Supplemental Material

Supplemental Methods

The progression function for each of the biomarkers was modeled as a hyperbola. This is essentially a simple changepoint model (2 lines) but with a smoothed intersection. (Hamiltonian Markov chain Monte-Carlo was used to obtain the solution via the STAN package, and that method requires a smooth first derivative.) This is nearly the simplest possible non-linear effect, but results show that it appears to be sufficient. We anticipate that other biomarkers may require a more flexible function such as monotone splines, e.g., if there is also an upper threshold.

The random effects for each individual were modeled as a multivariate t-distribution with 10 degrees of freedom. For each of the biomarkers we considered the possibility that there will be individuals who are non-progressors, i.e., will never reach a turning point in their progression curve. These can be accommodated in the model by allowing the random effect for that individual to be large, i.e., a turning point after age 100 say. The t-distribution better allows for such outlying values. However, investigation showed that the final result was insensitive to the number of degrees of freedom or replacing the t with a Gaussian. All other parameters used standard vague priors, i.e., as recommended in the rstan user manual.

The fit and computer code are configured to allow for different numbers and types of measurements for each individual. The data are presented where each row contains the participant id, age at measurement, type of measurement (amyloid-β, tau, etc.) and the value of the measurement, along with covariates of male sex, APOE ε4 positivity, education, and ADRC referral. If a particular participant has no tau scans, the tau offset for that participant is not connected to any data and the parameter becomes a random draw from the posterior distribution. (This has no detrimental effect on the solution, other than perhaps a slight increase in compute

time.) These free parameters, being uninformative, are omitted from the final tabulations and graphs of results. The model allows for amyloid-β non-progressors in a natural way: their posterior maximizes with an inflection point at an age that is well beyond the last observation in the sample. A person who is "due to " begin accumulating amyloid-β 10+ years from now is indistinguishable from one who will never accumulate amyloid-β, both in observed data and in the fitted model.

The model is:

$$y = f_{biomarker}(age + \alpha_{subject,\ biomarker} + male * \beta_{1,\ biomarker} + APOE * \beta_{2,\ biomarker} + education * \beta_{3,\ biomarker} + ADRC * \beta_4) + \varepsilon$$

with a separate function for each biomarker. The fitted functions are shown in **Figure 1**. An important strength of this formulation is that we can assess the correlation between biomarkers of the per-individual random effects (α). Each measurement is an observation; all available amyloid-β PET, tau PET, and plasma visits are included for participants meeting the inclusion criteria.

Models were fit using Hamiltonian Markov Chain Monte Carlo (MCMC) using the rstan package, R version 4.1.2. Code for the fits, along with further explanation, is available at github.com/Therneau/AFTmodel.

Supplemental Tables

Supplemental Table 1: Covariate effect estimates in years from the primary model. Values shown are mean (95% credible interval). The covariate effects for each measure report the estimated acceleration. For example, an estimate of 8.5 (7.2, 9.7) for APOE ε4 carriers implies an amyloid accumulation that begins, on average, 8.5 (7.2, 9.7) years earlier in APOE ε4 carriers than non-carriers.

	Amyloid-β PET	Tau PET	P-tau217	P-tau181	GFAP
APOE ε4 carrier	8.5 (7.2, 9.7)	4.4 (1.8, 7.1)	8.8 (7.2, 10.6)	4.0 (2.3, 5.6)	2.2 (1.0, 3.3)
Female sex	2.0 (0.9, 3.2)	1.4 (-0.8, 3.8)	-0.1 (-1.5, 1.3)	-3.1 (-4.6, -1.5)	3.4 (2.3, 4.4)
Education 1-yr	0.3 (0.1, 0.6)	0.7 (0.2, 1.2)	0.1 (-0.1, 0.4)	0.4 (0.1, 0.7)	0.2 (0.0, 0.4)
Referral to ADRC	11.4 (10.6, 12.3)	17.4 (15.0, 20.0)		10.2 (9.0, 11.5)	8.1 (7.3, 9.0)

Supplemental Table 2: Mean differences in years between threshold curves with CI (credible interval) using the lenient cutpoints based on the mean + 2SD method in the primary model. Times are listed as years from x (row) to y (column) variable.

	Tau PET	P-tau181	P-tau217	GFAP
Amyloid-β PET	13 (11, 15)	7 (6, 8)	5 (4, 6)	-8 (-9, -8)
Tau PET		-6 (-9, -4)	-8 (-10, -6)	-21 (-24, -19)
P-tau181			-2 (-3, -1)	-15 (-16, -14)
P-tau217				-13 (-14, -12)

Supplemental Table 3: Mean differences in years between threshold curves with CI (credible interval) using the conservative cutpoints based on the mean + 3 SD method in the primary model. Times are listed as years from x (row) to y (column) variable.

	Tau PET	P-tau181	P-tau217	GFAP
Amyloid-β PET	19 (16, 22)	9 (8, 11)	6 (5, 7)	-5 (-6, -4)
Tau PET		-9 (-13, -7)	-12 (-15, -10)	-24 (-27, -21)
P-tau181			-3 (-4, -2)	-14 (-16, -13)
P-tau217				-11 (-12, -10)

Supplemental Table 4: Correlation coefficient, R (95% credible interval), between individual-level adjustments for the model fit with tau PET Braak regions.

	Braak 1-2	Braak 3-4	Braak 5-6	P-tau217	P-tau181	GFAP
Amyloid-β PET	0.47 (0.42, 0.52)	0.41 (0.35, 0.45)	0.35 (0.30, 0.40)	0.66 (0.61, 0.70)	0.31 (0.25, 0.37)	0.21 (0.15, 0.27)
Braak 1-2		0.85 (0.83, 0.87)	0.76 (0.73, 0.78)	0.43 (0.36, 0.50)	0.26 (0.20, 0.33)	0.12 (0.06, 0.19)
Braak 3-4			0.97 (0.97, 0.98)	0.33 (0.26, 0.39)	0.20 (0.14, 0.26)	0.08 (0.02, 0.14)
Braak 5-6				0.22 (0.16, 0.29)	0.16 (0.10, 0.21)	0.04 (-0.02, 0.10)
P-tau217					0.59 (0.53, 0.64)	0.48 (0.42, 0.54)
P-tau181						0.41 (0.35, 0.48)

Supplemental Table 5: Covariate effect estimates in years for the model fit with tau PET Braak regions. Values shown are mean (95% credible interval). The covariate effects for each measure report the estimated acceleration. For example, an estimate of 8.0 (6.6, 9.1) for APOEε4 carriers implies an amyloid accumulation that begins, on average, 8.0 (6.6, 9.1) years earlier in APOEε4 carriers than non-carriers.

	Amyloid-β PET	Braak1-2	Braak3-4	Braak5-6	P-tau217	P-tau181	GFAP
APOE ε4 carrier	8.0 (6.6, 9.1)	4.8 (3.3, 6.1)	2.4 (1.1, 3.7)	0.7 (-0.7, 2.0)	8.4 (6.8, 9.9)	3.5 (2.1, 5.0)	2.2 (0.9, 3.4)
Female sex	2.1 (1.1, 3.2)	1.3 (-0.0, 2.5)	1.6 (0.3, 2.7)	1.7 (0.3, 2.9)	-0.0 (-1.5, 1.4)	-3.0 (-4.4, -1.7)	3.6 (2.5, 4.7)
Education 1-yr	0.3 (0.1, 0.6)	0.5 (0.2, 0.8)	0.6 (0.4, 0.9)	0.6 (0.4, 0.9)	0.2 (-0.1, 0.4)	0.3 (0.1, 0.6)	0.2 (-0.0, 0.5)
Referral	10.9 (10.2, 11.6)	13.3 (12.1, 14.6)	11.7 (10.4, 13.0)	10.8 (9.4, 12.2)		9.7 (8.7, 10.8)	8.7 (7.8, 9.6)

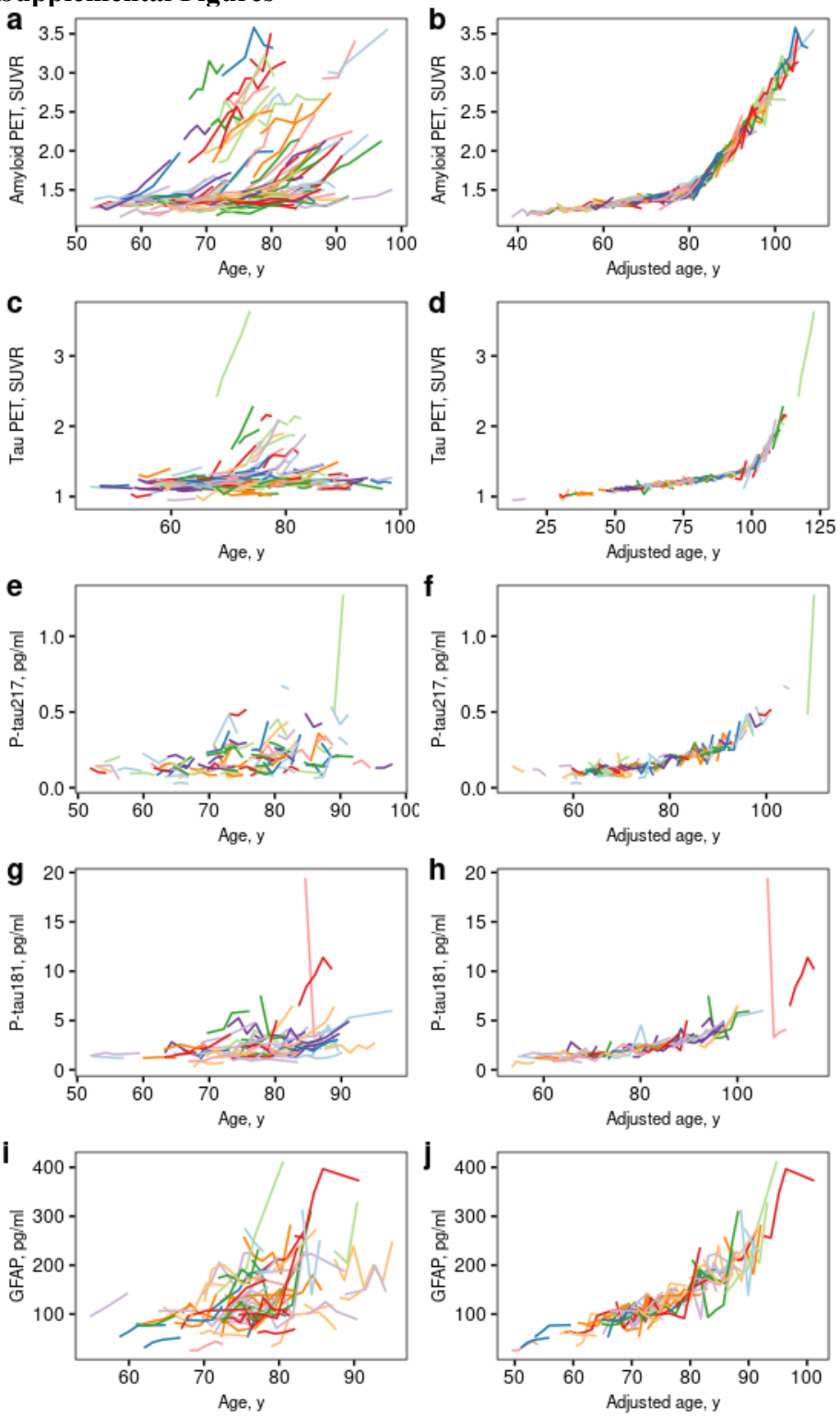
Supplemental Table 6: Correlation coefficient, R (95% credible interval), between individual-level adjustments for the model fit with amyloid-β PET regions.

	A2 amyloid-β	A3 amyloid-β	A4 amyloid-β	Tau PET	P-tau217	P-tau181	GFAP
A1 amyloid-β	1.00 (1.00, 1.00)	0.99 (0.99, 1.00)	0.98 (0.97, 0.98)	0.43 (0.38, 0.48)	0.61 (0.56, 0.65)	0.29 (0.23, 0.35)	0.17 (0.10, 0.23)
A2 amyloid-β		1.00 (0.99, 1.00)	0.98 (0.98, 0.98)	0.44 (0.40, 0.49)	0.63 (0.58, 0.67)	0.29 (0.24, 0.35)	0.19 (0.13, 0.25)
A3 amyloid-β			0.99 (0.99, 1.00)	0.46 (0.41, 0.50)	0.60 (0.54, 0.64)	0.27 (0.22, 0.33)	0.17 (0.11, 0.23)
A4 amyloid-β				0.48 (0.43, 0.52)	0.59 (0.54, 0.64)	0.26 (0.20, 0.31)	0.17 (0.10, 0.23)
Tau PET					0.34 (0.26, 0.41)	0.22 (0.16, 0.29)	0.08 (0.01, 0.15)
P-tau217						0.60 (0.54, 0.65)	0.49 (0.43, 0.55)
P-tau181							0.41 (0.35, 0.47)

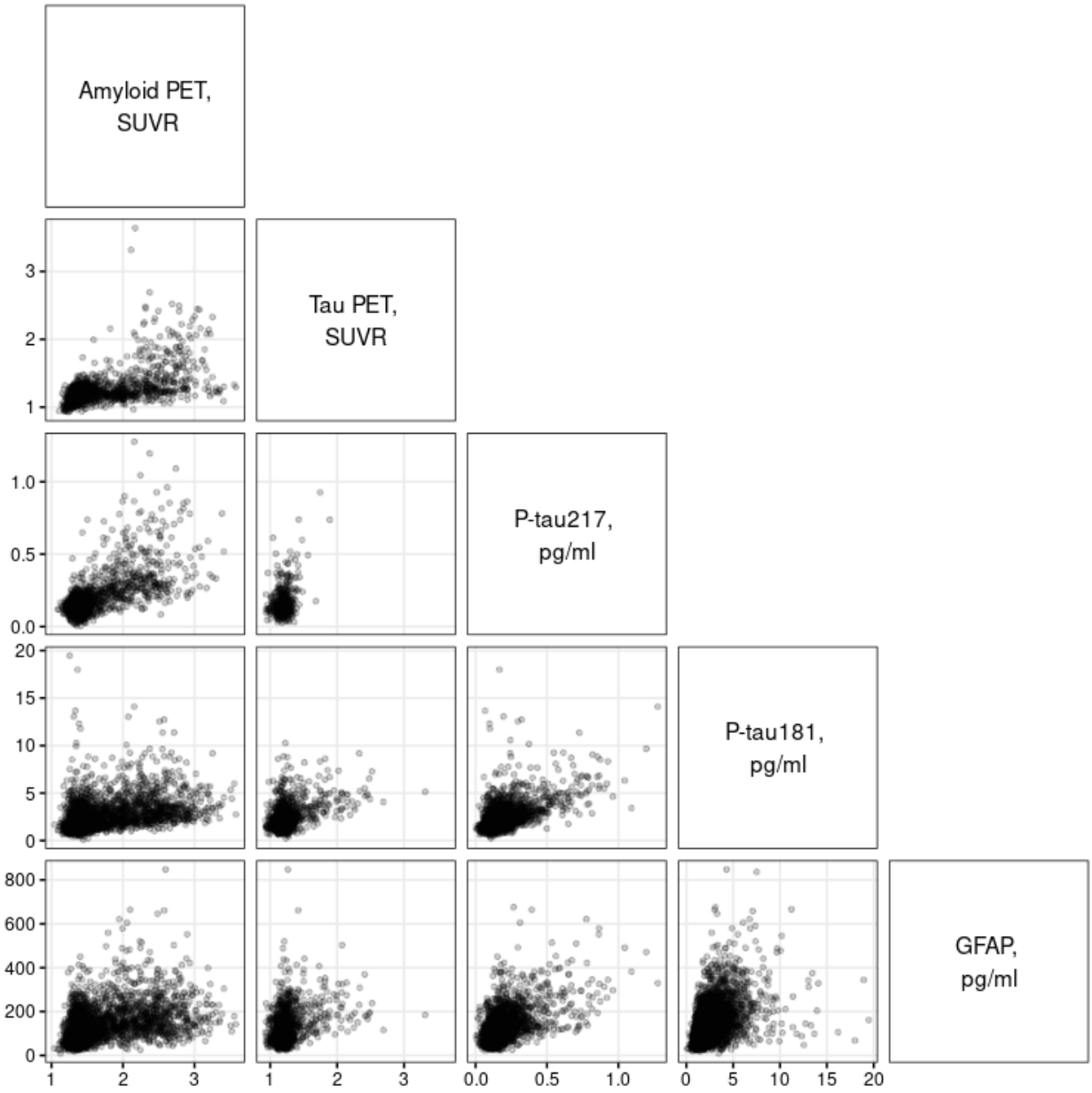
Supplemental Table 7: Covariate effect estimates in years for the model fit with amyloid-β PET regions. Values shown are mean (95% credible interval). The covariate effects for each measure report the estimated acceleration. For example, an estimate of 7.4 (6.5, 8.4) for APOEε4 carriers implies an amyloid accumulation that begins, on average, 7.4 (6.5, 8.4) years earlier in APOEε4 carriers than non-carriers.

	A1 amyloid-β	A2 amyloid-β	A3 amyloid-β	A4 amyloid-β	Tau PET	P-tau217	P-tau181	GFAP
APOE ε4 carrier	7.4 (6.5, 8.4)	7.5 (6.5, 8.5)	7.1 (6.2, 8.1)	6.9 (6.0, 7.9)	2.6 (1.1, 4.1)	8.0 (6.6, 9.4)	3.3 (1.9, 4.7)	2.1 (0.9, 3.4)
Female sex	2.7 (1.7, 3.7)	2.4 (1.3, 3.3)	2.4 (1.3, 3.3)	2.2 (1.1, 3.1)	1.3 (0.0, 2.8)	0.1 (-1.2, 1.3)	-3.0 (-4.3, -1.7)	3.7 (2.5, 4.8)
Education 1-yr	0.2 (0.1, 0.4)	0.3 (0.1, 0.4)	0.3 (0.1, 0.4)	0.3 (0.1, 0.4)	0.5 (0.3, 0.8)	0.1 (-0.1, 0.4)	0.3 (0.0, 0.5)	0.2 (0.0, 0.4)
Referral	10.5 (10.0, 11.0)	10.6 (10.0, 11.1)	10.8 (10.2, 11.2)	11.0 (10.4, 11.4)	13.5 (12.2, 14.9)		9.8 (8.8, 10.9)	8.8 (8.0, 9.8)

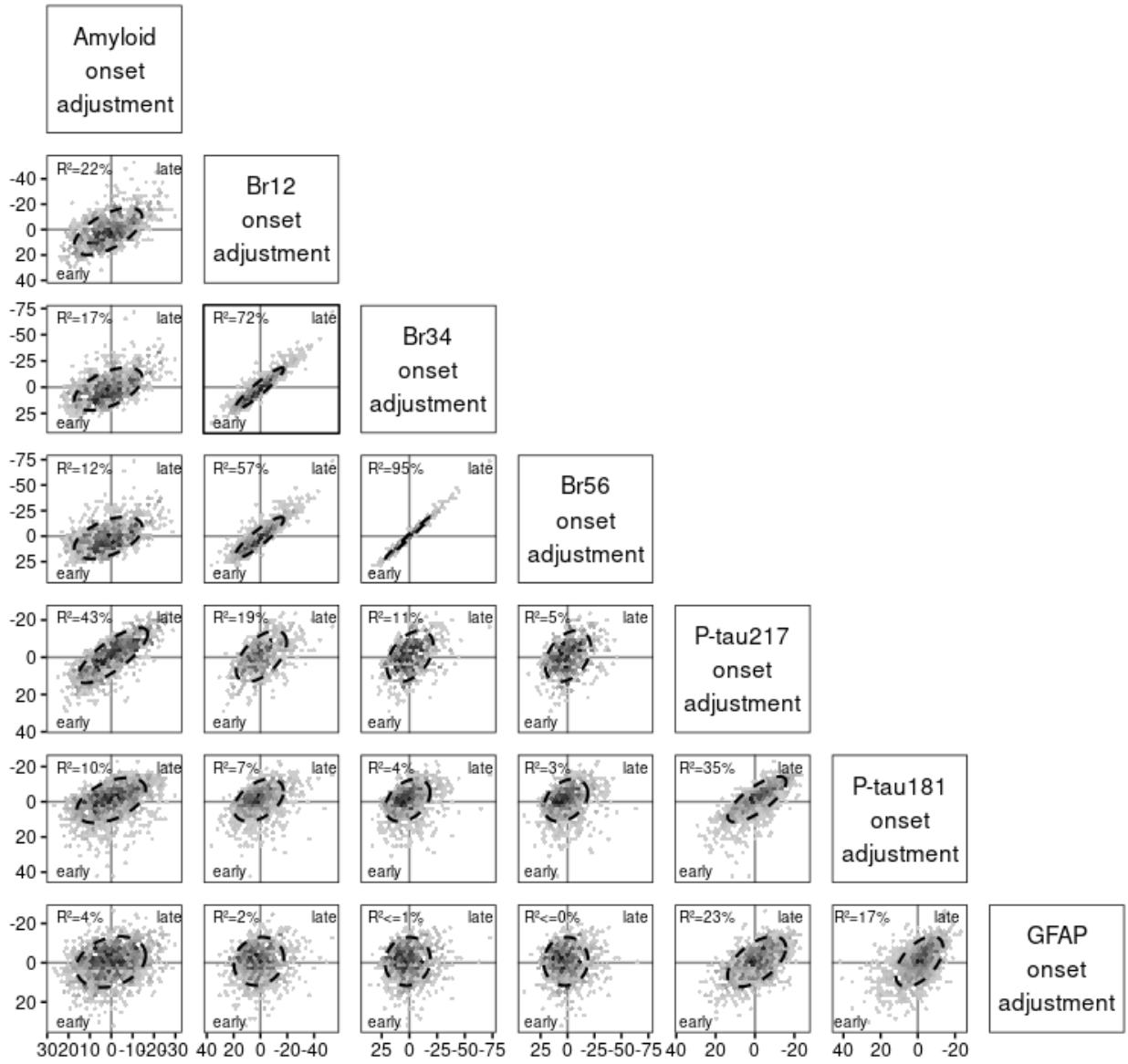
Supplemental Figures



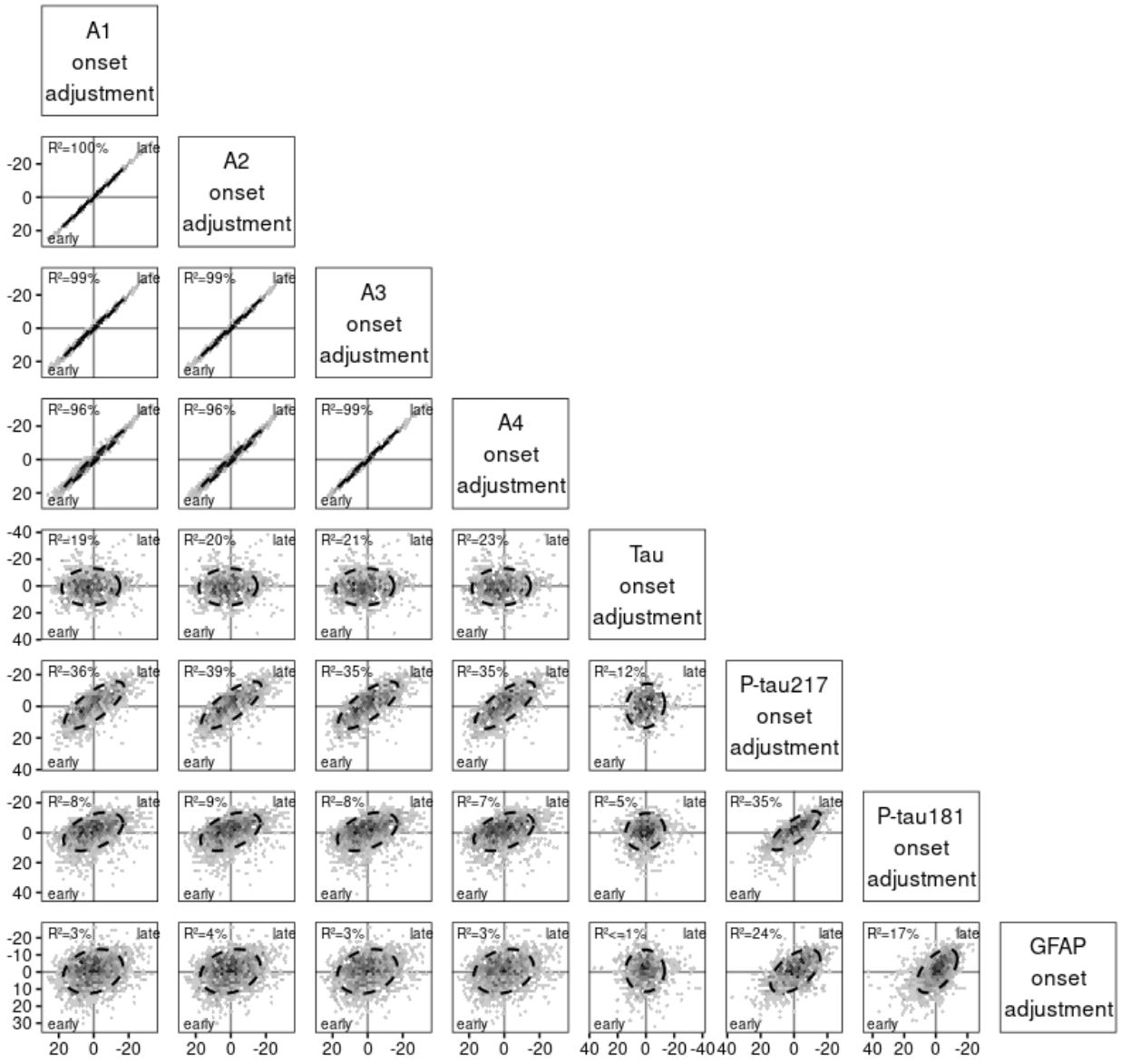
Supplemental Figure 1: Biomarker trajectories for a random subset of participants with three or more serial measurements. We show values at the observed age and at the adjusted age.



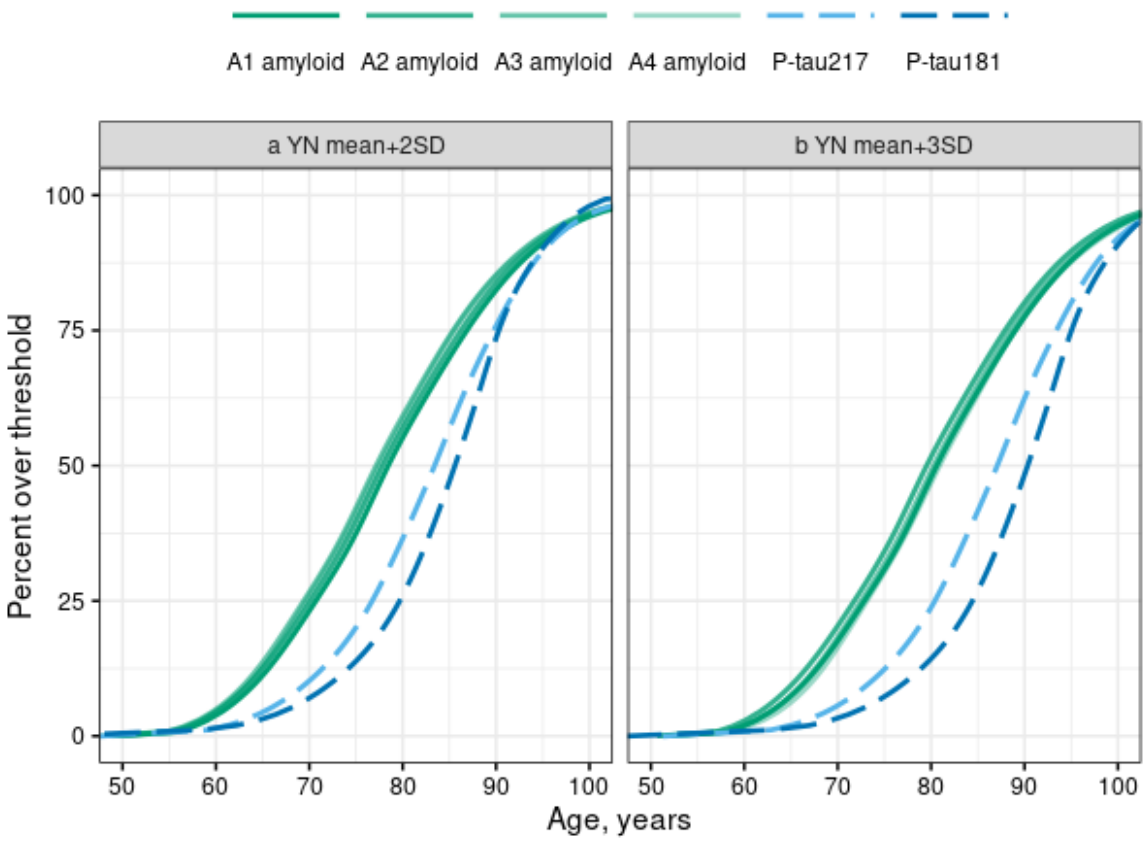
Supplemental Figure 2: Relationships between biomarker values. Each dot represents one observation and individuals having serial data contribute multiple observations. The number of data points in each comparison varies with data availability.



Supplemental Figure 3: Relationships of individual-level adjustments between amyloid PET meta-ROI, tau PET Braak 1-2, Braak 3-4, Braak 5-6, p-tau217 (MSD, Lilly), p-tau181 (Quanterix, Simoa), and GFAP (Quanterix, Simoa). An 80% ellipse is included with a perfect circle indicating no relationship between adjustments. The percent variation explained (square of the correlation*100) between individual-level adjustments is given in the upper left. The x-axes and y-axes are flipped for the individual adjustments. A higher positive value or earlier onset relative to the population mean is shown to the left of the x-axis and bottom of the y-axis. Each dot represents one participant, and the number of participants included in each comparison varies by data availability, as in **Figure 2**.



Supplemental Figure 4: Relationships of individual-level adjustments between A1 amyloid-β, A2 amyloid-β, A3 amyloid-β, A4 amyloid-β, tau PET meta-ROI, p-tau217 (MSD, Lilly), p-tau181 (Quanterix, Simoa), and GFAP (Quanterix, Simoa). An 80% ellipse is included with a perfect circle indicating no relationship between adjustments. The percent variation explained (square of the correlation*100) between individual-level adjustments is given in the upper left. The x-axes and y-axes are flipped for the individual adjustments. A higher positive value or earlier onset relative to the population mean is shown to the left of the x-axis and bottom of the y-axis. Each dot represents one participant, and the number of participants included in each comparison varies by data availability, as in **Figure 2**.



Supplemental Figure 5: By year of age, predicted proportion of MCSA participants having abnormal biomarker levels using (a) 2SD and (b) 3SD above the mean of young normal (YN) participants for the model using the A1-A4 amyloid-β regions in place of the amyloid-β metal-ROI, p-tau217, and p-tau181.