OPINION

Changing patterns in the epidemiology of traumatic brain injury

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Abstract | Traumatic brain injury (TBI) is a critical public health and socio-economic problem throughout the world. Reliable quantification of the burden caused by TBI is difficult owing to inadequate standardization and incomplete capture of data on the incidence and outcome of brain injury, with variability in the definition of TBI being partly to blame. Reports show changes in epidemiological patterns of TBI: the median age of individuals who experience TBI is increasing, and falls have now surpassed road traffic incidents as the leading cause of this injury. Despite claims to the contrary, no clear decrease in TBI-related mortality or improvement of overall outcome has been observed over the past two decades. In this Perspectives article, we discuss the strengths and limitations of epidemiological studies, address the variability in its definition, and highlight changing epidemiological patterns. Taken together, these analyses identify a great need for standardized epidemiological monitoring in TBI.

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Introduction

Traumatic brain injury (TBI) is a critical public health and socio-economic problem throughout the world. It is a major cause of death, especially among young adults,[1] and lifelong disability is common in those who survive. Although high-quality prevalence data are scarce, it is estimated that in the USA, around 5.3 million people are living with a TBI-related disability,[2] and in the European Union ('old' Member States), approximately 7.7 million people who have experienced a TBI have disabilities.[3] TBI commonly leads to neurocognitive deficits (such as impaired attention, inability to form visuospatial associations, or poor executive function) and psychological health issues; for example, 30–70% of TBI survivors develop depression. TBI survivors also exhibit increased impulsivity, poor decision-making and impulsive–aggressive behaviour. Such impairments in self-regulatory behaviours can affect interpersonal relationships and contribute to poor community, social and vocational integration, and may lead to long-term placement in an institutional setting.

Competing interests
The authors declare no competing interests.

TBI is considered a 'silent epidemic', as society is largely unaware of the magnitude of this problem.[2] In the USA, epidemiological monitoring of TBI is conducted by the Centers for Disease Control and Prevention (CDC), but standardized monitoring of TBI in Europe is deficient. Variability in both diagnostic criteria and case ascertainment in TBI further contributes to the inconsistency of incidence estimation and confounds comparison between studies. Nevertheless, clear evidence exists to show that epidemiological patterns of TBI are changing, linked to consequences of prevention strategies and health-care delivery. In this Perspectives article, we summarize available data on the worldwide incidence of TBI, discussing the limitations of such data and addressing problems related to the definition of TBI. We highlight changing epidemiological patterns and discuss discrepancies between perception and factual information on improvements in outcome.

Incidence

The incidence of TBI worldwide is rising, mainly owing to injuries associated with the increased use of motor vehicles, particularly in middle-income and low-income countries.[1] Estimates of TBI incidence show substantial variation between countries (Figure 1).[3–17] Data from the CDC indicate that each year in the USA, 1.7 million people sustain a TBI.[18] 1.4 million of these injured individuals are treated in emergency departments, with around 275,000 hospitalizations and 52,000 fatalities. A meta-analysis of reports from 23 European countries revealed a hospital admission incidence of 235 per 100,000 people.[3] However, substantial variation was found in the incidence of admission recorded in each study and country, ranging from 20 admissions per 100,000 people in studies that considered only neurosurgical cases to 536 admissions per 100,000 people in a report that included emergency department visits, hospital discharge and coroner reports. Such variability could be attributable to differences in inclusion criteria and/or variability with regard to policies on indications for hospital admission or neuroimaging. Reported estimates probably underestimate the 'real' incidence of TBI and should, therefore, be interpreted with caution.

Several key limitations of existing epidemiological studies are worth highlighting. First, high-quality epidemiological monitoring data are lacking. The available estimates are based on registration of emergency department visits, hospital admissions and discharge registries. In these registries, TBI is often identified using codes of the International Classification of Diseases (ICD). Notably, these definitions were more pathologically based in the ICD-9 compared with the more clinically orientated definitions in the new ICD-10. Both classifications are primarily intended for administrative use; consequently, their applications in epidemiological research are limited. Retrospective identification of patients with mild TBI by means of ICD coding produces substantial numbers of false-positive and false-negative results.[19] ICD codes seem to be sensitive for identification of severe TBI, although further classification by specific injury type is limited owing to variability in sensitivity and specificity of the codings.[20] Epidemiological estimates for TBI derived from databases that use ICD coding should, therefore, be interpreted with caution.

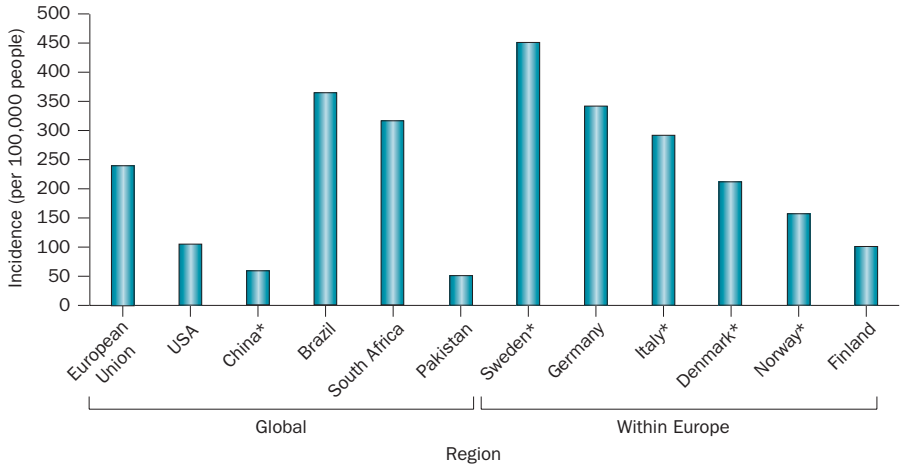

Figure 1 | Estimates of the global incidence of traumatic brain injury. *Mean of results from two studies.

A second limitation of epidemiological studies arises from under-reporting of the number of people who sustain TBI. Such under-reporting is likely as patients with mild TBI often do not seek medical help—especially in rural areas or in countries with less-developed health-care systems—and patients with very severe TBIs are often not registered if they die before reaching a hospital. The third limitation, discussed further below, is the fact that definitions of TBI are currently unclear and subject to debate.

Defining TBI and concussion

The term 'head injury' has been replaced with 'traumatic brain injury' as this new term captures the importance of the brain in these injuries. Although considered to be self-explanatory, in practice this terminology continues to be plagued by ambiguity, especially at the mild end of the severity spectrum of TBI. Several definitions for mild TBI have been proposed in recent decades (Box 1).[21–23]

ACRM and WHO definitions

The main difference between the American Congress of Rehabilitation Medicine (ACRM)[21] and WHO Task Force[22] definitions of TBI concern the inclusion of 'altered mental state'.[24] For diagnosis of TBI, the ACRM definition requires "any alteration of mental state at the time of accident (dazed, disoriented, or confused)," whereas the WHO Task Force has changed this definition to "confusion and disorientation." The ACRM and WHO definitions focus on mild TBI, excluding patients with more-severe injuries, and thus ignoring the clinical reality that TBI severity lies along a continuum. Furthermore, these definitions do not acknowledge additional injury mechanisms such as blast injuries—an aetiological mechanism of TBI that is of increasing importance to both civilians and military personnel in areas of military conflict.

The ACRM definition restricts causes of TBI to the following: the head being struck; the head striking an object; or the brain undergoing an acceleration–deceleration movement (such as whiplash) without direct external trauma to the head.[21] The WHO definition lists specific diagnostic exclusions, stating that the clinical features that lead to a diagnosis of mild TBI must not involve drugs, alcohol or medications; be attributable to other injuries or treatment for other injuries (such as systemic injuries, facial injuries or intubation); or be caused by other problems (for example, psychological trauma, language barrier or coexisting medical conditions) or by penetrating craniocerebral injury.[22] Given these limitations, the need for a more comprehensive definition of TBI that addresses emerging injury mechanisms and covers the entire spectrum of injury was recognized.

Common Data Elements definition

The Working Group on Demographics and Clinical Assessment of the International Interagency Initiative toward Common Data Elements for Research in TBI and Psychological Health recently proposed a broad definition of TBI that is applicable across all injury severities, and includes a wide range of injury mechanisms.[23] Their definition of TBI is "an alteration in brain function, or other evidence of brain pathology, caused by an external force." Three possible causes of TBI were specifically added to the ACRM definition: a foreign body penetrating the brain; forces generated from events such as a blast or explosion; and other force yet to be defined.

Despite inclusion of accompanying explanatory notes to provide more guidance, the definition of 'altered brain function' still lacked precision. Indeed, an accompanying discussion on the definitions recognized that 'mental symptoms' may have causes other than TBI (such as pain, medication, alcohol or drugs use or intoxication, or a post-traumatic stress disorder), which can be present either in isolation or in addition to an injury of the brain. Such symptoms may confound or complicate diagnosis of mild TBI, particularly when the patient presents late after the injury. The solution offered was to use distinct degrees of precision for consideration of a diagnosis of TBI and for establishment of the diagnosis, with the latter judgment involving less-ambiguous criteria.

Concussion

In a project funded by the CDC and US Department of Defence, coordinated by the Brain Trauma Foundation, the US Concussion Definition Consortium is working on a definition of concussion. The merit of a free-standing specific definition of concussion is of particular relevance to mild TBI, as experienced in many sports-related injuries,[25,26] but ensuring that characterization of concussion is integrated into a more holistic approach to definitions of TBI that can be applied across the severity spectrum has distinct advantages. One valuable outcome of this initiative would be to provide a more concise definition of 'altered mental state'.

Diagnostic criteria

Traditionally, patient history has been used as the gold-standard approach to enable diagnosis of TBI. The confounding factors listed above (particularly for mild TBI) and the late presentation of TBI that is inherent in some settings (such as with military-related injury) have, however, emphasized the need for supportive tests to help strengthen diagnostic certainty. Acutely, such tests include standardized symptom testing, the sensitivity of which is increased when changes are defined against a baseline score. Furthermore, certain symptoms may have stronger power than others for prediction of delayed symptom resolution after mild TBI. In one study, delayed recovery was associated with unconsciousness (odds ratio [OR] 4.15; 95% CI 2.12–8.15), post-traumatic

amnesia (OR 1.81; 95% CI 1.00–3.28), and more-severe acute symptoms (P <0.0001).[27]

In patients with TBI, analysis can involve formal—often computer-based—neurocognitive testing, processed EEG and evoked responses, blood biomarkers,[28] and both CT and MRI (in particular, susceptibility-weighted imaging and diffusion-tensor imaging). These measures have different efficiencies with regard to diagnosis of mild TBI and prognostication of outcome. For example, symptom inventories can be used not only to identify patients with concussion or persistent postconcussional symptoms, but also to track resolution of these symptoms.[29] Neurocognitive testing and EEG can reveal persisting abnormalities in the brain of recovering patients that can give cause for caution, particularly when making decisions on whether to allow clinically asymptomatic individuals to return to play in high-risk sports such as boxing or American football.[30,31]

Recent evidence suggests that many patients with mild TBI in whom CT scans are normal show abnormalities on subacute MRI. Such abnormalities are strong predictors of poor neurocognitive and neuropsychiatric outcomes.[32] In cases where late symptomatology is suggestive of a prior TBI, symptoms cannot be used to confirm the diagnosis, and EEG and evoked responses lack diagnostic specificity in this setting. Consequently, MRI (and perhaps blood biomarkers[28]) may provide useful confirmatory evidence that the symptoms are attributable to an earlier TBI. These emerging technologies offer opportunities for improved disease characterization in TBI, which will aid 'precision medicine'—a concept recently advocated by the US National Academy of Science that will facilitate targeted management and individualized approaches to treatment of patients with TBI.[33]

Box 1 | Definitions of mild TBI

ACRM (1993)[21]

A patient with mild TBI is a person who has had a traumatically induced physiological disruption of brain function, as manifested by at least one of the following:

- Any period of loss of consciousness ≤30 min
- Any loss of memory for events immediately before or after the accident (post-traumatic amnesia <24 h)
- Any alteration in mental state at the time of the accident (such as feeling dazed, disorientated or confused)
- Focal neurological deficit(s) that may or may not be transient
- GCS score 13–15 after 30 min

WHO (2004)[22]

Mild TBI is an acute brain injury resulting from mechanical energy to the head from external physical forces. Operational criteria for clinical identification include:

- Confusion or disorientation
- Loss of consciousness ≤30 min
- Post-traumatic amnesia ≤24 h
- And/or other transient neurological abnormalities such as focal signs, seizure and intracranial lesion not requiring surgery
- GCS score 13–15 after 30 min post-injury or later on presentation for health care

Common Data Elements working group on demographics and clinical assessments (2010)[23]

An alteration in brain function or other evidence of brain pathology caused by an external force

Abbreviation: GCS, Glasgow Coma Scale; TBI, traumatic brain injury.

Table 1 | Age of patients with TBI

Study	Year of study	*n*	Median age (years)	% of patients >50 years
Traumatic Coma Data Bank[44]	1984–1987	746	25	15
UK four-centre study[45]	1986–1988	988	29	27
European Brain Injury Consortium core data survey[46]	1995	847	38	33
Prospective Observational COhort Neurotrauma (POCON)[47]	2008–2009	339	45	43
Austrian severe TBI study[48]	1999–2004	415	48	45
Italian intensive care unit cohort[49]	1997–2007	1,478	45	44

Abbreviation: TBI, traumatic brain injury.

Changing epidemiology

Low-income vs high-income countries

A common perception is that the majority of TBI patients are young adult males who are injured in motor vehicle accidents. Many TBIs are indeed the result of motor-related accidents, but the pattern of injury varies across regions: in high-income countries, individuals with TBI are generally motor-vehicle occupants, whereas in middle-income and low-income countries patients with TBI are often vulnerable road-traffic users such as pedestrians, cyclists and motorcyclists. Increased motorization combined with inadequate traffic education and slow implementation of traffic safety regulations is the main cause of the increasing incidence of TBI in low-income and middle-income countries. In high income countries, improved safety regulations have led to a decline in traffic-related TBI.[1]

The success of safety regulations with regard to prevention of TBI was unequivocally demonstrated in Taiwan, where implementation of the motorcycle helmet law decreased the incidence of motorcycle-related TBI by 33%.[34] On analysis of patients recruited into the Medical Research Council CRASH trial, those who were injured in low-income and middle-income countries were younger and sustained more injuries in traffic incidents than their high-income country counterparts.[35] In high-income countries, alcohol consumption represents an important risk factor for TBI, and is suggested to be a contributory cause in up to 50% of all TBI admissions to intensive care units.[36]

In high-income countries, a shift in the population affected by TBI towards older age groups has been witnessed in recent decades. In an analysis of observational studies conducted between 1984 and 2004, comparison of median age and the proportion of patients over 50 years of age reveals a consistent increase in both variables over time (Table 1), which may be explained by a combination of factors. First, preventive measures have improved traffic safety and reduced the incidence of TBI related to traffic accidents, which primarily occur in younger individuals. Second, the absolute incidence of TBI among the elderly is increasing as a result of increased life expectancy and greater mobility in the elderly.[18] Data from the CDC show that individuals over 75 years of age have the highest incidence of TBI related

Table 2 | Outcome over time in observational studies

Study name	Year of study	*n*	Setting	GCS on admission	Mortality	% unfav.	Study
Older observational studies (prior to 1999)							
–	1968–1975	700	UK/NL/US	Coma ≥6 h	51%	62%	Jennett *et al.* (1977)[50]
Traumatic Coma Database (TCDB)	1984–1987	746	US	≤8	39%	58%	Foulkes *et al.* (1991)[44]
UK4 Centre	1986–1988	988	UK	≤8	39%	57%	Murray *et al.* (1999)[45]
European Brain Injury Consortium (EBIC) core data	1995	796 481*	Europe Europe	≤12 ≤8	31% 40%	49% 60%	Murray *et al.* (1999)[46]
Weighted average	–	–	–	–	42%	59%	–
Observational studies (1999–2005)							
Austria	1999–2004	492	Austria	≤8	38%	51%‡	Rusnak *et al.* (2007)[48]
Australasian Traumatic Brain Injury Study (ATBIS)	2000	363	Australia–New Zealand	≤8	32%	55%	Myburgh *et al.* (2008)[51]
–	1999–2004	672	Singapore	≤8	36%	51%	Ng *et al.* (2006)[52]
Weighted average	–	–	–	–	36%	52%	–
More recent studies (2005–2010)							
–	2005–2007	518	Paris	≤8	51%	66%	Darnoux *et al.* (2011)[53]
Prospective Observational COhort Neurotrauma (POCON)	2008–2009	339	NL	≤8	46%	60%	Andriessen *et al.* (2011)[47]
Ontario Prehospital Advance Life Support (OPALS) Major Trauma Study	?	538	Ontario (Canada)	≤8	33%‖	63%‖	Dowling *et al.* (2010)[54]
–	2008–2010	748	Latin America	≤8	31%	54%	Chesnut *et al.* (2011)[55]
Weighted average	–	–	–	–	39%	60%	–

*Severe subset (GCS ≤8 on admission). ‡Unknown in 16%. ‖Outcome assessed at discharge. Abbreviations: GCS, Glasgow Coma Scale; NL, The Netherlands; unfav., unfavourable. Reprinted with permission from *The Lancet*, **380**, Rosenfeld *et al.* Early management of severe traumatic brain injury, 1088–1098, © 2012, with permission from Elsevier.

hospitalizations, and are more likely to die from their injuries than any other age group. Older patients often present with multiple pretrauma morbidities[37] and are likely to be taking a range of medications, including anticoagulant therapy and platelet aggregation inhibitors, for pre-existing conditions; these medications are associated with a high risk of haemorrhagic contusions and subdural haematomas.

Paradigm shifts in our approaches to prevention, management and post-injury care for TBI in the elderly population will be necessary as the population ages. In low-income and middle-income countries, traffic safety education remains of paramount importance and requires further development.

Is mortality and outcome improving?

A general perception exists that improvements in the care of patients with TBI are leading to a decrease in mortality and improvements in outcome. This perception is largely based on comparisons between mortality rates in recent randomized controlled trials (RCTs) and mortality rates from older observational data sets such as the US Traumatic Coma Databank. From an epidemiological perspective, such comparisons are inappropriate, as selection strategies for these studies differ markedly: RCTs are strictly selective whereas observational studies have broad inclusion criteria.

One meta-analysis of 207 case series, involving over 140,000 patients with severe closed TBI over a time span of almost 150 years (1885–2006),[38] provides a methodologically sound assessment of mortality rate in TBI. The report revealed that overall mortality rate in TBI had decreased by approximately 50% over the entire period. This decrease was not uniform, however, and no change in mortality rate was noted during the period 1930–1970 or after 1990. The authors attributed static mortality rates between 1930 and 1970 to the increased use of motor vehicles in this period. The substantial decrease in mortality between 1970 and 1990 was attributed to the introduction of CT scanners and advances in intensive care, which led to improvements both in detection of TBI and in patient care. The static mortality after 1990 is surprising. One explanation for this outcome might be the epidemiological shift towards an elderly population—a group of individuals who are at risk of excessive pathologies (for example, haemorrhage due to falls) and comorbidities, and are, therefore, at high risk of mortality.

Similar conclusions were drawn in a recently published meta-analysis of observational studies that took place between 1980 and 2011, and involved over 300 patients with severe TBI in whom outcome was reported using the Glasgow Outcome Scale (Table 2).[39] Neither a clear reduction in mortality nor a decrease in the rate of unfavourable outcome over time was observed. Caution is needed in interpreting these findings, however, as the lack of access to individual data means that confounding effects relating to variability in initial patient characteristics and prognostic risk cannot be excluded. These considerations highlight the necessity for valid risk-adjustment models and uniform case-ascertainment processes to enable robust comparisons between studies. Furthermore, outcome studies should not stop at the acute phase (that is, at discharge from acute care) or postacute phase (rehabilitation). A recent study in

patients with TBI reported that the risk of death was increased up to sevenfold for at least 13 years after hospital admission.[40] This increase in mortality risk is multifactorial and, of note, some of the driving factors—such as post-traumatic epilepsy and endocrine dysfunction—are treatable.

Interest in the long-term cognitive consequences of TBI and the neuropathological associations that underpin these outcomes is increasing. TBI may, in some patients, trigger progressive cognitive decline or accelerate age-related cognitive decline.[41] The neuropathological substrates of such cognitive decline is uncertain, but tau deposition has been reported at postmortem analysis in individuals with recurrent mild TBI and in military personnel who sustained a blast injury.[42] Furthermore, accelerated age-related deposition of amyloid-β has been reported decades after injury in survivors of a single TBI.[43] The broad public health implications of these findings remain uncertain, but they are in agreement with an emerging consensus that TBI represents a substantial risk factor for development of Alzheimer disease, particularly in males and individuals who have a genetic predisposition to this disorder.[41] In any case, the emerging data highlight the need to consider whether TBI may, at least in some individuals, represent a chronic, progressive disease, and they underline the requirement for high-quality, long-term follow-up in TBI cohorts to establish the presence and magnitude of these pathological effects.

Conclusions

The epidemiology of TBI has changed over time. A shift towards older age of patients with TBI has been observed, especially in high-income countries, with falls representing the primary cause of TBI among the elderly, resulting in more contusional injuries. The high incidence of comorbidities and the frequent use of platelet aggregation inhibitors and oral anticoagulants among older patients have a negative influence on outcome following TBI. This is in agreement with the observation that the overall mortality rate of patients with severe TBI has not decreased since 1990 despite evidence that introduction of evidence-based guidelines for the management of TBI has led to an overall improvement in outcome.

The burden caused by TBI to patients, relatives, caregivers and societies remains high, but reliable quantification is difficult owing to a lack of adequate, standardized data on the incidence and outcomes of TBI, as well as a lack of generally accepted methods to systematically assess this burden. We recognize a great need for the development of high-quality epidemiological monitoring databases for reliable estimation of incidence, prevalence and outcome parameters. Long-term follow-up of large cohorts could provide definitive information about the cognitive consequences of acute TBI.

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Author contributions
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