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Plasma Immune Markers Associated with Hippocampal Volume: The Northern Manhattan Study

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KEY TAKE AWAY: Large-scale immune profiling in a multiethnic, community-based cohort identified potential blood-based immune markers of total hippocampal volume.

BACKGROUND

- Hippocampal atrophy = early biomarker of AD
- Blood immune markers may inform structural brain health.
- Large-scale studies remain limited.

Objective: Identify plasma immune markers associated with age-related hippocampal volume (HV) on MRI by large-scale immune profiling in a multiethnic, urban-dwelling Northern Manhattan Study (NOMAS).

METHODS

Population: MRI NOMAS subcohort; stroke-free, dementia-free; age ≥ 50

Outcomes (T2-MRI):

1. **HV:** Total hippocampal volumes (L and R) / total cranial volume (TCV)
2. **Age-standardized HV**

Exposure:

60 plasma immune markers (Luminex)

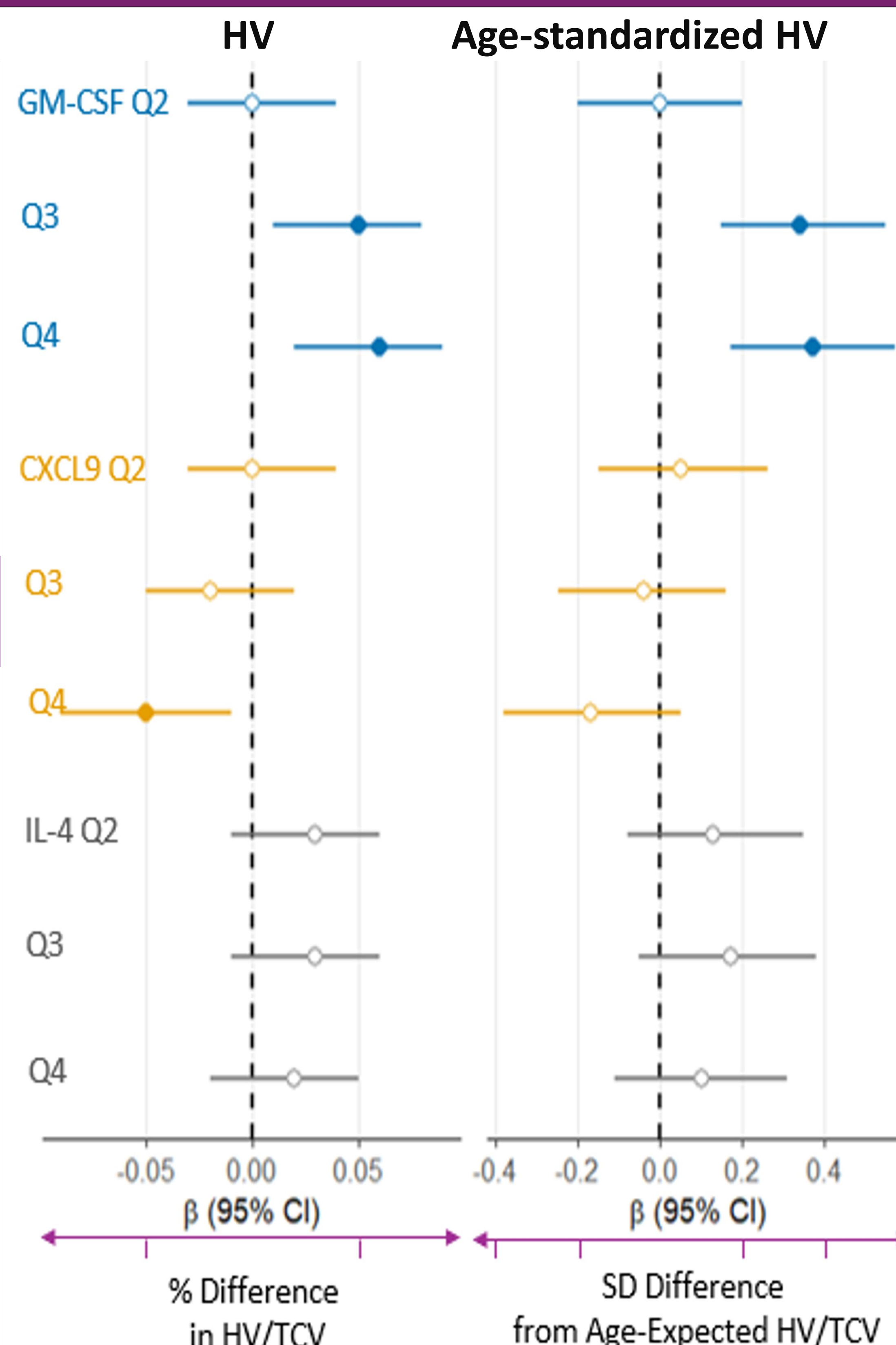
Analysis: Selected candidate markers by data reduction regression (LASSO) were modeled in quartiles using multivariable linear regression.

Final model adjustment:

Global vascular risk score (GVRs) incorporating demographic, clinical, and lifestyle factors, with addition of APOE $\epsilon 4$ status.

RESULTS

Adjusted associations of selected immune markers (quartiles) with HV



N=815 | Age 70 $\pm$ 9 | 60% female | 68% HTN | 67% Hispanic | 19% depression
Mean HV 7.29 $\pm$ 0.9 mL | Mean HV/TCV: 0.6% $\pm$ 0.08%

Abbreviations: GM-CSF = granulocyte-macrophage colony-stimulating factor (colony-stimulating factor 2; CSF2); CXCL9 = C-X-C motif chemokine ligand 9 (monokine induced by interferon- γ ; MIG); IL-4 = interleukin-4

Data reduction selected:

- GM-CSF
- CXCL9
- IL-4

In fully-adjusted analysis:

- **GM-CSF**
 - Each quartile $\uparrow$ ~ 0.14 SD larger age-standardized HV (95% CI 0.08–0.20)
 - $\uparrow$ GM-CSF quartiles (Q3 & Q4 vs. Q1) $\sim$ greater HV $\sim \uparrow$ HV than expected for age
- **CXCL9**
 - Each quartile $\uparrow$ in CXCL9 ~ 0.02 SD smaller HV (95% CI –0.03, –0.01)
 - Q4 (vs. Q1): $\sim 3.5\%$ lower HV ($\beta = -0.06$; 95%CI –0.09, –0.02)
- **IL-4**
 - no significant association

CONCLUSIONS

GM-CSF:

Dose-dependent association with larger hippocampal volume relative to age-expected values $\rightarrow$ possible neuroprotective effect.

CXCL9:

$\uparrow$ levels showed association with smaller HV (more atrophy).

GM-CSF and CXCL9 levels suggest:

- Active gray matter biological processes relevant for cognitive function and may inform future mechanistic studies and therapeutic targets.

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