

## Introduction

- Plasma p-tau217 is a recently established biomarker of Alzheimer's disease (AD)
- Investigating blood-based proteins associated with plasma p-tau217 could facilitate the detection of early pathogenetic processes in the preclinical stage

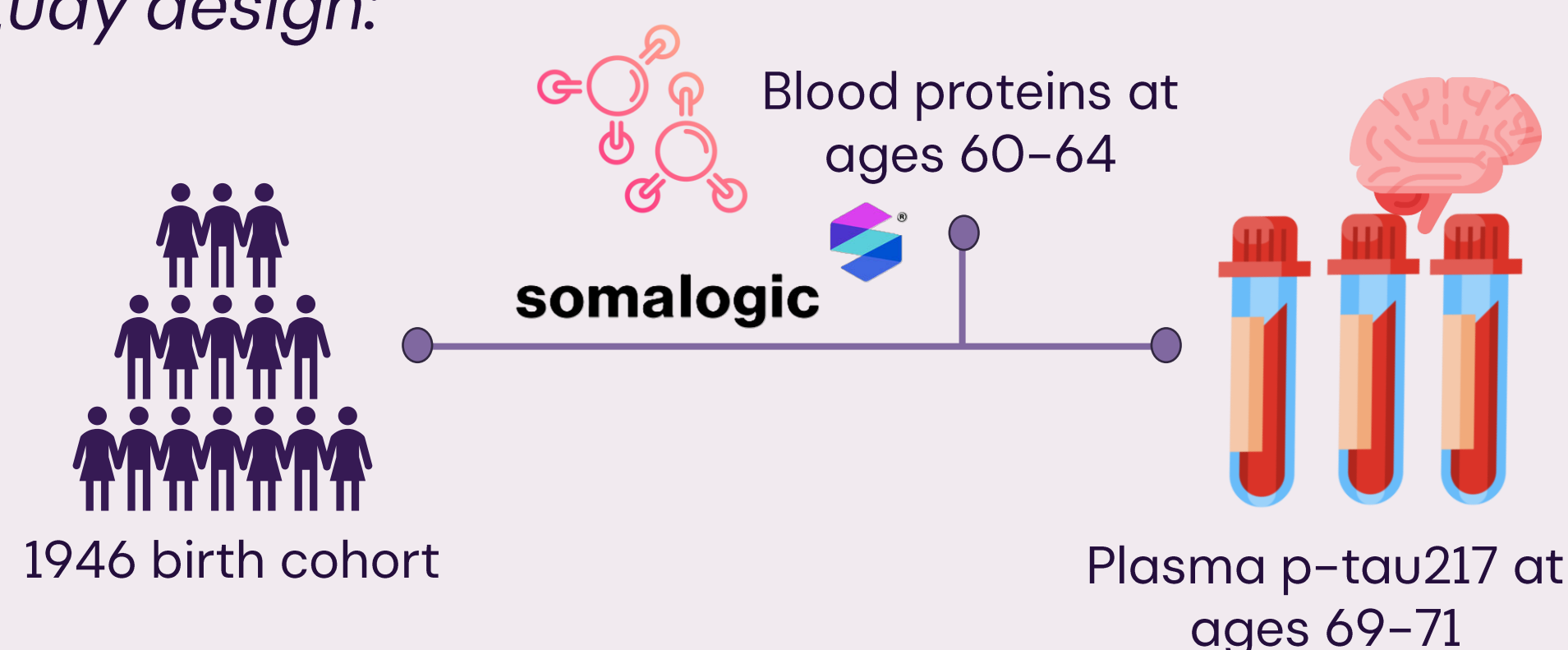


## Objectives

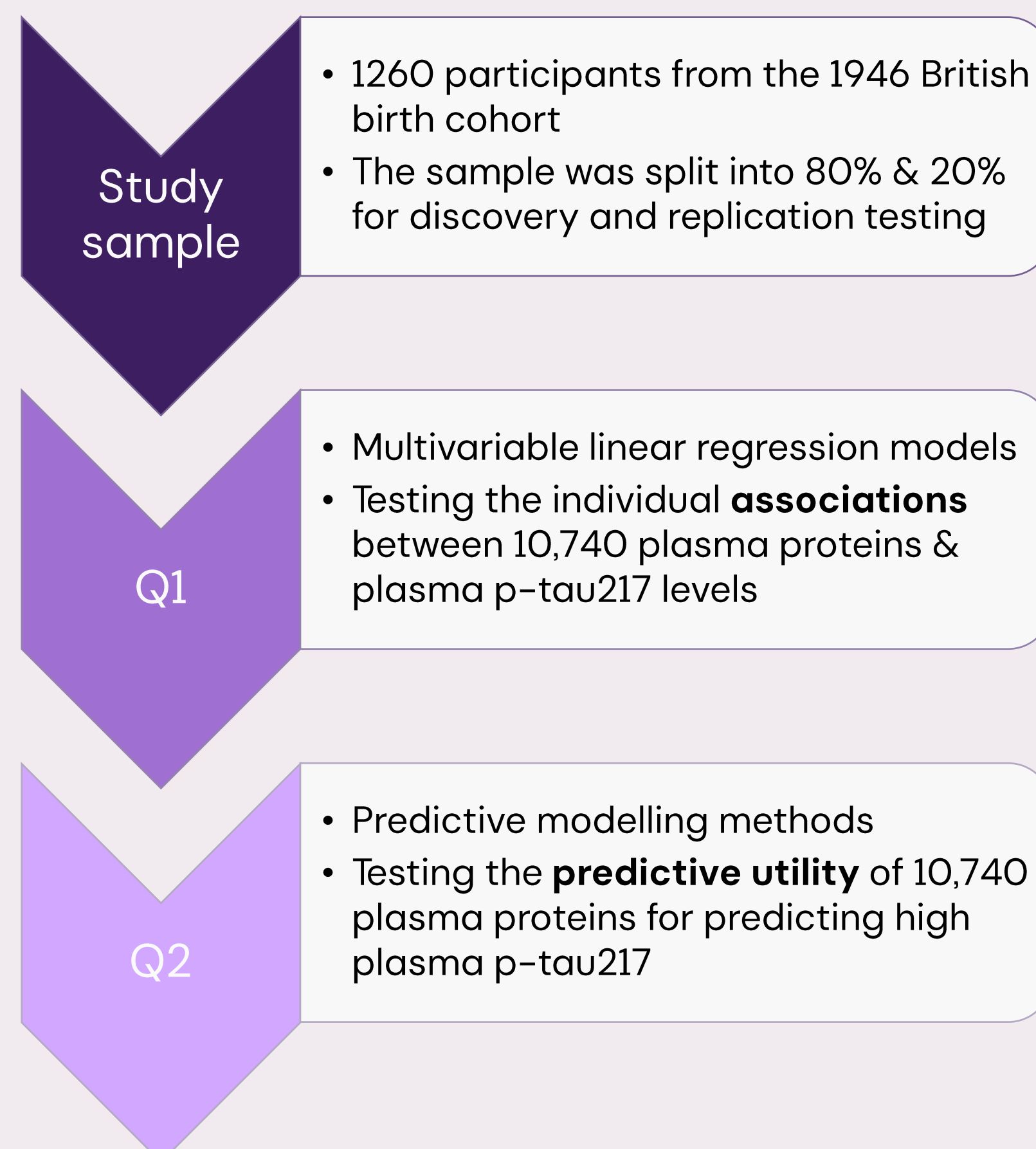
- Q1:** Are there early protein markers in the blood that are associated with plasma p-tau217 after ~5-11 years of follow-up?
- Q2:** Can early protein markers predict high plasma p-tau217 at a later timepoint?

## Methods

### Study design:



### Pipeline:



## Results

### Q1:

- 11 plasma proteins were robustly associated with plasma p-tau217 after ~5-11 years of follow-up
- Proteins: PUF60 and TWSG1 emerged as novel biomarkers of AD pathology
- PUF60 is involved in processes linked to cell death and gene expression & TWSG1 plays a role in embryonic development

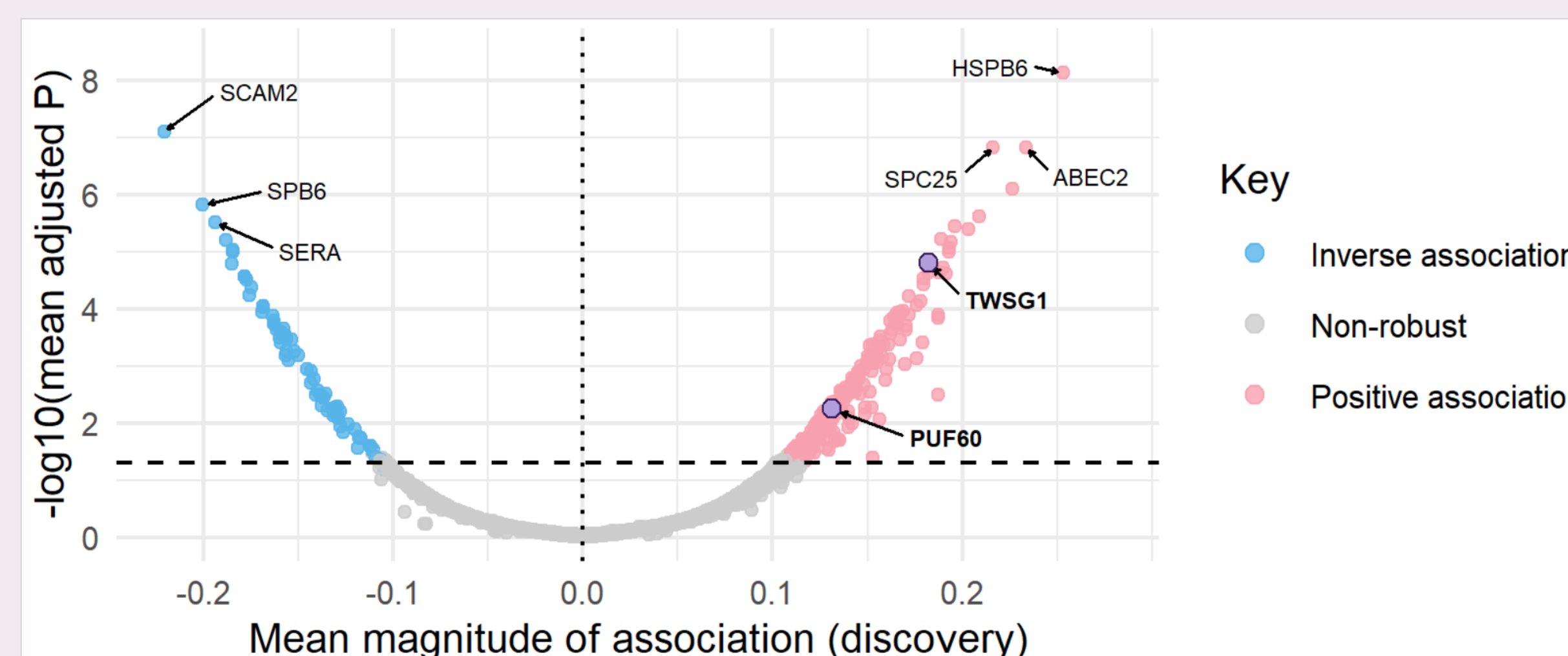


**Figure 1. Volcano plot assessing the relationship between 10,740 proteins with plasma p-tau217 in the discovery sample** Analyses were adjusted for age at blood sampling, sex, BMI, & eGFR. Bolded proteins (TWSG1 and PUF60) are plasma proteins which, to our knowledge, have not previously been observed in association with AD neuropathology

### Q2:

- There was limited utility of the plasma proteins for predicting high plasma p-tau217 in later life
- 13 proteins yielded an AUC (predictive performance) of 0.65 (95% CI 0.56-0.73) in a held-out sample
- AUC slightly improved to 0.67 (95% CI 0.60-0.75) when additionally testing for known risk factors of AD

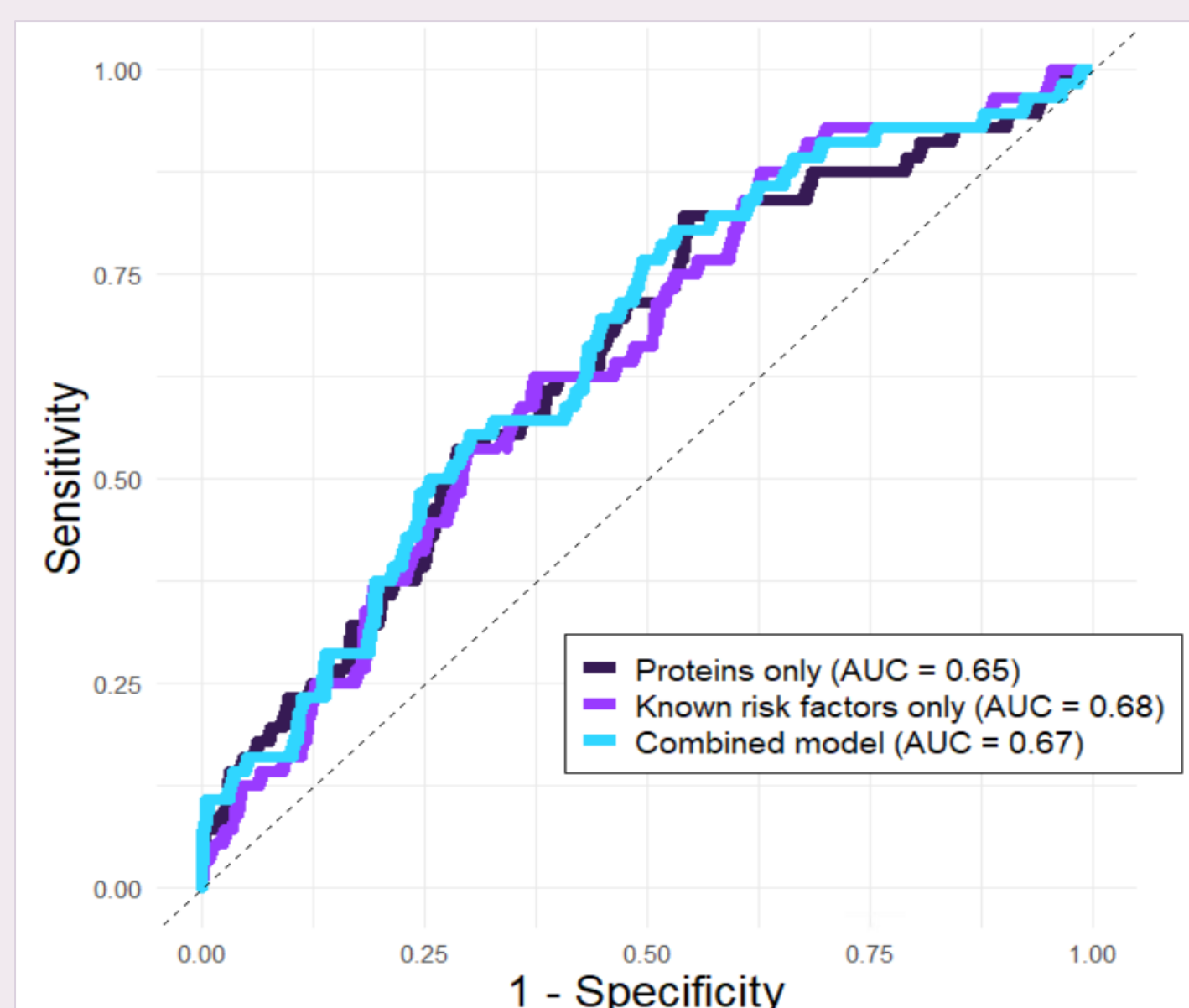


**Figure 2. Predictive performance of plasma proteins &/or known risk factors of AD for predicting high plasma p-tau217**

## Key findings & future directions

- We provide novel insights into early changes in the circulating proteome preceding AD dementia
- We replicated several proteins previously implicated in AD pathogenesis
- Additional pathway analyses showed robust proteins were significantly enriched in neurotransmitter signalling pathways
- We identified a number of novel proteins which should be explored further to provide additional insights into pathogenesis and potential targets for early disease intervention

### Contact details

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