

Characterizing the time interval between amyloid and tau onset

Julie Elisabeth Oomens¹, Ramiro E. Rea Reyes¹, Joyce Ruifen Chong¹, Nathaniel A. Chin¹, Hartmuth C. Kolb², Jessica Z.K. Caldwell¹, Rachael E. Wilson¹, Bradley Christian³, Matthew Zammit³, Henrik Zetterberg⁴, Tobey Betthausen¹, Sterling C. Johnson¹.

1 Wisconsin Alzheimer's Disease Research Center, University of Wisconsin School of Medicine and Public Health, Madison, WI, USA, 2 Enigma Biomedical Group, Knoxville, TN, USA, 3 Waisman Center, University of Wisconsin-Madison, Madison, WI, USA, 4 Department of Psychiatry and Neurochemistry, Institute of Neuroscience and Physiology, the Sahlgrenska Academy, University of Gothenburg, Molndal, Sweden



Wisconsin Alzheimer's
Disease Research Center
UNIVERSITY OF WISCONSIN
SCHOOL OF MEDICINE AND PUBLIC HEALTH

OBJECTIVES

The aim of the current project was to characterize the time between amyloid and tau onset (AT time) using Sampled Iterative Local Approximation (SILA).

METHODS

Participants and Imaging

- 906 participants from the Wisconsin Registry for Alzheimer's Prevention and the Wisconsin ADRC with ≥ 1 [¹⁸F]Florquinitau PET scan.
- CenTaur mesial ROI SUVR values were aligned to a duration scale using SILA (threshold: 1.35 SUVR)
- Amyloid Centiloid values were aligned to a duration scale using SILA (threshold: 18.53 centiloids)
- Participants crossing both thresholds were included in analyses (n=124).

AT Time Classification

- AT time = estimated age of tau onset – estimated age of amyloid onset.
- Participants classified as:
 - Tau positive before amyloid positive;
 - AT time 0–10 years;
 - AT time ≥ 10 years.

Statistical Analysis

- Compared demographic, vascular, and lifestyle factors across AT groups;
- Zero-inflated Gamma mixed-effects models (log link; random intercepts and slopes) to assess associations between AT group and CDR Sum of Boxes (CDR SOB)
 - Models were adjusted for APOE $\epsilon 4$ status and gender.
- Used the inverse of the Kaplan-Meier (KM) survival function to estimate the cumulative prevalence of tau PET positivity and conversion to cognitive impairment (CDR SOB > 1.5) as a function of amyloid time.

RESULTS

The mean estimated age of onset was 62.7 years for amyloid and 69.2 years for tau (**Figures 1 & 2**). **Figure 3** illustrates the time interval between amyloid and tau onset. There was no significant difference in AT time between APOE $\epsilon 4$ carriers and non-carriers (**Figure 4**). Comparisons of AT groups are presented in **Table 1**. AT group was associated with baseline CDR SOB scores, but not with the rate of decline (**Figure 5**). At 20+ years of amyloid chronicity, the estimated cumulative prevalence of tau PET positivity is > 90% and climbing (**Figure 6**).

ACKNOWLEDGEMENTS

We would like to thank WRAP participants and staff for their contributions to the WRAP study. Without their efforts this research would not be possible. This research is supported by NIA NIH R01 AG021155, R01 AG027161 and P30 AG062715

FIGURES & TABLES

Figure 1: Estimated age of amyloid onset (years)

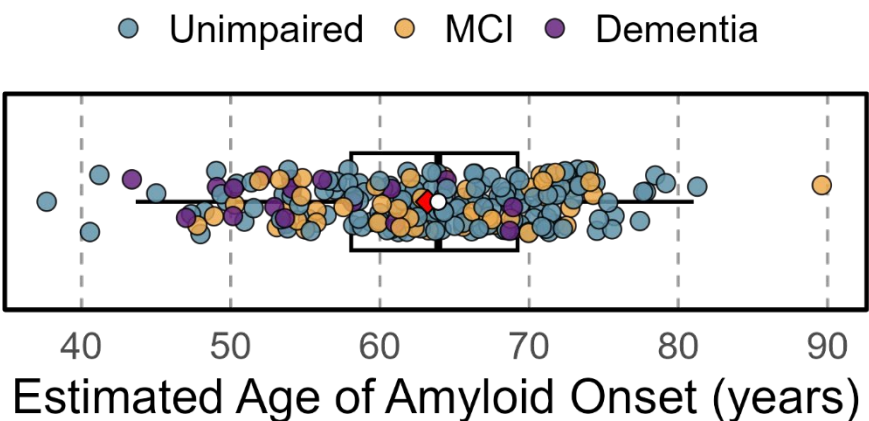


Figure 2: Estimated age of tau onset (years)

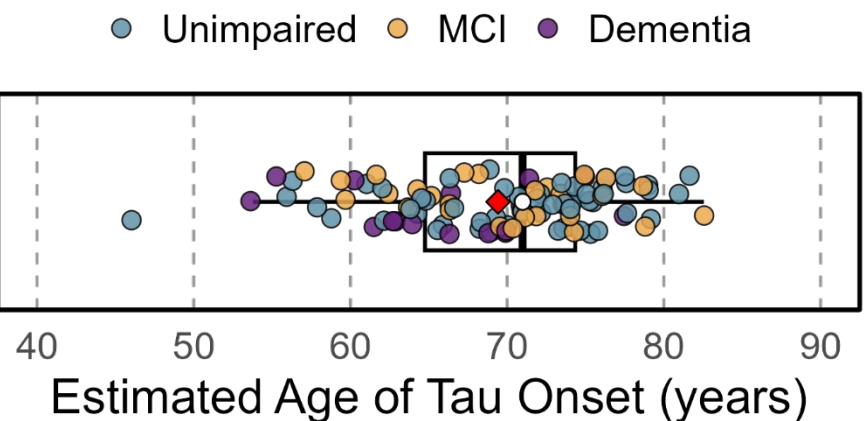


Figure 3: Time (years) between amyloid and tau onset.

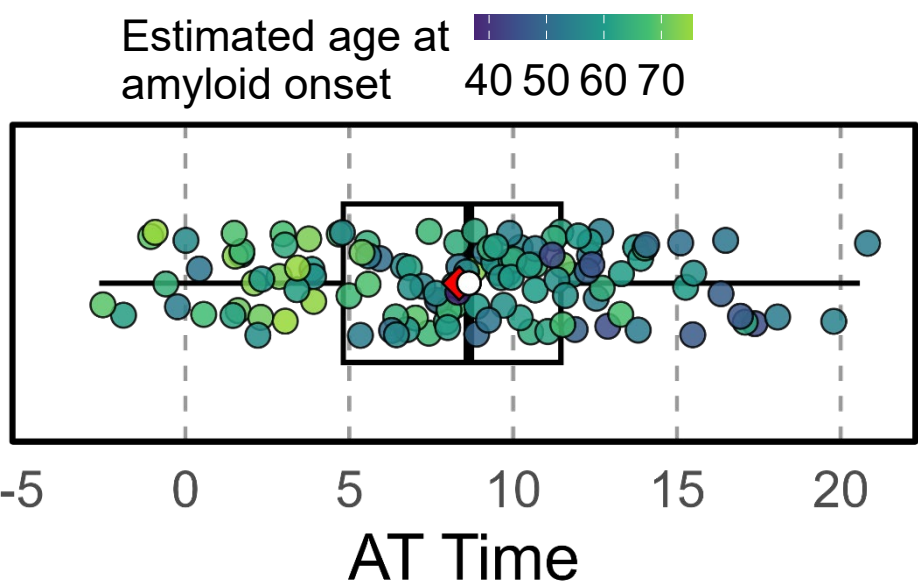


Figure 4: Time (years) between amyloid and tau onset, by APOE $\epsilon 4$ carrier status

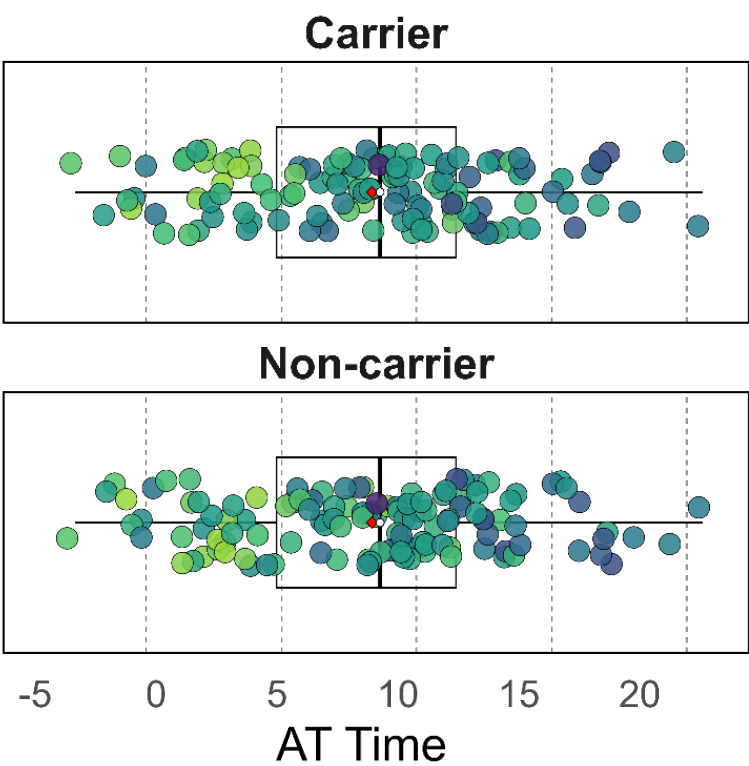


Figure 5: Predicted CDR-SB score over amyloid time, by AT group.

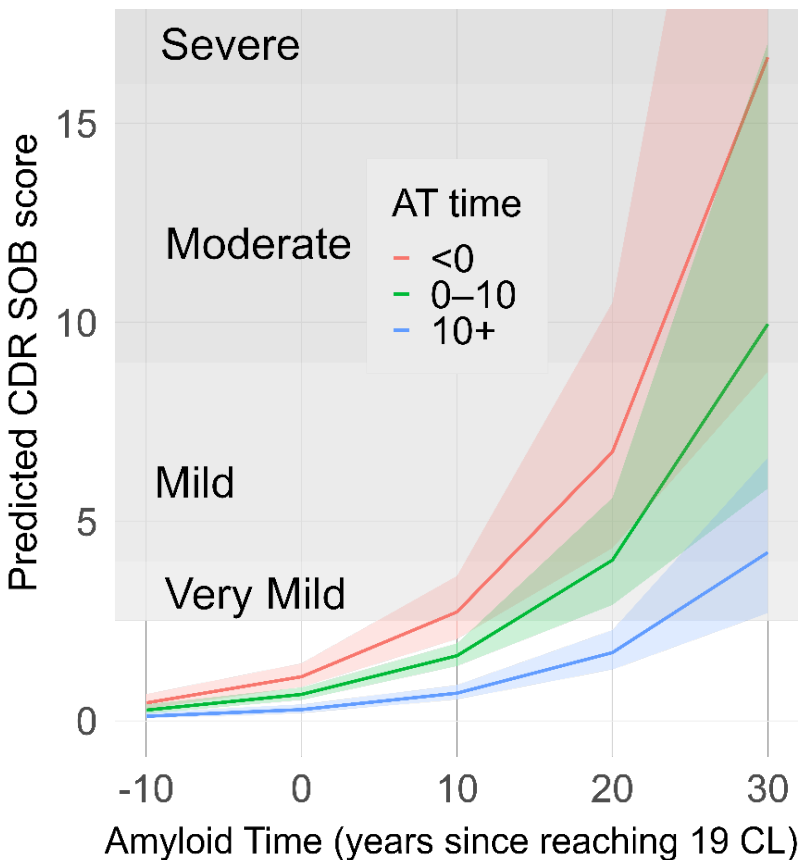


Figure 6: Cumulative prevalence of tau PET positivity and cognitive impairment as function of amyloid time.

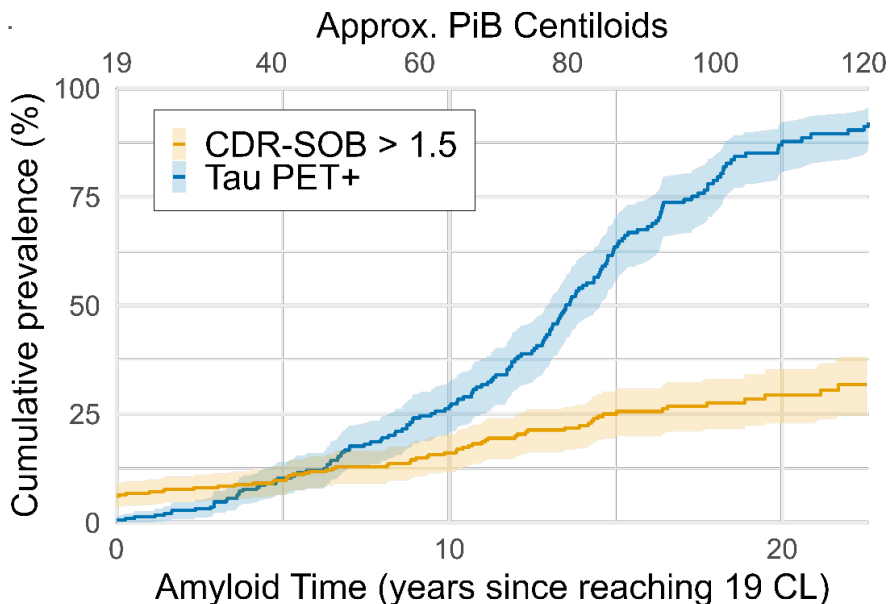


Table 1: Participant characteristics

	All, n = 124	Tau before amyloid, n = 8	0-10 years, n = 69	10+ years, n = 47
Age at amyloid reference scan, mean(SD)	73.6 (5.9)	70.7 (4.6)	73.4 (6.3)	74.4 (5.5)
Female, n(%)	84 (67.7%)	4 (50.0%)	48 (69.6%)	32 (68.1%)
APOE $\epsilon 4$ carrier, n(%)	90 (72.6%)	5 (62.5%)	50 (72.5%)	36 (76.6%)
Education years, median[range]	16 [10-18]	16 [12-18]	16 [10-18]	17 [12-18]
Non-Hispanic white, n(%)	108 (87.1%)	5 (62.5%)	62 (89.9%)	41 (87.2%)
Normal cognition, n(%)	62 (50.0%)	4 (50.0%)	34 (49.3%)	24 (51.1%)
MCI, n(%)	41 (33.1%)	1 (12.5%)	26 (37.7%)	14 (29.8%)
Dementia, n(%)	19 (15.3%)	3 (37.5%)	8 (11.6%)	8 (17.0%)
LIBRA score, median [range]*	-1.1 [-5.9-5.2]	0.13 [-2.0-3.2]	-1.1 [-4.3-4.5]	-1.3 [-5.9-5.2]

*missing for n = 49 (39.5%). LIBRA: Lifestyle for BRAin health Index.

CONCLUSIONS

We observed substantial heterogeneity in the time between amyloid and tau onset. AT group was associated with baseline CDR SOB scores, but not with the rate of decline. Further characterizing the time interval between amyloid and tau pathology onset will provide important insight into disease progression.