

Quantifying natural amyloid plaque accumulation using ADNI, BIOFINDER, A4 and LEARN datasets

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OBJECTIVE

- To establish a natural amyloid plaque accumulation model over lifetime
- To identify significant factors impacting natural amyloid plaque accumulation across a large number of participants

CONCLUSIONS AND DISCUSSION

- This natural amyloid plaque model, predicting the time course of Alzheimer's disease (AD) over decades, may be used in designing and interpreting novel AD trials in different patient populations
- *APOE* ε4 genotype was found to be predictive of age of onset of amyloid accumulation; the rate of amyloid accumulation is comparable between different ε4 genotypes
- Preventing amyloid accumulation may reduce downstream irreversible pathological changes, and ultimately cognitive and functional impairment due to AD

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BACKGROUND

Updating the study design of natural plaque accumulation models will help improve the understanding of the natural rate of accumulation over a lifetime

- Prior observational studies (using ADNI data) estimate approximately 3 CL/year amyloid plaque accumulation^{1,2}
 - Study participants' baseline amyloid levels were impacted by age, gender, *APOE* ε4 genotype, and disease stage
- Limitations of current natural accumulation models include:
 - Model time from study start
 - Baseline parameters describe enrollment criteria and are not meaningful for other populations
 - Models allow for unlimited accumulation of amyloid
 - Individuals may be at a different stage in their AD trajectory

STUDY DESIGN

Natural plaque accumulation model established across continuum of AD

- Participants included in model:
 - ADNI³: N=1745
 - BioFINDER 14⁴: N=265
 - A4/LEARN^{5,6} screening population: N=4492
- Cognitively unimpaired, mild cognitive impairment & dementia due to AD
- Two apparent sub-populations in data: amyloid accumulators (participants who accumulate amyloid over their lifetime) & amyloid non-accumulators (participants whose amyloid stays at baseline over their lifetime)
- Monolix (software version 2024R1) was used to model the data

ADNI: NCT00106889; BioFINDER: NCT01208675; LEARN: NCT02488720.

METHODS AND KEY RESULTS

Novel Structural Amyloid Accumulation Model

- Emax model with age of onset (when amyloid pathology starts increasing above baseline value) implemented as a lag time
- Mixture model applied on the Emax parameter to estimate two sub-populations of accumulators and non-accumulators (Emax=base)
- Normally distributed baseline describing the amyloid before accumulation starts
- Gamma was explored but with increasing sigmoidicity, the age of onset becomes increasingly early and less associated with the timing of meaningful amyloid accumulation
- Age of onset was logit transformed to constrain between 0-90 years of age; this improves the stability of the mixture model (without transformation, low amyloid, non-accumulating individuals can either be an accumulator with high age of onset e.g. 150 years or a non-accumulator)
- Parameter estimates, goodness of fit and visual predictive check are presented in Table 1, Figure 1 and Figure 2

$$Amyloid(from\ onset) = (Emax - base) * \frac{(Age - onset)}{EAge50 + (Age - onset)} + base$$

Covariate Analysis Methods

- Covariates tested: *APOE* ε4, genotype, sex, ethnicity, race, weight, and, BMI
- Parameters tested: age of onset, Emax, and EAge50
- Strategy: Monolix's automated covariate search strategy (COSSAC)

Covariate Analysis Results

- Increasing *APOE* ε4 allele prevalence associated with earlier age of onset and increased probability of being an amyloid accumulator
- Black and Asian races associated with lower Emax
- Males associated with slightly later EAge50 by ~2 years
- Covariate effects presented in Table 2/Figure 3

Table 1

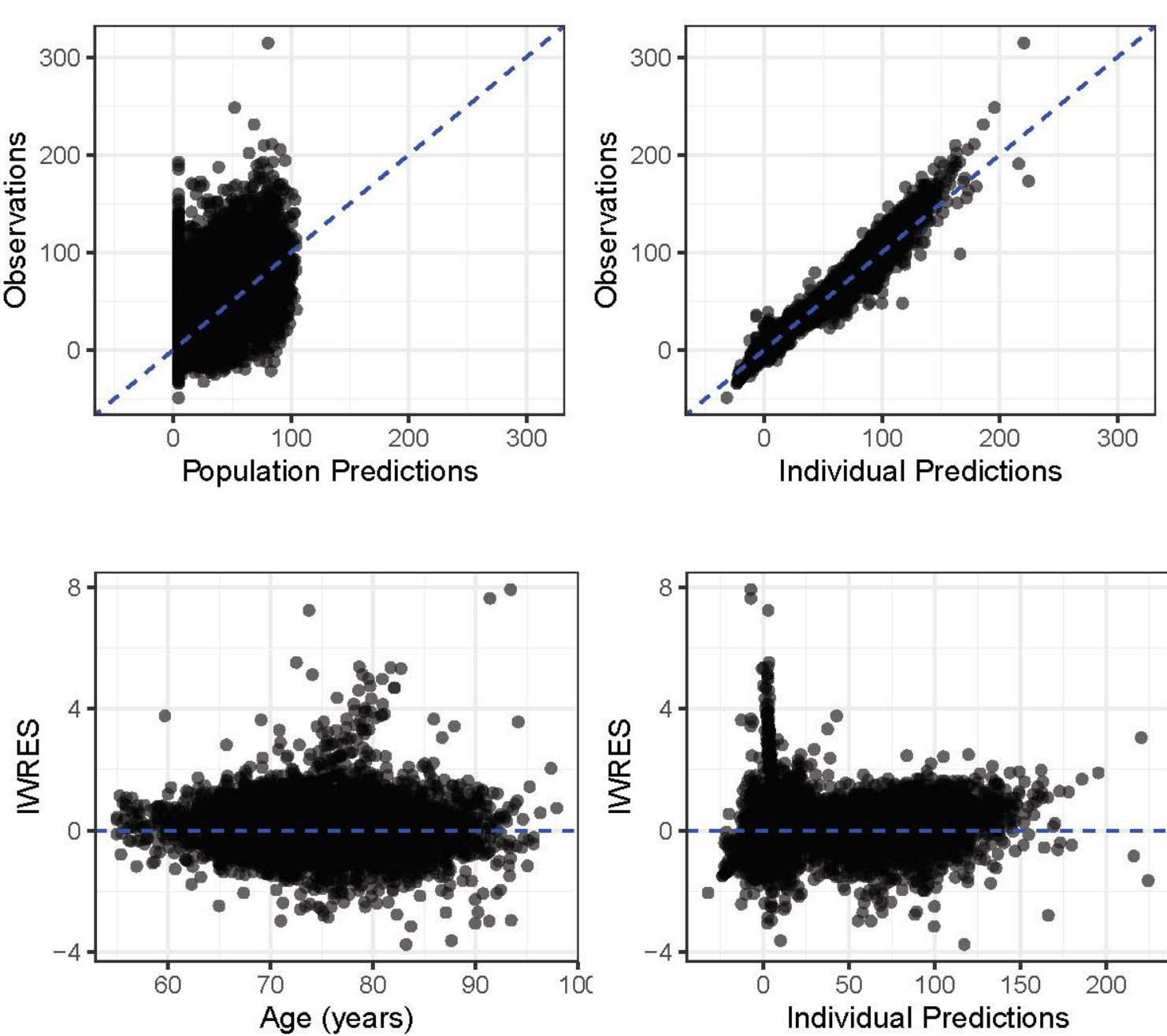
Covariate		Parameter			
		Age of Onset (years)	Emax (Centiloids)	EAge50 (years)	P(accumulator)
<i>APOE</i> ε4	Non-carrier/Unknown	71.5	185	.	0.466
	Heterozygote	64.1	185	.	0.847
	Homozygote	53.3	164	.	1
Race	White & Others	.	185	.	.
	Black	.	163	.	.
	Asian	.	131	.	.
Sex	Female	.	.	20.8	.
	Male	.	.	22.6	.

Model Parameters

Table 2	Parameter	Estimate	R.S.E. (%)	P2.5	P97.5
Population parameters	Age of onset (years)	71.5	0.789	70.4	72.6
	Baseline (Centiloids)	4.41	5.46	3.94	4.88
	Emax (Centiloids)	185	1.64	179	191
	EAge50 (years)	20.8	2.64	19.8	21.9
	Gamma	1	NA	NA	NA
	logit P(non-carrier)	-0.137	65.2	-0.311	0.0381
Covariate effects	logit P(heterozygous)	1.85	9.38	1.54	2.22
	logit P(homozygous)	176	NA	NA	NA
	Age of onset; <i>APOE</i> ε4; Heterozygote	-0.446	9.57	-0.53	-0.363
	Age of Onset; <i>APOE</i> ε4; Homozygote	-0.981	8.01	-1.14	-0.827
	Emax; <i>APOE</i> ε4; Homozygote	-0.121	28	-0.187	-0.0546
	Emax; Race; Black	-0.122	49	-0.238	-0.00486
Inter-individual variability	Emax; Race; Asian	-0.342	19.1	-0.47	-0.214
	EAge50; Sex; Male	0.0811	36.8	0.0226	0.14
	Omega Age of Onset	0.638	3.84	0.591	0.687
	Omega Baseline (years)	11.2	1.75	10.8	11.6
	Omega Emax	0.219	5.58	0.196	0.244
	Omega EAge50	0.188	8.65	0.159	0.223
Residual error	Additive error	4.57	NA	NA	NA
	Proportional error	0.119	2.93	0.112	0.126

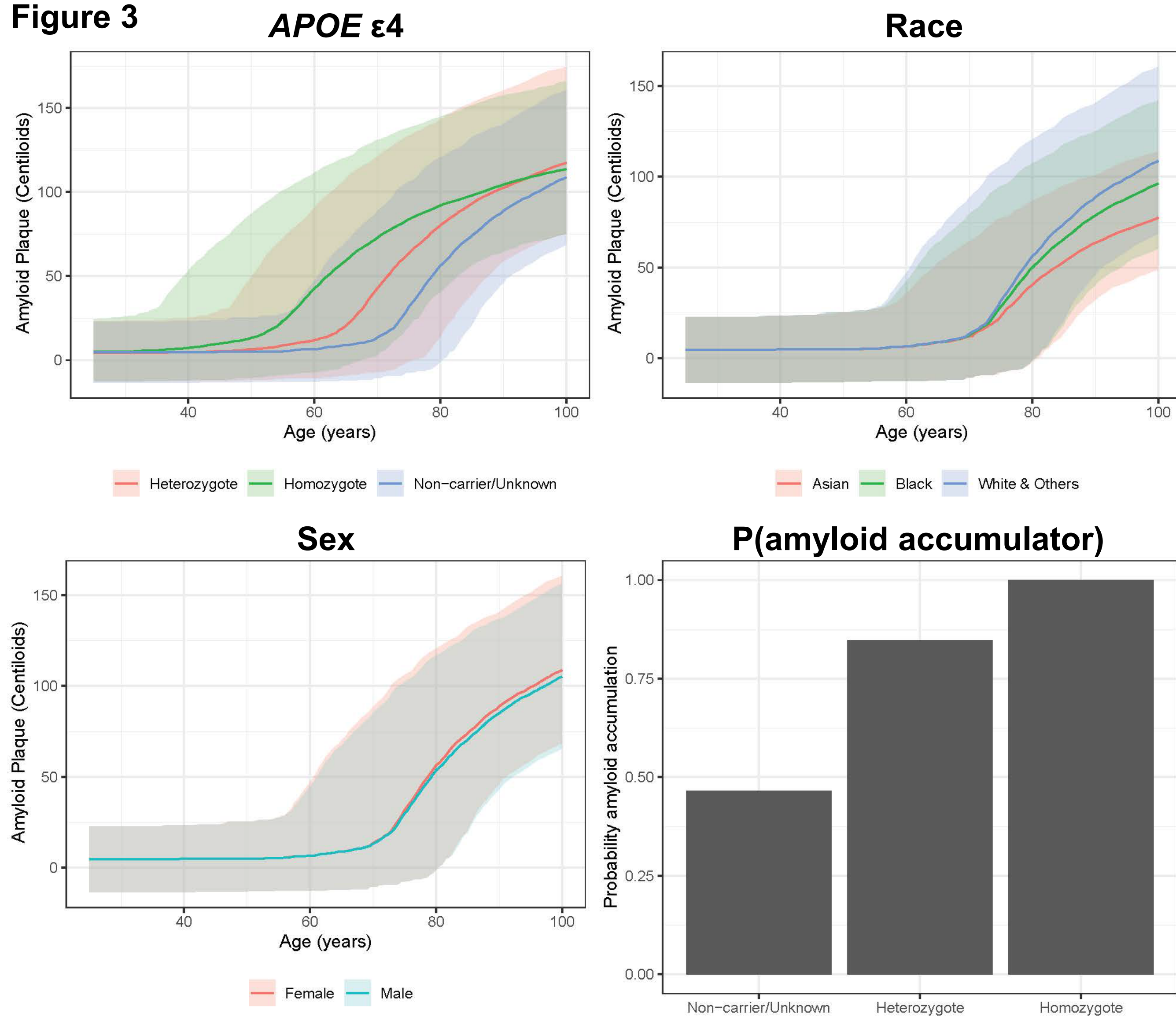
Model Goodness-of-Fit

Figure 1



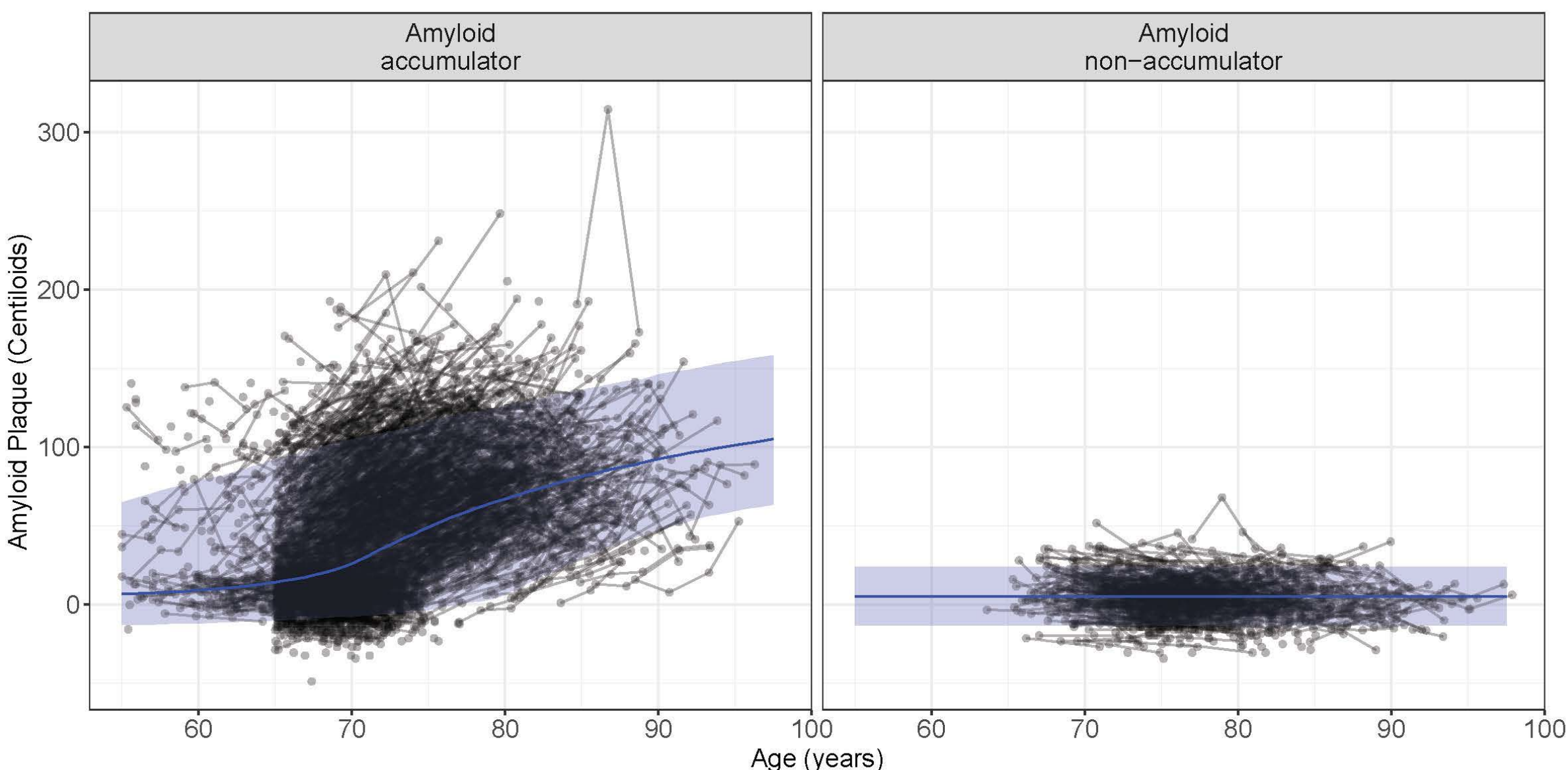
Impact of Covariates on Plaque Accumulation

Figure 3



Model Visual Predictive Check

Figure 2



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Disclosures: All authors are employees and minor shareholders of Eli Lilly and Company.
References: ¹Eliehnawy, et al. J. Pharmacokin. Pharmacodyn. 2024; ²Jagust WJ, et al. Neurology. 2021; ³Weiner MW et al Alzheimer's & Dementia. 2015; ⁴<https://clinicaltrials.gov/study/NCT01208675>; ⁵Sperling RA, et al. NEJM. 2023; ⁶Sperling RA, et al. JPAD. 2023.
Abbreviations: AD=Alzheimer's disease; *APOE*=apolipoprotein E; BMI=body mass index; CL=Centiloids; COSSAC=COnditional Sampling use for Stepwise Approach based on Correlation tests; EC50=half maximal effective concentration; Emax=maximum effect; IWRES=individual weighted residuals; N=number of participants; P=probability; R.S.E.=random study effect; SD=standard deviation.