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REVIEW

Toward More Holistic Early Traumatic Brain Injury Evaluation and Care: Recommendations from the 2024 National Institute of Neurological Disorders and Stroke Traumatic Brain Injury Classification and Nomenclature Initiative Psychosocial and Environmental Modifiers Working Group

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Abstract

Biopsychosocial and environmental factors play a major role in acute clinical presentation, recovery, and outcome of traumatic brain injury (TBI). As part of the 2024 National Institute of Neurological Disorders and Stroke (NINDS) TBI Classification and Nomenclature Initiative, the Psychosocial and Environmental Modifiers (PEM) Working Group was assembled to perform a narrative review and summary of expert opinions regarding how non-TBI factors influence the presenting features and outcomes of TBI and to make recommendations for incorporating these Modifiers into clinical care and research. With input from working group

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members and other interested parties, we summarize the membership, methods, and outcomes of the PEM Working Group activities. Modifiers were considered with the NINDS Social Determinants of Health Framework in mind and fall under three broad headings: individual-level variables (e.g., demographics, preinjury health, culture), injury-related variables (e.g., cause and context of injury, second insults), and community-/societal-level factors (e.g., family/community support, socioeconomic position, structural racism). Recommendations include steps to increase awareness of Modifiers in health care encounters, identify Modifier-related disparities in TBI-related care and outcomes, better understand the mechanisms by which Modifiers influence TBI-related clinical presentation and outcomes, and intervene to improve the health and well-being of persons exposed to TBI. These recommendations are intended to be a starting point that will evolve as knowledge grows and additional input is incorporated.

Keywords: CBI-M Model; classification; neuroimaging; blood-based biomarkers; clinical assessment; social determinants of health

Overview

The presenting features and outcomes of traumatic brain injury (TBI) are widely recognized to be influenced not only by the biomechanical characteristics and pathophysiological consequences of brain trauma but also by diverse biopsychosocial and environmental modifiers (Modifiers).¹ We use the term *Modifier* in a general sense to refer broadly to preinjury biopsychosocial characteristics and environmental factors that influence acute TBI presentation, recovery, or outcome. Modifiers influence the entire injury continuum, from risk of experiencing traumatic injuries^{2,3} to ability to access timely clinical care to acute presentation, clinical course, and long-term outcomes.

As part of the 2024 National Institute of Neurological Disorders and Stroke (NINDS) TBI Classification and Nomenclature Initiative,⁴ the Psychosocial and Environmental Modifiers (PEM) working group was formed with three primary objectives: (1) to evaluate evidence regarding Modifiers that influence early TBI classification (i.e., within the first 2 weeks of injury) or later outcome; (2) to make recommendations for incorporating Modifiers into clinical care decisions early after injury; and (3) to identify priorities for research regarding Modifiers in TBI. The Modifiers working group was one of six groups—alongside the Clinical, Imaging, Biomarkers, Retrospective Classification, and Knowledge-to-Practice groups 5–7—whose work jointly informed the development of a new CBI-M framework for the multidimensional characterization of TBI described in a separate article.⁴ The current article summarizes the membership and activities of the PEM working group, including the group's narrative literature review and recommendations.

Working Group and Process

Group membership and timeline

Our working group comprised 14 individuals from five countries, including clinicians, researchers, and representatives of two U.S. federal government agencies. Our membership included individuals with clinical training in

clinical psychology, emergency medicine, neurology, neuropsychiatry, neuropsychology, neurosurgery, rehabilitation counseling, and speech-language pathology, as well as researchers with varied expertise (e.g., clinical assessment, epidemiology, global health policy, health disparities, neuroscience, outcome measurement, public health, behavioral intervention). Three members identified a primary professional focus on pediatric TBI, and three members on older adults with TBI. Most of the group's work was performed over 9 months from Summer 2023 to Spring 2024.

Other contributors

The NINDS Classification and Nomenclature Initiative was led by NINDS representatives (H.O.A., A.D., N.U.) and a Steering Committee (K.D.O., G.T.M., M.A.M., A.I.R.M.), who determined the objectives of the initiative, developed six working groups—entitled Clinical, Imaging, Blood-Based Biomarkers, Psychosocial & Environmental Modifiers, Knowledge to Practice, and Retrospective Classification—and provided direction and collaboration throughout the initiative.^{5–8} Working groups had opportunities to give feedback on each other's evolving work. Additionally, the general public was invited to participate in the Initiative through participation in the January 2024 in-person workshop and through a Request for Information distributed by NINDS. Finally, our working group solicited content area expertise from several individuals during the development of this article (see the “Acknowledgments” section).

Scope of Work

Outcomes included in literature review

Our literature review was divided into two topics corresponding to our objective to summarize Modifiers that influence (a) acute presentation or classification of TBI severity and (b) TBI outcomes. Measures of acute TBI presentation were aligned with the focus areas of the Clinical, Imaging, and Biomarker working groups and emphasized widely used clinical and neuroimaging assessments as well as emerging blood-based biomarker measures available to

characterize TBI. Whereas these other working groups focused on the evidence and best practices for these assessments specifically, the Modifiers group focused on identifying non-TBI factors that could bias or confound these indicators. The specific acute assessments considered by the Modifiers group were as follows:

- 1) clinical signs and symptoms of TBI:
 - a) Glasgow Coma Scale (GCS) scores,
 - b) other classical signs indicative of disrupted brain function, including loss of consciousness (LOC), post-traumatic amnesia (PTA), and other alterations of mental state, and
 - c) self-report of TBI-related symptoms;
- 2) clinical neuroimaging findings (generally head computed tomography scans as the current clinical gold standard); and
- 3) blood-based biomarkers that are informative for diagnosis and classification (including prognostication; e.g., glial fibrillary acidic protein [GFAP], UCH-L1, tau, p-tau, NFL).

For the second topic of our literature review (outcomes), we included commonly reported clinical outcomes (e.g., symptoms, cognitive functioning, independence in daily life) as well as health care outcomes (e.g., access to follow-up care). In keeping with the Initiative's focus on acute/sub-acute TBI care, the goal of this work was to make recommendations for incorporating Modifiers into care soon (within 2 weeks) after TBI, recognizing that prognostic factors may influence pathways of care recommended by acute care providers.

Framework and list of Modifiers

The working group initially considered any biopsychosocial or environmental factor that contributes to individual differences in acute TBI presentation and outcome as a candidate Modifier. This broad lens was important given the group's role within the TBI classification initiative, which was to identify and emphasize individual-difference characteristics that may confound clinical, imaging, and biomarker assessments of TBI or that may inform best practices in acute TBI health care. We developed a list of specific Modifiers (Table 1) to review with a goal to balance comprehensiveness with the current state of the science.

The Modifiers are generally consistent with components of the NINDS Social Determinants of Health (SDOH) Framework for Addressing Health Inequities (Fig. 1).⁹ The NINDS SDOH Framework posits that diverse intrapersonal (e.g., mental health, health literacy), social status (e.g., race, income, social class), structural (e.g., racism), intermediate (e.g., community resources), and biological determinants impact neurological health. Although most SDOH models do not include biological determinants, the NINDS SDOH

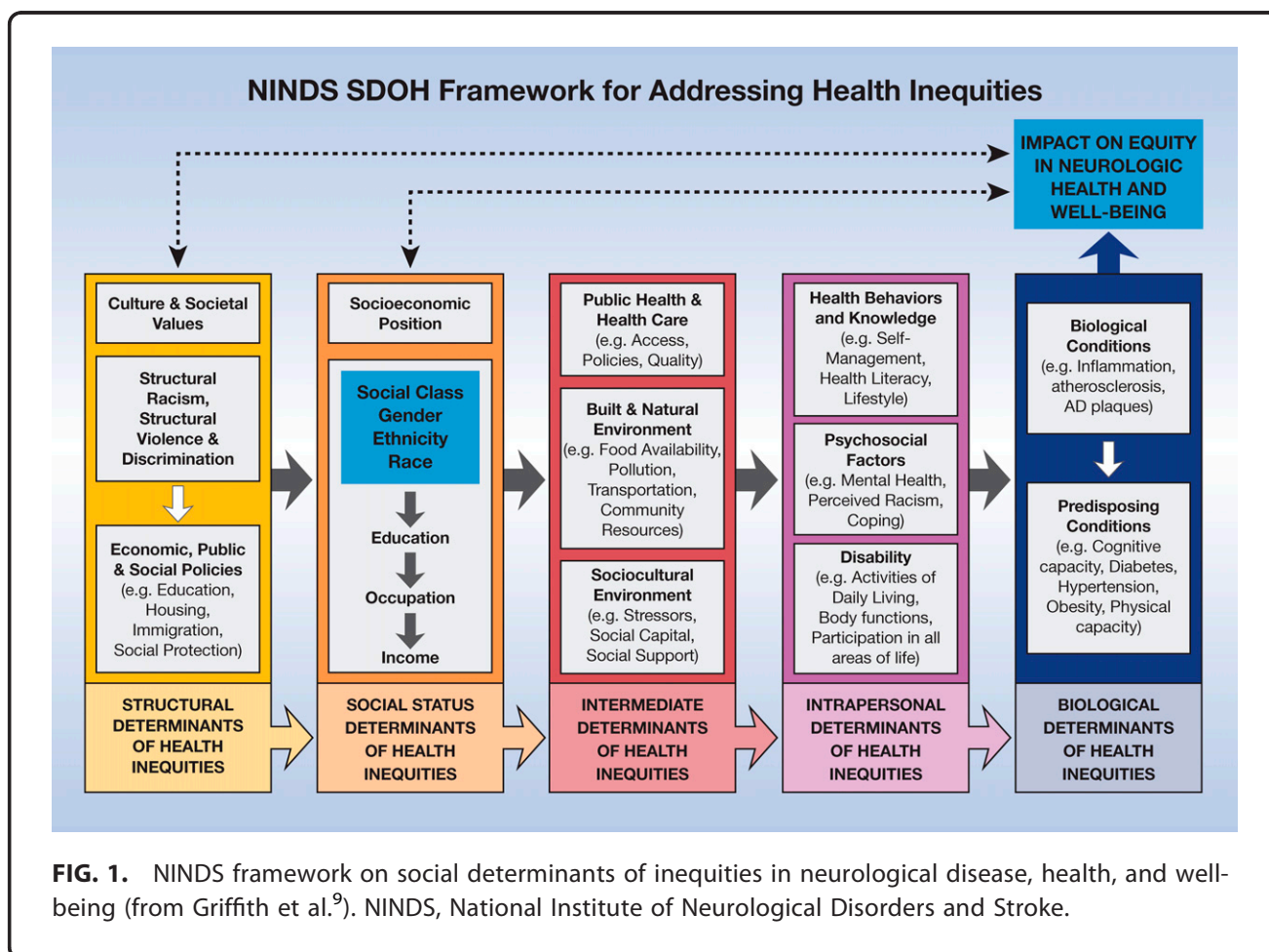
Table 1. List of Major Psychosocial and Environmental Modifiers Included in the Literature Review by the Working Group

<i>Level</i>	<i>Modifier</i>
Individual patient	Age Gender, sex Race Ethnicity Employment status Education Mental health Physical and neurological health (e.g., polypharmacy/medications, comorbid medical conditions, frailty; sensory/motor deficits) Individual socioeconomic position, including insurance coverage History of stress, trauma, injury exposure Language Culture
Injury	Injury cause/context (e.g., nonaccidental) Psychological trauma Comorbid extracranial injury Second insults: hypoxia and hypotension Alcohol and substance intoxication
Community/society	Racism Social/family support Neighborhood socioeconomic position System of care Access to care

Framework included such factors to acknowledge emerging evidence for the complex interplay of socioeconomic and biological factors (e.g., inflammation, predisposing health conditions, epigenetics) in neurological health. Similarly, we included factors consistent with the NINDS SDOH Framework's conceptions of biological determinants (e.g., age, preinjury health status, medications) given their clinical relevance to TBI. Finally, although most variables considered are generally measured preinjury, we also included select injury-related variables that in the NINDS SDOH Framework generally comprise intermediate determinants of health (stressors), intrapersonal determinants (alcohol and substance use), and biological determinants (predisposing non-TBI injuries and resulting second insults). Table 1 lists the Modifiers considered by our working group, which fall into three conceptual categories:

- 1) individual-level factors, including nonmodifiable intrinsic characteristics (e.g., demographics, language) and factors that might be modified with intervention (e.g., modifiable health conditions, health literacy);
- 2) injury-related factors (e.g., the cause and context of injury, comorbid extracranial injuries, second insults, and alcohol and other substance intoxication); and
- 3) community-/societal-level factors (e.g., family/community support, neighborhood socioeconomic position, structural racism, ageism, factors pertaining to one's local health care system).

The initial goals of the working group were to focus on lifespan TBI, and its summary of Modifiers of acute



Clinical, Imaging, and Biomarker characteristics, therefore included literature across the age span. Subsequently, following an increased focus of the Initiative on adult TBI, the working group adopted an emphasis on adult TBI (i.e., age 18 years and older); that focus was informed by a lifespan perspective and leveraged our working group's expertise in pediatric and geriatric TBI.

Key Findings

Role of biopsychosocial and environmental modifiers in acute TBI classification

This review emphasizes factors for which there is empirical support or clinical suspicion for altering the accuracy of the following TBI-related assessments used to recognize or characterize TBI. This portion of the working group's review focused on lifespan TBI.

Assessment of injury severity

Clinical assessments. Age can influence the accuracy of acute TBI assessments. The GCS is less reliable as a predictor of anatomical injury in younger children¹⁰ and older adults,¹¹ although these groups have the highest incidence of TBI.¹² The GCS and other clinical assessments—including interviews about acute

injury characteristics (e.g., LOC, PTA) and symptom checklists—can be unreliable or unattainable in young children, especially those who are preverbal, whose primary signs of TBI are typically observable changes (e.g., to behavior) recognized by parents rather than more widely known TBI symptoms.^{13–16} Multiple studies have demonstrated that, relative to younger adults, older adults are more likely to have more severe anatomical injury (evidence of structural brain injury on neuroimaging) at a GCS of 13–15, the conventional range of scores on this measure defining “mild TBI.”^{11,17,18} In fact, most older adults with TBI, even those with severe anatomical injury, present with GCS 14–15.¹⁹ The clinical usefulness of the GCS as a measure of TBI severity in older adults is limited by noninjury factors, including age-related cerebral atrophy, cognitive impairment, multimorbidity, and polypharmacy.²⁰ These factors, alone or in combination, may influence GCS scores and thereby foster misestimation of initial TBI severity.²⁰

Alcohol and substance intoxication are extremely common among people presenting to trauma centers²¹ and can decrease scores on the GCS (especially the verbal and motor scales).²⁰ Evidence regarding the influence of alcohol on GCS scores is mixed, however, at

least in part due to selection bias in study samples and variation in individual tolerance to substances.^{22–24} Some psychiatric disorders likely influence the GCS, although relevant research is limited.^{20,25,26} Presumably, only psychiatric disorders that are relatively severe at the time of initial presentation (e.g., severe or melancholic depression; hypomania or mania; active, and especially disorganized, psychosis; catatonia) and developmental disorders affecting movement, speech, and behavior would confound clinical assessments of mental state at the time of presentation with TBI and/or interfere with or limit a patient's ability to provide information needed to accurately assess initial TBI severity.

Co-occurring extracranial injuries can interfere with the identification of TBI, particularly among persons with injuries at the relatively mild end of the TBI severity continuum. Conversely, when extracranial injuries substantively confound interpretation of clinical findings used to identify altered mental status (AMS) (i.e., verbal, eye-opening, or motor responses, as on the GCS), they may be partially or fully misattributed to TBI, resulting in overestimation of initial TBI severity. For example, polytrauma increases the likelihood of second insults, such as hypoxia (due to pulmonary contusion, pneumothorax) and hypotension, which may impact the accuracy of GCS and fluid biomarkers and preclude neuroimaging.²⁷ Finally, the effects of treatment (e.g., sedation, paralytics, intubation, pain medications, including narcotics) can, and not infrequently do, confound clinical examinations.²⁰

Numerous factors can increase the likelihood and severity of neurobehavioral symptoms reported after trauma and TBI with GCS 13–15, including preinjury psychiatric history, female sex or gender identity, traumatic/violent injury mechanisms (although underreporting symptoms to mask injury is also possible), and more severe polytrauma.^{28–31} Other factors, such as mistrust of health care providers or other reasons for symptom denial, can reduce symptom reporting.^{32,33} Early symptom burden is among the strongest and most widely replicated predictors of eventual symptom recovery,^{34–36} suggesting it is an important prognostic factor that is valuable to recognize clinically rather than dismiss in persons with psychosocial risk factors for unusually high symptom burden.

Imaging. In circumstances that render clinical exams invalid for estimating the nature and extent of brain injury, the prospect of using objective injury biomarkers (e.g., neuroimaging, blood-based biomarkers where available) is especially appealing. However, some Modifiers may influence baseline objective injury biomarkers, making it important to investigate the validity of each biomarker in relation to variation in Modifiers. Neuroimaging, although less frequently performed in pediatric acute care settings, requires knowledge of age-appropriate reference standards given developmental changes in brain structure (e.g., relative reductions in gray-white matter differentiation on

conventional neuroimaging in infants when compared to older children or adults),³⁷ and interpretation benefits from pediatric neuroradiology expertise.³⁸

Across the lifespan, coagulopathies (whether acquired, such as due to taking anticoagulant or antiplatelet medications, or congenital) are associated with higher prevalence of acute intracranial findings after minor head trauma.³⁹ Moreover, being on antithrombotic medications is associated with delayed-onset intracranial lesions and progression of lesions.⁴⁰ Being on anticoagulant or antiplatelet medications (especially common among older adults) can enhance objective signs of intracranial injury, making it important for acute care providers to recognize and potentially amend medication regimens after injury.

In addition to age and coagulopathy, other Modifiers (e.g., drug or alcohol intoxication, dangerous mechanism of injury) are robustly associated with the presence of acute intracranial abnormalities on clinical neuroimaging, making recognition of such Modifiers along with predictive clinical signs important to clinical decision-making about obtaining neuroimaging.^{39,41–43}

Biomarkers. Baseline levels of blood-based TBI biomarkers—including GFAP, ubiquitin C-terminal hydrolase L1 (UCH-L1), neurofilament light (NfL), and S100B—may be elevated in younger children and older adults^{44–49} and may therefore have decreased range and limited specificity for detection of intracranial trauma at the extremes of age. Extracranial injuries influence the biomarker S100B,⁵⁰ and to a lesser extent GFAP and UCH-L1. Neurodegenerative conditions of the central nervous system (e.g., Alzheimer's disease, amyotrophic lateral sclerosis) increase levels of GFAP and/or NfL,^{51–55} while trauma or degenerative disorders of the peripheral nervous system may also increase levels of UCH-L1 (preclinical evidence only)⁵⁶ and NfL (substantial clinical evidence).^{57,58} These findings suggest that the accuracy of emerging blood-based biomarkers for TBI diagnosis will be limited in populations with comorbid nervous system diseases.⁵⁹ Additional research is needed to establish age-specific reference standards for blood-based TBI biomarkers across the lifespan and also to validate blood-based TBI biomarkers in populations with extracranial injury and degenerative nervous system diseases.

Other considerations at presentation

Racism, discrimination, and implicit bias. Very little research has explored the impact of racism, ageism, and other forms of discrimination on acute care pathways in TBI, relative to other areas of health care. A small but growing literature sheds light on the impact of these social factors on emergency and trauma care more generally. The time before trauma consultation has been found to be significantly longer for Black patients versus white patients, for women versus men, and for older versus younger adults.^{60–62} Black patients have also been found

to have longer lengths of stay in the emergency department and longer periods of time to trauma team activation as compared to non-Black patients.⁶³

Survey data and Implicit Association Test scores revealed unconscious racial and socioeconomic bias favoring white and upper social class persons among trauma and acute care surgeons in the United States; these biases were not, however, found to be associated with clinical assessments.⁶⁴ A systematic review of implicit bias among health care providers found evidence of implicit biases as a function of diverse Modifiers (e.g., age, gender, mental health, socioeconomic position, race, self-inflicted injuries) in countries across the globe.⁶⁵ The review also highlighted the diversity of findings in this area, which in part convey the complex, context-dependent nature of these biases. Increased diversity of trauma teams has been found to be associated with lower levels of bias, albeit with unclear impact on patient care.⁶⁶ However, several forms of communication bias based on differences in provider sex and race have been found to adversely impact trauma team communication and, ultimately, patient care.⁶⁷

Research on interactions of U.S. Black trauma patients with law enforcement before and during hospitalization reveals differential impacts on clinical care, including benefits when police expedited care and negative outcomes when police questioning was deemed disrespectful or stressful.⁶⁸ Racism has been reported to adversely impact emergency care among First Nations and indigenous populations in Canada through overt disrespect, neglect, and disparities in triage assessment.^{69,70} The lack of robust literature specifically exploring the impact of various forms of racism and discrimination on TBI evaluation and outcomes indicates a need for more research in this area, including in countries outside North America where differing racial factors are present (see below). Moreover, a recent call to action on improved demographic categorization in surgical research may provide a constructive means of addressing challenges in conducting this research while offering preliminary guidance on addressing sources of racism and discrimination in the acute phase of TBI care.⁷¹

Injury context, culture, health literacy, and environment. Culture, age,^{61,62} and health literacy, while understudied, appear to affect care seeking and symptom reporting.⁷² For example, cultures that value stoicism in the face of adversity or that tend to attribute symptoms to supernatural causes may differ in symptom reporting or clinical presentations.^{72,73} Health care providers may not adequately assess patients who do not appear to speak the provider's language, such as by not confirming their primary language and not completing injury interviews and clinical (GCS) assessments in that language.⁷⁴ Patients may not report all their symptoms and experiences to health care providers that do not share a similar background or values or when they do not understand what is being asked of them.

The injury context (e.g., emotional trauma, perceived life threat) and environmental features (e.g., accessibility of high-quality health care) can also affect acute TBI presentation. Abusive head trauma, the leading cause of TBI in children less than 2 years old and highly prevalent in adults experiencing interpersonal violence,^{75,76} may not be detectable due to misleading history, lack of physical exam findings, and variable, nonspecific symptoms on presentation. Abusive head trauma is further complicated by caregivers' failure to seek care for repeated significant injuries. Peritraumatic dissociation—a form of acute psychological stress reaction⁷⁷—reportedly causes amnesia and other signs of AMS, but more prospective research is needed to verify how it presents in acute care settings and to what degree it confounds TBI classification.^{78,79} Environmental factors such as living in a rural area or in a developing country are associated with delays in care that can increase mortality and morbidity and may be mediated by patient factors (e.g., health literacy and financial concerns that delay care) and geographical factors (e.g., time to get to a suitable hospital).^{80–84}

Role of biopsychosocial and environmental modifiers in clinical outcomes. Modifiers play a major role in recovery and outcomes from all types of TBI, making them important to consider in early and follow-up TBI care. For example, Modifiers may have a role in clinical decision support tools that stratify patients into groups based on risk for different outcomes to facilitate clinical management tailored to individual characteristics or risks. Modifiers may also be direct targets of intervention, such as the goal of hospital-based violence interruption programs^{85,86}; mental health screening and treatment; physician communication skills training to improve patients' health literacy^{87,88}; health care provider training in implicit bias^{89,90}; and efforts to identify and offer social services for food access, housing, transportation, and financial problems.^{91–93}

Modifiers may also define important subgroups that warrant investigation in previously completed, ongoing, and future interventional trials to improve TBI outcomes and guide Modifier-specific evidence-based management guidelines. Depending on the intervention and context, Modifiers may significantly impact the efficacy or safety of an intervention under study. The field of clinical trials for stroke provides clear examples of how Modifier-defined subgroup analysis (e.g., age, ethnicity, and premorbid health) led to Modifier-specific management guidelines.^{94–96}

However, nuances and gaps in the prognostic literature preclude simple summarization and definitive recommendations about how to incorporate Modifiers in early clinical care. The factors that predict outcomes vary by subpopulation of TBI (e.g., pediatric vs. adult vs. older adult, civilian vs. military vs. sport, TBI severity characteristics), type/nature of outcome (e.g., access to postacute rehabilitation, functional limitations, participation, symptoms, quality of life), and likely the features of

different systems of care (e.g., health care economics, local culture). The contributions of various Modifiers to outcomes following TBI have not replicated well across samples,^{28,34,97} highlighting the heterogeneity of TBI and the need to verify prognostic findings for intended subpopulations and contexts. Moreover, many Modifiers have not been measured in relation to each other to establish their independent prognostic value or their causal relationships.⁹ Nevertheless, below we summarize findings on the role of select Modifiers in clinical outcomes and make clinical and research recommendations that fit the state of the science on this topic. We also refer readers to other recent reviews on this topic^{98–101} as well as the paper presenting the NINDS SDOH Framework for Addressing Health Inequities (Fig. 1),⁹ which eloquently articulates the interdependencies and complexity of diverse Modifiers/SDOH in neurological disease.

Numerous Modifiers are well established to predict outcomes following TBI, with preinjury psychiatric disorders, age, gender or sex, and education among the most widely studied and replicated predictors.^{28,34,97,102–104} Other prognostic factors include but are not limited to preinjury employment status, race, health insurance (in the United States), family environmental/social support, environmental factors (e.g., neighborhood-level socioeconomic position),^{29,105} spiritual beliefs, and cultural background.^{82,105–108} Spiritual beliefs, such as feeling connected to a higher power, appear closely associated with a variety of outcomes, including mental health, physical health, life satisfaction, and functional independence.^{109,110} Moreover, receiving social support from one's religious congregation supports favorable outcomes, whereas religious practices (e.g., praying) are not associated with outcome.^{110,111} Cultural factors, while understudied, also appear important to diverse health care and clinical outcomes.^{72,73,112}

Our understanding of how Modifiers relate to clinical outcomes in pediatric and older adult samples is more limited. In children, parent and family functioning are important moderators of clinical outcomes. Among adults with more severe TBI (e.g., GCS 3–12 or inpatient rehabilitation samples), age is a commonly identified predictor of mortality and functional disability.¹¹³ However, several studies have found that multimorbidity/frailty independently predicted outcome above and beyond age.^{114–116} Even among those with severe TBI, many older adults can experience good recovery, including those who undergo surgical management.^{117,118} Among older adults, dementia and lower socioeconomic position consistently predict poorer recovery from TBI.^{119,120} Comorbidity burden also predicts poor long-term outcome among older adults. Recent reports have highlighted the importance of frailty, commonly operationalized as a deficit accumulation model, as a predictor

of outcome following TBI.^{99,121} Multiple frailty indices that sum various comorbidities and/or lab values are in current use and are distinct from the physical frailty phenotype described and validated in the aging literature, as well as emerging conceptions of social frailty.^{122,a} Consistent approaches to measuring and communicating about frailty would improve comparison across studies and prognostication.

Ethnoracial identity, cultural context, and linguistic diversity are other sociodemographic factors that have been associated with diverse and disparate clinical (e.g., functional limitations, PTSD)^{29,108,123} and health care outcomes (e.g., rates of hospitalization, mortality, referral to inpatient rehabilitation, engagement in community-based rehabilitation) following TBI.^{124–128} However, the putative mechanisms mediating racial and ethnic disparities in TBI outcome, such as racism, discrimination, and cultural incongruence, have been insufficiently studied. For example, structural racism, which refers to the totality of historically rooted, socially embedded mechanisms of fostering racial discrimination via mutually reinforcing inequitable systems,¹²⁹ is a determinant of inferior health outcomes in disenfranchised racial groups such as Black Americans; however, as in other neurological diseases,⁹ the role of structural racism in TBI severity and outcome disparities remains poorly understood.^{1,130}

Adults with TBI have elevated rates of preinjury psychiatric disorders, which contribute to poorer functional,^{97,102,108,131} neurobehavioral symptom,^{28,131,132} and mental health outcomes.^{133,134} TBI and trauma exposure are also risk factors for new-onset psychiatric disorders.^{133–135} Understanding of the mechanisms by which psychiatric history contributes to poor TBI outcome is extremely limited. However, psychological mechanisms such as coping styles appear to play a role.¹³⁶

Problematic alcohol use is common and has numerous negative consequences after TBI, including increased seizure risk, lower cognitive functioning and mood, and increased risk of re-injury, justifying the recommendation to reduce or abstain from alcohol, particularly among persons undergoing TBI rehabilitation for whom there is more consistent evidence of an adverse impact of

^aWhile multiple "frailty" indices that sum comorbidities and/or lab values are in current use, likely due to their ease of use in existing electronic medical record data, "multimorbidity frailty" is not synonymous with the "physical frailty" phenotype originally described and validated by Fried et al, which is based on measurement of exhaustion, grip strength, weight loss, slow walking, and low physical activity. Emerging evidence suggests that "physical frailty" may be a more specific predictor of mortality in the general older adult population than "multimorbidity frailty" alone; however, few TBI studies have rigorously quantified physical frailty. Recognition is emerging of a "social frailty" dimension that may have prognostic relevance as well. Consistent approaches to quantification of multimorbidity versus physical versus social frailty would improve comparison across studies and prognostication. Removal of excess frailty, previously conceptualized as removal of "excess disability," may be a useful construct for optimizing TBI rehabilitation in older adults that deserves further research in both observational and interventional studies.

alcohol use on outcomes.^{137–139} While data on alcohol use and outcomes after TBI are mixed,^{108,140,141} findings that consumption tends to decrease after TBI may support the early postinjury period as a window of opportunity to identify and treat problematic substance use.¹³⁹

Little is known about the effects of other SDOH. Health literacy can be low among persons with prior TBI,¹⁴² which may affect patient decision-making (e.g., selecting rehabilitation services) and be associated with patient-reported physical and mental health that is further reduced after TBI.^{143–145} Environmental factors (e.g., rural vs. urban dwelling; availability of acute health care postacute rehabilitation) also contribute greatly to mortality, morbidity, and clinical care outcome (e.g., hospital readmissions, length of rehabilitation stay).^{82,83,106,107,146} Moreover, socioeconomic position, demographic factors associated with socioeconomic position, and regional health care resources have important impacts on the amount and quality of rehabilitation that can be accessed,^{126,127,147,148} which may partly explain health disparities in clinical outcomes, particularly among those with severe TBI.^{149,150}

Recommendations

Table 2 lists recommendations that our working group deemed as ready for clinical implementation or as a high priority for research, based on our literature review, group discussions, and feedback from other participants in the initiative. In addition to setting an agenda for ongoing work on Modifiers in TBI, these recommendations will be incorporated, where relevant, into an article

synthesizing the output of the NINDS TBI Classification and Nomenclature Initiative's leadership and working groups. This overarching article will propose a new framework intended to better characterize acute TBI beyond the traditional "mild, moderate, and severe" nomenclature, with a focus on adult TBI and acute (e.g., first 24 h) classification of injury (reflecting Clinical, blood-based Biomarker, brain Imaging, and Modifiers; the "CBI-M" model). The CBI-M framework will advocate for characterizing clinical, biomarker, and imaging features of acute TBI with more granularity than historical conventions (which relied largely on the GCS total score) while emphasizing the clinical relevance of Modifiers in research and health care for TBI.

Recommendations for incorporating psychosocial and environmental factors into clinical care and health care system activities

The working group deemed the following clinical recommendations (CR) appropriate to pursue in health care settings based on available data, while also recognizing that parallel research efforts (e.g., community-based participatory research and implementation science) will be needed to employ, optimize, and determine the impact of these CR. To improve the routine detection and characterization of TBI, we recommend that clinical providers receive education in Modifiers that may confound the GCS (CR1) and objective tests used to characterize TBI (i.e., neuroimaging and, as they become more widely used clinically, fluid biomarkers [CR2]). We also recommend providers strive to provide trauma-informed and

Table 2. Recommendations for Incorporating Psychosocial and Environmental Modifiers into Early TBI Care and Research

Clinical recommendations

- CR1. Educate front-line providers that GCS scores do not directly translate to TBI severity. (i.e., recognize confounds such as older age, intoxication, dementia, polytrauma, some neurodevelopmental and psychiatric conditions).
- CR2. Educate front-line providers in the Modifiers that may confound characterization of TBI via neuroimaging and, as they become more widely used clinically, fluid biomarkers.
- CR3. Providers and health care systems should strive to provide trauma-informed care and culturally informed care. Examples:
 - a. Consider broader emotional and social context of injuries.
 - b. Assess patients in their native language whenever possible.
 - c. Learn about diverse cultures (including minoritized groups) relevant to one's health care setting and how they might influence patients' presentation, perceptions of care, values, and communication styles.
- CR4. Implement clinical quality assurance monitoring of hospital systems to ensure equity in timely, appropriate triage and reduce inequities in care and outcomes.
- CR5. Build into TBI encounter workflows the processes needed to screen and intervene for psychosocial and environmental barriers to recovery, repeat injury, and well-being. Examples:
 - a. Mental health screening and intervention (incl. substance use disorders)
 - b. Evidence-based injury prevention programs (e.g., violence interruption, elder abuse, fall prevention)
 - c. Screening for and addressing socioeconomic barriers (e.g., food insecurity, housing, transportation, social support, financial)

Research recommendations

TBI assessment and classification

- RR1. Identify strategies for detecting and classifying TBI more reliably in infants, children, and older adults
- RR2. Develop and validate reference standards for fluid biomarkers of TBI for subpopulations (e.g., age subgroups, polytrauma, comorbid conditions)
- RR3. Advance understanding of how and when possible confounding factors (e.g., acute intoxication, emotional response to trauma) influence acute presentation, such as clinical signs of altered mental state
- RR4. Validate clinical assessment tools in more diverse (e.g., non-Western) cultures, across languages, and across relevant TBI subpopulations

TBI outcomes

- RR5. Advance understanding of mechanisms by which psychosocial factors contribute to disparities in health care/clinical outcomes after TBI
- RR6. Identify interventions and strategies for clinical implementation to optimize outcomes and health equity
- RR7. Develop and refine tools and consensus for measuring psychosocial/environmental modifiers
- RR8. Incorporate into clinical trials preplanned PEM-informed subgroup analyses based on *a priori* hypotheses guided by current knowledge regarding Modifiers most likely to impact safety or efficacy of interventions under study

culturally humble care, such as by evaluating and considering the broader socioemotional context of patients' injuries (CR3a; e.g., nonaccidental trauma or concurrent injury to a loved one), assessing patients in their preferred language whenever possible (CR3b), and learning about cultures relevant to the local patient population to inform understanding of how culture and religion (including those aligned with racial/ethnic groups other than one's own) may influence patients' presentation, perceptions of care (including trust), values, and communication styles (CR3c).

We recommend health care systems implement clinical quality assurance monitoring that ensures equity in important domains such as timely and appropriate triage, equitable care (including rehabilitation access), and health care outcomes (CR4). The working group believed that while health care systems routinely monitor overall outcomes (e.g., timing of care and discharge), comparing subgroups to investigate equity among different subpopulations is less common but needed.

In line with movements to provide more holistic care that addresses SDOH,⁹³ we recommend that health care systems build into TBI clinical encounter workflows the processes needed to screen for and intervene on psychosocial and environmental barriers to TBI recovery, repeat injury, and general well-being (CR5), as identified in Table 1. This may include recognizing and offering intervention for under-addressed mental health problems (including anxiety, depression, and substance dependency disorders; CR5a), implementing and refining evidence-based injury prevention programs (CR5b; e.g., to address elder abuse, fall prevention, or violence prevention), and screening for and addressing broader socioeconomic barriers to care and outcomes (CR5c; e.g., food insecurity; social support; and housing, transportation, and financial barriers). While the potential personal and societal benefits of such efforts are apparent, the working group also recognized that efforts to incorporate Modifiers into health care documentation and workflows could potentially cause unintended harm (e.g., through promoting discrimination, or through documentation or outreach to someone involved in an abusive relationship).^{151–153} For this reason, efforts to incorporate SDOH/PEM screening and intervention into health care should be multidisciplinary and also engage persons with lived experience in the relevant areas to maximize the potential benefits—and minimize potential risks—of such programming.

Providing more holistic care by identifying and addressing broader barriers to health and wellness is a relatively new concept in health care that is receiving increasing interest across settings and countries.¹⁵⁴ Empirical support for specific screening and intervention practices varies across medical settings and socioeconomic domains, with relatively more literature addressing abuse and violence and relatively less addressing broader issues such as

financial insecurity, food insecurity, racism, and transportation and housing issues.^{93,155} However, our group felt that promoting clinical programs to address Modifiers in persons with TBI is justified based on several factors: (1) traumatic injury often signifies ongoing risks (e.g., of falls, violence exposure) that can be newly identified and addressed in TBI-related encounters to prevent cumulative morbidity, (2) a substantial and growing literature links diverse Modifiers to TBI outcomes, and (3) an increasing number of guidelines promote holistic approaches to health care targeting Modifiers.

For example, numerous professional organizations in the United States—including the National Academy of Medicine, the American College of Physicians, and the American Heart Association—encourage health care systems to embed screening for unmet social needs into health care visits.¹⁵⁴ In January 1, 2024, the U.S. Center for Medicare and Medicaid Services began to require health care organizations to screen for five social issues (food insecurity, housing instability, and transportation needs; interpersonal safety; and difficulty accessing utilities). Similarly, the 2008 report of the World Health Organization's (WHO) Commission on SDOH calls on the WHO and governments to take sweeping steps to eliminate the "social gradient"—that is, the relationship between socioeconomic position and health outcomes. As an example of TBI-related care that routinely addresses social factors, physicians in the United Kingdom—including emergency medicine providers—are required to receive training in "safeguarding," which encourages recognition of the antecedents of injury (e.g., violence, falls) and provision of appropriate referrals (e.g., to social workers) to help prevent repeat injuries. Despite more widespread acceptance of such SDOH screening, there are also active areas of debate and inquiry, such as whether screening for and documenting social issues is ethical when a health system is not yet prepared to intervene, what the best questions and strategies are to screen for various social domains, and whether such screening is the best place to target efforts to address health disparities (vs. more upstream structural drivers).^{93,151} Moreover, the success of health care system programming to address SDOH is likely to be limited without strong partnerships with community social service organizations and support by policymakers and other bodies (e.g., health insurance companies).

For clinicians and health care systems to address Modifiers of TBI outcome, a framework is needed that promotes recognition and documentation of Modifiers as part of routine clinical encounters for TBI. As a starting point toward developing such a framework, we devised a list of specific Modifiers that are recommended for clinical implementation, including Modifiers that are likely to be informative in provider-to-provider communication about

patients (Core) and a broader list of modifiers that, if documented in a patient's medical record, could support implementation of the aforementioned CR (Expanded; see Supplementary Data).

Recommendations for future research

Table 2 lists research recommendations (RR) on Modifiers in TBI, aiming both to fill knowledge gaps relevant to our CR and to identify additional future directions. First, we made four recommendations related to advancing understanding of the role of Modifiers in acute TBI assessment and classification. Considering the aforementioned challenges in recognizing and classifying TBI at the extremes of the lifespan, we recommend ongoing research to identify strategies for detecting and classifying TBI more reliably in infants, children, and older adults (RR1). As fluid biomarkers of TBI are becoming available for clinical use, there is an urgent need to validate appropriate reference standards for subpopulations of TBI for which normative biomarker levels vary (e.g., age subgroups, polytrauma, comorbid conditions [RR2]). Because of gaps in scientific data around how various Modifiers confound clinical assessment of AMS and the critical importance of AMS assessment to detecting and classifying TBI, we recommend ongoing research to learn how and when possibly confounding factors (e.g., acute intoxication, emotional response to trauma) influence acute presentation (RR3). Finally, recognizing the gaps in empirical validation of TBI clinical assessments in the literature, we recommend validating clinical assessments of TBI in more diverse (e.g., non-Western) cultures and in varied languages (RR4).

We devised four broad RR related to TBI outcomes. We identified an urgent need to elucidate the mechanisms by which Modifiers contribute to disparities in health care and clinical outcomes after TBI (RR5). This may require a variety of study methods, including qualitative and community-based participatory research studies that deepen understanding of the perspectives of individuals involved (e.g., patients, families, health care providers) and contribute to hypothesis building, as well as quantitative studies designed to test causal hypotheses. This deepened knowledge would be invaluable in helping to identify interventions and strategies for clinical implementation to optimize outcomes and health equity in TBI (RR6). Finally, this work will require further development, refinement, and validation of tools for measuring Modifiers across relevant end users (e.g., cultures, languages, and subpopulations of TBI) and using evolving knowledge on the mechanisms and measurement of Modifiers to develop consensus around best practices for measuring Modifiers (RR7). Finally, we recommended that clinical trials incorporate planned subgroup analyses to investigate how Modifiers—identified *a priori* through

the current state of knowledge—impact the safety and efficacy of interventions under study (RR8). This will require clinical trialists to discuss PEM-informed subgroup analyses with regulatory stakeholders to inform eventual PEM-guided personalized treatments, treatment labeling, and evidence-based management strategies.

Limitations

While this article outlined several key challenges in the assessment of TBI in children, the working group recognizes the need for a more thorough, targeted examination of PEM in children and adolescents with TBI in the future. For example, a variety of important developmental and family/caregiver factors are critical to assessing and treating pediatric TBI that were not sufficiently addressed in this article.

We also recognize our recommendations reflect the background and perspectives of our individual working group members and contributors. Although we endeavored to provide widely applicable recommendations, the review performed, issues identified, and recommendations made reflect the perspectives and potential biases borne of the group members' countries of origin, professional backgrounds and experiences, ethnoracial identities, and other factors. Several other professional disciplines whose day-to-day work is potentially affected by our recommendations were represented in our working group membership, including practicing social workers, case managers, other types of health care professionals (e.g., primary care, rehabilitation providers), and health care administration. We solicited feedback from community participants of the initiative (e.g., attendees of the in-person workshop, which included persons with lived experience and other health care professionals) that informed this work product, and we sought additional feedback in developing this article. However, ongoing work is needed to incorporate more diverse perspectives. Finally, we acknowledge that the literature reviewed primarily reflects high-income countries and that more work is needed to understand Modifiers in low- and middle-income countries.

Future Directions

This article summarizes the current state of knowledge on the role of Modifiers in TBI presentation and outcome. CR and RR are provided that reflect the current state of the scientific literature as well as the expertise and lived experiences of our working group members and contributors. We view our recommendations as preliminary and in need of ongoing refinement as more diverse perspectives (including from additional patients, families, and other interested parties) are incorporated and the scientific literature evolves. Furthermore, efforts to implement our recommendations, which are intended to be patient-centered and cross-disciplinary, will benefit from a

community-engaged approach to inform, contextualize, and increase uptake of CR and prioritize and refine RR.

Transparency, Rigor, and Reproducibility Summary

This narrative review was not preregistered. The goal of the working group was to summarize the literature and make recommendations based on the group's content area expertise, in conjunction with feedback from NINDS leadership, the Steering Committee of the TBI Classification and Nomenclature Initiative, as well as various parties with interest and experience in the topic who we consulted during the article's development. While we solicited relatively broad feedback, the findings and recommendations naturally reflect the perspectives and potential biases of the individuals who contributed to this work product. The recommendations are expected to evolve as the literature evolves and more diverse perspectives are incorporated.

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Authors' Contributions

Working group authors (J.S.A., D.B.A., E.J.B., S.N.F., R.C.G., S.B.J., L.D.N., M.R.P., J.P., D.G.T., L.W., and K.O.Y.): Conceptualization, methodology, investigation, and writing—original draft. Steering committee authors (A.I.R.M., C.D.'O., G.T.M., and M.A.M.): Conceptualization, supervision, and writing—review and editing. NINDS authors (H.O.A., A.D., and N.U.): Conceptualization, supervision, writing—review and editing, and funding acquisition.

Disclaimer

The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institute of Neurological Disorders and Stroke or the National Institutes of Health and the U.S. Department of Health and Human Services.

Author Disclosure Statement

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Supplementary Material

Supplementary Data

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