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Supplementary Materials for

Increased soluble TREM2 in cerebrospinal fluid is associated with reduced cognitive and clinical decline in Alzheimer's disease

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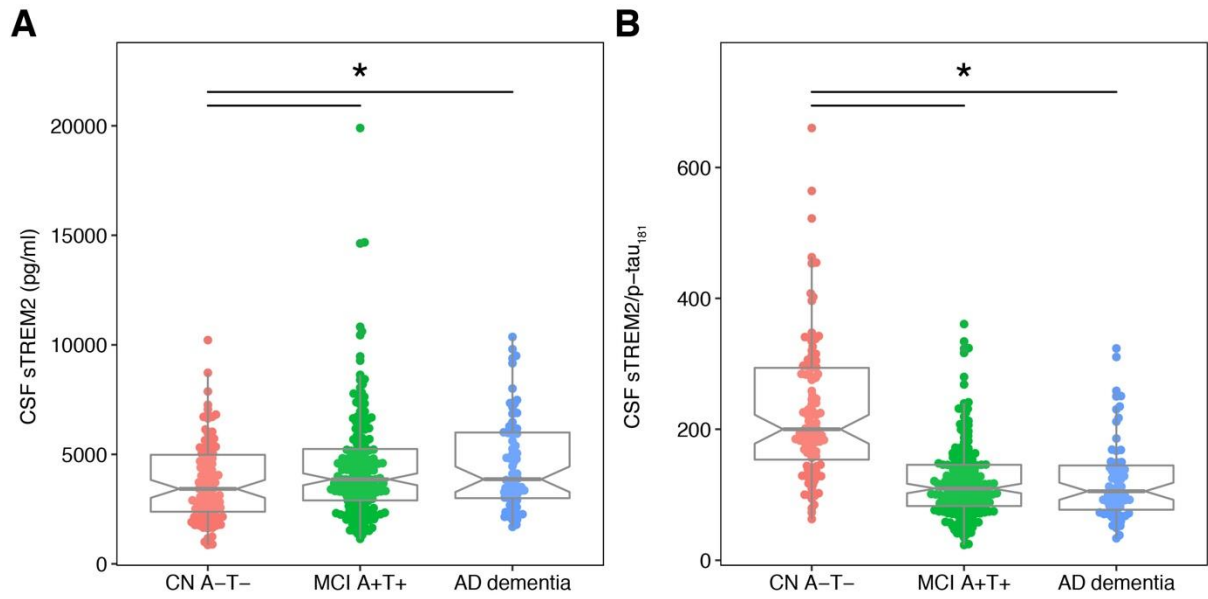
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Fig. S1. CSF sTREM2 and CSF sTREM2 to p-tau$_{181}$ ratio per group. The boxplots show the concentrations of CSF sTREM2 (A) and CSF sTREM2 to p-tau$_{181}$ (B) for each diagnostic group. After removal of 3 outliers of CSF sTREM2 in the MCI A+T+ group, the CSF sTREM2 level was still significantly higher in the MCI A+T+ group compared to CN A-T-. The asterisk indicates $p < 0.05$ for group differences tested by ANCOVA and post-hoc Tukey-test.
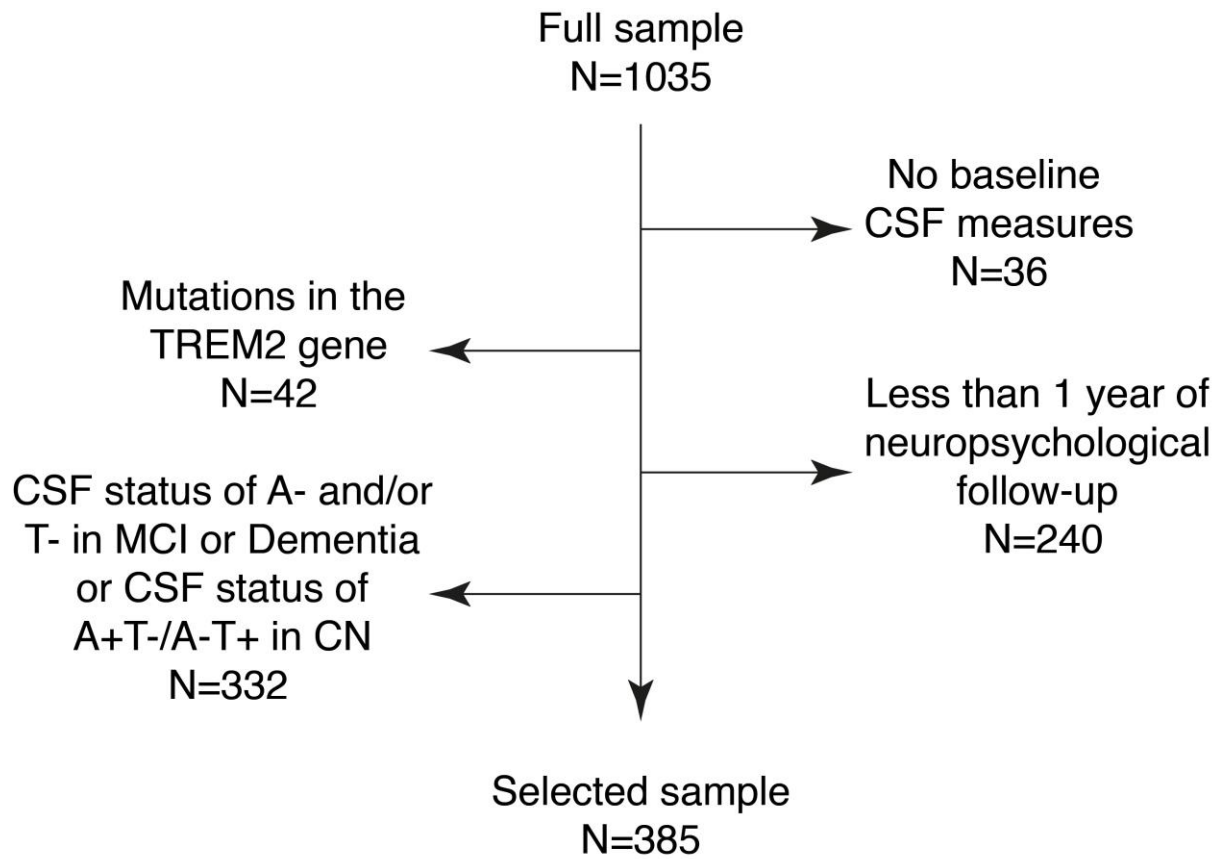
Fig. S2. Selection of the final subject group. Flow chart showing the exclusion of subjects from the full sample of 1035 subjects using CSF sTREM2 measurements.

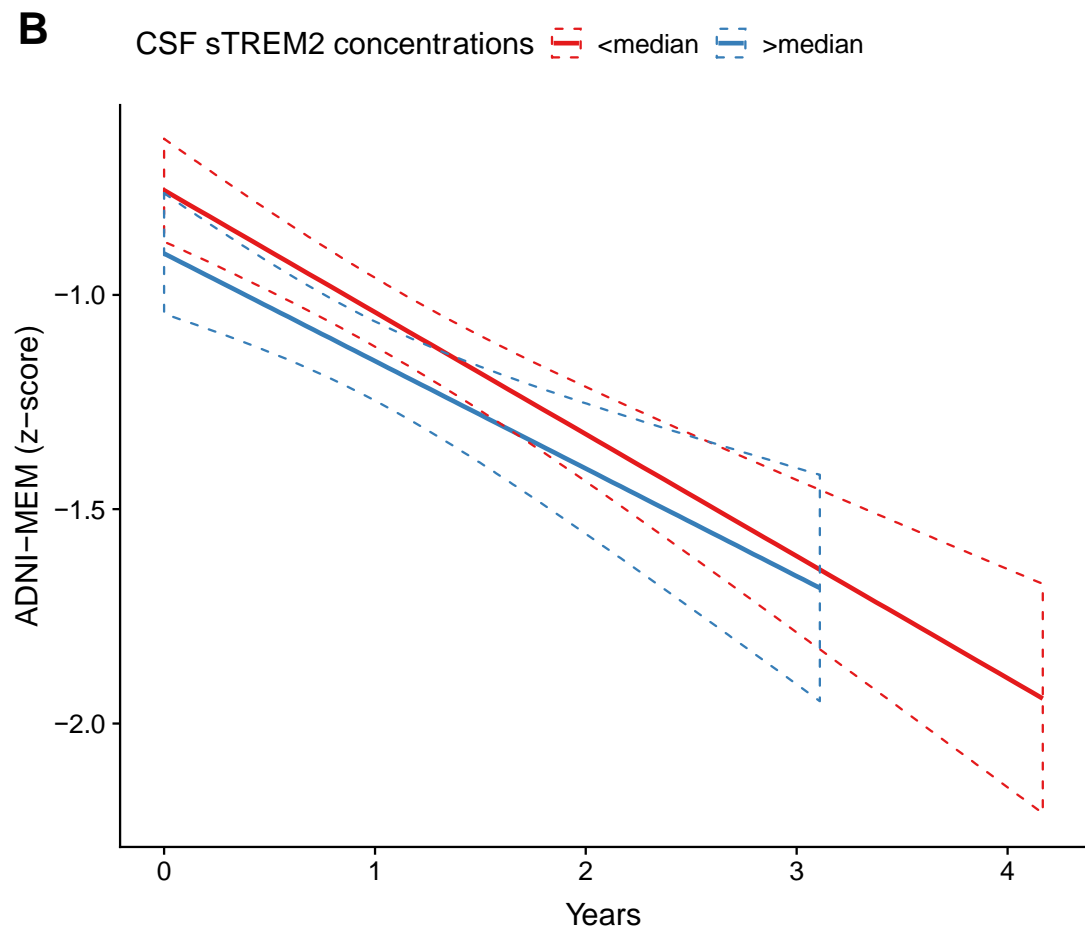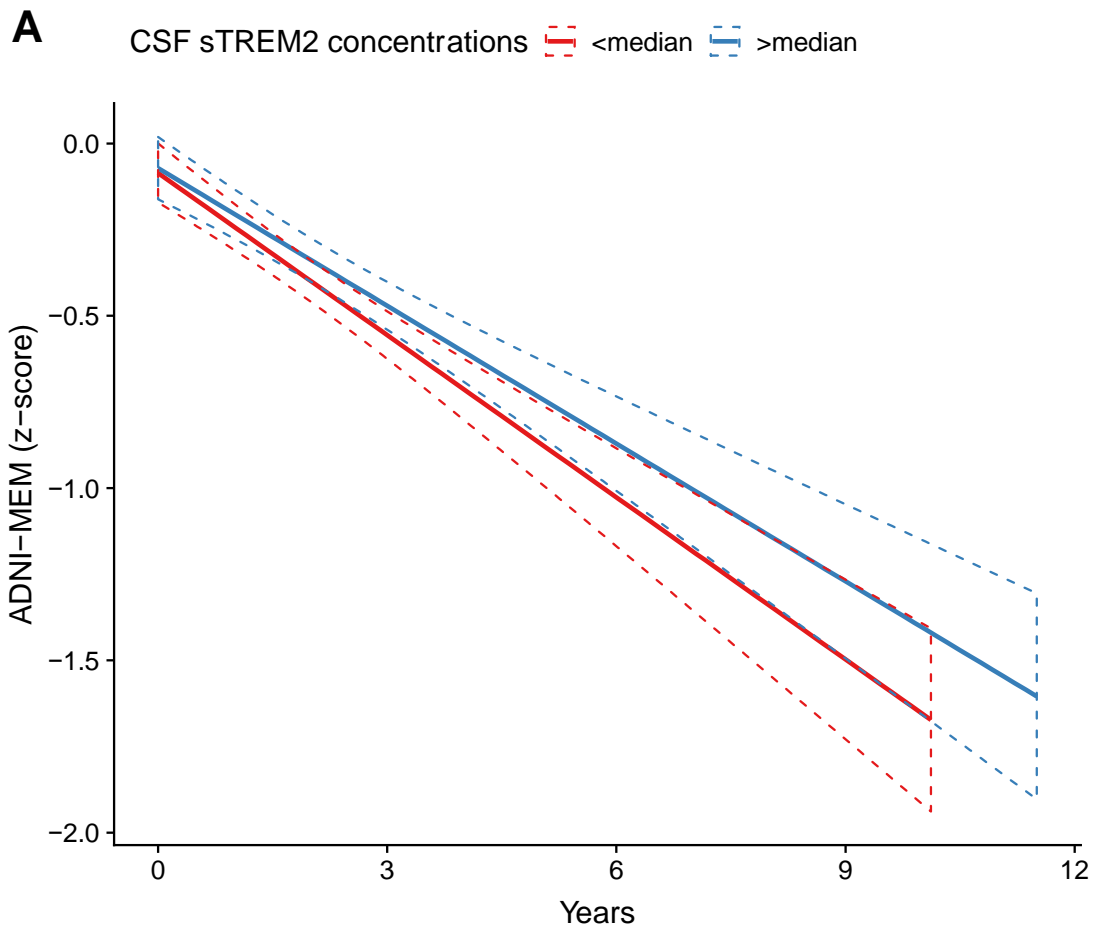**Fig. S3. Effect of CSF sTREM2 on changes in cognition in clinical subgroups.** Regression plot showing the change in episodic memory as a function of CSF sTREM2 concentrations in the MCI A+T+ (A, n = 184) and AD dementia A+T+ (B, n = 66) subgroups tested by linear mixed effects regression analyses.

A CSF sTREM2 concentrations — `<median` — `>median`

B CSF sTREM2 to p−tau ratio — `<median` — `>median`

Fig. S4. Effect of CSF sTREM2 measurements on hippocampal changes in MCI A+T+.
Regression plot showing the change in hippocampus volume change as a function of CSF sTREM2 concentrations (A) and CSF sTREM2 to p-tau$_{181}$ ratio (B) in the MCI A+T+ (A, n = 134) group as tested in mixed linear regression analyses.

Table S1. Regression analyses with additional control for CSF total tau. Regression statistics are shown for the effects of CSF sTREM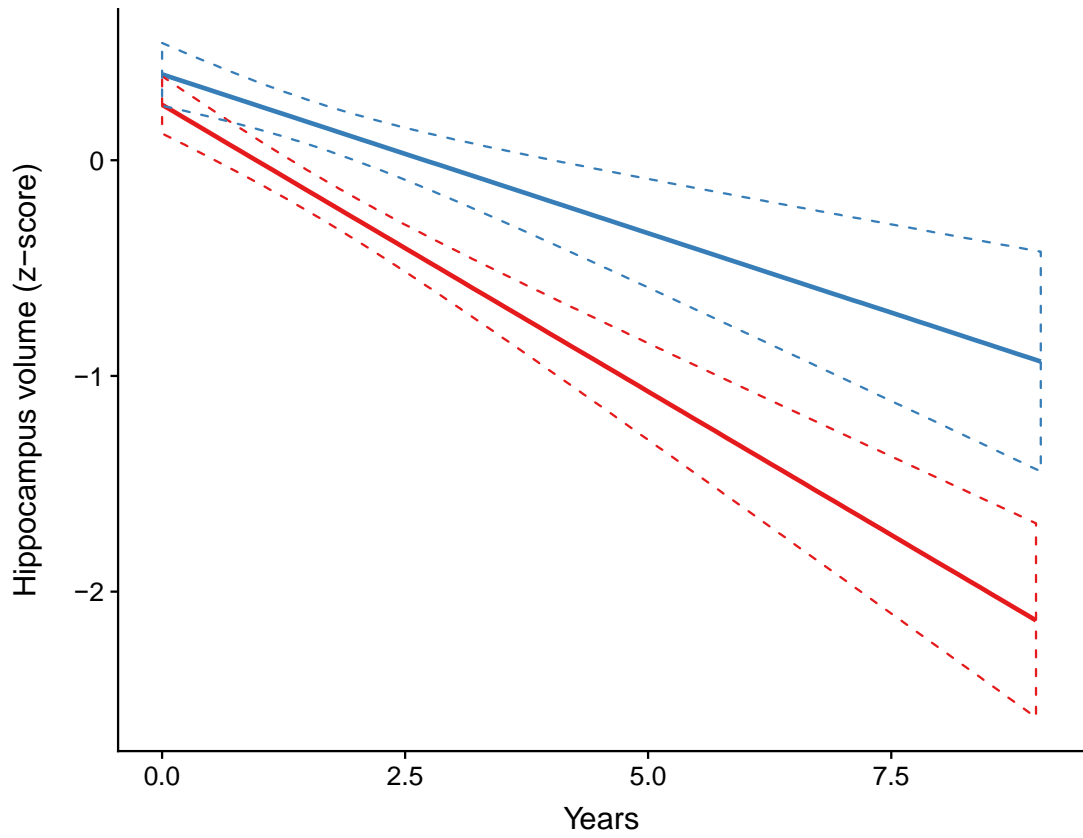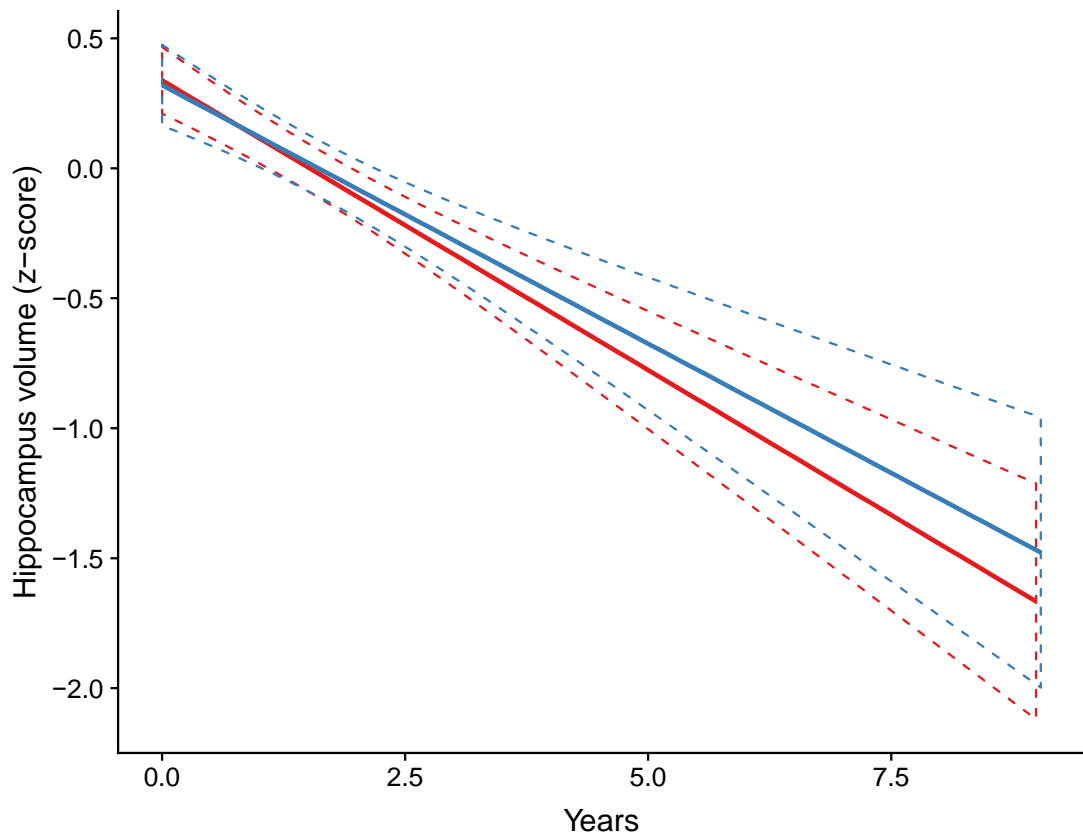2 on the rate of change in ADNI-MEM, ADAS-cog and hippocampal volume, *controlled for CSF total tau* in addition to CSF $A\beta_{1-42}$, and CSF p-tau$_{181}$.

ADNI-MEM	Interaction Term	B (SE)	95% CI	T-value	Cohens d	p	p-perm.
CN A-T-	CSF sTREM2 x Time	0.030 (0.047)	-0.060;0.120	<1	NA	0.530	0.500
	CSF sTREM2/p-tau x Time	0.039 (0.043)	-0.045;0.123	<1	NA	0.371	0.346
All A+T+	CSF sTREM2 x Time	0.074 (0.022)	0.031;0.116	3.380	0.45	<0.001	0.011
	CSF sTREM2/p-tau x Time	0.079 (0.021)	0.039;0.120	3.843	0.49	<0.001	0.003
MCI A+T+	CSF sTREM2 x Time	0.077 (0.028)	0.023;0.130	2.790	0.45	0.006	0.036
	CSF sTREM2/p-tau x Time	0.085 (0.026)	0.035;0.135	3.331	0.52	0.001	0.009
AD Dementia	CSF sTREM2 x Time	0.048 (0.023)	0.005;0.092	2.100	0.59	0.041	0.043
	CSF sTREM2/p-tau x Time	0.057 (0.024)	0.011;0.104	2.365	0.66	0.022	0.030

ADAS13	Interaction Term	B (SE)	95% CI	T-value	Cohens d	p	
CN A-T-	CSF sTREM2 x Time	0.092 (0.049)	-0.006;0.187	1.869	NA	0.070	0.086
	CSF sTREM2/p-tau x Time	0.071 (0.044)	-0.015;0.157	1.623	NA	0.116	0.164
All A+T+	CSF sTREM2 x Time	-0.079 (0.036)	-0.149;-0.001	-2.226	0.29	0.027	0.050
	CSF sTREM2/p-tau x Time	-0.083 (0.034)	-0.149;-0.018	-2.481	0.32	0.014	0.033
MCI A+T+	CSF sTREM2 x Time	-0.083 (0.046)	-0.172;0.001	-1.810	NA	0.072	0.172
	CSF sTREM2/p-tau x Time	-0.098 (0.042)	-0.181;-0.016	-2.317	0.36	0.022	0.036
AD dementia	CSF sTREM2 x Time	-0.046 (0.054)	-0.150;0.056	<1	NA	0.396	0.373
	CSF sTREM2/p-tau x Time	-0.040 (0.057)	-0.151;0.070	<1	NA	0.486	0.442

Hippocampus Volume	Interaction Term	B (SE)	95% CI	T-value	Cohens d	p	
CN A-T-	CSF sTREM2 x Time	-0.001 (0.014)	-0.036;0.017	<1	NA	0.484	0.428
	CSF sTREM2/p-tau x Time	-0.005 (0.013)	-0.030;0.020	<1	NA	0.680	0.646
All A+T+	CSF sTREM2 x Time	0.024 (0.010)	0.004;0.043	2.314	0.39	0.022	0.035
	CSF sTREM2/p-tau x Time	0.022 (0.009)	0.003;0.040	2.308	0.38	0.022	0.036
MCI A+T+	CSF sTREM2 x Time	0.035 (0.014)	0.009;0.061	2.602	0.49	0.011	0.012
	CSF sTREM2/p-tau x Time	0.030 (0.012)	0.007 (0.054)	2.487	0.47	0.014	0.016
AD dementia	CSF sTREM2 x Time	-0.007 (0.024)	-0.051;0.037	<1	NA	0.760	0.805
	CSF sTREM2/p-tau x Time	-0.002 (0.020)	-0.041;0.036	<1	NA	0.906	0.916

All models are controlled for age, gender, education, CSF p-tau$_{181}$ x Time, CSF total-tau x Time, CSF $A\beta_{1-42}$ x Time, CSF sTREM2, CSF $A\beta_{1-42}$, CSF total-tau, CSF p-tau$_{181}$ (fixed effects), plus random slope (i.e. Time) and intercept. Regular p-values are assessed using Satterthwaite's method. For non-parametric confirmation of results, p-values were further assessed using permutation testing with 1000 iterations (p-perm.). B = regression coefficient, SE = standard error, 95% CI = 95% confidence interval, T-value = t-test statistic, Cohen's d = effect size *d*, p-perm. = p-value from permutation test

Table S2. Regression analyses with additional control for hippocampus volume. Regression statistics are shown for the effects of CSF sTREM2 on the rate of change in ADNI-MEM, ADAS-cog and hippocampal volume, *controlled for hippocampus volume* in addition to CSF $A\beta_{1-42}$, and CSF p-tau$_{181}$.

ADNI-MEM	Interaction Term	B (SE)	95% CI	T-value	Cohens d	p	p-perm.
CN A-T-	CSF sTREM2 x Time	0.054 (0.049)	-0.040;0.148	1.101	NA	0.275	0.245
	CSF sTREM2/p-tau x Time	0.054 (0.046)	-0.035;0.143	1.165	NA	0.249	0.200
All A+T+	CSF sTREM2 x Time	0.074 (0.024)	0.026;0.121	3.039	0.43	0.003	0.009
	CSF sTREM2/p-tau x Time	0.088 (0.022)	0.045;0.131	3.950	0.53	<0.001	<0.001
MCI A+T+	CSF sTREM2 x Time	0.084 (0.031)	0.023;0.145	2.686	0.46	0.008	0.032
	CSF sTREM2/p-tau x Time	0.102 (0.028)	0.047;0.157	3.625	0.60	<0.001	0.003
AD Dementia	CSF sTREM2 x Time	0.024 (0.028)	-0.028;0.080	<1	NA	0.383	0.425
	CSF sTREM2/p-tau x Time	0.036 (0.026)	-0.014;0.087	1.339	NA	0.168	0.160

ADAS13	Interaction Term	B (SE)	95% CI	T-value	Cohens d	p	p-perm.
CN A-T-	CSF sTREM2 x Time	0.028 (0.046)	-0.060;0.115	<1	NA	0.539	0.55
	CSF sTREM2/p-tau x Time	0.025 (0.042)	-0.057;0.106	<1	NA	0.556	0.618
All A+T+	CSF sTREM2 x Time	-0.083 (0.040)	-0.160;-0.005	-2.084	0.29	0.038	0.049
	CSF sTREM2/p-tau x Time	-0.106 (0.036)	-0.176;-0.035	-2.935	0.40	0.004	0.025
MCI A+T+	CSF sTREM2 x Time	-0.102 (0.053)	-0.205;0.001	-1.940	NA	0.054	0.150
	CSF sTREM2/p-tau x Time	-0.126 (0.047)	-0.218;-0.033	-2.654	0.43	0.009	0.040
AD dementia	CSF sTREM2 x Time	0.005 (0.061)	-0.112;0.121	<1	NA	0.939	0.915
	CSF sTREM2/p-tau x Time	-0.028 (0.058)	-0.140;0.084	<1	NA	0.632	0.605

All models are controlled for age, gender, education, CSF p-tau$_{181}$ x Time, Hippocampal volume x Time, CSF $A\beta_{1-42}$ x Time, CSF sTREM2, CSF $A\beta_{1-42}$, Hippocampal volume, CSF p-tau$_{181}$ (fixed effects), plus random slope (Time) and intercept. Regular p-values are assessed using Satterthwaite's method. For non-parametric confirmation of results, p-values were further assessed using permutation testing with 1000 iterations (p-perm.). B = regression coefficient, SE = standard error, 95% CI = 95% confidence interval, T-value = t-test statistic, Cohen's d = effect size *d*, p-perm. = p-value from permutation test