

Supplemental Materials for Statistical Analyses

Demographic characteristics were compared between mutation carriers and mutation non-carriers or between symptomatic mutation carriers and asymptomatic mutation carriers using two sample t-tests or Person's chi-square tests as deemed appropriate.

Model Selection for Each Outcome

Part I: Search of the Change Point (the knot) in the Linear Spline Model.

A general linear mixed effects (LME) model was used to estimate each individual's rate of change over the follow-up (**the best linear unbiased estimators**) with fixed effects including mutation, time since baseline, interaction between mutation and random effects including random intercepts for each family and for each individual nested within families and a random slope for each individual. Then the individual rates of change were plotted over baseline EYO and a LOESS curve was fitted to determine the most likely pattern of biomarker change across the total EYO period, e.g. no association, linear, linear spline, or quadratic. If the figure indicated a linear spline pattern (like in the case of the cognitive composite, CDR SB, CSF p-tau, and hippocampal volumes), that is, if a linear association with two splines was observed, then the knot (hereafter referred to as the change point) which connected the two splines was searched using an empirical method to identify when, based on the baseline EYO, a CHANGE POINT in the rate of change occurred^{1,2}. Briefly, for any given baseline EYO (referred as the change point in baseline EYO) from -15 to five, a new variable CP-EYO was defined as the maximum between zero and the subtraction of baseline EYO from the change point in baseline EYO. We varied this change point in baseline EYO yearly from EYO -15 to five as it was the interval with the greatest density of observations. Next, a linear mixed effects models including fixed effects

for gender, education, mutation time since baseline, CP-EYO, a three-way interaction between baseline EYO, mutation, and time, and a three-way interaction between mutation, time and CPEYO, and random effects including intercepts for specific family and for each individual nested within families and a slope for each individual was constructed. A likelihood approach was used to compare the models based on the goodness-of-fit criterion as the Akaike information criterion (AIC) and Bayesian information criterion (BIC).^{2,3} The change point with the lowest AIC and BIC was accepted as the real change point and was used to calculate the CPEYO for the final analysis. The goodness-of-fit indices suggested a change point at baseline -7 EYO for CSF p-tau, -4 EYO for cognitive composite, -3 EYO for hippocampal volumes, and -1 EYO for CDR SB (Supplemental Figure 1)

Part I: Final Analysis Model Selection.

If a linear association with two splines was observed, both baseline EYO and the new variable were included in both the two-way and the three-way interaction with time and mutation, respectively (hereafter referred to as Model A).

Model A:

$$y_{ijk} = \beta_0 + \beta_1 \text{gender} + \beta_2 \text{Mutation} + \beta_3 \text{Mutation} * t_{ij} + \beta_4 \text{Baseline EYO} * \text{Mutation} + \beta_5 \text{Baseline EYO} * \text{Mutation} * t_{ij} + \beta_6 \text{CP EYO} * \text{Mutation} + \beta_7 \text{CP EYO} * \text{Mutation} * t_{ij} + b_{0i} + b_{1i} * t_{ij} + f_k + \epsilon_{ij}.$$

Where, $CP\ EYO = \max((Baseline\ EYO - EYO\ change\ point), 0)$. b_{0i} and b_{1i} are the

individual random intercept and random slope, and $\begin{pmatrix} b_{0i} \\ b_{1i} \end{pmatrix} \sim N\left(\mathbf{0}, \begin{pmatrix} \sigma_{b_0}^2 & \sigma_{b_0} \sigma_{b_1} \\ \sigma_{b_0} \sigma_{b_1} & \sigma_{b_1}^2 \end{pmatrix}\right)$. f_k is the

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random intercept for each family cluster, and $f_k \sim N(0, \sigma_k^2)$. ϵ_{ij} is the within-subject residual and conditioning on the random effect, $\epsilon_{ij} \sim N(0, \sigma_\epsilon^2)$. $\begin{pmatrix} b_{0i} \\ b_{1i} \end{pmatrix}$, f_k , and ϵ_{ij} are assumed to be independent for each participant.

If a linear association was observed with the rate of change, the baseline EYO was included as an interaction with both time and mutation in both the two-way and the three-way interaction (hereafter referred to as Model B).

Model B:

$$y_{ijk} = \beta_0 + \beta_1 \text{gender} + \beta_2 \text{Mutation} + \beta_3 \text{Mutation} * t_{ij} + \beta_4 \text{Baseline EYO} * \text{Mutation} \\ + \beta_5 \text{Baseline EYO} * \text{Mutation} * t_{ij} + b_{0i} + b_{1i} * t_{ij} + f_k + \epsilon_{ij}$$

If there was no obvious association between baseline EYO and the rate of change observed, the baseline EYO was included as an interaction with mutation only due to its effect on individual's baseline values (hereafter referred to as Model C).

Model C:

$$y_{ijk} = \beta_0 + \beta_1 \text{gender} + \beta_2 \text{Mutation} + \beta_3 \text{Mutation} * t_{ij} + \beta_4 \text{Baseline EYO} * \text{Mutation} \\ + b_{0i} + b_{1i} * t_{ij} + f_k + \epsilon_{ij}$$

If a quadratic association between baseline EYO and the rate of change observed, the baseline EYO was included as an interaction with both time and mutation in both the two-way and the three-way interaction and the square of baseline EYO (EYO*EYO) was also included as

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interaction with both time and mutation in both the two-way and the three-way interaction (hereafter referred to as Model D).

Model D:

$$\begin{aligned} y_{ijk} = & \beta_0 + \beta_1 \text{gender} + \beta_2 \text{Mutation} + \beta_3 \text{Mutation} * t_{ij} + \beta_4 \text{Baseline EYO} * \text{Mutation} \\ & + \beta_5 \text{Baseline EYO} * \text{Mutation} * t_{ij} + \beta_6 \text{Baseline EYO} * \text{Mutation} \\ & + \beta_7 \text{Baseline EYO} * \text{Mutation} * t_{ij} + b_{0i} + b_{1i} * t_{ij} + f_k + \epsilon_{ij} \end{aligned}$$

As gender is shown to be associated with the baseline values for several outcomes, gender is included in all the models.

Based on Figure 1, the linear-spline model were only appropriate for CSF p-tau₁₈₁, CDR sum boxes, MRI hippocampal volumes, and the DIAN cognitive composite score. The goodness-of-fit of Model A – Model D were compared using AIC and the results were presented in Table 1. Table 1 showed that the most appropriate model for CSF p-tau₁₈₁, CDR sum boxes, MRI hippocampal volumes, and the DIAN cognitive composite score was the linear spline model (Model A), for CSF AB₄₂ was the linear model (Model B), and for CSF Tau was Model C (no association between the baseline EYO and the rate of change in CSF Tau)). For Precuneus-FDG, Model C was selected, but Model B was used for the final analysis due to the significance of the interaction between time and the baseline EYO rather than baseline EYO square, indicating that the baseline EYO significantly affects the rate of change in Precuneus-FDG. For Amyloid PiB, Model C was selected, but Model B was used for the final analysis to include the interaction between the baseline EYO and time so that the rate of change for Amyloid PiB at each EYO point can be estimated. In summary, our model selection involves three aspects. First, we used the visualization of the unbiased estimated slopes over baseline EYO to help determine the

underlying model/trajectory. Second, we used AIC to choose or validate the underlying model/trajectory. Finally, if the linear spline model or the quadratic model is selected, we test the significance of the quadratic term or the line spline term in the model. If the test achieves significance, we use that as the final model, otherwise we drop that term and use what left as the final model.

Table e-1: Goodness of fit comparison between linear, linear spline, quadratic models, and no association with baseline EYO for each outcome

Model	CSF AB ₄₂	CSF Tau	CSF p-tau ₁₈₁	Precuneus-FDG	Amyloid PiB	CDR sum boxes	DIAN cognitive composite	Hippocampal volumes
	AIC							
A (linear Spline)	NA	NA	2454.8	NA	NA	3024.9	1119.7	7121.2
B (linear)	3427.0*	2674.3	2478.1	-450.7	783.6	3213.4	1166.3	7192.2
C (No)	3436.4	2669.6	2480.3	-456.1	760.4	3273.5	1177.6	7219.8
D (Quadratic)	3438.6	2696.6	2492.9	-405.4	1130.9	3169.0	1164.6	7358.4

* The bolded AICs are those for the final models

For each outcome of interest, we determined the optimal linear mixed effects model based on this process, and then using this optimal model for the final analysis. For all the models, fixed effects included gender, time since enrollment, mutation group, and baseline EYO; random effects included random intercepts for each family to account for the family cluster correlation, random intercepts and slopes for each individual with unstructured covariance matrix to account for correlation among repeated measures. When the association between baseline EYO and the rate of change is modeled (models A and B), all possible two or three-way interactions between baseline EYO, mutation group, and follow-up time were included in the model to allow the estimation of the rate of change at each EYO point. For each outcome, we evaluated: (1) the association between the rate of change and baseline EYO; (2) the EYO point where the rate of change became significantly different between MCs and NCs by comparing the rate of change at

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each EYP point using the test based on the LME model; (3) the EYO point where the significant difference occurred cross-sectionally between MCs and NCs by comparing the mean of MC with the mean of NMC at time 0 for each EYO point using the t test based on the LME model. We examined the normality assumption using the histogram and the QQ plot of the residuals outputted by the mixed effect model procedure. Overall, the normality assumption is met. Even though there are some deviations in the tail of the QQ plot for CDR SB, and CSF Ptau, considering that the deviation is not severe and the mixed model is very robust to violation of the normality assumption, we deemed the final model appropriate for data. For the covariate functional form, we examined the spaghetti plots with LOESS to evaluate the existence/appropriateness of the functional forms (either linear or quadratic) used in the model.

All p-values were based on two-sided tests and values <0.05 were considered significant. All analyses were conducted using SAS 9.4 (SAS Institute Inc., Cary, NC). All missing data were considered missing at random. The missing data mainly occurred in CSF due to the fact that many participants chose to bypass the lumbar puncture procedures to avoid the side effects (e.g. headache) (~40%) or due to the conflict of scheduling. There are less degree of missing data in imaging biomarkers (~15% to 25%). The reason for imaging missing data is similar to that for CSF. The DIAN study cohort is a relatively young cohort; most of the missing data is not related to disease progression. Therefore, the missing data in this cohort are likely to be missing at random. Whereas participants, who are symptomatic are more likely to dropout, our sensitivity analysis conducted on CDR 0 alone yielded largely consistent results. Because of the word limits, we have put these explanations into the supplemental materials instead of the main context.

Reference

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1. Hall CB, Lipton RB, Sliwinski M, Stewart WF. A change point model for estimating the onset of cognitive decline in preclinical Alzheimer's disease. *Statistics in medicine* 2000; 19(11-12): 1555-66.
2. Aguirre-Acevedo DC, Lopera F, Henao E, et al. Cognitive Decline in a Colombian Kindred With Autosomal Dominant Alzheimer Disease: A Retrospective Cohort Study. *JAMA neurology* 2016; 73(4): 431-8.
3. van den Hout A, Muniz-Terrera G, Matthews FE. Change point models for cognitive tests using semi-parametric maximum likelihood. *Computational statistics & data analysis* 2013; 57(1): 684-98.

Figure e-1.

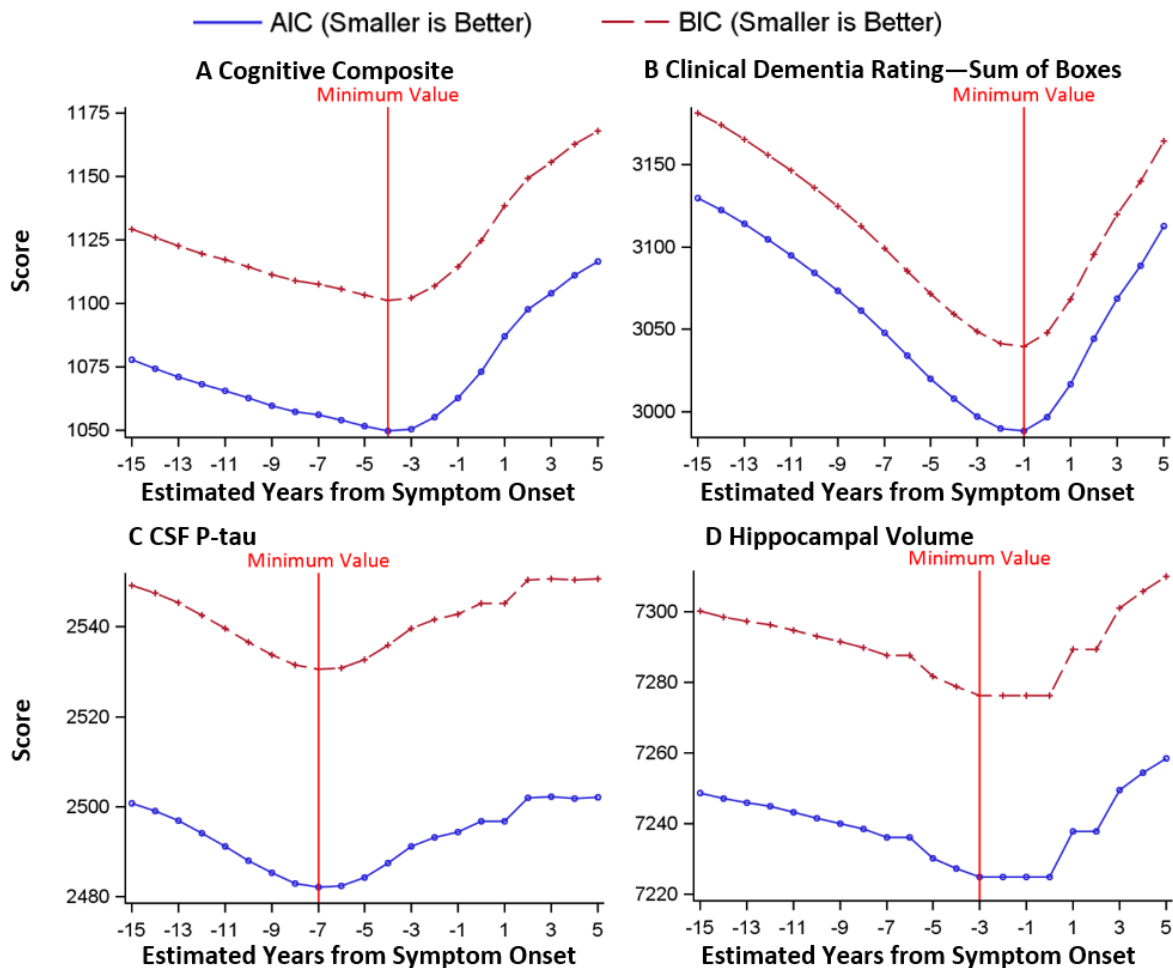


Figure e- 1: The goodness-of-fit AIC and BIC values estimated from the linear mixed effect model using the maximum likelihood method. The minimum value was used to select the knot in the linear spline model.

Table e-2: Estimates (SE) of the parameters associated with the rate of change for each model across EYO

Table e- 4 Part A: Rate of change in Cognitive composite for MCs, NCs, and its difference between MCs and NCs at each EYO point for Model A (p values were based on t-test using the LMEs with significant values at α level 0.05 were bold)

Cognitive Composite (Model A)										
EYO	MCs			NCs			MC-NC			EYO
	Mean	SE	P values	Mean	SE	P values	Mean	SE	P values	
-25	0.02711	0.03356	0.4212	-0.00757	0.04342	0.8620	0.03468	0.05487	0.5289	-25
-24	0.02349	0.03164	0.4596	-0.00760	0.04081	0.8526	0.03110	0.05164	0.5485	-24
-23	0.01988	0.02981	0.5065	-0.00763	0.03829	0.8424	0.02751	0.04852	0.5720	-23
-22	0.01626	0.02807	0.5637	-0.00767	0.03585	0.8311	0.02393	0.04553	0.6004	-22
-21	0.01265	0.02644	0.6335	-0.00770	0.03353	0.8189	0.02035	0.04270	0.6348	-21
-20	0.009033	0.02495	0.7181	-0.00773	0.03134	0.8057	0.01676	0.04006	0.6765	-20
-19	0.005417	0.02361	0.8190	-0.00776	0.02933	0.7918	0.01318	0.03765	0.7271	-19
-18	0.001802	0.02247	0.9362	-0.00779	0.02752	0.7776	0.009596	0.03552	0.7876	-18
-17	-0.00181	0.02155	0.9331	-0.00783	0.02595	0.7637	0.006013	0.03373	0.8589	-17
-16	-0.00543	0.02087	0.7953	-0.00786	0.02469	0.7510	0.002430	0.03233	0.9402	-16
-15	-0.00904	0.02046	0.6596	-0.00789	0.02377	0.7406	-0.00115	0.03136	0.9707	-15
-14	-0.01266	0.02035	0.5354	-0.00792	0.02323	0.7338	-0.00474	0.03088	0.8784	-14
-13	-0.01627	0.02053	0.4299	-0.00795	0.02310	0.7314	-0.00832	0.03090	0.7883	-13
-12	-0.01989	0.02099	0.3459	-0.00799	0.02339	0.7336	-0.01190	0.03143	0.7057	-12
-11	-0.02350	0.02173	0.2821	-0.00802	0.02409	0.7399	-0.01549	0.03244	0.6341	-11
-10	-0.02712	0.02270	0.2352	-0.00805	0.02515	0.7496	-0.01907	0.03388	0.5748	-10
-9	-0.03074	0.02389	0.2014	-0.00808	0.02654	0.7614	-0.02265	0.03571	0.5273	-9
-8	-0.03435	0.02526	0.1771	-0.00811	0.02821	0.7742	-0.02624	0.03786	0.4900	-8
-7	-0.03797	0.02679	0.1596	-0.00815	0.03010	0.7873	-0.02982	0.04029	0.4610	-7
-6	-0.04158	0.02844	0.1470	-0.00818	0.03219	0.8000	-0.03340	0.04295	0.4387	-6
-5	-0.04520	0.03020	0.1378	-0.00821	0.03443	0.8120	-0.03699	0.04580	0.4213	-5
-4	-0.04881	0.03206	0.1311	-0.00824	0.03680	0.8232	-0.04057	0.04880	0.4079	-4
-3	-0.07551	0.02742	0.0071	-0.00415	0.03400	0.9032	-0.07137	0.04367	0.1056	-3
-2	-0.1022	0.02360	<.0001	-0.00005	0.03155	0.9987	-0.1022	0.03939	0.0110	-2
-1	-0.1289	0.02104	<.0001	0.004046	0.02954	0.8914	-0.1330	0.03626	0.0004	-1
0	-0.1556	0.02022	<.0001	0.008142	0.02807	0.7724	-0.1638	0.03459	<.0001	0
1	-0.1823	0.02135	<.0001	0.01224	0.02723	0.6541	-0.1945	0.03460	<.0001	1
2	-0.2090	0.02415	<.0001	0.01633	0.02707	0.5476	-0.2253	0.03627	<.0001	2
3	-0.2357	0.02813	<.0001	0.02043	0.02760	0.4610	-0.2561	0.03941	<.0001	3
4	-0.2624	0.03286	<.0001	0.02453	0.02879	0.3964	-0.2869	0.04369	<.0001	4
5	-0.2891	0.03807	<.0001	0.02862	0.03056	0.3513	-0.3177	0.04882	<.0001	5
6	-0.3158	0.04358	<.0001	0.03272	0.03282	0.3212	-0.3485	0.05455	<.0001	6

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7	-0.3425	0.04929	<.0001	0.03682	0.03546	0.3018	-0.3793	0.06072	<.0001	7
8	-0.3692	0.05514	<.0001	0.04091	0.03843	0.2897	-0.4101	0.06721	<.0001	8
9	-0.3959	0.06109	<.0001	0.04501	0.04163	0.2824	-0.4409	0.07393	<.0001	9
10	-0.4226	0.06712	<.0001	0.04911	0.04503	0.2783	-0.4717	0.08083	<.0001	10

Table e- 2 Part A: Rate of change in CDR Sum of Boxes for MCs, NCs, and its difference between MCs and NCs at each EYO point for Model A (p values were based on t-test using the LMEs)

CDR SB (Model A)										
EYO	MCs			NCs			MC-NC			EYO
	Mean	SE	P values	Mean	SE	P values	Mean	SE	P values	
-25	-0.1171	0.1581	0.4605	-0.01496	0.1907	0.9376	-0.1021	0.2477	0.6809	-25
-24	-0.09428	0.1504	0.5320	-0.01085	0.1807	0.9522	-0.08343	0.2350	0.7233	-24
-23	-0.07145	0.1428	0.6178	-0.00673	0.1709	0.9686	-0.06472	0.2227	0.7719	-23
-22	-0.04863	0.1355	0.7203	-0.00262	0.1615	0.9871	-0.04601	0.2108	0.8276	-22
-21	-0.02581	0.1284	0.8411	0.001497	0.1524	0.9922	-0.02731	0.1993	0.8913	-21
-20	-0.00299	0.1217	0.9804	0.005612	0.1438	0.9689	-0.00860	0.1883	0.9637	-20
-19	0.01983	0.1153	0.8638	0.009727	0.1357	0.9430	0.01011	0.1781	0.9548	-19
-18	0.04265	0.1094	0.6974	0.01384	0.1282	0.9142	0.02881	0.1685	0.8645	-18
-17	0.06548	0.1040	0.5302	0.01796	0.1215	0.8827	0.04752	0.1599	0.7668	-17
-16	0.08830	0.09917	0.3752	0.02207	0.1156	0.8489	0.06622	0.1523	0.6645	-16
-15	0.1111	0.09503	0.2448	0.02619	0.1107	0.8135	0.08493	0.1459	0.5616	-15
-14	0.1339	0.09168	0.1468	0.03030	0.1070	0.7776	0.1036	0.1409	0.4635	-14
-13	0.1568	0.08919	0.0815	0.03442	0.1046	0.7427	0.1223	0.1374	0.3752	-13
-12	0.1796	0.08764	0.0428	0.03853	0.1035	0.7104	0.1411	0.1356	0.3004	-12
-11	0.2024	0.08708	0.0219	0.04265	0.1038	0.6821	0.1598	0.1355	0.2408	-11
-10	0.2252	0.08754	0.0114	0.04676	0.1056	0.6586	0.1785	0.1371	0.1956	-10
-9	0.2480	0.08899	0.0062	0.05088	0.1086	0.6403	0.1972	0.1403	0.1627	-9
-8	0.2709	0.09138	0.0037	0.05499	0.1128	0.6270	0.2159	0.1451	0.1397	-8
-7	0.2937	0.09465	0.0024	0.05911	0.1182	0.6179	0.2346	0.1513	0.1239	-7
-6	0.3165	0.09871	0.0018	0.06322	0.1245	0.6125	0.2533	0.1588	0.1134	-6
-5	0.3393	0.1035	0.0014	0.06734	0.1315	0.6097	0.2720	0.1673	0.1067	-5
-4	0.3622	0.1088	0.0012	0.07145	0.1393	0.6091	0.2907	0.1767	0.1027	-4
-3	0.3850	0.1147	0.0011	0.07557	0.1477	0.6099	0.3094	0.1869	0.1006	-3
-2	0.4078	0.1210	0.0010	0.07968	0.1565	0.6117	0.3281	0.1978	0.0999	-2
-1	0.4306	0.1277	0.0010	0.08380	0.1658	0.6142	0.3468	0.2092	0.1001	-1
0	0.7191	0.1075	<.0001	0.07800	0.1533	0.6120	0.6411	0.1872	0.0009	0
1	1.0076	0.09595	<.0001	0.07221	0.1440	0.6170	0.9354	0.1730	<.0001	1
2	1.2961	0.09628	<.0001	0.06641	0.1383	0.6319	1.2297	0.1685	<.0001	2
3	1.5846	0.1084	<.0001	0.06062	0.1367	0.6583	1.5240	0.1745	<.0001	3
4	1.8731	0.1290	<.0001	0.05482	0.1394	0.6949	1.8183	0.1900	<.0001	4
5	2.1616	0.1547	<.0001	0.04903	0.1462	0.7379	2.1125	0.2129	<.0001	5
6	2.4501	0.1834	<.0001	0.04323	0.1564	0.7828	2.4068	0.2411	<.0001	6
7	2.7386	0.2139	<.0001	0.03744	0.1696	0.8257	2.7011	0.2731	<.0001	7
8	3.0270	0.2456	<.0001	0.03164	0.1850	0.8645	2.9954	0.3075	<.0001	8
9	3.3155	0.2780	<.0001	0.02585	0.2021	0.8985	3.2897	0.3437	<.0001	9
10	3.6040	0.3108	<.0001	0.02005	0.2206	0.9277	3.5840	0.3812	<.0001	10

Table e- 2 Part A: Rate of change in CSF p- tau₁₈₁ for MCs, NMCs, and its difference between MCs and NCs at each EYO point for Model A (p values were based on t-test using the LMEs)

CSF P tau ₁₈₁ (Model A)										
EYO	MCs			NCs			MC-NC			EYO
	Mean	SE	P values	Mean	SE	P values	Mean	SE	P values	
-25*	-1.2101	2.9406	0.6824	3.3120	6.8627	0.6314	-0.4157	4.5303	0.9272	-25
-24	-1.1165	2.7596	0.6875	3.2247	6.6254	0.6285	-0.2348	4.2347	0.9560	-24
-23	-1.0230	2.5811	0.6935	3.1374	6.3895	0.6255	-0.05394	3.9433	0.9891	-23
-22	-0.9294	2.4055	0.7008	3.0501	6.1553	0.6224	0.1269	3.6572	0.9724	-22
-21	-0.8358	2.2337	0.7098	2.9628	5.9227	0.6191	0.3078	3.3778	0.9277	-21
-20	-0.7422	2.0665	0.7209	2.8755	5.6922	0.6156	0.4887	3.1069	0.8756	-20
-19	-0.6487	1.9051	0.7349	2.7882	5.4639	0.6121	0.6696	2.8468	0.8150	-19
-18	-0.5551	1.7512	0.7526	2.7008	5.2382	0.6084	0.8505	2.6009	0.7450	-18
-17	-0.4615	1.6069	0.7751	2.6135	5.0153	0.6045	1.0314	2.3735	0.6657	-17
-16	-0.3679	1.4750	0.8040	2.5262	4.7956	0.6006	1.2123	2.1705	0.5789	-16
-15	-0.2744	1.3592	0.8408	2.4389	4.5798	0.5967	1.3931	1.9994	0.4891	-15
-14	-0.1808	1.2638	0.8868	2.3516	4.3682	0.5927	1.5740	1.8688	0.4036	-14
-13	-0.08722	1.1939	0.9420	2.2643	4.1616	0.5887	1.7549	1.7878	0.3309	-13
-12	0.006360	1.1539	0.9956	2.1770	3.9607	0.5850	1.9358	1.7630	0.2774	-12
-11	0.09994	1.1471	0.9309	2.0897	3.7664	0.5814	2.1167	1.7970	0.2443	-11
-10	0.1935	1.1741	0.8697	2.0024	3.5799	0.5784	2.2976	1.8865	0.2289	-10
-9	0.2871	1.2325	0.8168	1.9151	3.4023	0.5760	2.4785	2.0241	0.2264	-9
-8	0.3807	1.3183	0.7739	1.8277	3.2353	0.5746	2.6593	2.2009	0.2325	-8
-7	0.4742	1.4265	0.7409	1.7404	3.0804	0.5745	2.8402	2.4082	0.2437	-7
-6	-0.1459	1.2862	0.9102	1.8927	3.1411	0.5495	2.0678	2.2217	0.3564	-6
-5	-0.7660	1.1521	0.5092	2.0450	3.2107	0.5270	1.2955	2.0471	0.5297	-5
-4	-1.3861	1.0267	0.1830	2.1973	3.2888	0.5071	0.5231	1.8879	0.7828	-4
-3	-2.0062	0.9135	0.0327	2.3495	3.3746	0.4894	-0.2493	1.7482	0.8872	-3
-2	-2.6263	0.8176	0.0023	2.5018	3.4677	0.4739	-1.0217	1.6330	0.5343	-2
-1	-3.2464	0.7458	<.0001	2.6541	3.5674	0.4603	-1.7941	1.5479	0.2518	-1
0	-3.8665	0.7054	<.0001	2.8064	3.6732	0.4484	-2.5664	1.4979	0.0927	0
1	-4.4866	0.7018	<.0001	2.9587	3.7846	0.4380	-3.3388	1.4867	0.0291	1
2	-5.1067	0.7357	<.0001	3.1109	3.9012	0.4289	-4.1112	1.5150	0.0091	2
3	-5.7268	0.8022	<.0001	3.2632	4.0224	0.4210	-4.8836	1.5808	0.0032	3
4	-6.3469	0.8941	<.0001	3.4155	4.1479	0.4141	-5.6560	1.6796	0.0014	4
5	-6.9670	1.0046	<.0001	3.5678	4.2773	0.4081	-6.4283	1.8061	0.0008	5
6	-7.5871	1.1280	<.0001	3.7200	4.4102	0.4029	-7.2007	1.9548	0.0006	6
7	-8.2072	1.2607	<.0001	3.8723	4.5464	0.3983	-7.9731	2.1212	0.0004	7
8	-8.8273	1.4000	<.0001	4.0246	4.6855	0.3944	-8.7455	2.3013	0.0004	8
9	-9.4474	1.5441	<.0001	4.1769	4.8273	0.3909	-9.5178	2.4922	0.0004	9
10	-10.0675	1.6918	<.0001	4.3292	4.9716	0.3880	-10.2902	2.6917	0.0004	10

*The minimum EYO for this outcome is -24.3, thus the estimation at EYO -25 was extrapolated using LMEs

Table e- 2 Part A: Rate of change in hippocampal volumes for MCs, NCs, and its difference between MCs and NCs at each EYO point for Model A (p values were based on t-test using the LMEs)

MRI Hippocampal Volumes (Model A)										
EYO	MCs			NCs			MC-NC			EYO
	Mean	SE	P values	Mean	SE	P values	Mean	SE	P values	
-25	3.1273	28.9934	0.9146	-3.8642	28.2316	0.8917	6.9915	40.2438	0.8628	-25
-24	1.1691	27.4237	0.9662	-4.2306	26.5468	0.8741	5.3997	37.9607	0.8875	-24
-23	-0.7891	25.8892	0.9758	-4.5970	24.9183	0.8544	3.8079	35.7427	0.9156	-23
-22	-2.7473	24.3963	0.9108	-4.9634	23.3580	0.8326	2.2161	33.6030	0.9477	-22
-21	-4.7055	22.9533	0.8385	-5.3298	21.8806	0.8086	0.6243	31.5573	0.9843	-21
-20	-6.6637	21.5702	0.7587	-5.6962	20.5038	0.7824	-0.9675	29.6252	0.9741	-20
-19	-8.6220	20.2592	0.6724	-6.0627	19.2494	0.7542	-2.5593	27.8304	0.9271	-19
-18	-10.5802	19.0353	0.5810	-6.4291	18.1428	0.7247	-4.1511	26.2010	0.8748	-18
-17	-12.5384	17.9163	0.4875	-6.7955	17.2124	0.6948	-5.7429	24.7698	0.8177	-17
-16	-14.4966	16.9231	0.3960	-7.1619	16.4881	0.6660	-7.3347	23.5727	0.7571	-16
-15	-16.4548	16.0789	0.3114	-7.5283	15.9980	0.6401	-8.9265	22.6472	0.6952	-15
-14	-18.4130	15.4083	0.2381	-7.8948	15.7639	0.6188	-10.5183	22.0272	0.6352	-14
-13	-20.3713	14.9346	0.1791	-8.2612	15.7971	0.6035	-12.1101	21.7391	0.5801	-13
-12	-22.3295	14.6770	0.1349	-8.6276	16.0961	0.5945	-13.7019	21.7960	0.5326	-12
-11	-24.2877	14.6469	0.1039	-8.9940	16.6465	0.5915	-15.2937	22.1953	0.4942	-11
-10	-26.2459	14.8456	0.0836	-9.3604	17.4245	0.5937	-16.8855	22.9190	0.4649	-10
-9	-28.2041	15.2642	0.0709	-9.7269	18.4012	0.5996	-18.4773	23.9377	0.4440	-9
-8	-30.1623	15.8854	0.0637	-10.0933	19.5469	0.6080	-20.0691	25.2158	0.4301	-8
-7	-32.1206	16.6865	0.0603	-10.4597	20.8338	0.6180	-21.6609	26.7160	0.4216	-7
-6	-34.0788	17.6430	0.0595	-10.8261	22.2373	0.6286	-23.2527	28.4031	0.4171	-6
-5	-36.0370	18.7312	0.0604	-11.1925	23.7368	0.6394	-24.8445	30.2459	0.4156	-5
-4	-37.9952	19.9294	0.0627	-11.5590	25.3152	0.6501	-26.4362	32.2177	0.4160	-4
-3	-39.9534	21.2191	0.0659	-11.9254	26.9586	0.6603	-28.0280	34.2962	0.4179	-3
-2	-60.6996	18.2036	0.0017	-11.0345	23.3587	0.6388	-49.6650	29.5983	0.1000	-2
-1	-81.4457	15.9322	<.0001	-10.1437	20.7671	0.6275	-71.3020	26.1566	0.0090	-1
0	-102.19	14.7527	<.0001	-9.2529	19.5883	0.6389	-92.9389	24.5060	0.0004	0
1	-122.94	14.9262	<.0001	-8.3620	20.0727	0.6789	-114.58	25.0039	<.0001	1
2	-143.68	16.4099	<.0001	-7.4712	22.1112	0.7369	-136.21	27.5340	<.0001	2
3	-164.43	18.8977	<.0001	-6.5804	25.3315	0.7962	-157.85	31.6120	<.0001	3
4	-185.18	22.0523	<.0001	-5.6896	29.3469	0.8471	-179.49	36.7259	<.0001	4
5	-205.92	25.6287	<.0001	-4.7987	33.8760	0.8880	-201.12	42.5033	<.0001	5
6	-226.67	29.4737	<.0001	-3.9079	38.7390	0.9201	-222.76	48.7089	<.0001	6
7	-247.41	33.4949	<.0001	111.39	684.91	0.8715	-244.40	55.1982	<.0001	7
8	-268.16	37.6360	<.0001	-2.1262	49.0643	0.9656	-266.03	61.8822	<.0001	8
9	-288.91	41.8613	<.0001	-1.2354	54.4131	0.9820	-287.67	68.7040	0.0001	9
10	-309.65	46.1477	<.0001	-0.3446	59.8418	0.9954	-309.31	75.6264	0.0002	10

Table e- 2 Part B: Rate of change in CSF A β 42 for MCs, NMCs, and its difference between MCs and NCs at each EYO point for Model B (p values were based on t-test using the LMEs)

CSF A β 42 (Model B)										
EYO	MCs			NCs			MC-NC			EYO
	Mean	SE	P values	Mean	SE	P values	Mean	SE	P values	
-25*	-46.4828	9.5927	<.0001	-8.5874	9.4051	0.3655	-37.8954	13.4342	0.0068	-25
-24	-45.2052	9.2013	<.0001	-8.3507	9.0357	0.3597	-36.8545	12.8960	0.0062	-24
-23	-43.9276	8.8129	<.0001	-8.1139	8.6718	0.3539	-35.8137	12.3640	0.0055	-23
-22	-42.6500	8.4282	<.0001	-7.8772	8.3141	0.3479	-34.7729	11.8389	0.0050	-22
-21	-41.3725	8.0475	<.0001	-7.6404	7.9635	0.3419	-33.7320	11.3217	0.0044	-21
-20	-40.0949	7.6714	<.0001	-7.4037	7.6209	0.3359	-32.6912	10.8134	0.0039	-20
-19	-38.8173	7.3007	<.0001	-7.1669	7.2875	0.3300	-31.6504	10.3155	0.0034	-19
-18	-37.5397	6.9363	<.0001	-6.9302	6.9645	0.3244	-30.6095	9.8295	0.0030	-18
-17	-36.2621	6.5792	<.0001	-6.6934	6.6536	0.3192	-29.5687	9.3572	0.0027	-17
-16	-34.9845	6.2306	<.0001	-6.4567	6.3564	0.3145	-28.5279	8.9008	0.0023	-16
-15	-33.7070	5.8920	<.0001	-6.2199	6.0750	0.3107	-27.4870	8.4630	0.0021	-15
-14	-32.4294	5.5654	<.0001	-5.9832	5.8116	0.3081	-26.4462	8.0467	0.0018	-14
-13	-31.1518	5.2528	<.0001	-5.7464	5.5689	0.3070	-25.4054	7.6555	0.0017	-13
-12	-29.8742	4.9571	<.0001	-5.5097	5.3497	0.3079	-24.3645	7.2934	0.0016	-12
-11	-28.5966	4.6813	<.0001	-5.2729	5.1569	0.3114	-23.3237	6.9649	0.0015	-11
-10	-27.3190	4.4292	<.0001	-5.0362	4.9936	0.3180	-22.2829	6.6750	0.0016	-10
-9	-26.0414	4.2050	<.0001	-4.7994	4.8628	0.3283	-21.2420	6.4289	0.0017	-9
-8	-24.7639	4.0135	<.0001	-4.5627	4.7671	0.3430	-20.2012	6.2318	0.0021	-8
-7	-23.4863	3.8595	<.0001	-4.3259	4.7088	0.3626	-19.1604	6.0885	0.0028	-7
-6	-22.2087	3.7476	<.0001	-4.0892	4.6891	0.3873	-18.1195	6.0028	0.0040	-6
-5	-20.9311	3.6817	<.0001	-3.8524	4.7086	0.4171	-17.0787	5.9772	0.0062	-5
-4	-19.6535	3.6642	<.0001	-3.6157	4.7668	0.4516	-16.0379	6.0125	0.0102	-4
-3	-18.3759	3.6959	<.0001	-3.3789	4.8623	0.4903	-14.9970	6.1076	0.0175	-3
-2	-17.0984	3.7755	<.0001	-3.1422	4.9930	0.5320	-13.9562	6.2598	0.0302	-2
-1	-15.8208	3.9000	0.0002	-2.9054	5.1561	0.5756	-12.9154	6.4651	0.0511	-1
0	-14.5432	4.0654	0.0008	-2.6687	5.3488	0.6200	-11.8745	6.7185	0.0831	0
1	-13.2656	4.2669	0.0031	-2.4319	5.5680	0.6641	-10.8337	7.0150	0.1287	1
2	-11.9880	4.4996	0.0103	-2.1952	5.8106	0.7072	-9.7929	7.3492	0.1886	2
3	-10.7104	4.7590	0.0288	-1.9584	6.0738	0.7484	-8.7520	7.7163	0.2620	3
4	-9.4328	5.0410	0.0671	-1.7217	6.3551	0.7876	-7.7112	8.1118	0.3463	4
5	-8.1553	5.3419	0.1330	-1.4849	6.6523	0.8243	-6.6704	8.5317	0.4379	5
6	-6.8777	5.6588	0.2298	-1.2481	6.9632	0.8585	-5.6295	8.9727	0.5332	6
7	-5.6001	5.9891	0.3542	-1.0114	7.2861	0.8901	-4.5887	9.4317	0.6287	7
8	-4.3225	6.3308	0.4978	-0.7746	7.6195	0.9194	-3.5479	9.9064	0.7217	8
9	-3.0449	6.6820	0.6505	-0.5379	7.9620	0.9464	-2.5070	10.3944	0.8104	9
10	-1.7673	7.0414	0.8028	-0.3011	8.3126	0.9712	-1.4662	10.8941	0.8935	10

*The minimum EYO for this outcome is -24.3, thus the estimation at EYO -25 was extrapolated using LMEs

Table e- 2 Part B: Rate of in Precuneus PiB SUVR change for MCs, NMCs, and its difference between MCs and NCs at each EYO point for Model B (p values were based on t-test using the LMEs)

Cortical Aβ PET (Model B)										
EYO	MCs			NCs			MC-NC			EYO
	Mean	SE	P values	Mean	SE	P values	Mean	SE	P values	
-25	0.06720	0.01873	0.0007	0.002619	0.02268	0.9085	0.06458	0.02941	0.0324	-25
-24	0.06785	0.01794	0.0004	0.002425	0.02166	0.9113	0.06542	0.02812	0.0238	-24
-23	0.06849	0.01717	0.0002	0.002232	0.02067	0.9144	0.06626	0.02686	0.0168	-23
-22	0.06914	0.01642	<.0001	0.002038	0.01970	0.9180	0.06710	0.02563	0.0115	-22
-21	0.06978	0.01570	<.0001	0.001844	0.01876	0.9221	0.06794	0.02445	0.0075	-21
-20	0.07043	0.01500	<.0001	0.001650	0.01785	0.9267	0.06878	0.02330	0.0047	-20
-19	0.07107	0.01433	<.0001	0.001457	0.01699	0.9320	0.06962	0.02220	0.0028	-19
-18	0.07172	0.01369	<.0001	0.001263	0.01617	0.9380	0.07045	0.02116	0.0016	-18
-17	0.07236	0.01310	<.0001	0.001069	0.01540	0.9449	0.07129	0.02019	0.0009	-17
-16	0.07301	0.01255	<.0001	0.000875	0.01469	0.9527	0.07213	0.01929	0.0004	-16
-15	0.07365	0.01205	<.0001	0.000681	0.01406	0.9615	0.07297	0.01848	0.0002	-15
-14	0.07430	0.01161	<.0001	0.000488	0.01350	0.9713	0.07381	0.01777	0.0001	-14
-13	0.07494	0.01123	<.0001	0.000294	0.01303	0.9821	0.07465	0.01717	<.0001	-13
-12	0.07559	0.01093	<.0001	0.000100	0.01267	0.9937	0.07549	0.01670	<.0001	-12
-11	0.07623	0.01071	<.0001	-0.00009	0.01241	0.9940	0.07633	0.01636	<.0001	-11
-10	0.07688	0.01057	<.0001	-0.00029	0.01228	0.9814	0.07717	0.01616	<.0001	-10
-9	0.07752	0.01051	<.0001	-0.00048	0.01226	0.9688	0.07800	0.01611	<.0001	-9
-8	0.07817	0.01054	<.0001	-0.00068	0.01236	0.9566	0.07884	0.01621	<.0001	-8
-7	0.07881	0.01066	<.0001	-0.00087	0.01258	0.9452	0.07968	0.01645	<.0001	-7
-6	0.07946	0.01087	<.0001	-0.00106	0.01291	0.9347	0.08052	0.01684	<.0001	-6
-5	0.08010	0.01115	<.0001	-0.00126	0.01335	0.9254	0.08136	0.01736	<.0001	-5
-4	0.08075	0.01151	<.0001	-0.00145	0.01388	0.9172	0.08220	0.01799	<.0001	-4
-3	0.08139	0.01193	<.0001	-0.00164	0.01449	0.9101	0.08304	0.01874	<.0001	-3
-2	0.08204	0.01242	<.0001	-0.00184	0.01518	0.9041	0.08388	0.01958	<.0001	-2
-1	0.08268	0.01295	<.0001	-0.00203	0.01593	0.8990	0.08472	0.02050	0.0001	-1
0	0.08333	0.01354	<.0001	-0.00223	0.01673	0.8947	0.08556	0.02150	0.0002	0
1	0.08398	0.01416	<.0001	-0.00242	0.01759	0.8911	0.08639	0.02256	0.0003	1
2	0.08462	0.01482	<.0001	-0.00261	0.01848	0.8881	0.08723	0.02367	0.0005	2
3	0.08527	0.01552	<.0001	-0.00281	0.01941	0.8856	0.08807	0.02483	0.0008	3
4	0.08591	0.01624	<.0001	-0.00300	0.02037	0.8834	0.08891	0.02603	0.0012	4
5	0.08656	0.01698	<.0001	-0.00319	0.02136	0.8817	0.08975	0.02727	0.0018	5
6	0.08720	0.01775	<.0001	-0.00339	0.02237	0.8802	0.09059	0.02854	0.0025	6
7	0.08785	0.01853	<.0001	-0.00358	0.02340	0.8789	0.09143	0.02983	0.0034	7
8	0.08849	0.01933	<.0001	-0.00378	0.02444	0.8778	0.09227	0.03115	0.0045	8
9	0.08914	0.02014	<.0001	-0.00397	0.02551	0.8769	0.09311	0.03249	0.0059	9
10	0.08978	0.02097	<.0001	-0.00416	0.02658	0.8761	0.09395	0.03385	0.0076	10

Table e-2 Part B: Rate of change in Precuneus FDG SUVR for MCs, NMCs, and its difference between MCs and NCs at each EYO point for Model B (p values were based on t-test using the LMEs)

FDG precuneus (Model B)										
EYO	MCs			NCs			MC-NC			EYO
	Mean	SE	P values	Mean	SE	P values	Mean	SE	P values	

Longitudinal Biomarkers in DIAN

-25	0.01263	0.009370	0.1825	0.02899	0.01197	0.0183	-0.01636	0.01518	0.2852	-25
-24	0.01059	0.008979	0.2429	0.02767	0.01141	0.0183	-0.01708	0.01450	0.2433	-24
-23	0.008539	0.008596	0.3244	0.02634	0.01087	0.0183	-0.01780	0.01384	0.2031	-23
-22	0.006492	0.008224	0.4329	0.02501	0.01034	0.0185	-0.01852	0.01319	0.1654	-22
-21	0.004445	0.007863	0.5739	0.02368	0.009830	0.0190	-0.01924	0.01257	0.1310	-21
-20	0.002398	0.007515	0.7507	0.02235	0.009341	0.0198	-0.01995	0.01197	0.1006	-20
-19	0.000351	0.007182	0.9612	0.02102	0.008876	0.0210	-0.02067	0.01140	0.0747	-19
-18	-0.00170	0.006867	0.8057	0.01969	0.008440	0.0229	-0.02139	0.01087	0.0535	-18
-17	-0.00374	0.006572	0.5710	0.01837	0.008036	0.0257	-0.02211	0.01037	0.0369	-17
-16	-0.00579	0.006299	0.3616	0.01704	0.007670	0.0300	-0.02283	0.009912	0.0246	-16
-15	-0.00784	0.006053	0.2002	0.01571	0.007347	0.0364	-0.02355	0.009507	0.0160	-15
-14	-0.00988	0.005835	0.0953	0.01438	0.007074	0.0463	-0.02427	0.009159	0.0102	-14
-13	-0.01193	0.005649	0.0387	0.01305	0.006856	0.0616	-0.02498	0.008875	0.0065	-13
-12	-0.01398	0.005500	0.0135	0.01172	0.006700	0.0851	-0.02570	0.008660	0.0043	-12
-11	-0.01603	0.005388	0.0042	0.01040	0.006608	0.1208	-0.02642	0.008520	0.0029	-11
-10	-0.01807	0.005318	0.0012	0.009067	0.006585	0.1735	-0.02714	0.008458	0.0021	-10
-9	-0.02012	0.005291	0.0003	0.007738	0.006630	0.2476	-0.02786	0.008478	0.0017	-9
-8	-0.02217	0.005307	<.0001	0.006410	0.006742	0.3454	-0.02858	0.008576	0.0015	-8
-7	-0.02421	0.005366	<.0001	0.005082	0.006918	0.4654	-0.02930	0.008753	0.0014	-7
-6	-0.02626	0.005466	<.0001	0.003753	0.007154	0.6017	-0.03001	0.009001	0.0014	-6
-5	-0.02831	0.005606	<.0001	0.002425	0.007443	0.7457	-0.03073	0.009317	0.0016	-5
-4	-0.03036	0.005782	<.0001	0.001096	0.007780	0.8884	-0.03145	0.009693	0.0019	-4
-3	-0.03240	0.005992	<.0001	-0.00023	0.008158	0.9774	-0.03217	0.01012	0.0023	-3
-2	-0.03445	0.006231	<.0001	-0.00156	0.008573	0.8561	-0.03289	0.01060	0.0029	-2
-1	-0.03650	0.006497	<.0001	-0.00289	0.009019	0.7498	-0.03361	0.01112	0.0036	-1
0	-0.03854	0.006787	<.0001	-0.00422	0.009492	0.6583	-0.03433	0.01167	0.0046	0
1	-0.04059	0.007097	<.0001	-0.00555	0.009988	0.5807	-0.03504	0.01225	0.0058	1
2	-0.04264	0.007425	<.0001	-0.00687	0.01050	0.5152	-0.03576	0.01286	0.0072	2
3	-0.04468	0.007769	<.0001	-0.00820	0.01104	0.4601	-0.03648	0.01350	0.0089	3
4	-0.04673	0.008127	<.0001	-0.00953	0.01158	0.4137	-0.03720	0.01415	0.0108	4
5	-0.04878	0.008496	<.0001	-0.01086	0.01214	0.3746	-0.03792	0.01482	0.0130	5
6	-0.05083	0.008876	<.0001	-0.01219	0.01271	0.3414	-0.03864	0.01550	0.0154	6
7	-0.05287	0.009266	<.0001	-0.01352	0.01329	0.3132	-0.03936	0.01620	0.0181	7
8	-0.05492	0.009663	<.0001	-0.01485	0.01388	0.2891	-0.04007	0.01691	0.0209	8
9	-0.05697	0.01007	<.0001	-0.01617	0.01448	0.2683	-0.04079	0.01763	0.0240	9
10	-0.05901	0.01048	<.0001	-0.01750	0.01508	0.2503	-0.04151	0.01836	0.0273	10

Table e-2 Part C: Rate of change in CSF total Tau for MCs, NMCs, and its difference between MCs and NCs at each EYO point for Model C (p values were based on t-test using the LMEs)

CSF total Tau (Model C)										
EYO	MCs			NCs			MC-NC			EYO
	Mean	SE	P values	Mean	SE	P values	Mean	SE	P values	
-25* to 10	0.4897	0.9908	0.6233	0.2032	1.2811	0.8746	0.2865	1.6192	0.8603	-25* to 10

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*The minimum EYO for this outcome is -24.3, thus the estimation at EYO -25 was extrapolated using LMEs. The rate of change is not associated with baseline EYO, thus the rate of change is the same from EYO -25 to 10.