

**Supplemental Table I. Rates of change comparisons in biomarkers between ADNI participants and DIAN mutation carriers, adjusted for APOE4, gender, education, and their interactions with cohort. Total sample size: ADNI=559, DIAN=292**

Biomarker	Slope Before Onset			Slope After Onset		
	ADNI	DIAN MC	Difference	ADNI	DIAN MC	Difference
CDR-SB	0.124 (0.027) [p<0.0001, t=4.58]	0.003 (0.010) [p=0.7457, t=0.32]	0.1206 {0.06378 to 0.1775} [p<0.0001, t=4.17]	0.707 (0.023) [p<0.0001, t=31.29]	1.000 (0.063) [p<0.0001, t=15.93]	-0.2924 {-0.4234 to -0.1614} [p<0.0001, t=-4.38]
Cognitive composite	-0.007 (0.007) [p=0.3427, t=-0.95]	-0.005 (0.004) [p=0.1783, t=-1.35]	-0.00137 {-0.01755 to 0.01480} [p=0.8678, t=-0.17]	-0.167 (0.007) [p<0.0001, t=-24.13]	-0.281 (0.020) [p<0.0001, t=-13.68]	0.1135 {0.07097 to 0.1561} [p<0.0001, t=5.24]
Hippocampal volume (mm <sup>3</sup> )	-114.110 (17.732) [p<0.0001, t=-6.44]	-16.249 (6.580) [p=0.0146, t=-2.47]	-97.8609 {-135.03 to - 60.6966} [p<0.0001, t=-5.17]	-218.450 (10.999) [p<0.0001, t=-19.86]	-348.830 (26.819) [p<0.0001, t=-13.01]	130.38 {73.3785 to 187.37} [p<0.0001, t=4.50]
Precuneus thickness (mm)	-0.003 (0.007) [p=0.7144, t=-0.37]	-0.014 (0.002) [p<0.0001, t=-6.41]	0.01123 {-0.00386 to 0.02633} [p=0.1443, t=1.46]	-0.035 (0.004) [p<0.0001, t=-8.33]	-0.104 (0.010) [p<0.0001, t=-10.84]	0.06949 {0.04879 to 0.09019} [p<0.0001, t=6.61]
Amyloid PET (mean CL)	1.342 (0.873) [p=0.1250, t=1.54]	1.948 (0.151) [p<0.0001, t=12.88]	-0.6058 {-2.3467 to 1.1351} [p=0.4944, t=-0.68]	2.208 (0.374) [p<0.0001, t=5.90]	4.176 (0.873) [p<0.0001, t=4.78]	-1.9673 {-3.8436 to -0.09100} [p=0.0400, t=-2.07]
CSF A $\beta_{42/40}$ (pg/mL for both CSF A $\beta_{42}$ and CSF A $\beta_{40}$ )	-0.001 (0.0005) [p=0.0754, t=-1.79]	-0.003 (0.0002) [p<0.0001, t=-11.30]	0.001573 {0.000493 to 0.002653} [p=0.0045, t=2.87]	-0.0005 (0.0002) [p=0.0019, t=-3.17]	0.0006 (0.0003) [p=0.1022, t=1.64]	-0.00107 {-0.00182 to - 0.00031} [p=0.0058, t=-2.79]
CSF tau (pg/mL)	6.215 (3.010) [p=0.0468, t=2.00]	6.356 (0.752) [p<0.0001, t=8.45]	-0.1411 {-6.4401 to 6.1579} [p=0.9648, t=-0.04]	7.722 (2.042) [p=0.0002, t=3.78]	1.4533 (3.952) [p=0.7134, t=0.37]	6.2689 {-2.4924 to 15.0302} [p=0.1600, t=-1.41]
CSF p-tau <sub>181</sub> (pg/mL)	1.004 (0.468) [p=0.0326, t=2.15]	1.097 (0.126) [p<0.0001, t=8.68]	-0.09317 {-1.0462 to 0.8599} [p=0.8476, t=-0.19]	0.639 (0.264) [p=0.0164, t=2.42]	-0.026 (0.511) [p=0.9593, t=-0.05]	0.6655 {-0.4673 to 1.7983} [p=0.2483, t=1.16]

Values in parentheses represent the standard error of the estimates. Values in brackets represent the p-value and t-statistic estimated with the Satterthwaite Method for testing whether the group-specific rates of change are equal to 0 with a two-sided t-test. The range in braces is the 95% confidence interval for the difference in slopes between the two cohorts. Adjusted analyses used unstructured covariance matrix among random effects, except CSF A $\beta_{42/40}$ , CSF p-tau<sub>181</sub>, Cognitive Composite, and CDR-SB which used variance components.

**Supplemental Table 2. Rates of change comparisons in biomarkers between ADNI participants and DIAN mutation carriers, adjusted for APOE4, gender, education, history of diabetes, history of depression, and history of hypertension. Total sample size: ADNI=559, DIAN=292**

Biomarker	Slope Before Onset			Slope After Onset		
	ADNI	DIAN MC	Difference	ADNI	DIAN MC	Difference
CDR-SB	0.178 (0.057) [p=0.0019, t=3.12]	0.065 (0.058) [p=0.2616, t=1.12]	0.1129 {0.05677 to 0.1691} [p<0.0001, t=3.95]	0.744 (0.051) [p<0.0001, t=14.61]	1.113 (0.068) [p<0.0001, t=16.28]	-0.3693 {-0.4960 to -0.2426} [p<0.0001, t=-5.72]
Cognitive composite	0.009 (0.016) [p=0.5645, t=0.58]	0.002 (0.017) [p=0.8820, t=-0.15]	0.006757 {-0.01012 to 0.02364} [p=0.4324, t=0.79]	-0.195 (0.016) [p<0.0001, t=-12.18]	-0.301 (0.022) [p<0.0001, t=-13.89]	0.1059 {0.06449 to 0.1473} [p<0.0001, t=5.02]
Hippocampal volume (mm <sup>3</sup> )	-139.410 (35.882) [p<0.0001, t=-3.89]	-51.113 (36.029) [p=0.1565, t=-1.42]	-88.2990 {-125.23 to - 51.3692} [p<0.0001, t=-4.69]	-251.110 (24.059) [p<0.0001, t=-10.44]	-340.630 (30.386) [p<0.0001, t=-11.21]	89.5248 {33.0687 to 145.98} [p=0.0020, t=3.12]
Precuneus thickness (mm)	0.007 (0.014) [p=0.6305, t=0.48]	0.004 (0.014) [p=0.7850, t=0.27]	0.003029 {-0.01192 to 0.01797} [p=0.6909, t=0.40]	-0.035 (0.009) [p<0.0001, t=-3.90]	-0.108 (0.011) [p<0.0001, t=-9.66]	0.07260 {0.05210 to 0.09310} [p<0.0001, t=6.97]
Amyloid PET (mean CL)	3.649 (1.862) [p=0.0505, t=1.96]	3.988 (1.849) [p=0.0314, t=2.16]	-0.3391 {-2.1312 to 1.4530} [p=0.7102, t=-0.37]	2.368 (0.828) [p=0.0046, t=2.86]	3.091 (1.032) [p=0.0030, t=3.00]	-0.7237 {-2.6569 to 1.2094} [p=0.4613, t=-0.74]
CSF A $\beta_{42/40}$ (pg/mL for both)	-0.002 (0.0009) [p=0.0784, t=-1.77]	-0.003 (0.0009) [p=0.0013, t=-3.24]	0.001382 {0.000223 to 0.002540} [p=0.0197, t=2.35]	-0.0005 (0.0003) [p=0.1376, t=-1.50]	0.0005 (0.0004) [p=0.2554, t=1.14]	-0.00093 {-0.00165 to - 0.00020} [p=0.0123, t=-2.54]
CSF A $\beta_{42}$ and CSF A $\beta_{40}$	7.716 (5.990) [p=0.1987, t=1.29]	4.791 (6.056) [p=0.4295, t=0.79]	2.9253 {-3.3898 to 9.2404} [p=0.3629, t=0.91]	7.314 (4.250) [p=0.0868, t=1.72]	2.849 (5.115) [p=0.5780, t=0.56]	4.4644 {-4.7910 to 13.7198} [p=0.3428, t=0.95]
CSF tau (pg/mL)	0.923 (0.861) [p=0.2846, t=1.07]	0.849 (0.870) [p=0.3302, t=0.98]	0.07474 {-0.8247 to 0.9742} [p=0.8703, t=0.16]	0.890 (0.538) [p=0.1000, t=1.65]	0.160 (0.649) [p=0.8055, t=0.25]	0.7296 {-0.4368 to 1.8961} [p=0.2189, t=1.23]

Values in parentheses represent the standard error of the estimates. Values in brackets represent the p-value and t-statistic estimated with the Satterthwaite Method for testing whether the group-specific rates of change are equal to 0 with a two-sided t-test. The range in braces is the 95% confidence interval for the difference in slopes between the two cohorts. Adjusted analyses used variance components error structure among random effects.

**Supplemental Table 3. Between-group comparisons of rates of change between ADNI participants (n=492) and DIAN mutation carriers (n=292) that does not include the n=67 ADNI participants that were symptomatic yet amyloid negative.**

	Slope Before Onset			Slope After Onset		
	ADNI	DIAN MC	Difference	ADNI	DIAN MC	Difference
CDR-SB	0.098 (0.027) [p=0.0003, t=3.66]	0.006 (0.009) [p=0.4695, t=0.72]	0.09175 {0.03630 to 0.1472} [p=0.0012, t=3.24]	0.763 (0.022) [p<0.0001, t=33.79]	1.112 (0.051) [p<0.0001, t=21.81]	-0.3483 {-0.4578 to -0.2388} [p<0.0001, t=-6.25]
Cognitive composite	-0.001 (0.007) [p=0.8932, t=-0.13]	-0.010 (0.004) [p=0.0070, t=-2.73]	0.009276 {-0.00560 to 0.02415} [p=0.2198, t=1.23]	-0.184 (0.008) [p<0.0001, t=-21.81]	-0.302 (0.017) [p<0.0001, t=-17.36]	0.1176 {0.07970 to 0.1556} [p<0.0001, t=6.09]
Hippocampal volume (mm <sup>3</sup> )	-119.050 (18.199) [p<0.0001, t=-6.54]	-20.453 (5.770) [p=0.0005, t=-3.54]	-98.5931 {-136.13 to - 61.0595} [p<0.0001, t=-5.16]	-239.710 (12.511) [p<0.0001, t=-19.16]	-316.520 (21.408) [p<0.0001, t=-14.79]	76.8046 {28.0260 to 125.58} [p=0.0021, t=3.10]
Precuneus thickness (mm)	-0.006 (0.008) [p=0.3959, t=-0.85]	-0.014 (0.002) [p<0.0001, t=-7.41]	0.007339 {-0.00803 to 0.02271} [p=0.3486, t=0.94]	-0.041 (0.005) [p<0.0001, t=-8.70]	-0.112 (0.008) [p<0.0001, t=-14.33]	0.07060 {0.05262 to 0.08859} [p<0.0001, t=7.73]
Amyloid PET (mean CL)	2.250 (0.930) [p=0.0160, t=2.42]	2.410 (0.219) [p<0.0001, t=11.01]	-0.1602 {-2.0390 to 1.7186} [p=0.8670, t=-0.17]	2.916 (0.422) [p<0.0001, t=6.91]	3.4758 (0.686) [p<0.0001, t=5.07]	-0.5592 {-2.1505 to 1.0321} [p=0.4886, t=-0.69]
CSF A $\beta_{42/40}$ (pg/mL for both)	-0.001 (0.0005) [p=0.0166, t=-2.41]	-0.002 (0.0002) [p<0.0001, t=-12.64]	0.001314 {0.000287 to 0.002341} [p=0.0124, t=2.52]	-0.0003 (0.0001) [p=0.0396, t=-2.13]	0.0003 (0.0002) [p=0.1231, t=1.56]	-0.000651 {-0.00118 to - 0.00013} [p=0.0162, t=-2.48]
CSF A $\beta_{42}$ and CSF A $\beta_{40}$	10.342 (2.863) [p=0.0004, t=3.61]	6.507 (0.674) [p<0.0001, t=9.66]	3.8348 {-1.9604 to 9.6300} [p=0.1936, t=1.30]	7.536 (2.339) [p=0.0015, t=3.22]	9.468 (3.318) [p=0.0048, t=2.85]	-1.9313 {-9.9396 to 6.0769} [p=0.6348, t=-0.48]
CSF p-tau <sub>181</sub> (pg/mL)	1.263 (0.398) [p=0.0018, t=3.17]	0.923 (0.086) [p<0.0001, t=10.69]	0.3398 {-0.4638 to 1.1435} [p=0.4055, t=0.83]	0.568 (0.316) [p=0.0745, t=1.80]	1.087 (0.429) [p=0.0121, t=2.53]	-0.5196 {-1.5720 to 0.5327} [p=0.3312, t=-0.97]

Values in parentheses represent the standard error of the estimates. Values in brackets represent the p-value and t-statistic, where degrees of freedom were estimated with the Satterthwaite Method for testing whether the group-specific rates of change are equal to 0 with a two-sided t-test. The range in braces is the 95% confidence interval for the difference in slopes for the two onsets within cohort. Unadjusted analyses used unstructured covariance matrix among random effects, except CSF A $\beta_{42/40}$  and CDR-SB which used variance components.

**Supplemental Table 4. Rates of change comparisons between pathogenic variants represented in DIAN mutation carriers (sample sizes: APP=46, PSEN1=224 and PSEN2=22).**

	Slope Before Onset				Slope After Onset			
	APP	PSEN1	PSEN2	Difference	APP	PSEN1	PSEN2	Difference
CDR-SB	-0.009 (0.022) [p=0.6937, t=-0.39]	0.008 (0.010) [p=0.4468, t=0.76]	-0.008 (0.036) [p=0.8156, t=-0.23]	NS	0.909 (0.141) [p<0.0001, t=6.42]	1.194 (0.059) [p<0.0001, t=20.38]	0.526 (0.256) [p=0.0405, t=2.06]	0.6683 {0.1522 to 1.1844} [p=0.0113, t=2.55] <sup>c</sup>
Cognitive composite	-0.012 (0.009) [p=0.2035, t=-1.28]	-0.009 (0.004) [p=0.0363, t=-2.11]	-0.006 (0.014) [p=0.6559, t=-0.45]	NS	-0.269 (0.047) [p<0.0001, t=-5.70]	-0.317 (0.020) [p<0.0001, t=-16.19]	-0.198 (0.083) [p=0.0174, t=-2.39]	NS
Hippocampal volume (mm <sup>3</sup> )	14.716 (14.476) [p=0.3106, t=1.02]	-24.989 (6.639) [p=0.0002, t=-3.76]	-9.320 (22.506) [p=0.6792, t=-0.41]	39.7049 {8.2907 to 71.1191} [p=0.0135, t=2.49] <sup>a</sup>	-399.440 (54.908) [p<0.0001, t=-7.27]	-309.840 (24.589) [p<0.0001, t=-12.60]	-218.300 (83.044) [p=0.0094, t=-2.63]	NS
Precuneus thickness (mm)	-0.014 (0.005) [p=0.0027, t=-3.03]	-0.015 (0.002) [p<0.0001, t=-6.96]	-0.007 (0.007) [p=0.3545, t=-0.93]	NS	-0.098 (0.020) [p<0.0001, t=-5.04]	-0.115 (0.009) [p<0.0001, t=-13.15]	-0.107 (0.030) [p=0.0005, t=-3.57]	NS
Amyloid PET (mean CL)	1.780 (0.401) [p<0.0001, t=4.44]	1.860 (0.149) [p<0.0001, t=12.47]	3.354 (0.515) [p<0.0001, t=6.51]	-1.5746 {-2.8707 to -0.2785} {-2.5608 to -0.4298} [p=0.0065, t=-2.79] <sup>c</sup>	4.568 (1.824) [p=0.0134, t=2.50]	4.172 (0.794) [p<0.0001, t=5.25]	4.176 (1.949) [p=0.0366, t=2.14]	NS
CSF A $\beta$ <sub>42/40</sub> (pg/mL for both A $\beta$ <sub>42</sub> and A $\beta$ <sub>40</sub> )	-0.003 (0.0005) [p<0.0001, t=-6.42]	-0.003 (0.0002) [p<0.0001, t=-11.30]	-0.002 (0.0006) [p=0.0053, t=-2.81]	NS	-0.001 (0.0009) [p=0.2465, t=-1.16]	0.0005 (0.0003) [p=0.0625, t=1.88]	0.0005 (0.0007) [p=0.4913, t=0.69]	NS
CSF tau (pg/mL)	4.531 (2.119) [p=0.0329, t=2.14]	7.283 (1.005) [p<0.0001, t=7.25]	4.036 (3.134) [p=0.1983, t=1.29]	NS	17.256 (9.754) [p=0.078, t=1.77]	7.963 (3.554) [p=0.0260, t=2.24]	2.216 (12.151) [p=0.8557, t=0.18]	NS
CSF p-tau <sub>181</sub> (pg/mL)	0.261 (0.228) [p=0.2587, t=1.14]	1.128 (0.101) [p<0.0001, t=11.19]	0.758 (0.312) [p=0.0167, t=2.43]	-0.8680 {-1.3682 to -0.3677} [p=0.0010, t=-3.48] <sup>a</sup>	3.259 (1.255) [p=0.010, t=2.60]	0.795 (0.448) [p=0.077, t=1.78]	-0.689 (1.467) [p=0.640, t=-0.47]	3.9475 {0.1288 to 7.7662} [p=0.0429, t=2.04] <sup>b</sup>

Values in parentheses represent the standard error of the estimates. Values in brackets represent the p-value and t-statistic estimated with the Satterthwaite Method for testing whether the group-specific rates of change are equal to 0 with a two-sided t-test. The range in braces is the 95% confidence interval for the difference in slopes for two mutation types. NS=not statistically significant. Unadjusted analyses used unstructured covariance matrix among random effects, except CDR-SB, CSF A $\beta$ <sub>42/40</sub>, and CSF tau which used variance components.

<sup>a</sup>APP vs PSEN1; <sup>b</sup>APP vs PSEN2; <sup>c</sup>PSEN1 vs PSEN2.

**Supplemental Table 5. Rates of change comparisons in PSEN1 mutation carriers before and after codon 200 (sample sizes: before codon 200=75 and after codon 200=149).**

	Slope Before Onset			Slope After Onset		
	Before Codon 200	After Codon 200	Difference	Before Codon 200	After Codon 200	Difference
CDR-SB	0.027 (0.018) [p=0.136, t=1.49]	-0.001 (0.013) [p=0.950, t=-0.06]	0.02799 {-0.01572 to 0.07170} [p=0.2093, t=1.26]	0.966 (0.104) [p<0.0001, t=9.29]	1.285 (0.069) [p<0.0001, t=18.62]	-0.3190 {-0.5641 to -0.07379} [p=0.0109, t=-2.56]
Cognitive composite	-0.013 (0.007) [p=0.0768, t=-1.77]	-0.010 (0.005) [p=0.0614, t=-1.87]	-0.00294 {-0.02101 to 0.01513} [p=0.7497, t=-0.32]	-0.295 (0.036) [p<0.0001, t=-8.19]	-0.320 (0.024) [p<0.0001, t=-13.43]	0.02510 {-0.05974 to 0.1099} [p=0.5616, t=0.58]
Hippocampal volume (mm <sup>3</sup> )	-32.400 (12.085) [p=0.0075, t=-2.68]	-22.984 (8.511) [p=0.0070, t=-2.70]	-9.4160 {-38.4246 to 19.5926} [p=0.5243, t=-0.64]	-346.880 (38.381) [p<0.0001, t=-9.04]	-285.770 (30.800) [p<0.0001, t=-9.28]	-61.1118 {-157.92 to 35.6972} [p=0.2152, t=-1.24]
Precuneus thickness (mm)	-0.014 (0.004) [p=0.0003, t=-3.61]	-0.016 (0.003) [p<0.0001, t=-5.69]	0.002271 {-0.00709 to 0.01164} [p=0.6341, t=0.48]	-0.130 (0.014) [p<0.0001, t=-9.38]	-0.104 (0.011) [p<0.0001, t=-9.41]	-9.4160 {-0.06068 to 0.008892} [p=0.1440, t=-1.46]
Amyloid PET (mean CL)	3.116 (0.448) [p<0.0001, t=6.95]	1.977 (0.326) [p<0.0001, t=6.06]	1.1383 {0.04943 to 2.2271} [p=0.0405, t=2.05]	5.220 (1.283) [p<0.001, t=4.07]	2.308 (1.080) [p=0.033, t=2.14]	2.9110 {-0.3934 to 6.2154} [p=0.0840, t=1.74]
CSF A $\beta_{42/40}$ (pg/mL for both CSF A $\beta_{42}$ and CSF A $\beta_{40}$ )	-0.003 (0.0004) [p<0.0001, t=-9.29]	-0.002 (0.0003) [p<0.0001, t=-8.34]	-0.00115 {-0.00202 to -0.00028} [p=0.0098, t=-2.63]	0.001 (0.0005) [p=0.0444, t=2.03]	0.0003 (0.0003) [p=0.3128, t=1.01]	0.000772 {-0.00050 to 0.002043} [p=0.2317, t=1.20]
CSF tau (pg/mL)	8.089 (1.715) [p<0.0001, t=4.72]	7.130 (1.279) [p<0.0001, t=5.58]	0.9582 {-3.2446 to 5.1610} [p=0.6544, t=0.45]	-7.028 (6.605) [p=0.2883, t=-1.06]	14.061 (4.224) [p=0.0010, t=3.33]	-21.0897 {-36.5343 to - 5.6452} [p=0.0076, t=-2.69]
CSF p-tau <sub>181</sub> (pg/mL)	1.377 (0.236) [p<0.0001, t=5.84]	1.223 (0.180) [p<0.0001, t=6.80]	0.1542 {-0.4283 to 0.7368} [p=0.6032, t=0.52]	-1.383 (0.838) [p=0.1001, t=-1.65]	1.042 (0.536) [p=0.0532, t=-1.94]	-2.4248 {-4.3842 to -0.4653} [p=0.0155, t=-2.44]

Values in parentheses represent the standard error of the estimates. Values in brackets represent the p-value and t-statistic estimated with the Satterthwaite Method for testing whether the group-specific rates of change are equal to 0 with a two-sided t-test. The range in braces is the 95% confidence interval for the difference in slopes before and after Codon 200. Unadjusted analyses used unstructured covariance matrix among random effects, except CDR-SB, CSF A $\beta_{42/40}$ , and CSF tau which used variance components.