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Recovery After Mild Traumatic Brain Injury in Patients Presenting to US Level I Trauma Centers

A Transforming Research and Clinical Knowledge in Traumatic Brain Injury (TRACK-TBI) Study

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IMPORTANCE Most traumatic brain injuries (TBIs) are classified as mild (mTBI) based on admission Glasgow Coma Scale (GCS) scores of 13 to 15. The prevalence of persistent functional limitations for these patients is unclear.

OBJECTIVES To characterize the natural history of recovery of daily function following mTBI vs peripheral orthopedic traumatic injury in the first 12 months postinjury using data from the Transforming Research and Clinical Knowledge in Traumatic Brain Injury (TRACK-TBI) study, and, using clinical computed tomographic (CT) scans, examine whether the presence (CT+) or absence (CT−) of acute intracranial findings in the mTBI group was associated with outcomes.

DESIGN, SETTING, AND PARTICIPANTS TRACK-TBI, a cohort study of patients with mTBI presenting to US level I trauma centers, enrolled patients from February 26, 2014, to August 8, 2018, and followed up for 12 months. A total of 1453 patients at 11 level I trauma center emergency departments or inpatient units met inclusion criteria (ie, mTBI [n = 1154] or peripheral orthopedic traumatic injury [n = 299]) and were enrolled within 24 hours of injury; mTBI participants had admission GCS scores of 13 to 15 and clinical head CT scans. Patients with peripheral orthopedic trauma injury served as the control (OTC) group.

EXPOSURES Participants with mTBI or OTC.

MAIN OUTCOMES AND MEASURES The Glasgow Outcome Scale Extended (GOSE) scale score, reflecting injury-related functional limitations across broad life domains at 2 weeks and 3, 6, and 12 months postinjury was the primary outcome. The possible score range of the GOSE score is 1 (dead) to 8 (upper good recovery), with a score less than 8 indicating some degree of functional impairment.

RESULTS Of the 1453 participants, 953 (65.6%) were men; mean (SD) age was 40.9 (17.1) years in the mTBI group and 40.9 (15.4) years in the OTC group. Most participants (mTBI, 87%; OTC, 93%) reported functional limitations (GOSE <8) at 2 weeks postinjury. At 12 months, the percentage of mTBI participants reporting functional limitations was 53% (95% CI, 49%-56%) vs 38% (95% CI, 30%-45%) for OTCs. A higher percentage of CT+ patients reported impairment (61%) compared with the mTBI CT− group (49%; relative risk [RR], 1.24; 95% CI, 1.08-1.43) and a higher percentage in the mTBI CT−group compared with the OTC group (RR, 1.28; 95% CI, 1.02-1.60).

CONCLUSIONS AND RELEVANCE Most patients with mTBI presenting to US level I trauma centers report persistent, injury-related life difficulties at 1 year postinjury, suggesting the need for more systematic follow-up of patients with mTBI to provide treatments and reduce the risk of chronic problems after mTBI.

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Supplemental content

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In the United States, about 2.8 million individuals are treated at hospitals annually for traumatic brain injuries (TBIs).[1] Most TBIs are classified as mild (mTBI) based on crude clinical signs, such as patients' gross levels of consciousness up hospital admission (eg, Glasgow Coma Scale [GCS] scores of 13-15). Although it is well accepted that moderate to severe TBIs may cause permanent disability,[2-4] controversy exists surrounding the expected course of clinical recovery for patients with mTBI. In particular, although mTBI commonly causes acute symptoms,[5-7] cognitive dysfunction,[6,8-12] and problems in day-to-day functioning,[13] findings vary as to whether patients continue to manifest sequelae of mTBI months to years postinjury.[14-16]

Limitations in research methods have been proposed as a major factor explaining inconsistencies in the observed natural history of mTBI. Seminal World Health Organization systematic reviews and others highlighted common methodologic problems, including small, nonprospective samples; cross-sectional study designs not well suited to characterize recovery; inadequate control groups; and insufficient statistical approaches (eg, limited attention to nonrandom patterns of attrition) called for large, carefully conducted prospective studies.[14,17-19] Another important issue that may explain variable findings is heterogeneity across patients. Given current diagnostic conventions,[20] mTBI encompasses a wide spectrum of TBI severity, from concussive injuries with subtle signs of brain dysfunction without evidence of structural injury on computed tomographic (CT) scans[21,22] to injuries with intracranial abnormalities shown on head CT scans.[16,23,24] Thus, in describing recovery from mTBI, one should consider subgroups of patients likely to vary in prognosis.[14,25]

The Transforming Research and Clinical Knowledge in TBI (TRACK-TBI) study[26] was designed to address calls to improve the quality of evidence in community-acquired TBI. This article describes the mTBI cohort's course of functional limitations, reported on the Glasgow Outcome Scale-Extended (GOSE) scale compared with patients with peripheral orthopedic traumatic injuries (orthopedic trauma control [OTC] group). Patients with mTBI were also stratified based on the presence (CT+) vs absence (CT−) of acute intracranial findings on head CT. In addition, we evaluated secondary outcomes of self-reported symptoms and neurocognitive performance. We hypothesized that rates of functional limitations would be maximal soon after injury and decline over time and that the mTBI group would continue to report more symptoms than the OTC group at 12 months postinjury.[16]

Key Points

Question How common are persistent, injury-related functional limitations following mild traumatic brain injury vs orthopedic trauma?

Findings In this cohort study of 1154 patients with mild traumatic brain injury and 299 patients with orthopedic trauma serving as controls, 53% of participants with mild traumatic brain injury reported impairment 12 months postinjury vs 38% of those with orthopedic trauma. Patients with intracranial abnormalities had the poorest outcomes; however, patients without abnormalities also reported problems at 12 months.

Meaning Many patients who present to level I trauma centers with mild traumatic brain injury experience difficulties at 12 months postinjury, suggesting that this injury is not always benign; better follow-up and treatment appear to be needed.

Methods

Participants and Study Design

TRACK-TBI is a prospective, multicenter study recruiting participants at 11 US level I trauma centers. Participants with mTBI who were enrolled between February 26, 2014, and May 4, 2016, and OTCs recruited by August 8, 2018, were considered for analyses. eFigure 1 in the Supplement depicts the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) diagram of the current TRACK-TBI sample (N = 1648) and the cohorts evaluated in this study (n = 1154 mTBI and n = 299 OTC). The study was approved by the institutional review board of each enrolling institution and was led by the University of California, San Francisco. Participants or their legally authorized representatives completed written informed consent and received financial compensation. Demographic, injury, and outcome variables were collected in accordance with the TBI Common Data Elements.[27,28] Demographic data were obtained through a combination of medical records and patient report. Outcome assessments occurred at 2 weeks and 3, 6, and 12 months postinjury. Three-month assessments were performed via telephone; other assessments were performed in person whenever feasible.

Inclusion Criteria

Inclusion criteria for TBI were for the patient to present within 24 hours of injury, have an acute head CT scan performed as part of clinical care, and show or report evidence of alterations in consciousness or amnesia. We restricted the cohort to GCS scores of 13 to 15 (ie, mTBI) on emergency department (ED) arrival. Patients in the OTC group presented with orthopedic injuries and showed no evidence of altered consciousness, amnesia, or other physical signs of head trauma. Exclusions included being in custody, pregnant, nonsurvivable physical trauma, debilitating mental health disorders, neurologic disease, or non-English speaking; however, some sites recruited Spanish-speaking participants. Although some sites recruited children, we focused on participants aged 17 years and older, given that they completed the outcome measures of interest.

Primary Outcome Measure

The GOSE score is a measure of the association between traumatic injuries and diverse aspects of daily functioning[27] and is commonly used as the primary outcome measure in TBI studies.[29] The possible range of scores is 1 (dead) to 8 (upper good recovery), with less than 8 reflecting some degree of functional limitation after injury. The scale is completed via interview with patients or proxies. Respondents are asked to report new injury-related dependence or difficulties (including

worsening of any preexisting problems) in major domains of life function: independence within (ie, activities of daily living) and outside (eg, shopping, travel) the home, work, social/leisure activities, family or friend relationships, and other injury-related symptoms or problems affecting daily life. Changes in function were counted irrespective of whether they resulted from TBI or other injury-related factors (eg, multiple trauma).

Secondary Outcome Measures

Secondary outcomes, collected at 12 months postinjury, comprised self-reported TBI-related symptoms (Rivermead Post Concussion Symptoms Questionnaire, with ratings of 1 not counted in total scores; possible range, 0-64; higher scores indicate more severe symptoms),[30] psychological distress (18-item Brief Symptom Inventory; mean [SD] T score normative for the general population, 50 [10]; possible range, 36-81; higher scores indicate more severe psychiatric symptoms),[31] and general life satisfaction (Satisfaction With Life scale; possible range, 0-35; higher scores indicate more life satisfaction).[32] In addition, participants performed neuropsychological measures of verbal episodic memory (Rey Auditory Verbal Learning Test; possible range for immediate memory, 0-80; higher scores indicate better memory; possible range for delayed recall, 0-16; higher scores indicate better memory),[33,34] processing speed (Wechsler Adult Intelligence Scale–Fourth Edition Processing Speed Index; mean [SD] normative score, 100 [15]; higher scores indicate better processing speed),[35] and executive functioning (Trail Making Test: number of seconds to complete; part A, maximum score is 90 seconds, lower score is faster/better; part B, maximum score is 300 seconds, lower score is faster/better).[36]

Statistical Analysis

Sample characteristics were compared between groups using Fisher exact tests (categorical variables) and Mann-Whitney tests (continuous variables). Primary analyses were adjusted for patterns of missing outcomes with propensity weights.[37] Propensity weights were derived separately by measure type (GOSE, self-report, neuropsychological) and time (2 weeks and 3, 6, 12 months) from boosted logistic regression models predicting completion vs noncompletion of outcomes from enrollment site and demographic, history, and injury variables. Weights were proportional to the inverse of the probability of measure completion and normed so the sum equaled the number of cases with the measure completed. Prevalence of functional difficulty by GOSE domain and report of injury-related symptoms on the Rivermead Post Concussion Symptoms Questionnaire (ie, ratings of 2-4) were evaluated through percentages and compared using Fisher exact tests for pairwise comparisons between groups (first, all mTBI vs OTC; second, pairwise comparisons among mTBI CT+, mTBI CT−, and OTC groups). Prevalence rates (percentages) and effect sizes of group differences (risk ratios [RRs]) are reported alongside 95% CIs.[38] Differences that remained significant after multiple comparison correction (within outcome domain and time point using a 5% false discovery rate)[39] are discussed.

Group comparisons on 12-month secondary outcome measures used 2-tailed, independent-samples, unpaired *t* tests for continuous self-report measures, with effect sizes reported as Cohen *d* (with 95% CIs). General linear models were used to compare groups on neuropsychological measures adjusting for age, sex, and educational level. Results were considered significant at $P < .05$.

Propensity probabilities were generated using the twang software package developed for R, version 3.2.2 (R Foundation for Statistical Computing), which was accessed via script files generated by an SAS, version 9.3 macro package (SAS Institute Inc). Other statistical analyses were conducted in SPSS Statistics for Windows, version 19 (IBM Corp).

Results

Participant Characteristics

Of the 1349 participants with TBI, 1154 patients (85.5%) met the criteria for mTBI. The mTBI group included 754 men (65.1%); mean (SD) age was 40.9 (17.1) years (**Table 1**). The OTC group (n = 299) included 199 men (66.6%); mean age was 40.9 (15.4) years. The mTBI sample size with available outcome data ranged from 975 to 768 at 2 weeks through 12 months postinjury, respectively (eFigure 1 in the Supplement). The number of OTCs with available outcome data ranged from 240 to 146 across the same time. The mTBI and OTC groups were well matched on demographic and history variables. Sample characteristics stratified by CT scan status are presented in eTable 1 in the Supplement. Because of differences in cause of injury between groups, sensitivity analyses were performed to confirm that covarying for this variable did not affect the results (eTables 6-10 in the Supplement).

Prevalence of Functional Limitations

The **Figure** illustrates the percentage and 95% CIs of participants in each group who reported injury-related functional problems in 1 or more areas of function on the GOSE score (ie, GOSE <8) at each assessment. Functional limitation rates were highest at 2 weeks postinjury (mTBI: 87%; 95% CI, 84%-89%; OTC: 93%; 95% CI, 89%-96%) and lowest at 12 months (mTBI: 53%; 95% CI, 49%-56%; OTC: 38%; 95% CI, 30%-45%). The mTBI and OTC groups were not significantly different from 2 weeks to 6 months postinjury: 2-week RR, 0.93 (95% CI, 0.89-0.98); 2-month RR, 0.92 (95% CI, 0.84-1.02); 6-month, RR, 1.14 (95% CI, 0.99-1.31). At 12 months, more participants in the mTBI group (53%; 95% CI, 49%-56%) continued to report functional limitations compared with the OTC group (38%; 95% CI, 30%-45%) (RR, 1.38; 95% CI, 1.12-1.71). In other words, 47.2% of patients with mTBI and 62.3% of the OTCs reported full return to preinjury levels of day-to-day functioning at 12 months postinjury ($P = .001$). Stratifying the CT+ and CT− subsamples of the mTBI group at 12 months (eFigure 2 in the Supplement) revealed a significantly higher percentage of patients with limitations in the mTBI CT+ group (61%) than the mTBI CT− group (49%) (RR, 1.24; 95% CI, 1.08-1.43), and a higher percentage in the mTBI CT− group (49%) vs the OTC group (38%) (RR, 1.28; 95% CI, 1.02-1.60).

Table 2 provides the percentage of participants in the mTBI and OTC groups who reported injury-related problems in each

Table 1. Unweighted Analysis of Sample Demographics and Injury Characteristics

Characteristic	No. (%)[a]		Effect Size (%)	*P* Value[a]
	mTBI (n = 1158)	OTC (n = 299)		
Age, y				
Mean (SD)	40.9 (17.1)	40.9 (15.4)	0	.50
Unknown	2	0		
Sex				
Men	754 (65.1)	199 (66.6)	−1	.68
Women	404 (34.9)	100 (33.4)	1	
Race/ethnicity				
White	882 (76.2)	231 (77.3)	−1	.78
Black	197 (17.0)	46 (15.4)	2	
Other/unknown	79 (6.8)	22 (7.4)	−1	
Hispanic				
No	904 (78.9)	220 (75.1)	4	.18
Yes	242 (21.1)	73 (24.9)	−4	
Unknown	12	6		
Insurance				
Insured	701 (63.7)	181 (65.1)	−1	.90
Uninsured	161 (14.6)	40 (14.4)	0	
Medicare/other	239 (21.7)	57 (20.5)	1	
Unknown	57	21		
Years of education				
Mean (SD)	13.5 (2.9)	13.8 (2.9)	−0.14	.047
Unknown	61	8		
Employment				
Full time	644 (58.6)	186 (65.0)	−6	.32
Part time	143 (13.0)	36 (12.6)	0	
Occasional/special/unemployed	96 (8.7)	21 (7.3)	1	
Retired/disabled/not working	154 (14.0)	31 (10.8)	3	
Other	62 (5.6)	12 (4.2)	1	
Unknown	59	13		
Living situation				
Independent living	922 (83.8)	236 (83.1)	1	.33
Living with others	172 (15.6)	45 (15.8)	0	
Homeless	0	1 (0.4)	0	
Other	6 (0.5)	2 (0.7)	0	
Unknown	58	15		
Previous TBI				
No	806 (77.1)	224 (83.3)	−6	.03
Yes	239 (22.9)	45 (16.7)	6	
Unknown	113	30		
Neurologic disorder (not TBI)				
No	988 (85.8)	252 (87.2)	−1	.57
Yes	164 (14.2)	37 (12.8)	1	
Unknown	6	10		
Neurodevelopmental disorder				
No	1045 (90.7)	268 (92.7)	−2	.30
Yes	107 (9.3)	21 (7.3)	2	
Unknown	6	10		

(continued)

Table 1. Unweighted Analysis of Sample Demographics and Injury Characteristics (continued)

Characteristic	No. (%)[a]		Effect Size (%)	*P* Value[a]
	mTBI (n = 1158)	OTC (n = 299)		
Mental health history				
No	909 (78.8)	225 (77.1)	2	.53
Yes	245 (21.2)	67 (22.9)	−2	
Unknown	4	7		
Headache history				
No	1115 (96.8)	276 (95.5)	1	.28
Yes	37 (3.2)	13 (4.5)	−1	
Unknown	6	10		
Migraine history				
No	1083 (94.0)	273 (94.5)	0	.89
Yes	69 (6.0)	16 (5.5)	0	
Unknown	6	10		
Cause of injury				
MVC (occupant)	418 (36.1)	50 (16.7)	19	<.001
MCC	92 (7.9)	32 (10.7)	−3	
MVC (cyclist or pedestrian)	189 (16.3)	22 (7.4)	9	
Fall	280 (24.2)	101 (33.8)	−10	
Assault	69 (6.0)	3 (1.0)	5	
Other/unknown	110 (9.5)	91 (30.4)	−21	
GCS				
13	41 (3.5)	0	4	<.001
14	214 (18.5)	0	18	
15	903 (78.0)	299 (100)	−22	
Loss of consciousness[b]				
No	167 (15.3)	292 (100)	−85	<.001
Yes	923 (84.7)	0	85	
Unknown	68	7		
Posttraumatic amnesia[b]				
No	229 (22.0)	292 (100)	−78	<.001
Yes	813 (78.0)	0	78	
Unknown	116	7		
Peripheral injury[c]				
No	153 (14.0)	1 (0.3)	14	<.001
Yes	940 (86.0)	285 (99.7)	−14	
Unknown	65	13		
AIS head/neck				
Mean (SD)	2.1 (1.3)	0.1 (0.4)	2.45	<.001
Median (IQR)	2 (1-3)	0 (0-0)		
Unknown	424	124		
ISS total				
Mean (SD)	12.0 (8.4)	7.7 (6.0)	0.82	<.001
Median (IQR)	10 (5-17)	5 (4-10)		
Unknown	424	124		
ISS peripheral				
Mean (SD)	5.6 (6.7)	7.5 (5.9)	−0.45	<.001
Median (IQR)	2 (1-9)	5 (4-10)		
Unknown	425	124		

(continued)

Table 1. Unweighted Analysis of Sample Demographics and Injury Characteristics (continued)

Characteristic	No. (%)[a] mTBI (n = 1158)	OTC (n = 299)	Effect Size (%)	*P* Value[a]
Highest level of care				
Emergency department	407 (35.1)	131 (43.8)	−9	<.001
Inpatient unit	479 (41.4)	147 (49.2)	−8	
Intensive care unit	272 (23.5)	21 (7.0)	16	
Litigation status at 12 mo				
No	586 (77.3)	129 (84.3)	−7	.07
Yes	172 (22.7)	24 (15.7)	7	
Unknown	400	146		

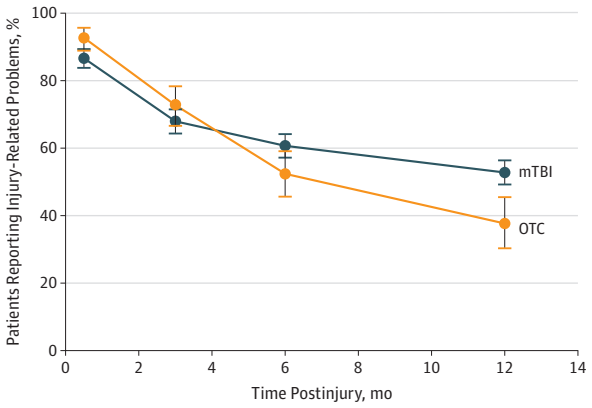
Abbreviations: AIS, abbreviated injury severity score; GCS, Glasgow Coma Scale; IQR, interquartile range; ISS, injury severity score; MCC, motorcycle crash; mTBI, mild traumatic brain injury; MVC, motor vehicle crash; OTC, orthopedic trauma control;.

[a] *P* values not adjusted for multiple comparisons. Statistical significance determined by Mann-Whitney and Fisher exact tests.

[b] Witnessed and suspected categories collapsed.

[c] Peripheral injury defined as either having an ISS nonhead (below the neck) greater than 0 or ever reporting peripheral injuries on a Glasgow Outcome Scale Extended score assessment.

Figure. Percentage of Patients in the Mild Traumatic Brain Injury (mTBI) and Orthopedic Trauma Control (OTC) Groups Reporting Injury-Related Limitations With Day-to-Day Functioning From 2 Weeks to 12 Months Postinjury on the Glasgow Outcome Scale–Extended Score Interview



Rates decreased from 87% (mTBI) and 93% (OTC) at 2 weeks to 53% (mTBI) and 38% (OTC) at 12 months postinjury. Group differences were nonsignificant at 2 weeks (RR, 0.93; 95% CI, 0.89-0.98), 3 months (RR, 0.92; 95% CI, 0.84-1.02), and 6 months (RR, 1.14; 95% CI, 0.99-1.31) postinjury. At 12 months postinjury, the mTBI group reported significantly higher rates of continued limitations with day-to-day functioning (RR, 1.38; 95% CI, 1.12-1.71).

GOSE score domain. **Table 3** provides effect sizes (RRs) for associated between-group comparisons. Overall, rates of dysfunction were highest for complex tasks, such as work (eg, mTBI: 61%; 95% CI, 57%-64%; OTC: 69%; 95% CI, 63%-74% at 2 weeks), and social/leisure functioning (eg, mTBI: 59%; 95% CI, 55%-62%; OTC: 70%; 95% CI, 63%-75% at 2 weeks) and lower in more basic activities, such as home independence (eg, mTBI: 12%; 95% CI, 9%-14%; OTC: 9%; 95% CI, 5%-13% at 2 weeks). Rates of dysfunction in each domain declined over time; for example, at 12 months, only 0% (95% CI 0%-3%) of the OTC group and 1% (95% CI, 1%-2%) of the mTBI group reported limitations in home independence; 17% of both groups (mTBI: 95% CI, 15%-20%; OTC: 95% CI, 12%-23%) reported problems with work and 17% (95% CI, 15%-20%) of the mTBI and 18% (95% CI, 13%-25%) of the OTC groups had limitations in social functioning. Compared with the OTC group, the mTBI group reported injury-related symptoms that affect daily life (from 73% vs 46% at 2 weeks: RR, 1.59; 95% CI, 1.37-1.84; to 48% vs 20% at 12 months: RR, 2.33;95% CI, 1.68-3.21) more frequently, with more family disruption reported at most time points. The OTC group reported more work and social dysfunction than the mTBI group through 6 months, but these group differences were no longer significant at 12 months.

eTables 3 and 4 in the Supplement present analyses of GOSE score domains by mTBI subgroup (CT+/CT−). At 2 weeks, the mTBI CT+ subgroup more commonly needed assistance at home (RR, 1.82; 95% CI, 1.17-2.81) and could not work (RR, 1.34; 95% CI, 1.09-1.65) compared with the CT− group. At 3, 6, and 12 months, the mTBI CT+ group reported higher rates of symptoms that affect daily life (RR, 1.21; 95% CI, 1.06-1.39; to RR, 1.29; 95% CI, 1.13-1.47). At select times, the mTBI CT+ group reported higher rates of psychological problems that affect relationships (at 6 months: RR, 1.43; 95% CI, 1.11-1.84) and more limitations with home independence (at 12 months: RR, 5.08; 95% CI, 1.33-19.47) and travel (at 12 months: RR, 6.54; 95% CI, 1.79-23.91) than the mTBI CT− group.

Group Differences in Symptoms and Cognitive Performance

Because the mTBI group continued to report substantial rates of injury-related problems at 12 months on the GOSE scale, we evaluated group differences in secondary outcome measures at 12 months to inform possible causes or consequences of chronic impairments. **Table 4** and eTable 11 in the Supplement present mTBI vs OTC comparisons. Participants with mTBI reported more severe symptoms on the Rivermead Post Concussion Symptoms Questionnaire (d = 0.46) and, to a lesser de-

Table 2. Prevalence of Functional Limitations (95% CI) Reported in Each GOSE Score Domain for mTBI and OTC Groups[a]

Variable	% (95% CI)							
	2 wk		3 mo		6 mo		12 mo	
	mTBI	OTC	mTBI	OTC	mTBI	OTC	mTBI	OTC
Independence								
Home	12 (9-14)	9 (5-13)	2 (1-4)	1 (0-3)	2 (1-3)	0 (0-3)	1 (1-2)	0 (0-3)
Shopping	12 (10-15)	9 (6-13)	3 (2-5)	0 (0-2)	2 (1-3)	0 (0-3)	1 (1-3)	0 (0-3)
Travel	12 (9-15)	10 (6-14)	3 (2-4)	1 (0-3)	2 (1-3)	0 (0-3)	2 (1-3)	0 (0-3)
Work[b]								
Reduced capacity[c]	61 (57-64)	69 (63-74)	31 (27-34)	40 (34-47)	20 (17-23)	22 (17-28)	17 (15-20)	17 (12-23)
Noncompetitive/unable to work	38 (34-42)	47 (40-53)	14 (11-16)	20 (15-26)	6 (5-8)	11 (7-16)	7 (6-9)	5 (2-9)
Social/leisure functioning								
A bit less[c]	59 (55-62)	70 (63-75)	32 (28-35)	46 (39-53)	20 (17-22)	31 (25-37)	17 (15-20)	18 (13-25)
Much less[c]	43 (39-47)	54 (48-60)	18 (16-22)	23 (18-29)	12 (10-15)	11 (7-16)	8 (6-10)	6 (3-11)
Unable	23 (20-27)	27 (22-33)	6 (5-8)	8 (5-12)	4 (3-5)	0 (0-2)	2 (1-4)	3 (1-6)
Family disruption								
Occasional[c]	26 (22-29)	18 (14-24)	26 (23-29)	20 (15-26)	26 (22-29)	17 (12-22)	24 (21-28)	8 (4-13)
Frequent[c]	19 (16-22)	12 (8-16)	19 (16-22)	14 (10-19)	18 (16-21)	10 (7-15)	16 (14-19)	5 (2-9)
Constant	8 (6-10)	2 (1-5)	6 (4-8)	4 (2-7)	5 (4-7)	1 (0-4)	4 (3-5)	1 (0-4)
Other disabling symptoms	73 (69-76)	46 (40-52)	56 (53-60)	38 (32-45)	54 (50-57)	32 (26-39)	48 (44-51)	20 (14-27)

Abbreviations: GOSE, Glasgow Outcome Scale Extended; mTBI, mild traumatic brain injury; OTC, orthopedic trauma control.

[a] Possible score range for GOSE score is 1 (dead) to 8 (upper good recovery), with a score less than 8 indicating some degree of functional impairment.

[b] Computed only for participants who were working before the injury.

[c] Refers to membership in the named impairment category or higher.

Table 3. Effect Sizes of mTBI vs OTC Group Differences in GOSE Score Domain Scores[a]

Variable	RR (95% CI)[b]			
	2 wk	3 mo	6 mo	12 mo
Independence				
Home	1.27 (0.81-2.01)	1.29 (0.43-3.84)	Inestimable	Inestimable
Shopping	1.27 (0.81-1.98)	7.21 (0.98-53.29)	Inestimable	Inestimable
Travel	1.15 (0.75-1.77)	2.92 (0.68-12.53)	Inestimable	Inestimable
Work[c]				
Reduced capacity[d]	0.88 (0.79-0.98)[e]	0.75 (0.62-0.92)[e]	0.88 (0.66-1.18)	0.97 (0.67-1.42)
Noncompetitive/unable to work	0.80 (0.67-0.95)[e]	0.64 (0.47-0.89)[e]	0.53 (0.33-0.86)[e]	1.58 (0.73-3.42)
Social/leisure functioning				
A bit less[c]	0.85 (0.76-0.94)[e]	0.69 (0.57-0.83)[e]	0.62 (0.48-0.80)[e]	0.92 (0.63-1.33)
Much less[c]	0.81 (0.70-0.94)[e]	0.79 (0.59-1.06)	1.05 (0.68-1.62)	1.11 (0.59-2.06)
Unable	0.88 (0.68-1.13)	0.83 (0.48-1.43)	7.50 (1.03-54.86)[e]	0.87 (0.29-2.56)
Family disruption				
Occasional[c]	1.35 (1.00-1.80)	1.20 (0.90-1.59)	1.48 (1.07-2.04)[e]	2.87 (1.68-4.91)[e]
Frequent[c]	1.58 (1.08-2.30)[e]	1.26 (0.88-1.81)	1.66 (1.09-2.54)[e]	3.20 (1.60-6.42)[e]
Constant	3.12 (1.35-7.20)[e]	1.55 (0.73-3.27)	3.35 (1.04-10.77)[e]	2.93 (0.71-12.20)
Other disabling symptoms	1.59 (1.37-1.84)[e]	1.45 (1.21-1.74)[e]	1.62 (1.32-2.00)[e]	2.33 (1.68-3.21)[e]

Abbreviations: GOSE, Glasgow Outcome Scale Extended; mTBI, mild traumatic brain injury; OTC, orthopedic trauma control; RR, risk ratio.

[a] Possible score range for GOSE score is 1 (dead) to 8 (upper good recovery), with a score less than 8 indicating some degree of functional impairment.

[b] Risk ratio 95% CIs estimated per Altman[38]; statistical significance by Fisher exact. Findings with zero in the denominator were inestimable.

[c] Computed only for participants who were students or in the workforce (ie, not homemakers, retired, or disabled) before injury.

[d] Refers to membership in the named impairment category or higher (ie, more impaired).

[e] Significant after correction for multiple comparisons.

gree, psychological distress (18-item Brief Symptom Inventory, d = 0.20) than the OTCs. The mTBI group demonstrated significantly poorer performance vs the OTC group in verbal learning and memory retrieval (d = 0.24-0.25) and on 1 measure of psychomotor processing speed (Trail Making Test, Part A; d = 0.30). Comparisons between the mTBI CT+ and

Table 4. Group Differences in Neuropsychological Performance and Self-reported Symptoms at 12 Months Postinjury

Variable	Mean (95% CI)		Group Difference, Cohen *d* (95% CI)
	mTBI	OTC	
Memory			
RAVLT immediate memory[a,b,c]	49.3 (48.4 to 50.2)	52.6 (50.9 to 54.4)	−0.25 (−0.43 to −0.07)[d]
RAVLT delayed recall[b,c]	9.6 (9.3 to 9.9)	10.6 (10.0 to 11.2)	−0.24 (−0.42 to −0.06)[d]
Processing speed			
WAIS-IV PS index[a,e]	103 (102 to 105)	104 (101 to 107)	−0.04 (−0.23 to 0.14)
Executive functioning			
Trails A time[a,b,f]	28.1 (27.0 to 29.2)	24.1 (22.4 to 25.8)	0.30 (0.11 to 0.48)[d]
Trails B time[a,b,f]	69.7 (66.6 to 72.8)	66.0 (59.9 to 72.1)	0.10 (−0.09 to 0.28)
Psychological distress (BSI-18 GSI)[g]	49.3 (48.5 to 50.1)	46.9 (45.1 to 48.6)	0.20 (0.03 to 0.37)[d]
Life satisfaction (SWLS)[b,h]	24.9 (24.4 to 25.5)	25.7 (24.6 to 26.8)	−0.10 (−0.27 to 0.07)
TBI symptoms (RPQ Score)[b,i]	12.5 (11.5 to 13.6)	6.0 (4.3 to 7.6)	0.46 (0.29 to 0.63)[d]

Abbreviations: BSI-18 GSI, 18-item Brief Symptom Inventory Global Severity Index; mTBI, mild traumatic brain injury; OTC, orthopedic trauma control; PS, processing speed; RAVLT, Rey Auditory Verbal Learning Test; RPQ, Rivermead Post Concussion Symptoms Questionnaire; SWLS, Satisfaction With Life Scale; WAIS-IV, Wechsler Adult Intelligence Scale-fourth edition.

[a] Group comparisons of cognitive functioning (RAVLT, WAIS-IV PSI, Trail Making Test variables) included age, sex, and education as covariates.

[b] Raw score.

[c] Possible range for immediate memory, 0 to 80; higher scores indicate better memory; possible range for delayed recall, 0 to 16; higher scores indicate better memory.

[d] Significant after correction for multiple comparisons.

[e] Standard mean (SD) score with general population, 100 (15); higher scores indicate better processing speed.

[f] Part A time, maximum score was 90 seconds in this study, lower score is faster/better; part B time, maximum score was 300 seconds in this study, lower score is faster/better.

[g] Mean (SD) T score normative for the general population, 50 (10); possible range, 36 to 81; higher scores indicate more severe psychiatric symptoms.

[h] Possible range, 5 to 35; higher scores indicate more life satisfaction.

[i] Possible range, 0 to 64; higher scores indicate more severe symptoms.

CT− groups (eTable 5 in the Supplement) were not statistically significant on any secondary outcome measure.

Discussion

In this longitudinal observational study of patients who presented to US level I trauma centers with mTBI, only 47.2% of patients with mTBI (defined as ED admission GCS score, 13-15) reported full return to preinjury levels of day-to-day functioning at 12 months postinjury vs 62.3% of OTCs (P = .001). In addition to more frequently reporting functional limitations at 12 months, patients with mTBI reported more persistent injury-related symptoms (eg, headaches, fatigue, depression, forgetfulness) and performed more poorly on cognitive tests than those in the OTC group.

Our findings highlight an apparent need for improved treatment of mTBI. Although there are currently no validated pharmacologic treatments for mTBI, nonpharmacologic interventions to provide psychoeducation and symptom management can help patients. For example, a number of studies support the efficacy of providing a clinical encounter soon (eg, 1 week) after injury to offer accurate and reassuring information about the expected symptoms and recovery course from mTBI.[40-43] In contrast, about half of patients with mTBI who present to the ED do not receive any TBI diagnosis,[44] a significant minority do not receive adequate discharge instructions,[45] and most do not receive follow-up care after their ED visit.[46] Thus, outcomes may be improved by increasing the rate of early identification of mTBI and providing patient education about the condition. In addition, given that many of the symptoms reported after mTBI (eg, headache, psychiatric symptoms) have validated treatments in other clinical populations,[47,48] such established treatments may be efficacious in the mTBI population but require more systematic validation in patients with mTBI.[49-51]

These data also suggest that patients who demonstrate acute intracranial CT scan findings of mTBI vs those without such findings more commonly report injury-related difficulties in several aspects of daily life even 1 year postinjury. This result is consistent with other findings that complicated (CT+) mTBI represents a more severe brain injury than uncomplicated (CT−) mTBI. However, across other outcome domains at 1 year (eg, self-report of symptoms, cognitive functioning), the CT+ and CT− subgroups were similar. In combination with the high degree of heterogeneity in outcomes, these results appear to support the need to further refine mTBI classification systems beyond current approaches focused on the crude variables of admission GCS score and normal vs abnormal head CT scan. Although we focused on these variables because of their broad clinical use, other pathophysiologic indicators of brain injury may soon inform diagnostic, treatment, and prognostic decisions. Beyond the presence of CT abnormalities, for example, the magnitude and nature of CT abnormalities may be relevant to mTBI classification.[52] Furthermore, a significant percentage of patients who present without evidence of brain injury on head CT scans show signs of intracranial injury on brain magnetic resonance imaging scans, and the findings from these scans predict outcomes.[53,54] In addition, peripheral blood biomarkers of brain injury may inform clinical decision making in the future.[55] These examples highlight the potential for neurobiological discoveries to improve the classification of

patients with mTBI and perhaps develop precision medicine treatment approaches. Ongoing studies, such as TRACK-TBI, are collecting the translational data needed to advance this goal in the coming years.

Data presented on the OTC group shed light on the relevance of peripheral injuries outcomes after traumatic injuries. In particular, 38% of the OTCs reported injury-related life difficulties at the 1-year study end point. Most patients with mTBI in this sample had some degree of peripheral injuries. The finding that some life problems were equally prevalent across the mTBI and OTC groups (eg, in work and social functioning at 12 months) may suggest that factors other than brain injury contributed to these types of problems. However, chronic symptoms and cognitive impairments were more prevalent in the patients with mTBI than OTC group, implying some contribution of mTBI toward these outcomes. Within the subsample of admitted patients for whom we could quantify peripheral injury severity, the mTBI CT+ group manifested less-severe peripheral injuries than the mTBI CT– and OTC groups (eTable 1 in the Supplement). This finding might imply that poorer functional outcomes in the mTBI CT+ subgroup may partly reflect the consequences of brain injury as opposed to peripheral trauma. These observations highlight the need for methods that parse the sequelae of brain vs peripheral injuries and underscore the recommendation that clinicians should consider the entirety of individual patients' injuries, histories, and life experiences when treating them after traumatic injuries. For example, in addition to physical injuries, patients with trauma may experience emotional distress and other life stressors after injury that affect their recoveries.[56-60] In addition, premorbid risk and resilience factors appear to contribute to injury response and recovery.[61-64] Although additional work is needed to understand the dynamic process by which diverse factors lead to resilient vs poor outcomes,[61,65] clinicians are encouraged to take a patient-centered treatment approach that addresses patients' symptoms and presenting concerns, regardless of their apparent source.[39]

Limitations

This study had several limitations. Because we only enrolled patients seen at level I trauma centers who received head CT scans, the findings may not generalize to the broader mTBI population, such as patients who meet criteria for mTBI but are triaged to a lower level of care and those who do not present to EDs.[66] However, the findings can be generalized to a large group of patients seen in acute care settings where CT imaging was clinically indicated to rule out more severe TBI. Although the OTC sample was relatively small at 12 months, groups were well matched at enrollment (except for select injury-related variables, such as the presence of orthopedic injuries, cause of injury, and highest level of care), and appropriate statistical analyses were used to ensure that any group differences at enrollment or possible nonrandom patterns of attrition did not bias results. Despite these efforts, there was significant heterogeneity within both the mTBI and OTC groups in the nature and severity of injuries, alongside limited available methods to quantify brain and peripheral injury severity. Thus, although these data shed some light on the potential contribution of brain and nonbrain injuries to outcomes, more work is needed to better understand how these and other factors (eg, preinjury risk factors, emotional trauma due to injury) affect recovery from traumatic injuries. Our primary outcome may be prone to response bias; however, we observed mTBI-related responses on objective cognitive performance measures, which strengthens our findings. Future work should clarify how variables other than head CT scan status (eg, other biomarkers, preinjury factors, multiple trauma, postinjury social and rehabilitative support) should inform clinical decisions for individual patients.

Conclusions

In this prospective, observational TRACK-TBI study cohort, patients with mTBI presenting to level I trauma centers commonly report difficulties in aspects of day-to-day functioning to at least 12 months postinjury, especially with TBI-related symptoms and interpersonal functioning, suggesting that this injury is not always benign. These findings contrast with the rapid recovery observed in prospective studies of sport-related concussion,[6,22] and appear to demonstrate that the natural history of mTBI recovery differs across patient populations. Furthermore, patients with mTBI with CT scan evidence of structural brain injury commonly have a higher prevalence of persisting functional limitations in some life areas but a similar degree of persistent symptoms compared with those with normal CT scan findings. The term *mild TBI* misrepresents the immediate and long-term burden of TBI and other cooccurring factors experienced by this patient population.

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REFERENCES

1. Taylor CA, Bell JM, Breiding MJ, Xu L. Traumatic brain injury-related emergency department visits, hospitalizations, and deaths—United States, 2007 and 2013. *MMWR Surveill Summ*. 2017;66(9):1-16. doi:10.15585/mmwr.ss6609a1

2. Dikmen SS, Machamer JE, Powell JM, Temkin NR. Outcome 3 to 5 years after moderate to severe traumatic brain injury. *Arch Phys Med Rehabil*. 2003;84(10):1449-1457. doi:10.1016/S0003-9993(03)00287-9

3. Colantonio A, Ratcliff G, Chase S, Kelsey S, Escobar M, Vernich L. Long-term outcomes after moderate to severe traumatic brain injury. *Disabil Rehabil*. 2004;26(5):253-261. doi:10.1080/09638280310001639722

4. Maas AI, Stocchetti N, Bullock R. Moderate and severe traumatic brain injury in adults. *Lancet Neurol*. 2008;7(8):728-741. doi:10.1016/S1474-4422(08)70164-9

5. Nelson LD, LaRoche AA, Pfaller AY, et al. Prospective, head-to-head study of three computerized neurocognitive assessment tools (CNTs): reliability and validity for the assessment of sport-related concussion. *J Int Neuropsychol Soc*. 2016;22(1):24-37. doi:10.1017/S1355617715001101

6. McCrea M, Guskiewicz KM, Marshall SW, et al. Acute effects and recovery time following concussion in collegiate football players: the NCAA Concussion Study. *JAMA*. 2003;290(19):2556-2563. doi:10.1001/jama.290.19.2556

7. Nelson LD, Furger RE, Ranson J, et al. Acute clinical predictors of symptom recovery in emergency department patients with uncomplicated mild traumatic brain injury (mTBI) or non-mTBI injuries. *J Neurotrauma*. 2018;35(2):249-259. doi:10.1089/neu.2017.4988

8. Rohling ML, Binder LM, Demakis GJ, Larrabee GJ, Ploetz DM, Langhinrichsen-Rohling J. A meta-analysis of neuropsychological outcome after mild traumatic brain injury: re-analyses and reconsiderations of Binder et al. (1997), Frencham et al. (2005), and Pertab et al. (2009). *Clin Neuropsychol*. 2011;25(4):608-623. doi:10.1080/13854046.2011.565076

9. Frencham KA, Fox AM, Maybery MT. Neuropsychological studies of mild traumatic brain injury: a meta-analytic review of research since 1995. *J Clin Exp Neuropsychol*. 2005;27(3):334-351. doi:10.1080/13803390490520328

10. Schretlen DJ, Shapiro AM. A quantitative review of the effects of traumatic brain injury on cognitive functioning. *Int Rev Psychiatry*. 2003;15(4):341-349. doi:10.1080/09540260310001606728

11. Belanger HG, Curtiss G, Demery JA, Lebowitz BK, Vanderploeg RD. Factors moderating neuropsychological outcomes following mild traumatic brain injury: a meta-analysis. *J Int Neuropsychol Soc*. 2005;11(3):215-227. doi:10.1017/S1355617705050277

12. Carroll LJ, Cassidy JD, Cancelliere C, et al. Systematic review of the prognosis after mild traumatic brain injury in adults: cognitive, psychiatric, and mortality outcomes: results of the International Collaboration on Mild Traumatic Brain Injury Prognosis. *Arch Phys Med Rehabil*. 2014;95(3)(suppl):S152-S173. doi:10.1016/j.apmr.2013.08.300

13. Rimel RW, Giordani B, Barth JT, Boll TJ, Jane JA. Disability caused by minor head injury. *Neurosurgery*. 1981;9(3):221-228.

14. Iverson GL. Outcome from mild traumatic brain injury. *Curr Opin Psychiatry*. 2005;18(3):301-317. doi:10.1097/01.yco.0000165601.29047.ae

15. Carroll LJ, Cassidy JD, Peloso PM, et al; WHO Collaborating Centre Task Force on Mild Traumatic Brain Injury. Prognosis for mild traumatic brain injury: results of the WHO Collaborating Centre Task Force on Mild Traumatic Brain Injury. *J Rehabil Med*. 2004;(43)(suppl):84-105. doi:10.1080/16501960410023859

16. Dikmen S, Machamer J, Temkin N. Mild traumatic brain injury: longitudinal study of cognition, functional status, and post-traumatic symptoms. *J Neurotrauma*. 2017;34(8):1524-1530. doi:10.1089/neu.2016.4618

17. Carroll LJ, Cassidy JD, Holm L, Kraus J, Coronado VG; WHO Collaborating Centre Task Force on Mild Traumatic Brain Injury. Methodological issues and research recommendations for mild traumatic brain injury: the WHO Collaborating Centre Task Force on Mild Traumatic Brain Injury. *J Rehabil Med*. 2004;(43)(suppl):113-125. doi:10.1080/16501960410023877

18. Dikmen SS, Corrigan JD, Levin HS, Machamer J, Stiers W, Weisskopf MG. Cognitive outcome following traumatic brain injury. *J Head Trauma Rehabil*. 2009;24(6):430-438. doi:10.1097/HTR.0b013e3181c133e9

19. Kristman VL, Borg J, Godbolt AK, et al. Methodological issues and research recommendations for prognosis after mild traumatic brain injury: results of the International Collaboration on Mild Traumatic Brain Injury Prognosis. *Arch Phys Med Rehabil*. 2014;95(3)(suppl):S265-S277. doi:10.1016/j.apmr.2013.04.026

20. Committee AMTBI. Definition of mild traumatic brain injury. *J Head Trauma Rehabil*. 1993;8(3):86-87. doi:10.1097/00001199-199309000-00010

21. Ponsford J, Cameron P, Fitzgerald M, Grant M, Mikocka-Walus A. Long-term outcomes after uncomplicated mild traumatic brain injury: a comparison with trauma controls. *J Neurotrauma*. 2011;28(6):937-946. doi:10.1089/neu.2010.1516

22. Nelson LD, Janecek JK, McCrea MA. Acute clinical recovery from sport-related concussion. *Neuropsychol Rev*. 2013;23(4):285-299. doi:10.1007/s11065-013-9240-7

23. Kashluba S, Hanks RA, Casey JE, Millis SR. Neuropsychologic and functional outcome after complicated mild traumatic brain injury. *Arch Phys Med Rehabil*. 2008;89(5):904-911. doi:10.1016/j.apmr.2007.12.029

24. Williams DH, Levin HS, Eisenberg HM. Mild head injury classification. *Neurosurgery*. 1990;27(3):422-428. doi:10.1227/00006123-199009000-00014

25. Borgaro SR, Prigatano GP, Kwasnica C, Rexer JL. Cognitive and affective sequelae in complicated and uncomplicated mild traumatic brain injury. *Brain Inj*. 2003;17(3):189-198. doi:10.1080/0269905021000013183

26. Yue JK, Vassar MJ, Lingsma HF, et al; TRACK-TBI Investigators. Transforming research and clinical knowledge in traumatic brain injury pilot: multicenter implementation of the common data elements for traumatic brain injury. *J Neurotrauma*. 2013;30(22):1831-1844. doi:10.1089/neu.2013.2970

27. Maas AI, Harrison-Felix CL, Menon D, et al. Common data elements for traumatic brain injury: recommendations from the interagency working group on demographics and clinical assessment. *Arch Phys Med Rehabil*. 2010;91(11):1641-1649. doi:10.1016/j.apmr.2010.07.232

28. Wilde EA, Whiteneck GG, Bogner J, et al. Recommendations for the use of common outcome measures in traumatic brain injury research. *Arch Phys Med Rehabil*. 2010;91(11):1650-1660.e17. doi:10.1016/j.apmr.2010.06.033

29. Jennett B, Snoek J, Bond MR, Brooks N. Disability after severe head injury: observations on the use of the Glasgow Outcome Scale. *J Neurol Neurosurg Psychiatry*. 1981;44(4):285-293. doi:10.1136/jnnp.44.4.285

30. King NS, Crawford S, Wenden FJ, Moss NE, Wade DT. The Rivermead Post Concussion Symptoms Questionnaire: a measure of symptoms commonly experienced after head injury and its reliability. *J Neurol*. 1995;242(9):587-592. doi:10.1007/BF00868811

31. Derogatis LR. *Brief Symptom Inventory 18 (BSI-18): Administration, Scoring, and Procedures Manual*. Bloomington, MN: Pearson; 2001.

32. Diener E, Emmons RA, Larsen RJ, Griffin S. The Satisfaction With Life scale. *J Pers Assess*. 1985;49(1):71-75. doi:10.1207/s15327752jpa4901_13

33. Rey A. L'examen psychologique dans les cas d'encephalopathie traumatique. *Arch Psychol*. 1941;28:215-285.

34. Schmidt M. *Rey Auditory Verbal Learning Test: A Handbook*. Loss Angeles, CA: Western Psychological Services; 1996.

35. Wechsler D. Wechsler Adult Intelligence Scale–Fourth Edition (WAIS-IV). Bloomington, MN: Pearson; 2008.

36. Reitan RM. Trail Making Test results for normal and brain-damaged children. *Percept Mot Skills*. 1971;33(2):575-581. doi:10.2466/pms.1971.33.2.575

37. McCaffrey DF, Ridgeway G, Morral AR. Propensity score estimation with boosted regression for evaluating causal effects in observational studies. *Psychol Methods*. 2004;9(4):403-425. doi:10.1037/1082-989X.9.4.403

38. Altman DG. *Practical Statistics for Medical Research*. London, England: Chapman and Hall; 1991.

39. Benjamini Y, Hochberg Y. Controlling the false discovery rate: a practical and powerful approach to multiple testing. *J R Stat Soc B*. 1995;57:289-300. Statistical Mehodology.

40. Ponsford J, Willmott C, Rothwell A, et al. Impact of early intervention on outcome after mild traumatic brain injury in children. *Pediatrics*. 2001; 108(6):1297-1303. doi:10.1542/peds.108.6.1297

41. Ponsford J, Willmott C, Rothwell A, et al. Impact of early intervention on outcome following mild head injury in adults. *J Neurol Neurosurg Psychiatry*. 2002;73(3):330-332. doi:10.1136/jnnp.73.3.330

42. Alves W, Macciocchi SN, Barth JT. Postconcussive symptoms after uncomplicated mild head injury. *J Head Trauma Rehabil*. 1993;8: 48-59. doi:10.1097/00001199-199309000-00007

43. Minderhoud JM, Boelens ME, Huizenga J, Saan RJ. Treatment of minor head injuries. *Clin Neurol Neurosurg*. 1980;82(2):127-140. doi:10.1016/0303-8467(80)90007-4

44. Powell JM, Ferraro JV, Dikmen SS, Temkin NR, Bell KR. Accuracy of mild traumatic brain injury diagnosis. *Arch Phys Med Rehabil*. 2008;89(8): 1550-1555. doi:10.1016/j.apmr.2007.12.035

45. Bazarian JJ, McClung J, Cheng YT, Flesher W, Schneider SM. Emergency department management of mild traumatic brain injury in the USA. *Emerg Med J*. 2005;22(7):473-477. doi:10.1136/emj.2004.019273

46. Seabury SA, Gaudette É, Goldman DP, et al; and the TRACK-TBI Investigators. Assessment and follow-up care after emergency department presentation for mild traumatic brain injury and concussion: results from the TRACK-TBI study. *JAMA Netw Open*. 2018;1(1):e180210. doi:10.1001/jamanetworkopen.2018.0210

47. Pampallona S, Bollini P, Tibaldi G, Kupelnick B, Munizza C. Combined pharmacotherapy and psychological treatment for depression: a systematic review. *Arch Gen Psychiatry*. 2004;61 (7):714-719. doi:10.1001/archpsyc.61.7.714

48. Palermo TM, Eccleston C, Lewandowski AS, Williams AC, Morley S. Randomized controlled trials of psychological therapies for management of chronic pain in children and adolescents: an updated meta-analytic review. *Pain*. 2010;148(3): 387-397. doi:10.1016/j.pain.2009.10.004

49. Comper P, Bisschop SM, Carnide N, Tricco A. A systematic review of treatments for mild traumatic brain injury. *Brain Inj*. 2005;19(11):863-880. doi:10.1080/02699050400025042

50. Fann JR, Hart T, Schomer KG. Treatment for depression after traumatic brain injury: a systematic review. *J Neurotrauma*. 2009;26(12):2383-2402. doi:10.1089/neu.2009.1091

51. Al Sayegh A, Sandford D, Carson AJ. Psychological approaches to treatment of postconcussion syndrome: a systematic review. *J Neurol Neurosurg Psychiatry*. 2010;81(10):1128-1134. doi:10.1136/jnnp.2008.170092

52. Lobato RD, Cordobes F, Rivas JJ, et al. Outcome from severe head injury related to the type of intracranial lesion. a computerized tomography study. *J Neurosurg*. 1983;59(5):762-774. doi:10.3171/jns.1983.59.5.0762

53. Yuh EL, Mukherjee P, Lingsma HF, et al; TRACK-TBI Investigators. Magnetic resonance imaging improves 3-month outcome prediction in mild traumatic brain injury. *Ann Neurol*. 2013;73(2): 224-235. doi:10.1002/ana.23783

54. Levin HS, Amparo E, Eisenberg HM, et al. Magnetic resonance imaging and computed tomography in relation to the neurobehavioral sequelae of mild and moderate head injuries. *J Neurosurg*. 2012;116:706-713.

55. Wang KK, Yang Z, Zhu T, et al. An update on diagnostic and prognostic biomarkers for traumatic brain injury. *Expert Rev Mol Diagn*. 2018;18(2):165-180. doi:10.1080/14737159.2018.1428089

56. Roden-Foreman K, Solis J, Jones A, et al. Prospective evaluation of posttraumatic stress disorder and depression in orthopaedic injury patients with and without concomitant traumatic brain injury. *J Orthop Trauma*. 2017;31(9):e275-e280. doi:10.1097/BOT.0000000000000884

57. deRoon-Cassini TA, Mancini AD, Rusch MD, Bonanno GA. Psychopathology and resilience following traumatic injury: a latent growth mixture model analysis. *Rehabil Psychol*. 2010;55(1):1-11. doi:10.1037/a0018601

58. Ruff R. Two decades of advances in understanding of mild traumatic brain injury. *J Head Trauma Rehabil*. 2005;20(1):5-18. doi:10.1097/00001199-200501000-00003

59. Bay E, de-Leon MB. Chronic stress and fatigue-related quality of life after mild to moderate traumatic brain injury. *J Head Trauma Rehabil*. 2011; 26(5):355-363. doi:10.1097/HTR.0b013e3181f20146

60. Stein MB, Jain S, Giacino JT, et al. Posttraumatic stress disorder and major depression after civilian mild traumatic brain injury: a TRACK-TBI study [published online January 30, 2019]. *JAMA Psychiatry*.

61. Nelson LD, Tarima S, LaRoche AA, et al. Preinjury somatization symptoms contribute to clinical recovery after sport-related concussion. *Neurology*. 2016;86(20):1856-1863. doi:10.1212/WNL.0000000000002679

62. Broshek DK, De Marco AP, Freeman JR. A review of post-concussion syndrome and psychological factors associated with concussion. *Brain Inj*. 2015;29(2):228-237. doi:10.3109/02699052.2014.974674

63. Ponsford J, Willmott C, Rothwell A, et al. Factors influencing outcome following mild traumatic brain injury in adults. *J Int Neuropsychol Soc*. 2000;6(5):568-579. doi:10.1017/S1355617700655066

64. Hoffman JM, Dikmen S, Temkin N, Bell KR. Development of posttraumatic stress disorder after mild traumatic brain injury. *Arch Phys Med Rehabil*. 2012;93(2):287-292. doi:10.1016/j.apmr.2011.08.041

65. Wood RL. Understanding the 'miserable minority': a diasthesis-stress paradigm for post-concussional syndrome. *Brain Inj*. 2004;18(11): 1135-1153. doi:10.1080/02699050410001675906

66. Sosin DM, Sniezek JE, Thurman DJ. Incidence of mild and moderate brain injury in the United States, 1991. *Brain Inj*. 1996;10(1):47-54. doi:10.1080/026990596124719