

Causal Discovery Of Alzheimer’s Disease Biomarkers Using The Fast Causal Inference Algorithm

Natalia Glazman¹, Ankit Gupta², Arėjas Užgiris², Jorge Cardoso¹

1 King’s College London

2 Siemens Healthineers

Constraint-based causal discovery recovered known Alzheimer's biomarker relationships, highlighted pTau217 as a biomarker directly linked to cognitive decline and suggested a potentially earlier pathological role for NfL that motivates further investigation.

INTRODUCTION

Traditional Alzheimer's disease (AD) biomarker research predominantly relies on associational analyses, limiting the ability to distinguish correlation from causation and infer underlying disease mechanisms. Causal discovery methods offer a framework for inferring directional relationships from observational data while accounting for latent confounding. Here, we apply **constraint-based causal discovery** to **plasma** and **neuroimaging biomarkers** to investigate the causal positioning of established AD markers within disease progression.

METHODS

- **Dataset:** Baseline data from the Alzheimer's Disease Neuroimaging Initiative (ADNI) were analysed (n = 550), comprising 289 cognitively normal (CN) participants, 192 individuals with mild cognitive impairment (MCI), and 69 individuals with Alzheimer's disease (AD).
- **Variables:** analysis incorporated key plasma biomarkers (pTau217, Aβ42/40, GFAP, and NfL), neuroimaging measures, demographic characteristics, and cognitive performance assessed using the ADAS-Cog13.
- **Causal discovery approach:** The Fast Causal Inference (FCI)¹ algorithm was applied using non-linear kernel conditional independence tests ($\alpha = 0.05$) to infer potential causal relationships from observational data while allowing for latent confounding.
- **Incorporation of prior knowledge:** Biological and temporal constraints were imposed by specifying demographic variables as root nodes (having no incoming edges) and ADAS-Cog13 as a sink node (having no outgoing edges).

RESULTS

- **Overall structure:** The inferred causal network was broadly consistent with established AD pathophysiology, supporting biological plausibility.
- **pTau217:** Showed a direct effect on cognitive outcomes not mediated by other measured variables and was consistently upstream of multiple cognitive measures and GFAP (64% bootstrap frequency).
- **NfL:** NfL unexpectedly appeared upstream of GFAP in 66% of bootstrap runs, contrasting with its typical characterisation as a late-stage neurodegeneration marker.
- **Stability:** NfL relationships with other biomarkers were generally unstable (max edge frequency with pTau217: 42%), suggesting potential sensitivity to unobserved confounding and warranting cautious interpretation.

CONCLUSIONS

- **Interpretation:** our findings support the role of pTau217 as a causally proximal biomarker of cognitive decline and are consistent with prior evidence linking GFAP more closely to amyloid–tau pathology than NfL.
- **NfL positioning:** The tentative upstream placement of NfL relative to GFAP suggests a possible earlier involvement in neuroinflammatory processes than typically assumed.
- **Implication:** This motivates further prospective and longitudinal studies to determine whether the observed causal ordering is stable across disease stages and cohorts.

REFERENCES

1. Spirtes, P., Glymour, C., & Scheines, R. (2000). *Causation, Prediction, and Search* (2nd ed.). MIT Press, Cambridge, MA.

CONTACT

Natalia Glazman, King’s College London
natalia.glazman@kcl.ac.uk

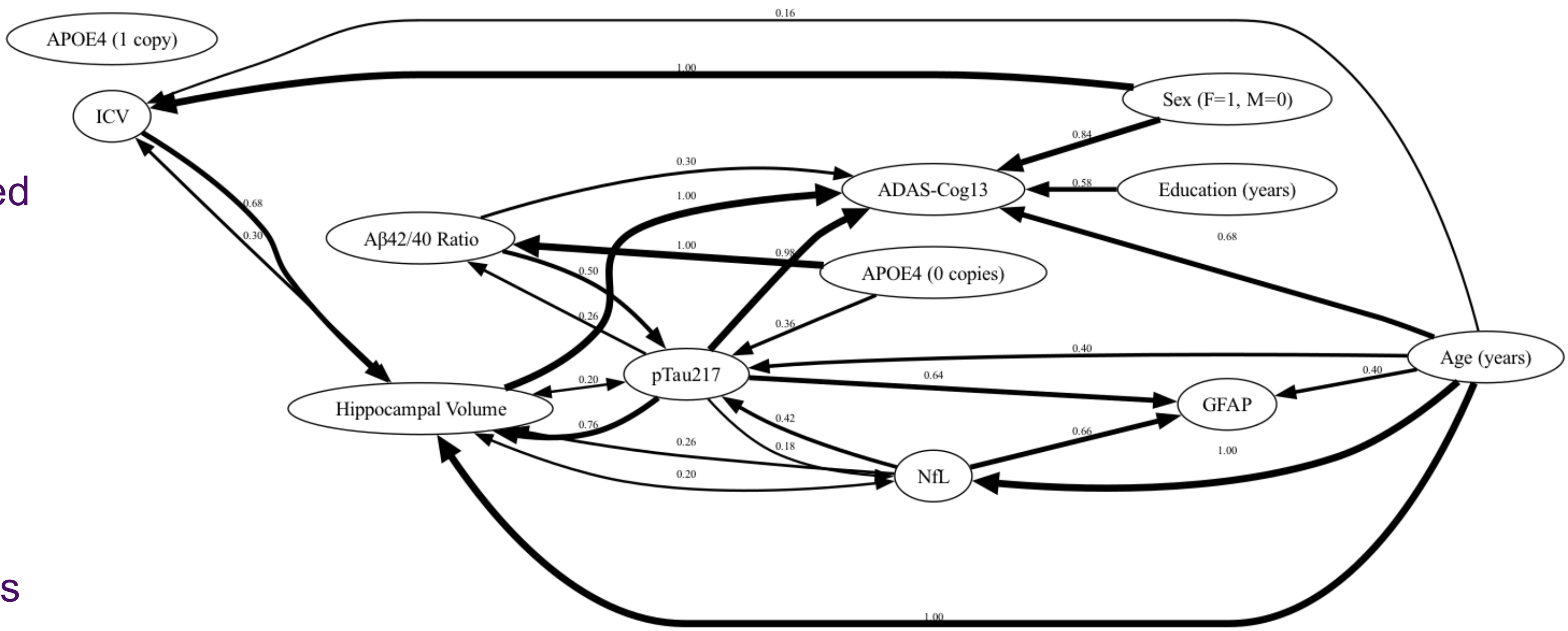


Figure 1. Estimated causal DAG across plasma biomarkers, neuroimaging, cognitive scores and demographic covariates; edge labels denote bootstrap edge frequency.