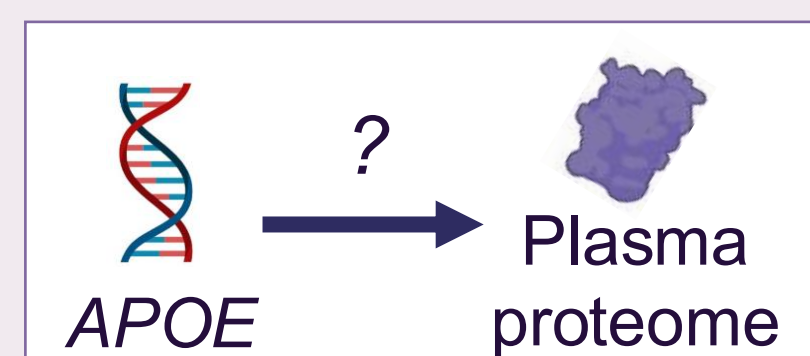


Background

- The *APOE* locus is the strongest genetic risk factor for late-onset Alzheimer's disease (AD), but its effects on the circulating proteome remain unclear
- Aim:** To compare the effects of *APOE* ϵ 4 and *APOE* ϵ 2 on the plasma proteome in middle and later life



Method

N = 42,642 (39.1–70.9 years)

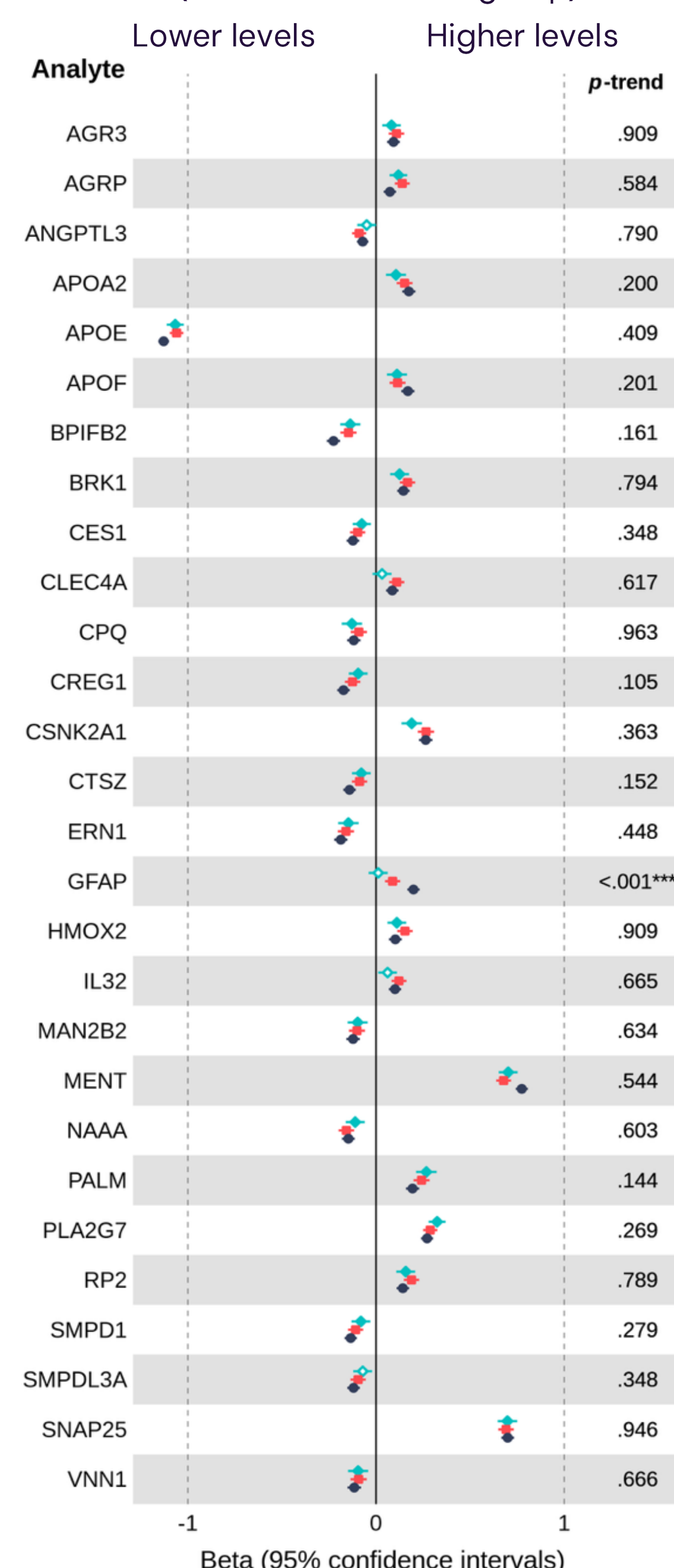


- ✓ Genetic data
- ✓ Plasma proteins assayed (n=2,923)
- ✓ Covariate data

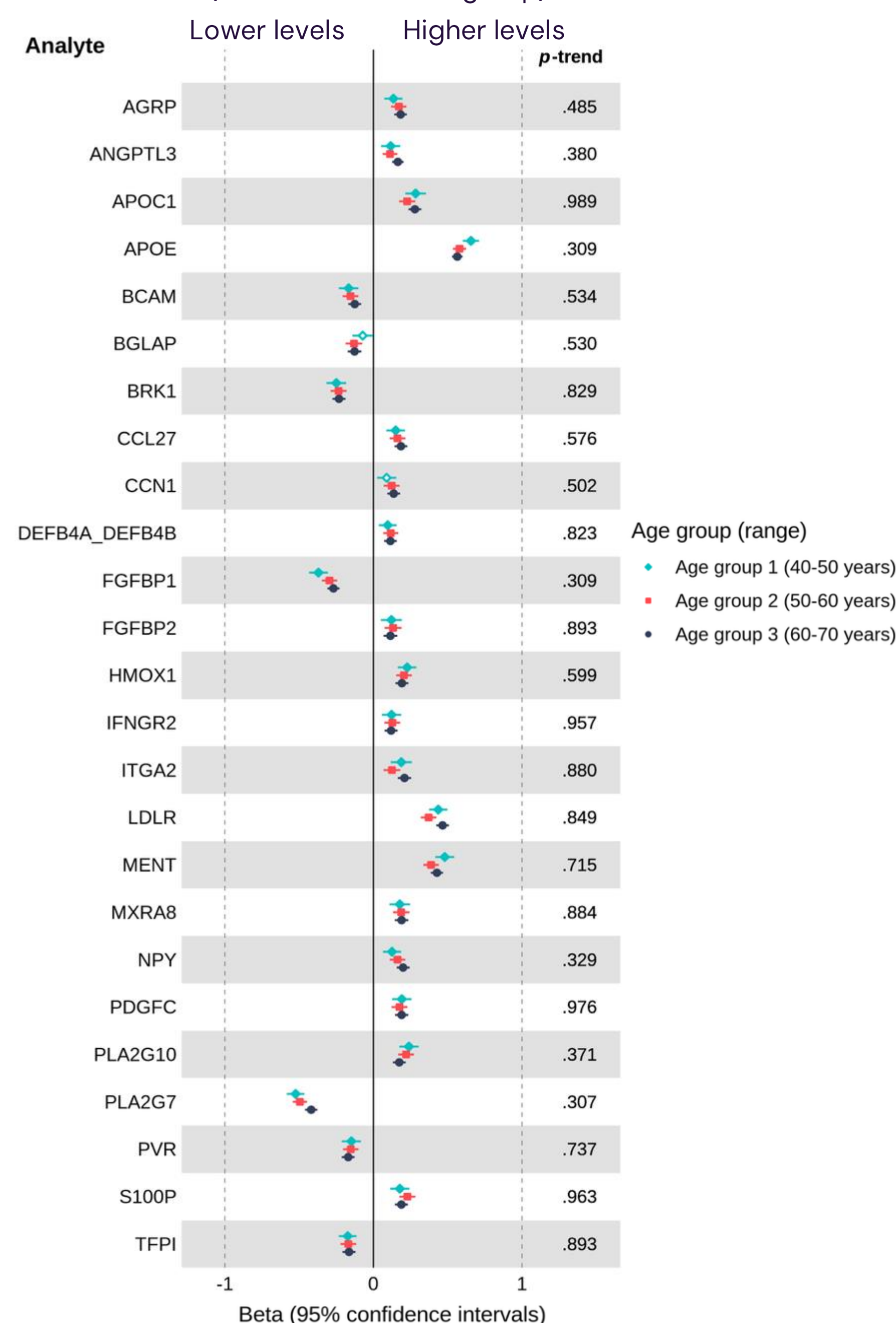


- Multivariable linear regression to compare *APOE* ϵ 4 or ϵ 2 carriers with ϵ 3 homozygotes from the UK Biobank^[1], adjusted for covariates
- Stratified by age (40–50 years; 50–60 years; 60–70 years) & ancestry (European, n = 40,092; African, n = 1,335; & South Asian, n = 971)
- Replication analyses in independent cohorts (i.e. INTERVAL, the 1946 National Birth Cohort)^[2,3], profiled using SomaLogic platforms

(A) ϵ 4-associated proteins in UKB (vs. ϵ 3/ ϵ 3 reference group)



(B) ϵ 2-associated proteins in UKB (vs. ϵ 3/ ϵ 3 reference group)



Age group (range)
 • Age group 1 (40–50 years)
 • Age group 2 (50–60 years)
 • Age group 3 (60–70 years)

Fig. 1 Proteins most robustly associated with ϵ 4 (A) and ϵ 2 (B) in Europeans ($P < .001$ in ≥ 2 age groups); ϵ 3/ ϵ 3 as reference group. Betas show adjusted mean differences in standardised protein levels (+ve = higher; -ve = lower). Filled points indicate FDR-adjusted $P < 0.05$; the right-hand side of each panel shows FDR-adjusted P values for age-related trends (*** $< .001$)

Results & Discussion

- 351 ϵ 2- & 480 ϵ 4-associated proteins identified (96 shared; European ancestry)
- Proteins identified included:
 - AD biomarkers (GFAP, NEFL^[4]) & proteins encoded by AD genetic risk loci (e.g. TREM2^[5])
 - Many linked broadly to neurodegenerative diseases, suggesting shared *APOE*-related pathways^[6,7,8]
 - Multiple, more novel UKB *APOE* signals that replicated in independent cohorts (e.g. ϵ 4- & ϵ 2-associated MENT & PLA2G7)

Conclusion

- APOE* ϵ 4 and ϵ 2 exert broad, partly age-dependent effects on the plasma proteome, detectable decades before typical AD diagnosis
- Further research should determine their role in AD pathophysiology & prediction



Acknowledgements

Full acknowledgements are provided in the manuscript (see QR code). This research was supported by funding from Alzheimer's Society (633, AS-PG-23-021) & Alzheimer's Research UK (ARUK-SRF2023B-008), and the Knight Initiative for Brain Resilience & funding from UCLH Biomedical Research Centre. UKB application number: 12113.

Contact details

Email: amy.packer.20@ucl.ac.uk
 LinkedIn: amy-packer-research

QR code

References & manuscript

