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A Proof-of-Concept Study Demonstrating How FITBIR Datasets Can be Harmonized to Examine Posttraumatic Stress Disorder-Traumatic Brain Injury Associations

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Abstract. Background: Although posttraumatic stress disorder (PTSD) is common following traumatic brain injury (TBI), the specific associations between these conditions is difficult to elucidate in part due to the diverse methodologies, small samples, and limited longitudinal data in the extant literature.
Objective: Conduct a proof-of-concept study demonstrating our ability to compile patient-level TBI data from shared studies in the Federal Interagency Traumatic Brain Injury Research (FITBIR) Informatics System to address these shortcomings and improve our understanding of TBI outcomes including rates of PTSD comorbidity.
Method: We searched the FITBIR database for shared studies reporting rates of probable PTSD among participants with no TBI, history of mild TBI, or history of moderate/severe TBI. We merged and harmonized data across the relevant studies and analyzed rates of probable PTSD across TBI history and severity categories.

Results: Four FITBIR studies with 2,312 participants included PTSD outcome data. The final sample for comparative analyses comprised 1,633 participants from two studies with TBI group comparison data. Approximately 79% had a history of mild TBI and 32-37% screened positive for probable PTSD. Participants with a history of mild TBI had 2.8 greater odds of probable PTSD compared to those without TBI (95% CI: 2.0, 3.7).
Conclusions: Only two FITBIR studies reported data examining PTSD outcomes for mild TBI as of January 2021. The analyses are consistent with prior literature, suggesting mild TBI is associated with higher rates of probable PTSD than no TBI. This study developed the methods, shared the harmonization and analysis code, and publicly shared the TBI and PTSD meta-dataset back to FITBIR for dissemination through their website, allowing future research teams to update these and other, related analyses as more studies are contributed to and shared via the FITBIR platform.

Keywords: Traumatic brain injury · Posttraumatic stress disorder · Evidence synthesis · Data repository · Meta-data.

1 Introduction

Approximately 12% of the population will experience traumatic brain injury (TBI) in their lifetime (Frost, Farrer, Primosch, & Hedges, 2013; Garber, Rusu, & Zamorski, 2014) with higher rates observed in at risk populations such as military members (Stroupe et al., 2013). TBI occurs when an external, impulsive force to the head or body causes brain dysfunction. Although definitions of TBI vary, Veterans Affairs (VA) and Department of Defense (DoD) guidelines from 2016 recommend considering structural imaging, alteration of consciousness, loss of consciousness, posttraumatic amnesia, and the Glasgow Coma Scale to determine TBI severity. From this information, TBI can be classified as mild or moderate-to-severe (VA/DoD, 2009). Physical symptoms are common in the aftermath of TBI, and may include, headache, dizziness, balance disorders, sensitivity to light/noise nausea, fatigue, and tinnitus (Marshall, Bayley, McCullagh, Velikonja, & Berrigan, 2012). TBI is also associated with a host of other negative outcomes including neurocognitive deficits (e.g., deficits in attention, concentration, memory processing speed, executive control; Karr, Areshenkoff, & Garcia-Barrera, 2014; Rabinowitz & Levin, 2014), reduced quality of life (Gormley et al., 2019; Polinder, Haagsma, van Klaveren, Steyerberg, & Van Beeck, 2015), and psychiatric comorbidity including depression, anxiety, substance use, and posttraumatic stress disorder (PTSD; Greer et al. 2020). Data suggests that the relationship between TBI and PTSD may be particularly strong (Greer et al., 2020).

A recent review estimated the prevalence of PTSD among civilian TBI samples at approximately 15.6% (Van Praag, Cnossen, Polinder, Wilson, & Maas, 2019). Meta-analytic data show that veterans with TBI are four times more likely to have a diagnosis of PTSD than those without (Loignon, Ouellet, & Belleville,

2020), and among those with mild TBI, rates of comorbid PTSD are around 33-39% (Carlson et al., 2011). Despite high rates of comorbidity, the association between TBI severity and PTSD remains unclear. Some studies reported higher rates of PTSD in mild TBI (Glaesser, Neuner, Lütgehetmann, Schmidt, & Elbert, 2004), while others reported higher rates following moderate-to-severe TBI (Stein et al., 2015; Yurgil et al., 2014), and a recent meta-analysis of civilian data reported no difference based on TBI severity (Van Praag et al., 2019).

1.1 Rationale

As described above, the symptoms of PTSD and TBI can differ for various populations, and the relationships among the two conditions and potentially moderating factors such as demographics can be difficult to tease apart. Additionally, the symptoms of TBI and PTSD overlap (e.g., concentration difficulties, insomnia), which could lead to artificially inflated comorbidity estimates or misdiagnosis (Tanev, Pentel, Kredlow, & Charney, 2014). Finally, the extant literature is limited by small samples and highly varied methodologies, which can make it challenging to reach firm conclusions about prevalence and risk. One way to address these concerns related to methodological variability across studies is by compiling existing research into a single data repository that is available for harmonization and pooled analyses. By harmonizing data from disparate sources, we can overcome the limitations of varied methodologies and improve sample size, which could allow for a more nuanced understanding of TBI and PTSD, akin to individual participant level data meta-analyses (Riley, Lambert, & Abo-Zaid, 2010). The present study is a proof-of-concept paper for such an approach. It summarizes data from the first phase of funded research to compile participant-level TBI data into a single repository with an emphasis on PTSD outcomes.

The Federal Interagency Traumatic Brain Injury Research (FITBIR) Informatics System is a collaborative effort between the National Institutes of Health (NIH) Institutes and Centers (ICs) and the US Army Medical Research and Development Command (USAMRDC) to develop a biomedical informatics system and data repository for TBI research `https://fitbir.nih.gov/`. FITBIR was first developed to share data across the TBI research field. It allows users to access publicly shared study data for new TBI research projects and collaborate with other researchers.

Our work to develop the methods necessary to harmonize, analyze, and disseminate compiled meta-data from the FITBIR database is titled, "FITBIR: Accelerating Synthesis of TBI Research Using Novel Methods (FASTRUN)," and is funded through the Department of Defense. The FASTRUN data harmonization project evaluated outcomes of TBI and psychological health and functioning (e.g., PTSD, depression, sleep, substance use disorders, cognition). We hypothesized that pooled analysis results from publicly available FITBIR studies would support the existing literature, which suggests that having a history of mild TBI versus no history of TBI is associated with higher rates of psychological disorders

and symptoms, in this case, PTSD. We hypothesized these associations would be influenced by patient and injury characteristics.

2 Methods

One of the overarching objectives of this project is the use of advanced software and analysis techniques to make TBI data more "FAIR" (Findable, Accessible, Interoperable, and Reusable; Wilkinson et al. 2016) by facilitating future utilization of FITBIR data and accelerating the synthesis of existing FITBIR data. We developed a model system for harmonizing data for key variables across FITBIR study datasets. Cross-sectional datasets were created by merging key variables, including TBI severity, demographic information, and PTSD outcomes. The methodological products including, harmonized cross-sectional datasets, methods, R syntax, and interactive data visualizations are shared on the FITBIR website (https://fitbir.nih.gov/). The PTSD-TBI meta-dataset and code from this study are available to those who have created a FITBIR account at http://fitbir.gov (navigate to the Meta Study tab, select study "FITBIR: Accelerating Synthesis is TBI Research Using Novel Methods", and click on the Data tab). The interactive data visualizations were created using R Shiny Apps and are publicly available on the FITBIR website, https://fitbir.nih.gov/meta_study_profile/223 (in the Data tab). The visualizations include a prevalence tab, with a visual summary of the outcomes, TBI severity, and demographic information, and an effect size tab, which displays associations between mild TBI and outcomes using logistic mixed effect regression models (O'Neil et al., 2024). Making these products publicly available allows future researchers, policymakers, and other stakeholders to access and utilize merged data for core FITBIR variables to advance TBI research and make informed decisions about TBI-related policy.

2.1 Study Approval

This research was reviewed and approved by the US Army Medical Research and Materiel Command (USAMRMC) Office of Research Protections (ORP), Human Research Protection Office (HRPO), prior to implementation. We complied with FITBIR, Congressionally Directed Medical Research Programs, and local institutional review board (IRB) standards and requirements, including using approved methods of maintaining data behind secure firewalls and transfer of data within and across sites. While use of deidentified data/records may be exempt from IRB review, we ensured that exemption was determined by the office of the institution's IRB of record and confirmed by USAMRMC HRPO.

2.2 Study Inclusion/Exclusion Criteria

At the initiation of this project in 2021, a total of 24 shared studies were identified and reviewed for inclusion from the FITBIR database. To be included, studies

had to report severity of TBI (mild, moderate/severe, no TBI) and demographic information, include adult participants (≥18 years), measure at least one of the psychological or functional health outcomes relevant to our overall FASTRUN project (e.g., PTSD, substance use disorders, sleep outcomes, etc.), and include an associated follow-up timepoint. Twelve studies were excluded for missing TBI severity, demographic information, baseline data without a corresponding follow-up timepoint, or lack of relevant outcome data. An additional three studies were excluded because they did not include adult participants, leaving nine shared studies to create new harmonized datasets (see Figure 1 for a flow diagram of excluded studies). Of these, four studies (Mac Donald et al., 2019; Roy et al., 2015; Walker et al., 2016; Yue et al., 2020) included PTSD outcomes (Table 1) and were included in the cross-sectional dataset.

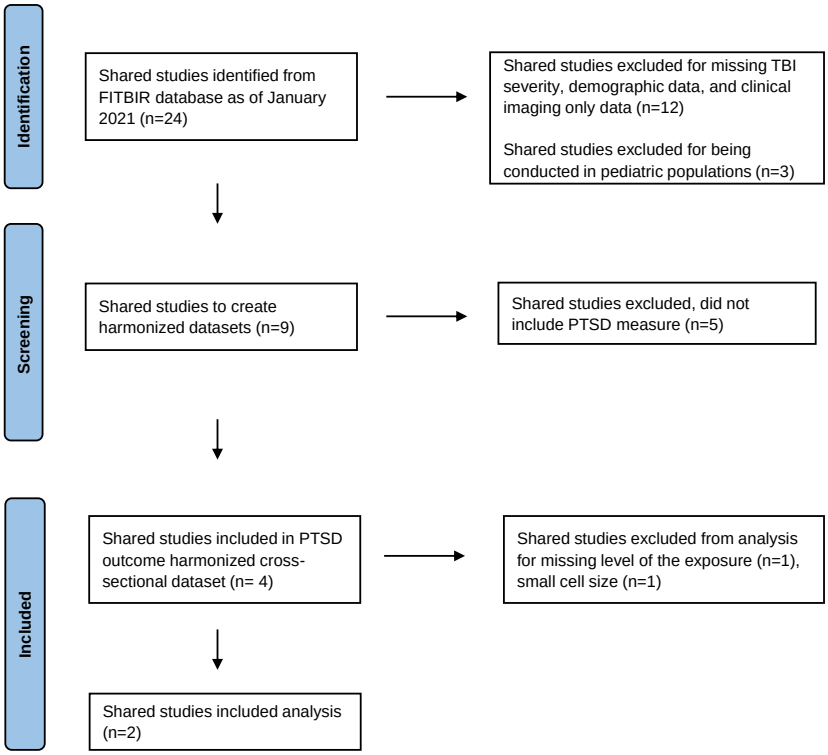

Figure 1. Flowchart

We based our data harmonization and analysis approach on methods used in individual participant level data meta-analysis to appropriately study differences when conducting multiple-study data combination (Riley et al., 2010; Ventresca et al., 2020). We combined data from numerous studies, forms, and variables

Table 1. FITBIR shared studies and measures - PTSD Outcome

Study ID	Title	Sample size	TBI severity	PTSD measure	PTSD variable	Cut point[1]	Included[2]
246 (Yue et al., 2020)	Transforming Research and Clinical Knowledge in Traumatic Brain Injury (TRACK-TBI) Pilot	599	mild TBI, moderate/ severe TBI	Posttraumatic Stress Disorder Checklist Civilian Version (PCLC_Standard)	PCLCTotlScore	No = 17-49 Yes = 50-85	No
254 (Roy et al., 2015)	Predictors of PTSD and Post Concussive Syndrome of OIF/OEF Veterans	80	mild TBI, no TBI	Clinical Administered PTSD Scale for DSM_IV (CAPS_IV)	CAPSPTSDCriteriaInd	No = 0 Yes = 1	No
254 (Roy et al., 2015)	Predictors of PTSD and Post Concussive Syndrome of OIF/OEF Veterans	80	mild TBI, no TBI	Posttraumatic Stress Disorder Checklist Military Version (PCLM)	PCLMTotalScore	No = 17-49 Yes = 50-85	No
263 (Walker et al., 2016)	CENC Study 1: Observational Study on Late Neurologic Effects of OEF/OIF/OND Combat	1,539	mild TBI, no TBI	PTSD Checklist for DSM-5 (PCL-5)	PCL5SymptmSeverityScore	No = 0-32 Yes = 33-80	Yes
264 (Mac Donald et al., 2019)	CENC Study 25: Assessment of Long-Term Outcome & Disability in Active-Duty Military Prospectively Examined Following Concussive TBI	94	mild TBI, no TBI	PCL_M_FITBIR	PCLMTotalScore	No = 17-49 Yes = 50-85	Yes
264 (Mac Donald et al., 2019)	CENC Study 25: Assessment of Long-Term Outcome & Disability in Active-Duty Military Prospectively Examined Following Concussive TBI	94	mild TBI, no TBI	CAPS_IV	CAPSBCDSubtotalsScore	No = 0-64 Yes = 65-128	Yes

Note. [1]Cut point for dichotomous PTSD variable, [2]Included in analysis.

in the FITBIR data repository by creating a function that would extract the variables of interest and their respective timepoint. The function produced a dataset in long format with each row containing the study ID, participant ID, value and timepoint of the measurement, and the name of the form, section, and variable. From this intermediate dataset, we filtered baseline values and dichotomized the outcome to create a cross-sectional dataset with one row per participant.

Separately, we created a demographic dataset and primary dataset. The primary dataset contained information on TBI injury severity, date of injury, time between TBI and the beginning of the study, and study-level data. The demographic dataset contained information on race, gender, age, veteran, military, or civilian status, ethnicity, income, educational attainment, and current employment. These datasets include one row per participant and can be combined with any dataset of interest. In the present study, the datasets were joined with the PTSD cross-sectional dataset for analysis.

2.3 Variables and Measures

When possible, TBI severity was determined using the International Classification of Diseases (ICD) – Post Concussive Syndrome (PCS) diagnostic criteria (ICDPCS). However, not all studies included the requisite data to evaluate these criteria, which led to TBI severity being determined on a study-by-study basis. For example, some studies included adequate data to differentiate between participants with no TBI, mTBI, or moderate/severe TBI and others did not, in which case other study design characteristics, such as inclusion criteria were used to establish TBI severity (e.g., some studies only included participants with mTBI, and therefore we were able to create variables reflecting this level of TBI severity in the dataset). In the final dataset, TBI severity included three levels: no TBI, mTBI, and moderate/severe TBI. The third group, moderate/severe TBI, combined data for any participant with history of either a moderate or severe TBI. Study 246 (Yue et al., 2020) used the Glasgow Coma Scale (GCS) total score to determine TBI severity. All participants had mild (GCS = 13-15) or moderate/severe TBI (GCS = 3-12). Studies 254, 263, and 264 (Mac Donald et al., 2019; Roy et al., 2015; Walker et al., 2016) included participants with either no TBI or mTBI, but did not include participants with moderate/severe TBI.

Across studies, several instruments were used to measure PTSD. In retrospective data harmonization, algorithmic transformation allows continuous and/or categorical variables with different, but comparable, ranges or categories to be combined into a categorical outcome to allow for cross-study comparisons (Fortier et al., 2017). Accordingly, we identified cut scores in the extant literature, and standardized and dichotomized PTSD variables into a "probable PTSD" outcome based on these cut scores (see Table 1). We used the following scores to indicate probable PTSD: a total score of 50-85 on the Posttraumatic Stress Disorder Checklist Civilian Version (PCL-C Weathers, Litz, Herman, Juska, & Keane, 1994) and Military Version (PCL-M Weathers et al., 1994),

a score of 33-80 on the PTSD Checklist for DSM-5 (PCL-5 Blevins, Weathers, Davis, Witte, & Domino, 2015; Weathers et al., 2013) and a score of 65-128 (with a positive Criterion A rating) on the Clinician Administered PTSD Scale for DSM-IV (CAPS-IV Blake et al., 1995; Weathers, Litz, Huska, & Keane, 2008). We used baseline measurements to create the dichotomous "probable PTSD" outcome variable. Baseline was defined as the earliest timepoint with a PTSD outcome measurement if the study had set timepoints. For studies without set timepoints, it was defined as the earliest observation with a PTSD outcome measurement for each participant. When a study used more than one PTSD variable, if any variable indicated the participant was likely experiencing PTSD, the participant was labeled as positive for "probable PTSD."

For the cross-sectional analysis, we dichotomized race and ethnicity to categorize participants as either Non-Hispanic White or Other, based on the available data. We used baseline age to create the continuous age variable, which was defined as the youngest age recorded for each participant. We coded gender based on the measure with the smallest amount of missing data in each shared study. Due to limitations of the existing data, both gender (male or female participants) and race/ethnicity were coded as binary variables.

2.4 Data Analysis

We used logistic regression models to measure the association between probable PTSD (yes/no) and mild TBI (yes/no). Studies were included in the analysis if they had both levels of TBI exposure (i.e., no history of TBI and a history of mild TBI). We built a separate model for each study with age, gender, and race included as covariates and a model with combined results, with study ID included as an additional covariate. Missing data were excluded via listwise deletion. All analyses were performed using SAS version 9.4.

Due to the limited overlap of harmonized variables across studies, there is a potential bias of unmeasured confounding in the analysis. Therefore, we calculated E-values to assess the potential contribution of unmeasured confounding on our results. The E-value is defined as the minimum strength of association that an unmeasured confounder would need to have with both the exposure and outcome, conditional on the measured covariates, to fully explain away a specific exposure-outcome association (VanderWeele & Ding, 2017). We used the E-value formula for odds ratios for common outcomes as prevalence of probable PTSD was higher than 15% in our sample (VanderWeele & Ding, 2017).

3 Results

Overall, 2,312 participants (ns ranging from 80 to 1,539) from four studies (Mac Donald et al., 2019; Roy et al., 2015; Walker et al., 2016; Yue et al., 2020) were screened for PTSD, and 32% screened positive. In total, 1,892 participants had a history of mild TBI, 21 had a history of moderate or severe TBI, and 399 had no history of TBI (Figure 2). Most participants from these four studies

identified as male (83%), White (63%), and veterans or military members (74%), and the largest age category was between 25 and 39 years old (47%, see Table 2). Due to the low number of participants with moderate or severe TBI we were unable to include this group in the final analyses.

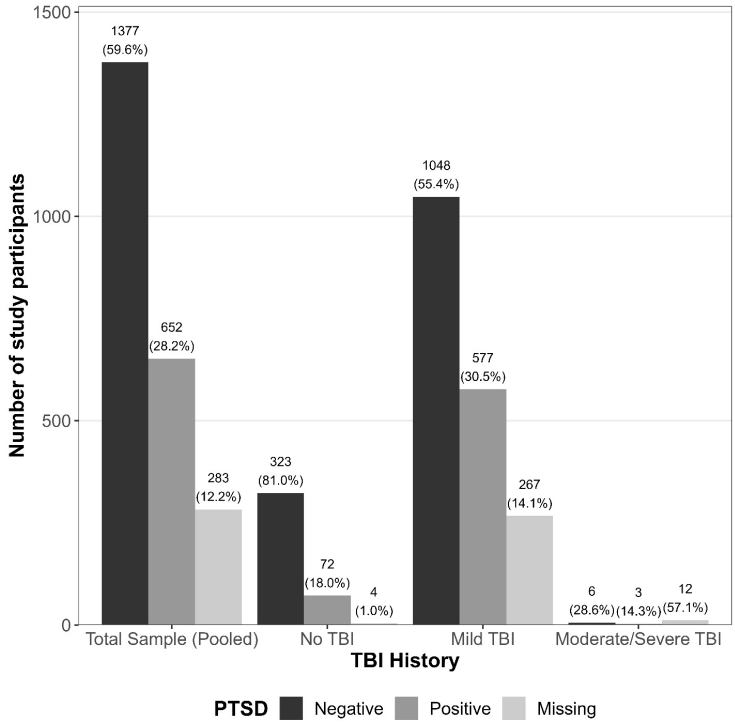

Figure 2. PTSD Outcomes by TBI history/severity in FITBIR; total across four included studies (N=2,312)

We then measured the association between history of mild TBI (yes/no) and probable PTSD (yes/no), examining only those studies with appropriate comparator data (i.e., similar groups within each study who differed in terms of their exposure to or severity of TBI). One study was excluded from this analysis due to not having comparative data on TBI presence or severity (Yue et al., 2020), and another study was excluded because the distribution of the outcome resulted in one of the groups having less than five participants, which precluded the ability to conduct the analysis (Roy et al., 2015).

Overall, 1,633 participants from two studies (Mac Donald et al., 2019; Walker et al., 2016) were included in the comparative analysis (Table 2). Most of the participants from these two studies were male (87%), between 25 and 39 years old (54%), and identified as Non-Hispanic White (61%). All participants from these

Table 2. Demographic Characteristics of PTSD participants in all four studies (Mac Donald et al., 2019; Roy et al., 2015; Walker et al., 2016; Yue et al., 2020)

TBI Category	Overall N = 2,312[1]	No TBI N = 399[1]	Mild TBI N = 1,892[1]	Moderate/Severe TBI N = 21[1]
PTSD				
Negative	1,377 (68%)	323 (82%)	1,048 (64%)	6 (67%)
Positive	652 (32%)	72 (18%)	577 (36%)	3 (33%)
Missing	283	4	267	12
Gender				
Male	1,922 (83%)	319 (80%)	1,587 (84%)	16 (76%)
Female	390 (17%)	80 (20%)	305 (16%)	5 (24%)
Age Category				
<25	174 (7.5%)	11 (2.8%)	158 (8.4%)	5 (24%)
25-39	1,077 (47%)	234 (59%)	838 (44%)	5 (24%)
40-49	553 (24%)	93 (23%)	458 (24%)	2 (9.5%)
50-64	407 (18%)	54 (14%)	346 (18%)	7 (33%)
65+	96 (4.2%)	5 (1.3%)	89 (4.7%)	2 (9.5%)
Missing	5	2	3	0
Race/ethnicity				
Non-Hispanic White	1,331 (63%)	163 (53%)	1,155 (65%)	13 (62%)
Other	787 (37%)	144 (47%)	635 (35%)	8 (38%)
Missing	194	92	102	0
Population type				
Veteran/Military	1,713 (74%)	399 (100%)	1,314 (69%)	0 (0%)
Civilian	599 (26%)	0 (0%)	578 (31%)	21 (100%)

Note. [1]n (%)

studies were military Veterans or active-duty service members. The prevalence of probable PTSD ranged from 32% to 37% (see Table 3). Participants with a history of mild TBI had 2.7 times greater odds of meeting criteria for probable PTSD than those without a history of TBI (95% CI: 2.0, 3.7, Table 4, Figure 3). When data from each study was analyzed separately, only history of mild TBI was associated with increased odds of screening positive for probable PTSD in both studies. Overall, approximately 79% of participants from these two studies had a history of mild TBI. Table 3 reports adjusted logistic regression models predicting probable PTSD. When the two studies were combined, participants with a history of mild TBI had greater odds of probable PTSD compared to those with no history of TBI (OR 2.8, 95% CI: 2.0, 3.7). White participants had decreased odds of screening positive for PTSD (OR 0.5, 95% CI: 0.4, 0.6) after adjusting for the effects of TBI, and none of the other included covariates had statistically significant associations with PTSD once TBI was accounted for in the models.

We conducted a sensitivity analysis on the association between history of mild TBI and probable PTSD by calculating an E-value. The E-Value for the observed odds ratio of 2.7 was 2.67. Therefore, it would take a strong unmeasured confounder that was associated with history of mild TBI and probable PTSD

Table 3. Descriptive Characteristics of PTSD Participants Included in Comparative Analyses (Mac Donald et al., 2019; Yue et al., 2020)

TBI Category	Overall N = 1,633[1]	No TBI N = 326[1]	Mild TBI N = 1,307[1]
PTSD			
Negative	1,014 (63%)	251 (78%)	763 (59%)
Positive	599 (37%)	72 (22%)	527 (41%)
Missing	20	3	17
Gender			
Male	1,425 (87%)	257 (79%)	1,168 (89%)
Female	208 (13%)	69 (21%)	139 (11%)
Age Category			
<25	30(1.8%)	5 (1.5%)	25 (1.9%)
25-39	881 (54%)	183 (56%)	698 (54%)
40-49	444 (27%)	81 (25%)	363 (28%)
50-64	259 (16%)	50 (15%)	209 (16%)
65+	14 (0.9%)	5 (1.5%)	9 (0.7%)
Missing	5	2	3
Race/ethnicity			
Non-Hispanic White	929 (61%)	163 (53%)	766 (63%)
Other	595 (39%)	144 (47%)	451 (37%)
Missing	109	19	90
Population type			
Veteran/Military	1,633 (100%)	326 (100%)	1,307 (100%)

Note. [1]n (%)

Table 4. Participant Factors Associated with Positive PTSD Screen (Mac Donald et al., 2019; Yue et al., 2020)

	OR	CI	P-value
Study 263			
Male	0.86	(0.6, 1.19)	.36
Non-Hispanic White	.5	(0.4, 0.6)	<0.0001
TBI	2.4	(1.8, 3.3)	<0.0001
Age	1.0	(0.99, 1.01)	0.28
Study 264			
Male	0.3	(0.02, 4.0)	.37
Non-Hispanic White	1.9	(0.3, 10.7)	.46
TBI	14.3	(3.2, 64.1)	0.0005
Age	1.0	(0.96, 1.13)	0.29
Combined			
Male	0.8	(0.6, 1.2)	.31
Non-Hispanic White	.5	(0.4, 0.6)	<0.0001
TBI	2.7	(2.0, 3.7)	<0.0001
Age	1.0	(0.98, 1.01)	0.29
263 vs. 264	0.8	(0.5, 1.4)	0.29

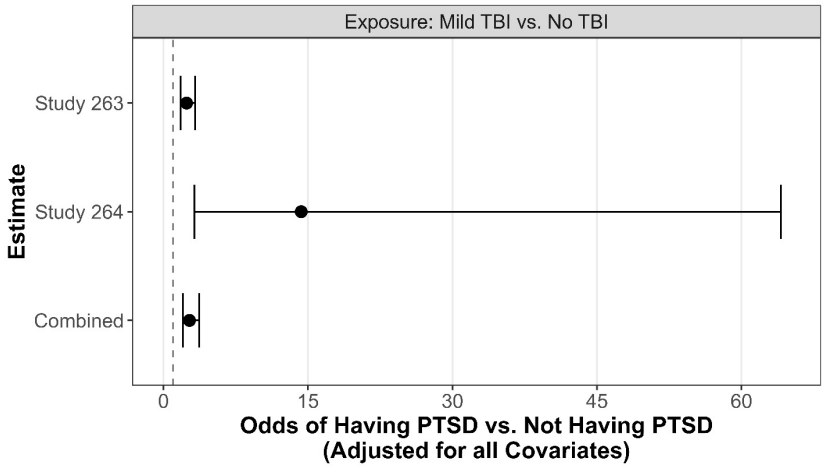

Figure 3. Effect of TBI on PTSD adjusted for participant demographics

by an odds ratio ≥2.67 each to explain away the association. The E-value for the lower confidence interval limit was calculated to be 2.18. Therefore, it would take a strong unmeasured confounder that was associated with history of mild TBI and PTSD by an odds ratio of ≥2.18 each for the confidence interval to cross the null value of 1.

4 Discussion

To overcome some of the significant challenges that exist in exploring and understanding the relationship between TBI and PTSD, we harmonized data from shared studies in the FITBIR database and explored associations between TBI, PTSD, and demographic variables. The final sample, derived from four shared studies, comprised civilian, veteran, and active-duty service member participants, 82% of whom had a history of TBI and 32% of whom screened positive for probable PTSD. These studies included participants seen in a wide range of medical disciplines, including physical medicine and rehabilitation, neurology, and mental health. Additionally, the studies used reliable and valid measures to screen and diagnose both TBI and PTSD, including careful delineation between TBI and PTSD-related symptomatology where relevant. Thus, these analyses represent the assimilation of data from a large number of participants across a range of research fields and are based on data that were collected using rigorous scientific methodology, and therefore offers greater clarity of the TBI-PTSD relationship. Of note, using this large sample of prospectively collected data from a range of research sites, a significant association between TBI and PTSD was identified.

The comparative analyses examining the association between TBI and probable PTSD was performed using data from 1,633 participants across eight U.S.

military and veteran research sites. The participants were 87% male, 61% white and predominantly between the ages of 25-50. Individuals with a history of mild TBI had nearly three times greater risk of developing PTSD compared to similar controls in the studies without a TBI history, more so if they were non-White, and the associations were present in both the individual studies and consolidated dataset. Given the range of sensitive screening tools and effective intervention strategies for PTSD, these associations are important for persons with TBI, their families, clinicians, and health care administrators to be aware of, to assist in early diagnosis and allow for adequate intervention. While recovery after mild TBI is typically rapid and complete, individuals with comorbid PTSD can often have a slower recovery, greater symptomatology, and need for additional, targeted services (Mac Donald et al., 2019; Walker et al., 2016). As the symptoms of PTSD and persistent mild TBI are similar, heightened awareness of their co-occurrence can assist patients, caregivers, and clinicians in accessing necessary individualized care. Our findings support the need for care for TBI and PTSD in individuals who have had a TBI exposure, particularly those whose symptoms are persistent. Additionally, given the disparity in resources for non-White individuals and the higher rate of PTSD in this population, healthcare administrators should be aware of these added risks and need for services. In general, clinicians who provide care to individuals with TBI exposures must be mindful of the increased risk of PTSD following injury and have skills to assess and manage individuals with the dual diagnosis of TBI and PTSD.

4.1 Limitations

While the analyses used were rigorous, there remain several limitations that warrant further investigation. FITBIR contains a significant number of prospective datasets involving individuals with TBI; however, most of the publicly shared studies available at the time of our search of the FITBIR database did not contain adequate information on PTSD to be useful for the pooled comparator analyses. Of the 12 available studies, only nine could be harmonized; only four contained PTSD outcome data similar enough for harmonization, and only two of those included comparators (i.e., mild TBI and no TBI groups from a similar cohort) to allow for group comparison. Similarly, data on individuals with moderate and severe TBI were too limited to allow for analysis, and therefore only participants with either mild TBI or no TBI could be compared. As described, we categorized TBI severity and PTSD in the original datasets and combined those categorical variables to allow for cross-study comparison. It is worth noting that there are other approaches for data combination that might be considered in future research. Namely, Bauer and Hussong (2009) describe the use of moderated nonlinear factor analysis, which can be used to combine scales with different item functioning across levels of severity. Readers should consider how variables were combined in their interpretation of these results and use of the FITBIR meta datasets. Regarding sample make-up, the two studies used to assess the associations between mild TBI and probable PTSD included service members and veteran participants, leaving civilian injuries under-represented. Similarly, female

participants represented a minority of the final dataset. Finally, given the limitations of data available in FITBIR, more detailed investigations into secondary demographic and clinical variables associated with both TBI and PTSD could not be performed. Thus, further analyses with the association between TBI and PTSD must be performed using either large, multi-center, prospective datasets that include military and civilian injuries or using unified individual participant level data repository sources, such as FITBIR, once additional datasets have been added and are publicly shared.

4.2 Conclusions

The use of publicly accessible data repositories for TBI allows for comprehensive analyses of large numbers of individuals with elevated risk for TBI exposure and/or PTSD. The available data supports that individuals with mild TBI exposure have a significantly elevated risk for the development of probable PTSD compared to similar individuals without a TBI history. Individuals with mild TBI, caregivers, clinicians, and healthcare administrators should be aware of this increased risk and identify ways of enhancing access to screening and management options. Further analyses of composite TBI data sets, including FITBIR, are encouraged.

Notes

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Data Availability Statement: The data that support the findings of this study are available on the FITBIR website (https://fitbir.nih.gov/). The PTSD-TBI meta-datasets and code are available to those who have created a FITBIR account at https://fitbir.gov (navigate to the Meta Study tab, select

study "FITBIR: Accelerating Synthesis is TBI Research Using Novel Methods", and click on the Data tab). The interactive data visualizations were created using R Shiny Apps and are publicly available on the FITBIR website,https://fitbir.nih.gov/meta_study_profile/223 (in the Data tab). The data are not publicly available due to privacy or ethical restrictions.

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