

The Long Reach of Blast: Leaky Gut as a Persistent Biomarker of Blast-Related TBI Years After Military Service in Veterans

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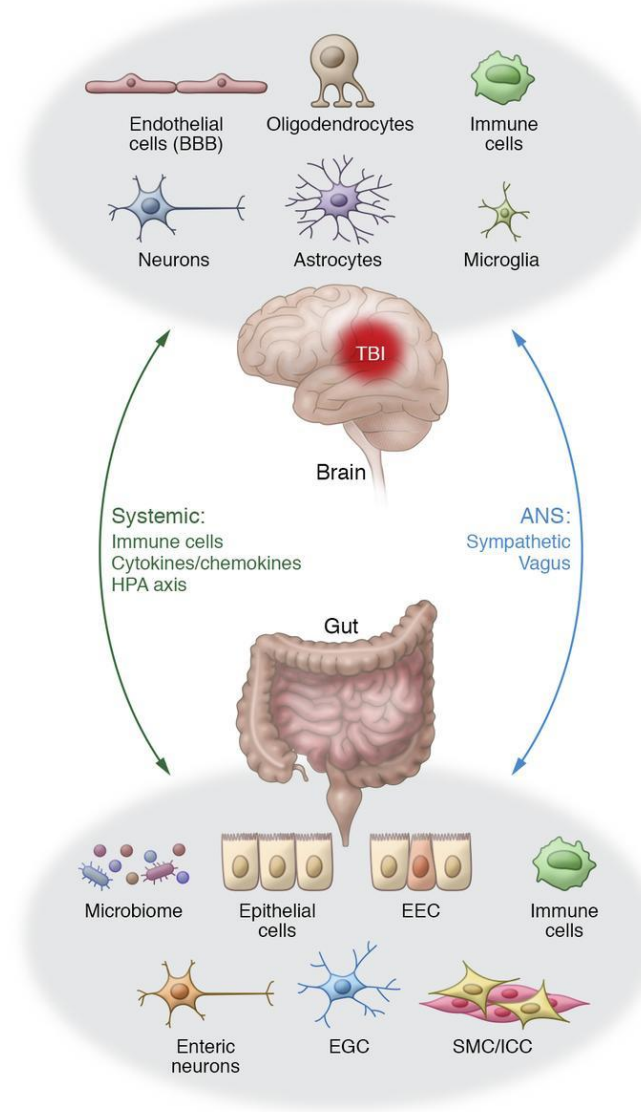
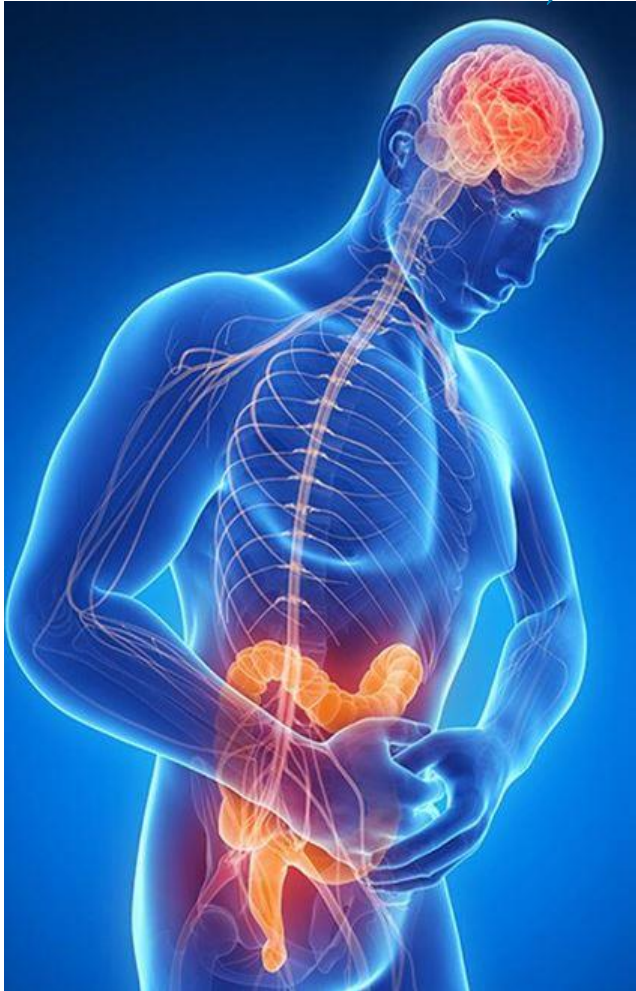


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- Dr. Haghighi has no relevant financial relationships with ineligible companies to disclose.
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TBI induced intestinal dysfunction

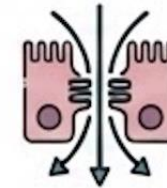
TBI



Intestinal dysfunctions induced by TBI:



Disruptions in gastrointestinal motility



Increase of gut permeability



Alteration of gut metabolites and microbiome

Sun, Y. et al., 2023.

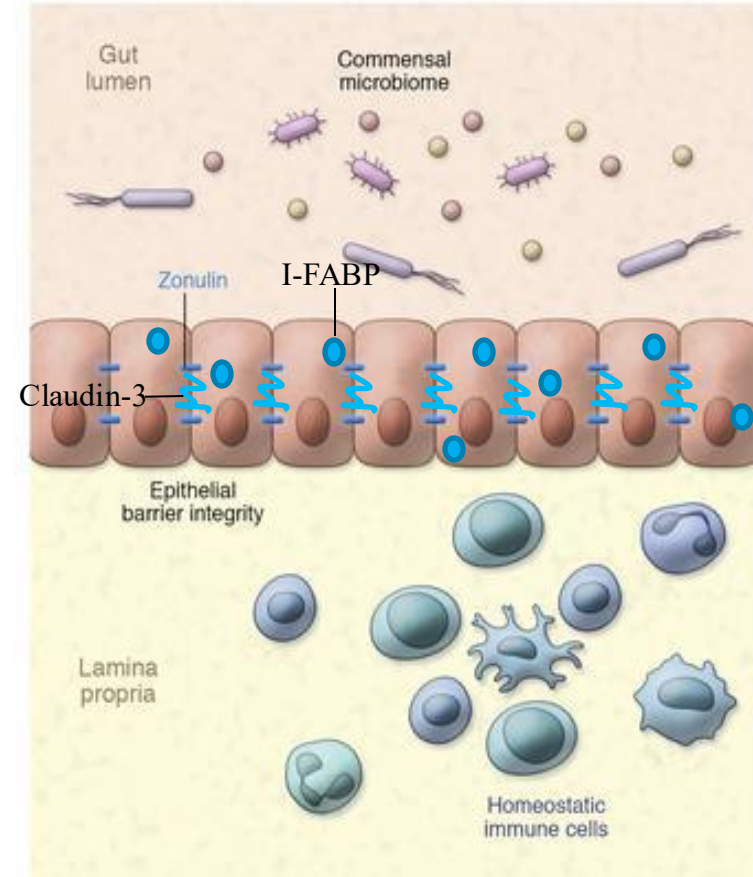
Rice MW, Pandya JD and Shear DA. 2019.

Schouten JW. 2007

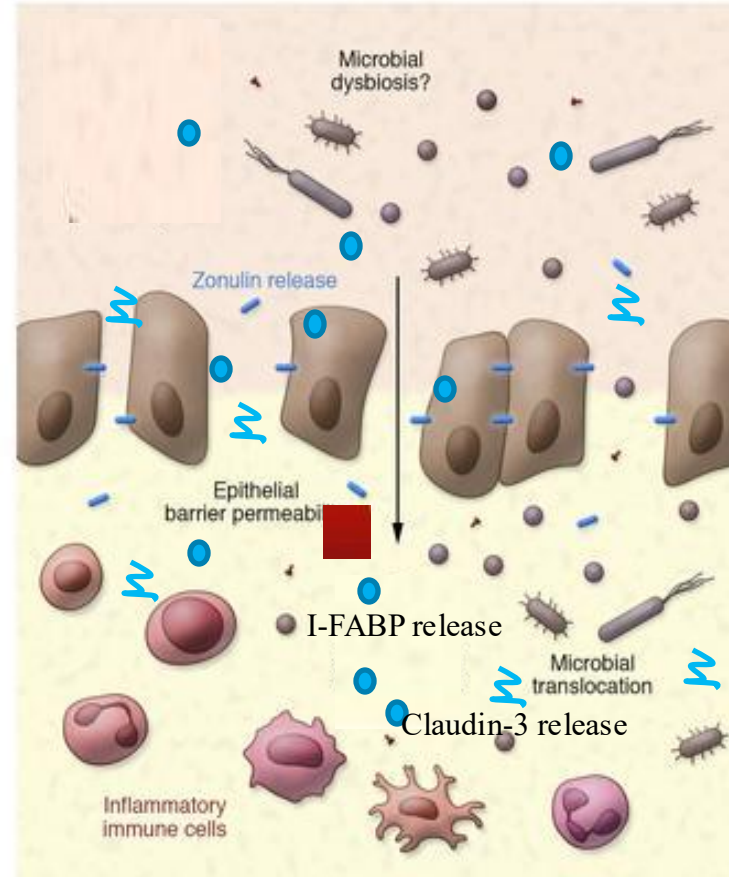
Hanscom M, Loane DJ, Shea-Donohue T. Brain-gut axis dysfunction in the pathogenesis of traumatic brain injury. J Clin Invest. 2021 Jun 15;131(12):e143777. doi: 10.1172/JCI143777. PMID: 34128471; PMCID: PMC8203445.

Schematic of Leaky Gut and Intestinal Permeability (IP) Biomarkers

Normal Gut

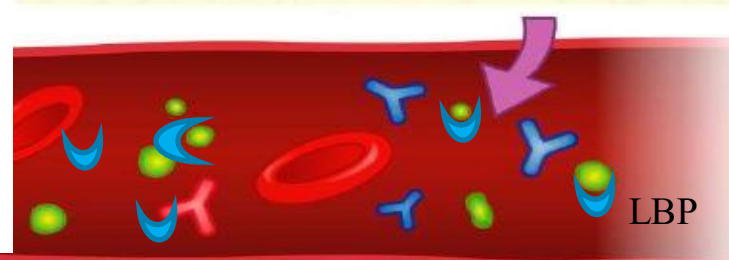


Leaky Gut



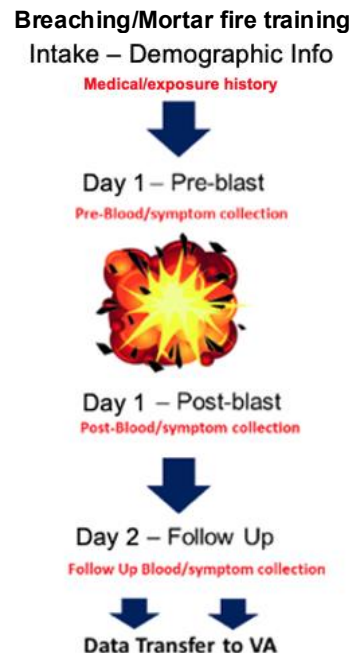
Leaky gut is associated with;

1. Release of Zonulin
2. claudin-3
3. Intestinal fatty acid binding protein (I-FABP)
4. Binding of Lipopolysaccharide binding protein (LBP) with LPS in blood stream

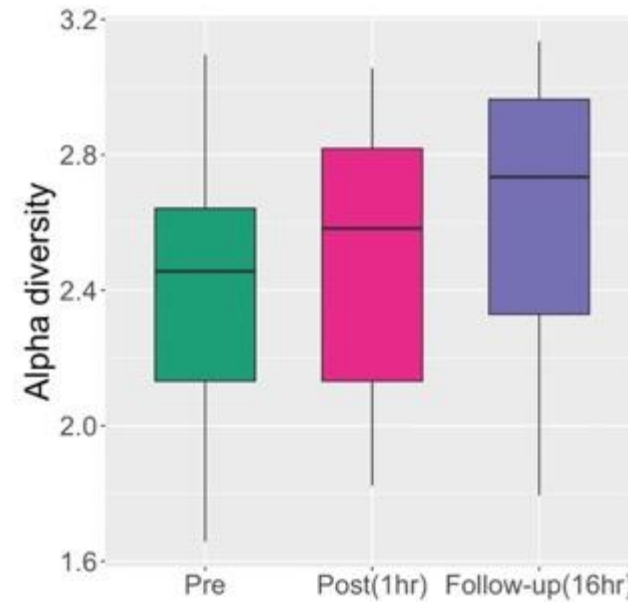
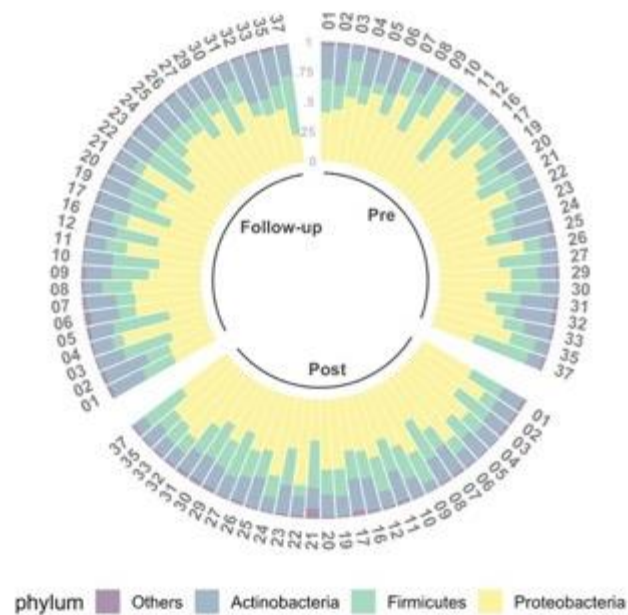


Blast-Induced Intestinal Permeability

- Blast injuries and subclinical effects are of significant concern in military operations and tactical training.
- Injuries and subclinical effects from exposure to low-level blasts are associated with transient concussion-like symptomology, and alterations in blood intestinal permeability biomarkers
- ***Our recent findings in Active-Duty Warfighters indicate blast impacts intestinal permeability.***

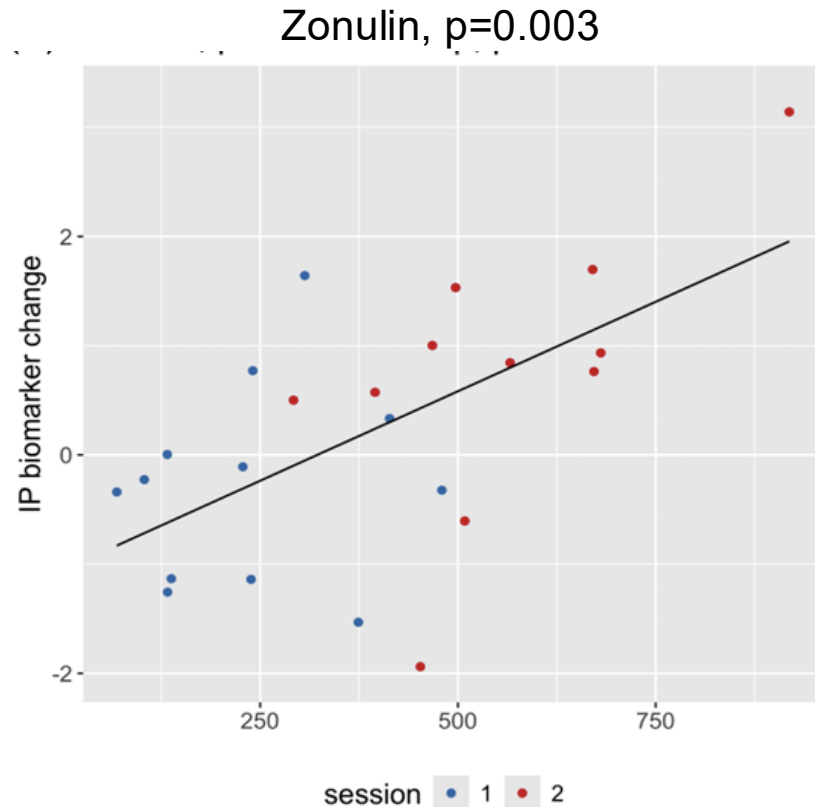


Warfighters: Blast Exposure from Heavy-wall breaching Associates with Bacterial Translocation During Tactical Training

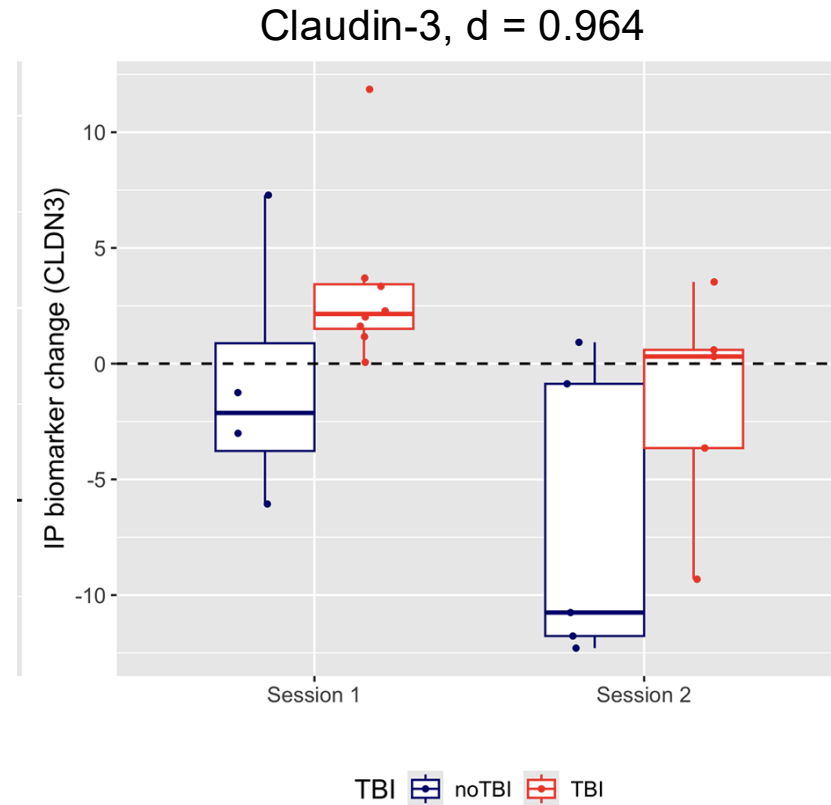


- Detected bacterial translocation into circulation using RNA sequencing data mapped to bacterial genomes.
- Abundance of the microbial communities within each sample, referred to as alpha diversity, showed significant stepwise increase following blast exposure.

Warfighters: Blast exposure confers changes in clinically validated IP blood biomarkers during mortar fire tactical training operations

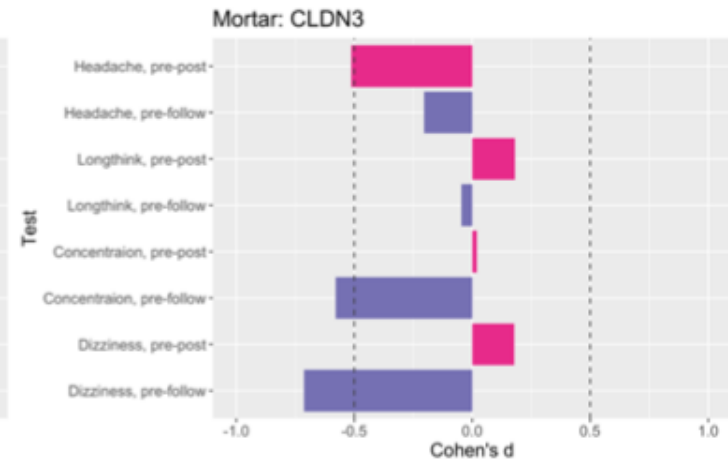
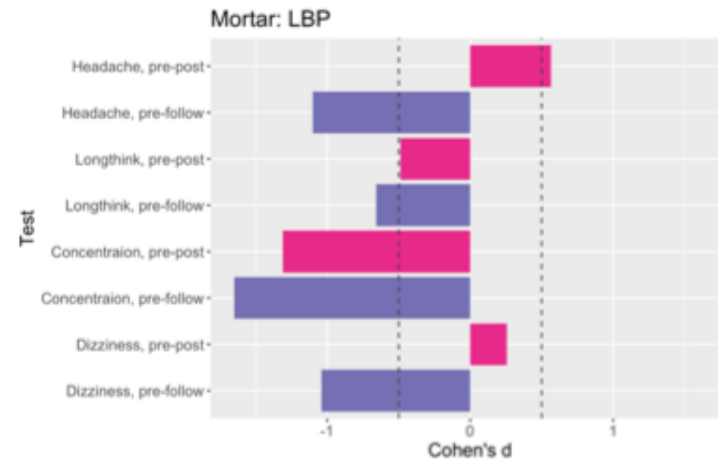
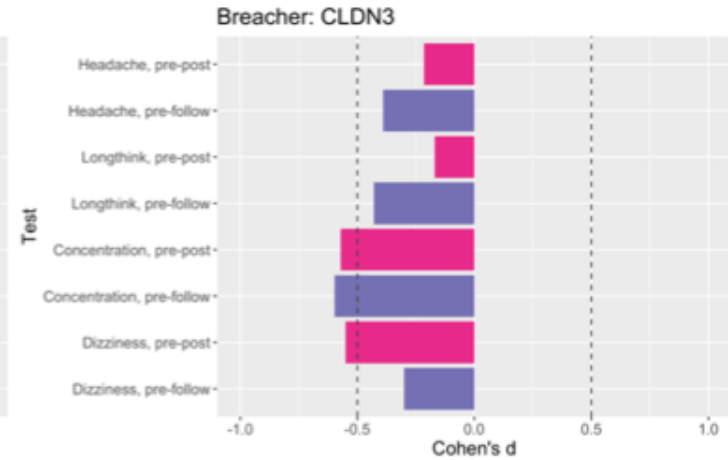
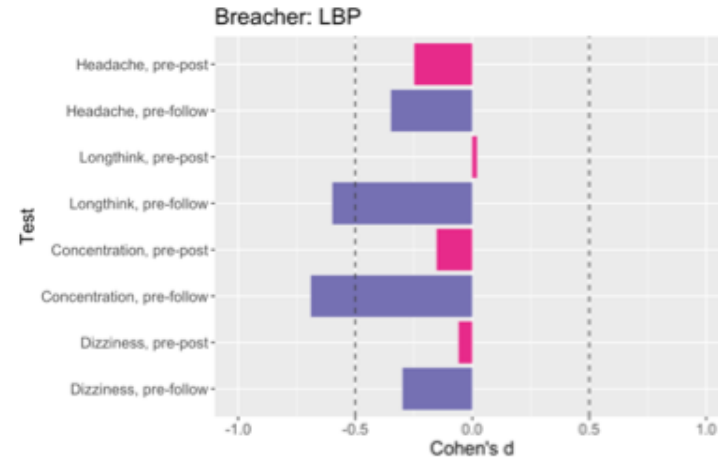
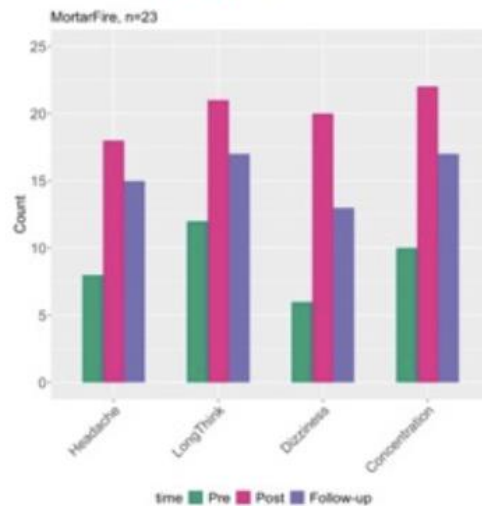
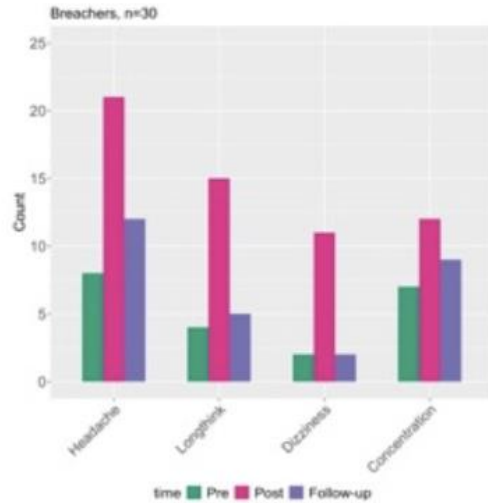


- Greater blast exposure is associated with larger cumulative changes in Zonulin across sessions 1 and 2.



- Warfighters with prior mTBI show greater blast-related increases in Claudin-3 than those without prior mTBI

Association of IP Biomarkers With Symptom Reporting After Blast Exposure



Time Pre-Post Pre-Follow

Veterans: Study Design

Participants: Blast-exposed Veterans with mild traumatic brain injury (N=140)

Blast and Combat Exposure Measures:

- BOOM: Blast Ordinance and Occupational Exposure Measure³
- Combat Exposure Scale (CES)

Clinical Measures:

- TBI history (OSU-TBI)
- Beck Depression Inventory (BDI)
- Beck Anxiety Inventory (BAI)
- PTSD Checklist for DSM-V (PCL-5)
- Insomnia Severity Index (ISI)
- Headache Impact Test (HIT)
- Epworth Sleepiness Scale (ESS)

- Tinnitus Handicap Inventory (THI)
- PROMIS Fatigue Scale (PROMIS)
- Pittsburgh Sleep Quality Index (PSQI)
- The Neurobehavioral Symptom Inventory (NSI)

Intestinal Permeability (IP) Measure: Using blood plasma collected from Veteran participants, Zonulin levels (an IP biomarker) were measured via ELISA: MyBiosource (catalog #MBS706368).

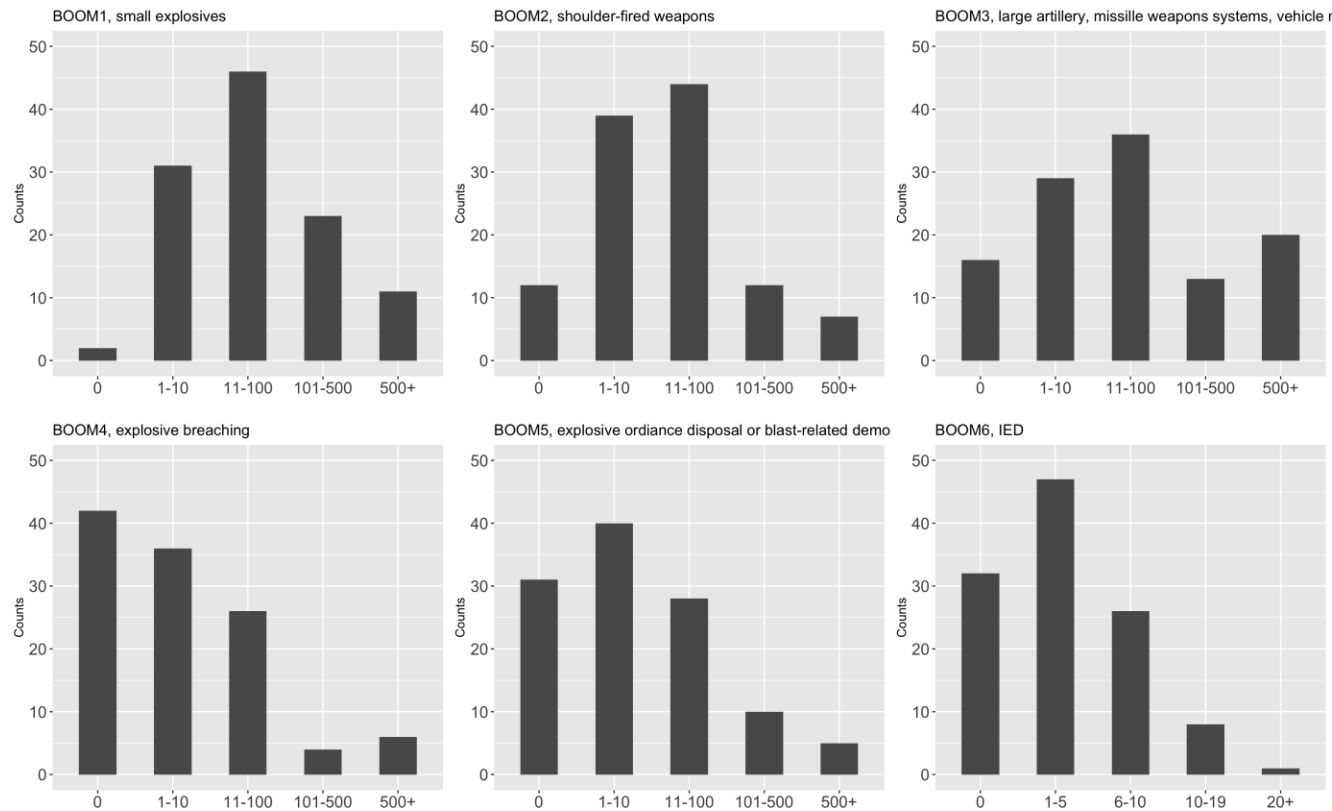
Data & Statistical Analyses: All analysis were performed in R 4.4.0. Effect size was calculated using R package *effsize*.

Demographics of Veteran Participants

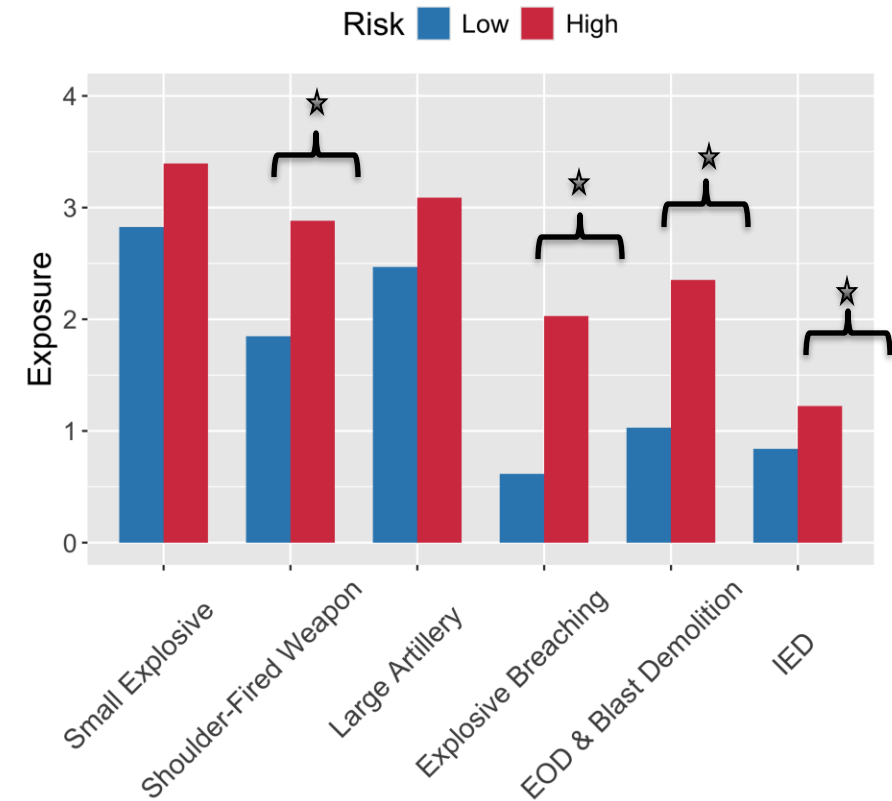
N	140
Age	45.1 +/- 9.1
Sex	
Male	130
Female	10
Service duration (months)	116.4+/-91.0
MOS Risk group	
Low	43
High	94
Branch	
Army	92
Marine	23
Air	14
Navy	11

Veterans: Blast Exposure Measured by Blast Ordinance and Occupational Exposure Measure (BOOM)

- BOOM: short self-report inventory developed with participation and feedback of clinical experts and service members to quantify lifetime blast exposures across various weapon systems.

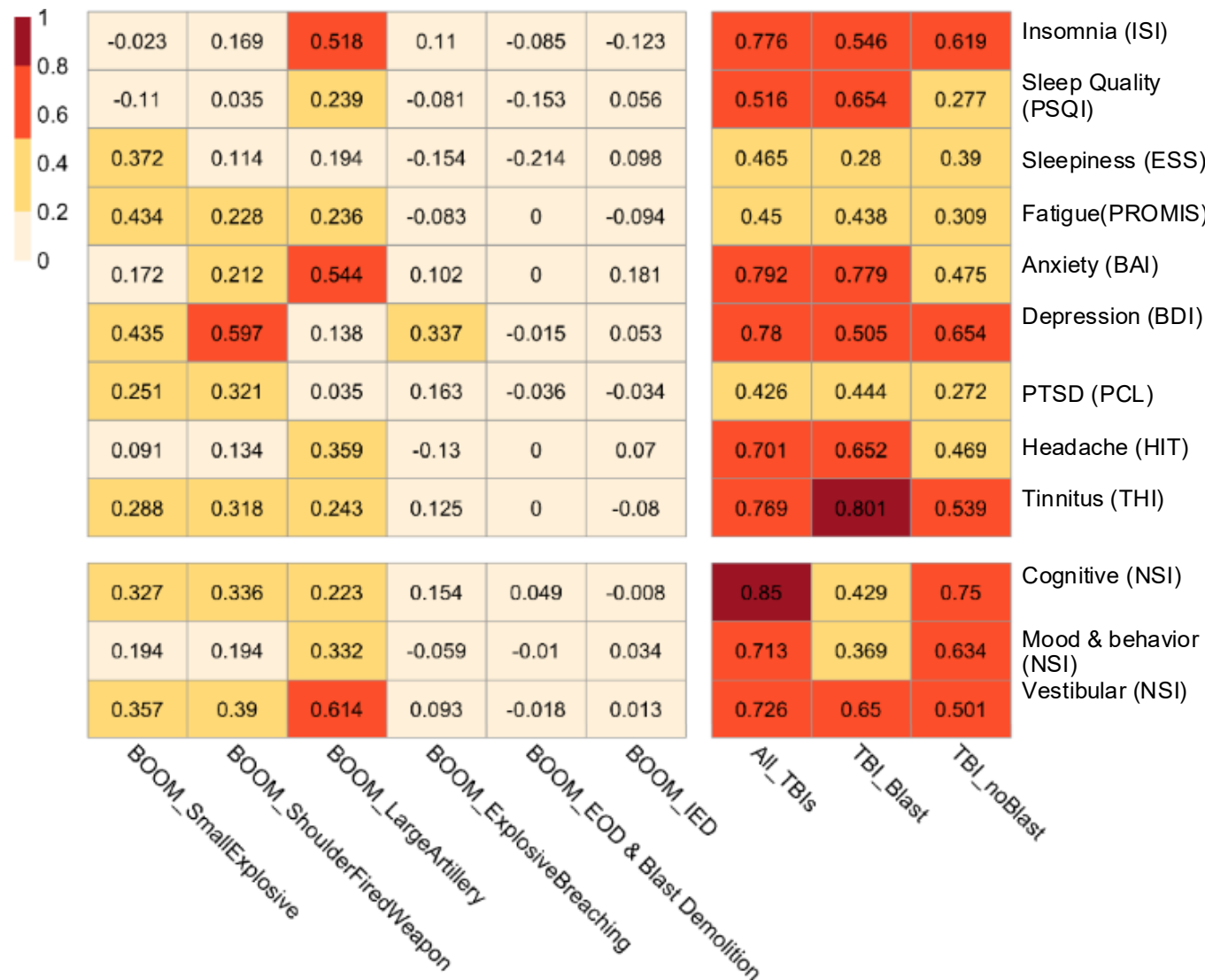


Distribution of self-reported blast exposure by weapons system.



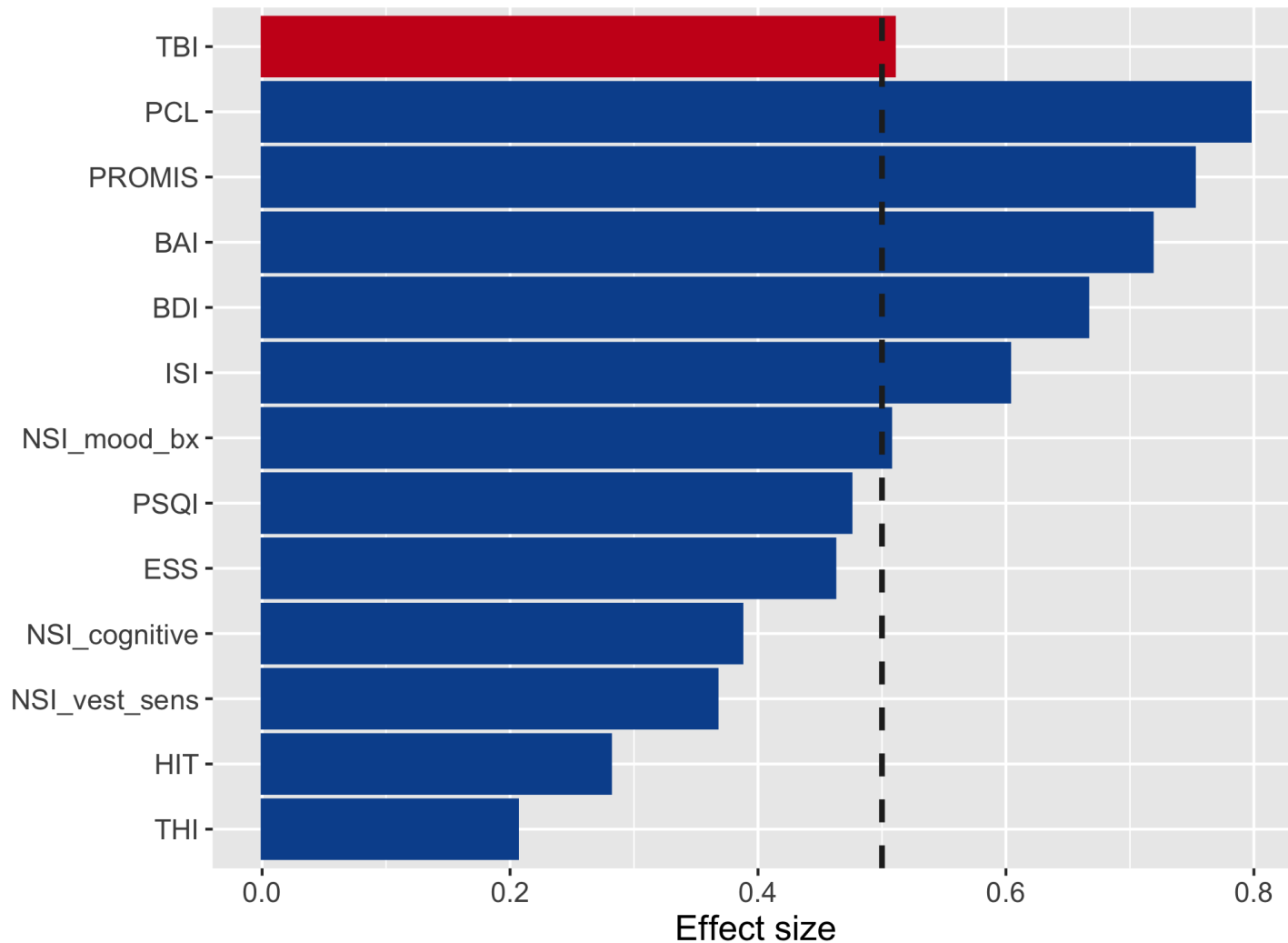
Distribution by weapon system in low vs high blast risk Military Occupational Specialty (MOS) with significant differences denoted by a star.

Veterans: Association of Blast and TBI with Clinical Symptoms



- Veterans with clinically significant anxiety and insomnia as well as higher neurological symptoms (i.e. vestibular and balance) endorse higher exposure to large artillery weapons systems, with moderate effect size, $d > 0.5$.
- Veterans with clinically significant depression symptoms endorse higher exposure to shoulder fired weapons, with moderate effect size, $d = 0.6$.
- In Veterans, history of TBI was associated with higher clinically significant anxiety, depression, sleep disturbance, pain, fatigue, and neurological symptoms.

Veterans: Association of IP (Zonulin) levels with Clinical Symptoms



- Effect sizes are provided for differences from comparisons of clinically significant vs. non-clinically significant groups (high vs. low groups, respectively)
- Higher IP (Zonulin) levels were observed in Veterans with clinically significant symptoms of insomnia, depression, anxiety, fatigue, and PTSD with moderate effect sizes
- IP (Zonulin) levels correlated with number of TBI (lifetime), and elevated neurological symptoms (NSI mood and behavior subscale) with moderate effect sizes

Conclusions

- In active-duty Warfighters exposed to blast during tactical trainings we found:
 - Acute changes in IP biomarker levels (Zonulin, LBP, Claudin-3, and I-FABP) 1 to 16 hours following blast exposure.
 - Transient increases in blast induced neurotrauma symptoms that also significantly associated with alteration in IP biomarker levels.
- In Veterans with chronic exposures to blast and mild TBI we found:
 - Chronically blast exposure across range of weapon systems were associated with worsening clinical symptoms (e.g., Insomnia, Depression, Anxiety, Neurological symptoms).
 - Chronically increase levels of IP biomarker (Zonulin) was higher in Veterans with clinically significant symptoms (i.e., PTSD, Anxiety, Depression, Insomnia, Fatigue, Neurological Symptoms)
- Study findings demonstrate that blast impacts gut permeability, underscoring the importance of investigating the role of gut-brain axis in blast injury, with broad therapeutic implications in how clinical symptoms associated with blast can be treated through the use of pre and/or probiotic interventions.

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