A Bayesian Disease Progression Model with Applications in Alzheimer's Disease

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Introduction

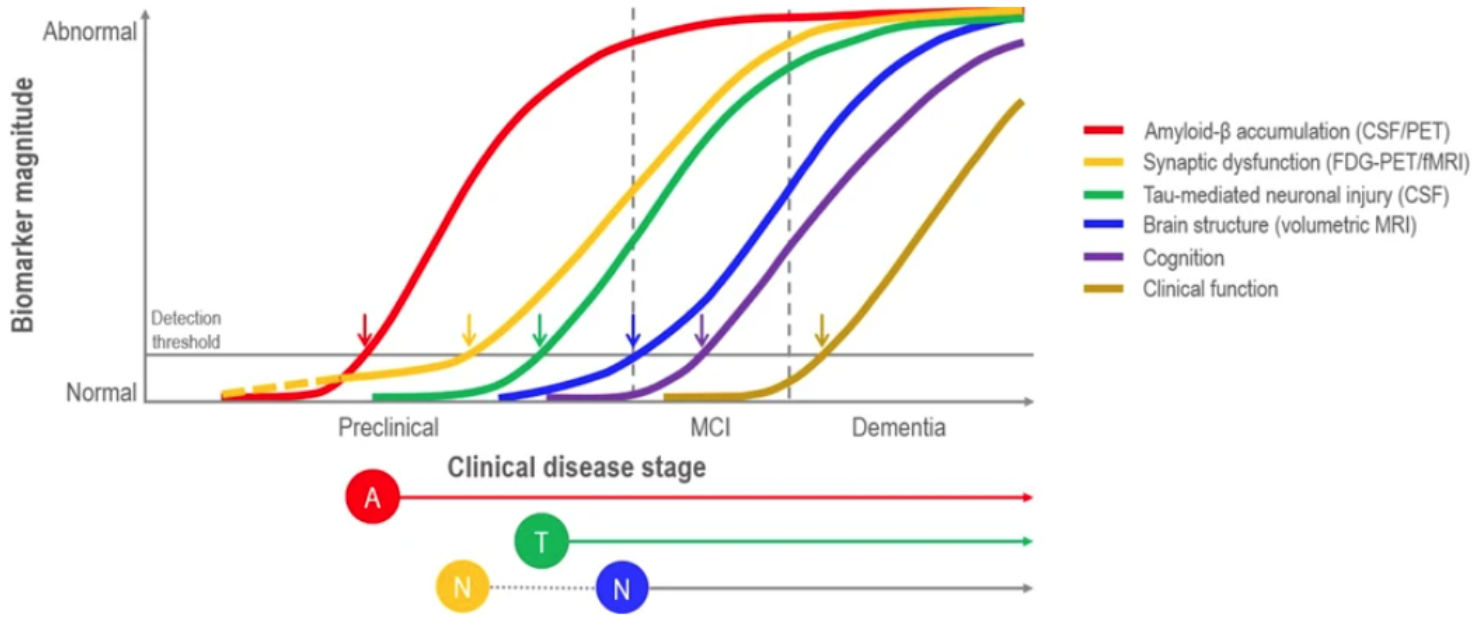
- Alzheimer disease (AD) is characterized neuropathologically by amyloid plaques and neurofibrillary tangles, which are thought to start accumulating approximately 20 years before the onset of dementia symptoms.
- Differences across individuals in the rate of disease progression make it difficult to characterize a quantitative template of biomarker changes
- Disease progression modeling (DPM) utilizes longitudinal or cross-sectional clinical data to characterize the patterns of disease state evolution over time and predict patients' future stages of progression
- This manuscript will introduce a Bayesian joint DPM and time-to-event model

Outline

1. Background and motivation
2. Bayesian joint DPM and time-to-event model
3. ADNI data analysis
4. Concluding remarks

Disease progression modeling

The translational research in Alzheimer's disease has supported a hypothetical model of Alzheimer's disease pathology in which key pathological processes unfold in a temporally ordered and monotonic manner, with early Aβ accumulation and plaque deposition preceding tau propagation, neuronal loss, and eventual clinical manifestations.



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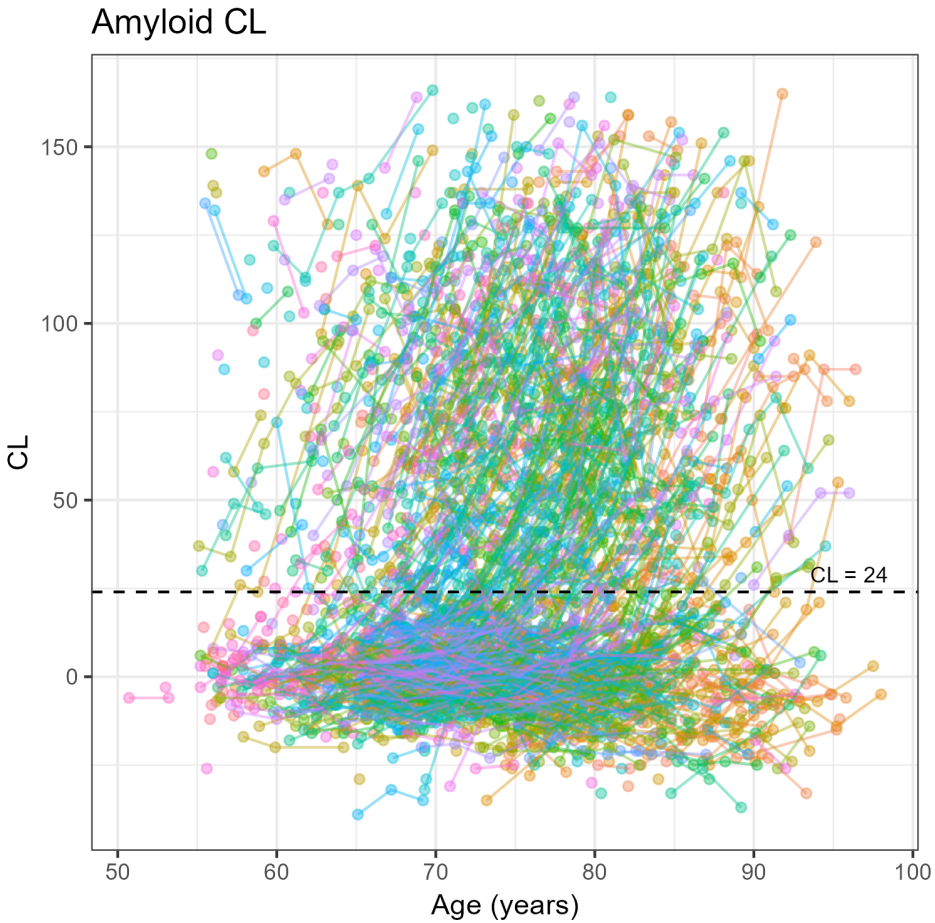
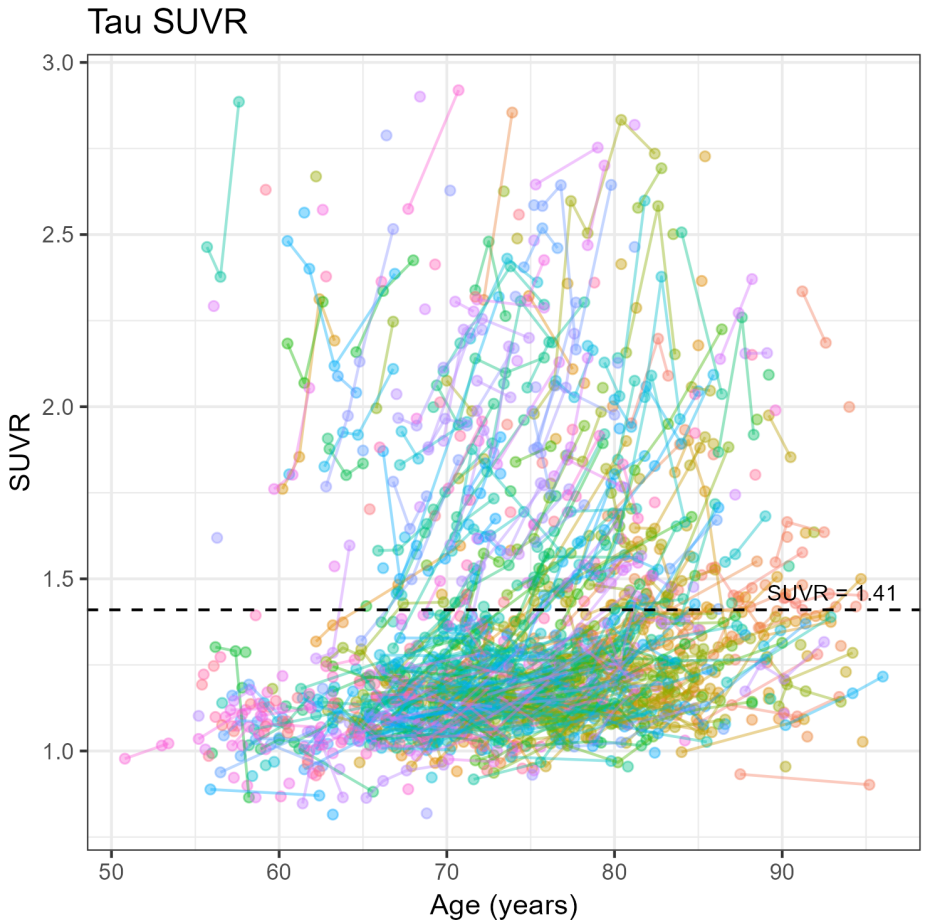
Motivation: ADNI study



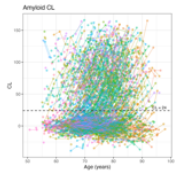


Proposed methodology

Rate vs time curve

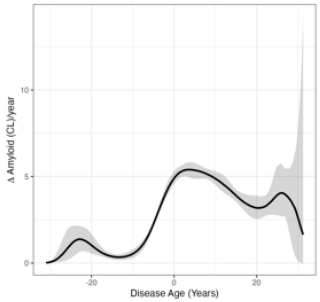
Value vs time curve

Age of Biomarker +

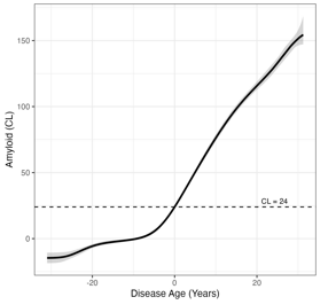


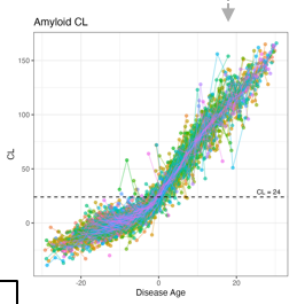
$$\alpha_{A,i} = x_i^t \gamma_A + \epsilon_{A,i}$$

Amyloid



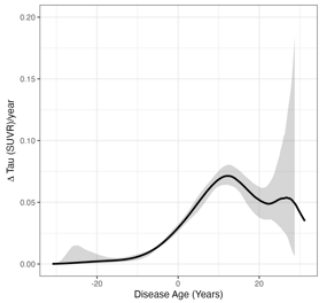
$\int \Delta A/\Delta d$





Biomarker Alignment

Tau



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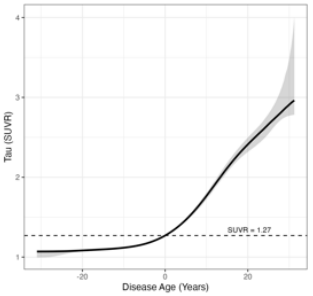
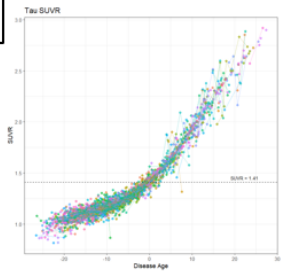
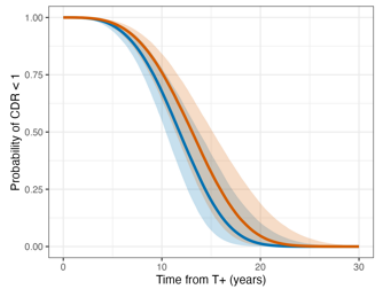




$$\alpha_{\tau,i} = x_i^t \gamma_\tau + \epsilon_{\tau,i}$$

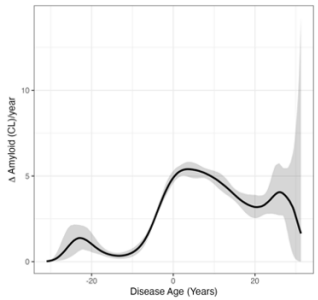
Survival Alignment and Analysis



Rate vs time curves

Rate vs time curve

Amyloid



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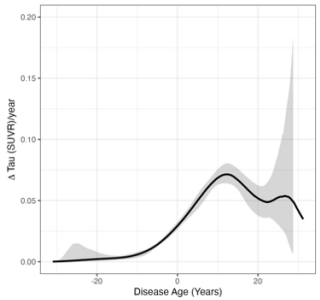
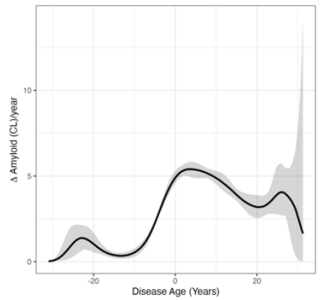


Value vs time curves

Rate vs time curve

Value vs time curve

Amyloid



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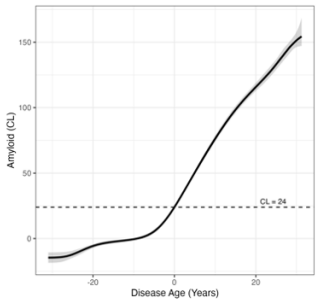

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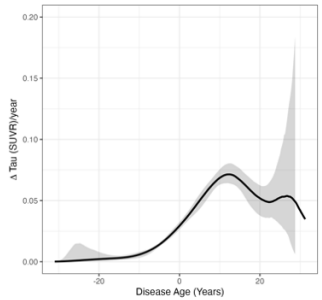

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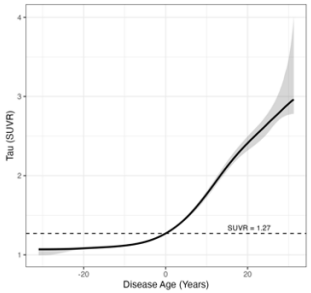
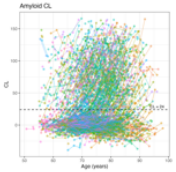


Age of symptom onset

Rate vs time curve

Value vs time curve

Age of Biomarker +



$$\alpha_{A,i} = x_i^t \gamma_A + \epsilon_{A,i}$$

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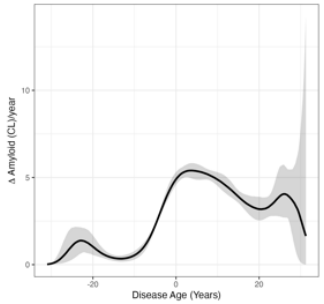

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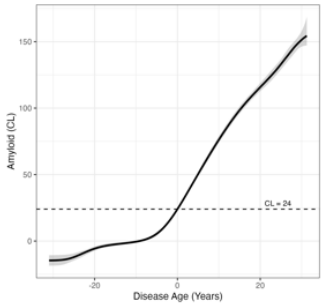
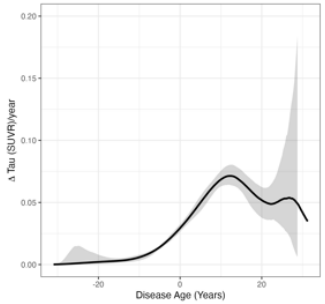


Biomarker Alignment

Tau



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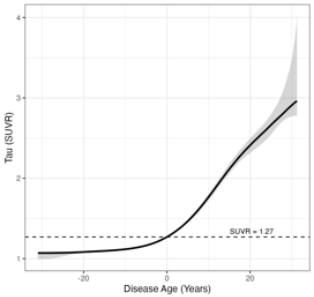


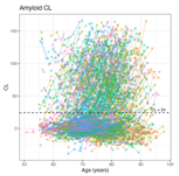
$$\alpha_{\tau,i} = x_i^t \gamma_\tau + \epsilon_{\tau,i}$$

Biomarker alignment

Rate vs time curve

Value vs time curve

Age of Biomarker +



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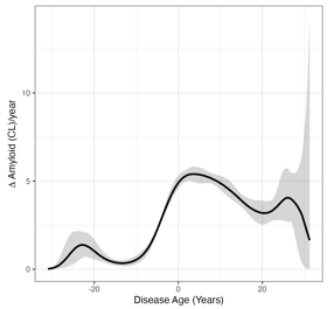
Amyloid



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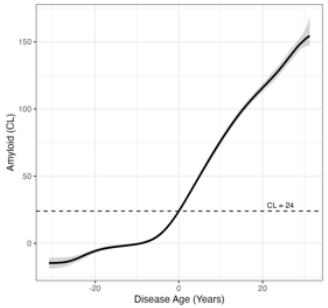
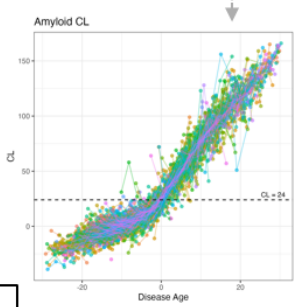
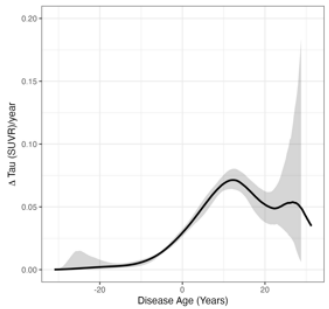




Biomarker Alignment

Tau



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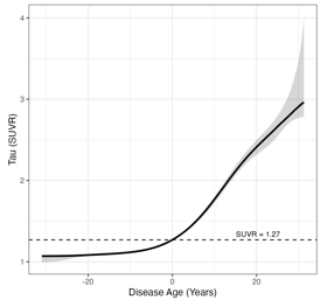

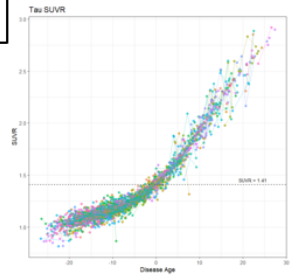

$$\alpha_{\tau,i} = x_i^t \gamma_\tau + \epsilon_{\tau,i}$$

Survival alignment and analysis

Rate vs time curve

Value vs time curve

Age of Biomarker +

Amyloid

Tau

$\int \Delta A/\Delta d$

$\int \Delta \tau/\Delta d$

$\alpha_{A,i} = x_i^t \gamma_A + \epsilon_{A,i}$

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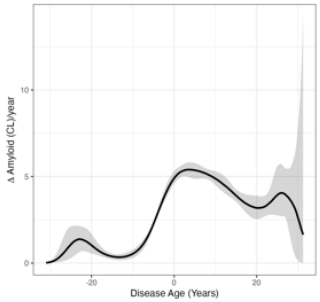
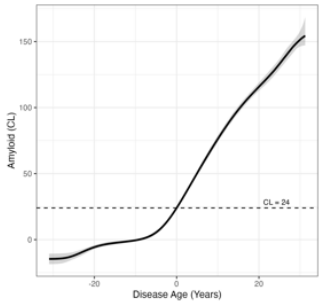
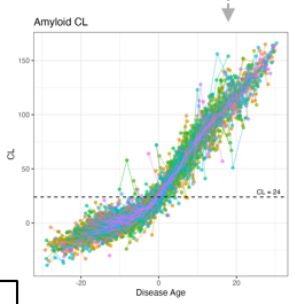
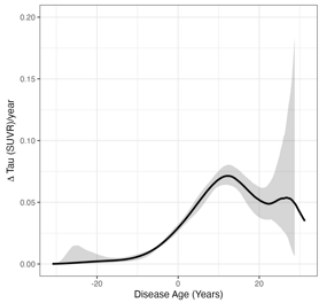
Biomarker Alignment

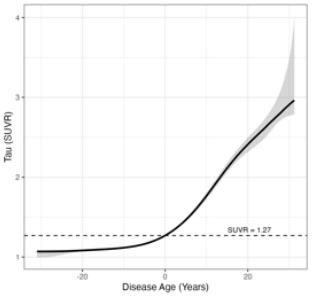
Survival Alignment and Analysis

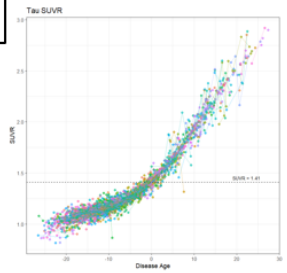


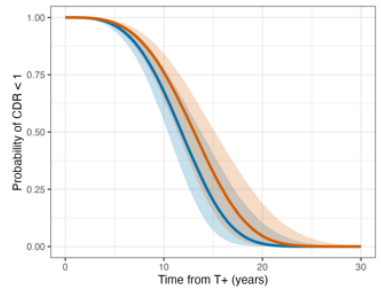












Posterior sampling and computation

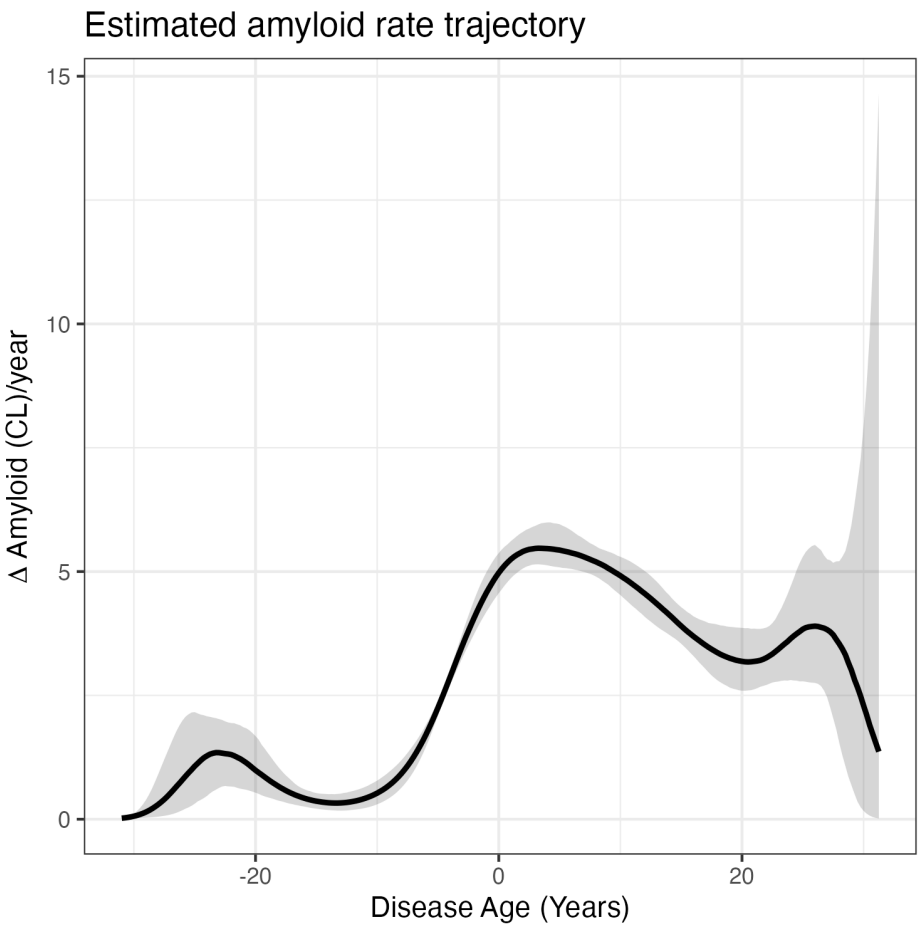
- Posterior sampling conducted in Nimble via MCMC
- Sampler run for 15,000 iterations with first 10,000 discarded as burn-in
- Chain mixing and effective sample size (ESS) assessed to be satisfactory

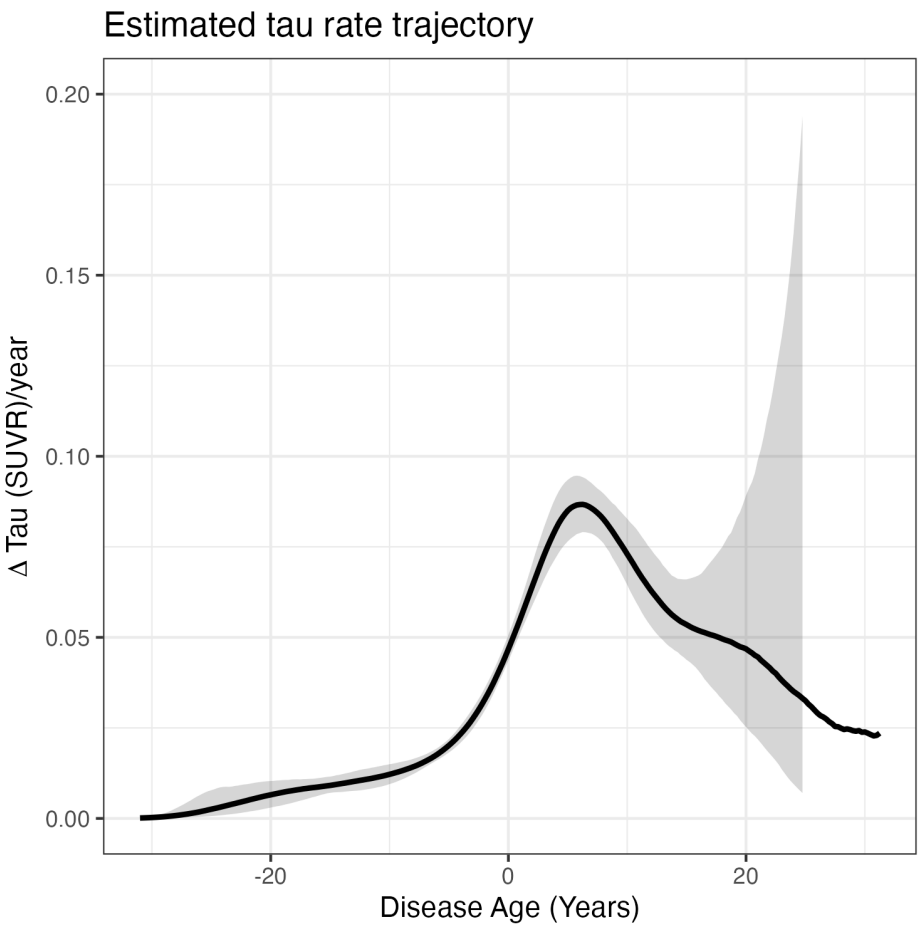
ADNI Study

ADNI Study Sample Characteristics

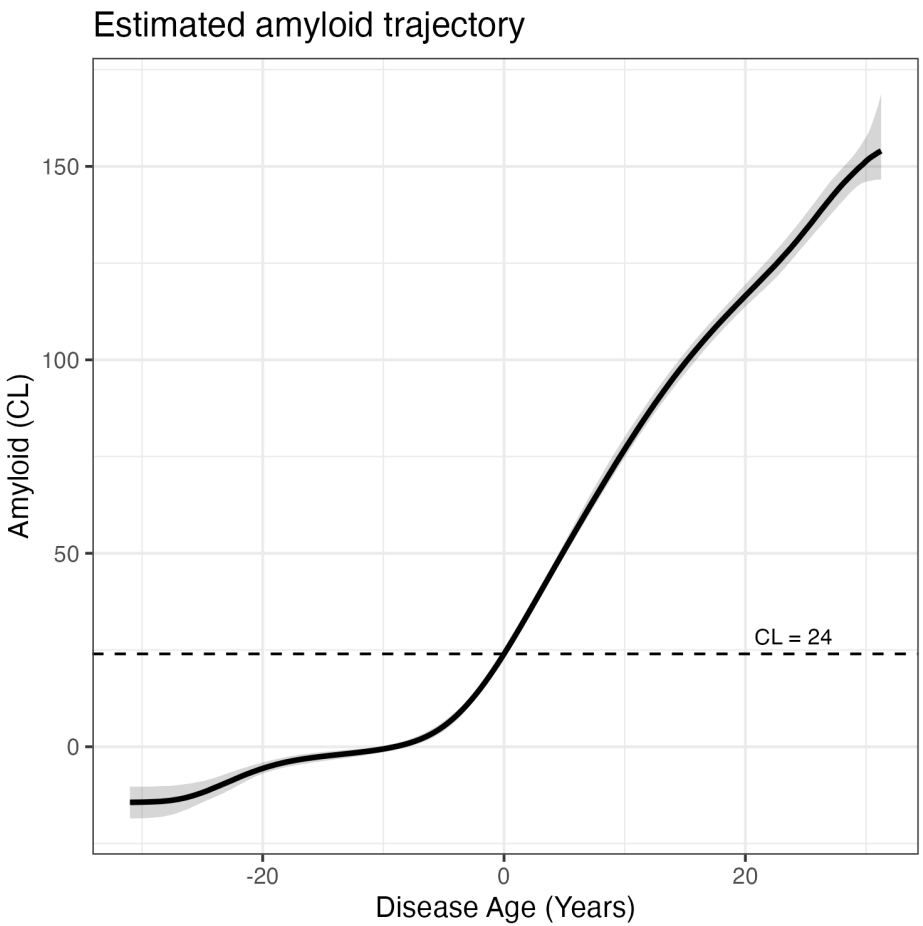
		Amyloid	Tau	Time from T+ to CDR>=0.5
n		1900 (955 A+)	991 (443 T+)	293
sex (%)	Male	944 (49.7)	464 (46.8)	128 (43.7)
	Female	956 (50.3)	527 (53.2)	165 (56.3)
race (%)	Asian	60 (3.2)	32 (3.3)	6 (2.1)
	Black or African American	170 (9.0)	117 (11.9)	21 (7.2)
	More than one race	25 (1.3)	15 (1.5)	7 (2.4)
	Unknown	16 (0.8)	9 (0.9)	3 (1.0)
	White	1613 (85.3)	808 (82.1)	254 (87.3)
	Other	7 (0.4)	3 (0.3)	
apoe_genotype (%)	2/2	6 (0.3)	2 (0.2)	1 (0.3)
	2/3	154 (8.1)	93 (9.4)	9 (3.1)
	2/4	41 (2.2)	21 (2.1)	7 (2.4)
	3/3	929 (48.9)	507 (51.2)	95 (32.4)
	3/4	614 (32.3)	301 (30.4)	136 (46.4)
	4/4	156 (8.2)	67 (6.8)	45 (15.4)
DX_baseline (%)	Unimpaired	763 (43.8)	466 (56.8)	72 (28.8)
	MCI	729 (41.9)	259 (31.5)	106 (42.4)
	Dementia	249 (14.3)	96 (11.7)	72 (28.8)
DX_final (%)	Unimpaired	638 (40.7)	444 (56.4)	52 (22.7)
	MCI	573 (36.6)	232 (29.5)	90 (39.3)
	Dementia	355 (22.7)	111 (14.1)	87 (38.0)
age_first_scan (mean (SD))		72.52 (7.69)	73.07 (8.17)	75.78 (7.76)
followup_years (mean (SD))		2.85 (3.35)	2.04 (2.53)	1.85 (2.34)
n_scans (%)	1	794 (41.8)	488 (49.2)	139 (47.4)
	2	487 (25.6)	254 (25.6)	67 (22.9)
	3	300 (15.8)	160 (16.1)	53 (18.1)
	4	154 (8.1)	61 (6.2)	21 (7.2)
	5	85 (4.5)	25 (2.5)	12 (4.1)
	6	64 (3.4)	1 (0.1)	1 (0.3)
	7	16 (0.8)	2 (0.2)	0 (0.0)

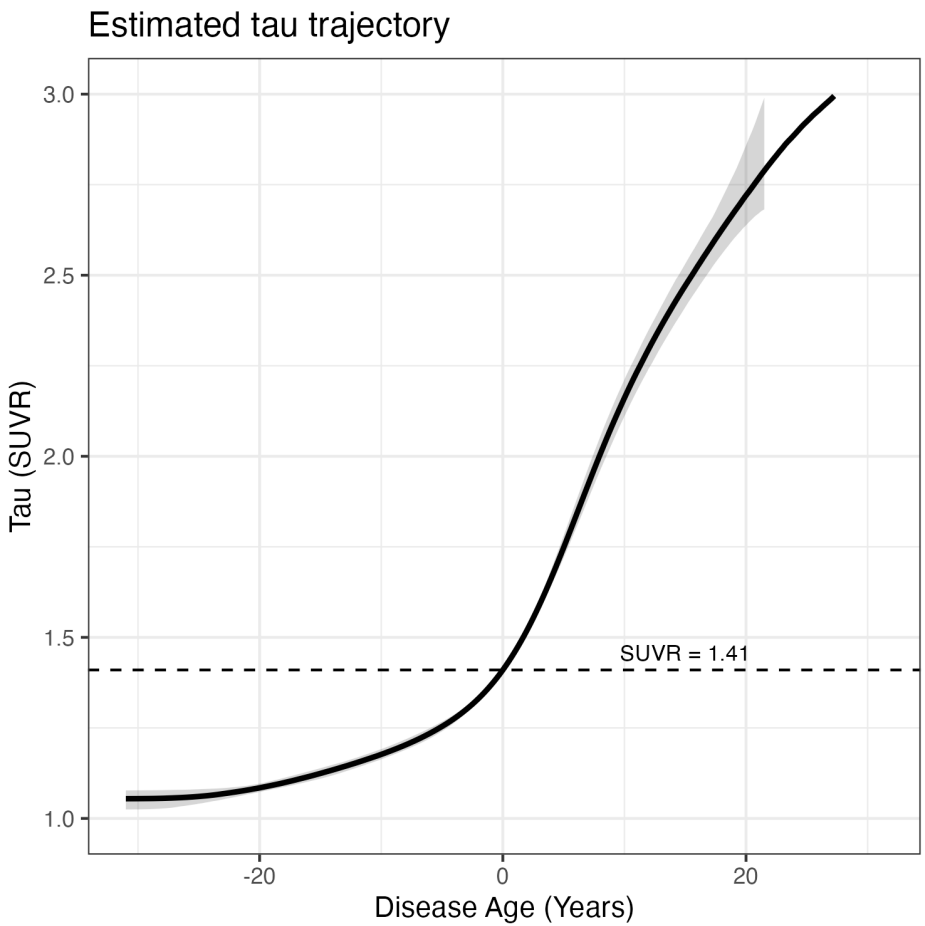
Rate vs time curve



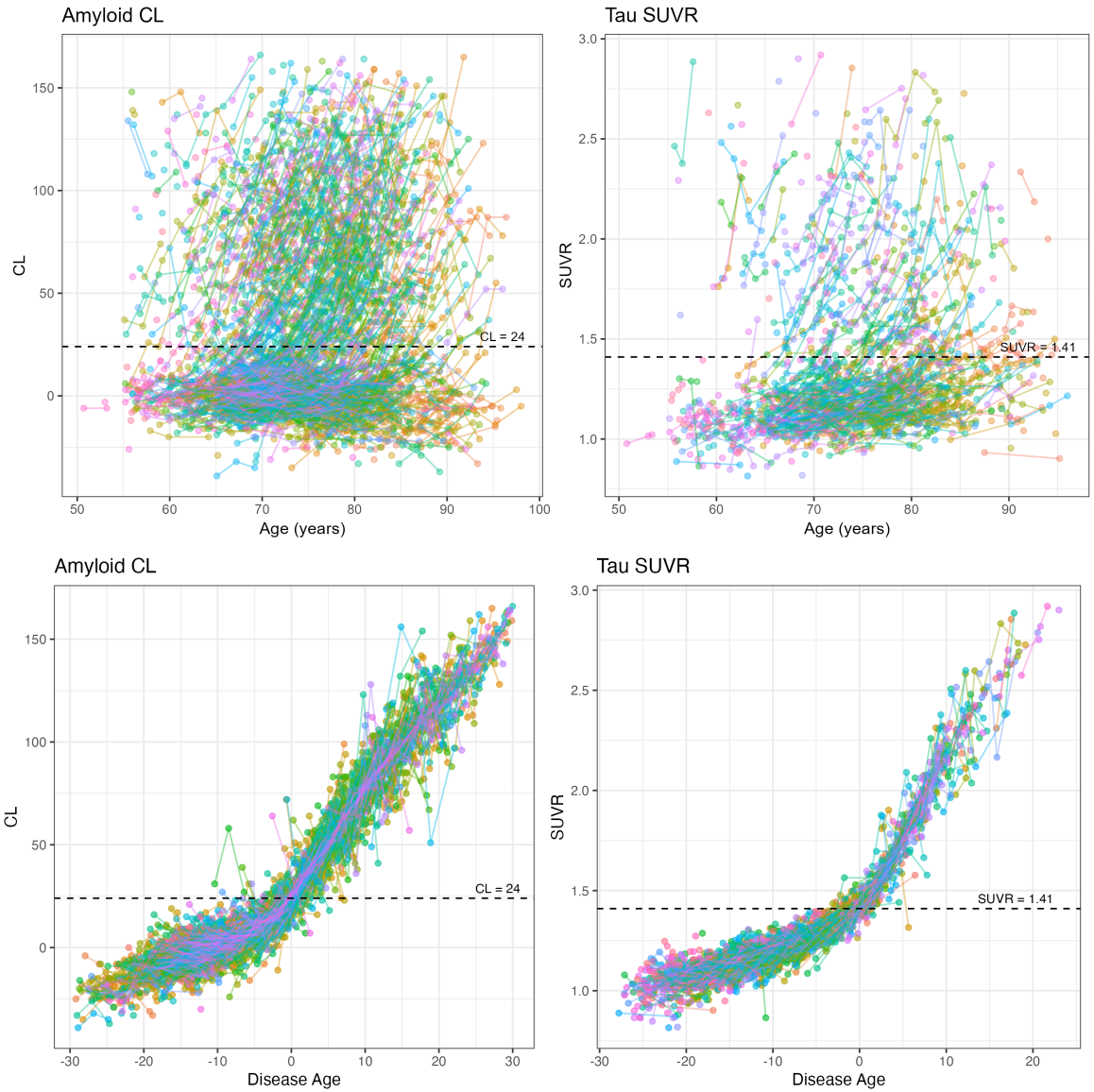


Value vs time curve

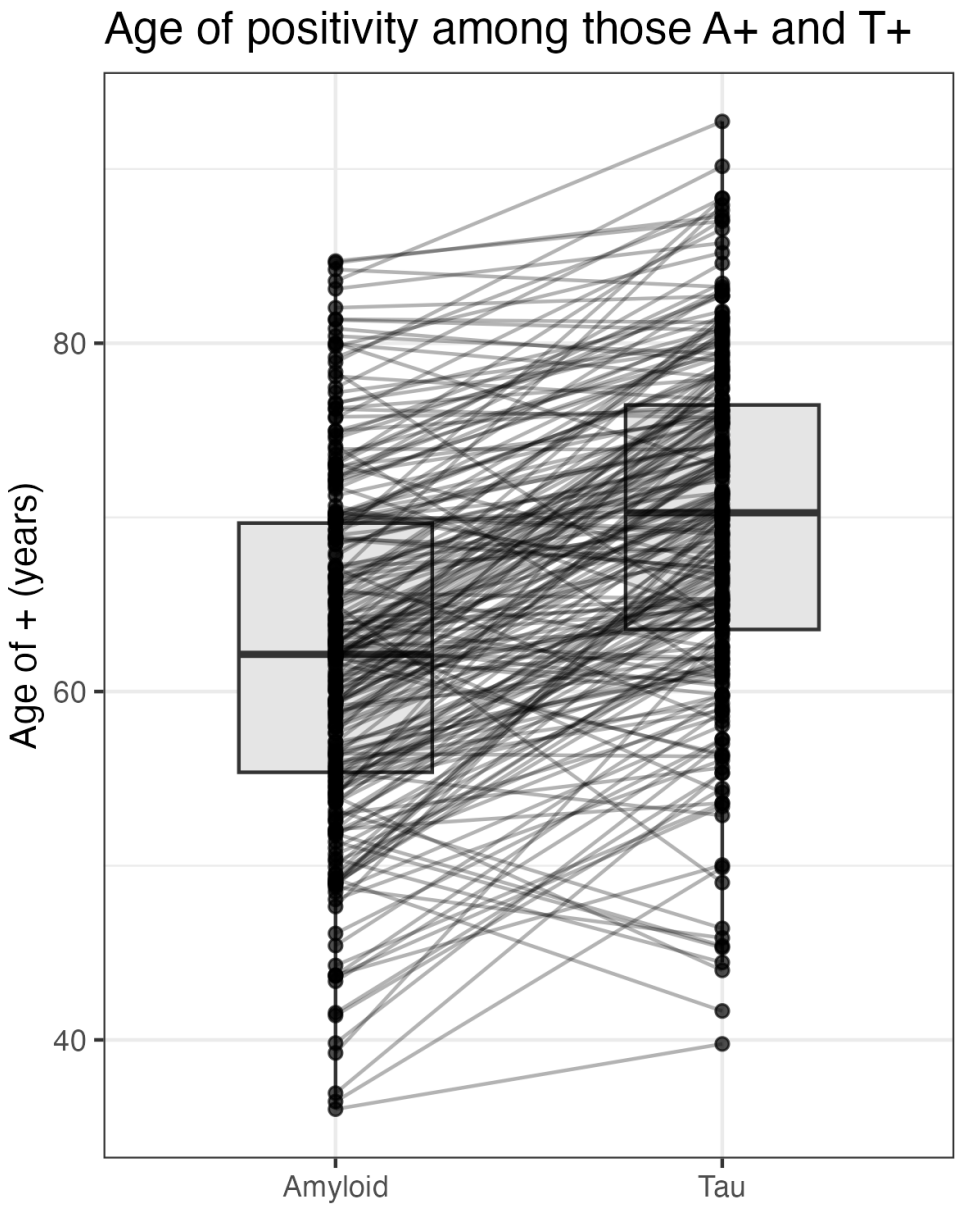




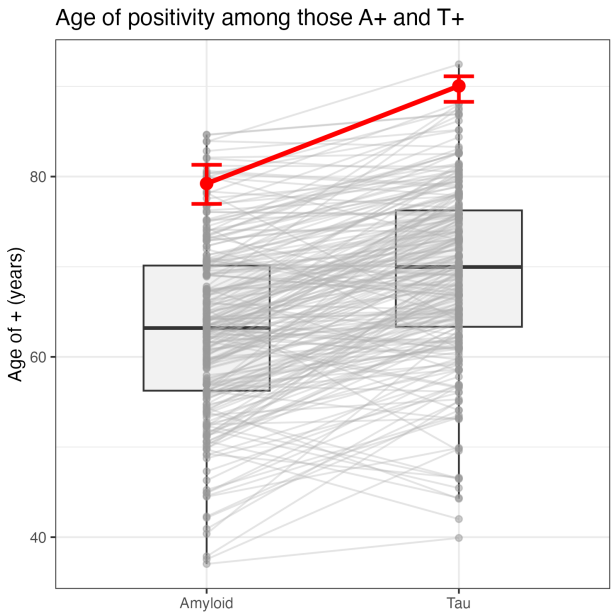
Age of symptom onset

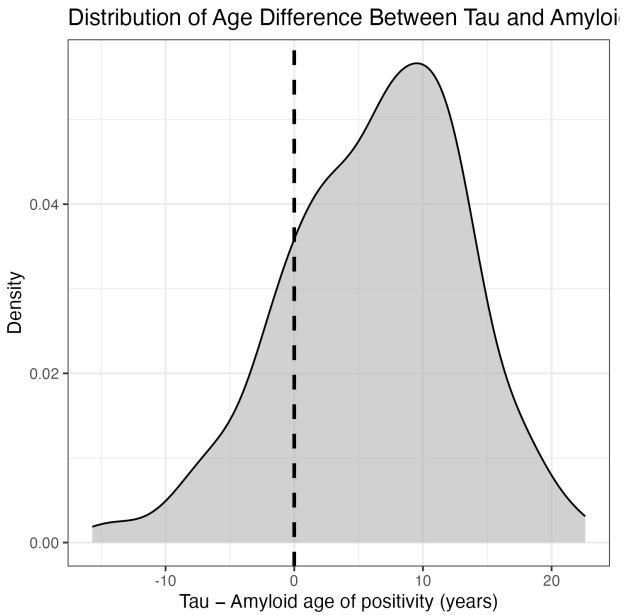


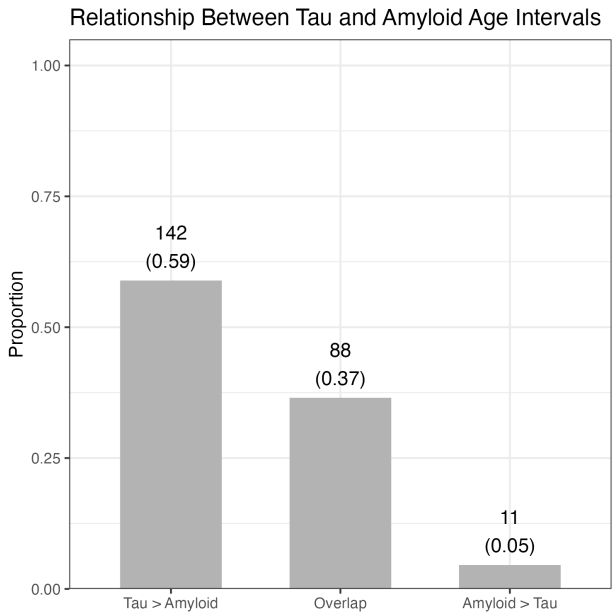
Age of symptom onset



Age of onset distributions







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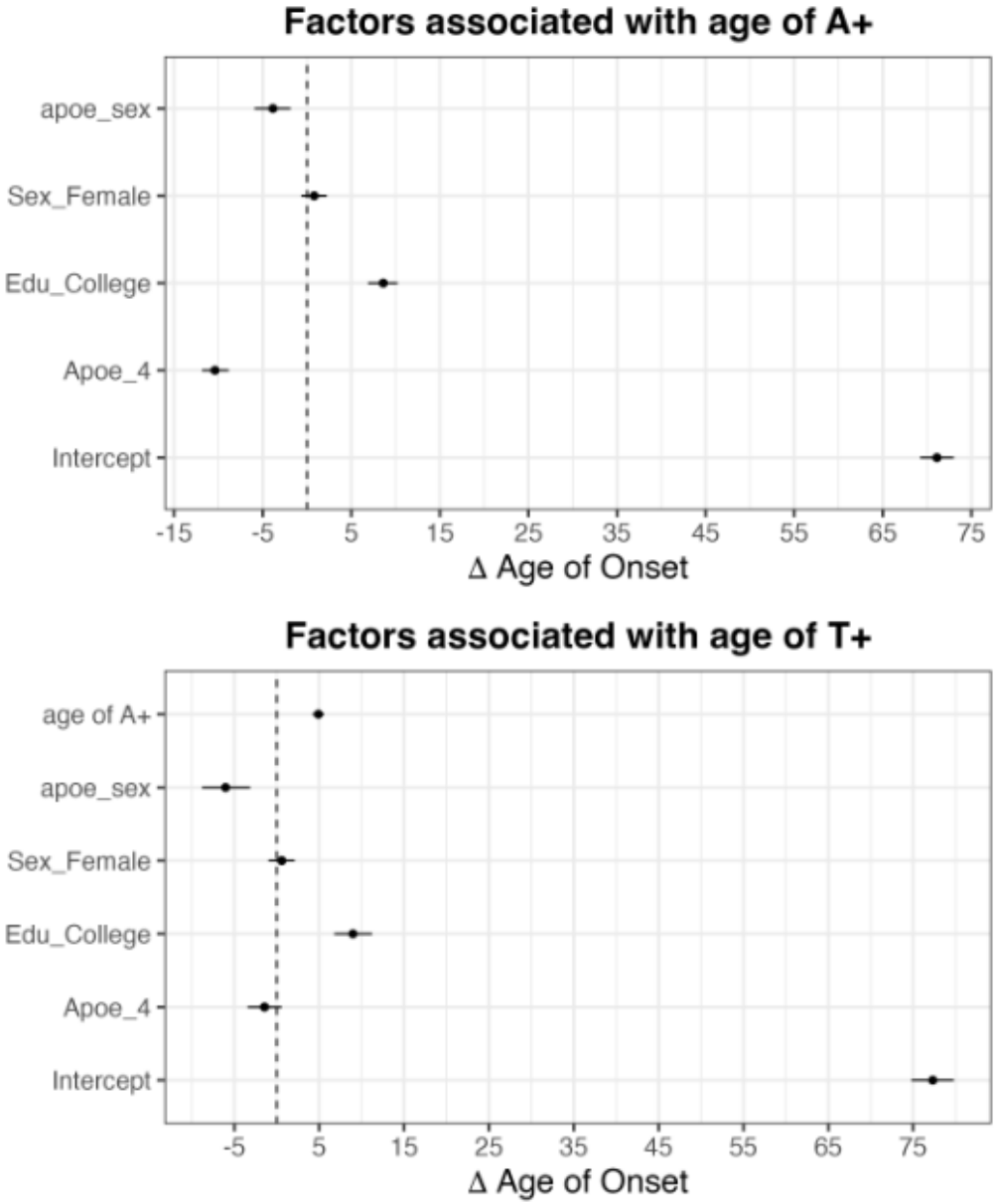

Time-to-event analysis

Covariates	Estimates	95% Credible Interval
Intercept	6.416	(3.830,8.968)
APOE_ε4	0.579	(-1.026,2.489)
College education	1.269	(-0.275,2.529)
Sex	-0.144	(-1.497,1.057)
APOE_ε4 & Sex	0.575	(-1.049,2.203)
α_τ	-0.049	(-0.085,-0.018)

Concluding Remarks

- Joint modeling of monotonic disease trajectories for amyloid and tau
- Individual symptom onset times with a time-to-event model
- Propagating uncertainty within a Bayesian framework

Acknowledgements

- Dr. Aaron Scheffler
- Dr. Jacqueline Torres
- Dr. Duygu Tosun-Turgut
- Isabella Hausle
- Dr. Margo Heston
- Dr. Renaud La Joie

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