Inflammatory Biomarkers Associated with Cognitive Function and Dementia:
Framingham Heart Study Offspring Cohort

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INTRO

- Systemic inflammation plays a critical role in cognitive decline and Alzheimer's disease (AD) development[1]
- We investigated associations of inflammatory biomarkers with cognitive aging phenotypes in a community-based cohort

METHODS

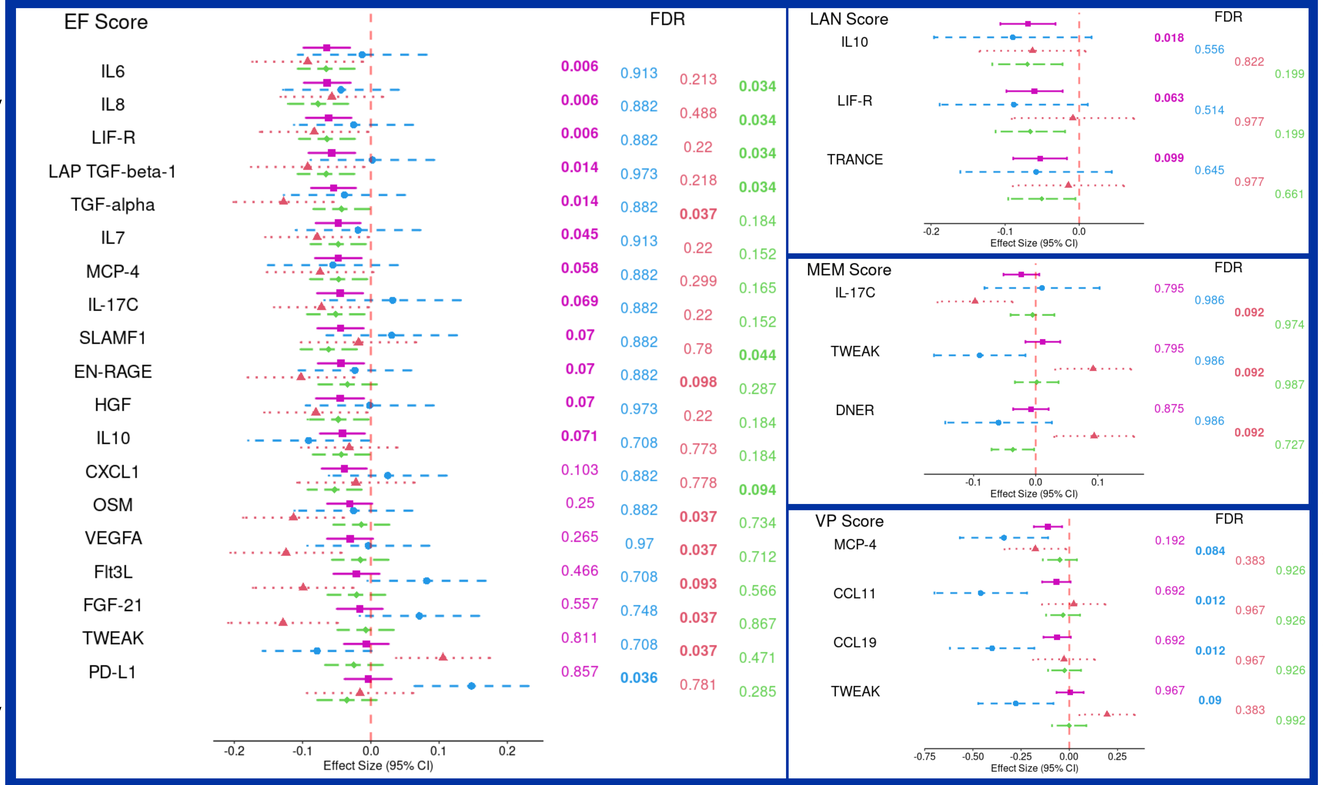
- Study sample: 879 Framingham Heart Study (FHS) Offspring participants who were dementia-free at Exam 7 (1998-2001)
  - Exclusion: 2 due to quality control, 8 without APOE genotype, 161 without neuropsychological tests within 5 years after Exam 7
  - Leaving a sample size of 708 for the cognitive score sample
- Assay: 68 protein biomarkers measured by OLINK Inflammation panel on stored plasma samples
- Outcomes of interest:
  - Cognitive scores[2] in four domains: memory (MEM), executive function (EF), language (LAN), and visual perceptual (VP) measured within 5 years after the plasma sample
  - Diagnoses of incident dementia, AD, or mild cognitive impairment (MCI) in up to 20 years of follow-up
- Statistical analyses:
  - Pairwise cross-sectional association analyses:
    - Between cognitive scores and individual protein levels using linear mixed-effects (LME) models
    - Between incident dementia-related outcomes and individual protein levels using Cox proportional hazards models
  - Covariates: sex, age, education level, the time difference between Exam 7 and cognitive testing date, a retest indicator, and APOE genotype
    - Full sample analysis adjusting for APOE genotype
    - Stratified analyses within three APOE genotype subgroups
  - False discovery rate (FDR)≤0.1 to declare significant associations

Table 1 Participant characteristics at Exam 7 at time of inflammatory biomarker measurement

Demographics	Cognitive score sample (n=708)
Female (%)	53%
Attended college (%)	79%
APOE ε2 carriers (%)	15%
APOE ε4 carriers (%)	22%
Age, mean (range)	61 (40,88)
MMSE, median (IQR)	29 (2)

Higher levels of 12 inflammatory proteins are significantly associated with **lower Executive Function** (EF) scores; 2 of these are also associated with **lower Language** (LAN) domain scores

TWEAK appears to have opposite effects in APOE-ε2 and ε4 carriers in **Executive Function**, **Memory** (MEM), and **Visual Perceptual** (VP) domains



RESULTS

- In the full sample
  - Higher levels of 12 and 3 proteins were associated with lower EF and LAN domain scores, respectively
  - IL10 and LIF-R were associated with scores in both domains
  - Higher levels of TNFB were associated with increased MCI, dementia, and AD hazards
- In ε2 carriers
  - Higher PD-L1 was associated with higher EF domain scores
  - Higher levels of CCL11, CCL19, MCP-4, and TWEAK were associated with lower VP domain scores
- In ε4 carriers
  - Higher levels of 6 proteins were associated with lower EF scores, and 1 was associated with higher scores; higher levels of 2 proteins were associated with higher MEM domain scores
    - Higher TWEAK levels were associated with both higher EF and MEM domain scores
    - Higher IL-17C levels were associated with lower MEM domain scores

DISCUSSION

- Many of the plasma proteins associated with decreased cognitive function have previously been associated with AD compared to controls in cerebrospinal fluid[3]
- TWEAK is a proinflammatory cytokine expressed in neurons, endothelial cells, microglia, and astrocytes that may cause inflammation, disrupt the blood-brain barrier, and increase neuronal cell damage leading to the cognitive phenotypes we are studying
- TWEAK shows significance in multiple domains, including the EF, MEM, and VP domains
- ε4 is associated with an additional 6 biomarkers (TGF alpha, EN-RAGE, OSM, VEGFA, Flt3L, FGF21) in the EF domain, all in a negative direction
- Limitations:
  - Causality cannot be inferred from cross-sectional analyses
  - Replication in larger and ethnically diverse samples is needed
- Study Strengths:
  - Community-based FHS Offspring with stored plasma samples, cognitive testing, and follow-up for MCI and dementias
  - OLINK targeted inflammation protein panel was measured with high quality
  - Ability to identify differential associations by APOE genotype strata

REFERENCES

1. Heneka el, et al. (2015). DOI: 10.1016/S1474-4422(15)70016-5
2. Scollard et al. (2022). DOI: 10.1037/neu0000835
3. Boström et al. (2021). DOI: 10.3233/JAD-201565

ACKNOWLEDGMENTS

The FHS participants and their study team.
R01 AG067457

Boston University School of Public Health
Department of Biostatistics

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