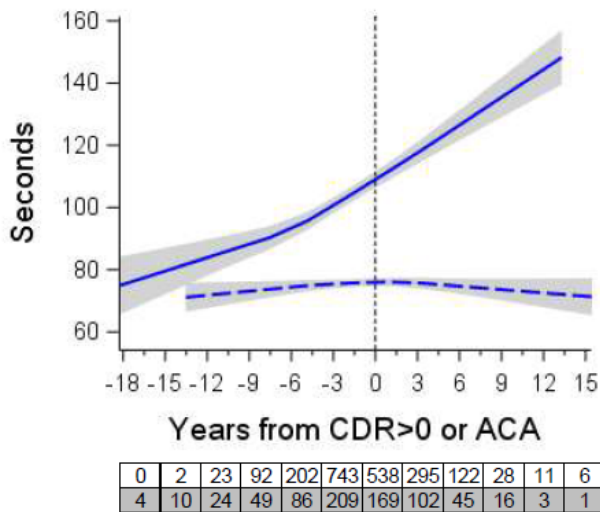
G. SRTFREE,  $p < .0001$



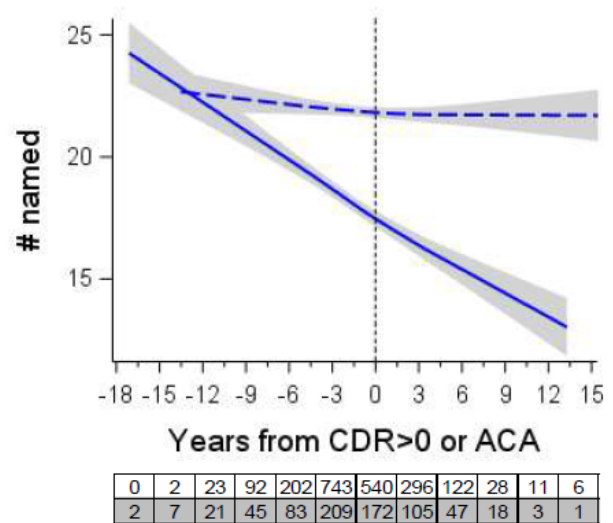
H. Trailmaking A,  $p < .0001$



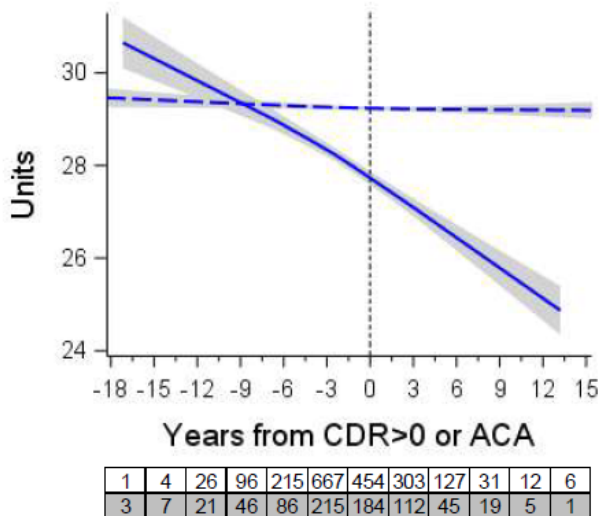
I. Trailmaking B,  $p < .0001$



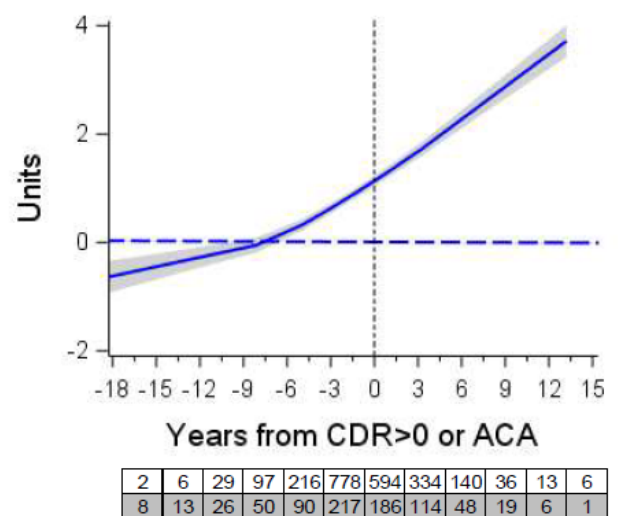
J. Animal Naming,  $p < .0001$



K. MMSE\*,  $p < .0001$

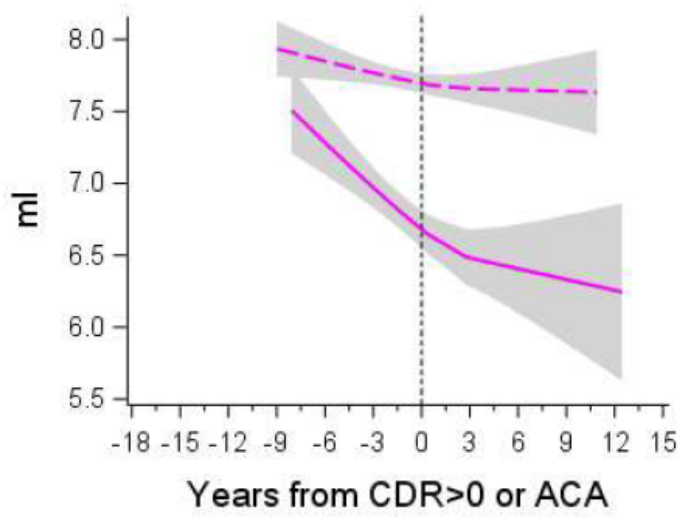


L. CDR Sum of Boxes\*,  $p < .0001$



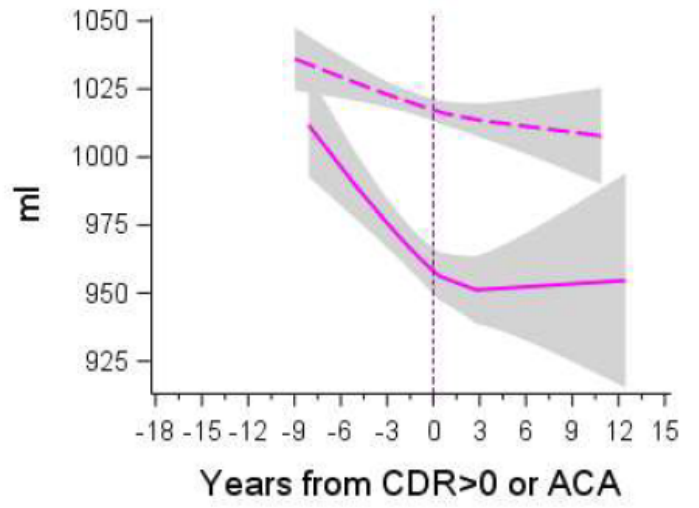
Supplementary Figure 5 (continued).

M. nHV,  $p < .0001$



0	0	0	48	128	522	331	188	78	21	3	0
0	0	0	12	34	101	50	28	15	5	1	0

N. nWBV,  $p = .0536$



0	0	0	48	128	521	332	188	78	21	3	0
0	0	0	12	34	101	50	28	15	5	1	0