

- **APOE4** is largest genetic risk factor for Alzheimer's disease (AD)
- Overall genetic risk for an individual can be captured with **Polygenic Risk Scores (PRS)**
- **Early amyloid burden** is enhanced by **APOE4** status and is of potential interest as a **target for preventative treatment**

- Early identification of individuals at risk of Alzheimer's disease (AD) is critical for prevention trials and biologically informed risk enrichment

- **Aim: Test whether biomarker- and neuropathology-informed PRS improve genetic stratification of amyloid pathology and cognition beyond a conventional AD-susceptibility PRS.**

BACKGROUND AND AIMS

PRS PIPELINE

867 subjects from AMYPAD¹ were included (Table 1).

Raw genetic data (GRCh37) underwent pre-imputation QC using **PLINK**. Imputation was performed using the **TOPMed server, Eagle Phasing, and TOPMed r3 reference panel**.

Post-imputation QC was performed, and cohorts were merged using **PLINK and merge-mode 2**.

PRSice was used to compute PRS of AD susceptibility, CSF-Aβ42 and ptau181 levels, Braak and CERAD neuropathology, and systemic domains (cerebrovascular health, metabolism, inflammation, biological ageing, and frailty) and European individuals (minus the Fins) from 1000 Genomes (1KG) as the reference for clumping.

Genome-wide PRS with and without the APOE region (19:44.4-45.5Mb), were computed at p -value threshold for SNP inclusion of 1×10^{-5} (AD-susceptibility, CSF-Aβ42 and ptau181, Braak, CERAD, inflammation, brain age, social frailty) or recommended SNP list (cerebrovascular health and metabolism).

Scores were corrected for **five genetic principal components** and **standardised** against EUR 1KG minus the Fins.

¹⁸F-Florbetaben (N=388) or ¹⁸F-Flutemetamol (N=570) PET were acquired and quantified using the **Centiloid** pipeline to obtain **global amyloid burden**⁴.

Table 1. Cohort characteristics. Continuous measures are shown as mean (SD), *Based on predefined cut-off of CL > 21

	Low (CL<12) (N=516)	Grey-zone (10<CL<30) (N=189)	High (CL>30) (N=162)	Overall (N=867)
Sex (female, N, %)	319 (61.8%)	105 (55.6%)	89 (54.9%)	513 (59.2%)
Age (years, median, range)	64 (49-89)	66 (50-93)	72 (54-88)	66 (49-93)
APOE-ε4 carriers (N, %)	169 (32.8%)	91 (48.1%)	108 (66.7%)	368 (42.4%)
Years of education (years, median, range)	15 (5-28)	15 (6-32)	15 (6-25)	15 (5-32)
Global CDR 0 (N, %)	460 (89.1%)	167 (88.4%)	111 (68.5%)	738 (85.1%)
MMSE (median, range)	29 (24-30)	30 (20-30)	29 (16-30)	29 (16-30)

Statistics: Linear regressions tested associations between each PRS and global amyloid PET burden or MMSE, adjusting for age, sex, and education, with Bonferroni correction. For PRS significantly associated with MMSE, mediation analyses assessed whether amyloid mediated these associations (N=793 with complete data). Unsupervised hierarchical clustering was applied to PRS from the full cohort to identify genetically distinct subgroups using Ward's minimum variance method (k=3).

RESULTS

1. **PRS-CSF-Aβ42 showed the strongest association with amyloid burden ($R^2=0.15$, $\text{padj}=8.46 \times 10^{-17}$), outperforming conventional PRS-AD-susceptibility ($R^2=0.14$, $\text{padj}=1.94 \times 10^{-15}$, Fig.1A). PRS-CERAD was the strongest predictor of MMSE ($R^2=0.05$, $\text{padj}=2.65 \times 10^{-4}$), outperforming PRS-AD-susceptibility ($R^2=0.04$, $\text{padj}=0.03$, Fig.1B).**

2. **Mediation analyses demonstrated that amyloid burden partially - up to 32% - mediated the relationship between PRS-CSF-Aβ42, PRS-CERAD, PRS-Braak, and PRS-CSFptau and MMSE (average causal mediation effect (ACME) $p<0.008$; average direct effect (ADE) $p<0.018$), whereas PRS-AD-Susceptibility demonstrated a full mediation effect of 43% (ACME $p=0.002$, ADE $p=0.156$).**

Conclusion

1. Biomarker-informed PRS capture mechanistic susceptibility to amyloid pathology and explain early cognitive differences in preclinical AD.
2. Integrating PRS with imaging and cognition supports scalable genetic pre-screening for precision prevention and trial recruitment.

Future work

1. We will compute cell-type and pathway PRS and investigate their relationship with longitudinal/regional amyloid burden and cognitive decline.

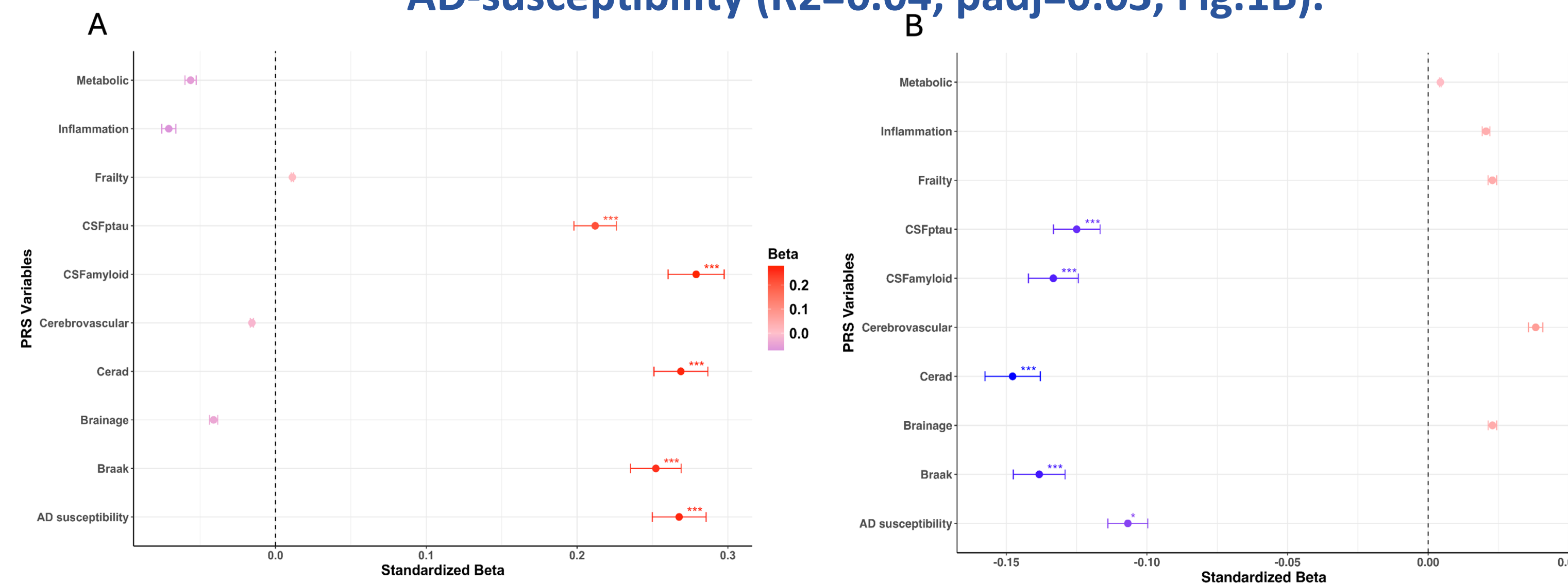


Figure 1: Association between PRS and global amyloid burden. The forest plots illustrate the standardised betas and confidence intervals, with corresponding Bonferroni-corrected P values. **A** With amyloid burden as outcome, **B** with MMSE as outcome.

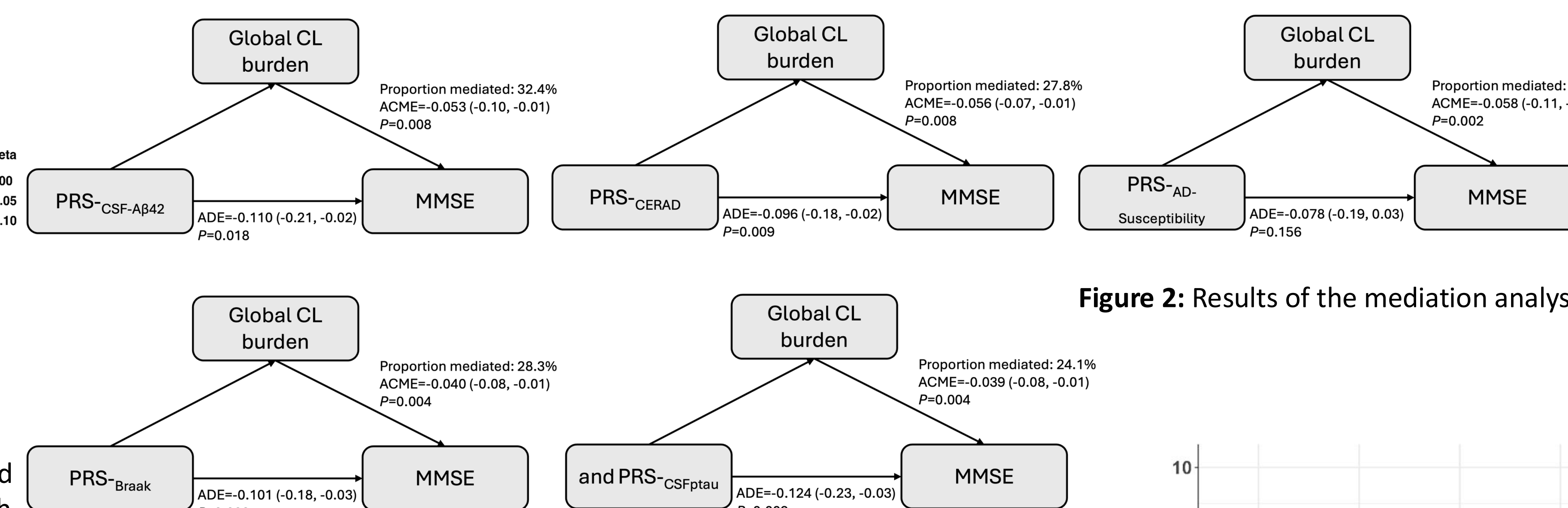


Figure 2: Results of the mediation analyses.

3. **Clustering analyses identified three distinct genetic subgroups: an “amyloid-tau-AD” cluster with high AD-specific PRS, high amyloid load, and elevated APOE-ε4 frequency; a “non-AD ageing” cluster with high PRS-Braak and low AD-specific PRS; a “low genetic risk” cluster with uniformly low PRS across domains.**

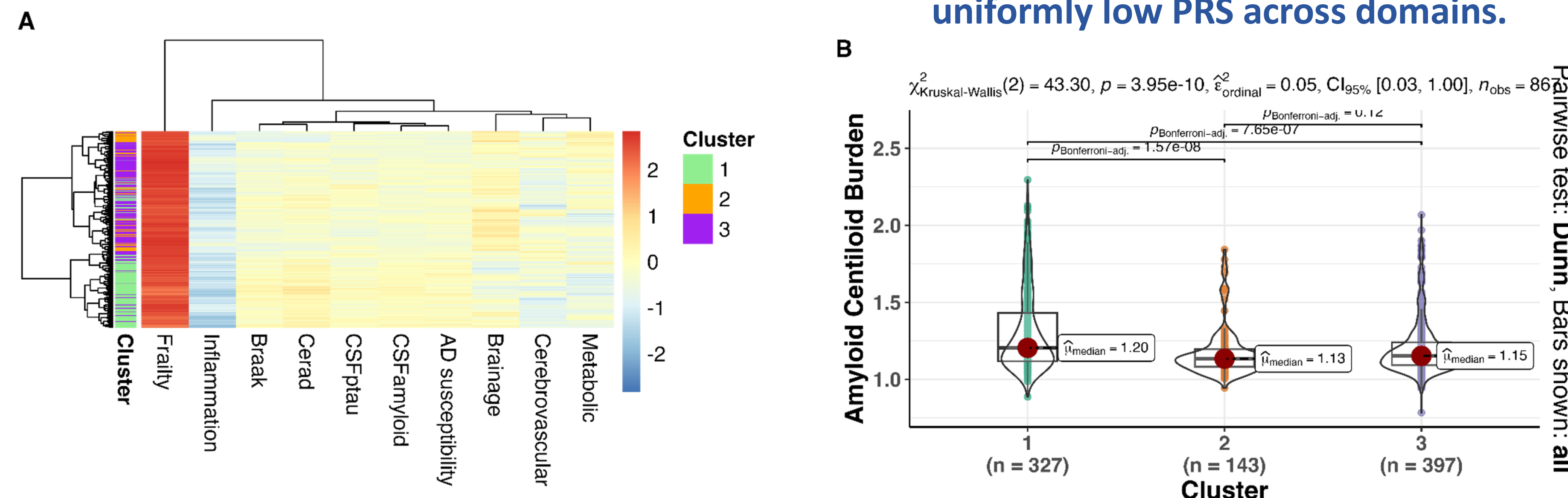


Figure 3: Hierarchical clustering of individuals based on polygenic risk profiles and corresponding differences in global amyloid burden and MMSE between derived clusters.

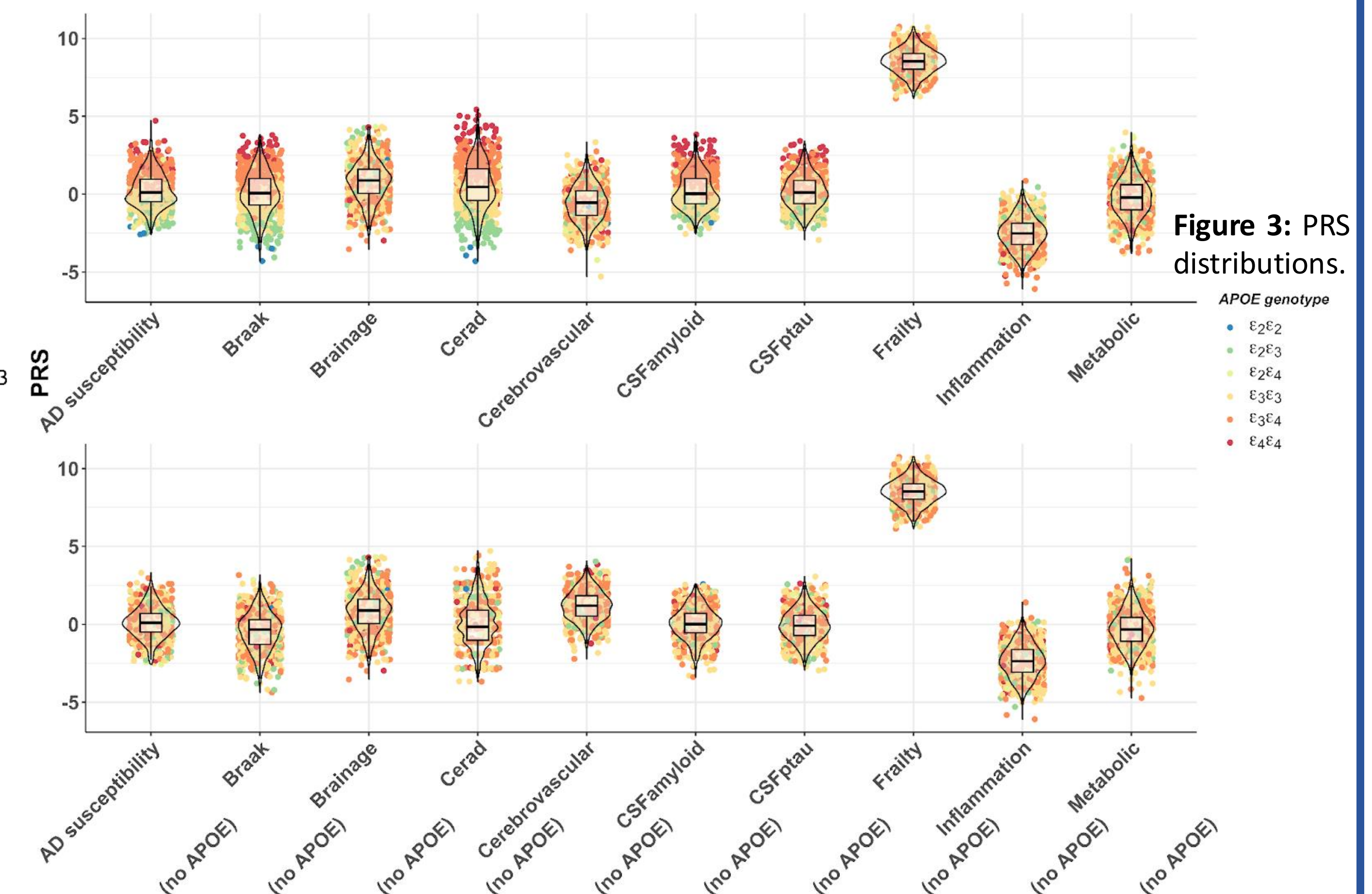


Figure 3: PRS distributions.