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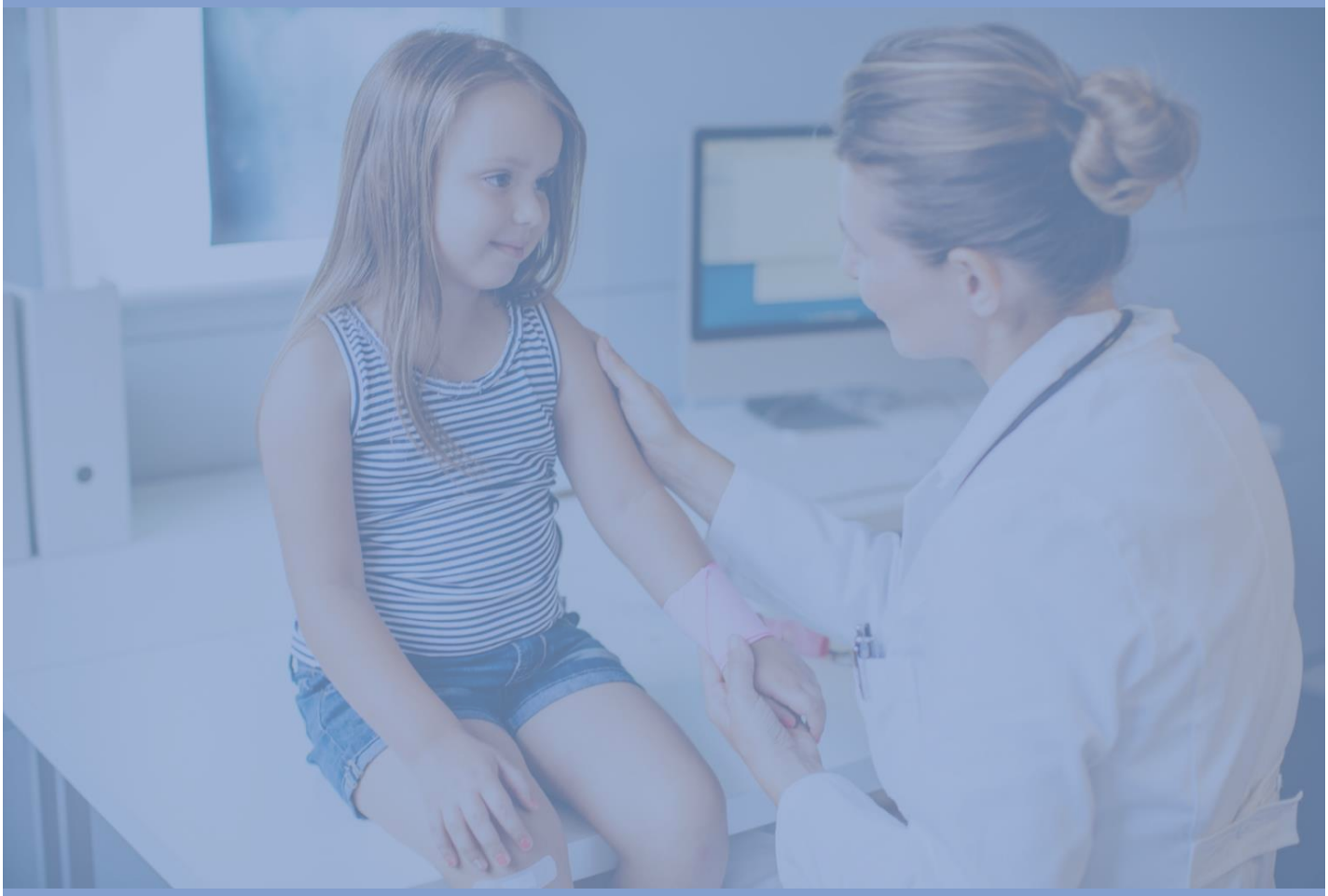
Report From the Pediatric Mild Traumatic Brain Injury Guideline Workgroup:

Systematic Review and Clinical Recommendations for Healthcare Providers on the Diagnosis and Management of Mild Traumatic Brain Injury Among Children



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REPORT AUTHORS

Lumba-Brown A; Yeates KO; Gioia G; Turner M; Benzel E; Suskauer S; Giza C; Joseph M; Broomand C; Weissman B; Gordon W; Wright DW; Moser RS; McAvoy K; Ewing-Cobbs L; Duhaime A; Putukian M; Holshouser B; Paulk D; Wade S; Herring S; Halstead M; Keenan H; Choe M; Christian CW; Guskiewicz K; Raksin P; Gregory A; Mucha A; Taylor HG; Callahan J; DeWitt J; Collins M; Kirkwood M; Ragheb J; Ellenbogen R; Spinks TJ; Ganiats TG; Sabelhaus L; Altenhofen K; Schoessler S; O'Connor RE; Timmons S.

EXECUTIVE SUMMARY

Mild traumatic brain injury (mTBI) in children is a public health concern. From 2005 to 2009, there were more than 2 million outpatient visits and almost 3 million emergency department (ED) visits for mTBI in children.[E1] In a subset of pediatric patients, postconcussive symptoms persist past 2 weeks and may continue for longer than 3 months.[E2] Pathophysiologic injury and symptomatology (both acute and long term) affect a child's ability to function physically, cognitively, and psychologically following mTBI.[E3-E5]

Despite the public health burden this injury presents, no evidence-based clinical guidelines exist on best practices for the diagnosis and management of pediatric mTBI in the United States that are inclusive of non-sports injury and younger age groups. Clinical guidance for healthcare providers on the identification, diagnosis, and management of pediatric mTBI is critical to improving the health and safety of this vulnerable population.

Through a standard protocol of identification and nomination, the National Center for Injury Prevention and Control's Board of Scientific Counselors at the Centers for Disease Control and Prevention established the Pediatric mTBI Guideline Workgroup, which included 21 Workgroup members. Given the size of the task, 21 Ad-Hoc experts were invited to participate in a consulting capacity. In addition, six federal representatives from the National Institutes of Health, the U.S. Department of Education, the Health Resources and Services Administration, the U.S. Department of Defense, and the Consumer Product Safety Commission were invited to observe the process.

The group's purpose was to create a report comprising a systematic review of the literature and clinical recommendations for healthcare providers on the identification, diagnosis, and management of mTBI among children ages 18 years and younger. Recommendations outlined in the Workgroup's report aim to provide healthcare providers in primary care, outpatient specialty, inpatient, and emergency care settings with guidance in their care of children with mTBI and promotion of evidence-based practices.

The Workgroup began development of their report by independently nominating pertinent clinical questions for consideration according to an analytic framework using the Patient-Intervention-Comparator

or Co-Intervention-Outcome format. Collated questions were presented to the entire group for ranking using a modified Delphi process during 3 rounds of voting. Through this process, the Workgroup ultimately selected six clinical questions pertaining to children 18 years of age and younger with mTBI for evaluation via systematic review.

1. For children with suspected mTBI, do specific tools, as compared with a reference standard, accurately diagnose mTBI?
2. For children presenting to the ED (or other acute care setting) with mTBI, how often does routine head imaging identify important intracranial injury?
3. For children presenting to the ED (or other acute care setting) with mTBI, which features identify patients at risk for important intracranial injury?
4. For children with mTBI, what factors identify patients at increased risk for ongoing impairment, more severe symptoms, or delayed recovery (< 1 year post-injury)?
5. For children with mTBI, which factors identify patients at increased risk of long-term (≥ 1 year) sequelae?
6. For children with mTBI (with ongoing symptoms), which treatments improve mTBI-related outcomes?

The systematic review and clinical recommendations for healthcare providers were developed using methods of the American Academy of Neurology and are compliant with the 2010 standards of the Institute of Medicine. An extensive literature search spanning 1990–2015 was conducted to identify evidence for each question, and more than 34,000 abstracts were reviewed by the Workgroup and Ad-Hoc experts, with agreement between two independent experts required at each step of abstract review, full text review, and data abstraction for evidence tables using the modified GRADE[E6] method.

The Workgroup was cognizant of the heterogeneity of presentations and outcomes of children with mTBI and aimed to prevent the exclusion of children representing the more severe end of the mTBI spectrum. For this reason, evidence analyzed included children described in the literature as having mTBI or "concussion" by historical definitions, encompassing Glasgow Coma Scale scores of 13-15, with and without the complication of intracranial injury on neuroimaging, and regardless of potentially requiring a hospital admission and/or neurosurgical intervention.[E7-E9]

Recommendations for healthcare providers regarding the clinical management of mTBI in children were developed and categorized into three topics: diagnosis, prognosis, and treatment. The recommendations were drafted based on evidence from the systematic review, as well as related evidence, scientific principles, and expert inference. Clinical recommendations were collated and distributed to the Workgroup in sequential rounds of voting to determine consensus. After four rounds, consensus was achieved on 46 clinical recommendations: 11 pertaining to diagnosis, 12 pertaining to prognosis, and 23 focused on treatment and management.

The diagnostic recommendations for healthcare providers examine the role of neuroimaging in mTBI identification. A key recommendation states that healthcare providers should use validated clinical decision rules to identify children at low risk for intracranial injury, in whom head computed tomography (CT) is not indicated, as well as to identify children who may be at higher risk for clinically important intracranial injury and, therefore, may warrant head CT. Several other imaging modalities, including magnetic resonance imaging, single photon emission CT, and skull x-ray, are not

endorsed by Workgroup recommendations as diagnostic tools in the acute evaluation of suspected or diagnosed mTBI based on analysis of the current evidence. Other diagnostic tools also considered include symptom scales, cognitive testing, and biomarkers. A key clinical recommendation established by the Workgroup states that healthcare providers should use age-appropriate, validated symptom scales for the purposes of diagnosis, and may also use validated, age-appropriate computerized cognitive testing. Insufficient evidence is available to support the use of serum biomarkers for diagnostic purposes at this time.

Clinical prognostic recommendations state that healthcare providers should counsel patients and families that most children with mTBI do not show significant difficulties that last more than 1-3 months post-injury, but that each child's recovery from mTBI is unique and will follow its own trajectory. Additionally, healthcare providers should assess the premorbid history of children, and counsel children and families that recovery from mTBI might be delayed in those presenting with specific risk factors. Further prognostic recommendations specify that healthcare providers should screen for a variety of known risk factors for persistent symptoms in children with mTBI. They may use validated prediction rules, which combine information about multiple risk factors for persistent symptoms, to provide prognostic counseling to children with mTBI evaluated in ED settings. Healthcare providers should use a combination of tools to assess recovery in children with mTBI. These should include validated symptom scales, and may include validated cognitive testing and balance testing. Based on premorbid history, demographics, and injury characteristics, as well as ongoing assessment of recovery, healthcare providers should monitor children with mTBI who are determined to be at high risk for persistent symptoms. When symptoms do not resolve as

expected with standard care (ie, within 4-6 weeks), healthcare providers should provide or refer for appropriate assessments and/or interventions.

Clinical treatment recommendations state that healthcare providers should offer education and reassurance to families, incorporating several specific informational elements: warning signs of more serious injury; description of injury and expected course of symptoms and recovery; instructions on how to monitor postconcussive symptoms; prevention of further injury; management of cognitive and physical activity/rest; instructions regarding return to play/recreation and school; and clear clinician follow-up instructions. Healthcare providers may emphasize social support as a key element in their education of caregivers. Subsequent clinical recommendations on treatment specify that healthcare providers should counsel a gradual stepwise progression, moving from rest to full resumption of activity. The progression may involve active rehabilitation programming with the intention to promote the return to full activity without significant symptom exacerbation.

Several clinical treatment recommendations focus on return to school. Medical and school-based teams should counsel students and families about the process of gradually increasing academic activities, with the goal of increasing participation without significantly exacerbating symptoms. Return-to-school protocols should be customized based on the severity of postconcussion symptoms, as monitored by the student, family, healthcare provider, and school teams, to jointly determine what modifications or accommodations are needed to maintain an academic workload without exacerbating symptoms. If a student has prolonged symptoms that interfere with academic performance, school-based teams should assess the educational needs of that student and determine the need for additional educational supports. The provision of supports should be adjusted on an ongoing basis until academic performance has returned to preinjury levels. Students who demonstrate prolonged symptoms and academic difficulties, despite appropriate educational supports, should receive a referral for a formal evaluation by a specialist in pediatric mTBI.

Other clinical treatment recommendations specifically address headache management. Healthcare providers in the ED should clinically observe and consider obtaining a head CT in children presenting with severe and worsening headache to evaluate for intracranial injury, in accordance with validated clinical decision rules. Children undergoing observation periods for headache with acutely worsening symptoms should undergo emergent neuroimaging. Non-narcotic analgesia should be provided to children with painful headache following acute mTBI, but with counseling as to the risks of analgesic overuse. Healthcare providers should refer children with chronic headache after mTBI for multidisciplinary evaluation and treatment.

Other treatment recommendations address concerns about dizziness and sleep problems. Specifically, healthcare providers may refer children with subjective or objective evidence of persistent vestibulo-ocular motor dysfunction for a program of vestibular rehabilitation. Also, healthcare providers should provide guidance on proper sleep hygiene methods. If sleep problems emerge or continue despite appropriate sleep hygiene measures, healthcare providers may refer children with mTBI to a sleep disorder specialist for further assessment.

The clinical treatment recommendations also address cognitive impairment after mTBI. Healthcare providers should attempt to determine the etiology of cognitive dysfunction, within the context of other symptoms, and should recommend treatment for cognitive dysfunction that reflects its presumed etiology. They may refer children with persisting complaints related to cognitive function for a formal neuropsychological evaluation to assist in determining etiology and recommending targeted treatment.

If implemented consistently, the Pediatric mTBI Workgroup Recommendations should improve healthcare for children, with evidence-based guidance for healthcare providers on the diagnosis and management of mTBI. Organized and consistent care for children with mTBI is critical to their recovery and re-integration into daily activities. Importantly, despite the increasing amount of published literature pertaining to mTBI, much more research needs to be done, as detailed in the Systematic Review.

SYSTEMATIC REVIEW: BACKGROUND AND INTRODUCTION

Traumatic brain injury (TBI) is a leading cause of death and disability in the United States, with significant public health implications.[S1-S4] Among children less than 15 years of age, pediatric TBI annually accounts for 3,000 deaths, 29,000 hospitalizations, and 473,947 emergency department (ED) visits in the United States.[S5]

At least 75% of all TBIs reported in the United States are classified as "minor," "mild," or "concussions," encompassing the spectrum of mild TBI (mTBI).[S1] Forty percent of *all* patients diagnosed with mTBI are children between the ages of 15 and 19 years old.[S6] Children are at risk for sustaining mTBIs due to their developing coordination, changing head-to-body ratio, risk-taking behaviors, and broad participation in sports and play.[S3,S7] From 2005 to 2009, there were more than 2 million outpatient visits and almost 3 million ED visits for mTBI in children.[S8] Sixty-nine percent of children diagnosed with mTBI are males and 30% of pediatric mTBIs are sports related.[S6] In a subset of patients, and via currently unclear processes, postconcussive symptoms persist past 2 weeks and continue for longer than 3 months.[S9] Such significant, long-term symptoms affect an individual's ability to function physically, cognitively, and psychologically.[S10-S12]

Mild TBI is one of the most common neurological disorders, but there is no universally accepted definition.[S1] The terms "concussion," "minor head injury," and "mTBI" are often used interchangeably in both the scientific literature and general media, but have different connotations for families, coaches, researchers, and healthcare providers, allowing for ambiguity and misinterpretation. In several studies, an injury described as a concussion was considered less severe than one described as an mTBI, potentially resulting in a premature return to activity in those diagnosed with concussion as compared to mTBI.[S13,S14] The Fourth International Conference on Concussion in Sport and the Institute of Medicine report that concussion "may result in neuropathological changes, but the acute clinical symptoms largely reflect a functional disturbance rather than a structural injury and, as such, no abnormality is seen on standard structural neuroimaging studies."[S15] This is distinct from the World Health Organization's definition of mTBI, which includes injuries with intracranial lesions.[S16] For these reasons, this report acknowledges the historical use of the term "concussion" and its continued use as a layman's term, but supports the clinical use of the term mTBI to most accurately reflect the pathophysiology of this neurologic injury. Importantly, the qualifier of "mild" does not suggest that an injury is trivial. Rather, the term is used to categorize the injury within the broader spectrum of mild, moderate, and severe traumatic injuries to the brain, allowing for clinical context.

Following mTBI, the brain's physiology is altered, as reflected in a variety of pathophysiological processes that may include oxidative stress, impaired axonal transport, and altered neurotransmission.[S17-S19] Such pathophysiological processes may be complicated by the presence of macroscopic injury, including intracranial hemorrhage. For most patients with mTBI, these

alterations in brain function are believed to resolve after a period of recovery, although they may persist or evolve in some cases (eg, complicated mTBI with macroscopic intracranial injury).[S19-S21]

For the purposes of *this* report, a wide clinical and functional definition of pediatric mTBI was employed in order to be cognizant of the heterogeneity of presentations and outcomes of children with mTBI and to prevent the exclusion of children representing the more severe end of the mTBI spectrum. Evidence analyzed included children described in the literature as having an mTBI or concussion by historical definitions, encompassing Glasgow Coma Scale (GCS) scores of 13-15, with and without the complication of intracranial injury on neuroimaging, and regardless of potentially requiring a hospital admission and/or neurosurgical intervention.[S1,S15,S16]

The past two decades have seen multiple efforts to increase awareness and understanding of mTBI. In 2000, Congress passed the *Children's Health Act of 2000* (Public Law 106-310) with the goal of delivering a national education and awareness campaign about TBI and charging the Centers for Disease Control and Prevention (CDC) with compiling the latest science on pediatric mTBI, creating a definition for mTBI, and determining the best methods to quantify its incidence and prevalence.[S22] In response, CDC formed the Mild Traumatic Brain Injury Workgroup, composed of experts in the field of brain injury, including those representing the Society for Academic Emergency Medicine, the Brain Injury Association of America, the American Congress of Rehabilitation Medicine, the American Academy of Neurology, and the National Institute on Disability and Rehabilitation Research.[S1] In 2003, the group produced a report that proposed conceptual and operational definitions of mTBI and made recommendations for mTBI surveillance needed to determine the full magnitude of mTBI and related impairments and disabilities for the general population, without pediatric specificity.[S1]

A number of guidelines have been developed related to the evaluation and care of specific types of mTBI. In 2008, CDC and the American College of Emergency Physicians produced neuroimaging and decision-making guidelines for adults with mTBI in the acute setting.[S23] These guidelines apply to patients age 16 and older who have a non-penetrating brain injury and a GCS score of 14 or greater. In 2012, a Canadian consensus guideline was published on managing patients' mTBI with persistent symptoms.[S24] In 2013, the American Academy of Neurology published an evidence-based guideline for the management of sports-related concussion in both children and adults.[S25] In 2014, the Institute of Medicine published "Sports-Related Concussions in Youth: Improving the Science, Changing the Culture," a major review of the science of sports-related concussion with recommendations to improve what is known about concussions and reduce their occurrence.[S26] Also in 2014, the Ontario Neurotrauma Foundation published evidence-based guidelines for diagnosing and managing pediatric concussion developed by a multidisciplinary team of experts in pediatric health.[S27]

Despite these large studies and guidelines published over the past 10 years, no evidence-based clinical guidelines exist regarding best practices for the diagnosis and management of pediatric mTBI that are specific to the United States and that are relevant to non-sports as well as sports injury and to younger as well as older age groups. Clinical guidance for healthcare providers on the diagnosis and management of pediatric mTBI will contribute to improving the health and safety of this vulnerable population.

PEDIATRIC MILD TBI GUIDELINE WORKGROUP

The CDC National Center for Injury Prevention and Control's (NCIPC) Board of Scientific Counselors (BSC), a federal advisory committee, established the Pediatric Mild TBI Guideline Workgroup in 2012. This Workgroup was charged with developing a report that comprises a systematic review and clinical recommendations for healthcare providers on diagnosis and management of mTBI among children and ages 18 and younger.

To identify potential Workgroup members, CDC medical officers and epidemiologists working in the field of TBI prepared a list of experts. This list was collated based on a review of relevant literature and TBI clinical practice guidelines. Expert nominations for the Workgroup were also obtained by receiving recommendations from various medical and health organizations. Once the initial list of experts was created, an online biography was obtained for each candidate and reviewed by the CDC/NCIPC staff. CDC/NCIPC staff rated each candidate as a high match, moderate match, or low match based on the following criteria:

1. Experience with TBI and pediatrics, as evidenced through biographies and publications obtained from literature searches.
2. Representation of a cross-section of professional settings, including clinical, research, healthcare systems, sports, and school environments.
3. Credentials and expertise in the following areas: pediatrics, family medicine, internal medicine, emergency medicine, neurology, neurosurgery, neuroimaging, neuropsychology, epidemiology, sports medicine, physiatry, nursing, physician assistant practice, emergency medical services, physical therapy and rehabilitation, athletic training, school health, and injury prevention (eg, motor vehicle safety, child maltreatment, falls safety, and sports safety).

The resulting list of potential Workgroup members consisted of experts who received the most high match ratings. The final list of Workgroup members was created in alignment with requirements contained within the Federal Advisory Committee Act, with review and approval by the NCIPC/BSC. In total, 21 non-federal members were selected for the Workgroup.

Given the size of the task, 21 additional Ad-Hoc experts were invited to participate in a consulting capacity throughout the course of the project. Ad-Hoc experts were identified using the same process and selection criteria outlined above for the Workgroup members. Both groups include broad representations among medical specialties and include allied healthcare professionals. Some members of the Workgroup and Ad-Hoc experts were former mTBI patients themselves or were family members of former mTBI patients. In addition, six federal representatives from the National Institutes of Health (NIH), the U.S. Department of Education, the Health Resources and Services Administration, the U.S. Department of Defense (DOD), and the Consumer Product Safety Commission were invited to observe the process.

DISCLOSURE OF RELATIONSHIPS

Workgroup members and Ad-Hoc experts were required to attest to financial and intellectual conflict of interest. Conflict of interest forms were requested from all participants at the inception of this process in 2012 and were again requested in 2016 to review any updated information. All Workgroup members and Ad-Hoc experts also completed a confidentiality form, which required disclosure of potential non-financial competing interests, financial interests, engagement in clinical practice overlapping with proposed clinical recommendations for clinicians, and ongoing research support.

The Workgroup members disclose that they have no financial conflicts of interest. Workgroup members

disclose the following related to the content of this guideline: Ed Benzel discloses 2012 Spine Prospective Clinical Research Grant #12-205, "Anatomical Differences and Protective Helmet Design in American Football," which he received from the Orthopedic Research and Education Foundation, and his work with Prevent Biometrics, where he was awarded DOD and U.S. Department of Transportation grants focusing on concussion dosimetry and behavioral deficits. Linda Ewing-Cobbs discloses her tuition waiver and travel expenses paid by the National Neurotrauma Society in June 2015, her work in performing neuropsychological evaluations of persons with TBI in research and clinical contexts, and her research awards from NIH and CDC in the areas of outcome following pediatric and adult injury. Gerard Gioia discloses his authorship and developer role of several of the free symptom measures, Child and Parent Post-Concussion Symptom Inventory and Acute Concussion Evaluation, and receiving royalties from his role as a test author for the Behavior Rating Inventory of Executive Function, Psychological Assessment Resources, Inc. Christopher Giza discloses his work with the California State Athletic Commission, his role as consultant to the National Football League (NFL)-Neurological Care Program, National Hockey League Players' Association, National Hockey League, Major League Soccer (MLS), National Basketball Association, U.S. Soccer Federation, and the National Collegiate Athletic Association (NCAA), his role as consultant on a NIH funded grant application for Neural Analytics, Inc., his work in the Medical Education Speakers Network, his medicolegal work on one or two cases annually, his clinical work on Sports Concussion at a mild TBI Clinic for one day per week, and his research support from the National Institute of Neurological Disorders and Stroke (NINDS), the DOD, NCAA, the Today and Tomorrow Children's Fund, the University of California, Los Angeles (UCLA) Brain Injury Research Center, the UCLA Faculty Grants Program, the UCLA Steve Tisch BrainSPORT program, and the NFL-GE. Wayne Gordon discloses his status as grant recipient (CDC, NIH, and the National Institute on Disability, Independent Living, and Rehabilitation Research [NIDILRR]). Mark Halstead discloses his lead authorship on the American Academy of Pediatrics policy statement on concussion. Stanley Herring discloses his past service on a medical advisory board for X2Biosystems and a payment from Vicis, a helmet manufacturer, in a joint initiative with the University of Washington. Angela Lumba-Brown discloses a stipend she received from UpToDate for publication review. Rosemarie Moser discloses book proceeds from her book Ahead of the Game and her engagement in clinical practice. Robert O'Connor discloses his salary from the University of Virginia School of Medicine and his position as Chair of the Board at the American College of Emergency Physicians. T.J. Spinks discloses his service on the Advisory Board for the Healthy Brain Foundation. Stacy Suskauer discloses travel expenses she received for presentations from the American Board of Physical Medicine and Rehabilitation; University of California San Diego; Hospital for Special Care, Connecticut; and All Children's Hospital, Florida; and her role as the medical director of the Neurorehabilitation Concussion Clinic at the Kennedy Krieger Institute, as well as physician provider at the Institute; her research support from NIH; and her research support from the Kennedy Krieger Institute. Shelly Timmons discloses her involvement on two professional organization boards and a speaker honorarium she received for speaking at courses related to neurotrauma for residents and practicing physicians. Michael Turner discloses two sources of corporate financial support from Medtronic Corporation and NICO corporation. David Wright discloses fees he received for his roles as speaker and consultant from Emory University School of Medicine, DOD, NINDS, Astrocyte Pharmaceuticals Inc. (Scientific Advisory Board), LPATH, Biogen Inc., European Congress of NeuroRehabilitation, Academy

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The Ad-Hoc experts disclose that they have no financial conflicts of interest. Experts disclose the following related to the content of this guideline: James Callahan discloses his role as a member of the Sub-Board of Pediatric Emergency Medicine for the American Board of Pediatrics and his role as a member of the Committee on Pediatric Emergency Medicine, American Academy of Pediatrics, and his honorarium for work as a member, Sub-Board of Pediatric Emergency Medicine for the American Board of Pediatrics Member, Committee on Pediatric Emergency Medicine, American Academy of Pediatrics from the American Board of Pediatrics. Meeryo Choe discloses her work as a consultant for the World Boxing Council, USA Swimming, Neural Analytics, her NIH Loan Repayment Program and research support from DOD, and her Brain and Behavior Foundation NARSAD Young Investigator Grant and The Friends of the Semel Institute/Drown Foundation Fellowship, research support from the NCAA, the UCLA Brain Injury Research Center, and the UCLA Steve Tisch BrainSPORT program. Cindy Christian discloses her medical-legal expert work in child abuse cases. Michael Collins discloses his Board Membership and role as Co-Developer for ImPACT applications. Tina Duhaime discloses her involvement in NIH's Transforming Research and

Acquiring Clinical Knowledge in Traumatic Brain Injury (TRACK) TBI study, which is a multi-site natural history data collection effort involving children and adults with traumatic brain injuries as well as her role as an investigator in the Food and Drug Administration's New England Pediatric Device Consortium, designed to promote development and commercialization of medical devices for children, in which she has no financial interest in any device. Richard Ellenbogen discloses his General Electric scientific board review, his NIH grant support, and his grant from the Paul G. Allen Family Foundation. Heather Keenan discloses her grant support from CDC and NIH. Michael Kirkwood discloses book royalties he received, a consultation to Psychological Assessment Resources, and multiple speaker honoraria, and his research grant support from the Patient-Centered Outcomes Research Institute and the National Institute on Disability and Rehabilitation Research, and his research grant support from Children's Hospital Colorado Research Institute. Anne Mucha discloses speaker fees she received. David Paulk discloses his travel compensation from his speaking engagement at the Virginia Academy of Pennsylvania's annual conference, as well as his legal consulting for a Pennsylvania practice. Margot Putukian discloses her role on the USA Football Medical Advisory Committee, NFL Head Neck & Spine Committee, US Lacrosse Sports Science & Safety Committee, NCAA Concussion Task Force, and the US Soccer, medical advisory committee, and her role as medical consultant for MLS; and her research grant support from the NCAA-DOD Grand Alliance and the National Operating Committee on Standards for Athletic Equipment. John Ragheb discloses his clinical practice that could be affected. Patricia Raksin discloses travel/expenses for oral board review courses. Gerry Taylor discloses clinical practice engagement, and his NIH and Patient-Centered Outcomes Research Institute grant support. Shari Wade discloses her NIH, NIDILRR, and Patient-Centered Outcomes Research Institute research grant support.

Two methodologists from the American Academy of Neurology (AAN) were contracted to support the project. The methodologists (Thomas Getchius and Dr. Gary Gronseth) disclose that they have no financial conflicts of interest. Thomas Getchius discloses his role as Chair of the Council of Medical Specialty Societies Clinical Practice Guideline Component Group, as well as his role as the incoming Chair of the Guidelines International Network North American Chapter, and his role as Agency for Healthcare Research and Quality grant recipient. Gary Gronseth discloses his salary from University of Kansas and Associate Editor honoraria and his contract with AAN guideline development.

CDC provided 100% of the funding for the supplemental evidence review tasks and meeting support. No foundation or industry support was accepted.

Overall Objective of the Pediatric Mild TBI Guideline Workgroup

The objective of the Pediatric Mild TBI Guideline Workgroup was to establish evidence-based recommendations for healthcare providers, developed using a rigorous scientific process that systematically reviewed the existing literature to address the lack of clinical consensus on the acute diagnosis and management of mTBI in children ages 18 and younger.

The Workgroup report represents the most comprehensive review of pediatric mTBI scientific evidence to date. Recommendations outlined in the Workgroup report will aim to provide healthcare providers caring for children in primary care, outpatient specialty, inpatient, and emergency care settings with guidance on the diagnosis and management of mTBI in children and help promote the use of evidence-based practices.

Selection of Clinical Questions

After presentation of an analytic framework and an introduction to the Patient-Intervention-Comparator or Co-Intervention-Outcome (PICO) format for questions, Workgroup members independently nominated questions for consideration. Candidate questions were collated and presented to the entire group. Using a modified Delphi process, questions were anonymously ranked on a 9-point ordinal scale of importance over three rounds of voting. Facilitated discussions among Workgroup members occurred between rounds of voting. Through this process, the Workgroup selected six clinical questions.

1. For children (18 years of age and younger) with suspected mild TBI, do specific tools, as compared with a reference standard, accurately diagnose mild TBI?

   Acceptable diagnostic reference standards for question 1 were not pre-specified. Reference standards used in the identified studies were tracked during the data extraction process.

2. For children (18 years of age and younger) presenting to the emergency department (or other acute care setting) with mild TBI, how often does routine head imaging identify important intracranial injury?

   Pertinent routine head imaging includes skull x-rays, head computed tomography (CT), and brain magnetic resonance imaging (MRI). Important intracranial injury abnormalities were defined as those that change acute treatment, such as abnormalities that prompt prolonged emergency room observation, hospitalization, or neurosurgical consultation (eg, intracranial hemorrhage, skull fractures).

3. For children (18 years of age and younger) presenting to the emergency department (or other acute care setting) with mild TBI, which features identify patients at risk for important intracranial injury?

4. For children (18 years of age and younger) with mild TBI, what factors identify patients at increased risk for ongoing impairment, more severe symptoms, or delayed recovery (< 1 year post-injury)?

5. For children (18 years of age and younger) with mild TBI, which factors identify patients at increased risk of long-term (≥ 1 year post-injury) sequelae?

   The literature relevant to both questions 4 and 5 was identified with a single search. The timing of the sequelae described from each identified study was tracked during the data extraction process.

6. For children (18 years of age and younger) with mild TBI (with ongoing symptoms), which treatments improve mild TBI-related outcomes?

LITERATURE SEARCH STRATEGY

The original database searches included MEDLINE (via PubMed), EMBASE, ERIC, SPORTDISCUS, and CINAHL. Two consecutive searches were limited by publication type and by date from January 1, 1990 to November 30, 2012 and an updated search from December 1, 2012 to July 31, 2015. Excluded publication types were comments, editorials, patient education handouts, newspaper articles, biographies, autobiographies, and case reports. All languages were included in the search result; non-English results were removed during the review process. In addition to a review of computerized bibliographic databases, experts reviewed the bibliographies of identified review articles.

The search strategies were developed and refined by performing test searches of MEDLINE (via PubMed). The sensitivity of the search was determined using a list of relevant index articles independently identified by the Workgroup. The specificity of the searches was determined by reviewing a randomly selected subset of the citations identified by the test searches. The finalized searches had a sensitivity of 100% relative to the index articles. Final question-specific search strategies are presented in the Appendix.

The original search strategy was used to model the updated search from December 1, 2012 to July 31, 2015. The databases searched include MEDLINE (via PubMed), EMBASE, ERIC, SPORTDISCUS, and CINAHL (via EBSCO). The updated search strategy was consistent with the original search; however, changes were required in the ERIC database search, as discussed below. Excluded publication types were comments, editorials, patient education handouts, newspaper articles, biographies, autobiographies, and case reports. All languages were included in the search result; non-English results were removed during the review process. To improve relevancy, the updated search was limited to human subjects.

In 2014, ERIC launched a new, more intuitive search algorithm to encourage the use of simple language, which the ERIC Thesaurus uses to produce search results. The changes to ERIC discourage large, specific, Boolean searches, and did not support the Keyword Identifier Tag used in the original strategy. The change in search algorithm required the removal of the Keyword Identifier Tag to achieve comparable search results.

EVIDENCE REVIEW PROCESS

Guideline Development Methodology

The Systematic Review and clinical recommendations for healthcare providers were developed using the guideline development methods of the American Academy of Neurology.[S28] These methods have been designed to be compliant with the 2010 standards of the Institute of Medicine.

To judge overall confidence in the evidence for each question, we used a modified GRADE process.[S28] This process explicitly considered the risk of bias in individual studies (class of evidence), consistency among studies, precision, directness, magnitude of effect relative to the risk of bias, presence of an expected dose-response relationship, and the direction of bias. Because of the small number of studies meeting the inclusion criteria, publication bias was not formally assessed.

Article Bias Ratings

The risk of bias in each study was determined using the classification of evidence scheme for screening, diagnostic, prognostic, and therapeutic questions found in the Appendix. Two experts abstracted study characteristics independently for each article selected for inclusion. A third expert adjudicated remaining disagreements. Evidence tables were constructed from abstracted study characteristics. All articles were reviewed by a minimum of two independent reviewers at each phase, requiring consensus for inclusion.

SYSTEMATIC REVIEW: CLINICAL QUESTIONS AND RATIONALE

Question 1: For children (18 years of age and younger) with suspected mild TBI, do specific tools, as compared with a reference standard, accurately diagnose mild TBI?

Introduction and Rationale

Following a blunt head injury, clinical decision-making hinges on the diagnosis of injury severity. A clinical decision rule guiding the use of head CT was recently published based on sign and symptom evaluation of more than 40,000 children with suspected mTBI.[S29] Although such evidence-based clinical decision rules are useful, challenges in the diagnosis of mTBI versus more significant TBI in acute care settings still exist.[S29] The decision to obtain head CT imaging following suspected mTBI remains a concern due to exposure to ionizing radiation. Advanced imaging techniques such as diffusion tensor imaging, magnetic resonance spectroscopy (MRS), perfusion weighted imaging, and functional MRI have shown changes in patients with mTBI, but their utility in management and feasibility of use has yet to be examined. Biomarker and imaging diagnostics for mTBI are reported in the literature and continue to be researched. There is a need to establish and analyze evidence regarding the reliability and validity of various tools and questionnaires to diagnose mTBI.

Inclusion Criteria

Studies of children (18 years of age and younger) with and without mTBI, where a putative diagnostic test was performed and was compared to an mTBI reference standard in both populations, were included.

Article Flow

A total of 6,849 research articles were identified by literature search. Of those, 787 full-text research articles were identified for full-text review for eligibility with 108 undergoing data extraction. Thirteen articles were ultimately included in the quantitative synthesis from data extraction based on the inclusion criteria. These 13 articles included no Class I studies, ten Class II studies, and three Class III studies. A single Class II study was ultimately rejected because the diagnostic test studied, the Chattecx Balance System, is no longer manufactured, and has not been commercially available for more than 15 years.

Description of the Evidence: Diagnostic Tool/Test Standard Category Outcome Pairs

Studies were organized by diagnostic tool/test: blood/serum tests, computerized cognitive tests, non-computerized cognitive tests, and symptom scales/checklists.

Blood/Serum Testing

➤ S100B

Two Class II studies[S30,S31] met the inclusion criteria. In the first study,[S30] the mTBI group was compared to a control group with long bone fractures. The study included mild, moderate, and severe TBI patients ages 0-13. Forty-four percent of the mTBI patients had abnormal serum S100B levels. No significant difference was observed in the percentage of children with abnormal S100B levels for the mild versus moderate TBI groups. Sensitivity was 0.44 (95% CI, 0.26-0.64) and specificity was 1.0 (95% CI, 0.76-1). The strength of the study was limited due to (1) the age restriction of less than 14 years of age, (2) the inclusion of inflicted trauma patients, and (3) the lack of a dose-response effect. The second study[S31] had two groups with a history of mTBI: one with postconcussive symptoms and a second with no symptoms. S100B and neuron-specific enolase (NSE) were measured within 6 hours in both groups. There was no difference in either marker between the two groups.

Confidence Level: Very low

***Conclusion:** There is insufficient evidence to determine whether serum S100B is a useful diagnostic indicator in distinguishing children with and without mTBI.*

➤ Serum Tau

A single Class II study met the inclusion criteria.[S32] Three groups were compared: mTBI with normal CT scan, mTBI with abnormal CT scan, and a control group. The control group was not defined. The difference in mean serum tau protein levels across the two mTBI groups and the control group were statistically significant ($P < 0.001$ and $P < 0.001$, calculated effect size Cohen's $d = 1.21$ (95% CI, 0.72-1.69)). Confidence in the evidence was downgraded due to the lack of definition of the control group, which compromised the generalizability of the findings.

Confidence Level: Very low

***Conclusion:** There is insufficient evidence to determine whether serum tau is a useful diagnostic indicator in distinguishing children with and without mTBI.*

➤ Serum Potassium (K), Sodium (Na), Glucose (Glu), White Blood Cell Count (WBC)

A single Class II study met the inclusion criteria.[S33] Three groups were compared: (1) patients admitted to the emergency department with a diagnosis of concussion, (2) patients admitted to the emergency department with long bone fractures without head injury, and (3) patients electively admitted for hernia repair. Significant results were K: Grp1v2, $d = -0.78$ (95% CI, 1.19-0.38), 1v3 $d = -1.1$ (95% CI, -1.5 to -0.67); Na: Grp1v2, $d = -0.67$ (95% CI, -1.1 to -0.26), 1v3 $d = -0.57$ (95% CI, -2.0 to -1.1); Glu: Grp1v2, $d =$ 0.18 (95% CI, -0.21 to 0.57), 1v3 $d = 1.17$ (95% CI, 0.75-1.6). Confidence in this evidence was downgraded as a clear definition of the inclusion criteria for the concussion study group was not provided.

Confidence Level: Very low

***Conclusion:** There is insufficient evidence to determine whether serum potassium, sodium, glucose, and white blood cell count are useful diagnostic indicators in distinguishing children with and without mTBI.*

➤ Autoantibodies Against Glutamate Receptors and Nitric Oxide Metabolites

A single Class II study met the inclusion criteria.[S34] Study subjects were divided into two TBI groups: mild (GCS 14-15) and severe (GCS 3-9). The control group had no identified central nervous system (CNS) disease and was either undergoing elective surgery or seen in a pediatric health clinic. Serum autoantibodies against glutamate receptors (AMPA $GluR_1$ and NMDA NR2A) and nitric oxide metabolites (nitrates and nitrites) were measured at three time points: 1-2 days, 4-5 days, and 7-10

days post-injury. Significant differences between the two TBI groups included Day 1-2 (GluR1) *d* = 3.4 (95% CI, 2.4-4.4) (NR2A) *d* = 5.8 (95% CI, 4.5-7.1); Day 4-5 (GluR1) *d* = 6.3 (95% CI, 4.9-7.7) (NR2A) *d* = 2.7 (95% CI, 1.8-3.6). Confidence in the evidence was downgraded because the study lacked a healthy control group. However, confidence in the evidence was upgraded for the magnitude of the effect of the significant findings.

Confidence Level: Low

***Conclusion**: Measurement of serum autoantibodies against glutamate receptors is possibly useful in the identification of children with and without mTBI.*

➤ Multiplex Bead Array Biomarkers

A single Class III study met the inclusion criteria.[S35] The study included a group of 16 infants (< 1 year of age) with inflicted TBI and a GCS of 15, and a control group consisting of two subgroups: (1) children undergoing elective surgery, and (2) children presenting to the emergency department with flu-like symptoms without diarrhea or fever, and no recent history of physical trauma. There were 16 TBI patients and 20 controls. Forty-four blood biomarkers were assayed, and 2 specific biomarker combinations were examined: vascular cellular adhesion molecule (VCAM) and IL-6, Sensitivity = 0.87 (95% CI, .60-.98), Specificity = 0.90 (95% CI, 0.67-0.98); LR+ = 8.8 (95% CI, 2.3-33.0); metallopeptidase-9 (MMP-9) and IL-6, Sensitivity = 0.81 (95% CI, 0.54-0.95), Specificity = 0.90 (95% CI, 0.67-0.98); LR+ = 8.1 (95% CI, 2.1-30.9). Because the data presented represented a single Class III study, confidence in this evidence was very low.

Confidence Level: Very low

***Conclusion**: There is insufficient evidence to determine whether a multiplex bead array serum assay of 44 blood biomarkers is a useful tool in distinguishing children with or without mTBI.*

➤ Ubiquitin Carboxyl-Terminal Hydrolase L1 (UCHL-1) and Glial Fibrillary Acid Protein (GFAP)

A single Class II study met the inclusion criteria.[S9] Twenty-three children ages 11-16 with isolated mTBI were compared to patients with orthopedic injuries. Mean serum UCHL-1 levels were not statistically different between the controls (M = 0.261 ng/ml, SD = 0.260) and the subjects (M = 0.177 ng/ml, SD = 0.219; *P* = 0.26). GFAP levels were significantly higher in the subjects (M = 0.072 ng/ml, SD = 0.087) than the controls (M = 0.014 ng/ml, SD = 0.022; *P* = 0.007). GFAP did not correlate with total symptom burden (R^2 = 0.05, *P* = 0.31); however, GFAP did correlate with PECARN risk stratification categories (R^2 = 0.44, *P* = 0.0005). Confidence in the evidence was downgraded from low to very low because of the absence of a consistent correlation between markers of mTBI severity (eg, symptom burden) and GFAP.

Confidence Level: Very low

***Conclusion:** There is insufficient evidence to determine whether serum UCHL-1 or GFAP are useful tools in distinguishing children with or without mTBI.*

➤ Computerized Cognitive Testing and Symptom Scales

Two Class II studies[S36,S37] met the inclusion criteria. Study participants included athletes with pre-season ImPACT cognitive testing and an observed mTBI in sports activities. Controls were non-brain-injured athletes who were actively participating in sports and sustaining physical contact. Analyses involved between-group comparisons at 36 hours for Memory *d* = -1.1 (-1.5, -0.56) and for Post-Concussion Symptoms (PCSx) *d* = 1.17 (95% CI, 0.67-1.7); at Day 4 for Memory *d* = -0.88 (95% CI, -1.4 to -0.39) and PCSx *d* = 0.74 (95% CI, 0.24-1.2); within 72 hours for PCSx: partial η^2 = 0.23; Verbal Memory = 0.19, Visual Memory = 0.20, Processing Speed = 0.24, Reaction Time = 0.31. Additional results included Combined Cognitive Test scores and PCSx Sensitivity

= 81.9% (95% CI, 0.71-0.90), Specificity = 89.4% (95% CI, 0.79-0.95); LR+ = 7.7 (95% CI, 3.8-15.7). Confidence in the evidence was not downgraded for indirectness (spectrum bias) because the controls included athletes actively participating in the contact sport and participating in the computer-based cognitive testing program in a manner similar to the patients.

Confidence Level: Moderate

Conclusion: *The combination of computerized cognitive testing and Post-Concussion Symptom Scale likely distinguishes children with and without mTBI.*

➤ Reaction Time Testing

A single Class III study[S38] met the inclusion criteria. The patient group included 7- to 16-year-olds, with a mean GCS of 14.8, hospitalized for a brain injury. The control group, matched for age, consisted of friends of the injured subjects. The measures of reaction time were derived from the Bruininks-Oseretsky Test of Motor Proficiency (BOTMP), using the response speed subtest, and from experimental computerized measures of reaction and movement time for upper and lower extremities in simple, choice, and reversed choice response time paradigms. Analyses revealed that children with mTBI performed significantly worse than the non-injured group on the BOTMP response speed subtest at 1 week post-injury ($P < .001$), but not at 4 or 12 weeks. The groups did not differ significantly on any of the experimental computerized measures. Because evidence represented a single Class III study, the confidence level was anchored at very low.

Confidence Level: Very low

Conclusion: *There is insufficient evidence to determine whether BOTMP reaction time is a useful tool to distinguish children with and without mTBI.*

➤ Computerized Cognitive Testing and Reaction Time (CNS Vital Signs)

A single Class III study on the CNS Vital Signs computerized cognitive test met the inclusion criteria.[S39] Seventy-seven children ages 8-17 with mTBI presenting to an emergency department were compared to an orthopedic injury control (OIC) group. All underwent four subtests from the CNS Vital Signs computerized neurocognitive assessment. There were no significant differences between the mTBI or OIC groups in the Verbal Memory Domain (F (2,99) = 2.63; P = 0.108; d = 0.36). There was no significant difference in the Cognitive Flexibility Domain (F (2,101) = 3.35; P = 0.070; d = 0.41). Subjects with mTBI were significantly worse on the Reaction Time Domain (RTD) (U = 725; Z = 2.56; P = 0.010; d = 0.60). Because evidence represented a single Class III study, the confidence level was anchored at very low.

Confidence Level: Very low

Conclusion: *There is insufficient evidence to determine whether the CNS Vital Signs neurocognitive test can distinguish between children with and without mTBI.*

➤ Non-Computerized Testing With Symptom Scale

A single Class II study[S40] met the inclusion criteria. The Standardized Assessment of Concussion (SAC) and Graded Symptom Checklist (GSC) were administered to 348 study participants. The study group included children 6-18 years of age who had sustained blunt head trauma in the previous 24 hours, and had a GSC > 12. They were subdivided into those with and without unambiguous evidence of altered mental status. Controls included children with minor extremity trauma and no concomitant head trauma. The GSC reliably identified mTBI symptoms for all children age 6 and older. SAC scores tended to be lower for case patients compared with controls, but did not reach significance. Confidence in evidence for the SAC was

low due to imprecision in SAC measurements. Confidence in the evidence for the GSC was upgraded due to the magnitude of effect in relation to the GSC and mTBI symptoms.

Confidence Level: SAC – Low; GSC – Moderate

***Conclusion for SAC**: The SAC possibly distinguishes children with and without mTBI.*

***Conclusion for GSC:** The GSC likely distinguishes between children with and without mTBI.*

➤ Vestibular/Ocular Motor Screening Assessment

A single Class II study[S41] met the inclusion criteria. The Vestibular/Ocular Motor Screening (VOMS) assessment test battery was administered to a total of 142 pediatric study participants. The study group included 64 children 9-18 years of age who had suffered sports-related concussion. Controls included healthy children with no concomitant head trauma. As a whole, the test battery demonstrated internal consistency and sensitivity in identifying subjects with concussion from controls with an accuracy of the predicted probability demonstrated by an AUC of 0.89 (95% CI, 0.84-0.95; $P < .001$). Confidence in evidence for the VOMS was low and was downgraded to very low due to indirectness from spectrum bias.

Confidence Level: Very low

***Conclusion for VOMS**: There is insufficient evidence to support whether the VOMS distinguishes between children with and without mTBI.*

➤ Missing Evidence

Because the inclusion criteria mandated that study participants be less than 19 years old and that the mTBI group include more than 15 patients, a large number of diagnostically focused studies were excluded. For example, studies of various neurocognitive tests and imaging techniques have been published on mixed age groups or adults only. MRI and diffusion tensor imaging (DTI) studies have been conducted, focusing on mTBI, but these studies did not meet the inclusion criteria. Recent studies of serum or blood biomarkers also did not meet the inclusion criteria. Studies of magnetoencephalography (MEG), eye tracking apparatus, and the newer more sophisticated balance apparatus were reviewed, but did not meet the inclusion criteria. Finally, measures such as electroencephalography (EEG), quantitative EEG (qEEG), and evoked and event-related potentials (EP/ERP) did not yield research for this review.

Recommendations for Future Research

Due to a paucity of well-controlled studies identifying diagnostic tools and techniques for mTBI in children, the following recommendations are offered:

1. Further research is needed in the area of specialized neuroimaging, such as fMRI and DTI, prior to implementation in clinical practice.
2. Further research is needed to refine and validate computerized cognitive testing and symptom scales, both together and separately, for use in all mTBI, whether sports or non-sports related, and in the younger population.
3. Newer tools, such as computerized balance testing and eye tracking procedures, require more development and research in the younger population.
4. Further research is needed involving blood biomarkers and electrophysiological neuromarkers prior to routine implementation in clinical practice.
5. Research to distinguish pediatric tools for use in the acute and chronic stages of mTBI would aid practitioners in the diagnosis and progressive care of mTBI.
6. More age-stratified research is needed to identify the efficacy of a multifaceted diagnostic approach to mTBI diagnosis across different stages of childhood.

Question 2: For children (18 years of age and younger) presenting to the emergency department (or other acute care setting) with mild TBI, how often does routine head imaging identify important intracranial injury?

Introduction and Rationale

As neuroimaging is readily available in most acute care settings, it may be used as a tool for evaluating children with mTBI. Theoretical risks associated with radiation exposure from head CT, as well as the health care costs of neuroimaging in general, require thoughtful consideration of what head imaging will add to the care of a child with mTBI. Decision-making requires an understanding of the rate of identification of trauma-related findings on head imaging among children with mTBI. Decision-making also requires an understanding of the rate of identification of findings that are associated with more intensive acute care needs.

Inclusion Criteria

Studies of children (18 years of age and younger) with mTBI evaluated in an ED (or other acute care setting) undergoing head imaging were included if the proportion of patients with traumatic intracranial abnormalities was reported for effect measure.

Article Flow

A total of 6,134 articles were identified by literature search. Of those, 212 articles were identified for full-text review for eligibility with 51 undergoing data extraction. Thirty articles were ultimately included for quantitative synthesis from data extraction based on the inclusion criteria. These 30 articles included no Class I studies, no Class II studies, and 30 Class III studies.

Description of the Evidence: Imaging Modality-Intracranial Outcome Pairs

All studies identified for inclusion used head CT and/or skull x-ray. For skull x-ray, there was only one modality-outcome pair (skull x-ray/skull fracture). For head CT, multiple outcomes were identified based on the data presented. Five outcomes were identified for head CT: (1) isolated skull fracture, (2) intracranial injury with/or without skull fracture, (3) intracranial injury or skull fracture, (4) investigator-defined clinically important outcomes, and (5) neurosurgical procedure reported.

Skull X-Ray/Skull Fracture

Two Class III studies[S42,S43] were included and both captured children younger than age 16 with mTBI. Respective cohort sizes were 421 and 916 patients; in one study, all patients received skull x-ray, and in the other study, nearly all patients received skull x-ray. The yield of identification of skull fracture was 7.14% (95% CI, 4.0%-10.3%). Overall confidence was anchored at low because of clinician bias in the selection of patients to image and/or unclear bias of clinical setting with regard to expertise in mTBI. The confidence level was not further modified.

Confidence Level: Low

***Conclusion**: Routine skull X-rays performed on children presenting to an acute care setting with mTBI possibly identify skull fracture in 7.14% (95% CI, 4.0%-10.3%) of patients.*

CT/Isolated Skull Fracture

Seven retrospective and prospective Class III studies[S44-S50] were identified that documented the rate of isolated skull fractures diagnosed on head CT. Inclusion ages were variable, but only patients under age 18 with mTBI were included in this data set. Skull fracture without intracranial abnormality was found in 18.2% (95% CI, 11.5%-24.9%). The overall confidence level for the data is low because only Class III studies were available and the selection for subject imaging was potentially complicated by clinician bias.

Confidence Level: Low

***Conclusion**: Routine head CT on children with mTBI in the acute care setting possibly identifies isolated skull fractures in 18.2% (95% CI, 11.5%-24.9%) of patients.*

CT/Intracranial Injury or Skull Fracture/Diastasis

Sixteen Class III studies[S29,S44,S47,S51-S63] were included, ranging from 25 to 14,969 patients with head CT following mTBI and using retrospective and prospective study designs. In one study,[S56] positive findings were from either head CT or skull x-ray and could not be separated by imaging modality. The effect size was 16.8% (95% CI, 14.3%-19.3%). Overall confidence was anchored at low because of clinician bias in the selection of patients to image and/or unclear bias of clinical setting with regard to expertise in mTBI.

Confidence Level: Low

***Conclusion:** Routine head CT performed on children presenting to an acute care setting with mTBI possibly identifies skull fracture or intracranial injury in as many as 16.8% (95% CI, 14.3%-19.3%) of patients.*

CT/Intracranial Injury Findings

Sixteen Class III, studies[S42-S49,S64-S71] were identified that documented the rate of intracranial abnormalities on head CT scan. These included combinations of epidural hematoma, subdural hematoma, intraparenchymal hemorrhage, subarachnoid hemorrhage, intraventricular hemorrhage, cerebral edema, and depressed skull fractures. Simple skull fractures were not included unless they occurred concomitantly with another intracranial finding. Only patients ages 18 and younger were included, but some studies did not include patients up to age 18. Intracranial findings were reported in 7.5% of patients undergoing CT (95% CI, 6.0%-9.1%). The overall confidence level for the data is low because only Class III studies were identified and due to potential clinician bias in selecting children for imaging.

Confidence Level: Low

***Conclusion:** Routine head CT on children with mTBI in the acute care setting possibly identifies intracranial injury in 7.5% (95% CI, 6.0%-9.1%) of patients.*

CT/Clinically Important Outcome

Sixteen Class III studies,[S29,S43,S46,S47,S49,S51,S53,S54,S57,S60,S61,S64,S65,S69,S70] were identified that reported the rate of clinically important outcomes for children with mTBI following head CT. For three studies[S29,S58,S60] this included a number of possible outcomes (death, neurosurgical intervention, intubation for more than 24 hours, or hospital admission of more than two nights for TBI). One study[S57] included hospital admission for one night. For another study,[S69] clinically important outcomes only referred to the placement of intracranial pressure monitors. For one study,[S61] the definition of clinically important outcome was not provided. For the remaining 10 studies,[S43,S46,S47,S49,S51,S53,S54,S64,S65,S70] the number of children requiring neurosurgery was reported. The

average effect size was 1.9% (95% CI, 1.3-2.5). Overall confidence was anchored at low because of clinician bias in the selection of patients to image and/or unclear bias of clinical setting with regard to expertise in mTBI.

Confidence Level: Low

***Conclusion:** Routine head CT performed on children presenting to an acute care setting with mTBI possibly identifies injuries with clinically important outcomes in 1.9% (95% CI, 1.3-2.5) of patients.*

CT/Neurosurgery

Fourteen Class III studies[S29,S43,S46,S47,S49,S51,S53,S54,S57,S60,S61,S64,S65,S69,S70] were identified that documented the incidence of neurosurgical intervention in response to positive CT scans in the acute care setting. Neurosurgical intervention was defined differently by the different authors, but included all craniotomies. Three studies[S29,S51,S69] included intracranial pressure monitors, and a fourth study[S53] included ventriculostomy placement. For four studies,[S43,S54,S60,S61] the procedures included in neurosurgical intervention were not specified. Only patients age 18 and younger were included, but some studies did not include patients up to age 18. Surgical intervention was performed on 0.9% of patients who underwent CT (95% CI, 0.5%-1.2%). The overall confidence level for the data is low because only Class III studies were used and because of the potential for clinician bias based on how children were selected for imaging.

Confidence Level: Low

***Conclusion:** Routine head CT on children with mTBI in the acute care setting possibly identifies abnormalities requiring neurosurgical intervention in 0.9% (95% CI, 0.5%-1.2%) of patients.*

Missing Evidence

We found no studies meeting inclusion criteria that described the frequency of abnormal MRI findings in the acute setting.

Recommendations for Future Research

1. Future research should include evaluation of the incidence and clinical meaningfulness of findings on MRI, including "ultra-fast" MRI studies which may replace head CT for acute imaging, and advanced MRI techniques.

Question 3: For children (18 years of age and younger) presenting to the emergency department (or other acute care setting) with mild TBI, which features identify patients at risk for important intracranial injury?

Introduction and Rationale

The identification of important risk factors that indicate which child has sustained more serious intracranial injury following mTBI is critical to effective management. For the purposes of this question, important intracranial injuries (ICI) have the potential to change acute management/ treatment and include the presence of an intracranial hemorrhage such as subdural, epidural, subarachnoid, intra-cerebral, or intra-ventricular bleeding.

Inclusion Criteria

Studies of children (18 years of age and younger) with mTBI evaluated in an ED (or other acute care setting) with and without a putative risk factor. The proportion of patients with traumatic intracranial abnormalities is reported in both populations.

Article Flow

A total of 6,134 articles were identified by a literature search. Of those, 375 were identified for full-text review for eligibility with 29 undergoing data extraction. Nine articles were ultimately included in the quantitative data synthesis from data extraction based on the inclusion criteria. These nine articles included six Class I studies, three Class II studies, and no Class III studies.

Effect Measure and Evidence Synthesis

The absolute difference in the percentage of ICI between children with and without the risk factor (risk difference [RD]) was the measure of effect. Positive values indicate a higher risk of ICI among children with the risk factor. When possible, the RD of children with ICI requiring surgical intervention was also described. Risk increases of 1%-5% were considered small, > 5%-10% moderate, and > 10% large. Ninety-five percent confidence intervals (95% CI) were used as the measure of precision. When more than one study measured the association between a risk factor and ICI, the results were pooled in a random effects meta-analysis. I-squared was used as the measure of heterogeneity.

Description of the Evidence: Factors and Injury Risk Outcome Pairs

The evidence was organized according to the putative risk factor. Class I and Class II studies are described in the text and documented in the corresponding Evidence Table (see Appendix E). Class III studies are included in the Evidence Table but may not be discussed in the text if multiple studies with higher levels of evidence are available.

Younger Age (Less Than 2 Years of Age)

A single Class I study[S29] demonstrated a higher risk of intracranial injury (ICI) among children < 2 years of age presenting to the acute care setting with suspected mTBI (RD 4.1%, 95% CI, 3.0%-5.2%). The injuries included subdural hematomas or intracranial hemorrhages. In this study, however, no significant increase was observed in the proportion of children < 2 years of age requiring surgery (RD 0.05%, 95% CI, -0.05% to 0.14%).

Confidence Level: Moderate

***Conclusion:** Age < 2 years at the time of the mTBI is likely associated with a small increased risk of ICI but is not likely associated with an increased risk of ICI requiring neurosurgical intervention.*

Vomiting

Four Class I studies[S29,S65,S66,S72] and one Class II[S73] study provided evidence regarding the presence of vomiting and the risk of ICI in children with mTBI. All studies demonstrated an increased risk of ICI in children with vomiting with absolute risk increases ranging from 1.8% to 9.3%. Pooling of the results of the Class I studies demonstrated a "typical" absolute risk increase of 3% (95% CI, 1.1%-4.9%; I^2 = 77%). One study[S29] did not demonstrate an increased risk of ICI in children with two or more episodes of vomiting, compared to any vomiting episode. Another study[S66] observed an increased risk of ICI needing surgical intervention in children with vomiting (RD 7.1%, 95% CI, 3.5%-10.8%) (single Class I study, Moderate confidence).

Confidence Level: High for risk of ICI; Moderate for ICI needing surgical intervention

***Conclusion**: Children with mTBI presenting with vomiting are highly likely to be at a small to moderate increased risk for ICI and are likely to be at a moderate increased risk for ICI requiring surgical intervention. Notably, an increased number of vomiting episodes is not associated with higher risk compared to any vomiting.*

Loss of Consciousness (LOC)

Loss of consciousness following mTBI was addressed in the data from three Class I studies.[S29,S65,S66] The combined data from the studies indicate a small increased risk for intracranial abnormalities. These data include all ages of children, < 2 years and ≥ 2 years. The pooled data from the studies resulted in an overall RD 4.44% (95% CI, 1.27%-7.62%). Because of inconsistency in the effects, the confidence in the evidence was downgraded to moderate.

Confidence Level: Moderate

***Conclusion:** Children presenting with LOC following mTBI are likely to be at a small increased risk for ICI.*

Severe Mechanism of Injury

Severe injury mechanism resulting in mTBI was addressed in two Class I studies[S29,S65]. The first study[S29] evaluated children in two age groups, < 2 years and ≥ 2 years. Severe mechanism of injury included motor vehicle crash with patient ejection, death of another passenger, or rollover; pedestrian or bicyclist without helmet struck by a motorized vehicle; falls of more than 1.5 meters (5 feet) for children age 2 and older, and more than 0.9 meter (3 feet) for those younger than age 2; or head struck by a high-impact object. For this study, severe mechanism of injury was associated with an increased risk for ICI in mTBI. The second study[S65] defined dangerous mechanism of injury as motor vehicle crash (MVC), fall from elevation ≥ 0.9 meter (3 feet) or five stairs, and fall from bicycle with no helmet. Pooling the results of these studies indicated that a severe mechanism of injury was associated with an increased risk of ICI of: 3.5% (95% CI, 1.4%-5.6%). Even though there were two Class I studies, the confidence in the evidence was downgraded to moderate because of variability in the definition of severe mechanism of injuries.

Confidence Level: Moderate

***Conclusion:** Children presenting with mTBI resulting from a severe mechanism of injury are likely to be at a small increased risk for ICI.*

Seizures

Seizures as a risk factor for ICI associated with mTBI was addressed in two Class I studies.[S65,S66] The data from the second study[S66] was presented as two groups, including a separate analysis of those requiring intervention. The pooled results across the two studies revealed an inconsistent association of risk for intracranial abnormality. The RD was 3.87% (95% CI, -4.6% to 12.31%). We downgraded confidence to very low because of imprecision and inconsistency. Only the second study[S66] assessed the risk of ICI requiring intervention, and they found a significant association, RD 18.1% (95% CI, -7.7% to 28.4%). However, confidence was downgraded to low because of a lack of directness (inability to confirm that mTBI caused seizures rather than the obverse).

Confidence Level: Very low for overall risk of ICI in association with seizures; Low for risk of ICI requiring intervention

***Conclusion:** There is insufficient evidence to determine an association between seizures and ICI. Children with seizures are possibly at increased risk for ICI requiring intervention.*

Headache

Headache at acute care center presentation following mTBI was addressed in three Class I studies[S29,S65,S66] and one Class II study.[S73] The pooled results from these studies demonstrate that a severe or worsening headache at presentation is associated with an increased risk for ICI. The small increased risk is reflected in an RD 1.86% (95% CI, 0.12%-3.59%).

Confidence Level: Moderate

***Conclusion:** Children presenting with a headache following mTBI, including worsening or severe headache, are likely at a small increased risk for ICI.*

Amnesia

Amnesia at presentation to the acute care center was addressed in two Class I studies.[S65,S66] In one study,[S66] results were further grouped into data for those requiring intervention and those who did not. The pooled results from both studies demonstrated that the presence of amnesia was associated with a small increased risk for intracranial abnormality overall with an RD 2.02% (95% CI, 0.38%-3.65%).

Confidence Level: Moderate

***Conclusion:** Children presenting with amnesia following mTBI are likely to have a small increased risk of ICI.*

Scalp Hematoma

Two Class I studies[S29,S66] and two Class II studies[S73,S74] demonstrated an increased risk of ICI in children with mTBI and scalp hematomas. The pooled RD from the Class I studies provided a small estimated effect of 0.80% (95% CI, 0.40%-1.20%), but there was substantial inconsistency in the magnitude between these studies (I^2 = 81%), which decreased our confidence in this evidence.

No significant association between scalp hematoma and ICIs needing intervention was reported in one Class I study.[S66] However, confidence intervals were too wide to exclude an important association (RD 1.13%, 95% CI, -3.14% to 5.41%).

Confidence Level: Moderate

***Conclusions:** Children presenting with non-frontal scalp hematomas following mTBI are likely to be at a small increased risk for ICI. The evidence is insufficient to determine whether scalp hematomas are associated with ICIs needing intervention.*

Skull Fracture

Two Class I studies[S29,S66] and two Class II studies[S73,S74] demonstrated an increased risk of ICI in children with mTBI and a clinical suspicion of skull fractures. The pooled RD from the Class I studies demonstrated a large estimated effect of 9.84% (95% CI, 6.97%-12.71%. There was inconsistency in the magnitude of the effect between the Class I studies (I^2 = 90%), but the magnitude of the effect was large in both (8.62%-28.1%). A significant association between skull fracture and ICIs needing intervention was observed in one Class I study[S66] (RD 39%, 95% CI, 27%-50%).

Confidence Level: High

***Conclusion:** Children presenting with the clinical suspicion of skull fracture following mTBI are highly likely to be at a large increased risk of ICI, including ICI requiring intervention.*

Glasgow Coma Scale Score at Presentation

Glasgow Coma Scale (GCS) at presentation to an acute care center following mTBI was addressed in two Class I studies.[S29,S65] A GCS < 15 was associated with a high increased risk for an intracranial abnormality. The pooled results from these studies revealed an association with high increased risk for intracranial abnormality with an RD 7.5% (95% CI, 6.2%-8.8%).

Confidence Level: High

***Conclusion:** Children presenting with GCS < 15 following mTBI are highly likely to be at a moderate increased risk for intracranial injuries (RD 7.5%, 95% CI, 6.2%-8.8%).*

Clinical Decision Rules

Several clinical decision rules for pediatric head injuries were developed based on elements of patient history, physical examination, or simple tests. Three Class I studies[S29,S65,S66] addressed prediction rules. These studies demonstrated that the prediction rules were useful in identifying children at low risk for important ICIs, negative predictive values from 99.7–100%. Because these prediction rules used different combinations of risk factors, a meta-analysis is not appropriate. Recently, a prospective study[S75] evaluated the

diagnostic accuracy of PECARN, CATCH, and CHALICE clinical decision rules and physician judgment for identifying clinically important TBI in children with mTBI presenting to the ED. In this prospective study[S75] of 1,009 injured children, only physician baseline ordering practice and PECARN identified all of the 21 clinically important TBI, with PECARN being slightly more specific. Physician risk estimation missed one injury, and two other decision rules were insufficiently sensitive. CHALICE was incompletely sensitive but the most specific of all rules. CATCH was incompletely sensitive and had the poorest specificity of all modalities.

Confidence Level: High

***Conclusion:** Validated prediction rules are highly likely to be useful in identifying children at low risk for ICI.*

Missing Evidence

We did not find studies meeting the inclusion criteria that addressed the association between focal neurological deficits and ICI. Most healthcare providers would consider obtaining a head CT in this situation. Evidence was limited by stratification of data by age, precluding analyses specific to very young children. There is lack of sufficient data associated with non-accidental trauma (NAT) injury mechanisms.

Recommendations for Future Research

1. Because children younger than 2 years of age are the most sensitive to radiation and because their assessment is clinically challenging, future research should focus on improving the detection of non-accidental trauma in young children presenting with mTBI and "trivial" mechanisms of injury.
2. Multicenter, large prospective studies for validation of clinical decision rules should include an assessment of rule performance in settings apart from the derivation study and a comparison of performance to physician estimates of injury. Additionally, healthcare providers must be provided with exact definitions of each predictor variable in the clinical decision rule to avoid inaccurate application of the rule to the population they are treating.
3. Validation of clinical decision rules in prospective studies should be conducted in various populations to evaluate the extent to which using the rule reduces the unnecessary use of head imaging in children with mTBI.

Question 4: For children (18 years of age and younger) with mild TBI, what factors identify patients at increased risk for ongoing impairment, more severe symptoms, or delayed recovery (< 1 year post-injury)?

Introduction and Rationale

Most mTBI causes acute symptoms that resolve over time. However, between 5% and 15% of children with mTBI develop persistent symptoms or impairments. This minority of patients is clinically important because they require ongoing medical care and intervention. This section systematically summarizes the evidence relating to factors associated with ongoing impairment, more severe early symptoms, or delayed recovery following pediatric mTBI, up to 12 months post-injury.

Inclusion Criteria

Studies of children (18 years of age and younger) with mTBI with and without a putative risk factor, measuring the strength of association between the risk factor and symptom severity or duration, were included. Studies did not meet the inclusion criteria if they included patients older than age 18 without presenting the results in the ≤ age 18 subgroup, or if they included children with more severe TBI without presenting results in the mTBI subgroup.

Article Flow

A total of 7,946 research articles were identified by a literature search. Of those, 490 articles were identified for full-text review for eligibility and underwent detailed methodological review with 82 undergoing data extraction. Twenty articles were ultimately included for quantitative data synthesis from data extraction based on the inclusion criteria. These 20 articles included 12 Class I studies, 8 Class II studies, and no Class III studies.

Effect Measure and Evidence Synthesis

For binary outcomes, the absolute difference in the percentage of children attaining an outcome between children with and without the risk factor (RD) was used as the measure of effect. For continuous outcomes, standardized mean differences (SMD) as the measure of effect were used. Ninety-five percent confidence intervals (95% CI) were used as the measure of precision. When more than one study measured the association between a risk factor and an outcome, we pooled the results in a random effects meta-analysis. I-squared was used as the measure of heterogeneity.

Description of the Evidence: Risk Factor Outcome Pairs

The evidence is organized according to the putative risk factor. Class I and Class II studies are described in the text and documented in the Evidence Table

(Appendix). Class III studies are included in the evidence tables, but may not be discussed in the text if multiple studies with higher levels of evidence are available.

Age

Five studies were identified that examined the association between age at injury and postconcussive symptoms. Three Class I studies used cohorts that presented to an ED. One study[S76] reported a non-significant trend for presence of headache 3 months following mTBI in ages 13-17 but not in ages 5-12. The second study[S77] showed symptoms more likely to persist in children > age 6 compared to those younger (OR in younger group 0.74, 95% CI, 0.62-0.89). The third study[S78] also examined the effects of age on psychosocial outcomes, including physical, social, emotional, and school functioning. This study found that older children ages 10-17 were more likely to self-report a decline in quality of life at 3 months compared with younger children 0-9 years of age (RR 2.905, 95% CI, 1.454-5.806). In all studies, the younger age group reported fewer symptoms. Two Class II studies[S79,S80] found no relationship between age and postconcussive symptoms lasting longer than 1 week in children age 11 and older.[S79,S80] The participants in the first of the two studies[S79] examined high school athletes from a national surveillance database. The participants from the second study[S80] were also from a database, but recruitment to that database was not explained.

Confidence in the evidence that younger children report fewer symptoms than older children was moderate among mTBI presenting to the ED and downgraded to low for mTBI in general due to directness. Within the teenage population, age was not found to be associated with postconcussive symptoms beyond 1 week in a sample of non-ED subjects. Confidence in this evidence was moderate for high school age children in a non-ED population and low for mTBI, in general, again due to directness.

Confidence Level: Moderate for mTBI presenting to an ED; Moderate for high school age children; Low for mTBI in general

***Conclusion:** Among children presenting to an ED, age is likely a factor in mTBI outcome, with younger children reporting fewer postconcussive symptoms than adolescents. However, among teenagers as a group, age likely does not differentiate those who are more likely to develop postconcussive symptoms. Among the general population of children with mTBI, older age is possibly associated with a higher likelihood of postconcussive symptoms.*

Gender

One Class I study and one Class II study examined the relationship between gender and headaches following mTBI.[S76,S81] Boys had fewer headaches at 3 months post-mTBI than girls by parental report (RD -0.22, 95% CI, -0.33 to -0.12) or by self-report (RD -0.26, 95% CI, -0.4 to -0.11).[76] Recurrent headache was less likely in boys than girls (RD -.074, 95% CI, -0.135 to -0.015). Combined analysis showed an RD of -10% (95% CI, -16% to -5%) in boys compared to girls. Boys had a higher rate of amnesia than girls after a new concussion (IPR: 2.37, 95% CI, 1.62-3.48).[S81] One Class I and four Class II studies examined postconcussive symptoms lasting more than 1 week. No association was found between gender and post-injury symptoms after 1 week in three Class II studies[S79,S80,S82]; academic, social, and physical problems after 3 months in one Class I study[S78] and one Class II study[S83]; neurocognitive change from baseline in one Class II study[S82]; or neurologic deterioration after a lucid interval in one Class II study.[S84]

Confidence Level: Moderate for headache; Low for amnesia; Moderate for symptoms beyond 7 days for teenagers, but low for younger children due to lack of evidence in this age group; Low for neurologic deterioration after a lucid interval and neurocognitive change from baseline to post-injury due to directness.

***Conclusion:** Girls are likely to experience more headaches than boys following mTBI. Boys possibly report post-traumatic amnesia more often than girls after a new (single) concussion. Among teenagers, gender is likely not associated with persistent self-reported symptoms. Gender possibly influences persistent self-reported symptoms in younger children but there is a lack of evidence. In children with mTBI, gender is possibly not associated with a different risk of change in neurocognitive function from baseline and academic, social, and physical problems after 3 months. Gender is possibly not associated with a different risk of neurological decline after a lucid interval.*

Race

One Class I study[S78] examined the relationship between race (separated into the categories: White, Black, Hispanic, Asian, other) and psychosocial outcome following mTBI in children. The study found that among a group of ED and inpatient subjects, those of Hispanic ethnicity as compared to White, Non-Hispanic ethnicity were significantly more likely to report a decline in quality of life, including social, academic, and/or physical functioning at 3 months post-injury (RR 3.37, 95% CI, 1.47-7.73). Confidence in this evidence is high for children presenting to the ED given the magnitude of the effect size.

Confidence Level: High for children presenting to the ED or as inpatients; Moderate for general mTBI.

***Conclusions:** Hispanic ethnicity as compared with White, non-Hispanic ethnicity is highly likely to be associated with a decline in quality of life (social, academic, and/or physical functioning) 3 months after mTBI in children who present to an ED.*

Hispanic ethnicity as compared with White, Non-Hispanic ethnicity is likely to be associated with a decline in quality of life (social, academic, and/or physical functioning) 3 months after mTBI among children with mTBI in general.

Weight

One Class II study[S79] explored the relationship between weight and concussive symptoms in a national sample of 817 male football players and 595 non-football players. They found that among the football players, weight at greater than the 90th percentile (> 90%) was significantly associated with symptoms lasting longer than 1 week (RR 1.7, 95% CI, 1.0-3.0). There was no association between weight and persistent concussive symptoms for non-football players weighing > 90% or for football players at less than the 10th percentile for weight (< 10%). Confidence in the evidence is low for athletes and very low for other mechanisms of mTBI injury.

Confidence Level: Low for athletes; Very low for other mechanisms of mTBI injury

***Conclusions:** Heavier weight (> 90%) is possibly associated with postconcussive symptoms lasting more than 1 week in male football players. Insufficient evidence is available to determine whether weight is associated with mTBI outcome with other mechanisms of injury.*

mTBI Severity

Four studies looked at the relationship between measures of mTBI severity and outcomes. One Class I study[S77] rated mTBI severity on the American Congress of Rehabilitation Medicine (ACRM) mTBI scale. This is a 6-point ordinal scale from A (mildest) to *F* (2-20 minutes LOC). Persistent symptoms were found to be more likely with increasing severity of injury (OR: 1.48, 95% CI, 1.2-1.9). Another Class I study[S85] examined the relationship between mTBI severity and adaptive functioning. In this study, mTBI that presented to the ED was divided into

three groups: I – mTBI CT negative; II – mTBI CT+ skull fracture; and III – mTBI CT+ intracranial hemorrhage. Different measures of adaptive functioning showed a trend for greater impairment with a higher rating of mTBI. A third Class I study[S86] using ED pediatric mTBI subjects found no relationship between acute measures of injury severity and dichotomous cognitive outcome (impaired versus not impaired) at 12 months. The fourth Class I study[S78] examined the relationship between injury severity and quality of life 3 months post-injury in a sample of ED subjects and inpatients. They found no relationship between social, academic, and physical functioning 3 months post-injury and mTBI with and without skull fracture, maximum head Abbreviated Injury Scale score, mechanism of injury, or whether they received emergency medical services (EMS) transport.

For the relationship between mTBI severity and postconcussive symptoms, confidence was moderate among mTBI presenting to the ED and low for mTBI in general. Increasing mTBI severity was associated with greater likelihood of longer symptoms. For the relationship between mTBI severity and adaptive functioning, confidence was low and may not be generalizable to all mTBI, but a small effect cannot be excluded. No relationship was found between mTBI severity and neurocognitive function, but confidence was low. For mTBI severity and quality of life, confidence was low in the ED and inpatient population, and very low in the general mTBI population.

Confidence Level: Moderate for mTBI presentations to the ED; Low for mTBI in general; Low for mTBI severity with impairment in adaptive functioning; Low for mTBI severity without relationship to neurocognitive functioning; Low for mTBI severity and decline in quality of life for ED/Inpatient population; Very low for general mTBI.

Conclusions: *For children presenting to an ED with mTBI, a higher ACRM severity score is likely associated with increased persistent postconcussive symptoms. For children with mTBI in general, severity is possibly associated with persistent symptoms. The severity of mTBI may possibly be associated with impairment in adaptive functioning. The severity of mTBI is possibly unrelated to neurocognitive functioning in children. The severity of mTBI is possibly unrelated to a decline in quality of life 3 months post-injury in patients presenting to an ED or an inpatient population. There is insufficient evidence to determine whether injury severity and decline in quality of life is associated with mTBI in children in general at 3 months post-injury.*

Imaging—Presence of Intracranial Hemorrhage

Two studies looked at the relationship between the presence of intracranial hemorrhage (ICH) on CT imaging and neurocognitive or psychosocial functioning. One Class I study[S87] using multiple neurocognitive tests after TBI reported significant decrements in 3-month CVLT-C and WISC-III, and 12-month WISC-III and WJTA letter-word scores in those with positive ICH compared to those without. However, other tests (N-back, SSRT, SCWIT, Grooved Pegboard Test, and WJTA calculation test) showed no differences between ICH- and ICH+ groups. One Class II study[S88] looked at the relationship between ICH on CT scan and post-traumatic stress disorder (PTSD) and depression and found a significantly increased score on the UCLA Reaction Index for PTSD in those with ICH+ (SMD: 1.13, 95% CI, 1.58-0.69).

Confidence in the association between ICH and neurocognitive impairment was downgraded from moderate to low due to lack of precision and lack of generalizability to all children with mTBI. Confidence in the association between ICH and PTSD was low in one Class II study,[S88] but upgraded to moderate due to the magnitude of the effect reported.

Confidence Level: Low for ICH and neurocognitive impairment; Moderate for ICH and PTSD

Conclusion: *Presence of ICH on CT scan in children with mTBI is likely associated with an increased risk of PTSD. The presence of ICH in mTBI is possibly related to neurocognitive impairment in children.*

Imaging— Single Photon Emission Computed Tomography (SPECT)

One Class I study[S89] looked at the presence of medial temporal hypometabolism (MTH) on SPECT within 3 days of concussion and its relationship to persistent postconcussion syndrome. This study found a significant risk difference (RD 0.732, 95% CI, 0.487-0.976) for children with MTH on early SPECT having postconcussion syndrome (12 postconcussion syndrome/14 early MTH) compared to only 2 postconcussion syndrome subjects in the group of 16 with no early MTH. Assessment of SPECT signal was blinded and semi-quantitative, with cerebellum referenced at 100%. SPECT was considered abnormal if cerebral perfusion was < 10% of the corresponding contralateral region or (if bilateral involvement) < 70% in cortex or basal ganglia, or < 50% in medial temporal lobe.

Confidence was downgraded to low due to significant issues with generalizability. Patient cohort was recruited from a department of neurosurgery in New Delhi and minor TBI was defined using ACRM criteria: (1) loss of consciousness (LOC) < 30 minutes; (2) after 30 minutes, initial GCS should be between 13 and 15; and (3) post-traumatic amnesia (PTA) < 24 hours. It is unclear what fraction of mTBI cases had any LOC or PTA, and all cases underwent CT imaging, suggesting that this cohort may be clinically more severe than other studies of mTBI/concussion.

Confidence Level: Low

Conclusion: *Medial temporal hypometabolism on SPECT within 72 hours of mTBI presenting to a hospital is possibly associated with development of postconcussion syndrome. There is insufficient data to determine whether this relationship exists for the more general population of mTBI (who do not present to the ED and/or do not get brain CT scans).*

Biomarker S100B

A single study[S90] examined the relationship of a positive serum S100B marker to a worse short-term outcome in pediatric mTBI patients presenting to an ED within 3 hours of injury. The outcome was dichotomous; good versus bad clinical evolution. Bad clinical evolution was defined as vomiting, facial paralysis, movement disorder, vertigo, photo motor reflex disorder, seizure, progressive

headache, or behavior change. This study showed an area under the curve (AUC) of 0.75 (95% CI, 0.70-0.79). Confidence was downgraded to very low because of concerns regarding generalizability. In particular, this study cohort was one of TBI presenting to the ED, and the distinction provided by S100B was to determine the likelihood of bad evolution, which included many clinical findings not typically seen in mTBI cases.

Confidence Level: Very low

***Conclusion**: There is insufficient evidence to determine the relationship between elevated serum S100B and bad clinical evolution after pediatric mTBI.*

Early Postconcussive Symptoms/Neurocognitive Outcomes or Behavioral Functioning

One Class I study[S86] and one Class II study[S91] assessed the relationship between early postconcussive symptoms and neurocognitive functioning. Both recruited pediatric mTBI subjects from an ED. No significant relationships were reported between early symptoms and performance on a battery of neuropsychological measures or behavioral scales. Confidence in the evidence was low for patients seen in the ED and reduced to very low because of lack of precision and indirectness (generalizability to mTBI patients at large).

Confidence Level: Low for mTBI presenting to ED; Very low for mTBI patients at large

***Conclusion:** Among children presenting to an ED with mTBI, early postconcussive symptoms are possibly unrelated to later neurocognitive outcomes or behavioral functioning. Insufficient data exists to determine a relationship between early postconcussive symptoms and later neurocognitive outcomes or behavioral functioning among the general population of pediatric mTBI.*

Early Postconcussive Symptoms/Symptoms Lasting Longer Than 1 Week

One Class II study[S79] assessed the relationship between early postconcussive symptoms and symptoms lasting beyond 1 week post-injury in both football players and non-football players. This study examined data from a national database that utilized an Internet platform to collect information entered by athletic trainers from 100 high schools from 8 different geographic regions. A significant relationship between light and noise sensitivity and persistent symptoms was found for non-football players. A significant relationship between drowsiness, concentration and confusion, and nausea at the time of injury was associated with symptoms after 1 week in both football and non-football players. Overall, having four or more symptoms was associated with symptoms after 1 week in both football (RR 2.1, 95% CI, 1.3-3.5) and non-football players (RR 2.5, 95% CI, 1.4-4.6). No significant relationships were reported between early symptoms of amnesia, LOC, irritability, headache, dizziness, or tinnitus and symptoms after 1 week. Confidence in the data was upgraded to moderate for high school athletes due to the magnitude of effect sizes and low for mTBI in general.

Confidence Level: Moderate for high school athletes; Low for mTBI in general

***Conclusion**: Early symptoms, including light and noise sensitivity, drowsiness, decreased concentration and confusion, and nausea, are likely related to postconcussive symptoms lasting longer than 1 week in high school athletes and are possibly related to persistent postconcussive symptoms in mTBI in general. Having four or more symptoms post-injury is likely related to postconcussive symptoms lasting longer than 1 week in high school athletes and is possibly associated with symptoms lasting beyond 1 week in mTBI in general.*

Premorbid Factors—Neurological/Psychiatric Problems

Two Class I studies and one Class II study measured the association between premorbid neurodevelopmental issues and subsequent academic, social, physical, and behavioral problems in ED or inpatient populations. The Class II study[S83] observed a significant association between ongoing physical symptoms and behavioral problems and the presence of pre-injury neurological/psychiatric problems (RD 19%, 95% CI, 2%-38%) and learning difficulties (RD 32%, 95% CI, 12%-52%). The first Class I study[S92] also found a significant association between postconcussion disorder at 6 months post-injury and pre-injury postconcussion-like symptoms (β: 0.6333, $P < .001$) and pre-injury psychosocial health-related quality of life (β: -0.550, $P < .001$). The other Class I study[S78] examined whether the number of preexisting neurodevelopmental comorbidities was associated with a decline in school, social, or physical functioning after 3 months. This study found no association between the number of neurodevelopmental comorbidities and decline in quality of life after mTBI.

For the association between premorbid neurodevelopmental issues and outcome, confidence in this evidence was high for children with mTBI presenting to an ED and moderate for children with mTBI in general, due to directness. For the association between number of comorbidities and decline in quality of life, confidence in the evidence is low for the ED population and very low for general mTBI.

Confidence Level: High for children with mTBI presenting to an ED; Moderate for children with mTBI in general; Low for number of comorbidities relating to outcome in children presenting to the ED; Very low for number of comorbidities relating to outcome for children with mTBI in general

Conclusion: *Premorbid factors such as neurological/psychiatric problems, learning difficulties, behavioral problems, and postconcussion-like symptoms are highly likely to be associated with an increased risk of persistent symptoms and behavioral problems 3-6 months post-injury in children with mTBI who present to an ED and likely associated with an increased risk in children with mTBI in general. The number of pre-injury comorbidities is possibly not associated with a decline in school, social, or physical functioning 3 months post-injury in those children who presented to an ED. There is insufficient evidence to determine whether an association exists between the number of pre-injury comorbidities and declines in school, social, or physical functioning 3 months post-injury for children with mTBI in general.*

Premorbid Factors—Socioeconomic Status (SES)

One Class I study[S78] examined the relationship between SES and quality of life 3 months after mTBI in children seen in the ED or inpatient units. Children with mTBI were more likely to experience a decline in social, academic, and/or physical functioning when they were from families whose income was < $30,000 versus > $100,000 (RR 2.73, 95% CI, 1.28-5.83); or their parents had less than a high school education versus post-college (RR 4.44, 95% CI, 1.55-12.76). Although this study included only ED and inpatients, which affects generalizability, the magnitudes of the effect sizes are significant (RR 1.571) and there is a demonstrated dose-response relationship between educational risk and worse outcome (Spearman's r 0.9, p =0.37). This study provided data for all risk strata allowing for analysis and elimination of spectrum bias. Therefore, confidence in the evidence is high for children seen in the ED or as inpatients, and moderate for mTBI in general.

Confidence Level: High for children seen in the ED or as inpatients; Moderate for mTBI in general

Conclusion: *Socioeconomic status as measured by lower parental income and lower parental education is highly likely to be associated with*

worse social, academic, and physical outcomes 3 months post-mTBI in children seen for mTBI in an ED setting or as inpatients. Socioeconomic status is likely associated with social, academic, and physical outcomes 3 months post-mTBI in the general population of children with mTBI.

Premorbid Factors—Family History and Functioning

Family history of migraine, general family functioning, and parent psychiatric symptoms were examined in relation to postconcussive symptoms in hospital/ED groups. One Class I study[S92] separated subjects into three groups: mTBI no imaging, mTBI uncomplicated (no lesions on imaging), and mTBI complicated (lesions on imaging but not requiring neurosurgery). They found that pre-injury parental hyperarousal was associated with a diagnosis of postconcussion disorder 6 months post-injury (β: 0.320, p .004); depression was associated with a diagnosis of postconcussion disorder 6 months post-injury in those children with uncomplicated mTBI (β: 0.513, p .001), while pre-injury parental anxiety was associated with postconcussion disorder at 6 months in children with complicated mTBI (β: 0.843, p .001). One Class II study[S84] found a relationship between family history of migraine in a first degree relative and neurological deterioration after a lucid interval (RR 1.896, 95% CI, 1.212-2.966). Another Class I study[S78] did not find an association between self-reported pre-injury general family functioning and social, academic, and/or physical functioning 3 months post-injury. Confidence in the evidence is low due to consistency and directness.

Confidence Level: Low for mTBI seen in ED or inpatient; Very low for mTBI in general

***Conclusion**: Family history of migraine in a first degree relative is possibly related to neurological deterioration after a lucid interval in children with mTBI presenting to an ED. Parental history of psychiatric symptoms such as hyperarousal, depression, and anxiety is possibly related to persistent postconcussive symptoms after mTBI in children presenting to an ED. Pre-injury family functioning is possibly not related to post-injury social, academic, and physical functioning 3 months post-injury in children with mTBI who presented to an ED. There is insufficient evidence to associate family history of migraine with neurological deterioration, parental history of psychiatric symptoms with postconcussive symptoms, or pre-injury family functioning with patient functioning 3 months post-injury in children with mTBI in general.*

Premorbid Factors—Apo E4 Genotype

Two Class I studies[S93,S94] explored the association between Apo E4 allele and neurocognitive outcomes or postconcussive symptoms after pediatric mTBI. There was no association between the Apo E4 genotype and these outcome measures, which included tests of academic skills, memory, and problem solving, as well as parent- and child-reported cognitive and somatic symptoms. Both studies did find a significant effect for constructional skills, but that difference was also seen on baseline measures, suggesting a premorbid difference between children with the E4 allele and those without the E4 allele. One study[S94] also found a relationship between Apo E4 and Glasgow Coma Scale (GCS) score. In children presenting to the ED, those with mTBI and a GCS of < 15 were more likely to have an E4 allele (OR: 3.61, 95% CI, 1.09-11.94). Although this finding was limited to an ED sample, the effect size was large and, thus, confidence in the evidence was high for children presenting to the ED and moderate for mTBI in general.

Confidence Level: Moderate for Apo E4 and neurocognitive outcomes or postconcussive symptoms in ED population; Low for general mTBI; High for Apo E4 and GCS presenting to the ED; Moderate for Apo E4 and GCS in mTBI in general

Conclusion: *Among children presenting to an ED with mTBI, the Apo E4 allele is likely not associated with neurocognitive outcomes or postconcussive symptoms. The Apo E4 allele is possibly not associated with poorer neurological outcome or postconcussive symptoms after mTBI in the general pediatric population.*

Among children presenting to the ED with mTBI, the Apo E4 allele is highly likely to be associated with lower GCS scores (GCS < 15) after injury. For children following mTBI in general, the Apo E4 allele is likely to be associated with lower GCS scores (GCS < 15) after injury.

Premorbid Factors—Prior History of mTBI

The systematic search revealed two Class II studies [S79,S81] that reported an effect of prior history of mTBI/concussion. Both studies involved a network of 100 nationally representative U.S. high schools where data was collected using the reporting information online (RIO) system. One study[S81] reported a higher proportion of athletes with loss of consciousness (LOC) (IPR/RR 1.76, 95% CI, 1.02-3.03) and light/noise sensitivity (IPR/RR 1.25, 95% CI, 1.01-1.55) after recurrent concussion as compared to a new concussion. More robustly, the athletes with a history of recurrent concussion had a higher rate of having symptom resolution between 1 week and 1 month (IPR: 1.52, 95% CI, 1.10-2.10), symptom resolution > 1 month (IPR: 10.35, 95% CI, 4.62-23.16), returning to play > 3 weeks post-injury (IPR: 1.95, 95% CI, 1.01-3.77), and ultimately being medically disqualified (IPR: 5.58, 95% CI, 3.50-8.88). The second study[S79] found that football players with a history of prior head injury were more likely to have symptoms for one week or longer (RR 2.1, 95% CI, 1.3-3.5), but this association was not significant for non-football players (RR 1.3, 95% CI, 0.7-2.3). Still another study[S83] looked for rate of physical or behavioral symptoms ("problems") in children with a history of prior concussion and did not find a relationship.

Confidence in the relationship between recurrent concussion and LOC or light/noise sensitivity in high school athletes was low and remained low when considering precision. Confidence in the effect of recurrent concussion on measures of concussion outcomes (either prolonged resolution or medical retirement) was moderate for high school athletes due to the magnitude of the effect sizes and low for mTBI in general. More specifically, the evidence suggests that high school athletes with a history of concussion may be more likely to have worse outcome when they sustain a repeat concussion. This may be especially true when the injury is sustained while playing football as compared to other sports. At this time, the confidence in evidence for the association between recurrent concussion and outcomes in mTBI in general is low due to inconsistency in evidence and indirectness.

Confidence Level: Moderate for the association between recurrent concussion and outcome (prolonged resolution of symptoms or medical retirement) in high school athletes; low for the association between recurrent concussion and outcome (prolonged resolution of symptoms or medical retirement) for mTBI in general; low for association between recurrent concussion and LOC or light/noise sensitivity in high school athletes; very low for association between recurrent concussion and LOC or light/noise sensitivity in mTBI in general.

Conclusion*: History of prior concussion is likely associated with a longer period until symptom resolution and higher rates of medical retirement in high school athletes after concussion and may be more likely when the injury is sustained while playing football. Additional evidence is needed to determine whether repeat concussion is associated with prolonged resolution of symptoms or higher rates of medical disqualification in mTBI in general. History of prior concussion is possibly associated with increased risk for LOC and light/noise sensitivity after repeat concussion.*

Premorbid Factors Predicting Novel Psychiatric Disorders

A single Class I study[S94] examined several factors that might potentially influence the development of new onset psychiatric disorders within 6 months of mTBI; however, none of them were significantly related including: age at injury, SES, adaptive behavior, family psychiatric history, general family functioning, psychosocial stressors, and whether there were injuries to other parts of the body. None of the analyses reached statistical significance. Confidence in the evidence is low due to directness.

Confidence Level: Low in the ED population; Very low for general mTBI

Conclusion: *Age at injury, SES, pre-injury adaptive functioning, family psychiatric history, general family functioning, pre-injury psychosocial stressors, and injuries to body parts other than the head are possibly unrelated to the development of new psychiatric disorders 6 months post-injury for children presenting to the ED. There is insufficient evidence to determine whether age at injury, SES, pre-injury adaptive functioning, family psychiatric history, general family functioning, pre-injury psychosocial stressors, and injuries to body parts other than the head are associated with the development of new psychiatric disorders 6 months post-injury for children with mTBI in general.*

Missing Evidence

The relationship between the timing of repeated mTBI and neurological catastrophe (ie, malignant brain edema or cerebral swelling leading to death) was not evaluated because no evidence met the criteria for this review. Similarly, the relationship between the timing of repeated mTBI and worsened short-term cognitive or behavioral outcomes was not evaluated for lack of evidence at the time of this search. Limited data examining the effect of prior mTBI on symptom resolution and return to play was reviewed; however, no data examining the impact of repetitive head trauma or multiple concussions on neurocognitive and behavioral outcomes was found. While some data were reviewed that examined the relationship between age and postconcussive symptoms, no evidence was found that examined the relationship between age at injury and objective measures of neurocognitive functioning within childhood.

Recommendations for Future Research

At the time of this review, little high-confidence data was found in the pediatric mTBI literature relating to risk factors for more severe early symptoms, ongoing impairment, or delayed recovery following pediatric mTBI. Many important areas for further investigation can be identified, including:

1. Effect of age at injury and gender on early symptoms or impairment after mTBI among children and youth.
2. Effects of severity and the timing of injuries, including repetitive injury, on the development of more severe early or subacute neurological, cognitive, or behavioral problems, including important intracranial injury or neurological catastrophe.
3. Relative effects of premorbid factors (eg, neurological, behavioral, cognitive, psychosocial) compared to injury factors (eg, mechanism, severity, timing, acute signs/symptoms) on the risk for more severe symptoms or delayed recovery.
4. Many existing studies rely on cohorts of children with mTBI identified from EDs, which creates concerns about generalizability to all children with mTBI. Studies examining mTBI cohorts from outside of the ED setting are challenging to conduct, but are an area where more quality data is needed.
5. Further research to identify sensitive and specific biomarkers (eg, blood, imaging, electrophysiological) that may be applied post-injury to help predict children at risk for prolonged or more severe impairments.

Question 5: For children (18 years of age and younger) with mild TBI, which factors identify patients at increased risk of long-term (≥ 1 year) sequelae?

Introduction and Rationale

Although most children recover from mTBI in a short period of time, a small proportion demonstrate persisting difficulties for a year or more post-injury. The identification of risk factors that increase the likelihood of such long-term difficulties will help to guide clinical assessment so that children at risk can be targeted for early intervention.

Inclusion Criteria

Studies of children (18 years of age and younger) with mTBI with and without a putative risk factor. The study examined the strength of association between the risk factor and long-tem (≥ 1 year) sequelae (or provided data that allowed the association to be computed).

Article Flow

A total of 7,946 articles were identified by a literature search. Of those, 635 were identified for full-text review for eligibility with 61 undergoing data extraction. Sixteen articles were ultimately included in the quantitative data synthesis from data extraction based on inclusion criteria.[S77,S78,S80,S85,S87,S88,S92,S93,S96-S103] These 16 articles included 13 Class I studies, 3 Class II studies, and no Class III studies. Many studies addressed multiple risk factors and multiple outcomes.

Description of the Evidence: Risk Factor-Outcome Pairs

Risk factors were grouped into 13 major categories: age at injury; presence/absence of Apo E4 allele; overall cognitive ability; presence/absence of extracranial injury; injury severity based on clinical characteristics; presence/absence of intracranial lesion on neuroimaging; pre-injury child psychiatric disorder; pre-injury child functioning; pre-injury family functioning; post-injury child functioning; post-injury family functioning; SES; and

demographics (gender, race). Outcomes were grouped into five major categories: general cognitive ability (IQ)/achievement; specific cognitive abilities; postconcussive symptoms; psychiatric outcome; and psychosocial adjustment. We report on all risk factor-outcome pairs for which evidence was available from the 16 identified studies. For this evidence, the term *extracranial injury* refers to non-head injuries and *novel disorders* refer to newly diagnosed disorders.

Age at Injury and General Cognitive Ability/Achievement

One Class I study[S96] longitudinally followed a prospective cohort of 76 children with mTBI between ages 8 and 17 years, and found that older age was significantly associated with a reduced likelihood of global neurocognitive impairment at 12 months (OR: 0.85, 95% CI, 0.745-0.964). One Class II study[S103] examined the relationship between age and general cognitive ability at age 18 among 960 males who sustained a single concussion between ages 0 and 11 versus ages 12 and 17. The group injured at an older age was significantly more likely than the group injured at a younger age to fail the military draft board's cognitive screening test (RD 0.05, 95% CI, 0.00-.011). The confidence in the evidence was judged to be very low given the inconsistent results; confidence was also downgraded for a lack of generalizability based on the restriction of the participants in the Teasdale study to males only.

Confidence Level: Very low

Conclusion: *There is insufficient evidence to determine whether age at injury is related to general cognitive ability/achievement more than 1 year after mTBI.*

Age at Injury and Postconcussive Symptoms

One Class I study[S77] examined the relationship between age and postconcussive symptoms during the first 600 days post-injury in 670 children between ages 0 and 18. The study reported that children injured when they were older than age 6 were more likely to remain symptomatic than children injured at age 6 or younger (approximately 5-10% risk difference: log rank [Mantel-Cox] = 51.64, $P < .001$). Another Class I study[S92] reported no significant relationship of age at injury to postconcussive symptoms at 18 months post-injury in a prospective cohort of 129 children ages 6-16 with mTBI, but the data were not reported in a manner that allowed for an effect size calculation. The confidence in the evidence was judged to be low; the level was lowered for imprecision because the results from this study were not reported in sufficient detail to allow for an effect size calculation.

Confidence Level: Low

***Conclusion:** Among children presenting to an ED, those injured after age 6 are possibly at a 5%-10% increased risk of remaining symptomatic at or after 12 months post-mTBI as compared to those injured at age 6 or younger.*

Age at Injury and Psychiatric Outcome

One Class I study[S100] examined the relationship between age at injury and novel psychiatric disorder in the interval 6-12 months after mTBI in a prospective cohort of 60 children between ages 5 and 14. Children with and without novel psychiatric disorder over that interval did not differ significantly in age at injury (*d* = -.29, 95% CI, -0.84 to 0.28).

Confidence Level: Moderate

***Conclusion:** Among children presenting to an ED with mTBI, age at injury is unlikely to predict who will develop a novel psychiatric disorder in the interval 6-12 months after injury.*

Age at Injury and Psychosocial Adjustment

One Class I study[S78] examined the relationship between age and declines in health-related quality of life (HRQoL) across the first 12 months after mTBI in a prospective cohort of 317 children between ages 0 and 17 recruited in an ED setting. Age (0-9 years versus 10-17 years) was unrelated to the likelihood of displaying a decline in HRQoL (RR 0.66, 95% CI, 0.37-1.19).

Confidence Level: Moderate

***Conclusion:** Among children presenting to an ED with mTBI, age at injury is unlikely to be associated with declines in HRQoL over the first 12 months post-injury.*

Presence/Absence of Apo E4 Allele and General Cognitive Ability/Achievement

One Class I study[S93] examined the relationship between the presence or absence of the Apo E4 allele and general cognitive ability/achievement at 12 months post-injury in 99 children between ages 8 and 15. The study reported that children with an Apo E4 allele and those without an Apo E4 allele did not differ in general cognitive ability/achievement (four dependent variables, mean *d* = .05, range of *d*: -.06 to .24). The confidence in the evidence was judged to be very low because of imprecision and because the sample was limited to patients presenting to the ED.

Confidence Level: Very low

***Conclusion:** There is insufficient evidence to determine whether the presence of an Apo E4 allele is associated with a risk of lower general cognitive ability/achievement after mTBI at 12 months post-injury.*

Presence/Absence of Apo E4 Allele and Specific Cognitive Ability

One Class I study[S93] examined the relationship between the presence or absence of the Apo E4 allele and specific cognitive abilities at 12 months post-injury in 99 children between ages 8 and 15. The study reported that children with an Apo E4 allele and those without an Apo E4 allele did not differ in specific cognitive ability (six dependent variables, mean *d* = .11, range of *d*: -.11 to .46). The confidence in the evidence was judged to be very low because of imprecision and because the sample was limited to patients presenting to the ED.

Confidence Level: Very low

***Conclusion:** There is insufficient evidence to determine whether the presence of an Apo E4 allele is associated with a risk of lower specific cognitive ability after mTBI at 12 months post-injury.*

Presence/Absence of Apo E4 Allele and Postconcussive Symptoms

One Class I study[S93] examined the relationship between the presence or absence of the Apo E4 allele and postconcussive symptoms 12 months post-injury in 99 children between ages 8 and 15. The study reported that children with an Apo E4 allele and those without an Apo E4 allele did not differ in the presence of postconcussive symptoms (six dependent variables, mean *d* = .04, range of *d*: -.10 to .16). The confidence in the evidence was judged to be very low because of imprecision and because the sample was limited to patients presenting to the ED.

Confidence Level: Very low

***Conclusion**: There is insufficient evidence to determine whether the presence of an Apo E4 allele is associated with a risk of more postconcussive symptoms 12 months following mTBI.*

Cognitive Ability and Postconcussive Symptoms

One Class I study[S97] examined the relationship between cognitive ability, assessed 1-2 weeks post-injury, and postconcussive symptoms during the first 12 months post-injury in 182 children ages 8-15. The study reported that, among children who had an intracranial lesion detected on MRI, those with lower cognitive ability were rated by their parents as exhibiting more cognitive symptoms at 12 months post-injury than children of higher cognitive ability. The relationship between symptoms and cognitive ability was significantly reduced in children without intracranial lesions on MRI (group X MRI status X cognitive ability interaction accounted for 6% of variance in linear change and 12% of variance in quadratic change in postconcussive symptoms). Another Class I study[S92] reported inconsistent relationships between specific cognitive abilities at 6 months post-injury and postconcussive symptoms at 18 months post-injury in a prospective cohort of 129 children between ages 6 and 16 with a history of mTBI. One test of executive functioning, the Contingency Naming Test, was marginally predictive; however, six other tests of other cognitive abilities were not significantly predictive. Confidence in the evidence was low; the level was lowered for imprecision because the results from this study were not reported in a manner that allowed for an effect size calculation.

Confidence Level: Low

***Conclusion:** Lower cognitive ability is possibly associated with an increased risk of increased cognitive symptoms after mTBI at 12 months post-injury, when it occurs in conjunction with an intracranial lesion.*

Cognitive Ability and General Cognitive Ability/Achievement

One Class I study[S96] longitudinally followed a prospective cohort of 76 children with mTBI between ages 8 and 17 recruited in an ED setting, and found that global neurocognitive impairment at 1 month post-injury was associated with an increased likelihood of global neurocognitive impairment at 12 months post-injury (OR: 0.72, 95% CI, 0.65-0.80). The confidence in the evidence was judged to be moderate.

Confidence Level: Moderate

Conclusion: *Neurocognitive impairment at 1 month after mTBI is likely associated with an increased risk of neurocognitive impairment at 12 months post-injury.*

Extracranial Injury and Psychiatric Outcome

One Class I study[S100] examined the relationship between extracranial injuries (Abbreviated Injury Scale score) and novel psychiatric disorder in a prospective cohort of 60 children between ages of 5 and 14 within 6-12 months following mTBI. Children with and without novel psychiatric disorder over that interval did not differ significantly in mean Abbreviated Injury Scale scores for non-head injuries (d = .33, 95% CI, -0.24 to 0.89). The confidence in the evidence was judged to be moderate.

Confidence Level: Moderate

Conclusion: *The severity of extracranial injury is unlikely to be associated with an increased risk of novel psychiatric disorder 12 months or longer post-injury.*

Extracranial Injury and Psychosocial Adjustment

One Class I study[S102] examined the relationship between the presence of non-head, extracranial injuries and total behavioral problems at 12 months post-injury in a prospective cohort of 176 children with mTBI recruited upon their presentation to an ED. The likelihood of displaying a clinically significant elevation in behavioral problems at 12 months post-mTBI was not significantly related to the presence of extracranial injuries at the time of injury. Confidence in this data was low; confidence was lowered for imprecision because data were not reported in a manner that permitted an effect size calculation.

Confidence Level: Low

Conclusion: *The presence of extracranial injury in association with mTBI is unlikely to be associated with an increased risk of significant behavioral problems at 12 months following mTBI.*

Injury Severity and Psychiatric Outcome

One Class I study[S98] examined the relationship between injury severity of mTBI sustained before 16 years of age and psychiatric outcome, measured by the Minnesota Multiphasic Personality Inventory-2 (MMPI-2) in 41 adults (mean age: 32.1 years) who were 23 years post-injury. The study reported increased psychopathology in subjects with injuries associated with both a period of post-traumatic amnesia longer than 30 minutes and EEG abnormality compared to those who displayed neither or only one of these risk factors (mean d = -.31, range of d: 0.66 to -1.20). Another Class I study[S100] examined the relationship between injury severity and novel psychiatric disorder in the interval 6-12 months following mTBI in a prospective cohort of 60 children between ages 5 and 14. Children with and without novel psychiatric disorder over that interval did not differ significantly in the likelihood of having a GCS score of 13 versus 14/15 (RR 1.69, 95% CI, 0.31-9.22), depressed skull fracture (RR 0.42, 95% CI, 0.05-3.25), or higher Abbreviated Injury Scale score for extracranial injury (*d* = .33, 95% CI, -0.24 to 0.89). The confidence in the evidence was low; confidence was downgraded because of multiple limitations to the first study, including imprecision from small sample size, lack of correction for multiple comparisons, and post hoc combination of selected risk factors.

Confidence Level: Low

Conclusion: *More severe mTBI is unlikely to be associated with an increased risk of novel psychiatric disorder 12 months or longer post-injury.*

Injury Severity and Postconcussive Symptoms

One Class I study[S77] examined the relationship between mTBI injury severity (six ordered categories based on clinical presentation) and postconcussive symptoms during the first 600 days post-injury in 670 children between ages 0 and 18. The study reported that children who sustained more clinically severe injuries associated with LOC and higher concussion grade were more likely to remain symptomatic after 1 year than children who sustained less severe injuries (approximately 60% risk difference between least and most severe after 1 year post-injury (log rank [Mantel-Cox] = 85.88, $P < .001$). Another Class I study[S92] reported no significant relationship between mTBI injury severity determined by clinical imaging (three groups: complicated mTBI, uncomplicated mTBI, and mTBI without imaging) and postconcussive symptoms at 18 months post-injury in a prospective cohort of 129 children between ages 6 and 16. Confidence in the evidence was low; the level was lowered for imprecision because the results from this study were not reported in a manner that allowed for an effect size calculation.

Confidence Level: Low

***Conclusion:** Among children presenting to an ED, those with more severe presentations of mTBI based on clinical characteristics are possibly more likely to remain symptomatic 12 or more months post-injury as compared to children with less severe presentations of mTBI.*

Injury Severity and Specific Cognitive Ability

One Class II study[S101] involved retrospective recruitment of a cohort of 52 children with mTBI who were injured before age 4 and assessed, on average, about 8 years post-injury. In that study, children with complicated mTBI (defined by positive LOC, Pediatric Coma Scale (PCS) score of 13-14, or two or more acute symptoms/signs) displayed inconsistent performance on five specific cognitive tasks as compared to children with uncomplicated mTBI (defined by no LOC, PCS score of 15, and no acute symptoms). Children with complicated mTBI performed worse on three of the tasks, although only one of those differences was statistically significant, and they performed better on two of the tasks, with one difference being significant. The confidence in the evidence was judged to be low; confidence was downgraded because of inconsistent results.

Confidence Level: Low

***Conclusion:** The severity of mTBI is possibly not associated with an increased risk of long-term cognitive deficits among children injured at less than 4 years of age.*

Injury Severity and General Cognitive Ability/Achievement

One Class I study[S96] longitudinally followed a prospective cohort of 76 children with mTBI between ages 8 and 17 recruited in an ED setting, and found that injury severity, determined by an Abbreviated Injury Scale score of 1 versus 2, as well as acute concussion symptoms, was not associated with an increased likelihood of global neurocognitive impairment at 12 months post-injury (OR: 1.23, 95% CI, 0.82-1.86; OR: 1.05, 95% CI, 0.74-1.49). The confidence in the evidence was moderate.

Confidence Level: Moderate

***Conclusion:** The severity of mTBI determined by the Abbreviated Injury Scale score and acute concussive symptoms is likely not associated with an increased risk of neurocognitive impairment at 12 months post-injury.*

Injury Severity and Psychosocial Adjustment

One Class I study[S78] examined the relationship between injury severity and declines in HRQoL across the first 12 months after mTBI in a prospective cohort of 317 children between ages 0 and 17 recruited in an ED setting. Injury severity was measured by the presence of skull fracture, injury mechanism, level of emergency medical transportation, or Abbreviated Injury Scale score. The likelihood of displaying a decline in HRQoL was unrelated to the presence of skull fracture (RR 0.35, 95% CI, 0.05-2.24), injury mechanism (motor vehicle versus other) (RR 2.35, 95% CI, 0.86-6.47), EMS level of transportation (advanced life support versus other) (RR 1.77, 95% CI, 0.64-4.10), or Abbreviated Injury Scale score for head injury (1 versus 2/3) (RR 1.59, 95% CI, 0.89-2.85). Another Class I studyS102 examined the relationship between injury severity and total behavioral problems at 12 months post-injury in a prospective cohort of 176 children with mTBI recruited in an ED setting. Injury severity was determined by the presence of LOC or admission to the hospital. The likelihood of displaying a clinically significant elevation in behavioral problems at 12 months was marginally significantly related ($P < 0.10$) to the presence of LOC at the time of injury (OR: 2.80, 95% CI, 0.92-8.56), and significantly related ($P < 0.05$) to hospital admission at the time of injury (OR: 3.50, 95% CI, 1.14-13.56). One Class II study[S101] involved retrospective recruitment of a cohort of 52 children with mTBI who were injured before age 4 and assessed, on average, about 8 years post-injury. In that study, children with complicated mTBI (defined by positive LOC, Pediatric Coma Scale (PCS) score of 13-14, or two or more acute symptoms/signs) did not differ on two parental ratings of everyday executive functioning as compared to children with uncomplicated mTBI (defined by no LOC, PCS score of 15, and no acute symptoms). The confidence in the evidence was judged to be moderate.

Confidence Level: Moderate

Conclusion: *Among children presenting to an ED with mTBI, injury severity based on clinical characteristics is unlikely to be associated with the likelihood of declines in HRQoL over the first 12 months post-injury or with long-term problems with everyday executive functioning, but is likely associated with the occurrence of behavioral problems at 12 months post-injury.*

Intracranial Lesion and Specific Cognitive Ability

One Class I study[S87] examined the relationship between the presence or absence of an intracranial lesion detected on head CT imaging obtained within 24 hours of mTBI and specific cognitive abilities in

80 children between ages 5 and 15. The study reported that children with an intracranial lesion performed worse on tests of specific cognitive ability at 12 months post-injury than children without such lesions (six dependent variables, mean *d* = -0.28, range of *d*: -0.17 to -0.46).

Confidence Level: Moderate

Conclusion: *Children with mTBI who display an intracranial lesion on acute head CT are likely to perform more poorly on tests of specific cognitive abilities at 12 months post-injury as compared to children with mTBI without an intracranial lesion on acute head CT.*

Intracranial Lesion and General Cognitive Ability/Achievement

One Class I study[S87] examined the relationship between the presence or absence of an intracranial lesion on acute head CT imaging obtained within 24 hours of mTBI and general cognitive ability/achievement in 80 children between ages 5 and 15. The study reported that children with an intracranial lesion did not perform consistently worse on tests of general cognitive ability/achievement at 12 months post-injury than children without such lesions (two dependent variables, mean *d* = -0.09, range of *d*: 0.28 to -0.46).

Confidence Level: Moderate

Conclusion: *Children with mTBI who have an intracranial lesion on acute head CT are unlikely to perform more poorly on tests of general cognitive ability/achievement at 12 months post-injury as compared to children with mTBI who do not have an intracranial lesion on acute imaging.*

Intracranial Lesion and Psychosocial Adjustment

One Class I study[S85] examined the relationship between the presence or absence of an unspecified intracranial hemorrhage on acute head CT imaging obtained within 24 hours of mTBI and psychosocial adjustment in 585 children between ages 0 and 17. The study reported that children with an intracranial hemorrhage exhibited modestly worse psychosocial adjustment at 12-24 months post-injury than children without a hemorrhage (eight dependent variables, mean *d* = -0.085, range of *d*: 0.11 to -0.25, six of eight effects negative). Another Class I study[S102] examined the relationship between the presence of abnormalities on brain MRI within 10 days of injury and total behavioral problems at 12 months post-injury in a prospective cohort of 176 children with mTBI recruited in an ED setting. The likelihood of displaying a clinically significant elevation in behavioral problems at 12 months was not associated with the presence of MRI abnormalities. Confidence in the evidence was moderate, but was downgraded due to lack of precision and incomplete reporting in the Taylor study.

Confidence Level: Low

Conclusion: *Children with mTBI who display an intracranial lesion on neuroimaging possibly display modest deficits in psychosocial adjustment at 12-24 months post-injury relative to children with mTBI without an intracranial lesion on neuroimaging.*

Intracranial Lesion and Postconcussive Symptoms

One Class I study[S97] examined the relationship between MRI abnormalities, assessed 1-2 weeks post-injury, and postconcussive symptoms during the first 12 months post-injury in 182 children ages 8-15 years. The study reported that, among children who had an intracranial lesion detected on MRI, those with lower cognitive ability were rated by their parents as exhibiting more cognitive symptoms at 12 months post-injury than children of higher cognitive ability. The relationship between symptoms and cognitive ability was significantly reduced in children without intracranial lesions on MRI (group X MRI status X cognitive ability interaction accounted for 6% of variance in linear

change and 12% of variance in quadratic change in postconcussive symptoms).

Confidence level: Moderate

Conclusion: *The presence of an intracranial lesion on MRI may be associated with an increased risk of increased cognitive symptoms after mTBI at 12 months post-injury, when it occurs in children of lower cognitive ability.*

Intracranial Lesion and Psychiatric Outcome

One Class I study[S88] examined the relationship between the presence or absence of an unspecified intracranial hemorrhage on acute head CT imaging obtained within 24 hours of mTBI and symptoms of PTSD and depression in 138 adolescents between ages 14 and 17. The study reported that adolescents with an intracranial hemorrhage displayed modestly worse psychiatric outcome, on average, at 12-24 months post-injury than adolescents without a hemorrhage, although the direction of effect was inconsistent (four dependent variables, mean *d* = -0.09, range of *d*: 0.62 to -1.13, two significant effects in opposite directions).

Another Class I study[S100] examined the relationship between the presence of abnormalities on head CT at the time of presentation and novel psychiatric disorder in the interval 6-12 months after mTBI in a prospective cohort of 60 children between ages 5 and 14. Children with and without novel psychiatric disorder over that interval did not differ significantly in the likelihood of an abnormality on head CT (RR 0.85, 95% CI, 0.38-1.92). Confidence in the evidence was downgraded to low due to the lack of precision in the first study.

Confidence Level: Low

Conclusion: *Children with mTBI who exhibit an intracranial hemorrhage on head CT at the time of presentation possibly are more likely to exhibit psychiatric disorder at 12-24 months post-injury than children with mTBI without intracranial hemorrhage on head CT.*

Pre-Injury Psychiatric Status and Psychiatric Outcome

One Class I study[S99] examined the relationship between the presence or absence of a premorbid psychiatric disorder during the year prior to injury and the incidence of new post-injury psychiatric illness in 490 children with mTBI between ages 0 and 14. The study reported that children with a premorbid psychiatric disorder displayed a higher incidence of new post-injury psychiatric illness (55%), on average, during the first 3 years post-injury than children without a premorbid psychiatric disorder (26%) (RD 29%, $P < .002$). Another Class I study[S100] examined the relationship between pre-injury lifetime psychiatric disorder and novel psychiatric disorder in the interval 6-12 months after mTBI in a prospective cohort of 60 children between ages 5 and 14. Children with and without novel psychiatric disorder over that interval did not differ in the likelihood of a pre-injury lifetime psychiatric disorder (RR 1.13, 95% CI, 0.50-2.55). Confidence was lowered because of imprecision.

Confidence Level: Low

Conclusion: *Children with mTBI with a premorbid psychiatric disorder possibly demonstrate a higher likelihood of novel psychiatric illness over the first 3 years post-injury than do children with mTBI who do not display a premorbid psychiatric disorder.*

Pre-Injury Child Functioning and General Cognitive Ability/Achievement

One Class I study[S96] longitudinally followed a prospective cohort of 76 children with mTBI between ages 8 and 17, and reported that parental ratings of children's pre-injury academic achievement and pre-injury learning problems were both significantly associated with the likelihood of global neurocognitive impairment at 12 months (OR: 0.79, 95% CI, 0.69-0.90 and OR: 1.46, 95% CI,

1.06-2.02, respectively). However, in the same study, parental ratings of children's pre-injury behavioral problems were not associated with the likelihood of global neurocognitive impairment at 12 months (OR: 1.030, 95% CI, 1.002-1.058). Confidence in this evidence was moderate.

Confidence Level: Moderate

***Conclusion:** Among children presenting to an ED with mTBI, pre-injury academic functioning likely predicts global neurocognitive impairment at 12 months post-injury, but pre-injury behavioral problems probably does not predict global neurocognitive impairment at 12 months.*

Pre-Injury Child Functioning and Postconcussive Symptoms

One Class I study[S92] reported no significant relationship of pre-injury symptoms to postconcussive symptoms at 18 months post-injury in a prospective cohort of 129 children ages 6-16 with mTBI. The confidence in the evidence was low; the level was lowered for imprecision because the results from the study were not reported in sufficient detail to allow for an effect size calculation.

Confidence Level: Low

***Conclusion:** Among children presenting to an ED, pre-injury symptoms possibly do not predict postconcussive symptoms at 18 months post-injury.*

Pre-Injury Child Functioning and Psychiatric Outcome

One Class I study[S100] examined the relationship between pre-injury adaptive functioning (Vineland Adaptive Behavior Scale [VABS] total score) and novel psychiatric disorder in the interval 6-12 months after mTBI in a prospective cohort of 60 children between ages 5 and 14. Children with and without novel psychiatric disorder over that interval did not differ significantly in their total VABS score (d = -0.38, 95% CI, -0.96 to 0.21). Confidence in this evidence was moderate.

Confidence Level: Moderate

***Conclusion:** Among children presenting to an ED with mTBI, pre-injury adaptive functioning is likely not associated with the presence of a novel psychiatric disorder in the 6-12 months after injury.*

Pre-Injury Child Functioning and Psychosocial Adjustment

One Class I study[S78] examined the relationship between parental reports of pre-injury comorbidities (from a list of 11), and parental ratings of pre-injury headache, sleep quality, and depressive symptoms, with declines in HRQoL across the first 12 months after mTBI in a prospective cohort of 317 children between ages 0 and 17 years recruited in an ED setting. Comorbidities (0-1 versus 2 or more) were not associated with significant declines in HRQoL (RR 1.75, 95% CI, 0.98-3.12). Pre-injury headache, sleep quality, and depressive symptoms also were not associated with declines in HRQoL, although these results were not reported in sufficient detail to permit effect size calculation. Confidence in this evidence was low; confidence was lowered because of the imprecision.

Confidence Level: Low

***Conclusion:** Among children presenting to an ED with mTBI, pre-injury child functioning is likely not associated with the likelihood of declines in HRQoL over the first 12 months post-injury.*

Pre-Injury Family Functioning and Postconcussive Symptoms

One Class I study[S92] reported that parents' pre-injury symptoms of avoidance (which are an indication of post-traumatic stress) were not predictive of postconcussive symptoms at 18 months post-injury in a prospective cohort of 129 children between ages 6 and 16 with mTBI. Parents'

pre-injury symptoms of anxiety were predictive of postconcussive symptoms for children with uncomplicated mTBI, but not for those with complicated mTBI or mTBI without imaging. Complicated mTBI was defined as the presence of a depressed skull fracture or intracranial lesion on neuroimaging not requiring surgery. The confidence in the evidence was very low; the level was lowered for imprecision, because the results from the study were not reported in sufficient detail to allow for an effect size calculation, and for inconsistency.

Confidence Level: Very low

***Conclusion:** There is insufficient evidence to determine whether parents' pre-injury symptoms of mental health problems and post-traumatic stress are predictive of postconcussive symptoms at 18 months post-injury in children with mTBI.*

Pre-Injury Family Functioning and Psychiatric Outcome

One Class I study[S100] examined the relationship between pre-injury family functioning (FAD General Functioning Scale, family psychiatric history, and pre-injury psychosocial adversity) and novel psychiatric disorder in the interval 6-12 months after mTBI in a prospective cohort of children between ages 5 and 14. Children with and without novel psychiatric disorder over that interval differed significantly with regard to pre-injury psychosocial adversity (d = 0.72, 95% CI, 0.12-1.30), and marginally significantly in pre-injury family functioning (d = 0.57, 95% CI, -0.03 to 1.14). They did not differ significantly in the severity of family psychiatric history, although the direction of effect was similar (d = 0.47, 95% CI, -0.15 to 1.07). Confidence in this evidence was moderate.

Confidence Level: Moderate

***Conclusion:** Poor pre-injury family functioning likely places children at elevated risk for novel psychiatric disorder 6-12 months after mTBI.*

Pre-Injury Family Functioning and Psychosocial Adjustment

One Class I study[S78] examined the relationship between pre-injury family functioning (total FAD score) and declines in HRQoL across the first 12 months after mTBI in a prospective cohort of 317 children ages 0-17 recruited in an ED setting. Total FAD scores did not differ significantly for children who did and did not show declines in HRQoL (d = -0.04, 95% CI, -0.37 to 0.29). Confidence was judged to be moderate.

Confidence Level: Moderate

***Conclusion:** Among children presenting to an ED with mTBI, pre-injury family functioning is unlikely to be associated with declines in HRQoL over the first 12 months post-injury.*

Post-Injury Child Functioning and General Cognitive Ability/Achievement

One Class I study[S96] longitudinally followed a prospective cohort of 76 children with mTBI between ages 8 and 17, and reported that parental ratings of children's behavioral problems at 12 months were significantly associated with the likelihood of global neurocognitive impairment at 12 months (OR: 1.03, 95% CI, 1.002-1.058). Confidence in this evidence was moderate.

Confidence Level: Moderate

***Conclusion:** Among children presenting to an ED with mTBI, concurrent behavioral problems likely predict the likelihood of global neurocognitive impairment at 12 months.*

Post-Injury Child Functioning and Postconcussive Symptoms

One Class I study[S92] examined the association between parental ratings of post-injury child functioning at 6 months (postconcussive symptoms HRQoL, and dissociative symptoms) and postconcussive symptoms at 18 months post-injury

in a prospective cohort of 129 children between ages 6 and 16 with mTBI. Postconcussive symptoms at 6 months were a significant predictor of postconcussive symptoms at 18 months (Significant F (1, 91) = 9.98, P < .002, η2 = 0.099); but neither HRQoL nor dissociative symptoms were significant predictors. One Class II study[S80] compared 47 children with mTBI who remained symptomatic at 7-10 days with 42 children with mTBI who were not symptomatic at 7-10 days, all of whom were recruited from a prospective database of 670 children injured from ages 0-18. They provided ratings of postconcussive symptoms at about 1-2 years post-injury. Children who were symptomatic post-acutely reported significantly more symptoms at 1-2 years post-injury than children who were not symptomatic post-acutely (d = 1.000, 95% CI, 0.558-1.441). The confidence in the evidence was judged to be low; the level was lowered for imprecision because the results from the first study were not reported in sufficient detail to allow for effect size and confidence interval calculations for all predictors.

Confidence Level: Low

***Conclusion:** The level of postconcussive symptoms reported 7-10 days or 6 months post-injury are possibly predictive of postconcussive symptoms at 1-2 years post-injury in children with mTBI. Post-injury HRQoL and dissociative symptoms are possibly not predictive of postconcussive symptoms at 18 months.*

Post-Injury Child Functioning and Psychosocial Adjustment

One Class II study[S80] compared 47 children with mTBI who remained symptomatic at 7-10 days with 42 children with mTBI who were not symptomatic at 7-10 days, all of whom were recruited from a prospective database of 670 children injured from ages 0-18. They provided ratings of depressive symptoms at about 1-2 years post-injury. Children who were symptomatic post-acutely reported significantly more symptoms at 1-2 years post-injury than children who were not symptomatic post-acutely (*d* = 0.172, 95% CI, -0.245 to 0.589). Confidence in the evidence was judged to be low.

Confidence Level: Low

***Conclusion:** Postconcussive symptoms reported 7-10 days or 6 months post-injury are possibly predictive of depressive symptoms at 1-2 years post-injury in children with mTBI.*

Post-Injury Family Functioning and General Cognitive Ability/Achievement

One Class I study[S96] longitudinally followed a prospective cohort of 76 children with mTBI between ages 8 and 17, and reported that parental ratings of family stress at 12 months were not associated with the likelihood of global neurocognitive impairment at 12 months (OR: 1.09, 95% CI, 0.92-1.28). Confidence in this evidence was moderate.

Confidence Level: Moderate

***Conclusion:** Among children presenting to an ED with mTBI, concurrent family stress likely does not predict the likelihood of global neurocognitive impairment at 12 months.*

Post-Injury Family Functioning and Postconcussive Symptoms

One Class I study[S92] examined the association between parents' somatic symptoms at 6 months and children's postconcussive symptoms at 18 months post-injury in a prospective cohort of 129 children ages 6-16 with mTBI. Parents' somatic symptoms at 6 months were a significant predictor of postconcussive symptoms at 18 months ($F(1, 91) = 9.98$, $P < 0.002$, $\eta 2 = 0.099$). The confidence in the evidence was low; the level was lowered for imprecision because the results from the study were not reported in sufficient detail to allow for effect size and confidence interval calculations for all predictors.

Confidence Level: Low

Conclusion: Parents' post-injury somatic symptoms at 6 months may possibly be predictive of children's postconcussive symptoms at 18 months post-injury in children with mTBI.

SES and General Cognitive Ability/Achievement

One Class I study[S96] longitudinally followed a prospective cohort of 76 children with mTBI between ages 8 and 17, and reported that parental education was marginally significantly ($P < 0.10$) associated with the likelihood of global neurocognitive impairment at 12 months (OR: 0.92, 95% CI, 0.84-1.002). Confidence in this evidence was low; confidence was lowered because of imprecision.

Confidence Level: Low

***Conclusion:** Among children presenting to an ED with mTBI, lower parental education possibly predict an increased likelihood of global neurocognitive impairment at 12 months.*

SES and Psychiatric Outcome

One Class I study[S100] examined the relationship between SES measured on the Hollingshead Index and novel psychiatric disorder in the interval 6-12 months after mTBI in a prospective cohort of 60 children between ages 5 and 14. Children with and without novel psychiatric disorder over that interval differed significantly in SES (d = -0.62, 95% CI, -1.20 to -0.03). Confidence in this evidence was moderate.

Confidence Level: Moderate

***Conclusion:** Lower SES is likely associated with an elevated risk for novel psychiatric disorder 6-12 months after mTBI.*

SES and Psychosocial Adjustment

One Class I study[S78] examined the relationship between SES (measured as health insurance status [Medicaid versus commercial], family income, and parental education) and declines in HRQoL across the first 12 months after mTBI in a prospective cohort of 317 children between ages 0 and 17 recruited in an ED setting. Children who showed

declines in HRQoL after mTBI showed lower SES on all indices (RR 2.2 [1.21-4.06] for insurance status; RR 3.10 [1.4-6.86] for family income; and RR 2.51 [1.09-6.10] for parental education. Confidence in this evidence was moderate.

Confidence Level: Moderate

***Conclusion:** Among children presenting to an ED with mTBI, lower SES is likely associated with a greater likelihood of declines in HRQoL over the first 12 months post-injury.*

Demographics and Postconcussive Symptoms

One Class I study[S92] examined the association between child gender and postconcussive symptoms at 18 months post-injury in a prospective cohort of 129 children with mTBI between ages 6 and 16. Gender was not a significant predictor of postconcussive symptoms. The confidence in the evidence was low; the level was lowered for imprecision because the results were not reported in sufficient detail to allow for effect size and confidence interval calculations for all predictors.

Confidence Level: Low

***Conclusion**: Children's gender is possibly not predictive of postconcussive symptoms at 18 months post-injury in children with mTBI.*

Demographics and Psychiatric Outcome

One Class I study[S100] examined the relationship between children's demographic characteristics (gender and race) and novel psychiatric disorder in the interval 6-12 months after mTBI in a prospective cohort of 60 children between ages 5 and 14. Children with and without novel psychiatric disorder over that interval did not differ in their distribution of gender or race (RR 0.96, 95% CI, 0.64-1.44 or RR 1.56, 95% CI, 0.79-3.07, respectively). Confidence in this evidence was moderate.

Confidence Level: Moderate

Conclusion: Neither gender nor race is likely to be associated with the risk of novel psychiatric disorder 6-12 months after mTBI in children.

Demographics and Psychosocial Adjustment

One Class I studyS78 examined the relationship between children's demographics (gender and race) and declines in HRQoL across the first 12 months after mTBI in a prospective cohort of 317 children between ages 0 and 17 recruited in an ED setting. Children who did and did not show declines in HRQoL after mTBI did not differ significantly in the distribution of gender or race (RR 1.03, 95% CI, 0.56-1.89 or RR 0.82, 95% CI, 0.44-1.54, respectively). Confidence in this evidence was moderate.

Confidence Level: Moderate

***Conclusion:** Among children presenting to an ED with mTBI, gender and race are not likely to be associated with a greater likelihood of declines in HRQoL over the first 12 months post-injury.*

Missing Evidence

Evidence was missing on a variety of risk factor-outcome pairs. Specifically, evidence was missing on the following pairs: age at injury/specific cognitive abilities; presence versus absence of Apo E4 allele with psychiatric outcomes and psychosocial adjustment; overall cognitive ability with specific cognitive abilities, psychiatric outcomes, and psychosocial adjustment; presence versus absence of extracranial injury with specific cognitive abilities, general cognitive ability and achievement, and postconcussive symptoms; pre-injury psychiatric status with specific cognitive ability, postconcussive symptoms, and psychosocial adjustment; pre-injury child functioning with specific cognitive ability; pre-injury family functioning with specific cognitive ability and

general cognitive ability; post-injury child functioning with specific cognitive ability and psychiatric outcome; SES with specific cognitive ability and postconcussive symptoms; and demographics with specific cognitive ability and general cognitive ability.

Recommendations for Future Research

1. More research is needed concerning the risks for long-term negative outcomes following mTBI in children, especially over intervals extending beyond 1 year post-injury.
2. Long-term outcome studies extending into adulthood are needed to better examine the likelihood of negative outcomes during adulthood and the risk factors that predict them.
3. Future studies ideally will examine multiple risk factors and multiple outcomes in large samples derived from multiple sites using prospective, longitudinal research designs.
4. Researchers are encouraged to supply data (ie, means and standard deviations, or counts/proportions) that are essential to the completion of systematic reviews/meta-analyses, either within the published papers or as online supplements.

Question 6: For children (18 years of age and younger) with mild TBI (with ongoing symptoms), which treatments improve mild TBI-related outcomes?

Introduction and Rationale

The current treatment for pediatric mTBI is supportive care with symptom management and avoidance of exertion that worsens symptoms. The purpose of this review was to evaluate studies on therapeutic intervention in pediatric mTBI and determine the best evidence for treatment practices with a goal of improved outcome in children. This is of particular importance for children with ongoing and/or severe symptoms following mTBI.

Inclusion Criteria

We included studies of children (ages 18 and younger) with mTBI who received or did not receive a treatment (randomization to treatment groups was not required). Studies included measured the association between treatment and mTBI-related outcomes.

Article Flow

A total of 2,879 articles were identified for potential inclusion. Of those, 395 were identified for full-text review eligibility with 14 undergoing data extraction. Four articles were ultimately included in the quantitative data synthesis from data extraction based on the inclusion criteria. These four articles included one Class I studies and three Class III studies.

Intervention-Outcome Pairs

Informational Booklet and 1-Week Clinician Follow-Up

A single Class III, controlled, multi-armed study[S104] evaluated the effect of a clinical visit within 1 week of mTBI and provision of an informational booklet about mTBI. Outcomes included reported

symptoms and neuropsychological assessments at 3 months following injury. Although some effect sizes were statistically significant, confidence in the clinical significance of the findings was low because the control groups show similar effects. For symptom scores, the difference between the mTBI intervention group and the mTBI non-intervention group was significant for headache (z = 2.96, 95% CI, 1.01-4.91), sleeping difficulty (z = 2.36, 95% CI, 0.37-4.35), and judgment problems (z = 2.04, 95% CI, 0.09-3.99). However, these changes in symptoms may not have applicable clinical significance or true association with the intervention. The Contingency Naming Test for patients ages 10-12 showed statistically significant improvements in scores in the mTBI intervention group compared to the mTBI non-intervention group (z = 1.14, 95% CI, 0.76-1.54). This improvement is unlikely to be clinically significant from a neuropsychological standpoint. Overall confidence is very low due to the classification of this study as Class III and the moderately high risk of bias in the study design and the lack of replication.

Confidence Level: Very low

Conclusion: *In children with mTBI, there is insufficient evidence to determine whether a clinical visit within 1 week and provision of an informational booklet on mTBI resulted in decreased symptom report at 3 months post-injury and mild improvements on the Contingency Naming Test in patients 10-12 years of age.*

Amantadine

A single Class III, retrospective, case-controlled study[S105] evaluated for the therapeutic efficacy of amantadine (100mg PO BID) in children with mTBI and persisting symptoms at 3 weeks. Patients were treated for 3-4 weeks and outcomes measured included self-reported symptoms and neurocognitive testing on ImPACT. The study showed improvement in self-reported symptoms following 3-4 weeks of therapy compared to the controls (*z* = 0.79, 95% CI, 0.22-1.37), as well as improvement in verbal memory on ImPACT testing following therapy compared to the controls (*z* = 0.74, 95% CI, 0.17-1.31). Although effect sizes were significant, patients with and without treatment had similar endpoints in total symptom score and verbal memory score improvement on ImPACT, suggesting uncertainty in clinical significance. Overall confidence is very low due to the classification of the study as Class III and the moderately high risk of bias in the study design and the lack of replication.

Confidence Level: Very low

Conclusion: *In children with mTBI with ongoing symptoms, there is insufficient evidence to determine the therapeutic efficacy of amantadine.*

Hypertonic Saline

A single Class I, double-blind, randomized control trial[S106] evaluated headache improvement in 44 children with mTBI following the administration of 3% hypertonic saline as compared to normal saline in the ED. Outcomes were assessed at 1 hour post-intervention and 3 days post-intervention. Effect sizes were significant immediately following the intervention, with a *z* score of 1.53 (95% CI, 0.85-2.20); however, the study failed to show an effect at 3 days post-intervention, with a *z* score of 0.79 (95% CI, 0.18-1.40). Overall confidence in this evidence was moderate, but was downgraded to low due to concerns regarding directness. The generalizability of the study is limited to patients perceived to have a more severe acute presentation of mTBI.

Confidence Level: Low

Conclusion: *In children with mTBI and acute headache, 3% hypertonic saline possibly decreases pain from headache in ED settings.*

Strict Rest

A single Class III, prospective, randomized trial[S107] of 88 children with mTBI evaluated the effects of strict rest compared to standard return to activity at 10 days for the following outcomes: symptom assessment with postconcussive symptoms score, neurocognitive assessment using ImPACT testing, and balance assessment using the Balance Error Scoring System.

Strict Rest/Postconcussive Symptom Score (Symptom Assessment)

For the strict rest-symptoms intervention outcome pair, this un-blinded study is Class III due to non-objective patient outcome assessment. The study reported an effect size relative to symptoms over 10 days, with a score of 56 points less in the non-bed rest group (95% CI, 5.4-106).

Overall confidence in this evidence is very low. Confidence was initially upgraded for magnitude of effect, but ultimately downgraded again due to concerns regarding precision. The generalizability of this outcome pair may be limited by the study's evaluation of older children presenting to an ED with ultimate ED discharge.

Confidence Level: Very low

***Conclusion:** There is insufficient evidence to support or refute an effect of strict rest on symptoms in children with mTBI.*

Strict Rest/Neurocognitive Testing (ImPACT) and Balance Scores (BESS)

For the strict rest-neurocognitive testing intervention outcome pair and the strict rest-balance testing intervention outcome pair, this study is Class II due to the objectivity of the outcome measure. For both outcome measures, there was no difference found for the strict rest compared to the standard-of-care group.

Confidence Level: Low

***Conclusion:** Strict rest possibly does not change postconcussion cognitive and balance recovery as measured by ImPACT testing and the Balance Error Scoring System (BESS) in children with mTBI.*

Missing Evidence

Currently, no evidence exists identifying and guiding specific populations that may benefit from recommendations for return to activities outside the standard of care.

Recommendations for Future Research

1. Further research using randomized controlled trials are needed to contribute to interpretable evidence for the best practices in treatment of children with mTBI, including interventions in the acute and chronic setting. Study designs, including case studies, case series, reviews, non-stratified studies of adults and children, and non-controlled studies, do not contribute to the current body of evidence supporting meaningful treatment recommendations.

CLINICAL RECOMMENDATIONS FOR HEALTHCARE PROVIDERS

Recommendations on the clinical care of pediatric mTBI in children were developed and categorized into three topics: diagnosis, prognosis, and management and treatment. These recommendations were drafted based on evidence from the systematic review, as well as related evidence, scientific principles, and expert inference. Clinical recommendations were collated and distributed to the Workgroup in sequential rounds of voting to determine consensus. After four rounds, consensus was achieved on 46 clinical recommendations: 11 pertaining to diagnosis, 12 pertaining to prognosis, and 23 focused on management and treatment. See the Appendix for further details pertaining to the methodology of formulating recommendations, assigning levels of obligation, and clinical contextual profiles.

Diagnosing Mild Traumatic Brain Injury Following Head Injury in Children (as compared to absence of brain injury or more severe injuries)

Three topical areas for the diagnosis of pediatric mild traumatic brain injury (mTBI) were identified:

A. Risk factor identification and imaging,
B. Neuropsychological tools, and
C. Serum biomarkers.

In an effort to provide a basis for these clinical recommendations for healthcare providers, the existing evidence and related evidence (studies of adult mTBI, child moderate-severe TBI, mixed age groups) were assembled to provide a rationale and support for each.

A. Risk Factor Identification and Imaging

- Risk Factors and Computed Tomography (CT)
- Brain Magnetic Resonance Imaging (MRI)
- Single Photon Emission Computed Tomography (SPECT)
- Skull X-ray

B. Neuropsychological tools

- Symptom Scales
- Computerized Cognitive Testing
- Standardized Assessment of Concussion

C. Serum Biomarkers

Level of obligation anchored to confidence in evidence is determined from the Delphi process:

- **Level A: The recommendation almost always should be followed.**
- **Level B: The recommendation usually should be followed.**
- **Level C: The recommendation may sometimes be followed.**
- **Level U: There is insufficient evidence to make a recommendation.**
- **Level R: The intervention generally should not be done outside of a research setting.**

A. Risk Factor Identification and Imaging

- ***Risk Factors for Intracranial Injury and CT***

Rationale:

Up to 7.5% of children with mTBI will have intracranial injury (ICI).[C1-C15] Identification of risk factors for ICI in children presenting with possible mTBI in the acute setting is important to the diagnosis of more severe forms of TBI, further directing observation and the possible need for emergent head CT. ICI further directs the prognosis of patients with mTBI (see Prognosis Recommendations). There is moderate evidence that several risk factors identify those patients with increased risk of ICI.[C3,C5,C16-C18] These risk factors include age younger than 2 years, vomiting, loss of consciousness, severe mechanism of injury, severe or worsening headache, amnesia, non-frontal scalp hematoma, Glasgow Coma Score less than 15, and clinical suspicion for skull fracture. Notably, upon literature review, there is insufficient evidence to report seizures as a risk factor for ICI at this time. There is strong clinical evidence that use of clinical decision rules are effective in identifying children at low risk for ICI.[C3,C5,C16,C18] The use of clinical decision rules may minimize the risk of failure to identify important ICI while avoiding unnecessary radiation exposure from head CT.

Head CT is the preferred diagnostic tool in acute care settings to rapidly identify ICI. However, higher doses of radiation attributable to this type of imaging in children have been associated with an increase in the lifetime cancer mortality risk.[C19-C22] Further, certain pediatric populations will require sedation in order to obtain adequate neuroimaging, increasing the overall risk related to imaging processes.[C23] Families require clinical counseling regarding these risks in order to understand best practices for the clinical care of their child.

Pediatric head CT following mTBI in the acute care setting may possibly identify ICI in 7.5% (95% CI, 6.0-9.1%) of patients in the acute setting based on 16 Class III studies.[C1-C15] However, this is likely an overestimate of the rate of findings due to bias in the selection of children for imaging. ICI included combinations of epidural hematoma, subdural hematoma, intracranial hemorrhage, subarachnoid hemorrhage, intraventricular hemorrhage, cerebral edema, and depressed skull fractures. Simple skull fractures were not included as ICI unless they occurred concomitantly with another intracranial finding.

In addition, head CT performed on children diagnosed initially with mTBI presenting to an acute care setting may possibly identify abnormalities resulting in clinically important outcomes in 1.9% (95% CI, 1.3-2.5) of patients based on 16 class III studies.[C1-C3,C8-C10,C12,C14,C16,C24-C30] Clinically important outcomes included, but were not limited to, death, neurosurgical intervention, intubation for more than 24 hours, hospital admission of more than two nights for TBI, placement of intracranial pressure monitor, or other neurosurgical procedures. This is probably an overestimation of the rate of findings due to bias in the selection of children for imaging. Routine head CT in the acute care setting is possibly associated with neurosurgical intervention in 0.9% (95% CI, 0.5-1.2%) of patients based on 14 Class III studies.[C1-C3,C8-C10,C12,C14,C16,C24-C30] Neurosurgical intervention was defined differently by the different authors, but included all craniotomies and occasionally intracranial pressure (ICP) monitors.

Following seemingly minor head injuries and mTBI, ICI resulting in the above stated clinically important outcomes is rare.[C1-C3,C8-C10,C12,C16,C24-C31] Clinical evaluation of the child with possible mTBI includes balancing the likelihood of potentially devastating complications of a more severe injury against the risks associated with head CT (as well as possible concomitant sedation for imaging).

CLINICAL RECOMMENDATIONS FOR HEALTHCARE PROVIDERS:

1. Healthcare providers *should not* routinely obtain head CT for diagnostic purposes in children with mTBI. (Level B)

2. Healthcare providers should use validated clinical decision rules to identify children at low risk for intracranial injury, in whom head CT is not indicated, as well as children who may be at higher risk for clinically important ICI, and therefore may warrant head CT. Existing decision rules combine a variety of risk factors, including the following:

- Age < 2 years old
- Vomiting
- Loss of consciousness
- Severe mechanism of injury
- Severe or worsening headache
- Amnesia
- Nonfrontal scalp hematoma
- Glasgow Coma Score < 15
- Clinical suspicion for skull fracture (Level B)

3. For children diagnosed with mTBI, healthcare providers should discuss the risks of pediatric head CT in the context of risk factors for ICI with the patient and his/her family. (Level B)

- ***Brain Magnetic Resonance Imaging (MRI)***

Rationale:

This review did not find any studies that met inclusion criteria addressing the use of brain MRI in the diagnosis of mTBI in children. MRI is more sensitive in identifying structural abnormalities than CT,[C32,C33] and MRI avoids the use of ionizing radiation associated with CT. However, MRI more often requires sedation due to longer imaging acquisition times, and is more expensive than CT, though recently rapid, non-sedated MRI has been successfully employed in children with suspected acute TBI.[C34] While current standard of care does not support the use of brain MRI in the diagnosis of pediatric mTBI for these reasons, specialized MRI imaging sequences such as functional MRI (fMRI), diffusion tensor imaging (DTI), Gradient recalled echo imaging (GREI), as well as others, have shown promise in research settings.[C35] Studies on mixed groups, including children and adults, have found that early brain MRI can stratify outcome in mTBI.[C36]

CLINICAL RECOMMENDATION FOR HEALTHCARE PROVIDERS:

4. There is currently insufficient evidence to recommend the use of brain MRI in the diagnosis of mTBI in children. Healthcare providers *should not* routinely use MRI in the acute evaluation of suspected or diagnosed mTBI. (Level B)

- ***Single Photon Emission Computed Tomography (SPECT)***

Rationale:

SPECT may demonstrate brain hypoperfusion or hypometabolism following mTBI, but the qualitative nature of the images results in significant variability.[C37-C39] A single Class I pediatric study looked at the presence of medial temporal hypometabolism on SPECT within 3 days of mTBI and reported a significant risk difference (RD: 0.732 [0.487–0.976]) for children with medial temporal hypometabolism having postconcussion syndrome.[C37] However, confidence in this evidence was low due to significant issues with the generalizability of the data and this study did not use SPECT to diagnose mTBI specifically. SPECT is not commonly used in the clinical setting of TBI in children, may require patient sedation employing additional risks, requires intravenous access in the child with the injection of a radiopharmeceutical, and may be more expensive than head CT alone as it is often employed in conjunction with CT. This review did not find any studies that met our inclusion criteria addressing the use of SPECT in the diagnosis of mTBI in children.

CLINICAL RECOMMENDATION FOR HEALTHCARE PROVIDERS:

5. Insufficient evidence currently exists to recommend the use of SPECT in the diagnosis of mTBI in children. Healthcare providers *should not* use SPECT in the acute evaluation of cases of suspected or diagnosed mTBI. (Level B)

- ***Skull X-ray***

Rationale:

This review identified two Class III studies evaluating the use of skull X-rays in children following minor head injury. The evidence identified a possible skull fracture in 7.14% (95% CI, 4.0-10.3%) of patients.[C2] Because related literature reports that skull X-ray has a 63% sensitivity for diagnosing a single skull fracture in children, X-ray cannot detect intracranial injuries such as hemorrhage, shift from midline, or edema, and because X-ray employs radiation for imaging, it is not the best test to diagnose skull fracture with ICI following mTBI.[C40] Clinical suspicion for skull fracture is a risk factor for other ICI following mTBI in children.[C5,C16-C18] Neuroimaging modalities, such as head CT, better detect intracranial injuries, including skull fractures, making it the more appropriate diagnostic imaging choice when imaging is clinically indicated to assess for acute TBI.[C40] In the instances where CT is not available, validated clinical decision rules are better than skull X-rays when screening patients with increased risk for ICI prior to determining the need for transfer to a facility with neuroimaging capabilities.[C3, C5,C16,C18,C41]

CLINICAL RECOMMENDATIONS FOR HEALTHCARE PROVIDERS:

6. Skull X-rays *should not* be used in the diagnosis of pediatric mTBI. (Level B)

7. Skull X-rays *should not* be used in the screening for ICI. (Level B)

B. Neuropsychological Tools

- ***Symptom Scales***

Rationale:

This review demonstrated with moderate confidence that the Graded Symptom Checklist (GSC) is useful in distinguishing children ages 6 years and older with mTBI from those without TBI within the first 2 days after injury.[C42] This review demonstrated with moderate confidence that the Postconcussion Symptom Scale used in the ImPACT neurocognitive testing battery distinguishes high school athletes with mTBI from those without TBI within the first 4 days after injury.[C43,C44] There are several other validated symptom scales that are reliable in the diagnosis of mTBI and have demonstrated validity at ages younger than high school.[C45] The consequences of missing a diagnosis of mTBI include failure to recommend appropriate treatment and management that may contribute to prolongation of symptoms and increased risk of re-injury. Symptom inventories can be applied quickly and inexpensively.

CLINICAL RECOMMENDATIONS FOR HEALTHCARE PROVIDERS:

8. Healthcare providers *should* use an age-appropriate, validated symptom rating scale as a component of the diagnostic evaluation in children presenting with acute mTBI. (Level B)

- ***Computerized Cognitive Testing***

Rationale:

This review identified two Class II studies meeting inclusion criteria evaluating computerized cognitive testing and the diagnosis of mTBI in children.[C43,C44] These studies only evaluated ImPACT cognitive testing and demonstrated that ImPACT cognitive testing probably distinguishes high school athletes with and without mTBI in the first 4 days post-injury and may add sensitivity to use of a symptom rating scale alone.[C43,C44] While these two studies only reviewed ImPACT testing, related evidence demonstrates that other validated computerized cognitive tests are also accurate in the diagnosis of mTBI in adults and children.[C46,C47] There is insufficient evidence to determine whether baseline testing in children better identifies mTBI post-injury as compared to post-injury scores alone, though evidence in adults currently suggests that baseline testing may be unnecessary in most cases.[C48,C49] The consequences of missing a diagnosis of mTBI include failure to recommend appropriate treatment and management that may contribute to prolongation of symptoms and increased risk of re-injury.

CLINICAL RECOMMENDATIONS FOR HEALTHCARE PROVIDERS:

9. Healthcare providers *may* use validated, age-appropriate computerized cognitive testing in the acute period of injury as a component of the diagnosis of mTBI. (Level C)

- ***Standardized Assessment of Concussion***

Rationale:

This review demonstrated that cognitive screening using the Standardized Assessment of Concussion (SAC) was not accurate in distinguishing those children with mTBI from those without mTBI due to lack of statistical significance from a single Class III study.[C42] Mixed literature in high school and collegiate athletes suggests that the SAC may detect effects of acute mTBI; however, these data were unable to be applied specifically to children in general or children specifically outside of the sports setting.[C50] The consequences of missing a diagnosis of mTBI include failure to recommend appropriate treatment and management and may contribute to prolongation of symptoms and increased risk of re-injury.

CLINICAL RECOMMENDATION FOR HEALTHCARE PROVIDERS:

10. There is insufficient evidence to support the use of the SAC in the diagnosis of children with mTBI, and this test *should not* be exclusively used to identify mTBI in children 6-18 years of age. (Level B)

C. Serum Markers

Rationale:

Blood serum markers that may aid in the diagnosis of pediatric mTBI would be beneficial due to their low-risk profile. In two Class II studies, S100B was shown to be associated with a low sensitivity but high specificity in severe TBI patients, with no discrimination in mild to moderate TBI.[C51,C52] Low sensitivity limits the usefulness of biomarkers, including S100B, for identifying or categorizing mTBI in children. In a Class II study, Tau was significantly different between pediatric mTBI patients with normal head CT, abnormal CT, and with non-TBI control subjects.[C53] The effect size was small, and the control group was poorly defined, thus limiting the application of the findings. Serum potassium, sodium, glucose, and white blood cell count were examined in a single Class II study.[C54] There were significant differences between these tests in children with mTBI versus the control groups.[C54] Because the effect sizes were small and the groups were ill-defined, conclusions from this study are limited. A single Class II study explored the use of autoantibodies against glutamate receptors and oxide metabolites as a marker to discriminate between severe and mild pediatric TBI.[C55] There was good discrimination between the two groups, but

there was no uninjured control group, and further data will be needed before the test's value in pediatric mTBI can be determined. A single Class III study examined multiplex bead array biomarkers in a small number of infants with TBI compared to controls and found significant differences in a number of biomarkers.[C56] The size of the study and the specialized population limit the applicability of the results. Related studies have demonstrated associations between neuronal ubiquitin C-terminal hydrolase-L1 and glial fibrillary acidic protein biomarker levels and ICI in adults following mild to moderate TBI.[C57-C60] This review evaluated a single Class II study of 23 children and determined that there is insufficient evidence to determine whether ubiquitin C-terminal hydrolase-L1 and glial fibrillary acidic protein biomarker levels are useful tools in distinguishing children with or without mTBI.[C61] Biomarker studies are not generally obtained in the clinical setting of mTBI and are costly. The time to report serum biomarker results represents a limitation in their clinical use in the acute setting. The risk of utilizing unvalidated biomarkers to clinically diagnose pediatric mTBI is false identification or under-identification of the injury.

CLINICAL RECOMMENDATION FOR HEALTHCARE PROVIDERS:

11. There is insufficient evidence to currently recommend any of the studied biomarkers for the diagnosis of mTBI in children. Healthcare providers should not perform these tests outside of a research setting at this time for the diagnosis of children with mTBI. (Level R)

Prognosis of mTBI in Children

Five topical areas for pediatric mTBI prognosis were identified based upon Workgroup recommendations for healthcare providers. In an effort to provide a basis for these clinical recommendations for healthcare providers, the existing evidence and related evidence (studies of adult mTBI, child severe TBI, mixed age groups) were assembled to provide a rationale and support for each.

A. General Healthcare Provider Counseling of Prognosis
B. Prognosis Related to Premorbid Conditions
C. Assessment of Cumulative Risk Factors and Prognosis
D. Assessment Tools and Prognosis
E. Interventions for mTBI With Poor Prognosis

A. General Healthcare Provider Counseling of Prognosis

Rationale:

Recovery from pediatric mTBI is variable,[C62-C64] and no factors can individually predict recovery of symptoms or outcome.[C65] Therefore, much of the variance in outcomes remains unaccounted for, even when multiple factors are considered. Evidence also suggests that the symptoms experienced by the majority of children with mTBI resolve within 1-3 months post-injury.[C62] A single Class III study reported that providing informational booklets to families that counseled on symptoms and coping strategies for children with mTBI resulted in improved patient outcomes at 3 months.[C66] Although some effect sizes were statistically significant, there is insufficient evidence to determine the clinical significance of this specific

intervention. However, related studies in children and adults with mTBI report direct patient benefits of counseling by healthcare providers.[C67,C68] Public health campaigns have emphasized the importance of parent and family education in mTBI because health outcomes in general are optimized through patient health literacy and the resulting behavior modifications.[C69-C71] Important aspects of healthcare provider counseling include education regarding warning signs of more serious injury (Centers of Disease Control and Prevention [CDC] Heads Up "12 Danger Signs"); review of expected symptoms, monitoring of postconcussive symptoms, prevention of further injury, cognitive and physical activity/rest, instructions regarding return to play/recreation and school (www.cdc.gov/HEADSUP), and clear clinician follow-up instructions.

CLINICAL RECOMMENDATIONS FOR HEALTHCARE PROVIDERS:

12. Healthcare providers *should* counsel patients and families that the large majority (70-80%) of children with mTBI do not show significant difficulties that last more than 1-3 months post-injury. (Level B)

13. Healthcare providers *should* counsel patients and families that although some factors predict an increased or decreased risk for prolonged symptoms, each child's recovery from mTBI is unique and will follow its own trajectory. (Level B)

B. Prognosis Related to Premorbid Conditions

Rationale:

Weak to strong evidence indicates that there is an increased risk of delayed recovery or prolonged symptoms associated with the following premorbid conditions in children with mTBI: premorbid history of concussion,[C72,C73] lower cognitive ability in pediatric mTBI with intracranial lesion,[C74] neurological or psychiatric disorder,[C75,C76] learning difficulties,[C63] increased preinjury symptoms,[C75-C77] and family and social stressors.[C77,C78] The assessment of premorbid history is likely to be most accurate when completed prior to injury (eg, as part of pre-participation athletic examinations) or as soon as possible post-injury to avoid biases or inaccuracies in recall.[C79] Healthcare providers can more effectively counsel patients with mTBI when they have assessed the risks of premorbid conditions for prognosis.

CLINICAL RECOMMENDATIONS FOR HEALTHCARE PROVIDERS:

14. Healthcare providers *should* assess the premorbid history of children either prior to injury as a part of pre-participation athletic examinations, or as soon as possible post-injury in children with mTBI, to assist in determining prognosis. (Level B)

15. Healthcare providers *should* counsel children and families completing pre-participation athletic examinations and children with mTBI as well as their families that recovery from mTBI might be delayed in those with:

- Premorbid histories of mTBI
- Lower cognitive ability (for children with an intracranial lesion)
- Neurological or psychiatric disorder
- Learning difficulties
- Increased pre-injury symptoms (ie, similar to those commonly referred to as "postconcussive")
- Family and social stressors (Level B)

C. Assessment of Cumulative Risk Factors and Prognosis

Rationale:

The outcomes of pediatric mTBI are known to be heterogeneous.[C62-C64] Weak to strong evidence indicates that a variety of demographic and injury-related factors predict outcomes in pediatric mTBI, including age, gender, ethnicity, severity of injury,

presence of ICI, and acute postconcussive symptoms. More specifically, symptoms may last longer for older children/adolescents,[C62,C80,C81] for children of Hispanic ethnicity as compared with White ethnicity,[C81] for children from lower socioeconomic status,[C78,C81] for children with more severe presentations of mTBI[C64,C82,C83] (including those associated with intracranial injury),[C82,C84] and for children who report higher level of acute postconcussion symptoms.[C63,C73,C85] Additionally, headaches persist longer in girls.[C80] However, no single factor is strongly predictive of outcome.[C65]

A 2016 prospective multicenter cohort study of 3,063 children with mTBI seen in emergency department (ED) settings demonstrated that an empirically derived and cross-validated prediction rule combining multiple risk factors stratified the risk of persistent postconcussion symptoms at 28 days.[C86] Healthcare providers can more effectively counsel patients with mTBI when they have assessed cumulative risk factors for prognosis.

CLINICAL RECOMMENDATIONS FOR HEALTHCARE PROVIDERS:

16. Healthcare providers *should* screen for known risk factors for persistent symptoms in children with mTBI. (Level B)

17. Healthcare providers *may* use validated prediction rules, which combine information about multiple risk factors for persistent symptoms, to provide prognostic counseling to children with mTBI evaluated in ED settings. (Level C)

D. Assessment Tools and Prognosis

Rationale:

No single assessment tool is strongly predictive of outcome in children with mTBI.[C65] However, multiple tools have shown utility in the assessment of individual patients and their recovery from mTBI.[C87-C89] Multiple tools are likely to be necessary because recovery trajectories can differ across specific domains of assessment, including symptom report, cognitive test performance, and balance.[C90,C91] Symptom scales and cognitive testing (including measures of reaction time) have the strongest evidence in terms of their contribution to diagnosis (see Diagnosis Recommendations, as well as predicting and assessing recovery[C92]). There is less evidence supporting balance testing as a predictor for prognosis in children, but it has shown utility in older adolescent athletes.[C93] Healthcare providers can more effectively counsel patients with mTBI when they have assessed risk factors for outcome and recovery.

CLINICAL RECOMMENDATIONS FOR HEALTHCARE PROVIDERS:

18. Healthcare providers *should* use a combination of tools to assess recovery in children with mTBI. (Level B)

19. Healthcare providers *should* use validated symptom scales to assess recovery in children with mTBI. (Level B)

20. Healthcare providers *may* use validated cognitive testing (including measures of reaction time) to assess recovery in children with mTBI. (Level C)

21. Healthcare providers *may* use balance testing to assess recovery in adolescent athletes with mTBI. (Level C)

E. Interventions for mTBI With Poor Prognosis

Rationale:

The symptoms experienced by the majority of children with mTBI resolve within 1-3 months post-injury,[C62] but some children are at risk for persistent symptoms and delayed recovery (ie, those who demonstrate certain premorbid characteristics and other risk factors; see rationales for recommendation items 5: Prognosis Related to

Premorbid Conditions and 6: Assessment of Cumulative Risk Factors and Prognosis. Children with mTBI who are at high risk for persistent symptoms or delayed recovery are more likely to require intervention than children at low risk. Healthcare providers can more effectively counsel patients with mTBI when they have assessed risks for prognosis.

CLINICAL RECOMMENDATIONS FOR HEALTHCARE PROVIDERS:

22. Healthcare providers *should* closely monitor children with mTBI who are determined to be at high risk for persistent symptoms based on premorbid history, demographics, and/or injury characteristics. (Level B)

23. For children with mTBI whose symptoms do not resolve as expected with standard care (ie, within 4-6 weeks), healthcare providers *should* provide or refer for appropriate assessments and/or interventions (see Recommendations for Treatment and Management). (Level B)

Management and Treatment of mTBI in Children

Eight topical areas for pediatric mTBI management and treatment were identified based upon Workgroup clinical recommendation for healthcare providers. The Systematic Review for Question 6 demonstrates a lack of definitive evidence to support all eight areas of management/treatment clinical recommendations for healthcare providers. In an effort to provide a basis for these clinical recommendations for healthcare providers, the existing evidence and related evidence (studies of adult mild TBI, child severe TBI, mixed age groups) were assembled to provide a rationale and support for each.

The eight areas of management/treatment are grouped into two domains:

General areas of treatment for patients and families

A. Patient/Family Education and Reassurance
B. Cognitive/Physical Rest and Aerobic Therapy
C. Psychosocial/Emotional Support
D. Return to School

Symptom/problem-specific treatment/ management:

A. Post-traumatic Headache Management
B. Vestibulo-oculomotor
C. Sleep
D. Cognitive impairment

A. Patient/Family Education and Reassurance

Rationale:

There is no definitive evidence to support specific methods of patient and family education and reassurance following pediatric mTBI that are associated with clear improvements in patient health outcomes. Regardless, public health campaigns have emphasized the importance of parent and family education in mTBI because health outcomes in general are optimized through patient health literacy and the resulting behavior modifications.[C69-C71]

Patient and family education and reassurance are key components of mTBI care initiatives and ED discharge instructions.[C66-C68,C94] Standardized processes of evaluation and discharge instruction provide significant benefit to pediatric mTBI patient outcomes.[C67] Important aspects of healthcare provider counseling include education regarding warning signs of more serious injury (CDC Heads Up "Danger Signs"), review of expected symptoms, monitoring of postconcussive symptoms, prevention of further injury, cognitive and physical activity/rest, instructions regarding return to play/recreation and school (www.cdc.gov/HEADSUP), and clear clinician follow-up instructions.

CLINICAL RECOMMENDATION FOR HEALTHCARE PROVIDERS:

24. In providing education and reassurance to the family, the healthcare provider *should* include the following information:

- Warning signs of more serious injury
- Description of injury and expected course of symptoms and recovery
- Instructions on how to monitor postconcussive symptoms
- Prevention of further injury
- Management of cognitive and physical activity/rest
- Instructions regarding return to play/recreation and school
- Clear clinician follow-up instructions (Level B)

B. Cognitive/Physical Rest and Aerobic Treatment

Rationale:

Historically, "rest" has been a foundation in the treatment of acute mTBI.[C95,C96] However, scientific evidence supporting its timing, duration, and efficacy is limited.[C97] A clear definition of rest is not provided in the literature and interpretations range from full bedrest to a reduced level of activity.[C97] Related evidence suggests that rest or reduction in cognitive/physical activity is beneficial immediately following mTBI and, for those who are slow to recover, may help accelerate recovery.[C98-C100] The rationale for rest is based on the attempted reduction of neurometabolic demand in the context of post-injury symptoms.[C101] Exertional, early post-injury activity increases the metabolic demand of impaired neural cells, and may result in increased symptom manifestation.[C101] Animal literature suggests that too much physical activity early post-injury may be counterproductive to recovery, but that later physical activity may accelerate recovery.[C102] The post-injury period is a posited temporal window of vulnerability for re-injury,[C103,C104] because the re-injury threshold is lower during recovery and the symptom burden may be greater.[C105,C107,C126] Re-injury during this window of vulnerability has been associated with catastrophic injury in rare pediatric cases via unclear mechanisms.[C108-C110]

Studies in children and adults with prolonged symptoms beyond 4 weeks demonstrate that physical exercise managed below symptom

exacerbation reduced postconcussive symptoms in active rehabilitation models.[C111-C114] Animal studies demonstrate that physical exercise facilitates key neurobiological factors (eg, increased brain derived neurotrophic factor, positive changes in neurotransmitters), which may support recovery from brain injury.[C102] However, these studies found that physical activity that was initiated early post-injury had worse outcomes and may compromise the positive effects of exercise. [C102] Related evidence demonstrates the deleterious effects of significant inactivity as well as significant health benefits of a regular program of exercise in other medical conditions in humans.[C97,C115-C119]

The optimal timing to initiate an aerobic program following pediatric mTBI has not been established and only limited studies have applied this treatment to patients with symptoms persisting past 4 weeks.[C111-C113] No evidence exists to provide guidance on the exact timing of activity onset, dosing (how much), and the progression of activity post-injury for a given symptom profile.[C97] Related evidence suggests that early rest within the first 3 days of the injury may be beneficial,[C95,C120] but that inactivity beyond this time period for most children may worsen their symptom report.[C121] As a result, the gradual resumption of noncontact activity that does not exacerbate symptoms has replaced the prescription of full rest until asymptomatic.

CLINICAL RECOMMENDATIONS FOR HEALTHCARE PROVIDERS:

25. Healthcare providers *should* counsel patients to observe more restrictive physical and cognitive activity during the first several days following mTBI in children. (Level B)

26. Following these first several days, healthcare providers *should* counsel patients and families to resume a gradual schedule of activity that does not exacerbate symptoms, with close monitoring of symptom expression (number, severity). (Level B)

27. Following the successful resumption of a gradual schedule of activity (see 26), healthcare providers should offer an active rehabilitation program of progressive reintroduction of noncontact aerobic activity that does not exacerbate symptoms, with close monitoring of symptom expression (number, severity). (Level B)

28. Healthcare providers *should* counsel patients to return to full activity when they return to premorbid performance if they have remained symptom free at rest and with increasing levels of physical exertion (see 25-27). (Level B)

C. Psychosocial/Emotional Support

Rationale:

Social support exerts a powerful influence on a variety of health issues, including chronic diseases.[C122,C123] Social support is positively associated with healthy behaviors and adherence, improved overall quality of life, and reduced deleterious effects of stress on health.[C122-C124] Conversely, lack of social support (perceived or actual) increases morbidity and a greater likelihood of hospital admissions or re-hospitalizations.[C124] Social isolation has been identified as an independent risk factor for all-cause mortality.[C125] It is reasonable to assume that the role of social support in any human interaction is beneficial.

Social support takes many forms, including emotional, with the provision of empathy, love, trust, and caring; instrumental, involving the provision of tangible aid/services directly assisting persons in need; informational, with its provision of suggestions, advice, or information used to address problems; and appraisal, which provides information useful for self-evaluation such as constructive feedback and positive affirmations. Social support has proven useful in the recovery of persons with TBI, particularly those with cognitive deficits.[C126,C127] Limited research with those who have suffered an mTBI demonstrates similar

benefits.[C128,C129] Direct, ancillary, and extrapolated evidence is strongly suggestive of the utility of social support in the management of mTBI.

CLINICAL RECOMMENDATION FOR HEALTHCARE PROVIDERS:

29. Healthcare providers *may* assess the extent and types of social support (ie, emotional, informational, instrumental, appraisal) in children with mTBI and emphasize social support as a key element in the education of caregivers and educators. (Level C)

D. Return to School

Rationale:

Return to school following mTBI must be carefully planned given the adverse effects (eg, headaches and fatigue interfering with learning, greater problems concentrating on schoolwork, difficulty taking notes) that can affect learning and performance.[C130,C131] Limited evidence exists to guide the timing or progression of return to activity in relation to academic activities.[C121] A subset of children with mTBI is at higher risk for more severe or prolonged postconcussive symptoms (see Prognosis Recommendations), which may interfere substantially with resumption of academic activities.[C62,C65,C73,C78,C80-C85,C132]

Consensus-based recommendations for returning to school after mTBI attempt to minimize cognitive and physical overexertion.[C96] Return to school protocols affirm the need for continued collaboration among medical, school, and family systems to gradually adjust interventions and return the child to full participation without significant worsening of symptoms.[C96,C130,C133-C136] The protocols target the student's symptoms as the focus of intervention, linking specific accommodations in efforts to limit symptom expression.

Because postconcussive symptoms resolve at different rates in different children after mTBI, individualization of return to school programming is necessary.

To protect their legal right for an appropriate education, children with mTBI who have greater symptom burden and prolonged recoveries may require formal educational planning incorporating protections under federal statutes.[C137,C138] These protections are provided to qualifying students under Section 504 of the Rehabilitation Act and the Traumatic Brain Injury guidelines under the Individuals with Disabilities Education Act.[C137]

CLINICAL RECOMMENDATIONS FOR HEALTHCARE PROVIDERS:

30. To assist children returning to school following mTBI, medical and school-based teams *should* counsel the student and family regarding the process of gradually increasing the duration and intensity of academic activities as tolerated, with the goal of increasing participation without significantly exacerbating symptoms. (Level B)

31. Return to school protocols *should* be customized based on the severity of postconcussion symptoms in children with mTBI as determined jointly by medical and school-based teams. (Level B)

32. For any student with prolonged symptoms that interfere with academic performance, school-based teams *should* assess the educational needs of that student and determine the student's need for additional educational supports, including those described under pertinent federal statutes (eg, Section 504, IDEA).[C137] (Level B)

33. Postconcussion symptoms and academic progress in school *should* be monitored collaboratively by the student, family, healthcare provider, and school teams, who jointly determine what modifications or accommodations are

needed to maintain an academic workload without significantly exacerbating symptoms. (Level B)

34. The provision of educational supports *should* be monitored and adjusted on an ongoing basis by the school-based team until the student's academic performance has returned to preinjury levels. (Level B)

35. For students who demonstrate prolonged symptoms and academic difficulties despite an active treatment approach, healthcare providers *should* refer the child for a formal evaluation by a specialist in pediatric mTBI. (Level B)

Symptom/problem-specific treatment/management

A. Post-traumatic Headache Management

Rationale:

Headache is the most common symptom of pediatric mTBI in the acute setting. Children presenting with a headache, including worsening or severe headache, following mTBI are probably at moderate risk for ICI reflected by risk difference of 1.86% (95% CI, 0.12%-3.59%) from three Class I studies and one Class II study.[C3,C5,C16,C18] This evidence supports that the risk of not identifying more severe forms of TBI presenting with a progressive, severe headache in a child with or without other risk factors outweighs the risk of ionizing radiation.

There is no evidence supporting a relationship between headache severity on postconcussion symptom assessment in the ED and neurocognitive function during the acute period of recovery. Additionally, insufficient data exists to determine a relationship between early postconcussion symptoms, including headache, and later neurocognitive outcomes or behavioral function among children with mTBI.[C132,C139] There is no evidence to support a relationship between age and headache following mTBI. However, among children presenting to an ED following mTBI, those injured above the age

of 6 years are probably at a 5-10% increased risk of remaining symptomatic (including headache) for 12 months or longer as compared to children 6 years of age or younger.[C62] There was a relationship between gender and headache with girls reporting recurrent and persisting headache after 3 months compared with boys.[C80,C140]

Painful headache in children requires intervention. Non-narcotic analgesics such as ibuprofen and acetaminophen are often effective in treating headaches in children and opioids are not generally recommended as therapy for headaches.[C141-C143] While common clinical practice supports use of non-narcotic analgesics and avoidance of exertional activities for the treatment of headache secondary to pediatric mTBI, there is no evidence to support the success of such interventions in the acute setting or their impact on headache recurrence in the subacute or chronic setting.[C144] Non-narcotic analgesic overuse carries important risks of toxicity and rebound headache.[C145]

A single Class I study evaluated 3% hypertonic saline as a treatment for headache in children following acute mTBI presenting to an ED.[C146] In children with mTBI and headache, hypertonic saline possibly decreases pain with headache immediately following the intervention, with a Z score of 1.53 (95% CI, 0.85-2.200), though the study failed to show an effect at 3 days post intervention.[C146] However, there are limitations in the study's sample size and inability to show sustained effect on pain improvement, as well as lack of related evidence and concerns for risks versus benefits of intravenous medication administration in children that preclude further recommendation at this time.

CLINICAL RECOMMENDATIONS FOR HEALTHCARE PROVIDERS

36. Healthcare providers in the ED *should* clinically observe and consider obtaining a head CT in

children presenting with severe and worsening headache following mTBI to evaluate for ICI requiring further management in accordance with validated clinical decision making rules. (Level B)

37. Children undergoing observation periods for headache with acutely worsening symptoms *should* undergo emergent neuroimaging. (Level B)

38. Healthcare providers and caregivers *should* offer non-narcotic analgesia (ie, ibuprofen or acetaminophen) to children with painful headache following acute mTBI, but also provide counseling to the family regarding the risks of analgesic overuse, including rebound headache. (Level B)

39. There is insufficient evidence to currently recommend the administration of 3% hypertonic saline as a treatment for acute headache following mTBI in children. Healthcare providers should not administer this medication to children with mTBI for treatment of symptoms outside of a research setting at this time. (Level R)

40. Chronic headache following mTBI is likely to be multifactorial, and, therefore, healthcare providers *should* refer children with chronic headache after mTBI for multidisciplinary evaluation and treatment, with consideration of analgesic overuse as a contributory factor. (Level B)

B. Vestibulo-oculomotor Dysfunction

Rationale:

Dizziness is a pervasive and debilitating symptom reported following mTBI in children. A single Class II study reported that vestibular and oculomotor dysfunction may contribute to the diagnosis of mTBI and longer symptom duration.[C147] Gaining interest as an area for screening, as well as treatment, limited evidence suggests that early vestibular physical therapy may be of benefit for patients presenting with subjective complaints (symptom of dizziness) or objective physical examination findings.[C148-C151] The optimal time to initiate vestibular physical therapy, the specific order and intensity of exercises, and longitudinal outcomes have yet to be studied.

CLINICAL RECOMMENDATION FOR HEALTHCARE PROVIDERS:

41. Healthcare providers *may* refer children with subjective or objective evidence of persistent vestibulo-oculomotor dysfunction following mTBI to a program of vestibular rehabilitation. (Level C)

C. Sleep

Rationale:

Sleep disturbance is a common problem following TBI, and may lead to ongoing disability.[C152-C157] Sleep disturbance may impede the recovery process given the critical need for the availability of appropriate energy to support neurobiological recovery and daily functioning, and worsen symptoms. Related evidence in adolescents with mTBI reported poorer sleep quality and demonstrated significantly shorter actigraphic-measured sleep duration, poorer sleep efficiency, and more wake time after onset of sleep, compared with healthy adolescents (all, $p<0.05$).[C158] Receiving adequate sleep has been shown to facilitate health,[C159] and when not appropriate, adversely affects medical conditions, including TBI.[C154,C160,C161]

Practices that promote healthy sleep include (1) age-appropriate and consistent bedtimes and wake times, (2) establishing bedtime routines, (3) maintaining appropriate lighting and sound control in the bedroom, (4) engaging in appropriate daytime exercise and an appropriate diet with limited caffeine consumption, (5) no electronics in the bedroom or before bed, (6) positivity, (7) independence when falling asleep, and (8) meeting the child's emotional needs during the day.[C162-C164] Related evidence from studies in adults with TBI discuss potential treatments including cognitive behavior therapy supporting lifestyle modifications, pharmacologic treatments with modafinil and melatonin, and light therapy.[C152,C165,C166] While limited evidence supports a recommendation for sleep hygiene specifically in children with mTBI, related evidence in adults with TBI indicates benefits, suggesting that the maintenance of appropriate sleep and management of disrupted sleep may be a critical target of treatment for the child with mTBI.

CLINICAL RECOMMENDATIONS FOR HEALTHCARE PROVIDERS:

42. Healthcare providers *should* provide guidance on proper sleep hygiene methods to facilitate recovery from pediatric mTBI. (Level B)

43. If sleep problems emerge or continue despite appropriate sleep hygiene measures, healthcare providers *may* refer children with mTBI to a sleep disorder specialist for further assessment. (Level C)

D. Cognitive Impairment

Rationale:

Cognitive impairment occurs following mTBI and includes the following areas: attention, memory and learning, response speed, and aspects of executive functions.[C43,C44,C167,C168] Dysfunctional attention or memory may result in significant problems with learning in school or social interactions.[C131,C134,C168] Current literature is insufficient to determine whether cognitive impairment is directly related to the pathology of the brain injury (ie, impaired neurotransmission) or secondary effects of the plethora of other symptoms (eg, ongoing headache pain, fatigue/low energy, low frustration tolerance), which, as a result of their distracting effects, may produce a disruption in cognitive processing. Understanding the etiology of the cognitive dysfunction is important to direct treatment/management appropriately. For example, primary cognitive impairment suggests the need to apply direct therapeutic interventions to the affected cognitive process (eg, teaching memory or attentional strategies). In contrast, if the cognitive dysfunction is secondary to another symptom (eg, headache pain), then the primary therapeutic intervention would be directed toward the reduction of the headaches. Neuropsychological evaluations can assist in determining etiology of cognitive impairment and directing treatment.[C168]

CLINICAL RECOMMENDATIONS FOR HEALTHCARE PROVIDERS:

44. Healthcare providers *should* attempt to determine the etiology of cognitive dysfunction, within the context of other mTBI symptoms. (Level B)

45. Healthcare providers *should* recommend treatment for cognitive dysfunction that reflects its presumed etiology. (Level B)

46. Healthcare providers *may* refer children with persisting complaints related to cognitive function for a formal neuropsychological evaluation to assist in determining etiology and recommending targeted treatment. (Level C)

LIST OF MEMBERS OF THE PEDIATRIC MTBI WORKGROUP, AD-HOC EXPERTS, FEDERAL REPRESENTATIVES, AND ACKNOWLEDGMENTS

Pediatric mTBI Workgroup and Ad-hoc Experts

Chair: Shelly D. Timmons, MD, PhD, FACS, FAANS

Workgroup Members and Ad-Hoc Experts: Katrina Altenhofen, MPH, Paramedic, CME, CCPSTI; Edward C. Benzel, MD; Catherine Broomand, PhD, ABPP-CN; James M. Callahan, MD; Meeryo C. Choe, MD; Cindy W. Christian, MD; Micky Collins, PhD; John DeWitt, PT, DPT, SCS, ATC; Ann-Christine Duhaime, MD; Richard G. Ellenbogen, MD, FACS; Linda Ewing-Cobbs, PhD; Theodore G. Ganiats, MD; Gerard A. Gioia, PhD; Christopher C. Giza, MD; Wayne A. Gordon, PhD, ABPP-CN; Andrew Gregory, MD, FAAP, FACSM; Kevin Guskiewicz, PhD, ATC; Mark E. Halstead, MD; Stanley A. Herring, MD; Barbara Holshouser, PhD; Madeline Matar Joseph, MD, FACEP, FAAP; Heather Keenan, MDCM, MPH, PhD; Michael Kirkwood, PhD, ABPP-CN; Angela Lumba-Brown, MD, FAAP; Karen McAvoy, PsyD; Rosemarie Scolaro Moser, PhD, ABN, ABPP-RP; Anne Mucha, PT, DPT, MS, NCS; Robert E. O'Conner, MD; David Paulk, PA-C, EdD, DFAAPA; Margot Putukian, MD, FACSM; John Ragheb, MD, FACS, FAAP; Patricia B. Raksin, MD; Linda Sabelhaus, MLS; Sally Schoessler, MEd, BSN, RN; T.J. Spinks, MD; Stacy Suskauer, MD; H. Gerry Taylor, PhD; Michael Turner, MD; Shari Wade, PhD; Barbara Weissman, MD; David W. Wright, MD, FACEP; Keith Owen Yeates, PhD.

Federal Representatives: A. Cate Miller, PhD; Deborah Hirtz, MD; Elizabeth A. Edgerton, MD, MPH; James Kelly, MD; Jason Goldsmith, PhD; Therese A. West, DNP, APN, BC.

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APPENDICES

(Due to their size, the Appendices may be found in a separate file.)

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