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REVIEW ARTICLE

Systematic Review of Self-Reported Prognosis in Adults After Mild Traumatic Brain Injury: Results of the International Collaboration on Mild Traumatic Brain Injury Prognosis

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Abstract

Objective: To update the mild traumatic brain injury (MTBI) prognosis review published by the World Health Organization Task Force in 2004.

Data Sources: MEDLINE, PsycINFO, Embase, CINAHL, and SPORTDiscus were searched from 2001 to 2012. We included published, peer-reviewed studies with more than 30 adult cases.

Study Selection: Controlled trials and cohort and case-control studies were selected according to predefined criteria. Studies had to assess subjective, self-reported outcomes. After 77,914 titles and abstracts were screened, 299 articles were eligible and reviewed for scientific quality. This includes 3 original International Collaboration on MTBI Prognosis (ICoMP) research studies.

Data Extraction: Eligible studies were critically appraised using the Scottish Intercollegiate Guidelines Network criteria. Two reviewers independently reviewed each study and tabled data from accepted articles. A third reviewer was consulted for disagreements.

Data Synthesis: Evidence from accepted studies was synthesized qualitatively into key findings, and prognostic information was prioritized according to design as exploratory or confirmatory. Of 299 reviewed studies, 101 (34%) were accepted and form our evidence base of prognostic studies. Of these, 23 addressed self-reported outcomes in adults, including 2 of the 3 original ICoMP research studies. These studies show that common postconcussion symptoms are not specific to MTBI/concussion and occur after other injuries as well. Poor recovery after MTBI is

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associated with poorer premorbid mental and physical health status and with more injury-related stress. Most recover over 1 year, but persistent symptoms are more likely in those with more acute symptoms and more emotional stress.

Conclusions: Common subjective symptoms after MTBI are not necessarily caused by brain injury per se, but they can be persistent in some patients. Those with more initial complaints and psychological distress recover slower. We need more high-quality research on these issues.

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Mild traumatic brain injury (MTBI) is a common injury after falls and traffic collisions.[1] It represents 70% to 90% of all TBI and has been estimated to affect more than 600 adults per 100,000 each year.[2] MTBI or concussion has received increasing attention mostly because of contact sports, especially American football and ice hockey.[3] As a result, there is more public attention and concern about potential long-lasting effects. Clinicians must deal with concerned patients who want to know how long their symptoms might last and what to expect in the future. These concerns can only be addressed by high-quality prognostic studies that follow up defined cohorts of injured subjects and use valid measures of prognostic factors and outcomes.

In 2004, the World Health Organization (WHO) Collaborating Centre Task Force on MTBI published the first systematic review[4] of the literature on the course and prognosis after MTBI. They searched MEDLINE, PsycINFO, CINAHL, and Embase up to the year 2000 and found 427 research articles on prognosis. After critically reviewing these studies, 120 (28%) were found to be of sufficient scientific quality to be included in their best-evidence synthesis. Of these studies, 16 focused on subjective symptoms in adults. The Task Force concluded that self-reported symptoms such as headache, fatigue, self-perceived cognitive deficits, and other symptoms reported after concussive events are also common in the acute stage of other injuries, and they are not specific to MTBI. Furthermore, these subjective symptoms are commonly associated with pain, depression, anxiety, posttraumatic stress, litigation, and other injury-related factors. Therefore, the Task Force recommended that postconcussion symptoms be assessed in the light of all contributing psychosocial factors and not be automatically attributed to brain injury per se. In addition, the use of terms such as postconcussion syndrome (PCS) might be misleading because of doubts about the etiology of some subjective postconcussion symptoms. The Task Force found that most patients recover within 3 months to a year but that compensation-related litigation can prolong recovery. Other factors associated with prolonged symptoms were preexisting physical limitations, prior brain injury, prior neurologic problems, psychiatric problems, stress, being a student, sustaining an MTBI in a motor vehicle collision, and age >40 years. They found evidence to suggest that premorbid personality and prior psychiatric history contribute to post-MTBI stress and psychological problems, which in turn are associated with more self-reported symptoms. Also, those with more severe MTBI (eg, Glasgow Coma Scale [GCS] score of 14 or 13 and MTBI complicated by intracranial lesions and/or depressed skull fracture) have more disability than those with a GCS score of 15. Overall the Task Force concluded that self-reported symptoms were common, but there was a need for more high-quality studies on their cause, course, and prognosis.

The International Collaboration on MTBI Prognosis (ICoMP) is a team of clinicians and scientists assembled to update the WHO Collaborating Centre Task Force findings on MTBI.[5] ICoMP includes many of the same members who served on that task force, and were selected for their expertise in epidemiology of MTBI, clinical management of MTBI, or both. Our purpose here is to update the WHO findings on course and prognosis in adults with respect to self-reported outcomes.

List of abbreviations:

APOE	**apolipoprotein E**
ED	**emergency department**
GCS	**Glasgow Coma Scale**
ICoMP	**International Collaboration on MTBI Prognosis**
LOC	**loss of consciousness**
MTBI	**mild traumatic brain injury**
PCS	**postconcussion syndrome**
PRISMA	**Preferred Reporting Items for Systematic Reviews and Meta-Analyses**
PTA	**posttraumatic amnesia**
PTHA	**posttraumatic headache**
PTSD	**posttraumatic stress disorder**
RPSQ	**Rivermead Postconcussion Symptoms Questionnaire**
SF-36	**Medical Outcomes Study 36-Item Short-Form Health Survey**
WHO	**World Health Organization**

Methods

The literature search and critical review strategy are outlined in detail elsewhere. Briefly, the electronic databases MEDLINE, PsycINFO, Embase, CINAHL, and SPORTDiscus were systematically searched from January 1, 2001, to June 30, 2011.[6] These searches were updated on February 10, 2012. The reference lists of all reviews and meta-analyses related to MTBI, and articles meeting the eligibility criteria were screened for additional studies. ICoMP members also provided studies they had knowledge about. Articles were screened for eligibility according to predefined criteria. Included were original, published, peer-reviewed research reports in English, French, Swedish, Norwegian, Danish, and Spanish, and human participants of all ages. Studies had to have a minimum of 30 MTBI cases, and for this report, had to assess self-reported outcomes after adult MTBI. The definition of MTBI had to fall within the WHO Collaborating Centre Task Force[7] or the Centers for Disease Control and Prevention definitions.[5] Excluded were publication types other than systematic reviews and meta-analyses that included an assessment of the methodological quality of the included studies, randomized controlled trials, cohort studies, and case-control studies. We also excluded basic science, animal, cadaveric, biomechanical, and laboratory studies. Although we screened systematic review reference lists for primary studies, we did not include systematic reviews in our critical review.

All eligible articles were critically appraised using a modification of the Scottish Intercollegiate Guidelines Network criteria.[8] Two reviewers performed independent, in-depth methodological reviews of each eligible study, and a third reviewer was consulted

for disagreements. Two reviewers independently extracted data from accepted articles into evidence tables, and this evidence was synthesized to provide clear and useful conclusions linked to the evidence tables. ICoMP members also undertook 3 original research projects, and 2 are included in the results of this article.

We prioritized the evidence on prognostic factors using the framework described by Côté et al.[9] Phase I studies are hypothesis generating and explore associations between potential prognostic factors and disease outcomes in a descriptive, or crude univariate way. Phase II studies are exploratory analyses that focus on sets of prognostic factors or markers to discover which have the highest independent prognostic value. Phase III studies are confirmatory studies with explicit hypotheses and focused examination of the strength, direction, and independence of proposed causal relationships. Phase III studies are considered the strongest evidence for prognostic factors followed by phase II studies. Phase I studies are considered more preliminary.

Our review was conducted and is reported in compliance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[10] Our protocol was registered with the International Prospective Register of Systematic Reviews (registration no. CRD42011001410) and published in *Systematic Reviews*.[5]

Results

After applying the inclusion and exclusion criteria to 77,914 titles and abstracts, 2170 full-text articles were assessed for eligibility. There were 173 eligible articles that assessed MTBI prognosis in adults, excluding studies of sport and military injuries, which are reported elsewhere.[11,12] Of the 173 articles on prognosis, 51 (29%) were evaluated as having a low risk of bias, and 21 of these included subjective, self-reported outcomes. The other studies reported on objective outcomes and are reported elsewhere.[13] We also include 2 original studies addressing subjective outcomes in adult prognosis done by ICoMP members.[14,15] In total, 23 studies with self-reported outcomes, including 22 cohort studies and 1 nonrandomized experimental study, form the basis of this report (fig 1). Of the cohort studies, 1 is phase III, 16 are phase II, and 5 are phase I studies. All are English publications. We report our findings according to the length of follow up in these studies, including 1, 3, 6, 12, or more than 12 months of follow up.

Up to 1-month follow up

We accepted 3 cohort studies from the United States that followed up patients for up to 1 month (table 1). Outcomes included self-reported irritability and executive functions, neurobehavioral function and symptoms, bodily pain, mental health, and postconcussion symptoms. One is a phase I study[16] and the other 2 are phase II studies.[17,18] All 3 studies recruited patients from hospitals, and 2 included an orthopedic injury group.[17,18]

With respect to recovery, Brewer et al[16] found that 30% of patients continued to complain of irritability and 20% continued to complain of concentration problems at 1 month. Landre et al[17] found that patients with MTBI had similar Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36) scores (bodily pain and mental health subscales) and frequency and intensity of postconcussion symptoms as patients with other traffic injuries. Rush et al[18] reported a similar result comparing neurobehavioral function and symptoms at discharge between those with MTBI and those with orthopedic injuries. These results indicate that postconcussion symptoms, pain, and mental health are similar across acute injuries and not unique or specific to MTBI.

With respect to prognosis, Brewer[16] suggests that the presence of loss of consciousness (LOC) does not impact self-reported irritability or concentration problems measured 1 month postinjury but might impact other executive functions. However, these findings are preliminary phase I findings. Landre[17] found that postconcussion symptoms reported within the first week after injuries are correlated to mental health but not bodily pain. This suggests these symptoms are related to emotional distress but not to pain severity. Rush[18] reported that neurobehavioral function and symptoms were not associated with self-ratings of personality. However, both studies are phase II and exploratory with respect to prognosis.

Up to 3 months' follow up

The 3-month follow-up period is important because the *Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision* stipulates that the criteria for a diagnosis of PCS include objective evidence of declines on neuropsychological testing, including difficulty in attention or memory, and 3 or more subjective symptoms present for at least 3 months (ie, fatigue; disordered sleep; headache; vertigo or dizziness; irritability or aggression with little or no provocation; anxiety, depression, or affective liability; changes in personality [eg, social or sexual inappropriateness]; or apathy or lack of spontaneity).[19] We accepted 5 studies[20-24] that followed up patients for up to 3 months. Outcomes included various subjective symptoms (table 2). Two studies[20,24] were from the United States, 2[21,22] were from Canada, and 1 study[23] was from Sweden. All are phase II cohort studies except for the study by Nygren-de Boussard et al,[23] which is a phase I cohort study.

Four of these studies[20-23] compared patients with MTBI to uninjured controls, and Davis[20] also included a second control group of patients with other injuries. Four studies[20,21,23,24] recruited acute patients seen at hospitals, but Lange et al[22] recruited patients referred to an early intervention clinic. Two of these studies[20,21] found little difference in postconcussion symptoms reported after injury when comparing patients with MTBI and controls, although Davis[20] found that patients with MTBI tended to underreport existing symptoms before their injury when compared with healthy controls. They also found that patients with MTBI attribute more of their preinjury somatic symptoms to the injury and endorse more memory symptoms. Kashluba et al[21] found that patients with MTBI improved substantially and did not endorse significantly more postconcussion symptoms than controls at 3 months postinjury. However, they did have a higher incidence of doing things more slowly, fatiguing quickly, and having poor balance compared with controls. Also, more patients with MTBI endorsed at least 1 symptom in the severe range compared with controls (39% vs 15%). However, Lange[22] showed that even though patients with MTBI endorse more symptoms than healthy controls, they recall fewer symptoms than controls before injury. They concluded that patients with MTBI misperceive their preinjury status as better than the average, and they called this the "good-old-days" bias because of the potential of misattributing symptoms to the injury. The weight of this evidence suggests that postconcussion symptoms are not specific to MTBI, and clinicians should be cautious about attributing common

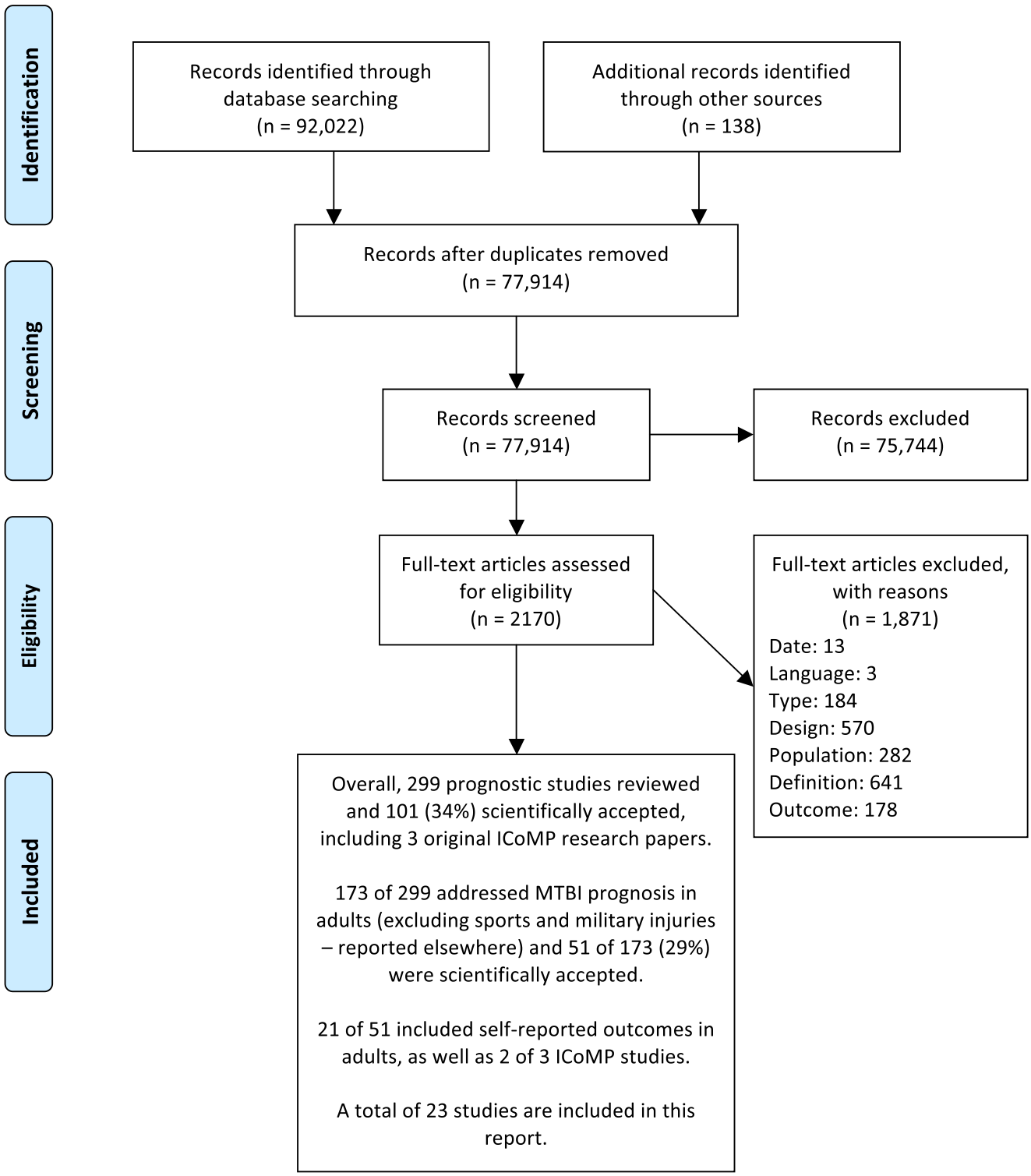

Fig 1 PRISMA flow diagram of literature inclusion/exclusion.

postinjury symptoms to the MTBI. This calls into question the validity of diagnosing PCS.

Nevertheless, postconcussion symptoms are troublesome for patients. Dischinger et al[24] followed up 180 patients with MTBI to see how many developed PCS 3 months after the injury. They defined PCS as having 4 or more symptoms that could include any of 6 physical symptoms (headache, dizziness, blurry/double vision, fatigue, sensitivity to light, sensitivity to noise), 3 cognitive symptoms (difficulty concentrating, memory problems, trouble thinking), or 3 emotional symptoms (anxiety, depression, irritability). At baseline, 84.2% had 4 or more postconcussion symptoms. At 3 months, 41.4% had PCS, and it was associated with

Table 1 Prognostic studies of self-reported outcomes in adults with up to 1 month of follow up

Author, Year, Country	Source Population, Study Size, Participation, F/U	Inclusion/Exclusion Criteria	MTBI Case Definition	Prognostic Factors/Self-Reported Outcomes	Findings
Brewer et al,[16] 2002; U.S.	Convenience sample from university hospital ED (n=40) F/U: 24h, 48h, and 1mo	Inclusion: age 18–59y, 21 male, 19 female, understand English, sufficient motor facility to manipulate Tinkertoys and paper and pencil. 25/40 (63%) had LOC. Exclusion: history of MTBI in last 6mo, substance abuse, domestic abuse, major psychiatric disorder, general anesthesia within 5y, or taking prescription drugs that alter cognition	Physiological disruption of brain function followed by disturbance or LOC <10min; PTA <24h; mild alteration in mental status (eg, feeling dazed, disoriented, confused immediately after injury); GCS (if available) 13–15	Prognostic factors: LOC present or absent Outcomes: irritability measured by items from 3 inventories: PHIQ (2 questions), MDI, and AFI (2 questions). Subjective measures of executive function were made using the AFI and PHIQ.	30% self-reported irritability at 24h postinjury, and it was still 30% at 1mo. 60% self-reported concentration problems at 24h compared with 20% by 1mo. Phase I cohort: LOC did not impact self-reported irritability or concentration on the MDI. More LOC patients complained of more executive-type difficulties on the PHIQ at 1mo (28% LOC vs 18% no LOC).
Landre et al,[17] 2006; U.S.	Consecutively admitted trauma patients at a level 1 trauma center recruited August 1998 through May 2000 MTBI group: n=37; 34 had other injuries, 86% were injured in an MVC, and 63% had some LOC. Trauma group: n=39; 65% injured in an MVC Average F/U of 4–5d postinjury	Inclusion: between the ages of 18 and 60y, fluent in English, and obtained a minimum score of 20 on the Mini-Mental State Examination Exclusion: positive findings on brain CT, histories of premorbid neurologic disorder (including moderate to severe TBI), psychiatric disorder, developmental disability; presence of MTBI case definition exclusion criteria	American Congress of Rehabilitation Medicine, 1993: at least 1 of the following: (1) any period of LOC; (2) any loss of memory for events immediately before or after the accident; (3) any alteration in mental state at the time of the accident (eg, feeling dazed, disoriented, or confused); (4) focal neurologic deficit(s) that may or may not be transient. Exclusions: (1) LOC >30min; (2) GCS <13 after 30min; (3) PTA >24h	Prognostic factors: injury status (MTBI vs control) Outcomes: bodily pain and mental health subscales of the SF-36 and a modified version of the PCSC	Phase II cohort: There were no significant differences between groups on the SF-36 bodily pain or mental health subscale scores. Both groups scored low on the PCSC, and there was no difference between them with respect to frequency, intensity, or duration of symptoms. PCSC scores were correlated to the SF-36 mental health subscale, but not the bodily pain subscale. This suggests that PC symptoms are related to emotional distress but not to pain severity.
Rush et al,[18] 2004; U.S.	Consecutive hospital admissions for MTBI (n=87) or OI (n=82) F/U: to hospital discharge	Inclusion: consented to participate, sustained either OI or MTBI requiring hospitalization	Diagnosis of TBI (as evidenced by abnormality on neurologic examination consistent with external trauma); GCS ≥13; absence of injury-related intracranial abnormality on CT scan	Prognostic factors: preinjury personality traits (NEO-PI-R completed by injured and significant other) Outcomes: neurobehavioral function and symptoms measured by the NFI	Phase II cohort: Self-ratings on the NFI did not differ between the OI and the MTBI groups. Self-ratings of personality did not predict NFI scores. Results suggest that early neurobehavioral symptoms after MTBI are related to the injury experience rather than the MTBI.

Abbreviations: AFI, Attention Function Index; CT, computed tomography; F/U, follow-up; MDI, Multiscore Depression Inventory; MVC, motor vehicle collision; NEO-PI-R, NEO Personality Inventory—Revised; NFI, Neurobehavioral Functioning Inventory; OI, orthopedic injury; PC, postconcussion; PCSC, Postconcussion Symptom Checklist; PHIQ, Philadelphia Head Injury Questionnaire; U.S., United States.

Table 2 Prognostic studies of self-reported outcomes in adults with up to 3 months of follow up

Author, Year, Country	Source Population, Study Size, Participation, F/U	Inclusion/Exclusion Criteria	MTBI Case Definition	Prognostic Factors/Self-Reported Outcomes	Findings
Davis,[20] 2002; U.S.	Acutely injured patients (n=171) were recruited at University of California, Davis, Medical Center MTBI: n=102 Other injuries: n=69 Age-matched controls (uninjured): n=115 recruited from community. Baseline measures were made 1wk postinjury for all groups, and the MTBI group was followed up at 3mo.	Inclusion: age 18–65y, English speaking, completion of preinjury and postinjury PCSQ, and biographic information 1wk after the injury Exclusion: past psychiatric hospitalization, hospitalization for substance abuse or dependency, or prior hospitalization for head injury	American College of Rehabilitation Medicine criteria for MTBI—at least 1 of the following: (1) any period of LOC; (2) any loss of memory for events before/after accident; (3) any alteration in mental status at time of accident; (4) focal neurologic injuries that may or may not be transient. Severity of injury must not exceed (1) LOC for 30min; (2) initial GCS 13–15 at 30min after injury; and (3) PTA of 24h.	Prognostic factors: injury status (MTBI vs other injuries) Outcomes: symptoms reported on the PCSQ Participants were asked to rate their preinjury symptoms and their postinjury symptoms at 1wk. MTBI group was also measured at 3mo.	There were no significant differences between groups on postinjury PCSQ scores at 1wk. At 3mo, the MTBI group attributed more of their preinjury somatic symptoms to the injury and endorsed more memory symptoms. Phase II cohort: When compared with controls, both trauma groups endorsed significantly fewer symptoms in describing their preinjury status.
Dischinger et al,[24] 2009; U.S.	180 MTBI patients admitted to a level 1 trauma center Baseline measures were made within 3–10d postinjury and F/U at 3mo postinjury.	Inclusion: age 18–64y, acceptable score on Mini-Mental State Examination, and English speaking Exclusion: brain lesion requiring intervention; moderate/severe multiple injuries; focal neurologic findings; skull fracture requiring clinical intervention; cerebrospinal fluid leak requiring clinical intervention; prior moderate or severe brain injury; new or prior seizures; history of psychiatric disorder requiring hospitalization, or hallucinations; recent history of substance abuse; current probation/parole; and active duty in military	American College of Rehabilitation Medicine definition: see previous	Prognostic factors: PCS—6 physical (headache, dizziness, blurry/double vision, fatigue, sensitivity to light, sensitivity to noise), 3 cognitive (difficulty concentrating, memory problems, trouble thinking), and 3 emotional (anxiety, depression, irritability). Also sociodemographic factors: age, sex, education, history of substance abuse and depression Outcomes: PCS defined by 4 or more PC symptoms.	At baseline, 84.2% had 4 or more PC symptoms, and 41.4% reported PCS at 3mo. Phase II cohort: PCS was associated with noise sensitivity (OR=3.06; 95% CI, 1.09–9.04) and female sex (OR=2.4; 95% CI, 1.10–5.32). Anxiety was associated with PCS in women only (OR=48.66; 95% CI, 7.50–315.8).
Kashluba et al,[21] 2004; Canada	MTBI patients were drawn from consecutive admissions to 2 hospital emergency wards to participate in an RCT (n=118). Control group: n=118 uninjured adult	Inclusion: 118 MTBI patients and controls enrolled in an RCT Exclusion: history of inpatient treatment for psychiatric disorder, mental retardation, inability to read English,	American Congress of Rehabilitation Medicine (1993)*	Prognostic factors: PCL, which measures incidence and severity of symptoms of PCS Outcome: PCL at 3mo	Overall, the MTBI patients improved substantially by 3mo and did not differ much from healthy controls. Phase II cohort: At F/U, MTBI patients did not endorse

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Table 2 (*continued*)

Author, Year, Country	Source Population, Study Size, Participation, F/U	Inclusion/Exclusion Criteria	MTBI Case Definition	Prognostic Factors/Self-Reported Outcomes	Findings
	participants recruited from university, hospital, and municipal government workplaces; matched on age, sex, years of education, and socioeconomic status to patients F/U: to 3mo	history of TBI more severe than an MTBI, an MTBI within 1y before study, any central nervous system disorder, and concurrent pregnancy			significantly more PCL symptoms than controls (group means: 14.09±10.77 vs 12.56±8.46). MTBI patients had a higher incidence of doing things more slowly, fatiguing quickly, and having poorer balance than controls. More MTBI patients endorsed at least 1 symptom in the severe range compared with controls (39% vs 15%). Poor balance and slowness best differentiated MTBI from controls.
Lange et al,[22] 2010; Canada	MTBI patients (n=86) referred to a hospital-based, early intervention concussion clinic Controls (n=177) recruited from university and local community Patients were evaluated on average 1.8mo after their injury.	Inclusion: patients evaluated within 8mo of injury (most evaluated within 3mo of injury) and fluent in English Controls excluded if they had mental health problems, substance abuse, or neurologic problems	WHO Collaborating Centre Task Force on MTBI, including: (1) 1 or more of the following: confusion or disorientation, LOC ≤30min, PTA <24h, and/or other transient neurologic abnormalities such as focal signs, seizure, and IC lesion not requiring surgery; and (2) GCS 13–15 after 30min postinjury or later on presentation for health care	Prognostic factor: litigation Outcomes: preinjury and postinjury frequency and intensity of 13 PC symptoms measured by BC-PSI	MTBI patients' preinjury BC-PSI total scores were significantly lower than control subjects' total scores (small effect size, .27). Preinjury symptoms most frequently present: Control group: fatigue (39%), headache (26.6.%), and poor sleep (32.8%) MTBI group: fatigue (25.6%), irritability (25.6%), headache (20.9%), and poor sleep (30.2%) Postinjury, the MTBI group complained of more symptoms: fatigue (76.7%), irritability (74.4%), headache (80.2%), and poor sleep (73.3%). Phase II cohort: Patients in litigation (n=34) reported more postinjury symptoms (medium-large effect size, .63), even though they did not have a more serious injury at baseline (ie, LOC, PTA, or abnormal CT scan

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Table 2 (*continued*)

Author, Year, Country	Source Population, Study Size, Participation, F/U	Inclusion/Exclusion Criteria	MTBI Case Definition	Prognostic Factors/Self-Reported Outcomes	Findings
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Nygren-de Boussard et al,[23] 2005; Sweden	MTBI patients (n=122) consecutively recruited from 3 hospital EDs from January 2000 through December 2001 Noninjured controls (n=35) of similar age, sex, and socioeconomic status used to standardize S100 serum protein levels F/U: 3mo	Included patients with blunt trauma to the head seen within 24h of injury, and age 15–65y. Included controls aged 15–65y, in good health, and no history of recent head trauma Excluded patients with no clear history of blunt trauma, or other major injuries, or major neurologic disorders. Those with prior or current psychiatric illness or alcohol dependence were not excluded.	MTBI: blunt head trauma with GCS 14–15, LOC no more than 30min, PTA no more than 24h	Prognostic factors: S100B and S100A1B (reference values determined as ≤97.5 percentile of uninjured controls) Outcome: PC symptoms assessed by RPSQ	31% of patients had S100B concentrations above the cutoff, and 48% had S100A1B concentrations above cutoff. 44% reported at least 1 cognitive symptom on the RPSQ at day 1, 45% on day 7, 27% on day 14, and 26% at 3mo. Phase I cohort: no association between S100 and cognitive symptoms. Self-reported cognitive symptoms were not associated with objective cognitive testing results.

Abbreviations: BC-PSI, British Columbia Postconcussion Symptom Inventory; CI, confidence interval; CT, computed tomography; F/U, follow up; IC, intracranial; OR, odds ratio; PC, postconcussion; PCL, Problem Checklist; PCSQ, Postconcussion Symptom Questionnaire; RCT, randomized controlled trial; RPSQ, Rivermead Postconcussion Symptoms Questionnaire; U.S., United States.

* Mild Traumatic Brain Injury Committee, Head Injury Interdisciplinary Special Interest Group, American Congress of Rehabilitation Medicine. Definition of mild traumatic brain injury. J Head Trauma Rehabil 1993;8:86-7.

female sex, baseline noise sensitivity, and baseline anxiety in women only. Furthermore, Lange et al[22] found that patients in litigation report more postconcussion symptoms than MTBI nonlitigants. All this highlights the complexity of symptom attribution after MTBI and the interactions of biopsychosocial issues.

Finally, Nygren-de Boussard et al[23] reported a phase I study of the relationship between the serum concentrations of proteins S100A1B and S100B and prognosis. S100 proteins are biochemical markers of acute brain injury, and if present and associated with cognitive impairment, might be used as a prognostic marker. Baseline S100A1B and S100B serum concentrations were elevated in 48% and 31% of the patients, respectively, and 44% reported at least 1 cognitive symptom at baseline and 26% at 3 months. However, there was no association between elevated S100 levels and cognitive symptoms at any time point. This suggests that these markers are not useful in MTBI prognosis with respect to subjective outcomes.

Up to 6 months' follow up

Six studies were accepted that reported follow up of patients for up to 6 months, including 2 from the United Kingdom,[25,26] and 1 each from Israel,[27] New Zealand,[28] The Netherlands,[29] and Canada.[30] Five are phase II studies and 1 is a phase I study. Outcomes included functional disability measured by the Glasgow Outcome Scale, posttraumatic symptoms, posttraumatic stress disorder (PTSD), PCS (ie, defined by ≥3 symptoms on the Rivermead Postconcussion Symptoms Questionnaire [RPSQ]), self-reported symptoms, and community integration (table 3). None of these studies included control groups, and they all included acute patients recruited from hospitals.

With respect to course and prognosis, Gil et al[27] showed that by 6 months, 14% of patients with MTBI had developed PTSD. It was more prevalent in those with a memory of the injury event (23%) than those without memory (6%). This difference was primarily due to the "reexperiencing" cluster of symptoms. PTSD was also associated with acute posttraumatic symptoms, anxiety, depression, and a history of psychiatric disorder. Hou et al[26] found that PCS was present in 22% of patients at 3 months and 21% at 6 months. Fatigue, forgetfulness, and sleep disturbance were most commonly reported at 3 months, and PCS was associated with self-reported activity levels. Headache, fatigue, and sleep disturbance were most commonly reported at 6 months, and PCS at 6 months was associated with negative head injury perceptions. These results suggest that cognitive and behavioral responses to MTBI might be more important in the development of PCS than demographics, injury severity, and other emotional and social factors. Norrie et al[28] found that fatigue prevalence diminished from 67.3% at 1 week to 29.6% at 3 months and 26.4% at 6 months. Further, fatigue severity and depression measured at 3 months were associated with fatigue prevalence at 6 months. All of these studies indicate that postconcussion symptoms continue to persist in 14% to 26% of patients with MTBI at 6 months.

Table 3 Studies of self-reported outcomes in adults with up to 6 months of follow up

Author, Year, Country	Source Population, Study Size, Participation, F/U	Inclusion/Exclusion Criteria	MTBI Case Definition	Prognostic Factors/Self-Reported Outcomes	Findings
de Silva et al,[25] 2009; UK/global	8927 TBI patients from 46 high-, middle-, and low-income countries from the multicentered CRASH trial; n=2676 with MTBI F/U: to 6mo postinjury	Inclusion: ≥16y of age and GCS ≤14. Exclusion: patients who had a disability that was not caused by their TBI	GCS 13–14	Prognostic factors: countries were classified using the *World Bank Atlas* as either high-income (GNP* ≥$10,066) or middle-/low-income country (GNP* ≤$10,065). Outcomes: GOS: disability defined as anything less than good recovery	60% of MTBI patients in high-income countries had good recovery compared with 78% in middle-/low-income countries. Phase II cohort: The risk of moderate disability (OR=.41; 95% CI, .30–.56) and severe disability (OR=.41; 95% CI, .23–.72) was less for MTBI patients in middle-/low-income vs high-income countries.
Gil et al,[27] 2005; Israel	120 MTBI patients recruited from 2 surgical wards of a hospital F/U: 1wk, 1mo, and 6mo	Inclusion criteria: age 18–50y and fluent in Hebrew Exclusion criteria: actively receiving psychiatric care, prior history of head trauma, cognitive deficit, substance abuse, and major untreated medical condition	MTBI defined as GCS 13–15 at the time of admission. None had LOC at the time of admission.	Prognostic factors: memory of the injury event within the first 24h of injury. Also, measures of depression and anxiety at 1wk using BDI and BAI, acute posttraumatic symptoms using PTSS and the CA-PTSDS, history of psychiatric disorder, age, sex, education, Injury Severity Score, marital status, country of origin, history of physical illness Outcome: PTSD diagnosis based on CA-PTSDS and PTSS	By 6mo, 14% had developed PTSD. PTSD was more prevalent in those with a memory of the injury event (23%) than those without memory (6%). This difference was primarily due to "reexperiencing" cluster of symptoms. Phase II cohort: PTSD was associated with memory of event (OR= 2.2; 95% CI, 1.0–10.1), acute posttraumatic symptoms (OR=5.3; 95% CI, 1.1–9.3 for CA-PTSDS; and OR=5.2; 95% CI, 1.0–9.4 for PTSS), anxiety (OR=4.9; 95% CI, 1.0–9.1), depression (OR=5.1; 95% CI, 1.0–9.2), and history of psychiatric disorder (OR=3.7; 95% CI, 1.1–8.9)
Hou et al,[26] 2012; UK	MTBI patients (N=126) seen at an ED of a general hospital F/U: 3 and 6mo	Inclusion: age 18–60y Exclusion: those with multitrauma requiring hospitalization and those with major neurologic or psychiatric disorders	Traumatically induced physiological disruption of brain function with at least 1 of the following: LOC ≤15min, PTA ≤60min, any alteration in mental state at the time of the injury, lack of focal neurologic deficit, and GCS 13–15	Prognostic factors: BIPQ measures patients' perceptions of their injury, BRIQ measures behavior after onset of illness/injury and the "all or nothing" subscale measures patterns of activity and rest, HADS, IES measures distress after the injury, Brief SSQ measures perceived social support including availability and satisfaction, sex, age, GCS 14	PCS was present in 22% at 3mo and 21% at 6mo. Fatigue, forgetfulness, and sleep disturbance were most commonly reported at 3mo. Headache, fatigue, and sleep disturbance were most commonly reported at 6mo. No significant recovery from PCS occurred from 3 to 6mo. Phase II cohort: At 3mo, the baseline

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Table 3 (*continued*)

Author, Year, Country	Source Population, Study Size, Participation, F/U	Inclusion/Exclusion Criteria	MTBI Case Definition	Prognostic Factors/Self-Reported Outcomes	Findings
				or 15, LOC, PTA, education, marital status, occupation, and litigation status Outcome: PCS defined by ICD-10 criteria of ≥3 of headache, dizziness, fatigue, irritability, insomnia, concentration problems, memory difficulty, or intolerance of stress, emotion or alcohol measure using RPSQ	"all or nothing" subscale score of the BRIQ was the only variable associated with PCS (OR=1.14; 95% CI, 1.05–1.24; *P*=.002). At 6mo, negative head injury perceptions from the BIPQ were associated with PCS (OR=1.05; 95% CI, 1.01–1.10; *P*=.02). Cognitive and behavioral responses to head injury might be more important in the development of PCS than emotional and social factors.
Norrie et al,[28] 2010; New Zealand	MTBI patients (N=159) seen in the ED of a hospital over a 2-y period. F/U: 3 and 6mo	Inclusion: patients with full F/U data and did not report confounding temporary illnesses over the F/U period Exclusion: abnormal CT scan findings, intake of psychoactive drugs or history of drug abuse, central neurologic or psychiatric condition, skull/facial fracture, and trauma to other parts of body	GCS 13–15, LOC <20min, and PTA <24h	Prognostic factors: early fatigue severity assessed at 1wk by the FSS, depression and anxiety measured by the HADS Outcome: fatigue prevalence defined as a F/U score of ≥2 on the RPSQ –item 6 about fatigue	Fatigue prevalence diminished from 67.3% at 1wk to 29.6% at 3mo. It remained relatively stable at 26.4% at 6mo. Phase II cohort: Fatigue severity and depression at 3mo were associated with fatigue prevalence at 6mo. Anxiety at 3mo was not associated with fatigue at 6mo.
Stulemeijer et al,[29] 2008; The Netherlands	MTBI patients (N=201) admitted to a level 1 trauma center F/U: 6mo postinjury	Inclusion: age 18–60y, able to speak and write in Dutch, no premorbid mental retardation or dementia Exclusion: questionnaires that were completed >6wk postinjury	European Federation of Neurological Societies' definition of MTBI: history of impact to head with or without LOC ≤30min, with or without PTA, and admission GCS of 13–15	Prognostic factors: 1. Preinjury: age, sex, education, emotional problems, physical comorbidities, or prior head injury 2. Peri-injury: GCS, LOC, PTA duration, brain CT abnormality, early symptoms (ie, dizziness, nausea/vomiting, headache), additional extracranial injuries (ie, score ≥2 on the AISS) 3. Early postinjury: PC symptoms (RPSQ), posttraumatic stress (IES	64% reported full recovery (ie, absence of PC symptoms). Phase II prediction rule: Absence of comorbid physical problems (OR=3.5; 95% CI, 1.6–7.8), low levels of early PC symptoms (OR=5.5; 95% CI, 2.3–13.2), and low levels of early posttraumatic stress (OR=10.0; 95% CI, 2.3–42.9) predicted low PC symptoms

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Table 3 (*continued*)

Author, Year, Country	Source Population, Study Size, Participation, F/U	Inclusion/Exclusion Criteria	MTBI Case Definition	Prognostic Factors/Self-Reported Outcomes	Findings
				with scores >26 classified as severe), severe fatigue (AFQ with a cutoff value of 20), pain severity score in 5 body regions), self-efficacy (ie, GSES median split) Outcome: RPSQ: recovered defined as a score <3 on at least 13 of 16 PC symptoms	(ie, 90% chance of remaining free of PCS). Discriminative ability was good with AUC=.73. The rule identified patients with a 90% probability of low PC symptoms at 6-mo F/U.
Tellier et al,[30] 2009; Canada	MTBI patients (N=125) presenting to the ED of a trauma center F/U: 6mo	Inclusion: patients presenting to ED and agreed to participate	MTBI defined as lowest GCS 13−15, LOC <30min, and PTA up to 24h	Prognostic factors: GCS 15 vs GCS 13−14; PTA length (≤30min, >30min), prior TBI Outcomes: self-reported symptoms assessed with the NFI, CIQ Productivity Scale, and a postconcussive checklist developed by the authors, including measures of fatigue, disordered sleep, headaches, vertigo or dizziness, irritability, and changes in mood or personality	Phase I cohort: GCS score was not associated with symptom differences at 6mo. At 6mo, those with longer PTA showed greater aggressive and disinhibited behaviors on the NFI. Prior TBI not associated with self-reported outcomes

Abbreviations: AFQ, Abbreviated Fatigue Questionnaire; AISS, Abbreviated Injury Severity Score; AUC, area under the curve; BAI, Beck Anxiety Inventory; BDI, Beck Depression Inventory; BIPQ, Brief Illness Perception Questionnaire; BRIQ, Behavioral Response to Illness Questionnaire; CA-PTSDS, Clinician-Administered Posttraumatic Stress Disorder Scale; CI, confidence interval; CIQ, Community Integration Questionnaire; CRASH, Corticosteroid Randomization After Significant Head injury; CT, computed tomography; FSS, Fatigue Severity Scale; F/U, follow up; GNP, gross national product; GOS, Glasgow Outcome Scale; GSES, General Self-Efficacy Scale; HADS, Hospital Anxiety and Depression Scale; ICD-10, *International Statistical Classification of Diseases, 10th Revision*; IES, Impact of Event Scale; NFI, Neurobehavioral Functioning Inventory; OR, odds ratio; PC, postconcussion; PTSS, Posttraumatic Stress Scale; RTW, return to work; SSQ, Social Support Questionnaire; UK, United Kingdom.

* Millions of U.S. dollars.

However, all of these studies are phase II and require confirmation.

Three other studies followed up patients for up to 6 months. De Silva et al[25] compared functional outcomes after more severe MTBI (GCS score, 13−14) across low-, middle-, and high-income countries using the Glasgow Outcome Scale. In this phase II study they found that 6-month recovery was better in patients from low-income countries compared with high-income countries (78% vs 60%). They speculate that sociocultural or environmental factors are responsible. Tellier et al[30] compared 6-month outcomes in patients with MTBI with GCS scores of 13 or 14 with those with a GCS score of 15 and found no difference in postconcussion symptom prevalence. However, they did find that those with longer posttraumatic amnesia (PTA) showed greater aggressive and disinhibited behaviors. This is a phase I study, and the results should be viewed as exploratory.

Finally, the study by Stulemeijer et al[29] deserves special attention. They developed and internally validated a clinical prediction rule for good recovery, defined as a score of 0 (no problem), 1 (not a problem anymore), or 2 (mild problem but not interfering with daily activities) on 13 of 16 postconcussion symptoms measured by the RPSQ. If the patient did not have any preinjury comorbid physical problems, had low levels of early postconcussion symptoms (ie, a score of 0 [no problem], 1 [not a problem anymore], or 2 [mild, but not interfering with daily activities] on at least 13 of the 16 postconcussion symptoms measured by the RPSQ), and had low levels of early posttraumatic stress, they had a 90% chance of a good recovery. LOC, GCS, PTA, and abnormal computed tomography findings did not predict recovery. These results show that early identification of patients with MTBI who are likely to have good recovery is feasible, but Stulemeijer's prediction rule needs to be validated in another setting before it can be recommended for widespread use.

Up to 1-year follow up

Six accepted cohort studies reported 1-year follow up of patients, including 3 studies from Canada,[14,15,31] 2 from the United States,[32,33] and 1 study from Lithuania[34] (table 4). One is a phase III study,[32] 3 are phase II studies,[14,33,34] and 2 are phase I studies.[15,31] Outcomes include self-reported recovery, levels of fatigue, perceived activities and behaviors, satisfaction with reintegration to normal living, posttraumatic stress, psychiatric impairment, postconcussion symptoms, depressive symptomatology, health care use, PCS as defined by >3 symptoms on the RPSQ, and the prevalence of posttraumatic headache (PTHA).

Two studies report on a population-based cohort of MTBI after traffic collisions from the Canadian province of Saskatchewan. Cassidy et al[14] found that the median time to self-reported recovery was 100 days in this cohort, and about 23% reported not being recovered by 1 year. Hartvigsen et al[15] found that the most common symptoms reported by those not recovered at 1 year were sleep disturbances (44%), tiredness (39%), forgetfulness (27%), dizziness (25%), neck pain (25%), and low back pain (19%). Some of these symptoms might be due to coexisting whiplash injuries to the spine. They also reported that more than 50% of these symptomatic participants reported more than 3 symptoms. Most who continued to seek care for their symptoms at 1 year postinjury were seeing medical doctors, although a substantial number were also seeking care from physical therapists, registered massage therapists, and chiropractors. In a phase II analysis of prognostic factors from the same cohort, Cassidy[14] found that prolonged recovery was associated with age >50 years, less education, poor expectations for recovery, depressive symptomatology, hearing problems, arm numbness, confusion, headache intensity, low back pain intensity, and mid-back pain intensity. Sex, LOC, and PTA were not associated with recovery. Overall, these results suggest that traffic-related MTBI occurs with other injuries to the neck and back, and expectation for recovery, depression, and somatic complaints determine the outcome.

The remaining 4 studies all had control groups to compare to patients with MTBI recruited from emergency departments (EDs). One phase III prognostic study[32] focused on fatigue and compared 173 patients with MTBI and no PTA or LOC, with 58 patients with LOC ≤30 minutes and/or PTA <24 hours and 128 patients with other mild nonhead injuries. By 1-year follow up, levels of fatigue were slightly higher in the group with MTBI and no LOC or PTA, but all groups were still within population norms indicating low levels of fatigue. Worse fatigue at 1-year follow up was associated with preinjury fatigue, marital status, lawyer involvement, and baseline poor medical and mental health, but not with type of injury. These results confirm that postinjury fatigue is no worse in MTBI than in other injuries and is associated with psychosocial factors.

Using the same injury cohort as de Leon et al,[32] McLean et al[33] examined prognostic factors associated with persistent PCS 1 year after injury. They compared 251 patients with MTBI to 256 patients with minor nonhead injuries. Outcomes included PCS defined as ≥3 symptoms rated as at least mild on the RPSQ, mental and physical health measured by the SF-36, and level of cognitive symptoms measured by the Sickness Impact Profile—Alertness Behavior subscale. Compared with non−head-injured patients, those with MTBI had slightly worse mental and physical health at 1 year. They also reported more postconcussion symptoms (RPSQ, 13.9 vs 3.7) and had a higher incidence of PCS (≈56% vs ≈28%) at 1 year postinjury. In the combined cohort of 507 patients, baseline mental and physical health was associated with PCS and cognitive symptoms, but having an MTBI was not. The findings of this phase II study are in agreement with those of previous studies with short-term outcomes that suggest that the development of PCS and cognitive symptoms are not specific to head injury. In another study, Friedland and Dawson[31] came to a similar conclusion after comparing 64 patients with MTBI to 35 non−head-injured patients and following them up to between 6 and 9 months postinjury. In this phase I study, patients with symptoms of posttraumatic stress did not do well in terms of functional outcome regardless of injury type. The patients with MTBI were not particularly worse off compared with those with other injuries, but they did have lower psychosocial scores on the Sickness Impact Profile but no other significant difference on outcomes.

Finally, Stovner et al[34] used historical and prospective cohort designs to measure the prevalence of PTHA in patients with MTBI and patients with orthopedic injuries. Both studies indicate that PTHA prevalence is similar in patients with MTBI and in orthopedic-injured patients. In the historical cohort, more than 90% of all patients had recovered from their PTHA by 1 month. In the prospective cohort, 10% of patients with MTBI and 12% of orthopedic-injured patients complained of persistent headache (ie, >15d/mo) after 1 year. Although photophobia was more common in patients with MTBI, there were no other differences among groups with respect to frequency or types of symptoms at 1 year. The authors conclude that headache occurring more than 3 months

Table 4 Studies of self-reported outcomes in adults with up to 1 year of follow up

Author, Year, Country	Source Population, Study Size, Participation, F/U	Inclusion/Exclusion Criteria	MTBI Case Definition	Prognostic Factors/Self-Reported Outcomes	Findings
Cassidy et al,[14] 2013; Canada	MTBI patients (N=1716) treated after a traffic injury F/U: 6wk, 3, 6, 9, and 12mo	Inclusion: all Saskatchewan residents aged ≥18y or older who were treated for, or made an insurance claim for, a traffic injury over a 2-y period Exclusion: those who made a claim, or were treated for a traffic injury more than 42d after the collision, or sustained a serious injury (ie, died, could not answer questionnaire because of injury), or could not understand English. Also excluded were workers' compensation claims and those with LOC >30min.	Answered yes to "Did you hit your head in the collision" and answered "yes" or "don't know" to 1 of the following: LOC, PTA, disorientation or confusion. Also had to answer, "yes" to having at least 1 of the following symptoms: dizziness or unsteadiness, memory problems or forgetfulness, and concentration or attention problems.	Prognostic factors: demographics (age, sex, income, marital status, education), position in vehicle, days in hospital, symptoms (checklist of PC symptoms), fractured bones, LOC, PTA, pain intensity (NRS-11: neck, headache, face, low back, midback, arms, hands, leg, foot, and abdomen, chest, or groin), prior health, current health, expectations for recovery, depression (CES-D cut point 16), and number of comorbid health conditions. Outcomes: self-reported recovery (ie, "all better or cured" or "very much improved")	Course: Median time to recovery was 100d (95% CI, 97–103). Phase II cohort: Factors associated with recovery were age >50y vs 18–23y (HRR=.76; 95% CI, .63–.91); > high school education vs some high school (HRR=1.24; 95% CI, 1.07–1.44); expectations for recovery—(1) never get better (HRR=.26; 95% CI, .14–.50), (2) don't know when will get better (HRR=.52; 95% CI, .43–.63), and (3) will get better slowly (HRR=.79; 95% CI, .67–.94) compared with (4) get better soon; depression (HRR=.99; 95% CI, .99–1); arm numbness (HRR=.83; 95% CI, .73–.94); hearing problems (HRR=.75; 95% CI, .59–.96); confusion after collision—don't know (HRR=.78; 95% CI, .62–.96) vs none; low back pain intensity (HRR=.97; 95% CI, .95–.98); headache intensity (HRR=.98; 95% CI, .96–1); and mid-back pain intensity (HRR=.97; 95% CI, .95–.99).
de Leon et al,[32] 2009; U.S.	Patients (N=359) from level 2 trauma center at community hospital ED. N1=58: MTBI with LOC ≤30min, and/or PTA <24h. N2=173 MTBI with no PTA/LOC. N3=128 other mild non-head injuries (25% sprains, 24%	Inclusion: age ≥18y, presented within 24h of injury, GCS ≥13, did not require adult trauma team, discharged directly from ED, Mini-Mental State Examination of at least 18, and able to describe elements of the study to a research assistant. Exclusion: transfer from another hospital, non-English speaking, being incarcerated, hospital admission, evidence of still being in a state of PTA, LOC ≥30min, or LOC	CDC criteria: GCS ≥13 on ED arrival and ≥1 of the following: (1) LOC ≤30min, (2) PTA, or (3) ≥2 PC symptoms (symptoms rated at least "mild" on RPSQ). Patients without direct head impact injury but with LOC/PTA caused by trauma were classified as having MTBI if there was no other demonstrable cause for LOC.	Prognostic factors: injury group, preinjury health status variables including baseline fatigue; medical variables including having a past medical disability or a history of psychological or mental health problems, ISS, injury characteristics and cause; demographic variables including age, sex, education, marital status, employment status, and ethnicity; and litigation status Outcome: fatigue measured by SF-36	SF-36 vitality scores for all injured patients were within population norms by 12-mo F/U. The less severe MTBI group (N2) with no PTA/LOC had more fatigue (lower mean score ± SD) at 12mo than the other groups: N1=52.3±12.22; N2=49.6±11.83; N3=53.0±10.37. Phase III cohort: Worse fatigue at 12mo was associated with preinjury fatigue, marital status (ie,

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Table 4 (*continued*)

Author, Year, Country	Source Population, Study Size, Participation, F/U	Inclusion/Exclusion Criteria	MTBI Case Definition	Prognostic Factors/Self-Reported Outcomes	Findings
	contusions, 16% lacerations, 21% closed fractures, 14% others). F/U: 12mo	not attributable to trauma		vitality subscale.	separated, divorced, or widowed), lawyer involvement, and baseline poor medical and mental health. Having a head injury did not result in more fatigue than having a non-head injury. Psychosocial factors were associated with more fatigue.
Friedland et al,[31] 2001; Canada	MTBI patients (n=64) admitted to tertiary hospital after MVC Non–head-injured controls (n=35) admitted to the same hospital after MVC F/U: 6 to 9mo	Inclusion criteria: admission to hospital after an MVC, age 19–65y, and English speaking Exclusion: prior history of head injury, neurologic disease or hospitalization for psychiatric illness, severe disfigurement, amputation, or spinal cord injury. Non-TBI group excluded if they had LOC, PTA, GCS <15, abnormal CT scan findings if taken, or documented brain injury in medical chart	American Congress of Rehabilitation Medicine criteria: GCS of 13–15 after 30min, LOC ≤30min, or PTA ≤24h	Prognostic factors: type of injury (MTBI vs other) Outcomes: SIP and RNL, IES to measure posttraumatic stress, and GHQ-12 to measure psychiatric impairment	Phase I cohort: MTBI group had lower psychosocial scores on SIP (21.1 vs 10.9) than the non-head injury group. There was no difference on the RNL or GHQ-12 across injury groups. MTBI and non-MTBI group had similar levels of posttraumatic stress. Those with no symptoms of posttraumatic stress were less likely to have lost consciousness.
Hartvigsen et al,[15] 2013; Canada	MTBI patients (N=1716) treated after a traffic injury F/U: 6wk, 3, 6, 9 and 12mo	Inclusion: all Saskatchewan residents aged ≥18y who were treated for, or made an insurance claim for, a traffic injury over a 2-y period. Exclusion: those who made a claim, or were treated for a traffic injury more than 42d after the collision, or sustained a serious injury (ie, died, could not answer questionnaire because of injury), or could not understand English. Also excluded were workers' compensation claims and those with LOC >30min.	Answered yes to "Did you hit your head in the collision" and answered "yes" or "don't know" to 1 of the following: LOC, PTA, disorientation or confusion. Also had to answer "yes" to having at least 1 of the following symptoms: dizziness or unsteadiness, memory problems or forgetfulness, and concentration or attention problems	Prognostic factors: none Outcomes: symptoms (checklist of PC symptoms, depression using CES-D cut point 16, pain at various body regions) and type of health practitioner care at follow-up interviews (MD, PT, DC, and RMT)	Most common symptoms: At 6wk: sleep disturbance (65%), tiredness (59%), neck pain (50%), headache (39%), dizziness (39%), and low back pain (35%). 75% of those with symptoms reported more than 3 symptoms. At 1y: sleep disturbances (44%), tiredness (39%), forgetfulness (27%), dizziness (25%), neck pain (25%), and low back pain (19%). More than 50% of symptomatic persons reported more than 3 symptoms. Phase I cohort: health utilization By 6wk: MD (95%), PT (42%), DC (20%), and RMT (24.4%) By 1y: >90% were seeing MDs, but combinations of care were seen in

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Table 4 (*continued*)

Author, Year, Country	Source Population, Study Size, Participation, F/U	Inclusion/Exclusion Criteria	MTBI Case Definition	Prognostic Factors/Self-Reported Outcomes	Findings
					the majority, especially MD-PT.
McLean et al,[33] 2009; U.S.	MTBI patients (n=251) from level II trauma center ED Patients (n=256) with minor injuries seen at the ED of a level II trauma center F/U: 1, 3, and 12mo	Inclusion: patients aged ≥18y and presented within 24h of minor injury Exclusion: patients scoring below 19 on the Mini-Mental Status Examination or below 76 on the Galveston Orientation and Amnesia Test indicating current PTA; non-English speaking, prisoners, hospital transfers or admissions, clinically unstable, LOC ≥30min, or not competent to consent	CDC criteria: GCS ≥13 on ED arrival and ≥1 of the following: (1) LOC ≤30min, (2) PTA, or (3) ≥2 PC symptoms (symptoms rated at least "mild" on RPSQ). Patients without direct head impact injury, but with LOC/PTA caused by trauma were classified as having MTBI if there was no other demonstrable cause for LOC.	Prognostic factors: injury group, baseline mental and physical health measured by the SF-36 Mental Component (MnCS) and Physical Component Summary (PhCS) scales, initial postconcussion symptoms measured by the RPSQ, and type of injury (MTBI vs non-head injury) Outcomes: PCS defined ≥3 symptoms rated as at least mild on the RPSQ. SIP— Alertness Behavior (ab) subscale to evaluate cognitive symptom outcomes	Compared with minor injury patients, MTBI patients had slightly worse mental (SF-36 MnCS 48 vs 51) and physical (SF-36 PhCS 50 vs 53) health. MTBI patients had more PC symptoms (RPSQ 13.9 vs 3.7) and had a higher incidence of PCS than other minor injuries (≈56% vs ≈28% at 1y postinjury). Phase II cohort: In the combined cohort of 507 patients, baseline MnCS and PhCS were associated with PCS and cognitive symptoms, but having an MTBI was not. PCS and cognitive symptoms are not specific to head injury.
Stovner et al,[34] 2009; Lithuania	Historic cohort: MTBI patients (n=131) admitted to emergency wards in a city Prospective cohort: MTBI patients (n=217) admitted to the same emergency wards in the city Patients (n=221) with orthopedic injuries not involving the head or neck admitted to the same emergency wards F/U: 3mo and 1y	Inclusion: Historical cohort: age 18—67y admitted to emergency wards 22—35mo before the study Prospective cohort: age 18—60y for MTBI patients Historical and prospective cohort: orthopedic injury patients were age and sex matched to the MTBI patients. Exclusion: orthopedic controls with head or neck injury	Head trauma with LOC <15min	Prognostic factor: MTBI vs orthopedic injury Outcomes: prevalence of PTHA measured by ICHD-2 criteria and headache severity on a visual analog scale	Phase II historical cohort: All MTBI patients presented with PTHA, but 92% had recovered by 1wk postinjury and 96% after 1mo. The prevalence of PTHA was similar between head-injured and non—head-injured patients, but MTBI patients complained of more photophobia than those with other injuries (41% vs 30%). Phase II prospective cohort: no significant difference in the prevalence of PTHA between MTBI and non—head-injured patients at 3mo and 1y. Fewer MTBI patients than orthopedic-injured patients had a history of headache before the trauma (44% vs 72%). The prevalence of persistent headache (ie, >15d/mo) in MTBI patients was similar to that in other patients at 3mo and 1y (16% vs 10% and 12%

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Table 4 (*continued*)

Author, Year, Country	Source Population, Study Size, Participation, F/U	Inclusion/Exclusion Criteria	MTBI Case Definition	Prognostic Factors/Self-Reported Outcomes	Findings
					vs 13%, respectively). No important differences among groups were found in headache diagnosis, frequency, or symptoms at 1y after trauma, except photophobia was more prevalent in concussed patients. Headache occurring ≥3mo after injury is unlikely caused by brain injury.

Abbreviations: CDC, Centers for Disease Control and Prevention; CES-D, Center for Epidemiologic Studies Depression Scale; CI, confidence interval; CT, computed tomography; DC, doctor of chiropractic; GHQ-12, General Health Questionnaire-12; HRR, hazard rate ratio; ICHD-2, *International Classification of Headache Disorders. 2nd Edition*; IES, Impact of Event Scale; ISS, Injury Severity Score; MD, medical doctor; MnCS, Mental Component Summary; MVC, motor vehicle collision; NRS, numeric rating scale; PC, postconcussion; PhCS, Physical Component Summary; PT, physical therapist; RMT, registered massage therapist; RNL, Reintegration to Normal Living Index; SIP, Sickness Impact Profile; U.S., United States.

after MTBI is unlikely caused by brain injury per se. The results of this phase II study should be interpreted with caution, since other authors have found a very low rate of expectation of any chronic sequelae after MTBI in Lithuania.[35] These results suggest that PTHA is not a problem in Lithuania after MTBI, but studies from other jurisdictions do not necessarily agree.

More than 1-year follow up

We accepted 2 phase II cohort studies[36,37] and 1 nonrandomized experimental study[38] with follow up for more than 1 year post-injury, including 1 study each from Brazil, Canada, and Sweden (table 5). Outcomes included postconcussion symptoms measured by the RPSQ, health-related quality of life, anxiety, depression, self-reported cognitive function, self-reported memory, fatigue, sleep disturbance, and loneliness.

The 2 phase II studies included uninjured controls to look at the prognostic value of S100B[36] and the apolipoprotein E (APOE) ε4 genotype.[37] De Almeida Lima et al[36] followed up 38 cases of MTBI treated at an ED for 18 months and compared them with 39 household controls. They found no correlation between S100B protein levels and abnormal findings on a computed tomography scan, or between S100B and health-related quality of life or depression at follow up, confirming the results of Nygren-de Boussard et al[23] that S100B is not a useful prognostic marker in patients with MTBI. Sundström et al[37] looked at the prognostic value of APOE in 31 patients with MTBI and compared them with matched controls. Outcomes included simple questions about various postconcussion symptoms. Postinjury fatigue was more common in MTBI cases with APOE ε4 than without it (58% vs 32%). Among carriers of APOE ε4, those with MTBI had more fatigue than controls without MTBI (58% vs 17%). These results are preliminary and need to be confirmed in a phase III study.

Finally, Ozen and Fernandes[38] conducted a nonrandomized experiment with undergraduate university students to determine whether expectations of MTBI symptoms influence self-reported symptoms. Students were initially surveyed about past head injuries, and then a subset of those with and without head injury were surveyed again under 2 separate scenarios. Under a "diagnosis threat" scenario, 22 students with and 21 students without past head injury were tested with the knowledge that the tests were focused on comparing outcomes between those with and without past MTBI. Under the "neutral" scenario, 21 students with and 23 students without past head injury were tested without knowledge that the tests were focused on past MTBI status. The diagnosis threat group with past MTBI reported more cognitive errors and memory failures than all others. The neutral scenario group with past MTBI reported more anxiety than others. These results suggest that expectations influence self-reported cognitive and memory results.

Discussion

Our results support the previous finding of the WHO Collaborating Centre Task Force on MTBI that self-reported symptoms such as headache, fatigue, self-perceived cognitive deficits and other so-called postconcussion symptoms are common in the acute stage of injury but are not specific to MTBI.[4] When compared with uninjured controls, patients with MTBI do report more postconcussion symptoms at 3 months[21,22] and at 1 year.[36,37] However, postconcussion symptoms are equally

Table 5 Studies of self-reported outcomes in adults with more than 1 year of follow up

Author, Year, Country	Source Population, Study Size, Participation, F/U	Inclusion/Exclusion Criteria	MTBI Case Definition	Prognostic Factors/Self-Reported Outcomes	Findings
de Almeida Lima et al,[36] 2008; Brazil	MTBI patients (n=39) treated at a hospital ED of a trauma center Household controls (n=39) F/U: 18mo	Cases had isolated head trauma treated at an ED trauma center from September to October 2004. Controls lived in the same household as patients and had no history of head trauma and had to preferably be of the same sex and similar age.	GCS 13–15 and at least 1 of the following symptoms at admission to the ED: headache, vertigo, amnesia, nausea, vomiting, or LOC <15min	Prognostic factor: S100B protein levels and injury status Outcomes: PC symptoms (RPSQ), HRQL (SF-36), anxiety and depression (HADS)	No correlation between S100B protein levels at ED visit and positive CT scan or with HRQL, anxiety, or depression at 18-mo F/U Phase II cohort: Patients had worse SF-36 domain scores of functional capacity, pain, vitality, social aspects, and mental health compared with controls. Patients complained of more depression and anxiety than controls (47% vs 22% for anxiety; 25% vs 11% for depression). Compared with controls, patients complained of more loss of balance (42.1% vs 20%), dry mouth (44.7% vs 20%), arm pain (39.5% vs 11.4%), loss of memory (36.8% vs 14.3%), and dizziness (60.5% vs 37.1%).
Ozen and Fernandes,[38] 2011; Canada	Participants: university students (n=87) assigned to 2 groups: 1. Diagnosis threat group (n=43): informed that study to examine negative effects of head injury on cognitive functioning. Included 22 with past MTBI and 21 with no history of MTBI. 2. Neutral group (n=44): unaware of effects of MTBI on cognitive functioning. Included 21 with past MTBI and 23 with no history of MTBI Variable F/U: on average, 5.1–7.5y after injury	Inclusion: healthy students fluent in English with normal or corrected-to-normal hearing and vision Exclusion: past diagnosis of psychological or neurologic disorder, or diagnosis of depression or anxiety	Any strike to the head or acceleration/deceleration whiplash force that resulted in LOC and occurred at least 6mo before the study testing. Severity was determined by duration of LOC, PTA, disorientation, and/or confusion. MTBI was defined by PTA <24h and LOC ≤30min.	Prognostic factors: symptom expectation—diagnosis threat group vs neutral group Outcomes: self-reported depression (BDI), anxiety (STAI), cognitive errors (ARCES), and memory failures (MFS)	Nonrandomized experiment: Diagnosis threat group with past MTBI reported more cognitive errors and memory failures than all others. Neutral group with past MTBI reported more anxiety than others. No other significant differences detected between groups. These results suggest that expectations influence self-reported cognitive and memory results.

(*continued on next page*)

Table 5 (*continued*)

Author, Year, Country	Source Population, Study Size, Participation, F/U	Inclusion/Exclusion Criteria	MTBI Case Definition	Prognostic Factors/Self-Reported Outcomes	Findings
Sundström et al,[37] 2007; Sweden	Random sample of adults from a population registry in northern Sweden forming the Betula Longitudinal Cohort on Aging MTBI (n = 31) Age-, sex-, education-, and APOE-matched controls (n = 62) F/U: every 5y (minimum 10y of F/U)	Inclusion: age 35–85y and past MTBI. For each MTBI, 2 non–head-injured controls were chosen matched for age, sex, education, and APOE genotype. Exclusion: psychiatric illness, memory disturbance, stroke, brain infection, neurologic disorders, Mini-Mental State Examination scores <23, subjects with missing data, and developing dementia cases	MTBI: self-reported to have met the American Congress of Rehabilitation Medicine criteria	Prognostic factors: injury status (MTBI vs control) and presence of APOE ε4 genotype. Outcome: single questions about the presence of fatigue, anxiety, sleep disturbance, loneliness, and depression	Compared with preinjury, those with MTBI had more fatigue (16.1% vs 41.9%). There was no increase in fatigue in the control group over time. Phase II cohort: Postinjury fatigue was more common in MTBI cases with APOE ε4 (58% vs 32%). Among carriers of APOE ε4, those with MTBI had more fatigue than those without (58% vs 17%). No significant differences in other outcomes.

Abbreviations: APOE, apolipoprotein E; ARCES, Attention-Related Cognitive Error Score; BDI, Beck Depression Inventory; CT, computed tomography; F/U, follow up; HADS, Hospital Anxiety and Depression Scale; HRQL, health-related quality of life; MFS, Memory Failures Scale; PC, postconcussion; STAI, State-Trait Anxiety Inventory.

prevalent in those with other nonhead injuries.[17,18,20,31,32,34] Most of the postconcussion symptoms could be viewed as common reactions to the stress of injury, or other mental or physical health stressors. For example, Landre et al[17] showed that acute postconcussion symptoms are associated with emotional distress, but not type of injury. De Leon et al[32] found that fatigue severity at 1-year follow up was associated with baseline fatigue, past mental health issues, past medical disability, marital status, and being involved in litigation, but not the type of injury (ie, MTBI vs nonhead injury). All this evidence calls into question the validity of the PCS as a specific diagnosis and sequelae of MTBI. These symptoms are common in the general population,[39] in patients with chronic pain,[40] and after whiplash injury to the neck.[41,42] In addition, 2 studies[20,22] we reviewed show that patients with MTBI tend to minimize symptoms that they have before being injured. Thus, we recommend that the term *postconcussion syndrome* be replaced with *posttraumatic symptoms* because they are common to all injuries.

Even though posttraumatic symptoms are not specific to MTBI, they are a problem for patients and clinicians. The literature reviewed by the WHO Collaborating Centre Task Force suggested that most patients recover within 3 months to 1 year.[4] Our update supports this, but there is evidence that a significant minority continue to have subjective complaints. Hou et al[26] found that 22% of patients had 3 or more posttraumatic symptoms at 3 months, and there was no significant recovery by 6 months. Norrie et al[28] found that 30% of patients complained of fatigue at 3 months, and this remained relatively stable at 26% by 6 months. Stulemeijer et al[29] found that 36% of patients with MTBI continued to have 3 or more posttraumatic symptoms at 6 months. Cassidy et al[14] reported that the median time to self-reported recovery was 100 days in patients with MTBI after traffic collisions, and that about 23% report not being recovered by 1 year. However, these same studies show that persistent posttraumatic symptoms are associated with psychosocial factors such as depression,[28] posttraumatic stress,[29] negative injury perceptions,[26] and poor expectations for recovery.[14] Other psychosocial factors associated with posttraumatic symptoms at follow up include mental health status,[17,32,33] anxiety in women,[24] and litigation or lawyer involvement.[22,32] In fact, these psychosocial factors are more strongly associated with outcomes than the traditional biomedical factors thought to determine recovery. For example, several studies[14,26,29,32] found that LOC and PTA were not associated with recovery from self-reported symptoms. The results of our review suggest that patients with persistent posttraumatic symptoms might benefit from psychosocial interventions, and this should be a focus of future intervention studies.

One purpose of prognosis is the early recognition of patients at risk of a poor or good outcome. Clinical prediction rules are prognostic tools that can help stratify patients into different risk sets at the onset of a disorder and can inform the clinician and patient of the likely course of recovery and aid in treatment decisions.[43] Our review found 1 clinical prediction rule. Stulemeijer[29] developed a clinical prediction rule in patients admitted to the ED with MTBI in The Netherlands. They defined a good outcome as a score of less than 3 on at least 13 of 16 posttraumatic symptoms measured by the RPSQ. An absence of comorbid physical problems, low levels of early posttraumatic symptoms, and low levels of early posttraumatic stress predicted a good outcome at 6 months with a probability of 90%. However,

these results need to be validated in another setting before being recommended for widespread use.

Study limitations and strengths

Our study has some limitations and strengths. Although we followed a strict PRISMA-compliant protocol, our conclusions are only as good as the literature that we have accepted, and we found it to be generally weak and heterogeneous. Of the 173 studies we reviewed on adult prognosis of MTBI, only 51 (29%) were considered to have a low risk of bias, and 21 of these included self-reported outcomes relevant to this article. It is disappointing that so few good prognostic studies have been published since the WHO Task Force reviewed the same literature up to the year 2000. Also, only 1 of our accepted articles was a phase III confirmatory prognostic study. However, we may have excluded some good studies that included intentional injuries, or included both adults and children without stratifying the results. We a priori decided to do this because we think children and those with intentional injuries may have a different trajectory for recovery. In addition, most of the prognostic studies we reviewed did not take into account potential confounding effects of varying levels of treatment on prognosis. However, since there is little evidence of treatment effectiveness in MTBI, we do not think this is a major problem.[44] Although our search strategy was comprehensive, we may have missed some good studies that were not in the searched databases or not in languages included in our protocol.

A strength of the ICoMP is that our group includes a mix of methodological and clinical scientists with a spectrum of experience in systematic reviews and clinical care of MTBI. Our group also carefully considered the strength of the evidence on MTBI prognosis and report only on studies that have a low risk of bias. Thus, our results include only the best current evidence.

Conclusions

Since the prognosis review of the WHO Collaborating Centre Task Force, there has been some progress in understanding MTBI prognosis. Our results add to the growing evidence that postconcussion symptoms are not specific to MTBI and occur commonly in the general population and after other nonhead injuries. Our results also confirm the importance of psychosocial determinants of recovery. We conclude that self-reported symptoms can be persistent after MTBI, and there is a need for more intervention research targeting modifiable prognostic factors. Finally, we found only 1 study of a clinical prediction rule, and we recommend more focus on this issue because it holds the potential of identifying those at risk of a poor recovery who might benefit from more focused clinical attention.

Keywords

Craniocerebral trauma; Prognosis; Recovery of function; Rehabilitation

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