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Characterizing Sex Differences in Clinical and Functional Outcomes Among Military Veterans with a Comprehensive Traumatic Brain Injury Evaluation (CTBIE): A Million Veteran Program (MVP) Study

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Abstract

Using a diverse sample of military Veterans enrolled in the VA's Million Veteran Program (N=14,378; n=1,361 females [9.5%]; all previously deployed), we examined sex differences on the Comprehensive Traumatic Brain Injury Evaluation (CTBIE), a structured traumatic brain injury (TBI) interview routinely administered within the VA. Confirmed TBI diagnoses were more frequent among males than females (65% vs. 58%). Additionally, when compared to females, a greater proportion of males with CTBIE-confirmed TBI histories experienced blast-related injuries and were employed. In contrast, a greater proportion of females reported experiencing falls, sustaining a TBI since deployment, and having more severe neurobehavioral symptoms (particularly affective-related symptoms). Results indicate that males and females experience differential clinical and functional outcomes in the aftermath of military TBI. Findings underscore the need to increase female representation in TBI research to increase understanding of sex-specific experiences with TBI and to improve the clinical care targeted to this vulnerable population.

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Author Contributions

VCM developed the study concept. All authors contributed to the study design. Data curation was performed by CCC with assistance from MSS and VCM, and VCM performed the data analysis and interpretation in consultation with AJJ and LDW. VCM drafted the paper, and CCC, MSS, AJJ, and LDW provided edits, feedback, and revisions. All authors approved the final version of the paper for submission.

Conflicts of Interest

Conflicts of Interest: None

Keywords

gender; female Veterans; military; Veterans Health Administration; CTBIE

Introduction

The military conflicts in Iraq and Afghanistan have led to a renewed interest in understanding clinical outcome and recovery following traumatic brain injury (TBI). In particular, accurate detection and diagnosis of TBI as well as tracking and monitoring of post-injury sequelae have been two primary areas of scientific exploration. Through these efforts, it has been well established that a host of “post-concussive” or neurobehavioral symptoms such as headache, sleep difficulties, and forgetfulness are frequently endorsed following TBI (Merritt et al., 2020; Scholten, Sayer, Vanderploeg, Bidelspach, & Cifu, 2012; Schwab et al., 2017). Although there is ongoing debate regarding the precise etiology of these symptoms, these sequelae have been shown to significantly interfere with service members’ day-to-day functioning and overall quality of life (McMahon et al., 2014; Schiehser et al., 2015). Given the pervasiveness of neurobehavioral symptoms and the negative impact of these sequelae on functioning, there has been increasing interest in better understanding the factors that contribute to the development and maintenance of symptoms and poor clinical outcome following injury.

Examining the influence of biological sex on post-injury outcome and recovery has recently emerged as an issue of special importance within the broader traumatic brain injury (TBI) literature (Gupte, Brooks, Vukas, Pierce, & Harris, 2019; Merritt, Padgett, & Jak, 2019; Mollayeva, Mollayeva, & Colantonio, 2018). However, this area of investigation has been severely understudied within the context of military Veterans, resulting in the development of clinical practice guidelines that are based predominantly on evidence gathered from androcentric studies (Cogan, McCaughey, & Scholten, 2020; Kim et al., 2018; Valera et al., 2021). Although military service was, historically, a male-dominated occupation, the number of female service members has increased substantially over the past several decades (Amoroso & Iverson, 2017; Armed Forces Health Surveillance Branch, 2019; Defense Manpower Data Center, 2019; Reynolds & Shendruk, 2018). Consequently, the Veterans Health Administration (VHA) has experienced a sizable increase in the number of women Veterans seeking care; currently, roughly 10% of VHA users are now females, and this number is only expected to grow substantially in the coming years (Frayne et al., 2014; Kim et al., 2018). In order to better serve the female Veteran population, robust studies with adequate female representation are critically needed so that we can better understand women’s experience with TBI and improve the clinical care offered to this population.

Mechanistically, there are also a number of reasons why sex may modify outcome and recovery in the context of TBI including differences in musculature, hormones, and social experience (Mollayeva et al., 2018; Solomito, Reuman, & Wang, 2019; Späni, Braun, & Van Eldik, 2018). For example, females generally have weaker neck muscles than males, which has been shown to contribute to greater angular acceleration of the head/neck upon injury (Tierney et al., 2008; Tierney et al., 2005). Furthermore, a combined animal and in

vitro modeling study examining traumatic axonal injury showed that females exhibit greater axonal pathology following neurotrauma (Dollé et al., 2018). Both oral contraceptive use and phase of menstrual cycle at the time of injury have also been associated with differential clinical outcomes following TBI (Gallagher et al., 2018; Mihalik, Ondrak, Guskiewicz, & McMurray, 2009; Wunderle, Hoeger, Wasserman, & Bazarian, 2014). Finally, it has long been hypothesized that environmental and cultural norms may differentially influence females' and males' experience of TBI and clinical presentation following injury (Granito Jr, 2002), and prior studies have shown that females and males differ with respect to both injury-disclosure behaviors (Kerr, Register-Mihalik, Kroshus, Baugh, & Marshall, 2016; Kerr et al., 2014; Kroshus, Baugh, Stein, Austin, & Calzo, 2017) and treatment engagement (Kim et al., 2018; Mollayeva et al., 2018).

The VA's Million Veteran Program (MVP) offers a unique opportunity to examine sex differences in military Veterans. MVP is a nationwide VA research initiative that seeks to incorporate genomic data with electronic health record and self-report survey data to learn how these factors influence health and illness in Veterans (Gaziano et al., 2016). A recent study conducted within MVP characterized sex differences with regard to MVP enrollment rates, healthcare utilization, and health conditions among the entire MVP cohort (Harrington et al., 2019). The present study extends prior work by examining sex differences with respect to various TBI outcomes among MVP-enrolled Veterans who screened positive for TBI on the VA TBI Screen (Department of Veterans Affairs, 2010) and subsequently completed the Comprehensive Traumatic Brain Injury Evaluation (CTBIE), a clinician-administered VA interview that assesses historical, deployment-related TBIs (Scholten et al., 2012). Outcomes of interest included (a) CTBIE diagnostics, (b) injury-related characteristics, (c) neurobehavioral symptoms and medical comorbidities, and (d) functional outcomes.

Given the dearth of research examining sex differences in military Veterans, we evaluated sex differences in two phases—Aim 1 evaluated all Veterans who *screened positive* for TBI on the VA TBI Screen and completed the CTBIE (i.e., the "full CTBIE sample"), and Aim 2 evaluated only those Veterans with a *CTBIE-confirmed history of TBI* (see Method section for details). Prior research has shown that Veterans who screen positive for TBI, regardless of whether they are ultimately diagnosed with TBI on the CTBIE, experience high rates of neurobehavioral symptoms and psychiatric disorders (Carlson et al., 2010; Scholten et al., 2012). Therefore, evaluating sex differences in both the full CTBIE sample *and* the CTBIE-confirmed TBI sample could offer valuable clinical information. Our final aim (Aim 3) focused exclusively on neurobehavioral symptom reporting and evaluated sex differences with respect to symptom domain and symptom interference summary scores while adjusting for demographic/social construct data and injury-related characteristics.

Methods

Procedures

Million Veteran Program (MVP).—MVP is a nationwide research initiative offering Veterans the opportunity to participate in research that seeks to examine how genes impact health and disease (Gaziano et al., 2016). Any Veteran is eligible to participate in MVP as

long as they are able to provide informed consent. The specific MVP project from which this study's data were collected ("MVP026") received VA Central IRB approval in 2019. Data for this study was obtained from the VA's Corporate Data Warehouse (Fihn et al., 2014) between October 2007 and October 2019.

Participants

Participants were selected from a larger sample of Veterans who (1) enrolled in MVP (N=702,740) and (2) screened positive on the VA TBI Screen (i.e., "TBI Clinical Reminder Screen") and completed the CTBIE (N=17,496). To maximize the number of participants included in this study, Veterans having a missing (n=2,866) or uncertain (n=293) response to the "CTBIE diagnosis" variable (see below under "Measures" for details) was the only additional exclusion criterion; thus, the final sample for Aim 1 included 14,378 Veterans. Regarding Aim 2, only those Veterans with a *CTBIE-confirmed history of TBI* were included (N=9,243). Finally, in order to be included in Aim 3, participants must have had a CTBIE-confirmed history of TBI and passed symptom validity testing (N=7,635; see below under "Measures" for details). See Figure 1 for a flow diagram illustrating the inclusion/exclusion criteria for this study.

Measures

VA TBI Screen and CTBIE.—The VA TBI Screen was initiated within the VHA in April 2007 and the CTBIE in October 2007 to improve the tracking and monitoring of deployment-related TBI (Belanger, Vanderploeg, Soble, Richardson, & Groer, 2012; Department of Veterans Affairs, 2007, 2010; Scholten et al., 2012). The psychometric properties of the VA TBI Screen and CTBIE have been extensively studied (Belanger, Vanderploeg, & Sayer, 2016; Belanger et al., 2012; Donnelly et al., 2011; Fortier, Amick, Kenna, Milberg, & McGlinchey, 2015; Pape et al., 2018; Radigan, McGlinchey, Milberg, & Fortier, 2018), with results showing the two instruments demonstrate moderate-to-good sensitivity (56%−90%) with variable specificity (13%−93%) (Belanger et al., 2012; Pape et al., 2018; Radigan et al., 2018).

The VA TBI Screen is administered to Operation Enduring Freedom/Operation Iraqi Freedom (OEF/OIF)-era Veterans who have experienced deployment and were not previously diagnosed with a TBI (Belanger et al., 2012). The screen is administered to Veterans upon enrollment in the VHA, usually by a primary care provider, and consists of four-sections: (1) identification of injury event(s) (e.g., blast or explosion, bullet); (2) immediate signs/symptoms (e.g., losing consciousness, not remembering the event); (3) acute symptoms (e.g., memory problems, headache); and (4) current symptoms (e.g., memory problems, headache). All four sections must be endorsed to screen positive for TBI; positive screens result in a referral to a TBI specialist who then completes the CTBIE (Belanger et al., 2012; Scholten et al., 2012).

The CTBIE is conducted by trained clinicians within polytrauma clinics or by specialists with "appropriate background and skills" (e.g., physiatrists, neurologists, etc.) who have expertise in the diagnosis and assessment of TBI (Department of Veterans Affairs, 2010). As part of the CTBIE, the clinician follows a structured interview template

to gather demographic and social construct data (e.g., age, race/ethnicity, pre-military education), functional outcomes (e.g., employment status), as well as information about any OEF/OIF deployment-related injuries. Specifically, detailed information is collected about mechanism(s) of injury (e.g., bullet, vehicular, fall, blast) and the number and duration of any episodes of loss of consciousness (LOC), alteration of consciousness (AOC), and post-traumatic amnesia (PTA). There are additional questions to assess whether the Veteran has experienced any TBIs outside of deployment (i.e., "Prior to your OEF/OIF deployment, did you experience a brain injury or concussion" and "Since your OEF/OIF deployment, have you experienced a brain injury or concussion"). The CTBIE also includes administration of the Neurobehavioral Symptom Inventory (described below); an assessment of psychiatric symptoms (i.e., a single item on the CTBIE where the clinician makes a determination about whether the Veteran is currently experiencing psychiatric symptoms by marking "yes" or "no") and pain (i.e., the clinician asks the patient "In the last 30 days, have you had any problems with pain?" and must select either "yes" or "no); and a physical examination.

At the conclusion of the CTBIE, the clinician is prompted to answer two diagnostic questions, one related to the presence/absence of a historical TBI (referred to as "CTBIE diagnosis" below) and the other related to current symptom etiology (referred to as "CTBIE symptom etiology" below). Regarding the CTBIE diagnosis, the clinician selects either "yes" or "no" to the question, "Based on the history of the injury and the course of clinical symptoms, did the Veteran sustain a TBI during OEF/OIF deployment?" The clinician is instructed to answer this question based on LOC, AOC, and PTA status, consistent with VA and Department of Defense (DoD) guidelines for TBI (The Management of Concussion/mTBI Working Group, 2016). Regarding CTBIE symptom etiology, clinicians are asked to make a determination about the *cause* of the Veteran's current symptom presentation, selecting one of the following options: "symptom resolution"; "TBI residual problems"; "behavioral health conditions"; "a combination of TBI residual problems and behavioral health conditions"; or "other".

Neurobehavioral Symptom Inventory (NSI).—The NSI—a 22-item self-report measure designed to measure neurobehavioral, or "post-concussive," symptoms following TBI (Cicerone & Kalmar, 1995)—was administered as part of the CTBIE. Veterans rate the extent to which they have been affected by each symptom "over the last 30 days" using the following scale: 0 (*None*); 1 (*Mild*); 2 (*Moderate*); 3 (*Severe*), and 4 (*Very Severe*). Veterans are also asked to rate the extent to which these symptoms have interfered with their life in the last 30 days ("symptom interference") using the following scale: 0 (*Not at all*); 1 (*Mildly*), 2 (*Moderately*), 3 (*Severely*), and 4 (*Extremely*). The following NSI-derived variables were examined for this study: symptom domain scores, symptom interference, and symptom validity (i.e., Validity-10).

Symptom Domain Scores: Using the results of a prior factor analysis conducted on the NSI in a similar military cohort (Vanderploeg et al., 2015), symptom domain scores were computed reflecting vestibular (items 1–3, range: 0–12; Cronbach's $\alpha = 0.84$), somatic/sensory (items 4–7 and 9–11; range: 0–28; Cronbach's $\alpha = 0.82$), cognitive (items 13–16; range: 0–16; Cronbach's $\alpha = 0.90$), and affective (items 17–22; range: 0–24; Cronbach's α

= 0.89) symptoms. These scores were then transformed into “scaled scores” by taking into account the total number of items per domain (i.e., each symptom domain total score was divided by the total number of items in that domain) to ensure that all scores were on the same metric (i.e., this transformation resulted in a possible range of 0–4 for all symptom domain scores). Consistent with prior research (Bouldin et al., 2021; Iverson et al., 2011), the symptom domain scaled scores were dichotomized into high (“severe”) and low (“not severe”) symptom groups, using 3 as the cutoff to define groups (i.e., scores ≥ 3 were classified as “severe” symptoms, and scores < 3 were classified as “not severe” symptoms).

Symptom Interference: The symptom interference score (described above; range: 0–4) was dichotomized into high (“severe”) and low (not severe”) interference groups, again using 3 as the cutoff to define groups (i.e., scores ≥ 3 were classified as “severe” interference, and scores < 3 were classified as “not severe” interference).

Symptom Validity: To assess symptom validity, the NSI Validity-10 scale was used (Vanderploeg et al., 2014). The Validity-10 contains 10 items from the NSI that are considered to be infrequently endorsed symptoms (items 1–3, 5–6, 8–9, 11, 15, and 16). To compute the Validity-10 scale, the 10 items are added together to create a total score; a score of >22 reflects symptom over-reporting (Vanderploeg et al., 2014). Using this cutoff, symptom validity test (SVT) pass and fail groups were created—a Validity-10 score ≤22 was classified as “SVT-Pass” and a Validity-10 score >22 was classified as “SVT-Fail.”

Supplemental Table 1 displays descriptive statistics associated with the NSI variables.

Statistical Analyses

All analyses were conducted using Stata (Stata/MP 15.1 for Windows). Biological sex served as the independent variable in all analyses. Aim 1 analyses included Veterans who *screened positive* for TBI (i.e., the full CTBIE sample; n=14,378); dependent variables for Aim 1 were grouped as follows (all categorical data): (a) CTBIE diagnostics (CTBIE diagnosis, CTBIE symptom etiology), (b) injury-related characteristics (mechanism of injury: bullet, vehicular, fall, and blast; LOC, AOC, and PTA status; and TBI history prior to and since deployment), (c) neurobehavioral symptoms and medical comorbidities (symptom domain scores: vestibular, somatic/sensory, cognitive, and affective; symptom interference; symptom validity; psychiatric symptoms; problems with pain), and (d) functional outcomes (employment status). Aim 2 analyses included only those Veterans with a *CTBIE-confirmed history of TBI* (N=9,243); dependent variables for Aim 2 were identical to Aim 1, with the exception of CTBIE diagnostics, as Aim 2 only included CTBIE+ Veterans. Finally, Aim 3 analyses included only those Veterans with a *CTBIE-confirmed history of TBI* who *passed symptom validity testing* (N=7,635); dependent variables included the NSI symptom domain and symptom interference scores.

Descriptive statistics were computed for the overall sample, and females and males were compared using chi-square analyses to evaluate group differences across demographic and social construct data. For Aims 1 and 2, chi-square analyses were used to compare females and males across the CTBIE variables of interest (i.e., CTBIE diagnostics, injury-related characteristics, neurobehavioral symptoms and medical comorbidities, and functional

outcomes). Effect sizes for all chi-square analyses are presented as Cramer's *V* or phi values. To account for multiple comparisons, we used a Bonferroni-corrected *p*-value (20 unique analyses in Aim 1 and 19 unique analyses in Aim 2 resulted in an adjusted alpha of ~.003). Stata performs computations on all available data; thus, chi-square analyses were computed based on the total number of non-missing cases.

For Aim 3, logistic regression analyses were conducted to evaluate the association between sex and neurobehavioral symptoms while adjusting for demographic/social construct data (i.e., age, race/ethnicity, education, marital status, and employment status). Specifically, we estimated the odds of having "severe" symptoms (defined using a cutoff of ≥3 on NSI outcomes of interest) as a function of sex. Before running each model, missing data were evaluated; there was less than 10% overall missingness for each model and less than 3% missingness for each variable included within a model. All logistic regression analyses were run on complete cases. As a sensitivity analysis, mechanism of injury (i.e., blast and fall) was added to the model; while this did not significantly change the results, the sample size was substantially reduced because of missingness on the mechanism of injury variables; therefore, we did not retain mechanism of injury as a covariate in our final model. Odds ratios (with 95% confidence intervals [CI's]) reflect the odds of females having "severe" symptoms relative to males. To account for multiple comparisons, we again used a Bonferroni-corrected *p*-value (5 unique analyses resulted in an adjusted alpha of .01).

Results

Sample Characteristics

The final sample included 14,378 Veterans with a history of deployment who completed the CTBIE; of these, 1,361 were females (9.5%) and 13,017 were males (90.5%). Demographic and social construct data for the sample are presented in Table 1. Females and males significantly differed with respect to age distribution (females tended to be slightly older than males), race/ethnicity (a greater proportion of females identified as non-Hispanic Black or African-American, and a greater proportion of males identified as non-Hispanic White as well as Hispanic), pre-military education level (females tended to have higher educational attainment than males), and marital status (at the time of CTBIE completion, a greater proportion of males were married or partnered relative to females).

Aim 1: Sex Differences on CTBIE Outcomes Among Veterans Screening Positive for TBI (Full CTBIE Sample; N=14,378)

Results of the chi-square analyses evaluating females and males across CTBIE outcomes utilizing the full CTBIE sample are presented in Table 2, and statistically significant findings are summarized below.

CTBIE Diagnostics: With regard to TBI status ("CTBIE diagnosis"), a greater proportion of males were diagnosed with TBI compared to females ($p < .001$).

Injury Characteristics: There was a significant relationship between sex and the following mechanisms of injury: bullet ($p = .001$), fall ($p < .001$), and blast ($p < .001$).

A significantly greater proportion of females experienced falls whereas a significantly greater proportion of males experienced bullet and blast-related injuries. With regard to TBI characteristics, there was a significant relationship between sex and AOC status ($p < .001$), such that a significantly greater proportion of males reported experiencing AOC compared to females. Finally, a greater proportion of females endorsed experiencing a TBI *since* deployment compared to males ($p = .001$).

NSI Symptoms and Medical Comorbidities: There was a significant relationship between sex and all NSI symptoms (all p's $< .001$). Relative to males, a significantly greater proportion of females endorsed severe (or clinically significant) vestibular, somatic/sensory, cognitive, and affective symptoms, as well as more severe symptom interference with daily life. Additionally, a significantly greater proportion of females failed symptom validity testing (i.e., Validity-10). Finally, there was a significant relationship between sex and psychiatric symptoms ($p = .001$); relative to males, a greater proportion of females were classified as having psychiatric symptoms on the CTBIE.

When the SVT-Fail group (n=2,146) was removed from the NSI analyses, significant sex differences continued to be observed for the cognitive and affective symptoms clusters (both p's $< .001$) and a trend finding was observed for the somatic symptom cluster ($p = .014$), such that a greater proportion of females endorsed clinically significant symptoms relative to males. There was also a significant association between sex and symptom interference ($p < .001$).

Functional Outcomes: There was a significant relationship between sex and employment status ($p < .001$); specifically, a greater proportion of males were employed at the time of CTBIE completion relative to females. In contrast, a greater proportion of females were unemployed and *not* looking for work compared to males, and more females than males were students.

Aim 2: Sex Differences on CTBIE Outcomes Among Veterans with a CTBIE-Confirmed History of TBI (N=9,243)

Results of the chi-square analyses evaluating females and males across CTBIE outcomes utilizing only those Veterans with a CTBIE-confirmed history of TBI are presented in Table 3. Statistically significant findings are summarized below, as well as any changes observed between the full CTBIE sample (i.e., those *screening positive* for TBI) and those with a CTBIE-confirmed history of TBI.

Injury Characteristics: There continued to be significant relationships between sex and the following mechanisms of injury: fall ($p < .001$) and blast ($p < .001$); a significantly greater proportion of females experienced falls whereas a significantly greater proportion of males experienced blast-related injuries. The proportion of females and males experiencing bullet-related injuries was no longer statistically significant when examining just the CTBIE-confirmed TBI sample. With regard to TBI characteristics, there were no longer significant differences between sex and AOC status. However, sex differences remained with regard to

experiencing a TBI *since* deployment, with females still more likely than males to have had a TBI since deployment ($p = .001$).

NSI Symptoms and Medical Comorbidities: There continued to be a significant relationship between sex and the following NSI variables when examining the CTBIE-confirmed TBI sample: vestibular ($p=.001$), somatic/sensory ($p<.001$), and affective ($p<.001$) symptoms. As before, a significantly greater proportion of females endorsed severe (or clinically significant) symptoms relative to males. There were no longer statistically significant sex differences with respect to cognitive symptoms, symptom interference, symptom validity, or psychiatric symptoms, though all relationships trended in the same direction (females > males; $p's = .004–.040$).

When the SVT-Fail group (n=1,556) was removed from the NSI analyses, significant sex differences were observed for the affective symptom cluster ($p < .001$) and a trend finding was observed for the cognitive symptom cluster ($p = .038$), such that a greater proportion of females endorsed clinically significant symptoms relative to males.

Functional Outcomes: There continued to be a significant relationship between sex and employment status ($p < .001$). Specifically, a greater proportion of males were employed at the time of CTBIE completion relative to females. Additionally, more females were unemployed and *not* looking for work compared to males, and more females than males were students.

Aim 3: Adjusted Logistic Regression Models Evaluating Sex Differences on Neurobehavioral Symptoms (N=7,635)

Results of the logistic regression analyses examining the effect of sex on neurobehavioral symptoms while adjusting for demographic/social construct data (i.e., age, race/ethnicity education, marital status, and employment status) are presented in Table 4. Only Veterans with a CTBIE-confirmed history of TBI who passed symptom validity were included in these analyses. After adjusting for covariates, significant sex differences were observed on the affective symptom cluster; relative to males, females were about 1.5 times more likely than males to report severe affective symptoms ($p<.001$).

Discussion

The primary purpose of this study was to examine sex differences on CTBIE outcomes in military Veterans enrolled in MVP. Sex differences were evaluated across four CTBIE domains—CTBIE diagnostics, injury-related characteristics, neurobehavioral symptoms and medical comorbidities, and functional outcomes. Results showed that males and females experience differential clinical and functional outcomes—both among Veterans *screening positive* for TBI and among those with *CTBIE-confirmed TBI histories*. Results underscore the need for additional studies to be conducted on female Veterans so that we can continue to better understand women's experience with TBI and improve the clinical care being offered to this population.

We evaluated sex differences in two phases—Aim 1 evaluated Iraq/Afghanistan-era Veterans who screened positive for TBI on the VA TBI Screen and completed the CTBIE (i.e., the "full CTBIE sample") and Aim 2 evaluated only Veterans with a CTBIE-confirmed history of TBI. Within the full CTBIE sample (i.e., those screening positive for TBI), confirmed TBI diagnoses were more frequent among males than females (65% vs. 58%). This is generally consistent with the broader TBI literature that has demonstrated higher rates of TBI in males relative to females (Center for Disease Control and Prevention, 2016; Frost, Farrer, Primosch, & Hedges, 2013; Giza et al., 2013). However, within the context of military TBI, comparatively limited research has evaluated associations between sex and TBI prevalence/incidence. An older study by Schneiderman and colleagues (2008) examined Iraq/Afghanistan-era service members following deployment and reported that males and females had a roughly similar prevalence of TBI (males = 11–13%; females = 8–12%). In another study, Hendricks et al. (2013) evaluated military personnel who had completed the VA TBI Screen and showed that males were more likely than females to *screen positive* for TBI (~23% vs. 11%).

In the present study, we evaluated Veterans who had screened positive for TBI on the VA TBI Screen and were subsequently administered the CTBIE; under these specific conditions, we found that males were more likely than females to have a *clinician-confirmed* history of TBI. However, what we are unable to determine from this data is whether this reflects a true sex difference in TBI prevalence or if this instead highlights possible limitations associated with the VA TBI Screen and/or CTBIE methodology (i.e., a possible *under*-confirmation of TBI in females or an *over*-confirmation of TBI in males). It is also possible that provider bias (when completing the CTBIE) may have influenced these results. For example, observer expectation bias or interviewer bias occurs when the interviewer records observations or interprets patients' responses in a manner that aligns with their expectations or anticipated outcomes (Cook, 2010). While the CTBIE template has built-in "checks" to minimize error (i.e., if the clinician selects "no" to LOC, AOC, and PTA, but then enters "yes" for TBI diagnosis, a dialog box will pop up on the screen questioning the diagnosis), provider bias may still exist. Moreover, despite there being universal instructions and specific guidelines for how to administer and score the VA TBI Screen and CTBIE, there may be some variability with respect to how providers were trained, which could similarly influence CTBIE diagnostics. Certainly, future research is needed to better understand TBI prevalence rates among male and female Veterans, but the current data suggest that meaningful sex differences do exist.

Significant sex differences were also observed across several other CTBIE outcomes. Specifically, among Veterans screening positive for TBI, a greater proportion of males experienced bullet and blast-related injuries, reported AOC, and were more often employed at the time of CTBIE completion. In contrast, a greater proportion of females experienced falls; reported having a TBI since their deployment; endorsed clinically significant neurobehavioral symptoms (i.e., vestibular, somatic, cognitive, and affective symptoms) as well as symptom interference with daily life, failed symptom validity testing, and were assessed as having comorbid psychiatric symptoms on the CTBIE. Among Veterans with a *CTBIE-confirmed history of TBI*, sex differences continued to be observed (in the same direction) for mechanism of injury (i.e., fall and blast), experiencing a TBI since

deployment, neurobehavioral symptoms (i.e., vestibular, somatic, and affective symptoms), and employment status. These findings extend our understanding of sex differences in the context of Veterans who (1) screened positive for TBI and (2) were clinically confirmed to have history of TBI upon further analysis, and results provide important targets for future research.

When considering our findings in the context of existing literature, there are few military-related TBI studies available for comparison. Indeed, recent reviews focused on sex differences in TBI have highlighted female underrepresentation in TBI outcome studies (Cogan, McCaughey, et al., 2020; Kim et al., 2018; Merritt et al., 2019; Valera et al., 2021), especially within Veteran samples. Among the published studies that have examined sex differences in the context of military-related TBI, the majority have explored neurobehavioral symptom reporting and have found that female Veterans tend to endorse greater symptoms compared to male Veterans (Brickell et al., 2017; Gray et al., 2020; Iverson et al., 2011; Lippa et al., 2018). Studies have also simultaneously characterized sex differences with respect to psychiatric comorbidities in Veterans with TBI histories; with some exceptions, studies have mostly found that females were more likely than males to have comorbid psychiatric diagnoses and/or endorse greater psychiatric symptoms (Brickell et al., 2017; Iverson et al., 2011). However, Iverson et al. (2011) noted that blast exposure may account for some of the observed sex differences and the influence of provider bias or patient bias also cannot be ruled out (Cook, 2010).

While our findings provide further evidence to suggest that females experience higher rates of *severe* neurobehavioral symptomatology relative to males—both in the full CTBIE sample and in Veterans with a CTBIE-confirmed history of TBI—it is important to note that when we adjusted for demographic/social construct data, the significant effect of sex on neurobehavioral symptoms only remained for the affective symptom cluster. We also evaluated sex differences with respect to symptom validity (using the NSI Validity-10 index) and found that females were significantly more likely than males to be classified in the SVT-Fail group—at least in Veterans screening positive for TBI. Though there remains much debate regarding the clinical utility of the Validity-10 index in this population (Armistead-Jehle et al., 2018; Lange, Brickell, & French, 2015), the greater tendency for females to demonstrate Validity-10 scores above cutoff relative to males is notable and may reflect a propensity for women to be more forthcoming about their symptoms relative to men (Kerr et al., 2014; Kroshus et al., 2017). Ultimately, it is difficult to discern whether symptom validity failure reflects true exaggeration of symptoms, somatization, or other psychological factors such as anxiety sensitivity (Albanese, Boffa, Macatee, & Schmidt, 2017; Vanderploeg et al., 2014). Regardless, the higher rates of symptom invalidity in females suggest the need for (1) expanded research on sex disparities in assessment and care; (2) additional health services targeting women, particularly within the VA; and (3) tailoring psychoeducation and psychotherapy interventions to meet the unique needs of female Veterans.

A final caveat to note is that when we examined the *types* of symptoms endorsed at a severe-to-very severe degree, both females and males tended to endorse high rates of cognitive and affective symptoms but lower rates of vestibular and somatic/sensory symptoms. For

example, in our CTBIE-confirmed TBI sample, when collapsed across sex, roughly one out of every three Veterans endorsed severe cognitive and affective symptoms, whereas one out of every 20 Veterans endorsed severe vestibular and somatic/sensory symptoms. This is particularly important data to consider when designing therapeutic interventions for this population.

Beyond symptom reporting and psychiatric comorbidities, another notable finding pertained to mechanism of injury. In Veterans with a CTBIE-confirmed history of TBI, we found that a significantly greater proportion of females experienced falls whereas a significantly greater proportion of males experienced blast-related injuries. Although not consistently reported in the military TBI literature, mechanism of injury has been linked with behavioral outcomes (i.e., symptom reporting, cognitive functioning) as well as brain structure and function following TBI (Clark et al., 2018; MacDonald et al., 2014; Reid et al., 2014; Sullivan et al., 2021). Furthermore, the finding that females are more likely than males to experience falls may be linked to female Veterans' trauma and/or assault history (i.e., military sexual trauma [MST], intimate partner violence [IPV]), which may coincide with the higher level of affective symptoms reported by women (Iverson, Dardis, Grillo, Galovski, & Pogoda, 2019; Iverson & Pogoda, 2015; Valera et al., 2021). This previous work, combined with our finding of significant sex differences on mechanism of injury, suggests the need for follow-up studies to examine the interactive relationships between biological sex and mechanism of injury on clinical outcomes following military TBI, as it is likely that biological sex may be an important moderator or mediator of these associations. Furthermore, it is also important to note that the "mechanism of injury" categories that are listed within the CTBIE (i.e., bullet, vehicular, fall, and blast) are not fully inclusive of all mechanisms of injury. In particular, the CTBIE precludes causes of injury that may be a primary means of head injury in women—that is, MST/IPV or other "struck by" events (Amoroso & Iverson, 2017; Iovine-Wong et al., 2019; Iverson et al., 2020). Understanding the mechanisms of injury that are most common among female Veterans would greatly help to inform rehabilitation and treatment efforts for this population.

Finally, we evaluated employment status and found that males were more likely than females to be employed at the time of CTBIE completion. While this may not be entirely surprising, and is consistent with recent research (Cogan, Smith, et al., 2020), this does bring to light the importance of considering the vocational needs of female Veterans with positive TBI screens and CTBIE-confirmed histories of TBI. It is certainly conceivable that employment provides a significant benefit (i.e., feeling useful/having a sense of purpose, greater self-efficacy, better quality of life, etc.) that may be absent for women who are not employed (Greer, 2017; Zivin et al., 2011). Furthermore, it is notable that a greater proportion of women in our sample were unemployed and *not* looking for work compared to men, and that more females than males were in school. Although the VHA has successfully implemented evidenced-based vocational rehabilitation programs (Carlson et al., 2018; Pogoda, Carlson, Gormley, & Resnick, 2018; Wyse, Pogoda, Mastarone, Gilbert, & Carlson, 2020), more emphasis could be placed on understanding barriers and facilitators associated with seeking employment that are unique to female Veterans, as well as expanding employment training and opportunities for women. Furthermore, it may be beneficial for the VA to offer career

counseling as well as career interest and aptitude inventories, especially for women who are in school.

There are limitations associated with this study that must be considered when interpreting the results. First, the sample was limited to only Iraq/Afghanistan-era Veterans with a history of deployment who completed the TBI Screen and CTBIE. Thus, the results may not generalize to civilians or Veterans who were never deployed or who served in other eras. Likewise, our results may not generalize to Iraq/Afghanistan-era Veterans who were diagnosed with TBI *during* deployment, as the TBI Screen and CTBIE were specifically designed to evaluate and capture Veterans who were deployed but never diagnosed with TBI (VHA Directive 2010–012). This produced a sample with generally mild injuries which are overwhelmingly common and represent the largest severity group across all-cause TBI in both military personnel and civilians. We also did not specifically evaluate TBI severity or time since injury and therefore are not able to speak to how our findings may generalize across the TBI severity spectrum or over time. Nevertheless, given the VHA's method for systematically evaluating TBI in Iraq/Afghanistan-era Veterans after enrollment in the VA Healthcare System (Belanger et al., 2012; Scholten et al., 2012) as well as the base rates of military-related mild TBI (Defense and Veterans Brain Injury Center, 2020), it is presumed that the majority of Veterans included in the sample had a history of remote mild TBI. Furthermore, although all Veterans who complete the CTBIE have a history of deployment, data pertaining to deployment duration, number of deployments, or time since deployment were not available. We also did not have data on lifetime number of TBIs. Future research will need to evaluate the extent to which deployment-related factors and other injury characteristics influence the association between biological sex and clinical outcomes following TBI.

Another study limitation was the use of retrospective, cross-sectional clinical data gathered from the VA's electronic health record. Though there are obvious limitations associated with using clinical data (Scholten et al., 2012), the ability to assess important clinical outcomes utilizing "big data" is a clear benefit. Additionally, although the VA TBI Screen and CTBIE are widely administered throughout the VHA and certainly have clinical utility, there are some limitations associated with these measures, including (1) the possibility for some variability across VA sites with respect to clinician training (i.e., potential administration and scoring differences across sites) and (2) the psychometric variability (e.g., sensitivity, specificity) reported by prior research (Belanger et al., 2016; Pape et al., 2018; Radigan et al., 2018). It is also worth highlighting that we examined neurobehavioral symptoms in a binary fashion (i.e., severe vs. not severe) using previously determined symptom clusters. Future research is needed to determine whether similar findings would be observed if different cutoffs were used or if different symptom domains were evaluated. Indeed, research examining measurement invariance of the NSI by biological sex is needed. Furthermore, many of the symptoms that are measured on the NSI are not specific to TBI (Porter et al., 2018); as such, our results should be interpreted with these caveats in mind. Relatedly, we limited our evaluation to exploring only CTBIE outcomes, and future research is needed to more comprehensively examine sex differences following TBI and the various factors that can influence these associations. A final limitation of our study was that we specifically focused on biological sex and did not consider the influence of gender (Giordano, Rojas-

Valencia, Bhargava, & Lifshitz, 2020; Mollayeva et al., 2018). It will be necessary for future research to explore both sex *and* gender differences in the context of TBI outcomes, as well as possible interactions with culture and geographic background.

Conclusions & Future Directions

Findings showed sex differences across a number of CTBIE outcomes including rates of CTBIE-confirmed TBI diagnoses, injury-related characteristics, symptom endorsement, and employment status. Understanding the extent to which females and males experience differential outcomes following TBI is a critical first step for identifying how treatments and interventions may be tailored to better serve Veterans with a history of TBI. Findings underscore the importance of increasing studies that focus on TBI in women while, at the same time, bolstering female representation in military TBI research. Although more research is clearly needed in this domain, our findings support the need for tailoring treatment and intervention programs for male and female Veterans with a history of TBI, and they highlight the possible benefit of provider-specific trainings/seminars on treating female Veterans who screen positive for TBI and/or have confirmed TBI histories. Future studies are planned using MVP data to further explore sex differences in military TBI, with the ultimate goal of improving sex-specific evidenced-based treatments for Veterans with a TBI history.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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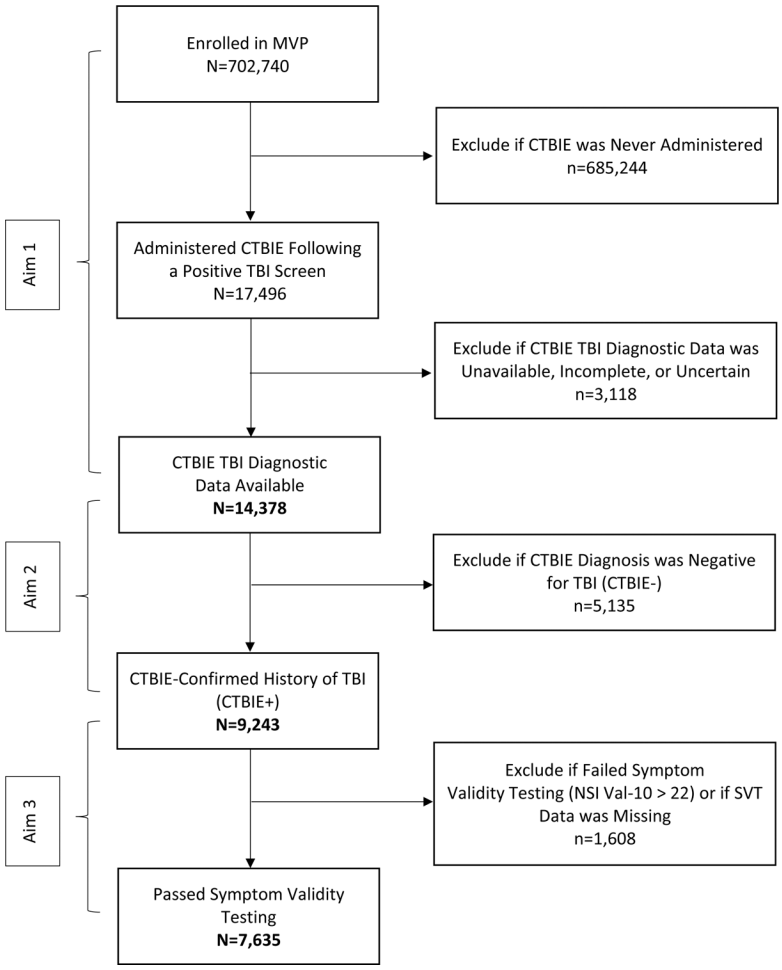

Fig. 1.
Flow diagram representing study inclusion/exclusion criteria.

Table 1.

Sample characteristics: descriptive statistics for overall sample and by sex.

Variables	Overall Sample		Females		Males		
	N	%	N	%	N	%	*p*
Age at CTBIE							
18–29	5,012	35.3%	397	29.4%	4,615	35.9%	
30–39	4,753	33.5%	503	37.3%	4,250	33.1%	<.001
40–49	3,105	21.9%	307	22.7%	2,798	21.8%	
50+	1,337	9.4%	143	10.6%	1,194	9 .3 %	
Race/Ethnicity							
White	7,703	53.6%	617	45.3%	7,086	54.4%	
Hispanic	2,325	16.2%	187	13.7%	2,138	16.4%	
Black or African American	2,248	15.6%	348	25.6%	1,900	14.6%	<.001
Asian	351	2.4%	28	2.1%	323	2.5%	
Other	761	5.3%	101	7.4%	660	5.1%	
Not Reported/Unknown	990	6.9%	80	5.9%	910	7.0%	
Pre-Military Education Level							
High School or Less	8,126	58.1%	571	43.7%	7,555	59.6%	<.001
Some College	4,833	34.6%	574	44.0%	4,259	33.6%	
College Degree or More	1,026	7 .3 %	161	12.3%	865	6.8%	
Marital Status at CTBIE							
Single/Never Married	3,272	22.8%	378	28.0%	2,894	22.3%	
Married or Partnered	7,454	52.0%	484	35.8%	6,970	53.7%	<.001
Divorced or Separated	3,548	24.7%	471	34.8%	3,077	23.7%	
Widowed	67	0.5%	19	1.4%	48	0.4%	

Abbreviations: CTBIE = Comprehensive Traumatic Brain Injury Evaluation. *Notes*: N=14,378; Females: n=1,361, Males: n=13,017; however, n's may not total 14,378 due to missing data.

Table 2.

Results of chi-square analyses comparing females and males across CTBIE outcome variables[†] among Veterans screening positive for TBI (full CTBIE sample).

Variables	Females		Males		Test Result	
	N	% [95% CI]	N	% [95% CI]	*p*	*Cramer's V/ Phi*
CTBIE Diagnostics						
CTBIE Diagnosis[‡]						
Yes (CTBIE+)	789	58.0% [54.5–61.5%]	8,454	65.0% [64.0–66.0%]	<.001	.04
No (CTBIE−)	572	42.0% [37.9–46.1%]	4,563	35.1% [33.7–36.5%]		
CTBIE Symptom Etiology[‡]						
Symptom Resolution	69	5.8% [1.6–14.2%]	742	6.8% [5.0–8.8%]	.014	.03
TBI Residual Problems	59	5.0% [1.1–14.1%]	613	5.6% [3.9–7.7%]		
Behavioral Health Conditions	587	49.6% [45.5–53.7%]	5,242	47.7% [46.3–49.1%]		
TBI & Behavioral Health	299	25.3% [20.6–30.7%]	3,112	28.3% [26.7–29.9%]		
Other	170	14.4% [9.3–20.3%]	1,290	11.7% [10.0–13.6%]		
Injury Characteristics						
Mechanism of Injury: Bullet[^]						
Yes	15	1.8% [0–21.8%][*]	346	3.9% [2.0–6.3%]	.001	.03
No	840	98.3% [97.2–99.1%]	8,433	96.1% [95.7%−96.5%]		
Mechanism of Injury: Vehicular[^]						
Yes	228	24.9% [19.5–31.1%]	2,579	27.7% [26.0–29.5%]	.071	.02
No	688	75.1% [71.7–78.3%]	6,738	72.3% [71.2–73.4%]		
Mechanism of Injury: Fall[^]						
Yes	415	42.7% [37.8–47.6%]	3,131	33.3% [31.7–35.0%]	<.001	.06
No	556	57.3% [53.1–61.5%]	6,280	66.7% [65.5–67.9%]		
Mechanism of Injury: Blast[^]						
Yes	540	55.6% [51.3–59.8%]	7,958	76.7% [75.8–77.6%]	<.001	.14
No	431	44.4% [39.6–49.1%]	2,417	23.3% [21.6–25.0%]		
LOC Present						

Variables	Females		Males		Test Result	
	N	% [95% CI]	N	% [95% CI]	*p*	*Cramer's V/ Phi*
Yes	414	42.6% [37.7–47.4%]	4,751	47.9% [46.5–49.3%]	007	03
No	470	48.4% [43.7–52.9%]	4,379	44.1% [42.6–45.6%]	.007	.04
Uncertain	87	9.0% [4.1–17.3%]	791	8.0% [6.2–10.1%]		
AOC Present						
Yes	797	75.1% [72.0–78.1%]	8,663	80.6% 79.7–81.4%]	<.001	.04
No	227	21.4% [16.4–27.5%]	1,749	16.3% [14.6–18.1%]		
Uncertain	38	3.6% [0–13.8%]	334	3.1% [1.4–5.4%]		
PTA Present						
Yes	237	27.9% [22.2–34.0%]	2,682	31.1% [29.3–32.9%]	.151	02
No	520	61.2% [56.8–65.4%]	5,084	58.9% [57.5–60.2%]		
Uncertain	93	10.9% [5.3–18.9%]	871	10.1% [8.2–12.3%]		
TBI Prior to Deployment						
Yes	285	21.0% [16.5–26.3%]	2,958	22.8% [21.2–24.3%]		
No	989	72.9% [70.7–75.7%]	9,262	71.3% [70.4–72.2%]	.533	.01
Uncertain	60	4.4% [1.0–13.9%]	555	4.3% [2.8–6.4%]		
Not Assessed	23	1.7% [0–14.8%] *	220	1.7% [0.5–4.6%]		
TBI Since Deployment						
Yes	201	14.8% [10.3–20.6%]	1,442	11.1% [9.5–12.8%]		
No	1,096	80.7% [78.2–83.0%]	10,961	84.4% [83.7–85.1%]	.001	.03
Uncertain	42	3.1% [0.0–12.6%]	405	3.1% [17–5.4%]		
Not Assessed	19	1.4% [0–17.6%] *	187	1.4% [0.3–4.6%]		
Neurobehavioral Symptoms and Medical Comorbidities						
Vestibular Symptoms §						
Severe	102	7.5% [3.4–14.9%]	651	5.0% [3.5–7.0%]	<.001	.03
Not Severe	1,251	92.5% [90.9–93.3%]	12,284	95.0% [94.6–95.3%]		
Somatic/Sensory Symptoms §						
Severe	106	7.8% [3.3–14.3%]	619	4.8% [3.2–6.8%]	<.001	.04
Not Severe	1,252	92.2% [90.5–93.6%]	12,375	95.2% [94.8–95.6%]		

Variables	Females		Males		Test Result	
	N	% [95% CI]	N	% [95% CI]	*p*	*Cramer's V/ Phi*
Cognitive Symptoms[§]						
Severe	434	32.0% [27.7–36.6%]	3,260	25.1% [23.6–26.6%]	<.001	.05
Not Severe	923	68.0% [64.9–71.0%]	9,737	74.9% [74.0–75.8%]		
Affective Symptoms[§]						
Severe	531	39.1% [35.0–43.5%]	4,102	31.6% [30.2–33.0%]	<.001	.05
Not Severe	827	60.9% [57.5–64.3%]	8,892	68.4% [67.4–69.4%]		
Symptom Interference[§]						
Severe	603	47.4% [43.4–51.5%]	4,959	40.1% [38.7–41.5%]	<.001	.04
Not Severe	669	52.6% [48.8–56.5%]	7,401	59.9% [58.8–61.0%]		
Symptom Validity (Validity-10)[¥]						
SVT-Pass	1,096	80.9% [78.5–83.2%]	11,053	85.4% [84.7–86.1%]	<.001	.04
SVT-Fail	259	19.1% [14.3–24.2%]	1,887	14.6% [13.1–16.3%]		
Psychiatric Symptoms						
Yes	749	70.5% [67.1–73.7%]	6,921	66.6% [65.5–67.7%]		
No	101	9.5% [4.9–17.5%]	1,235	11.9% [10.1–13.8%]	.001	.04
Suspected/Probable	129	12.1% [7.3–19.4%]	1,574	15.1% [12.4–17.0%]		
Not Assessed	84	7.9% [3.4–16.4%]	670	6.4% [4.7%−8.5%]		
Problems with Pain						
Yes	1,277	94.1% 992.7–95.4%]	11,970	92.2% [91.7–92.7%]	.010	.02
No	80	5.9% [2.1–14.0%]	1,019	7.9% [6.4–9.8%]		
Functional Outcomes						
Employment Status						
Employed	475	35.5% [31.3–40.1%]	5,519	43.3% [42.0–44.6%]		
Unemployed - Looking	235	17.6% [12.8–22.9%]	2,574	20.2% [18.7–21.8%]	<.001	.09
Unemployed - Not Looking	289	21.6% [16.9–26.6%]	2,412	18.9% [15.0–18.2%]		
Student	286	21.4% [16.7–26.5%]	2,107	16.5% [15.0–18.2%]		
Volunteer/Homemaker	52	3.9% [0.5–13.2%]	145	1.1% [0.2–4.9%]		

Abbreviations: CI = confidence interval; CTBIE = Comprehensive Traumatic Brain Injury Evaluation; LOC = loss of consciousness; AOC = alteration of consciousness; PTA = post-traumatic amnesia; NSI = Neurobehavioral Symptom Inventory; SVT = symptom validity test.

Notes: N=14,378; Females: n=1,361, Males: n=13,017; however, n's may not total 14,378 due to missing data. To account for multiple comparisons, a Bonferroni-corrected *p*-value was applied (20 unique analyses resulted in a *p*-value of .003 [.05/20]).

† All data presented within this table were derived from the CTBIE.

‡ "CTBIE Diagnosis" represents the clinician's determination about whether a TBI occurred based on the data gathered within the CTBIE and "CTBIE Symptom Etiology" represents the clinician's determination about the cause of the veteran's current symptom presentation.

^ Not mutually exclusive categories; Veterans may have experienced more than one mechanism of injury; therefore, n's will not add up to 14,378.

§ The NSI symptom domain scores were transformed so that they range from 0–4 (consistent with the NSI individual items), with "0" reflecting no symptoms and "4" reflecting very severe symptoms; symptom domain scores were then dichotomized to reflect "severe" vs. "not severe" symptoms; scores ≥ 3 were classified as "severe" symptoms and scores < 3 were classified as "not severe" symptoms. The symptom interference item was also dichotomized to reflect "severe" vs. "not severe" symptom interference using the same criteria noted above.

¥ Scores >22 on the NSI Validity-10 reflect symptom over-reporting; using this cutoff, "SVT-pass" and "SVT-fail" groups were created; a Validity-10 score ≤22 was classified as "SVT-Pass" and a Validity-10 score >22 was classified as "SVT-Fail."

* Reflects one-sided, 97.5% confidence interval.

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Table 3.

Results of chi-square analyses comparing females and males across CTBIE outcome variables[†] among Veterans with a CTBIE-confirmed history of TBI.

Variables	Females		Males		Test Result	
	N	% [95% CI]	N	% [95% CI]	*p*	*Cramer's V/ Phi*
CTBIE Diagnostics						
CTBIE Symptom Etiology[‡]						
Symptom Resolution	35	5.4% [0.6–19.2%]	411	6.0% [4.0–8.8%]		
TBI Residual Problems	57	8.7% [2.9–19.3%]	591	8.6% [6.5–11.2%]	.652	.02
Behavioral Health Conditions	229	35.1% [28.8–41.5%]	2,472	35.8% [33.9–37.7%]		
TBI & Behavioral Health	287	44.0% [38.1–49.9%]	3,042	44.1% [42.3–45.9%]		
Other	45	6.9% [1.4–18.3%]	381	5.5% [3.4–8.3%]		
Injury Characteristics						
Mechanism of Injury: Bullet[^]						
Yes	11	1.8% [0–28.5%][*]	255	3.9% [1.9–71%]	.011	.03
No	590	98.2% [96.7–99.1%]	6,339	96.1% [95.6–96.6%]		
Mechanism of Injury: Vehicular[^]						
Yes	167	26.1% [19.8–33.7%]	1,952	28.1% [26.1–30.2%]	.278	.01
No	473	73.9% [69.8–77.9%]	4,994	71.9% [70.6–73.1%]		
Mechanism of Injury: Fall[^]						
Yes	289	43.4% [37.5–49.2%]	2,384	34.0% [32.1–36.0%]	<.001	.06
No	377	56.6% [51.3–61.6%]	4,627	66.0% [64.6–67.4%]		
Mechanism of Injury: Blast[^]						
Yes	366	54.7% [49.4–59.8%]	5,903	77.5% [76.4–78.6%]	<.001	.14
No	303	45.3% [39.5–51.0%]	1,716	22.5% [20.5–24.5%]		
LOC Present						
Yes	374	53.9% [48.8–59.1%]	4,375	57.8% [56.3–59.3%]	.048	.03
No	245	35.3% [29.1–41.4%]	2,546	33.7% [31.9–35.6%]		
Uncertain	75	10.8% [4.7–19.9%]	644	8.5% [6.5–11.0%]		
AOC Present						

Variables	Females		Males		Test Result	
	N	% [95% CI]	N	% [95% CI]	*p*	*Cramer's V/ Phi*
Yes	690	92.1% [89.8–93.9%]	7,423	92.7% [92.1–93.3%]	.452	.01
No	40	5.3% [0.6–16.9%	432	5.4% [3.4–7.9%]		
Uncertain	19	2.5% [0–17.6%] *	150	1.9% [0.4–5.7%]		
PTA Present						
Yes	223	37.3% [30.9–43.9%]	2,553	39.2% [37.3–41.1%]	.431	.02
No	300	50.2% [44.5–56.1%]	3,242	49.8% [48.1–51.6%]		
Uncertain	75	12.5% [5.6–21.6%]	717	11.0% [8.8–13.5%]		
TBI Prior to Deployment						
Yes	154	19.6% [13.5–26.6%]	1,827	21.6% [19.8–23.6%]		
No	592	75.2% [71.5–78.6%]	6,168	73.0% [71.9–74.1%]	.582	.01
Uncertain	31	3.9% [0–16.7%	338	4.0% [2.3–6.9%]		
Not Assessed	10	1.3% [0–30.8%] *	115	1.4% [0.2–6.1%]		
TBI Since Deployment						
Yes	125	15.9% [10.1–23.6%]	935	11.1% [9.2–13.3%]		
No	628	79.7% [76.4–82.9%]	7,167	84.9% [84.1–85.7%]	.001	.04
Uncertain	27	3.4% [0.1–19.0%]	253	3.0% [1.4–61%]		
Not Assessed	8	1.0% [0–36.9%] *	92	1.1% [0–5.9%]		
Neurobehavioral Symptoms and Medical Comorbidities						
Vestibular Symptoms §						
Severe	67	8.5 % [3.4–18.5%]	471	5.6 % [3.6–8.0%]	.001	.03
Not Severe	718	91.5% [89.2–93.4%]	7,936	94.4 % [93.9–94.9%]		
Somatic/Sensory Symptoms §						
Severe	70	8.9% [3.2–17.7%]	470	5.6% [3.6–8.0%]	<.001	.04
Not Severe	718	91.1% [88.8–93.1%]	7,974	94.4% [93.9–94.9%]		
Cognitive Symptoms §						
Severe	255	32.4% [26.8–38.7%]	2,339	27.7% [25.9–29.6%]	.005	.03
Not Severe	532	67.6% [63.5–71.6%]	6,109	72.3% [71.2–73.4%]		
Affective Symptoms §						

Variables	Females		Males		Test Result	
	N	% [95% CI]	N	% [95% CI]	*p*	*Cramer's V/ Phi*
Severe	333	42.3% [37.0–47.8%]	2,869	34.0% [32.3–35.8%]	<.001	.05
Not Severe	455	57.7% [53.1–62.4%]	5,576	66.0% [64.7–67.2%]		
Symptom Interference[§]						
Severe	359	48.6% [43.2–53.8%]	3,478	43.3% [41.6–45.0%]	.006	.03
Not Severe	380	51.4% [46.2–56.4%]	4,550	56.7% [55.2–58.1%]		
Symptom Validity (Validity-10)[¥]						
SVT-Pass	623	79.4% [76.1–82.6%]	7,012	83.4% [82.5–84.3%]	.004	.03
SVT-Fail	162	20.6% [14.5–27.4%]	1,394	16.6% [14.7–18.6%]		
Psychiatric Symptoms						
Yes	449	73.0% [68.7–77.1%]	4,738	69.6% [68.3–70.9%]		
No	51	8.3% [2.2–18.9%]	734	10.8% [8.6–13.2%]	.040	.03
Suspected/Probable	67	10.9% [4.3–20.3%]	899	13.2% [11.1–15.6%]		
Not Assessed	48	7.8% [2.3–20.0%]	435	6.4% [4.3–9.2%]		
Problems with Pain						
Yes	748	94.9% [93.1–96.4%]	7,908	93.7% [93.1–94.2%]	.165	.01
No	40	5.1% [0.6–16.9%]	534	6.3% [4.4–8.8%]		
Functional Outcomes						
Employment Status						
Employed	266	34.3% [28.5–40.3%]	3,439	41.4% [39.8–43.1%]		
Unemployed - Looking	134	17.3% [11.2–24.6%]	1,701	20.5% [18.6–22.5%]	<.001	.08
Unemployed - Not Looking	181	23.3% [17.3–30.3%]	1,591	19.2% [17.3–21.2%]		
Student	165	21.2% [15.2–28.2%]	1,482	17.8% [15.9–19.9%]		
Volunteer/Homemaker	30	3.9% [0.1–17.2%]	96	1.2% [0–5.7%]		

Abbreviations: CI = confidence interval; CTBIE = Comprehensive Traumatic Brain Injury Evaluation; LOC = loss of consciousness; AOC = alteration of consciousness; PTA = post-traumatic amnesia; NSI = Neurobehavioral Symptom Inventory; SVT = symptom validity test.

Notes: N=9,243; Females: n=789, Males: n=8,454; however, n's may not total 9,243 due to missing data. To account for multiple comparisons, a Bonferroni-corrected *p*-value was applied (19 unique analyses resulted in a *p*-value of .003 [.05/19]).

[†]All data presented within this table were derived from the CTBIE.

[‡]"CTBIE Symptom Etiology" represents the clinician's determination about the cause of the veteran's current symptom presentation.

^Not mutually exclusive categories; Veterans may have experienced more than one mechanism of injury; therefore, n's will not add up to 9,243.

§The NSI symptom domain scores were transformed so that they range from 0–4 (consistent with the NSI individual items), with "0" reflecting no symptoms and "4" reflecting very severe symptoms; symptom domain scores were then dichotomized to reflect "severe" vs. "not severe" symptoms; scores ≥ 3 were classified as "severe" symptoms and scores < 3 were classified as "not severe" symptoms. The symptom interference item was also dichotomized to reflect "severe" vs. "not severe" symptom interference using the same criteria noted above.

¥Scores >22 on the NSI Validity-10 reflect symptom over-reporting; using this cutoff, "SVT-pass" and "SVT-fail" groups were created; a Validity-10 score ≤22 was classified as "SVT-Pass" and a Validity-10 score >22 was classified as "SVT-Fail."

*Reflects one-sided, 97.5% confidence interval.

Table 4.

Results of logistic regression analyses[†] evaluating associations between sex and NSI variables in Veterans with CTBIE-confirmed histories of TBI who passed symptom validity testing.

Variable	OR	95% CI	*p*
Vestibular	1.09	0.89–1.35	.400
Somatic/Sensory	1.12	0.47–2.65	.794
Cognitive	1.23	1.02–1.58	.032
Affective	1.49	1.24–1.81	<.001
Symptom Interference	1.21	1.00–1.45	.046

Abbreviations: OR = odds ratio; CI = confidence interval.

Notes: N=7,635; Females: n=623, Males: n=7,012; however, n's may not total 7,635 due to missing data.

[†]Logistic regression was used to estimate the odds of having "severe" symptoms (defined using a cutoff of ≥3 on each NSI outcome of interest) as a function of sex. Only Veterans with a CTBIE-confirmed history of TBI who passed symptom validity were included in these analyses. Odds ratios reflect the odds of females having "severe" symptoms relative to males. All models are adjusted for age at CTBIE (18–29, 30–29, 40–49, and 50+), race/ethnicity (White, Hispanic, Black or African American, Asian, Other, Not Reported/Unknown), pre-military education level (high school or less, some college, college degree or more), marital status (single/never married, married or partnered, divorced or separated, widowed), and employment status (employed, unemployed, student, volunteer/homemaker).