

Blood-based biomarkers and risk of clinically diagnosed Alzheimer's disease up to 25 years later in the EPIC-Oxford cohort study

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Introduction

- Alzheimer's disease (AD) pathology typically progresses sub-clinically up to 20 years prior to symptomatic presentation and diagnosis.
- Effective markers for the early identification of at-risk individuals are necessary for enrollment into preventative trials for AD and to prepare for a future where emerging treatments and interventions become widely available.
- Blood-based biomarkers represent cost-effective and accessible measures for AD risk stratification, however there is a need to determine the utility of blood-based biomarkers for risk prediction many years prior to an AD diagnosis.

Aim: To investigate the association between 131 blood-based biomarkers measured in a population-based cohort and risk of AD diagnosed in a clinical setting up to 25 years later.

Methods

Population: Participants were selected from EPIC-Oxford, a population-based cohort of women and men recruited throughout the UK between 1993-2001.

Blood-based biomarkers: 131 proteins were measured using the NULISaseq CNS panel (Alamar Biosciences), including p-tau isoforms, A β 40 and 42, GFAP, NFL and a range of proteins implicated in neuro-related processes and pathology. The panel also includes newly available measures of brain-derived p-tau isoforms which are specific to the central nervous system and account for p-tau arising from the periphery.

Cases: 213 AD cases were identified from longitudinally collected electronic hospital inpatient and death records available up to 2019.

Controls: 213 participants free-from incident all-cause dementia were matched 1:1 with AD cases on age at blood draw, sex and date of blood-draw.

Characteristics, %	AD cases (N=213)	Non-AD controls (N=213)
Age at blood draw, mean	63 years	63 years
Women	71%	71%
Degree level qualification	20%	16%
Never smoker	51%	50%
Alcohol g/day, mean	8.6 g/day	7.5 g/day
Moderately or very physically active	23%	17%
BMI, mean	24.7	24.9
Presence of one or more health condition	37%	35%

Baseline characteristics of the final sample

Analysis: Conditional logistic regression was used to determine the association between all biomarkers and AD risk, with correction for multiple comparisons using a false discovery rate. Risk prediction was assessed using the Area Under the Curve (AUC) of the Receiver Operator Curve.

Results

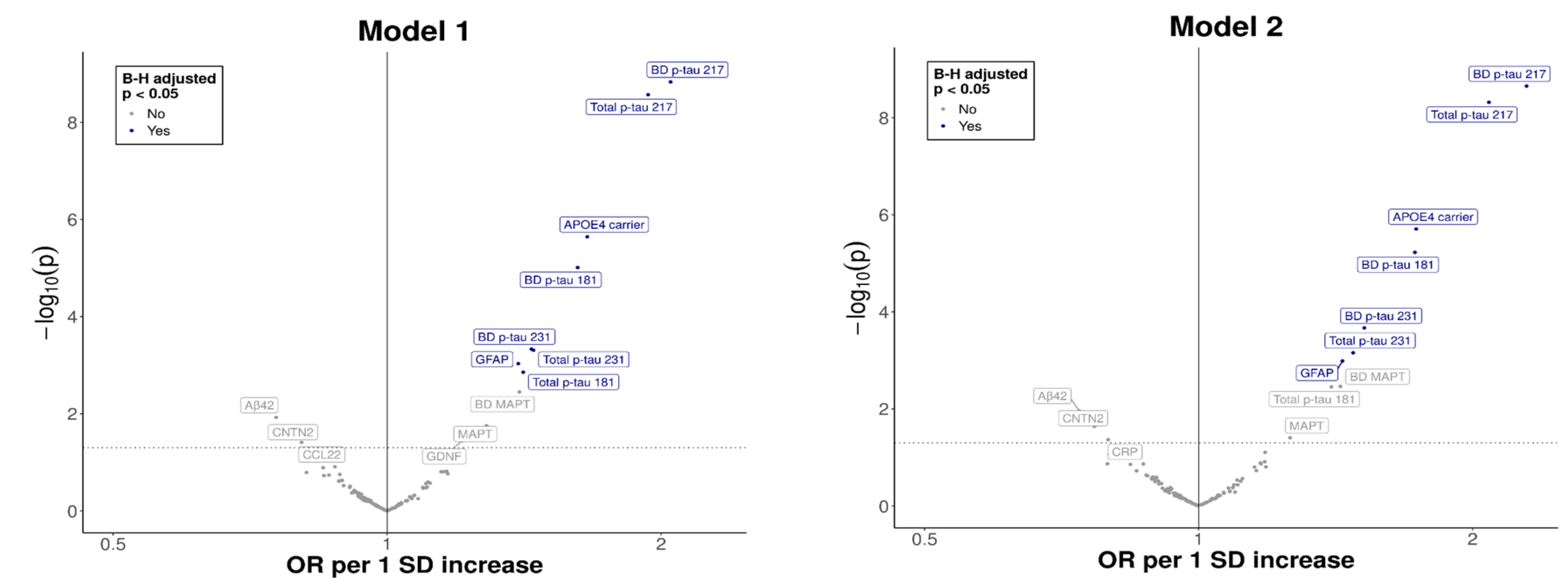
The median time from blood draw to AD diagnosis was 19 years, the range was 10 to 25 years (interquartile range = 17-22 years).

Blood-based biomarker associations with AD

Higher concentrations of brain-derived p-tau 181, 217, 231, and total p-tau 181, 217, 231, as well as GFAP, were associated with AD risk (Model 1).

Results were highly similar when adjusting for education, smoking status, alcohol intake, physical activity index, BMI, and presence of a self-reported health condition (Model 2). Except for total p-tau 181, which was not statistically significant after false discovery rate correction.

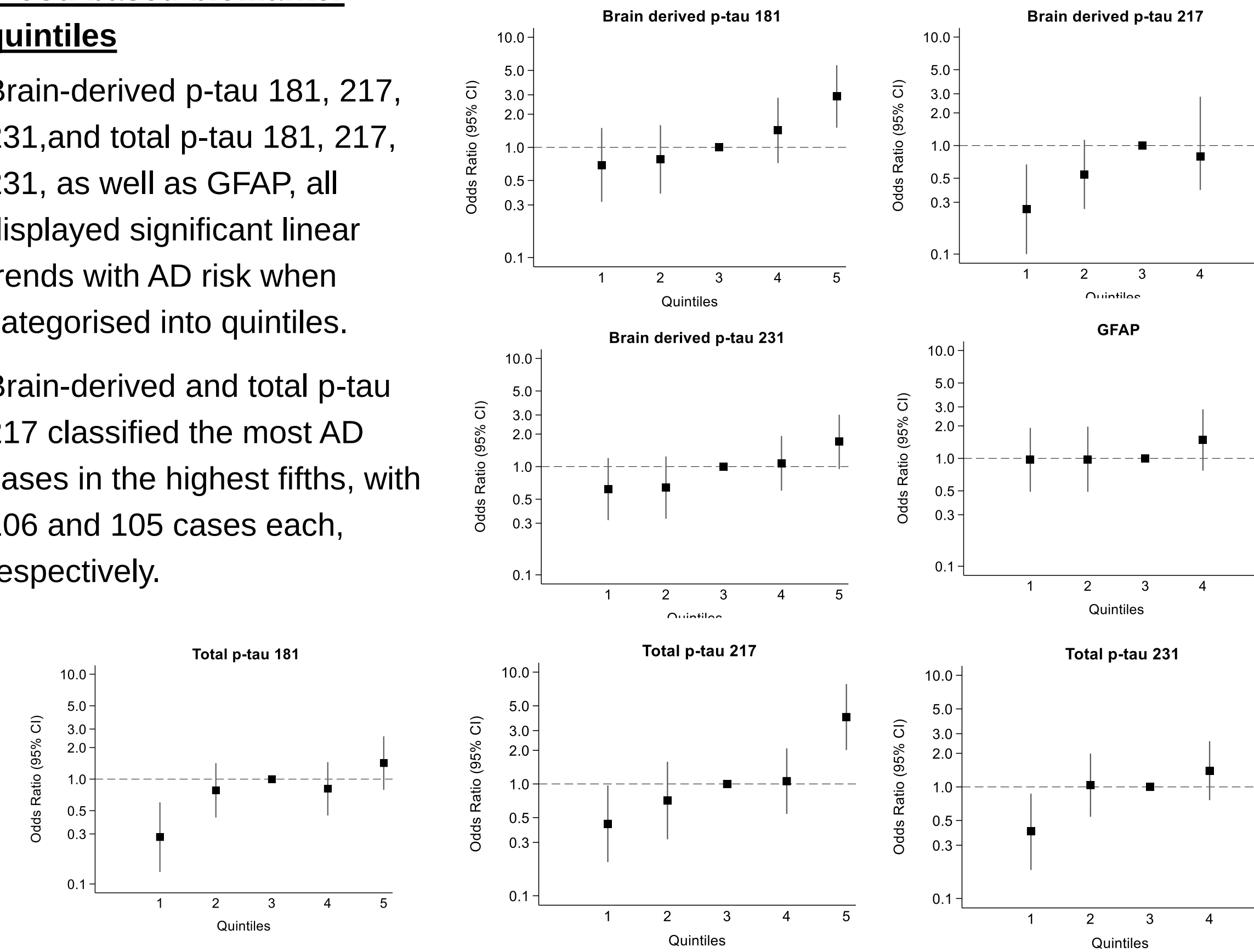
The proteins labelled in grey in the figures on the right are statistically significant at $p < 0.05$ but not after FDR correction.



Blood-based biomarker quintiles

Brain-derived p-tau 181, 217, 231, and total p-tau 181, 217, 231, as well as GFAP, all displayed significant linear trends with AD risk when categorised into quintiles.

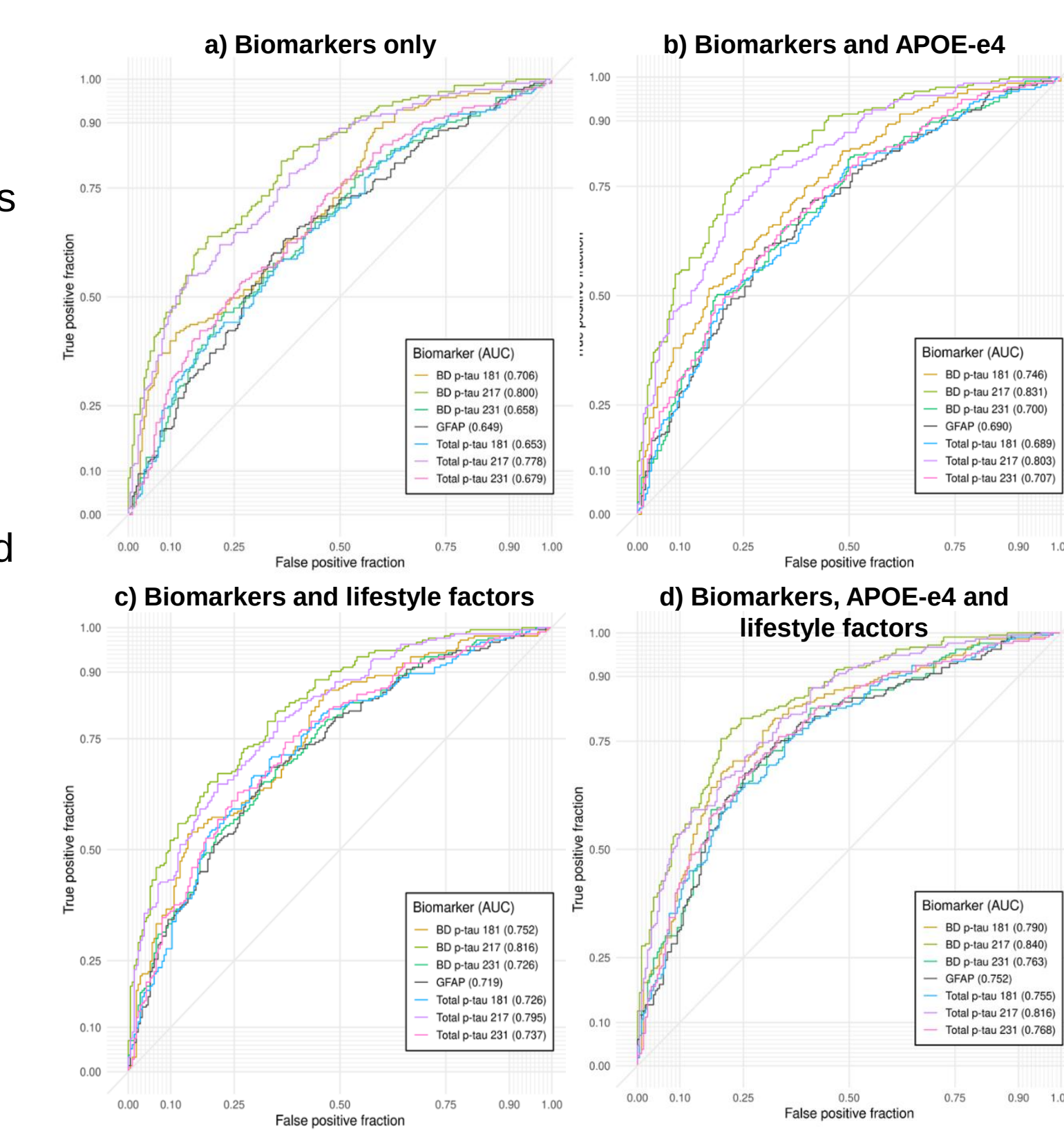
Brain-derived and total p-tau 217 classified the most AD cases in the highest fifths, with 106 and 105 cases each, respectively.



AD risk prediction

Brain-derived p-tau 217, was the strongest risk predictor for AD in models which included a) matching factors only (age and sex), b) APOE-e4, c) lifestyle factors adjusted for in Model 2, and d) both APOE-e4 and lifestyle factors.

In a LASSO regression model with 5-fold cross-validation, brain-derived p-tau 217 was highly predictive of AD with minimal change in AUC when incorporating additional biomarkers.



Conclusions

- Multiple blood-based biomarkers measured in a population-based cohort setting were associated with AD risk over a 25 year follow-up period.
- The strongest association was observed for brain-derived p-tau 217, which remained even after adjustment for sociodemographic and lifestyle factors.
- Brain-derived p-tau 217 was also the strongest risk predictor for AD, with the inclusion of additional biomarkers adding minimal predictive value to brain-derived p-tau 217 alone.
- Blood-based biomarkers could identify individuals at-risk of AD at least two decades pre-diagnosis. This has important implications for the assessment of early interventions that aim to ameliorate the pathological processes leading to AD.

Acknowledgments

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