ERABI
EVIDENCE-BASED REVIEW
of moderate to severe
ACQUIRED BRAIN INJURY

EPIDEMIOLOGY AND LONG-TERM OUTCOMES

POST ACQUIRED BRAIN INJURY

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Funding

This work is funded by the Ontario Neurotrauma Foundation. All work produced by ERABI is editorially independent from its funding source.

Conflict of Interest

In the context of ERABI development, the term “conflict of interest” (COI) refers to situations in which an author or ERABI staff member’s financial, professional, intellectual, personal, organizational or other relationships may compromise their ability to independently conduct this evidence-based review. No limiting conflicts were identified.

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Greetings from Dr. Robert Teasell,

Professor and Chair-Chief of Physical Medicine and Rehabilitation

The Collaboration of Rehabilitation Research Evidence (CORRE) team is delighted to present the Evidence-Based Review of moderate to severe Acquired Brain Injury (ERABI) *Mental Health Issues post Acquired Brain Injury.* Through collaboration of researchers, clinicians, administrators, and funding agencies, ERABI provides an up-to-date review of the current evidence in brain injury rehabilitation. ERABI synthesizes the research literature into a utilizable format, laying the foundation for effective knowledge transfer to improve healthcare programs and services.

We offer our heartfelt thanks to the many stakeholders who are able to make our vision a reality. Firstly, we would like to thank the Ontario Neurotrauma Foundation, which recognizes ERABI's capacity to lead in the field of brain injury evidence-based reviews and is committed to funding it. We would also like to thank the co-chairs of ERABI, Dr. Mark Bayley (University of Toronto) and Dr. Shawn Marshall (University of Ottawa) for their invaluable expertise and stewardship of this review. Special thanks to the authors for generously providing their time, knowledge and perspectives to deliver a rigorous and robust review that will guide research, education and practice for a variety of healthcare professionals. We couldn't have done it without you! Together, we are building a culture of evidence-based practice that benefits everyone.

We invite you to share this evidence-based review with your colleagues, patient advisors that are partnering within organizations, and with the government agencies with which you work. We have much to learn from one another. Together, we must ensure that patients with brain injuries receive the best possible care every time they require rehabilitative care – making them the real winners of this great effort!

Robert Teasell, MD FRCPC

TABLE OF CONTENTS

Preface

About the Authors

ERABI is internationally recognized and led by a team of clinicians and researchers with the goal of improving patient outcomes through research evidence. Each ERABI module is developed through the collaboration of many healthcare professionals and researchers.

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Purpose

The Evidence-Based Review of Acquired Brain Injury (ERABI) is a systematic review of the rehabilitation literature of moderate to severe acquired brain injuries (ABI). It is an annually updated, freely accessible online resource that provides level of evidence statements regarding the strength of various rehabilitation interventions based on research studies. The ERABI is a collaboration of researchers in London, Toronto and Ottawa. Our mission is to improve outcomes and efficiencies of the rehabilitation system through research synthesis, as well as from providing the foundational research evidence for guideline development, knowledge translation, and education initiatives to maximize the real-world applications of rehabilitation research evidence.

Key Concepts

Acquired Brain Injury

For the purposes of this evidence-based review, we used the definition of ABI employed by the Toronto Acquired Brain Injury Network (2005). ABI is defined as damage to the brain that occurs after birth and is not related to congenital disorders, developmental disabilities, or processes that progressively damage the brain. ABI is an umbrella term that encompasses traumatic and non-traumatic etiologies.

TABLE 1 | Defining Acquired Brain Injury

Included in ABI definition	Excluded from ABI definition
Traumatic Causes • Motor vehicle accidents • Falls • Assaults • Gunshot wounds • Sport Injuries **Non-traumatic Causes** • Tumours (benign/meningioma only) • Anoxia • Subarachnoid hemorrhage (non-focal) • Meningitis • Encephalitis/encephalopathy (viral, bacterial, drug, hepatic) • Subdural Hematoma	**Vascular and Pathological Incidents** • Intracerebral hemorrhage (focal) • Cerebrovascular accident (i.e., stroke) • Vascular accidents • Malignant/metastatic tumours **Congenital and Developmental Problems** • Cerebral Palsy • Autism • Developmental delay • Down's syndrome • Spina bifida with hydrocephalus **Progressive Processes** • Alzheimer's disease • Pick's disease • Dementia • Amyotrophic Lateral Sclerosis • Multiple Sclerosis • Parkinson's disease • Huntington's disease

Given that 'ABI' can have multiple definitions, studies with an 'ABI' population can be equally heterogeneous in terms of the sample composition. Such studies may include any combination of persons with TBI, diffuse cerebrovascular events (i.e., subarachnoid hemorrhage) or diffuse infectious disorders (i.e., encephalitis or meningitis). The vast majority of individuals with ABI have a traumatic etiology; therefore, much of the brain injury literature is specific to TBI. The terms ABI and TBI have been used intentionally throughout ERABI to provide more information about populations where relevant.

Moderate to Severe Brain Injury

ABI severity is usually classified according to the level of altered consciousness experienced by the patient following injury (Table 2). The use of level of consciousness as a measurement arose because the primary outcome to understand the severity of an injury is the Glasgow Coma Scale. Consciousness levels following ABI can range from transient disorientation to deep coma. Patients are classified as having a mild, moderate or severe ABI according to their level of consciousness at the time of initial assessment. Various measures of altered consciousness are used in practice to determine injury severity. Common measures include the Glasgow Coma Scale (GCS), the duration of loss of consciousness (LOC), and the duration of post-traumatic amnesia (PTA). Another factor used to distinguish moderate and severe brain injury is evidence of intracranial injury on conventional brain imaging techniques which distinguish severity of injury from a mild or concussion related brain injury.

TABLE 2 | Defining Severity of Traumatic Brain Injury, adapted from Veterans Affairs Taskforce (2008) and Campbell (2000)

Criteria	Mild	Moderate	Severe	Very Severe
Initial GCS	13-15	9-12	3-8	Not defined
Duration LOC	< 15minutes*	<6 hours	6-48 hours	>48 hours
Duration PTA	< 1hour*	1-24 hours	1-7 days	>7 days
	*This is the upper limit for mild traumatic brain injury; the lower limit is any alteration in mental status (dazed, confused, etc.).			

Methods

An extensive literature search using multiple databases (CINAHL, PubMed/MEDLINE, Scopus, EMBASE, and PsycINFO) was conducted for articles published in the English language between 1980–December 2018 that evaluate the effectiveness of any intervention/treatment related to ABI. The references from key review articles, meta-analyses, and systematic reviews were reviewed to ensure no articles had been overlooked. For certain modules that lacked research evidence the gray literature, as well as additional databases, were searched in order to ensure the topic was covered as comprehensively as possible.

Specific subject headings related to ABI were used as the search terms for each database. The search was broadened by using each specific database's subject headings, this allowed for all other terms in the database's subject heading hierarchy related to ABI to also be included. The consistent search terms

used were “head injur*”, “brain injur*”, and “traumatic brain injur*”. Additional keywords were used specific to each module. A medical staff librarian was consulted to ensure the searches were as comprehensive as possible.

Every effort was made to identify all relevant articles that evaluated rehabilitation interventions/ treatments, with no restrictions as to the stage of recovery or the outcome assessed. For each module, the individual database searches were pooled, and all duplicate references were removed. Each article title/abstract was then reviewed; titles that appeared to involve ABI and a treatment/intervention were selected. The remaining articles were reviewed in full.

Studies meeting the following criteria were included: (1) published in the English language, (2) at least 50% of the study population included participants with ABI (as defined in Table 1) or the study independently reported on a subset of participants with ABI, (3) at least three participants, (4) ≥50% participants had a moderate to severe brain injury (as defined in Table 2), and (5) involved the evaluation of a treatment/intervention with a measurable outcome. Both prospective and retrospective studies were considered. Articles that did not meet our definition of ABI were excluded.

EPIDEMIOLOGY AND LONG-TERM OUTCOMES

POST ACQUIRED BRAIN INJURY

Introduction

Acquired brain injury (ABI), particularly traumatic brain injury (TBI), is one of the leading causes of death and lifelong disability in North America (Greenwald et al., 2003; Pickett et al., 2001; Thurman & Guerrero, 1999). In the United States between 1.4 and 1.7 million people sustain a TBI every year (Faul et al., 2010; Zaloshnja et al., 2008), with more than 120,000 people expected to develop long-term disability (Zaloshnja et al., 2008). In the province of Ontario, more than 80,000 individuals sustained a TBI between 2002 and 2006 (Colantonio et al., 2010). Among low and middle income countries, the lifetime prevalence of TBI ranges from 0.3% in China to 14.6% in rural Mexico (Khan et al., 2015); however, the global incidence of TBI is increasing primarily due to the increased use of motor vehicles in low and middle income countries (Maas et al., 2008). Recently, in high income countries, the epidemiological patterns of TBI have been shifting (Roozenbeek et al., 2013). An increase in the absolute incidence of TBI among older age individuals and an increase in the median age of TBI has been observed. Accordingly, the primary cause of TBI in the elderly is falls (Maas et al., 2008; Roozenbeek et al., 2013). In high income countries, improvements in safety regulations have been associated with a reduction in traffic related TBI (Redelmeier et al., 2003), however, motor vehicle accidents (MVA) remain one of the most common causes of TBI (Andriessen et al., 2011). Furthermore, in European countries, individuals were identified as being under the influence of alcohol at the time of their TBI in 24-51% of cases (Tagliaferri et al., 2006).

Most individuals with TBI are classified as having a mild injury, but residual deficits in these patients are not uncommon (Thornhill et al., 2000). However, 10-15% of patients with TBI have more serious injuries requiring specialist care (Maas et al., 2008). In Canada, brain injury is the leading cause of death in individuals under 40 years old (Northern Brain Injury Association, 2018), with recent incidence rates of moderate to severe ABI as high as 500 per every 100 000 individuals (Northern Brain Injury Association, 2018).

Much of the data pertaining to ABI is collected when patients present at a specific point of care (i.e., emergency departments, inpatient rehabilitation, and outpatient services). It should be noted that these studies do not explore the number of patients treated in other healthcare settings. Furthermore, the individuals who do not seek medical care, commonly those with mild TBI, are not accounted for (Roozenbeek et al., 2013). In addition, individuals with very severe TBI who die before reaching a hospital are often not registered (Roozenbeek et al., 2013). For these reasons, the number of individuals with a brain injury is likely to be higher than these figures suggest (Langlois et al., 2006).

This module will discuss demographic characteristics within the ABI patient population as well as how these characteristics relate to injury etiology. In addition, factors that influence rate of recovery and prognosis during the acute and chronic post injury time periods will be reviewed. The following information is not meant to be prescriptive in any way, as each ABI case should be considered individually when attempting to predict outcome and when determining the best course of treatment. The

information in this module is designed to help clinicians better understand the complex relationships between patient characteristics, injury characteristics and outcomes post ABI.

Sex Differences in ABI

The rate and etiology of injury seem to differ according to patient sex, with TBI being more common in males than females (CIHI, 2008; Colantonio et al., 2009; Colantonio et al., 2010; Greenwald et al., 2003). A study conducted in the United States found TBI to be nearly 1.4 times more common among males than females (Faul et al., 2010). Data from Ontario, Canada is consistent with this finding and also shows greater rates of TBI among males (Chan et al., 2013a). The increased incidence in males may in part be due to greater participation in risk-taking activities, exposure to occupational hazards, and more engagement in violent behaviours than females. A cohort study found that fall-related TBIs were more common among females than males (51.7% versus 36.2%, respectively), conversely, being struck by or against an object was more common among males than females (Colantonio et al., 2010). Females have also been shown to have 33.1% lower odds of mortality after adjusting for covariates than males post brain injury (Haring et al., 2015). However, these results are in contrast to one study in Spain, which found no association between sex and outcome after severe TBI (Herrera-Melero et al., 2015).

Age and ABI

Evidence suggests that the etiology of TBI varies with age. Among children aged 0-4 years, up to two thirds of severe brain injuries are attributable to non-accidental trauma (Greenwald et al., 2003). Between 2002 and 2010 rates of TBI emergency department visits in the United States declined for all males aged below 65, however for males above the age of 65 rates increased by 17% (Fu et al., 2016). In the same study it was found that rates for all females (except those aged 5-14) decreased between 2002 and 2010 (Fu et al., 2016). Falls are a common cause of TBI in both children and older adults (Colantonio et al., 2009; Faul et al., 2010). An epidemiological study conducted in the United States showed that falls accounted for 50.2% of TBIs in children (aged 0-14 years) and 60.7% of TBIs in adults aged 65 years or older (Faul et al., 2010). For those 85 years of age or older, the rate of hospitalization in Ontario for TBI due to a fall was as high as 90% (Chan et al., 2013b, 2013c). The increased risk of falls in the elderly may be linked to factors such as substance use, decreased balance and/or age-related neurological conditions such as dementia (Wagner, 2001).

Overall, motor vehicle or other transportation related accidents and falls are the most common causes of TBI (Faul et al., 2010). Based on literature, falls account for approximately 35% to 42% of TBIs whereas MVAs are responsible for 12% to 17% (Colantonio et al., 2010; Faul et al., 2010). These trends have been consistent for approximately ten years (Fu et al., 2016; Roozenbeek et al., 2013).

With increasing age, the prevalence of brain injury due to non-traumatic causes also increases. Non-traumatic brain injury (nTBI), which excludes patients with a primary diagnosis of stroke, is more prevalent in those over the age of 40 years. In Ontario, hospitalization rates for nTBI increase with age; rates of 365 persons per 100,000 have been reported for those 65-74 years old, compared to 561 persons per 100,000 for those above 85 years old (Chan et al., 2013b, 2013c). Vascular insults (not captured in other national studies on stroke), brain tumours, meningitis, encephalitis, and anoxia have been found to be the most frequent causes of nTBI (Chan et al., 2013b).

Recently, an increase in the rate of TBI among the elderly has been noted which is heavily influenced by the fact that they are the fastest growing sector of the population (Chan et al., 2013a; Roozenbeek et al., 2013). A recent examination of the Ontario ABI Dataset found that between 2003 and 2010, there was a significant increase in TBI cases among patients aged 65 to 74 years (11%), 75 to 84 years (50%) and 85 years and older (63%) (Chan et al., 2013a).

Impact of Older Age on TBI and Subsequent Recovery

Those who sustain a TBI, regardless of age, may develop circulatory, digestive, or respiratory problems, have an increased risk of infection, and may experience neurological complications such as endocrine abnormalities, seizures, and swallowing difficulties (Flanagan, 2008). Individuals with a TBI may also develop mental health concerns such as depression or anxiety (Colantonio et al., 2011).

Evidence suggests that age influences the trajectory of one's recovery following injury. Individuals in the older age bracket generally had poorer outcomes when compared to younger individuals (Marquez de la Plata et al., 2008). Pennings et al. (1993) found individuals over the age of 60 required a greater number of resources to obtain favourable outcomes compared to younger patients (≤40 years old) with a similar severity of injury. For those in the older age group, a longer length of stay in hospital was often necessary to address their slower rate of functional recovery (Chan et al., 2013a; Cifu et al., 1996). Both admission and discharge Functional Independence Measure scores from inpatient rehabilitation were lower among older adults (Chan et al., 2013b). Consequently, older adults also had a lower rate of discharge to the community (Colantonio et al., 2009). Watanitanon et al. (2018) studied patients with moderate TBI (defined as admission GCS of 9-13), compared to those aged 18-44 years, patients aged 45-64 years had an almost two-fold increased risk and those 80 years or older had an almost five-fold increased risk of a poor outcome.

Older age at the time of injury has also been associated with poorer performance in various cognitive domains (Senathi-Raja et al., 2010). A study by Ashman and Mascialino (2008) noted that deficits in encoding and retention of verbal information, as well as inattention, were more common and more serious post TBI in those over the age of 65 years. It has been postulated, for those who are older at the time of injury, that less neuronal plasticity may negatively affect the brain's ability to compensate or adapt in the same way a younger brain does post injury (Senathi-Raja et al., 2010).

Mosenthal et al. (2002) found older individuals (>64 years of age) had a significantly higher mortality rate than their younger peers at all levels of TBI severity ($p<0.001$). Study authors suggested this increase in mortality may be attributable to multiple factors including pre-existing comorbidities, post injury complications, and the intrinsic properties of aging itself (Mosenthal et al., 2002). Evidently, for older patients with TBI, their recovery may be challenging, as aging is often accompanied by a number of chronic comorbidities (e.g., diabetes, arthritis, cardiovascular disease and/or cerebrovascular disease) (Colantonio et al., 2011). Such factors are rarely taken into account when assessing the impact an ABI has on an older person (Colantonio et al., 2004; Rapoport & Feinstein, 2000), however, these pre-existing health issues may impede the recovery of patients living with an ABI if left unresolved.

A study examined the recovery of patients with TBI in inpatient rehabilitation facilities (Dijkers et al., 2013). The study found that adults aged 65 years or older had lower brain injury severity but more medical comorbidities than the younger participants. In addition, these older patients received fewer hours of therapy per day (especially from psychology and therapeutic recreation) and had shorter lengths of stay in both acute care and rehabilitation compared to the younger patients (Dijkers et al., 2013). Older individuals with TBI also showed less functional gains both during and after rehabilitation when compared with younger patients (Dijkers et al., 2013). Furthermore, older individuals with TBI had a higher death rate both 3 and 9 months post rehabilitation discharge than younger patients (Dijkers et al., 2013). Hence, issues regarding therapy intensity and care may be important when examining recovery among older adults.

Aging with an Established ABI

It is important to consider that persons with TBI may be at risk for subsequent falls due to balance, mobility, and cognitive impairments, as well as environmental challenges such as building infrastructure. Coupled with the effects of aging, these risk factors may result in a patient sustaining yet another injury (Chan et al., 2013c). For more information on older age and ABI, please refer to the *Older Adults and Acquired Brain Injury* module.

The Impact of ABI on Survivors and the Healthcare System

Assessing the impact that an ABI may have on individuals as they age is difficult, as survivors can live for several decades post injury. This is particularly true for children and adolescents who sustain an injury. Unfortunately, longitudinal studies assessing the impact of the injury on the individual and their families are challenging due to the cost and the number of participants lost to follow-up.

Chen et al. (2012) studied direct costs – emergency department visits, acute care admissions, inpatient rehabilitation stays, complex continuing care stays, home care services and physician visits – from the

government payer's perspective for patients with ABI discharged from Ontario acute care hospitals between 2004 and 2008. Total medical costs in the first year of follow up amounted to approximately $120.7 million for patients with TBI and $368.7 million for the nTBI population. However, the most significant cost during the first year was the acute care stay. This translates into a mean cost during the first year of $32,132 per patient with TBI and $38,018 per patient with nTBI (A. Chen, K. Bushmeneva, et al., 2012). It is important to note that this study did not account for any indirect or directs costs to the patient or family such as lost income or out-of-pocket expenses. Most costs were incurred during the first follow up year; however, patients continued to require regular use of health care resources during the second- and third-year post ABI.

ABI is costly to the healthcare system and unfortunately some costs are the result of alternative level of care (ALC) days. ALC is when patients occupy hospital beds even when they do not require the level of intensity of resources/services being provided in that particular care setting (A. Chen, B. Zagorski, et al., 2012). For example, this commonly occurs while patients are awaiting a placement in a long-term care facility. In Ontario, during fiscal years 2007/08 to 2009/10, the total number of days spent as ALC increased from 15,606 to 22,637 among patients with TBI and from 39,918 to 48,267 among patients with nTBI (A. Y. Chen et al., 2012). This study also showed increased odds of having an ALC day was associated with increasing patient age, female sex, psychiatric comorbidity, and having been injured in an MVC.

Furthermore, the use of health care resources may also depend on multiple other factors. Fu et al. (2015) found, in Canada, there was a 29% increase in fall-related hospitalization rates among those aged 65 years or older with TBI between the years 2006 and 2011. Hammond et al. (2015) identified a 28% rehospitalization rate during the first 9 months following TBI rehabilitation discharge; older age at the time of injury, number of previous brain injuries, greater non-brain injury severity of illness score, and history of seizure before or during inpatient rehabilitation were all predictors of experiencing $\geq$1 rehospitalization. Rural residence and psychiatric comorbidity have also been shown to be predictors of rehospitalization (Saverino et al., 2016).

Unfortunately, data indicates that a large proportion of individuals with a brain injury do not appear to be accessing all the rehabilitation services that they need. The Ontario Brain Injury Association survey conducted in 2005 examined the number of individuals using services compared to those who weren't (OBIA, 2007). The main reasons given for the gaps between service need and use were long waiting lists, lack of available and appropriate services, lack of training about the cognitive and behavioural needs of patients, and poor coordination of services (A. Y. Chen et al., 2012; Minnes et al., 2010). Particularly, the apparent lack of access to services for psychological issues. Those with pre-existing comorbid conditions, such as psychosocial and psychiatric problems, are at an increased risk of mortality following injury (Colantonio et al., 2009); thus, it is very important for patients to be able to access appropriate care in a timely manner.

Mortality and ABI

Few studies have examined the effects of ABI on life expectancy; however, it has been suggested that a person with TBI who recovers during the acute period may still have a substantially reduced life expectancy and a poorer outcome than those that do not have a brain injury (Colantonio et al., 2009; Ratcliff et al., 2005). One of the strongest predictors of post-acute mortality is the patient's age at the time of injury, such that those of higher age have a higher risk of mortality in the acute phase of ABI (Colantonio et al., 2009). Further, Ratcliff et al. (2005) found an ABI doubled long-term mortality risk for all age groups, even though many survived 20 or more years post injury.

Harrison-Felix et al. (2015) found that, between 2001 and 2010, individuals with TBI were 2.23 times more likely to die compared to individuals similar in age, sex, and race. In addition, those patients with TBI had an average reduced life expectancy of 9 years. Older age, male sex, being unemployed at the time of injury, being married at the time of injury, and having less than a high school education have all been shown to be risk factors for earlier death among those with ABI (Cuthbert et al., 2015; Harrison-Felix et al., 2015).

In a population of individuals with severe TBI followed for the first 14 days post injury, mortality rates ranged from 24.5% among persons <65 years of age to 40.9% among persons >65 years of age (Walder et al., 2013). Fifty-four percent of adults over 55 years died within 6 months of discharge and 68% within 1 year (Peck et al., 2014). Owens et al. (2018) reported the 12-month all-cause mortality rate as 12% in a retrospective cohort study of patients admitted to a regional trauma unit in Ireland with TBI from 2008-2013 and length of stay >48 hours. Watanitanon et al. (2018) reported a 7.2% mortality rate in a population of patients with moderate TBI (defined as admission GCS of 9-13).

Prognostic Indicators

It is important to know which factors are significantly related to outcomes post ABI. Prognostic indicators can include such variables as injury severity, etiology of injury, age, rehabilitation length of stay, duration of post-traumatic amnesia, etc. Table 3 summarizes the most common TBI prognostic indicators identified in the literature.

TABLE 3 | Common Prognostic Indicators for ABI

Patient Related Indicators	Injury Related Indicators	Treatment Related Indicators
• Age • Sex • Presence of prior brain injury • Presence of comorbidities	• Injury severity • Length of coma • Initial GCS • Duration of PTA • Mechanism of injury • Nature of injury (TBI or nTBI)	• Timing of rehabilitation • Intensity of rehabilitation

Bushnik et al. (2003) studied a variety of etiologies, such as MVAs, assaults, and falls. They demonstrated that individuals involved in MVAs initially incurred more severe injuries than individuals injured by assaults, falls, or other causes. However, at one year post injury, individuals with TBI related to MVAs reported the best functional and psychosocial outcomes, while individuals with violence-related TBI reported the highest unemployment rates and lowest Community Integration Questionnaire scores (Bushnik et al., 2003). Individuals with TBI related to falls or 'other' etiologies had outcomes that fell somewhere between those injured by MVAs and assaults. This occurred despite the fact there were no functional differences between the groups at discharge from rehabilitation.

Asikainen et al. (1998) focused on the effects of hospital admission Glasgow coma scale (GCS) score, length of coma, and duration of post-traumatic amnesia on outcomes post TBI. These three factors are all correlated with level of injury severity. While hospital admission GCS score positively correlated with functional outcome as measured by Glasgow Outcome Scale score, length of coma and duration of post-traumatic amnesia correlated with both functional and occupational outcomes. Watanitanon et al. (2018) found – even in a population of patients with moderate TBI – that lower GCS was a risk factor for poor outcome. Poor scores on functional measures (e.g., mobility, eating, or grooming) have also been found to be significant predictors of premature death (Colantonio et al., 2008). Notably, limitation in eating was one of the most important predictors of mortality (Ratcliff et al., 2005).

The nature of the injury seems to play a predictive role in patient outcomes as well. For instance, Colantonio et al. (2011) reported that the diagnosis of nTBI was associated with a lower Functional Independence Measure rating at both admission and discharge, more comorbidities, and longer lengths of stay in inpatient rehabilitation. Significantly more individuals with nTBI died in acute care, whereas more patients with TBI were discharged home, to inpatient rehabilitation, or to a long-term care facility (Chan et al., 2013c). In addition, TBI with diffuse axonal injury has been shown to have a threefold higher risk of an unfavourable outcome (Glasgow Outcome Scale (GOS) 1-3 or Glasgow Outcome Scale-Extended (GOSE) 1-5) when compared to patients with TBI without diffuse axonal injury. Overall, 38% of patients with diffuse axonal injury were classified as having an unfavourable outcome (van Eijck et al., 2018). This study also found that lesions affecting the corpus callosum in particular were more likely to be associated with an unfavourable outcome.

The presence of comorbidities may affect patient outcome as well. An increase in Charlson Comorbidity Index category increased the odds of having an ALC day by 9% in the TBI population. Furthermore, having a psychiatric comorbidity increased the odds of having an ALC day among patients with TBI by 73% (A. Y. Chen et al., 2012). Similarly, A study by Rapoport et al. (2000) demonstrated that major depression in older adults in the first months after TBI had persisting adverse effects on outcome. This finding is particularly problematic since studies have demonstrated that major depression is quite common in the TBI population, and associated with a poorer prognosis (Rogers & Read, 2007). In addition, Folkerson et al. (2018) demonstrated that individuals with penetrating TBI had a higher mortality compared to those blunt TBI and were more coagulopathy. In this study, coagulopathy was found to be an early predictor of mortality and thus presents an opportunity for intervention. Watanitanon et al. (2018) also identified

admission hypotension and polytrauma as risk factors of a poor outcome in a study population of individuals with moderate TBI.

Long-Term Outcomes

There is increasing concern about the potential for development of neurodegenerative diseases many years after sustaining a TBI due to the physiological changes that occur following injury. The National Academy of Medicine (2008) has concluded that moderate and severe TBI is associated with the development of Alzheimer's and Parkinson's disease. Veterans that sustained a TBI were at an increased risk for Alzheimer's disease and dementia (Plassman et al., 2000). In individuals over the age of 55 years, this pattern was present even after a single presentation of moderate to severe TBI (Gardner et al., 2014). Furthermore, individuals that sustained a TBI were at an increased risk for Parkinson's disease, particularly with multiple TBIs (Goldman et al., 2006). This is in contrast with a meta-analysis performed in 2018 by Huang et al., (2018) which reported TBI as a potential risk factor for dementia, frontotemporal dementia, and TDP-43 aggregation-associated disease but not Alzheimer's dementia, Parkinson's disease, or APOE-associated neurodegeneration. Additional research is needed to further elucidate the relationship between TBI and the development of neurodegenerative diseases.

In an attempt to examine the long-term impact of ABI, some of the most salient studies related to long-term outcomes were identified and reviewed. Study follow-up periods ranged from three months to more than ten years. The studies included in the review below have been separated into two groups according to the participants' injury severity: 1) moderate to severe ABI (when both moderately and severely injured participants were included in the study) and 2) severe ABI (when only severely injured participants were included in the study). Studies were also separated according to three follow-up periods: 1) three months to two years, 2) three to five years, and 3) greater than five years. Results are summarized in Table 4 to 7 below.

TABLE 4 | Long-Term Outcomes Up to Two Years Post Injury

Author Year Country Sample Size	Study Summary
Moderate to Severe ABI	
Einarsen et al. (2018) Norway N= 395	**Population:** 395 individuals with moderate TBI, GCS of 9-13. **Follow-up**: 1yr. **Findings:** At 1 year, 8% of individuals were severely disabled as measured by the GOS-E. Linear regression modelling showed that older age, lower initial GCS, no day-of-injury alcohol intoxication, subdural hematoma, preinjury disability, and occurrence of hypoxia and/or hypotension were significant predictors of moderate disability or worse (GOS-E ≤6) at 1 year.

Author Year Country Sample Size	Study Summary
Gross & Amsler (2018) Switzerland N= 326	**Population:** 110 older (≥65yr) and 216 younger (16-64yr) individuals at the time of their TBI. **Follow-up:** 1yr. **Findings:** There was no significant difference in 1-year outcome between younger and older TBI participants as measured by the GOS, EQ-5D, QOLIBRI, and TOP. However, the two physical oriented sub scores on the SF-36 showed significantly lower values in the older group. Further analysis showed poorer outcomes on the QOLIBRI among patients aged greater than 80yr.
Andersson et al. (2017) Sweden N=95	**Population**: 95 individuals with TBI, GCS ≤8 **Follow-up:** 1yr and 10-15yr post injury **Findings:** There was no significant difference in GOS scores from 1yr and 10-15yr post ABI. Poorer GOS scores were correlated to age at both 1yr ($p<0.001$), and 10-15yr ($p=0.021$). At 10-15yr follow-up 70% of patients reported mental fatigue. From first to second follow-up the TBI group had significantly higher rates of mortality ($p<0.001$, $p<0.001$) compared to healthy controls.
Novack et al. (2000) USA N=72	**Population**: 72 individuals with TBI; >50% severe injury. **Follow-up:** 6 and 12mo post injury. **Findings:** For individuals with severe TBI, driving status improved only marginally from 6 mo (n=11) to 12mo (n=16) ($p=0.05$); the total number of individuals with >20 hr/wk employment increased from 1 (2.0%) at 6mo to 5 (10.2%) at 12mo; and a trend towards increased productive activities was observed (8.2% at 6mo versus 16.8% at 12mo, $p=0.04$).
Malec et al. (1993) USA N=29	**Population:** 29 individuals with ABI (TBI=20) participating in post-acute rehabilitation. Mean age at admission=33.1yr; mean time post injury=1463.9 days. **Follow-up:** 1yr (n=21). **Findings:** Eighty-six percent of patients were living with no supervision compared to 48% on admission. 48% of patients were in an independent work placement and 29% were unemployed.
Cope et al. (1991) USA N=145	**Population**: 145 individuals with ABI (TBI=113) admitted to post-acute rehabilitation; mean age=35yr; mean time post injury=448 days; mean disability rating score=6.03. **Follow-up**: 6, 12, and 24mo post discharge. **Findings:** From admission to follow-up there was an increase in residence at home (44.8% to 69.7%), an increase in competitive employment or academic involvement (5.6% to 34.5%), a decrease in 'no productive activity' (92.3% to 27.6%), and an increase in the percentage of patients independent throughout a 24hr period (25% to. 78.6%). All differences were significant ($p<0.0001$).
Severe ABI	
Beck et al. (2018) Australia N=1966	**Population:** 1966 individuals with severe TBI. **Follow-up:** 6mo post-injury. **Findings:** A majority of individuals had an unfavorable outcome on the GOS-E (</=4) at 6mo post-injury (70%). After adjusting for confounders, there were no change in functional outcomes ($p=0.35$) and no change in odds of death (GOS-E=1; $p=0.08$) after severe TBI between 2006 and 2015 in a mature trauma system.
Bonow et al. (2018) Argentina N=550	**Population:** 550 individuals with severe TBI in lower- and middle-income countries. **Follow-up:** 6mo post-injury. **Findings:** A majority of individuals had an unfavorable outcome on the GOS-E (</=4) at 6mo (66%). Higher GCS motor and epidural hematoma were associated with higher scores on the GOS-E at 6mo. Advanced age and cisternal effacement were associated with a lower GOS-E at 6mo. Study site and race ($p<0.05$) significantly predicted outcome at 6 months, in some cases outweighing clinical variables such as hypotension and pupillary exam.

Author Year Country Sample Size	Study Summary
Mills et al. (1992) USA N=42	**Population:** 42 patients with TBI; GCS score <9. **Follow-up:** 6mo (n=32), 12mo (n=13), and 18mo (n=18) post discharge from a community cognitive rehabilitation program. **Findings:** At 6mo follow-up, 87.5% of patients maintained or improved their status in the home and community, and 90% maintained or improved their status in leisure and vocational function. These gains were maintained or improved at a follow-up of 12 and 18mo.

TABLE 5 | Long-Term Outcomes at Three to Five Years Post Injury

Author Year Title Country Sample Size	Study Summary
Severe ABI	
Lu et al. (2018) Norway N= 121	**Population:** 121 individuals with moderate-to-severe TBI. **Follow-up:** 3mo, 1yr, 5yr post-injury. **Findings:** Longitudinally, using the Functional Independence Measure motor and cognitive subscales, patients were classified into 3 motor functional and 4 cognitive trajectories. For the Functional Independence Measure motor scores, 8.2% followed a stable low recovery trajectory, 9.2% demonstrated an elevated good recovery trajectory, and 82.6% demonstrated a stable good recovery trajectory. For the Functional Independence Measure cognitive, 4.1% followed a stable low recovery trajectory, 12.6% demonstrated a delayed moderate recovery trajectory, 28.7% demonstrated an elevated good recovery trajectory, and 54.6% demonstrated a stable good recovery trajectory. Across the trajectory subgroups, statistically significant differences were observed in PTA duration, GCS, CT classification, and hospital length of stay; indicators of increased injury severity were associated with membership in the less favourable recovery trajectory groups.
Ruet et al. (2018) France N= 133	**Population:** 133 individuals with severe TBI. **Follow-up:** 4yr post-injury. **Findings:** 38% of participants were employed; 80% of these individuals worked >20 hours per week. Only half of those individuals who were employed at the time of their TBI were still employed 4 years later. Predictors of employment included: preinjury employment, higher initial GCS score, shorter length of ICU stay, and higher GOS-E score at 1-year post-injury. The employment rate of individuals who were students at the time of their injury was low. The most common self-reported difficulties that impacted work included fatigue, slowness, and problems with maintaining concentration.
Odgaard et al. (2017) Denmark N=3134	**Population:** 3134 patients with severe TBI. **Follow-up:** 2yr and 5yr post TBI **Findings:** The majority of return to work occurred within the first-year post TBI, at 5yr follow-up 70% of patients were receiving public assistance benefits.
Katz et al. (2009) USA N=36	**Population:** 36 patients with ABI (TBI=22). **Follow-up:** 2yr and 4yr. **Findings:** Of 16 patients who were assessed at 2yr follow-up, Disability Rating Scale (DRS) scores continued to improve compared to admission in 56% of patients. Between 2yr and 4yr, improvement was seen in 3 of 8 patients. Of 23 patients followed 1 to 4yr, 43% achieved household independence, and 22% returned to work or school.

Author Year Title Country Sample Size	Study Summary
Kaitaro et al. (1995) Finland N=19	**Population:** 19 patients with severe TBI. **Follow-up:** 5yr. **Findings:** None of the participants required institutional care. Sixty-eight percent of patients were living with their families or spouses. Eighty-nine percent of patients were retired despite attempts to work.
Harrick et al. (1994) Canada N=21	**Population:** 21 individuals with severe TBI. **Follow-up:** 3yr. **Findings:** At discharge, 67% (versus 34% at admission) were engaged in productive activity. Financially, 15% (versus 5% at admission) were self-supported, 15% (versus 5% at admission) were both self-supported and aided, and 73% (versus 81% at admission) were aided. Moreover, 77% (versus 68% at admission) received informal support, 24% (versus 10% at admission) received partial support, and no one (versus 24% at admission) required institutional support.

TABLE 6 | Long-Term Outcomes at Greater than Five Years Post Injury

Author Year Title Country Sample Size	Study Summary
Moderate to Severe ABI	
Grauwmeijer et al. (2018) The Netherlands N=119	**Population:** 50 individuals with moderate-severe TBI. **Follow-up:** 10yr post-injury. **Findings:** 20% of individuals at the 10yr follow-up showed symptoms of depression on the CES-D. These patients were more often admitted to rehabilitation or nursing homes and had more psychiatric symptoms at initial hospital discharge ($p<0.05$). Individuals with depressive symptoms demonstrated significantly worse scores in 6/8 SF-36 subdomains as well as on the physical component and mental component summary scores ($p=0.001$, $p=0.008$). Patients with depressive symptoms reported more subjective cognitive complaints with the CFQ; however, they did not perform any worse on neuropsychological tests – except for the d2 test – than those without symptoms.
Andersson et al. (2017) Sweden N=95	**Population**: 95 individuals with TBI, GCS ≤8 **Follow-up:** 1yr and 10-15yr post injury **Findings:** There was no significant difference in GOS scores from 1yr and 10-15yr post ABI. Poorer GOS scores were correlated to age at both 1yr ($p<0.001$), and 10-15yr ($p=0.021$). At 10-15yr follow-up, 70% of patients reported mental fatigue. From first to second follow-up, the TBI group had significantly higher rates of mortality ($p<0.001$, $p<0.001$) compared to healthy controls.
Klonoff et al. (2001) USA N=164	**Population:** 164 patients with ABI (TBI=113). **Follow-up:** 11yr. **Findings**: At follow-up, 83.5% were productive in some capacity; 46.3% were gainfully employed full-time, 11.6% were in full-time school or school/work, 9.2% were in part-time gainful work or school, and 12.2% worked as volunteers. 16.5% were not productive in any capacity. Additionally, younger age ($p=0.009$), being male ($p=0.025$), and higher staff working alliance ratings of patients ($p=0.024$) and their families ($p=0.017$) were associated with better vocational/school outcomes.

Severe ABI	
Possl et al. (2001) Germany N=43	**Population**: 43 participants with severe ABI. **Follow-up:** 7-8yr. **Findings:** At follow-up, 37% had achieved stable re-employment at pre-injury levels, 16% had achieved stable re-employment with work modifications, 19% continued to have persistent vocational adjustment problems, and 28% opted for retirement.
Johnson (1998) UK N=64	**Population:** 64 patients with severe head injury. **Follow-up:** 10yr or more. **Findings:** At follow-up, 42% had re-established employment, 20% had an irregular pattern of work, and the remainder were not in the workforce.
Wilson (1992) UK N=25	**Population:** 25 patients. **Follow-up:** 5-10yr. **Findings:** At follow-up, 81% were living in their own homes either alone, with relatives, or with friends. Those remaining were in long-term residential care, residential college, or warden controlled accommodation. 42% were in paid employment; 1 of 11 were in paid employment that was comparable to their preinjury status.

Table 7 summarizes whether each long-term outcome study reported a positive or negative outcome regarding participants' productivity, independence, and place of residence. Productivity outcomes were defined as positive if the majority (≥50%) of participants were involved in any form of paid or unpaid labour, including volunteer work. If the majority of participants were not taking part in any of the aforementioned types of productive activity (e.g., they were retired) then it was considered a negative outcome**.** Independence was related to the level of supervision required. A positive outcome was noted as long as the majority of participants did not require institutional care or support. However, if the majority of participants did require this type of assistance, it was deemed a negative outcome. Positive place of residence outcomes were noted when the majority of participants in the study were not living in an institutionalized setting. Otherwise, it was considered to be a negative outcome. Positive trends and increases regarding productivity, independence, and place of residence were also viewed as positive outcomes.

TABLE 7 | Long-Term Outcomes for Productivity, Independence, and Place of Residence

Author Year Country	Injury Severity	Follow-Up Period	Productivity	Independence	Place of Residence
Ruet et al. (2018) France	Severe TBI	4yr	+ (38% achieved paid employed)	n/a	n/a
Cope et al. (1991) USA	moderate to severe ABI	3mo-2yr	+ (no deterioration in positive trends from 6-24 mo)	+ (no deterioration in positive trends from 6-24 mo)	+ (no deterioration in positive trends from 6-24 mo)
Malec et al. (1993) USA	moderate to severe ABI	3mo-2yr	+ (72%)	+ (96%)	n/a

Author Year Country	Injury Severity	Follow-Up Period	Productivity	Independence	Place of Residence
Klonoff et al. (2001) USA	moderate to severe ABI	>5yr	+ (83.5%)	n/a	n/a
Novack et al. (2000) USA	severe ABI	3mo-2yr	+ (12.6% increase in those involved in productive activity from 6-12mo)	n/a	n/a
Mills et al. (1992) USA	severe ABI	3mo-2yr	+ (90%)	n/a	n/a
Harrick et al. (1994) Canada	severe ABI	3mo-2yr	+ (62%)	+ (100%)	+ (100%)
Harrick et al. (1994) Canada	severe ABI	3-5yr	+ (67%)	+ (100%)	+ (100%)
Kaitaro et al. (1995) Finland	severe ABI	3-5yr	- (89%)	n/a	+ (100%)
Wilson (1992) UK	severe ABI	>5yr	- (42%)	+ (81%)	+ (81%)
Johnson (1998) UK	severe ABI	>5yr	+ (62%)	n/a	n/a

Note: +=positive outcome; -=negative outcome; n/a=not applicable; (%)=Percentage of participants who experienced positive/negative outcome.

Conclusion

In summary, although methodological differences between studies exploring the long-term outcomes post ABI do not permit direct comparison, it is generally true that those who have moderate to severe ABI appear to fare better than those with exclusively severe ABI; this was particularly true when looking at the dimension of productivity. In terms of employment, approximately 40% of those with severe TBI were able to return to employment at 7-10 years post TBI (Johnson & Davis, 1998; Possl et al., 2001). This is in comparison to those with moderate TBI where over 60% were in full-time positions either at work or school 11 years post TBI (Klonoff et al., 2001). However, even those with severe ABI might expect to have generally favorable outcomes with respect to return to independent living.

References

Andersson, E., Rackauskaite, D., Svanborg, E., Csajbok, L., Ost, M., & Nellgard, B. (2017, May). A prospective outcome study observing patients with severe traumatic brain injury over 10-15 years. *Acta Anaesthesiol Scand, 61*(5), 502-512.

Andriessen, T. M., Horn, J., Franschman, G., van der Naalt, J., Haitsma, I., Jacobs, B., Steyerberg, E. W., & Vos, P. E. (2011, Oct). Epidemiology, severity classification, and outcome of moderate and severe traumatic brain injury: a prospective multicenter study. *J Neurotrauma, 28*(10), 2019-2031.

Ashman, T. A., Cantor, J. B., Gordon, W. A., Sacks, A., Spielman, L., Egan, M., & Hibbard, M. R. (2008, May-Jun). A comparison of cognitive functioning in older adults with and without traumatic brain injury. *J Head Trauma Rehabil, 23*(3), 139-148.

Asikainen, I., Kaste, M., & Sarna, S. (1998). Predicting late outcome for patients with traumatic brain injury referred to a rehabilitation programme: a study of 508 Finnish patients 5 years or more after injury. *Brain Inj, 12*(2), 95-107.

Beck, B., Gantner, D., Cameron, P. A., Braaf, S., Saxena, M., Cooper, D. J., & Gabbe, B. J. (2018). Temporal Trends in Functional Outcomes after Severe Traumatic Brain Injury: 2006-2015. *J Neurotrauma, 35*(8), 1021-1029.

Bonow, R. H., Barber, J., Temkin, N. R., Videtta, W., Rondina, C., Petroni, G., Lujan, S., Alanis, V., La Fuente, G., Lavadenz, A., Merida, R., Jibaja, M., Gonzales, L., Falcao, A., Romero, R., Dikmen, S., Pridgeon, J., & Chesnut, R. M. (2018, Mar). The Outcome of Severe Traumatic Brain Injury in Latin America. *World Neurosurg, 111*, e82-e90.

Bushnik, T., Hanks, R. A., Kreutzer, J., & Rosenthal, M. (2003). Etiology of traumatic brain injury: Characterization of differential outcomes up to 1 year postinjury. *Archives of physical medicine and rehabilitation, 84*(2), 255-262.

Campbell, M. (2000). *Rehabilitation for traumatic brain injury: physical therapy practice in context* (2 ed.). Churchill Livingstone

Chan, V., Zagorski, B., Parsons, D., & Colantonio, A. (2013a). Older adults with acquired brain injury: a population based study. *BMC Geriatr, 13*, 97.

Chan, V., Zagorski, B., Parsons, D., & Colantonio, A. (2013b, October). Older adults with acquired brain injury: Functional independence measures after inpatient rehabilitation. *Archives of physical medicine and rehabilitation, 94 (10)*, e9.

Chan, V., Zagorski, B., Parsons, D., & Colantonio, A. (2013c). Older adults with acquired brain injury: outcomes after inpatient rehabilitation [Research Support, Non-U.S. Gov't]. *Canadian Journal on Aging, 32*(3), 278-286.

Chen, A., Bushmeneva, K., Zagorski, B., Colantonio, A., Parsons, D., & Wodchis, W. P. (2012). Direct cost associated with acquired brain injury in Ontario. *BMC neurology, 12*(1), 76-76.

Chen, A., Zagorski, B., Chan, V., Parsons, D., Laan, R. V., & Colantonio, A. (2012). Acute Care Alternate-Level-of-Care Days Due to Delayed Discharge for Traumatic and Non-Traumatic Brain Injuries. *Healthcare Policy/Politiques de Santé, 7*(4), 41-55.

Chen, A. Y., Zagorski, B., Parsons, D., Vander Laan, R., Chan, V., & Colantonio, A. (2012). Factors associated with discharge destination from acute care after acquired brain injury in Ontario, Canada. *BMC Neurol, 12*, 16.

Cifu, D. X., Kreutzer, J. S., Marwitz, J. H., Rosenthal, M., Englander, J., & High, W. (1996). Functional outcomes of older adults with traumatic brain injury: a prospective, multicenter analysis. *Archives of physical medicine and rehabilitation, 77*(9), 883-888.

CIHI, C. I. f. H. I. (2008). The Burden of Neurological Diseases. *Disorders and Injuries in Canada*.

Colantonio, A., Escobar, M. D., Chipman, M., McLellan, B., Austin, P. C., Mirabella, G., & Ratcliff, G. (2008, Apr). Predictors of postacute mortality following traumatic brain injury in a seriously injured population. *J Trauma, 64*(4), 876-882.

Colantonio, A., Gerber, G., Bayley, M., Deber, R., Yin, J., & Kim, H. (2011). Differential profiles for patients with traumatic and non-traumatic brain injury [Research Support, Non-U.S. Gov't]. *Journal of Rehabilitation Medicine, 43*(4), 311-315.

Colantonio, A., McVittie, D., Lewko, J., & Yin, J. (2009, Oct). Traumatic brain injuries in the construction industry. *Brain Inj, 23*(11), 873-878.

Colantonio, A., Ratcliff, G., Chase, S., & Vernich, L. (2004). Aging with traumatic brain injury: long-term health conditions. *International Journal of Rehabilitation Research, 27*(3), 209-214.

Colantonio, A., Saverino, C., Zagorski, B., Swaine, B., Lewko, J., Jaglal, S., & Vernich, L. (2010, Nov). Hospitalizations and emergency department visits for TBI in Ontario. *Can J Neurol Sci, 37*(6), 783-790.

Cope, D. N., Cole, J. R., Hali, K. M., & Barkan, H. (1991). Brain injury: analysis of outcome in a post-acute rehabilitation system. Part 1: general analysis. *Brain Inj, 5*(2), 111-125.

Cuthbert, J. P., Harrison-Felix, C., Corrigan, J. D., Bell, J. M., Haarbauer-Krupa, J. K., & Miller, A. C. (2015). Unemployment in the United States after traumatic brain injury for working-age individuals: prevalence and associated factors 2 years postinjury. *The Journal of head trauma rehabilitation, 30*, 160-174.

Dijkers, M., Brandstater, M., Horn, S., Ryser, D., & Barrett, R. (2013). Inpatient rehabilitation for traumatic brain injury: the influence of age on treatments and outcomes. *NeuroRehabilitation, 32*, 233-252.

Einarsen, C. E., van der Naalt, J., Jacobs, B., Follestad, T., Moen, K. G., Vik, A., Haberg, A. K., & Skandsen, T. (2018, Jun). Moderate Traumatic Brain Injury: Clinical Characteristics and a Prognostic Model of 12-Month Outcome. *World Neurosurg, 114*, e1199-e1210.

Faul, M., Xu, L., Wald, M., & Coronado, V. (2010). Traumatic Brain Injury in the United States. *Centers for Disease Control and Prevention, National Center for Injury Prevention and Control. Atlanta, GA*.

Flanagan, S. (2008). Post-TBI life expectancy and health: A systematic review. *Brain Injury Professional, 5, 22, 23*.

Folkerson, L. E., Sloan, D., Davis, E., Kitagawa, R. S., Cotton, B. A., Holcomb, J. B., Tomasek, J. S., & Wade, C. E. (2018). Coagulopathy as a predictor of mortality after penetrating traumatic brain injury. *American Journal of Emergency Medicine, 36*(1), 38-42.

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Fu, T. S., Jing, R., Fu, W. W., & Cusimano, M. D. (2016). Epidemiological Trends of Traumatic Brain Injury Identified in the Emergency Department in a Publicly-Insured Population, 2002-2010. *PloS one, 11*(1), e0145469-e0145469.

Fu, T. S., Jing, R., McFaull, S. R., & Cusimano, M. D. (2015). Recent trends in hospitalization and in-hospital mortality associated with traumatic brain injury in Canada: A nationwide, population-based study. *The journal of trauma and acute care surgery, 79*, 449-454.

Gardner, R. C., Burke, J. F., Nettiksimmons, J., Kaup, A., Barnes, D. E., & Yaffe, K. (2014, Dec). Dementia risk after traumatic brain injury vs nonbrain trauma: the role of age and severity. *JAMA Neurol, 71*(12), 1490-1497.

Goldman, S. M., Tanner, C. M., Oakes, D., Bhudhikanok, G. S., Gupta, A., & Langston, J. W. (2006, Jul). Head injury and Parkinson's disease risk in twins. *Ann Neurol, 60*(1), 65-72.

Grauwmeijer, E., Heijenbrok-Kal, M. H., Peppel, L. D., Hartjes, C. J., Haitsma, I. K., de Koning, I., & Ribbers, G. M. (2018, 2018 Jul 01 2019-02-14). Cognition, health-related quality of life, and depression ten years after moderate to severe traumatic brain injury: A prospective cohort study. *J Neurotrauma, 35*(13), 1543-1551.

Greenwald, B. D., Burnett, D. M., & Miller, M. A. (2003). Congenital and acquired brain injury. 1. Brain injury: epidemiology and pathophysiology. *Archives of physical medicine and rehabilitation, 84*(3 Suppl 1), S3-7.

Gross, T., & Amsler, F. (2018). One-year outcome following brain injury: a comparison of younger versus elderly major trauma patients. *Archives of Orthopaedic & Trauma Surgery, 138*(10), 1375-1387.

Hammond, F. M., Horn, S. D., Smout, R. J., Seel, R. T., Beaulieu, C. L., Corrigan, J. D., Barrett, R. S., Cullen, N., Sommerfeld, T., & Brandstater, M. E. (2015). Rehospitalization During 9 Months After Inpatient Rehabilitation for Traumatic Brain Injury. *Archives of physical medicine and rehabilitation, 96*, S330-339.e334.

Haring, R. S., Narang, K., Canner, J. K., Asemota, A. O., George, B. P., Selvarajah, S., Haider, A. H., & Schneider, E. B. (2015). Traumatic brain injury in the elderly: morbidity and mortality trends and risk factors. *The Journal of surgical research, 195*, 1-9.

Harrick, L., Krefting, L., Johnston, J., Carlson, P., & Minnes, P. (1994). Stability of functional outcomes following transitional living programme participation: 3-year follow-up. *Brain Inj, 8*(5), 439-447.

Harrison-Felix, C., Pretz, C., Hammond, F. M., Cuthbert, J. P., Bell, J., Corrigan, J., Miller, A. C., & Haarbauer-Krupa, J. (2015). Life Expectancy after Inpatient Rehabilitation for Traumatic Brain Injury in the United States. *J Neurotrauma, 32*, 1893-1901.

Herrera-Melero, M. C., Egea-Guerrero, J. J., Vilches-Arenas, A., Rincon-Ferrari, M. D., Flores-Cordero, J. M., Leon-Carrion, J., & Murillo-Cabezas, F. (2015). Acute predictors for mortality after severe TBI in Spain: Gender differences and clinical data. *Brain Inj, 29*, 1439-1444.

Huang, C. H., Lin, C. W., Lee, Y. C., Huang, C. Y., Huang, R. Y., Tai, Y. C., Wang, K. W., Yang, S. N., Sun, Y. T., & Wang, H. K. (2018, Nov 5). Is traumatic brain injury a risk factor for neurodegeneration? A meta-analysis of population-based studies. *BMC Neurol, 18*(1), 184.

Institute of Medicine Committee on Gulf, W., Health: Brain Injury in, V., & Long-Term Health, O. (2008). In *Gulf War and Health: Volume 7: Long-Term Consequences of Traumatic Brain Injury*. National Academies Press (US) Copyright 2009 by the National Academy of Sciences. All rights reserved.

Johnson, K., & Davis, P. K. (1998). A supported relationships intervention to increase the social integration of persons with traumatic brain injuries. *Behavior modification, 22*(4), 502-528.

Kaitaro, T., Koskinen, S., & Kaipio, M.-L. (1995). Neuropsychological problems in everyday life: a 5-year follow-up study of young severely closed-head-injured patients. *Brain Inj, 9*(7), 713-727.

Katz, D. I., Polyak, M., Coughlan, D., Nichols, M., & Roche, A. (2009). Natural history of recovery from brain injury after prolonged disorders of consciousness: outcome of patients admitted to inpatient rehabilitation with 1-4 year follow-up. *Prog Brain Res, 177*, 73-88.

Khan, A., Prince, M., Brayne, C., & Prina, A. M. (2015). Lifetime Prevalence and Factors Associated with Head Injury among Older People in Low and Middle Income Countries: A 10/66 Study. *PloS one, 10*, e0132229.

Klonoff, P. S., Lamb, D. G., & Henderson, S. W. (2001). Outcomes from milieu-based neurorehabilitation at up to 11 years post-discharge. *Brain Inj, 15*(5), 413-428.

Langlois, J. A., Rutland-Brown, W., & Wald, M. M. (2006). The Epidemiology and Impact of Traumatic Brain Injury: A Brief Overview. *The Journal of head trauma rehabilitation, 21*(5), 375-378.

Lu, J., Roe, C., Sigurdardottir, S., Andelic, N., & Forslund, M. (2018, 2018 Jul 15 2018-07-12). Trajectory of functional independent measurements during first five years after moderate and severe traumatic brain injury. *J Neurotrauma, 35*(14), 1596-1603.

Maas, A. I. R., Stocchetti, N., & Bullock, R. (2008, 8//). Moderate and severe traumatic brain injury in adults. *The Lancet Neurology, 7*(8), 728-741.

Malec, J. F., Smigielski, J. S., DePompolo, R. W., & Thompson, J. M. (1993). Outcome evaluation and prediction in a comprehensive-integrated post-acute outpatient brain injury rehabilitation programme. *Brain Inj, 7*(1), 15-29.

Marquez de la Plata, C. D., Hart, T., Hammond, F. M., Frol, A. B., Hudak, A., Harper, C. R., O'Neil-Pirozzi, T. M., Whyte, J., Carlile, M., & Diaz-Arrastia, R. (2008). Impact of age on long-term recovery from traumatic brain injury. *Archives of physical medicine and rehabilitation, 89*(5), 896-903.

Mills, V. M., Nesbeda, T., Katz, D. I., & Alexander, M. P. (1992). Outcomes for traumatically brain-injured patients following post-acute rehabilitation programmes. *Brain Inj, 6*(3), 219-228.

Minnes, P., Woodford, L., Carlson, P., Johnston, J., & McColl, M. A. (2010). The needs of aging parents caring for an adult with acquired brain injury [Research Support, Non-U.S. Gov't]. *Canadian Journal on Aging, 29*(2), 185-192.

Mosenthal, A. C., Lavery, R. F., Addis, M., Kaul, S., Ross, S., Marburger, R., Deitch, E. A., & Livingston, D. H. (2002). Isolated traumatic brain injury: age is an independent predictor of mortality and early outcome. *Journal of Trauma-Injury, Infection, and Critical Care, 52*(5), 907-911.

Northern Brain Injury Association. (2018). *Brain Injury Statistics*.

Novack, T. A., Alderson, A. L., Bush, B. A., Meythaler, J. M., & Canupp, K. (2000). Cognitive and functional recovery at 6 and 12 months post-TBI. *Brain Inj, 14*(11), 987-996.

OBIA, O. B. I. A. (2007). *Caregiver Information and Support Link: 2005 A year in review*. Ontario Brain Injury Association.

Odgaard, L., Johnsen, S. P., Pedersen, A. R., & Nielsen, J. F. (2017, May 2017 – Jun May 2017 - Jun 2017 2017-09-25). Return to work after severe traumatic brain injury: A nationwide follow-up study. *The Journal of head trauma rehabilitation, 32*(3), E57-E64.

Owens, T. S., Corkill, R., Berg, R. M. G., & Bailey, D. M. (2018, October). Traumatic brain injury and dementia. *The Lancet Psychiatry, 5*(10), 782.

Peck, K. A., Calvo, R. Y., Sise, C. B., Johnson, J., Yen, J. W., Sise, M. J., Dunne, C. E., Badiee, J., Shackford, S. R., & Lobatz, M. A. (2014). Death after discharge: predictors of mortality in older brain-injured patients. *The journal of trauma and acute care surgery, 77*, 978-983.

Pennings, J. L., Bachulis, B. L., Simons, C. T., & Slazinski, T. (1993). Survival after severe brain injury in the aged. *Archives of Surgery, 128*(7), 787-794.

Pickett, W., Ardern, C., & Brison, R. J. (2001, Aug 7). A population-based study of potential brain injuries requiring emergency care. *Cmaj, 165*(3), 288-292.

Plassman, B. L., Havlik, R. J., Steffens, D. C., Helms, M. J., Newman, T. N., Drosdick, D., Phillips, C., Gau, B. A., Welsh-Bohmer, K. A., Burke, J. R., Guralnik, J. M., & Breitner, J. C. (2000, Oct 24). Documented head injury in early adulthood and risk of Alzheimer's disease and other dementias. *Neurology, 55*(8), 1158-1166.

Possl, J., Jurgensmeyer, S., Karlbauer, F., Wenz, C., & Goldenberg, G. (2001, Jan). Stability of employment after brain injury: a 7-year follow-up study. *Brain Inj, 15*(1), 15-27.

Rapoport, M. J., & Feinstein, A. (2000). Outcome following traumatic brain injury in the elderly: a critical review. *Brain Inj, 14*(8), 749-761.

Ratcliff, G., Colantonio, A., Escobar, M., Chase, S., & Vernich, L. (2005). Long-term survival following traumatic brain injury. *Disability & Rehabilitation, 27*(6), 305-314.

Redelmeier, D. A., Tibshirani, R. J., & Evans, L. (2003, Jun 28). Traffic-law enforcement and risk of death from motor-vehicle crashes: case-crossover study. *Lancet, 361*(9376), 2177-2182.

Rogers, J. M., & Read, C. A. (2007, Dec). Psychiatric comorbidity following traumatic brain injury. *Brain Inj, 21*(13-14), 1321-1333.

Roozenbeek, B., Maas, A. I., & Menon, D. K. (2013, Apr). Changing patterns in the epidemiology of traumatic brain injury. *Nat Rev Neurol, 9*(4), 231-236.

Ruet, A., Jourdan, C., Bayen, E., Darnoux, E., Sahridj, D., Ghout, I., Azerad, S., Pradat Diehl, P., Aegerter, P., Charanton, J., Vallat Azouvi, C., & Azouvi, P. (2018, Sep). Employment outcome four years after a severe traumatic brain injury: results of the Paris severe traumatic brain injury study. *Disabil Rehabil, 40*(18), 2200-2207.

Saverino, C., Swaine, B., Jaglal, S., Lewko, J., Vernich, L., Voth, J., Calzavara, A., & Colantonio, A. (2016). Rehospitalization After Traumatic Brain Injury: A Population-Based Study. *Archives of physical medicine and rehabilitation, 97*, S19-25.

Senathi-Raja, D., Ponsford, J., & Schönberger, M. (2010). Impact of age on long-term cognitive function after traumatic brain injury. *Neuropsychology, 24*(3), 336.

Tagliaferri, F., Compagnone, C., Korsic, M., Servadei, F., & Kraus, J. (2006, Mar). A systematic review of brain injury epidemiology in Europe. *Acta Neurochir (Wien), 148*(3), 255-268; discussion 268.

Thornhill, S., Teasdale, G. M., Murray, G. D., McEwen, J., Roy, C. W., & Penny, K. I. (2000, Jun 17). Disability in young people and adults one year after head injury: prospective cohort study. *Bmj, 320*(7250), 1631-1635.

Thurman, D., & Guerrero, J. (1999). Trends in hospitalization associated with traumatic brain injury. *Jama, 282*(10), 954-957.

van Eijck, M. M., Schoonman, G. G., van der Naalt, J., de Vries, J., & Roks, G. (2018). Diffuse axonal injury after traumatic brain injury is a prognostic factor for functional outcome: a systematic review and meta-analysis. *Brain Inj, 32*(4), 395-402.

Wagner, A. K. (2001). Functional prognosis in traumatic brain injury. *Physical Medicine and Rehabilitation: state of the arts reviews, 15*, 245-265.

Walder, B., Haller, G., Rebetez, M. M. L., Delhumeau, C., Bottequin, E., Schoettker, P., Ravussin, P., Brodmann Maeder, M., Stover, J. F., Zurcher, M., Haller, A., Wackelin, A., Haberthur, C., Fandino, J., Haller, C. S., & Osterwalder, J. (2013). Severe traumatic brain injury in a high-income country: an epidemiological study. *J Neurotrauma, 30*, 1934-1942.

Watanitanon, A., Lyons, V. H., Lele, A. V., Krishnamoorthy, V., Chaikittisilpa, N., Chandee, T., & Vavilala, M. S. (2018, 01 May). Clinical epidemiology of adults with moderate traumatic brain injury. *Critical Care Medicine, 46*(5), 781-787.

Wilson, B. (1992). Recovery and compensatory strategies in head injured memory impaired people several years after insult. *Journal of Neurology, Neurosurgery & Psychiatry, 55*(3), 177-180.

Zaloshnja, E., Miller, T., Langlois, J. A., & Selassie, A. W. (2008). Prevalence of long-term disability from traumatic brain injury in the civilian population of the United States, 2005. *The Journal of head trauma rehabilitation, 23*(6), 394-400.