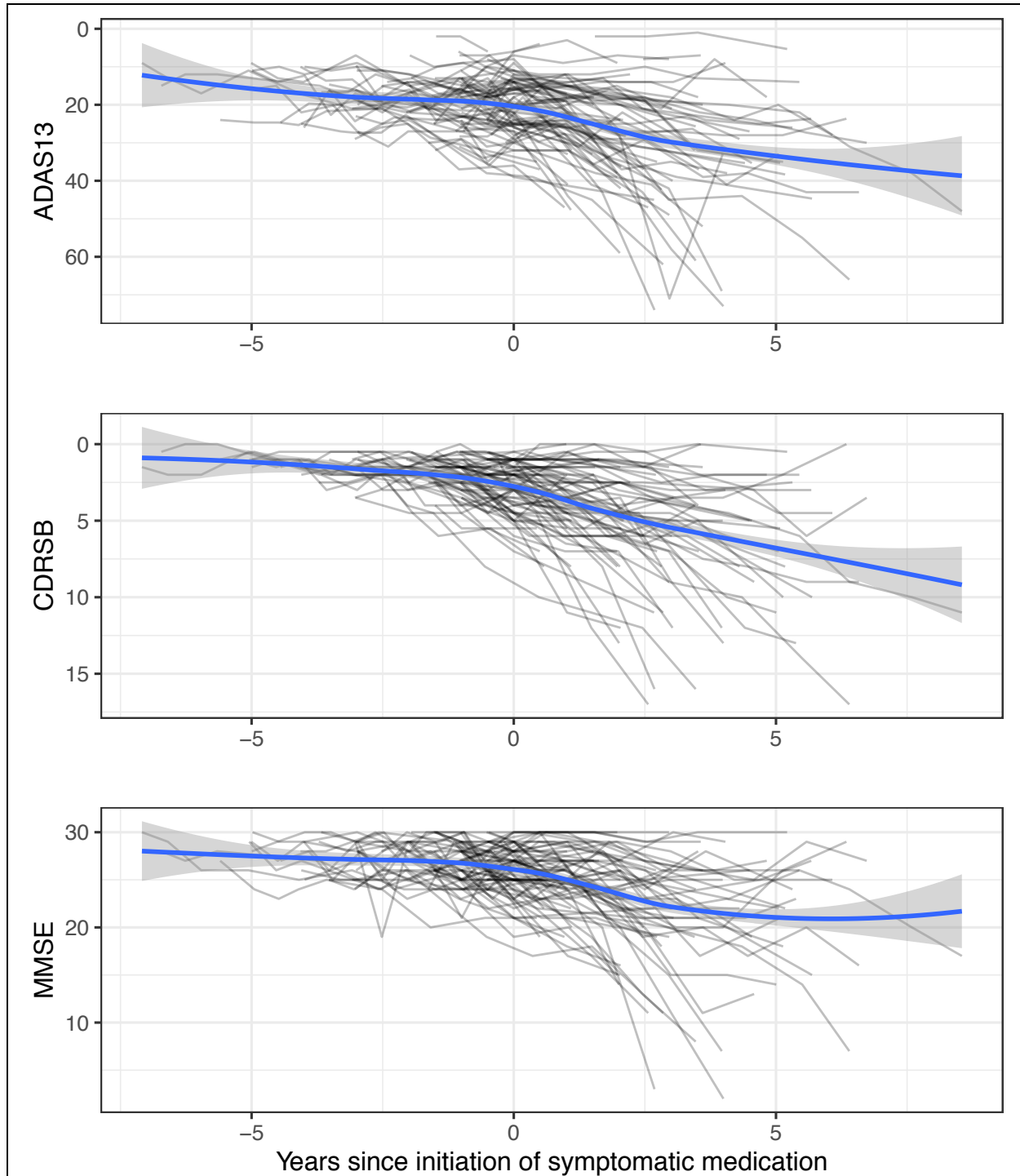


**The Initiation of Symptomatic Medications during Clinical Trials for  
Mild Cognitive Impairment:  
Supplemental Material**

Table A1. Characteristics of ADNI Prodromal participants grouped by whether or not the participant initiated a symptomatic medication during the course of follow-up. P-values are from Pearson's  $\chi^2$  test or Kruskal-Wallis test.

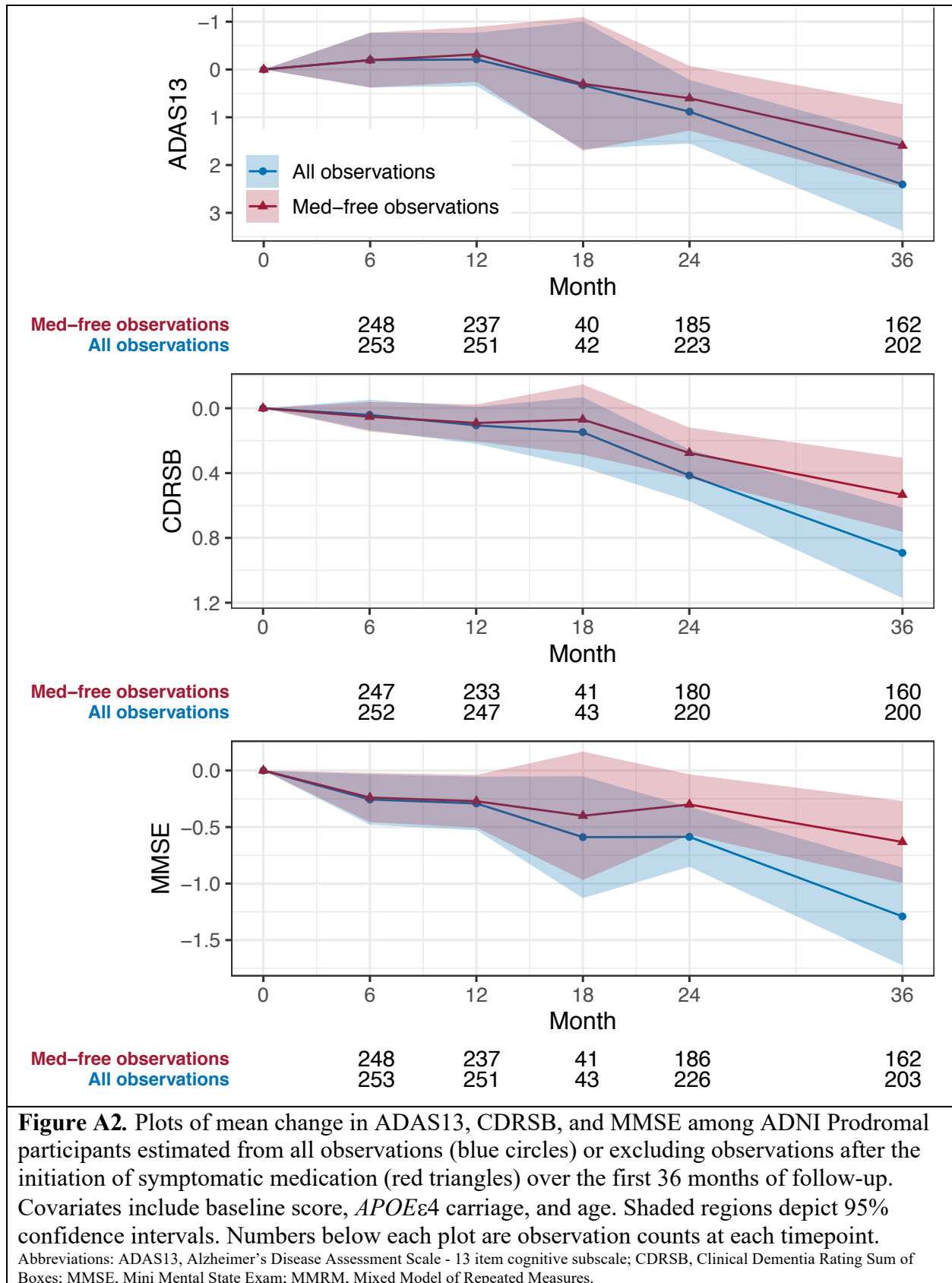
	N	On symptomatic medication at baseline (N=154)	Initiated symptomatic medication (N=75)	Never Initiated symptomatic medication (N=204)	Combined (N=433)	P-value
eMCI at baseline	433	51 (33%)	37 (49%)	121 (59%)	209 (48%)	<0.001
Age (years)	433	72.23 (6.72)	73.49 (6.87)	72.22 (7.61)	72.45 (7.18)	0.301
Sex (female)	433	61 (40%)	33 (44%)	96 (47%)	190 (44%)	0.372
Education (years)	433	16.10 (2.90)	15.59 (2.62)	15.97 (2.89)	15.95 (2.85)	0.316
Ethnicity	433					0.526
Not Hispanic/Latinx		148 (96%)	73 (97%)	200 (98%)	421 (97%)	
Hispanic/Latinx		6 (4%)	2 (3%)	3 (1%)	11 (3%)	
Unknown		0 (0%)	0 (0%)	1 (0%)	1 (0%)	
Race	433					0.436
Am. Indian/Alaskan		0 (0%)	0 (0%)	0 (0%)	0 (0%)	
Asian		0 (0%)	1 (1%)	3 (1%)	4 (1%)	
Hawaiian/Pacific Islander		0 (0%)	0 (0%)	1 (0%)	1 (0%)	
Black		2 (1%)	1 (1%)	9 (4%)	12 (3%)	
White		150 (97%)	71 (95%)	188 (92%)	409 (94%)	
More than one		2 (1%)	2 (3%)	3 (1%)	7 (2%)	
Unknown		0 (0%)	0 (0%)	0 (0%)	0 (0%)	
Marital status	433					0.142
Divorced		10 (6%)	5 (7%)	29 (14%)	44 (10%)	
Married		128 (83%)	60 (80%)	145 (71%)	333 (77%)	
Never married		4 (3%)	1 (1%)	7 (3%)	12 (3%)	
Widowed		12 (8%)	9 (12%)	21 (10%)	42 (10%)	
Unknown		0 (0%)	0 (0%)	2 (1%)	2 (0%)	
APOE $\epsilon$ 4 alleles	430					0.051
0		60 (40%)	26 (35%)	99 (49%)	185 (43%)	
1		63 (42%)	39 (52%)	85 (42%)	187 (43%)	
2		28 (19%)	10 (13%)	20 (10%)	58 (13%)	
CSF A $\beta$ <sub>1-42</sub> (pg/ml)	363	800 (379)	826 (387)	1150 (476)	969 (461)	<0.001
Florbetapir PET (SUVR)	347	1.367 (0.213)	1.337 (0.197)	1.244 (0.207)	1.300 (0.215)	<0.001
CDR Sum of Boxes	433	1.740 (0.933)	1.627 (0.847)	1.235 (0.763)	1.483 (0.872)	<0.001
ADAS-Cog 13	433	18.55 (6.61)	18.29 (6.71)	13.69 (5.79)	16.21 (6.68)	<0.001
MMSE	432	27.44 (1.76)	27.52 (1.74)	28.04 (1.66)	27.73 (1.73)	0.001
Hippocampus (/ICVx1,000)	433	4.370 (0.757)	4.404 (0.727)	4.795 (0.760)	4.576 (0.779)	<0.001
Follow-up (years)	365	4.37 (2.82)	5.32 (2.09)	4.25 (2.77)	4.48 (2.70)	0.004
Exposure to symptomatic medication (years)	433	-	3.218 (1.801)	-	-	-

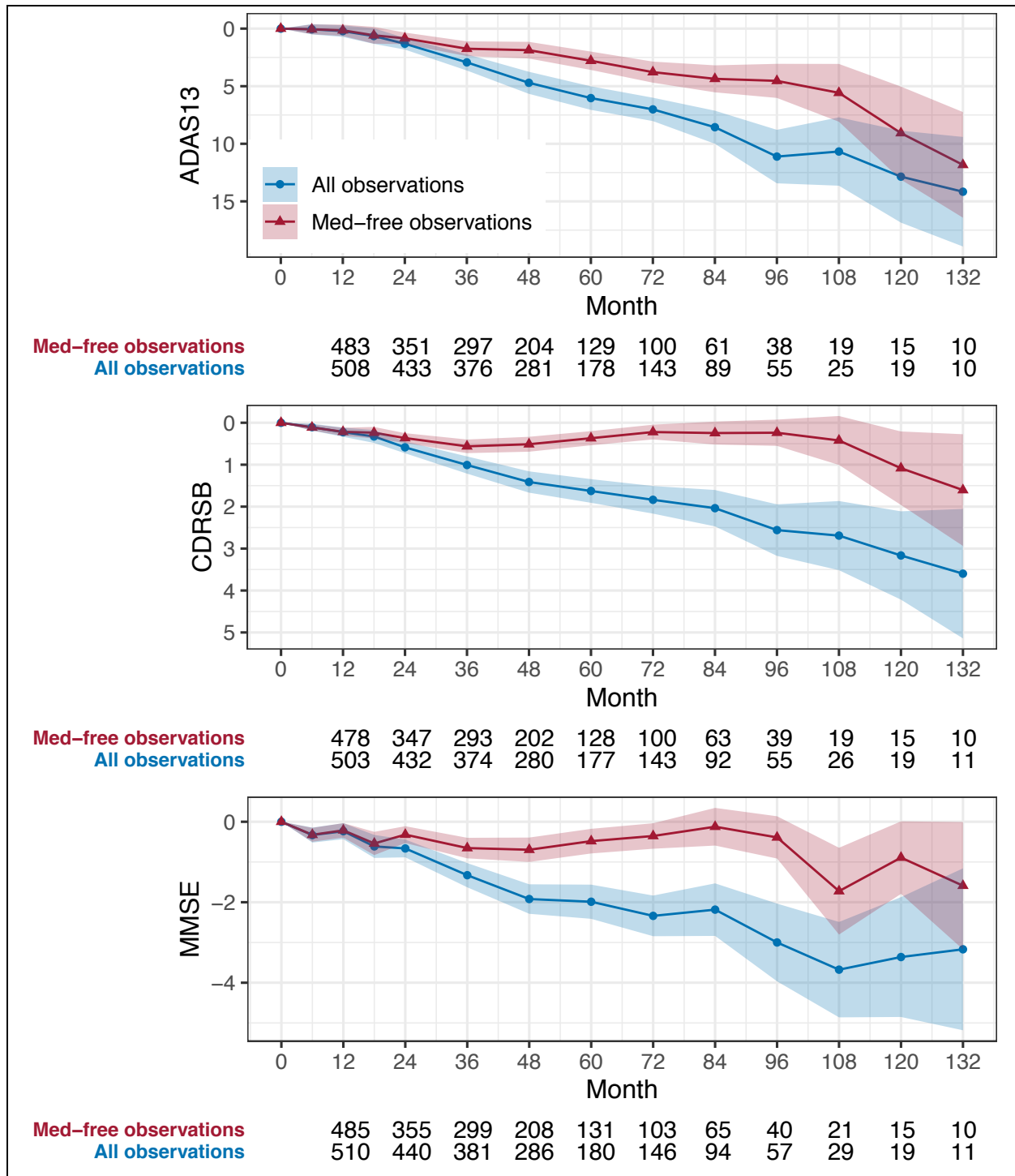
Abbreviations: eMCI, Early Mild Cognitive Impairment; PET, positron emission tomography; SUVR, standard uptake value ratio; CDR, Clinical Dementia Rating; ADAS-Cog, Alzheimer's Disease Assessment Scale – Cognitive subscale; MMSE, Mini Mental State Exam; ICV, Intracranial Volume



**Figure A1.** Spaghetti plots of ADAS13, CDRSB, and MMSE relative to time of initiation of symptomatic medication for ADNI Prodromal participants who initiated symptomatic medication. The blue trend lines estimated by LOESS do not demonstrate a cognitive *improvement* soon after time 0, even though a benefit relative to no treatment cannot be ruled out. Shaded regions depict 95% confidence intervals, not accounting for repeated measures.

Abbreviations: ADAS13, Alzheimer's Disease Assessment Scale - 13 item cognitive subscale; CDRSB, Clinical Dementia Rating Sum of Boxes; MMSE, Mini Mental State Exam; LOESS, LOcally Estimated Scatterplot Smoothing.





**Figure A3.** Plots of mean change in ADAS13, CDRSB, and MMSE among ADNI MCI participants estimated from all observations (blue circles) or excluding observations after the initiation of symptomatic medication (red triangles) over 132 months of follow-up. Covariates include baseline score, *APOE* $\epsilon$ 4 carriage, and age. Shaded regions depict 95% confidence intervals. Numbers below each plot are observation counts at each timepoint.

Abbreviations: ADAS13, Alzheimer’s Disease Assessment Scale - 13 item cognitive subscale; CDRSB, Clinical Dementia Rating Sum of Boxes; MMSE, Mini Mental State Exam; MMRM, Mixed Model of Repeated Measures.

