The Biology of Deployment Trauma: Blood-based Biomarkers and the Diagnosis of a Complex Multi-Morbid Condition

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Translational Research Center for TBI and Stress Disorders

VA Boston Healthcare System

Poll: How much experience do you have working with blood-based biomarkers related to traumatic brain injury?

a) I am currently working with blood-based biomarkers related to brain injury.

b) I am planning on including blood-based biomarkers in my research.

c) I work with patients with brain injury.

d) I am interested in the topic but do not have directly related experience.

Translational Research Center for TBI & Stress Disorders (TRACTS)

- Ongoing comprehensive assessment of post-9/11 Veterans.
  - 2009 – present
  - 2 sites: Boston & Houston (combined *n* = 850)
  - Longitudinal: Baseline, ~1-year (*n* = 322) and 5-year follow-ups (*n* = 89)
- Extensive longitudinal cohort study focused on the impact of traumatic brain injury (TBI) and common clinical comorbidities that impact functional outcomes.
  - Clinical Interviews
  - Medical/biological evaluation
  - Neuropsychological Assessments
  - Structural and Functional Brain Imaging

TRACTS Core Assessment at Baseline, 1-year, and 5-year Visits.

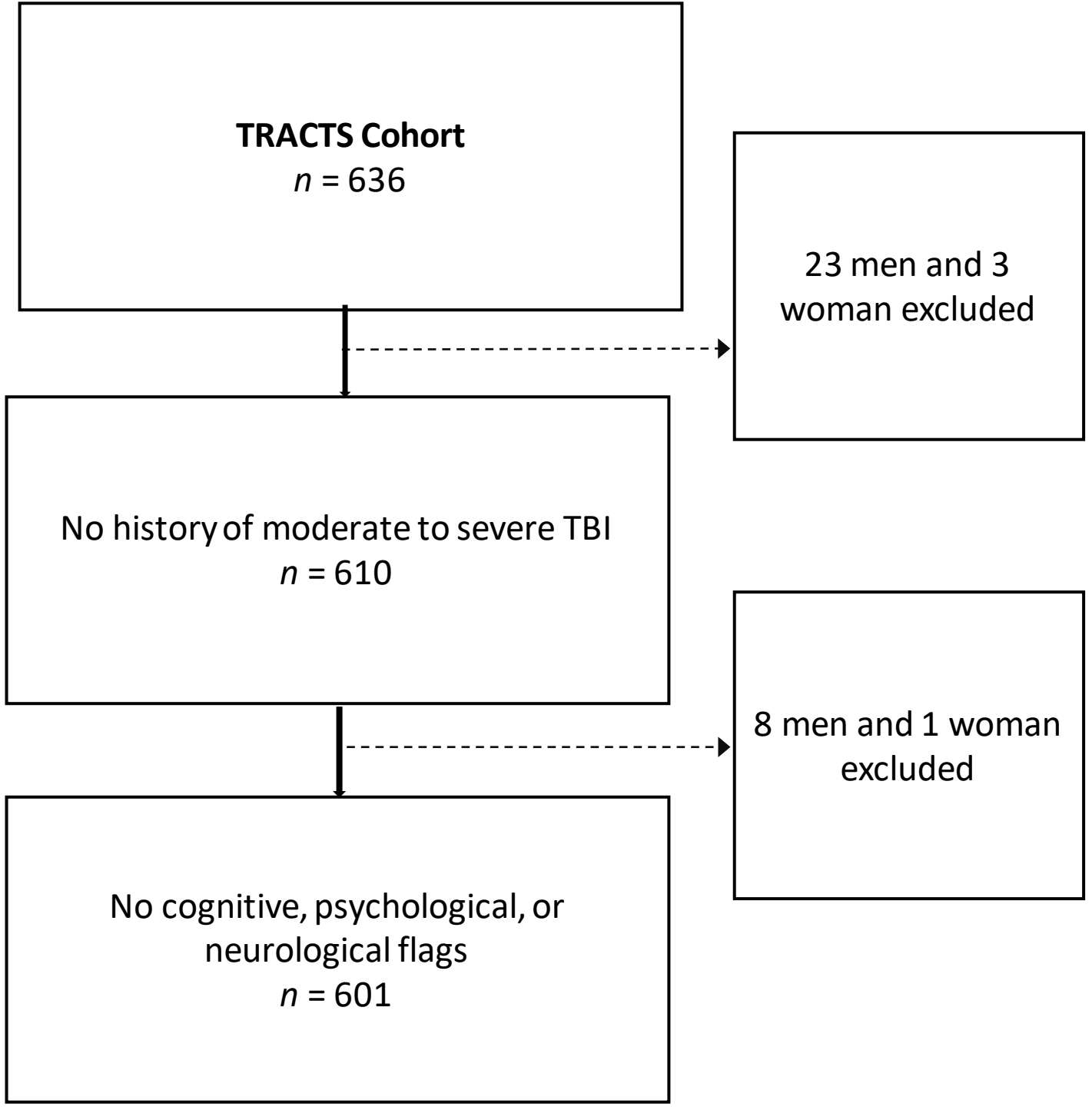
Medical/Biological	Neuropsych Domains	Affective/Psychosocial	Blast/TBI	Neuroanatomy S/F MRI
Blood Chemistry	Simple/Divided Attention	PTSD: CAPS & PCL-C	Boston Assessment of TBI-Lifetime	Cortical Volume
GWAS	Information Processing Speed	DSM-IV AXIS I: SCID	Ohio State University TBI ID	Cortical Thickness
Neuro-steroid	Executive Function	Traumatic Life Events Questionnaire	Neurobehavioral Symptom Inventory	Diffusion Tensor
Neural Injury	Declarative/Procedural Memory	Deployment Risk & Resiliency Inventory		Resting-State Networks
	Pre-morbid Function	Depression, Anxiety & Stress Scale-21		Functional Connectivity
	Perception	Pittsburg Sleep Quality Index		Task-Based fMRI
	Symptom Validity	McGill Pain Questionnaire		
	Psychomotor Speed	Alcohol, Nicotine		

How we measure TBI Severity

Criteria	Mild			Moderate	Severe
	Grade I	Grade II	Grade III		
Loss of Consciousness	None	< 5 minutes	> 5 minutes and < 30 minutes	> 30 minutes and < 24 hours	> 24 hours
Alteration of Mental Status	0 – 15 minutes	> 15 minutes and < 24 hours	> 24 hours	> 24 hours; severity based on other criteria	
Post Traumatic Amnesia	0 – 15 minutes	> 15 minutes and < 24 hours	> 24 hours	> 1 day and < 7 days	> 7 days
Glascow Coma Scale	13 - 15			9 - 12	< 9

Department of Veterans Affairs and Department of Defense. (2009). VA/DOD clinical practice guideline for the management of concussion/mild traumatic brain injury. Retrieved from http://www.healthquality.va.gov/mtbi/concussion_mtbi_full_1_0.pdf.

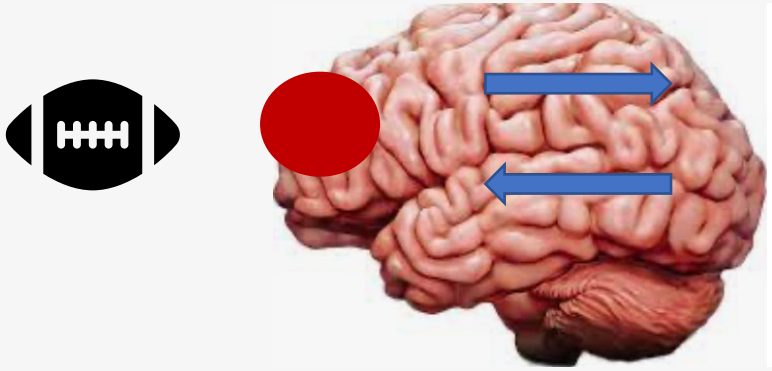
Exclusions


TRACTS Cohort
n = 636
23 men and 3 woman excluded
No history of moderate to severe TBI
n = 610
8 men and 1 woman excluded
No cognitive, psychological, or neurological flags
n = 601

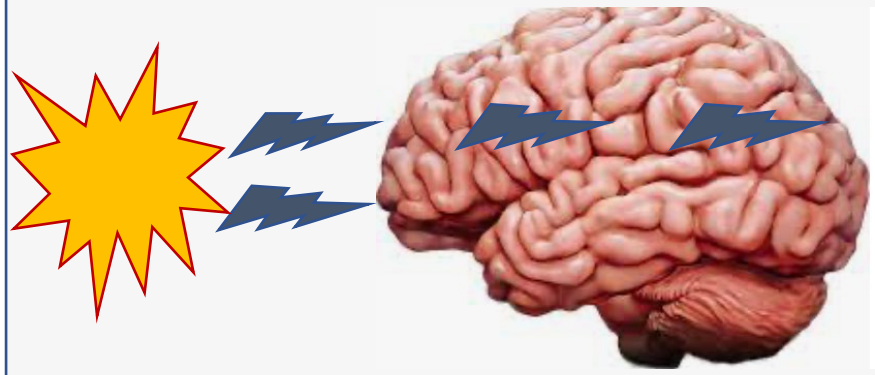
Mechanisms of Traumatic Brain Injury

No mTBI (*n* = 183)

Blunt mTBI *n* = 245

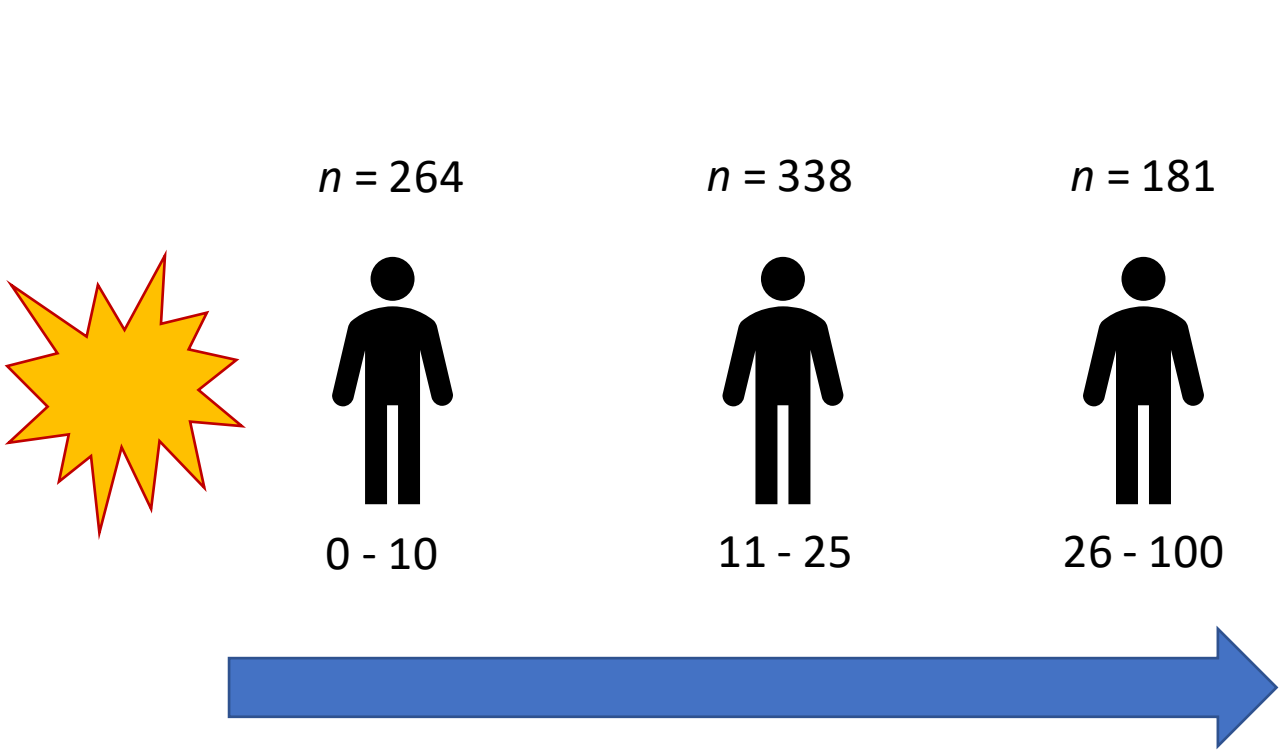


Blast mTBI *n* = 173

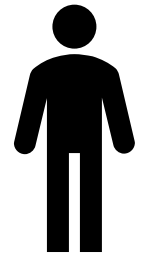


Military mTBI *n* = 279

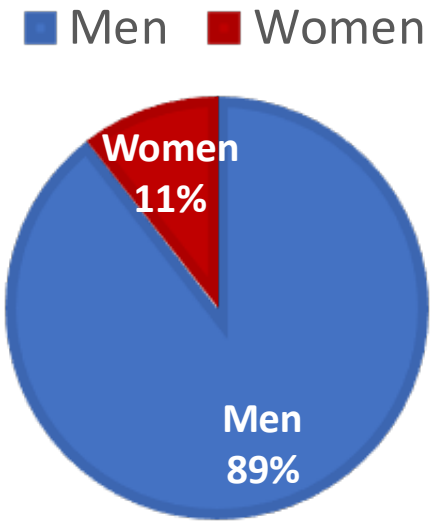
Proximity to Blast



No Blast exposure
(*n* = 128)

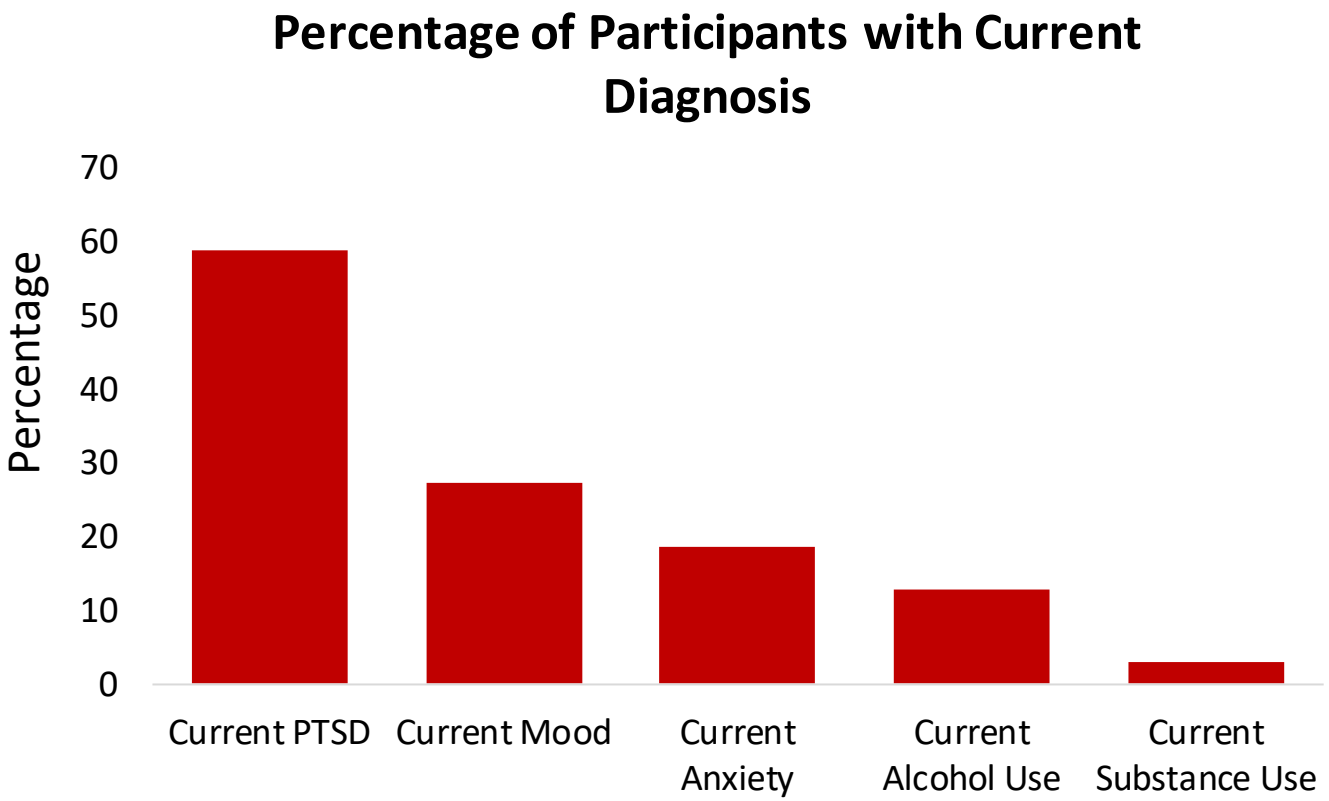


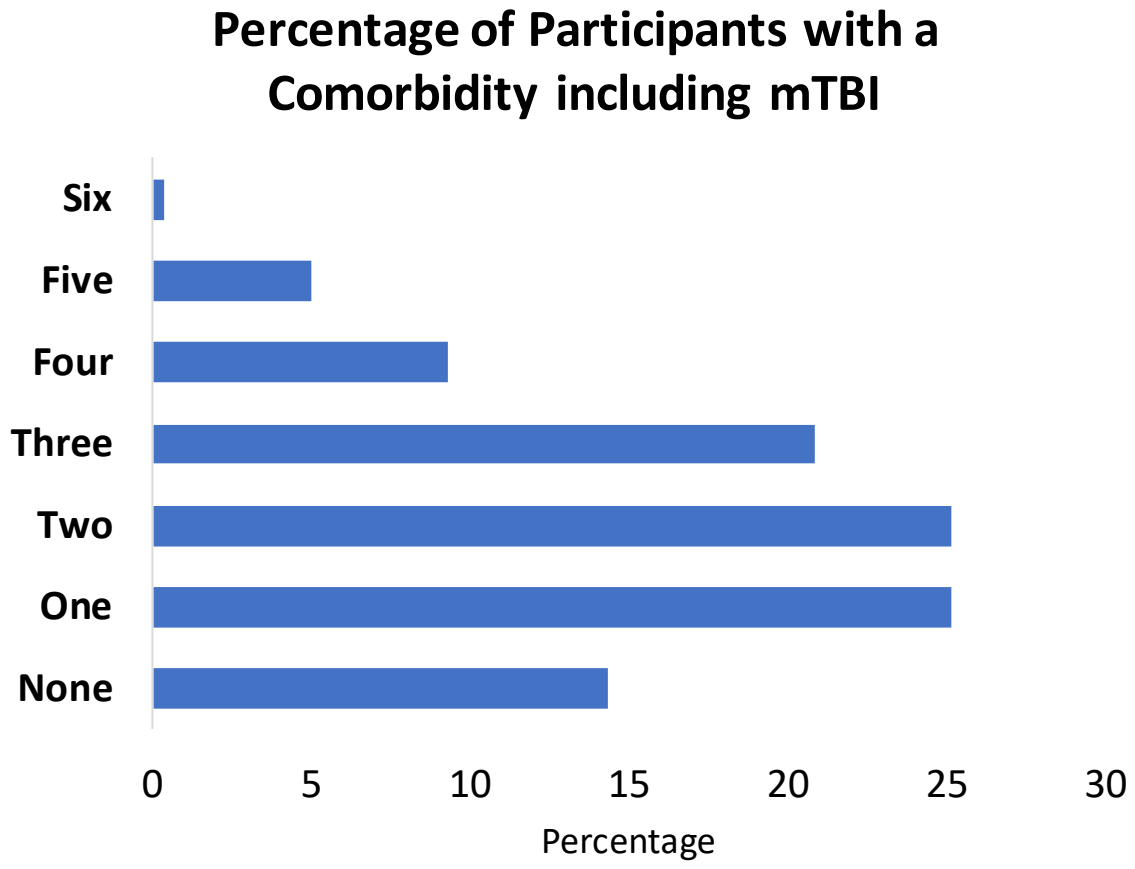
Total exposed to any blast *n* = 473



Demographic Characteristics

Ages ranges from 19-64 (M = 33.40, SD = 9.01)





TRACTS Biomarker Innovation

- Large well-characterized longitudinal sample of Veteran men and women.
- Extensive panel of blood-based biomarkers related to brain injury.
- Innovative Quanterix Simoa assay technology.
- Extensive brain imaging data.
- Extensive medical/biological data.

TRACTS Biomarkers Markers

Biomarker	Type	Function
Tumor Necrosis Factor α (TNFα)	Cytokine	Pro-inflammatory
Interleukin 6 (IL-6)	Cytokine	Pro-inflammatory
Interleukin 10 (IL-10)	Cytokine	Anti-inflammatory
Eotaxin	Chemokine	Coordination of inflammatory cells and allergic inflammation
Brain Derived Neurotrophic Factor (BDNF)	Neurotrophin	Neuroprotective
Amyloid ß 40 (Aß40)	Peptide	Component of amyloid plaques related to neurodegenerative diseases
Amyloid ß 42 (Aß42)	Peptide	Component of amyloid plaques related to neurodegenerative diseases
Total Tau & p-Tau181	Protein	Marker of microtubule damage
Neuron Specific Enolase (NSE)	Enzyme	Marker of axonal damage
Neurofilament Light (NfL)	Protein	Marker of axonal damage
Phosphorylated Neurofilament Heavy (pNF Heavy)	Protein	Marker of axonal and dendritic damage and degeneration
Glial Fibrillary Acidic Protein (GFAP)	Protein	Marker of astrocyte damage

Translational Psychiatry

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Plasma biomarkers associated with deployment trauma and its consequences in post-9/11 era veterans: initial findings from the TRACTS longitudinal cohort

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Study Aims

Examine blood-based biomarkers related to brain injury and chronic TBI and blast exposure in a poly-morbid population of post-9/11 Veterans.

Understand relationships between markers of brain injury and deployment-related comorbidities.

Mechanism of Mild Traumatic Brain Injury

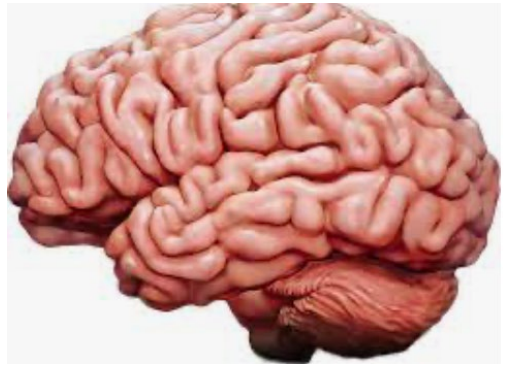
Analyses of covariance (ANCOVA) controlling for age

Exclusions

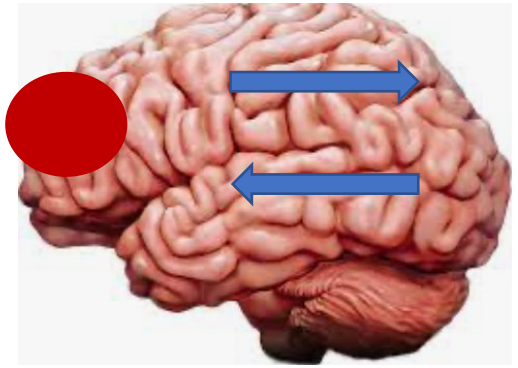
- Cognitive, neuropsychological, psychiatric flags; moderate-severe TBI
- Coefficient of variation (CV) above 20%

Groups examined

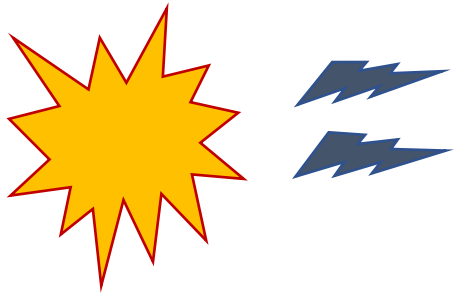
- mTBI mechanism of injury
  - No history of mTBI (*n* = 183)
  - Blunt mTBI (*n* = 224)
  - Blast mTBI (*n* = 173)

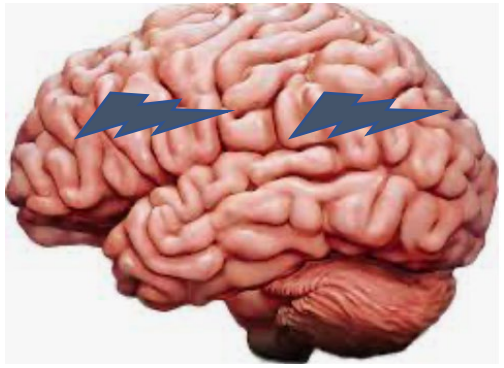


No mTBI



Blunt mTBI





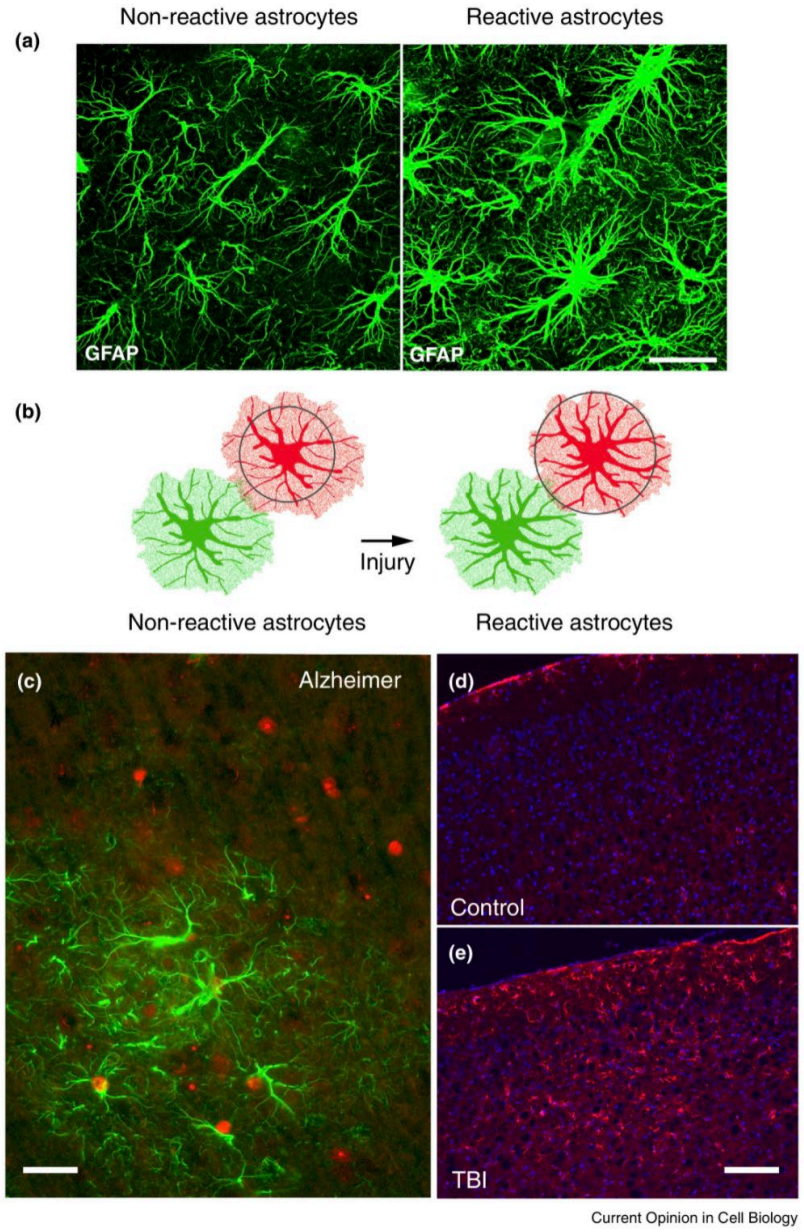
Blast mTBI

Table 3. Mean level differences in plasma biomarkers related to military mTBI and mechanism of injury.

	Military TBI				Mechanism of TBI				
	Non-mTBI	**mTBI**	***p*-value**	***q*-Value**	**No TBI**	**Blunt TBI**	**Blast TBI**	***p*-value**	***q*-Value**
Neuroprotection									
BDNF	7.06 (1.16)	7.23 (1.13)	0.142	0.142	7.16 (1.26)	7.04 (1.08)	7.24 (1.12)	0.261	0.261
Anti-Inflammatory									
IL-10	−0.31 (0.67)	−0.34 (0.54)	0.631	0.631	−0.33 (0.64)	−0.33 (0.65)	−0.32 (0.53)	0.977	0.977
Pro-Inflammatory									
IL-6	0.32 (0.65)	0.39 (0.68)	0.151	0.453	0.31 (0.57)	0.30 (0.67)	0.46 (0.72)	0.025	0.075
TNFα	0.99 (0.33)	0.99 (0.33)	0.955	0.955	0.99 (0.33)	0.97 (0.33)	1.02 (0.32)	0.425	0.425
Eotaxin	3.69 (0.37)	3.73 (0.36)	0.364	0.546	3.71 (0.39)	3.68 (0.34)	3.74 (0.36)	0.358	0.425
Neurodegeneration									
Aß40	5.35 (0.22)	5.33 (0.18)	0.553	0.885	5.34 (0.23)	5.34 (0.20)	5.35 (0.17)	0.872	0.872
Aß42	2.07 (0.21)	2.07 (0.21)	0.886	0.886	2.08 (0.21)	2.05 (0.20)	2.08 (0.21)	0.368	0.822
Tau	0.35 (0.56)	0.32 (0.54)	0.664	0.885	0.33 (0.59)	0.36 (0.51)	0.29 (0.56)	0.617	0.822
NSE	9.35 (0.49)	9.39 (0.47)	0.270	0.885	9.34 (0.49)	9.34 (0.50)	9.44 (0.46)	0.575	0.822
Neuronal damage									
NfL	1.71 (0.47)	1.64 (0.52)	0.181	0.319	1.72 (0.44)	1.67 (0.50)	1.64 (0.53)	0.438	0.876
pNF-H	3.25 (0.99)	3.12 (0.96)	0.319	0.319	3.19 (0.96)	3.20 (1.02)	3.17 (0.95)	0.961	0.961
Glial damage									
GFAP	4.16 (0.36)	4.07 (0.37)	0.009*	0.009*	4.18 (0.39)	4.14 (0.33)	4.03 (0.37)	0.013	0.013

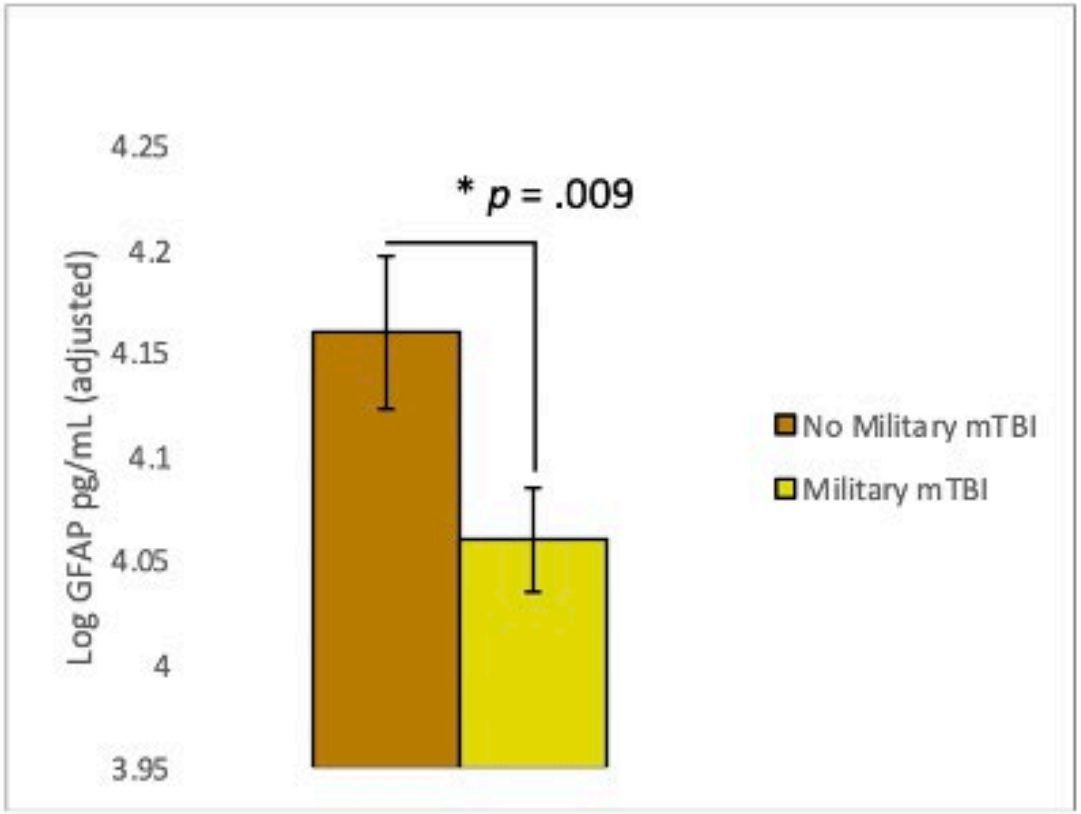
Glial Fibrillary Acidic Protein (GFAP)

- Released by Astrocytes
- Reactive Astrogliosis
  - Brain damage & neurodegenerative diseases
  - Stress & inflammation.
- Upregulation of GFAP
  - hallmark of reactive astrogliosis
  - Restores homeostasis after injury/stress/etc.
    - limits tissue damage too
  - If chronic, leads to negative outcomes
    - Can lead to scarring
    - Disruptions in neural communication
      - involved in long term potentiation (LTP)
      - involved in disruptions to neuronal signaling in mice models of Alzheimer's Disease



Hol & Penky (2015)

Military mTBI



Mechanism of mTBI

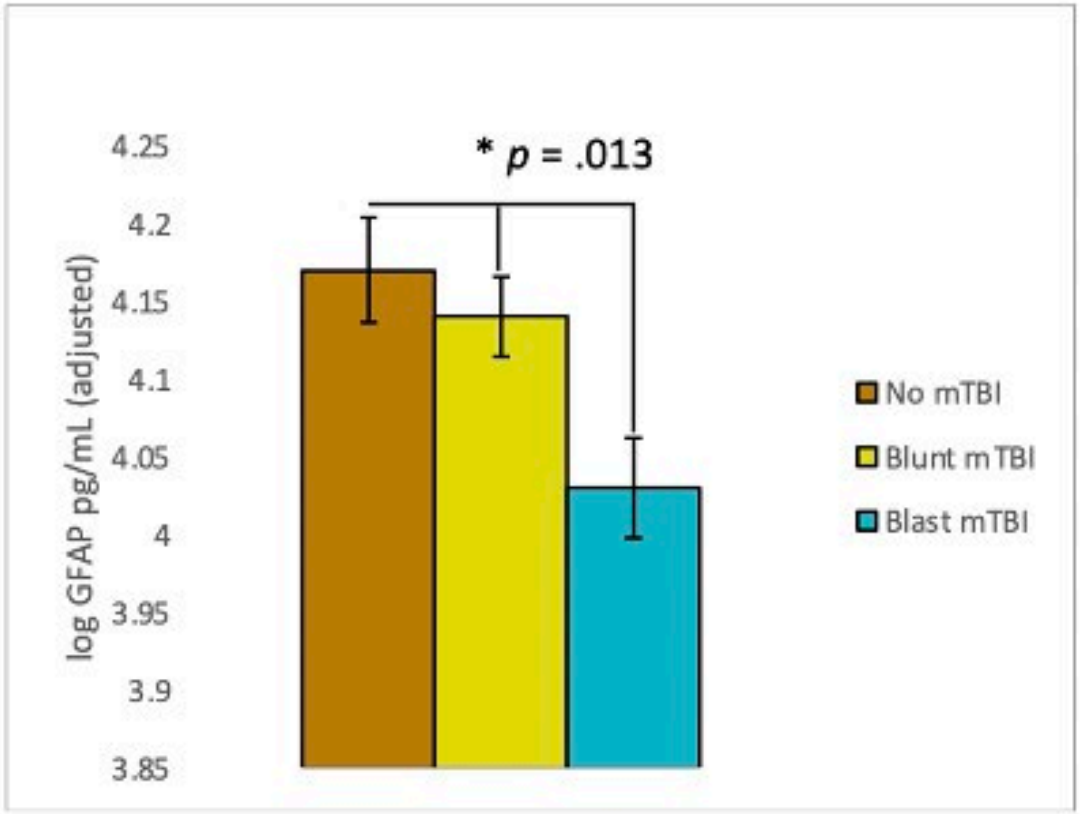


Table 3. Mean level differences in plasma biomarkers related to military mTBI and mechanism of injury.

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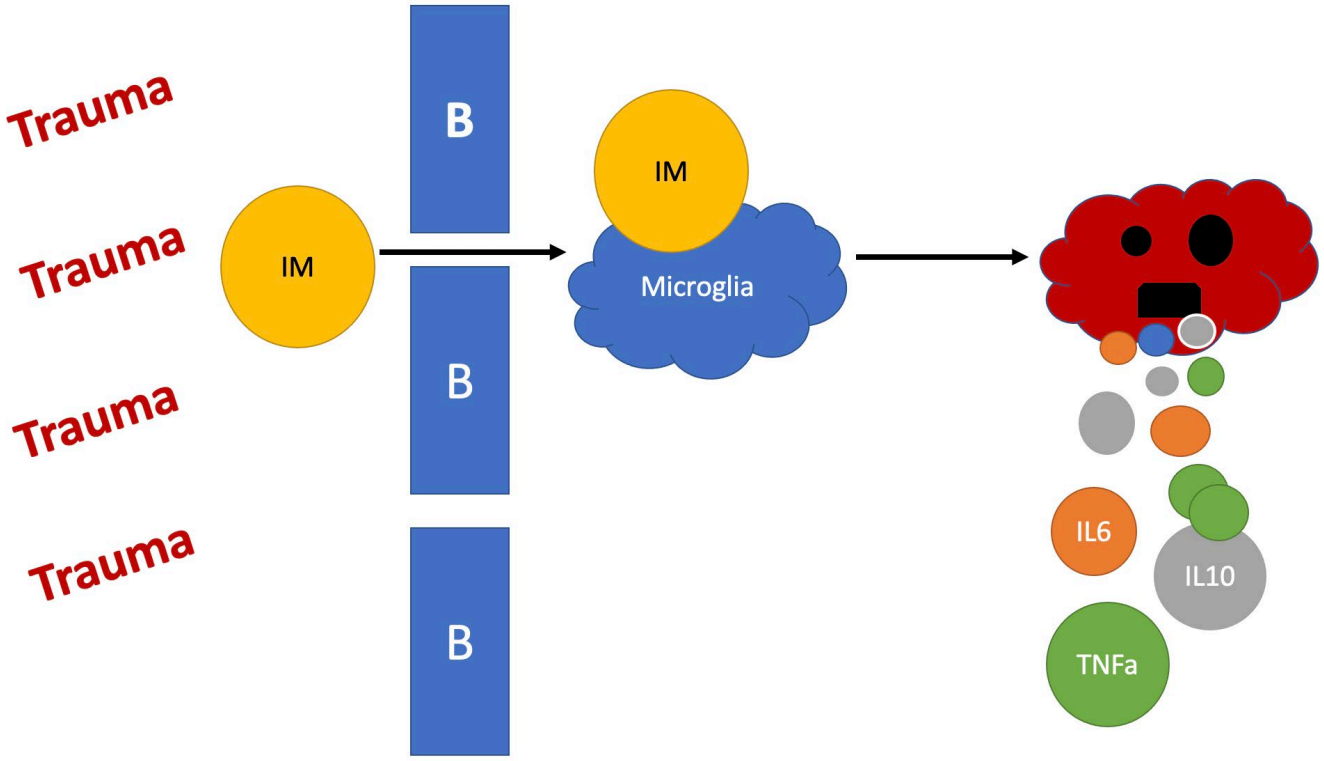
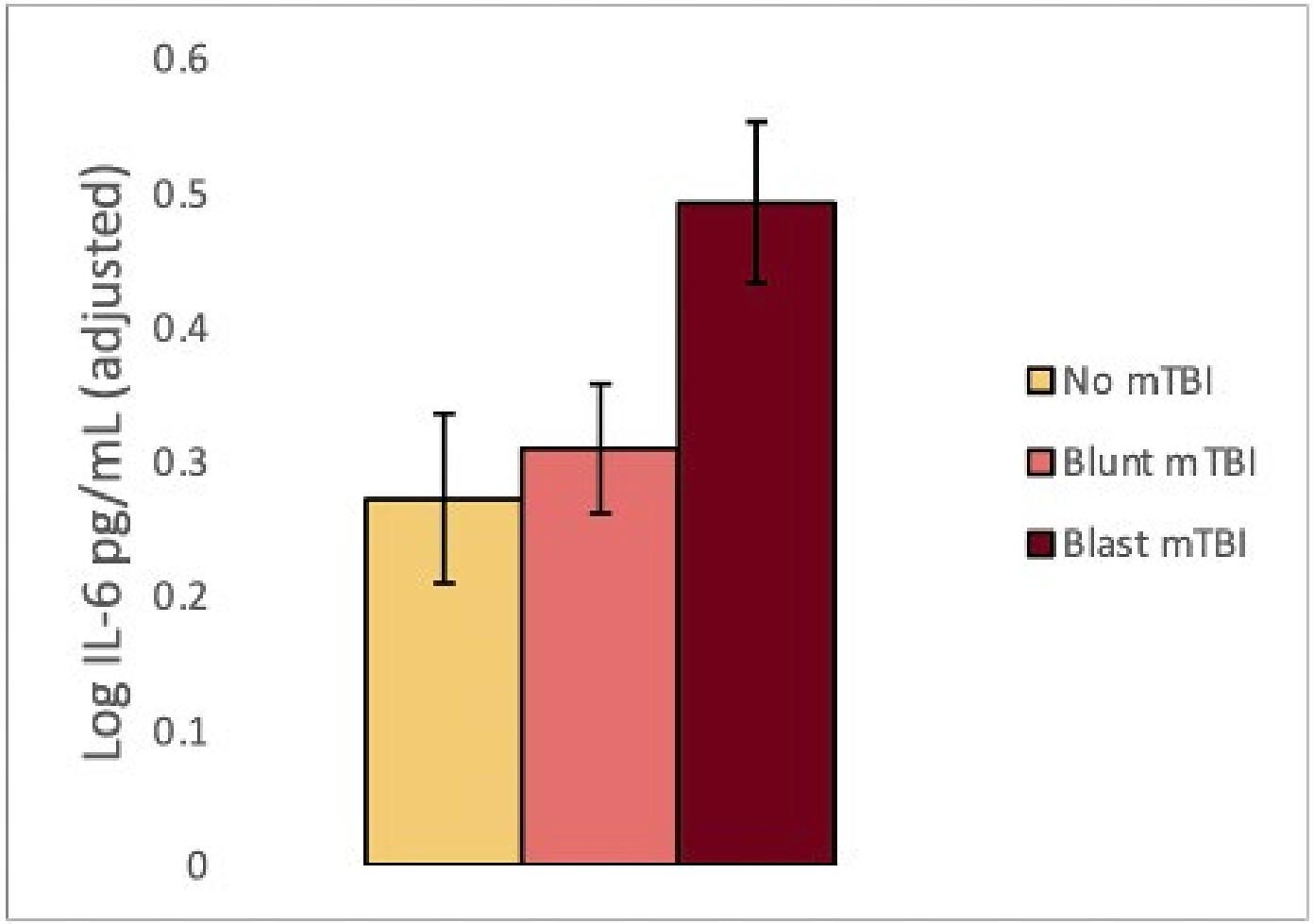
Glial damage									
GFAP	4.16 (0.36)	4.07 (0.37)	0.009*	0.009*	4.18 (0.39)	4.14 (0.33)	4.03 (0.37)	0.013	0.013

Inflammatory Response to Trauma



- Cytokines modulate inflammation in response to a stressor like trauma and pathogens.
  - Coordination of immune response.
  - Regulate cell growth, proliferation, and differentiation.
  - Chronic inflammation can lead to neural degeneration.

Trend in higher IL6 in individuals with Blast-Related mTBI compared to no mTBI.



Proximity to Blast

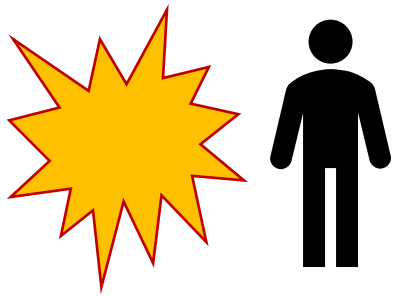
Analyses of covariance (ANCOVA) controlling for age

Exclusions

- Cognitive, neuropsychological, psychiatric flags; moderate-severe TBI
- Coefficient of variation (CV) above 20%

Groups examined

- Blast proximity
  - No history blast exposure (*n* = 128)
  - Blasts between 0-10 meters (*n* = 234)



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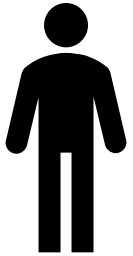

No blast

Table 2. Mean level differences in plasma biomarkers related to reported close blast exposure.

	No Blast *M* (SD)	Close Blast *M* (SD)	*p*-Value	*q*-Value
Neuroprotection				
BDNF	7.02 (1.18)	7.25 (1.08)	0.084	0.084
Anti-Inflammatory				
IL-10	−0.38 (0.51)	−0.31 (0.59)	0.401	0.401
Pro-Inflammatory				
IL-6	0.22 (0.54)	0.40 (0.72)	0.012	0.036
TNFa	0.93 (0.29)	1.02 (0.30)	0.040	0.040
Eotaxin	3.64 (0.36)	3.72 (0.35)	0.024	0.036
Neurodegeneration				
Aß40	5.36 (0.16)	5.34 (0.17)	0.861	0.874
Aß42	2.07 (0.17)	2.06 (0.22)	0.874	0.874
Tau	0.43 (0.58)	0.27 (0.55)	0.038	0.094
NSE	9.29 (0.43)	9.42 (0.49)	0.047	0.094
Neuronal damage				
NfL	1.73 (0.47)	1.62 (0.50)	0.201	0.201
pNF-H	3.10 (0.98)	3.23 (0.97)	0.178	0.201
Glial damage				
GFAP	4.22 (0.35)	4.06 (0.37)	0.003	0.003

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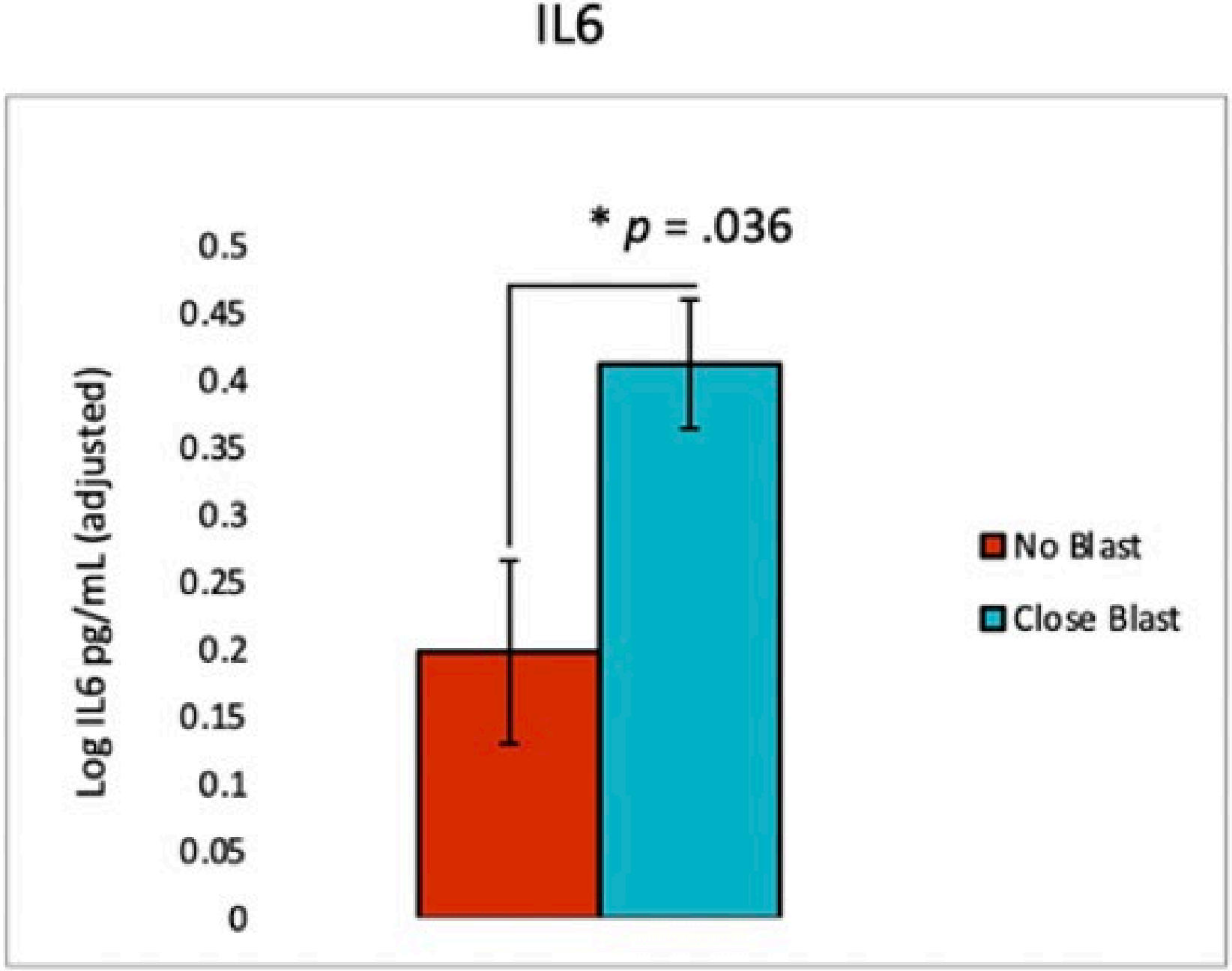
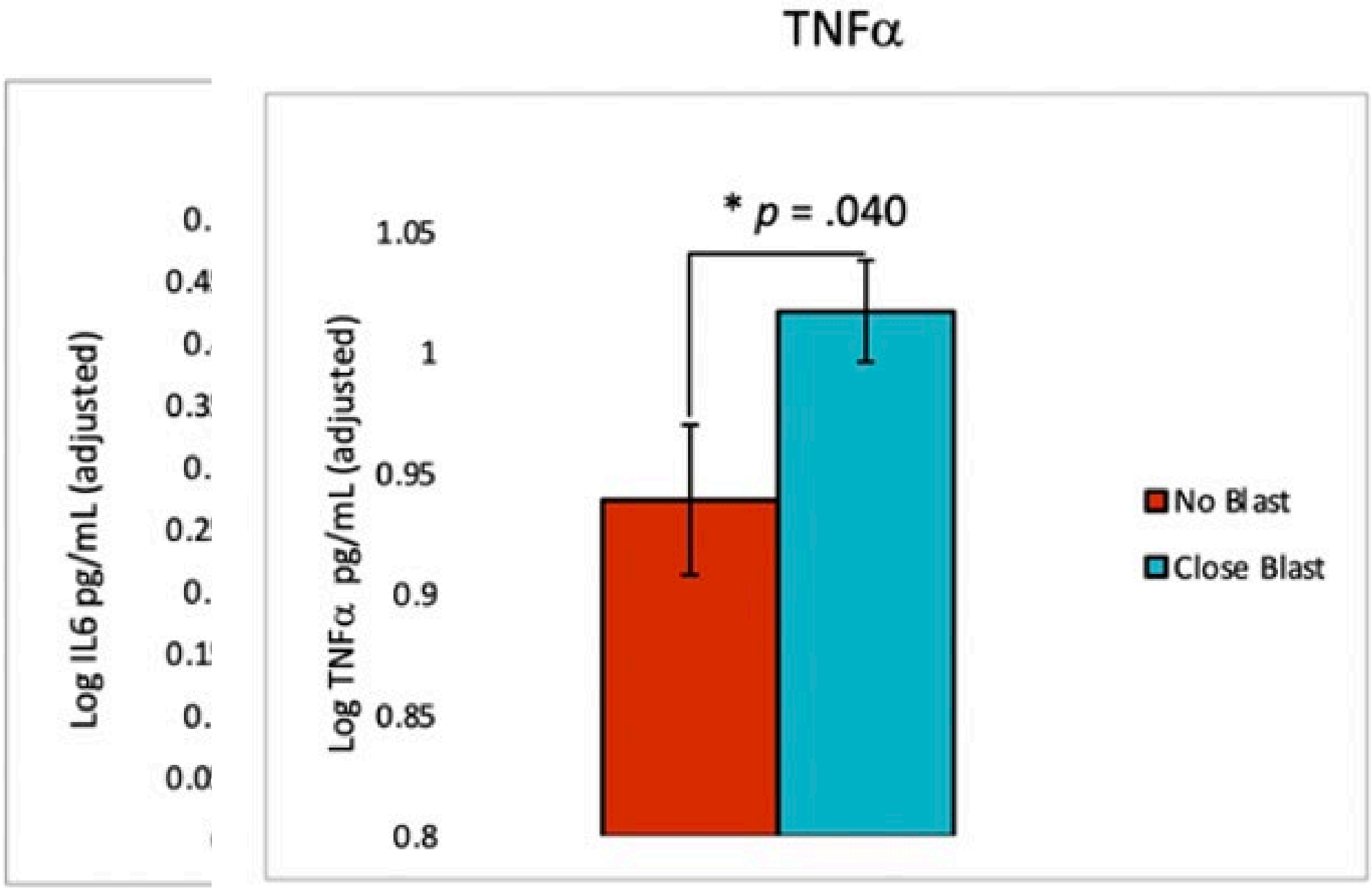
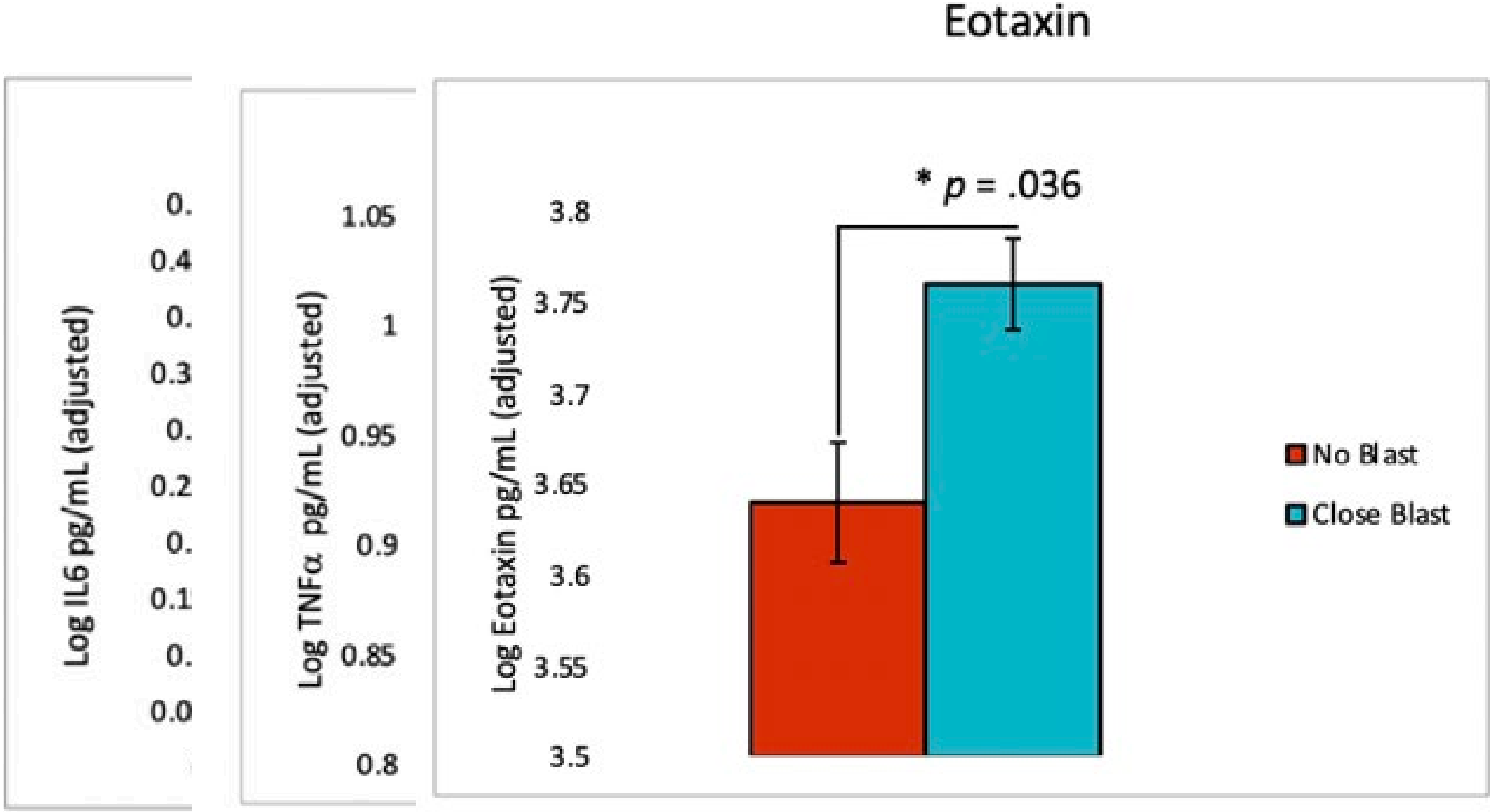

IL6
* p = .036
Log IL6 pg/mL (adjusted)
0.5
0.45
0.4
0.35
0.3
0.25
0.2
0.15
0.1
0.05
0
No Blast
Close Blast

A


TNFα
Log IL6 pg/mL (adjusted)
0.
0.4
0.
0.3
0.
0.2
0.
0.1
0.
0.0
Log TNFα pg/mL (adjusted)
1.05
1
0.95
0.9
0.85
0.8
* p = .040
No Blast
Close Blast

A


Log IL6 pg/mL (adjusted)
0.
0.4
0.
0.3
0.
0.2
0.
0.1
0.
0.0
Log TNFα pg/mL (adjusted)
1.05
1
0.95
0.9
0.85
0.8
Eotaxin
* p = .036
Log Eotaxin pg/mL (adjusted)
3.8
3.75
3.7
3.65
3.6
3.55
3.5
No Blast
Close Blast

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Aß40	5.36 (0.16)	5.34 (0.17)	0.861	0.874
Aß42	2.07 (0.17)	2.06 (0.22)	0.874	0.874
Tau	0.43 (0.58)	0.27 (0.55)	0.038	0.094
NSE	9.29 (0.43)	9.42 (0.49)	0.047	0.094
Neuronal damage				
NfL	1.73 (0.47)	1.62 (0.50)	0.201	0.201
pNF-H	3.10 (0.98)	3.23 (0.97)	0.178	0.201
Glial damage				
GFAP	4.22 (0.35)	4.06 (0.37)	0.003	0.003

Close Blast

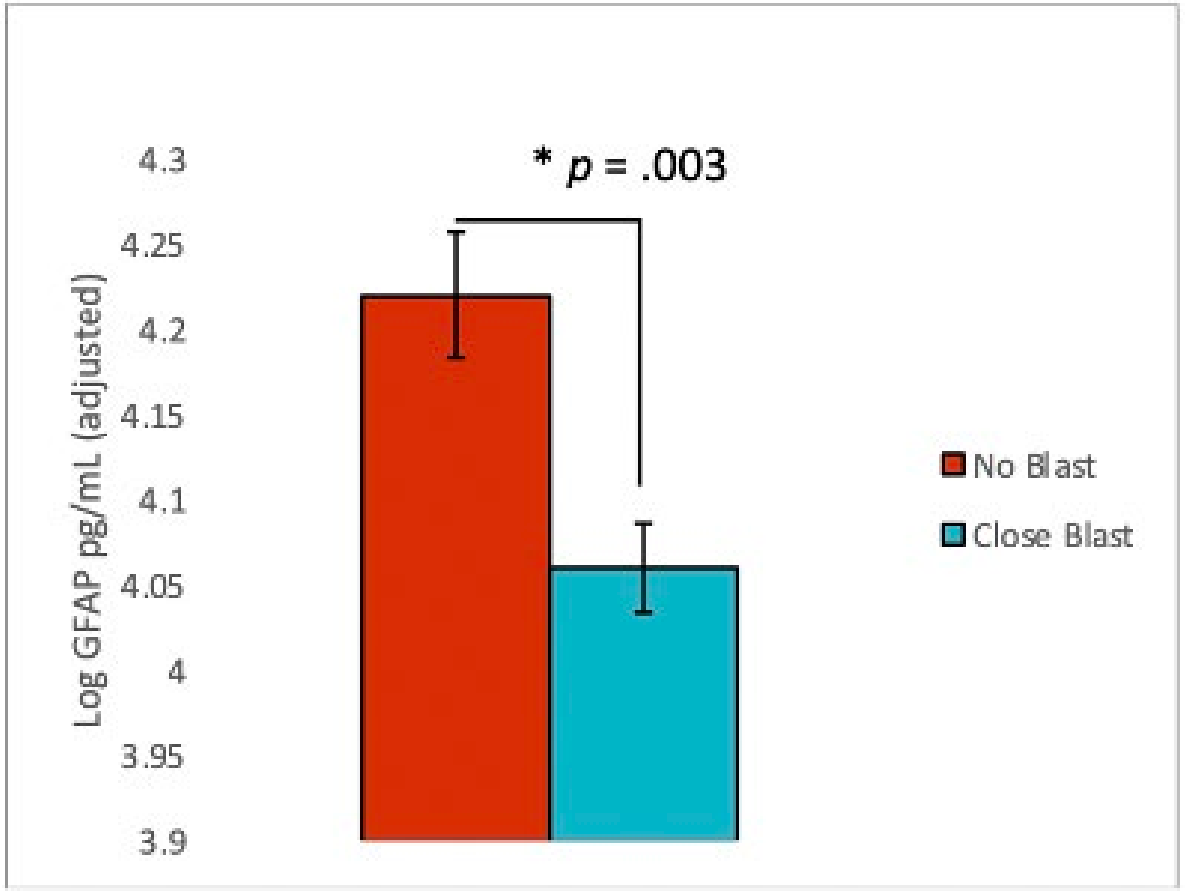
* p = .003
Log GFAP pg/mL (adjusted)
4.3
4.25
4.2
4.15
4.1
4.05
4
3.95
3.9
No Blast
Close Blast

Table 4

Relationships between Plasma Biomarkers and Psychiatric Comorbidities

	BDNF	IL-10	IL-6	TNFα	Eotaxin	Aß40	Aß42	Tau	NSE	NfL	pNF-H	GFAP
PTSD Symptom Severity (CAPS)	.042	-.023	.155***	.062	.066	-.032	-.031	-.003	.044	-.043	-.025	-.100*
DRRI Subscale Total Score												
Combat	.067	.028	.081	.107*	.105*	.007	.029	-.065	.083	-.046	.043	-.186***
Other War Experiences	.070	-.007	.080	.053	*.112*	-.011	-.028	-.086	.031	-.010	.034	-.120*
Depression Anxiety and Stress Scale												
Anxiety Total	.050	.012	*.113*	.082	.061	-.013	.000	-.035	.036	-.046	.006	-.123*
Depression Total	.048	.112*	.138*	.092	.074	-.009	-.032	-.018	.017	-.046	-.033	-.057
Stress Total	.017	-.008	.105	.043	.031	-.037	-.047	-.025	.023	-.043	.029	-.112*
Lifetime Drinking History												
Total (weight corrected)	.031	.057	.065	.117*	.076	-.001	-.061	-.088	.048	-.049	-.011	-.097*
Average Drinks	-.009	.011	.177***	.132**	.057	.030	-.024	-.070	.019	-.061	-.011	-.083
Maximum Drinks	.034	.017	.157***	.136**	.057	-.048	-.060	-.081	.044	-.061	-.026	-.090
SMAST Total Lifetime Score	.034	.059	.057	.058	.023	-.008	-.139*	-.152*	-.039	-.076	.031	-.054
Fagerstrom Test of Nicotine Dependence												
Total Cigarette Score	-.046	-.005	-.064	.035	.043	.145	.092	.082	.035	.141	.023	-.158
Total Chew Score	-.068	-.025	.027	.017	.043	.099	.102	-.149	.033	.010	-.006	-.155
NSI: Total Score	.046	.037	.143**	.116*	.070	.010	.017	-.061	.039	-.030	-.013	-.107*
WHODAS Complex Total Score	.051	.052	.122*	.103*	.071	-.047	-.023	-.058	.031	-.057	-.053	-.085
McGill: Current Overall Pain	-.001	.030	.059	.074	.006	-.011	-.024	.044	.066	-.067	-.029	-.102*
PSQI: Global Score	.078	-.020	.178***	.112*	.068	-.012	.026	-.035	.104*	.003	.045	-.076

Note. Partial correlations controlling for age and sex. * < .05; ** < .01, *** < .001. All significance indicators reflect Benjamini-Hochberg corrected values.

Table 5

Relationships between Plasma Biomarkers and Medical Comorbidities

	BDNF	IL-10	IL-6	TNFα	Eotaxin	Aß40	Aß42	Tau	NSE	NfL	pNF-H	GFAP
Age	.101*	-.011	.074	.048	.122*	-.077	-.072	-.123*	.104*	.348***	.187***	.277***
Mean Arterial BP	.211***	-.061	.078	-.046	.093	-.073	-.064	-.002	.217***	-.171***	-.019	-.113*
Systolic BP	.222***	-.036	.093	-.037	.089	-.083	-.079	-.043	.241***	-.141**	.009	-.126**
Diastolic BP	.174***	-.070	.057	-.046	.083	-.057	-.045	.026	.174***	-.168***	-.035	-.088
Body Mass Index	.083	-.020	.345***	.198***	-.038	-.104*	-.149**	-.030	.135**	-.320***	-.079	-.218***
Waist to Hip Ratio	.091	.043	.219***	.214***	-.036	.009	-.039	-.029	.136***	-.194***	-.001	-.189***
Total Cholesterol	.087	-.092	-.086	-.083	.041	.002	.019	.025	.145**	-.141**	-.037	-.081
HDL Cholesterol	-.037	-.149**	-.184***	-.270***	-.010	-.040	-.055	.012	-.079	.140**	.085	.094
LDL Cholesterol	.086	-.054	-.017	-.052	.051	-.054	-.034	.005	.054	-.159***	-.090	-.058
Triglycerides	.075	.027	.021	.127**	.015	.091	.100*	.055	.215***	-.056	.010	-.104*
Homocysteine	.076	.089	.003	.067	.049	.080	.116*	-.016	.080	.085	.026	.080
Glucose	.127*	-.016	.042	.020	.069	-.012	-.028	-.068	-.010	.085	.040	-.096*
A1C	.093	-.040	.077	.020	.045	.039	.031	-.045	.027	.051	.037	-.065
C-Reactive Protein	.011	.186***	.427***	.341***	-.034	.040	.036	.047	-.001	-.113*	-.009	-.144**

Note. Partial correlations controlling for age and sex. * < .05; ** < .01, *** < .001. Partial correlation for age was corrected for sex. All significance indicators reflect Benjamini-Hochberg corrected values. BP refers to blood pressure, HDL refers to high-density lipoprotein and LDL refers to low-density lipoprotein.

Conclusions

- Blast, particularly close blast, is associated with chronic alterations in inflammation and glial degeneration.
  - Chronic decreases in GFAP, maybe indicating a downregulation of astrocyte function, is associated with blast-related TBI and close blast.
  - Increased systemic inflammation was associated with close blast, indicating that close blast exposure may lead to Chronic elevations in multiple markers of inflammation.
- Inflammatory markers and GFAP were associated with psychological and health comorbidities.
  - Increased inflammation and decreased GFAP was associated with higher levels of severity in several psychological disorders and metabolic variables.

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ARTICLE

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The association between blast exposure and transdiagnostic health symptoms on systemic inflammation

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Study Aims

Inflammation is observed in a wide variety of physiological and psychological conditions.

Given that post-9/11 veterans have a high rate of comorbidities, particularly in our sample, they might be vulnerable to the negative long-term effects of inflammation.

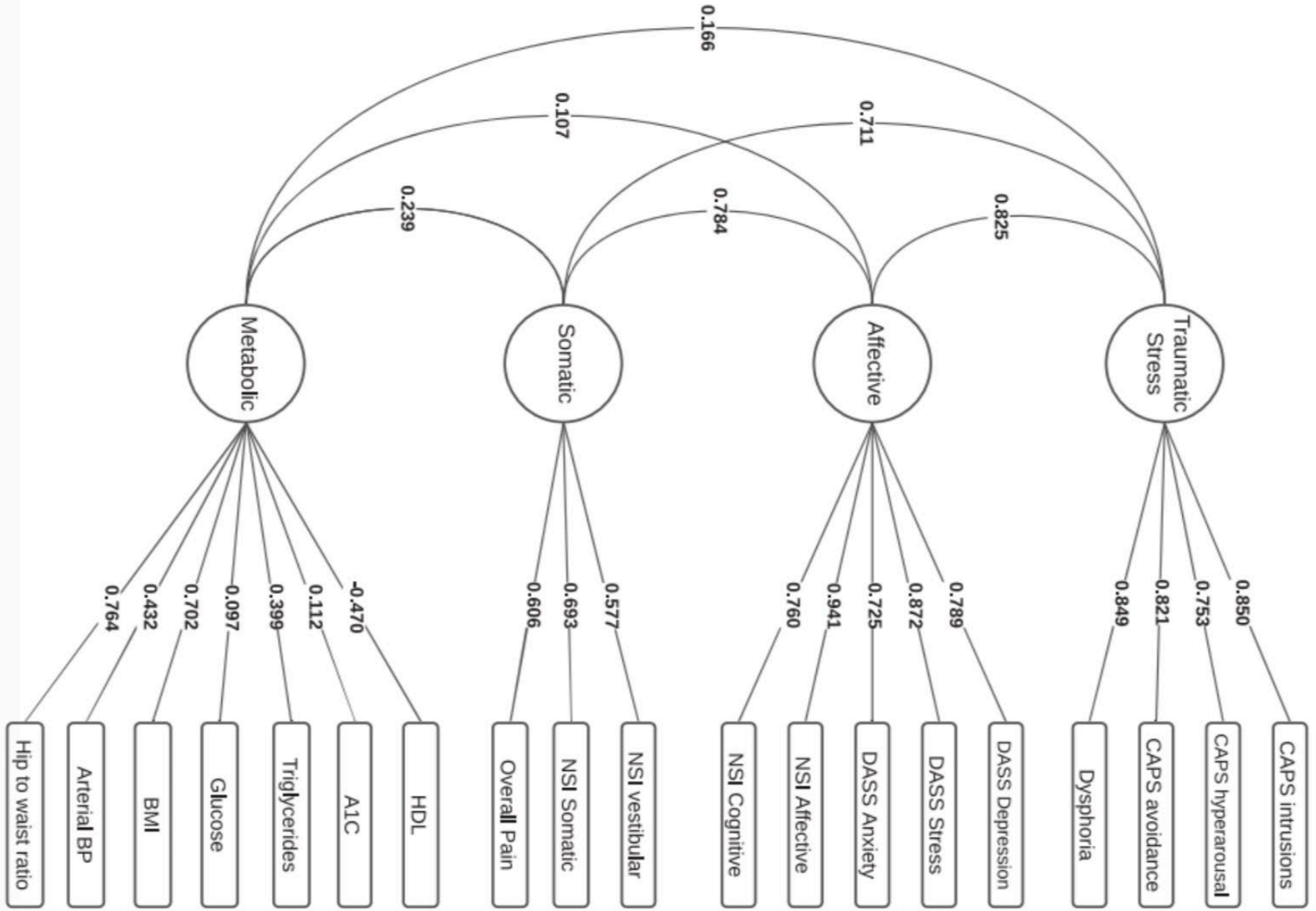
We examined if mTBI or blast exposure moderated the relationships between inflammation and psychological and physical health symptoms.

Transdiagnostic Factors Associated with Deployment Trauma

Previous research from TRACTS utilized factor analysis to create empirically derived clinical components consisting of psychological disorders and mTBI (Lippa et al., 2015; Amick et al., 2018; Esterman et al., 2019).

We sought to expand upon this previous research by including metabolic health symptoms.

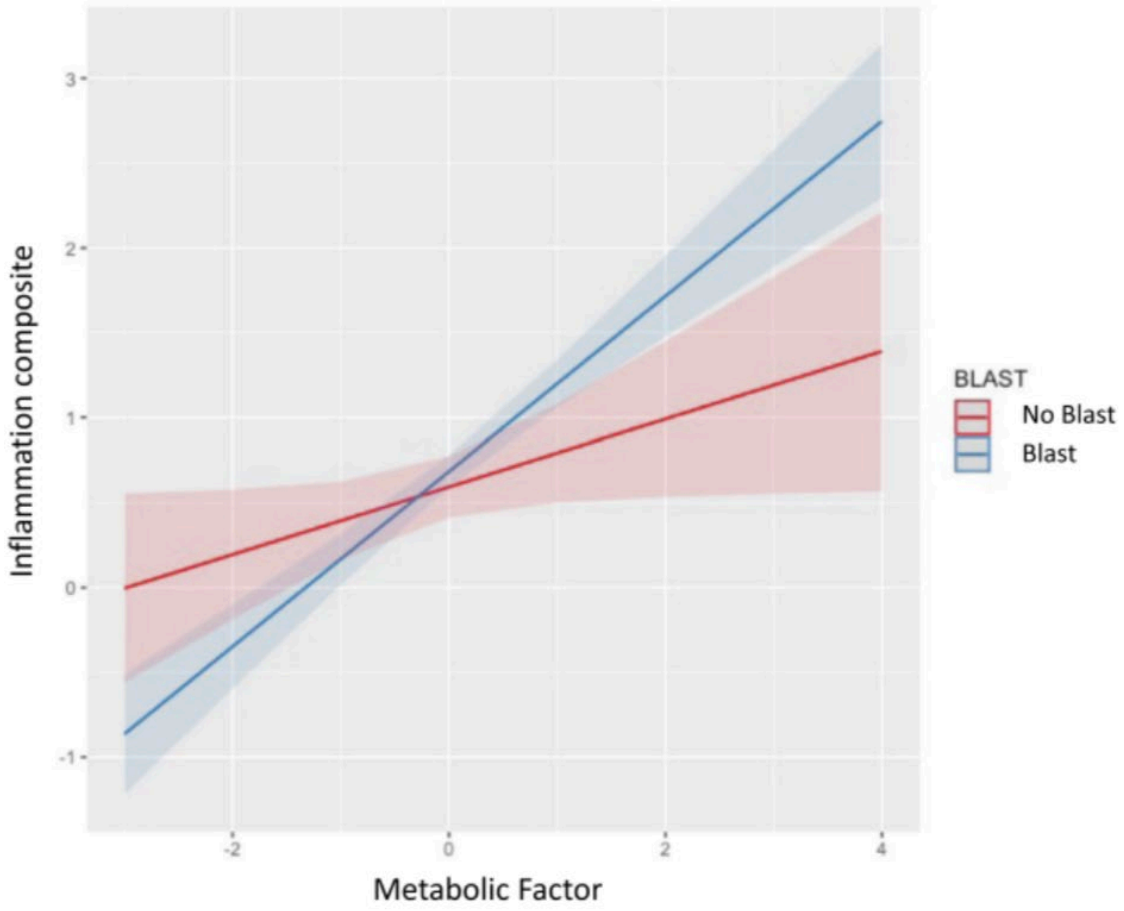
We conducted a confirmatory factor analysis to examine model strength using factors of Traumatic Stress, Affective, Somatic, and Metabolic symptoms.



Transdiagnostic Symptom Latent Model

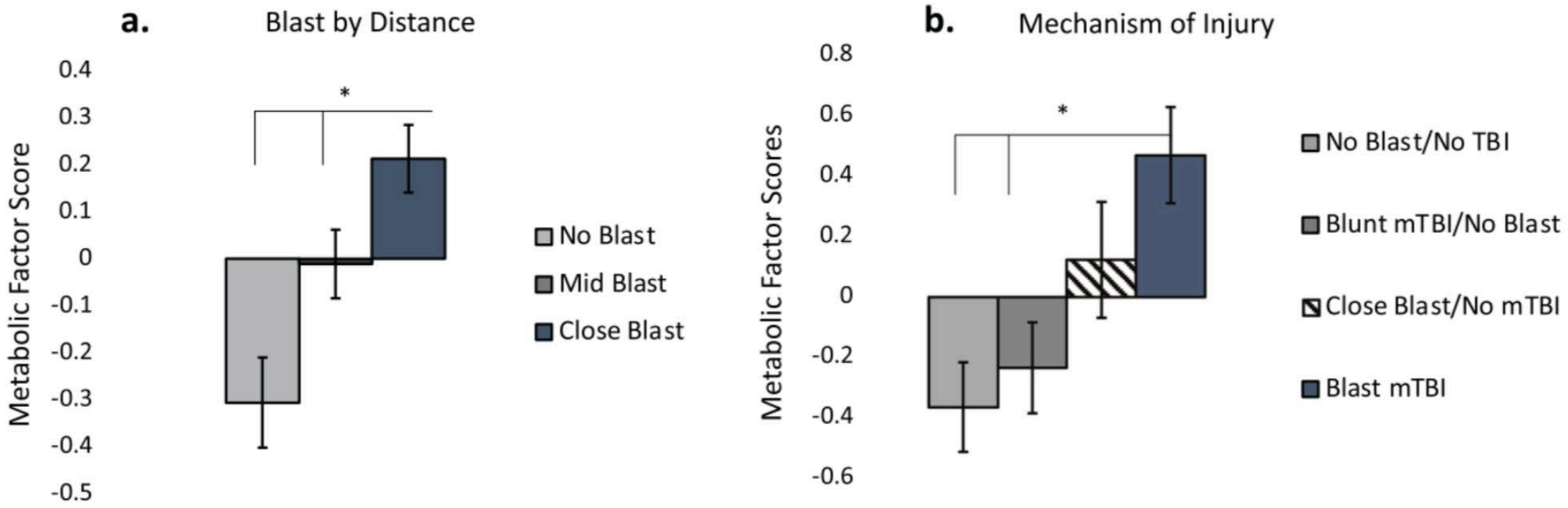
- Good model fit
- CFI = 0.96, TLI = 0.95, SRMR = 0.04, RMSEA = 0.52
- Each latent variable was associated with indicator variables $p < .001$
- Standardized betas ranged from -.471 to .937

	Metabolic					
Step 1: Age	0.046	0.385	0.385	0.046	0.385	0.385
Step 2: Metabolic	0.418	<0.001*	<0.001*	0.424	<0.001*	<0.001*
Step 2: Blast/mTBI	0.016	0.747	0.747	−0.065	0.185	0.613
Step 3: Metabolic × Blast/mTBI	0.268	0.005*	0.040*	0.126	0.162	0.259



- There were main effects observed for Traumatic Stress, Affective, Somatic, and Metabolic.
- mTBI did not moderate the relationship between the transdiagnostic factors and inflammation.
- Blast moderated the relationship between Metabolic factor and inflammation.

Metabolic Symptom Severity by Blast and Mechanism of Injury



Conclusions

- The strongest relationship with inflammation was among those exposed to blast and had metabolic dysregulation.
- Blast exposure was associated with metabolic dysregulation in a dose response manner.
- This provides a greater understanding of the health pathways that link blast injury to systemic inflammation.

Thank you!

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