

# A Scoping Review of Registered Clinical Studies on Mild Traumatic Brain Injury and Concussion (2000 to 2019)

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**BACKGROUND:** While many patients with mild traumatic brain injury (mTBI) or concussion recover completely, prolonged postconcussion symptoms remain a challenge for patients and an opportunity for clinical research. This has led to numerous research initiatives over the last 2 decades.

**OBJECTIVE:** To review the characteristics of clinical studies on management of mTBI/concussion; and to examine their definitions of mTBI/concussion.

**METHODS:** This scoping review included all clinical studies on diagnosis and management of patients with mTBI/concussion registered at [www.clinicaltrials.gov](http://www.clinicaltrials.gov) from 2000 to June/2019. The terms “mild TBI/concussion” were used for the primary search. Definitions of mTBI/concussion were obtained from the protocols. When a definition was missing in the website, the study’s investigators were contacted for clarification.

**RESULTS:** There were 225 interventional and 95 observational studies. Most of the studies are focused on treatment (54.7%) or diagnosis (37.5%), while 3.4% examined preventive measures, 2.8% evaluated prognostic instruments, and 1.6% developed registries. Most of the studies in this American database were single-center initiatives led by American and Canadian institutions. The definitions of mTBI/concussion differed widely among 109 studies.

**CONCLUSION:** The results of this review suggest that most of the clinical studies are focused on diagnosis and non-pharmacological therapies for patients with mTBI/concussion. The large number of differing definitions of mTBI/concussion among the studies creates significant limitations when comparing studies. The requirements for registering research protocols on mTBI/concussion should include the necessity to state the definition being used. There is a need for consensus on a uniform definition of concussion.

**KEY WORDS:** Mild traumatic brain injury, Concussion, Neurotrauma, Definitions

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**T**raumatic brain injury (TBI), according to the report from the World Health Organization (WHO), is the leading cause of death and disability in children and young adults worldwide, and is accountable for almost half of all trauma-related deaths.<sup>1</sup> In a systematic review, Tagliaferri et al<sup>2</sup> summarized the results of 23 prior studies on the epidemiology of TBI

in Europe. The authors reported an estimated incidence rate of 235 per 100 000 inhabitants based on aggregate data from hospitalized plus fatal TBI.<sup>2</sup> There was no estimation of the prevalence rate of TBI among the 23 European studies.<sup>2</sup> The minority of TBIs are considered “severe”, whereas the vast majority of the TBIs are classified as “mild” (approximately 90%).<sup>3</sup> The most commonly used classification of TBIs is based on the Glasgow Coma Scale (GCS) based on a point system to assess the best ocular, verbal and motor responses.<sup>1</sup> According to the WHO criteria, individuals with mild TBI have a GCS score from 13 to 15, whereas individuals with

**ABBREVIATIONS:** ACRM, American Congress of Rehabilitation Medicine; GCS, Glasgow Coma Scale; mTBI, mild traumatic brain injury; NIH, National Institutes of Health; TBI, Traumatic brain injury

moderate TBI have a GCS from 9 to 12, and individuals with severe TBI have a score from 3 (the worst cases) to 8.<sup>1</sup> While the classification of mild TBI according to WHO criteria represents a heterogeneous group of patients including concussion, many other definitions of mild TBI have been proposed.

In a recent population-based study, Langer et al<sup>4</sup> reported an estimated incidence of concussion of 1153 per 100 000 residents in the province of Ontario (Canada) in a given year (or approximately 1.2% per year). This was the highest rate of concussion ever reported in the literature, which raises the question of possible methodological discrepancies, especially related to definition of mild traumatic brain injury (mTBI)/concussion among the prior studies. While TBI in general has become a pressing public health issue there is also concern about a silent “epidemic” of mTBI/concussion for more than a decade, and furthermore the true incidence and prevalence of mTBI/concussion remain unclear.<sup>4-6</sup>

The lack of uniformity in the definition of mTBI/concussion has created major difficulties for researchers and clinicians many experts in the field.<sup>7,8</sup> This variability of definitions may have a significant impact on the epidemiological analysis and generalizability of the registered studies of the management of patients with mTBI/concussion. To examine this issue of definition, we analysed data from recently completed and ongoing clinical studies registered in the ClinicalTrials.gov website. A scoping review was performed: (a) to analyze and summarize the characteristics of clinical studies on management of mTBI/concussion; and (b) to examine the definitions of mTBI/concussion used in these studies.

## METHODS

This scoping review included all clinical studies on the management of mTBI/concussion registered in the ClinicalTrials.gov website from the date when the website became publicly available in February 2000 to June 29, 2019. The term “mTBI/concussion” was used to identify the clinical studies focused on management of mTBI/concussion.

All definitions of mTBI/concussion used in the clinical studies were collected and analyzed. When there was no definition of mTBI/concussion in the study description in the website, the principal investigator was contacted via email with a request to provide the definition used in the study. A reminder was sent 2 wk later if there was no response to the initial request.

### ClinicalTrials.gov Website

ClinicalTrials.gov is a Web-based resource publicly available to anyone wishing to search for clinical studies on many diseases and conditions including TBI.<sup>9</sup> The website was established following the Food and Drug Administration Modernization Act of 1997 (FDAMA) that ordered the U.S. Department of Health and Human Services to create “a registry of clinical trials information for both federally and privately funded trials conducted under investigational new drug applications to test the effectiveness of experimental drugs for serious or life-threatening diseases or conditions.”<sup>9</sup> The National Institutes of Health (NIH), through the National Library of Medicine, was delegated the task to create and maintain the website. By combining forces, the NIH and

the Food and Drug Administration (FDA) developed the website that became available to the public in February 2000.<sup>9</sup>

The sponsor or principal investigator of the clinical study is responsible for providing and updating the website with study information. All listed studies include human volunteers who participate in a research protocol led by an institution located in the United States or in 193 other countries.<sup>9</sup> While the majority of registered studies are clinical trials where human volunteers are assigned to interventions (so-called “interventional studies”), the website also includes observational studies on investigational drugs outside of clinical trials (expanded access).<sup>9</sup> Not all clinical studies in the United States are required by law to be registered in the website. For example, observational studies and clinical trials that are not focused on a drug, biologic agent, or device do not have to be registered. There has been an escalation of registered studies as more investigators and sponsors have voluntarily recorded their studies.<sup>9</sup>

## RESULTS

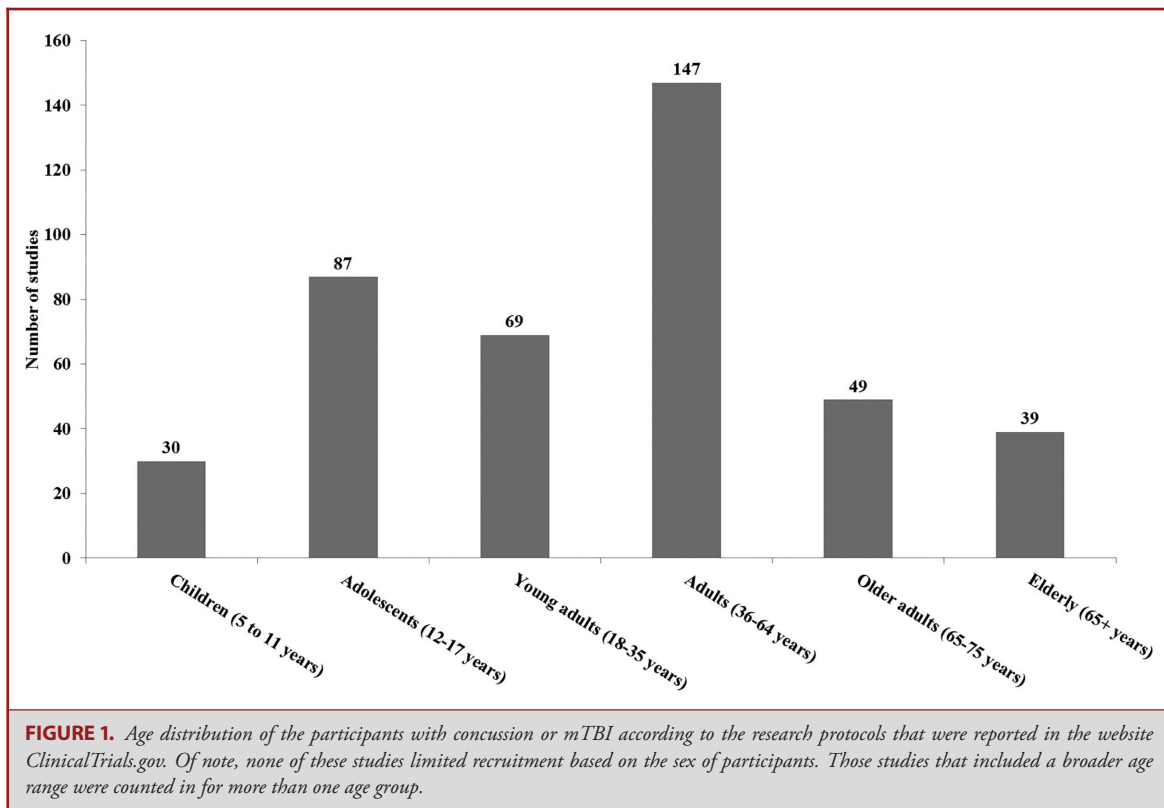
Our search captured 320 studies on mTBI/concussion registered in the website, and most involved a single center (n = 251), whereas there were 69 multicenter studies. The vast majority of studies were led by institutions situated in the United States (n = 230) followed by: Canada (n = 43); Denmark (n = 9); France (n = 7); Israel and Norway (n = 4 each); Austria, China, Ireland, Taiwan (n = 3 each), Afghanistan and England (n = 2 each); and Brazil, Finland, Indonesia, Iraq, Malaysia, Sweden, Switzerland (n = 1 each).

### Demographics and Characteristics of the Participants

Demographic data of the participants in the studies were available in the inclusion criteria in 228 out of 320 research protocols that were documented in the website. Adults were the most commonly recruited participant group for the studies followed by adolescents (ages 12-17), younger adults (18-35), elderly ( $\geq 65$ ) and children ( $\leq 11$ ) (Figure 1). Specific groups of participants were recruited in a few studies that focused on military personnel (n = 11), females older than 14 yr of age (n = 1), male adults (n = 1), and civilians (n = 1).

### Characteristics of the Clinical Studies

Of the 320 studies, 225 were classified as interventional (including clinical trials), and 95 were designated as observational. Most were focused on treatment (54.7%) or diagnosis of mTBI/concussion (37.5%), while 3.4% examined preventive measures, 2.8% evaluated prognostic instruments, and 1.6% involved development of a registry. Of the 175 studies focused on treatment, several different therapeutic modalities were studied including exercise-based therapy (20.5%), pharmacological therapy (16.8%) and neuromodulation (9.7%) among others (Figure 2). The pharmacological and neuromodulation therapy studies are shown in Table 1. Of the 120 studies focused on diagnosis, most protocols used clinical assessments, neuroimaging analyses, or other technology-based assessments for diagnosis of mTBI/concussion (Figure 3).



### Definitions of Concussion or mTBI

A definition of mTBI or concussion was available in 86 of the 320 studies (26.9%) posted in the website. Information on the definitions used was obtained from the investigators in 23 additional studies who responded to our request. A definition of mTBI or concussion was obtained for 109 of the 320 (34.1%) studies (Table 1). However, among these 109 studies, there were several different definitions: in 33 a variety of definitions based on selected clinical criteria without following a previously reported definition; in 19 the definition was a GCS between 13 and 15 at presentation; and in 16 a combination the two former criteria. Among those 33 definitions within the variety group (“clinical criteria that were not previously cited in the literature” in Table 1), there were relatively simple definitions of mTBI/concussion such as: “Reported or observed signs (Loss of consciousness, amnesia, disorientation/confusion) at time of injury, and Current reported symptoms and/or impairment (cognitive, balance, visual)”. On the other hand, there are also more complex definitions such as: “A TBI induced by biomechanics forces, which was caused by either a direct or indirect blow to the head, face, neck or elsewhere on the body with an impulsive force transmitted to the head, which may or may not have involved loss of consciousness, and included one or more of the following clinical domains: symptoms (eg, headache, nausea, fatigue, feeling like in a fog, difficulty concentrating or remembering, and/or emotional lability); physical signs

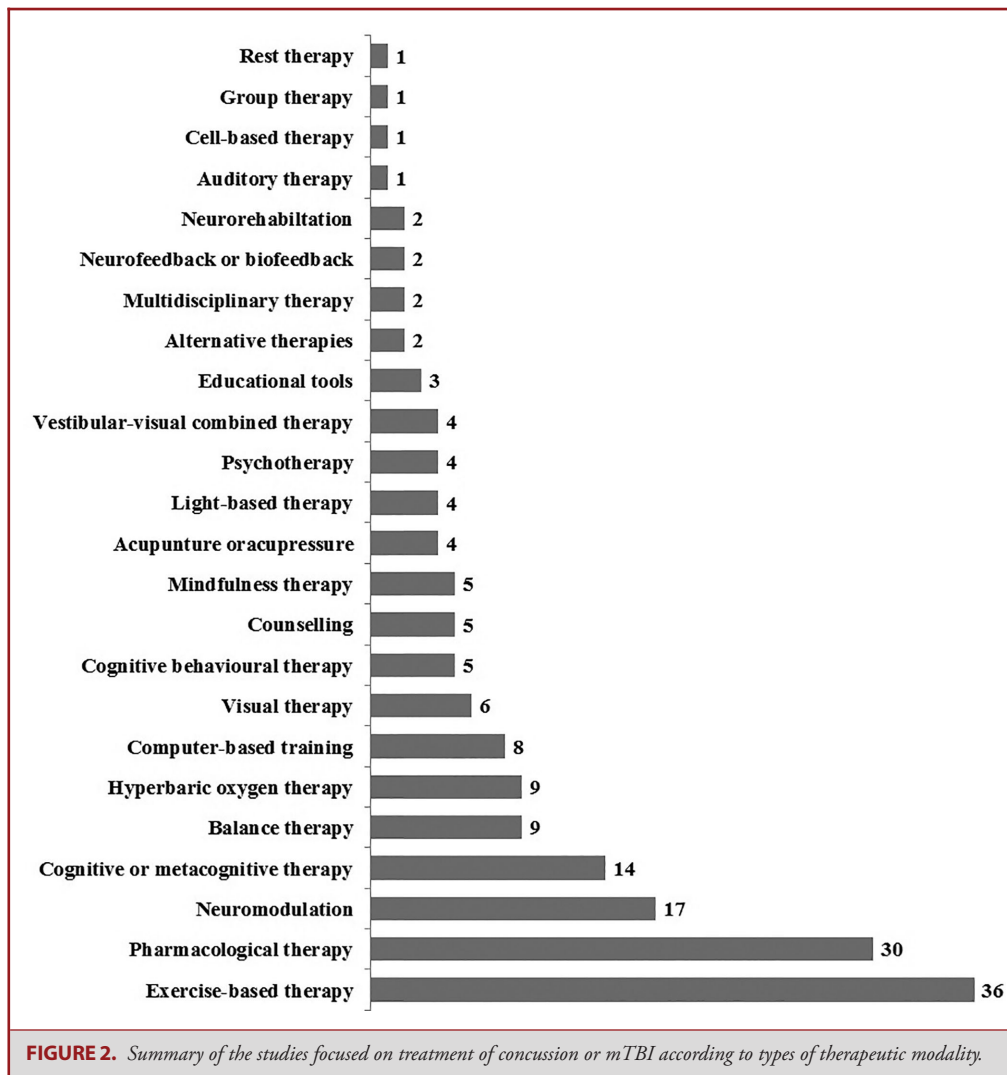
(eg, loss of consciousness, amnesia, neurological deficit); balance impairment (eg, gait unsteadiness); behavioural changes (eg, irritability); cognitive impairment (eg, slowed reaction times); sleep/wake disturbance (eg, somnolence, drowsiness).” There were at least 11 other definitions of mTBI or concussion used in the study protocols (Table 2).

### DISCUSSION

Our review of the clinical studies on mTBI/concussion revealed that the vast majority of the recently completed or ongoing investigations are led by North American institutions. In 72% of the study protocols, participants of both sexes were included when the mTBI/concussion occurred in their adolescence or adulthood. While the majority of the research protocols are investigational and focused on therapies or diagnostic tools for mTBI/concussion, fewer investigations were focused on preventive measures, prognostic instruments, and development of registries for future research. Moreover, the lack of consensus on the definitions for mild TBI and concussion remains a major challenge in this research field.

### Demographics and Characteristics of the Participants

Although the clinical studies in this review predominantly included adults and adolescents of both sexes with



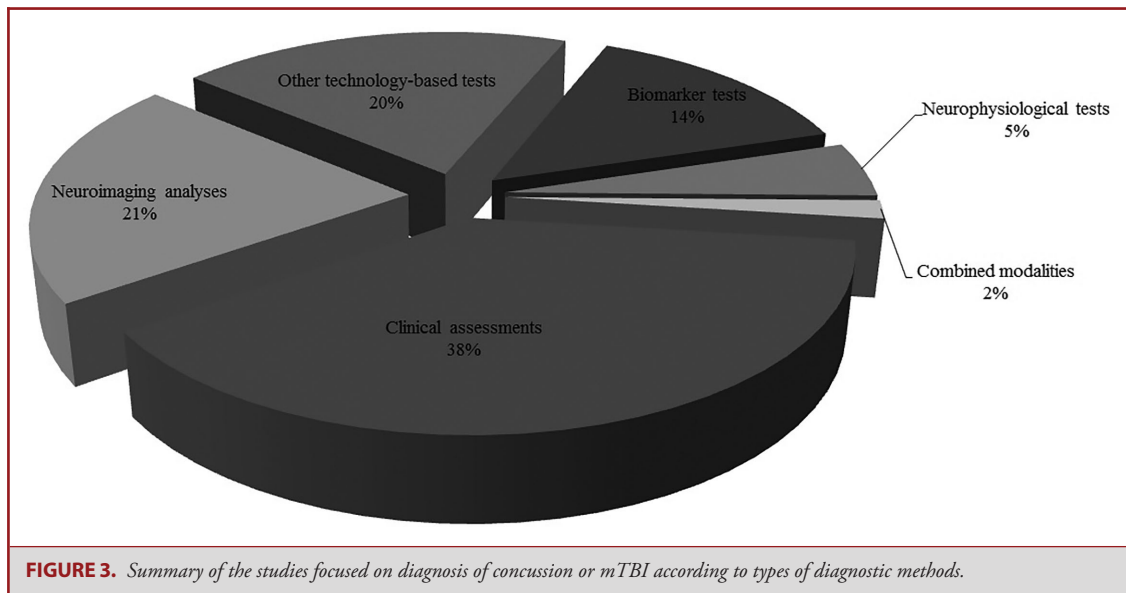
mTBI/concussion, fewer research protocols included all other age groups. The reasons for preferentially studying adults and adolescents could be related to the causes of mTBI/concussion in those age groups that raise greater interest in workplace- and sports-related injuries and their consequences in their ability to return to work and to return to play, respectively.<sup>10,11</sup> In a recent systematic review, Iverson et al stressed that the current research is largely focused on sports-related mTBI/concussion.<sup>12</sup> As an example of the impact of the escalation on research in this field, there have been improvements in the management of young athletes with sports-related mTBI/concussion over the past 15 yr that allow additional time for brain recovery after injury, and reducing the risk of repetitive concussion during the critical period of brain susceptibility.<sup>13</sup> Work-related mTBI/concussion is another area of great interest in the research and medical community due to the potential societal impact related to the delay in return to work. This impression is supported for instance by the results of

a recent nationwide cohort study with 5-yr follow-up period in Denmark where 43% of the patients with mTBI/concussion were not attending regular work 5 yr after injury and received health and social transfer benefits.<sup>10</sup>

Despite the apparent lack of sex-related preference in the inclusion criteria for the studies that were documented in the ClinicalTrials.gov website, the actual enrolment may favour a disproportionately greater involvement of the male population in the research studies on mTBI/concussion. In a recent review analysing data from 1501 interventional studies listed in the ClinicalTrials.gov website, Prakash et al reported that females were under-represented in recent clinical trials that were funded by either NIH or industry.<sup>14</sup> There is a growing body of evidence for sex- and gender-related differences in the epidemiology and outcomes of mTBI/concussion, which emphasises the need for proper representation of males and females and sex-stratified data analyses in future clinical studies.<sup>15,16</sup>

**TABLE 1.** Description of the Pharmacological Therapies (n = 30) and Neuromodulation Therapies (n = 17). The Number of Studies Focused on the Same Therapy is Shown in Parentheses; Otherwise, There has Been Only one Study for Each of the Other Therapies

Primary outcome measures	Pharmacological therapies	Neuromodulation therapies
General symptoms or post-concussive symptoms	Magnesium (n = 2), Ibuprofen vs Acetaminophen, hypertonic saline, Atorvastatin, Ondansetron, Melatonin, Sildenafil citrate, anti-oxidant substances,	Magnetic EEG/EKG resonance therapy, high-definition transcranial direct stimulation (n = 2), pulsed electromagnetic field, transcranial high-intensity LED
Cognitive function	Citicoline, Glycyl-L-2-Methylpropyl-L-Glutamic Acid, branched chain amino acids, hyperosmolar sodium lactate, Resveratrol	Transcranial direct stimulation (n = 3)
Headache	Prazosin, calcitonin gene-related peptide (CGRP), Erenumab, Metoclopramide, Onabotulinumtoxin A, salt-water solution	Transcranial magnetic stimulation
Return to play or functional recovery	Docosahexaenoic acid (DHA), Omega 3 fatty acid (n = 2)	No studies
Brain blood oxygenation	Sildenafil citrate, Tolcapone	No studies
Post-traumatic stress disorder	Lithium	Intermittent theta burst stimulation
Cerebrovascular reactivity	Sildenafil citrate	No studies
Inflammatory markers	Probiotics	No studies
Depressive mood	Citalopram	Transmagnetic brain stimulation
Performance fatigue	Recombinant growth hormone	No studies
Balance and gait performance	No studies	Cranial-nerve non-invasive brain stimulation (n = 2)
Neurobehavior	No studies	Acoustic stimulation
Alcohol craving	No studies	Transmagnetic brain stimulation
Number of abnormal magnetoencephalography (MEG) slow-waves	No studies	Transcranial direct electrical stimulation



**FIGURE 3.** Summary of the studies focused on diagnosis of concussion or mTBI according to types of diagnostic methods.

### Clinical Studies on mTBI or Concussion

The results of this review suggest that research on diagnosis, treatment, prognosis and prevention of mTBI/concussion is a global endeavour, even though most of the studies in this American database were from institutions situated in the United

States and Canada. In a recent review on the PubMed database using Clinical Queries, Hon et al<sup>17</sup> also documented that, despite the global efforts, the majority of the publications on concussion in the pediatric population was led by institutions in the United States and Canada. MTBI/concussion represents a major public

**TABLE 2. Definitions of Concussion or mTBI Reported in the Study Protocols**

Definition	n	Percentage
Not specified	211	65.9%
Clinical criteria that were not previously cited in the literature	33	10.3%
GCS from 13-15	19	5.9%
GCS and clinical criteria	16	5.0%
ACRM <sup>a</sup>	9	2.8%
US Department of Defense <sup>a</sup>	8	2.5%
Clinical impression and pathophysiological aspects	6	1.9%
Zurich Consensus Statement <sup>b</sup>	6	1.9%
Clinical impression and neuroimaging	4	1.3%
Danish Consensus Report on Commotio Cerebri	2	0.6%
World Health Organization <sup>a</sup>	2	0.6%
GCS from 9-15	1	0.3%
GCS 14 and 15	1	0.3%
Rancho Los Amigos Scale score of 7 or above	1	0.3%
2017 Berlin International Consensus Conference	1	0.3%

<sup>a</sup>Included studies that adopted the published definition 'as is' and studies that cited the published definition but applied a modified version still containing all original criteria;

<sup>b</sup>Consensus statements from different International Conferences on Concussion in Sport were used.

health issue worldwide that requires a global contribution in the efforts of prevention, diagnosis, treatment and prognosis of this condition. This point of view is further reinforced by the fact that different jurisdictions may face particularities in terms of epidemiology, risk factors, social and economic status, safety legislation and regulation, and healthcare access and coverage. For instance, research studies on the use of helmets during American football or hockey matches is not relevant for a country where those sports are not practiced but soccer is the most popular sport.

The research protocols captured in our website-based search are mainly focused on the development of new therapies and diagnostic instruments for mTBI/concussion. Among 175 studies on treatment for mTBI/concussion captured in our review, there was a wide-range of therapeutic modalities including exercise-based therapy (20.5%), pharmacological therapy (17.5%), neuromodulation (11.9%), among others. Using data from Clinical.Trials.gov and 7 additional WHO registries, Burke et al<sup>18</sup> also documented several different categories of treatment for concussion that were studied until 2013. Research and clinical practice have been evolving with the increasing recognition that mTBI/concussion is a heterogeneous condition with distinct clinical profiles affected by several modifying factors.<sup>19</sup> In this new conceptual framework, more comprehensive and multimodal assessments are required in order to

facilitate the development of more personalized and targeted therapies that can potentially improve outcomes of individuals after mTBI/concussion.<sup>19</sup>

Data from this review indicate that preventive measures were the focus of only 3.4% clinical studies that were registered in ClinicalTrials.gov. Despite important educational initiatives on the prevention of mTBI/concussion such as Parachute, *Think-First* Canada Smart Hockey, and Heads Up Football programmes, there is a need for further studies on prevention in order to reduce the risks for individuals and the societal burden of mTBI/concussion.<sup>20-22</sup> In a recent review analyzing data from 14 prospective studies on prevention of mTBI/concussion, Schneider et al<sup>21</sup> found only one study on education program that examined the effects of the Heads Up Football programme which emphasizes proper tackling technique.<sup>23</sup> Furthermore, Schneider et al<sup>21</sup> concluded that the relative risk of concussion in athletes wearing novel protective equipment did not differ from those athletes wearing standard equipment.

Overall, the recently completed and ongoing research studies on mTBI/concussion have been predominantly enrolling adolescents and adults who often sustained a sports-related or work-related trauma. In addition, development of new therapies and diagnostic instruments for mTBI/concussion has been the focuses of the majority of the research studies in this field according to data largely collected in North America.

## Definitions of mTBI and Concussion

The results of this scoping review revealed that the majority of the study descriptions (73.1%) in the Clinical.Trials.gov website did not include a definition of mTBI/concussion. Moreover, there was a great diversity of definitions of mTBI/concussion among the study protocols when this information was provided by the investigators. Similarly, the WHO Collaborating Centre for Neurotrauma Task Force on mTBI carried out a comprehensive review that identified 38 different case definitions of mild TBI in the literature published between 1980 and 2002.<sup>24</sup> Those findings led the WHO Task Force to develop an operational definition following many criteria suggested in the definition from the mTBI Committee of the Head Injury Interdisciplinary Special Interest Group of the American Congress of Rehabilitation Medicine (ACRM).<sup>24,25</sup> In a more recent review, Kristman et al<sup>26</sup> documented a greater variation in the definition of mild TBI (n = 101) where, although the ACRM and WHO Task Force criteria were frequently applied, the use of additional, distinct diagnostic criteria often resulted in the selection of subsets of patients with mild TBI for clinical studies.

In the context and purpose of the Clinical.Trials.gov website, the lack of a definition and the heterogeneity of definitions of mTBI/concussion represent important challenges for the research community in terms of consistent recruitment of study participants and accurate clinical application of the results of the studies on patients with mTBI/concussion. The lack of consensus on

the definitions of mild TBI and concussion causes selection of heterogeneous patient populations for clinical research which compromises the generalizability of the results.<sup>27</sup> Similarly, the heterogeneity of definitions of mTBI and concussion represents one of the major challenges in the determination of the true incidence and prevalence of this clinical entity.<sup>7</sup> Similarly, the lack of consensus on the definition has implications for accurate diagnosis and management of mTBI/concussion.<sup>27</sup> In a recent analysis, Crowe et al<sup>28</sup> applied 17 different definitions of mild TBI in a large observational cohort study (ie, Australian Paediatric Head Injury Rules Study) that included 11 907 children with age at the time of brain injury between 3 and 16 yr. The authors reported that the proportion of children classified as having sustained mild TBI varied widely from less than 10% to more than 90% of the study population of TBI of any degree.<sup>28</sup>

An additional problem is that the terms “mild TBI” and “concussion” are frequently used interchangeably in the medical literature and clinical practice, even though patients may perceive them as distinct entities.<sup>27</sup> In fact, the implications of the terminology affect the patients’ perception of the severity of the injury and its prognosis. In an interesting prospective study, 105 undergraduate students who had acute brain trauma were randomly assigned as patients with either “mild TBI” or “concussion”.<sup>29</sup> While both study groups showed no significant differences regarding anxiety, symptomatology, timeline, or consequence scales, those assigned to the “mTBI” group were allocated more days to return to play than their counterparts with “concussion”, likely because the perceptions of the severity of the injury were different between the 2 participant groups and concussion may not be perceived as an actual brain injury.<sup>29</sup> Furthermore, there is still a debate in the literature between those who claim concussion is the constellation of symptoms that can arise from any mTBI, and those who argue concussion is “a distinct pathophysiological entity with its own diagnostic and management implications”.<sup>30</sup>

We believe that the definition of “mTBI/concussion” denotes different populations of patients. Furthermore, mTBI may not be as useful a term as concussion for clinical trials because many patients with GCS of 13 and 14 have focal brain lesions such as cerebral contusions, brain microhemorrhages or subarachnoid hemorrhage which are identifiable on computed tomography and magnetic resonance imaging. In contrast, the modern definition of concussion as enunciated by the periodic Consensus Conferences of the Concussion in Sport Group, the last of which was in Berlin in 2016 excludes patients with focal neurological deficits and patients with structural lesions identified by imaging.<sup>31</sup> Therefore, in our view concussion encompasses a more homogeneous group of patients than the group of individuals with mTBI.

In summary, the diversity and incorrectly presumed equivalence of the definitions of mTBI and concussion remains a common and serious problem in clinical research. The effects of this lack of appreciation of the differences in the two definitions impair clinical trials of diagnosis and treatment of this type of

brain injury. As well, the lack of uniformity of definition also impairs studies of the prevention and prediction of prognosis of mild brain injuries.

### Study Limitations

Although this scoping review included up-to-date information on clinical research on mTBI/concussion, there are some limitations. First, this review was based solely on information from the ClinicalTrials.gov website and, hence, the accuracy and comprehensiveness of the data depend upon the individuals who registered the studies. Concerns about the quality assurance for all entries in this publicly available website were raised many years ago, which led to regulatory modifications to make data insertion more complete, timely, accurate, and informative.<sup>32,33</sup> Second, the search for this review was based on the term “mTBI/concussion” that is a feature available in the ClinicalTrials.gov website. The lack of a clear definition in most of the registered studies precluded any distinction between the two clinical entities, mTBI and concussion. Third, this scoping review using data from the ClinicalTrials.gov is essentially a cross-sectional analysis of the recently completed or current/ongoing clinical studies at one point in time that may over-represent observational interventional studies in the field. Finally, the ClinicalTrials.gov website is an American initiative containing predominantly registered studies from the United States and Canada followed by other high-income countries. While the low- and middle-income countries experience more burden from TBI, the high-income countries provide disproportionately greater funding support of research on this subject.<sup>34</sup>

### CONCLUSION

The results of this scoping review assess the characteristics of the recently completed and ongoing clinical studies on mTBI/concussion. North American institutions have been leading most of the clinical studies in this American database, but the results from studies conducted in higher-income countries such as United States and Canada may not necessarily reflect the reality in the low- and middle-income countries where the epidemiology of mTBI/concussion, healthcare access and coverage, and legislation for prevention of trauma can be substantially different from the United States and Canada. The epidemiological, medical, and regulatory discrepancies among jurisdictions worldwide should also be considered when evaluating the relevance of the clinical studies registered in the ClinicalTrials.gov website, which were largely focused on adolescents and adults who sustain sports-related or work-related mTBI/concussion. Although the large proportion of research studies on novel diagnostic and therapeutic modalities address the clinical need for advances in the management of mTBI/concussion, the paucity of investigational initiatives on prevention of trauma persists as an unmet need in the research community. When registering clinical studies in ClinicalTrials.gov, investigators should be explicitly

required to provide a definition of mTBI or concussion. Lastly, the lack of consensus in the definitions of mTBI and concussion is a methodological challenge that has existed for several decades. The authors of this review strongly favor the use of the current definition of concussion rather than mild TBI for all clinical trials and other studies of this type of brain injury.

## Disclosures

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## REFERENCES

- WHO. *Neurological Disorders: Public Health Challenges*. Switzerland: World Health Organization, 2006.
- Tagliaferri F, Compagnone C, Korsic M, Servadei F, Kraus J. A systematic review of brain injury epidemiology in Europe. *Acta Neurochir (Wien)*. 2006;148(3):255-268; discussion 268.
- CDC. Report to Congress on Traumatic Brain Injury in the United States: Epidemiology and Rehabilitation. Atlanta, GA: Centers for Disease Control and Prevention. National Center for Injury Prevention and Control; Division of Unintentional Injury Prevention, 2015.
- Langer L, Levy C, Bayley M. Increasing incidence of concussion: true epidemic or better recognition? *J Head Trauma Rehabil*. 2020;35(1):E60-E66.
- Buck PW. Mild traumatic brain injury: a silent epidemic in our practices. *Health Soc Work*. 2011;36(4):299-302.
- Hyder AA, Wunderlich CA, Puvanachandra P, Gururaj G, Kobusingye OC. The impact of traumatic brain injuries: a global perspective. *NeuroRehabilitation*. 2007;22(5):341-353.
- Tator CH. Let's standardize the definition of concussion and get reliable incidence data. *Can J Neurol Sci*. 2009;36(4):405-406.
- Tator CH, Davis HS, Dufort PA, et al. Postconcussion syndrome: demographics and predictors in 221 patients. *J Neurosurg*. 2016;125(5):1206-1216.
- NLM. ClinicalTrials.gov [online]. Available at: <https://support.nlm.nih.gov/knowledgebase/article/KA-03869/en-us>. Accessed June 06, 2019.
- Graff HJ, Siersma V, Moller A, et al. Labour market attachment after mild traumatic brain injury: nationwide cohort study with 5-year register follow-up in Denmark. *BMJ Open*. 2019;9(4):e026104.
- Asken BM, Hack DC, McCrea MA. The modern landscape of sport-related concussion research: key achievements and future directions. *Handb Clin Neurol*. 2018;158:269-278.
- Iverson GL, Gardner AJ, Terry DP, et al. Predictors of clinical recovery from concussion: a systematic review. *Br J Sports Med*. 2017;51(12):941-948.
- McCrea M, Broglio S, McAllister T, et al. Return to play and risk of repeat concussion in collegiate football players: comparative analysis from the NCAA concussion study (1999-2001) and CARE consortium (2014-2017). *Br J Sports Med*. 2019;54(2):102-109.
- Prakash VS, Mansukhani NA, Helenowski IB, Woodruff TK, Kibbe MR. Sex bias in interventional clinical trials. *J Womens Health (Larchmt)*. 2018;27(11):1342-1348.
- Mollaveya T, El-Khechen-Richandi G, Colantonio A. Sex & gender considerations in concussion research. *Concussion*. 2018;3(1):CNC51.
- Cancelliere C, Donovan J, Cassidy JD. Is sex an indicator of prognosis after mild traumatic brain injury: a systematic analysis of the findings of the World Health Organization collaborating centre task force on mild traumatic brain injury and the international collaboration on mild traumatic brain injury prognosis. *Arch Phys Med Rehabil*. 2016;97(2 Suppl):S5-S18.
- Hon KL, Leung AKC, Torres AR. Concussion: a global perspective. *Semin Pediatr Neurol*. 2019;30:117-127.
- Burke MJ, Fralick M, Nejatbakhsh N, Tartaglia MC, Tator CH. In search of evidence-based treatment for concussion: characteristics of current clinical trials. *Brain Inj*. 2015;29(3):300-305.
- Charek DB, Collins M, Kontos A. Office-based concussion evaluation, diagnosis, and management: adult. *Handb Clin Neurol*. 2018;158:91-105.
- August J, Torres A. Prevention of concussion. *Semin Pediatr Neurol*. 2019;30:99-106.
- Schneider DK, Grandhi RK, Bansal P, et al. Current state of concussion prevention strategies: a systematic review and meta-analysis of prospective, controlled studies. *Br J Sports Med*. 2017;51(20):1473-1482.
- Cook DJ, Cusimano MD, Tator CH, Chipman ML. Evaluation of the think-first canada, smart hockey, brain and spinal cord injury prevention video. *Inj Prev*. 2003;9(4):361-366.
- Kerr ZY, Yeargin S, Valovich McLeod TC, et al. Comprehensive coach education and practice contact restriction guidelines result in lower injury rates in youth american football. *Orthop J Sports Med*. 2015;3(7):2325967115594578.
- Carroll LJ, Cassidy JD, Holm L, Kraus J, Coronado VG, Injury WHOCCT-FoMTB. 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.
- ACRM. Definition of mild traumatic brain injury. *J Head Trauma Rehabil*. 1993;8(3):86-87.
- 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.
- Sussman ES, Pendharkar AV, Ho AL, Ghajar J. Mild traumatic brain injury and concussion: terminology and classification. *Handb Clin Neurol*. 2018;158:21-24.
- Crowe LM, Hearn S, Anderson V, et al. Investigating the variability in mild traumatic brain injury definitions: a prospective cohort study. *Arch Phys Med Rehabil*. 2018;99(7):1360-1369.
- Kelly K, Erdal K. Diagnostic terminology, athlete status, and history of concussion affect return to play expectations and anticipated symptoms following mild traumatic brain injury. *J Clin Exp Neuropsychol*. 2017;39(6):587-595.
- Sharp DJ, Jenkins PO. Concussion is confusing us all. *Pract Neurol*. 2015;15(3):172-186.
- McCroory P, Meeuwisse W, Dvorak J, et al. Consensus statement on concussion in sport—the 5(th) international conference on concussion in sport held in berlin, october 2016. *Br J Sports Med*. 2017;51(11):838-847.
- Zarin DA, Tse T, Williams RJ, Califf RM, Ide NC. The clinicaltrials.gov results database—update and key issues. *N Engl J Med*. 2011;364(9):852-860.
- Zarin DA, Tse T, Williams RJ, Carr S. Trial reporting in clinicaltrials.gov - The Final rule. *N Engl J Med*. 2016;375(20):1998-2004.
- Kolias AG, Rubiano AM, Figaji A, Servadei F, Hutchinson PJ. Traumatic brain injury: global collaboration for a global challenge. *Lancet Neurol*. 2019;18(2):136-137.

## COMMENT

An accepted definition of an ailment seems fundamental to its diagnosis, treatment, and study. It is striking that this was not done for 'traumatic brain injury' until 2010<sup>1</sup> and that it has yet to be achieved for concussion. No wonder advancement in head injury is lagging so far behind other areas of medicine. There are over 40 different definitions of concussion, but an evidence-based definition has yet to be widely accepted.<sup>2</sup> As concussion has moved from its historic place at the fringes of medicine to a major public health concern, it seems high time to unite everyone behind a single definition.

This study provides a couple of important and – I think – remarkable findings. The first is confirmation that ongoing research does not seem to be unifying behind a single nor a small number of concussion definitions. This means that recent calls for a unified definition have been



unsuccessful and that the literature will continue to be problematic for years to come. Also important but less surprising is the paucity of research aimed at prevention of concussion. I think we can agree that preventing concussion would be preferred to treating it.

The authors suggest that [clinicaltrials.gov](https://clinicaltrials.gov) should mandate the provision of a definition of concussion in registered studies. I think this would be valuable. Perhaps the best way to bring unity to the concussion definition would be to have agreed upon definitions of concussion and mild traumatic brain injury mandated by funding agencies. This 'mandatory use' approach has seemed a very

effective way of improving the uptake of head injury common data elements.

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1. Menon DK, Schwab K, Wright DW, et al. Position statement: definition of traumatic brain injury. *Arch Phys Med Rehabil.* 2010;91(11):1637-1640.
  2. Carney N, Ghajar J, Jagoda A, et al. Concussion guidelines step 1: systematic review of prevalent indicators. *Neurosurgery.* 2014;75 (Suppl 1): S3-S15.