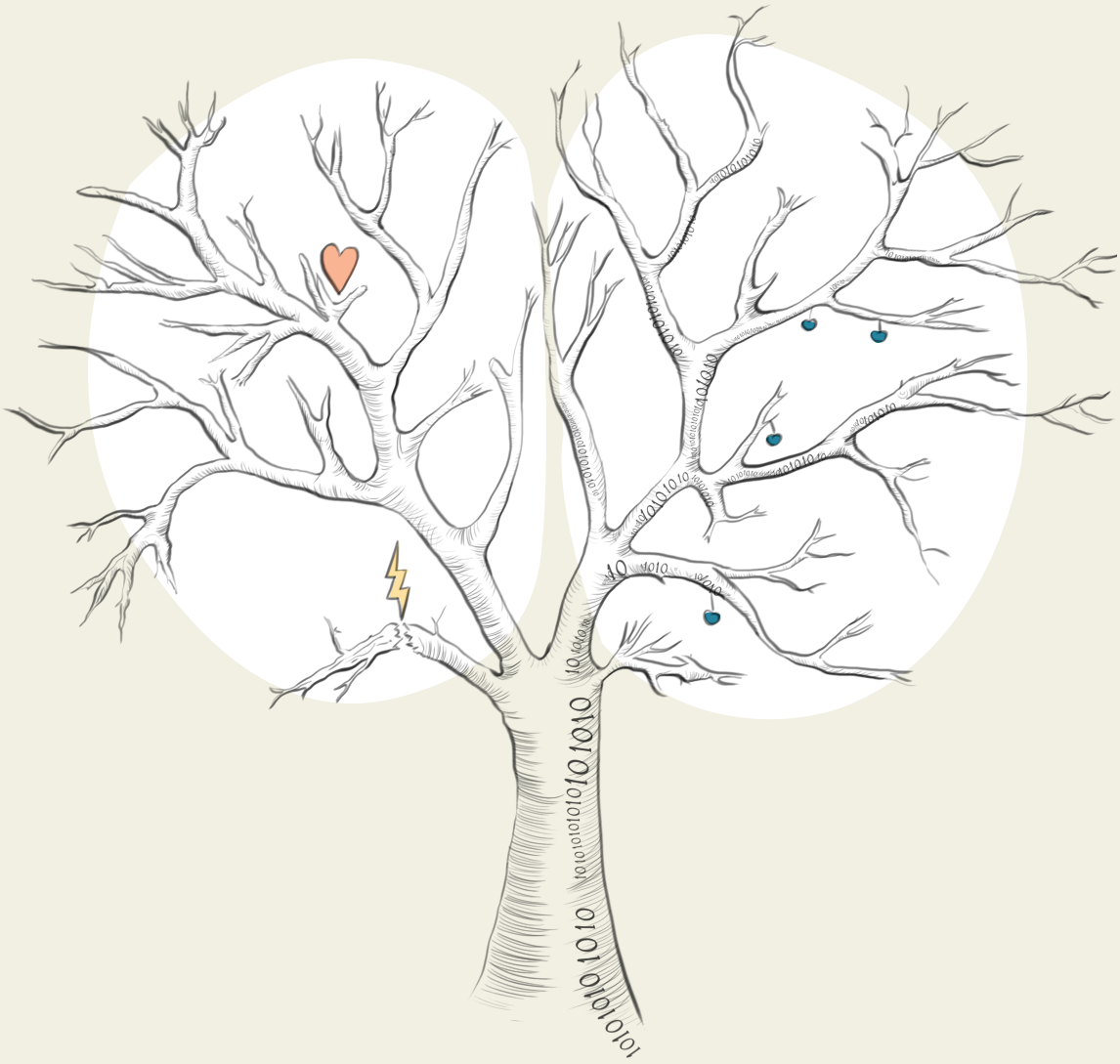
Outcome following Traumatic Brain Injury

Assessment and Preferences



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Outcome following Traumatic Brain Injury – Assessment and Preferences

Uitkomsten na traumatisch hersenletsel – Vaststellen en Preferenties

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Chapter 1

General Introduction

An acquired brain injury is an injury caused to the brain since birth, which means it is not hereditary, congenital, degenerative or induced by birth trauma. Acquired brain injury can be classified as either a traumatic (e.g. traumatic brain injury (TBI)) or non-traumatic injury (e.g. subarachnoid hemorrhage (SAH), tumor, stroke, encephalitis)[1]. Acquired brain injury is a rapidly growing public health problem, and affects clinical outcome and quality of life of survivors[2]. It has profound implications for individuals, relatives and society, since it often results in physical, cognitive, emotional and social changes[3]. The most common causes of acquired brain injury include TBI and stroke, which are leading causes of injury-related death and disability worldwide[2, 4-7].

In the past decades, mortality due to TBI and stroke have decreased substantially, however, equivalent reductions in disability have remained behind[8, 9]. Additionally, besides the fact that TBI and stroke are major public health problems, they also impose high health care costs on individuals and society and the consequential economic burden on patients and health care systems are tremendous[10-12]. Economic evaluations have become an integral part in decision making for patients with TBI and stroke. Well-founded evaluations of implementation of cost-effective treatments, allocation of resources, prevention intervention, identifying best practices and quality of care, and assessing future care demand have become essential for informing decisions by policy- and decision makers[10]. More research into health (e.g. functional outcome and quality of life) and economic outcomes of TBI and stroke is fundamental.

In this thesis we address two important and majorly discussed subjects in TBI and stroke research. First, we focus on outcome assessment following mild TBI, with an emphasis on prevalence, risk factors, classification and pre-injury reporting of post-concussion symptoms. Second, we focus on individual preferences for specific TBI and stroke related outcomes.

This chapter will introduce concepts related to assessing outcome and preferences for TBI and stroke. Subsequently, the research questions will be addressed and an outline of this thesis will be provided.

Acquired Brain Injury

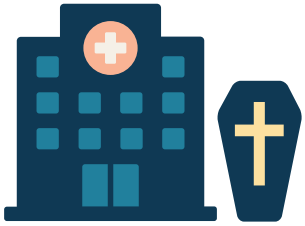
Traumatic Brain Injury

Traumatic Brain Injury (TBI) is defined as "an alteration in brain function, or other evidence of brain pathology, caused by an external force"[13, 14]. TBI has tremendous economic repercussions, considering it is costing the global economy approximately $US400 billion per year[4]. Annually, 50-60 million new TBI cases occur worldwide and over 80% are in developing countries[4]. Approximately one out of two people in the world's population will experience a TBI during their lifetime. In the European Union (EU; 28 Member States), around 2.5 million new cases of TBI occur each year(1)(Panel 1).

Panel 1. Statistics concerning traumatic brain injury

50 million people suffer from a TBI worldwide every year - over 80% in developing countries

Annual global costs of care and consequences of TBI are up to US$400 billion



57 000 TBI-related deaths and 1.5 million hospitalisations occur in the EU-28 every year

Source: Infographic CENTER-TBI
Abbreviations. TBI, traumatic brain injury; US, United States; EU, European Union.

The severity of TBI ranges from mild TBI (mTBI) to moderate and severe.[1] The vast majority of patients presenting to hospital with a TBI are diagnosed as having mild TBI (mTBI; Glasgow Coma Score (GCS): 13-15).[4, 15] Furthermore, additional diagnostic criteria such as loss of consciousness (LOC) and the presence and duration of posttraumatic amnesia (PTA) are frequently used.[16] On top of this, mTBI could also be conceptualized into subgroups, since some patients may have intracranial abnormalities on the computed tomography (CT) performed on presentation to hospital.[17] Using this information, a more detailed differentiation for patients with mTBI can be made: patients with a complicated (intracranial abnormalities present on CT) and uncomplicated (no intracranial abnormalities present on CT) mTBI.[17]

Stroke

Stroke is defined by The World Health Organization (WHO) as: *"a clinical syndrome consisting of rapidly developing clinical signs of focal (or global in case of coma) disturbance of cerebral function lasting more than 24 hours or leading to death with no apparent cause other than a vascular origin."* The arteries leading to and within the brain are affected by this disease. It is the second leading cause of death worldwide[18] and its incidence is increasing due to an ageing population.[7] Strokes can be divided up in two types: ischemic or hemorrhagic, and the majority (80%) of strokes are ischemic.[19]

Functional outcome in case of stroke outcome is measured by the modified Rankin Scale (mRS), which is the most widely used clinical outcome measure in clinical trials concerning stroke.[20, 21] The mRS evaluates the degree of disability or dependence in daily life, and is measured on an ordinal scale consisting of seven grades ranging from 0 (no symptoms) to 6 (death) (Figure 1).[22]
Even though the causes of TBI and stroke are different, the consequences and effects are often very similar, since both result in physical, cognitive and psychological, and social dysfunction.[23]

Figure 1. All instruments and measurement scales used in this thesis

Instrument		Number of items/ grades	Content	Scale/Levels	Scoring
Clinical outcome					
Traumatic brain injury	GOS	5	To assess functional outcome after TBI	1=Dead, 2=Vegetative state, 3=Severe disability, 4=Moderate disability, 5=Good recovery	Not applicable
	GOSE	8	To assess functional outcome after TBI	1=Dead, 2=Vegetative state, 3=Lower severe disability, 4=Upper severe disability, 5=Lower moderate disability, 6=Upper moderate disability, 7=Lower good recovery, 8=Upper good recovery	GOSE Score ≤ 6 = functional impairment
Stroke	mRS	7	Evaluates the degree of disability or dependence in daily life	0=No symptoms at all, 1=No significant disability despite symptoms, 2=Slight disability, 3=Moderate disability , 4=Moderate severe disability, 5=Severe disability, 6=Dead	mRS score 3-6 = “Dead or dependent” mRS score 0-2 = “Independent”
Post-concussion symptoms and syndrome					
	RPQ	16	Symptoms: Headaches, Dizziness, Nausea/ Vomiting, Noise sensitivity, Sleep disturbance, Fatigue, Being irritable, Feeling depressed or tearful, Feeling frustrated or impatient, Forgetfulness, Poor concentration, Taking longer to think, Blurred vision, Light sensitivity, Double vision and Restlessness	5- point Likert scale: 0=not experienced at all, 1=not a problem, 2=mild problem, 3=moderate problem, and 4=severe problem	Total score is the sum of all items Total score ≥ 12 = Post-Concussion Syndrome

	HISC	21	Symptoms: Headache, Dizziness, Balance problems, Tinnitus, Hearing loss, Drowsiness, Fatigue, Forgetfulness, Poor concentration, Slowness, Irritability, Noise intolerance, Alcohol intolerance, More Anxious, Dry mouth, Neck pain, Neck Stiffness, Arm pain, Itching, Problems with falling asleep, Problems with sleeping through	3-point scale: 0=never, 1=sometimes, 2=often	For each symptom a difference score is calculated by subtracting the pre-injury score from the current score. 0 = no increase in complaints > 1 = any increase in complaints
HRQoL instruments					
Generic	SF-36/SF-12	36/12	8 domains: Physical functioning, Role limitations related to physical functioning, Bodily pain, General health perception, Vitality, Social functioning, Role limitations related to emotional problems, and Mental health	Dependent on item	Total score is the sum of all items Total scores of 45-55 = average range Total scores of 40-45 = borderline Total scores < 40 = impaired
	PQoL	19	3 domains: Physical health, Cognitive health and Social health	11-point scale ranging from 0 (extremely dissatisfied) to 10 (extremely satisfied)	Total score is the mean of all 19 item scores Total score < 7.5 = “Dissatisfied” Total score > 7.5 = “Satisfied”
	EQ-5D	6	Two components: EQ VAS + EQ-5D-3L/5L 5 dimensions: Mobility, Self-care, Usual activities, Pain/ Discomfort, and Anxiety/Depression	*EQ-5D-3L:* no problems, some problems and extreme problems (3 levels) *EQ-5D-5L:* no problems, slight problems, moderate problems, severe problems and extreme problems (5 levels)	Total summary score is computed by a value set A total score < 0 = worse than dead Possibolity to compare with population normscores and limitations per dimension

Disease specific	QOLIBRI	37	6 dimensions: Four 'Satisfaction' items: Cognition, Self, Daily Life and Autonomy and Social Relationships Two 'Bothered' items: Emotions and Physical Problems	5-point Likert scale ranging from "not at all satisfied/bothered" to "very satisfied/ bothered	Total score is the sum of all responses on each scale Total scores of 67-82 = average range Total scores of 60-66 = borderline Total scores < 60 = impaired
	QOLIBRI-OS	6	Physical condition, How brain is working in terms of concentration, memory and thinking, Feelings and emotions, Ability to carry out day to day activities, Personal and social life, Current situation and future prospects	5-point Likert scale ranging from "not at all satisfied/bothered" to "very satisfied/ bothered	Total score is computed by the mean of the six items Total scores of 61-79 = average range Total scores of 52-60 = borderline Total scores < 52 = impaired

GOS, Glasgow Outcome Scale; GOSE, Glasgow Outcome Scale Extended; mRS, Modified Rankin Scale; SF-36, Short Form 36-Questionnaire Health Survey; SF-12, Short Form 12-Questionnaire; RPQ, Rivermead Post-Concussion Symptoms Questionnaire; HISC, Head Injury Symptom Checklist; EQ-5D-3L, EuroQol five-dimensional questionnaire with 3 levels; EQ-5D-5L, EuroQol five-dimensional questionnaire with 5 levels; PQoL, Perceived Quality of Life; QOLIBRI, Quality of Life after Brain Injury; QOLIBRI-OS, Quality of Life after Brain Injury overall scale.

Part I - Outcome assessment following traumatic brain injury

TBI is considered as “the most complex disease in the most complex organ”[24] and it is known that no two TBIs are rendered exactly the same, thus the recovery after TBI leads to variability and uncertainty.[1] Consequently, it remains unclear why TBI affects some patients for a short period of time and others remain permanently disabled.[1, 25]

Over the past 25 years, a spotlight has been put on the need and importance of research into TBI and billions of dollars have been spent on research investment in TBI,[24] which has resulted in a better comprehension of the disease. However, besides all these efforts, substantial improvement in outcome for patients has been lagging behind.[24, 26] In addition, many questions remain unanswered regarding the impact of mTBI in specific. Mortality rates in patients after sustaining a mTBI are low, nevertheless, a considerable amount of patients experience several cognitive, somatic and emotional problems lasting for months or even years. Additionally, besides the objective burden, the experienced burden as described by patients themselves has become crucial in outcome research. For these reasons, outcome assessment in current research has undergone a transformation from focusing on mortality as an endpoint, to other outcome measurements such as clinical outcome, health-related quality of life (HRQoL) and post-concussion symptoms.[26, 27] Figure 1 shows an overview of the most important instruments and measurements scales used throughout this thesis.

Clinical outcome

Clinical outcome describes the level of functioning, recovery and residual disability for TBI and stroke survivors.[28, 29] Levels of functioning in case of TBI outcome are frequently measured by use of the Glasgow Outcome Scale (GOS)[30] or the Glasgow Outcome Scale Extended (GOSE) [8, 29, 31] with a 5-point and an 8-point scale, respectively. These scales are both specifically designed to assess functional outcome after TBI and allocate patients who suffered acute brain damage into broad categories of functional outcome.[29] The GOSE instrument evaluates functional outcome through eight categories encompassing consciousness, independence at home and outside the home, work, social and leisure activities, family and friendship, and return to normal life.[30] An eight point scale ranging from 1 (dead) to 8 (completely recovered) is established from these categories, which has the ability to distinguish among functional outcomes (Figure 1). The GOS/GOSE are the most widely used functional measurement scales after TBI, however, they have been criticized since they do not represent a patient’s self-reported experience of their health[31] and especially for patients with mTBI, the majority of patients will be categorized in the upper level categories.[32]

Post-concussion symptoms and syndrome

Many patients following mTBI experience post-concussion symptoms, which manifest as physical symptoms (e.g., headaches, dizziness, blurred vision, fatigue, and sleep disturbances), cognitive deficits (e.g., poor memory, and attention and executive difficulties), and behavioral/emotional symptoms (e.g., depression, irritability, anxiety-related disorders, and emotional lability).[16, 33] For the majority of patients these symptoms will resolve and/or diminish spontaneously within weeks to months after the injury[34]. However, a subgroup of patients (estimated between 5%–43%[35-38]), have lasting post-concussion symptoms for weeks, months or even longer. When a set of these symptoms persist for over 3 months, it is often referred to as post-concussion syndrome (PCS).[37, 38] The presence of PCS is generally determined by the International Classification of Diseases,10th revision (ICD-10)[39] and the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV).[33] Post-concussion symptoms are usually measured by self-report questionnaires. The Rivermead Post-Concussion Symptoms Questionnaire (RPQ) is a frequently used instrument to assess the presence and severity of post-concussion symptoms.[40] Patients are asked to rate the severity of 16 different post-concussion symptoms, commonly found after TBI, over the past 24 hours in comparison to before the injury (Figure 1). There is currently no gold standard concerning the use of the RPQ to classify PCS, and besides the RPQ total score,[40] there are multiple different evaluation methods including: dividing the scale up in two (RPQ3 and RPQ13),[41] or dividing it up in three (cognitive, emotional and somatic) subscales.[42, 43] Furthermore, aside from heterogeneity in usage of the RPQ for classification of PCS, there is currently no ground rule in place on whether symptoms should be incorporated if they are rated as 2 (mild problem or worse) or only if they are rated as 3 (moderate problem or worse). Another instrument to assess post-concussion symptoms is the Head Injury Symptom Checklist (HISC), which consists of 21 frequently reported symptoms after TBI, and patients are asked to rate these symptoms for the situation before the injury and after the injury, e.g. during the last week (Figure 1). [44]

Health-related quality of life (HRQoL)

The WHO has defined Quality of Life (QoL) as follows: *"an individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns. It is a broad ranging concept affected in a complex way by the person's physical health, psychological state, personal beliefs, social relationships and their relationship to salient features of their environment".*[45] The definition of QoL is very broad and for this reason the concept of HRQoL was introduced.[46] HRQoL reflects an individual's perception of how an illness and its treatment affect the physical, mental, and social aspects of his or her life.[46-48] When comparing HRQoL to functional outcomes scales, it is seen as a more thorough approach in measuring outcome.[26]

Previously, it was assumed that HRQoL could not be rated adequately by patients

with TBI, since the brain damage, and especially the cognitive impairments, might influence a patients' ability to self-report on their functioning and overall well-being.[49] However, nowadays, it has become a central part in outcome assessment following TBI.[47, 50] Additionally, two patients with TBI and exactly the same GOSE score, may have dramatically different HRQoL responses. These responses are influenced by the perspective on their own subjective health. This amplifies the importance of HRQoL measurement in TBI research.

Generic versus disease specific measurements

HRQoL can be measured by two approaches: generic and disease specific instruments (Figure 1). Generic HRQoL questionnaires, such as the 36-item Short-Form Health Survey (SF-36), Perceived Quality of Life Scale (PQoL) and EuroQol 5D (EQ-5D), allow for comparison of health across disease states and populations. The SF-36 instrument is a multidimensional self-report questionnaire consisting of 36 questions assessing eight domains of health.[51] A physical and mental health summary component scores can be generated from the weighted sums of the subscales.[52] The SF-36 has been determined as the most widely used instrument to assess HRQoL after TBI.[47]

The PQoL instrument is seen as a measure of global life satisfaction and particularly measures an individual's satisfaction with their functional status. It contains 19 items in three different domains (physical health, cognitive health and social health) and has an 11-point scale ranging from 0 (extremely dissatisfied) to 10 (extremely satisfied).[53] Good internal reliability was shown for the PQoL in a TBI population.[54]

The EQ-5D[55] consists of two different components: the EQ-5D descriptive system (health state description) and the EQ visual analogue scale (EQ VAS)(evaluation). The EQ-5D descriptive system covers five dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression). Nowadays, there are two formats of the EQ-5D descriptive classification systems: EQ-5D-3L and EQ-5D-5L.[56] Differences between the two are based on the number of response categories per dimension. The expansion to five levels was done to increase the sensitivity and reduce the ceiling effect.[57] The EQ VAS is a vertical scale ranging from 0 (worst imaginable health state) to 100 (best imaginable health state).[55]

Nonetheless, generic HRQol questionnaires have been sharply criticized,[48, 58] since generic instruments may not always be particularly sensitive to or adequately assess specific aspects of HRQoL associated with a disease,[50] such as cognitive functioning in the case of TBI.[48, 59] Therefore, condition-specific questionnaires have been developed. The Quality of Life after Brain Injury (QOLIBRI)[48] and Quality of Life after Brain Injury overall scale (QOLIBRI-OS)[60] are TBI-specific instruments. This means they assess HRQoL of individuals by measuring areas and domains of health typically affected after sustaining a TBI.[61]

The QOLIBRI consists of 37 items covering six dimensions of HRQoL after TBI, which measure physical, psychological, daily life and psychosocial changes typical

for TBI.[23] The six dimensions encompasses four “satisfaction” and two “feeling bothered” dimensions.[62] The QOLIBRI-OS is a short, six-item version of QOLIBRI and assesses a single overall score, which provides a brief summary measure of HRQoL.[60] For both instruments, a 5-point Likert scale ranging from “not at all satisfied/bothered” to “very satisfied/bothered” is used to record responses. These condition-specific instruments are on occasion used in combination with generic measures.

Generally, self-rating is used to acquire measurements of these HRQoL instruments, however, when a patient has severely impaired cognition, proxies, or in other words, someone who knows the patient well (e.g. parent/partner), are used.[31]

Part II - Preferences for outcome in traumatic brain injury

Economic evaluation studies

A method for evaluating choices and decision making in reimbursement, health care resource allocation, and quality of care and clinical effectiveness measurements is economic evaluation.[63] Economic evaluations are a quantitative evaluation between two or more interventions on both the costs and outcomes.[63] It gives a complete overview of the impact on, and representation of a cost-effective use of limited health care resources. Different types of economic evaluation techniques exist, and the type is dependent on how the outcome is assessed. The four major types of economic evaluation methods are: cost-effectiveness analysis (CEA), cost-utility analysis (CUA), cost-benefit analysis and cost-minimization analysis (CMA). In CEA the outcomes are measured by natural units (e.g. life years gained, years of life saved, hospital days prevented etc.).[64] Cost-effectiveness analyses have become an integral part of decision making processes in TBI[10, 11] and stroke[12] research since both diseases have high economic costs. CUA measures outcomes in units that relate to a person’s level of wellbeing. It determines costs in terms of utilities, and measures outcomes in terms of quantity and quality.[65] Ultimately, it combines this into a single measure (e.g. Quality-adjusted life year (QALY)).[66]

QALY

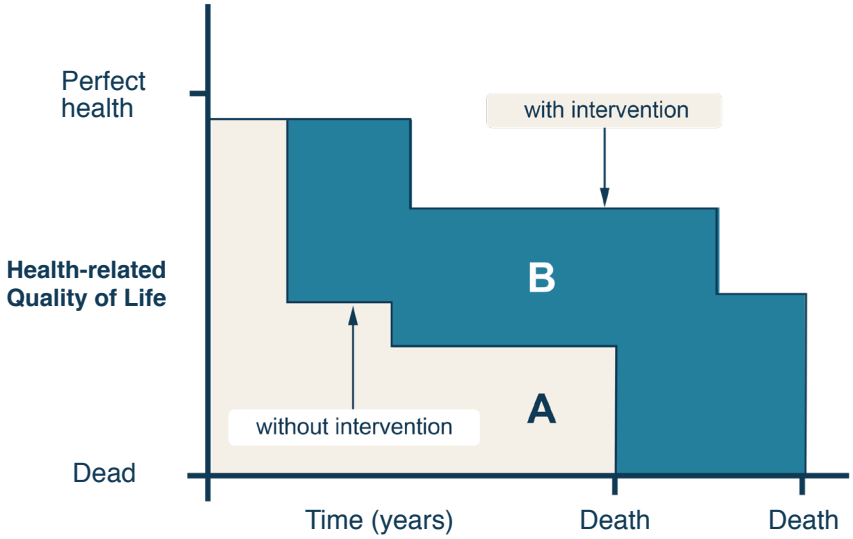
QALY is a measure in which a quantitative measure (months/years gained) and qualitative measure (e.g. EQ-5D) are combined[67] into a single index.[68] It permits comparisons of interventions across different disease states. QALY’s are derived from the number of life years multiplied by the quality of life experienced during these years, which is expressed in health utility weights (Figure 2).[63] Calculating QALYs is done by use of the following formula:

$$\mathrm{QALY} = \mathrm{y} * \mathrm{v(q)}$$

In this formula, y is the amount of life years lived in a health state, v(q) is the utility value associated with a given health state.[69] In a number of countries, such as the

Netherlands and United Kingdom, the ED-5D is specified as its preferred method of utility measurement.[70]

Figure 2. Quality-adjusted life year (QALY)



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Health utility indices

The responses on generic and disease specific measurements represent preferences for health states measured by these instruments. Nevertheless, to be able to use these responses in economic evaluations, they have to be converted into utility weights. Utilities are anchored on a scale ranging from 0 (death) to 1 (perfect health). A less than 0 value is given to health states which are reported to be worse than dead.[71] Utility weights represent the relative preference for a year of life in a given health state. Preferences can be equated with value or desirability,[72] which means that health state utilities are based on preferences for these diverse health states. Furthermore, a greater weight is given to a more desirable/preferred health state,[63, 73] which leads to a ranking of health states.

Value set

To assign utilities to each health state described by generic or disease specific measurements, an algorithm is used, which is called a value set.[74] A value set converts each health state into a single index value, which means that each of the levels in each dimension has a value (weight) assigned to it. In other words, a value set is a collection of index values for all possible health states described in an instrument. When looking at the EQ-5D, a value set provides weights to

each of the levels in each EQ-5D dimension.[75] Additionally, a value set has the ability to summarize general population preferences for health states that could be experienced by patients and the HRQoL of patients can be compared with other (patient) groups. Nowadays, in economic evaluations, value sets for generic instruments (e.g. EQ-5D)[76] are widely available and are used extensively.[74] Every so often, there is no value set available for an instrument, and to make these instruments suitable for use in economic evaluations, a value set needs to be generated by means of a preference elicitation method.

Preferences in a value set can be based on a variety of preference elicitation methods and the valuation of preferences could be performed by different groups of people.

Preference elicitation methods

There are different preference elicitation methods for deriving preference based weights for a health state. These methods could be direct or indirect.[73] Direct methods for data collection on utilities include the Visual Analogue Scale (VAS), standard gamble (SG), time trade-off (TTO) and discrete choice experiment (DCE).[77-79] The VAS is a valuation technique that records participants' views about hypothetical health states on a scale from 0 (worst imaginable health state) to 100 (best imaginable health state)(Figure 3).[80]

DCEs are increasingly being promoted among elicitation methods,[78] and makes it possible to generate values for alternatives in hypothetical situations or conditions that cannot be judged in the real world[81]. DCE questions consist of a pair of health states (labelled Health state A and Health state B, Figure 4) with no implication concerning the time of the health states, and respondents have to decide which health state they would prefer. Ultimately, the responses are utilized to generate preferences and to estimate the impact of altering severity and different combinations of health states on these preferences.[80]

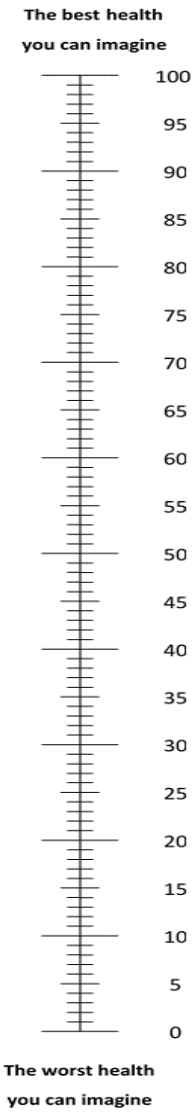
Indirect methods obtain health state values by indirectly mapping preferences onto the utility scale via a HRQoL questionnaire and afterwards predetermined value sets are applied to these questionnaire responses.[82] The main indirect methods of utility measurement are: the use of generic preference instruments (e.g. EQ-5D, SF-36); the use of disease specific measures (e.g. QOLIBRI, QOLIBRI-OS, GOSE); and mapping or cross-walking from disease specific instrument to a generic instrument (e.g. SF-36 to GOSE).[83]

Figure 3. Visual Analogue Scale (VAS)

We would like to know how good or bad your health is TODAY.

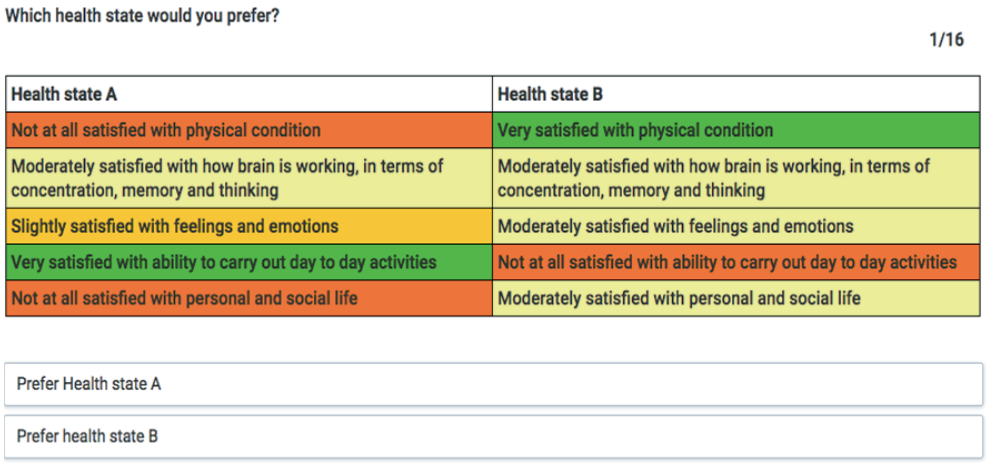
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark on the scale to show how good or bad your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



Adapted from: the EuroQol Group: www.euroqol.org

Figure 4. Discrete Choice Experiment (DCE)



Which health state would you prefer?

1/16

Health state A	Health state B
Not at all satisfied with physical condition	Very satisfied with physical condition
Moderately satisfied with how brain is working, in terms of concentration, memory and thinking	Moderately satisfied with how brain is working, in terms of concentration, memory and thinking
Slightly satisfied with feelings and emotions	Moderately satisfied with feelings and emotions
Very satisfied with ability to carry out day to day activities	Not at all satisfied with ability to carry out day to day activities
Not at all satisfied with personal and social life	Moderately satisfied with personal and social life

Prefer Health state A

Prefer health state B

General population versus patient valuation

The valuation of preferences using different preference elicitation methods can be performed by either patients, patient proxies, members of the general population, or health professionals.[84] The responses on the valuation task reflect the preferences between different health states,[85] and are eventually used to generate and model value sets. The general public values a health state usually lower ('worse') compared to the values for equivalent health states elicited from patients.[86] There are arguments in favor and against either valuation population, however, valuations based on preferences of the general population are currently being used in practice in the United Kingdom.[73]

DALY

In current CUA research, besides QALYs, there is also another outcome measure being used frequently, which is portrayed in disability adjusted life years (DALYs) (Figure 5).[87] The difference between QALYs and DALYs is that QALYs measure years lived in perfect health and DALYs measure years in perfect health lost.[88] DALYs represent the overall disease burden expressed in the number of years lost due to ill-health, disability or death, and combines mortality and morbidity in one single index measure. DALYs are the sum of two components: the Years of Life Lost (YLL) due to premature death, and the Years Lost due to Disability (YLD) for people living with the health condition or its consequences.[89] DALYs are calculated by use of the following formula:

$$\mathrm{DALY} = \mathrm{YLL}^{1} + \mathrm{YLD}^{2}$$

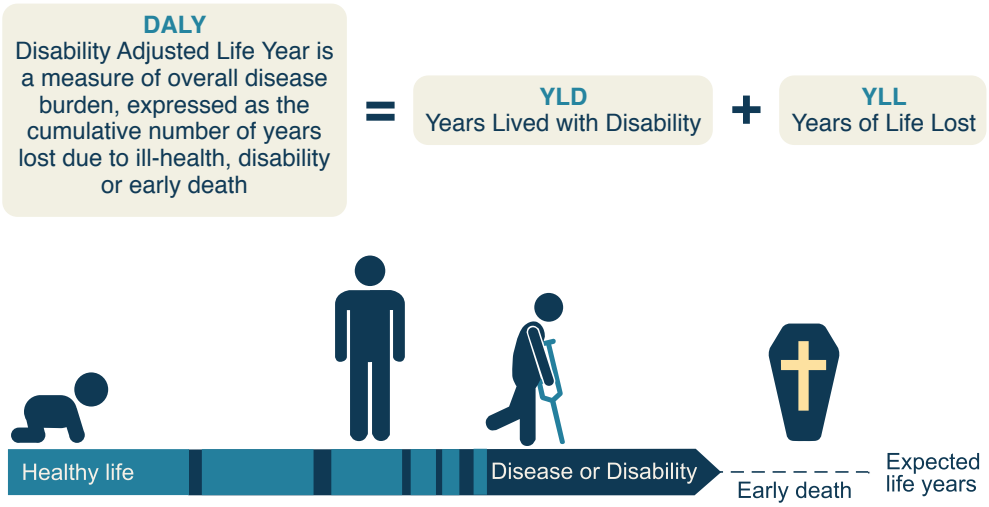
$$^{1}\ \mathrm{YLL} = \mathrm{n} * \mathrm{l}$$

n is the number of deaths due to the disease and l is the standard life expectancy at age of death in years

$$^{2}\mathrm{YLD} = \mathrm{i} * \mathrm{dw} * \mathrm{l}$$

i is the number of incident cases, dw is disability weight and l is the average duration of the case until remission or death in years.[69, 89, 90]

Figure 5. Disability adjusted life year (DALY)



Adapted from: PlanemadVector:Radio89 - This file was derived from: DALY disability affected life year infographic.png:, CC BY-SA 3.0, https://commons.wikimedia.org/w/index.php?curid=20278903

Disability weights

Levels of loss of functioning caused by diseases is represented in disability weights, which are a key component in DALY calculations. The disability weight demonstrates the impact of a disease or injury and is measured on a scale with values ranging from 0, corresponding to perfect health, to 1, corresponding to death.[91] Disability weights are assigned to health states by a panel of judges, which could be patients, proxies, medical experts, or members from the general population, but can also be derived using multi-attribute utility instruments.

Aims and outline of this thesis

The main aim of this thesis is to expand our knowledge on assessing outcome following traumatic brain injury, and measuring outcome preferences for traumatic brain injury and stroke among patients and the general population. We used a wide range of methods, including analysis of prospective observational longitudinal patient data, survey data of the general population, and a simulation study.

The aim of this thesis is operationalized in the following research questions:

1. What is the association between post-concussion symptoms and HRQoL in mTBI?
a. What is the outcome in divergent mTBI patient groups?
b. What are the prevalence and risk factors of post-concussion symptoms in mTBI patients and the general population?
c. How can we classify post-concussion symptoms and post-concussion syndrome after mTBI and to what extent are pre-injury ratings reliable?

2. What are preferences and utility weights for TBI and stroke health states and how could they be applied?
a. What are preferences of the general population for disease specific outcome measures for TBI and which utility weights can be assigned to TBI value sets?
b. How can value sets and patient data be u used to determine utility and/or disability weights for TBI and stroke health states?

This thesis consists of two parts. Part I (Chapter 2-8) describes the association between post-concussion symptoms and HRQoL in mTBI and assesses the outcome following mTBI, the prevalence and risk factors of post-concussion symptoms in patients with mTBI and the general population and lastly, classifies post-concussion symptoms.
Chapter 2 provides the prevalence and risk factors of post-concussion symptoms, and functional outcome of mTBI patients and an overview on different classification methods for post-concussion syndrome. **Chapter 3** examines the impact of post-concussion symptoms on HRQoL for patients with mTBI. **Chapter 4 and 5** study the prevalence rates of post-concussion symptoms and outcome following divergent mTBI patient groups. **Chapter 6** describes the prevalence and risk factors of post-concussion-like symptoms in the general population of three European countries. **Chapter 7** determines the prevalence and prediction of post-concussion symptoms in children and adolescents with mTBI. **Chapter 8** assesses the ratings of pre-injury symptoms in patients with mTBI over time.

In Part II (Chapter 9-12) of this thesis we examine the preferences and utility weights for TBI and stroke health states and their application. **Chapter 9** starts with the elicitation of preferences and development of value sets for a TBI specific instrument

to measure HRQoL in three European countries. **Chapter 10** describes the assessment of impact following TBI by developing disability weights for a functional outcome instrument and uses HRQoL data of patients with TBI to achieve this. **Chapter 11** describes a simulation study in which we evaluate statistical efficiency of a new outcome measure in stroke research. Reference values from the general Dutch and United Kingdom population are developed for a TBI specific instrument to assess HRQoL in **Chapter 12**.

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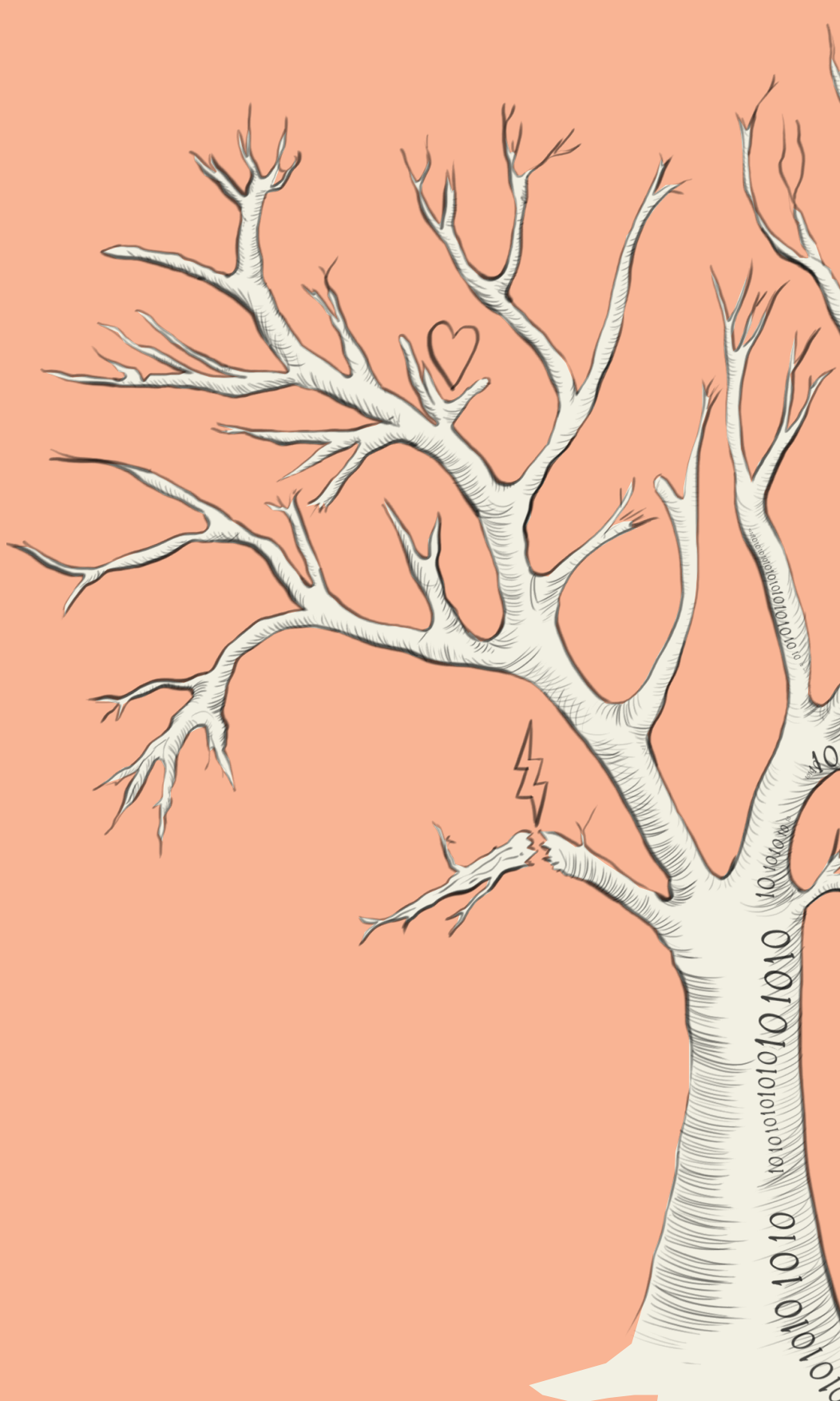

PART I

OUTCOME ASSESSMENT FOLLOWING TRAUMATIC BRAIN INJURY

Chapter 2

Divergent Classification Methods of Post-Concussion Syndrome After Mild Traumatic Brain Injury: Prevalence Rates, Risk Factors and Functional Outcome

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Abstract

Mild traumatic brain injury (mTBI) is a common diagnosis and approximately one third of mTBI patients experience a variety of cognitive, emotional, psychosocial, and behavioral post-concussion symptoms. When a cluster of these symptoms persists for more than 3 months they are often classified as post-concussion syndrome (PCS). The objective of this study was to determine prevalence rates, risk factors and functional outcome associated with PCS 6 months after mTBI, applying divergent classification methods. Follow-up questionnaires at 6 months after mTBI included the Rivermead Post-Concussion Symptoms Questionnaire (RPQ) and the Glasgow Outcome Scale Extended (GOSE). The RPQ was analyzed according to different classification methods: the mapped International Classification of Diseases, 10th revision (ICD-10)/Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV), the RPQ total score, the RPQ3 and the three-factor model using two different cutoff points (mild or worse and moderate or worse). Our results from a sample of 731 mTBI patients showed that prevalence rates of PCS ranged from 11.4% to 38.7% using divergent classification methods. According to all eight methods, 6.3% (n=46) of mTBI patients experienced PCS. Applying the divergent classification methods resulted in a different set of predictors being statistically significantly associated with PCS, and a different percentage of overlap with functional impairment, measured with the GOSE. In conclusion, depending on the classification method and rating score used, prevalence rates of PCS deviated considerably. For future research, consensus regarding the diagnostic criteria for PCS and the analysis of the RPQ should be reached, to enhance comparability of studies regarding PCS after mTBI.

Introduction

Traumatic brain injury (TBI) is a leading cause of death and disability worldwide with an annual incidence of 262 per 100,000 admitted TBI patients in Europe.[1] The large majority (70-80%) of all TBI cases are evaluated as mild TBI (mTBI). In the first weeks following mTBI, many patients experience post-concussion symptoms comprising physical symptoms (e.g., headaches, dizziness, blurred vision, fatigue and sleep disturbances), cognitive deficits (e.g., poor memory, and attention and executive difficulties), and behavioral/emotional symptoms (e.g., depression, irritability, anxiety-related disorders, emotional lability).[2] For most patients, these symptoms will diminish spontaneously,[3] but for a subset of patients (estimated between 5%–43%[4-9]) symptoms last for months and sometimes even longer. When a set of symptoms persists for >3 months, it is often referred to as post-concussion syndrome (PCS).

It is challenging to define PCS, because there is no consensus as to the criteria for diagnosis.[10] The most used criteria for diagnosis are those specified in the International Classification of Diseases, 10th revision (ICD-10)[11] and the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV).[2] Even though the ICD-10 and DSM-IV classifications deviate, they both include a brain injury with potential loss or alteration of consciousness, and the existence of certain symptoms. A frequently used instrument to assess the presence and severity of post-concussion symptoms is the Rivermead Post-Concussion Symptoms Questionnaire (RPQ).[12] The RPQ was developed by King and colleagues, who proposed to use the total scale score for analyses.[12] Subsequently, other evaluation methods have been applied. Potter and colleagues proposed a ≥ 12 cutoff for the total scale score.[13] Eyres and colleagues suggested the use of a two subscale version, one scale containing three items (RPQ3) and one containing 13 items (RPQ13), because of a possible lack of unidimensionality for the RPQ total scale.[14] Smith-Seemiller and colleagues recommended a modified scoring system with three subscales (cognitive, emotional and somatic symptoms) or two subscales (collapsing somatic and emotional symptoms versus cognitive symptoms) to be more sensitive.[13, 15] The majority of studies, however, mapped the ICD-10 or DSM-IV criteria to the RPQ.[16-18]. Patients are subsequently classified with PCS if they report at least three out of the following symptoms: headaches, dizziness, fatigue, irritability, impaired memory, impaired concentration, and insomnia. In addition to heterogeneity in classification methods, there is also no consensus on whether symptoms should be incorporated in the rating for PCS if they are rated as 2 (mild problem) or worse or only if they are rated as 3 (moderate problem) or worse.[19, 20]

An abundance of studies are being done in the field of PCS regarding predictors and prediction modeling.[20-22] We investigated whether classification methods have different predictors or have more predictive power, and expected that different risk factors would be significant depending on the classification method used. Advances and developments in prediction modeling are difficult, because an unambiguous definition for PCS is missing, and it is possible that different predictors

are associated with PCS according to divergent classification methods.[20]
The application of different classification methods and cutoffs may lead to incomparability of studies assessing PCS. The main objective of this study was to examine how the four divergent classification methods and two different rating scores as cutoff defining PCS using the RPQ differ among patients 6 months after mTBI. First, descriptive analyses were done according to the four classification methods. Subsequently, the sample was analyzed on whether the risk factors predicting PCS differed across PCS classification methods, and lastly, the association with the clinically relevant Glasgow Outcome Scale Extended (GOSE) and different classification methods was observed. We expect differences in prevalence of PCS per classification method. We also hypothesize differences in predictors associated with PCS according to the divergent classification methods. Additionally, it was hypothesized that the functional outcome, measured by the GOSE, would differ, depending on the classification method used.

Methods

Study design

Data were obtained from the prospective observational Radboud University Brain Injury Cohort Study (RUBICS).[23-26] All patients with mild, moderate or severe TBI admitted between January 1998 and December 2010 to the emergency department (ED) of the Radboud University Medical Centre (RUNMC), a level I trauma center in the Netherlands, were included in the database. The ethical standards committee of the RUNMC had approved this study.

Study participants

In the current study, 797 patients were selected from the RUBICS database based on the following inclusion criteria: patients' age was ≥16 years, written informed consent was given by patients (or guardians), patients had mTBI and were admitted to the ED of RUNMC between January 2003 and June 2010. Diagnosis of mTBI was based on a Glasgow Coma Scale (GCS) score of 13-15 after initial resuscitation or followed by sedation and intubation during resuscitation for a non-neurological cause. Exclusion criteria were alcohol or drug abuse or dementia, unknown address, and not being able to speak or write Dutch. We selected 92% (n=731) of mTBI patients who completed the RPQ (filled in all items) at 6 month follow-up for all analyses throughout this study.

Measurements

Clinical data were registered in the ED at admission by a neurologist and/or neurosurgeon and entered by a research nurse into the RUBICS databank. Demographic data (age, sex, and educational level), trauma mechanism, hospitalization, clinical variables, comorbidities, functional outcome (GOSE), and the RPQ were all collected with a postal questionnaire, which was self-rated by patients or guardians at 6 months after the trauma. Structured interviews during regular visits to the outpatient clinic or during consultation by telephone were used to determine GOSE scores.[27]

Assessment of persistent post-concussion symptoms and diagnosis of PCS

The prevalence rates and severity of persistent post-concussion symptoms were assessed with the postal RPQ at 6 month follow-up. Patients were asked to rate the severity of 16 different symptoms, commonly found after TBI, over the past 24 h. In each case, the symptoms were compared with how severe they had been before the injury occurred (premorbid). The patient was asked to rate the symptoms on a five-point Likert scale: 0 (not experienced at all), 1 (not a problem), 2 (mild problem), 3 (moderate problem) and 4 (severe problem).

In the literature, there is not a gold standard concerning the use of the RPQ. Therefore, we used the following classification methods to classify patients as having PCS: mapped ICD-10/DSM-IV, RPQ total score[12], RPQ 3,[14] and three-factor model (Table 1).[15] The mapped ICD-10/DSM-IV requires that three or more symptoms in the list in Table 1 reach cutoff, the RPQ3 requires that one or more symptoms in the list in Table 1 reach cutoff, the RPQ total score requires a sum

Table 1. Classification methods regarding Post-Concussion Syndrome

Classification methods	**Mapped ICD-10/DSM-IV**	**RPQ Total score**[13]	**RPQ3**[14]	**Three-factor model**[15]	
	At least 3 symptoms from the list below	All symptoms from the list below	At least 1 symptom from the list below	At least 1 symptom from each scale from the list below	
Eligible symptoms from the RPQ	Headache	Headache	Headache	Cognitive	Forgetfulness, poor memory
	Dizziness	Dizziness	Dizziness		Poor concentration
	Sleep disturbance	Nausea and/or vomiting	Nausea and/or vomiting		Taking longer to think
	Fatigue	Noise sensitivity		Emotional	Being irritable, easily angered
	Being irritable, easily angered	Sleep disturbance			Feeling depressed or tearful
	Forgetfulness, poor memory	Fatigue			Feeling frustrated or impatient
	Poor concentration	Blurred vision			Restlessness
		Light sensitivity		Somatic	Headache
		Double vision			Dizziness
		Forgetfulness, poor memory			Nausea and/or vomiting
		Poor concentration			Noise sensitivity
		Taking longer to think			Sleep disturbance
		Being irritable, easily angered			Fatigue
		Feeling depressed or tearful			Blurred vision
		Feeling frustrated or impatient			Light sensitivity
		Restlessness			Double vision
Cutoff; rating score 2	Three items with score ≥ 2	≥ 12 (only symptoms ≥ 2) [a]	One item with score ≥ 2		Each scale has one item ≥ 2
Cutoff; rating score 3	Three items with score ≥ 3	≥ 12 (only symptoms ≥ 3)	One item with score ≥ 3		Each scale has one item ≥ 3

[a] *Example: Six symptoms with rating score 2 qualify as having PCS.*

Abbreviations. ICD, International Classification of Diseases; DSM, Diagnostic and Statistical Manual; RPQ, Rivermead Post-Concussion Symptoms Questionnaire; PCS, Post-Concussion Syndrome.

score of all items of the RPQ of ≥ 12, and the three- factor model requires that one or more items within each of the cognitive, emotional, and somatic scales reaches cutoff. For each classification method, we used two different rating scores as cutoff (≥ 2 and ≥ 3), resulting in eight different classification methods in total. Because no clear cutoff was found in the literature for the RPQ13, this scale was not taken into consideration. It should also be noted that the RPQ is based on self-report rather than clinical examination, and does not include information on the duration of the symptoms and clinically significant impairment. Therefore, it cannot accurately diagnose PCS.[20]

Risk factors

Looking at the available data in our dataset and using previous literature [20-22], the variables age, gender, level of education, injury mechanism (assault vs. other mechanisms), Injury Severity Scale (ISS), Abbreviated Injury Score of the Head (AISH), comorbidity, traumatic abnormalities on the head computed tomography (CT) scan, and whether the patient was admitted to the hospital were considered as risk factors. We hypothesized that older age, female gender, lower years of education, higher ISS and AISH scores, comorbidity, abnormalities on CT, and being hospitalized would be associated with PCS.

Functional outcome

Functional outcome was assessed using the 6 month GOSE, which was completed as a postal questionnaire. The GOSE is a functional measurement scale specifically designed for TBI.[28, 29] The instrument evaluates functional outcome through eight categories encompassing consciousness, independence at home and outside the home, work, social and leisure activities, family and friendship and return to normal life.[30] After accumulating these categories an eight point scale ranging from 1 (dead) to 8 (completely recovered) is established, which has the ability to distinguish among functional outcomes. For 20 patients included in our study, the GOSE score was missing. When there was no available outcome at exactly 6 months, outcomes measured within a 2 month range were also approved. Functional impairment was classified as a GOSE score of ≤6.[27]

Statistical analysis

For demographic data (age, sex and educational level), trauma mechanisms, hospitalization, clinical injury variables and comorbidities, descriptive analyses were performed. Patients included in the current study were compared with those having incomplete RPQ data on demographic (gender, age, educational level) and clinical variables using Chi-Square tests (categorical variables) and Student's *t* tests (continuous variables).

Prevalence of PCS using the eight divergent classification methods was determined by computing the percentage of patients meeting the specific criteria of each classification method. We subsequently determined overlap between classification methods by calculating the number and percentage of patients diagnosed with PCS according to multiple classification methods.

The univariable associations between predictors and PCS according to multiple classification methods were explored by using Chi-Square tests (categorical variables) and an independent samples t test (continuous variables). All variables were included in a stepwise backwards multivariable logistical regression to identify significant risk factors ($p < 0.05$) of PCS. The association between PCS and functional impairment (GOSE ≤6) was determined by calculating the percentage of patients for each classification method of PCS that was functionally impaired. McNemar tests were used to see if the classification methods differed significantly in PCS/no PCS pattern at the population level, and a Cochran's Q test was used to see if the classification methods differed significantly ($p < 0.05$) at an individual level. Multiple imputation technique with five datasets was used to impute missing data for the following predictor variables: education (182 missing), comorbidity (237 missing) and hospital admission (2 missing).
All statistical analyses were performed using SPSS version 21 for Windows (IBM SPSS Statistics, SPSS Inc, Chicago, IL).

Results

Study population

In total, 731 mTBI patients were included in this study. Patients with a missing 6 month RPQ (n = 66) did not differ from those included in this study, except that their median age was 54.5 (interquartile range [IQR]: 42.75-68), which was significant on a $p < 0.01$ level. The characteristics of our study sample are shown in Table 2. The median age of the respondents was 44 years and 63% were male. Almost half (48%) of the patients were injured in road traffic accidents and a third were injured due to falls. One out of five people had one or more comorbid conditions and ~ 13% showed abnormalities on the CT scan. Approximately 50% of the respondents were admitted to the hospital, and they were hospitalized for an average of 3 days. A total of 35 patients were admitted to the intensive care unit (ICU).

Six-month persistent post-concussion symptoms

The three most frequently reported symptoms on the 6 month RPQ were fatigue, forgetfulness/poor memory and poor concentration (Fig. S1) (see online supplementary material at http://www.liebertpub.com). Fatigue was experienced by 308 patients (42.1%), and 32 (4.4%) patients evaluated this as a severe problem. Nausea and/or vomiting was the least reported symptom (n=42, 5.7%). Approximately one-third of the patients (n=242) experienced none of the symptoms (total RPQ score of 0), whereas three patients had an RPQ score of 59, which means they experienced severe problems 6 months after the injury with almost every symptom on the list. Around 30% (n=234) had a total RPQ score of ≥ 12. The median score on the RPQ for the study population was 4 (IQR, 4 -15).

Prevalence rates of PCS according to the different classification methods

The use of divergent classification methods resulted in prevalence rates for 6 month PCS ranging from 11.4% (three-factor model with rating score 3) to 38.7% (mapped ICD-10/DSM-IV with rating score 2; Figure 1 A and B). Classification methods overlapped substantially; for example, 95.6% (n =108) of patients who met the criteria for PCS according to the mapped ICD-10/DSM-IV with rating score 2 also met the criteria for PCS according to the RPQ total score with rating score 2. The lowest amount of overlap was found for the classification methods RPQ3 and three-factor model with rating score 3 (n = 49, 51%) A total of 46 (6.3%) patients met the criteria for PCS according to all classification methods. When looking at the difference in PCS/no PCS pattern for the classification methods with rating score 2, a significant result was found for all classification methods, except for the mapped ICD-10/DSM-IV compared with the RPQ3 (p = 0.07) and the RPQ total score compared with the three-factor model (p = 0.81). For the classification methods with rating score 3, all had significant differences in pattern, except for the mapped ICD-10/DSM-IV compared with the RPQ3 (p = 0.78) and the RPQ3 compared with the three-factor model (p = 0.18). The lack of significant differences in PCS/no PCS pattern were characterized by the shared symptom overlap between the RPQ3 and the three-factor model, and the mapped ICD-10/DSM-IV. A Cochran's Q test determined that all classification methods differed significantly from each other. These results demonstrated that the choice of classification method influenced PCS diagnosis both at a population level, and at an individual level.

Table 2. Characteristics of the study population

n	731
Gender (male)	463 (63.3%)
Age[a] (years)	44 (27-57)
Education	
Primary education	21 (2.9%)
Secondary education	336 (46.0%)
Higher professional education	108 (14.8%)
Academic education	84 (11.5%)
Unknown	182 (24.9%)
Injury Mechanism	
Road traffic accident	351 (48.0%)
Fall	240 (32.8%)
Sports	77 (10.5%)
Assault	41 (5.6%)
Other/Unknown	22 (3.0%)
Injury characteristics	
ISS[a]	6 (4-14)
AISH[a]	2 (2-2)
Head AIS 3	93 (12.7%)
Head AIS 4	57 (7.8%)
Head AIS 5	11 (1.5%)
Comorbidity[b]	
No pre-existing disease	329 (45.0%)
1 comorbid disease	92 (12.6%)
2 comorbid disease	33 (4.5%)
3 or more comorbidities	40 (5.5%)
Unknown	237 (32.4%)
CT scan	
No CT scan	45 (6.2%)
CT scan, no abnormalities	591 (81.0%)
CT scan, abnormalities	94 (12.9%)
Hospitalization[c]	
Hospital admission	373 (51.0%)
Number of days hospitalized[a]	3 (1-8)
ICU admission	35 (4.8%)

GCS[a]	15 (14-15)
13	40 (5.5%)
14	152 (20.8%)
15	539 (73.7%)
GOSE[a]	7 (6-8)
RPQ total score[a]	4 (4-15)

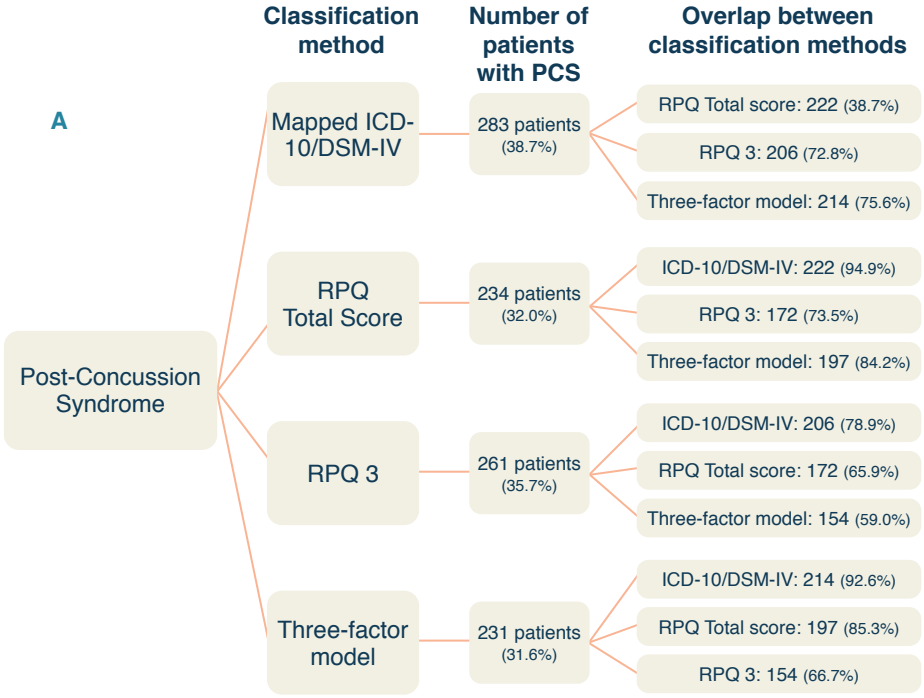
[a] *Data are displayed as median, with the first and third quartile given in parentheses.*

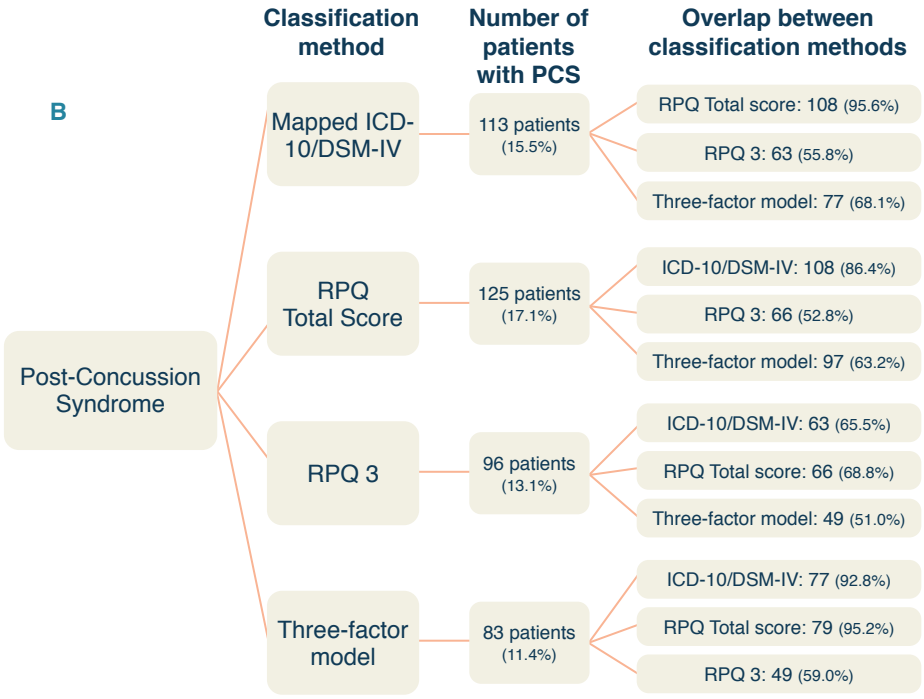
[b] *Comorbidity is defined as the presence of any co-existing diseases or disease processes additional to injury that the traumatic brain injury (TBI) patients sustained. The following diseases were assessed as comorbid disease: asthma, chronic bronchitis, chronic nonspecific lung disease (not asked about), heart disease, diabetes, back hernia or chronic backache, osteoarthritis, rheumatoid arthritis, and cancer.*

[c] *Hospital or ICU admission for ≥1 day or more after arrival at emergency department.*

Abbreviations. ISS, Injury Severity Score; AISH, Abbreviated Injury Scale of the Head; AIS, Abbreviated Injury Scale; CT, Computed Tomography; ICU, Intensive Care Unit; GOSE, Glasgow Outcome Scale Extended; RPQ, Rivermead Post-Concussion Symptoms Questionnaire.

Figure 1 A and B.





Risk factors for PCS

Assault was significantly associated with 6 month PCS according to all classification methods, whereas traumatic abnormalities on the head CT scan and age were not statistically significantly associated with PCS according to any of the classification methods (Table 3, Tables S1-S4) (see online supplementary material at http://www.liebertpub.com). Female gender and lower education were significantly associated with all classification methods, except for the three-factor model with rating score 3. The significance of the predictors ISS, AISH, comorbidity and hospital admission, however, depended on the classification method used; for example, hospital admission was a significant predictor for PCS using six out of eight classification methods. Multivariable prediction models explained 6-14% (Nagelkerke R^2) of the variation in PCS according to the different classification methods.

PCS and functional outcome

A total of 198 (27.1%) patients were functionally impaired (GOSE ≤6) 6 months post-injury. There was a significant association between PCS according to all classification methods and functional impairment ($p < 0.01$). The highest percentage of functional impairment for patients with PCS was found for the RPQ total scale with rating score 3 (72.8%, $n = 91$), whereas the RPQ3 with rating score 2 recorded the lowest percentage (46.0%, $n = 120$) (Table 4).

Table 3. Significant predictors in multivariable model of 6 month PCS using divergent classification methods on a $p < 0.05$ level

	Mapped ICD-10/DSM-IV		RPQ total score		RPQ3		Three-factor model	
Predictor	≥ 2*	≥ 3**	≥ 2	≥ 3	≥ 2	≥ 3	≥ 2	≥ 3
Gender	0.53	0.48	0.53	0.54	0.38	0.4	0.59	
Age								
Education (Primary/Secondary)	1.73	1.8	1.69	1.82	1.55	1.8	1.62	
Injury mechanism (Assault vs. other mechanisms)	0.38	0.26	0.25	0.34	0.34	0.21	0.27	0.29
ISS			1.03					
AISH	1.21		1.24		1.29		1.22	1.29
CT abnormalities								
Comorbidity	0.54		0.51	0.6	0.65	0.59	0.52	
Hospital admission	0.45	0.45	0.61	0.43			0.52	0.53
R^2	0.13	0.09	0.14	0.11	0.1	0.1	0.11	0.06

Note. Cells in grey indicate that the predictor is statistically significantly ($p < 0.05$) associated with PCS in multivariable logistic regression analysis and in the cells are the odds ratios. Cells in white indicate that the predictor is not statistically significantly associated with PCS.

** For each classification method, we used two different rating scores as cutoff: rating score 2 (* ≥ 2) and rating score 3 (** ≥ 3)*

Abbreviations. PCS, Post-Concussion Syndrome; ICD, International Classification of Diseases; DSM, Diagnostic and Statistical Manual; RPQ, Rivermead Post-Concussion Symptoms Questionnaire; CT, Computed Tomography; ISS, Injury Severity Scale; AISH, Abbreviated Injury Severity Scale of the Head.

Table 4. MTBI patients with PCS and functionally impaired (GOSE ≤6)

	Mapped ICD-10/ DSM-IV	RPQ total score	RPQ3	Three-factor model
Rating score 2[a]	51.6% (146)	58.1% (136)	46.0% (120)	54.5% (126)
Rating score 3[b]	71.7% (81)	72.8% (91)	67.7% (65)	71.7% (59)

[a] *mild or worse.*

[b] *moderate or worse.*

Note: p<0.01 on all associations.

Abbreviations. MTBI, mild traumatic brain injury; GOSE, Glasgow Outcome Scale Extended; DSM, Diagnostic and Statistical Manual; ICD, International Classification of Diseases; PCS, Post-Concussion Syndrome; RPQ, Rivermead Post-Concussion Symptoms Questionnaire.

Discussion

The prevalence of PCS 6 months following mTBI ranged from 11.4% to 38.7%, depending on the classification method and rating score applied. The divergent classification methods in this study additionally influenced the statistical significance of predictors and the association with functional outcome, as measured with the GOSE.

The prevalence rates of PCS in our study are in line with preceding studies, which reported that prevalence rates of PCS after mTBI fluctuate and are estimated to range from 5% to 43%.[4-9] The prevalence rates that were found in the literature were dependent on many aspects, such as case mix of the sample and setting, but they were also dependent on the rating score applied and the classification method used to identify mTBI patients with PCS. Yeates has pointed out that the inconsistency in definition and classification criteria interferes with the righteous classification and identification of patients with PCS,[31] which ultimately leads to incommensurable prevalence rates and outcomes. Additionally, Waljas and colleagues have also stated that the rate of PCS diagnosis varies greatly based on which rating scale is being used,[19] which substantiates the decision during the writing of this article to research two different rating scores as cutoff points. Recently, the DSM criteria for PCS have been revised substantially. As this definition deviates significantly from the DSM-IV (e.g. the term mild neurocognitive impairment (MNI) from TBI was introduced instead of PCS),[32] it is likely that this will result in even more heterogeneity in prevalence rates. Tator and colleagues have recently emphasized "a refinement of the definition of PCS,"[33] and also the lack of consensus with regard to the definitions of PCS has previously been identified as a problem.[8] This problem presented itself as an opportunity in our study to explore and compare prevalence rates, risk factors and functional outcome when divergent cutoff rating scores and classification methods of the RPQ are applied.

When comparing divergent classification methods, different patients were identified as having PCS. There was a difference of almost 30% in prevalence rates between the classification method with the highest (mapped ICD-10/DSM-IV with rating score 2; 38.7%) and lowest (three-factor model with rating score 3; 11.4%) percentage. Forty-six patients experienced PCS according to all eight classification methods. The most overlap in identifying the same patients experiencing PCS was found between the mapped ICD-10/DSM-IV and the RPQ total score (95.6%), both with rating score 3. This can be explained by the overlap between symptoms included in both classification methods and by the fact that six out of seven eligible symptoms from the RPQ enclosed in the mapped ICD-10/DSM-IV are in the top eight most reported symptoms in this population. The lowest percentage of overlap was found between the RPQ3 and the three-factor model (51.0%) when a rating score of 3 was used as a cutoff. This can be explained by the fact that the RPQ3 only defines three somatic symptoms, whereas four out of the five most reported symptoms (forgetfulness/poor memory, poor concentration, taking longer to think, feeling frustrated or impatient) in this study population are cognitive or emotional, which are

captured in the three-factor model. This also is in line with the thought that the RPQ3 measures symptoms that occur more often in the acute phase after a mTBI.[18]

In this study, we found that the classification method used influenced the statistical significance of predictors; that is, several predictors were statistically significantly associated with PCS using some classification methods but not using others. This might be one of the reasons for the substantial heterogeneity in studies on predictors and prediction modelling for PCS,[21, 22] hampering prognostic research. However, the results also showed that assault was associated with all classification methods, and female gender and lower education with all but one classification method.

Although PCS was statistically significantly associated with functional impairment (GOSE ≤6), there was variation in the amount of overlap between PCS and functional impairment dependent on the classification methods applied, ranging from 46.0% to 72.8%. Restricting PCS to only those symptoms that were reported as being 'moderate or worse' resulted in higher overlap between PCS and functional impairment. This may indicate that symptoms reported as moderate or worse are more likely to represent clinically relevant symptomatology than symptoms reported as mild. This is in line with the findings by Waljas and colleagues,[19] who reported that when using rating score 3 as a cutoff, patients with head injury were successfully distinguished from healthy controls, whereas when rating score 2 was used as cutoff, this resulted in a substantial proportion of healthy controls being diagnosed with PCS.

The present study is unique because eight divergent classification methods for PCS were applied, and the statistical effect this might have had on predictors associated with PCS and the different percentages seen as functionally impaired, measured by the GOSE, were assessed.

Our study had several limitations. First, Ruff declared that PCS concerns a complex interplay of biological, psychological and social factors that include prior health, life stressors and compensation/litigation issues.[8] This implies that an overview of many aspects of a patient's current, but also previous life before the trauma, is required for correct assessment.
Our study was a post-hoc analysis of prospectively collected data of individuals after mTBI, and there were no pre-injury data available except for pre-existing comorbidity. Additionally, post-concussion symptoms in our study were self-reported, which might have led to more or fewer reported symptoms on the questionnaire than if the respondents had been interviewed by a physician.[34] Response bias might also have played a role during our study. Respondents with symptoms may have been more likely to participate in the 6 month follow-up questionnaires than patients who were currently not experiencing/or had never experienced any symptoms.
Further, it has been argued that the RPQ is not the most ideal instrument to use in an mTBI population,[35] but there is currently no consensus on what would be a better instrument to use. Looking at the RPQ total scale, one should keep in mind that even though the total RPQ score has been proposed by the developer of the instrument

and is used in most articles until now, Eyres and colleagues have revalidated the RPQ, and have pointed out that the various items of the RPQ have very low construct validity and in consequence of this, should not be computed into a sum score[14], but into two subscales. During this study, we have decided to not take the RPQ13 into consideration, because no clear cutoff was found in the literature. For future studies, it would be interesting to look at the RPQ13 and establish a cutoff in view of the fact that a large number of the reported symptoms at 6 months are considered cognitive, provided that enough clinical data and concurrent evidence are available to define and diagnose TBI.
A limitation concerning the use of mapped ICD-10/DSM-IV in this study was that we imposed them as the same, because we do not have the required data to differentiate between the ICD-10 and DSM-IV. This might have led to over/under reporting of prevalence rates, and limited the ability to report about the differences among the most applied definitions. Previous studies have shown that DSM-IV usually leads to lower prevalence rates, because the diagnostic criteria seem to be more stringent [36, 37], yet McCauley and colleagues have stated that there should be no clinical preference for any one of the diagnostic criteria.[38] In previous research, the variability in instruments used to diagnose mTBI has also been considered a difficulty. Depending on the diagnosis criteria used, different individuals will be classified as having mTBI, which may lead to inconsistencies and might influence the results.[22, 39-42] In our study, this could possibly mean that we have included patients who would not have been diagnosed with mTBI using other diagnostic criteria, which could affect the risk factors and functional outcome of this population.

In our study we used a relatively low threshold ($p = 0.05$) for the inclusion of predictors in the backward selection procedure. Higher levels (e.g., $p = 0.20$ or $p = 0.157$ [43, 44]) as well as advanced statistical methods such as shrinkage and bootstrap validation are usually recommended to enhance the internal and external validity of prediction models.[43] Therefore, the results on predictors in our study should be interpreted as a proof of principle (there are different predictors associated with PCS according to different definitions) rather than considered applicable for clinical practice. Regarding the results of the regression, these could have been weakened by the fact that we looked at assault compared with all other injury mechanisms combined. More detailed information on the circumstances of the injury is essential to comprehend the real effect of the injury mechanism on the outcome.
Additionally, lower education and comorbidity were considered significant risk factors for PCS, which could have been impacted by the large amount of imputed values.
A final limitation of our study is that data were collected in one academic hospital, which limits the generalizability of the results, because of differences in the case mix and because patients with severe trauma are more likely to be admitted to the ED of an academic hospital.

During the last decade, a shift from identifying PCS and interpreting it as an exclusive syndrome to recognizing it as being a highly complex and ever-changing

condition in different settings/populations, can be observed. This development leads to more and more specific research in the area of PCS or, as now suggested, persistent post-concussive symptoms. This debate and inconsistency concerning definitions, diagnostic criteria, assessment and evaluation of PCS hampers its research and therapy. Standardizing and improving diagnosis and assessment of PCS will facilitate to identify opportunities for intervention when patients experience the disabling PCS symptoms, or even prevent mTBI patients from developing PCS. In addition, it is recommended to perform sensitivity and specificity analyses on the different classification methods for the RPQ to evaluate their classification accuracy. [18]

Conclusion

Our study showed that prevalence rates of PCS 6 months after mTBI deviated considerably, depending on the classification method and rating score used. In addition, applying divergent classification methods resulted in a different set of predictors being statistically significantly associated with PCS, and a different percentage of overlap with functional impairment, measured with the GOSE.
These findings highlight the need for a universal guideline with respect to diagnostic criteria for PCS, and a gold standard for analysis of the RPQ, to enhance comparability of studies regarding PCS after mTBI.

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Appendix

Supplementary Table S1. Characteristics of the study population with Post-Concussion Syndrome per classification method with rating score 2

	Mapped ICD-10/DSM-IV			*RPQ Total score*			*RPQ3*			*Three-factor model*		
	PCS	*No PCS*	*P-value*	*PCS*	*No PCS*	*P-value*	*PCS*	*No PCS*	*P-value*	*PCS*	*No PCS*	*P-value*
n	283	448		234	497		261	470		231	500	
Gender (male)	161 (56.9%)	302 (67.4%)	< .01	133 (56.8%)	330 (66.4%)	0.01	132 (50.6%)	331 (70.4%)	< .01	133 (57.6%)	330 (66.0%)	0.03
Age[a] (years)	45 (31-56)	43 (26-57)	0.14	47 (32-57)	42 (25.5-56)	0.01	44 (30.5-56.5)	43 (26-57)	0.26	45 (31-56)	43.5 (26-57)	0.32
Education			< .01			< .01			0.01			< .01
Primary	6 (2.1%)	15 (3.3%)		5 (2.1%)	16 (3.2%)		7 (2.7%)	14 (3.0%)		2 (0.9%)	19 (3.8%)	
Secondary	142 (50.2%)	194 (43.3%)		122 (52.1%)	214 (43.1%)		127 (48.7%)	209 (44.5%)		123 (53.2%)	213 (42.6%)	
Higher professional	32 (11.3%)	76 (17.0%)		27 (11.5%)	81 (16.3%)		35 (13.4%)	73 (15.5%)		28 (12.1%)	80 (16.0%)	
Academic	18 (6.4%)	66 (14.7%)		14 (6.0%)	70 (14.1%)		17 (6.5%)	67 (14.3%)		14 (6.1%)	70 (14.0%)	
Unknown	85 (30.0)	97 (21.7%)		66 (28.2%)	116 (23.3%)		75 (28.7%)	107 (22.8%)		64 (27.7%)	118 (23.6%)	
Injury Mechanism			0.03			< .01			0.01			< .01
Road traffic accident	139 (49.1%)	212 (47.3%)		113 (48.3%)	238 (47.9%)		134 (51.3%)	217 (46.2%)		109 (47.2%)	242 (48.4%)	
Fall	96 (34.9%)	144 (32.1%)		77 (32.9%)	163 (32.8%)		77 (29.5%)	163 (34.7%)		79 (34.2%)	161 (32.2%)	
Sports	19 (6.7%)	58 (12.9%)		14 (6.0%)	63 (12.7%)		18 (6.9%)	59 (12.6%)		13 (5.6%)	64 (12.8%)	
Assault	22 (7.8%)	19 (4.2%)		22 (9.4%)	19 (3.8%)		22 (8.4%)	19 (4.0%)		22 (9.5%)	19 (3.8%)	

Other/Unknown	7 (2.6%)	14 (3.3)		8 (3.4%)	14 (2.8%)		10 (3.8%)	12 (2.6%)		8 (3.5%)	14 (2.8%)	
Injury characteristics												
ISS[a]	8 (5-16)	5 (4-13)	< .01	9 (5-17)	5 (4-12)	< .01	6 (4-14)	6 (4-14)	0.67	8 (5-17)	5 (4-13)	< .01
AISH[a]	2 (2-3)	2 (1-2)	< .01	2 (2-3)	2 (1-2)	< .01	2 (2-3)	2 (1-2)	0.02	2 (2-3)	2 (1-2)	< .01
Head AIS 3	42 (14.8%)	51 (11.4%)		35 (15.0%)	58 (11.7%)		39 (14.9%)	54 (11.5%)		30 (13.0%)	63 (12.6%)	
Head AIS 4	30 (10.6%)	27 (6.0%)		30 (12.8%)	27 (5.4%)		25 (9.6%)	32 (6.8%)		26 (11.3%)	31 (6.2%)	
Head AIS 5	6 (2.1%)	5 (1.1%)		7 (3.0%)	4 (0.8%)		5 (1.9%)	6 (1.3%)		7 (3.0%)	4 (0.8%)	
Comorbidity[b]			< .01			< .01			0.1			< .01
No pre-existing disease	102 (36.0%)	227 (50.7%)		82 (35.0%)	247 (49.7%)		101 (38.7%)	228 (48.5%)		82 (35.5%)	247 (49.4%)	
1 comorbid disease	36 (12.7%)	56 (12.5%)		29 (12.4%)	63 (12.7%)		27 (10.3%)	65 (13.8%)		30 (13.0%)	62 (12.4%)	
2 comorbid disease	13 (4.6%)	20 (4.5%)		11 (4.7%)	22 (4.4%)		15 (5.7%)	18 (3.8%)		12 (5.2%)	21 (4.2%)	
3 or more comorbidities	24 (8.5%)	16 (3.6%)		23 (9.8%)	17 (3.4%)		21 (8.0%)	19 (4.0%)		22 (9.5%)	18 (3.6%)	
Unknown	108 (38.2%)	129 (28.8%)		89 (38.0%)	148 (29.8%)		97 (37.2%)	140 (29.8%)		85 (36.8%)	152 (30.4%)	
CT scan			0.95			0.37			0.86			0.86
No CT scan	17 (6.0%)	28 (6.3%)		11 (4.7%)	34 (6.8%)		16 (6.2%)	29 (6.2%)		13 (5.7%)	32 (6.4%)	
CT scan, no abnormalities	223 (78.8%)	368 (82.1%)		181 (77.7%)	410 (82.5%)		207 (79.6%)	384 (81.7%)		178 (77.4%)	413 (82.6%)	
CT scan, abnormalities	42 (14.8%)	52 (11.6%)		41 (17.6%)	53 (10.7%)		37 (14.2%)	57 (12.1%)		39 (17.0%)	55 (11.0%)	

Hospitalization[c]												
Hospital admission	180 (63.6%)	193 (43.1%)	< .01	149 (63.7%)	224 (45.1%)	< .01	143 (54.8%)	230 (48.9%)	0.12	145 (62.8%)	228 (45.6%)	< .01
Number of days[a]	4 (1-9)	3 (1-6)	0.37	5 (1-10)	2 (1-6)		3 (1-9)	3 (1-7.25)		4 (1-9)	3 (1-7)	
ICU admission	22 (7.8%)	13 (2.9%)	< .01	20 (8.5%)	15 (3.6%)	< .01	15 (5.7%)	20 (4.3%)	0.37	18 (7.8%)	17 (3.4%)	0.01

[a] *Data are displayed as median, with the first and third quartile given within parentheses.*

[b] *Comorbidity is defined as the presence of any co-existing diseases or disease processes additional to injury that the TBI 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.*

[c] *Hospital or IC admission for one day or more after arrival at emergency department.*

Abbreviations. ICD, International Classification of Diseases; DSM, Diagnostic and Statistical Manual; RPQ, Rivermead Post-Concussion Symptoms Questionnaire; PCS, Post-Concussion Syndrome; ISS, Injury Severity Scale; AISH, Abbreviated Injury Severity Scale Head; AIS, Abbreviated Injury Scale; CT, Computed Tomography; ICU, Intensive Care Unit.

Supplementary Table S2. Characteristics of the study population with Post-Concussion Syndrome per classification method with rating score 3

	Mapped ICD-10/DSM-IV			RPQ Total score			RPQ3			Three-factor model		
	PCS	No PCS	P-value	PCS	No PCS	P-value	PCS	No PCS	P-value	PCS	No PCS	P-value
n	113	618		125	606		96	635		83	648	
Gender (male)	59 (52.2%)	404 (65.4%)	< .01	68 (54.4%)	395 (65.2%)	0.02	46 (47.9%)	417 (65.7%)	< .01	48 (57.8%)	415 (64.0%)	0.27
Age[a] (years)	43 (30.5-54)	44 (27-57)	0.83	46 (31.5-55.5)	43 (27-57)	0.32	46.5 (34.3-53.8)	43 (26-57)	0.42	42 (26-53)	44 (27-57)	0.46
Education			< .01			< .01			0.02			0.03
Primary	1 (0.9%)	20 (3.2%)		3 (2.4%)	18 (3.0%)		2 (2.1%)	19 (3.0%)		-	21 (3.2%)	
Secondary	63 (55.8%)	273 (44.2%)		68 (54.4%)	268 (44.2%)		50 (52.1%)	268 (45.0%)		48 (51.8%)	293 (45.2%)	
Higher professional	11 (9.7%)	97 (15.7%)		12 (9.6%)	96 (15.8%)		10 (10.4%)	98 (15.4%)		7 (8.4%)	101 (15.6%)	
Academic	6 (5.3%)	78 (12.6%)		7 (5.6%)	77 (12.7%)		5 (5.2%)	79 (12.4%)		5 (6.0%)	79 (12.2%)	
Unknown	32 (28.3%)	150 (24.3%)		35 (28.0%)	147 (24.3%)		29 (30.2%)	153 (24.1%)		28 (33.7%)	154 (23.8%)	
Injury Mechanism			< .01			< .01			< .01			0.02
Road traffic accident	53 (46.9%)	298 (48.2%)		57 (45.6%)	294 (48.5%)		44 (45.8%)	307 (48.3%)		40 (48.2%)	311 (48.0%)	
Fall	37 (32.7%)	203 (32.8%)		44 (35.2%)	196 (32.3%)		32 (33.3%)	208 (32.8%)		27 (32.5%)	213 (32.9%)	
Sports	5 (4.4%)	72 (11.7%)		5 (4.0%)	72 (11.9%)		5 (5.2%)	72 (11.3%)		3 (3.6%)	74 (11.4%)	
Assault	13 (11.5%)	28 (4.5%)		12 (9.6%)	29 (4.8%)		13 (13.5%)	28 (4.4%)		10 (12.0%)	31 (4.8%)	
Other/Unknown	5 (4.4%)	17 (2.6%)		7 (4.0%)	14 (2.5%)		2 (2.1%)	20 (3.1%)		2 (2.4%)	18 (2.9%)	

Injury characteristics												
ISS[a]	9 (4-17)	6 (4-13)	0.01	9 (4.5-17)	6 (4-13)	< .01	6 (5-15.5)	6 (4-14)	0.8	9 (4-17)	6 (4-13)	0.04
AISH[a]	2 (1-3)	2 (2-2)	0.02	2 (1-3)	2 (2-2)	0.02	2 (2-2)	2 (2-2)	0.19	2 (2-3)	2 (1.25-2)	< .01
Head AIS 3	11 (9.7%)	82 (13.3%)		16 (12.8%)	77 (12.7%)		8 (8.3%)	85 (13.4%)		6 (7.2%)	87 (13.4%)	
Head AIS 4	18 (15.9%)	39 (6.3%)		18 (14.4%)	39 (6.4%)		10 (10.4%)	47 (7.4%)		14 (16.9%)	43 (6.6%)	
Head AIS 5	4 (3.5%)	7 (1.1%)		4 (3.2%)	7 (1.2%)		4 (4.2%)	7 (1.1%)		4 (4.8%)	7 (1.1%)	
Comorbidity[b]			0.32			0.04			0.1			0.6
No pre-existing disease	43 (38.1%)	286 (46.3%)		44 (35.2%)	285 (47.0%)		35 (36.5%)	294 (46.3%)		31 (37.3%)	298 (46.0%)	
1 comorbid disease	8 (7.1%)	84 (13.6%)		12 (9.6%)	80 (13.2%)		8 (8.3%)	84 (13.2%)		8 (9.6%)	84 (13.0%)	
2 comorbid disease	6 (5.3%)	27 (4.4%)		8 (6.4%)	25 (4.1%)		6 (6.3%)	27 (4.3%)		4 (4.8%)	29 (4.5%)	
3 or more comorbidities	13 (11.5%)	27 (4.4%)		14 (11.2%)	26 (4.3%)		12 (12.5%)	28 (4.4%)		6 (7.2%)	29 (4.5%)	
Unknown	43 (38.1%)	194 (31.4%)		47 (37.6%)	190 (31.4%)		35 (36.5%)	202 (31.8%)		34 (41.0%)	203 (31.3%)	
CT scan			0.37			0.45			0.36			0.29
No CT scan	4 (3.6%)	41 (6.6%)		5 (4.0%)	40 (6.6%)		4 (4.2%)	41 (6.5%)		3 (3.6%)	42 (6.5%)	
CT scan, no abnormalities	86 (76.8%)	505 (81.7%)		96 (77.4%)	495 (81.7%)		79 (82.3%)	512 (80.8%)		60 (72.3%)	531 (82.1%)	
CT scan, abnormalities	22 (19.6%)	72 (11.7%)		23 (18.5%)	71 (11.7%)		13 (13.5%)	81 (12.8%)		20 (24.1%)	74 (11.4%)	

Hospitalization[c]												
Hospital admission	73 (64.6%)	300 (48.5%)	< .01	83 (66.6%)	290 (47.9%)	< .01	49 (51.0%)	324 (51.0%)	0.93	54 (65.1%)	319 (49.2%)	< .01
Number of days[a]	4 (2-13.5)	3 (1-7.75)		2 (0-7.75)	3 (1-7)		4 (2-11.5)	3 (1-8)		3 (1.75-10.75)	3 (1 - 8)	
ICU admission	7 (6.2%)	28 (4.5%)	0.45	11 (8.8%)	24 (4.0%)	0.02	6 (6.3%)	29 (4.6%)	0.47	7 (8.4%)	28 (4.3%)	0.1

[a] *Data are displayed as median, with the first and third quartile given within parentheses.*

[b] *Comorbidity is defined as the presence of any co-existing diseases or disease processes additional to injury that the TBI 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.*

[c] *Hospital or IC admission for one day or more after arrival at emergency department.*

Abbreviations. ICD, International Classification of Diseases; DSM, Diagnostic and Statistical Manual; RPQ, Rivermead Post-Concussion Symptoms Questionnaire; PCS, Post-Concussion Syndrome; ISS, Injury Severity Scale; AISH, Abbreviated Injury Severity Scale Head; AIS, Abbreviated Injury Scale; CT, Computed Tomography; ICU, Intensive Care Unit.

Supplementary Table S3. Determinants in relation to PCS/No PCS at 6 months after TBI with rating score 2

Post-Concussion Syndrome	*Mapped ICD-10/DSM-IV*		*RPQ Total score*		*RPQ3*		*Three-factor model*	
	OR	*95% CI*	*OR*	*95% CI*	*OR*	*95% CI*	*OR*	*95% CI*
Patient demographics								
Gender (male)	0.532	0.382 - 0.721***	0.529	0..374 - 0.748***	0.379	0.273- 0.525***	0.586	0.417 - 0.825***
Education								
Primary/Secondary	1.732	1.111 - 2.701**	1.685	1.098 - 2.585**	1.551	1.039 - 2.316**	1.619	1.041 - 2.516**
Injury mechanism								
Assault (no)	0.376	0.190 - 0.743***	0.252	0.127 - 0.501***	0.344	0.177 - 0.669***	0.272	0.138 - 0.538***
Injury characteristics								
ISS			1.03	1.004 - 1.056**				
AISH	1.209	1.007 - 1.452**	1.239	1.002 - 1.531**	1.292	1.087 - 1.535***	1.219	1.011 - 1.469**
Other								
Comorbidity (no)	0.536	0.378 - 0.761***	0.513	0.354 - 0.743***	0.65	0.463 - .912**	0.52	0.362 - 0.748***
Hospital Admission (no)	0.447	0.317 - 0.631***	0.611	0.414 - 0.903**			0.518	0.361 - 0.742***
n	731		731		731		731	
R^2	0.131		0.138		0.1		0.111	

*** $p < 0.01$; ** $p < 0.05$;
* $p < 0.1$

Abbreviations. PCS, Post-Concussion Syndrome; ICD, International Classification of Diseases; DSM, Diagnostic and Statistical Manual; RPQ, Rivermead Post-Concussion Symptoms Questionnaire; OR, Odds Ratio; 95% CI, 95% Confidence Interval; ISS, Injury Severity Scale; AISH, Abbreviated Injury Severity Scale Head.

Supplementary Table S4. Determinants in relation to PCS/No PCS at 6 months after TBI with rating score 3

Post-Concussion Syndrome	*Mapped ICD-10/DSM-IV*		*RPQ Total score*		*RPQ3*		*Three-factor model*	
	OR	*95% CI*	*OR*	*95% CI*	*OR*	*95% CI*	*OR*	*95% CI*
Patient demographics								
Gender (male)	0.482	0.315 - 0.737***	0.542	0.360 - 0.816***	0.399	0.253 - 0.630***	0.636	0.497 - 0.813*
Education								
Primary/Secondary	1.802	1.110 - 2.925**	1.821	1.102 - 3.008**	1.796	1.014 - 3.182**		
Injury mechanism								
Assault (no)	0.264	0.128 - 0.547***	0.337	0.160 - 0.709***	0.211	0.101 - 0.443***	0.291	0.173 - 0.491**
Injury characteristics								
AISH					1.232	0.974 - 1.559*	1.296	1.025 - 1.640**
Other								
Comorbidity (no)			0.023	0.599 - 0.385**	0.591	0.366 - 0.954**		
Hospital Admission (no)	0.45	0.291 - 0.694***	0.426	0.280 - 0.649***			0.532	0.316 - 0.895**
n	731		731		731		731	
R^2	0.092		0.109		0.096		0.06	

*** $p < 0.01$; ** $p < 0.05$;
* $p < 0.1$

Abbreviations. PCS = Post-Concussion Syndrome; ICD = International Classification of Diseases; DSM = Diagnostic and Statistical Manual; RPQ = Rivermead Post-Concussion Symptoms Questionnaire; OR = Odds Ratio; 95% CI = 95% Confidence Interval; ISS = Injury Severity Scale; AISH = Abbreviated Injury Severity Scale Head.

Chapter 3

The Association Between Post-Concussion Symptoms and Health-Related Quality of Life in Patients with Mild Traumatic Brain Injury

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Abstract

A subset of mild traumatic brain injury (mTBI) patients experience post-concussion symptoms. When a cluster of post-concussion symptoms persists for over three months, it is referred to as post-concussion syndrome (PCS). Little is known about the association between PCS and Health-Related Quality of Life (HRQoL) after mTBI. The aims of this study were to assess the implications of PCS on HRQoL six months after mTBI and the relationship between PCS and HRQoL domains. A prospective observational cohort study was conducted among a sample of mTBI patients. Follow-up postal questionnaires at six months after emergency department (ED) admission included socio-demographic information, the Rivermead Post-Concussion Symptoms Questionnaire (RPQ), and HRQoL measured with the 36-item Short-Form Health Survey (SF-36) and the Perceived Quality of Life Scale (PQoL). In total, 731 mTBI patients were included, of whom 38.7% were classified as suffering from PCS. Patients with PCS had significantly lower scores on all SF-36 domains, lower physical and mental component summary scores and lower mean PQoL scores compared to patients without PCS. All items of the RPQ were negatively correlated to all SF- 36 domains and PQoL subscale scores, indicating that reporting problems on any of the RPQ symptoms was associated with a decrease on different aspects of an individual's HRQoL. To conclude, PCS is common following mTBI and patients with PCS have a considerably lower HRQoL. A better understanding of the relationship between PCS and HRQoL and possible mediating factors in this relationship could improve intervention strategies, the recovery process for mTBI patients and benchmarking.

Introduction

Traumatic brain injury (TBI) represents a substantial burden worldwide and reported annual incidence rates vary from 47 to 849/100,000 in the European population.[1] TBI is defined as "an alteration in brain function, or other evidence of brain pathology, caused by an external force."[2] The greater part (70-80%) of all TBI cases can be classified as mild TBI (mTBI). Despite the term 'mild', many patients experience post-concussion symptoms such as somatic symptoms (e.g. headaches, dizziness, blurred vision, fatigue and sleep disturbances), cognitive complaints (e.g. poor memory, attention and executive difficulties), and behavioral or emotional symptoms (e.g. depression, irritability, anxiety-related disorders, emotional lability).[3] When a subset of these symptoms persist for over three months,[4, 5] it is typically referred to as post-concussion syndrome (PCS). In previous literature, the prevalence rates of PCS vary considerably (5-43%), dependent on timing, measurement and classification method used.[4-8] Additionally, van der Naalt et al. have determined an incomplete recovery in almost half mTBI patients six months after injury.[9]
Generally, the International Classification of Diseases (ICD)-10[10] or Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV[11] diagnostic criteria are used to determine the presence of PCS. In the literature, PCS continues to be a subject of discussion and remains controversial, because of diverging definitions and classification methods,[8] disagreement regarding etiology and no clear impartial neurologic results.
Health-related quality of life (HRQoL) has been acknowledged as an important outcome, reflecting to what degree a medical condition and its treatment affect the physical, mental and social aspects of someone's life perceived from an individual's perspective.[12] Previous studies have shown that many people suffering from mTBI experience a reduction in HRQoL, because of physical, cognitive and/or emotional impairments.[13, 14] Furthermore, PCS may result in loss of functional health, which prohibits return to work after injury and leads to additional economic and societal costs[15] and it may hamper someone's psychosocial functioning.[16] However, the topic of HRQoL and outcomes for people with PCS after mTBI is important and under-researched. Furthermore, to date no large comprehensive study has addressed the association between PCS and HRQoL and its subscales in the general adult mTBI population. This information could also add to the discussion concerning the clinical relevance of PCS; i.e. a strong association between PCS symptoms and a decreased quality of life may indicate that PCS is a clinical relevant syndrome.
More insight is needed in the relationship between PCS and HRQoL. Therefore, the objectives of this study were to assess the association between PCS and HRQoL six months after mTBI and the correlation between post-concussion symptoms and HRQoL domains.

Materials and Methods

Study design

In this study, data were acquired through the Radboud University Brain Injury Cohort Study (RUBICS),[17-20] which is a prospective observational cohort study. Patients who attended the emergency department (ED) of the Radboud University Nijmegen Medical Center (RUNMC) between January 2003 and June 2010 with a diagnosis of mild, moderate or severe TBI were included in the RUBICS database. The clinical data registered in the ED by a neurologist and/or neurosurgeon were entered into the RUBICS databank by a research nurse. Demographic data (age, sex and education), trauma mechanism, hospital admission and length of hospitalization, clinical variables and comorbidities are reflected in the RUBICS databank and follow-up postal questionnaires were utilized to obtain this data. The clinical variables described are the Glasgow Coma Scale (GCS), abbreviated injury scale (AIS) and injury severity score (ISS). The AIS is used to classify and describe the severity of injury to trauma patients in every body region on a six-point ordinal scale[21] and the AIS head (AISH) is classified as the AIS score specific for the head. The ISS[22, 23] is derived from the AIS and represents the severity of the trauma. The questionnaires were self-rated by patients or guardians of patients six months after the injury. This study has been approved by the ethical standards committee of the RUNMC. For more details on the RUBICS dataset, see Scholten et al[13] and Haagsma et al.[20]

Study participants

In the current study, mTBI was diagnosed by a GCS score of 13-15 in the ED after initial resuscitation or followed by sedation and intubation during resuscitation for non-neurological cause. Exclusion criteria were: being 16 years and younger, no written informed consent given by patients/guardians, abusive use of drugs or alcohol, diagnosed with dementia, unknown address of the patient, and inability to speak or write Dutch. A total of 731 patients, which were classified as having mTBI and had completed all items of the RPQ at six-month follow-up, were selected for the current analyses.

Post-concussion symptoms and diagnosis of PCS

The RPQ was applied to identify the existence and severity of post-concussion symptoms at six-month follow-up. The RPQ describes 16 post-concussion symptoms frequently identified after TBI including headaches, dizziness, nausea/vomiting, noise sensitivity, sleep disturbance, fatigue, being irritable, feeling depressed or tearful, feeling frustrated or impatient, forgetfulness, poor concentration, taking longer to think, blurred vision, light sensitivity, double vision and restlessness. Patients were asked to assess the severity of these symptoms over the past 24 h compared with the pre-injury situation. The symptoms are rated on a 5-point Likert scale, which covers responses from 0 (not a problem) to 4 (severe problem). A higher total score, which ranges from 0 to 64, on the RPQ represents a higher and more severe number of symptoms to be in place.[24] Rating scores of one did not contribute to the total score of the RPQ as recommended by King et al.[24]

In this study, we mapped the symptoms of the ICD-10 diagnostic criteria[25] on the RPQ. Patients were classified as having PCS when they reported three or more of the following symptoms with a rating score of two (mild) or higher: headache, dizziness, fatigue, irritability, insomnia, concentration difficulty, and memory difficulty (Panel 1). Additionally, the ICD-10 diagnostic criteria also requires reduced tolerance to stress, emotional excitement or alcohol as one of the criteria. However, this information is not available in the RPQ nor in the RUBICS database.

Panel 1. Classification method regarding Post-Concussion Syndrome

Mapped ICD-10	
Eligible symptoms from the RPQ	*At least 3 symptoms from the list below* Headache Dizziness Sleep disturbance Fatigue Being irritable, easily angered Forgetfulness, poor memory Poor concentration
Cut-off; rating score 2	Three items with score ≥ 2

Abbreviations. ICD, International Classification of Diseases; RPQ, Rivermead Post-Concussion Symptoms Questionnaire.

Health-related quality of life

The paper-and-pencil version of the 36-Item Short-Form (SF-36) Health Survey (Version 1)[26] was self-rated by the patients included in the databank at six months post-injury. The SF-36 instrument has been validated in a TBI population and has demonstrated good internal consistency and validity,[27, 28] and is the most used generic HRQoL instrument in TBI research.[29] It is a 36 item multidimensional self-reported survey of patient's health that reflects the physical, mental and social functioning. It consists of eight domains of health status: physical functioning (PF), role limitations related to physical functioning (RP), bodily pain (BP), general health perception (GH), vitality (VT), social functioning (SF), role limitations related to emotional problems (RE), and mental health (MH).[26] The weighted sums of the item responses for each domain are linearly transformed to a score ranging from 0 to 100. The physical and mental health summary component scores are calculated by first standardizing the patients' scores, specifically by subtracting the subscale means for the general Dutch population sample from each individual's subscale scores and dividing the results by the standard deviation of the Dutch sample to generate Z-scores.[30] Second, to facilitate international comparison, Z-scores are multiplied by the subscale factor coefficients for physical and mental health summary component scores of the U.S. sample and summed over eight subscales into the physical and mental health summary component scores. Finally, both sums were re-scaled into T-scores, with a mean of 50 and standard deviation of 10 for the

U.S. norm.[31] Mean values of the respondents' completed items in the same scale were used as replacement for the missing values at six months, under one condition that at least 50% of the items within that scale had been completed.[26]

The Perceived Quality of Life Scale (PQoL) is also a generic HRQoL instrument, initially developed as a cognitive appraisal of life satisfaction for patients after intensive medical care.[32] The instrument has previously been used in adults with chronic neurologic disability and additionally in stroke and TBI.[33, 34] The PQoL showed good internal reliability in a TBI population.[35] The PQoL measures an individuals' satisfaction with his or her functional status on an 11-point scale ranging from 0 (extremely dissatisfied) to 10 (extremely satisfied). It contains 19 items in three different domains (physical health, cognitive health and social health), estimating the level of functioning in 10 different areas, 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 is established by the mean of the 19 item scores and seen as a measure of global life satisfaction, in which a score of < 7.5 is considered as "Dissatisfied" and a score > 7.5 as "Satisfied".[32] For our analyses, the mean score (range 0 to 10) was chosen. Hot deck imputation per domain was used to estimate the missing values at six months, provided that at least 50% of the items within that domain had been completed, applying similar scores on the items in that specific domain. This was done because PQoL scores are only allowed to be computed in case of complete information on all items.[32]
The PQoL can be divided in physical, social and cognitive subscales. The physical subscale includes physical health (item 1), take care of yourself (item 2), amount of walking (item 4), getting outside the house (item 5) and amount and kind of sleep (item 19). The social subscale consists of see or talk to family and friends (item 8), help from family and friends (item 9), help you give to family and friends (item 10), contribution to community (item 11), work situation (item 12), kind and amount of recreation or leisure (item 13), level or lack of sexual activity (item 14), income meets your needs (item 15), respected by others (item 16), meaning and purpose of your life (item 17) and amount of variety in your life (item 18), and the cognitive subscale entails think and remember (item 3) and carry on a conversation (item 6).[32]

Statistical analysis
Descriptive analyses were conducted on the demographic (age, sex and educational level), trauma mechanism, hospitalization, clinical injury variables and comorbidities. Patients diagnosed with mTBI and who had completed the entire RPQ were included in the analyses. To distinguish on socio-demographic and injury-related variables between mTBI patients experiencing PCS and not experiencing PCS, chi-squared tests (dichotomous variables) and t-tests were applied. Mann Whitney U tests were used to evaluate the differences in SF-36 domain scores and PQoL scores between mTBI patients with and without PCS. Statistical significance was determined by a p-value of $p<.05$. Spearman's correlation coefficients were utilized to evaluate the linear relationship and correlation between the RPQ and

the various SF-36 domains and PQoL subscales. Cohen's Set Correlation and Contingency Tables were used to differentiate between strong, moderate and weak correlations. A correlation was considered strong when the coefficient was above 0.5, moderate when the coefficient was between 0.3 and 0.5, and weak when the coefficient was below 0.3.[36] Missing data for the following variables: education (182 missing), comorbidity (237 missing), and hospital admission (2 missing) were imputed using multiple imputation technique with five datasets. Multiple regression was performed to adjust for differences in case-mix between patients with and without PCS.

All statistical analyses were performed using SPSS version 24 for Windows (IBM SPSS Statistics, SPSS Inc, Chicago, IL).

Results

Patient characteristics

In total, 797 mTBI patients were selected from the RUBICS database, of which 731 were included in this study. There were no significant differences in characteristics between the 731 patients with complete outcome data and the 66 patients with missing items on the RPQ, except that the median age of the 66 patients was significantly higher 54.5 (Interquartile range (IQR): 42.75-68, $p<.01$). Table 1 shows the characteristics of our study sample. The median age of the respondents was 44 years and 63% were male. Road traffic accidents (48%) and falls (33%) were the most reported causes of injury. The median ISS and AISH scores were respectively 6 (IQR 4-14) and 2 (IQR 2-2). Forty-five per cent of the patients had no pre-existing disease and 81% received a computed tomography (CT) scan of the head in which no abnormalities were found. Approximately 51% of the mTBI patients were admitted to hospital with an average length of stay of 3 days (range 1 to 8 days). Furthermore, 35 patients (4.8%) were admitted to the intensive care unit (ICU).

The prevalence of PCS in this population according to our criteria was 38.7%, which defines a total of 283 patients as experiencing PCS six months after the injury. Patients with PCS were significantly more often female, had a lower education, were more likely to be injured by assault compared with other causes of injury, had higher ISS and AISH scores, were more likely to be hospitalized and had a higher RPQ total score (Table 1).

Table 1. Characteristics of the study population

	Total	PCS	No PCS	P-value
N	731	283	448	
Gender (male)	463 (63.3%)	161 (56.9%)	302 (67.4%)	<.01
Age[1] (years)	44 (27-57)	45 (31-56)	43 (26-57)	0.14
Education				<.01
Primary education	21 (2.9%)	6 (2.1%)	15 (3.3%)	
Secondary education	336 (46.0%)	142 (50.2%)	194 (43.3%)	
Higher professional education	108 (14.8%)	32 (11.3%)	76 (17.0%)	
Academic education	84 (11.5%)	18 (6.4%)	66 (14.7%)	
Unknown	182 (24.9%)	85 (30.0)	97 (21.7%)	
Injury Mechanism				0.03
Road traffic accident	351 (48.0%)	139 (49.1)	212 (47.3%)	
Fall	240 (32.8%)	96 (33.9%)	144 (32.1%)	
Sports	77 (10.5%)	19 (6.7%)	58 (12.9%)	
Assault	41 (5.6%)	22 (7.8%)	19 (4.2%)	
Other/Unknown	22 (3.0%)	7 (2.6%)	14 (3.3)	
Injury severity				
ISS[1]	6 (4-14)	8 (5-16)	5 (4-13)	<.01
AISH[1]	2 (2-2)	2 (2-3)	2 (1-2)	<.01
Head AIS 3	93 (12.7%)	42 (14.8%)	51 (11.4%)	
Head AIS 4	57 (7.8%)	30 (10.6%)	27 (6.0%)	
Head AIS 5	11 (1.5%)	6 (2.1%)	5 (1.1%)	
Comorbidity[2]				<.01
No pre-existing disease	329 (45.0%)	102 (36.0%)	227 (50.7%)	
1 comorbid disease	92 (12.6%)	36 (12.7%)	56 (12.5%)	
2 comorbid disease	33 (4.5%)	13 (4.6%)	20 (4.5%)	
3 or more comorbidities	40 (5.5%)	24 (8.5%)	16 (3.6%)	
Unknown	237 (32.4%)	108 (38.2%)	129 (28.8%)	
CT scan				0.2
No CT scan	46 (6.3%)	18 (6.4%)	28 (6.3%)	
CT scan, no abnormalities	591 (80.8%)	223 (78.8%)	368 (82.1%)	
CT scan, abnormalities	94 (12.9%)	42 (14.8%)	52 (11.6%)	
Hospitalization[2]				
Hospital admission	373 (51.0%)	180 (63.6%)	193 (43.1%)	<.01
Number of days hospitalized[1]	3 (1-8)	4 (1-9)	3 (1-6)	0.37
ICU admission	35 (4.8%)	22 (7.8%)	13 (2.9%)	<.01

GCS[1]	15 (14-15)	15 (14-15)	15 (15-15)	<.01
13	40 (5.5%)	22 (7.8%)	18 (4.0%)	
14	152 (20.8%)	71 (25.1%)	81 (18.1%)	
15	539 (73.7%)	190 (67.1%)	349 (77.9%)	
RPQ total score[1]	4 (0-15)	18 (12-28)	0 (0-4)	<.01

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

[2] Comorbidity was defined as the presence of any co-existing diseases or disease processes additional to injury that the TBI 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.

Abbreviations. PCS, Post-Concussion Syndrome; ISS, Injury Severity Score; AISH, Abbreviated Injury Scale of the Head; AIS, Abbreviated Injury Scale; CT, Computed Tomography; ICU, Intensive Care Unit; GCS, Glasgow Coma Scale; RPQ, Rivermead Post-Concussion Symptoms Questionnaire; TBI, traumatic brain injury.

PCS and Health-related quality of life

SF-36 – Table 2 shows the median SF-36 and PQoL scores for mTBI patients with and without PCS six months post-injury. Patients with mTBI and PCS had significantly lower scores on all domains of the SF-36 compared to mTBI patients without PCS. The lowest mean score for mTBI patients with PCS compared to patients without PCS was reported on the role limitations related to physical functioning domain, which represents problems with work / daily activities as a result of physical health (mean: 40, SD: 42 vs. mean: 82, SD: 33, p<.001). The median physical component summary score was 44 (IQR 35-53) and 56 (IQR 49-59), respectively for patients with PCS and without PCS (p<.001). Furthermore, the median mental component summary score was 43 (IQR 32-52) for patients experiencing PCS and 54 (IQR 50-58) for patients without PCS (p<.001) (Appendix A).

PQoL – The median PQoL score for patients with PCS was 6.7 (IQR 5.3-7.8) and significantly lower compared to the median PQoL of patients without PCS (8.6 (IQR 7.7-9.5), p<.001) (Appendix B). Approximately, 45% of patients with PCS were dissatisfied with their functioning (PQoL< 7.5), whereas only 14% of patients without PCS were dissatisfied with their functioning.

After adjusting for case-mix differences, there were still significant differences between patients with and without PCS.

Table 2. Data on health-related quality of life at six months after mTBI

	PCS				No PCS					
	N	*Observed range*	*Mean (SD)*	*Median (IQR)*	*N*	*Observed range*	*Mean (SD)*	*Median (IQR)*	*Unadjusted mean difference (95% CI)*	*Adjusted mean difference (95% CI)**
SF-36 (0-100)										
Physical Functioning	277	0-100	68.9 (27.9)	75 (50-95)	432	0-100	88.7 (20.4)	100 (90-100)	19.8 (16.2-23.4)	15.2 (11.7-18.8)
Role Physical	279	0-100	40.0 (42.1)	25 (0-75)	437	0-100	82.2 (33.1)	100 (75-100)	42.2 (36.7-47.8)	36.4 (30.7-42.1)
Bodily Pain	283	0-100	58.8 (25.6)	62 (41-74)	446	0-100	82.8 (21.5)	100 (72-100)	24.0 (20.5-27.4)	20.3 (16.7-24.0)
General Health	281	5-100	56.9 (22.0)	57 (40-72)	442	6-100	77.6 (18.5)	80 (67-92)	20.7 (17.7-23.6)	19.1 (16.0-22.1)
Vitality	283	0-100	49.2 (18.7)	50 (40-65)	443	15-100	73.0 (16.7)	75 (60-85)	23.8 (21.2-26.4)	22.2 (19.5-25.0)
Social Functioning	283	0-100	61.5 (27.0)	63 (50-87.5)	447	25-100	89.7 (16.1)	100 (75-100)	28.2 (25.0-31.3)	25.9 (22.6-29.2)
Role Emotional	279	0-100	58.2 (42.3)	67 (0-100)	438	0-100	92.6 (22.6)	100 (100-100)	34.4 (29.7-39.2)	31.9 (26.9-36.9)
Mental Health	283	0-100	62.2 (20.3)	64 (48-76)	443	28-100	81.7 (13.7)	84 (76-92)	19.6 (17.1-22.0)	19.1 (16.5-21.7)
Physical CS	271	Sep-69	43.2 (11.4)	44 (35-53)	423	16-70	52.5 (9.0)	56 (49-59)	9.2 (7.7-10.8)	7.3 (5.8-8.9)
Mental CS	271	Jul-66	41.1 (12.5)	43 (32-52)	423	16-73	52.7 (7.5)	54 (50-58)	11.6 (10.1-13.1)	11.6 (10.0-13.2)
PQoL (0-10)	192	10-Jan	6.5 (1.9)	6.7 (5.3-7.8)	347	0-10	8.4 (1.5)	8.6 (7.7-9.5)	1.9 (1.6-2.2)	1.6 (1.2-1.9)

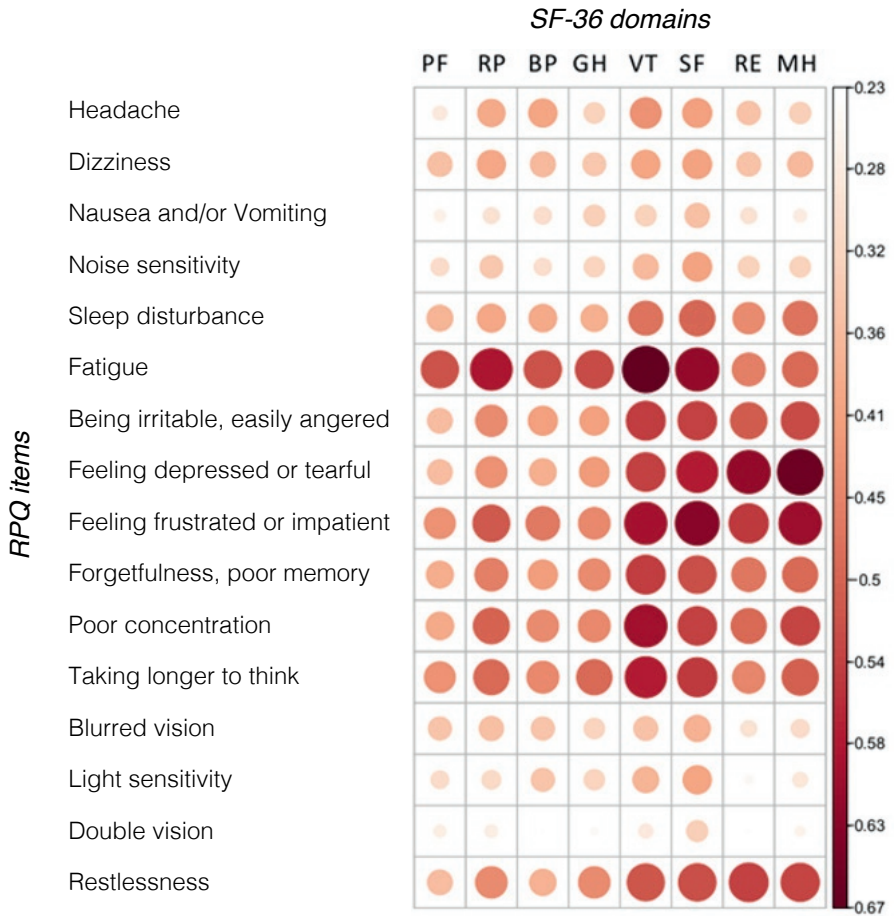
**Variables adjusted for: gender, age, education, ISS, comorbidity, hospital admission, GCS and yes/no PCS.*

Abbreviations. mTBI, mild Traumatic Brain Injury; PCS, post-concussion syndrome; IQR, interquartile range; CI, confidence interval; SF-36, Short-Form-36; Physical CS, physical component score; Mental CS, mental component score; PQoL, Perceived Quality of Life; ISS, Injury Severity Score; GCS, Glasgow Coma Scale.

Correlation of RPQ with SF-36

In Figure 1 the Spearman's correlation coefficients of the RPQ items and the eight domains of the SF-36 are shown. All items of the RPQ were negatively correlated to the SF-36 domains, indicating that reporting problems on any of the RPQ items is associated with a decrease on different aspects of an individuals' HRQoL. The strongest negative correlation (-0.671, p<.001) was found between fatigue and the vitality (VT) domain of the SF-36. Double vision was determined as having the weakest correlations with all domains. Moreover, fatigue was observed as having a strong negative correlation with all domains except for role limitations related to emotional problems (RE) and mental health (MH). All correlations were statistically significant on a p<.001 level.

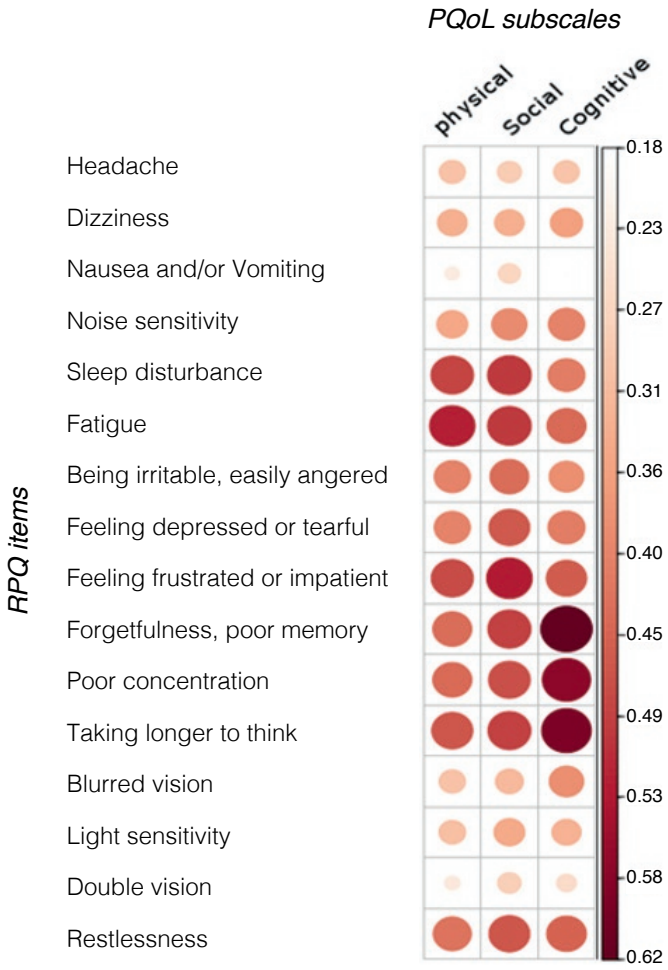
Figure 1. Correlation RPQ items and SF-36 domains



Correlation of RPQ with PQoL

The Spearman's correlation coefficients of the RPQ items and the three PQoL subscales are shown in Figure 2. All the items of the RPQ were negatively correlated with the PQoL subscales. All correlations were statistically significant on a p<.001 level. The strongest correlation (-0.621, p<.001) was found between forgetfulness and the PQoL cognitive subscale. Double vision was observed as having the weakest correlation with all subscales, which is in line with the SF-36 domain correlations.

Figure 2. Correlation RPQ items and PQoL subscales



Discussion

The objectives of this paper were to elucidate the association between PCS and HRQoL six months after mTBI and the correlation between the RPQ items with SF-36 domains and PQoL subscale scores. Almost 40% of our mTBI cohort were experiencing PCS six months post-injury and PCS was negatively associated with HRQoL as measured with both the SF-36 and PQoL. MTBI patients with PCS had a 20% lower HRQoL on average, compared with mTBI patients without PCS. Almost half of mTBI patients with PCS were dissatisfied with their functioning. When adjusting for possible confounding effects of baseline differences between the two groups, it was shown that PCS decreases HRQoL. Additionally, significant negative correlations between all RPQ items and SF-36 domains and PQoL subscale scores were found, indicating that reporting problems on any of the RPQ items was associated with a decrease on different aspects of an individual's HRQoL.

These results are in line with previous literature, where Emanuelson et al. have found a significant correlation between higher rates of symptoms and low SF-36 scores in patients 16-60 years of age living in western Sweden.[14] However, they did not use the RPQ to assess post-concussion symptoms. Patients could only rate each symptom as existing (yes) or non-existing (no), which meant they weren't able to identify the severity of post-concussion symptoms and they didn't use the term PCS throughout their paper. Patients with mTBI and PCS had lower SF-36 scores on all domains compared to the Dutch population norm.[30] However, when looking at patients without PCS, mean SF-36 scores were higher on all domains compared to the Dutch population norm. This is in line with a previous study by Scholten at al. where it was reported that respondents with mTBI reached outcomes comparable to the Dutch population norm on all the SF-36 domains at one year follow-up.[13] In previous literature, a reduction of HRQoL was found for mTBI patients,[13] nevertheless there is a gap in the literature concerning the factors that cause this reduction. This study shows that a decrease in HRQoL for mTBI patients could be affected by PCS. We adjusted for the most important factors, however, there may also be an intricate role of other factors influencing the relationship between PCS and HRQoL. Both, the reporting of post-concussion symptoms with the RPQ and functional impairments with the SF-36 may be mediated by pre-injury psychological, personality, psycho-social factors and the severity of the injury.[29, 37, 38] Additionally, 14% of patients without PCS demonstrated dissatisfaction with their functioning, which implies that other factors play a role.

Several limitations have been encountered during this study. Firstly, an abundance of information was requested from TBI patients to acquire the RUBICS database, which may have resulted in lower quality responses. Secondly, RPQ, SF-36 and PQoL were all reported through self-administration. For HRQoL self-report is inherent in the concept. However, as the general population already had difficulties to fill out the SF-36 in its entirety,[38] this might be even more complex for the TBI population; these patients may experience cognitive problems and may have more difficulties

answering complicated and extensive questions. Concerning the RPQ, previous research has revealed that self-report might lead to under- or over-reporting of symptoms.[39] By asking explicitly for the existence of symptoms patients might furthermore be made aware of a symptom they would have otherwise not reported or they may not understand the meaning of a symptom and may just simply endorse it anyway.[39] Researchers have questioned whether the sensitivity and specificity of most instruments (e.g. RPQ) are sufficient for mTBI patients, because they have been developed for more severe cases of TBI.[29] Stulemeijer et al. have shown that additional extracranial injuries could also have an impact on lowered SF-36 scores.[40] Furthermore, even though questionnaires are very convenient in the clinical and research context, the RPQ alone cannot be used to diagnose PCS, a full clinical evaluation by a health professional is necessary. Lastly, the cohort data were collected in an academic hospital where it is more likely that patients with severe trauma have been admitted to the ED, which is shown in the high percentage of patients admitted to the hospital (51%). Additionally, no pre-injury data with the exception of pre-existing comorbidity was available in the dataset. Therefore, the cohort is likely to not be representative for the overall mTBI population.
This study gives us more information on PCS and the association with HRQoL, which could ultimately lead to a better comprehension of recovery and burden of PCS after mTBI. A better understanding of the relationship between PCS and HRQoL and possible mediating factors in this relationship could improve intervention strategies and the recovery process. TBI outcome covers a broad spectrum of HRQoL[38] and more knowledge about the specific effects on the HRQoL domains will justify future decisions concerning quality of life measures and interventions. Nevertheless, the role of mediating factors in the relationship between PCS and generic and disease-specific HRQoL is not clear. For future studies it would be interesting to look at the role of pre-injury psychological, personality and psychosocial factors which may influence both, the report of post-concussion symptoms and physical, mental and social functioning measured with the SF-36.

Conclusions

To conclude, PCS is common after mTBI and patients suffering from PCS have a considerably lower HRQoL. These findings highlight that better assessment and intervention strategies for PCS are needed, because intervention and support strategies can be targeted more appropriately when mTBI patients with PCS are detected shortly after sustaining the injury.[40] More insight is needed in the role of pre-injury psychological, personality and psychosocial factors that may influence both the report of post-concussion symptoms and physical, mental and social functioning.

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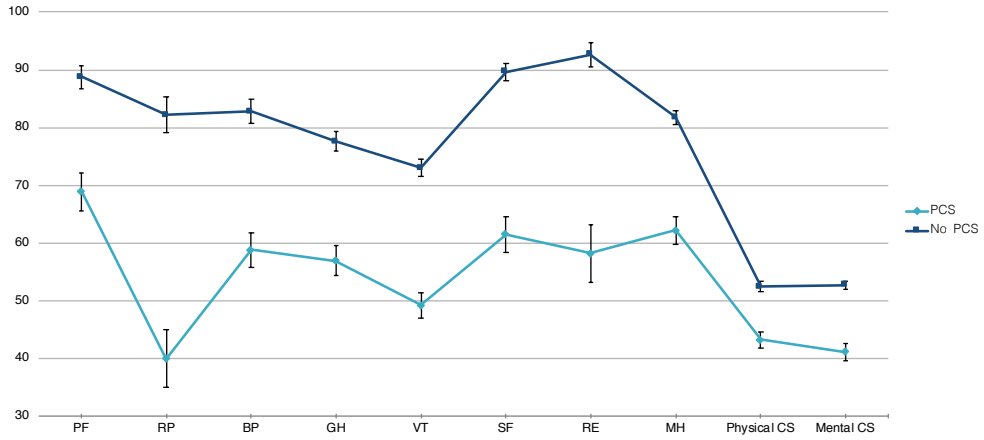
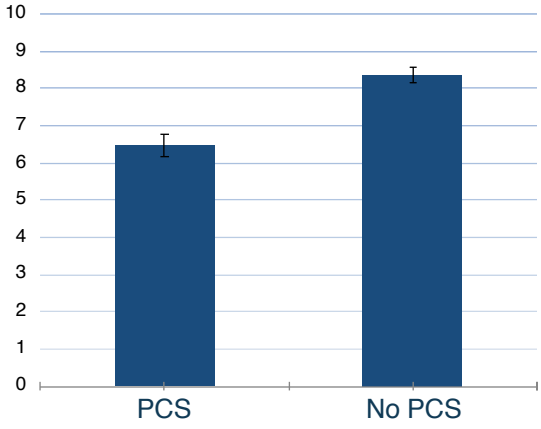
Appendix

Appendix A. SF-36 mean scores at six months after mTBI.



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.

Appendix B. PQoL mean scores at six months after mTBI.



PQoL: Perceived Quality of Life.

Chapter 4

Post-Concussion Symptoms in Complicated vs. Uncomplicated Mild Traumatic Brain Injury Patients at Three and Six Months Post-Injury: Results from the CENTER-TBI Study

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Abstract

The aim of this study was to assess the occurrence of post-concussion symptoms and post-concussion syndrome (PCS) in a large cohort of patients after complicated and uncomplicated mild traumatic brain injury (mTBI) at three and six months post-injury. Patients were included through the prospective cohort study: Collaborative European NeuroTrauma Effectiveness Research (CENTER-TBI). Patients enrolled with mTBI (Glasgow Coma Scale 13-15) were further differentiated into complicated and uncomplicated mTBI based on the presence or absence of computed tomography abnormalities, respectively. The Rivermead Post-Concussion Symptoms Questionnaire (RPQ) assessed post-concussion symptoms and PCS according to the mapped ICD-10 classification method. The occurrence of post-concussion symptoms and syndrome at both time points was calculated. Chi square tests were used to test for differences between and within groups. Logistic regression was performed to analyse the association between complicated versus uncomplicated mTBI and the prevalence of PCS. Patients after complicated mTBI reported slightly more post-concussion symptoms compared to those after uncomplicated mTBI. A higher percentage of patients after complicated mTBI were classified as having PCS at three (complicated: 46% vs. uncomplicated: 35%) and six months (complicated: 43% vs. uncomplicated 34%). After adjusting for baseline covariates, the effect of complicated versus uncomplicated mTBI at three months appeared minimal: odds ratio 1.25 (95% confidence interval: 0.95-1.66). Although patients after complicated mTBI report slightly more post-concussion symptoms and show higher PCS rates compared to those after uncomplicated mTBI at three and six months, complicated mTBI was only found a weak indicator for these problems.

Introduction

In the European Union, around 2.5 million new cases of traumatic brain injury (TBI) occur each year.[1] The vast majority of patients presenting to hospital with a TBI are diagnosed as having mild TBI (mTBI; Glasgow Coma Score (GCS): 13-15).[1] Some of these patients may have traumatic intracranial abnormalities on the computed tomography (CT) performed on presentation which could potentially be associated with worse outcomes compared to those who do not have any traumatic intracranial abnormalities. For this reason, Williams et al.[2] addressed a subgroup conceptualization of these injuries, which has been shown to provide more detail on level of outcome.[3] According to this approach a differentiation can be made between patients with a complicated (intracranial abnormalities present on CT) and uncomplicated (no intracranial abnormalities present on CT) mTBI.
In addition to heterogeneity with regard to the manifestation of mTBI, outcome may also vary between patients. Many patients with mTBI experience post-concussion symptoms in the first couple of weeks and months following the brain injury. However, the type, amount and severity of these symptoms differ between patients and may fluctuate over time.[4] These post-concussion symptoms could be physical, cognitive, emotional and/or behavioural.[5] When a patient experiences a certain combination of symptoms for longer than three months, they may be diagnosed with post-concussion syndrome (PCS).[6, 7] Generally, the International Classification of Diseases (ICD)-10[8], or Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV[9] criteria are used to diagnose PCS.[6, 10] PCS has been a critically debated topic and the question has been raised if we can, or even should, identify this as a unique syndrome for TBI,[4, 5, 11, 12] however, the concept is still used in the majority of post-concussion symptom research.

A certain percentage of patients (estimated between 5% and 43%)[13-18] after mTBI report and experience post-concussion symptoms for months and sometimes even longer post-injury.[3, 19] However, the literature concerning similarities and dissimilarities of post-concussion symptoms between complicated mTBI and uncomplicated mTBI is inconclusive. McMahon et al. noted that patients after complicated mTBI reported significantly more post-concussion symptoms compared to patients after uncomplicated mTBI at both six and twelve months.[20] On the contrary, Iverson et al. have determined that patients after complicated mTBI reported fewer depression and post-concussion symptoms compared to patients after uncomplicated mTBI.[21] When considering PCS, McCauley et al. demonstrated that abnormalities on CT were not associated with PCS at 3 months following injury.[22] Additionally, Iverson et al. have reported: 'no significant difference in the percentages of patients in the uncomplicated versus complicated mTBI groups who met ICD-10 criteria for PCS.'[21] Furthermore, in previous research, limited information has been documented on the different care paths patients after complicated and uncomplicated mTBI may have followed and if reporting of post-concussion symptoms differs between these care paths.

Despite a growing body of literature on complicated versus uncomplicated mTBI,

to date, most studies that compared self-reported symptoms following complicated and uncomplicated mTBI were limited in sample size, and there is a relative paucity of recent data.

We hypothesize that patients after complicated mTBIs report more post-concussion symptoms and have higher prevalence rates of PCS at both time points compared to those with uncomplicated mTBI. Additionally, we anticipated a larger number of patients after complicated mTBI admitted to hospital ward compared to those discharged home from the emergency room (ER) stratum, and aimed to explore if such patients may constitute an "enriched" population in terms of occurrence of PCS and a higher number of post-concussion symptoms. This would be particular relevant when planning a clinical trial investigating efficacy of approaches to treat PCS symptoms.

The objectives of this study were to assess the occurrence of post-concussion symptoms and PCS in a large sample of patients after complicated and uncomplicated mTBI at three and six months post-injury.

Methods

Study design

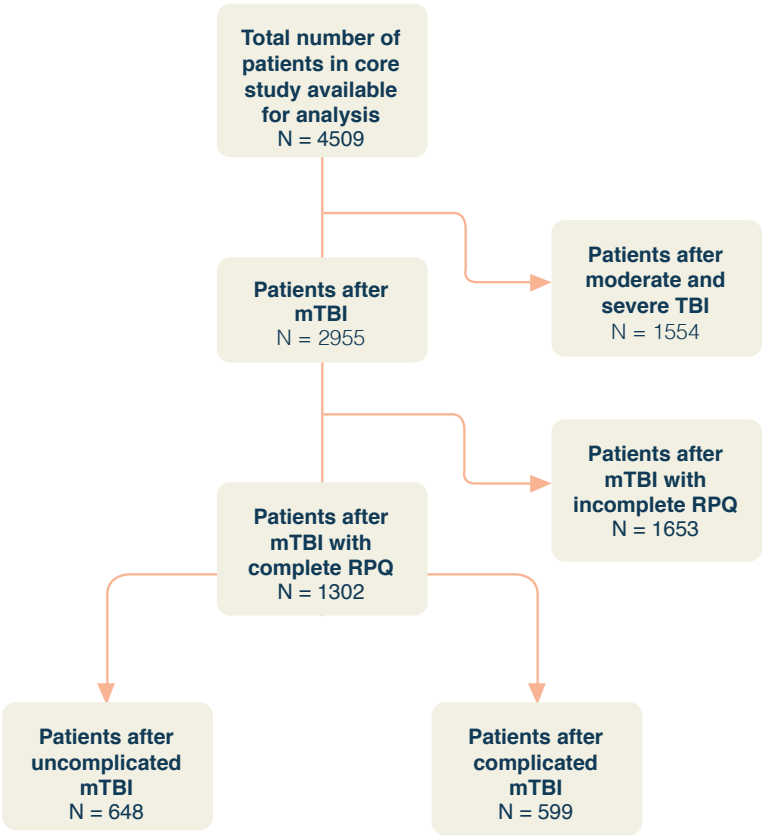
Patients were included in the Collaborative European NeuroTrauma Effectiveness Research (CENTER-TBI) research project, which is a multicentre, prospective observational longitudinal cohort study, conducted in Europe and Israel.[1, 23] The core study enrolled patients with all severities of TBI who presented to centres between December 19, 2014 and December 17, 2017. Inclusion criteria were a clinical diagnosis of TBI, an indication for CT scanning, presenting to a centre within 24 hours of injury, and obtained informed consent adhering local and national requirements: prior to inclusion, either personally, or through a legally designated representative.[23] Participants were free to withdraw at any point in time during the study without stating a reason.[23] Patients were excluded when there was a severe pre-existing neurological disorder i.e., cerebrovascular accident, transient ischemic attacks, and epilepsy, which could potentially invalidate outcome assessments. Three strata were used to prospectively differentiate patients by care path: ER (patients evaluated in the ER and discharged afterwards), admission (patients admitted to hospital ward) and intensive care unit (ICU) (patients who were primarily admitted to the ICU).[23] The main descriptive findings of CENTER-TBI have been published.[24]

Study participants

In the current study, only patients with a mTBI diagnosis were included (Glasgow Coma Scale (GCS) 13-15). They were divided in complicated mTBI, which was defined as GCS 13-15 and presence of any intracranial injury on first CT and uncomplicated mTBI, which was defined as GCS 13-15 and absence of any intracranial injury on first CT. For analyses of post-concussion symptoms including

PCS, we performed a complete case analysis, selecting all patients after mTBI who completed the Rivermead Post-Concussion Symptoms Questionnaire (RPQ)[25] at three and six months follow-up (N =1,302) (Figure 1).

Figure 1. Flowchart sample size



N, number; mTBI, mild traumatic brain injury; TBI, traumatic brain injury; RPQ, Rivermead Post-Concussion Symptoms Questionnaire

Measurement-Instrument

Post-concussion symptoms were assessed by the (RPQ),[25] which evaluates the frequency and severity of 16 post-concussion symptoms. Symptoms evaluated included headaches, dizziness, nausea/vomiting, noise sensitivity, sleep disturbance, fatigue, being irritable, feeling depressed or tearful, feeling frustrated or impatient, forgetfulness, poor concentration, taking longer to think, blurred vision, light sensitivity, double vision, and restlessness. Patients rated the severity of the post-concussion symptoms on a five-point Likert scale, where 0 represents a rating corresponding to “not experienced at all”, 1 “no more of a problem than before the TBI”, 2 “a mild problem”, 3 “a moderate problem” and 4 “a severe problem.”[25]

To obtain the total score, the ratings of all 16 items are summated, excluding the ratings of 1.[25] The RPQ was administered at three and six months following injury, and patients were asked to rate the severity of the symptoms over the last 24 hours.

Various approaches to defining PCS exist.[26] For this study, we primarily focussed on the mapped ICD-10 classification method, in which we defined patients as having PCS when they reported any three of the seven symptoms described in the ICD-10 criteria (e.g. headache, dizziness, sleep disturbance, fatigue, being irritable/ easily angered, forgetfulness/poor memory, and poor concentration).[8] As previous research is inconclusive concerning which severity rating should be applied as a cut-off,[26] two different cut-offs were assessed: rating score 2 (≥ 2), corresponding to symptoms rated as mild or worse, and rating score 3 (≥ 3), corresponding to symptoms rated as moderate or worse.
The RPQ was collected by telephone and face-to-face interviews, or per postal or web-based questionnaires (Appendix A). The questionnaire was translated into 18 languages and linguistically validated.[23, 27]

Ethical approval
The CENTER-TBI study (EC grant 602150) has been conducted in accordance with all relevant laws of the EU if directly applicable or of direct effect, and all relevant laws of the country where the Recruiting sites were located, including, but not limited to, the relevant privacy and data protection laws and regulations (the "Privacy Law"), the relevant laws and regulations on the use of human materials, and all relevant guidance relating to clinical studies from time to time in force including, but not limited to, the ICH Harmonised Tripartite Guideline for Good Clinical Practice (CPMP/ICH/135/95) ("ICH GCP") and the World Medical Association Declaration of Helsinki entitled "Ethical Principles for Medical Research Involving Human Subjects". Ethical approval was obtained for each recruiting site. Informed Consent was obtained for all patients recruited in the Core Dataset of CENTER-TBI and documented in the e-CRF. The list of sites, Ethical Committees, approval numbers and approval dates can be found on the official Center TBI website (www.center-tbi.eu/project/ethical-approval).

Statistical analysis
For all analyses, data was extracted from the INCF Neurobot tool (INCF, Sweden), a clinical study data management tool. Version 2.0 of the CENTER-TBI dataset (data frozen in January 2019) was used in this manuscript. The number and percentage of patients who were classified as having experienced mTBI (complicated and uncomplicated mTBI) were assessed by stratum and per GCS level. Descriptive analyses for demographic data (age, gender and education) injury mechanism, GCS at baseline, first CT scan, and RPQ total score were performed and examined for patients with mTBI, complicated and uncomplicated mTBI at 3 and 6 months post-injury. Chi-square tests for categorical variables and Student's t tests for continuous variables were used to compare patients with mTBI who completed the

RPQ (filled in all items) with those with incomplete RPQ data (not all items filled in). Additionally, these tests were also performed to compare patients with complicated versus uncomplicated mTBI. To assess whether there was a relation between having a completed RPQ at three and/or six months, a McNemar test was performed.

At each time point, we computed the prevalence and percentages of post-concussion symptoms and of patients who were classified as having PCS according to our mapped ICD-10 classification method, and we explored whether there were differences between the complicated and uncomplicated group. For all analyses, a p-value of $p<0.05$ was considered significant.

For the analysis of the effect of complicated versus uncomplicated mTBI on PCS, data for the following predictor variables: age, GCS, stratum, education, gender, psychiatric medical history and cause of injury were first multiply imputed. We assumed missing at random as the mechanism of missingness. For the component variables considering psychiatric medical history (anxiety, depression, sleep disorders, schizophrenia, substance abuse disorder and other) missings were treated as absence of this diagnosis, since investigators could only enter components if the main category (e.g. psychiatric medical history" had been scored positive. All potential confounders, which were based on clinical relevance, the outcome (PCS) and exposure (complicated TBI) were included in the imputation model. Only the cases with observed outcomes were analysed in the main analysis. The Multivariate Imputation by Chained Equations (mice) package, which imputes incomplete multivariate data by chained equations,[28] was used to create five datasets.[29] Results of each imputed data set were combined according to Rubin's rules.[30]

To analyse the association of complicated versus uncomplicated mTBI on the presence of PCS, logistic regression was performed. We adjusted for the following baseline covariates: age, gender, education, injury mechanism, GCS, complicated vs. uncomplicated, and stratum. The unadjusted and adjusted effects were displayed as odds ratios (OR) with 95% confidence intervals (95% CI).

All statistical analyses were performed using SPSS version 25 for Windows (IBM SPSS Statistics, SPSS Inc, Chicago, IL) and R (version 3.2.2 or higher, the R Foundation for Statistical Computing, Vienna, Austria).

Results

Study population

Within CENTER-TBI, most patients were classified as mTBI (N=2,955; 65.5%), and these patients constituted the vast majority of patients in the ER (97%) and admission (93%) strata, but were also present in the ICU (34%) stratum (Table 1). Complicated mTBI was identified in 12%, 45% and 73% of mTBI in the ER, admission and ICU strata, respectively.

Figure 2 shows the total number of patients per stratum and provides additional differentiation by GCS score for complicated and uncomplicated mTBI. A larger number of patients with complicated mTBI were found in the admission and ICU strata compared to the ER stratum. Many patients had a significantly lower GCS score when looking at complicated versus uncomplicated mTBI ($p < 0.01$).

A total of 1,302 patients with mTBI and a completed RPQ from the CENTER-TBI database were included in this study (Figure 1). Table 2 shows the characteristics of our study sample. The median age of patients after mTBI was 53 years (interquartile range (IQR); 35-66) and 64% were male. The median number of years of education was 14 (IQR; 11-17) and almost half (47%) of the patients were injured due to an incidental fall, followed by road traffic incidents (39%). Approximately 46% showed any intracranial injury on the first CT and was defined as complicated mTBI.

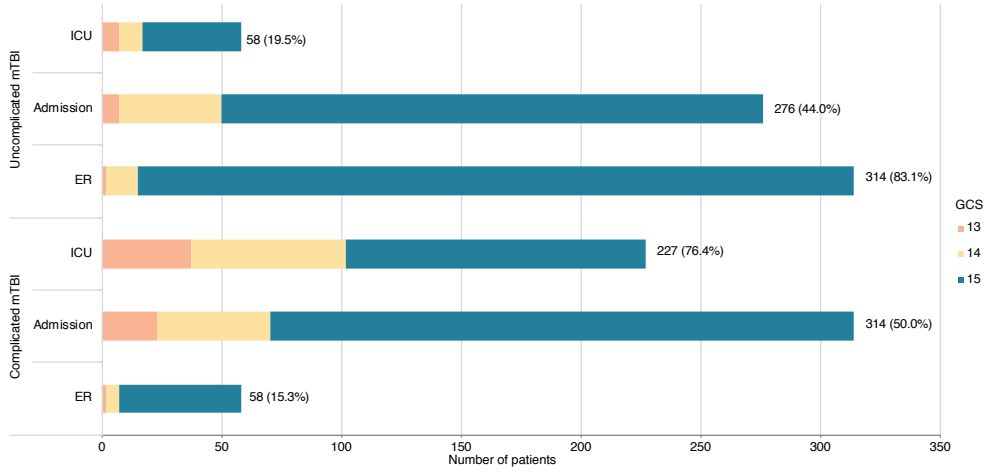
Patients after complicated mTBI were significantly older ($p<0.01$) and had a higher total RPQ score ($p < 0.01$: 11.8 vs. 9.4) compared to patients after uncomplicated mTBI. Patients after mTBI who completed the RPQ were not significantly different from those with incomplete RPQ data, except that they had a slightly higher number of education years ($p < 0.01$: 13.9 vs. 12.6) and more patients reported to have had a psychiatric medical history ($p < 0.01$) (Appendix B). Additionally, there was no statistically significant difference between patients who had a completed RPQ at three and/or six months ($p = 0.17$).

Table 1. Number of mTBI, uncomplicated and complicated mTBI per stratum

	Total mTBI	Uncomplicated mTBI	Complicated mTBI
ER *N (%)*	826 (97.4%)	699 (84.6%)	97 (11.7%)
Admission *N (%)*	1409 (92.5%)	686 (48.7%)	627 (44.5%)
ICU *N (%)*	720 (33.7%)	144 (20.0%)	527 (73.2%)
Total	2955 (65.5%)	1529 (51.7%)	1251 (42.3%)

Note: for 175 mTBI patients the CT scan was not available
Abbreviations. mTBI, mild traumatic brain injury; ER, emergency room; ICU, intensive care unit.

Figure 2. Number of uncomplicated and complicated mTBI patients with complete RPQ data per GCS level 13-15 per stratum



mTBI, mild traumatic brain injury; GCS, Glasgow Coma Score; ICU, intensive care unit; ER, emergency room.n=1302; complete case analysis.

Table 2. Characteristics of the study population

	Total mTBI with completed RPQ	Uncomplicated	Complicated	P-value
N	1302	648	599	
Gender (male)	827 (63.5%)	398 (61.4%)	396 (66.1%)	0.085
Age[1] (years)	53 [35-66]	51 [31.25-64]	58 [39-68]	<0.01
Education[1] (years)	14 [11-17]	14 [12-17]	13 [11-17]	0.054
Injury Mechanism				0.394
Road traffic accident	504 (38.7%)	255 (39.4%)	227 (37.9%)	
Incidental fall	616 (47.3%)	300 (46.3%)	289 (48.2%)	
Other non-intentional	72 (5.5%)	41 (6.3%)	29 (4.8%)	
Violence/assault	43 (3.3%)	22 (3.4%)	19 (3.2%)	
Act of mass violence	1 (0.1%)	-	1 (0.2%)	
Suicide attempt	7 (0.5%)	2 (0.3%)	5 (0.8%)	
Other	42 (3.2%)	23 (3.5%)	18 (3.0%)	
Unknown	17 (1.3%)	5 (0.8%)	11 (1.8%)	
Psychiatric Medical History	146 (11.2%)	68 (10.5%)	73 (12.2%)	0.329
Anxiety	36 (24.7%)	13 (19.1%)	22 (30.1%)	0.13
Depression	89 (61.0%)	46 (67.6%)	41 (56.2%)	0.161
Sleep disorders	19 (13.0%)	8 (11.8%)	10 (13.7%)	0.731
Schizophrenia	3 (2.1%)	1 (1.5%)	2 (2.7%)	0.602
Substance abuse disorder	17 (11.6%)	5 (7.4%)	9 (12.3%)	0.324
Other	19 (13.0%)	9 (13.2%)	9 (12.3%)	0.872
GCS baseline[1]	15 [15-15]	15 [15-15]	15 [14-15]	<0.01
Computed Tomography				
Any intracranial injury on first CT	599 (46.0%)	648 (0.0%)	599 (100.0%)	<0.01
RPQ total score[1]				
3 months	6 [0-17]	4 [0-14]	7 [2-20]	<0.01
6 months	5 [0-15]	4 [0-14]	7 [2-17]	<0.01

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

Note: only completed RPQ (all items of the questionnaire filled out).

Abbreviations. mTBI, mild traumatic brain injury; RPQ, Rivermead-Post-Concussion Symptoms Questionnaire; CT, Computed Tomography.

Post-concussion symptoms and PCS

The median RPQ score for patients after complicated mTBI at three and six months was 7 (IQR 3 months; 2-20/ IQR 6 months; 2-17), which was significantly higher than the median score for patients after uncomplicated mTBI (IRQ: 0-14) ($p < 0.01$). Figure 3.1 shows that patients after complicated mTBI reported significantly more feelings of dizziness, noise sensitivity, fatigue/tiring more easily, feeling depressed/tearful, feeling frustrated or impatient, forgetfulness/poor memory, poor concentration, taking longer to think, and restlessness compared to uncomplicated mTBI at three months ($p < 0.05$).

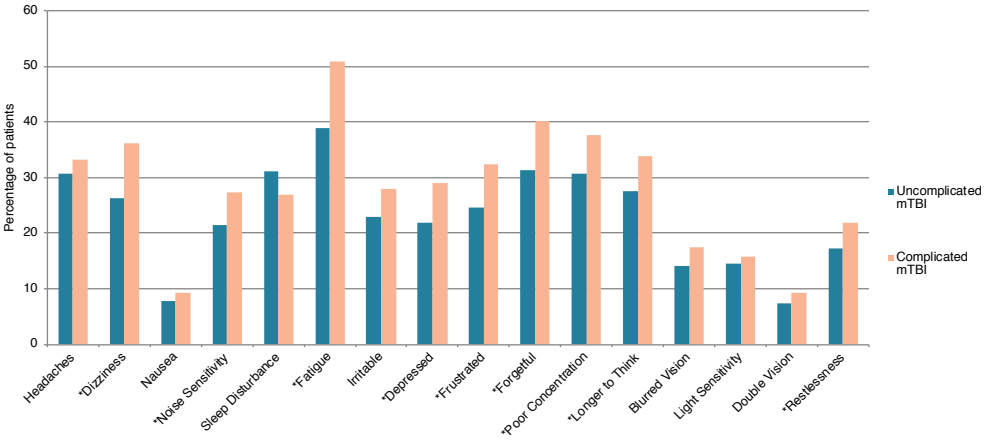
Additionally, when inspecting data at six months, patients in both groups reported a lower percentage of symptoms and less symptoms were found to be significant, compared to the 3-month time point (Figure 3.2). Nevertheless, differences in symptom reporting between complicated and uncomplicated remain.

PCS prevalence, when using rating score 2 as a cut-off, for patients after complicated mTBI were 45.6% (95% CI: 41.6 – 49.6) and 42.7% (95% CI: 38.7 - 46.7) at three and six months, respectively, which showed a significant decrease ($p < 0.01$) (Figure 4). A significant difference was also found when comparing the prevalence rates for patients after uncomplicated mTBI, which were 35.3% (95% CI: 31.6 - 39.0) at 3 months and 34.4% (95% CI: 30.7 - 38.1) at 6 months. Additionally, significant difference was found between the two groups at both follow up points (3 months: $p < 0.01$ and 6 months: $p < 0.01$).

When using rating score 3 as a cut-off, post-concussion symptom percentages (Appendix C.1 and C.2) and PCS prevalence rates were reduced by half for both complicated and uncomplicated mTBI. Furthermore, there was no significant difference anymore between patients with complicated and uncomplicated mTBI (3 months: $p=0.055$ and 6 months: $p=0.303$).

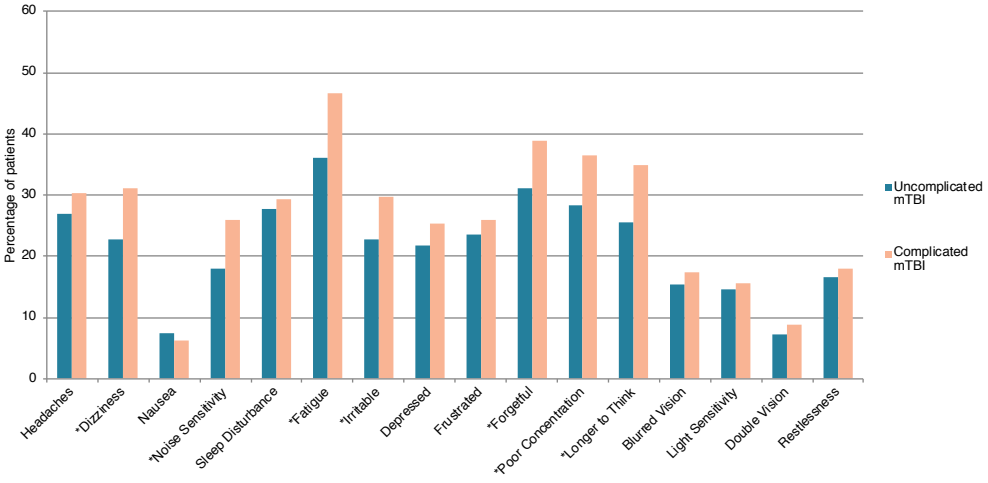
Since the absolute percentages within both groups did not differ much from three to six months, we looked more specifically into the patterns behind the significant difference, which could be explained by the transitioning of patients with PCS between three and six months. Figure 5 shows the trajectories of patients after complicated and uncomplicated mTBI classified with PCS over time. When looking at the complicated mTBI group, there are 272 patients who did not, and 202 patients who did meet the PCS criteria at 3 and 6 months. Seventy-one patients with PCS at 3 month follow-up did not classify as having PCS at 6 month follow-up.
Furthermore, 54 patients did not have PCS at 3 months, however, they did classify at 6 month follow-up. In general, the absolute number of patients transitioning between 3 and 6 month follow up for uncomplicated and complicated mTBI are almost even.

Figure 3.1. Frequency of post-concussion symptoms with a severity rating of 2 (mild problem) or higher at 3 months



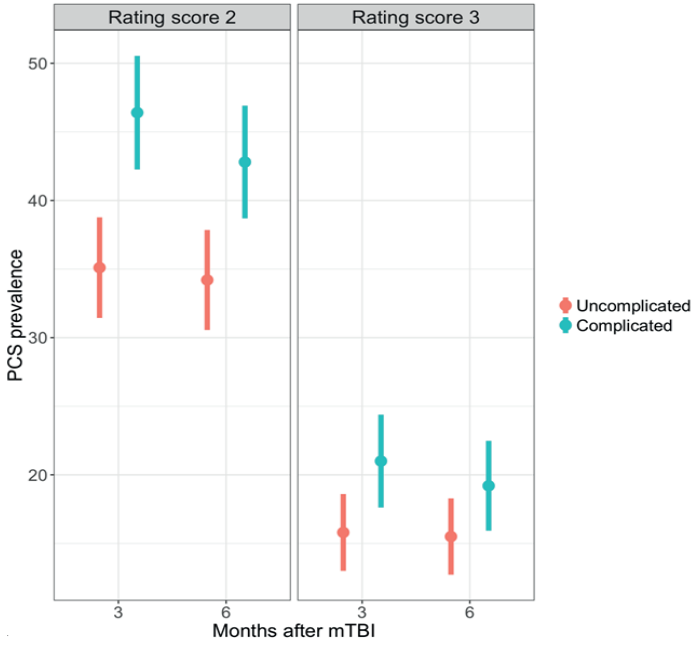
** significant ($p < 0.05$)*

Figure 3.2. Frequency of post-concussion symptoms with a severity rating of 2 (mild problem) or higher at 6 months



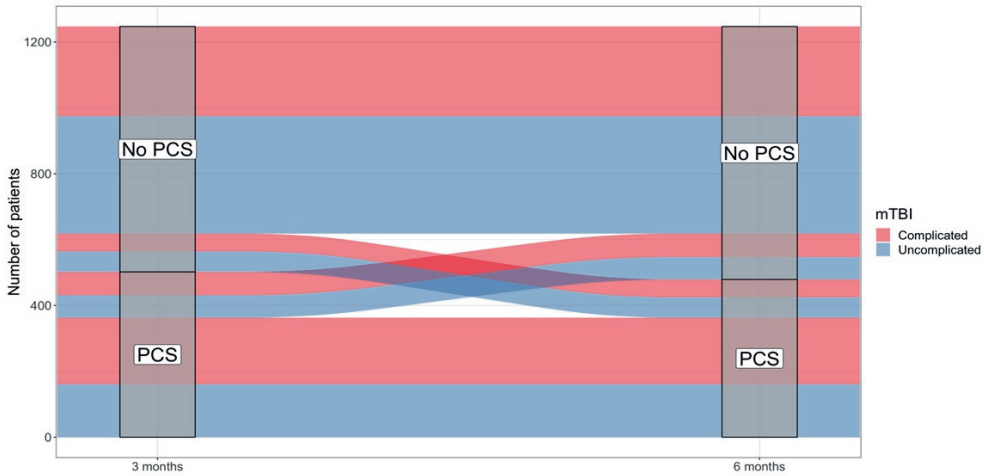
** significant ($p < 0.05$)*

Figure 4. Prevalence of PCS for patients after uncomplicated and complicated mTBI at 3 and 6 months



PCS, Post-Concussion Syndrome; mTBI, Mild Traumatic Brain Injury
Rating score 2 = mild or worse; Rating score 3 = moderate or worse

Figure 5. Trajectories of patients after uncomplicated and complicated mTBI with PCS at 3 and 6 month follow up



mTBI, Mild Traumatic Brain Injury; PCS, Post-Concussion Syndrome; n = number of patients

Figure 6.1 shows the differentiation per stratum for patients after complicated and uncomplicated mTBI classified as having PCS. The PCS prevalence for patients after complicated mTBI were 43.6% and 51.1% for the admission and ICU strata, respectively. These percentages were higher than the 37.7% admission and 48.3% ICU PCS prevalence rates which were found for patients after uncomplicated mTBI. When looking at 6 months, the reported percentages of patients classified as having PCS for both groups were very similar within the admission stratum, however, the ER and ICU stratum stayed around the same (Figure 6.2).

Figure 6.1. Number and percentage of uncomplicated and complicated mTBI with PCS differentiated by strata at 3 months

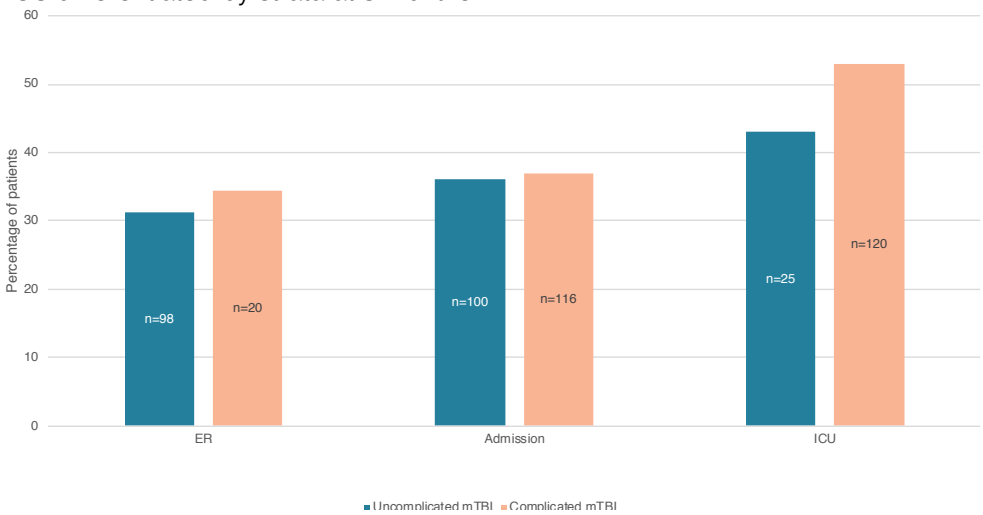
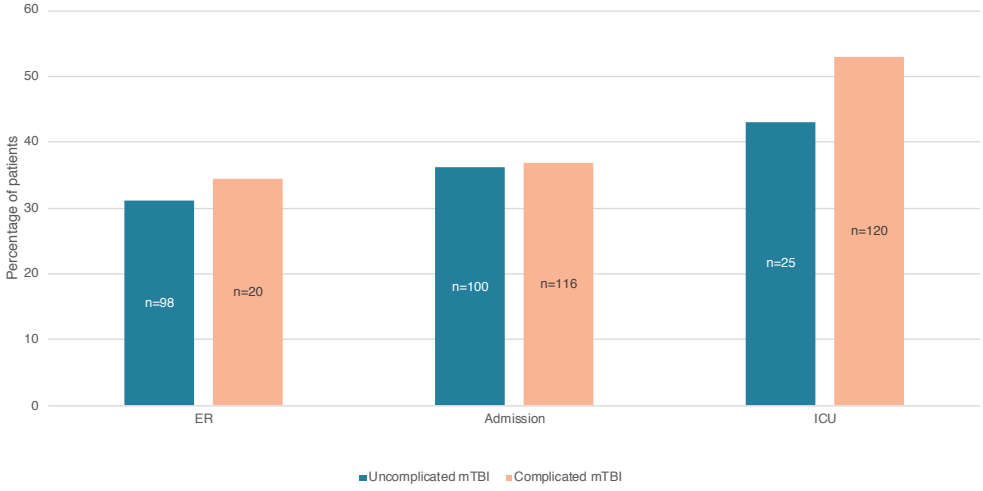


Figure 6.2. Number and percentage of uncomplicated and complicated mTBI with PCS differentiated by strata at 6 months



mTBI, mild traumatic brain injury; PCS, post-concussion syndrome; ER, emergency room; ICU, intensive care unit.

Table 3 shows a summary of a covariate adjusted analysis for the association of complicated and uncomplicated mTBI on the presence of PCS. After adjusting for baseline covariates, the association of complicated versus uncomplicated mTBI at 3 month follow up was of only borderline significance with an odds ratio (OR) of 1.25 (95% CI: 0.95 – 1.66). This implies that the difference in PCS prevalence between complicated versus uncomplicated mTBI at 3 months can be influenced by differences in baseline characteristics. However, at 6 month follow up, the association was rendered insignificant (OR: 1.07, 95% CI: 0.80-1.42) (Appendix D).

Table 3. Summary of covariate adjusted analysis for the association between complicated versus uncomplicated mTBI on the presence of PCS at 3 months and 6 months

	3 months		*6 months*	
	OR	**95% CI**	**OR**	**95% CI**
Unadjusted	1.54	1.22 - 1.94	1.39	1.10 - 1.76
Adjusted	1.25	0.95 - 1.66	1.07	0.80 - 1.42

Baseline covariates adjusted for: age, gender, education, injury mechanism, GCS, complicated vs. uncomplicated, psychiatric medical history and stratum.

Abbreviations. mTBI, mild traumatic brain injury; PCS, post-concussion syndrome; OR, Odds Ratio; 95% CI, 95% confidence interval.

Discussion

This study focussed on the three and six month prevalence rates of post-concussion symptoms and PCS of patients after complicated and uncomplicated mTBI included in a large European database. Overall, we demonstrated that patients after complicated mTBI report significantly more symptoms and have higher prevalence rates of PCS at these points in time. The differences observed at three months (complicated: 45.6% vs. uncomplicated: 35.3%) and six months (complicated: 42.7% vs. uncomplicated 34.4%), were in line with a previous study done by McMahon et al.[20] However, we found a decrease in symptom reporting from three to six months for both groups, and this is in contrast with McMahon et al. since they determined that patients after uncomplicated mTBI were stable in their symptom reporting across the follow-up times, whereas patients after complicated mTBI reported significantly higher symptoms at six and 12 months compared to three months. Additionally, we found that complicated and uncomplicated mTBI patients transition between being classified with PCS at 3 and 6 month follow up, which meant that some patients with PCS 'recover' after 3 months and some enter the threshold of PCS from 3 to 6 months. Depending on the analysis approach taken, rating score 2 or rating score 3, we observed variability in results. However, our results confirm a higher prevalence of PCS in patients after complicated compared

to uncomplicated mTBI across both approaches. When looking at the association of complicated and uncomplicated mTBI on the presence of PCS, it became less clear after adjusting for baseline covariates, which suggests that the reported differences in this study may be explained by differentiations in baseline characteristics. Lastly, a larger number of complicated mTBI patients were found in the admission and ICU strata, and the percentages of patients classified as having PCS was also higher for both these strata when comparing patients after complicated and uncomplicated mTBI. In terms of PCS occurrence, patients in the admission and ICU strata would appear to represent an "enriched" population, but it is not clear if targeting patients with complicated mTBI would lead to substantial additional enrichment.

In previous research, contradictions in reporting differences regarding post-concussion symptom and syndrome following complicated and uncomplicated mTBI has led to a conundrum, which is based on the question if patients after complicated mTBI are similar or dissimilar based on symptom reporting compared to uncomplicated mTBI patients. Furthermore, the discussion still stands if post-concussion symptoms are TBI specific[31] and regarding the existence of post-concussion syndrome.[4, 32, 33] There is no gold standard regarding defining PCS and which severity rating should be used as a cut-off,[26] and different approaches to analysis, classification and quantification of PCS exist and lead to variability in results.[26] This has also been demonstrated in this study, where the different severity rating scores have shown to have a substantial impact on the results, since the symptom percentages and PCS prevalence drop down to half when using rating score 3 as a cut-off.

The current study is unique compared to previous studies, because none of them have looked at a large sample such as in this study to compare self-reported symptoms from patients after complicated and uncomplicated mTBI nor did they assess both concepts, post-concussion symptoms and PCS alongside each other. A number of limitations of our study should be recognized. No information was available considering if patients were involved in a litigation. Lees-Haley et al. have accentuated the need for caution when relying on self-reported symptoms as evidence of brain damage in patients involved in litigation, since they are more likely to endorse post-concussion symptoms.[34] Additionally, response bias might also be portrayed in this study. Patients who did not complete the RPQ might be less likely to partake in the follow up than patients who did experience symptoms.[26] There was no detailed information on pre-morbid personality traits [35, 36] and limited on the psychological distress of patients.[37] These factors could all potentially influence the reported outcome after mTBI. Furthermore, the RPQ was collected through various ways, and the method of administration could have influenced patients' symptom reporting.[23, 38] Lastly, there is a broad spectrum of abnormalities within the complicated mTBI group and doctors might treat patients differently when objective evidence for the brain injury was found.[21] Moreover, the confirmation of structural damage to the brain provided by imaging studies showing traumatic abnormalities (e.g. complicated mTBI) might lead to a higher rate of self-reported symptoms.

For future research it would be recommended to look at the localization of abnormalities in CT or MRI data and see how this may effect post-concussion symptom reporting since in previous research CT abnormalities have been found to be related to outcome.[39] Additionally, brain imaging methods and technology are advancing and this could potentially help to revolutionize and improve our understanding and detection of small changes in the brain following mTBI.[3, 24] Furthermore, looking into the differences in treatment and treatment policies between complicated and uncomplicated mTBI would establish a better understanding considering the outcome. It would also be interesting to determine the occurrence of post-concussion symptoms and PCS at one year or even later follow-up times. Lastly, the DSM-V edition did not include PCS, but introduced the term mild neurocognitive impairment [MNI] due to TBI instead, which shows there is a move away from using PCS in mTBI research.

Conclusions

This study showed that patients after complicated mTBI reported more post-concussion symptoms and have higher PCS prevalence rates compared to patients with uncomplicated mTBI at three and six months, which presents complicated mTBI as an indicator for these problems. However, the differences between both patient groups are small, and after adjusting for baseline covariates, this association could be explained by differences in baseline characteristics. These findings highlight the need to take the long-term impact on outcome for patients diagnosed with mTBI into consideration, and both patient groups are in need of clinical follow-up.

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Appendix

Appendix A. Method of administration of the Rivermead Post-Concussion Symptoms Questionnaire

	Telephone interview	Postal questionnaire	Web-based completion	Face-to-face interview	Not completed/ missing
3 months	97 (3.3%)	784 (26.5%)	2 (0.07%)	418 (14.1%)	1653 (55.9%)
6 months	45 (1.5%)	594 (20.1%)	4 (0.14%)	659 (22.3%)	1653 (55.9%)

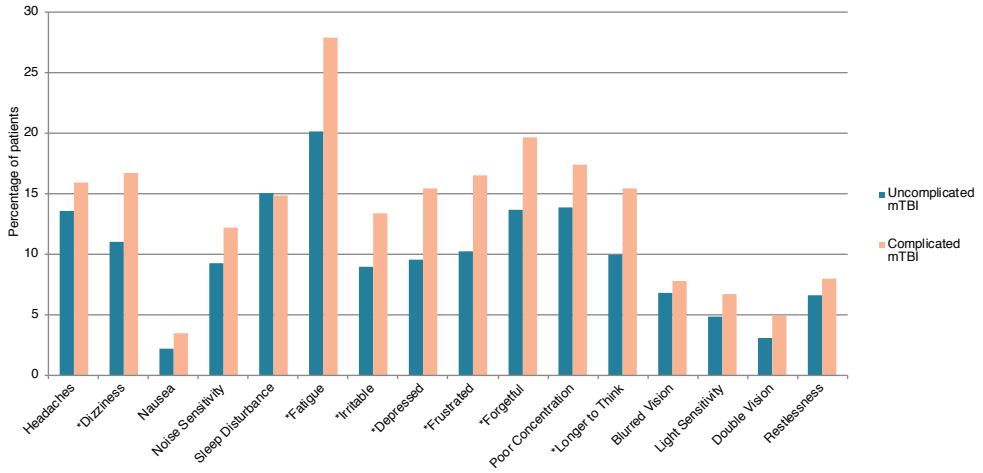
Appendix B. Characteristics of mTBI patients with complete and incomplete RPQ

	Complete RPQ	Incomplete RPQ	P-value
N	1302	1653	
Gender (male)	827 (63.5%)	1076 (65.1%)	0.374
Age[1] (years)	53 [35-66]	49 (29-69)	0.207
Education[1] (years)	14 [11-17]	12 (10-15)	<0.01
Injury Mechanism			<0.01
Road traffic accident	504 (38.7%)	506 (30.6%)	
Incidental fall	616 (47.3%)	825 (49.9%)	
Other non-intentional	72 (5.5%)	91 (5.5%)	
Violence/assault	43 (3.3%)	140 (8.5%)	
Act of mass violence	1 (0.1%)	3 (0.2%)	
Suicide attempt	7 (0.5%)	8 (0.5%)	
Other	42 (3.2%)	50 (3.0%)	
Unknown	17 (1.3%)	30 (1.8%)	
Psychiatric Medical History	146 (11.2%)	249 (15.1%)	<0.01
Anxiety	36 (24.7%)	77 (30.9%)	0.183
Depression	89 (61.0%)	146 (58.6%)	0.65
Sleep disorders	19 (13.0%)	34 (13.7%)	0.857
Schizophrenia	3 (2.1%)	2 (0.8%)	0.283
Substance abuse disorder	17 (11.6%)	62 (24.9%)	<0.01
Other	19 (13.0%)	43 (17.3%)	0.262
GCS baseline[1]	15 [15-15]	15 (14-15)	0.037
Computed Tomography			
Any intracranial injury on first CT	599 (46.0%)	652 (39.4%)	<0.01

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

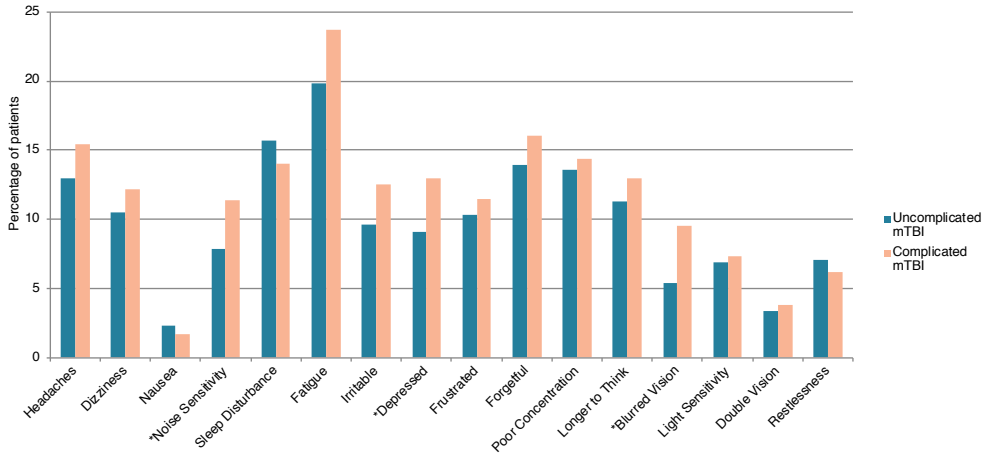
Abbreviations. mTBI, mild traumatic brain injury; RPQ, Rivermead-Post-Concussion Symptoms Questionnaire; CT, Computed Tomography.

Appendix C.1 Frequency of post-concussion symptoms with a severity rating of 3 (moderate problem) or higher at 3 months



** significant (p<0.05)*

Appendix C.2 Frequency of post-concussion symptoms with a severity rating of 3 (moderate problem) or higher at 6 months



** significant (p<0.05)*

Appendix D. Significant predictors in a multivariable model on the association of complicated versus uncomplicated mTBI on the presence of PCS (with a severity rating of 2 (mild problem) or higher)

Post-Concussion Syndrome	*3 months*			*6 months*
Predictor	**OR**	**95% CI**	**P-value**	**OR**
Age	0.995	0.989 - 1.001	0.083	1.002
Gender (male)	0.588	0.460 - 0.749	<0.01	0.617
Education	0.998	0.970 - 1.027	0.894	0.979
Stratum (ER)				
Admission	1.517	1.127 - 2.044	<0.01	1.254
ICU	2.013	1.371 - 2.956	<0.01	2.128
GCS baseline	0.925	0.753 - 1.137	0.459	0.927
Injury Mechanism (other)				
Road traffic accident	1.105	0.722 - 1.692	0.644	1.045
Incidental fall	1.252	0.967 - 1.620	0.088	1.623
Violence/assault/suicide	1.012	0.543 - 1.888	0.968	1.353
Psychiatric Medical History (yes)	1.592	0.698 - 3.632	0.269	2.8
Anxiety (yes)	1.198	0.516 - 2.783	0.674	0.687
Depression (yes)	1.146	0.513 - 2.559	0.74	0.832
Sleep disorders (yes)	1.631	0.557 - 4.782	0.372	0.817
Substance abuse disorder (yes)	1.272	0.414 - 3.915	0.674	2.092
Other	1.063	0.354 - 3.188	0.913	0.509
Any intracranial injury on first CT (yes)	1.252	0.945 - 1.658	0.117	1.084
N	1302			1302
Nagelkerke R^2	0.072			0.085

Note: schizophrenia was taken out of the analyses due to limited number of patients; violence/assault, act of mass violence and suicide attempt were grouped together into 'violence/assault/suicide'; other non-intentional and other were grouped together into 'other'.

Abbreviations. mTBI, mild traumatic brain injury; PCS, post-concussion syndrome; OR, Odds Ratio; 95% CI, 95% confidence interval; PCS, post-concussion syndrome; ER, emergency room; ICU, intensive care unit; RTA, road traffic accident; CT, computed tomography.

Chapter 5

Outcome Following Complicated and Uncomplicated Mild Traumatic Brain Injury Patients at Three and Six Months Post-Injury: Results From the CENTER-TBI Study

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Abstract

The objective of this study was to provide a comprehensive examination of the relation of complicated and uncomplicated mild traumatic brain injury (mTBI) with multidimensional outcomes at three and six months after TBI. We analyzed data from the Collaborative European NeuroTrauma Effectiveness Research (CENTER-TBI) research project. Patients after mTBI (Glasgow Coma scale (GCS) score of 13-15) enrolled in the study were differentiated into two groups based on computed tomography (CT) findings: complicated mTBI (presence of any traumatic intracranial injury on first CT) and uncomplicated mTBI (absence of any traumatic intracranial injury on first CT). Multidimensional outcomes were assessed using seven instruments measuring generic and disease-specific health-related quality of life (HRQoL) (SF-36 and QOLIBRI), functional outcome (GOSE), and psychosocial domains including symptoms of post-traumatic stress disorder (PTSD) (PCL-5), depression (PHQ-9), and anxiety (GAD-7). Data were analyzed using a multivariate repeated measures approach (MANOVA-RM), which inspected mTBI groups at three and six months post injury. Patients after complicated mTBI had significantly lower GOSE scores, reported lower physical and mental component summary scores based on the SF-36 version 2, and showed significantly lower HRQoL measured by QOLIBRI compared to those after uncomplicated mTBI. There was no difference between mTBI groups when looking at psychological outcomes, however, a slight improvement in PTSD symptoms and depression was observed for the entire sample from three to six months. Patients after complicated mTBI reported lower generic and disease-specific HRQoL and worse functional outcome compared to individuals after uncomplicated mTBI at three and six months. Both groups showed a tendency to improve on outcome from three to six months after TBI. The complicated mTBI group included more patients with impaired long-term outcome than the uncomplicated group. Nevertheless, patients, clinicians, researchers, and decisions-makers in health care should take account of the short and long-term impact on outcome for patients after both uncomplicated and complicated mTBI.

Introduction

In the European Union 1.5 million hospitalizations result from traumatic brain injury (TBI) annually [1, 2]. Approximately 70-90% of patients presenting to hospital are diagnosed with mild TBI (mTBI), which is generally classified with a Glasgow Coma Scale (GCS) score of 13 to 15 [1]. Williams et al. have elaborated further on this description of mTBI and proposed that intracranial abnormalities on the computed tomography (CT) on presentation should be taken into account. This resulted in distinguishing patients after complicated (presence of trauma-related intracranial abnormalities and/or depressed skull fracture on CT) and uncomplicated (absence of intracranial abnormalities and/or depressed skull fracture on CT) mTBI[3]. The sensitivity of CT has improved over the years, and an abnormal scan may no longer have the same significance.

Previous research concerning the impact of complicated and uncomplicated mTBI on outcome has been contradictory. On the one hand, the presence or absence of intracranial abnormalities is seen as relevant to prognosis, since complicated mTBI has been associated with cognitive and functional outcome comparable to patients after moderate TBI (GCS 9-13) [3-6]. In contrast, other studies have shown no relationship between complicated mTBI and cognitive and functional outcome [7-9]. Additionally, previous research reported divergent results concerning longitudinal outcome after complicated and uncomplicated mTBI. In some studies, patients after complicated mTBI reported worse outcome than individuals after uncomplicated mTBI [7, 10, 11]. While others observed improvement in patients after complicated mTBI over time and showed slower recovery in the uncomplicated mTBI group [12]. A few studies even found no significant differences between the two groups [7, 9]. In previous research, the focus in complicated and uncomplicated mTBI research has mainly been on neurocognitive and functional outcome, and post-concussion symptoms [4, 5, 7, 11, 13-15]. However, nowadays, generic and disease-specific health-related quality of life (HRQoL) have been acknowledged as an important outcome after TBI [16, 17] for both patients and clinicians. HRQoL reflects an individual's perception of how an illness and its treatment affect the physical, mental, cognitive and social aspects of someone's life [16, 18, 19].

Despite an abundance of studies and decades of research on complicated and uncomplicated patients after mTBI, only few studies have examined HRQoL outcomes in patients after complicated and uncomplicated mTBI [20] and differences regarding outcome between these groups remain poorly understood. There has not yet been a study with a large sample size, taking longitudinal changes into account, and the ability to compare patients on different outcome domains: generic and disease specific HRQoL, functional outcome and symptomatology, such as post-traumatic stress, depression and anxiety. Moreover, the authors of the present study are not aware of any studies using a multivariate approach when exploring HRQoL, functional and psychological outcomes in adult patients [21]. As (m)TBI may affect different areas simultaneously, it is important to investigate the differences between groups by using multidimensional approaches [22].

We hypothesize that patients after complicated mTBI report lower generic and disease-specific HRQoL and worse functional outcome compared to uncomplicated mTBI at three and six months. Additionally, we do not expect considerable improvement in outcome from three to six months.

More insight is needed regarding the impact of complicated mTBI compared to uncomplicated mTBI on outcome from a longitudinal perspective. Therefore, the objective of this study was to provide a comprehensive multidimensional approach in analyzing the effects of complicated and uncomplicated mTBI on outcome in a large sample of individuals at three and six months post-injury.

Materials and Methods

Study design

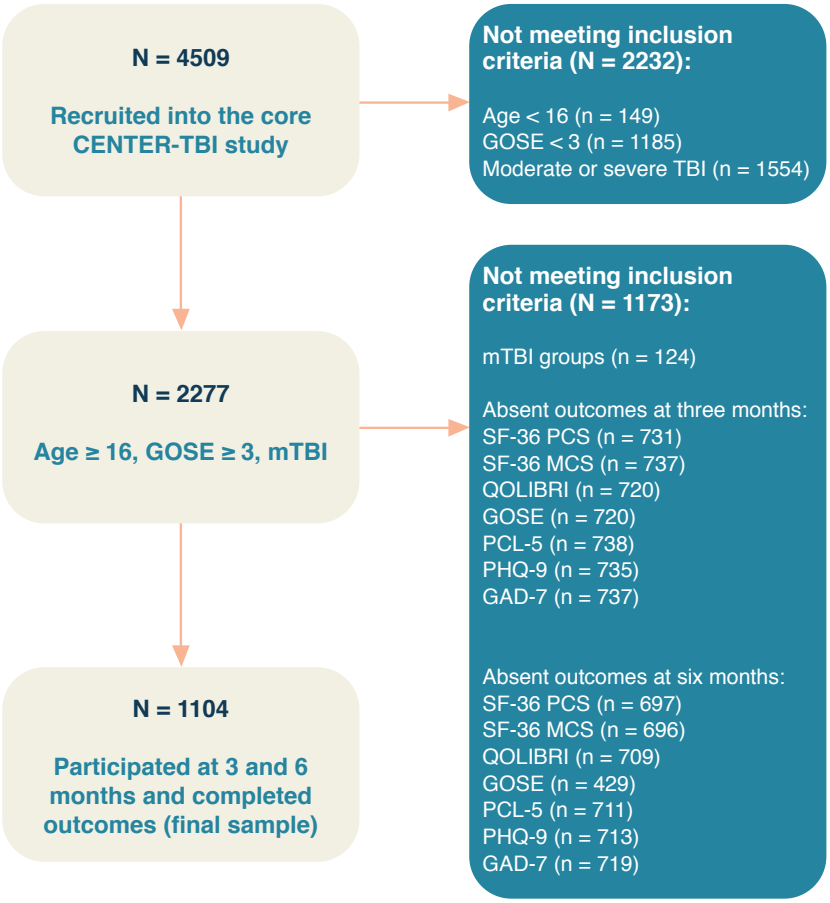
In this study we analyzed patients who were enrolled in the Collaborative European NeuroTrauma Effectiveness Research (CENTER-TBI) research project. This is a multicenter, prospective, observational, longitudinal cohort study, which was conducted in Europe and Israel [1, 23]. Patients with all severities of TBI who presented to hospital were included between 19 December 2014 and 17 December 2017. A clinical diagnosis of TBI, an indication for a CT scan, presenting to a center within 24 hours after the injury, and informed consent were used as inclusion criteria. Informed consent, adhering to local and national requirements, had to be obtained prior to inclusion, either personally or through a legally acceptable representative. At any point in time during the study patients were free to withdraw without stating a reason. Patients with severe pre-existing neurological disorders, which could invalidate assessment of outcomes, were excluded. Patients were recruited in three strata: emergency room (ER; patients evaluated at the ER and discharged afterwards), admission (ADM; patients admitted to hospital ward), and intensive care unit (ICU; patients who were primarily admitted to the ICU) [23]. The main descriptive findings of CENTER-TBI can be found in Steyerberg et al. [24].

Study participants

In the current study analysis, participants were included if they had mTBI (GCS 13-15). They were differentiated in two groups: complicated and uncomplicated mTBI. Complicated mTBI was specified as presence of any traumatic intracranial abnormalities on first CT scan and uncomplicated was specified as absence of any traumatic intracranial abnormality on first CT. The presence of intracranial abnormality was defined as the detection of at least one of the following twelve findings on the CT scan: mass lesion, extra axial hematoma, epidural hematoma, acute or chronic subdural hematoma, one or multiple subdural collections/ mixed density hematomas, contusion, traumatic axonal injury (TAI), traumatic subarachnoid hemorrhage, intraventricular hemorrhage, midline shift, or cisternal compression. In the current study, a linear or depressed skull fracture, in the

absence of structural intracranial abnormalities, was not considered as a criterion for complicated mTBI, however, this has been used as a determinant of intracranial abnormalities in previous research. Furthermore, participants had to be ≥ 16 years of age and classified as GOSE ≥ 3.
The American Society of Anesthesiologists Physical Status Classification System (ASA-PS) was used to assess individuals' health status before the injury[25].
For all analyses, a complete case analysis for the following variables at three and six months was performed: SF-36, QOLIBRI, GOSE, PCL-5, PHQ-9 and GAD-7. For more details, see Figure 1.

Figure 1. Flowchart sample size



Abbreviations. N = number; mTBI = mild traumatic brain injury; GOSE = Glasgow Outcome Scale Extended; TBI = traumatic brain injury; SF-36 PCS = Short Form (36) Health Survey (physical component score); SF-36 MCS = Short Form (36) Health Survey (mental component score); QOLIBRI = Quality of Life after Brain Injury; PCL-5 = Posttraumatic Stress Disorder Checklist; PHQ-9 = Patient Health Questionnaire; GOSE = Glasgow Outcome Scale - Extended; GAD-7 = Generalized Anxiety Disorder questionnaire.

Instruments

Outcome was assessed as a multidimensional construct by using seven instruments measuring generic and disease-specific HRQoL, functional outcome, and psycho-social domains including post-traumatic stress, depression and anxiety. The following measures were analyzed:

Health-related quality of life (HRQoL)

Generic HRQoL. The 36-item Short Form (SF-36v2) Health Survey is a multidimensional self-report questionnaire measuring the subjective health state including physical, mental, and social functioning [26]. The questionnaire comprises 36 items covering eight domains and applies different response scales from a dichotomous ("yes"/"no") to a polytomous five-point Likert scale. For more information see Ware et al.[26]. For our analyses, we used the two summary component scores: physical component summary (PCS) and mental component summary (MCS) score, which measure physical functioning and mental health, respectively. The total score of the SF-36 ranges from 0 to 100, whereby higher values indicate higher HRQoL, and total scores below 40 are considered impaired [27].

Disease specific HRQoL. The Quality of Life after Brain Injury (QOLIBRI) is a 37-item self-report instrument which measures level of satisfaction with various aspects of TBI-specific HRQoL [28]. It entails six scales evaluating key aspects of life: the first four scales assess 'satisfaction' with cognition, self, daily life and autonomy and social relationships and the last two scales measure 'feeling bothered' with emotions and physical problems. Responses are given on a five-point Likert scale which extends from 0 ("not at all") to 4 ("very"). The total score was transformed linearly to range from 0-100; higher values indicate better HRQoL[28]. For the QOLIBRI, scores below 60 are considered impaired [29].

Functional outcome

Glasgow Outcome Scale Extended (GOSE) measures functional outcome after TBI. Functional outcome is rated by a clinician on an eight point scale: 1 (dead), 2 (vegetative state), 3 (lower sever disability), 4 (upper severe disability), 5 (lower moderate disability), 6 (upper moderate disability), 7 (lower good recovery) and 8 (upper good recovery) and is derived from eight questions [30]. In the present study, functional impairment was classified as a GOSE score ≤ 6 [31]. Structured interviews and self-report questionnaires were used to collect the GOSE. A multistate model was used to impute the 180-day GOSE when patients scores were outside the 5 to 8 month window (msm R package) [32]. Patients with GOSE 1 (dead) were excluded from analyses, and GOSE levels 2 and 3 were collapsed into one.

Post-traumatic stress, depression and anxiety

The Posttraumatic Stress Disorder Checklist-5 (PCL-5) [33] measures 20 symptoms of post-traumatic stress disorder (PTSD) based on the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-V) [34] by using a five-point scale (from 0 "not at all" to 4 "extremely"). The total score ranges from 0 to 80, whereby higher values indicate greater impairment and a score of ≥ 33 is considered

indicative of clinically relevant PTSD[35].
The Patient Health Questionnaire (PHQ-9) [36] is a nine item self-assessment instrument evaluating depression symptoms in the past two weeks using a four-point Likert scale (from 0 “not at all” to 3 “nearly every day”) based on DSM-IV criteria [37]. The maximum score is 27 and the higher the score, the greater the indication for depressive symptoms. A score of ≥ 10 is seen as a strong indication for clinically relevant depressive symptoms and cutoffs of 5, 10 and 15 and 20 indicate mild, moderate, and moderately severe to severe depressive symptoms, respectively [36, 38].
The Generalized Anxiety Disorder questionnaire (GAD-7) [39] measures anxiety symptoms in the past two weeks by using seven items with a four-point scale (from 0 “not at all” to 3 “nearly every day”). The total score ranges from 0 to 27. A score of ≥ 10 is generally seen as an indicator for the presence of anxiety disorder and cutoffs 5, 10 and 15 indicate mild, moderate, and severe anxiety, respectively[39].

Ethical approval
The CENTER-TBI study (EC grant 602150) has been conducted in accordance with all relevant laws of the EU if directly applicable or of direct effect, and all relevant laws of the country where the Recruiting sites were located, including, but not limited to, the relevant privacy and data protection laws and regulations (the “Privacy Law”), the relevant laws and regulations on the use of human materials, and all relevant guidance relating to clinical studies from time to time in force including, but not limited to, the ICH Harmonised Tripartite Guideline for Good Clinical Practice (CPMP/ICH/135/95) (“ICH GCP”) and the World Medical Association Declaration of Helsinki entitled “Ethical Principles for Medical Research Involving Human Subjects”. Ethical approval was obtained for each recruiting site. Informed Consent was obtained for all patients recruited in the Core Dataset of CENTER-TBI and documented in the e-CRF. The list of sites, Ethical Committees, approval numbers, and approval dates can be found on the official Center TBI website www.center-tbi.eu/project/ethical-approval.

Statistical analyses
For all analyses, data was extracted from the INCF Neurobot tool (INCF, Solna, Sweden), a clinical study data management tool. Core data set version 2.1 (data frozen in January 2019) was used for all analyses in this manuscript. Descriptive analyses for care paths, demographic and socio-economic characteristics, pre-injury health status and medical history, cause of injury, clinical presentation, CT characteristics, SF-36 MCS and SF-36 PCS, PCL-5, PHQ-9, GAD-7, QOLIBRI, and GOSE were performed and analyzed for patients with complicated and uncomplicated mTBI at three and six months post-injury. Descriptive statistics show the number (N) and percentages (%) for categorical variables and median and interquartile range (IQR) for continuous and ordinal variables. To compare individuals after complicated mTBI to uncomplicated mTBI, Chi-square tests

and Mann-Whitney U-tests were used for categorical and continuous variables, respectively.

We compared individuals with a least one impaired outcome with those classified as not impaired at all (i.e., each outcome value did not exceed respective cut-off value). For analyses of individuals who were classified as impaired according to the cut-off values of unfavorable outcome for each outcome variable, new variables with classification (impaired vs. not impaired) were calculated for each dependent variable separately. See the instrument descriptions for the respective selected cut-off values. Distributions of individuals classified as reporting impaired outcome within mTBI groups were compared by using Chi-square tests for both three and six months after TBI.

Data were analyzed using a multivariate repeated measures approach (MANOVA-RM), suitable for non-normal data with covariance heterogeneity, to provide robust test statistics [40, 41]. The outcome construct (dependent variables) consisted of seven instruments assessing outcomes (SF-36 MCS and SF-36 PCS, PCL-5, PHQ-9, GAD-7, QOLIBRI, and GOSE). The between effect was defined by complicated and uncomplicated mTBI groups. The within effect was defined by time points (three and six months after mTBI).

For post hoc comparisons, we used repeated measures ANOVAs for non-normal data and significance was assessed at $\alpha < 0.007$ applying a Bonferroni-adjustment ($\alpha_{adj} = \frac{0.05}{7}$).
All analyses were conducted using R version 3.6.1 [42] with application of the MANOVA-RM package [40] for both MANOVA-RM and post-hoc repeated measures ANOVAs. Appendix A gives a detailed overview of the methodology. The significance level was determined as $\alpha < 0.05$ for Chi-square tests, Mann-Whitney U-tests, and multivariate analysis and $\alpha < 0.007$ for post hoc comparisons between groups.

Results

Study sample

The total CENTER-TBI cohort included 2,955 patients after mTBI and our study sample consisted of 1104 patients (37.4%) who were interviewed at both time points (3 and 6 months after mTBI) and completed all seven outcomes. Included patients were admitted to the ER (30.6%), ADM (47.6%), or the ICU (21.8%) and had sustained either uncomplicated mTBI (48.5%) or complicated mTBI (51.5%). The mean age of individuals after mTBI was 52.3 years (SD = 18.8) and 63.4% were male. The majority were injured by a fall (47%) or traffic incident (39%) and approximately 11% reported having experienced a TBI previously. Patients after complicated mTBI were significantly older (mean age: 54.5 vs. 50.3) compared to those after uncomplicated mTBI and were less likely to be classified as 'working', however, they less often reported a previous TBIs ($p < 0.01$). Patients after complicated mTBI were more often classified with a GCS score of 13 and 14. For more details, see Table 1.

Table 1. Characteristics of the study sample

	Study sample	Uncomplicated	Complicated	P-value
N	1104	569 (51.5%)	535 (48.5%)	
Care paths				< 0.01
ER	338 (30.6%)	286 (50.3%)	52 (9.7%)	
Admission	525 (47.6%)	236 (41.5%)	289 (54.0%)	
ICU	241 (21.8%)	47 (8.3%)	194 (36.3%)	
Demographic characteristics				
Gender (male)	700 (63.4%)	352 (61.9%)	348 (65.0%)	0.272
Age[1] (years)	54 [37.25-67]	51 [35-65]	58 [40-68]	< 0.01
Socio-economic characteristics				
Education[1] (years)	14 [12-17]	14 [12-17]	14 [11-17]	0.054
Employment status before injury				
Working[2]	593 (53.7%)	331 (58.2%)	262 (49.0%)	< 0.01
Pre-injury health status and medical history				
Pre-injury ASA-PS classification				0.175
A patient with mild systemic disease	377 (34.1%)	181 (31.8%)	196 (36.6%)	
A patient with severe systemic disease	106 (9.6%)	60 (10.5%)	46 (8.6%)	
Previous TBI	129 (11.7%)	84 (14.8%)	45 (8.4%)	< 0.01
Cause of injury				

Injury Mechanism				0.409
Road traffic accident	429 (38.9%)	222 (39.0%)	207 (38.7%)	
Incidental fall	517 (46.8%)	265 (46.6%)	252 (47.2%)	
Other non-intentional	60 (5.4%)	36 (6.3%)	24 (4.5%)	
Violence/assault	38 (3.4%)	19 (3.3%)	19 (3.6%)	
Act of mass violence	1 (0.1%)	-	1 (0.2%)	
Suicide attempt	7 (0.6%)	2 (0.4%)	5 (0.9%)	
Other	36 (3.3%)	20 (3.5%)	16 (3.0%)	
Unknown	16 (1.4)	5 (0.9%)	11 (2.1%)	
Clinical presentation				
GCS baseline[1]	15 [15-15]	15 [15-15]	15 [14-15]	< 0.01
13	65 (5.9%)	9 (1.6%)	56 (10.5%)	
14	155 (14.0%)	53 (9.3%)	102 (19.1%)	
15	884 (80.1%)	507 (89.1%)	377 (70.5%)	
CT characteristics				
Computed Tomography				
Any intracranial injury on first CT	535 (48.5%)	0 (0.0%)	535 (100%)	< 0.01

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

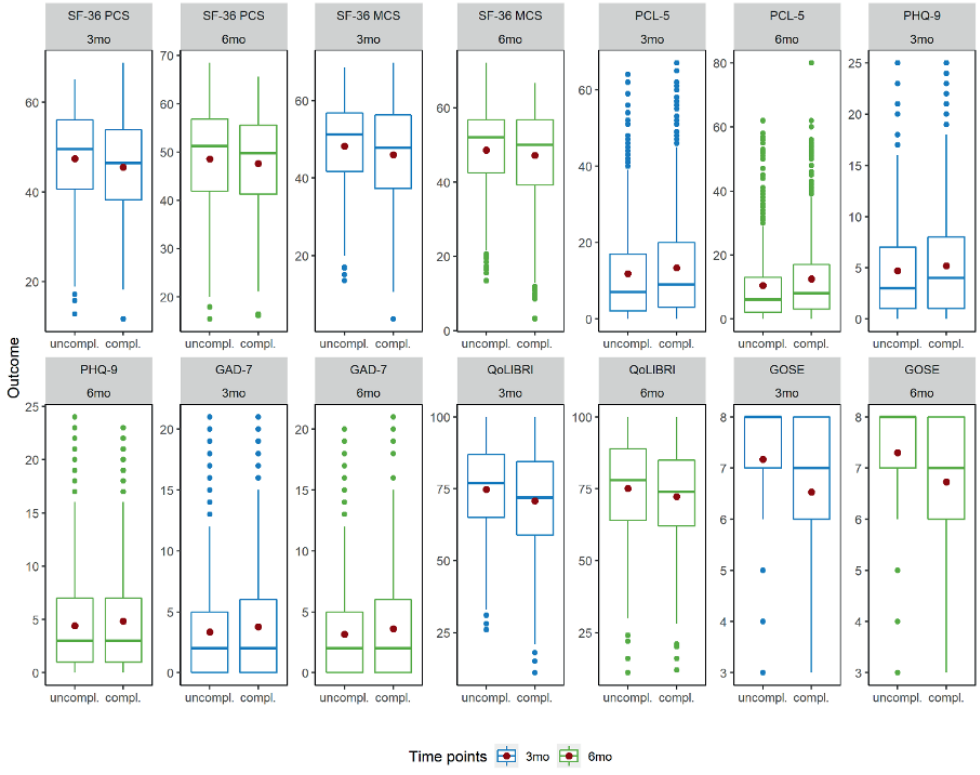
[2] *Working = working 35 hours or more per week; working 20-34 hours per week; working less than 20 hours per week and/or special employment/sheltered employment*

Abbreviations. mTBI, mild traumatic brain injury; ER, emergency room; ICU, intensive care unit; ASA-PS, The American Society of Anaesthesiologists (ASA) Physical Status Classification System; TBI, traumatic brain injury; GCS, Glasgow Coma Scale; CT, Computed Tomography.

Descriptive statistics of outcomes

Figure 2 provides an overview on outcome instruments and uncomplicated and complicated mTBI groups and time points. Patients after complicated mTBI reported both lower generic (PCS and MCS scores) and lower disease-specific HRQoL (QOLIBRI), lower functional outcome (GOSE), higher PCL-5, PHQ-9, and GAD-7 scores compared to individuals after uncomplicated mTBI at both time points. In general, small differences were observed for both groups between 3 and 6 months.

Figure 2. Boxplots for outcomes by time points and uncomplicated and complicated mTBI groups



Note. The Y-axis of the boxplots are adapted to the scales of the outcomes. Red dots within boxplots indicate the mean value.

Abbreviations. mTBI, mild traumatic brain injury; SF-36 PCS, Short Form (36) Health Survey (physical component score); SF-MCS, Short Form (36) Health Survey (mental component score); PCL-5, Posttraumatic Stress Disorder Checklist; PHQ-9, Patient Health Questionnaire; GAD-7, Generalized Anxiety Disorder questionnaire; QOLIBRI, Quality of Life after Brain Injury; GOSE, Glasgow Outcome Scale – Extended; 3mo, 3 months; 6mo, 6 months.

Appendix B provides mean values (M) and standard deviations (SD) for the seven outcomes clustered in the two mTBI groups and time points.

Patients were considered impaired when the corresponding cut-offs were reached. The percentage of impaired individuals (i.e., with at least one of the seven outcomes being impaired) in the total sample was 53% at three months and 49% at six months after TBI. In the uncomplicated mTBI group, 51% and 49% were classified as impaired at three and six months, respectively. In the complicated mTBI group, 53% at three months and 48% at six months had at least one impaired outcome. For development of impaired outcomes in individuals after uncomplicated and complicated mTBI at three and six months see Appendix C.

For both mTBI groups, there were patients included in our study sample who could be considered as reporting impaired outcomes. Therefore, these individuals with impaired outcomes were inspected separately. Table 2 gives an overview for each dependent variable by uncomplicated and complicated mTBI groups at three and six months post-injury.

Table 2. Percentages of impaired individuals according to the respective cut-off values

Outcome	Time points	Uncomplicated mTBI (n = 569)
SF-36 PCS	3mo	24%
	6mo	21%
SF-36 MCS	3mo	22%
	6mo	21%
PCL-5	3mo	10%
	6mo	8%
PHQ-9	3mo	16%
	6mo	16%
GAD-7	3mo	11%
	6mo	8%
QOLIBRI	3mo	19%
	6mo	19%
GOSE	3mo	23%
	6mo	16%

Note. Cut-off values: SF-36 PCS and SF-36 MCS < 40, PCL-5 ≥ 33, PHQ-9 ≥ 10, GAD-7 ≥ 10, QOLIBRI < 60, GOSE ≤ 6.

Abbreviations. mTBI, mild traumatic brain injury; 3mo, 3 months; 6mo, 6 months; SF-PCS, Short Form (36) Health Survey (physical component score); SF-MCS, Short Form (36) Health Survey (mental component score); PCL-5, Posttraumatic Stress Disorder Checklist; PHQ-9, Patient Health Questionnaire; GAD-7, Generalized Anxiety Disorder questionnaire; QOLIBRI, Quality of Life after Brain Injury; GOSE, Glasgow Outcome Scale - Extended; n, number of cases.

At three months post TBI, there were significantly more individuals with impaired outcomes after complicated mTBI according to SF-36 MCS score, QOLIBRI, and GOSE ($p < 0.05$). Concerning the GOSE scale, 41% of patients after complicated mTBI were considered to be impaired (cut-off value ≤ 6) and 23% of the individuals after uncomplicated mTBI. Additionally, more patients with impaired generic (SF-36 MCS < 40) and disease-specific (QOLIBRI < 60) HRQoL were observed within the complicated mTBI group (for details, see Table 2).

At six months after TBI, we observed significantly more individuals with impaired outcomes after complicated mTBI according to the GOSE scale ($p < 0.05$). More than one third of the patients after complicated mTBI showed impairments on the GOSE, compared to 16% of individuals after uncomplicated mTBI. Among the other outcomes, the distribution within mTBI group was equal.

MANOVA-RM

MANOVA-RM showed significant differences between complicated and uncomplicated mTBI groups as well as between time points. No significant interaction was found between both main effects. There were significant differences between mTBI groups in three (generic and disease-specific HRQoL and functional outcome) out of seven outcomes. All but one domain (i.e., anxiety) differed between both time points (see Table 3 for test statistics).

Table 3. Results of repeated measures MANOVA and repeated measures ANOVA

Analysis	Dependent variable(s)	Independent variable	(M)ATS	*df1*	*df2*	*p*
MANOVA RM	Multiple outcomes*	mTBI	197.538	-	-	**< 0.001**
		Time points	34.708	-	-	**< 0.001**
		mTBI : Time points	2.932	-	-	0.158
ANOVA RM	SF-36 PCS	mTBI	5.897	1	1365.422	0.015
		Time points	61.133	1	-	**< 0.001**
		mTBI : Time points	4.361	1	-	0.037
	SF-36 MCS	mTBI	7.879	1	1399.985	**0.005**
		Time points	10.502	1	-	**0.001**
		mTBI : Time points	3.058	1	-	0.08

	mTBI	5.481	1	1366.071	0.019
PCL-5	Time points	16.902	1	-	**< 0.001**
	mTBI : Time points	0.653	1	-	0.448
	mTBI	2.632	1	1386.136	0.114
PHQ-9	Time points	9.075	1	-	**0.005**
	mTBI : Time points	0.032	1	-	0.848
	mTBI	3.216	1	1425.187	0.073
GAD-7	Time points	3.137	1	-	0.077
	mTBI : Time points	0.026	1	-	0.872
	mTBI	12.25	1	1337.174	**< 0.001**
QOLIBRI	Time points	8.588	1	-	0.003
	mTBI : Time points	2.98	1	-	0.084
	mTBI	80.944	1	1444.067	**< 0.001**
GOSE	Time points	26.15	1	-	**< 0.001**
	mTBI : Time points	1.057	1	-	0.304

Note. TBI severity = between effect (uncomplicated and complicated mTBI); Time = within effect (time points 3 and 6 months after TBI); p = p-value based on parametric bootstrapping ((M)ATS). Bold p-values are significant on α = 0.05 for MANOVA-RM and αadj = 0.007 for ANOVA-RM, respectively.

** Multiple outcomes = all seven outcomes combined as a dependent variable*

Abbreviations. (M)ATS, (multivariate) ANOVA-type statistic; df1/df2, degrees of freedom; p, p-value; TBI, traumatic brain injury; SF-PCS, Short Form (36) Health Survey (physical component score); SF-MCS, Short Form (36) Health Survey (mental component score); PCL-5, Posttraumatic Stress Disorder Checklist; PHQ-9, Patient Health Questionnaire; GAD-7, Generalized Anxiety Disorder questionnaire; QOLIBRI, Quality of Life after Brain Injury; GOSE, Glasgow Outcome Scale - Extended.

Post-hoc comparisons

Table 4 provides an overview on differences between mTBI groups, time points, and interaction between both effects according to the results of ANOVA-RM.

Post hoc comparisons revealed, in contrast to the multivariate results, a more detailed insight into differences between the main effects and their interaction for each dependent variable. Therefore, differences between mTBI groups and time points for the seven outcomes are reported separately. It is important to note that, with the exception of the mean depression score in the complicated mTBI group, all other outcomes were on average above the clinically relevant cut-off points.

Table 4. Overview of differences between mTBI groups, time points, and interaction between both effects

Outcome	mTBI	Time points	Interaction
SF-36 PCS	--	++	--
SF-36 MCS	++	++	--
PCL-5	--	++	--
PHQ-9	--	++	--
GAD-7	--	--	--
QOLIBRI	++	++	--
GOSE	++	++	--

Note. ++ = significant on α = 0.007, -- not significant

Abbreviations. mTBI, mild traumatic brain injury; SF-PCS, Short Form (36) Health Survey (physical component score); SF-MCS, Short Form (36) Health Survey (mental component score); PCL-5, Posttraumatic Stress Disorder Checklist; PHQ-9, Patient Health Questionnaire; GAD-7, Generalized Anxiety Disorder questionnaire; QOLIBRI, Quality of Life after Brain Injury; GOSE, Glasgow Outcome Scale - Extended.

Health-related quality of life

Generic HRQoL. The PCS (SF-36) showed a significant within effect with an increase in HRQoL from three (M = 46.52, SD =10.43) to six months (M = 48.10, SD = 10.21) after TBI.

The MCS (SF-36) revealed significant differences between both the mTBI groups and the observed time points. Individuals after uncomplicated mTBI (M = 48.43, SD = 11.01) reported significantly higher HRQoL compared to those after complicated mTBI (M = 46.61, SD = 12.07). There was a slight but significant increase of MCS score from three (M = 47.14, SD = 11.57) to six months (M = 47.95, SD = 11.56) after mTBI.

Disease-specific HRQoL. For the QOLIBRI significant differences between both mTBI groups and time points were reported. HRQoL was significantly higher in the uncomplicated mTBI group (M = 74.97, SD = 16.82) compared to the complicated mTBI group (M = 71.56, SD = 17.33). In addition, an increase of HRQoL was observed between three (M = 72.84, SD = 17.05) and six months (M = 73.79, SD = 17.24) following mTBI for both groups.

Functional outcome

For the GOSE, significant differences in both the between and the within effects were detected. Patients after complicated mTBI showed significantly higher disability levels (M = 6.63, SD = 1.37) compared to those with uncomplicated mTBI (M = 7.24, SD = 1.08). A significant increase concerning recovery was observed for both groups from three (M = 6.86, SD =1.301) to six months (M = 7.02, SD = 1.23).

Post-traumatic stress, depression and anxiety

Results showed a significant decrease of PTSD related symptoms (PCL-5) from three (M = 12.54, SD = 13.44) to six months (M = 11.41, SD = 12.98) after mTBI. Depression related symptoms measured by the PHQ-9 were slightly but significantly higher for three (M = 4.93, SD = 5.04) compared to six months (M = 4.61, SD = 5.01) after mTBI. Anxiety measured by GAD-7 revealed no significance neither between mTBI groups nor between time points.

Discussion

This study focused on outcome of patients after complicated and uncomplicated mTBI at three and six month post-injury, included in a large European database. Results may contribute significantly to existing literature concerning this topic. A better understanding of the relation between complicated and uncomplicated mTBI and different outcomes may improve intervention strategies and the recovery process of patients after mTBI.

When comparing individuals after complicated and uncomplicated mTBI, patients after complicated mTBI reported lower generic and disease-specific HRQoL and worse functional outcome at both time points. Nevertheless, we did not find considerable improvement in outcomes from three to six months as mean scores on all outcome measures were within average range and not classified as impaired. The mean PHQ-9 score for patients after complicated mTBI at three months post-injury reached the cut-off for mild depressive symptoms, which indicates the need for an appropriate follow-up and early treatment. It is noteworthy that the number of individuals with impaired functional and psychological outcomes was considerably higher in the complicated mTBI group than in the uncomplicated group, especially three months post-injury. Therefore, one should ensure that these patients are detected early and their health status should be monitored longitudinally, to provide targeted and timely treatment. Ultimately, the differences between some measures were small and significant baseline differences between the groups might contribute to the reported findings. Especially, when keeping in mind that patients after complicated mTBI were often more severely injured according to the GCS score.

In previous research, nearly 40% of patients with mTBI reported depressive symptoms within three to six months post-injury[43]. In addition, 33% of patients with mTBI were functionally impaired three months post-injury[13]. When specifically focusing on individuals after complicated and uncomplicated mTBI, contradictory results have been reported regarding the impact of complicated and uncomplicated mTBI on outcome. Ponsford et al. found that the majority of individuals after uncomplicated mTBI make a good recovery on average 7 months post-injury, when focusing on post-concussion symptoms, depression/anxiety and mental and physical quality of life scores [44]. In various studies, complicated mTBI is seen as a key component when predicting outcome [3-6]. However, other research did not find any relation between functional outcome and complicated mTBI [7-9]. Furthermore, HRQoL has

been under-investigated in previous research and a multidimensional approach to outcome assessment such as in this study has been lacking.
The present study is novel because there has not yet been a study with such a large sample size and simultaneously having the ability to compare patients on different outcome levels such as generic and disease-specific HRQoL, functional outcome, and symptomatology. Moreover, the methodology used in this study strengthened the results, since a multivariate statistical approach suitable for non-normal distributed data with less assumptions and restrictions as in most other research was applied. In particular, the method combines information from multiple outcome measures and is also be suitable for non-normal data.

Several limitations concerning this study should be taken into account. It is important to note that the effects sizes were small for the PCS and MCS scores and PHQ-9, statistical significance was most likely due to the sample size used in this study. Resilience and coping, which was not measured in this study, might have impacted outcome. Maestas et al. reported that pre-injury coping in the sense of strengthening resilience could impact outcome after uncomplicated and complicated mTBI as coping may impact resilience [20]. Williams' classification of complicated versus uncomplicated may underestimate the presence and type of TBI abnormalities as routine magnetic resonance imaging was proven to be far more sensitive and is the preferable tool [45]. Generalizability of the results presented in this study is restricted since adjustment for baseline covariates between the two groups was not provided. In the current study implications of treatment after mTBI have not been accounted for, which could influence the course of recovery after mTBI. Lastly, patients who are still experiencing lower HRQoL and lower functional outcome might have been more likely to participate, resulting in response bias [46].

For future research it would be interesting to look at outcome at later follow-up times such as five to ten years post-TBI. In addition, return to work or school after complicated and uncomplicated mTBI should be assessed since this could influence subjective well-being [47], and has major impact on societal costs [1]. Furthermore, research into biomarkers and localization of the abnormality on the CT or magnetic resonance imaging scan can could refine the conclusions drawn in this study [1, 10]. Lastly, to establish a better understanding considering outcome after complicated and uncomplicated mTBI, outcomes in this study should be compared to patients with non-brain injured trauma as well as the general population, and complicated and uncomplicated mTBI groups should be further differentiated by GCS score.

Conclusions

To conclude, the present results indicate that patients after complicated mTBI reported lower generic and disease-specific HRQoL and worse functional outcome compared to patients after uncomplicated mTBI at three and six months. However, differences between some measures were small and there were significant baseline differences between the groups that might contribute to the findings. Both groups showed a tendency to improve on outcome from three to six months after TBI. Additionally, the complicated mTBI group comprised more patients with impaired outcomes than the uncomplicated group. Considering this, patients, clinicians, researchers, and decisions-makers in health care should be taking the short and long-term effects on outcome for patients after both uncomplicated and complicated mTBI into account. At the same time, individually tailored therapy should be provided early on for those who show deficiencies in recovery, HRQoL, psychological and psychosocial outcomes.

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Appendix

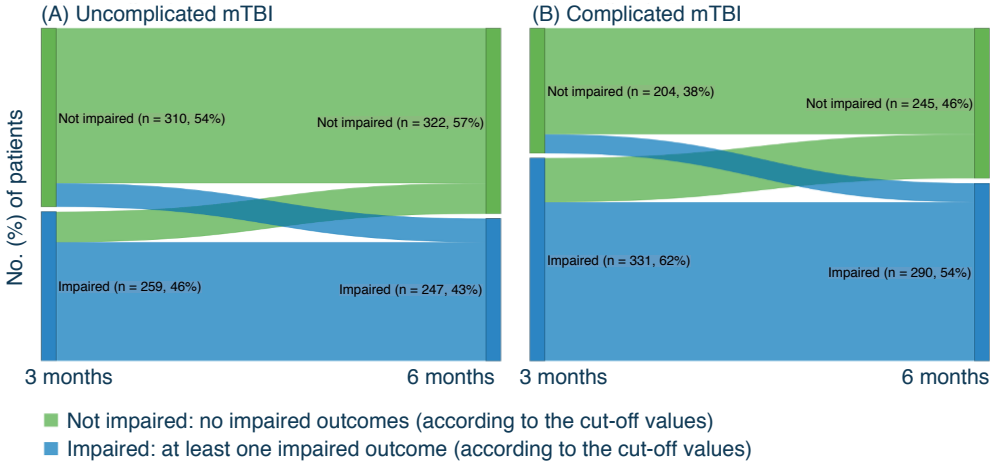
Appendix A. Statistical Model and Methods (available per request)

Appendix B. Descriptive statistics on outcomes by uncomplicated and complicated mTBI groups

		Uncomplicated mTBI (*n* = 569)		**Complicated mTBI** (*n* = 535)	
Outcome	**Time points**	*M*	*SD*	*M*	*SD*
SF-36 PCS	3mo	47.41	10.56	45.56	10.22
	6mo	48.58	10.37	47.59	10.01
SF-36 MCS	3mo	48.24	10.89	45.98	12.14
	6mo	48.62	11.12	47.24	11.98
PCL-5	3mo	11.8	13	13.33	13.86
	6mo	10.45	12.39	12.42	13.51
PHQ-9	3mo	4.69	4.9	5.17	5.18
	6mo	4.4	4.92	4.84	5.1
GAD-7	3mo	3.35	4.25	3.77	4.65
	6mo	3.15	4.02	3.61	4.64
QOLIBRI	3mo	74.77	16.46	70.79	17.45
	6mo	75.17	17.18	72.32	17.2
GOSE	3mo	7.17	1.1	6.53	1.42
	6mo	7.3	1.06	6.73	1.32

Abbreviations. mTBI, mild traumatic brain injury; 3mo, 3 months; 6mo, 6 months; SF-PCS, Short Form (36) Health Survey (physical component score); SF-MCS, Short Form (36) Health Survey (mental component score); PCL-5, Posttraumatic Stress Disorder Checklist; PHQ-9, Patient Health Questionnaire; GAD-7, Generalized Anxiety Disorder questionnaire; QOLIBRI, Quality of Life after Brain Injury; GOSE, Glasgow Outcome Scale - Extended; n, number of cases; M, mean; SD, standard deviation.

Appendix C. Development of impaired outcomes in individuals after uncomplicated and complicated mTBI at three and six months



Chapter 6

Prevalence of Post-Concussion-like Symptoms in the General Population in Italy, The Netherlands and the United Kingdom

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Abstract

Objectives: To evaluate the frequency of post-concussion symptoms and prevalence and risk factors of post-concussion syndrome (PCS) in the general population, investigate the association between the Rivermead Post-Concussion Symptoms Questionnaire (RPQ) and self-perceived health, and evaluate differences between three European countries.

Methods: A web-based survey including the RPQ and EQ-5D was conducted among representative samples in three European countries.

Results: A total of 11,759 respondents completed the questionnaire. The most frequently reported symptom was fatigue (49.9%). Almost half (45.1%) of the respondents were classified as having PCS considering rating score 2 (three RPQ items with score ≥ 2) as a cut-off. Chronic health complaints were found as a significant risk factor for PCS. All items of the RPQ were positively correlated with the EQ-5D and the strongest positive correlation (0.633, $p<0.001$) was between RPQ item 'feeling depressed or tearful' and EQ-5D domain 'anxiety/depression'.

Conclusions: We found a high frequency of post-concussion-like symptoms and PCS in the general population, indicating that these symptoms are not specific for patients with traumatic brain injury (TBI), and PCS is not a unique syndrome after TBI. Therefore, the use of post-concussion symptoms and PCS as outcome following mild TBI should be interpreted with caution.

Introduction

Post-concussion symptoms following a traumatic brain injury, and especially mild traumatic brain injury (mTBI), are very common.[1] Post-concussion symptoms can be categorized in physical symptoms, cognitive deficits and behavioral/emotional symptoms.[2] In general, many patients with mTBI make a full recovery within one year after injury,[3] but when several post-concussion symptoms persist over time, patients are considered as having a post-concussion syndrome (PCS). One of the most prominent diagnostic criteria of PCS is the International Classification of Diseases (ICD-10).[4] The Rivermead Post-Concussion Symptoms Questionnaire (RPQ) is a frequently applied instrument to assess the existence and severity of post-concussion symptoms.[5]

Over the last decennia, the concept of PCS has been debated in an abundance of studies. The prevalence rates of PCS throughout the literature vary greatly[6] and depend on the definition used[7] as well as the applied classification method.[8] Researchers and clinicians who have performed extensive research concerning the etiology of PCS have still not been able to successfully identify the pre- and post-injury-related factors as well as the underlying structure of post-concussion symptoms.[9] All controversy[10] and uncertainty leads to a growing concern whether PCS really does exist and if post-concussion symptoms are unique for patients with mTBI. Multiple studies have concluded that the etiology of the post-concussion symptoms and/or syndrome might probably not resort back to the brain damage itself.[11-13] Moreover, self-reported symptoms may be nonspecific symptoms, which are not exclusively associated with patients with mTBI.[14] Post-concussion symptoms can be caused by various factors, and it is complex to interpret which components may be linked specifically to the brain injury and to which extent symptoms already existed before the injury. Additionally, previous studies have shown that post-concussion-like symptoms exist in healthy populations[13, 15-19] as well as in patients with a non-head injury trauma,[11, 14] patients with chronic pain[12] and personal injury claimants.[20] However, all previous studies had relatively small sample sizes and samples were not representative for general populations, since the populations studied mainly consisted of university students or patient groups.[11-18, 21] Furthermore, all studies were only conducted in one country at a time and most research was done in North-America,[12, 13, 16, 18-21] with exceptions of China,[15] France[14] and Australia.[11, 17]

Wang and colleagues have suggested that the differences in frequency of post-concussion symptoms could be due to cultural differences.[15] Additionally, Zakzanis and colleagues[16] have shown that the influence of culture and language should be taken into consideration in PCS research. Consequently, prevalence rates in healthy populations may differ between countries. Apart from culture and language, a linkage between post-concussion symptoms and lower levels of life satisfaction[22] and lower health-related quality of life (HRQoL)[23] have been reported. Nonetheless, the patient populations in both these researches consisted

of patients with TBI. A strong link between post-concussion symptoms and HRQoL may suggest that PCS is debilitating. However, a weak association could point out that PCS consists of common symptoms that everyone experiences at some time which do not explicitly have a major effect on HRQoL. Whether this linkage also exists in healthy populations remains to be investigated.

The aims of this paper were to (a) evaluate the frequency of post-concussion symptoms and prevalence of PCS in general healthy populations, (b) assess the risk factors for PCS, (c) compare the RPQ with general HRQoL (EQ-5D), and (d) inspect the differences between three European countries.

Methods

Participants

A web-based survey was conducted among a representative sample in three European countries, namely the United Kingdom (UK), the Netherlands and Italy. The respondents were recruited by Survey Sampling International (SSI), a market research agency, who distributed and launched the questionnaires. Existing large internet panels were used and these samples were designed to be representative of the population aged 18 to 70 in the selected countries with regard to age, gender and education. Data were obtained between June 29th and July 31st 2017. A total of 11,759 respondents filled out the questionnaire, which was comprised of 4,646 respondents in UK, 3,564 respondents in the Netherlands and 3,549 respondents in Italy.

Patient consents

All participants, as members of a web-based panel, had already provided informed consent to participate in online surveys. Informed consent for the present survey was obtained from all those agreeing to complete the survey. Participants were informed on the welcome page that the survey aimed to better understand the consequences of traumatic brain injury, that it would take approximately 20 min to complete, and that all responses were confidential and anonymous. Consent was obtained when respondents clicking the 'Go to Survey' button from this page. This study was part of the CENTER-TBI study (EC grant 602150) and ethical approval was obtained from the Leids Universitair Centrum – Commissie Medische Ethiek (approval P14.222/NV/nv).

Measures

Prevalence and severity of post-concussion symptoms were evaluated by the use of the RPQ. A total of 16 different post-concussion symptoms are described in the RPQ, which include headaches, dizziness, nausea/vomiting, noise sensitivity, sleep disturbance, fatigue, being irritable, feeling depressed or tearful, feeling frustrated or impatient, forgetfulness, poor concentration, taking longer to think, blurred vision, light sensitivity, double vision and restlessness. During the questionnaire respondents were asked to assess the severity of the symptoms over the last 24 h on a 5-point Likert scale: 0 (not experienced at all), 1 (no more of a problem), 2 (a mild problem), 3 (a moderate problem) and 4 (a severe problem).[5] The RPQ total score is the sum of all 16 items excluding ratings of 1.[5] During this study, the criteria described in the ICD-10 are mapped onto the RPQ scale and respondents were classified as having PCS when they reported at least three out of the following symptoms: headaches, dizziness, fatigue, irritability, impaired memory, impaired concentration, and insomnia.[4] There is not a set standard available in the literature for which severity rating to uses as a cut-off, which resulted in two possible cut-offs; mild or higher (≥ rating score 2) and moderate or higher (≥ rating score 3) (Panel 1).[8] In this study, we looked at both cut-offs separately.

HRQoL was measured by the EQ-5D. The EQ-5D constitutes of two parts: the EQ-5D descriptive system and the EQ visual analog scale (EQ VAS). The EQ-

5D descriptive system encompasses five dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression). The EQ-5D-5L was introduced in 2009 and gives respondents the opportunity to score the dimensions on five levels (no problems, slight problems, moderate problems, severe problems and extreme problems). The EQ-VAS consists of a vertical VAS rating scale, where 0 is labeled as "The worst health you can imagine" and 100 as "The best health you can imagine" and documents the respondent's self-rated health. The EQ-5D utility scores, which are on a scale from 0 (dead) to 1 (full health), for each country were calculated by the use of the Dutch value set.[24]

Panel 1. Severity rating cut-offs regarding Post-Concussion Syndrome

Cut-off rating score 2	Cut-off rating score 3	Eligible symptoms
Three RPQ items with score ≥ 2	*Three RPQ items with score ≥ 3*	Headache Dizziness Sleep disturbance Fatigue Being irritable, easily angered Forgetfulness, poor memory Poor concentration

Abbreviations. RPQ, Rivermead Post-Concussion Syndrome Questionnaire

Risk factors

Age, gender, education level, work status, income level, the experience of serious illness in respondents themselves; or their immediate family, whether respondents cared for others, and the experience of chronic health complaints were considered risk factors. This selection was based on the available data in our dataset and by looking at risk factors in previous literature.[25-27] The categorizations for the risk factors can be found in Appendix B.

Statistical analysis

Descriptive analyses were performed for demographic data (age, gender, education, work status, annual household income, the experience of serious illness in yourself, immediate family and caring for others, and chronic health complaints). The frequency of post-concussion-like symptoms was assessed by computing the percentages for respondents, and the prevalence of PCS was calculated by identifying the percentage of respondents that complied with our classifications.
Differences in mean EQ-5D utility and EQ-5D VAS scores per country were assessed by the use of the Kruskal Wallis H test, followed by post-hoc analyses where the significance values were adjusted by the Bonferroni correction for multiple tests. Statistical significance was determined by a p-value of $p<0.05$.

By the use of Mann Whitney U tests, we inspected the difference for respondents with and without PCS in mean EQ-5D utility and mean EQ-5D VAS. To evaluate the correlation between the various EQ-5D dimensions and EQ-5D total score and the RPQ items, which were not normally distributed, the Spearman's correlation coefficients were administered. Strong, moderate and weak correlations were differentiated between by Cohen's Set Correlation and Contingency Tables: a coefficient above 0.5 the correlation was considered strong, a coefficient between 0.3 and 0.5 moderate, and when the coefficient was below 0.3 it was considered as weak.[28]

The survey was translated from English into Dutch and Italian using translation software and subsequently translated back into English. Bilingual native speakers verified the translations independently.

All analyses were done for the complete database and per country. SPSS version 24 for Windows (IBM SPSS Statistics, SPSS Inc, Chicago, IL) was used to perform all statistical analyses.

Data availability

The data that support the findings of this study are available from the corresponding author, [DV], upon reasonable request. Anonymized data will be shared.

Results

Study population

In total 11,759 respondents were included in this study. The characteristics of our study sample are shown in Table 1. The median age of the respondents was 44 years (interquartile range (IQR); 32–57 years) and women and men were evenly represented. The educational level of the respondents can be divided up in 28.3% (low), 47.2% (middle) and 25.3% (high). Approximately 50% was employed and just over a half (52.2%) had experienced serious illness in their immediate family. One in two (50.9%) respondents has reported to have one or more chronic health complaints.

Frequency of post-concussion-like symptoms and prevalence of PCS

The most frequently reported symptom was fatigue (49.9%) followed by sleep disturbance (42.4%) (Figure 1). The least reported symptom was double vision (10.7%). The patterns for the reported post-concussion symptoms in the individual countries were quite similar. Fatigue was also the most frequently reported symptom in each country (UK: 52.6%, the Netherlands: 48.4% and Italy: 48.1%), followed by sleep disturbance (UK: 47.0%, the Netherlands: 40.1%), except for Italy where being irritable was the second most reported symptom (Italy: 44.0%). When using

rating score 3 as a cut-off the same pattern is detected (Appendix A).

Almost half (45.1%) of the respondents were classified as having PCS considering rating score 2 (three RPQ items with score ≥ 2) as a cut-off (Table 2). When using rating score 3 (three RPQ items with score ≥ 3) as a cut-off, this prevalence rate dropped substantially to 17.5%. When we inspected all respondents with chronic health complaints, higher PCS prevalence rates were found for every single complaint compared to the sample as a whole. Furthermore, respondents with memory problems due to a neurological disease/dementia had the highest percentage of PCS prevalence for rating score 2 (81.9%) and rating score 3 (53.4%). The prevalence of PCS differed per country with the UK (47.8%) having the highest prevalence rates. When using rating score 3 as a cut-off, the biggest drop in prevalence rate is seen in Italy, which implies that Italians report less frequently moderate problems.

Figure 1. Frequency of post-concussion symptoms with a severity rating of 2* or higher per country

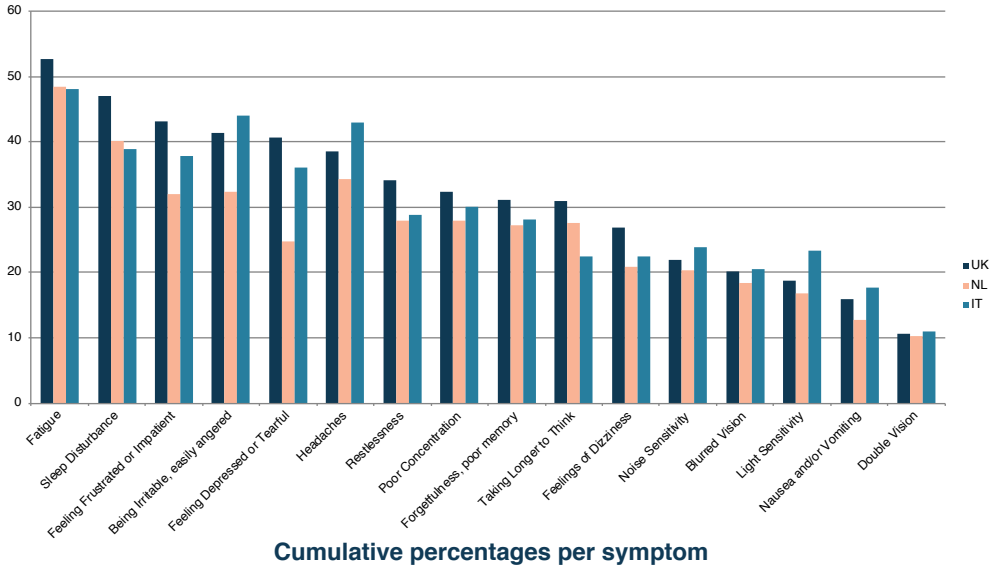


Table 1. Characteristics of the study population

	All respondents	UK	The Netherlands	Italy
	(N=11759) *N (%)*	(N=4646) *N (%)*	(N=3564) *N (%)*	(N=3549) *N (%)*
Age[1] (years)	44 [32-57]	44 [31-57]	45 [32-57]	45 [33-57]
Gender (male)	5840 (49.7%)	2288 (49.2%)	1782 (50.0%)	1770 (49.9%)
Education[2]				
Low	3330 (28.3%)	1066 (22.9%)	1064 (29.9%)	1200 (33.8%)
Middle	5555 (47.2%)	1986 (42.7%)	1601 (44.9%)	1968 (55.5%)
High	2874 (24.4%)	1594 (34.3%)	899 (25.2%)	381 (10.7%)
Work status[3]				
Employed	6038 (51.3%)	2428 (52.3%)	1891 (53.1%)	1719 (48.4%)
Unemployed	1648 (14.0%)	417 (9.0%)	384 (10.8%)	847 (23.9%)
Looking after others[4]	601 (5.1%)	313 (6.7%)	149 (4.2%)	139 (3.9%)
Student	772 (6.6%)	287 (6.2%)	245 (6.9%)	240 (6.8%)
Retired	1743 (14.8%)	733 (15.8%)	452 (12.7%)	558 (15.7%)
Unable to work	957 (8.1%)	468 (10.1%)	443 (12.4%)	46 (1.3%)
Annual household income[5]				
Low	2722 (23.1%)	999 (21.5%)	648 (18.2%)	1075 (30.3%)
Middle	2853 (24.3%)	1409 (30.3%)	614 (17.2%)	830 (23.4%)
High	4325 (36.8%)	1735 (37.3%)	1525 (42.8%)	1065 (30.0%)
Do not know/do not want to tell	1859 (15.8%)	503 (10.8%)	777 (21.8%)	579 (16.3%)
Experience of serious illness				
In you yourself (yes)	3115 (26.5%)	1640 (35.3%)	917 (25.7%)	558 (15.7%)
In your immediate family (yes)	6138 (52.2%)	2845 (61.2%)	2484 (69.7%)	809 (22.8%)
In caring for others (yes)	2822 (24.0%)	1520 (32.7%)	795 (22.3%)	507 (14.3%)
Chronic health complaints (yes)[6]	5983 (50.9%)	2487 (53.5%)	1887 (52.9%)	1609 (45.3%)
RPQ total score[1]	8 [0-20]	8 [0-22]	6 [0-18]	8 [2-18]

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

[2] *Education was divided up in low (junior school), middle (comprehensive school) and high (college and university).*

[3] *Work status was categorized as employed (employee and self-employed), unemployed (consisting out of work for more than and less than 1 year), looking after others (e.g. a carer or parent), a student, retired and unable to work.*

[4] *E.g. carer or parent.*

[5] *Income was grouped as follows low (UK; less than £14.000, Italy and the Netherlands; less than €20.000), middle (UK; £14.000-£27.999, Italy and the Netherlands; €20.000-€39.999) and high (UK; more than £27.999, Italy and the Netherlands; more than €39.999).*

[6] *Chronic health complaints were defined as: asthma, chronic bronchitis, severe heart disease, consequences of a stroke, diabetes, severe back complaints, arthrosis, rheumatism, cancer, memory problems due to neurological disease/dementia, memory problems due to ageing, depression or anxiety disorder, and other chronic health complaints.*

Table 2. Prevalence of Post-Concussion Syndrome in the general population

	Rating score 2		Rating score 3	
Country	*PCS*	*No, PCS*	*PCS*	*No, PCS*
All respondents	5301 (45.1%)	6458 (54.9%)	2057 (17.5%)	9702 (82.5%)
UK	2221 (47.8%)	2425 (52.2%)	971 (20.9%)	3675 (79.1%)
NL	1442 (40.5%)	2122 (59.5%)	581 (16.3%)	2983 (83.7%)
IT	1638 (46.2%)	1911 (53.8%)	505 (14.2%)	3044 (85.8%)

Abbreviations. UK, United Kingdom; NL, the Netherlands, IT, Italy; PCS, Post-Concussion Syndrome.

Risk factors

Lower age, female gender, low education, unable to work, low-income level and when respondents indicated they experienced serious illness in respondents themselves, their immediate family, and when they cared for others, and chronic health complaints are all significantly associated with PCS (Appendix B). The most pronounced effects on PCS are “being a student” or “retired” compared to being “unable to work” and chronic health complaints. Multivariable prediction models explained 26% (rating score 2) and 24% (rating score 3) (Nagelkerke R2) of the variance in PCS.

EQ-5D utility

The mean EQ-5D utility score was 0.81. The lowest utility measured in this sample was –0.45% and 33.5% of the respondents reported no problems on any of the EQ-5D domains. As expected, the mean utility score was significantly lower for respondents with PCS compared to respondents without PCS (0.70 vs. 0.90; $p<0.001$) (Table 3). The mean EQ-5D VAS score was 74.7 (Table 4) and was also found to significantly differ between respondents with and without PCS (66.8 vs. 81.2; $p<0.001$).

The highest mean utility score was found for Italian respondents ($\mu = 0.86$, SD = 0.16), followed by Dutch respondents ($\mu = 0.83$, SD = 0.21) and lastly British respondents ($\mu = 0.77$, SD = 0.28). The lowest mean utility score was found for respondents from the UK with PCS according to rating score 3. There were statistically significant differences in EQ-5D utility and total scores between countries ($p<0.05$), except for

the utility between the Netherlands and Italy (p=0.051). Tables 3 and 4 also show the mean utility scores for respondents with and without PCS according to the two cut-offs and per country. The biggest difference in utility was determined for British respondents without PCS and with PCS according to rating score 3.

For the EQ-5D VAS scores, the same order was found as for the mean utility score, which means Italian respondents rate their own health the highest and British respondents the lowest, with the Dutch respondents in between both of them. The EQ-5D-VAS was determined to be significantly different for respondents with and without PCS in all countries (p<0 .001).

RPQ and EQ-5D

Figure 2 shows Spearman's correlation coefficients between RPQ items and EQ-5D dimensions indicating that all items of the RPQ are positively correlated with the EQ-5D dimensions. The strongest positive correlation (0.633, p< .001) was found between 'feeling depressed or tearful' and the anxiety/depression dimension. The weakest correlation was between 'headache' and the mobility dimension. Fatigue has a moderate correlation with all EQ-5D dimensions, with the exception of the self-care dimension. All correlations were statistically significant on a p<0.001 level. Lastly, when looking at correlations between the EQ-5D total score and all RPQ items separately, fatigue (0.546, p<0.001) was determined as the strongest positive correlation and double vision (0.278, p<0.001) showed the weakest correlation with the EQ-5D total score.

Table 3. Mean EQ-5D utility scores calculated by the Dutch value set for respondents with and without Post-Concussion Syndrome per country

	EQ-5D utility score											
	All respondents			UK			The Netherlands			Italy		
	N	*Mean (SD)*	*P-value*	*N*	*Mean (SD)*	*P-value*	*N*	*Mean (SD)*	*P-value*	*N*	*Mean (SD)*	*P-value*
Total	11759	0.81 (0.23)		4646	0.77 (0.28)		3564	0.83 (0.21)		3549	0.86 (0.16)	
PCS (RS2)	5301	0.70 (0.28)	p<0.001	2221	0.63 (0.33)	p<0.001	1442	0.71 (0.25)	p<0.001	1638	0.79 (0.18)	p<0.001
No, PCS (RS2)	6458	0.90 (0.14)		2425	0.89 (0.16)		2122	0.90 (0.14)		1911	0.91 (0.12)	
PCS (RS3)	2057	0.58 (0.32)	p<0.001	971	0.49 (0.36)	p<0.001	581	0.62 (0.27)	p<0.001	505	0.72 (0.21)	p<0.001
No, PCS (RS3)	9702	0.86 (0.18)		3675	0.84 (0.20)		2983	0.87 (0.17)		3044	0.88 (0.14)	

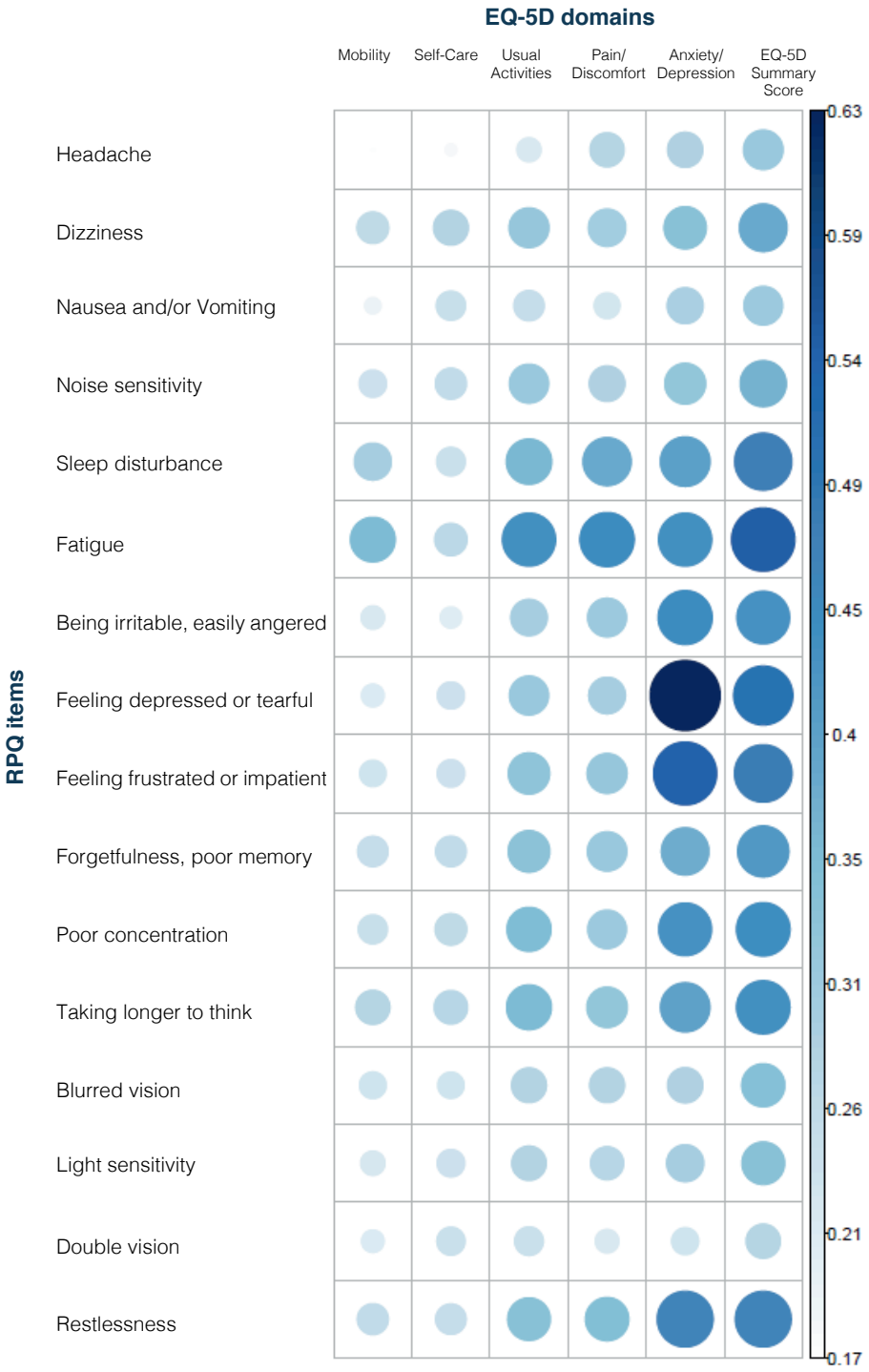
Abbreviations. UK, United Kingdom; NL, the Netherlands, IT, Italy; 95% CI, 95% Confidence Interval; PCS, Post-Concussion Syndrome; RS2, rating score 2; RS3, rating score 3

Table 4. Mean EQ-5D VAS scores for respondents with and without Post-Concussion Syndrome per country.

	EQ-5D VAS score											
	All respondents			UK			The Netherlands			Italy		
	N	*Mean (SD)*	*P-value*	*N*	*Mean (SD)*	*P-value*	*N*	*Mean (SD)*	*P-value*	*N*	*Mean (SD)*	*P-value*
Total	11759	74.7 (19.6)		4646	71.3 (21.6)		3549	77.6 (17.4)		3564	76.2 (18.4)	
PCS (RS2)	5301	66.8 (21.1)	p<0.001	2221	62.5 (22.8)	p<0.001	1638	71.8 (18.8)	p<0.001	1442	67.6 (19.4)	p<0.001
No, PCS (RS2)	6458	81.2 (15.6)		2425	79.3 (16.8)		1911	82.5 (14.4)		2122	82.1 (15.0)	
PCS (RS3)	2057	58.7 (22.9)	p<0.001	971	54.3 (24.3)	p<0.001	505	64.7 (20.9)	p<0.001	581	60.7 (20.6)	p<0.001
No, PCS (RS3)	9702	78.1 (17.0)		3675	75.8 (18.4)		3044	79.7 (15.8)		2983	79.2 (16.3)	

Abbreviations. UK, United Kingdom; NL, the Netherlands, IT, Italy; 95% CI, 95% Confidence Interval; PCS, Post-Concussion Syndrome; RS2, rating score 2; RS3, rating score 3

Figure 2. Correlation between RPQ items and EQ-5D domains.



Discussion

This study provides the first examination of the frequency of post-concussion-like symptoms and the prevalence of PCS in a large and representative sample of the general population, and within and across three European countries. We found a high base rate of post-concussion-like symptoms and respondents with memory problems due to a neurological disease/dementia had the highest prevalence rate for PCS. The use of post-concussion symptoms and PCS as outcome following mTBI should be interpreted with caution.

Our findings correspond to those of preceding studies. Wang and colleagues investigated a group of university students, in which they found fatigue as the highest reported symptom with a frequency of 38.1%.[15] During this study, we also determined fatigue (49.9%) as the highest reported symptom for all respondents in the database. The prevalence rate of PCS was 45.1% considering rating score 2 as a cut-off, however; when using rating score 3 the prevalence for PCS decreased to 17.5%, which is comparable to prevalence rates found by Lagarde and colleagues in patients with head injuries (28.7%) and patients with non-head injuries (22.9%).[14]

The following risk factors were all significantly associated with PCS: lower age, female gender, low education, work status, low-income level, chronic health complaints, and when respondents experienced serious illness in themselves, their immediate family, and when they cared for others, and chronic health complaints. These findings are in line with previous studies.[25-27] Being a “student” or “retired” compared to being “unable to work” and chronic health complaints had the most noticeable effect on PCS. Statistically significant differences in EQ-5D utility, total scores, and EQ-5D VAS scores were found for patients with and without PCS. This indicates that being classified with PCS had a strong impact on the respondent’s HRQoL. In addition, correlations between all RPQ items and EQ-5D dimensions were high.

The current study is unique compared to previous studies, because none of them have looked at large samples such as in this study nor did they compare three different countries at the same time. Additionally, the database used is also representative for the general population with regards to age, gender, and educational level, where in previous studies mostly healthy university students were used.[13, 15-19]
Limitations include that for the calculation of the utility scores of the EQ-5D, Dutch value sets were used for all countries included in the analysis, mainly because there is no value set available yet for Italy. Using the same tariff for each country could potentially limit the representativeness of these scores in the separate countries, as the relative value of dimensions and levels may differ from those in the Netherlands. However, it does substantiate the comparability across the three countries. When comparing the population norms with the mean EQ-5D utility and VAS scores, the reported mean scores were comparable for the Netherlands and Italy. However, the

mean UK scores, 0.77 and 71.3, respectively, are lower than the population norms; 0.86 and 82.8.[29]

Our study was conducted by the use of a web-based checklist, which might have led to 'over' reporting of symptoms, because according to Edmed & Sullivan, the method used to assess PCS symptoms influences the number and type of symptoms reported.[17] On the other hand, the RPQ is the most frequently applied instrument to classify PCS. By also incorporating this method in our study, our prevalence rates are comparable with previous mTBI studies. Another limitation is based on the fact that there were no questions asked if respondents had experienced a concussion, TBI or brain injury in their life or trauma's in general. However, the expected TBI prevalence is 639.2 (UK), 278.6 (the Netherlands) and 214.5 (Italy), extrapolated from reported country-specific age-adjusted hospital discharge rates per 100.000 due to TBI by Majdan and colleagues.[30] This is considerably lower than the found prevalence rates for PCS in this population. Nevertheless, the found pattern is similar to PCS distribution, where the UK was the highest and IT the lowest. Additionally, previous literature has determined that respondents suffering from depression and/ or burn-out or PTSD, or being involved in a litigation at the time of the questionnaire assessment are factors that could be associated with PCS.

However, in the current study, there is no information representing these aspects.[1, 13] There is also no information available if respondents are enduring intolerance of stress, emotion or alcohol, which is the last criterion described in the ICD-10 criteria. [4] Furthermore, we do not know to what extent our samples are representative for the population in the three countries with regards to characteristics other than age, gender, and educational level. Additionally, the people who partake in a market research panel might not be illustrative of the general population.
We were able to look at the representativeness of the sample with regards to HRQoL by comparing our scores with the population norms. However, it could be that our sample is not representative with regards to other factors and characteristics that impact the likelihood of developing PCS, and which should be taken into account when pooling representative samples. Moreover, the maximum age in our study sample was 70, whereas the TBI epidemiology is changing with a greater deal of patients aged 70 and older.[31]

More research is needed into which cut-off point is sufficient for PCS research, because the current literature is inconclusive concerning the severity rating score that should be used as a cut-off when the RPQ is applied to classify PCS. As shown during this study, and previous studies, the results change considerably depending on the cut-off.[8] Rating score 2 seems to be less discriminating as healthy adults are also being diagnosed with PCS, which points towards a high percentage of false-positives. Additionally, to correctly diagnose people with PCS, a clinical examination should take place rather than basing it on self-report of symptoms by the patient. Clinicians should be aware of the high post-concussion-like symptom endorsement and prevalence of PCS in the healthy population and the possible contributing risk factors in a specific country, and take this into consideration during

their clinical examination.[13] Considering the issues with current PCS assessment tools, more and more research is being done into new methods that may be better suited in the assessment of PCS (e.g. ocular motor assessment[32] and robotic technology[33]). It is very clear that a high base rate of PCS symptoms is present in the general population, so when looking at patients with TBI, one should wonder which part of the reported symptoms are actually due to the injury. There is a plethora of research being performed in the field of PCS, however, this study shows that there is no clear view on what is really being researched. Furthermore, this is supported by the fact that the prevalence rates of PCS halved when we looked at the respondents without any chronic health complaints and that prevalence depended substantially on the distribution of risk factors in a population that are not specific for TBI. The terminologies post-concussion symptoms and PCS should be modified as they are deceptive, since they incorrectly assume that the underlying principle of the symptoms and/or syndrome is a brain injury.[11]

Conclusions

This study showed that post-concussion-like symptoms are frequently reported, and the prevalence of PCS is prominent in the general population, indicating that post-concussion-like symptoms are not specific for patients with TBI, and PCS is not a unique syndrome after TBI. Post-concussion-like symptoms are highly correlated with EQ-5D dimensions. This suggests that post-concussion-like symptoms are debilitating and that also in the healthy population these symptoms have a major effect on HRQoL.

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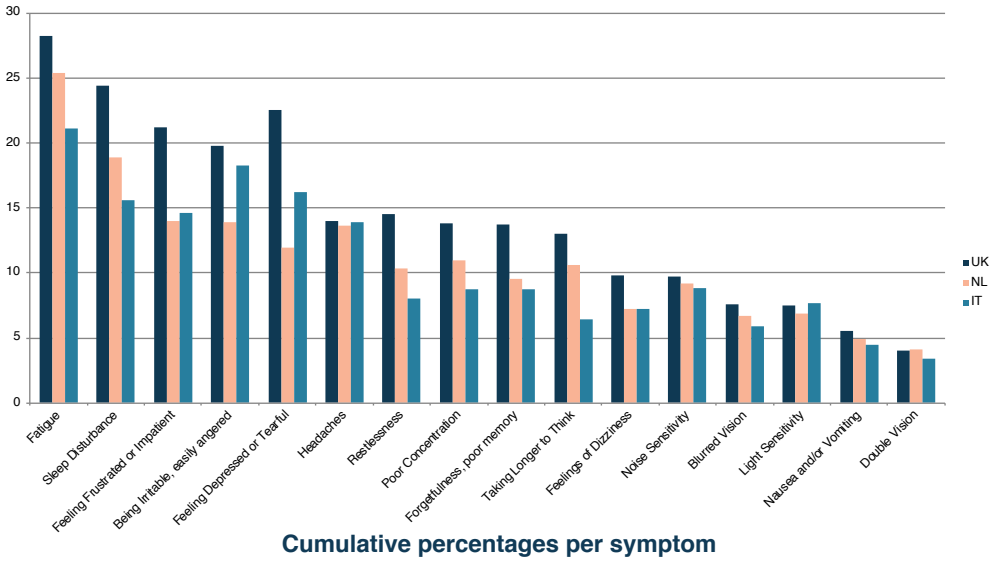
Appendix

Appendix A. Frequency of post-concussion symptoms with a severity rating of 3* or higher per country



Appendix B. Significant predictors in a multivariable model of PCS using two cut-offs

Post-Concussion Syndrome	**Rating Score 2***		**Rating score 3****	
Predictor	*OR*	*95% CI*	*OR*	*95% CI*
Age	0.98	0.98 - 0.98	0.98	0.97 - 0.98
Gender (male)	0.58	0.53 - 0.64	0.664	0.59 - 0.75
Education (high)				
Low	1.34	1.18 - 1.53	1.306	1.11 - 1.54
Middle	1.25	1.12 - 1.40	1.085	0.94 - 1.26
Work status (unable to work)				
Employed	0.49	0.40 - 0.60	0.417	0.35 - 0.50
Unemployed	0.67	0.54 - 0.83	0.553	0.45 - 0.68
Carer	0.54	0.41 - 0.70	0.44	0.33 - 0.58
Student	0.36	0.27 - 0.48	0.275	0.20 - 0.38
Retired	0.39	0.32 - 0.49	0.333	0.26 - 0.43
Income level (low) [1]	1.34	1.22 - 1.47	1.267	1.12 - 1.44
Have you experienced serious illness in				
you yourself (yes)	1.78	1.60 - 1.99	2.13	1.88 - 2.41
in your immediate family (yes)	1.15	1.04 - 1.27	1.234	1.09 - 1.40
in caring for others (yes)	1.31	1.17 - 1.46	1.35	1.18 - 1.53
Chronic health complaints (yes)	3.67	3.33 - 4.04	3.94	3.41 - 4.55
N	9900			9900
Nagelkerke R^2	0.26			0.24

[1] *Income was categorised in low (UK; less than £28.000, Italy and the Netherlands; less than €20.000 and high (UK; £28.000 and more, Italy and the Netherlands; €20.000 and more).*

Two different rating scores were used as cut-off: rating score 2 (* ≥ mild) and rating score 3 (≥ moderate)*

Abbreviations. PCS, Post-Concussion Syndrome.

Chapter 7

Persistent Post-Concussive Symptoms and Health Related Quality of Life in Children and Adolescents with Mild Traumatic Brain Injury Requiring Initial Head Computed Tomography

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Alexander Younsi

Submitted

Abstract

Objective: To evaluate the prevalence of post-concussive symptoms and their relation to health-related quality of life (HRQoL) in pediatric and adolescent patients with mild traumatic brain injury (mTBI) and that received head computed tomography (CT) imaging during initial assessment.

Methods: Patients aged between 5-21 years with mTBI (GCS 13-15) and available Rivermead Post-Concussion Questionnaire (RPQ) at six months followup in the multi-center, prospectively collected CENTER-TBI study were included. Prevalence of post-concussive symptoms was assessed and the occurrence of post-concussive syndrome (PSC) based on the ICD-10 criteria, was analyzed. HRQoL was compared in patients with and without PCS using the Quality of Life after Brain Injury (QOLIBRI) questionnaire.

Results: A total of 196 adolescent or pediatric mTBI patients requiring head CT imaging were included. High-energy trauma was prevalent in more than half of cases, abnormalities on head CT scans were detected in 44% and admission to the regular ward or intensive care unit was necessary in 78%. Six months post-injury, 36% of included patients had experienced at least one moderate or severe symptom of the RPQ. PCS was present in 13% of adolescents and children when considering symptoms of at least moderate severity and those patients had significantly lower QOLIBRI total scores, indicating lower HRQoL, compared to young patients without PCS.

Conclusions: Adolescent and pediatric mTBI patients requiring head CT imaging show signs of increased trauma severity. Post-concussive symptoms are present in up to one third of those patients and PCS can be diagnosed in 13% six months after the injury. Moreover, PCS is significantly associated with decreased HRQoL.

Introduction

Mild traumatic brain injury (mTBI) is a common injury in children and adolescents that frequently leads to clinical presentation. An epidemiological study including children from 0-17 years requiring medical contact reported an estimated incidence of 304 cases per 100.000 child-years.[1] Ninety-seven percent of included patients in that study were classified as mTBI,[1] which is defined according to the American Congress of Rehabilitation Medicine (ACRM) by a Glasgow Coma Scale (GCS) of 13-15, a maximum loss of consciousness (LOC) of 30 minutes and post-traumatic amnesia (PTA) less than 24 hours after the brain impact.[2, 3] Acute post-concussive symptoms after mTBI can be severe and might include somatic symptoms such as headaches, cognitive symptoms such as difficulty concentrating, and affective symptoms such as irritability. In a considerable fraction of patients, symptoms can chronically persist for weeks, months, or even years.[4] The prevalence of prolonged post-concussive symptoms in young patients varies depending on the diagnostic criteria used and the population studied, but has been reported to be as high as 31%.[5] Although the knowledge about such post-concussive symptoms in the pediatric and adolescent population has considerably increased over the past years and now includes insights from large, multi-center studies,[5, 6] there remains an important subgroup of patients that has not been studied in detail: Young mTBI patients requiring a head computed tomography (CT) during initial assessment following the brain injury. While the majority of adolescents and children do not receive CT imaging after mTBI in order to avoid radiation exposure, it might be nevertheless indicated when e.g. a history of high-energy injury mechanisms, suspicious clinical findings, or other risk factors are present. In such patients, a more severe subtype of mTBI might therefore be present. Mild TBI in general can already have profound negative impacts on the lives of affected adolescents and children.[7] Moreover, young patients experiencing a combination of persistent post-concussive symptoms of somatic, cognitive and affective nature can be diagnosed with post-concussion syndrome (PCS), a diagnosis encoded in the ICD-10.[8] Between 11% and 55% of adolescents and children have been reported to develop PCS following mTBI.[9] In those patients, the persistent post-concussive symptoms can have serious consequences and could significantly decrease their overall health-related quality of life (HRQoL).[10] The objectives of this study, therefore, were to examine the prevalence of such persistent post-concussive symptoms, to analyze the occurrence of PCS and to assess its association with HRQoL in the potentially more complicated subgroup of adolescent and pediatric patients who were classified as mTBI but who required head CT imaging after presenting to the emergency department (ED).

Methods

Study design and patient selection

For the present study, data from the Collaborative European NeuroTrauma Effectiveness Research in TBI (CENTER-TBI) core study was analyzed. CENTER-TBI is a multi-center, observational, longitudinal cohort study of patients with a clinical diagnosis of TBI (all severities) and, notably, the indication for head CT imaging (defined at the discretion of each study center), who presented to a participating study center within 24 hours after the injury. Patients for the CENTER-TBI core study were enrolled from December 2014 to December 2017 in 59 centers across Europe and Israel.[11, 12] The study protocol was approved by national and local ethics committees for each recruiting site and informed consent was obtained by the legal representative or next of kin for all enrolled patients. For this analysis, we included all pediatric and adolescent patients between the age of 5 and 21 years from the CENTER-TBI core study database that presented with mTBI (Glasgow Coma Scale [GCS] 13-15) and had completed the Rivermead Post-Concussion Questionnaire (RPQ) at six months post-injury.

Data collection

Data was accessed through the clinical study data management tool Neurobot (INCF-Neurobot, RRID:SCR_017004). The CENTER Core version 2.1 was used for this study. The variables age, sex, GCS at admission, presence of any intracranial abnormality on initial CT brain imaging (CT abnormalities), post-traumatic amnesia (PTA), loss of consciousness (LOS), major extracranial injury, admission to the intensive care unit (ICU), high-energy trauma as well as RPQ and Quality of Life after Brain Injury (QOLIBRI) scores at six months were collected. Major extracranial injury was defined as an abbreviated injury scale (AIS) of at least 3 in any body region. High-energy trauma was defined as an accelerating/decelerating trauma of high velocity or falls > 1m.

Outcome measurements

Rivermead Post-Concussion Questionnaire

The RPQ was used to assess the presence and severity of post-concussive symptoms following mTBI.[13] This assessment instrument evaluates 16 different symptoms that can be divided into three categories: somatic symptoms (headaches, blurred vision, double vision, noise sensitivity, light sensitivity, dizziness, nausea, sleep disturbances, fatigue), affective symptoms (irritability, depression, frustration, restlessness), and cognitive symptoms (forgetfulness, poor concentration, slowed thinking). Patients rate the severity of each symptom on a 5-point Likert scale (not experienced at all (0), no more of a problem (1), a mild problem (2), a moderate problem (3), a severe problem (4)). Patients were specifically instructed to rate the severity of their symptoms over the last 7 days in comparison to the pre-injury levels, thus giving the instrument a time and an event anchor.[14] For the analysis, scores 0 and 1 were comprised into one category as proposed in previous works,[13, 15, 16] yielding a 4-point scale ranging from currently absent symptoms (0), mild

symptoms (2), moderate symptoms (3) to severe symptoms (4). The total RPQ score was calculated by adding the scores of each RPQ symptom to a sum with a maximum total score of 64. Presence of PCS was defined according to ICD-10 criteria, which meant that patients had to experience at least three of the following symptoms: headaches, dizziness, sleep disturbance, fatigue, being irritable/easily angered, forgetfulness/poor memory, and poor concentration.[8] As there is currently no consensus on whether to include only symptoms of at least moderate severity (rating score ≥3) or even of mild severity (rating score ≥2) when assessing patients for PCS, the prevalence of PCS was analyzed for both definitions in this study.

Health-related Quality of Life (HRQoL)
To assess HRQoL, the QOLIBRI questionnaire was used, which consists of 37 items covering six aspects of disease-specific HRQoL after TBI (cognition, self, daily life & autonomy, social relationships, emotions, and physical problems).[17] The QOLIBRI instrument is a health-related, disease specific and internationally validated instrument to assess HRQoL in patients following brain injury.[17, 18] The responses to each questionnaire item were summed to the QOLIBRI total score ranging from 0, meaning worst, to 100, meaning best possible HRQoL (https://qolibrinet.com/scoring/). A QOLIBRI total score of 60 or greater represents good HRQoL; a score below 60 indicates an unsatisfactory outcome with an increased risk for one or even two psychiatric disorders.[18]

Statistical analysis
Baseline demographical and clinical variables are presented as median and interquartile ranges (IQR) for continuous variables and numbers and percentages for categorical variables. Correlation between total RPQ scores and QOLIBRI total scores were tested with Spearman's rank sum test. Differences in QOLIBRI total scores between patients with and without PCS were tested using the non-parametric Mann-Whitney U test. The level of significance was set at $p < 0.05$. All analyses were conducted with the statistical software R (version 3.6.1).[19]

Results

Patient characteristics

Among recruited CENTER-TBI core study participants, 324 mTBI patients were between the age of 5 and 21 at the time of enrollment of which 196 patients (60%) completed the RPQ at six months after the brain impact and were included in this study (Figure 1). Those patients were enrolled at 32 different centers across Europe and by definition of the CENTER-TBI core study inclusion criteria had received a head CT scan during initial assessment in the ED. The median age was 17 years (IQR: 14-19; range: 6-21) and 72% of included patients were males. A GCS score of 15 was recorded for 144 patients (73%). LOC and PTA were very common in this cohort with 52% and 58% of patients, respectively. A total of 54% of patients were involved in a high-energy trauma, and 19% additionally suffered from major extracranial injuries with an AIS ≥ 3. Finally, CT abnormalities were detected in 44% of patients on brain CT imaging. Of all patients, 22% were discharged home from the ED, while 49% and 29% were admitted to the regular ward or intensive care unit, respectively (Table 1).

Figure 1. Flowchart of patient selection

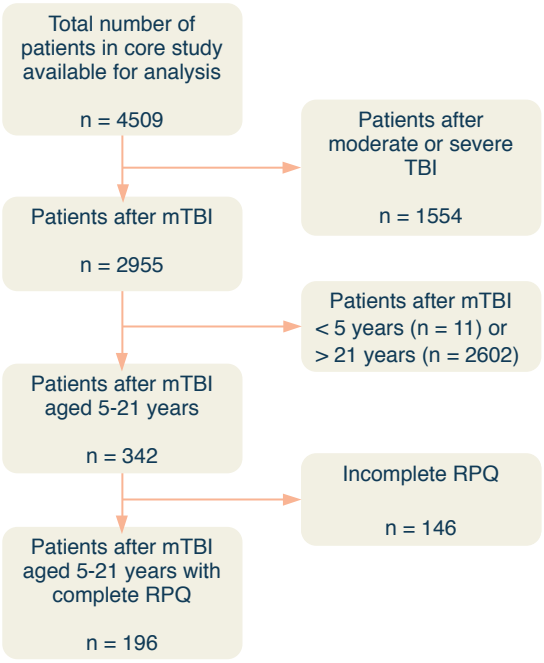


Table 1. Characteristics of the study population

Characteristic	n=196
Demographic characteristics	
Age[1] (years)	17 [14-19]
Sex (male)	142 (72%)
Stratum	
ER	44 (22%)
Admission	96 (49%)
ICU	56 (29%)
Trauma energy	
High-energy trauma	106 (54%)
Pre-injury health status	
Previous history of headaches	10 (5%)
Previous psychiatric history	8 (4%)
Previous TBI	24 (13%)
Clinical presentation	
GCS = 15	144 (73%)
PTA	102 (52%)
LOC	114 (58%)
Major extracranial injury	37 (19%)
CT characteristics	
CT abnormalities	80 (44%)
Influence of alcohol and drugs	
Blood alcohol >80 mg/dL	6 (3%)
Drug abuse	5 (3%)

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

Abbreviations. ER, Emergency room; ICU, Intensive Care Unit; TBI, traumatic brain injury; GCS, Glasgow Coma Scale; PTA, post-traumatic amnesia; LOC, loss of consciousness; CT, computed tomography.

Prevalence of post-concussive symptoms and occurrence PCS

Prevalence of mild, moderate or severe post-concussive symptoms were assessed at six months after mTBI in our adolescent and pediatric patient cohort (Figure 2). More than one third of patients (36%) reported having at least one of the 16 symptoms assessed in the RPQ with at least moderate severity. When including symptoms of mild severity, this number exceeded 60% (Figure 3). The most commonly reported symptoms were headaches, fatigue, poor concentration, and forgetfulness, i.e. poor memory. At least one of the nine somatic symptoms of at least moderate severity were reported by 30% of patients, while 20% had at least one of the three cognitive and four psychological symptoms. Those numbers increased to 54% for any somatic symptom, 40% for any cognitive symptom, and 37% for any psychological symptom when including also mild symptoms. Among patients reporting post-concussive symptoms at six months, the median number of moderate or worse symptoms was 2 (IQR: 2-4) and 5 (2-7) for mild or worse symptoms. By our definition requiring at least three moderate RPQ symptoms on the basis of ICD-10 criteria, 26 patients (13%) were classified as having PCS six months after the injury. Notably, this number substantially increased to 34% when applying the definition that at least three symptoms of at least mild severity were required.

Figure 2. Prevalence of mild, moderate or severe post-concussive symptoms

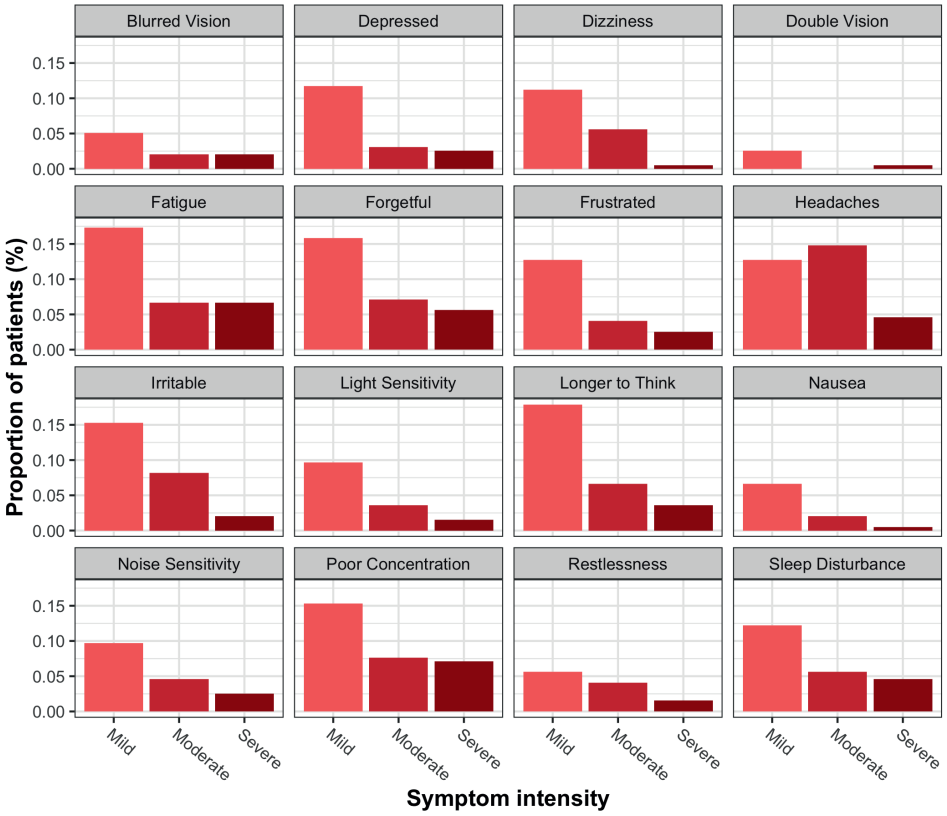
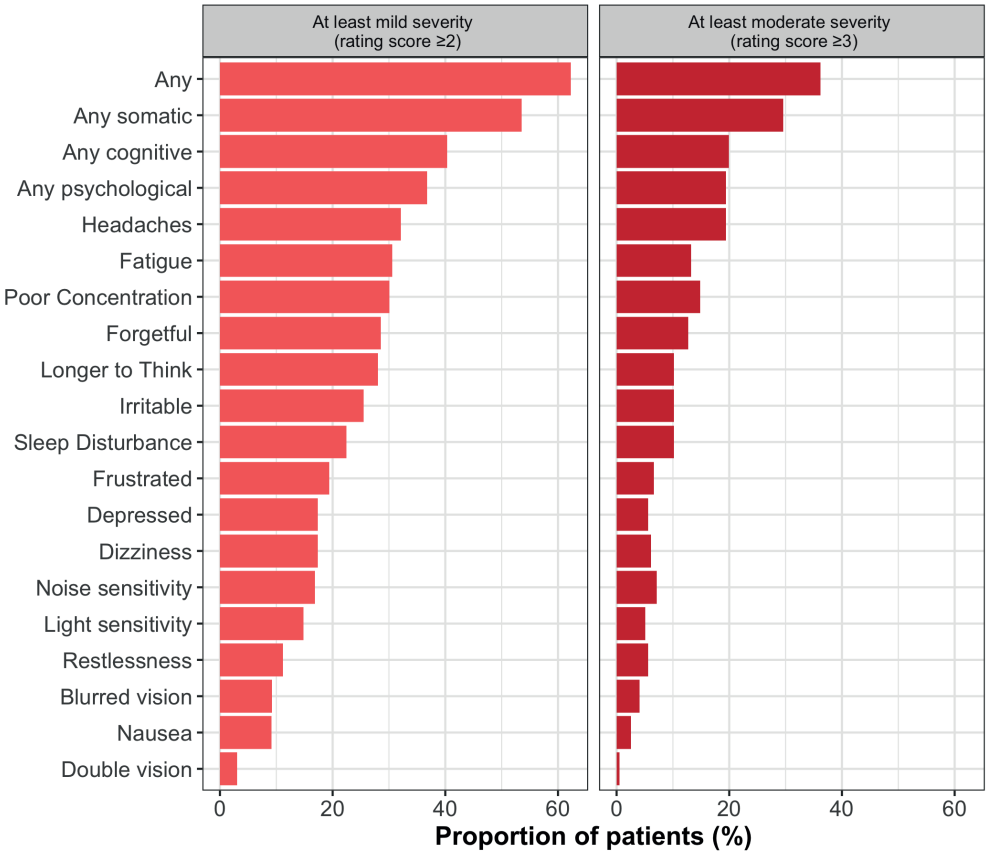


Figure 3. Symptoms assessed in the RPQ with at least mild or moderate severity



PCS and quality of life

A total of 172 patients (88%) included in this study completed a QOLIBRI assessment at six months follow-up. The median QOLIBRI total score was 82 (IQR: 68-91), representing good quality of life. In 67 patients (34%) with PCS considering at least mild severity, the median QOLIBRI total score was 66 (IQR: 53-76). Of those, 23 patients (34%) had a QOLIBRI total score < 60, representing unsatisfactory HRQoL. Patients without PCS following this classification (n=129, 66%) reported a median QOLIBRI total score of 86 (IQR: 79-94) which was significantly higher compared to the patients with PCS considering at least mild severity (p<0.001). As opposed to patients with PCS, only 4 patients (3%) without PCS had a QOLIBRI rating <60. When applying the definition of at least three symptoms of moderate severity, similar results were obtained: Patients classified as suffering from PCS (n=26) had a median QOLIBRI total score of 57 (IQR: 49-72) and 14 of those 26 patients (54%) reported a QOLIBRI total score < 60. Patients without PCS following this classification (n=170, 87%) showed a median QOLIBRI total score of 83 (IQR: 73-92) which was significantly higher compared to the patients with PCS) in patients without PCS,

displaying a significant difference between these two groups (p<0.001). Only 13 patients (8%) without PCS reported a QOLIBRI total score < 60. For both severity cut-offs, this means that patients with PCS have lower HRQoL compared to patients without PCS. Moreover, total RPQ scores and QOLIBRI total scores showed a significant, moderately strong negative correlation (r=-0.62, p<0,001).

Discussion

Mild Traumatic brain injury represents one of the most common injuries in the young population but only a small minority of patients will receive CT scans in an effort to avoid potentially harmful radiation in this particular patient population. The analysis of patient characteristics in our cohort showed that adolescents and children who require CT imaging indeed form a more severe and complex subgroup of mTBI patients. More than half of the patients in this study were involved in high-energy trauma and abnormalities on CT imaging were detected in 44%. Nearly 30% of patients were primarily admitted to the ICU in this cohort which is notable because the TBI was at presentation classified as mild in all patients. This might reflect the higher injury severity in this particular group of patients and possible explanations for the high ICU admission rate despite mTBI include the high prevalence of concurrent extracranial injuries. While previous reports of post-concussive symptoms focused on young mTBI patients in general and thus included only a small portion of patients who received head CT scans (and/or excluded them altogether when detecting abnormalities on CT imaging), with head CT imaging as an inclusion criterion, the CENTER-TBI study offers the unique possibility to analyze this particular subgroup of adolescents and children as a separate entity.

For young mTBI patients who require head CT-imaging during initial post-injury assessment, we report high prevalence numbers of post-concussive symptoms: One third of patients reported at least one symptom of at least moderate severity six months after brain injury. Thirteen percent of patients met the criteria for our more demanding definition of PCS that considered only at least moderate symptoms, which falls well into the range of results from previous studies that included pediatric mTBI patients in general.[4, 20, 21] Especially somatic symptoms were very common in our study (30% of children and adolescents) and this number increased to more than 50% when including also mild symptoms. Naturally, when including mild symptoms, the results are likely to be less specific and more susceptible to confounding influences, as mild somatic symptoms such as mild headaches and fatigue are also common in non-injured individuals.[22-24] The high prevalence of symptoms of moderate and severe severity in adolescents and children with mTBI and an indication for head CT imaging, however, emphasizes the presumption that mTBI in this subgroup might not be so “mild” after all but can have serious long-term sequelae.
In our study, adolescent and pediatric patients with PCS had significantly lower

QOLIBRI total scores indicating lower or even unsatisfactory HRQoL compared to young patients without PCS. Those findings are in line with results from previous studies showing that HRQoL is influenced across several domains (physical, emotional, social, school etc.) in patients with PCS.[10] In addition, the reported significant correlation between the RPQ and QOLIBRI total scores in our study illustrates the close association between post-concussive symptoms and HRQoL, and therefore demonstrates the clinical importance of recognizing post-concussive symptoms in this particular subgroup of adolescents and children who obtained CT imaging after mTBI. While there are some preliminary promising therapeutic approaches such as brief cognitive therapy and other medical and non-medical interventions that could be effective and beneficial in children and adolescents with persistent post-concussive symptoms,[25, 26] further high-quality studies are needed to closer investigate the possible impact and efficacy of these interventions. [25]

We note several limitations to our study. First of all, while CENTER-TBI included patients of all ages, pediatric and adolescent patients were underrepresented as participating centers were mainly general hospitals and not specialized pediatric centers. Therefore, the sample size is relatively small when compared to the older patient cohort in the CENTER-TBI study.

Furthermore, a non-response bias limiting external validity is possible as a considerable proportion of patients were lost to follow-up (40%). Results from our study also need to be interpreted with caution when considering the assessment tool used. The RPQ was initially validated in adolescents and adults aged equal or above 16 years.[13] It has been suggested to remain a basic common data element in TBI research as it correlates with cognitive impairment,[13, 14, 27] although it remains a controversial assessment tool that might, amongst other concerns, be prone to recall bias as patients might underestimate post-concussive-like symptoms they experienced before the injury. Lastly, the use and utility of simple change scores for diagnosis of post-concussive symptoms in children have recently been questioned.[28] Therefore, the results from this study should merely be seen as an exploratory analysis. However, our results support the fact that further studies designed to acquire a better understanding of post-concussive symptoms are needed, as those symptoms might be highly prevalent in mTBI patients and directly affect patients' HRQoL.

In conclusion, this analysis of the multi-center, prospectively collected CENTER-TBI dataset, we found a high prevalence of 30 to 60% of post-concussive symptoms at six months post-injury in adolescents and children with mTBI who received CT imaging upon presentation to the hospital. Depending on the definition, 13-34% were classified as experiencing a PCS. Those patients had a significantly decreased HRQoL compared to patients without PCS.

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Chapter 8

Rating of Pre-Injury Symptoms over Time in Patients with Mild Traumatic Brain Injury: the Good-Old-Days Bias Revisited

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Abstract

Objective: Post-concussion syndrome (PCS) occurs following mild traumatic brain injury (mTBI). Patients with mTBI are often assessed using self-report instruments that rely on perception of current symptoms compared to how they felt and functioned pre-injury. The objective was to examine reliability of patients' post-injury reporting of their pre-injury symptoms.

Methods: We included two control groups (trauma patients without brain injury history and healthy controls) who were recruited at an outpatient surgical clinic and among the working and social environment of the researchers, respectively. The Head Injury Symptom Checklist (HISC) was used to assess pre-injury and current symptoms at four time points post injury. We included 836 patients with mTBIs, 191 trauma patients without brain injury history, and 100 healthy controls.

Results: Patients with mTBI reported significantly more pre-injury symptoms than both control groups ($p<.001$). Forty-five percent of patients with mTBI were inconsistent in their pre-injury ratings across four assessments. Patients with post-injury PCS reported much greater pre-injury symptoms and were more often inconsistent.

Conclusion: Accurately assessing PCS by comparing pre with post-injury complaints is difficult, and may have implications for diagnosis when using self-report instruments. Therefore, post-injury PCS diagnosis should be interpreted with caution and PCS should ideally be examined using clinical examination.

Introduction

Traumatic brain injury (TBI) is a leading cause of death and disability worldwide and half of the world's population will experience one or more TBIs over their lifetime.[1] The large majority of TBIs (70-90%) can be classified as mild (mTBI),[1] which is often indicated by a Glasgow Coma Scale (GCS) score between 13 and 15 at admission to the emergency department. Most patients report complete symptom resolution following mTBI;[2, 3] however, a subset of patients report post-concussion symptoms, which can be defined as somatic, cognitive, and emotional symptoms that may last for months or even years.[4-6] When three or more post-concussion symptom categories are present, a patient can be diagnosed with 'postconcussional syndrome' (PCS) according to the definition by the International Classification of Diseases (ICD)-10.[7] The diagnosis of PCS is highly controversial because symptoms do not always cluster in a consistent and predictable manner.[8] In addition, post-concussion symptoms, such as fatigue, concentration difficulties, and headaches, are not specific to TBI and are also reported among trauma patients without brain injury history [9-11] and healthy adults.[12, 13] The method of assessment of post-concussion symptoms and PCS, such as using a clinical interview versus a self-reported questionnaire, is another topic of controversy.[14, 15] Nevertheless, post-concussion symptoms are generally examined with self-report questionnaires.

The use of self-report may have several limitations in a mTBI population, because symptom endorsement on self-report questionnaires might be influenced by expectation bias; i.e. following mTBI, patients may expect that they will experience some post-concussion symptoms and may therefore be more likely to endorse these symptoms.[16] Additionally, it might be difficult to make a distinction between the two, considering PCS could also be a part of or a result from emotional distress, which commonly occurs in the aftermath of TBI.[10, 17, 18] Furthermore, some self-report instruments (e.g., the Rivermead post-concussion questionnaire (RPQ) [19]) investigate a comparison of current symptoms with symptoms experienced before injury. The reliability and validity of pre-injury symptom ratings might be complicated because patients may not remember symptoms that occurred months earlier in an accurate manner.[20] Moreover, following a negative event, patients may have the tendency to underestimate past problems and to view oneself as healthier in the past, which is referred to as the 'good-old-days' bias.[21] Previous studies examined the occurrence of the 'good-old-days bias' in patients with mTBI. [20-24] They consistently found that patients with mTBI remembered their pre-injury functioning as better compared to healthy controls. As a consequence of this cognitive bias, patients may misattribute the experience of common symptoms to the mTBI, and thereby increase the possibility of an incorrect PCS diagnosis[25]. These previous studies assessing the reliability and validity of pre-injury symptom ratings are, however, limited by small sample sizes[20, 23, 24] and the use of non-representative patient groups.[21, 22] In addition, previous studies assessed the pre-injury symptom-level only once or twice,[24] whereas repeated measurements may provide further insight into the test-retest reliability of pre-injury ratings.

Especially since test-retest reliability was noted as less than optimal for most common and emerging concussion assessment tools.[26, 27]

This study aimed to assess the reliability and validity of post-injury ratings of symptoms compared with pre-injury symptoms in a large and representative sample of patients with mTBI at several time points during the first year following injury. Additionally, these ratings of patients with mTBI were compared to both trauma patients without brain injury history and healthy controls. We specifically tested the three hypotheses, based on previous research and clinical experience, listed below.

1. Both patients with mTBI and trauma patients without brain injury history will underestimate their pre-injury symptom level (i.e., 'good-old-days bias') by reporting fewer symptoms than healthy controls.

2. The consistency (i.e., test-retest reliability[28]) of ratings of pre-injury symptoms at different time points will be low in patients with mTBI.

3. Patients with mTBI who have post-injury PCS will be more likely to underestimate their pre-injury symptoms and will be less consistent in their ratings compared to patients with mTBI without post-injury PCS.

Methods

Study population

Data from patients with mTBI were obtained from the prospective UPFRONT study, which collected baseline, clinical, and outcome data across three level I trauma centers in the Netherlands between 2013 and 2015.[29] Patients were included if they presented to the emergency department of one of the participating centers with an admission GCS score of 13-15.

Trauma patients without brain injury history were recruited at the outpatient surgical clinic of the University Medical Center Groningen between June and October 2013. Patients were included if they sustained minor injury to one of the extremities, for which they had visited the emergency department. Patients were excluded if they completed the questionnaire more than six months (> 185 days) after the injury.

Healthy controls were recruited among the working and social environment of the investigators involved with the UPFRONT study. They were included if they were at least 16 years old and they had sufficient comprehension of the Dutch language. Patients were excluded if they were addicted to drugs or alcohol, homeless, or diagnosed with dementia. The study was approved by the medical ethics committee of the University Medical Center in Groningen and all participants provided written informed consent. For more information on the UPFRONT study or the study population, see previous publications.[18, 29, 30]

Assessment of post-concussion symptoms and PCS

Post-concussion symptoms and PCS were assessed using the Head Injury Symptom Checklist (HISC).[18] The HISC consists of 21 frequently reported symptoms after a TBI, which can be rated on a 3-point scale (never, sometimes, often). Eight symptoms from the ICD-10 are included in the checklist: headache, dizziness, fatigue, irritability, sleep problems, concentration problems, memory problems, and intolerance of alcohol or stress. Stress intolerance is not a symptom included in the HISC, so for this we used the more anxious symptom. For each patient, we recorded the total number of ICD-10 symptoms endorsed as 'sometimes' or 'often'. In addition, we classified patients as having PCS if they indicated that at least three out of eight symptoms were experienced 'sometimes' or 'often'. Because it has not been established whether symptoms should be included if they are endorsed as 'sometimes' or only when they are endorsed as 'often',[31] we also estimated prevalence rates of post-concussion symptoms and PCS including only those symptoms that were endorsed as 'often'. For this study, we defined screening positively for ICD-10 PCS as endorsing any 3 of the 8 symptoms.

For patients with mTBI, the HISC was administered two weeks, three months, six months, and twelve months following injury. At each time period, patients were asked to rate both their current and pre-injury symptoms. The trauma patients without brain injury history completed the HISC once for both their current and pre-

injury symptoms at approximately three weeks post injury. The healthy controls completed the HISC twice with a two-week interval and were asked to rate their current symptoms.

Statistical analyses

Baseline characteristics of patients with mTBI, trauma patients without brain injury history, and healthy controls were reported by frequencies and percentages, or medians and interquartile range for continuous variables. At each time point, we presented the number and percentage of participants who endorsed post-concussion symptoms and screened positively for the ICD-10 diagnosis of PCS, on both their retrospective pre-injury and current symptom ratings. Analyses were performed using SPSS statistics version 24.0.

Hypothesis 1: Both patients with mTBI and trauma patients without brain injury history will underestimate their pre-injury symptom level (i.e., show the 'good-old-days bias') by reporting fewer post-concussion symptoms than healthy controls.
We used a chi-square test to compare the number of patients with three or more pre-injury post-concussion symptoms among patients with mTBI, trauma patients without brain injury history, and healthy controls. Non-parametric Kruskall-Wallis tests were used to compare the total number of ICD-10 symptoms across groups. For the patients with mTBI, we used the two-week assessment because this was most comparable to the assessment of the trauma patients without brain injury history (3 weeks). For the healthy controls we used their first rating (random selection). Post-hoc tests were performed to assess which of the three groups differed statistically significantly. A p-value of 0.02 (0.05/3) was considered statistically significant in the post-hoc analyses.

Hypothesis 2: The consistency (i.e., test-retest reliability) of pre-injury ratings will be low in patients with mTBI.
We performed chi-square tests to compare the number of patients with three or more pre-injury post-concussion-like symptoms across all four time points (2 weeks, 3 months, 6 months, and 12 months) in patients with mTBI. Because this comprises six related comparisons, a p-value of 0.008 (0.05/6) was considered statistically significant. Spearman's correlation was used to compare the total number of ICD-10 symptoms across four time points. A correlation <0.5 can be interpreted as a weak correlation, a correlation 0.5-0.7 as a moderate correlation, and a correlation >0.7 as a high correlation. In addition, we calculated the number and percentage of patients with mTBI who consistently reported three or more symptoms over all four time points. Inconsistency was defined as reporting three or more symptoms on one or more of the pre-injury ratings but not on the preceding questionnaires. Multivariable logistic regression analysis was used to explore whether baseline characteristics and pre-injury comorbidities were predictive of inconsistency.

Hypothesis 3: Patients with mTBI who have post-injury PCS will be more likely to underestimate their pre-injury symptoms and will be less consistent in their ratings

compared to patients with mTBI without post-injury PCS.
We used the chi-square test to examine whether patients with and without PCS at six months differed on their pre-injury rating (also assessed at six months). The Mann-Whitney U test was used to examine whether the total number of pre-injury symptoms differed among patients with and without a diagnosis of PCS at six months post injury. Ratings at six months were chosen for this purpose because this is a common time point to evaluate persistent PCS. We additionally performed multivariable logistic regression analysis to adjust the effect of post-injury PCS diagnosis for age, sex, education, and pre-injury physical and psychological comorbidities. Patients were classified in the following four groups: persistent PCS (PCS present at two weeks and six months),[32] late-onset PCS (PCS not present at two weeks, but present at six months), resolved PCS (PCS present at two weeks, but not at six months), and no PCS (no PCS at both two weeks and six months). A chi-square test was performed to compare pre-injury ratings among these four groups.
To examine whether post-injury PCS was associated with inconsistency in pre-injury ratings, we used the chi-square test to check whether inconsistency (see hypothesis 2) was different for those with versus without PCS at six months. In addition, we also checked for differences between the four patient groups described above (no PCS, persistent PCS, late-onset PCS, and resolved PCS). Multivariable logistic regression analysis was performed to adjust the effect of post-injury PCS for age, sex, education, and pre-injury physical and psychological comorbidities.

Results

Study population

A total of 1,151 patients with mTBI were included in the UPFRONT study, of whom 836 completed either the retrospective pre-injury or the current rating of symptoms at two weeks post injury. Patients included in this study were older (46 years) than those who were not included (38 years). Patients' median age was 48 years (interquartile range (IQR): 27-62) and 61% were male. Patients were most often injured by a fall (n = 550, 66%) and the majority experienced loss of consciousness (n = 710, 85%) and/or posttraumatic amnesia (n = 682, 87%). A total of 509 patients (61%) were admitted to the hospital (Table 1).

The non-brain-injured trauma control group consisted of 206 patients, among whom 204 completed the HISC. Thirteen patients were excluded from the analyses because they completed the questionnaire more than six months (> 185 days) after the injury, which ultimately left 191 trauma patients without brain injury history. These patients had a median age of 35 years (IQR: 23-52) and 54.5% were male. Fall was the most common cause of injury (n = 92, 48.2%), and 35 patients (18.3%) were admitted to the hospital ward. The healthy control group consisted of 100 healthy volunteers, who all completed the HISC at two different time points. Healthy controls had a median age of 29 years (IQR: 24-48) and half of them were male. More than half of the healthy volunteers (n = 65, 65%) had a high education level (Table 1).

Post-concussion symptoms in mTBI and trauma patients without brain injury history during the first year post injury

Post-concussion symptoms were often endorsed among patients with mTBI during the first year post injury. Fatigue was the most commonly reported symptom at all time points (79% at 2 weeks, 66% at 3 months, 68% at 6 months, and 66% at 12 months). The majority of patients endorsed three or more out of eight post-concussion symptoms, and thereby fulfilled our criteria for the ICD-10 diagnosis of PCS (84% at 2 weeks, 72% at 2 months, 78% at 6 months, 75% at 12 months; Table 2). Among the trauma patients without brain injury history, 38% (n = 73) were classified as having PCS approximately three weeks post injury. The most often reported symptoms included sleep problems (n = 90, 47%) and fatigue (n = 84, 44%).

Including only those symptoms that were endorsed as 'often' rather than 'sometimes or often', resulted in substantially lower prevalence rates (median number of symptoms among patients with mTBI=1, median number of symptoms among trauma patients without brain injury history =0). Among the patients with mTBI, 22-32% fulfilled our criteria for ICD-10 PCS post injury, whereas only a minority of the trauma patients without brain injury history (6%) met the criteria (Table 2).

Table 1. Characteristics of the study sample.

	Patients with mTBI (n = 836)*	Trauma patients without brain injury history (n = 191)	Healthy controls (n = 100)
Age (median, interquartile range)	48 (27-62)	35 (23-52)	29 (24-48)
Male sex	512 (61%)	104 (54.5%)	50 (50%)
Education level		Not measured	6 (6%)
- Low	158 (19%)		29 (29%)
- Middle	329 (40%)		65 (65%)
- High	342 (41%)		
Pre-injury physical disorders ‡	257 (31%)	71 (37.2%)	*Not measured*
Pre-injury psychiatric disorders ⊥	94 (11%)	10 (5.2%)	*Not measured*
Cause of injury			NA
- Motor vehicle accident	193 (23%)	5 (2.6%)	
- Fall	550 (66%)	92 (48.2%)	
- Violence	40 (5%)	7 (3.7%)	
- Other	53 (6%)	87 (45.5%)	
Loss of Consciousness	710 (85%)	*Not present by definition*	NA
Post-Traumatic Amnesia	682 (82%)	*Not present by definition*	NA
Hospital admission	509 (61%)	35 (18.3%)	NA

‡ *Includes cerebrovascular accident, heart diseases, hypertension, diabetes, asthma or other respiratory diseases, epilepsy, or any malignant disorder.*
⊥ *Includes any psychiatric disorder necessitating treatment by a psychologist or psychiatrist or use of psychotropic medication, or both.*
**All patients with mild TBIs that have either a pre-injury or a current rating at 2 weeks post injury*

Abbreviations. mTBI, mild traumatic brain injury.

Table 2. Overview of pre-injury and current post-concussion symptoms for mild TBI patients, trauma patients without brain injury, and healthy controls at different time points.

			Post-concussion symptoms according to the ICD-10								Total number of PCS symptoms	Meeting the ICD-10 criteria for PCS**
	Time period	N	Headache %	Fatigue %	Concentration problems %	Memory problems %	Dizziness %	Sleep problems %	Irritability %	Intolerance to alcohol or more anxious %	Median [IQR]	%
mTBI pre-injury symptoms	2 weeks	819	32% (4%)*	39% (9%)	35% (7%)	35% (4%)	21% (2%)	41% (12%)	35% (3%)	36% (8%)	2 [1-4]	49% (5%)
	3 months	789	32% (2%)	34% (6%)	30% (4%)	32% (4%)	21% (1%)	40% (9%)	27% (2%)	28% (7%)	2 [1-4]	43% (3%)
	6 months	638	34% (3%)	40% (8%)	35% (4%)	38% (3%)	23% (2%)	41% (10%)	32% (3%)	35% (8%)	2 [1-4]	49% (4%)
	12 months	593	33% (4%)	37% (6%)	30% (4%)	33% (3%)	24% (2%)	38% (8%)	31% (2%)	31% (8%)	2 [1-4]	45% (4%)
mTBI current symptoms	2 weeks	806	69% (27%)	79% (43%)	67% (25%)	61% (18%)	69% (23%)	57% (25%)	46% (12%)	47% (15%)	5 [3-7]	84% (32%)
	3 months	770	53% (16%)	66% (28%)	54% (19%)	56% (18%)	52% (11%)	55% (21%)	43% (11%)	43% (14%)	4 [2-6]	72% (22%)
	6 months	628	55% (15%)	68% (30%)	63% (20%)	63% (20%)	51% (11%)	61% (25%)	51% (13%)	49% (16%)	5 [3-7]	78% (25%)
	12 months	586	52% (13%)	66% (31%)	58% (20%)	63% (21%)	51% (12%)	59% (23%)	48% (13%)	48% (15%)	5 [3-7]	75% (24%)
Trauma patients without brain injury history symptoms ‡	Pre-injury	191	25% (5%)	29% (8%)	18% (4%)	13% (3%)	12% (1%)	34% (8%)	22% (3%)	20% (8%)	1 [0-3]	28% (3%)
	Current	191	28% (4%)	44% (16%)	26% (6%)	14% (4%)	19% (2%)	47% (16%)	28% (4%)	23% (9%)	2 [0-4]	38% (6%)
Healthy controls	Time 1	100	23% (4%)	21% (6%)	19% (5%)	16% (1%)	12% (0%)	31% (8%)	17% (1%)	29% (8%)	2 [1-2]	24% (1%)
	Time 2	100	26% (4%)	29% (7%)	25% (4%)	20% (1%)	13% (0%)	36% (7%)	19% (2%)	27% (3%)	2 [1-3]	33% (1%)

*Number of patients who endorsed the symptom as 'sometimes' or 'often'; in parentheses are the number of patients who endorsed the symptom as 'often' .

**Number of patients who endorsed three out of eight post-concussion symptoms as 'sometimes' or 'often'.

‡ The questionnaire was completed by the trauma patients without brain injury history at approximately 3 weeks post-injury (IQR 1-7, range 0-51).

Note: a more red square means that a higher percentage of patients endorsed the symptom

Hypothesis 1: Both patients with mTBI and trauma patients without brain injury history will underestimate their pre-injury symptom level (i.e., 'good-old-days bias') by reporting fewer symptoms than healthy controls
Patients with mTBI reported more pre-injury symptoms and more often indicated having experienced three or more pre-injury symptoms compared to both trauma patients without brain injury history and healthy controls ($p < .001$). There were no statistically significant differences between trauma patients without brain injury history and healthy controls in the total number of ICD-10 symptoms ($p = 0.343$) or the number of patients experiencing three or more symptoms ($p = 0.322$).

Hypothesis 2: The consistency (i.e., test-retest reliability) of pre-injury ratings will be low in patients with mTBI
All four pre-injury ratings of post-concussion-like symptoms (2 weeks, 3 months, 6 months, and 12 months) differed significantly from each other (all $p < .001$; Table 3). As seen in Table 3, there were weak to moderate correlations between the total number of pre-injury symptoms across the four time points. A total of 444 patients completed all four pre-injury ratings. Among these patients, only half (n = 242, 55%) consistently reported three or more symptoms across all time points. The remaining 202 patients (45%) endorsed three or more pre-injury symptoms at some of the time points but not at other time points, and thus showed inconsistent pre-injury ratings. Inconsistency was not associated with demographic or pre-injury characteristics (Table 4).

Table 3. A comparison of pre-injury ratings of patients with mTBI among the four different time points.

Rating	3 months	6 months	12 months
2 weeks	Similar rating: 75% PCS at 2w, not at 3m: 16% PCS at 3m, not at 2w: 9% p < .001 r* = 0.66	Similar rating: 74% PCS at 2w, not at 6m: 12% PCS at 6m, not at 2w: 14% P < .001 r = 0.64	Similar rating: 71% PCS at 2w, not at 12m: 15% PCS at 12m, not at 2w: 14% P < .001 r = 0.49
3 months	-	Similar rating: 75% PCS at 3m, not at 6m: 9% PCS at 6m, not at 3m: 16% P < .001 r = 0.67	Similar rating: 75% PCS at 3m, not at 12m: 11% PCS at 12m, not at 3m: 14% P < .001 r = 0.54
6 months		-	Similar rating: 77% PCS at 6m, not at 12m: 14% PCS at 12m, not at 6m: 9% P < .001 r = 0.59

**r = the Spearman correlation between the number of ICD-10 symptoms across different time periods.*

Abbreviations. w, weeks; m, months.

Hypothesis 3: Patients with mTBI and post-injury PCS will be more likely to underestimate their pre-injury symptoms and be less accurate compared to patients with mTBI without post-injury PCS

Patients with PCS at six months reported substantially more pre-injury symptoms (median = 3, IQR = 2-5, mean = 3.3) compared to patients without PCS at six months (median = 1, IQR = 0-2, mean = 0.94, p< .001). Additionally, three or more pre-injury symptoms were also reported more often by patients with PCS at six months (62% vs. 3%, p < .001). Comparing patients with persistent PCS (PCS at both 2 weeks and 6 months), late-onset PCS (no PCS at 2 weeks, PCS at 6 months), resolved PCS (PCS at 2 weeks, no PCS at 6 months), and no PCS (no PCS at both 2 weeks and 6 months) also revealed statistically significant differences (p < .001). The percentage of patients that reported three or more pre-injury symptoms was highest among those with late onset PCS (65%) and those with persistent PCS (62%). Patients without PCS or those with resolved PCS both had very low percentages pre-injury symptoms (2% and 4%, respectively). In multivariable analyses, PCS at six months remained a strong predictor of reporting three or more pre-injury symptoms (Odds ratio (OR) = 43.2, 95% Confidence Interval (CI) 15.5 – 119.8). In addition, reporting three or more pre-injury symptoms was associated with older age (OR = 1.01, 95% CI 1.00 – 1.03) and pre-injury psychiatric disorders (OR = 4.05, 95%CI 1.89 – 8.67; Table 4).

Table 4. Exploratory analysis of factors associated with inconsistency of pre-injury ratings and reporting three or more pre-injury symptoms (measured at six months post injury) in patients with mild TBI.

Variable	Inconsistency of pre-injury ratings *OR (95% CI)*	Three or more pre-injury symptoms *OR (95% CI)*
PCS diagnosis at 6 months		**43.2 (15.5-119.8)**
Female sex	1.15 (0.78 – 1.70)	1.37 (0.92-2.05)
Age (per year)	1.01 (0.99 – 1.02)	**1.01 (1.00-1.03)**
Education		
Low	*Reference*	*Reference*
Middle	0.84 (0.48 – 1.45)	1.18 (0.68-2.07)
high	0.80 (0.46 – 1.39)	1.23 (0.70 – 2.17)
Pre-injury physical disorders‡	1.12 (0.70 – 1.80)	0.93 (0.60 – 1.60)
Pre-injury psychiatric disorders⸸	0.68 (0.35 – 1.32)	**4.05 (1.89-8.67)**

‡Includes cerebrovascular accident, heart diseases, hypertension, diabetes, asthma or other respiratory diseases, epilepsy, or any malignant disorder.
⸸Includes any psychiatric disorder necessitating treatment by a psychologist or psychiatrist, use of psychotropic medication, or both.
Note: OR, 95% CIs that do not cross 1 are bolded.

Abbreviations. OR, Odds ratio; 95% CI, 95% Confidence interval; PCS, post-concussion syndrome.

We also assessed whether PCS at six months was associated with inconsistency. patients with PCS at six months were more often inconsistent in their pre-injury assessment than patients without PCS (50% vs. 31%, p = .001). The association between PCS at six months and inconsistency remained statistically significant after correcting for sex, age, education, and pre-injury physical and psychiatric complaints (OR = 2.33, 95% CI 1.40 – 3.87). Comparing the four different groups revealed that patients with late-onset PCS were most often inconsistent (69%), followed by patients with persistent PCS (48%) and resolved PCS (45%). Patients without post-injury PCS had the lowest inconsistency (10%, p < .001).

Discussion

Post-concussion symptoms, and PCS, are usually conceptualized by the patient or health care provider by comparing current symptoms with how the person felt and functioned prior to the injury. This is done by having the person think back, and retrospectively conceptualize or rate, pre-injury symptoms. During this study, we investigated the reliability and validity of such retrospective ratings of pre-injury symptoms among a representative sample of patients with mTBI in the Netherlands, and we compared their ratings to those of trauma patients without brain injury history and healthy controls. The accuracy of pre-injury ratings is critically important, because some self-report instruments (e.g., the RPQ[19] and the HISC[18]) require patients to compare their current symptom level with their symptom level pre injury. When patients do not remember their pre-injury status accurately or demonstrate cognitive bias (e.g., the good-old-days bias), this may increase the possibility of an incorrect PCS diagnosis after injury. Interestingly, we did not find evidence for the good-old-days bias in our sample. In fact, we found almost the opposite—those people who endorsed the greatest number of symptoms at six months following their injury were also most likely to endorse greater symptoms before their injury. We found that approximately half of the patients with mTBI were inconsistent in their retrospective assessment of symptoms over different time periods following injury, and a post-injury diagnosis of PCS was strongly associated with inconsistency in retrospective ratings of pre-injury symptoms.

In this study, we included post-concussion symptoms and post-concussion-like symptoms endorsed as ‘sometimes’ or ‘often’, resulting in a very high prevalence in reporting a constellation of symptoms among all groups, both before and after injury. Nevertheless, prevalence rates were on the high end of the spectrum, particularly for studies in which compensation is not involved. However, they were in line with previous studies performed in patients with mTBI using the RPQ with the cut-off of ‘mild or worse’.[4, 6, 33, 34] It is open to question whether all patients identified or ‘diagnosed’ with PCS in these studies truly reflect a subgroup with clinically significant symptomatology. Possibilities to reduce the potential high rate of false-positives include the calculation of difference scores between pre- and post-injury assessment, which was performed in a previous investigation using the

UPFRONT data.[35] Another possibility might be to restrict analyses to symptoms endorsed as 'often' on the HISC or 'moderate or worse' on the RPQ. In this study, we found preliminary evidence that this cut-off may better discriminate between patients with mTBI and both control groups, and also between the pre- and post-injury assessments of patients with mTBI. The fact that the HISC was used in this study instead of the RPQ, which is the most applied questionnaire for both research and clinical purposes, should not be seen as a limitation, because we focused on certain symptoms that fit the diagnosis of PCS and did not look at the total number of symptoms, for which the RPQ is normally used.[19]

Based on previous research, we hypothesized that both patients with mTBI and trauma patients without brain injury history would report fewer pre-injury symptoms than healthy controls, congruent with the 'good-old-days' bias theory. In contrast, however, we found that patients with mTBI reported significantly more pre-injury symptoms than both control groups, whereas the trauma patients without brain injury history did not differ significantly from the healthy controls. Thus, we did not find evidence of the good-old-days bias in this large cohort of patients with mTBI. There might be several reasons for this. The patients with mTBI in the UPFRONT study were older in comparison to both control groups and one-third of the sample reported pre-existing physical comorbidities. Because post-concussion-like symptoms are non-specific, the endorsement of a large number of pre-injury symptoms in our sample might be the direct consequence of physical comorbidities, other age-related symptoms, or life stressors that were experienced pre injury. Notwithstanding, the age of the patients with mTBI in our sample (median age = 48 years) was comparable to the age of the patients with mTBI included in the study by Iverson et al.[21] (mean age = 41.5 years). Iverson and colleagues[21] report, however, that only 20% of the patients with mTBI endorsed three or more pre-injury symptoms as 'mild or worse', while we found a percentage of 43-49%. A major difference between the two cohorts is that we included a sample of patients with mTBI who presented to the emergency department of level I trauma centers, whereas Iverson et al.[21] included injured workers who received compensation benefits. Such a population might be more vulnerable to a true good-old-days bias[20] or might distort or misrepresent their pre-injury symptoms and functioning in relation to their compensation claim.

Another reason for the significant difference between the pre-injury ratings of the patients with mTBI and the healthy controls is that the healthy controls in this study might not be representative of the general population. They are relatively young and highly educated, and therefore, they may have endorsed fewer symptoms. Previous research in healthy adults or trauma patients without brain injury history showed higher rates of post-concussion symptoms,[10, 21] comparable to those found in our sample of patients with mTBI.

Similar to the study by Silverberg et al.,[20] we found that patients with post-injury PCS reported substantially more pre-injury symptoms compared to those without post-injury PCS. Pre-injury symptom ratings among patients with PCS were also substantially higher than reported in the general population.[21] The endorsement of pre-injury symptoms was also associated with older age and pre-injury psychiatric

disorders. Because post-concussion-like symptoms are non-specific,[10] it is likely that pre-existing mental health problems or age-related complaints have influenced both the pre-injury and current symptom ratings in this group.

In this study, we also assessed the consistency of pre-injury ratings over time. In concordance with our hypothesis, we found that approximately half of the patients with mTBI inconsistently reported their pre-injury symptom level during the first year following injury. Our results are in line with the study by Yang et al.[24] who studied pre-injury ratings at both one and three months post injury. They found a trend towards an increase in pre-injury symptoms reported at three months compared to one-month following injury. Inconsistency of pre-injury ratings might be influenced by the fact that memories have to be reconstructed and might be influenced by subjective beliefs and perception. Some people may have simply forgotten whether they experienced certain symptoms in the past or they may have reframed them.[36] Inconsistency was especially apparent for patients with post-injury PCS; even those with resolved PCS (i.e., PCS at 2 weeks but not at 6 months) had a higher rate of inconsistency than those who never fulfilled the criteria for PCS post injury. It is possible that patients with post-injury PCS are dealing with recall bias, which means that they have difficulties remembering when the symptoms first occurred (i.e., did the symptoms start pre injury or post injury?). In addition, some of the post-concussion symptoms themselves (e.g., fatigue, concentration problems, memory problems) may directly influence the ability to accurately complete a self-report questionnaire and thereby may have influenced the consistency of the pre-injury assessment. It is possible that some people in this study who reported the greatest symptoms at six months following injury are more likely to conceptualize those symptoms as longstanding and due to factors separate from their mTBI.

Strengths of our study include the large number of patients with mTBI and the representativeness of the study sample. In addition, pre-injury symptoms were assessed at four different time points and ratings were compared to both trauma patients without brain injury history and healthy controls. Therefore, the current study represents the most up to date and comprehensive study in assessing the reliability of pre-injury symptom reporting among patients with mTBI. The main limitation of our study was that the healthy control group was not comparable to both patient groups. Therefore, the relatively low number of symptoms reported might be the direct consequence of the younger age and the higher education level in this group. Healthy controls were recruited via the personal and occupational network of the investigators of the UPFRONT study, which could have introduced bias. An alternative approach might be to include 'friend controls', a method that is currently used by the TRACK-TBI study.[37] A second limitation concerns the number of patients that were lost to follow-up during the 12-month period. A total of 806 patients completed the two-week assessment, whereas 586 were still involved at 12 months. All pre-injury ratings were completed by 444 patients. Although attrition is common in mTBI studies,[4, 6, 38] it might have resulted in selection bias that could have influenced our study results; i.e. if patients with post-injury PCS are more likely to participate in the follow-up assessment and these patients are less

consistent in their pre-injury assessment, it is possible that the large percentage of inconsistent ratings in our study is in fact an overestimation. Additionally, the confidence interval for PCS diagnosis at six months as a predictor of three or more pre-injury symptoms was wide. Lastly, the RPQ is the most often used questionnaire to assess PCS and is recommended in the common data elements[39]. However, in this study we used the HISC, which could make the results of this study more difficult to compare with previous literature although it was possible to delineate patients with PCS based on the available symptoms.

Our study reveals the difficulty in accurately obtaining pre-injury ratings of symptoms among patients with mTBI. More than half of the patients inconsistently reported their pre-injury functioning over time. Patients with post-injury PCS had strikingly high ratings of pre-injury symptoms and were also more likely to report symptoms inconsistently over time. This has implications for the accuracy of self-report measurements designed to assess post-concussion symptoms and PCS in patients with mTBI. When patients are not able to accurately recall their pre-injury status, the validity of their perceived post-injury status could also be doubted. Another problem is that the overlap with psychiatric disorders is not captured in a self-report questionnaire. Patients with pre-injury PCS more often had psychiatric premorbidity and this premorbidity also showed a strong association with post-injury PCS. Therefore, some of the post-injury PCS diagnoses might actually be the consequence of pre-existing psychiatric problems rather than the sustained mTBI. For clinical purposes, we recommend assessing post-concussion symptoms in a more comprehensive way by using a semi-structured or structured interview. In such an interview, a clinician may investigate the frequency and severity of symptoms and whether these symptoms influence functioning and quality of life. A clinician may also examine when the symptom first occurred and whether there is overlap with psychological factors such as emotional distress. For research purposes, however, such an approach might not be feasible.

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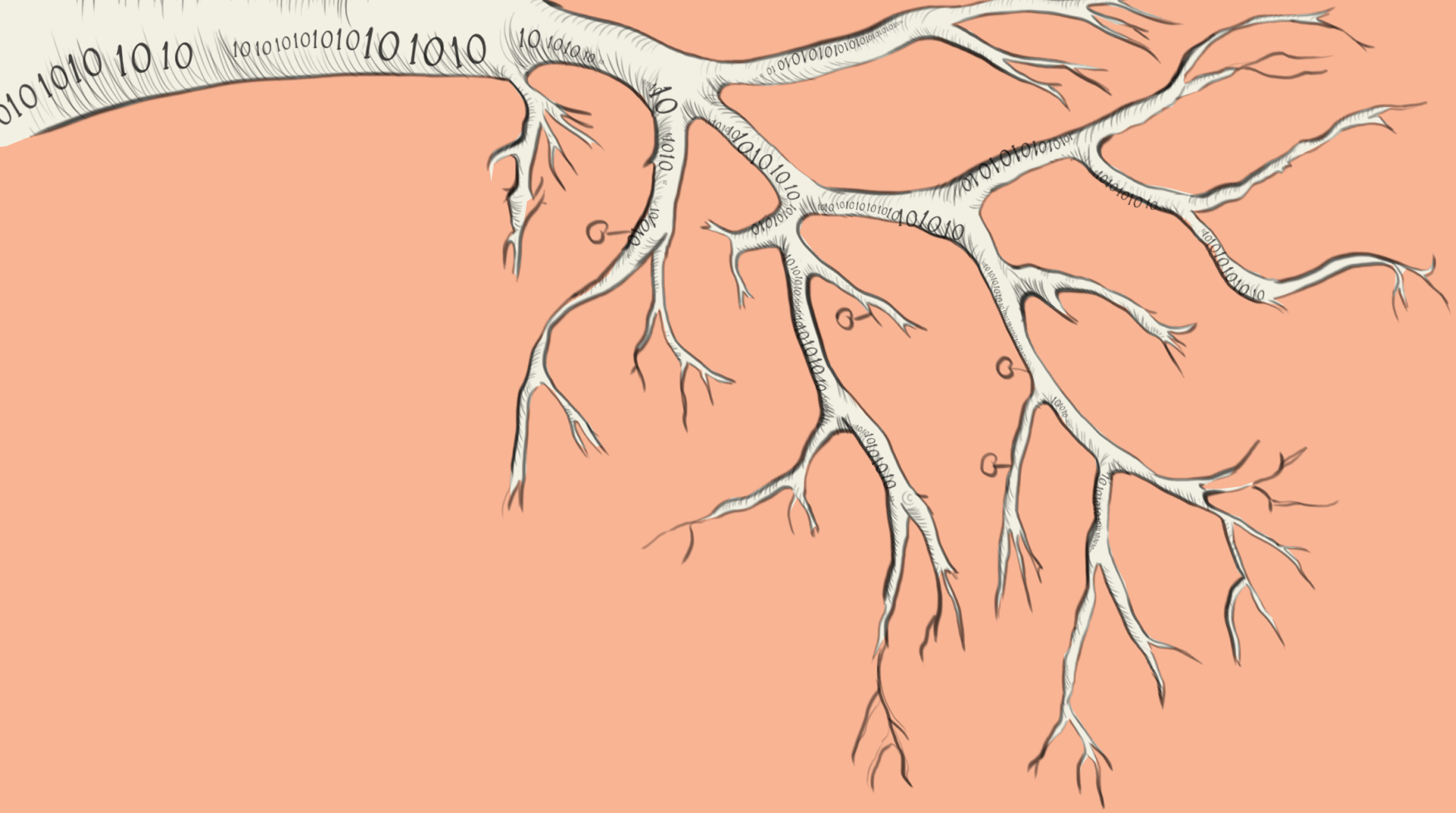

PART II

PREFERENCES FOR OUTCOME IN TRAUMATIC BRAIN INJURY

Chapter 9

Health-Related Quality of Life after Traumatic Brain Injury: Deriving Value Sets for the QOLIBRI-OS for Italy, The Netherlands and The United Kingdom

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Abstract

Purpose: The Quality of Life after Brain Injury overall scale (QOLIBRI-OS) measures health-related quality of life (HRQoL) after traumatic brain injury (TBI). The aim of this study was to derive value sets for the QOLIBRI-OS in three European countries, which will allow calculation of utility scores for TBI health states.

Methods: A QOLIBRI-OS value set was derived by using discrete choice experiments (DCEs) and visual analogue scales (VAS) in general population samples from the Netherlands, United Kingdom and Italy. A three stage procedure was used: (1) A selection of health states, covering the entire spectrum of severity, was defined; (2) General population samples performed the health state valuation task using a web-based survey with three VAS questions and an at random selection of sixteen DCEs; (3) DCEs were analysed using a conditional logistic regression and were then anchored on the VAS data. Utility scores for QOLIBRI-OS health states were generated resulting in estimates for all potential health states.

Results: The questionnaire was completed by 13,623 respondents. The biggest weight increase for all attributes is seen from "slightly" to "not at all satisfied", resulting in the largest impact on HRQoL. "Not at all satisfied with how brain is working" should receive the greatest weight in utility calculations in all three countries.

Conclusion: By transforming the QOLIBRI-OS into utility scores we enabled the application in economic evaluations, and in summary measures of population health, which may be used to inform decision-makers on the best interventions and strategies for TBI patients.

Introduction

Traumatic Brain Injury (TBI) is generally defined as “an alteration in brain function or other evidence of brain pathology, caused by an external force”.[1] TBI is one of the leading causes of death and disability worldwide.[2] Annually, TBI costs approximately $US 400 billion worldwide and imposes a massive burden on society.[3] Economic evaluations in health care interventions are increasingly being used to inform governments, healthcare funders and policy makers and to prioritize resource allocation.[4] Nonetheless, for economic evaluations, preference-based measures (PBMs) are a requirement[5] and values have to be assigned to the health states these measures describe.[6] Many popular PBMs are generic. However, generic instruments do not always adequately assess specific aspects of health-related quality of life (HRQoL) that are affected by a disease, such as for example cognition.[7] Therefore, generic measures, such as the EuroQol-5D (EQ-5D) and Short Form-36 (SF-36), are often combined with condition-specific questionnaires. A TBI-specific instrument is the Quality of Life after Brain Injury overall scale (QOLIBRI-OS).[8] The QOLIBRI-OS instrument is a disease-specific tool for assessing HRQoL after sustaining TBI, which covers areas that are typically affected by TBI.[9] It was developed in 2012 and since then has been widely applied in TBI[8]. By generating a condition-specific preference based measure (CSPBM) for TBI, it will potentially provide a more accurate assessment of the impact of heterogeneous outcomes after TBI and a more sensitive measure of the benefit of interventions.

The QOLIBRI-OS is a non-preference-based instrument that yields ordinal data, and therefore has limitations for economic evaluation studies. Transforming QOLIBRI-OS into utility scores will enable the application in economic evaluations, and in summary measures of population health (e.g. quality-adjusted life years (QALYs)). Furthermore, a value set for the QOLIBRI-OS will introduce the ability to summarize general population preferences for health states that could be experienced by TBI patients and the HRQoL of TBI patients can be compared with other (patient) groups.

To be able to use health state values in QALYs calculations,[10] they have to be anchored on a scale from 0 (dead) to 1 (full health). A less than 0 value is given to health states which are reported to be worse than dead. Ultimately, a value set can be generated, which means that each item level of the QOLIBRI-OS has a weight (utility) assigned to it. A lower utility means a higher impact on HRQoL. Each QOLIBRI-OS health state can be converted into a single summary index value with a value set.

Value sets for generic instruments (e.g. EQ-5D and Health Utility Index 2 (HUI2))[11] are widely available and are being used extensively in economic evaluations.[12] However, the QOLIRBI-OS currently does not have utilities, which means the instrument cannot be used for QALY calculations.[13] To make the QOLIBRI-OS suitable for use in economic evaluations, the health states need to be valued with a preference-elicitation method. Widely used methods are discrete choice experiments (DCE)[14, 15] and visual analogue scales (VAS).[16] The DCE and

VAS technique are used to quantify health outcomes.[17-21] DCEs are based on stated preferences and are seen to be a simpler method than the conventional methods such as time trade off (TTO) and standard gamble (SG).[22] The DCE approach makes it possible to predict values for alternatives in hypothetical situations or conditions that cannot be judged in the real world.[23] The VAS is a valuation technique that records participants' views about hypothetical health states on a scale from 0 (worst imaginable health state) to 100 (best imaginable health state).[16]

The objective of this study was to develop health utility indices for the QOLIBRI-OS health states. In order to do this we aimed to develop value sets for the QOLIBRI-OS in three European countries by the use of a web-based DCE and VAS valuation study, which will allow calculation of utility values for the health states measured with the QOLIBRI-OS.

Methods

The QOLIBRI-OS is a short, six-item version of the Quality of Life after Brain Injury (QOLIBRI), which provides a profile of HRQoL in domains typically affected by brain injury. It addresses wellbeing and functioning and the psychometric properties have been determined satisfactory to good.[8] The QOLIBRI-OS assesses a single overall score, which provides a brief summary measure of HRQoL.[8] The six items are satisfaction with physical condition; how brain is working, in terms of concentration, memory and thinking; feelings and emotions; ability to carry out day to day activities; personal and social life; current situation and future prospects. Responses are on a 5-point Likert scale ranging from "not at all satisfied" to "very satisfied". Ultimately, the current situation and future prospects item from the QOLIBRI-OS was excluded because a general sample might answer this item too subjectively, which may hamper the use of the QOLIBRI-OS value set in populations other than TBI patients. By use of Rasch analysis, the psychometric validity of the QOLIBIR-OS scale was tested and well-functioning items of the QOLIBRI-OS were identified, which ultimately resulted in measures of item difficulty and fit of the QOLIBRI-OS. The scale was examined for redundancy and removing the current situation and future prospects item did not change the properties of the scale (Appendix A). In the end, the QOLIBRI-OS scale included 5 items, each with 5 levels, which are shown in Table 1.

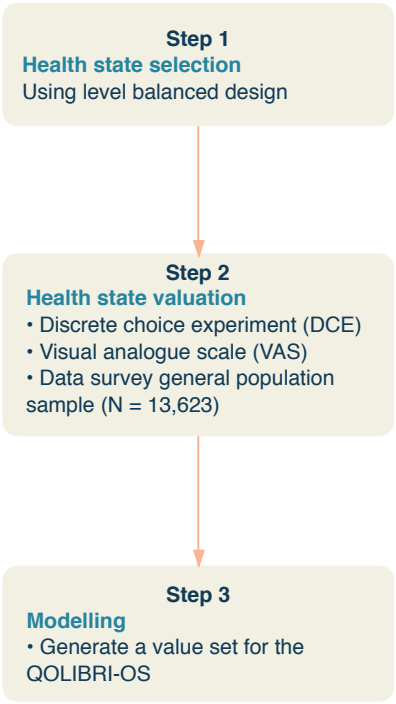
Developing value sets for the QOLIBRI-OS required three methodological steps (Figure 1). Each of these steps is described in more detail in the following sections.

Table 1. Five selected items of QOLIBRI-OS[$]

QOLIBRI-OS
1. Satisfied with physical condition
2. Satisfied with how brain is working, in terms of concentration, memory and thinking
3. Satisfied with feelings and emotions
4. Satisfied with ability to carry out day to day activities
5. Satisfied with personal and social life

[$] *Item levels: 1-Not at all; 2-Slightly; 3-Moderately; 4-Quite; 5-Very*

Figure 1. Steps taken to yield a QOLIBRI-OS value set which enables calculation of utility weights for the health states measured with this instrument.



Step-by-step

Step 1: Health state selection

Even after reducing the items from the QOLIBRI-OS from 6 to 5, the selected items can generate a large number of possible health states. The 5-item QOLIBRI-OS can generate 3125 (55) possible health states, since each dimension has five levels, and this makes it impossible to ask the respondents for a valuation all of them. [13] We therefore made a selection of health states to be used in the health state valuation task. For the DCE valuation of the QOLIBRI-OS, 392 health states were selected, which were presented in 196 pairs, based on a method devised by Oppe and van Hout.[24] These health states cover the spectrum of severity. For this we used a level-balanced design,[13] meaning that all levels of each item occurred with the same frequency. The same 392 states were used in the EuroQol EQ-5D-5L value set valuation study.[24-26] The best and worst health states plus death were selected for the visual analogue scale (VAS) valuation.

Step 2: Health state valuation – study design

During this step a panel of judges evaluated the selected health states. The general population was asked to evaluate the possible QOLIBRI-OS health states by assuming what they would consider their quality of life to be, if they were in one of these specific health states. The responses from the general population sample were used to generate the health state values.

Health state valuation – survey

The web-based questionnaire included questions regarding the demographics of the respondent (e.g. age, sex, educational and income level, chronic health complaints), sixteen DCE questions and three VAS questions. The DCE pairs were randomly assigned to the participants. During this study, no DCE or VAS data was excluded. The survey and description of health states were translated from English into Dutch and Italian using translation software and subsequently translated back into English. Bilingual native speakers verified the translations independently. The panel of judges consisted of members of the general public aged 18 to 75 years from the United Kingdom (UK), Italy and the Netherlands, which provided an international spread. The samples were also representative of the population in the countries with regard to age, gender and education. A total number of 13,623 respondents filled out the questionnaire (Italy: 5,270 respondents; Netherlands 4,183 respondents; UK 4,170 respondents). The questionnaires were distributed by a market research agency (Survey Sampling International (SSI), nowadays called Dynata) via internet during the period June 29th till July 31st 2017. A second round of data collection took place between February 3rd and February 16th 2018 to collect some more responses for the VAS data, especially for the health state 'dead', and these were all respondents who had already completed the survey the first round (recontacts).

Valuation techniques

The responses from the general population sample reflect preferences between different health states[10] and these were used to generate and model the value sets.

One of the methods used to evaluate the health states was a DCE,[27-29] which is an ordinal measurement method. With this method, a pair of health states (labelled A and B, Figure 2), with no reference to the duration of the states, is presented, and respondents have to decide which health state they consider to be better. No indifference option was included. The assumption of a DCE is that the choices among sets of divergent health states are driven by differences in the levels of the dimensions from the QOLIBRI-OS which define the health states. Furthermore, by asking respondents to choose between health states with altering severity levels and different combinations, the opportunity arises to estimate the impact of the preferences based on the changes in levels.[30] We used colours in the online survey to indicate the severity level of the attribute, ranging from green indicating very satisfied to red indicating not at all satisfied.

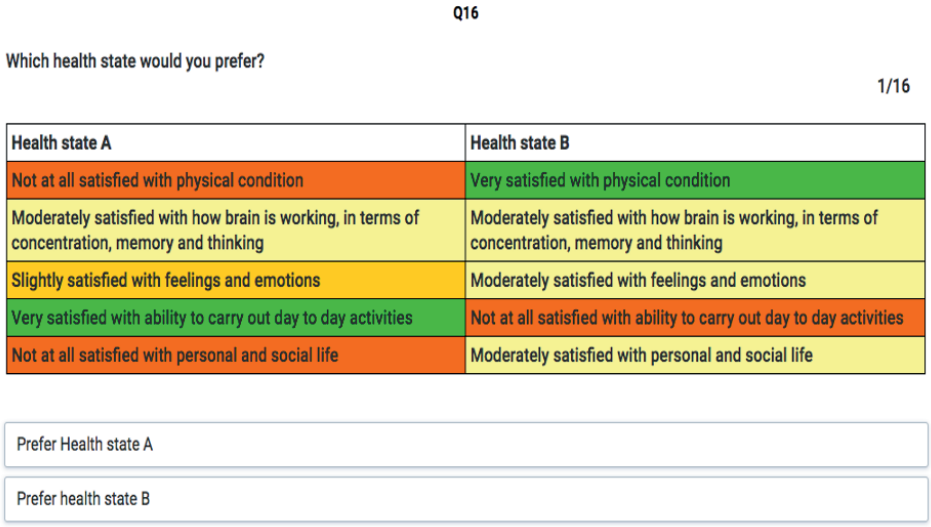
The second method used was the VAS, which is a valuation technique that requires participants to score the injury stage on a vertical scale graded from 0 (worst

imaginable health state) to 100 (best imaginable health state). As done previously by Stolk et al.,[23] a rescaled VAS, based on dead and the best and worst health states. was developed; health preference valuations of 0 to 100 on the VAS were rescaled from 0 to 1. This was done by the use of the following formula:

$$VAS\ rescaled = 100 \times \frac{VAS\ mean - VAS\ dead}{VAS\ 11111 - VAS\ dead}$$

It was necessary to rescale the VAS values in such a way that the value for death was explicitly set at 0 and the best health state (11111) to 1.[23]

Figure 2. Example of a QOLIBRI-OS DCE question



Step 3. Modelling the DCE health state valuations

Statistical modelling was used to estimate the values for all potential health states according to the responses for the selected health states. The coefficients for each level and attribute were estimated by regression techniques. Whether a level has a positive or negative effect on utility depends on the sign of the coefficient. The relative importance of the level is revealed by the value of the coefficient. A level is considered to be important when the coefficient has been determined to be statistically significant ($p<0.05$).[31] Afterwards, the values for all the health states described by the QOLIBRI-OS were generated from these coefficients.[32] A utility score for the QOLIBRI-OS health states is generated from the DCE responses anchored on the VAS. DCE responses were defined as binary outcomes.

As described by Feng et al.,[32] a 20 parameter model (4 levels x 5 dimensions = 20 parameters) was generated for the QOLIBRI-OS, which estimated four parameters for each dimension and one parameter per level, with the "very satisfied" level used as the reference. This model allowed for the coefficients to differ between dimensions,

and for the importance of each level of problems to differ between dimensions.[32] Regression models were estimated for the DCE in all three countries separately. DCE answers were analysed using a conditional logistic regression. Subsequently, we derived health state values from the DCE data on the QALY scale by anchoring the values on the estimated VAS value for the worst state (55555). The following formula was used for this process:

$$\beta_{anchored\ DCE\ model} = \frac{\beta_{20\ parameter\ DCE\ model} \times estimated\ VAS_{worst\ state}}{estimated\ DCE_{worst\ state}}$$

Where $\beta_{20\ parameter\ DCE\ model}$ is the coefficient from the conditional logistic regression DCE model, *estimated* $VAS_{worst\ state}$ is the pooled mean value given to the worst health state by all respondents, *estimated* $DCE_{worst\ state}$ is the intercept and all "not at all" level coefficients from the DCE model summed up, which generates a $\beta_{anchored20\ parameter\ DCE\ model}$ for each attribute and level as output. The utilities are based on and have been calculated by the use of these anchored DCE coefficients.

In addition, we implemented a generalized additive logistic regression using the bamlss package of R[33, 34] to relax the assumption of the standard logistic regression on the linear relationship between the predictors and the log-odds of the outcome. We compared the non-parametric model specifying an additive (but otherwise unknown) utility function to the standard model assuming linear utility.

Statistical analysis

For the statistical analyses, responses on the QOLIBRI-OS were recoded with 1 reflecting "very satisfied" and 5 reflecting "not at all satisfied" (similar to the convention used for the EQ-5D). Therefore 11111 was seen as the 'best health state' and 55555 as the 'worst health state'.

Rasch analysis was performed using Winsteps 3.92 (Winsteps.com, Chicago Illinois, USA).

All other analyses were performed using SPSS version 24 for Windows (IBM SPSS Statistics, SPSS Inc, Chicago, IL) and R (R Core Team (2013). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria).

Results

Study population

The characteristics of the survey respondents are shown in Table 2. A total of 13,623 respondents divided over three countries completed the questionnaire. The median age of the respondents was 45 years old. Approximately half of the respondents (51.2%; N=6981) were employed and 15% (N=2068) were retired. One out of two respondents have experienced serious illness in their immediate family and/or reported to have chronic health complaints.

DCE data

An upward trend was shown in probability of respondents choosing health state A when the difference in sum score of health state A and B (e.g. probability of choosing health state 11111; sum score = 5 over health state 12345; sum score = 15) becomes bigger and more positive, which is what was expected (Appendix B).

VAS data

Table 3 shows the summary statistics for the three VAS health states considering the QOLIBRI-OS data. The lowest mean value was 38.01 (health state dead) and highest mean value was 81.49 (health state 11111 e.g. very satisfied with every attribute). As expected, when the summary score of the of the health state decreased (e.g. severity of health state becomes lower), which means the health state was comprised of lower attribute levels, the utility mean increased.

Value sets

Table 4 shows the 20 parameters model per country for the QOLIBRI-OS which was based on the conditional logistic regression for the DCE data and the anchoring of the DCE coefficients. For all respondents and both the Netherlands and Italy, the lowest estimate for the DCE and anchored DCE data was found for 'Quite satisfied with feelings and emotions' and the highest estimate for 'Not at all satisfied with how brain is working in terms of concentration, memory and thinking.' When looking at the model specifically for the UK, the lowest estimate was found for 'Moderately satisfied with personal and social life' and the highest for 'Not at all satisfied with how brain is working in terms of concentration, memory and thinking'. The biggest increase in weight for all attributes is seen from level four (slightly satisfied) to level five (not at all satisfied). Table 5 introduces an example for the QOLIBRI-OS value set based on the DCE and anchored DCE models. This enables the calculation of a utility weight per health state, which is how the utilities for the QOLIBIR-OS data can be obtained. The utility scores of the anchored DCE model of the QOLIBRI-OS range from 0.383 for health state 55555 to 1.0 for health state 11111. Table 6 shows an example of values for a mild, moderate and severe health state. Generally speaking, Italians value these health states lower compared to their counterparts in UK and the Netherlands. Appendix C shows the non-parametric models per country for the QOLIBRI-OS and Appendix D shows an example of values for a mild, moderate and severe health state based on the non-parametric models.

Table 2. Characteristics of the study population

	All respondents	UK	The Netherlands	Italy
	(N=13623)	(N=5270)	(N=4183)	(N=4170)
	N (%)	*N (%)*	*N (%)*	*N (%)*
Age[1] (years)	45 [33-57]	44 [32-57]	46 [33-58]	45 [34-57]
Gender (male)	6736 (49.4%)	2597 (49.3%)	2069 (49.5%)	2070 (49.6%)
Education[2]				
Low	3797 (27.9%)	1205 (22.9%)	1232 (29.5%)	1360 (32.6%)
Middle	6499 (47.7%)	2265 (43.0%)	1901 (45.4%)	2333 (55.9%)
High	3327 (24.4%)	1800 (34.2%)	1050 (25.1%)	477 (11.4%)
Work status[3]				
Employed	6981 (51.2%)	2759 (52.4%)	2214 (52.9%)	2008 (48.2%)
Unemployed	1915 (14.1%)	475 (9.0%)	447 (10.7%)	993 (23.8%)
Looking after others[4]	699 (5.1%)	358 (6.8%)	177 (4.2%)	164 (3.9%)
Student	849 (6.2%)	294 (5.6%)	270 (6.5%)	285 (6.8%)
Retired	2068 (15.2%)	855 (16.2%)	545 (13.0%)	668 (16.0%)
Unable to work	1111 (8.2%)	529 (10.0%)	530 (12.7%)	52 (1.2%)
Annual household income[5]				
Low	3131 (23.0%)	1126 (21.4%)	759 (18.1%)	1247 (29.9%)
Middle	3315 (24.3%)	1604 (30.4%)	728 (17.4%)	983 (23.6%)
High	5076 (37.3%)	1994 (37.8%)	1787 (42.7%)	1295 (31.1%)
Do not know/do not want to tell	2100 (15.4%)	546 (10.4%)	909 (21.7%)	645 (15.5%)
Experience of serious illness				
In you yourself (yes)	3517 (25.8%)	1834 (34.8%)	1068 (25.5%)	615 (14.7%)
In your immediate family (yes)	7066 (51.9%)	3231 (61.3%)	2864 (68.5%)	971 (23.3%)
In caring for others (yes)	3224 (23.7%)	1689 (32.0%)	924 (22.1%)	611 (14.7%)
Chronic health complaints (yes)[6]	6896 (50.6%)	2778 (52.7%)	2223 (53.1%)	1895 (45.4%)

[1] *Data are displayed as median, with the first and third quartile given within brackets.*
[2] *Education was divided up in low (junior school), middle (comprehensive school) and high (college and university).*
[3] *Work status was categorized as employed (employee and self-employed), unemployed (consisting out of work for more than and less than 1 year), looking after others (e.g. a carer or parent), a student, retired and unable to work.*
[4] *E.g. carer or parent.*
[5] *Income was grouped as follows low (UK; less than £14,000, Italy and the Netherlands; less than €20,000), middle (UK; £14,000-£27,999, Italy and the Netherlands; €20,000-€39,999) and high (UK; more than £27,999, Italy and the Netherlands; more than €39,999).*
[6] *Chronic health complaints were defined as: asthma, chronic bronchitis, severe heart disease, consequences of a stroke, diabetes, severe back complaints, arthrosis, rheumatism, cancer, memory problems due to neurological disease/dementia, memory problems due to ageing, depression or anxiety disorder, and other chronic health complaints.*

Table 3. QOLIBRI-OS summary statistics for the 3 selected VAS health states

Health state	Observations (N)	Mean VAS	SD	Rescaled mean	Utility mean
dead	116	38.01	40.71	0	0
55555*	138	54.64	33.56	38.26	0.38
11111**	245	81.49	22.15	100	1

** worst possible health state; all attributes have 'not at all satisfied' level*
*** best possible health state; all attributes have 'very satisfied' level*

Table 5. QOLIBRI-OS example: the value for health state 21232

	DCE	Anchored DCE
Full health (constant/intercept)	1	1
Minus constant	0	0
Quite satisfied with physical condition	0.143	0.015
Very satisfied with how brain is working, in terms of concentration, memory and thinking	0	0
Quite satisfied with feelings and emotions	0.05	0.005
Moderately satisfied with ability to carry out day to day activities	0.306	0.031
Quite satisfied with personal and social life	0.109	0.011
Utility weight health state 21232	0.392	0.938

[1]*Calculation of utilities: utility = 1 - value*

Note: all respondents

Table 6. Example of values for a mild, moderate and severe health state

	Anchored DCE			
	All respondents	UK	The Netherlands	Italy
Best health state: 11111	1	1	1	1
Mild health state: 21232	0.902	0.94	0.955	0.918
Moderate health state: 34343	0.631	0.853	0.799	0.801
Severe health state: 55455	0.449	0.465	0.472	0.396
Worst health state: 55555	0.383	0.383	0.383	0.383

Abbreviations. DCE, Discrete Choice Experiment

Table 4. QOLIBRI-OS 20 parameters model per country

	All respondents			UK			The Netherlands			Italy		
	DCE-data		Anchored DCE	DCE-data		Anchored DCE	DCE-data		Anchored DCE	DCE-data		Anchored DCE
	Estimate	*SE*	*Estimate*[1]	*Estimate*	*SE*	*Estimate*[1]	*Estimate*	*SE*	*Estimate*[1]	*Estimate*	*SE*	*Estimate*[1]
Physical condition												
Quite	0.143	0.028***	0.015	0.171	0.048***	0.017	0.093	0.047*	0.01	0.158	0.051**	0.016
Moderately	0.313	0.028***	0.032	0.345	0.048***	0.035	0.311	0.047***	0.032	0.269	0.050***	0.028
Slightly	0.522	0.028***	0.053	0.5	0.049***	0.051	0.488	0.049***	0.05	0.568	0.051***	0.058
Not at all	1.306	0.031***	0.134	1.339	0.053***	0.137	1.08	0.053***	0.11	1.54	0.057***	0.157
How brain is working, in terms of concentration, memory and thinking												
Quite	0.2	0.027***	0.02	0.25	0.046***	0.026	0.105	0.047*	0.011	0.24	0.048***	0.025
Moderately	0.464	0.028***	0.047	0.426	0.047***	0.044	0.433	0.049***	0.044	0.542	0.051***	0.055
Slightly	0.663	0.025***	0.068	0.64	0.044***	0.065	0.609	0.043***	0.062	0.746	0.046***	0.076
Not at all	1.68	0.030***	0.172	1.688	0.052***	0.173	1.369	0.050***	0.14	2.033	0.054***	0.208
Feelings and emotions												
Quite	0.05	0.028 .	0.005	0.071	0.047	0.007	-0.013	0.048	-0.001	0.11	0.050*	0.011
Moderately	0.218	0.027***	0.022	0.159	0.046***	0.016	0.211	0.047***	0.022	0.328	0.050***	0.034
Slightly	0.29	0.026***	0.03	0.207	0.045***	0.021	0.416	0.045***	0.043	0.264	0.046***	0.027
Not at all	0.938	0.029***	0.096	0.967	0.049***	0.099	0.922	0.049***	0.094	0.969	0.052***	0.099
Ability to carry out day to day activities												
Quite	0.159	0.028***	0.016	0.136	0.049**	0.014	0.111	0.049*	0.011	0.232	0.051***	0.024
Moderately	0.306	0.028***	0.031	0.263	0.049***	0.027	0.259	0.047***	0.026	0.408	0.051***	0.042

Slightly	0.347	0.029***	0.035	0.268	0.050***	0.027	0.45	0.049***	0.046	0.356	0.052***	0.036
Not at all	1.131	0.028***	0.116	1.164	0.049**	0.119	1.143	0.049***	0.117	1.113	0.051***	0.114
Personal and social life												
Quite	0.109	0.028***	0.011	0.082	0.047 .	0.008	0.104	0.048*	0.011	0.121	0.050*	0.012
Moderately	0.225	0.031***	0.023	0.03	0.053	0.003	0.382	0.053***	0.039	0.252	0.056***	0.026
Slightly	0.421	0.028***	0.043	0.241	0.048***	0.025	0.698	0.049***	0.071	0.33	0.051***	0.034
Not at all	0.986	0.029***	0.101	0.833	0.050***	0.085	1.163	0.050***	0.119	0.963	0.052***	0.098
Constant/intercept	0		0	0		0	0		0	0		0

[1] *β anchored DCE model = (β 20 parameter DCE model × (estimated VAS 55555 / estimated DCE 55555))*

*P-value: *** < 0.001. ** < 0.01. * < 0.05. . < 0.1*

Discussion

Our study demonstrates the first value sets for the QOLIBRI-OS. The main outcomes according to the preferences of our general sample suggested the biggest increase in weight was found when making the step from level slightly satisfied to level not at all satisfied within an attribute, which results in the largest impact on HRoQL. This is also in line with previous EQ-5D value set research.[32] Additionally, it was also found that 'Not at all satisfied with how brain is working in terms of concentration, memory and thinking' should receive the greatest weight in utility calculations in all three countries.

When looking at the face validity of the value set it was shown that a lower level of satisfaction within a health state also corresponded to a lower utility.
Strengths of our study include the representativeness of the study sample and the large number of survey respondents included in our survey. A general population sample was used instead of a brain injury group, because then the benefit gained has been determined from a public perspective, who ultimately are the taxpayers and potential patients.

During this study, DCEs were used and as mentioned in previous research, this valuation technique has advantages in measuring health state valuations over methods such as standard gamble (SG) and time trade off (TTO) in terms of simplicity[35] and understandability. There are several methods of administration to conduct health state valuation studies, such as face-to-face using paper-and-pencil methods and web-based questionnaires. The choice for a web-based survey during this study also implied using health state valuation methods that were amenable to online administration, in this case DCEs and VAS. Compared to personal interviews, web-based surveys are equipped to get answers from large samples in a relatively short time, have a flexible sampling frame, enable a range of background characteristics of non-respondents to be obtained, the order of the questions can be randomized, allow complex routing of questions, the time it takes a respondent can be recorded, and the errors associated with data entry are minimized.[36] Some limitations considering DCE research are the fact that a main effects only design, assuming that all attributes were value-independent of each other (i.e., all interactions between attributes were zero) was used. This may, however, be reasonable since main effects typically account for 70-90% of the explained variance in DCE.[37] Additionally, the complexity of a DCE can potentially cause some extra selection bias compared with general questionnaire surveys.[38] Furthermore, we have also encountered some limitations specific to our study. To ultimately get to five items for the QOLIBRI-OS, we based eliminating the last item on subjective researcher judgement, which could potentially lead to bias. Considering it was a web-based survey, we had no control on checking if respondents completely understood the task at hand. For future studies it would be advisable to build in a tool, to be able to check answers while respondents are taking the survey, for example to check if they are using the VAS correctly and are not turning it upside down. Additionally, face-to-face surveys will deliver higher

quality data, but also require larger monetary resources. However, web-based is the mostly used administration method in DCE research, especially because of the high costs associated with the face-to-face method. We based our health states and pairs on previous EQ-5D research; however, it could be that for the QOLIBRI-OS instrument different health states should have been asked and for future research it would be advised to develop an experimental design where the pairs of health states are selected specifically for the QOLIBIR-OS. Another problem is that the respondents saw a complete 'clean' VAS for every new question. In a situation where their given answers are shown on the scale during the following questions, the respondents can scale their own answers more easily, which ultimately leads to a better scale division. The VAS and DCE are different tasks; what people imagine when they use the VAS may vary relative to a DCE. Using the VAS to scale, such as was done in this study, makes mathematical sense, but does it also make sense when using it to scale coefficients giving utilities? In addition, the worst health state (health state 55555 e.g. not at all satisfied with every attribute) was given a mean VAS value of 54.64, which was expected to be lower, and could influence the rescaling. Furthermore, VAS scores used for rescaling in this study were not based on country-specific data due to small sample size. Future research could solve these limitations linked to the VAS values used in this study by doing a small TTO valuation task in each of the three countries, to provide anchors for the DCE scale. In addition, for the UK value set, an inconsistent coefficient in the final algorithm ("moderately satisfied with personal and social life") was reported, which should be looked at in more detail in future research. Moreover, the DCE and VAS questions were completely randomized. The quality of the data would have most likely been higher, if we asked the DCE and VAS questions in blocks, which would be randomly assigned to the respondents and every block consisted of one of the better health states and the worst health state.[24] This makes for a more balanced way of asking the questions, because everyone gets a well-balanced set of questions, which accounts for the whole range of severity. In addition, red-green color blindness could have influenced our respondents while answering the DCE questions, however, color-coding does improve the results.[39] Building upon these findings, it would be recommended for future research to provide anchors for the DCE and to use different colors than red and green. Since we used a market research company to recruit our sample, some individuals might be 'professional' respondents: those who answer a large number of surveys, and whose responses are not typical for the general public and we do not know to what extent our samples are representative for the population in the three countries with regards to characteristics other than age, gender, and educational level. Nonetheless, this study is the first one to determine a value set for the QOLIBRI-OS in three different European countries and introduced the opportunity to compare HRQoL of TBI patients with other (patient) groups. Similar studies have been performed for the EQ-5D,[25, 32] and are used daily in HRQoL research.

Conclusions

By transforming the QOLIBRI-OS into utility scores we have enabled the potential application in economic evaluations, and in summary measures of population health, which may inform decision-makers on the best interventions and strategies for TBI patients.

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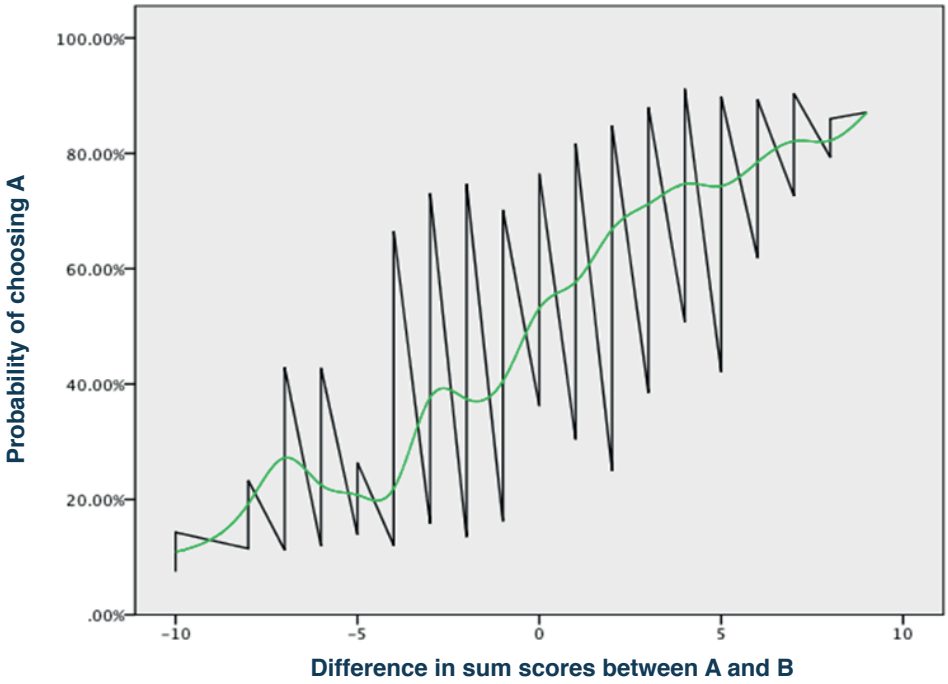
Appendix

Appendix A. Measures of Item Difficulty and Fit from Rasch Analysis of the QOLIBRI-OS

QOLIBRI-OS items	Item difficulty measure	Infit MNSQ	Infit Z	Outfit MNSQ	Outfit Z
Physical condition	0.32	1.05	0.9	1.07	1.4
How brain is working, in terms of concentration, memory and thinking	0.23	1.11	2.2	1.12	2.3
Feelings and emotions	-0.01	1.04	0.8	1.02	0.5
Ability to carry out day to day activities	-0.35	0.99	-0.3	0.94	-1.2
Personal and social life	-0.38	1	0.1	0.93	-1.4
Current situation and future prospects	0.19	0.81	-4.1	0.8	-4.4
Six items:					
Person real separation: 1.57					
Reliability: 0.71					
Five items:					
Person real separation: 1.63					
Reliability: 0.73					

** when the current situation and future prospects item has been excluded.*

Appendix B. The probability of choosing health state A when looking at the difference in sum scores between health state A and B.



Appendix C. QOLIBRI-OS non parametric model per country

	All respondents				UK				The Netherlands				Italy			
	Unanchored		Anchored		Unanchored		Anchored		Unanchored		Anchored		Unanchored		Anchored	
	Mean	*95% CI*	*Mean*	*95% CI*	*Mean*	*95% CI*	*Mean*	*95% CI*	*Mean*	*95% CI*	*Mean*	*95% CI*	*Mean*	*95% CI*	*Mean*	*95% CI*
Physical condition																
Quite	0.121	0.057-0.182	0.012	0.006-0.019	0.135	0.029-0.241	0.014	0.003-0.025	0.090*	-0.017-0.195	0.010*	-0.002-0.021	0.128	0.017-0.240	0.012	0.002-0.023
Moderately	0.289	0.219-0.357	0.030	0.023-0.037	0.290	0.171-0.405	0.030	0.0178-0.042	0.317	0.211-0.422	0.034	0.023-0.045	0.260	0.135-0.375	0.025	0.013-0.036
Slightly	0.548	0.483-0.613	0.057	0.050-0.063	0.521	0.411-0.630	0.054	0.043-0.066	0.482	0.377-0.585	0.052	0.041-0.063	0.624	0.505-0.749	0.060	0.049-0.072
Not at all	1.349	1.275-1.421	0.139	0.132-0.146	1.419	1.290-1.549	0.148	0.1360.159	1.124	1.002-1.248	0.121	0.110-0.132	1.517	1.395-1.643	0.146	0.135-0.156
How brain is working, in terms of concentration, memory and thinking																
Quite	0.157	0.091-0.224	0.016	0.009-0.023	0.241	0.137-0.348	0.025	0.014-0.036	0.081*	-0.028-0.189	0.009*	-0.003-0.020	0.173	0.049-0.289	0.017	0.005-0.028
Moderately	0.380	0.308-0.451	0.039	0.032-0.046	0.376	0.259-0.488	0.039	0.027-0.051	0.353	0.228-0.476	0.038	0.025-0.051	0.459	0.336-0.579	0.044	0.032-0.055
Slightly	0.704	0.640-0.769	0.073	0.066-0.079	0.719	0.609-0.835	0.075	0.063-0.088	0.630	0.531-0.734	0.068	0.057-0.079	0.793	0.688-0.903	0.076	0.066-0.087
Not at all	1.619	1.548-1.691	0.167	0.160-0.173	1.597	1.486-1.716	0.167	0.156-0.177	1.354	1.239-1.476	0.146	0.135-0.157	1.959	1.836-2.086	0.188	0.177-0.199
Feelings and emotions																
Quite	0.166	0.100-0.235	0.017	0.010-0.024	0.253	0.141-0.369	0.026	0.015-0.038	-0.002*	-0.105-0.108	0.000*	-0.011-0.011	0.243	0.120-0.369	0.023	0.011-0.035
Moderately	0.223	0.159-0.288	0.023	0.017-0.030	0.168	0.062-0.275	0.018	0.007-0.029	0.225	0.117-0.336	0.024	0.013-0.036	0.301	0.185-0.419	0.029	0.018-0.040
Slightly	0.336	0.270-0.401	0.035	0.028-0.041	0.267	0.157-0.379	0.028	0.016-0.040	0.403	0.299-0.502	0.043	0.032-0.054	0.341	0.224-0.458	0.033	0.021-0.044
Not at all	0.940	0.877-1.005	0.097	0.091-0.103	0.936	0.835-1.045	0.098	0.089-0.107	0.911	0.807-1.020	0.098	0.088-0.108	1.013	0.896-1.135	0.097	0.088-0.107
Ability to carry out day to day activities																
Quite	0.132	0.058-0.205	0.014	0.006-0.021	0.127	0.007-0.249	0.013	0.001-0.026	0.077*	-0.046-0.197	0.008*	-0.005-0.021	0.223	0.100-0.346	0.021	0.010-0.033
Moderately	0.228	0.162-0.295	0.023	0.017-0.030	0.218	0.110-0.324	0.023	0.012-0.034	0.212	0.100-0.321	0.023	0.011-0.034	0.314	0.190-0.439	0.030	0.018-0.042
Slightly	0.330	0.261-0.404	0.034	0.027-0.041	0.236	0.124-0.354	0.025	0.013-0.037	0.440	0.327-0.557	0.047	0.035-0.060	0.343	0.210-0.489	0.033	0.020-0.046
Not at all	1.108	1.037-1.177	0.114	0.108-0.121	1.152	1.035-1.267	0.120	0.109-0.131	1.134	1.011-1.254	0.122	0.110-0.134	1.106	0.985-1.227	0.106	0.096-0.117
Personal and social life																
Quite	0.097	0.026-0.165	0.010	0.003-0.017	0.064*	-0.055-0.176	0.007*	-0.006-0.018	0.090*	-0.031-0.203	0.010*	-0.003-0.021	0.128	0.007-0.246	0.012	0.001-0.023
Moderately	0.251	0.174-0.330	0.026	0.018-0.034	0.025*	-0.1-0.156	0.003*	-0.010-0.016	0.376	0.254-0.494	0.040	0.028-0.053	0.348	0.198-0.497	0.033	0.019-0.047
Slightly	0.370	0.311-0.433	0.038	0.032-0.045	0.192	0.094-0.293	0.020	0.010-0.030	0.616	0.512-0.723	0.066	0.055-0.078	0.329	0.216-0.488	0.032	0.021-0.043
Not at all	0.989	0.925-1.051	0.102	0.096-0.108	0.915	0.801-1.026	0.095	0.085-0.106	1.140	1.036-1.245	0.123	0.113-0.133	0.923	0.811-1.033	0.089	0.079-0.098

**Not significant: p-value < 0.05*
95% CI credible interval

Appendix D. Example of values for a mild, moderate and severe health state

	All respondents	UK	The Netherlands	Italy
Mild health state: 21232	0.95	0.948	0.96	0.942
Moderate health state: 34343	0.833	0.879	0.789	0.827
Severe health state: 55455	0.446	0.452	0.442	0.445

Chapter 10

Deriving Disability Weights for the Glasgow Outcome Scale Extended from Health-Related Quality of Life Data from Traumatic Brain Injury Patients: a Mapping Study

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Chapter 11

The Utility-Weighted Modified Rankin Scale as Outcome in Stroke Trials: A Simulation Study

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Abstract

Background and purpose: The utility-weighted modified Rankin Scale (UW-mRS) has been proposed as a new patient-centered primary outcome in stroke trials. We aimed to describe utility weights for the mRS health states and to evaluate the statistical efficiency of the UW-mRS to detect treatment effects in stroke intervention trials.

Methods: We used data of the 500 patients enrolled in the MR CLEAN (Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands). Utility values were elicited from the EuroQol Group 5-Dimension Self-Report Questionnaire assessed at 90 days after inclusion, simultaneously with the mRS. Utility weights were determined by averaging the utilities of all patients within each mRS category. We performed simulations to evaluate statistical efficiency. The simulated treatment effect was an odds ratio of 1.65 in favor of the treatment arm, similar for all mRS cutoffs. This treatment effect was analyzed using 3 approaches: linear regression with the UW-mRS as outcome, binary logistic regression with a dichotomized mRS (0-1/2-6, 0-2/3-6, and 0-4/5-6), and proportional odds logistic regression with the ordinal mRS. The statistical power of the 3 approaches was expressed as the proportion of 10 000 simulations that resulted in a statistically significant treatment effect ($P \leq 0.05$).

Results: The mean utility values (SD) for mRS categories 0 to 6 were: 0.95 (0.08), 0.93 (0.13), 0.83 (0.21), 0.62 (0.27), 0.42 (0.28), 0.11 (0.28), and 0 (0), respectively, but varied substantially between individual patients within each category. The UW-mRS approach was more efficient than the dichotomous approach (power 85% versus 71%) but less efficient than the ordinal approach (power 85% versus 87%).

Conclusions: The UW-mRS as primary outcome does not capture individual variation in utility values and may reduce the statistical power of a randomized trial.

Introduction

The modified Rankin Scale (mRS) is the most widely used primary outcome measure in trials for acute stroke interventions.[1, 2] The mRS is an ordinal scale ranging from 0 (no symptoms) to 6 (death) measuring the degree of disability or dependence in everyday life.[3] Previously, dichotomizing the mRS into dead or dependent (mRS, 3–6) versus independent (mRS, 0–2) was common, but this results in a reduction in statistical power to detect relevant treatment effects.[4] Therefore, statistical approaches preserving the ordinal nature of outcome measures, such as proportional odds logistic regression, have been recommended for stroke and other neurological disorders.[1, 5-8] Currently, the importance of incorporating quality of life (QoL) in outcome analysis in stroke trials is increasingly recognized.[9-11] For the mRS to reflect both treatment effect and patient perception, the utility-weighted mRS (UW-mRS) has been proposed and used as primary end point.[2, 12, 13] In the UW-mRS, utilities based on the EuroQol Group 5-Dimension Self-Report Questionnaire (EQ-5D-3L) values are assigned to the mRS health states. Two prior studies reported utility weights for the mRS health states: 1 representing the values of patients and 1 representing the values of clinicians. The utility weights that were proposed for the UW-mRS are based on these 2 studies.[12] Compared with the ordinal mRS, the UW-mRS showed similar statistical power to detect treatment effects in empirical data in a wide range of stroke trials.[12] However, because in empirical data, the true treatment effect is unknown, the only valid method to assess statistical power is simulation. We aimed to describe utility weights for the mRS health states and to evaluate the statistical efficiency of the UW-mRS to detect treatment effects in stroke trials.

Methods

Anonymized trial data and analytic methods that support our study findings are available from the principal investigator (e-mail: mrclean@erasmusmc.nl) on reasonable request.

Study Population

We used individual patient data of the 500 patients enrolled in the MR CLEAN (Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands). MR CLEAN was a phase III, multicenter randomized clinical trial, designed to evaluate whether intra-arterial treatment (within 6 hours of symptom onset) plus usual care would be more effective than usual care alone in patients with acute ischemic stroke and a proximal arterial occlusion in the anterior cerebral circulation. The primary outcome was the mRS at 90 days, and the secondary outcome was the EQ-5D-3L at 90 days. In MR CLEAN, ethics approval was obtained from the local institutional review boards of the participating centers, and written informed consent was obtained from patients or legal representatives before randomization.[14]

Modified Rankin Scale

The mRS is a measure of functional outcome after stroke, evaluating the degree of disability or dependence in daily life. The scale is derived from clinical assessment by a trained nurse or a physician and consists of 7 grades ranging from 0 (no symptoms) to 6, with 5 indicating severe disability and 6 indicating death. A score of ≤2 indicates functional independence.[3]

Utilities

Utilities represent preferences for mRS health states and range from 0 (death) to 1 (perfect health). Utility values of poor outcome categories might even be negative, indicating that they are valued worse than death.[15] In MR CLEAN, utility values were elicited using the EQ-5D-3L responses of patient, proxy, or healthcare provider assessed at 90 days after inclusion, simultaneously with the mRS. The EQ-5D-3L consists of 5 dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) with 3 levels each (no problems, some problems, and extreme problems), thus defining 243 (35) distinct health states.[16] Converting the EQ-5D-3L responses into utility values was done according to the Dutch tariff—a country-specific value set established based on the time trade-off method.[17] Patients who died before the follow-up interviews at 90 days received a utility value of zero. The utility values ranged from −0.33 to 1.00. We determined utility weights for each mRS category by averaging the derived utilities (including the negative values) of all patients within each mRS health state (eg, the utility weight for mRS=1 is the average of the utilities of all patients with mRS=1). Additionally, we matched the utility values proposed by Chaisinanunkul et al,[12] who collapsed mRS 5 to 6 by assigning a utility weight of zero to both categories, to our mRS values.

Simulations for Statistical Efficiency

Statistical efficiency was evaluated based on simulations that utilized the MR CLEAN database. For a single simulation, 500 patients were sampled at random with replacement. For each patient, the predicted probability of each possible outcome on the 7-point ordinal mRS was modeled as a function of the baseline covariates. These covariates were identical to those in MR CLEAN and included age, stroke severity (National Institutes of Health Stroke Scale) at baseline, time from stroke onset to randomization, status with respect to previous stroke, atrial fibrillation, diabetes mellitus, and occlusion of the internal carotid artery terminus (yes/no).[14]

Using these estimated probabilities, an actual outcome in terms of an mRS or UW-mRS was simulated. Treatment (yes/no) was randomly assigned, and the simulated treatment effect was an odds ratio (OR) of 1.65 (β=0.5) in favor of the treatment arm, similar for all mRS cutoffs. We also evaluated a scenario with no treatment effect, by simulating a treatment effect of OR=1.0 (β=0). During this process, samples of 500 subjects were generated representing 250 patients from the control group and 250 from the intervention group, with a known treatment effect. This was then repeated 10 000×.

The data were analyzed by 3 different statistical approaches. First, we dichotomized the 90-day mRS in 3 different ways of favorable versus unfavorable outcome: 0 to 1 versus 2 to 6, 0 to 2 versus 3 to 6, and 0 to 4 versus 5 to 6. The treatment effect on the dichotomized mRS was determined using binary logistic regression. Second, we used proportional odds logistic regression for analysis of the treatment effect on the ordinal mRS. We fitted a proportional odds logistic regression model with the 7-point ordinal mRS scale as outcome. The proportional odds model estimates a common OR over all health state transitions within the mRS. According to the proportional odds assumption, the common OR is an accurate reflection of the overall treatment effect if the ORs are the same for each health state transition. If there is agreement regarding the ordinality of the mRS, the common OR can be interpreted as a summary measure of treatment effect even if the proportional odds assumption is violated.[18] Third, treatment effect on the UW-mRS was analyzed using linear regression, as proposed by Chaisinanunkul et al.[12]
Each of the 3 approaches yielded either a significant ($P \leq 0.05$) or a nonsignificant treatment effect ($P > 0.05$, 2 sided). The power (or type 1 error in case of no treatment effect) of each statistical approach was estimated as the proportion of the 10 000 analyses, which resulted in a statistically significant treatment effect.

Associations were expressed as ORs or β with 95% confidence intervals (CIs), averaged over all simulations. All analyses were performed unadjusted and adjusted for the prespecified covariates identical to those mentioned above. Statistical analyses were performed with R software, version 3.3.2 (R Foundation for Statistical Computing, Vienna, Austria). Missing data on time from stroke to randomization (0.4%) and level of vessel occlusion (0.2%) was statistically imputed using simple imputation (replacement by mean or mode, as applicable).

Results

Study Population

All 500 participants from the MR CLEAN trial were included in our analysis. The mRS at 90 days was available for all patients. The EQ-5D-3L assessments, and consequently the utility values, were available in 457 patients (including 108 patients who died before follow-up). In 43 patients (8.6%), mRS assessment could not be followed by an EQ-5D-3L assessment. In 192 patients (38%), the EQ-5D-3L was completed by a proxy.

The total study population had a mean age of 65 years (SD, 14 years), and most patients (58%) were men (Table 1).

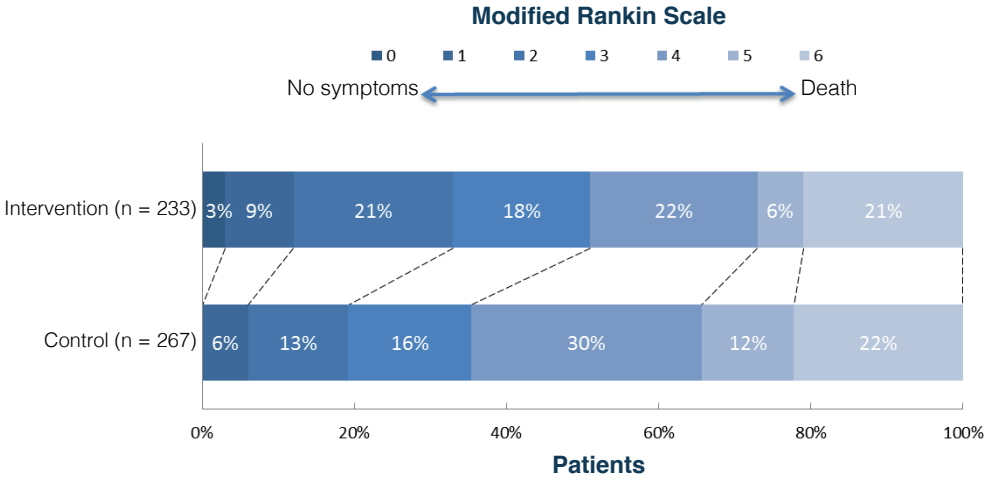
Table 1. Baseline characteristics of the 500 patients in the MR CLEAN trial.

Baseline variable	Intervention (n = 233)	Control (n = 267)
	Intra-arterial treatment plus usual care	*Usual care*
Age, y; median (IQR)	65.8 (54.5-76.0)	65.7 (55.5-76.4)
Male sex	135 (58%)	157 (59%)
NIHSS score, median (IQR)	17 (14 - 21)	18 (14 - 22)
Previous ischemic stroke	29 (12%)	25 (9%)
Atrial fibrillation	66 (28%)	69 (26%)
Diabetes mellitus	34 (15%)	34 (13%)
Prestroke mRS		
0	190 (82%)	214 (80%)
1	21 (9%)	29 (11%)
2	12 (5%)	13 (5%)
> 2	10 (4%)	11 (4%)
Treatment with IV alteplase	203 (87%)	242 (91%)
Time from stroke onset to start of IV alteplase, min; median (IQR)	85 (67-110)	87 (65-116)
Occlusion of the internal carotid artery terminus*	59 (25%)	75 (28%)
Time from stroke onset to randomization, min; median (IQR) †	204 (152 - 251)	196 (149 - 266)
Time from stroke onset to groin puncture, min; median (IQR)	260 (210-313)	NA

** No vessel imaging in one patient in the control group.*
*** Data were missing for two patients in the intervention group.*
Abbreviations. IQR, interquartile range; IV, intravenous; mRS, modified Rankin Scale; NA, not applicable; and NIHSS, National Institutes of Health.

The intervention and control groups were similar in terms of baseline and treatment characteristics. The number of patients with poor outcome (mRS, 3–6) at 90 days was lower in the intervention group than in the control group (Figure 1).

Figure 1. Distribution of the mRS at 90 days among intervention and control group.



Utility Weights

The mean utility values (SD) for mRS categories 0 to 6 were: 0.95 (0.08), 0.93 (0.13), 0.83 (0.21), 0.62 (0.27), 0.42 (0.28), 0.11 (0.28), and 0 (0), respectively (Table 2). We observed substantial variation in utility values within each mRS category (Figure 2). Within MR CLEAN, the mean UW-mRS for the intervention group was significantly higher when compared with the control group (Table 2).

Outcome Analysis in MR CLEAN

Ordinal analysis of the mRS showed improved functional outcomes in favor of the intervention, consistent throughout all categories of the mRS except for death (adjusted common OR, 1.67; 95% CI, 1.21–2.30; Figure 1). The dichotomous approach led to slightly stronger treatment effects for cutoffs mRS 0 to 1 and 0 to 2 (adjusted OR, 2.07 [95% CI, 1.07–4.02] and 2.16 [95% CI, 1.39–3.38], respectively). The fact that the ORs were not equal for the different cutoffs might imply that the proportional odds assumption did not hold perfectly in the empirical data. Linear analysis of the UW-mRS resulted in an adjusted β of 0.086 (95% CI, 0.033–0.131).

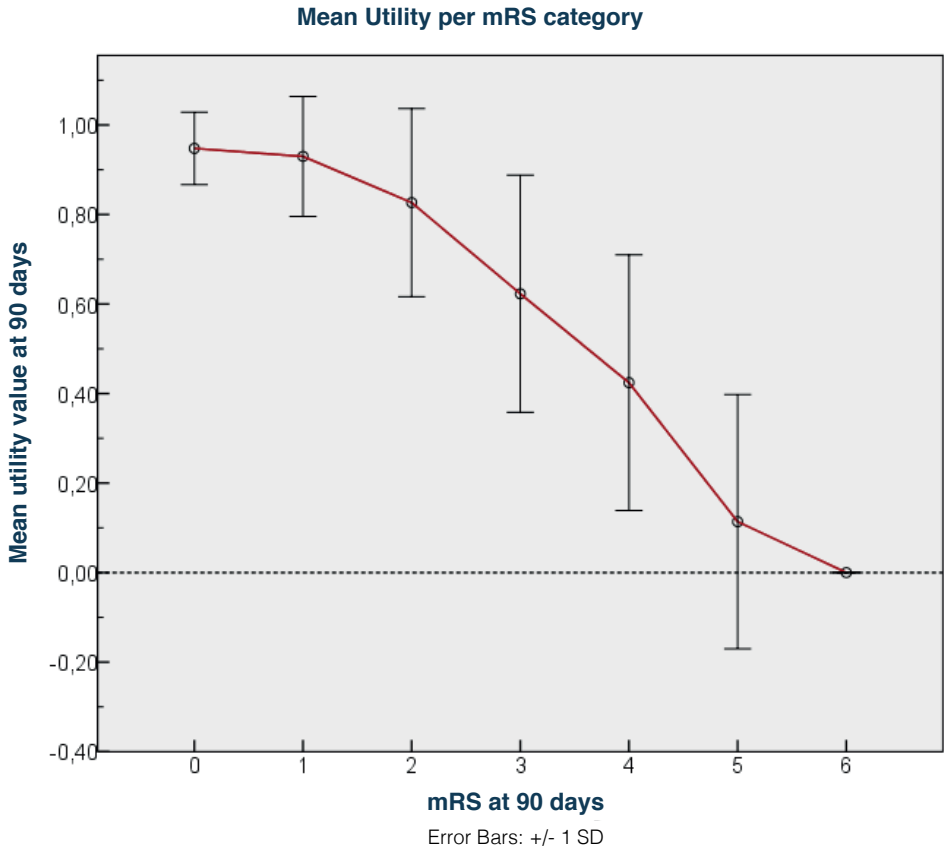
Table 2. Mean utility values per mRS category and mean UW-mRS in MR CLEAN and the Study by Chaisinanunkul et al.

	No. of Patients MR CLEAN	Mean (SD)	Chaisinanunkul et al[12], Mean Utility Values
mRS			
0	7	0.95 (0.081)	1
1	36	0.93 (0.133)	0.91
2	84	0.83 (0.210)	0.76
3	87	0.62 (0.265)	0.65
4	133	0.42 (0.286)	0.33
5	45	0.11 (0.284)	0
6	108	0	0
UW-mRS			
Overall	500	0.45 (0.322)	0.4
Intervention group	233	0.50 (0.33)**	0.46
Control group	267	0.41 (0.31)	0.36

** Mean utility for the intervention group vs control group within MR CLEAN: P=0.002 (Mann-Whitney U test).*

Abbreviations. MR CLEAN, Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands; mRS, modified Rankin Scale; and UW, utility weighted.

Figure 2. Mean utility value per mRS category.



Simulations

For all 3 prespecified mRS dichotomizations, intra-arterial treatment was positively associated with better outcomes (adjusted OR, 1.66–1.68; Table 3). The estimated treatment effects were similar to the simulated (true) treatment effect of 1.65. When comparing the 3 different mRS cutoffs, the statistical efficiency for the cutoff of mRS 0 to 2 versus 3 to 6 was highest (power 71% versus 62% for mRS 0–1 and 35% for mRS 0–4). This could be explained by an almost equal distribution of patients among both categories for this cutoff (Table 3).

Ordinal analysis of the mRS estimated an adjusted treatment effect of common OR=1.66 (95% CI, 1.41–1.95; Table 3), similar to the dichotomous approach. However, the ordinal approach was statistically more efficient (power 87% versus 71%).

Linear regression analysis of the UW-mRS estimated an adjusted beneficial treatment effect of β=0.075 (95% CI, 0.027–0.125; Table 3). The UW-mRS approach was statistically less efficient in detecting treatment effects compared with the ordinal approach (power 85% versus 87%). Matching the utilities of Chaisinanunkul et al to

Table 3. Univariable and multivariable treatment effects in simulations for proportional odds logistic regression analysis of the mRS and linear regression analysis of the UW-mRS and utilities.

		SE	Power		SE	Power
Binary logistic regression	Univariable OR (95% CI)*			Multivariable OR (95% CI)*†		
0-1 vs 2-6						
0-1 (n=146)	1.54 (1.29-1.83)	0.205	56%	1.67 (1.08-2.61)	0.226	62%
2-6 (n=354)	reference			reference		
0-2 vs 3-6						
0-2 (n=272)	1.51 (1.30-1.74)	0.181	63%	1.66 (1.12-2.48)	0.203	71%
3-6 (n=228)	reference			reference		
0-4 vs 5-6						
0-4 (n=448)	1.58 (1.21-2.07)	0.303	32%	1.68 (0.89-3.19)	0.326	35%
5-6 (n=52)	reference			reference		
Proportional odds logistic regression	Univariable OR (95% CI)			Multivariable OR (95% CI)*		
mRS at 90 days	1.53 (1.34-1.75)	0.159	76%	1.66 (1.41-1.95)	0.163	87%
Linear regression	Univariable β (95% CI)			Multivariable β (95% CI)*		
UW-mRS with MR CLEAN utilities	0.075 (0.020-0.131)	0.028	76%	0.076 (0.027-0.125)	0.025	85%
UW-mRS with utilities from Chaisinanunkul et al.	0.076 (0.020-0.133)	0.029	75%	0.077 (0.026-0.128)	0.026	84%

**Simulated treatment effect β=0.5 (OR, 1.65).*

†Adjusted for age, NIHSS at baseline, time from stroke onset to randomization, status with respect to previous stroke, atrial fibrillation, diabetes mellitus, and occlusion of the internal carotid artery terminus (yes/no)

Abbreviations. CI, confidence interval; MR CLEAN, Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; OR, odds ratio; and UW, utility weighted.

the mRS values in MR CLEAN led to similar results (Tables 2 and 3). However, the assumptions of the linear model were not met because there was non-normality of the residuals (Figure I in the online-only Data Supplement).
In the simulations without a treatment effect, a proportion of false-positives (type 1 error) of around 5% was estimated for all 3 statistical approaches (data not shown).

Discussion

We evaluated the UW-mRS—a recently proposed patient-centered outcome measure in stroke. Our study, based on a Dutch stroke intervention trial, showed that the UW-mRS does not capture the individual variation in utility values within each mRS category. Moreover, our simulations revealed that the UW-mRS approach was more efficient in detecting treatment effects than dichotomous analysis of the mRS but less efficient than the ordinal approach.

Widely used functional outcome measures in stroke intervention trials, such as the mRS, have been extensively studied concerning their feasibility in measuring disability after stroke.[19, 20] Nevertheless, more attention has recently been aimed at incorporating patient-reported QoL in stroke outcome measures.[10, 11]

As part of this trend, the UW-mRS has been proposed as a new primary patient-centered outcome measure in acute stroke intervention trials. In empirical data, the UW-mRS was equally statistically efficient in detecting treatment effects compared with ordinal analysis of the mRS.[12] Based on that study, the UW-mRS was recently used as the primary end point in the DAWN trial (Diffusion-Weighted Imaging or Computerized Tomography Perfusion Assessment With Clinical Mismatch in the Triage of Wake Up and Late Presenting Strokes Undergoing Neurointervention With Trevo),[13] and it is expected that more trials will follow. However, the study by Chaisinanunkul et al was only based on analyses of empirical sets of data. Because the true treatment effect in empirical data is unknown and different treatment effects on different outcome measures could be caused by random variation, the only valid method to assess the power of a statistical approach is a simulation study, as we performed.

Intuitively, patient-centered outcomes, such as the UW-mRS, are clinically useful because they concern patient-reported measures combined with the perception of the general public. These outcomes reflect patient perception and respect the nonequality of health state transitions on an ordinal scale. Nevertheless, averaging utility values for each mRS category does not reflect individual valuation of these health states: all patients within 1 mRS category receive the same utility weight, irrespective of their own valuation of this health state (Figure 2). So, the UW-mRS is in fact a revaluation of the mRS. Moreover, the utility distribution with mRS=5 being worse than death for some patients does not support collapsing mRS categories 5 to 6 as proposed by Chaisinanunkul et al. To reflect true individual valuation of health states, QoL instruments should rather be used as outcome. However, utility values derived from the EuroQol Group 5-Dimension Self-Report Questionnaire may not cover the full range of limitations relevant to patients with stroke[21] and may, therefore, overestimate QoL in this group. An alternative would be to use utility values derived from QoL instruments designed specifically for patients with neurological disorders, such as Neuro-QoL.[22] Nevertheless, because QoL depends on many external factors, it might introduce noise, making it less suitable

as a primary outcome measure.[23, 24]

Our simulations revealed that the UW-mRS is not as statistically efficient as ordinal analysis of the mRS and may, therefore, cause a reduction in statistical power when used in randomized trials. Chaisinanunkul et al12 analyzed the UW-mRS with a t test, implying a continuous outcome variable. We used linear regression, which is a comparable approach but allows for multivariable analysis. In theory, linear analysis is expected to be more efficient than ordinal analysis when the assumptions of the linear model are met. A linear model assumes that the errors between observed and predicted values, that is, the residuals of the regression, are normally distributed. In our analyses, however, we found non-normality of the residuals of the linear model for the UW-mRS. Because the UW-mRS remains a scale with 7 outcome categories, the assumption of normally distributed residuals can never be met. Non-normality of the residuals might cause bias because of underestimation of the standard error. Therefore, the actual power of the UW-mRS approach will be even <85%. Ordinal analysis also makes an assumption (the proportional odds assumption), but it should be noted that the assumption of a normal distribution of the residuals in a linear model is more difficult to fulfill than the assumption of ordinality in proportional odds analyses. In line with theoretical expectations, the UW-mRS showed to be exactly as efficient as the mRS when it was analyzed with a proportional odds model (data not shown).

Defining a beneficial treatment effect in terms of the UW-mRS, and, therefore, clinical interpretability, might be difficult. Treatment effect on the UW-mRS scale is expressed as a difference in mean UW-mRS between treatment and control groups.[12] This difference can be converted into quality-adjusted life-years (QALYs) gained or lost by a certain treatment.[12, 25] The QALY measure assumes that a year of life lived in perfect health is worth 1 QALY, and a year of life lived in a state less than perfect health is worth <1 QALY, proportional to its utility value (QALY=years of life×utility). QALYs can be used to calculate cost-effectiveness to select a certain intervention for funding.[26] Also, the QALY measure has been argued to be more intuitive to patients (healthy life-years gained) and, therefore, to improve communication of treatment effects.[12, 25] However, when not converted into QALYs, treatment effects expressed as utility differences remain difficult to interpret. Moreover, clinicians and researchers are now used to working with the (common) OR.

Ordinal outcome scales are also used in other neurological disorders besides stroke. Examples are the Glasgow Outcome Scale in traumatic brain injury and the Guillain-Barre syndrome disability score in Guillain-Barre syndrome.[6, 7, 27] These ordinal outcomes could be transformed to patient-centered outcomes using utility values, similar to the UW-mRS. For randomized trials in patients with other neurological diseases, such as traumatic brain injury and Guillain-Barre syndrome, our study might, therefore, also implicate that ordinal analysis should remain the gold standard.

Our study has several strengths. The simulation study was based on data from the MR CLEAN trial, with relatively broad inclusion criteria.[14] As such, our findings should be generalizable to future stroke trials. Furthermore, simulation is the most adequate method to evaluate statistical power. Also, we used utility values derived using the recommended time trade-off method, which should be less prone to bias compared with other elicitation methods.[24]

Some limitations should also be acknowledged. As with all simulation studies, we do not know how far our findings may be extrapolated beyond the modeled situations. For instance, we only simulated a model with a uniform treatment effect across all mRS health state transitions, which, therefore, adheres perfectly to the proportional odds assumption. However, if the proportional odds assumption would be violated, and treatment effect would not be uniform across the different outcome categories, ordinal analysis would still be the most efficient.[6] Nevertheless, further validation of our results is required. Finally, we used the EuroQol Group 5-Dimension Self-Report Questionnaire assessed at 90 days after inclusion, which reflects neither short-term QoL nor the final health state. A better reflection of patient perception could be achieved by calculating QALYs based on multiple QoL measurements in 1 patient. Nevertheless, the aim of this study is not to describe QoL but to evaluate efficiency in detecting treatment effects.

In conclusion, the UW-mRS has been received as a promising new patient-centered outcome in stroke research. However, the UW-mRS does not capture individual variation in utilities within each mRS health state. Also, interpretation of treatment effect on the UW-mRS scale might be more challenging than was first suggested. Finally, clinicians and researchers should be aware of the reduction in power compared with ordinal analysis of the mRS when they use the UW-mRS as outcome measure in acute stroke intervention trials. More thorough evaluation of the UW-mRS in terms of its added value, analytic approach, and interpretation is required.

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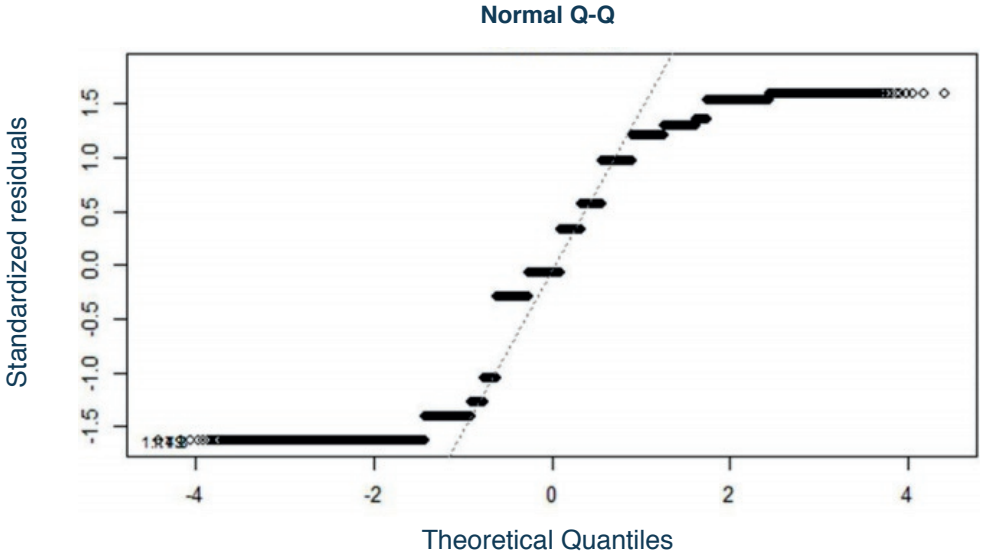
Appendix

Appendix A. Q-Q plot to test normality of the residuals of the UW-mRS in simulations.



Legend: Univariable linear model with UW-mRS as outcome and treatment effect as variable. (Standardized) residuals are the errors between observed and predicted values in a model. Theoretical quantiles are the residuals as theoretically expected when they are normally distributed. In a Q-Q plot, the residuals are normally distributed when they fall on the dashed line.

Chapter 12

Reference Values of the QOLIBRI from General Population Samples in the United Kingdom and the Netherlands

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Abstract

The Quality of Life after Traumatic Brain Injury (QOLIBRI) instrument is an internationally validated patient-reported outcome measure for assessing disease-specific health-related quality of life (HRQoL) in individuals after traumatic brain injury (TBI). However, no reference values for general populations are available yet for use in clinical practice and research in the field of TBI. The aim of the present study was, therefore, to establish these reference values for the United Kingdom (UK) and the Netherlands (NL). For this purpose, an online survey with a reworded version of the QOLIBRI for general populations was used to collect data on 4403 individuals in the UK and 3399 in the NL. This QOLIBRI version was validated by inspecting descriptive statistics, psychometric criteria, and comparability of the translations to the original version. In particular, measurement invariance (MI) was tested to examine whether the items of the instrument were understood in the same way by different individuals in the general population samples and in the TBI sample across the two countries, which is necessary in order to establish reference values. In the general population samples, the reworded QOLIBRI displayed good psychometric properties, including MI across countries and in the non-TBI and TBI samples. Therefore, differences in the QOLIBRI scores can be attributed to real differences in HRQoL. Individuals with and without a chronic health condition did differ significantly, with the latter reporting lower HRQoL. In conclusion, we provided reference values for healthy individuals and individuals with at least one chronic condition from general population samples in the UK and the NL. These can be used in the interpretation of disease-specific HRQoL assessments after TBI applying the QOLIBRI on the individual level in clinical as well as research contexts.

Introduction

Traumatic brain injury (TBI) is often a source of long-lasting impairments and functional limitations.[1] It can affect participation in daily activities[2] and may lead to a stagnation in working life for several years[3] or permanently prevent a return to work.[4] TBI can have dramatic consequences for cognitive, behavioral, and emotional life domains, and increases the risk of experiencing other health-related problems such as increased alcohol consumption and depression.[5] However, a person's perception of TBI sequelae, compared to an objectively assessed functional state, is a subjective dimension, and the relationship between these two types of measurement is not always straightforward.[6] Subjective assessments of health deficits and self-rated health-related quality of life (HRQoL) provide valuable additional information to clinical health examinations and ratings. Thus, patient-reported outcomes (PROs) have now become widely used in assessing HRQoL in the field of TBI. HRQoL measures provide aggregated information on diverse health components, such as physical, psychological (mental and emotional), social and daily life aspects, and are, therefore, able to capture the multidimensionality of individually experienced consequences of TBI.[7]

A systematic review of assessments of HRQoL after TBI, covering the period from 1991 to 2013, found that the most frequently used instruments were the generic Short Form (36) Health Survey (SF-36)[8] and the TBI-specific Quality of Life after Traumatic Brain Injury (QOLIBRI).[1] Both instruments display satisfactory to very good psychometric properties in TBI populations, with the QOLIBRI having higher discriminative powers when separate domains of the QOLIBRI and SF-36 are compared.[7, 9]

To gain a more in-depth understanding of TBI-specific consequences, one may apply a TBI-specific HRQoL instrument. However, from the perspective of rehabilitation after TBI, applying generic instruments may offer an advantage due to the availability of population-based reference values. Bearing in mind the unspecific nature of some post-TBI symptoms, such as headaches and nausea,[10] a comparison with general population samples is essential in order to evaluate the rehabilitation progress. Additionally, population-based reference values play a key role in differentiating between individuals after TBI with and without impaired HRQoL.

In previous research, the QOLIBRI was developed and validated exclusively in samples of individuals after TBI to establish its sensitivity for the TBI condition.[11] In the interest of enhancing the interpretability of its scores in clinical practice and research after TBI, we collected QOLIBRI scores from general population samples in the UK and the NL to provide respective reference values.

Thus, the aims of the present study are:

To ensure the comparability of QOLIBRI translations between general and TBI samples by determining the measurement invariance (MI) in general population samples (healthy individuals and individuals with a chronic health condition) and TBI samples from the UK and the NL.

To provide reference values for healthy individuals and individuals with at least one chronic health condition from the UK and the NL.

Only when MI has been verified, reference values will be provided for healthy individuals (and individuals with a chronic health condition) from Dutch and UK general population samples. Separate reference values will be given for the presence and absence of chronic health conditions, age, sex, and level of education.

Methods

Study Design

The present study is a web-based, self-reported, cross-sectional study based on quota sampling of general population samples from the UK and the NL (see below). Additional data of patients after TBI, needed for the MI analyses, were retrieved from the multicenter, prospective, longitudinal, observational Collaborative European Neuro Trauma Effectiveness Research in Traumatic Brain Injury (CENTER-TBI) study.[12] These data were collected at three months post-TBI.

Setting

General Population Samples

Data Collection

The general population sample data were collected through a web-based survey. Respondents were recruited by a market research agency (https://www.dynata.com/), which distributed the questionnaires and collected the data. The samples were based on existing large internet panels designed to be representative for individuals from the general population from the UK and the NL with regard to age, sex, and education. Data collection was carried out between 29 June and 31 July 2017. The recruitment integrated several sources, e.g., proprietary loyalty partnerships (members of loyalty programs across travel, entertainment, retail, and other sectors), open recruitment to traditional online panels (e.g., via online banners, online all panels, cable TV advertising, mailings, social media influencers, and other methods), and integrated partnerships with online communities, publishers, and social networks. A broad variety of sources was chosen to reach participants from different social milieus to thereby increase the representativeness of the sample.

To avoid a self-selection bias, no specific project details were included in the invitation: participants were invited to "take a survey". Details were disclosed later, after the system had selected the individuals for participation according to the given selection criteria. After completing the survey, participants received an incentive in the form of cash, points, prizes, or sweepstakes from the market research company. Respondents, who were identified by the agency as "speeders" (e.g., who took the survey in less than five minutes), were deleted. The electronic data capture system did not allow missing answers, thus respondents had to answer every question. The recruitment process continued until the required quotas were reached.

Informed Consent

Informed consent for the present survey was obtained by the agency from all those agreeing to complete the online survey. The process is described in the privacy agreement available at https://www.dynata.com/privacy-policy/. Participants were informed on the welcome page of the survey that its aim was a better understanding of the consequences of TBI on patients' lives, that it would take approximately 20 min to complete, and that all responses were confidential and anonymous. Data

were anonymized and each participant was assigned a number in the order of questionnaire completion.

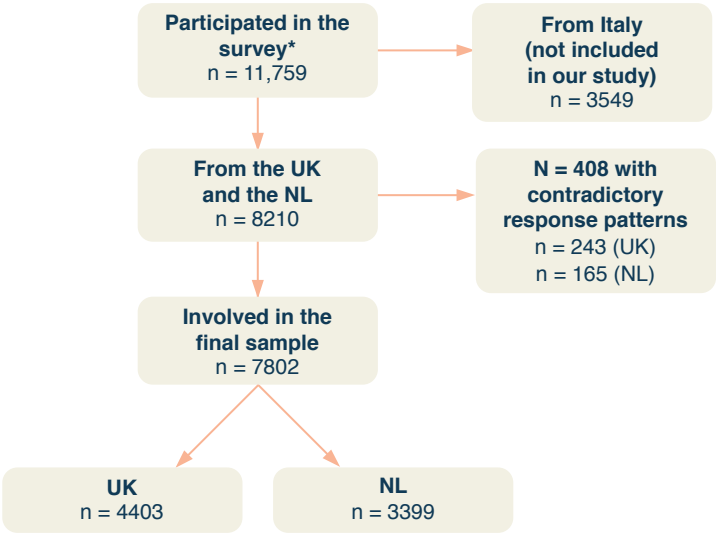
Sample Composition
From a total of 11,759 survey participants, 4646 individuals from the UK and 3564 from the NL were included for further analyses. Recruitment was carried out until the required quotas for age, gender, and education had been achieved, which ensured that samples were as comparable as possible to the general populations of the two countries. Nonresponse rates were below 20% (UK: 14.4%, NL: 19.5%). A more detailed analysis of these individuals was not possible due to the recruitment system used.
Prior to the analyses, responses to QOLIBRI items were examined for obvious contradictory response patterns in both general population samples, for example, the choice of the response option "not at all" for all items, meaning that responders were not at all satisfied and at the same time not at all bothered. This indicated that the person had chosen only left-hand side response options, ignoring the item polarity. Due to contradictory response patterns, the data of 243 individuals from the UK and of 165 individuals from the NL general population samples were excluded from further analyses. The individuals included and excluded were compared using chi-square (χ2-) tests with Yates correction for nominal variables and independent t-test for continuous variables. In both countries, excluded individuals were predominantly male and younger compared with the total sample (M = 35, SD = 12) and had a middle level of education. In the end, 7802 individuals from the general population (UK: 4403; NL: 3399) were included in the final analyses (see Figure 1).

TBI sample

Data Collection
Individuals after TBI were investigated in the (CENTER-TBI) study.[13] They were recruited between 9 December 2014 and 17 December 2017. The inclusion criteria were a clinical diagnosis of TBI, presentation to hospital within 24 h after the injury, a clinical indication for a computed tomography (CT) scan, and provision of informed consent adhering to local and national requirements. Data were collected applying an electronic case report form (e-CRF, QuesGen Systems Incorporated, Burlingame, CA, USA) either during the hospital visit, in a face-to-face visit, a telephone interview, or by mail combined with a telephone interview. The data were exported from the CENTER-TBI database, Neurobot version 2.0, on 8 November 2018. Further study details can be found elsewhere.[12]

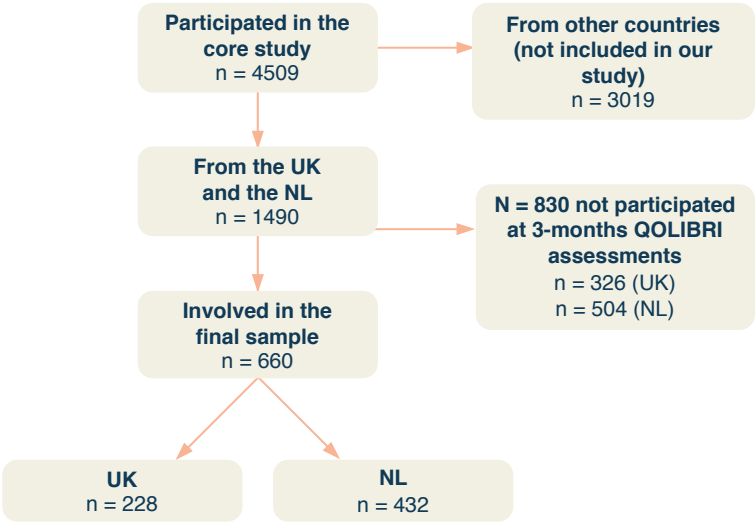
Informed Consent
Informed consent was obtained according to local and national requirements for all patients recruited in the Core Dataset of CENTER-TBI and documented in the e-CRF.[13]

Figure 1. Sample attrition chart (general population).



non-responder rates for the survey were below 20% (UK:14.4%, NL: 19.5%)

Figure 2. Sample attrition chart (traumatic brain injury (TBI) sample).



Sample Composition
Out of the total of 4509 CENTER-TBI core study participants, 554 individuals after TBI from the UK and 936 from the NL participated in the assessments at three months post-TBI and were included in the present study. When there were less than 30% of missing answers per QOLIBRI subscale, scores were calculated by using the prorating method.[14] Of the 1490, 830 individuals did not complete the QOLIBRI at three months.
Chi-square tests with Yates correction for nominal variables and independent t-test for continuous variables showed that participants from the NL had a higher level of education, were mostly female, working or studying, and had predominantly sustained a mild TBI (84% in the NL and 72% in the UK) with a good recovery rated by the Glasgow Coma Scale Extended (GOSE),[15] compared to those who did not complete the QOLIBRI. Analyses of contradictory response patterns did not reveal any peculiarities. No exclusion based on QOLIBRI response patterns was necessary for the TBI sample. A total of 660 individuals (UK: 228, NL: 432) were, therefore, included in the further analyses. For more details on TBI sample attrition, see Figure 2.

Ethical Approvals

General Population Sample
The study on the general population sample was part of the CENTER-TBI study and ethical approval was obtained from the Leids Universitair Centrum—Commissie Medische Ethiek (approval P14.222/NV/nv).

TBI Sample
The CENTER-TBI study (EC grant 602150) was conducted in accordance with all relevant laws of the European Union, which were directly applicable or had a direct effect, and all relevant laws of the countries in which the recruiting sites were located, including but not limited to, the relevant privacy and data protection laws and regulations (the "Privacy Law"), the relevant laws and regulations on the use of human materials, and all relevant guidance relating to clinical studies including, but not limited to, the ICH Harmonised Tripartite Guideline for Good Clinical Practice (CPMP/ICH/135/95, "ICH GCP") and the World Medical Association Declaration of Helsinki entitled "Ethical Principles for Medical Research Involving Human Subjects". Ethical approval was obtained for each recruiting site. The list of sites, ethical committees, approval numbers, and approval dates can be found on the project's website https://www.center-tbi.eu/project/ethical-approval.

Sociodemographic and Health Status Data
All study participants provided information regarding their age, sex, and level of education. Individuals from the general population samples were asked if they had one or more chronic health conditions (asthma, heart disease, stroke, diabetes, back complaints, arthrosis, rheumatism, cancer, memory problems due to a neurological condition like dementia, memory problems due to aging, depression,

or other problems). Multiple answers were allowed.
The severity of TBI was rated by attending clinical personnel using the Glasgow Coma Scale (GCS), with values of 3–8 indicating severe, 9–12 moderate, and 13–15 mild TBI.[16] Recovery after TBI was rated using the Glasgow Outcome Scale Extended (GOSE) with scores of 3–4 indicating severe, 5–6 moderate disability, and 7–8 good recovery. Scores of 2 indicate a vegetative state and a score of 1 death.[15]

Disease-Specific Health-Related Quality of Life after Brain Injury (QOLIBRI)
HRQoL was assessed administering the TBI-specific QOLIBRI questionnaire, which was developed and validated in accordance with the World Health Organization definition of health.[14, 17] It covers six life domains (Cognition, Self, Autonomy and Daily life, Social Relationships, Emotions and Physical Problems). Items contributing to the domains Emotions and Physical problems are negatively worded ("How bothered are you by…?"), the remaining items positively ("How satisfied are you with…?"). Thirty-seven items are rated on a 5-point Likert scale ("Not at all" = 1, "Slightly" = 2, "Moderately" = 3, "Quite" = 4, "Very" = 5) and reverse coding was performed for negatively worded items. The QOLIBRI total score is scaled to vary between 0 (worst possible HRQoL) and 100 (best possible HRQoL).[14]
As not all items were directly applicable to the general population, three items were reworded to remove any reference to a TBI: "How satisfied are you with what you have achieved recently (instead of "since your brain injury")?", "How bothered are you by the effects of any injuries you sustained? (instead of "any other injuries you sustained at the same time as your brain injury")", and "Overall, how bothered are you by the effects of any health problems? (instead of "brain injury")".

Statistical Analyses
The statistical analyses comprised the following steps: (1) examination of the psychometric properties of the QOLIBRI on the item and scale level in the general population; (2) MI analyses between groups of individuals from the TBI and general population samples and between the countries, to ensure that the same concept of HRQoL was being measured; (3) multivariate linear regression analyses, which examined whether country of residence, age, sex, level of education, and the presence of chronic health conditions affected the HRQoL/QOLIBRI total score; (4) based on the regression results, computation of reference values for individuals with and without chronic health conditions for the QOLIBRI total score and subscales with respect to age, sex, and level of education.
Descriptive statistics (mean, standard deviation, response frequencies) were used to describe participants' sociodemographic and health-related data.

Item Characteristics of the QOLIBRI in the General Populations
As the main focus of this study was to provide reference values for the QOLIBRI from general population samples, item properties such as mean, standard deviation, skewness, and ceiling effects are only reported for the general population samples. Items with absolute skewness values between 1.0 and 1.3 were interpreted as

moderately skewed and not affecting further analysis.[10, 18] Due to the high variation in cut-off values for ceiling effects (15–60%) in the current literature,[10, 19] we set the cut-off value at 40% (twice as high as by chance, 1/5 = 20%) for the maximum response category “very”. Additionally, we checked if there were items with less than 10% of responses in the two lower response categories “not at all” and “slightly”.

Scale Characteristics of the QOLIBRI in the General Populations

The scales’ internal consistency was determined using Cronbach’s alpha, with values between 0.7 and 0.95 indicating good to excellent internal consistency. [19] An item was defined as inconsistent when the corrected item-total correlation coefficient (CITC) exceeded 0.4.[20] Correlations between the QOLIBRI domains were investigated using Pearson correlation coefficients, with values ranging from 0.36 to 0.67, indicating a moderate linear association.[21]

Construct Validity of the QOLIBRI in the General Populations

As a prerequisite for MI testing, construct validity was investigated in the general population samples to ensure the comparability of the reworded and the original QOLIBRI using confirmatory factor analysis (CFA) with the robust weighted least squares estimator (WLSMV, calculated with the lavaan-package in R [22]). Model fit was assessed by means of the scaled chi-square statistics, Comparative Fit Index (CFI), and root mean square error of approximation (RMSEA) with a 90-percent confidence interval. As the standard cut-offs for CFI (>0.95) and RMSEA (<0.06),[23,24] indicating good model fit, have not been validated for the WLSMV estimator, and they should be interpreted with caution.[25] To address this issue, we compared fit indices across models with different factorial structures (one common factor, two correlated factors—one containing all positively worded “satisfaction” items, and the other one all negatively worded “bothered” items, and six correlated factors) with higher CFI values and lower RMSEA values indicating a better model.
2.5.4. Measurement Invariance in All Samples

By using modern statistical techniques, such as MI testing, it is possible to verify whether the questionnaire score differences between individuals, e.g., with and without TBI experience, can be attributed to true differences in HRQoL or rather to differences in interpretation of the items and response categories, as well as differences in items difficulty and their importance.[26]

Therefore, MI testing in the framework of CFA was applied to examine whether TBI experience and cultural/language differences influenced the comprehension of the QOLIBRI items. First, we examined the influence of the TBI experience on the invariance of model parameters by comparing groups of individuals from the TBI and general population samples separately for each country. To overcome estimation problems due to the large number of estimated parameters and relatively small sizes of the two TBI samples, the QOLIBRI items were dichotomized. The response categories “not at all”, “slightly” and “moderately” were coded as 0, and “quite” and “very” as 1. We then investigated the effect of the country by comparing

UK and NL general population samples.
The strategy for analyzing ordinary scaled response categories suggested by Wu and Estabrook (2016) was applied, resulting in three steps: testing of the (1) configural, (2) partial, and (3) full invariance model. For more details, see Wu and Easterbrook.[27]

For MI analyses, at least N = 200 observations per group are necessary to obtain reliable results.[28] All estimations for invariance testing (WLSMV-estimator, theta-parameterization) were performed within the lavaan-package (version 0.6-3).[22] For model comparisons, we applied a scaled chi-square difference test with the significance level set to $\alpha = 0.05$. As this test has been criticized for being very powerful in detecting small, possibly irrelevant effects in large samples,[29] in case of invariance violation, we estimated whether the effect had a practical significance for estimating the probability of choosing a particular response category. For example, if the full invariance model (invariant thresholds) had a significantly worse fit than the partial invariance model (noninvariant thresholds), the probabilities of individuals from general population samples choosing a particular response category were estimated in both models, and then compared. If the differences did not exceed 5%, we considered the thresholds to be invariant.[30]

Reference Values from General Population-Based Samples

As clinicians may be interested in the subjective health status and HRQoL of a single patient after TBI, population-based reference values were calculated as percentiles. Percentiles indicate the value below which a given percentage of observations falls. Based on this information, one can determine whether the QOLIBRI score of an individual after TBI is below, equal to, or above the value of the reference population. The following percentiles are provided for a patient-level interpretation: 2.5%, 5%, 16%, 30%, 40%, 50%, 60%, 70%, 85%, 95%, and 97.25%. HRQoL is considered to be impaired when scores are one standard deviation below the average of the general population sample,[31] which corresponds to the 16%-quantile when the data are assumed to be normally distributed. Examples are given in the results section.
Previous research has shown that 50 to 75 cases for each subgroup can already be sufficient to provide norm values.[32] However, as several factors can influence the required sample size (e.g., which type of norms are provided [33]), we have decided to report reference values when the number of cases was at least N = 100. All analyses were performed in R 3.6.0.[34]

Results

Sociodemographic and Health-Related Data

General Population Sample

Study participants (N = 4403 from the UK and N = 3399 from the NL) from the general population samples were analyzed. Individuals without a chronic health condition (UK: 2016; NL: 1572) were differentiated from individuals with chronic health conditions (UK: 2387; NL: 1827; for details, see Table 1). In both countries, up to 55% of individuals from the general population samples indicated that they had at least one chronic health condition, and, in comparison with the TBI samples, significantly more individuals described themselves as being unable to work (UK: 10%, NL: 12.8%).

TBI Sample

The TBI sample contained 660 individuals (N = 228 from the UK and N = 432 from the NL), who had filled in the QOLIBRI at three months post-TBI. The majority of individuals from both TBI samples had experienced a mild TBI (71.9% and 84.1 % in the UK and NL, respectively). In the UK, almost half of all individuals after TBI made a good recovery 48.7% (NL: 66.2%) and 20% were still severely disabled (NL: 8.8%) at three months post-TBI. Sociodemographic and health-related data for all samples are presented in Table 1.

Table 1. Sociodemographic and health-related data.

	UK			NL		
	Gen. pop. Sample	TBI Sample		Gen. pop. Sample	TBI Sample	
	N = 4403	N = 228	p	N = 3399	N = 432	p
Age in years						
mean ± SD	44.52 ± 15.66	49.73 ± 17.79	<0.001	45.2 ± 15.3	55.4 ± 18.8	<0.001
Age category						
18–40	1885 (42.8%)	67 (29.4%)	<0.001	1338 (39.4%)	98 (22.7%)	<0.001
41–64	1954 (44.4%)	113 (49.6%)		1651 (49.6%)	175 (40.5%)	
65+	564 (12.8%)	48 (21.1%)		410 (11.0%)	159 (36.8%)	
Gender						
Male	2134 (48.5%)	152 (66.7%)	<0.001	1665 (49.0%)	253 (58.6%)	<0.001
Female	2269 (51.5%)	76 (33.6%)		1734 (51.0%)	179 (41.4%)	
Educational level						
Low	1002 (22.8%)	7 (3.1%)	<0.001	1024 (30.1%)	14 (3.3%)	<0.001
Middle	1884 (42.8%)	99 (43.4%)		1526 (44.9%)	239 (55.3%)	
High	1517 (34.5%)	98 (43%)		849 (25.0%)	137 (31.7%)	
NA		24 (10.5%)			42 (9.7%)	

Work status (before TBI)						
In work	2267 (51.5%)	145 (63.6%)	<0.001	1776 (52.3%)	202 (46.8%)	<0.001
Out of work	399 (9.0%)	7 (3.1%)		374 (11.0%)	12 (2.8%)	
Looking after others	305 (6.9%)	1 (0.4%)		145 (4.3%)	7 (1.6%)	
Student	265 (6.0%)	10 (4.4%)		223 (6.6%)	34 (7.9%)	
Retired	725 (16.5%)	50 (21.9%)		446 (13.1%)	143 (33.1%)	
Unable to work	442 (10.0%)	3 (1.3%)		435 (12.8%)	7 (1.6%)	
NA		12 (5.3%)			27 (6.2%)	
Type of chronic health condition *						
Asthma	602 (13.0%)	-	-	336 (9.4%)	-	-
Heart disease	109 (2.3%)	-		102 (2.9%)	-	
Stroke	74 (1.6%)	-		81 (2.3%)	-	
Diabetes	390 (8.4%)	-		274 (7.7%)	-	
Back conditions	567 (12.2%)	-		355 (10.0%)	-	
Arthrosis	141 (3.0%)	-		346 (9.7%)	-	
Rheumatisms	192 (4.1%)	-		218 (6.1%)	-	
Cancer	128 (2.8%)	-		140 (3.9%)	-	
Memory problems (dementia)	82 (1.8%)	-		94 (2.6%)	-	
Memory problems (aging)	205 (4.4%)	-		82 (2.3%)	-	
Depression	1254 (27%)	-		423 (11.9%)	-	
Other	493 (10.6%)	-		628 (19.3%)	-	
Number of chronic health conditions						
None	2016 (45.8%)	-	-	1572 (46.2%)	-	-
One	1379 (31.3%)	-		1088 (32.0%)	-	
Two and more	1008 (22.9%)	-		739 (21.8%)	-	
TBI-severity (GCS)						
Mild	-	164 (71.9%)	-	-	366 (84.7%)	-
Moderate	-	7 (3.1%)		-	27 (6.3%)	
Severe	-	51 (22.4%)		-	29 (6.7%)	
NA	-	6 (2.6%)		-	10 (2.3%)	
Recovery status (GOSE) at 3 months postinjury						
Good recovery	-	111 (48.7%)	-	-	286 (66.2%)	-
Moderate disability	-	68 (29.8%)		-	107 (24.8%)	
Severe disability	-	47 (20.6%)		-	38 (8.8%)	
NA	-	2 (0.9%)		-	1 (0.2%)	

Note. Type of chronic health condition: multiple answers were allowed, therefore percentages were calculated separately for each complaint based on the total sample size; 65+: general population sample: 65–75, TBI-sample: 65–95; - : when data was not assessed; In work: general population sample: employee and self-employed, TBI-sample: 35+ h/week and 20–34 h/week and <20 h/week and currently on sick leave and special employment; Out of work: general population sample: for more than 1 year and less than 1 year, TBI-Sample: unemployed; Housekeeper: general population sample: looking after others, e.g., kids or parents; Education level: TBI-sample: "low": currently in school and primary school, "middle": currently in diploma and secondary school/high school and post-high school, "high": college/ university.

Abbreviations. UK = the United Kingdom; NL = the Netherlands; Gen. pop. = general population sample; TBI = TBI sample; p = p-value obtained with independent samples t-test for age or with chi-square test with Yates correction for gender, educational level, and work status; GCS = Glasgow Coma Scale; GOSE = Glasgow Outcome Scale Extended.

Comparison of the General Population Samples with TBI Samples

In both countries, significant differences were identified between the general population samples and the TBI samples concerning age, sex, educational level, and work status. In both general population samples, individuals were younger than in the TBI samples (with an average age difference of five years in the UK and of 10 years in the NL) and had a lower male incidence (UK: 48.5% vs. 66.7%, NL: 49.0% vs. 58.6%). The rate of individuals with a high level of education (diploma, secondary/high school, or post-high school) was lower in the general population samples compared with the TBI samples (UK: 34.5% vs. 43%; NL: 25% vs. 31.7). In the UK, the number of working individuals was lower in the general population sample compared with the TBI sample (51.5% vs. 63.6%, respectively), whereas in the NL the general population sample contained more employed individuals compared with the TBI sample (52.3% vs. 46.8%, respectively).

Item Characteristics of the QOLIBRI in the General Population Samples

On a descriptive level, there were some differences between countries concerning the item characteristics: individuals from the UK general population sample scored lower on average but with higher dispersion and mean values varying from 3.0 (satisfaction with sex life) to 4.1 (satisfaction with the ability to find a way around; NL: from 3.5 to 4.2); items were less skewed ((−1; −0.2), NL: (−1.3; −0.3)), and a ceiling effect was observed for only six items, compared with 10 in the NL sample. All items in the UK sample and 22 items in the NL sample had over 10% responses in two adjusted response categories "not at all" and "slightly". For more detailed information, see Appendix A Table A1.

Scale Characteristics of the General Population Samples

The total scale Cronbach's alpha was high in both general population samples (UK: 0.94, NL: 0.96), and per-scale alpha coefficients ranged between 0.86 (Emotions) and 0.95 (Cognition) in the UK general population sample, and between 0.86 and 0.92 in the NL, indicating a very good internal consistency of the scales. Also based on CITC, all items were found to be consistent in both samples. QOLIBRI domains

were moderately to highly correlated (UK: 0.39–0.77, NL: 0.46–0.76). For more detailed information, see Appendix A Table A2.

Construct Validity of the General Population QOLIBRI

Based on CFA results, a six-factorial structure was most appropriate for the QOLIBRI in the UK ($\chi 2(614) = 15{,}441$, $p < 0.001$, CFI = 0.957, RMSEA = 0.074, 90%CI (0.073; 0.075)) and also in the NL ($\chi 2(614) = 10{,}276$, $p < 0.001$, CFI = 0.952, RMSEA = 0.068, 90%CI (0.067; 0.069)) general population samples. For more detailed information, see Appendix A Table A3.

Measurement Invariance

When the general population and TBI samples were compared for each country, the fit of the model with six correlated factors was not negatively affected by constraining equal intercepts, loadings, and residuals across all groups (UK: $\Delta\chi 2(\Delta df) = 23.00$ (25), $p = 0.577$, NL: $\Delta\ \chi 2(\Delta df) = 8.27$ (25), $p = 0.999$). However, assuming equality of thresholds resulted in significantly higher chi-square values, indicating that some thresholds may not be invariant across groups. When UK and NL general population samples were compared, significant, yet very small, and thus, negligible chi-square differences ($\Delta\chi 2(\Delta df) = 87.27$ (25), $p < 0.001$) were observed.[32] The model fit deteriorated meaningfully when the thresholds were restricted to be equivalent across groups ($\Delta\chi 2(\Delta df) = 2395.26$ (148), $p < 0.001$). For details, see Appendix A Table A4.

More detailed analyses on the estimated thresholds using the partial invariance model showed that the thresholds obtained in the general population sample were significantly higher than those in the TBI sample. Comparing the UK and NL general population samples, the thresholds obtained from the UK sample were lower in all cases (see Appendix A, Figure A1). However, for individuals from the general population samples, differences in the probabilities of choosing a particular response category did not exceed 5% (Appendix A, Table A5). Therefore, the violation of the threshold invariance may be interpreted as not significant. This implies that the QOLBRI scores can be compared between countries, and between the general population and TBI samples. More important, differences in the QOLIBRI scores should be attributed to “real” differences in HRQoL.

Reference Values for the General Population Samples

A significant difference in HRQoL as indicated by the QOLIBRI total score, was found between the countries. The NL sample experienced a significantly higher HRQoL compared with the UK general population sample ($\beta = 8.76$, $p < 0.001$). Regression analyses identified a significant effect of age, level of education, presence of at least one chronic health condition, and interactions between age and sex and health status in both general population samples. No significant effects for sex were found in both general population samples (Table 2).

Table 2. Results of the multiple regression analyses (total sample, UK, and the NL).

		Total Sample		UK		NL	
Predictors and Interactions	**Reference Group**	**B**	**p**	**β**	**p**	**β**	**p**
NL	UK	8.76	**<0.001**	-	-	-	-
Age (41–64)	Age (18–40)	7.57	**<0.001**	9.36	**<0.001**	5.41	**<0.001**
Age (65–75)		13.11	**<0.001**	15.26	**<0.001**	9.91	**<0.001**
Sex (female)	Sex (male)	0.63	0.257	0.67	0.393	0.13	0.863
Education (middle)	Education (low)	3.07	**<0.001**	2.55	**<0.001**	3.57	**<0.001**
Education (high)		5.3	**<0.001**	5.35	**<0.001**	5.35	**<0.001**
Chronic health conditions (yes)	Chronic health conditions (no)	–16.38	**<0.001**	–16.70	**<0.001**	–15.88	**<0.001**
Age (41–64) × Chronic health conditions (yes)	Age (18–40) × Chronic health conditions (no)	–0.43	0.598	–2.80	**0.015**	2.02	0.066
Age (65–75) × Chronic health conditions (yes)		4.89	**<0.001**	4.91	**0.004**	4.98	**0.004**
Sex (female) × Chronic health conditions (yes)	Sex (male) × Chronic health conditions (no)	–0.19	0.805	–2.05	0.057	2.58	**0.012**

Note. β: regression coefficient; p: p-value; bold: p-values are significant on α = 0.05.

Reference values of the general population-based samples for the QOLIBRI total score are presented in Table 3 for the UK and Table 4 for the NL. The tables with the reference values for the QOLIBRI subscales can be found in the Online Supplement Materials (Table S1: UK; Table S2: NL).

Table 3. Reference values for the Quality of Life after Traumatic Brain Injury (QOLIBRI) total score obtained from the general population UK sample stratified by sex, health status, age, and education.

	Sex × Health status × Age			Low HRQoL		−1 SD			Md			+1 SD	High HRQoL	
Sex	**Health Status**	**Age**	**N**	**2.50%**	**5%**	**16%**	**30%**	**40%**	**50%**	**60%**	**70%**	**85%**	**95%**	**97.25%**
Female	Healthy	Age: 18–40	434	40	43	51	61	65	71	75	80	88	96	99
		Age: 41–64	408	49	50	60	71	76	80	84	88	94	100	100
		Age: 65–75	119	51	55	69	79	83	86	90	92	96	99	100
	At least one chronic condition	Age: 18–40	547	16	20	33	42	46	50	56	61	71	81	87
		Age: 41–64	587	12	19	36	46	50	55	61	68	79	90	94
		Age: 65–75	174	31	38	50	63	66	71	76	81	88	96	99
Male	Healthy	Age: 18–40	497	40	46	51	57	63	67	73	78	86	95	99
		Age: 41–64	442	49	50	59	70	75	80	83	87	95	100	100
		Age: 65–75	116	54	61	72	79	83	85	88	91	96	100	100
	At least one chronic condition	Age: 18–40	407	18	23	36	44	48	50	54	58	70	83	89
		Age: 41–64	517	14	19	36	46	52	57	64	71	83	93	98
		Age: 65–75	155	29	39	52	62	68	72	76	82	90	97	98

Sex × Health status × Education				Low HRQoL		−1 SD			Md			+1 SD	High HRQoL	
Sex	**Health Status**	**Education**	**N**	**2.50%**	**5%**	**16%**	**30%**	**40%**	**50%**	**60%**	**70%**	**85%**	**95%**	**97.25%**
Female	Healthy	education: low	193	44	49	54	65	71	77	81	85	93	97	100
		education: middle	383	46	49	57	67	73	79	82	87	94	100	100
		education: high	385	43	48	57	66	72	76	80	86	92	98	100
	At least one chronic condition	education: low	332	17	23	36	45	50	55	61	67	79	91	96
		education: middle	526	11	19	34	45	49	54	60	66	76	89	92
		education: high	450	16	21	38	45	50	56	62	69	78	87	93
Male	Healthy	education: low	197	41	46	54	61	71	78	81	85	95	100	100
		education: middle	493	45	49	54	63	69	74	79	83	91	99	100
		education: high	365	47	50	57	66	72	78	81	84	92	98	100
	At least one chronic condition	education: low	280	17	21	33	46	50	53	59	66	78	93	97
		education: middle	482	15	20	36	45	50	54	61	69	82	92	96
		education: high	317	25	28	44	50	54	58	63	71	83	92	97
		Total	4403	20	28	44	52	58	65	71	78	88	96	99

Note. 50% percentiles represent 50% of the distribution corresponding to the median (Md); Values from −1 standard deviation (16%) to +1 standard deviation (85%) are within the permissible range (i.e., not impaired HRQoL). Values below 16% (no symbols) indicate impaired HRQoL and values above 85% indicate outstanding HRQoL.
Abbreviations. HRQoL = health-related quality of life; SD = standard deviation.

Table 4. Reference values for the QOLIBRI total score obtained from the general population NL sample stratified by sex, health status, age, and education.

Sex × Health Status × Age				Low HRQoL		–1 SD			Md			+1 SD	High HRQoL	
Sex	**Health status**	**Age**	**N**	**2.50%**	**5%**	**16%**	**30%**	**40%**	**50%**	**60%**	**70%**	**85%**	**95%**	**97.25%**
Female	Healthy	Age: 18–40	338	50	52	63	71	75	79	83	86	92	98	100
		Age: 41–64	292	50	58	69	75	79	83	86	90	96	100	100
		Age: 65–75	66	61	61	75	79	81	84	88	90	96	98	99
	At least one chronic condition	Age: 18–40	364	32	37	49	55	60	63	68	73	81	87	92
		Age: 41–64	527	38	44	54	62	66	71	75	79	87	94	96
		Age: 65–75	147	47	52	63	69	73	75	80	83	88	93	94
Male	Healthy	Age: 18–40	388	49	50	57	69	74	77	81	86	94	100	100
		Age: 41–64	396	53	56	68	75	79	83	89	92	96	100	100
		Age: 65–75	92	65	73	77	81	84	88	91	93	96	99	100
	At least one chronic condition	Age: 18–40	248	30	38	48	52	54	57	60	67	77	88	91
		Age: 41–64	436	31	37	50	58	63	69	73	77	86	95	98
		Age: 65–75	105	47	51	61	69	75	80	83	86	92	96	97

Sex × Health Status × Education				Low HRQoL		–1 SD			Md			+1 SD	High HRQoL	
Sex	**Health status**	**Education**	**N**	**2.50%**	**5%**	**16%**	**30%**	**40%**	**50%**	**60%**	**70%**	**85%**	**95%**	**97.25%**
Female	Healthy	education: low	171	49	50	61	70	75	79	82	86	94	99	100
		education: middle	341	50	56	68	75	78	81	84	88	95	100	100
		education: high	184	51	59	69	75	79	84	86	88	93	98	99
	At least one chronic condition	education: low	374	34	41	52	59	65	68	73	78	84	91	96
		education: middle	477	34	42	52	60	64	69	73	78	85	92	96
		education: high	187	43	48	54	63	67	71	76	80	86	92	95
Male	Healthy	education: low	202	50	50	60	71	76	79	82	88	95	99	100
		education: middle	394	50	54	65	74	77	81	85	92	96	100	100
		education: high	280	50	52	66	75	79	83	88	91	96	100	100
	At least one chronic condition	education: low	277	30	35	50	57	61	66	70	75	83	93	96
		education: middle	314	32	41	49	56	59	66	72	77	86	96	98
		education: high	198	36	42	50	57	62	68	72	79	87	92	95
		Total	3399	39	46	55	65	71	75	79	83	92	98	100

Note. 50% percentiles represent 50% of the distribution corresponding to the median (Md); Values from –1 standard deviation (16%) to +1 standard deviation (85%) are within the permissible range (i.e., not impaired HRQoL). Values below 16% (no symbols) indicate impaired HRQoL and values above 85% indicate outstanding HRQoL.
Abbreviations. HRQoL = health-related quality of life; SD = standard deviation.

The following example illustrates how to apply these norms. After a TBI, a 70-year-old woman from the UK without any chronic health condition reports a QOLIBRI total score of 75. The table depicts that around 20% of healthy individuals in her age group reported the same level of HRQoL or a lower HRQoL. In other words, 80% of the reference population experience better HRQoL. Should a chronic health condition be known, 60% of the reference population from her age and health status group report better HRQoL and 40% of the general population with similar conditions experience a better HRQoL than she does.
Based on the 16%-percentile cut-off value, HRQoL is interpreted as impaired for female healthy individuals in the age range of 64–75 years when the QOLIBRI total score is under 69, or under 50 if any chronic health condition is reported. The score of 75 exceeds both cut-off values and can, therefore, be interpreted as indicating that she is not impaired (compared with individuals from the UK general population aged between 65–75 years with and without any chronic health condition).

Discussion

The aim of our study was to enhance the interpretability of disease-specific HRQoL after TBI using the QOLIBRI by establishing reference values from general population samples in the UK and the NL, based on representative quotas with regard to sex, age, and educational level. The representation of these characteristics corresponds to their distribution in the UK and the NL general populations (e.g., see the Organisation for Economic Co-operation and Development (OECD) [35] for sociodemographic characteristics in European countries). In this respect, the data from our general population samples are comparable to the general population of each country. This study is unique, as such general population-based reference values are currently not available for the QOLIBRI.

The results indicated that the reworded QOLIBRI is applicable to general population samples and displays good psychometric properties. Measurement invariance testing demonstrated that for the six HRQoL subdomains, all QOLIBRI items have the same meaning for individuals with and without a TBI experience and in the different countries. Therefore, we conclude that the QOLIBRI scores can be compared across general population samples and TBI samples in the UK and the NL. The differences in the scores have to be explained by “real” differences in HRQoL and not by other factors, such as differences in the understanding of items or response categories. Thus, we were able to establish population-based reference values.

In previous research, individuals from the NL general population reported higher mental summary component scores in the SF-36 in comparison to seven other countries, including five European countries.[36] Lower HRQoL was associated with the presence of chronic health conditions.[37] Our results replicate these findings,

with individuals from the NL general population sample reporting significantly higher HRQoL compared to those from the UK. Previous findings concerning the association of HRQoL with age are ambiguous: in the general populations of Norway and Canada, higher age was positively associated with the mental summary component score of the SF-36 and negatively with the physical summary component.[38,39] Our data showed that older individuals from the general population samples from both countries and subsamples with and without chronic health conditions report better HRQoL. Our study did not identify any sex differences in the two countries, with the exception of the subgroups with and without any chronic health conditions in the NL sample. This finding is also comparable to a study assessing the generic HRQoL by means of the SF-36: here only the general health perception scale was sensitive to sex differences, with females reporting lower generic HRQoL.[8,40]
Previously, the interpretation of the QOLIBRI total score was facilitated through a cross-walk analysis with the mental component summary score of the SF-36, for which US population-based norms were used.[41] HRQoL was considered to be impaired when scores were one standard deviation below the average of the general population sample.[35] Therefore, QOLIBRI values under 60 indicated impaired disease-specific HRQoL.[41] Our reference values provide a country-adapted basis because they were obtained from general population samples. Here, cut-off values of 56 for the UK and 65 for the NL should be taken to identify impaired TBI-specific HRQoL when comparing individuals after TBI with healthy individuals. As we found significant differences between the countries, we strongly recommend using the respective population-based reference values presented in the current study when the QOLIBRI is applied.

Strengths and Limitations

A strength of the present study is the large size of the general population samples, which allowed for high-powered statistical analyses. The stratification into healthy individuals and those having reported at least one chronic health complaint offers an additional possibility for the interpretation of HRQoL of individuals after TBI.
The representativeness of the recruited samples may be questioned. First, the selection of participants was based on different web-based panels. This might have led to different selection biases, even when several platforms were used for recruiting in order to increase the representativeness of different groups. Second, no information was available from the survey agency concerning participants who were contacted but did not take part in the survey. In other words, it was not possible to determine how many and which individuals could have potentially participated in the study, as a means of demonstrating a selection bias. Third, answers given in the online survey could be associated with (self-)selection and nonresponse bias,[42,43] as some individuals may systematically participate in online surveys.
Yet, the sampling procedure was strictly based on demographic characteristics such as age, sex, and education, and on a very large panel involving individuals from different sources. The quota sampling with respect to age, sex, and level of education corresponded to the distribution in the general populations of the two countries (see OECD statistics [35]). Therefore, the samples seem valid for providing

reference values to evaluate the degree of impairment of HRQoL in individuals after TBI.

Another limitation was the lack of precise information concerning previously experienced TBIs in the general population samples. However, the estimated TBI prevalence based on reported age-adjusted hospital discharge rates due to TBI is quite low and reaches 312.7 per 100,000 in the UK and 173.7 per 100,000 in the NL.[44] Thus, the presence of individuals, who experienced TBI in the general population samples, was very unlikely to cause a bias concerning the reference values and evaluation of HRQoL.

The baseline characteristics of the general and the TBI sample displayed differences with regard to sex, age, and education status. However, such differences are unavoidable bearing in mind the two times higher prevalence of TBI among males [45] and increasing TBI incidence in elderly people,[46] resulting in differences in work status distribution, and in higher rates of retired individuals in the TBI samples. Furthermore, the relatively small sizes of the TBI samples required dichotomization of the QOLIBRI response categories for MI testing, which is associated with a loss of information concerning response patterns. However, the TBI sample was only used to ensure the methodological comparability of the QOLIBRI in general population samples by MI analyses. It turned out that the factorial structure and the understanding of the HRQoL construct measured by the QOLIBRI were comparable between the general population samples and the TBI samples in both countries. Thus, the reference values established here are reliable.

Conclusions

This paper aimed to provide a basis for a better understanding of HRQoL after TBI in research and clinical practice. For this purpose, population-based reference values were developed to add value to the interpretation and clinical meaningfulness of QOLIBRI scores of individuals after TBI. Significant differences in the reported levels of HRQoL were found between the UK and the NL general population samples as well as between the TBI and the general population samples. Therefore, we have presented population-based reference values separately for the two countries. We recommend establishing population-based reference values also for other countries in future research, especially for lower-income countries, as these are a key component for understanding therapeutic progress in individual cases and enabling research on HRQoL.

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Appendix

Table A1. Characteristics of the QOLIBRI items.

General Population Sample								
	UK	NL	UK	NL	UK	NL	UK	NL
QOLIBRI Items	**mean ± SD**		**Skewness**		**Ceiling (%)**		**% "not at all" and "slightly"**	
Cognition	71.1 ± 24.4	78.4 ± 18.1	–0.8	–0.9	15.1	16.8	-	-
Concentrate	3.7 ± 1.2	4.0 ± 0.9	–0.6	–1	30.4	34.5	17	7
Express yourself	3.8 ± 1.1	4.1 ± 0.9	–0.8	–1.1	35.2	38	13	6
Memory	3.7 ± 1.1	4.1 ± 0.9	–0.6	–1	26.8	33.8	15	6
Plan and problem solve	3.9 ± 1.1	4.2 ± 0.9	–0.8	–1.2	35	41	12	5
Decisions	3.9 ± 1.1	4.1 ± 0.9	–0.9	–1.1	38.6	39	11	5
Navigate	4.1 ± 1.1	4.2 ± 0.9	–1	–1.2	46.2	44.7	10	4
Speed of thinking	3.9 ± 1.1	4.2 ± 0.9	–0.8	–1.2	32.7	39.6	12	5
Self	54.8 ± 27.4	68.6 ± 20.3	–0.2	–0.7	6.2	6.4	-	-
Energy	3.2 ± 1.2	3.5 ± 1.0	–0.3	–0.6	13	15.1	27	15
Motivation	3.2 ± 1.2	3.7 ± 1.0	–0.3	–0.7	15.4	21.2	26	11
Self-esteem	3.2 ± 1.3	3.8 ± 1.0	–0.2	–0.8	17.2	28.2	30	11
Appearance	3.1 ± 1.2	3.8 ± 1.0	–0.2	–0.8	13.4	20.2	31	10
Achievements	3.2 ± 1.2	3.8 ± 1.0	–0.2	–0.8	16.2	25.8	29	11
Self-perception	3.2 ± 1.2	3.8 ± 1.0	–0.3	–0.9	14.8	21.7	28	11
Future	3.2 ± 1.2	3.7 ± 1.0	–0.2	–0.8	15.4	21.5	29	12
Daily life and autonomy	66.5 ± 26.2	75.5 ± 19.4	–0.6	–0.8	11.9	13.2	-	-
Independence	3.7 ± 1.2	4.1 ± 1.0	–0.7	–1	33.3	38.4	16	7
Get out and about	3.8 ± 1.2	4.2 ± 0.9	–0.8	–1.3	40.2	45.3	16	5
Domestic activities	3.9 ± 1.2	4.1 ± 1.0	–0.8	–1.1	40.7	42.5	15	7
Run personal finances	3.8 ± 1.2	4.2 ± 0.9	–0.8	–1.2	36.7	43.5	16	6
Participation work	3.5 ± 1.3	3.8 ± 1.2	–0.5	–0.9	27.4	30.6	22	15
Social and leisure activities	3.3 ± 1.3	3.8 ± 1.1	–0.3	–0.8	21.5	26.9	28	13
In charge of life	3.6 ± 1.2	4.0 ± 0.9	–0.6	–1	28.8	35	18	7
Social relationships	63.9 ± 26.0	74.0 ± 19.6	–0.5	–0.8	11	11.5	-	-
Affection towards others	3.8 ± 1.2	4.2 ± 0.9	–0.7	–1.2	34	43.9	15	6
Family	3.8 ± 1.2	4.0 ± 1.0	–0.7	–1	33.8	35.9	15	8
Friends	3.6 ± 1.2	4.0 ± 0.9	–0.6	–1.1	28.8	34.9	18	7

Partner	3.7 ± 1.3	4.0 ± 1.1	–0.7	–1.1	37.1	43	19	10
Sex life	3.0 ± 1.4	3.5 ± 1.2	–0.1	–0.7	20.6	23.9	35	19
Attitudes of others	3.4 ± 1.1	3.9 ± 0.9	–0.4	–0.9	19.7	26.4	19	7
Emotions	59.4 ± 28.0	68.4 ± 24.4	–0.2	–0.4	11.6	15.4	-	-
Feel lonely	3.5 ± 1.3	3.5 ± 1.3	–0.4	–0.3	32.1	29.2	24	25
Feel bored	3.4 ± 1.3	3.6 ± 1.2	–0.3	–0.5	26.2	28.2	26	20
Feel anxious	3.3 ± 1.4	3.7 ± 1.2	–0.2	–0.6	25.1	35.2	32	15
Feel sad	3.3 ± 1.4	3.7 ± 1.3	–0.2	–0.6	27	35.5	31	18
Feel angry	3.6 ± 1.3	3.9 ± 1.2	–0.5	–0.8	34.7	41.6	22	13
Physical problems	66.8 ± 27.0	70.0 ± 23.5	–0.5	–0.5	15.6	15.3	-	-
Slow/clumsiness	3.8 ± 1.2	3.9 ± 1.1	–0.7	–0.7	40.8	38.8	17	14
Effects injuries	3.9 ± 1.2	3.9 ± 1.2	–0.8	–0.9	46.4	47.2	15	16
Pain	3.5 ± 1.3	3.6 ± 1.2	–0.4	–0.4	28.6	28.8	23	22
See/hear	4.0 ± 1.2	4.0 ± 1.1	–0.9	–0.8	46	40.1	14	11
Effects health problems	3.5 ± 1.3	3.7 ± 1.2	–0.4	–0.5	28.8	31.1	23	19
QOLIBRI total score	63.8 ± 20.6	72.8 ± 16.6	–0.3	–0.5	1.6	1.9	-	-

Note. Ceiling effects are expressed as a percentage and represent the proportion of individuals who chose the response category "very" on the QOLIBRI items or reached the maximum of 100 on the respective QOLIBRI scales.

Abbreviations. Mean = mean value; SD = standard deviation.

Table A2. Psychometric properties of the QOLIBRI scales.

	Cronbach's Alpha	Item-Total Correlation Range	Correlations between Subscales Scores				
UK general population sample							
QOLIBRI domain			**(1)**	**(2)**	**(3)**	**(4)**	**(5)**
Cognition (1)	0.94	0.77–0.83	1				
Self (2)	0.95	0.76–0.87	0.67	1			
Daily life and autonomy (3)	0.93	0.71–0.81	0.75	0.77	1		
Social relationships (4)	0.9	0.60–0.76	0.65	0.73	0.71	1	
Emotions (5)	0.87	0.62–0.79	0.46	0.51	0.49	0.47	1
Physical problems (6)	0.88	0.61–0.74	0.5	0.44	0.55	0.39	0.48
NL general population sample							
QOLIBRI domain			**(1)**	**(2)**	**(3)**	**(4)**	**(5)**
Cognition (1)	0.92	0.69–0.77	1				
Self (2)	0.92	0.70–0.81	0.68	1			
Daily life and autonomy (3)	0.89	0.61–0.73	0.7	0.76	1		
Social relationships (4)	0.86	0.60–0.72	0.58	0.66	0.66	1	
Emotions (5)	0.88	0.72–0.82	0.54	0.57	0.56	0.55	1
Physical problems (6)	0.86	0.54–0.78	0.52	0.57	0.62	0.45	0.49

Table A3. Results of confirmatory factor analyses.

UK General Population Sample							
					Model Comparison		
Model with Factors	**CFI**	**RMSEA (90%CI)**	**χ^2 (df)**	**p**	**Model with Factors**	**$\Delta\chi^2$ (Δdf)**	**p**
one	0.802	0.156 (0.155; 0.157)	68,302 (629)	<0.001			
two	0.889	0.117 (0.116; 0.118)	38,601 (628)	<0.001	one vs. two	3111.5 (1)	<0.001
six	0.957	0.074 (0.073; 0.075)	15,441 (614)	<0.001	two vs. six	5696.1 (14)	<0.001
NL General Population Sample							
					Model Comparison		
Model with Factors	**CFI**	**RMSEA (90%CI)**	**χ^2(df)**	**p**	**Model with Factors**	**$\Delta\chi^2$(Δdf)**	**p**
one	0.8	0.137 (0.136; 0.138)	40,659 (629)	<0.001			
two	0.868	0.111 (0.110; 0.113)	27,135 (628)	<0.001	one vs. two	1725.3 (1)	<0.001
six	0.952	0.068 (0.067; 0.069)	10,276 (614)	<0.001	two vs. six	4313.8 (14)	<0.001

Abbreviations. CFI = scaled Comparative Fit Index; RMSEA (90%CI) = scaled root mean square error of approximation with 90% confidence interval; χ2 = scaled chi-square statistics; df = scaled degrees of freedom; p = p-value of chi-square (difference) statistics; Δχ2 = difference in chi-square statistics under Sattora.Bentler.2001 correction; Δdf = difference in degrees of freedom.

Table A4. Results of measurement invariance testing.

UK: General Population Sample vs. TBI Sample						
				Model Comparison		
CFI	**RMSEA (90%CI)**	**χ^2 (df)**	**p**	**Invariance Models**	**$\Delta\chi^2$ (Δdf)**	**P**
0.989	0.033 (0.032; 0.034)	4264 (1228)	<0.001			
0.991	0.029 (0.028; 0.031)	4740 (1253)	<0.001	Configural vs. partial	23.00 (25)	0.577
0.991	0.029 (0.028; 0.030)	4854 (1290)	<0.001	Partial vs. full	66.95 (37)	0.002
NL: General Population Sample vs. TBI Sample						
				Model Comparison		
CFI	**RMSEA (90%CI)**	**χ^2 (df)**	**p**	**Invariance Models**	**$\Delta\chi^2$ (Δdf)**	**P**
0.983	0.032 (0.031; 0.034)	3409 (1228)	<0.001			
0.986	0.029 (0.027; 0.030)	3544 (1253)	<0.001	Configural vs. partial	8.27 (25)	0.999
0.986	0.029 (0.028; 0.030)	3702 (1290)	<0.001	Partial vs. full	108.10 (37)	<0.001
UK vs. NL: General Population Samples						
				Model Comparison		
CFI	**RMSEA (90%CI)**	**χ^2 (df)**	**p**	**Invariance Models**	**$\Delta\chi^2$ (Δdf)**	**P**
0.956	0.071 (0.071; 0.072)	16696 (1228)	<0.001			
0.966	0.062 (0.061; 0.063)	17884 (2153)	<0.001	Configural vs. partial	87.27 (25)	<0.001
0.962	0.062 (0.061; 0.063)	20051 (1410)	<0.001	Partial vs. full	2395.26 (148)	<0.001

Note. Identification constraints for the invariance models: Configural: item intercepts = 0, residual variances = 1, latent factor means = 0, latent factor variances = 1 Partial: item intercepts = 0, residual variances = 1. Only in the reference group latent factor means = 0 and variances = 1; Full: item intercepts = 0, residual variances = 1. Only in the reference group factor means = 0, factor variances = 1.

Abbreviations. CFI = scaled Comparative Fit Index; RMSEA (90%CI) = scaled root mean square error of approximation with 90% confidence interval; $\chi2$ = scaled chi-square statistics; df = scaled degrees of freedom; p = p-value of chi-square (difference) statistics; $\Delta\chi2$ = difference in chi-square statistics under Sattora-Bentler (2001) correction; Δdf = difference in degrees of freedom.

Table A5. Response probabilities (RP) of the UK and NL general population samples to choose a response category estimated in the partial invariance model and their differences to the response probabilities estimated within the full invariance model.

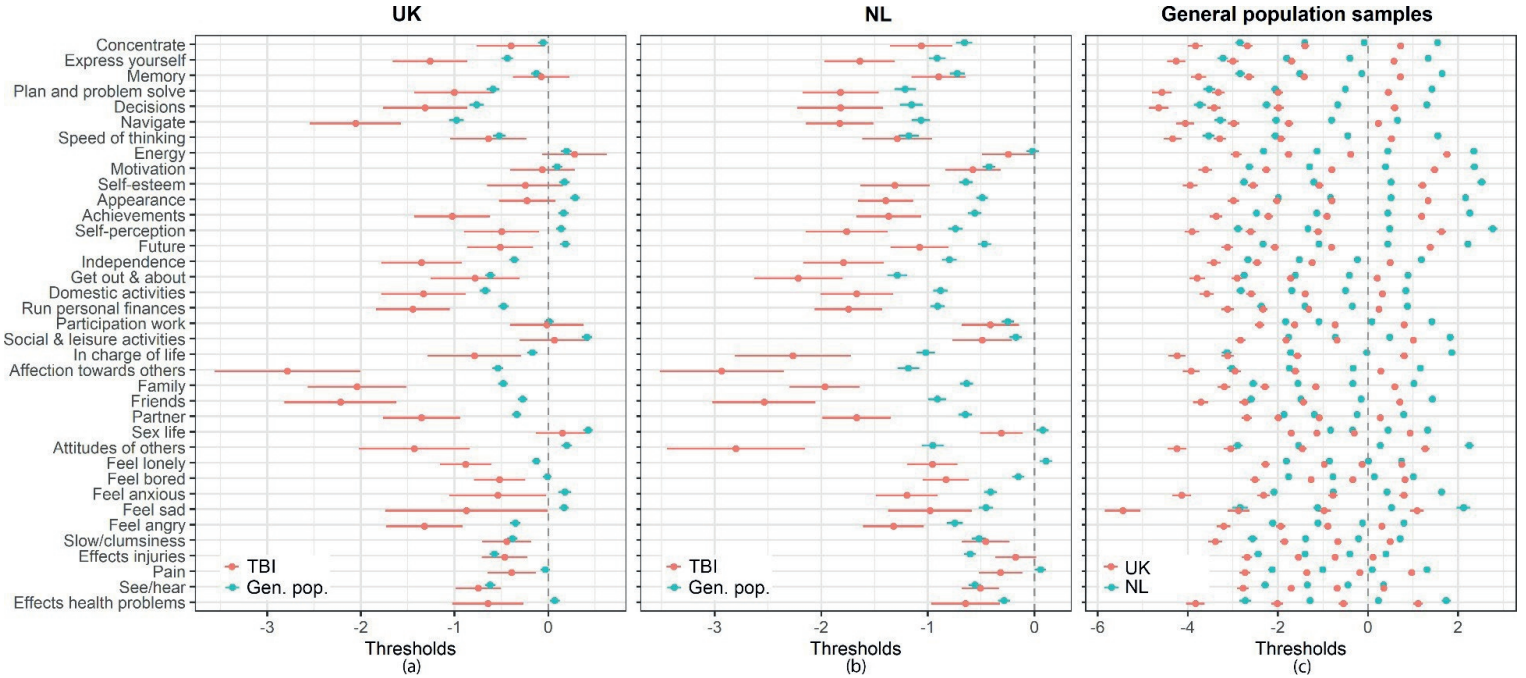
	UK Gen. pop. (TBI As a Ref.) [a]	NL Gen. pop. (TBI As a Ref.) [b]	NL Gen. pop. (UK As a Reference) [c]				
Cognition	**1** [d]	**1** [d]	**Not at all**	**slightly**	**moderately**	**quite**	**very**
Concentrate	0.614 (0.001)	0.777 (0.001)	0.050 (–0.001)	0.124 (0.012)	0.213 (0.014)	0.309 (–0.039)	0.304 (0.013)
Express yourself	0.670 (–0.003)	0.814 (–0.004)	0.038 (–0.001)	0.097 (0.005)	0.195 (0.013)	0.318 (–0.041)	0.352 (0.023)
Memory	0.624 (0.004)	0.793 (0.004)	0.042 (–0.001)	0.109 (0.009)	0.225 (0.022)	0.355 (–0.027)	0.268 (–0.003)
Plan and problem solve	0.685 (0.001)	0.841 (–0.001)	0.033 (–0.001)	0.086 (0.005)	0.196 (0.020)	0.334 (–0.035)	0.350 (0.011)
Decisions	0.705 (0.000)	0.824 (–0.001)	0.034 (–0.004)	0.080 (0.001)	0.181 (0.008)	0.319 (–0.043)	0.386 (0.038)
Navigate	0.747 (–0.004)	0.843 (–0.005)	0.026 (–0.002)	0.071 (0.001)	0.157 (0.001)	0.285 (–0.049)	0.462 (0.049)
Speed of thinking	0.677 (0.003)	0.836 (0.006)	0.032 (–0.004)	0.086 (0.007)	0.205 (0.022)	0.350 (–0.029)	0.327 (0.005)
Self							
Energy	0.431 (0.006)	0.589 (0.007)	0.116 (–0.014)	0.157 (–0.012)	0.296 (0.010)	0.300 (–0.005)	0.130 (0.020)
Motivation	0.448 (0.003)	0.667 (0.008)	0.109 (–0.003)	0.156 (–0.006)	0.288 (0.017)	0.294 (–0.021)	0.154 (0.013)
Self-esteem	0.438 (0.001)	0.696 (0.000)	0.129 (–0.003)	0.173 (0.006)	0.260 (0.020)	0.266 (–0.022)	0.172 (0.000)
Appearance	0.409 (–0.001)	0.69 (–0.008)	0.136 (0.004)	0.178 (0.018)	0.277 (0.022)	0.275 (–0.048)	0.134 (0.004)
Achievements	0.438 (–0.006)	0.69 (–0.003)	0.120 (–0.006)	0.166 (0.005)	0.275 (0.025)	0.276 (–0.025)	0.162 (0.001)
Self-perception	0.443 (–0.001)	0.701 (–0.003)	0.118 (–0.007)	0.166 (0.006)	0.273 (0.024)	0.295 (–0.031)	0.148 (0.008)
Future	0.433 (–0.002)	0.677 (–0.001)	0.123 (–0.008)	0.163 (0.005)	0.282 (0.025)	0.279 (–0.033)	0.154 (0.011)

Daily life & Autonomy							
Independence	0.623 (–0.003)	0.771 (–0.003)	0.056 (–0.003)	0.105 (0.005)	0.216 (0.009)	0.290 (–0.028)	0.333 (0.017)
Get out and about	0.655 (0.003)	0.836 (–0.001)	0.060 (0.001)	0.100 (0.012)	0.185 (0.014)	0.253 (–0.052)	0.402 (0.025)
Domestic activities	0.672 (–0.001)	0.791 (–0.001)	0.052 (–0.004)	0.095 (0.002)	0.182 (–0.001)	0.265 (–0.036)	0.407 (0.039)
Run personal finances	0.650 (–0.003)	0.81 (–0.004)	0.057 (0.000)	0.099 (0.009)	0.194 (0.013)	0.283 (–0.033)	0.367 (0.011)
Participation work	0.554 (0.003)	0.677 (0.007)	0.115 (–0.012)	0.100 (–0.010)	0.231 (0.022)	0.280 (–0.018)	0.274 (0.017)
Social and leisure activities	0.472 (0.001)	0.662 (0.005)	0.129 (0.007)	0.153 (0.010)	0.246 (0.016)	0.257 (–0.034)	0.215 (0.002)
In charge of life	0.584 (0.000)	0.773 (–0.001)	0.069 (–0.003)	0.114 (0.009)	0.233 (0.018)	0.296 (–0.033)	0.288 (0.010)
Social relationships							
Affection towards others	0.627 (–0.002)	0.806 (–0.001)	0.050 (–0.004)	0.105 (0.008)	0.218 (0.012)	0.287 (–0.030)	0.340 (0.014)
Family	0.633 (–0.001)	0.758 (–0.005)	0.057 (–0.007)	0.096 (–0.003)	0.213 (0.003)	0.295 (–0.035)	0.338 (0.042)
Friends	0.593 (–0.002)	0.784 (–0.002)	0.072 (0.000)	0.110 (0.007)	0.225 (0.013)	0.305 (–0.044)	0.288 (0.023)
Partner	0.615 (0.000)	0.758 (0.000)	0.102 (–0.001)	0.092 (–0.001)	0.191 (0.005)	0.244 (–0.032)	0.371 (0.028)
Sex life	0.425 (0.005)	0.591 (0.010)	0.234 (0.021)	0.120 (0.001)	0.221 (0.000)	0.218 (–0.039)	0.206 (0.017)
Attitudes of others	0.517 (0.000)	0.766 (0.000)	0.070 (0.001)	0.124 (0.010)	0.289 (0.031)	0.320 (–0.053)	0.197 (0.010)

Emotions							
Feel lonely	0.529 (–0.004)	0.534 (–0.010)	0.079 (–0.003)	0.160 (–0.035)	0.232 (–0.002)	0.208 (–0.006)	0.321(0.046)
Feel bored	0.494 (0.000)	0.589 (–0.003)	0.089 (0.006)	0.171 (–0.010)	0.245 (0.002)	0.232 (–0.023)	0.262(0.026)
Feel anxious	0.463 (0.002)	0.633 (–0.001)	0.136 (0.022)	0.181 (0.008)	0.219 (–0.010)	0.212 (–0.021)	0.251 (0.001)
Feel sad	0.474 (0.003)	0.620 (0.010)	0.138 (0.018)	0.171 (–0.007)	0.217 (–0.005)	0.204 (–0.018)	0.270 (0.011)
Feel angry	0.567 (–0.002)	0.695 (0.002)	0.082 (0.008)	0.136 (–0.001)	0.214 (0.003)	0.22 (–0.022)	0.347 (0.012)
Physical problems							
Slow/clumsiness	0.612 (0.002)	0.649 (0.002)	0.055 (0.008)	0.118 (–0.005)	0.214 (0.003)	0.204 (–0.021)	0.408 (0.015)
Effects injuries	0.658 (0.005)	0.679 (0.013)	0.048 (–0.004)	0.105 (–0.011)	0.189 (0.014)	0.194 (–0.003)	0.464 (0.004)
Pain	0.545 (–0.002)	0.542 (–0.010)	0.088 (0.006)	0.146 (–0.010)	0.221 (–0.007)	0.260 (0.009)	0.286 (0.002)
See/hear	0.674 (0.000)	0.688 (0.002)	0.041 (0.004)	0.098 (0.001)	0.187 (–0.008)	0.215 (–0.029)	0.460 (0.032)
Effects health problems	0.534 (–0.004)	0.595 (–0.006)	0.090 (0.011)	0.143 (–0.004)	0.233 (0.009)	0.245 (–0.010)	0.288 (–0.007)

Note. a Probabilities estimated for the NL general population sample from the invariance model comparing TBI and general population sample; b Probabilities estimated for the UK general population sample from the invariance model comparing TBI and general population sample; c Probabilities estimated for the NL general population sample from the invariance model comparing UK and NL general population samples; d For measurement invariance testing with TBI samples response categories "not at all" and "slightly" were recorded as 1.

Figure A1. (a) Comparison of the thresholds estimated with the partial invariance model for the UK TBI and general population samples; (b) Comparison of the thresholds estimated with the partial invariance model for the NL TBI and general population samples; (c) Comparison of the thresholds estimated with partial invariance model for the UK and NL general population samples.



Chapter 13

General Discussion

General Discussion

"Recovering from mild traumatic brain injury has been my biggest challenge. And after a very difficult 17 months I have come to realize that my priorities have changed and I can no longer be the athlete I have been, so proudly and for so long. The challenge of returning to play following my head injury is too much, and the risks too high. With my head injury and a different outlook on life, my family old and new are now my priority." -- Alex Danson, Olympic hockey Gold and Bronze medalist

The above quote perfectly portrays why research into mild traumatic brain injury is essential. Life can be turned upside down completely because of something that is classified as a 'mild' injury. Currently, there is no clear view on which patients will experience symptoms and longer lasting problems related to the injury, which is one of the main focus points of this thesis. The aim of this thesis was to study outcome assessment following traumatic brain injury (TBI) and measure outcome preferences in the fields of TBI and stroke. An overview of the main findings for the specific research questions presented in Chapter 1 can be found in Box 1. This chapter describes the main findings of this thesis. These findings will be discussed separately for assessing outcome and measuring outcome preferences, followed by recommendations for future research, research policy and clinical practice.

Box 1. Overview of main findings per research question.

1. What is the association between post-concussion symptoms and HRQoL in mTBI?

We observed an association between post-concussion syndrome (PCS) and lower health-related quality of life (HRQoL) for adult and paediatric patients. Approximately 20% of adult patients with mTBI suffering from PCS had a considerably lower HRQoL compared to patients without PCS at 6 months post-injury.

a. What is the outcome in divergent mTBI patient groups?

Approximately 30% of adult patients after mTBI were functionally impaired. Furthermore, patients after complicated mTBI reported worse functional outcome and lower generic and disease-specific HRQoL at three and six months post-injury compared to patients after uncomplicated mTBI. We observed no considerable improvement in outcomes from three to six months.

b. What are the prevalences and risk factors of post-concussion symptoms in mTBI patients and the general population?

Prevalence - Fatigue (42%), forgetfulness/poor memory (38%), and poor concentration (33%) were the most prevalent post-concussion symptoms reported by adult mTBI patients at six months post-injury. More than 60% of paediatric patients reported having at least one post-concussion symptom of at least mild severity. Remarkably high frequencies of post-concussion-like symptoms, such as fatigue (50%) and sleep disturbance (42%), were also found in the general population.

Risk factors - We identified female gender, education, injury severity, assault, hospitalization, complicated mTBI and post-concussion symptoms as risk factors for PCS in adult mTBI patients. For paediatric patients specifically, female gender was identified. For the general population age, female gender, education, work status, income level, chronic health complaints were identified as risk factors.

c. *How can we classify post-concussion symptoms and post-concussion syndrome after mTBI and to what extent are pre-injury ratings reliable?*

The choice of classification method and rating score both influenced PCS diagnosis at a population and at an individual level. Currently, there is no unambiguous and universal classification of PCS, however, we believe that patients should be evaluated for post-concussion symptoms and syndrome by the use of a combination between self-report and clinical evaluation (e.g. a multidimensional comprehensive assessment). In addition, we believe rating score 2 should be applied as cut-off for severity in self-report instruments.

Pre-injury ratings are not reliable since we found that more than half of patients were inconsistent in their post-injury ratings over time when reporting their pre-injury functioning.

2. What are preferences and utility weights for TBI and stroke health states and how could they be applied?

The responses on generic and disease specific measurements represent preferences for health states measured by these instruments, which ultimately means that preferences represent the value or desirability for individual health states. Preference elicitation methods can be used to assign utility weights to each item level of a preference-based instrument. Responses from the general population sample reflect preferences between different health states. Utility weights represent the relative preference for a year of life in a given health state and a greater weight is given to a more desirable/preferred health state. Value sets are needed to apply these utility weights in economic evaluations.

a. *What are preferences of the general population for disease specific outcome measures for TBI and which utility weights can be assigned to TBI value sets?*
The preferences of the general population determined that the biggest weight increase for all attributes of a disease specific outcome measure for TBI (e.g. QOLIBRI-OS) should be from the level 'slightly' to 'not at all satisfied', which consequently results in the largest impact on HRQoL. Health states values have to be anchored on a scale from 0 (dead) to 1 (full health) to be able to assign utility weights to value sets.

b. How can value sets and patient data be used to determine utility and/or disability weights for TBI and stroke health states?
A value set represents the collection of utility values for all possible health states described in a preference-based measure, which means that each health state can be converted into a single summary index. Patient data can be used to determine utility weights by averaging the derived utilities of all patients within each health state, after which this patient data can be used in a simulation study to evaluate statistical efficiency. Disability weights can be derived by mapping HRQoL data to preference-based instruments.

Main findings and interpretation

Part I - Outcome assessment following traumatic brain injury

In this part of the thesis, we focused on outcome assessment following mild TBI (mTBI) and described the association between post-concussion symptoms and health-related quality of life (HRQoL) in mTBI with an emphasis on prevalence and risk factors of post-concussion symptoms in mTBI patients and the general population. In addition, we focused on the classification of post-concussion symptoms and post-concussion syndrome (PCS) after mTBI and assessed to what extent pre-injury ratings of post-concussion symptoms are reliable. Lastly, we assessed the outcome in divergent mTBI patient groups.

Post-concussion symptoms and post-concussion syndrome

The majority (70-90%) of all TBI cases can be classified as mTBI. Many patients following mTBI experience post-concussion symptoms such as physical symptoms (e.g., headaches, dizziness, blurred vision, fatigue, and sleep disturbances), cognitive deficits (e.g., poor memory, and attention and executive difficulties), and behavioral/emotional symptoms (e.g., depression, irritability, anxiety-related disorders, and emotional lability)(1, 2). These symptoms will resolve and/or diminish for most patients within weeks to months after the injury, however, a subgroup of patients (estimated between 5%–43%(3-6)), will continue to report these symptoms for weeks, months or sometimes even longer. When a set of these symptoms persist for over 3 months, it is generally referred to as post-concussion syndrome (PCS) (5, 6).

Prevalence

In this thesis, considerable differences were found in prevalence rates for post-concussion symptoms and post-concussion syndrome (PCS). Prevalence rates are dependent on population, case-mix of the sample, setting, measurement instrument, and diagnostic criteria and classification methods applied (Chapter 2, 3, 4, 6, 7, 8). Fatigue, forgetfulness/poor memory, and poor concentration were the most prevalent post-concussion symptoms reported by adult patients (age ≥ 16) after mTBI at six months post-injury (Chapter 2). Almost 40% of adult patients were experiencing PCS six months post-injury (Chapter 3).

The most commonly reported symptoms by paediatric patients were headaches, fatigue, poor concentration, and forgetfulness and more than one third of paediatric patients reported at least one symptom of moderate or severe intensity. Roughly 55% of paediatric patients were experiencing PCS six months post-injury (Chapter 7).

Representative respondents from the United Kingdom, the Netherlands and Italy were used as norm population. Concentrating on the general population, we found high frequencies of post-concussion-like symptoms. Symptoms such as fatigue and sleep disturbance were the most frequently reported. Forty-five percent of respondents were classified as having PCS (Chapter 6).

When looking specifically at complicated (Glasgow Coma Scale (GCS) 13-15 and presence of computed tomography (CT) abnormalities) and uncomplicated (GCS 13-15 and absence of CT abnormalities) mTBI patients, patients after complicated mTBI reported slightly more post-concussion symptoms compared to those after uncomplicated mTBI. Approximately 43% of patients after complicated mTBI were classified as having PCS at six months compared to 34% of patients after uncomplicated mTBI (Chapter 4).

In this thesis, we found high prevalence rates of post-concussion symptoms and PCS in adult and paediatric patients after mTBI six months post-injury. Additionally, we found high prevalence rates of post-concussion-like symptoms and PCS in the general population, indicating that these symptoms are not specific for patients following mTBI and PCS is not a unique syndrome after mTBI. Consequently, implying that other factors play a role. For this reason, these concepts should be interpreted with caution and should never solely be used as outcome following mTBI.

Health-related quality of life
With regard to health-related quality of life (HRQoL), six months following mTBI, one in five adult patients suffering from PCS had a considerably lower HRQoL compared to patients without PCS and almost half of these patients were dissatisfied with their functioning (Chapter 3). Furthermore, paediatric patients with PCS had significant lower Quality of Life after Traumatic Brain Injury (QOLIBRI) total scores, indicating lower HRQoL, compared to patients without PCS. Lastly, in the general population, patients classified with PCS had lower EQ-5D utility and total scores, and EQ-5D visual analogue scale (VAS) scores (Chapter 6), which again indicates that PCS has strong impact on an individuals' HRQoL.

We evaluated the correlation between post-concussion symptoms and different HRQoL instruments, to assess the relation between these symptoms and the various HRQoL instruments. We found negative correlations between all items of the Rivermead Post-Concussion Symptoms Questionnaire (RPQ) and the 36-Item Short Form (SF-36) domains, Perceived Quality of Life (PQoL) subscales and QOLIBRI total scores, and positive correlations between all RPQ items and EQ-5D dimensions, illustrating that reporting problems on any items of the RPQ is associated with decreasing HRQoL (Chapter 3), which is also in line with previous research(7).
Better assessment tools and intervention strategies for PCS are needed, because intervention and support strategies can be targeted more appropriately when mTBI patients with PCS are detected shortly after sustaining the injury. Additionally, a better understanding of the relationship between PCS and HRQoL and possible mediating factors in this relationship could improve intervention strategies and the recovery process (Chapter 3).

Classification
Post-concussion symptoms and PCS can be assessed by different instruments and classification methods, which mostly rely on subjective endorsement of symptoms by patients. A frequently used instrument to assess the presence and severity of post-concussion symptoms is the RPQ (8), and despite the majority of studies using this instrument, there is currently no gold standard regarding the use and analysis of the RPQ. In addition, specifically looking at the severity ratings, there is currently no set standard available for which rating score should be used as a cut-off when using the RPQ, resulting in two possible cut-offs: rating score 2, indicating items with score ≥ 2 (symptoms mild or higher) or rating score 3, indicating items with score ≥ 3 (symptoms moderate or higher). Not only that, an unambiguous and universal classification of PCS is also missing(9) (Chapter 2). Furthermore, in previous research, it has already been described that the inconsistency in definition, classification criteria and rating score interferes with the righteous classification and identification of patients with PCS(10). This ultimately leads to inconsistencies, over- and/or underestimation of symptoms, incommensurable prevalence rates and outcome, and hampers research and therapy(4) (Chapter 2).

The majority of studies use the International Classification of Diseases, 10th revision (ICD-10)(11) and or the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV)(12) as criteria to diagnose PCS. Throughout this thesis, we have mainly utilized the mapped ICD-10/DSM-IV definition to classify PCS, which requires the endorsement of three or more post-concussion symptoms (Chapter 2). More classification methods can be found in Chapter 2.

Previous research reported prevalence rates of PCS ranging from 5% to 43%(5, 6, 13-16). Notwithstanding, we found prevalence rates for six month PCS ranging from 11% to 40%, depending on the classification method used and rating score applied. Furthermore, research in this thesis determined that the choice of classification method and rating score influenced PCS diagnosis both at a population and at an individual level (Chapter 2). In addition, the association between PCS and functional outcome was significantly influenced by the divergent classification methods. This was shown by the fluctuating percentages (46% to 73%) of patients with PCS being classified as functionally impaired dependent on the classification method applied (Chapter 2).

We believe that patients should be evaluated for post-concussion symptoms and syndrome by the use of a combination between self-report and clinical evaluation (e.g. a multidimensional comprehensive assessment).

In this thesis, it was shown that the rating score has a significant impact on the reported prevalence rates for post-concussion symptoms and PCS. When using the more stringent cut-off (e.g. rating score 3) we found that in most cases the prevalence rates dropped substantially and were sometimes even reduced by half (Chapter 2, 3, 4, 6, 7). Some argue that symptoms reported as moderate or worse are more likely to represent clinically relevant symptomatology than symptoms

reported as mild because patients with head injury were distinguished more easily from healthy controls when using rating score 3 as cut-off (17). In addition, when rating score 2 is used a substantial proportion of healthy individuals from the general population are diagnosed with PCS (Chapter 6).

At present, we cannot give a well-supported verdict on which classification method is the best and should become the gold standard. This is mainly related to the fact that there is currently no way to objectively evaluate patients on post-concussion symptoms and assess which method classifies the 'correct' patients (e.g. false-negatives vs. false-positives) for PCS. PCS was taken out of the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-V) and instead they have introduced the terms "major or mild neurocognitive disorder due to TBI"(18), and clinicians are instructed to base their diagnosis depending on the severity of cognitive deficits and functional disability present(19). We do not agree with this and highly recommend to reinstate PCS. In this thesis, we have shown that high prevalence rates of post-concussion symptoms and PCS were found for diverse patient groups, which were not solely based on cognitive deficits and functional disability, and it remains a very relevant problem after mTBI. The first step would be to develop a universal guideline to classify PCS and reach consensus regarding the usage of the RPQ, which is highly needed to enhance and facilitate comparability across studies. In addition, more research into the usage of biomarkers and more refined imaging studies in patients with mTBI is required, since this might shine light into the black box of objective assessment of post-concussion symptoms. Furthermore, we believe that rating score 2 should be applied as cut-off, even though we determined that these symptoms might not be specific for mTBI. We believe this for the following two reasons: first, when patients are asked to self-report their symptoms after mTBI, they are always asked to compare this with their situation before the injury. Second, even mild symptoms can have a significant impact on individuals' HRQoL, as was shown in this thesis, and this cannot be disregarded. Ultimately, we believe that patients should be evaluated for post-concussion symptoms and syndrome by the use of a combination between self-report and clinical evaluation (e.g. a multidimensional comprehensive assessment). All of the above will result in improved insights in post-concussions symptoms and PCS.

Pre-injury ratings

Symptoms are often assessed by using a self-report instrument and patients after mTBI are asked to rate their current symptoms compared to their pre-injury situation. Nonetheless, patients have the tendency to remember their pre-injury functioning as better, underestimate their past problems and might have a hard time to remember pre-injury symptoms accurately(20), which is commonly specified as the 'good-old-days' bias(21).

Patients may misattribute post-concussion symptoms to their sustained injury (e.g mTBI) since these symptoms might be non-specific and do not have to be exclusively associated with injury(22), and this increases the likelihood of inaccurate

post-concussion symptoms and PCS prevalence rates(23). We found that more than half of patients were inconsistent in their post-injury ratings over time when reporting their pre-injury functioning, which was evaluated by assessing pre-injury and current symptoms at four times post injury. In addition, we determined that pre-existing psychiatric morbidity is strongly associated with a PCS diagnosis post-injury, which reflects that PCS might not be a consequence of the sustained mTBI but a result from pre-existing psychiatric problems (Chapter 8). For future research, a good alternative for recruiting healthy controls in this type of research is the 'friend controls' approach (24), which could limit potential bias.

Risk factors

Identifying individuals at high risk for post-concussion symptoms and syndrome is desirable and clinically very relevant. Knowing beforehand which patients might experience symptoms, will allow patients and clinicians to act accordingly.

We found that PCS was more often experienced by females, those with lower education, those with higher injury severity scores (ISS) and abbreviated injury scale (AISH) scores, those who were injured by assault compared with other causes of injury, those who were hospitalized, those with complicated mTBI, and those who reported a higher RPQ total score (Chapter 3, 4 and 7). For paediatric patients specifically, female gender was identified as a significant predictive factor (Chapter 7). Furthermore, the following risk factors were found to be associated with PCS in the general population: lower age, female gender, low education, work status, low-income level, chronic health complaints, and when individuals experience serious illness in themselves and or in their immediate family, and when they care for others. These risk factors should also be taken into consideration when studying post-concussion symptoms and PCS (Chapter 6). When adjusting for possible confounding effects of baseline differences between patients with and without PCS, it was shown that PCS decreases HRQoL. In addition, when specifically looking at patients after complicated and uncomplicated mTBI, the effect of complicated versus uncomplicated mTBI appeared to be minimal (Chapter 3 and 4).

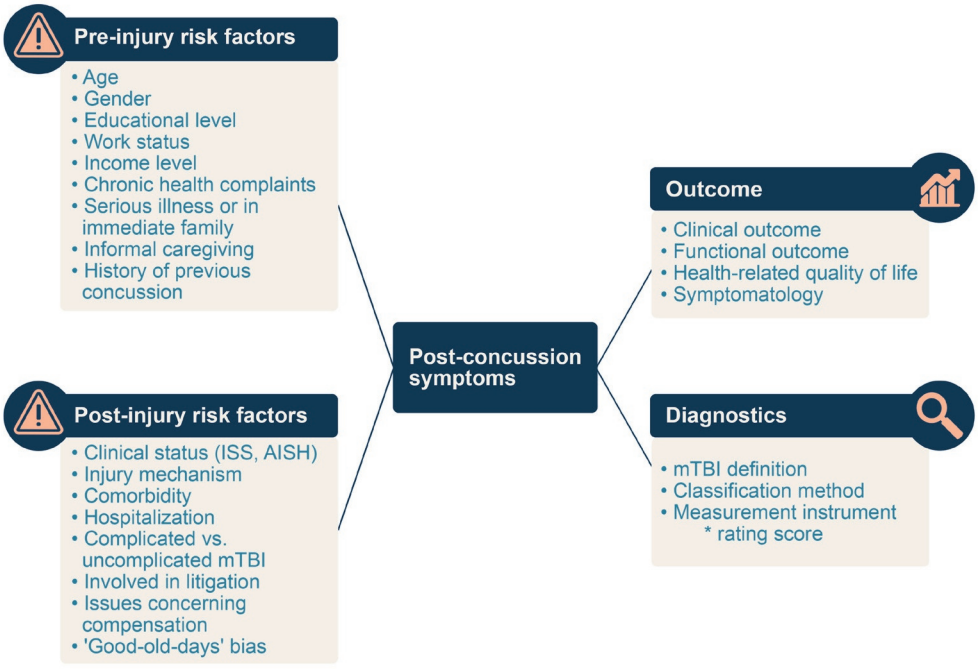
Multivariable prediction models explained 6-14% (Nagelkerke R2) of the variance in six-month PCS according to different classification methods (Chapter 2). In the general population, 26% (rating score 2) and 24% (rating score 3) of the variance in PCS was explained. A prediction model for post-concussive symptoms and PCS in paediatric patients using only baseline clinical and demographical factors, directly available in the emergency department performed reasonably (area under the receiver operating characteristics curve (AUC) rating score 2: 0.75; rating score 3: 0.79; Chapter 7). To enhance the internal and external validation of prediction models, advanced statistical methods such as shrinkage and bootstrap validation should be explored.

Post-injury care could considerably be improved by e.g. scheduling closer follow-up meetings, prolonging rest periods or establishing additional psychological or educational support. Besides the clinical relevance, patients, care givers (e.g. families) and employers would all benefit from this.

Overall conclusion post-concussion symptoms and post-concussion syndrome

To conclude, we determined that the RPQ is based on self-report rather than clinical examination, and does not include information on the duration of the symptoms and clinically significant impairment, and for this reason cannot accurately diagnose PCS (25) (Chapter 2). Nevertheless, it is essential that definitions, classification methods and terminology regarding post-concussion symptoms and PCS are standardized, since it was shown that all these factors lead to differences in prevalence rates and risk factors. It should be required for all researchers to clearly describe how self-report measurements were used and which cut-off points were employed. To enhance our knowledge regarding the different RPQ classification methods which could be used to classify PCS, sensitivity and specificity analyses should be performed. Post-concussion symptoms and PCS entail a difficult interaction between biological, psychological and social factors, which also include pre-injury health, such as pre-injury psychological, personality, psycho-social factors, severity of the injury, troubles in life, and issues concerning compensation and litigation (26-28). In addition, clinicians should be aware of the high endorsement of post-concussion-like symptoms and prevalence of PCS in the general population, anticipate on the concept of the 'good-old-days' bias and try to keep the patients' specific circumstances and risk factors in mind with a key focus on a patients' pre-injury situation(10). Ultimately, all these factors should be considered and taken into account when dealing with post-concussion symptoms and PCS (Figure 1) (Chapter 2, 3, 4, 6).

Figure 1. A model for the study of post-concussion symptoms after mTBI



Outcome following mild traumatic brain injury

Aside from post-concussion symptoms and syndrome, outcome can also be assessed by other outcome measurements such as clinical outcome and HRQoL. A better understanding of the relation between mTBI and outcome may improve intervention strategies and the recovery process in divergent mTBI patient groups. Six months post-injury, approximately 30% of adult patients after mTBI were functionally impaired (GOSE ≤6) (Chapter 2). However, functional measurement scales as the GOSE have been criticized since they just describe the clinical outcome and do not represent a patient's subjective experience of their health(29). Especially for patients with mTBI, the majority of patients will be categorized in the upper level categories (GOSE > 6), because they will not be assessed by a clinician as functionally impaired in their daily life(30). However, these patients could be affected in various other aspects of life and could be limited physically, mentally, cognitively and socially(26, 31, 32). For this reason, we used a variety of outcome measures and to achieve a comprehensive multidimensional approach outcome was assessed by generic and disease-specific HRQoL, functional outcome and symptomatology, such as post-traumatic stress, depression and anxiety. Moreover, we compared individuals after complicated mTBI and uncomplicated mTBI and analysed the effects on outcome by the use of a comprehensive multidimensional approach. We concluded that patients after complicated mTBI reported worse functional outcome and lower generic and disease-specific HRQoL at three and six months post-injury. Nevertheless, when specifically concentrating on the longitudinal effects, considerable improvement in outcomes from three to six months were not found (Chapter 5).

A recommendation for future research would be to develop mobile phone applications, which could track patient's post-concussion symptoms and certain outcomes in the months following their injury. This would be an easy way to track patients who reach a certain cut-off point and to ask these patients to come and see a clinician, who could, together with the patient, come up with an individualized rehabilitation plan. Subsequently, the growing usage of social media (e.g. Twitter, Instagram and Facebook) could be utilized to inform patients about everything surrounding a brain injury and create a community online of patients, care givers and clinicians. However, privacy-sensitive data and confidential information regarding individuals are principles that we must hold dear in this context. In addition, return to work or school should be used as a measure of outcome assessment, since this might objectively portray how an individual copes with the sustained injury in their everyday life.

Ultimately, the short and long-term impact on outcome for patients diagnosed with mTBI should be taken into consideration by patients, clinicians, researchers and decision-makers in health care and should not be taken lightly by anyone. Clinical follow-up should be provided to all patients after mTBI and complicated and uncomplicated mTBI groups should not be treated differently. New treatments options should be explored such as aerobic exercises: "pushing through symptoms". Rehabilitation services and concussion treatment centres for mTBI in

specific should be realized and organized, since these patients often fall through the cracks of care under the misplaced ideology that it is just a 'mild' injury. Lastly, we should always keep in mind that: "there are no two identical TBIs", and the implications and repercussions for a top sport athlete compared to an elderly are very diverse and for this reason precision rehabilitation should be provided.

Part II - Preferences for outcome in traumatic brain injury

In the second part of this thesis, we focused on preferences and utility weights for TBI and stroke health states and determined what was needed to apply them. We specifically focused on preferences of the general population for disease specific outcome measures for TBI and which utility weights can be assigned to TBI value sets. Additionally, we assessed how value sets and patient data can be used to determine utility and/or disability weights for TBI and stroke health states.

Preferences

Cost-effectiveness analyses have become an integral part of decision making processes in TBI(33, 34) and stroke(35) research since both diseases have high economic costs. With a growing health care demand and the rate of increase in healthcare costs currently exceeding economic growth, using limited health care resources sufficiently are at the center of attention (36, 37). The responses on generic and disease specific measurements represent preferences for health states measured by these instruments, which ultimately means that preferences represent the value or desirability for individual health states(38). Nevertheless, to be able to use the responses on HRQoL measurements in economic evaluations, they first have to be converted into utility weights.

Health utility indices

Utility weights represent the relative preference for a year of life in a given health state and a greater weight is given to a more desirable/preferred health state(39, 40). Utilities are always anchored on a scale ranging from 0 (death) to 1 (perfect health) and a less than 0 value is given to health states which are reported to be worse than dead(41).

In this thesis, we have determined utility weights for the most widely used outcome measure in trials for acute stroke interventions, which is the modified Ranking Scale (mRS)(42, 43). In previous research, the utility-weighted mRS (UW-mRS) was developed, to reflect both treatment and patient perception, and this has since then been used as primary outcome in a clinical trial. We established utility weights for the mRS health states and evaluated the statistical efficiency of the UW-mRS by the usage of a simulation study. Utility weights were derived for each mRS category and it was shown that these do not capture the individual variation within each category. Our simulation study disclosed that the original ordinal analysis of the mRS was more efficient in detecting treatment effects than the newly proposed UW-mRS approach. This shows the importance of evaluating the statistical efficiency

of a new patient-centred outcome measure first, before it is widely implemented into research or clinical practice. Future research should focus on a more thorough evaluation of the UW-mRS in terms of its added value, analytical approach and interpretation, and subsequently validating our results.

Value sets

A value set is a collection of utility values for all possible health states described in an instrument, which are needed to be able to use the health states described by this instrument in economic evaluations. Chapter 9 presents the first value sets for the QOLIBRI-OS, since before this study, utilities were not available for the QOLIBRI-OS. With the development of value sets for three different European countries, we have enabled the application of the QOLIBRI-OS in economic evaluations and in summary measures of population health. We determined that the biggest weight increase for all attributes of the QOLIBRI-OS was from the level 'slightly' to 'not at all satisfied', which consequently results in the largest impact on HRQoL. Table 1 shows an example of utility weights per QOLIBRI-OS health state, which have been generated from a value set.

Table 1. Example of values for a mild, moderate and severe health states from the QOLIBRI-OS

	Anchored DCE			
	All respondents	UK	the Netherlands	Italy
Best health state: 11111	1	1	1	1
Mild health state: 21232	0.902	0.94	0.955	0.918
Moderate health state: 34343	0.631	0.853	0.799	0.801
Severe health state: 55455	0.449	0.465	0.472	0.396
Worst health state: 55555	0.383	0.383	0.383	0.383

Note: See Chapter 9 for the full description.

Abbreviations. DCE, Discrete Choice Experiment; UK, United Kingdom.

The generated value sets were based on health states and pairs of previous EQ-5D research, however, it could be that for the QOLIBRI-OS instrument different health states should have been included. For future research in generating value sets, it would be recommended to perform health state and pair selection per instrument separately, to ensure that the right set of health states specifically important to these preference-based health state measures are being valued. There are several methods of administration to conduct health state valuation studies, such as face-to-face, paper-and-pencil methods and web-based questionnaires. When choosing a web-based survey it also implies using health state valuation methods that are amenable to online administration, such as discrete choice experiments (DCEs) and VAS. Compared to personal interviews, web-based surveys are equipped to get answers from large samples in a relatively short time, have a flexible sampling

frame, enable a range of background characteristics of non-respondents to be obtained, the order of the questions can be randomized, allow complex routing of questions, the time it takes a respondent can be recorded, and the errors associated with data entry are minimized.(44) However, during a web-based survey one cannot check if respondents completely understood the task at hand. For this reason it would be advisable to starting with some rounds of face-to-face to test the web-based survey to identify the teething troubles. Additionally, building in a tool to be able to check answers while respondents are taking the survey, for example to check if they are using the VAS correctly and are not turning it upside down, would also be suggested. Nevertheless, face-to-face surveys will deliver higher quality data, but will also require larger monetary resources.

Norm scores

Currently, with the focus in research increasingly being on HRQoL, and on top of that explicitly focusing on disease-specific HRQoL, the QOLIBRI has been an instrument the majority of researchers have started using to assess disease-specific HRQoL after TBI. Nevertheless, to achieve a better understanding of HRQoL after TBI and to be able to interpreted the QOLIBRI scores in research and clinical practice, population-based norms need to be generated. In Chapter 12, we established these population-based norms from representative general population samples in the United Kingdom and the Netherlands, and samples of individuals after TBI from these same countries were used as a reference. Foremost, we found that the QOLIBRI has good psychometric properties in the general population samples and showed measurement invariance across countries and in TBI and general population samples. Surprisingly, individuals after mTBI at three months post-injury did not have significantly different HRQoL compared to individuals from the general population. Nevertheless, it was determined that functional disability and symptoms of emotional disorder, which are common after mTBI, negatively affect HRQoL (Chapter 12). Future research should focus on developing population-based norms for all HRQoL instruments used in TBI and stroke research specifically per country and to limit costs, options for 'crosswalking' should be explored.

Disability

In current research, disability-adjusted life year (DALY) are increasingly being used and researchers have concluded that, in case of injury, disability weights should be derived from empirical HRQoL follow up data from individual patients (45-48). An advantage of using HRQoL data to derive disability weights is that they can be linked to epidemiological date more precisely and are able to capture the heterogeneity within an injury group (49). A logical and homogeneous grouping is the preferred option, such as the Glasgow Outcome Scale Extended (GOSE) which was specifically designed and has been a widely used instrument to describe outcome for TBI patients (29, 50-53) . Utilities for the GOSE are widely available (39), however, we were the first ones to develop disability weights per GOSE level. We found that HRQoL disability weights increased with increasing severity level of GOSE. In addition, since there is currently no gold standard available on which

preference-based measure of health to use, we derived HRQoL utility and disability weights from three different preference based measures of health. This resulted in different weights and hampers generalizability, which shows the importance for future research establishing assessment criteria for which instrument would be best to derive disability weights from. Generating disability weights per GOSE severity level have enabled the evaluation and comparison of disease burden across countries and effectiveness of health care and economic evaluations. The results from Chapter 10 will provide a promising framework to enhance our knowledge on DALYs and for future research seeking to apply DALYs in cost-effectiveness analyses and policy making (Chapter 10).

Overall conclusion Part II

Several aspects should be considered when assessing utility and disability weights. First, one should recognize that patients after TBI may suffer from pre-existing chronic disease (11% in the CENTER-TBI cohort), which could contaminate the HRQoL utility and disability weights. Second, researchers should always acknowledge the strengths and limitations of different elicitation methods and preferably use face-to-face interviews performed by experienced researchers in this field, which will deliver high quality data. Lastly, every respondent in a health state valuation task should see a well-balanced set of health states representing the whole range of severity and given answers on the VAS should be shown during the following questions so respondents can scale their answers based on previous responses, which provides them with a better overview.

Limitations

The cohort data in this thesis is mainly collected in academic hospitals/research settings and these patients are not representative for the overall mTBI population (Chapter 3), especially in the CENTER-TBI study where included patients were required to have an indication for CT imaging as eligibility criterion (Chapter 7). In addition, patients who have confirmed structural damage to the brain as shown on a CT or MRI scan (e.g. complicated mTBI) might act differently and report more and give higher ratings to self-report symptoms since they are aware of the objective evidence of the brain injury. Correspondingly, health care providers might treat these patients differently and this might be completely subconsciously (Chapter 4).

Further, a considerable fraction of patients after TBI was lost to follow-up, e.g. attrition, and this might imply selection bias, which could have important implications for the interpretation of our results. While this number within CENTER-TBI is comparable to other large, prospective studies, a non-response bias limiting external validity is possible (Chapter 7 and 8).

Self-report is the most frequently used mechanism of symptom reporting within this thesis, nevertheless, this may lead to under- or over reporting of symptoms (Chapter 3). Patients who are not experiencing symptoms might be less likely to get involved in a study because they might have moved on and might not see the importance of participating (Chapter 4 and 5). Additionally, recall bias might play a role as patients might underestimate their pre-injury symptoms (Chapter 7). It has been debated whether TBI patients, especially patients with cognitive impairment, are able to provide useful and complete answers to questionnaires (Chapter 3, 5 and 10). Moreover, method of administration of questionnaires (e.g. web-based, face-to-face or postal) could influence the type and amount of symptoms reported (Chapter 4 and 6).

Our findings, when using the web-based survey data, should be interpreted with caution since it is not known how much respondents involved in a market research panel influence the results, since they might be 'professional' in taking and filling out surveys and it could also be questioned how representative these respondents are for the general population (Chapter 6, 9 and 12). Additionally, the usage of complex DCE questions might potentially cause extra selection bias compared with general questionnaire surveys (Chapter 9).

Recommendations

Based on our main findings and interpretation regarding outcome assessment and measuring outcome preferences in TBI and stroke, we have summarized specific recommendations for the next steps in future research, policy and clinical practice below.

Recommendations for research

Research on outcome assessment following traumatic brain injury

- Develop one universal guideline regarding definitions, classification methods and terminology for post-concussion symptoms and syndrome.
- For reporting, clearly describe how self-report measurements were used and especially for the RPQ which cut-off points were utilized
- Examine the pathophysiology of post-concussion symptoms and syndrome in patients after mTBI and especially take pre-injury factors into account
- Study use of biomarkers and more refined imaging studies when assessing outcome in patients with mTBI
- Assess outcome after TBI through a multidimensional approach including clinical outcome, HRQoL and symptomatology such as GOSE, SF-36/12, QOLIBRI/-OS, RPQ and psychological tests
- Study outcome after mTBI longitudinally and at follow-up times later than 1 year post-injury
- Perform multidimensional analyses to investigate outcome differences between TBI groups
- Perform advanced statistical methods such as shrinkage and bootstrap validation to enhance the internal and external validity of prediction models
- Study differences in treatment and treatment policies and investigate the possibilities for personalized intervention strategies

Research on preferences for outcome in traumatic brain injury

- Consider using ‘shorter’ versions of a questionnaire
- Recognize comorbidity when assessing utility and disability weights
- Perform health state and pair selection for the QOLIBRI/-OS
- Consider the strengths and limitations of the preference elicitation method used
- Summarize state-of-the-knowledge for development of value sets
- Develop a universal guideline considering assessment criteria to compare different utility instruments
- Explore options of ‘crosswalking’ and develop population-based norms for all HRQoL instruments per country

Recommendations for policy

- Do not focus all attention on severe TBI, since mTBI often gets forgotten: provide funding for research projects focusing on outcome after mTBI
- Provide funding to generate country-specific utility and disability weights for disease-specific HRQoL instruments for TBI and stroke.
- Make the population more aware of the consequences of TBI and mTBI in specific
- Obligate researchers to report how they used an outcome instrument (e.g. cut-off points) and add this to the STROBE criteria.
- Allow for different rehabilitation programs to be covered by health insurance (e.g. a life coach)

Recommendations for clinical practice

- Inform patients after mTBI about the potential consequences of the injury
- Evaluate patients for post-concussion syndrome by the use of a combination between self-report and clinical evaluation, e.g. a multidimensional comprehensive assessment
- Use a biopsychosocial model to assess symptoms after mTBI
- Acknowledge potential outcome differences between divergent mTBI groups and act accordingly
- Provide precision rehabilitation (e.g. individualized precision medicine)

Overall conclusion

The aim of this thesis was to expand our knowledge on assessing outcome following TBI, and measuring outcome preferences for TBI and stroke among patients and the general population.

In the first part of this thesis, we initially described the association between post-concussion symptoms and HRQoL in mTBI patients with an emphasis on the prevalence, risk factors and pre-injury reporting of post-concussion symptoms and the classification of post-concussion symptoms and PCS. After this, we assessed the outcome in divergent mTBI patient groups.

Prevalence rates for post-concussion symptoms and PCS fluctuated extensively and dependent on population, case-mix of the sample, setting, measurement instrument, and diagnostic criteria and classification methods applied. Nevertheless, high prevalence rates of post-concussion symptoms and PCS six months post-injury in adult and paediatric patients were found, which shows that even though the injury might be classified as 'mild', patients still experience debilitating problems months after sustaining the injury. Outcome after mTBI is multidimensional and defined by a difficult interaction between biological, psychological and social factors and has a different effect on each individual. Ultimately, a patients specific situation should be taken into account and precision rehabilitation should be provided.

In the second part of this thesis, we examined the preferences and utility weights for TBI and stroke health states and assessed to what extent these could be applied. Generating utility and disability weights for disease-specific HRQoL instruments will enable the evaluation and comparison of disease burden across countries and effectiveness of health care and the application in economic evaluations and in summary measures of population health.

MTBI is very complex and a good example of a patient group that could really benefit from a coordinated collaboration between health care providers. The physical, psychological, social and economic impact on the patients after mTBI, but also the caregivers, families, friends and society, is tremendous. Given this, it is imperative that new research into the evaluation of costs and the relation with outcome, will help to ameliorate the impact of mTBIs. – Daphne Cloë Voormolen

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Summary

Summary

Introduction
Traumatic brain injury (TBI) is a leading cause of death and disability worldwide with 2.5 million new cases in the European Union (EU; 28 Member States) each year. In addition, it is costing the global economy approximately $US400 billion per year. The large majority of patients (70-90%) are diagnosed with mild TBI (mTBI). However, despite the term 'mild', patients after mTBI can also experience long-lasting symptoms. Other than all the research efforts in the last couple decades, substantial improvement in outcome for patients has been lagging behind and many questions remain unanswered regarding the impact of mTBI. Health-related quality of life (HRQoL) has been the focus of outcome assessment in current research endeavors, since this reflects an individual's perception of how an illness and its treatment affect the physical, mental, and social aspects of his or her life.

Stroke is the second leading cause of death worldwide, with an increasing incidence due to an ageing population. Even though the causes of TBI and stroke are different, the consequences and effects are often very similar, since both result in physical, cognitive, psychological, and social dysfunction.

TBI and stroke both have high economic costs and because of this cost-effectiveness analyses have become an integral part of decision making processes in both diseases. Nevertheless, essential components to be able to perform economic evaluations, namely quality-adjusted life years, health-utility indices, value sets and population based norms, are missing in current TBI and stroke research.

This thesis consists of two parts. Part I focused on assessing outcome following mTBI, with an emphasis on prevalence, risk factors, classification and pre-injury reporting of post-concussion symptoms and post-concussion syndrome (PCS). In part II, we examined the preferences and utility weights for TBI and stroke health states and their application. Prospective observational longitudinal patient data, survey data of the general population, and a simulation study were used. The aim of this thesis is operationalised in the following research questions:

1. What is the association between post-concussion symptoms and HRQoL in mTBI?
    a. What is the outcome in divergent mTBI patient groups?
    b. What are the prevalence and risk factors of post-concussion symptoms in mTBI patients and the general population?
    c. How can we classify post-concussion symptoms and post-concussion syndrome after mTBI and to what extent are pre-injury ratings reliable?

2. What are preferences and utility weights for TBI and stroke health states and how could they be applied?

    a. What are preferences of the general population for disease specific outcome measures for TBI and which utility weights can be assigned to TBI value sets?

    b. How can value sets and patient data be used to determine utility and/or disability weights for TBI and stroke health states?

Part I - Outcome assessment following traumatic brain injury

In **Chapter 2** and **3** a total of 731 mTBI patients from a prospective observational cohort study performed in the Netherlands were included. In **Chapter 2** we examined how four divergent classification methods and two different rating scores as cutoff defining post-concussion syndrome (PCS) differ among patients six months after mTBI. The Rivermead Post-Concussion Symptoms Questionnaire (RPQ) was used to assess post-concussion symptoms and the following classification methods were used to classify patients as having PCS: the RPQ mapped to the ICD-10/ DSM-IV, the RPQ total score, the RPQ-3 and the RPQ three-factor model. We found prevalence rates of PCS ranging from 11% to 39%, a different set of risk factors to be statistically significantly associated with PCS, and a different percentage of overlap with functional impairment. These differences in results were all dependent on the classification method and rating score used. In **Chapter 3** we assessed the association between PCS and health-related quality of life (HRQoL) six months after mTBI and we additionally looked at the correlation between post-concussion symptoms, assessed by the RPQ, and different HRQoL domains. HRQoL was measured with the 36-item Short-Form Health Survey (SF-36) and the Perceived Quality of Life Scale (PQoL). We found that 39% of patients were classified as suffering from PCS, and these patients had significantly lower HRQoL, e.g. lower scores on all SF-36 domains and lower mean PQoL scores. Furthermore, all RPQ items were negatively correlated to all SF-36 domains and PQoL subscale scores, which indicates a decreasing effect on different aspects of an individuals' HRQoL when reporting problems on any of the RPQ symptoms.

In **Chapter 4, 5** and **7** we presented results based on the Collaborative European NeuroTrauma Effectiveness Research in TBI (CENTER-TBI) study, which is a large multicenter, prospective observational longitudinal cohort study conducted in Europe and Israel. In **Chapter 4** and **5** we differentiated patients in complicated (intracranial abnormalities present on computed tomography (CT)) and uncomplicated (no intracranial abnormalities present on CT) mTBI. In **Chapter 4** we assessed the occurrence of post-concussion symptoms and PCS in a large sample of patients

with complicated and uncomplicated mTBIs at three and six months post-injury. A complete case analysis was performed and a total of 1302 patients with mTBI who completed the RPQ were included. Approximately 46% of patients were identified as complicated mTBI and they reported significantly more symptoms and have higher PCS prevalence rates compared to patients after uncomplicated mTBI at three and six months. However, when adjusting for baseline covariates, e.g. age, gender, education, injury mechanism, Glasgow Coma Score, complicated vs. uncomplicated, psychiatric medical history and stratum, the differences between both patient groups became less clear and this indicated that the association could be explained by differentiations in baseline characteristics. In **Chapter 5** we compared outcome of patients after complicated and uncomplicated mTBI at three and six months post-injury. Outcome was assessed as a multidimensional construct to compare patients on different outcome levels: generic and disease specific HRQoL, functional outcome and symptomatology such as post-traumatic stress, depression and anxiety measured by the following instruments: SF-36 and Quality of Life after Brain Injury (QOLIBRI), Glasgow Outcome Scale Extended (GOSE), Posttraumatic Stress Disorder Checklist-5 (PCL-5), Patient Health Questionnaire (PHQ-9) and Generalized Anxiety Disorder questionnaire (GAD-7), respectively. A complete case analyses was performed and a total of 1104 patients with mTBI who completed the seven assessed outcome instruments were included. The results of this study showed that patients after complicated mTBI reported lower generic and disease-specific HRQoL and worse functional outcome compared to patients after uncomplicated mTBI at three and six months post-injury. Nevertheless, no significant differences were found between time points.

In **Chapter 6** we evaluated the frequency of post-concussion-like symptoms and prevalence and risk factors of PCS, determined the relationship between the items of the RPQ with self-perceived health (EQ-5D) and ultimately investigated differences in the general population of three European countries, e.g. Italy, the Netherlands, and the United Kingdom. We conducted a web-based survey among representative samples in three European countries, and a total of 11,759 respondents who completed the RPQ and EQ-5D were included. The most frequently reported symptom was fatigue (50%), approximately half of the respondents were classified as having PCS and chronic health complaints was found to be a significant risk factor for PCS. These results indicate that post-concussion-like symptoms are not specific for patients with TBI, and PCS is not a unique syndrome after TBI. Furthermore, positive correlations were determined between all RPQ items and EQ-5D dimensions and summary score. This suggest that post-concussion-like symptoms are debilitating and they also have a major effect on HRQoL in the general population.

In **Chapter 7** we analyzed the prevalence and associated risk factors for the development of post-concussion symptoms, and the relationship with Quality of life (QoL) in pediatric and adolescent patients with mTBI at six months post-injury. We used data from the CENTER-TBI study and included 196 patients who completed the RPQ at six months post-injury. At least one moderate or severe symptom of

the RPQ was experienced by 36% of patients and PCS was present in 13% when considering symptoms of at least moderate severity (score > 2). A prediction model for PCS using only baseline clinical and demographical factors, directly available in the emergency department, was developed and regression analyses identified females as a significant risk factor. Pediatric patients with PCS had lower QoL compared to patients without PCS since they had significant lower QOLIBRI total scores.

In **Chapter 8** we assessed the reliability of patient's post-injury ratings of symptoms compared with their pre-injury ratings in a large and representative sample of patients with mTBI at several time points during the first year following injury. We included 836 patients with mTBI, 191 trauma patients without brain injury history and 100 healthy controls and the latter two groups served as control groups. To assess pre-injury and current symptoms the Head Injury Symptom Checklist (HISC) was used. Almost half of all patients with mTBI inconsistently reported their pre-injury functioning over time. Patients who were classified with post-injury PCS reported higher percentages of pre-injury symptoms and were often more inconsistent. Patients who were classified with pre-injury PCS more often had psychiatric morbidity and this premorbidity also showed a strong association with post-injury PCS.

Part II - Preferences for outcome in traumatic brain injury

Chapter 9 describes the development of value sets for the Quality of Life after Brain Injury overall scale (QOLIBRI-OS), which is a TBI specific instrument to measure HRQoL. A web-based valuation study was performed in the Netherlands, United Kingdom and Italy. We found that the biggest weight increase for all attributes of the QOLIBRI-OS is seen from "slightly" to "not at all satisfied", resulting in the largest impact on HRQoL. In addition, the item "Not at all satisfied with how brain is working" should receive the greatest weight in utility calculations in all three countries. By transforming the QOLIBRI-OS into utility scores we have enabled the potential application in economic evaluations, and in summary measures of population health, which may ultimately be used to inform decision makes on the best interventions and strategies for TBI patients.

In **Chapter 10** we described the impact following TBI by developing disability weights for the GOSE, which is a functional outcome instrument after TBI, and we used HRQoL data of patients with TBI to achieve this. Data were obtained through CENTER-TBI research project and a total of 2200 patients after TBI were included. Generic HRQoL was assessed with the Short Form 36-Questionnaire Health Survey version 2 (SF-36v2) and a crosswalk was performed to convert this to the Short Form 12-Questionnaire Health Survey version 2 (SF-12v2). After this we mapped the SF-12 onto three different preference-based measures of health: the Short Form Six-Dimension (SF-6D), EQ-5D-3L and Health Utility Index Mark 3 (HUI3). Thereafter,

we assessed the SF-6D, EQ-5D and HUI3 utility scores per patient. Ultimately, we derived the following mean disability weights ranging from 0.045, 0.010, 0.008 (GOSE 8; upper good recovery) to 0.185, 0.142, 0.200 (GOSE 3; lower severe disability), respectively for SF-6D, EQ-5D and HUI3. We determined that HRQoL disability weights increased with increasing severity levels of GOSE. The results of this study enable the evaluation and comparison of disease burden across countries and the effectiveness of health care and economic evaluations. Moreover, future researchers can use these results when applying disability-adjusted life years in cost-effectiveness analyses and policy making.

In **Chapter 11** we evaluated the statistical efficiency of a new patient-centred outcome measure in stroke research (utility-weighted modified Rankin Scale (UW-mRS)) and describe this by the use of a simulation study. The simulation study was based on individual data from 500 patients from the MR CLEAN trial, which is a multicentre clinical trial evaluating the effectiveness of intra-arterial treatment in ischemic stroke. The linear analysis of the UW-mRS (power 85%) was more efficient in detecting treatment effects than dichotomous analysis of the mRS (power 71%) but less efficient than the ordinal analysis of the mRS (power 87%). Additionally, the individual variation in utility within each mRS category is not captured by the UW-mRS.

In **Chapter 12** we provided a basis for better understanding of HRQoL after TBI in research and clinical practice. We established population-based norms from representative general population samples in the United Kingdom and the Netherlands and samples of individuals after TBI from the United Kingdom and the Netherlands were used as a reference. Data was obtained through a web-based survey and CENTER-TBI data for the general population and TBI samples, respectively. The QOLIBRI showed good psychometric properties in the general population samples and measurement invariance was demonstrated across countries and in TBI and general population samples. We found that HRQoL of individuals after mTBI at three months post-injury did not differ significantly from HRQoL assessed in the general population. However, we did determine that post-TBI factors such as functional disability and symptoms of emotional disorder affected HRQoL negatively.

Discussion

The aim of this thesis is to expand our knowledge on assessing outcome following TBI, and measuring outcome preferences for traumatic brain injury and stroke among patients and the general population.

Despite an abundance of studies, there is currently no gold standard regarding the use and analysis of instruments assessing post-concussion symptoms. Not only that, an unambiguous and universal classification of PCS is missing as well. This leads to large variation in reported prevalence rates, inconsistencies, incommensurable outcome, and hampers research and therapy. Utility and disability weights, population-based norms and value sets are currently not available for all generic and disease-specific outcome measurements after TBI, which limits the utilization of these instruments in economic evaluations.

We found that prevalence rates for post-concussion symptoms and PCS fluctuated extensively dependent on population, case-mix of the sample, setting, measurement instrument, and diagnostic criteria and classification methods applied. Furthermore, since we found high prevalence rates of post-concussion symptoms in adult and paediatric patients six months post-injury, we can conclude that mTBI could be debilitating months after the injury. Outcome after mTBI is multidimensional and defined by a difficult interaction between biological, psychological and social factors and impacts every individual differently.

Generating utility and disability weights for disease-specific HRQoL instruments enables the evaluation and comparison of disease burden across countries and effectiveness of health care and the application in economic evaluations and in summary measures of population health.

Specific recommendations for future research, policy and clinical practice were formulated, based on the interpretation of the main results of the studies included in this thesis. These recommendations include one universal guideline regarding definitions, classification methods and terminology for post-concussion symptoms and syndrome and researchers should clearly describe how self-report measurements were used and especially for the RPQ which cut-off points were utilized. In addition, outcome after TBI should be assessed through a multidimensional approach including clinical outcome, HRQoL and symptomatology and we recommend to investigate the possibilities for personalized intervention strategies. For research on preferences for outcome in traumatic brain injury, we recommend to summarize the state-of-the-knowledge for development of value sets in a systematic review and to develop a universal guideline considering assessment criteria to compare different utility instruments. For clinical practice, we recommend a multidimensional comprehensive assessment in which patients are evaluated for post-concussion syndrome by the use of a combination between self-report and clinical evaluation, to take patient specific situations into account and to provide precision rehabilitation.

Samenvatting

Samenvatting

Introductie
Traumatisch hersenletsel is wereldwijd een van de meest voorkomende oorzaken van de dood en/of gezondheidsverlies met 2,5 miljoen nieuwe gevallen in de Europese Unie (EU; 28 lidstaten) per jaar. Bovendien kost het de wereldwijde economie gemiddeld 400 miljard dollar per jaar. Het grootste gedeelte (70-80%) van deze patiënten wordt gediagnosticeerd met mild/licht traumatisch hersenletsel (LTH). Echter, ondanks de benaming 'mild', kunnen patiënten met LTH langdurig symptomen ervaren. De afgelopen tientallen jaren is er veel onderzoek gedaan naar LTH, maar echte substantiële verbeteringen in de uitkomst van patiënten blijft achter en veel vragen rondom de impact van LTH blijven onbeantwoord. Onderzoek omtrent uitkomsten na LTH focust vandaag de dag veel meer op gezondheids-gerelateerde kwaliteit van leven (GKvL), omdat dit een betere weerspiegeling geeft van de perceptie van een individu over hoe een ziekte en de behandeling hiervan invloed heeft op fysieke, mentale en sociale aspecten in zijn/haar leven.
Beroerte is wereldwijd de tweede belangrijke doodsoorzaak, waarvan de incidentie nog steeds stijgt vanwege een vergrijzende populatie. Ondanks dat de oorzaken van traumatisch hersenletsel en een beroerte verschillen, lijken de consequenties vaak erg op elkaar, omdat beide resulteren in fysieke, cognitieve en psychologische, en sociale disfunctie.
Traumatisch hersenletsel en beroerte hebben beiden hoge economische en maatschappelijke kosten en om deze reden spelen kosteneffectiviteitsanalyses een grote rol wanneer keuzes gemaakt moeten worden rondom beide ziektebeelden. Niettemin, in het huidige traumatisch hersenletsel- en beroerteonderzoek ontbreken essentiële componenten om economische evaluaties te kunnen uitvoeren, namelijk voor kwaliteit gecorrigeerde levensjaren (quality-adjusted life year, QALY), utiliteiten, waardensets en populatie-gebaseerde normen.

Onderzoeksvragen
Het hoofddoel van dit proefschrift is om onze kennis uit te breiden over het vaststellen van uitkomsten na traumatisch hersenletsel, en het meten van preferenties bij patiënten en de algemene bevolking voor traumatisch hersenletsel en beroerte. We hebben een breed scala aan methoden gebruikt, waaronder het analyseren van prospectieve observationele longitudinale patiëntgegevens, analyseren van survey-data van de algemene bevolking, en een simulatieonderzoek.

Deze doelen zijn geoperationaliseerd in de volgende onderzoeksvragen:
1. Wat is het verband tussen postcommotionele symptomen en gezondheids-gerelateerde kwaliteit van leven (GKvL) in licht traumatisch hersenletsel (LTH)?
    a. Wat is de uitkomst in diverse groepen van patiënten met LTH?
    b. Wat is de prevalentie en wat zijn de risicofactoren van postcommotionele symptomen bij patiënten met LTH en in de algemene bevolking?
    c. Hoe kunnen we postcommotionele symptomen en het Post

Commotioneel Syndroom na LTH classificeren en in hoeverre zijn beoordelingen – over de situatie vóór het ongeluk - achteraf betrouwbaar?

2. Wat zijn preferenties en utiliteiten voor gezondheidstoestanden binnen traumatisch hersenletsel en beroerte en hoe kunnen deze toegepast worden?
   a. Wat zijn de preferenties van de algemene bevolking voor ziekte specifieke uitkomstmaten binnen traumatisch hersenletsel en welke utiliteiten kunnen worden toegewezen aan waardensets voor traumatisch hersenletsel?
   b. Hoe kunnen waardensets en patiëntgegevens gebruikt worden om utiliteiten en/of wegingsfactoren voor gezondheidstoestanden binnen traumatisch hersenletsel en beroerte te bepalen?

Deel I - Vaststellen van uitkomst na traumatisch hersenletsel

In **Hoofdstuk 2** en **3** zijn in totaal 731 patiënten met LTH geïncludeerd uit een prospectief observationeel cohortonderzoek uitgevoerd in Nederland. In **Hoofdstuk 2** hebben we onderzocht hoe vier uiteenlopende classificatiemethoden en twee verschillende beoordelingsscores als grenswaarde voor het definiëren van postcommotioneel syndroom (PCS) verschillen aantonen tussen patiënten zes maanden na LTH. De Rivermead Post-Concussion Symptoms Questionnaire (RPQ) werd gebruikt om postcommotionele symptomen vast te stellen. De volgende classificatiemethoden zijn gebruikt om patiënten met PCS te classificeren: de RPQ items gelinkt aan de ICD-10 / DSM-IV criteria, de RPQ totaal score, de RPQ-3 en het RPQ drie-factorenmodel. We hebben PCS prevalenties gevonden variërend van 11% tot 39%. Bovendien hebben wij geconstateerd dat een andere set risicofactoren statistisch significant geassocieerd is met PCS, en een verschil in overlap met functionele beperkingen en deze verschillen in resultaten waren allemaal afhankelijk van de classificatiemethoden en de gebruikte beoordelingsscore. In Hoofdstuk 3 hebben we de associatie tussen PCS en gezondheids-gerelateerde kwaliteit van leven (GKvL) zes maanden na LTH beoordeeld en hebben we ook gekeken naar de correlatie tussen postcommotionele symptomen, gemeten door de RPQ, en verschillende GKvL -domeinen. GKvL is gemeten met de 36-item Short-Form Health Survey (SF-36) en de Perceived Quality of Life Scale (PQoL). De prevalentie voor patiënten met PCS was 39%, en deze patiënten hadden een significant lagere GKvL, b.v. lagere scores op alle SF-36-domeinen en lagere gemiddelde PQoL-scores. Bovendien waren alle RPQ-items negatief gecorreleerd aan alle SF-36-domeinen en de sub schaal scores van de PQoL, wat wijst op het feit dat het rapporteren van problemen op de RPQ een negatief effect heeft op verschillende aspecten van een individu's GKvL.

In **Hoofdstuk 4, 5** en **7** hebben wij resultaten gepresenteerd op basis van het Collaborative European NeuroTrauma Effectiveness Research in TBI (CENTER-TBI) -onderzoek, een groot multicenter, prospectief observationeel longitudinaal cohortonderzoek uitgevoerd in Europa en Israël. **In Hoofdstuk 4** en **5** hebben we onderscheid gemaakt tussen patiënten met gecompliceerd (intracraniële afwijkingen aanwezig op de computertomografie (CT)-scan) en ongecompliceerd (geen intracraniële afwijkingen aanwezig op de CT-scan) LTH. In **Hoofdstuk 4** hebben we het optreden van postcommotionele symptomen en PCS bij een grote steekproef van patiënten met gecompliceerd en ongecompliceerd LTH op drie en zes maanden na het letsel beoordeeld. In totaal hebben we 1302 patiënten met LTH die de RPQ volledig hadden ingevuld geïncludeerd. Ongeveer 46% van de patiënten werd geïdentificeerd met gecompliceerd LTH en deze patiënten rapporteerden significant meer symptomen en hadden een hogere PCS prevalentie vergeleken met patiënten met ongecompliceerd LTH drie en zes maanden na het letsel. Niettemin, nadat wij gecorrigeerd hebben voor basisvariabelen zoals leeftijd, geslacht, opleiding, trauma mechanisme, Glasgow Coma Score, gecompliceerd vs. ongecompliceerd LTH, psychiatrische voorgeschiedenis en stratum, werden de verschillen tussen beide patiëntengroepen minder duidelijk en gaf dit aan dat de associatie verklaard kon worden door differentiaties in basiskenmerken tussen beide groepen. In **Hoofdstuk 5** hebben we de resultaten vergeleken van patiënten met gecompliceerd en ongecompliceerd LTH op drie en zes maanden na het letsel. Uitkomst is vastgesteld door middel van een multidimensionaal concept om patiënten te kunnen vergelijken op verschillende uitkomstniveaus: generieke en ziekte specifieke GKvL, functionele uitkomst en symptomatologie zoals posttraumatische stress, depressie en angst. In totaal zijn 1104 patiënten met LTH, die alle zeven beoordeelde uitkomstinstrumenten in zijn volledigheid hadden ingevuld, geïncludeerd in onze studie. Patiënten met gecompliceerd LTH rapporteerden een lagere generieke en ziekte specifieke GKvL en slechtere functionele uitkomst dan patiënten met ongecompliceerd LTH drie en zes maanden na het letsel. Desondanks werden er geen significante verschillen gevonden tussen de twee genoemde tijdpunten.

In **Hoofdstuk 6** hebben we de frequentie van postcommotionele symptomen en de prevalentie en risicofactoren van PCS in de algemene populatie geëvalueerd. Daarnaast hebben we de relatie tussen de items van de RPQ met de zelf ervaren gezondheid (EQ-5D) bepaald en onderzochten we de verschillen in de algemene bevolking van drie Europese landen (Italië, Nederland en het Verenigd Koninkrijk). We hebben een online enquête uitgevoerd om representatieve steekproeven uit deze drie Europese landen te verkrijgen, en in totaal hebben 11.759 respondenten de RPQ en EQ-5D voltooid. Het meest frequent gerapporteerde symptoom was vermoeidheid (50%), ongeveer de helft van de respondenten werd geclassificeerd met PCS en chronische gezondheidsklachten bleken een significante risicofactor voor PCS. Deze resultaten geven aan dat postcommotionele symptomen niet specifiek zijn voor patiënten met traumatisch hersenletsel en dat PCS niet een uniek syndroom is na traumatisch hersenletsel. Bovendien zijn positieve correlaties bepaald tussen alle RPQ-items en EQ-5D-dimensies- en totaal score.

Dit suggereerde dat postcommotionele symptomen slopend zijn en ook een groot effect hebben op de GKvL van mensen in de algemene bevolking.

In **Hoofdstuk 7** hebben we de prevalentie en bijbehorende risicofactoren voor de ontwikkeling van postcommotionele symptomen en de relatie met kwaliteit van leven (KvL) bij pediatrische en adolescente patiënten met LTH zes maanden na het letsel geanalyseerd. We gebruikten gegevens van de CENTER-TBI-studie en includeerden 196 patiënten die de RPQ zes maanden na het letsel voltooiden. Ten minste één matig of ernstig symptoom van de RPQ werd door 36% van de patiënten ervaren en PCS was aanwezig bij 13% wanneer symptomen van ten minste matige ernst werden overwogen (score> 2). Het ontwikkelde voorspellingsmodel voor PCS wat uitsluitend klinische en demografische basisgegevens gebruikte die direct beschikbaar zijn op de spoedeisende hulp afdeling, identificeerde door middel van een regressieanalyse vrouwen/meisjes als een significante risicofactor voor PCS. Pediatrische patiënten met PCS hadden een lagere Kvl in vergelijking met patiënten zonder PCS, omdat ze significant lagere traumatisch hersenletsel gerelateerde KvL totaal scores hadden.

In **Hoofdstuk 8** hebben we de betrouwbaarheid beoordeeld van symptomen die patiënten na het letsel rapporteren in vergelijking met de symptomen die zij na het letsel rapporteren van hoe zij er voor het letsel aan toe waren, in een grote en representatieve steekproef van patiënten met LTH op verschillende tijdstippen in het eerste jaar na het letsel. De studie bestond uit 836 patiënten met LTH, 191 traumapatiënten zonder voorgeschiedenis van hersenletsel en 100 gezonde controles, waar de laatste twee groepen als controlegroepen dienden. Om symptomen van zowel voor als na het letsel te beoordelen, werd de Head Injury Symptom Checklist (HISC) gebruikt. Bijna de helft van alle patiënten met LTH rapporteerden hun functie voor het letsel inconsequent door de tijd heen. Patiënten die werden geclassificeerd met PCS na het letsel, rapporteerden hogere percentages symptomen vóór het letsel en waren vaker inconsequent. Patiënten die geclassificeerd werden met het hebben van PCS vóór het letsel hadden vaker psychiatrische morbiditeit en deze premorbiditeit vertoonde ook een sterke associatie met PCS na het letsel.

Deel II - Preferenties voor traumatisch hersenletsel

Hoofdstuk 9 beschrijft de ontwikkeling van waardensets voor de QOLIBRI-OS en dit is een instrument specifiek ontwikkeld om GKvL na traumatisch hersenletsel te kunnen meten. In Nederland, het Verenigd Koninkrijk en Italië is een online waarderingsonderzoek uitgevoerd. We ontdekten dat de grootste gewichtstoename voor alle kenmerken van de QOLIBRI-OS wordt gezien op de levels van “licht” tot “helemaal niet tevreden”, wat resulteert in de grootste impact op de GKvL. Bovendien zou het item “Helemaal niet tevreden over hoe de hersenen werken” in alle drie de

landen het grootste gewicht moeten krijgen bij de berekeningen van utiliteiten. Door de QOLIBRI-OS om te zetten in utiliteiten, hebben we de mogelijkheid gecreëerd om dit instrument te in economische evaluaties en in samenvattende metingen van de volksgezondheid toe te passen, die uiteindelijk weer kunnen worden gebruikt om beslissingen te nemen over de beste interventies en strategieën voor patiënten met traumatisch hersenletsel.

In **Hoofdstuk 10** hebben we de impact na traumatisch hersenletsel omschreven door het ontwikkelen van wegingsfactoren voor de GOSE, een functioneel uitkomstinstrument na traumatisch hersenletsel. Hiervoor hebben we GKvL-gegevens van patiënten met traumatisch hersenletsel gebruikt. Voor deze studie zijn de gegevens verkregen via het CENTER-TBI-onderzoeksproject en een totaal van 2.200 patiënten met traumatisch hersenletsel zijn geïncludeerd. Generieke GKvL werd beoordeeld met de Short Form 36-Questionnaire Health Survey versie 2 (SF-36v2) en dit is omgezet naar de Short Form 12-Questionnaire Health Survey versie 2 (SF-12v2). Hierna hebben we de SF-12 drie verschillende, op voorkeur gebaseerde gezondheidsmetingen toegepast: de Short Form Six-Dimension (SF-6D), EQ-5D-3L en Health Utility Index Mark 3 (HUI3). Daarna hebben we de SF-6D-, EQ-5D- en HUI3-scores per patiënt uitgerekend. Uiteindelijk hebben we de volgende gemiddelde wegingsfactoren afgeleid: 0,045, 0,010, 0,008 (GOSE 8; goed herstel) tot 0,185, 0,142, 0,200 (GOSE 3; lagere ernstige invaliditeit), voor de SF-6D, EQ-5D en HUI3 respectievelijk. We hebben vastgesteld dat GKvL-wegingsfactoren toenemen met toenemende ernst van de GOSE. De resultaten van deze studie maken de evaluatie en vergelijking van ziektelast tussen landen en het meten van de effectiviteit van gezondheidszorg en economische evaluaties mogelijk. Bovendien kunnen toekomstige onderzoekers deze resultaten gebruiken bij het vergelijken van de ziektelast en bij het toepassen van kosteneffectiviteitsanalyses en beleidsvorming.

In **Hoofdstuk 11** hebben we de statistische efficiëntie van een nieuwe patiëntgerichte uitkomstmaat in beroerteonderzoek (utility-weighted modified Rankin Scale (UW-mRS)) geëvalueerd en hebben we dit gedaan door middel van een simulatieonderzoek. Het simulatieonderzoek was gebaseerd op individuele gegevens van 500 patiënten uit het MR CLEAN-onderzoek, een multicenter klinisch onderzoek dat de effectiviteit van intra-arteriële behandeling bij ischemische beroerte evalueert. De lineaire analyse van de UW-mRS (power 85%) was efficiënter in het detecteren van behandelingseffecten dan de dichotome analyse van de mRS (power 71%), maar minder efficiënt dan de ordinale analyse van de mRS (power 87%). Bovendien wordt de individuele variatie in bruikbaarheid binnen elke mRS-categorie niet vastgelegd door de UW-mRS.

In **Hoofdstuk 12** hebben we de basis gelegd het begrip GKvL na traumatisch hersenletsel beter te gaan begrijpen in onderzoek en in de klinische praktijk. We hebben populatie-gebaseerde normen opgesteld op basis van representatieve steekproeven uit de algemene bevolking in het Verenigd Koninkrijk en Nederland,

en steekproeven van patiënten met traumatisch hersenletsel uit het Verenigd Koninkrijk en Nederland zijn gebruikt als referentie. Gegevens voor de algemene populatie zijn verkregen via een online enquête en CENTER-TBI-gegevens zijn gebruikt voor de traumatisch hersenletsel patiënten. De QOLIBRI vertoonde goede psychometrische eigenschappen in de steekproeven van de algemene populatie en de gemeten invariantie werd aangetoond in alle landen en in steekproeven van de traumatisch hersenletsel patiënten en de algemene bevolking. De GkvL van individuen met traumatisch hersenletsel verschilt drie maanden na het letsel niet significant van de beoordeelde GKvL in de algemene bevolking. Factoren die na het hersenletsel opspelen, zoals functionele ongemakken en symptomen van emotionele stoornis beïnvloeden GKvL negatief.

Discussie

Het doel van dit proefschrift is het uitbreiden van onze kennis over het vaststellen van de uitkomsten na traumatisch hersenletsel, en het meten van de preferenties voor traumatisch hersenletsel en beroerte bij patiënten en de algemene bevolking. Ondanks dat er een overvloed aan onderzoek gedaan wordt, is er momenteel geen gouden standaard voor het gebruik en de analyse van instrumenten die postcommotionele symptomen beoordelen. Niet alleen dat, ook een eenduidige en universele classificatie van PCS ontbreekt. Dit leidt tot grote variatie in gerapporteerde prevalentiecijfers, inconsistenties, onvergelijkbare uitkomsten en belemmert onderzoek en therapie. Utiliteiten en wegingsfactoren, populatie-gebaseerde normen en waardensets zijn momenteel niet beschikbaar voor alle generieke en ziekte specifieke uitkomstmaten na traumatisch hersenletsel, wat het gebruik van deze instrumenten in economische evaluaties beperkt.

In dit proefschrift hebben wij geconcludeerd dat de prevalentiecijfers voor postcommotionele symptomen en PCS sterk fluctueerden, afhankelijk van de populatie, case-mix van de geïncludeerde patiënten, setting, meetinstrument en diagnostische criteria en toegepaste classificatiemethoden. Bovendien, aangezien we hoge prevalenties van postcommotionele symptomen bij volwassen en pediatrische patiënten zes maanden na het letsel hebben gevonden, kunnen we concluderen dat LTH maanden na het ongeluk nog steeds een rol kan spelen in alle aspecten van het leven. De uitkomst na LTH is multidimensionaal en wordt gekenmerkt door een moeilijke interactie tussen biologische, psychologische en sociale factoren en beïnvloedt elk individu anders.
Het genereren van utiliteiten en wegingsfactoren voor ziekte specifieke GKvL-instrumenten maakt de evaluatie en vergelijking van ziektelast tussen landen en het meten van de effectiviteit van de gezondheidszorg mogelijk. Bovendien kan dit ook toegepast worden in economische evaluaties en gebruikt worden in samenvattende metingen van de volksgezondheid.
Gebaseerd op de interpretatie van de belangrijkste resultaten van de studies die in dit proefschrift zijn opgenomen, hebben we specifieke aanbevelingen

voor toekomstig onderzoek, beleid en de klinische praktijk geformuleerd. Deze aanbevelingen bevatten het volgende: één universele richtlijn met betrekking tot definities, classificatiemethoden en terminologie voor postcommotionele symptomen en PCS, en onderzoekers moeten duidelijk beschrijven hoe een meetinstrument gebruikt moet worden/is en vooral voor de RPQ welke afkappunten gebruikt zijn. Bovendien moet de uitkomst na traumatisch hersenletsel beoordeeld worden door middel van een multidimensionale benadering, waar klinische uitkomst, GKvL en symptomatologie allemaal aan bod komen, en we raden aan om de mogelijkheden voor gepersonaliseerde interventiestrategieën te onderzoeken. Voor onderzoek naar preferenties voor traumatisch hersenletsel raden we aan om een overzicht te creëren omtrent de ontwikkeling van waardensets en dit samen te vatten in een systematische review. Daarnaast moet er een universele richtlijn met beoordelingscriteria ontwikkeld worden om verschillende meetinstrumenten, die utiliteiten genereren, te kunnen vergelijken. Voor de klinische praktijk raden we een uitgebreid multidimensionaal onderzoek aan waarbij patiënten worden geëvalueerd op postcommotionele symptomen door een combinatie van een klinische evaluatie en de patiënt die zelf een vragenlijst invult. Dit alles om rekening te houden met patiënt specifieke situaties en om het revalidatietraject aan te kunnen passen aan het individu.

Dankwoord

Dankwoord

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Daphne Voormolen, Rotterdam augustus 2020.

List of Publications

List of publications

This thesis

Chapter 2 **Voormolen, D.C.**, Cnossen, M.C., Polinder, S., von Steinbuechel, N., Vos, P.E., Haagsma, J.A. (2018) Divergent Classification Methods of Post-Concussion Syndrome after Mild Traumatic Brain Injury: Prevalence Rates, Risk Factors, and Functional Outcome. Journal of Neurotrauma, 35(11):1233-1241.

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About the Author

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Daphne Cloë Voormolen was born on November 5th, 1991 in Rotterdam, the Netherlands. In 2010 she passed her secondary school exams at Erasmiaans Gymnasium in Rotterdam. She was then granted a full scholarship to play field hockey and study at the University at Albany in New York, the United States of America. In 2014 she obtained her double bachelors: Bachelor of Arts in Public Health (Summa Cum Laude) and Bachelor of Science in Business Administration (Magna Cum Laude).

After obtaining these bachelor degrees, Daphne moved back to Rotterdam in September 2014 and started a pre-masters at Erasmus University Rotterdam. Right after this she started the Health Economics Policy and Law (HEPL) master's program. Her master thesis focused on the validation of the CarerQol in informal caregivers of people with dementia in eight different European countries. She obtained her master's degree in July 2016.

In 2016 Daphne started her PhD. project at the Department of Public Health of the Erasmus MC under supervision of dr. Suzanne Polinder, dr. Juanita Haagsma and prof. dr. Ewout Steyeberg. She worked for the Collaborative European NeuroTrauma Effectiveness Research in Traumatic Brain Injury (CENTER-TBI) research project, which ultimately resulted in this thesis.
In April 2020, Daphne started working as a postdoctoral researcher at Erasmus School of Health Policy & Management (ESHPM) at Erasmus University Rotterdam.

PhD Portfolio

PhD portfolio

Name PhD student: Daphne Cloë Voormolen
Department: Public Health
Promotor: Prof.dr. E.W. Steyerberg
Copromotors: Dr. S. Polinder and Dr. J.A. Haagsma
PhD period: May 2016 – March 2020
ECTS: 34.90

	Year	Workload (ECTS)
1. PhD training		
General academic skills		
Systematic literature retrieval/Endnote - W. Bramer	2016	0.6
Research integrity	2018	0.3
Consultation Center for Patient Oriented research (CPO)	2017	0.3
Time management course	2016	0.2
Research skills		
BROK	2017	1
(deel-)BKO	2018 - 2019	2
Reviewing research articles for scientific journals	2019	1
NIHES courses, Rotterdam, the Netherlands		
Principles of Epidemiologic Data-analysis - K. Rothman	2017	0.7
Courses for the Quantitative Researcher - J. van Rosmalen	2017	1.4
From Problem to Solution in Public Health - J. Haagsma	2017	0.55
Logistic Regression - S. Lemeshow	2017	1.4
Presentations at national and international conferences		
Impact of Post-Concussion Symptoms on Health-Related Quality of Life of Patients with Mild Traumatic Brain Injury lolaHESG 2017, Rotterdam, the Netherlands (presentation)	2017	1
The Association between Persisting Post-Concussion Symptoms and Health-Related Quality of Life in Patients with Mild Traumatic Brain Injury Eurosafe Conference, Amsterdam, the Netherlands (presentation)	2017	1
Workpackage 11 - Health utility indices and population health Center-TBI General Assembly, Antwerp, Belgium (presentation)	2017	1

Divergent Classification Methods of Post-Concussion Syndrome after Mild Traumatic Brain Injury: Prevalence Rates, Risk Factors, and Functional Outcome	2017	1
Medical Decision Making, Dep. Public Health, Erasmus MC, Rotterdam, the Netherlands (research meeting)		
Health-related quality of life after traumatic brain injury: Deriving a value set for the QOLIBRI-OS and QOLIBRI in 3 European countries	2018	1
SMDM, Leiden, the Netherlands (poster)		
Prevalence of post-concussion-like symptoms in the general population in Italy, The Netherlands and the United Kingdom		
Health-related quality of life after traumatic brain injury: Deriving a value set for the QOLIBRI-OS and QOLIBRI in 3 European countries	2018	1
NeuroTrauma 2018, Toronto, Canada (posters)		
"The PhD-student as a teacher"		
Gastroenterology & Hepatology PhD-day, Erasmus MC, Rotterdam, the Netherlands (presentation)	2018	1
Health-related quality of life after traumatic brain injury: Deriving a value set for the QOLIBRI-OS	2019	1
CENTER-TBI monthly meeting, Erasmus MC, Rotterdam, the Netherlands (research meeting)		
Prevalence of post-concussion-like symptoms in the general population in Italy, The Netherlands and the United Kingdom	2019	1
Health Science Research Day, Rotterdam, the Netherlands (poster)		
Post-Concussion Symptoms in Complicated vs. Uncomplicated Mild Traumatic Brain Injury Patients at Three and Six Months Post-Injury: Results from the CENTER-TBI Study	2019	1
NNC 2019, Lund, Sweden (poster)		
"De Sporter met hersenletsel"		
Refereeravond Spoedeisende Hulp: 'De sporter op de spoed', Erasmus MC, Rotterdam, the Netherlands (presentation)	2020	1
Seminar and workshops		
Research seminars, Dep. Public Health, Erasmus MC, Rotterdam, the Netherlands	2016-2019	9
Research meetings Medical Decision Making, Dep. Public Health, Erasmus MC, Rotterdam, the Netherlands	2016-2019	1
Research meetings Health Technology Assessment and Implementation, Dep. Public Health, Erasmus MC, Rotterdam, the Netherlands	2017-2019	
MGZ Career day	2017	0.5
PhD Day	2017-2018	1
Organisation Career Event, Erasmus MC	2018-2019	1

Conference ZONMW/NWO “Evolution or Revolution”, The Hague, the Netherlands	2019	0.2

2. Teaching activities

Courses		
Basisdidactiek voor docenten (Teach the Teacher I)	2018	0.2
Workshop Hoe ontwikkel ik een e-module	2018	0.2
Workshop Het ontwerpen van vragen voor schriftelijke tentamens	2018	0.2
Training VO Gezondheidsvoorlichting	2018	0.2
Lecturing		
VO Hoe houden we de zorg betaalbaar	2018 - 2020	1.2
VO Keuzen in de zorg	2018 - 2019	0.8
VO Gezondheidsvoorlichting	2018 - 2019	0.8
Supervising		
Supervisor medical students theme 3.C.1 (community projects)	2016 - 2019	1.2
Other teaching activities		
Coordinator of ED resident education	2019	0.2
Correction of the ‘GENBA2A1-V01 - Ba2A Oncologie’ exam	2018 - 2019	0.5
Coordinator CENTER-TBI workshop	2018	

3. Other activities

Committees		
Promeras board member (Secretary and Communication)	2018 - 2019	1
Social Committee, Dep. Public Health, Erasmus MC, Rotterdam, the Netherlands	2018 - 2019	0.5
Acquisition		
Erasmus trustfonds (applicant: €500,- granted)	2018	

BROK: Basiscursus Regelgeving en Organisatie voor Klinisch onderzoekers; NIHES: National Institute for Health Sciences; IolaHESG: The lowlands Health Economists' Study Group; SMDM: Society for Medical Decision Making; CENTER-TBI: Collaborative European NeuroTrauma Effectiveness Research in Traumatic Brain Injury; ED: emergency department.