



Evaluating Sex Differences in Neuroendocrine Responses to Traumatic Brain Injury in Active-Duty Service Members: A NEXUS Study

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INTRODUCTION

- Among military personnel, Psychological Health (PH) symptoms disproportionately effect woman.
- Sex may be a risk factor for post-traumatic stress disorder (PTSD) among active-duty servicemembers.
- Allostatic burden (AlloB), a physiological and psychological index of chronic stress, may contribute to PH and PTSD.
- It remains unclear whether sex and allostatic load relate to PTSD and PH outcomes within the military population.

HYPOTHESIS

Sex is a determinant of AlloB and PH symptoms among active-duty personnel.

OBJECTIVE

Compare PH (PTSD, Anxiety, Depression) along with AlloB (stress and resilience measures) and examine the relationships between TBI, allostatic load, and PH.

METHODS

N=560 active-duty personnel (290 male, 270 female) were enrolled and screened for PH and AlloB using the following self reported metrics:

- PH
 - Generalized Anxiety Disorder-7 (GAD-7)
 - Patient Health Questionnaire-9 (PHQ-9)
 - Post-Traumatic Stress Disorder Checklist-5 (PCL-5)
- AlloB
 - Combat Exposure (CES)
 - Trauma History Screen (THS)
 - Adverse Childhood Experiences (ACEs)

Serum cortisol (CORT) was also measured by ELISA following manufacturers protocol (Calbiotech)

STATISTICAL ANALYSIS

- Participants were grouped into AlloB clusters (Resilient, Vulnerable) using k-means clustering using FSSQ, CD-RISC-25, PSS-10, and UCLA-LS scores.
- Multivariable linear regression was used to examine associations between time-adjusted cortisol and four psychological outcomes (GAD-7, PHQ-9, PCL-5, NSI) in active-duty service members, adjusting for age, sex, cluster group, ACE, CES, and TBI exposure.
- To evaluate sex differences in neuroendocrine response, primary interaction models tested cortisol by sex, sex by age, and cortisol by AlloB cluster.
- Additional moderating effects, including ACE, CES, and service associated TBI history, were also explored.
- Significance was set at $p < 0.05$.

RESULTS

- Women have significantly higher scores for anxiety (GAD-7), depression (PHQ-9), and traumatic stress (PCL-5) compared to men when adjusting for covariates (**Figure 1**).
- AlloB cluster moderated the CORT-symptom relationship for GAD-7 ($p=0.045$) and PHQ-9 ($p=0.009$) (**Figure 2**).
 - In the **Resilient** group, higher CORT was linked to lower symptoms.
 - In the **Vulnerable** group, higher CORT was linked to higher symptoms.
- After adjusting for covariates, women showed significantly higher symptom scores than men across GAD-7 ($p=0.002$), PHQ-9 ($p=0.042$), and PCL-5 ($p<0.0001$) (**Figure 3**).
- Cluster also moderated the effect of CES on PHQ-9 ($p=0.031$) and PCL-5 ($p=0.024$) and there was a trend-level association with GAD-7 scores ($p=0.060$).
 - In the **Resilient** group, higher CES was associated with more symptoms.
 - In the **Vulnerable** group, CES had little effect on symptoms.

Figure 1. Multivariable regression adjusted for demographics, cortisol, and trauma-related variables.

Bold = $p < 0.05$ *Italics = $p > 0.05$*

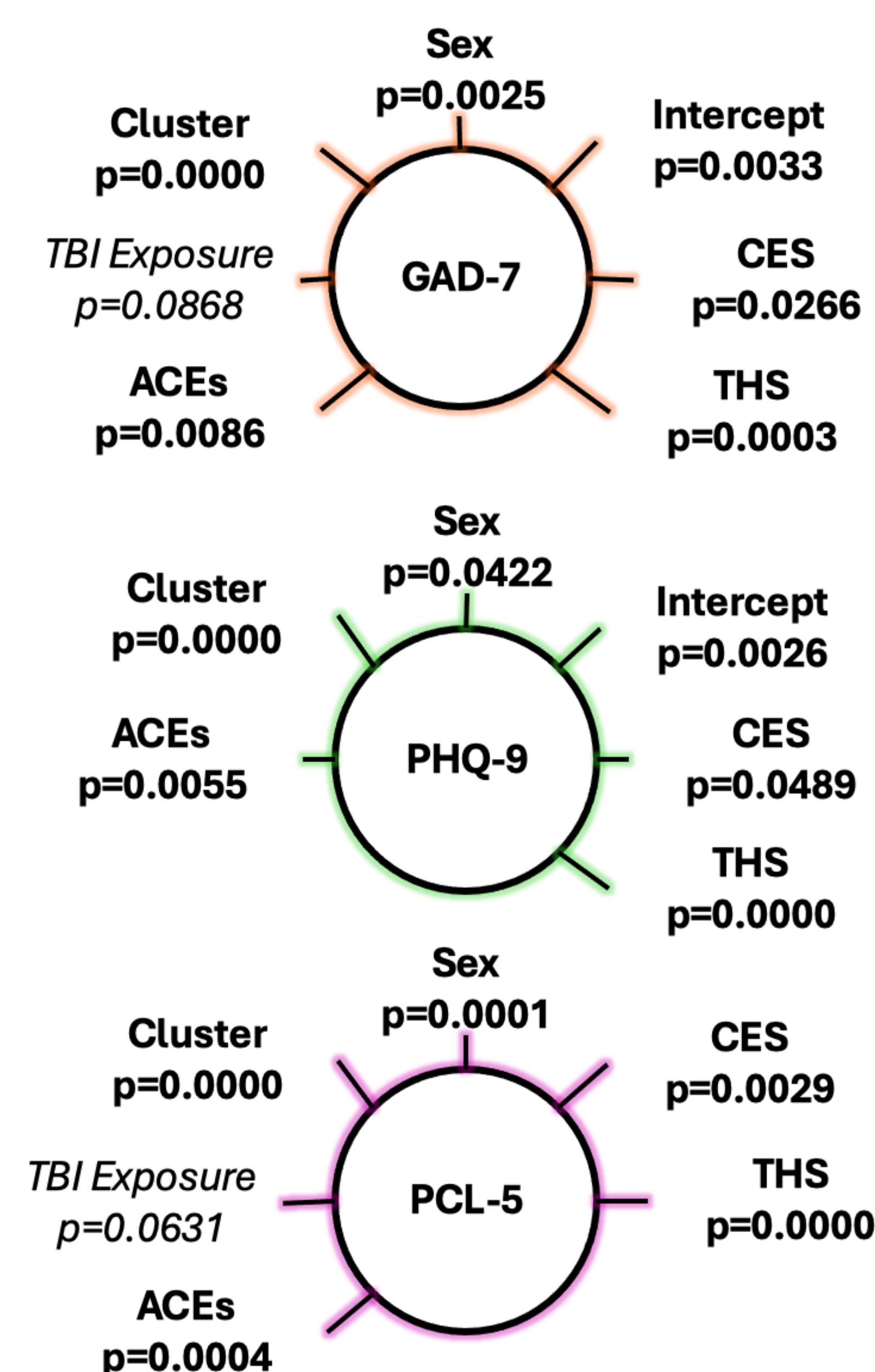


Figure 2. Covariate-Adjusted Regression: Cortisol by Allostatic Burden Moderation

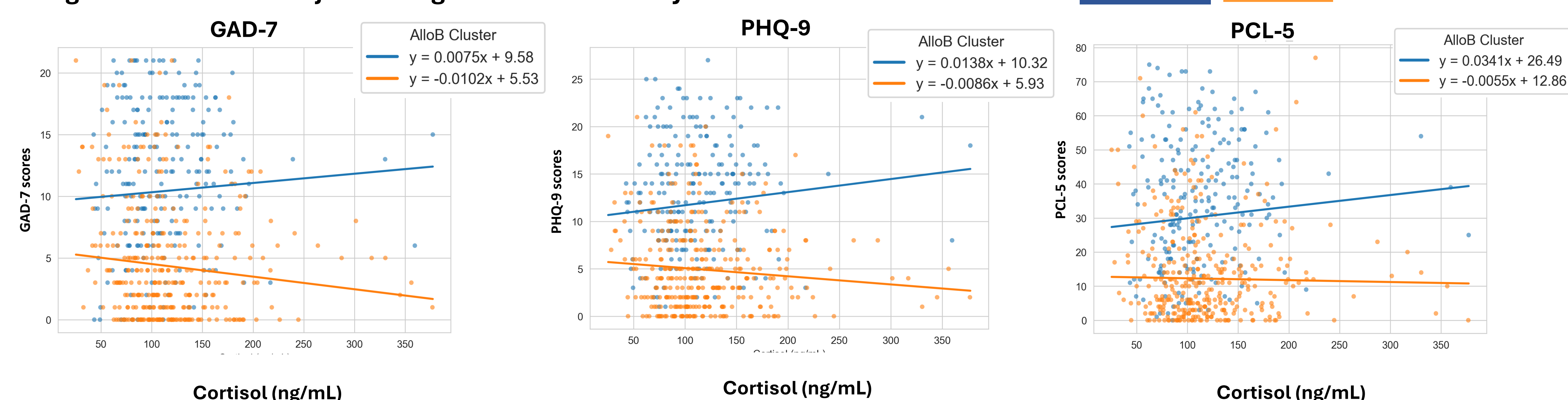
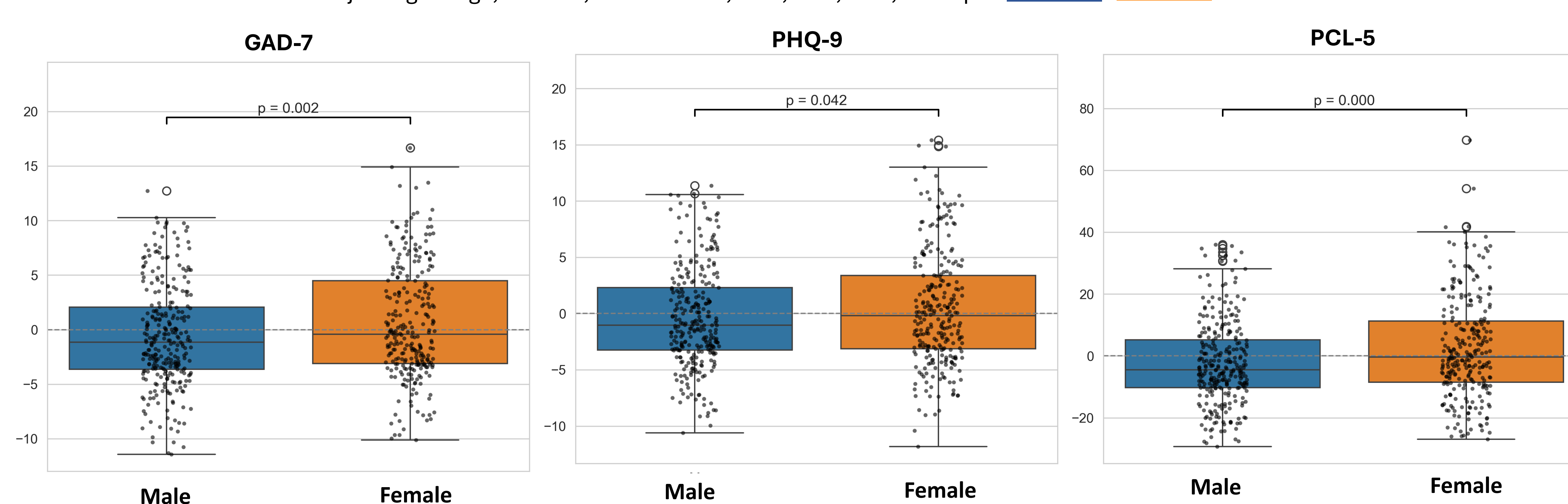


Figure 3. Covariate-adjusted differences in outcomes by sex

Y-axis = Total residuals after adjusting for age, cortisol, AlloB cluster, ACE, THS, CES, TBI exposure



CONCLUSIONS

- Defining AlloB based on social support (FSSQ), resilience (CD-RISC-25), stress (PSS-10) loneliness (UCLA-LS), enables characterization of vulnerability and resilience among active-duty personnel.
- Multiple factors underlying differences in PH and AlloB measures were supported including:
 - PH symptoms were higher in females and moderated by age, suggesting that younger woman may be at greater risk.
 - CORT was associated with PH symptoms irrespective of sex and age.
- Further research investigation is warranted to understand the biological interactions between age, sex and TBI in relation to AlloB and PH.

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