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## Traumatic brain injury: progress and challenges in prevention, clinical care, and research

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See Online for appendix

This Commission is an update of the first Lancet Neurology TBI Commission: *Lancet Neurol* 2017; 16: 987–1048

For more on resolution  
WHA73.10 see [https://apps.who.int/gb/ebwha/pdf\\_files/WHA73/A73\\_R10-en.Pdf](https://apps.who.int/gb/ebwha/pdf_files/WHA73/A73_R10-en.Pdf)

### Executive summary

Traumatic brain injury (TBI) has the highest incidence of all common neurological disorders, and poses a substantial public health burden. TBI is increasingly documented not only as an acute condition but also as a chronic disease with long-term consequences, including an increased risk of late-onset neurodegeneration. The first *Lancet Neurology* Commission on TBI, published in 2017, called for a concerted effort to tackle the global health problem posed by TBI. Since then, funding agencies have supported research both in high-income countries (HICs) and in low-income and middle-income countries (LMICs). In November 2020, the World Health Assembly, the decision-making body of WHO, passed resolution WHA73.10 for global actions on epilepsy and other neurological disorders, and WHO launched the Decade for Action on Road Safety plan in 2021. New knowledge has been generated by large observational studies, including those conducted under the umbrella of the International Traumatic Brain Injury Research (InTBIR) initiative, established as a collaboration of funding agencies in 2011. InTBIR has also provided a huge stimulus to collaborative research in TBI and has facilitated participation of global partners. The return on investment has been high, but many needs of patients with TBI remain unaddressed. This update to the 2017 Commission presents advances and discusses persisting and new challenges in prevention, clinical care, and research.

In LMICs, the occurrence of TBI is driven by road traffic incidents, often involving vulnerable road users such as motorcyclists and pedestrians. In HICs, most TBI is caused by falls, particularly in older people (aged  $\geq 65$  years), who often have comorbidities. Risk factors such as frailty and alcohol misuse provide opportunities for targeted prevention actions. Little evidence exists to inform treatment of older patients, who have been commonly excluded from past clinical trials—consequently, appropriate evidence is urgently required.

Although increasing age is associated with worse outcomes from TBI, age should not dictate limitations in therapy. However, patients injured by low-energy falls (who are mostly older people) are about 50% less likely to receive critical care or emergency interventions, compared with those injured by high-energy mechanisms, such as road traffic incidents.

Mild TBI, defined as a Glasgow Coma sum score of 13–15, comprises most of the TBI cases (over 90%) presenting to hospital. Around 50% of adult patients with mild TBI presenting to hospital do not recover to pre-TBI levels of health by 6 months after their injury. Fewer than 10% of patients discharged after presenting to an emergency department for TBI in Europe currently receive follow-up. Structured follow-up after mild TBI should be considered good practice, and urgent research is needed to identify which patients with mild TBI are at risk for incomplete recovery.

The selection of patients for CT is an important triage decision in mild TBI since it allows early identification of lesions that can trigger hospital admission or life-saving surgery. Current decision making for deciding on CT is inefficient, with 90–95% of scanned patients showing no intracranial injury but being subjected to radiation risks. InTBIR studies have shown that measurement of blood-based biomarkers adds value to previously proposed clinical decision rules, holding the potential to improve efficiency while reducing radiation exposure. Increased concentrations of biomarkers in the blood of patients with a normal presentation CT scan suggest structural brain damage, which is seen on MR scanning in up to 30% of patients with mild TBI. Advanced MRI, including diffusion tensor imaging and volumetric analyses, can identify additional injuries not detectable by visual inspection of standard clinical MR images. Thus, the absence of CT abnormalities does not exclude structural damage—an observation relevant to litigation procedures, to management of mild TBI, and when CT scans are insufficient to explain the severity of the clinical condition.

Although blood-based protein biomarkers have been shown to have important roles in the evaluation of TBI, most available assays are for research use only. To date, there is only one vendor of such assays with regulatory clearance in Europe and the USA with an indication to rule out the need for CT imaging for patients with suspected TBI. Regulatory clearance is provided for a combination of biomarkers, although evidence is accumulating that a single biomarker can perform as well as a combination. Additional biomarkers and more clinical-use platforms are on the horizon, but cross-platform harmonisation of results is needed. Health-care efficiency would benefit from diversity in providers.

In the intensive care setting, automated analysis of blood pressure and intracranial pressure with calculation of derived parameters can help individualise management of TBI. Interest in the identification of subgroups of patients who might benefit more from some specific therapeutic approaches than others represents a welcome shift towards precision medicine. Comparative-effectiveness research to identify best practice has delivered on expectations for providing evidence in support of best practices, both in adult and paediatric patients with TBI.

Progress has also been made in improving outcome assessment after TBI. Key instruments have been translated into up to 20 languages and linguistically validated, and are now internationally available for clinical and research use. TBI affects multiple domains of functioning, and outcomes are affected by personal characteristics and life-course events, consistent with a multifactorial bio-psycho-socio-ecological model of TBI, as presented in the US National Academies of Sciences, Engineering, and Medicine (NASEM) 2022 report. Multi-dimensional assessment is desirable and might be best based on measurement of global functional impairment. More work is required to develop and implement recommendations for multidimensional assessment. Prediction of outcome is relevant to patients and their families, and can facilitate the benchmarking of quality of care. InTBIR studies have identified new building blocks (eg, blood biomarkers and quantitative CT analysis) to refine existing prognostic models. Further improvement in prognostication could come from MRI, genetics, and the integration of dynamic changes in patient status after presentation.

Neurotrauma researchers traditionally seek translation of their research findings through publications, clinical guidelines, and industry collaborations. However, to effectively impact clinical care and outcome, interactions are also needed with research funders, regulators, and policy makers, and partnership with patient organisations. Such interactions are increasingly taking place, with exemplars including interactions with the All Party Parliamentary Group on Acquired Brain Injury in the UK, the production of the NASEM report in the USA, and interactions with the US Food and Drug Administration. More interactions should be encouraged, and future

discussions with regulators should include debates around consent from patients with acute mental incapacity and data sharing. Data sharing is strongly advocated by funding agencies. From January 2023, the US National Institutes of Health will require upload of research data into public repositories, but the EU requires data controllers to safeguard data security and privacy regulation. The tension between open data-sharing and adherence to privacy regulation could be resolved by cross-dataset analyses on federated platforms, with the data remaining at their original safe location. Tools already exist for conventional statistical analyses on federated platforms, however federated machine learning requires further development. Support for further development of federated platforms, and neuroinformatics more generally, should be a priority.

This update to the 2017 Commission presents new insights and challenges across a range of topics around TBI: epidemiology and prevention (section 1); system of care (section 2); clinical management (section 3); characterisation of TBI (section 4); outcome assessment (section 5); prognosis (Section 6); and new directions for acquiring and implementing evidence (section 7). Table 1 summarises key messages from this Commission and proposes recommendations for the way forward to advance research and clinical management of TBI.

## Introduction

The first *Lancet Neurology* Commission on traumatic brain injury (TBI),<sup>1</sup> published in 2017, provided a comprehensive resource for subsequent research, clinical care, and policy development. The Commission did more than just collate data; it provided an integrated picture of TBI in 2017, identified gaps in knowledge, and presented recommendations to improve clinical care and research from the perspectives of policymakers, clinicians, and researchers. This resource provided the foundation for a substantial body of subsequent research, informed the strategies of major funding organisations (such as the EU and the US National Institutes of Health [NIH]), and was used to brief legislators and inform policy.<sup>2</sup>

The 2017 Commission documented that TBI was estimated to remain one of the top three causes of injury-related death and disability up to 2030. Overall, 50 million–60 million people have a TBI each year, costing the global economy around US\$400 billion annually. Of all common neurological disorders, TBI has the highest incidence and poses a substantial public health burden (figure 1). In Europe, more than 2 million people are admitted to hospital each year because of TBI, and about 82 000 die.<sup>3</sup> Care for all severities of TBI was noted to be inconsistent across centres, regions, and countries, both for acute and post-acute care. The 2017 Commission recognised that the substantial between-centre variability in treatment and outcome in TBI offered unique opportunities for comparative-effectiveness research to improve the strength of evidence. Methods for diagnosis

For more on the **Decade for Action on Road Safety** see <https://www.who.int/teams/social-determinants-of-health/safety-and-mobility/decade-of-action-for-road-safety-2021-2030>

For the **NASEM 2022 report** see <https://nap.nationalacademies.org/catalog/25394/traumatic-brain-injury-a-roadmap-for-accelerating-progress>

	Key messages	Recommendations
Section 1	Worldwide, TBI is a leading cause of injury-related death and disability, with devastating effects on patients and their families	Continue concerted efforts to address this vast global health problem and focus on better prevention, improved access to care, and promotion of clinical research to improve treatment standards
Section 1	More than 90% of patients presenting to hospital with TBI have so-called mild TBI (GCS 13–15), but evidence to inform treatment of patients with mild TBI is scarce	Increase public health interest and establish a research focus on mild TBI
Section 1	In HICs, older patients (≥65 years) who are mostly injured by falls account for 30–40% of hospital admissions for TBI. Frailty and alcohol abuse contribute to falls causing TBI in older people	Target fall prevention for older citizens in HICs
Sections 1, 2	People in LMICs are disproportionately affected by TBI, with most injuries caused by road traffic incidents. Substantial disparities in care exist, with little infrastructure available for emergency pre-hospital care and very little access to post-acute care	Deliver on implementation of road safety goals, described in WHO's <i>Decade for Action on Road Safety</i> plan launched in 2021. Improve emergency pre-hospital care and develop an infrastructure for post-acute care
Section 2	Disparities in care also exist in HICs and relate to: older people injured by low-energy mechanisms (falls); access to rehabilitation for patients with moderate to severe TBI (GCS ≤12); and follow-up in patients with mild TBI	Address disparities through close collaboration between policymakers and clinicians; Approaches to consider include: critical appraisal of triage tools used in emergency settings; involvement of rehabilitation services at an early stage of the in-hospital treatment for TBI; and establishment of structured follow-up after mild TBI as good practice
Sections 2, 4	Use of blood-based biomarkers is on the verge of a breakthrough for diagnostic and prognostic use in TBI, but few assay platforms have been approved for clinical use and substantial variability exists between platforms	Stimulate the development, validation, and approval of clinical-use platforms, and facilitate cross-platform harmonisation of biomarker assays
Section 3	Older patients often have co-morbidities, but very little evidence exists to inform their treatment	Stimulate a research focus on older patients with TBI
Section 3	Access to rehabilitation services is inconsistent and no protocols for treating long-term problems exist	Improve access to rehabilitation services and develop evidence-based treatments for long-term problems—including fatigue, and cognitive and behavioural changes
Section 4	Substantial advances have been made towards individualised management with improved characterisation and understanding of disease processes in TBI, but physicians are not yet sufficiently able to match therapies to subgroups of patients	Stimulate research to identify subgroups of patients who would be most likely to benefit from specific interventions
Section 5	Around 50% of patients with mild TBI presenting to hospital do not recover to pre-TBI levels of health and wellbeing by 6 months after injury	Implement care pathways to ensure structured follow-up of patients with mild TBI, and stimulate research to identify patients with mild TBI at high risk for incomplete recovery, which would allow timely evaluation and treatment
Section 5	Outcome in women after TBI is poorer than in men	Facilitate research to help explain this sex and gender difference and inform intervention strategies
Section 6	Prognostic models have been developed and extensively validated for moderate and severe TBI. No well-validated models exist for mild TBI, nor do models exist that are applicable across all ranges of TBI severity	Initiatives should be stimulated to develop models applicable across the range of TBI severity. Availability of such models would constitute a huge step forward and facilitate implementation into clinical practice
Section 6	Quality indicators developed for TBI are restricted to the ICU setting and are not yet ready for translation into practice	Research should be stimulated to refine, validate, and implement quality indicators for TBI
Section 7	Costs of data curation and deep harmonisation in preparation for sharing research data are underestimated and can amount to up to 20% of a study budget	For completed studies, mechanisms should be developed to facilitate maintenance of the data and to provide guidance to external researchers wishing to analyse the data. For new studies, inclusion of an appropriate budget to prepare data for sharing should be foreseen in the grant award
Section 7	TBI is often characterised by both an acute mental incapacity of patients to provide informed consent for participation in research and an emergency situation. Although GDPR recognises the issue of absence of capacity to provide consent, no provisions are included that are relevant to patients with an acute absence of capacity or to emergency situations	Develop better regulatory guidance. Consider mandating that researchers obtain objective proof of mental capacity of the study participant, who might have been temporarily mentally incapacitated, before requesting informed consent.
Section 7	Data sharing and analyses across different datasets do not necessarily require data transfer and can be done on a federated platform. Use of a federated platform facilitates broad use of data and reduces the risks for violation of data security and privacy regulation	Support is required for the development of platforms for federated analysis, particularly for development and implementation of machine-learning techniques on such platforms

TBI=traumatic brain injury. HICs=high-income countries. LMICs=low-income and middle-income countries. GCS=Glasgow Coma sum score. ICU=intensive care unit. GDPR=general data protection regulation.

**Table 1: Key messages and recommendations**

For more on **GDPR** see <https://gdpr-info.eu/>

For more on **InTBIR** see <https://intbir.incf.org>

and classification of patients with TBI were noted to be insufficient to permit targeting of current and new therapies to the needs of individual patients. The Commission underlined the need for multidimensional outcome constructs that quantify the overall burden of disability from TBI, to guide improved clinical management, and to support high-quality research.

Since publication of the 2017 Commission, much has changed in the field of TBI. Studies have provided new

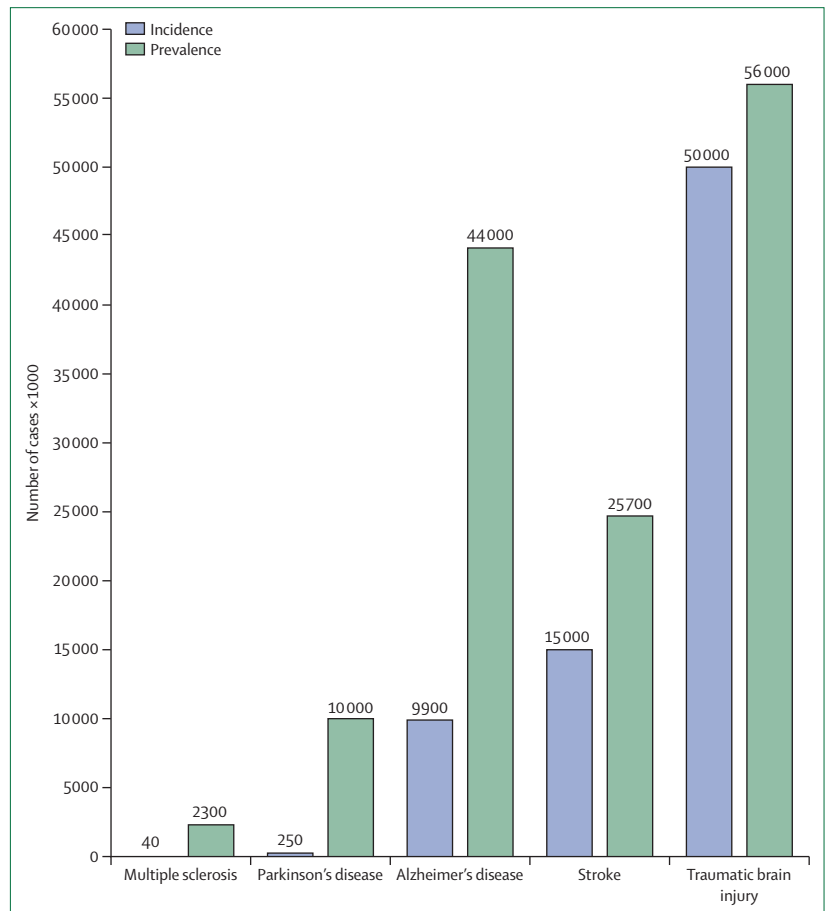
data on epidemiology and casemix of TBI in the hospital setting, and new insights regarding the effects of systems of care on TBI management and outcome. Clinical care has been informed by the results of a substantial body of research since that Commission, much of which was supported by the International TBI Research (InTBIR) initiative, a coalition of major funding bodies that came together in 2011 to support neurotrauma research.<sup>4,5</sup> Although there have been advances in the characterisation

of TBI with the use of advanced neuroimaging, blood biomarkers, and genomics, these advances have not yet been fully translated into clinical care. However, there is increasing evidence that these advances will facilitate identification of patients with TBI who share specific disease mechanisms, treatment response characteristics, or prognosis, thus providing a basis for individualised management. Progress has also occurred in the prediction and characterisation of outcome following TBI, and although these advances are still being developed in research settings, their clinical application will likely occur over the next few years. Challenges remain, particularly in low-income and middle-income countries (LMICs), relating to prevention of TBI, access to care, and provision of clinical guidelines that can be implemented in resource-limited contexts. It is also crucial that we ensure equitable integration of researchers from LMICs in neurotrauma research. Disparities in care provision have also been identified in high-income countries (HICs). In the research context, developments both within the TBI field and insights into novel approaches to trial design from the COVID-19 pandemic have highlighted exciting new approaches and opportunities for generating evidence to support clinical care. Many of these new approaches are dependent on collaborative research and data-sharing, a process that can be constrained by regulatory requirements and facilitated by novel data analysis techniques.

This 2022 update on the Commission for TBI describes advances along with attendant challenges and opportunities, and provides a staging post in ongoing efforts to improve clinical care and outcomes.

### Section 1: Epidemiology and prevention of TBI

The first *Lancet Neurology* Commission on TBI<sup>1</sup> highlighted the huge public health burden posed by TBI. Reported population-based incidence rates in New Zealand and North America were between 811 and 979 per 100 000 people per year and hospital discharge rates in the EU were 287·2 per 100 000 people per year, with substantial variation between Member States. We highlighted how methodological variations confound comparisons of TBI epidemiology patterns between regions, countries, and continents, and emphasised the need for standardised epidemiological monitoring and international consensus on definitions and approaches. Since then, the Global Burden of Diseases, Injuries, and Risk Factors (GBD) study has provided estimates of global TBI incidence rates using a standardised approach.<sup>6</sup> CENTER-TBI and TRACK-TBI—two large-scale, real-world observational studies on TBI of all severities—have provided insight into TBI-related disability and characteristics of patients currently presenting to hospital. The COVID-19 pandemic has had clear effects on both TBI incidence and presenting causes of injury. In this section, we discuss these new findings on the incidence, mechanisms, and burden of TBI. We additionally focus on four subpopulations



**Figure 1: Global incidence and prevalence of traumatic brain injury compared with other common neurological diseases**

Data are from multiple sources. Incidence is quantified as the number of cases per year, and prevalence as the number of cases at a given time point. The numbers provided are best estimates. However, it should be recognised that data collection and reporting are inconsistent across different parts of the world, and that data reported for the various diseases do not always reflect exactly the same time period. Modified from a draft provided by Carl Long, NeuroTrauma Sciences.

of increasing relevance: older people, children and adolescents, criminal offenders, and sports participants, also highlighting specific targets for prevention and ongoing prevention initiatives.

For data provided by NeuroTrauma Sciences see <https://neurotraumasciences.com>

### Incidence and mechanisms

The age-adjusted incidence of all severities of TBI from epidemiological population-based studies published between 2015 and 2020 ranged between 476 per 100 000 individuals in South Korea<sup>7</sup> to 787 per 100 000 individuals in the USA.<sup>8</sup> However, these incidence studies might still underestimate the true extent of the problem. A Canadian study of concussion<sup>9</sup> (a subset of mild TBI) revealed a higher annual incidence rate of 1153 per 100 000 individuals. Small regional or single-centre studies reported a decrease in TBI incidence during periods of COVID-19 lockdowns, reflecting decreased mobility, reduced participation in sports and recreational activities, and possibly reluctance to seek medical

For more on the CENTER-TBI study see <https://www.center-tbi.eu>  
For more on the TRACK-TBI study see <https://tracktbi.ucsf.edu>

treatment for milder injuries.<sup>10,11</sup> A few cohort studies reported<sup>12,13</sup> an increase in suspected head trauma in children and gunshot wounds to the head. Although there has been an increase in intimate partner violence during the pandemic,<sup>14,15</sup> there are no specific data on TBI in this context.

For the pre-COVID-19 era, GBD reported a worldwide age-standardised TBI incidence of 369 per 100 000 people (95% CI 331–412) in 2016.<sup>6</sup> Updated rates for 2019 are 346 per 100 000 people (298–401).<sup>16</sup> These rates are lower than previously reported in population-based studies and closer to those reported for hospital admissions. A likely explanation is that GBD mainly accesses data from hospital presentations and uses an indirect approach to capturing TBI incidence involving identification of external causes of injury and linking the nature of the most severe injury to the external cause. Therefore, TBI might not be captured in cases with severe extracranial injuries.

Assessing temporal trends and national variations in TBI incidence is complex and confounded by methodological diversity. We previously found a ten-fold difference in the reported incidence of hospital admissions for TBI between countries in Europe,<sup>3</sup> probably reflecting nation-specific differences in data capture and reporting methods. A major strength of the GBD approach is that it uses a standardised approach across all global regions and calculates age-adjusted incidence rates, enabling cross-country comparisons. Nevertheless, GBD also reported substantial between-country differences in incidence rates. A common denominator in both approaches is the use of hospital International Classification of Diseases (ICD) injury coding for data extraction. Inconsistencies within and between hospitals in ICD coding might be a main cause of the large variations observed. These considerations highlight a crucial need to standardise conduct and reporting of incidence studies. The main injury mechanisms causing TBI are falls, road traffic incidents,

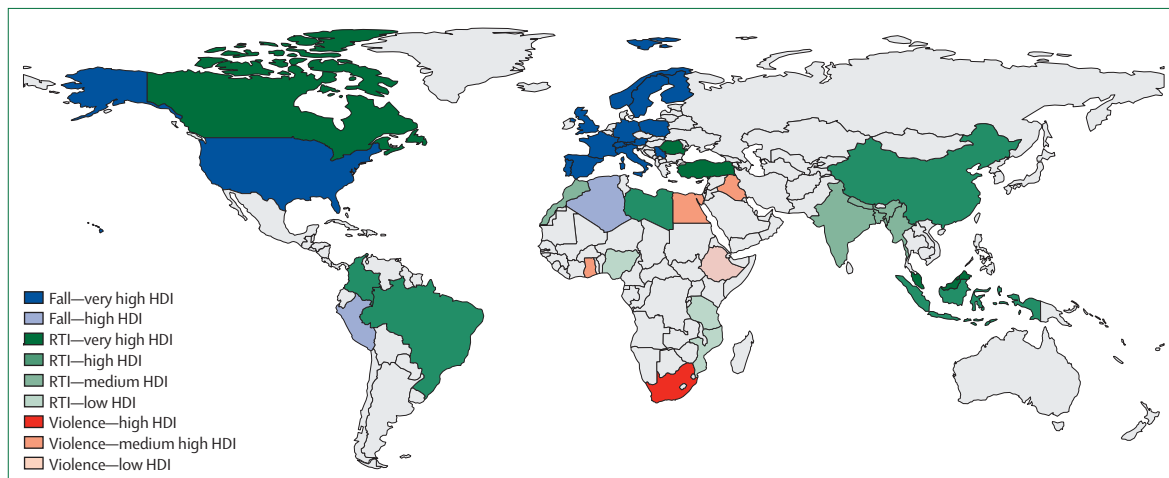
and violence. GBD reported that, overall, their relative contributions have remained stable between 1990 and 2019, with falls being the most common cause (52% in 1990 and 54% in 2019). These average numbers might, however, mask shifts within regions. Global modelling suggests that the incidence of TBI in LMICs is significantly higher than in HICs,<sup>6,17</sup> and is mainly driven by road traffic collisions, particularly those involving motorcyclists. These findings were confirmed in the Global Neurotrauma Outcomes Study,<sup>18</sup> showing a clear relationship between the mechanism of injury and the UN's Human Development Index (a composite index of life expectancy, education, and per person income indicators, which is used to rank countries into four tiers of human development: low, medium, high, and very high; figure 2).

By contrast with findings in LMICs, the CENTER-TBI registry,<sup>19</sup> which mainly collected data from HICs, reported that 12 127 (56%) of 21 681 patients with TBI were injured by falls, of whom 71% had a low-energy (ground-level) fall. Compared with 13 059 patients injured by high-energy transfer, those injured through low-energy falls were older (median 74 years [IQR 56–84] vs 42 years [25–60]), and more often female (50% [95% CI 48–51] vs 32% [31–34]). The CENTER-TBI Core study<sup>20</sup> reported alcohol involvement in 28% of incidental falls versus 17% in road traffic incidents. Although these findings illustrate the success of traffic-related alcohol prevention campaigns, they also emphasise the importance of campaigns to prevent fall-related injuries (panel 1). Alcohol and cannabis abuse were particularly prominent in violence-related TBI (64% and 15%, respectively).

### The burden of TBI

The true consequences of TBI go beyond the dynamics of their occurrence or fatality, and are better reflected in measures of disease burden—ie, years of lost life (YLLs) and years lived with disability (YLDs). GBD reports

For guidance on falls from the US CDC see [https://www.cdc.gov/falls/programs/community\\_prevention.html](https://www.cdc.gov/falls/programs/community_prevention.html)



**Figure 2: Between-country variations in mechanism of traumatic brain injury according to the Human Development Index**  
Figure modified from Clark et al with permission.<sup>18</sup> HDI=Human Development Index. RTI=road traffic incident.

**Panel 1: Targets for prevention and ongoing prevention actions for traumatic brain injury**

**Targets for prevention identified in the Lancet Neurology Commissions on traumatic brain injury (TBI)**

- Road traffic safety: of particular relevance to low-income and middle-income countries (LMICs).
- Older people: fall prevention, including campaigns to increase awareness of increased risk with excessive alcohol use; address frailty.
- Children and adolescents: targeted prevention with a particular focus on car safety, traffic education, and protection of juvenile sporters; early intervention and support to prevent violent head trauma.
- Criminal offenders: implementation of rehabilitative justice systems; provision of special considerations to support offenders who have had TBI or intimate partner violence, or both.
- Sports: implementation of measures to mitigate risks in contact sports; development of a consensus on sideline assessment protocols across different sports and uniform return-to-play guidelines; improvement of design and mandated use of helmets in individual sports, such as horse-riding and cycling.

**Ongoing prevention actions**

*WHO Decade for Action on Road Safety in 2021*

The initiative aims to reduce traffic related deaths and injuries by at least 50% by 2030, with clear recommendations for safer traffic systems, measures needed to implement these systems, and allocation of key responsibilities for such implementation.

*US Centers for Disease Control and Prevention (CDC): Older adult Fall Prevention*

In the USA, falls result in around 3 million hospital attendances, 800 000 hospitalisations, and 34 000 deaths each year—most

commonly for hip fracture or TBI—with total medical costs that exceed US \$50 billion. Recognition of this burden has led to comprehensive recommendations for both health professionals and the lay public for measures to prevent falls.

*CDC STEADI Initiative (Stopping Elderly Accidents, Deaths and Injuries) for health-care providers*

This initiative describes a coordinated approach for health-care providers to implement guidelines for fall prevention, and includes three core elements:

- Screen patients for risk of falls,
- Assess modifiable risk factors, and
- Intervene to reduce risk by using effective clinical and community strategies.

*UK National Health Service (NHS) guidance. Falls: applying All Our Health*

This guidance document for health professionals and the lay public covers the multifactorial causes of falls, estimates their costs to the NHS, and suggests strategies for mitigation.

**Sport-related concussion**

- Rugby union: introduction of law changes around tackle height and related sanctions for foul play under the Head Contact Process.<sup>21,22</sup>
- Ice hockey: removal of body checking at youth-participation level to reduce concussion risk.<sup>23</sup>
- Soccer: introduction of restrictions to heading training from youth to professional levels by several national associations.
- Various sports: deployment of mouthguard sensors during training and match-play that gather head kinematic data around head impacts and injury to inform risk-reduction measures.

For the CDC STEADI see <https://www.cdc.gov/steady/about.html>

For UK NHS guidance on falls see <https://www.gov.uk/government/publications/falls-applying-all-our-health/falls-applying-all-our-health>

For more on TBI in rugby see [https://resources.world.rugby/worldrugby/document/2021/03/10/e597c9c8-e852-4e19-875f-18e02e7f7e24/Head\\_Contact\\_Process\\_EN\\_v1.pdf](https://resources.world.rugby/worldrugby/document/2021/03/10/e597c9c8-e852-4e19-875f-18e02e7f7e24/Head_Contact_Process_EN_v1.pdf)

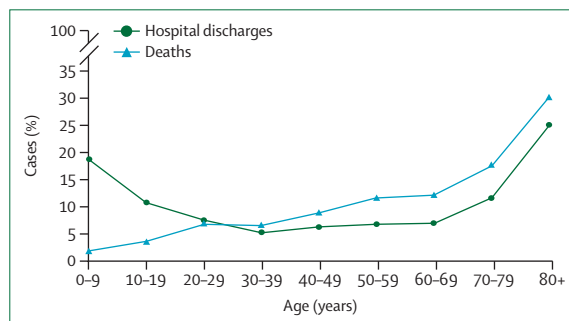
For more on TBI in soccer see <https://www.thefa.com/news/2021/jul/28/20210728-new-heading-guidance-published>

For CDC recommendations on falls prevention see <https://www.cdc.gov/falls/index.html>

that TBI was a cause of 8·1 million YLDs in 2016. YLLs due to TBI have been reported for selected countries or population groups. European data captured from 16 countries suggests that each TBI death is associated with about 24 YLLs. This extrapolates to a pooled age-standardised rate of about 160 YLLs per 100 000.<sup>24</sup> Few studies have estimated both the fatal and non-fatal burden of TBI, quantified as disability-adjusted life years (DALYs). In New Zealand, estimates revealed 20 300 DALYs attributable to TBI, accounting for 27% of total injury-related health loss and 2·4% of DALYs from all causes. A total of 71% of TBI DALYs resulted from fatal TBI.<sup>25</sup> More studies on the disease burden of TBI are required.

*TBI in older adults*

The frequency of hospital admissions for TBI is highest in older people (aged ≥65 years), followed by children and adolescents (figure 3).<sup>3</sup> Rates of TBI in older people are rising and exceed population growth in some countries.<sup>26</sup> Relative to their younger counterparts,



**Figure 3: Estimated frequency of hospital discharges and deaths in cases of traumatic brain injury by age group in Europe**  
Figure created using data from Majdan et al.<sup>3</sup>

older adults more often sustain TBI from falls and have more severe cognitive and functional impairments,<sup>27</sup> and might be at greater risk for post-recovery functional decline.<sup>28</sup> However, psychological outcomes can be better, perhaps because older individuals have had more opportunity to develop coping skills, achieve life

goals, and might have less pressure to resume economic productivity.<sup>29</sup>

Consistent with epidemiological studies in HICs, the proportion of older patients (ie, aged  $\geq 65$  years) enrolled in CENTER-TBI was high (28% in the Core study, 38% in the registry), but lower in TRACK-TBI (12%). Nevertheless, the CDC report that older adults account for 43.9% of all TBI-related hospital admissions in the USA.<sup>30</sup> In the China registry,<sup>31</sup> older patients accounted for 2500 (18.3%) of 13627 enrolled participants. The increasing number of older patients with TBI is of direct relevance to policy makers and clinicians. Most previous clinical trials excluded patients older than 65 years. Consequently, very little—if any—evidence exists to inform the clinical management of older patients. TBI in older adults can have a distinct pathophysiology and injury severity indices used in younger adults might be less appropriate in older people.<sup>32</sup> Additionally, older patients often have comorbidities requiring multiple medications. Together with age-related physical and cognitive decline, the presence of comorbidities can complicate acute and long-term management, rehabilitation care needs, and outcome measurement.

The association between age and outcome is partly indirect; risk, mechanism, and type of injury, as well as recovery potential, are intricately linked to the concept of frailty. Frailty is a consequence of cumulative decline in physiological systems across a lifetime. It reflects, as a state of vulnerability, the poor resolution of homeostasis after a stressor event (eg, TBI), resulting in increased risk of poor health outcomes. CENTER-TBI developed a novel TBI-specific frailty measurement index using a cumulative deficit approach.<sup>33</sup> The overall median frailty index score in CENTER-TBI was 0.07 (IQR 0.03–0.15), with a median score of 0.17 (0.08–0.27) in older adults aged at least 65 years. Higher frailty scores were significantly associated with unfavourable outcome. External validation on data from TRACK-TBI supported the robustness of these findings. Evidence that TBI in older adults is biologically distinct and recognition of the relevance of frailty underscore the need for research to inform acute and long-term care in older adults.

#### *TBI in children and adolescents*

The paediatric and adolescent age group (age range 0–19 years) has the second-highest incidence of hospital admissions for TBI.<sup>34</sup> Approximately 345 children or adolescents per 100 000 are admitted to hospitals in the EU per year, and about 3 per 100 000 die as a consequence of a TBI, resulting in around 184 YLLs per 100 000<sup>34</sup> individuals. In the USA, approximately 1 million–2 million children and adolescents have a mild TBI annually, and youths with a previous concussion have a four-fold risk of having a recurrent concussion.<sup>35</sup> Moreover, children and young people (aged 5–18 years) have a significantly increased risk of mental health issues, psychiatric

hospitalisation, and self-harm after TBI compared with those after an orthopedic injury.<sup>36</sup> Although the paediatric and adolescent age group shows the lowest TBI mortality overall (about 5% of all TBI deaths), the burden of these deaths is substantial: about 3000 TBI-related deaths occurring in the EU each year result in nearly 200 000 YLLs.<sup>24</sup> These findings suggest that targeted prevention of TBI in this group could result in substantial gains in quality of life and in decrease of YLLs (panel 1).

#### *Violence, crime, and TBI*

Violence is an important cause of TBI; and in turn, having had a TBI can predispose an individual to violent behaviour and criminal offending. Violence is the third-most common cause of TBI. In the CENTER-TBI Core and TRACK-TBI studies, 6.7% (293/4388 and 171/2537, respectively) of injuries were caused by violence. In the CENTER-TBI China registry, which collected data only for patients admitted to hospital, 1714 (13%) of 13138 had a TBI resulting from violence.<sup>37</sup> Populations in precarious circumstances are especially at risk for violence-related TBI—eg, communities affected by conflict (including migrants and refugees) and indigenous populations who are socially disadvantaged.<sup>38,39</sup> The prevalence of TBI within prison populations is also high: up to 64%<sup>40</sup> of male inmates and 78% of female inmates have a history of TBI. Intimate partner violence is the most frequently reported cause<sup>41</sup> of previous TBI in incarcerated women, with many experiencing their first injury in childhood or adolescence. When compared with other causes of TBI due to interpersonal violence, intimate partner violence far more commonly affects women than men (75% vs 5%), more often results in severe TBI (27% vs 5%), and is associated with nearly three times the mortality (14% vs 5%).<sup>42</sup> Young people with TBI in the criminal justice system often did not have appropriate parenting support, and were excluded from school or exposed to gang violence, or both. Without appropriate support, TBI in incarcerated individuals is associated with poor engagement in rehabilitation and reconviction. In the UK, Brain Injury Link Workers enable neuro-rehabilitation practices in some prisons, with promising outcomes—an initiative that deserves broader implementation and validation.

TBI can lead to impaired social communication and behavioural dysregulation associated with an increased risk of crime, especially reactive violence in response to a perceived threat.<sup>43</sup> Epidemiological studies from various high-income jurisdictions (eg, Sweden, Canada, and Australia) indicate an approximate 2–3 fold increased risk of serious crime in individuals after a TBI compared with non-injured controls. The UN General Comment (no 24) urges States to implement rehabilitative justice systems, rather than focusing on a punitive approach.<sup>44</sup> England and Wales in the UK have developed guidelines for sentencing adults with mental disorders, development disorders, or neurological impairments.<sup>45</sup> These examples

For more on Brain Injury Link Workers see [https://barrowcadbury.org.uk/wp-content/uploads/2016/07/Disability\\_Trust\\_linkworker\\_2016Lores.pdf](https://barrowcadbury.org.uk/wp-content/uploads/2016/07/Disability_Trust_linkworker_2016Lores.pdf)



reflect a need for a holistic approach uniting health, education, social care, and justice systems, to strengthen preventative and proactive measures (panel 1).

#### *Sport-related TBI*

Sport-related TBI has received considerable media attention. There is increasing awareness of the risk of adverse brain-health consequences caused by TBI and repetitive head impacts in sport.<sup>46–48</sup> A retrospective cohort study<sup>49</sup> compared mortality from neurodegenerative disease in 7676 former professional soccer players with that of 23 028 matched controls from the general population, and found that mortality from neurodegenerative disease was around three times higher in former soccer players compared with controls (subhazard ratio 3.45; 95% CI 2.11–5.62;  $p < 0.001$ ). However, mortality from other common diseases (eg, ischaemic heart disease and lung cancer) was lower in the former soccer players.

Several studies report on the incidence of sport-related concussions, but establishing comparative risks within and between sports is challenging. Reportedly, the risk of sport-related concussion is highest among collision sports, particularly rugby and American football.<sup>50,51</sup> In CENTER-TBI, sports and recreational activities were reported as a cause of TBI in 312 (7%) of 4509 cases. Of these, horse-riding (19%), skiing or snowboarding (16%), cycling (11%), and soccer (11%) were the main activities involved. In TRACK-TBI, 218 (8.7%) of 2520 injuries occurred during sport and recreational activities. Of note, these data reflect a selected cohort of patients with injuries motivating hospital attendance and are not representative of the overall risk of sport-associated TBI. The community-based BIONIC study<sup>52</sup> in New Zealand collected data over a 12-month period for 1369 patients with TBI across all ages in a population of 173 205 people, and reported that 21% of injuries were related to sports and recreational activities.

Substantial advances in the immediate management and rehabilitation of sport-related concussion in the past decade have resulted in increased detection and notable decreases of same-season repeat concussions (see section 2).<sup>53–55</sup> Various global sports organisations have developed initiatives to better understand risk factors for sport-related concussion and to implement measures to mitigate risks. For example, a review of match data from the professional rugby union showed that around half of sport-related concussions occur during the tackle, mostly involving the player making the tackle.<sup>56</sup> Leveraging this information, World Rugby have embarked on targeted initiatives to address the risk of concussion associated with tackling<sup>57</sup> (panel 1). Data from the CARE Consortium study indicate that concussion risk and head-impact exposures are highest among American college footballers in pre-season and in practice, triggering targeted initiatives to reduce the risk for these athletes.<sup>58,59</sup> However, there remains a need for continued data

collection to inform public health policy and practice changes designed to maximise athlete health and safety. Large, multicentre, prospective surveillance projects are ongoing (appendix p 3), and will provide further insight on the risks of sport-related TBI. Current initiatives are mainly directed at rugby, American football, and soccer, but the CENTER-TBI and TRACK-TBI data suggest the need for an additional focus on individual sports, such as horse-riding and cycling, where simple preventive measures (eg, improved helmet design and use) can make a substantial difference.<sup>60,61</sup>

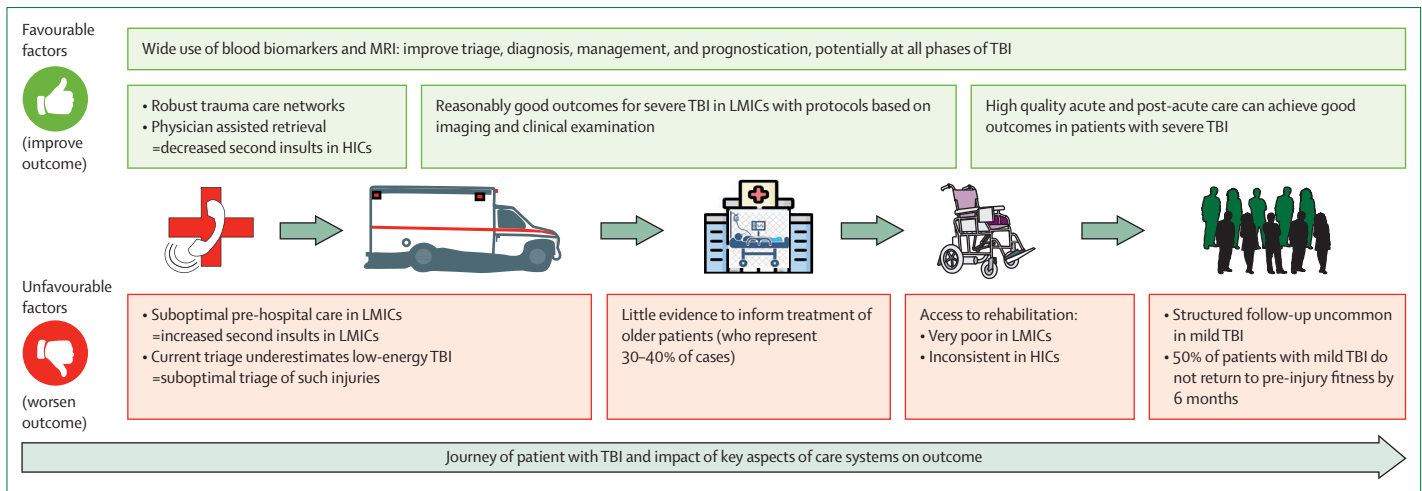
### **Main messages and recommendations**

#### *Main messages*

- (1) Worldwide, TBI is a leading cause of injury-related death and disability, with devastating effects on patients and their families.
- (2) Wide variations exist in global estimates of TBI incidence and in reported incidence, prevalence, and mortality rates between regions and countries. Variations in approaches to data capture and interpretation probably contribute to these variations, confounding comparisons.
- (3) More than 90% of patients presenting to hospital with TBI have mild TBI, but there is little evidence to inform treatment of patients with mild TBI.
- (4) In HICs, older patients ( $\geq 65$  years) who are mostly injured by falls account for 30–40% of hospital admissions for TBI. Frailty and alcohol abuse contribute to falls causing TBI in older people.
- (5) People in LMICs are disproportionately affected by TBI, with most injuries caused by road traffic incidents. There are substantial disparities in care, with little infrastructure for emergency pre-hospital care and very little access to post-acute care.
- (6) Although there is a strong focus on the risk of sport-related concussion and repetitive head impacts in team sports, most patients seen in hospital with sport-related concussion have sustained the injury during individual sports or recreational activities.
- (7) TBI and criminal offending are closely and bidirectionally related. TBI associated with intimate partner violence affects women more commonly and is associated with worse outcomes compared with other interpersonal violence.

#### *Recommendations*

- (1) Continue concerted efforts to address this vast global health problem and focus on better prevention, improved access to care, and promotion of clinical research to improve treatment standards.
- (2) Develop a uniform process for data capture and reporting of TBI epidemiology that is agreed upon by governments and institutions.
- (3) Increase public health interest and establish a research focus on mild TBI.
- (4) Target fall prevention for older people in HICs and make preparations for subsequent implementation of



**Figure 4: Advances and remaining challenges in the provision of health care for people with traumatic brain injury along the trauma chain**  
Continuity of care along the chain of trauma health care is of paramount importance to achieve good outcomes. If pre-hospital care is inadequate, secondary damage might be so severe that outcome will be poor, no matter how good the in-hospital treatment might be. Conversely, benefits accrued from excellent in-hospital treatment might be lost if they are not consolidated by good post-acute care. Note that many challenges relate to transitions across the links of the trauma chain. TBI=traumatic brain injury. HICs=high-income countries. LMICs=low-income and middle-income countries.

successful strategies in LMICs as demographics change.

(5) Deliver on implementation of Road Safety goals, described in WHO’s Decade for Action on Road Safety plan launched in 2021. Improve emergency pre-hospital care and develop an infrastructure for post-acute care.

(6) Continue education and public pressure on governing bodies to ensure consistent implementation of safe-play rules that are compliant with guidelines. Reinforce preventive measures in individualised sports, such as cycling and horse-riding.

(7) Implement rehabilitative justice systems; provide special considerations to support criminal offenders who have had a TBI. Develop and implement initiatives to recognise, reduce, and manage intimate partner violence.

## Section 2: Systems of care for TBI

In the 2017 Commission on TBI, we highlighted inconsistencies in access to acute and post-acute care between centres, regions, and countries, and reported substantial variations in systems and quality of care. We recommended that measures to improve systems of care for patients with TBI, ensuring continuity of care, should be high on policy agendas. In this section, we present new data on persisting variations in care, identify disparities in care provision, and discuss their implications for health policy, differentiated for the pre-hospital setting, the emergency departments, and post-acute care. Figure 4 presents a summary overview of advances and challenges in care for TBI along the trauma chain. We additionally provide a discussion on the management of sport-related concussions, a field in which substantial progress has been made towards protecting the brains of athletes, and on the specific persisting challenges of TBI care in LMICs. By contrast

with the first Commission, we do not discuss cost-effectiveness, as few new data are available.

### Pre-hospital care

The pre-hospital phase (eg, care at the scene of the incident and during transport to hospital) is a time of high risk for hypoxia, hypotension, and expanding intracranial mass lesions. Emergency medical services implement resuscitative interventions to prevent secondary brain injuries and decide whether the patient requires specialist care in a regional trauma centre. Such specialist care might require prolonged transportation from a closer non-specialist hospital. These time-critical assessments are complicated by other causes of impaired consciousness in injured patients, including extracranial injury, metabolic derangement, intoxication, or pre-existing chronic neurological impairments.

The CENTER TBI core study collected detailed data on current pre-hospital practices in Europe. In patients with moderate or severe TBI,<sup>62</sup> pre-hospital hypoxia (in 64 [5.5%] of 1160 individuals) and hypotension (in 124 [10.6%] of 1160) were less common than previously reported in the IMPACT studies<sup>63</sup> (hypoxia in 1150 [20.3%] of 5661 individuals, and hypotension in 1211 [18.3%] of 6629). Secondary insults were associated with major extracranial injuries (odds ratio [OR] 3.6, 95% CI 2.6–5.0 for hypotension and 4.4, 2.9–6.7 for hypoxia). Pre-hospital intubation was associated with better functional outcome in patients with higher abbreviated injury scores in the thoracic and abdominal regions (p=0.009 and p=0.02, respectively). There was substantial variation between countries and centres in all aspects of pre-hospital care (at scene interventions, time spent at scene, and en route), which were not sufficiently explained by patient characteristics and did

not clearly translate to differences in outcome.<sup>62,64</sup> The greatest driver of longer on-scene time was intubation (mean increase 8.3 min, 95% CI 5.6–11.1). Substantial variation was observed in secondary referrals, with a median OR of 1.69 between countries.<sup>64,65</sup> Of 1347 patients with moderate or severe TBI, 195 (14.5%) were admitted after secondary referral, and presented more often with CT abnormalities than patients who were admitted directly: mass lesions (52% vs 34%), midline shift (54% vs 36%), and acute subdural haematoma (77% vs 65%)—reflecting the main reasons for secondary referral. Secondary referral was not significantly associated with functional outcome (adjusted OR 1.07, 95% CI 0.78–1.69), or with survival at discharge (OR 1.05, 0.58–1.90).

These results appear to contrast with the evidence provided in the 2017 Commission on TBI,<sup>1</sup> which supported direct transport of more severely injured patients to regional trauma centres. We recognise that CENTER-TBI did not capture information on patients who stayed in regional hospitals and that this limitation might have confounded results. Our interpretation is that, within a system of care that embeds appropriate and rapid transfer following initial presentation to a regional hospital, the outcome is similar to that observed in patients directly transported to a trauma centre. Current triage tools,<sup>66,67</sup> such as the Field Triage Decision Scheme established by the American College of Surgeons Committee on Trauma,<sup>68</sup> for identifying patients requiring direct (prolonged) primary transportation to a regional trauma centre are heavily weighted towards patients with high-energy injury mechanisms.<sup>69</sup> Older patients with intracranial injury often go undetected by current triage tools because they often have a discordantly high GCS at the scene of the incident in relation to the severity of intracranial injury shown on subsequent neuroimaging,<sup>70</sup> and typically have had a low-energy injury through falling. The potential severity of such injuries should not be underestimated, and any decrease in conscious level should motivate transport to a trauma centre where neurosurgical treatment is available. Nevertheless, the data from CENTER-TBI, showing similar outcomes in patients directly or secondarily transferred, indicate that most patients with a stable and high GCS can be safely initially assessed at the emergency department of the closest hospital, and then referred to a specialist hospital, if required, according to neuroimaging findings.

### Emergency department

On arrival to an emergency department, the role of emergency physicians and nurses is to continue efforts to minimise the risk of secondary brain injury while unravelling the diagnostic conundrum of whether the patient's condition is due to TBI or other injuries and illnesses. Prioritisation is a main feature in this approach,

following the principle of treat first what kills first. Evidence-based guidance and protocolised approaches according to the principles of Advanced Trauma Life Support<sup>71</sup> are the main pillars in this phase of care<sup>72</sup> to ensure a systematic and structured approach. Intubation is recommended in the pre-hospital guidelines of the Brain Trauma Foundation<sup>73</sup> for all patients with a GCS of 8 or less. Evidence from CENTER-TBI shows that in-hospital intubation had a significant beneficial effect on functional outcome in patients with GCS of 10 or lower ( $p=0.01$ ).<sup>74</sup> In combination with the findings from CENTER-TBI in the pre-hospital setting, these results suggest that major extracranial injury should drive the decision to intubate in the pre-hospital setting, and that indications for intubation in-hospital should be broadened to also include patients with a GCS of 9 or 10. Large, international, multicentre, randomised trials have examined the efficacy of tranexamic acid as part of haemorrhage control in injured patients. Although there is significant benefit of tranexamic acid in patients with trauma with clinically significant extracranial bleeding, including those who also have TBI,<sup>75</sup> the evidence in isolated TBI is still under debate.<sup>76,77</sup>

Additionally, in the emergency-department setting, the main focus is on patients with high-energy injuries and on those with severe TBI. CENTER-TBI found disparities in care for patients injured by low-energy mechanisms: compared with 13059 patients injured by high-energy transfer, those injured through low-energy falls had similar rates of CT brain scan abnormalities and in-hospital mortality, but were 50% less likely to receive critical care or emergency interventions.<sup>19</sup> From a perspective of systems of care, a major decision made in the emergency department phase relates to triaging for CT scanning. A strategy of imaging all patients with a head injury would guarantee not missing any clinically relevant structural damage, but would be costly, expose many patients to unnecessary radiation, and increase crowding in the emergency department. Clinical decision rules have been developed to select patients for CT scanning. Examples include the New Orleans criteria, the Canadian CT head rule,<sup>78</sup> the UK National Institute for Health and Care Excellence (NICE) guideline for head injury, and the CT in Head Injury Patients rule.<sup>79</sup> These clinical decision rules substantially reduce the number of CT scans but are still inefficient, as 90–95% of scans performed show no intracranial injury.<sup>80</sup> The assessment of certain protein-based blood biomarkers has the potential to improve the performance of these rules. In 2013, the Scandinavian Neurotrauma guidelines<sup>81</sup> incorporated S100 calcium-binding protein B (S100B) to reduce CT scan usage in low-risk patients with mild TBI and reported that, even with incomplete implementation, the approach saved €39 per patient<sup>82</sup> managed. A systematic review supported the clinical use of S100B for detecting intracranial abnormalities,<sup>83</sup> and the ALERT trial<sup>84</sup> provided evidence in favour of using

For the NICE guideline on head injury see <https://www.nice.org.uk/guidance/cg176>

glial fibrillary acidic protein (GFAP) and ubiquitin carboxy-terminal hydrolase L1 (UCH-L1). Based on these data, the GFAP and UCH-L1 tandem biomarker-based plasma test has been cleared by the FDA to rule out the need for CT imaging in patients with mild TBI.<sup>85</sup> The same test recently obtained a CE mark in the EU, indicating conformity with European health and safety standards.<sup>86</sup>

TRACK-TBI, reporting on 1359 patients with GCS 3–15, found that GFAP showed better diagnostic performance for predicting intracranial abnormalities than did S100B.<sup>87</sup> The regulatory landscape for the diagnostic use of blood-based biomarkers is presented in detail in the appendix (p 4). One company has received regulatory clearance for a point-of-care device. Use of such devices will permit faster turnover times in the emergency department, and will also facilitate application in out-of-hospital settings. Regulatory clearance is, however, restricted to a specific combination of biomarkers (GFAP and UCH-L1). Data currently available suggest that there is no clear diagnostic benefit from combinations of biomarkers, as GFAP in isolation performs as well as all biomarkers combined. The clinical utility of biomarkers will depend on their added value compared with clinical decision rules, and this added value has insufficiently been addressed in previous studies. One study<sup>88</sup> published in 2022 explored the value of adding GFAP and UCH-L1 to three clinical decision rules (the New Orleans criteria, the Canadian CT head rule, and the National Emergency X-ray Utilisation Study) in a cohort of 349 patients with mild TBI (GCS 13–15) presenting to the emergency department within 4 h of injury. At predefined cutoff thresholds, GFAP outperformed UCH-L1 (area under the receiver operating characteristic curve [AUC] 0·83, 95% CI 0·73–0·93 vs 0·72, 0·61–0·82) for predicting CT abnormalities. Adding continuous GFAP to the clinical decision rules improved the AUC, particularly for the Canadian CT head rule (to 0·88, 95% CI 0·81–0·95). A limitation of this study, however, was the low number of events (CT positivity in 23 [7%] of 349 individuals). Stronger evidence in support of adding biomarkers to clinical decision rules was provided by CENTER-TBI. Six biomarkers (S100B, GFAP, UCH-L1, neuron-specific enolase [NSE], neurofilament light [NfL], and total tau) were analysed in 1889 patients with mild TBI (CT positivity in 874 [46%] of 1889) and their diagnostic accuracy for predicting CT abnormalities compared with four clinical decision rules (the Canadian CT head rule, the CT in Head Injury Patients, NICE, and New Orleans criteria). GFAP outperformed other biomarkers and all clinical decision rules in predicting CT abnormalities (AUC for GFAP 0·85, 95% CI 0·83–0·87 vs 0·71–0·74 for the multivariable models containing components of the rules). Combining GFAP with the rule components marginally increased their discriminative ability to AUC (0·86–0·87 [95% CI 0·85–0·88]). The addition of other biomarkers did not

provide added value over GFAP. A limitation of CENTER-TBI was that most blood samples were not obtained within the first few hours after injury (median sampling time 11·8 h, IQR 5·4–18·6). However, results were consistent when modelling was used to estimate biomarker concentrations 2 h after injury. These results support the development of novel clinical decision rules, combining GFAP with clinical characteristics. Clinical implementation will require robust assay platforms for clinical use, and further validation studies are needed, in broader populations with early sampling, to determine cost-effectiveness.

### Post-acute care

The frequent occurrence of impairments in functioning and participation in daily life activities after TBI (see section 5) highlights the need for continued rehabilitation efforts. The US National Institute for Disability, Independent Living, and Rehabilitation Research has funded the TBI Model Systems of Care since 1987, a clinical care and research infrastructure network that enrolls individuals with moderate to severe TBI at the time of in-patient rehabilitation and follows them up at 1, 2, and 5 years, and every 5 years thereafter.<sup>89</sup> The Monash Epworth Rehabilitation Research Centre in Australia has led a similarly designed study investigating rehabilitation outcomes up to 30 years after a TBI.<sup>90</sup> Both studies have shown that early and continuous rehabilitation can consolidate the progress gained in the acute clinical phase, and reduce the length of stay in hospital and socioeconomic burden. Individuals who experience discontinuity of care between the acute and post-acute phase have poorer functional outcomes and satisfaction with care than those who receive a continuous chain of rehabilitation.<sup>91,92</sup> Moreover, fragmented systems of care can cause patients and caregivers to feel unsupported and uncertain about how to access resources and negotiate care transitions.<sup>93</sup> Despite broad recognition among clinicians of the needs for appropriate post-acute care, CENTER-TBI, which reported on 1206 individuals with moderate to severe disability at 6 months after injury, showed that 90% reported rehabilitation needs, but only 30% received in-patient rehabilitation and 15% received out-patient rehabilitation.<sup>94</sup>

At the milder end of the TBI spectrum, where inpatient rehabilitation needs are different, the need for post-discharge rehabilitation is even more neglected. Results from CENTER-TBI showed that only a fifth of individuals with mild TBI who had persisting symptoms received outpatient rehabilitation at 6 months post-injury.<sup>95</sup> Both CENTER-TBI and TRACK-TBI found further deficiencies in care with regard to the discharge policy from the emergency department. Provider profiling in CENTER-TBI showed that 90% of centres do not routinely schedule a follow-up appointment for patients with TBI discharged home from the emergency department, and around 50% do not follow patients up

after discharging them from the ward.<sup>96</sup> The CENTER-TBI Core study data show that only 26% of patients discharged from an emergency department received written information and 6% received a follow-up appointment in hospital. In TRACK-TBI, fewer than half of the participants received educational material at discharge from the emergency department and saw a health-care provider within 3 months after mild TBI.<sup>97</sup> Yet both studies showed that 30% of patients discharged from an emergency department did not attain full recovery by 6 months.

Taken together, the evidence suggests that access to rehabilitation and structured follow-up care following TBI remains suboptimal and underlines the need for increased knowledge about TBI consequences, the assessment of functional impairments and corresponding rehabilitation needs, and referrals to rehabilitation.

### Sport-related concussions

Triage decisions play a prominent part in the management of confirmed and suspected sport-related concussion, regarding removal from play, treatment considerations, and decisions on return to play. Broad consensus exists among international experts and global sports organisations that, at all levels of sport, any athlete with clear signs or symptoms of concussion—so-called red flags—should be immediately removed from play.<sup>98,99</sup> Exclusion of a possible sport-related concussion is more challenging. Although various sideline assessment tools and protocols have been developed to aid in concussion recognition,<sup>100–102</sup> no perfect sideline assessments tools exist for its diagnosis or, importantly, its exclusion, with most tools showing substantial observer variability.<sup>100</sup> Assessments of symptoms and multimodality testing protocols have the highest sensitivity and specificity for concussion detection,<sup>103,104</sup> and are incorporated into the widely used Sport Concussion Assessment Tool,<sup>105</sup> elements of which are included in the extensive, multimodal Head Injury Assessment protocol.<sup>106</sup> Although several global consensus statements endorse recommendations of the rugby union based around the notion of ‘if in doubt, sit them out’, there is remarkable variability in how these recommendations are translated to clinical practice.<sup>107</sup> An editorial in the *British Journal of Sports Medicine* raised a red flag towards the professional soccer association Fédération Internationale de Football Association because of their variable policies that might compromise athlete care, and made a strong plea for adoption of standards introduced into other fields of sport.<sup>108</sup> We suggest that efforts should be made to operationalise consensus statements on the management of sport-related concussion to increase consistency of sideline assessment protocols across sports.

Sport-related concussion rehabilitation and follow-up protocols use a multidimensional approach to monitoring symptom resolution and return to functional baseline before resuming return-to-play progression,

with return to normal life prioritised (eg, education and work) before returning to sport.<sup>55,98</sup> Typically, return-to-play protocols begin with low-intensity exercise, gradually progressing to sport-specific contact activities, with a growing trend toward early subthreshold exercise and domain-specific rehabilitation. These protocols are mainly pragmatically oriented, while research studies using advanced blood and neuroimaging biomarkers continue to improve our understanding of sport-related concussion.

Continued investment in research remains crucial to determining factors that might contribute to potential adverse brain-health outcomes associated with sport-related concussion and repetitive head impacts. In parallel, efforts to reduce the incidence of concussion and head impact exposure in athletes should continue (see section 1).<sup>58</sup>

### Challenges in LMICs

The 2019 GBD study<sup>109</sup> estimated that almost 90% of the 4 million global deaths due to injuries occurred in LMICs, with autopsy studies suggesting that TBI is responsible for a substantial proportion of these deaths.<sup>110</sup> Increasing industrialisation and changing demographics in LMICs are associated with an epidemiological shift from communicable, maternal, neonatal, and nutritional diseases towards non-communicable diseases and injuries, with a predicted increasing burden of injuries in LMICs over the coming years.<sup>109,111,112</sup> Quality of care and outcomes of TBI vary throughout the world. In the 2017 Commission on TBI, we reported a 3·3 times difference in the odds of unfavourable outcome between centres at the extremes of the outcome range (2·5th vs 97·5th percentiles) in the IMPACT studies, but this difference increased to a 6·6 times difference on analysis of data from the CRASH trial, which included patients from LMICs. The Global Neurotrauma Outcomes Study,<sup>18</sup> an observational cohort study of 1635 patients across 57 countries receiving emergency neurosurgery for TBI, found significant differences in management and short-term mortality between countries with different levels of human development index (HDI). Patients in countries with medium and low levels of HDI had temporal delays to surgery as well as limited access to CT scanning, intensive care, and intracranial pressure monitoring.

An absence of beds in an intensive care unit (ICU) often results in severe TBI being managed in the emergency department or wards with less monitoring, physiological support, or medical attention. ICU beds are generally allocated on a first-come, first-serve basis in the absence of triage support (often for ethical reasons). Management and outcomes from this large group of patients with severe TBI managed outside the ICU are completely unstudied. The most crucial limitations to care are not the absence of advanced technology, but the availability of ICU beds, basic

**Panel 2: Initiatives specifically in low-income and middle-income countries to decrease the incidence of traumatic brain injury, improve the care for patients, and stimulate collaborative research**

**Global institutional and Governmental initiatives with a primary aim on road traffic safety**

*WHO Decade for Action on Road Safety plan*

The initiative, launched in 2021, aims to reduce traffic-related deaths and injuries by at least 50% by 2030. It was implemented following the adoption of resolution A/RES/74/299 "Improving global road safety" by the UN General Assembly.

*The Federation Internationale de l'Automobile Action for Road Safety*

This campaign was launched in support of the UN Decade of Action for Road Safety and involves four key priorities: advocacy at the highest levels, action by clubs on the ground, involvement of the motor sport community, and campaigns and partnerships.

*The National Highways Authority India (NHAI)*

NHAI is seeking bids for providing free emergency clinical care for automotive incidents occurring on highways connecting the Delhi–Mumbai–Chennai, Chennai–Kolkata, Kolkata–Agra, and Agra–Delhi corridors (the so-called golden quadrilateral).

*The World Bank Road Safety Project in Bangladesh*

The project will pilot comprehensive road safety measures, including improved engineering designs, signing and marking, pedestrian facilities, speed enforcement, and emergency care on two major highways in Bangladesh.

*Guide to implementation of the Toward Zero Deaths (TZD) national strategy on highway safety (2022)*

The TZD national strategy, initiated in 2014, previously had a high level focus on national leadership and direction, with details of implementation in the USA left to individual states. However, the persistent number of traffic fatalities led to publication of this report, which provides guidance to states and other highway safety stakeholders to advance the implementation of the TZD national strategy through programmes, tools, and techniques.

**Investigator-led initiatives to advance the care for traumatic brain injury (TBI) in low-income and middle-income countries (LMICs) and to stimulate collaborative research**

*UK National Institute for Health and Care Research Global Health Research Group on Neurotrauma<sup>18</sup>*

Its overarching mission is to improve global neurotrauma care. Four main themes are identified: mapping TBI care, understanding TBI care, innovation in TBI, and measuring and nurturing research capacity. A total of 57 countries are involved in the collaboration.<sup>18</sup>

*The US National Institutes of Health and Fogarty-International-Research-Institute-funded Global Neurotrauma Research Group*

The main focus is on Spanish-speaking countries in Central and South America, with a central aim to build capacity and implement and test protocols for TBI management in LMICs.

For more on the TZD national strategy see <https://doi.org/10.17226/26627>

physiological support devices (eg, bedside monitors, ventilators, etc), and access to CT imaging.

On comparison of data collected in the context of CENTER-TBI between India and Europe, we found large differences in the provision of pre-hospital and post-acute care: despite a similar distribution of injury severity classified by the GCS, 89.6% of patients received emergency care at the scene of incident in Europe versus only 5.8% in India. In Europe, 16.3% were discharged from hospital to a rehabilitation facility versus 0.4% in India. Such differences highlight the need for systems-wide approaches to improving TBI care in LMICs,<sup>113–115</sup> as

well as clinical practice guidelines tailored to the resources available<sup>116</sup> (see section 3). Various initiatives have been developed over the past 5 years in this direction at global institutional, governmental, and investigator-driven levels (panel 2). Global institutional and governmental initiatives appropriately have a main focus on road traffic safety, whereas investigator-driven initiatives are more directed at improving care provision and stimulating research. Investigator-led initiatives have been hugely successful in involving clinicians and researchers from LMICs in neurotrauma research, in developing advocacy initiatives, and in implementing educational activities and protocols to improve the care for patients with TBI in LMICs (see appendix, p 6 for key accomplishments). Some unpublished studies from LMICs in Latin America have shown that protocolised care (eg, the CREVICE protocol:<sup>117</sup> see section 3) in the absence of intracranial pressure monitoring can produce 6-month outcomes superior to those predicted by the CRASH prognostic model for low-income countries (LICs), and similar to those predicted for HICs by the IMPACT and CRASH models (Chesnut R, personal communication). Improving prevention, advancing care, and stimulating research in LMIC settings are urgent unmet needs. Current efforts should be strengthened and new efforts developed.

**Main messages and recommendations**

*Main messages*

- (1) Disparities in care exist in HICs and relate to: older people injured by low-energy mechanisms (falls), access to rehabilitation for patients with moderate-to-severe TBI, and follow-up in patients with mild TBI.
- (2) Current triage tools used in emergency settings are heavily focused on high-energy injuries and might insufficiently identify the severity of brain injury resulting from low-energy mechanisms.
- (3) Blood-based biomarkers, particularly GFAP, provide added value to clinical decision rules for selecting patients with mild TBI for CT scanning. However, few assay platforms have been approved for clinical use and substantial variability exists between platforms.
- (4) Implementation of safe-play protocols to protect participants in sports from acute and long-term adverse effects of brain injury is highly variable across different team sports.

*Recommendations*

- (1) Address disparities through close collaboration between policymakers and clinicians. Approaches to consider include: critical appraisal of triage tools used in emergency settings, involvement of rehabilitation services at an early stage of the in-hospital treatment for TBI, and establishment of structured follow-up after mild TBI as good practice.
- (2) Critical appraisal of triage tools used in emergency settings is needed.

(3) Develop and seek regulatory approval for robust clinical use platforms. Establish cross-platform harmonisation of assay results, avoiding unnecessary use of combinations of biomarkers.

(4) Operationalise consensus statements on the management of sport-related concussion to increase consistency of sideline assessment and return-to-play protocols across sports.

### Section 3: Clinical management of TBI

Patients with moderate-to-severe TBI are a minority (around 10%) of all patients with TBI presenting to hospital, with the remainder (around 90%) having mild TBI (GCS 13–15). However, although the proportion of patients with moderate-to-severe TBI is smaller, many patients are admitted to the ICU and receive acute inpatient therapeutic interventions, and more severe injury results in the greatest burden of death and disability for individual patients. The first 2017 Commission emphasised the scarce evidence supporting the management in patients with severe TBI; highlighted substantial between-centre variances in practice; and showed that physiological management targets were based on population averages and took little account of heterogeneity in pathophysiology and therapy responsiveness.

In this section, we describe how casemix and clinical practice have evolved since the 2017 Commission for patients with TBI admitted to an ICU, summarise how emerging evidence and insights have refined and individualised current management in HICs, and discuss advances and persisting challenges in LMICs. Section 4 provides greater detail regarding future prospects for identifying subgroups of patients who might benefit from specific therapeutic approaches.

#### The current picture of TBI in the ICU

Data from over a decade ago had led to the perception that most patients with TBI in an ICU are young and have severe TBI (GCS  $\leq 8$ ). Even at the time of the 2017 Commission, there were emerging data suggesting that the demographics of TBI were changing, and these insights have been confirmed by large observational studies (see section 1). In CENTER-TBI,<sup>20</sup> the median age in the ICU stratum was 49 years (IQR 29–65), compared with a median 30 years (21–45) in the IMPACT studies,<sup>118</sup> and 26% of patients were older than 65 years. This change in demographics is important, as age can impair physiological reserve, and many older patients are on treatments for comorbidities, which can modulate disease course and outcome.<sup>119,120</sup> Fewer than half of patients admitted to ICU for TBI in HICs have severe TBI and more than a third have mild TBI (GCS 13–15). ICU admission of patients with mild TBI is often prompted by factors other than TBI severity, in particular major extracranial injuries (abbreviated injury scale  $\geq 3$  in any extracranial body part), which were seen in 55% of

ICU admissions with TBI.<sup>121</sup> These extracranial injuries typically involved the thorax (35%), spine (18%), and extremities (17%), and often required surgical interventions (29%). However, other patients with mild TBI were admitted to an ICU because of a perceived risk for clinical and neurological deterioration. Although some of these admissions might have been appropriately prudent, others represent costly over-triage, estimated at 17% of cases in a US study.<sup>122</sup>

#### TBI as a systemic disease

Systemic organ dysfunction in TBI can result from extracranial injury, but TBI itself, and therapies for intracranial hypertension, also contribute. Systemic complications include respiratory failure (see later in this section), renal failure,<sup>123</sup> adrenal insufficiency,<sup>124</sup> myocardial injury,<sup>125</sup> and potentially multiple organ dysfunction.<sup>126</sup> Acute kidney injury occurs in about 12% of patients with TBI in an ICU and is associated with worse outcome. Osmotic therapy and hyponatremia are important modifiable risk factors (hazard ratios 2.08 and 1.88, respectively), attention to which could reduce the incidence of acute kidney injury.<sup>123</sup> These data underline the importance of general ICU management in addition to the specific management of TBI, and further establish TBI as a systemic condition.<sup>127,128</sup>

#### Individualising clinical targets for ICU management

TBI still does not have interventions targeting disease mechanisms; management in the ICU remains focused on physiological targets, including intracranial pressure and cerebral perfusion pressure (ie, the difference between mean arterial pressure and intracranial pressure), and in some centres, multimodality monitoring (see later in this section and section 4).<sup>129,130</sup> The BEST TRIP randomised trial, published before the last Commission in 2017, recruited 324 patients with severe TBI from South American centres, and did not show any benefit of a protocol based on intracranial pressure monitoring when compared with management based on clinical examination and serial imaging.<sup>131</sup> However, the more recent SYNAPSE-ICU study, published in 2021, undertook comparative-effectiveness analysis of intracranial pressure monitoring in 146 ICUs across the world including 1287 patients with TBI, and showed that the use of intracranial pressure monitoring was associated with increased therapy intensity, lower mortality, and better functional outcome at 6 months.<sup>132</sup> Understanding these apparently contrasting results requires further exploration, but the differences could be related to the settings where the studies were conducted.

The harm associated with intracranial pressure elevation is unlikely to be uniform across patients and over time. Although existing guidelines suggest treating an intracranial pressure that is greater than 22 mm Hg and keeping cerebral perfusion pressure between 60 and 70 mm Hg,<sup>133</sup> these thresholds are not absolute.

CENTER-TBI confirmed earlier research<sup>134</sup> showing that both intensity and duration of intracranial pressure insults are associated with poorer outcomes,<sup>135</sup> and identified an intracranial pressure treatment threshold of 18 mm Hg ( $\pm 4$  mm Hg), consistent with other evidence for treatment thresholds of less than 20 mm Hg.<sup>136,137</sup> This concept of so-called intracranial pressure dose, that integrates both the intensity and duration of an intracranial pressure event, is increasingly gaining recognition. Moreover, the evolution of intracranial pressure over time should be taken into consideration to guide management decisions. Tolerance of intracranial pressure insults is reduced by impaired cerebral autoregulation (ie, the ability to maintain cerebral blood flow in the face of changing cerebral perfusion pressure), and assessment of autoregulatory status is increasingly used to titrate cerebral perfusion pressure targets (see also section 4 and appendix p 14).

Characterisation of ongoing pathophysiology can be facilitated by the monitoring of partial pressure of brain tissue oxygen (PbtO<sub>2</sub>) and cerebral metabolism using microdialysis. Observational studies show that low PbtO<sub>2</sub>,<sup>138–140</sup> elevated lactate-to-pyruvate ratio, and low brain tissue glucose concentrations<sup>141</sup> are associated with a poor outcome after severe TBI, but evidence for targeting these parameters to improve outcomes is still accumulating. The phase 2 study BOOST-2,<sup>142</sup> done in 119 patients with severe TBI, showed that management incorporating monitoring of PbtO<sub>2</sub> in addition to intracranial pressure reduced brain tissue hypoxia, and might improve TBI outcomes. Three ongoing phase 3 randomised trials comparing management with or without PbtO<sub>2</sub> monitoring will recruit a total of 2274 patients with severe TBI and should provide definitive answers (details provided in appendix p 8). Cerebral microdialysis is less widely used than PbtO<sub>2</sub> monitoring, despite promising data from prospective observational studies and small randomised trials suggesting that metabolic derangements detected by cerebral microdialysis are associated with worse TBI outcomes.<sup>143</sup> A fundamental limitation of these monitors is their focal nature, which only indirectly measures a heterogeneous and diffuse pathophysiology.<sup>144–146</sup>

### Managing TBI and suspected raised intracranial pressure in settings with few resources

A major finding from the BEST TRIP trial<sup>131</sup> was the achievement of satisfactory outcomes from TBI despite resource limitations. In settings with few resources, the management approach typically involves more physician input, using more frequent clinical examinations and CT scanning than in high-income settings because there is less monitoring capacity and a smaller role is afforded to nurses in guiding patient care. This greater physician involvement might increase the clinical detection of neurological changes, reinforcing the crucial value of on-site intensivists in non-monitored TBI care. In the BEST

TRIP trial, patients in the control group were treated according to a protocol based on imaging and clinical examination (ICE). This standardised approach in combination with high physician involvement is likely to have contributed to the satisfactory outcomes observed.

Following the BEST TRIP trial, a prospective two-phase NIH-funded study (R01-NS-058302) investigated the efficacy of the ICE protocol outside of a trial setting. In the phase 1 of the study, outcomes from a new group of centres in resource-limited settings not using set protocols were compared with those from a group of the original BEST TRIP investigators using the ICE protocol. Subsequently, a consensus conference comprising the investigators and other clinicians developed a more comprehensive version of the ICE protocol—the Consensus-Revised ICE (CREVICE) protocol,<sup>117</sup> which was then prospectively tested in both groups. Preliminary analysis of the findings showed that protocolised care is superior to non-protocolised care.<sup>147</sup>

CREVICE filled in many gaps in the ICE protocol, including formalising the decision-tree leading to the diagnosis of suspected intracranial hypertension (panel 3). In one study,<sup>148</sup> investigators examined the correlation of these criteria with an intracranial pressure greater than 22 mm Hg in the BEST TRIP trial monitored group and found a sensitivity of 93·9% and a specificity of 42·4%. This approach will treat most intracranial hypertension cases but there might be overtreatment of patients with subthreshold intracranial pressure.

Managing monitor-documented intracranial hypertension involves intervention in direct response to supra-threshold values. By contrast, treating suspected intracranial hypertension involves scheduled or non-reflex interventions (eg, periodic hypertonic agent infusions). This so-called tranquility approach contrasts with the crisis-management approach for monitored

#### Panel 3: Diagnosis of suspected intracranial hypertension

Intracranial hypertension is suspected and treatment is recommended in the presence of one of the following major or two of the following minor criteria:

##### Major criteria

- Compressed cisterns (CT classification of Marshall diffuse injury III; see appendix p 12)
- Midline shift greater than 5 mm (Marshall diffuse injury IV)
- Non-evacuated mass lesion

##### Minor criteria

- Glasgow Coma sum motor score of 4 or less
- Pupillary asymmetry
- Abnormal pupillary reactivity
- CT classification of Marshall diffuse injury II (ie, basal cisterns are present with midline shift 0–5 mm or a high-density or mixed-density lesion of 25 cm<sup>3</sup> or less, or both)



		GCS motor score and pupillary exam							
		GCS-M 6		GCS-M 5		GCS-M 4		GCS-M 1-3	
		NP	AP	NP	AP	NP	AP	NP	AP
During first 24 h	DI 1-2								
	EML/DI 1-2								
	DI 3								
	EML/DI 3								
		NP	AP	NP	AP	NP	AP	NP	AP
Around 48 h	DI 1-2								
	EML/DI 1-2								
	DI 3								
	EML/DI 3								
		NP	AP	NP	AP	NP	AP	NP	AP
Around 72 h	DI 1-2								
	EML/DI 1-2								
	DI 3								
	EML/DI 3								
		NP	AP	NP	AP	NP	AP	NP	AP
After 72 h	DI 1-2								
	EML/DI 1-2								
	DI 3								
	EML/DI 3								
		NP	AP	NP	AP	NP	AP	NP	AP

**Figure 5: Consensus-derived matrix for de-escalation of therapy in suspected intracranial hypertension**

This decision-support heatmap matrix represents tendencies to wean ongoing treatment for intracranial pressure on the basis of the most recent Marshall CT scan classification and clinical status exam (GCS motor score and pupillary exam) in patients who have been stable for 24, 48, 72, or more than 72 h. Green cells in the table indicate a decision to initiate weaning; red cells indicate a decision to continue treatment; and yellow cells indicate an indeterminate situation, where further consideration is needed (modified with permission from Chesnut et al).<sup>117</sup> GCS=Glasgow Coma Scale. NP=normal pupils. AP=abnormal pupils, without worsening since injury. DI=diffuse injury (graded by the Marshall CT classification—see appendix p 12). EML=evacuated mass lesion.

patients. As treatment cannot be predicated on quantitative intracranial pressure values, it can be difficult to decide when treatment for suspected intracranial hypertension can be tapered. The CREVICE consensus conference addressed this challenge by creating a heatmap describing their aggregate treatment-related practice tendencies for weaning treatment based on duration of acceptable ICE evaluations<sup>117</sup> (figure 5). The uncertainty (yellow fields) apparent in this heatmap reveals the importance of developing better indicators for tapering treatment. A detailed flow chart for weaning of intracranial pressure-directed therapy for suspected intracranial hypertension is presented in the appendix (p 7). Non-invasive methods of estimating intracranial pressure, such as measurement of optic nerve sheath diameter,<sup>149</sup> could help to guide decisions to initiate, escalate, and wean treatment for suspected intracranial hypertension, possibly decreasing the inefficiencies of non-monitored management (eg, overtreatment, increased length of stay, more decompressions, etc). CT imaging is central to the CREVICE approach. However, in many

low-resource settings the patient and their family bear the imaging costs, limiting CT usage. Additionally, availability and functional status of CT devices in LMIC settings are often problematic. Unrestricted access to at least a few CT studies should be considered crucial to effective implementation of the CREVICE protocol. What to do in settings without CT access remains an important unresolved question.

Overall, even if the standard in high-resource settings is monitoring intracranial pressure in severe cases, evidence is accumulating that attentive teams of intensivists and neurosurgeons can achieve a reasonably good outcome from severe TBI in low-resources settings using institutional protocols that include imaging and clinical examination (eg, ICE and CREVICE). However, good post-acute care would appear essential to consolidate these benefits. These considerations should direct allocation of available finances within trauma centres in low-resource settings and the funding of research aimed at improving the outcome from severe TBI where it is most common, but also the most under-resourced.

**Frameworks for care: the role of rigorous evidence-based recommendations versus expert consensus**

Over the past two decades, several guidelines have been produced for the management of TBI, and an analysis in 2021 suggested that their use was associated with improved patient outcomes.<sup>150</sup> However, increasing rigour in grading evidence resulted in fewer strong recommendations, loss of clinical appeal, and reduced support for decision making.<sup>151</sup> This paradox illustrates the realities of clinical practice when strong evidence is unavailable or insufficient. Consensus-based efforts help to bridge this gap (see panel 4). In general, deviations from guidelines are discouraged, but some deviations might represent individualisation of care, driving better outcomes. Consequently, guidelines are best thought of as frameworks for care, rather than prescriptive instructions for management. However, analysis of the use of more intensive (and potentially hazardous) intracranial pressure therapies in CENTER-TBI suggests substantial practice variation between centres, and many clinicians use more hazardous therapies before exhausting safer options.<sup>156</sup> To remain current, guidelines must be continuously updated to reflect evolving evidence: living guidelines (in parallel with living systematic reviews)<sup>157</sup> could be one way to address this need. Transforming guidelines into a so-called living document will, however, require long-term support by an authoritative organisation or funding body.

**New evidence and insights regarding critical care management**

*Ventilatory management and tracheostomy*

Tracheal intubation and mechanical ventilation can be necessary in TBI because of extracranial injuries, airway compromise, depressed consciousness, or to

manipulate carbon dioxide (PaCO<sub>2</sub>) for intracranial pressure management. However, both TBI and mechanical ventilation can potentially worsen pulmonary injury,<sup>158</sup> and positive pressure ventilation has complex and multifactorial interactions with intracranial dynamics.<sup>159,160</sup> Optimal ventilation strategies in TBI remain variable and are under investigation.<sup>161</sup> CENTER-TBI showed substantial between-centre variability in PaCO<sub>2</sub> concentrations, and nearly two thirds of patients without intracranial hypertension had PaCO<sub>2</sub> concentrations below 4.7 kPa (35 mm Hg) for most of the time. Although such hyperventilation was not clearly associated with poorer outcome, concerns about inducing brain hypoxia by hypocapnia remain.<sup>162</sup> We suggest that hyperventilation might be indicated in patients with raised intracranial pressure due to vasodilation and hyperaemia (identified, for example, by PbtO<sub>2</sub> monitoring), but not in patients with raised intracranial pressure from other causes, and this concept should be further explored.

Although CENTER-TBI showed that in-hospital intubation had a significant beneficial effect on outcome in patients with a GCS of 10 or lower (p=0.01;<sup>74</sup> see also section 2), 20% of mechanically ventilated patients developed ventilator-associated pneumonia, which

prolonged ICU stay but did not affect TBI outcome.<sup>163</sup> Tracheostomy was required in 31% of ventilated patients with TBI, but there was considerable inter-centre variation in its use (mean OR 2.2) and timing. Late tracheostomy (undertaken >7 days post injury) was associated with a longer mean ICU stay (49 vs 39 days; p=0.003) and greater odds of a worse outcome (OR 1.69, 95% CI 1.07–2.67; p=0.018).<sup>164</sup> However, these and other<sup>165,166</sup> data do not show causality—supporting the case for a robust randomised trial of tracheostomy timing. A randomised trial on this topic has been conducted in the area of stroke and did not show a benefit of an early tracheostomy.<sup>167</sup>

#### Fluid and haemodynamic management

Haemodynamic management in TBI usually depends on cerebral perfusion pressure targets, and includes fluid therapy and vasoactive drugs, neither of which are addressed in current guidelines.<sup>133</sup> Comparative-effectiveness research analysis in CENTER-TBI showed that higher positive mean daily fluid balances were associated with worse clinical outcomes, both in patient-level and hospital-level analyses after accounting for confounders.<sup>168</sup> Furthermore, despite slightly more favourable prognostic characteristic in centres with lower-than-median fluid balances, more patients had cardiac output monitoring, which might have contributed to more restrictive fluid administration. However, cardiac output is routinely monitored in less than 20% of patients with a TBI in an ICU. It would be important to investigate implementation of comprehensive haemodynamic monitoring to optimise management and assess effects on outcome.

#### Venous thromboembolism prophylaxis

Pharmacological prophylaxis of venous thromboembolism must balance the risk of venous thromboembolism against concerns that treatment might precipitate or worsen intracranial bleeding.<sup>169</sup> CENTER-TBI reported substantial inter-centre variation in policies for pharmacological venous thromboembolism prophylaxis,<sup>170</sup> unaccounted for by casemix differences. The use of pharmacological prophylaxis was moderately associated with more favourable outcome (OR 1.4, 95% CI 1.1–1.7, and OR 1.5, 1.1–2.0, in multivariable and propensity-adjusted analyses, respectively). However, a retrospective analysis of data from patients with TBI who were managed surgically, collected between 2012 and 2016 from US trauma centres, showed that prophylaxis delay was associated with increased venous thromboembolism (adjusted OR 1.08, 95% CI 1.04–1.12), but decreased the risk of repeated neurosurgery (adjusted OR 0.72, 0.59–0.88 per day of delay in pharmacological venous thromboembolism prophylaxis).<sup>171</sup> These persisting uncertainties regarding optimal dose, timing, and selection of patients for pharmaceutical thromboprophylaxis following TBI<sup>172</sup> have resulted in a [call for a large randomised trial on this topic](#).

#### Panel 4: Established and recent guidelines for the intensive care unit management of traumatic brain injury

##### Brain Trauma Foundation Guidelines

- Management of severe traumatic brain injury (TBI; update to fourth edition in 2016)<sup>133</sup>
- Surgical management (2006)<sup>152</sup>

##### Trauma Quality Improvement Program guidelines of the American College of Surgeons (2015)<sup>153</sup>

- Present best practices in the management of traumatic brain injury, including recommendations for physiological targets. This document is scheduled for an update in 2023.

##### The Seattle International Brain Injury Consensus Conference

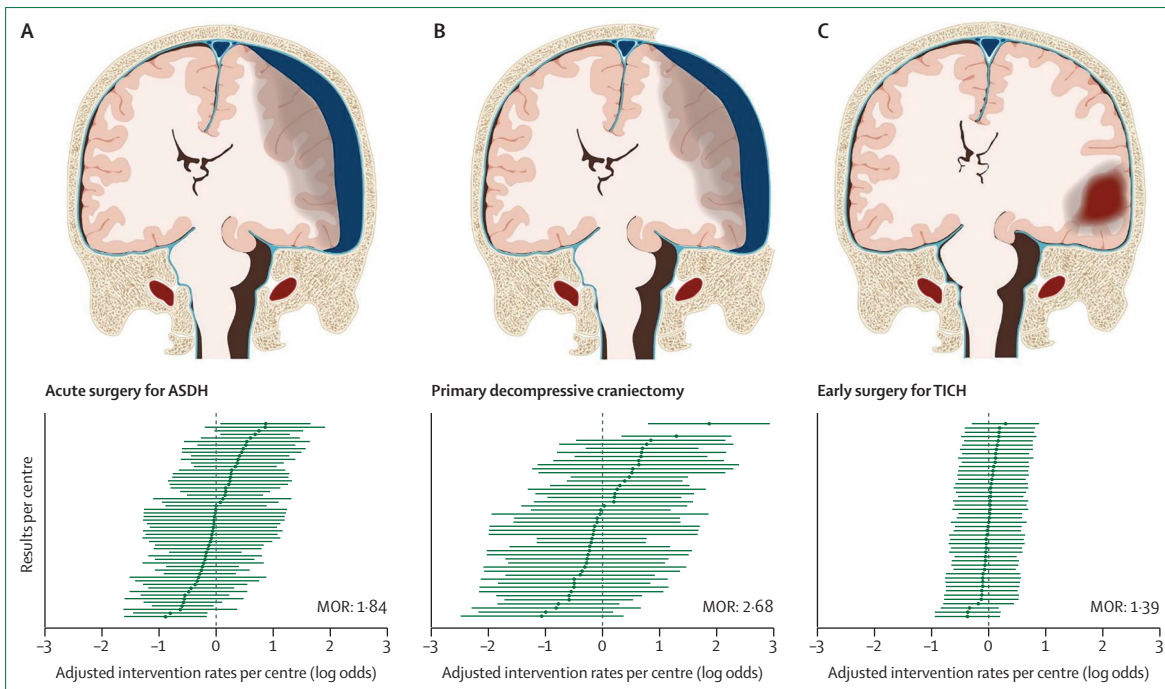
Used expert consensus to integrate existing treatments into management algorithms:

- Based on intracranial pressure and cerebral perfusion pressure (2019),<sup>154</sup> or
- Based on intracranial pressure and cerebral perfusion pressure in combination with brain tissue oxygen partial pressure (2020)<sup>155</sup>

##### Consensus REvised Imaging and Clinical Examination guidelines

- Present a useful approach for managing suspected intracranial hypertension based on imaging and clinical observation in settings where there are few facilities for monitoring intracranial pressure and cerebral perfusion pressure (2020)<sup>117</sup>

For more on pharmacological thromboprophylaxis after TBI see <https://www.nihr.ac.uk/documents/21588-timing-of-pharmacological-thromboprophylaxis-in-traumatic-brain-injury-commissioning-brief/29197>



**Figure 6: Between-centre differences in surgery in acute traumatic brain injury**

(A) Acute surgery in acute subdural haematoma, (B) primary decompressive craniectomy in acute subdural haematoma, and (C) early surgery in traumatic intracerebral haematoma. A logistic random-effects model, adjusted for predefined confounders, was used to estimate the acute surgery preference per centre, with corresponding 95% CIs. The MOR reflects the between-centre variation. An MOR equal to 1 represents no variation; the larger the MOR, the larger the variation. The proportion of patients with an acute subdural haematoma undergoing acute surgery ranged from 7% to 52% (IQR 13–35) between centres, with an MOR of 1.84, suggesting an almost two-fold difference in the likelihood of an identical patient receiving surgery in different centres. Furthermore, the type of surgery for acute subdural haematoma varied between centres: the proportion of primary decompressive craniectomies (as opposed to craniotomies) ranged from 6% to 67% (IQR 12–26), with an adjusted MOR for primary decompressive craniectomies of 2.68 ( $p < 0.0001$ ). Of 367 patients with a large traumatic intracerebral haematoma, the proportion who received acute surgery ranged from 13% to 48%, with an MOR of 1.39 ( $p = 0.27$ ). ASDH=acute subdural haematoma. MOR=median odds ratio. TICH=traumatic intracerebral haematoma.

### Coagulopathy and its management

About 20% of patients with isolated TBI show abnormalities on conventional tests of haemostasis,<sup>120</sup> and these are associated with greater progression of intracranial haematomas,<sup>119</sup> higher mortality, and worse functional outcomes, compared with patients with a normal coagulation profile.<sup>120</sup> Advanced testing of platelet function, fibrinolysis, and viscoelastic testing can better characterise haemostatic defects than conventional tests,<sup>173</sup> but current management remains largely based on conventional laboratory parameters.<sup>174</sup>

### Surgical management

Timely evacuation of an expanding traumatic intracranial haematoma in a patient with deteriorating consciousness is lifesaving. However, many patients present with a stable low-level or high-level of consciousness. Uncertainty exists, particularly in patients with an acute subdural haematoma or a traumatic intracerebral haematoma, on indications and timing of surgery, reflected in large practice variations (figure 6). In CENTER-TBI, comparative-effectiveness research analyses in patients with an acute subdural haematoma showed that centre preference for an acute

surgical strategy compared with that of initial conservative treatment was not significantly associated with better outcome (OR 0.92, 95% CI 0.77–1.09).<sup>175</sup> However, 11% of patients in the initial conservative group required delayed surgery (at a median of 19.1 h, IQR 8.1–84.6). These data suggest that, where surgical equipoise exists, early evacuation of acute subdural haematoma does not lead to a better outcome compared with a strategy favouring initial conservative treatment.

For patients with a large traumatic intracerebral haematoma ( $n=367$ ), comparative-effectiveness research showed no overall clear benefit of early surgery (OR 1.05, 95% CI 0.63–1.73). However, subgroups with moderate TBI (GCS 9–12) or isolated traumatic intracerebral haematoma had a better outcome (OR 1.50, 95% CI 1.10–1.98 and 1.84, 1.27–2.53, respectively) after early surgery than with initiative conservative management. Conversely, conservative management in patients with mild TBI and in those with a smaller traumatic intracerebral haematoma ( $<33$  cc) was associated with better outcome (OR 0.61, 95% CI 0.36–0.94 and 0.75, 0.48–1.00, respectively). These results are consistent with findings of the STITCH(Trauma) trial,<sup>176</sup> which randomly assigned 170 patients with TBI with

For the US CDC TBI report see <https://www.cdc.gov/traumaticbraininjury/pdf/CDC-NIDILRR-Self-Report-508.pdf>

traumatic intraparenchymal haemorrhage to conservative management or early surgery. The study findings were inconclusive because of low recruitment, leading to premature termination by the funder. Thus, there seems to be no uniform effect of surgery in acute subdural haematoma and traumatic intracranial haemorrhage. Meta-analyses of data from CENTER-TBI, TRACK-TBI, and STITCH (Trauma) could provide more definitive evidence to inform guidelines.

There is also uncertainty regarding the benefits of decompressive craniectomy, a procedure that aims to mitigate the effects of raised intracranial pressure by removing part of the skull. Decompressive craniectomy can be a primary procedure (combined with evacuation of a haematoma) or a secondary procedure (to decompress the brain). In a population of patients with TBI in the ICU, who were recruited to CENTER-TBI and the harmonised Australian OzENTER study, decompressive craniectomy was performed in 320 (13.7%) of 2336 patients; craniectomy was performed as a primary procedure in 81% of these 320 patients.<sup>177</sup> Previous trials have investigated the effectiveness of decompressive craniectomy as a secondary procedure and suggest that it provides no benefit when used relatively early,<sup>178</sup> but that it might improve survival with acceptable functional outcome as a rescue therapy for refractory intracranial hypertension.<sup>179,180</sup> Until recently, no evidence was available to support the use of decompressive craniectomy as a primary procedure. RESCUE-ASDH, a multicentre randomised trial comparing craniotomy versus decompressive craniectomy for patients undergoing evacuation of a traumatic acute subdural haematoma has completed recruitment of 462 individuals, and is undergoing analysis (Kolias A, personal communication). Results are awaited and will hopefully provide support or refute the efficacy of primary decompressive craniectomy. In LMICs across many parts of the world, decompressive craniectomy is performed even more frequently than in HICs. In the China CENTER registry, decompressive craniectomy was performed also mostly as a primary procedure in 1354 (48%) of 2804 patients with severe TBI, compared with 222 (20.8%) of 1068 with severe TBI in CENTER-TBI.<sup>37</sup> In the BEST TRIP trial, conducted in Bolivia and Ecuador, decompressive craniectomy was performed in 93 (29%) of 323 patients,<sup>131</sup> and similar rates (28%) were seen in all groups of the intracranial pressure/CREVICE study (Chesnut R, personal communication). In LMICs, use of decompressive craniectomy appears to be often determined by resource limitations, including ICU beds being unavailable. This perceived third indication for decompression is completely unstudied, and indications for and results from such common practice are unknown.

#### Post-acute care

Long-term outcome studies completed over the past 10 years make clear that TBI symptoms can persist or

worsen over time, and more than 50% of patients with moderate to severe TBI receiving in-hospital rehabilitation have a decline in daily function or die within 5 years of injury, suggesting that TBI should be viewed as a chronic disease. Between 1 and 5 years after injury, decline occurs as frequently as improvement. Despite these data, multidisciplinary rehabilitation is underused after TBI, with many individuals reporting unmet rehabilitation needs and long-term service use below the prevalence of morbidity.<sup>94,181</sup> A review by the National Academies of Sciences, Engineering, and Medicine<sup>182</sup> published in 2022 concluded that TBI care in the USA frequently fails to meet the needs of individuals, families, and communities affected by this condition, despite the substantial burden it poses. Similar findings were reported by CENTER-TBI (see section 2), which found large inconsistencies in provision of rehabilitation services between centres, regions, and countries. Although existing evidence suggests that rehabilitation is more effective when started acutely and offered continuously,<sup>183</sup> only approximately a third of patients reporting cognitive and psychological impairments received interventions in these domains.<sup>94,184</sup> Significant negative predictors for receipt of rehabilitation were pre-injury unemployment (OR 0.80, 95% CI 0.67–0.95), living in central or eastern Europe (0.42, 0.20–0.87), admission to a hospital ward (0.47, 0.37–0.59; reference: admission to ICU), or direct discharge from the emergency room (0.24,<sup>94,184</sup> 0.17–0.33). These and other data<sup>185,186</sup> suggest that rehabilitation referral is not only driven by clinical needs, but also by demographic, social, and organisational factors, raising issues regarding equitable access to appropriate rehabilitation care. In the USA, provision of follow-up care appears to be affected by social factors such as insurance coverage and race.<sup>187</sup>

There is also a huge need to address long-term problems such as fatigue and sleep disturbance; cognitive impairments affecting memory, attention, and executive function; behavioural problems; and anxiety and depression; and provide services to facilitate return to work, study, and driving, all of which are significantly affected for at least 5–10 years post-injury. There is a need for the development, evaluation, and implementation of treatment protocols for these problems that are adapted for TBI.<sup>188</sup> International guidelines for the treatment of cognitive and communication impairments following TBI, including post-treatment amnesia, originally published by the INCOG group in 2014, have been updated in 2022, but there is a need for many more large-scale controlled studies to validate interventions.<sup>189</sup> Taken together, there is an extensive and pressing need for improving post-acute care in the long-term perspective after TBI.

#### Understanding TBI outcome in the ICU population

The overall 6-month mortality for ICU admissions in CENTER-TBI was 21%, the rate of unfavourable outcome

43%, and only 16% made a complete recovery (Glasgow Outcome Scale-Extended [GOSE] 8).<sup>121</sup> Between-centre variations in 6-month outcome (median odds ratio [MOR] 1.2) were substantially less compared with previous studies (MOR 3.3).<sup>190</sup> This finding signals that treatment standards have probably improved over time, and that high-quality care might be more important than specific interventions.

Interpretation of mortality rates might be confounded by current policies related to withdrawal of life-sustaining measures, a topic not addressed in the 2017 Commission. Yet, most deaths (54%–70%) in patients with very severe TBI result from such decisions.<sup>191,192</sup> CENTER-TBI reported that withdrawal of life-sustaining measures occurred in 86% of patients who died after TBI, ranging from no deaths in some centres to almost 100% in others,<sup>193</sup> mirroring previous data from Canada (rates of 45%–87%).<sup>191</sup> Although withdrawal of life-sustaining measures is appropriate in many situations, there has been concern that such decisions<sup>194,195</sup> are not always equitable,<sup>196</sup> and can lead to a self-fulfilling prophecy of death,<sup>197</sup> a particular concern when the withdrawal is performed too early. In CENTER-TBI, withdrawal of life-sustaining measures was instituted within 72 h of the TBI in almost half the patients who died after decisions made about withdrawal of life-sustaining measures. These decisions were primarily made in patients with severe TBI affecting brainstem reflexes. However, some patients with very severe brain injuries can achieve favourable outcomes over time. TRACK-TBI followed 271 patients with severe TBI and found that 52% were able to function independently at home by 12 months, with 19% reporting no disability.<sup>198</sup> 78% of patients in a vegetative state at 2 weeks recovered consciousness by 12 months, and 25% regained orientation. These figures from TRACK-TBI are consistent with past data from the TBI Models Systems in the USA, where 68% of those with a GCS of 3 in the emergency department regained consciousness during in-patient rehabilitation, and 21% of survivors were able to live independently following discharge.<sup>199</sup> Acute severe impairment does therefore not universally imply poor functional outcome. Although delaying withdrawal of life-sustaining measures could lead to prolonged suffering and impose unnecessary burden on patients, caregivers, and clinicians, instituting it too early can sometimes result in the death of patients who might otherwise have eventually achieved an outcome that was acceptable<sup>200</sup> for their families. Clinicians should be aware of uncertainties surrounding prognosis<sup>201</sup> and avoid premature decisions on withdrawal of life-sustaining measures when prognosis is uncertain.<sup>202,203</sup>

### Main messages and recommendations

#### Main messages

(1) Older patients often have comorbidities, but very little evidence exists to inform their treatment.

(2) Guidelines for the management of TBI are best thought of as frameworks for care. To remain current, guidelines must be continuously updated to reflect evolving evidence.

(3) In low-resource settings, in the absence of facilities for monitoring intracranial pressure, a reasonably good outcome from severe TBI can be obtained using institutional protocols that include imaging and clinical examinations.

(4) Substantial between-centre differences exist for the acute surgical management of patients with traumatic intracranial haematoma.

(5) Access to rehabilitation services is inconsistent and there is an absence of protocols for treating long-term problems.

(6) Withdrawal of life-sustaining measures is common in patients who die after TBI, but—if undertaken prematurely—can lead to self-fulfilling prophecies and increase the risk for unnecessary deaths.

#### Recommendations

(1) Stimulate a research focus on older patients with TBI.

(2) Guidelines should be transformed into a living document that will require long-term support by an authoritative organisation or funding body.

(3) In low-resource settings, funding is needed for research aimed at improving the outcomes from severe TBI, where it is most common, but also most under-resourced.

(4) Meta-analyses across studies are required to provide stronger evidence to inform which patients are most likely to benefit from early surgery.

(5) Access to rehabilitation services needs to be improved, and evidence-based treatments for long-term problems—including fatigue, and cognitive and behavioural changes—developed.

(6) Clinicians should be aware of uncertainties surrounding prognosis and avoid premature decisions on withdrawing life-sustaining measures (eg, within 72 h after injury) when prognosis is uncertain.

### Section 4: Characterisation of TBI—the path to precision medicine

The 2017 Commission on TBI made the case for precision medicine in the ICU setting—ie, targeting a specific treatment to a subset of patients, with a common biological basis of disease, who are most likely to benefit from these approaches. The Commission highlighted the fact that interventions that might be beneficial in some patients can also result in harms in others, and there has been limited success in matching therapies to patients. We also identified the clinical heterogeneity and complexity of TBI as key barriers that limited our ability to target patients for existing therapies, or to effectively show the benefit of new therapies that might be efficacious only in a subset of patients. We described how this clinical heterogeneity was underpinned by widely

varied pathophysiological processes, which are present to variable extents in different patients, at different stages in the same patient, and in different parts of the brain in a single patient at a given time. Response to therapy, disease course, and outcome can also be substantially affected by variations in intrinsic host biology, comorbidities, and pre-TBI therapies. We recognised that better tools were needed to characterise the severity and type of acute TBI than those provided by available clinical classification systems, such as the GCS, or CT classification schemes in isolation.

In this section, we report on advances in improved characterisation, achieved by incorporation of clinical variables beyond the GCS, as well as advanced neuroimaging, multimodality monitoring, blood biomarkers, and genomics. These advances, in some instances, have identified key subsets of patients who would not have been recognised using conventional tools (eg, detection of severe diffuse axonal injury by MRI which would have been missed by CT). In other instances, such as with the use of multimodality physiological monitoring, we are closer to achieving individualised approaches by titrating the choice and intensity of (often hazardous) treatments, not just between patients, but over time in individual patients, while taking account of pre-injury comorbidities, extracranial injuries, and crucially, the choices expressed by patients and families about acceptable outcomes.

#### Clinical characterisation and classification

The GCS remains the main instrument for classifying the severity of TBI as mild (GCS 13–15), moderate (GCS 9–12), or severe (GCS  $\leq$ 8). However, it does not capture the specific pathoanatomical features or pathophysiology in individual patients, and is confounded by factors such as drug and alcohol use, medications, and tracheal intubation.<sup>20,204</sup> The duration of post-traumatic amnesia is widely used as an indicator of injury severity and reported to be a strong predictor of outcome in survivors of TBI.<sup>205,206</sup> However, accurate determination of the duration of post-traumatic amnesia is not possible early after injury in patients who are still in post-traumatic amnesia, and post-traumatic amnesia is therefore more relevant to rehabilitation settings. Additional clinical variables (see also section 2) are important modulators of TBI course and outcome. Major extracranial injury, often associated with high-energy trauma, is known to influence the course, complications, management, and outcome of TBI.<sup>207</sup> However, a recent analysis from CENTER-TBI published in 2021<sup>19</sup> has also drawn attention to the risks of substantial intracranial injury even from low-energy mechanisms, particularly in older patients, which might be underestimated by the initial GCS and, in the context of a comorbid cohort, result in poor outcomes.<sup>19</sup> For mild TBI, neck pain, early post-concussional symptoms, and mental health can increase the risk of incomplete recovery.<sup>208,209</sup>

There is also a need to identify specific patient groups that might benefit from individual treatments.<sup>210–212</sup> CENTER-TBI and TRACK-TBI applied unsupervised clustering methods to identify such groups or disease endotypes (ie, a subtype of a health condition that is defined by a distinct functional or pathobiological mechanism, first described in the context of asthma). CENTER-TBI identified GCS, extracranial injuries, and mechanism of injury as important distinguishing factors for subgroups of patients with TBI across all injury severities.<sup>213</sup> Clustering of biomarkers revealed two subgroups of patients with TBI who showed differences in injury severity.<sup>214</sup> In the subgroup of patients admitted to the ICU, six early endotypes could be distinguished by GCS and degree of metabolic derangement, primarily described by pH, lactate, SpO<sub>2</sub>, pCO<sub>2</sub>, blood glucose, creatinine, and body temperature.<sup>215</sup> A US study<sup>216</sup> identified potential endotypes using mainly haematological and coagulation factors, such as platelet count, haemoglobin, haematocrit, prothrombin time, international normalised ratio, and glucose. Among patients with mild TBI, TRACK-TBI identified five subgroups distinguished by demographic factors, CT characteristics, blood pressure, substance use, fall injuries, administration of intravenous fluids, and history of neurological and psychiatric disease.<sup>211,217</sup> These advanced analysis tools suggest that there are clinical subgroups with potential clinical and therapeutic relevance and that require further investigation. An early demonstration of this approach comes from a secondary analysis of the PAMPer randomised trial of pre-hospital thawed plasma in high risk trauma patients, which showed that the overall benefit demonstrated in the trial was confined to patients who had TBI, and was specifically seen in an endotypic subgroup characterised by multiomic analysis.<sup>212</sup>

#### Neuroimaging

Results of CT and MRI inform treatment decisions and have prognostic significance. Imaging common data elements, originally developed by a multidisciplinary task force of the US National Institutes of Health-National Institute of Neurological Disorders and Stroke (NIH-NINDS), has now been well validated (appendix p 9),<sup>218–220</sup> and improve reporting consistency compared with data extraction from local radiology reports.<sup>218</sup> Basic, or core, common data elements appear to have the most prognostic value,<sup>221</sup> whereas supplementary or advanced and emerging imaging common data elements have less consistent relevance to outcome. Common data elements also permit the creation of large neuroimaging databases, which facilitate large-scale meta-analyses.<sup>217,222</sup> The frequency of co-occurrences of CT abnormalities, assessed according to the common data elements, was explored in the CENTER-TBI (n=4087) and TRACK-TBI (n=2670) studies (figure 7). CT abnormalities were present in CENTER-TBI in 1345 (49 %) of 2744 patients with mild

TBI and in 1112 (93%) of 1193 with moderate to severe TBI, and in TRACK-TBI in 789 (38%) of 2104 patients with mild TBI and in 470 (90%) of 520 with moderate to severe TBI.

Various CT classification schemes exist (appendix p 12) and have been evaluated in terms of their prognostic value.<sup>223</sup> The Helsinki CT score and the Stockholm CT score seem to be more accurate in predicting outcome (AUC 0.75–0.80), but are more complex to score than the Rotterdam CT score and the Marshall CT classification. Although developed in adult TBI cohorts, these classification systems also perform well in evaluating paediatric TBI.<sup>224–226</sup> A role is emerging for quantitative CT in diagnosing and following up TBI, an application facilitated by artificial-intelligence-based automated image interpretation.<sup>227–229</sup> The use of new approaches to analyse existing data is as important as the availability of new imaging modalities. For example, one study<sup>217</sup> showed three distinct CT-based clusters in mild TBI: presence of contusion and subarachnoid haemorrhage or subdural haematoma, or both; intraventricular or petechial haemorrhage, or both; and epidural haematoma. This result was largely reproduced in CENTER-TBI and related to outcome at 1-year post-TBI.

Major advances have resulted from the application of MRI to TBI, with a role for identifying injuries that are not visible on CT imaging. Both CENTER-TBI and TRACK-TBI reported structural traumatic abnormalities on MRI, performed at 2–3 weeks after injury, in approximately 30% of patients with mild TBI who had a normal CT on presentation.<sup>20,230</sup> Advanced MRI techniques, such as diffusion tensor imaging and susceptibility weighted imaging (both of which are now routinely available on clinical scanners) are more sensitive at detecting superficial contusions, traumatic axonal injury,<sup>231</sup> and traumatic vascular injury<sup>232</sup>—additionally, traumatic axonal injury and traumatic vascular injury are now recognised as distinct entities with pathophysiological and outcome impact. Quantitative assessments of MRI, such as volumetric analyses,<sup>233,234</sup> reductions in fractional anisotropy, and increases in mean diffusivity can identify injury not detectable by visual inspection of MR images. Such injuries can be particularly relevant in mild TBI, because fractional anisotropy and diffusivity abnormalities identify patients who are likely to have persistent post-concussional symptoms and long-term disability.<sup>235–237</sup> Crucially, the timing of imaging is important, and imaging within 3 days of a TBI might be more sensitive than imaging in the second week.<sup>236</sup> Quantitative diffusion tensor imaging has strong predictive value in people more severe TBI, in whom diffuse axonal injury might represent the substrate for disorders of consciousness.<sup>238</sup> Functional MRI<sup>239</sup> and MR spectroscopy<sup>240</sup> might add additional sensitivity, but these are currently still making the transition from research techniques to clinical tools. In the chronic phase of TBI, there is increasing interest in using MRI to detect

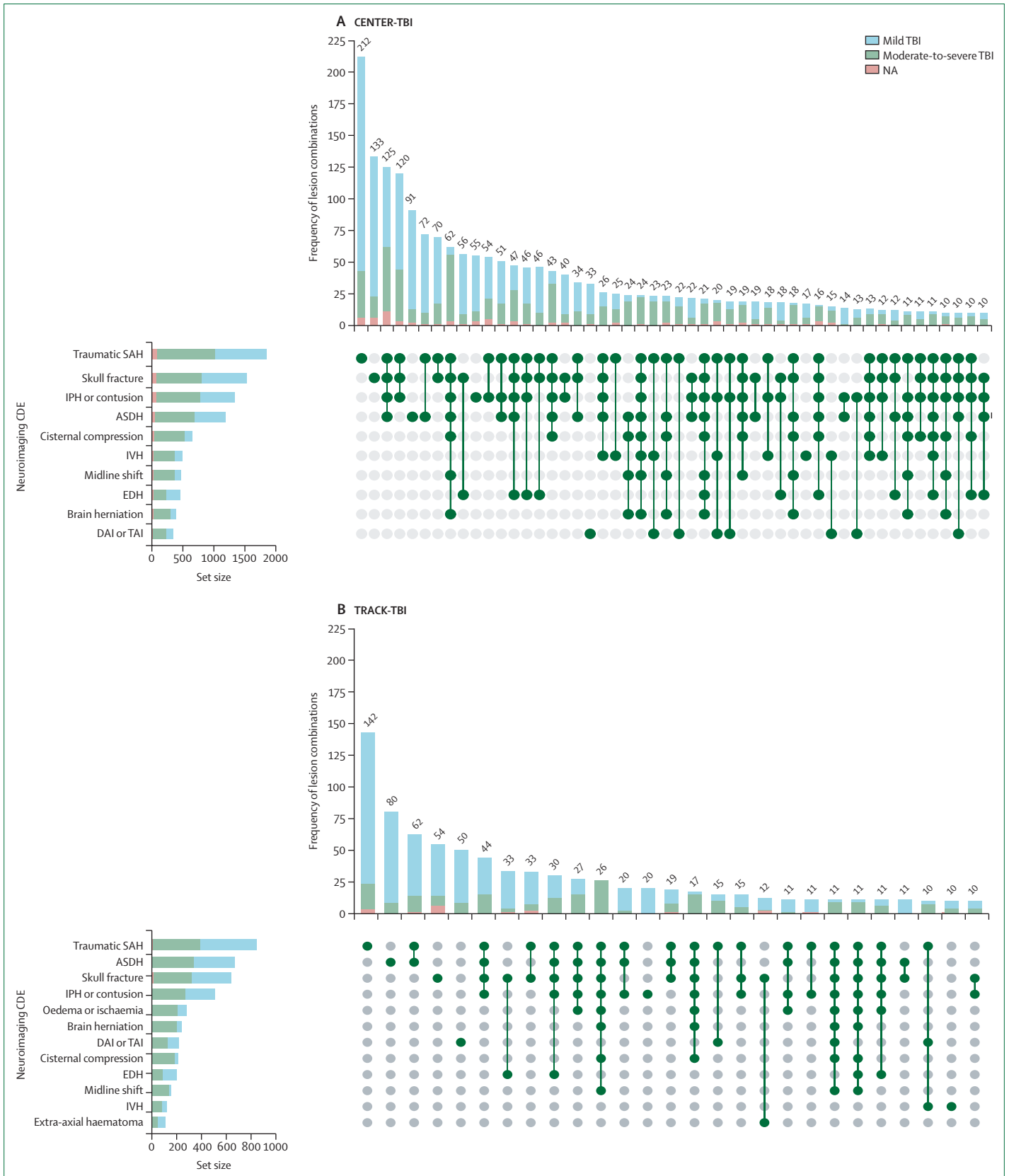
global and regional loss of brain volume, which could represent accelerated brain ageing.<sup>241–243</sup> Such late volume loss is related to, and can be predicted by, brain injury biomarkers up to a decade after TBI.<sup>243,244</sup>

## Body fluid biomarkers

### Protein biomarkers

Among the technologies to improve phenotyping of TBI, blood biomarkers are the closest to being implemented into routine clinical care. Building on past results that primarily focused on S100B, a quartet of new brain injury biomarkers (GFAP, NfL, UCH-L1, and tau) have been evaluated in several studies of TBI.<sup>83</sup> Biomarkers perform well in predicting CT and MRI positivity, outperforming clinical decision rules (see section 2). The combination of GFAP and UCH-L1 has received FDA clearance in the context of aiding in the identification of CT-detectable brain lesions within 12 h of mild TBI (initial GCS 13–15).<sup>87,245</sup> GFAP on its own has emerged as an excellent brain injury biomarker for prediction of CT positivity<sup>246,247</sup> and MRI positivity in CT-negative individuals.<sup>230</sup> However, a direct comparison of GFAP against S100B is confounded by the more rapid kinetics of S100B and by the fact that samples in some of the larger studies were variably analysed in plasma or serum, and sometimes obtained relatively late—possibly outside the timeframe that would be relevant to selecting patients for CT. Initial expectations that patterns of biomarker elevation might differentiate focal from diffuse injury<sup>248,249</sup> have not been confirmed, and some data suggest that biomarkers correlate more with the burden of injury than with different pathoanatomical types of TBI.<sup>214</sup> In addition to diagnosing CT positivity, biomarkers have been shown to prognosticate late outcomes in large cohorts of patients (see also section 6).<sup>244,247,250</sup> CENTER-TBI reported the highest incremental value for UCH-L1, S100B, NfL, and total tau for predicting mortality or unfavourable outcome.<sup>251</sup> When compared with more severe TBI, biomarkers were less predictive of outcomes in mild TBI and of incomplete recovery overall. TRACK-TBI likewise reported lower incremental value of GFAP and UCH-L1 for predicting incomplete recovery, when compared with the prediction of mortality or unfavourable outcome.<sup>252</sup> The use of several different platforms means that substantial cross-platform calibration and regulatory approval will be required before quantitative thresholds can come into routine clinical use.<sup>253,254</sup> However, when applied to outcome prognostication, the relative merits of discrete thresholds versus a continuous scale of biomarker concentrations remains an open question.

Other circulating biomarkers (such as amyloid beta species, phospho-tau, heart fatty acid binding protein, and IL-10)<sup>255–257</sup> are also in the process of investigation as prognostic biomarkers. Integrated characterisation of the innate and adaptive host response might be able to separate subsets of patients with different inflammatory





endotypes,<sup>212,258</sup> or to detect the presence of autoantibodies against brain and extracranial antigens,<sup>259</sup> leading to the rational selection of patients for anti-inflammatory and immunomodulatory therapies. Subacute and chronic trends of biomarker concentrations are increasingly being investigated as markers of disease evolution and chronicity in TBI. S100B has been used by some centres to detect disease evolution and second insults in patients with more severe TBI,<sup>260</sup> and emerging evidence shows that similar insights might be provided by secondary rises in GFAP and other biomarkers, both in mild TBI<sup>261</sup> and in more severe injury.<sup>260</sup> However, the biomarkers of interest in TBI have very different apparent half-lives (ranging from hours for S100B to weeks for NfL) and expected times to peak concentrations following a single insult, and it is important that any assessment of their performance accounts for these factors.<sup>260,261</sup> Beyond the acute phase, NfL values correlate with (and predict) accelerated brain volume loss, functional trajectories, and cognitive performance for months to years after TBI.<sup>243,244</sup>

#### Metabolomics and microRNAs

TBI is characterised by a mismatch between the requirement and production of metabolic energy in the brain—referred to as an energy crisis—and by metabolic dysregulation, both of which are reflected in mass spectrometry-based analysis of serum. Such analyses reveal varied and complex alterations in the metabolome, including in the lipidome (ie, the characterisation of molecular lipids) and the glycome (ie, the characterisation of glycan structures). Specific metabolic signatures have been shown to be associated with a diagnosis of TBI, imaging findings on CT<sup>262,263</sup> and MRI,<sup>264</sup> injury severity,<sup>262,265</sup> and patient outcomes.<sup>262,265–267</sup> These findings

extend across the severity spectrum of TBI, including patients with mild TBI<sup>268</sup> and sport-related concussion.<sup>269</sup> Deciphering the striking diversity of the metabolome is an important goal of precision medicine in TBI. Future large-scale prospective studies with broad analytical coverage are warranted. There is also emerging interest in the measurement in blood and saliva of microRNAs, the amounts of which are rapidly altered in the brain in experimental TBI.<sup>270–272</sup>

#### Genomics

A range of methods can be used to obtain evidence on the effect of the patient's genetics on TBI outcome. Rare but highly penetrant variants in genes such as *CACNA1A* cause life-threatening brain swelling in response to a trivial head injury.<sup>273</sup> Multiple candidate gene-association studies<sup>274,275</sup> have investigated whether more common variants in different genes might influence TBI outcomes. The choice of genetic variants in these studies has been driven by a-priori hypotheses regarding TBI pathophysiology. However, candidate gene studies have recognised shortcomings,<sup>276</sup> including low genetic coverage, selection bias, cryptic population stratification, high false-positive rates, publication bias, and poor replication—many of which are overcome by genome-wide association studies. One large genome-wide association study of TBI outcome in around 5000 patients<sup>277</sup> estimated that 26% of outcome variance in TBI might be heritable, well within the range seen in common neurological diseases with recognised genetic associations. Although no genome-wide association study hits reached genome-wide significance, several achieved statistical thresholds that merit further investigation. However, with one exception, this study failed to replicate any hits from past candidate gene studies, including the previously reported association of poor outcomes with *APOE*  $\epsilon 4$  carriage.<sup>274</sup> The one successful replication was for variations in *MBL2*, the gene for mannose-binding lectin, which has previously been associated with significant variations in the host inflammatory response and TBI outcome.<sup>278</sup>

The failure to replicate other past candidate gene hits might be because previous reports were false-positives, but at least some of these past studies examined outcomes other than GOSE—such as cognition and psychological health, which require further investigation. However, perhaps the most important role of candidate gene studies is the understanding of disease biology and identifying enriched populations of patients for trials and treatment with novel or repurposed agents.<sup>279,280</sup> For example, one study<sup>280</sup> showed that variation in two genes, *ABCC8* (*SUR1*) and *TRPM4*, contributed to progression of intracerebral haemorrhage after severe TBI, and the addition of genetic information significantly improved prediction of haemorrhage progression when compared with baseline models. Such results are important because they reflect biology in experimental models and

#### Figure 7: UpSet plot of pathoanatomic common data elements reported on early CT, by traumatic brain injury severity

(A) Data are from the CENTER-TBI study. (B) Data are from the TRACK-TBI study. Of a potential of 17 imaging CDEs, 14 were included in the analysis. Ventricular compression, mixed density subdural haematoma, and penetrating injuries were excluded as these were either not reported or not included in TRACK-TBI. The vertical bar graphs depict the absolute frequencies of lesion combinations. Combinations with fewer than ten occurrences and CDEs that appeared exclusively in such infrequent combinations are not shown. The horizontal bar graphs depict the absolute frequency of each CDE in the cohort. Traumatic subarachnoid haemorrhage, skull fracture, intraparenchymal haemorrhage (haematoma or contusion), and acute subdural haematoma were the most frequently occurring abnormalities in both studies. Although there are some differences in co-occurrence of abnormalities, five of the top six combinations in each study are consistent. Differences in co-occurrence were probably affected by differences in casemix. However, cisternal compression was less frequently scored in TRACK-TBI and oedema or ischaemia were more frequently scored than in CENTER-TBI, which might reflect differences in reporting. In both studies, co-occurrence of abnormalities was dependent on the severity of the initial injury. CDE=common data elements. TBI=traumatic brain injury. NA=not applicable. SAH=subarachnoid haemorrhage. IPH=intraparenchymal haemorrhage. ASDH=acute subdural haematoma. IVH=intraventricular haemorrhage. EDH=epidural haematoma. DAI=diffuse axonal injury. TAI=traumatic axonal injury.

clinical studies, and can provide a basis for mechanistic enrichment in developing trials of SUR-1 antagonists.

### Physiological monitoring

Substantial advances have been made towards precision medicine approaches based on physiological monitoring. In patients with more severe TBI, tolerance of intracranial pressure dose (see section 3) is reduced by impaired autoregulation, which is more common with diffuse intracranial injury.<sup>281–284</sup> Autoregulatory status can be assessed by evaluating intracranial pressure responses to induced or spontaneous variations in arterial blood pressure (appendix p 14). Variations in autoregulatory status are commonly quantified by the pressure reactivity index (ie, a correlation coefficient between intracranial pressure and cerebral perfusion pressure), which shows strong independent associations with 6-month outcomes.<sup>137,281,285–288</sup> The parabolic relationship between cerebral perfusion pressure and the pressure reactivity index allows the derivation of a personalised optimal cerebral perfusion pressure and clinically actionable thresholds.<sup>289–295</sup> The COGITATE phase 2 trial<sup>295</sup> explored the feasibility and safety of targeting a personalised optimal cerebral perfusion pressure, and phase 3 trials are now in planning.

Intracranial pressure monitoring is increasingly being supplemented by PbtO<sub>2</sub> monitoring<sup>157</sup> and (less frequently) by microdialysis.<sup>141</sup> Comprehensive metabolic profiling, along with assessment of autoregulation, provides a more nuanced picture of cerebrovascular physiology in TBI, particularly when intracranial pressure thresholds are close to treatment thresholds. Abnormal brain biochemistry can prompt aggressive treatment of intracranial pressure even when intracranial pressure is not markedly elevated, or in other cases can allow clinicians to withhold such treatment escalation if biochemistry is not deranged. The latter approach is particularly important when considering de-escalation of therapy, or in withholding interventions when patients are particularly vulnerable to their side effects (eg, vasopressors for cerebral perfusion pressure augmentation in patients with pre-existing coronary artery disease or injury). Commonly accepted thresholds for different monitoring modalities (appendix p 18) can be used to inform management strategies.<sup>129</sup>

### Data integration for individualised management

The preceding parts of this section describe the rich range of data that are available for better characterisation of TBI. Newer blood biomarkers, such as GFAP, can help to refine decisions about which patients with mild TBI receive a CT, or require an MRI if CT is normal, and the combination of biomarkers, quantitative CT, and MRI can help to identify patients who are at risk of persistent symptoms and require more frequent follow up. In more severe TBI, discordantly high biomarker concentrations in the presence of a CT with little or no abnormality might

change patient management pathways—leading to ICU admission, and suggesting greater care with physiological stability, or consideration for early MRI to detect CT-occult diffuse axonal injury and informing discussion with families about prognosis and therapy choices. Identification of patients at risk of refractory intracranial hypertension at an early stage would be desirable, both to calibrate expectations of progress and to select patients for trials of novel therapies to lower intracranial pressure.<sup>296,297</sup> However, current clinical, imaging, and monitoring variables explain less than 10% of the variation in the need for second-tier intracranial pressure therapies.<sup>152</sup>

Much work is still required to identify group differences in underlying pathophysiology or disease mechanisms. Advanced analyses of the inflammatory host response might identify patients with other inflammatory and host responses,<sup>212,258</sup> and facilitate creation of enriched populations or endotypes for anti-inflammatory therapies.<sup>212,298–300</sup> Genetic variations that associate with disease course or outcome could have prognostic significance, and might identify key pathobiological pathways as therapeutic targets for novel drug development. However, such endotypic subgroups will necessarily be of a smaller size than the overall cohort, and large sample sizes and well characterised phenotypes are needed to draw statistically robust inferences, and to ensure that rare (but still biologically relevant) genetic variations are not missed. Collection of such large datasets would be facilitated if funders required that all clinical research studies—both observational and interventional—should bank blood for genomic analysis alongside collection of common data element-based data at presentation and outcome.

As highlighted in the 2017 Commission, identification of meaningful subgroups (ie, endotypes) for targeting therapeutic approaches warrants the application of machine-learning techniques and artificial intelligence, given the size and complexity of available databases. Some progress in this direction has been made, but most studies to date have been exploratory<sup>301</sup> or had a specific focus on prognostic modelling.<sup>302</sup> A substantial stimulus is needed to implement neuroinformatics to support clinical decision-making in the field of TBI.

### Main messages and recommendations

#### Main messages

- (1) Substantial advances have been made towards individualised management, with improved characterisation and understanding of disease processes in TBI, but we are not yet sufficiently able to match acute care therapies to subgroups of patients.
- (2) Identification of meaningful subgroups (endotypes) for targeting therapeutic approaches warrants the application of machine-learning techniques and artificial intelligence.
- (3) A normal CT scan on presentation after TBI does not mean the absence of structural traumatic abnormalities.

MRI and blood biomarker measurement can have a major role for identifying injuries that are not visible on CT imaging.

(4) Current intracranial pressure thresholds for treatment neglect the harmful effects of more modest and prolonged elevation of intracranial pressure (intracranial pressure dose) and the modulation of such harm by variations in cerebrovascular physiology and brain metabolism.

(5) Approximately 26% of outcome variance in TBI might be heritable, in line with the range seen in common neurological diseases with recognised genetic associations.

#### Recommendations

(1) Research needs to aim to identify subgroups of patients who would be most likely to benefit from specific interventions.

(2) A substantial stimulus is needed to implement neuro-informatics to support clinical decision-making in the field of TBI.

(3) Lawyers involved in litigation procedures should be aware that absence of CT abnormalities does not mean absence of TBI. Research should be stimulated to determine which patients with a normal CT scan would benefit from MRI.

(4) Consider initiation of intracranial pressure therapy for intracranial pressure at lower thresholds, and autoregulatory status and brain chemistry as ancillary guides to titrate therapy.

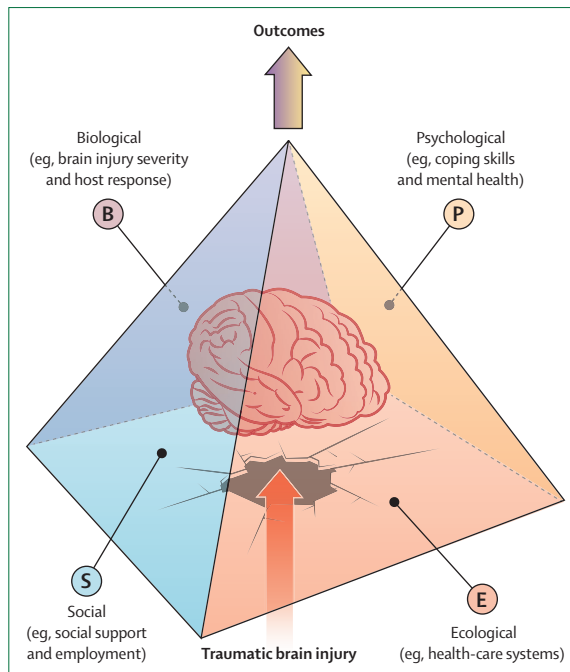
(5) Research should be stimulated to better understand the effects of genetic variation on disease biology and how this variation might allow identification of enriched populations of patients for trials and treatment with novel or repurposed agents. Establishment of the required large datasets could be stimulated if funders would encourage all clinical research studies to bank blood for genomic analysis alongside common data element-based data collection at presentation and outcome.

### Section 5: Assessment of TBI outcome

In the 2017 Commission on TBI in 2017, we highlighted how trauma to the brain affects multiple outcome domains and suggested that multidimensional constructs are needed to better quantify the consequences of TBI. Since then, various studies, including CENTER-TBI and TRACK-TBI, have produced a body of empirical data to inform the development of multidimensional approaches. In this section, we present these data with an additional focus on the relevance of post-traumatic stress disorder (PTSD) in civilian TBI, on outcome after mild TBI, on sex and gender differences in outcome, and on the relation of TBI to late dementia.

#### A holistic approach to outcome after TBI

There are inherent challenges to studying the associations of a remote exposure (ie, TBI) with outcomes of interest, particularly as the interval between exposure and outcome



**Figure 8: Outcomes after a traumatic brain injury: the bio-psycho-socio-ecological model**

The pyramid represents how BPSE factors capture individual differences that can substantially affect the outcome trajectory after a traumatic brain injury, in some cases leading to a better outcome and in others leading to a worse than expected outcome. B=biological (eg, brain injury severity, host response, and genetics); P=psychological (eg, coping skills and mental health); S=social (eg, social support and employment); and E=ecological (eg, health-care systems). BPSE=bio-psycho-socio-ecological.

increases. Effects of the TBI are overlaid upon personal characteristics, such as age, preinjury mental health, coping skills, and the influence of other life course events, such as litigation and access to health care. Disentangling these relationships requires the study of large and heterogeneous cohorts.<sup>303</sup> Interdisciplinary collaboration, including neurology, psychology, psychiatry, and sociology is needed to improve the understanding of the chronic consequences of TBI.<sup>304</sup> This process would be facilitated by the use of modern psychometric methods<sup>305</sup> (eg, to define endpoints), advanced statistical approaches (such as latent profile analysis to identify neurobehavioural phenotypes),<sup>306</sup> and life-course epidemiological methods that consider TBI in the context of other environmental and genetic exposures. This approach reflects the increasing recognition by clinicians and policy makers of the relevance of a multifactorial bio-psycho-socio-ecological model to TBI, as enunciated in a report of the National Academies of Science, Engineering and Medicine in the USA<sup>182</sup> (figure 8).

#### Standardisation of outcome assessments

The introduction and widespread adoption of common data elements (see also Section 7) for assessing outcomes<sup>307</sup> has enabled a crucial infrastructure for TBI

For more on the NIH-NINDS common data elements initiative see <https://www.commondataelements.ninds.nih.gov/Traumatic%20Brain%20Injury#pane-162>

outcome research. The common data elements initiative, coordinated by NIH-NINDS, aims to standardise data collection and coding by recommending the most relevant outcome instruments for use in TBI. However, challenges have become apparent following their implementation into research. Differing conventions across TBI subpopulations (eg, paediatric vs adult or sport-related vs non-sport-related TBI) have led to distinct common data elements even for similar outcomes. Impediments to global adoption include an absence of validated translations of instruments originally developed in English and of cross-cultural norms, and copyright and proprietary issues. Outcome instruments, designated as core common data elements (ie, those recommended across studies) should be freely available to facilitate widespread use, including in settings with few resources, but some of these instruments are proprietary. Linguistic validation and psychometric evaluation of 11 outcome instruments in up to 20 languages was performed in the context of CENTER-TBI.<sup>308</sup> Psychometric and validity analyses showed satisfactory to excellent reliability of all instruments, and showed that correlations between measures were consistent across languages.<sup>309</sup> These translations provide a solid basis for multinational TBI research and practice, and are available on the CENTER-TBI website.

Particular subgroups will require specific assessment approaches—eg, most outcomes in the common data elements cannot be completed for patients with disorders of consciousness. In this population of patients, the Coma Recovery Scale–Revised has been recommended by international guidelines.<sup>310–312</sup> The incorporation of common data elements into paediatric TBI research requires unique considerations. Children have individual differences in abilities and capacities to comprehend and respond to patient-reported questionnaires, and thus parents or caregivers will often act as an interlocutor. During childhood, attention, language, executive skills, and psycho-social functioning rapidly change. Age-specific norms need to be established in TBI and non-TBI control groups with and without pre-existing comorbid conditions (eg, attention-deficit hyperactivity disorder, anxiety, and depression). Future directions for the common data element initiative on outcomes should focus on the frequency and effects of impairments to determine which elements have practical utility, on decreasing redundancy among measures, and on identifying those elements that are most responsive in specific TBI subgroups (see also section 7).

#### *Standardisation and imputation of outcome instruments*

Standardisation of the administration and scoring of outcome common data elements is more complex than might appear. Many measures exist in more than one version or have variations in administration. Studies thus need to develop a manual of operations and implement training for investigators to ensure

consistency; methods should be shared to promote transparency and reproducibility.

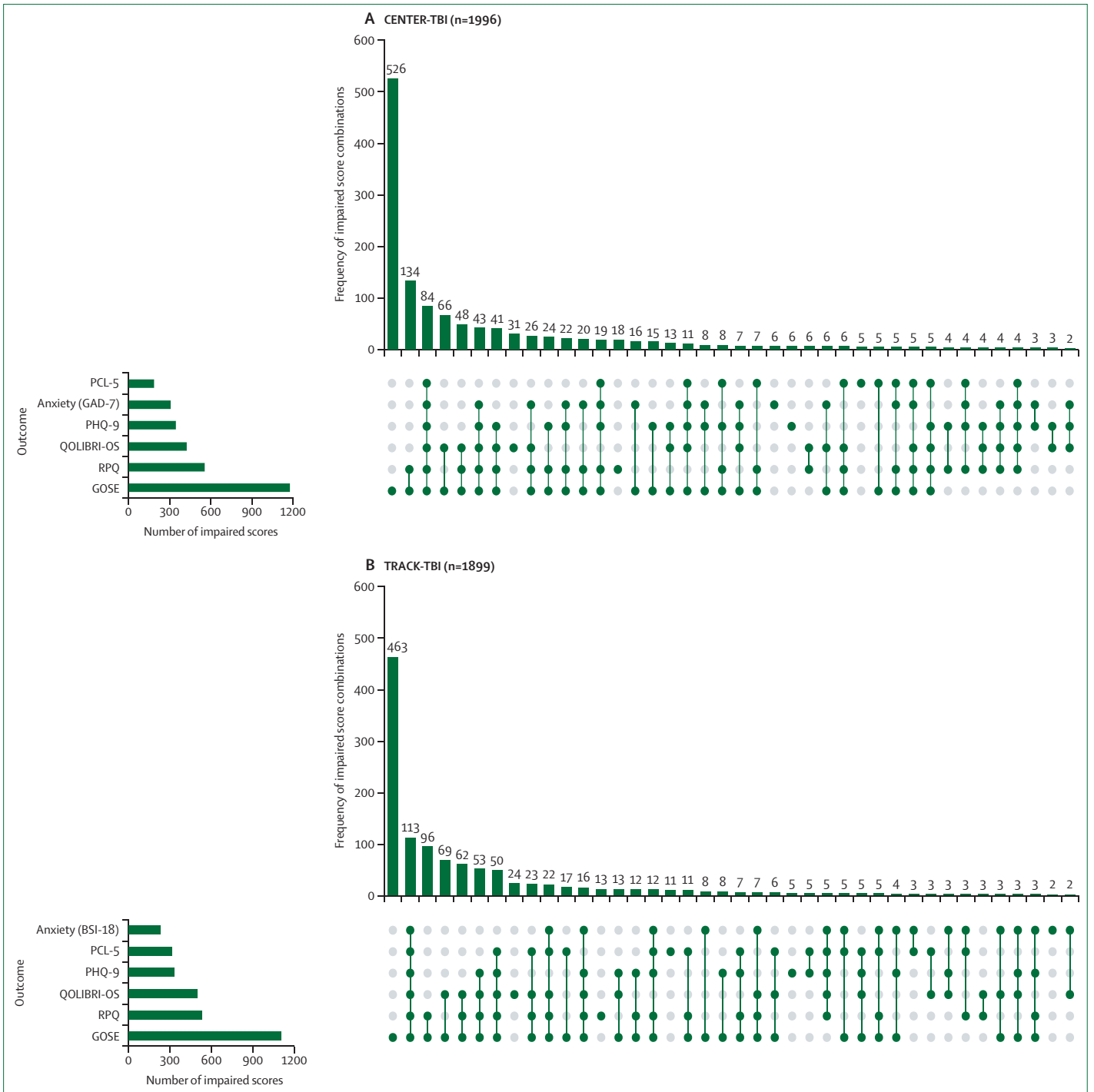
Differences in scoring the GOSE have been found between studies in Europe and the USA.<sup>313</sup> In Europe, the GOSE rating has typically encompassed all disabilities related to injury (GOSE-ALL) including extracranial injuries; however, in the USA studies have commonly focused on the effects of brain injury (GOSE-TBI), excluding disability from other sources.<sup>314</sup> Both approaches have pros and cons: when compared with GOSE-ALL, GOSE-TBI might more specifically relate to the consequences of TBI (rather than extracranial injury). However, GOSE-TBI might be confounded by the subjectivity and expertise of the assessor. Differences also exist between adult and paediatric versions of GOSE: the paediatric GOSE adopts a contrary convention for numbering the scale, with 8 corresponding to being dead and 1 to complete recovery.<sup>315</sup> These examples illustrate the challenges of harmonising outcomes and highlight the need for deep harmonisation, going beyond the simple alignment of coding of variables and ensuring that, for example, instrument versions, methods of administration, and interpretation of scores are similar before performing meta-analyses across studies (see section 7). Recommendations for scoring the GOSE are provided in a CENTER-TBI and TRACK-TBI publication.<sup>316</sup>

Satisfactory completion rates for outcome instruments are crucial to guard against bias, maintain statistical power, and increase generalisability. Analysis of all data (eg, using imputation) is preferred over selection of complete cases. Historically, the last observation carry forward method has been accepted by regulators, but this approach is problematic and can underestimate current functioning due to ongoing recovery.<sup>317</sup> Alternative approaches that take account of trajectories of outcomes over time should be considered. Single imputation of the GOSE based on modelling data at one or more timepoints was successfully implemented in CENTER-TBI,<sup>317</sup> and propensity weighting methods were applied in other studies.<sup>314</sup> The TBI research field has begun adopting such techniques, but there is a need for consensus on approaches and their extension to assessments other than functional outcome.

#### *Towards a multidimensional outcome assessment*

The Evidence-Based Clinical Outcome assessment Platform, a systematic approach for ascertaining the suitability of a TBI outcome for a specific purpose and population of interest (ie, context of use)<sup>318</sup> provides some guidance for the selection of TBI endpoints. However, there are many gaps in the psychometrics available for TBI outcomes. A primary motivation for implementing multidimensional outcome assessment is to obtain greater detail than that provided by global scales such as the GOSE. Although the GOSE tends to be the assessment that most commonly captures impairment (figure 9), other instruments provide better

For more on validated translations in CENTER-TBI see <https://www.center-tbi.eu/project/validated-translations-outcome-instruments>



**Figure 9: UpSet plots of impaired scores on outcomes from (A) the CENTER-TBI study and (B) the TRACK-TBI study**  
 Horizontal bars depict the frequencies of impairment on individual assessments; vertical bar scores depict the frequencies of profiles of impairment across all assessments (group sizes fewer than ten are not shown). Both samples include all severities of traumatic brain injury and cases with complete data on all six outcome measures at the 6-month follow-up. Impairment was defined as a Glasgow Outcome Scale-Extended score of less than 8, a Rivermead Post Concussion Symptoms Questionnaire score of at least 16, a Quality of Life After Brain Injury-Overall Scale score of less than 52, a Patient Health Questionnaire-9 Depression Scale score of more than 9, a Generalized Anxiety Disorder-7 score of more than 7, an 18-item Brief Symptom Inventory Anxiety Scale T score of at least 63, and a Post-traumatic Stress Disorder Checklist for DSM-5 score of at least 33. In both datasets, the GOSE is the outcome on which impaired scores are most frequent, followed by the Rivermead Post Concussion Symptoms Questionnaire, the Quality of Life After Brain Injury-Overall Scale, and mental health scales. Heterogenous combinations of impairment are apparent, with a similar order of clinical outcome profiles across studies. The top panel showing data for CENTER-TBI is modified with permission from Wilson et al.<sup>319</sup> PCL-5=Post-traumatic Stress Disorder Checklist for DSM-5. GAD-7=Generalized Anxiety Disorder-7. PHQ-9=Patient Health Questionnaire-9. QOLIBRI-OS=Quality of Life After Brain Injury-Overall Scale. RPQ=Rivermead Post Concussion Symptoms Questionnaire. GOSE=Glasgow Outcome Scale-Extended. BSI-18=18-item Brief Symptom Inventory.

**Panel 5: The relevance of multidimensional outcome assessment in mild traumatic brain injury**<sup>309,314,315,320,321</sup>

Outcome and recovery after mild traumatic brain injury (TBI) are affected by a combination of variables (see also section 6), including acute injury characteristics, the type and extent of TBI pathology, concomitant polytrauma, demographic characteristic (eg, age and sex), and psychosocial factors (eg, premorbid or coexisting psychological health problems). Global functional outcome measures do not have the precision and detail needed for characterising the heterogeneous impairments found after mild TBI. These measures should be complemented by a multidimensional outcome-assessment approach providing more sensitive and comprehensive measurement, which can guide TBI systems of care and improve clinical trial endpoints. As findings from the CENTER-TBI and TRACK-TBI studies show, recovery is often slow or incomplete after mild TBI, and thus timely multidimensional outcome evaluation and therapy should be offered when possible.

characterisation of impairments, particularly in patients with mild TBI, and scores on individual instruments might be the only evidence of impairment (see panel 5). Structural modelling from TRACK-TBI indicated that mental-health-related symptoms can be reconfigured to reflect core dimensions of psychopathology underlying diverse symptoms assessed across different common data elements,<sup>322</sup> such as internalising factors (eg, depression, anxiety, and fear), and somatic symptoms (eg, sleep disturbances, pain, and physical complaints). Conversely, data from single instruments, such as the Rivermead Post-Concussion Symptoms Questionnaire, can be treated as unidimensional, that is measuring a general factor (severity of symptoms), or can be decomposed into subfactors reflecting different types of symptoms (emotional, cognitive, and visual). In the latter case it is employed as a multidimensional scale. Treating instruments as unidimensional (ie, reflecting a single construct or attribute) offers simplicity, whereas encompassing the multidimensional structure of single common data elements provides insight into the breadth of clinical sequelae after TBI. The overall structure of TBI outcomes, however, still remains to be elucidated, and better understanding of their architecture will inform advances in methods and guidelines for outcome assessment.

Comparison of the GOSE score with cognitive, mental health, and quality of life outcomes indicates that cognitive impairment most strongly differentiates between patients with moderate and severe disability, whereas adverse mental health outcomes differentiate between patients at the upper levels of functional outcome (between good recovery and moderate disability).<sup>323</sup> These findings suggest that patients in different disability categories require different

approaches to outcome assessment, and that the choice of instruments can be guided by the rating on the GOSE. For example, the assessment strategy appropriate for individuals who are severely disabled is different from that used to identify possible impairment in patients reporting good recovery but persisting symptoms.<sup>319</sup> One example of the need for targeting assessment is mild TBI (panel 5). An alternative approach to incorporating multiple outcomes is the creation of composite endpoints, and some progress has been made in this direction. The Brief Test of Adult Cognition by Telephone is feasible in individuals with moderate to severe TBI,<sup>324</sup> and was shown to be essentially unidimensional (ie providing a measure of general cognitive function) using data from TRACK-TBI and an overall composite score was derived, thus simplifying its use in analyses.<sup>325</sup> Different methodological approaches have been summarised and their theoretical strengths and weaknesses discussed.<sup>305</sup> Rich datasets should be leveraged to empirically evaluate composite endpoints derived by different methodological approaches or from different measures. Both multidimensional approaches and composites need to be validated for qualification by regulatory bodies as a primary endpoint for relevant contexts of use.

#### PTSD and TBI

For many years it was thought that individuals with a TBI seldom develop PTSD, as they often have amnesia for the event. This is a misconception—extensive evidence shows that military personnel repeatedly exposed to blast explosions or combat injuries show high rates of PTSD.<sup>326</sup> Since the 2017 Commission, PTSD is now increasingly recognised as being prevalent also in civilians with TBI. Two systematic reviews found prevalence rates for PTSD respectively of 16·3% across all TBI severities,<sup>327</sup> and of 13·8% following mild TBI and 11·8% following moderate to severe TBI<sup>328</sup> at 6 months after injury. A similar rate was found in CENTER-TBI, with 13·5% across all severities.<sup>329</sup> In TRACK-TBI, the rate at 6 months of probable PTSD for individuals with mild TBI was somewhat higher, at 19·2%.<sup>330</sup> Risk factors for PTSD after mild TBI include lower education, antecedent psychiatric disorder, and injury resulting from violence. Individuals with comorbid PTSD and mild TBI reported lower quality of life, were more likely to be admitted to the hospital and use rehabilitation care, and have lower return-to-work rates compared with individuals with mild TBI only.<sup>95</sup> A screening tool, such as the PTSD Checklist for the Diagnostic and Statistical Manual of Mental Disorders-5 (DSM-5) can identify individuals at risk for PTSD to initiate adequate and timely intervention. Currently, the risk for PTSD and its co-occurrence with TBI is likely to be high in the people of Ukraine, both in military and civilian populations (panel 6).

### Mild TBI

More than 90% of all TBI cases are classified as mild, based on a GCS of 13–15. A common perception is that almost all such patients will make a full recovery, but this is not the case. TRACK-TBI reported that 53% (95% CI 49–56) of patients with mild TBI had functional limitations at 12 months after injury.<sup>314</sup> Common impairments included reduced work capacity, problems with social function, family disruption, and other disabling symptoms. CENTER-TBI reported that 1215 (51%) of 2374 patients with mild TBI had a GOSE score of less than 8 at 6 months after injury.<sup>338</sup> The concept of incomplete recovery was further explored in a cohort of 1612 patients with mild TBI in whom other measures were available, and 63% of patients showed impairments on one or more instruments. These data illustrate that the persisting effects of mild TBI are common and well outside the conventional perception of mild. A major research challenge is to identify patients at risk for incomplete recovery early after mild

TBI to facilitate timely intervention to improve outcome.

### Sex and gender differences

Sex and gender, as factors representing biological and sociocultural human characteristics, respectively, interact with injury cause, injury severity, age, and outcome in complex ways. TBI is more common in young males, who also sustain on average more severe injuries than their female counterparts. However, compared with older men, there is a higher incidence of TBI due to falls in older women and a growing awareness of intimate partner violence as a cause of mild TBI in women. The risk for concussion is higher<sup>30,339</sup> among female athletes when compared with male athletes, with evidence of longer recovery times.<sup>340</sup> The association between sex and outcome is less clear. Studies in moderate to severe TBI, reporting on survival or functional status, generally show similar outcomes in men and women, or better outcomes in women.<sup>341</sup> Studies in mild TBI, collecting data on

#### Panel 6: The Russian invasion of Ukraine: high risk for traumatic brain injury and post-traumatic stress disorder

The risk for post-traumatic stress disorder (PTSD)—and its co-occurrence with traumatic brain injury (TBI)—is likely to be high in the people of Ukraine, both in military and civilian populations. Extensive studies on blast TBI (TBI caused by explosions) and PTSD have been conducted in the USA on military personnel and veterans who were involved in the Iraq and Afghanistan conflicts. Blast TBI was considered the signature injury of these conflicts, with reports showing that around 20% of veterans returning from deployment had a single or multiple blast TBI injuries.<sup>326</sup> Reported prevalence rates of PTSD in veterans were between 11% and 20%, but were much higher in veterans who had had a blast TBI, with reported rates between 33% and 65%.<sup>331</sup> In the initial phases of the Iraq and Afghanistan conflicts, substantial delays of up to 1 year or more occurred between the events and definitive diagnosis.<sup>332–334</sup> We know that PTSD is also common after civilian TBI, with reported rates between 12% and 19%.<sup>330</sup> These issues are now being reprised in the Russian invasion of Ukraine, with risks being experienced not just by military personnel, but also civilians who are victims of artillery and rocket attacks. Additionally, experts are recognising a third category of individuals who are at particularly high risk of PTSD—those who are directly involved in the conflict but are not professional soldiers, termed civilian combatants—who often do not have the preparation and training of military personnel.<sup>335</sup>

We echo alerts from PTSD experts to the imminent mental health problems that are emerging across these populations at risk, and support their calls for addressing this issue as soon as the situation permits. We emphasise the coexistence of PTSD with TBI and the overlap in presentation (and possibly even biology)<sup>336</sup> additionally underlines the need to consider both diagnoses in individuals who present with either. To our

knowledge, no studies have yet been implemented in Ukraine to document the frequency of blast TBI and PTSD.

We also call for awareness of the risk for TBI, PTSD, and related mental health problems in refugees, and suggest that this should be urgently addressed both by screening people at risk and by implementing surveillance studies. The EU Agency for Asylum provides guidance and practical tools to Member States to help screen asylum seekers for vulnerability, and is also operationally assisting some Member States with this task through the deployment of vulnerability experts on the ground. However, there is a difference in procedures between applicants for international protection (ie, asylum seekers) and beneficiaries of temporary protection (eg, refugees from Ukraine). Although temporary protection beneficiaries already benefit from protection status with provision of the same rights and access to services as national citizens, including health care, vulnerability screening is not mandated as in the case of asylum seekers. Consequently, there is no systematic and common approach across Member States for screening or for provision of medical and psychological care. Even if screening for vulnerability is performed, this does not specifically focus on identifying PTSD in combination with TBI. We suggest that refugees from Ukraine who have been exposed to explosions, physical insults, or psychological stressors of warfare, are screened for both TBI and PTSD (as well as for major depression, which frequently accompanies both disorders).<sup>337</sup> To not do so in patients with a diagnosis of TBI might miss a treatable psychological health condition. Conversely, if PTSD is diagnosed, not detecting concomitant TBI might result in suboptimal treatment and overlook other TBI-related complications. Screening alone is not sufficient, and the principles of identification, assessment, and referral should be followed to allow appropriate intervention.

For more on the **EU Agency for Asylum** see <https://euaa.europa.eu/asylum-knowledge/vulnerability>

For **PTSD prevalence rates in veterans** see <https://www.ptsd.va.gov/>

For more on the **emerging risk of PTSD in Ukraine** see <https://www.scientificamerican.com/article/ukrainians-face-lasting-psychological-wounds-from-russian-invasion/>

self-reported cognitive and psychological symptoms, mostly report worse outcomes in women.<sup>342,343</sup> In CENTER-TBI, women reported more severe post-concussion and mental health symptoms, and poorer health-related quality of life (HRQOL). 6 months after mild TBI (but not after moderate to severe TBI), women also had a higher likelihood of worse GOSE scores.<sup>344</sup> The outcome differences after mild TBI could not be explained by differences in care pathways or sociodemographic characteristics, and were only partly mediated by psychiatric history.<sup>345</sup> TRACK-TBI reported more PTSD symptoms in women, and a greater TBI-related symptom burden.<sup>342</sup> Importantly, the effect of gender on TBI-related symptoms seen in people with TBI was not present in an orthopaedic trauma control sample. The interactions between sex, gender, and outcomes might also be related to hormonal and genetic responses to injury.<sup>341</sup> A detailed discussion on endocrine dysfunction after TBI is presented in the appendix (p 20).

#### Relation to late neurodegenerative disease

TBI is recognised as a potentially modifiable risk factor for neurodegenerative disease.<sup>46,346,347</sup> Estimates suggest that at least 3% of dementia cases in the general population are attributable to TBI,<sup>346</sup> and there is growing evidence of a higher risk among former elite-level contact sports athletes.<sup>49,348–350</sup> Nevertheless, the associated clinical presentations are heterogeneous and remain poorly defined,<sup>351,352</sup> partly because of the complex interrelationship between the acute injury and the evolving pathological processes contributing to progressive decline.<sup>352</sup> Emerging descriptions of TBI-related neurodegeneration document multiple proteinopathies, typically associated with wider neurodegenerative disease,<sup>353–355</sup> in addition to the more TBI-specific pathology of chronic traumatic encephalopathy.<sup>356</sup>

Unlike many widely studied neurodegenerative disorders for which disease onset is typically unknown,<sup>357</sup> exposure to TBI or repetitive head impacts, or both, can be identified and studied prospectively. The Late Effects of TBI study, initiated in 2015 and longitudinal follow-up initiated in 2019, is a longitudinal prospective brain donor programme that aims to characterise chronic post-traumatic neuropathology and to identify in-vivo biomarkers of post-traumatic neurodegeneration.<sup>358</sup> In sports medicine, progress has been made toward strategies for early detection of disease, including the use of PET imaging<sup>359,360</sup> in at-risk athletes, but the ability to predict late neurological health problems in former athletes remains uncertain. Studies in individuals with a history of repeated TBI or head impacts present unique opportunities to identify neuropathological signatures, neurobehavioral features (such as cognitive impairment and mental health problems), and novel biomarkers of adverse brain health, with direct relevance to understanding both neurodegeneration following TBI and neurodegenerative disease.<sup>103,361</sup>

#### Main messages and recommendations

##### Main messages

- (1) Around 50% of patients with mild TBI presenting to hospital do not recover to pre-TBI levels of health and wellbeing by 6 months after injury.
- (2) Outcome in women after TBI is poorer compared with men.
- (3) PTSD occurs in 13–19% of civilians with TBI.
- (4) There is little understanding of individual differences in recovery after TBI.
- (5) Age-specific norms are absent for many outcome instruments.
- (6) Although around 3% of dementia cases in the general population are attributable to TBI, and there is growing evidence of higher risk of dementia among former elite-level contact sports athletes, the associated clinical presentations are heterogeneous and remain poorly defined.

##### Recommendations

- (1) Care pathways should be implemented to ensure the structured follow-up of patients with mild TBI, and research should be stimulated to identify patients with mild TBI at high risk for incomplete recovery, which would allow timely evaluation and treatment.
- (2) Research should be facilitated to help explain sex and gender differences and inform intervention strategies.
- (3) Awareness of the risk of PTSD after TBI needs to be increased, and implementation of routine screening procedures considered.
- (4) Research on multifactorial influences on outcome should be stimulated.
- (5) Research should be stimulated to develop age-specific and population-specific standards for outcome instruments commonly used in TBI.
- (6) Studies in individuals with a history of repeated TBI or head impacts to identify neuropathological signatures, neurobehavioral characteristics, and novel biomarkers of adverse brain health should be stimulated.

#### Section 6: Prognosis in TBI

Prognosis is an essential element of medicine. Realistic counselling on expected outcomes is of utmost relevance to patients and their relatives. Major applications of prognostic analysis are at the level of the individual patient. Moreover, group-level application can be used for calculating a baseline risk as a reference for evaluating quality of care, and for stratification and covariate adjustment in clinical trials.<sup>362</sup> Prognostic models provide risk estimates from multiple patient and disease characteristics that are based on systematic analysis of empirical data. Robust and externally validated models exist for moderate and severe TBI, but not for mild TBI. The 2017 Commission on TBI concluded that (1) existing models for moderate to severe TBI require refinement, (2) there is a need for further development and validation of models in mild TBI, (3) models should be developed to



	IMPACT models			CRASH models	
	Core*	Extended†	Lab‡	Basic§	CT¶
<b>CENTER-TBI</b>					
Mortality	0.81 (0.79–0.84; n=1173)	0.85 (0.82–0.87; n=1030)	0.85 (0.82–0.87; n=1006)	0.86 (0.83–0.88; n=1742)	0.88 (0.86–0.90; n=1542)
Unfavourable outcome	0.77 (0.74–0.80; n=1173)	0.80 (0.78–0.83; n=1030)	0.81 (0.78–0.84; n=1006)	0.82 (0.80–0.84; n=1742)	0.84 (0.82–0.86; n=1542)
<b>TRACK-TBI</b>					
Mortality	0.79 (0.74–0.84; n=441)	0.84 (0.79–0.88; n=406)	0.81 (0.76–0.86; n=406)	0.88 (0.83–0.91; n=841)	0.91 (0.87–0.94; n=841)
Unfavourable outcome	0.77 (0.72–0.81; n=441)	0.82 (0.77–0.85; n=406)	0.82 (0.78–0.85; n=406)	0.86 (0.83–0.89; n=841)	0.88 (0.85–0.91; n=841)

Data are discriminatory performance (expressed as AUC with 95% CIs) of the models. Validation cohorts were selected to be consistent with the development populations. For validation of the IMPACT models, patients with moderate to severe TBI (GCS  $\leq$  12) aged at least 14 years in CENTER-TBI and at least 17 years in TRACK-TBI were selected. For validation of the CRASH models, patients with a GCS of less than 15 aged more than 15 years in CENTER-TBI and at least 17 years in TRACK-TBI were selected. AUCs cannot be directly compared between the IMPACT and CRASH validations, as they are based on different selections of patients. AUC=area under the receiver operating characteristic curve. GCS=Glasgow Coma sum score. \*IMPACT Core model: age, GCS motor score, and pupillary reactivity. †IMPACT extended model: core predictors plus hypoxia, hypotension, Marshall CT classification, presence of traumatic subarachnoid haemorrhage, and presence of epidural haematoma. ‡IMPACT Lab model: predictors extended model plus glucose and haemoglobin concentrations from samples obtained at presentation. §CRASH basic model: age, GCS total score, pupillary reactivity, and major extracranial injury. ¶CRASH CT model: basic model plus petechial haemorrhages, obliteration of third ventricle or basal cisterns, presence of traumatic subarachnoid haemorrhage, midline shift of more than 5 mm, and non-evacuated haematoma.

**Table 2: External validation of the IMPACT and CRASH prognostic models on data from the CENTER-TBI and TRACK-TBI studies**

predict outcome beyond mortality and GOSE scores, and (4) a need was identified to develop a set of quality indicators in TBI. In this section we describe the advances towards accomplishing these four goals.

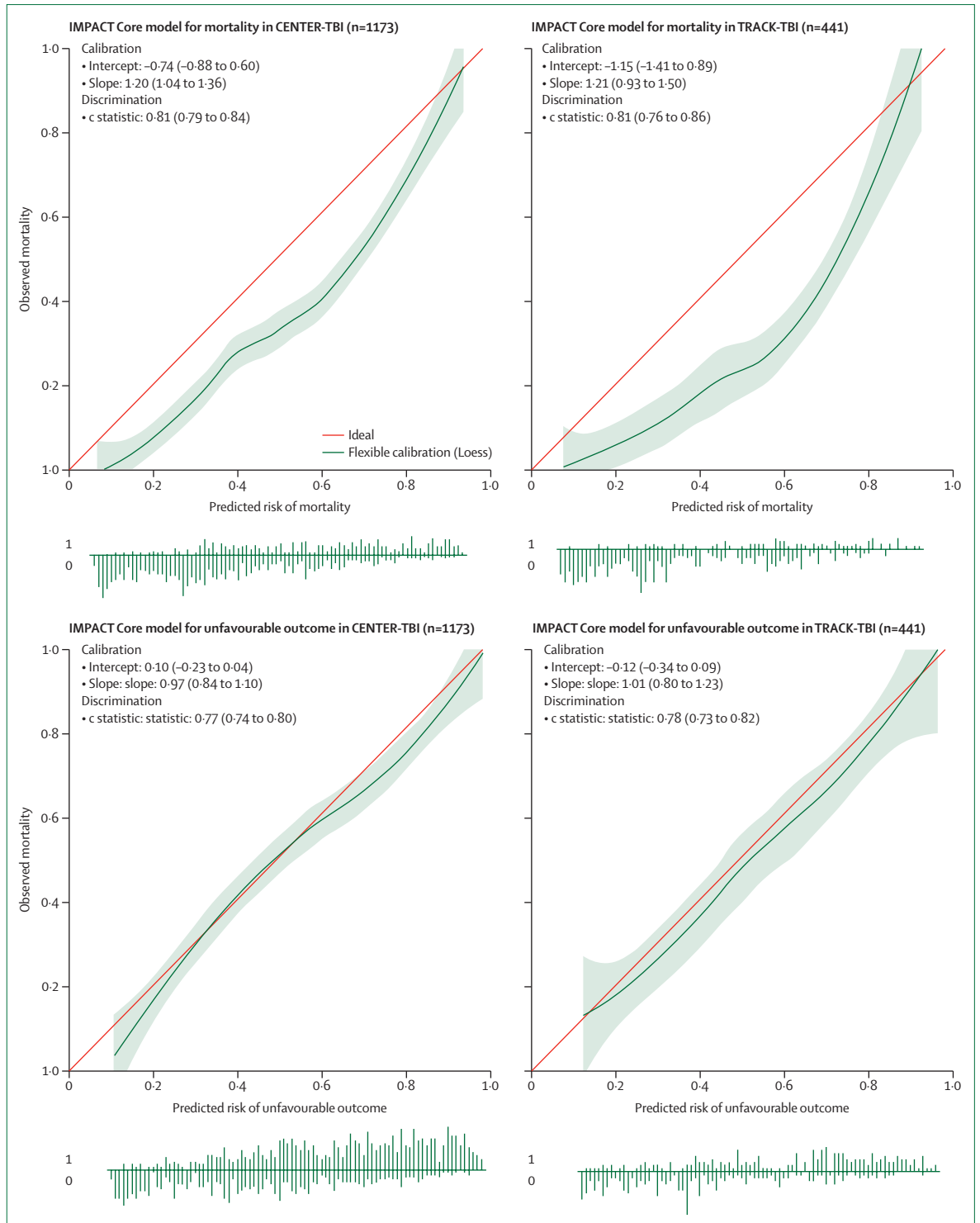
### Prognostic models in moderate to severe TBI

Most prognostic models have been developed for patients with moderate to severe TBI. A systematic review<sup>363</sup> identified 58 papers describing the development, validation, or extension of 67 different multivariable prognostic models for functional outcome in these patient groups, published between 2006 and 2018. There were 149 external validations of prognostic models. The International Mission on Prognosis and Analysis of Clinical trials in Traumatic brain injury (IMPACT)<sup>364</sup> and Corticoid Randomisation After Significant Head injury (CRASH)<sup>365</sup> prognostic models were developed on the largest cohorts (8509 and 10008 individuals, respectively) and have been most often externally validated (56 and 24 times, respectively). IMPACT developed three models and CRASH two models (table 2). Overall, these models showed good discrimination (ie, the ability of a prediction model to separate subjects with and without the outcome of interest; AUCs around 0.8). However, calibration (ie, how well observed outcomes relate to a predicted outcome) was variable and partly influenced by selection of the validation population (casemix). More complex models showed slightly better discrimination compared with the IMPACT Core model (including age, GCS motor score, and pupillary reactivity) and basic CRASH models (age, GCS total score, pupillary reactivity, and major extracranial injury). No competing models are available that have withstood the test of multiple external validations. The IMPACT and CRASH models remain the most widely used in clinical TBI research. However, the IMPACT models were developed on data accrued 25–38 years ago (before the implementation of guidelines) and the CRASH models on data collected around 20 years ago. The validity of model predictions in current

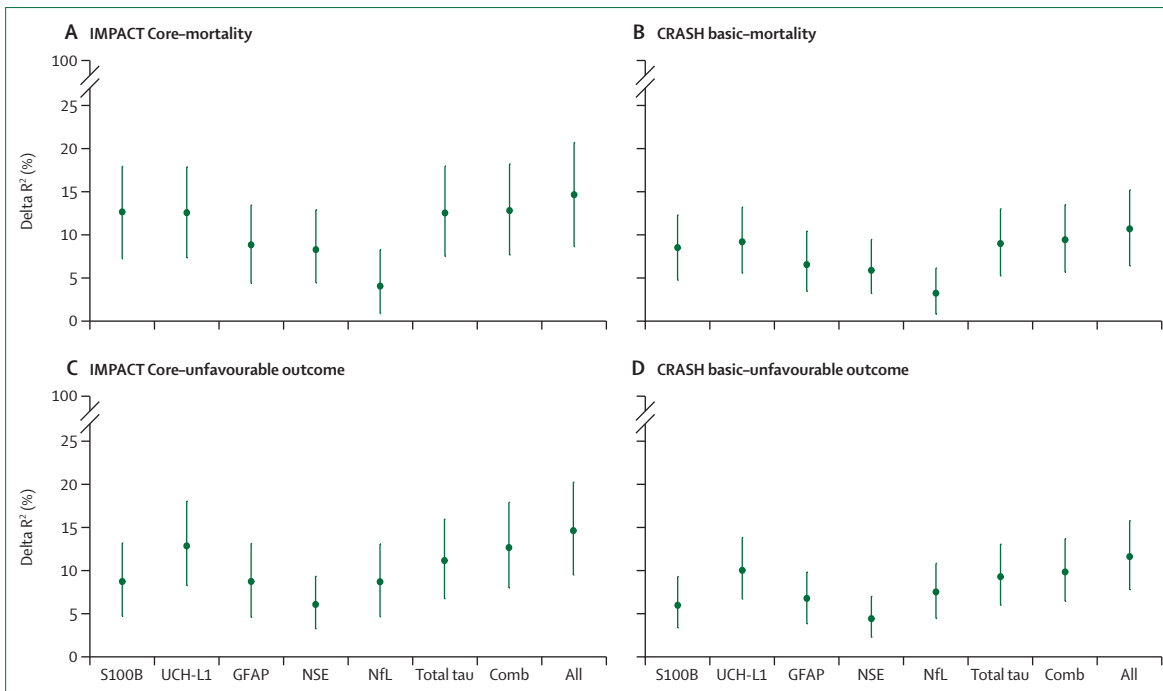
practice might therefore be under question. Both CENTER-TBI<sup>366</sup> and TRACK-TBI assessed the performance of these models on their contemporary data, collected between 2014 and 2020, and, as with the systematic review, found good discrimination (table 2), although mortality was lower than expected (figure 10).

The calibration plots in figure 10 reflect comparisons between observed and expected outcomes, which can inform benchmarking of quality of care. At the group level, the rate of unfavourable outcome (GOSE <5) was 55%, similar to that predicted by the IMPACT core prognostic model (observed–expected ratio 1.06, 95% CI 0.97–1.14), but mortality was lower than expected (observed–expected ratio 0.70, 95% CI 0.62–0.76). These findings were replicated in an analysis of 441 adult patients from TRACK-TBI, and showed that over time, mortality decreased but that came at a cost of more survivors with severe disability at 6 months. These analyses are robust, as they are adjusted for differences in casemix by the model, but we noted that comparison of contemporary data with historical series is problematic (appendix p 22). The good discrimination of the IMPACT and CRASH models shows that they are still valuable for current-day research. The lower-than-expected mortality, however, indicates a need for updating the models.<sup>367</sup> Moreover, the IMPACT models only explain 35% of variance in outcome. This could be increased by extending the models, either by adding new predictors or by adding dynamic information on current predictors as it becomes available over time (dynamic modelling). Data from CENTER-TBI show that adding UCH-L1 to the IMPACT and CRASH models substantially increased the percentage of variability in the outcome that is explained by the predictors (expressed as R<sup>2</sup>) for predicting mortality: by 12.5% (95% CI 7.3–17.8) when added to IMPACT Core and by 9.2% (5.6–13.2) when added to CRASH (figure 11).

The aim in developing the IMPACT and CRASH models was to establish a baseline prognostic risk before



**Figure 10: Calibration plots for external validation of the IMPACT lab models for mortality and unfavourable outcome on data from the CENTER-TBI and TRACK-TBI studies**  
 The correspondence between observed outcomes and predicted risks is shown as LOESS smoothed curves with 95% CI. The red line is the reference with perfect agreement (calibration intercept 0, slope 1). The distribution of predicted risks is shown at the bottom of each graph, stratified by outcome (1 vs 0). LOESS=Locally Estimated Scatterplot Smoothing.



**Figure 11: Absolute incremental value (delta R<sup>2</sup>) of biomarkers when added to the (left) IMPACT Core and (right) CRASH basic models for predicting mortality and unfavourable outcome**

For IMPACT, we selected patients with moderate to severe TBI (Glasgow Coma sum score  $\leq 12$ ;  $n=737$ ) and for CRASH, patients with a Glasgow Coma sum score of less than 15, thus also including patients with mild TBI ( $n=1083$ ). Six biomarkers are considered separately, in combination (Comb: GFAP plus UCH-L1), and altogether (All). The vertical lines depict the 95% CIs around the estimates. The explained variance (R<sup>2</sup>) for the models without biomarkers was as follows: IMPACT Core: 30.7% [95% CI 23.5–37.7] for mortality and 22.6% [15.6–29.1] for unfavourable outcome; CRASH basic: 35.2% [95% CI 28.8–41.8] for mortality and 33.8% [28.4–39.7] for unfavourable outcome. UCH-L1, S100B, and total tau have the greatest incremental value. Combinations of biomarkers appear to have little added value. S100B=S100 calcium-binding protein B. UCH-L1=ubiquitin C-terminal hydrolase L1. GFAP=glial fibrillary acidic protein. NSE=neuron-specific enolase. NFL=neuro-filament light chain. Comb=combination.

enrolment of a patient in a clinical trial. Hence, they are static models using only characteristics available upon admission. In the 1970s, one study<sup>368</sup> showed that prognostic estimates become more accurate when adding information obtained on days 2–3 and days 4–7 after injury. Since then, however, very few studies have attempted dynamic modelling. The systematic review cited above reported 12 extensions in five studies, including the APACHE II score, intracranial pressure, and vital parameters obtained within the first 24 h. More recently, autoregulatory indices have shown potential in terms of prognostication (see section 4). The logic of dynamic prediction is already intuitively used in clinical practice, where experienced clinicians constantly re-estimate a patient's prognosis considering new information.

Despite the broad acceptance of prognostic models in TBI research, their use in clinical practice is low. Barriers to clinical implementation include broad CIs around prognostic estimates and the fact that most models are based on predictors assessed on presentation, whereas clinicians typically consider the clinical course after admission. Following updates and extensions of existing models, efforts are needed to facilitate broader implementation by educating clinicians on their relevance for clinical practice (eg, for provision of reliable

expectations to patients and their relatives, and for benchmarking quality of care).

#### Prognostic models for functional outcome in mild TBI

Few prognostic models have been developed for mild TBI.<sup>209,365,369</sup> We identified five methodologically sound models for the GOSE, reported in three studies. The best known are the CRASH (for GCS  $\leq 14$ ) and the UPFRONT models. Published models contain different predictors to those on moderate to severe TBI and include, besides age, GCS, extra-cranial injuries, and alcohol intoxication, sex and gender, education, and pre-injury mental health. Broadly speaking, prognosis in mild TBI is driven to a greater extent by what the patient brings to the injury (eg, pre-injury comorbidities and mental health) than in moderate and severe TBI. This observation was confirmed in the CENTER-TBI and TRACK-TBI studies, which found pre-injury health (including mental health) and sociodemographic characteristics (eg, education, employment, sex, and race and ethnicity) to be prominent predictors of outcome in mild TBI. Injury severity, however, remained one of the strongest predictors of GOSE, showing that what injury brings to the patient (eg, injury severity) is also relevant for global outcome after mild TBI.

Validation of existing models for predicting the GOSE in CENTER-TBI data showed poor performance, with discrimination varying between 0.66 and 0.79, and highly variable calibration. Broader issues in prediction after mild TBI are whether the traditional split of GOSE into unfavourable versus favourable outcome as commonly used for moderate and severe TBI, is appropriate, and whether models should be based only on acute symptoms. After mild TBI, few patients have unfavourable outcome as defined by a GOSE of less than 5 (11% in CENTER-TBI). Some publications<sup>370</sup> suggest considering a split between lower and upper good recovery (eg, GOSE <8 vs GOSE=8, best defined as incomplete recovery) or the use of GOSE as an ordinal variable (1–8) as most appropriate for predictive modelling in mild TBI. The percentage of patients with incomplete recovery 6 months after mild TBI was substantial in the UPFRONT study (44%),<sup>209</sup> in CENTER-TBI (51%),<sup>20</sup> and in TRACK-TBI (60%).<sup>314</sup> The UPFRONT model found that including symptoms recorded at 2 weeks post-injury (dynamic modelling) increased discrimination from an AUC of 0.69 to 0.77, and the explained variance (Nagelkerke R<sup>2</sup>) from 14% to 27%. Also in CENTER-TBI, post-injury symptoms, assessed in a subset of 640 patients with mild TBI discharged from an emergency department, showed incremental value for the prediction of functional outcome following mild TBI, increasing the AUC from 0.63 to 0.74 and Nagelkerke R<sup>2</sup> from 7% to 21%. Whereas post-injury symptoms increase model performance, other categories of predictors showed inconsistent or minor incremental predictive ability. In CENTER-TBI, some blood-based biomarkers (eg, NfL) showed associations with the GOSE, but did not substantially improve prediction of incomplete recovery. The role of CT abnormalities is uncertain: in the UPFRONT study, CT abnormality was not a predictor of incomplete recovery, but in both CENTER-TBI and TRACK-TBI some CT and MRI findings were predictive of the GOSE.<sup>217,236,371</sup> Other studies have shown a strong association between the duration of post-traumatic amnesia and outcome.<sup>205</sup>

#### Predicting outcomes beyond the GOSE

Outcome after TBI is multidimensional (see section 5). Despite the value of the GOSE for describing functional outcome, it lacks detail in characterising the heterogeneous nature of impairments, particularly those resulting from mild TBI. Global functional outcome measures should be complemented by domain-specific instruments, providing more comprehensive assessment. Persisting post-concussion symptoms, HRQOL, depression, and PTSD have been analysed in the prognostic context,<sup>372,330</sup> mostly in patients with mild TBI. We identified three prognostic models for predicting persisting post-concussion symptoms,<sup>209,369,373</sup> but each of these studies used different approaches to defining these symptoms.<sup>338</sup> Models

developed by two different groups that included symptoms measured early after injury, in addition to socio-demographic and medical variables, reported good performance in predicting persisting post-concussion symptoms (AUC 0.75 and 0.76, respectively).<sup>208,209</sup> New models for predicting persisting post-concussion symptoms were developed in CENTER-TBI in a cohort of 1605 patients with complete outcome assessment at 6 months. The Core model explained only 4% of variance; extending this model with other variables available at admission increased the explanation of variance to 9%–12%, and adding information obtained at 2–3 weeks in a cohort of 476 patients, for whom this information was available, increased the explained variance from 6% to 37%. CENTER-TBI further explored prediction of HRQOL in 2666 adult patients who had completed the SF36 version 2 and QOLIBRI questionnaires at 6 months after injury and found that medical and injury related characteristics were more important for the prediction of the physical component summary score, whereas patient-related characteristics were more important for prediction of the mental component summary score and the QOLIBRI following TBI. However, the proportion of variance explained (R<sup>2</sup>) was relatively low (19% for the physical component score of SF36, 9% for mental component score, and 13% for the QOLIBRI). Inclusion of HRQOL assessments at 2–3 weeks after injury, which were available in 436 patients, substantially increased the R<sup>2</sup> to 37% for the SF-PCS, to 36% for the SF-MCS, and to 48% for QOLIBRI.

#### Development of quality indicators

Measurement of quality of care can guide quality improvement initiatives and benchmarking—ie, with feedback on performance, between-centre discussions on policies, and opportunities to study best practice. Improvement of care and outcomes through quality measurement requires valid quality indicators, which are measurable aspects of quality of care. Quality indicators have been developed in other clinical areas, for example in sepsis, stroke, and in children with TBI, but are absent for general use in TBI. CENTER-TBI developed a set of quality indicators specific to TBI and explored benchmarking quality of care by comparing observed to predicted outcomes. Quality indicators were developed in an extensive Delphi process and consisted of 17 structure indicators, 16 process indicators, and nine outcome indicators.<sup>374</sup> The indicators were subsequently validated using data from 2006 adult patients enrolled to the ICU stratum of CENTER-TBI.<sup>375</sup> 26 of the initial 42 indicators could be validated in the CENTER-TBI data. The other 16 indicators related to organisational aspects, which could not be evaluated on patient data. Overall, nine structure and five process indicators showed potential for quality improvement purposes for patients with TBI in the ICU (appendix p 23). Other indicators might, however, have value in other settings, for example time until CT

scan for mild TBI in the emergency department. The indicator set developed in CENTER-TBI is an important first step towards benchmarking and quality improvement programmes for patients with TBI, but requires further validation and refinement.

### Main messages and recommendations

#### Main messages

- (1) Despite the broad acceptance of prognostic models in TBI research, they are not often used in clinical practice. This discrepancy might be partly due to the low precision of prediction in individual patients.
- (2) Prognostic models have been developed and extensively validated for moderate and severe TBI. No well-validated models exist for mild TBI, nor do models exist that are applicable across all ranges of TBI severity.
- (3) Robust prognostic models exist for moderate to severe TBI, but these only account for 35% of the variance in outcome.
- (4) Prognostic models for mild TBI are less developed than those for moderate to severe TBI, and their performance can be enhanced by including information obtained at 2–3 weeks after injury.
- (5) Incomplete recovery in mild TBI (GOSE <8) represents a prognostic endpoint with clinical, research, and societal relevance. Models for predicting post-concussion symptoms after mild TBI have used different approaches to defining post-concussion symptoms.
- (6) Quality indicators developed for TBI are restricted to the ICU setting and are not yet ready for translation into clinical practice.

#### Recommendations

- (1) Efforts are needed to facilitate broader implementation of prognostic models by educating clinicians on their relevance for clinical practice. Clinical acceptance and use of prognostic models would be facilitated by greater precision of prediction for individual patients.
- (2) Initiatives should be stimulated to develop models applicable across the range of TBI severity. Availability of such models would constitute a huge step forward and facilitate implementation into clinical practice.
- (3) Research should be stimulated to update and extend these models, either by adding new predictors (eg, biomarkers) or by adding dynamic information on current predictors as it becomes available over time (dynamic modelling).
- (4) Researchers developing prognostic models for mild TBI should focus on dynamic modelling by including information obtained in the first few weeks after injury.
- (5) Initiatives should be stimulated to develop a consensus on the definitions of outcomes, such as persistent post-concussion symptoms, to support the development of clinically relevant prognostic models for mild TBI.
- (6) Research should be stimulated to refine, validate, and implement quality indicators for TBI.

## Section 7: New directions for acquiring and implementing evidence

### Introduction

The 2017 Commission on TBI in 2017 highlighted the need for internationalisation of the common data elements to ensure standardised data collection, the opportunities for comparative-effectiveness research, and the need for globally coordinated research efforts. In this section, we discuss accomplishments towards these aims and identify new challenges. We particularly focus on consent procedures, data sharing in the context of current privacy regulation, novel approaches to evidence generation, and international collaboration.

### Study approvals, consent procedures, and the regulatory environment

In May 2018, the General Data Protection Regulation (GDPR: 2016/679) entered into force in the EU and, although broadly addressing privacy and human rights laws, contains provisions also for health research. Specifically, health data are designated as a special category of data, requiring explicit consent for collection and processing. Exemptions include general epidemiological studies serving a public health purpose. Consent is restricted to the aims of the study and the use of data outside this context requires specific consent. GDPR recognises the issue of absence of mental capacity to provide consent, and specific provisions are made in the case of children. However, no provisions are included relevant to patients with an acute absence of capacity or to emergency situations. In TBI (and in other acute neurological diseases), there is both an absence of capacity and an emergency situation. Although conducted before GDPR entered into force, the experiences of CENTER-TBI are relevant to informing regulatory policy. The protocol for CENTER-TBI was evaluated by institutional review boards of 66 centres in 18 European countries, of which 14 considered the study to be observational and two (France and Hungary) considered the study to be interventional, because the study involved blood sampling and outcome assessments that would not be part of clinical routine. Two countries (the Netherlands and Serbia) considered it as both observational and interventional.<sup>376</sup> A primary institutional review board assessment was conducted centrally in 11 (61%) of 18 countries and locally in seven (39%) of 18 countries. Although central review is intended to be directly applicable to all national centres, local institutional review board approval was required in six (55%) of 11 countries with central procedures. Local institutional review board approval is generally considered a feasibility check, but full review was often conducted, extending the median duration of final IRB approval in centres participating in CENTER-TBI to 114 days (IQR 75–224 days), with a range from 1 to 535 days. This substantial variation reflects an absence of clear directions in European countries, especially in national legislation, and can adversely affect efficiency of multinational clinical

For more on GDPR see <https://gdpr-info.eu/>

For more on **clinical trials regulation** see <https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=celex%3A32014R0536>

For more on the **clinical trials information system** see <https://euclinicaltrials.eu/home>

For more on the **data-sharing policy implemented by the NIH** see <https://sharing.nih.gov/>

For the **current common data elements iteration** see <https://www.commondataelements.ninds.nih.gov/Traumatic%20Brain%20Injury#pane-89>

research on TBI. We suggest that the EU should develop and implement directives that regulate central and additional local approval.

Obtaining consent for patients with possible acute mental incapacity poses challenges. In CENTER-TBI, informed consent from the patient was obtained for 805 (95%) of 844 patients enrolled in the emergency room stratum and for 1266 (83%) of 1517 in the admission stratum.<sup>377</sup> These patients all had mild TBI and were considered to have sufficient mental capacity to provide consent. Nevertheless, formal documentation of mental capacity, for example by administering the Galveston Orientation and Amnesia test, should be considered before requesting consent. This capacity was documented in TRACK-TBI, where 2216 (87%) of 2550 patients with mild TBI provided consent themselves. In patients with reduced mental capacity, alternatives in CENTER-TBI included proxy consent (eg, by a family member) and deferred consent. Proxy consent was applied in 1377 (64%) of 2137 patients and deferred consent in 334 (16%) of 2137 patients.<sup>377</sup> A relative disadvantage of proxy consent is that relatives might not be available soon after injury or might be too overwhelmed to provide valid proxy consent.<sup>378</sup> Deferred consent was used only in around a third of centres where it was considered valid, but it might be the preferred option in observational studies in which risks to patients are minimal or absent. In TRACK-TBI, alternative consent procedures for patients with reduced mental capacity included proxy consent by a legally authorised representative or a waiver of consent (at approved institutions). Waiver of consent was used in 327 (10%) of 3284 patients in the total cohort. Proxy consent was the most frequently used alternative in patients with moderate to severe TBI (470 [70%] of 674).

In January 2022, the clinical trials regulation (536/2014) entered into force in the EU and the clinical trials information system was implemented by the European Medicines Agency. To our knowledge, it does not apply to observational studies. The concern is that this more complex regulation might be inappropriately applied to studies such as CENTER-TBI, since two EU nations classified it as an interventional study. A uniform regulatory definition of what should be considered an interventional and an observational study in the EU is needed. In the US, NIH classifies essentially all prospective human studies as trials, and from Jan 25, 2023, all data will need to be deposited in an approved repository.

### Internationalisation of common data elements

Standardisation of data collection and data coding received a strong impetus with the publication of the first version of the common data elements for TBI in 2010.<sup>379</sup> The current iteration of the common data elements (version 2.0; panel 7) was published in 2012, but since then various issues have arisen.

Absence of evidence-based criteria for common data element designation has led to proliferation of the number of elements, especially in the supplemental category, and redundancy across element domains. Importantly, common data elements cannot be universally used because of a variety of factors including legal and regulatory issues, semantic or cultural considerations, inconsistent or duplicative categorisation of data elements, and idiosyncratic modes of administration. For example, several core common data elements do not meet GDPR standards as they include potential patient identifiers (eg, date of birth). The core elements of race and ethnicity and the basic elements of educational level of the patient and caregiver are US-centric, and many outcome common data elements are available only in the English language or are copyrighted (see section 5).<sup>222</sup> To address these and other issues raised by investigators across the world, NIH-NINDS is planning to convene a work group in 2023, which will be tasked to advise on updating the TBI common data elements to version 3.0. This update is long overdue but can now be informed by the empirical experience in the CENTER-TBI and TRACK-TBI studies to determine which elements have most practical utility, to decrease redundancy, and to identify outcome common data elements that are most responsive in specific TBI subgroups. The version 3.0 update is anticipated to improve global utility of TBI common data elements, but broad international input will be essential to transform the elements to global standards.

### Data collection and curation

Data collection according to the common data elements should permit cross-validation of study results<sup>33,217</sup> and

#### Panel 7: Classification of traumatic brain injury common data elements

##### Core elements

A small set of 29 data elements that are relevant to all traumatic brain injury (TBI) clinical studies.

##### Basic elements

Data elements beyond the core elements, which are recommended for studies of:

- Concussion or mild TBI (n=114\*)
- Acute hospitalisation (n=105\*)
- Rehabilitation for moderate or severe TBI (n=143\*)
- Epidemiology (n=110\*)

##### Supplementary elements

Additional data elements for which inclusion depends upon the particulars of the study.

\*These numbers are inflated as various common data elements might relate to one variable. For example, the paediatric Glasgow Outcome Scale-Extended contains 17 CDEs.

facilitate meta-analyses across multiple studies to answer research questions that would be difficult to address with single studies alone. However, meta-analysis across CENTER-TBI and TRACK-TBI has taught us that simple alignment of data coding is insufficient and that a deeper level of harmonisation is required, which we designate as deep harmonisation (appendix p 24). For example, outcome data such as the GOSE can be collected inclusive or exclusive of the influence of extra-cranial injuries on function, and interpretation of a given GOSE score is possible only with knowledge of how data were collected (see section 5). Detailed documentation of meta-data is essential and procedures to ensure data quality should run from design through data collection to analysis. Post-processing of data is important to facilitate analyses. For example, the imputation of missing baseline covariates<sup>380</sup> or outcome timepoints<sup>317</sup> after TBI is statistically challenging,<sup>381,382</sup> but predicates the reproducibility of all subsequent analyses. These procedures all belong to the process of data curation, which should involve both domain experts and data scientists. The aim of data curation is to create a final dataset that is well documented and as complete and free from errors as possible. This goal is already demanding in HICs with adequate resources (detailed discussion provided in appendix p 24), but becomes even more challenging in LMICs (panel 8). Data curation in CENTER-TBI and TRACK-TBI was much more complex and time consuming than initially anticipated, and motivated the development of consensus guidelines for Data Acquisition, Quality and Curation for Observational Research Designs<sup>391</sup> as a framework for robust data curation applicable beyond TBI. Costs involved in data curation and deep harmonisation in preparation of data sharing are substantial and have been estimated to amount to 15–20% of the study budget.<sup>392</sup> Few funding mechanisms exist to support work to make data reusable, and this should be an area for further development of data science policy.

### Data sharing and privacy regulation

Data curation and provision of meta-data are essential for data sharing and their reuse, adhering to the FAIR principles: Findable, Accessible, Interoperable, and Reusable.<sup>393,394</sup> Although the original study investigators are responsible for ensuring the FAIR principles of interoperability and reusability, the good use of data should be considered a joint responsibility of both the original investigators and researchers reusing the data. This joint responsibility would also be in line with GDPR, which stipulates that the data controller (ie, original investigators or sponsor) remains responsible for what is done with the data. Moreover, insufficient knowledge of study design can lead to erroneous interpretation of findings. For example, in CENTER-TBI a researcher reported substantial between-centre variation in admission rates for mild TBI, ranging from 0 to 100%. This variation could, however, be explained by

the fact that some centres only enrolled patients in the emergency room stratum (never admitted to hospital) and others only to the admission stratum (always admitted). Interactions between researchers seeking to access the data and the original investigators should be strongly encouraged and mechanisms developed to cover the costs involved.

Data sharing provides opportunities for other researchers to confirm previous findings or to address new research questions and, most importantly, facilitates meta-analysis across studies. Policymakers strongly support data sharing, as this approach optimises the returns from invested public funding. Meta-analyses can be performed on pooled study results or on individual patient data. The former approach is common in systematic reviews, where larger sample sizes permit greater precision than individual studies. Meta-analysis of individual patient data offers greater opportunities compared with meta-analysis of pooled study results: new study questions can be addressed and heterogeneity between studies can facilitate comparative-effectiveness research. Pooled analysis of individual patient data (one-step process) has been successful in TBI, as shown by the IMPACT studies, for which initially data from eight randomised controlled trials and three observational studies were pooled and analysed centrally.<sup>395</sup> However, the regulatory environment has become more stringent since these data were collected over 25 years ago, raising barriers to direct pooling of data across institutions and countries, even among willing partners.<sup>396–398</sup> An

### Panel 8: Challenges of data collection in low-income and middle-income countries

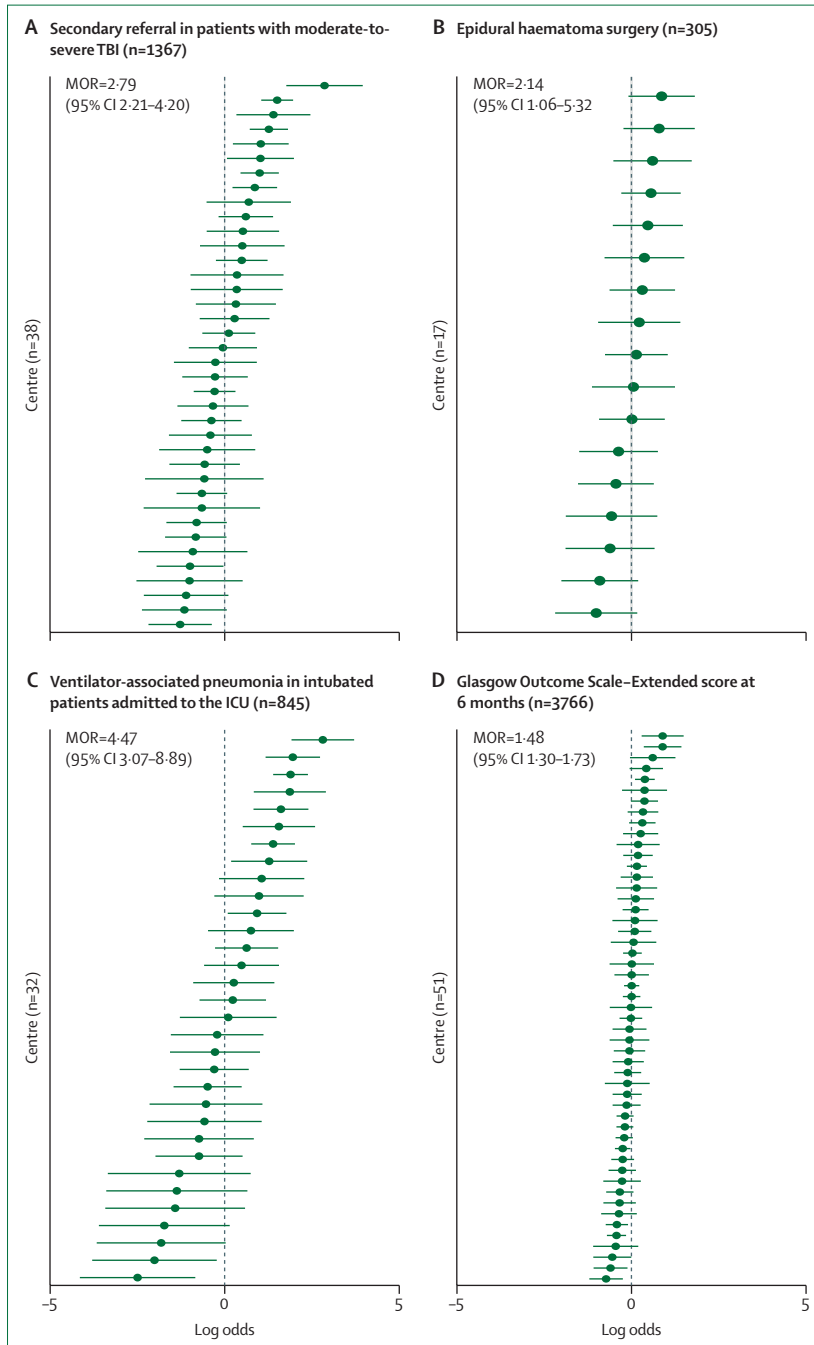
The substantial burden of traumatic brain injury (TBI) in low-income and middle-income countries (LMICs) represents both a clinical need and a research opportunity. However, resource limitations affect medical record keeping,<sup>383</sup> civil registration systems, and clinical research, making accurate determinations of TBI hospital admissions and deaths challenging.<sup>384,385</sup> Researchers in LMICs cite insufficient funding, incentives, training, and institutional support as barriers to conducting high-quality research,<sup>386</sup> with patient follow-up being logistically challenging.<sup>387</sup> Considerable heterogeneity exists within LMICs, which, despite the described limitations, include several centres of excellence that have also provided unique and valuable contributions to scientific knowledge.<sup>331</sup> Understanding these varied systems of TBI care requires mixed-methods approaches<sup>388</sup> to data collection, and more recognition by peers and policy makers of the value of qualitative research.<sup>389</sup> Both clinical outcome instruments and qualitative methods require adaptation to account for linguistic and cultural heterogeneity. Finally, it is crucial that LMIC researchers are fully involved in scientific aspects of research, rather than just providing samples for what has been termed "helicopter research".<sup>390</sup>

alternative to pooling of data is to perform federated analysis (ie, centralised analysis with individual-level data remaining on local servers). In this approach, the data remain at their original location and a platform is constructed for decentralised coanalysis. Data federation strikes a balance between protection of patient privacy<sup>399,400</sup> and public health interests by bringing the analysis to the data, instead of the data to the analysis. This approach allows a two-stage meta-analytical process (which has a similar statistical interpretation as a one-

stage meta-analysis: see appendix p 27), and other decentralised analyses. Tools already exist for implementation of standard statistical analyses on federated platforms and implementation of machine learning approaches are under development. CENTER-TBI is now in the process of implementing a platform for federated analysis, allowing external researchers to access and analyse the data without any need for transfer of the data. Federated analyses offer novel venues to augment and accelerate TBI research worldwide and are potentially applicable to conditions beyond TBI.

**Comparative-effectiveness research**

In the 2017 Commission on TBI, we identified a particular potential for observational comparative-effectiveness research in the field of TBI, and suggested that evidence from high-quality observational studies could be as valuable as that from randomised trials because of their greater generalisability. CENTER-TBI has extensively applied observational comparative-effectiveness research to identify effective treatments for TBI by leveraging existing variation in treatment and outcomes between centres and countries. Large variations in different treatment approaches were observed (see section 3), but variation in outcome in the ICU stratum (median OR 1·2 [median OR represents the relative odds of the outcome in two randomly sampled centres])<sup>121</sup> was smaller than in previous studies on moderate and severe TBI (median OR 3·3; figure 12).<sup>190</sup> This finding does not necessarily



**Figure 12: Caterpillar plots of between-centre differences in interventions and outcomes in the CENTER-TBI study**  
 (A) Secondary versus primary referral to a specialised neuro-trauma centre in patients with moderate-to-severe traumatic brain injury. (B) Epidural haematoma surgery during hospitalisation in patients with an epidural haematoma on the admission CT. (C) Ventilator-associated pneumonia in intubated patients admitted to the ICU. (D) Glasgow Outcome Scale-Extended score at 6 months (higher scores on the ordinal scale). To estimate centre-specific effects, a random-effect regression model was created for each intervention and outcome. Each model was adjusted for casemix severity using variables from the International Mission for Prognosis and Analysis of Clinical Trials in TBI (IMPACT) Lab model: age, Glasgow Coma Scale-motor score, pupillary response, hypoxia, hypotension, Marshall CT classification, presence of traumatic subarachnoid haemorrhage, presence of epidural haematoma (omitted in the model for epidural haematoma surgery), and first glucose and first haemoglobin measurements from blood samples obtained on presentation. Multiple imputation was used for missing values of adjustment variables. For each intervention and outcome, only centres that enrolled at least ten patients from the target subgroup (eg, patients with an epidural haematoma in [B], intubated ICU patients in [C]) were included. As such, the number of centres on the y-axis differs between plots. Centres are ordered by their estimated random effect. For (A), (B), (C), (D), the origin of the x-axis represents the overall log-odds of experiencing the intervention and outcome for all patients from all centres for each respective plot. Random effects of more than 0 mean an increased likelihood and less than 0 mean a decreased likelihood of experiencing the intervention and outcome for a given centre. The MOR is a summary measure of the overall between-centre variation and is interpreted as the odds ratio of experiencing the intervention and outcome for the same patient, when comparing two randomly selected centres. An MOR of 1 indicates no between-centre differences, and larger MORs indicate higher variation. The MORs 95% CIs were derived from the profile likelihood CIs of the random effect SDs. ICU=intensive care unit. TBI=traumatic brain injury. MOR=median odds ratio.



preclude meaningful analysis, as different treatment preferences might affect an outcome in different directions.<sup>401</sup>

A particular challenge to drawing causal inferences from observational comparative-effectiveness research analysis is the risk for confounding by indication. Broadly speaking, two mitigation approaches can be differentiated: adjustment-based methods (eg, propensity scores and covariate adjustment) and so-called quasi-experimental designs (eg, an instrumental variable approach).<sup>402</sup> Both approaches were used in CENTER-TBI. We identified best practices in, for example, fluid management in the ICU and surgery for acute subdural haematoma (see section 3). The ADAPT study successfully applied comparative-effectiveness research to the analysis of the relative effectiveness of hypertonic saline and mannitol for managing intracranial pressure and cerebral perfusion pressure in paediatric patients with severe TBI.<sup>403</sup> Nevertheless, residual confounding might remain and was likely in the exploration of benefits of monitoring intracranial pressure by a ventricular catheter (allowing for drainage of CSF) versus by an intraparenchymal sensor.<sup>404</sup> A clear comparative-effectiveness research analysis plan before data collection, which considers all variables that are likely to interact with treatment effects, can ensure that all relevant data are collected and used to minimise residual confounding.

Causal interpretation of observational comparative-effectiveness research studies depends on methodological rigour, which can make interpretation and scientific review complex. CENTER-TBI had substantial problems during the peer-review process of multiple submissions for publication. These problems suggest that comparative-effectiveness research is not yet considered mainstream and highlight the need for reviewers with sufficient understanding of such research methods to judge their quality and to recognise when comparative-effectiveness research is an appropriate approach to answer a specific question.

CENTER-TBI and ADAPT<sup>403,405</sup> have shown that observational comparative-effectiveness research in TBI meets expectations. Nevertheless, challenges were encountered and lessons were learned (panel 9). The strength of evidence resulting from well-conducted comparative-effectiveness research studies can be considered high. Such studies, using robust methodology showing results that are mechanistically plausible, can be causally interpreted. They can inform clinical practice<sup>408</sup> and can complement randomised trials, specifically in situations for which there is no clinical equipoise or the standard treatment is difficult to define.

### Novel approaches to randomised trials

Although observational comparative-effectiveness research is increasingly recognised as relevant to the field of TBI, randomised trials remain the standard for

#### Panel 9: Comparative effectiveness research analyses: challenges and recommended solutions based on the experience from the CENTER-TBI study

##### Post-hoc study question

Problem: insufficient parameters to adjust for differences between treatment groups for a specific question.

Potential solution: pre-specification of study question and collection of all variables that are likely to relate to the selection of treatments.

##### Confounding by indication

Problem: residual confounding.

Potential solution: application of different approaches to analysis with different assumptions; for example, instrumental variable approach and propensity matching.

##### Small between-centre differences in outcome

Problem: decreases likelihood of identifying best practices.

Potential solution: none.

##### Peer-reviewers of submitted manuscripts insufficiently familiar with comparative-effectiveness research

Problem: multiple revisions or rejection from journals.

Potential solution: improved understanding of comparative effectiveness research methods among peers.

##### Strength of comparative-effectiveness research results undervalued compared with those from randomised trials

Problem: low interest and poor understanding of comparative-effectiveness research.

Potential solution: emphasise the relevance of real-world data. The COVID-19 pandemic has accelerated the implementation and acceptance of new research paradigms and increased awareness of the relevance of real-world data and real-world evidence.<sup>406,407</sup>

determining efficacy of interventions. Historical controls (ie, patients from cohorts in previous studies) are accepted by regulatory authorities in rare diseases with small but homogeneous patient populations, but TBI is not rare and patients are highly heterogeneous. A discussion on the use of cohort studies is included in the appendix (p 29). The classic design of a randomised trial involves strict enrolment criteria and randomised, blinded allocation of patients to two treatment groups. Randomised trials are costly and labour intensive. Means to make the conduct of these trials more efficient are needed. For these reasons, interest in non-classic designs is increasing with lessons learned from other fields. We discuss various approaches below.

#### Platform trial design

Platform trials,<sup>409-413</sup> used with great effectiveness in the COVID-19 pandemic to identify effective treatments, provide infrastructures to study several interventions in a specific patient population simultaneously, avoiding

For the ADAPT study see <https://www.adapttrial.org/>

multiple independent trials. Interventions with similar mechanisms of action can form a specific domain or category of treatment. Patients can be randomly assigned in more than one domain, but to only one intervention of a specific domain. The approach also allows addition of new domains, or interventions within domains, when novel interventions emerge or research priorities change. Although their applicability in TBI remains untested, platform designs might enhance the efficiency of trials in this population.

#### Adaptive design

The long interval between intervention and final outcome assessment in TBI trials poses challenges for determining efficacy of an acute intervention and increases costs. Trial efficiency can potentially be increased by using adaptive designs, in which some features of the design can be dropped (eg, study drugs that show early futility) or other study agents inserted (ie, adapted as part of the trial design). Criteria for such changes need to be pre-specified and require interim analyses by an independent statistical team and decisions following a-priori determined thresholds (superiority, inferiority, or futility). By necessity, an adaptive design involves repeated interim analyses, incrementing the risk of a type 1 error. Bayesian statistics have been successfully used to mitigate this risk.<sup>409,414</sup> Implementing an adaptive design in TBI trials would, however, involve the use of early endpoints. To date, such early endpoints, which need to be related to final outcome, are exploratory in TBI. Work published in 2022 suggests that blood-based biomarkers and

advanced MRI imaging, captured in the acute postinjury phase, are associated with patient outcome (see section 4),<sup>251,252,415</sup> suggesting that these might serve as endpoints for proof of concept that a drug is hitting a target in an adaptive design. The TRACK-TBI Network is designing a phase 2 adaptive platform randomised control trial using a master protocol to test three drugs against placebo. With the adaptive design, the investigators aim to discover early utility or futility using biomarker endpoints along with functional, cognitive, and symptom measures. The potential of an adaptive randomisation design is also being explored in the context of the HOBIT trial on hyperoxia.<sup>416</sup>

#### Pragmatic mega-trials

Pragmatic mega-trials recruit large patient numbers, use simple data collection forms, and target small treatment effects that apply across the population of patients studied or in identifiable subgroups with adequate sample size following stratified randomisation to deliver statistical power. To date, they have been one of the more successful approaches in TBI. Examples of pragmatic mega-trials in TBI are in the appendix (p 30). Mega-trials can detect small treatment effects that apply to an unselected population of TBI patients, but questions have been raised about their clinical relevance.<sup>417</sup> Furthermore, their pragmatic design and limited data collections often make identification of discrete treatment-responsive subgroups impossible. Past mega-trials have all tested relatively inexpensive drugs already approved for other indications, and would appear less appropriate for complex interventions or for

For more on **APPG ABI** see <https://publications.parliament.uk/pa/cm/cmllparty/220504/acquired-brain-injury.htm>

For more on **UKABIF** see <https://ukabif.org.uk/>

For more on **CPIM** see <https://www.fda.gov/drugs/new-drugs-fda-cders-new-molecular-entities-and-new-therapeutic-biological-products/critical-path-innovation-meetings-cpim>

For more on **biomarker candidates** see <https://www.fda.gov/drugs/new-drugs-fda-cders-new-molecular-entities-and-new-therapeutic-biological-products/critical-path-innovation-meetings-cpim>

For more on **MDDT** see <https://www.fda.gov/medical-devices/science-and-research-medical-devices/medical-device-development-tools-mddt>

For more on **FDA development of treatments for traumatic brain injury** see <https://www.fda.gov/news-events/fda-brief/fda-brief-fda-takes-new-step-help-advance-development-novel-treatments-traumatic-brain-injury>

For more on **OsiriX** see <https://www.osirix-viewer.com/>

### Panel 10: Examples of regulatory and policy engagement in traumatic brain injury research

The UK All Party Parliamentary Group on Acquired Brain Injury (APPG ABI), a non-partisan group of UK members of parliament, was launched in 2017. All UK members of parliament were provided with a copy of the 2017 Commission on traumatic brain injury (TBI), and the APPG, chaired by member of parliament Chris Bryant, obtained input from a range of experts in brain injury, in a process facilitated by the UK Acquired Brain Injury Forum (UKABIF), an organisation that advocates for patients with acute brain injury. In 2018, the APPG launched the *Time for Change* report based on these deliberations, which addressed issues in neurorehabilitation, education, the criminal justice system, sport-related concussion, and welfare benefits. This report and testimonies from the APPG ABI have informed parliamentary debates and the development of government policy in the area, and these procedures have become recognised as a model for progress.<sup>2</sup>

The TRACK-TBI study group has engaged with regulators and US policy makers. TRACK-TBI has used each of the Critical Path for Innovation Meetings (CPIM), submission of letters of support for promising biomarker candidates, obtained qualification of medical device development tools (MDDTs), and convened

public consensus conferences with participation from the US Food and Drug Administration to develop and disseminate evidentiary standards aimed at improving efficiency and achieving success in drug and device development. For example, in 2019, approval as an MDDT was provided for an OsiriX Common Data Element package, which assists health-care providers, such as neuroradiologists, to better identify eligible patients for enrolment in mild TBI clinical trials.

TRACK-TBI leadership has had extensive engagement with the US National Academies of Sciences, Engineering, and Medicine (NASEM). In 2020, concerned about the under-studied, high burden, and complex health issues attendant to TBI, NASEM convened a Committee on Accelerating Progress in Traumatic Brain Injury Research and Care. Composed of a broad membership of stakeholders, the Committee, including several clinical and research experts from TRACK-TBI, analysed barriers and opportunities to improve TBI research and the currently fractured care systems from the perspectives of researchers, public institutions, industry, and importantly, patients and caregivers. The Committee's report,<sup>182</sup> released in 2022, presents a roadmap to guide the field over the next decade.

	Original recommendation	Progress since the 2017 Commission	New and persisting challenges	Work for next decade
Worldwide, TBI is a leading cause of injury-related death and disability, with a devastating effect on patients and their families	Concerted efforts to address this vast global health problem should focus on policies aimed at reducing the burden and effects of TBI, through better prevention, improved access to care, and promotion of clinical research to improve treatment standards	Increased attention to road safety in LMICs: WHO's Decade for Action on Road Safety launched in 2021. Substantial support for TBI research from funding agencies, including the European Commission, NIH-NINDS and the Department of Defence in the USA, NHMRC in Australia, and the MRC in the UK. No clear evidence of change in mortality or disability outcomes from TBI, despite advances in care and research. However, these advances are likely to have a latent period before they have an effect on these key statistics	LMICs are disproportionately affected by TBI. Populations at increased risk include children, older people, and criminal offenders. Adverse brain health consequences caused by TBI and repetitive head impacts in sport	Deliver on implementation of Road Safety goals of 50% reduction in traffic-related injuries and deaths by 2030. Target prevention and intervention actions to populations at increased risk. Harmonise safe-play rules across team sports and increase prevention focus for individual sports
Coordinated research efforts on a global basis are needed to address the growing public health problem of TBI	A commitment of governmental and non-governmental funding bodies, as well as industrial partners, is needed to foster global collaborations and to establish national and international biorepositories and databases that can facilitate future TBI research	Substantial success with large collaborative studies in InTBIR—large bodies of research with valuable databases, image repositories, and biobanks. Some follow-up funding, but this is less integrated. Clear evidence of engagement with policy makers and regulators. New TBI funding initiatives (eg, Mission TBI in Australia) and engagement of global partners in LMICs (eg, NIHR Global Neurotrauma Initiative)	There is no structured follow-up funding to support maintenance of the databases and to facilitate meta-analyses across the datasets	Exploiting the results and (perhaps more importantly) the networks of these studies will require collaborations supported by ongoing funding. Discussions are underway—both between individual study partners and globally through InTBIR. Continue to engage with policy makers and funders, but further involvement of patient advocacy organisations is also needed. Encourage governments and funders to integrate efforts—'how' is at least as important as 'how much'
In LMICs, the incidence of TBI due to traffic incidents is increasing, while in HICs, TBI increasingly affects elderly people, mostly resulting from falls; however, methodological variations confound comparisons of epidemiological patterns of TBI between regions, countries, and continents	An international consensus is needed on definitions and standardised epidemiological monitoring of TBI to allow accurate measurement of incidence, prevalence, and mortality, and comparison of rates of access to community, hospital, and residential care	Still no accepted framework for epidemiological data collection and reporting, with resulting wide variations in global estimates of TBI incidence (2017 Commission estimate of 50 million–60 million per year; vs Global Burden of Disease study estimate of 24 million–30 million per year) without objective evidence of which is correct	Inconsistencies within and between hospitals in ICD coding could contribute to the large variations observed	There is a need for an accepted process for data capture and reporting of TBI epidemiology, agreed upon by governments and institutions
TBI results in substantial health care and societal costs	More effective strategies for TBI prevention are urgently needed and could deliver cost savings that help to fund research and improve access to health care for TBI	Most ongoing prevention actions are directed at road traffic safety. Only a few new studies on the cost burden of TBI have been published since the 2017 Commission	Increased recognition of the relevance of frailty and alcohol abuse as factors contributing to falls causing TBI in older people	Target fall prevention for older people in HICs. Need to develop fall prevention strategies more universally, and as demographics in LMICs change, ensure implementation also in these countries. Develop a research focus on the cost burden of TBI and cost-effectiveness of diagnostics (including biomarkers) and treatment
Access to health care is often inconsistent between centres, regions, and countries, especially for acute and post-acute care	Health-care policies should aim to improve access to acute and post-acute care to reduce the effects of TBI on patients, families, and society	No clear improvement in access to acute and post-acute care. Some improvements in engagement of LMIC partners in Global Health Research in TBI and development of protocols for acute TBI management suitable for deployment in resource-limited settings. Epidemiology of TBI might have changed during the COVID-19 pandemic. Reports of the effects of COVID-19 on TBI care and outcome are variable	Disparities in care identified in high-income countries for: older people injured by low-energy mechanisms (falls), who are less often taken to a trauma centre, receive less critical care, and fewer neurosurgical interventions compared with patients injured by high-energy mechanisms. Access to rehabilitation for patients with moderate to severe TBI. Absence of structured follow-up for mild TBI, despite more than 50% of patients do not recover to pre-TBI levels of health and wellbeing by 6 months after injury. Near-total absence of adequate pre-hospital and post-acute care in LMICs	Reappraisal of triage tools used in emergency settings, aiming to decrease the current strong focus on high-energy mechanisms. Involve rehabilitation services at an early stage of the in-hospital treatment for TBI. All patients discharged from hospital after mild TBI should be scheduled for follow-up. Develop and implement health-care policies in LMICs to correct this disparity. Need to monitor the effects of COVID-19 on TBI care and address these if clinically significant.

TBI=traumatic brain injury. LMICs=low-income and middle-income countries. NIH-NINDS=US National Institutes of Health-National Institute of Neurological Disorders and Stroke. NHMRC=Australian National Health and Medical Research Council. MRC=UK Medical Research Council. InTBIR=International Traumatic Brain Injury Research. NIHR=UK National Institute for Health and Care Research. HICs=high-income countries. ICD=International Classification of Diseases.

**Table 3: Summary overview of progress and outstanding issues, based on the key messages of particular relevance to policymakers and recommendations presented in the 2017 Commission**

new drugs or interventions, for which safety monitoring is more relevant.

For the list of new InTBIR studies see <https://intbir.incf.org/list-of-studies>

For the InTBIR initiative see <https://intbir.incf.org/>

For the CReACTIVE study see <http://creactive.marionegri.it/>

For the NIHR Group on Neurotrauma see <https://neurotrauma.world/>

**International collaborations**

The formation of the InTBIR initiative, established in 2011 initially as a collaboration of funding agencies,<sup>5</sup> formed a major step forward towards international collaborations to support innovative study design. 10 years after inception, the InTBIR initiative has become an international open science ecosystem in clinical TBI research. Major studies conducted under the auspices of InTBIR included CENTER-TBI, TRACK-TBI, CReACTIVE, and ADAPT, and several other multicentre studies and trials. CENTER-TBI evolved from a primarily European-based project to a global study with linked data collections in Australia, China, and India. Since its inception, the operating model of InTBIR has evolved, and it is now a collaborative consortium of neurotrauma researchers, with funding bodies having a less directive role in its function than previously. Models of collaborative research networks, such as the Canadian Traumatic Brain Injury consortium, could be emulated globally with InTBIR.

This new phase of InTBIR, which is still in evolution, promises to provide a platform for international and transdisciplinary collaboration, with a new tranche of collaborative studies in development. These studies will include projects conducted in Australia in the context of the Mission for TBI, announced by the Australian Government in 2019 to dedicate grant funding of 50 million Australian dollars over a 10-year period. The Mission for TBI aims to accelerate Australian-led TBI research to develop and deliver innovative and effective treatments that improve health outcomes, in partnership with people with TBI and carers. Global collaborations are needed with researchers from LMICs because the greatest burden of TBI occurs in these countries. An example is the NIHR Global Health Research Group on Neurotrauma, which is already showing high productivity<sup>18</sup> (see also section 2).

**Interactions with regulators, research funders, and policy makers**

Neurotrauma researchers have traditionally pursued academic outputs and sought translation of their findings through clinical guidelines (usually in conjunction with

	Original recommendation	Progress since the 2017 Commission	New and persisting challenges	Work for next decade
Second or subsequent concussions that occur before recovery from an initial concussion can be associated with more severe symptoms and more prolonged recovery than a single injury of similar severity	Any risk of an early second injury after even a mild TBI should be avoided; professional sporting organisations should set an example for children and amateur athletes by immediately removing from play anyone with a suspected concussion	Increasing visibility of dangers of concussion and most professional sporting bodies have (or are moving towards having) good concussion protocols. Substantial new knowledge on sport-related concussion from very large observational studies	Implementation of protocols is still incomplete across different team sports, and isolated poor practice is still visible during high-profile televised events. Although there is a strong focus on the risk of sport-related concussion and repetitive head impacts in team sports, most patients seen in hospital with sport-related concussion have sustained the injury during individual sports or recreational activities	Need to ensure broad adoption of sport-related concussion protocols. Continue education and public pressure on governing bodies to ensure consistent practice that is compliant with guidelines. Re-enforce preventive measures in individualised sports such as cycling and horse-riding
Methods of diagnosis and classification of patients with TBI are insufficient to permit targeting of current and new therapies to the needs of individual patients	Research is needed to improve the precision of diagnosis, classification, and characterisation of TBI using multidomain approaches	There have been substantial gains from a large body of research reported in the past 5 years, much of it from large collaborative studies, incorporating advanced neuroimaging and blood biomarker data. Approaches to individualised titration of ICU care using multimodality monitoring are now being tested in clinical trials. Insights from genomic medicine and measurement of host inflammatory response are less developed, but datasets are available for exploitation	Identification of groups of patients who would be most likely to benefit from specific interventions. Use of blood-based biomarkers is on the verge of a breakthrough for diagnostic and prognostic use in TBI, but implementation in practice is adversely affected by an absence of clinical-use assays and cross-platform harmonisation	Use advanced analytic techniques, including artificial intelligence approaches to derive clinically relevant insights. Integration of new data sources to identify patient endotypes for trials of existing and new therapies. Translate these research advances into real-world approaches to individualised management of patients
Evidence underpinning guidelines for medical, surgical, and rehabilitation interventions for TBI is weak	Robust evidence is needed to inform guidelines on medical, surgical, and rehabilitation interventions, and hence improve outcomes for patients with TBI	Evidence from randomised clinical trials available in some areas (mainly surgical), and additional trials are now underway or in preparation. Comparative-effectiveness research is making increasing contributions. New generation of expert consensus-based guidance to supplement rigorous evidence-based guidelines	Although comparative-effectiveness research analyses have proven to provide strong evidence, the methodology is complex and often insufficiently understood or appreciated	Continue to seek highest quality of evidence (from randomised controlled trials) wherever possible, but understand the opportunities and limitations of comparative-effectiveness research and expert consensus. Consider platform trials and adaptive designs to accelerate evidence generation. Better publicise the potential of comparative-effectiveness research analyses

(Table 4 continues on next page)

	Original recommendation	Progress since the 2017 Commission	New and persisting challenges	Work for next decade
(Continued from previous page)				
Substantial between-centre variability in treatment and outcome in TBI offers unique opportunities for comparative-effectiveness research to improve the strength of evidence	Comparative-effectiveness research should be supported to identify best practices and to improve the level of evidence for systems of care and diagnostic and therapeutic interventions	Between-centre variability in practice confirmed in large observational studies, and comparative-effectiveness research analyses have permitted identification of best practices (eg, fluid management, hyperosmolar therapy, thrombosis prophylaxis, and surgical approaches)	Outcome variance between centres is less substantial than expected. Some scepticism experienced from peer-reviewers during the publication process	Better quantitation of opportunities and limitations of comparative-effectiveness research approaches—we need to understand when a result from comparative-effectiveness research is the best evidence available and when it should serve to set a hypothesis as a prelude to a formal randomised clinical trial
Trauma disturbs the brain in complex ways, affecting multiple outcome domains	Multidimensional outcome constructs that quantify the overall burden of disability from TBI need to be developed and validated to guide improved clinical management and support high-quality research	Translation and linguistic validation of outcome instruments, previously only available in English, into multiple languages. New tools to understand and compensate for missingness of outcome data. Better understanding of how different outcome assessments (eg, GOSE, quality of life, mental health, and cognition) fit together and affect the overall outcome	Uncertainty if multidimensional assessment should focus on the use of multiple instruments or on development of a composite outcome score	Implement systems of outcome assessment that integrate different instruments, understand the benefits and limitations of such approaches, and then find ways to refine them
TBI might represent an important modifiable risk factor for epilepsy, stroke, and late-life neurodegenerative diseases	Studies are needed in children and adults to better understand links between TBI of all severities and an increased risk of later neurological diseases	Further data on epidemiological links between repeated concussions and late neurodegeneration, supported by a few studies examining medium term outcomes of acute TBI over a decade. Large collaborative efforts ongoing to collate late neuropathology data for TBI-related neurodegeneration WHO initiative on epilepsy in the context of other diseases (including TBI); and guidelines on TBI-related pituitary dysfunction	Absence of early clinical criteria to determine the onset of late-life neurodegenerative diseases	Continue to look for and correct treatable late consequences of TBI. Need definitive studies with a long follow-up to address the long-term consequences of TBI. Combine post-mortem neuropathology with ante-mortem molecular imaging to understand the mechanisms of TBI-related neurodegeneration
A validated set of quality indicators is essential for the benchmarking of quality of care, but none exists for TBI	Efforts are needed to develop a set of quality indicators for TBI that includes structure, process, and outcome metrics	Some progress with development of quality indicators	Quality indicators developed are restricted to the ICU setting. Not ready yet for translation into practice	Refine, validate, and implement quality indicators
TBI=traumatic brain injury. ICU=intensive care unit. GOSE=Glasgow Outcome Scale-Extended.				
<b>Table 4: Summary overview of progress and outstanding issues, based on the key messages mainly directed at clinical management and research and recommendations presented in the first Commission</b>				

professional bodies) and new diagnostic and therapeutic interventions (usually through collaboration with industry partners). However, it has become increasingly obvious that to affect clinical care and outcomes, there is also a need to interact with regulators (appendix p 31), policy makers, and research funders. The release of the 2017 Commission in the European Parliament exemplified such engagement, and provided an ongoing stimulus for researchers to pursue engagement outside the academic bubble. Panel 10 lists three examples of such outputs that have materialised since the Commission was published.

**Main messages and recommendations**

*Main messages*

(1) TBI is often characterised by both an acute loss of mental capacity of patients to provide informed consent for participation in research and by an emergency situation. Although GDPR recognises the issue of absence of capacity to provide consent, no provisions are included that are relevant to patients with acute lack of capacity or to emergency situations.

(2) Standardisation of clinical data collection, based on the TBI common data elements, provides a common language for research, but the common data elements need to be made internationally applicable when aiming for global standardisation of clinical data collection. There is substantial redundancy and duplication in current common data elements.

(3) Data sharing and analyses across different datasets do not necessarily require data transfer and can be done on a federated platform. Use of a federated platform facilitates broad use of data, while reducing the risks for violation of data security and facilitating privacy regulation.

(4) Costs of data curation and deep harmonisation in preparation for sharing research data are under-estimated and can amount to up to 20% of a study budget.

(5) Comparative-effectiveness research has delivered on expectations by identifying best practices and providing strong evidence in support of treatments, but its interpretation can be complex, contributing to a perception that the strength of results from such research is lower than that of results from randomised clinical trials.

### Recommendations

- (1) Regulatory guidance should be developed. Consider mandating that researchers document objective proof of mental capacity in the study participant, who might have temporarily lost capacity, before seeking informed consent.
- (2) NIH-NINDS, as the coordinating agency for the TBI common data elements, needs to ensure appropriate international input when developing the next update of the common data elements to version 3.0. Updates to and refinement of TBI common data elements should be informed by the pragmatic experience of large-scale studies conducted under the InTBIR initiative.
- (3) Support is required for the development of platforms for federated analysis, particularly for the development and implementation of machine-learning techniques on such platforms.
- (4) For completed studies, mechanisms should be developed to facilitate the maintenance of the data and provision of guidance to external researchers wishing to analyse the data. For new studies, inclusion of an appropriate budget to prepare data for sharing should be foreseen in the grant award.
- (5) Educational and outreach efforts are needed to improve the understanding of comparative-effectiveness research methods and their interpretation.

### Conclusions: Looking backward and looking forward

This update provides an overview of progress since the publication of the 2017 Commission on TBI in 2017 and outlines remaining challenges. Tables 3 and 4 summarise key messages and recommendations from the original Commission, the progress made over the past 5 years in addressing these, and persisting and new challenges identified as part of this update. Table 3 contains key messages of particular relevance to policymakers, whereas table 4 contains key messages mainly directed at clinical management and research.

There has clearly been progress in the past 5 years, mostly due to the collaborative efforts triggered by the InTBIR initiative. However, many of these advances have yet to achieve routine clinical implementation and major issues persist in the care of patients with TBI in LMICs. Substantial progress has been made in incorporating novel clinical variables, blood biomarkers, and neuroimaging into patient characterisation, and implementation of these advances into clinical practice is currently underway. However, additional progress is needed in terms of achieving precision medicine approaches to TBI management. Although further evidence is needed, these approaches might include incorporation of molecular and genomic information into clinical practice, assisted by new approaches to data analysis. Finally, engagement with funders, policy makers, and regulators, and closer partnership with patient representative groups could address important strategic issues in TBI research and delivery of care.

The final columns of tables 3 and 4 suggest a work plan to address challenges over the next decade. We hope that a following update of the Commission on TBI in 5–10 years might document further progress in all of these areas, including TBI prevention, clinical management, and patient outcomes.

### Contributors

All authors contributed to drafting parts of the text, and have seen and approved the final version. AIRM, DKM, and GTM led the *Lancet Neurology* Commission on traumatic brain injury, oversaw the collation of sections, and performed the final general editing of the manuscript. They contributed equally. The main authors provided draft text and contributed to (parts of) the various sections. Authors for section 1 were BLB, MJB, TB, BC, DJC, GC, KDO'C, RMC, EF, FMH, JAH, HK, FL, MMa, MMc, JP, WS, AT, AU, WHW, and RZ. Authors for section 2 were NA, RD-A, AB, AK, BLB, DC, EC, GC, KDO'C, RMC, BG, BF, DG, PH, FL, AMi, MMc, SM, JP, CRø, WS, and KKWW. Authors for section 3 were CÂ, MA, NA, DJC, GC, MC, RMC, AE, TavE, AF, BF, DG, FG, GG, JG, GH, PH, J-yj, Mvdj, AK, EJOK, FL, AMi, GM, MM, DN, LDN, WP, CRo, CRø, NS, PS, EvV, EJAW, AU, AY, FAZ, and RZ. Authors for section 4 were CÂ, RD-A, AB, EC, MC, AE, BG, AnM, PM, SM, DN, VN, DO, MO, DP, LP, JR, RR, EWS, PS, IT, JV, TVV, KKWW, ELY, JY, and FAZ. Authors for section 5 were MJB, YGB, JG, MG, FMH, PH, Soj, Swj, AMi, MMc, LDN, KDO'C, DP, JP, DVP, DJS, EWS, MBS, WS, NvS, NT, OT, LW, JY, MZ, and RZ. Authors for section 6 were AE, AMi, Soj, Swj, HFL, AM, SP, EWS, and LW. Authors for section 7 were MA, DJC, GC, AE, ATE, MF, PH, ARF, EJOK, VDK, HFL, AMa, DP, EWS, PS, AFT, EvV, SRW, and JY. The group authors—287 contributors designated as the International Initiative for Traumatic Brain Injury Research (InTBIR) Participants and Investigators, listed at the end of the paper—contributed by means of interacting with and providing their insights and experience to main authors. Many of the contributors participated in recently completed InTBIR studies—the results of which have substantially informed this Commission. All group contributors were offered the opportunity to provide comments on the final draft. The final version of the manuscript was reviewed and approved by all main authors and group contributors.

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