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Review

Sex Differences in Traumatic Brain Injury: What We Know and What We Should Know

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Abstract

There is growing recognition of the problem of male bias in neuroscience research, including in the field of traumatic brain injury (TBI) where fewer women than men are recruited to clinical trials and male rodents have predominantly been used as an experimental injury model. Despite TBI being a leading cause of mortality and disability worldwide, sex differences in pathophysiology and recovery are poorly understood, limiting clinical care and successful drug development. Given growing interest in sex as a biological variable affecting injury outcomes and treatment efficacy, there is a clear need to summarize sex differences in TBI.

This scoping review presents an overview of current knowledge of sex differences in TBI and a comparison of human and animal studies. We found that overall, human studies report worse outcomes in women than men, whereas animal studies report better outcomes in females than males. However, closer examination shows that multiple factors including injury severity, sample size, and experimental injury model may differentially interact with sex to affect TBI outcomes. Additionally, we explore how sex differences in mitochondrial structure and function might contribute to possible sex differences in TBI outcomes. We propose recommendations for future investigations of sex differences in TBI, which we hope will lead to improved patient management, prognosis, and translation of therapies from bench to bedside.

Keywords: biological sex; chromosomal factors; mitochondria; sex hormones; TBI

Introduction

Traumatic Brain Injury (TBI) is a growing public health concern with an estimated 1.7 million Americans suffering a TBI every year.[1] With approximately 5 million people in the United States currently living with a TBI-related disability, the cost of care estimates range from $60 to $221 billion per year.[2] Epidemiological data suggest that men are approximately 40% more likely to suffer a TBI compared with women in the general adult population, although the sex difference disappears above 75 years of age.[1,2] National Collegiate Athletic Association data indicate that women suffer more concussions than men of a comparable age playing the same sport.[3] Although women have a lower prevalence of deployment-related TBI than men, as a growing number of women choose to serve in active military duty, their relative risk of sustaining combat-related injuries is likely to increase compared with their civilian counterparts.[4,5] Given the increasing risk of sports- and combat-related TBI in women, biological sex is an important variable that needs to be considered in the context of TBI outcomes.

The question of whether there are differences in outcome from TBI in men and women can be approached in different ways. First, are there differences in how men and women acquire their injuries? The answer appears to be yes, with women more likely to receive injuries from assault or violence in interpersonal relationships and men more likely to receive work-related injuries from falls and motor vehicle collisions.[6–8] Second, are there differences in how the brains of men and women respond to an injury at the cellular and molecular level? Again, the answer appears to be yes, with genetics and sex hormones likely to influence inflammation, edema, oxidative stress, excitotoxicity, and mitochondrial function.[9–15] Third, are there differences in the brain repair and recovery processes of men and women and in the associated recovery of function? The data also support this premise, with studies indicating sex-based differences in neuroplasticity.[16,17] Fourth, there may also be sex-specific patterns of extracerebral trauma accompanying TBI and predilection to post-injury complications. Each and all of these factors might influence outcome in studies of sex differences in TBI.

A better understanding of the effects of biological sex in TBI may help improve treatments and patient outcomes. There are no effective therapies specific to TBI, because promising pre-clinical therapies for TBI have repeatedly failed to translate to successful

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human trials. This has been attributed in part to inadequate pre-clinical efforts to recapitulate the complexity of the human injury.[18,19] For example, a recent review reported that 93–95% of pre-clinical studies have failed to include biological sex as a variable.[20] Fewer women than men are enrolled in clinical trials of TBI, in part because the incidence of TBI in men is far greater than in women. Moreover, results are not always analyzed by sex.[19,21,22]

Because brain anatomy, cellular pathways, and drug pharmacokinetics can be affected by biological sex,[21,22] the limited representation of females in animal studies and women in human trials is problematic for developing successful treatments. The absence of females in pre-clinical trials means that possible sex differences in pathophysiological mechanisms are not being targeted during drug development. Subsequently, the paucity of women in clinical trials means that promising treatments are not being tested against the real biological substrate and may hamper translational success. A workshop convened in December 2017 by the United States National Institutes of Health on ''Understanding Traumatic Brain Injury in Women'' focused on how current knowledge of sex differences in epidemiology, pathophysiology, recovery, and response to treatments can provide solutions to improve research practices in the field of TBI. The workshop acknowledged that findings to date have been mixed, and concluded that numerous knowledge gaps still exist regarding the effects of sex in TBI. As one workshop participant summarized, ''The more we look for sex differences, the more we find.'' The collective conclusion was that more research is needed to fill the gaps using carefully designed, multidisciplinary studies that include sex as a biological variable.

The purpose of this review is to provide an overview of sex-specific differences in TBI pathophysiology, functional outcomes, and recovery, and to highlight a possible role of mitochondria in mediating these differences. First, we perform a scoping review to summarize the current state of human and animal research on sex differences in TBI. Next, we discuss some of the major unresolved questions that need to be addressed to advance understanding of sex differences in TBI. Finally, we examine mitochondrial dysfunction as a potential contributor to sex differences in TBI pathophysiology.

Methods

Terminology

Sex includes the biological attributes that distinguish males and females based on reproductive organs and chromosome complement, whereas *gender* reflects non-biological traits, behaviors, and expectations that society ascribes to men and women.[23] However, across the scientific literature the terms *sex* and *gender* are often used interchangeably. Although it is recognized that some behavioral outcomes in clinical studies might be influenced by social constructs, this review largely examines biological differences and as such we will use ''sex differences'' in our discussion of both human and animal studies. We refer to men and women in human studies and males and females in animal studies.

Search strategy for literature review

To identify published medical literature regarding sex differences and TBI, PubMed was searched without limitations as to publication date or language. Because sex and gender have been used interchangeably we included both terms in our search strategy. The following search strategy was devised: (sex factors[mesh] OR sex characteristics[mesh] OR ''gender dependent'' OR ''sex dependent'' OR ''gender differences'' OR ''sex differences'' OR ''sexual dimorphism'' OR ''sex related'' OR ''gender related'') AND (''Brain Injuries, Traumatic''[Mesh:noexp] OR ''Brain Concussion''[Majr] OR ''Brain Contusion''[Majr] OR ''traumatic brain injury''[All Fields] OR ''traumatic brain injuries''[All Fields]) NOT (Review[publication type] OR ''Systematic review''[All Fields] OR Meta-analysis[publication type] OR ''literature review''). This search generated 601 results in July 2018. An additional 15 items were identified through manual cross-reference searching (Fig. 1).

Study inclusion and exclusion criteria

Only original research articles were included in the final analysis—reviews and meta-analyses were excluded. Human studies that included adolescents and/or adults of reproductive age were included. Clinical studies that included adults of reproductive age but also spanned younger and older ages were also included. Clinical and pre-clinical studies that focused solely on pediatric TBI (patients ages ≤12 years only and rodents post-natal day 0–21 or pigs 0–4 weeks old) or solely on geriatric TBI (patients ages ≥65 years only and rodents ≥20 months old) were excluded. Articles that only studied epidemiology of human TBI, but not mechanisms or outcomes of injury were excluded. Studies on injuries other than TBI (e.g., general trauma, stroke, spinal cord injury, etc.) and journal articles in a language other than English were also excluded.

Classification of studies

Human and animal studies were classified into four categories based on functional, physiological, or neuropathological outcome measures: 1) worse outcomes in women/females, 2) better outcomes in women/females, 3) no difference between sexes, or 4) mixed results between sexes. Studies that reported better or worse performance in women/females on at least one outcome measure and no significant difference between sexes on other outcome measures were grouped under ''better outcomes in women/females'' or ''worse outcomes in women/females'' categories, respectively. When no differences were reported between men/males and women/females on any of the outcome measures tested, studies were grouped under ''no difference.'' Studies that showed women/females performing better on one or more measure(s) and men/males on others, or those reporting different post-TBI symptoms by sex were categorized under ''mixed results.'' Such a system of classification is unbiased because it avoids judgments on the relative importance of each outcome/symptom.

Studies of patients with a Glasgow Coma Scale (GCS) of 9–15 were classified into the ''Mild–moderate'' category. Studies with GCS <12 were grouped into the ''Moderate–severe'' category. Studies that included all injury severities (GCS 3–15) or where data on injury severity were not available were grouped under ''Non-stratified.'' Measures that reflected injury mechanisms such as edema, cerebral blood flow, oxidative stress, tissue integrity, neural activity, brain region connectivity, and heart rate variability were classified under ''Neuropathology and physiology'' (Table 1). Mortality, Glasgow Outcome Score (GOS), duration of hospital stay, work capacity, and behavioral, motor, or neurocognitive assessments were classified as ''Functional outcomes.''

Results

Sex effects on TBI outcomes in humans

Using the search criteria outlined above, we found 156 published studies that compared outcomes between men and women following TBI. For each study, the following data were extracted: injury severity, total number of subjects and number of women in the study, age of subjects, comorbidities and systemic injury status, functional outcomes, and proposed neuropathological mechanisms

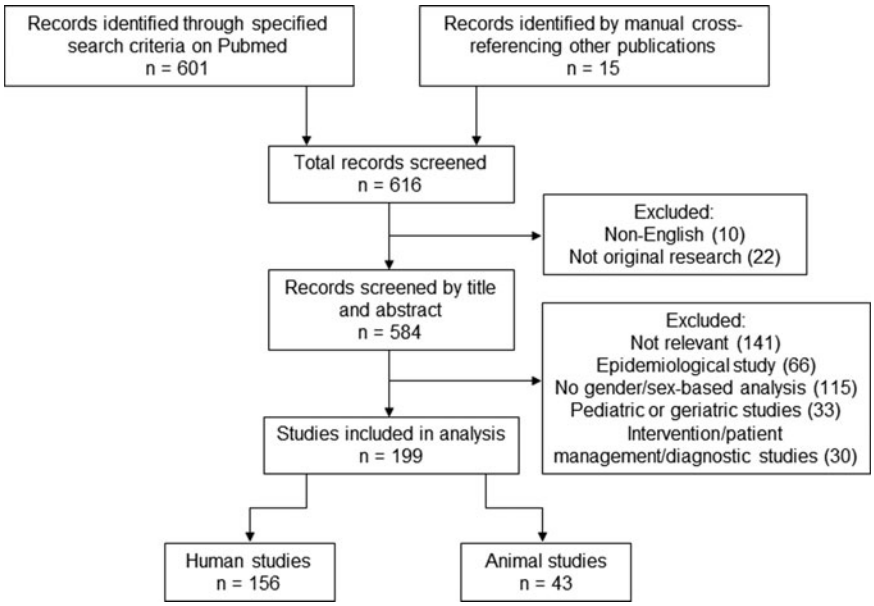

FIG. 1. Flowchart for search strategy and study inclusion criteria.

contributing to observed outcomes. The main sex difference findings from these studies are summarized in Table 1.

Across all human studies, the largest fraction (47%) reported worse outcomes in women than men. 26% found better outcomes, in women, 18% found no sex difference, and only about 9% reported mixed results with women performing better on certain outcome measures and men on others (Fig, 2, upper panel). These studies reflect the heterogeneity of human TBI, with injury severities ranging from mild to severe. Non-stratified studies that did not segregate patients by injury severity were split between those that showed women faring better (33%) and those that showed women faring worse than men (40%), with 19% reporting no sex differences in TBI outcomes or pathology (Fig. 2, lower left). However, when we categorized studies by injury severity, certain trends became apparent. For example, a majority of studies of mild–moderate TBI found that women fared worse than men (60%), whereas only 9% of these reported better outcomes in women (Fig. 2, lower middle). In contrast, among studies of moderate–severe TBI, 34% found that women fared worse than men and a greater proportion (46%) showed that women fared better (Fig. 2, lower right). This analysis suggests that injury severity may interact with biological sex in determining outcomes following TBI.

Because the number of patients enrolled in an individual study impacts the statistical power for making reliable predictions, we categorized studies into 1) Small (0–1000 patients; 118 studies), 2) Medium (1000–10,000 patients; 23 studies), and 3) Large (>10,000 patients; 15 studies). A majority of the smaller studies (52%) reported worse outcomes in women compared with men, with fewer (23%) reporting better outcomes in women (Fig. 3, left). Among medium-sized studies, 39% showed women faring worse than men and among large studies only 13% reported women faring worse. Moreover, most large studies reported that women did better than men (67%; Fig. 3, right). These large studies obtained data retrospectively from national registries that included patients from multiple trauma centers and classified TBI based on criteria outlined in the *International Classification of Diseases*.

Our analysis therefore suggests that studies with larger sample sizes, perhaps better representing a less-biased view of the population at large, tended to report better outcomes in women than smaller studies with limited enrollment. However, other factors such as recruitment methods, inclusion/exclusion criteria, type of statistical analyses, ratio of men to women, and inclusion of age-matched controls can influence the study quality and merit further consideration that is outside the scope of this review.

Given the breadth of assessments used to measure functional outcomes across human studies, we further categorized these measures into three broad domains: Community Integration (CI), including activities of daily living, return to work/school/sporting activity, or GOS (44 studies); Social-Behavioral (SB), including cognitive function and symptoms such as depression, anxiety, memory, and attention (99 studies); or Survival (S; 27 studies; Table 1). We found interactions between outcome category and each of injury severity and sample size. For example, 76% of studies of >10,000 patients used either S or CI as outcomes, whereas smaller studies relied on SB measures (66%, Table 2). This is likely because smaller studies can collect data prospectively from individual patients, whereas very large studies tend to extract data retrospectively from existing databases including medical records. When comparing these trends with sex difference findings across study size (Fig. 3), it seems that SB outcome measures used in smaller studies correspond to worse outcomes in women. In contrast, larger studies that use CI and S were more likely to report women faring better than men.

The severity of TBI in the patients studied was associated with the type of outcome measure used. We found that >88% of studies of mild–moderate injury used SB outcome measures including self-reported symptoms (Table 2). In studies of moderate–severe injury 52% used CI and/or S as outcomes, whereas only 30% included SB measures (Table 2). This may be because patients surviving severe TBI are less likely to complete detailed cognitive testing, whereas a study of survival in patients with mild TBI might suffer from ceiling effects because few patients will die. Combining these findings with the distribution of sex differences by injury severity

Table 1. Human Studies of TBI Comparing Outcomes by Sex

Reference	*Severity (GCS)*	*Total # (F)*	*Age (years)*	*Comorbidities and systemic injury*	*Results: neuropathology and physiology (in women vs. men)*	*Results: functional outcomes (in women vs. men)*
			Worse outcomes in women (n = *73*)			
(Rutherford et al., 1979)[151]	Mild	131 (48)	No data	No data	-	More women reported symptoms 1 year post-concussion; SB
(Edna and Cappelen, 1987)[152]	Mild–severe (3–15)	200 (91)	15–64	No data	-	More post-concussive symptoms in women 3–5 years after TBI; SB
(Bazarian et al., 1999)[52]	Mild (≥13)	71 (35)	Avg: 29.04	Prior head/neck trauma excluded	-	Higher incidence of post-concussive symptoms in women 3 months post-TBI; SB
(Kraus et al., 2000)[153]	Moderate–severe (3–12)	795 (143)	≥16	Chronic comorbidities and lower spinal cord injuries excluded	-	Higher mortality post-admission and poorer GOS indicative of higher rates of persistent vegetative state and severe disability in women 3 years post-TBI; S, CI
(Glenn et al., 2001)[154]	Mild–severe (<9 to 15)	41 (14)	18–75	Prior neurological diseases excluded	-	Higher risk of depression in women 3 months post-TBI; SB
(Levin et al., 2001)[155]	Mild–moderate (9–15)	69 (20)	35.06 ± 14.69	Prior TBI and neurological disorders excluded	-	Higher risk of depression in women 3–6 months post-TBI; SB
(Seibert et al., 2002)[156]	Moderate–severe (<12)	33 (14)	13–61	No data	-	More women reported poorer quality of life 6 months to 1 year post-injury; CI
(Balestreri et al., 2003)[24]	No data	392 (82)	No data	No data	Lower CPP and higher ICP in women	Higher mortality in women >50 years of age; S
#(Farin et al., 2003)[13]	Severe (3–8)	957 (220)	15–79	Systemic and nervous system comorbidities excluded	Greater frequency of brain swelling and intracranial hypertension in women early after injury, especially in those <51 years	Non-significant trend toward higher incidence of unfavorable GOS outcomes in women 1 month post-TBI; CI
(Kirkness et al., 2004)[57]	Moderate–severe	157 (33)	≥16	No data	No significant differences in intracerebral hemorrhage, MAP, CPP, ICP	Lower GCS in women at admission; women ≥30 years had poorer GOS-E and functional status at 6 months post-TBI; similar in-hospital mortality between women and men; CI
(Morrison et al., 2004)[157]	Mild–severe	16,437 (6016)	0–19	Extracranial injuries included	-	Girls had longer duration of ICU stay, worse functional impairment (vision, speech, hearing, feeding, bathing, etc.), and trend toward higher mortality; S, CI
(Broshek et al., 2005)[158]	Mild	131 (37)	14–24	No data	-	Greater decline in neurocognitive performance and more post-concussive symptoms in women athletes; SB
(Greenspan et al., 2006)[159]	Mild–severe	198 (67)	≥16	No data	-	More symptoms of post-traumatic stress in women at 6 and 12 months post-TBI; SB
(Ng et al., 2006)[160]	Severe (≤8)	672 (147)	No data	Multiple injuries included	-	Higher mortality and poorer GOS outcomes at 6 months post-injury in Asian women; CI, S
(Corrigan et al., 2007)[161]	Mild–severe	3444 (957)	18–64	No data	-	Lower return to employment 1 year post-TBI in women; CI
(Czosnyka et al., 2008)[25]	Mild–severe	469 (98)	34 ± 17	No data	Worse cerebrovascular pressure reactivity in women <50 years of age. No difference in ICP, CPP, MAP	Higher 6-month mortality in women <50 years of age; S
(Ponsford et al., 2008)[162]	Severe (<9) with hypotension	229 (78)	>17	Extracranial injuries included, chronic comorbidities excluded	No differences in CPP or ICP between men and women	Lower 6-month survival rate, but no difference in GOS-E between surviving men and women; CL, S
(Bay et al., 2009)[163]	Mild–moderate (9–15)	159 (77)	18–60	Prior TBI included, other neurological disorders excluded	-	Higher depressive symptoms, chronic stress, motor, cognitive, and somatic symptoms in women 1–6 months post-TBI; SB
(Colvin et al., 2009)[122]	Mild	234 (141)	8–24	Prior psychiatric disorders excluded	-	Worse neurocognitive performance and more post-concussion symptoms in women soccer players; SB
(Kraus et al., 2009)[164]	Mild	687 (244)	18–64	Prior head injury and chronic comorbidities included	-	Higher post-concussion symptoms in women 3 months post-TBI; SB
(Liossi and Wood, 2009)[165]	Mild–severe (3–15)	150 (75)	20–60	Prior head injury, neurological disorders, or chronic comorbidities excluded	-	Greater cognitive deficits in visual and verbal memory that were exacerbated with age in women only. No difference in anxiety, depression, attention, or executive function; SB
(Ottochian et al., 2009)[68]	Severe	1807 (406)	No data	Extracranial injuries excluded	-	Higher mortality in post-menopausal women (≥55 years); S

(*continued*)

Table 1. (Continued)

Reference	Severity (GCS)	Total # (F)	Age (years)	Comorbidities and systemic injury	Results: neuropathology and physiology (in women vs. men)	Results: functional outcomes (in women vs. men)
(Preiss-Farzanegan et al., 2009)[166]	Mild (≥13)	215 (128)	4–59	No data	-	More post-concussive symptoms in adult women (ages 18–59) but not minor girls (ages 4–17), at 3 months post-TBI compared with men: SB
(Bazarian et al., 2010)[167]	Mild (≥13)	1425 (643)	≥3	No data	-	More post-concussive symptoms in women at 3 months post-TBI, mainly during child-bearing age; SB
(Su et al., 2010)[168]	Severe (<8)	47 (18)	4 weeks to 16 years	No data	Higher CSF levels of α-synuclein, indicative of neuronal damage and mitochondrial dysfunction	-
(Whelan-Goodinson et al., 2010)[169]	Mild–severe (<15)	100 (29)	19–74	Prior TBI and neurological disorders excluded	-	Higher risk of post-injury depression in women; SB
(Ponsford et al., 2011)[28]	Mild–severe (3–15)	651 (215)	13–82	Prior TBI and neurological disorders excluded	-	Worse GOS-E 24 h post-TBI in women carrying the APOE4 allele than men with APOE4; CI
(Covassin et al., 2012b)[170]	Mild	296 (93)	14–25	Prior psychiatric disorders excluded	-	More post-concussive symptoms and worse performance on visual memory tasks in women athletes up to 2 weeks post-TBI; SB
(Covassin and Bay, 2012)[171]	Mild–moderate (9–13)	72 (36)	18–65	Prior neurological disorders excluded	-	More verbal memory deficits in women but no differences on cognitive tasks, neurobehavioral symptoms, or chronic stress; SB
(Hu et al., 2012)[172]	Moderate–severe (3–12)	358 (101)	18–56	Spinal cord injury excluded	-	Worse mental health scores in Chinese women 2 years post-TBI; SB
(Kontos et al., 2012b)[173]	Mild	1438 (477)	13–24	No data	-	More post-concussive symptoms in women up to 7 days post-TBI; SB
(Sander et al., 2012)[174]	Mild – severe (≤8 – 15)	223 (58)	37.0±15.1	Prior neurological disorders excluded	-	More impaired sexual function in women 1 year post-TBI; CI
(Ahman et al., 2013)[175]	Mild	163 (68)	18–64	No data	-	More severe post-concussion symptoms and anxiety in women; SB
(Berz et al., 2013)[176]	Mild	37 (No data)	11–17	No data	-	More post-concussion symptoms in women, but no differences in recovery rate, loss of consciousness, amnesia, or confusion; SB
(Covassin et al., 2013)[177]	Mild	95 (56)	Men: 17.69±2.1; Women: 17.78±2.3	Prior psychiatric/neurological disorders excluded	-	More concussion symptoms, worse verbal and visual memory, and more migraine, cognition, fatigue, and sleep-related symptoms in women soccer players 1 week post-TBI; SB, CI
(Iverson et al., 2013)[178]	No data	2348 (1209)	Men: 37.0±10.1; Women: 34.4±8.9	No data	-	Higher correlation between TBI and mental and physical health symptoms including depression, anxiety, PTSD, pain, and dizziness in women veterans; SB
(Lannsjo et al., 2013)[179]	Mild (15)	1262 (511)	≥6	No data	-	More post-concussion symptoms and worse GOS-E in women at 3 months post-injury; SB; CI
(Mihalik et al., 2013)[180]	Mild	296 (55)	12–25	Prior psychiatric disorder excluded	-	More women reported posttraumatic migraine symptoms up to 3 months post-TBI; SB
(Sander et al., 2013)[181]	Moderate–severe (<13)	255 (68)	≥18	Prior neurological disorders excluded	-	Higher risk of sexual impairment in women 1 year after TBI; CI
(Styrke et al., 2013)[182]	Mild (13–5)	214 (68)	18–64	No data	-	More women experienced post-concussion symptoms and disability, but no differences in life satisfaction 3 years post-injury; SB; CI
(Tham et al., 2013)[183]	Mild–severe (3–15)	144 (44)	14–17	No data	-	Higher risk of persistent pain up to 3 years post-TBI in women; SB
(van der Horn et al., 2013)[184]	Mild–severe (3–15)	242 (65)	15–78	Prior TBI excluded	-	More women with minor TBI were depressed and had incomplete return to work 6–12 months post-TBI than men with similar injury severity; SB; CI
(Moen et al., 2014)[185]	Moderate–severe	65 (17)	16–66	Prior neurological disorders excluded	-	Lower scores on high-level motor skills >1-year post-TBI in women; SB
(Zuckerman et al., 2014)[186]	Mild	244 (122)	16.1±2	Prior psychiatric/neurological disorders excluded	-	Greater symptom severity and longer time to return to baseline performance in women athletes; CI, SB
(Benedict et al., 2015)[187]	Mild	206 (No data)	10–77	No data	-	Higher severity and more concussion symptoms in women. No differences in eye coordination or balance; SB
(Bramley et al., 2015)[188]	Mild	400 (152)	13–18	No data	-	More post-traumatic headaches and longer recovery time 1–3 weeks post-TBI in women; SB
(Herrera-Melero et al., 2015)[189]	Severe (≤8)	629 (94)	> 18	Cross-gender hormonal treatment and pregnancy excluded	-	Higher mortality in the ICU and 6 months post-TBI in women. No differences in GOS at discharge or 6 months post-TBI; S

(*continued*)

Table 1. (Continued)

Reference	*Severity (GCS)*	*Total # (F)*	*Age (years)*	*Comorbidities and systemic injury*	*Results: neuropathology and physiology (in women vs. men)*	*Results: functional outcomes (in women vs. men)*
(Hsu et al., 2015)[55]	Mild (15)	60 (30)	≥17	Prior TBI, neurological or psychiatric disorder, chronic systemic comorbidities excluded	Sustained hypoactivation in fMRI activity during memory tasks in women	No differences in cognitive tests between men and women; SB
(Rabinowitz et al., 2015)[190]	Mild (13–15)	66 (24)	12–30	Prior head injury, neurological/psychiatric disorder excluded	-	Prolonged post-concussive symptoms 3 months post-TBI in women; SB
(Covassin et al., 2016)[3]	Mild	1702 (903)	No data	No data	-	Higher rates of injury and longer recovery times in women soccer and basketball players; CI
(Henry et al., 2016)[191]	Mild	66 (24)	14–23	Prior concussion, neurological/psychiatric disorders excluded	-	More vestibulo-oculomotor impairment and longer time to symptom resolution in women. No differences in neurocognitive recovery; SB
#(Miller et al., 2016)[192]	Mild	168 (39)	13.7 ± 2.5	Concussion from severe mechanisms excluded	-	Higher risk of delayed recovery with symptoms lasting more than 28 days in girls; SB
(Ono et al., 2016)[193]	Mild	176 (41)	10–18	No data	-	More post-concussive symptoms in women athletes 1 month post-TBI. No differences in recovery time; SB
(Sung et al., 2016)[194]	Mild (13–15)	181 (109)	≥20	Chronic comorbidities excluded	Heart rate variability (indicative of autonomic nervous system dysfunction) early after TBI was associated with late depression in women	Higher risk of late depression 6 months to 1.5 years post-TBI in women. Depression exacerbated over time in women, but resolved over time in men; SB
(Widerstrom-Noga et al., 2016)[195]	Mild–severe (6–15)	45 (15)	27.9 ± 8.27	Prior TBI, neurological/psychiatric disorders excluded	-	More severe pain in women up to 2 months post-TBI. No differences in incidence of neuropathic pain following TBI; SB
(Zemek et al., 2016)[196]	Mild	3063 (1205)	5–18	No data	-	Higher risk of persistent post-concussion symptoms in girls at 28 days post-injury; SB
(Albanese et al., 2017)[197]	Mild–severe	59 (30)	18–87	Chronic comorbidities, neurological/psychiatric disorders excluded	-	More post-concussive symptoms due to increased anxiety sensitivity in women; SB
(Brickell et al., 2017)[198]	Mild	172 (86)	28.9 ± 8.1	Extracranial injury included	-	More nausea, light sensitivity, change in taste/smell and appetite, fatigue, and poor sleep-related symptoms in women vs. age-matched men; SB
(Cheng et al., 2017)[199]	No data	93,793 (No data)	All ages	No data	-	Higher risk of mortality in women in China; S
(Dillard et al., 2017)[200]	Mild	157 (67)	12–19	No data	-	Higher number and severity of post-concussion symptoms in women 1 month post-injury; SB
(Gabrys et al., 2017)[201]	Mild	219 (138)	17–31	No data		More depressive symptoms in women; SB
(Howell et al., 2017)[202]	Mild	35 (18)	15 ± 2.1	Extracranial injury, neurological/psychiatric disorders excluded	-	Decreased cadence on a dual gait-cognition task in adolescent girls indicating impaired executive function up to 2 weeks post-TBI. No differences in post-concussion symptom severity or single gait task; SB
(Hutchison et al., 2017)[56]	Mild	52 (20)	18–28	No data	More heart rate variability indicative of greater impairment in autonomic nervous system function in women athletes	No difference in post-concussive symptoms or recovery time; SB
(Neidecker et al., 2017)[203]	Mild	212 (102)	11–18	Extracranial injuries excluded		Longer duration of post-concussion symptoms in women athletes; SB
(Oyegbile et al., 2017)[204]	Mild	1284 (732)	10–35	No data	-	Increased sleep disturbance after single concussion in women, especially those above age 15. Stronger correlation between sleep disturbance and headaches, mood changes, and cognitive dysfunction in women. No difference in sleep disturbance after multiple concussions; SB
(Salottolo et al., 2017)[205]	Severe (3)	481 (129)	≥18	Chronic comorbidities, extracranial injuries included	-	Higher mortality in women victims of falls; S
(Sandel et al., 2017)[206]	Mild	224 (112)	13–17	Prior neurological disorders excluded	-	Worse neurocognitive performance and more post-concussion symptoms in girls; SB

(*continued*)

Table 1. (Continued)

Reference	*Severity (GCS)*	*Total # (F)*	*Age (years)*	*Comorbidities and systemic injury*	*Results: neuropathology and physiology (in women vs. men)*	*Results: functional outcomes (in women vs. men)*
(Sufrinko et al., 2017)[207]	Mild	64 (28)	9–18	Multiple prior concussions, neurological/psychiatric disorders excluded	-	More post-concussion symptoms and greater impairment in vestibular ocular reflexes in girls up to 3 weeks post-TBI. No differences in neurocognitive functions or balance impairment; SB
(van Markus-Doornbosch et al., 2017)[208]	Mild–severe	50 (28)	12–39	Chronic co-morbidities excluded	-	Less time spent on moderate–vigorous physical activity by women >6 months post-TBI; CI
(Gallagher et al., 2018)[209]	Mild	90 (50)	19.8 ± 1.2	Chronic comorbidities, neurological/psychiatric disorders excluded	-	Longer recovery times in women athletes. No difference in symptom severity; CI
(Sicard et al., 2018)[210]	Mild	196 (98)	~21	Non-sports head injuries, neurological/psychiatric disorders excluded	-	Greater impairment in executive function in women athletes 6 months post-TBI; SB
(Singh et al., 2018)[211]	Mild–severe	774 (239)	>17	Patients with prior TBI and dementia history excluded	-	Higher risk of depression in women 3 months post-TBI; SB
(Zupan et al., 2018)[212]	Severe (≤8)	160 (44)	21–65	Patients with premorbid neurological/psychiatric disorders excluded	-	More impaired empathy in women post-TBI; SB
				Better outcomes in women (n =41)		
(Groswasser et al., 1998)[213]	Severe	334 (72)	5–65	No data	-	Better work capacity outcomes in women; CI
(Steadman-Pare et al., 2001)[214]	Moderate–severe	275 (81)	≥14	No data	-	Better quality of life 8–24 years after TBI in women; CI
(Donders and Hoffman, 2002)[215]	Mild–severe (3–15)	60 (30)	6–16	Prior neurological and psychiatric disorders excluded	-	Better scores on verbal memory in girls at 1 year post-injury; SB
(Donders and Woodward, 2003)[216]	Mild–severe (3–15)	70 (35)	6–16	Prior neurological/ psychiatric diseases excluded	-	Better visual and verbal memory scores in girls at 1 year post-injury; SB
(Geraldina et al., 2003)[217]	Moderate–severe	96 (23)	0–18	Chronic comorbidities and neurological disorders excluded	-	Less withdrawal and better social skills in girls 1 year post-TBI; SB
(Slewa-Younan et al., 2004)[218]	Moderate–severe (≤12)	108 (54)	No data	Prior head injury and psychiatric disorder excluded	-	Shorter duration of post-traumatic amnesia in women. No differences in GOS or mortality; CI, SB, S
#(Wagner et al., 2004)[14]	Severe (≤8)	68 (No data)	16–65	No data	Lower oxidative damage in women within 48 h of injury; level of oxidative damage correlated with GOS in women but not men	No differences in GOS 5 days post-TBI; CI
(Doctor et al., 2005)[219]	Mild–severe (3–15)	418 (84)	<25 to >50	Prior brain injury or neurological disorders excluded	-	Lower risk of unemployment 1 year post-TBI in women; CI
(Wagner et al., 2005)[15]	Severe (≤8)	123 (30)	16–65	No data	Lower excitotoxic oxidative damage in women within 48 h post-TBI	-
(Davis et al., 2006)[72]	Moderate–severe	13,437 (3178)	≥15	No data	-	Better survival rates in post-menopausal women. No differences in pre-menopausal women and age-matched men; S
(Gujral et al., 2006)[220]	Mild–severe	20,465 (6827)	All ages	No data	-	Lower mortality in women after blunt force injury; S
(Wood and Liossi, 2006)[221]	Moderate–severe (<12)	134 (33)	37 ± 12.18	Prior head injury and neurological/psychiatric disorders excluded	-	Lower incidence of aggression in women 1–3 years post-injury; SB
(Niemeier et al., 2007)[222]	Moderate–severe (8.7 ± 4.2)	1331 (359)	18–49	Prior brain injury and neurological disorders *included*	-	Better executive function in women; SB

(*continued*)

Table 1. (Continued)

Reference	*Severity (GCS)*	*Total # (F)*	*Age (years)*	*Comorbidities and systemic injury*	*Results: neuropathology and physiology (in women vs. men)*	*Results: functional outcomes (in women vs. men)*
(Wagner et al., 2007)[223]	Severe (≤8)	63 (15)	16–70	Chronic comorbidities, extracranial injuries excluded	Higher CSF dopamine levels in women with DAT 10/10 genotype; no association between DAT genotype and dopamine levels in men. Higher levels of dopamine metabolites in CSF of women	-
(Ost et al., 2008)[29]	Severe (≤8)	96 (26)	8–81	No data	-	Worse 1-year GOS-E outcomes in men with APOE4 than those without. No effect of APOE4 allele in women; CI
(Slewa-Younan et al., 2008)[224]	Moderate–severe (≤12)	70 (25)	15–50	Prior head injury, psychiatric disorder excluded	Blood levels of sex hormones declined in both men and women 24 h post-TBI	Shorter length of hospital stay and better outcomes on 3-month GOS and in women; CI
(Berry et al., 2009)[71]	Moderate–severe	72,294 (22,276)	14–89	Extracranial injuries excluded	-	Lower 1-year mortality, shorter duration of hospital and ICU stay, and fewer post-TBI complications in women, with improved survival peri- and post-menopausal; CL, S
(Harrison-Felix et al., 2009)[225]	No data	1678 (399)	Avg: 32	No data	-	Lower risk of mortality in women compared with men; S
(Covassin et al., 2010)[226]	Mild	188 (88)	Men: 18.35±2.77; Women: 18.29±2.29	Prior neurological/ psychiatric disorder excluded	-	Faster processing speed and reaction time in women athletes. Better verbal and visual memory in women than men with multiple concussions; SB
(Moore et al., 2010)[227]	Mild–severe	158 (75)	48±14	Non-TBI brain injury excluded	-	Better visual memory in women. No sex differences in processing speed, executive function, or other types of memory; SB
(Saban et al., 2011)[228]	Severe (3–8)	297 (84)	16–50	Comorbidities and extracranial injuries included	-	Better cognitive outcomes in women 1 year post-TBI. No differences in motor outcomes or perceived life satisfaction; SB
(Liao et al., 2012)[229]	No data	16,635 (7467)	≥20	Psychiatric disorders included	-	Lower risk of post-injury mortality in women; S
(Saadat et al., 2012)[230]	Mild–severe	2274 (480)	30.1±19.11	Extracranial injuries included	-	Lower mortality in women; S
(Collins et al., 2013)[231]	Mild–severe (3 – 15)	342 (107)	<17	No data	More subdural hematomas in girls; more extradural hematomas in boys	Lower mortalityin girls; S
(Ley et al., 2013)[67]	Moderate–severe	20,280 (6754)	≤18	Extracranial injuries excluded	Systolic blood pressure was lower in pubescent and pre-pubescent girls than in boys; More girls than boys had SBP <90 mm Hg	Lower in-hospital mortality in pubescent girls vs. age-matched boys; S
(Matsukawa et al., 2013)[232]	Mild–severe	419 (92)	Avg: 54	Extracranial injuries excluded	-	Lower incidence of disability in women 6 months post-TBI; CI
(Yeh et al., 2013)[233]	Mild–severe	19,336 (8625)	≥15	Prior neurological disorders excluded	-	Lower risk of post-TBI epilepsy in women; CI
(Zimmer et al., 2013)[234]	Mild	437 (164)	19.61±1.64	No data	-	Better post-concussion performance in women; SB
(de Guise et al., 2014)[235]	Mild–severe (3–15)	5642 (1728)	Men: 49.2±21.2; Women: 57.2±23.6	Extracranial injuries, neurological/psychiatric illness included	-	Lower risk of mortality in women than age-matched men with similar injury severity. No differences in length of hospital stay, GOS-E, or functional independence 3.5 years post-TBI; CI, S
(Fakhran et al., 2014)[26]	Mild	90 (33)	10–50	Prior neurological disorder excluded	Higher fractional anisotropy (indicative of white matter integrity) in women	Shorter time to post-TBI symptom resolution in women; SB
(Helmer et al., 2014)[236]	Mild	45 (20)	Men: 23±2; Women: 21±4	No data	Fewer cerebral micro-bleeds post-concussion in women hockey players	-
(Niemeier et al., 2014)[237]	Moderate–severe	121 (40)	42.83±18.76	No data	-	Better executive function in women due to greater self-awareness of injury-related deficits; SB
(Brooks et al., 2015)[238]	Moderate–severe	12,481 (No data)	≥10	Comorbidities and extracranial injuries included	-	Lower risk of long-term (≥1 year post-TBI) mortality in women; S

(*continued*)

Table 1. (Continued)

Reference	*Severity (GCS)*	*Total # (F)*	*Age (years)*	*Comorbidities and systemic injury*	*Results: neuropathology and physiology (in women vs. men)*	*Results: functional outcomes (in women vs. men)*
(McGlade et al., 2015)[27]	Mild–severe	41 (17)	18–55	Prior neurological/ psychiatric disorders excluded	Higher connectivity between brain regions in women, that was associated with less physical aggression	Less physical aggression in women veterans but no differences in anxiety or depression; SB
(Rigon et al., 2016)[239]	Moderate–severe	53 (25)	18–65	Prior psychiatric disorders included	-	Better emotion recognition in women. No differences in neurocognitive abilities; SB
(Saverino et al., 2016)[240]	Mild–severe (AIS 1 to ≥4)	29,265 (10,014)	<15 to >65	Prior TBI excluded	-	Lower risk of re-hospitalization in women 3 years post-TBI; CI
(Barker et al., 2017)[241]	Mild	303 (99)	10–19	Prior neurological/ psychiatric disorders excluded	-	No difference in symptom reporting in women. Lower rates of dizziness, fogginess, memory impairment, and concentration problems in women; SB
(Eaton et al., 2017)[242]	Mild–severe (3 –15)	280 (35)	28.8 ± 16.3	Patients with extracranial injuries included	-	Lower mortality, vegetative state, or severe disability in sub-Saharan African women at admission and 24 h post-TBI; CI, S
(Leveille et al., 2017)[243]	Mild	22 (12)	19–28	Non-sports TBI, prior neurological/ psychiatric disorders excluded	-	Less impaired recognition of negative emotions in women, whereas men needed more emotional intensity to recognize the same emotions up to 1 year post-TBI; SB
(Shibahashi et al., 2017)[244]	Moderate–severe (AIS 3–5)	24,833 (8202)	≥16	Patients with extracranial injuries excluded	-	Lower in-hospital mortality in women; S
(Li et al., 2018)[245]	Mild–severe	52,877 (21,514)	≥18	No data	-	Lower risk of 30-, 60-, and 90-day re-hospitalization in women; CI
			No significant difference between men and women (n = *28*)			
(Millis and Dijkers, 1993)[246]	Moderate–severe (3–11)	36 (13)	17–65	Prior neurological disorder excluded	-	No difference in memory impairment; SB
(Mount et al., 2002)[247]	No data	72 (24)	33.8 ± 10.8	No data	-	No difference in visuo-spatial abilities; SB
(Coimbra et al., 2003)[248]	Mild–severe (<9 –15)	1830 (914)	18–64	No data	-	No differences in mortality, injury severity, or incidence of acute complications post-TBI; SB, S
(Kadyan et al., 2004)[249]	Mild–severe	158 (38)	16–86	No data	-	No differences in length of hospital stay, duration of rehabilitation, cognition, and frequency, duration, presentation, or extent of post-traumatic agitation 48 h post-TBI; CI,SB
(Mushkudiani et al., 2007)[250]	Moderate–severe	8720 (2009)	≥14	No data	-	No difference in 6-month GOS; S
(Tsushima et al., 2009)[251]	Mild (13–15)	102 (40)	41.99 ± 4.71	Penetrating brain injury, chronic comorbidities, and psychological trauma excluded	-	No difference in neuropsychological performance 2 years post-TBI; SB
(Cantu et al., 2010)[83]	Mild	215 (68)	19.19 ± 8.53	Non-sports TBI excluded	-	No difference in duration of symptoms, loss of consciousness or depression; SB
(Leitgeb et al., 2011)[252]	Moderate–severe	439 (134)	Men: 50.4 ± 21.5; Women: 61.4 ± 22.6	Extracranial injuries excluded	No sex differences in lesions on CT scans	No differences in mortality or unfavorable outcomes; S
(Yeung et al., 2011)[30]	Mild–severe (<9 to >13)	2979 (627)	12–45	Extracranial injury included	Higher incidence of brain edema in Asian but not Australian women	No difference in mortality; S
(Kontos et al., 2012a)[253]	Mild	75 (24)	High school and college students	Prior neurological/ psychiatric disorders excluded	-	No differences in number of post-concussive symptoms, neurocognitive test scores or depression up to 2 weeks post-injury; SB

(*continued*)

Table 1. (Continued)

Reference	*Severity (GCS)*	*Total # (F)*	*Age (years)*	*Comorbidities and systemic injury*	*Results: neuropathology and physiology (in women vs. men)*	*Results: functional outcomes (in women vs. men)*
#(Renner et al., 2012)[254]	Mild–severe	427 (108)	18–90	Prior head injury, neurological/psychiatric disorders, severe comorbidities excluded	No sex difference in diffuse axonal injury, brain edema, hypoxia, ICP, contusional bleeding; skull fractures were more common in men than women	No differences in injury severity, GOS, or length of stay in rehabilitation; CI
(Zuckerman et al., 2012)[255]	Mild	80 (40)	15.8 ± 1.9	Prior neurological/ psychiatric disorders excluded	-	No difference in neurocognitive ability or number of symptoms in high school soccer players; SB
(Iverson and Koehle, 2013)[256]	No data	1234 (496)	20–69	No data	-	No difference in balance and postural stability; CI
(Kozlowski et al., 2013)[257]	Mild	34 (17)	25.9 ± 10.9	Prior neurological disorders and extracranial injuries excluded	-	No difference in exercise intolerance in men and women with post-concussion syndrome 3 months post-TBI; CI, SB
(Brooks et al., 2014)[258]	Mild	615 (98)	13–17	Prior concussion, psychiatric disorder excluded	-	No differences in concussion symptom reporting or cognition in hockey players 6 months post-injury; SB
#(Ehsaei et al., 2015)[259]	Mild–severe	98 (No data)	No data	Extracranial injury included	No difference in serum markers of oxidative stress 24 h post-trauma	-
(Falk et al., 2015)[260]	Severe (<8)	651 (148)	>15	No data	-	No difference in mortality or GOS at discharge. Non-significant trend toward shorter ICU stay for women; CI, S
(Chan et al., 2016)[261]	Mild–severe	1730 (519)	All ages	No data	-	No difference in rehabilitation outcomes within 1 year of TBI; CI
(Hugentobler et al., 2016)[262]	Mild	71 (29)	14.14 ± 2.44	Extracranial injury and prior neurological disorder excluded	-	No difference in postural control and balance post-TBI; CI
(Meng and Shi, 2016)[263]	Moderate–severe (≤13)	136 (55)	15–65	Extracranial injuries and chronic comorbidities excluded	No difference in incidence of hyponatremia post-TBI	-
(Mollayeva et al., 2016)[264]	Mild	94 (36)	≥18	No data	-	No difference in insomnia prevalence or severity 3 months post-TBI; SB
(Black et al., 2017)[265]	Mild	75 (42)	19.34 ± 1.81	Psychiatric disorders excluded	-	No difference in symptom recovery or cognitive recovery; SB
(Lavoie et al., 2017)[266]	Moderate–severe (≤13)	175 (44)	≥16	No data	-	No differences in mild depression 1-year post-injury; SB
(Mollayeva et al., 2017a)[267]	Mild	94 (36)	45.2 ± 9.94	No data	-	No differences in frequency or severity of chronic pain; SB
(Mollayeva et al., 2017b)[268]	Mild	40 (18)	47.54 ± 11.30	No data	-	No difference in sleep architecture; SB
(Ren et al., 2017)[269]	Severe (≤8)	129 (30)	33.3 ± 14.6	No data	-	No difference in trajectory of depressive symptoms, anxiety, and life satisfaction up to 24 months post-TBI; SB
(Amara et al., 2018)[5]	Mild–severe	63,795 (3807)	18 to ≥40	No data	-	No difference in unemployment rate between men and women veterans; CI
(Brooks et al., 2018)[270]	Mild	9314 (4572)	13–18	Prior concussion, neurological disorder excluded	-	No difference in cognition or symptoms in soccer players 6 months post-TBI; SB
			Mixed results in men and women (n = *14*)			
(Comerford et al., 2002)[123]	Mild (13–15)	56 (16)	Men: 25.4 ± 9.7; Women: 31.69 ± 13.3	No data	-	Shorter comprehension times in men; better memory and immediate recall in women; SB
(Covassin et al., 2007)[271]	Mild	79 (38)	College students	No data	-	Better visual memory in men athletes; lower post-concussive vomiting and sadness in women up to 10 days post-injury; SB
(Ratcliff et al., 2007)[272]	Mild–severe (3–15)	325 (100)	16–45	Patients with previous learning deficits excluded	-	Shorter hospital stay and better attention, working memory, and language skills 1 year post-TBI in women; better visual analytic skills in men; CI, SB
(Colantonio et al., 2010)[111]	Moderate–severe	306 (93)	≥14	No data	-	More headaches and dizziness in women; more noise sensitivity and sleep disturbances in men 8–24 years post-TBI; SB

(*continued*)

Table 1. (Continued)

Reference	*Severity (GCS)*	*Total # (F)*	*Age (years)*	*Comorbidities and systemic injury*	*Results: neuropathology and physiology (in women vs. men)*	*Results: functional outcomes (in women vs. men)*
(Frommer et al., 2011)[102]	Mild	812 (202)	15.9 ± 0.7	No data	-	More drowsiness and noise sensitivity in girls; more amnesia and confusion in boys; no differences in number of symptoms, symptom resolution time or return to play time; CI, SB
(Iverson et al., 2011)[8]	Mild	12,605 (654)	30.9 ± 8.4	Non-deployment TBI excluded	-	Higher risk of depression, non-PTSD anxiety, and more than one psychiatric diagnosis following deployment-related TBI in women; higher PTSD risk in men; SB
(Covassin et al., 2012a)[273]	Mild	1616 (512)	High school and college students	Prior concussion, neurological/psychiatric disorder excluded	-	More sleep, emotion, and cognitive symptoms in women athletes; worse verbal memory and motor processing speed in men; SB
(Eramudugolla et al., 2014)[112]	Mild–severe	6333 (3309)	20–24, 40–44, 60–64	Patients with prior cerebrovascular disorders and epilepsy excluded	-	Following childhood TBI, better verbal abilities in women than men in their 20s; worse memory and slower processing speed in women in their 40s compared with similar-age men; SB
(Lax et al., 2015)[274]	Mild	211 (62)	8–15	Prior concussion, psychiatric disorder excluded	-	Greater cognitive flexibility immediately after injury in boys; faster neurocognitive improvement 1 month post-injury in girl hockey players; SB
(Xiong et al., 2016)[275]	No data	209 (60)	>15	No data	-	Higher risk of post-TBI anxiety in women; higher risk of substance abuse in men; SB
(Davis-Hayes et al., 2017)[276]	Mild	1200 (378)	19 ± 1	Non-high-risk sport concussion excluded	-	Prolonged recovery and more sleep disturbances post-concussion in women athletes; non-significant trend toward more memory impairment in men; SB
(Sayko Adams et al., 2017)[277]	No data	19,240 (1152)	17 to >40	No data	-	Lower risk of frequent binge drinking in women with TBI only. Higher risk of frequent binge drinking in women with TBI and other mental health problems 3–9 months post-deployment; SB
(Tanveer et al., 2017)[103]	Mild	1971 (848)	10–20	No data	-	Higher post-concussion symptom score and more visual memory impairment in girls; more frequent loss of consciousness, confusion, and amnesia in boys; SB
(Goodrich-Hunsaker et al., 2018)[278]	Mild	94 (31)	8–15	No data	Sex differences in white matter integrity in several brain regions	-

References marked with # were obtained by manual cross-referencing.

Functional outcome categories: CI, Community Integration; SB, Social-Behavioral; S, Survival.

AIS, Abbreviated Injury Scale; CPP, cerebral perfusion pressure; CT, computed tomography; fMRI, functional magnetic resonance imaging; GCS, Glasgow Coma Scale; GOS, Glasgow Outcome Scale; GOS-E, Glasgow Outcome Scale Extended; ICU, intensive care unit; MAP, mean arterial pressure; PTSD, post-traumatic stress disorder.

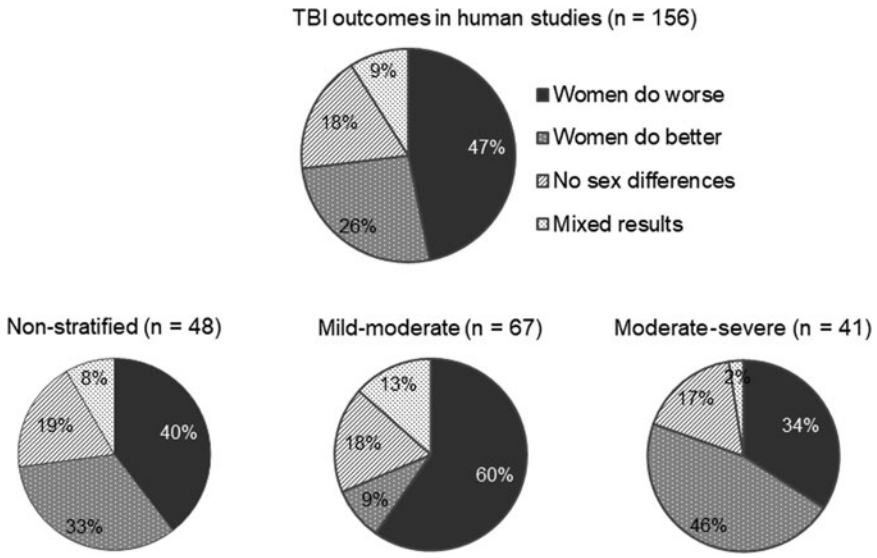

FIG. 2. Sex effects on TBI in human studies: distribution by severity. All human studies identified by our search criteria were classified based on post-TBI outcomes (upper panel). The total studies were then analyzed based on injury severity. Studies that included patients of all injury severities (GCS 15–3) or where data on injury severity were not available, were grouped under ''Non-stratified'' (lower left). Studies that recruited patients with GCS 9–15 were classified into the ''Mild–moderate'' category (lower middle). Studies with GCS <12 were grouped into the ''Moderate–severe'' category (lower right). In each category, we quantified percentage of studies showing worse outcomes in women than men, studies showing better outcomes in women than men, those showing no significant difference between men and women, and studies reporting mixed results where women do better on some outcome measures and men on others. GCS, Glasgow Coma Scale; TBI, traumatic brain injury.

(Fig. 2), suggests some interesting interactions. Studies of mild–moderate TBI that were more likely to use SB outcomes also tended to show worse outcomes in women than men. Moreover, studies of severe TBI were more likely to use CI and S as outcome measures and to show better outcomes in women.

Although functional outcomes were reported in 149 of the 156 human studies, physiological/neuropathological measures were only reported in 24. Lower cerebral perfusion pressure, higher intracranial pressure, and greater frequency of cerebral edema may contribute to higher mortality and unfavorable GOS 1 month post-TBI in women.[13,24,25] Another study reported that greater preservation of white matter integrity was associated with shorter duration of post-TBI symptoms in women compared with men.[26] Moreover, higher connectivity between various brain regions was associated with less physical aggression in women veterans than men post-TBI.[27]

Genetic factors may interact with sex and injury severity to affect TBI outcomes. For example, women carrying the APOE4 allele had worse Glasgow Outcome Scale-Extended (GOS-E) scores than men carriers in a study of 651 patients with mild to severe TBI.[28] A smaller study of severe TBI reported that men who were carriers of APOE4 had worse GOS-E scores than those lacking the

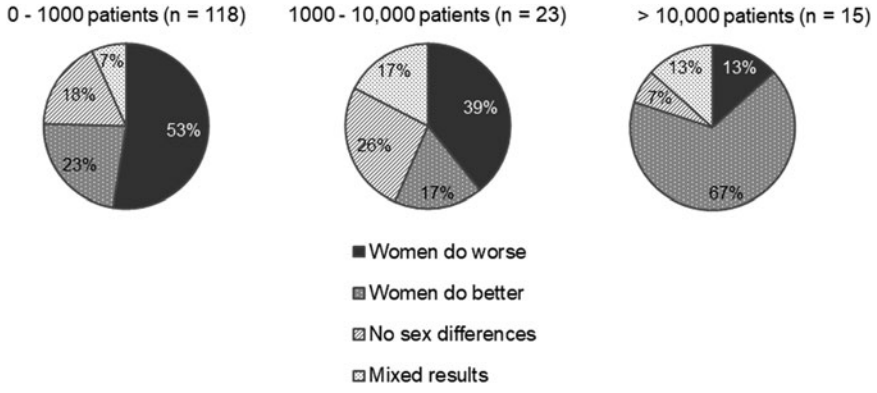

FIG. 3. Sex effects on TBI in human studies: distribution by sample size. We categorized the human studies identified by our search criteria based on the number of patients recruited. Small studies enrolled no more than 1000 patients (left), medium-sized studies enrolled 1000–10,000 patients (middle), and large studies enrolled more than 10,000 patients (right). In each category, we quantified percentage of studies showing worse outcomes in women than men, studies showing better outcomes in women than men, those showing no significant difference between men and women, and studies reporting mixed results where women do better on some outcome measures and men on others. TBI, traumatic brain injury.

Table 2. Outcome Domains in Human Studies: Distribution by Study Size and TBI Severity

References	*Community integration*	*Social-behavioral*	*Survival*
Size of study			
0–1000 patients	23.6%	66.1%	10.2%
1000–10,000 patients	30.8%	50.0%	19.2%
>10,000 patients	35.3%	11.8%	52.9%
TBI severity			
Mild–moderate	11.4%	88.6%	0.0%
Moderate–severe	37.0%	30.4%	32.6%
Non stratified	35.2%	42.6%	22.2%

Community Integration includes activities of return to work/school/-sport, daily living, quality of life, and length of hospitalization. Social-Behavioral includes cognitive (memory, attention, executive function), psychiatric (depression, anxiety, aggression, binge drinking), and neurological (pain, sleep) measures.

TBI, traumatic brain injury.

allele, whereas no such effect was detected in women.[29] Additionally, race may interact with sex to influence TBI outcomes, with a study of nearly 3000 patients with mild to severe TBI finding higher incidence of brain edema in women sampled in Hong Kong but not those in Australia.[30] However, because detailed data on race were not collected, inferences regarding race and sex differences can only be inferred for a predominantly Asian versus a predominantly non-Asian population. These differences could be attributed to race-specific single nucleotide polymorphisms in genes affecting inflammation and predisposition to genetic diseases.[31,32] However, given the number of women typically enrolled and low minor allele frequency of such polymorphisms, very large sample sizes would be required to detect any meaningful race and sex-specific interactions in TBI.

Comorbidities and extracerebral injuries can affect the clinical course and outcomes of TBI.[33,34] Although many studies explicitly exclude patients with history of neurological/psychiatric disorders and/or severe comorbidities, a surprising number (37%) of the studies we reviewed provided no data on exclusions. Further, only 15% of studies specifically reported extracranial injury status, with similar numbers including versus excluding these patients. Because comorbidities and extracranial injuries might have different prevalence in men versus women,[33,35] the absence of widespread reporting of these factors is an important limitation in interpreting findings of sex differences. Accordingly, we recommend that future studies make greater efforts to document pre-existing and concurrent clinical conditions.

Sex effects on TBI outcomes in animal studies

Animal models of TBI allow control of such factors as age, genetics, injury type, and comorbidities, providing an opportunity to better understand the mechanisms of secondary damage after head trauma and to investigate novel therapies. The most commonly used TBI models are controlled cortical impact (CCI), fluid percussion injury (FPI), closed head injury (CHI), penetrating ballistic-like brain injury (PBBI), and blast injury. These models aim to mimic the various types of TBI reported in humans and have been reviewed in detail elsewhere.[36] In brief, CCI produces a focal contusion injury, whereas FPI results in a mixed focal cortical injury and diffuse subcortical injury. Blast injury and PBBI mimic the types of injuries most frequently sustained by military service members. Repeated CHI models the diffuse injury of sport concussions.[36]

Our search found 43 studies that compared outcomes between male and female animals following TBI. The following information was extracted from each study: TBI model, injury severity, species, age, functional outcomes, and neuropathological mechanisms. The main findings of these studies are summarized in Table 3. Functional outcomes, defined as mortality or behavioral assessments of cognition or sensorimotor ability, were reported in 24 of the 43 animal studies. Neuropathological mechanisms including edema, cerebral blood flow regulation, oxidative stress, inflammation, glial activation, and tissue damage or cell death were identified in 36 studies.

Among all animal studies, 44% reported that females fared better than males, 14% reported that females fared worse, with the remaining studies showing no sex differences (28%) or mixed results (14%; Fig. 4, top). Segregating studies by injury severity suggested a possible interaction between sex and severity similar to that identified in human studies. Specifically, among studies of mild TBI, only 17% showed better outcomes in females than males, whereas in moderate–severe TBI a larger proportion (55%) showed better outcomes in females. Conversely, the percentage of studies reporting females doing worse decreased with severity (Fig. 4, lower).

We next considered whether effects of sex on injury outcome might differ across pre-clinical injury models. Most of the CCI studies (55%) reported better outcomes in females than males, with none showing males doing better (Fig. 5). In studies using CHI, 31% found females doing better and 23% showed females doing worse. In the small number of studies using lateral FPI, 40% showed females doing better and 60% females doing worse. Due to the small number of studies employing some injury models, interpretation of trends should be viewed as preliminary.

Overall, more animal studies report better outcomes in females than those reporting worse or mixed results. However, results when comparing males and females appear to depend upon the specific measures recorded, when they are recorded after injury, and in what brain region they are sampled. Mixed results within an animal study may also result from pre-set group sizes that are powered to detect sex differences in some assessments but might be inadequate for others. Females performed better than males on sensorimotor tasks but not on cognitive tasks following moderate to severe CCI.[37–40] Regarding time-course, females showed less edema than males at 5 h, 3 days, and 5 days after impact acceleration injury, but more edema at 24 h post-injury.[41] Impact acceleration injury also resulted in an earlier peak of neurodegeneration in male mice (3 days) versus a 14-day peak in females.[42] However, severe CCI did not show significant difference in time-course of neurodegeneration or in overall tissue damage between males and females.[43] Neuropathological measures varied based on the type of injury and brain region sampled. Sex-dependent changes in messenger ribonuleic acid (mRNA) expression of growth factors and inflammatory markers were different between the prefrontal cortex and the hippocampus.[44] Gene expression in males and females also varied based on the direction of acceleration and rotational forces and number of head impacts.[44,45]

Animal studies offer the ability to control many experimental variables, to study cellular and molecular mechanisms, and to directly test the link between mechanisms and functional outcomes. However, the extent to which these models accurately reflect the human condition has been debated.[46,47] Although comparisons across different animal species, strains, injury models, and severities are helpful in understanding the complexity of human TBI,

Table 3. Animal Studies of TBI Comparing Outcomes by Sex

Reference	*TBI model*	*Severity*	*Species*	*Age group*	*Results: neuropathology and physiology (in F vs. M)*	*Results: functional outcomes (in F vs. M)*
			Worse outcomes in females (n = 6)			
#(Emerson and Vink, 1992)[279]	Lateral FPI	Moderate (2.8 atm)	Rat	Adult	Lower free Mg^{2+} levels in female brain post-TBI	Higher mortality in females
(Emerson et al., 1993)[280]	Lateral FPI	Moderate (2.8 atm)	Rat	Adult	-	Higher mortality in females
(Bramlett et al., 2009)[281]	Lateral FPI	Moderate (1.7–2.2 atm)	Rat	Adult	Increased cleavage of the anti-apoptotic protein XIAP in intact females compared with males and Ovx females	-
(Mychasiuk et al., 2014)[282]	CHI	Mild (150 g, 0.5 m)	Rat	Adolescent	-	More social avoidance behavior in females
#(White et al., 2017)[16]	CHI	Mild (200 g, 10 cm)	Rat	Adolescent	More immediate and prolonged reduction in long-term potentiation in females	-
#(Lyons et al., 2018)[131]	CHI	Mild (5 m/sec, 1 mm depth)	Mouse	Adult	Reduction in hippocampal metabolites of mitochondrial function in females post-TBI	-
			Better outcomes in females (n = 19)			
#(Roof et al., 1993)[11]	Bilateral CCI	Moderate (2.25 m/sec, 2 mm depth)	Rat	Adult	Less cerebral edema in intact and pseudopregnant females than males	-
(Roof and Hall, 2000)[60]	CHI	Moderate (500 g, 1.5 m drop)	Rat	Adult	Better cortical blood flow and mean arterial pressure in females	Lower mortality in females
(Bramlett and Dietrich, 2001)[61]	Lateral FPI	Moderate (1.7–2.2 atm)	Rat	Adult	Smaller brain contusions in intact females than in males or Ovx females	-
(Igarashi et al., 2001)[283]	CCI	Moderate (4m/sec, 1 mm depth)	Mouse	Adult	Smaller cortical lesion and less neuronal loss in thalamic nuclei of females. No sex difference in loss of hippocampal neurons	-
(Kupina et al., 2003)[42]	CHI	Moderate–severe (100 g, 10.5 cm drop)	Mouse	Adult	Less cytoskeletal damage and delayed time course of neurodegeneration in females	Lower mortality in females
(Suzuki et al., 2003)[284]	Lateral FPI	Moderate (1.7–2.2 atm)	Rat	Adult	Smaller contusion volume and more neuronal marker staining in females	-
#(Wagner et al., 2004)[38]	CCI	Moderate (4m/s, 2.7 mm depth)	Rat	Adult	-	Less sensorimotor impairment in females. No sex differences in spatial memory
(Wagner et al., 2005)[285]	CCI	Moderate (4m/sec, 2.7 mm depth)	Rat	Adult	Less decline in post-TBI dopamine transporter expression in females	-
(O'Connor et al., 2006)[41]	CHI	Moderate (450 g, 2 m drop)	Rat	Adult	Better BBB integrity and delayed edema formation in intact females compared with males and Ovx females	-
(Wagner et al., 2007)[223]	CCI	Moderate (4m/sec, 2.7 mm depth)	Rat	Adult	-	Less impairment on beam balance and beam walk in females. No sex differences on open field novelty task and Morris water maze
(Xiong et al., 2007)[40]	CCI	Moderate (4 m/sec, 0.8 mm depth)	Mouse	Adult	Greater cell proliferation in injured cortex of females than males. No sex differences in neurogenesis, angiogenesis, or tissue loss	Less sensorimotor impairment in females. No sex differences in spatial learning
(Gunther et al., 2015)[10]	Penetrating brain injury	Severe	Rat	Adult	Less inflammation and apoptosis in females	-
(Lazarus et al., 2015)[132]	CCI	Severe (5 m/sec, 2mm depth)	Rat	Adult	Lower protein carbonylation, a measure of oxidative stress, in females at brain regions distal to the injury. No sex differences at injury site	-
(Free et al., 2017)[37]	CCI	Moderate (4 m/sec, 2.8 mm depth)	Rat	Adult	Smaller cortical lesions in females than males	Less impairment on beam balance in females. No sex differences on beam walk and Morris water maze
#(Taylor et al., 2017)[287]	CCI	Moderate (2.8 m/sec, 2 mm depth)	Rat	Adult	Shorter duration of hyperthermia and neuroinflammation in females	-
(Tucker et al., 2017)[51]	CCI	Mild (5m/sec, 1 mm depth) or severe (5 m/sec, 2 mm depth)	Mouse	Adult	No sex differences in lesion volume	Females ambulated greater distances. Less anxiety in females in the light-dark box and elevated zero maze. No sex differences in the open-field test

(*continued*)

Table 3. (Continued)

Reference	*TBI model*	*Severity*	*Species*	*Age group*	*Results: neuropathology and physiology (in F vs. M)*	*Results: functional outcomes (in F vs. M)*
(Velosky et al., 2017)[288]	Repetitive CHI	Mild (5 m/sec, 1.2 mm depth)	Mouse	Adult	Less reactive astrogliosis in the optic tract but not corpus callosum of females	Less cognitive impairment in females
(Villapol et al., 2017)[12]	CCI	Moderate–severe (5.25 m/sec, 1.5 mm depth)	Mouse	Adult	Less macrophage activation and infiltration, neuroinflammation, and cell death. Smaller lesion volumes in females	-
(Clevenger et al., 2018)[62]	CCI	Moderate–severe(3 m/sec, 2 mm depth)	Mouse	Adult	Smaller lesion volume and less microglial activation and astrogliosis in intact females than males or Ovx females	Less sensorimotor impairment in intact females than males or Ovx females
No significant difference between males and females (n = *6*)						
#(Duvdevani et al., 1995)[289]	Bilateral CCI	Moderate (2.25 m/sec, 2 mm depth)	Rat	Adult	No difference in BBB integrity between males, normally cycling females, and pseudopregnant females	-
(Grossman and Stein, 2000)[290]	CCI	Moderate (2.25 m/sec, 2 mm depth)	Rat	Adult	-	No difference in asymmetrical forelimb use and number of foot faults in males, normally cycling females, or pseudopregnant females
(Hall et al., 2005)[43]	CCI	Severe (3.5 m/sec, 1 mm depth)	Mouse	Adult	No difference in brain damage or time-course of neurodegeneration	-
(Bruce-Keller et al., 2007)[291]	CCI	Moderate (3.5 m/s, 0.5 mm depth) or severe (3.5 m/s, 1 mm depth)	Mouse	Adult	No difference in cortical or hippocampal injury. No difference in microglial activation based on sex or hormonal status	-
#(Grant et al., 2017)[292]	Repetitive CHI	Mild (36 psi,8 mm depth)	Rat (Tg APP/PS1)	Adolescent	No sex difference in β-amyloid deposition	-
(Rubenstein et al., 2017)[293]	CHI	Severe (6.3 m/sec, 3 mm depth)	Mouse	Adult	No sex differences in biomarker concentrations (Tau and GFAP)	No sex differences in cognitive function
Mixed results in males and females (n = *12*)						
(O'Connor et al., 2003)[50]	CHI	Moderate (450 g, 2 m drop)	Rat	Adult	-	Anesthesia-dependent differences in female mortality: no sex difference with halothane, less mortality with isoflurane, higher mortality with pentobarbital. Worse rotarod performance in females. No sex difference on Morris water maze
(Chen et al., 2005)[294]	CCI	Moderate (4m/sec, 2.7 mm depth)	Rat	Adult	Increased BDNF expression in cortex of males but not females. Similar changes in BDNF expression in ipsilateral hippocampus of both sexes. Increased BDNF expression in contralateral hippocampus of females but not in males	-
(Mychasiuk et al., 2016)[282]	Lateral injury and modified CHI	Mild (100 g, pneumatic pressure or 150 g, 1 m drop)	Rat	Adult	Biomarker genes (BDNF, Eno2, GFAP, tau, TERT) were differentially expressed based on injury type, brain region, and sex	No sex differences in time-to-right, beam walk, novel context mismatch, or forced swim test. Females did better on open field test and elevated plus maze
(Tucker et al., 2016)[49]	CCI	Mild (5 m/sec, 1 mm depth) or severe (5 m/sec, 2 mm depth)	Mouse	Adult	No sex difference in lesion volume	Larger deficits in females on Y-maze. Smaller deficits in females on open-field test. No sex differences in Morris Water maze or rotarod
(Xu et al., 2016)[39]	CCI	Severe (4 m/sec, 2 mm depth)	Mouse	Adult	-	Better locomotion in females, despite lower striatal dopamine
(Semple et al., 2017)[295]	CCI	Moderate–severe (4.5 m/sec, 1.7 mm depth)	Mouse	Adult	Less reduction in dendritic complexity in females than males	Fewer deficits in social recognition in females than males. Higher sociosexual avoidance in females

(*continued*)

Table 3. (Continued)

Reference	*TBI model*	*Severity*	*Species*	*Age group*	*Results: neuropathology and physiology (in F vs. M)*	*Results: functional outcomes (in F vs. M)*
(Wright et al., 2017)[45]	Single and repetitive CHI	Mild (100 g, 5.5 m/sec)	Rat	Adolescent	Greater brain volume atrophy in females; lower white matter integrity in males. Sex-dependent changes in GFAP and tau mRNA levels	Females performed worse after sTBI but better after rTBI on beam walk. Worse performance on forced swim in females with rTBI. Better performance on novel context mismatch in females with sTBI and rTBI
(Wirth et al., 2017)[296]	Acceleration with impact	Mild	Rat	Adult	Lower hippocampal neurogenesis in females post-TBI	Shorter time-to-right, higher activity, and less anxiety in females. More persistent deficits on the Morris water maze in females
(Yamakawa et al., 2017)[297]	Repetitive CHI	Mild (50 g, 7.4 m/sec)	Rat	Adolescent	Higher hypothalamic expression of *Clock* gene but lower *Bmal1* expression in females	Less open-field ambulation in females. Better performance on elevated plus maze in females
#(Jullienne et al., 2018)[298]	CCI	Moderate (2 m/sec, 1.5 mm depth)	Mouse	Adult	No sex differences in lesion volume, neurodegeneration, BBB alteration, and microglia activation. More astrogliosis in females. Higher endothelial activation, vessel number, and vessel complexity in males	No sex differences in motor activity post-TBI
(Russell et al., 2018)[58]	Blast TBI	Mild	Mouse	Adult	Different mechanisms of hypothalamic-pituitary-adrenal axis dysfunction: dysregulation of pre-autonomic neurons in females, disruption of limbic pathways in males	No sex differences in righting reflex
(Taylor et al., 2018)[299]	CCI	Moderate (2.8 m/sec, 2 mm depth)	Rat	Adult	Shorter duration of hyperthermia in females; higher plasma corticosterone and hippocampal IL-6 in females	-

References marked with # were obtained by manual cross-referencing.
BBB, Blood–brain barrier; CCI, controlled cortical impact; CHI, closed head injury; FPI, fluid percussion injury; Ovx, ovariectomized; rTBI, repetitive TBI; sTBI, single TBI; TBI, traumatic brain injury.

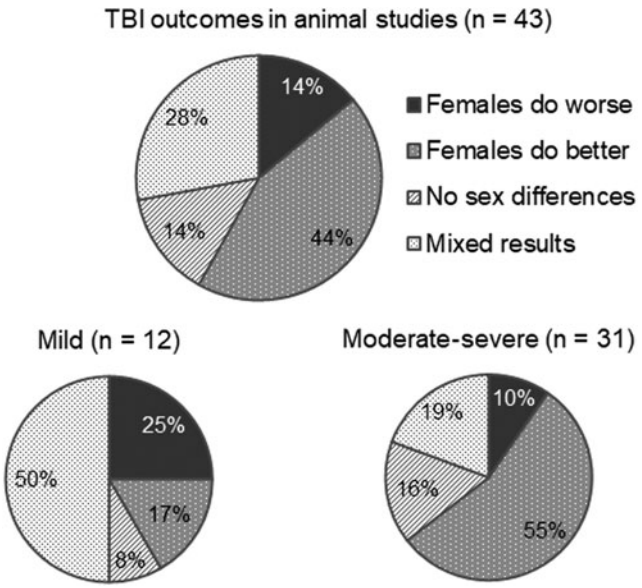

FIG. 4. Sex effects on TBI in animal studies: distribution by severity. All animal studies identified by our search criteria were classified based on post-TBI outcomes (upper panel). Animal studies were then categorized into those investigating mild (lower left) or moderate–severe (lower right) injury severity. In each category, we quantified percentage of studies showing worse outcomes in females than males, better outcomes in females than males, no sex differences, or mixed results where females do better on some outcome measures and males on others. TBI, traumatic brain injury.

greater inclusion of females in pre-clinical modeling is also essential. There remain concerns among investigators that estrous cycle changes may introduce variability in pre-clinical studies, although this has been debated.[48,49] Such concerns can, however, be addressed by using ovariectomized animals, time-locking experiments to cycle, or by measuring sex hormone levels for inclusion in post hoc statistical analysis. Future animal studies of sex differences in TBI should also consider the potential for hidden confounds, such as differential response to anesthetics, sex differences in body and/or skull size, and sex differences in motivation to perform behavioral tasks.[49–51]

Discussion

Considering the current body of research on sex differences in TBI, the overall picture is not a straightforward one that points to better outcomes in one sex versus the other. Rather, the findings we have reviewed from human and animal studies are complicated and often contradictory. A closer examination of these findings provides opportunity for new insights that we hope will move the field forward in a meaningful way. Below we will review what we have learned from studies to date, discuss some of the major unresolved questions related to sex effects in TBI, and make recommendations for future directions.

Human versus animal studies

As Figure 6 summarizes, among all human studies, women tend to do worse following TBI, whereas in animal studies, females tend to do better. However, closer examination reveals similar trends across both clinical and pre-clinical studies. For example, limiting the scope of studies to moderate to severe TBI suggests better outcomes in women/females than in men/males (Figs. 2 and 4). In contrast, mild TBI is associated with worse outcomes in women in clinical studies but mixed results in animal studies (Figs. 2 and 4). Differences in outcome measures used in humans and animals might account for this. Most human studies of mild TBI report that women experience a greater number, severity, and/or duration of post-concussive symptoms, such as headaches, fatigue, sleep disturbances, dizziness, irritability, aggressiveness, anxiousness, depression, work or relationship troubles, or short-term memory impairment.[52] Such symptoms are usually self-reported and may be influenced by societal gender stereotypes resulting in men reporting symptoms differently from women.[53,54] Outcome measures in animal studies of mild TBI may be less susceptible to this type of bias. Inclusion of more objective measures that are sensitive to mild TBI, such as biofluid and imaging biomarkers, would benefit both animal and human studies.

As noted above, human studies more commonly report functional outcomes after TBI, whereas animal studies more frequently report measures related to cellular or molecular mechanism. Across the body of literature exploring sex effects in TBI, studies incorporating *both* mechanistic and functional outcome measures remain relatively sparse. From the limited data available, it is important to note that sex differences in mechanistic measures of neuropathology or physiology are not always associated with differences in functional or

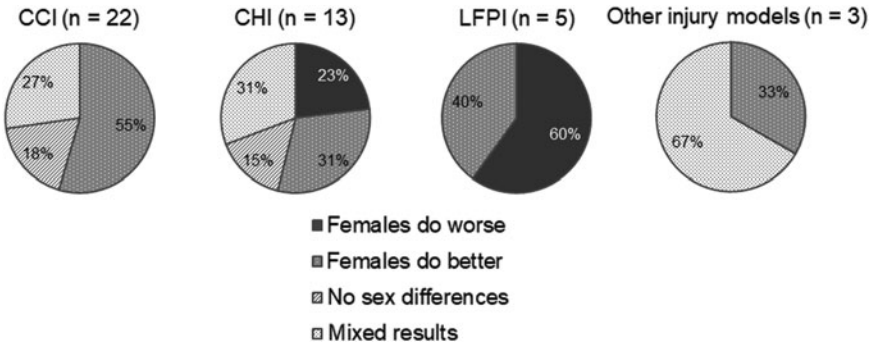

FIG. 5. Sex effects on TBI in animal studies: distribution by injury model. Animal studies were classified based on injury model used: CCI, CHI, LFPI, and other injury models. In each category, we quantified percentage of studies showing worse outcomes in females than males, better outcomes in females than males, no sex differences, or mixed results where females do better on some outcome measures and males on others. CCI, controlled cortical impact; CHI, closed head injury; LFPI, lateral fluid percussion injury; TBI, traumatic brain injury.

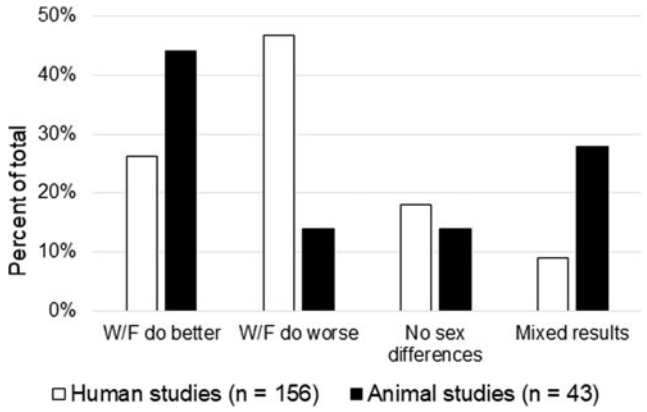

FIG. 6. Comparison of TBI outcomes in human versus animal studies. All human studies (white bars) and animal studies (black bars) were divided into four categories based on study findings: 1) those showing women/females do better than men/males, 2) studies showing women/females do worse than men/males, 3) no sex differences, and 4) those reporting mixed results by sex. TBI, traumatic brain injury.

neurocognitive outcome. Indeed, sex-related differences in functional magnetic resonance imaging (fMRI) activity, heart rate variability, edema, and intracranial hypertension were reported even in the absence of differences in cognition, post-concussive symptoms, duration of recovery, and GOS.[13,55,56] Differences in gene expression following mild TBI in male and female rats were not associated with deficits in motor function.[44] Conversely, mortality and GOS-E were found to be different between sexes despite similar cerebral perfusion pressure and intracranial pressure.[57] In addition, female mice had better ambulation and displayed less anxiety post-TBI although sex differences in brain lesion volumes were not detected.[49,51] One explanation for these divergent findings may be different sensitivities of the physiological versus functional outcome measures used.

Occasionally, both sexes may converge to the same functional outcome despite having divergent underlying neuropathology.[48] For instance, cell death following brain injury is triggered by caspase activation in females but by caspase-independent mechanisms in males.[9] In mice, dysfunction of the hypothalamic-pituitary-adrenal (HPA) axis following blast TBI is caused by dysregulation of pre-autonomic neurons in females, but by disruption of limbic pathways in males.[58] Because therapeutic interventions are targeted toward underlying mechanisms, elucidating the role of sex in TBI pathophysiology is crucial.

Hormonal versus non-hormonal factors

One of the most compelling and widely studied hypotheses of the cause of sex differences in TBI is that the injury response is modulated by sex hormones, as recently reviewed by Spani and colleagues.[20] A simplified overview of hormonal changes across the life span is that following a period of low hormonal levels after birth, boys and girls experience a pubertal surge in male and female sex hormones, respectively.[59] Whereas women experience cyclic production of estrogen and progesterone until menopause, testosterone production in men declines incrementally over time and is markedly reduced in older men.

Whether better outcomes in female animals are due to the neuroprotective effects of estrogen and/or progesterone has been extensively examined. Normally cycling females had significantly better survival rates, blood–brain barrier integrity, improved cortical blood flow, fewer sensorimotor deficits, less brain edema, and smaller contusion volumes than age-matched males after TBI.[11,60–62] In pseudo-pregnant rats, post-TBI cerebral edema was even lower than in normally cycling females, suggesting that female sex hormones may exert a dose-dependent neuroprotective response.[11]

One study suggests that the better post-injury outcome in pseudopregnant females compared with both males and intact females might be due to their 50–100 times higher levels of progesterone and its metabolites at the time of injury.[63] Similarly, female rats in the proestrous phase of their cycles had less brain edema and lower intracranial pressure after TBI compared with non-proestrous females presumably due to elevated serum levels of estrogen and progesterone.[64] Conversely, sex-dependent neuroprotective effects were extinguished in ovariectomized females with low levels of circulating estrogen and progesterone, but rescued by exogenous treatment with these hormones.[11,60,61] Sex may also influence the response to exogenous hormone treatments as seen in a rat model of pediatric TBI, where progesterone improved mitochondrial respiratory control ratio and glutathione levels in males but reduced lesion volumes in females.[65] In adolescent male mice with TBI, progesterone improved motor performance but exacerbated deficits in female mice.[66]

If female sex hormones provide endogenous neuroprotection in women, then we might predict that women in their reproductive years would have a neuroprotective advantage over men that would not be seen before puberty or after menopause. This prediction is supported by a study of over 20,000 patients showing that post-pubescent teenage girls had lower mortality than age-matched boys after moderate to severe TBI.[67] Further, a study with approximately 1800 patients showed higher mortality following severe TBI in post-menopausal women compared with age-matched men.[68] Notably, both of these studies excluded patients with extracranial injury, removing the potential confound of non-brain causes of mortality.

However, several studies have questioned the importance of female sex hormones following TBI. Estrous stage at injury did not influence contusion volumes or behavioral outcomes in female rats.[38,61] Moreover, newborn female piglets had better cerebral perfusion pressure regulation after injury than males, despite their reproductively immature state.[69] These pre-clinical studies suggest that phase of menstrual cycle at injury may not by itself have a large influence on TBI outcomes. Certain human studies also support this notion. Menstrual cycle phase and oral contraceptive use did not affect post-concussion cognition or postural stability in a study of college-aged women.[70] Peri- and post-menopausal, but not younger (reproductive age) women had better outcomes including lower mortality than age-matched men in more than 72,000 survivors of moderate to severe TBI.[71] Another large, multi-center study found lower mortality in women than men above 50 years of age.[72] Finally, the disappointing results of progesterone in Phase III clinical trials has called into question the importance of sex hormones in determining TBI outcome.[73,74] Together, these findings support the notion that factors beyond sex hormones are likely to be important contributors to sex differences after TBI.

In addition to the effects of sex hormones on injury pathophysiology, it is also important to consider the reverse, that is, the effects of brain trauma on endogenous hormone levels. Acute and chronic hypogonadism due to HPA axis dysfunction has been reported in approximately 20–30% of TBI patients.[75–78] Patients with hypogonadism had low GCS, indicating that more severe TBI may be associated with greater suppression of the HPA axis.[79] Whether

there are differences in the magnitude and prevalence of hypogonadism between men and women is not known. It may however be hypothesized that even after gonadal suppression, the low levels of female sex hormones may be sufficient to mediate neuroprotection because a large proportion of moderate–severe TBI studies show better outcomes in women than men (Fig. 2, lower right).

The influence of estrogen and progesterone on injury pathways and outcomes has been far more extensively characterized than that of male androgens. The limited data available suggest that testosterone too may exert neuroprotection. Lower testosterone levels at admission were associated with longer duration of hospital stay and worse functional independence measures in men with moderate–severe TBI.[80,81] Testosterone promotes neurogenesis in uninjured male rats[82] and neuronal survival in male and female rats following axonal injury.[83,84] However, because testosterone is converted to estradiol by aromatase, there is a possibility that the observed effects are at least partly conferred by its estrogenic metabolite. In contrast, chronically treating mice with an androgenic-anabolic steroid cocktail containing testosterone prior to induction of repeated, mild TBI exacerbated TBI-mediated axonal injury and white matter microgliosis but not behavioral deficits.[85] Data from a clinical trial testing the effects of physiological doses of testosterone on men with low testosterone levels following moderate–severe TBI is currently awaited (ClinicalTrials.gov identifier NCT01201863). More studies are clearly needed to delineate the role of testosterone on the neuropathological and functional outcomes of TBI.

Although many studies have focused on the hormonal basis of sex differences in TBI, chromosomal differences remain underexplored. Sex differences may, however, arise from chromosomal sources wherein XX or XY complement genes drive brain development.[86] Biologically, organisms with XX chromosomes are considered female and those with XY chromosomes are male. *In utero*, one of the X chromosomes in female embryos undergoes inactivation to balance gene expression between sexes.[87] However, some genes escape X-inactivation, remaining transcriptionally active in both the active and inactive X chromosome, resulting in higher expression of these genes in females.[88,89] Because the X chromosome is enriched in genes often expressed in neural tissues, ''escape genes'' that affect brain function may contribute to sex differences in susceptibility to, and recovery from, neurological disorders and injuries. Indeed, most escape genes identified in mice play a role in neuronal differentiation, cell survival, dendritic outgrowth, and regulation of synaptic density.[88,90]

Efforts are underway to separate the hormonal and chromosomal underpinnings of sex differences in brain structure and function. The Four Core Genotypes mouse model uncouples chromosomal effects (X and Y) from gonadal influences (ovaries and testes), allowing each to be studied separately by generating four genotypes: XX mice with ovaries, XX mice with testes, XY mice with ovaries, and XY mice with testes.[91] High-resolution MRI in these mice found that sex differences in the volumes of certain brain regions were influenced exclusively by gonadal hormones, whereas differences in others were exclusively under chromosomal control. The same study showed that spatial learning and memory was solely under hormonal control, independent of sex chromosomes.[92] The Four Core Genotype mouse model may be a valuable tool to unravel sex-based differences in TBI.[93] However, because fewer genes escape inactivation in mice (3%) compared with humans (15%),[94,95] the chromosomal basis of sex differences may be understated in rodent studies compared with humans.

In humans, chromosomal and hormonal influences on the brain can be dissected by comparing individuals with Klinefelter syndrome (XXY males) with XX females and XY males. Accordingly, sex differences in cerebellar and pre-central gray matter volumes were associated with X-chromosome load, whereas sex differences in the amygdala, parahippocampus, and occipital cortex were linked to testosterone levels.[96] Given the importance of the amygdala, hippocampus, and prefrontal cortex for stress responses and mood,[97–99] it is possible that anatomical differences in these regions may contribute to post-TBI symptoms, as women report greater anxiety and depression and men report more amnesia and confusion.[8,100,101]

At the ultrastructural level, axons of cultured neurons isolated from females were consistently smaller and contained fewer microtubules than those from males. Also, following a stretch-induced injury *in vitro*, axons from females exhibited greater swelling and loss of calcium signaling compared with those from males.[102] The effect of sex hormones on neurogenesis and spine density has also been studied,[103–105] and could modulate synaptic plasticity during recovery from TBI. By contrast, how sex chromosomes may affect these phenomena has not been well studied. Whether impaired synaptic plasticity observed in juvenile female rats following mild TBI is due to chromosomal control of synaptic ion channel expression or synaptic spine density needs further investigation.[16] *In vitro* approaches offer an opportunity to examine cells isolated from males or females without the influence of circulating sex hormones,[102] and offer considerable potential for better understanding chromosomal influence on injury response.

Interpreting mixed results

One finding of our analysis is the substantial fraction of both human and animal studies yielding mixed results, that is, women/females had better outcomes on some measures and worse outcomes on others. Figures 2 and 4 indicate that 9% of human studies and 28% of animal studies yielded mixed results per our definition. However, many of these studies only used a single outcome measure. Restricting analysis to studies reporting more than one outcome indicates that 19% of human and 37% of animal studies reported mixed results.

One factor that might contribute to mixed results is that men and women perform differently on some cognitive and behavioral tasks at baseline. For instance, baseline testing on the Immediate Post-Concussion Assessment and Cognitive Test showed that women outperformed men on verbal memory and reaction times.[106,107] Similarly, rodents show sex differences in baseline performance on spatial learning tasks such as the Morris water maze and radial arm maze.[108]

In addition, the selection of outcome measures clearly matters and can affect conclusions. For example, female mice had fewer deficits in social recognition, but increased sociosexual avoidance compared with males following CCI,[51] and also showed greater ambulation but more severely depleted striatal dopamine compared with males.[39] Female rats subjected to repeated, mild TBI exhibited greater prefrontal cortical atrophy, whereas males exhibited greater white matter disruption in the corpus callosum. Behavioral studies in the same rats also found increased depression-like behaviors in females and working memory deficits in males.[45] Studies in humans also show mixed results. For example, although women veterans were less likely to be diagnosed with post-traumatic stress disorder following TBI, they were more likely to suffer from depression or anxiety.[8] Post-TBI symptoms differed between sexes with women reporting more headaches, dizziness, and drowsiness and men reporting more

amnesia and confusion.[100,109] Further, age interacted with sex leading to better verbal abilities in women than men in their twenties but slower processing speed in women than men in their forties.[110]

These studies, which show *within a given population sample* that males fare better on some outcome measures and females better on others, encourage us to think about sex effects in TBI beyond a single dimension. A useful framework for understanding sex differences in TBI may be a ''mosaic'' model in which distinct anatomical/functional domains may each respond differently to injury in males versus females. Such a model can account for mixed results, and highlights the benefits of study design that includes multiple outcome measurements.[48,111] Although studies relying on a single outcome measure might be useful for gross outcomes such as mortality and are easier to interpret, they do not fully represent the anatomical and physiological complexity of sex effects in TBI. Accordingly, we advocate for study batteries of multiple measures reflecting both mechanisms and behavioral responses, ideally with multiple time-points, and with more brain regions sampled. Clinical databases such as TRACK-TBI, FITBIR, and IMPACT that serve as integrated repositories for multi-dimensional outcome assessments, genomic/proteomic data, neuroimaging and blood biomarkers for civilian, sports, and military TBI are becoming important tools in evaluating the impact of sex on TBI outcomes and experimental treatments.[112–114] This ability to access, share, analyze, and aggregate common data elements allows for rigorous comparison of multiple methodologies and outcome measures in studies of sex differences.

Sex differences in TBI: Do mitochondria play a role?

Brain mitochondrial dysfunction and the resulting bioenergetic disruption are fundamental to the injury cascade of TBI. Mitochondria are crucial to energy production, as well as calcium homeostasis, free radical production, neurotransmitter synthesis, and apoptosis in neurons and glia.[115] Accumulating evidence suggests that mitochondria might perform these processes differently in males than females, both under physiological conditions and under conditions of cellular stress such as TBI.[116]

Under physiological conditions, sex-specific differences in mitochondrial respiration, bioenergetics, and reactive oxygen species production have been reported in both human and animal studies. In healthy human subjects, women had higher levels of *N*-acetylaspartate, a marker of neuronal bioenergetics, in gray and white matter.[117] Although mitochondria extracted from brain, liver, and cerebral arteries of female rodents displayed more efficient oxidative phosphorylation than in males,[118–122] higher maximal respiration was reported in cortical astrocytes derived from male rats than females.[123] Further, brain mitochondria of female rodents had lower oxidative stress than those from males associated with greater expression and activity of antioxidant enzymes.[119,124,125]

These physiological differences in mitochondrial respiration, energy production, and oxidative stress may be exacerbated under pathological conditions. For example, during high-stress conditions males preferentially rely on carbohydrates and amino acids as a fuel source for energy production, whereas females use fats.[116,126–128] Cellular stressors such as nutrient deprivation may elicit a differential response in mitochondria from males and females resulting in decreased mitochondrial respiration, increased autophagy, and enhanced neuronal death in male rats.[128] Conversely, female mice showed greater deficits in bioenergetic markers such as phosphocreatine and *N*-acetylaspartate following mild TBI, compared with male mice.[129] Protein carbonylation, a marker of oxidative damage, was also lower in the brains of female rats compared with males post-TBI.[130]

How mitochondrial fission/fusion dynamics can affect mitochondrial health, protein quality control, and neuronal survival is a relatively new and active area of TBI research.[131] Mitochondrial fusion allows for greater adenosine triphosphate (ATP) production during conditions of high metabolic activity, whereas fission facilitates transport of mitochondria to regions of high energy demand and removal of damaged mitochondria by autophagy.[132,133] Although it is reported that mitochondria from male rodents have increased propensity to undergo fission following TBI,[134,135] mitochondrial dynamics following TBI have not been studied in females. Notably, sex differences in the regulation of genes controlling mitochondrial dynamics have been reported in mice following ischemic injury, a condition that shares pathophysiological features with TBI.[136] If mitochondrial dynamics are also differentially altered in males and females following TBI, this could be a possible mechanism underlying observed sex differences in mitochondrial respiration, oxidative stress, and cell death.

Sex hormones affect mitochondrial biogenesis and gene expression via estrogen, progesterone, and androgen receptors expressed on the mitochondrial membrane.[137] Conversely, mitochondria play an essential role in sex steroid biosynthesis by promoting the

Table 4. Review Highlights

- A better understanding of the effects of biological sex in TBI will help improve treatments and patient outcomes.
- Among studies reviewed, the largest fraction of human studies reported worse outcomes in women, whereas the largest fraction of animal studies reported better outcomes in females.
- Human and animal studies of more severe TBI were more likely than studies of milder injury to report better outcomes in women/females than men/males.
- Larger clinical studies were more likely than smaller studies to report better outcomes in women.
- Injury severity, genetic factors, and age may interact with biological sex to determine TBI outcomes.
- Comorbidities and extracerebral injuries, which may have different prevalence in women and men, are frequently unreported.
- Sex differences in TBI may be considered as a ''mosaic'' where women/females fare better on some measures and men/males on others.
- Few studies have investigated potential effects of androgens or chromosomal contributions to sex differences in TBI outcomes.
- Sex differences in mitochondrial function and dynamics may be important sources of sex differences in TBI.
- More research is needed to characterize both the underlying pathophysiology of TBI and treatment efficacy in women. Study designs need to be adequately powered to detect possible sex differences.

TBI, traumatic brain injury.

production of the sex hormone precursor pregnenolone from cholesterol.[138] Estrogen and progesterone contributed to sex differences in cellular respiration and anti-oxidative functions of brain mitochondria in uninjured female rodents.[119,124,139–141] They upregulated transcription of fission and fusion genes in astrocytes of uninjured female mice, but decreased the transcription of these genes in males.[142] Progesterone treatment reversed TBI-mediated impairment in mitochondrial respiration and neuron loss in ovariectomized adult females and prevented loss of the antioxidant glutathione in juvenile male rats, but not in females.[65,143] Although not as well-characterized as the effects of progesterone, neuroprotective effects of testosterone including inhibition of apoptosis, reduction in oxidative stress, improved mitochondrial respiration, and maintenance of mitochondrial membrane potential have also been reported.[144–146]

In summary, multiple aspects of mitochondrial function appear to be different between males and females under physiological conditions, and differences may be exacerbated by stress or injury.[126–128,136] However, sex differences in mitochondrial function in the context of TBI have only been explored to a limited extent. Given the central importance of mitochondria in TBI pathophysiology, this is an area that warrants further investigation.

Conclusion

This review of the literature in humans and animal models suggests that sex differences in TBI outcomes are likely, but these effects are not universal. The largest fraction of human studies report worse outcomes in women than men, whereas the largest fraction of animal studies report better outcomes in females than males. However, a more nuanced picture emerges upon closer examination of additional factors that may interact with sex differences to influence TBI outcomes. Table 4 presents highlights of our main findings.

In clinical studies, injury severity might affect TBI outcomes in a sex-dependent manner. Although only a few of the studies on milder TBI reported better outcomes in women, a larger proportion of the studies focusing on more severe injury report better outcomes in women. TBI outcomes also varied based on the size of study. Most human studies were small, enrolling fewer than 1000 patients. Whereas half of these smaller studies reported worse outcomes in women, a majority of large studies enrolling more than 10,000 patients reported better outcomes in women. Because larger sample size affords greater statistical power and might better represent the general population, these large studies might be more reliable predictors of sex differences in TBI outcomes.

Animal studies showed a similar trend across injury severities as that in TBI patients, with greater injury severity being associated with better outcomes in females than males. Our review of animal studies suggests that sex differences may also depend on the specific TBI model used. Most studies using the CCI model indicate that females do better and none show males with better outcomes. Fewer studies use other models and so conclusions pertaining to sex differences should be approached with caution. However, an overall problem in the field is that few studies include females as an integral comparison group. More studies are required to probe the specific effects of sex on TBI outcomes, particularly in animal models of diffuse and repetitive injury.

An array of outcome measures has been used to study sex differences in TBI in both humans and animals. Given the substantial number of studies reporting mixed results, it is obvious that the selection of outcome measures can affect conclusions. Neuroimaging and blood biomarkers that are TBI-specific yet robust across injury type and translatable from pre-clinical to clinical studies have not been applied to the study of sex differences.[147] Future studies in both animals and humans would benefit from the use of validated, objective biomarkers.

Because mitochondria are central to TBI pathophysiology and have marked sex differences, we believe this is an important area for future investigation. Specifically, clear elucidation of how sex differences in mitochondrial respiration, antioxidant status, and mitochondrial dynamics may affect functional outcomes is essential. Further research is clearly required to unravel the hormonal and chromosomal basis of sex differences in TBI and how these may influence mitochondrial function.

Historically, preclinical studies in neurotrauma have been performed exclusively in males and women have been under-represented in clinical studies. Because disease etiology, underlying neuropathology, and cellular mechanisms of recovery differ between sexes, such under-representation likely has a negative impact on clinical care and limits successful drug development. Recent National Institutes of Health guidelines to include both sexes or to justify exclusion of either sex in cell and animal studies[148] are a promising step to help reduce male bias in pre-clinical TBI. As these guidelines drive our understanding of mechanisms of injury and recovery in both sexes, there will also be an increasing need to translate this knowledge into adequately powered clinical trials in both sexes. A better understanding of how biological sex dictates TBI pathophysiology and outcomes is critical to improving patient care and the development of treatments for both men and women.

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