Comparison of clinical outcomes 1- and 5-years post-injury following combat concussion

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ABSTRACT

Objective: To compare 1-year and 5-year clinical outcomes in two groups of combat-deployed
non-brain-injured service members to two groups of combat-related concussion to better
understand long-term clinical outcome trajectories.

Methods: This prospective, observational, longitudinal multi-cohort study examined four
combat-deployed groups: non-head-injured controls with or without blast exposure, and patients
with combat concussion arising from blast or blunt trauma. 1-year and 5-year clinical
evaluations included identical batteries for neurobehavioral, psychiatric, and cognitive outcomes.
347 participants completed both time points of evaluation. Cross-sectional and longitudinal
comparisons were assessed. Overall group-effect was modelled as a four-category variable with
rank regression adjusting for demographic factors using a two-sided significance threshold of
.05, with post-hoc Tukey p-values calculated for the pairwise comparisons.

Results: Significant group differences in both combat concussion groups were identified cross-
sectionally at 5-year follow-up compared to controls in domains of neurobehavioral-NRS
(Cohen’s-d, -1.10 to -1.40, CIs (-0.82:-1.32) to (-0.97:-1.83) by group), and psychiatric-CAPS
(Cohen’s-d, -0.91 to -1.19, CIs (-0.63:-1.19) to (-0.76:-1.62) by group) symptoms with minimal
differences in cognitive performance. Both combat concussion groups also showed clinically
significant decline from 1-to-5-year evaluation (66-76% neurobehavior-NRS; 41-54%
psychiatric-CAPS by group). Both control groups fared better but a subset also had clinically
significant decline (37-50% neurobehavior-NRS; 9-25% psychiatric-CAPS by group).
**Conclusions:** There was an evolution not resolution of symptoms from 1-to-5-year evaluation challenging the assumption that chronic stages of concussive injury are relatively stable. Even some of the combat-deployed controls worsened. The evidence supports new considerations for chronic trajectories of concussion outcome in combat-deployed service members.

**INTRODUCTION**

Questions remain regarding the long-term outcome trajectories of service members who sustain traumatic brain injuries (TBI) in combat. Recent publications suggest these trajectories are not fully understood in particular for mild TBI\(^1,2\). One challenge of prior efforts has been the reliance on self-report of brain injury that may have occurred months to years before\(^3,4\). Furthermore, comprehensive assessments for co-occurring conditions complicating clinical course are often lacking\(^5\). Substantial research has attempted to elucidate these outcomes which has provided important insights and paved the way for future efforts. However, it has primarily be reliant upon self-report\(^6-10\) or retrospective records\(^8,11\), with single time point of assessment\(^6,10-13\), and lumping together all chronic injury\(^8,12,14\).

Some longitudinal studies have been performed but they largely focused on sub-acute to early chronic time frame post-injury\(^15\) with remote surveys or focused only on chronic phases of injury\(^16\) more subject to recall bias. Through collaborative efforts in combat, following medical evacuation, and in the United States, we have been provided the opportunity to follow the same service members both with and without blast concussion from the sub-acute, 1-year, and 5-year outcome. We recently reported varying neuroimaging trajectories in this cohort where a subset of the concussive blast patients were found to have secondary worsening of brain white matter microstructure motivating consideration of the implications on clinical outcomes\(^17\).
objective of the current study was to compare 1-year and 5-year clinical outcomes in these service members to better understand trajectories of long-term clinical outcome.

METHODS

Participants in this study were originally enrolled into one of four previous cohorts between 2008 and 2013. This is the 5-year evaluation in an ongoing prospective, observational, longitudinal research study. In this publication, we report the longitudinal clinical outcomes across our four participant groups, two primary and two exploratory; (1) combat-deployed controls without history of blast exposure ‘non-blast control,’ and (2) concussive blast TBI ‘blast TBI,’ (primary), and (3) combat-deployed controls with history of blast exposure ‘blast control,’ and (4) patients sustaining a combat concussion arising not from blast ‘non-blast TBI’ (exploratory). Inclusion criteria have been reported elsewhere. Briefly, participants were service members, deployed to the combat theatre, between 2008 and 2013, in which original enrollment was completed either directly in Afghanistan or following medical evacuation to Landstuhl Regional Medical Center in Germany. Diagnosis of head injury was determined by trained medical personnel working in the TBI clinics in Afghanistan or Germany using the same protocol. First the Military Acute Concussion Evaluation (MACE) was administered by clinic staff followed by further examination for diagnosis corroboration by a TBI Neurologist. For the concussive blast TBI group, all available clinical histories indicated blast exposure plus another mechanism of head injury such as a fall, motor vehicle crash, or being struck by a blunt object. None suffered an isolated blast injury. All concussive blast and non-blast TBI patients met the Department of Defense definition for mild, uncomplicated traumatic brain injury defined as GCS 13-15, LOC 0-30 minutes, AOC less than 24 hours, PTA less than 24 hours, unremarkable CT or MRI at the time of evaluation. All combat-deployed
controls were clinically evaluated to be free of signs and symptoms of head injury for both the ‘non-blast’ and ‘blast’ control groups and additionally no history of blast exposure for the ‘non-blast control’ group. Prior psychiatric and TBI diagnoses were exclusions for all groups.

Through these efforts 575 participants have been prospectively enrolled and assessed at the acute (0-7 days, median 4, Study 4), and sub-acute time points (0-30 days, median 7-9, Study 2-3; 0-90 days, median 14, Study 1); 347 of whom completed further clinical examination at 1-year and 348 at 5-year post-injury; with 281 completing both follow-up evaluations. Note that due to funding restrictions only a subset of Study 4 could be followed. Reasons for non-participation at follow up primarily were due to continued service responsibilities. It was intentional in the study design to assess both medically evacuated (Studies 1-3) and non-medically evacuated (Study 4) combat casualties so that direct comparisons in outcome measures could be determined. Surprisingly, at the 1-year follow-up no difference in clinical outcome measures was found comparing the TBI patients from each of these groups so their data were combined for further analysis. Figure 1 shows the enrollment flow diagram summarizing enrollment including details of the specific groups evaluated.

**Standard Protocol Approvals, Registrations, and Patient Consents**

This study was approved by the University of Washington Institutional Review Board with additional approval from the US Army Medical Research and Materiel Command Institutional Review Board and carried out in accordance with the approved protocol. Reconsent for each follow-up evaluation was provided by all participants according to the Declaration of Helsinki; no surrogate consent was allowed. Active-duty military were not paid for participation per government guidelines, though travel expenses to the follow-up evaluations were covered.
Clinical Assessments

In-person clinical assessments at the 5-year evaluation included a structured neurobehavioral interview, structured psychiatric evaluation, and neuropsychological battery consisting of 10 cognitive tests identical to the 1-year follow up with additional self-administered questionnaires. Evaluations lasted approximately 5 hours; 1 hour of standardized neurobehavioral evaluation and 2 hours both for cognitive testing and psychiatric evaluation. During the evaluations, participants took their regularly scheduled medications. All tests were performed between 8 am and 5 pm in private, quiet, well-lighted rooms. All examiners underwent standardized training for evaluation consistency and were blinded to other clinical information, though during the interviews it often became clear which group participants were in given endorsements of prior events. Per patient, the examiners for each evaluation battery were different, meaning the patient would see three different examiners for the three different assessments (neurobehavioral, neuropsychological, psychiatric). In order to evaluate multiple patients on a single day, assessment order for the neurobehavioral and psychiatric evaluations varied making sure to always complete the neuropsychological assessment in the first half of the day.

Overall global disability was assessed using the Glasgow Outcome Scale Extended (GOS-E). The GOS-E is scored from 1-8: 1=dead, 2=vegetative, 3-4=severe disability, 5-6=moderate disability, 7-8=good recovery. Moderate disability (GOS-E = 5-6) is defined as one or more of the following: 1) inability to work to previous capacity 2) inability to resume much of regular social and leisure activities outside the home 3) psychological problems which have frequently resulted in ongoing family disruption or disruption of friendships. Severe disability (GOS-E = 3-4) is defined as one or more of the following: 1) inability to drive and/or travel
locally without assistance 2) inability to shop or run errands without assistance 3) support required for activities of daily living. Standardized, structured interviews were performed per published guidelines. Participants were instructed to consider deployment as the reference point for this interview.

The neurological assessment included a structured interview designed for TBI patients (Neurobehavioral Rating Scale-Revised, NRS), two headache interviews capturing frequency and intensity (Migraine Disability Assessment, MIDAS, Headache Impact Test, HIT-6), the Neurological Outcome Scale for TBI (NOS-TBI) designed to assess focal neurological deficits associated with TBI, and a TBI history intake interview modified from the Brain Injury Screening Questionnaire (BISQ), to confirm life history of head injury exposure and identify new head injuries sustained since last evaluation. Participants also completed the Quality of Life after Brain Injury questionnaire capturing life satisfaction.

The psychiatric evaluation included structured interviews and self-administered questionnaires. The Clinician-Administered PTSD Scale for DSM-IV (CAPS) and Montgomery-Asberg Depression Rating Scale (MADRS) for depression were administered as structured interviews before the participant completed the: PTSD Checklist-Military (PCL-M), Beck Depression Inventory (BDI), Brief Symptom Inventory-Anxiety module (BSI-A), Insomnia Severity Index, and Michigan Alcohol Screening Test (MAST). The CAPS was scored using the standards from Blake et al.

The neuropsychological test battery assessed cognitive domains of attention, executive functioning, memory, and motor functioning. The Wechsler Test of Adult Reading was used as an estimate of pre-injury intellectual abilities. Cognitive measures included: the Conner’s Continuous Performance Test II (CPT-II), a computer-based assessment of attention,
impulsivity, reaction time, and vigilance; the California Verbal Learning Test II (CVLT-II)\textsuperscript{39}, an assessment of verbal declarative memory; the Ruff-Light Trail Learning Test\textsuperscript{40}, an assessment of visual-spatial memory; the Trail Making Test\textsuperscript{41}, an assessment of visual scanning and mental flexibility; the Controlled Oral Word Association test\textsuperscript{42}, an assessment of verbal fluency; the Iowa Gambling Test, a computer-based assessment of impulsivity and decision making; the D-KEFS Color-Word Interference Test (D-KEFS CWI)\textsuperscript{43}, a measure of response inhibition similar to the Stroop test; the Grooved Pegboard test\textsuperscript{44}, an assessment of upper extremity motor speed and coordination; and a timed 25-foot walk, an assessment for motor strength, balance, and coordination. Participant effort and engagement was assessed using embedded measures (e.g., CVLT-II forced choice).

**Statistical Analysis**

Overall differences in subject characteristics across the four groups were assessed for statistical significance using Fisher’s exact and Kruskal-Wallis tests as appropriate. 5-year cross-sectional analysis considered the entire cohort that completed this follow-up evaluation (n=348) while longitudinal analysis only considered those who completed both the 1-year and 5-year evaluations (n=281). Since many of the 5-year outcome measures had skewed distributions, differences among the groups were assessed non-parametrically using rank-regression in which the actual measured values are replaced by the corresponding within-sample ranks. All outcome models adjusted for age, education, gender, branch of service, and subsequent head injury exposure that may have occurred since last study evaluation. The overall group-effect was modelled as a four-category variable using a two-sided significance threshold of .05, with post-hoc Tukey p-values calculated for the pairwise comparisons of the four groups. All resulting

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\textsuperscript{39} California Verbal Learning Test II: A measure of verbal declarative memory.
\textsuperscript{40} Ruff-Light Trail Learning Test: An assessment of visual-spatial memory.
\textsuperscript{41} Trail Making Test: An assessment of visual scanning and mental flexibility.
\textsuperscript{42} Controlled Oral Word Association Test: An assessment of verbal fluency.
\textsuperscript{43} D-KEFS Color-Word Interference Test: A measure of response inhibition similar to the Stroop test.
\textsuperscript{44} Grooved Pegboard Test: An assessment of upper extremity motor speed and coordination.
probability values were interpreted for significance across multiple measures within each outcome domain using a 5% false-discovery rate per Benjamini-Hochberg.

**Data Availability**

Data from this study are available through data use agreements submitted by interested parties to the corresponding author. Following study completion, data will also be available and has been submitted to the Federal Interagency Traumatic Brain Injury Research data repository per NIH-NINDS guidelines for funded studies.

**RESULTS**

A 5-year follow-up, 109 non-blast control and 170 concussive blast TBI patients, as well as 41 blast control and 28 non-blast TBI patients completed evaluation of which 80 non-blast control, 136 concussive blast TBI, 39 blast control and 26 non-blast TBI completed both 1-year and 5-year follow-up. Participants across studies by group were combined across original studies 1-4 as there were no demographic differences identified within each group. Of note, the overall study sustained 7 deaths from the 1-year to 5-year follow-up as reported in Figure 1. All of these untimely deaths were blast-exposed patients, the vast majority of which were death by suicide, followed by accidents. Across groups, as shown in Table 1, there were significant demographic differences. Specifically, differences were identified in age, education, gender, branch of service, and military rank. As military rank is a surrogate for education, all statistical comparisons were adjusted for age, education, gender, branch of service, in addition to subsequent head injury exposure sustained between the 1-year and 5-year evaluation to account for any possible impact on clinical outcome. All subsequent head injury exposures identified across groups met the clinical criteria for concussion and were primarily due to ground level
falls, low speed motor vehicle crashes, and fights. At the time of 5-year evaluation, there was also a significant difference in the percent of individuals by group that had separated from the service with close to 70% of the concussive blast TBI, non-blast TBI, and blast control patients already separated while only 43% of the non-blast control had completed service separation. Percent disability was also significantly higher in the concussive blast TBI, and non-blast TBI patients but also in the blast controls in comparison to the non-blast controls. In contrast, no patient or participant had separated from the service at 1-year evaluation.

5-Year cross-sectional analysis of global outcome

Overall 5-year follow-up global outcome and quality of life were substantially impaired in the concussive blast TBI patients as well as the non-blast TBI patients in comparison to the non-blast controls as evidenced by the GOS-E and Quality of Life Satisfaction questionnaire (All adjusted post-hoc p<0.0001, Figure 2). Blast controls were also significantly impaired compared to non-blast controls on global disability but not quality of life after adjustment and statistical correction for multiple comparisons (GOSE adjusted post-hoc p=0.002, QoL adjusted post-hoc p=0.09). 70% of the concussive blast TBI, 86% of non-blast TBI and 56% of blast control patients met criteria for moderate to severe disability on the GOS-E in contrast to only 16% of non-blast controls.

Longitudinal comparison between 1-year and 5-year global outcome

For comparison to the 1-year follow-up we defined ‘worse’ as any GOS-E score that at 5-year follow-up fell into a lower disability bracket than the previous score; ‘better’ as any GOS-E score that fell into a higher disability bracket than the previous score; ‘no change’ as any GOS-E score that was in the same disability bracket as the previous score (good recovery, moderate
disability, severe disability, death). While the non-blast controls were found to have 72% of participants unchanged, 23% getting better, and 5% getting worse, there was a substantially greater number of blast and non-blast TBI patients who declined during this same time frame. In fact, 30% of blast TBI and 34% of non-blast TBI declined into a worse disability bracket which is particularly striking given at 1-year\textsuperscript{21} 79% of blast TBI and 78% of non-blast TBI were already in the moderate to severe disability range. In addition, 17% of concussive blast TBI and 7% of non-blast TBI got better by 5-year evaluation. Blast controls were more in line with the TBI groups with 23% getting worse, 20% getting better and 57% remaining the same as their 1-year evaluation\textsuperscript{19, 21} where 58% already met criteria for moderate to severe disability.

5-Year cross-sectional analysis of neurobehavior

Overall neurobehavioral symptoms in addition to focal neurological deficits and headache frequency and intensity were significantly elevated in concussive blast TBI and non-blast TBI compared to non-blast controls at 5-year follow-up (All adjusted post-hoc p<0.0001, Figure 3). Blast controls were not significantly more impaired in these domains compared to non-blast controls after adjustment, pairwise post-hoc analysis followed by correction for multiple comparisons (NRS adjusted post-hoc p=0.02, MIDAS adjusted post-hoc p=0.73, HIT-6 adjusted post-hoc p=0.16, NOS-TBI adjusted post-hoc p=0.68).

Longitudinal comparison between 1-year and 5-year neurobehavior

In comparison to 1-year follow-up\textsuperscript{19, 21}, worsening of neurobehavioral symptoms, defined as a 5-point increase or greater, was found in 66% of concussive blast TBI, and 76% of non-blast TBI patients, while 50% of blast controls also met this criteria in contrast to only 37% of non-blast controls. Increases in focal neurological exam findings were found in 81% of concussive
blast TBI, 88% of non-blast TBI, 80% of blast controls, and 55% of non-blast controls during this same time frame and were primarily in domains of hearing, olfaction, and sensory deficits to an extremity. Using the clinical cutoff of 11 for the Migraine Disability Assessment (MIDAS) and 50 for the Headache Impact Test (HIT-6), 5-year moderate to severe headache impairment was identified in 52% (MIDAS) and 82% (HIT-6) of concussive blast TBI patients as well as 75% (MIDAS) and 86% (HIT-6) of non-blast TBI patients in contrast to 15% (MIDAS) and 44% (HIT-6) of non-blast controls. 27% (MIDAS) and 68% (HIT-6) of blast controls were also found to have moderate to severe headache disability at 5-year follow-up. In comparison to the 1-year evaluation\(^{19,21}\), all groups were found to have an increase in the number of participants meeting criteria for both the MIDAS (concussive blast TBI 30% 1yr vs. 52% 5yr; non-blast TBI 64% 1yr vs. 75% 5yr; blast control 23% 1yr vs. 27% 5yr; non-blast control 3% 1yr vs. 15% 5yr) and HIT-6 (concussive blast TBI 46% 1yr vs. 82% 5yr; non-blast TBI 78% 1yr vs. 86% 5yr; blast control 50% 1yr vs. 68% 5yr; non-blast control 13% 1yr vs. 44% 5yr).

5-Year cross-sectional analysis of psychiatric symptoms

There was also significant psychological impairment identified at 5-year follow-up in the domains of post-traumatic stress, depression, and anxiety in both concussive blast TBI and non-blast TBI patients compared to non-blast controls (All adjusted post-hoc p<0.0001, Figure 4). Significant impairment was identified by both the structured clinical interview (Figure 4A) and self-administered questionnaire (Figure 4B) for PTSD as well as for depression (Figure 4C-D) in both TBI groups but not for the blast controls compared to non-blast controls after statistical adjustment, pairwise post-hoc analysis, and correction for multiple comparisons (Blast controls to non-blast controls, adjusted post-hoc p-values range: 0.02-0.82). While elevated symptoms of anxiety were significantly different between both TBI groups compared to non-blast controls.
(Both adjusted post-hoc p<0.0001), there was not a significant difference comparing blast-control to non-blast control (adjusted post-hoc p=0.36, Figure 4E). In parallel sleep impairment followed the same pattern with significant impairment in both TBI groups compared to non-blast control (Both adjusted post-hoc p<0.001) while there was no difference comparing blast control to non-blast control after proper adjustment, pairwise post-hoc analysis, and correction for multiple comparisons (adjusted post-hoc p=0.82, Figure 4F). In contrast alcohol misuse was largely similar across groups (omnibus adjusted p=0.16, adjusted post-hoc pairwise comparisons p-values range: 0.23-0.99, Figure 4G). This is consistent with the 1-year follow-up where there were no differences in alcohol misuse across any of the groups\textsuperscript{19,21}.

**Longitudinal comparison between 1-year and 5-year psychiatric symptoms**

Overall comparison of 1-year to 5-year outcome in these domains identified an increase in the number of patients or participants meeting criteria for moderate to severe impairment. Using the clinical cutoff of 65 on the CAPS, the percentage of each group, including the non-blast controls but to a lesser extent, meeting criteria for moderate to severe PTSD symptoms was found to noticeably increase during this time frame (concussive blast TBI 26% 1yr vs. 41% 5yr; non-blast TBI 39% 1yr vs 54% 5yr; blast control 25% 1yr vs 39% 5yr, non-blast control 0% 1yr vs 9% 5yr). Using the clinical cutoff of 21 on the MADRS, the percentage of each group, including the non-blast controls but to a lesser extent, meeting criteria for moderate to severe depression symptoms was also found to noticeably increase during this time frame (concussive blast TBI 23% 1yr vs. 32% 5yr; non-blast TBI 36% 1yr vs 43% 5yr; blast control 23% 1yr vs 43% 5yr, non-blast control 4% 1yr vs 9% 5yr). It should be noted that these increases in symptoms from 1-year to 5-year follow-up were not for lack of trying to get help on the part of the patient or participant. In fact, 80% of concussive blast TBI, 79% of non-blast TBI, 82% of blast controls,
and 48% of non-blast controls endorsed seeking assistance with a licensed mental health provider. However, only 30% of concussive blast TBI, 45% of non-blast TBI, 34% of blast controls, and 49% of non-blast controls who sought help and completed treatment reported positive benefit with sustained resolution. In contrast, alcohol misuse, which was also collected at both time points was differentially increased by group. Using the clinical cutoff of 6 for moderate to severe alcohol impairment on the MAST identified preferential increases in impairment in the TBI groups compared to the control groups (concussive blast TBI 6% 1yr vs. 17% 5yr; non-blast TBI 7% 1yr vs 18% 5yr; blast control 7% 1yr vs 3% 5yr, non-blast control 5% 1yr vs 4% 5yr) despite no group differences in MAST score at either timepoint.

5-Year cross-sectional analysis of cognitive performance

Overall neuropsychological performance was largely similar across the groups at 5-year follow-up (Table 2). Only performance on the grooved pegboard and 25-foot walk were found to be significantly different although there is not a good embedded reliability measure for these assessments so we interpret these findings with caution (Grooved pegboard omnibus adjusted p<0.0001, 25ft walk omnibus adjusted p=0.004). Post-hoc pairwise analysis followed by correction for multiple comparisons only identified non-blast TBI patients as performing significantly worse than non-blast controls on the grooved pegboard (adjusted post-hoc p=0.001).

Longitudinal comparison between 1-year and 5-year cognitive performance

Comparing 1-year to 5-year neuropsychological function revealed marginal fluctuations in performance for most cognitive measures. The average change in performance for both TBI and both control groups was 0-10% meaning there was less than a 10% difference in test
performance when comparing the data from each patient between these two time points and then taking the average change for each group. There were two exceptions, omission errors t-score indicating attentional lapses on the Connor’s Continuous Performance Test, and the scaled score for Trial 4 (inhibition switching condition) on the DKEFS Color Word Interference (DKEFS-CWI) Test of executive function. For omission errors t-score, while both the non-blast control and blast control groups showed on average a 4% worsening in performance, the concussive blast TBI patients had an average of 25% worsening and the non-blast TBI patients had a 39% worsening in performance over the same time frame. Examining the DKEFS-CWI Trial 4 for inhibition switching, non-blast controls performed on average 3% worse at 5-year verses 1-year follow up while blast-controls performed 4% better in contrast to concussive blast TBI who performed on average 37% worse and non-blast TBI who performed 12% worse comparing this same time frame.

DISCUSSION

Overall, careful examination of the very same cohort of service members from the point of injury to 1-year and 5-year follow-up identified an evolution not resolution of symptoms including selective worsening of cognitive performance in two domains. While prior efforts examining concussion mostly in collegiate athletes and other civilian cohorts have not predominantly reported lasting cognitive deficits, very little work has been done to understand trajectories in the active duty service population. Our current results challenge the historical consideration of ‘chronic’ injury as one group and underscore the need to consider clinically significant fluctuations even after the 6 to 12-month outcome. Findings from this study support the notion that one should not merely lump all mild TBI patients who are past 1-year post-injury together as these trajectories of outcome continue to evolve, and can complicate additional
conditions unrelated to the brain injury as these service members age. Furthermore, that there may be a unique contribution of these concussion exposures to long term outcome even in the absence of a comorbid mental health condition such as PTSD. Prior evidence for dynamic trajectories in chronic outcome has been reported from large longitudinal studies of moderate to severe civilian brain injury through the TBI Model Systems study\textsuperscript{45} as well as penetrating head injury of veterans from previous conflicts through the Vietnam Head injury Study\textsuperscript{46}. To our knowledge we provide the first evidence of such in combat deployed mild TBI service members complementing prior work in more severely injured civilian and military patients.

We extend this trajectory comparison to also consider longitudinal outcomes in those who do not sustain a head injury but are combat-deployed. In fact, we also observed worsening trajectories in a proportion of our non-blast controls in particular in the domains of headache impairment, focal neurological deficits, and mental health problems to a lesser extent than the concusive blast TBI and non-blast TBI patients but still showing decline. Additionally, the consistent and comparable findings in both TBI patient groups imply that mechanism of injury in combat may not differentially impact long term outcome, rather a concussive brain injury in combat by any mechanism may increase a service member’s risk for a complicated clinical course with poor outcome. Last, we note that in our parallel neuroimaging study of these very same patients and participants, it was striking to find that 20% of the concussive blast TBI patients also were found to have a delayed worsening in their brain white matter microstructure from 1-year to 5-year follow up evidenced by DTI\textsuperscript{17}. This supports the notion that these clinical declines may be indicative of continued underlying pathophysiological changes that may corroborate recent theories regarding accelerated brain aging and early life head injury exposures linking to later life neurodegeneration\textsuperscript{47}.
Strengths of the study include the use of a prospectively assessed, longitudinal study design enrolling deployed services members at the point of injury or immediately following medical evacuation from the combat theatre, the relative robust sample size in our two primary groups of non-blast controls and concussive blast TBI, utilization of two different control groups to be able to directly examine impact of combat exposure alone verses combat exposure plus head injury, as well as impact of sub-concussive blast injuries in our blast control patients, consideration of additional head injury exposures that may have ensued since original enrollment in the study, and examination by trained clinicians blinded to the clinical status of the patient or participant at each time point.

Limitations of the study include the relatively modest group size of our exploratory patient groups of non-blast TBI and blast-control, the heterogeneity of treatment centers in the United States in which our patients and participants sought care, lack of ability to corroborate ensuing medical diagnosis and treatment between the 1-year and 5-year follow up, lack of comprehensive preinjury clinical data for comparison to long term outcome, heterogeneity in service separation across groups, and unmeasured covariates that may have influenced the clinical course and findings.

In conclusion, clinical outcome trajectories following combat concussion were not stable 1-year to 5-years post-injury with many patients exhibiting continued clinical decline. There are over 18 million US veterans of all previous conflicts alive today with TBI diagnosis from these conflicts and mild TBI in particular from recent conflicts impacting 20% – 40% of this population. These findings have direct public health implications as many of these service members have decades of life to live with the hope that these would be good quality years. Understanding varying outcome trajectories will aid clinicians in identifying individuals
requiring more targeted screening and treatment in order to help maintain better quality of life for our service men and women throughout their lifespan.

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Tables and Figure Legends (in order of appearance in the manuscript)

Figure 1. Consort diagram of longitudinal enrollment.
Table 1. Participant Characteristics at 5-Year Follow-Up

Figure 2. Global outcome and Quality of Life Satisfaction at 5-year follow-up. Overall global disability was significantly different across groups with greater numbers of concussive blast TBI and non-blast TBI in the moderate or severe disability range compared to both control groups (A). In parallel, lower quality of life satisfaction was observed in the concussive blast TBI and non-blast TBI patients compared to both control groups (B). Omnibus test for group comparisons with rank regression adjustment for age, education, gender, branch of service, subsequent head injury exposure followed by Tukey’s pairwise post-hoc comparison and correction for multiple comparisons. Omnibus and post-hoc findings (noted with an asterisk) are only reported as significant if they survived adjustment and correction.
Figure 3. Neurobehavioral outcomes and headache impairment at 5-year follow-up.

Concussive blast TBI and non-blast TBI patients exhibited significantly more neurobehavioral symptoms than either of the control groups at 5-year follow-up (A). This was also the case for focal neurological deficits (B) as well as headache frequency (C) and headache intensity (D). Omnibus test for group comparisons with rank regression adjustment for age, education, gender, branch of service, subsequent head injury exposure followed by Tukey’s pairwise post-hoc comparison and correction for multiple comparisons. Omnibus and post-hoc findings (noted with an asterisk) are only reported as significant if they survived adjustment and correction.
Figure 4. Psychological health, sleep, and alcohol misuse outcomes at 5-year follow-up.

Symptoms of post-traumatic stress were significantly elevated in both TBI groups compared to both groups of controls observed via clinical evaluation (A) and self-endorsement (B). Symptoms of depression were also significantly elevated in both TBI groups compared to both control groups via clinical evaluation (C) and self-endorsement (D). Symptoms of anxiety (E) and sleep impairment (F) were also significantly increased in both TBI groups compared to both control groups. There was not a significant different across groups on alcohol misuse (G). Dashed lines indicate clinical cutoff for moderate to severe impairment on each measure.

Omnibus test for group comparisons with rank regression adjustment for age, education, gender, branch of service, subsequent head injury exposure followed by Tukey’s pairwise post-hoc comparison and correction for multiple comparisons. Omnibus and post-hoc findings (noted with an asterisk) are only reported as significant if they survived adjustment and correction.
Table 2. Neuropsychological Test Performance at 5-Year Follow-up
## Table 1. Participant Characteristics at 5-Year Follow-Up

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Non-blast CTL (n=109)</th>
<th>Blast-Exposed CTL (N= 41)</th>
<th>Concussive Blast TBI (n=170)</th>
<th>Non-blast TBI (N=28)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age in years:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mean (stdev)</td>
<td>33.6 ± 7.8</td>
<td>38.7 ± 7.9</td>
<td>31.9 ± 6.9</td>
<td>34.9 ± 9.2</td>
<td>&lt;0.001&lt;sup&gt;a,d&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>Education in years:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mean (stdev)</td>
<td>16.0 ± 3.1</td>
<td>14.6 ± 2.2</td>
<td>13.7 ± 1.7</td>
<td>14.6 ± 2.0</td>
<td>&lt;0.001&lt;sup&gt;a,b&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>Gender - no (%):</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>92 (84%)</td>
<td>40 (98%)</td>
<td>163 (96%)</td>
<td>25 (90%)</td>
<td>0.004&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Female</td>
<td>17 (16%)</td>
<td>1 (2%)</td>
<td>7 (4%)</td>
<td>3 (10%)</td>
<td></td>
</tr>
<tr>
<td><strong>Race/ethnicity - no (%):</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>83 (76%)</td>
<td>32 (78%)</td>
<td>125 (74%)</td>
<td>19 (69%)</td>
<td></td>
</tr>
<tr>
<td>African American</td>
<td>16 (15%)</td>
<td>6 (15%)</td>
<td>13 (8%)</td>
<td>6 (21%)</td>
<td>0.82&lt;sup&gt;*&lt;/sup&gt;</td>
</tr>
<tr>
<td>Hispanic/Latino</td>
<td>10 (9%)</td>
<td>2 (5%)</td>
<td>27 (16%)</td>
<td>2 (7%)</td>
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</tr>
<tr>
<td>Asian/Pacific Islander</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>4 (2%)</td>
<td>1 (3%)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>0 (0%)</td>
<td>1 (2%)</td>
<td>1 (1%)</td>
<td>0 (0%)</td>
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<tr>
<td><strong>Branch of Service - no (%):</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>US Army</td>
<td>61 (56%)</td>
<td>36 (88%)</td>
<td>145 (85%)</td>
<td>24 (86%)</td>
<td>&lt;0.001&lt;sup&gt;*&lt;/sup&gt;</td>
</tr>
<tr>
<td>US Air Force</td>
<td>17 (16%)</td>
<td>2 (5%)</td>
<td>2 (1%)</td>
<td>2 (7%)</td>
<td></td>
</tr>
<tr>
<td>US Marine Corps</td>
<td>9 (8%)</td>
<td>3 (7%)</td>
<td>21 (12%)</td>
<td>2 (7%)</td>
<td></td>
</tr>
<tr>
<td>US Navy</td>
<td>22 (20%)</td>
<td>0 (0%)</td>
<td>2 (1%)</td>
<td>0 (0%)</td>
<td></td>
</tr>
<tr>
<td><strong>Military Rank - no (%):</strong></td>
<td></td>
<td></td>
<td></td>
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<td>&lt;0.001</td>
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<tr>
<td>Enlisted</td>
<td>86 (79%)</td>
<td>36 (88%)</td>
<td>163 (96%)</td>
<td>27 (97%)</td>
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<tr>
<td>Officer</td>
<td>23 (21%)</td>
<td>5 (12%)</td>
<td>7 (4%)</td>
<td>1 (3%)</td>
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<tr>
<td><strong>Deployments</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.02&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>mean (stdev)</td>
<td>2.1 ± 1.6</td>
<td>2.7 ± 2.0</td>
<td>1.8 ± 1.1</td>
<td>2.5 ± 2.3</td>
<td></td>
</tr>
<tr>
<td><strong>Subsequent HIE&lt;sup&gt;4&lt;/sup&gt; by 5 years</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001&lt;sup&gt;a,b&lt;/sup&gt;</td>
</tr>
<tr>
<td>mean (stdev)</td>
<td>0.2 ± 0.7</td>
<td>1.2 ± 2.8</td>
<td>0.9 ± 2.3</td>
<td>0.5 ± 0.7</td>
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</tr>
<tr>
<td><strong>Service Separation - no (%):</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001&lt;sup&gt;a,b,c&lt;/sup&gt;</td>
</tr>
<tr>
<td>No</td>
<td>62 (57%)</td>
<td>12 (30%)</td>
<td>51 (31%)</td>
<td>9 (32%)</td>
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</tr>
<tr>
<td>Yes</td>
<td>47 (43%)</td>
<td>28 (70%)</td>
<td>113 (69%)</td>
<td>19 (68%)</td>
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</tr>
<tr>
<td><strong>Percent Disability</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001&lt;sup&gt;a,b,c&lt;/sup&gt;</td>
</tr>
<tr>
<td>mean (stdev)</td>
<td>32 ± 37.4</td>
<td>55 ± 41.5</td>
<td>69.3 ± 35.9</td>
<td>73.2 ± 37.2</td>
<td></td>
</tr>
</tbody>
</table>

Statistical significance by Kruskal-Wallis and Fisher’s Exact as appropriate

<sup>1</sup>Dichotomous comparison reported for race (white vs other) and branch (army vs other)

<sup>2</sup>HIE, Head Injury Exposure, all subsequent exposures met the clinical definition for concussion

Post-hoc pairwise significance <.05 (Tukey)

a = non-blast CTL vs blast TBI
b = non-blast CTL vs blast CTL
c = non-blast CTL vs non-blast TBI
d = blast control vs blast TBI
e = blast control vs non-blast TBI
f = blast TBI vs non-blast TBI
<table>
<thead>
<tr>
<th>Assessment</th>
<th>Non-blast CTL (n=109)</th>
<th>Blast-Exposed CTL (N= 41)</th>
<th>Concussive Blast TBI (n=170)</th>
<th>Non-blast TBI (N=28)</th>
<th>Adjusted p-value*</th>
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<tbody>
<tr>
<td><strong>Wechsler Test of Adult Reading (Standard Score)</strong></td>
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<tr>
<td><em>(Estimate of Pre-injury Verbal Intelligence)</em></td>
<td>106.8 ± 11.9</td>
<td>103.2 ± 12.6</td>
<td>104 ± 11.9</td>
<td>103.8 ± 9.8</td>
<td>0.86</td>
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<tr>
<td><strong>Conners’ Continuous Performance Test II</strong></td>
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<td></td>
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<tr>
<td>Omission Errors (T-score): <em>Attention Lapses</em></td>
<td>46.4 ± 4.6</td>
<td>48 ± 6.5</td>
<td>48.1 ± 7.1</td>
<td>47.9 ± 3.4</td>
<td>0.24</td>
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<tr>
<td>Commission Errors (T-score): <em>Impulsivity</em></td>
<td>48.6 ± 9</td>
<td>53 ± 9.7</td>
<td>51.8 ± 9.6</td>
<td>52.5 ± 10.6</td>
<td>0.28</td>
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<tr>
<td>Hit Rate (T-score): <em>Reaction Time</em></td>
<td>51.4 ± 7.6</td>
<td>49.8 ± 7.8</td>
<td>51.9 ± 8</td>
<td>53.8 ± 7.1</td>
<td>0.13</td>
</tr>
<tr>
<td>Hit Rate Block Change (T-score): <em>Sustained Vigilance</em></td>
<td>52 ± 8.5</td>
<td>51.3 ± 7.3</td>
<td>52.2 ± 10</td>
<td>53.2 ± 8.9</td>
<td>0.85</td>
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<tr>
<td><strong>California Verbal Learning Test II</strong></td>
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<tr>
<td>Long-Delay Free Recall (Standard Score): <em>Verbal Memory</em></td>
<td>0.3 ± 1</td>
<td>0.1 ± 1.3</td>
<td>-0.2 ± 1.1</td>
<td>-0.2 ± 1.2</td>
<td>0.22</td>
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<tr>
<td>Total Intrusions (Standard Score): <em>Falsely Recalled Items</em></td>
<td>-0.1 ± 1</td>
<td>0 ± 1.3</td>
<td>0 ± 1</td>
<td>0.3 ± 1.6</td>
<td>0.96</td>
</tr>
<tr>
<td>List B vs. List A (Standard Score): <em>Proactive Memory Interference</em></td>
<td>-0.2 ± 1.2</td>
<td>-0.1 ± 1.1</td>
<td>0 ± 0.9</td>
<td>-0.3 ± 1</td>
<td>0.22</td>
</tr>
<tr>
<td><strong>Ruff Light Trail Learning Test</strong></td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>Total Trials Correct (T-score): <em>Visuospatial Learning</em></td>
<td>51.8 ± 9.6</td>
<td>49.4 ± 10.3</td>
<td>49.2 ± 10</td>
<td>47.3 ± 12.6</td>
<td>0.02</td>
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<tr>
<td>Long Delay Trial Correct: <em>Visuospatial Memory</em></td>
<td>14.4 ± 1</td>
<td>14.4 ± 1</td>
<td>14.1 ± 1.4</td>
<td>13.9 ± 1.3</td>
<td>0.39</td>
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<tr>
<td><strong>Trail Making Test</strong></td>
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<tr>
<td>Trails A time (seconds): <em>Visual Scanning, Coordination</em></td>
<td>22.4 ± 6</td>
<td>22.6 ± 7.4</td>
<td>25.8 ± 10.7</td>
<td>30.1 ± 16.6</td>
<td>0.01</td>
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<tr>
<td>Trails B time (seconds): <em>Mental Flexibility</em></td>
<td>56.1 ± 16.9</td>
<td>60.7 ± 17</td>
<td>64.8 ± 23.9</td>
<td>77.5 ± 46.7</td>
<td>0.16</td>
</tr>
<tr>
<td>Controlled Oral Word Association Total Score: <em>Verbal Fluency</em></td>
<td>45.4 ± 11</td>
<td>43 ± 10.7</td>
<td>43.9 ± 11.9</td>
<td>41.2 ± 9.8</td>
<td>0.39</td>
</tr>
<tr>
<td>**Iowa Gambling Task Net Trials (T-score): <em>Monetary decision making</em></td>
<td>51.1 ± 10.1</td>
<td>51.2 ± 9.9</td>
<td>49.7 ± 10.9</td>
<td>47.7 ± 9.5</td>
<td>0.57</td>
</tr>
<tr>
<td><strong>DKEFS Color Word Interference: <em>Executive Function</em></strong></td>
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<td></td>
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<tr>
<td>Trial 1 + Trial 2 (scaled score): <em>Naming, Reading</em></td>
<td>19.7 ± 4.8</td>
<td>19.3 ± 5.6</td>
<td>18.7 ± 5.9</td>
<td>18.3 ± 7</td>
<td>0.84</td>
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<tr>
<td>Trial 3 (scaled score): <em>Inhibition</em></td>
<td>11 ± 2.6</td>
<td>10.3 ± 2.9</td>
<td>10 ± 3.3</td>
<td>8.7 ± 4</td>
<td>0.26</td>
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<tr>
<td>Trial 4 (scaled score): <em>Inhibition Switching</em></td>
<td>10.5 ± 2.5</td>
<td>10 ± 2.5</td>
<td>9.3 ± 3.1</td>
<td>9 ± 4</td>
<td>0.71</td>
</tr>
<tr>
<td><strong>Grooved Pegboard (Motor Speed &amp; Coordination)</strong></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Average Dom &amp; Non-Dom Time (seconds)</td>
<td>66.8 ± 13</td>
<td>69.6 ± 13.2</td>
<td>71.9 ± 15.3</td>
<td>80.8 ± 20.7</td>
<td>&lt;0.001**</td>
</tr>
<tr>
<td>25-Foot Walk (seconds): <em>Motor Strength, Balance, Coordination</em></td>
<td>4.2 ± 0.8</td>
<td>4.4 ± 0.8</td>
<td>4.5 ± 1.1</td>
<td>4.9 ± 1.2</td>
<td>0.004</td>
</tr>
</tbody>
</table>

*Accepted*
Omnibus statistical significance with rank regression adjustment for age, education, gender, branch of service, and subsequent head injury exposure. Bold p-value indicates significance after adjustment and correction for multiple comparisons.

Post-hoc pairwise significance <.05 (Tukey)

a = non-blast CTL vs blast TBI
b = non-blast CTL vs blast CTL
c = non-blast CTL vs non-blast TBI
d = blast control vs blast TBI
e = blast control vs non-blast TBI
f = blast TBI vs non-blast TBI
## Appendix 1. Author

<table>
<thead>
<tr>
<th>Name</th>
<th>Location</th>
<th>Contribution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Christine Mac Donald, PhD</td>
<td>University of Washington</td>
<td>Design and conceptualized study; interpreted the data; drafted the manuscript, study PI</td>
</tr>
<tr>
<td>Jason Barber, MS</td>
<td>University of Washington</td>
<td>Analyzed the data; performed biostatistical review of results; drafted the manuscript for intellectual content</td>
</tr>
<tr>
<td>Jana Patterson</td>
<td>University of Washington</td>
<td>Major role in the acquisition of data</td>
</tr>
<tr>
<td>Ann Johnson</td>
<td>Washington University</td>
<td>Major role in the acquisition of data</td>
</tr>
<tr>
<td>Carolyn Parsey, PhD</td>
<td>University of Washington</td>
<td>Interpreted the data; revised the manuscript for intellectual content</td>
</tr>
<tr>
<td>Beverly Scott, MD</td>
<td>University of Washington</td>
<td>Interpreted the data; revised the manuscript for intellectual content</td>
</tr>
<tr>
<td>Jesse Fann, MD MPH</td>
<td>University of Washington</td>
<td>Interpreted the data; revised the manuscript for intellectual content</td>
</tr>
<tr>
<td>Nancy Temkin, PhD</td>
<td>University of Washington</td>
<td>Performed biostatistical review of results; revised the manuscript for intellectual content</td>
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</table>
REFERENCES

Comparison of clinical outcomes 1- and 5-years post-injury following combat concussion
Christine L. Mac Donald, Jason Barber, Jana Patterson, et al.
Neurology published online November 11, 2020
DOI 10.1212/WNL.0000000000011089

This information is current as of November 11, 2020

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