

### Introduction:

- Plasma vascular cell adhesion molecule-1 (VCAM-1) and glial fibrillary acidic protein (GFAP) are blood-based markers of endothelial activation and astrocytic injury, respectively, and are increasingly linked to cognitive performance in aging.
- Both reflect interrelated aspects of blood–brain barrier and neurovascular unit integrity associated with preclinical cognitive performance.
- However, VCAM-1 and GFAP are typically examined independently, and it remains unclear whether endothelial activation modifies the association between astrocytic injury and cognitive performance, particularly among Black adults, who experience a high burden of vascular and neurovascular risk.
- We therefore examined whether endothelial activation modifies the association between astrocytic injury and cognitive performance in Black adults.

### Methods:

- We analyzed cross-sectional baseline data from 334 Black adults aged ≥45 years enrolled in the Aging Research Characterizing Health Exposome via Social Drivers (ARCHES) study. Cognitive performance was assessed using the Preclinical Alzheimer Cognitive Composite (PACC).
- Plasma VCAM-1, GFAP, and platelet-derived growth factor receptor beta (PDGFRβ) were quantified using IP-MS and NULISA™ assays. Generalized linear models evaluated associations of VCAM-1 and GFAP and their interaction with cognitive performance, adjusted for age, sex, and education.
- Sensitivity analyses included models incorporating APOE ε4 genotype, Area Deprivation Index (ADI), PDGFRβ.

### Results:

- Among participants (mean age 66·9 years [SD 10·1]; 76·3% women), the VCAM-1×GFAP interaction was significantly associated with PACC scores ( $\beta = -1\cdot36\times10^{-6}$ ;  $p=0\cdot013$ ; FDR  $p=0\cdot030$ ), while neither VCAM-1 ( $p=0\cdot093$ ) nor GFAP ( $p=0\cdot317$ ) showed significant independent associations.
- In sensitivity analyses, the VCAM-1×GFAP interaction remained statistically significant after adjustment for APOE ε4 genotype ( $\beta = -1\cdot35\times10^{-6}$ ;  $p=0\cdot025$ , FDR  $p=0\cdot079$ ) and ADI ( $\beta = -1\cdot39\times10^{-6}$ ;  $p=0\cdot013$ , FDR  $p=0\cdot048$ ). In neurovascular–pericytic models, VCAM-1 showed a significant main association with PACC ( $\beta = -8\cdot1\times10^{-4}$ ;  $p<0\cdot01$ , FDR  $p<0\cdot01$ ), while the VCAM-1×PDGFRβ interaction was not significant ( $p=0\cdot519$ ).

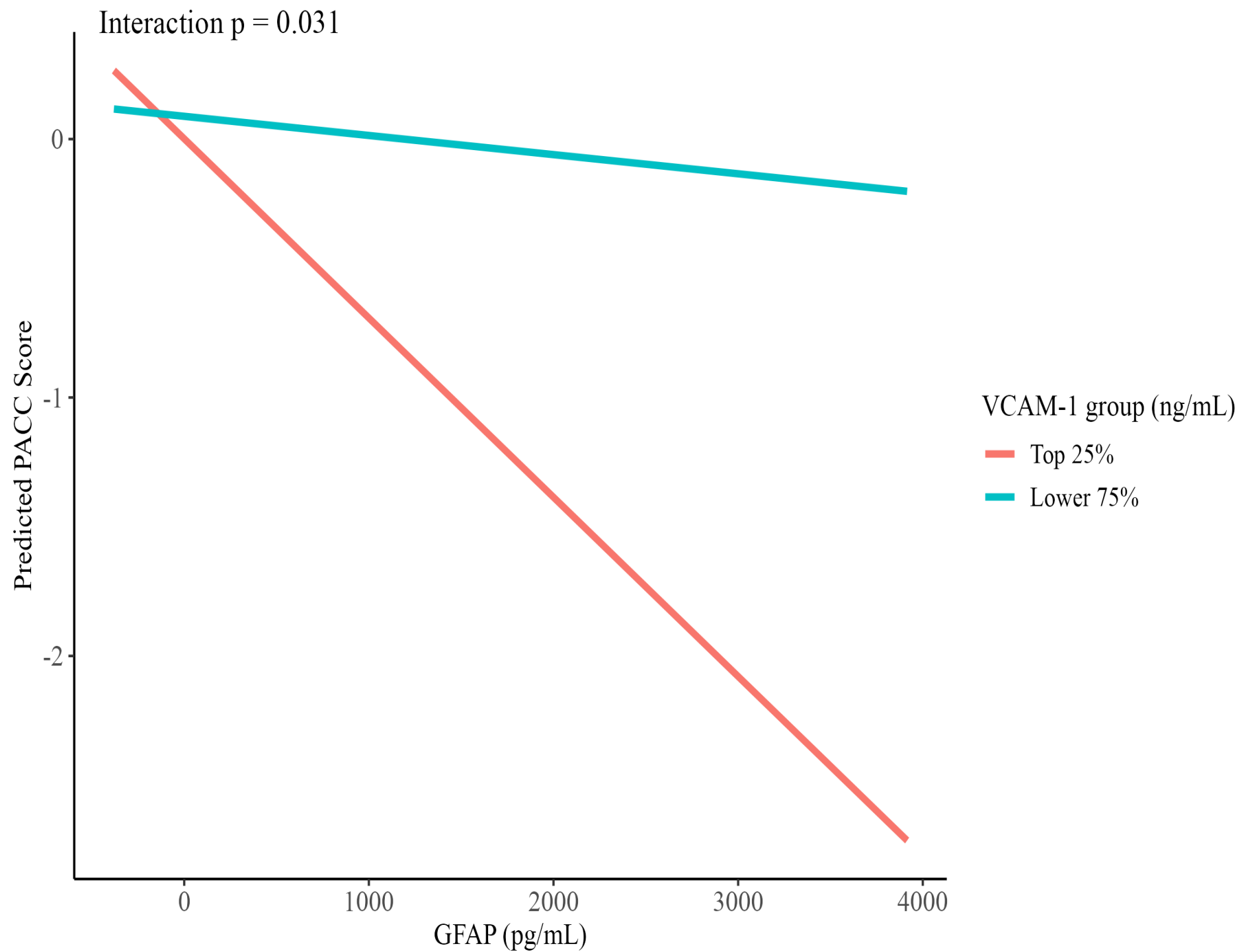
Table1. Neurovascular Inflammation and Astrocytic Injury in Relation to Cognitive Performance

| Predictor            | $\beta$ Estimate        | Std. Error             | t value | p value    | FDR-adjusted p |
|----------------------|-------------------------|------------------------|---------|------------|----------------|
| Intercept            | 0.572                   | 0.330                  | 1.732   | 0.084      | 0.109          |
| VCAM-1               | $-4.200 \times 10^{-4}$ | $2.500 \times 10^{-4}$ | −1.680  | 0.093      | 0.109          |
| GFAP                 | $-1.200 \times 10^{-4}$ | $1.100 \times 10^{-4}$ | −1.002  | 0.317      | 0.317          |
| Age (years)          | −0.015                  | 0.004                  | −3.703  | < 0.001*** | < 0.01**       |
| Sex (Male vs Female) | −0.222                  | 0.092                  | −2.395  | 0.017*     | 0.030*         |
| Education (years)    | 0.034                   | 0.014                  | 2.406   | 0.016*     | 0.030*         |
| VCAM-1 × GFAP        | $-1.360 \times 10^{-6}$ | $5.400 \times 10^{-7}$ | −2.492  | 0.013*     | 0.030*         |

**Notes:** Notes: Model N = 311; model R<sup>2</sup> = 0.144; AIC = 635.91. Age and education were modeled in years; sex was coded as male vs female.  $\beta$  (SE) denotes the estimated regression coefficient and its standard error. FDR–adjusted p values were calculated using the Benjamini–Hochberg procedure. The VCAM-1 × GFAP interaction term reflects whether endothelial inflammation modifies the cross-sectional association between astrocytic injury and cognitive performance. Abbreviations: AIC, Akaike Information Criterion; FDR, false discovery rate; GFAP, glial fibrillary acidic protein; PACC, Preclinical Alzheimer Cognitive Composite; SE, standard error; VCAM-1, vascular cell adhesion molecule-1. \*\*\* $p < 0.001$ ; \*\* $p < 0.01$ ; \* $p < 0.05$ .

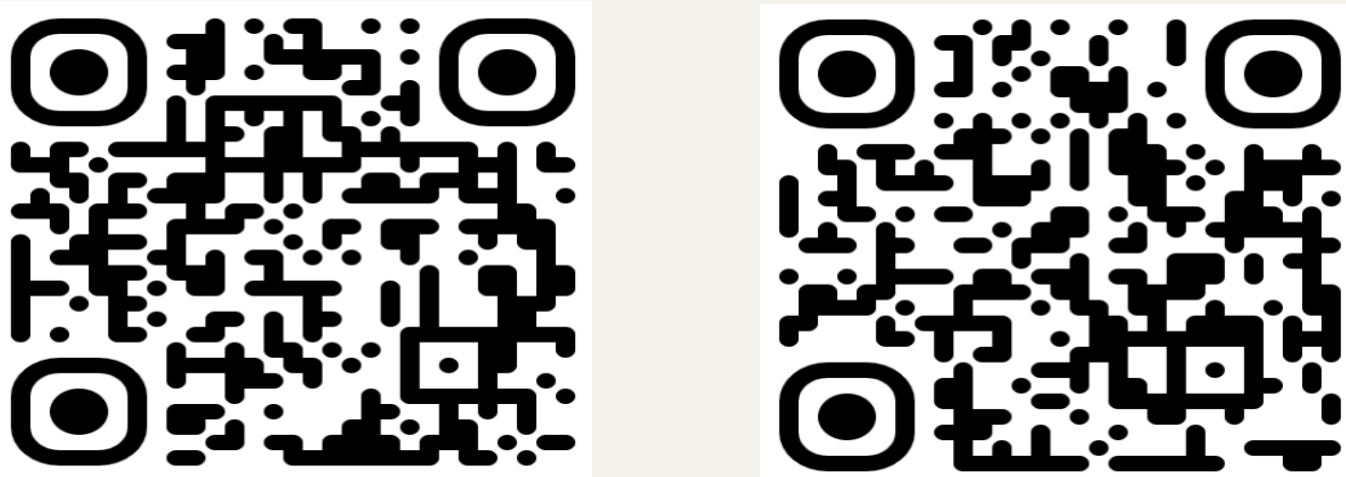
Figure 1. Interaction between Plasma VCAM-1 and GFAP in Relation to Cognitive Performance.

Interaction Between VCAM-1 and GFAP in Relation to Cognitive Performance



- VCAM-1, vascular cell adhesion molecule-1; GFAP, glial fibrillary acidic protein; PACC, Preclinical Alzheimer Cognitive Composite.
- VCAM-1 was categorized into higher (top 25%) and lower (remaining 75%) concentration groups based on its distribution; GFAP: modeled as a continuous variable; Cognitive outcome: PACC; Covariates adjusted for: age, sex, and education; Biomarkers mean-centered prior to analysis.
- Two-way interaction significant at  $p < 0.05$ .

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### Conclusions:

- VCAM-1 modifies the association between GFAP and cognitive performance in Black adults, suggesting heterogeneity in neurovascular and astrocytic biomarker–cognition relationships. These findings suggest that astrocytic biomarkers such as GFAP may be most informative when interpreted in the context of vascular endothelial status, highlighting the potential value of incorporating neurovascular markers when characterizing cognitive performance and prioritizing individuals for vascular-focused monitoring and follow-up.

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