

# Prognostic Indicators of Persistent Post-Concussive Symptoms after Deployment-Related Mild Traumatic Brain Injury: A Prospective Longitudinal Study in U.S. Army Soldiers

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## Abstract

Mild traumatic brain injury (mTBI), or concussion, is prevalent in the military. The course of recovery can be highly variable. This study investigates whether deployment-acquired mTBI is associated with subsequent presence and severity of post-concussive symptoms (PCS) and identifies predictors of persistent PCS among US Army personnel who sustained mTBI while deployed to Afghanistan. We used data from a prospective longitudinal survey of soldiers assessed 1–2 months before a 10-month deployment to Afghanistan (T0), on redeployment to the United States (T1), approximately 3 months later (T2), and approximately 9 months later (T3). Outcomes of interest were PCS at T2 and T3. Predictors considered were: sociodemographic factors, number of previous deployments, pre-deployment mental health and TBI history, and mTBI and other military-related stress during the index deployment. The study sample comprised 4518 soldiers, 822 (18.2%) of whom experienced mTBI during the index deployment. After adjusting for demographic, clinical, and deployment-related factors, deployment-acquired mTBI was associated with nearly triple the risk of reporting any PCS and with increased severity of PCS when symptoms were present. Among those who sustained mTBI, severity of PCS at follow-up was associated with history of pre-deployment TBI(s), pre-deployment psychological distress, more severe deployment stress, and loss of consciousness or lapse of memory (versus being “dazed” only) as a result of deployment-acquired mTBI. In summary, we found that sustaining mTBI increases risk for persistent PCS. Previous TBI(s), pre-deployment psychological distress, severe deployment stress, and loss of consciousness or lapse of memory resulting from mTBI(s) are prognostic indicators of persistent PCS after an index mTBI. These observations may have actionable implications for prevention of chronic sequelae of mTBI in the military and other settings.

**Key words:** concussion; deployment; mental health; military; stress; traumatic brain injury

## Introduction

MILD TRAUMATIC BRAIN INJURY (mTBI) or concussion, previously believed to be an almost uniformly benign and reversible event, is increasingly recognized as a prelude to adverse functional outcomes in a subset of individuals.<sup>1–4</sup> Although most persons who sustain mTBI recover within days to weeks with no sequelae, a sub-

group of approximately 5% of individuals experiences persistent post-concussive symptoms (PCS) such as headaches, light or noise sensitivity, dizziness, sleep problems, concentration or memory problems, fatigue, irritability, and other somatic, cognitive, and affective symptoms.<sup>5</sup> Establishing prognostic indicators of PCS and other outcomes of mTBI is critical for research efforts to test preventive interventions and, ultimately, to identify best practices for clinical care.<sup>4</sup>

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Several studies have examined predictors of persistent PCS. One study of patients admitted to a level 1 trauma center examined 3-month outcomes of 62 patients whose traumatic injury included mTBI and 58 patients whose traumatic injury did not include TBI.<sup>6</sup> The mTBI did not predict persistent PCS, whereas female sex and pre-injury depressive or anxiety disorders did. Another study of emergency department patients evaluated 3-month outcomes of 123 patients who sustained mTBI and 100 control patients whose injury did not involve TBI. Again, female sex and pre-morbid psychiatric illness were predictive of PCS whereas mTBI was not.<sup>7</sup> The failure of mTBI to predict PCS in some studies raises questions about the specificity of PCS symptoms to the post-concussion state, or whether these symptoms are entirely nonspecific in nature.

In the military, there have also been questions about whether persistent PCS should be considered a consequence of mTBI or a by-product of other factors. A cross-sectional study of United Kingdom (UK) military personnel found that whereas self-reported mTBI was related to subsequent PCS, self-reported exposure to other factors (e.g., depleted uranium; helping the wounded) were just as likely to be associated.<sup>8</sup> More recently, a study of Canadian military personnel similarly failed to find an association between mTBI and PCS (after adjusting for confounders) approximately 4 months later.<sup>9</sup>

A United States (US) military study in polytrauma patients concluded that emotional distress—but not injury-related factors—was uniquely predictive of persistent PCS; this study, however, was not able to assess the impact of pre-injury characteristics.<sup>10</sup> A recent systematic review of predictors of mTBI outcomes emphasizes the prognostic value of pre-injury mental health and early post-injury psychological symptoms (e.g., anxiety).<sup>11</sup>

In the present study, we use data from a large, prospective study of US Army soldiers to examine the association between deployment-related mTBI and persistent PCS approximately 3- and 9- months later. We use pre-deployment (i.e., sociodemographic factors, mental health status), and deployment-related (self-reported mTBI; severity of mTBI based on whether the individual lost consciousness or was only dazed; extent of exposure to combat stress) information, based on the extant literature, to develop predictive models for PCS at both follow-up time points.

We did not include in the models information about other post-deployment disorders (e.g., post-traumatic stress disorder [PTSD] or major depressive episode [MDE]) because it has already been well established that there is considerable cross-sectional overlap between the various symptom domains,<sup>12,13</sup> and our goal here was to predict PCS on the basis of pre-deployment and deployment-related factors, not concurrent symptomatology. We did, however, also evaluate models among soldiers without concurrent post-deployment MDE or PTSD to determine whether predictors of PCS were the same/similar in the absence of these disorders.

## Methods

### *Overview of the Pre/Post Deployment Study (PPDS) of the Army Study to Assess Risk and Resilience in Servicemembers (Army STARRS)*

Detailed information about the design and conduct of Army STARRS is available in a separate report.<sup>14</sup> The PPDS of Army STARRS is a multiwave panel survey that collected baseline data (T0; self-administered questionnaire [SAQ]) from US Army soldiers in three brigade combat teams (BCTs) during the first quarter of 2012, within approximately 6 weeks of their deployment to Afghanistan. Follow-up data collections for these same respon-

dents were available for this report at three times after they returned from deployment: within 1 month of their return (T1; SAQ and blood samples), and then approximately 3 months (T2; SAQ), and 9 months (T3; SAQ) later.

The baseline (T0) SAQ was an extensive survey of socio-demographic characteristics, lifetime and past-30-day mental disorders, and additional other potential risk and resilience factors including but not limited to past civilian and military experiences. The T1 follow-up SAQ included only a brief assessment of experiences that occurred during deployment (including deployment stressors and TBI). The T2 and T3 SAQ, which were virtually identical, covered mainly subsequent experiences such as post-concussive and other symptoms.

### *Participants*

The PPDS study population consisted of all soldiers in three BCTs whose members deployed to Afghanistan (average duration of deployment was 10 months) shortly after completing the baseline (T0) PPDS data collection. All participants gave their informed, written consent to participate. These procedures were approved by the Human Subjects Committees of all collaborating organizations. At the baseline (T0), a total of 9949 soldiers were present for duty in the three BCTs. Of these, 9488 (95.3%) consented to participate in the survey with 8558 (86.0%) providing complete T0 survey responses and consent to link their survey responses to their administrative records.

The T0 longitudinal analysis cohort for this investigation was restricted to the subpopulation ( $n=7742$ ) of these T0 study participants who subsequently deployed to Afghanistan. A total of 4645 (60.0%) of the 7742 T0 study participants who deployed to Afghanistan provided complete data at all three post-deployment assessments (i.e., T1, T2, and T3).

To compensate for T1, T2, and/or T3 attrition losses from the eligible baseline sample of 7742 participants, response propensity (based on T0 measures available for all baseline respondents) and post-stratification (based on comparisons of distributions for key sociodemographic and Army career variables from administrative data available for the entire Army as well as for survey respondents) weighting factors<sup>15</sup> were developed and applied in all analyses of the multiwave data.

Finally, because this investigation focuses on sequelae of mTBI, 127 of the eligible soldiers with complete data were excluded because they met study criteria for “more-than-mild” (i.e., moderate or severe) TBI (see Measures below). This resulted in a final sample size of 4518 for the current analysis.

### *Measures*

**Baseline (T0) assessment.** At baseline (T0), PPDS respondents self-administered a computerized version of the Composite International Diagnostic Interview screening scales (CIDI-SC)<sup>16</sup> to assess 10 lifetime *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition mental disorders. The sum of all past 30-day depression, anxiety, and irritability items from the screening scales (24 items each ranging 0–4) was calculated to create a past-month general distress score (range 0–96). Also collected at the T0 assessment were sociodemographic information and a query about previous TBI(s). The latter was assessed by a series of questions similar to those described below for the T1 assessment. For purposes of the analyses described here, any pre-deployment reporting of probable TBI of any level of severity was counted as being positive for probable TBI history before the index deployment.

#### *First post-deployment (T1) assessment*

**Deployment stress.** The T1 survey included 15 questions that assessed the frequency of specific deployment experiences that

were stressful or traumatic in nature [e.g., *During your deployment how many times did you...Go on combat patrols or have other dangerous duty (e.g., route clearance, clearing buildings, disarming civilians, working in areas that had improvised explosive devices)? or ...Fire rounds at the enemy or take enemy fire (either direct or indirect fire)?*]. Responses to these questions were discretized (yes/no), and positive responses were summed to create a total (0–15) deployment stress severity score.

**Deployment-acquired TBI.** Probable TBI was determined by the probe [*How many times during your recent deployment did you have a head, neck, or blast injury that...*] followed by a series of questions pertaining to alteration or loss of consciousness (LOC) and lapse of memory that followed. We used the highest level of severity of response(s) to characterize each respondent as having had one of: (1) No TBI; (2) probable “very mild” TBI (alteration but no LOC [*“didn’t knock you out but caused you to be dazed or ‘see stars’”*]) and no lapse of memory); (3) probable “mTBI” (LOC [*“knocked you out”*]) for less than 30 min and/or lapse of memory for less than 30 min; or (4) probable “more-than-mTBI” (LOC for 30 min or more or lapse in memory lasting 30 min or more).

Using these criteria, TBIs classified as very mild or mild would match up with most standard and widely used definitions of mTBI (e.g., <http://tbiaw.com/acrm-brain-injury-definition.html>). The majority of TBIs classified as more-than-mild would fall into a higher category (i.e., moderate or severe) of clinical severity and were therefore not included in the present analyses. We evaluated the effects of level of mTBI severity (i.e., very mild vs. mild), as well as “any” deployment-acquired mTBI compared with none.

#### Second (T2) and third (T3) post-deployment assessments

**PCS.** Included at T2 and again at T3 were eight items that reflect the array of PCS: balance problems or dizziness; sensitivity to noise; sensitivity to light; memory problems; irritability; difficulty concentrating; headaches; and feeling tired out or being easily fatigued. Past 30-day occurrence of these symptoms was assessed in a survey section that inquired generally about “health problems” without any reference to TBI or other injury or event. Respondents rated each symptom on a 5-point frequency scale that ranged from “None of the time (0)” through “All or almost all of the time (4).”

Summing these ratings yielded an eight-item PCS score (PCS-8) ranging from 0–32, with good internal consistency (Cronbach alpha=0.88). For the purpose of sensitivity analysis, we also calculated an alternative PCS measure (PCS-5; range=0–20) that excluded symptoms that are also commonly associated with anxiety and depressive disorders (i.e., irritability, difficulty concentrating, and feeling tired or easily fatigued).

#### Statistical methods

Using the total sample ( $N=4518$ ), we conducted zero-inflated negative binomial (ZINB) regression analyses to jointly model the effect of predictors of interest on presence (yes/no) and severity (for nonzero scores) of PCS symptoms (as measured by the PCS-8) at T2 and T3, respectively. Some of the predictors of interest were assessed before the index deployment; these were age (30-or-younger vs. older), sex, race (white vs. black vs. Asian vs. other), ethnicity (Hispanic vs. other), number of previous deployments (none vs. one vs. two or more), previous lifetime TBI, and pre-deployment past-month general distress.

Two additional predictors reflected experiences during the index deployment and were collected immediately on return to the United States at T1; these were severity of deployment stress and deployment-acquired mTBI. BCT was also dummy-coded and adjusted for in the analyses. Duration of index deployment and the interaction of lifetime TBI and deployment-acquired mTBI were

included in preliminary models but did not predict PCS and were thus excluded from the final models.

In the subsample of soldiers who reported mTBI during the index deployment ( $n=822$ ), linear regression was conducted to evaluate associations between the pre- and peri-deployment factors listed above and severity of PCS (as measured by the PCS-8) at T2 and T3. Given that all soldiers in the subsample had sustained mTBI, level of severity of deployment-acquired TBI (very mild vs. mild) was entered as a predictor instead of any mTBI versus none.

To evaluate the robustness of findings, all ZINB and linear regression analyses were repeated using PCS-5 (see Measures) as the outcome. This sensitivity analysis was conducted to evaluate the possibility that observed associations between mTBI and PCS were attributable to symptoms that could also be explained by co-occurring anxiety or depression. An additional set of sensitivity analyses were conducted by excluding persons with concurrent MDE or PTSD. The purpose of this set of analyses was to determine whether the observed associations between mTBI and PCS were attributable to the presence of these comorbid mental health conditions.

All analyses were weighted to account for T1, T2, and T3 survey attrition from the eligible T0 soldier cohort. Because the PPDS data are both clustered by BCT and administration session and weighted, the design-based Taylor series linearization method was used to estimate standard errors. Multivariate significance was examined using design-based Wald  $\chi^2$  tests. All statistical analyses were conducted using the software R (version 3.0.2; R Development Core Team, 2011) or STATA Version 14.0. The  $p$  values less than 0.05 (two-tailed) were considered statistically significant.

## Results

### Participant characteristics at pre-deployment baseline (T0)

All reported percentages and means are weight-adjusted. The sample was predominantly male (94.7%, standard error [SE]=0.6%) and less than 30 years of age (71.5%, SE=1.4%). The majority of participants were white (71.8%, SE=0.9%), with smaller proportions identifying their race as other (12.2%; SE=0.6%), black (12.0%; SE=0.7%), and Asian (4.0%; SE=0.3%); and 16.0% (SE=0.7%) identifying their ethnicity as Hispanic. For 44.8% (SE=1.3%) of soldiers, the index deployment to Afghanistan was their first, with others reporting one (23.1%, SE=0.7%) or multiple (32.0%, SE=1.1%) previous deployments.

Before the index deployment, mean past month general distress was 10.97 (standard deviation [SD]=14.50; median 6, range 0–96; interquartile range [IQR]=2–13). Approximately one-third of soldiers reported having sustained TBI(s) before the index deployment (34.0%; SE=1.0%).

### Deployment stress and deployment-acquired TBI

The mean number of deployment stressors in the index deployment endorsed by respondents at T1 was 3.97 (SD=2.74; median 4, range 0–15, IQR=2–6). Nearly one in five soldiers reported having sustained probable mTBI(s) during the index deployment with 13.3% (SE=0.6%) endorsing probable very mild TBI (i.e., dazed only, no LOC or amnesia) and 4.8% (SE=0.4%) endorsing probable mild TBI.

### Post-concussive symptoms at T2 and T3

At the T2 follow-up, the mean PCS-8 score was 12.26 (SD=7.31, median=11, IQR=7–17) in soldiers with a deployment-acquired mTBI ( $n=822$ ) vs. 7.74 (SD=6.22, median=7, IQR=3–11) in

those without a deployment-acquired mTBI ( $n=3696$ ;  $p<0.0001$ ). At the T3 follow-up, the mean PCS-8 score was 10.31 (SD=6.96, median=10, IQR=5–15) in soldiers with a deployment-acquired mTBI ( $n=822$ ) vs. 6.76 (SD=6.31, median=5, IQR=2–11) in those without a deployment-acquired mTBI ( $n=3696$ ;  $p<0.0001$ ).

#### Prognostic indicators of PCS in the total sample

**T2 Follow-up.** In a ZINB regression adjusting for age group, race, ethnicity, BCT, and number of previous deployments, it was observed that worse pre-deployment general distress, more severe deployment stress during the index deployment, and having sustained an mTBI during the index deployment, were all significantly associated with increased odds of nonzero score on the PCS-8 (i.e., having some post-concussive symptoms vs. none; see AORs for “3 months post-deployment [T2]” in Table 1), as well as with significant increases in PCS-8 score when symptoms were present (i.e., higher score when PCS-8 score was nonzero; see FCs for “3 months post-deployment [T2]” in Table 1). Female sex and history of TBI before the index deployment also were significantly associated with increased PCS-8 score when symptoms were present (Table 1).

**T3 Follow-up.** In a ZINB regression adjusting for age group, race, ethnicity, BCT, and number of previous deployments, it was observed that pre-deployment history of TBI, worse pre-deployment general distress, more severe deployment stress during the index deployment, and having sustained an mTBI during the index deployment were all significantly associated with increased odds of nonzero score on the PCS-8 (i.e., having some post-concussive symptoms vs. none; see AORs for “9 months post-deployment [T3]” in Table 1) as well as with significant increases in PCS-8 score when symptoms were present (i.e., higher score when PCS-8 score was nonzero; see FCs for “9 months post-deployment [T3]” in Table 1). Female sex also was associated with higher score on the PCS-8 when symptoms were present (Table 1).

#### Prognostic indicators of PCS in soldiers who sustained mTBI during the index deployment

Having established that mTBI during the index deployment was a strong predictor of PCS symptoms at follow-up, we next determined whether severity of mTBI (i.e., very mild [“dazed only”] vs. mild [including LOC and/or lapse in memory]) influenced PCS outcomes. Among soldiers who had sustained an mTBI during the index deployment ( $n=822$ ), including the same covariates as in the model above, having had a mild versus very mild TBI during deployment was significantly associated with increased PCS-8 score at T2 and at T3 (Table 2). History of TBI before the index deployment, worse pre-deployment past-month general distress, and more severe deployment stress also predicted higher PCS-8 score at T2 and at T3 (Table 2).

#### Sensitivity analyses with PCS-5

When ZINB regression models of PCS were rerun with PCS-5 as the outcome, deployment-acquired mTBI remained a highly significant predictor of presence and severity of PCS at follow-up. Magnitudes of associations were comparable to those observed in the PCS-8 models, except at T2, deployment-acquired TBI appeared an even stronger predictor of nonzero score on PCS-5 (AOR=3.85; 95% CI 2.20–6.73;  $p<0.001$ ; cf. Table 1). The other predictors of interest displayed associations with PCS-5 that were similar to those they had with PCS-8. Exceptions were that presence of PCS-5 symptoms at T2 was additionally predicted by history of lifetime TBI (AOR=1.50; 95% CI 1.08–2.09;  $p=0.018$ ), but not significantly predicted by deployment stress severity ( $p=0.081$ ), and presence of PCS-5 symptoms at T3 was additionally predicted by female sex (AOR=2.22; 95% CI 1.38–3.60;  $p=0.002$ ). Also contrasting with the PCS-8 results was the finding that severity of symptoms on PCS-5 was not significantly predicted by sex at T2 ( $p=0.11$ ; cf. Table 1).

When linear regression models of PCS-5 were run in the subsample of soldiers who sustained deployment-acquired mTBI, results were comparable to those of the PCS-8 models. Severity of

TABLE 1. RESULTS OF WEIGHTED ZERO-INFLATED NEGATIVE BINOMIAL REGRESSION EVALUATING EFFECTS OF SEX, PRE-DEPLOYMENT GENERAL DISTRESS, PRE-DEPLOYMENT TRAUMATIC BRAIN INJURY HISTORY, DEPLOYMENT STRESS SEVERITY, AND DEPLOYMENT-ACQUIRED TRAUMATIC BRAIN INJURY\* ON PRESENCE (YES/NO; ADJUSTED ODDS RATIO) AND SEVERITY (FOR NONZERO SCORES; FOLD CHANGE) OF POST-DEPLOYMENT POST-CONCUSSIVE SYMPTOMS IN SOLDIERS WITH AND WITHOUT MILD TRAUMATIC BRAIN INJURY (N=4518)

	3 months post-deployment (T2)						9 months post-deployment (T3)					
	AOR <sup>a</sup>	95% CI	p	FC <sup>b</sup>	95% CI	p	AOR <sup>a</sup>	95% CI	p	FC <sup>b</sup>	95% CI	p
Female sex	1.34	0.50–3.58	0.551	1.19	1.07–1.33	0.002	1.46	0.91–2.32	0.110	1.23	1.10–1.37	0.001
Pre-deployment past-month general distress	1.39	1.11–1.73	0.005	1.01	1.01–1.01	<0.001	1.14	1.06–1.22	0.001	1.01	1.01–1.01	<0.001
Deployment stress severity	1.09	1.00–1.19	0.050	1.05	1.04–1.06	<0.001	1.10	1.04–1.16	0.001	1.04	1.03–1.05	<0.001
Any lifetime pre-deployment TBI	1.34	0.91–1.98	0.133	1.10	1.05–1.15	<0.001	1.59	1.19–2.11	0.002	1.10	1.03–1.17	0.004
Any deployment-acquired mild TBI	2.88	1.64–5.05	<0.001	1.31	1.24–1.39	<0.001	2.92	1.82–4.68	<0.001	1.23	1.16–1.31	<0.001

AOR, adjusted odds ratio; CI, confidence interval; FC, fold change. Post-concussive symptoms (PCS) were measured with the PCS-8, which assessed severity of: balance problems or dizziness, sensitivity to noise, sensitivity to light, memory problems, irritability, difficulty concentrating, headaches, and feeling tired out or being easily fatigued.

\*Models also adjust for age group (<30 years vs. older), race, ethnicity, brigade combat team, and number of previous deployments.

<sup>a</sup>For ease of interpretation, AORs reported in the table indicate odds of a nonzero score on the PCS-8 (i.e., presence of any symptoms) that are associated with each hypothesized predictor. These AORs were calculated by taking the inverse of the AORs for odds of a zero score (not shown in Table).

<sup>b</sup>FCs indicate the fold increase or decrease in PCS-8 score associated with each predictor when any symptoms are present (i.e., when PCS-8 score is nonzero).

TABLE 2. RESULTS OF LINEAR REGRESSION EVALUATING EFFECTS OF SEX, PRE-DEPLOYMENT PSYCHOLOGICAL DISTRESS, PRE-DEPLOYMENT TRAUMATIC BRAIN INJURY HISTORY, DEPLOYMENT STRESS SEVERITY, AND SEVERITY OF DEPLOYMENT-ACQUIRED TRAUMATIC BRAIN INJURY\* ON POST-DEPLOYMENT POST-CONCUSSIVE SYMPTOMS IN SOLDIERS WITH MILD TRAUMATIC BRAIN INJURY (N = 822)

	3 months post-deployment (T2)				9 months post-deployment (T3)			
	B	SE B	t	p	B	SE B	T	p
Female sex	-0.33	1.43	-0.23	0.82	-0.22	1.20	-0.18	0.86
Pre-deployment past-month general distress	0.16	0.01	11.68	< 0.001	0.10	0.01	7.87	<0.001
Deployment stress severity	0.40	0.11	3.66	0.001	0.34	0.09	3.76	0.001
Any lifetime pre-deployment TBI	1.03	0.43	2.40	0.025	1.08	0.44	2.43	0.023
Deployment-acquired TBI involved LOC or amnesia (versus “dazed” only)	2.48	0.65	3.80	0.001	2.40	0.67	3.60	0.002

TBI, traumatic brain injury; LOC, loss of consciousness.

Post-concussive symptoms (PCS) were measured with the PCS-8, which assessed severity of: balance problems or dizziness, sensitivity to noise, sensitivity to light, memory problems, irritability, difficulty concentrating, headaches, and feeling tired out or being easily fatigued.

\*Models also adjust for age group (<30 years vs. older), race, ethnicity, brigade combat team, and number of previous deployments.

mTBI (very mild vs. mild) during the index deployment remained a highly significant predictor of PCS severity at T2 (B=2.03; SE=0.44; t=4.57; p<0.001) and at T3 (B=1.71; SE=0.43; t=3.98; p=0.001). The only notable discrepancy with the PCS-8 models was that the association of lifetime TBI with PCS-5 score at T2 slightly exceeded the threshold for statistical significance (B=0.55; SE=0.27; t=2.05; p=0.052).

*Sensitivity analyses among soldiers without concurrent post-deployment MDE or PTSD*

A parallel set of analyses was conducted excluding soldiers in whom MDE or PTSD had developed at T2 or T3, respectively. With these models (data not shown), the only minor difference is that when MDE/PTSD subjects are excluded, the p values for effects of deployment stress climb just above the threshold for significance for the T2 ZINB model of PCS in the full sample (p=0.07); and for the two linear regression models of PCS in the subgroup exposed to mTBI (p=0.07 for T2; p=0.06 for T3).

**Discussion**

In this prospective, longitudinal study of US soldiers surveyed before and subsequent to an average 10-month deployment to Afghanistan, we found clear evidence that mTBI predicted persistent PCS. Further support for this association comes from the finding of a dosage effect wherein soldiers with mTBI that involved LOC or lapse in memory had more severe PCS than those whose mTBI involved only alteration in consciousness (i.e., being dazed). Confidence in these findings is enhanced by sensitivity analyses that confirmed these effects using a more conservative measure of PCS (i.e., excluding symptoms that are also defining features of anxiety and mood disorders).

The current findings stand in contrast to some (but not most) studies of military personnel that have found mTBI to be no more predictive of PCS than other nonbrain injury factors.<sup>6-9</sup> This literature may be influenced by a type of publication bias wherein studies that fail to find an association between mTBI and PCS are published, given how apparent this association would otherwise seem to be. Our finding that sustaining mTBI during an index deployment was indeed a determinant of presence and severity of PCS at 3 and 9 months post-deployment highlights the need for continued investigation of persistent PCS as a potential sequela of mTBI.

This study also aimed to identify risk factors for persistent PCS among persons who sustained mTBI during deployment. A variety of potential risk factors have been examined, ranging from genetic factors, such as apolipoprotein E epsilon-4 allele<sup>17</sup> to neurocognitive and imaging parameters (e.g., diffusion tensor imaging),<sup>18</sup> none of which has yet been well replicated or shown to be conclusively predictive. Other blood-based biomarkers are also being evaluated,<sup>4</sup> some of which may eventually be confirmed as predictive biomarkers of PCS (e.g., serum Tau-A or SNTF).<sup>19,20</sup>

In this study, we focused on risk factors for which there is a consistent precedent in the literature,<sup>11</sup> and indeed confirmed that previous TBI(s) and pre-injury (or, in this military context, pre-deployment) psychological distress predicted increased severity of PCS at follow-up. Importantly, extent of deployment-related stress also was a predictor of PCS, suggesting that the degree of stress exposure also contributes to PCS and that the implementation of buffers to these stresses may be an avenue toward prevention. As has been noted in some studies, female sex was also associated with increased risk of poor recovery from mTBI.<sup>21</sup>

We did not look at sleep disturbance, per se, as a specific predictor of PCS. Given recent findings that sleep difficulties pre- and post-injury were predictive of poorer functional outcomes in a cohort of adults with mTBI,<sup>22</sup> future research should pay special attention to insomnia as a potential intervention target.

Strengths of this study are its large sample size and its detailed, systematic longitudinal prospective assessment of three Army BCTs about to be deployed to Afghanistan. Another strength is the way the questions about PCS were asked: they were included in a separate survey section from the questions about mTBI and, in fact, were not asked about in the context of having experienced a TBI. This aspect of the survey design may have mitigated the tendency for persons who reported mTBI to then go on to identify symptoms as a result of that injury.

Our study also has a number of limitations. First and foremost is the reliance on self-report for reporting of mTBI. Whereas external and independent corroboration of mTBI is desirable, it is rarely achievable in this type of study. In fact, our review of medical records suggested that only a small fraction of TBIs were captured in the medical administrative data, and most of these were moderate to severe. This is the nature of mTBI in general, and perhaps particularly in the military, where most mTBIs are undocumented.<sup>23</sup>

Another potential limitation is the absence of information in the survey about blast versus nonblast mechanisms of injury. A recent study suggests, however, that adverse functional outcomes in TBI may have little to do with mechanism (blast v. non-blast) of injury.<sup>24</sup> Still, this and other injury-related factors such as co-occurring extracranial injury—which, along with pre-existing mental health conditions has been found to predict poor outcome after mTBI<sup>25</sup>—may well be important and should be considered in future studies.

A third potential limitation has to do with the timing of administration of the survey questions about mTBI. A recent study of UK military personnel suggests that in-theater reporting of TBI yields lower rates than when reporting takes place post-deployment.<sup>26</sup> We attempted to mitigate recall bias by asking about deployment-related mTBI very early on (1–2 days) after redeployment to the United States. Whether or not the timing of reporting of mTBI influenced the findings is a subject for future study. A fourth potential limitation is our use of a novel measure of PCS for this study. Additional psychometric work is needed to ensure that this measure is a valid and longitudinally reliable indicator of PCS severity.

Worthy of further study is the frequent finding that PCS and post-traumatic stress symptoms are often seen in tandem as sequelae to mTBI. Interestingly, many of the prospective risk factors for post-traumatic stress symptoms after TBI also have been found to be risk factors for PCS; these include female sex, pre-injury mental health status, and extent of deployment-related stress.<sup>27</sup> Given the striking similarity of risk factors, these observations should encourage additional research into shared pathophysiological mechanisms (e.g., inflammatory)<sup>28</sup> for PCS and post-traumatic stress symptoms.

What are potentially actionable implications of our findings beyond those pertaining to predictive analytics for PCS? Our results show that persons with more severe mTBI (i.e., with LOC or amnesia), previous history of TBI, pre-injury mental health symptoms, and more severe stress surrounding the TBI are more vulnerable to PCS, implying that patients with TBI presenting with one or more of these features may comprise the ideal group for targeted prevention or early intervention efforts. Previous history of TBI, which for many soldiers in this study originated in pre-military concussions sustained from sports or other injuries, is especially prevalent and worthy of further attention as a vulnerability factor for PCS.

The optimal approach to prevention and early intervention, however, is yet to be determined.<sup>29</sup> Interestingly, a recent randomized controlled trial (RCT) of strict rest versus usual care after acute concussion (in 11–22-year-olds) found no benefit (on balance or neurocognitive outcomes) of strict rest and, in fact, some evidence of harm because those assigned to acute rest reported more PCS.<sup>30</sup> A potential explanation is that strict rest provides an opportunity to focus on existing symptoms and thereby intensify them. Indeed, a recent review suggests that excessive prescription of rest may result in attentional biases and symptom misattribution that can worsen PCS.<sup>31</sup>

These observations raise the question of whether or not cognitive-behavioral therapies and related attention-modifying approaches would be useful for patients with TBI at risk for persistent PCS. Patients with pre-injury emotional disorders, symptoms of anxiety/depression early in the post-injury period, or severe life stress (i.e., those predicted to have increased odds of PCS developing based on our findings) are likely more vulnerable to threat-focused attentional biases and catastrophic interpretations of symptoms<sup>32</sup> and would be hypothesized to derive particular benefit from these treatment approaches.

Such interventions also could alleviate symptoms of stress and/or emotional disorders, producing additional clinical benefits. Indeed, findings from a recently published RCT suggest that cognitive behavioral therapy is effective for reducing anxiety and depression symptoms after TBI.<sup>33</sup> Given the previous finding of increased PCS in patients prescribed rest after mTBI,<sup>30</sup> however, it would be important to also monitor for potential adverse effects of increasing focus on symptoms through certain elements of cognitive-behavioral or attention-modification treatments (e.g., self-monitoring). These hypotheses merit evaluation in future experimental studies and RCTs.

## Conclusion

Data from a prospective, longitudinal study of US soldiers (surveyed pre- and post-deployment) provided evidence that mTBI is a determinant of persistent PCS. Moreover, a dosage effect was observed wherein soldiers with mTBI that involved LOC or lapse in memory reported more severe PCS than those whose mTBI involved only alteration in consciousness (i.e., being dazed). The current study also replicates and extends previous work on predictors of PCS by identifying history of previous TBI, worse pre-injury mental health status, and acute stress (in this case, deployment stress) as key prognostic factors in the development of persistent PCS after an index TBI.

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Dr. Stein has in the last 3 years been a consultant for Healthcare Management Technologies, Tonix Pharmaceuticals, Janssen, and Pfizer. In the past 3 years, Dr. Kessler has been a consultant for Hoffman-La Roche, Inc., Johnson & Johnson Wellness and Prevention, and Sonofi-Aventis Groupe. Dr. Kessler has served on advisory boards for Mensante Corporation, Plus One Health Management, Lake Nona Institute, and U.S. Preventive Medicine. Dr. Kessler owns 25% share in DataStat, Inc. For the remaining authors report, no competing financial interests exist.

### References

- Peskind, E.R., Brody, D., Cernak, I., McKee, A., and Ruff, R.L. (2013). Military- and sports-related mild traumatic brain injury: clinical presentation, management, and long-term consequences. *J. Clin. Psychiatry* 74, 180–188.
- McMahon, P., Hricik, A., Yue, J.K., Puccio, A.M., Inoue, T., Lingsma, H.F., Beers, S.R., Gordon, W.A., Valadka, A.B., Manley, G.T., Okonkwo, D.O., Casey, S.S., Cooper, S.R., Dams-O'Connor, K., Menon, D.K., Sorani, M.D., Yuh, E.L., Mukherjee, P., Schnyer, D.M., and Vassar, M.J. (2014). Symptomatology and functional outcome in mild traumatic brain injury: results from the prospective TRACK-TBI study. *J. Neurotrauma* 31, 26–33.
- Bahraini, N.H., Breshears, R.E., Hernandez, T.D., Schneider, A.L., Forster, J.E., and Brenner, L.A. (2014). Traumatic brain injury and posttraumatic stress disorder. *Psychiatr. Clin. North Am.* 37, 55–75.
- Levin, H.S., and Diaz-Arrastia, R.R. (2015). Diagnosis, prognosis, and clinical management of mild traumatic brain injury. *Lancet Neurol*, 14, 506–517.
- Boyle, E., Cancelliere, C., Hartvigsen, J., Carroll, L.J., Holm, L.W., and Cassidy, J.D. (2014). Systematic review of prognosis after mild traumatic brain injury in the military: results of the International Collaboration on Mild Traumatic Brain Injury Prognosis. *Arch. Phys. Med. Rehabil.* 95, Suppl 3, S230–S237.
- Meares, S., Shores, E.A., Taylor, A.J., Batchelor, J., Bryant, R.A., Baguley, I.J., Chapman, J., Gurka, J., and Marosszeky, J.E. (2011). The prospective course of postconcussion syndrome: the role of mild traumatic brain injury. *Neuropsychology* 25, 454–465.
- Ponsford, J., Cameron, P., Fitzgerald, M., Grant, M., Mikocka-Walus, A., and Schonberger, M. (2012). Predictors of postconcussive symptoms 3 months after mild traumatic brain injury. *Neuropsychology* 26, 304–313.
- Fear, N.T., Jones, E., Groom, M., Greenberg, N., Hull, L., Hodgetts, T.J., and Wessely, S. (2009). Symptoms of post-concussional syndrome are non-specifically related to mild traumatic brain injury in UK Armed Forces personnel on return from deployment in Iraq: an analysis of self-reported data. *Psychol. Med.* 39, 1379–1387.
- Garber, B.G., Rusu, C. and Zamorski, M.A. (2014). Deployment-related mild traumatic brain injury, mental health problems, and post-concussive symptoms in Canadian Armed Forces personnel. *BMC Psychiatry* 14, 325.
- Waldron-Perrine, B., Hennrick, H., Spencer, R.J., Pangilinan, P.H., and Bieliauskas, L.A. (2014). Postconcussive symptom report in polytrauma: influence of mild traumatic brain injury and psychiatric distress. *Mil. Med.* 179, 856–864.
- Silverberg, N.D., Gardner, A.J., Brubacher, J.R., Panenka, W.J., Li, J.J., and Iverson, G.L. (2015). Systematic review of multivariable prognostic models for mild traumatic brain injury. *J. Neurotrauma* 32, 517–526.
- Stein, M.B., and McAllister, T.W. (2009). Exploring the convergence of posttraumatic stress disorder and mild traumatic brain injury. *Am. J. Psychiatry* 166, 768–776.
- Lange, R.T., Brickell, T.A., Kennedy, J.E., Bailie, J.M., Sills, C., Asmussen, S., Amador, R., Dilay, A., Ivins, B., and French, L.M. (2014). Factors influencing postconcussion and posttraumatic stress symptom reporting following military-related concurrent polytrauma and traumatic brain injury. *Arch. Clin. Neuropsychol.* 29, 329–347.
- Ursano, R.J., Colpe, L.J., Heeringa, S.G., Kessler, R.C., Schoenbaum, M. and Stein, M.B. (2014). The Army Study to Assess Risk and Resilience in Servicemembers (Army STARRS). *Psychiatry* 77, 107–119.
- Heeringa, S.G., West, B.T., Berglund, P.A. (2010). *Applied Survey Data Analysis*. Chapman Hall/CRC Press: Boca Raton, FL.
- Kessler, R.C., and Ustun, T.B. (2004). The World Mental Health (WMH) Survey Initiative Version of the World Health Organization (WHO) Composite International Diagnostic Interview (CIDI). *Int. J. Methods Psychiatr. Res.* 13, 93–121.
- Lawrence, D.W., Comper, P., Hutchison, M.G., and Sharma, B. (2015). The role of apolipoprotein E epsilon (epsilon)-4 allele on outcome following traumatic brain injury: A systematic review. *Brain Inj.* 29, 1018–1031.
- Waljas, M., Iverson, G.L., Lange, R.T., Hakulinen, U., Dastidar, P., Huhtala, H., Liimatainen, S., Hartikainen, K., and Ohman, J. (2015). A prospective biopsychosocial study of the persistent post-concussion symptoms following mild traumatic brain injury. *J. Neurotrauma* 32, 534–547.
- Shahim, P., Linemann, T., Inekci, D., Karsdal, M.A., Blennow, K., Tegner, Y., Zetterberg, H., and Henriksen, K. (2015). Serum tau fragments predict return to play in concussed professional ice hockey players. *J. Neurotrauma*. Epub ahead of print.
- Siman, R., Shahim, P., Tegner, Y., Blennow, K., Zetterberg, H., and Smith, D.H. (2015). Serum SNTF increases in concussed professional ice hockey players and relates to the severity of postconcussion symptoms. *J. Neurotrauma* 32, 1294–1300.
- Rabinowitz, A.R., Li, X., McCauley, S.R., Wilde, E.A., Barnes, A., Hanten, G., Mendez, D., McCarthy, J.J., and Levin, H.S. (2015). Prevalence and predictors of poor recovery from mild traumatic brain injury. *J. Neurotrauma* 32, 1488–1496.
- Theadom, A., Copley, M., Parmar, P., Barker-Collo, S., Starkey, N., Jones, K., Feigin, V.L.; BIONIC Research Group. (2015). Sleep difficulties one year following mild traumatic brain injury in a population-based study. *Sleep Med.* 16, 926–932.
- Chase, R.P., and Nevin, R.L. (2015). Population estimates of undocumented incident traumatic brain injuries among combat-deployed US military personnel. *J. Head Trauma Rehabil.* 30, E57–E64.
- Mac Donald, C.L., Johnson, A.M., Wierzechowski, L., Kassner, E., Stewart, T., Nelson, E.C., Werner, N.J., Zonies, D., Oh, J., Fang, R., and Brody, D.L. (2014). Prospectively assessed clinical outcomes in concussive blast vs nonblast traumatic brain injury among evacuated US military personnel. *JAMA Neurol.* 71, 994–1002.
- Lingsma, H.F., Yue, J.K., Maas, A.I., Steyerberg, E.W., Manley, G.T.; TRACK-TBI Investigators. (2015). Outcome prediction after mild and complicated mild traumatic brain injury: external validation of

- existing models and identification of new predictors using the TRACK-TBI pilot study. *J Neurotrauma* 32, 83–94.
26. Jones, N., Fear, N.T., Rona, R., Fertout, M., Thandi, G., Wessely, S., and Greenberg, N. (2014). Mild traumatic brain injury (mTBI) among UK military personnel whilst deployed in Afghanistan in 2011. *Brain Inj.* 28, 896–899.
  27. Stein, M.B., Kessler, R.C., Heeringa, S.G., Jain, S., Campbell-Sills, L., Colpe, L.J., Fullerton, C.S., Nock, M.K., Sampson, N.A., Schoenbaum, M., Sun, X., Thomas, M.L., Ursano, R.J.; Army STARRS collaborators. (2015). Prospective longitudinal evaluation of the effect of deployment-acquired traumatic brain injury on posttraumatic stress and related disorders: results from the Army Study to Assess Risk and Resilience in Servicemembers (Army STARRS). *Am. J. Psychiatry* 172, 1101–1111.
  28. Rathbone, A.T., Tharmaradinam, S., Jiang, S., Rathbone, M.P., and Kumbhare, D.A. (2015). A review of the neuro- and systemic inflammatory responses in post concussion symptoms: introduction of the “post-inflammatory brain syndrome:” PIBS. *Brain Behav. Immun.* 46, 1–16.
  29. Marshall, S., Bayley, M., McCullagh, S., Velikonja, D., Berrigan, L., Ouchterlony, D., and Weegar, K. (2015). Updated clinical practice guidelines for concussion/mild traumatic brain injury and persistent symptoms. *Brain Inj.* 29, 688–700.
  30. Thomas, D.G., Apps, J.N., Hoffmann, R.G., McCrea, M., and Hammeke, T. (2015). Benefits of strict rest after acute concussion: a randomized controlled trial. *Pediatrics* 135, 213–223.
  31. Broshek, D.K., De Marco, A.P., and Freeman, J.R. (2015). A review of post-concussion syndrome and psychological factors associated with concussion. *Brain Inj.* 29, 228–237.
  32. MacLeod, C., and Mathews, A. (2012). Cognitive bias modification approaches to anxiety. *Annu. Rev. Clin. Psychol.* 8, 189–217.
  33. Ponsford, J., Lee, N.K., Wong, D., McKay, A., Haines, K., Alway, Y., Downing, M., Furtado, C., and O’Donnell, M.L. (2015). Efficacy of motivational interviewing and cognitive behavioral therapy for anxiety and depression symptoms following traumatic brain injury. *Psychol. Med.* 46, 1079–1090.

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