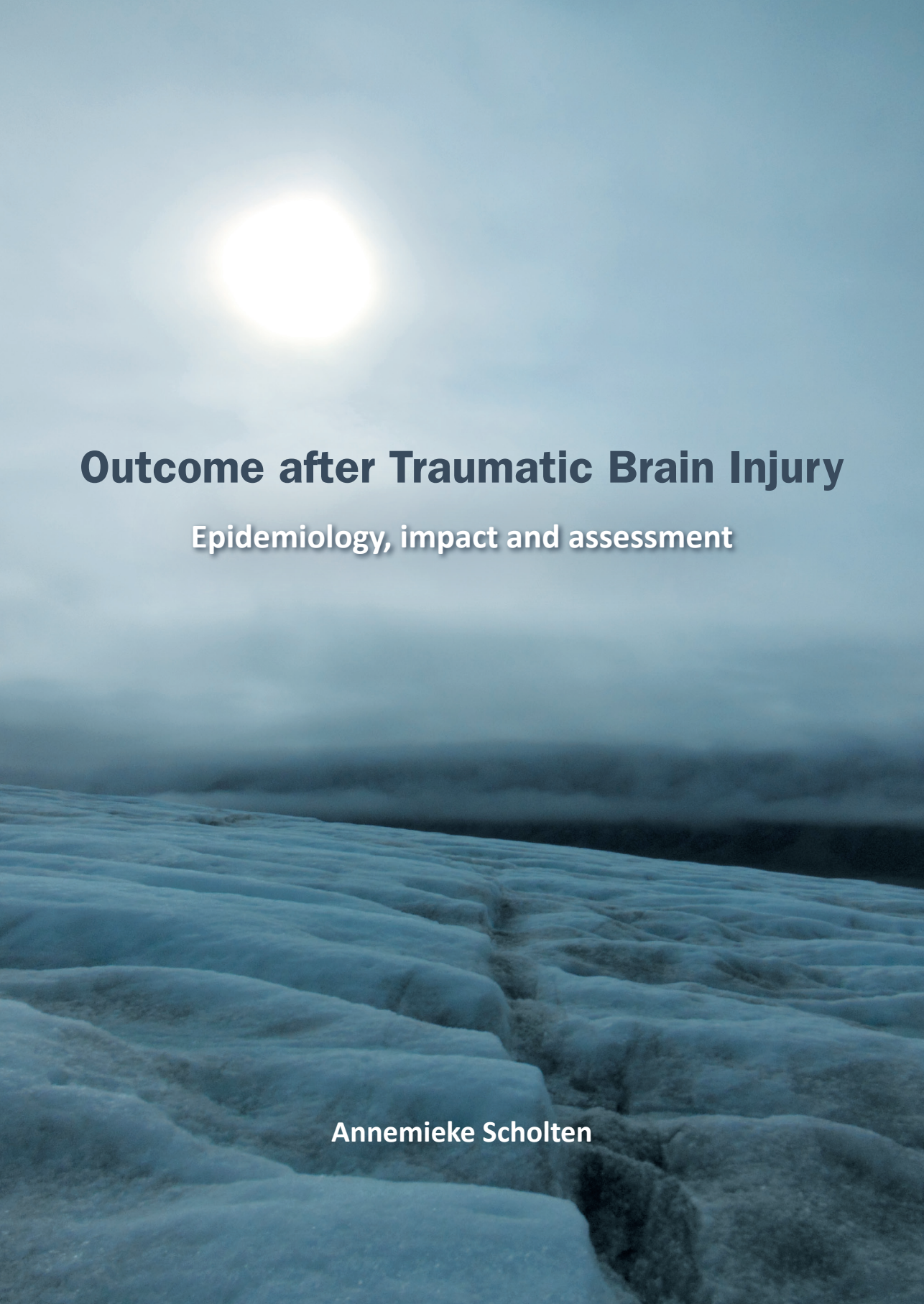

Outcome after Traumatic Brain Injury

Epidemiology, impact and assessment

Annemieke Scholten

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Outcome after Traumatic Brain Injury: Epidemiology, impact and assessment
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Chapter 1

General introduction

GENERAL INTRODUCTION

Injuries are among the leading causes of death and disability in the world, often affecting young people.[1] In road traffic alone, about 1.25 million people die each year on the world's roads and millions more sustain non-fatal injuries.[2,3] In Europe, yearly more than 230,000 people die and about 5.7 million people are hospitalised due to an intentional (e.g. self-harm, assault) or unintentional injury.[4] Injury may lead to great personal suffering and economic costs. Almost all injury survivors experience some level of short-term or long-term impairment or disability,[5] which affects their health-related quality of life (HRQL)[5] and frequently inhibits them to return to full employment.[6] In addition, survivors of injury may require specialised emergency care and long-term rehabilitation.

An important severe injury that often affects young people is a traumatic brain injury (TBI). TBI, especially the more severe cases, can have a significant and long-term impact on a person's life and imposes a substantial economic burden on individuals and society.[7,8] According to the World Health Organisation, TBI is predicted to surpass many diseases as a major cause of death and disability by the year 2020.[9,10]

The number of survivors of severe injuries has rapidly risen,[1] due to major advances in trauma systems, amongst others. This resulted in a shift in attention from mortality towards disability. Policymakers and clinicians are recognising the importance of quantifying the health impact and costs of injuries in order to identify, measure, value, and compare the costs and consequences of prevention strategies and treatments. This information enables them to prioritise prevention and provides essential input for the development of treatment guidelines. Consequently, insight into the incidence, trends, risk groups, costs, disease burden, and impact of an injury on patients' health is essential in order to compare the burden of injuries between patient subgroups and with other diseases, optimise health care policy and prevention, and develop effective health care and rehabilitation services.

The papers in this thesis deal with the incidence, health-related quality of life, psychiatric consequences and economic consequences of TBI, and address the methodological challenges in assessing outcome after injury, including TBI.

This chapter will introduce some concepts related to the assessment of the health impact and costs of injuries, and consequently will address the research questions and outline of this thesis.

1.1 TRAUMATIC BRAIN INJURY

Traumatic brain injury (TBI) occurs when a sudden trauma causes damage to the brain. One commonly used definition of TBI is from an international expert group on TBI (Box 1.1).[11]

Annually, 10 million people worldwide sustain a TBI that warrants some form of health care (incidence rate 144 per 100,000).[1] In Europe, approximately 2.5 million people experience a TBI each year, of whom 1 million are admitted to the hospital and 75,000 die.[12] Overall, males are about twice as likely as females to experience a TBI,[13] and show overall higher mortality rates than females.[14] Additionally, TBI often involves young children, young adults and the elderly.[13] Motor vehicle-related crashes and falls are the most common events leading to a TBI.[13]

Box 1.1 Definition of traumatic brain injury (TBI)

TBI is defined as an alteration in brain function, or other evidence of brain pathology, caused by an external force.[11] ***An alteration in brain function*** is defined as one of the following clinical signs: any period of loss of or a decreased consciousness; any loss of memory for events immediately before or after the injury; neurologic deficits such as muscle weakness, loss of balance and coordination, disruption of vision, change in speech and language, or sensory loss; any alteration in mental state at the time of the injury such as confusion, disorientation, slowed thinking, or difficulty with concentration. ***Other evidence of brain pathology*** may include visual, neuro-radiologic, or laboratory confirmation of damage to the brain. ***Caused by an external force*** may include any of the following events: the head being struck by an object; the head striking an object; the brain undergoing an acceleration/deceleration movement without direct external trauma to the head; a foreign body penetrating the brain; forces generated from events such as a blast or explosion; or other force yet to be defined.[11]

TBI survivors often experience a substantial burden of functional, physical, emotional, cognitive, behavioral, and/or social disability,[15,16] which disrupts the lives of victims and relatives and imposes huge costs to individuals and society.[17-19]

Symptoms of TBI can be classified as mild, moderate, or severe, depending on the extent of the damage to the brain. The majority (70–80%) of TBI cases involve mild TBI,[13] often comprising a concussion. Although classified as 'mild', individuals with mild TBI may suffer from several physical impairments (e.g. headaches, dizziness, visual disturbances), cognitive problems (e.g. attention deficits, memory problems), and/or emotional or behavioral problems (irritability, anxiety, depression).[16,20] Moderate or severe TBI often occurs due to penetrating injuries or more severe shaking of the brain inside the bony skull, compressing and stretching the fragile nerve cells in the brain. These injuries may result in contusion (bleeding), bruising, swelling, and/or tearing of the brain tissue and blood vessels, leading to a loss of consciousness of several minutes or a prolonged unconscious state or coma.[21]

After a TBI, as swelling decreases and blood flow and brain chemistry improve, the function of the brain usually improves. TBI, however, often results in long-term or lifelong disability.[15] In the US, almost half of all hospitalised TBI survivors[22] and about 2% of the US population[15] experience TBI-related long-term or lifelong disability, which drastically reduced their HRQL[23,24] and complicated recovery and rehabilitation.[25]

Over the past decades, the number of survivors of severe TBI has rapidly grown due to major advances in trauma systems,[1] amongst others. However, the disability due to TBI has not appreciably reduced.[26] This has resulted in a shift in attention from mortality towards disability of TBI survivors.

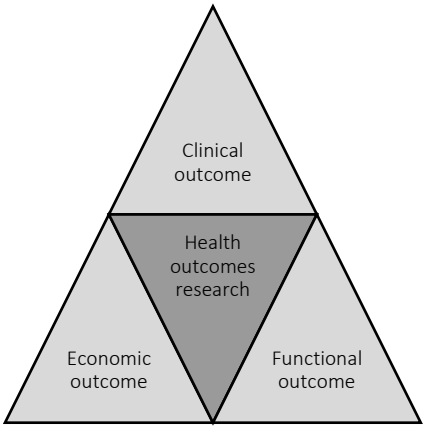
1.2 OUTCOME AFTER INJURY

Historically, the medical community was oriented towards clinical outcomes, such as mortality and side effects of treatments.[27] The escalation of health care expenditures in the 1970s and 1980s,[28] amongst others, induced a need for mechanisms to reduce these cost increases and a need for accountability for expenses and health outcome.[27] As a consequence, there has been an increased interest in expanding the objective clinical outcomes with assessments of subjective patient-reported outcomes

and the measurement of economic outcomes.[27] This resulted in the development of a model that classifies health outcomes along three dimensions: clinical outcome, functional outcome, and economic outcome.[29]

The model can be translated to measure outcome after injury (Figure 1.1). In this thesis, clinical outcomes comprise the medical events that occur as a result of injury (e.g. hospital admission) and the objective outcome after injury as assessed by physicians. Functional outcomes are the consequences of injuries on a patient's health-related quality of life (HRQL). Economic outcomes include the direct, indirect, and intangible costs of injuries.

Figure 1.1 Measuring outcome after injury



Integrated knowledge on the clinical outcomes, functional outcomes, and costs of injuries are essential to gain insight into the total impact of injuries, to identify high-risk groups and in its turn to set priorities for prevention and trauma care. So far, most efforts on assessing the outcome after injury, including TBI, have been limited to either its clinical outcome,[13] functional outcome,[30] or costs.[7,31] By focusing on all three dimensions, the papers in this thesis provide insight into the medical events and the objective outcome after injury (clinical outcome), the impact of an injury on a patient's life and specifically the psychiatric consequences (functional outcome), and the associated costs of injuries (economic outcome).

Clinical outcome

Injuries frequently warrant some form of specialised emergency care. This may involve consulting a general physician, treatment at the emergency department or intensive care, and/or admission to the hospital. Most injury patients, especially those who experienced a TBI, also require additional treatment after hospital discharge and often require rehabilitation services for the rest of their life. Rehabilitation aims to help injury patients to achieve the highest possible level of physical, mental, and social functioning.

In case of TBI, these levels of functioning are often objectively assessed by physicians using the Glasgow Outcome Scale Extended (GOSE).[26,32] The GOSE classifies outcome into an 8-point scale from 1 (dead) to 8 (complete recovery), using eight questions covering consciousness, independence at home, major

social roles, and return to normal life.[33] However, a criticism of scales such as the GOSE is that they fail to capture the subjective perspective (e.g. HRQL) of injury patients.[34]

Functional outcome

Health care and prevention strategies have the ultimate goal to restore or preserve functioning and well-being related to health.[35] Functional outcome addresses not only activities of daily living but also the other aspects that constitute quality of life.[36] Quality of life expresses an overall sense of well-being, comprising aspects of happiness and satisfaction with life as a whole.[37]

Health-related quality of life

The concept of health-related quality of life (HRQL) has evolved since the 1980s and refers to a wide range of aspects of life that affect health (Box 1.2).[38]

Box 1.2 Definition of health-related quality of life (HRQL)

HRQL reflects an individual's perception of how an illness and its treatment affect physical, mental and social aspects of his or her life.[39] HRQL measurement is aimed to quantify the degree to which the medical condition (e.g. injury) impacts the individual's life in a valid and reproducible way.[40]

HRQL is generally measured with questionnaires (e.g. the SF-36 or EQ-5D) consisting of a number of questions on several domains of functioning (e.g. physical health, mental health, pain, mobility, self-care, cognition, and social functioning).[38] By means of HRQL measures patients can indicate whether and to which extend they have problems on one or several of these domains.

Some HRQL instruments generate a single summary score (or utility score) that represents the total health status of a person on a scale that usually extends from 0 (death) to 1 (full health), although negative scores representing states worse than death are possible.[38] This way, HRQL measures can be used to quantify the gap between measured and perfect HRQL or the net change in HRQL over time.[38]

HRQL has been recognised as an important outcome after injuries, as it provides well-standardised information on the recovery patterns and frequency, nature, severity and duration of the functional consequences of injuries.[41] This information is needed to quantify the impact of injuries on population health over time. Additionally, HRQL measures enable comparison of health outcome after injury with other diseases, pre-injury health state and the general population, and their outcome can be used in economic evaluations.[38]

Psychiatric consequences

The psychiatric consequences of injury have already been acknowledged since the 1940s.[42] Several of these first studies investigated the mental problems occurring as a consequence of head injuries and burn injuries.[42-44] To date, mental health has been recognised as an important component of HRQL after injury. However, little is known about to what extent patients with TBI are diagnosed with mental health problems after their injury, what the risk factors are for developing these psychiatric problems, and what the impact of these problems is on patients' recovery.

Research showed that a significant proportion of injury survivors is diagnosed with psychiatric disorders, with major depression and post-traumatic stress disorder (PTSD) being the most commonly diagnosed

and studied disorders.[10] Notable variation exists in the prevalence rates of these disorders following TBI. For example, depression prevalence rates after injury have been assessed that vary from 8% to 60% shortly after injury, and 9% to 31% up to one year after the injury.[45] PTSD prevalence rates have been reported that range from 18% to 42% within the first half year after injury, and 2% to 33% after one year.[45]

Overall, psychiatric consequences are found to play an important role in the development and maintenance of long-term disability in injury survivors and have a substantial effect on their physical health, functioning, HRQL and capacity to work,[46,47] imposing high costs to both individuals and society.

Economic outcome

Injuries, especially TBI, are a major cause of health care costs in the Western world. In Europe, the medical costs of hospital treated injuries is estimated to be at least 78 billion Euro per year.[4] In case of TBI, the annual lifetime costs of patients requiring medical treatment add up to an estimated 406 billion US dollars (about 431 Euro) in the US[17] and an estimated 147 million US dollars in New Zealand.[18] The majority (80%) of these costs is attributed to lifetime lost productivity, while a relatively minor share (20%) is estimated for medical costs.

Most of the assessments of the economic costs of injuries are based on the cost of illness approach (Box 1.3).

Box 1.3 Definition of cost of illness

The cost of illness approach was formalised in the 1960s, and divides the economic consequences of illnesses into direct costs, indirect costs, and intangible costs.[48,49] ***Direct costs*** include the expenses incurred because of the illness (e.g. medical care in hospitals and rehabilitation centers).[48] ***Indirect costs*** represent the value of lost production because of reduced working time or impaired performance at the workplace.[48] ***Intangible costs*** comprise the costs of pain and disability that cannot be directly measured in monetary form.[48] Generally, direct and indirect costs are summed to provide the overall cost the illness imposed on society.[49]

The papers in this thesis describe the direct health care costs, indirect productivity costs, and estimates of the total costs of injuries. These cost estimates provide a measure that enables comparison of the economic consequences of several types of injury with different injury severity and health care need. An overview of the costs of injuries by socio- and injury-related demographics easily provides insight into the opportunity for savings and needs for preventive action or treatment strategies. This information is essential for setting priorities in injury prevention and trauma care, and allocating resources in health care.

1.3 METHODOLOGICAL CHALLENGES

Injury, especially TBI, is characterised by a heterogeneous patient population of all ages and with a wide variety of causes, severity levels, outcome, and recovery patterns. This heterogeneity in patients and outcomes makes health outcomes research in the area of injuries challenging, and puts specific demands on the methodology of assessing outcome after injury.

The most important challenges in the outcome assessment of injuries, and especially TBI, comprise the difficulties in obtaining ratings from patients with severe injury, cognitive impairments, and those of very young age.[50] These patients might not be able to self-report on their HRQL, and in certain conditions proxy-report might be useful. Additionally, a large variation of measures and instruments exists to quantify the health impact of injuries.[51] Especially in TBI, there has been much debate on the use of generic instruments and/or measures that have been developed for TBI specifically, in order to measure all relevant domains of functioning (e.g. cognitive functioning).[50]

Other challenges in the field of injuries involve the measurement of pre-injury health status, the shift in outcome assessment from mortality towards disability, and the assessment of change in health status due to an injury, which will be addressed in the second part of this thesis.
In order to produce valid estimates of the health impact of injuries and the decrease in HRQL due to an injury, information on the patient's pre-injury health status is needed. This information is, however, often not available due to the difficulty to prospectively collect information on the patients' pre-injury health status. To date, it is not clear which alternative methods should be used to measure and incorporate the pre-injury HRQL of injury patients to estimate the change in health status.
Moreover, it remains challenging to obtain information on the consequences of injury and assessing the outcome of injuries beyond mortality. Most trauma registries document information on the acute phase of hospital care and in-hospital mortality, but not on the consequences of non-fatal trauma. Additionally, information on the medical events after trauma is often registered in different databases, which generally all have their own purposes (e.g. injury prevention, trauma care evaluation, providing death statistics). As a consequence, none of these databases provides the full picture of medical events resulting from injury. Linkage of data from multiple sources may overcome these problems and may be used to obtain insight into the consequences of injury.
Finally, different methods exist to quantify the consequences of injury, for example, the burden of disease. To estimate the years lived with disability due to an injury, disability weights are needed. Disability weights can be obtained from existing sets of disability weights, or derived from HRQL data from individual injury patients. Although both methods have their advantages and disadvantages, little is known about the differences between the disabilities weights derived by both methods and their effect on estimations of the change in health status.

1.4 GUIDELINES

Insights into the health- and economic impact of injuries is essential for the development of treatment guidelines. The trauma care for patients with injuries, especially TBI, is often complex and multidisciplinary. As a consequence, guidelines, protocols and care pathways have been developed to reduce variation in practice, improve quality of care, and ensure that evidence-based care is optimally implemented (Box 1.4).

Box 1.4 Guidelines

Guidelines incorporate the current best evidence in making decisions about the care of individual patients. This way, guidelines enable the integration of the best available external clinical evidence from systematic research and consensus recommendations made by a panel of experts, with individual clinical expertise and patient values.[52,53]

The proportion of patients treated according to these guideline recommendations is generally low,[54-56] showing substantial variation in guideline adherence between centers[56,57] and medical condition,[58] amongst others. Consequently, patients may not receive evidence based care or receive unnecessary care. The studies included in this thesis specifically assess the guidelines adherence in TBI, and in the pain management of injury patients in the chain of emergency care.

1.5 AIM AND OUTLINE OF THIS THESIS

The main aim of this thesis is to expand our knowledge on the incidence and health- and economic impact of injuries and TBI in specific, and the possible improvements of outcome assessment in the field of injuries. We will apply an integrated approach of assessing all three domains of health outcomes research to identify important risk groups as input for prevention strategies.
The aim of this thesis was operationalised in the following research questions:

1. What are the incidence, health impact and costs of TBI, and which risk groups in TBI can be identified?
2. How can the assessment of outcomes after injury be improved?
3. What is the impact of TBI on HRQL, and what is the prevalence of psychiatric disorders after TBI?
4. What is the extent of adherence to guidelines in injury patients?

This thesis consists of four parts. Part I (Chapter 2 and 3) addresses research question 1 and describes the incidence, health impact, and costs of TBI, and thereby provides insight into the risk groups in TBI. Chapter 2 provides estimates of the incidence, costs and disease burden of TBI in the Netherlands, using an integrated approach which enables detection of important risk groups in TBI. As bicyclists are one of the main risk groups in TBI, Chapter 3 addresses the incidence and costs of bicycle-related TBI across various age groups, and in comparison to all injuries from cycling.
Part II (Chapter 4 and 5) addresses the methodological issues in assessing outcome after injury, and aims to answer research question 2. Chapter 4 provides an overview of the current measures to assess pre-injury HRQL and the differences in pre-injury HRQL scores between measures. Chapter 5 provides insight into the opportunities of expanding trauma registries that generally contain only clinical outcomes, with follow-up data on the functional and economic outcomes after injury. In Chapter 6, two methods to derive disability weights of TBI are compared which are used to estimate the years lived with disability after TBI.
Part III (Chapter 7 to 10) examines the outcome after TBI. Chapter 7 assesses the recovery pattern differences between mild, moderate, and severe TBI and examines the relationship between objective functional impairment and subjective HRQL. Chapter 8 provides an overview of the prevalence and risk factors of anxiety and depression following TBI. Chapter 9 elaborates on the predictors and prediction

models of major depression and posttraumatic stress disorder after TBI. In Chapter 10, the impact of depression and posttraumatic stress symptoms on functional outcome and HRQL of patients with TBI is assessed. These chapters aim to answer research question 3.

Part IV (Chapter 11 and 12) addresses the adherence to guidelines in injury patients, and aims to answer research question 4. Chapter 11 quantifies the guideline adherence in TBI, explores the factors influencing adherence, and examines the associations between guideline adherence and outcome. In Chapter 12 the compliance of current practice with a guideline on the pain management for trauma patients in the chain of emergency care is assessed, and the early and initial pain management for adult trauma patients in emergency care is evaluated.

These parts are followed by the general discussion, which summarises the main findings of the papers in this thesis, answers the four research questions, and consequently addresses the methodological considerations, practical implications and recommendations for future research.

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PART I

Epidemiology of traumatic brain injury

Chapter 2

Traumatic brain injury in the Netherlands: incidence, costs and disability-adjusted life years

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ABSTRACT

Background Traumatic brain injury (TBI) is a major cause of death and disability, leading to great personal suffering and huge costs to society. Integrated knowledge on epidemiology, economic consequences and disease burden of TBI is scarce but essential for optimising health care policy and preventing TBI. This study aimed to estimate incidence, cost-of-illness and disability-adjusted life years (DALYs) of TBI in the Netherlands.

Methods This study included data on all TBI patients who were treated at an Emergency Department (ED - National Injury Surveillance System), hospitalised (National Medical Registration), or died due to their injuries in the Netherlands between 2010–2012. Direct health care costs and indirect costs were determined using the incidence-based Dutch Burden of Injury Model. Disease burden was assessed by calculating years of life lost (YLL) owing to premature death, years lived with disability (YLD) and DALYs. Incidence, costs and disease burden were stratified by age and gender.

Results TBI incidence was 213.6 per 100,000 person years. Total costs were €314.6 (USD $433.8) million per year and disease burden resulted in 171,200 DALYs (on average 7.1 DALYs per case). Men had highest mean costs per case (€19,540 versus €14,940), driven by indirect costs. 0–24-year-olds had high incidence and disease burden but low economic costs, whereas 25–64-year-olds had relatively low incidence but high economic costs. Patients aged 65+ had highest incidence, leading to considerable direct health care costs. 0–24-year-olds, men aged 25–64 years, traffic injury victims (especially bicyclists) and home and leisure injury victims (especially 0–5-year-old and elderly fallers) are identified as risk groups in TBI.

Conclusions The economic and health consequences of TBI are substantial. The integrated approach of assessing incidence, costs and disease burden enables detection of important risk groups in TBI, development of prevention programmes that target these risk groups and assessment of the benefits of these programmes.

2.1 INTRODUCTION

Traumatic brain injury (TBI) – defined as an alteration in brain function, or other evidence of brain pathology, caused by an external cause[1] – is a leading cause of morbidity, disability, and mortality worldwide. In Europe, the annual incidence rate of hospitalised and fatal TBI is about 235 per 100,000 person years.[2] TBI survivors almost all experience some level of impairment or disability,[2] which drastically reduces their health-related quality of life (HRQL).[3,4]

In addition to the often long-term impact of TBI on a person's life, the economic consequences of TBI for both individuals and society are substantial.[5,6] TBI patients require specialised pre-hospital care, transport, in-hospital (emergency) care, and often long-term rehabilitation. Survivors of more severe TBI are often unable to return to full employment.[7,8] TBI therefore leads to significant direct health care costs in terms of pre-hospital care, emergency care, hospitalisation, long-term outpatient care and rehabilitation, and indirect costs due to loss of productivity. The total direct and indirect costs of TBI occurring in Europe were estimated to €33 billion (approximately USD $45.4 billion).[9]

Most efforts on assessing the impact of TBI have been limited to either its epidemiology,[2,10,11] costs[5,6,9,12-18] or disease burden.[17,19,20] Integrated knowledge on epidemiology, economic consequences and disease burden of TBI is scarce but essential for optimising health care policy, allocating scarce resources, preventing TBI, and developing effective health care and rehabilitation services. Up till now, an insight of the total population impact of TBI is lacking. The purpose of this study was to 1) estimate the incidence, cost-of-illness and disability-adjusted life years (DALYs) of TBI in the Dutch population, and 2) detect important risk groups in TBI.

2.2 METHODS

Data sources

This surveillance-based study included data on all patients with TBI treated at an emergency department (ED) and/or admitted to hospital in the Netherlands in the period 2010–2012. TBI cases were extracted from the Dutch Injury Surveillance System (LIS)[21] and the National Hospital Discharge Registry (LMR),[22] to include data of TBI patients treated at the ED and hospitalised TBI patients respectively.

LIS is an ongoing monitoring system which records data of all unintentional and intentional injured patients who attend the ED. LIS is based upon the registration of 13 hospitals in the Netherlands (12–15% coverage) that are considered to be representative for the total Dutch injury-related ED visits. To generate national estimates of the injury-related ED visits in the Netherlands, an extrapolation factor was calculated in which the number of ED treatments due to injury registered by the participating hospitals is multiplied by the quotient of the number of hospital admissions due to injury in the Netherlands divided by the number of hospital admissions due to injury registered in the participating hospitals.[23] The required data on the number of hospital admissions due to TBI in the Netherlands is obtained from the LMR, which collects data from all Dutch hospitals regarding patient information from hospital admission to discharge.

In this study, data from LIS was used to assess socio-demographic (age at injury and sex), injury (type of injury, external cause of injury, multiple injury), and health care related characteristics (hospitalisation

and length of stay). To avoid double counting, only the LMR was used to obtain data of hospitalised patients on the type of injury (ICD-9-codes) and for costs calculations.

Definition of TBI

For patients treated at the ED, TBI was defined as having a "Concussion" or "Other skull – brain injury" in at least one of the three injuries that can be recorded in LIS. This study therefore included all cases in which TBI was registered as first, second or third injury. In case of multiple injuries, an hierarchy derived from the literature was used to determine the most severe injuries.[24] This hierarchy prioritised spinal cord injury over skull or brain injury (except concussions), hip fracture, and other lower extremity fractures, respectively.

For hospitalised patients, TBI was defined using the International Classification of Diseases, ninth revision (ICD-9-CM). This study included ICD-9-codes related to concussion (850), fractures (800–801, 803, 804), lesion (851–854), late effects (905, 907), nerve injury (950), and unspecified head injury (959).

Cost-of-illness

Short- and long-term direct costs (e.g. health care costs) and indirect costs (e.g. productivity loss) of TBI were calculated with use of the incidence-based Dutch Burden of Injury Model.[23,25] This model calculates patient numbers, health care consumption, and related costs for predefined patient groups that are homogenous in terms of health service use. Data on health care consumption was obtained from the LIS and LMR database, rehabilitation centers (LIVRE), nursing homes (SIVIS), and a patient follow-up survey conducted in 2007–2008.[23,26,27]

Direct health care costs of TBI were calculated by multiplying incidence by health care volumes (e.g. length of stay), transition probabilities (e.g. probability of hospital admission), and unit costs (e.g. costs per day in hospital). All unit costs were estimated according to national guidelines for health care costing,[28] reflecting real resource use (Table 2.1).

Indirect costs of TBI were calculated for all TBI patients in the working age 15 to 64 years treated at the ED or hospitalised, based on information on work absence and return to work from the patient follow-up questionnaire conducted in 2007–2008.[23,26,27]

In order to compare the costs of TBI in the Netherlands with previous cost studies conducted in other countries and at varying points in time, all costs estimates were adjusted for inflation with use of the Consumer Price Index[29-31] and converted into 2012 Euros (as at 31 December 2012 €1.00 = USD $1.3203).

Burden of TBI

The national disease burden of TBI was measured using the disability-adjusted life year (DALY), a summary measure of population health.[32] To calculate the burden of disease, information on premature mortality, and morbidity and disability due to non-fatal health outcome is combined into one single number. This number represents the health gap between the current state of a population's health compared to an ideal situation where individuals would live to the standard life expectancy in full health, i.e. free of disease and disability. DALYs are the sum of the years of life lost due to premature mortality (YLLs) and years lived with disability (YLDs).

Table 2.1 Unit costs (2012)

	Resource	Unit costs
General Practitioner	Practice consultation	€33.70
	Consultation by telephone	€16.90
	Home visit	€67.40
	Referral patient treated at the ED	€35.00
	Referral hospitalised patient	€44.00
	Follow-up care patient treated at the ED	€33.70
	Follow-up care hospitalised patient	€37.80
Ambulance	Emergency journey	€538.20
	Scheduled journey	€206.20
Hospital	Attendance of ED	Injury specific fees[1]
	Hospitalisation general hospital	€460.40/day
	Hospitalisation academic hospital	€629.00/day
	Intensive care	€1,751.50/day
	Day care	€310.30/day
	Outpatient department visit	€178.10/visit
	Medical procedures	Reimbursement fees
Long-term care	Nursing home	€264.60/day, 138.80/day care
	Rehabilitation	€469.10/day
	Physiotherapy	€38.00/treatment
Home care	Domestic care	€30.60/hour
	Care	€39.10/hour
	Nursing	€67.60/hour
	Nursing & care	€46.40/hour
Labor costs	15–19 year	€13.50/hour
(including VAT)	20–24 year	€24.70/hour
	25–29 year	€32.80/hour
	30–34 year	€39.30/hour
	35–39 year	€43.30/hour
	40–44 year	€45.40/hour
	45–49 year	€46.80/hour
	50–54 year	€48.50/hour
	55–59 year	€49.70/hour
	60–64 year	€50.70/hour
	Overall mean	€40.90/hour

[1] Unit costs for attendance of emergency department are calculated per type of injury in an annually unit cost study indexing the tariffs per minute of nurses, physicians and specialists. ED: emergency department; VAT: value added tax.

YLLs were calculated by multiplying the number of deaths at each age by a standard life expectancy at that age. The number of deaths at each age were calculated with use of the average European case-fatality rate of 11%; about 3% in-hospital and 8% out-of-hospital.[2,33] To allow for international comparisons, the life expectancy was calculated using the Coale-Demeny model West life tables, with a life expectancy at birth of 80 years for males and 82.5 years for females.[34]

YLDs were calculated in three steps.[35] First, data was gathered on the incidence, age and sex distribution of patients treated at the ED or hospitalised due to TBI. Second, the incidence data was divided into the injury categories "Concussion" and "Skull-brain injury" of the EUROCOST classification system.[36] Finally, the grouped incidence data was combined with the disability weights and durations developed within the framework of the European INTEGRIS (Integration of European Injury Statistics) study.[35] Registered cases were multiplied with the 1-year disability weight, the proportion of lifelong consequences (Concussion: 4% ED, 21% hospitalised; Skull-brain injury: 13% ED, 23% hospitalised) and the duration (life expectancy at age of injury, by sex). The mean 1-year disability weights included the temporary and lifelong consequences for cases seen in EDs and those recorded in hospital discharge registers for both concussions (Temporary: 0.015 ED, 0.100 hospitalised; Lifelong: 0.151) and skull-brain injuries (Temporary: 0.090 ED, 0.241 hospitalised; Lifelong: 0.323). To compare the impact of TBI with that of other injuries, YLDs for the other injuries were also calculated with disability weights obtained from the

INTEGRIS study. The disability weights were derived from empirical follow-up data on the health-related quality of life of individual trauma patients, and adjusted for population norms, age and gender.[35]

Data and statistical analysis

All statistical analyses were carried out using the statistical package SPSS for Windows, version 21 (IBM SPSS Statistics, SPSS Inc, Chicago, IL). Descriptive statistics were used to provide insight in the characteristics of TBI patients. Continuous variables were described by presenting the median and interquartile range. Incidence rates per 100,000 person years were calculated using population data from Statistics Netherlands.[37] A value of $p<0.05$ was used to determine statistical significance. All data reported in this article are national estimates.

2.3 RESULTS

Incidence

In the period 2010–2012, annually 34,681 patients visited the ED due to TBI (Table 2.2), comprising about 4% of the total injury-related ED visits per year in the Netherlands. The overall incidence rate of ED visits due to TBI was 213.6 per 100,000 person years, 241.9 for males and 175.3 for females respectively. Incidence rates were highest in children (268.2), young adults (271.6) and older patients in the age of 75–84 years (307.6) or 85 and older (578.2).

The majority of patients sustained a TBI because of a home and leisure injury (47.9%) or traffic injury (33.5%). Patients that sustained a TBI due to a traffic accident often concerned bicyclists (56.9%) and passenger vehicle occupants (16.5%). Home and leisure injuries often concerned a fall among 0–5-year-olds and elderly patients (aged 60 years and older). ED visits due to TBI often included the diagnoses concussion (44.7%), intracranial injury of other or unspecified nature (25.5%) and cerebral laceration or contusion (9.8%). Almost one in three TBI patients were treated for more than one injury and more than half of the patients were hospitalised, most frequently for 1 or 2 days (61.7% of the hospitalised patients).

Cost-of-illness

The estimated total costs of TBI in the Netherlands was €314.6 million per year (Table 2.3). Total direct health care costs (€158.6 million) were comparable to indirect costs (€155.9 million), whereas in the working population per case mean direct health care costs were more than 3 times lower than the indirect costs.

Overall, the mean total costs per case were €18,030, and were higher for men (€19,540) than for women (€14,940). This difference is mostly driven by the difference in indirect costs per TBI patient (males €15,416; females €10,257; $p<0.001$). The estimated total amount of omitted work days among TBI patients with paid employment was 44 days per case, and significantly differed between men (mean 46 days) and women (mean 38 days) ($p<0.001$). Both direct and indirect costs per TBI patient increased with the length of hospital stay.

The average direct costs per case increased with age (Figure 2.1). Mean direct costs per case were higher (up to €950) for men than for women in the ages up to 74 years, while in individuals aged over 75 years women had much higher mean direct costs per case (up to € 3,210) than men. Indirect costs

(applicable to individuals aged 15–64 years old) also increased with age, and were higher (up to €6,280) for men than for women.

Table 2.2 Incidence and characteristics of traumatic brain injuries in the Dutch population (2010-2012)[1]

	Dutch Injury Surveillance System n=3,762 (%)	National estimate n=34,681 (%)	Incidence (per 100,000) Total: 213.6
Gender			
Male	2,162 (57.5)	19,937 (57.5)	241.9
Female	1,600 (42.5)	14,744 (42.5)	175.3
Age			
0–14	846 (22.5)	7,793 (22.5)	268.2
15–24	601 (16.0)	5,538 (16.0)	271.6
25–44	714 (19.0)	6,584 (19.0)	148.7
45–64	789 (21.0)	7,281 (21.0)	156.1
65–74	332 (8.8)	3,062 (8.8)	211.4
75–84	287 (7.6)	2,648 (7.6)	307.6
85+	192 (5.1)	1,775 (5.1)	578.2
Accident category, type of road user			
Home and leisure	1,806 (48.0)	16,628 (47.9)	
Traffic	1,256 (33.4)	11,616 (33.5)	
Pedestrian	66 (5.3)	613 (5.3)	
Bicyclist	706 (56.9)	6,522 (56.9)	
Moped occupant	151 (12.2)	1,406 (12.3)	
Motor vehicle/scooter occupant	63 (5.1)	575 (5.0)	
Passenger vehicle occupant	205 (16.5)	1,898 (16.5)	
Other	49 (4.0)	455 (4.0)	
Unknown	*16*	*148*	
Sport	307 (8.2)	2,824 (8.1)	
Occupational	109 (2.9)	1,003 (2.9)	
Assault	247 (6.6)	2,269 (6.5)	
Self-mutilation	18 (0.5)	171 (0.5)	
Other	19 (0.5)	172 (0.5)	
Type of brain injury[2,3]			
Concussion		8,983 (44.7)	
Fracture			
Vault		317 (1.6)	
Base		1,319 (6.6)	
Other/unqualified		330 (1.6)	
Multiple fractures		130 (0.6)	
Lesion			
Cerebral laceration/contusion		1,977 (9.8)	
Subarachnoid/sub-/extradural hemorrhage		1,598 (7.9)	
Other/NFS intracranial hemorrhage		262 (1.3)	
Intracranial injury, other/NFS nature		5,116 (25.5)	
Late effects			
Musculoskeletal and connective tissue		46 (0.2)	
Nervous system		18 (0.1)	
Nerve injury			
Optic nerve and pathways		3 (<0.1)	
Unknown		*14,581 (42.0)*	
Number of injuries			
1 injury	1,065 (28.3)	9,766 (28.2)	
2 injuries	2,033 (54.0)	18,773 (54.1)	
≥3 injuries	664 (17.7)	6,142 (17.7)	
Hospitalisation			
Not admitted	1,633 (43.5)	15,024 (43.4)	
Unknown	*8*	*70*	
1–3 days	1,424 (70.4)	13,146 (70.4)	
≥4 days	597 (29.6)	5,529 (29.6)	
N days unknown	*106*	*982*	

[1] Mean number per year in the period 2010–2012.

[2] Traumatic brain injury diagnoses (ICD-9 codes): *Concussion:* Concussion (850): *Cranial fracture:* Fracture of vault of skull (800); Fracture of base of skull (801); Other and unqualified skull fractures (803); Multiple fractures involving skull or face with other bones (804): *Lesion:* Cerebral laceration and contusion (851); Subarachnoid, subdural, and extradural hemorrhage after injury (852); Other and unspecified intracranial hemorrhage after injury (853); Intracranial injury of other and unspecified nature (854): *Late effects:* Late effects of musculoskeletal and connective tissue injuries (905); Late effects of injuries to the nervous system (907): *Nerve injury:* Injury to optic nerve and pathways (950): *Head injury, unspecified* (959, n=0).

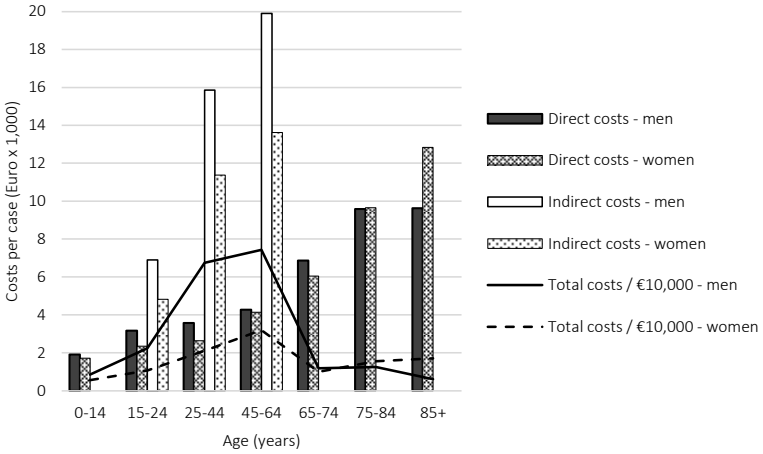
[3] Data on injury type (ICD) only known for hospitalised patients in the LMR database (National estimate: n=20,100).

Table 2.3 Cost-of-illness by hospitalisation and gender (2010-2012)

	Hospitalisation	Direct costs per case[1]	Indirect costs per case[1]	Total costs per case[1]	Total costs (€)
Total	0–7 days	3,584	12,454	16,040	234,259,230
	>7 days	9,854	21,431	31,280	64,608,290
	Total	**4,361**	**13,668**	**18,030**	**314,592,930**
Men	0–7 days	3,413	14,116	17,530	149,815,870
	>7 days	8,809	22,216	31,020	41,805,590
	Total	**4,128**	**15,416**	**19,540**	**202,953,300**
Women	0–7 days	3,812	9,479	13,290	84,443,360
	>7 days	11,433	18,638	30,070	22,802,690
	Total	**4,680**	**10,257**	**14,940**	**111,639,630**

[1] Mean costs per case: indirect costs per case are presented as an average of only the working population (15 to 65 years).

Figure 2.1 Mean direct and indirect costs per case and total costs by age and gender (2010–2012)



Disability-adjusted life years

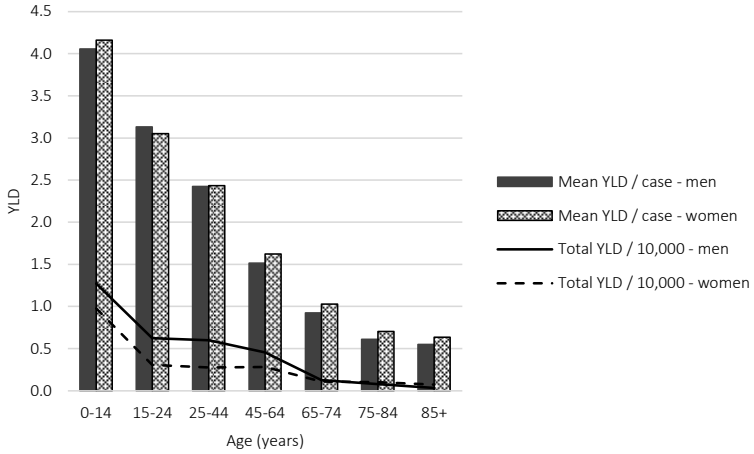
TBI resulted in 52,998 YLD and 118,207 YLL respectively, amounting to 171,205 DALYs (on average 7.07 DALYs per TBI patient, Table 2.4). Overall, 69% of the total burden was caused by premature mortality. The burden due to permanent (lifelong) disability was high compared with temporary (short-term) disability. Men were responsible for 59% of the total burden of TBI, and had higher YLDs, YLLs and DALYs per case than women (YLD per case: 2.29 in men vs 2.05 in women; YLL per case: 4.97 vs 4.76; DALY per case: 7.27 vs 6.81). Mean YLD decreased with age in both men and women, and was highest among 0–14-years-olds (Figure 2.2).

Table 2.4 Total temporary and lifelong years lived with disability, years of life lost and disability-adjusted life-years per 1-year interval (2010–2012)

		YLD ED visits		YLD hospital admission				
	N	Temporary	Lifelong	Temporary	Lifelong	YLL	Total DALYs[1]	DALYs per case
Men	13,877	56	1,077	2,098	28,603	69,022	100,856	7.27
Women	10,330	47	941	1,470	18,706	49,185	70,348	6.81
Concussion	12,580	54	1,023	897	13,540	118,207	171,205	7.07
Skull-brain injury	11,631	50	995	2,670	33,769			
Total	**24,211**	**104**	**2,018**	**3,567**	**47,309**	**118,207**	**171,205**	**7.07**

[1] Disability-adjusted life-years (DALYs) per year.
YLD: years lived with disability; ED: emergency department; YLL: years of life lost.

Figure 2.2 Mean years lived with disability by age and gender (2010–2012)



YLD: years lived with disability.

TBI in comparison to other injury categories

In the period 2007–2011, TBI accounted 10% of the total YLDs and 12% of the lifelong YLDs caused by all injuries in the Netherlands (data not shown). Concussion and skull-brain injury both were ranked in the top 5 of injuries with highest total YLDs, after fractures of the knee or lower leg, ankle, and foot or toes (Table 2.5). Skull-brain injury accounted for the highest YLDs per case after spinal cord injury: 2.89 and 14.68 respectively (data not shown).

Table 2.5 Top ten injuries with highest disability in the Netherlands by accident category (2007–2011)[1]

Rank	Home and leisure	Traffic	Sport	Occupational	Total
1	Fract ankle	Fract knee/lower leg	Fract knee/lower leg	Fract foot/toes	Fract knee/lower leg
2	Fract foot/toes	**Skull-brain injury**	Fract ankle	Fract knee/lower leg	Fract ankle
3	Fract knee/lower leg	**Concussion**	Fract foot/toes	Fract ankle	Fract foot/toes
4	**Concussion**	Fract ankle	Lux/dist ankle/foot	Spinal cord injury	**Skull-brain injury**
5	**Skull-brain injury**	Spinal cord injury	Lux/dist knee	**Skull-brain injury**	**Concussion**
6	Hip fract	Fract foot/toes	**Concussion**	Complex arm/hand	Spinal cord injury
7	Spinal cord injury	Hip fract	Fract wrist	Lux/dist ankle/foot	Hip fract
8	Fract upper arm	Fract shoulder	**Skull-brain injury**	**Concussion**	Lux/dist ankle/foot
9	Lux/dist ankle/foot	Fract upper arm	Fract upper arm	Lux/dist knee	Fract upper arm
10	Fract wrist	Fract upper leg	Fract shoulder	Open wound	Lux/dist knee

[1] Ranked by total years lived with disability (YLD) for short- and long-term disability.
Fract: fracture; Lux/dist: luxation/distortion.; Complex arm/hand: complex soft tissue arm/hand.

2.4 DISCUSSION

The purpose of this paper was to estimate the incidence, cost-of-illness and disability-adjusted life years (DALYs) of TBI in the Netherlands. Our study revealed that TBI imposes a substantial economic and disease burden (on average 7.1 DALYs per TBI patient) on the Dutch population, accounting for more than 4% of injury-related ED visits, 9% of the injury-related costs and 10% of the injury-related YLDs in the Netherlands.

The integrated approach of our study showed that the incidence and burden of disease among children and young adults aged 0–24 years is high, whereas the economic consequences for this group were low

due to relatively shorter hospitalisation and almost no indirect costs (Figure 2.3). The reverse is shown in the 25–64-year-olds, who have relatively low incidence and high economic costs, driven by loss of productivity. Older patients aged 65+ had highest incidence of TBI, leading to considerable direct health care costs, and a relatively low disease burden.

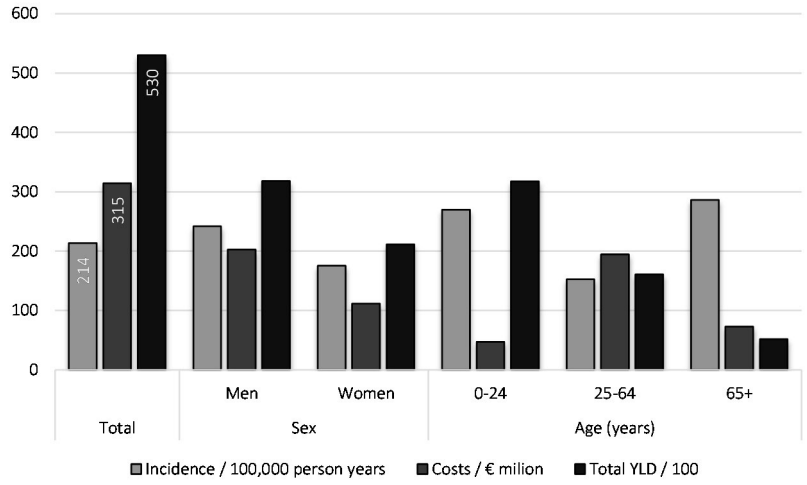
Comparison of results to other studies

Incidence

Our estimated incidence rate of ED treated, hospitalised and fatal TBI for the Netherlands of about 214 per 100,000 person years was lower than the estimated rate of hospitalised and fatal TBI for Europe of about 235 per 100,000 persons years.[2] This difference may partly be explained by the time period covered in the studies. The European rate was derived from studies with data over 1974 to 2000, with incidence rates ranging from 150 to 300 per 100,000 person years,[2] whereas our study included data from 2010 to 2012. Compared to the US, the Dutch estimated incidence rates of ED visits, hospital admissions and deaths are considerably lower. It is estimated that the incidence of TBI in the US is 577 per 100,000 person years in 2006,[38] comprising about 1,365,000 ED visits (81%), 275,000 hospitalisations (16%) and 52,000 deaths (3%). However, other population-based studies suggest that the incidence of TBI in the US is somewhat lower, between 180 to 250 per 100,000 person years in 1965 to 1996.[2,11]

Consistent with prior research,[2,38] TBI incidence was higher among men than women, and highest among children and older people. Whereas motor vehicle accidents and falls were the most common mechanisms of injury in previous studies in Europe[2] and the US,[6,17,38] our sample showed a high number of ED treatments among bicyclists in the traffic setting. Cycling is a very popular form of transport and recreation in the Netherlands, as up to 28% of all trips nationwide are made by bicycle.[39] The popularity of cycling however also imposes a high burden on society, due the large number of (brain) injuries among cyclist.[40-42] Bicycle helmets are not compulsory in the Netherlands and are only commonly used among road cyclist, mountain bikers and young children.

Figure 2.3 Economic and disease burden of traumatic brain injury in the Netherlands (2010–2012)



YLD: years lived with disability.

Cost-of-illness

TBI accounted for 9% of total costs of all injuries in the Netherlands (about €3.5 billion). The direct health care costs of TBI are on average €4,300 per case. This is in line with the outcomes of a previous study on the costs of all types of injuries in the Netherlands in 2004 that estimated the average direct health care costs of skull and brain injury cases at €3,100.[12] This is approximately €4,100 when converting 2004 Euros to 2012 Euros using consumer price index.

Compared to other European countries our estimation of direct health care costs of TBI are somewhat higher:[5] from €2,700 in whole Europe, to €2,930 in Germany, €3,490 in Spain and €3,453 in Sweden after adjustment for inflation up to 2012. Estimates from the US are however more than two times the estimates in our present study: about €23,500 acute hospital charges per TBI,[15] €6,200 per TBI in Missouri,[17] and €8,500 to €35,000 for mild to severe hospitalised patients[6] - all scaled to 2012 price levels and 2012 Euro. These differences can partly be explained by differences in cost calculations. The European cost calculations were limited to inpatient costs while the current study included also extramural health care costs, and most US studies used charges instead of unit costs. Although the methodology of cost calculations varied considerably, our study confirms that indirect costs of TBI are far higher than direct health care costs of TBI,[9,17,43,44] costs of TBI are higher among men than women and increase with age [5] and that the costs increase with the length of hospital stay.[6] The latter suggests that the economic burden of TBI varies considerably by TBI severity.

Overall, TBI imposes a high economic burden on society and, together with hip fracture, is a leading source of hospital costs[13] and direct health care costs[12] in the Netherlands due to high health care costs per patient.

Disability-adjusted life years

TBI accounted for 10% of total YLD and 12% of the lifelong YLD caused by all injuries in the Netherlands, due to lifelong consequences in a relative young patient group. TBI resulted in both high temporary and lifelong YLD among road traffic injuries and home and leisure injuries, as confirmed in the literature.[19,45]

TBI is one of the leading causes of disease burden compared to other injuries and diseases in the Netherlands. TBI imposes a disease burden comparable to that of depression, diabetes, and lung cancer, which are all in the top 10 diseases with highest total DALY in the Netherlands.[46]

Mean YLD decreased with age and was highest among children (0–14 years). This can partly be explained by the use of the expected number of years of life remaining as the duration of TBI in the YLD calculation. This method assumes that a proportion of the TBI patients will live with disability outcomes for the remainder of their expected lifetime. Therefore the duration used in the YLD calculation equaled the life expectancy at age based on the Coale-Demeny model West life tables;[34] in our sample on average 45 years in men and 43 in women. This may have led to a higher estimate of the years lived with disability after TBI in comparison to the use of a fixed average duration for TBI.

Limitations

The number of deaths due to TBI in the Netherlands could not be generated from national death statistics, because these are only available for specific diseases (e.g. type of cancer, cardiovascular diseases) or injuries specified by cause (e.g. traffic accidents, falls, drowning, self-mutilation). Therefore, the YLL component of the total DALY was estimated with use of the European average case fatality rate

of TBI, derived from 18 studies. This overall case fatality rate was on average about 11 per 100 persons with TBI; about 3% in-hospital and 8% out-of-hospital deaths among patients with TBI.[2,33] Due to the use of the average European overall case fatality rate, the number of YLLs and thereby the disease burden of TBI may be over- or underestimated. However, actual case fatality rates and disease burden of TBI may be even higher due to higher excess mortality in the long-term.[47-49] In order to improve the YLL and disease burden estimates of TBI and other injuries and diseases in the Netherlands, specific (long-term) mortality data should be registered and available for future research.

Other limitations concern the classification of TBI and the calculation of costs. TBI patients treated at the ED were registered as having a "Concussion" or "Other skull – brain injury". No additional data was available on ICD-codes, AIS-codes or a Glasgow Outcome Scale to uniformly determine TBI; data that was available for the majority of the hospitalised patients.

The ICD-9 codes used to determine the type of TBI among hospitalised patients slightly differed from those recommended by the Center for Disease Control (CDC),[50] in that this study also included the late effects of TBI (ICD-9 codes 905, 907, 950). These late effects however comprise far less than 1% of all hospitalised traumatic brain injuries in the Netherlands, and therefore will not complicate comparison of our results to those of other studies in which the CDC ICD-9 codes for TBI were used.

The cost-of-illness of TBI may have been overestimated because of the use of a patient follow-up survey to obtain information on health care consumption and labor status. Comparison of the hospital discharge data and the patient follow-up data indicated that there is a higher response among the more severe injured patients. This may lead to an overestimation of the costs and disease burden of TBI.

On the other hand, our estimation of indirect costs of TBI comprised only costs of lost work productivity for TBI patients of working age. Other potential sources of indirect costs, such as the work productivity and finances of families and caregivers were not incorporated in this study. Previous research showed that TBI imposes a significant level of financial burden on families and caregivers,[51,52] which is directly related to the severity of TBI.[51] Total indirect costs of TBI will therefore be far higher than estimated in this study, particularly among children and elderly with caregivers in the working age.

Our study is limited to TBI patients that were treated at the ED or admitted to hospital. Patients who consulted a GP were not included in our overview. Hence, incidence rates, cost-of-illness and burden of TBI may be even higher.[53] According to registries from Dutch general practice, in 2012 about 7,600 persons contacted their General Practitioner (GP) or after-hours General Practitioner Co-operation (GPC) due to TBI.[54] Assuming that direct health care costs of GP visits are on average €39 per contact (Table 2.1; mean costs for practice or telephone consultation, and home visit), and the indirect costs and disease burden of TBI will not be larger than that of ED-treated patients, they will add about 7–8% only to our cost estimate and about 1–2% only to our DALY estimate.

Recommendation for future research

The results of our study reveal that TBI imposes a relatively high economic and health impact compared to all injuries and diseases in the Netherlands. TBI is a growing worldwide problem, as recent reports suggest a rapid increase in ED visits and hospitalisations resulting from traumatic brain injury, especially fall-related TBI in older adults[55-57] and traffic-related TBI.[58,59]

There is a need for prevention programmes targeting on the reduction of incidence and severity of TBI. On the bases of our study, we conclude that especially children and young adults aged 0–24 years, men

aged 25–64 years and traffic injury victims (in the Netherlands especially bicyclists) and home and leisure injury victims are an important target for intervention. In the working population, screening for risk of problems to return to work and immediate rehabilitation after TBI may help to minimise lost productivity.[60]

Future research should examine how helmet use among cyclists can be increased. Bicycle helmets have shown to be highly effective in preventing head, brain, and facial injuries to cyclist.[61,62] Previous research in Canada showed that helmet legislation may be an effective tool in the prevention of childhood bicycle-related head injuries.[63]

Overall, future research on the population impact of TBI in terms of costs and disease burden should also include patients who receive no treatment or out-of-hospital treatment (e.g. from a GP or by sports trainers).

Conclusions

This study provided comprehensive population-based estimates on the epidemiology, costs and disease burden (in DALYs) of ED-treated and hospitalised persons with TBI over 2010–2012 in the Netherlands. The study included all age groups, all TBI severities, and both patients treated at the ED and hospitalised patients.

The economic and health consequences of TBI are substantial. Prevention programmes are needed to reduce incidence and severity of TBI. The integrated approach of assessment of incidence, costs and disease burden (in DALYs) of TBI enables the detection of all important risk groups in TBI.

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Chapter 3

Incidence and costs of bicycle-related traumatic brain injuries in the Netherlands

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ABSTRACT

Background The main cause of death and serious disability in bicycle accidents is traumatic brain injury (TBI). The aim of this population-based study was to assess the incidence and costs of bicycle-related TBI across various age groups, and in comparison to all bicycle-related injuries, to identify main risk groups for the development of preventive strategies.

Methods Data from the National Injury Surveillance System and National Medical Registration was used for all patients with bicycle-related injuries and TBI who visited a Dutch emergency department (ED) between 1998 and 2012. Demographics and national, weighted estimates of injury mechanism, injury severity and costs were analysed per age group. Direct health care costs and indirect costs were determined using the incidence-based Dutch Burden of Injury Model.

Results Between 1998 and 2012, the incidence of ED treatments due to bicycle-related TBI strongly increased with 54%, to 43 per 100,000 persons in 2012. However, the incidence of all bicycle-related injuries remained stable, from 444 in 1998 to 456/100,000 in 2012. Incidence of hospital admission increased in both TBI (92%) and all injuries from cycling (71%). Highest increase in incidence of both ED treatments and hospital admissions was seen in adults aged 55+. The injury rate of TBI per kilometre travelled increased (44%) except in children, but decreased (–4%) for all injuries, showing a strong decrease in children (–36%) but an increase in men aged 25+, and women aged 15+. Total costs of bicycle-related TBI were €74.5 million annually. Although bicycle-related TBI accounted for 9% of the incidence of all ED treatments due to cycling, it accounted for 18% of the total costs due to all bicycle-related injuries (€410.7 million). Children and adolescents (aged 0–24) had highest incidence of ED treatments due to bicycle-related injuries. Men in the working population (aged 15–64) had highest indirect costs following injuries from cycling, including TBI. Older cyclists (aged 55+) were identified as main risk group for TBI, as they had highest ED attendance, injury rate, injury severity, admission to hospital or intensive care unit, and costs.

Conclusions Incidence of ED treatments due to cycling are high and often involve TBI, imposing a high burden on individuals and society. Older cyclists aged 55+ were identified as main risk group for TBI to be targeted in preventive strategies, due to their high risk for (serious) injuries and ever-increasing share of ED visits and hospital admissions.

3.1 INTRODUCTION

Cycling is a popular form of transport and recreation worldwide, and especially in the Netherlands, where there are more bicycles than residents.[1,2] In the Netherlands, cycling is a common mode of transport among all age groups and socio-economic classes, in both urban and rural areas.[2] The Netherlands has a good cycling infrastructure with cyclists enjoying segregated cycle facilities and protected intersections.[2,3] Despite the high levels of road safety, in the Netherlands (with 16.7 million inhabitants) approximately 350,000 injuries occur due to cycling each year.[4]

Traumatic brain injury (TBI) is the main cause of mortality and severe morbidity among bicycle accidents,[5-12] which is most often seen in children,[7,8,10] adolescents[8] and older adults.[7,8,11,13] Almost all survivors of TBI experience some level of impairment or disability,[14] which drastically reduces their health-related quality of life,[15,16] increases their requirement of specialised health care,[17] and often restricts adults in returning to full employment.[18,19] TBI therefore imposes significant direct health care costs in terms of pre-hospital care, emergency care, hospitalisation, long-term outpatient care and rehabilitation, and indirect costs due to loss of productivity.[20]

Although the literature on the epidemiology and consequences of bicycle-related TBI is growing, by our knowledge, detailed population-based information on the costs of bicycle-related TBI is scarce and often limited for use in studies on the cost-effectiveness of bicycle helmet campaigns or laws.[21-23] Such information is however vital for the development of prevention programmes that are aimed at patient groups at greater risk of TBI. This article presents the results of a population-based study in the Netherlands. It provides demographics and national, weighted estimates of the injury mechanism, injury severity and costs, by age group, of all patients with bicycle-related injuries and TBI in specific, who visited Dutch emergency departments (EDs). The purposes of this study were to 1) assess the incidence, direct costs and indirect costs of bicycle-related TBI between 1998 and 2012 across various age groups, 2) compare these estimates with all bicycle-related injuries treated in Dutch EDs between 1998 and 2012, and 3) identify main risk groups to develop preventive strategies that target bicycle-related TBI.

3.2 METHODS

Study setting

This retrospective study included data on all patients with bicycle-related injuries treated at Dutch EDs and/or hospitalised between 1998 and 2012. Data on ED treatments due to bicycle-related TBI was obtained from the Dutch Injury Surveillance System (LIS).[24] Data on hospital admissions was obtained from the National Hospital Discharge Registry (LMR).[25]

LIS is an ongoing monitoring system which records data of all unintentional and intentional injured patients who attend the ED. LIS is based upon the registration of 13 hospitals in the Netherlands (12–15% coverage), that are considered to be representative for the total Dutch injury-related ED visits.[24] The LMR contains data from all Dutch hospitals regarding patient information from hospital admission to discharge.[25]

National, weighted estimates of bicycle-related TBI presenting to Dutch EDs were derived by calculating an extrapolation factor. This factor multiplies the number of ED treatments due to bicycle-related injury registered by the participating hospitals, by the quotient of the number of hospital admissions due to

bicycle-related injury divided by the number of hospital admissions due to bicycle-related injury registered in the participating Dutch hospitals.[26]

Data from the LIS databank was used to assess socio-demographic (age at injury and sex), injury (type of injury besides TBI, injury mechanism), and health care related characteristics (hospitalisation and length of stay). The LMR was used to obtain data on hospitalisation and injury severity (MAIS: maximum abbreviated injury scale).

Definitions

A bicycle-related injury was defined as an injury sustained to the cyclist either during cycling or getting on or off a bicycle. A cyclist was defined as a user of a non-motorised two wheeled vehicle, and also included electrically assisted bicycles, road bikes, mountain bikes and cyclo-cross bicycles.

TBI was defined as having a concussion (ICD10 code S06.0) or other skull-brain injury (S02.0–1, S02.7, S02.9, S06.1–9, S04.0–9, S07.1–9, T02.0, T04.0) in one of the three injuries that can be recorded in LIS. This study included all bicycle-related TBI that were registered as first, second or third injury.

Cost-of-illness

Direct costs (e.g. health care costs) and indirect costs (e.g. productivity loss) of bicycle-related injuries and TBI were calculated with use of the incidence-based Dutch Burden of Injury Model.[26,27]

Direct health care costs were calculated by multiplying incidence by health care volumes (e.g. length of stay), transition probabilities (e.g. probability of hospital admission), and unit costs (e.g. costs per day in hospital). Health care volumes were estimated with use of age- and injury-specific data from the LIS and LMR database, rehabilitation centres (LIVRE), nursing homes (SIVIS), and a patient follow-up survey conducted in 2007–2008.[26,28,29] All unit costs were estimated according to national guidelines for health care costing,[30] reflecting real resource use (Appendix Table 3.A).

Indirect costs were calculated for all patients in the working age 15 to 65 treated at the ED or hospitalised, based on age- and injury- specific estimates on work absence and return to work from the patient follow-up questionnaire conducted in 2007–2008.[26,28,29] A full description of the calculation of the cost per hour worked, based on data from the patient follow-up survey, has been published elsewhere.[31,32]

All costs estimates were converted into 2012 Euros (as at 31 December 2012 €1.00 = USD $1.3203). The direct and indirect costs of bicycle-related TBI were compared with the costs of all bicycle-related injuries treated at Dutch EDs, including TBI.

Data and statistical analysis

All statistical analyses were carried out using the statistical package SPSS for Windows, version 21 (IBM SPSS Statistics, SPSS Inc., Chicago, IL). Descriptive statistics were used to provide insight in the characteristics of injured cyclists. Continuous variables were described by presenting the median and interquartile range. Chi square statistics were used for between-group comparisons on injury mechanism variables. Univariate logistic regression analysis was used to explore the association between patient demographics and injury mechanism with regard to a diagnosis of TBI and the severity of TBI. Secondly, multivariate logistic regression analysis (enter method) including socio-demographics (block 1) and injury mechanism (block 2) was used to further identify independent predictors of bicycle-related TBI and TBI severity.

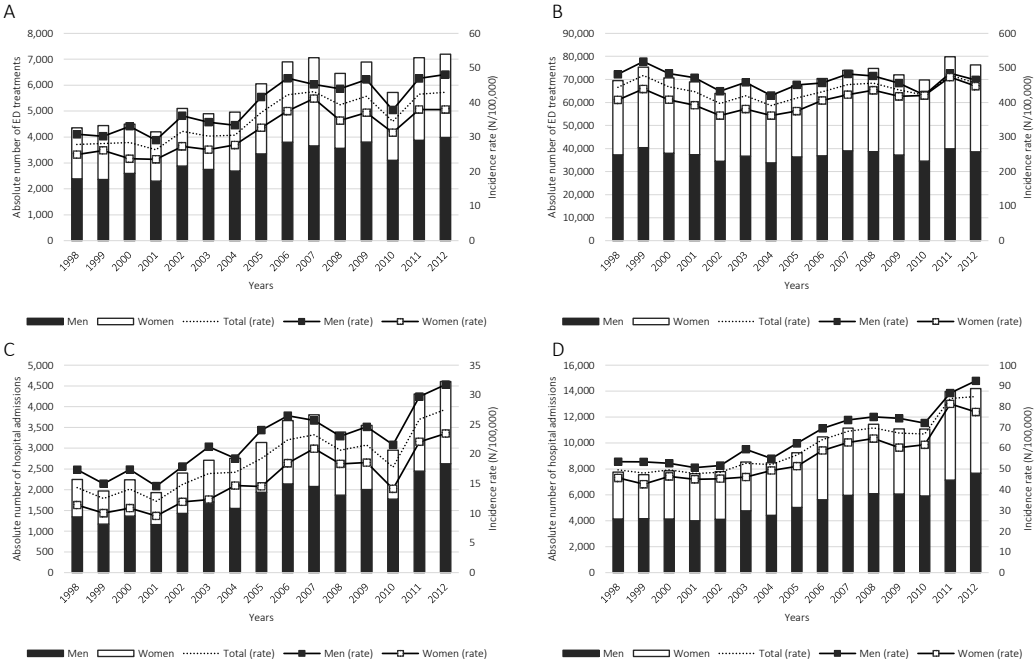
Incidence rates per 100,000 person years were calculated for men and women separately, using population data from the Dutch Central Bureau of Statistics.[33] Data on cycle use, as measured by the average annual number of kilometres travelled per cyclist, was obtained by age groups from the Dutch National Travel Survey.[34] To overcome differences in age group classifications, data from the Dutch National Travel Survey (0–11; 12–17; 18–24; 25–29; followed by 10-year age groups until 75+) was divided into the age groups of this study. Injury rate of bicycle-related TBI and all bicycle-related injuries per kilometre travelled was calculated by age group, by dividing the number of cyclists with respectively TBI and all injuries in each age group by the total number of kilometres travelled within that age group. The overall growth in the number of ED visits, hospital admissions, cycle use, and injury rate was calculated for 2012 in percentages relative to the year 1998. A value of $p<0.05$ was used to determine statistical significance. All data reported in this article are national estimates.

3.3 RESULTS

Incidence and trends

Between 1998 and 2012, the incidence of ED treatments due to bicycle-related TBI increased with 54% from 28 to 43 per 100,000 persons (Figure 3.1A). The highest increase was seen in adults aged 55+ (151%), though incidence decreased in girls aged 0–14 (–6%; Appendix Figure 3.A (A and B). The incidence of hospital admissions due to bicycle-related TBI increased in all age groups (92% from 14 to 28/100,000 in 2012 – Figure 3.1C), with also highest increase in adults aged 55+ (186% – data not shown).

Figure 3.1 Absolute number of ED treatments (A and B), hospital admissions (C and D), and incidence (per 100,000 person-years) for bicycle-related TBI (A and C) and all bicycle-related injuries (B and D) in the Dutch population (1998–2012)



ED: emergency department.

In contrast to the strong increase of bicycle-related TBI between 1998 and 2012, the incidence of ED treatments of all bicycle-related injuries remained stable from 444/100,000 in 1998 to 456/100,000 in 2012 (Figure 3.1B). However, we see a decrease in children (–30%), but increase in adults aged 55+ (43%) and especially in 75+ year-old women (89%; Appendix Figure 3.A (C and D)). Similar to bicycle-related TBI, the incidence of hospital admissions due to all bicycle-related injuries increased in all age groups (71% from 50 to 85/100,000 – Figure 3.1D), and especially in adults aged 55+ (93% – data not shown).

In the same period, cycle use increased with only 14% (on average 13% in men and 16% in women). Cycle use in those aged 15–54 remained stable over time (0% to +5%), however strongly increased in adults aged 55+ (on average 56% in 55–74, and 68% in 75+ – data not shown).

Between 1998 and 2012, the injury rate of TBI per kilometre travelled increased with on average 44% from 0.34 per million kilometres travelled in 1998 to 0.49 in 2012 (48% in men, 41% in women). Like the incidence rates, injury rates of TBI per kilometre travelled decreased in children (–12%) but increased in all other age groups (from 34% in 25–54 to 125% in 75+), with highest increase in the elderly aged 75+ (141% in men, 121% in women). In the same period, the overall injury rate of all bicycle-related injuries decreased (–4%, from 5.40 to 5.19 per million kilometres travelled) due to a decrease in children (–36%) and men aged 15–24 (–10%), but increased in all other age groups with highest increase in men aged 55–74 (44%) and women aged 75+ (49% – data not shown).

Cause of injury

In 2012, 7,190 bicycle-related TBI were treated at Dutch EDs (43/100,000 persons), comprising 9% of all 76,325 bicycle-related injuries (456/100,000; Table 3.1). Half of the patients with bicycle-related TBI were injured due to a fall or single bicycle crash (51%). Collisions with a 4-wheeled vehicle (26% of all causes) often involved a passenger car (86% of all collisions). Collision with a passenger car was most common in children (26% of all causes in this age group), adolescents aged 15–24 (30%), and elderly cyclists aged 75+ (26%). Almost two third of all collisions with a 2-wheeled vehicle (16% of all causes) comprised a collision with another cyclist (73%). This was the most common cause in children (14% of all causes in this age group) and adults aged 55–74 (14%).

Table 3.1 Injury mechanism of bicycle-related TBI (2012)

	0–14 (%)	15–24 (%)	25–54 (%)	55–74 (%)	75+ (%)	Total TBI (%)	Total all bicycle-related injuries (%)
N (N)	1,215	1,010	2,169	2,095	701	7,190	76,325
Traffic (N, %)	**1,206 (99.3)**	**963 (95.3)**	**2,102 (97.0)**	**2,095 (100.0)**	**701 (100.0)**	**7,066 (98.3)**	**74,752 (98.0)**
Fall (single bicycle crash)	45.0	43.0	54.4	54.8	49.4	50.7	63.2
Collision with 4-wheeled vehicle[1]	28.9	37.8	22.6	21.6	29.3	26.3	13.7
Collision with 2-wheeled vehicle[2]	16.0	13.3	15.4	17.4	18.3	16.1	12.7
Collision with obstacle[3] / pedestrian / animal	3.3	5.9	7.6	6.2	3.0	5.7	5.0
Fall out of child seat	6.8	–	–	–	–	1.2	0.4
Fall when getting on or off the bicycle	0.0	0.0	0.0	0.0	0.0	0.0	0.3
Entrapment between bicycle spokes / wheel	0.0	0.0	0.0	0.0	0.0	0.0	4.8
Not specified/unknown (N)	*115*	*95*	*348*	*321*	*96*	*975*	*12,870*
Sport (N, %)	**9 (0.7)**	**47 (4.7)**	**47 (2.2)**	**0 (0.0)**	**0 (0.0)**	**1.4**	**1,232 (1.6)**
Other (N, %)	**0 (0.0)**	**0 (0.0)**	**18 (0.8)**	**0 (0.0)**	**0 (0.0)**	**0.3**	**316 (0.4)**

[1] Including passenger cars, buses, pick-up trucks, trucks and trams.
[2] Including bicycles, mopeds and motor cycles.
[3] Including tree, wall, stationary car (door), (light) pole or edge of sidewalk.

In contrast to all bicycle-related injuries, bicycle-related TBI less often involved a fall (Chi^2=242.2, p<0.001), but more often were caused by a collision with a 4-wheeled vehicle (Chi^2=1018.8, p<0.001; OR 2.7, 95%CI [2.2–3.3], p<0.001), 2-wheeled vehicle (Chi^2=92.9, p<0.001; OR 1.6, 95%CI [1.3–2.0], p < 0.001), or obstacle (Chi^2=17.5, p<0.001; OR 1.5, 95%CI [1.2–1.9], p=0.001), or by a fall out of a child seat (Chi^2=151.3, p<0.001; OR 6.6, 95%CI [4.6–9.3], p<0.001 – Appendix Table 3.B).

Patient characteristics and outcome

Incidence of ED treatments due to bicycle-related TBI was highest in older cyclists aged 55–74 (57/100,000 persons) and 75+ (59/100,000, Table 3.2). In contrast, incidence of ED treatments due to all injuries from cycling were highest in children aged 0–14 (540/100,000), and adolescents aged 15–24 (623/100,000). In both bicycle-related TBI and all bicycle-related injuries, lowest incidence was reported in cyclists aged 25–54 (32/100,000 and 340/100,000). Elderly cyclist (75+) had the highest injury rate per kilometre travelled of both TBI and all injuries from cycling (annual injury rate of respectively 1.45 and 12.64 per million kilometres travelled). Bicycle-related TBI patients were significantly older than all injured cyclists (mean age 43 (SD 24.2) versus 39 (SD 24.0), p<0.001), and more likely to be male (55% versus 51%, p<0.001).

Over half (59%) of the ED treatments due to bicycle-related TBI comprised a concussion, and one third (30%) a skull-brain injury. Concussions were often caused by a fall (48.1% concussion versus 33.9% skull-brain injury; Chi^2=124.7, p<0.001; OR of severe TBI 0.4, 95%CI [0.3–0.7], p<0.001), or a collision with an obstacle (5.4% versus 4.3%; Chi^2=4.1, p<0.04; OR 0.5, 95%CI [0.3–0.8], p=0.003), whereas a collision with a 4-wheeled vehicle often led to skull-brain injuries (33.5% versus 18.1% concussion; Chi^2=204.1, p<0.001 – Appendix Table 3.B).

In 11% of the ED treatments due to bicycle-related TBI, patients had a primary injury other than TBI. These injuries often involved upper extremity fractures (40%, common in all age groups), facial fractures (17%, only in patients aged 15–74), and internal organ injury (10%, common in all age groups except the elderly). In contrast, all bicycle-related injuries often comprised superficial injury (31%), and fractures to the upper (26%) or lower extremity (9%).

Bicycle-related TBI often represented severe injuries (MAIS 2+, 98%), whereas all bicycle-related injuries often comprised minor or moderate injuries (MAIS 1–2, 76%). According to the MAIS, 482 of all cyclists (4%) died in the hospital because of their injuries, the majority comprising bicycle-related TBI (452, 94%; total in-hospital mortality rate in bicycle-related TBI: 14%).
In both bicycle-related TBI and all bicycle-related injuries, injury severity (type of injury and MAIS), hospitalisation, days of hospitalisation, and IC admission increased with older age. However, those diagnosed with TBI were more often warranted admission to a hospital (64% versus 19%). Although patients with bicycle-related TBI had a shorter length of hospital stay than all bicycle-related injuries (on average 2.3 days (SD 0.74) versus 2.4 (SD 0.73)), they were more often admitted to the intensive care (IC; 7% versus 1%).

Table 3.2 Characteristics of bicycle-related TBI (2012)

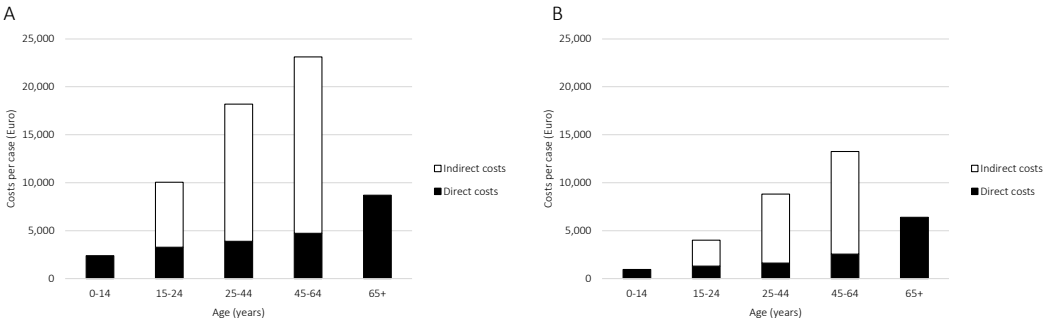
	0–14 (%)	15–24 (%)	25–54 (%)	55–74 (%)	75+ (%)	Total TBI (%)	Total all bicycle-related injuries (%)
N (N (%))	1,215 (16.9)	1,010 (14.0)	2,169 (30.2)	2,095 (29.1)	701 (9.7)	7,190 (100)	76,325
Incidence rate (per 100,000)	41.9	49.3	31.5	56.6	58.8	43.0	456.2
Cycle use[1] **(billion km)**	2.7	2.7	5.5	3.3	0.5	14.7	14.7
Injury rate[2]	0.45	0.38	0.39	0.63	1.45	0.49	5.19
Sex							
Men	57.7	48.1	61.6	53.1	49.4	55.4	50.5
Women	42.3	51.9	38.4	46.9	50.6	44.6	49.5
Type of injury							
Traumatic brain injury							
Concussion	70.0	62.0	59.1	53.6	53.3	59.2	5.6
Skull-brain injury	23.8	25.0	29.3	34.0	41.3	30.3	2.9
Other injury[3]							
Facial fracture	0.0	28.7	15.2	18. 0	0.0	16.9	2.1
Facial injury, other	0.0	0.0	0.0	0.0	0.0	0.0	6.1
Spine, vertebrae	0.0	0.0	7.8	10.7	0.0	6.6	1.1
Internal organ injury	19.6	7.0	19.3	3.4	0.0	10.3	0.9
Rib/thorax fracture	0.0	0.0	0.0	14.2	51.4	7.8	1.2
Upper extr. fracture	19.6	21.7	53.9	39.5	48.6	40.4	25.5
Upper extremity, other	0.0	0.0	0.0	0.0	0.0	0.0	4.6
Hip fracture	0.0	0.0	0.0	14.2	0.0	5.2	2.5
Lower extr.fracture	0.0	20.9	3.7	0.0	0.0	5.0	9.2
Lower extremity, other	60.9	14.7	0.0	0.0	0.0	6.6	3.9
Superficial injury	0.0	7.0	0.0	0.0	0.0	1.3	30.6
Other	0.0	0.0	0.0	0.0	0.0	0.0	3.9
Injury severity[4]							
MAIS 1	1.0	1.7	2.3	1.7	2.5	1.8	15.3
MAIS 2	85.1	69.0	67.2	52.3	48.1	64.4	60.9
MAIS 3	4.7	9.5	13.4	16.1	13.0	11.9	18.2
MAIS 4	2.8	7.1	5.1	12.0	18.0	8.3	2.1
MAIS 6	6.5	12.6	12.1	18.0	18.3	13.5	3.5
Unknown (N)	*0*	*0*	*1*	*0*	*0*	*0*	*360*
Hospitalisation[5]							
Hospital admission	58.5	58.3	60.8	68.8	78.6	64.1	18.6
Number of hospital days[6]	2 (2–2.75)	2 (1–3)	2 (2–3)	3 (2–3)	3 (2–3)	2 (2–3)	3 (2–3)
1 day	15.8	33.3	23.4	9.7	6.7	17.2	14.4
2 days	59.2	38.1	34.7	30.5	28.9	36.9	27.6
≥3 days	25.0	28.6	41.8	59.8	64.4	45.9	58.0
IC admission	3.0	4.7	6.9	8.9	8.0	6.6	1.1

[1] Cycle use (annual number of kilometres travelled) per age group: relevant for both bicycle-related TBI and all bicycle-related injuries.
[2] Annual injury rate per million kilometres: calculated by dividing the number of cyclists with TBI or all injuries from cycling in each age group, by the annual number of kilometres travelled.
[3] Bicycle-related TBI: primary injury besides TBI.
[4] Data on MAIS only known for hospitalised patients in the LMR database (all injuries: n=14,177; TBI: n=3,357).
[5] Hospital admission or IC admission for one day or more after arrival at emergency department.
[6] Data is displayed as median, with the first and third quartile given within brackets.
Km: kilometres, MAIS: maximum abbreviated injury score, IC: intensive care.

Cost-of-illness

Total costs of bicycle-related TBI in the Netherlands were €74.5 million annually, comprising 18% of the costs of all bicycle-related injuries (€410.7 million). Total costs per patient were far higher in bicycle-related TBI (€19,620 per patient) than in all bicycle-related injuries (€10,130 per patient, Figure 3.2). This is due to both higher mean direct costs (€4,940 versus €2,610 per patient) and mean indirect costs (€14,680 versus €7,530 per patient), because TBI patients were more often warranted to the hospital and intensive care, and were longer absent from work (on average 46 versus 24 work days in all injuries). The direct costs and indirect costs (only applicable to the working population aged 15 to 65 years) per patient increased with age (Figure 3.2).

Figure 3.2 Age-related costs per case for bicycle-related TBI (A) and all bicycle-related injuries (B) in 2012



In both TBI (Table 3.3) and all injuries from cycling, the mean indirect costs per case were up to three times higher than the mean direct costs per case. Also, in both groups, total costs per case were higher in men than in women (TBI: €21,290 versus €17,120 per patient; all injuries: €11,160 versus €8,840 per patient). Men had higher indirect costs per case than women (TBI: €16,520 versus €11,990 per patient; all injuries: €8,850 versus €5,940 per patient), because they had to omit more days from work than women (TBI: 47 versus 44 work days; all injuries: 26 versus 21 work days).

Indirect costs per case due to bicycle-related TBI were highest in men in the working population (aged 15–64), and overall in adults aged 45–64 (on average €20,350 in men and €15,320 in women). Direct costs per case due to bicycle-related TBI were highest in cyclists aged 65+ (on average €8,530 per patient in men and €8,850 per patient in women).

Table 3.3 Costs of bicycle-related TBI (2012)

	Age (years)	N	Direct costs per case[1]	Indirect costs per case[1]	Total costs per case[1]	Total costs TBI
Total	0–14	1,215	2,400	–	2,400	2,734,650
	15–24	1,010	3,280	6,780	10,050	6,741,570
	25–44	1,299	3,890	14,300	18,190	18,467,500
	45–64	2,047	4,730	18,400	23,120	32,000,700
	65+	1,617	8,690	–	8,690	14,594,180
	Total	**7,190**	**4,940**	**14,680**	**19,620**	**74,538,610**
Men	0–14	701	2,700	–	2,700	1,825,610
	15–24	486	3,750	7,802	11,550	3,630,390
	25–44	813	3,682	15,261	18,940	12,336,920
	45–64	1,169	4,438	20,350	24,790	20,130,920
	65+	813	8,527	–	8,530	7,158,850
	Total	**3,983**	**4,770**	**16,520**	**21,290**	**45,082,680**
Women	0–14	514	1,950	–	1,950	909,040
	15–24	524	2,820	5,930	8,750	3,111,180
	25–44	486	4,233	12,502	16,740	6,130,590
	45–64	879	5,091	15,320	20,410	11,869,790
	65+	804	8,852	–	8,850	7,435,330
	Total	**3,207**	**5,140**	**11,990**	**17,120**	**29,455,920**

[1] Mean costs per case: indirect costs are only applicable to the working population (15 to 65 years).

3.4 DISCUSSION

Cycling is a popular form of transport and recreation in the Netherlands. Although cycling improves fitness and health, it is not without risks. The purpose of this paper was to assess the incidence and costs of bicycle-related traumatic brain injury across various age groups, and compared them with data on all bicycle-related injuries treated at Dutch EDs between 1998 and 2012. We conclude that incidence

of ED treatments due to cycling are high (456/100,000 persons) and often involve TBI (9%; 43/100,000). Between 1998 and 2012, the incidence of ED treatments due to bicycle-related TBI strongly increased, while this incidence due to all bicycle-related injuries remained stable. The incidence of hospital admissions, however, increased in both TBI and all injuries from cycling. In the same period, the injury rate of TBI per kilometres travelled increased in all age groups (44%) except children (–12%), whereas the overall injury rate of all injuries decreased (–4%) especially in children (–36%). Although bicycle-related TBI accounted for 9% of the incidence of all ED treatments due to cycling, it accounted for 18% (€74.5 million) of the total costs due to all bicycle-related injuries (€410.7 million). Both direct and indirect costs per patient were far higher for cyclists diagnosed with TBI than all injuries from cycling, as TBI patients had more severe injuries, were more often admitted to a hospital or intensive care, and were longer absent from work. Our study identified children and adolescents aged 0–24 to have the highest incidence of ED treatments due to bicycle-related injuries. Although incidence of all bicycle-related injuries and TBI was relatively low in cyclists aged 25–54, men in the working population (age 15–64) had highest indirect costs due to their loss of productivity. Older cyclists aged 55+ were identified as main risk group for TBI, as they represented highest ED attendance, injury severity, admission to hospital or intensive care unit, and economic costs.

The strength of our study lies in the detailed data on demographics, injury mechanism, injury severity (MAIS) and costs of bicycle-related injuries treated at Dutch EDs. Our study therefore provides population-based weighted estimates of the incidence and costs of injuries among all types of cyclists (sports and non-sports) in the Netherlands. In addition, our data provides insight into the trends of ED treatments and hospital admissions due to injuries from cycling over a period of 15 years. In contrast to cost estimations in previous studies, our cost-of-illness assessment included both direct and indirect costs, which were calculated with use of information on real health care volumes, work absence and return to work obtained from patient follow-up surveys.

Incidence and trends

Our estimated incidence of 456 ED treatments per 100,000 persons due to injuries from cycling was much higher than previously reported population-based incidence of ED treatments elsewhere in the world; <1/100,000 persons in Tanzania[35] and Sweden,[8] 10 in Iran,[36] 50 in Canada,[37] 80 in France,[6] and 163 in the United States.[38] This higher Dutch incidence is most likely caused by the more frequent use of bicycles and therefore higher risk of bicycle-related injuries in the Netherlands than in other countries: in the Netherlands one third of all journeys are made by bike.[33] In contrast, in other European countries approximately 2–20% of all journeys are made by bike.[2] In car-oriented countries such as Canada and the United States, only 1% of daily trips are made by bike.[39]

The finding that bicycle-related TBI accounted for 9% of all bicycle-related injuries, is lower than the proportion of head injuries reported in other studies, namely 22–35% in the USA, Sweden, and Finland.[5,10,11] This difference in proportion is likely explained by the disparity in TBI definition. Whereas this study only included patients diagnosed with traumatic brain injury, other studies included all head injuries (including facial fractures, and open wounds or superficial injuries to the head). In addition, the difference in proportion of head injuries may be explained by differences in cycling populations, as in the abovementioned Northern European countries cycling levels remain high, even among the elderly.[40]

Our study showed a strong increase in the incidence of ED treatments due to bicycle-related TBI between 1998 and 2012. In this period, the number of hospital admissions due to bicycle-related TBI and all injuries from cycling increased in all age groups in the Netherlands. Such findings have also been reported for adolescents (aged 13–17) and adults (aged 18+) without head injuries in Alberta, Canada.[41] The increase in hospital admissions in the Netherlands is likely explained by an increase in injury severity of patients visiting an ED, as the number of patients with multiple injuries and the number of patients admitted to the intensive care increased over time. In addition, estimates of the Global Burden of Diseases, Injuries, and Risk Factors Study 2010 (GBD 2010) showed a constant increase in the number of years lived with disability (YLDs – the non-fatal component of disability adjusted life-years (DALYs)) from pedal cycling in Western Europe, approximately 30% from 1990 to 2010.[42]

Patient characteristics and outcome

Our finding that in all age groups the majority of bicycle-related TBI and all bicycle-related injuries were caused by a fall or collision with a motor vehicle is in line with results of other studies.[6-10,43]

Our study indicated that the incidence of ED treatments due to bicycle-related TBI are highest in adults aged 55+, which is in line with previous studies that reported that older cyclists tended to have a higher risk of (serious) injuries from cycling than the younger age groups.[7,8,11,13] This confirms our finding that bicycle-related TBI imposed far more severe injuries (98% MAIS 2+) than all bicycle-related injuries. In our sample, the majority (76%) of all bicycle-related injuries involved minor or moderate injuries (MAIS 1-2), which is in line with other findings in injured cyclists.[5,12] The difference in injury severity between TBI and all injuries from cycling may explain the fact that we found far higher hospital admission rates in cyclists diagnosed with TBI (64%) than in all injured cyclists (19%).

Direct and indirect costs

Total direct and indirect costs of bicycle-related injuries treated at EDs were €10,130 per patient, which was higher than estimates in other European countries: €3,180 in Finland[5] and €4,290 in Sweden[11] after adjustment for inflation up to 2012. Although the Finnish study estimated the same costs and included both costs of treatment and labour absenteeism, the Swedish study estimated only the costs of out- and inpatient care in older adults (65+ years). However, a study in Norway estimated costs of health care and lost output per cyclist injured or killed, similar to estimates in our study: ranging from €1,470 for minor injuries (AIS1) to €19,610 for moderate injuries (AIS2)[12] after adjustment for inflation up to 2012.

In addition to previous studies, we found the total costs of survivors of bicycle-related TBI to be even higher (on average €19,620 per patient), because these TBI patients were more often warranted to the hospital and intensive care, and were longer absent from work (on average 46 days). Our estimates were higher than those of head injured cyclists used for cost-effectiveness of bicycle helmet campaigns or laws, estimating acute medical treatment costs as being €64 per patient,[22] and direct medical costs of hospitalisation as being €1,310 in children aged 5–12, €1,350 in adolescents aged 13–18, and €1,130 in adults aged 18+.[23]

According to our study, in both bicycle-related TBI and all injuries from cycling, the mean indirect costs per case were up to three times higher than the mean direct costs per case, and higher in men than in women (on average 3–5 more omitted workdays). Previous research on minor bicycle accidents in

Belgium, also indicated productivity loss to be the most important component of total cost due to cycling injuries.[44] The difference in omitted workdays and indirect costs between men and women can be explained by the fact that in the Netherlands many women, especially mothers, work part-time: 75% of women aged 25 to 54 with dependent children work part-time, compared to only 26% in France.[45]

Limitations

The epidemiology and costs of bicycle-related TBI and all bicycle-related injuries reported in this study are conservative since they represent only injury patients who were treated at the ED and/or hospitalised. Estimates of the Dutch Consumer and Safety Institute indicate that for every injured cyclist treated at the ED, 1 to 2 consulted a general practitioner, and 2 did not seek medical care.[4] Hence, the actual incidence and cost-of-illness due to bicycle-related TBI and all bicycle-related injuries may be even higher. It should also be noted that this study could not provide complete information on mortality among injured cyclists, because national death statistics are only available for specific diseases or specific injury mechanisms. However, information on the injury severity (MAIS) showed that 482 (4%) of all cyclists died (MAIS 6) in the hospital because of their injuries. The majority of these patients (n=452, 94%) was diagnosed with TBI. According to the MAIS, total in-hospital mortality rate in bicycle-related TBI was 14%. Overall mortality rates are expected to be even higher, because the MAIS only provides information on the in-hospital mortality.

The incidence of bicycle-related TBI and all injuries from cycling were not kilometre-adjusted. However, we did include information on cycle use and the injury rate of both bicycle-related TBI and all injuries from cycling per kilometre travelled. This data showed that between 1998 and 2012, cycle use increased in the Netherlands. In the same period, the injury rate of bicycle-related TBI increased (except in children), whereas the overall injury rate of all bicycle-related injuries decreased.

A final limitation of our study is that since helmet use is not registered in the LIS database, the effects of helmet use could not be studied.

Implications for prevention

This study showed older cyclists (aged 55+ years) to have a higher risk of (serious) injuries from cycling than younger cyclists, both with respect to incidence and injury rate, and identified them as an important risk group for TBI. However, so far, prevention strategies in the Netherlands have been mainly focussing on children and the use of bicycle-helmets in these young and vulnerable cyclists. This has led to an increase in the purchase and/or use of bicycle helmets in children.[46-48] Efforts to increase helmet use may have been effective, as our study showed a 30% decrease in ED treatments due to all bicycle-related injuries and a 12% decrease in the injury rate of TBI per kilometre travelled in 0–14-year olds between 1998 and 2012, and a 6% decrease in ED treatments due to bicycle-related TBI in girls aged 0–14. Also, preliminary results of a campaign in the southern part of the Netherlands, in which free bicycle helmets are provided to all children in primary schools, indicate that after the implementation of this campaign the number of young cyclists with TBI decreased.[46] The latter provides further support for the effectiveness of community based helmet promotion programmes.

Bicycle helmets may also be of use among older cyclists. In the Netherlands, nowadays, helmet use is not mandatory and is unusual among most cyclists. Bicycle helmets are only used during sports among road cyclists and mountain bikers, and by young children. However, it has been shown in other countries

that bicycle helmets reduce the incidence, proportion and severity of head injuries among helmet users.[5,9,36,49,50]

Finally, as older cyclists showed higher injury rates of TBI per kilometre travelled compared to other age groups, and increased cycling is expected to increase TBI in the older age groups, prevention strategies should target on education and training for the physical vulnerable elderly in traffic, especially those using electrical bicycles. Our finding that both the number of ED treatments due to injuries from cycling and injury rate per kilometre travelled increased in adults aged 55+, may be caused by the increasing popularity of electrically assisted bicycles[1,51,52] in this age group.[53] In 2011, 13% of all ED treatments due to bicycle-related injuries in the Netherlands involved users of an electrical bicycle, often aged 60+ (72%).[54] Although injury characteristics seemed similar, in contrast to users of classical bikes, elderly users of electrical bikes were more often injured due to a fall (18% versus 12%). A possible explanation could be the weight of the electrical bicycle, which the elderly indicated to be too high.[54] Also, results of a recent study on the road safety implications of the use of electric bicycles in the Netherlands suggest that users of electric bicycles are more at risk of having a crash that requires treatment at an ED than users of classical bicycles.[55] Further research is needed to minimise the risk and maximise the health benefits for users of electric bicycles. Overall, education and training for the elderly, and improvements in the cycle infrastructure, may reduce the injury severity, ED attendance, and hospitalisation of elderly cyclists.

Conclusions

This study examined the incidence and costs of bicycle-related TBI and compared them with data on all bicycle-related injuries treated at Dutch EDs between 1998 and 2012. We found that incidence of ED treatments due to cycling are high and often involve TBI, imposing a high burden on individuals and society. Older cyclists aged 55+ were identified as main risk group for TBI to be targeted in preventive strategies, due to their high risk for (serious) injuries and ever-increasing share of ED visits and hospital admissions.

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APPENDIX

Table 3.A Unit costs (2012)

	Resource	Unit costs
General Practitioner	Practice consultation	€33.70
	Consultation by telephone	€16.90
	Home visit	€67.40
	Referral patient treated at the ED	€35.00
	Referral hospitalised patient	€44.00
	Follow-up care patient treated at the ED	€33.70
	Follow-up care hospitalised patient	€37.80
Ambulance	Emergency journey	€538.20
	Scheduled journey	€206.20
Hospital	Attendance of ED	Injury specific fees[1]
	Hospitalisation general hospital	€460.40/day
	Hospitalisation academic hospital	€629.00/day
	Intensive care	€1,751.50/day
	Day care	€310.30/day
	Outpatient department visit	€178.10/visit
	Medical procedures	Reimbursement fees
Long-term care	Nursing home	€264.60/day, 138.80/day care
	Rehabilitation	€469.10/day
	Physiotherapy	€38.00/treatment
Home care	Domestic care	€30.60/hour
	Care	€39.10/hour
	Nursing	€67.60/hour
	Nursing & care	€46.40/hour
Productivity loss	15–19 year	€13.50/hour
(including VAT)	20–24 year	€24.70/hour
	25–29 year	€32.80/hour
	30–34 year	€39.30/hour
	35–39 year	€43.30/hour
	40–44 year	€45.40/hour
	45–49 year	€46.80/hour
	50–54 year	€48.50/hour
	55–59 year	€49.70/hour
	60–64 year	€50.70/hour
	Overall mean	€40.90/hour

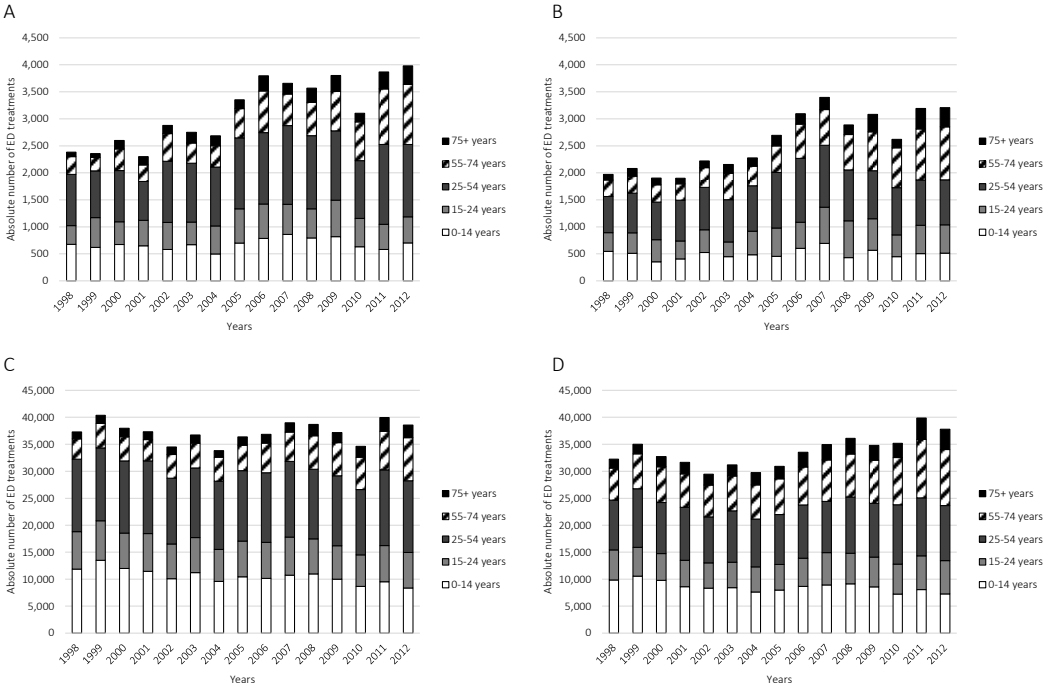
[1] Unit costs for attendance of emergency department are calculated per type of injury in an annually unit cost study indexing the tariffs per minute of nurses, physicians and specialists. ED: emergency department; VAT: value added tax.

Table 3.B Predictors of bicycle-related TBI and TBI severity[1]

	OR	95%CI	p-value
Bicycle-related TBI[2]			
Age[3]	1.01	1.01–1.01	<0.05
Male gender	1.33	1.27–1.40	<0.05
Fall (single bicycle crash)	0.95	0.77–1.16	0.601
Collision with 4-wheeled vehicle[4]	2.67	2.17–3.30	<0.05
Collision with 2-wheeled vehicle[5]	1.63	1.32–2.01	<0.05
Collision with obstacle[6], pedestrian or animal	1.48	1.18–1.86	<0.05
Fall out of child seat	6.56	4.64–9.26	<0.05
TBI severity[7]			
Age[3]	1.01	1.01–1.02	<0.05
Male gender	1.11	1.00–1.23	0.059
Fall (single bicycle crash)	0.43	0.29–0.66	<0.05
Collision with 4-wheeled vehicle[4]	1.24	0.82–1.88	0.317
Collision with 2-wheeled vehicle[5]	0.55	0.36–0.85	<0.05
Collision with obstacle[6], pedestrian or animal	0.49	0.31–0.79	<0.05
Fall out of child seat	1.46	0.79–2.72	0.231

[1] Analysis based on stepwise multivariate regression analysis with socio-demographics (age and gender) as step 1; and injury mechanism as step 2.
[2] Bicycle-related TBI versus all bicycle-related injuries.
[3] Continuous variable.
[4] Including passenger cars, buses, pick-up trucks, trucks and trams.
[5] Including bicycles, mopeds and motor cycles.
[6] Including tree, wall, stationary car (door), (light) pole or edge of sidewalk.
[7] Concussion versus skull-brain injuries.
OR: odds ratio; 95%CI: 95% confidence interval; IC: intensive care.

Figure 3.A Absolute number of ED treatments and incidence (per 100,000 person-years) for bicycle-related TBI (A and B) and all bicycle-related injuries (C and D) in the Dutch population (1998–2012)
Data is shown for men (A and C) and women (B and D).



ED: emergency department.

PART II

Methodological challenges in assessing outcome after injury

Chapter 4

Assessment of pre-injury health-related quality of life: a systematic review

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Submitted

ABSTRACT

Background Insight into the change from pre- to post-injury health-related quality of life (HRQL) of trauma patients is important to derive estimates of the impact of injury on HRQL. Prospectively collected pre-injury HRQL data is, however, often not available due to the difficulty to collect this data before the injury. We performed a systematic review on the current methods used to assess pre-injury health status and to estimate the change from pre- to post-injury HRQL due to an injury.

Methods A systematic literature search was conducted in EMBASE, MEDLINE, and other databases. We identified studies that reported on the pre-injury HRQL of trauma patients. Articles were collated by type of injury and HRQL instrument used. Reported pre-injury HRQL scores were compared with general age- and gender-adjusted norms for the EQ-5D, SF-36 and SF-12.

Results We retrieved results from 31 eligible studies, described in 41 publications. All but two studies used retrospective assessment and asked patients to recall their pre-injury HRQL, showing widely varying timings of assessments (soon after injury up to years after injury). These studies commonly applied the SF-36 (n=13), EQ-5D (n=9) or SF-12 (n=3) using questionnaires (n=14) or face-to-face interviews (n=11). Two studies reported prospective pre-injury assessment, based on prospective longitudinal cohort studies from a sample of initially non-injured patients, and applied questionnaires using the SF-36 or SF-12. The recalled pre-injury HRQL scores of injury patients consistently exceeded age- and gender-adjusted population norms, except in a limited number of studies on injury types of higher severity (e.g. traumatic brain injury and hip fractures). All studies reported reduced post-injury HRQL compared to pre-injury HRQL. Both prospective studies reported that patients had recovered to their pre-injury levels of physical and mental health, while in all but one retrospective study patients did not regain the reported pre-injury levels of HRQL, even years after injury.

Conclusions So far, primarily retrospective research has been conducted to assess pre-injury HRQL. This research shows consistently higher pre-injury HRQL scores than population norms and a recovery that lags behind that of prospective assessments, implying a systematic overestimation of the change in HRQL from pre- to post-injury due to an injury. More prospective research is necessary to examine the effect of recall bias and response shift. Researchers should be aware of the bias that may arise when pre-injury HRQL is assessed retrospectively or when population norms are applied, and should use prospectively derived HRQL scores wherever possible to estimate the impact of injury on HRQL.

4.1 INTRODUCTION

Insight into the change from pre- to post-injury health status of trauma patients is important in order to derive population estimates of the impact of injury on health-related quality of life (HRQL). However, prospectively collected information on the pre-injury HRQL of injury patients is difficult to obtain.
This has led researchers to use alternative methods to assess the contrast between pre-injury and post-injury HRQL, such as use of patient recall or retrospective baseline scores. In other words, pre-injury HRQL that is assessed after sustaining the injury. However, retrospective baseline scores of pre-injury health status are potentially subject to bias.[1,2] Patients may remember their pre-injury HRQL as better or worse than it actually was (recall bias).[1] Moreover, patients' perception on HRQL may change after the injury, due to a change in internal standards or values (response shift).[3] This change in perception of HRQL after the injury may also affect the retrospectively assessed pre-injury HRQL.
Other methods are the application of general population norms (i.e. using normative values from the general population as a reference point for the health status before the injury), or the use of a matched non-injured comparison group as a baseline to assess the reduction in health due to the injury. The application of population norms or a matched non-injured comparison group may lead to an inaccurate estimate of the change in health status as injured people may differ from the general non-injured population.[4,5] Research indicated that injured people have a higher prevalence of comorbidity, hospitalisation and health service utilisation prior to their injury in comparison to non-injured people.[4] This suggests that pre-injury health status is worse compared to population norms and conflicts with the reported better pre-injury health status compared to the general population.[5-7] On the other hand, the injured population might be healthier and more likely to participate in activities, exposing them to a higher risk of injuries.[8]

The current systematic review identifies the methods that are used to assess pre-injury health status of trauma patients and to estimate the change from pre- to post-injury HRQL due to an injury. Moreover, bias that may occur from these methods is examined, by comparing the reported pre-injury HRQL scores with population norms. The objectives of this study are to 1) assess the methods which are used to measure pre-injury HRQL, 2) compare the reported pre-injury HRQL scores with general age- and gender-adjusted norms, 3) study the pre-injury HRQL scores per HRQL instrument and injury type, 4) examine the change between pre- and post-injury HRQL in injury patients, and 5) formulate recommendations for future studies on (pre-injury) HRQL.

4.2 METHODS

Relevant studies were identified through systematic literature searches in the databases EMBASE, MEDLINE (via Ovid SP), Cochrane Central, Pubmed, Web of Science, SCOPUS, PsycINFO, CINAHL, Lilacs, Scielo, ScienceDirect, and ProQuest. Grey literature was examined via Google Scholar. Search strategies were developed in consultation with a search expert, and included a combination of subheadings and text words (Appendix A). Reference lists and citation indices of the included papers and relevant reviews were inspected to identify additional relevant citations.

Study selection

We included studies that assessed the pre-injury HRQL of injury patients, published in English in peer-reviewed journals until July 6 2015. We included studies on general injury populations, as well as injury specific studies (e.g. traumatic brain injury or hip fractures). There was no restriction in the methods of patient selection used in the studies (e.g. samples drawn from to the ED, hospital or outpatient programmes). HRQL was conceptualised as an individual's perception of how an illness and its treatment affect physical, mental and social aspects of his/her life.[9] Studies that assessed only some domains of HRQL (e.g. functional status, activities of daily living, mobility, mental health) were excluded. We included studies that assessed the HRQL of patients before the injury, whether assessed before the injury or retrospectively. Studies that solely used population norms, as a substitute of pre-injury HRQL, were excluded. For studies using data from the same study sample, one study was chosen as reference study by giving priority to the study that focused on reporting pre-injury HRQL summary scores or utility scores (e.g. instead of percentage of problems per HRQL domain).

Data extraction and methodological quality

The first review author (AS) screened all titles and abstracts and deleted obviously irrelevant papers. Two independent review authors (AS and SP) screened the remaining citations on title and abstract and those obtained in full text. Results from both reviewers were compared by a third review author (JH) and any disagreement was be resolved by discussion between the three authors.

We extracted information on the participants (age, gender), injury (type, severity, and mechanism), the assessment of pre-injury HRQL (instrument, procedure, and timing) and recovery of injury patients (change between pre- and post-injury HRQL).

The methodological quality of the studies was evaluated with four elements of the STROBE checklist[10] which were most relevant to the quality of reported pre-injury HRQL by injury type: setting, participants, data sources/measurement and study size. In addition, risk of bias was assessed using items from the Research Triangle Institute item bank for observational studies on attrition bias (Impact missing data adequately assessed) and reporting bias (No important primary outcomes missing).[11]

Statistical analysis

Pre-injury HRQL scores from the study samples were compared with norm scores derived from the general population. Norms by age and sex groups of the EQ-5D (UK population),[12] SF-36[13] and SF-12[14] (US population) were used to calculate age- and gender-adjusted norms based on the demographics in the study samples.

Heterogeneity between pre-injury HRQL scores was assessed with the Q-statistic and I^2-statistic, using a random-effects model in a Microsoft Excel spreadsheet.[15] The Q-statistic is a Chi^2-test for heterogeneity, which assesses whether observed differences in results are compatible with chance alone. A significant Q (low p-value) indicates heterogeneity among the effect sizes and a variation in effect sizes that is beyond chance.[16] The I^2-statistic describes the percentage of variation across studies that is due to heterogeneity rather than chance, with an I^2 value of ≤25% indicating low heterogeneity, and ≥50% indicating substantial heterogeneity.[17]

4.3 RESULTS

Literature search

The extensive search strategy identified 2,286 unique titles of potentially relevant articles (Figure 4.1). Screening of the titles and abstracts resulted in a selection of 383 articles that appeared to meet all selection criteria. After screening and selection of the full text papers, we retrieved 31 studies described in 41 publications. The main reasons for exclusion were not measuring pre-injury health status, not reporting on injuries or only reporting part of the outcomes on HRQL.

Study characteristics

Of the 31 studies included in our systematic review, most were conducted in the US (n=8),[18-25] Australia (n=5),[5,26-29] and Canada (n=5)[30-34] (Table 4.1). Eight studies measured the pre-injury HRQL of patients with a hip fracture,[24,30,34-39] followed in frequency by extremity injury (n=6),[19,23,32,37,40,41] general injury (n=5)[7,29,31,42,43] and traumatic brain injury (TBI, n=4).[22,25,27,44] Sample sizes of the studies varied widely, ranging between 34[33] and 2,842[7] participants, with most studies having sample sizes between 100 and 600 (n=17). The majority of the participants were males (>50% men in 20 out of the 31 studies). The nine studies that included more women than men[18,23,30,34,36,38,39,45,46] often focused on hip fractures (n=5),[30,34,36,38,39] or reported on the outcomes after a motor vehicle crash of a longitudinal (annual) survey (n=2).[18,46] The mean age of the participants in the included studies ranged between 10[19] and 87[30], with an average of 30 to 54 in half (n=16) of the studies and 75+ in six of the 31 included studies. Four studies measured the pre-injury HRQL for children and adolescents,[19,22,25,31] of which the author names are indicated in bold in Table 4.1

Figure 4.1 Study selection

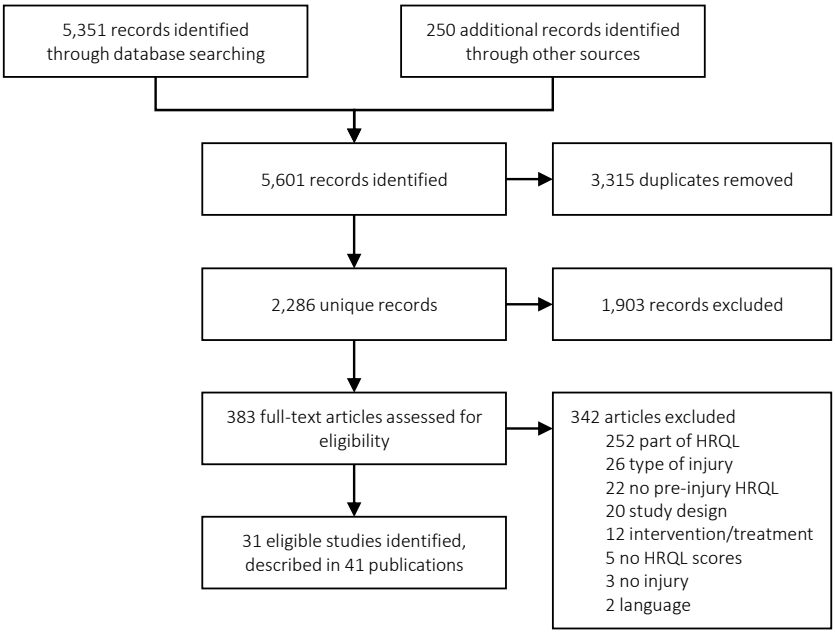


Table 4.1 Study characteristics (**Bold author names are studies of children**; ***Studies in bold and italics prospectively measured pre-injury HRQL***)

Author, year, country, design	Type of injury	Setting *Cohort*	Study sample *Inclusion / exclusion* *N (response); age; % men; severity*	Instrument	Assessment *Method* *Timing*	Focus of pre-injury and follow-up assessments	Analysis *Comparison groups*
Alghnam, 2014, US [18 A]	***Motor vehicle injury vs no MVC***	***Medical expenditure panel survey (MEPS)***	***18+y*** ***n=993; MVC: 18–45y 68%; 46%*** ***No MVC: 18–45y 51%; 47%***	***SF-12***	***Questionnaires*** ***Pre: prospective*** ***Post: max 9m***	***NR***	***MVC vs no MVC***
Andrew, 2012, Australia [26 A]	Orthopedic injury (sport/recreation)	Trauma services / Hospital (VOTOR)	18–75y n=317 (73%); 40y (13); 73% ISS>15 19%	SF-36 (v2)	Telephone interviews Pre: 1–2w Post: 12m	Pre: 4w before injury Post: NR	Type of sport/ recreation
Beaupre, 2012, Canada [30 A]	Hip fracture	Nursing home facilities	65+y; Previously ambulatory nursing home residents n=60 (65%); 87y (8), 62–104; 30%	EQ-5D	(Telephone) Interviews Pre: NR Post: 3m, 6m, 12m	Pre: just before injury Post: NR	Survival status
Brussoni, 2013, Canada [31 D]	General injury	Pediatric ED / hospital	0–16y n=232 (67%); 0–4y 33%, 5–16y 67%; 61% boys	EQ-5D (3L, VAS)	Questionnaires (child/proxy)	Pre: 1d before injury Post: NR	Length of hospital stay
Buecking, 2014, Germany [35 A]	Hip fracture (Proximal femoral)	Hospital / Surgical fracture treatment	>60y; No ISS≥16; No malignancy-related fractures n=350 (65%); 81y (8), 60–99; 73%	EQ-5D (3L, VAS) German norms	Questionnaires Pre: at admission Post: at discharge	Pre: before injury Post: current status	
Busse, 2012, Canada [32 E]	Tibia fracture	Multicenter (SPRINT)	Operative fixation intramedullary nail n=1319; 39y (16); 74%	SF-36	Questionnaires Pre: at the time of enrollment Post: 2w, 12m	Pre: before injury Post: NR	
Ding, 2006, US [19 A]	Extremity fracture (Long bone or pelvic)	Pediatric hospital	5–15y, Hospitalised ≥1d; No TBI n=100 (85%); 10y (3); 66%; NISS: 8 (5)	PedsQL	Telephone interviews Pre: soon after injury (median 9d) Post: 3m, 12m	Pre: before injury Post: post-injury	Upper/lower extremity; HRQL domains
Dvorak, 2005, Canada [33 B,C]	Vertebral fracture (C1, Jefferson)	Databases	18+y; No neurological injury; Disruption of anterior and posterior atlantal arches n=34 (60%); 48y (21); 68%	SF-36 Canadian norms	Questionnaire (by mail/phone) Not reported	Pre: before injury Post: current status	Canadian norms

Table 4.1 (continued) (**Bold author** names are studies of children; ***Studies in bold and italics prospectively measured pre-injury HRQL***)

Author, year, country, design	**Type of injury**	**Setting** *Cohort*	**Study sample** *Inclusion / exclusion* *N (response); age; % men; severity*	**Instrument**	**Assessment** *Method* *Timing*	**Focus of pre-injury and follow-up assessments**	**Analysis** *Comparison groups*
Fauerbach, 1999, US [20 A]	Burn injury	Burn center	Adults n=86; 42y (15); 78	SF-36	Questionnaire Pre: first 73h after admission Post: 2m after discharge	Pre: month before injury Post: past month	Post Traumatic Distress (PTD) vs no PTD; HRQL domains; US norms
Gabbe, 2007, Australia [8 A]	Orthopedic injury	Hospital (VOTOR)	18+y; New orthopedic injury n=1839 (77%); 45y, 21–65; 60%	SF-12	Interviews/Questionnaires Pre: in-hospital/soon after discharge Post: NA	Pre: week before injury Post: NA	Men vs women Australian norms
Greenspan, 2002, US [21 A]	Gunshot injury	Hospital	18–64y; <24h after injury n=60 (38%); 30y (9); 92% ISS 1–9 57%; MAIS 3 48%	SF-36	(Telephone) Interviews Pre: in-hospital/soon after discharge Post: 8m after discharge	Pre: pre-injury status Post: current status	HRQL domains; UK norms
Griffin, 2015, UK [36 A]	Hip fracture	Hospital	60+y; operatively managed n=741 (83%); 80+y 67%; 25%	EQ-5D (3L)	(Telephone) Interviews No response: questionnaires (post) Pre: in-hospital/soon after discharge Post: 4w, 4m, 12m	Pre: pre-injury status Post: NR	Age
Gross, 2012, Switzerland [44 A]	TBI vs no TBI	ICU	≥2 AIS regions, ISS>16; GCS<14, AISH>2 No secondarily admissions n=170 (65%); 40y (21); 75% ISS 28 (8); GCS 11 (5)	EQ-5D (3L, VAS) German norms SF-36 (v1)	Postal questionnaires Pre & post: 2y	Pre: pre-injury status Post: post-injury status	TBI vs non-TBI
Hagino, 2009, Japan [37 A]	Hip fracture Vertebral fracture Wrist fracture	Hospital	Women; 45+y; No malignancy-related fractures; Lower-energy; Minor trauma n=122; Hip 76 (10), 49–91; Vertebral 73 (10), 48–91; Wrist 69 (10), 49–88	EQ-5D Japanese norms	Questionnaires Pre: first visit/admission Post: 2w, 3m, 6m, 12m	Pre: period before injury Post: NR	Hip vs vertebral vs wrist
Innocenti, 2014, Italy[43 A]	General injury	ED-HDU	n=153 (51%); 54y (22); 67% ISS 12 (9)	SF-12 Italian norms	Telephone interviews Pre & post: 6m after ED discharge	Pre: before injury Post: current status	Change HRQL domains Italian norms

Table 4.1 (continued) (**Bold author names are studies of children**; ***Studies in bold and italics prospectively measured pre-injury HRQL***)

Author, year, country, design	Type of injury	Setting *Cohort*	Study sample *Inclusion / exclusion* *N (response); age; % men; severity*	Instrument	Assessment *Method* *Timing*	Focus of pre-injury and follow-up assessments	Analysis *Comparison groups*
Jaglal, 2000, Canada [34 E]	Hip fracture	Hospital	Living independently; No cognitive impairment n=43; 81y (8); 19%	SF-36	(Telephone) Interviews Pre: in-hospital Post: 6w, 6m after injury	Pre: before injury Post: NR	HRQL domains
Jimenez, 2013, US [22 A]	TBI	Hospital (CHAI)	<18y; discharged alive from ED Hispanic or non-Hispanic white n=531 (73%); 0–9 50%; 65% boys; MAIS 1 46%	PedsQL (Spanish)	(Telephone) Interviews Pre: soon after injury (median 37d) Post: 3m, 12m, 24m, 36m	Pre: period before injury Post: NR	Hispanic vs non-Hispanic white
Lyrtzis, 2013, Greece [41 A]	Ankle sprain (2nd degree)	Not reported	Injury at 1 limb; No previous ankle injury; No fracture; <24h after injury; no analgesic n=78 (98%); 36y (13); 74%	SF-36	Questionnaires Pre: day of injury Post: 10d	Pre: before injury Post: 10d since injury	HRQL domains
McGuine, 2014, US [23 A]	Knee injury	Sports medicine center/clinic	Women; 13–23y; Injury during regular fitness or sport activities n=255 (91%); 17y (2), 13–23; 0%	SF-12 (v2)	Questionnaires Pre: initial visit (median 12d) Post: diagnosis, 3m, 6m, 12m	Pre: 1w before injury Post: since injury	US norms
Ottosson, 2007, Sweden [45 A]	Musculoskeletal injury	ED	15+y n=318 (39%); 39y (15); 46%	SF-36	Questionnaires Pre: at inclusion Post: 1m, 6m	Pre: week before injury Post: NR	Swedish norms
Peterson, 2008, US [24 E]	Hip fracture	Hospital Hip fracture surgery	>65y; Not mentally impaired; Living independently n=105 (NR); alive – 79 (8); NR	SF-36 (v1)	Questionnaires Pre: NR Post: 1st w after operation	Pre: 4w before injury Post: NR	Survival status; HRQL domains
Pieper, 2014, US [25] **Related: [47 A]**	TBI vs no TBI	Pediatric ED (Self-selected sample)	5–17y; discharge <24h n=40 mBTI, 40 no TBI TBI: 12y (3); 80%; no TBI: 10y (3); 63%	PedsQL (4.0 Generic)	(Telephone) Interviews Pre: initial contact Post: 1m, 3m, 6m, 12m	Pre: week before injury Post: NR	mTBI vs no TBI vs no injury; Children vs parents (proxy); HRQL domains

Table 4.1 (continued) (**Bold author names are studies of children**; ***Studies in bold and italics prospectively measured pre-injury HRQL***)

Author, year, country, design	**Type of injury**	**Setting** *Cohort*	**Study sample** *Inclusion / exclusion* *N (response); age; % men; severity*	**Instrument**	**Assessment** *Method* *Timing*	**Focus of pre-injury and follow-up assessments**	**Analysis** *Comparison groups*
Ponsford, 2011, Australia [27 A] Related: [48]	TBI vs no TBI	Hospital	18+y; <24h after injury n=123 (63%) mTBI, 100 (30%) no TBI mTBI: 35y (13); 74%; no TBI: 35y (11); 64%	SF-36	Questionnaires Pre: within 48h after injury Post: 1w, 3m	Pre: before injury Post: current, past 4w	mTBI vs no TBI
Pons-Villanueva, 2011, Spain [46 A]	***Motor vehicle injury vs no MVC***	***University graduates (SUN)***	***n=64 MVC, 3297 no MVC (91%) 40y; 38%***	***SF-36***	***Questionnaires Pre: prospective Post: 4y, 8y***	***NR***	***MVC vs no MVC; HRQL domains***
Skoog, 2001, Sweden [40]	Tibia shaft fracture	Hospital	No pathologic fractures or fractures adjacent to implant n=64; 45y (19), 14–93; 56%	SF-36	Interviews/Questionnaires Pre: during hospitalisation Post: 4m, mean 13m	Pre: before injury Post: not reported	Swedish norms
Sugeno, 2008, Japan [38 A]	Hip fracture	Hospital	No severe cognitive decline n=50 (44%); 77y (10); 20%	EQ-5D (3L, VAS)	Interviews Pre: 1/2d after admission Post: discharge, 3m, 6m, 12m after admission	NR	
Tidermark, 2002, Sweden [39 A]	Hip fracture (Falls)	ED	65+y; Living independently n=90; 80y (7), 66–92; 37%	EQ-5D (3L, VAS) UK norms	Interviews/Questionnaires (post) Pre: first days after injury Post: 1w, 4m, mean 17m (2))	Pre: week before injury Post: NR	Age (60-88); Gender; Fracture outcome; Survival status; Swedish norms
Ulvik, 2008, Norway [42 A]	General injury	Closed ICU (neurosurgery)	>18y n=210 (92%); 39y (17), 18–83; 81% ISS (median) 25; 4–54	EQ-5D	Telephone interviews Pre & post: 2–7y (median 4y)	Pre: before injury Post: current status	
Wasiak, 2014, Australia [28 A]	Burn injury	Burn center	18+y; TBSA>10% n=99 (79%); 42y (2); 75%	SF-36 (v2)	Questionnaires Pre: not reported Post: 12m	NR	Australian norms

Table 4.1 (continued) (**Bold author** names are studies of children; ***Studies in bold and italics prospectively measured pre-injury HRQL***)

Author, year, country, design	**Type of injury**	**Setting** *Cohort*	**Study sample** *Inclusion / exclusion* *N (response); age; % men; severity*	**Instrument**	**Assessment** *Method* *Timing*	**Focus of pre-injury and follow-up assessments**	**Analysis** *Comparison groups*
Watson, 2005, Australia [29] A Related: [49]	General injury	Hospital	18–74y; No self-inflicted injury; No neurological deficit n=221 (88%); 38y; 72%	SF-36	Interviews Pre: in hospital / 1st w Post: 6w, 3m, 6m, 12m	Pre: previous week Post: previous week	Age; Gender; Work status; Employment; Australian norms
Wilson, 2012, New Zealand [7] A Related: [50-52]	General injury	Accident Compensation Corporation entitlement claims register	18–64y; No self-harm or sexual assault n=2.842; 18–34y 35%, 35–64y 47%; 61%	EQ-5D New Zealand norms	Interviews Pre: 3.2m Post: 4.6m, 12.3m	Pre: before injury Post: current status	Recovery status; New Zealand norms

Design: A Prospective cohort, B Retrospective cohort, C Cross-sectional, D Validation study, E Randomised controlled trial.
h=hour; d=day; w=week; m=month; y=year.
AIS: Abbreviated Injury Scale; ED: emergency department; GCS: Glasgow Coma Scale; NR: not reported; MVC: injury due to motor vehicle crash; Ortho: orthopedic injury; TBI: traumatic brain injury.

Methodological quality

Over half (n=19) of the 31 articles included in our review reported on attrition. Most studies faced several problems in the participation of eligible patients, as patients refused to participate (n=15), could not be contacted (n=6), did not complete the HRQL assessment (n=6), had died (n=5), or were not able to respond to the questionnaires (e.g. due to the consequences of the trauma, n=3). Overall, response rates ranged from 60% to 98% in 17 of the 22 studies that reported on response rates.

Limited variation existed in the selection of samples between the studies. Most patients were recruited during or after a treatment in a (pediatric) hospital (n=21), while others were selected from a specialised burn center (n=2),[20,28] sports center (n=1),[23] or nursing home facility (n=1).[30]

In four out of the 31 studies, the measurement of pre-injury HRQL was one of the primary aims,[7,8,18,46] while in all other studies pre-injury HRQL scores were used to assess the change in HRQL after the injury or to validate HRQL instruments.

Methods to measure pre-injury HRQL

The 36-item Short-Form (SF-36, n=14)[21,24,26-29,32-34,40,41,45,46,53] was the most frequently used instrument to assess the pre-injury HRQL of injury patients, followed by the EuroQol-5 Dimension Questionnaire (EQ-5D, n=9),[7,30,31,35-39,42] and the SF-12 (n=4)[5,18,23,43] (Table 4.1). The remaining studies used the Pediatric Quality of Life Inventory (PedsQL, n=3),[19,22,25] or a combination of the EQ-5D and SF-36 (n=1).[44] The majority of the studies assessed the participants' pre-injury HRQL by using a questionnaire (n=16)[8,18,20,22-24,27,28,31-33,35,37,41,44-46] or a face-to-face interview (n=11).[7,8,21,25,29,30,34,36,38-40] At follow-up, most studies used questionnaires (n=17)[18,23,24,27,28,31-33,35,37,39-41,44-46,53] followed by the use of telephone interviews (n=10).[19,21,22,25,26,30,34,36,42,43]

All but two studies in this review retrospectively assessed the pre-injury HRQL of patients, by asking them to recall their HRQL before the injury occurred. Only two studies provided prospectively collected pre-injury health status of participants[18,46] (articles in bold and italics in Table 4.1): the Medical Expenditure Panel Survey (MEPS)[18] and the Seguimiento Universidad de Navarra (SUN)[46] cohort. These studies used data from longitudinal cohort studies in which participants who were initially non-injured were followed for several years, by means of questionnaires comprising the SF-36[46] or SF-12[18]. In addition, only one of the included studies measured the recalled pre-injury health status of trauma patients and not their post-injury HRQL,[5] while all other studies measured both pre- and post-injury HRQL.

Pre-injury scores were often reported as assessed 'soon after' injury or admission (n=12), in-hospital or 'soon after' discharge (n=5),[8,21,29,34,36] at inclusion or initial contact/visit (n=5),[23,25,32,37,45] within 6 months after ED discharge (n=2),[7,43] or years after injury (n=2).[42,44] The focus of the questionnaire and/or interviews (i.e. a specified period prior to the injury) was often not specifically defined (e.g. 'before the injury', n=15) or not reported (n=2).[28,38] The studies that specified the period of their pre-injury assessment used a day before injury (n=1),[31] 'just' before injury (n=1),[30] a week before injury (n=4),[8,25,39,45] the previous week (n=2),[23,29] or the month or 4 weeks before injury (n=3).[20,24,26]

Most studies (n=16) made a comparison of pre-injury HRQL between injury patients or with controls (e.g. TBI vs no TBI),[18,19,25,27,37,44,46] between subgroups (e.g. by age, gender, ethnicity),[5,22,29,36,39] or between survival or recovery status (e.g. survived vs dead, recovered vs not recovered).[7,24,30,39] In

addition, twelve studies compared the participants' pre-injury health status with general population norms.[7,8,20,21,23,28,29,33,39,40,43,45]

Comparison of pre-injury HRQL between injury patients and with population norms

Within-study comparisons between retrospectively collected pre-injury HRQL and general population norms indicated that self-reported pre-injury HRQL scores were consistently higher than population norm scores (n=3).[7,29,54] Three studies found that scores were higher in either the physical domains (n=3)[20,21,28] or mental domains (n=1)[20] or in certain age or sex groups (n=1).[8] Five studies found no differences between the recalled pre-injury HRQL and population norms (n=5)[33,39,40,43,45] (Table 4.2).

The self-reported pre-injury HRQL scores also exceeded the calculated age- and gender-adjusted population norm scores on the EQ-5D[7,37-39,42,44] (Figure 4.2), as well as the physical and mental domains of the SF-36 and SF-12 (Figure 4.3). Exceptions were injury types of higher severity, including elderly hip fracture patients (aged 80+ years),[30,35,36] or patients with a motor vehicle injury,[18,46] vertebral fracture,[33] or TBI.[27]

Within-study comparisons of pre-injury HRQL between injury patients or with controls showed that patients that injured due to a motor vehicle injury or that sustained a TBI have significantly lower mental health at baseline[18,27,44,46] and lower scores across all HRQL domains[46] compared to those without a motor vehicle injury or TBI (Table 4.2). Higher pre-injury HRQL was found in those who survived than those who eventually died during follow-up (significant differences found on the SF-36 PF, RP and GH,[24] no significant differences found between EQ-5D scores[30]) and in those recovered than those not recovered at follow-up (not significant).[7]

Pre-injury HRQL scores per HRQL instrument and injury type

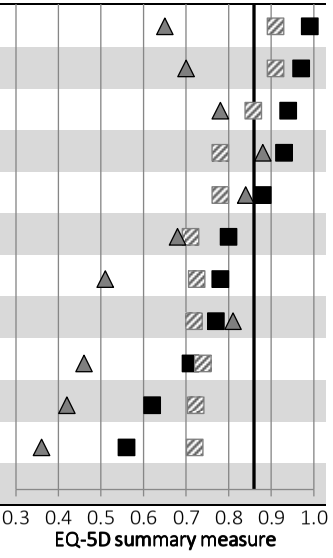
There was a large variation in the presentation of the pre-injury HRQL of patients (Table 4.2). Most studies reported the total scale scores on the EQ-5D (n=10)[7,30,31,35-39,42,44] or PedsQL (n=3).[19,22,25] The studies that used the SF-36 or SF-12 often presented the physical (PCS) and mental component scores (MCS) (n=10),[8,18,27-29,32,33,43,44,54] while some studies provided an oversight of all domain scores without summary scores.[20,21,24,34,41]

Pre-injury HRQL scores varied between patients with a hip fracture, ranging from 0.56 in an operatively managed sample of primarily 80+ year old females[36] to 0.80 in a hospitalised sample of women aged 45+.[37] Highest pre-injury EQ-5D scores were seen in study populations who experience a TBI,[44] major trauma,[42] unintentional injury[7] or wrist or vertebral fracture[37] (mean EQ-5D 0.94, SD 0.04) while lowest pre-injury EQ-5D scores were reported in hip fracture populations[30,35-39] (mean EQ-5D 0.71, SD 0.10); two-sample t(9)=5.01, 95% confidence interval (CI) [0.13-0.34], p=0.001. Overall, pre-injury EQ-5D scores decreased with age, from 0.99 in populations with a mean age of 40 years (SD 21)[44] to 0.56 in those aged 80+ years.[30,35,36]

Patients with a vertebral injury reported lowest pre-injury PCS (SF-36, PCS 49),[33] while those with orthopedic injury reported highest pre-injury PCS scores (SF-36, PCS 59).[26] Lowest pre-injury MCS on both the SF-36 (MCS 47)[46] and SF-12 (MCS 49)[18] was reported in the two studies that prospectively assessed the pre-injury HRQL of participants before the occurrence of a motor vehicle injury. Overall, rather similar pre-injury HRQL scores were reported in all studies, showing low heterogeneity (PCS: I^2=12%, MCS: I^2=7%), with generally better pre-injury PCS than MCS (mean 54.6 vs 52.9).

Figure 4.2 Pre-injury EQ-5D scores by injury type and in comparison to population norm scores

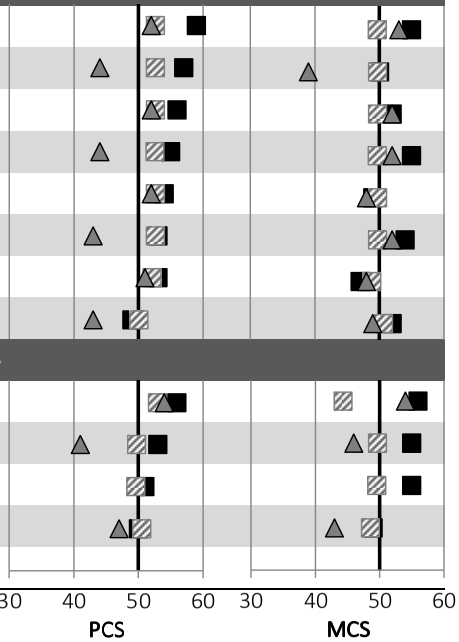
Author (year)	Injury	N	Age (mean, SD, range)	Men (%)	Norm score[1]	Pre-injury score	Post-injury score[2]
Gross (2012)	TBI	170	40y (21)	75%	0.91	0.99	0.65
Ulvik (2008)	General	210	39y (17), 18–83	81%	0.91	0.97	0.70
Wilson (2012)	General	2842	18–34y 35%, 35–64y 47%	61%	0.86	0.94	0.78
Hagino (2009)	Wrist	122	69 (10), 49–88	0%	0.78	0.93	0.88
Hagino (2009)	Spine	122	73 (10), 48–91	0%	0.78	0.88	0.84
Hagino (2009)	Hip	122	76 (10), 49–91	0%	0.71	0.80	0.68
Tidermark (2002)	Hip	90	80y (7), 66–92	37%	0.72	0.78	0.51
Sugeno (2008)	Hip	50	77y (10)	20%	0.72	0.77	0.81
Buecking (2014)	Hip	350	81y (8), 60–99	73%	0.74	0.71	0.46
Beaupre (2012)	Hip	60	87y (8), 62–104	30%	0.72	0.62	0.42
Griffin (2015)	Hip	741	80+y 67%	25%	0.72	0.56	0.36
UK norm	**No injury**				**0.86**		



[1] Adjusted by the age and sex distribution in the study population, based on the weighted health state index by age and sex.[12]
[2] Final post-injury measurement: at discharge,[35] 1 year post-injury,[7,30,36-39] 2 years post-injury,[44] or 2-7 years post-injury.[42]

Figure 4.3 Pre-injury SF-36 and SF-12 scores by injury type and in comparison to population norm scores

Author (year)	Injury	N	Age (mean, SD, range)	Men (%)	Norm score[1]		Pre-injury score		Post-injury score[2]	
SF-36					**PCS**	**MCS**	**PCS**	**MCS**	**PCS**	**MCS**
Andrew (2012)	Ortho	317	40y (13)	73%	52.6	49.7	59	55	52	53
Gross (2012)	TBI	170	40y (21)	75%	52.6	49.7	57	50	44	39
Wasiak (2014)	Burn	99	42y (2)	75%	52.6	49.7	56	52	52	52
Watson (2005)	General	221	38y, 18–74	72%	52.6	49.7	55	55	44	52
Ponsford (2011)	TBI	123	35y (13)	74%	52.6	49.7	54	49	52	48
Busse (2012)	Extremity	1319	39y (16)	74%	52.6	49.7	53	54	43	52
Pons-Villanueva (2011)	***MVC***	***64***	***40y***	***38%***	***52.1***	***48.8***	***53***	***47***	***51***	***48***
Dvorak (2005)	Spine	34	48y (21)	68%	50.1	50.7	49	52	43	49
SF-12					**PCS**	**MCS**	**PCS**	**MCS**	**PCS**	**MCS**
McGuine (2012)	Knee	255	17y (2), 13–23	0%	53.0	44.3	56	56	54	54
Innocenti (2014)	General	153	54y (22)	67%	49.8	49.7	53	55	41	46
Gabbe (2007)	Ortho	1839	45y, 21–65	60%	49.6	49.6	51	55	-	-
Alghnam (2014)	***MVC***	***993***	***18–45y 68%***	***46%***	***50.5***	***48.6***	***50***	***49***	***47***	***43***
US norm	**No injury**				**50**	**50**	**50**	**50**		



Studies in bold and italics prospectively measured pre-injury HRQL

[1] Adjusted by the age and sex distribution in the study population, based on the weighted health state index by age and sex.[13,14]

[2] Final post-injury measurement: at 3[27], 6[43] or ***maximal 9 months post-injury***,[18] 1 year post-injury,[26,28,29,32,33,54] 2 years post-injury,[44] or ***4-8 years post-injury***.[46]

Heterogeneity: PCS Chi^2=12.48, df=11, (p=0.33), I^2=12%; MCS Chi^2=11.88, df=11, (p=0.37), I^2=7%.

MVC: injury due to motor vehicle crash; Ortho: orthopedic injury; TBI: traumatic brain injury.

Table 4.2 Pre- and post-injury HRQL **(Bold author names are studies of children; *Studies in bold and italics prospectively measured pre-injury HRQL*)**

Author, year, country	Instrument	Pre-injury HRQL	Post-injury HRQL	Change *Post-injury vs pre-injury*	Findings
General injury					
Brussoni, 2013, Canada [31]	EQ-5D	Not admitted: 0.97 1–3d: 0.94 4+d: 0.93	Not admitted: 0.90 1–3d: 0.76 4+d: 0.61	Not admitted: –0.07 1–3d: –0.18 4+d: –0.32	All categories of length of stay in hospital had significantly lower HRQL at follow-up than at baseline
Ulvik, 2008, Norway [42]	EQ-5D	0.97	0.70	–0.27*	Significant decrease in HRQL in all dimensions
Wilson, 2012, New Zealand [7]	EQ-5D	0.94	5m: 0.75 12m: 0.78	5m: –0.19 12m: –0.16	Significantly higher pre-injury HRQL than New Zealand norms. Recovered had significantly higher post-injury HRQL than norms. Non-recovered had significantly lower HRQL than norms.
Watson, 2005, Australia [29]	SF-36	PCS 55; MCS 55	1w: PCS 25; MCS 46 6w: PCS 34; MCS 53 12w: PCS 38; MCS 55 26w: PCS 43; MCS 52 52w: PCS 44; MCS 52	1w: PCS –30; MCS –9 6w: PCS –21; MCS –2 12w: PCS –17; MCS 0 26w: PCS –12; MCS –3 52w: PCS –11; MCS –3	Consistently higher pre-injury scores than Australian norms. Males had higher pre-injury PCS and MCS than females. 18-24y and 65-74y had highest pre-injury MCS. Those with pre-injury paid-employment had significantly higher pre-injury PCS than those without.
Innocenti, 2014, Italy [43]	SF-12	PCS 53 (7), 24–64 MCS 55 (7), 28–63	6m: PCS 41 (12), 14–64 6m: MCS 46 (13), 16–67	PCS –12* MCS –9*	93% pre-injury PCS and MCS in normal range according to Italian norms. Significant worse HRQL after 6m.
Traumatic brain injury					
Gross, 2012, Switzerland [44]	EQ-5D SF-36	TBI: 99 (4); no TBI: 95 (14) *TBI* PCS 57 (6); MCS 50 (11) *no TBI* PCS 56 (7); MCS 51 (12)	TBI: 65 (28); no TBI: 76 (21) TBI - PCS: 44 (12); MCS: 39 (13) *no TBI* - PCS: 45 (11); MCS: 48 (13)	TBI: –34; no TBI: –19 *TBI* PCS –13; MCS –11 *no TBI* PCS –11; MCS –3	TBI had significantly worse HRQL compared with no TBI (on EQ VAS, EQ-5D, MCS, but not on PCS)
Ponsford, 2011, Australia [27]	SF-36	*mTBI* PCS 54 (6); MCS 49 (8) *no TBI* PCS 54 (6); MCS 53 (7)	1w: *mTBI* PCS: 38 (10); MCS: 44 (11) 1w: *no TBI* PCS:36 (10); MCS: 49 (11) 3m: *mTBI* PCS: 52 (9); MCS: 48 (10) 3m: *no TBI* PCS: 50 (9); MCS: 53 (7)	1w: *mTBI* PCS: –16; MCS: –5 1w: *no TBI* PCS: –18; MCS: –4 3m: *mTBI* PCS: –2; MCS: –1 3m: *no TBI* PCS: –4; MCS: 0	mTBI had significantly poorer mental HRQL pre-injury. Significant change in PCS in mTBI and no TBI, MCS only in mTBI. Scores dropped dramatically at 1w, returned to pre-injury levels at 3m.

Table 4.2 (continued) **(Bold author names are studies of children; *Studies in bold and italics prospectively measured pre-injury HRQL*)**

Author, year, country	Instrument	Pre-injury HRQL	Post-injury HRQL	Change *Post-injury vs pre-injury*	Findings
Jimenez, 2013, US [22]	PedsQL	NHW: 86 Hispanic: 90	NR	0–3m: NHW –5; Hispanic –16 0–12m: NHW –5; Hispanic –13 0–24m: NHW –5; Hispanic –13 0–36m: NHW –5; Hispanic –16	Pre-injury scores were higher for Hispanic than NHW. Post-injury scores were significantly lower for Hispanic compared with NHW.
Pieper, 2014, US [25]	PedsQL	mTBI: 82 (13) no TBI: 81 (14)	mTBI: 82 (15) no TBI: 82 (16)	mTBI 0 no TBI: 1	No significant differences were identified among mTBI, NBI, and uninjured groups. Cognitive HRQL after mTBI trended lower from 3-12 months post-injury.
Hip fracture					
Beaupre, 2012, Canada [30]	EQ-5D	0.62 (0.20) *Survived* 0.63 (0.20) *Deceased* 0.61 (0.20)	*Survivors* 3m: 0.42 (0.25) 6m: 0.46 (0.24) 12m: 0.42 (0.30)	3m: –0.21 6m: –0.17 12m: –0.21	At 1y, those alive had higher pre-injury HRQL than those that died. Significant loss in HRQL at 3m that remained relatively unchanged 6m and 12m postoperatively.
Buecking, 2014, Germany [35]	EQ-5D	0.71	Discharge: 0.46	Discharge: –0.25	Significantly reduced HRQL during hospitalisation.
Griffin, 2015, UK [36]	EQ-5D**	0.56	4w: 0.28[A] 4m: 0.32[A] 12m: 0.36[A]	4w: –0.28 4m: –0.24 12m: –0.2	Significantly lower HRQL at one year than pre-injury. HRQL significantly improved after 4w in those aged ≤80y, but not in >80y.
Hagino, 2009, Japan [37]	EQ-5D	0.80 (0.17)	2w: 0.37 (0.27) 3m: 0.64 (0.16) 6m: 0.63 (0.18) 12m: 0.68 (0.24)		Hip fracture had lower pre-injury HRQL than wrist facture (significant) or vertebral fracture.
Sugeno, 2008, Japan [38]	EQ-5D	0.77 (0.24)	Discharge: 0.67 (0.21) 12m: 0.81 (0.17)	Discharge: –0.10 12m: 0.04	HRQL decreased post-injury, but recovered to pre-facture levels 1y following hospitalisation.
Tidermark, 2002, Sweden [39]	EQ-5D	0.78 (0.21) *Survived* 0.79 (0.21) *Deceased* 0.73 (0.22)	*Survivors* 1w: 0.44 (0.33) 4m: 0.55 (0.37) 12m: 0.51 (0.36)	1w: –0.34 4m: –0.23 12m: –0.27	Similar pre-injury HRQL compared to Swedish population norms. Decrease in HRQL from pre- to post-injury. Patients did not regain their pre-injury HRQL.
Jaglal, 2000, Canada [34]	SF-36	PF 74 (24); RP 68 (46); BP 92 16); GH 79 (20); VT 63 (22); SF 86 (21); RE 86 (34); MH 73 (20)	6w: PF 44 (18); RP 2 (7); BP 68 (20); GH 75 (19); VT 54 (18); SF 75 (23); RE 85 (36); MH 79 (16) 6m: PF 59 (22); RP 63 (48); BP 78 (24); GH 77 (25); VT 59 (23); SF 77 (25); RE 96 (21); MH 82 (13)	6w: PF –30*; RP –66*; BP –24*; GH –4; VT –9; SF –11*; RE –1*; MH 6 6m: PF –15*; RP –5*; BP –14*; GH –2; VT –4; SF –9; RE 10; MH 9*	Significant decrease in HRQL from pre- to post-injury in all domains (ex GH, VT, MH). Significantly lower PF, RP, BP but higher MH at 6m than pre-injury.

Table 4.2 (continued) **(Bold author names are studies of children; *Studies in bold and italics prospectively measured pre-injury HRQL*)**

Author, year, country	Instrument	Pre-injury HRQL	Post-injury HRQL	Change *Post-injury vs pre-injury*	Findings
Peterson, 2008, US [24]	SF-36	*Survived* PF 56 (36); RP 81 (33); BP 84 (24); GH 75 (21); VT 65 (22); SF 86 (23); RE 93 (26); MH 76 (20) *Died* PF 41 (29); RP 60 (43); BP: 82 (24); GH 62 (26); VT 55 (23); SF 84 (24); RE 85 (32); MH 79 (22)	NA		At recruitment, no differences in domain scores between those living at 5 years and those dead (though small N, large SD). At 5y, significantly higher PF, RP and GH in those alive than those that died.
Extremity injury					
Ding, 2006, US [19] (Extremity)	PedSQL	89	3m: 73 12m: 80	3m: –16 12m: –9	Similar pre-injury HRQL for upper- and lower- extremity fractures. Significantly lower HRQL post-injury than pre-injury.
Busse, 2012, Canada [32] (Tibia)	SF-36	PCS 53 (9) MCS 54 (9)	2w: PCS 28 (8); MCS 46 (13) 12m: PCS 43 (11); MCS 52 (12)	2w: PCS –25; MCS –8 12m: PCS –10; MCS –2	Decrease in HRQL from pre- to post-injury. Patients did not regain their pre-injury HRQL.
Skoog, 2001, Sweden [40] (Tibia)	SF-36**	PF 72; RP 83; BP 80; GH 80; VT 75; SF 83; RE 88; MH 82	4m: PF 60; RP 45; BP 63; GH 74; VT 62; SF 70; RE 58; MH 77 12m: PF 68; RP 58; BP 66; GH 70; VT 57; SF 70; RE 76; MH 73	4m: PF –12*; RP –38*; BP –17; GH –6; VT –13; SF –13*; RE –30*; MH –5 12m: PF –4; RP –25; BP –14*; GH –10*; VT –18*; SF –13; RE –12; MH –9	Pre-injury HRQL was comparable to Swedish healthy population. SF-36 domain scores were lower at 4m and 12m, compared to pre-injury HRQL.
Lyrtzis, 2013, Greece [41] (Ankle)	SF-36	89 (6); 68–97 PF 96; RP 95; BP 91; GH 76; VT 79; SF 92; RE 93; MH 87	10d: 68 (11); 52–82 PF: 64; RP: 72; BP: 71; GH: 54; VT: 78; SF: 77; RE: 82; MH: 68	10d: –21 PF –32; RP –23; BP –20; GH –22; VT –1; SF –15; RE –11; MH –19	Significant worsening of HRQL 10d after injury, compared to pre-injury HRQL.
McGuine, 2014, US [23] (Knee)	SF-12	PCS 56 (5) MCS 56 (7)	Diagnosis: PCS 41 (11); MCS 51 (12) 3m: PCS 48 (9); MCS 53 (10) 6m: PCS 53 (7); MCS 53 (9) 12m: PCS 54 (6); MCS 54 (8)	Diagnosis: PCS –15; MCS –5 3m: PCS –8; MCS –3 6m: PCS –3; MCS –3 12m: PCS –2; MCS –2	Pre-injury HRQL was higher than population norms in all domains. HRQL change from preinjury through an entire 12m after injury.
Hagino, 2009, Japan [37] (Wrist)	EQ-5D	0.93 (0.13)	2w: 0.72 (0.14) 3m: 0.81 (0.18) 6m: 0.87 (0.15) 12m: 0.88 (0.15)	2w: –0.21 3m: –0.12 6m: –0.06 12m: –0.05	Hip fracture had lower pre-injury HRQL than wrist facture (significant) or vertebral fracture. Scores showed recovery after 6m. After 1y, scores were not significantly different from pre-fracture.

Table 4.2 (continued) **(Bold author names are studies of children; *Studies in bold and italics prospectively measured pre-injury HRQL*)**

Author, year, country	Instrument	Pre-injury HRQL	Post-injury HRQL	Change *Post-injury vs pre-injury*	Findings
Other injury					
Pons-Villanueva, 2011, Spain [46] (MVC)	SF-36	*MVC* PCS 53; MCS 47 PF 95; RP 87; BP 74; GH 73; VT 65; SF 89; RE 80; MH 71 *No MVC* PCS 53; MCS 49 PF 95; RP 91; BP 79; GH 76; VT 66; SF 92; RE 87; MH 76	*MVC* PCS 51; MCS 48 PF 93; RP 83; BP 69; GH 71; VT 63; SF 91; RE 82; MH 73 *No MVC* PCS 53; MCS 50 PF 95; RP 92; BP 78; GH 77; VT 66; SF 94; RE 90; MH 77	*MVC* PCS –2; MCS 1 PF –2; RP –4; BP –5; GH –2; VT –2; SF –2; RE 2; MH 2 *No MVC* – PCS 0; MCS 1 PF 0; RP 1; BP –1; GH 1; VT 0; SF 2; RE 3; MH 1	All physical scales declined in participants reporting a MVC, while mental health dimensions increased. Patients who did not have any MVC had significantly higher HRQL than those who suffered a MVC on RP, BP, GH, RE, MH, MCS and PCS.
Alghnam, 2014, US [18] (MVC)	SF-12	*MVC* PCS 50; MCS 49 *No MVC* PCS 50; MCS 51	*MVC* PCS 47; MCS 49 *No MVC* PCS 50; MCS 51	*MVC* PCS –3; MCS 0 *No MVC* PCS 0; MCS 0	Similar baseline PCS in MVC and no MVC. Significant lower baseline MCS in MVC than no MVC.
Ottosson, 2007, Sweden [45] (Muscosk)	SF-36**	Recovered 1m: PF 93; RP 93; BP 92; GH 85; VT 75; SF 92; RE 94; MH 85 Not recovered: PF 85; RP 83; BP 80; GH 83; VT 73; SF 91; RE 83; MH 85	1m: *Rec 1m* PF 95; RP 93; BP 89; GH 85; VT 73; SF 95; RE 93; MH 85 *No rec* PF 63; RP 30; BP 43; GH 68; VT 45; SF 68; RE 85; MH 67 6m: *No rec* PF 70; RP 45; BP 53; GH 65; VT 51; SF 76; RE 60; MH 70	1m: *Rec 1m* PF 2; RP 0; BP –3; GH 0; VT –2; SF 3; RE –1; MH 0 *No rec* PF –22; RP –53; BP –37; GH –15; VT –28; SF –23; RE –30; MH –18 6m: *No rec* PF –15; RP –38; BP –27; GH –18; VT –22; SF –15; RE –23; MH –15	Pre-injury HRQL was comparable to Swedish norm population. At 1m patients who reported no recovery had significantly lower scores on all domains, compared to those reporting recovery.
Andrew, 2012, Australia [26] (Ortho)	SF-36	PCS 59 (4); MCS 55 (7) PF 57 (3); RP 56 (4); BP 60 (6); GH 60 (6); VT 60 (8); SF 56 (5); RE 55 (5); MH 55 (7)	PCS 52 (10); MCS 53 (10) PF 52 (8); RP 50 (10); BP 52 (10); GH 55 (10); VT 52 (10); SF 52 (10); RE 53 (7); MH 52 (9)	PCS –7; MCS –2 PF –5; RP –6; BP –7; GH –5; VT –7; SF –4; RE –2; MH –3	Significant reductions in all SF-36 subscale scores, with RP and BP reporting the most reductions.
Gabbe, 2007, Australia [8] (Ortho)	SF-12	PCS 51; Men 53; Women 48 MCS 55; Men 55; Women 54	NA		Significantly higher PCS (stratified men 25-54y) and MCS (men 18-24y, women 18-24y, 25-34y or 45-54y) than Australian norms.
Dvorak, 2005, Canada [33] (Spine)	SF-36	PCS 49 (13) MCS 52 (10)	PCS 43 (13) MCS 49 (14)	PCS –6 MCS –3	No significant differences between patients' recalled PCS and MCS and Canadian norms.
Hagino, 2009, Japan [37] (Spine)	EQ-5D	0.88 (0.17)	2w: 0.53 (0.17) 3m: 0.76 (0.18) 6m: 0.75 (0.16) 12m: 0.84 (0.17)	2w: –0.35 3m: –0.12 6m: –0.13 12m: –0.04	Hip fracture had lower pre-injury HRQL than wrist (significant) or vertebral fracture. Scores at 6m were significantly lower than pre-injury. After 1y, scores were not significantly different from pre-fracture values.

Table 4.2 (continued) **(Bold author names are studies of children; *Studies in bold and italics prospectively measured pre-injury HRQL*)**

Author, year, country	Instrument	Pre-injury HRQL	Post-injury HRQL	Change *Post-injury vs pre-injury*	Findings
Fauerbach, 1999, US [20] (Burn)	SF-36	*PTD* PF 87 (24); RP 85 (34); BP 87 (28); GH 77 (25); VT 66 (20); SF 88 (24); RE 85 (32); MH 77 (14) *No PTD* PF: 92 (20); RP 91 (22); BP 81 (30); GH 87 (11); VT: 73 (20); SF 94 (19); RE 97 (16); MH 88 (9)	2m: *PTD* PF 66 (27); RP 29 (39); BP 41 (19); GH 68 (24); VT 52 (24); SF 75 (30); RE 76 (38); MH 67 (22) *No PTD* PF 85 (22); RP 56 (49); BP 47 (21); GH 83 (15); VT 69 (23); SF 92 (18); RE 92 (34); MH 87 (12)	2m: *PTD* PF –21; RP –56; BP –46; GH –9; VT –14; SF –13; RE –9; MH –10 *No PTD* PF –7; RP –35; BP –34; GH –4; VT –4; SF –2; RE –5; MH –1	Higher pre-injury HRQL in PTD (BP) and non-PTD (MH, VT, RE, SF, GH) than US norms.
Wasiak, 2014, Australia [28] (Burn)	SF-36	PCS 56 (9) MCS 52 (12)	PCS 52 (13) MCS 52 (11)	PCS –4 (1) MCS 0 (1)	Pre-burn PCS was higher than Australian norms, MCS was comparable. HRQL at 12m were consistent with the Australian norms. Significant lower PCS at 12m compared with pre-injury.
Greenspan, 2002, US [21] (Gunshot)	SF-36	PF 96 (14); RP 89 (29); BP 93 (19); GH 85 (20); VT 70 (21); SF 86 (27); RE 83 (34); MH 76 (24)	8m: PF 71 (28); RP 43 (42); BP 63 (32); GH 58 (27); VT 52 (28); SF 67 (31); RE 64 (43); MH 68 (25)	PF –25; RP –46; BP –30; GH –27; VT –18; SF –19; RE –19; MH –8	Pre-injury scores were similar to population norms, except for PF and GH (higher). Significant declines in PCS and MCS, and across all domains compared to pre-injury (especially PF, RP, BP, GH, and VT).

* Significant change between pre- and post-injury HRQL scores.
** Scores obtained from graph(s) (not reported in text or tables).

Change between pre- and post-injury HRQL

Most studies used a longitudinal design (n=23) with multiple follow-up measurements over time (n=18), often measuring post-injury HRQL at 3 months, 6 months and/or 12 months. All studies showed a decrease in post-injury HRQL compared to their pre-injury levels of HRQL (Table 4.2). Looking at the EQ-5D, only one out of the 12 studies showed full recovery to pre-injury HRQL at one year after the injury,[38] while the other studies still reported reduced levels of HRQL post-injury. Looking at the SF-36 and SF-12, injuries showed to have the highest impact on the physical component of HRQL (reduction in PCS with 15 to 30 points from pre-injury to first post-injury assessment) compared to the mental component of HRQL (reduction in MCS with 5 to 9 points).[23,27,29,32] At the final follow-up measurement, both prospective studies showed almost full recovery to pre-injury HRQL levels on the PCS and full recovery on the MCS,[18,46] while only one retrospective study showed such recovery on the PCS[54] or MCS.[28]

4.4 DISCUSSION

This systematic review summarised the methods that were used to assess pre-injury health status and to estimate the change from pre- to post-injury HRQL. All but two of the 31 studies in our review used retrospective assessment (recall) to assess pre-injury HRQL. The studies most often applied the SF-36, followed by the EQ-5D or SF-12, by means of questionnaires or face-to-face interviews. Recalled pre-injury HRQL scores consistently exceeded general population norms, except in a limited number of studies on injury types of higher severity (e.g. traumatic brain injury and hip fractures). All studies reported reduced post-injury HRQL compared to pre-injury HRQL. Both prospective studies reported that patients had recovered to their pre-injury levels of physical and mental health, while in all but one retrospective study patients had not returned to their reported pre-injury levels of HRQL, even years after the injury.

Prospective assessment is the preferred method to determine pre-injury HRQL as it is not subject to bias that may occur due to experiencing an injury. In our review, only two out of the 31 studies used prospective assessment of pre-injury HRQL. These studies used longitudinal data from the Medical Expenditure Panel Survey (MEPS) among the US general population[18] and the Seguimiento Universidad de Navarra (SUN) cohort comprising university graduates in Navarra, Spain.[46] Both prospective studies reported lowest pre-injury mental health on the SF-36 (MCS 47)[46] as well as SF-12 (MCS 49)[18] of all studies in our review, which otherwise all used retrospective assessment.

Our review shows that the retrospectively assessed pre-injury HRQL systematically differed from the age- and gender-adjusted norms we calculated based on population data on the EQ-5D, SF-36, and SF-12. Despite the use of different HRQL instruments, recalled pre-injury HRQL scores in our review consistently exceeded these adjusted population norms. An exception to this were samples including patients with a hip fracture,[30,35,36,39] motor vehicle injury,[18,46] vertebral fracture[33] or TBI,[27] that reported poorer pre-injury HRQL than our calculated adjusted norms. These injury patients are likely to be less healthy than their counterparts,[18,27,44,46] in terms of socio-economic status,[18] comorbidity[18,55] or frailty and older age.[12,55,56]

The difference between retrospectively assessed pre-injury HRQL and population norm scores might be caused by several reasons.

Recall bias may have influenced the outcomes of the retrospective assessment, as patients may have remembered their pre-injury HRQL differently than it actually was.[1,57,58] Patients may, for example, have overestimated their health status before the injury, resulting in higher recalled pre-injury HRQL than seen in the general population.

Response shift might have occurred, as patients' perception of HRQL may have changed due to the injury and a change in health.[3] After having had experience with poor HRQL, patients may have inflated the rating of their health status before the injury.[59]

Nevertheless, some researchers argue for the use of retrospective assessment of pre-injury HRQL, as this method applies one internal standard of HRQL values (reference point) in the assessment of both pre-injury HRQL and post-injury HRQL.[3,59] According to them, such a reference point is essential for the interpretation of the change from pre- to post-injury HRQL, since patients may have changed their judgement of HRQL due to new insights since the injury (e.g. although a patient has a serious injury, he/she has seen others who are far worse off), or patients have become used to their new health state. However, both recall bias and response shift might result in an overestimation of the pre-injury HRQL by patients. This is underpinned by our finding that, even years after the injury, in all but one retrospective study patients had not returned to their reported levels of pre-injury PCS and MCS, while recovery to pre-injury HRQL levels was seen in both prospective studies.

Moreover, selection bias may have threatened the validity of the findings from the studies included in our review, as the study populations were often not randomly selected from the injury population for which the findings are reported.[60] For example, studies had excluded patients with pre-existing morbidities (e.g. physical illness, cognitive impairment), as it was anticipated that these patients would be difficult to follow-up. Exclusion of patients with impairments before the injury may have increased the overall pre-injury HRQL scores of these study samples, as healthier participants were recruited.

In contrast, attrition bias may have decreased the overall pre-injury HRQL scores measured in the studies, as a higher proportion of the non-participants were less educated,[26] cognitive impaired,[38] victim of intentional injury,[5] shorter hospitalised[21] and had lower injury severity,[28,29,44] less pain,[34] better mental health.[34] These factors are all expected to be associated with better HRQL and incorporation of these patients would have resulted in higher pre-injury HRQL scores. Additionally, pre-injury HRQL levels may have increased after loss of follow-up, resulting in higher pre-injury HRQL in the final study sample with complete response compared to the eligible study sample.[32]

Finally, retrospectively assessed pre-injury HRQL scores may differ from the population norms as injury populations may differ from the general population. The findings of the retrospective assessments (recall) in our review suggest that injured populations are generally healthier than the general population. Previous studies reported that, as injured populations might be healthier, they are more likely to participate in activities, exposing them to a higher risk of injuries.[8] However, the comparisons of injury patients with matched controls in our review showed injury patients to be less healthy than their counterparts, as they reported significantly lower pre-injury mental health than controls[18,27,44,46] and lower scores across all HRQL domains.[46] Previous research showed that injury patients had a higher occurrence of comorbidity, higher admission rates to the hospital, higher health service utilisation and a lower socio-economic status prior to their injury in comparison to uninjured people.[4,18] It is argued that the general population has not been exposed to a similar injury experience as the injury population,

which emphasises the use of retrospective assessments over the application of general population norms to estimate the impact of injury on HRQL.[49]

Strengths and limitations

Our review included studies on the pre-injury HRQL from children, adolescents and adult patients, with various injury types, using a range of HRQL instruments. Moreover, this review compared the reported pre-injury HRQL scores with general population norms, calculated for each study based on the reported mean age and gender distribution of the study sample, to identify bias that may occur from the different methods to asses pre-injury HRQL.

There are limitations to this review that need to be addressed. First, there was no restriction in the methods of patient selection used in the studies. Therefore, the studies in this review included samples retrieved from a variety of injury settings (e.g. hospital or outpatient programmes). Their conclusion may not be applicable to injury patients from other injury settings. However, most studies selected their patients during or after treatment in a (pediatric) hospital or specialised treatment center, which may enhance the generalisability of their results to patient populations with similar case-mix.

Second, the review included studies with patient samples from a broad range of injury types and injury severity levels, which may have complicated the comparability of the results between studies. Nonetheless, this way we were able to provide a full oversight of the pre-injury health status of injury patients and the differences in pre-injury HRQL between injury types.

In addition, there are limitations to the studies included in our review. First, more than half of the included studies had difficulties in recruiting research participants, as patients often could not be contacted, had died, refused to participate, or did/could not complete questionnaires. The studies often reported limited generalisability of their results due to differences between the eligible patients and study participants, loss to follow-up, their limited number of subjects, and recruitment of participants from a single center.

In some studies pre-injury HRQL was assessed after a long period of time since the injury, for example several months up to years after the injury.[7,42,44] This longer time frame may have increased the recalled pre-injury HRQL scores,[31] as these studies also reported the highest pre-injury HRQL scores on the EQ-5D (0.94-0.99) compared to the studies that used shorter time frames. However, these three studies assessed the HRQL of a relatively young injury population. Moreover, no differences were found between the time frame and pre-injury HRQL on the SF-36 and SF-12.

Finally, unfortunately not all studies reported the HRQL scores in the text or tables (e.g. only in graphs). After contacting the authors, in three publications HRQL scores had to be manually obtained from the graphs presented in the article.[36,40,45] This may have resulted in some small differences in the levels of pre- and/or post-injury HRQL.

Recommendations for future research

Our review clearly showed that recalled pre-injury HRQL systematically exceeded population norms. These differences in pre-injury HRQL may generate different estimates of the change in HRQL from pre- to post-injury due to an injury.

Researchers should use prospectively derived pre-injury HRQL scores wherever possible to estimate the impact of injury on HRQL. If it is not feasible to prospectively assess the pre-injury health status of

trauma patients, researchers should be aware of the bias that may arise when pre-injury HRQL is assessed retrospectively or when population norms are applied. Overall, more research is needed to examine the effect of recall bias and response shift on the reported levels of pre-injury HRQL among trauma patients, in which different methods to assess pre-injury HRQL are compared and within-study comparisons between reported pre-injury HRQL and population norms are made.

In general, when assessing pre-injury HRQL, researchers should carefully consider and specify the timing of the assessment of pre-injury HRQL and the period of the pre-injury assessment. The time period shows to be one of the essential factors influencing patient recall, as recall bias is generally worse when asking for a recall over longer periods.[61] A short time frame within the injury and retrospective assessment of pre-injury HRQL may increase recall and may increase the correlation between pre- and post-injury measures.[31] This implies that pre-injury HRQL should be assessed as soon as possible after the injury, preferably within the first week after the injury.[62] Whether or not the measurement of pre-injury HRQL is the primary purpose of studies, publications on the measurement of HRQL should include information on the applied methods to measure HRQL.

Levels of pre-injury HRQL also may have been influenced by the use of telephone interviews. In our review, the highest or one of the highest pre-injury HRQL on the EQ-5D,[42] SF-36 (PCS and MCS)[26] or SF-12[43] were reported by studies that had conducted telephone interviews to assess the pre-injury levels of HRQL. Previous research indicated that telephone-administered questionnaires provide higher HRQL scores than self-administered questionnaires.[63-65] Preferably, the same method should be used for the assessment of both pre-injury and post-injury HRQL throughout the study, at all post-injury HRQL measurements and among all individuals.

Researchers should choose a validated HRQL instrument that showed good performance in the type of injury under study, and that is sensitive to changes in HRQL and differentiates well between health states. In order to assess the change from pre- to post-injury HRQL, the same HRQL instrument should be applied throughout the study. Preferably, a HRQL instrument should be chosen for which national age- and gender-adjusted population norms are available. In order to enable comparison of the impact of injuries on HRQL between studies, injury types and other diseases, it is recommended to report the pre- and post-injury HRQL scores for specific age and sex groups, which correspond to the age and sex distribution of the norm groups for the applied instrument.

Finally, to examine the change in HRQL due to the injury, a longitudinal design is recommended with multiple follow-up measurements over time (e.g. at 1–3 months, 3–6 months, and 6–24 months post-injury).[62]

Conclusions

So far, primarily retrospective research has been conducted to assess pre-injury HRQL. This research shows consistently higher pre-injury HRQL scores than population norms and a recovery that lags behind that of prospective assessments, implying a systematic overestimation of the change in HRQL from pre- to post-injury due to an injury. More prospective research is necessary to examine the effect of recall bias and response shift. Researchers should be aware of the bias that may arise when pre-injury HRQL is assessed retrospectively or when population norms are applied, and should use prospectively derived HRQL scores wherever possible to estimate the impact of injury on HRQL.

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Chapter 5

The future of trauma registries: focus on the consequences of non-fatal injuries

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Submitted

ABSTRACT

Background Trauma-related mortality has rapidly dropped over the past decades. Most trauma registries document information on the acute phase of hospital care and in-hospital mortality, but not on the consequences of non-fatal trauma. This pilot provides insight into the opportunities of expanding the trauma registry with extensive follow-up data. The aim of our study was to assess the hospitalisation, health care costs, productivity costs and health-related quality of life (HRQL) by injury type and injury severity, and to identify injury types with highest impact.

Methods We linked data of trauma patients (aged 16+) hospitalised between 2007–2008 from the Dutch National Injury Surveillance System, Trauma Registry, and patient follow-up survey. Socio-demographic and trauma-related characteristics, hospitalisation, health care costs (in-hospital and after discharge), return to work and associated productivity costs, and HRQL (EQ-5D) were analyzed by injury type and injury severity score (ISS).

Results Injury patients with ISS 9–15 (moderate) showed higher mean costs than patients with ISS≥16 (severe), mainly due to their longer admission to a nursing home or revalidation center and high need for home care; health care costs (€13,440/patient, IQR €6,030 to €22,020 vs €8,800, IQR €6,710 to €9,710: p=0.001), productivity costs (€23,720/patient, IQR €16,800 to €32,670 vs €20,920, IQR €17,900 to €24,960: not significant). Injury patients with ISS 9–15 also reported poor HRQL at 2.5 months post-injury (EQ-5D 0.56), comparable to that of patients with ISS 25+ (EQ-5D 0.49). Isolated hip fractures (100% ISS<16) were among the injury types with the highest mean health care costs (€19,740/patient vs €8,630/patient in other injuries, p<0.001), with patients reporting poor HRQL (EQ-5D 0.48).

Conclusions The integrative approach of assessing the consequences of non-fatal trauma revealed that injury patients with ISS 9–15 had one of the highest impact on both individuals and society. Our findings emphasise the importance of documenting the consequences of all hospitalised trauma cases in trauma registries and incorporating these outcomes in the evaluation of trauma care to obtain insight into the quality of survival after trauma and to compare the consequences of trauma across patient subgroups.

5.1 INTRODUCTION

Injuries are a major public health problem, yearly leading to more than 5.7 million hospitalisations and 230,000 deaths in Europe,[1] and over 560,000 deaths in high-income countries.[2] In order to evaluate and improve the care delivered to individual trauma patients, the results of trauma care are documented in trauma registries.[3] Trauma registries generally contain information on patient demographics, pre-hospital care and transport, emergency department and in-hospital treatment, diagnosis, in-hospital mortality, and patient discharge destination.[3] These databases generally focus on severe trauma (e.g. hospitalised trauma patients, or only those with severe injuries).[3]

Trauma registries were initially developed to reduce preventable mortality. Therefore, they generally document information on the acute phase of hospital care and focus on mortality as main patient outcome. In order to compare mortality rates between trauma groups, risk adjustment models are used to adjust for the differences in baseline risk of death between trauma patients. A key element in these risk adjustment models is the severity of the injury, which is often measured with the Injury Severity Score (ISS).[4]

During the last decades, however, trauma-related mortality has rapidly dropped due to advances in trauma care,[5] amongst others. As more and more trauma patients survive, mortality does no longer provide the true quality indicator of trauma systems. Although survival after injury may further improve, largest gains will come from improved outcome of survivors.[6] Therefore, there is an increased interest in other trauma outcomes such as the costs of medical care use, productivity costs due to the absence from work, and the health-related-quality of life (HRQL) of injury survivors. Nevertheless, trauma registries generally provide very limited information on the post-hospital care of patients other than their discharge destination.[3]

Moreover, although the injury severity scoring tools like the ISS were developed to predict mortality after injury,[7] many studies still use these threat-to-life measures in their assessment of the long-term consequences after injury, whether as threshold for inclusion (e.g. ISS>15) or as predictor of outcome.[8] Assessment of the outcomes of trauma other than mortality is important to obtain insight into the recovery of patients following trauma, the quality of survival after trauma, and to compare the (long-term) consequences of trauma across patient subgroups. The current study therefore provides insight into the opportunities of expanding the trauma registry with follow-up data on the long-term consequences of non-fatal injuries among hospitalised trauma patients. In a pilot, we therefore linked data of adult trauma patients hospitalised between 2007–2008 from the Dutch National Injury Surveillance System, the Dutch Trauma Registry, and a patient follow-up survey.

We aim to 1) assess the hospitalisation, health care costs, productivity costs and HRQL by injury type and ISS, and 2) identify injury types with highest impact.

5.2 METHODS

Study design

In a pilot, we linked data from the Dutch National Injury Surveillance System (LIS), the Trauma Registry (TR) of the Regional Emergency Health care Network Nijmegen (AZO, The Netherlands), and a patient follow-up survey of the LIS (Figure 5.1).[9,10]

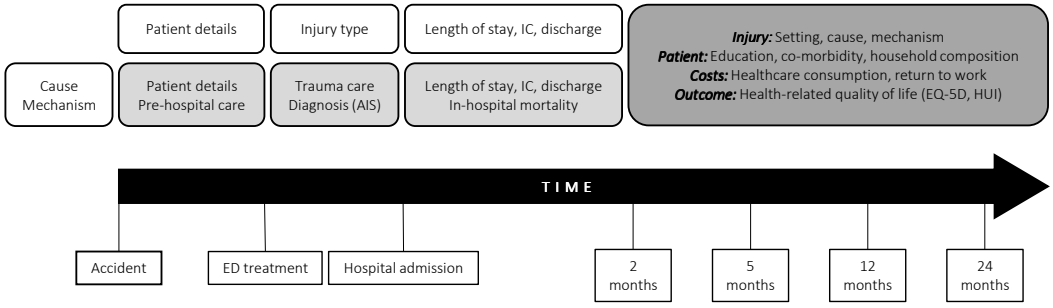
The LIS is an ongoing monitoring system which focuses on injury prevention and records data of all injured patients who attend the emergency department (ED). It is based upon the registration of 13 hospitals throughout the Netherlands (12–15% coverage), and registers detailed information on the cause and mechanism of injuries, patient characteristics, type of injury, and hospitalisation.

The TR focuses on the quality of trauma care and provides data on the (pre)hospital treatment of hospitalised trauma patients and the epidemiology of the trauma population. It is an important tool for trauma evaluation and improvement of trauma care. The TR contains detailed information on trauma patients admitted to the hospital within 48 hours after the ED treatment and registers their Abbreviated Injury Scale (AIS) revised 1990, update 98 (AIS-98),[11] length of stay in hospital, admission to intensive care, and in-hospital mortality.

During the period February 1, 2007 to January 31, 2008 a patient follow-up survey was sent to a random sample of patients registered in LIS,[9] to collect information on socio-demographics and data on the consequences of trauma in terms of health care consumption and associated health care costs, return to work and associated productivity costs, and the HRQL of patients at 2.5 months after trauma.

Four hospitals of the TR of AZO also participated in the LIS: Radboud university medical center, Nijmegen (Level I trauma center, 950 beds); Canisius-Wilhelmina hospital, Nijmegen (Level II, 650 beds); Gelderse Vallei hospital, Ede (Level II, 510 beds); Maasziekenhuis Pantein hospital, Boxmeer hospital (Level III, 190 beds).

Figure 5.1 Data in the national Injury Surveillance System, the Trauma Registry, and the patient follow-up survey 2007–2008



National Injury Surveillance System: information used on patient details, injury type, length of stay, intensive care (IC).
Trauma Registry: information used on injury severity (ISS).
Patient follow-up survey: information used on health care consumption, return to work, HRQL (EQ-5D).

Study participants

This pilot included data of hospitalised patients aged 16+ years, who were injured due to unintentional injury or interpersonal violence and were registered in both LIS and the TR, and responded to the 2.5 month patient follow-up survey.

Linkage of data

Data of the TR and patient follow-up survey (respondents of first questionnaire) was linked to the LIS data, using data that was not reducible to individual patients (e.g. date of arrival at ED, patient's age in months, patient's sex and detailed cause-of-injury. Informed consent was obtained from the patients

participating in the patient follow-up survey. Ethical approval for the linkage of data was obtained from the ethical committee of the Radboudumc.

Injury severity

Information on injury severity was obtained from the TR. Abbreviated Injury Scale (AIS) codes were assigned to all injuries by a trained staff member using information from patient medical records. The AIS describes the type of injury, affected body region, and injury severity in a 7-digit code for each injury the patient has sustained.[12] The AIS ranges from 1 (minor injury) to 6 (nonsurvivable).[11] The AIS scores of patients with multiple injuries were combined into a single score, with use of the maximum AIS (MAIS)[13] and Injury Severity Score (ISS).[7] The MAIS was computed as the highest AIS score off all injuries.[13] In case of multiple injuries with the same AIS, an algorithm was applied, giving priority to head injuries, followed by injuries to the spine, extremity, and thorax/abdomen.[13] Like the AIS, the MAIS ranges from 1 (minor injury) to 6 (nonsurvivable). Additionally, the ISS was computed by allocating AIS scores to six body regions and taking the sum of squares for the highest AIS score in each of the three most severely injured body regions.[7] The ISS ranges from 1 (minor injury) to 75 (nonsurvivable). The ISS was categorised as mild (<9), moderate (9–15), severe (16–24), and profound (25+).[14]

Injury type

The type of injury was obtained from LIS in which up to three injuries can be recorded. In case of multiple injuries, like with the MAIS, the most severe injury was determined by giving priority to head injuries, followed by injuries to the spine, extremity, and thorax/abdomen.[13] Injuries were classified into 8 main injury groups: head injury (including injuries to face/neck), spine injury, thorax/abdomen injury, upper extremity injury, hip fracture (AIS 8518083 (2%), 8518103 (19%), and 8518123 (79%)),[15] lower extremity injury (excluding hip fracture), superficial injury (including open wound), and other injury (burns, unspecified).

Health care and productivity costs

Information on the health care consumption was obtained from LIS (short-term) and the patient follow-up survey (long-term). Short- and long-term direct health care costs and indirect productivity costs of injuries were calculated with use of the incidence-based Dutch Burden of Injury Model.[16,17] This prediction model is based on the incidence of injuries treated in emergency departments, as recorded in LIS. The prediction model is used to calculate the health care consumption within the hospital and after discharge, and related costs for predefined patient groups that are homogenous in terms of health service use (e.g. age, gender, injury type/location and injury severity/mechanism).[17] Data on health care consumption (in-hospital and after discharge) was obtained from LIS, the National Hospital Discharge Registry, rehabilitation centers (LIVRE), nursing homes (SIVIS), and a patient follow-up survey conducted in 2007–2008.[9,10,16,17]

The length of stay in hospital (LOS) and admission to the Intensive Care (IC) were determined using the LIS database (missing values were obtained from the TR).

Direct costs of all health care consumption within the hospital and after discharge were computed by multiplying incidence by health care volumes (e.g. length of stay) and unit costs (e.g. costs per day in

hospital). Unit costs were estimated according to national guidelines for health care costing[18] reflecting real resource use (Appendix Table 5.A).
Indirect productivity costs were calculated for all hospitalised trauma patients in the working population (aged 15 to 64 years), using the same prediction model based on information on return to work from the patient follow-up questionnaire.[9,10,16] People with paid jobs were asked questions related to work absence, absence duration, and return to work, which were strongly related to the 'usual activities' dimension of the EQ-5D but are more detailed.[19]

Health-related quality of life

HRQL was measured 2.5 months after trauma using the EQ-5D by means of the patient follow-up survey.[9,10] The EQ-5D defines health along five domains (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) with each three levels of severity (no/moderate/extreme problems).[20] EQ-5D summary scores, ranging from 0 (dead) to 1 (full health), were calculated with the Dutch tariff based on time-trade-off preferences from the general Dutch population.[21] The EQ-5D is a feasible and valid instrument for the measurement of functioning in trauma patients, and is well able to describe a heterogeneous trauma population and to discriminate among specific injuries.[10,19,22,23]

Statistical analysis

Analysis of variance (ANOVA) and Chi-square statistics (dichotomous variables) were used for between-group comparisons. A value of $p<0.05$ was used to determine statistical significance.
Linear regression analysis was used to assess which factors were predictors of HRQL (EQ-5D) at 2.5 months after trauma. We included the socio-demographic factors gender (male/female), age (continuous), a dummy-coded variable for low (reference)/middle/higher education, household composition (alone/not alone), and comorbidity (continuous), and the trauma-related characteristics injury type (head yes/no, etc.), and ISS (continuous). Variables associated with outcome ($p<0.20$ in univariable analysis) were included in stepwise multivariable linear regression analyses.[24,25] All statistical analyses were carried out using the statistical package SPSS for Windows, version 21 (IBM SPSS Statistics, SPSS Inc, Chicago, IL).

5.3 RESULTS

Study population

Linkage of data resulted in 1,995 hospitalised patients treated between 2007 and 2008 who were registered in both the LIS and TR (Appendix Table 5.B). Of these patients, 891 (45%) were invited for participation in a patient follow-up survey. In total, 411 (46%) patients responded to the 2.5 month follow-up survey, and formed the basis of our pilot. No significant differences on socio-demographic characteristics and injury characteristics were found between responders and non-responders to the follow-up survey.
The 411 participants in our pilot were on average 57 years old (SD 21.6), and 48% were men (Table 5.1). About one third of the patients had one or more comorbid disease(s) (39%). Frequently reported causes of injury were home and leisure accidents (53%) or traffic accidents (30%). Most patients had a single injury (68%), with a moderate injury severity (43% MAIS3/ISS9) with an average ISS of 8.7 (SD 7.2). Lower

extremity injury (excluding hip fractures; n=126, 31%) was the most common injury type, followed by an upper extremity injury (16%), head injury (16%), or hip fracture (15%).

Table 5.1 Patient demographics, injury mechanism and injury severity by injury type (%)

	Total	Head	Spine	Thorax/ Abdomen	Upper Extremity	Hip Fracture	Lower Extremity	Superficial	Other
N (%)	411 (100)	64 (15.6)	26 (6.3)	31 (7.5)	66 (16.1)	61 (14.8)	126 (30.7)	30 (7.3)	7 (1.7)
Patient demographics									
Age at injury (mean, SD)	57 (21.6)	50.8 (21.3)	60.4 (21.2)	47.8 (22.5)	55.9 (20.3)	76.0 (12.6)	55.2 (21.4)	56.3 (20.3)	47.4 (22.5)
Sex (male)	48.4	54.7	42.3	58.1	50.0	26.2	51.6	46.7	100
Comorbid diseases									
None	61.1	73.4	50.0	71.0	65.2	37.7	63.5	56.7	85.7
1	24.3	15.6	38.5	19.4	13.6	36.1	26.2	30.0	14.3
≥2	14.6	10.9	11.5	9.7	21.2	26.2	10.3	13.3	0.0
Injury mechanism									
Home and leisure	52.6	39.1	65.4	41.9	48.5	78.7	54.0	33.3	42.9
Traffic	30.2	42.2	23.1	35.5	33.3	18.0	22.2	56.7	28.6
Occupational	4.9	6.3	3.8	0.0	7.6	0.0	6.3	6.7	0.0
Sport	10.5	6.3	7.7	12.9	10.6	3.3	16.7	3.3	28.6
Intentional	81.9	6.3	0.0	9.7	0.0	0.0	0.8	0.0	0.0
Injury severity									
Multiple injury									
1	67.5	26.6	73.1	58.1	50.0	96.7	81.7	76.7	85.7
2	19.1	32.8	23.1	19.4	30.3	3.3	13.5	16.7	14.3
≥3	13.4	40.6	3.8	22.6	19.7	0.0	(4.8	6.7	0.0
MAIS (median, IQR)	3 (2–3)	3 (2–4)	2 (2–2)	2 (2–3)	3 (2–3)	3 (3–3)	2 (2–3)	2 (1–2.5)	2.5 (1.3–3)
ISS (median, IQR)	9 (4–9)	9 (5–17)	4 (4–8)	9 (4–16)	9 (4–10)	9 (9–9)	5 (4–9)	4 (1–7)	6.5 (1.8–15)
ISS 1–8	45.3	45.5	79.2	45.2	41.0	1.7	54.1	75.9	50.0
ISS 9–15	45.3	25.5	16.7	25.8	55.7	98.3	40.2	24.1	25.0
ISS 16–24	4.9	9.1	0.0	22.6	3.3	0.0	3.3	0.0	25.0
ISS 25+	4.4	20.0	4.2	6.5	0.0	0.0	2.5	0.0	0.0
Unknown (N)	*27*	*9*	*2*	*0*	*5*	*3*	*4*	*1*	*3*

IQR: interquartile range.
Head: including head, face and neck; Lower extremity injury: excluding hip fractures; Superficial injury: open wounds, superficial injuries; Other injury: burns, unspecified.

Patient characteristics by injury type

Patients with a hip fracture were more likely to be older than patients with other injuries (mean age 76 vs 54 years, F=60.6, df=1, p<0.001), female (74% vs 48%, Chi2=14.1, p<0.001), live alone (58% vs 28%, Chi2=19.0, p<0.001), and have comorbidity (62% vs 35%, Chi2=16.4, p<0.001).

In contrast, patients with thorax/abdomen injury were more likely to be younger (mean age 48 vs 58 years in other injuries, F=6.8, df=1, p=0.010), male (58% vs 48%), without comorbidity (71% vs 60%), and to have multiple injuries (42% vs 32%), though the latter differences were not significant.

Patients with head injuries were assigned highest injury severity (ISS median 9, interquartile range (IQR) 5–17) followed by thorax/abdomen injuries (median 9, IQR 4–16), whereas lowest injury severity was assigned to patients with superficial injuries (median 4, IQR 1–7).

Consequences of non-fatal trauma

Hospitalisation

Highest mean length of stay (LOS) in hospital was documented in patients with skull-brain injuries (on average 20 days), a fracture of the upper leg (12 days), or a hip fracture (12 days, Table 5.2). Lowest mean LOS was seen in patients with hand/finger injury (on average 1–2 days), a concussion (2 days), a luxation/distortion of the knee, ankle or foot (2–3 days), or superficial injuries (3–4 days).

IC admission was highest among patients with a head injury (28%), especially those with a skull-brain injury (n=18, 62% admitted, mean ISS 23.5, SD 15.1), followed by thorax/abdomen injuries (19%).

Health care and productivity costs

Expanding the data of the TR with follow-up data from the patient survey indicated that highest mean direct health care costs were seen in patients with a fracture of the upper leg (on average €20,800, interquartile range (IQR) €12,630 to €25,150) and those with a hip fracture (€19,740, IQR €15,650 to €23,800 vs €8,630/patient, IQR €4,380 to €10,880 in other injuries: F=136.6, df=1, p<0.001, Table 5.2). These patients with an upper leg fracture or hip fracture showed a higher need for home care in the first 2.5 months post-injury than other injuries (on average 1.9 weeks vs 1 week, F=8.9, df=1, p=0.003; for on average 2 hours/week vs 0.8 h/w, F=9.8, df=1, p=0.002).

Although the incidence of patients with an isolated hip fracture in the working population was low (n=10), these patients lost on average the highest number of work days (on average 107 days, (SD 2.8) vs 70 days (SD 20.2) in other injuries) and accordingly showed highest mean productivity costs (€35,380, IQR €32,180 to €38,910 vs €20,860/patient, IQR €15,870 to €26,270 in other injuries: F=28.0, df=1, p<0.001). Overall, hip fractures accounted for 15% of our hospitalised study sample but accounted for 28% of the total direct health care costs and 38% of the total productivity costs.

Lower extremity injury (excluding hip fractures) accounted for the highest total direct health care costs (€1.2 million, 32% of total direct costs), mainly due to their high incidence (31% of our study sample).

Highest mean total costs per patient were seen in patients with a fracture to the knee/lower leg (on average €30,290, IQR €20,540 to €39,800), foot/toes (€29,790, IQR €20,670 to € 41,830), upper leg (€28,300, IQR €23,660 to €27,000), spine (€27,580, IQR €18,620 to €38,020) or pelvis (€27,580, IQR €18,640 to €38,240), followed by hip fractures (€26,540, IQR €22,020 to €26,230). Overall, total direct and indirect costs were the highest in hip fractures (€1.4 million) and other lower extremity injuries (€2.9 million), together accounting for 52% of the total costs due to injuries (compared to 46% of the study sample).

Health-related quality of life (HRQL)

There was a wide variety of EQ-5D scores per injury severity level (Figure 5.2), indicating low injury severity but poor HRQL and vice versa, especially in patients with ISS 9–15. Patients with ISS 9–15 reported lower HRQL (EQ-5D 0.56) than patients with more severe injuries coded with ISS 16–24 (EQ-5D 0.63). Respondents with ISS<16 (indicating minor to moderate injury severity) but poor HRQL (EQ-5D<0.30, n=44) often involved females (84%), aged 60+ (77%), diagnosed with a hip fracture (27%) or other lower extremity injury (30%). Univariable regression revealed age, gender, education, comorbidity, living alone, diagnosis of hip fracture, and ISS to be significantly related to HRQL (all p<0.002).

Table 5.2 Hospitalisation, costs and HRQL by injury type

	Total	Head	Spine	Thorax/ Abdomen	Upper Extremity	Hip Fracture	Lower Extremity	Superficial	Other
N (%)	411 (100)	64 (15.6)	26 (6.3)	31 (7.5)	66 (16.1)	61 (14.8)	126 (30.7)	30 (7.3)	7 (1.7)
Hospitalisation									
Length of stay (mean, SD)	7.8 (10.1)	10.4 (14.2)	5.4 (3.9)	5.4 (3.7)	5.6 (6.8)	11.6 (9.6)	8.0 (11.6)	3.7 (3.2)	4.1 (3.6)
1–3 days	42.9	50.8	30.8	37.9	65.0	3.4	41.8	73.3	71.4
4–7 days	25.0	12.7	50.0	37.9	10.0	33.9	29.5	13.3	14.3
8–14 days	20.2	17.5	11.5	24.1	15.0	39.0	18.9	10.0	14.3
>14 days	11.9	19.0	7.7	0.0	10.0	23.7	9.8	3.3	0.0
IC admission	6.6	28.1	0.0	19.4	1.5	1.6	0.8	0.0	0.0
Costs (€)									
Health care costs									
Total costs	3,675,800	367,000	249,700	224,700	449,600	1,026,300	1,181,500	140,200	36,800
Costs/patient (mean)	10,240	6,330	11,890	8,640	7,620	19,740	10,840	5,190	5,250
IQR	4,630–14,590	3,080–8,500	5,760–18,620	6,650–9,390	3,970–12,280	15,650–23,800	4,650–14,590	2,470–5,440	2,920–8,450
Productivity costs									
Total costs	4,401,100	746,900	329,500	314,600	733,500	353,800	1,678,900	216,900	27,000
Costs/patient (mean)	21,570	17,780	29,960	16,560	20,960	35,380	25,830	12,760	5,400
IQR	16,260–27,700	13,020–22,400	25,110–37,760	10,790–22,730	17,100–24,130	32,180–38,910	20,660–32,630	12,750–14,540	2,270–8,090
Total costs									
Total costs	8,076,900	1113,900	579,300	539,300	1,183,100	1,380,200	2,860,300	357,100	63,800
Costs/patient (mean)	22,490	19,210	27,580	20,740	20,050	26,540	26,240	13,230	9,110
IQR	14,460–28,300	11,130–27,110	18,620–38,020	12,860–29,020	12,840–26,700	22,020–26,230	19,240–35,550	8,680–16,380	6,530–12,670
Health-related quality of life									
EQ-5D at 2.5 months	0.62	0.66	0.69	0.74	0.64	0.49	0.59	0.71	0.73

Head: including head, face and neck; Lower extremity injury: excluding hip fractures; Superficial injury: open wounds, superficial injuries; Other injury: burns, unspecified.
IQR: interquartile range (25th percentile to 75th percentile).

After adjusting for confounders in the multivariable model, older age, female gender, lower education, higher comorbidity, and higher ISS were found to statistically significantly predict lower EQ-5D scores at 2.5 months post-injury ($F(5, 348)=22.45$, $p<0.001$, $R^2=0.24$).

Lowest HRQL at 2.5 months after trauma was reported by patients with a fracture of the upper arm (EQ-5D 0.36), a pelvic fracture (EQ-5D 0.48) or hip fracture (100% ISS<16, EQ-5D 0.49, Figure 5.3). Hip fracture patients specifically reported significantly more problems than other injuries on mobility (93% vs 58%, $Chi^2=27.6$, df=1, $p<0.001$), self-care (71% vs 40%, $Chi^2=19.5$, df=1, $p<0.001$), usual activities (88% vs 73%, $Chi^2=6.2$, df=1, p=0.007), anxiety/depression (48% vs 32%, Chi2=5.3, df=1, p=0.017), and cognition (37% vs 26%, $Chi^2=3.5$, df=1, p=0.047). In contrast, patients with thorax/abdomen injury reported one of the highest HRQL (71% ISS<16, EQ-5D 0.74), comparable to the HRQL of patients with superficial injuries (100% ISS<16, EQ-5D 0.71).

Looking at the EQ-5D domains (Appendix Figure 5.A (A)), a substantial number of respondents with ISS 1–8 and ISS 9–15 reported to have problems on mobility (ISS 1–8: 56%; ISS 9–15: 74%), self-care (34%; 83%) usual activities (68%; 83%), pain/discomfort (74%; 76%) and anxiety/depression (21%; 43%). Respondents with ISS<16 reported more problems than those with ISS≥16 on multiple domains, though these differences were not significant (Appendix Figure 5.A (B)). This indicated that, although ISS<16 indicates minor to moderate severity, these injuries had a substantial impact on the patient's HRQL.

Figure 5.2 EQ-5D summary scores at 2.5 months after injury by ISS category

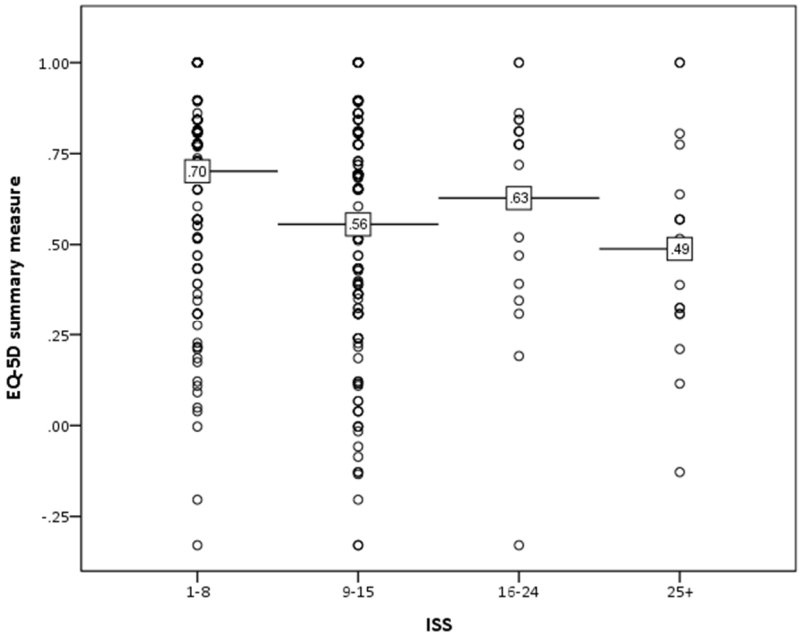
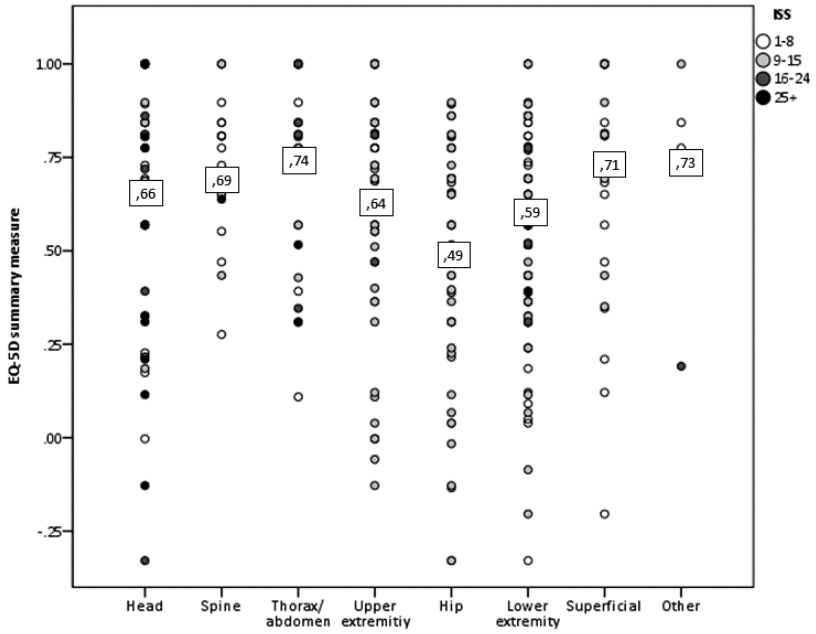


Figure 5.3 EQ-5D summary sores at 2.5 months after injury by injury type and ISS category

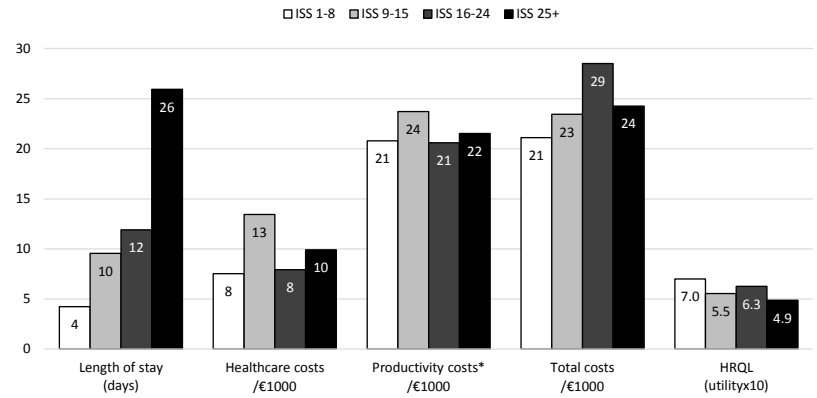


Head: including head, face and neck; Lower extremity injury: excluding hip fractures; Superficial injury: open wounds, superficial injuries; Other injury: burns, unspecified.

Injuries with highest impact

Comparison of the consequences of trauma (from LIS and the patient follow-up survey) by injury severity (obtained from the TR) revealed a generally linear pattern, with minor injuries (ISS 1–8) showing the lowest impact on all measures towards severe injuries (ISS 25+) showing the highest impact (Figure 5.4). Patients with ISS 25+ had the highest mean LOS (on average 26 days, SD 17.7), and lowest HRQL (EQ-5D 0.49).

Figure 5.4 Mean length of stay in hospital, costs, and HRQL by injury severity



* Mean productivity costs per case are presented as an average of only the working population (in our sample aged 16 to 65 years). In patients aged 65 and older, mean total costs per case only comprised the direct health care costs.

The integrative assessment of the consequences of trauma, however, also highlighted the major impact of trauma in patients with ISS 9–15. Although these injuries were given moderate severity by the AIS-coding system, patients with ISS 9–15 had significant higher mean health care costs compared to patients with ISS≥16 (on average €13,440, IQR €6,030 to €22,020 vs €8,800/patient, IQR €6,710 to €9,710: F=11.2, df=1, p=0.001) as well as higher mean productivity costs (on average €23,720, IQR €16,800 to €32,670 vs €20,920/patient, IQR €17,900 to €24,960: F=1.8, df=1, not significant). Patients with ISS 9–15 specifically were longer admitted to a nursing home or rehabilitation center than patients with ISS≥16 (on average 25.4 days vs 11.5 days; F=3.4, df=1, not significant). In addition, patients with ISS 9–15 reported one of the poorest outcomes on the EQ-5D (EQ-5D 0.56), comparable to the HRQL of patients with ISS 25+.

5.4 DISCUSSION

Trauma registries generally focus mainly on mortality as the main patient outcome. To show the opportunities of expanding the trauma registry with follow-up data on the consequences of trauma, we linked data of the National Injury Surveillance System, a trauma registry, and a patient follow-up survey. Assessment of the consequences of trauma beyond mortality is important to obtain insight into patients' recovery after trauma, their quality of survival, and to compare the (long-term) outcomes of trauma across patient subgroups. By linkage of data from multiple sources, we were able to combine information of a heterogeneous sample of adult injury patients and on a broad spectrum of outcome measures. Our integrative approach revealed injuries with ISS 9–15 to have one of the highest impact on individuals and society.

According to the results of our pilot study, injury patients with ISS 9–15 (moderate severity) showed higher mean health care costs (p=0.001) and productivity costs (not significant) than patients with ISS≥16 (severe injury). Moreover, the HRQL of injury patients with ISS 9–15 was generally poor and comparable to that of patients with ISS 25+. Patients with an isolated hip fracture (100% ISS<16) showed one of the highest mean health care costs and also reported one of the poorest HRQL at 2.5 months post-injury. Overall, the ISS insufficiently classified injuries according to their probable degree of functional problems after trauma.

Limitations

This pilot study was restricted to patients hospitalised in one of the four hospitals participating in both LIS and the TR, which included Level I, II, and III trauma centers situated in the eastern part of the Netherlands with rural and (sub)urban catchment areas. The characteristics of our study population were, however, comparable to the national trauma population registered in the Dutch trauma registry between 2007 and 2008 in terms of treatment at a trauma center with level I to III, age (mean 57 ± SD 21.6 in our sample vs 52 ± SD 28 in the total national sample), gender (48% males vs 50%), injury severity (median ISS 9, IQR 4–9 vs median 9), length of hospital stay (in both samples on average 8 days), and admission to the intensive care (6.6% vs 6.8%).[26] This indicates that the results of our study are generalisable to the Dutch trauma population.

Another limitation of this study was the response rate for the 2.5 month follow-up survey (46%), primarily due to the use of postal questionnaires and the limited opportunities to increase response rates (i.e. no contact information available to the researchers). The low response rates may have led to

selection bias, and under- or overestimation of the consequences of injury. However, comparison of the characteristics of responders and non-responders to the 2.5 month follow-up survey showed no significant differences in patient and injury characteristics.

Additionally, our pilot study only included trauma patients with a response to the 2.5 month follow-up survey, and therefore did not comprise the outcomes of trauma patients who had died due their injuries in the period before the first follow-up assessment. We therefore may have missed the high health care costs of injury patients who died after a long stay in the hospital and/or IC. This may have led to an underestimation of the consequences of injuries in our study, especially the severe ones. However, according to the Dutch national trauma registry, the overall in-hospital mortality rate of injury patients is low; about 3% in 2007–2008 and 2% in recent years.[26] In addition, missing of these consequences of fatal injuries may have had limited impact on our results, as mortality not only occurs in patients with injuries of high injury severity (e.g. ISS≥16), but also in patients with a low injury severity score (e.g. hip fracture patients, ISS<16)[27]. It is however recommended to, shortly after the injury, assess the consequences of all hospitalised trauma patients documented in the trauma registries, in order to obtain full insight into the impact of injuries.

Moreover, information on injury severity was obtained from AIS codes assigned by a trained staff member. The AIS coding system is known to be rater-subjective, especially in case of patients with multiple injuries, leading to considerable variations in AIS codes between raters for identical injuries.[28-30] However, the AIS codes in our study were assigned by a single rater, which is expected to enhance the comparability of the severity rating of injuries included in our sample.

In addition, no risk adjustment was used in the assessment of the hospitalisation or costs after injury. Research showed that there are many other factors which influence the outcome after injury, for example including patients' health status before the injury, age, or injury severity.[8,31] Unfortunately, in this pilot study, we were not able to collect information on the pre-injury HRQL of patients. However, we did use a multivariable model to assess the predictors of poor HRQL after injury, which indicated age, gender, education, comorbidity, and ISS to be independent predictors of lower EQ-5D scores post-injury.

Finally, although the EQ-5D showed to be a feasible and valid instrument for the measurement of functioning in injury patients,[10,19,22,23] it lacks a cognitive dimension and is in some populations outperformed by other measures.[22,32] We therefore included a separate item on cognitive ability. Preferably, the EQ-5D should be combined with other instruments when used in patient-related outcome measurement.

The future of trauma registries

Our study provides directions for the development of trauma registries, showing the opportunities of expanding these registries and document data on the consequences of non-fatal trauma.

As trauma registries were originally designed to monitor and improve the quality of care delivered to trauma patients[3], in-hospital mortality is generally the only available and easy accessible patient outcome in these databases. Mortality comprises a relatively rare outcome among all trauma patients and does no longer provide the true quality indicator of trauma systems. As a consequence, trauma registries that focus on mortality as the main patient outcome have become outdated.

Consequently, the outcomes of non-fatal trauma have increasingly become important. Trauma survivors often experience some level of impairment or disability after their trauma. The economic consequences of injuries are substantial, as survivors of severe trauma often require specialised health care and long-term rehabilitation and are in some cases unable to return to full employment. Insight into the economic consequences, and impact of a trauma on patients' health outcome is essential for optimising health care policy and prevention, and developing effective health care and rehabilitation services.

More specifically, patient-reported outcome measures (e.g. HRQL instruments) can be used in clinical decision making after the acute phase of trauma care. For instance, HRQL information may enable clinicians to detect unrecognised problems, monitor the impact of a trauma and the provided trauma care, and may also lead to improvements in the patient's health status and/or satisfaction with trauma care.[33]

Our study highlights that data on the consequences of non-fatal trauma should be integrated in the evaluation of health care delivered to trauma patients, and should be documented in trauma registries. Worldwide, the first trauma registry to measures the long-term outcomes of trauma survivors after discharge is the Victorian State Trauma Registry (VSTR) in Australia. The VSTR routinely collects information on the long-term functional status, work disability, and HRQL of trauma patients over 2 years post-discharge,[34] reaching follow-up rates of over 80% using telephone interviews.[35] Results from the VSTR indicate that even years after injury survivors of major trauma still experience impairments due to the injury, as only one fourth of all patients returned to their pre-injury level of function after two years of follow-up.[36] In line with our findings, data from the VSTR also indicated that patients with abdominal injury showed high levels of recovery and as well as highest return to work or study after injury.[36]

Like other trauma registries, the VSTR focuses on the more severe injuries and major trauma patients (e.g. ISS≥16).[3,34] Our results, however, indicated that the highest impact on both individual patients and society was found in injuries coded with ISS 9–15 (indicating moderate severity). It is therefore recommended to broaden the inclusion criteria of trauma registries by including all hospitalised trauma patients (as in the Dutch National Trauma Registry[26] and the National Trauma Data Bank® of the US).[37]

Information on the health outcome of patients could be gathered and documented for all patients on discharge using questionnaires. The EuroSafe Group has developed guidelines for the conduction of follow-up studies measuring trauma-related disability, and recommended the use of the EQ-5D in combination with the Health Utilities Index mark 3.[38] These instruments were thought to include most of the relevant health domains for trauma patients, when measuring the consequences of non-fatal trauma.[38] Another instrument that is frequently used among trauma patients is the 36-item Short Form health survey (SF-36).[8,39] The SF-36 and EQ-5D both have shown to be able to discriminate between the health status of patients with different types of injuries.[8] More specific, disability and activity limitations after injury can be assessed with use of the World Health Organisation Disability Assessment Schedule (WHODAS);[40] a self-administered instrument which captures six major life domains and a summary score of functioning and disability.[40] The WHODAS has been shown to be a reliable and valid instrument, with scores highly correlated with scores on physical component score (PCS) of the SF-36.[40] However, in contrast to the EQ-5D, the SF-36 and WHODAS may be too time-consuming for patients to fill out, which may negatively affect the response rates. Therefore, the shorter SF-12 health survey can be used,

which like the SF-36, captures information about the mental and physical HRQL,[41] and is applied in the VSTR.[34]

Some trauma registries, like the Dutch trauma registry, have implemented the Utstein Template for uniform reporting of data following trauma,[42] in which besides the 30-day mortality also the Glasgow Outcome Scale (GOS) is recorded; an objective measure to assess the recovery of trauma patients.[43] An extended version of the GOS is used in the Australian VSTR,[34] the GOSE, which classifies patients into eight levels of function from death to full recovery.[44] However, a criticism of scales such as the GOSE is that they fail to capture the subjective perspective of trauma patients.[45]

In practice, hospitals could send follow-up questionnaires to all hospitalised patients registered in the trauma database, in order to provide information on the long-term consequences of trauma of all patients. It may however be costly and time-consuming to contact all registered trauma patients, to obtain their informed consent, and to collect their response to the follow-up questionnaires. Previous research indicated that the use of telephone interviews may increase response and reduce the costs of data collection.[46] Moreover, (part of) the HRQL assessment could be incorporated into the daily care provided within the hospital and/or outpatient setting (e.g. during contact with the clinician). In addition, the burden of follow-up measurement may be reduced by drawing random samples from all registered trauma patients to obtain a representative sample of the treated trauma population. Moreover, due the high share of Internet users worldwide (82% of individuals in developed countries),[47] web-based and mobile phone technologies (e.g. online questionnaires or use of smartphone apps) may be used for set up and follow-up of a cohort of injury patients, creating significant cost and time savings in comparison to traditional research methods.[48]

Besides assessing the HRQL of trauma patients, these assessments of outcomes after trauma should also include items on the health care consumption, and return to work or normal activities after trauma. Depending on the length of stay of individual trauma patients, follow-up measurement of all these items is advised at 1 month (acute treatment phase, range 0–8 weeks), 2 months (rehabilitation phase, range 1–3 months), 4 months (adaptation phase, range 3–6 months), and 12 months (stable end situation, range 6–24 months) after the trauma.[38] To produce estimates of the decrease in HRQL due to the trauma, it is recommended to retrospectively assess the preinjury HRQL of trauma patients within the first week after the injury.[38]

Conclusions

The integrative approach of assessing the consequences of non-fatal trauma revealed that injury patients with ISS 9–15 had one of the highest impact on both individuals and society. Our findings emphasise the importance of documenting the consequences of all hospitalised trauma cases in trauma registries and incorporating the outcomes of non-fatal trauma in the evaluation of trauma care to obtain insight into the quality of survival after trauma and to compare the consequences of trauma across patient subgroups.

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APPENDIX

Table 5.A Unit costs (2012) estimated according to national guidelines for health care costing

	Resource	Unit costs
General Practitioner	Practice consultation	€33.70
	Consultation by telephone	€16.90
	Home visit	€67.40
	Referral patient treated at the ED	€35.00
	Referral hospitalised patient	€44.00
	Follow-up care patient treated at the ED	€33.70
	Follow-up care hospitalised patient	€37.80
Ambulance	Emergency journey	€538.20
	Scheduled journey	€206.20
Hospital	Attendance of ED	Injury specific fees[1]
	Hospitalisation general hospital	€460.40/day
	Hospitalisation academic hospital	€629.00/day
	Intensive care	€1,751.50/day
	Day care	€310.30/day
	Outpatient department visit	€178.10/visit
	Medical procedures	Reimbursement fees
Long-term care	Nursing home	€264.60/day, 138.80/day care
	Rehabilitation	€469.10/day
	Physiotherapy	€38.00/treatment
Home care	Domestic care	€30.60/hour
	Care	€39.10/hour
	Nursing	€67.60/hour
	Nursing & care	€46.40/hour
Labor costs	15–19 year	€13.50/hour
(including VAT)	20–24 year	€24.70/hour
	25–29 year	€32.80/hour
	30–34 year	€39.30/hour
	35–39 year	€43.30/hour
	40–44 year	€45.40/hour
	45–49 year	€46.80/hour
	50–54 year	€48.50/hour
	55–59 year	€49.70/hour
	60–64 year	€50.70/hour
	Overall mean	€40.90/hour

[1] Unit costs for attendance of emergency department are calculated per type of injury in an annually unit cost study indexing the tariffs per minute of nurses, physicians and specialists. ED: emergency department; VAT: value added tax.

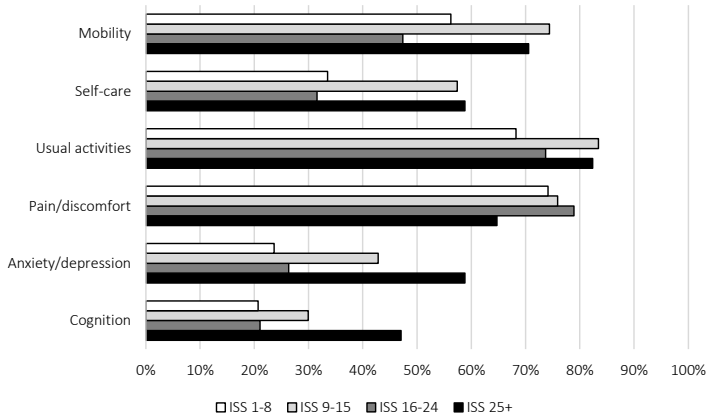
Table 5.B Study population (aged 16 years and older)

Hospital	Level[1]	National Injury Surveillance System[2]	Trauma Registry[3]	Linked files[4]	Follow-up survey[5]	Response
Radboud university medical center, Nijmegen	I	975	750	747	309	91
Canisius-Wilhelmina hospital, Nijmegen	II	918	474	413	186	152
Gelderse Vallei hospital, Ede	II	1,088	477	424	194	78
Maasziekenhuis Pantein hospital, Boxmeer	III	532	431	411	202	90
Total		**3,513**	**2,132**	**1,995**	**891**	**411**

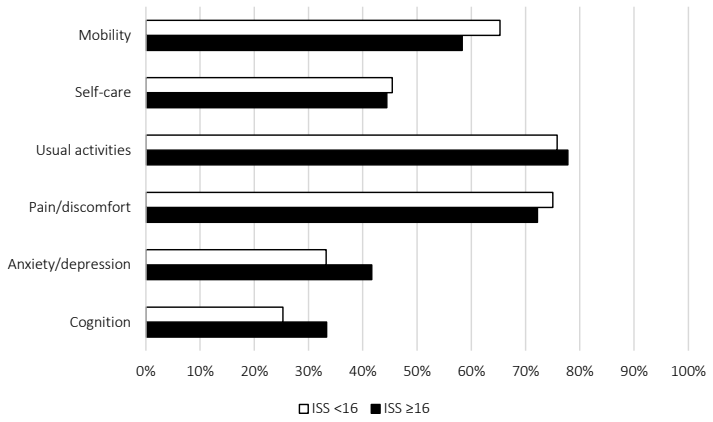
[1] Trauma center level, from Level-I (highest) to Level-III (lowest).
[2] Number of hospitalised patients (16+ years) registered in the LIS.
[3] Number of hospitalised patients (16+ years) registered in the TR.
[4] Number of hospitalised patients (16+ years) registered in both the LIS and TR.
[5] Number of hospitalised patients (16+ years) with linked files who were sent a follow-up survey.

Figure 5.A Prevalence of limitations (moderate or severe) of the EQ-5D health domains by ISS category
Data is shown by the four ISS categories (A) and ISS<16 versus ISS≥16 (B).

A



B



Chapter 6

Assessing the burden of traumatic brain injury with disability weights derived from health-related quality of life data

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Submitted

ABSTRACT

Background The disability-adjusted life year (DALY) measures the burden of disease, which serves as crucial input for policy decisions. Disability weights are necessary to estimate DALYs. The aims of this study were to 1) quantify differences between two methods to derive disability weights for traumatic brain injury (TBI), and 2) compare DALY estimations calculated with both sets of disability weights given the same TBI incidence data.

Methods HRQL disability weights were assessed using SF-36 data from a postal survey among 996 TBI patients 6 and 12 months after attending the emergency department of a hospital. Differences between health-related quality of life (HRQL) and existing Global Burden of Disease (GBD) study disability weights were calculated by TBI severity class (mild, moderate, severe). The GBD 2013 and HRQL disability weights were applied to the same incidence data to assess YLD due to TBI in the Netherlands to estimate the burden of TBI.

Results The findings showed that the GBD and HRQL disability weights for TBI were in the same order of magnitude apart from the disability weight for severe TBI, where long-term consequences were weighted 2.5 times more severe according the GBD. When the HRQL disability weights were used, the majority (62%) of the total number of DALYs were lost due to mild TBI, whereas with the GBD disability weights 51% of the total number of DALYs were lost due to mild TBI.

Conclusions We conclude that differences are small between the disability weights and YLD estimations derived in a standard way or from empirical HRQL follow-up data from individual TBI patients.

6.1 INTRODUCTION

The disability-adjusted life year (DALY) measures the burden of disease, i.e. it is a time-based measure that aggregates the total health loss due to mortality, morbidity and disability at population level into a single index by summarising a) years of life lost due to premature death (YLL), and b) years lived with disability (YLD).[1] This allows comparison of the size of a certain health problem to comparable data of other health problems and this feature makes the DALY very suitable for guiding decision-making on prevention and control.[2,3] Landmark studies that used the DALY are the Global Burden of Disease and Injury (GBD) 1996 study and its subsequent updates.

An essential component for DALY calculations is the disability weight. The disability weight is a scaling factor that expresses the impact of a disease with a value ranging from 0, indicating best possible health state, to 1, indicating worst possible health state.[4] By multiplying the disability weight of a condition by its incidence and its average duration (or prevalence in case of chronic disease), the healthy time lost due to living with disability (YLD) is calculated.

Disability weights are derived by a panel of judges that value a number of health states and these health state valuations are then used to calculate disability weights for the health states.[5] These judges may be patients, proxies, health experts or lay people from the population. Up till now few panel studies have been conducted, of which the GBD disability weighs studies,[6-8] the Dutch Disability Weights (DDW) study,[9] Integrated Burden of Injury (IBIS) study[10] and INTEGRIS[11] disability weights are of significance for traumatic brain injury (TBI) and its consequences.

An important difference between these existing sets of TBI disability weights is the subdivision into TBI categories, ranging from one category to six categories. For instance, the set of GBD 1996 disability weights included one disability weight for intracranial injury, which was applied to concussion, moderate and severe brain injury, whereas the set of GBD 2013 disability weights included five disability weights for TBI. An overview of existing sets of TBI disability weights and the subdivision into TBI categories is shown in Appendix Table 6.A and 6.B.

However, a disadvantage of the application of standard disability weights is that these disability weights may be unable to capture the heterogeneity within a certain injury group. In other words, there may be a misfit between the epidemiological data that is used for the YLD calculations and the disability weight that is applied to the epidemiological data, leading to an underestimation of the burden of TBI. Consequently, increasingly, researchers conclude that, in case of injury, disability weights derived from health-related quality of life (HRQL) data from individual trauma patients are the preferred option.[12-15]

Deriving HRQL disability weights consists of two steps. First patients report their own health state with a generic health state classification (e.g. EQ-5D, Health Utilities Index, Short Form(SF)-36).[16] Combined with previously population elicited attribute weights these responses render a HRQL summary score. Subsequently, the HRQL summary score of the cases is converted to a disability weight.

Using HRQL data to derive disability weights has the advantage that disability weights can be linked to epidemiological injury data more precisely, provided that a logical and homogeneous grouping of patients is used.[11] In case of TBI a logical and homogeneous grouping would be the Glasgow Outcome Scale Extended (GOSE). GOSE is a functional measurement scale with eight categories that has been designed for TBI specifically.[17] GOSE has demonstrated good construct and discriminant validity and is

a widely used instrument to describe outcome in a group of TBI cases.[18,19] However, the GOSE classification has not yet been used to assess disability weights for TBI.
The aims of this study were to 1) generate HRQL disability weights for TBI by severity level measured by GOSE level based on SF-6D data of a cohort of TBI patients, 2) quantify differences between (a) HRQL disability weights and (b) GBD 2013 disability weights, and 3) compare YLD estimations calculated with both sets of disability weights given the same incidence data.

6.2 METHODS

Cohort of TBI patients

The data for this study was obtained from the Radboud University Brain Injury Cohort Study (RUBICS).[20-22] RUBICS is a prospective observational cohort study on the association between demographic and clinical variables, posttraumatic complaints, and functional outcome. The RUBICS database included data of all patients with TBI admitted to the emergency department (ED) of the Radboud University Nijmegen Medical Centre (RUNMC), a level I trauma center. The RUBICS database recorded socio-demographic variables, cause of injury, the Abbreviated Injury Scale (AIS), Glasgow Coma Scale (GCS), Abbreviated Injury Scale of the Head (AISH) score, Injury Severity Score (ISS) and health care that was provided. Of the 3,888 patients with TBI admitted to the ED of the RUNMC between June 2003 and June 2010 were eligible for inclusion. Of these patients, 2,286 were sent a questionnaire. For this study, all patients with TBI aged 18 years and older were selected from the RUBICS database. For more details on the RUBICS, see Scholten and colleagues.[23]

Glasgow Outcome Scale Extended

The GOSE scores functional outcome with eight questions covering consciousness, independence inside and outside the home, major social roles (work, social and leisure activities, family and friendships), and return to normal life.[24] Aggregating these questions results in an 8-point scale that classifies functional outcome from 1 (dead) to 8 (complete recovery). The GOSE was assessed using a structured interview during regular visits to the outpatient clinic or during consultation by telephone.[17] Assessment of the GOSE often took place at 6 and 12 months post-injury. If GOSE scores at 6 months post-TBI were missing, the 6 month GOSE was composed by taking the mean of GOSE scores assessed at 5 or 7 months, or at 4 or 8 months. In case of missing GOSE scores at 12 months post-TBI, the 12 month GOSE was composed by taking the mean of GOSE scores assessed at 11 or 13 months, or at 10 or 14 months.

Health-related quality of life data

HRQL data was collected by postal questionnaires at 6 and 12 months after injury. The questionnaires included items regarding socio-demographics (age, sex, educational level and household composition), clinical outcome and HRQL determined with the 36-item Short-Form Health Survey (SF-36).[25] The SF-36 is one of the HRQL instruments recommended by the TBI consensus groups.[26] The SF-36 is a 36-item questionnaire that covers eight domains of health status: physical functioning (PF), role limitations related to physical health problems (RP), bodily pain (BP), general health perception (GH), vitality (VT), social functioning (SF), role limitations related to emotional problems (RE), and mental health (MH).[25]

The SF-36 has been used previously to evaluate HRQL in TBI patients.[27,28] For each domain, a summation of item responses is linearly transformed into a score ranging from 0–100.

Converting SF-36 data into disability weights

Assessing HRQL disability weights requires two steps. Firstly, patients described their health state by choosing a functional level for each attribute of the HRQL instrument. Using tariff weights for the separate attributes, the reported functional level on the attributes is then converted into a utility weight which usually fits within the 0–1 range. The method of scoring the SF-36 is not based on preferences, and therefore cannot be used directly as a single utility score which is needed to construct disability weights. Single utility scores were obtained by deriving SF-6D utility scores out of the SF-36. The SF-6D reduces the eight dimensions of the SF-36 to six dimensions by excluding the general health item and combining both role limitation dimensions.[29] The reduced and less complex SF-6D defines 249 health states, which were valued by a representative sample of 611 members of the UK general population using standard gamble.[30,31] Preference data from this study was used in a SF-6D algorithm. The SF-6D algorithm was applied to responses to the SF-36 generating SF-6D utility scores for each TBI patient, ranging from full health (1) to death (0).

The second step in assessing HRQL disability weights is to convert the utility weights into disability weights. The method that we applied to convert SF-6D utility scores to disability weights (dw) is as follows: $dw = SF\text{-}6D_{population} - SF\text{-}6D_{patient}$

In this formula, the SF-6D utility score of the general population of a country (HRQL<1) is used as the baseline in the calculation of the disability weight of the health state. With this formula, it is possible to adjust for the effects of age and/or sex on HRQL. We used the population norm scores for the SF-6D for the UK.[32]

GBD 2013 disability weights

For the GBD 2013 study a Disability Weights Measurement study was carried out using household sample surveys in five countries (Bangladesh, Indonesia, Peru, Tanzania, USA) supplemented by an open-access online survey and a web-survey that was held among a representative sample of the general population of four European countries (Hungary, Italy, the Netherlands and Sweden).[7,33,34] The primary mode of data collection was via a simple paired comparison question in which respondents were asked to consider two hypothetical individuals, each with a particular health condition described briefly in terms of its main functional consequences and symptoms, and to indicate which of the two individuals they would regard as being healthier. An additional type of question asked respondents to compare the population health benefits in two different hypothetical health programmes, and this information was used to anchor the results from the paired comparison data such that all weights were located on a scale between zero and one. This resulting in a set of 235 disability weights based on the responses from 61,890 people in 167 countries.[7,33,34] The GBD 2013 includes five disability weights for TBI 1) concussion; 2) minor TBI, long-term consequences; 3) moderate TBI, long-term consequences; 4) severe TBI, short-term consequences; 5) severe TBI, long-term consequences.

Mapping of disability weights and calculating Disability-Adjusted Life Years

The injury severity classes were grouped post hoc according to the GOSE categories (GOSE 2–3: severe disability; GOSE 4–5: moderate disability; GOSE 6–7: minor disability; GOSE 8: no disability) (Table 6.1).

Table 6.1 Mapping of TBI severity classes, duration and severity distribution of TBI cases according to GOSE

GBD disability weight	GOSE points	Duration	Severity distribution of cases from the RUBICS study
Short-term consequences			
No disability	8	-	42.3%
Concussion	6–7	<12 months	43.2%
Moderate disability, short-term consequences	4–5	<12 months	13.9%
Severe disability, short-term consequences	2–3	<12 months	0.7%
Long-term consequences			
No disability	8	-	56.7%
Minor disability, long-term consequences	6–7	≥12 months	14.6%
Moderate disability, long-term consequences	4–5	≥12 months	2.2%
Severe disability, long-term consequences	2–3	≥12 months	0.5%

To estimate the burden of TBI. the GBD 2013 and HRQL disability weights have been applied to the same incidence data to assess YLD due to TBI in the Netherlands. Incidence data on all patients with TBI treated at an ED and/or admitted to hospital in the Netherlands in the period 2010–2012 was extracted from the Dutch Injury Surveillance System (LIS)[35] and the National Hospital Discharge Registry (LMR)[36] to include data of TBI patients treated at the ED and hospitalised TBI patients respectively. See Scholten and colleagues for more details on the incidence of TBI in the Netherlands.[37] The distribution of the TBI severity level (assessed by GOSE points) of RUBICS cases was calculated using the RUBICS dataset (Table 6.1). This distribution was then applied to incidence data on all patients with TBI treated at an ED and/or admitted to hospital in the Netherlands. Apart from incidence data and disability weights, duration is needed to assess YLDs. Duration of injury is the period of time that there is disability due to the injury. In our conceptual model we distinguish between short-term and long-term consequences of TBI. Short-term consequences are the consequences that a TBI patient experiences immediately after until 364 days after sustaining the TBI. Long-term consequences are the consequences that a patients experiences one year after injury. In our study, the short- and long-term consequences of TBI are captured with the 6 month and 12 months follow-up study respectively.

Data and statistical analysis

For analysis of the data the Statistical Package for the Social Sciences version 21 was used (SPSS Inc, Chigaco, Ill). The SF-36 and SF-6D summary scores can be calculated if all items are completed. If one or two items were missing, the item was estimated using a hot deck imputation technique. The missing data was then imputed by the estimated values.[38] If more than two of the SF-36 items were missing, data was not imputed.

Differences between HRQL and GBD disability weights and ratios were calculated by TBI severity class (minor, moderate, severe). The intraclass correlation coefficient was calculated to test if the ranking based on the mean HRQL and GBD disability weights of the TBI health states were associated.

6.3 RESULTS

Respondents

The response rates were 44% (n=996) at 6 months and 17% (n=386) at 12 months post-injury (Table 6.2). Of the TBI patients that completed the patient surveys 6 months after attending the ED 63% was male and mean age was 44 years old. The majority (80%) of TBI patients had a GCS score ≥13. After visiting the ED, 60% of the respondents were admitted to hospital and 17% were admitted to the IC.

Table 6.2 Characteristics of the study population

	6 month follow-up	12 month follow-up
N	996	386
Patient demographics		
Age[1]	44 [27–57]	47 [28–58]
Male sex	628 (63.1%)	232 (60.1%)
Injury characteristics		
ISS[1]	9 [5–18]	10 [5–22]
AISH		
Head AIS 0–1	208 (20.9%)	73 (18.9%)
Head AIS 2–3	602 (60.4%)	234 (60.6%)
Head AIS 4–5	186 (18.7%)	79 (20.5%)
Admitted to hospital	596 (59.8%)	263 (68.1%)
GCS		
Mild (GCS≥13)	797 (80.0%)	282 (73.1%)
Moderate (GCS=9–12)	50 (5.0%)	22 (5.7%)
Severe (GCS≤8)	149 (15.0%)	82 (21.2%)

[1] Data is displayed as median, with the first and third quartile given within brackets.

HRQL disability weights

Table 6.3 shows that the HRQL disability weight increases with increasing level of GOSE. Mean 6 month HRQL disability weights ranged from 0.04 (GOSE 7; lower good recovery) to 0.254 (GOSE 3; lower severe disability). Mean 12 month HRQL disability weights ranged from 0.08 (GOSE 7; lower good recovery) to 0.263 (GOSE 3; lower severe disability).

Table 6.3 Mean HRQL disability weights by GOSE category

GOSE	6 month follow-up					12 month follow-up				
	N	SF-6D mean	SF-6D SD	DW	SD	N	SF-6D mean	SF-6D SD	DW	SD
2	0	NA	NA	NA	NA	0	NA	NA	NA	NA
3	4	0.541	0.051	0.254	0.09	4	0.542	0.075	0.263	0.07
4	43	0.607	0.070	0.185	0.09	6	0.625	0.109	0.210	0.04
5	90	0.635	0.091	0.167	0.09	14	0.593	0.112	0.202	0.10
6	170	0.663	0.087	0.137	0.08	49	0.642	0.105	0.149	0.10
7	196	0.760	0.112	0.040	0.11	70	0.719	0.114	0.079	0.12

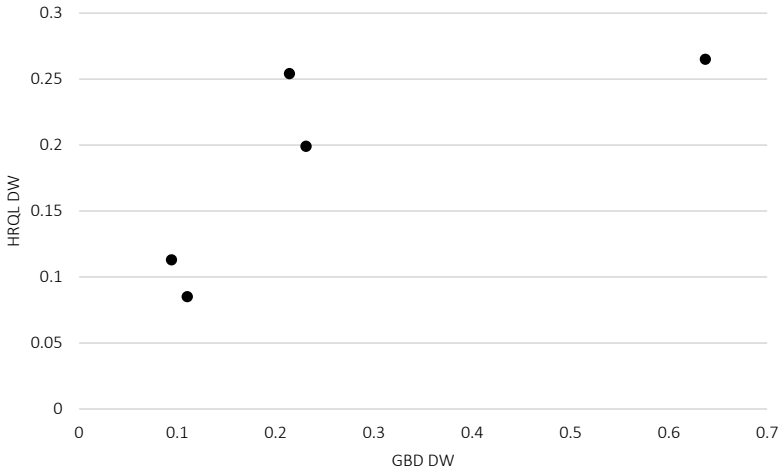
N: number of respondents; SF-6D mean: mean SF-6D utility weight; SD: standard deviation; DW: disability weight (0 indicates best possible health state and 1 indicates worst possible health state); NA: not available.

Comparison of HRQL and GBD 2013 disability weights

Figure 6.1 shows a Bland-Altman plot of the GBD and HRQL disability weights. Table 6.4 shows that absolute differences and SF-6D/GBD disability weights ratio increased with increasing level of severity. Correlation coefficients between SQM and APM disability weights were high, intraclass correlation was 0.65 (p=0.166). The GBD and HRQL disability weights are in the same order of magnitude, apart from

the disability weight for severe TBI, long-term consequences for which the GBD disability weights is 2.5 times higher.

Figure 6.1 Comparison of GBD and HRQL disability weights for TBI



Each point represents the TBI disability weight per GOSE category.
DW: disability weight; 0 indicates best possible health state and 1 indicates worst possible health state.

Table 6.4 TBI disability weights derived with the HRQL and GBD disability weights measurements study

TBI health state	HRQL DW	GBD DW	Δ[1]	Ratio
Short-term				
Concussion	0.085	0.110	–0.03	0.8
Severe traumatic brain injury, short-term	0.254	0.214	0.04	1.2
Long-term				
TBI, long-term consequences, minor	0.113	0.094	0.02	1.2
TBI, long-term consequences, moderate	0.199	0.231	–0.03	0.9
TBI, long-term consequences, severe	0.265	0.637	–0.37	0.4

[1] Δ: absolute difference between SQM and APM disability weights.
DW: disability weight; 0 indicates best possible health state and 1 indicates worst possible health state.

Comparison of YLD estimations

Annually, 34,682 patients visited the ED due to TBI in the Netherlands. Table 6.5 shows the YLD estimations calculated with (a) the set of HRQL disability weights and (b) the set of GBD disability weights. Application of the HRQL disability weights resulted in 102,381 YLDs (short-term TBI: 2,725 YLDs; long-term: 99,656 YLDs), whereas application of the GBD disability weights resulted in 108,732 YLDs (short-term TBI: 2,682 YLDs; long-term: 106,050 YLDs).

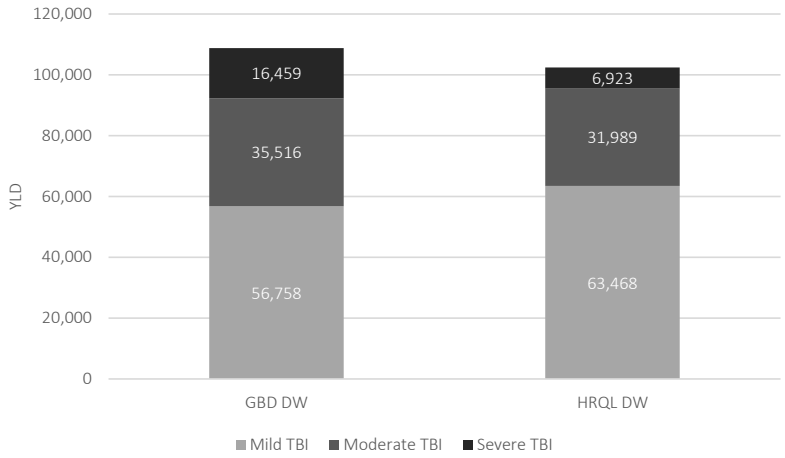
As shown in Figure 6.2, with the application of HRQL disability weights, the majority (62%) of the total number of YLDs were lost due to mild TBI, whereas with the GBD disability weights 52% of the total number of YLDs were lost due to mild TBI.

Table 6.5 YLD estimations calculated with (a) the set of SF-6D disability weights and (b) the set of GBD disability weights

GOSE category	Incidence	Duration (years)	HRQL DW	YLD HRQL DW	GBD DW	YLD GBD DW
Short-term (<12 months)						
2	0	1	NA	0	0.214	0
3	771	1	0.254	196	0.214	165
4	2,253	1	0.185	417	0.110	248
5	4,565	1	0.167	762	0.110	502
6	7,292	1	0.137	999	0.110	802
7	8,774	1	0.04	351	0.110	965
8	11,027	1	0	0	0	0
Total	*34,682*			*2,725*		*2,682*
Long-term (≥12 months)						
2	0	47.9	NA	0	0.637	0
3	534	47.9	0.263	6,727	0.637	16,294
4	1,067	47.9	0.21	10,733	0.231	11,806
5	2,075	47.9	0.202	20,077	0.231	22,960
6	4,743	47.9	0.149	33,851	0.094	21,356
7	7,470	47.9	0.079	28,267	0.094	33,634
8	18,793	47.9	0	0	0	0
Total	*34,682*			*99,656*		*106,050*
Total				**102,381**		**108,732**

DW: disability weight; 0 indicates best possible health state and 1 indicates worst possible health state.
YLD: years lived with disability.

Figure 6.2 YLDs due to mild, moderate and severe TBI, calculated with GBD and HRQL disability weights



DW: disability weight; 0 indicates best possible health state and 1 indicates worst possible health state.
YLD: years lived with disability.

6.4 DISCUSSION

The results showed that the ranking of both sets of disability weights were concordant and that the HRQL and GBD disability weights for TBI were in the same order of magnitude, apart from the disability weight for severe TBI long-term consequences for which the GBD disability weight was 2.5 times more severe.

In many areas of medicine, disability weights are not tailored to incidence or prevalence. Disability weights for certain health outcomes may not be available or not 'appropriate'. If, for example, the health status of the population is less or more severe than the health status represented by the

'disability weights' used in the formula the linkage between the incidence data and functional outcomes is flawed.

This problem is amplified in case of TBI. TBI encompasses a variety of consequences and recovery patterns ranging from mild and short-term to severe and lifelong. To assess the burden of TBI, the Global Burden of Disease (GBD) study developed a set of five disability weights.[7] Application of these disability weights means that TBI incidence data, classified into many ICD codes, have to be collapsed into five groups to link the data to the disability weights. Important to note for instance is that there was no GBD disability weight for short-term consequences of moderate TBI (14% of TBI patients) and we applied the disability weight for concussion to these cases, resulting in an underestimation of the YLD of the short-term consequences of moderate TBI.

More and more researchers conclude that the fit between injury incidence data and disability weights is improved if disability weights are derived from empirical HRQL follow-up data from individual trauma patients.[12-14] An advantage of using disability weights based on empirical HRQL follow-up data is that the HRQL disability weights are able to capture the heterogeneity within an injury group. However, the results of our study showed that although disability weights based on HRQL data provides solutions for problems with the GBD disability weights, it also has limitations.

Firstly, the HRQL disability weights might be contaminated by comorbidity, since one in four TBI patients from our sample suffered from comorbid disorders.[23] This means that the disability weights based on empirical HRQL follow-up data might reflect the impact of the TBI plus one or more comorbid diseases. Apart from this, HRQL may be affected by age and sex of the respondent, follow-up time, type of instrument that is used to measure HRQL, etc.

A second aspect that might affect HRQL disability weights is adaptation to the health state. Especially in case of chronic conditions, such as long-term consequences of TBI, adaptation to the health state plays an important role, because this may cause TBI patients to perceive their health state as less severe after living with the condition for some time.[39] This may be an explanation for the relatively low HRQL disability weights for severe TBI compared to the HRQL disability weights for moderate and mild TBI.

Another explanation for the relatively low HRQL disability weights for severe TBI may be the use of self-report HRQL data to assess disability weights for TBI patients. TBI patients had to fill out the SF-36, which is lengthy and has complex questions. It has been debated whether TBI patients have the ability to provide useful and complete answers to complex questions.[40] The more complex HRQL instruments, such as the SF-36, have been shown to be difficult to complete by the general populations,[41] let alone for TBI patients who may have cognitive problems. The use of self-report SF-36 questionnaires may have led to an underestimation of impact on functional outcome and HRQL, since patients with a higher degree of cognitive problems may have not been able to fill in the questionnaire. Comparison of the response rate of patients with a GSC>8 and GSC≤8 in the RUBICS dataset showed that latter group of patients were significantly less likely to respond to the 6 month follow-up questionnaire. Also, the low response rates at 6 and 12 month follow-up may have led to selection at the two follow-up moments of the study.

Furthermore, the HRQL disability weight for severe TBI is based on a small number of patients (n=4). This underlines the challenge of using HRQL data to assess disability weights, namely that the number of patients per grouping needs to be relatively large to derive a HRQL disability weight for the whole

spectrum of patients within the grouping. This may be difficult in case of less frequently occurring injury, such as severe TBI.

The YLD of TBI assessed in the current paper is twice as high as the YLD reported in a previous study on the incidence and burden of disease in the Netherlands.[37] This difference can be explained by differences in several aspects of the YLD calculation. Firstly, our study used a more detailed subdivision of TBI (six categories versus two categories), different sets of disability weights and a longer duration of long-term consequences of TBI. This translates into a higher YLD per case (3.0–3.1 YLD per case in the current study versus 1.5 YLD per case in Scholten and colleagues).[37]

A limitation of our YLD calculations is that we applied information on the distribution of GOSE level of the TBI cases seen in one academic hospital to all TBI cases in the Netherlands. This academic hospital functions as a tertiary referral hospital. This may result in a relatively high proportion of more severe cases of TBI, which limits extrapolation to all TBI in the Netherlands.

Conclusions

Taking the results of our study, with little difference between the disability weights and YLD estimations, and the limitations of disability weights derived from empirical HRQL follow-up data from individual TBI patients, we conclude that using the GBD disability weights to assess the burden of TBI is the preferred option.

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APPENDIX

Table 6.A Overview of disability weights for traumatic brain injury

Study	Label	No of TBI health states	Subdivision	Description of study*
GBD study Murray (1996) [6]	Intracranial injury	3	Short-term: 0.358 Lifelong age 0–59: 0.350 Lifelong age 60+: 0.404	Panel study PC: Experts (n=10) HSD: Disease label HSV: 1% PTO/99% VAS
DDW study Stouthard (1997) [9,42]	Skull-brain injury (permanent impairments)	3	Mild skull/brain injury: 0.37 Moderately severe skull/brain injury: 0.73 Severe skull/brain injury: 0.74	Panel study PC: Experts (n=34) HSD: Disease label + EQ-5D+ HSV: 10% PTO/100% VAS
IBIS Haagsma (2008) [10]	Concussion Brain injury	4	Concussion: 0.020 Moderate brain injury: 0.193 Severe brain injury, acute phase: 0.540 Severe brain injury, stable phase: 0.429	Panel study PC: Population (n=143) HSD: Disease label + description + EQ-5D+ HSV: 100% TTO/100% VAS
INTEGRIS Haagsma (2012) [11]	Concussion Other skull-brain injury	6	Concussion ED short-term: 0.015 Concussion HA short-term: 0.100 Concussion long-term: 0.151 Other skull-brain injury ED short-term: 0.090 Other skull-brain injury HA short-term: 0.241 Other skull-brain injury long-term: 0.323	Based on EQ-5D of patients reported at 2.5, 5, 9 and 24 months following injury
GBD 2010 study Salomon (2013) [7]	Traumatic brain injury	4	Severe TBI short-term consequences: 0.235 TBI, minor, long-term consequences: 0.106 TBI, moderate, long-term consequences: 0.224 TBI, severe, long-term consequences: 0.625	Panel study PC: Population (n=30,230) HSD: Description of impairments HSV: 100% Pairwise comparison/15% population health equivalence
Euro DW study 2013 Haagsma (2015) [43]	Traumatic brain injury	5	Concussion: 0.104 Severe TBI short-term consequences: 0.192 TBI, minor, long-term consequences: 0.089 TBI, moderate, long-term consequences: 0.214 TBI, severe, long-term consequences: 0.604	Panel study PC: Population (n=30,660) HSD: Description of impairments HSV: 100% Pairwise comparison/11% population health equivalence

* PC: panel composition; HSD: health state description; HSV: health state valuation technique.
ED: emergency department treatment; HA: hospital admission; PTO: person-trade-off; TBI: traumatic brain injury; TTO: time-trade-off; VAS: visual analogue scale.

Table 6.B GBD disability weights, health state description and severity classes according to GOSE and duration

GBD disability weight[7]	GBD Health state description[7]	GOSE points	Duration
No disability	–	8	-
Concussion	has headaches, dizziness, nausea and difficulty concentrating	6–7	<12 months
Minor TBI, long-term consequences	has episodes of headaches, memory problems, and difficulty concentrating.	6–7	>12 months
Moderate TBI, long-term consequences	has frequent headaches, memory problems, difficulty concentrating, and dizziness. The person is often anxious and moody.	4–5	>12 months
Severe TBI, short-term consequences	cannot concentrate and has headaches, memory problems, dizziness, and feels angry.	2–3	<12 months
Severe TBI, long-term consequences	cannot think clearly and has frequent headaches, memory problems, difficulty concentrating and dizziness. The person is often anxious and moody, and depends on others for feeding, toileting, dressing and walking.	2–3	>12 months

PART III

Outcome after traumatic brain injury

Chapter 7

Health-related quality of life after mild, moderate and severe traumatic brain injury: Patterns and predictors of suboptimal functioning during the first year after injury

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ABSTRACT

Background The Glasgow Outcome Scale Extended (GOSE) is the established functional outcome scale to assess disability following traumatic brain injury (TBI), however does not capture the patient's subjective perspective. Health-related quality of life (HRQL) does capture the individual's perception of disability after TBI, and has therefore been recognised as an important outcome in TBI. In contrast to GOSE, HRQL enables comparison of health outcome across various disease states and with healthy individuals. We aimed to assess functional outcome, HRQL, recovery, and predictors of 6 and 12 month outcome in a comprehensive sample of patients with mild, moderate or severe TBI, and to examine the relationship between functional impairment (GOSE) and HRQL.

Methods A prospective cohort study was conducted among a sample of 2,066 adult TBI patients who attended the emergency department (ED). GOSE was determined through questionnaires or structured interviews. Questionnaires 6 and 12 months after ED treatment included socio-demographic information and HRQL measured with Short-Form Health Survey (SF-36; reflecting physical, mental and social functioning) and Perceived Quality of Life Scale (PQoL; measuring degree of satisfaction with functioning).

Results 996 TBI survivors with mild, moderate or severe TBI completed the 6 month questionnaire. Functional outcome and HRQL after moderate or severe TBI was significantly lower than after mild TBI. Patients with moderate TBI showed greatest improvement. After one year, the mild TBI group reached outcomes comparable to population norms. TBI of all severities highly affected SF-36 domains physical and social functioning, and physical and emotional role functioning. GOSE scores were highly related to all SF-36 domains and PQoL scores. Female gender, older age, comorbidity and high ISS were strongest independent predictors of decreased HRQL at 6 and 12 months after TBI.

Conclusions HRQL and recovery patterns differ for mild, moderate and severe TBI. This study indicates that GOSE, although clinically relevant, fails to capture the subjective perspective of TBI patients, which endorses the use of HRQL as valuable addition to established instruments in assessing disability following TBI. Influence of TBI severity on recovery, together with female gender, older age, comorbidity and high ISS should be considered in long-term follow-up and intervention programmes.

7.1 INTRODUCTION

Traumatic brain injury (TBI) is a leading cause of death and long-term disability, particularly in young adults. TBI can cause assorted impairments and disabilities in functional, physical, emotional, cognitive, and social domains which drastically reduce health-related quality of life (HRQL).[1,2] Because of major improvements in trauma care, the number of survivors of severe TBI has rapidly grown.[3] However, the disability due to TBI has not appreciably reduced.[4] This has resulted in a shift in attention from mortality towards disability of TBI patients.

Disability following TBI is often assessed by functional measurement scales that have been designed for TBI specifically, e.g. the Glasgow Outcome Scale (GOS) and the GOS Extended (GOSE).[4,5] The GOS is a descriptive outcome scale with 5 categories. Five categories are believed to be too few to represent the wide range of mental and physical disability a patient can suffer following TBI.[6,7] Therefore, the GOS was extended to 8 categories, by dividing 3 categories into a lower and upper one. The GOSE is more sensitive to change than the GOS,[6,8] is quick to administer, can be applied to all cases, and has clinically relevant categories. These practical advantages have led to its widespread adoption in early management studies and clinical trials. However, one criticism of scales such as the GOSE is that they fail to capture the subjective perspective (e.g. HRQL) of TBI patients.[8]

HRQL reflects an individual's perception of how an illness and its treatment affect physical, mental and social aspects of his/her life.[9] HRQL has been recognised as an important outcome in TBI, because it provides well-standardised information on recovery patterns and frequency, nature, and predictors of disabilities.[10] In contrast to the GOSE, HRQL measures enable comparison of health outcome after TBI with other diseases and the general population, and their outcome in terms of an health status on a scale from 0 (death) to 1 (perfect health) scale can be used in economic evaluations. Research has shown that even years after injury, many TBI patients still report significantly lower HRQL than the general population.[1,2,11-14] Most studies however, focus on recovery after mild[15-17] or moderate and severe[1,12,13,18,19] TBI. HRQL and recovery pattern differences between mild, moderate and severe TBI are not often studied.

Large variation exists in the use of HRQL instruments to quantify the impact of TBI on population health over time. The most widely used instrument to estimate HRQL after TBI is the 36-Item Short-Form (SF-36) Health Survey;[20] a multidimensional questionnaire, reflecting features of health including physical, mental, and social functioning. Another HRQL instrument that has previously been used in TBI,[21,22] is the Perceived Quality of Life Scale (PQoL); a measure of the degree to which the individual is satisfied with his/her functioning, or global life satisfaction.[23] Findings from earlier studies suggest similar SF-36 and PQoL patterns after TBI.[7,21,24]

Due to the heterogeneity of TBI patients and their wide array of short- and long-term recovery patterns, accurate measurement of HRQL and the impact of all severities of TBI over time is needed. Furthermore, more insight is needed in the assessment of HRQL following TBI as a potential addition to established instruments, such as the GOSE. Therefore, the current study focused on HRQL after mild, moderate and severe TBI, and on the relationship between functional outcome measured with GOSE and HRQL measured with the SF-36 (including all domains) and PQoL.

The objectives of the present prospective cohort study were to 1) assess the functional outcome (GOSE), HRQL (SF-36 and PQoL), and recovery patterns at 6 and 12 months after mild, moderate and severe TBI,

2) assess the relationship and discrepancies between GOSE and HRQL for all TBI severity levels, and 3) test socio-demographic and injury-related characteristics as predictors for suboptimal functioning after TBI.

7.2 METHODS

Study design

Data for the present study was obtained from the Radboud University Brain Injury Cohort Study (RUBICS).[25-27] RUBICS is a prospective observational cohort study on the association between demographic and clinical variables, posttraumatic complaints, and functional outcome of patients with brain injury. This study encompassed multiple outcome measures (GOSE, SF-36 and PQoL) of patients 6 and 12 months after mild, moderate and severe TBI.

Between 1998 and 2010, patients admitted to the emergency department (ED) of the Radboud University Nijmegen Medical Centre (RUNMC), a level I trauma centre, with a diagnosis of mild, moderate or severe TBI were included in the RUBICS database. TBI was defined as an acute insult to the brain caused by an external physical force.[28] Mild and moderate TBI were defined by an ED Glasgow Coma Scale (GCS) score of, respectively, 13–15[29] and 9–12[30] after initial resuscitation at the ED or an admission GCS of, respectively, 13–15 and 9–12 followed by sedation and intubation during resuscitation for a non-neurological cause. Severe TBI was characterised by an ED GCS ≤8[31] after resuscitation. Clinical data registered by a neurologist and/or neurosurgeon in the ED was collected by a research nurse and entered into the RUBICS database. The RUBICS database comprised demographic data, trauma mechanism, hospitalisation, clinical injury variables, and comorbidities. Comorbidity was defined as the presence of any co-existing medical diseases or disease processes additional to the injury that the injury patients sustained. The following diseases were assessed as comorbid disease: asthma, chronic bronchitis, chronic non-specific lung disease (not questioned), heart disease, diabetes, back hernia or chronic backache, osteoarthritis, rheumatoid arthritis, and cancer. Further, Abbreviated Injury Scale of the Head (AISH) revised 1990 (AIS-90),[32] Injury Severity Score (ISS), and GOSE were recorded.

Study participants

In the current study, all patients, aged 16 years and older, with mild, moderate and severe TBI, admitted to the ED of RUNMC, between June 2003 and June 2010, who completed the 6 month questionnaire, were selected from the RUBICS database. Exclusion criteria were no informed consent, alcohol or drug abuse or dementia, unknown address, and inability to speak or write Dutch. Furthermore, patients who died within 6 months were excluded. Written informed consent was obtained from all participating patients.

Functional outcome measure

The GOSE scores functional outcome with eight questions covering consciousness, independence at home, major social roles (work, social and leisure activities, family and friendships), and return to normal life.[33] It results in an 8-point scale classifying functional outcome from 1 (dead) to 8 (complete recovery). GOSE scores were determined using a structured interview during regular visits to the outpatient clinic or during consultation by telephone.[34] Patients not visiting the outpatient clinic were sent a GOSE

questionnaire by regular mail, and when not returned a reminder was sent.[35] Finally, we attempted to reach all non-responding patients by telephone to acquire an outcome score. Assessment often took place at 6 (70%) and 12 (66%) months post-injury. Outcomes obtained within a 2 months range were also accepted if no outcome at exactly 6 or 12 months was available. Patients with a GOSE score of 1 (dead) were excluded from this study.

Health-related quality of life measures

HRQL was determined using the SF-36 (Version 1) and PQoL. Patients were asked to fill in a questionnaire, which included the HRQL measurements at 6 and 12 months post-injury.

The SF-36 is the most frequently used HRQL instrument in TBI and showed positive results for internal consistency and validity in a TBI population.[36,37] It is a 36-item questionnaire that covers eight domains of health status: physical functioning (PF), role limitations related to physical health problems (RP), bodily pain (BP), general health perception (GH), vitality (VT), social functioning (SF), role limitations related to emotional problems (RE), and mental health (MH).[38] For each domain, a summation of item responses is linearly transformed into a score ranging from 0 to 100. Physical (PCS) and mental summary scores (MCS) are calculated by standardising patients' scores, by subtracting Dutch subscale means from each individual's subscale scores and dividing the result by Dutch standard deviation to generate Z-scores.[39] In order to facilitate international comparison,[40] Z-scores are multiplied by United State (US) subscale factor coefficients for PCS and MCS and summed over all eight subscales into PCS and MCS sums. Both sums were re-scaled into T-scores, with a mean of 50 and standard deviation of 10 for the US norm population.[40] Missing values at 6 and 12 months of 10.8% and 10.7% of the respondents were replaced by the mean value of the respondents' completed items in the same scale, provided that at least 50% of the items within that scale had been completed.[38]

The PQoL was initially developed as a cognitive appraisal of life satisfaction for patients after intensive medical care.[41] It has been used for adults with chronic neurologic disability[21,42] and showed good internal reliability in a TBI population.[22] PQoL measures the degree to which the individual is satisfied with his/her functioning on an 11-point scale ranging from 0 (extremely dissatisfied) to 10 (extremely satisfied). It consists of 19 items in 3 domains (physical, cognitive and social), assessing 10 areas of functioning including physical health, thinking and remembering, family relationships, community participation and leisure, work and income, and meaning and purpose of life. PQoL scores may be considered a measure of global life satisfaction, with PQoL <7.5 ''Dissatisfied'' and PQoL >7.5 ''Satisfied''.[23] A previous study showed that the PQoL scores in adults without chronic conditions, range between 8.3 and 8.5.[42] We used the mean score (range of 0 to 10) in our analyses. Because PQoL scores can only be computed in case of complete information on all items, missing values of 11.4% respondents at both 6 and 12 months were estimated by hot deck imputation per domain if at least 50% of the items within that domain had been completed, using the reported values of respondents with similar scores on the items that were reported in that domain.[43]

Data and statistical analysis

Analysis of variance (ANOVA), Chi-square statistics (dichotomous variables), and Student's t tests (continuous variables) were used for between-group comparisons on socio-demographic and injury-related variables, and the influence of AISH (<3 versus ≥3) on HRQL in patients with mild TBI. A paired t

test was used to evaluate the difference between 6 and 12 month patients' SF-36 scores. The relationship between GOSE and HRQL was determined by comparing the mean SF-36 domain scores and PQoL scores across GOSE categories using ANOVA (degrees of freedom = 5). Correlations were analysed with Spearman's r. Additional analyses were done to look for discrepancies between GOSE and HRQL outcomes, comparing patients with and without poor functional outcome (defined as GOSE ≤4) with high SF-36 domain scores (defined per SF-36 domain score as higher than or equal to third quartile of overall domain score), or patients with and without good functional outcome (defined as GOSE ≥7) with low SF-36 domain scores (defined per SF-36 domain score as lower than or equal to first quartile of overall domain score). A value of $p<0.05$ was used to determine statistical significance.

Socio-demographic and injury-related characteristics were tested as predictors of HRQL measured with the SF-36 domains and PQoL score 6 and 12 months after TBI in a simple linear regression analysis. We included the socio-demographic variables gender (male/female), age (continuous), a dummy-coded variable for primary/secondary (reference), higher and academic education, and comorbidity (continuous). The injury-related variables were a dummy-coded variable for GCS 13–15 (mild TBI, reference), GCS 9–12 (moderate TBI), and GCS 3–8 (severe TBI), ISS (continuous), and AISH (continuous). Variables associated with outcome ($p<0.20$ in the univariable analysis) were included in stepwise multivariable linear regression analyses.[44,45] Analysis of the variance inflation factor (VIF) showed low VIF-values (all VIFs<1.9), indicating that higher order collinearity was not problematic in this study. None of the variables showed high correlations between each other (all variables $r<0.7$).

All statistical analyses were carried out using the statistical package SPSS for Windows, version 21 (IBM SPSS Statistics, SPSS Inc, Chicago, IL).

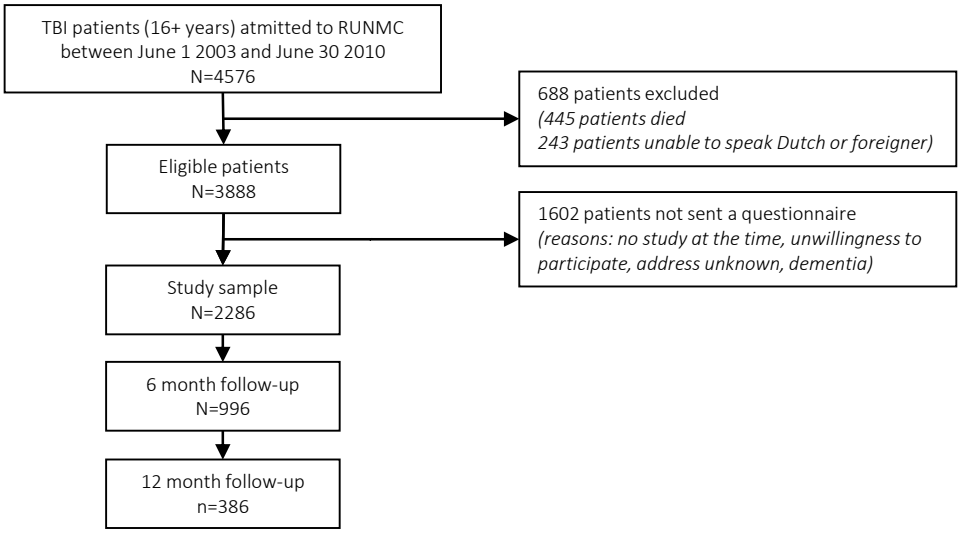
7.3 RESULTS

Patient characteristics

Between June 2003 and June 2010, 4,576 patients with TBI of 16 years old and older were admitted to the ED of the Radboud University Nijmegen Medical Centre (Figure 7.1). Of these patients, 688 were excluded from the database due to inability to speak Dutch, or death. Mortality for mild, moderate and severe TBI was, respectively, 4.1%, 17.2%, and 35.7%. Of the 3,888 eligible patients, 1,602 did not receive a first questionnaire due to various reasons (e.g. dementia, unknown address). Of the 2,286 TBI patients that received a 6 month questionnaire, 996 (44%) completed the 6 month questionnaire, of whom 386 (39%) filled in the 12 month questionnaire.

Of the 996 respondents, 797 had mild (80%), 50 moderate (5%) and 149 severe (15%) TBI (Table 7.1). The median age of the respondents was 44 years and 63% were male. Respondents with severe TBI were significantly younger than respondents with mild or moderate TBI (median age 39 years versus 45 years and 47 years, $F=5.5$, $df=2$, $p=0.004$). Respondents with moderate TBI more often were female (56%, $F=6.4$, $df=2$, $p=0.002$).

Figure 7.1 Flow chart of patient inclusion throughout the study



Respondents who also filled in the 12 month follow-up questionnaire (74% mild, 6% moderate and 21% severe TBI) had a significantly higher head AIS-score (F=4.6, df=1, p=0.033), GCS score (F=21.4, df=1, p<0.001), and were significantly more often admitted to hospital (Chi^2=17.6, p<0.001) and more often admitted to the Intensive Care (IC; Chi^2=6.2, p=0.009) than non-respondents. Furthermore, comparison of the characteristics of responders and non-responders to the 12 month follow-up survey showed that respondents who filled in both the 6 and 12 month questionnaire were older and more likely to be female, though these differences were not significant.

Functional outcome and HRQL for mild, moderate and severe TBI

According to the GOSE scores, at 6 and 12 months 36% and 23% of all respondents had an unfavourable outcome (GOSE ≤6). GOSE was significantly lower for respondents with moderate or severe TBI than for those with mild TBI (6 months F=53.1, 12 months F=28.3, df=2, both p<0.001, Table 7.2). The majority of the respondents (54% and 55% at 6 and 12 months, respectively) reported on the SF-36 a higher PCS than MCS. Respondents with moderate or severe TBI had significantly lower outcomes than mild TBI on PCS, physical functioning, role physical, social functioning and role emotional (F=8.5–20.4, df=2, all p<0.001).

All SF-36 domains showed improvement over time after mild, moderate and severe TBI (Figure 7.2), except mental health for respondents with severe TBI. Individual patients' scores revealed significant improvement for only mild and moderate TBI, on the domains physical functioning, role physical, bodily pain, social functioning and PCS (t(340–378)= –5.10 to –3.52, 95%CI [–11.70 to –2.23, –4.14 to –0.81]; all p<0.001), and lowest change for all severities on general health, vitality, mental health and MCS. Respondents with moderate TBI showed greatest improvement over time. This group went from lowest 6 month scores on all SF-36 domains except physical functioning, to higher 12 month scores than severe TBI on all SF-36 domains except social functioning and role emotional, and even higher 12 month scores than mild TBI on physical functioning, general health and vitality.

Table 7.1 Characteristics of the study population

	All	Severe (GCS≤8)	Moderate (GCS=9-12)	Mild (GCS≥13)
N	996	149 (15.0)	50 (5.0)	797 (80.0)
Gender (male)	628 (63.1)	107 (71.8)	22 (44.0)	499 (62.6)
Age[1] (years)	44 (27–57)	39 (22.5–54.5)	47 (27–61.3)	45 (28–57)
Education				
Primary education	34 (3.4)	4 (2.7)	5 (10.0)	25 (3.1)
Secondary education	515 (51.7)	114 (76.5)	35 (70.0)	366 (45.9)
Higher professional education	143 (14.4)	20 (13.4)	5 (10.0)	118 (14.8)
Academic education	95 (9.5)	4 (2.7)	3 (6.0)	88 (11.0)
Unknown	*209 (21.0)*	*7 (4.7)*	*2 (4.0)*	*200 (25.1)*
Injury mechanism				
Road traffic accidents	493 (49.5)	94 (63.1)	24 (48.0)	375 (47.1)
Fall	330 (33.0)	34 (22.8)	22 (44.0)	273 (34.3)
Sports	93 (9.3)	9 (6.0)	2 (4.0)	82 (10.3)
Assault	47 (4.7)	4 (2.7)	0 (0.0)	43 (5.4)
Other/unknown	*34 (3.4)*	*8 (5.4)*	*2 (4.0)*	*24 (3.0)*
Injury severity				
ISS[1]	9 (5–18)	29 (20–38)	20.5 (10–29)	6 (4–14)
AISH[1]	2 (2–3)	4 (3–5)	4 (2–4)	2 (2–2)
Head AIS 3	152 (15.5)	43 (29.7)	10 (20.4)	99 (12.5)
Head AIS 4	123 (12.5)	45 (31.0)	16 (32.7)	62 (7.9)
Head AIS 5	63 (6.4)	41 (28.3)	10 (20.4)	12 (1.5)
Comorbidity[2]				
No pre-existing disease	489 (49.1)	98 (65.8)	26 (52.0)	365 (45.8)
1 comorbid disease	135 (13.6)	23 (15.4)	13 (26.0)	99 (12.4)
2 comorbid diseases	43 (4.3)	6 (4.0)	3 (6.0)	36 (4.5)
3 or more comorbidities	52 (5.2)	4 (2.7)	2 (4.0)	43 (5.4)
Unknown	*277 (27.8)*	*18 (12.1)*	*5 (10.0)*	*254 (31.9)*
Hospitalisation[3]				
Hospital admission	597 (59.9)	144 (96.6)	46 (92.0)	407 (51.1)
Number of days hospitalised[1]	6 (2–14)	17.5 (7.3–32)	11 (6–20.5)	3 (1–8)
IC admission	167 (16.8)	118 (79.2)	14 (28.0)	35 (4.4)
Number of days on IC[1]	4 (2–10)	6 (2–10.3)	6 (2–16.3)	2 (1–5)

[1] Data is displayed as median, with the first and third quartile given within brackets.
[2] Comorbidity is defined as the presence of any co-existing medical diseases or disease processes additional to the injury that the injury patients sustained. The following diseases were assessed as comorbid disease: asthma, chronic bronchitis, chronic non-specific lung disease (not questioned), heart disease, diabetes, back hernia or chronic backache, osteoarthritis, rheumatoid arthritis, and cancer.
[3] Hospital or IC admission for one day or more after arrival at emergency department.

At one year follow-up, only respondents with mild TBI reached outcomes comparable to the Dutch population norm on all the SF-36 domains. Comparison of patients' scores with the Dutch general norm showed that mild, moderate and severe TBI all highly affected the domains physical functioning, role physical, social functioning, and role emotional.

PQoL scores showed that, at 6 and 12 months 40% and 37% of all respondents were dissatisfied with their functioning (PQoL<7.5). Mean PQoL scores ranged from 7.4 and 7.3 after severe or moderate TBI to 7.6 after mild TBI, compared to mean PQoL scores of 8.3 to 8.5 measured in adults without chronic conditions.[42] Of the 346 respondents who filled in both 6 and 12 month PQoL, 50% reported a decreased PQoL over time (from 8.0 to 7.1). In total, at 6 and 12 months 31 (4.0%) and 12 (3.2%) respondents scored at the scale ceiling.

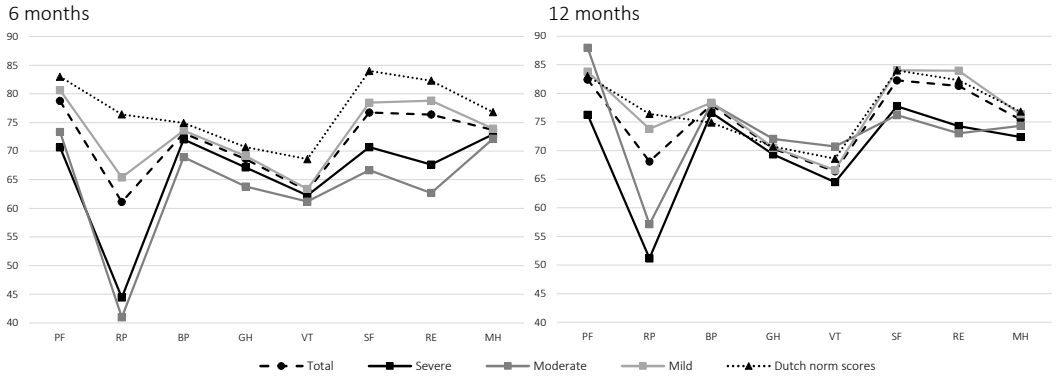
Additional analyses on multiple organ injury showed no statistical difference in SF-36 or PQoL scores between respondents with or without polytrauma besides TBI, except for SF-36 physical functioning at 6 months (t(885)=2.36, 95%CI [0.86, 9.66]; p=0.019). The GOSE also showed statistical difference between respondents with and without polytrauma at 6 months (t(963)=3.11, 95%CI [0.11, 0.50]; p=0.002).

Table 7.2 Data on clinical outcome and health related quality of life at 6 and 12 months after TBI

	Severe (GCS≤8)				Moderate (GCS 9–12)				Mild (GCS≥13)			
	N	Observed range	Mean (SD)	Median	N	Observed range	Mean (SD)	Median	N	Observed range	Mean (SD)	Median
6 months												
GOSE[1](1-8)	142	3-8	–	6.0	50	3-8	-	6.0	773	3-8	-	7.0
3	7 (4.7)				1 (2.0)				3 (0.4)			
4	14 (9.4)				6 (12.0)				28 (3.5)			
5	27 (18.1)				5 (10.0)				71 (8.9)			
6	49 (32.9)				17 (34.0)				116 (14.6)			
7	21 (14.1)				12 (24.0)				189 (23.7)			
8	24 (16.1)				9 (18.0)				366 (45.9)			
SF-36 (0-100)												
PF	142	0–100	70.7 (30.0)	80.0	48	5–100	73.4 (25.8)	80.0	754	0–100	80.6 (25.8)	95.0
RP	139	0–100	44.4 (40.9)	25.0	47	0–100	41.0 (41.8)	25.0	762	0–100	65.4 (42.2)	100.0
BP	145	12–100	72.0 (24.0)	74.0	49	22–100	68.9 (25.3)	62.0	786	0–100	73.6 (25.8)	74.0
GH	143	10–100	67.2 (20.1)	67.0	49	20–100	63.8 (20.9)	67.0	775	0–100	69.2 (22.2)	72.0
VT	143	0–100	62.3 (19.1)	65.0	47	15–100	61.2 (21.4)	65.0	779	0–100	63.4 (21.0)	65.0
SF	145	0–100	70.7 (27.2)	75.0	48	12.5–100	66.7 (28.6)	62.5	787	0–100	78.5 (25.0)	87.5
RE	139	0–100	67.6 (41.5)	100.0	46	0–100	62.7 (44.6)	100.0	761	0–100	78.8 (36.1)	100.0
MH	143	8–100	72.9 (19.0)	76.0	47	24–100	72.1 (22.7)	75.0	778	0–100	73.9 (19.1)	80.0
PCS	133	20.0–61.7	45.0 (9.9)	45.4	46	22.3–59.2	45.2 (9.7)	45.4	732	9.5–69.5	48.8 (11.0)	52.4
MCS	133	17.2–68.5	47.2 (11.6)	50.1	46	18.9–62.2	45.5 (13.3)	47.7	732	7.2–72.7	48.1 (11.2)	51.7
PQoL (0–10)	134	1–10	7.4 (1.8)	7.6	48	3–10	7.3 (1.9)	7.5	584	0–10	7.6 (1.9)	8.1
12 months												
GOSE[1](1–8)	105	3–8	–	7.0	33	4–8	–	7.0	364	3–8	–	8.0
3	4 (2.7)				–				2 (0.3)			
4	5 (3.4)				1 (2.0)				5 (0.6)			
5	9 (6.0)				2 (4.0)				18 (2.3)			
6	32 (21.5)				7 (14.0)				28 (3.5)			
7	24 (16.1)				8 (16.0)				74 (9.3)			
8	31 (20.8)				15 (30.0)				237 (29.7)			
SF-36 (0–100)												
PF	80	0–100	76.3 (25.7)	85.0	20	40–100	87.9 (17.9)	95.0	273	0–100	83.8 (23.3)	95.0
RP	79	0–100	51.2 (43.2)	50.0	21	0–100	57.1 (48.2)	100.0	275	0–100	73.8 (38.6)	100.0
BP	82	12–100	76.6 (22.2)	77.0	21	22–100	78.2 (24.6)	84.0	280	0–100	78.4 (24.9)	84.0
GH	82	15–100	69.3 (20.2)	72.0	20	15–100	72.1 (23.6)	73.5	278	0–100	70.6 (21.1)	72.0
VT	82	13.3–100	64.5 (18.5)	65.0	21	10–100	70.7 (26.8)	80.0	278	15–100	66.6 (19.8)	70.0
SF	82	37.5–100	77.7 (19.3)	81.3	21	37.5–100	76.2 (25.0)	87.5	280	12.5–100	84.0 (21.4)	100.0
RE	79	0–100	74.3 (39.2)	100.0	21	0–100	73.0 (43.0)	100.0	277	0–100	83.9 (33.1)	100.0
MH	82	24–100	72.4 (17.9)	74.0	21	20–100	74.3 (25.0)	80.0	279	20–100	76.3 (18.5)	80.0
PCS	76	21.5–67.1	47.4 (10.1)	50.2	19	26.3–59.3	49.7 (8.9)	51.6	268	9.4–68.8	50.4 (10.4)	54.8
MCS	76	20.1–63.1	48.1 (10.8)	50.8	19	12.7–63.0	46.8 (15.8)	51.0	268	9.8–68.6	49.6 (10.5)	52.3
PQoL (0–10)	81	2–10	7.3 (1.6)	7.7	18	4–10	7.9 (1.8)	8.7	279	0–10	7.7 (1.9)	8.1

[a] Data is displayed as number (N), with the percentage given within brackets. GOSE: Glasgow Outcome Score Extended; SF-36: Short-Form-36; PF: physical functioning; RP: role physical; BP: bodily pain; GH: general health; VT: vitality; SF: social functioning; RE: role emotional; MH: mental health; PCS: physical component score; MCS: mental component score; PQoL: Perceived Quality of Life.

Figure 7.2 SF-36 at 6 and 12 months for mild, moderate and severe TBI

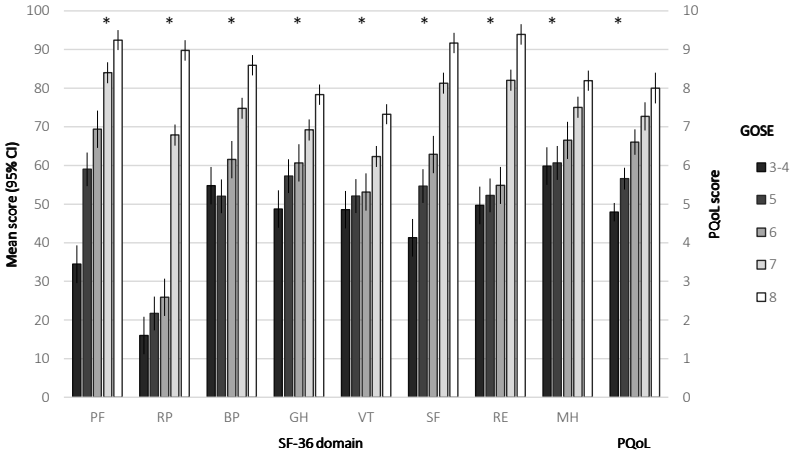


SF-36: Short-Form-36; PF: physical functioning; RP: role physical; BP: bodily pain; GH: general health; VT: vitality; SF: social functioning; RE: role emotional; MH: mental health; Dutch norm scores from Aaronson and colleagues (1998)

HRQL compared to GOSE levels

The mean 6 and 12 month SF-36 scores were generally appropriately ordered for each GOSE category (Figure 7.3). There was a particularly strong relationship between the GOSE and the SF-36 domains physical functioning (r=0.62, p<0.001), role physical (r=0.68, p<0.001) and social functioning (r=0.61, p<0.001). The mean scores of all eight SF-36 domains significantly increased with higher GOSE categories at 6 months (F=43.2–163.8, df=5, all p<0.001) and 12 months (F=10.8–46.3, df=5, all p<0.001). The PQoL also showed a significant increase with higher GOSE categories at 6 months (F=53.7, df=5, p<0.001) and 12 months (F=29.5, df=5, p<0.001).

Figure 7.3 Comparison of SF-36 domain scores and PQoL with GOSE 6 months after TBI



* Significant increase of domain score with more favourable GOSE category (multiple ANOVA, all p<0.001).
Mean (error bars: 95% confidence interval [CI]) SF-36 domain scores, and Perceived Quality of Life (PQoL) plotted against Glasgow Outcome Score – Extended (GOSE) category; 3: Lower severe disability; 4: Upper severe disability; 5: Lower moderate disability; 6: Upper moderate disability; 7: Lower good recovery; 8: Upper good recovery; SF-36: Short-Form-36; PF: physical functioning; RP: role physical; BP: bodily pain; GH: general health; VT: vitality; SF: social functioning; RE: role emotional; MH: mental health.

Additional analysis on discrepancies between GOSE and SF-36 showed that at 6 months a small number of patients reported high SF-36 domain scores while having a low GOSE score, ranging from no differences on the social functioning domain to 3.1% on bodily pain and 3.2% on the role emotional domain. Patients more often reported low SF-36 domain scores at 6 months while having a high GOSE score, with smallest differences on the role physical domain (8.3%) and largest differences on general health (24.8%), mental health (25.1%) and vitality (31.1%). High SF-36 domain scores while having a low GOSE score was significantly related to injury-related characteristics and more common among patients with more severe TBI according to the GCS (in general health and vitality; t(792–828)=3.96 to 4.24, 95%CI [0.20 to 0.24, 0.60 to 0.66]; both p<0.001), higher ISS (in bodily pain, vitality, role emotional and mental health; t(782–876)= –6.60 to –4.87, 95%CI [–13.70 to –11.32, –7.36 to –4.80]; all p<0.001) and higher AISH (in bodily pain, general health and mental health; t(828–876)=–4.46 to –2.18, 95%CI [–1.10 to –0.63, –0.42 to –0.03]; all p<0.05). The reporting of low SF-36 domain scores while having a high GOSE score was significantly related to socio-demographic characteristics and more often occurred among females (in bodily pain, general health and vitality; Chi^2=4.4–9.5, all p<0.05), older patients (in physical functioning and bodily pain; t(831–885)=–4.78 to –2.29, 95%CI [–15.56 to –6.71, –6.50 to –0.59]; all p<0.05), less educated patients (in bodily pain; Chi^2=11.3, p=0.003) and patients with multiple comorbid diseases (in all SF-36 domains except social functioning, role emotional and mental health; t(594–640)=–3.71 to –2.35, 95%CI [–1.58 to –0.53, –0.45 to –0.05]; all p<0.02).

Predictors for HRQL after TBI

At 6 months, females tended to have lower outcome on all SF-36 domains, except general health and role emotional (both not significant), as well as lower PCS, MCS and PQoL (t(764–978)=2.09 to 4.79, 95%CI [0.06 to 4.20, 0.63 to 12.72]; all p<0.05, Table 7.3). Older respondents showed lower outcome on all SF-36 domains, except vitality, social functioning, mental health and MCS (t(764–978)=–5.93 to –2.03, 95%CI [–13.83 to –0.64, –6.95 to –0.09]; all p<0.05). Respondents with comorbid diseases tended to have lower outcome on all SF-36 domains, except role emotional and mental health, as well as lower PCS and PQoL (t(651–705)=–8.29 to 0.47, 95%CI [–28.78 to –1.63, –17.52 to 3.08]; all p<0.005). The more severe injured patients (higher ISS) showed lower outcome on all SF-36 domains, PCS, MCS and PQoL (t(763–976)=–9.03 to –2.37, 95%CI [–31.23 to –0.78, –20.08 to –0.22]; all p<0.02).

After one year (data not shown), females still had lower outcome on the presented items, with exception of SF-36 physical functioning, role physical, PCS and PQoL (t(361–381)=1.99 to 3.80, 95%CI [0.02 to 4.02, 4.72 to 12.64]; all p<0.05). Older respondents still showed lower outcome on physical functioning, general health and PCS (t(361–378)=–3.09 to –3.56, 95%CI [–13.47 to –5.11, –3.87 to –0.87]; all p<0.01). Respondents with comorbidity still showed lower outcome on all SF-36 domains, except social functioning, role emotional and mental health, as well as lower PCS and PQoL (t(317–336)=–5.93 to –2.35, 95%CI [–31.86 to –1.70, –13.36 to –0.47]; all p<0.05). In contrast to lower outcome on all 6 month items, after one year, respondents with higher ISS scores showed lower outcome on only SF-36 domains physical functioning, role physical, social functioning and role emotional (t(370–380)=–3.87 to –2.17, 95%CI [–25.38 to –10.52, –8.28 to –0.53]; all p<0.05).

Table 7.3 Determinants in relation to health-related quality of life at 6 months after TBI

Determinants	SF-36 domains										PQoL
	PF n=944	RP n=948	BP n=980	GH n=967	VT n=969	SF n=980	RE n=946	MH n=968	PCS n=911	MCS n=911	n=766
Socio-demographic characteristics											
Gender (male reference)	–0.068*	–0.079*	–0.141*	–0.059	–0.150*	–0.105*	–0.060	–0.097*	–0.095*	–0.088*	–0.087*
	*–0.072**	*–0.132**	*–0.151**	–	*–0.171**	*–0.144**	–	*–0.106**	*–0.108**	*–0.096**	*–0.091**
Age at injury (years)	–0.276*	–0.131*	–0.122*	–0.228*	–0.027	–0.087*	–0.126*	–0.033	–0.235*	–0.014	–0.157*
	*–0.213**	–	–	*–0.178**	–	–	*–0.129**	–	*–0.155**	–	*–0.087**
Education	*	*	*	*	–	*	*	–	*	–	*
Primary/Secondary (reference)	0	0	0	0	0	0	0	0	0	0	0
Higher professional	0.161*	0.126*	0.122*	0.102*	0.059	0.102*	0.103*	0.073*	0.147*	0.056	0.103*
	*0.133**	*0.090**	*0.115**	–	–	–	–	–	*0.118**	–	*0.099**
Academic education	0.168*	0.170*	0.154*	0.072*	0.048	0.125*	0.092*	0.047	0.187*	0.027	0.119*
	*0.106**	*0.112**	*0.130**	–	–	–	–	–	*0.133**	–	*0.095**
Comorbidity[1] (number of diseases)	–0.281*	–0.143*	–0.262*	–0.261*	–0.155*	–0.138*	–0.072	–0.023	–0.306*	0.002	–0.207*
	*–0.221**	*–0.171**	*–0.259**	*–0.214**	*–0.164**	*–0.160**	–	–	*–0.261**	–	*–0.171**
Injury characteristics											
GCS	*	*	–	–	–	*	*	–	*	–	–
Mild (GCS≥13, reference)	0	0	0	0	0	0	0	0	0	0	0
Moderate (GCS 9–12)	–0.060	–0.124*	–0.040	–0.054	–0.023	–0.099*	–0.092*	–0.020	–0.073*	–0.050	–0.041
	–	–	–	–	–	–	–	–	–	–	–
Severe (GCS≤8)	–0.133*	–0.173*	–0.022	–0.033	–0.019	–0.107*	–0.105*	–0.018	–0.125*	–0.029	–0.047
	–	–	–	–	–	–	–	–	–	–	–
ISS (0 no, 1 minor – 75 untreatable)	–0.231*	–0.287*	–0.132*	–0.102*	–0.093*	–0.208*	–.0160*	–0.098*	–0.234*	–0.095*	–0.129*
	*–0.353**	*–0.304**	*–0.262**	*–0.130**	*–0.139**	*–0.259**	*–0.163*	*–0.106**	*–0.347**	*–0.103**	*–0.125**
AISH (0 no, 1 minor – 5 critical)	–0.067*	–0.171*	0.016	–0.058	–0.042	–0.133*	–0.127*	–0.046	–0.076*	–0.085*	–0.057
	*0.195**	–	*0.182**	–	–	–	–	–	*0.169**	–	–
Multivariable linear regression											
N	*668*	*678*	*697*	*694*	*695*	*707*	*946*	*968*	*647*	*911*	*690*
R^2	*0.220*	*0.154*	*0.153*	*0.112*	*0.069*	*0.080*	*0.042*	*0.021*	*0.214*	*0.018*	*0.088*
Sign	*<0.001*	*<0.001*	*<0.001*	*<0.001*	*<0.001*	*<0.001*	*<0.001*	*<0.001*	*<0.001*	*<0.001*	*<0.001*

Standard beta coefficients are presented: simple linear regression analysis (1st row), multivariable regression analysis in *italics* (2nd row). Variables associated with outcome in simple linear regression analysis, were included in multivariable regression analyses. 95% confidence interval. * Significant difference at p<0.05.

[1] Comorbidity is defined as the presence of any co-existing medical diseases or disease processes additional to the injury that the injury patients sustained. The following diseases were assessed as comorbid disease: asthma, chronic bronchitis, chronic non-specific lung disease (not questioned), heart disease, diabetes, back hernia or chronic backache, osteoarthritis, rheumatoid arthritis, and cancer. SF-36: Short-Form-36; PF: physical functioning; RP: role physical; BP: bodily pain; GH: general health; VT: vitality; SF: social functioning; RE: role emotional; MH: mental health; PCS: physical component score; MCS: mental component score; PQoL: Perceived Quality of Life; GCS: Glasgow Coma Scale; ISS: Injury Severity Score: AISH: Abbreviated Injury Scale Head.

7.4 DISCUSSION

The purpose of this paper was to assess HRQL and recovery patterns at 6 and 12 months after mild, moderate and severe TBI to examine the relationship between GOSE and HRQL, and to test predictors for suboptimal functioning after TBI. We found that TBI of all severities strongly affected functional outcome and HRQL, with only patients with mild TBI reaching outcomes comparable to general population norms at one year follow-up. In line with our expectations, HRQL and recovery patterns differed after mild, moderate and severe TBI. GOSE scores were highly related to all SF-36 domains and PQoL scores. Female gender, older age, comorbidity and high ISS were strongest independent predictors of decreased HRQL at 6 and 12 months after TBI.

In contrast to most other studies, this study examined HRQL in a comprehensive sample of TBI patients of all severity levels. Surprisingly, at 6 months moderate TBI patients scored lower on almost all SF-36 domains and reported lower PQoL scores than severe TBI. This intriguing trend toward greater difficulty after moderate TBI than after severe TBI was also reported in other studies.[21,46,47] A possible explanation for this finding may be that survivors of severe injuries perceive some of their problems as less difficult, or their appreciation of being alive might outweigh their concerns about functioning. Those with moderate injuries would both have problems and be distressed about them.[21]

SF-36 patterns at 6 and 12 months for all 3 severities reflect those reported in earlier studies on HRQL after TBI.[20] All SF-36 domain scores for all 3 TBI severities increased over time, suggesting improvement on the whole spectrum of HRQL after mild, moderate and severe TBI. However, comparison of SF-36 outcome at one year follow-up with Dutch population norms[39] revealed outcomes in line with studies in which HRQL was lower for TBI patients than for the general population.[2,11-13] This study used Dutch population norms, which vary from US population norms.[40] The Dutch population reported lower physical domain scores and higher mental domain scores than the US population, with largest differences in the domains role physical (–4.2; Dutch: 77.0 vs US: 81.2) and vitality (+7.1; Dutch: 68.2 vs US: 61.1).[39,40] Comparison of patients' scores with the US population norms, however, revealed the same outcomes, in that TBI of all severities strongly affected HRQL and that only patients with mild TBI reached outcomes comparable to the general population at one year follow-up. The latter was also indicated in a study of MacKenzie and colleagues, in which trauma patients with an AISH of 2, considered as mild TBI, reached outcomes at one year follow-up comparable to the US population norms on all SF-36 domains, except bodily pain and general health.[48]

Our study also provided insight in the assessment of HRQL following TBI as a potential addition to GOSE. The significant relationship of increasing scores with more favourable GOSE category across all SF-36 domains confirms results of earlier studies.[8,36] This study was the first to examine the relationship between GOSE and PQoL, which also showed a significant increase with higher GOSE categories. Analysis on discrepancies between GOSE and SF-36 showed that at 6 months only a few patients reported high HRQL while having poor functional outcome, which was significantly more common among patients with more severe TBI in terms of GCS, ISS and AISH (especially in bodily pain, general health and mental HRQL domains). However, on some HRQL domains up to one third of the patients reported low HRQL while having good functional outcome, which significantly more often occurred among females, older patients, less educated patients, and patients with multiple comorbid diseases (especially physical HRQL domains). Our study therefore indicates that although functional outcome

(measured with the GOSE) is highly associated with HRQL, the discrepancies between GOSE and HRQL endorse the use of HRQL as valuable addition to established instruments in assessing disability following TBI. HRQL measures have the advantages over instruments like the GOSE, that they capture the individual's perception of disability following TBI, enable comparison of health outcome across various disease states and with healthy individuals, and can be used in economic evaluations.

Subsequent to initiation of our study, a disease specific HRQL measure for TBI, the Quality of Life after Brain Injury (QOLIBRI), has been developed.[49] It captures the individuals' well-being and satisfaction, and provides a profile of HRQL in 6 domains together with an overall score. The QOLIBRI consists of 37 items and measures physical, psychological (emotional and cognitive), social and functional changes typical of TBI.[49] The QOLIBRI seems a promising instrument to measure HRQL after TBI with good correlation with the GOSE and providing additional information to the SF-36.[50]

Additionally, we tested predictors for suboptimal functioning 6 and 12 months after TBI. Female gender was the most striking. Multiple studies have reported poorer outcomes after TBI among females.[51-53] A possible explanation for this finding may be disruption of hormone production after injury in females.[53] However, the mechanism behind gender differences in outcome after TBI is not entirely clear.

The presented results made no distinction between outcome after TBI with or without additional multiple organ injury. Our study showed no statistical difference in SF-36 or PQoL scores between respondents with or without polytrauma besides TBI, except for SF-36 physical functioning at 6 months. The GOSE, which according to our findings was strongly related to SF-36 physical functioning, also showed statistical difference between respondents with and without polytrauma at 6 months. Similar results with regard to SF-36 have previously been reported,[54,55] suggesting outcome after TBI is not influenced by polytrauma.

Apart from these promising findings, there are some potential validity problems with administering HRQL measurement questionnaires to patients with cognitive impairments.[56] In severely impaired persons, awareness of cognitive and other deficits may be reduced. Therefore, measuring a construct such as HRQL in persons with cognitive deficits via self-rated questionnaires represents a major methodological challenge. However, recent research indicated that although lack of awareness is expected among people with severe TBI soon after the injury, most people with TBI, even those with severe functional limitations, are aware of those deficits 6 months after injury and rate their satisfaction accordingly.[57]

In our study, the severity of TBI was defined by the GCS. Although the GCS is the established instrument to define TBI severity, a small sample of patients with mild TBI in our study had an AISH 3 or higher. The severity of these injuries however did not affect HRQL, except the SF-36 domains role physical and role emotional. The higher scores of patients with an AISH 3 or higher on these role functioning scales may be influenced by the use of SF-36 version 1, which has dichotomous response choices instead of the five-level response choices in version 2. During the preparation of this study, a validated Dutch SF-36 version 2 was not yet available.

It is a limitation that this study was restricted to TBI patients of one hospital. The results do not necessarily apply to patients treated at other Dutch hospitals. A national multicentre study comparing the outcome of TBI patients could possibly improve the understanding of HRQL and the impact of all severities of TBI over time.

Finally, this study had to cope with a low response rate of 39% at 12 month follow-up. Comparison of the characteristics of responders and non-responders to the 12 month follow-up survey showed that respondents who filled in both the 6 and 12 month questionnaire were older and more likely to be female, though these differences were not significant. The low response rates may have led to selection bias and in its turn to under- or overestimation of the functional outcome and HRQL after TBI. Despite the low response rate, a strength of our study is that we used a relatively large study sample, with even 386 participants at 24 months.

Conclusions

TBI of all severities strongly affects HRQL, leading to lower HRQL of TBI patients compared to the general population. HRQL and recovery patterns differ for mild, moderate and severe TBI. This study indicates that the GOSE, although clinically relevant, fails to capture the subjective perspective of TBI patients, which endorses the use of HRQL as valuable addition to established instruments in assessing disability following TBI. Influence of TBI severity on recovery, together with female gender, older age, comorbidity and high ISS should be considered in long-term follow-up and intervention programmes.

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Chapter 8

Prevalence of and risk factors for anxiety and depressive disorders after traumatic brain injury: a systematic review

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ABSTRACT

Background This review examined pre- and post-injury prevalence of, and risk factors for, anxiety disorders and depressive disorders after traumatic brain injury (TBI), based on evidence from structured diagnostic interviews.

Methods A systematic literature search was conducted in EMBASE, MEDLINE, Cochrane Central, PubMed, PsycINFO, and Google Scholar. We identified studies in civilian adults with TBI reporting on the prevalence of anxiety and depressive disorders using structured diagnostic interviews and assessed their quality. Pooled pre- and post-injury prevalence estimates of anxiety disorders and depressive disorders were computed.

Results A total of 34 studies described in 68 publications were identified, often assessing anxiety disorders (n=9), depressive disorders (n=7), or a combination of disorders (n=6). Prevalence rates of psychiatric disorders varied widely. Pooled prevalence estimates of anxiety and depressive disorders were 19% and 13% before TBI and 21% and 17% in the first year after TBI. Pooled prevalence estimates increased over time and indicated high long-term prevalence of Axis I disorders (54%), including anxiety disorders (36%) or depressive disorders (43%). Females, those without employment, and those with a psychiatric history before TBI were at higher risk for anxiety and depressive disorders after TBI.

Conclusions We conclude that a substantial number of patients encounter anxiety and depressive disorders after TBI, and that these problems persist over time. All health care settings should pay attention to the occurrence of psychiatric symptoms in the aftermath of TBI to enable early identification and treatment of these disorders and to enhance the recovery and quality of life of TBI survivors.

8.1 INTRODUCTION

Traumatic brain injury (TBI) often imposes long-term consequences that complicate recovery and rehabilitation.[1] A significant proportion of TBI survivors is diagnosed with psychiatric disorders, with post-traumatic stress disorder (PTSD) and major depression (MD) being the most commonly diagnosed and studied disorders.[1-3]

Anxiety disorders and depressive disorders have a major impact on functional outcome of patients with TBI, and drastically reduce their health-related quality of life (HRQL).[4-9] Because of the high incidence of TBI and the common diagnosis of anxiety and depressive disorders post-TBI, this pathology imposes substantial disease burden and economic consequences to both individuals and society.

Early identification and treatment of psychiatric disorders in patients with TBI may improve their outcome, psychosocial functioning, and HRQL.[10,11] For early prevention and treatment, insight in the prevalence of and risk factors for anxiety and depressive disorders is needed.

Anxiety and depressive disorders can be diagnosed with use of standard criteria such as the Diagnostic and Statistical Manual of Mental Disorders (DSM)[12] or the International Statistical Classification of Diseases and Related Health Problems (ICD).[13] These criteria specify clinical disorders (so-called Axis I disorders in DSM) that represent acute symptoms that need treatment. Axis I disorders include a wide range of psychological diagnostic categories, for example, substance use, schizophrenia, psychotic disorders, dementia, and so on. Common Axis I disorders include anxiety disorders (generalised anxiety disorder (GAD), acute stress disorder (ASD), panic disorder, agoraphobia, specific phobia, social phobia, obsessive-compulsive disorder (OCD), and PTSD), and depressive disorders (dysthymia, bipolar disorder, and MD).

Previous reviews on psychiatric outcomes post-TBI reported a wide range of anxiety and depressive disorders among TBI survivors,[3,14-17] and large variation in prevalence rates.[3,15,17] These reviews found prevalence rates of anxiety as high as 70%[15] and rates of depressive disorders varying from 25% to 50%.[3,18] The existing reviews, however, focused solely on post-TBI prevalence rates of PTSD,[17,19,20] anxiety disorders,[15] or depressive disorders[18,21] or included studies with prevalence rates based on both self-report measures and structured diagnostic interviews.[18,22] Research, however, indicated that self-reports from TBI patients may be unreliable because of the overlap between psychiatric symptoms and disorders, memory deficits associated with TBI, and evidence that TBI patients tend to underestimate their functional problems.[10,15] In contrast to self-reports, the use of structured diagnostic interviews enables the clinical examination for the presence of psychiatric disorders according to standard criteria such as the DSM or ICD.[23] Use of these criteria in structured diagnostic interviews leads to more accurate prevalence estimates compared to self-report measures.[18,24] Self-report measures may provide an overestimation of psychiatric disorders post-TBI, given that they do not take into account the pre-existing or comorbid conditions of TBI patients and enable patients to report more symptoms by prompting them with specific questions.[25,26]

The current review was conducted to improve our knowledge on psychiatric outcomes post-TBI, which may enable early identification and treatment of these psychiatric disorders and may enhance the recovery and HRQL of patients with TBI. This review provides a full oversight of the prevalence of and risk factors for anxiety and depressive disorders in civilian adults with TBI, based on evidence from structured diagnostic interviews. The current study therefore analyzed existing research that has

examined the 1) pre- and/or post-injury prevalence of clinically diagnosed anxiety and depressive disorders post-TBI and/or 2) risk factors influencing the development of anxiety and depressive disorders post-TBI.

8.2 METHODS

Relevant studies were identified through systematic literature searches in the databases EMBASE, MEDLINE, Cochrane Central, PubMed, and PsycINFO. Grey literature was examined by Google Scholar. Search strategies were developed in consultation with a search expert and included a combination of subheadings and text words (Appendix 8.A). Reference lists and citation indices of the included papers and relevant reviews were inspected to identify additional relevant citations. We restricted searches to English-language articles, published in peer-reviewed journals until November 2, 2015.

Study selection

Study design – We included retrospective and prospective cohort studies, cross-sectional studies, and case-control studies. Reviews, case reports, editorials, and intervention studies were excluded.

Participants – Studies were included if they were conducted in civilian adults (16+ years) with TBI. Studies including a mixed population (e.g. all trauma patients) were only included if they analyzed their results for TBI patients separately. TBI was defined as an alteration in brain function or other evidence of brain pathology, caused by an external cause.[27] There was no restriction in the diagnosis of TBI (e.g. self-reported) or severity of TBI. There was also no restriction in the methods of patient selection (e.g. samples drawn from the emergency department (ED) or hospital, referral clinics, or outpatient programmes).

Psychiatric disorders – We included studies that examined all Axis I disorders or reported on the prevalence of at least one of the underlying anxiety disorders (including GAD, ASD, panic disorder, agoraphobia, specific phobia, social phobia, OCD, and PTSD) or depressive disorders (dysthymia, bipolar disorder, and MD) – see Table 8.1. All information on risk factors for anxiety or depressive disorders (from uni- or multivariable analysis) were extracted from the included studies.

Structured diagnostic interviews – We included studies that used structured diagnostic interviews for the diagnosis of disorders (see Table 8.2). Studies solely using self-report measures (e.g. checklist or rating scales) or other measures to determine disorders (e.g. told by doctor, own classification system) were excluded.

Multiple publications – To avoid double counting of prevalence rates, we identified publications that were related to the same sample of patients. For studies using data from an overlapping sample, one study was chosen as reference study by giving priority to the largest sample size (e.g. whole sample instead of specific age group or injury mechanism), the assessment of most disorders (e.g. Axis I over solely PTSD), and the focus on reporting prevalence rates (instead of predictors of disorders, or their impact on outcome). Information from all articles was used for analysing the risk factors for psychiatric disorders post-TBI.

Table 8.1 Overview of anxiety disorders and depressive disorders according to the DSM-5*

Disorder	Definition	Symptoms	Duration
Axis I			
	Clinical disorders	Acute symptoms that need treatment	
Anxiety			
Generalised anxiety disorder (GAD)	Excessive anxiety and worry about a number of events or activities	Restlessness or feeling keyed up or on edge; being easily fatigued; difficulty concentrating or mind going blank; irritability; muscle tension; sleep disturbance	Occurring more days than not and for ≥6 months
Acute stress disorder (ASD)	Exposure to actual/threatened death, serious injury, or sexual violation	Intrusion; negative mood; dissociation; avoidance; arousal	3 days to 1 month after trauma exposure
Panic disorder	Recurrent unexpected panic attacks (abrupt surge of intense fear or discomfort)	Palpitations; sweating; shaking; shortness of breath; choking; chest pain; nausea; dizziness; chills or heat sensations; numbness or tingling; derealisation; fear of losing control; fear of dying	≥1 attack followed by ≥1 month of persistent worry, or maladaptive change in behavior
Agoraphobia	Marked fear or anxiety about using public transportation; being in open or enclosed spaces, outside of the home alone, in a crowd; standing in line	Fear or anxiety; avoidance of situation	Persistent, typically lasting ≥6 months
Specific phobia	Marked fear or anxiety about an object or situation	Immediate fear or anxiety; avoidance of object or situation	Persistent, typically lasting ≥6 months
Social phobia	Marked fear or anxiety about ≥1 social situations with exposure to possible scrutiny by others	Fear to act in a way or show anxiety symptoms that will be negatively evaluated; avoidance of social situations	Persistent, typically lasting ≥6 months
Obsessive-compulsive disorder (OCD)	Presence of obsessions, compulsions, or both	Experience and ignorance or suppression of recurrent and persistent thoughts, urges, or images; repetitive behaviors or mental acts	Time-consuming (>1h/day) or interfere with functioning
Post-traumatic stress disorder (PTSD)	Direct experience or witnessing traumatic event, exposure to aversive details or involved friends or family	Persistent re-experiencing of event; avoidance of stimuli; negative alterations in cognitions and mood associated with event; alterations in arousal and reactivity	>1 month, interfere with functioning
Depression			
Dysthymia	Persistent depressive disorder	Poor appetite/overeating; insomnia/hypersomnia; low energy/fatigue; low self-esteem; poor concentration/difficulty making decisions; feelings of hopelessness	Occurring for most of the day, for more days than not, for ≥2 years
Bipolar disorder	Current or past hypomanic episode and major depressive episode	Inflated self-esteem or grandiosity; diminished need for sleep; more talkative than usual or pressure to keep talking; racing thoughts	Interfere with functioning
Major depression (MD)		Depressed mood; diminished interest/pleasure; significant weight loss/gain; insomnia/hypersomnia; agitation/retardation; fatigue/loss of energy; worthlessness/guilt; diminished ability to think/ concentrate; recurrent thoughts of death, suicidal ideation	Most of the day, nearly every day, interfere with functioning

* Obtained from: American Psychiatric Association (2013). *Diagnostic and statistical manual of mental disorders, (DSM-5®)*. American Psychiatric Pub.

Table 8.2 Structured diagnostic interviews

Disorder	Interview		Criteria	Assessment
Anxiety and depression				
	CIDI[28]	Composite International Diagnostic Interview	DSM/ICD	Trained lay interviewers
	DIS[29]	Diagnostic Interview Schedule	DSM	Trained lay interviewers
	MINI[30]	Mini International Neuropsychiatric Interview	DSM/ICD	Trained lay interviewers
	SADS-L[31]	Schedule for Affective Disorders and Schizophrenia-Lifetime	DSM	Trained psychiatrists / psychologists
	SCAN/PSE[32]	Schedules for Clinical Assessment in Neuropsychiatry (or Present State Examination)	DSM/ICD	Trained interviewers (clinicians)
	SCID[33]	Structured Clinical Interview for DSM Disorders	DSM	Mental health professional
ASD				
	ASDI[34]	Acute Stress Disorder Interview	DSM	Trained lay interviewer
PTSD				
	CAPS[35]	Clinician-Administered PTSD Scale	DSM	Trained subprofessionals
	PSS[36]	PTSD Symptom Scale	DSM	Trained lay interviewers
	PDS	Post-traumatic Diagnostic Scale	DSM	Trained lay interviewers
	PTSD-I[37]	Posttraumatic Stress Disorder Interview	DSM	Trained subprofessionals

ASD: acute stress disorder; DSM: Diagnostic and Statistical Manual of Mental Disorders; ICD: International Statistical Classification of Diseases and Related Health Problems; PTSD: posttraumatic stress disorder.

Data extraction and risk of bias assessment

The first review author (AS) screened all titles and abstracts and deleted obvious irrelevant citations. After initial selection, the reviewer (AS) screened the remaining citations on title and abstract and full-text. Any doubt on inclusion was resolved by consulting a second author (JH). Two reviewers (AS and MC) extracted data and assessed the risk of bias of the included studies. Any discrepancies were resolved by discussion or consulting a third author (SP).

We extracted information on the participants (age, gender, injury severity, and injury mechanism), and the assessment (interview, procedure, and timing), prevalence (before and/or after TBI), and risk factors (assessed and significant variables) for the studied psychiatric disorders. For each study, risk of bias was assessed using items on attrition bias (management of loss to follow-up) and reporting bias (primary outcomes missing) from the Research Triangle Institute item bank for observational studies,[38] complemented by items on the assessment of psychiatric disorders (e.g. inter-rater reliability, or assessor blinded to psychiatric history, medical file history, and/or hospitalisation variables of participants), study limitations, and statements on causality.

Statistical analysis

TBI severity was assessed and categorised into severity levels (mild, minor, moderate, severe) with use of the classification methods reported in the studies. TBI severity can be classified with use of the Glasgow Coma Scale (GCS),[39] which is often categorised into mild or minor (GCS 13–15), moderate (GCS 9–12), and severe TBI (GCS 3–8).[40] Additionally, the American Congress of Rehabilitation Medicine (ACRM) defined mild TBI as a traumatically induced physiological disruption of brain function with a loss of consciousness (LOC) of approximately 30 minutes or less, an initial GCS of 13–15 after 30 minutes, and posttraumatic amnesia (PTA) not greater than 24 hours.[41]

Pooled prevalence estimates per disorder were determined for three time points: before TBI (pre-injury), during the first year (first year), and after one year (>1 year). A step-by-step guide was followed to perform a meta-analysis using a random-effects model in a Microsoft Excel spreadsheet.[42] This meta-

analysis using Microsoft Excel showed to achieve results comparable with that of using Comprehensive Meta-Analysis Software, a commercial software package specifically developed to conduct meta-analyses.[42] If studies reported prevalence rates equal to 0%, a prevalence rate of 0.1% was used in our calculations. Studies with a sample size of fewer than 30 patients were excluded from the calculation of pooled prevalence estimates to minimise outlier estimates resulting from small sample sizes. Additionaly, studies that used a sample with self-reported TBI[43,44] or retrospective recall over decades post-injury to assess the prevalence of disorders preceding TBI (pre-injury)[45] or the year after injury (first year)[45] were excluded from the calculation of pooled prevalence estimates, as suggested by the Cochrane Collaboration.[46] When only a small number of studies (n≤2) reported on the prevalence of a disorder, no pooled prevalence estimates were calculated for that disorder.

Heterogeneity was assessed with the Q-statistic and I^2-statistic. The Q-statistic is a Chi^2-test for heterogeneity, which assesses whether observed differences in results are compatible with chance alone. A significant Q (low p-value) provides evidence of heterogeneity among the effect sizes and indicates that the variation in effect sizes is beyond chance.[47] The I^2-statistic describes the percentage of variation across studies that is to heterogeneity rather than chance.[48] An I^2 value of 25% or lower is associated with low heterogeneity, 50% is associated with moderate heterogeneity, and 75% or higher is associated with high heterogeneity.[48]

8.3 RESULTS

Literature search

In January 2015, a total of 4,800 unique titles of potentially relevant articles were identified through the extensive search strategy (Figure 8.1). In November, the search strategy was updated and an additional 539 new, unique titles of potentially relevant articles were identified. Screening of the titles and abstracts resulted in a selection of 291 articles that appeared to meet all selection criteria. After screening and selection of the full text papers, we retrieved 34 studies described in 68 publications. The main reasons for exclusion were not using a structured interview, not reporting about TBI patients (separately), or not reporting prevalence rates. Twelve out of the 34 included studies were multiple publications on the same sample of patients, with the number of related studies ranging from 1 (n=5)[2,43,44,49,50] to 7 (n=1).[51] The 34 studies formed the basis of our review.

Study characteristics

Of the 34 studies, most were conducted in Australia (n=9),[2,5,52-58] followed by the United States (n=8),[43,44,51,59-63] the United Kingdom (n=4),[24,49,64,65] and Canada (n=3)[11,66,67] (Table 8.3 and Appendix Table 8.A). Sample sizes varied widely, ranging between 16[68] and 476[56] participants. The majority of the participants were males (except in 3 studies with 40–46% males),[64,66,69] with an average age of 29–42 years (in 27 out of the 34 studies). Traffic accidents comprised over half of all causes in 16 of the 22 studies that reported on injury mechanism.

TBI severity was often classified using the GCS (n=15),[5,44,49-51,53,54,59-61,66,68,70-72] the definition of mild TBI by the ACRM (n=8),[11,55-58,63,67,73] or the duration of PTA (n=3).[24,52,64] Fifteen studies included all TBI severity levels, and 12 only mild TBI.

Axis I disorders (n=11),[2,5,43-45,49,50,54,58,70,74] ASD and/or PTSD (n=9),[24,52,53,55,56,64,65,69,75] (major) depression (n=7),[11,51,60-62,67,73] and a combination of anxiety disorders and depressive disorders (n=6)[57,59,63,66,68,72] were the most frequently studied disorders per sample. The three studies on ASD also assessed PTSD, and only included patients with mild TBI (n=3).[52,56,64] In contrast, 15 of the remaining 31 studies included all TBI severity levels in their assessment of Axis I disorders, PTSD, (major) depression, or both anxiety disorders and depressive disorders.

The most frequently used structured interview was the Structured Clinical Interview for DSM Disorders (SCID, n=15),[5,11,43,44,50,54,59-62,67,68,73,74,76] followed by the Clinician-Administered PTSD Scale (CAPS, n=6),[2,24,55,56,58,65] Schedules for Clinical Assessment in Neuropsychiatry / Present State Examination (SCAN/PSE, n=5),[45,49,51,60,70] and/or Mini International Neuropsychiatric Interview (MINI, n=3).[2,57,58] Axis I disorders were often assessed with the SCID (n=6),[5,43,44,50,54,74] or SCAN/PSE (n=3).[45,49,70] ASD and/or PTSD were diagnosed with use of a range of interviews, including the CAPS (n=4),[24,55,56,65] Acute Stress Disorder Interview (ASDI, n=2),[52,64] and PTSD Symptom Scale (PSS, n=2),[64,69] whereas depressive disorders were commonly assessed with use of the SCID (n=8).[11,59-62,67,68,73] Five studies used multiple instruments in their assessment of Axis I disorders (MINI and CAPS),[2,58] ASD and PTSD (ASDI and PSS[64] or Composite International Diagnostic Interview (CIDI)[52]), and MD (SCAN/PSE and SCID).[60] Eleven studies reported that the interviews were conducted by one trained (neuro) psychiatrist or psychologist.

Figure 8.1 Study selection

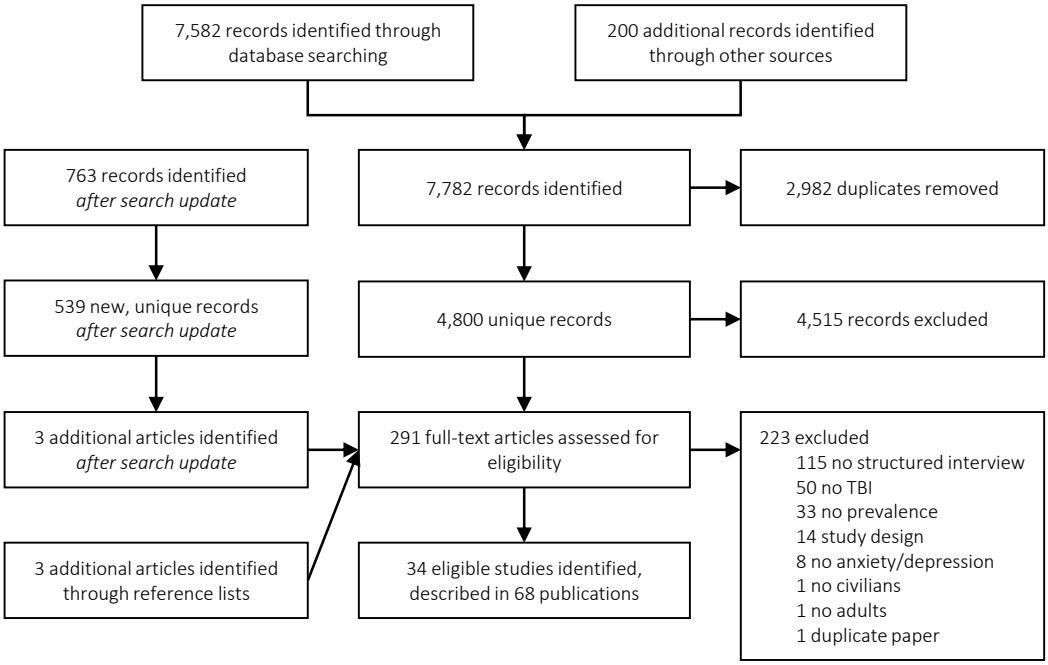


Table 8.3 Study characteristics

Author, year, country, design	Study population	Inclusion/Exclusion	Sample	Disorder	Interview	Assessment
Bryant, 2010, Australia, A [2] Related [77,78]	Mild (ACRM) Admitted to hospital (n=437)	16–70y Not psychotic or suicidal Randomly selected, stratified by LOS	<45y 73%, 45+y 28% Male 72%; MVA 76%	Axis I	MINI (DSM-IV, ICD-10) CAPS (DSM-IV)	Telephone interview by trained researchers
Meares, 2011, Australia, A [58]	Mild (ACRM) Admitted to hospital (n=62)	18–65y Admission <24h, initial assessment<14d, IQ≥74 No physical injury due to self-harm; psychotic; pre-existing cognitive impairment; pregnant	35.7y (14.5) Male 68%; MVA: 82% GCS 13 3%, 14 11%, 15 86% PTA <5m 40%, 6–60m 21% 61m–24h 29%	Axis I	MINI (DSM-IV) CAPS (DSM-IV)	Four trained supervised postgraduate-level psychologists, and Meares. Reimbursement fee $40.00. Multiple imputation (n=6)
Gil, 2005, Israel, A [74]	Mild Admitted to hospital (n=120)	18–50y No history of TBI; psychiatric care at time of injury; cognitive deficit; substance abuse; major untreated medical condition	31.4y (2.7) Male 58%; Traffic 90% Upper range GCS 13–15	Axis I	SCID (DSM-IV)	Trained clinician
Gould, 2011A, Australia, A [5] Related [79-84]	Compl mild to severe Admitted to rehab. hospital (n=122)	16–80y No history of TBI; neurological disorder	34.9y (16.2), 16–77 Male 79%; GCS 9.2 (4.3), 3–15; PTA 23.6 (22.6), 0.05–121d	Axis I	SCID (DSM-IV-TR)	Not reported
Whelan-Goodinson, 2009, Australia, B/C [54] Related [85,86]	Minor to severe (GCS<15) Admitted to hospital (n=100)	17–75y No history of TBI; neurological disorder; neurodegenerative disease	*37.2y (14.2), 19–74 Male 71%; MVA 86% GCS 9.1 (4.1), 3–14 PTA 20.8 (17.9), 1–77	Axis I	SCID (DSM-IV)	Clinical computerised version, blinded to medical file history
Deb, 1999, UK, A [49] Related: [87]	Minor to severe (GCS<15) Admitted to hospital (n=164)	17+y ICD-9 diagnosis of TBI; Period of LOC; Radiological evidence	Median 43.5y, IQR 28, 18–94; Male 67% GCS 13–14 82%, 3–12 18%	Axis I	SCAN/PSE (ICD-10)	Two trained psychiatrists
Koponen, 2002, Finland, B [45]	Mild to severe Neuropsychiatric evaluation (n=60)	Neurological symptoms lasting ≥1w & LOC≥1m; PTA≥30m; neurol sympt (ex headache; nausea) first 3d; neurorad findings suggesting TBI No history of neurological disorder	29.4y (10.9), 10–53 Male 68% PTA <24h 50%, >7d 32%	Axis I	SCAN/PSE (DSM-IV)	Trained research psychiatrist
Koponen, 2011, Finland, A [70]	Mild to severe Attended ED (n=38)	16–70y Acute brain trauma (<3d); LOC≥1m; PTA≥30m; neurol sympt (ex headache; nausea) first 3 days, neurorad findings suggesting TBI	41.6y (17.0), 16–67 Male 71%; MVA 26% GCS 13–15 & PTA <24h 71%	Axis I	SCAN/PSE (DSM-IV)	Trained research psychiatrist

Table 8.3 (continued)

Author, year, country, design	Study population	Inclusion/Exclusion	Sample	Disorder	Interview	Assessment
Hibbard, 1998, US, A [43] Related [88]	Mild to severe Selection quality of life survey (n=100)	18–65y at time of interview Self-identified TBI ≥1y prior to interview No history of neurological disorder	*39.8y (10.2) Male 53%; MVA 62% LOC <20m 30%, >1mo 24%	Axis I	SCID (DSM-IV)	Licensed psychologist with extensive background in clinical neuropsych and brain injury
Ashman, 2004, US[1,3] [44] Related [4]	Mild to severe Hospital, brain injury associations, advertisements, website (n=188)	18–87y Self-identified TBI No history of neurocognitive disorder; psychotic disorder	40.4y (15.1) Male 53% GCS 13–15 29%, 3–8 62%	Axis I	SCID (DSM-IV)	Clinicians with ≥3y clinical experience
Diaz, 2014, Brazil, A [50] Related [6]	Severe Admitted to ICU (n=43)	16+y No gunshot wounds	31.2y (11.9); Male 84%; Traffic: 72%; GCS 7–8 37%, 5–6 27%, 3–4 37% PTA ≤1mo 51%, >1mo 49%	Axis I	SCID (DSM-IV)	Two board-certified psychiatrists, blinded to hospitalisation variables, additional information by patient relative
Jones, 2005, UK, A [64]	Mild (ACRM) Attended ED (n=131)	18–65y RTA No alcohol/drugs at RTA; psychiatric care at time of injury; fatality involved in RTA	36.8y (12.8), 18–65 Male 40%; Traffic 71%	ASD PTSD	ASDI (DSM-IV) PSS (DSM-IV)	ASDI: Trained masters-level psychologist. PSS: Chartered clinical psychologist with >10y experience in trauma assessment
Bryant, 1999C, Australia, A [52] Related [89-92]	Mild (PTA<24h) Admitted to hospital (n=79)	16–65y MVA	29.5y (12.6) Male 70%; MVA 100% PTA 9.4 (9.1), 5m–24h	ASD PTSD	ASDI (DSM-IV) CIDI (DSM-III)	Doctoral clinical psychologist with 5y experience in assessing traumatised individuals
Broomhall, 2009, Australia, A [56]	Mild (ACRM) Admitted to hospital (>24h) (n=476)	16–65y Not suicidal or psychotic	38y (14.2) Male 73%; MVA 64%	ASD PTSD	CAPS (DSM-IV)	Trained interviewers by a clinical psychologist
Creamer, 2005, Australia, A [55]	Mild (ACRM) Admitted to hospital (>24h) (n=189)	18–70y No current psychotic disorder	37.0y (13.7) Male 76%	PTSD	CAPS (DSM-IV)	Telephone interview, trained mental health clinicians
Roitman, 2013, Israel, A [69]	Mild (LOC<30m) Attended ED (n=402)	Single MVA Not arrived in coma; LOS>30m; LOS>7d	HI 37.2y (12.7), LOC: 37.2y (12.4) Male HI: 46%, LOC: 63%	PTSD	PSS (DSM-IV)	Telephone interview

Table 8.3 (continued)

Author, year, country, design	Study population	Inclusion/Exclusion	Sample	Disorder	Interview	Assessment
Caspi, 2005, Israel, B [76]	Mild to moderate Neurocognitive clinic (n=120)	18–50y No history of TBI; major psychiatric illness; cognitive deficit; substance abuse; chronic medical condition	35.8y (5.9); Male 59%; Car 84%	Anxiety	SCID (DSM-IV)	Same team of interviewers
Barker-Collo, 2013, New-Zealand, A/B [75]	Mild to severe Multiple sources (BIONIC) (n=296)	16+y	37.0y (17.9) Male 60%; Traffic 17% Worst GCS 14.1 (2.3) PTA 21.8d (36.4)	PTSD	PDS (DSM-IV)	Trained researcher
Turnbull, 2001, UK, A/C [65]	Mild to severe Attended ED (n=41)	16–65y No chronic alcohol abuse with repeated ED attendance	35y (11) Male 87%; Traffic 32% PTA none 4%, <1h 56%, 1–24h 22%, >1d 18%	PTSD	CAPS (DSM-IV)	Telephone interview by postgraduate psychologist, if >20 on IES-R subscales
Sumpter, 2005, UK, A [24]	Severe (PTA>1d) Out-patient and rehabilitation services, voluntary organisations (n=34)	18+y Severe TBI (PTA>1d) ≥3mo before assessment No scores <27 on MMSE; severe dysphasia; dyslexia; current treatment for psychosis	*40y (11), 20–60 Male 88%; Traffic 47% PTA 11w (13w), 26h–52w	PTSD	CAPS (DSM-IV)	Not reported
Bryant, 2000 Australia, A [53] Related [93-95]	Severe Admitted to rehabilitation unit (n=96)		34.3y (12.8), 16–71 Male 80%; GCS 8.0 (3.8) PTA 37.0 (30.7), 7–143d	PTSD	PTSD-I (DSM-III-R)	Trained rehabilitation consultant
McCauley, 2005, US, A [59] Related [96-98]	Mild to moderate Attended ED/admitted to hospital (n=340)	16+y Arrival to hospital <24h; blood alcohol level <200mg/dL No history of substance dependence; mental retardation; major psychiatric disorder; CNS disturbance	DSM PCD: 36.4y (13.6) No PCD: 31.4y (13.3) Male 71%; MVA 70% GCS DSM PCD: 14.7 (1.0); No PCD: 14.6 (1.1)	PTSD Depression	SCID (DSM-IV)	Conducted by bachelors-/masters-level research assistant in the patient's primary language (English or Spanish)
Ponsford, 2011, Australia, A/D [57]	Mild (ACRM) Attended ED (n=90)	18+y No intubation; anesthesia; breath alcohol >0.05mg/L; illicit substances; focal neurological signs, seizures, CT abnormalities; upper limb injury (use computer mouse); spinal precautions; history of cognitive impairment, neurological illness, substance abuse, psychiatric impairment affecting functioning	35.0y (13.1) Male 74%; MVA: 41% PTA 103m (191m), 0–24h	Anxiety Depression	MINI (DSM-IV)	Not reported

Table 8.3 (continued)

Author, year, country, design	Study population	Inclusion/Exclusion	Sample	Disorder	Interview	Assessment
Al-Adawi, 2007, Oman, A [72]	Mild to severe Neurocogn functioning evaluation (n=68)	No history of psychiatric disorder; neurological disorder	M: 29.5y (6.9), 17–45; F: 34.9y (7.6), 22–50 Male 69%; MVA 67% GCS 13–15 9%, 9–12 3%, 3–8 41%	Anxiety Depression	CIDI (DSM-IV, ICD-10)	Two trained authors, blinded to results to the HADS
Fann, 1995, US, A [63]	Mild to severe Brain injury rehabilitation clinic (n=50)	Closed head injuries	38.0y (13.0); Male 74% GCS 13–15 58%, 3–12 42%	Anxiety Depression	DIS (DSM-III)	Psychiatrist
Van Reekum, 1996, Canada, A [66]	Mild to severe TBI rehabilitation program (n=18)	<50y MVA≥2y pre-injury No pre-TBI psychiatric history; pre-TBI cognitive deficit Selection female : male ratio 3:1	31.2y (8.5), 19–49 Male 44% GCS 13–15 28%, 9–12 17%, 3–8 56%	Anxiety Depression	SADS-L (DSM-III)	Experienced registered psychiatric nurse
Mauri, 2014, Italy, A/D [68]	Mild to severe Admitted to neurosurgery (n=16)	18–65y Closed head injury; lesion on CT; LOC≥1m; PTA≥30m No history of unstable neurol conditions; pathol conditions of cardioresp system; psychiatric disorders; substance abuse	40.4y (14.0) Male 63%; MVA 81% GCS 13–15 38%, 9–12 38%, 3–8 25%	Anxiety Depression	SCID (DSM-IV-TR)	Expert clinicians
Rao, 2010, US, D [62]	Mild (LOC<30m) Attended ED (n=43)	18+y Closed head injury; GCS<15 soon after injury No history of TBI; neurological disorder; mood disorder	44.5y (17.5) Male 53%; MVA 45%	Depression	SCID (DSM-IV)	Neuropsychiatrist
Konrad, 2011, Germany, A/D [73]	Mild (ACRM) Attended ED (n=33)	18–65y No psychopharmacological medication; neurological diseases; MRI contra-indications	*36.7y (12.4) Male 52%; Traffic 55%	Depression	SCID (DSM-IV)	Not reported
Kennedy, 2005, US, A [61]	Mild to moderate Outpatient follow-up system; Living assistance program (n=78)	18+y ≥3mo post-injury	38y (12.2), 18–69 Male 69%; MVA 77% GCS 9.3 (4.8), 13–15 45%, 9–12 12%, 3–8 43%	Depression	SCID (DSM-IV)	Three trained research team members, additional information by significant other and medical records

Table 8.3 (continued)

Author, year, country, design	Study population	Inclusion/Exclusion	Sample	Disorder	Interview	Assessment
Fedoroff, 1992, US, A [51] Related [99-105]	Mild to severe Admitted to shock trauma center (n=64)	18+y Acute closed head injury No significant multiple system injuries	MD: 26.8y (5.8); No MD: 29.5y (10.7) Male 86%; GCS 12–15 17%, 8–15 & intracran surg or focal lesions >25cc 58%, 3–7 15%	Depression	SCAN/PSE (DSM-III)	Trained research psychiatrist
Rapoport, 2003A, Canada, A [11] Related [10,106,107]	Mild (ACRM) Appointment at TBI clinic (n=210)	18+y No history of focal brain disease; acute medical illness; schizophrenia; bipolar disorder; dementia	47.3y (19.6), 19–91 Male 60%; MVA 61%	MD	SCID (DSM-IV)	Psychiatrist
Chamelian, 2006, Canada, A [67]	Mild to moderate TBI clinic, tertiary referral center (n=63)	18–60y	33y (11.7); Male 56% GCS 13.7 (no complicat.) PTA <24h 78%, >24<1w 22%	MD	SCID (DSM-IV)	Clinic's neuropsychiatrist, blinded to subjects' cognitive data
Jorge, 2004, US, A/D [60]	Mild to severe Admitted to hospital (n=91)	Closed head injury No spinal cord injury	36.4y (15.7); Male 59%; MVA 75%; GCS 13–15 44%, 9–15 & intracran surg or focal lesions >15mL 33%, 3–8 23%	MD	SCAN/PSE (DSM-III-R, ICD-10) SCID (DSM-IV)	Psychiatrist

A: Prospective; B: Retrospective; C: Cross-sectional; D: (Nested) Case-control. m=minute; h=hour; d=day; w=week; mo=month; y=year; * Age at assessment.
ACRM: American Congress of Rehabilitation Medicine; ASD: acute stress disorder; ASDI: Acute Stress Disorder Interview; CAPS: Clinician-Administered PTSD Scale for DSM-IV; CIDI: Composite International Diagnostic Interview; DIS: Diagnostic Interview Schedule; CNS: central nervous system; DSM: Diagnostic and Statistical Manual of Mental Disorders; ED: emergency department; GCS: Glasgow Coma Scale; HADS: Hospital Anxiety and Depression Scale; HI: head injury; ICU: intensive care unit; IES-R: Impact of Event Scale – Revised; IQR: interquartile range; LOC: loss of consciousness; LOS: length of stay in hospital; MD: major depression; MINI: Mini International Neuropsychiatric Interview; MMSE: Mini-Mental State Examination; MVA: motor vehicle accident; PCD: post-concussive disorder; PDS: Posttraumatic Stress Diagnostic Scale; PTSD-I: Posttraumatic Stress Disorder Interview; PSE: Present State Examination; PSS: PTSD Symptom Scale; PTA: post-traumatic amnesia; PTSD: post-traumatic stress disorder; RTA: road traffic accident; SADS-L: Schedule for Affective Disorders and Schizophrenia-Lifetime; SCAN: Schedules for Clinical Assessment in Neuropsychiatry; SCID: Structured Clinical Interview for DSM Disorder.

Risk of bias

Overall, 21 of the 34 studies reported on attrition and faced problems of patients who refused to participate (n=17, 8–58% of study sample),[2,45,50,52-58,64,68,70,73-76] patients who could not be contacted (n=11, 2–58%),[2,5,45,50,52,53,64,65,70,73,75] and patients who deceased or did not attend appointments (n=6, 3–36%).[45,49,50,60,73,76] According to these studies, participants often did not differ from those who did not participate. A few studies, however, showed differences in age (participants were older[2,57,60] or younger[69,75] compared to non-responders), and TBI severity (participants had higher[2,75] or lower[53] TBI severity level compared to non-responders).

With respect to patient selection, two of the 34 studies included patients with self-reported TBI (not medically documented),[43,44] and in another 16 studies participants were drawn from a variety of settings like specialty referral clinics or outpatient programmes.

Only six out of the 34 studies provided information on the inter-rater reliability of the structured diagnostic interviews, which ranged between 80% (n=2)[44,61] and 100% (n=4).[2,54-56]

Prevalence rates

Prevalence rates of anxiety and depressive disorders were assessed retrospectively (pre-injury, n=15),[5,43-45,51,54,57,58,61,63,66,70,73,74,76] and at approximately 3 months (n=8),[2,57-60,62,64,68] 6 months (n=8),[52,53,60,65,67-69,74] 1 year (n=10),[2,5,44,45,49,55,60,62,70,75] or more than one year post-TBI (n=12)[24,43-45,50,54,61,63,66,72,73,76] (Figure 8.2). Of the 12 studies with long-term follow-up, six studies had follow-up periods between 1 and 3 years,[44,50,54,63,72,76] five studies comprised periods of 5–8 years post-TBI,[24,43,61,66,73] and one study 31 years post-TBI.[45]

Overall, a wide range of prevalence rates was reported for Axis I disorders, anxiety disorders and depressive disorders (Table 8.4).

Figure 8.2 Time points at which prevalence of psychiatric disorders was assessed

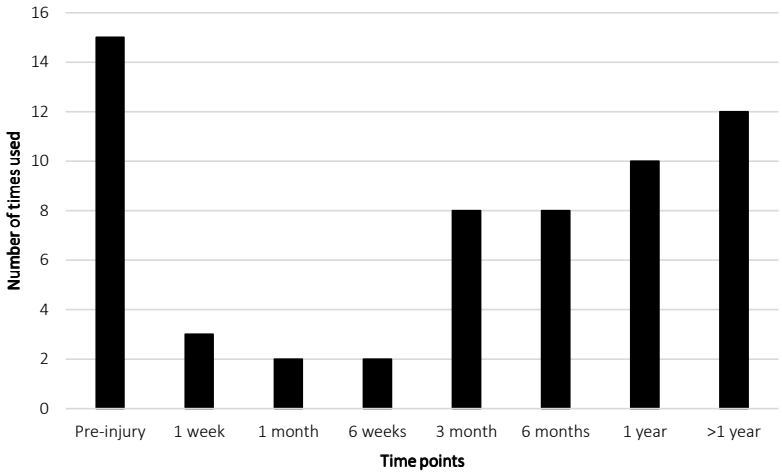


Table 8.4 Prevalence rates of psychiatric disorders pre- and post-TBI

Disorder	Study	Severity	Pre-injury	<3 months	3–6 months	1 year	>1 year	Follow-up (mean, (SD), range)
Axis I								
	Bryant, 2010 [2]	Mild				34.3		1y
	Meares, 2011 [58]	Mild	44.6*		32.1			~106.2d (14.9)
	Gil, 2005 [74]	Mild	40.8*		10.0			6mo
	Gomez-Hernandez, 1997 [105]	Mild to severe	13.8*					[1mo–1y]
	Gould, 2011A [5]	Compl mild to severe	54.1*			45.9[c]		1y (1mo)
	Whelan-Goodinson, 2009 [54]	Minor to severe					65.0	3.0y (1.5); 0.5–5.5y
	Deb, 2007 [87]	Minor to severe				27.6		1y (1mo)
	Koponen, 2002 [45]	Mild to severe	21.7*				40.0	>10y
	Koponen, 2011 [70]	Mild to severe	39.5**			47.4		1y
	Hibbard, 1998 [43]	Mild to severe	51.0*					[7.6y (7.1); 1–37y]
	Ashman, 2004 [44]	Mild to severe	5.0*	9.0		5.0	0.0	Base, 1, 2y; 3mo–4y
	Diaz, 2014 [50]	Severe					56.0	17.8mo (5.7)
Anxiety								
	Meares, 2011 [58]	Mild	41.1*		32.1			~106.2d (14.9)
	Ponsford, 2011 [57]	Mild	16.1*	12.5[b]				3mo
	Caspi, 2005 [76]	Mild to moderate	19.0*					[2.9y (3.7); 1mo–5y]
	Gould, 2011A [5]	Compl mild to severe	22.1*	13.9	24.6	28.7[c]		6w[81], 6mo[82], 6mo–1y
	Whelan-Goodinson, 2009 [54]	Minor to severe	13.0*				38.0	3.0y (1.5); 0.5–5.5y
	Ashman, 2004 [44]	Mild to severe	16.0*	27.0		19.0	9.0	Base, 1, 2y; 3mo–4y
	Al-Adawi, 2007 [72]	Mild to severe					50.0	18.2mo (12.2); 0mo–5y
	Van Reekum, 1996 [66]	Mild to severe	16.7*				38.9	4.9y; 2–9y
	Diaz, 2014 [50]	Severe					20.9	17.8mo (5.7)
GAD	Bryant, 2010 [2]	Mild			9.8	13.4		3mo, 1y
	Meares, 2011 [58]	Mild	14.3*		10.7			~106.2d (14.9)
	Gould, 2011C [80]	Compl mild to severe	1.0*			2.0		1y
	Whelan-Goodinson, 2009 [54]	Minor to severe	5.0*				17.0	3.0y (1.5); 0.5–5.5y
	Deb, 1999 [49]	Minor to severe				1.8		~1y (4w)
	Koponen, 2002 [45]	Mild to severe	0.0*			0.0	1.7	<1y, >10y
	Hibbard, 1998 [43]	Mild to severe	1.0*				8.0	7.6y (7.1); 1–37y
	Fann, 1995 [63]	Mild to severe					24.0	32.5mo (35.1); 1–128mo
	Van Reekum, 1996 [66]	Mild to severe	5.6*				27.8	4.9y; 2–9y
	Jorge, 1993D [102]	Mild to severe		10.6	3.0	1.5		31d (IQR 32), 3mo, 1y
	Jorge, 2004 [60]	Mild to severe				15.4[d]		1y
	Diaz, 2012 [6]	Severe	0.0*				15.1	18.4mo (6)

Table 8.4 (continued)

Disorder	Study	Severity	Pre-injury	<3 months	3–6 months	1 year	>1 year	Follow-up (mean, (SD), range)
ASD	Jones, 2005 [64]	Mild		21.2				6.0d (1.9)
	Bryant, 1999C [52]	Mild		13.9				7.2d (5.3); 2–25d
	Harvey, 2000 [91]	Mild		13.9				1mo
	Broomhall, 2009 [56]	Mild		4.6				6.7d (6.9)
	Gould, 2011C [80]	Compl mild to severe	0.0*			1.0		1y
	Whelan-Goodinson, 2008 [85]	Minor to severe					11.0	3.0y (1.5); 0.5–5.5y
Panic	Bryant, 2010 [2]	Mild			7.4	7.5		3mo, 1y
	Meares, 2011 [58]	Mild	10.7*		10.7			~106.2d (14.9)
	Gould, 2011C [80]	Compl mild to severe	2.0*			2.0		1y
	Whelan-Goodinson, 2009 [54]	Minor to severe	1.0*				6.0	3.0y (1.5); 0.5–5.5y
	Deb, 1999 [49]	Minor to severe				6.7		~1y (4w)
	Koponen, 2002 [45]	Mild to severe	0.0*			1.7	6.7	<1y, >10y
	Hibbard, 1998 [43]	Mild to severe	4.0*				4.0	7.6y (7.1); 1–37y
	Fann, 1995 [63]	Mild to severe					4.0	32.5mo (35.1); 1–128mo
	Van Reekum, 1996 [66]	Mild to severe					5.6	4.9y; 2–9y
	Jorge, 2004 [60]	Mild to severe				2.2[d]		9.4mo (4.2)
	Diaz, 2012 [6]	Severe	3.0*				3.0	18.4mo (6)
Agoraphobia	Bryant, 2010 [2]	Mild			14.8	12.8		7.2d (9.6), 3mo, 1y
	Meares, 2011 [58]	Mild	12.5*		7.1			~106.2d (14.9)
	Gould, 2011C [80]	Compl mild to severe	0.0*			2.0		1y
	Whelan-Goodinson, 2009 [54]	Minor to severe	1.0*				1.0	3.0y (1.5); 0.5–5.5y
	Hibbard, 1998 [43]	Mild to severe	4.0*				5.0	7.6y (7.1); 1–37y
	Fann, 1995 [63]	Mild to severe					2.0	32.5mo (35.1); 1–128mo
Specific phobia	Gould, 2011C [80]	Compl mild to severe	5.9*			6.9		1y
	Whelan-Goodinson, 2009 [54]	Minor to severe	0.0*				7.0	3.0y (1.5); 0.5–5.5y
	Koponen, 2002 [45]	Mild to severe	8.3*			5.0	13.3	<1y, >10y
	Koponen, 2011 [70]	Mild to severe	5.3**					[1y]
	Hibbard, 1998 [43]	Mild to severe	4.0*				5.0	7.6y (7.1); 1–37y
Social phobia	Bryant, 2010 [2]	Mild			6.1	9.0		7.2d (9.6), 3mo, 1y
	Meares, 2011 [58]	Mild	10.7*		3.6			~106.2d (14.9)
	Gould, 2011C [80]	Compl mild to severe	7.8*			2.9		1y
	Whelan-Goodinson, 2009 [54]	Minor to severe	2.0*				6.0	3.0y (1.5); 0.5–5.5y
	Koponen, 2002 [45]	Mild to severe	5.0*			0.0	5.0	<1y, >10y
	Koponen, 2011 [70]	Mild to severe	5.3**					1y
	Hibbard, 1998 [43]	Mild to severe	4.0*				5.0	7.6y (7.1); 1–37y

Table 8.4 (continued)

Disorder	Study	Severity	Pre-injury	<3 months	3–6 months	1 year	>1 year	Follow-up (mean, (SD), range)
OCD	Bryant, 2010 [2]	Mild			3.2	4.0		3mo, 1y
	Meares, 2011 [58]	Mild	10.7*		7.1			~106.2d (14.9)
	Gould, 2011C [80]	Compl mild to severe	0.0*			1.0		1y
	Whelan-Goodinson, 2009 [54]	Minor to severe	1.0*				1.0	3.0y (1.5); 0.5–5.5y
	Deb, 1999 [49]	Minor to severe				1.2		~1y (4w)
	Hibbard, 1998 [43]	Mild to severe	1.0*				9.0	7.6y (7.1); 1–37y
	Van Reekum, 1996 [66]	Mild to severe					5.6	4.9y; 2–9y
PTSD	Bryant, 2010 [2]	Mild			12.7	13.0		3mo, 1y
	Meares, 2011 [58]	Mild	17.9*		19.6			~106.2d (14.9)
	Jones, 2005 [64]	Mild		30.4	17.2			44.0d (2.6), 94.3d (2.9)
	Bryant, 1999C [52]	Mild			23.8			6mo
	Creamer, 2005 [55]	Mild				15.0		1y
	Gil, 2005 [74]	Mild			14.2			6mo
	Roitman, 2013 [69]	Mild			31.6[a]			224.9d (39.1)
	Caspi, 2005 [76]	Mild to moderate	1.7*				18.3	2.9y (3.7); 1mo-5y
	McCauley, 2005 [59]	Mild to moderate			11.5			86.4d (17.4)
	Whelan-Goodinson, 2009 [54]	Minor to severe	4.0*				14.0	3.0y (1.5); 0.5–5.5y
	Deb, 1999 [49]	Minor to severe				2.4		~1y (4w)
	Koponen, 2002 [45]	Mild to severe					0.0	31.4y (4.4); 27–48y
	Koponen, 2011 [70]	Mild to severe	0.0**			2.6		1y
	Hibbard, 1998 [43]	Mild to severe	6.0*				10.0	7.6y (7.1); 1–37y
	Ashman, 2004 [44]	Mild to severe	10.0*	30.0		18.0	21.0	Base, 1, 2y; 3mo–4y
	Barker-Collo, 2013 [75]	Mild to severe				17.9		1y
	Turnbull, 2001 [65]	Mild to severe			17.1			5mo (3)
	Mauri, 2014 [68]	Mild to severe		6.3	6.3			1mo, 3mo
					0.0			6mo
	Jorge, 2004 [60]	Mild to severe				7.7[d]		1y
	Alway, 2015A [83]	Moderate to severe	0.5	1.9	4.3	9.4	8.9	56.4d (39.9), Initial–3mo, 3–6mo, 6mo–1y, 1–2y
							8.7	2–3y
							5.6	3–4y
							5.0	4–5y
	Diaz, 2012 [6]	Severe	3.0*				3.0	18.4mo (6)
	Sumpter, 2005 [24]	Severe					2.9	6y (7); 0.6–34y
	Bryant, 2000 [53]	Severe			27.1			6.3mo (1.3); 5–7mo

Table 8.4 (continued)

Disorder	Study	Severity	Pre-injury	<3 months	3–6 months	1 year	>1 year	Follow-up (mean, (SD), range)
Depression								
	Meares, 2011 [58]	Mild	25.0*		10.7			~106.2d (14.9)
	Ponsford, 2011 [57]	Mild	27.0*	13.5[b]				3mo
	Rao, 2010 [62]	Mild			16.3	9.3		3mo, 1y
	Kennedy, 2005 [61]	Mild to moderate	50.0*					[76mo (94); 3mo–36y]
	Caspi, 2005 [76]	Mild to moderate	8.0*					[2.9y (3.7); 1mo–5y]
	Gould, 2011A [5]	Compl mild to severe	23.0*	8.2	18.0[c]	32.8		6w[81], 6mo[82], 6mo–1y
	Whelan-Goodinson, 2009 [54]	Minor to severe	17.0*				46.0	3.0y (1.5); 0.5–5.5y
	Deb, 1999 [49]	Minor to severe				12.8		~1y (4w)
	Koponen, 2011 [70]	Mild to severe	0.0**			5.3		1y
	Ashman, 2004 [44]	Mild to severe	20.0*	35.0		24.0	21.0	Base, 1, 2y; 3mo–4y
	Al-Adawi, 2007 [72]	Mild to severe					57.4	18.2mo (12.2); 0mo–5y
	Jorge, 2004 [60]	Mild to severe				51.6[d]		1y
	Gomez-Hernandez, 1997 [105]	Mild to severe	0.0*					[1mo–1y]
	Diaz, 2014 [50]	Severe					27.9	17.8mo (5.7)
Dysthymia	Meares, 2011 [58]	Mild	0.02*		0.0			~106.2d (14.9)
	Gould, 2011C [80]	Compl mild to severe	3.9*			1.0		1y
	Whelan-Goodinson, 2009 [54]	Minor to severe	0.0*				1.0	3.0y (1.5); 0.5–5.5y
	Koponen, 2002 [45]	Mild to severe*					0.0	31.4y (4.4); 27–48y
	Hibbard, 1998 [43]	Mild to severe	1.0*				3.0	7.6y (7.1); 1–37y
	Fann, 1995 [63]	Mild to severe					14.0	32.5mo (35.1); 1–128mo
	Fedoroff, 1992 [51]	Mild to severe	0.0*	3.0	7.7	7.0		~36.6d (15.8), 3mo[100], 1y[100]
					2.3			6mo[100]
	Jorge, 2004 [60]	Mild to severe				9.9[d]		1y
Bipolar disorder	Gould, 2011C [80]	Compl mild to severe	0.0*			2.0		1y
	Koponen, 2002 [45]	Mild to severe	0.0*			0.0	1.7	31.4y (4.4); 27–48y
	Koponen, 2011 [70]	Mild to severe	5.3**					[1y]
	Hibbard, 1998 [43]	Mild to severe	0.0*				2.0	7.6y (7.1); 1–37y
	Fann, 1995 [63]	Mild to severe					0.0	32.5mo (35.1); 1–128mo
	Van Reekum, 1996 [66]	Mild to severe	0.0*				16.7	4.9y; 2–9y
	Jorge, 1994 [104]	Mild to severe		1.9				31d (IQR 32)
	Diaz, 2012 [6]	Severe	3.0*				6.1	18.4mo (6)

Table 8.4 (continued)

Disorder	Study	Severity	Pre-injury	<3 months	3–6 months	1 year	>1 year	Follow-up (mean, (SD), range)
MD	Bryant, 2010 [2]	Mild			17.9	17.4		7.2d (9.6), 3mo, 1y
	Meares, 2011 [58]	Mild	23.2*		10.7			~106.2d (14.9)
	Konrad, 2011 [73]	Mild	3.0*				9.1	6.0y; 4.8–7.3y
	Rapoport, 2003A [11]	Mild		16.7				49.0d (30.0)
	McCauley, 2005 [59]	Mild to moderate			15.0			86.4d (17.4)
	Kennedy, 2005 [61]	Mild to moderate	14.0*				30.0	76mo (94); 3mo–36y
	Chamelian, 2006 [67]	Mild to moderate				7.9		6mo
	Gould, 2011C [80]	Compl mild to severe	13.7*			29.4		1y
	Whelan-Goodinson, 2009 [54]	Minor to severe	17.0*				45.0	3.0y (1.5); 0.5–5.5y
	Koponen, 2002 [45]	Mild to severe	0.0*			10.0	10.0	31.4y (4.4); 27–48y
	Koponen, 2011 [70]	Mild to severe	10.5**			7.9		1y
	Hibbard, 1998 [43]	Mild to severe	17.0*				61.0	7.6y (7.1); 1–37y
	Fann, 1995 [63]	Mild to severe	12.0*				26.0	32.5mo (35.1); 1–128mo
	Van Reekum, 1996 [66]	Mild to severe	22.2*				61.1	4.9y; 2–9y
	Mauri, 2014 [68]	Mild to severe		62.5	50.0			1mo, 3mo
					43.8			6mo
	Fedoroff, 1992 [51]	Mild to severe	0.0*	25.8				~36.6d (15.8)
	Jorge, 2004 [60]	Mild to severe		16.5	9.9			Initial, 3mo
					6.6			6mo
	Diaz, 2012 [6]	Severe	6.1*				30.3	18.4mo (6)

Axis I also includes disorders other than anxiety or depressive disorders (e.g. substance use, schizophrenia, psychotic disorders, dementia, etc.).
* Lifetime pre-injury prevalence.
** Prevalence in 12 month period pre-TBI.
[a] Assessed at on average 7 months post-TBI.
[b-d] Prevalence measured over a period of time: last 3 months[b]; 6 to 12 months[c]; during 1st year[d] d=day; w=week; mo=month; y=year.
ASD: acute stress disorder; GAD: Generalised Anxiety Disorder; HI: head injury; IQR: interquartile range; MD: major depression; OCD: Obsessive Compulsive Disorder; PTSD: post-traumatic stress disorder.

Pre-injury

In total, 14 of the 15 studies that assessed the history of psychiatric disorders pre-TBI used the same diagnostic interview to assess the pre- and post-injury disorders, while one study used questions to assess the personal history of psychiatric disorders.[105] The 15 studies showed widely varying prevalence rates of pre-injury Axis I disorders (5–54%, with 40–54% in 5 out of 8 studies),[5,43,58,70,74] anxiety disorders (13–41%), and depressive disorders (0–50%, with 17–27% in 5 of the 9 studies reporting on pre-injury rates),[5,44,54,57,58] irrespective of TBI severity. The 15 studies also reported varying pre-injury rates of the other disorders: GAD 0–14%, panic 0–11%, agoraphobia 0–13%, specific phobia 0–8%, social phobia 2–11%, OCD 0–11%, PTSD 0–18%, dysthymia 0–4%, bipolar disorder 0–5%, MD 0–23%, and absence of ASD (0%, n=1).[80] A history of dysthymia or bipolar disorders preceding TBI was rarely reported. A few studies reported absence of disorders (a prevalence rate of 0%), which may be explained because of the assessment of disorders after a long period of time,[6,45,54] the measure used for diagnosis of disorders (PSE),[51,105] or inclusion of only patients with severe TBI,[6] with causes other than motor vehicle accident (MVA),[70] or those admitted to a rehabilitation hospital.[80] Additionally, two studies that assessed Axis I disorders in patients with mild TBI generally reported relatively high prevalence rates of all disorders, which may be related to their measures used for diagnosis of the disorders (MINI/CAPS).[2,58]

Post-injury

In the first year post-TBI, prevalence rates of Axis I disorders ranged from 10–34% in mild TBI, to 5–47% in studies with all TBI severity levels. Additionally, substantial prevalence rates were reported of post-injury anxiety disorders (13–32%), especially ASD (14–21% in 3 of the 5 studies)[52,64,91] and PTSD (12–32% in 12 of the 17 studies),[2,44,52,53,55,58,59,64,65,69,74,75] or depressive disorders (5–52%, 11–35% in 6 of the 8 studies),[5,44,49,57,58,62] especially MD (7–63%, 15–29% in 6 of the 11 studies).[2,11,51,59,60,80] MD tended to be more frequently diagnosed in patients with more severe TBI, given that 8–18% of the patients with mild TBI received this diagnosis versus 7–63% in patients with all TBI severity levels.

Even years post-TBI, patients were diagnosed with psychiatric disorders, with prevalence rates of Axis I disorders as high as 40% (more than 10 years post-TBI)[45] and 65% (3 years post-TBI).[54] Prevalence of anxiety ranged from 9–50% after on average 1.5–5 years of follow-up,[44,50,54,66,72] and rates for depressive disorders were up to 21–57% after follow-up periods of on average 1.5–3 years.[44,50,54,72] Long-term prevalence rates were almost all higher than (or equal to) the rates before TBI, in all studies that measured both pre-injury and long-term prevalence of psychiatric disorders.[6,43-45,54,61,63,66,73,76]

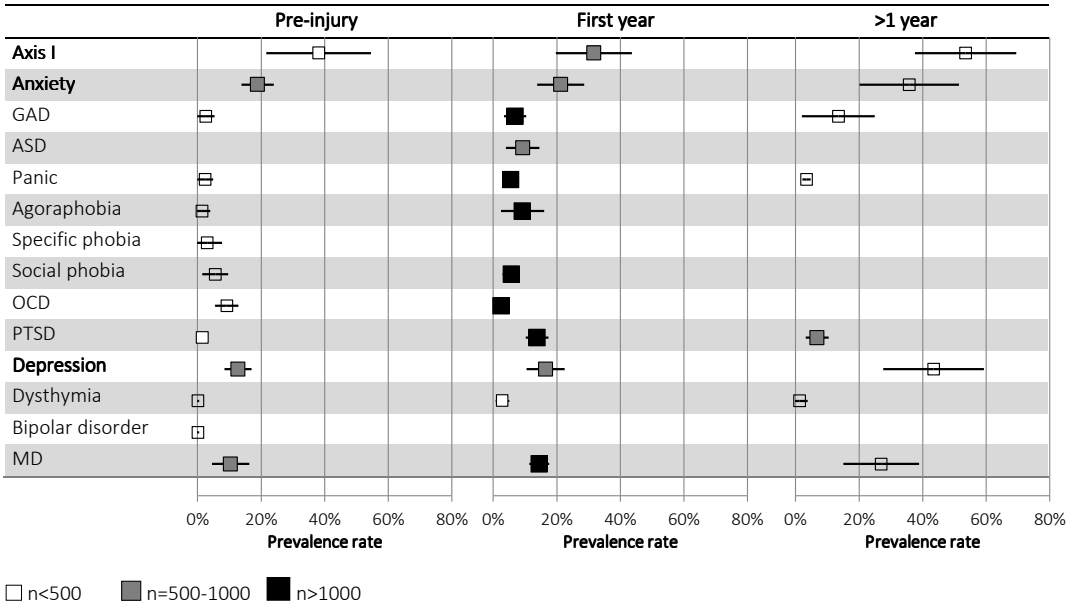
Although the prevalence of dysthymia after TBI was generally low (0–3% in 5 of the 8 studies),[43,45,54,58,80] a few studies also reported a prevalence rate of 0% (absence of disorder) for GAD, social phobia, PTSD, and bipolar disorder. These studies, however, had a long follow-up period (more than 30 years post-TBI),[45] a small sample size (n=16),[68] or included solely patients admitted to neurosurgery[68] or a TBI rehabilitation clinic.[63]

Pooled prevalence estimates

Figure 8.3 provides an overview of the overall pooled prevalence estimates per disorder by time point (also see Appendix Table 8.B). Highest variation in prevalence rates across studies were seen before TBI in agoraphobia (moderate heterogeneity: I^2=66%, p=0.05), and depressive disorders (high heterogeneity: I^2=82%, p<0.01). Highest pooled prevalence rates were retrieved for Axis I disorders

(n=5, 38% pre-TBI; n=6, 32% in the first year; n=3, 54% after one year), including anxiety disorders (n=6, 19%; n=5, 21%; n=3, 36%), and depressive disorders (n=8, 13%; n=10, 17%; n=3, 43%). Overall, the pooled prevalence rates increased over time in all disorders, except panic disorder, PTSD, and dysthymia (slight decrease).

Figure 8.3 Forest plot of pooled prevalence rates per psychiatric disorder



Axis I also includes disorders other than anxiety or depressive disorders (e.g. substance use, schizophrenia, psychotic disorders, dementia, etc.

Risk factors

In total, 30 articles assessed risk factors for psychiatric disorders, including 24 (71%) of the 34 reference studies and 6 related articles.[2,50,52,54,83,84] The most often assessed risk factors were age (n=22), gender (n=19), education (n=18), marital or relationship status (n=12), and TBI severity or GCS (n=14). Other frequently studied factors were personal history of psychiatric disorders preceding TBI (n=11), employment, ethnicity, duration of PTA, and time post-injury (all n=10), history of alcohol or substance abuse before TBI (n=6), and involvement in litigation (n=6). Females,[43,44,75,85] those without employment,[5,60,86,93] and those with a history of psychiatric disorders[5,43,49,51,60,74,75,80,84-87,89,99,103,107] or substance abuse pre-TBI[11,49,75,87,99] were at higher risk for psychiatric disorders post-TBI (Table 8.5). Location of the brain lesion showed to be related to the risk of depressive disorders.[51,60,62,100,102] Further, psychiatric disorders were associated with worse outcomes on measures like the Glasgow Outome Scale (GOS),[49,87] Mini-Mental State Examination (MMSE),[49,87] or complications such as post-concussion symptoms/disorder (PCS/PCD)[59,92,97] and memory of the traumatic event.[65,74,76] Contrasting findings were reported with respect to patients age, showing an increased risk of psychiatric disorders in older[5,62,74,79,86,98,107] and younger[11,49,87] patients.

Table 8.5 Risk factors associated with psychiatric disorders post-TBI*

Disorder	Patient-related	Injury-related	Follow-up related
Axis I	Younger age (18–64 year)[49,87] (2|8)	More severe TBI[43] (1|7)	Shorter[44], longer[80] time post-injury (2|2)
	Less education[49,87] (2|6)		Poorer GOS[49,87] (2|2)
	Pre-injury unemployment[5] (1|3)		Lower MMSE score[49,87] (2|2)
	History of psychiatric disorders[43,49,80,87] (4|5)		
	History of alcohol consumption[49,87] (2|2)		
Anxiety	Older age[5,79,86] (3|6)	Less[66], more (symptoms)[68] severe TBI (1|4)	
	Female gender[43,44] (2|6)		
	Pre-injury unemployment[86] (1|2)		
	Pre-injury anxiety disorders[5,85,86] (3|4)		
ASD	History of psychiatric disorders[89] (1|2)		Shorter[89], longer[56] hospitalisation (2|2)
PTSD	Older age[74] (1|9)	Higher LOC[69] (PTSD severity)[75] (2|2)	Shorter time post-injury[44] (1|4)
	Female gender[44] (PTSD severity)[75] (2|5)	Shorter PTA duration[83] (1|8)	PCS/PCD[59,92,97] (3|3)
	History of psychiatric disorders[74,83] (PTSD severity)[75] (3|4)		Memory of traumatic event[65,74,76] (3|3)
			Poorer GOSE[83] (1|1), Lower QOLI[83] (1|1)
Depression	Older age[62,98] (2|12)	Lesion location[62,100,102] (3|3)	Shorter[44], longer[85] time post-injury (2|5)
	Female gender[44,85] (2|11)	Abnormal CT result[98] (1|3)	
	Less education[85] (1|11)		
	History of psychiatric disorders[99,103] (2|6), depression[85] (1|2)		
	History of substance abuse[99] (1|4)		
MD	Older[107], younger (16–59 year)[11] age (2|6)	MVA[10] (1|3)	PCS/PCD[59,97] (2|2)
	Pre-injury unemployment[60] (1|4)	Lesion location[51,60,100] (3|3)	
	(No)[43] History of psychiatric disorders[51] (2|2), depression[51,60,107] (3|3)		
	History of substance abuse[11] (1|6)		

Axis I also includes disorders other than anxiety or depressive disorders (e.g. substance use, schizophrenia, psychotic disorders, dementia, etc.).
* Only risk factors which appear to be significant in 2 or more studies were presented.
In brackets: Number of studies in which the risk factor reached significance | Number of studies in which the risk factor was assessed.
ASD: acute stress disorder; GOS: Glasgow Outcome Scale; MMSE: Mini-Mental State Examination; LOC: loss of consciousness; MD: major depression; MVA: motor vehicle accident; PCS/PCD: post-concussion symptoms/disorder (e.g. concentration deficits, dizziness, fatigue, headaches, sensitivity to sound, and visual disturbances); PTSD: post-traumatic stress disorder.

8.4 DISCUSSION

Our systematic review aimed to provide insight into the prevalence of, and risk factors for, anxiety disorders and depressive disorders post-TBI, collected with structured diagnostic interviews. Our findings showed that a substantial number of patients had a history of anxiety disorders (19%) or depressive disorders (13%) pre-TBI or were diagnosed with those disorders in the first year post-TBI (21% and 17%). Pooled prevalence estimates of psychiatric disorders increased over time and indicated that years post-TBI, half of the participants (54%) were diagnosed with Axis I disorders, including anxiety disorders (36%) or depressive disorders (43%). Females, those without employment, and those with a history of psychiatric disorders or substance abuse pre-TBI seem to be at higher risk for anxiety or depressive disorders post-TBI.

Quality of the evidence

Several limitations of the included studies need to be considered. First, the studies faced difficulties in differential diagnosis of overlapping disorders (e.g. ASD and post-concussive effects) and overlapping symptoms between TBI and disorders, which may have led to higher[89] or lower[108] prevalence rates of disorders. The included studies, however, all used structured diagnostic interviews to examine the presence of psychiatric disorders according to standard criteria like the DSM or ICD. The use of structured diagnostic interviews by clinical experts (e.g. one trained psychiatrist or psychologist) enables more stringent assessment of psychiatric outcomes post-TBI than self-report measures.[18] However, regardless of the method of assessment, patients may report more symptoms because of concerns about pending litigations.[109]

Second, the history of psychiatric disorders pre-TBI was often retrospectively assessed (e.g. with use of the structured interview), in some studies even years post-TBI. Relying on recall of symptoms over such long periods may be less reliable.[110]

Third, several studies reported on a small number of subjects,[6,24,62,66,68,73,90,92] and their conclusions may not apply to all patients with TBI. Although most of the 34 included studies had difficulties in contacting and interviewing all eligible patients, there is a need for a thorough and reliable assessment of the psychiatric outcome in all survivors of a TBI. Participation rates may be increased by using face-to-face recruitment and data collection, using mail and Internet for contacting and informing patients, and lowering the participant burden (e.g. by conducting interviews at home).[111]

Prevalence rates

Consistent with findings in the literature,[1-3] anxiety disorders (mainly PTSD) and depressive disorders (mainly MD) were the most common, frequently studied disorders post-TBI.

There was considerable variation in the post-injury prevalence rates of disorders among the patient samples of the included studies. The wide variation in prevalence rates of pre- and post-injury prevalence rates of anxiety and depressive disorders between studies has been reported previously[1,3,15,112] and can be explained by differences in study design, characteristics of the patients, definitions, methods of assessment, and measures used to assess the psychiatric outcomes.

Our findings indicate that a history of psychiatric disorders before the TBI was common in TBI survivors, given that approximately 1 in 3 adults (38%) had pre-injury Axis I disorders (often including substance abuse disorder), 1 in 5 (19%) a history of anxiety disorders, and 1 in 8 (13%) a history of depressive disorders pre-TBI. According to our pooled prevalence estimates, prevalence rates of anxiety disorders were lower pre-TBI (19%) than in the first year post-TBI (21%). In contrast, three studies that reported on pre- and post-injury prevalence rates of depressive disorders, indicated prevalence of depressive disorders to be higher pre-TBI than in the first year post-TBI.[5,57,58] In line with these findings, the included studies in our review that also reported on the community base rate of psychiatric disorders showed that patients with TBI had lower pre-injury rates of anxiety disorders than the general population (e.g. PTSD: 6% pre-TBI vs 8% in US adults[43]; 2% pre-TBI versus 6% in Australian population[80]), but higher pre-injury rates of depressive disorders (e.g. MD: 17–20% pre-TBI versus 6% in US adults[43,44]; 14% pre-TBI versus 11% in Australian population[80]).

Although a history of psychiatric disorders pre-TBI was common, several studies reported a substantial share of novel disorders.[2,45,54] These studies showed that numerous participants experienced Axis I

disorders (78%), including anxiety disorders (74%) or depressive disorders (72%) for the first time post-injury.[45,54] However, a history of psychiatric disorders pre-TBI was significantly associated with a higher risk for psychiatric disorders in the aftermath of a TBI.[5,43,49,51,60,74,75,80,85-87,89,99,103,107]

A few of the included studies reported on the prevalence of comorbid psychiatric disorders and indicated that 72–77% of those with a post-injury depressive disorder also had a comorbid anxiety disorder and 69% of those with an anxiety disorder also had a comorbid depressive disorder.[54,60,80] According to findings of Gould and colleagues, anxiety disorders tended to precede or emerge at the same time as depressive disorders.[80]

Pooled prevalence estimates of psychiatric disorders indicated that psychiatric disorders did increase over time, even after mild TBI. The increase of prevalence rates of disorders over time was a phenomenon that was also found within some of the included studies.[2,5] This may be explained by the ongoing stressors and problems that may occur after the traumatic event, which may add to the maintenance of disorders post-TBI.[2,113] Additionally, the delayed onset of psychiatric disorders may occur because of psychosocial changes, given that after the physical recovery insight into social, cognitive, and emotional disability develops.[80,114,115] Another explanation may be that a greater cognitive resource (e.g. higher education level before a TBI) may decrease the vulnerability to cognitive deficits post-TBI and may have a protective role in the development of psychiatric disorders.[116] Although the included studies in our review assessed education level[5,6,11,24,44,49,51,60-63,68,74,76,86,88,93,98] and pre-morbid IQ[24,68,107] as risk factors for psychiatric disorders post-TBI, only few of them reached significance showing less education to be associated with higher prevalence of anxiety and depressive disorders post-TBI.[49,85,87] In contrast, longitudinal results of Ashman and colleagues showed that the risk of having an Axis I disorder decreased 3–6 years post-injury.[44] However, Koponen and colleagues found high rates of current psychiatric disorders 30 years post-TBI,[45] which suggests that the vulnerability of developing psychiatric disorders may remain throughout the life of a person with TBI.

Our pooled estimates of depressive disorders (MD: 15% first year, 27% >1 year; dysthymia: 3% and 1%) were in line with those of a recent review of Osborn and colleagues, in which 27% of the TBI survivors were clinically diagnosed with MD and/or dysthymia post-TBI.[18] We, however, computed pooled prevalence estimates over time, showing lower estimates of MD and dysthymia in the first year post-TBI (15% and 3%), but higher estimates in the long-term (27% and 1%). Additionally, a review of Van Reekum and colleagues overall reported higher mean prevalence rates of MD and PTSD compared to our pooled estimates: MD 44%[22] versus 15% in the first year and 27% after one year in our review; PTSD 14%[22] versus 14% and 7% in our review. Their review, however, did not specify prevalence of disorders over time, and included data from both structured diagnostic interviews and self-report measures.[22] Osborn and colleagues showed that, in comparison to structured diagnostic interviews, use of self-report measures leads to far higher prevalence rates.[18]

Risk factors

The included studies in our review reported different directions of risk factors such as the patients' age,[11,107] TBI severity level,[43,66,68] time post-injury,[44,80,85] and length of stay in the hospital.[56,89] However, these findings are not necessarily inconsistent. For example, in the studies that reported that younger people were more at risk of having a psychiatric disorder post-TBI, the younger group comprised all those aged 18–64 years,[49,87] or 16–59 years.[11] However, the relationship between age and psychiatric

disorders post-TBI is controversial, with studies showing contrasting findings on whether[62,98] or not[11] older patients are at increased risk of psychiatric disorders post-TBI.

Additionally, inconsistent findings were reported on TBI severity, because more-severe TBI was related to a higher risk for Axis I disorders[43] and the number of anxiety symptoms,[68] whereas less-severe TBI was related to higher risk for anxiety disorders.[66]

The studies in our review tended towards higher prevalence rates of MD among patients with more-severe TBI, as 8–18% of the patients with mild TBI received this diagnosis versus 7–63% in patients with all TBI severity levels. However, the severity of TBI has not emerged as a significant risk factor for depressive disorders in previous studies.[5,18,61,63,66,86,96,99,105]

Female gender was identified as a risk factors for psychiatric disorders post-TBI in several studies.[43,44,85] This is underpinned by the fact that the included studies with a high share of women (≥70%, n=5) tended to report somewhat higher prevalence rates of anxiety disorders than the samples with relatively more men (on average 6–12% higher rates), OCD (2–6%), PTSD (3–8%), depressive disorders (4–12%), and MD (<1–5%).

Finally, several studies included in this review reported depressive disorders being associated with lesion location, with higher rates of disorders in patients with left frontal abnormality,[51,60,62,99,102] left anterior lesions,[51,99,100,102] left[51] or right hemisphere lesions,[51,102] cortical lesions,[51] and parieto-occipital lesions.[51] Although investigations determining the relationship between lesion location and depressive symptoms have proven inconsistent,[1] lesion site may influence the nature of depression, but does not fully explain the occurrence and severity of depressive disorders.[117]

Strengths and limitations

Our review adds to the knowledge on psychiatric outcomes of TBI in civilian adults, by providing pooled prevalence estimates over time and insight into the risk factors associated with the full spectrum of anxiety disorders and depressive disorders. Our findings are based on evidence from structured diagnostic interviews and emphasise that the prevalence of anxiety and depressive disorders post-TBI is high and persists over time.

This review has limitations. First, because of our decision to only include studies on anxiety and depressive disorders post-TBI, other psychiatric outcomes (e.g. including substance use disorders, schizoaffective disorders, or psychotic disorders) were not specifically taken into account. Second, the review solely focused on the prevalence of psychiatric disorders post-TBI in civilian adults aged 16 years or older. Therefore, information on the prevalence of anxiety and depressive disorders among children or adolescents and military personnel is missing. Military personnel and veterans have a higher exposure to emotional trauma,[25] and therefore show higher rates of psychiatric disorders (e.g. PTSD) than the civilian populations.[26] Third, this review did not elaborate on the cognitive impairments (e.g. deficits in attention, processing speed, and working memory) or post-concussion symptoms (e.g. dizziness, fatigue, and headaches) which may contribute or interact with psychiatric outcome post-TBI.[79,107] Fourth, only a few of the studies included in this review reported on the percentage of novel disorders post-TBI.[2,45,54,70] Research is needed to gain more insight into the prevalence of new versus recurrent anxiety disorders and depressive disorders post-TBI. Finally, it was difficult to compare study results because of the differences in study objectives, design, methodology, and study population, including differences in definitions of TBI, inclusion and exclusion criteria, and interviews used to assess

psychiatric disorders. Some of the studies in this review included participants with self-reported TBI (not medically documented) or from a variety of outpatient or rehabilitation settings. The studies assessed disorders in patients with varying TBI severity levels. Because mild TBI is likely to be very different from severe TBI on many aspects, pooling of the data across these TBI severity levels may lead to an under- or overestimation of the prevalence rates amongst different cohorts. In addition, some studies (n=3) reported prevalence over a period of time instead of point prevalence and sometimes used different diagnostic criteria. Research showed that the latter variation in diagnostic criteria surprisingly provided different prevalence estimates, despite the overlap between these criteria.[18] All the previous factors might have influenced the prevalence estimates of anxiety disorders and depressive disorders provided in this review. To enable comparisons between studies, consensus should be reached on standard definitions (e.g. for TBI and TBI severity levels), study methods (e.g. which structured interview to use and which time points), and reporting styles (e.g. how to report on pre- and post-injury prevalence rates).

Implications for practice and research

Our review showed that, even years post-TBI, a substantial number of patients experience psychiatric disorders. This underscores the need for recognition and treatment of anxiety and depressive disorders in all health care settings.[10,11,68] Ideally, the routine treatment of patients with TBI should include a psychiatric evaluation and follow-up. Overall, early identification and treatment of psychiatric disorders may enhance the recovery of TBI survivors, their capacity to work, their HRQL and functional outcome, and may reduce the high costs associated with disability in TBI.[118-120]

As only a few of the studies included in this review reported on the percentage of novel disorders post-TBI,[2,45,54,70] research is needed to gain more insight into the prevalence of new versus recurrent anxiety and depressive disorders post-TBI.

Additionally, because of the increased risk of psychiatric disorders over time, it is recommended to assess the psychiatric outcome of patients soon after TBI (within 1 month), and after 3, 6, 12, and 24 months.

Future studies on the psychiatric outcomes of TBI survivors should assess the prevalence of the full range of anxiety disorders and depressive disorders, with use of structured diagnostic interviews, and should investigate the increased risk for these disorders among females, the unemployed, and those with a history of psychiatric disorders pre-TBI.

Conclusions

Research conducted with the best available assessment instruments shows that a substantial number of patients encounter anxiety and depressive disorders pre- and post-TBI and that prevalence rates increase with time post-injury. The pooled prevalence estimates provide insight into the magnitude of anxiety disorders and depressive disorders post-TBI and indicate that these disorders persist over time. All health care settings should pay attention to the occurrence of psychiatric symptoms in the aftermath of TBI, especially in females, those without employment, and those with a history of psychiatric disorders or substance abuse pre-TBI.

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APPENDIX

Appendix 8.A Literature search strategies

Date: January 15, 2015
Update: November 2, 2015

	January 15, 2015		November 2, 2015	
Database	**Records**	**Unique records**	**Records**	**Unique, new records**
Embase.com	3623	3606	307	
Medline (OvidSP)	2288	511	173	
PsycINFO (OvidSP)	1448	461	107	
PubMed publisher	161	114	174	
Cochrane	69	15	2	
Google scholar	200	93	–	
Total	**7782**	**4800**	**763**	**539**

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Medline (OvidSP)
(exp Craniocerebral Trauma/ OR Glasgow Coma Scale/ OR coma/ OR (((brain OR head OR crani* OR intracrani* OR skull* OR cerebr* OR capitis OR hemisphere*) ADJ3 (injur* OR trauma* OR posttrauma* OR damag* OR lesion* OR fracture*)) OR concus* OR contus* OR neurotraum* OR tbi OR mtbi OR coma*).ab,ti.) AND (exp Wounds and Injuries/ OR exp Stress Disorders, Traumatic/ OR exp accidents/ OR exp Emergencies/ OR exp Emergency Treatment/ OR exp Emergency Service, Hospital/ OR exp violence/ OR (trauma* OR posttrauma* OR injur* OR tbi OR mtbi OR accident* OR emergen* OR violen*).ab,ti.) AND (exp anxiety/ OR exp mood disorders/ OR exp anxiety disorder/ OR exp depression/ OR exp

mental health/ OR Personal Satisfaction/ OR "Diagnostic and Statistical Manual of Mental Disorders" OR (anxi* OR ((mood OR affective) ADJ3 (disorder* OR disturb*)) OR phobi* OR agoraphobi* OR panic OR ocd OR (obsessi* ADJ3 compulsi*) OR depress* OR ((posttraumatic OR post-traumatic OR postconcussion* OR post-concussional OR post-concussion) ADJ3 (stress* OR syndrom*)) OR dysthymi* OR ptsd OR ((psychologic* OR neuropsychologic* OR emotion*) ADJ3 (outcome* OR develop* OR well-being OR wellbeing OR disabil* OR progres* OR adjust* OR function* OR consequenc* OR sequel*)) OR mental health OR dsm).ab,ti.) AND (exp prevalence/ OR exp incidence/ OR Prognosis/ OR exp Interviews as Topic/ OR epidemiology/ OR epidemiology.xs. OR exp risk factors/ OR (incidenc* OR prevalen* OR predict* OR prognos* OR interview* OR (risk ADJ3 factor*) OR epidemiolog* OR ((indicator* OR variable* OR characteristic* OR examination* OR assessment* OR measure* OR association* OR determinant*) ADJ3 psycholog*) OR psychometric*).ab,ti.) NOT (letter OR news OR comment OR editorial OR congresses OR abstracts).pt. AND english.la. NOT (exp animals/ NOT humans/)

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(exp Head Injuries/ OR Brain Damage/ OR coma/ OR (((brain OR head OR crani* OR intracrani* OR skull* OR cerebr* OR capitis OR hemisphere*) ADJ3 (injur* OR trauma* OR posttrauma* OR damag* OR lesion* OR fracture*)) OR concus* OR contus* OR neurotraum* OR tbi OR mtbi OR coma*).ab,ti.) AND (exp Injuries/ OR exp Posttraumatic Stress Disorder/ OR exp accidents/ OR exp trauma/ OR exp Emergency Services/ OR exp Emergency Management/ OR exp violence/ OR (trauma* OR posttrauma* OR injur* OR tbi OR mtbi OR accident* OR emergen* OR violen*).ab,ti.) AND (exp anxiety/ OR exp affective disorders/ OR exp anxiety disorders/ OR exp "Depression (Emotion)"/ OR exp mental health/ OR Satisfaction/ OR "Diagnostic and Statistical Manual" OR (anxi* OR ((mood OR affective) ADJ3 (disorder* OR disturb*)) OR phobi* OR agoraphobi* OR panic OR ocd OR (obsessi* ADJ3 compulsi*) OR depress* OR ((posttraumatic OR post-traumatic OR postconcussion* OR post-concussional OR post-concussion) ADJ3 (stress* OR syndrom*)) OR dysthymi* OR ptsd OR ((psychologic* OR neuropsychologic* OR emotion*) ADJ3 (outcome* OR develop* OR well-being OR wellbeing OR disabil* OR progres* OR adjust* OR function* OR consequenc* OR sequel*)) OR mental health OR dsm).ab,ti.) AND (Prognosis/ OR exp Interviews/ OR exp epidemiology/ OR exp risk factors/ OR (incidenc* OR prevalen* OR predict* OR prognos* OR interview* OR (risk ADJ3 factor*) OR epidemiolog* OR ((indicator* OR variable* OR characteristic* OR examination* OR assessment* OR measure* OR association* OR determinant*) ADJ3 psycholog*) OR psychometric*).ab,ti.) NOT book.pt. AND english.la. NOT (exp animals/ NOT humans/)

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((((brain OR head OR crani* OR intracrani* OR skull* OR cerebr* OR capitis OR hemisphere*) NEAR/3 (injur* OR trauma* OR posttrauma* OR damag* OR lesion* OR fracture*)) OR concus* OR contus* OR neurotraum* OR tbi OR mtbi OR coma*):ab,ti) AND ((trauma* OR posttrauma* OR injur* OR tbi OR mtbi OR accident* OR emergen* OR violen*):ab,ti) AND ((anxi* OR ((mood OR affective) NEAR/3 (disorder* OR disturb*)) OR phobi* OR agoraphobi* OR panic OR ocd OR (obsessi* NEAR/3 compulsi*) OR depress* OR ((posttraumatic OR post-traumatic OR postconcussion* OR post-concussional OR post-concussion) NEAR/3 (stress* OR syndrom*)) OR dysthymi* OR ptsd OR ((psychologic* OR neuropsychologic* OR emotion*) NEAR/3 (outcome* OR develop* OR well-being OR wellbeing OR disabil* OR progres* OR adjust* OR function* OR consequenc* OR sequel*)) OR 'mental health' OR dsm):ab,ti) AND ((incidenc* OR prevalen* OR predict* OR prognos* OR interview* OR (risk NEAR/3 factor*) OR epidemiolog* OR ((indicator* OR variable* OR characteristic* OR examination* OR assessment* OR measure* OR association* OR determinant*) NEAR/3 psycholog*) OR psychometric*):ab,ti)

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"brain|head|cranial|cerebral injury|trauma|fracture"|concussion|contussion|coma trauma|traumatic|posttraumatic|injury|accident anxiety|"mood disorder"|depression|"mental health"|psychological|dsm prevalence|incidence|epidemiology|"risk factor"|prognosis

Table 8.A Study characteristics of related studies

Author, year, country	Study population	Inclusion/Exclusion	Sample	Disorder	Interview	Assessment
Bryant, 2009, Australia, A [77]	Mild (ACRM) Admitted to hospital (>24h) (n=478)	16–70y Not psychotic or suicidal Randomly selected, stratified by LOS	<45y 73%, 45+y 28% Male 72%; MVA 74% PTA 2.4h (1.6)	PTSD	CAPS (DSM-IV)	Telephone interview by trained researchers
Bryant, 2015, Australia, A [78]	Mild (ACRM) Admitted to hospital (>24h) (n=437)	16–70y Not psychotic or suicidal Randomly selected, stratified by LOS	<45y 72%, 45+y 28% Male 72%; MVA 76%	PTSD	MINI (DSM-IV, ICD-10) CAPS (DSM-IV)	Telephone interview
Gould, 2011C, Australia, A [80]	Compl mild to severe Admitted to rehab. hospital (n=102)	16–80y No history of TBI; neurological disorder	34.6y (15.7), 16–73 Male 76%; MVA: 64% GCS 13–15 40%, 9–12 16%, 3–8 43% PTA 24.9 (23.7), 0.006–121d	Axis I	SCID (DSM-IV-TR)	Not reported
Gould, 2011B, Australia, A [81]	Compl mild to severe Admitted to rehab. hospital (n=122)	16–80y No history of TBI; neurological disorder	34.9y (16.2), 16–77 Male 79%; GCS 9.2 (4.3), 3–15; PTA 23.6 (22.6), 0.05–121d	Axis I	SCID (DSM-IV-TR)	Not reported
Schonberger, 2011, Australia, A [82]	Compl mild to severe Admitted to rehab. hospital (n=122)	16–80y No history of TBI; neurological disorder	34.9y (16.2), 16–77 Male 79%; GCS 9.2 (4.3), 3–15; PTA 23.6 (22.6), 0.05–121d	Axis I	SCID (DSM-IV-TR)	Not reported
Gould, 2014, Australia, A [79]	Moderate to severe (PTA≥24h) Admitted to rehab. hospital (n=66)	16–80y No history of TBI; ADHD; neurological disorder	*33.0y (13.2), 18–61 Male 79%; MVA 77% PTA 1–7d 21%, 8–28d 53%, >28d 24%	Anxiety	SCID (DSM-IV-TR)	Not reported
Alway, 2015A, Australia, A [83]	Moderate to severe (PTA>24h) Admitted to rehab. hospital (n=203)	16–80y No history of TBI; neurological disorder	34.4y (16.0), 16–76 Male 78%; MVA 80% PTA 1–7d 34%, >7d 66%	PTSD	SCID (DSM-IV)	Face-to-face interview (initial), telephone interview (follow-up)
Alway, 2015B, Australia, A [84]	Moderate to severe (PTA>24h) Admitted to rehab. hospital (n=85)	16–80y No history of TBI; neurological disorder; All 6 (follow-up) assessments completed	PTSD: 35.2y (14.9) No PTSD: 35.9 (17.0) Male 79%; MVA 77% PTSD: PTA 1–7d 40%; No PTSD: 24%	PTSD	SCID (DSM-IV)	Interview by trained psychologist
Whelan-Goodinson, 2008, Australia, B/C [85]	Minor to severe (GCS<15) Admitted to hospital (n=100)	17–75y No history of TBI; neurological disorder; neurodegenerative disease	*37.2y (14.2), 19–74 Male 71% GCS 9.1 (4.1), 3–14 PTA 20.8 (17.9), 1–77	Anxiety	SCID (DSM-IV)	Clinical computerised version, blinded to medical file history
Whelan-Goodinson, 2010, Australia, B/C [86]	Minor to severe (GCS<15) Admitted to hospital (n=100)	17–75y No history of TBI; neurological disorder; neurodegenerative disease	*37.2y (14.2), 19–74 Male 71%; MVA 86% GCS 9.1 (4.1), 3–14 PTA 20.8 (17.9), 1–77	Axis I	SCID (DSM-IV)	Clinical computerised version, blinded to medical file history
Deb, 2007, UK, A [87]	Minor to severe (GCS<15) Admitted to hospital (n=165)	17+y ICD-9 diagnosis of TBI; Period of LOC; Radiological evidence	18–65y: 35.5y, 65+ 79.2y; Male 67%	Axis I	SCAN/PSE (ICD-10)	Only patients with abnormal score on CIS-R, GHQ-28 or PSQ

Table 8.A (continued)

Author, year, country	Study population	Inclusion/Exclusion	Sample	Disorder	Interview	Assessment
Sliwinski, 1998, US, A [88]	Mild to severe Selection quality of life survey (n=100)	18–65y at time of interview Self-identified TBI ≥1y prior to interview No history of neurological disorder	*39.8y (10.2) Male 53%; MVA 62% LOC <20m 30%, >1mo 24%	Depression	SCID (DSM-IV)	Licensed psychologist with extensive background in clinical neuropsych and brain injury
Hibbard, 2004, US, A/C [4]	Mild to severe Hospital, brain injury associations, advertisements, website (n=188)	18–87y Self-identified TBI No history of neurocognitive disorder; psychotic disorder	40.4y (15.1); Male 53% GCS 13–15 29%, 3–8 62%	Depression	SCID (DSM-IV)	Clinicians with ≥3y clinical experience
Diaz, 2012, Brazil, A [6]	Severe (GCS≤8 <48h of admission) Admitted to ICU (n=33)	18+y No gunshot wounds	32.3y (11.7); Male 88% GCS 7–8 42%, 5–6 29%, 3–4 29%	Axis I	SCID (DSM-IV)	Two board-certified psychiatrists, blinded to hospitalisation variables, additional information by patient relative
Harvey, 1998A, Australia, A [89]	Mild (ACRM) Admitted to hospital (n=79)	16–65y MVA	29.0y (12.0), 16–60; Male 70%; MVA 100% GCS 14.9 (0.4) PTA 9.4 (9.1), 5m–24h	ASD	ASDI (DSM-IV) CIDI (DSM-III-R)	Not reported Doctoral clinical psychologist with 5y experience in assessing traumatised individuals
Harvey, 1998B, Australia, A [90]	Mild (ACRM) Admitted to hospital (n=48)	16–65y MVA	29.1y (13.0), 16–60; Male 69%; MVA 100% GCS 14.7 (0.7) PTA 9.4 (9.1), 5m–24h	ASD	ASDI (DSM-IV)	Doctoral clinical psychologist with 5y experience in assessing traumatised individuals
Harvey, 2000, Australia, A [91]	Mild (ACRM) Admitted to hospital (n=50)	16–65y MVA	27.0y (10.6), 17–58; Male 62%; MVA 100% PTA 9.4 (9.1), 5m–24h	ASD PTSD	ASDI (DSM-IV) CIDI (DSM-III-R)	Doctoral clinical psychologist with 5y experience in assessing traumatised individuals
Bryant, 1999B, Australia, A [92]	Mild (ACRM) Admitted to hospital (n=46)	16–65y; MVA Not psychotic or suicidal Randomly selected, stratified by LOS	28.5y (12.3); Male 70%; MVA 100%	PTSD	CIDI (DSM-III-R)	Clinical psychologist
Bryant, 2000A, Australia, A [93]	Severe Admitted to rehabilitation unit (n=96)		34.3y (12.8), 16–71; Male 80% GCS 8.0 (3.8) PTA 37.0 (30.7), 7–143d	PTSD	PTSD-I (DSM-III-R)	Trained rehabilitation consultant
Bryant, 1999A, Australia, A [94]	Severe Admitted to rehabilitation unit (n=96)		34.3y (12.8), 16–71; Male 80% GCS 8.0 (3.8) PTA 37.0 (30.7), 7–143d	PTSD	PTSD-I (DSM-III-R)	Trained rehabilitation consultant

Table 8.A (continued)

Author, year, country	Study population	Inclusion/Exclusion	Sample	Disorder	Interview	Assessment
Bryant, 2001, Australia, A [95]	Severe Admitted to rehabilitation unit (n=96)		34.3y (12.8), 16–71; Male 80% GCS 8.0 (3.8) PTA 37.0 (30.7), 7–143d	PTSD	PTSD-I (DSM-III-R)	Trained rehabilitation consultant
Levin, 2001, US, A [96]	Mild to moderate Attended ED/admitted to hospital (n=69)	16+y Arrival to hospital <24h; blood alcohol level <200mg/dL No history of substance dependence; mental retardation; major psychiatric disorder; CNS disturbance	35.1y (14.7); Male 71%; MVA 64% GCS 4.4, 9–15; 13–15 87%, 9–12 13%	MD	SCID (DSM-IV)	Research technician and supervising psychologist (English or Spanish)
McCauley, 2001, US, A [97]	Mild to moderate Attended ED/admitted to hospital (n=115)	16+y Arrival to hospital <24h; blood alcohol level <200mg/dL No history of substance dependence; mental retardation; major psychiatric disorder; CNS disturbance	33.4y (13.7); Male 21%; MVA 76% GCS 13–15 83%, 9–12 17%)	PTSD MD	SCID (DSM-IV)	Trained research associates under supervision of study psychiatrist
Levin, 2005, US, A [98]	Mild to moderate Attended ED/admitted to hospital (n=129)	16+y Arrival to hospital <24h; blood alcohol level <200mg/dL No history of substance dependence; mental retardation; major psychiatric disorder; CNS disturbance	31.5y (12.8); Male 67%; MVA 67% GCS 14.8 (0.5)	Depression	SCID (DSM-IV)	Conducted by bachelors-/masters-level research assistant in the patient's primary language (English or Spanish)
Rapoport, 2003B, Canada, A [10]	Mild (ACRM) Appointment at TBI clinic (n=170)	18+y No history of focal brain disease; acute medical illness; schizophrenia; bipolar disorder; dementia	44.2y (20.1), 15–91; Male 65%; MVA 65%	MD	SCID (DSM-IV)	Psychiatrist
Rapoport, 2005, Canada, A [107]	Mild to moderate Appointment at TBI clinic (n=74)	<65y No history of focal brain disease; acute medical illness; schizophrenia; bipolar disorder; dementia	34.9y (13.1), 18–64 GCS MD 14.4 (0.7), No MD 13.9 (1.4)	MD	SCID (DSM-IV)	Psychiatrist
Rapoport, 2006, Canada, A [106]	Mild to moderate Appointment at TBI clinic (n=77)	50+y No history of focal brain disease; acute medical illness; schizophrenia; bipolar disorder; dementia	67.1y (8.4), 50–89; Male 49% GCS 13–15 57%, 9–2&PTA<1w 43%	MD	SCID (DSM-IV)	Not reported

Table 8.A (continued)

Author, year, country	Study population	Inclusion/Exclusion	Sample	Disorder	Interview	Assessment
Jorge, 1993A, US, A [99]	Mild to severe Admitted to shock trauma center (n=66)	18+y Acute closed head injury No significant multiple system injuries; DSM-III-R delirium; impaired consciousness or severe comprehension deficits	Acute (A): 26.8y (5.8); Delayed (D): 28.9y (6.4), No depression (N): 29.5y (11.7) Male 82% (A), 73% (D), 88 (N) GCS A: 9.0 (3.3), D: 8.3 (3.0), N: 10.6 (3.3)	Depression	SCAN/PSE (DSM-III-R)	Fully trained psychiatrist
Jorge, 1993B, US, A [100]	Mild to severe Admitted to shock trauma center (n=66)	18+y Acute closed head injury No significant multiple system injuries	MD: 26.8y, No MD: 30.1y; Male 84% GCS median 10, IQR 6	Depression	SCAN/PSE (DSM-III-R)	Not reported
Jorge, 1993C, US, A [101]	Mild to severe Admitted to shock trauma center (n=66)	18+y Acute closed head injury No significant multiple system injuries; DSM-III-R delirium; decreased LOC or substantial aphasia	Mania: 30.3y (18.4); MD: 27.7y (6.1),None: 29.6y (10.0); Male 84% GCS 12–15 17%, 8–15 & intracran surg or focal lesions >25cc 58%, 3–7 15%	Depression (mania)	SCAN/PSE (DSM-III-R)	Not reported
Jorge, 1993D, US, A [102]	Mild to severe Admitted to shock trauma center (n=64)	18+y Acute closed head injury No significant multiple system injuries; decreased LOC or substantial aphasia	GAD&MD: 25.0y (5.0), MD: 29.4y (6.2), None: 30.1 (10.8); Male 84% GCS median 10, IQR 6	GAD, MD	SCAN/PSE (DSM-III-R)	Not reported
Jorge, 1993E, US, A [103]	Mild to severe Admitted to shock trauma center (n=66)	18+y Acute closed head injury No significant multiple system injuries; decreased LOC or substantial aphasia	Depressed: 25.0 (8.4), None: 27.0y (13.5) Male 85%	Depression	SCAN/PSE (DSM-III-R)	Not reported
Jorge, 1994, US, A [104]	Mild to severe Admitted to shock trauma center (n=52)	18+y Acute closed head injury No significant multiple system injuries; decreased LOC or substantial aphasia	Not reported	MD	SCAN/PSE (DSM-III-R)	Not reported
Gomez-Hernandez, 1997, US, A [105]	Mild to severe Admitted to shock trauma center (n=65)	18+y Acute closed head injury No significant multiple system injuries	Depressed: 27.3y (8.4), None: 29.3y (10.3) Male 86% GCS median 10, IQR 6	Depression	SCAN/PSE (DSM-III-R)	Research psychiatrist

A: Prospective; B: Retrospective; C: Cross-sectional; D: (Nested) Case-control. m=minute; h=hour; d=day; w=week; mo=month; y=year. * Age at assessment.
ACRM: American Congress of Rehabilitation Medicine; ASD: acute stress disorder; ASDI: Acute Stress Disorder Interview; CAPS: Clinician-Administered PTSD Scale for DSM-IV; CIDI: Composite International Diagnostic Interview; DIS: Diagnostic Interview Schedule; CNS: central nervous system; DSM: Diagnostic and Statistical Manual of Mental Disorders; ED: emergency department; GCS: Glasgow Coma Scale; HADS: Hospital Anxiety and Depression Scale; HI: head injury; ICU: intensive care unit; IES-R: Impact of Event Scale – Revised; IQR: interquartile range; LOC: loss of consciousness; LOS: length of stay in hospital; MD: major depression; MINI: Mini International Neuropsychiatric Interview; MMSE: Mini-Mental State Examination; MVA: motor vehicle accident; PCD: post-concussive disorder; PDS: Posttraumatic Stress Diagnostic Scale; PTSD-I: Posttraumatic Stress Disorder Interview; PSE: Present State Examination; PSS: PTSD Symptom Scale; PTA: post-traumatic amnesia; PTSD: post-traumatic stress disorder; RTA: road traffic accident; SADS-L: Schedule for Affective Disorders and Schizophrenia-Lifetime; SCAN: Schedules for Clinical Assessment in Neuropsychiatry; SCID: Structured Clinical Interview for DSM Disorder.

Table 8.B Overall pooled prevalence rates (95%CI) per disorder by time point

Disorder	Pre-injury				First year				>1 year			
	N	Pooled rate (95%CI)	I^2 (%)	p-value	N	Pooled rate (95%CI)	I^2 (%)	p-value	N	Pooled rate (95%CI)	I^2 (%)	p-value
Axis I	5	38.1% (21.6%, 54.6%)	0.0	0.61	6	31.6% (19.6%, 43.6%)	0.0	0.52	3	53.5% (37.5%, 69.4%)	0.0	0.42
Anxiety	6	18.9% (13.8%, 23.9%)	31.9	0.20	5	21.2% (13.8%, 28.6%)	4.5	0.38	3	35.8% (20.2%, 51.4%)	7.8	0.34
GAD	5	2.6% (–0.1%, 5.3%)	45.6	0.12	9	6.9% (3.4%, 10.4%)	4.4	0.40	4	13.5% (2.0%, 25.0%)	0.0	0.57
ASD	–	–[1]	–	–	5	9.2% (4.0%, 14.5%)	47.0	0.11	–	–[1]	–	–
Panic	4	2.4% (0.1%, 4.9%)	26.3	0.25	6	5.0% (3.0%, 8.0%)	0.0	0.42	5	3.5% (2.2%, 4.8%)	0.0	0.91
Agoraphobia	3	1.4% (–1.2%, 4.0%)	65.5	0.05*	4	9.2% (2.4%, 16.0%)	0.0	0.53	–	–[1]	–	–
Specific phobia	3	3.0% (–1.5%, 7.6%)	0.0	0.49	–	–[1]	–	–	–	–[1]	–	–
Social phobia	4	5.5% (2.0%, 8.3%)	0.0	0.48	4	5.7% (3.0%, 8.3%)	2.1	0.38	–	–[1]	–	–
OCD	3	9.2% (5.5%, 12.8%)[2]	64.1	0.06	5	2.6% (1.1%, 4.0%)	10.1	0.35	–	–[1]	–	–
PTSD	6	1.5% (–0.1%, 3.2%)	55.8	0.05*	20	13.8% (10.2%, 17.4%)	12.8	0.30	9	6.8% 3.2%, 10.4%)	0.0	0.46
Depression	8	12.7% (8.5%, 16.9%)	82.3	0.00*	10	16.5% (10.5%, 22.5%)	42.4	0.07	3	43.4% (27.6%, 59.3%)	7.7	0.34
Dysthymia	4	0.1% (–0.3%, 0.5%)	21.7	0.28	7	2.9% (0.7%, 5.1%)	25.3	0.24	3	1.2% (–1.3%, 3.8%)	64.7	0.06
Bipolar disorder	4	0.1% (–0.3%, 0.5%)	0.0	0.42	–	–[1]	0.0	0.32	–	–[1]	–	–
MD	9	10.4% (4.5%, 16.3%)	0.0	0.75	12	14.5% (11.4%, 17.6%)	21.6	0.23	7	26.9% (15,0%, 38,9%)	6.3	0.38

Axis I also includes disorders other than anxiety or depressive disorders (e.g. substance use, schizophrenia, psychotic disorders, dementia, etc.).
I^2: percentage of variation across studies that is attributed to heterogeneity rather than chance: $I^2 \leq 25\%$ indicates low heterogeneity, 50% moderate heterogeneity, and ≥75% high heterogeneity.[48]
p-value: outcome of the Q-statistic, a Chi^2-test for heterogeneity. A low p-value indicates that the variation in effect sizes is beyond chance.[47]
* Including studies with prevalence rate of 0% (absence of disorder), or wide range of prevalence rates.
[1] Small number of studies (n≤2).
[2] Fixed effects model.
ASD: acute stress disorder; GAD: Generalised Anxiety Disorder; MD: major depression; OCD: Obsessive Compulsive Disorder; PTSD: post-traumatic stress disorder.

Chapter 9

Predictors of major depression and post-traumatic stress disorder following traumatic brain injury:

a systematic review and meta-analysis

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Submitted

ABSTRACT

Background While major depressive disorder (MDD) and post-traumatic stress disorder (PTSD) are prevalent after traumatic brain injury (TBI), little is known about which patients are at risk of developing these psychiatric conditions. This systematic review examined predictors of and prognostic models for MDD and PTSD after TBI.

Methods We searched EMBASE, MEDLINE, Cochrane Central, PubMed, PsycINFO, and Google Scholar in September 2015. We sought to include studies in adults with TBI reporting on predictors or prognostic models for MDD and/or PTSD, using structured diagnostic interviews. Risk of bias of individual studies was assessed using the QUIPS tool. Overall quality of the evidence underpinning predictors was assessed using a modified GRADE framework.

Results We included 24 observational studies assessing predictors or prognostic models for MDD (n=14), PTSD (n=8) or both (n=2). Risk of bias ratings for most studies were acceptable although studies that developed a prognostic model (n=9) were at risk for statistical overfitting. MDD was probably predicted by pre-injury depression and may also be predicted by female gender, higher Glasgow Coma Scale and post-injury unemployment. PTSD was probably predicted by a shorter post-traumatic amnesia and a memory of the traumatic event. The effect of other possible predictors was uncertain due to low or very low quality evidence.

Conclusions The overall evidence on predictors of MDD and PTSD after TBI is weak, and currently available prognostic models suffer from methodological shortcomings. Future prognostic models for PTSD and MDD should be developed with adequate sample size and solid methodology.

9.1 INTRODUCTION

There is growing awareness that traumatic brain injury (TBI) may result in post-injury psychiatric disorders[1,2] among which major depressive disorder (MDD) and post-traumatic stress disorder (PTSD) are the most frequently reported.[2-5] A recent systematic review reported pooled prevalence estimates of 21% for MDD and 17% for PTSD in the first year after TBI.[5]

MDD and PTSD after TBI are associated with functional impairments[1,6,7] and a decrease in health-related quality of life (HRQL).[7] They subsequently interfere with rehabilitative interventions and negatively affect recovery from TBI.[1] Moreover, they are associated with high direct and indirect costs,[8-10] resulting in a tremendous individual and societal burden.

Although the significance of MDD and PTSD after TBI is well established, the literature yields limited information about which patients are at risk of developing these psychiatric conditions. This knowledge could be used to flag patients who might benefit from additional monitoring or (preventive) therapeutic interventions, which have shown to be effective in people at risk for MDD and PTSD.[11-13] Prognostic models, which combine a number of characteristics to predict MDD or PTSD, are particularly useful for this purpose.

To our knowledge, there is currently no systematic review investigating prognostic models for MDD or PTSD in patients with TBI. There is one systematic review assessing psychological and psychosocial predictors of PTSD.[14] The authors found that comorbid depression and anxiety, acute stress disorder (ASD), psychological processes (coping styles and attribution) and psychosocial variables (role impairment and reintegration) were associated with PTSD post-TBI.[14] The authors however included all factors *associated with* PTSD, rather than factors *predicting* PTSD. It is therefore unclear whether these specific factors predicted PTSD or were predicted by PTSD. Moreover, they included self-reported measurements to diagnose PTSD. Self-reported measurements might not be reliable in a TBI population due to overlap between psychiatric symptoms and TBI symptoms, memory deficits, low self-awareness, attention problems and evidence that TBI patients tend to underestimate their problems.[15-18] Structured diagnostic interviews, such as the Structured Clinical Interview for Diagnostic and Statistical Manual of mental disorders (SCID), constitute a better alternative as these interviews distinguish psychopathology symptoms from TBI symptoms and are less influenced by TBI-related problems such as memory deficits.[16] Potential predictors of MDD and PTSD are further discussed in three narrative reviews of psychiatric sequelae after TBI.[1,6,16] However, these reviews did not include systematic searches nor analyses to identify predictors.

The objective of this systematic review and meta-analysis was to examine predictors of and prognostic models for MDD and/or PTSD following TBI using structured diagnostic interviews.

9.2 METHODS

Information sources

We conducted a comprehensive literature search on September 1st 2015. The search strategy was developed in consultation with a search expert using a combination of subheadings and text words (Appendix 9.A). The following databases were searched: EMBASE, MEDLINE, Cochrane Central, PubMed, PsycINFO and Google Scholar. Reference lists and citation indices of included papers and

relevant reviews were further inspected to identify any additional publications. The search strategy was restricted to studies published in peer-reviewed English language journals. We did not use any date restrictions.

Study selection

We selected studies examining predictors of and/or prognostic models for MDD and PTSD after TBI. We used the following inclusion and exclusion criteria to determine eligibility of a study:

Participants – Civilian adults (age ≥16) who sustained TBI. TBI was defined as "an alteration in brain function or other evidence of brain pathology, caused by an external force".[19] We included patients with mild, moderate and severe TBI (as defined by the study authors).

Outcome measurement – MDD and/or PTSD according to the Diagnostic and Statistical Manual of Mental Disorders (DSM) or International Classification of Diseases (ICD) classification systems. We restricted our inclusion criteria to studies that used a structured diagnostic interview to diagnose MDD and PTSD, as structured diagnostic interviews are regarded as the gold standard in diagnosing psychopathology.[17] Moreover, structured diagnostic interviews are less influenced by potential memory deficits, low self-awareness and over- or underestimation by TBI patients.

Predictors – We selected studies that examined at least one predictor of or prognostic model for MDD or PTSD after TBI. To be included, studies had to report at least one of the following: 1) baseline differences between the diagnosed and undiagnosed groups, 2) descriptive statistics (e.g. results t-test, chi square test, p-value) or 3) results of the prognostic model (e.g. odds ratio, Nagelkerke R^2). To be included as a predictor, these factors must have preceded the diagnosis of MDD or PTSD. Preceding was defined as either 1) being measured earlier than the psychiatric diagnose or 2) obviously preceding the diagnosis such as gender, age and computed tomography (CT) abnormalities. Prognostic models were defined as models that combined at least two factors to predict a clinical outcome,[20,21] in our case MDD or PTSD.

Study design – We included retrospective- and prospective cohort studies, cross-sectional studies, and case-control studies.

Data extraction and assessment of risk of bias

One author (MC or ASc) screened citations on title and abstract, and then again on full-text, excluding those that did not meet the inclusion criteria. Any doubts were resolved by consulting a senior member of the team (JH or SP). As an audit of performance, a random 20% of the full text screening was repeated by the other reviewer (MC or ASc) and concordance rates were calculated accordingly. The search process was documented according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flowchart.[22]

We developed a data extraction form based on the Critical Appraisal and Data Extraction for Systematic Reviews of Prediction Modelling Studies (CHARMS) checklist[23] and subsequently extracted information on type of prediction modelling study, target population, participants, outcome measurements, candidate predictors, sample size, handling of missing values and model development methods. We additionally extracted baseline information on univariable associations between predictors and outcome by collecting means and standard deviation (SD) for MDD+/PTSD+ and MDD-/PTSD- group (continuous predictors) or number of patients with and without the predictor in MDD+/PTSD+ and

MDD-/PTSD- groups (categorical predictors). We further extracted univariable and multivariable statistics and effect measurements, if available.

Risk of bias was assessed using the Quality in Prognostic Studies (QUIPS) risk of bias tool. The QUIPS has been recommended by the Cochrane Prognosis Methods Groups and has acceptable inter-rater reliability.[24] We included information on the following domains: study participation, study attrition, prognostic factor measurement, outcome measurement, study confounding and statistical analysis and presentation. Each domain was subsequently rated as 'low', 'moderate' or 'high' risk of bias. A domain obtained the score 'low risk' if all individual items of the domain were rated as 'low risk'. A domain was rated as 'moderate risk' if at least one and maximum 50% of the items implied a high risk of bias or an unknown risk of bias, and a study received a score of high risk if >50% of the items implied a high risk of bias or an unknown risk of bias. We applied a quality threshold for study inclusion in the meta-analyses; i.e. studies were omitted from the meta-analyses if they obtained a high score on at least two out of six QUIPS domains. Such a strategy is recommended by Cochrane.[25] Since we performed the meta-analyses with univariable predictors, we omitted studies with a high score on at least two out of five QUIPS domains, excluding study confounding. Study confounding indicates whether the effect of the predictor(s) studied might be explained by other variables and is therefore not relevant for univariable associations.

The data extraction and risk of bias were done independently by one author (MC) with the data and decisions checked by a second author (ASc). Any discrepancies were resolved by discussion with a senior member of the team (SP).

Data synthesis

We performed meta-analyses of univariable predictors of MDD and PTSD. Predictors were included in the meta-analysis if univariable data (mean (SD) or numbers in MDD+/PTSD+ and MDD-/PTSD- groups) were reported in two or more studies measuring the same predictor. Predictors were excluded from the meta-analyses if a study measured the predictor differently from any other study (e.g. age dichotomised into two age groups instead of continuous) or obtained a high risk of bias on at least two QUIPS domains (excluding confounding). Predictors that were not included in the meta-analyses were narratively described and their results were included in the overall rating of the effect. If a study assessed predictors for multiple time points or multiple outcomes (e.g. chronic depression, late onset depression and recovered depression) scores were combined, or if this was not possible, the time point or outcome that was closest to that in the other studies in the same meta-analysis was chosen. We used Review manager (Revman) version 5.3[26] to perform the meta-analyses. For all analyses, random effect models were used as we expected heterogeneity in time span and measurements. For dichotomous predictors, we reported the pooled odds ratio (pOR) and confidence interval (CI) and for continuous predictors, we reported the mean difference (MD) and CI. Heterogeneity was determined using I^2. Heterogeneity was defined as high when I^2 was ≥ 50% (substantial heterogeneity according to Cochrane[27]). In that case, pooled results should not be calculated, or at the very least, be interpreted with caution.

Prognostic models of MDD and PTSD were narratively described by comparing model performance (e.g. Area Under the Receiver Operating Curve (AUC) / Nagelkerke R^2 / calibration) and methods (e.g. number

of candidate predictors). We also narratively described the effect of individual predictors corrected for other variables in the model.

Assessing the quality of evidence

We used an approach modified from the GRADE framework[28] to assess the overall quality of evidence underpinning the identified predictors of and prognostic models for MDD or PTSD.[29,30] For every predictor that was assessed in at least two studies including at least 200 patients in total, we provided summary information from the meta-analysis, narrative synthesis and multivariable analysis, together with a GRADE rating of the overall quality. The quality of predictors that were studied in less than two studies or less than 200 patients in total, was on forehand rated as 'very low' and therefore not included in the GRADE assessment.

According to the GRADE approach, quality of the evidence can be rated as high, moderate, low or very low. Since we included predominately exploratory studies that identified potential prognostic factors, which may be vulnerable to type I errors,[29] we started our GRADE rating at 'moderate quality' instead of 'high quality'. The GRADE rating was subsequently upgraded or downgraded according to the evaluation of study limitations, inconsistencies, indirectness, imprecision, publication bias, effect size and dose-response effects. See Huguet and colleagues[29] and Iorio and colleagues[30] for more information about these criteria. GRADE rating was performed by one review author (MC) and checked by a second review author (ASy), both of whom were trained in the GRADE approach. The pooled results and narrative syntheses for each predictor, along with its GRADE rating (with reasons), were presented in table form.

Multiple publications

Multiple publications refer to more than one article that has been written based on the same study data.[31] Multiple publications were dealt with by selecting one main study based on the following criteria: 1) the study that uses multivariable analyses or developed a prognostic model; 2) the study with the largest number of patients included; 3) the study with the largest numbers of predictors. Any other articles based on the same study database were used to extract any additional predictors.

9.3 RESULTS

Study selection

A total of 8,449 citations were identified through the electronic search strategy (Figure 9.1). After removing duplicates, 5,374 were screened on title and abstract and 5,075 citations were excluded. We obtained 299 citations in full-text of which 270 were subsequently excluded. The most common reason for exclusion was using self-reported measurements instead of a structured diagnostic interview (n=140). The 20% audit on full-text screening obtained a concordance rate of 100% between two review authors. Five additional citations were found via reference lists and citation indices. We included 24 studies (reported in 34 publications) in the narrative synthesis. Of these, 17 studies were included in the meta-analysis.

Figure 9.1 PRISMA flowchart of the selection process

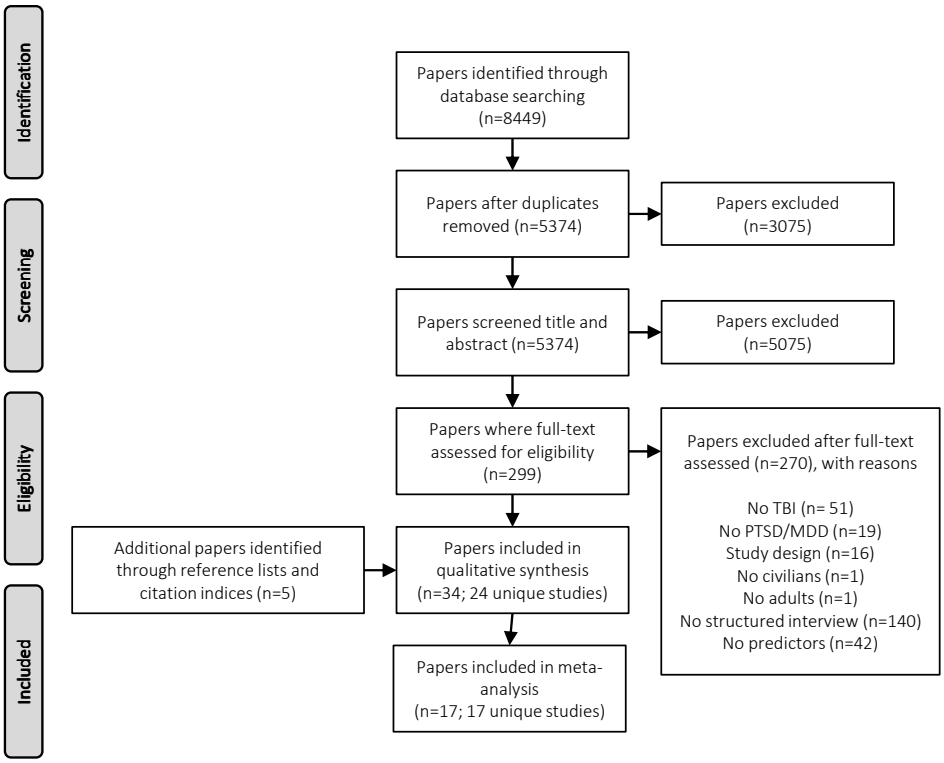

Figure is adapted from Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097.
MDD: Major Depressive Disorder; PTSD: Posttraumatic Stress Disorder; TBI: traumatic brain injury.

Study characteristics

Of the 24 studies included, the majority (n=15) were prospective cohort studies.[17,32-45] Four studies used a retrospective cohort,[46-49] three a cross-sectional design,[50-52] and two were case-control studies.[3,53] Studies were published between 1992 and 2015 and were conducted all over the globe, but mainly in high-income countries such as the United States (n=7) and Australia (n=4). The large majority of studies derived their patients from a single hospital or rehabilitation center (n=20).[3,17,32-39,41-44,46-50,52]

Fourteen studies examined predictors of MDD,[3,17,33,37-39,41-43,47,48,51-53] eight studies examined predictors of PTSD[32,34-36,44-46,49] and two studies examined both.[40,50] Nine studies included multiple predictors in a prognostic model to predict MDD (n=5), PTSD (n=3) or both (n=1).

Studies included on average 117 patients (range 16 to 402). Studies that assessed predictors of MDD included on average 24 (range 9 to 48) patients with MDD ('cases') and 67 patients without MDD. Studies that assessed predictors of PTSD included on average 32 (range 7 to 127) patients with PTSD ('cases') and 132 patients without PTSD. The majority of studies included predominately male patients with a mean age between 30 and 40 years. Motor vehicle accidents (MVA) were the most reported cause of injury.

Most predictors were measured during emergency department (ED) visit or very soon after discharge. Outcome was measured between one month and six years post-injury with the majority of studies measuring MDD/PTSD between three months and one year post-injury (Table 9.1).

Table 9.1 Study characteristics of 24 studies examining predictors of or prognostic models for MDD and PTSD after TBI

Study	Study design, setting	Study population	Inclusion and exclusion criteria	Patient characteristics*	No. predic-tors	Disorder (no. pt)	Interview	Timing Outcome	Assessment
Alway, Y. (2015) *Related: Alway (2015b)*	Pros cohort, Australia	Consecutive mod and sev TBI admitted to hospital (n=203)	PTA > 24h; age 16–80y; no prior TBI/neurological disorder; residence in Australia, sufficient English language	Age: 34y; 16y 78% male GCS: 9.3; 4.3 80% MVA	5	PTSD (n=27)[A]	SCID-I	3m–5y	Face-to face interview at initial assessment; telephone interview at follow-up.
Ashman, T.A. (2004) *Related: Hibbard (2004)*	Cross-sectional, longitudinal, and cross-sequential, US	Self-identified mild to sev TBI from community (n=188)	US residents in the community 3m–4y post-injury; age 18–87; capable of giving informed consent; no acquired brain injury/neurocognitive disorder/psychotic disorder	Age: 40y; 15y 53% male GCS 13–15: 29%, 3–12: 62%	3 MDD / 3 PTSD	MDD (n=66)[B] &PTSD (n=56)[B]	SCID-I	1y–6y	Interview by clinician with ≥ 3y experience
Barker-Collo (2013)	Pros and retro cohort, New-Zealand	Mild to sev TBI, from a large incidence and outcome study or self-referred (n=296)	Age ≥16	Age: 37y; 18y 60% Male Worst GCS: 14.1; 2.3 30% falls, 24% assault, 17% traffic	17	PTSD (n=53)	PDS	1y	Interview by trained researchers
Bryant, R.A. (1998) *Related: Harvey (2000)*	Pros cohort, Australia	Consecutive MVA victims admitted to trauma hospital (n=63)	Exclusion: inability to be interviewed with aid of an interpreter; not medically fit; taking narcotic analgesia 4weeks after trauma; PTA>24h	Age: 29y; 13y[C] 70% Male[C]	25	PTSD (n=15)	CIDI	6m	Interview by clinical psychologist blinded for ASD status
Bryant, R.A. (2000)	Pros cohort, Australia	Sev TBI admitted to rehab unit (n=96)	Exclusion: inability to be interviewed with aid of an interpreter; insufficient cognitive abilities	Age: 34y; 13y 80% Male	5	PTSD (n=26)	PTSD-I	6m	Interview by rehab consultant
Caspi, Y. (2005)	Retro cohort, Israel	Mild to mod TBI admitted to neurocogn clinic (n=120)	Age: 18–50y, fluent in Hebrew; no active chronic medical condition; no pre-injury psychiatric illness, substance abuse, cognitive deficits or brain damage	Age: 36y; 6y 59% Male 84% car accident	4	PTSD (n=22)	SCID-I	3y	Interview

Table 9.1 (continued)

Study	Study design, setting	Study population	Inclusion and exclusion criteria	Patient characteristics*	No. predic-tors	Disorder (no. pt)	Interview	Timing Outcome	Assessment
Deb, S. (2007)	Pros cohort, UK	Minor to sev TBI admitted to hospital (n=165)	Any of the following: unconsciousness; evidence of skull fracture on X-rays; contusion/hemorrhage on CT or MRI; focal neurological signs; GCS < 15	Age: young group: 36; elderly group: 79 67% Male 82% mild, 13% mod, 5% sev TBI	1	MDD (n=24)	SCAN	1y	Interview by two trained psychiatrists
Diaz, A.P. (2012)	Pros cohort, Brazil	Consecutive sev TBI admitted to ICU (n=33)	GCS ≤ 8 within 48h; age ≥ 18y; resident of the Florianopolis metropolitan area; no gunshot injury	Age: 31y; 11y 88% Male GCS: 7–8 46%; 5–6 30%; 3–4 24%	7	MDD (n=10)	SCID-I	18m	Interview by two board-certified psychiatrist, blinded for hospital data
Fedoroff, J. P. (1992) *Related: Jorge 1993, Jorge 1993b*	Pros cohort, US	Consecutive mild to sev TBI admitted to shock trauma center (n=64)	Acute closed HI; no open HI, no spinal cord injury, no multiple system injury, no decreased consciousness or aphasia	Age: MDD 27y; 6y; no MDD: 30y; 11y 86% male GCS: 12–15 17%; 8–15 & intracran surg or focal lesions>35 cc 58%; 3–7 15%	25	MDD (n=17)	PSE	1m	Interview by trained research psychiatrist
Gil, S. (2005)	Pros cohort, Israel	Mild TBI admitted to surgical ward (n=120)	Age 18–50y; fluent in Hebrew Exclusion: psychiatric care at time of injury; prior HI; cognitive deficits; substance abuse; major untreated medical condition	Age: 31y; 3y 58% male 90% traffic accident GCS: 13–15 100%	16	PTSD (n=17)	SCID-I	6m	Interview by trained clinician
Gould, K.R. (2011) *Related: Gould (2011b) and Schonberger (2011)*	Pros cohort, Australia	Consecutive TBI admissions to a rehab hospital (n=122)	Mild, mod or sev TBI; age 16–80; no previous TBI/ neurological disorder; residence in Australia; sufficient cognitive and English ability	Age: 35; 16y GCS: 9.15; 4.3	7	MDD (n=40)	SCID-I	12m	Interview
Hibbard, M.R. (1998)	Pros cohort, US	Mild to sev TBI randomly selected for quality of life survey (n=100)	TBI ≤ 1y prior to interview; age 18–65; resident of New York State; living in the community; no nontraumatic brain injury	Age^{D}:40y; 10y 53% Male 62% MVA	5 MDD / 1 PTSD	MDD (n=48) & PTSD (n=17)	SCID-I	8y	Interview by licensed psychologist with background in clinical neuropsychology and brain injury

Table 9.1 (continued)

Study	Study design, setting	Study population	Inclusion and exclusion criteria	Patient characteristics*	No. predic-tors	Disorder (no. pt)	Interview	Timing Outcome	Assessment
Jorge, R.E. (2004) *Related: Jorge, R.E. (2007)*	Pros case-control, US	Consecutive mild to sev TBI admitted to hospital (n=91)	Exclude: penetrating HI; spinal cord injury; sev comprehension deficits	Age: 36y; 16y 59% Male 44% mild, 33% mod, 23% sev TBI 75% MVA	32	MDD (n=30)	PSE and SCID-I	9m	Interview by psychiatrist
Kennedy, R.E. (2005)	Pros cohort, US	Mild to mod TBI admitted to neuropsych clinic (n=78)	3m post-injury; age ≥ 18	Age: 38y; 12y 69% male Mean GCS: 9.3; 4.8 77% MVA	10	MDD (n=23)	SCID-I	76m	Interview by three trained research team members
Koponen, S. (2002) *Related: Koponen 2005*	Retro cohort, Finland	Mild to sev TBI seen for neuropsych evaluation (n=60)	TBI causing neurological symptoms ≥ 1 week; one of the following: 1) LOC ≥ 1min, 2) PTA ≥ 30 min, 3) neurological symptoms during the first 3d 4) neuroradiological findings suggesting TBI. No nontraumatic neurological illness	Age: 29y; 11y 68% Male	2	MDD (n=16)	SCAN	31y	Interview by trained research psychiatrist
Levin, H.S. (2005)	Pros cohort, US	Consecutive mild TBI admitted to level I trauma hospital (n=129)	Hospital arrival ≤ 24h; BAL ≤ 200 mg/dl; age ≥16y; fluent in English or Spanish; resident in catchment area Exclusion: undocumented alien; incarcerated; homeless; active military service; spinal cord injury; previous TBI requiring hospitalisation; pre-injury substance dependence, mental retardation, psychiatric disorders or other central nervous system disturbances; no preexisting condition preventing outcome measurement	Age: 32; 13y 67% male GCS: 14.8; 0.5 67% MVA	8	MDD (n=15)	SCID-I	3 m	Interview

Table 9.1 (continued)

Study	Study design, setting	Study population	Inclusion and exclusion criteria	Patient characteristics*	No. predic-tors	Disorder (no. pt)	Interview	Timing Outcome	Assessment
Mauri, M. C. (2014)	Pros case-control, Italy	Consecutive closed HI admitted to neurosurgery (n=16)	LOC ≥1m; PTA ≥30 min; neuroradiological evidence of TBI; no pre-injury neurological / cardiorespiratory / psychiatric conditions; no substance abuse	Age: 40y; 14y 63% Male GCS 10.6; 4.4 81% MVA	4	MDD (n=10)	SCID-I	1m	Interview by expert clinician
Rao, V. (2010)	Cross-sectional, US	Closed HI recruited by advertisements in local newspapers (n=17)	Age ≥18y; TBI 3–60m prior to evaluation; no history of diagnosable mood disorder; MMSE>18, stable medical history; sufficient cognitive capacity	Age: MDD: 53; no MDD 27	38	MDD (n=10)	SCID-I	3–60m	Interview
Rapoport, M.J. (2003) *Related: Rapoport (2003b)*	Pros cohort, Canada	Consecutive mild TBI with appointment at TBI clinic (n=210)	Non-penetrating mild TBI Exclusion: pre-injury focal brain disease; serious acute medical illness; schizophrenia; bipolar disorder; dementia	Age: 47y; 20y 60% Male 61% MVA	10	MDD (n=35)	SCID-I	49d	Interview by psychiatrist
Rapoport, M.J. (2005)	Crosssectional, Canada	Mild and mod TBI attending a TBI clinic (n=74)	Exclusion: premorbid focal brain disease; serious medical illness; schizophrenia; bipolar disorder; dementia	Age: 35y; 13y	16	MDD (n=21)	SCID-I	200d	Interview
Reekum, R. van (1996)	Pros cohort, Canada	Mild to sev TBI admitted to TBI rehab program. Patients were contacted with a female: male ratio of 3:1 (n=18)	TBI due to MVA ≥2y prior to the study; age <50y; sufficient language, motor and perceptual skill to permit testing; no pre-injury psychiatric disorder; living in the community	Age: 31y; 9y 44% Male GCS 13–15: 28%; 9–12: 17%; 3–8 56%	4	MDD (n=9)	SADS-L	5y	Interview by experienced registered psychiatric nurse
Roitman, P. (2013)	Pros cohort, Israel	Consecutive mild TBI attended ED (n=402)	MVA survivors Exclusion: arrived to the hospital in coma; LOC >30 min; admitted to the hospital >7days	Age: 37y; 13y 52% male	1	PTSD (n=127)	PSS-I	8m	Telephone interview

Table 9.1 (continued)

Study	Study design, setting	Study population	Inclusion and exclusion criteria	Patient characteristics*	No. predic-tors	Disorder (no. pt)	Interview	Timing Outcome	Assessment
Turnbull, S.J. (2001)	Retro cohort, Scotland	Mild to sev TBI attended ED who respond to a postal questionnaire (n=53)	Age 16–65; evidence of TBI; no chronic alcohol abuse	Age: 35y; 11y 87% Male 32% traffic; 60% assault	1	PTSD (n=11)	CAPS	6m	Telephone interview by postgraduate psychologist
Whelan-Goodinson, R. (2010)	Retro crosssectional, Australia	Mild to sev TBI admitted to rehab unit (n=100)	GCS <15; cognitive capable; reliable historians according to treating doctor/ neuropsychologis, sufficiently proficient in English; no previous TBI/neurological disorder	Age: 37y; 14y 71% male GCS: 9.1; 4.1 86% MVA	13	MDD (n=46)	SCID-I	0.5–5.5y	Face-to-face or telephone interview

*Patient characteristics: we reported age: mean; SD unless otherwise specified. For injury mechanism, we reported the most occurring.
[A] 27 patients were diagnosed with PTSD during the 5 year follow-up period.
[B] MDD or PTSD at any time point during the 5y follow-up period.
[C] These results represent 79 patients included in the study; 14 of them were however not included in the prediction analysis due to loss to follow-up. These patients did not differ significantly from the original sample.
[D] Age at assessment.
Abbreviations. ASD: acute stress disorder; BAL: blood alcohol level; CAPS: Clinician Administrated PTSD scale; CT: computed tomography; HI: head injury; CIDI: Composite International Diagnostic Interview; GCS: Glasgow Coma Scale; LOC: loss of consciousness; MDD: major depressive disorder; MRI: magnetic resonance imaging; MVA: motor vehicle accident; PDS: Posttraumatic Diagnostic Scale; PSE: Present State Examination; PSS: PTSD symptom scale; PTA: posttraumatic amnesia; PTSD: posttraumatic stress disorder; PTSD-I: posttraumatic stress disorder interview; SADS-L: Schedule for Affective Disorders and Schizophrenia; SCAN: Schedules for Clinical Assessment in Neuropsychiatry; SCID-I: Structured Clinical Interview for DSM-IV; US: United States.

Risk of bias of the studies

The majority of studies (n=16)[3,17,33,35,37,38,40,43-45,47,49,51-54] were scored as high risk of bias for study confounding because they only assessed the effect of predictors in univariable analyses (Table 9.2). It is therefore unknown whether the effect of the predictor is independent of other factors. As we sought to perform a meta-analysis with univariable data, we did not exclude any studies based on a high risk of study confounding from the meta-analysis.

Except for the high risk of study confounding, methodological quality of the included studies was acceptable. Study participation[17,40,51] and attrition[37,43,49] were rated at high risk of bias in three studies. Additionally, one study was judged at high risk of bias for prognostic factor measurement[3] and outcome measurement[49], and five studies were rated at high risk of bias on statistical analysis and reporting.[3,39,44,46,49] Nevertheless, the majority of studies obtained a moderate risk of bias score for two or three domains. Two studies[3,49] were rated at high risk on two out of five (excluding study confounding) domains and were therefore omitted from the meta-analyses.

Table 9.2 Risk of bias assessment

Study	Study participation	Study attrition	Prognostic factor measurement	Outcome measurement	Study confounding	Statistical analyses and presentation
Alway, Y. (2015)	Moderate	Moderate	Low	Low	Low	Low
Ashman, T.A. (2004)	Moderate	Moderate	Moderate	Low	Low	Moderate
Barker-Collo, S. (2013)	Moderate	Moderate	Low	Low	High	Low
Bryant, R.A. (1998)	Low	Low	Low	Low	High	Low
Bryant, R.A. (2000)	Low	Moderate	Low	Low	High	Low
Caspi, Y. (2006)	Low	Moderate	Low	Low	Low	High
Deb, S. (2007)	Low	High	Low	Moderate	High	Low
Diaz, A.P. (2012)	Low	Low	Low	Low	High	Low
Federoff, J.P. (1992)	Low	Low	Low	Low	High	Low
Gil, S. (2005)	Low	Moderate	Low	Low	Low	Low
Gould, K.R. (2011)	Low	Moderate	Low	Low	Low	High
Hibbard, M.R. (1998)	High	Moderate	Moderate	Low	High	Moderate
Jorge, R.E. (2004)	Low	Low	Low	Low	High	Low
Kennedy, R.E. (2005)	High	Moderate	Low	Low	High	Low
Koponen, S. (2002)	Moderate	Moderate	Moderate	Low	High	Low
Levin, H.S. (2005)	Low	Moderate	Low	Low	Low	Low
Mauri, M.C. (2014)	Moderate	Low	High	Low	High	High
Rao, V. (2010)	High	Low	Low	Low	High	Moderate
Rapoport, M.J. (2003)	Moderate	Low	Moderate	Low	Low	Low
Rapoport, M.J. (2005)	Moderate	Low	Moderate	Low	High	Low
Reekum, R. (1996)	Moderate	High	Low	Low	High	Low
Roitman, P. (2013)	Moderate	Low	Moderate	Low	High	High
Turnbull, S.J. (2001)	Moderate	High	Moderate	High	High	High
Whelan-Goodinson, R. (2010)	Moderate	Low	Low	Low	Moderate	Moderate

Table presents risk of bias assessment according to the Quality in Prognostic Studies (QUIPS) tool.

Predictors of MDD and PTSD

The included studies examined a total of 109 predictors of MDD and 54 predictors of PTSD (Figure 9.2). Age and gender were most often assessed. The majority of predictors were assessed in only one study.

Figure 9.2 Frequency of predictors of MDD and PTSD following TBI

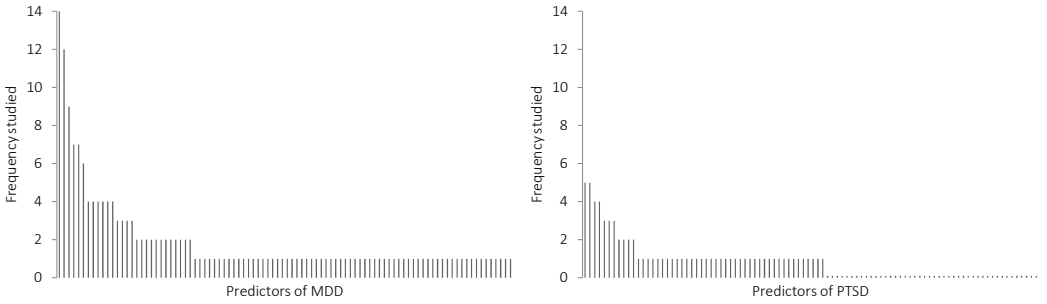

Figure shows how frequent predictors were studied across the included studies. For example, for MDD one predictor (age) is studied in fourteen studies and one predictor (gender) is studied in thirteen studies. The majority of predictors (e.g. MRI abnormalities) were assessed in one study.

Predictors of MDD

In the meta-analysis of univariable data, we found that the presence of a pre-injury depression was associated with a higher odds of developing MDD in five studies of 470 patients (pOR=3.86; 95%CI [2.26 – 6.59], moderate quality evidence, Table 9.3). This was confirmed by one of the studies in the narrative synthesis. Two studies[42,48] included pre-injury depression in a multivariable model. One study[48] reported that the odds of MDD was more than five times higher in those with a pre-injury depression compared to those without a pre-injury depression (OR=6.5, p<0.01), while the other study[42] reported an opposite effect (OR=0.28, p>0.05, Table 9.3 and 9.4). Overall, the evidence for pre-injury depression as a predictor for MDD was rated as moderate, meaning that pre-injury depression *probably* predicts MDD and that we are moderately confident in the effect estimate.

Three other predictors were found to be associated with MDD based on their pooled results. These include female gender (pOR=1.78; 95%CI [1.22 – 2.60], 9 studies, 786 participants, low quality evidence), higher GCS ($MD_{admission\ GCS}$=0.49; 95%CI [0.02 – 0.97]; $MD_{24h\ GCS}$=0.13; 95%CI [–1.29 – 1.56], 4 studies, 289 participants, very low quality evidence) and post-injury unemployment (pOR=2.04; 95%CI [1.10 – 3.79], 3 studies, 211 participants, very low quality evidence). For GCS, we found that MDD is more common in those with moderate TBI (GCS 9–12) compared to those with severe TBI (GCS 3–8, Appendix 9.B). However, the quality of the evidence underpinning all these associations was judged as low or very low, meaning that we are (very) uncertain about these estimates and therefore cannot make firm conclusions about the role of female gender, higher GCS and post-injury unemployment in the prediction of MDD.

Other possible predictors of MDD studied were: age, education, race, marital status, income, pre-injury psychiatric disorder, pre-injury alcohol or substance abuse, pre-injury unemployment, family history of psychiatric disorders, pre-injury TBI, mechanism of injury, posttraumatic amnesia (PTA), bodily injuries, computed tomography (CT) abnormalities and post-injury litigation situation (Table 9.3). None of these predictors showed a significant association with MDD on pooled or narratively synthesised estimates. In addition, the quality of the evidence for these predictors was rated as either low or very low, meaning that we are (very) uncertain about these estimates. This means that, while we have no evidence to suggest they play a role in the development of MDD, it would be premature at this stage to conclude that they do not. The forest plots of the meta-analyses and narrative synthesis are presented in Appendix 9.B and 9.C.

Predictors of PTSD

In the meta-analysis of univariable data, PTA was associated with PTSD in three studies of 477 patients (MD –8.07;95%CI [–15.46 – –0.69], moderate quality evidence, Table 9.3). The association was also found in one study[34] that used a multivariable model, although the association was no longer statistically significant (OR=0.98; p>0.05). Patients with a memory of the traumatic event were more likely to develop PTSD than those without a memory of the event in two studies in both univariable analysis (pOR=5.15; 95%CI [2.37 – 11.21], 240 patients, moderate quality evidence) and in a multivariable model (ORs 2.2 and 2.8, both p<0.05). Evidence for PTA and memory of the traumatic event were rated as moderate quality, meaning that they *probably* predict PTSD and that we are moderately confident in the effect estimates.

Other possible predictors include age, education, pre-injury psychiatric disorders and loss of consciousness (Table 9.3). The quality of evidence underpinning these predictors was rated as either low or very low. This means that we are (very) uncertain about these estimates and it would be premature to conclude that any of these predictors do or indeed, do not play a role in the development of MDD. The forest plots of the meta-analyses and narrative synthesis are presented in Appendix 9.B and 9.C.

Prognostic models of MDD and PTSD

Six studies used a multivariable model to predict MDD (Table 9.4). On average, models included 6.3 (range 1.2–22) cases for every predictor in the model. None of the studies described whether there were missing values in predictors and if so, how they were handled. Nagelkerke R^2 was calculated in three models,[39,42,48] and ranged from 0.18–0.35. The Area Under the Receiver Operating Curve (AUC) was calculated in one study[41] and indicated good discriminative ability (AUC=0.86). This model included age, depressive symptoms after one week post-injury and CT results.

Four studies used a multivariable model to predict PTSD (Table 9.4). Models included on average 7.7 (range 1.1–19) cases per predictor. Again, none of the studies described how they handled missing values in predictors. Nagelkerke R^2 was reported for two models[32,46] and ranged from 0.38–0.42. Both models included memory of the traumatic event and history of psychiatric disorders.

Table 9.3 Summary of findings of predictors of and prognostic models for MDD and PTSD after TBI

	Univariable associations			Multivariable association			
Predictor	**No. of participants (cohorts)**	**Pooled effect size meta-analysis****	**Narrative synthesis***	**No. of participants (cohorts)**	**Narrative synthesis**	**Quality of evidence (GRADE)**	**Interpretation**
MDD							
Age	1156 (14)	MD 1.20y (–1.96 to 4.36) in 7 studies	Contradictory findings in 6 studies	527 (3)	Contradictory findings in 3 studies with OR ranging from 0.99 to 1.05	☺ Very low[1,2,3]	Association between age and MDD is very uncertain
Female gender	977 (12)	1.78 (1.22 to 2.60) in 9 studies	No statistically significant differences in gender between MDD+ and MDD- in 3 studies [A]	310 (2)	OR_{female} ranged from 1.61 to 2.01, p>.05 in 2 studies	☺☺ Low[1]	Female gender may be associated with a higher odds of MDD after TBI, the association is however uncertain
Education	554 (7)	MD –0.50y (–1.37 to 0.37) in 4 studies	No statistically significant difference in education between MDD+ and MDD- in 3 studies	320 (2)	Contradictory findings in 2 studies using a multivariable model, with OR ranging from 0.52 (education higher than high school, p>.05) to 6.5 (years of education, p=.01)	☺☺ Low[2]	Association between education and MDD is uncertain
Caucasian race	407 (4)	1.04 (0.61 to 1.75) in 3 studies	No statistically significant difference in race between MDD+ and MDD- in 1 study	–	–	☺ Very low[2,3]	Association between race and MDD is very uncertain
Marital status (married/relationship vs. unattached)	784 (8)	1.20 (0.82 to 1.75) in 6 studies	No statistically significant differences in marital status between MDD+ and MDD- in 2 studies [A]	–	–	☺☺ Low[1]	Association between marital status and MDD is uncertain
Annual income	255 (2)	–	Patients with MDD more often reported a low salary (annual salary <20.000 or <21.000) in 2 studies (p>.05)	–	–	☺ Very low[1,3,4]	Association between annual income and MDD is very uncertain

Table 9.3 (continued)

	Univariable associations			Multivariable association			
Predictor	**No. of participants (cohorts)**	**Pooled effect size meta-analysis****	**Narrative synthesis***	**No. of participants (cohorts)**	**Narrative synthesis**	**Quality of evidence (GRADE)**	**Interpretation**
Pre-injury depression	782 (7)	3.86 (2.26 to 6.59) in 5 studies	Pre-injury depression is associated with a higher odds of MDD post-injury in 1 study (OR 5.25, p=.005), a second study did not report any significant differences [A]	310 (2)	Pre-injury depression is associated with a higher odds of MDD post-injury in 1 study (OR: 6.5, p<.01), a second study did not report any significant differences (OR 0.28, p>.05)	☺☺☺ Moderate[3,5]	Pre-injury depression is probably associated with a higher odds of MDD after TBI
Pre-injury psychiatric disorders	352 (4)	1.58 (0.42 to 5.99) in 4 studies	–	122 (1)	Pre-injury counseling is associated with a higher odds of MDD in 1 study (OR 2.34, p= .07)	☺ Very low[2,3]	Association between pre-injury psychiatric disorders and MDD is very uncertain
Pre-injury alcohol abuse	318 (3)	1.49 (0.61 to 3.69) in 2 studies	No statistically significant differences in 1 study[A]	–	–	☺☺ Low[3]	Association between pre-injury alcohol abuse and MDD is uncertain
Pre-injury substance abuse	440 (4)	2.02 (0.75 to 5.42) in 2 studies	No statistically significant differences in 2 studies[A]	–	–	☺☺ Low[3]	Association between pre-injury substance abuse and MDD is uncertain
Pre-injury unemployment	418 (4)	3.80 (0.34 to 42.09) in 2 studies	No statistically significant differences in 2 studies[A]	–	–	☺ Very low[1,2,3]	Association between pre-injury unemployment and MDD is very uncertain
Family history of psychiatric disorders	382 (4)	1.06 (0.52 to 2.14) in 2 studies	No statistically significant differences in 2 studies[A]	210 (1)	Family history of depression is associated with a lower odds of MDD in 1 study (OR 0.28, p>.05)	☺☺ Low[4]	Association between family history of psychiatric disorders and MDD is uncertain
Pre-injury TBI	244 (2)	–	No statistically significant differences in 2 studies[A]	–	–	☺ Very low[1,3,4]	Association between pre-injury TBI and MDD is very uncertain

Table 9.3 (continued)

	Univariable associations			Multivariable association			
Predictor	**No. of participants (cohorts)**	**Pooled effect size meta-analysis****	**Narrative synthesis***	**No. of participants (cohorts)**	**Narrative synthesis**	**Quality of evidence (GRADE)**	**Interpretation**
Mechanism of injury	362 (3)	–	One study reported that violent injury was associated with a higher odds of MDD (p>.05), another study reported that MVA was associated with a higher odds of MDD (p>.05)	210 (1)	MVA is associated with a higher odds of MDD in 1 study (OR 1.66, p>.05)	☺ Very low[1,2,3,6]	Association between mechanism of injury and MDD is very uncertain
GCS	507 (7)	Admission GCS: MD 0.49 (0.02 to 0.97) in 2 studies 24h GCS: MD 0.13 (-1.29 to 1.56) in 2 studies	A higher GCS / moderate TBI vs severe TBI might be associated with a higher odds of MDD in 7 studies, although the differences are not statistically significant in the majority of studies	–	–	☺ Very low[1,2,3]	Higher GCS on admission may be associated with a higher odds of MDD post-injury, the association is however very uncertain
PTA	234 (3)	–	No statistically significant differences in 3 studies. 1 study reported less PTA>24 h in MDD+ (53%) than in MDD- (43%)	–	–	☺ Very low[1,3,4]	Association between PTA and MDD is very uncertain
Bodily injuries	296 (3)	–	Number of bodily injuries was associated with MDD in 1 study. In 2 studies, there were no statistically significant differences[A]	–	–	☺ Very low[1,3,4]	Association between bodily injuries and MDD is very uncertain

Table 9.3 (continued)

	Univariable associations			Multivariable association			
Predictor	**No. of participants (cohorts)**	**Pooled effect size meta-analysis****	**Narrative synthesis***	**No. of participants (cohorts)**	**Narrative synthesis**	**Quality of evidence (GRADE)**	**Interpretation**
CT abnormalities	259 (3)	0.70 (0.35 to 1.43) in 3 studies	–	403 (3)	In 2 studies, CT abn were significantly associated with a higher odds of MDD ($OR_{CT\ abn}$ 7.68, p<.05 in 1 study and 6 lesion locations X^2 = 31.39, p<.01 in 1 study). In 1 other study, CT abn were associated with a lower odds of MDD (OR 0.77, p>.05)	☺ Very low[2,3]	Association between CT abnormalities and MDD is very uncertain
Post-injury unemployment	311 (3)	2.04 (1.10 to 3.79) in 2 studies	No statistically significant differences in 1 study	310 (2)	Post-injury unemployment is associated with a higher odds of MDD in 2 studies (OR range 1.61 to 2.04, p>.05)	☺ Very low[1,3]	Post-injury unemployment may be associated with a higher odds of MDD after TBI, the association is however very uncertain
Post-injury litigation situation	202 (2)	0.64 (0.16 to 2.53) in 2 studies	–			☺ Very low[2,3]	Association between post-injury litigation situation and MDD is very uncertain
PTSD							
Age	717 (5)	MD 1.02y (–1.46 to 3.49) in 5 studies	–	511 (3)	Contradictory findings in 3 studies with OR ranging from 0.98 to 1.2	☺ Very low[2,3]	Association between age and PTSD is very uncertain
Female gender	809 (5)	1.27 (0.83 to 1.96) in 4 studies	Women are more likely to develop PTSD than men in 1 study (p=.04)	323 (2)	Contradictory findings in 2 studies with OR ranging from 0.31 to 2.0 (p>.05)	☺☺ Low[2]	Association between gender and PTSD is uncertain
Education	421 (4)	MD 0.15y (–0.61 to 0.92) in 3 studies	No statistically significant differences in 1 study [A]	203 (1)	More years of education is associated with PTSD post-injury (OR: 1.06, p>.05)	☺ Very low[2,3]	Association between education and PTSD is very uncertain

Table 9.3 (continued)

	Univariable associations			Multivariable association			
Predictor	**No. of participants (cohorts)**	**Pooled effect size meta-analysis****	**Narrative synthesis***	**No. of participants (cohorts)**	**Narrative synthesis**	**Quality of evidence (GRADE)**	**Interpretation**
Pre-injury psychiatric disorder	425 (4)	1.32 (0.63 to 2.77) in 4 studies	–	443 (3)	Pre-inj psychiatric disorder is associa-ted with a higher odds of PTSD in 1 study (OR: 3.7, 95%CI 1.1-8.9) but not in 2 other studies (OR range 0.50 to 0.84, p>.05)	☺ Very low[1,2,3]	Association between pre-injury psychiatric disorders and PTSD is very uncertain
PTA	477 (3)	MD –8.07 (–15.46 to –0.69) in 3 studies	–	203 (1)	More days PTA is associated with a lower odds of PTSD (OR 0.98, p>.05)	☺☺☺ Moderate[1,5]	Shorter PTA is probably associated with a higher odds of PTSD after TBI
LOC	698 (2)	–	The presence of LOC was associated with a higher odds of PTSD (OR 1.72, p<.05). However, patients that developed PTSD had less days of PTA (mean: 4.0) than those without PTSD (mean: 9.0)	–	–	☺ Very low[1,2,3]	Association between LOC and PTSD is very uncertain
Memory of the traumatic event	240 (3)	5.15 (2.37 to 11.21) in 2 studies	No statistically significant differences in 1 study [A]	240 (2)	Memory of the traumatic event is significantly associated with a higher odds of PTSD (OR range 2.2 to 2.8)	☺☺☺ Moderate[4,5]	Memory of the traumatic event is probably associated with a higher odds of PTSD post-injury

*In the narrative synthesis, we describe studies that could not be pooled in the meta-analysis because they measured the predictor differently. **OR (95%CI) unless otherwise specified. [A] None of the studies in the narrative synthesis reported the direction of effect. MD: mean difference; MDD: major depressive disorder; OR: odds ratio; TBI: traumatic brain injury; GCS: Glasgow Coma Scale; PTA: posttraumatic amnesia; CT: computed tomography; PTSD: posttraumatic stress disorder; LOC: loss of consciousness.

GRADE working group grades of evidence[29]: *High quality*: Further research is very unlikely to change our confidence in the estimate of effect; *Moderate quality*: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate; *Low quality*: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate; *Very low quality*: We are very uncertain about the estimate. [1]Quality of the evidence is downgraded by one level for study limitations since the majority of studies have a moderate/high risk of bias in the majority of domains; [2]Quality of evidence is downgraded by one level for inconsistency since the direction of effect varies across studies; [3]Quality of evidence is downgraded by one level for imprecision since the confidence interval around the mean difference is large or the number of studies or total number of participants is too small; [4]Level of inconsistency could not be determined since studies did not report data on the direction of effect or confidence interval. We did not downgrade; [5]Quality of evidence is upgrated by one level because of a moderate or large effect size; [6]Quality of evidence is downgraded by one level for indirectness since not all levels of the predictor are included.

Table 9.4 Prognostic models of MDD and PTSD after TBI

Study	Timing model use	No. of patients	No. of cases*	No. of candidate predictors	Selection procedure predictors	Statistical model	Outcome measurement and timing	Summary statistics	Final predictors in model
MDD									
Ashman, T.A. (2004)	Unknown	188	35;24;21[A]	3	Not reported	Linear random effects longitudinal model	SCID-I 3m–4y	Not reported	Age (OR: 1.00; p=.77), time post-injury (OR: 0.88, p=.23) and time of enrolment in the study (OR: 0.59, p<.001)
Federoff, J.P. (1992)	ED	64	17	14	All CT lesion location variables measured	Logistic regression model with backwards selection (p>.05)	PSE 1m	X^2=31.39, df=6, p=0.0001	Left hemisphere (b:–2.84, p=0.04); right hemisphere (b: 2.40, p=0.03); cortical (b: –3.67, p=0.01); frontal (b: –3.58, p=.01); left anterior (b: 5.90, p=0.0003); parietal-occipital (b: 3.75, p=.009)
Gould, K.R. (2011)	At discharge	122	40	7	Not reported	Two logistic regression models ((1) pre-injury variables; (2) injury-related variables). Significant variables were entered into a final regression model	SCID-I 12m	Nagelkerke R^2=0.20; correct classification rate: 70.7%	Pre-injury counseling (OR: 2.34, p=.073); limb injury (OR: 4.07, p=.009); depressive disorder at initial assessment (OR: 6.04, p=0.039)
Levin, H.S. (2005)	1 wk	129	15	8	Not reported	Logistic regression with backwards selection (p>.05)	SCID-I 3m	AUC=0.86	Age (OR: 1.05; 95%CI 1.00 to1.1); CES-D score 1wk (OR: 1.11; 95%CI 1.04 to 1.17); Abnormal CT scan (OR: 7.68; 95%CI 1.36–43.48)

Table 9.4 (continued)

Study	Timing model use	No. of patients	No. of cases*	No. of candidate predictors	Selection procedure predictors	Statistical model	Outcome measurement and timing	Summary statistics	Final predictors in model
Rapoport, M.J. (2003)	ED	210	35	11	Significant differences in univariable analyses	Hierarchical logistic regression model with time post-injury as covariate	SCID-I 49d	Nagelkerke R^2=0.18	Age (OR: 0.99, SE: 0.05, p>.05); pre-injury depression (OR: 0.28, SE: 0.67, p>.05), substance abuse (OR: 0.25, SE: 0.67, p<.05), time post-injury (OR: 1.00, SE: .001, p>.05); gender (OR: 0.50, SE: 0.52, p>.05); employment (OR: 0.49, SE: 0.71, p>.05); education (OR: 0.52; SE: 0.48, p>.05), family history of depression (OR: 0.28, SE: 0.67, p>.05), medical history (OR: 1.49, SE: 0.55, p>.05), focal CT abnormalities (OR: 0.77, SE: 0.55, p>.05), mechanism of injury (OR: 1.66, SE: 1.62, p>.05)
Whelan-Goodinson, R. (2010)	ED	100	46	13	Significant in univariable analyses	Logistic regression model	SCID-I at 0.5–5y	X^2(6)=29.10, p<.001, Nagelkerke R^2=0.35;correct classification absent depression: 80.4%; correct classification presence depression: 67.4%; overall correct classification: 74.2%	Gender (B=0.48; p=.10); pain (B=–0.97, p=.06); post-injury unemployment (B=0.48; p=.39); pre-injury depression (B=1.87; p=.01); years of education (B=1.87; p= .01); time post-injury (B=0.32, p= .06)
Alway, Y. (2015)	ED	203	27	5	Not reported	Multivariable random-effects logistic regression model adjusting for time post-injury	SCID-I at different follow-up points 3m–5y	Not reported	Age (OR: 0.99; 95%CI: 0.95 to 1.03); female gender (OR: 0.31; 95%CI: 0.05 to 2.08); years of education (OR: 1.06; 95%CI: 0.80 to 1.42); pre-injury psychiatric disorder (OR: 0.84; 95%CI: 0.23 to 3.15); PTA (days; OR: 0.98; 95%CI 0.95 to 1.02)

Table 9.4 (continued)

Study	Timing model use	No. of patients	No. of cases*	No. of candidate predictors	Selection procedure predictors	Statistical model	Outcome measurement and timing	Summary statistics	Final predictors in model
PTSD									
Ashman, T.A. (2004)	Unknown	188	30;18;21[A]	3	Not reported	Linear random effects longitudinal model	SCID-I 3m–4y	Not reported	Age (OR: 0.98; p=.22), time post-injury (OR: 1.07, p=.74) and time of enrolment in the study (OR: 0.59; p=.003)
Caspi, Y. (2006)	2.9y post-injury	120	22	4	Not reported	Logistic regression model adjusted for co-occuring depressive (BDI) and anxiety (BAI) symptoms	SCID-I 3y	Goodness of fit: 83.42, p<.001; Nagelkerke R^2=0.42, p<.001	Memory for the traumatic event (OR: 2.8; 95%CI 1.8–8.9); male gender (OR: 0.5; p>.05); history of psychiatric illness (OR: 0.5, p>.05), age (OR: 1.2, p>.05)
Gil, S. (2005)	1m post-injury	120	17	16	Significant in univariable analyses	Logistic regression model with variables that had shown significant association in univariable analyses	SCID-I 6m	Nagelkerke R^2=0.38; p<.001	Memory of traumatic event (OR: 2.2, 95%CI 1.0 to 10.1); acute posttraumatic symptoms (CAPS; OR: 5.3; 95%CI 1.1 to 9.3); acute posttraumatic symptoms (PSS; OR: 5.2; 95%CI 1.0 to 9.4); depressive symptoms (1wk; OR: 5.1; 95%CI 1.0 to 9.2); anxiety symptoms (1 wk; OR: 4.9, 95%CI 1.0 to 9.1), history of psychiatric disorders (OR: 3.7; 95%CI 1.1-8.9)

*Case = number of patients with the outcome of interest, in this case MDD or PTSD.
[A]Number of patients with MDD or PTSD at three time points.
AUC: Area Under the Receiver Operating Curve; BAI: Beck Anxiety Inventory; BDI: Beck Depression Inventory; CAPS: Clinician Administrated PTSD scale; CES-D: Center for Epidemiologic Studies Depression Scale; CT: computed tomography; ED: emergency department; MDD: major depressive disorder; PSE: Present State Examination; PTSS: PTSD symptom scale; PTA: posttraumatic amnesia; PTSD: posttraumatic stress disorder; SCID=IV: Structured Clinical Interview for DSM-IV.

9.4 DISCUSSION

This systematic review provides an overview of predictors of and prognostic models for MDD and PTSD following TBI. We included 24 studies and found that pre-injury depressive disorder is a probable predictor of MDD. Additionally, female gender, higher GCS and post-injury unemployment may also be predictors of MDD but the low or very low quality of the evidence precludes firm conclusions. PTSD was probably predicted by a shorter PTA and a memory of the traumatic event. Only a few studies used a multivariable model to predict MDD or PTSD, of which the majority was of limited quality. All other studied predictors were non-significant and graded as low or very low quality, precluding firm conclusions.

Quality of the evidence

This systematic review included studies over the last 23 years from all over the globe and therefore provides a complete overview of current knowledge about predictors and prognostic models for MDD and PTSD following TBI. Some notes should however be made regarding the completeness and applicability of the evidence. Firstly, the large majority of predictors were examined in only one study and therefore could not be included in our meta-analyses. For many predictors, we consequently cannot draw conclusions. A possible solution might have been to include studies with all self-reported outcome measurements since these studies are more common and usually include more patients. However, self-reported measurements are less reliable in TBI patients.[14-16] A 2006 study found that the diagnosis of PTSD varied from 59–3% when using self-reported measurements and structured diagnostic interviews respectively.[18]

Secondly, as only a minority of studies used a multivariable model, the majority of our results are based on univariable associations. As a consequence, we cannot exclude the possibility that some of the associations we found were influenced by other factors. Lastly, the majority of studies included patients from a single site, limiting generalisability of results in prognostic research.[55]

The risk of bias of most studies developing prognostic models was high. Models included on average six to eight cases for every predictor, while it is recommended to include at least ten.[56,57] Including too many predictors enhances the risk of finding too extreme estimates (‘statistical overfitting’), limiting generalisability of findings.[58] Additionally, the majority of studies did not report how they handled missing data and how they selected candidate predictors. Although this is common in prognostic studies in TBI,[55] it may have resulted in bias, further limiting generalisability. For the studies on predictors, the risk of bias of included studies was acceptable, except for the high risk of study confounding.

In terms of quality of the evidence for each predictor, the majority was rated as ‘very low’, indicating that we are very uncertain about the estimates. This was mainly due to study limitations, inconsistencies in results across studies, small number of studies and small sample sizes. It would however be difficult to obtain high evidence ratings in this research area since studies are usually underpowered due to relatively low prevalences of psychiatric disorders in combination with the use of labor-intensive structured diagnostic interviews. Three predictors obtained a moderate quality score. In all cases this was because we upgraded for a moderate or high effect size according to the GRADE criteria. It can however be debated whether the evidence of studies with a moderate or large effect size is indeed stronger than that of studies with a smaller effect size. Large effect sizes can also indicate random errors

or biases. Whether the size of an effect indicates high quality merely depends on whether the effect size is commensurate with prior knowledge rather than whether the effect size is above a certain cut-off point.[59]

Predictors of MDD and PTSD

We found that MDD was probably associated with the presence of a pre-injury depression, which might be due to the high recurrence rates in MDD. A large prospective study reported that even 85% of the patients with prior MDD developed a new MDD episode during a 15 years follow-up period.[60] Recurrence of MDD can be triggered by a stressful life event, such as a TBI, although causation is usually multifactorial.[61,62]

We further found a possible association between female gender and the likelihood of developing MDD. This is in line with systematic reviews about gender and depression in the general population; females approximately have a twice as high risk of developing major depression as males.[63,64] Higher GCS, referring predominately to moderate TBI patients compared to severe TBI patients, might also be associated with a higher odds of MDD. A recent study about HRQL after TBI also reported a lower quality of life in patients with moderate TBI than in patients with severe TBI.[65] The authors elaborated that this might be caused by severe TBI patients' appreciation about being alive, which might outweigh difficulties caused by the TBI and thereby influence their quality of life to a lesser extent compared to patients with moderate TBI. It could however also be explained by potential selective lost to follow-up among severe TBI patients with severe psychopathology or differences in rehabilitative treatment interventions between moderate and severe TBI patients. Lastly, MDD was more prevalent among those reporting post-injury unemployment. This has also been shown in systematic reviews in the general population.[66,67] Unemployment can results in reduced social interactions and status which may subsequently result in depression.[68] Unemployment is also related to a lower socio-economic status, which is also associated with a higher risk of depression.[69]

PTSD was more likely among patients with a shorter PTA and those with a memory of the traumatic event. It is suggested that amnesia for the traumatic events minimises the establishment of cognitive representations and so reduces the likelihood of intrusive symptoms.[46] There are no other studies yet investigating this association.

Strengths and limitations

Strengths of this systematic review include the comprehensive search strategy, the restriction to structured diagnostic interviews and the use of GRADE to evaluate the quality of the evidence. This novel approach provides an explicit, transparent and rigorous assessment of the strength of the evidence of predictors.[30] Additionally, we combined results from the meta-analyses, narrative syntheses and multivariable models to obtain conclusions about the significance of predictors. We thereby integrated all available sources of evidence.

The use of meta-analytic techniques might have been a limitation in this review since there was between-study variation in time span, TBI severity and outcome measurement. This might have resulted in estimates that are difficult to interpret. However, a meta-analysis is the most adequate and efficient possibility to provide insight in prognosis of psychiatric sequelae after TBI. A second limitation concerns our screening process, which was conducted by one study author. We however performed an audit and

found a 100% concordance rate between study authors, indicating that screening by two independent reviewers would probably not have resulted in the inclusion of any additional studies. A last limitation is that we only included studies published in peer-reviewed English language journals.

Implications for practice and research

The results of this systematic review imply that there is still limited knowledge about which patients develop MDD and PTSD after TBI. We therefore cannot recommend yet which patients should receive additional follow-up or preventive treatment and advise physicians to be aware in all patients that sustained TBI. Physicians could be extra aware in those with a pre-injury history of depression. Additionally, female patients, those with a higher GCS (predominately moderate TBI patients) and those who are unemployed, might be at enhanced risk of developing MDD. Furthermore, patients with a shorter PTA and a clear memory of the traumatic event might be at higher risk of developing PTSD post-TBI.

More research is needed to confirm the relevance of these predictors of MDD and PTSD after TBI, and develop a prognostic model that could be implemented in hospitals and rehabilitation centers. Future prognostic studies should ideally include a large sample size and a limited set of candidate predictors. Selection of candidate predictors could be based on current review, theory or clinical knowledge about aetiology of psychiatric disorders. Additionally, the confirmation of specific predictions among different patient samples is critically important to increase our knowledge about predictors of psychiatric sequelae post-TBI.

Conclusions

Our systematic review showed that MDD after TBI was predicted by gender, pre-injury depressive disorder, GCS and post-injury unemployment while PTSD was predicted by PTA and memory of the traumatic event. However, currently available prognostic models of MDD and PTSD after TBI suffer from methodological shortcomings. These findings, together with clinical knowledge about aetiology of psychiatric disorders, could form the basis for future development of a prognostic model from a large sample of TBI patients using solid methodology.

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APPENDIX

Appendix 9.A Literature search strategy

Date: September 1, 2015

Embase.com

('brain injury'/exp OR 'brain injury assessment'/exp OR 'head injury'/exp OR concussion/exp OR coma/exp OR (((brain OR head OR crani* OR intracrani* OR skull* OR cerebr* OR capitis OR hemisphere*) NEAR/3 (injur* OR trauma* OR posttrauma* OR damag* OR lesion* OR fracture*)) OR concus* OR contus* OR neurotraum* OR tbi OR mtbi OR coma*):ab,ti) AND (injury/exp OR 'posttraumatic stress disorder'/exp OR accident/exp OR emergency/exp OR 'emergency care'/exp OR 'emergency ward'/exp OR violence/exp OR (trauma* OR posttrauma* OR injur* OR tbi OR mtbi OR accident* OR emergen* OR violen*):ab,ti) AND (anxiety/exp OR 'mood disorder'/de OR 'anxiety disorder'/exp OR

depression/exp OR 'mental health'/de OR 'psychological well being'/de OR "Diagnostic and Statistical Manual of Mental Disorders" OR (anxi* OR ((mood OR affective) NEAR/3 (disorder* OR disturb*)) OR phobi* OR agoraphobi* OR panic OR ocd OR (obsessi* NEAR/3 compulsi*) OR depress* OR ((posttraumatic OR post-traumatic OR postconcussion* OR post-concussional OR post-concussion) NEAR/3 (stress* OR syndrom*)) OR dysthymi* OR ptsd OR ((psychologic* OR neuropsychologic* OR emotion*) NEAR/3 (outcome* OR develop* OR well-being OR wellbeing OR disabil* OR progres* OR adjust* OR function* OR consequenc* OR sequel*)) OR 'mental health' OR dsm):ab,ti) AND (prevalence/exp OR incidence/exp OR 'prediction and forecasting'/exp OR interview/exp OR epidemiology/de OR 'risk factor'/exp OR (incidenc* OR prevalen* OR predict* OR prognos* OR interview* OR (risk NEAR/3 factor*) OR epidemiolog* OR ((indicator* OR variable* OR characteristic* OR examination* OR assessment* OR measure* OR association* OR determinant*) NEAR/3 psycholog*) OR psychometric*):ab,ti) NOT ([Conference Abstract]/lim OR [Letter]/lim OR [Note]/lim OR [Conference Paper]/lim OR [Editorial]/lim) AND [english]/lim NOT ([animals]/lim NOT [humans]/lim)

Medline (OvidSP)
(exp Craniocerebral Trauma/ OR Glasgow Coma Scale/ OR coma/ OR (((brain OR head OR crani* OR intracrani* OR skull* OR cerebr* OR capitis OR hemisphere*) ADJ3 (injur* OR trauma* OR posttrauma* OR damag* OR lesion* OR fracture*)) OR concus* OR contus* OR neurotraum* OR tbi OR mtbi OR coma*).ab,ti.) AND (exp Wounds and Injuries/ OR exp Stress Disorders, Traumatic/ OR exp accidents/ OR exp Emergencies/ OR exp Emergency Treatment/ OR exp Emergency Service, Hospital/ OR exp violence/ OR (trauma* OR posttrauma* OR injur* OR tbi OR mtbi OR accident* OR emergen* OR violen*).ab,ti.) AND (exp anxiety/ OR exp mood disorders/ OR exp anxiety disorder/ OR exp depression/ OR exp mental health/ OR Personal Satisfaction/ OR "Diagnostic and Statistical Manual of Mental Disorders" OR (anxi* OR ((mood OR affective) ADJ3 (disorder* OR disturb*)) OR phobi* OR agoraphobi* OR panic OR ocd OR (obsessi* ADJ3 compulsi*) OR depress* OR ((posttraumatic OR post-traumatic OR postconcussion* OR post-concussional OR post-concussion) ADJ3 (stress* OR syndrom*)) OR dysthymi* OR ptsd OR ((psychologic* OR neuropsychologic* OR emotion*) ADJ3 (outcome* OR develop* OR well-being OR wellbeing OR disabil* OR progres* OR adjust* OR function* OR consequenc* OR sequel*)) OR mental health OR dsm).ab,ti.) AND (exp prevalence/ OR exp incidence/ OR Prognosis/ OR exp Interviews as Topic/ OR epidemiology/ OR epidemiology.xs. OR exp risk factors/ OR (incidenc* OR prevalen* OR predict* OR prognos* OR interview* OR (risk ADJ3 factor*) OR epidemiolog* OR ((indicator* OR variable* OR characteristic* OR examination* OR assessment* OR measure* OR association* OR determinant*) ADJ3 psycholog*) OR psychometric*).ab,ti.) NOT (letter OR news OR comment OR editorial OR congresses OR abstracts).pt. AND english.la. NOT (exp animals/ NOT humans/)

PsycINFO (OvidSP)
(exp Head Injuries/ OR Brain Damage/ OR coma/ OR (((brain OR head OR crani* OR intracrani* OR skull* OR cerebr* OR capitis OR hemisphere*) ADJ3 (injur* OR trauma* OR posttrauma* OR damag* OR lesion* OR fracture*)) OR concus* OR contus* OR neurotraum* OR tbi OR mtbi OR coma*).ab,ti.) AND (exp Injuries/ OR exp Posttraumatic Stress Disorder/ OR exp accidents/ OR exp trauma/ OR exp Emergency Services/ OR exp Emergency Management/ OR exp violence/ OR (trauma* OR posttrauma* OR injur* OR tbi OR mtbi OR accident* OR emergen* OR violen*).ab,ti.) AND (exp anxiety/ OR exp affective disorders/ OR exp anxiety disorders/ OR exp "Depression (Emotion)"/ OR exp mental health/ OR Satisfaction/ OR "Diagnostic and Statistical Manual" OR (anxi* OR ((mood OR affective) ADJ3 (disorder* OR disturb*)) OR phobi* OR agoraphobi* OR panic OR ocd OR (obsessi* ADJ3 compulsi*) OR depress* OR ((posttraumatic OR post-traumatic OR postconcussion* OR post-concussional OR post-concussion) ADJ3 (stress* OR syndrom*)) OR dysthymi* OR ptsd OR ((psychologic* OR neuropsychologic* OR emotion*) ADJ3 (outcome* OR develop* OR well-being OR wellbeing OR disabil* OR progres* OR adjust* OR function* OR consequenc* OR sequel*)) OR mental health OR dsm).ab,ti.) AND (Prognosis/ OR exp Interviews/ OR exp epidemiology/ OR exp risk factors/ OR (incidenc* OR prevalen* OR predict* OR prognos* OR interview* OR (risk ADJ3 factor*) OR epidemiolog* OR ((indicator* OR variable* OR characteristic* OR examination* OR assessment* OR measure* OR association* OR determinant*) ADJ3 psycholog*) OR psychometric*).ab,ti.) NOT book.pt. AND english.la. NOT (exp animals/ NOT humans/)

Cochrane
((((brain OR head OR crani* OR intracrani* OR skull* OR cerebr* OR capitis OR hemisphere*) NEAR/3 (injur* OR trauma* OR posttrauma* OR damag* OR lesion* OR fracture*)) OR concus* OR contus* OR neurotraum* OR tbi OR mtbi OR coma*):ab,ti) AND ((trauma* OR posttrauma* OR injur* OR tbi OR mtbi OR accident* OR emergen* OR violen*):ab,ti) AND ((anxi* OR ((mood OR affective) NEAR/3 (disorder* OR disturb*)) OR phobi* OR agoraphobi* OR panic OR ocd OR (obsessi* NEAR/3 compulsi*) OR depress* OR ((posttraumatic OR post-traumatic OR postconcussion* OR post-concussional OR post-concussion) NEAR/3 (stress* OR syndrom*)) OR dysthymi* OR ptsd OR ((psychologic* OR neuropsychologic* OR emotion*) NEAR/3 (outcome* OR develop* OR well-being OR wellbeing OR disabil* OR progres* OR adjust* OR function* OR consequenc* OR sequel*)) OR 'mental health' OR dsm):ab,ti) AND ((incidenc* OR prevalen* OR predict* OR prognos* OR interview* OR (risk NEAR/3 factor*) OR epidemiolog* OR ((indicator* OR variable* OR characteristic* OR examination* OR assessment* OR measure* OR association* OR determinant*) NEAR/3 psycholog*) OR psychometric*):ab,ti)

PubMed publisher
(Craniocerebral Trauma[mh] OR Glasgow Coma Scale[mh] OR coma[mh] OR (((brain OR head OR crani*[tiab] OR intracrani*[tiab] OR skull*[tiab] OR cerebr*[tiab] OR capitis OR hemisphere*[tiab]) AND (injur*[tiab] OR trauma*[tiab] OR posttrauma*[tiab] OR damag*[tiab] OR lesion*[tiab] OR fracture*[tiab])) OR concus*[tiab] OR contus*[tiab] OR neurotraum*[tiab] OR tbi OR mtbi OR coma*[tiab])) AND (Wounds and Injuries[mh] OR Stress Disorders, Traumatic[mh] OR accidents[mh] OR Emergencies[mh] OR Emergency Treatment[mh] OR Emergency Service, Hospital[mh] OR

violence[mh] OR (trauma*[tiab] OR posttrauma*[tiab] OR injur*[tiab] OR tbi OR mtbi OR accident*[tiab] OR emergen*[tiab] OR violen*[tiab])) AND (anxiety[mh] OR mood disorders[mh] OR anxiety disorder[mh] OR depression[mh] OR mental health[mh] OR Personal Satisfaction[mh] OR "Diagnostic and Statistical Manual of Mental Disorders" OR (anxi*[tiab] OR ((mood OR affective) AND (disorder*[tiab] OR disturb*[tiab])) OR phobi*[tiab] OR agoraphobi*[tiab] OR panic OR ocd OR (obsessi*[tiab] AND compulsi*[tiab]) OR depress*[tiab] OR ((posttraumatic OR post-traumatic OR postconcussion*[tiab] OR post-concussional OR post-concussion) AND (stress*[tiab] OR syndrom*[tiab])) OR dysthymi*[tiab] OR ptsd OR ((psychologic*[tiab] OR neuropsychologic*[tiab] OR emotion*[tiab]) AND (outcome*[tiab] OR develop*[tiab] OR well-being OR wellbeing OR disabil*[tiab] OR progres*[tiab] OR adjust*[tiab] OR function*[tiab] OR consequenc*[tiab] OR sequel*[tiab])) OR mental health OR dsm)) AND (prevalence[mh] OR incidence[mh] OR Prognosis[mh] OR Interviews as Topic[mh] OR epidemiology[mh] OR epidemiology[sh] OR risk factors[mh] OR (incidenc*[tiab] OR prevalen*[tiab] OR predict*[tiab] OR prognos*[tiab] OR interview*[tiab] OR (risk AND factor*[tiab]) OR epidemiolog*[tiab] OR ((indicator*[tiab] OR variable*[tiab] OR characteristic*[tiab] OR examination*[tiab] OR assessment*[tiab] OR measure*[tiab] OR association*[tiab] OR determinant*[tiab]) AND psycholog*[tiab]) OR psychometric*[tiab])) NOT (letter[pt] OR news[pt] OR comment[pt] OR editorial[pt] OR congresses[pt] OR abstracts[pt]) AND english[la] NOT (animals[mh] NOT humans[mh]) AND publisher[sb]

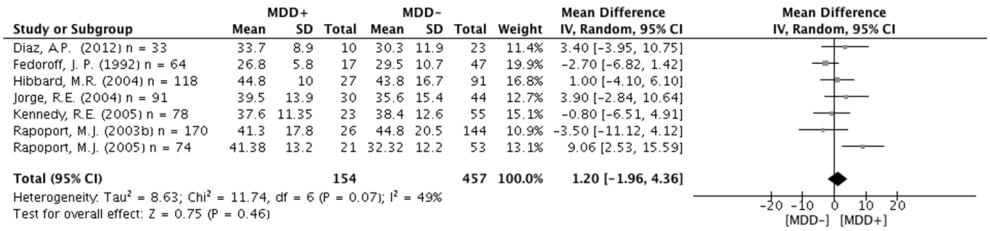
Google scholar
"brain|head|cranial|cerebral injury|trauma|fracture"|concussion|contussion|coma
trauma|traumatic|posttraumatic|injury|accident anxiety|"mood disorder"|depression|"mental health"|psychological|dsm prevalence|incidence|epidemiology|"risk factor"|prognosis

Appendix 9.B Meta-analyses of univariable predictors of MDD and PTSD

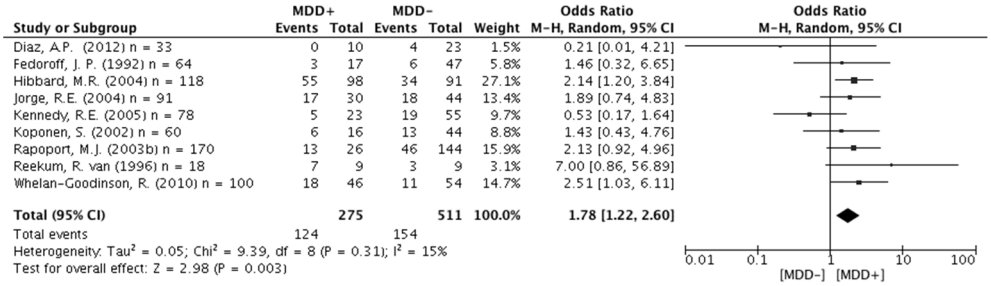
MDD

Demographics

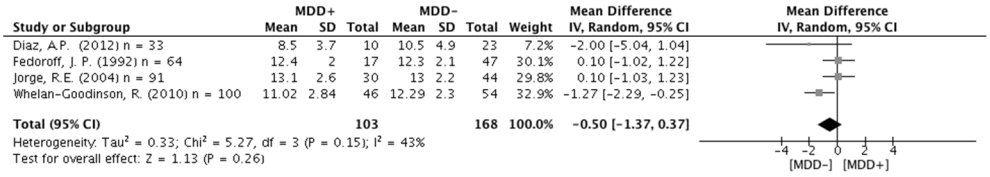
1. Age (continuous, in years) as predictor of MDD



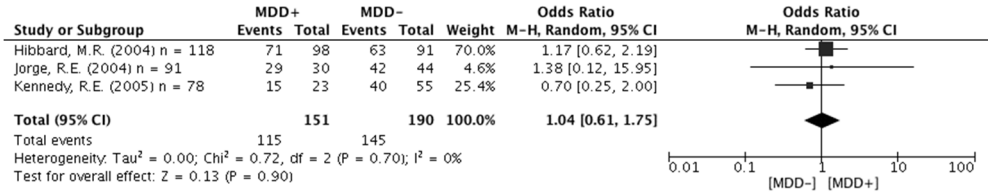
2. Female gender as predictor of MDD



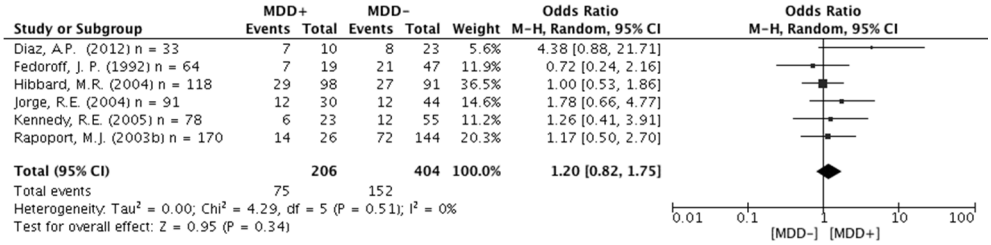
3. Education (continuous, in years) as predictor of MDD



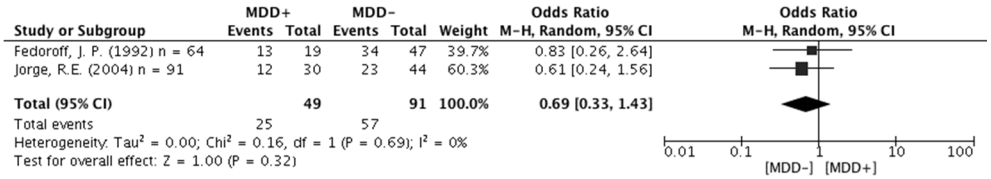
4. Caucasian race as predictor of MDD



5. Marital status (married / relationship vs. unattached) as predictor of MDD

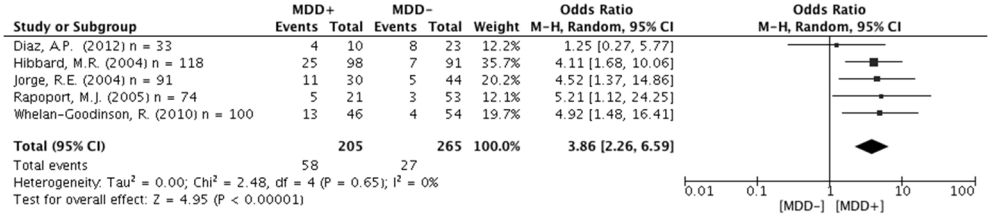


6. Socio-economic status (Hollinghead classes IV and V vs. lower) as predictor of MDD

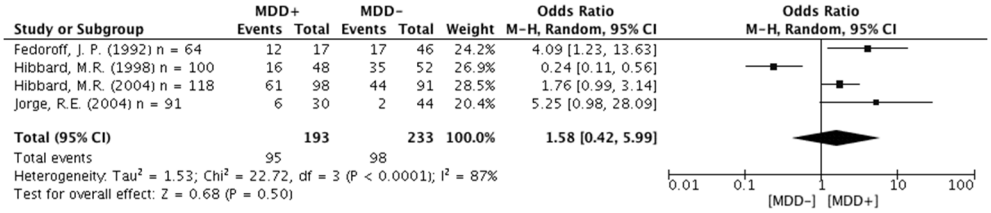


Pre-injury variables

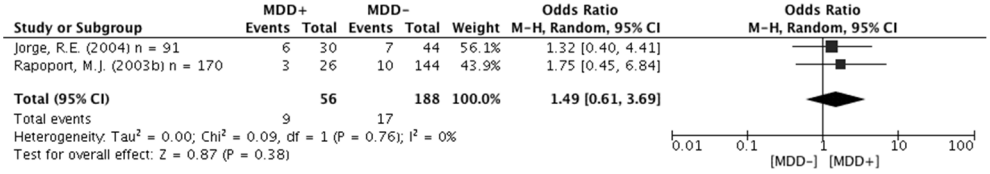
7. Pre-injury depression as predictor of MDD



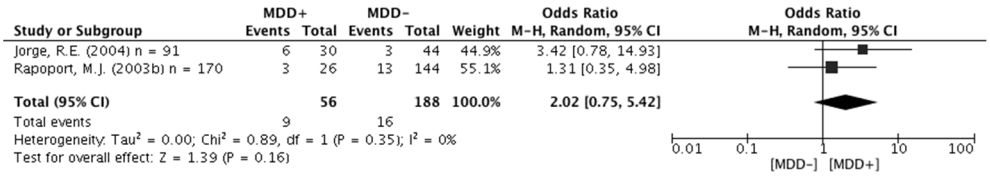
8. Pre-injury psychiatric disorders as predictor of MDD



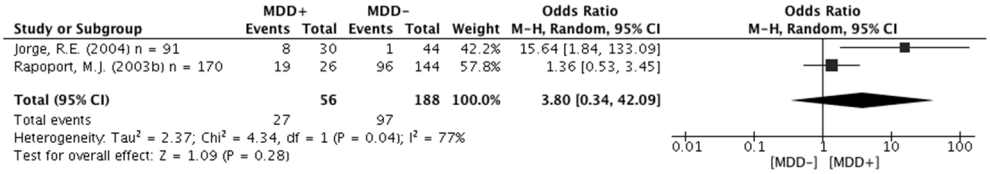
9. Pre-injury alcohol abuse as predictor of MDD



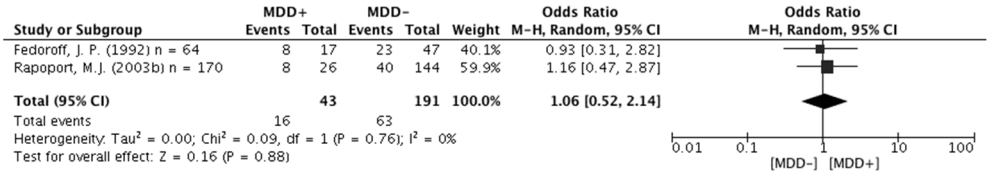
10. Pre-injury substance abuse as predictor of MDD



11. Pre-injury unemployment as predictor of MDD

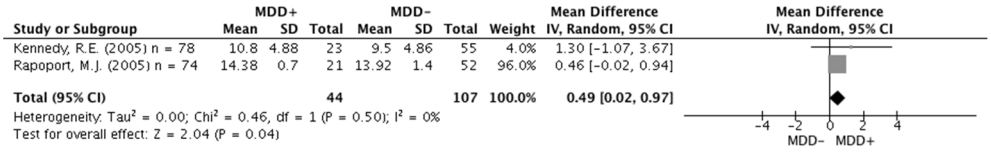


12. Family history of psychiatric disorders as predictor of MDD

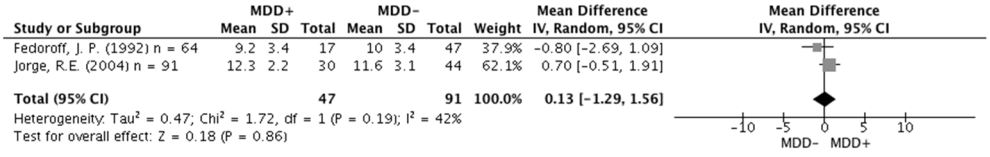


Clinical variables and imaging

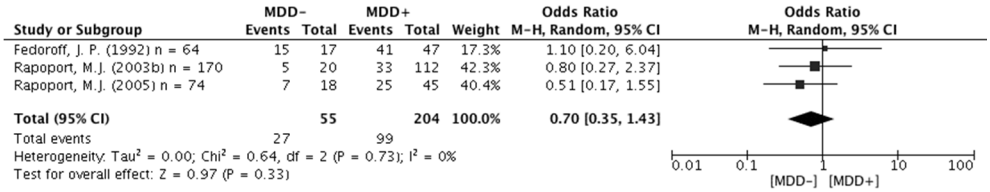
13. Admission GCS as predictor of MDD



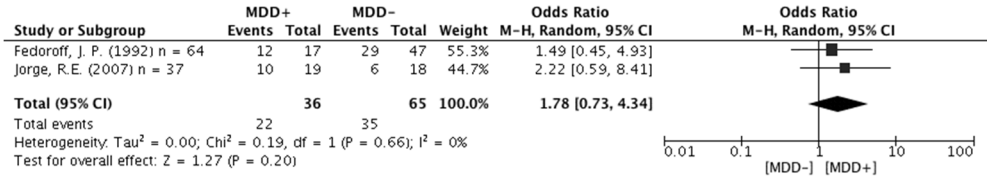
14. GCS after 24h post-injury as predictor of MDD



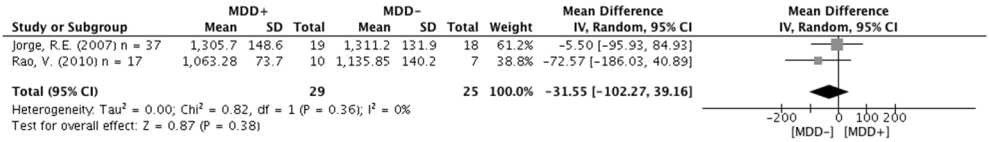
15. CT abnormalities as predictor of MDD



16. Brain Contusion as predictor of MDD

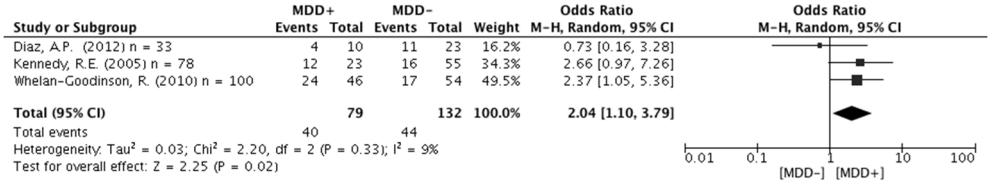


17. Total brain volume as predictor of MDD

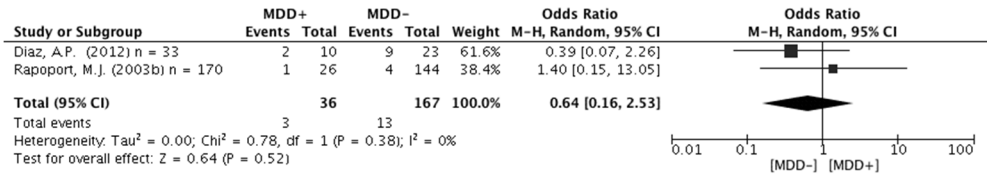


Post-injury variables

18. Post-injury unemployment as predictor of MDD



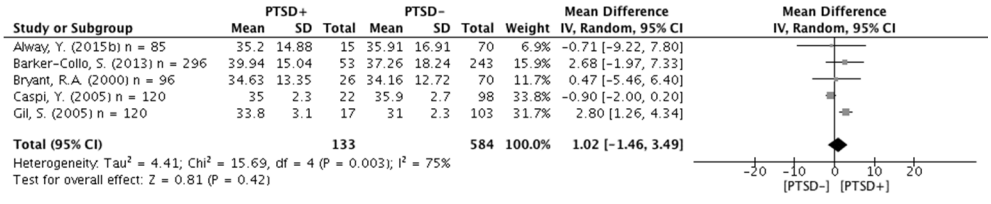
19. Post-injury litigation situation as predictor of MDD



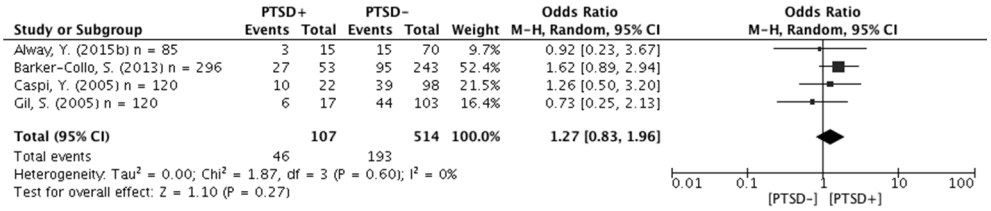
PTSD

Demographics

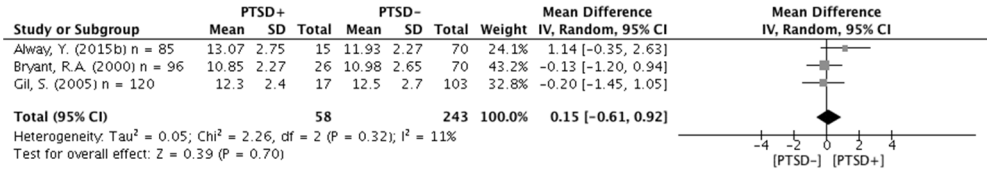
1. Age (continuous) as predictor of PTSD



2. Female gender as predictor of PTSD

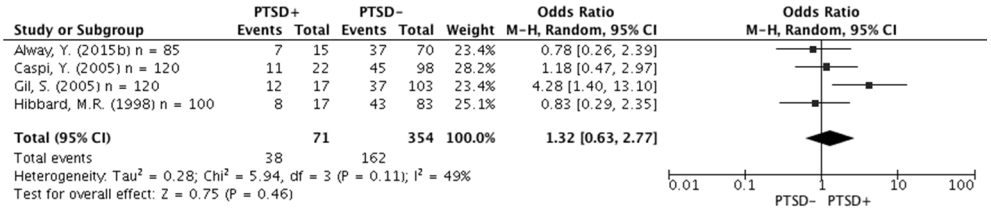


3. Education (continuous) as predictor of PTSD



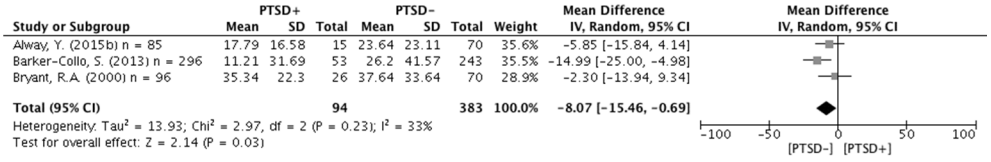
Pre-injury variables

4. Pre-injury psychiatric disorder as predictor of PTSD



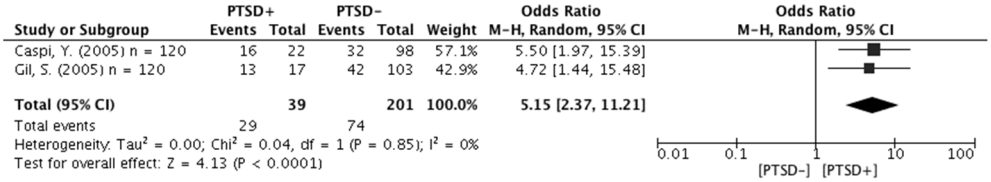
Clinical variables

5. PTA (continuous) as predictor of PTSD



Post-injury variables

6. Memory of the traumatic event as predictor of PTSD



Appendix 9.C Variables not included in the meta-analysis

MDD

Variable	Study	Results
Demographics		
Age	Deb, S. (2007)	Percentage patients with young age (18–65y) in MDD+ group: 79%, in MDD- group 72%, p>.05
	Hibbard, M. (1998)	No statistically significant differences
	Jorge, R.E. (1993)	*No statistically significant differences*
	Jorge, R.E. (1993b)	*Mean age MDD+: 25.0 (SD=8.0); MDD-: 27.0 (SD=13.5), p>.05*
	Mauri, M.C. (2014)*	Mean age MDD+: 37.1 (SD=15), MDD-: 47.5 (SD=13), p>.05
	Rao, V. (2010)	Mean age MDD+ 52.4 (SD=unknown); MDD- 27.3 (SD=unknown), p<.001
	Rapoport, M.J. (2003)	*Percentage patients with old age (>60y): MDD+ 11%, MDD- 24%. OR = 4.04 (95%CI: 1.36–11.99)*
	Reekum, R. (1996)	Percentage patients under age 30: MDD+ 56%, MDD- 33%, p>.05
	Whelan-Goodinson, R (2010)	No statistically significant differences
Gender	*Ashman, T.A. (2004)*	*Significantly more women than men (p= .02) develop MDD post-injury*
	Hibbard, M. (1998)	No statistically significant differences
	Jorge R.E. (1993)	*No statistically significant differences*
	Jorge R.E. (1993b)	*Percentage women: MDD+ 16%, MDD= 13%, p>.05*
	Rao, V. (2010)	No statistically significant differences
	Rapoport, M.J. (2005)	No statistically significant differences
Education	Hibbard, M. (2004)	No statistically significant differences
	Jorge, R.E. (1993)	*No statistically significant differences*
	Jorge, R.E. (1993b)	*Median years of education: MDD+ 12 (IQR: 3); MDD- 12 (IQR: 3), p>.05*
	Kennedy, R.E. (2005)	In MDD+ group: less than high school 23%, high school graduate or some college 46%, college graduate or higher 32%; in MDD- group: less than high school 16%, high school graduate or some college 56%, college graduate or higher 27%, p=.67
	Mauri, M.C. (2014)*	Mean years of education: MDD+ 13 (SD=2.9), MDD- 13 (SD=4.2), p>.05
Race	Federoff, J.P. (1992)	Percentage of black patients: MDD+ 29%, MDD= 23%, p>.05
	Jorge, R.E. (1993)	*No statistically significant differences*
	Jorge, R.E. (1993b)	*No statistically significant differences*
Marital status	Rapoport, M.J. (2005)	No statistically significant differences
	Whelan-Goodinson, R. (2010)	No statistically significant differences
Socioeconomic status	*Jorge, R.E. (1993b)*	*Percentage Hollingshead classes IV and V: MDD+ 78%, MDD- 72%, p>.05*
	Jorge, R.E. (2007)	*Percentage Hollingshead classes IV and V: MDD+ 65%, MDD- 56%, p>.05*
Income	Hibbard, M. (2004)	Annual salary < 20.000 dollar: MDD+ 36%, MDD- 30%, p>.05
	Jorge, L.E. (2004)	Annual salary < 21.000 dollar: MDD+ 46%, MDD- 24%, p>.05
Intelligence coefficient	Mauri. M.C. (2014)*	Mean IQ MDD+ 104 (SD=11), MDD- 112 (SD=15), p>.05
	Rao, V. (2010)	Mean IQ MDD+ 105 (SD=15); MDD- 102 (SD=9), p=.67
	Rapoport, M.J. (2005)	No statistically significant differences
Location of residence	Whelan-Goodinson, R. (2010)	No statistically significant differences
Left handedness	Federoff, J.P. (1992)	Percentage left handedness: MDD+ 6%, MDD- 9%, p>.05
	Jorge, R.E. (1993b)	*Percentage left handedness: MDD+ 6%, MDD- 8%, p>.05*

Appendix 9.C - MDD (continued)

Variable	Study	Results
Pre-injury variables		
Pre-injury depression	Gould, K.R. (2011b)	OR = 5.25 (95%CI: 1.66 to 16.64), p=.005
	Rapoport, M.J. (2003)	Chi square = 1.35 (df = 1), p=.25
Pre-injury psychiatric disorder (any)	*Jorge, R.E. (1993)*	*Significantly more MDD+ patients had a pre-injury psychiatric disorder than MDD- patients at 1 month post-injury; no differences at 3, 6 and 12 months post-injury*
	Jorge, R.E. (1993b)	*Percentage patients with pre-injury psychiatric disorder: MDD+ 68%, MDD- 37%, p=.01*
Pre-injury anxiety	Jorge, L.E. (2004)	Percentage patients with pre-injury anxiety disorder: MDD+ 20%, MDD- 5%, p=.05
Pre-injury alcohol abuse	Rapoport, M.J. (2005)	No statistically significant differences
Pre-injury substance abuse	Gould, K.R. (2011)	Chi square = 3.10 (df=1, n=114), p=.78
	Rapoport, M.J. (2005)	No statistically significant differences
Pre-injury substance- or alcohol abuse	Federoff, P.J. (1992)	*Percentage pre-injury substance or alcohol abuse: MDD+ 47%, MDD- 24%, p > .05*
	Jorge, R.E. (1993)	*No statistically significant differences*
	Jorge, R.E. (1993b)	*Percentage pre-injury substance or alcohol abuse: MDD+ 42%, MDD- 24%, p=.01*
Pre-injury unemployment	*Rapoport, M.J. (2003)*	*No statistically significant differences*
	Rapoport, M.J. (2005)	No statistically significant differences
	Whelan-Goodinson, R. (2010)	No statistically significant differences
Family history of psychiatric disorders	*Jorge, R.E. (1993)*	*No statistically significant differences*
	Jorge, R.E. (1993b)	*Percentage family history of psychiatric disorders: MDD+ 42%, MDD- 49%, p>.05*
	Jorge, R.E. (2004)	No statistically significant differences
	Rapoport, M.J. (2005)	No statistically significant differences
Pre-injury counselling	Gould, K.R. (2011)	Higher percentage pre-injury counselling in those with MDD: Chi square = 5.43 (df = 1, n=118), p=.02
Pre-injury medical problems	Rapoport, M.J. (2003)	No statistically significant differences
	Rapoport, M.J. (2003b)	Pre-injury medical problems: MDD+ 42%, MDD- 48%, p>.05
Pre-injury TBI	Rapoport, M.J. (2003b)	Percentage pre-injury TBI: MDD+ 23%, MDD- 23%, p>.05
	Rapoport, M.J. (2005)	No statistically significant differences
Peri-injury variables		
Mechanism of injury	Kennedy, R.E. (2005)	Percentage violent injury: MDD+ 22%, MDD- 9%, p=0.13
	Rapoport, M.J. (2003)	No statistically significant differences
	Rapoport, M.J. (2003b)	*MVA: MDD+ 65%, MDD= 44%, p<.05*
	Rapoport, M.J. (2005)	MVA: MDD+ 71%, MDD- 60%, Chi square = 0.79 (df = 1), p >.05
Trauma severity	Mauri, M.C. (2014)	Trauma severity score: MDD+ 2.3 (SD=0.9), MDD- 1.4 (SD=0.7), p>.05
Clinical variables		
GCS (continuous)	Jorge R.E. (1993)	Mean GCS obtained at 24h post-injury: no statistically significant differences
	Jorge, R.E. (2007)	Mean GCS after 24h post-injury: MDD+ 12.1 (SD=2.4), MDD- 12.0 (SD=2.3)
	Kennedy, R.E. (2005)	Lowest GCS score: MDD+ 10.0 (SD=4.4), MDD- 9.0 (SD=5.0), p>.05
	Whelan-Goodinson, R. (2010)	No statistically significant differences (measurement = lowest preintubation GCS)

Appendix 9.C - MDD (continued)

Variable	Study	Results
GCS (division into mild, moderate and severe)	Federoff, P.J. (1992)	MDD+: GCS12–15 35%; GCS 8–11 24%; GCS 3–7 41% MDD-: GCS 12–15 43%; GCS 8–11 26%; GCS 3–7 32%, p>.05
	Hibbard, M. (1998)	No statistically significant differences
	Jorge, L.E. (2004)	MDD+: mild: 47%, moderate 40%, severe 13% MDD-: mild 48%, moderate 25%, severe 27%, p>.05
	Kennedy, R.E. (2005)	MDD+ GCS 13–15: 38%, GCS 9–12: 31%, GCS <9 31% MDD-: GCS 13–15 33%, GCS 9–12 18%, GCS <9 49%, p=.67
	Reekum, R. (1996)	MDD+: severe TBI 56%, moderate TBI 22%, mild TBI 22% MDD-: severe TBI 56%, moderate TBI 11%, mild TBI 33%, p>.05
PTA	Koponen, S. (2002)	No statistically significant differences
	Rapoport, M.J. (2005)	PTA > 24h: MDD+ 43%, MDD- 53%, Chi square = 0.6 (df = 1), p=.32
	Whelan-Goodinson, R. (2010)	No statistically significant differences
LOC	Kennedy, R.E. (2005)	MDD+: none 53%, 1–2h 26%, 3–14h 21%, >14h 0% MDD-: none 43%, 1–2h 12%, 3–14h 22%, >14h 22%, p=.10
Bodily injuries	Gould, K. R. (2011)	MDD+ more bodily injuries than MDD- , p=.049
	Rapoport, M.J. (2005)	Fractures or other significant injuries: MDD+ 60%, MDD- 67%, p>.05
	Whelan-Goodinson, R. (2010)	No statistically significant differences
Pain	Whelan-Goodinson, R. (2010)	Percentage with pain: MDD+ 57%; MDD- 28%, OR = 3.38 (95%CI: 1.47 to 7.78), p=.004
AIS score	Jorge, L.E. (2004)	MDD+ 16.7 (SD=5.7); MDD- 18.0 (SD=8.1), p>.05
Comorbidities	Rapoport, M.J. (2003b)	MDD+: no comorbidity 15%, soft tissue only 50%, fractures 35% MDD-: no comorbidity 22%, soft tissue 52%, fractures 26%, p>.05
Imaging variables		
CT abnormalities	*Rapoport, M.J. (2003)*	*No statistically significant differences*
MR abnormalities	Jorge, L.E. (2004)	% of gray matter at MR image - L orbitofrontal cortex: MDD+ 2.1 (SD=0.25), MDD- 2.1 (0.25), p>.05 % of gray matter at MR image - L medial frontal cortex: MDD+ 1.5 (SD=0.24), MDD- 1.6 (SD=0.37), p>.05 % of gray matter at MR image - L lateral frontal cortex: MDD+ 5.6 (SD =0.7); MDD-: 4.5 (SD=0.9), Chi square = 10.5, p=.001 % of gray matter at MR image - L superior frontal gyrus: MDD+ 2.2 (SD=0.4), MDD- 1.9 (SD=0.3), p>.05 % of gray matter at MR image - L middle frontal gyrus: MDD+ 2.2 (SD=0.5), MDD- 1.7 (SD=0.7), p>.05 % of gray matter at MR image - L inferior frontal gyrus: MDD+ 1.2 (SD=0.2); MDD- 0.9 (SD=0.2), Chi square = 7,1, p=.008 % of gray matter at MR image - R orbitofrontal cortex: MDD+ 2.1 (0.20); MDD- 2.1 (SD=0.46), p>.05 % of gray matter at MR image - R medial frontal cortex: MDD+ 1.6 (SD=0.30), MDD- 1.7 (SD=0.43), p>.05 % of gray matter at MR image - R lateral frontal cortex: MDD+ 5.4 (SD=0.7), MDD- 4.9 (SD=1.2), p >.05

Appendix 9.C - MDD (continued)

Variable	Study	Results
MR abnormalities (continued)	Jorge, L.E. (2004)	% of gray matter at MR image - R superior frontal gyrus: MDD+ 2.1 (SD=0.3); MDD+ 1.9 (0.3), p>.05 % of gray matter at MR image - R middle frontal gyrus: MDD+ 2.2 (SD=0.6); MDD- 2.0 (SD=0.8), p>.05 % of gray matter at MR image - R inferior frontal gyrus: MDD+ 1.1 (SD=0.2), MDD- 1.0 (SD=0.3), p>.05
Diffuse injury at CT or MRI scan	Jorge, R.E (2007)	Percentage diffuse injury: MDD+ 37%, MDD- 67%, p>.05
Intracranial hemorrhages	Jorge, R.E. (2007)	Percentage intracranial hemorrhages: MDD+ 32%, MDD- 22%
Frontal lesions	Jorge, R.E. (2007)	Percentage frontal lesion: MDD+ 42%, MDD- 28%
Brain volume	Rao, V. (2010)	Total gray brain volume: MDD+ 474.98 (SD=72.8), MDD- 564.96 (SD=93.9), p =.07 Total white brain volume: MDD+ 588.08 (SD=31.8); MDD- 590.78 (SD=61.2), p=.91 Total left frontal lobe: MDD+ 150.47 (SD=14.4); MDD- 153.31 (SD=26.2), p=.79 Left frontal lobe white matter: MDD+ 90.63 (SD=10.2), MDD- 81.1 (SD=13.1), p=.14 Left frontal lobe grey matter: MDD+ 59.84 (SD=10.3); MDD- 72.19 (SD=14.6), p =.08 Total right frontal lobe: MDD+ 155.49 (SD=12.6); MDD- 160.55 (SD=20.1), p=.56 Right frontal lobe white matter: MDD+ 95.13 (SD=11.2); MDD- 84.26 (SD=9.0), p=.07 Right frontal lobe grey matter: MDD+ 60.4 (SD=8.9), MDD- 76.3 (SD=13.6), p=.02 Total left limbic lobe: MDD+ 54.02 (SD=3.5), MDD- 54.9 (SD=8.7), p=.78 White left limbic lobe: MDD+ 26.8 (SD=3.6), MDD- 25.0 (SD=4.5), p=.40 Gray left limbic lobe: MDD+ 27.14 (SD=2.8); MDD- 29.90 (SD=5.6), p=.30 Total right limbic lobe: MDD+ 50.0 (SD=3.8); MDD- 52.03 (SD=5.9), p=.43 White right limbic lobe: MDD+ 22.5 (SD=2.6); MDD- 20.8 (SD=2.7), p=.23 Gray right limbic lobe: MDD+ 27.50 (SD=4.4); MDD- 31.27 (SD=4.25), p=.12 Total left occipital lobe: MDD+ 41.99 (SD=5.2); MDD- 53.48 (SD=7.31), p=.004 White left occipital lobe: MDD+ 24.49 (SD=3.37); MDD- 29.65 (SD=6.1), p=.06 Gray left occipital lobe: MDD+ 17.50 (SD=4.12); MDD- 23.82 (SD=4.3), p=.01 Total right occipital lobe: MDD+ 42.57 (SD=9.06), MDD- 50.57 (SD=8.46), p=.11 White right occipital lobe: MDD+ 24.63 (SD=5.07), MDD- 27.66 (SD=6.1), p=.32 Gray right occipital lobe: MDD+ 17.93 (SD=5.8), MDD- 22.9 (SD=4.7), p=.11 Total left temporal lobe: MDD+ 74.11 (SD=5.7); MDD- 81.69 (SD=9.6), p=.08 White left temporal lobe: MDD+ 33.96 (SD=2.15), MDD- 35.63 (SD=4.96), p=.39 Gray left temporal lobe: MDD+ 40.14 (SD=5.4); MDD- 46.06 (SD=5.90), p=.07 Total right temporal lobe: MDD+ 74.24 (SD=9.12); MDD- 81.60 (SD=9.9), p=.16 White left temporal lobe: MDD+ 33.59 (SD=4.51); MDD- 34.82 (SD=5.68), p=.65 Gray left temporal lobe: MDD+ 40.65 (SD=6.36); MDD- 46.77 (SD=5.87), p=.08 Total left parietal lobe: MDD+ 53.84 (SD=6.37), MDD- 59.20 (SD=5.32), p=.11 White left parietal lobe: MDD+ 29.56 (SD=3.4), MDD- 29.03 (SD=5.1), p=.81 Gray left parietal lobe: MDD+ 24.28 (SD=6.16), MDD- 30.17 (SD=4.24), p=.06 Total right parietal lobe: MDD+ 57.04 (SD=9.26); MDD- 63.44 (SD=6.36), p=.17 White right parietal lobe: MDD+ 31.46 (SD=2.7), MDD- 31.09 (SD=6.59), p=.88 Gray right parietal lobe: MDD+ 25.58 (SD=6.9), MDD- 32.34 SD=5.06), p=.06

Appendix 9.C - MDD (continued)

Variable	Study	Results
Brain volume (continued)	Jorge, R.E. (2007)	Left frontal lobe grey matter (% of TIV): MDD+ 8.9 (SD=0.6), MDD- 9.4 (SD=0.6), F = 7.8, p=.009 Right frontal lobe grey matter (% of TIV): MDD+ 9.4 (SD=0.9), MDD- 9.7 (SD=0.6), Hippocampal volume (left): MDD+ group has significantly lower hippocampal volumes, p=.04 Hippocampal volume (right): MDD+ group has significantly lower hippocampal volumes, p=.03
Choline/creatine ratio in the right basal ganglia	Rao, V. (2010)	MDD+ 1.6 (SD=2.0), MDD- 2.0 (SD=0.43), p=.02
N-acetylaspartate/creatine ratio	Rao, V. (2010)	MDD+ 1.7 (SD=0.36), MDD- 2.2 (SD=0.68), p=.06
Post-injury variables		
Post-injury unemployment	Hibbard, M. (1998)	No statistically significant differences
Post-injury rehabilitation	Reekum, R. (1996)	Inpatient rehabilitation: MDD+ 33%, MDD- 56%
Post-injury depression	Gould, K.R. (2011)	Post-injury depression is related to MDD Measured with SCID: p=.006 Measured with HADS: p=.031
Post-injury anxiety	Gould, K.R. (201)	No statistically significant differences
Alexithymia	Koponen, S. (2005)	Score on TAS-20: MDD+ 69.0 (SD – 13.1); MDD- 52.5 (SD=12.6), p>.05
Neuropsychological test results	Jorge, L.E. (2004)	Rey auditory verbal learning test: MDD+ 8.33 (SD=2.77), MDD- 9.93 (SD=3.14), Cohen's d = 0.52, p >.05 Rey complex figure test score: MDD+ 14.50 (SD= 8.10), MDD- 17.64 (SD=5.31), Cohen's d = 0.52, p <.05 Wisconsin card sorting test (perseverative errors): MDD+ 13.92 (SD=11.09), MDD- 7.95 (SD=5.17), Cohen's d = 0.82, p=.03 Wisconsin card sorting test (categories achieved): MDD+ 2.25 (SD= 1.60), MDD- 3.33 (SD=1.49), Cohen's d = 0.69, p>.05 Trail making test (A): MDD+ 37.08 (SD=15.18), MDD- 31.90 (SD=15.24), Cohen's d = 0.34, p >.05 Trail making test (B/A ratio): MDD+ 3.44 (SD=1.60), MDD- 2.49 (SD=.80), Cohen's d = 0.87, p=.02 Stroop test: MDD+ 31.83 (SD=10.30), MDD- 38.05 (SD=9.92), Cohen's d = 0.61, p >.05 Multilingual aphasia examination score: MDD+ 34.08 (SD=12.06), MDD- 36.29 (SD=12.73), Cohen's d = 0.18, p>.05

*Study excluded from meta-analysis because high risk of bias.
Studies in *italic* refer to multiple publications. Another publication from the same dataset is already being used for the meta-analysis or already mentioned in the table.

Appendix 9.C - PTSD

Variable	Study	Results
Demographics		
Age	*Alway, Y. (2015)*	*No statistically significant differences*
Gender	*Alway, Y. (2015)*	*No statistically significant differences*
	Ashman, T.A.. (2000)	Significantly more women than men fit the criteria for PTSD (p=.04)
Education (years)	*Alway, Y. (2015)*	*No statistically significant differences*
	Caspi, Y. (2005)	No statistically significant differences
Ethnicity	Barker-Collo, S. (2013)	Percentage European ethnicity: PTSD+ 57%, PTSD- 68%, p=.38
Marital Status	Gil, S. (2005)	Percentage married: PTSD+ 52%, PTSD- 49%, p>.05
Country of origin	Gil, S. (2005)	Percentage native Israeli: PTSD+ 64%, PTSD- 68%, p >.05
Pre-injury variables		
Pre-injury employment	Bryant, R.A. (2000)	Percentage employed: PTSD+ 79%, PTSD- 81%, p > .05
Pre-injury physical injury	Gil, S. (2005)	Percentage physical injury: PTSD+ 23%, PTSD- 20%, p>.05
Pre-injury psychiatric disorders	*Alway, Y. (2015)*	*No statistically significant differences*
Pre-injury PTSD	Barker-Collo, S. (2013)	None of the patients had a pre-injury PTSD
Pre-injury depression	Barker-Collo, S. (2013)	Percentage pre-injury depression: PTSD+ 28%, PTSD- 19%, p=0.51
Pre-injury anxiety	Barker-Collo, S. (2013)	Percentage pre-injury anxiety disorder: PTSD+ 15%, PTSD- 6%, p=.05
Peri-injury variables		
Injury mechanism	Barker-Collo, S. (2013)	PTSD+: traffic 21%, fall 26%, assault 30% PTSD-: traffic 17%, fall 31%, assault 20%, p=.90
	Caspi, Y. (2005)	No statistically significant differences
Place of injury	Barker-Collo, S. (2013)	PTSD+: home 28%, street 32%, work 17% PTSD-: home 33%, street 28%, work 11%
Intentional injury	Barker-Collo, S. (2013)	Percentage intentional injury: PTSD+ 34%, PTSD- 22%, p=.25
Alcohol involved in injury	Barker-Collo, S. (2013)	Percentage alcohol involved: PTSD+ 25%, PTSD- 26%, p=.24
Drugs involved in injury	Barker-Collo, S. (2013)	Percentage drugs involved: PTSD+ 11%, PTSD- 6%, p=.01
Clinical variables and imaging		
GCS	Always (2015b)	Mean GCS: PTSD+ 13.91 (SD=2.22), PTSD- 14.13 (SD=2.32), p=0.43 PTSD+:GCS 13–15: 53%, GCS 9–12: 13%, GCS 3–8 27% PTSD-: GCS 13–15: 33%, GCS 9–12 13%, GCS 3–8 34%, p>.01
	Barker-Collo, S. (2013)	Mean worst GCS PTSD+: 13.91 (SD=2.22), PTSD- 14.13 (SD=2.32), p=0.43 PTSD+: mild TBI 91%, PTSD-: mild TBI 95%, p=0.84
	Bryant, R.A.	Mean GCS: PTSD+ 6.92 (SD=3.52), PTSD- 2.60 (SD=1.79), p>.05
PTA	*Alway, Y. (2015)*	*No statistically significant differences*
	Alway, Y. (2015b)	*PTSD+: 1–7d 40%, 8–28d 33%, >28d 20%* *PTSD-: 1–7d 24%, 8–28d 44%, >28d 31%*
LOC	Roitman, P. (2013)	Percentage patients with LOC: PTSD+ 39%, PTSD- 24%, OR = 1.72 (95%CI: 1.22–2.42)
	Barker-Collo, S. (2013)	Mean days LOC: PTSD+ 4.0 (SD=6.16), PTSD- 9.04 (SD=28.57), p=.07
ISS	Gil, S. (2005)	Mean ISS: PTSD+ 6.0 (SD=3.9), PTSD- 5.8 (SD=3.3), p>.05
CT abnormalities	Barker-Collo, S. (2013)	No lesion: PTSD+ 93%, PTSD- 96%, p=.24
Surgery	Barker-Collo, S. (2013)	PTSD+: neurosurgery 4%, orthopedic surgery 4%, other surgery 6% PTSD-: neurosurgery 0.4%, orthopedic surgery 4%, other surgery 2%, p=.18

Appendix 9.C - **PTSD** (continued)

Variable	Study	Results
Post-injury variables		
Memory of the traumatic event	Turnbull, S.J. (2001)*	No statistically significant differences
Acute PTSD symptoms	Gil, S. (2005)	PTSD according to CAPS 1 wk post-injury: PTSD+ 39%, PTSD- 32%, p >.05 PTSD according to CAPS 1 month post-injury: PTSD+ 43%, PTSD- 34%, p <.01 PTSD according to PSS 1 wk post-injury: PTSD+ 38%, PTSD- 34%, p > .05 PTSD according to PSS 1 month post-injury: PTSD+ 39%, PTSD- 30%, p <.01
ASD	Bryant, R.A. (1998)	Percentage patients with ASD: PTSD+ 60%, PTSD- 4% Percentage patients with fearful response (ASD symptom): PTSD+ 53%, PTSD- 27%, Chi square = 2.46, p > .003 Percentage patients with helplessness (ASD symptom): PTSD+ 40%, PTSD- 38%, Chi square = 0.02, p < .003 Percentage patients with numbing (ASD symptom): PTSD+ 67%, PTSD- 15%, Chi square = 13.20, p < .003 Percentage patients with reduced awareness (ASD symptom): PTSD+ 53%, PTSD- 15%, Chi square = 7.44, p > .003 Percentage patients with derealisation (ASD symptom): PTSD+ 67%, PTSD- 21%, Chi square = 9.07, p > .003 Percentage patients with depersonalisation (ASD symptom): PTSD+ 47%, PTSD- 4%, Chi square = 13.57, p <.003 Percentage patients with dissociative amnesia (ASD symptom): PTSD+ 100%, PTSD- 100% Percentage patients with recurrent images and thoughts (ASD symptom): PTSD+ 47%, PTSD- 6%, Chi square = 11.12, p <.003 Percentage patients with nightmares (ASD symptom): PTSD+ 40%, PTSD- 8%, Chi square = 6.37, p > .003 Percentage patients with sense of reliving the trauma (ASD symptom): PTSD+ 20%, PTSD- 2%, Chi square = 3.52, p > .003 Percentage patients with distress on exposure (ASD symptom): PTSD+ 67%, PTSD- 21%, Chi square = 9.07, p > .003 Percentage patients with avoidance of thoughts or talk (ASD symptom): PTSD+ 60%, PTSD- 8%, Chi square = 15.61, p <.003 Percentage patients with avoidance of places of people (ASD symptom): PTSD+ 67%, PTSD- 13%, Chi square = 14.95, p <.003 Percentage patients with insomnia (ASD symptom): PTSD+ 87%, PTSD- 27%, Chi square = 14.37, P < .003 Percentage patients with irritability (ASD symptom): PTSD+ 73%, PTSD- 23%, Chi square = 10.66, p < .003 Percentage patients with poor concentration (ASD symptom): PTSD+ 67%, PTSD- 29%, Chi square = 5.32, p > .003 Percentage patients with hypervigilance (ASD symptom): PTSD+ 87%, PTSD- 52%, Chi square = 4.36, p > .003 Percentage patients with exaggerated startle response (ASD symptom): PTSD+ 53%, PTSD- 13%, Chi square = 8.79, p > .003 Percentage patients with motor restlessness (ASD symptom): PTSD+ 33%, PTSD- 0%, Chi square = 13.12, p < .003
	Harvey, A.G. (2000)	*Percentage patients with ASD: PTSD+ 73%, PTSD- 5%*
Dissociative reactions	Gil, S. (2005)	No statistically significant differences
Post-injury depression	Gil, S. (2005)	More post-injury depression in those with PTSD compared to those without PTSD post-injury
Post-injury anxiety	Gil, S. (2005)	More post-injury anxiety in those with PTSD compared to those without PTSD post-injury
Pending compensation	Harvey, A.G. (2000)	No statistically significant differences

*Study excluded from meta-analysis because high risk of bias
Studies in *italic* refer to multiple publications. Another publication from the same dataset is already being used for the meta-analysis or already mentioned in the table.

Chapter 10

Impact of depression and post-traumatic stress disorders on functional outcome and health-related quality of life of patients with mild traumatic brain injury

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ABSTRACT

Background The impact of disability following traumatic brain injury (TBI), assessed by functional measurement scales for TBI or by health-related quality of life (HRQL), may vary because of a number of factors, including presence of depression or post-traumatic stress disorder (PTSD). The aim of this study was to assess prevalence and impact of depression and PTSD on functional outcome and HRQL six and 12 months following mild TBI.

Methods We selected a sample of 1,919 TBI patients who presented to the emergency department (ED) followed by either hospital admission or discharge to the home environment. The sample received postal questionnaires six and 12 months after treatment at the ED. The questionnaires included items regarding socio-demographics, the 36-item Short-Form Health Survey (SF-36), the Perceived Quality of Life Scale (PQoL), the Beck Depression Inventory, and the Impact of Event Scale.

Results A total of 797 (42%) TBI patients completed the 6 month follow-up survey. Depression and PTSD prevalence rates at both the 6 and 12 month follow-up were 7% and 9%, respectively. Living alone was an independent predictor of depression and/or PTSD at 6 and 12 month follow-up. Depression and PTSD were associated with a significantly decreased functional outcome (measured with Glasgow Outcome Scale Extended) and HRQL (measured using the SF-36 and the PQoL).

Conclusions We conclude that depression and/or PTSD are relatively common in our sample of TBI patients and associated with a considerable decrease in functional outcome and HRQL.

10.1 INTRODUCTION

Traumatic brain injury (TBI) is an important cause of mortality and disability in modern Western societies. In Europe annually, 1.6 million patients with TBI are admitted to the hospital.[1] About half of these patients experience some level of disability caused by TBI.[2] The impact of disability following TBI may be assessed by functional measurement scales that have been designed for TBI specifically (e.g. the Glasgow Outcome Scale (GOS) or the GOS Extended (GOSE)) or by health-related quality of life (HRQL). HRQL reflects an individual's perception of how a disorder and its treatment affect the physical, mental, and social aspects of his or her life. HRQL has been recognised as a potentially important outcome variable in TBI, because it provides well-standardised information on recovery patterns and frequency, nature, and predictors of disabilities.

Functional outcome and HRQL may vary because of a number of factors, including the severity of the brain injury, time since injury and comorbid sequelae due to the injury, such as presence of depression or post-traumatic stress disorder (PTSD). Depression and PTSD frequently occur among TBI patients. Among TBI patients, depression prevalence rates have been assessed that vary from 17–61%[3,4] and PTSD prevalence rates from 0–50%.[5]

Recently, a study of injury patients by O'Donnell and colleagues[6] revealed that psychiatric symptoms play a substantial role in the development and maintenance of long-term disability measured with the World Health Organisation Disability Assessment Schedule. Among TBI patients, research has shown that depression and PTSD have a substantial effect on functioning and HRQL.[7-11]

The current study focused on a comprehensive population of adult patients with mild TBI and on the impact of depression and PTSD on both functional outcome and HRQL. The aims of this study were to 1) assess the prevalence and predictors of depression and PTSD among patients with mild TBI, 2) assess the association between depression and PTSD and functional outcome measured with the GOSE, and 3) assess the association between depression and PTSD and HRQL measured by the SF-36 and the PQoL.

10.2 METHODS

Study design

The data for this study was obtained from the Radboud University Brain Injury Cohort Study (RUBICS).[12-14] RUBICS is a prospective observational cohort study on the association between demographic and clinical variables, post-traumatic complaints, and functional outcome. The RUBICS database included information for all patients with TBI admitted to the emergency department (ED) of the Radboud University Nijmegen Medical Centre (RUNMC), a Level I trauma center, between January 1998 and December 2010. Approval for this study was obtained from the ethical standards committee of the RUNMC. Clinical data was registered by a neurologist and/or neurosurgeon at the ED, and thereafter collected by a research nurse and registered on prespecified forms and entered into the RUBICS databank.

The RUBICS databank comprised demographic data (age and sex), trauma mechanism, hospital admission and length of hospitalisation, clinical injury variables, and comorbidities. Mild TBI was defined by a Glasgow Coma Scale (GCS) score in the ED of 13–15 after initial resuscitation or followed by sedation and intubation during resuscitation for a non-neurological cause. The injury diagnosis was

verified at the individual level with information from the hospital discharge register according to the Abbreviated Injury Scale (AIS), 1990 Revision, update 1998.[15] The AIS is used to assess patients' Injury Severity Score (ISS), which indicates the risk of mortality. Further, the GCS score, the Abbreviated Injury Scale of the Head score, the ISS, and GOSE were recorded. Initially, several sub-studies were conducted, in which TBI patients registered in the RUBICS database received a survey. Later on, all patients in the RUBICS database received postal follow-up surveys six months and 12 months after initial treatment.

Study participants

In the current study, 3,631 patients with mild TBI admitted to the ED of the RUNMC between June 2003 and June 2010 were eligible for inclusion. Of these patients, 1,919 were sent a questionnaire. Exclusion criteria were age younger than 16 years, no informed consent given for previous RUBICS sub-studies, alcohol or drug abuse or dementia, no possibility of follow-up (unknown address), and inability to speak or write Dutch.Written informed consent was obtained from all patients (or guardians of patients) participating in the study.

Functional outcome

The GOSE assesses functional outcome via eight questions that cover consciousness, independence inside and outside the home, major social roles (work, social and leisure activities, family and friendships), and return to normal life.[16] Aggregating these questions results in an 8-point scale that classifies functional outcome from 1 (dead) to 8 (complete recovery). The GOSE was assessed using a structured interview during regular visits to the outpatient clinic or during consultation by telephone.[17] Assessment of the GOSE often took place at six (70%) and 12 (66%) months post-injury. If GOSE scores at six months post-TBI were missing, the six month GOSE was composed by taking the mean of GOSE scores assessed at five or seven months (25%), or at four or eight months (4%). In case of missing GOSE scores at 12 months post-TBI, the 12 month GOSE was composed by taking the mean of GOSE scores assessed at 11 or 13 months (29%), or at 10 or 14 months (5%).

Health-related quality of life

Generic HRQL was determined using the SF-36[18] and the Perceived Quality of Life Scale (PQoL).
The SF-36 is one of the HRQL instruments recommended by the TBI consensus groups.[19] The SF-36 is a 36-item questionnaire that covers eight domains of health status: physical functioning, role limitations related to physical health problems, bodily pain, general health perception, vitality, social functioning, role limitations related to emotional problems, and mental health.[18] The SF-36 has been used previously to evaluate HRQL in TBI patients.[20,21] For each domain, a summation of item responses is linearly transformed into a score ranging from 0–100.
The physical (PCS) and mental health summary component scores (MCS) are calculated by first standardising the patients' scores, specifically by subtracting the subscale means for the general United States population sample from each individual's subscale scores and dividing the result by the standard deviation of the US sample to generate Z-scores. Second, Z-scores are multiplied by the subscale factor coefficients for PCS and MCS of the US sample and summed over all eight subscales into the PCS and MCS summary scores. Finally, the obtained PCS and MCS sums were re-scaled into T-scores, with a mean of 50 and standard deviation of 10 for the US norm.[22]

The PQoL was initially developed as a cognitive appraisal of life satisfaction for patients after intensive medical care.[23] The instrument has been used for adults with chronic neurologic disability, including stroke and TBI.[24,25] The PQoL measures the degree to which the individual is satisfied with his/her functioning on an 11-point scale ranging from 0 ("extremely dissatisfied") to 10 ("extremely satisfied"). The measurement consists of 19 items that assess 10 different areas of functioning, including physical health, thinking and remembering, family relationships, community participation and leisure, work and income, and meaning and purpose of life. The overall PQoL score based on the mean of the 19 item scores may be considered a measure of global life satisfaction, where a score <7.5 is "Dissatisfied" and a score >7.5 is "Satisfied".[26] We used the mean score (range of 0 to 10) in our analyses. The PQoL showed to have good internal reliability in a sample of 97 people who had sustained a TBI at least six months previously and who are living in the community.[27]

Self-report inventories on depression and anxiety

Symptoms of depression were assessed with the Beck Depression Inventory (BDI). The BDI consists of 21 items that measure symptoms relating to depression (e.g. hopelessness and irritability), cognitions (e.g. guilt), and physical symptoms. By combining the items the total BDI score can be calculated. The total BDI score can range from 0 through 63. For TBI patients, a cut-off score of 19 for depression is recommended.[28]

The Impact of Event Scale (IES) was used to assess symptoms of post-traumatic stress indicative of PTSD.[29] The IES consists of 15 items, which measure intrusive re-experiences of the trauma and avoidance of trauma-related stimuli. By combining the 15 items the total IES score, ranging from 0 through 75, can be calculated. Wohlfarth and colleagues30 showed that a cut-off score of 34 on the total IES score produced a sensitivity of .89, and a specificity of .94 against the *Diagnostic and Statistical Manual of Mental Disorders, 4th. Edition* (DSM-IV) criteria for PTSD as the gold standard.[30] Therefore, we assumed that an IES score of 35 or higher (IES ≥35) represents symptoms of post-traumatic stress indicative of PTSD.

Data and statistical analysis

For analysis of the data the Statistical Package for the Social Sciences version 21 was used (SPSS Inc, Chicago, IL). The BDI and IES scores can be calculated if all items are completed. If one or two items of the BDI or IES were missing, the missing item was estimated using a hot deck imputation technique. The missing data was then imputed by the estimated values.[31] If more than two of the BDI or IES items were missing, data was not imputed. Chi-square statistics (dichotomous variables) and Student's t-tests (continuous variables) were used to test for differences between TBI patients with IES scores higher or lower than 35 and for TBI patients with BDI scores higher or lower than 19.

We used univariate logistic regression analysis to explore the association between patient demographics, presence of comorbid diseases and health care with regard to depression (BDI ≥19) and PTSD (IES ≥35) at six and 12 months post-trauma. Secondly, multiple logistic regression analyses (enter method) was applied to further investigate the association between socio-demographics (block 1), hospitalisation and comorbidity (block 2), and depression (BDI ≥19) and PTSD (IES ≥35).

For the analysis of the association between BDI ≥19 and/or IES ≥35 and functional outcome and HRQL, we selected participants that filled in the GOSE, SF-36, and the PQoL. We used the Mann-Whitney U

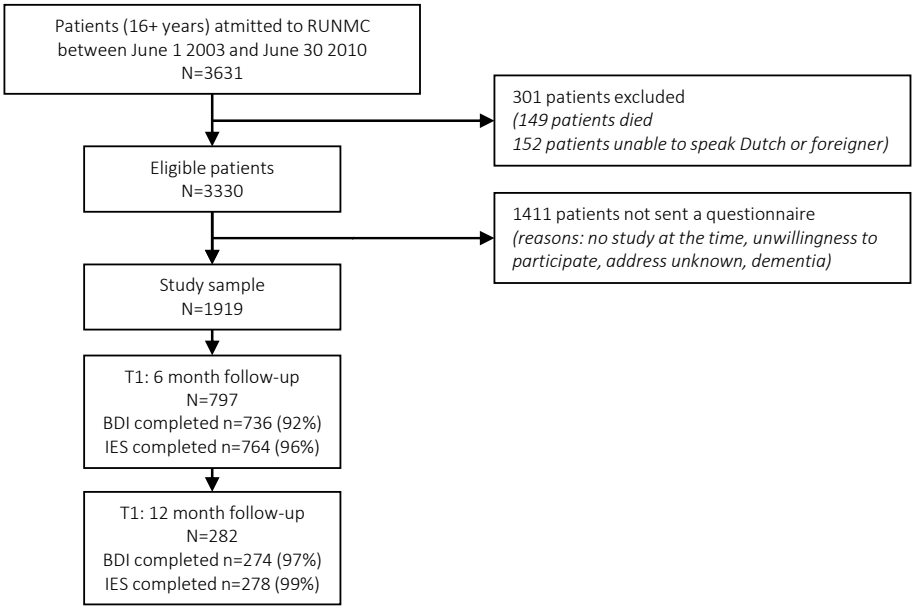
test to assess differences with and without depression and/or PTSD and GOSE. To test differences between participants with and without depression and/or PTSD, SF-36 and PQoL summary scores were analyzed with a one-way ANOVA. Because two outcome measures were tested against four variables, a Bonferroni adjusted significance level of 0.00625 was calculated to account for the increased possibility of type I error. A p value of less than 0.00625 was considered to indicate statistical significance.

10.3 RESULTS

Study population

During the study period, 3,631 patients with mild TBI aged 16 years and older were admitted to the RUNMC. The average age of the TBI patients was 43 years (interquartile range (IQR), 25–61). Of these patients, 1,919 were sent a questionnaire. The response rates were 41.5% (n=797) at six months post-injury and 15% (n=282) at 12 months post-injury. A flow chart of study participants demonstrates the number of respondents and the number of respondents that completed the BDI and IES at each time-point (Figure 10.1).

Figure 10.1 Flow-chart of study participants and the number of respondents that completed the BDI and IES



RUNMC, Radboud University Nijmegen Medical Centre; BDI, Beck Depression Inventory; IES, Impact of Event Scale.

With regard to the respondents of the 6 month follow-up questionnaire, the average age was 45 years old and 63% were male (Table 10.1). Almost one-half (47%) of TBI patients was injured due to traffic accidents and one in three (34%) was injured due to home and leisure accidents. After treatment at the ED, 51% of the respondents were admitted to the hospital and 4% were admitted to the intensive care unit.

Comparison of the characteristics of responders and non-responders to the 6 month follow-up survey showed that respondents who filled in the 6 month questionnaire were significantly older (non-responders, 38 years (IQR, 25–54); responders, 45 tears (IQR, 28–57).

Respondents who also filled in the 12 month follow-up questionnaire were significantly more often admitted to hospital (Chi^2=8.8; p<0.05), compared with non-respondents. Further, comparison of the characteristics of responders and non-responders to the 12 month follow-up survey showed that respondents who filled in both the 6 and 12 month questionnaire were older and more likely to be female, though these differences were not significant.

Table 10.1 Characteristics of the study population

	Patients (16+ years) admitted to RUNMC	6 month follow-up		12 month follow-up	
		Respondents	Filled in BDI and IES	Respondents	Filled in BDI and IES
N	3,631	797	721	282	270
Patient demographics					
Age	43 [25–61]	45 [28–57]	45 [28–57]	48.5 [33–58]	48.5 [32.8–58]
Male sex		62.6	62.3	58.8	58.5
Injury mechanism					
Road traffic accident		47.1	46.0	42.6	42.6
Fall		34.3	35.0	35.1	35.9
Sports		10.3	11.0	11.7	11.9
Assault		5.4	5.3	5.3	4.8
Other/unknown		*3.0*	*2.8*	*5.3*	*4.8*
Injury characteristics					
ISS[1]		6 [4–14]	6 [4–14]	8 [5–14]	8 [5–14]
AISH[2]					
Head AIS 0–1	27.5	25.2	25.2	24.5	23.7
Head AIS 2–3	65.8	65.5	65.6	67.0	67.8
Head AIS 4–5	6.7	9.3	9.2	8.5	8.5
CT scan[2]					
No CT scan		6.6	6.5	7.4	7.0
CT scan, no abnormalities		81.1	80.7	78.0	78.5
CT scan, abnormalities		12.3	12.8	14.5	14.4
Admitted to hospital[3]		51.1	51.4	58.2	58.5
Admitted to IC[2]		4.4	4.7	5.3	5.6

[1]Data is displayed as median, with the first and third quartile given within brackets.
[2] p < 0.05 (comparison between respondents 6 month and respondents 12 month follow-up questionnaire).
[3] p < 0.001 (comparison between non-respondents and respondents 6 month and respondents 12 month follow-up questionnaire).
RUNMC, Radboud University Nijmegen Medical Centre; BDI, Beck Depression Inventory; IES, Impact of Event Scale; ISS injury Severity Score; AISH, Abbreviated Injury Scale of the Head; AIS, Abbreviated Injury Scale; CT, computed tomography; IC, intensive care.

Prevalence of depression and PTSD

With reference to the respondents that completed the 6 month follow-up questionnaire, BDI and IES scores were available for 92% and 96% of the patients (Figure 10.1). At the 12 month follow-up, BDI and IES scores were available for 97% and 99% of the patients, respectively. Table 10.2 shows the characteristics of the respondents with a BDI score of 19 or higher, which indicates the likely presence of depression, and respondents with an IES score of 35 or higher, which indicates the likely presence of PTSD. At 6 month follow-up, 6.5% of the respondents had depression and 8.7% of the respondents had probable PTSD. A total of 3.4% of the patients met the criteria of both depression and probable PTSD. At 12 month follow-up, the prevalence rates of depression and PTSD were 6.8% and 8.5%, respectively and 2.5% met the criteria for both depression and PTSD. In total, this means that at six months, 11.8% had and IES and/or BDI score that indicated PTSD and/or depression, and at 12 month follow-up, 12.8% had depression and/or PTSD.

Table 10.2 Characteristics of the respondents, in jury and post-injury care, stratified by presence of depression and/or probable PTSD

	No depression/PTSD		Depression, no PTSD		PTSD, no depression		Depression and PTSD	
	6 months (%)	12 months (%)	6 months (%)	12 months (%)	6 months (%)	12 months (%)	6 months (%)	12 months (%)
Total	78.7%	84.0%	3.1%	4.3%	5.3%	6.0%	3.4%	2.5%
N	627	237	25	12	42	17	27	7
Mean IES-score[1] (SD)	7.0 (8.9)	6.6 (9.0)	18.0 (9.8)	15.3 (11.4)	44.9 (6.0)	44.7 (7.3)	47.9 (11.7)	48.7 (12.2)
Powerful impact (IES=35–43)	–	–	–	–	50.0	58.8	44.4	42.9
Severe impact (IES≥44)	–	–	–	–	50.0	41.2	55.6	57.1
Mean BDI-score[1] (SD)	4.1 (4.6)	3.7 (4.1)	24.8 (6.1)	27.0 (7.0)	9.5 (5.0)	9.0 (4.8)	28.1 (8.5)	27.9 (9.1)
Mild (BDI=19–20)	–	–	24.0	25.0	–	–	14.8	28.6
Moderate (BDI=21–30)	–	–	60.0	41.7	–	–	51.9	28.6
Severe (BDI≥31)	–	–	16.0	33.3	–	–	33.3	42.9
Socio-demographics								
Age								
<50	59.6	53.2	56.0	58.3	57.1	35.3	66.7	57.1
≥50	40.4	46.8	44.0	41.7	42.9	64.7	33.3	42.9
Sex								
Male	64.1	60.3	56.0	50.0	50.0	47.1	44.4	28.6
Female	35.9	39.7	44.0	50.0	50.0	52.9	55.6	71.4
Household composition								
Alone	23.1	21.6	35.3	18.2	19.4	37.5	47.1	42.9
Not alone	76.9	78.4	64.7	81.8	80.6	62.5	52.9	57.1
Unknown	*150*	*6*	*8*	*1*	*6*	*1*	*10*	*0*
Educational level								
Primary and lower	23.9	25.3	31.6	33.3	43.2	46.7	50.0	28.6
Middle and higher	76.1	74.7	68.4	66.7	56.8	53.3	50.0	71.4
Unknown	*146*	*4*	*6*	*0*	*5*	*2*	*7*	*0*
Physical								
Comorbid disease								
No comorbidity	69.5	68.0	64.7	66.7	42.9	16.7	58.8	57.1
Comorbid disease(s)	30.5	32.0	35.3	35.3	57.1	83.3	41.2	42.9
Unknown	*191*	*31*	*8*	*0*	*7*	*5*	*10*	*0*
Injury mechanism								
Road traffic accident	46.1	41.4	36.0	50.0	55.0	52.9	46.2	28.6
Fall	34.9	35.9	48.0	25.0	30.0	47.1	34.6	28.6
Sports	12.4	13.5	0.0	8.3	2.5	0.0	0.0	0.0
Assault	4.3	4.6	12.0	0.0	10.0	0.0	15.4	28.6
Other	2.2	4.6	4.0	16.7	2.5	0.0	3.8	0.0
Unknown	*0*	*0*	*0*	*0*	*2*	*0*	*1*	*0*

Table 10.2 (continued)

	No depression/PTSD		Depression, no PTSD		PTSD, no depression		Depression and PTSD	
	6 months (%)	12 months (%)	6 months (%)	12 months (%)	6 months (%)	12 months (%)	6 months (%)	12 months (%)
Injury severity								
ISS[1]	6 (4–13)	8 (5–14)	9 (4.5–16.5)	9.5 (3.3–22.3)	10 (5–21)	6.0 (4.5–21.5)	8 (5 –17)	2 (2–8)
AISH[1]	2 (2–2)	2 (2–2)	2 (1.5–2.5)	2 (1–2.8)	2 (1–3)	2 (1.5–3)	2 (1–2)	1 (1–2)
Head AIS 0–1	24.6	23.2	24.0	33.3	35.7	23.5	25.9	71.4
Head AIS 2–3	67.1	68.8	60.0	50.0	50.0	58.8	59.3	28.6
Head AIS 4–5	8.3	8.0	16.0	16.7	14.3	17.6	14.8	0.0
CT scan								
No CT scan	6.7	7.2	4.0	0	7.1	5.9	3.7	14.3
CT scan, no abnormalities	82.0	78.1	72.0	83.3	64.3	76.5	85.2	85.7
CT scan, abnormalities	11.3	14.8	24.0	16.7	28.6	17.6	11.1	0.0
Care								
Admitted to hospital	51.4	58.6	60.0	75.0	73.8	58.8	74.1	57.1
Admitted to IC	4.1	5.5	12.0	8.3	7.1	5.9	7.4	0.0

[1] Continuous variable.

PTSD, post-traumatic stress disorder; IES, Impact of Event Scale; BDI, Beck Depression Inventory; ISS, Injury Severity Score; AISH, Abbreviated Injury Scale of the Head; CT, computed tomography; IC, intensive care; SD, standard deviation.

Risk factors for developing depression and PTSD

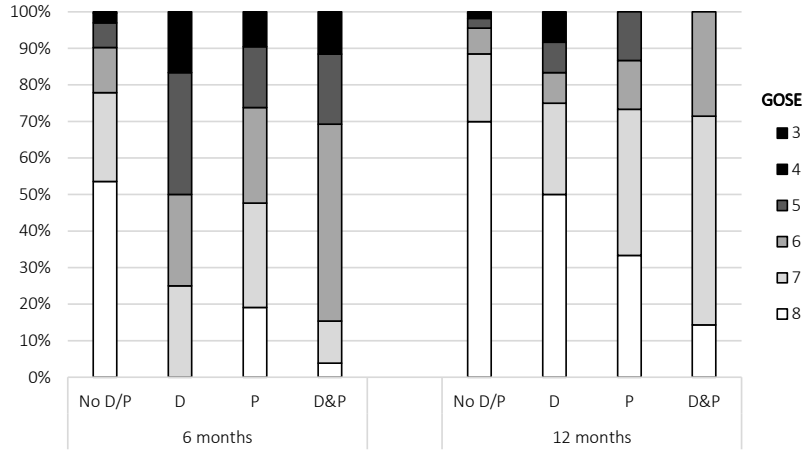
Univariate logistic regression analyses showed that lower educational level, living alone, comorbid disease, and hospital admission (all, p<0.006) were significantly associated with depression and/or probable PTSD at 6 month follow-up. At 12 month follow-up, lower education was significantly associated with depression and/or probable PTSD. Multivariate logistic regression analysis, including socio-demographic, physical and health care variables, indicated that living alone was an independent predictor of depression and/or probable PTSD (6 month OR=3.8; 95%CI [1.4 – 9.9]; p<0.006; 12 month OR=10.2; 95%CI [2.2 – 47.4]; p<0.006).

Functional outcome

TBI patients with depression and/or PTSD had significantly lower GOSE scores, compared with TBI without depression and probable PTSD (6 month Z=-9.3, p<0.001; 12 month Z=-3.9; p<0.001). The outcomes on the GOSE 6 and 12 months after sustaining the injury are presented in Figure 10.2.

To examine the correlation between depression and PTSD and functional outcome, we performed a logistic regression analysis of admission variables (age, sex, GCS, number of days in hospital) and BDI and IES scores against GOSE. The results showed that apart from number of days in hospital, BDI score is correlated with unfavorable outcome at 6 and 12 month follow-up (6 month OR=1.15; 95%CI [1.11 – 1.21]; 12 month OR=1.06; 95%CI [1.02 – 1.11]). IES score is correlated with unfavorable outcome at 6 month follow-up (OR=1.03; 95%CI [1.01 – 1.04]).

Figure 10.2 Mean Glasgow Outcome Scale Extended (GOSE) scores at 6 and 12 month follow-up of mild TBI patients with and without depression and post-traumatic stress disorder (PTSD)



No D/P: no depression and/or PTSD; D: depression but no PTSD; P: PTSD but no depression; D&P: depression and PTSD.

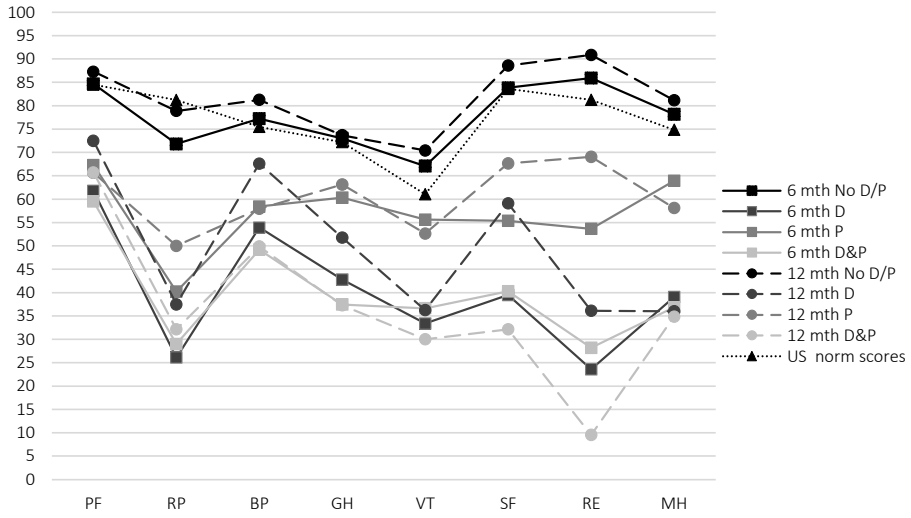
Health-related quality of life

SF-36

At 6 and 12 month follow-up, TBI patients with depression and/or probable PTSD had significantly lower scores in all SF-36 categories. At 6 and 12 month follow-up, TBI patients with depression and/or PTSD had lowest mean scores on the role emotional (difference in mean score six months (Δ, 22–81), social functioning (Δ, 21–57), and role physical (Δ, 25–47). The mean physical and mental health summary

scores of TBI patients without depression/PTSD were 49 and 53, respectively, whereas for patients with depression/PTSD the mean summary scores ranged from 41–42 for physical health and 30–44 for mental health. Figure 10.3 illustrates the SF-36 scores for TBI patients with and without depression and/or PTSD at six and 12 months post-injury, and the US norm scores.[18]

Figure 10.3 Mean scores on the 36-item Short-Form Health Survey (SF-36) at 6 and 12 month follow-up of mild TBI patients with and without depression and post-traumatic stress disorder (PTSD)



No D/P: no depression and/or PTSD; D: depression but no PTSD; P: PTSD but no depression; D&P: depression and PTSD; PF: physical functioning; RP: role physical; BP: bodily pain; GH: general health; VT: vitality; SF: social functioning; RE: role emotional; MH: mental health.

PQoL

At 6 month follow-up the mean PQoL score for TBI patients without depression/PTSD was 8.1, with 28% of patients who were dissatisfied with their functioning (PQoL <7.5). For TBI patients with depression, PTSD, or both, the mean PQoL scores were 4.6, 6.9, and 4.2 respectively ($F=49.3$; $p<0.001$). Of these patients, 53% to 100% were dissatisfied with their functioning. At 12 month follow-up, the mean PQoL scores for TBI patients without depression, with depression, without PTSD, and with PTSD were 8.1, 5.8, 6.4, 3.9 respectively ($F=16.2$; $p<0.001$), with 25%, 90%, 64%, and 100% of patients who were dissatisfied with their functioning.

10.4 DISCUSSION

Depression and PTSD are common in a comprehensive population of Dutch patients with mild TBI. Six months after sustaining the injury 12% had an IES and/or BDI score that indicated PTSD and/or depression. At 12 month follow-up, 13% had depression and/or PTSD. The depression and PTSD prevalence rates found in this study were higher than the depression (5.2–5.8%) and PTSD (3.3–3.8%) prevalence rates in the general Dutch population.[32-35]

Reported prevalence rates of PTSD and depression following TBI vary widely. Depression prevalence rates vary from 17–61%,[3,4] and PTSD prevalence rates range from 0–50%.[5] The prevalence rates that were found are dependent on many aspects, including cause and severity of the TBI, patient subgroup,

methods used to assess depression, and PTSD and follow-up time.[36] The majority of studies that focused on PTSD following TBI found prevalence rates lower than 20%.[37] The PTSD prevalence rates that we found are comparable to those reported by studies that included a self-report inventory to assess PTSD symptoms at 6 month follow-up.[38-42] Bombardier and colleagues[38] found that 11% of 124 TBI patients of all severity levels met PTSD criteria some time during the first six months, however, point prevalence at six months was between 2% and 3%, which is much lower than the PTSD prevalence rates we found. Greenspan and colleagues,[41] on the other hand, found a point prevalence of 11% at 6 month follow-up among 198 TBI patients. Williams and colleagues[42] reported a PTSD prevalence rate of 18% among a sample of 66 injury patients and Ohry and colleagues[40] found a much higher prevalence rate of 33% among a sample of severe brain injury patients. Depression prevalence rates assessed with the BDI varied even more. Three studies reported depression prevalence rates of 11%,[43] 24%,[44] and 46%,[45] respectively.

Detection of depression and PTSD in patients with traumatic brain injury is complicated, because several symptoms that result from TBI are similar to those of PTSD or depression.[46] As a result, a patient with TBI and depression or PTSD may be diagnosed with only one of the two conditions, or with both conditions while there is only one condition.[47-50] In addition, patients with TBI may have difficulty answering questions from the questionnaire used to diagnose depression and PTSD. Therefore, it is of great importance that accurate screening tools are used with acceptable sensitivity and specificity.

An independent predictor of depression was living alone. Previous research has shown that living alone increases the likelihood of depressive symptoms both among TBI patients and the general population, as well as in certain other subgroups, such as the elderly, immigrants or patients who suffer the consequences of a stroke or myocardial infarction. Insight into the predictors of depression and PTSD may help health care providers identify TBI patients at risk for depression and/or PTSD. Further investigation of predictors of depression and PTSD among TBI patients, particularly of subgroups of TBI patients (e.g. young adults or adults), may provide opportunities for prevention and early treatment of depression and PTSD.

Risk factors for psychiatric illness following TBI that are often reported are female sex, young age, lower educational level, lower GCS scores, and previous psychiatric illness or alcohol abuse.[51-53] In our study, previous psychiatric illness may be captured in the variable comorbidity. Unfortunately, the data on comorbidity did not allow the identification of TBI patients with psychiatric comorbidity for a more detailed analysis of the relationship between psychiatric comorbidity and depression and/or PTSD. However, it should be noted that psychiatric illness and TBI may share risk factors.[53]

Regarding functional outcome and HRQL, we found that among respondents, depression and/or PTSD was associated with a significantly lower mean GOSE, SF-36 and PQoL summary score. Previous studies showed similar significant effects of PTSD and depression on functional outcome and HRQL among injury patients.[10,11,21,52,54-58] Although these studies used different instruments to measure functional outcome or HRQL (e.g. SF-36, Quality of Well Being Self-Administered Scale, the EuroQOL five dimensions questionnaire, etc.), each of these studies reported a considerable decrease of HRQL at each time-point of measurement, even after correction for possible confounders, such as comorbidity and hospitalisation. This concurs with the findings by O'Donnell and colleagues,[6] who found that psychiatric symptoms play a substantial role in the development and maintenance of longterm disability measured with the World Health Organisation Disability Assessment Schedule. However, it should be

noted that in the current study, it was not possible to ascertain a cause-effect relationship between depression and/or PTSD and impaired functional outcome and HRQL. Depression and PTSD may raise a barrier for physical recovery or conversely, severe injury, and no or a slow recovery may induce depression and/or PTSD.

Strengths and limitations

A main limitation of our study was the low response rate of 15% at 12 month follow-up and that there may be selection bias at the two follow-up moments of the study. Therefore, the finding that depression and PTSD prevalence rates among TBI patients are higher, compared with the general population, cannot be extrapolated to the mild TBI population. Comparison of the characteristics of responders and non-responders to the 12 month follow-up survey showed that respondents who filled in both the 6 and 12 month questionnaire were older and more likely to be female, though these differences were not significant. The low response rates may have led to selection bias and in turn, to underestimation or overestimation of the prevalence of depression and PTSD.[32] In our study, there was the risk of underestimation of depression, since patients who met the threshold for depression at 6 month follow-up were significantly less likely to respond to the 12 month questionnaire.

In the current study, a large number of outcome measures were included in the follow-up questionnaire. This may affect statistical power, because there is an increased risk of attaining a significant finding. To adjust for this, the use of adjusted p values has been recommended, though other researchers have debated that this may lead to incorrect conclusions.[59,60] In this study, the p values were adjusted for the multiple outcome measurement.

This study used a self-report questionnaire to identify cases of depression and PTSD. It should be noted that self-report questionnaires are not designed to diagnose mental disorders according to the DSM-IV. As a result, cases identified with symptoms of depression or PTSD may not meet the DSM-IV criteria of clinical depression or PTSD, and conversely. In our study, the IES was used to measure PTSD. The IES measures symptoms of two of the three main PTSD criteria.[61] To avoid over-diagnosing PTSD in a comprehensive population with a relative low PTSD prevalence, we used a high IES cut-off to increase specificity.

Another issue with the use of self-report instruments to measure functional outcome, HRQL, depression, and PTSD is that TBI patients had to fill out lengthy and complex questions. It has been debated whether TBI patients have the skills to provide useful and complete answers to complex questions.[62] The more complex HRQL instruments, such as the SF-36, have been shown to be difficult to complete by the general population,[63] let alone by TBI patients who may have cognitive problems. The use of self-report questionnaires may have led to an underestimation of impact on functional outcome and HRQL, since patients with a higher degree of cognitive problems may not have been able to fill in the questionnaire. Comparison of the response rate of patients with a GSC >8 and GSC ≤8 showed that the latter group of patients were significantly less likely to respond to the 6 month follow-up questionnaire. Further, because the SF-36 and PQoL were self-reported by patients, it is unclear if and to what extent the self-reported assessments of HRQL are biased by depression and/or PTSD and consequently, resulted in lower HRQL.

Unlike the PQoL and the SF-36, the GOSE was assessed by health care professionals and may therefore have been less prone to subjectivity. A limitation of the GOSE, however, is that it measures functional

outcome with eight rather broad categories that are insensitive to subtle changes in functional outcome and quality of life.[17]

Conclusions

We conclude that among respondents with mild TBI, depression and/or PTSD are associated with a considerable decrease in functional outcome and HRQL. The cause-effect relationship between depression and/or PTSD and impaired functional outcome and HRQL should be further investigated, as well as predictors of depression and PTSD to enhance early diagnosis and treatment.

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PART IV

Guidelines and adherence

Chapter 11

Adherence to guidelines in adult patients with traumatic brain injury:

a living systematic review

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ABSTRACT

Background Guidelines aim to improve the quality of medical care and reduce treatment variation. The extent to which guidelines are adhered to in the field of traumatic brain injury (TBI) is unknown. The objectives of this systematic review were to (1) quantify adherence to guidelines in adult patients with TBI, (2) examine factors influencing adherence, and (3) study associations of adherence to clinical guidelines and outcome.

Methods We searched EMBASE, MEDLINE, Cochrane Central, Pubmed, Web of Science, PsycINFO, SCOPUS, CINAHL, and grey literature in October 2014. We included studies of evidence-based (inter)national guidelines that examined the acute treatment of adult TBI patients. Methodological quality was assessed using the Research Triangle Institute item bank and Quality in Prognostic Studies Risk of Bias Assessment Instrument.

Results Twenty-two retrospective and prospective observational cohort studies, reported in 25 publications, were included, describing adherence to 13 guideline recommendations. Guideline adherence varied considerably between studies (range 18–100%) and was higher in guideline recommendations based on strong evidence compared to those based on lower evidence, and lower in recommendations of relatively more invasive procedures such as craniotomy. A number of patient-related factors, including age, Glasgow Coma Scale and intracranial pathology, were associated with greater guideline adherence. Guideline adherence to Brain Trauma Foundation guidelines seemed to be associated with lower mortality.

Conclusions Guideline adherence in TBI is suboptimal and wide variation exists between studies. Guideline adherence may be improved through the development of strong evidence for guidelines. Further research specifying hospital and management characteristics that explain variation in guideline adherence is warranted.

11.1 INTRODUCTION

Traumatic brain injury (TBI) is a major public health concern affecting approximately 150–300 per 100,000 people annually in Europe.[1] The World Health Organisation has predicted that TBI will be one of the leading causes of death and disability worldwide by the year 2020.[2]

The care for TBI patients is often complex and multidisciplinary. Guidelines, protocols and care pathways have been developed to improve quality of care, to reduce variation in practice and to ensure that evidence-based care is optimally implemented.[3]

A 2013 systematic review[4] found that the use of protocols in the management of severe TBI in the intensive care unit (ICU) led to improved patient outcomes. However, the findings were based on observational studies that did not report on adherence rates. Without an understanding of adherence rates, the improved outcomes stated in the review cannot be directly attributed to the use of protocols.

Guideline adherence can be defined as the proportion of patients treated according to a guideline recommendation, which often represents evidence-based or best practice care. Previous studies have found that guideline adherence in medicine is generally low[5-7] and varies widely across centers,[7,8] medical condition,[9] types of guideline,[10,11] and time period.[8,10] As a result, many patients do not receive evidencebased care, while others receive unnecessary care that may even be harmful.[5] To date, no systematic review of the literature about guideline adherence in TBI has been conducted.

The aim of this systematic review was to provide a comprehensive overview of professionals' adherence to guidelines in adult TBI patients. The objectives were to 1) quantify adherence to guidelines in adult patients with TBI, 2) explore factors influencing adherence to TBI guidelines in those studies reporting on adherence, and 3) examine the association between adherence to guidelines and outcome in patients with TBI in those studies reporting on adherence.

11.2 METHODS

This review was conducted and reported in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement.[12] Details of the protocol for this systematic review were registered on PROSPERO (registration number CRD42014012863) and can be accessed at http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42014012863.

This review is being prepared as a '*living systematic review*' as part of the CENTER-TBI project[13] (www.center-tbi.eu). A living systematic review is a high quality, up-to-date, online summary of health research that is updated as new research becomes available.[14] This means that the searches will be re-run frequently and new studies will be incorporated into the review, with revisions to recommendations as appropriate. We will seek to publish regular updates.

Information sources

A comprehensive literature search was conducted on October 22nd 2014. Search strategies were developed in consultation with search experts using a combination of subheadings and text words (Appendix 11.A). The databases EMBASE, MEDLINE (via Ovid SP), Cochrane Central, Pubmed as supplied by publisher, Web of Science, PsycINFO, SCOPUS and CINAHL were searched. In addition, grey literature was examined via Google Scholar, opengrey.eu and dissertation databases (openthesis.org,

dissertation.com). Reference lists and citation indices of the included papers and relevant reviews were inspected to identify additional relevant citations. All selected studies were downloaded to the reference management database Endnote X5[15] and duplicates were removed. We restricted the search to original articles published in English. There was no date restriction.

Inclusion and exclusion criteria and study selection

We used the following inclusion and exclusion criteria to select studies:

Study designs: We included retrospective and prospective cohort studies, cross-sectional studies, time series and controlled clinical trials. Reviews, qualitative studies, case reports and editorials were excluded.

Participants: Studies were included if they were conducted in adult patients with suspected or confirmed TBI. Studies including a mixed population (e.g. all trauma patients) were only included if they presented their results for TBI patients separately. Studies solely about children were excluded as other factors, such as radiation, might play a role in guideline adherence in this group. If studies presented results for children and adults separately, only the information on adults was extracted.

Guidelines: Evidence-based international and national clinical TBI guidelines were included. Evidence-based guidelines were defined as guidelines for which evidence was found in quantitative research. We included studies analysing adherence to a complete guideline or protocol as well as studies analysing adherence to one or more single guideline recommendations. Local and regional guidelines, and guidelines based on expert opinion were excluded. Studies were further excluded if they assessed adherence to guidelines not published or implemented during the study period.

Adherence: Adherence or compliance was conceptualised as the percentage of patients that were treated according to a guideline, a subset of guidelines or an individual recommendation of a guideline. This definition was chosen to enable comparison of adherence to different guidelines or guideline recommendations. Studies using self-reported adherence were excluded due to the risk of overestimation.[16]

Setting: Studies were included if they examined the acute curative care of TBI patients, in the prehospital setting, emergency department (ED), hospital ward care and intensive care unit (ICU).

The first review author (MC) screened all titles and abstracts and deleted obviously irrelevant citations. After the initial selection, two independent reviewers (MC and ACS) screened the remaining citations on title and abstract and obtained those selected in full text. Results were compared and any disagreement was resolved by discussion or consulting a third author (SP). The search process was documented according to the PRISMA flowchart.[12]

Data collection and assessment of methodological quality

Two reviewers (MC and ACS) independently extracted data and assessed the risk of bias of included studies. Any discrepancies were resolved by discussion or consulting a third author (SP).

A data extraction form was developed based on the Effective Practice and Organisation of Care Cochrane Review Group (EPOC) data collection checklist,[17] and the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement.[18] Additionally, topic-relevant criteria about guidelines, adherence, and influencing factors were extracted. Guideline recommendations were classified as ‘strong’ or ‘weak/moderate’ recommendations. Strong recommendations were defined as

being based on good quality randomised controlled trials (RCTs). Weak or moderate recommendations were defined as being based on moderate or poor quality RCTs, cohort studies, case control studies or case series.

We developed three risk of bias forms to rate the risk of bias in quantifying adherence (objective 1), exploring factors influencing adherence (objective 2) and examining the association between adherence and outcome (objective 3). Risk of bias forms were based on items from the Research Triangle Institute (RTI) Item Bank for observational studies[19,20] (objective 1 and 3) and the Quality in Prognostic Studies (QUIPS) risk of bias tool[21] (objective 2). The risk of bias was assessed for each of the three objectives separately as different risks are relevant in the three objectives. Moreover, it was possible that studies assessing more than one review objective had a low risk of bias for one objective but a high risk for another.

Risk of bias items were subdivided into six categories for every objective: selection bias/confounding, performance bias, attrition bias, detection bias, reporting bias and information bias[19,22] (Appendix 11.B). For every category, individual items were scored as high, low or unclear risk of bias.

If at least one item in a bias category was scored as high, the risk of bias within this category was scored as 'moderate risk'. If at least 50% of the items in a bias category were scored as high, the risk of bias category was scored as 'high risk'. Every study received a total risk of bias score for every objective which was equal to the highest score obtained in all risk of bias criteria.

Risk of bias was presented with a table divided by objective. Attrition and detection bias were not reported for objective 1 since these were considered irrelevant for the percentage adherence obtained. We accounted for risk of bias by narratively describing studies with a low (none of the criteria was rated as high risk of bias) and moderate (<50% of the criteria was rated as high risk of bias) risk of bias separately for the three objectives.

In order to enhance inter-rater reliability, data extraction and risk of bias forms were pilot-tested on three studies that were likely to be included in the review. Inter-rater reliability was assessed by calculating concordance rates between the two independent reviewers in data screening, data extraction and risk of bias assessment.

Data synthesis

Due to heterogeneity in settings, guidelines, populations, statistical methods and outcomes, meta-analytic techniques were not used. Instead, we conducted a narrative synthesis of results stratified by objective.

For every guideline recommendation that was examined in at least two studies, mean guideline adherence was calculated by adding up the total number of patients treated according to the guideline recommendation and subsequently dividing them by the total number of patients eligible for the guideline. In addition, the percentage adherence was presented separately for strong and moderate/weak recommendations. We also compared the differences in percentage adherence for relatively more invasive (e.g. intracranial pressure monitoring and intracranial operation) and less invasive (e.g. computer tomography scanning and anti-seizure prophylaxis) procedures separately. A total percentage adherence was not calculated, as there was considerable variation in guidelines and patient severity.

An overview of factors influencing adherence was conducted. We examined whether associations between predictive factors and adherence were positively or negatively directed and whether they were statistically significant ($p<0.05$). Additionally, we conducted an overview of the association between adherence and outcome and reported whether associations were positively or negatively directed and statistically significant.
All eligible studies were used for objective 1. Those that also reported factors influencing adherence and/or outcome were further analyzed for objective 2 and/or 3. There were no further specific inclusion criteria for these objectives. All results are presented before and after the exclusion of studies that were judged as high risk of bias.

Treatment of studies with multiple publications

Multiple publications refer to the situation where more than one article has been written based on the same dataset.[23] Multiple publications assessing the same guideline in an overlapping time period and setting were dealt with by extracting information from the study that could be used for the most study objectives. If the number of objectives was similar across studies with multiple publications, the article that included the largest number of patients was chosen. Articles from the same dataset that assessed different guidelines or that were conducted during a different study period or in a different setting, were analysed separately.

11.3 RESULTS

Study selection

A total of 1,903 citations were identified through the extensive search strategy (Figure 11.1). After removing duplicates, 912 were screened on citation and 518 obviously irrelevant records (determined on title) were removed. We screened 394 citations on title and abstract and excluded 310. We obtained 84 citations in full text of which 62 were excluded. Three additional citations were found via reference lists and citation indices. For an overview of related studies excluded at the full text stage, see Appendix 11.C. The concordance rates between the two independent reviewers were generally high in screening of title and abstract (91%), screening of full text (81%), and data extraction (93%).

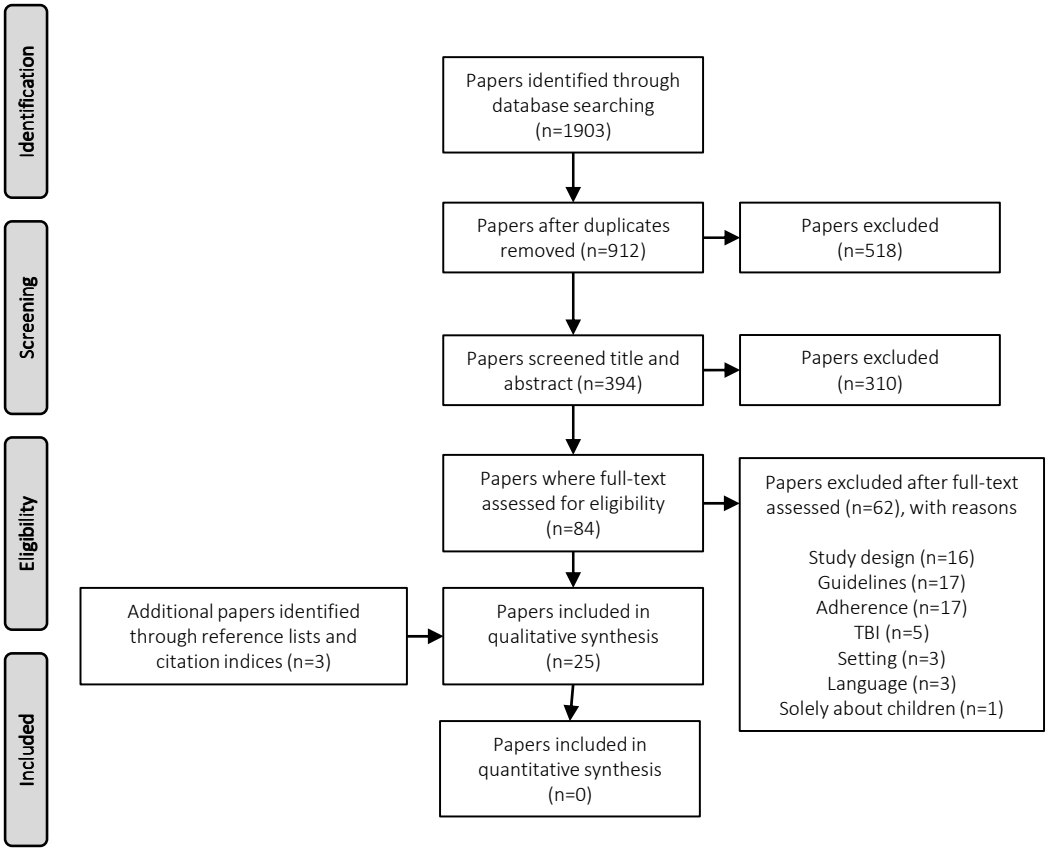
Study characteristics

We included 22 studies, reported in 25 publications (Table 11.1). Three articles were removed from the analyses because of multiple publications.[10,24,25] Two more studies were based on the same dataset,[26,27] but the study describing the least number of objectives[26] was still included for extracting the amount of adherence to another guideline recommendation.
All included studies used an observational cohort design with fourteen being retrospective[28-41] and eight being prospective.[26,27,42-47] Twelve studies described multicentre studies[26-31,34,36,40,41,44,46] with a median of eight (range 2–155) hospitals included. All studies were conducted in North America (n=9) or Europe (n=13) and were published between 2002 and 2014. Six of the included studies[33,40,41,43,44,46] examined adherence to more than one guideline recommendation (mean number of guideline recommendations in studies describing more than one guideline recommendation: 3.6; range 2–6). The sample size in the included studies ranged from n=27[38] to n=10,628[28] patients.

Adherence to a total of thirteen guideline recommendations was assessed, including those from the Brain Trauma Foundation (BTF),[48] National Institute of Health and Clinical Excellence (NICE)[49] and Scandinavian guidelines for the initial management of minimal, mild and moderate head injury.[50] The most frequently studied guideline recommendation was the BTF guideline for Incracranial Pressure (ICP) monitoring (n=9). Other guidelines that were studied in more than one study were the NICE guidelines for CT scanning (n=5), the BTF guidelines for prehospital intubation (n=7), transport (n=2), steroids (n=2) and resuscitation (n=2), and the Scandinavian guidelines for computer tomography (CT) scanning and hospital admission (n=2).

Six studies were performed during ICU admission, seven during an emergency department (ED) visit and three during the prehospital phase. The remainder (six studies) reported on a combination of these settings. The majority of studies reported on guideline recommendations that were judged as weak/moderate. Only seven studies included strong recommendations. The majority of studies were funded by government organisations. One study[29] was funded by the BTF.

Figure 11.1 PRISMA flowchart of the selection process



Reasons for exclusion full text: *Study design*: the study was no prospective or retrospective cohort study, RCT, clinical trial, cross-sectional study or time series; *Guideline*: the study did not describe a guideline, the guideline was local or not evidence-based, the guideline was not implemented or disseminated before the study period; *Adherence*: the study did not measure adherence per patient, adherence was self-reported; *TBI*: the study was not about TBI patients; *Setting*: the study was not conducted during the hospital and prehospital setting; *Language*: the study was not published in English; *Solely about children*: the study did not include adults.
TBI: traumatic brain injury.
Figure is adapted from Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097.

Table 11.1 Characteristics of the included studies (n=22)

Study ID	Objective	Study design & Setting	Patients	Guideline & topic	Strength of recommen-dation*	Adherence operationalisation	Adherence (% (n adherent / n total))
Alali (2013)	1,2,3	Retrospective cohort (US, Canada) in 155 centers	Severe TBI, age ≥16	BTF (2007) – ICP monitoring	M/W	ICP monitor inserted	18% (1874/10628)
Andriessen (2011)	1[A]	Same dataset as Biersteker (2012)	Severe TBI, age ≥16	BTF (2007) – Prehospital intubation	M/W	Prehospital intubation performed	69% (234/339)
Biersteker (2012)	1,2,3	Prospective cohort (The Netherlands) in 5 centers	Severe TBI, age ≥16, intracranial pathology or 2/3 criteria: age >40, ED motor score ≤3 or systolic blood pressure <90mmHg	BTF (2007) – ICP monitoring	M/W	ICP monitor inserted	46% (123/265)
Bulger (2002)	1,3	Retrospective cohort (US) in 33 centers	Severe TBI, multitrauma, age ≥18. ICP monitoring: abnormal head CT	BTF (1995) – Prehospital intubation and ICP monitoring	M/W	Prehospital intubation performed ICP monitor inserted	43% (79/182) 58% (105/182)
Fakhry (2004)	1,3	Prospective cohort with historical control group (US)	Severe TBI, age >14	BTF (1995) – ICU management of severe TBI[B]	M/W	Following ICU protocol***	76% (466/611)
Farahvar (2012) *Gerber (2013)*	1,2,3	Retrospective analysis of prospectively collected database (US) in 22 centers	Severe TBI, intracranial pathology or 2/3 criteria: age >40, hypotension or GCS motor score ≤3; ICP lowering treatment on the first 2 days	BTF (2000) – ICP monitoring	M/W	ICP monitor inserted	83% (1084/1307)
Franschman (2012) *Franschman (2009)*	1	Retrospective cohort (The Netherlands) in 3 centers	Severe, CT scan confirmed TBI, age >10	BTF (2000) – prehospital intubation	M/W	Prehospital intubation performed	88% (NR/372)
Griesdale (2010)	1,2,3	Retrospective cohort (Canada)	Severe TBI, intracranial pathology	BTF (2000) – ICP monitoring	M/W	ICP monitoring with EVD inserted	61% (98/161)
Harr (2011) *Heskestad (2012)*	1,2	Retrospective cohort (Norway)	ICD-10 diagnosis head injury, age ≥15	Scandinavian guidelines (2000) – CT scanning & hospital admission	M/W	CT scanning and hospital admission according to algorithm	61% (520/860)
Härtl (2006)	1,2,3	Same dataset as Farahvar (2012)	Severe TBI	BTF (2000) – Direct transport	M/W	Direct transfer to trauma center	77% (864/1118)

Table 11.1 (continued)

Study ID	Objective	Study design & Setting	Patients	Guideline & topic	Strength of recommen-dation*	Adherence operationalisation	Adherence (% (n adherent / n total))
Haydon (2013)	1	Retrospective cohort (UK)	Head injury, age ≥16, received a CT scan	NICE CG 56 (2007) – CT scanning	S	Documentation of ≥1 CT scan requirements Performing CT scan ≤1 hour of request for all but three of indications Performing CT scan ≤8 hours in three other risk factors	84% (129/153) 86% (93/108) 100% (21/21)
Heskestad (2008)	1,2	Prospective cohort (Norway)	ICD-10 diagnosis head injury	Scandinavian guidelines (2000) – CT scanning & hospital admission	M/W	CT scanning and hospital admission according to algorithm	51% (259/508)
Mauritz (2008)	1,2,3	Prospective cohort in 13 tertiary care centers (Austria, Slovakia, Bosnia and Macedonia)	Severe TBI	BTF (1995) – Prehospital intubation, direct transport, steroid use	M/W M/W M/W S	Following BTF guidelines for: Prehospital intubation Direct transfer Steroids not used	 58% (673/1172) 72 (534/746) 83% (468/564)
Mooney (2011)	1	Retrospective cohort (UK) in 2 centers	Head injury	NICE CG56 (2007) – CT scanning	S	CT performed according to criteria	97 (741/762)
Prowse (2009)	1	Retrospective cohort (UK)	Isolated head injury	NICE CG56 (2007) – CT scanning	S	NICE criteria reported in patients that had a CT scan performed	70% (23/33)
Ravindran (2007)	1	Retrospective cohort (UK)	Head injury	NICE CG4 (2003) – CT scanning	S	NICE criteria reported in patients that had a CT scan performed out of hours	100% (27/27)
Rognas (2013)	1	Prospective cohort (Denmark)	Severe TBI	BTF (2007) and Scandinavian Guidelines on prehospital management of TBI (2008) – prehospital intubation	M/W	Prehospital intubation performed	93% (50/54)
Rusnak (2007)	1,3	Prospective cohort (Austria) in 5 centers	Severe TBI	BTF (1995) – various recommendations	 M/W M/W M/W M/W S M/W	Following BTF guidelines (see Rusnak (2007) Table 11.2) for: Resuscitation of BP & O2 Indications for ICP monitoring Hyperventilation Barbiturates Steroids Anti-seizure prophylaxis	 79% (217/274) 68% (283/415) 92% (363/393) 83% (269/326) 89% (362/409) 89% (360/407)

11.1 (continued)

Study ID	Objective	Study design & Setting	Patients	Guideline & topic	Strength of recommen-dation*	Adherence operationalisation	Adherence (% (n adherent / n total))
Shafi (2014)	1,2,3	Retrospective cohort (US) in 11 centers	Severe TBI patients, age <99, intracranial pathology	BTF (2007) – various recommendations		Following BTF guidelines (see Shafi (2014) Table 11.1):	
					M/W	Endotracheal intubation	92% (1890/2056)
					M/W	Resuscitation	75% (48/64)
					M/W	ICP monitoring	52% (818/1569)
					M/W	ICP directed therapy	76% (742/978)
Shafi (2014b)	1	Retrospective cohort (US) in 5 hospitals	Severe TBI, age ≥16	BTF – various recommendations	M/W	Prehospital intubation performed	94% (468/497)
					M/W	Intracranial pressure monitoring in trauma patients with a GCS ≤8 and intracranial bleed on head CT and endotracheal intubation	39% (100/257)
					M/W	Craniotomy in patients with GCS ≤8 and intracranial bleed on head CT	20% (66/326)
Shravat (2006)	1	Retrospective cohort (UK)	Head injury	NICE CG56 (2007) – CT scanning	S	Whether CT had been requested within existing NICE criteria	100% (472/472)
Talving (2013)	1,2,3	Prospective cohort (US)	Severe TBI, age >18, meeting BTF criteria for ICP monitoring	BTF (2007) – ICP monitoring	M/W	ICP monitor inserted	47% (101/216)

*S = strong recommendation, the guideline recommendation was based on good quality randomised controlled trials; M/W = strong/weak recommendation, the guideline recommendation was based on lower level evidence.

[A] Due to multiple publications, only the amount of intubation adherence is assessed from Andriessen. For ICP monitoring see Biersteker (2012).

[B] See appendix Fakhry (2004) for the ICU protocol.

[C] Authors stated that 98 out of 171 patients got an ICP monitor placed. They also stated that 10 of the patients that got no ICP monitor placed, did not had an indication. We therefore recalculated the percentage adherence without those 10 patients.

TBI: traumatic brain injury; NR: not reported; AIS: Abbreviated Injury Scale; BTF: Brain Trauma Foundation; ICP: intracranial pressure; LOS: length of stay; GCS: Glasgow Coma Scale; ED: emergency department; GOSE: Glasgow Outcome Scale Extended; US: United States of America; CT: computed tomography; ICU: intensive care unit; RLAS: Rancho Los Amigos Scale; ISS: Injury Severity Score; EVD: external ventricular drainage; ICD: International Classification of Diseases; HI: head injury; NICE: National Institute of health and Clinical Excellence; HIC: high income country; UMIC: upper middle income country; LMIC: lower middle income country; BP: blood pressure; O_2: oxygen; RBC: red blood cell; SBP: systolic blood pressure; CPP: cerebral perfusion pressure.

Severe TBI = GCS <9.

Methodological quality

Overall, the methodological quality of studies was good, with the majority of studies judged at low risk of bias in most domains (Table 11.2). For studies measuring the amount of adherence to guidelines (objective 1, n=22), 19 had an overall low risk of bias. The remainder (n=3)[34,36,38] received a high risk of bias score, due to high scores on selection bias / confounding.

For studies exploring factors influencing adherence to guidelines (objective 2, n=10), respectively three and four studies received a low and moderate overall risk of bias score. Three studies[34,43,44] were judged as being at high risk of bias due to selection bias / confounding.

None of the studies examining the association between adherence to guidelines and outcome (objective 3, n=11) had an overall low risk of bias. Nine studies received a moderate risk of bias score and two studies[42,46] a high risk of bias score. This was due to selection bias / confounding, performance bias and information bias. None of the studies sufficiently isolated the impact of the guideline studied from concurrent interventions. In addition, some studies used inappropriate control groups or did not adjust for confounders while others calculated adherence- or quality scores that were based on non-validated scoring mechanisms or partly based on guideline recommendations that were not evidence-based nor (inter)national.

Concordance rates between independent reviewers in assessing risk of bias was high (92%) and any discrepancies were resolved by discussion or consulting a third author.

Amount of adherence to guidelines

The amount of guideline adherence was reported in all included studies (Table 11.1) and varied considerably between (range 18%–100%) and within (range 0%–100%) studies. Excluding studies with a high risk of bias[34,36,38] did not influence this variation.

Among the guidelines that were examined by more than one study, adherence was the highest in NICE CT-scan guidelines[35-39] (mean 87%, range 70–100%) and the lowest in BTF Intracranial Pressure (ICP) monitoring guidelines[10,26,28-30,32,40,41,46,47] (mean 31%, range 18–83%). Studies about the NICE CT scan guidelines were all performed at the ED in the United Kingdom and included patients with head injury. The majority had a single-center design. Studies about ICP monitoring were performed in Europe and Northern America and performed during ICU admission. Most studies used a multi-center design. The studies with the lowest and highest percentage adherence to ICP monitoring guidelines were comparable multi-center studies performed in Northern America. The study with the highest percentage adherence was based on the TBI-Trac database, which is a database from the BTF aiming to track and improve adherence, while the study with the lowest percentage was based on general trauma databases. A visual display of adherence per guideline is provided in Figure 11.2. After removing studies with a high risk of bias (n=3), adherence to the NICE guidelines was 75%. Adherence to other guidelines did not differ substantially.

To assess whether strength of recommendation was related to guideline adherence, we divided guidelines into strong, and moderate/weak recommendations. Strong recommendations consisted of NICE CT scan guidelines, reported in five studies, and BTF steroids guidelines, reported in two studies. All other guideline recommendations were based on low levels of evidence. Mean adherence to strong recommendations was 93% (range 70%–100%) while adherence to moderate/weak recommendations was considerable lower (mean 49%, range 18%–94%). Percentages did not differ substantially after

removing studies that were found to be at high risk of bias. One study[42] was excluded from this analysis as it reported adherence to an ICU protocol that was based on both strong and moderate/weak recommendations.

In addition, we considered whether the invasiveness of the intervention was related to adherence. Across studies, relatively invasive interventions such as ICP monitoring and intracranial operations obtained a mean adherence rate of 30% (range: 8–83%), while less invasive interventions such as CT scanning and anti-seizure prophylaxis obtained a much higher adherence rate (mean: 79%, range 51–100%).

Figure 11.2 Percentage guideline adherence for various guideline recommendations

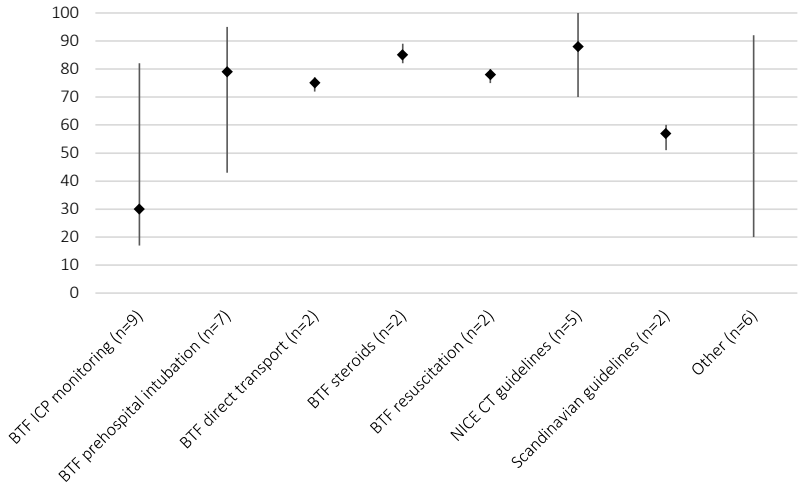


Figure displays lowest, highest and mean percentages adherence for various guideline recommendations. Numbers correspond with number of guideline recommendation and not to individual studies since some studies reported on multiple guideline recommendations. "Other" is a summary measure of following: BTF ICU protocol for patients with severe TBI,[42] BTF hyperventilation,[46] BTF barbiturates,[46] BTF anti-seizure prophylaxis,[46] BTF ICP directed therapy[40] and BTF craniotomy.[41] BTF: Brain Trauma Foundation; ICP: intracranial pressure; NICE: National Institute for Health and Care Excellence; CT: computer tomography.

Factors influencing guideline adherence

Ten studies identified factors influencing adherence (Table 11.3). Most studies assessed patient demographics and clinical characteristics. Three studies assessed treatment, hospital or country characteristics. Taking the results together, the BTF guidelines, in particular the ICP monitoring recommendations, were consistently more often adhered to in younger patients with extracranial injury and more severe TBI (indicated by Glasgow Coma Scale (GCS), Head Abbreviated Injury Scale (HAIS), abnormal pupillary reactions and intracranial pathology). The Scandinavian guidelines were more often adhered to in older patients with moderate head injury in comparison to mild and minimal head injuries. Among studies with a relatively low risk of bias that assessed factors influencing adherence using multivariable analyses, age was significantly associated with adherence in all studies (younger age is associated with greater adherence in severe TBI patients; older age is associated with greater adherence in minimal, mild and moderate TBI patients). Studies about ICP monitoring further reported that adherence was more often accomplished in patients with a lower GCS and the occurrence of intracranial pathology.

Table 11.2 Risk of bias assessment

Study ID	Selection bias / Confounding			Performance bias			Attrition bias		Detection bias		Reporting bias			Information bias			Highest score	Highest score	Highest score
	OB1	OB2	OB3	OB1	OB2	OB3	OB2	OB3	OB2	OB3	OB1	OB2	OB3	OB1	OB2	OB3	OB1	OB2	OB3
Alali (2013)	L	M	L	L	L	M	L	L	L	L	L	L	L	L	L	L	L	M	M
Andriessen (2011)	L	–	–	L	–	–	–	–	–	–	L	–	–	L	–	–	L	–	–
Biersteker (2012)	L	L	L	L	L	M	L	L	L	L	L	L	L	L	L	L	L	L	M
Bulger (2002)	L	–	L	L	L	M	–	L	–	L	L	–	L	L	–	L	L	–	M
Fakhry (2004)	L	–	H	L	–	H	–	L	–	L	L	–	L	L	–	L	L	–	H
Farahvar (2012)	L	M	L	L	L	M	L	L	L	L	L	L	L	L	L	L	L	M	M
Franschman (2012)	L	–	–	L	–	–	–	–	–	–	L	–	–	L	–	–	L	–	–
Griesdale (2010)	L	M	M	L	L	M	L	L	L	L	L	L	L	L	L	L	L	M	M
Harr (2011)	L	M	–	L	L	–	L	–	L	–	L	L	–	L	L	–	L	M	–
Härtl (2006)	H	H	L	L	L	M	L	L	L	L	L	L	L	L	L	L	H	H	M
Haydon (2013)	L	–	–	L	–	–	–	–	–	–	L	–	–	L	–	–	L	–	–
Heskestad (2008)	L	H	–	L	L	–	L	–	L	–	L	L	–	L	L	–	L	H	–
Mauritz (2008)	L	H	L	L	L	M	L	L	L	L	L	L	L	L	L	M	L	H	M
Mooney (2011)	H	–	–	L	–	–	–	–	–	–	L	–	–	L	–	–	H	–	–
Prowse (2009)	L	–	–	L	–	–	–	–	–	–	L	–	–	L	–	–	L	–	–
Ravindran (2007)	H	–	–	L	–	–	–	–	–	–	L	–	–	L	–	–	H	–	–
Rognas (2013)	L	–	–	L	–	–	–	–	–	–	L	–	–	L	–	–	L	–	–
Rusnak (2007)	L	–	L	L	–	M	–	H	–	L	L	–	L	L	–	M	L	–	H
Shafi (2014)	L	L	L	L	L	M	L	L	L	L	L	L	L	L	L	M	L	L	M
Shafi-b (2014)	L	–	–	L	–	–	–	–	–	–	L	–	–	L	–	–	L	–	–
Shravat (2006)	L	–	–	L	–	–	–	–	–	–	L	–	–	L	–	–	L	–	–
Talving (2013)	L	L	L	L	L	M	L	L	L	L	L	L	L	L	L	L	L	L	M

Table represents the risk of bias for the three objectives.
OB1: objective 1 (assessing the amount of adherence).
OB2: objective 2 (assessing factors influencing adherence).
OB3: objective 3 (assessing the association between adherence and outcome).
L: Low risk of bias; M: Moderate risk of bias; H: High risk of bias.

Factors that were studied but not significantly associated with adherence included race,[28,40] certain severity indices (GCS motor score[28]; Acute Physiology and Chronic Health Evaluation (APACHE) II score[32]), certain laboratory values (international normalised ratio and prothrombin time[47]; blood alcohol level[33]) certain complications (tachycardia[47]; hypoxia[47]), referral status[27] and structural hospital characteristics (hospital type[28]; number of beds[28]; trauma center designation[28]). For an overview of factors significantly associated with adherence in at least one study see Table 11.3. For a complete overview of all factors studied, see Appendix 11.D.

The association between guideline adherence and outcome

Eleven studies examined the association between guideline adherence and outcome (Table 11.4). All studies examined the BTF guidelines with six studies investigating ICP monitoring guidelines, one study examining direct transfer, and the remainder combining various BTF recommendations into a compliance or quality score.

Outcome measurements included in-hospital mortality,[28,29,32,40,42,47] two-week mortality,[30,34] 28-day mortality,[32] six-month mortality,[27] Glasgow Outcome Scale (GOS) and Rancho Los Amigos Scale (RLAS) at discharge,[42] 90-day Extended Glasgow Outcome Scale (GOSE),[46] six-month GOSE,[27] ICU survival,[44,46] and ICU and hospital length of stay (LOS).[27,29,42,47]

The majority of studies (n=8) analysed the adherence-outcome association with multiple regression adjusted for relevant confounders[30,34,40,44,46] or for propensity scores.[27,32,47] Two multi-center studies analysed the association on hospital level by dividing hospitals into quartiles based on their percentage adherence[28] or by dividing hospitals into having an aggressive or nonaggressive approach.[29] One study univariately assessed the association.[42]

Eight out of eleven studies reported a statistically significant association between adherence and a reduction in mortality with odds ratios ranging from 0.15 to 0.96.[28-30,34,40,42,44,47] One study additionally described an association between adherence and higher scores on GOSE and RLAS.[42] One study reported increased in-hospital mortality in those treated according to the guideline but no significant differences between groups in 28-day mortality.[32]

For ICU and hospital LOS, three studies[27,32,47] reported an association with longer LOS and one study reported an association with shorter LOS.[42] All other associations were non-significant.

After adjusting for the risk of bias by removing studies with a high risk of bias on at least one of the criteria and outcomes that have been univariately assessed, all but one of the nine remaining studies[32] reported an association between adherence and a reduction in mortality. Functional outcome was assessed in one study,[27] showing non-significant results. The association with LOS was assessed with multivariable analyses in two studies[29,47] showing contradictory results. Statistical methods and results can be found in Appendix 11.E.

Table 11.3 Factors significantly associated with adherence to guidelines in at least one study

	BTF – ICP monitoring					BTF – direct transport	BTF – various recommendations		Scandinavian guidelines	
	Alali (2013)	Biersteker (2012)	Farahvar (2012)	Griesdale (2010)	Talving (2013)	Härtl (2006)	Mauritz (2008)	Shafi (2014)	Harr (2011)	Heskestad (2008)
Patient and clinical characteristics										
Age	—[A]	—	—[A]	—[A]	—	+		—	++	+/–[A]
Male gender	—[A]	+	+[A]	+[A]	+[A]			++	+	+/–[A]
Insurance status	++[A1]							+/–		
Injury mechanism	++/—[A]	+/–[A]								
GCS	–[A]	—	–[A]	—[A]	—[2]			+/–[A]		
HISS									++	++[A]
HAIS	+[A]				+			++		
Comorbidity	—[A]							+/–[A]		
Extracranial injury		+[B]			++			+/–[A]		
Abnormal pupillary reactions		++	++[A]		–[A]					
Hypotension	—[A]	–[A]	–[A]	+[A]	—			—[4]		
Intracranial pathology	++[A]	++	+[A]	++[A]	++			++		
PTT					—					
Process, hospital and country characteristics										
Decompressive craniotomy/ craniectomy				++[A]	++[3]					
Teaching status	++[A]									
Gross national product							++[A]			

+ = Positive, non-significant effect; – = Negative, non-significant effect; ++ = Positive, significant effect; — = Negative, significant effect; +/– = Direction or statistical significance unknown. [A] predictor is solely univariately assessed; [B] predictor is significant in univariate analyses, but not in multivariable analyses.

[1] Commercial insurance vs noncommercial insurance (United States).

[2] Lowest GCS within 24 hours is statistically associated with adherence; median GCS was not statistically associated.

[3] Decompressive craniotomy within 4 hours is associated with adherence in univariate and multivariable analysis, decompressive craniotomy within 24 hours is only associated in univariate analysis.

[4] Authors measured systolic blood pressure. Higher systolic blood pressure is associated with more adherence.

GCS: Glasgow Coma Scale; HISS: Head Injury Severity Scale; HAIS: Head Abbreviated Injury Scale; PTT: Partial Thromboplasting Time.

Table 11.4 The association between adherence to guidelines and patient outcome

Study ID	Outcome variables	Direction of association[1]
Alali (2013)	In-hospital mortality	—
Biersteker (2012)	6 month mortality	–
	6 month unfavorable outcome	+
	ICU LOS	++*
	Hospital LOS	++*
Bulger (2002)	In-hospital mortality	—
	Hospital LOS	–
Fakhry (2004)	Mortality	—*
	ICU LOS	—*
	Hospital LOS	—*
	Unfavorable outcome (GOSE) at discharge	—*
	Lower RLAS at discharge	—*
Farahvar (2012) *Gerber (2013)*	2-weeks mortality	—
Griesdale (2010)	In-hospital mortality	++
	28-days mortality	+
	ICU LOS	++*
Härtl (2006)	2-weeks mortality	—
Mauritz (2008)	ICU mortality	–/—
Rusnak (2007)	ICU mortality	–
	90 days unfavorable outcome (GOS)	–
	ICU LOS	+*
	Hospital LOS	–*
Shafi (2014)	In-hospital mortality	—
Talving (2013)	In-hospital mortality	—
	ICU LOS	++
	Hospital LOS	++

[1] + = Positive, non-significant effect; – = negative, non-significant effect; ++ = positive, significant effect; — = negative, significant effect. The direction of the multivariable analyses were noted. If there was no multivariable analysis performed, the univariate analysis was reported and a * was noted.
* Univariate association adherence – outcome.

11.4 DISCUSSION

This systematic review provides an overview of adherence to guidelines, its determinants and association with outcomes in TBI patients. We included 22 studies, reported in 25 publications. Guideline adherence in TBI was found to be suboptimal overall, and varied widely between studies (from 18–100%) and within multi-center studies. Guideline recommendations based on strong evidence were more often adhered to in comparison with recommendations based on lower level evidence. Guideline adherence was also influenced by age and severity (indicated by intracranial pathology and lower GCS). Importantly, guideline adherence appears related to patient outcomes, as adherence to BTF (especially ICP monitoring) guidelines was associated with a reduction in mortality in all but one study after correction for risk of bias.

This systematic review included three objectives, and thereby provided an overview of the entire scope of adherence to guidelines in TBI. However, four important notes should be made regarding the completeness and applicability of the evidence. Firstly, despite the existence of over 100 evidence-based guideline recommendations,[51] adherence was assessed for only thirteen recommendations. Results can therefore not be generalised to all guideline recommendations. Similarly, the variability in adherence might have been confounded by the invasiveness of the recommended intervention. We found a lower adherence rate in studies about invasive interventions such as ICP monitoring and craniotomy in comparison to studies with less invasive interventions. Invasive interventions require more experience and skills within the institution and therefore may face greater barriers to be

implemented than less invasive interventions. Thirdly, no definitive conclusion about the efficacy of guidelines can be drawn from this review as we did not include any cluster RCTs. These results should encourage the conduct of cluster RCTs to more rigorously examine the efficacy of guidelines for TBI. Additionally, all included studies were conducted in Europe and North America. Hence, our findings are not generalisable to non-Western countries since lack of resources restricts the routine use of aggressive treatment strategies in these countries.[52] Related, our findings cannot be generalised to children as it is known that guideline adherence in children varies from guideline adherence in adults[36] and might also be influenced by other factors such as concern about radiation. Lastly, the majority of current TBI guidelines are not based on high quality evidence. TBI is however emerging as an important topic in research with large-scaled, high-quality multicenter studies conducted all over the globe.[13] These are likely to result in revised guidelines based on more rigorous evidence.[13] The findings of this review might not be generalisable to a situation in which TBI guidelines are based on robust evidence, which underlines the importance of keeping this systematic review, as well as other systematic reviews in the field of TBI, 'living'.

Overall, the methodological quality of the studies was good. The association between adherence to guidelines and outcome was however highly suspect for performance bias, as none of the studies sufficiently isolated the impact of the guideline studied from concurrent interventions. It is nevertheless plausible that patients who had, for example, an ICP monitoring inserted, also had a higher chance of receiving ICP lowering treatment, and that this therapy might have caused the association with outcome.

Although selection bias / confounding did not seem a major threat to validity in the association between adherence and outcome, the risk of bias form we used did not account for confounding by indication. Observational studies in critical care may easily suffer from confounding by indication, i.e. a different *a priori* risk of unfavourable outcome between those treated and those not treated according to the guideline.[53,54] Although the majority of studies made attempts to reduce the risk of confounding by multivariable analysis or propensity score adjustment, these methods may still insufficiently resolve the problem of confounding by indication as they do not account for unmeasured confounders.[54-56] This is in contrast to an RCT, where comparability between groups is achieved on measured and unmeasured characteristics. In this review, two studies defined guideline adherence at the level of the hospital, which is more likely to provide a valid estimate of the effect of adherence on outcome.

Suboptimal adherence and between center variation have been reported in other systematic reviews about guideline adherence in critical care.[6,57] Ebben[6] reported a variation as large as 0 to 98% in a systematic review about guideline adherence in the prehospital and emergency care.

The large between-center variation suggests that guideline adherence is a management or structural characteristic, which is consistent with a qualitative study about guideline adherence in the ICU.[58] These authors reported that unit culture and communication were among the most important factors in guideline adherence. Furthermore, the availability of electronic protocols, education, reminders and an audit-feedback system were identified by participants as important determinants of guideline adherence. Surprisingly, only one of the included studies in this review assessed the association between hospital characteristics and adherence.[28]

In this review we found that strong recommendations were more often adhered to than recommendations based on lower level evidence. This is consistent with the findings of a study about

oncology guidelines.[59] This may imply that clinicians are not convinced by the benefit of moderate and weak guideline recommendations, which is supported by our finding that intracranial pathology is associated with adherence to ICP monitoring guidelines. The recommendation to place an ICP monitoring in patients without CT abnormalities but with additional risk factors stems from one prospective study published in 1982,[60] while the recommendation to place an ICP monitor in patients with an abnormal head CT is, albeit still controversial, based on more robust evidence.

Other clinical characteristics that were associated with guideline adherence were age and GCS. The negative association between age and adherence in severe TBI patients is conceivable as older age is associated with medical comorbidity and premorbid anticoagulant- or antiplatelet use.[61] It has been suggested that these patients should not be treated aggressively,[62] although the BTF guidelines do not specify any subgroups in their recommendations.

The positive association between lower GCS and adherence to BTF guidelines is in line with findings from methodological studies about confounding by indication in critical care, which describe that the most intensive treatments, such as ICP monitoring, are often reserved for the most ill.[53,63]

The association between adherence and a reduction in mortality is consistent with a systematic review of protocolised management of patients with TBI in the ICU[4] and a cost-benefit analysis about the effectiveness of the BTF guidelines.[64] Although these findings are consistent, they should be interpreted with caution because of the high risk of confounding by indication and performance bias in these studies.

Strengths and limitations

Strengths of this systematic review include the use of a comprehensive search strategy and independent screening, data extraction and quality assessment by two review authors. As there is no gold standard for risk of bias assessment in observational studies,[65] we developed and piloted our own form. This could be considered a review limitation, however, we attempted to describe the six threats to validity as described by the Cochrane Collaboration and used two validated forms. In addition, concordance rates in assessing bias were high suggesting unambiguous items. Finally, despite an extensive search strategy, we found no unpublished studies. Although the performance of audits to test and improve guideline adherence is well practiced,[66] these reports are seldom published in international journals. Combined with the fact that we excluded non-English language studies, it is likely that some publication bias exists within this review.

The results of this review imply that guideline adherence in TBI is suboptimal. Certain subgroups, such as older patients or severe TBI patients with a relatively high GCS are even less likely to be treated according to the guidelines. One solution may be for guideline developers to take into account specific subgroups of patients and tailor their recommendations accordingly.

The fact that strong guideline recommendations were more often followed than those based on less robust evidence, speaks to the need for adequate investment in high-quality research to evaluate treatment efficacy and effectiveness, and for this research to be incorporated rapidly into guidelines. We would recommend high quality RCTs and large-scale comparative effectiveness design using robust methods to adjust for confounding by indication for this purpose.

The large variation found in this systematic review highlights the importance of hospital characteristics and/or management strategies in guideline adherence. Although this has been reported in qualitative

studies, further quantitative research may shed greater light on its importance and elucidate which characteristics inhibit clinicians from adhering to guidelines.

In this systematic review, we found an association between adherence to current guidelines and reduced mortality. These results should be interpreted as preliminary because only two studies accounted for confounding by indication and none could eliminate the effect of concurrent interventions. It is important that future studies investigating guideline adherence or treatment effectiveness use robust methods to adjust for confounding by indication and concurrent treatment interventions to estimate effectiveness.

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APPENDIX

Appendix 11.A Search strategy

Date: October 22, 2014

Embase.com

('protocol compliance'/de OR (((adher* OR complian* OR conform* OR deviat* OR nonadher* OR noncomplian* OR nonconform* OR nondeviat*) NEAR/11 (protocol* OR guideline* OR pathway* OR 'good clinical practice' OR polic* OR procedure* OR recommend* OR definition* OR rule* OR 'evidence based'))):ab,ti) AND ('brain injury'/exp OR 'head injury'/de OR concussion/exp OR 'nervous system injury'/de OR (((brain OR head OR crani* OR cerebr* OR capitis OR hemisphere*) NEAR/3 (injur* OR trauma* OR posttrauma* OR damag*)) OR concus* OR contus* OR neurotraum* OR tbi OR mtbi):ab,ti)

Medline (OvidSP)

("Guideline Adherence"/ OR (((adher* OR complian* OR conform* OR deviat* OR nonadher* OR noncomplian* OR nonconform* OR nondeviat*) ADJ11 (protocol* OR guideline* OR pathway* OR "good clinical practice" OR polic* OR procedure* OR recommend* OR definition* OR rule* OR "evidence based"))).ab,ti.) AND (exp "Brain Injuries"/ OR "Craniocerebral Trauma"/ OR "Trauma, Nervous System"/ OR exp "Cerebrovascular Trauma"/ OR (((brain OR head OR crani* OR cerebr* OR capitis OR hemisphere*) ADJ3 (injur* OR trauma* OR posttrauma* OR damag*)) OR concus* OR contus* OR neurotraum* OR tbi OR mtbi).ab,ti.)

Cochrane central

((((adher* OR complian* OR conform* OR deviat* OR nonadher* OR noncomplian* OR nonconform* OR nondeviat*) NEAR/11 (protocol* OR guideline* OR pathway* OR 'good clinical practice' OR polic* OR procedure* OR recommend* OR definition* OR rule* OR 'evidence based'))):ab,ti) AND ((((brain OR head OR crani* OR cerebr* OR capitis OR hemisphere*) NEAR/3 (injur* OR trauma* OR posttrauma* OR damag*)) OR concus* OR contus* OR neurotraum* OR tbi OR mtbi):ab,ti)

Web-of-science

TS=(((((adher* OR complian* OR conform* OR deviat* OR nonadher* OR noncomplian* OR nonconform* OR nondeviat*) NEAR/11 (protocol* OR guideline* OR pathway* OR "good clinical practice" OR polic* OR procedure* OR recommend* OR definition* OR rule* OR "evidence based")))) AND ((((brain OR head OR crani* OR cerebr* OR capitis OR hemisphere*) NEAR/3 (injur* OR trauma* OR posttrauma* OR damag*)) OR concus* OR contus* OR neurotraum* OR tbi OR mtbi)))

Scopus

TITLE-ABS-KEY(((((adher* OR complian* OR conform* OR deviat* OR nonadher* OR noncomplian* OR nonconform* OR nondeviat*) W/11 (protocol* OR guideline* OR pathway* OR "good clinical practice" OR polic* OR procedure* OR recommend* OR definition* OR rule* OR "evidence based")))) AND ((((brain OR head OR crani* OR cerebr* OR capitis OR hemisphere*) W/3 (injur* OR trauma* OR posttrauma* OR damag*)) OR concus* OR contus* OR neurotraum* OR tbi OR mtbi)))

PsycINFO (OvidSP)

((((adher* OR complian* OR conform* OR deviat* OR nonadher* OR noncomplian* OR nonconform* OR nondeviat*) ADJ11 (protocol* OR guideline* OR pathway* OR "good clinical practice" OR polic* OR procedure* OR recommend* OR definition* OR rule* OR "evidence based"))).ab,ti.) AND (exp "Brain Damage"/ OR (((brain OR head OR crani* OR cerebr* OR capitis OR hemisphere*) ADJ3 (injur* OR trauma* OR posttrauma* OR damag*)) OR concus* OR contus* OR neurotraum* OR tbi OR mtbi).ab,ti.)

Cinahl
(MH "Guideline Adherence+" OR (((adher* OR complian* OR conform* OR deviat* OR nonadher* OR noncomplian* OR nonconform* OR nondeviat*) N11 (protocol* OR guideline* OR pathway* OR "good clinical practice" OR polic* OR procedure* OR recommend* OR definition* OR rule* OR "evidence based")))) AND (MH "Brain Injuries+" OR MH "Head Injuries+" OR (((brain OR head OR crani* OR cerebr* OR capitis OR hemisphere*) N3 (injur* OR trauma* OR posttrauma* OR damag*)) OR concus* OR contus* OR neurotraum* OR tbi OR mtbi))

PubMed publisher
((((adher*[tiab] OR complian*[tiab] OR conform*[tiab] OR deviat*[tiab] OR nonadher*[tiab] OR noncomplian*[tiab] OR nonconform*[tiab] OR nondeviat*[tiab]) AND (protocol*[tiab] OR guideline*[tiab] OR pathway*[tiab] OR good clinical practice*[tiab] OR polic*[tiab] OR procedure*[tiab] OR recommend*[tiab] OR definition*[tiab] OR rule*[tiab] OR evidence based*[tiab])))) AND ((((brain[tiab] OR head[tiab] OR crani*[tiab] OR cerebr*[tiab] OR capitis[tiab] OR hemisphere*[tiab]) AND (injur*[tiab] OR trauma*[tiab] OR posttrauma*[tiab] OR damag*[tiab])) OR concus*[tiab] OR contus*[tiab] OR neurotraum*[tiab] OR tbi[tiab] OR mtbi[tiab])) AND publisher[sb]

Google scholar
adherence|compliance|nonadherence|noncompliance protocol|protocols|guideline|guidelines "brain|head injury|injuries|trauma"|concussion|tbi|mtbi

Opengrey.eu
Handsearch (use criteria google scholar)

Dissertations
Handsearch (use criteria google scholar)

Reference lists of included papers / relevant reviews
Handsearch after the initial selections of papers

ISI web of science
Handsearch after the initial selections of papers

Appendix 11.B Risk of bias form

Bias	Issues to consider for judging overall rating of "Risk of Bias"	A	B	C
Instruction to assess the risk of each potential bias	These issues will guide your thinking and judgment about the overall risk of bias within each of the 6 domains. Some issues may not be relevant to the specific study or review question. These issues are taken together to inform the overall judgment of potential bias for each of the 6 domains			
1. SELECTION BIAS / CONFOUNDING				
RQ1				
2. Are critical inclusion/exclusion criteria clearly stated (does not require the reader to infer)?	Provide direction to abstractors by listing individual criteria of a priori significance and minimal requirements for criteria to be considered "clearly stated". List the criteria			
RQ2				
1. Is the study design prospective, retrospective or mixed? QUIPS:Are baseline study characteristics adequately described? (QUIPS) If there are groups: does the analysis control for baseline differences between groups? QUIPS: All important confounders including treatment, are measured QUIPS: important potentional confounders are accounted for in the study design or in the analysis	Cohort study = low risk; case-control/historifcal control group = high risk			
RQ3				
1. Is the study design prospective, retrospective or mixed? 4. Did the study apply inclusion/exclusion criteria uniformly to all comparison groups/arms of the study? 9. Is the selection of the comparison group appropriate? 10. Any attempt to balance the aollocation between the groups (eg stratification, matching, propensity scores) OR study accounted for imbalance by post hoc analyses or multivariate analysis 20. Does the analysis control for baseline differences between groups? 22. Were important confounding and effect modifying variables taken into account in the design and/or analysis (e.g through matching, stratification, interaction terms, multivariate analysis, or other statistical adjustment)	Cohort study = low risk; case-control/historifcal control group = high risk groups should be selected from the same source (eg hospital)			
TOTAL SELECTION BIAS RQ1				
TOTAL SELECTION BIAS RQ2				
TOTAL SELECTION BIAS RQ3				

Appendix 11.B (continued)

Bias	Issues to consider for judging overall rating of "Risk of Bias"	A	B	C
2. PERFORMANCE BIAS				
RQ1,2,3 Did execution of the study vary from the intervention protocol proposed by the investigators and therefore compromise the conclusion of the study?				
RQ3 5. Was the strategy for recruiting partiicpants into the study the same across study groups/arms 7. What is the level of detail in describing the intervention or exposure? 11. Did researchers isolate the impact from a concurrent intervention or an unintended exposure that might bias results, e.g. through multivariate analysis, stratification, or subgroup analysis?	This question is likely to be more releevant for prospective or mixed designs than retropsective designs			
TOTAL PERFORMANCE BIAS RQ1				
TOTAL PERFORMANCE BIAS RQ2				
TOTAL PERFORMANCE BIAS RQ3				
3. ATTRITION BIAS				
RQ2 QUIPS: what is the response rate? (the proportion of study sample completing the study and providing outcome data) QUIPS: Did the study authors make attempts to collect information on partiicpatns who dropped out of the study? QUIPS: Are reasons for loss to follow-up provided? QUIPS: are participants who are lost to follow-up adequately described + are there baseline differences?				
RQ3 16. Is the length of follow-up the same for all groups? 17. Is the length of time following the intervention/exposure sufficient to support the evaluation of primary outcomes and harms? 18. Did attrition from any group exceed 20% (<1 year) or 30% (≥1 year)? 19. Did attrition differ between groups more than 20% 23. In cases of high loss to follow-up, is the impact assessed? (through sensitivity analysis or other adjustment methods)				
TOTAL ATTRITION BIAS RQ2				
TOTAL ATTRITION BIAS RQ3				
4. DETECTION BIAS				
RQ2 QUIPS: a clear definition of outcome is provided, including duration of follow-up & no systematic differences in outcome assessment among comparison groups				
RQ3 13. were the outcome assessors blinded to the intervention or exposure status of the participants?				
TOTAL DETECTION BIAS RQ2				
TOTAL DETECTION BIAS RQ3				

Appendix 11.B (continued)

Bias	Issues to consider for judging overall rating of "Risk of Bias"	A	B	C
5. REPORTING BIAS				
RQ1				
29. is the source of funding identified?				
24. are any important primary outcomes missing from the results?	Identify all primary outcomes, including timing of measurement, that one would expect to be reported in the study			
RQ2				
QUIPS: there is not selecting reporting of results				
RQ3				
8. Are the important outcomes prespecified by the researchers? Do not consider harms in answering this question unless they should have been pre-specified				
26. Are any important harms or adverse events that may be a consequence of the intervention/exposure missing from the results?				
TOTAL REPORTING BIAS RQ1				
TOTAL REPORTING BIAS RQ2				
TOTAL REPORTING BIAS RQ3				
6. INFORMATION BIAS				
RQ1				
3. Are the inclusion/exclusion criteria measured using valid and reliable measures?	Subjective measures based on self-report tend to have lower reliability and validity than objective measures such as clinical reports and lab findings			
RQ2				
QUIPS: Are the predictors well defined?	A clear definition of each predictor should be provided			
QUIPS: Are predictors assessed using valid and reliable measures, implemented consistently across all study participants				
QUIPS: The method and setting of measurement of predictors are the same for all study participants				
QUIPS: Appropriate methods of imputation are used for missing predictor variables				
RQ3				
14. Are interventions/expsoures assessed using valid and reliable measures, implemented consistently across all study participants				
15. are outcomes assessed using valid and reliable measures, implemented consistently across all study participants?				
21. Are confounding and/or effect modifying variables assessed using valid and reliable measures across all study participants?				
TOTAL INFORMATION BIAS RQ1				
TOTAL INFORMATION BIAS RQ2				
TOTAL INFORMATION BIAS RQ3				

A = **Study methods and comments**: Provide comments of tekst exerpts in the boxed below, as necessary, to facilitate the consensus process that will follow.
B = **Rating of risk of bias**: Rate the risk of bias for the subquestion as: high risk, low risk, unsure or not applicable in the blue boxes.
C = **Rating of total risk of bias**: Rate the total risk of bias for the question as: high, moderate and low risk. Moderate risk = if at least one of the criteria is scored with high risk; High risk = if >50% is scored as high risk.

Appendix 11.C Table of related studies that were excluded

Reason exclusion	Studies
Study measured guideline adherence in a group of patients of which a part did not fit the guideline criteria	Arabi (2010); Frohlich (2011); Myburgh (2008); Raj (2013); Watts (2012)
Study was about a local guideline	Crandall (2010); Mossop (2009)
Study had a qualitative design (survey)	Duus (1997); Strand (2012)
Study included all trauma patients and results for TBI patients were not reported separately	Gage (2012)
Study examined how many CT scans would have been performed if guidelines were implemented	Harris (2006); Hassan (2005)
Study examined adherence to more than one guideline of which none was implemented	Gupta (2014); Kerr (2010); Korley (2013); Melnick (2012)
Study included all patients with blunt force trauma above the neck (including facial injuries)	Kerr (2005); Kerr (2010)
Study measured adherence not per patient but per measurement	Neumann (2008); Griesdale (2014); Thompson (2006)
Study did not measure adherence	Palmer (2001)
Study measured deviations from the protocol in clinical characteristics (e.g. hypotension, hypocapnia) and did not measure whether patients have been treated adequately	Schirmer-Mikalsen (2012); Schirmer-Mikalsen (2013)
Study is about a consensus guideline	Thomas (2002)
Study measured whether neurological observations were prescribed according to the guidelines; but not if they were conducted (while authors describe that they could have been performed if they weren't prescribed)	Qureshi (2005)

Appendix 11.D Factors influencing adherence

Domain	Predictor	Study	Effect (direction, OR, p-value)
Baseline patient characteristics	Age	Alali (2013)	*** Younger age is significantly associated with adherence to BTF ICP monitoring guidelines.** **Median (IQR) ICP+ = 43 (26-56); ICP- 53 (31-72) standardised difference = 0.45**
		Biersteker (2012)	*** Younger age is significantly associated with adherence to BTF ICP monitoring guidelines.** **Median (IQR) ICP+ = 44 (26-54); ICP- = 53 (37-69). Unadjusted (Mann-Whitney test): p < 0.001; Adjusted OR (adjusted for baseline demographic and clinical variables) = 0.96 (95%CI 0.94-0.98) p < 0.001**
		Farahavar (2012)	*** Younger age is significantly associated with adherence to BTF ICP monitoring guidelines.** **Mean age (SD): ICP+ 38.3 (17.5), ICP- 45.9 (21.8). Unadjusted (T-test): p <0.0001** *** Less patients above age 60 is associated with adherence to ICP monitoring guidelines.** **N(%) ICP+ 141 (13.0%); ICP- 65 (29.1%). Unadjusted (Chi square): p < 0.0001**
		Griesdale (2010)	*** Younger age is significantly associated with adherence to BTF ICP (EVD) monitoring** **Mean age (SD): EVD+ 35 (15.4), EVD- 42 (18.0). Independent t-test: p < .01**
		Harr (2011)	*** Older age is significantly associated with adherence to Scandinavian guidelines for CT-scan and hospital admission guidelines.** **Unadjusted (logistic regression): OR = 1.01 (1.00-1.02, p < .01),** **Multivariate (adjusted for gender, HISS score, weekday of admission, alcohol consumption and BAC): OR = 1.01 (1.01-1.02, p < .001)**
		Härtl (2006)	** No significant association between age and adherence to transport guidelines.* *Age (mean): direct transport 36.5; indirect transport 34.4* *Chi square P value = 0.21*
		Heskestad (2008)	** No significant association between age and adherence to Scandinavian guidelines for head CT and hospital admission* *No statistics or direction reported*
		Shafi (2014)	*** Younger age is significantly associated with higher BTF adherence scores (based on endotracheal intubation, resuscitation, correction of coagulopathy, BTF ICP monitoring guidelines, ICP directed therapy, and physical therapy & rehabilitation after discharge).** **Adjusted OR (adjusted for sex, race/ethnicity, insurance status, comorbidities, SBP and heart rate on admission, ISS, GCS score at admission, head AIS score, and Marshall score on initial head CT) = 0.98 (95%CI 0.98-0.99)**
		Talving (2013)	*** Younger age is significantly associated with adherence to BTF ICP monitoring guidelines.** **Mean age (SEM): ICP+ 40.1 (1.9); ICP- 48.0 (2.4). Unadjusted (Chi square) p = 0.011.** **Adjusted OR (adjusted for sex, presence of IPH on CT, loss of gray and white differential on CT, presence of reactive pupils during the first physical examination, PT and INR values on admission, initiation of nutrition in the first 7 days, head AIS score of 3, head AIS score of 5, evacuation of a mass lesion within the first 24 hours, decompressive craniectomy within 4 hours, extremity AIS score of 3 or higher, increasing PTT on admission, best GCS score within 24 hours of admission, hypotension on admission and SAH) = 0.97 (95%CI 0.96-0.99), p = 0.001**
	Gender	Alali (2013)	*** Gender is significantly associated with adherence to BTF ICP monitoring guidelines** **Female (%): ICP+ 420 (22.4), ICP- 2611 (29.8). Standardised difference = 0.17**
		Biersteker (2012)	** Gender is not significantly associated with adherence to BTF ICP monitoring guidelines* *Male (%): ICP+ 90 (73%); ICP- 90 (63%). Unadjusted (chi square): p = 0.09;* *Adjusted OR (adjusted for baseline demographic and clinical variables) = 1.87 (95%CI: 0.87-4.03), p = 0.11*
		Farahavar (2012)	** Gender is not significantly associated with adherence to BTF ICP monitoring guidelines* *Male (%): ICP+ 843 (77.8%); ICP- 164 (73.5%). Unadjusted (Chi square): p = 0.17*

Appendix 11.D (continued)

Domain	Predictor	Study	Effect (direction, OR, p-value)
		Griesdale (2010)	** Gender is not significantly associated with adherence to BTF ICP monitoring guidelines* *Female gender (n,%): EVD+ 21 (21.4%), EVD- 18 (24.7%). Independent t-test: p > 0.05*
		Harr (2011)	** Gender is not significantly associated with adherence to Scandinavian guidelines for CT scanning and hospital admission.* *Unadjusted (logistic regression): OR female = 0.84 (95%CI 0.61–1.16)* *Multivariate (adjusted for age, HISS score, weekday of admission, alcohol consumption and BAC): OR female = 0.87 (0.65–1.16).*
		Heskestad (2008)	** No significant association between gender and adherence to Scandinavian guidelines for head CT and hospital admission* *No statistics or direction reported*
		Shafi (2014)	*** Male sex is significantly associated with higher BTF adherence scores (based on endotracheal intubation, resuscitation, correction of coagulopathy, ICP monitoring, ICP directed therapy, and physical therapy & rehabilitation after discharge).** **Adjusted: OR (adjusted for age, race/ethnicity, insurance status, comorbidities, SBP and heart rate on admission, ISS, GCS score at admission, head AIS score, and Marshall score on initial head CT) (females) = 0.76 (95%CI: 0.66-0.87)**
		Talving (2013)	** Gender is not significantly associated with adherence to BTF ICP monitoring guidelines* *Male (%): ICP+ 80 (79.2%); ICP- 81 (70.4%). Unadjusted (Chi square) P = 0.160*
	Race	Alali (2013)	** Race is not significantly associated with adherence to BTF ICP monitoring guidelines* *Black (%) ICP+ 183 (9.8%), ICP- 958 (10.9%); White (%): ICP+ 1334 (71.2%), ICP- 6316 (72.2%)* *Other race (%): ICP+ 247 (13.2%), ICP- 1084 (12.4%); Unknown (%) ICP+ 110 (5.9%), ICP- 396 (4.5%).* *Standardised difference 0.07*
		Shafi (2014)	** Race is not significantly associated with BTF adherence scores (based on endotracheal intubation, resuscitation, correction of coagulopathy, ICP monitoring, ICP directed therapy, and physical therapy & rehabilitation after discharge).* *No statistics reported.*
	Insurance status	Alali (2013)	*** Commercial insurance (US) is significantly associated with adherence to BTF ICP monitoring guidelines.** **Commercial (%): ICP+ 721 (38.5%), ICP- 2590 (29.6%); Noncommercial (%) ICP+ 1072 (57.2%), ICP- 5343 (61%)** **Unknown (%) ICP+ 81 (4.3%), ICP- 821 (9.4%)** **Standard difference = 0.25.**
		Shafi (2014)	*** No insurance is significantly associated with lower compliance with BTF adherence scores (based on endotracheal intubation, resuscitation, correction of coagulopathy, ICP monitoring, ICP directed therapy, and physicial therapy & rehabilitation after discharge).** **Adjusted OR (adjusted for age, sex, race/ethnicity, insurance status, comorbidities, SBP and heart rate on admission, ISS, GCS score at admission, head AIS score, and Marshall score on initial head CT) (uninsured) = 0.81 (0.70–0.93)**
	Alcohol consumption	Harr (2011)	*** Alcohol consumption is associated with adherence to Scandinavian guidelines for CT scanning and hospital admission. This association is not significant after adjusting for age, gender, HISS score, and weekday of admission)** **Unadjusted (logistic regression): OR alcohol consumption=0.67 (95%CI 0.49-0.93), p < 0.05.** *Multivariate: OR alcohol consumption=0.92 (0.69–1.22)*
Injury mechanism		Alali (2013)	*** Injury mechanism is significantly associated with adherence to BTF ICP monitoring guidelines** **Fall (%): ICP+ 765 (40.8%), ICP- 4800 (54.8%); Motor vehicle collision(%) ICP+ 398 (21.2%); ICP- 1442 (16.5%)** **Motorcycle ICP+ 166 (8.9%), ICP- 500 (5.7%); Pedestrian (%): ICP+ 209 (11.2%), ICP- 636 (7.3%)** **Other(%) ICP+ 336 (17.9%), ICP- 1376 (15.7%)** **Standard difference = 0.29.**

Appendix 11.D (continued)

Domain	Predictor	Study	Effect (direction, OR, p-value)
		Biersteker (2012)	** Injury mechanism is not significantly associated with adherence to BTF ICP monitoring guidelines.* *Traffic (%) ICP+ 68 (55%); ICP- 65 (46%); Fall (%) ICP+ 48 (39%); ICP- 57 (40%)* *Violence(%) ICP+ 5 (4%); ICP- 16 (11%); Other/Unknown(%): IPC+ 2 (2%); ICP- 4 (3%)* *Chi square: p = 0.12*
TBI severity indices	GCS	Alali (2013)	** GCS is not statistically associated with adherence to BTF ICP monitoring guidelines.* *Median (IQR) ICP+ 3 (3–5), ICP- 3 (3–6)* *Standardised difference = 0.02*
		Biersteker (2012)	*** Lower GCS at injury scene is associated with adherence to BTF ICP monitoring guidelines. The association is not significant anymore after adjustment for baseline demographic and clinical variables.** **≤ 8 (%): ICP+ 107 (87%); ICP- 95 (67%); >8 (%): ICP+ 12 (9.8%); ICP- 24 (17%); Unknown: ICP+ 4 (3.3%); ICP- 23 (16%)** **Unadjusted (Chi-square): p < 0.001** *GCS ≤ 8 adjusted: OR = 0.98 (95%CI 0.36-2.64) p = 0.97;* **GCS unknown adjusted OR = 0.20 (95%CI 0.04-0.96) p = 0.05** *** Lower GCS at ED is associated with adherence to BTF ICP monitoring guidelines** **Median GCS (IQR): ICP+ = 3 (3–3); ICP- 3 (3–6)** **Unadjusted (Mann-Whitney U test): p < 0.01;** **Adjusted OR (adjusted for baseline demographic and clinical variables) = 0.72 (95%CI 0.56-0.93) p = 0.01**
		Fahravar (2012)	** Initial GCS is not statistically associated with adherence to BTF ICP monitoring guidelines.* *GCS 6-8 (%): ICP+ 449 (43.5%); ICP- 96 (48.5%)* *GCS 3-5 (%) ICP+ 583 (56.5%); ICP- 102 (51.5%).* *Chi square: p = 0.20*
		Griesdale (2010)	*** Best GCS in 12 hours is significantly associated with adherence to BTF ICP (EVD) monitoring guidelines** **GCS < 6 n(%): EVD+ 42 (42.9%), EVD- 10 (13.7%). Fisher's exact test: p < .01** **GCS 6-8 n(%): EVD+ 51 (52.0%); EVD- 53 (72.6%). Fisher's exact test: p < .01** **GCS 9-12 n(%): EVD+ 5 (5.1%); EVD- 10 (13.7%). Fisher's exact test: p < .01**
		Shafi (2014)	** GCS is not statistically associated with adherence to BTF adherence scores (based on endotracheal intubation, resuscitation, correction of coagulopathy, ICP monitoring, ICP directed therapy, and physical therapy & rehabilitation after discharge).* *Statistics not reported.*
		Talving (2013)	** GCS is not statistically associated with adherence to BTF ICP monitoring guidelines.* *Median (IQR) ICP+ 4 (3–8), ICP- 4 (3–8). Unadjusted (Mann-Whitney U test) p = 0.762* *** Lower best GCS scores within 24 hours of admission is significantly associated with adherence to BTF ICP monitoring guidelines** **Adjusted OR (adjusted for sex, presence of IPH on CT, loss of gray and white differential on CT, presence of reactive pupils during the first physicial examination, PT and INR values on admission, initiation of nutrition in the first 7 days, head AIS score of 3, head AIS score of 5, evacuation of a mass lesion within the first 24 hours, decompressive craniectomy within 4 hours, extremity AIS score of 3 or higher, increasing age, increasing PTT on admission, hypotension on admission and SAH) 0.81 (0.71–0.93), p = 0.002**

Appendix 11.D (continued)

Domain	Predictor	Study	Effect (direction, OR, p-value)
	GCS motor score	Alali (2013)	** GCS motor score is not significantly associated with adherence to BTF ICP monitoring guidelines.* *Median (IQR) ICP+ 1(1-3), ICP- 1(1–3)* *Standardised difference = 0.01*
	HISS	Harr (2011) *Heskestad (2012)*	*** HISS is significantly associated with adherence to Scandinavian guidelines for CT scanning and hospital admission.** **Mild vs minimal head injury:** **Unadjusted (logistic regression): OR = 1.61 (95%CI:1.05–2.45) p < .05** *Multivariate(adjusted for age, gender, weekday of admission, alcohol consumption and BAC): OR = 1.46 (95%CI: 0.97-2.20), p > .05* **Moderate vs minimal head injury:** **Unadjusted (logistic regression): OR = 61.97 (95%CI: 18.29–209.96), p < .001** **Multivariate (adjusted for age, gender, weekday of admission, alcohol consumption and BAC): OR = 53.20 (95%CI: 15.96–117.38), p < .001**
		Heskestad (2008)	*** HISS is associated with adherence to Scandinavian guidelines for CT scanning and hospital admission** **N(%): Minimal HI: 47 (31%); mild HI: 197 (58%); moderate HI: 16 (100%)** **No statistics reported**
	Head AIS	Alali (2013)	** Head AIS is not significantly associated with adherence to BTF ICP monitoring guidelines.* *AIS 3 (%) ICP+ 109 (5.8%), ICP- 111 (12.7%)* *AIS 4 (%): ICP+ 676 (36.1%), ICP- 3678 (42.0%)* *AIS 5 (%) ICP+ 1089 (58.1%), ICP- 3965 (45.3%).* *Standardised difference = 0.31*
		Shafi (2014)	*** Head AIS is significantly associated with adherence to BTF adherence scores (based on endotracheal intubation, resuscitation, correction of coagulopathy, ICP monitoring, ICP directed therapy, and physical therapy & rehabilitation after discharge).** **Adjusted OR (adjusted for age, sex, race/ethnicity, insurance status, comorbidities, SBP and heart rate on admission, ISS, GCS score at admission, head AIS score, and Marshall score on initial head CT) = 1.17 (1.08–1.28)**
		Talving (2013)	** Head AIS scores 3 and 4 are not significantly associated to adherence to BTF ICP monitoring guidelines* *HAIS 3 (%): ICP+ 42 (41.6%), ICP- 35 (30.4%)* *Unadjusted (chi square): p = 0.153* *HAIS 4 (%): ICP+ 22 (21.8%), ICP- 21 (18.3%)* *Unadjusted (chi square): p = 0.609,* *** HAIS 5 is significantly associated to adherence to BTF ICP monitoring guidelines in Unadjusted analysis but not after adjustment for sex, presence of IPH on CT, loss of gray and white differential on CT, presence of reactive pupils during the first physicial examination, PT and INR values on admission, initiation of nutrition in the first 7 days, evacuation of a mass lesion within the first 24 hours, decompressive craniectomy within 4 hours, extremity AIS score of 3 or higher, increasing age, increasing PTT on admission, best GCS score within 24 hours of admission, hypotension on admission and SAH.** **HAIS 5 (%)ICP+ 37. (36.6%); ICP- 59 (51.3%)** **Unadjusted (chi square): p = 0.039.** *Multivariate: not significant, no statistics reported*
	APACHE II score	Griesdale (2010)	** APACHE II score is not significantly associated with BTF ICP (EVD) monitoring guidelines* *Mean (sd): EVD+ 23.5 (4.5); EVD- 23.4 (5.0)* *Independent t-test: p > 0.05*

Appendix 11.D (continued)

Domain	Predictor	Study	Effect (direction, OR, p-value)
(Severity of) Comorbidity	Comorbidity	Alali (2013)	*** Less comorbidity is associated with adherence to BTF ICP monitoring guidelines.** **Coronary artery disease ICP+ 49 (2.6%), ICP- 447 (5.2%). Standardised difference = 0.13.** **Hypertension ICP+ 379 (20.4%), ICP- 2360 (27.3%). Standardised difference = 0.16.** **Diabetes ICP+ 159 (8.6%); ICP- 2360 (11.3%). Standardised difference = 0.09.** **On dialysis ICP+ 15 (0.8%), ICP- 87 (1.0%). Standardised difference = 0.02.** **CVA with residual deficit ICP+ 49 (2.6%), ICP- 335 (3.9%). Standardised difference = 0.06.** **Cancer ICP+ 3 (0.2%); ICP- 121 (1.4%). Standardised difference = 0.14.** **Bleeding disorder ICP+ 73 (3.9%), ICP- 717 (8.3%). Standardised difference = 0.18.** **Chronic respiratory diseases ICP+ 74 (4.0%); ICP- 485 (5.6%). Standardised difference = 0.07.** **Functionally dependent ICP+ 11 (0.6%); ICP- 103 (1.2%). Standardised difference = 0.07.**
		Shafi (2014)	** Comorbidity is not significantly associated with BTF adherence scores (based on endotracheal intubation, resuscitation, correction of coagulopathy, ICP monitoring, ICP directed therapy, and physical therapy & rehabilitation after discharge). Statistics not reported.*
Extracranial injury	Major Extracranial Injury	Biersteker (2012)	*** Major Extracranial injury is associated with adherence to BTF ICP monitoring guidelines. The association is not significant anymore after adjustment for baseline demographic and clinical variables.** **N(%): ICP+ 69 (57%); ICP- 54 (39%). Unadjusted: Chi square: p < 0.01.** *Adjusted: OR 1.68 (95%CI 0.78–3.61); p = 0.18*
	ISS	Shafi (2014)	** ISS is not significantly associated with adherence to BTF adherence scores (based on endotracheal intubation, resuscitation, correction of coagulopathy, ICP monitoring, ICP directed therapy, and physical therapy & rehabilitation after discharge). Statistics not reported.*
		Talving (2013)	** ISS is not significantly associated with adherence to BTF ICP monitoring guidelines* *Mean (SEM): ICP+ 25 (1), ICP- 25 (1)* *Unadjusted (Mann-Whitney): p = 1.000*
	Chest AIS	Talving (2013)	** Chest AIS 3 or higher is not significantly associated with adherence to BTF ICP monitoring guidelines* *N(%) ICP+ 38 (37.6%), ICP- 36 (31.3%)* *Unadjusted (Chi square) p = 0.389*
	Abdomen AIS	Talving (2013	** Abdomen AIS 3 or higher not significantly associated with adherence to BTF ICP monitoring guidelines.* *N(%) ICP+ 11 (10.9%), ICP- 8 (7.0%)* *Unadjusted (Chi square): p = 0.343*
	Extremity AIS	Talving (2013)	*** Extremity AIS scores 3 or higher is significantly associated with adherence to BTF ICP monitor guidelines:** **N(%) ICP+ 18 (17.8%), ICP- 9 (7.8%)** **Unadjusted (chi square) p = 0.038.** **Adjusted OR (adjusted for sex, presence of IPH on CT, loss of gray and white differential on CT, presence of reactive pupils during the first physicial examination, PT and INR values on admission, initiation of nutrition in the first 7 days, head AIS score of 3, head AIS score of 5, evacuation of a mass lesion within the first 24 hours, decompressive craniectomy within 4 hours, increasing age, increasing PTT on admission, best GCS score within 24 hours of admission, hypotension on admission and SAH) = 3.01 (1.09 – 8.32), p = 0.033**

Appendix 11.D (continued)

Domain	Predictor	Study	Effect (direction, OR, p-value)
Clinical characteristics	Pupillary reactions	Biersteker (2012)	*** Abnormal pupillary reactions is associated with adherence to BTF ICP monitoring guidelines.** **Both reacting (%): ICP+ 49 (40%); ICP- 90 (63%)** **One reacting (%): ICP+ 13 (11%); ICP- 11 (7.7%)** **Both nonreacting (%): ICP+ 50 (41%); ICP- 34 (24%)** **Unadjusted (Chi square) p < 0.01.** **Adjusted (adjusted for baseline demographic and clinical variables): One pupil reacting OR = 4.30 (95%CI 1.29-14.3) p = 0.02; both nonreacting: OR = 3.64 (95%CI 0.78–3.61) p < 0.01**
		Fahravar (2012)	*** Abnormal pupillary reactions is associated with adherence to BTF ICP monitoring guidelines.** **Abnormal pupils: ICP+ 245 (23.0%); ICP- 72 (32.6%).** **Unadjusted (Chi square): p = 0.003**
		Talving (2013)	** Fixed, dilated pupils on admission is not significantly associated with adherence to BTF ICP monitoring guidelines* *N(%): ICP+ 23 (22.8%), ICP- 35 (30.4%)* *Unadjusted (chi square): p = 0.221*
	Blood pressure & hypotension	Alali (2013)	*** Hypotension (SBP<90 mmHg) is associated with adherence to BTF ICP monitoring guidelines.** **N(%) ICP+ 52 (2.8%); ICP- 532 (6.1%)** **Standard difference = 0.16**
		Biersteker (2012)	** An hypotensive episode is not significantly associated with adherence to BTF ICP monitoring guidelines.* *N(%): ICP+ 27 (22%); ICP- 37 (26%)* *Unadjusted (Chi square): p = 0.44*
		Farahvar (2012)	** Hypotension on day 1 is not significantly associated with adherence to BTF ICP monitoring guidelines* *N(%): ICP+ 170 (15.8%); ICP- 38 (17.0%)* *Unadjusted (Chi square): p = 0.63*
		Griesdale (2010)	** Systolic blood pressure < 90 mmHg is not significantly associated with adherence to BTF ICP (EVD) monitoring guidelines* *N (%): EVD+ 20 (20.4%), EVD- 12 (16.4%)* *Fisher's exact test: p > 0.05*
		Shafi (2014)	*** Systolic blood pressure is associated with BTF adherence scores (based on endotracheal intubation, resuscitation, correction of coagulopathy, ICP monitoring, ICP directed therapy, and physical therapy & rehabilitation after discharge).** **Adjusted OR (adjusted for age, sex, race/ethnicity, insurance status, comorbidities, SBP and heart rate on admission, ISS, GCS score at admission, head AIS score, and Marshall score on initial head CT) = 1.001 (1.00-1.003)**
		Talving (2013)	** Mean Blood Pressure on admission is not associated with adherence to BTF ICP monitoring guidelines* *N(SEM): ICP+ 142 (3), ICP- 137 (3)* *Unadjusted (Mann-Whitney U test): p = 0.267*
		Talving (2013)	*** Hypotension on admission is significantly associated with adherence to BTF ICP monitoring guidelines** **N(%) ICP+ 2 (2.0%), ICP- 10 (8.7%),** **Unadjusted (chi square): p = 0.040.** **Adjusted OR (adjusted for sex, presence of IPH on CT, loss of gray and white differential on CT, presence of reactive pupils during the first physicial examination, PT and INR values on admission, initiation of nutrition in the first 7 days, head AIS score of 3, head AIS score of 5, evacuation of a mass lesion within the first 24 hours, decompressive craniectomy within 4 hours, extremity AIS score of 3 or higher, increasing age, increasing PTT on admission, best GCS score within 24 hours of admission, and SAH) = 0.13 (0.02–0.86), p = 0.034**

Appendix 11.D (continued)

Domain	Predictor	Study	Effect (direction, OR, p-value)
	Hart rate / tachycardia	Talving (2013)	** Heart rate on admission is not associated with adherence to BTF ICP monitoring guidelines* *mean(SEM): ICP+ 104 (3), ICP- 105 (3)* *Unadjusted (Mann-Whitney U test) p = 0.811*
		Talving (2013)	** Tachycardia (HR>120bpm) on admission is not significantly associated with adherence to BTF ICP monitoring guidelines* *N(%) ICP+ 26 (25.7%), ICP- 37 (32.2%)* *Unadjusted (Chi square): p = 0 .370*
	Respiratory rate / hypoxia	Biersteker (2012)	** An hypoxic episode is not significantly associated with adherence to BTF ICP monitoring guidelines* *N(%) ICP+ 29 (25%); ICP- 30 (23%)* *Unadjusted (Chi square): p = 0.65*
		Griesdale (2010)	** PaO2 < 70 mmHg is not significantly associated with adherence to BTF ICP (EVD) monitoring guidelines* *N(%): EVD+ 10 (10.2%), EVD- 5 (6.8%)* *Fisher's exact test: p > .05*
		Talving (2013)	** Respiratory rate is not significantly associated with adherence to BTF ICP monitoring guidelines* *Mean(SEM): ICP+ 18 (1), ICP- 18 (1)* *Unadjusted (Mann Whitney U test): p = 1.000*
Intracranial pathology		Alali (2013)	*** Intracranial lesions are associated with adherence to BTF ICP monitoring guidelines.** **Epidural hematoma: ICP+ 242 (12.9%), ICP- 767(8.8%)** **Standardised difference = 0.13** **Subdural hematoma ICP+ 1274 (68.0%), ICP- 5401 (61.7%) Standardised difference = 0.13.** **Traumatic subarachnoid hemorrhage ICP+ 1038 (55.4%), ICP- 4104 (46.9%). Standardised difference = 0.17.** **Intracerebral mass lesion ICP+ 167 (8.9%), ICP- 417 (4.8%). Standardised difference = 0.16.** **Compressed/absent basal cisterns ICP+ 102 (5.4%), ICP- 238 (2.7%). Standardised difference = 0.14.** **Brainstem/cerebellar lesion ICP+ 213 (11.4%), ICP- 835 (9.5%). Standardised difference = 0.06.**
		Biersteker (2012)	* Adherence with BTF ICP monitoring guidelines is almost five times lower in patients with a normal CT scan and two or more risk factors (10%) compared to patients with visible intracranial pathology (49%)
		Biersteker (2012)	*** Severe intracranial pathology is significantly associated with adherence to BTF ICP monitoring guidelines in some Unadjusted analyses. The association is not significant anymore after adjustment for baseline demographic and clinical variables.** *** Subarachnoid hemorrhage ICP+ 76 (62%), ICP- 61 (44%). Unadjusted (Mann-Whitney): p < 0.01** *Adjusted OR = 1.28 (95%CI 0.57–2.85; p = 0.55)* *** Subdural hemorrhage ICP+ 72 (59%); ICP- 55 (40%). Unadjusted (Mann-Whitney) p < 0.01** *Adjusted OR = 1.13 (95%CI 0.40–3.25; p = 0.82)* *Epidural hemorrhage ICP+ 21 (17%); ICP- 13 (9.4%). Unadjusted (Mann-Whitney): p = 0.70* *** Intraparenchymal lesion ICP+ 80 (65%); ICP- 63 (46%). Unadjusted (Mann-Whitney): p < 0.01** *Adjusted OR 2.36, (95%CI 0.90–3.25), p = 0.08* *** Punctate hemorrhages ICP+ 48 (39%); ICP= 36 (26%). Unadjusted (Mann Whitney) p = 0.03** *Adjusted OR = 2.11 (95%CI 0.99–4.51), p = 0.06* *** More severe midline shift is significantly associated with adherence to BTF ICP monitoring guidelines in Unadjusted analyses. The association is not significant anymore after adjustment for baseline demographic and clinical variables.**

Appendix 11.D (continued)

Domain	Predictor	Study	Effect (direction, OR, p-value)
		Biersteker (continued)	*** No shift (%): ICP+ 60 (49%), ICP- 93 (65%); < 5 mm (%): ICP+ 21 (17%), ICP- 11 (34%); 5-15 mm (%): ICP+ 33 (27%), ICP- 20 (14%); > 15 mm (%): ICP+ 9 (7%), ICP- 14 (10%).** **Unadjusted (Mann Whitney): p = 0.002** *Adjusted OR < 5mm = 1.51 (0.45–5.10) p = .50; adjusted OR 5–15 mm OR = 0.65 (0.16–2.76) p = 0.56; adjusted OR > 15 mm 0.27 (0.03–2.40) p = 0.25* *** Ambient Cisterns are significantly associated with adherence to BTF ICP monitoring guidelines.** **Compressed (%) ICP+ 34 (27%), ICP- 22 (16%); Absent (%) ICP+ 4 (3%); ICP- 8 (6%).** **Unadjusted (Mann Whitney) p = 0.03.** **Adjusted OR: (adjusted for baseline demographic and clinical variables) 13.2 (95%CI 3.3-52.6) p < .001**; *absent adjusted OR 3.25 (95%CI 0.69–15.2), p = .13* *** Compressed and absent fourth ventricles are significantly associated with adherence to BTF ICP monitoring guidelines.** **Compressed (%): ICP+ 43 (35%); ICP- 10 (7%); Absent (%): ICP+ 27 (27%); ICP- 28 (20%)** **Unadjusted (Mann Whitney) p < 0.001.** *Adjusted OR compressed (adjusted for baseline demographic and clinical variables) = 0.33 (95%CI: 0.09–1.22), p = 0.10;* Adjusted OR absent (adjusted for baseline demographic and clinical variables) = 0.07 (95%CI: 0.01–0.50) p < 0.01 *** Moderate lesion volume is significantly associated with adherence to BTF ICP monitoring guidelines**
		Biersteker (2012)	**No lesion (%): ICP+ 20 (16%); ICP- 49 (35%); <25ml (%): ICP+ 42 (34%); ICP- 45 (32%); 25–100ml (%): ICP+ 39 (32%); ICP- 18 (13%); 100–200ml (%): ICP+ 13 (11%); ICP- 14 (10%); > 200 ml (%): ICP+ 9 (7%); ICP- 12 (9%)** **Unadjusted (Mann-Whitney): p < 0.01.** **Adjusted OR (adjusted for baseline demographic and clinical variables): 25–100 ml OR = 6.22 (95%CI: 1.17–33.0), p = 0.03.** *<25 adjusted OR (adjusted for baseline demographic and clinical variables) = 1.18 (95%CI: 0.33–4.24) p = 0.81; 100–200 ml adjusted OR = 5.85 (95%CI: 0.63–54.7), p = 0.12, > 200 adjusted OR (adjusted for baseline demographic and clinical variables) = 4.10 (95%CI: 0.38–43.8) p = 0.25*
		Fahravar (2012)	** CT abnormalities is not significantly associated with adherence to BTF ICP monitoring guidelines* *N(%) ICP+ 35 (3.3%); ICP- 9 (4.1%).* *Unadjusted (Chi square): p = 0.52*
		Griesdale (2010)	** Traumatic SAH is not significantly associated with BTF ICP (EVD) monitoring adherence* *N(%): EVD+ 49 (50.0%); EVD- 42 (57.5%). Fisher's exact test > .05.* ** Diffuse Axonal injury is not significantly associated with BTF ICP (EVD) monitoring adherence* *N(%): EVD+ 33 (33.7%), EVD- 19 (26.0%). Fisher's exact test > .05.* *** Subdural hematoma is significantly associated with adherence to BTF ICP (EVD) monitoring guidelines** **N(%): EVD+ 46 (46.9%), EVD- 20 (27.4%). Fisher's exact test p< .01.** *** Features of increased ICP at the head CT is significantly associated with adherence to BTF ICP (EVD) monitoring guidelines** **N(%): EVD+ 62 (63.3%), EVD- 25 (34.2%). Fisher's exact test p < .01.** ** Basal Skull fracture is not significantly associated with adherence to ICP (EVD) monitoring guidelines* *N(%): EVD+ 23 (23.5%), EVD- 19 (26.0%). Fisher's exact test: p > .05.*

Appendix 11.D (continued)

Domain	Predictor	Study	Effect (direction, OR, p-value)
		Shafi (2014)	*** Marshall score ≤ 2 is significantly associated with adherence to BTF scores (based on endotracheal intubation, resuscitation, correction of coagulopathy, ICP monitoring, ICP directed therapy, and physical therapy & rehabilitation after discharge).** **Adjusted OR (adjusted for age, sex, race/ethnicity, insurance status, comorbidities, SBP and heart rate on admission, ISS, GCS score at admission and head AIS score) = 1.38 (1.20–1.58)**
		Talving (2013)	** Brain contusion is not associated with adherence to BTF ICP monitoring guidelines.* *N(%) ICP+ 75 (74.3%), ICP- 82 (71.3%). Unadjusted (chi square): p = 0.649* ** SDH is not associated with adherence to BTF ICP monitoring guidelines.* *N(%) ICP+ 55 (54.5%), ICP- 59 (51.3%). Unadjusted (chi square): p = 0.683.* *** SAH is significantly associated with adherence to ICP monitoring guidelines** **N(%): ICP+ 59 (58.4%), ICP- 40 (34.8%). Unadjusted (Chi square): p = 0.001.** **Adjusted OR (adjusted for sex, presence of IPH on CT, loss of gray and white differential on CT, presence of reactive pupils during the first physical examination, PT and INR values on admission, initiation of nutrition in the first 7 days, head AIS score of 3, head AIS score of 5, evacuation of a mass lesion within the first 24 hours, decompressive craniectomy within 4 hours, extremity AIS score of 3 or higher, increasing age, increasing PTT on admission, best GCS score within 24 hours of admission, hypotension on admission) = 2.07 (1.09–8.32) p = 0.033;** *** IPH is significantly associated with adherence to BTF ICP monitoring guidelines in Unadjusted analyses,** *but not after adjustment for sex, presence of IPH on CT, loss of gray and white differential on CT, presence of reactive pupils during the first physical examination, PT and INR values on admission, initiation of nutrition in the first 7 days, head AIS score of 3, head AIS score of 5, evacuation of a mass lesion within the first 24 hours, decompressive craniectomy within 4 hours, extremity AIS score of 3 or higher, increasing age, increasing PTT on admission, best GCS score within 24 hours of admission, hypotension on admission and SAH)* ***ICP+ 37 (36.6%), IPC- 22 (19.1%).* Unadjusted (chi square): p = 0.006.** *Adjusted: no statistics available* ** Epidural hematoma is not significantly associated with adherence to BTF ICP monitoring guidelines* *ICP+ 18 (17.8%), ICP- 17 (14.8%). Unadjusted (chi square): p = 0.582* ** Midline shift is not significantly associated with adherence to BTF ICP monitoring guidelines.* *N(%) ICP+ 6 (5.9%), ICP- 8 (7.0%). Unadjusted (Chi square): p = 0.790* ** Loss of basal cistern is not associated with adherence to BTF ICP monitoring guidelines.* *N(%): ICP+ 31 (30.7%), ICP- 39 (33.9%), Unadjusted (Chi square): p = 0.663* ** Cerebral edema is not significantly associated with adherence to BTF ICP monitoring guidelines.* *N(%): ICP+ 74 (73.3%), ICP- 91 (79.1%). Unadjusted (Chi square): p = 0.338* ** Loss of gray/white differential is not significantly associated with adherence to BTF ICP monitoring guidelines.* *N(%) ICP+ 35 (34.7%), ICP- 28 (24.3%). Unadjusted (Chi square): p = 0.102*
Laboratory Values	PTT	Talving (2013)	*** PTT on admission is significantly associated with adherence to ICP monitoring guidelines.** **N(SEM): ICP+ 30.4 (0.7), ICP- 40.3 (3.7). Unadjusted (Mann-Whitney U test): p = 0.010.** **Adjusted OR (adjusted for sex, presence of IPH on CT, loss of gray and white differential on CT, presence of reactive pupils during the first physical examination, PT and INR values on admission, initiation of nutrition in the first 7 days, head AIS score of 3, head AIS score of 5, evacuation of a mass lesion within the first 24 hours, decompressive craniectomy within 4 hours, extremity AIS score of 3 or higher, increasing age, best GCS score within 24 hours of admission, hypotension on admission and SAH) = 0.96 (0.92-0.99) p = 0.021**

Appendix 11.D (continued)

Domain	Predictor	Study	Effect (direction, OR, p-value)
	PT	Talving (2013)	** PT on admission is not significantly associated with adherence to BTF ICP monitoring guidelines* *N(SEM): ICP+ 15.7 (0.3), ICP- 16.9 (0.8).* *Unadjusted (Mann-Whitney U test): p= 0.082*
	INR	Talving (2013)	** INR is not significantly associated with adherence to BTF ICP monitoring guidelines* *N(SEM): ICP+ 1.21 (0.03), ICP+ 1.40 (0.09)* *Unadjusted (Mann-Whitney U test): p = 0.058*
	Blood alcohol level	Harr (2011)	** BAC is nog significantly associated with adherence to Scandinavian guidelines for CT scanning and hospital admission.* *Unadjusted (logistic regression): OR = 0.93 (0.65–1.35)* *Multivariate (adjusted for age, gender, HISS score and, weekday of admission) OR = 1.30 (0.96–1.75), p > 0.05*
Process/treatment characteristics	Referral status	Biersteker (2012)	** Secondary referral is not significantly associated with adherence to BTF ICP monitoring guidelines* *N(%) ICP+: 17 (14%); ICP- 30 (21%)* *Unadjusted (Chi square): p = 0.12*
	Craniotomy	Griesdale (2010)	*** Craniotomy is statistically associated with adherence to BTF ICP (EVD) monitoring guidelines** **N(%): EVD+ 44 (44.9%), EVD- 21 (28.8%). Fisher's exact test p < .05**
	Decompressive craniectomy	Talving (2013)	*** Decompressive craniectomy in the first 24 hours is statistically associated with adherence to BTF ICP monitoring guidelines but not after correcting for sex, presence of IPH on CT, loss of gray and white differential on CT, presence of reactive pupils during the first physicial examination, PT and INR values on admission, initiation of nutrition in the first 7 days, head AIS score of 3, head AIS score of 5, decompressive craniectomy within 4 hours, extremity AIS score of 3 or higher, increasing age, increasing PTT on admission, best GCS score within 24 hours of admission, hypotension on admission and SAH.** **N(%) ICP+ 42 (41.6%), ICP- 18 (15.7%). Unadjusted (Chi square): p < 0.001** *Adjusted: no statistics reported* ***Decompressive craniectomy in the first 4 hours is significantly associated with adherence to BTF ICP monitoring guidelines** **N(%) ICP+ 32 (31.7%), ICP- 17 (14.8%). Unadjusted (Chi square): p = 0.003** **Adjusted OR (adjusted for sex, presence of IPH on CT, loss of gray and white differential on CT, presence of reactive pupils during the first physicial examination, PT and INR values on admission, initiation of nutrition in the first 7 days, head AIS score of 3, head AIS score of 5, evacuation of a mass lesion within the first 24 hours, extremity AIS score of 3 or higher, increasing age, increasing PTT on admission, best GCS score within 24 hours of admission, hypotension on admission and SAH) 3.85 (1.82-8.14) p < 0.001**
	Early nutrition	Talving (2013)	***Early nutrition is significantly associated with adherence to BTF ICP monitoring guidelines in Unadjusted analysis but not after adjustment for (adjusted for sex, presence of IPH on CT, loss of gray and white differential on CT, presence of reactive pupils during the first physical examination, PT and INR values on admission, initiation of nutrition in the first 7 days, head AIS score of 3, head AIS score of 5, evacuation of a mass lesion within the first 24 hours, decompressive craniectomy within 4 hours, extremity AIS score of 3 or higher, increasing age, increasing PTT on admission, best GCS score within 24 hours of admission, hypotension on admission and SAH)** **N(%) ICP+ 85 (84.2%), ICP- 66 (57.4%). Unadjusted (Chi square): p < 0.001** *Multivariate: no statistics available*

Appendix 11.D (continued)

Domain	Predictor	Study	Effect (direction, OR, p-value)
Structural characteristics	Hospital type	Alali (2013)	** Hospital type (profit vs non profit) is not significantly associated with adherence to BTF ICP monitoring guidelines* *Nonprofit (%): ICP+ 1770 (94.5%); ICP= 8331 (95.2%)* *For profit (%): ICP+ 104 (5.6%), ICP- 423 (4.8%)* *Standardised difference = 0.03*
	Number of beds	Alali (2013)	** Number of hospital beds is not significantly associated with adherence to BTF ICP monitoring guidelines* *≤ 200 beds (%): ICP+ 62 (3.3%), ICP- 171 (2.0%); 201–400 beds (%): ICP+ 350 (18.7%), ICP- 1577 (18.0%);* *401–600 beds (%): ICP+ 557 (29.7%), ICP- 2388 (27.3%); >600 beds (%) ICP+ 905 (48.3%), ICP- 4618 (52.8%)* *Standardised difference = 0.11*
	Teaching status	Alali (2013)	*** Teaching status of the hospital is significantly associated with adherence to BTF ICP monitoring guidelines** **University hospital (%): ICP+ 1155 (61.6%); ICP= 5288 (60.4%)** **Community hospital (%): ICP+ 657 (35.1%); ICP- 2906 (33.2%)** **Nonteaching hospital (%): ICP+ 62 (3.3%), ICP- 560 (6.4%) Standardised difference = 0.15**
	Level trauma center	Alali (2013)	** Level trauma center designation (level I versus level II) is not significantly associated with adherence to BTF ICP monitoring guidelines* *Level I (%): ICP+ 1449 (77.3%), ICP- 6885 (78.7%); level II (%) ICP+ 425 (22.7%), ICP- 1869 (21.4%)* *Standardised difference = 0.03*
Country characteristics	Bruto National Product	Mauritz (2008)	*** Per capita gross domestic product is associated with adherence to prehospital intubation, direct transport and steroid use guidelines (HI = higher income, GDP = 37213 USD; UMI = upper middle income, GDP = 7724 and 8803 USD; LMI = lower middle income, GDP = 2183 and 2637 USD)** *** Prehospital intubation (%): HI 334 (82%); UMI 118 (35%); LMI = 221 (52%)** **Unadjusted (Chi square): p < 0.0001** *** Direct transport: HI 343 (84%); UMI 201 (60%); LMI 235 (55%)** **Unadjusted (Chi square): p < 0.0001** *** Steroids not used: HI 389 (96%); UMI 318 (94%); LMI 153 (36%)** **Unadjusted (Chi square): p < 0.0001**

Bold = statistically significant association; *Italic* = statistically non-significant association.

BTF: Brain Trauma Foundation; ICP: intracranial pressure; IQR: interquartile range; ICP+: patients in which ICP monitoring guidelines were adhered to; ICP-: patients in which ICP monitoring guidelines were not adhered to; OR: odds ratio; EVD: external ventricular drain; CT: computed tomography; HISS: Head Injury Severity Score; BAC: blood alcohol concentration; SBP: systolic blood pressure; ISS: Injury Severity Score; GCS: Glasgow Coma Scale; AIS: Abbreviated Injury Score; IPH: intraparenchymal hemorrhage; PT: prothrombin time; INR: international normalised ratio; PTT: partial thromboplasting time; SAH: subarachnoid hemorrhage; HAIS: Head Abbreviated Injury Score; APACHE: Acute Physiology and Chronic Health Evaluation; CVA: cerebrovascular accident; SDH: subdural hemorrhage; GDP: gross domestic product; HI: high income; UMI: upper middle income; LMI: lower middle income.

Appendix 11.E Adherence and outcome

Study ID	Statistical method (outcome)	Outcome variables	Statistics
Alali (2013)	Two random intercept multilevel logistic regression models with respectively ICP monitoring as a patient-level factor and a hospital-specific ICP utilisation rate (categorised into quartiles) adjusted for patient- and hospital-level covariates	In-hospital mortality	Patient level model (adj.) OR death ICP+ 0.44 (95%CI: 0.31–0.63); Hospital-level model (adj.): OR death ICP+ (highest – lowest quartile): 0.52 (95%CI: 0.35–0.78)
Biersteker (2012)	Chi^2 and two multivariate logistic regression analyses with 6 month outcome dichotomised as dead (yes/no) and unfavorable outcome (yes = GOSE 1–4/no = GOSE 5–8) adjusted for patient's propensity score of receiving an ICP monitor inserted	6 month mortality (n, %) 6 month unfavorable outcome (n, %) ICU LOS (median, IQR) Hospital LOS (median, IQR)	Mortality ICP+ 59 (48%); ICP- 52 (37%), p = .07 OR death (adj.) 0.93 (95%CI: 0.47–1.85) ICP+ 81 (74%), ICP- 67 (53%), p< .001 OR unfav (adj.) 1.81 (95%CI: 0.88–3.73) ICP+ 10.8 (4.2–21); ICP- 2.65 (1.00–6.9), p<.001 ICP+ 22.0 (8.3–44), ICP- 7.48 (1.9–20), p<.001
Bulger (2002)	Aggressive centers (ICP monitoring in > 50% of patients with a BTF indication) are compared with non-aggressive centers (ICP monitoring ≤ 50% of the patients with a BTF indication) using a Cox proportional hazards model adjusted for baseline characteristics and treatment characteristics. The association with LOS was calculated using linear regression controlling for ISS< head AIS, age, and hypotension on admission	In-hospital mortality Hospital LOS	Hazard Ratio = 0.43 (95%CI: 0.27–0.66) Mean difference = –6 (95%CI: (–14) – 2), p = .143
Fakhry (2004)	Comparison of a historical control group (1991–94), low adherence (1995–96, 50% adherence) and high adherence (1997–00, 88% adherence) using F test and Tukeys honest significant difference multiple comparison (post hoc) for significant results	Mortality (%) ICU LOS (mean) Hospital LOS (mean) Favorable outcome (GOSE, % good recovery) at discharge RLAS (% appropriate) at discharge	91–94: 17.8%; 95–96: 18.6%; 97–00: 13.8%, p = .047 91–94: 9.7; 95–96: 8.4; 97–00: 7.9, p = .021 91–94: 21.2; 95–96: 16.7; 97–00: 15.8, p = .001 91–94:43.4%; 95–96: 50.3%; 97–00: 61.5%, p<.001 91–94: 43.9%; 95–96: 44.0%; 97–00: 56.6%, p = .004
Farahvar (2012) *Gerber (2013)*	Chi^2 and multivariate logistic regression analysis to adjust for age, hypotension status on day 1, pupillary status on day 1, initial GCS score, and CT results with 2 weeks mortality as dependent variable	Two-weeks mortality (n, %)	ICP+ 212 (19.6%); ICP- 74 (33.2%); p<.001 OR = 0.64 (.41–1.00), p = .05
Griesdale (2010)	Fisher's exact test, t-test, Wilcoxon rank-sum tests and multivariate logistic regression analysis adjusted for GCS and the propensity score of having an EVD monitor inserted	In-hospital mortality (n, %) 28-day mortality (mean, SD) ICU LOS (median, SD)	ICP+ 28 (28.6%), ICP- 9 (12.3%), p < .01 OR (adj.): 2.8 (1.1–7.1) ICP+ 22 (22.4%), ICP- 9 (12.3%), p = .07 OR (adj.): 2.1 (0.80–5.6) ICP+ 14 (11), ICP= 6 (8). P < .001
Härtl (2006)	Logistic regression analysis adjusted for age, pupillary status on day 1, hypotension status on day 1 and GCS score on day 1	Two-weeks mortality (%)	Unadj: Indirect 25.6%, direct 20.7%, p = .10 OR(adj.) = 0.68 (0.47–0.97)
Mauritz (2008)	Logistic regression to identify factors associated with survival. Authors developed a scoring system to measure quality of care (high quality = what is stated in the guideline) and adjusted for UMIC, LMIC, age, first GCS, ISS score and system factors	ICU survival	Quality score prehospital[A]: OR = 0.99 (0.95–1.03) Quality score hospital[B]: OR = 1.04 (1.01–1.06)

Appendix 11.E (continued)

Study ID	Statistical method (outcome)	Outcome variables	Statistics
Rusnak (2007)	Logistic regression adjusted for age, ISS and GCS. Authors developed a scoring system to measure guideline adherence	ICU survival	Total score[C]: OR = 1.01 (0.98–1.03)
		90 days Favorable outcome (GOS)	Total score: 1.02 (0.99–1.04)
		ICU LOS	Unit difference ICU = 0.05 (p< .05)
		Hospital LOS	Unit difference hospital = –0.04 (p<.05)
Shafi (2014)	Multivariate model with compliance scores as independent variable adjusted for age, sex, insurance status, SBP, ISS, GCS score, head AIS score, Marshall score≤ 2, craniotomy, decompressive craniectomy	In-hospital mortality	Compliance score[D] (per 10% increase): OR = 0.88 (0.81–0.95)
Talving (2013)	Logistic regression analysis adjusted for age, presence of hypotension on admission, head AIS of 5, extremity AIS ≥ 3, presence of IPH or SAH on CT, PTT on admission, early nutrition, decompressive craniectomy/craniotomy within 4 hours and decompressive craniectomy/craniotomy within 24 hours, and the probability of receiving ICP monitoring	In-hospital mortality	ICP+ 33 (33%), ICP- 62 (54%) OR (unadj.): 0.42 (0.24–0.72); OR (adj): 0.15 (0.03–0.74)
		ICU LOS (mean)	ICP+ 16.8, ICP- 8.2 Mean difference (unadj.): –8.62 (–11.83 – (–5.41)) Mean difference (adj): –6.04 (–9.46 – (– 1.69))
		Hospital LOS	ICP+ 19.4, ICP- 10.1 Mean difference (unadj.): –9.26 (–13.10 – (– 5.42)) Mean difference (adj): –7.14 (–11.14 – (–2.08))

[A] Quality score prehospital is based on airway management (endotracheal intubation, other airway management), direct transfer to study centre and helicopter transfer (Mauritz, 2008).
[B] Quality score hospital is based on CT scan, Intracranial pressure monitoring, Ventilation, Body Temperature below 38.5◦C and steroids (Mauritz, 2008).
[C] Total score is based on prehospital resuscitation, resuscitation of BP and O_2, Indication of ICP, ICP treatment threshold, type of monitoring, CPP, Hyperventilation, Mannitol, Barbiturates, Steroids and Anti-seizure Prophylaxis (Rusnak, 2007).
[D] Compliance score is based on Endotracheal intubation, resuscitation, correction of coagulopathy, ICP monitoring, ICP directed therapy, and physical therapy and rehabilitation (Shafi, 2014).
ICP: intracranial pressure; OR: odds ratio; 95%CI: 95% confidence interval; adj.: adjusted; ICP+: patients in which was adhered to ICP monitoring guidelines; ICP-: patients in which was not adhered to ICP monitoring guidelines; LOS – length of stay; GOSE: Glasgow Outcome Scale Extended; Unfav: unfavorable outcome; ICU: intensive care unit; IQR: interquartile range; BTF: Brain Trauma Foundation; ISS: Injury Severity Score; AIS: Abbreviated Injury Scale; RLAS: Ranchos Los Amigos Scale; GCS: Glasgow Coma Scale; CT: computed tomography; EVD: external ventricular drainage; UMIC: upper middle income country; LMIC: lower middle income country; GOS: Glasgow Outcome Scale; SBP: systolic blood pressure; IPH: intraparenchymal hemorrhage; SAH: subarachnoid hemorrhage; PTT: partial thromboplastin time.

Chapter 12

Pain management in trauma patients in (pre)hospital based emergency care: Current practice versus new guideline

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ABSTRACT

Background Acute pain in trauma patients in emergency care is still undertreated. Early pain treatment is assumed to effectively reduce pain in patients and improve long-term outcomes. In order to improve pain management in the chain of emergency care, a national evidence-based guideline was developed. The aim of this study was to assess whether current practice is in compliance with the guideline 'Pain management for trauma patients in the chain of emergency care' from the Netherlands Association for Emergency Nurses (in Dutch NVSHV), and to evaluate early and initial pain management for adult trauma patients in emergency care.

Methods Chart reviews were conducted in three regions of the Netherlands using electronic patient files of trauma patients from the chain of emergency care. We included one after-hours General Practitioner Co-operation (GPC), one ambulance Emergency Medical Services (EMS), two Helicopter Emergency Medical Services (HEMS), and three Emergency Departments (EDs). Organisation of pain management, pain assessment, and pain treatment was examined and compared with national guideline recommendations, including quality indicators.

Results We assessed a random sample of 1,066 electronic patient files. The use of standardised tools to assess pain was registered in zero to 52% of the electronic patient files per organisation. Registration of (non-)pharmacological pain treatment was found in less than half of the files. According to the files, pharmacological pain treatment deviated from the guideline in 73–99% of the files. Time of administration of medication was missing in 73–100%. Reassessment of pain following pain medication was recorded in half of the files by the HEMS, but not in files of the other organisations.

Conclusions The (registration of) current pain management in trauma patients in the chain of emergency care varies widely between health care organisation, and deviates from national guideline recommendations. Although guideline compliance differs across groups of health care professionals, maximum compliance rate with indicators registered is 52%. In order to improve pain management and evaluate its effectiveness, we recommend to improve pain registration in patient files. Furthermore, we advise to identify barriers and facilitators related to the implementation of the national guideline in all emergency care organisations.

12.1 INTRODUCTION

Treatment of acute pain in emergency care still gets insufficient attention.[1] Acute pain and trauma are often closely related to one another, as pain is induced by noxious stimuli at the site of tissue damage.[2] Recent studies show that the prevalence of pain in trauma patients in the Dutch (pre-hospital) emergency care setting is 70–91%.[1,3] In contrast to the improved treatment of postoperative and chronic pain,[4,5] the treatment of acute pain in emergency care is low;[1] only 19–30% of trauma patients receive pharmacological pain treatment.[1,3]

Emergency care for trauma patients encompasses the care for patients with recent (within 24h) suspected injuries caused by blunt or penetrating forces, falls, explosions, heat/cold or chemical toxicants. In the Netherlands, emergency care is provided by General Practitioners (Co-operations) (GP(C)s), ambulance Emergency Medical Services (EMS), Helicopter Emergency Medical Services (HEMS), and Emergency Departments (EDs). Collaboration between health care professionals in the chain of emergency care with respect to pain management is not optimal, making it very difficult to guarantee continuity of care. As a consequence, pain treatment is not always applied, not continued or contradicts the pain management by the preceding professional partner in the chain.[6] The undertreatment of acute pain can have an adverse effect on the outcome of the treatment, e.g. a delay in wound healing, and causes a longer period of recovery.[7] Furthermore, poorly treated acute pain can result in chronic pain.[8] Early pain treatment is therefore of great importance.

To improve pain management in trauma patients, a national evidence-based guideline 'Pain management for trauma patients in the chain of emergency care' was developed in 2010.[9] This multidisciplinary guideline from the Netherlands Association for Emergency Nurses (in Dutch NVSHV) provides clear recommendations and quality indicators for early pain management in evaluable, adult trauma patients in the chain of emergency care, concerning pain assessment, (non-)pharmacological pain treatment, and the organisation of pain management.

The objective of this study is to 1) assess whether current practice is in compliance with the Dutch guideline recommendations, and 2) evaluate early and initial pain management for adult trauma patients in the chain of emergency care. The evaluation provides insight into the extent to which the guideline is already used by health care professionals in the chain of emergency care. It identifies the adherence and deviations in current practice from the quality indicators in the guideline, and provides a starting point for the implementation of the guideline.

12.2 METHODS

Design

Between January and March 2012 (HEMS from October 2011 to March 2012) chart reviews were conducted, assessing electronic patient files of trauma patients from seven organisations in the chain of emergency care, in three regions of the Netherlands; one after-hours GPC (suburban), one EMS (suburban), two HEMS (suburban and urban), and three EDs (rural/suburban, suburban and urban). Trauma patients were defined as patients with (suspected) injuries, due to mechanisms of blunt or penetrating forces, falls, explosions, heat/cold or chemical toxicants.[10] Patient files were used to assess whether current practice is in compliance with the guideline 'Pain management for trauma patients in

the chain of emergency care' from the NVSHV and to evaluate pain assessment and current pain management for adult trauma patients in emergency care.

Setting

The target group of the guideline consists of GPs, physicians and nurses in ambulance EMS and the ED, and team members of the HEMS. Dutch GPs organise their after hours primary care – weekdays 5PM to 8AM and weekend – in large-scale GPCs.[11] Telephone triage nurses assess the urgency of patient's health problem and decide – based on triage protocols[12] and guidelines – the appropriate action to be taken,[11] e.g. using paracetamol. In addition, out-of-hospital emergency care is also provided by nurses in EMS; registered nurses who followed a national training programme and deliver pre-hospital care autonomously, based on national protocols. These national protocols assist the nurses in the limited use of Fentanyl, Ketanest (S-Ketamine), and Midazolam in case of a trauma.[13] However, nurses may decide to deviate from the protocol (stating reasons) based on the patient's condition and circumstances, or follow advices from regional protocols, e.g. using paracetamol. Care provided by EMS nurses can be complemented by team members of a HEMS. Four HEMS, which are available on a 24/7 basis for the whole country, are equipped with a specially trained team including a HEMS physician (trauma surgeon or anaesthesiologist), a registered flight nurse, and a pilot. This team is capable of delivering hospital-level medical care and advanced pain management at the accident site, including the use of anaesthesia and certain analgesics. At the ED, a triage nurse assigns an urgency level to the patient's health problem,[14] and may decide to give a patient certain pain medications before treatment by a physician. Care at the ED is provided by registered physicians and nurses who followed additional training in emergency medicine.

Guideline

The national evidence-based guideline was developed in 2010 by a multidisciplinary working group consisting of representatives from all relevant professionals working in emergency care: general practitioners, EMS nurses, HEMS physicians and nurses, physicians and nurses working in the ED, nurse practitioners, physician assistants, anaesthesiologists and physicians of surgical and orthopaedic traumatology departments. The guideline offers professionals recommendations and indicators, concerning pain assessment, initial (non-)pharmacological pain treatment, and the organisation of pain management in the chain of emergency care. The guideline has been distributed among these organisations, but has not yet been actively implemented nationwide.

The guideline recommends to register pain scores, initial (non-)pharmacological pain treatment and time of administration of medication in the medical records. The guideline suggests to use the verbal Numeric Rating Scale (NRS), a scale from zero to ten with zero as no pain and ten as unbearable pain, to assess pain score. Pain needs to be assessed at least three times; at arrival, after (non-)pharmacological intervention, and at the end of the medical visit. Non-pharmacological treatment of patients with fractures, contusions, and soft tissue injuries should be delivered according to the RICE#-criteria – Rest, Ice, Compression and Elevation.

According to the guideline, initial pharmacological pain management should be given as indicated by algorithms, designed specifically for ambulance EMS, HEMS, GP(C) and ED (Figure 12.1 to 12.3).

Figure 12.1 Algorithm for pharmacological pain management in ambulance EMS

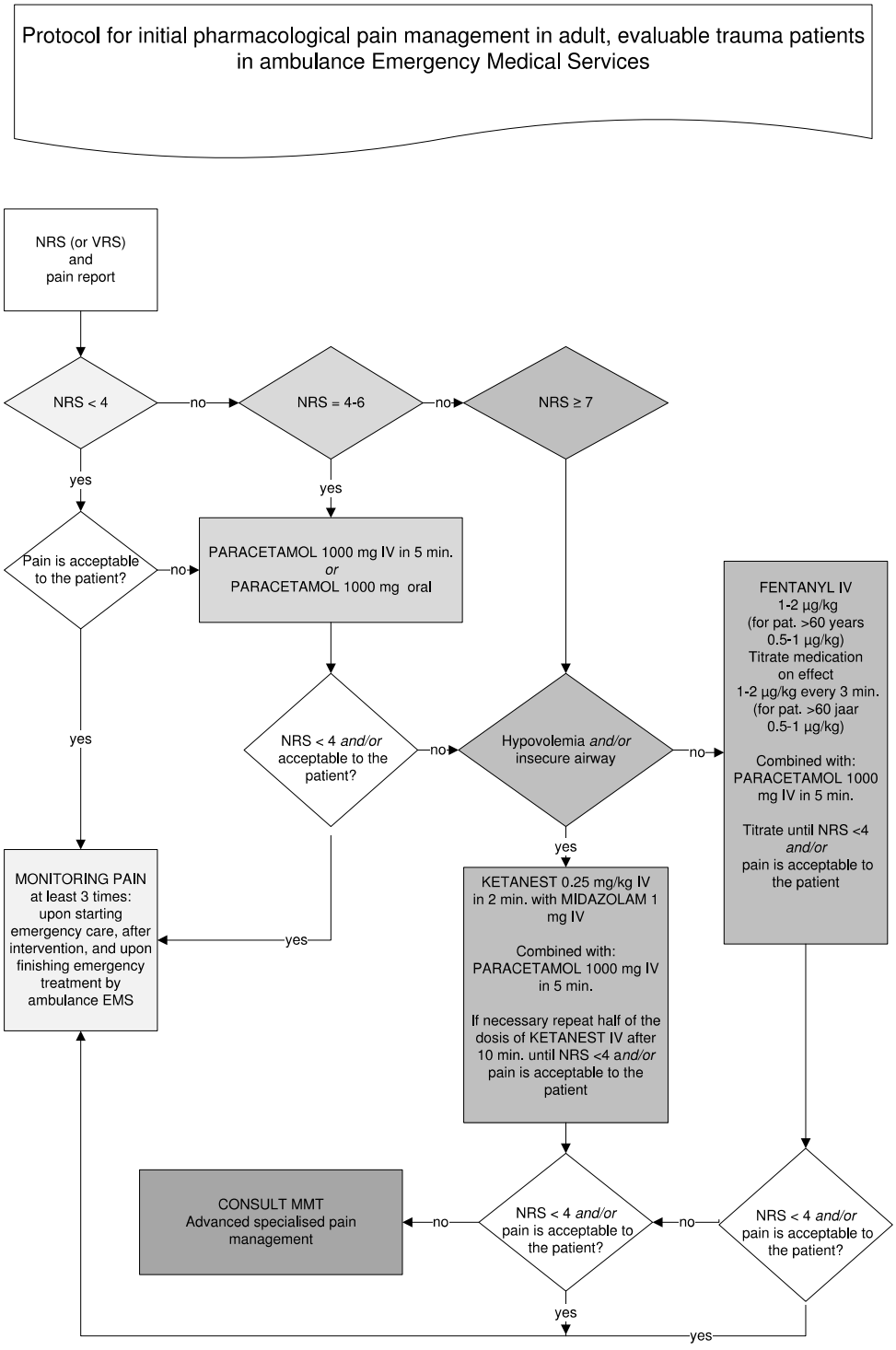


Figure 12.2 Algorithm for pharmacological pain management in HEMS

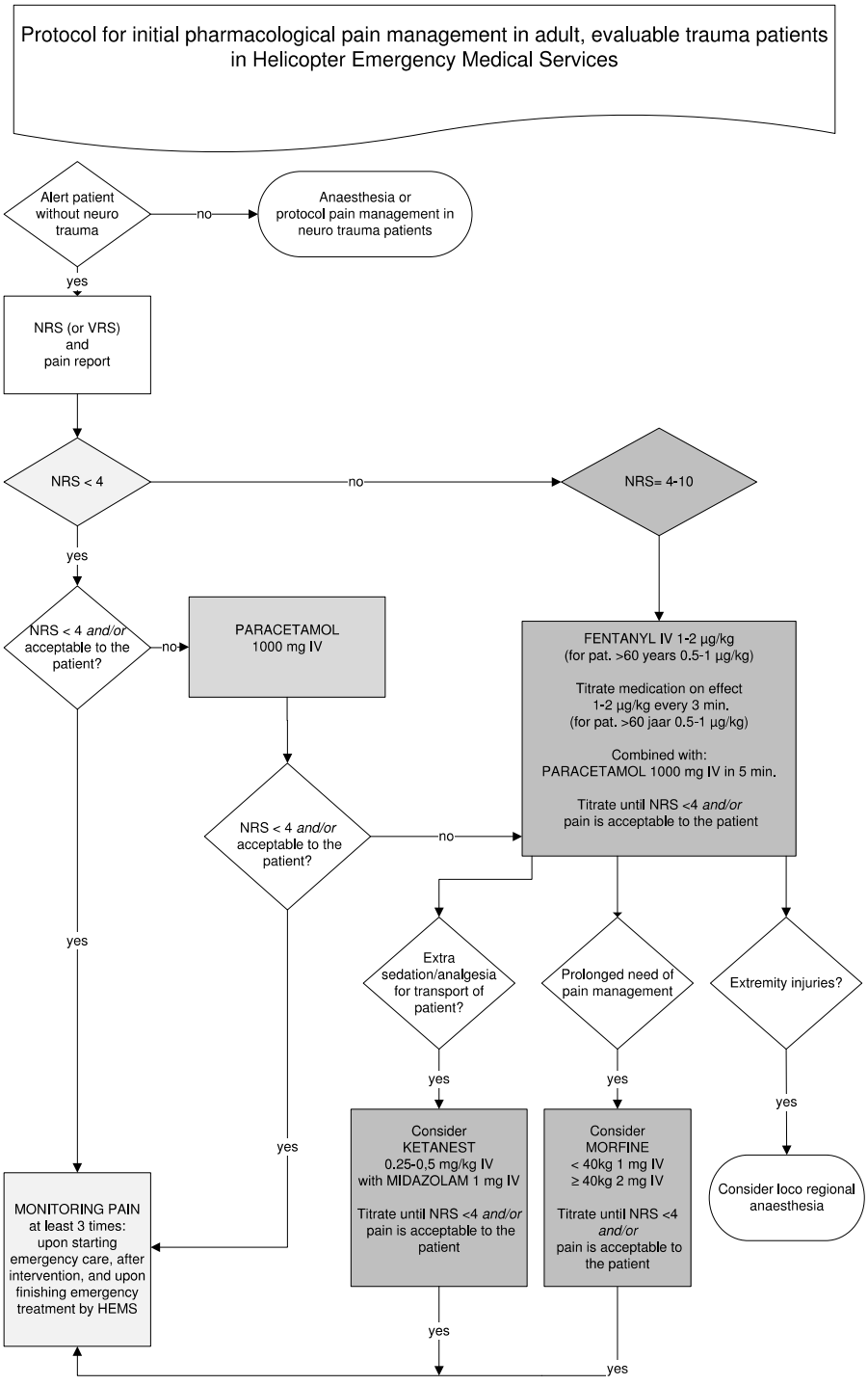
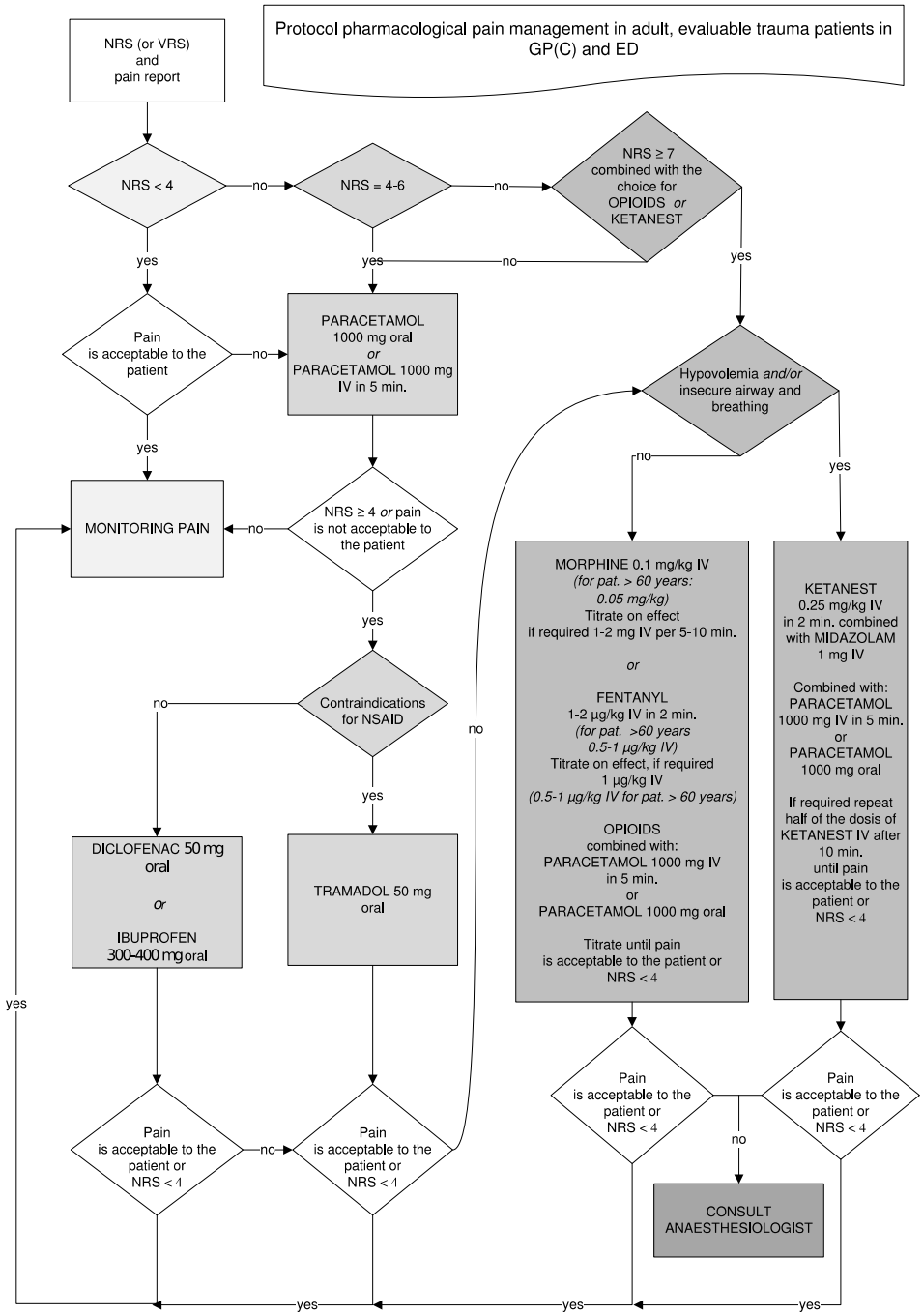


Figure 12.3 Algorithm for pharmacological pain management in GP(C) and ED



These algorithms consist of several routes concerning pain treatment for mild (NRS <4), moderate to severe (NRS 4–7) and unbearable pain (NRS >7). In the guideline, paracetamol is the pharmacological treatment of first choice, if necessary with additional use of non-steroidal anti-inflammatory drugs (NSAIDs) or opioids. Fentanyl and Morphine can be given for severe to unbearable pain during emergency care. Administering Ketanest can be considered in case of severe or unbearable pain in combination with hypovolemia.
In order to measure pain management performance by professionals and organisations in emergency care, the recommendations in the guideline are translated into essential indicators (Table 12.1).

Table 12.1 Indicators of guideline 'Pain management for trauma patients in the chain of emergency care'

Indicator	Numerator /Denominator
Organisation of pain management	
Pain treatment within 10 min after ABCD assessment	Number of patients pain treatment started ≤10 min after triage or intake / Patients with pain
Registration of pain score	Number of patients with registered pain score / Total number of patients
Registration of non-pharmacological pain treatment	Number of patients with registered non pharmacological pain treatment / Total number of patients
Registration of pharmacological pain treatment	Number of patients with registered pharmacological pain treatment / Total number of patients
Registration of time administration of medication	Number of patients with registered time of administration of medication / Total number of patients
Pain assessment	
Using Numeric Rating Score (NRS)	Number of patients pain assessed with NRS / Total number of patients
Using NRS after administration of analgesics	Number of patients with pain score after pain medication / Patients with pain medication
Acceptable pain level after treatment	Number of patients acceptable pain NRS <4 after medication / Patients pain score after medication
Using NRS three times during treatment	Number of patients pain assessed at least three times / Total number of patients
Pharmacological treatment	
Paracetamol for moderate to severe pain (NRS≥4)	Number of patients with NRS 4–10 receiving paracetamol / Patients with NRS 4–10
Treatment according to algorithms in guideline	Number of patients receiving treatment according to guideline flowcharts / Total number of patients

Data collection and selection of patient files

Patient files were handled anonymously – without patient identification, e.g. name or address. For each organisation, databases were preselected before a random sample for analysis was drawn. The preselection was based on the following inclusion criteria: patient in need of emergency care due to a recent trauma – less than 24h before admission – aged 18 or older, ABCD-stabile, and verbally responsive (Glasgow Coma Scale ≥14) at least once during treatment. Due to the severity of trauma treated by the HEMS and the lower number of HEMS calls (on average 45 non-cancelled flights per month in the study period), the preselection of the HEMS included patients with a Glasgow Coma Scale ≥8. This included also unresponsive patients, in contrast to the other organisations. Exclusion criteria were: patients that had drowning injuries, had attempted suicide, were victim of domestic violence, and visited ED for wound inspection or removal of stitches. After pre-selecting the electronic patient files, around 150 cases were randomly selected from each database.

In order to assess the electronic patient files for essential indicators, the quality indicators and recommendations from the guideline were translated into a measuring tool which was used to screen information in the patient files. The quality indicator 'treatment according to guideline algorithms' was assessed through a step by step analysis of the information per patient on pain as measured by the NRS, followed by the advised pharmacological treatment (dose not taken into account).

Data analysis

We used descriptive statistics (percentages, means and standard deviations (SDs)) to analyse the results. Data was analysed using SPSS 21 (SPSS Inc., Chicago, IL).

12.3 RESULTS

This study included a random sample of 1,066 files out of the 12,407 assessed electronic files of patients treated by the seven organisations in the emergency care, including 155 files of GPC, 176 of EMS, 238 of HEMS, and 497 of ED (Table 12.2).

Table 12.2 Pre-selection, inclusion and random sample per organisation

Region[1]	Organisation	Period	Patient files	Sample
Rural/suburban	ED - general	January – March 2012	8,741	195
Suburban	GPC	January – March 2012	1,224	155
	EMS	January – March 2012	807	176
	HEMS	October 2011 – March 2012	287	120
	ED – academic	January – March 2012	690	157
Urban	HEMS	January – March 2012	245	118
	ED – academic[2]	January – March 2012	413	145
Total			12,407	1,066

[1] Defined by number of inhabitants per agglomeration: rural/suburban 159.000; suburban 168.000, urban 1.000.000.[15]
[2] Selection of patients with primary transport by EMS to the ED.

Characteristics of patients

Table 12.3 shows the characteristics of the 1,066 trauma patients, of whom most were men (51.1% at EMS to 73.1% at HEMS). The age of the trauma patients ranged from 18 to 100, and varied from a mean age of 41.9 (SD 17.2) in the GPC to 57.3 (SD 23.2) in the EMS. Most patients treated in the GPC had injuries due to sports, while patients treated by the (H)EMS or ED often had injuries that occurred at home or during leisure, or in traffic. Mechanism of injuries often included a fall or collision (data not shown).

Most patients had injuries to their extremities (up to 72.1% in the GPC). Patients treated by the (H)EMS and ED often had injuries to head/neck (up to 29.4%). The GPC often treated patients with superficial injury (24.5%), while the (H)EMS and ED often treated patients with fractures (up to 52.7%). In 1.3% (GPC) to 10.1% (ED) of the electronic patient files it was registered that patients were under the influence of alcohol and/or drugs. Most electronic patient files did not contain information about the mental state of patients (data not shown).

Guideline adherence and current practice of pain management

Adherence to the guideline is presented in Table 12.4 and 12.5 reports current pain management practice based on the chart review.

Table 12.3 Characteristics of trauma patients

Organisation (N electronic patient files)	GPC, N(%) n=155	EMS, N(%) n=176	HEMS, N(%) n=238	ED, N(%) n=497
Gender				
Men	96 (61.9)	90 (51.1)	174 (73.1)	303 (61.0)
Women	59 (38.1)	86 (48.9)	64 (26.9)	194 (39.0)
Age				
Mean (SD)	41.9 (17.2)	57.3 (23.2)	45.1 (18.9)	45.1 (20.8)
18–19	10 (6.5)	5 (2.8)	17 (7.1)	31 (6.2)
20–39	62 (40.0)	44 (25.0)	95 (39.9)	209 (42.1)
40–59	59 (38.1)	41 (23.3)	75 (31.5)	121 (24.3)
60 or older	24 (15.5)	86 (48.8)	51 (21.4)	136 (27.4)
Cause of injury				
Home and leisure	7 (16.7)	77 (55.4)	37 (23.6)	218 (47.7)
Traffic	5 (11.9)	41 (29.5)	95 (60.5)	103 (22.5)
Sports	20 (47.6)	15 (10.8)	10 (6.4)	50 (10.9)
Work	10 (23.8)	2 (1.4)	9 (5.7)	54 (11.8)
Violence	0 (0.0)	4 (2.9)	6 (3.8)	32 (7.0)
Unknown/Not registered	*113*	*36*	*81*	*40*
Location of injury				
Head/neck	10 (6.8)	41 (20.1)	130 (29.4)	100 (18.6)
Face	24 (16.3)	6 (2.9)	63 (14.3)	61 (11.3)
Thorax	7 (4.8)	17 (8.3)	71 (16.1)	27 (5.0)
Abdomen	0 (0.0)	10 (4.9)	39 (8.8)	10 (1.9)
Spinal cord	0 (0.0)	19 (9.3)	28 (6.3)	26 (4.8)
Extremities	106 (72.1)	111 (54.4)	111 (25.1)	315 (58.4)
Unknown/Not registered	*8*	*11*	*21*	*52*
Observed assumed injury				
Fracture	9 (5.8)	48 (52.7)	109 (23.8)	146 (29.0)
Dislocation/luxation	21 (13.5)	20 (22.0)	7 (1.5)	39 (7.8)
Intracranial injury	0 (0.0)	0 (0.0)	69 (15.1)	35 (7.0)
Internal injury[1]	3 (1.9)	0 (0.0)	31 (6.8)	17 (3.4)
Open wound	16 (10.3)	9 (9.9)	26 (5.7)	53 (10.5)
Injury to blood vessel	17 (11.0)	6 (6.6)	31 (6.8)	7 (1.4)
Superficial injury	38 (24.5)	1 (1.1)	63 (13.8)	77 (15.3)
Contusion	0 (0.0)	2 (2.2)	71 (15.5)	64 (12.7)
Other	51 (32.9)	5 (5.5)	51 (11.1)	65 (12.9)
Unknown/Not registered	*0*	*93*	*24*	*80*
Under influence				
Alcohol	2 (1.3)	8 (4.5)	19 (8.0)	50 (10.1)
Drugs	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Alcohol and drugs	0 (0.0)	1 (0.6)	1 (0.4)	5 (1.0)
Unknown/Not registered	*153*	*167*	*218*	*441*

[1] Internal injury of thorax, abdomen and/or pelvis.

Organisation of pain management

According to the registration in patient files, one fifth of patients of the HEMS and ED received pain treatment within 10 min after the ABCD assessment. For the GPC and the EMS this indicator could not be calculated due to missing time and pain score registrations. Registration of pain scores was lacking in the GPC, and varied from 15% in the EMS up to 52% in the ED. The registration of non-pharmacological pain treatment varied from 14% in the EMS up to 49% in the HEMS. Pharmacological pain treatment was registered in 13% in the GPC up to 48% in the (H)EMS. Finally, the registration of the time of administration of analgesia was not or poorly reported in the GPC (0%), EMS (1%) and HEMS (13%). However, over one in four electronic files in the ED contained a time of administration of analgesia (27%).

Table 12.4 Guideline adherence

Organisation (N electronic patient files)	GPC, N(%) n=155	EMS, N(%) n=176	HEMS, N(%) n=238	ED, N(%) n=497
Organisation of pain treatment				
Pain treatment within 10 min after ABCD assessment[1]	*	*	10 (18)	23 (20)
Registration of pain score (any scoring instrument)	0 (0)	26 (15)	68 (29)	259 (52)
Registration of non-pharmacological pain treatment	47 (30)	24 (14)	117 (49)	50 (46)
Registration of pharmacological pain treatment	20 (13)	84 (48)	115 (48)	228 (46)
Registration of time administration of medication	0 (0)	2 (1)	31 (13)	132 (27)
Pain assessment				
Using Numeric Rating Score (NRS)	0 (0)	26 (15)	68 (29)	126 (25)
After administration of pain medication[2]	*	*	27 (48)	*
Acceptable pain level after treatment[3]	*	*	14 (52)	*
At least three times during treatment	*	3 (2)	25 (11)	13 (3)
Pharmacological treatment				
Paracetamol for moderate to severe pain (NRS≥4)[4]	*	6 (32)	1 (3)	37 (50)
Treatment according to algorithms in guideline	*	22 (13)	3 (1)	132 (27)

Percentages are presented and calculated by the number divided by the total number of patients per organisation.
[1] Divided by number of patients with pain (HEMS: 56, ED: 115). [2] Divided by number of patients with pain medication (HEMS: 56). [3] Divided by number of patients with a pain score after medication (HEMS: 27). [4] Divided by number of patients with NRS 4-10 (EMS: 19, HEMS: 39, ED: 74).
* Cannot be calculated due to missing, not registered or unknown data.

Pain assessment

The files of the GPC and one HEMS indicated that a systematic pain score with the NRS was not used. In the EMS professionals registered the NRS in 15% of the patients, while for the ED in 25% and the other HEMS in 57% of the files a pain score was reported. If pain was assessed, it was mostly registered as assessed once during treatment. Indicators on the effectiveness of pain management (pain assessment after medication, and acceptable pain level after treatment) could not be calculated for the GPC, EMS and ED, due to the missing time registrations of the pain score and administration of pharmacological pain treatment. For the HEMS half of the patients (52%) had an acceptable pain score registered after pharmacological interventions.

(Non-)pharmacological treatment

Non-pharmacological treatment of patients treated by the GPC often consisted of a bandage (57.4%), while treatment at the ED (64.5%) and HEMS (77.8%) often consisted of immobilisation by splint or cast (Table 12.5). Pharmacological pain treatment was administered and registered in accordance to the algorithms of the guideline in 1% (HEMS) up to 27% (ED) of the patients. Guideline adherence for the GPC could not be assessed, because the recommendations regarding pain management in the guideline are based on intensity of pain, and the GPs reported no pain scores in the files.

In general, only the registered pain treatment at the ED often included paracetamol (35.5%) or a combination with paracetamol (49.6%). Half of the patients with severe or unbearable pain in the ED received paracetamol (50%); this was in contrast with the HEMS, where no or hardly any paracetamol was (registered to be) administered to patients in severe or unbearable pain. Due to the often life-threatening injuries, patients in the HEMS were mostly treated without paracetamol (51.3%), and were provided with more stronger analgesia like Ketanest or anaesthesia. The files indicated that patients of all severities received paracetamol (45.0%), NSAID (40.0%) or a combination of medications including paracetamol (15.0%) in the GPC, and Fentanyl in the EMS (36.9%) and HEMS (47.0%).

Overall, the chart review showed that the current registration of pain management mainly (but poorly) focused on the administration of analgesia and not on the pain assessment and evaluation, with a maximum compliance rate of 52%.

Table 12.5 Current practice of pain management

Organisation (N electronic patient files)	GPC, N(%) n=155	EMS, N(%) n=176	HEMS, N(%) n=238	ED, N(%) n=497
Type of scale				
NRS	0 (0.0)	26 (100)	68 (100)	126 (47.5)
VRS	0 (0.0)	0 (0.0)	0 (0.0)	117 (44.2)
NRS and VRS	0 (0.0)	0 (0.0)	0 (0.0)	16 (6.0)
Other	0 (0.0)	0 (0.0)	0 (0.0)	6 (2.3)
No/Unknown/Not registered[1]	*155*	*150*	*170*	*232*
Number of assessments				
Once	0 (0.0)	18 (69.2)	28 (35.4)	229 (88.4)
Twice	0 (0.0)	5 (19.2)	26 (32.9)	17 (6.6)
3 times	0 (0.0)	3 (11.5)	25 (31.6)	13 (5.0)
Unknown/Not registered[1]	*155*	*150*	*159*	*238*
Non-pharmacological				
No	1 (2.1)	6 (25.0)	22 (18.8)	2 (0.9)
Immobilisation	0 (0.0)	10 (41.7)	91 (77.8)	149 (64.5)
Ice	5 (10.6)	0 (0.0)	0 (0.0)	1 (0.4)
Compression	8 (17.0)	0 (0.0)	0 (0.0)	35 (15.2)
Elevation	1 (2.1)	1 (4.2)	0 (0.0)	11 (4.8)
Bandage	27 (57.4)	7 (29.2)	2 (1.7)	18 (7.8)
Other	5 (10.6)	0 (0.0)	2 (1.7)	15 (6.5)
Unknown/Not registered[1]	*108*	*152*	*121*	*266*
Pharmacological				
Paracetamol	9 (45.0)	15 (17.9)	0 (0.0)	81 (35.5)
NSAID	8 (40.0)	0 (0.0)	0 (0.0)	6 (2.6)
Fentanyl	0 (0.0)	31 (36.9)	54 (47.0)	13 (5.7)
Morfine	0 (0.0)	2 (2.4)	0 (0.0)	9 (3.9)
Nitrous 50%/ oxygen 50%	0 (0.0)	3 (3.6)	0 (0.0)	0 (0.0)
Other	0 (0.0)	6 (7.1)	0 (0.0)	0 (0.0)
Combination with paracetamol	3 (15.0)	14 (16.7)	2 (1.7)	113 (49.6)
Combination without paracetamol	0 (0.0)	13 (15.5)	59 (51.3)*	6 (2.6)
Unknown/Not registered[1]	*135*	*92*	*123*	*269*

[1] Missing information can have several meanings; assessment/treatment has not been done/provided unfairly, has not been done/provided with good reasons, was not needed at all, or has been done/provided but not registered.
* HEMS provides advanced pain treatment, while the guideline is limited to initial pain treatment.

12.4 DISCUSSION

Our study showed that (registration of) current pain management in trauma patients in the chain of emergency care varies widely between health care organisations, and is suboptimal. The assessment of pain scores using standardised tools was only registered in zero to 52% of the electronic patient files per organisation. Registration of (non-)pharmacological pain treatment was found in less than half of the files. According to the available information in the electronic patient files, pharmacological pain treatment was not in accordance with the guideline in 73–99% of the files. The time of administration of medication was missing in 73–100% of the patient files. Reassessment of pain following administration of pain medication was recorded in half of the patient files by the HEMS, but not in any of the patient files of the other organisations.

Although the Dutch guideline has been distributed among the organisations in emergency care, it has not yet been actively implemented nationwide. As a first step in the implementation of the guideline,

this study assessed where current practice deviates from the guideline recommendations. It is important to note that any differences found are not interpreted as violations, but rather as issues for which the reasons need to be explored. Thus, a next step is to explore reasons for deviations from the guideline, which may depend on the circumstances, patient characteristics and injury severity. For example, the HEMS provides care to patients with often life-threatening injuries and unstable vital signs, and their advanced pain management often does not start with the administration of paracetamol and reaches beyond the algorithm for initial pain management in the guideline. Before deciding on an implementation strategy, barriers and facilitators for guideline adherence in the chain of emergency care need to be identified.

A limitation of this study was the use of chart review to assess current practice. The data registered by the emergency care organisations was not primarily gathered for research purposes, and not all organisations had the ability to register all relevant data on pain management in their electronic patient files, because their databases were not designed for this purpose. For example, the GPC had no pain scores registered in their electronic patient files. Guideline adherence for the GPC could therefore not be assessed, because the guideline recommendations regarding pain management are based on intensity of pain.

In addition, it is known that chart reviews are prone to underreporting. It is therefore highly plausible that missing registration on certain factors of pain assessment or pain treatment does not mean that these proceedings did not occur in practice; i.e. not performed or not registered. The lack of registration of information can have several meanings; assessment and treatment has not been done but should have been provided, has not been done and has not been provided with good reasons, was not needed at all, or has been done and is provided but not registered. This challenges the determination of guideline adherence. Overall, compliance with the guideline in practice, particularly with regard to registration of pain management, could be higher. Uniform registration of data by all organisations on the organisation of pain, pain assessment, and pain treatment, is key to accurately evaluate early pain management in the chain of emergency care.

With these limitations in mind, our study is to our knowledge the first to report on pain management in trauma patients in a comprehensive sample of organisations in the chain of emergency care. Most studies on pain management in trauma patients focused on one specific organisation in the emergency care setting.

The finding that (registration of) current practice of pain management in trauma patients in emergency care is suboptimal, is not new. Earlier retrospective document and prospective cohort studies among respectively 1,407 and 450 patient of the EMS and ED showed that in the ambulance only 30% of the patients receive pain medication,[3] and in the ED this is even less (19%),[1] and 69–86% still report pain at discharge.[1] Furthermore, a high prevalence of oligoanalgesia (40%) was identified in adult trauma victims transported by the HEMS.[16] Although pain is the major complaint for patients seeking emergency care,[17] research showed that only 20% of the patients with minor trauma actually received adequate pain management, while 40% of these patients expected to receive analgesia in the ED.[18] In contrast, our study shows a much larger amount of patients for whom pain medication is registered at admission; GPC (15%), EMS (48%), HEMS (48%), and ED (46%). Although compliance with the guideline differs across groups of health care professionals, the maximum compliance rate with the indicators

registered is 52%. The deviations in current practice from the quality indicators of the guideline were however expected, as the guideline has not yet been implemented nationwide.

The pain guideline requires professionals in the chain of emergency care to collaborate and synchronise their pain management strategies. This might pose a problem as these professionals are used to work autonomously. Their differences in professional background, working culture, organisation and financial incentives may influence their guideline adherence.[19,20] As with all guidelines, it is not self-evident that the guideline will implement itself. Therefore, the development of a tailored implementation strategy for the multidisciplinary pain guideline is necessary. This implementation strategy should be based on a thorough analysis of the specific setting of the chain of emergency care and the different organisations involved in pain management.

Conclusions

In conclusion, this study showed that (registration of) current pain management in trauma patients in the chain of emergency care varies widely between health care organisations, and deviates from the Dutch guideline recommendations. In order to improve pain management and evaluate its effectiveness, we recommend to improve pain registration in electronic patient files and to identify barriers and facilitators related to the implementation of the Dutch national guideline in all emergency care organisations.

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General discussion and summary

Chapter 13

General discussion

GENERAL DISCUSSION

The aim of this thesis was to study the incidence, health-related quality of life (HRQL), psychiatric consequences and costs of traumatic brain injury (TBI), and to contribute to the improvement of outcome assessment in the injury field. This chapter will describe the main findings of the papers in this thesis and consequently will address the possible shortcomings and methodological considerations. The chapter ends with the implications of the papers and recommendations based on the findings.

13.1 MAIN FINDINGS

Part I - Epidemiology of traumatic brain injury

The first part of this thesis studies the epidemiology of TBI, addressing research question 1:

1. *What are the incidence, health impact and costs of TBI, and which risk groups in TBI can be identified?*

In the Netherlands, yearly about 35,000 patients visit the emergency department (ED) due to a TBI, equal to an incidence of 214/100,000 person years. Most cases of TBI in the Netherlands are caused by a fall or traffic accident, the latter often involving cyclists. Over the past decade, Dutch numbers of ED visits and hospital admissions due to bicycle-related TBI strongly increased (54% and 92%), especially among older cyclists aged 55+ (151% and 186%, Chapter 3). Overall, TBI imposes a substantial disease burden (patients loose on average 7 disability-adjusted life years due to ill-health, disability or early death) and huge economic costs (in total €315 million per year, on average €18,000 per patient). Our integrated approach of assessing incidence, health impact and costs of TBI identified different risk groups for each indicator. Children and adolescents (up to 24 years) had high incidence and disease burden but low economic costs, whereas 25–64-year-olds had relatively low incidence but high economic costs. Overall, patients aged 65+ (often involving cyclists and fallers) had highest incidence, leading to considerable health care costs.

Part II - Methodological challenges in assessing outcome after injury

The second part of this thesis addresses some methodological challenges in assessing outcome after injury, answering research question 2:

2. *How can the assessment of outcomes after injury be improved?*

In Chapter 4, evidence from the international literature was reviewed to study and clarify the differences between the methods which are currently used to assess the pre-injury HRQL of injury patients. Retrospectively assessment (recall) showed consistently higher pre-injury HRQL scores than population norms and a recovery that lags behind that of prospective assessments, implying a systematic overestimation of the change in HRQL from pre- to post-injury due to an injury. Researchers should be aware of the bias that may arise when pre-injury HRQL is assessed retrospectively or when population norms are applied, and should use prospectively derived HRQL scores wherever possible to estimate the impact of injury on HRQL.

Overall, the assessment of outcome after injury has become increasingly important, due to the growing number of injury patients that survives their injury.[1] Although trauma registries were initially developed

to improve preventable mortality after trauma, our research shows the possibilities of extending these registries with valuable follow-up data on the consequences of injuries beyond mortality, and incorporating these outcomes in the evaluation of trauma care (Chapter 5). This way, insight in the outcome of trauma survivors can be obtained, and comparisons of the consequences of trauma across patient subgroups can be made.

Estimates of the outcomes after injury may further be improved by choosing the right elements in, for example, calculating the healthy time that is lost due to living with disability (YLD) due to TBI. An essential component of these YLD calculations is the disability weight.[2] YLD estimates can be derived using different methods, involving the use of a set of standard disability weights (e.g. from the Global Burden of Disease study) or disability weights derived from HRQL follow-up data of individual TBI patients. As described in Chapter 6, both methods yield similar estimates of the YLD due to TBI in the Netherlands. Although researchers increasingly recommend the use of HRQL disability weights,[3-6] as these capture the heterogeneity within TBI patients and match with the epidemiological data of the sample under study,[7] HRQL data might be affected by factors like the patient's comorbidity, age, sex and adaptation to a certain health state, and the follow-up time or instrument used to assess HRQL.

Part III - Outcome after traumatic brain injury

The third part of this thesis studies the health outcome after TBI, addressing research question 3:

3. What is the impact of TBI on HRQL, and what is the prevalence of psychiatric disorders after TBI?

Historically, studies on the impact of TBI on HRQL primarily have focused on the consequences of moderate and severe TBI instead of mild TBI, due to a lack of consensus on the diagnosis of mild TBI and limited methods for detecting and classifying less severe grades of TBI.[8] Over time, studies have advanced our knowledge on the outcomes and recovery patterns after mild TBI,[8,9] although studies often still focus on the outcomes after either mild TBI or moderate and severe TBI.[10] As described in Chapter 7, data from a longitudinal cohort study indicates that TBI of all severities strongly affects HRQL, showing different recovery patterns between TBI severity levels with only patients with mild TBI reaching outcomes comparable to population norms at one year follow-up. Consistent with risk factors identified in general injury populations,[11] our results show that poor HRQL after TBI is predicted by female gender, older age, comorbidity and a higher injury severity.

Our results emphasise that TBI has a more negative association with patients' mental functioning than physical functioning.[10] As described in Chapter 8, review of the international literature shows that a high number of patients encounter anxiety and depressive disorders following TBI, often involving post-traumatic stress disorder (PTSD) and major depression disorder (MDD). These problems persist over time, as over one third of the patients are diagnosed with an anxiety or depressive disorder more than one year after TBI. The meta-analysis described in Chapter 9 shows that patients with a shorter post-traumatic amnesia and those with a memory of the traumatic event are at higher risk to be diagnosed with PTSD after TBI. Moreover, MDD after TBI is associated with pre-injury depression, female gender, moderate TBI, and post-injury unemployment.

These psychiatric consequences, in their turn, have a great impact on the HRQL in TBI patients. It was shown in Chapter 10 that both PTSD and MDD are associated with significantly decreased objective clinical outcomes as well as subjective HRQL.

Part IV - Guidelines and adherence

The fourth part of this thesis addresses the adherence to guidelines in the field of injury, answering research question 4:

4. What is the extent of adherence to guidelines in injury patients?

Our findings indicate that TBI, and injury in general, is not just an acute event, but can result in long-term consequences. Although our knowledge on the epidemiology and impact of injuries has increased over time, guideline adherence remained suboptimal. Review of the international literature (Chapter 11) and medical charts (Chapter 12) shows that guideline adherence in injury patients is generally low and varies widely between studies and between health care organisations. In case of TBI, adherence is found to be higher in guideline recommendations that are based on strong evidence rather than lower level evidence. Guidelines are also more often adhered to in younger patients and those with more severe TBI. Adherence to guidelines is associated with more favorable patient outcomes, showing a reduction in mortality. The clinical management and trauma care for injury patients and evaluation of its effectiveness can be improved by a complete registration of guideline recommendations and quality indicators in patient files.

In summary, the studies in this thesis clearly indicate that TBI has a substantial impact on both individuals and society. TBI has large and often long-term consequences for the persons' functioning and HRQL, resulting in a high disease burden. Subsequently, TBI imposes huge economic costs due to the often long-term need for specialised medical care and loss of productivity.

13.2 METHODOLOGICAL CONSIDERATIONS

Considerable methodological variation exists in the methods to measure outcome after TBI[10] as well as injury in general,[11] including differences in settings, study populations, instruments, follow-up periods and timings of assessments. These design choices limit the comparability between study results, and limit our insight into the national, regional, and global burden of injuries.

Clinical outcome

Over the past decades, our knowledge on the causes and consequences of injuries has rapidly grown, especially in case of TBI. This resulted in the recognition of the impact of milder injuries and the development of criteria to diagnose and classify TBI.[8,12]

TBI severity is often classified with use of scores on the Glasgow Coma Scale (GCS). Since 1974, the GCS is the most common scoring system used to describe the level of consciousness after TBI.[13] The GCS can be translated into three severity categories: mild, moderate, and severe TBI. There is however considerable variation within these severity categories, especially at the ends of the scale.[14] Research shows that the GCS as a single variable may have limited value as a predictor of outcome after TBI, and suggests the use of other variables for this purpose (e.g. the duration of post-traumatic amnesia).[15,16]

Only recently, an expert group published a position statement including a clear-cut definition of TBI and related diagnostic criteria.[12] Notwithstanding, research on the epidemiology of TBI still lacks standardisation and does not incorporate all TBI cases.

Most estimates on the incidence of TBI are based on data from only a sample of hospitals in a certain nation or region, and include only TBI cases that warranted treatment at an ED or admission to a hospital. As a consequence, these estimates do not include the thousands of persons with TBI who consult their general physician[17] or another specialists (e.g. physiotherapist), or those not seeking medical help but experiencing a change in their ability to function after the injury.

Epidemiological data is known to be incomplete, as patients with mild injuries may be missed in current epidemiologic monitors. Combination of data from prospective and retrospective surveillance systems in New Zealand shows that the incidence of TBI, especially mild TBI, may be substantially greater than would be estimated from previous findings.[18] To get full insight into the true size of the TBI problem, data from multiple overlapping sources (e.g. surveillance systems, national registries, study databases, medical records, etc.) that hold information on TBI cases treated by health care professionals need to be combined. These data sources should also comprise accurate information on the TBI-related mortality.

Beyond mortality, outcome following TBI is generally assessed with the Glasgow Outcome Scale Extended (GOSE).[19] This 8-point scale enables clinicians to objectively score the patient's recovery.[19] Data from the Radboud University Brain Injury Cohort Study (RUBICS) showed that HRQL levels significantly increased with more favorable GOSE categories (Chapter 7), in line with other studies.[20,21] However, we found discrepancies between the objective perspective of clinicians on the patient's recovery on the one hand, and the subjective perspective of patients on certain aspects of their HRQL on the other hand. Specifically, one third of the patients showed poor outcomes on the domains general health, mental health or vitality, while being assigned good recovery levels by the clinician on the GOSE. Research on the observer variation in GOSE scores shows that clinicians may tend to rate patients as less disabled than indicated by the GOSE criteria.[22] If correctly rated, the GOSE does however incorporate the pre-injury health status of patients, by ignoring areas in which there has been no change with respect to the situation before the injury.

Functional outcome

Our insight into the impact of injuries on individuals can be improved by incorporating the patients' subjective perception of how an injury and its treatment affect physical, mental and social aspects of his/her life, by assessing their HRQL.[23] Data on these domains of functioning make it possible to obtain insight into the recovery patterns after injuries and the disability that injury patients experience over time. This provides ways to quantify the impact of injury on population health over time and enables comparison of health outcome between injury patients, different types of injuries, and between injuries and other diseases. However, measuring the impact of injuries remains challenging.

A recent systematic review shows considerable variation in the HRQL instruments that are used to assess the HRQL of patients with TBI.[10] Depending on the study setting and injury population, researchers may choose different HRQL instruments. This makes it difficult to compare the outcomes of studies, as different HRQL instruments measure different domains of HRQL and may result in different valuations of similar health states. Guidelines and recommendations are required to standardise the follow-up studies on the HRQL after TBI.

Moreover, the patient's HRQL after an injury may be influenced by factors other than the injury. Research shows that HRQL scores are for example associated with injury severity, injury type, gender,

patients' mental health and comorbidity.[11] For instance, pre-existing comorbidity may contaminate our estimates of the injury-related disability, since HRQL scores might incorporate the impact of one or more comorbid diseases instead of solely reflecting the impact of the injury. Consequently, these factors may all influence our measurement of what the impact of an injury is on the patient's HRQL.

Therefore, information on the pre-injury HRQL is needed to make valid estimates of the change from pre- to post-injury HRQL due to the injury. Studies may compare the HRQL reported by patients after an injury with general population norms. This way, we were able to show that TBI of all severities strongly affects HRQL (Chapter 7). However, general population norms may not reflect the pre-injury health status of injury patients, as pre-injury HRQL scores of injury patients often deviate from the HRQL scores in general populations. An alternative can be to use retrospective assessment (recall) to assess pre-injury HRQL. Retrospectively assessment however showed consistently higher pre-injury HRQL scores than the general population norms and a recovery that lags behind that of prospective assessments (Chapter 4). Users should be aware of the bias these methods may have on their estimate of the impact of injury on the HRQL of patients.

Measuring the effects of serious injuries, like TBI, on the mental functioning of patients may be even more challenging. On the one hand, there is overlap in symptoms caused by TBI and symptoms caused by psychiatric disorders. Patients with TBI may for example experience fatigue or difficulties in concentrating or social functioning, which are symptoms of TBI as well as psychiatric disorders. This impedes attribution of symptoms after TBI to the brain injury or other frequently comorbid conditions such as anxiety or depression. Differential diagnosis of the psychiatric consequences of TBI may be enhanced by using structured diagnostic interviews. In contrast to self-report measures, structured diagnostic interviews enable the clinical diagnosis of psychiatric disorders according to standard criteria. However, structured diagnostic interviews are time consuming for health care professionals as well as patients, and require specific training and experience. Although self-report measures are not designed to diagnose psychiatric disorders according to standard criteria, and their use may lead to less accurate prevalence estimates,[24-27] self-report questionnaires can be used as a screening tool to detect psychiatric symptoms. Consequently, only screening tools that have proven to be sensitive and specific in measuring psychiatric symptoms should be used. In addition, high cut-off scores need to be used to avoid over-diagnosing of psychiatric symptoms and the prevalence of probable psychiatric disorders.

On the other hand, it is difficult to determine causality between TBI, psychiatric disorders and impaired functioning. Our results show that a history of psychiatric disorders before a TBI is strongly related to the presence of psychiatric disorders after TBI (Chapter 8 and 9). In their turn, psychiatric disorders are associated with decreased functioning and HRQL (Chapter 8 and 10). According to previous research, post-injury psychiatric symptoms may be caused by the history of pre-injury psychiatric disorders, rather than due the TBI.[28] Moreover, psychiatric disorders may be caused directly by the injury, but may also occur as a consequence of the experienced disability after TBI.[29-31] Further research is necessary to determine the cause-effect relationship between the development of psychiatric disorders and impaired outcome after TBI.

Economic outcomes

The clinical and functional implications of injuries have a huge economic impact on both individuals and society. Generally, considerable methodological variation exists between studies that report on the

economic outcomes after injury. For example, cost calculations may be limited to inpatient costs or may also include the extramural health care costs. These differences in cost calculations make it difficult to compare the economic burden of injuries between countries or health care settings.

In this thesis we were able to assess both the direct medical costs and indirect productivity costs due to TBI, using the Dutch Burden of Injury Model. This model includes data on the medical expenses from pre-hospital care (e.g. emergency medical care) to out-of-hospital care (e.g. physiotherapy and home care) that is needed to estimate the direct health care costs of injuries. This information is, however, based on ED treated and/or hospitalised injury cases, and does not contain information on the costs of patients who seek care outside the hospital or did not use medical care.

Besides information on the direct health care costs, the applied cost model also includes data on the costs due to lost productivity. These indirect productivity costs represent the indirect economic burden of injuries resulting from absence from work due to an injury. To date, only a few population-based studies have included both the direct medical costs and indirect productivity costs of injuries. Their results underpin our findings that, especially in serious injuries like TBI, the productivity costs constitute a considerable proportion of the total economic burden (Chapter 2 and 3).[32-34] This indicates that information on the productivity costs is essential input for policy decision making and the development of preventive strategies.

Notwithstanding, the economic burden of injuries is expected to be even higher if other potential sources of indirect costs are included. Specifically in TBI, the occurrence of such a severe injury imposes a substantial financial burden to family members and caregivers, who are often confronted with loss of work productivity and financial issues in taking care of their injured relative.[35,36]

Patient follow-up data

Overall, we were able to use data from patient surveys from multiple studies in this thesis. There are, however, methodological considerations with respect to administering questionnaires to injury patients, especially in case of severe injuries like TBI.

There has been debate whether patients with cognitive impairments, like in TBI, have the skills to complete questionnaires, answering complex questions and providing useful information on their health outcome.[37,38] This may affect the measurement of constructs such as HRQL in severely impaired persons, and may have led to biased estimates of the health impact of TBI. Despite this, research indicated that lack of awareness is expected among patients with severe TBI soon after the injury, though most people are aware of those deficits six months after injury.[39]

Specifically in long-term conditions like TBI, questionnaire response may be affected by the adaptation of patients to a certain health state. Patients who live with certain conditions for some time may perceive their health state as being less severe.[40] This may lead to an underestimation of the true injury-related disability.

The most commonly threat to longitudinal studies on the outcomes after TBI is the loss due to follow-up.[41] The loss of subjects to follow-up may affect the generalisability of the findings, when those lost differ from those found and responding. These differences may occur in the outcomes themselves (e.g. higher response among older patients, reporting poorer HRQL) as well as in the factors affecting outcomes (e.g. higher response among those with a higher socio-economic status, reporting better HRQL).

Moreover, low response rates may affect the representativeness of the study findings to other patients. Response rates may be affected by the use of lengthy follow-up questionnaires, that are often used to assess a large number of outcome measures. However, contradictory findings have been published on the effect of questionnaire length on response rates and data quality.[42-44]

13.3 IMPLICATIONS AND FUTURE RESEARCH

In this thesis we estimated the incidence, disease burden and economic costs of TBI based on an extrapolation of data from the Dutch National Injury Surveillance System (ED treated cases, 12-15% coverage Dutch EDs) and the Dutch Hospital Registry (hospitalised cases, all Dutch hospitals) between 2007 and 2012. This way, we were able to generate national estimates of the incidence, disease burden and costs of TBI in the Netherlands (Chapter 2 and 3). In addition, we used regional data from a trauma registry (Chapter 5), longitudinal cohort study (Chapter 6, 7 and 10) and medical charts (Chapter 12) from an academic trauma center and health care organisations in the Eastern part of the Netherlands. The results of these studies do not necessarily apply to patients treated at other hospitals or health care settings. Additionally, thorough reviews of the available evidence from different countries and health care settings were used to provide an overview of the pre-injury HRQL in injury populations (Chapter 4), the prevalence and predictors of anxiety and/or depression following TBI (Chapter 8 and 9), and the adherence to TBI guidelines (Chapter 11). Although these systematic reviews included all eligible studies published in peer-reviewed English language journals, most studies reported on findings from high-income countries such as the United States, Australia, the UK or Canada. However, their findings may also be of use in developing countries. Overall, the studies presented in this thesis have important implications for policy makers, health care professionals and researchers.

Implications for policy and health care

Education and communication

TBI is often described as an silent epidemic, with patients and families who experienced a TBI knowing how devastating its effects can be, yet awareness among the public and even health care specialist remains low.[45] Prevention programmes are needed to inform the public on the devastating consequences a TBI can have, even in case of milder injuries, and should educate the population about how injuries can be avoided. Victims of a TBI seeking medical care should be clearly informed by their health care professional on the symptoms that may occur in the period after their injury, and their recovery should be closely monitored. Special attention should be given to the outcomes of injuries in patients with milder injuries, as patients but also health care professionals might underestimate the consequences a mild TBI can have. Overall, early recognition, treatment and monitoring of the physical as well as psychiatric consequences of TBI may enhance the recovery of TBI survivors, their capacity to work, and may reduce the high costs associated with disability after TBI.[30,46]

Setting priorities for prevention

Our research shows that TBI imposes a substantial disease burden and huge economic costs to individuals and society, supporting findings from other countries.[32,33,47] Our studies provide directions on how the burden of TBI can be reduced by identifying important risk groups in TBI that should be

targeted in prevention programmes. Worldwide, TBI is still highly prevalent among children, adolescents and older adults aged 55 years and older,[18,48-50] with falls and traffic accidents being its leading causes.[51,52] Especially in children, TBI can have a tremendous lifelong impact. The younger brain is more flexible and modifiable, and it was thought that healthy tissue could take over the functions of damaged tissue. It was only recently acknowledged that TBI can have a more devastating impact on children and adolescents than similar injuries may have on adults.[53,54] Children and young adults may face lifetime physical and psychological challenges, and experience problems in functioning and learning due to their TBI. Beyond the high incidence and disease burden among children, our findings show that TBI imposes a substantial loss of productivity among the working population leading to considerable productivity costs, and high health care costs among the elderly cyclists and fallers. Overall, this calls for the development of preventive strategies to reduce the number of serious injuries in these risk groups in order to reduce the TBI-related burden.

Patient's perspective

The studies in this thesis provide evidence that it is important to assess the subjective perspective of patients on their functioning and recovery following the injury. Information from patient-reported outcome measures (e.g. HRQL instruments) can be used in clinical decision making and may enable clinicians to detect unrecognised problems, monitor the impact of injuries and evaluate the provided care. Research shows that incorporation of the patient's perspective may lead to improvements in HRQL and satisfaction with care.[55]

Implications for future research

Data linkage

For future research, one of the challenges in assessing the outcomes after injury remains that epidemiological data on all TBI cases and data on the long-term medical events resulting from injury (e.g. long-term rehabilitation or even death) is often not readily available. Generally, multiple registration systems and databases exist that contain information on injuries and injury patients (e.g. national injury surveillance systems, national hospital discharge registries, trauma registries, hospital records, or cause of death registries). These registries all have their own purposes (e.g. prevention of injuries, or evaluation of trauma care) and therefore may document only specific information of the injury (e.g. data on the acute phase of trauma care, the number and cause of death, or the long-term outcomes after injury). As a consequence, none of these registries provides the full picture of medical events resulting from injury. Linkage of data from multiple sources may overcome these problems. Future research may benefit from data linkage to obtain full insight into the incidence, risk groups, costs, and impact of injuries on population health over time.

Long-term follow-up

Data on the long-term outcomes of trauma is often not available, or limited to a certain period of follow-up. Our research shows that most patients do not recover in the first year after TBI. TBI symptoms may persist for many years and may even cause growing problems over time.[56,57] This emphasises the need for longitudinal follow-up studies in TBI patients to obtain insight into the long-term consequences and recovery patterns after TBI. Additionally, challenges remain in rehabilitation research. To date, there is

only limited understanding of the rehabilitation process after TBI and the effectiveness of interventions.[58] The rehabilitation process plays an important role in the long-term outcomes of TBI survivors, as early and continuous rehabilitation improves long-term functional outcomes and reduces the economic burden of TBI.[59,60]

Productivity costs

Our results showed that the productivity costs dominate the economic burden after TBI, especially in men of the working age. However, the productivity costs related to paid work are not systematically included in injury research, and there is ongoing debate on whether and how indirect productivity costs should be included in economic evaluations.[61] Productivity costs strongly affect economic outcomes after injury, accounting for on average 75% of the total costs of TBI per patient (Chapter 2). On average 20% of the injury survivors, especially victims of severe injury like TBI, are unable to work or to return to full employment and become depended on social security.[62-64] Consequently, the productivity costs of injuries are often several times higher than the direct medical costs of injuries.[32] Future research should incorporate the productivity costs in their assessment of the economic burden of injuries, as information on the magnitude of productivity losses is important input for policy decisions and enables priority setting based on the total direct and indirect expenses due to injuries.

Integrated outcome assessment

Overall, studies on the incidence and outcomes after injury or other diseases should apply an integrated approach in assessing the incidence, health impact and economic costs. Incorporation of all three dimensions of outcome is essential to gain a comprehensive insight into the size of the injury or disease problem, to identify high-risk groups and to set priorities for prevention and treatment.

Standardisation of research

TBI is considered to be the most complex disease in our most complex organ. It is characterised by large heterogeneity, in terms of mechanisms, severity, and treatment, with a large range of outcomes. Our findings indicate that TBI of all severities strongly affects outcome after injury, which endorses the assessment of the outcomes after all severity levels of TBI in future research.[10,47] The heterogeneity imposes several methodological challenges, and endorse the need for standardisation in TBI research. Consensus should be reached on definitions, classifications, methodology (including timings of assessments and follow-up), and reporting of study results to enable comparisons between studies and to obtain insight into the true size of the TBI problem.

According to our findings, it is important to incorporate information on the patients pre-injury HRQL before the injury to assess the change between pre- and post-injury HRQL. Researchers should be aware of the bias that may arise when pre-injury HRQL is assessed retrospectively or when population norms are applied, and should use prospectively derived HRQL scores wherever possible to estimate the impact of injury on HRQL.

Financial support

Without support for research on the outcomes of TBI, there will be limited knowledge on the recovery patterns after TBI, the associated disease burden and costs, and the way to improve prevention and

rehabilitation of TBI victims. The growing number of TBI victims due to falls in the aging population and road traffic injuries in developing countries, endorses the need for financial support and funding of TBI research. Like the treatment for TBI patients, research should be a collaborative effort.

13.4 CONCLUSIONS

To conclude, the papers in this thesis quantified the incidence, health impact and costs of TBI, and contributed to the improvement of outcome assessment in the injury field. The incidence data, HRQL data, and cost data provided in this thesis is essential input for policy makers to set priorities in health care policy and prevention, and enables health care professionals to develop effective treatments, rehabilitation services and guideline recommendations. In addition, the findings of our papers and the methodological considerations presented in this thesis may enable researchers to further improve the assessment of outcomes after TBI. A collaborative effort of policy makers, health care professionals and researchers may tame the globally growing numbers of TBI victims, and improve the care and outcomes for injury patients.

13.5 RECOMMENDATIONS

Based on this thesis some specific recommendations can be made for policy makers, health care professionals and researchers who work in the injury field, especially related to TBI.

Policy makers

- Inform the public on the substantial consequences TBI may have, and educate the population about how injuries can be avoided.
- Develop preventive strategies to reduce TBI, targeting 0–24-year-olds, men in the working population aged 25–64 years, and elderly cyclists and fallers.
- Provide funding and support for research to assess the size and impact of the TBI problem.

Health care professionals

- Inform patients on the physical and mental symptoms that may occur after a TBI.
- Closely monitor the recovery of TBI victims over a long time of follow-up as TBI symptoms may persist for many years and may cause growing problems over time.
- Pay attention to the psychiatric consequences TBI may have.
- Do not underestimate the consequences of mild TBI.
- Incorporate the subjective perspective of patients on their functioning and recovery following injury in clinical decision making.
- Use guidelines in providing care to patients, and register all necessary items of the guideline recommendations and quality indicators in patient files.

Researchers

- Apply an integrated approach to assess the clinical, functional and economic outcomes after injuries and diseases, including the health-related quality of life (HRQL) and psychiatric consequences.
- Link data from multiple sources to obtain full insight into the size and impact of injuries and diseases.
- Incorporate the productivity costs to assess the economic burden of injuries and diseases.
- Assess the pre-injury HRQL of patients to estimate the change in health status due to an injury.
- Assess the long-term consequences and recovery patterns after TBI.
- Use multiple follow-up measurements over time (preferably lifelong), as recovery patterns and occurrence of symptoms may vary over time.
- Standardise TBI research by using uniform definitions, classifications, methodology (e.g. timings of assessments and follow-up), and reporting of study results to enable comparisons between studies.

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Summary

INTRODUCTION

Injuries are among the leading causes of death and disability in the world, often imposing great personal suffering and economic costs. An important severe injury that often affects young people is a traumatic brain injury (TBI). TBI occurs when a sudden trauma causes damage to the brain. Globally, the incidence of TBI has rapidly grown in scale over the past decade due to increasing motor vehicle use in low- and middle income countries and the growing number of falls among elderly in higher income countries.
TBI is often described as a silent epidemic, with patients and families who experienced a TBI knowing how devastating its effects can be, yet awareness among the public and even health care specialist remains low. Almost all TBI survivors experience some level of short-term or long-term impairment or disability, which disrupts the lives of victims and relatives, reduces their health-related quality of life (HRQL), complicates their recovery and rehabilitation, and imposes a huge economic burden to both individuals and society.
Over the past decades, the number of survivors of severe TBI has rapidly grown, though the disability due to TBI has not appreciably reduced. This has resulted in a shift in attention from mortality towards disability. Policymakers and clinicians are recognising the importance of quantifying the outcomes after TBI to assess the effects of prevention strategies and treatments. Consequently, insight into the incidence, health impact and costs of TBI is essential in order to compare the burden of injuries between patient subgroups and with other diseases, optimise health care policy and prevention, and develop effective health care and rehabilitation services.

Aims and research questions

In this thesis we assessed the incidence, health-related quality of life, psychiatric consequences and costs of injuries, especially TBI, and the possible improvements of outcome assessment in the injury field. The thesis consists of four parts, including eleven studies, that each address a specific research question:

- What are the incidence, health impact and costs of TBI, and which risk groups in TBI can be identified?
- How can the assessment of outcomes after injury be improved?
- What is the impact of TBI on HRQL, and what is the prevalence of psychiatric disorders after TBI?
- What is the extent of adherence to guidelines in injury patients?

Part I - Epidemiology of traumatic brain injury

In part I the incidence, costs and disease burden of TBI in the Netherlands were studied, and important risk groups in TBI were identified, using data from the Dutch Injury Surveillance System and National Hospital discharge. In **Chapter 2**, we demonstrated that yearly about 35,000 patients in the Netherlands visit the emergency department (ED) due to a TBI, equal to an incidence of 214/100,000 person years. We found that TBI imposes a substantial disease burden (TBI patients loose on average 7 disability-adjusted life years due to ill-health, disability or early death) and huge economic costs (in total €315 million per year in the Netherlands, on average €18,000 per patient). By applying an integrated approach of assessing incidence, health impact and costs of TBI, we identified different risk groups for each indicator. Children and adolescents (up to 24 years) had high incidence and disease burden but

low economic costs, whereas 25–64-year-olds had relatively low incidence but high economic costs. Overall, patients aged 65+ (often involving cyclists and fallers) had highest incidence, leading to considerable health care costs. In **Chapter 3**, we further explored the incidence and impact of TBI due to cycling. We identified a strong increase in the number of hospital treatments due to bicycle-related TBI over the past decade (55%), especially among older cyclists (55+, 151%).

Part II - Methodological issues in assessing outcome after injury

Part II addresses ways to improve outcome assessment in the injury field. The literature review in **Chapter 4** reviewed the methods that are currently used to assess pre-injury health status. We found that retrospectively assessment (recall) showed consistently higher pre-injury HRQL scores than population norms and a recovery that lags behind that of prospective assessments, implying a systematic overestimation of the change in HRQL from pre- to post-injury due to an injury. Researchers should be aware of the bias that may arise when pre-injury HRQL is assessed retrospectively or when population norms are applied, and should use prospectively derived HRQL scores wherever possible to estimate the impact of injury on HRQL.

In **Chapter 5** we performed a pilot study, linking trauma data from complementary registers to patient follow-up data. We showed the opportunities of expanding trauma registries with follow-up data on the consequences of injuries beyond mortality. This way, insight in the outcome of injury survivors can be obtained, enabling comparisons of the consequences of trauma across patient subgroups. Information on the (long-term) outcomes of injury survivors should be incorporated in the evaluation of trauma care.

In **Chapter 6** we compared two methods to derive disability weights for several TBI health states: a set of standard disability weights from the Global Burden of Disease (GBD) study and disability weights derived from HRQL follow-up data of individual TBI patients. A disability weight is a weight factor that reflects the severity of the health losses due to an injury or disease on a scale from 0 (implying no loss of health) to 1 (implying a health loss equivalent to death). These disability weights are used to calculate the number of years lost due to disability (YLD) after TBI. We showed that both methods yield similar disability weights for TBI health states, except for long-term consequences of severe TBI, for which the GBD disability weight was much higher (more severe), which will ultimately result in higher YLD.

Part III - Outcome after traumatic brain injury

In Part III the impact of TBI on HRQL, and the psychiatric consequences of TBI were studied. In **Chapter 7** we assessed the recovery pattern differences between mild, moderate, and severe TBI and examined the relationship between clinicians' outcome assessment and patient-reported outcomes in a cohort of TBI patients. We found that TBI of all severities strongly affects HRQL, showing different recovery patterns between TBI severity levels. Poor HRQL was predicted by female gender, older age, comorbidity and a higher injury severity. Patient-reported outcomes were generally poorer than clinicians' outcome assessments, showing the importance of the patient's perspective on functioning and HRQL in assessing disability.

The literature review in **Chapter 8** provides insight into the prevalence and risk factors of anxiety and depression after TBI. We found that prevalence rates of psychiatric disorders after TBI varied widely, often involving post-traumatic stress disorder (PTSD) and major depression disorder (MDD). About one

fifth of all patients with TBI had a history of anxiety (19%) or depressive disorders (13%) before the injury, and slightly more were diagnosed with these disorders in the year after TBI (respectively 21% and 17%). Pooled prevalence estimates increased over time, and indicated high long-term prevalence of anxiety (36%) and depressive disorders (43%).

The meta-analysis in **Chapter 9** provides an overview of the predictors of PTSD and MDD after TBI. We found that patients with a shorter post-traumatic amnesia and those with a memory of the traumatic event are at higher risk to be diagnosed with PTSD after TBI. MDD after TBI is associated with pre-injury depression, female gender, moderate TBI, and post-injury unemployment.

In **Chapter 10** the impact of PTSD and MDD on patients' functioning and HRQL was assessed, using data from a longitudinal cohort study among TBI patients. We found that PTSD and MDD both are associated with significantly decreased functioning and HRQL after TBI.

Part IV - Guidelines and adherence

Part IV studied the adherence to guidelines in injury patients. The literature review in **Chapter 11** quantifies the guideline adherence in TBI, explores the factors influencing adherence, and examines the associations between guideline adherence and outcome. In **Chapter 12** chart reviews of health care organisations involved in the emergency care of injury patients are used to assess whether current practice is in compliance with a new guideline on pain management for injury patients. In both studies, guideline adherence was generally low and varied widely between health care organisations. In case of TBI, adherence was found to be higher in younger patients, more severe TBI, and in guideline recommendations that are based on strong evidence rather than lower level evidence. Review of the international evidence showed guideline adherence to be associated with more favorable patient outcomes, including reduced mortality.

DISCUSSION

The aim of this thesis was to study the incidence, HRQL, psychiatric consequences and costs of TBI, and to contribute to the improvement of outcome assessment in the injury field.

We found that TBI has a substantial impact on both individuals and society. TBI has large and often long-term consequences for the persons' functioning and HRQL, resulting in a high disease burden. Subsequently, TBI imposes huge economic costs due to the often long-term need for specialised medical care and loss of productivity. Current epidemiological data is, however, known to be incomplete, as epidemiologic monitors do not incorporate all cases of TBI (e.g. milder injuries treated outside the hospital are missed). Moreover, data on long-term medical events resulting from injury (e.g. rehabilitation or even death) is often not readily available. This limits our insight into the actual size of the TBI problem.

Our analyses showed that research on the epidemiology and outcomes of TBI is seriously challenging due to the large heterogeneity in causes, severity, treatment, and outcome, and still lacks standardisation. Considerable methodological variation exists in the methods to measure outcome after TBI, including differences in settings, study populations, instruments, follow-up periods and timings of assessments. These design choices limit the comparability between study results. Moreover, we found

that different methods may result in different valuations of similar health states, and may yield different estimates of the change in health status.

Implications

Our findings have several implications for policy makers, health care professionals and future research. From a policy perspective, prevention programmes are needed to inform the public on the consequences that TBI can have, even in case of milder injuries, and to educate them on how such injuries can be avoided. Based on our findings, preventive strategies should be developed to reduce the incidence and impact of TBI in children, adolescents, men in the working age, and victims from falls (children and elderly) or traffic injury (especially cyclists). The growing number of TBI victims due to falls in the aging population and traffic injuries endorses the need for financial support and funding of TBI research. Without this support for research, there will be limited knowledge on the outcomes and recovery after TBI, and ways to improve prevention and rehabilitation of TBI victims.

Health care professionals should be aware of the consequences TBI may have and should inform their patients on the symptoms that may occur after a TBI. They should closely monitor the recovery of TBI victims, including those with milder injuries. Health care professionals may benefit from the use of patient-reported outcome measures (e.g. HRQL instruments), which enable them to detect unrecognised problems and monitor the impact of injuries. Incorporation of patient's perspective on their functioning and recovery in clinical decision making, may enhance the patient's rehabilitation and HRQL. Overall, as guideline adherence is associated with better outcomes, health care professionals should use guideline recommendations in their care for injury patients. The trauma care for injury patients and evaluation of its effectiveness can be improved by a complete registration of guideline recommendations and quality indicators in patient files.

Future research

Future research should apply an integrated approach of assessing incidence, health impact and economic consequences of injuries, to identify important risk groups. Incorporation of all three dimensions of outcome is essential to gain insight into the size of the injury problem, to identify high-risk groups and to set priorities for prevention and treatment. Researchers may benefit from linkage of data from multiple registries to obtain full insight into the incidence and impact of injuries on population health over time. Assessments of outcome of injury, especially TBI, should incorporate the productivity losses due to the injury and the associated costs, as productivity costs dominate the economic burden of severe injuries like TBI. These assessments should also incorporate information on the patients' pre-injury HRQL, as HRQL may be influenced by a range of factors (e.g. comorbidity). Researchers should however be aware of the bias that may arise when pre-injury HRQL is assessed retrospectively or when population norms are applied, and should use prospectively derived HRQL scores wherever possible to estimate the impact of injury on HRQL.

Further insight into the long-term consequences and recovery patterns after TBI is needed and longitudinal follow-up studies can provide this valuable information. These studies should use multiple follow-up measures over time, as TBI symptoms may aggravate or vary over time. TBI research should be standardised in terms of the use of uniform definitions, classifications, and methodology. It is

however also important for researchers to uniformly report on study results to improve comparison of results of studies.

Recommendations

To call attention to the devastating consequences a TBI may have, and to improve prevention, treatment and outcomes research in TBI, some specific recommendations can be made based on this thesis:

Policy makers

- Inform the public on the substantial consequences TBI may have, and educate the population about how injuries can be avoided.
- Develop preventive strategies to reduce TBI, targeting 0–24-year-olds, men in the working population aged 25–64 years, and elderly cyclists and fallers.
- Provide funding and support for research to assess the size and impact of the TBI problem.

Health care professionals

- Inform patients on the physical and mental symptoms that may occur after a TBI.
- Closely monitor the recovery of TBI victims over a long time of follow-up as TBI symptoms may persist for many years and may cause growing problems over time.
- Pay attention to the psychiatric consequences TBI may have.
- Do not underestimate the consequences of mild TBI.
- Incorporate the subjective perspective of patients on their functioning and recovery following injury in clinical decision making.
- Use guidelines in providing care to patients, and register all necessary items of the guideline recommendations and quality indicators in patient files.

Researchers

- Apply an integrated approach to assess the clinical, functional and economic outcomes after injuries and diseases, including the health-related quality of life (HRQL) and psychiatric consequences.
- Link data from multiple sources to obtain full insight into the size and impact of injuries and diseases.
- Incorporate the productivity costs to assess the economic burden of injuries and diseases.
- Assess the pre-injury HRQL of patients to estimate the change in health status due to an injury.
- Assess the long-term consequences and recovery patterns after TBI.
- Use multiple follow-up measurements over time (preferably lifelong), as recovery patterns and occurrence of symptoms may vary over time.
- Standardise TBI research by using uniform definitions, classifications, methodology (e.g. timings of assessments and follow-up), and reporting of study results to enable comparisons between studies.

Samenvatting

INTRODUCTIE

Letsels vormen wereldwijd een groot probleem voor de volksgezondheid. Ze behoren tot de belangrijkste doodsoorzaken en hebben vaak ernstige gevolgen, wat leidt tot hoge kosten voor de samenleving. Traumatisch hersenletsel is een letsel met een relatief hoge sterftekans en een aanzienlijk risico op blijvende lichamelijke beperkingen. Deze vorm van niet-aangeboren hersenletsel ontstaat plotseling door een oorzaak buiten het lichaam, bijvoorbeeld een verkeersongeval of val van de trap.
Traumatisch hersenletsel wordt vaak beschreven als een stille epidemie. Patiënten en familieleden die ervaring hebben met dit letsel weten hoe ernstig de gevolgen kunnen zijn. In de samenleving en zelfs onder zorgaanbieders is dit bewustzijn echter nog steeds laag. Bijna alle overlevenden van een traumatisch hersenletsel ondervinden lichamelijke of mentale beperkingen. Deze beperkingen hebben een grote impact op de kwaliteit van leven van patiënten en hun herstel. Daarnaast hebben hersenletselpatiënten vaak moeite om hun werk of studie volledig te hervatten. De langdurige zorg en verminderde productiviteit brengen hoge kosten met zich mee voor de patiënt en de samenleving.
De afgelopen decennia is een sterke stijging zichtbaar van het aantal patiënten dat een ernstig traumatisch hersenletsel overleeft. De beperkingen en ziektelast ten gevolge van dit letsel zijn echter niet aanzienlijk afgenomen. Hierdoor is er meer aandacht gekomen voor het meten van de (lange-termijn) uitkomsten na letsels, in aanvulling op sterfte. Er is een toegenomen belangstelling onder beleidsmakers en zorgaanbieders om de uitkomsten na letsels te kwantificeren om de effecten van preventieprogramma's en behandelingen te kunnen meten. Inzicht in de incidentie, gezondheidsimpact en economische gevolgen van letsels, zoals traumatisch hersenletsel, is noodzakelijk om de ziektelast van letselpatiënten onderling of met andere aandoeningen te vergelijken, gezondheidsbeleid en preventie te optimaliseren en effectieve (revalidatie)zorg te ontwikkelen.

In dit proefschrift worden de incidentie, gezondheidsgerelateerde kwaliteit van leven, psychische gevolgen en kosten van traumatisch hersenletsel en de mogelijkheden voor verbetering van uitkomstmeting na letsel onderzocht. Daarbij staan de volgende onderzoeksvragen centraal:

- Wat zijn de incidentie, gezondheidsimpact en kosten van traumatisch hersenletsel en welke risicogroepen kunnen geïdentificeerd worden?
- Hoe kan het meten van uitkomsten na letsel worden verbeterd?
- Wat is de impact van traumatisch hersenletsel op de kwaliteit van leven van patiënten en hoe vaak komen psychiatrische stoornissen voor na traumatisch hersenletsel?
- In welke mate worden richtlijnen opgevolgd in de zorgverlening aan letselpatiënten?

Deel I - Epidemiologie van traumatisch hersenletsel

In deel I wordt de omvang van het hersenletselprobleem in Nederland onderzocht. Op basis van informatie over de incidentie, kosten en ziektelast van traumatisch hersenletsel worden belangrijke risicogroepen voor preventie geïdentificeerd. Uit de gegevens van het Nederlandse Letsel Informatie Systeem (patiënten gezien op de Spoedeisende Hulp-afdeling van een ziekenhuis) en de Landelijke Medische Registratie (patiënten opgenomen in het ziekenhuis) in **hoofdstuk 2** blijkt dat jaarlijks 35.000 patiënten met traumatisch hersenletsel op de Spoedeisende Hulp behandeld worden: een incidentie van 214 per 100.000 persoonsjaren. Traumatisch hersenletsel leidt tot een aanzienlijke ziektelast:

hersenletselpatiënten verliezen gemiddeld 7 levensjaren door ziekte, beperkingen of vroegtijdige sterfte. Daarnaast brengt dit type letsel hoge kosten met zich mee: in totaal €315 miljoen per jaar in Nederland, met een gemiddelde van €18.000 per patiënt. Het risico op traumatisch hersenletsel en diens gezondheids- en economische gevolgen waren het hoogst in kinderen en jongvolwassenen (tot 24 jaar), mannen (25–64 jaar) en slachtoffers van privé-ongevallen (met name valincidenten bij 0–5 jarigen en ouderen) en verkeersongevallen (in het bijzonder fietsers). In **hoofdstuk 3** onderzochten we de incidentie en gevolgen van hersenletsel onder fietsers. We vonden dat het aantal patiënten dat opgenomen werd naar aanleiding van een hersenletsel door een fietsongeval de afgelopen tien jaar sterk is gestegen, met name onder oudere fietsers (55+).

Deel II - Methodologische uitdagingen in uitkomstmeting na letsel

Deel II gaat in op de mogelijkheden voor verbetering van uitkomstmeting na letsel. De systematische literatuurstudie in **hoofdstuk 4** onderzoekt hoe de gezondheidsgerelateerde kwaliteit van leven voorafgaand aan een letsel gemeten wordt. Aangezien het vaak niet mogelijk is om deze informatie vóór een ongeval te meten, wordt veelal na het ongeval (retrospectief) aan patiënten gevraagd hoe zij hun gezondheidstoestand van vóór het ongeval herinneren. Een andere methode is om de algemene populatie als norm te gebruiken voor de gezondheidstoestand van patiënten vóór het ongeval. De retrospectieve methode levert echter voor de meeste letseltypen een hogere waardering van de kwaliteit van leven vóór het ongeval op in vergelijking met de algemene populatienorm. Daarnaast blijft het herstel in de gezondheidsgerelateerde kwaliteit van leven na het ongeval in de retrospectieve metingen achter op de prospectieve metingen, wat duidt op een systematische overschatting van de verandering in de gezondheidsgerelateerde kwaliteit van leven als gevolg van een letsel. Onderzoekers moeten bedacht zijn op de bias die gepaard gaat met het gebruik van deze retrospectieve methode en het toepassen van algemene populatienormen en moeten waar mogelijk de gezondheidsgerelateerde kwaliteit van leven voorafgaand aan een ongeval prospectief meten om de impact van een letsel op de gezondheidsgerelateerde kwaliteit van leven van een patiënt te bepalen.

In de pilot studie in **hoofdstuk 5** hebben we data van meerdere registraties gekoppeld aan gegevens van een vervolgvragenlijst onder patiënten. We lieten hiermee zien wat uitbereiding van traumaregistraties met follow-up gegevens over de uitkomsten na letsels verder dan alleen sterfte kan opleveren. Deze koppeling van gegevens biedt inzicht in de uitkomsten van letselpatiënten en maakt het mogelijk om de gevolgen van letsels onderling en tussen patiënten te vergelijken. Informatie over de (lange-termijn) uitkomsten na letsels zouden geïntegreerd moeten worden in de evaluatie van traumazorg.

In **hoofdstuk 6** vergeleken we twee methoden om wegingsfactoren van traumatisch hersenletsel te bepalen. Een wegingsfactor is een maat voor de ernst van de gevolgen van het letsel voor het functioneren van patiënten, uitgedrukt op een schaal van 0 (geen nadelige gevolgen) tot 1 (zeer ernstige nadelige gevolgen). Door de wegingsfactor voor de ernst van de gevolgen van het letsel te vermenigvuldigen met het aantal mensen dat letsel heeft en het aantal mensen dat blijvende beperkingen heeft door letsel, kan het aantal verloren levensjaren door het letsel worden berekend (ziektejaarequivalenten). In deze studie vergeleken we standaard wegingsfactoren vastgesteld in de Global Burden of Disease (GBD) studie 2013 met wegingsfactoren vastgesteld op basis van follow-up gegevens over de kwaliteit van leven van individuele patiënten met traumatisch hersenletsel. Beide methoden leveren vergelijkbare schattingen op van het aantal ziektejaarequivalenten door traumatisch

hersenletsel in Nederland, behalve voor de lange-termijn gevolgen van zwaar traumatisch hersenletsel, die veel zwaarder meewogen in de GBD wegingsfactoren, wat zal resulteren in een hoger aantal verloren levensjaren.

Deel III - Uitkomsten na traumatisch hersenletsel

In deel III onderzochten we de impact van traumatisch hersenletsel op de kwaliteit van leven van patiënten en het voorkomen van psychiatrische stoornissen na traumatisch hersenletsel. In **hoofdstuk 7** brachten we de herstelpatronen na licht, middelzwaar en zwaar hersenletsel in kaart en onderzochten we het verband tussen de functionele uitkomsten na letsel volgens clinici en de patiënt-gerapporteerde uitkomsten. We vonden dat hersenletsel van alle ernstniveaus sterk de gezondheidsgerelateerde kwaliteit van leven beïnvloedt en dat het herstelpatroon verschilt per ernstniveau. Vrouwelijk geslacht, oudere leeftijd, comorbiditeit en een zwaarder letsel bleken voorspellers te zijn voor een lagere kwaliteit van leven. Patiënt-gerapporteerde uitkomsten vielen over het algemeen slechter uit dan de meting van clinici. Het is daarom belangrijk om het patiënt perspectief mee te nemen in de uitkomstmeting na letsels.

De systematische literatuurstudie in **hoofdstuk 8** geeft inzicht in de prevalentie van angst- en depressieve stoornissen na traumatisch hersenletsel. We vonden een grote variatie in de prevalentie van psychische stoornissen tussen de verschillende studies. Posttraumatische stress (PTSS) en depressie waren de meest voorkomende stoornissen ten gevolge van traumatisch hersenletsel. Ongeveer één op de vijf patiënten had een geschiedenis van een angst- (19%) of depressieve stoornis (13%) vóór het ongeval en bij een groter aantal patiënten werden deze stoornissen gediagnosticeerd in het jaar na het letsel (respectievelijk 21% en 17%). De gepoolde prevalenties uit de verschillende studies namen toe over tijd met een hoge prevalentie van angst- (36%) en depressieve stoornissen (43%) in de lange termijn.

De meta-analyse in **hoofdstuk 9** geeft inzicht in de risicofactoren van PTSS en depressie ten gevolge van traumatisch hersenletsel. We vonden dat patiënten met een kortere toestand van verwarring (post-traumatische amnesie) en patiënten die zich het ongeval kunnen herinneren een hoger risico hebben op een diagnose van PTSS na traumatisch hersenletsel. Depressie werd geassocieerd met een geschiedenis van een depressieve stoornis vóór het ongeval, vrouwelijk geslacht, middelzwaar hersenletsel en werkloosheid na het ongeval.

In **hoofdstuk 10** onderzochten we de impact van PTSS en depressie op de gezondheidsgerelateerde kwaliteit van leven van patiënten met hersenletsel. Zowel PTSS als depressie werden geassocieerd met een significante daling in de functionele uitkomsten en kwaliteit van leven na traumatisch hersenletsel.

Deel IV - Opvolging van richtlijnen

Deel IV onderzoekt de opvolging van richtlijnen in de behandeling van letselpatiënten. In de systematische literatuurstudie in **hoofdstuk 11** onderzochten we de mate waarin richtlijnen worden opgevolgd bij patiënten met traumatisch hersenletsel, de factoren die het opvolgen van richtlijnen beïnvloeden en de relatie tussen het opvolgen van richtlijnen en de uitkomsten voor de patiënt. In **hoofdstuk 12** onderzochten we medische dossiers van zorginstellingen in de acute zorg om na te gaan in welke mate de huidige hulpverlening overeenkomt met een nieuwe richtlijn over pijnbehandeling bij traumapatiënten in de spoedzorgketen. Uit beide studies bleek dat de richtlijnen over het algemeen

matig werden opgevolgd en dat de mate van opvolging sterk varieerde tussen zorginstellingen. We vonden dat bij traumatisch hersenletsel de opvolging van richtlijnen hoger was bij jongere patiënten, zwaarder hersenletsel en bij aanbevelingen uit richtlijnen die onderbouwd waren met overtuigend wetenschappelijk bewijs dan bewijs van een lager niveau. Opvolging van richtlijnen werd geassocieerd met betere uitkomsten voor de patiënt, onder andere lagere sterfte.

DISCUSSIE

Het doel van dit proefschrift was om de incidentie, gezondheidsgerelateerde kwaliteit van leven, psychische gevolgen en kosten van traumatisch hersenletsel en de mogelijkheden voor verbetering van uitkomstmeting na letsel te onderzoeken.

Onze studies toonden aan dat traumatisch hersenletsel een substantiële impact heeft op zowel de individuele patiënt als de samenleving. Traumatisch hersenletsel heeft grote en veelal langdurige gevolgen voor het functioneren en de gezondheidsgerelateerde kwaliteit van leven van patiënten, wat leidt tot een hoge ziektelast. Daarnaast brengt traumatisch hersenletsel hoge kosten met zich mee door de lange-termijn behoefte aan specialistische zorg en het verlies aan productiviteit. Echter, de huidige epidemiologische gegevens zijn niet volledig aangezien niet alle hersenletselpatiënten worden geregistreerd in de bestaande registraties. Deze registraties missen bijvoorbeeld de patiënten met licht hersenletsel die buiten het ziekenhuis worden behandeld, of geen medische hulp zoeken. Daarnaast zijn gegevens over de lange-termijn gevolgen en hulpverlening na letsels (zoals revalidatie of zelfs sterfte) niet altijd gemakkelijk beschikbaar. Hierdoor is ons inzicht in de daadwerkelijke omvang van het hersenletselprobleem nog niet volledig.

We vonden dat het onderzoek naar de epidemiologie en gevolgen van traumatisch hersenletsel belemmerd wordt door de sterke heterogeniteit in oorzaken, ernst, behandeling en uitkomsten van hersenletsel en dat onderzoek naar traumatisch hersenletsel nog steeds niet gestandaardiseerd is. Er zijn aanzienlijke verschillen in methoden om uitkomsten na traumatisch hersenletsel te meten, zoals verschillende studie populaties, meetinstrumenten en de periode en timing van vervolgonderzoek. Dit beperkt de vergelijkbaarheid van resultaten tussen studies. Daarnaast kunnen verschillende methoden leiden tot verschillende waarderingen van dezelfde gezondheidstoestanden en daarmee verschillende schattingen van de letsel-gerelateerde ziektelast tot gevolg hebben.

Implicaties

Onze resultaten hebben implicaties voor beleidsmakers, zorgaanbieders en toekomstig onderzoek. Preventieprogramma's zijn nodig om de samenleving te informeren over de gevolgen die traumatisch hersenletsel kan hebben, ook de lichtere letsels, en hoe deze letsels voorkomen kunnen worden. Preventiemaatregelen zouden zich moeten richten op het verlagen van de incidentie en impact van hersenletsel onder kinderen, jongvolwassenen, mannen (25–64 jaar) en slachtoffers van privé-ongevallen (valincidenten onder kinderen en ouderen) en verkeersongevallen (fietsers). De toename van het aantal hersenletselpatiënten door verkeersongevallen en valincidenten in de vergrijzende samenleving benadrukken de noodzaak voor financiële steun van hersenletselonderzoek. Zonder deze steun zal er beperkt inzicht zijn in de uitkomsten en het herstel van deze patiënten, evenals in de manier waarop preventie en revalidatie van traumatisch hersenletsel kan worden verbeterd.

Zorgaanbieders moeten bedacht zijn op de gevolgen die traumatisch hersenletsel kan hebben en moeten hun patiënten informeren over de symptomen en klachten die na dit letsel zouden kunnen ontstaan. Het herstel van patiënten zou nauwkeurig gevolgd moeten worden, ook na licht hersenletsel. Zorgaanbieders kunnen hierbij gebruik maken van patiënt-gerapporteerde uitkomsten, bijvoorbeeld uit kwaliteit van leven instrumenten. Deze informatie maakt het hen mogelijk om functionele problemen bij patiënten op te sporen en de gevolgen van letsels te monitoren. Door dit patiënt perspectief op het functioneren en herstel na het letsel onderdeel te laten uitmaken van de besluitvorming over de behandeling, kunnen zorgaanbieders de uitkomsten voor patiënten verbeteren. De uitkomst voor de patiënt kan tevens worden verbeterd door aanbevelingen uit wetenschappelijk onderbouwde richtlijnen toe te passen in de dagelijkse zorg aan patiënten. Om het effect van deze zorg te kunnen evalueren is het van belang om een complete registratie van de aanbevelingen uit richtlijnen en kwaliteitsindicatoren bij te houden.

Toekomstig onderzoek

Het meten van zowel de incidentie, functionele uitkomsten als kosten van letsels is noodzakelijk om inzicht te krijgen in de omvang van het letselprobleem en om prioriteiten te kunnen stellen voor de preventie en behandeling van letsels. Daarom is het cruciaal dat onderzoekers een integrale aanpak toepassen en alle drie uitkomsten na letsels meten om belangrijke risicogroepen voor preventie te identificeren. Daarbij kan gebruik worden gemaakt van het koppelen van bestaande gegevens uit verschillende registraties. Daarnaast is het van belang, zeker in geval van traumatisch hersenletsel, om niet alleen de directe medische kosten van letsels te bepalen, maar ook de kosten in kaart te brengen die gepaard gaan met het verlies aan productiviteit door letsels. Deze productiviteitskosten bepalen namelijk het overgrote deel van de totale economische gevolgen van zware letsels zoals traumatisch hersenletsel. Om de invloed van andere factoren op het functioneren (zoals comorbiditeit) uit te sluiten is informatie nodig over de gezondheidstoestand van de patiënt vóór het ongeval. Verschillende methoden kunnen gebruikt worden om de gezondheidsgerelateerde kwaliteit van leven vóór een ongeval te meten, bijvoorbeeld door retrospectief te meten of de algemene populatie als norm te gebruiken. Onderzoekers moeten echter bedacht zijn op het effect dat deze methoden kunnen hebben op hun schatting van de impact van een letsel op de gezondheidsgerelateerde kwaliteit van leven van patiënten.

Er is meer longitudinaal onderzoek nodig naar de lange-termijn gevolgen en herstelpatronen na traumatisch hersenletsel. Daarbij zijn meerdere follow-up momenten over tijd nodig, aangezien symptomen van hersenletsel kunnen toenemen en variëren over tijd. Hersenletselonderzoek zou gestandaardiseerd moeten worden door gelijke definities, classificaties en methoden te gebruiken. Daarbij is het van belang om resultaten op een uniforme manier te rapporteren om zo de vergelijkbaarheid van resultaten tussen studies te verhogen. Tot slot moet de belasting van onderzoek voor patiënten worden gereduceerd, zeker in geval van zware letsels.

Aanbevelingen

Om meer aandacht te vragen voor de aanzienlijke gevolgen die traumatisch hersenletsel kan hebben en om de preventie, behandeling en uitkomstmeting na hersenletsel te verbeteren, doen wij enkele aanbevelingen op basis van dit proefschrift:

Beleidsmakers

- Informeer de samenleving over de gevolgen die traumatisch hersenletsel kan hebben en hoe deze letsels voorkomen kunnen worden.
- Ontwikkel preventiemaatregelen om de incidentie en impact van hersenletsel te verlagen, gericht op 0–24-jarigen, mannen in de leeftijd 25–64 jaar en slachtoffers van verkeersongevallen en valincidenten.
- Bied financiële ondersteuning voor onderzoek om inzicht te krijgen in de omvang en impact van het hersenletselprobleem.

Zorgaanbieders

- Informeer patiënten over de fysieke en mentale klachten die kunnen ontstaan na een traumatisch hersenletsel.
- Volg nauwkeurig het herstel van slachtoffers van een traumatisch hersenletsel op de lange termijn, aangezien klachten meerdere jaren kunnen aanhouden en problemen kunnen variëren over tijd.
- Wees bedacht op de psychische gevolgen die een traumatisch hersenletsel kan hebben.
- Onderschat de gevolgen van licht traumatisch hersenletsel niet.
- Laat het perspectief van de patiënt over diens functioneren en herstel na het letsel onderdeel uitmaken van de besluitvorming over de behandeling.
- Pas aanbevelingen uit wetenschappelijk onderbouwde richtlijnen toe in de dagelijkse zorg aan patiënten en registreer de aanbevelingen uit richtlijnen en kwaliteitsindicatoren.

Onderzoekers

- Pas een integrale aanpak toe en onderzoek zowel de incidentie, functionele uitkomsten als kosten van letsels en ziekten, inclusief de kwaliteit van leven en psychische gevolgen.
- Koppel data van verschillende registraties om inzicht te krijgen in de omvang en impact van letsels en ziekten.
- Onderzoek ook de productiviteitskosten om de economische impact van letsels en ziekten te bepalen.
- Meet de gezondheidstoestand van patiënten vóór het ongeval om de letsel-gerelateerde ziektelast te bepalen.
- Onderzoek de lange-termijn uitkomsten en herstelpatronen na traumatisch hersenletsel.
- Gebruik meerdere follow-up moment over tijd, aangezien symptomen van hersenletsel kunnen toenemen en variëren over tijd.
- Standaardiseer hersenletselonderzoek en verhoog de vergelijkbaarheid tussen studies door uniforme definities, classificaties, methoden en rapportage van studieresultaten te gebruiken.

List of publications

LIST OF PUBLICATIONS

Publications and manuscripts printed in this thesis

Scholten AC, Haagsma JA, Panneman MJM, van Beeck EF, Polinder S. Traumatic brain injury in the Netherlands: Incidence, costs and disability-adjusted life years. PLOS ONE. 2014 Oct;9(10):e110905.

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Dankwoord

DANKWOORD

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Bedankt!
Annemieke

Curriculum Vitae

CURRICULUM VITAE

Annemieke Christine Scholten was born in Opende, Groningen, the Netherlands on May 18th, 1986. After graduation from secondary school 'CSG Liudger Raai' in Drachten in 2004, she started studying Health Sciences at the University of Twente in Enschede. In 2010, she obtained her Masters of Science degree in Health Sciences. Her Master thesis focused on early cardiopulmonary resuscitation and use of automated external defibrillators by laypersons in out-of-hospital cardiac arrest using an SMS alert service.

From the beginning of 2010, Annemieke worked as a Scientific Researcher at the Regional Emergency Health care Network of the Radboud university medical center, Nijmegen. Here, she was involved in the evaluation and improvement of trauma care and surveillance of patient flow in the chain of emergency care. In 2013 she started a PhD project on the outcome after traumatic brain injury at the Department of Public Health at the Erasmus MC in Rotterdam, which resulted in this thesis. At this moment, Annemieke is working as a Strategic Intelligence Advisor at the Department of Strategy & Proposition Development of health insurance company Menzis, Wageningen.

PhD portfolio

PHD PORTFOLIO

Name PhD student: Annemieke Scholten
Erasmus MC department: Public Health
PhD period: 2013 – 2015

Promotor: Prof.dr. E.W. Steyerberg
Copromotors: Dr. S. Polinder and Dr. J.A. Haagsma

	Year	Workload (ECTS)
1. PhD training		
Research skills		
Legislation and Organisation for Clinical Researchers	2013	1.7
English Biomedical Writing and Communication	2014–2015	4.0
Introduction R	2014	1.0
Systematical literature retrieval in PubMed	2015	0.6
Time management course	2015	0.2
NIHES courses, Rotterdam, the Netherlands		
Cohort Studies	2013	0.7
Quality of Life Measurement	2014	0.9
Regression Analysis	2014	1.9
Advanced Analysis of Prognosis Studies	2015	0.7
Methods of Health Services Research	2015	0.7
Health Economics	2015	0.7
Presentations at national and international conferences		
Traumatic brain injury in the Netherlands: incidence, costs and disease burden WEON 2014, Leiden, the Netherlands (poster)	2014	1.0
Lange termijn gevolgen ervaren door traumapatiënten in Acute Zorgregio Oost LNAZ Symposium 2014, Amersfoort, the Netherlands	2014	1.0
Health-related quality of life after mild, moderate and severe TBI ISOQOL 2014, Berlin, Germany	2014	1.0
Incidence and costs of bicycle-related traumatic brain injuries in the Netherlands Healthy Living Conference 2015, Maastricht, the Netherlands (poster)	2015	1.0
Incidence, costs, and quality of life after traumatic brain injury Research meeting, Dep. Public Health, Erasmus MC, Rotterdam, the Netherlands	2015	1.0
Gevolgen voor en volgens de patiënt: verbreding uitkomstmetingen, LNAZ Symposium 2015, Utrecht, the Netherlands	2015	1.0
National and international conferences		
WEON 2014, Leiden, the Netherlands	2014	0.6
LNAZ Symposium 2014, Amersfoort, the Netherlands	2014	0.1
ISOQOL 2014, Berlin, Germany	2014	1.2
Healthy Living Conference 2015, Maastricht, the Netherlands	2015	0.9
LNAZ Symposium 2015, Utrecht, the Netherlands	2015	0.1
Seminars and workshops		
Research seminars, Dep. Public Health, Erasmus MC, Rotterdam, the Netherlands	2013–2015	3.0
CMB/Club Meth, Rotterdam, the Netherlands	2013–2015	1.0
2. Teaching activities		
Supervisor medical students theme 3.C.4 (community projects)	2013–2015	4.5
Lecturer medical students course 'From Problem to Solution in Public Health'	2014	0.3
Checking examinations course 'GEN3C1 - Arts en volksgezondheid (REG)'	2014	0.3

CMB: Medical Decision Making; ISOQOL: International Society for Quality of Life Research; LNAZ: Dutch Network for Emergency Care; NIHES: National Institute for Health Sciences; WEON: Working Group on Epidemiological Research Netherlands.