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Estimated Age of Amyloid Onset in Participants with Early- versus Late-Onset Alzheimer's Disease: Results from the LEADS & ADNI Studies

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Abstract

Background: Aβ deposition is thought to start decades prior to symptom onset. Previous studies have shown that mathematical modeling enables reconstruction of Aβ-PET trajectory and age estimation at Aβ-PET positivity in Aβ-positive patients. We aimed to apply this approach to determine Aβ duration and estimate age at Aβ-PET positivity in sporadic early- (<65yo) and late- (≥65yo) onset AD (EOAD/LOAD).

Method: We combined PET data from the Longitudinal Early-Onset AD Study (LEADS, n = 288) and ADNeuroimaging Initiative (ADNI, n = 915). First, we selected Aβ+ (baseline Centiloids ≥24) cognitively impaired patients with ≥2 Florbetaben-PET scans to compare baseline and longitudinal amyloid-PET in EOAD versus LOAD using linear mixed effects regression (Figure 1). Then, we used ADNI participants with ≥2 Florbetapir-PET scans to assess the relationship between Aβ-PET Centiloids and time (Figure 2). We estimated the Aβ temporal trajectory by integrating a reciprocal of the spline model from the accumulation rate and Centiloidmid-point. Finally, we used the resulting Aβ trajectory to estimate Aβ duration and age at Aβ-PET positivity onset for patients with EOAD and LOAD (Figure 3).

Result: EOAD patients had higher baseline Aβ burden than LOAD patients. Amyloid-PET increased at similar rates in the two groups (Figure 1), allowing us to operate under the assumption that EOAD and LOAD follow the same Aβ trajectory, with a temporal shift. Aβ trajectory was estimated in ADNI Florbetapir-PET, showing an almost linear dependency between Centiloids and Aβ duration (Figure 2). The model suggests that Aβ-PET positivity (CL = 24) is reached after 7 years, and an additional 26 years are needed to reach 100 CL. When applied to the Florbetaben sample, we determined that 75yo LOAD patients became Aβ-PET positive around 52yo, while 60yo patients with EOAD dementia were Aβ-PET positive around age 31 (Figure 3).

Conclusion: Based on available data, the dynamic of Aβ accumulation seems similar in EOAD and LOAD, with a temporal shift indicating that EOAD patients might transition to Aβ-PET-positive in their early 30s. Prospective studies on early phases of Aβ accumulation in EOAD patients will be important for validation of these findings since existing data is limited.

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Figure 1 Step 1. Comparison of baseline Aβ burden and accumulation rate in subset of Cohort A: significant difference in baseline but not the annual change in EO- vs. LOAD.

LEADS and ADNI [^{18}F]Florbetaben PET data with available FU

A

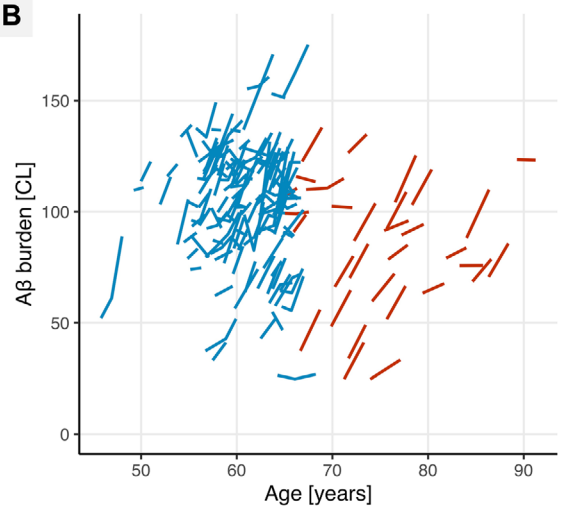
	N	Age [years]	FU duration [years]	Dx
EOAD	131	59.7	1.67	MCI = 38 Dementia = 93
LOAD	31	74.3	2.15	MCI = 19 Dementia = 11

C

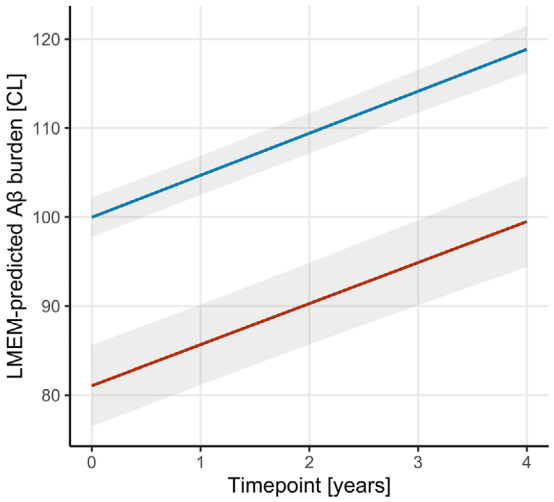
Aβ burden ~ Onset*Time + (Time|ID)

	Estimate	Std. Error	t-value	P-value
Intercept	99.96	2.21	45.21	**<0.001**
Onset [Early vs. Late]	-18.92	5.06	-3.73	**<0.001**
Time	4.72	0.44	10.52	**<0.001**
Onset:Time	-0.11	0.89	-0.12	0.90

B



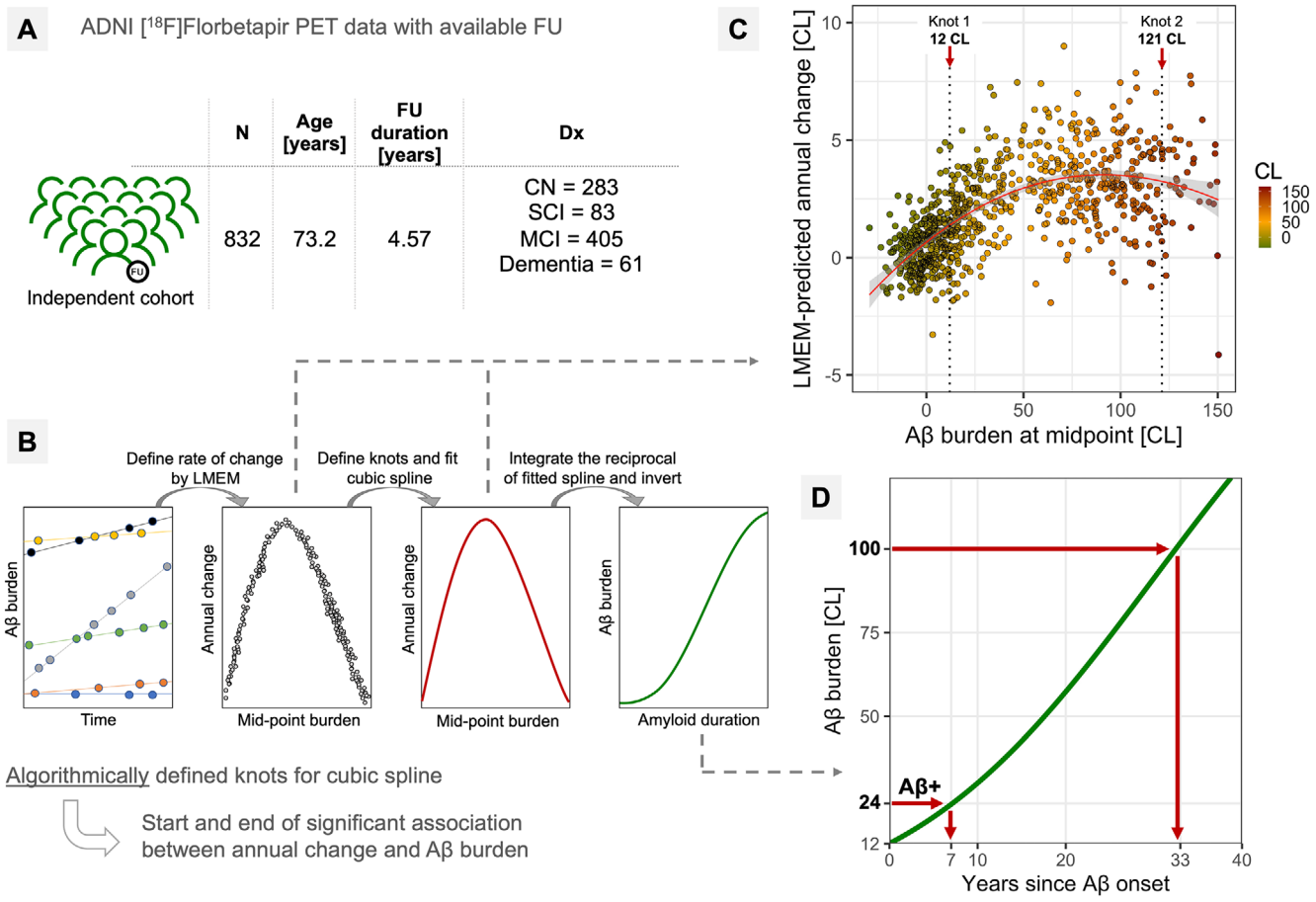
D



A. *Demographic characteristics of the analyzed cohort.* ***B.*** *Longitudinal trajectories of Aβ PET in EOAD and LOAD.* ***C.*** *Results of the linear mixed effects model (LMEM) analysis exploring the association between Aβ burden and FU time depending on the onset group.* ***D.*** *Aβ burden by time Interaction in EO- and LOAD.*

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Figure 2 Step 2. Definition of amyloid trajectory in an independent cohort with long available follow-up: almost linear relationship between Aβ burden and time in Aβ+ range of CL



A. Demographic characteristics of the analyzed cohort. B. Trajectory modelling workflow. C. Midpoint Aβ burden by annual change scatter plot with the cubic spline fit. D. Aβ trajectory curve, indicating around 26 y to reach 100 CL after turning Aβ+ (cutoff = 24 CL).

Figure 3

Step 3. Application of derived model to a combined cohort of EOAD and LOAD: estimated age at Aβ+ PET is significantly lower in patients with early-onset AD.

LEADS and ADNI [^{18}F]Florbetaben PET data: cross-sectional and longitudinal

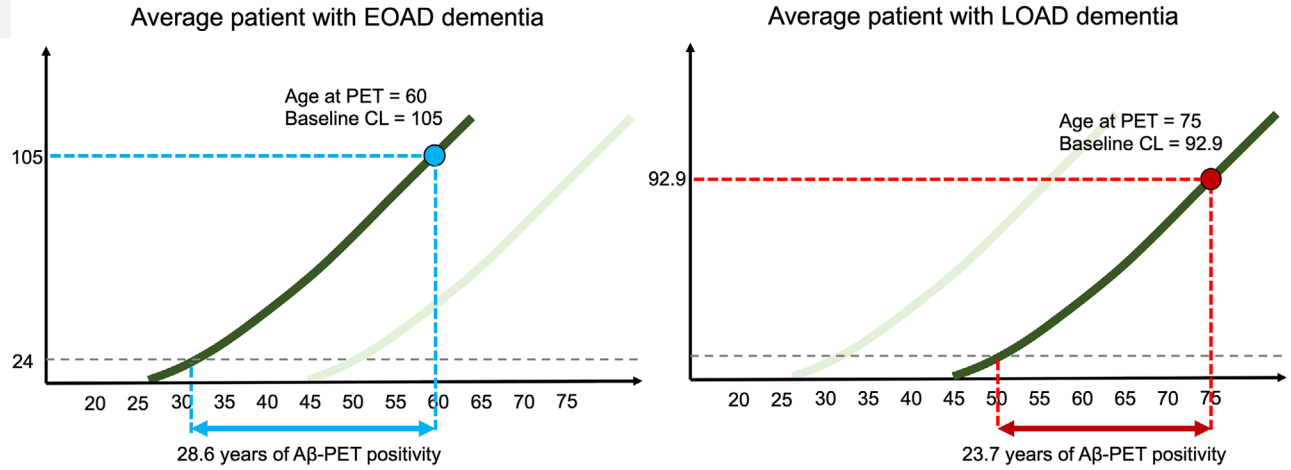
A

	N	Age [years]	Dx
EOAD	291	59.0	MCI = 86 Dementia = 205
LOAD	80	74.9	MCI = 47 Dementia = 33

C

	Dx	Average age at PET [years]	Measured Aβ burden [CL]	Time since Aβ+ PET [years]	Estimated age at Aβ+ PET [years]
EOAD					
	MCI	58.7	89.9	22.7	37.0
	Dementia	59.6	105.0	28.6	31.0
LOAD					
	MCI	74.5	72.3	16.6	57.9
	Dementia	75.4	92.9	23.7	51.7

B



A. *Demographic characteristics of the analyzed cohort.* ***B.*** *Schematic illustration of Aβ trajectory in patients with dementia in EO- and LOAD* ***C.*** *Average age at PET, measured Aβ burden, and estimated markers from trajectory modelling for MCI and AD dementia patients based on onset.*