



Functional Form Matters: How Model Specification Shapes Conclusions About Alzheimer's Disease Biomarker Relationships



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Background

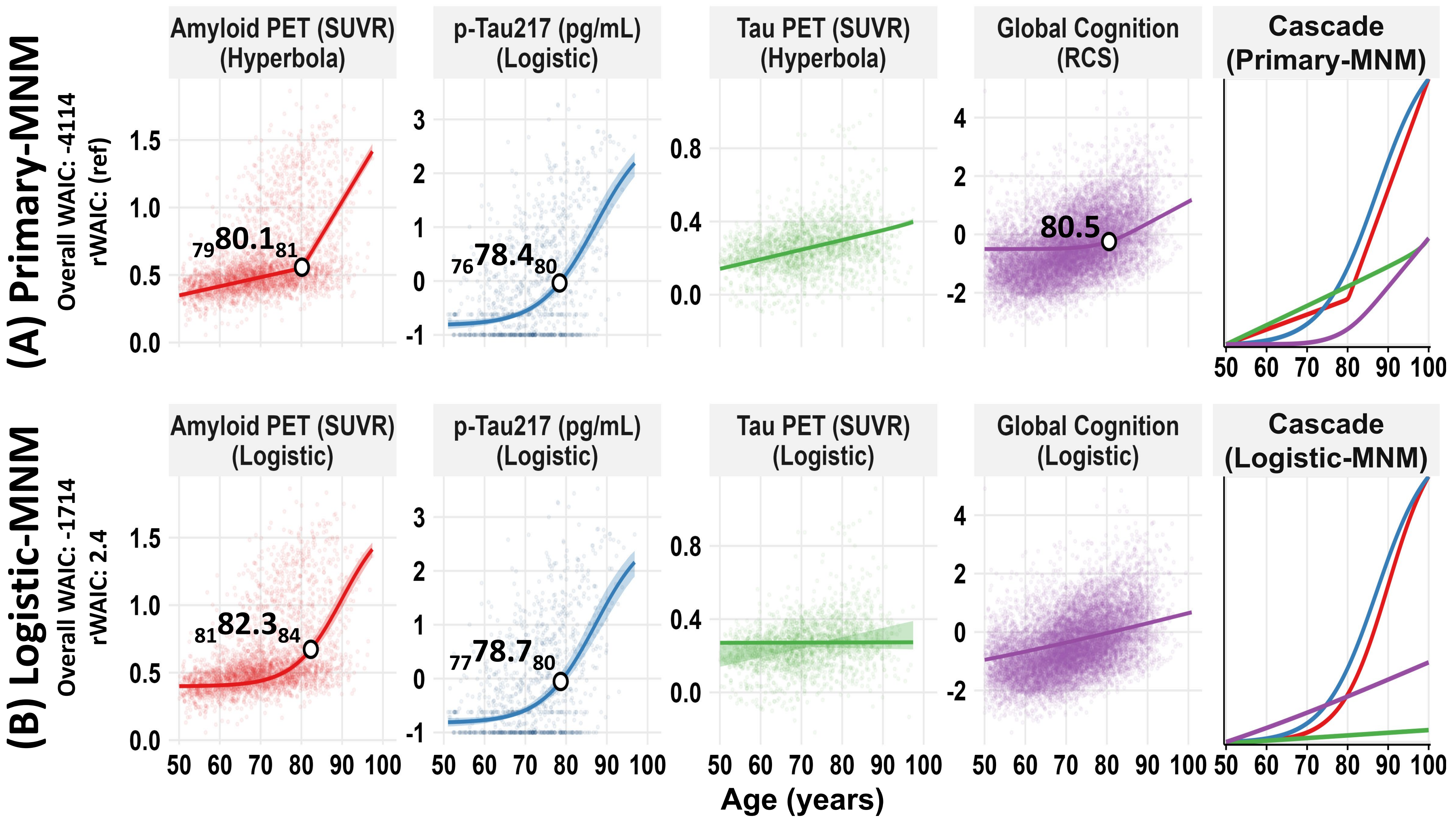
- Alzheimer's Disease (AD) pathology progression is often characterized by sequential S-shaped shifts in biomarkers from normal to abnormal.
- Advanced modeling approaches are needed to capture nonlinear changes in multiple biomarkers simultaneously over time using longitudinal data.
- Key challenges in estimation include:
 - Selecting optimal sigmoidal (S-shaped) functions for each biomarker
 - Ensuring algorithmic convergence
 - Producing interpretable and clinically meaningful estimates.

Objectives

- We examine the sensitivity of AD cascade conclusions to functional form choice in Multivariate Nonlinear Mixed Effect Models (MNM). We compare best-fitting, outcome-specific functional forms (Primary-MNM) selected using Watanabe-Akaike Information Criterion (WAIC) vs. assuming logistic functional forms across outcomes (Logistic-MNM).

Results

Figure 1. Comparison of estimated AD-cascade functions and maximum-acceleration points from (A) Best-Supported and (B) Logistic MNMs



Methods

Study population: The Mayo Clinic Study of Aging (MCSA) is a prospective cohort from Olmsted County, Minnesota, ages 50 to 101 years (see Table 1).

Final samples:

- 1,576 PET amyloid SUVR measures
- 495 plasma p-tau217 measures
- 1,416 tau PET measures
- 2,598 global cognition

Biomarkers: PET Amyloid SUVR (¹¹C-PiB PET, normalized to cerebellar gray matter), p-tau217 (C2N PrecivityAD2 LC-MS assay), Tau PET, Global Cognition

Sigmoidal Functions:

- Logistic – Symmetric s-shaped¹
- Hyperbola Function – Non s-shaped focusing on acceleration²
- Restricted Cubic Splines (RCS)

Statistical Analysis: MNMs with subject-specific age-shifts model longitudinal trajectories across age, adjusting for sex and APOE4 status. Estimates are presented as Bayesian posterior means with 95% credible intervals.

Discussion

- Model choices can greatly affect results about the ordering of biomarker changes
 - Best-Supported MNM supports biology more than assumed Logistic-MNM
 - Cross-outcome correlations differed substantially between Primary-MNM and Logistic-MNM, particularly for tau PET with PET amyloid and plasma p-tau217
- Limitations:**
- ~5% of participants had MCI/dementia, which may affect bend-point estimations

References

1. Gottschalk, P. G., & Dunn, J. R. (2005). The five-parameter logistic: a characterization and comparison with the four-parameter logistic. *Analytical biochemistry*, 343(1), 54-65.
2. Therneau, Terry M., David S. Knopman, Val J. Lowe, Hugo Botha, Jonathan Graff-Radford, David T. Jones, Prashanthi Vemuri et al. (2021). Relationships between β -amyloid and tau in an elderly population: An accelerated failure time model. *Neuroimage*, 242.

Acknowledgements

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Table 1. MCSA Study Participant Baseline Visit Characteristics

Variables	Total (n=2,725)
Age (years)	67 (10.2)
Male, n (%)	1,356 (50%)
APOE4+, n (%)	559 (26%)
Amyloid SUVR	1.5 (0.3)
P-Tau217 (pg/mL)	1.2 (1.5)
Tau SUVR	1.2 (0.1)
Global Cognition	0.2 (1.0)

†Cells represent mean (SD) for continuous data and counts (%) for categorical data

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Figure 2. Subject-Specific Random Effect Correlation Matrices Comparing (A) Best-Supported and (B) Logistic MNMs

