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Sex Differences in Outcome after Mild Traumatic Brain Injury

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Abstract

The objective of this study was to estimate the independent association of sex with outcome after mild traumatic brain injury (mTBI). We performed an analysis of a subset of an established cohort involving 1425 mTBI patients presenting to an academic emergency department (ED). The associations between sex and three outcomes determined 3 months after the initial ED visit were examined: post-concussive symptom (PCS) score (0, 1–5, 6–16, and >16), the number of days to return of normal activities (0, 1–7, and >7), and the number of days of work missed (0, 1–7,and >7). Logistic regression analyses were used to determine the relationship between sex and each outcome after controlling for 12 relevant subject-level variables. Of the 1425 subjects, 643 (45.1%) were female and 782 (54.9%) were male. Three months after mTBI, males had significantly lower odds of being in a higher PCS score category (odds ratio [OR] 0.62, 95% confidence interval [CI]: 0.50, 0.78); this association appeared to be more prominent during child-bearing years for females. Males and females did not significantly differ with respect to the odds of poorer outcome as defined by the number of days to return of normal activities or the number of days of work missed. Female sex is associated with significantly higher odds of poor outcome after mTBI, as measured by PCS score, after control for appropriate confounders. The observed pattern of peak disability for females during the child-bearing years suggests disruption of endogenous estrogen or progesterone production. Attempts to better understand how mTBI affects production of these hormones acutely after injury and during the recovery period may shed light on the mechanism behind poorer outcome among females and putative therapeutic interventions.

Key words: mild traumatic brain injury; outcome; post-concussive symptoms; sex; unemployment

Introduction

Mild traumatic brain injury (mTBI) has recently emerged as a major public health problem, affecting over 1.2 million Americans each year (Jager et al., 2000) The annual incidence of emergency department-attended mTBI is 503/100,000 in the U.S. (Bazarian et al., 2005). The unemployment rate at 3 months post-injury is significant, ranging from 12–34% (Englander et al., 1992; Rimel et al. 1981). Additionally, one-quarter of all mTBI patients—an estimated 320,000 per year—have post-concussive symptoms or other cognitive deficits that persist beyond 1 year (Alves et al., 1993; Middelboe et al., 1992). This number is greater than the annual incidence of multiple sclerosis, Parkinson's disease, myasthenia gravis, and Huntington's disease combined (Alexander, 1995). In fact, a 1999 National Institutes of Health Consensus Development Panel concluded that mTBI is significantly underdiagnosed, and that research surrounding risk stratification and outcome prediction was needed (National Institutes of Health, 1999).

There are several factors associated with poor outcome after mTBI, but the most controversial is sex. Controlled experiments in animals have shown improved survival and cognitive function among females after TBI compared to males (Bramlett and Dietrich, 2001; O'Connor et al., 2003; Wagner et al., 2004), suggesting that female sex is somehow neuroprotective. However, multiple observational studies in humans have reported poorer outcomes among females after both severe TBI (Cifu et al., 1997; Donders and Woodward, 2003; Edna and Cappelen, 1987; Kaplan and Corrigan, 1992; Kirkness et al., 2004; Kraus et al., 2000; Levin et al., 1987; McMordie et al., 1990; Morrison et al., 2004; Wilberger et al., 1991), and mTBI (Bazarian and Atabaki, 2001; Bazarian et al., 1999; Jensen and Nielsen, 1990; Rutherford et al., 1977, 1979).

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Indeed, a meta-analysis of eight studies and 20 outcome variables revealed poorer outcome for women in 85% of the measured variables with an average effect size of −0.15 (Farace and Alves, 2000).

The reason for the discrepancy between controlled experiments in animals and observational studies in humans is not clear. In animal studies (predominantly rodent models), the genetic make-up of the subjects and the mechanically-induced TBI they receive are both controlled. Thus the relationship between sex and post-TBI outcome is not obscured by any individual differences in the animals. The disadvantage of animal studies lies in the fact that the TBI incurred is typically more severe than that experienced in human mTBI (Leker et al., 2002), and that there are substantial differences between the brains of humans and rodents. Functional outcome measurement in animals is also far less sensitive than in humans, relying on direct observation of motor skills or performance of cognitive tasks such as maze navigation. It remains technically impossible to assess subjective symptoms of TBI in animal models. This is a major shortcoming because humans with post-concussive syndrome often perform normally in neuropsychological testing. Nonetheless, these animal studies have been used to advance the hypothesis that gonadal steroids such as estrogen and progesterone are neuroprotective (Djebaili et al., 2004, 2005; Roof et al., 1994; Stein and Hoffman, 2003), which has led to two clinical trials of progesterone after moderate to severe TBI in humans (Wright et al., 2007; Xiao et al., 2008). Therefore resolving the discrepancy between human and animal studies has implications for future clinical trials in humans.

If female sex is indeed associated with improved outcome after TBI in humans, continued efforts to explore gonadal steroids as potential treatment seems warranted. Why have observational studies in humans failed to confirm that females have better post-TBI outcomes? One possible explanation is that human observational studies, unlike controlled animal experiments, have failed to control for subject-level factors other than sex that affect functional outcome after TBI. Functional outcome after TBI, and after mTBI in particular, has been postulated to be related to a combination of subject-level factors stemming from three broad areas: pre-injury brain function, the severity of the brain injury, and post-injury brain recovery (Stulemeijer et al., 2008) (Supplementary Figure 1; see online supplementary material at http://www.liebertonline.com). In this model, sex is considered a pre-injury factor. In animal models, these factors can be controlled by using genetically similar animals, inducing head injury in a consistent and reproducible fashion using an accepted model, and providing an identical environment post-injury. Without control for these factors, the true relationship between sex and outcome in human observational studies might have been obscured.

The primary objective of the current study was to estimate the independent association of sex with outcome 3 months after mTBI. The secondary goal was to identify other important predictors of outcome after mTBI.

Methods

We conducted an analysis of a subset of mTBI patients derived from a larger, established cohort accrued through the emergency department (ED) of the University of Rochester between January 2003 and September 2004. The larger cohort was assembled to better understand the epidemiology of mTBI and was funded by the National Institutes of Health. Patients of all ages were eligible for the parent study if they met the case definition of mTBI as determined by the Mild Traumatic Brain Injury Committee of the American Congress of Rehabilitation Medicine (American Congress of Rehabilitation Medicine, 1993). This definition consists of a blow to the head or acceleration/deceleration movement of the head resulting in one or more of the following: loss of consciousness (LOC) for less than 30 min, amnesia for less than 24 h, or any alteration in mental state at the time of injury. All subjects must have had a Glasgow Coma Scale (GCS) score $\geq$13 measured 30 min or more after the injury. Because the focus of the current analysis was outcome, the subset cohort was restricted to subjects $\geq$3 years of age who we were able to contact at 3 months post-injury for follow-up.

In order to accrue the parent cohort, patients entering the ED with mTBI were identified by trained research assistants. Board-certified ED physicians attending to the patients confirmed the suspected cases of mTBI. Research assistants collected clinically relevant data from the patient or caregiver, including demographic factors (race, sex, age, ethnicity, and employment status), historical factors (LOC, amnesia, dizziness, nausea, and headache), physical exam factors (GCS score and extracranial injuries), mechanism of injury, psychosocial factors (drug or alcohol intoxication), and results of imaging studies. Head-injured patients using ethanol or other psychoactive drugs remained eligible for inclusion in this study.

Three months after the initial ED visit, outcome was determined by telephone interview. The interviewer was blinded to the details of the initial ED visit. Three aspects of neurological outcome were evaluated: post-concussive symptoms, the number of days to return to normal activities, and the number of days of work missed.

Post-concussive symptoms were assessed using the Rivermead Post Concussion Questionnaire (RPCQ). This 16-question survey has been previously validated among mTBI patients (Crawford et al., 1996; King et al., 1995). Each of the 16 questions asks subjects to rate the severity of a post-concussive symptom (such as headache), compared to pre-injury, on a Likert scale ranging from "0" (absent) to "4" (severe). Subjects were asked to report their current symptoms in relation to the way they felt before the head injury. Total scores thus ranged from 0–64. The RPCQ was administered directly to subjects if they were >14 years of age, and to a parent or caregiver if they were 3–14 years of age.

The number of days to return to normal activities was assessed by asking subjects to recall the number of days between the time of injury and resumption of activities typical of their daily routine, such as bathing, dressing, food preparation, interacting with friends, and recreational activities. This question was administered directly to subjects if they were >14 years of age, and by a parent or caregiver if they were 3–14 years of age. Because follow-up occurred at 3 months, the number of days to return of normal activities ranged from 0–90.

The number of workdays missed was determined by asking subjects to recall the number of days between the time of injury and resumption of employment. Subjects not employed at the time of injury (i.e., pre-schoolers, students, retirees, and

the unemployed) were excluded from the analysis of the number of days of work missed. Subjects were considered employed if they had reported at the time of injury that they were involved in full-time or part-time work for pay, were self-employed, or were homemakers. This follow-up question was administered directly to subjects. Because follow-up occurred at 3 months, the number of days of work missed ranged from 0–90.

Selection of covariates for multivariate analysis

In order to isolate the independent associations of sex with post-concussive symptoms, activity days lost, and workdays lost, we sought to identify and control for other subject-level factors that impact these outcomes. While there is no accepted group of variables that are known to account for all of the variation in outcome, multiple studies report single variables that appear to influence outcome. In general these variables can be categorized into those that occur pre-injury, those that that occur at the time of injury, and those that occur post-injury (Supplementary Figure 1; see online supplementary material at http://www.liebertonline.com).

Pre-injury. Advanced age and prior TBI have been shown to be associated with an increase in post-concussive symptoms and neurobehavioral deficits after mTBI (Ponsford et al., 2000; Rutherford, 1989). A history of prior TBI was defined as the patient's report of a prior ED visit or hospitalization for head injury. Race and ethnicity are also important. Hispanics are less likely than non-Hispanics to develop post-concussive symptoms after mTBI (McCauley et al., 2001). Both race and ethnicity were elicited directly from subjects. Low socioeconomic status (SES) has also been linked to poor outcome after mTBI (Rutherford, 1989). SES was estimated by household income, which in turn was determined by applying the median household income in the zip code of residence from U.S. Census data (www.census.gov).

Injury. The severity of TBI, even within the category of mTBI, has a significant influence on outcome. There are several ways to estimate the severity of mTBI. The first is with initial mTBI symptoms such as LOC and amnesia. While it is widely accepted that a head injury resulting in transient LOC or amnesia is more severe than one that just produces a sense of being stunned or dazed, the evidence for this is conflicting (American Congress of Rehabilitation Medicine, 1993; Thurman et al., 1995). Wenden and associates and Rutherford found that patients with post-traumatic amnesia had significantly more post-concussive symptoms than patients without amnesia (Rutherford, 1989; Wenden et al., 1998). Several authors, however, have found neither amnesia nor LOC to be associated with poor outcome after mTBI (Harad and Kerstein, 1992; Hinton-Bayre and Geffen, 2002; Ratan et al., 2001; Strugar et al., 1993). These initial mTBI symptoms (LOC, amnesia, and feeling stunned) were elicited from subjects or caregivers at the time of initial presentation to the ED by trained patient enrollers.

The second way to capture mTBI severity is with the initial GCS score. mTBI patients with a GCS score of 13 or 14 have higher intracranial injury rates and poorer overall outcomes than mTBI patients with a GCS score of 15 (Culotta et al., 1996; McCullagh et al., 2001). The initial GCS score was elicited at the time of the ED visit from the emergency physician caring for the subject.

A final way to capture mTBI severity is with the initial head CT scan. Traumatic abnormalities on CT scan, although typically revealing hemorrhage, may be related to the severity of underlying brain injury. Several authors have found that mTBI patients with cerebral contusions on head CT scan have worse cognitive and neurobehavioral outcomes than mTBI patients with normal CT scans (Borgaro et al., 2003; Iverson, 2006; Kashluba et al., 2008; Levin et al., 2008; Williams et al., 1990). Abnormal CT scan was defined as revealing any of the following traumatic abnormalities: acute hemorrhage (subarachnoid, subdural, epidural, or contusion), edema, or skull fracture.

Mechanism of injury is another injury-related factor that influences outcome after mTBI. Compared to other mechanisms, motor vehicle crashes and assaults are associated with a higher number of post-concussive symptoms (Bazarian and Atabaki 2001; McCauley et al., 2001; Ponsford et al., 2000; Wenden et al., 1998). Mechanism of injury was elicited from subjects or caregivers at the time of initial presentation to the ED by the patient enrollers. Finally, extracranial injuries such as fractures and internal organ injuries can produce pain and alterations in daily functions that impact post-TBI outcome (Wenden et al., 1998). Significant extracranial injuries were defined as any bone fractures, solid organ injuries, sprains, strains, contusions, or lacerations requiring sutures. These were determined by retrospectively examining the International Classification of Disease–9th edition codes assigned by billing coders to each ED chart.

Post-injury. Pharmacological agents given in the immediate post-injury period have the potential to impact the sequence of cellular events leading from the initial mTBI (traumatic axonal injury) to neuronal death, synaptic reorganization, and thus outcome. Selective inhibitors of the enzyme cyclooxygenase-2 in particular have been shown to have a beneficial effect on outcome after experimentally-induced TBI in animals (Hurley et al., 2002). Other non-selective inhibitors of cyclooxygenase such as indomethacin and ibuprofen have also been shown to affect outcome (Banik et al., 2000; Fu et al., 2007; Slavik and Rhoney 1999). Analgesics such as these are commonly given to mTBI patients in the ED. Patients were considered to have received an analgesic medication in the ED if the medication fell into one of the following categories: acetaminophen, aspirin, nonsteroidal anti-inflammatory agents, cyclooxygenase-2 inhibitors, opiates, or muscle relaxants.

A patient's ability to cope with a change in brain function post-TBI has been shown to be an important factor in recovery and outcome (Anson and Ponsford ,2006). Although we did not formally assess subjects' coping styles, we used a self-report of taking a prescribed analgesic on a routine basis pre-injury as a surrogate for poor coping style. Patients were considered to be on an analgesic medication before injury if the medication fell into one of the following categories: nonsteroidal anti-inflammatory agents, cyclooxygenase-2 inhibitors, opiates, or muscle relaxants.

Thus, the following 12 independent variables were included in the multivariate models in order to minimize the effects of confounding on the relationship between sex and post-mTBI outcome: age, race, ethnicity, SES, initial GCS

score, extracranial injuries, initial symptoms (LOC, amnesia, or feeling stunned), initial head CT, mechanism of injury, coping style (taking prescribed analgesics on a routine basis before injury), history of prior TBI, and analgesics given in the ED.

Bivariate analysis

Pre-injury, injury, and post-injury factors were compared between males and females using *t*-tests for continuous variables that were approximately normally distributed, and chi-square tests for categorical variables. A Wilcoxon rank-sum test was used to compare males and females with respect to age because of its skewed (non-normal) distribution (Supplementary Figure 2; see online supplementary material at http://www.liebertonline.com). We also compared those included in the study with those excluded with respect to age, sex, initial GCS score, and head CT scan results using Wilcoxon rank-sum tests (for age), and chi-square tests (for sex, initial GCS score, and head CT scan results). To evaluate the magnitude and direction of the unadjusted associations between sex and the outcomes of interest, we used logistic regression models. Although all three outcome variables are continuous, the distribution of each is highly skewed (Supplementary Figure 2; see online supplementary material at http://www.liebertonline.com); therefore, we chose to categorize each outcome variable. Post-concussive symptom (PCS) scores were divided into four categories: 0, 1–5, 6–16, and 17–64. The number of activity days missed and number of workdays missed were divided into three categories: 0 days, 1–7 days, and 8–90 days. These cut-points were dictated in part by the distributions of the outcome variables, but decisions regarding the cut-points were made before examining the associations between the independent variables and outcomes. The logistic regression models for PCS score and number of activity days missed assumed a proportional odds model. In this model, the odds ratio for sex (or any covariate) is assumed to be the same for all possible dichotomizations of the outcome using the chosen cut-points (e.g., 0 days versus 1–90 days, or 0–7 days versus 8–90 days for the number of activity days missed) (Hosmer, 2000). The proportional odds assumption was found to be violated (using the score test; $p = 0.004$) for the number of workdays missed outcome, so a multinomial logit model was used instead. This model specifies separate odds ratios for sex (or any covariate) for the outcome dichotomized as 0 days versus 1–7 days, and 0 days versus 8–90 days (Hosmer, 2000).

Multivariate analysis

Multivariate logistic regression analyses were used to examine the independent associations between sex and each of the three outcome variables controlling for the 12 aforementioned demographic and clinical factors. Proportional odds or multinomial logit models were used as described above. Results are reported as adjusted odds ratios along with their associated 95% confidence intervals and p values. The association between sex and outcome was tested using a significance level of $p < 0.05$. The interaction between sex and age was tested for each outcome variable by adding the appropriate interaction term to the model. All analyses were performed using SAS statistical software, version 9.1 (SAS Institute, Inc., Cary, NC).

Results

There were 1911 subjects in the parent cohort, 486 (25%) of whom were either less than 3 years old or could not be contacted at 3 months. Subjects who were contacted at 3 months but only provided information on one or two of the outcome variables were included in the analysis. Thus, the analysis cohort consisted of 1425 subjects. Compared to those excluded, the subjects included in the analysis cohort were of similar mean age and proportion female, and had similar initial GCS scores. However, those excluded were more likely to have had a traumatic abnormality on initial head CT (12.5% versus 3.9%; $p < 0.0001$).

Of these 1425 subjects, 643 (45.1%) were female and 782 (54.9%) were male, and the mean age was 30.0 years (SD 19.5 years, median 24 years). Compared to males with mTBI, females were significantly older, less likely to undergo head CT scanning, less likely to be injured participating in a sport, more likely to be injured in a motor vehicle collision, and more likely to be on analgesics before injury (surrogate for poor coping style; Table 1.

The median PCS score was 5.0 (interquartile range [IQR] 0–16). Approximately 28.2% of subjects had a PCS score of 0, 23.7% had a score of 1–5, 23.3% had a score of 6–16, and 24.9% had a score >16. The median number of days to return of normal activities was 4.0 days (IQR 0–16 days). Approximately 7.7% of subjects reported no missed activity days, 59.2% reported 1–7 missed activity days, and 33.1% reported >7 missed activity days. Among the 715 subjects who were employed before their head injury, the median number of days to return of work was 3.0 days (IQR 1–14 days). Approximately 23% of subjects employed pre-injury reported no missed workdays post-injury, 45.9% reported 1—7 missed workdays, and 31.1% reported >7 missed workdays. Compared to males, females were more likely to have a PCS score >16 and to miss >7 days of daily activities and work (Table 2).

Sex and 3-month post-concussive symptom scores

Males had lower 3-month PCS scores than females. The median PCS score for males was 4.0 (IQR 0–14) and for females was 7.0 (IQR 1–21). The unadjusted odds ratio (OR) for sex (male versus female) from the proportional odds model was 0.63 (95% CI: 0.52, 0.76).

Not all subjects were included in the multivariate analysis of PCS scores. Of the 1425 in the analysis cohort, 51 were missing a value for PCS score, and 248 were missing one or more independent variables, leaving 1126 subjects available for multivariate analysis. Those included in the multivariate analysis did not differ from those excluded in the proportion female, mean age, proportion with initial GCS score <15, and proportion with traumatic injury on initial head CT scan (Supplementary Table 1; see online supplementary material at http://www.liebertonline.com).

After adjustment for confounders, sex was found to be a significant predictor of 3-month PCS score. Using a proportional odds model, males were found to have significantly reduced odds of being in a higher PCS score category (OR 0.62, 95%; CI: 0.50, 0.78; $p < 0.0001$; Table 3). The interaction between age and sex was found to be significant ($p = 0.01$) and is described in Figure 1. The association between sex and PCS score category appeared to be more prominent between the ages of 14 and 56 years. Subjects were also less likely to be

Table 1. Baseline Demographic and Clinical Characteristics by Sex

Variable		*Female* (n = *643*)	*Male* (n = *782*)	P *Value*
Income, mean (SD)		$46,260 ($15,587)	$46,670 ($16,034)	0.48
Age, mean (SD) years		31.6 (20.1)	28.8 (18.9)	0.008
Race and ethnicity	Non-white, Non-Hispanic, *n* (%)	184 (28.7)	175 (22.4)	0.03
	Non-white, Hispanic, *n* (%)	8 (1.2)	11 (1.4)	
	White, Non-Hispanic, *n* (%)	421 (65.6)	567 (72.5)	
	White, Hispanic, *n* (%)	29 (4.5)	29 (3.7)	
Initial GCS score	13/14, *n* (%)	35 (5.5)	53 (6.8)	0.30
	15, *n* (%)	607 (94.6)	729 (93.2)	
Extracranial injuries or illnesses	No, *n* (%)	109 (17.0)	144 (18.4)	0.48
	Yes, *n* (%)	533 (83.0)	638 (81.6)	
Initial symptoms	Stunned only, *n* (%)	147 (23.2)	165 (21.3)	0.40
	LOC or amnesia, *n* (%)	487 (76.8)	609 (78.7)	
Head CT	Normal, *n* (%)	320 (50.7)	446 (58.4)	0.003
	Not done, *n* (%)	291 (46.1)	284 (37.2)	
	Abnormal, *n* (%)	20 (3.2)	34 (4.5)	
Mechanism of injury	Sport or cycling, *n* (%)	97 (15.1)	201 (25.7)	<0.0001
	Pedestrian struck/other, *n* (%)	53 (8.3)	94 (12.0)	
	Fall, *n* (%)	173 (27.0)	195 (25.0)	
	Assault, *n* (%)	39 (6.1)	46 (9.5)	
	Motor vehicle crash, *n* (%)	277 (43.2)	220 (28.1)	
	Motorcycle crash, *n* (%)	3 (0.5)	26 (3.3)	
Received analgesics in ED	No, *n* (%)	206 (32.8)	346 (45.3)	<0.0001
	Yes, *n* (%)	423 (67.3)	418 (54.7)	
Prior TBI	No, *n* (%)	482 (76.0)	565 (73.2)	0.24
	Yes, *n* (%)	153 (24.1)	207 (26.8)	
On analgesics before injury (poor coping style)	No, *n* (%)	569 (88.6)	708 (90.5)	0.29
	Yes, *n* (%)	73 (11.4)	74 (9.5)	

ED, emergency department; GCS, Glasgow Coma Scale score; LOC, loss of consciousness; CT, computed tomography; SD, standard deviation; TBI, traumatic brain injury.

in a higher PCS score category if they reported high income or did not undergo head CT scanning. Subjects were more likely to be in a higher PCS score category if they had extracranial injuries, were on analgesics before injury (surrogate for poor coping style), or if they received analgesics in the ED. There was also a significant quadratic relationship between age and PCS score category.

Table 2. Distributions of Outcomes 3 Months after mTBI

		Sex (n, %)	
Outcome		*Female*	*Male*
PCS score ($n = 1373$)[a]	0	144 (23.2%)	242 (32.2%)
	1–5	144 (23.2%)	181 (24.1%)
	6–16	142 (22.9%)	178 (23.7%)
	>16	191 (30.8%)	151 (20.1%)
Days of return to normal activities ($n = 1286$)[a]	0	40 (6.9%)	59 (8.3%)
	1–7	342 (59.2%)	419 (59.2%)
	>7	196 (33.9%)	230 (32.5%)
Days of work missed ($n = 660$)	0	56 (17.9%)	96 (27.6%)
	1–7	148 (47.4%)	155 (44.5%)
	>7	108 (34.6%)	97 (27.9%)

[a]One subject was not included due to a missing value for sex.
PCS, post-concussive symptom; mTBI, mild traumatic brain injury.

Sex and number of days to return to normal activities

During the first 3 months after mTBI, males missed fewer activity days than females. The median number of activity days missed for males was 3.0 (IQR 1–14 days), compared to 5.0 (IQR 2–14 days) for females. The unadjusted OR for sex (male versus female) from the proportional odds model was 0.91 (95% CI: 0.74, 1.14).

Not all subjects were included in the multivariate analysis of number of activity days missed. Of the 1425 in the analysis cohort, 138 were missing a value for the number of days to return to normal activities, and 232 were missing one or more independent variables, leaving 1055 subjects available for multivariate analysis. Those included in the multivariate analysis were significantly younger than those excluded (28.6 ± 18.9 versus 34.3 ± 20.5 years), but were similar in terms of the proportion of females, proportion with GCS score <15, and proportion with traumatic injury on initial head CT scan (Supplementary Table 1; see online supplementary material at http://www.liebertonline.com).

After adjustment for confounders, sex was not significantly associated with activity days missed after mTBI. Using a proportional odds model, males and females did not significantly differ regarding the odds of being in a higher activity days missed category (OR 0.84, 95%; CI: 0.64, 1.08; $p = 0.17$; Table 4). There were, however, several other significant predictors of the number of activity days missed. Subjects were more likely to be in a higher activity days missed category if

Table 3. Predictors of PCS Score, Proportional Odds Model ($N = 1126$)

Variable	*Odds ratio (95% confidence interval)*	p *Value*
Sex, male versus female	0.62 (0.50, 0.78)	<0.0001
Age[a]	1.15 (1.07, 1.25)	0.0002
Age[a]	0.96 (0.93, 0.98)	0.0014
Income[b]	0.89 (0.82, 0.96)	0.003
Race/ethnicity	0.35	
▪ Non-white, Hispanic versus non-white, non-Hispanic	1.02 (0.41, 2.53)	
▪ White, non-Hispanic versus non-white, non-Hispanic	0.76 (0.54, 1.06)	
▪ White, Hispanic versus non-white, non-Hispanic	0.97 (0.55, 1.72)	
Glasgow Coma Scale score (15 versus 13/14)	0.83 (0.52, 1.32)	0.42
Mechanism of injury	0.15	
▪ Fall versus sports/cycling	1.23 (0.88, 1.74)	
▪ Pedestrian struck/other versus sports/cycling	1.33 (0.88, 2.02)	
▪ Assault versus. sports/cycling	1.98 (1.21, 3.24)	
▪ Motor vehicle collision versus sports/cycling	1.34 (0.98, 1.82)	
▪ Motorcycle collision versus sports/cycling	1.41 (0.66, 3.04)	
Extracranial injuries or illness	1.51 (1.11, 2.06)	0.009
LOC or amnesia versus no LOC or amnesia	0.86 (0.66, 1.12)	0.26
Head CT scan	0.0001	
• Abnormal versus normal	1.14 (0.65, 2.02)	
• Not done versus normal	0.61 (0.48, 0.77)	
On analgesics before injury	1.73 (1.21, 2.46)	0.003
Received analgesics in ED	1.44 (1.14, 1.82)	0.002
Prior TBI	1.20 (0.94, 1.54)	0.14

[a]For every 10-year increase in age.
[b]For every $10,000 increase in income.
ED, emergency department; PCS, post-concussive symptom; LOC, loss of consciousness; CT, computed tomography; TBI, traumatic brain injury.

they had a traumatic abnormality on head CT scan, were on analgesics before injury (surrogate for poor coping style), or received analgesics in the ED. Subjects were less likely to be in a higher activity days missed category if they did not undergo CT scanning in the ED. As with PCS score, there was a significant quadratic relationship between age and activity days missed category. No significant interaction was found between age and sex for this outcome ($p = 0.21$).

Sex and number of missed days of work

During the first 3 months after mTBI, males missed fewer workdays than females. The median number of workdays missed for males was 2.0 (IQR 0–10 days), compared to 4.0 (IQR 1–14 days) for females. The unadjusted ORs for sex (male versus female) from the multinomial logit model were 0.52 (95% CI: 0.34, 0.80) for >7 days, versus 0 days and 0.61 (95% CI: 0.41, 0.91) for 1–7 days versus 0 days.

Not all subjects were included in the multivariate analysis of workdays missed. Of the 1425 in the analysis cohort, 715 were employed before injury (47% female). Of these, 55 were missing a value for the number of workdays missed, and 119 were missing one or more independent variables, leaving 541 subjects available for multivariate analysis. Those included in the multivariate analysis did not differ from those excluded in the proportion female, mean age, proportion with initial GCS score <15, and proportion with traumatic injury on initial head CT scan (Supplementary Table 1; see online supplementary material at http://www.liebertonline.com).

After adjustment for confounders, sex was not significantly associated with the number of missed days of work. Using a multinomial logit model, males and females did not significantly differ regarding the odds of being in a higher missed days of work category (OR 0.57, 95%; CI: 0.33, 0.97 for >7 days versus 0 days, and OR 0.64, 95%; CI: 0.39, 1.03 for 1–7 days versus 0 days; $p = 0.09$; Table 5). Subjects were less likely to be in a higher missed days of work category if they had higher incomes or did not undergo CT scanning in the ED. Subjects were more likely to be in a higher missed days of work category if they were injured in a motor vehicle collision or motorcycle collision or fall, had extracranial injuries, or received analgesics in the ED. There was no evidence of a relationship between age and missed days of work category, and no significant interaction was found between age and sex for this outcome ($p = 0.67$).

Limitations

There are several important limitations to our findings. First, those excluded from the analysis subset of the parent cohort had a significantly higher rate of traumatic abnormalities on initial head CT scan than those included. This would imply that the subjects we analyzed were less severely injured. Second, subjects included in the multivariate analyses of activity days lost were significantly younger than those excluded from these analyses. The effect of this on our findings is unclear.

Although we attempted to control for potential confounders of the association between sex and outcome after mTBI, several important covariates were not included in our multivariate model. Pre-existing medical and psychiatric illnesses have been found to be associated with an increase in post-concussive symptoms (McCauley et al., 2001; Ponsford et al., 2000). We did not collect this information at the time of the ED visit. Patients' intention to sue after the injury has also been found to be associated with a greater number and longer duration of post-concussive symptoms (Paniak et al., 2002; Feinstein et al., 2001). We did collect this variable during the 3-month follow-up contact, but elected not to include it in our multivariate models. We found no significant difference between males and females in the proportion who said at 3 months that they were pursing litigation (12.1% of females and 11.1% of males; $p = 0.56$). In addition, because a subject's intention to sue or actual involvement in a lawsuit is not known at the time of injury (i.e., it develops at some point after the injury), this variable is best considered a dependent variable rather than an independent variable. Furthermore, the development of post-traumatic stress disorder after any injury can have a strong negative impact on quality of life and outcome. Although post-traumatic stress is an important

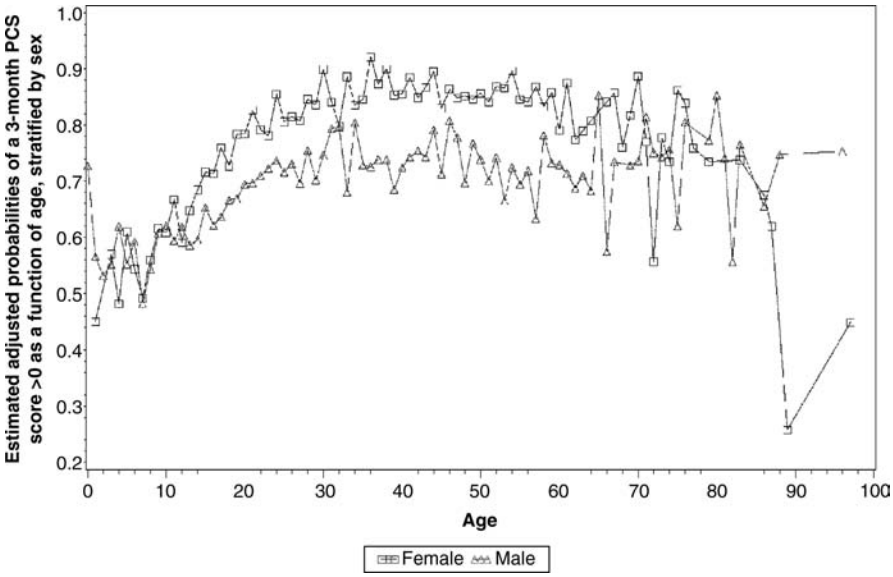

FIG. 1. Estimated adjusted probabilities of a 3-month post-concussive symptom (PCS) score >0 as a function of age, stratified by sex. The average adjusted probability of a 3-month PCS score >0 is given for each age for females (squares) and males (triangles).

predictor of post-TBI outcome in military populations (Hoge et al., 2008; Schneiderman et al., 2008), it does not appear to be linked to outcome in civilian populations (Bryant and Harvey, 1999; Creamer et al., 2005), and was therefore excluded from consideration in our models. Given our finding that sex outcome differences varied by age, knowledge of where female subjects were in the menstrual cycle at the time of their injury might have helped clarify this relationship. Are poor outcomes related to points in the cycle at which estrogen/progesterone levels are presumed to be high, or to points in the cycle where these hormones are low? Unfortunately, menstrual cycle information was not collected during the recruitment of the parent cohort. Finally, we elected not to remove subjects suspected of using drugs or alcohol at the time of injury. The cognitive effects of chronic, long-term alcohol use are well known (Vickery et al., 2008). However, many patients presenting to an ED, and especially young adults such as those that comprise this cohort, have used alcohol but are not necessarily chronic abusers. The effect of episodic alcohol use on cognitive outcome is less clear. In fact, several studies suggest that alcohol use in the setting of TBI may confer a survival advantage in humans (O'Phelan et al., 2008; Salim et al., 2009). In addition, cognitive deficits after TBI in rats are actually attenuated by the pre-injury administration of alcohol (Dash et al., 2004; Janis et al., 1998). Moreover, when we re-analyzed our dataset by excluding those suspected of drug/alcohol use ($n = 88$), or in whom this variable was not collected ($n = 80$), we found little change in the magnitudes of the associations (i.e., odds ratios and 95% confidence intervals) between sex and each of the three outcomes studied. There was also very little change in the magnitudes of the age-sex interactions.

Discussion

Animal studies of traumatic brain injury have consistently revealed better outcomes among females than in males. These studies have been used to advance the hypothesis that gonadal steroids such as estrogen and progesterone may provide neuroprotection after TBI (Djebaili et al., 2004, 2005; Roof et al., 1994; Stein and Hoffman, 2003). However, our results suggest that female sex, after appropriate control for confounders, is associated with a significantly higher risk of poor outcome after mTBI in humans. Three months after injury, males had reduced odds of being in a higher PCS score category (OR = 0.62; $p < 0.0001$), and of being in a higher missed days of work category (OR = 0.57 for 0 days versus 1–7 days, and OR = 0.64 for 0 days versus >7 days), although the latter association did not reach statistical significance ($p = 0.09$). Males and females did not significantly differ, however, with respect to the number of days to return to normal daily activities.

Our results are consistent with those of several other observational studies in humans that show worse outcome among females after TBI. However, unlike these studies, we attempted to control for factors that could potentially confound the relationship between sex and outcome. We hypothesized that proper control for these factors would uncover a pattern of recovery similar to that found in animal studies, in which female sex was associated with good, not poor, outcome. Despite this control for confounders, however, we found just the opposite. What could account for the apparent discrepancy between the results of animal studies and our results?

There are several potential explanations. Animal models of TBI differ substantially from the clinical disease seen in humans. With animals, it is possible to control precisely for variables such as age, genetic background, and injury mechanism, that are likely to play important roles in the pathophysiology of TBI. Clinical TBI is heterogeneous, typically comprising multiple types of injury within the same patient, whereas animal models allow for the study of isolated subtypes of injury, such as diffuse axonal injury or contusion. The discrepant results between humans and animals may also be

Table 4. Predictors of Number of Days to Return to Normal Activities, Proportional Odds Model ($N = 1055$)

Variable	*Odds ratio (95% confidence interval)*	p *Value*
Sex, male versus female	0.84 (0.64, 1.08)	0.17
Age[a]	1.14 (1.04, 1.25)	0.005
Age[a]	0.96 (0.93, 0.99)	0.02
Income[b]	0.92 (0.84, 1.00)	0.06
Race/ethnicity	0.84	
▪ Non-white, Hispanic versus non-white, non-Hispanic	1.54 (0.51, 4.70)	
▪ White, non-Hispanic versus non-white, non-Hispanic	1.08 (0.72, 1.61)	
▪ White, Hispanic versus non-white, non-Hispanic	0.94 (0.49, 1.81)	
Glasgow Coma Scale score (15 versus 13/14)	0.76 (0.44, 1.30)	0.32
Mechanism of injury	0.11	
▪ Fall versus sports/cycling	0.65 (0.44, 0.96)	
▪ Pedestrian struck/other versus sports/cycling	0.76 (0.47, 1.23)	
▪ Assault versus sports/cycling	0.87 (0.50, 1.52)	
▪ Motor vehicle collision versus sports/cycling	0.96 (0.67, 1.32)	
▪ Motorcycle collision versus sports/cycling	1.74 (0.74, 4.11)	
Extracranial injuries or illness	1.31 (0.95, 1.90)	0.09
LOC or amnesia versus no LOC or amnesia	1.13 (0.83, 1.54)	0.43
'Head CT scan	<0.0001	
• Abnormal versus normal	3.63 (1.79, 7.36)	
• Not done versus normal	0.51 (0.39, 0.67)	
On analgesics before injury	1.55 (1.02, 2.38)	0.04
Received analgesics in ED	1.58 (1.20, 2.07)	0.001
Prior TBI	0.88 (0.66, 1.18)	0.38

[a]For every 10-year increase in age.
[b]For every $10,000 increase in income.
ED, emergency department; PCS, post-concussive symptom; LOC, loss of consciousness; CT, computed tomography; TBI, traumatic brain injury.

due to species-specific differences in brain anatomy and the vulnerability of specific brain structures to damage from TBI. Moreover, studies using animal models of TBI typically focus on short-term outcomes, usually within days of injury, while our study looked at longer-term, 3-month outcome. Finally, measurement of outcome after mTBI in humans is difficult to objectively quantify and relies on subjective symptom reporting and cognitive testing. While it is possible to assess cognitive function in animal models, it is likely that these measurements are even less sensitive than those made in humans. It is not at all possible to assess subjective symptoms in animals, making it unlikely that a correlate to the poor outcome assessed in our cohort could be seen in animals.

Our results may differ from those of animal studies for several reasons. First, women may be more likely to report post-TBI symptoms than males. Our finding that activity levels in males and females were similar despite increased post-concussive symptoms among women supports this idea. Increased symptom reporting by women relative to men has been demonstrated in several other disease states. Women with coronary artery disease, hypertension, and musculoskeletal disorders report more symptoms than their male counterparts.(Barsky et al., 2001). In addition, we observed that poor coping style (which was much more prevalent among women) was associated with increased post-concussive symptoms and activity days missed. Last, societal pressures on men, who still outnumber women as primary wage earners (Winkler et al., 2005), to return to work could explain why they are more likely to return to work given similar activity levels as women (Corrigan et al., 2007).

These observations raise the question: Do females have worse outcomes than males, or are they simply more willing to report subtle feelings that males would dismiss altogether? Our results may provide some clues to the answer. Increased symptom reporting would not explain the pattern of disability as a function of age that we observed among females, but not males. Among females, mean adjusted PCS scores exceed those of males beginning around menarche, peak during the child-bearing years, and then return to the level of males after menopause (Fig. 1). This observation suggests that post-mTBI outcome may be more physiological than sociological.

A major physiological difference between women and men in this age range, as well as between pre- and post-menopausal women, is that menstruating women experience cyclical changes in the gonadal steroids estrogen and progesterone. It is tempting to speculate that post-traumatic alterations in the normal physiology of these gonadal steroids may underlie the relatively poor outcomes observed. Central endocrine regulation of female gonadal steroids is mediated by the anterior pituitary gland. Experimentally-induced TBI in animals does not appear to result in injury to the anterior pituitary gland, whereas mTBI in humans does (Kelly et al., 2006; Klose et al., 2007). Injury to the anterior pituitary, which produces follicle-stimulating hormone (FSH) and luteinizing hormone (LH), could disrupt endogenous estrogen and/or progesterone production, and reduce the neuroprotective effect of these hormones, or even cause "withdrawal" in human females of child-bearing age (Davis et al., 2006). The production of both FSH and LH have been shown to be reduced substantially after TBI in both men (Lee et al., 1994; Woolf et al., 1986), and women (Agha and Thompson, 2005; Joele and Endtz, 1975). Amenorrhea has also been reported after TBI in humans (Ripley et al., 2008).

Indirect support for the hypothesis that post-traumatic alterations in the normal physiology of gonadal steroids underlie poor outcomes comes from human studies. These studies compare post-TBI outcome in males and females, and report that females are more likely to have poor outcomes during child-bearing years, but not during the pre-menarche or post-menopause years. For example, compared to males, Morrison and colleagues found a longer ICU stay for post-menarche teens (13–19 years of age), but not for pre-menarche girls (Morrison et al., 2004). Farin and associates found increased cerebral edema and intracranial hypertension in

Table 5. Predictors of Number of Days of Work Missed, Multinomial Logit Model ($n = 541$)

Variable	*Workdays missed*	*Odds ratio (95% confidence interval)*	p *Value*
Sex, male versus female	>7 versus 0	0.57 (0.33, 0.97)	0.09
	1–7 versus 0	0.64 (0.39, 1.03)	
Age[a]	>7 versus 0	1.00 (0.84, 1.20)	0.94
	1–7 versus 0	1.03 (0.87, 1.21)	
Income[b]	>7 versus 0	0.82 (0.67, 0.99)	0.02
	1–7 versus 0	1.04 (0.88, 1.23)	
Race/ethnicity		0.97	
▪ Non-white, Hispanic versus non-white, non-Hispanic	>7 versus 0	1.23 (0.11, 14.09)	
	1–7 versus 0	0.55 (0.04, 7.14)	
▪ White, non-Hispanic versus non-white, non-Hispanic	>7 versus 0	0.87 (0.38, 2.00)	
	1–7 versus 0	0.87 (0.39, 1.91)	
▪ White, Hispanic versus non-white, non-Hispanic	>7 versus 0	0.67 (0.18, 2.51)	
	1–7 versus 0	0.91 (0.29, 2.93)	
Glasgow Coma Scale score (15 versus 13/14)	>7 versus 0	0.72 (0.21, 2.48)	0.87
	1–7 versus 0	0.80 (0.23, 2.72)	
Mechanism of injury		0.02	
▪ Fall versus sports/cycling	>7 versus 0	2.91 (1.16, 7.29)	
	1–7 versus 0	2.71 (1.24, 5.91)	
▪ Pedestrian struck/other versus sports/cycling	>7 versus 0	1.64 (0.54, 4.96)	
	1–7 versus 0	1.69 (0.69, 4.16)	
▪ Assault versus sports/cycling	>7 versus 0	1.25 (0.39, 2.96)	
	1–7 versus 0	1.16 (0.43, 3.14)	
▪ Motor vehicle collision versus sports/cycling	>7 versus 0	3.58 (1.66, 7.71)	
	1–7 versus 0	2.01 (1.06, 3.80)	
▪ Motorcycle collision versus sports/cycling	>7 versus 0	9.31 (1.62, 53.52)	
	1–7 versus 0	2.22 (0.36, 13.72)	
Extracranial Injuries or Illness	>7 versus 0	1.12 (0.38, 3.27)	0.002
	1–7 versus 0	0.33 (0.14, 0.76)	
LOC or amnesia versus no LOC or amnesia	>7 versus 0	1.42 (0.79, 2.55)	0.12
	1–7 versus 0	1.75 (1.03, 2.99)	
Head CT scan		0.0004	
• Abnormal versus normal	>7 versus 0	4.70 (0.54, 40.86)	
	1–7 versus 0	1.73 (0.19, 15.95)	
• Not done versus normal	>7 versus 0	0.38 (0.22, 0.66)	
	1–7 versus 0	0.86 (0.53, 1.39)	
On analgesics before injury	>7 versus 0	1.03 (0.44, 2.40)	0.20
	1–7 versus 0	0.55 (0.24, 1.26)	
Received analgesics in ED	>7 versus 0	2.07 (1.14, 3.74)	0.01
	1–7 versus 0	0.95 (0.58, 1.56)	
Prior TBI	>7 versus 0	1.65 (0.94, 2.91)	0.16
	1–7 versus 0	1.14 (0.68, 1.92)	

[a]For every 10-year increase in age.
[b]For every $10,000 increase in income.
ED, emergency department; PCS, post-concussive symptom; LOC, loss of consciousness; CT, computed tomography; TBI, traumatic brain injury.

pre-menopausal females, but not in post-menopausal females (Farin et al., 2003; Farin and Marshall, 2004). Davis and co-workers reported lower post-TBI mortality in post-menopausal females, but not in pre-menopausal females (Davis et al., 2006).

Further indirect support for this hypothesis comes from one of the two published Phase II trials of progesterone after human TBI. Although the first trial did not report outcome differences by sex (Wright et al., 2007), the subsequent study did (Xiao et al., 2008). The difference in favorable 6-month Glasgow Outcome Scale score between the progesterone and placebo groups was considerably larger among females (66% versus 35%, respectively) than among the cohort as a whole (42% versus 31%, respectively). Outcome results for males were not reported (Xiao et al., 2008). These data, viewed in light of our findings, might lead one to speculate that progesterone replacement may be more likely to benefit women than men. Without a detailed subset analysis of both Phase II trials, we will be forced to wait for the results of the planned Phase III trial for further support of our hypothesis.

These observations suggest that a better understanding of the relationship between sex and outcome could be gained through an assessment of pituitary structure and function immediately after mTBI and throughout the recovery period. Structural imaging of the anterior pituitary as well as longitudinal assessment of endogenous FSH, LH, estrogen, and progesterone levels could shed light on mechanisms underlying the poorer outcome exhibited by females. These efforts

might also suggest potential therapeutic interventions either to mitigate pituitary injury or to replace deficient hormones. Given the lack of available treatments, these efforts could be a fruitful avenue for reducing the disability associated with mTBI.

Several other factors found to be associated with poor outcome after mTBI deserve mention. Those who did not get a CT scan had a substantially reduced risk of poor outcome compared to those with a normal CT for all three outcome variables. The process by which emergency providers select mTBI patients for these head CT scans also appears to be good at predicting outcome. While several decision rules exist to help guide CT selection, it is unclear to what extent they are used by emergency providers (Carpenter, 2008). Of interest, those with a traumatic injury on CT were similar to those with a normal CT with regard to PCS score and workdays missed, but had increased odds of being in a higher activity days missed category. It is unclear if this is because of physician recommendation to refrain from normal daily activities in the face of an identified CT lesion, or the subject's inability to perform these activities due to neurologic injury.

The receipt of analgesics (received by 59.0% of the cohort) in the ED was strongly associated with poor 3-month outcome. Most subjects received a nonsteroidal anti-inflammatory drug, followed by a narcotic, and then acetaminophen. It is possible that subjects who received analgesics in the ED were more symptomatic at the time of injury because they had a more severe brain injury, and that this severity was not captured by the other severity covariates we used in the multivariate model (LOC, amnesia, CT scan result, GCS score, and mechanism of injury). Alternatively, analgesics may have had an adverse affect on outcome. Almost a third of the subjects in our cohort received a narcotic in the ED. Narcotics have been shown by several authors to adversely affect hemodynamic parameters after severe TBI in humans, and to increase mortality after TBI in rats (de Nadal et al., 2000; Statler et al., 2006). In addition, a third of our cohort received a nonsteroidal anti-inflammatory drug—primarily oral ibuprofen and intramuscular ketorolac—in the ED. Although several authors report favorable outcome after indomethacin in animals, one author reported that ibuprofen worsened cognitive performance after TBI in rats (Browne et al., 2006). Although cyclooxygenase inhibitors potentially improve outcome, none of our subjects received these medications. Clearly more research is needed in this area. Given the high incidence of mTBI and the liberal administration of analgesics in the ED setting, studies clarifying the relationship between the acute use of analgesics and outcome could be of tremendous public health benefit.

In summary, female sex is associated with significantly higher odds of being in a higher PCS score category after mTBI, after controlling for appropriate confounders. The observed pattern of peak increased PCS reporting for females during the child-bearing years relative to males suggests disruption of endogenous estrogen or progesterone production. Attempts to better understand how mTBI affects production of these hormones acutely after injury and during the recovery period may shed light on the mechanism behind poorer outcome among females and allow potential therapeutic interventions. In addition, the effects of analgesic medications given acutely after mTBI on post-mTBI recovery also deserve careful evaluation.

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