



Exploratory Shiny App

Timing of First Neuroimaging in Alzheimer's Disease

A Multicenter Competing-Risk Analysis of Genetic, Cognitive, and Social Determinants



★ Joshua T. Korley^{1,†}, Enock A. Bonsu²

¹ Arnold School of Public Health, University of South Carolina, Columbia, SC, USA

² Mel and Enid Zuckerman College of Public Health, University of Arizona, Tucson, AZ, USA

[†] Correspondence: jkorley@email.sc.edu

Background & Motivation

MRI is central to Alzheimer's disease research and clinical evaluation, yet the timing of a participant's first post-baseline MRI varies widely across centers and patient groups.

In aging cohorts, many participants die before imaging; treating death as noninformative censoring can distort inference about neuroimaging access and selection into imaging-based analyses.

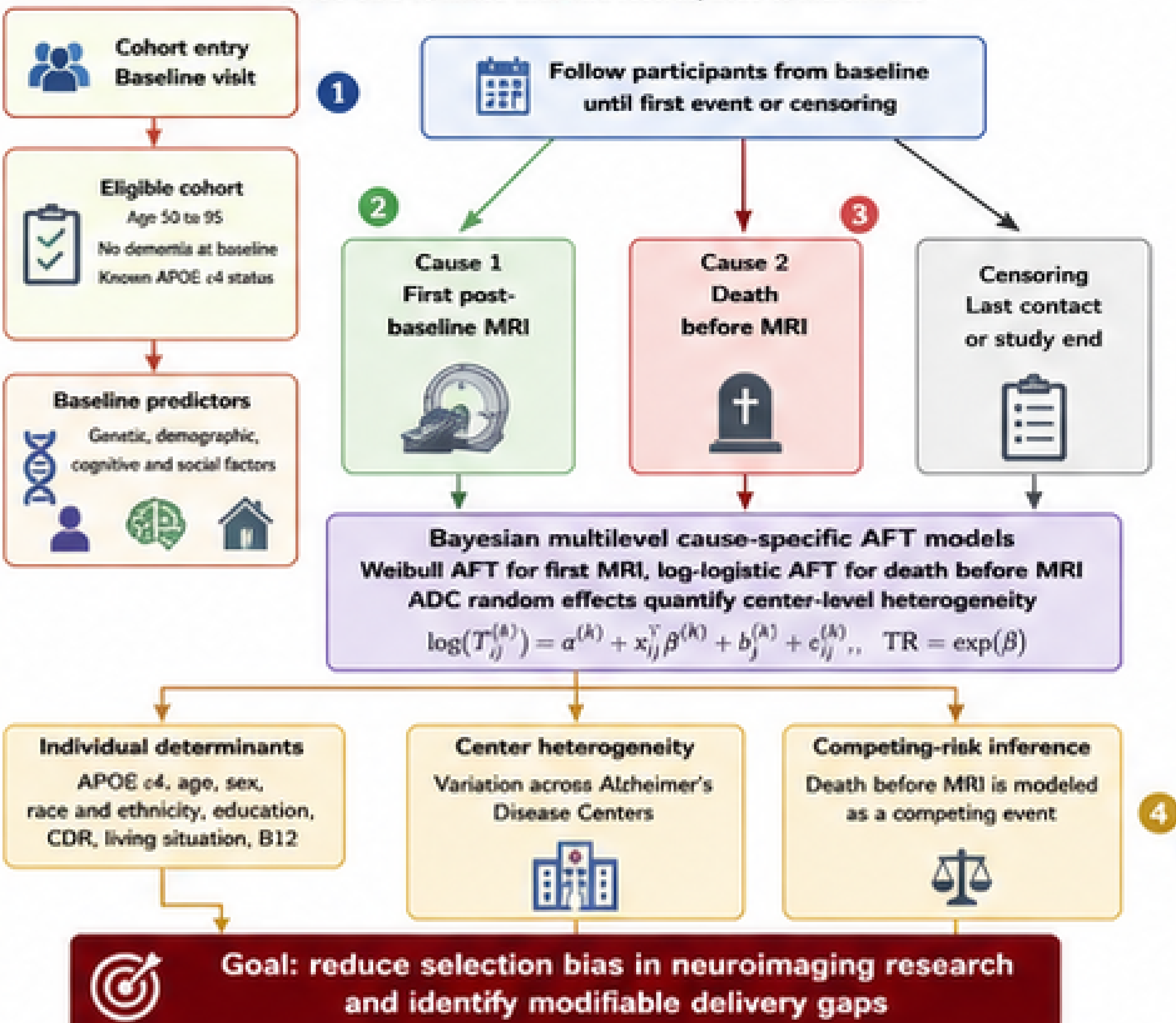
Clinical relevance: Linked multicenter data can identify system-level heterogeneity and social determinants that shape the pathway from cohort entry to neuroimaging, connecting Alzheimer's disease research with equitable imaging delivery.

Objective

Quantify individual-level determinants and center-level heterogeneity in time to first post-baseline MRI while accounting for the competing risk of death before MRI.

Study Design

Research Flow: Timing of First Neuroimaging in Alzheimer's Disease
NACC UDS v3 linked with MRI records, 2015 to March 2025



Cohort & Measures

- **Data:** NACC UDS v3 linked with MRI records from 2015 to March 2025.
- **Eligibility:** ages 50 to 95, no dementia at baseline, known APOE ε4 status.
- **Sample:** 20,867 participants across multiple Alzheimer's Disease Centers.
- **Outcomes:** first MRI after baseline and death before MRI.
- **Baseline covariates:** APOE ε4 count, age group, sex, race and ethnicity, education, global functional impairment, living situation, and vitamin B12 deficiency.

Statistical Methods (Bayesian multilevel cause-specific AFT)

We fit two cause-specific accelerated failure time (AFT) models:

Cause 1 (First MRI): Weibull AFT

Cause 2 (Death before MRI): Log-logistic AFT

Let T_{ij} be time-to-event for participant i in center j and $k \in \{1, 2\}$ index the cause. For each cause:

$$\log(T_{ij}^{(k)}) = \alpha^{(k)} + x_{ij}^T \beta^{(k)} + b_j^{(k)} + \epsilon_{ij}^{(k)}, \quad b_j^{(k)} \sim \mathcal{N}\{0, (\sigma_b^{(k)})^2\}.$$

Interpretation: $\exp(\beta_\epsilon^{(k)})$ is a time ratio (TR).

TR > 1 indicates longer time to event; TR < 1 indicates shorter time to event.

Why multilevel Bayesian modeling matters

- ▶ **Center effects are part of the research question:** heterogeneity across Alzheimer's Disease Centers reflects differences in imaging pathways and study operations.
- ▶ **Partial pooling improves estimation:** Bayesian multilevel modeling stabilizes center-specific effects and provides interpretable credible intervals.
- ▶ **Death is not ordinary censoring:** treating death as a competing event reduces bias in aging cohorts.

Main Results (Bayesian AFT time ratios)

Table 2. Bayesian accelerated failure time models for time to first MRI (Cause 1) and time to death before MRI (Cause 2).

Risk Factors	First MRI (Cause 1)		Death before MRI (Cause 2)	
	TR	95% CrI	TR	95% CrI
APOE ε4: One vs None	0.98	0.85 to 1.13	0.98	0.85 to 1.02
APOE ε4: Two vs None	0.79	0.68 to 1.08	0.67	0.52 to 0.97
Age: 65–79 vs <65	0.99	0.85 to 1.15	0.69	0.64 to 0.73
Age: ≥80 vs <65	2.77	2.10 to 3.51	0.34	0.26 to 0.41
Undergraduate vs ≤HS	0.74	0.61 to 0.90	1.09	1.03 to 1.15
Graduate vs ≤HS	0.63	0.51 to 0.77	1.18	1.12 to 1.25
Black vs White	1.66	1.17 to 2.36	0.85	0.71 to 1.04
Other vs White	1.86	1.47 to 2.35	0.69	0.60 to 0.78
Female vs Male	1.09	0.96 to 1.24	1.25	1.20 to 1.30
CDR Global ≥ 1 vs 0	1.15	1.00 to 1.31	1.52	1.47 to 1.58
Live with spouse vs alone	0.92	0.79 to 1.06	1.09	1.05 to 1.14
Other household vs alone	0.91	0.76 to 1.10	0.97	0.84 to 0.99
Vitamin B12 deficiency (Yes vs No)	0.91	0.71 to 1.18	0.94	0.84 to 0.97

TR denotes time ratio from Bayesian accelerated failure time models. Values >1 indicate longer time to event, while values <1 indicate shorter time. 95% CrI: 95% credible interval.

Key Findings

- ▶ **APOE ε4 was not credibly associated with MRI timing (Cause 1), but ε4 homozygosity predicted earlier death before MRI (Cause 2).**
- ▶ **Older age** was associated with longer time to MRI and shorter time to death before MRI.
- ▶ **Black participants and other racial minorities** experienced longer time to MRI relative to White participants.
- ▶ **Graduate education** was associated with shorter time to MRI.
- ▶ **Large center-to-center variability** indicates that site processes strongly shape time-to-imaging.
- ▶ **Sensitivity analyses** using frequentist AFT and Cox models supported the main qualitative conclusions.

Center-Level Heterogeneity (ADC random effects)

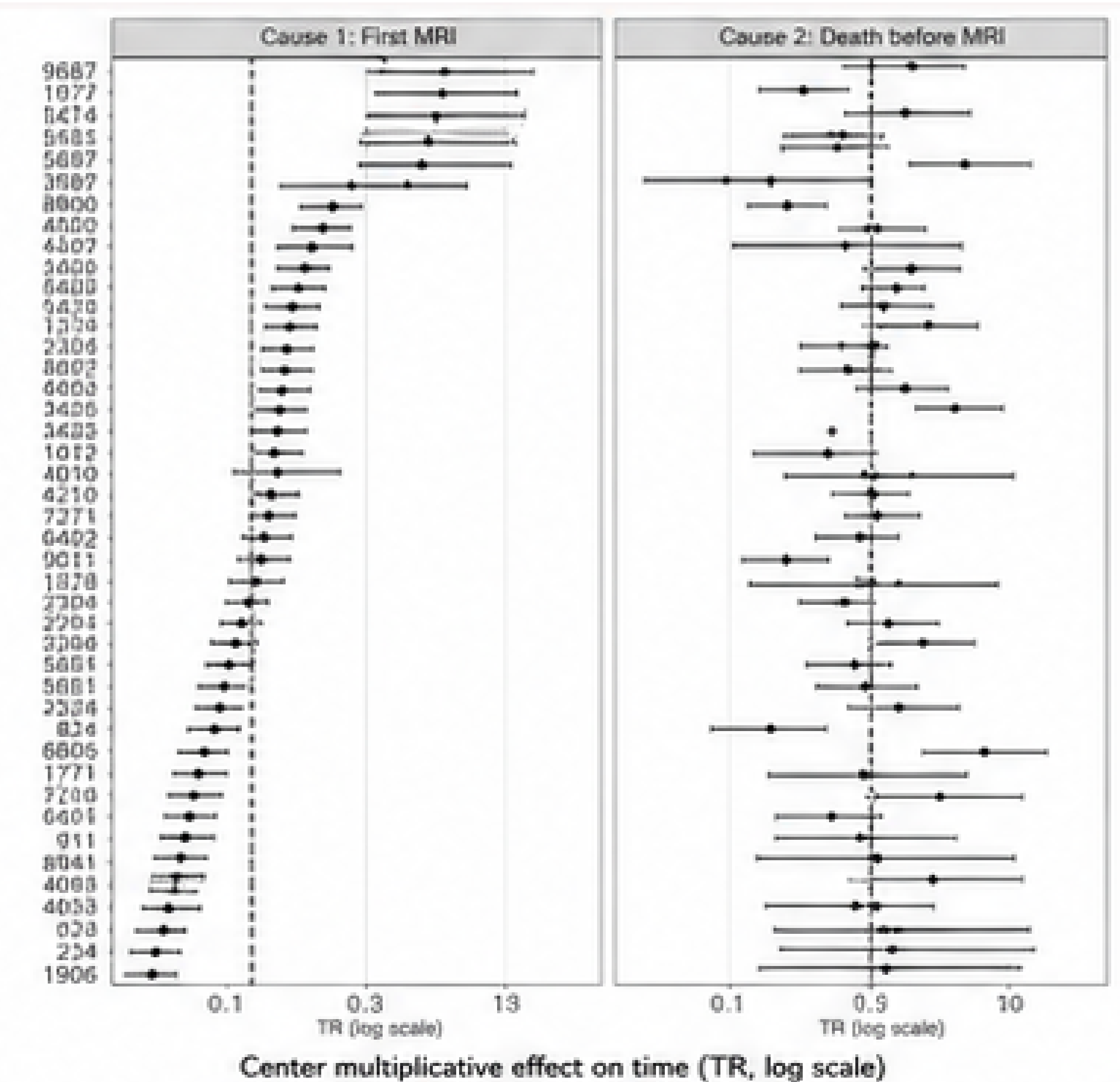


Figure 5. Center-specific multiplicative effects on event times from Bayesian AFT models. point represents the posterior mean time ratio (TR) for an Alzheimer's Disease Center, with horizontal bars indicating 95% credible intervals. The vertical dashed line denotes the overall average center effect (TR = 1). Left: time to first MRI. Right: time to death before MRI.

Interpretation for "Discovery to Delivery"

- ▶ **Discovery:** Genetic risk through APOE is important for Alzheimer's disease biology, but it did not explain when participants received MRI after cohort entry.
- ▶ **Delivery:** Demographic and social determinants, including age, race, ethnicity, education, living situation, and center-level processes, were primary drivers of time-to-imaging.
- ▶ **Equity signal:** Delayed imaging was linked more strongly to age, race and ethnicity, education, and center-level practice than to APOE genotype.
- ▶ **Robustness:** Conclusions were unchanged in sensitivity analyses using frequentist AFT and Cox models.
- ▶ **Implication:** Imaging-based studies may overrepresent participants with faster access and underrepresent those with delayed imaging or higher competing mortality, which can bias downstream biomarker discovery.

Limitations

- ▶ Observational access patterns may reflect unmeasured center policies and local imaging capacity.
- ▶ Covariates reflect baseline status; time-varying clinical and access factors may further explain delays.
- ▶ MRI availability does not guarantee identical imaging protocols across centers.

Conclusion

Timing of first MRI in Alzheimer's research cohorts was driven primarily by **demographic, social, and center-level factors** rather than genetic risk. Accounting for competing mortality and site heterogeneity is necessary to reduce selection bias in neuroimaging samples and to support more equitable Alzheimer's research. Scan the QR code for the exploratory Shiny app.

Selected References

1. Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. *JASA*. 1999;94(446):496–509.
2. Austin PC, Lee QS, Fine JP. Introduction to the analysis of survival data in the presence of competing risks. *Circ Cardiovasc Qual Outcomes*. 2016;9(4):e002767.
3. National Alzheimer's Coordinating Center (NACC). Uniform Data Set Researcher's Data Dictionary, Version 3, 2023.

Acknowledgements

Data source: National Alzheimer's Coordinating Center (NACC).