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Strengthening the Evidence Base: Recommendations for Future Research Identified Through the Development of CDC's Pediatric Mild TBI Guideline

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Abstract

Objective: The recently published Centers for Disease Control and Prevention evidence-based guideline on pediatric mild traumatic brain injury (mTBI) was developed following an extensive review of the scientific literature. Through this review, experts identified limitations in existing pediatric mTBI research related to study setting and generalizability, mechanism of injury and age of cohorts studied, choice of control groups, confounding, measurement issues, reporting of

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results, and specific study design considerations. This report summarizes those limitations and provides a framework for optimizing the future quality of research conduct and reporting.

Results: Specific recommendations are provided related to diagnostic accuracy, population screening, prognostic accuracy, and therapeutic interventions.

Conclusion: Incorporation of the recommended approaches will increase the yield of eligible research for inclusion in future systematic reviews and guidelines for pediatric mTBI.

Keywords

child; concussion; guideline; mild traumatic brain injury; pediatrics; study design

PEDIATRIC MILD TRAUMATIC BRAIN INJURY (mTBI), including concussion, is a significant public health concern. In 2014, traumatic brain injury in children, inclusive of mTBI, accounted for more than 800 000 emergency department visits (1103.9 per 100 000 children) and 23 000 hospitalizations (31.4 per 100 000).[1] Data suggest that almost 90% of children with mTBI enter the healthcare system in nonemergency department outpatient settings,[2] and 65% of children with mTBI may not seek care in any organized healthcare setting.[3] Most children recover from postconcussive symptoms within the first few months following injury; however, a significant subset reports long-term sequelae.[4] The International Consensus Statements on Concussion in Sport, among others, highlighted the need for continued research and evidence-based strategies to improve diagnosis, prognostication, and treatment of mTBI to help improve outcomes for children with mTBI.[5]

The Centers for Disease Control and Prevention (CDC) responded to this need by publishing an evidence-based guideline in 2018.[6] This guideline is inclusive of clinical recommendations spanning diagnosis, prognosis, and management/treatment that are applicable to healthcare professionals working in all settings. In developing the CDC guideline, the authors identified limitations in research including related to study settings and generalizability, mechanism of injury, age, control groups, confounding, measurement issues, result reporting, and specific study design considerations. This report addresses those limitations and provides a framework for optimizing the future quality of research conduct and reporting to better inform next iterations of guideline recommendations.

DEVELOPMENT OF THE CDC PEDIATRIC mTBI GUIDELINE

The CDC Pediatric mTBI Guideline was developed through a rigorous stepwise process guided by the American Academy of Neurology methodology and 2010 National Academy of Sciences methodology for the development of evidence-based guidelines.[6,7] This evidence-based guideline was directed by an extensive review of the scientific literature[7] focused on 6 clinical questions (see Table 1). The literature search spanned 25 years (January 1, 1990, to July 31, 2015). Using a modified Grading of Recommendations Assessment Development and Evaluation (GRADE) methodology, guideline investigators reviewed studies of mTBI that provided analyzable data on youth 18 years and younger. The inclusion of youth through 18 years of age allowed for applicability of results to older high school populations still commonly cared for in pediatric practices. A broad definition of mTBI was utilized encompassing Glasgow Coma Scale scores of 13 to 15, regardless of the

presence of intracranial imaging findings and related care needs, to better understand outcomes and provide inclusive recommendations for the management of children representing the full spectrum of children diagnosed with concussion/mTBI, including children at the more severe end of that spectrum who are at risk for "falling through the cracks" of services.[8]

Of the more than 37 000 abstracts identified through the literature search, the guideline authors selected over 2900 articles in a dual-reviewer process that met the inclusion criteria for full-text review. Approximately 345 articles were deemed sufficiently relevant for data extraction, and ultimately datasets from 66 studies were included in the text of the systematic review, which formed the basis of the guideline. Included studies were classified according to risk bias with varying strengths of evidence. Confidence in the evidence was evaluated across studies *per clinical question* and was downgraded or upgraded based on consistency, precision, plausibility, directness, reporting bias, magnitude of effect, dose response, and the direction of bias.[9]

CURRENT LIMITATIONS AND OPPORTUNTIES FOR FUTURE RESEACH IDENTIFIED THROUGH GUIDELINE DEVELOPMENT

Limitations identified generally focused on study design, data presentation (such as not separating findings by age and TBI severity level), use of small sample sizes and exclusion of control groups, and generalizability and applicability of research findings (such as due to unclear inclusion/exclusion criteria and unrepresentative samples). Table 1 summarizes limitations in the evidence consistently identified by the guideline authors for each of the 6 clinical questions.

Opportunities to optimize the conduct and reporting of future research, applicable to all study designs, are discussed below and summarized in Table 2.

Study settings and generalizability

Capturing a broad spectrum of youth with mTBI is critical for study outcome generalizability to clinical populations. This will require recruitment of children with mTBI from a range of healthcare settings (eg, pediatric offices, subspecialty clinics, varying types of emergency departments, or urgent care settings) and also outside of healthcare settings, such as in schools. The importance of capturing youth from varying settings is underscored by data demonstrating that site of care varies based on children's age, race/ethnicity, and socioeconomic status.[2] The severity and duration of symptoms are also likely to influence whether and where care is sought. In all cases, clear inclusion and exclusion criteria must be used and reported for the purposes of evaluating generalizability, as well as facilitating replication and comparison across studies.

Mechanism of injury

Most studies focus on sports-related injuries; however, 30% to 50% of children treated for mTBI in healthcare settings sustain injuries through other mechanisms (eg, falls and motor vehicle crashes).[10,11] While the distribution of sports- versus non-sports-related mechanisms

of injury will vary by age and setting, it is important to study children with mTBI of all etiologies and to understand mechanism-related differences and similarities.

Age range

To date, mTBI research has been particularly limited in young children, despite their high rate of TBI[12] and high risk for behavioral and learning problems following mTBI.[13–16] One challenge that needs to be addressed is how to reliably diagnose mTBI in infants and toddlers incapable of articulating their symptoms, especially in the setting of nonspecific symptoms such as vomiting, fussiness, or irritability. Currently available postconcussive symptom inventories have not been validated for children younger than 5 to 6 years.[17,18] Research is needed to define symptoms and signs of mTBI in very young children and to validate age-appropriate symptom inventories inclusive of younger age groups. In addition, the identification of objective diagnostic tools, such as serum biomarkers, is likely to play a critical role in young children.

Control groups

Selection of control groups in mTBI research is important. Even in study designs for which non-mTBI controls may not be necessary for addressing the primary question (eg, questions 2, 4, and 5 included in the systematic review), the inclusion of controls allows contextualization of outcomes in the mTBI cohort. Utilization of an injured comparison group that experienced nonhead trauma controls for factors related to a child's likelihood of sustaining an injury as well as for nonspecific physiologic and emotional responses to trauma. However, as brain injury can occur secondary to translational forces in the absence of direct blows to the head, as in body-checking during hockey or tackling in football, deliberate care should be taken to identify and exclude control group children with subtle signs of mTBI. Noninjury control groups will not provide an understanding of the effects of mTBI relative to trauma more generally but may provide a clearer understanding of how children with mTBI compare to a broader sample of their peers. When possible, use of a child's own preinjury data for comparison purposes best controls for interindividual variability, although nonhead injury controls are still useful in this context for establishing normative expectations for reliable change over time.[19]

Accounting for confounding

Across participants with mTBI and controls, identification of and accounting for confounding factors is critical to quality research. Factors to consider include a child's preinjury functioning (eg, preinjury symptom level, academic performance, medical, and/or mental health diagnoses), family functioning (eg, socioeconomic status and parenting styles), and other exposures (eg, prior mTBI and nonconcussive head trauma). A priori sample size calculations need to account for inclusion of multiple confounders in analyses.

Measurement issues

Careful attention is needed in the selection of measures used to describe mTBI populations with respect to preinjury and postinjury status. Consistent use of the same, validated measures (eg, NIH Common Data Elements[20–22]) to assess common constructs (eg, post

concussive symptoms, cognitive functioning, and behavioral adjustment) will facilitate comparison of results across studies, including through meta-analysis techniques. Given the evolving nature of evaluation and management of mTBI, however, the call for common data elements must be balanced against the continued need to evaluate and report on novel measures that may show improved sensitivity to subtle findings, such as changes in school performance that may not be reflected in traditional standardized measures of academic achievement and novel imaging acquisitions/analyses that may more fully capture disruption of structure and function as compared with standard clinical imaging. For findings to be optimally translatable into clinical practice, diagnostic and prognostic measures should be publicly available and feasible for widespread use.

Reporting of results

When publishing research, key reporting features will optimize inclusion of results in systematic reviews and meta-analyses and thereby promote future guideline development. If the research cohort includes participants spanning adolescence through early adulthood or with more severe forms of TBI, data should be presented for the subset of participants who are 18 years and younger or have mTBI. In addition, sufficient raw data must be provided in the text or as supplemental files to allow calculation of effect sizes and inclusion in meta-analyses; 95% confidence intervals are a preferred measure of precision[9] and should be provided.

Specific study design considerations

To address study design-specific strategies for optimizing research quality, recommended approaches were compiled for each of the 6 questions included in the systematic review (see Tables 3-6). Each table addresses 1 or 2 of the questions included in the systematic review. For each question, a recommended approach is provided for critical elements of study design and reporting. These recommended approaches represent a translation of general study design and reporting principles to pediatric mTBI-specific language and concepts and are intended to aid researchers by providing models for designing high-quality studies and optimizing dissemination of findings. The systematic review questions were used for convenience purposes and are not intended to reflect a recommendation for a specific research agenda.

Other research directions/gaps

While this article describes limitations in research related to the specific, focused questions utilized in the CDC Pediatric Mild TBI Guideline, other questions related to identification of risk for mTBI, prevention of mTBI, and reduction in possible long-term adverse outcomes remain important areas in need of quality research. In addition, children live in home and school environments that may contribute to their long-term outcomes. Factors such as family education, parental income, and parenting styles, as well as receipt of appropriate support at school, contribute to the risk and outcomes of mTBI. Data collection about a child's environment is important to consider in future research. Prospective study of a broad, nationally representative cohort over time to determine which children with mTBI have good versus poor outcomes is needed. In addition, high-quality research is needed to understand the effects of blows to the head in the absence of diagnosed mTBI.

CONCLUSION

Pediatric mTBI is a significant public health concern representing a research priority that warrants increased attention. Fortunately, the literature related to pediatric mTBI continues to expand rapidly, and continued updates of evidence-based systematic reviews and guidelines will be needed, as the amount and quality of research grows. Incorporation of the concrete approaches outlined here would increase the yield of eligible research for inclusion in future systematic reviews and recommendations for pediatric mTBI, thereby directing optimized standard care in this vulnerable population.

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TABLE 1

Limitations identified in the evidence by clinical question

Clinical question	Study design	Data presentation	Sample size and control groups	Generalizability
Applicable to all research reviewed	Lack of randomization	Data not presented separately for participants 18 y and younger Data not presented separately for mTBI (vs moderate and/or severe TBI)	Small sample sizes	Lack of clear inclusion/exclusion criteria Unrepresentative samples (eg, cohorts of only patients evaluated in emergency departments, lack of inclusion of young children)
Question 1 For children (18 y and younger) with suspected mTBI, do specific tools, as compared with a reference standard, assist in accurately diagnosing mTBI?	Lack of clarity regarding objectivity of diagnosis of mTBI	Uncertainty regarding masking (blinding) of raters	Lack of extracranial injury control group	Measures not able to be assessed in acute postinjury period
Question 2 For children (18 y and younger) presenting to the emergency department (or other acute care setting) with mTBI, how often does routine head imaging identify intracranial injury?	Bias of sampling from emergency departments at institutions with specialized interest in TBI			Nonsystematic selection of participants biased toward positive imaging findings
Question 3 For children (18 y and younger) presenting to the emergency department (or other acute care setting) with mTBI, which features identify patients at risk for important intracranial injury?	Retrospective study design Bias of sampling	Risk factors assessed in isolation without comparing their unique effect relative to other risk factors		Nonsystematic selection of participants for imaging Lack of precision or inconsistency across studies
Questions 4 and 5 For children (18 y and younger) with mTBI, what factors identify patients at increased risk for ongoing impairment, more severe symptoms, or delayed recovery <1 y (question 4) or ≥1 y (question 5) postinjury?	Retrospective or cross-sectional study design	Data not presented in sufficient detail to permit calculation of effect sizes		Lack of precision Nonsystematic selection of participants
Question 6 For children(18 y and younger) with mTBI (with ongoing symptoms), which treatments improve mTBI-related outcomes?	Lack of randomization Absence of objective or masked outcome measures			Lack of precision, directness, or small magnitude of effect Dearth of research on therapeutic intervention following pediatric mTBI

Abbreviations: mTBI, mild traumatic brain injury; TBI, traumatic brain injury.

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TABLE 2

Research design and reporting elements relevant across types of mTBI studies

Population	Include broad mTBI population • Recruitment from a variety of sites and populations – Within healthcare settings – Outside of healthcare settings – Rural vs urban – Community vs academic centers – Facilitate racial/ethnic diversity • Broad age range, 0-18 y • Broad definition of mTBI – Sports and non-sports injuries – Full range of mTBI severity – Inclusion of youth with and without intracranial imaging findings Optimize control group • Orthopedic/extracranial injury controls account for nonspecific trauma-related factors • Noninjured, healthy controls allow comparison to uninjured peers • Within-individual preinjury evaluation best accounts for interindividual variability; non-mTBI controls are still needed in this context to establish normative expectations for reliable change • Controls are optimally recruited from the same settings as the mTBI cohort • Controls are screened for prior TBI exposure Determine eligibility by clearly defined inclusion/exclusion criteria Identify and describe relevant co-morbidities and plan for exclusion or analyses to account for these factors • Mental health diagnoses • Preinjury symptoms (eg, headaches) • Cognitive/educational diagnoses Determine sample size based on a priori power calculation
Reporting	By TBI severity • If mixed severity of TBI studied, provide data separately for mTBI group • Provide data separately for youth with mTBI and intracranial imaging findings By age • If participants 18 y and older included, provide data separately for participants 18 y and younger

	• Provide data separately for youth 4 y and younger. Include analyses accounting for sex and gender Provide sufficient raw data for effect size calculations Provide 95% confidence intervals where possible Presentation of negative findings is important to avoid bias in the literature
Data sharing	Share data via publicly available archive

Abbreviations: mTBI, mild traumatic brain injury; TBI, traumatic brain injury.

TABLE 3

Diagnostic accuracy in mTBI: Recommended approaches

	Recommended approach
Setting	Captures broad spectrum of youth with suspected mTBI
mTBI population	Broad spectrum of youth with mTBI captured early after injury (for acute diagnostic purposes) Random, consecutive, or systematic selection of participants
Control population	Orthopedic injury controls, to distinguish trauma in general from mTBI specifically
Tool selection	Diagnostic test identifies mTBI vs no mTBI Diagnostic measures should be readily available in most settings where children with mTBI receive care Reference standard is objective or made without knowledge of results of diagnostic measure
Data collection and reporting	Prospective data collection within 24-48 h postinjury Individual administering and/or evaluating the diagnostic test must be masked (blinded) to study group/results from reference standard. Method for ensuring masking should be described At least 80% of enrolled participants should have both the diagnostic test and the reference standard completed For continuous data, report means and standard deviations for mTBI and control groups. For binary outcomes, report number and percentage of mTBI and control participants with positive outcome
Study reporting standards	STARD checklist[23]

Abbreviation: mTBI, mild traumatic brain injury; STARD, Standards for Reporting of Diagnostic Accuracy.

TABLE 4

Population screening in mTBI: Recommended approaches

	Recommended Approach
Setting	Optimal design is to prospectively capture all youth with mTBI treated in a defined setting within a given geographical region
Population	Broad definition of mTBI based on current practice to avoid bias toward youth with higher likelihood of imaging findings Control population of youth treated in emergency departments without a history of head trauma to compare frequency of nonspecific findings
Imaging modality	Modality available/practical for routine use for clinical practice Optimal study includes imaging obtained for >80% of eligible youth
Outcome	Consider evaluating 2 levels of outcome: (1) Any injury-related imaging finding (divided into subcategories of findings) (2) Clinically important intracranial injury per standardized definition When reporting, state what intracranial findings were evaluated and report numbers of positive findings for each type of intracranial finding In addition, report the number of youth with multiple findings For important intracranial injury, use existing definitions in the literature (eg, PECARN definition). In all cases, provide specifics regarding what findings define “clinically important”
Study reporting standards	STROBE checklist[24]
To additionally address question 3 (prognostic accuracy): For children (18 y and younger) presenting to the emergency department (or other acute care setting) with mTBI, which features identify patients at risk for important intracranial injury?	
Risk factors evaluated for imaging findings	Incorporate existing clinical rules Each risk factor must be objectively defined
Outcome evaluated	“Important intracranial injury” is objectively measured and/or determined without knowledge of risk factors Reporting needs: Provide raw numbers or sufficient data to allow calculation: • Total number of youth imaged • Number with each risk factor who met criteria for imaging by decision rule • Number with each risk factor who met criteria for important intracranial injury Provide 95% confidence intervals
Study reporting standards	TRIPOD checklist[25]

Abbreviations: mTBI, mild traumatic brain injury; STROBE, Strengthening the Reporting of Observational Studies in Epidemiology; TRIPOD, Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis.

TABLE 5

Prognostic accuracy in mTBI: Recommended approaches

	Recommended approach
Setting	Optimal design is to prospectively capture as many youth as possible with mTBI in a defined setting or geographical region (not limited to emergency departments or specific sports)
Population	Participation rate is either 80% of eligible population or participants can be compared with nonparticipants on key characteristics to determine comparability Minimal attrition (<10% per year) over time Control population (preferably youth with extracranial injury) should be included to compare outcomes in concussion group relative to peers (reliance on normative data for comparison is less ideal)
Predictors	Determined by investigator. May include 1 or more of the following: • Age • Sex • Gender • Race • Weight • Injury severity • Imaging findings • Biomarkers • Early symptoms • Premorbid factors (family functioning, SES, neuropsychological functioning, genetic factors, medical history, psychiatric history) • Mechanism of injury
Outcome	Outcome measures should be objective and determined without knowledge of risk factor status Reporting needs: • Total number of youth examined • Description of group status for each risk factor (number with/without risk factor or distribution of ratings) • Measure of entire group on outcome measure (eg, number with/without outcome or mean and standard deviation) • For dichotomous predictor variables: – For dichotomous outcome variables: number of participants with/without risk factor who are positive for specified outcome – For continuous outcome variables: mean and standard deviation of outcome for groups with/without risk factor • For continuous predictor variables: measure of statistical association of predictor and outcome
Study reporting standards	STROBE checklist[24]

Abbreviations: mTBI, mild traumatic brain injury; SES, socioeconomic status; STROBE, Strengthening the Reporting of Observational Studies in Epidemiology.

TABLE 6

Therapeutic interventions in mTBI: Recommended approaches

	Recommended approach
Design	Randomized controlled trial
Setting	Optimal design is to capture all youth with mTBI treated in a defined setting Special emphasis should be placed on children with risk factors for prolonged recovery, including more severe symptoms at presentation
Population	Optimal population reflects broad definition of mTBI 80% of enrolled participants complete trial Baseline characteristics equivalent between groups Control data: • Baseline measurements in injured participants • Randomized control group receiving placebo medication or intervention
Therapeutics	Investigator-selected Some examples: Medication Prescription for activity or rest Vestibulo-ocular therapies Balance rehabilitation
Outcome	Improvement as measured by validated diagnostic tools such as: Symptom scales Neurocognitive testing Health-related quality-of-life questionnaires Physical assessments of balance or vestibular/ocular function Sleep questionnaires Brain imaging, including specialized MRI
Study reporting standards	CONSORT checklist[26] Clinical trials registry

Abbreviations: CONSORT, Consolidated Standards of Reporting Trials; MRI, magnetic resonance imaging; mTBI, mild traumatic brain injury.