

APOE ε4 and inflammatory biomarkers in former American football players



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BACKGROUND

- Chronic traumatic encephalopathy (CTE) is a neurodegenerative disease associated with repetitive head impact (RHI) exposure.
- Apolipoprotein E (APOE) ε4 has been linked to more severe CTE pathology among autopsy-confirmed cases, particularly among older donors.
- The mechanisms by which APOE confers risk for neurodegeneration include neuroinflammation and tau deposition but its relationship with inflammatory processes in the context of RHI exposure remains unclear.

OBJECTIVE

This study examined whether *APOE* ε4 is associated with inflammatory and neurodegenerative biomarkers in former elite American football players using data from the DIAGNOSE CTE Research project

METHODS

- DIAGNOSE CTE Research Project was designed to develop biomarkers, characterize the clinical presentation, and examine genetic and RHI risk factors for CTE.

n=115
former
professional

174 male
former
American
football
players

n=59
former
college

Sample Characteristics

	N	Total (n=174)	APOE E4 Negative (n=121)	APOE E4 Positive (n=53)	p-value ²
Demographics					
Age (years) ¹	174	57.06 (8.04)	57.34 (8.39)	56.42 (7.21)	0.629
Self-Reported Race					
Black n(%)	174	60 (34%)	35 (29%)	25 (47%)	0.020
Education (years) n(%)	174	16.72 (1.45)	16.90 (1.60)	16.30 (0.93)	0.007
Medical History					
BMI ¹	174	32.52 (4.53)	32.42 (4.72)	32.74 (4.09)	0.545
rFRSP ¹	165	0.03 (0.03)	0.03 (0.03)	0.03 (0.04)	0.824
Total AUDIT Score	174	5.06 (5.76)	5.54 (6.13)	3.96 (4.69)	0.038
Football Exposure					
Highest Level of Play	174				0.480
NFL		115 (66%)	82 (68%)	33 (62%)	
College		59 (34%)	39 (32%)	20 (38%)	
Total Years of Play ¹	174	15.79 (4.27)	15.80 (4.41)	15.77 (3.98)	0.793

Table 1. Sample Characteristics

¹Mean (SD)
²Wilcoxon rank sum test; Pearson's Chi-squared test
BMI: Body mass index
rFRSP: revised Framingham stroke risk profile
APOE: Apolipoprotein E

Sample Acquisition

- Participants completed fasting blood-draws and lumbar punctures.
- V-PLEX Proinflammatory Panel I from Meso Scale Diagnostics assays were conducted for plasma and cerebrospinal fluid (CSF) inflammatory biomarkers GFAP, IL-1β, IL-6, IL-17A, TNFα, INFG, eotaxin-1, and neurodegenerative biomarkers p-tau181, p-tau231, NfL, total tau.
- APOE was genotyped from whole blood.

Statistical Analysis

- Biomarkers were log-transformed.
- Multivariable linear regression models** examined associations of APOE ε4 carrier status with fluid biomarker concentrations.
- Stratified by median age and FDR-corrected.**
- Covariates included age, race, rFSRP and AUDIT score.
- Exploratory models** tested association between duration of play and biomarker outcomes, stratified by APOE ε4 status.

RESULTS

Subgroup	Fluid	Biomarker	Domain	B [95% CI]	p-value	P _{adj}
Age ≥56	CSF	IL-1β	Cytokines	0.945 [0.383 – 1.507]	0.001	0.007
Age <56	CSF	IL-1β	Cytokines	-0.645 [-1.300 – 0.010]	0.054	0.270

Table 2a. Significant associations of APOE ε4 carrier status with fluid biomarkers stratified by age

Subgroup	Fluid	Biomarker	Domain	B [95% CI]	p-value
APOE ε4-positive	CSF	Eotaxin-1*	Chemokines	-0.051 [-0.092 – -0.009]	0.017
APOE ε4-negative	CSF	Eotaxin-1*	Chemokines	0.015 [-0.023 – 0.053]	0.432

Table 2b. Significant associations of duration of play with fluid biomarkers stratified by APOE ε4 carrier status

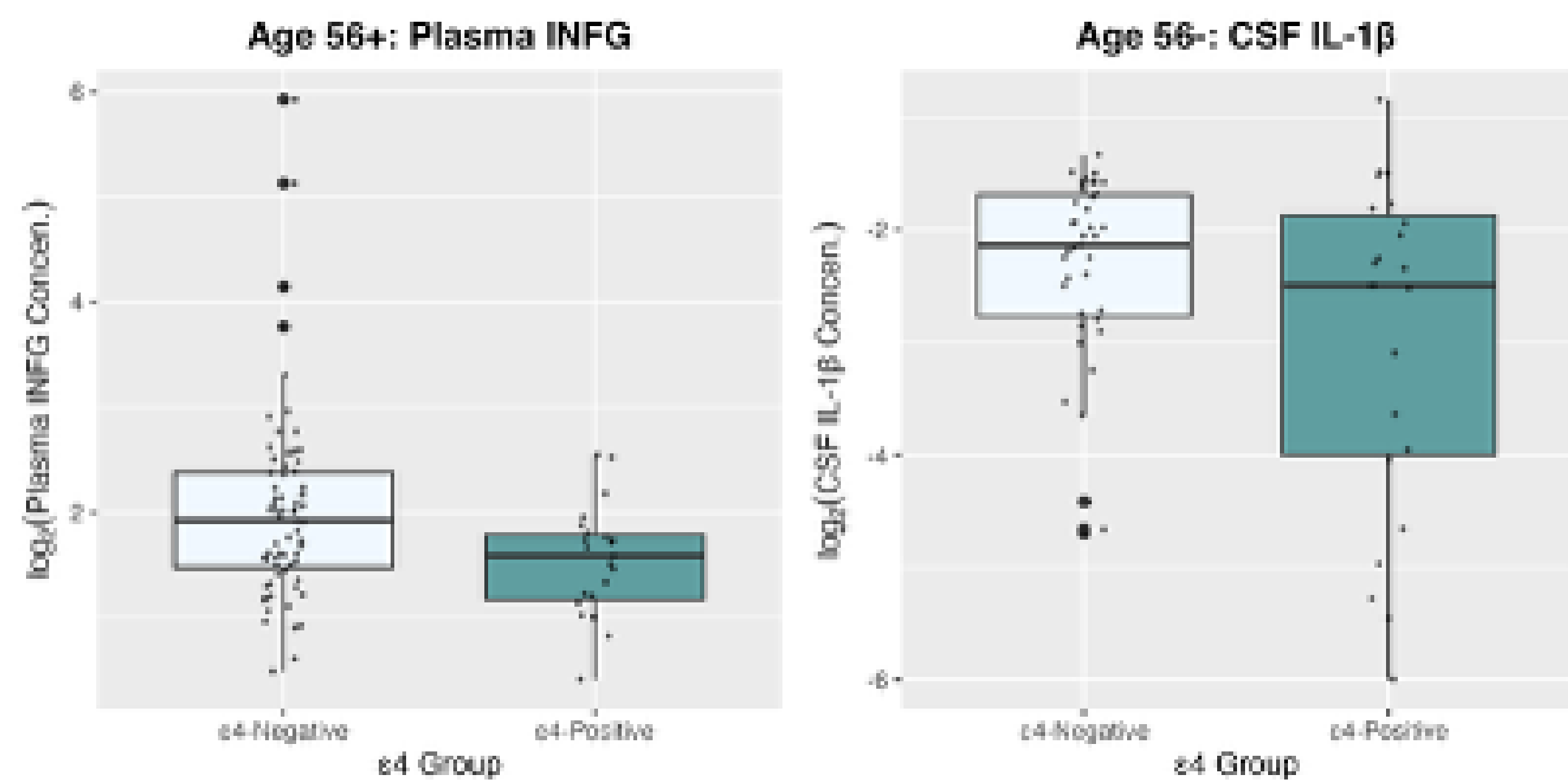


Figure 1a. Distribution of CSF IL-1β with APOE ε4 carrier status in former football players ≥56 years old.

RESULTS

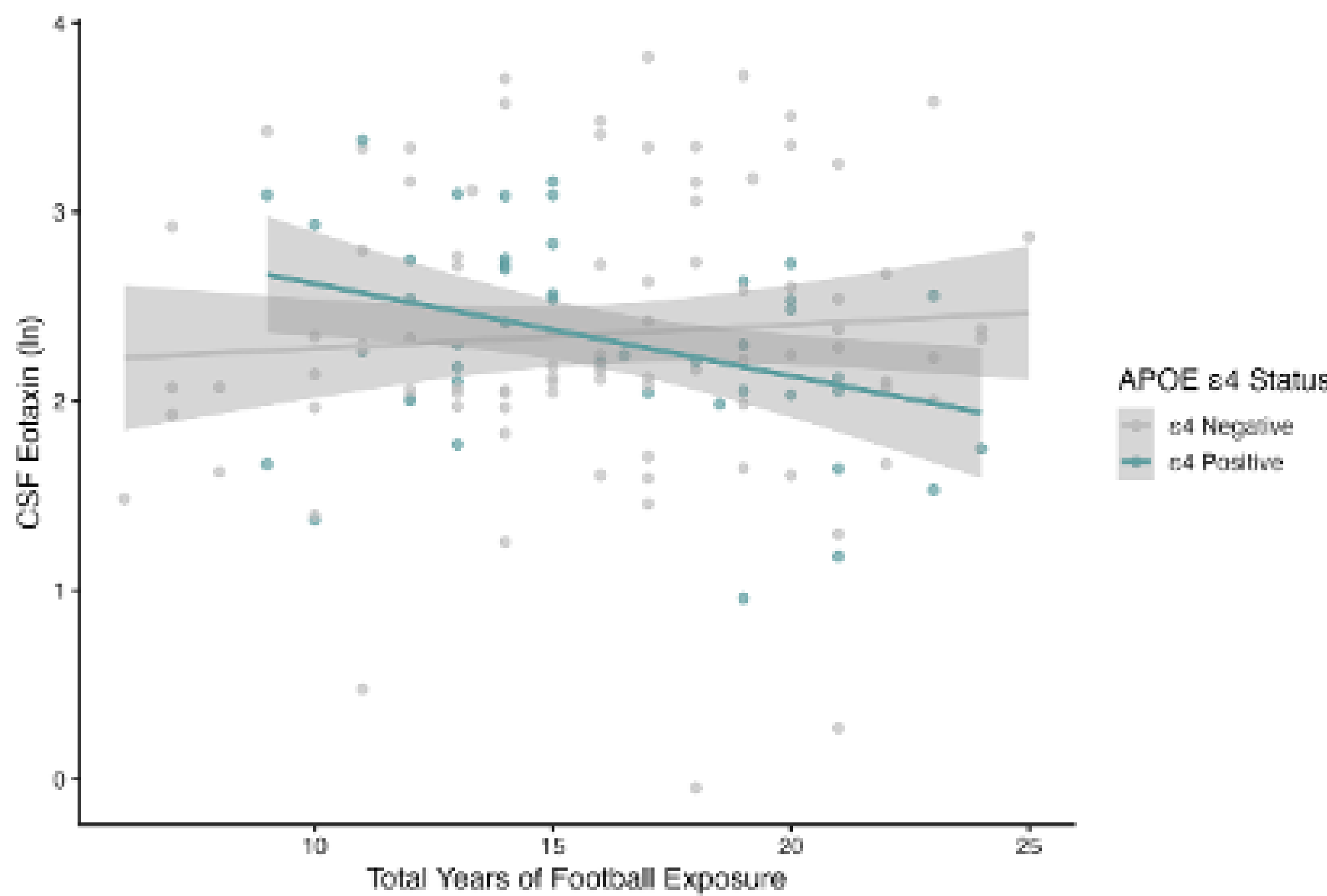


Figure 1b. Association between total years of football play and CSF eotaxin-1 concentrations in former football players who are APOE ε4 allele carriers.

In the overall sample, ε4 status was not significantly associated with any fluid biomarker.

Among participants aged ≥56 years only, ε4 status was associated with higher CSF IL-1β (B=0.945, padj=0.007); Table 2a, Figure 1a.

Among ε4 carriers only, greater total years of play were significantly associated with lower CSF eotaxin-1 (B=-0.051, p=0.017). Table 2b, Figure 1b.

APOE ε4 carrier status interacted with age- and duration of play to influence CSF concentrations of inflammatory biomarkers. Findings may implicate inflammation as a mechanism linking APOE to RHI-exposed individuals.

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