Predictors of long-term outcome after severe traumatic brain injury

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If we knew what it was we were doing, it would not be called research would it?

− Albert Einstein

ABSTRACT

Aim: A complex interaction between several factors may influence and explain the variance in outcome after traumatic brain injury (TBI). The overall aim of this thesis was to explore, in individuals with severe TBI, the impact of posttraumatic hypopituitarism (PTHP), a history of unemployment or sick leave, and care pathways on long-term global outcome. Further, to investigate short- and long-term all-cause mortality after severe TBI.

Methods: The studies reported in this thesis included a total of 280 participants with severe TBI. In study I and II, a retrospective follow-up was performed of 51 consecutive individuals, age 16–65 years, who were admitted with severe TBI to Sahlgrenska University Hospital, Gothenburg, from 1999 to 2002.The impact of PTHP and of unemployment or sick leave before injury on functioning and health related quality of life (HRQL) was explored. Data from the time of injury were combined into a validated prognostic model to adjust for injury severity. Outcome was measured once, 2 -11 years after trauma, and included hormonal testing, the Short Form-36 Health Survey, the Glasgow Outcome Scale –Extended (GOSE), and a self-report questionnaire specifically designed for these studies. Data on sick leave and unemployment were gathered from the Swedish social insurance agency. Study III was a multi-centre, prospective, observational study of 114 individuals, age 18-65 years, with severe TBI from six neurosurgical centers in Sweden and Iceland, with a follow up one year after the injury. The study assessed the relationship between care pathways (length of stay in intensive care, time between intensive care discharge and rehabilitation admission), and global outcome (GOSE). A validated prognostic model was used to adjust for injury severity. In study IV, a comparison of the cumulative death rates and causes of death between 166 individuals admitted to Sahlgrenska and a community control group, was conducted retrospectively at 10 years after the severe TBI. The data was ascertained from the Swedish National Board of Health and Welfare register.

Results: A history of sick leave or unemployment before severe TBI was found to predict a worse long-term global outcome, more problems with activities of daily living and reduced HRQL at follow-up. A higher body mass index and overweight at follow-up was partially explained by PTHP. Otherwise no significant correlation was found between PTHP, functioning and HRQL. A longer length of stay in intensive care, and longer time between discharge from intensive care and admission to inpatient rehabilitation, were both associated with a worse global outcome at one year after injury. The risk of death was increased from a variety of causes for at least 10 years after severe TBI.

Conclusion: The participants with severe TBI reported lasting disability, and low HRQL, with a complex range of physical, cognitive, behavioral and emotional disturbance. This may increase risk for secondary medical morbidity and explain the increased risk of death for many years after the injury. The results of the studies should be considered when refining long-term outcome predictions and optimizing rehabilitation interventions (prevention, surveillance and treatment) and care pathways after severe TBI. These findings highlight the need to provide special interventions for individuals with a history of unemployment or sick leave before severe TBI and they indicate that screening for PTHP might be warranted to specific subgroups such as overweight individuals. Measures to establish well-timed rehabilitation admission may improve outcomes after severe TBI.

Key words: Severe Traumatic brain injury; Prognosis; Hypopituitarism; Pre-morbid; Rehabilitation; Health Facility Planning; Long-term outcome; Functioning; Quality of life; Survival analysis.

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Ten-year mortality after severe traumatic brain injury in western Sweden, a case-control study.

Submitted

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ABBREVIATIONS

ADL	Activities of Daily Living
BMI	Body Mass Index
CRASH	Corticosteroid Randomization After Significant Head Injury
CT	Computed Tomography
FK	Swedish Social Insurance Agency (Försäkringskassan)
GCS	Glasgow Coma Scale
GH	Growth Hormone
GHD	Growth Hormone Deficiency
GOS	Glasgow Outcome Scale
COSE	Glasgow Outcome Scale –Extended
HRQL	Health-Related Quality of Life
ICD-10	International Classification of Diseases, tenth revision
ICF	Classification of Functioning, Disability and Health
ICP	Intracranial Pressure
LORS	Length of Inpatient Rehabilitation Stay
LOSIC	Length of Stay in Intensive Care
NICU	Neuro-intensive Care Unit
PTHP	Posttraumatic Hypopituitarism
SCB	Statistics Sweden (Statistiska Centralbyrån)
SF-36	The Short Form-36 Health Survey
SoS	Swedish National Board of Health and Welfare (Socialstyrelsen)
SU	Sahlgrenska University Hospital
TBI	Traumatic Brain Injury
WHO	World Health Organization

INTRODUCTION

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, as a consequence of direct impact, rapid acceleration or deceleration, a penetrating object (e.g. gunshot), or blast waves from an explosion (1). The nature, intensity, direction, and duration of these forces determine the pattern and extent of brain damage (2).

Traditionally, TBI has been classified by mechanism (closed vs. penetrating), by clinical severity (Glasgow Coma Scale, GCS), and by assessment of structural damage (neuroimaging) (2-4). Multiple classification schemes for TBI severity appear in the literature. Historically, the GCS has been the most widely used clinical TBI severity classification tool (4, 5). It is based on the patient' s responses of eye opening, verbal function, and motor function to various stimuli and consists of the sum score (range 3–15) of the three components (eye, motor, and verbal scales). A score of 13–15 is considered a mild, 9–12 is considered a moderate, and 3–9 is considered a severe TBI. The Reaction Level Scale (RLS), is a hierarchically ordered classification scale with 8 categories ("reaction levels"); higher scores denote worse responsiveness, and a score ≥4 denotes a nonresponsive patient (6). The eight point RLS is widely used in Sweden and at the Neuro-intensive Care Unit (NICU) at Sahlgrenska University Hospital (SU) in Gothenburg it is used instead of the GCS. RLS scores can be converted to GCS scores as described (7). GCS scores of 3–8 and RLS scores of 8–4 indicate similar levels of consciousness, reflecting the severity of injury; however, the RLS has somewhat better inter-rater reliability than the GCS (7). The RLS and GCS are scored in opposite directions, with the highest RLS score of 8 reflecting the most severe injuries (7, 8). Ordering of severity with the RLS and GCS has been shown to be consistent (9); the RLS and GCS are highly correlated (r=–0.94) and assess similar behavioral features reflecting consciousness (10). However, in the acute settings, the elapsed time from injury, hemodynamic parameters, medical sedation, paralysis and intoxication often confound GCS and RLS scoring (5, 11, 12). Assessment of structural damage by neuroimaging is not influenced by these confounders, but has limitations. These limitations include among others that It can only capture momentary snapshots of the dynamically evolving process of TBI, and important lesions that occur at the microscopic level, such as diffuse axonal injury (DAI) and ischemic damage, cannot be visualized (13). TBI can be isolated, but is associated with extracranial injuries (limb fractures, thoracic or abdominal injuries) in about 35% of cases, which increases the risk of secondary brain damage due to hypoxia, hypotension, pyrexia, and coagulopathy (14). The recording of the severity of extracranial injuries should therefore form anintegral part of TBI classification. An alternative approach is to classify patients by prognostic risk. Although not new, this is an approach under development. Recent, well validated models, developed on large patient samples, have become available to facilitate this approach (15-19) These models allow covariate adjustment to reduce the effect of prognostic heterogeneity (18). By combining the predictive value of computed tomography (CT)-findings and some of the clinical parameters into such a model, prognostic classification can serve as an objective basis for evaluating the impact of different outcome predictors for TBI patients. The CRASH (Corticosteroid Randomization After Significant Head Injury) acute prognostic model is developed from

study of over 10 000 patients worldwide and has been externally validated against another large data set of over 8 000 patients (20). CRASH incorporates ten acute variables: age, pupil reaction, acute GCS, country, presence or absence of major extracranial injury, presence or absence of 5 specified acute CT-brain findings.

According to the World Health Organization (WHO), TBI will surpass many diseases as the major cause of death and disability by the year 2020, mainly due to increasing road traffic accidents in the developing world, as well as increasing trends for political and civil violence in certain regions (21, 22). With an estimated 10 million people affected annually by TBI, the burden of mortality and morbidity that this condition imposes on society, makes TBI a pressing public health and medical problem (21, 22). The general incidence of TBI in developed countries is stated to range from 150 to 250 per 100 000 people/year, and the incidence of fatal TBI-related trauma to range from 12 to 20 per 100 000 people/year. The ratio of mild to moderate to severe TBI has been found to be 22: 1.5: 1; which equals about 10 cases of severe TBI/100 000 people/year (23-25). This estimate typically includes only TBI patients admitted to hospitals, resulting in underestimation of the frequency of mild TBI (26). Studies, accounting more accurately for the mild TBI, report an incidence of up to 500 per 100 000 people/year in USA and Europa (27, 28), and 790 per 100 000 people/year in New Zealand (29). In Sweden, approximately 15 000 TBI patients are admitted to hospitals per year (30). Incidence peaks in early childhood, late adolescence/early adulthood, and in the elderly. Males are uniformly at higher risk of TBI than females, with the highest male-to-female ratios typically occurring in adolescence and young adulthood, being > 2:1(23-25, 31). The most common event leading to a TBI are falls and motor vehicle related causes. Violence is also a common and an increasing cause of TBI (23-25, 31).

Approaches to management

Pre-hospital and admission emergency care

The main goals of pre-hospital management are to prevent hypoxia and hypotension, because these systemic insults lead to secondary brain damage (32, 33). The primary aims of admission care are stabilization and diagnostic assessment, and from a neurosurgical perspective, the immediate priority is rapid detection and treatment of operable lesions (32).

Intensive care management

A major focus for neurointensive care is to prevent and limit ongoing brain damage and to provide the best conditions for natural brain recovery by reducing brain swelling and raised intracranial pressure (ICP) (32, 34-36). Optimum oxygenation, perfusion, nutrition, glycaemic control, and temperature homoeostasis are indicated, as in general intensive care. Furthermore, the brain must be protected from overt or silent seizures. Sedation and artificial ventilation are used to reduce brain swelling and raised ICP in patients with severe head injuries. Osmotherapy is currently preferred as the first agent in the medical management of raised ICP (36). Further steps in the treatment of raised ICP are drainage of cerebral fluid from a ventriculostomy and if the ICP levels are still unacceptable, decompressive craniectomy (37). Surgical evacuation of the hematomas may be necessary. There are standardized protocol-driven therapies, but they vary across different centers.

Rehabilitation

Recovery of function after severe TBI depends not only on resolution of injury related pathology, e.g. resolution of oedema, clearing of inflammatory infiltrate, resolution of disruption to functional networks. It also depends on neuroplasticity - the brain's ability to reorganize itself by forming new neural connections through changes in synapses, glia modulation, axonal sprouting and neurogenesis. Neuroplasticity can be influenced by active rehabilitation interventions (38, 39). Rehabilitation is defined by the WHO as follows: “Rehabilitation of people with disabilities is a process aimed at enabling them to reach and maintain their optimal physical, sensory, intellectual, psychological and social functional levels. Rehabilitation provides disabled people with the tools they need to attain independence and self-determination” (40) .

As well as contributing to improved function through optimization of neuroplastic processes, rehabilitation also aids the patient in compensating for any persisting deficits and as such minimizing activity limitations and maximizing possibilities for participation. Evaluations of TBI rehabilitation interventions are still in development, but there is now a substantial body of high-quality research evidence for the effectiveness, and indeed the cost-effectiveness, of multidisciplinary rehabilitation following TBI (41-44). A systematic review provided "strong evidence" that more intensive programs are associated with more rapid functional gains, and further, that early or late rehabilitation, and specialist programs (e.g. vocational or neuro-behavioural rehabilitation) are effective, as well as evidence for the cost-benefits of rehabilitation (44). An example of more specific interventions is cognitive rehabilitation for patients with TBI, targeting problems like strategy training for mild memory impairment or attention deficits (41) and computerized working memory training for patients with acquired brain injury to improve impaired working memory, cognition and psychological health (45, 46).

The rehabilitation in Sweden is generally built on a policy of continuum of care, like a chain in a support system with subsequent interventions over time from “coma to community”. Early rehabilitation interventions after severe brain injury include assessment and treatment to improve a patient’s level of function and to prevent secondary complications (47, 48). The interventions must be extremely sensitive to the patient’s medical status and needs at the time. The patients are mobilized to sitting and standing positions as soon as possible, even if they still need respiratory assistance. Preventing complications such as infections and contractures is essential.

The aim of the initial inpatient rehabilitation process is to assure medical stability. The ultimate goal is to enable the patient to regain the highest possible degree of physical and psychological performance in order to achieve functional independence necessary for returning home so that the participation in their community life can be attained. In the long term, it requires the patient to participate actively in the process of understanding the complexity of his/her neuropsychological deficits and his/her personal reactions to those deficits. Relatives or significant others are actively involved in the rehabilitation activities. The inpatient rehabilitation continues with outpatient rehabilitation programs for those who have such needs. In ideal cases the chain goes through several phases with the goal of achieving community reintegration, vocational rehabilitation, and a good quality of life (49).

Short- and long –term outcome after severe traumatic brain injury

The term outcome, in the context of this thesis, reflects a consequence of an initial trauma (50). The outcome after TBI can range from complete recovery to death (26, 51-54).

Early in the rehabilitation process, functional abilities such as levels of independency in activities of daily living, e.g. manageability in self-care, are prominent, while outcome in a later phase is more often described in terms of social role fulfillment, e.g. ability to engage in leisure and work activities. The later phase is characterized by the ambition to return to an optimal level of participation in the community, and to be socially reintegrated (55).

Functioning and disability

Current perspectives on outcomes often use the WHO's taxonomy entitled International Classification of Functioning, Disability and Health (ICF) (56).

In ICF, the term functioning refers to all body functions, activities and participation, while disability is similarly an umbrella term for impairments, activity limitations and participation restrictions (figure 1).

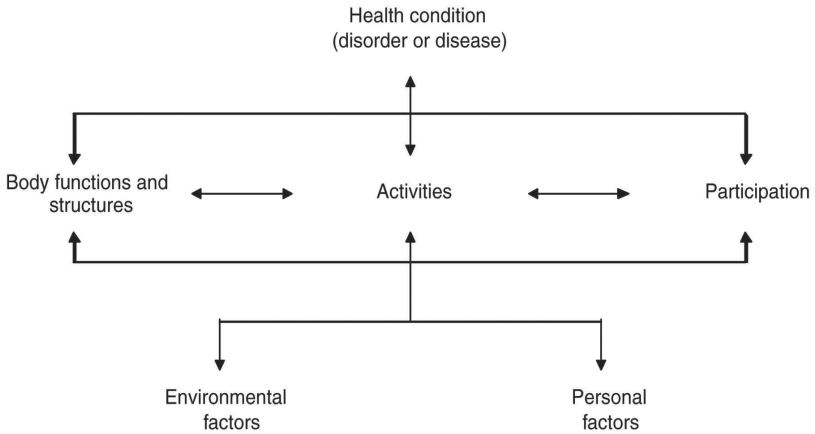

Figure 1. Components of the International Classification of Functioning, Disability and Health

The ICF takes a bio-psychosocial view on functioning consisting of four domains divided into two parts: Part 1: i) body functions, ii) body structures, iii) activities and participation, and Part 2 (Contextual factors): iv) environmental factors and personal factors, e.g. age, sex, lifestyle, etc., are included in the conceptual framework, but not classified due to the large individual differences that exist.

A European epidemiological study found that TBI was the most common cause of permanent disability after injury (57). Especially after severe injury, serious cognitive, behavioral, emotional, and sensorimotor impairments can occur that have major consequences for the

patient's activity patterns, social participation, and quality of life (51, 52, 54, 58-62). Cognitive, and psychosocial problems have been shown to be more common and more serious than physical problems after severe TBI (52, 63-66). Particularly common are problems with memory, attention and mental fatigue, as well as irritability, reported in more than two-thirds of the patients (62). Similarly, depression and anxiety are common, reported in about half of the patients(62, 67-71). Balance problem is one of the most common persistent neurological symptoms after severe TBI, reported in more than half of the patients (62), and sensorimotor impairments are common, reported in more than one-third of the patients (62, 72).

The ICF model would be expected to allow an approach to characterize the consequences of TBI, and the extent of disability many years after the TBI.

Health-related quality of life

Measures of outcomes may be regarded as incomplete if the subjective well-being of the individual is not considered (73). An international TBI consensus group noted that patients' self reported health-related quality of life (HRQL) values are necessary in TBI research (74). Quality of life as an outcome measure is important for both patients and clinicians as one of the primary goals of rehabilitation is to help TBI survivors to gain a meaningful existence and a life within their expectations (75). Factors that contribute to HRQL could guide interventions for improving physical, cognitive and emotional status along with environmental factors.

Mortality

Although a significant proportion of deaths from head injury occur shortly after the injury (14, 24, 76, 77), a patient with severe TBI who recovers may still have a substantially reduced life expectancy for many years thereafter (53, 78-88). TBI can result in disabilities that may increase the risk for secondary medical morbidity and mortality (54, 59, 61, 62, 78, 85, 87). Some studies suggest that the causes of death in patients with TBI who survive the acute phase differ from those in the general population, but this is not a consistent finding (53, 78, 83, 85). Many studies of late mortality after TBI have suffered from recruitment bias, including the use of unrepresentative samples of the head injury population, such as patients from a rehabilitation unit, patients with persisting disabilities, or patients from age-restricted samples (85, 87-92). Further, only few studies have compared the occurrence of deaths after head injury with the death rate in the population from which the TBI patients come; patients are often young men from socially deprived backgrounds (93). Late mortality after TBI should be studied in different geographic areas and care settings to determine whether earlier findings can be generalized to other populations. No Scandinavian study has examined late all-cause mortality among patients with severe TBI.

Predictors of outcome after severe traumatic brain injury

Only a proportion of the variance in late outcome is accounted for by the initial severity of the brain injury, a relationship that may weaken over time (61, 87). Instead, a complex interaction between several factors such as premorbid characteristics (including genetic variability and co-morbidities), injury factors (including secondary systemic and neuroinflammatory response), post injury impairments, and personal and environmental

factors may influence and explain the variance in late outcome. (54, 59, 61, 87, 94-97). Analysis of factors impacting on outcome after severe TBI is therefore merited.

Posttraumatic hypopituitarism (PTHP)

Hypopituitarism is defined as either partial or complete deficiency of anterior or posterior pituitary hormone secretion, or both (98). Several studies from the last decade have shown that TBI put patients at substantial risk of subsequent hypopituitarism (99-106). However, the prevalence of reported PTHP is highly dependent on the diagnostic setup and varies widely among published studies (105, 107-109). A meta-analysis reported a pooled prevalence of PTHP in the chronic phase after TBI of 30% (110).

Several mechanisms have been suggested for the PTHP, including hypoxic insult or direct mechanical injury to the hypothalamus, pituitary stalk, or the pituitary gland; compression from hemorrhage, edema, or increased intracranial pressure; and vascular injury to the hypothalamus or the pituitary gland (111). Recently published studies suggest that PTHP long –term after TBI might be du to autoimmunity (112, 113).

Although the clinical symptoms of hypopituitarism are usually unspecific, it can cause life-threatening events and lead to increased mortality (114-117). Identification of growth hormone (GH) and corticotrophin deficiency generally requires a stimulation test, whereas basal hormones in combination with clinical judgment can detect other deficiencies. Patients with TBI have many somatic, psychiatric, and neurological symptoms that could well mask the typical signs and symptoms of hypopituitarism, such as decreased muscle mass and strength, weight change, fatigue, depression, and impairment of attention and memory (114). Researchers have begun to investigate the effect of PTHP on outcome after TBI, with a particular focus on neuropsychological sequelae (118). However, such studies have measured outcome in a heterogeneous group of patients with a wide range of TBI severity (119-131). Few studies have considered the relative contribution of injury severity to functional outcome (118).

A worse functional outcome (e.g., greater functional dependency and activity limitation) and worse cognitive functions (e.g., greater deficits in attention, executive functioning, memory, and emotion) has been reported in TBI patients with PTHP, particularly those with growth hormone deficiency (GHD), compared to those without PTHP (122, 123, 130). A few studies have also reported a worse health-related quality of life (HRQL) in patients with PTHP, particularly those with GHD (e.g., poorer sleep and energy levels and an increased sense of social isolation) (120, 125, 127, 131).

The above-mentioned studies evaluated patients up to 2 years after the injury. However, in one study of TBI patients with long-lasting cognitive disorders followed for a mean of 6.5 years after the initial injury, late functional outcomes, activity performance, and cognitive function after TBI were worse in patients with PTHP, especially those with GHD. However, the impact of PTHP on functional outcome, cognitive disorders, and HRQL is controversial (124). Some studies have shown results that have questioned the current opinion on hypopituitarism after TBI. They reported no evidence for an association between impaired cognitive function and GHD in adult TBI patients, between neuropsychological impairments, HRQL and PTHP, or between TBI, fatigue, and GHD (119, 121, 129).

Given the discrepancies in the limited data on PTHP and outcome, the clinical importance of PTHP needs to be examined further in a well-defined group of patients with severe brain injury and a long follow-up time.

Pre-morbid factors

Factors that predate the injury should be considered in rehabilitation after TBI (132-135). Co-morbidities such as substance abuse and pre-morbid demographic characteristics such as age, education, and employment are important for outcome (136-145). A systematic review of prospective cohort studies investigating prognostic factors at least 1 year after injury found strong evidence that pre-injury unemployment and pre-injury substance abuse predict disability and non-productivity in patients with TBI (94). In a study of the specific sick leave pattern before TBI in patients with various injury severities at the SU in Gothenburg, the strongest factor predicting long-term sick leave after TBI was being on sick leave on the day of the trauma (146).

Although several studies have investigated the long-term prognosis after TBI, little is known about pre-morbid factors in adults with severe TBI, and a significant effect of pre-morbid factors have not always been noted in these patients (132, 136, 137).

Care pathways

Although less common than mild and moderate TBI, severe TBI may require a lengthy hospital stay and cause long-term disability.

Initial injury severity, post-acute complications, and rehabilitation interventions all have the potential to impact on outcome. The literature on acute care and on rehabilitation for individuals with severe TBI has however largely developed along separate paths. The acute care literature has focused on increasingly nuanced analysis of markers of acute injury severity of importance for predicting outcome (16, 19) but largely ignored any impact of rehabilitation interventions, whilst the rehabilitation literature has relied on relatively simplistic definition of injury severity (e.g. by acute GCS), to define study populations, without reference to recent developments in acute prognostic models (58, 94, 133).

Access to rehabilitation for patients surviving severe TBI is variable across the world. A recent French study found that more than a third of patients surviving severe TBI in Paris were not even referred to rehabilitation (147). In some countries, access to rehabilitation depends on the individual's medical insurance status, and rehabilitation may be unavailable to uninsured patients (148). This thesis assessed care pathways in Sweden and Iceland where there is universal health insurance, and as such no formal access barriers to rehabilitation. However acute and rehabilitation care have historically developed separately, without a planned, unified pathway of care. They also belong to different organisations, and clinical experience is that delays in admission to rehabilitation units are common.

Evidence is now emerging for the benefits of a continuous chain of care after severe traumatic brain injury (from neurosurgical intensive care to inpatient rehabilitation to discharge) (149-151). These were recently demonstrated in a Norwegian quasi-randomised study of severe traumatic brain injury (150). Better outcomes one year after injury were demonstrated for patients receiving early and continuous rehabilitation starting in the intensive care unit, compared to a group who received usual care. The usual care also

incorporated inpatient rehabilitation, but not via a defined, continuous pathway of care.

Elsewhere in Europe, Denmark has had a defined care pathway for patients after severe traumatic brain injury for over a decade, centralized to two national centres. The most severely injured patients receive highest priority regarding transfer to inpatient rehabilitation. Outcomes after introduction of this defined care pathway with centralized rehabilitation were better than outcomes for historical controls (151).

In Sweden, rehabilitation after severe TBI may be offered in several forms (152). Specialised inpatient rehabilitation is primarily offered in rehabilitation medicine departments based in university departments of rehabilitation medicine, and in some county hospitals. These are found in each of the six health care regions and have traditionally offered specialised, post-acute rehabilitation to adults of working age. Other forms of inpatient rehabilitation exist in some regions, for example in county hospitals, in some cases integrated with Geriatric services, and as such lacking a primary focus on the needs of working adults. Care pathways vary, and these county units may either act as step-down units for continued rehabilitation after discharge from specialised units, or in some cases may receive patients directly. There are no national guidelines regarding appropriate care pathways for TBI patients and improved evidence base is needed to support appropriate developments in this field (152).

AIM

The overall aim of this thesis was to explore the impact of PTHP, a history of unemployment or sick leave, and care pathways on the long-term global outcome in individuals with severe traumatic brain injury (TBI). Further, to investigate the short- and long-term all-cause mortality after severe TBI.

The specific aims where:

Paper I

To evaluate the relationship between pituitary function, self-reported HRQL and functioning in a series of retrospectively identified working age individuals 2–11 years after severe TBI.

Paper II

To determine whether being unemployed or on sick leave before injury influences self-reported HRQL and functioning in a retrospectively identified working age individuals 2–11 years after severe TBI.

Paper III

To assess prospectively the relationship between care pathways for working age individuals in the first year after severe TBI, and global outcome at one year.

Paper IV

To investigate the 10-year mortality rate in a retrospectively identified cohort of individuals with severe TBI admitted to a hospital in western Sweden and in a matched community control group. Our goals were to ascertain the patterns of short- and long-term all-cause mortality for this cohort and to examine the rates of the primary causes of death.

METHODS

Design

Paper I and II

Retrospective, observational single-center studies of PTHP, pre-morbid working status and outcomes after severe TBI in working age individuals in western Sweden.

Paper III

A prospective, observational, multi-centre study of care pathways and outcomes after severe TBI in working age individuals in Sweden and Iceland.

Paper IV

A retrospective case-control, single-center study in western Sweden of causes and rates of death between individuals admitted to hospital after a severe TBI and a community control group.

Study participants

Participants with severe TBI

The studies reported in the thesis included a total of 280 participants with severe TBI.

For **studies I, II**, **and IV**, participants were enrolled from the catchment region of SU in Gothenburg which includes about 1.65 million inhabitants in the Västra Götaland region in western Sweden, with roughly 550 000 in the city of Gothenburg. Between January 1, 1999, and December 31, 2002, 419 individuals with TBI (ICD-10 diagnostic codes S06.1–S06.9) were admitted to the NICU at SU. Their medical files were reviewed retrospectively to collect data on the level of consciousness upon arrival at the hospital. Consciousness was evaluated with the RLS, and RLS scores converted to GCS scores as described (7).

In **studies I, and II**, 104 working age individuals of the 419 admitted to NICU, met the inclusion criteria and were invited by letter to participate in the study (figure 2). Those who did not respond within 1 month received another letter, a phone call, or both. Fifty-three individuals were lost to follow-up, and 51 individuals were included in the studies (13 women and 38 men) (figure 2). The 53 individuals who did not participate were similar to the 51 study participants in terms of mean age (40.7 vs. 37.9 years; 95% CI = -2.8 – 8.4), injury severity, according to CRASH (68.0% vs. 63.1% risk of unfavorable outcome; 95% CI = -3.9 – 13.7) or gender (14 F/39 M vs. 13 F/38 M; p = 1.00).

In **study IV**, 170 of the 419 individuals met the inclusion criteria of a GCS score ≤8. Four of those individuals did not have a Swedish residence, thus 166 participants were included in the study. Exclusions were not made on the basis of age (figure 3).

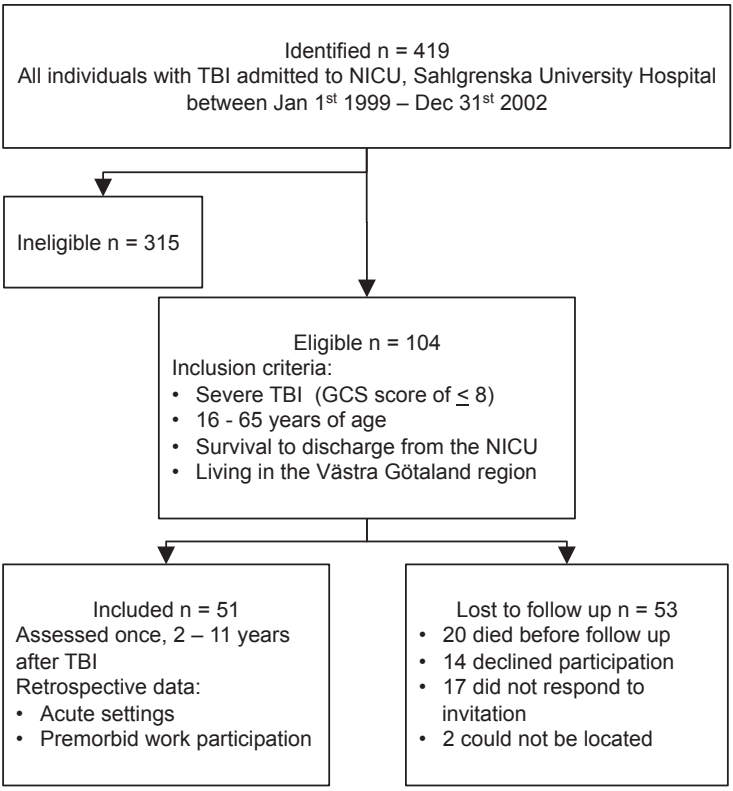

Figure 2. Flow chart of derivation of cohort in studies I, and II.

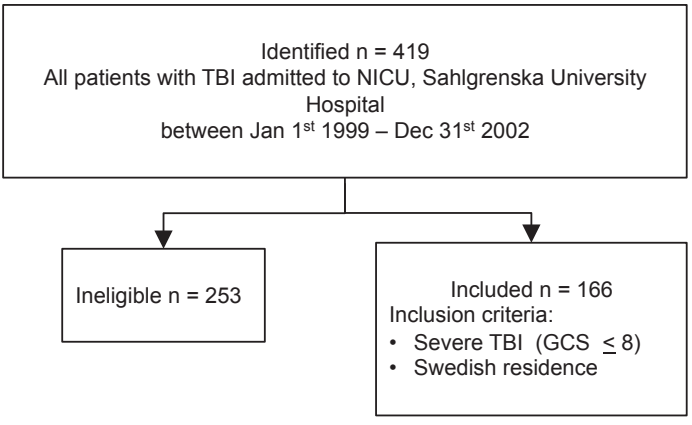

Figure 3. Flow chart of derivation of cohort in study IV.

For **study III,** 114 working age individuals were recruited prospectively from five NICUs in Sweden and one in Iceland (six out of possible seven) from January 2010 until June 2011, with extended recruitment until December 2011 at two centres (figure 4). The participating centres provide neurosurgical care to more than 80% of the population of Sweden, and the whole population of Iceland, in total approximately 4.7 million adults aged 18-65 years. The Southern region of Sweden chose not to participate. The NICUs were contacted on a weekly basis to identify eligible participants. Inclusion criteria were:

1. Severe, non-penetrating, traumatic brain injury, with a lowest non-sedated GCS score of 3-8 or RLS score of 4-8 in the first 24 hours after injury.
2. Age at injury 18-65 years
3. Injury requiring neurosurgical intensive care.

Exclusion criteria were death or expected death within 3 weeks of injury.

Follow up rates were 98% to 3 weeks after injury (97% alive, 1% dead), 96% to 3 months after injury (92% alive, 4% dead), 84% to one year after injury (78% alive, 6% dead). Individuals who withdrew were similar to those who continued in terms of median age (34.5 vs. 42.0 years; p=0.7) and median acute GCS or RLS-derived GCS (4 vs. 5; p=0.3).

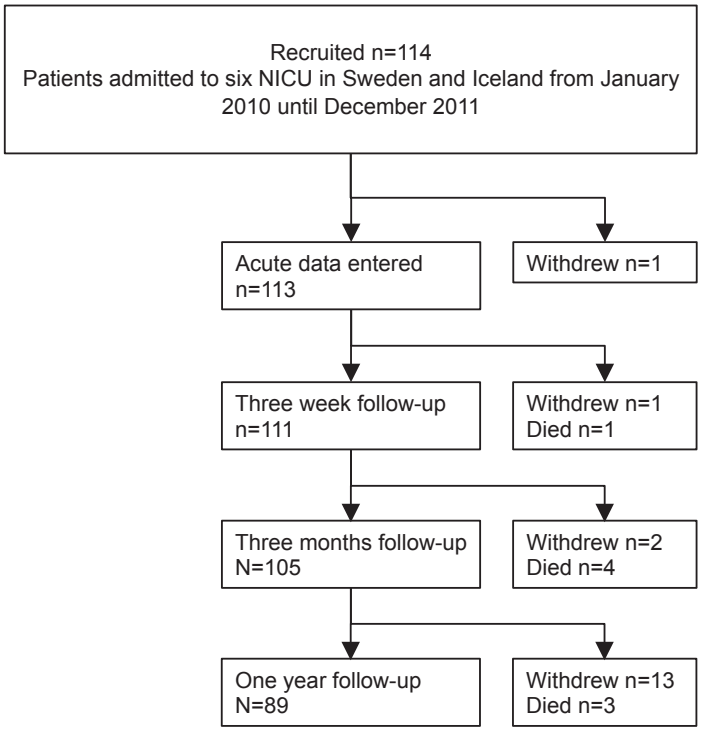

Figure 4. Flow chart of derivation of cohort in study III.

Community control group

For **study IV,** identification of a community control group was undertaken by Statistics Sweden (Swedish: Statistiska centralbyrån, SCB), the Swedish government agency responsible for producing official statistics regarding Sweden, by matching to the postcode area of the head injured group at the time of injury, by age and by gender. SCB identified the control group of n = 809 based on 5:1 matching with the head injury cohort.

Assessments

For **study I and II**, all participants were assessed once, between September 2004 and June 2010, 2–11 years after their TBI (median = 5 years, 8 months). No statistical difference was found in months to follow up between the group with PTHP or not (95% CI = -24.6 – 8.4), and similarly not between the group with a history of sick leave/unemployment or not (95% CI = -13.3 – 17.4). The participants were assessed without knowledge of their hormonal status or pre-morbid work participation, in the endocrinology department in a quiet setting over a 2–3-hour period. A physician performed the health assessment (physical examination and medical history), and completed the questionnaires by interviewing the patient (n = 45) or, if that was not possible due to severe sequelae of the TBI, the physician interviewed a relative or personal assistant of the patient (n = 6).

Data on co- morbidity and sociodemographic characteristics at the time of injury were recorded retrospectively from the medical files. The injury characteristics were obtained from the acute care medical files and the findings from each patient's first and second CT scans after arrival at the hospital were registered. In order to control for acute injury severity, the CRASH acute prognostic model was used to obtain a composite representing risk of unfavourable outcome: After conversion of RLS scores to GCS (7) we used the online calculator for the CRASH to calculate the percentage risk of an unfavourable outcome at six months for each patient, which refers to dead, vegetative state or severe disability as defined by the Glasgow Outcome Scale (GOS) (20, 153).

For **study III,** after inclusion, acute and socioeconomic data were obtained from medical records. Additional background socioeconomic data and medical history were collected via interview of relatives (if the patient remained unable to communicate) as soon as possible after inclusion. The participants were considered to have a co-existing medical problem at the time of injury if any of the following were present: hypertension, diabetes mellitus, cardiac disorder, psychiatric disorder, renal failure, chronic obstructive airways disease, other significant medical problem, as judged by a rehabilitation physician.

The participants underwent prospective clinical assessments, at three time points, three weeks (18-24 days), three months (75-105 days) and one year (350-420) days after injury. Assessments took place in the patient's current care setting where possible, which in some cases was in the patient's home, or in a local outpatient department. Baseline and follow-up was therefore designed to be independent of any decisions regarding care-pathways and of any decision regarding admission to inpatient rehabilitation. Rehabilitation physicians performed assessments with assistance from rehabilitation nurses, psychologists, physiotherapists and occupational therapists.

The presence or absence of medical complications was recorded at each study time point.

Those complications present three weeks after injury were considered in relation to both possible delays in transfer to rehabilitation, and to outcome. The following possible complications were recorded: infection meningitis, sepsis, wound infection, urinary tract infection, pneumonia, other stated infection, hydrocephalus, deep vein thrombosis, pulmonary embolism, heterotopic ossification, new fracture or new brain injury since the incident injury, other complication, defined by a rehabilitation physician. The presence of a tracheostomy, on-going artificial ventilation, or administration of oxygen at these time points were considered surrogates for respiratory complications in terms of difficulties in weaning from ventilation and/or persisting respiratory difficulties, and were therefore also coded as representing complications.

Predictors of outcome

In **study I** anterior and posterior pituitary hormonal testing was performed. All participants arrived in the morning after fasting since 12 am. Fasting blood samples were obtained between 8-9 am for tests of anterior pituitary function, including free thyroxine (f-T4), thyroid stimulating hormone, cortisol, adrenocorticotrophic hormone, testosterone (males), estrogen (females), sexual hormone binding globulin, luteinizing hormone, follicle-stimulating hormone, prolactin, insulin-like growth factor-1 and GH in connection to an arginine-growth hormone-releasing hormone (arginine-GHRH) stimulation test. Urine osmolality and history of increased thirst and/or increased urine volumes were obtained in all participants and a history of the menstrual status in all females.

In order to provide a valid comparison of the injury characteristics as outcome predictors versus hormonal status, the CRASH acute prognostic model was used as previously described.

In **study ll,** data on sick leave and unemployment were gathered from the Swedish social insurance agency (Swedish: Försäkringskassan, FK), which keeps records of all economic compensations to individuals funded by the state. FK is the authority that administers the various types of insurance and benefits, which make up social insurance in Sweden. The Swedish social security system is a tax-based system that covers everyone who lives or works in Sweden (154-156). It provides financial security for families and children, for disabled persons and in connection with illness, work injury and old age (http://www.forsakringskassan.se).

For participants categorized as being on sick leave/unemployed at the day of the TBI, data on sick leave and unemployment over a 1-year period before the TBI were gathered. Included in the term ‘‘sick leave’’ were full-time and part-time daily sickness allowances and disability pensions. Included in the term “unemployment” were full-time and part-time unemployment benefits and welfare benefits.

In **study III,** data on care pathways were updated at follow-up, at three time points, three weeks (18-24 days), three months (75-105 days) and one year (350-420) days after injury, in order to gather complete care-pathway data during the first year after injury, as far as possible.

Outcome measures

In **study I and II,** the primary outcome measures were assessment of functioning, disability, and HRQL.

A specifically designed patient-reported questionnaire

Body functions, activities, and some aspects of participation (work, studies and hobbies) were assessed with a patient-reported questionnaire specifically designed for these studies (appendix), using the framework of the ICF (56). The questionnaire consists of 50 "yes-no" questions, 38 questions about physical and psychological functions, and 12 questions about personal and instrumental activities of daily living. The questionnaire also gathers socio-demographic information, including household, work, and studies, and the need for support (personal, economical, or technical), and information on co-morbidities (cardiovascular disease, diabetes mellitus, epilepsy, cancer, gastrointestinal disease, kidney disease, rheumatic disease, respiratory disease, endocrine disease, and significant injury other than TBI), medications, smoking, alcohol consumption, and drug abuse.

The Short Form-36 Health Survey (SF-36)

HRQL was assessed with SF-36, a widely used health outcome measure, validated for the TBI population (157-160). The 36 questions are designed to measure patient-reported health-related functioning and well-being along eight subscales, each graded 0–100 (worst to best). Despite the ordinal nature of the SF-36, it has been recommended that the subscales of the SF-36 be aggregated into summary scores that represent the two main dimensions of health: the physical component summary and the mental component summary, calculated as weighted sums of the subscales scores, with a mean reference score being 50 points and lower scores indicating worse HRQL than the reference population (157-160). A 5-point difference is considered to reflect a minimal clinically important difference (161, 162).

Glasgow Outcome Scale–Extended (GOSE)

Global outcome of TBI was assessed with the eight-point GOSE, in which information from the specifically designed questionnaire was interpreted together with the physical examination and medical history, obtained by physician according to the study protocol (163). The GOS was constructed to present the "degree of neurological deficits and day-to-day living abilities" after severe brain damage (153). It is an ordinal scale and has been used widely all over the world (164). The GOSE is a further developed version of the GOS, where the upper three criteria are subdivided, and extends the original 5 GOS categories to 8. The categories are: 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, and 8=Upper Good Recovery. The GOS and the GOSE cover the components of body functions, activity and aspects of participation, as classified by the ICF. The GOSE has good inter-rater reliability (165) and validity (166), and is an established measure of global outcome after TBI.

In **study III,** the primary outcome at one year was measured using the GOSE. A standardised interview was used (165). The GOSE findings were dichotomised into "good" and "bad" outcome. This division was made in accordance with the definition of "good" and "bad" outcome used in the CRASH study (20). GOSE 2-4 was considered a "bad" outcome, and GOSE 5-8 a "good" outcome.

In **study IV,** survival outcome and cause of death for the head injury group and the controls were ascertained 10 years after the injury from the Swedish National Board of Health and Welfare (Swedish: Socialstyrelsen, SoS) register.

Statistical analysis

For **studies I and II,** all statistical analyses were performed with PASW (Chicago, IL) version 18.0. Functioning, disability, and health were compared between the groups in study I who were or were not deficient in one or more hormonal axes, and in study II between groups who were or were not unemployed or on sick leave before injury. Fisher's exact test and independent-samples *t* test were used to compare the groups. Data from the specifically designed questionnaire on functional impairment and activity limitation were analysed by factor analysis. Principal components analysis with Varimax rotation based on the correlation matrix was used to make informed decisions on reducing the number of variables while retaining as many variables as needed to describe performance and dependency. Principal components analysis gives the number of variables (components) needed to capture most of the variance in the original data set. The determination of the specific variables to be extracted was both a statistical and a qualitative decision of the first author. The correlation matrix was used to determine which variables clustered together in a meaningful way and may measure aspects of the same underlying dimension (factor). Components were extracted according to Kaiser's criterion; thus, variables with loading values ≥ 0.6 were included from the rotated component matrix, and clustered into the following four domains, measuring different outcomes:

1. Physical function. Included components: arm function, leg function, swallowing, talking, sensory functions and headache.
2. Psychological function. Included components: depression, anxiety, sleep, concentration and sexual drive.
3. Routine activities of daily living (ADL) Included components: walk, climb stairs, get dressed, manage personal hygiene, manage elimination needs, read, and maintain a home.
4. Leisure and community activities. Included components; drive, manage transportation, engage in hobbies, watch a movie and manage household economy.

Multivariate analyses were performed to determine whether hormonal status and a history of sick leave/unemployment before TBI independently predicted outcome; multiple regression was used to control for the outcome predictors of injury severity, age, gender, substance abuse and co-morbidity. The independent variables controlled for were not highly intercorrelated (Tolerance > 0.6, Variance inflation factor < 1.5).

For **study III,** non-parametric methods were used, as data were not normally distributed. Statistical analysis was performed with SPSS version 20. Summary statistics (median, range) were obtained and correlations with outcome were analysed (Spearman's rho). To assess the

possible respective impacts of injury severity according to CRASH, duration of intensive care, the presence of complications at the 3-week assessment, and length of time between intensive care and rehabilitation admission, a logistic regression model was developed, with stepwise introduction of the variables. Correlation matrices were inspected in order to evaluate possible multicolinearity, which was not found to any important degree (highest correlation of 0.26 between length of stay in intensive care (LOSIC) and time between intensive care and admission to rehabilitation).

In **study IV**, a hazard function was used to describe the momentary risk of death and give the number of deaths per time unit, as in terms of predictors of post- acute mortality, age at time of injury and time since injury have been shown to be important (78, 80, 83, 167). The hazard function was allowed to depend on the current (updated) age, sex and group (control or case). Furthermore, the function was allowed to change by time since start of follow-up for the cases. The impact of sex was allowed to be different for the two groups. To achieve a continuous and smooth curve some spline functions of time since start of follow-up were used. The hazard function is exp (S $b_i \cdot x_i$), where the betas are constants and x_1, x_2, … are equal to 1 (constant) or the value of the corresponding variable. The distribution of the causes of deaths in cases and controls was compared by chi-square tests.

Ethical considerations

In studies I, II, and III, the patient gave informed consent in cases where he/she had capacity. When the patient lacked capacity the patient's nearest relative gave consent to inclusion. None of the assessments were potentially harmful to the participants. No adverse advents occurred during any of the tests. Studies I, II and IV were approved by the regional ethical review board of Västra Götaland (case nr 634-09, nr 330-02, and nr 089-13), and study III approved by the regional ethical review board of Stockholm (case nr 2009/1644 – 31/3).

RESULTS

Study I

Participants' characteristics

Age, gender, injury severity and body mass index (BMI) of the participants at injury are presented in table 1. There were no statistical differences between participants with or without PTHP in this regard (paper I; table 1). However, a subgroup analysis showed that the participants with GHD were older at the time of injury (table 1). The participants with GHD were more often overweight than those without GHD (table1). No statistical differences were found in the injury severity (according to CRASH) (table 1), or in the causes of TBI between the groups. The most common causes of TBI were traffic accidents (53%), falls (29%), and assault (12%).

Table 1. Demographic data, injury characteristics and the BMI of the participants at the time of the injury. The participants are categorized as GHD or not, at follow up.

	All particip (n=51)	GHD (n=11)	No GHD (n=40)	95% CI / p value[a]
Age (years)	37.9 (16-64)	52.3 (34-63)	34.0 (16-64)	8.5 - 28.0 [b]
Gender	13 F/38 M	1 F/10 M	12 F/28 M	p = 0.25
BMI (n=40)	24.0 (18-29)	25.8 (23-28)	23.5 (18-29)	0.7 – 4.0 [b]
BMI >25	16/40 (40%)	7/9 (78%)	9/31 (29%)	p = 0.02 [b]
Risk of unfav outcome [c]	63.1%	74.0%	60.0%	-29.5 – 2.3

Data are given as mean (range) or absolute number (%). BMI, body mass index; GHD, growth hormone deficiency; M, male; F, female;
[a] 95% confidence interval of the difference between the groups / p-value.
[b] A significant difference between the groups.
[c] According to the "CRASH prognostic model" (see text). Unfavourable outcome refers to dead, vegetative state and severe disability according to GOS.

Hormone deficiency

A pituitary insufficiency was diagnosed in 14 (27.5%), in one third of the men, but in just one of 13 women (fig. 5). All the participants with PTHP had isolated deficiencies; 11 (21.6%) had GHD, 2 men (3.9%) had gonadotrophic deficiency, and 1 man (2%) had a thyrotrophic deficiency.

Functioning and quality of life at the time of follow-up

The study participants reported lasting disability with a complex range of physical, cognitive, behavioral and emotional disturbance at follow up (table 2).

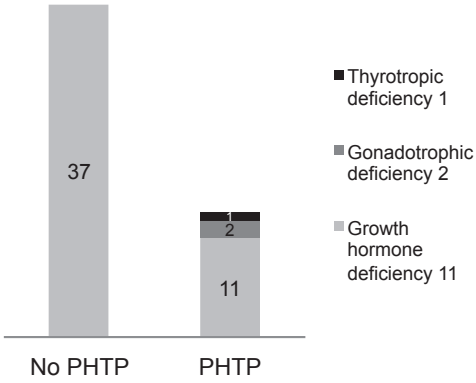

Figure 5. Number of participants with posttraumatic hypopituitarism (PTHP), and the pattern of different pituitary hormone deficiency, 2-11 years after injury.

Thirteen participants (26%) had an unfavorable outcome (GOSE ≤ 4) needing personal support to manage ADL. The mean physical health score for the participants reporting HRQL measured by SF-36 was 45.4 points (range=17-61; 95% CI=42.3-48.4) and the mean mental health score was 42.8 points (range=8-63; 95% CI=38.9-46.7). The mean scores of all the SF-36 subscales are shown in paper I, table 2. Twenty-one participants (41%) were working/studying, and 10 (20%) were working/studying full time.

Participants with or without PTHP showed no statistically significant differences in HRQL scores, or in the number with unfavorable outcome. Further, the two groups showed no statistically significant differences in perceived problems with cognitive, emotional, or physical functions, dependence in activities, and participation in work/studies.

The participants with PTHP and within that group, individuals with GHD, were more often overweight at the time of follow-up (82% vs. 33%; p=0.01). The groups did not differ in weight gain after the trauma.

When multivariate analyses were performed controlling for other outcome predictors, PTHP partly explained a higher BMI, although the fraction of variance explained was small (R^2 change = 0.07, p = 0.001) (paper I; table 3).

Interestingly, PTHP and GHD also partly explained a better global outcome measured by GOSE even though the fraction of variance explained was small (paper I; table 3).

TBI participants suffering from PTHP and especially those with GHD more often had cardiovascular disease or diabetes mellitus (55% vs. 13%; p=0.01). No association was found between PTHP and smoking, alcoholism, drug abuse, epilepsy, or use of antiepileptic drugs.

Table 2. The participants' symptoms, signs and diseases at follow up, 2-11 years after injury.

Psychological functions [a]	Participants n=51	Physical functions [a]	Participants n=51
Fatigue	42 (82%)	Weight gain	21 (41%)
Concentration problem	37 (73%)	Arm motor impairment	19 (37%)
Memory problem	36 (70%)	Leg motor impairment	18 (35%)
Depression	25 (49%)	Chronic pain	18 (35%)
Irritability	23 (45%)	Hearing impairment	18 (35%)
Communication problem	23 (45%)	Visual impairment	17 (33%)
Sleep disturbances	19 (37%)	Impaired touch sense	17 (33%)
Impotence (men, n=38)	14 (37%)	Problem talking (n=50)	17 (33%)
Reduced libido (n=50)	18 (35%)	Dizziness	15 (29%)
Anxiety	17 (33%)	Impaired smell sense	14 (28%)
Smoking addiction	16 (31%)	Diabetes/cardiovascular disease	11 (22%)
Alcohol/drug abuse	14 (28%)	Epilepsy	10 (20%)
		Problem swallowing	6 (11%)
		Irregular menses (n=12)	1 (8%)

Data are given as absolute number (%).
[a] According to the questionnaire specifically designed for the study.

Study II

Participants' characteristics

The age and gender of the 51 participants in the study are presented in table 1.

Nineteen participants (37%) were either on sick leave (10 participants) or unemployed (9 participants) before the trauma. Comparisons were made between the groups who were or were not on sick leave/unemployed before injury. The participants on sick leave/ unemployed were further divided into three subgroups; I) on sick leave/unemployed ≥ 12 months, II) on sick leave, III) unemployed), and each subgroup compared to all the other participants. No statistical differences were found in age, gender, or injury severity between participants who were on sick leave/ unemployed before the injury and those who were not (paper II; table 1). A history of alcohol and drug abuse was significantly more common in individuals who were unemployed at the time of injury (56% vs. 17%; p=0.03). Assault was a cause of injury in one third of the unemployed participants; however, the difference was not significant between the groups (p=0.06).

Functioning and quality of life at the time of follow-up

The study participants reported lasting disability with a complex range of physical, cognitive, behavioral and emotional disturbance at follow up (table 2). Thirteen participants (26%) had an unfavorable outcome (GOSE ≤ 4) needing personal support to manage ADL. The mean

Table 3. Effects of sick leave/unemployment before injury on outcome adjusted for age, gender, injury severity, co-morbidity [a], and substance abuse, 2-11 years after injury.

	Explanatory variables at the time of injury							
	Sick leave/unemployment (n=19)				Sick leave/unemployment ≥ 12 months (n=10)			
	Unstandardized coefficients		p-value	Fraction of variance explained (R^2 change)	Unstandardized coefficients		p-value	Fraction of variance explained (R^2 change)
Outcome	B	SE			B	SE		
GOSE [b]	–0.7	0.4	0.08	0.046	–1.3	0.5	0.01	0.089
Routine-ADL [c]	1.4	0.7	0.04	0.077	1.9	0.9	0.04	0.083
SF-36 physical function [d]	–20.7	8.3	0.02	0.101	–23.9	10.9	0.03	0.080

[a] Including cardiovascular disease, diabetes mellitus, epilepsy, cancer, gastrointestinal disease, kidney disease, rheumatic disease, respiratory disease, endocrine disease, and significant injury other than TBI.
[b] Glasgow Outcome Scale–Extended: 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.
[c] Routine activities of daily living, assessed with a questionnaire specifically designed for the study. Higher scores denote more impairment or limitation. Scores 0–7.
[d] Short Form Health Survey-36. Lower scores indicate a worse health-related quality of life. Scores 0–100.

physical health score for the participants reporting HRQL measured by SF-36 was 45.4 points (range=17-61; 95% CI=42.3-48.4) and the mean mental health score was 42.8 points (range=8-63; 95% CI=38.9-46.7). The mean scores of all the SF-36 subscales are shown in paper I, table 2. Twenty-one participants (41%) were working/studying, and 10 (20%) were working/studying full time.

In a multivariate analysis, a history of sick leave/unemployment seemed to predict a worse outcome, measured as perceived problems with routine activities of daily living and as decreased HRQL measured with the SF-36 subscale for physical functioning (table 3). Being unemployed or on sick leave for 12 months or more before TBI seemed to predict a worse global outcome, measured with the GOSE (table 3). However, a history of sick leave/ unemployment did not seem to influence the outcome measures of leisure and community activities physical function or psychological function.

When outcomes were analyzed separately in patients who were unemployed and those who were on sick leave before TBI, only unemployment seemed to predict a worse global outcome ($p = 0.01$; R^2 change = 0.089). Participants who were unemployed and/or on sick leave before the injury reported less participation in work at follow-up (79% vs. 47%; p=0.04). These individuals also more often reported depression at follow-up (68% vs. 38%; p=0.04). A history of alcohol and drug abuse at follow-up was more common in participants with a history of unemployment before TBI (78% vs. 16%; p=0.01). Participants who had a history of alcohol and drug abuse before TBI reported decreased HRQL at follow-up, on the SF-36 subscale for physical functioning (60.2; 95% CI = 0.9–38.7). Participants with a history of unemployment before the injury more often lived alone at follow-up (p=0.03).

Study III

Participants' characteristics

Demographic details and summary statistics on severity of injury are given in table 4.

Care pathways

Median LOSIC during the acute period (i.e. until the first discharge from intensive care) was 17 days (table 4). 97 patients were transferred to an inpatient brain injury rehabilitation unit at some point during the first year after injury. Of these, 81 were alive and followed up at one year, two died having received some inpatient rehabilitation but before follow up at one year, 13 had withdrawn from the study and data were missing for one. Another 5 patients died without having been transferred to a rehabilitation unit. Eight surviving patients (7%) were not transferred to an inpatient brain injury rehabilitation service: one participated in early out-patient rehabilitation, two received non-specialist rehabilitation in a nursing home or a geriatric unit, one received rehabilitation interventions within a neurology service, and 4 (3,5%) did not receive rehabilitation. One further patient declined transfer to a rehabilitation unit and care pathway data was missing for 3 (3%) patients. The four patients who did not receive rehabilitation were slightly older (median 43 years, range 24-59) than those receiving rehabilitation (median 38,5 years, range 17-64), difference not significant (Mann-Whitney p=0,55) and had slightly more severe injuries as assessed by the CRASH, with a risk of a bad outcome based on acute prognostic variables being a median of 84.5% for those not receiving

Table 4. Demographic data and injury characteristics of the participants in study III.

Median age at injury	42 years	(range 17-65)
Median worst un-sedated GCS* first 24 hours	5	(range 3-8)
Cause of injury	Transport accident, n=46 (41%)	
	Fall, n=50 (44%)	
	Other, n=13 (11%)	
	Missing data, n=5, (4%)	
Median Length of stay – intensive care	17 days	(range 1-78)
Median duration of ventilation	12 days (range 0-101) *(range 0-36, with one outlier at 101 days)*	
Economic support at time of injury	Employed/self-employed full time, n=57 (50%)	
	Study grant, n=7 (6%)	
	Unemployment benefit or social support, n=11 (10%)	
	Sick pay, n=16 (14%)	
	Other**, n=8 (7%)	
	Part time employment/self-employment, n=6 (5%)	
	Unknown, n=3 (3%)	
	Missing data, n=6 (5%)	
Previous brain injury requiring hospitalisation	n=18 (16%)	
Known drug or alcohol misuse at injury	n= 34 (28%)	
Gender	men n=75, women n=26, missing data n=13	

*Or derived GCS using conversion from Reaction Level Scale Score (RLS, table I) for patients exclusively assessed with the RLS (n=42).
** "Other" includes parental pay, pension, other economic support, and combinations of other categories.

rehabilitation (range 76-95%) and a median of 72.5% (range 23-98% for those receiving rehabilitation (not significant, Mann-Whitney p=0.14). However length of intensive care was shorter for those not receiving rehabilitation (median 6 days, range 5-17) compared to those receiving rehabilitation (median 17 days, range 1-78). Further analysis was not appropriate or possible given the small group size.

For the 97 patients admitted to inpatient brain injury rehabilitation units during the first year after injury, median time from injury to first admission to inpatient rehabilitation was 28 days (range 9-198). Median time from first discharge from intensive care to admission to inpatient rehabilitation was 13 days (range 0-176), with a substantial proportion of patients waiting several weeks.

The relationship between acute injury severity and time between intensive care and the inpatient rehabilitation is shown in paper III figure II, and was only weakly correlated. The cohort experienced a variety of care pathways. Considering those patients who were eventually transferred to inpatient rehabilitation (n=97), the most common care pathway was from intensive care to a neurosurgical ward to a rehabilitation unit (n=25). Nearly as many patients were transferred directly to a rehabilitation unit from intensive care (n=23), and a similar number from intensive care to a surgical ward to a rehabilitation unit (n=20). The remaining 29 patients (30% of those eventually transferred to rehabilitation) had a wide variety of different care pathways, receiving care on between one and five different intervening care units after intensive care discharge and before eventual transfer to a rehabilitation unit. During the period between discharge from intensive care and admission to rehabilitation, patients received care in a median of one other care unit (range 1-5).

Outcomes

Of the 89 participants alive and followed up one year after injury (including those who did not receive inpatient rehabilitation), 36 (40%) had a bad outcome (Glasgow Outcome Scale Extended [GOSE] 2,3 or 4), 50 (56%) had a good outcome (GOSE 5,6,7 or 8) and data on GOSE were missing for three (4%). Predictions from the CRASH acute prognostic model correlated only poorly with actual outcome at one year (Spearman's rho correlation coefficient -0.12*)*. However both LOSIC (correlation coefficient -0.52) and length of time between intensive care and admission to rehabilitation (correlation coefficient -0.33) showed somewhat stronger correlations with outcome. The number of intervening care units between intensive care and rehabilitation was however not significantly related to outcome at one year. Of the 81 participants who were alive, followed-up to one year, and received some inpatient rehabilitation, 60 had one or more sub-acute complication, 19 did not, and data was missing for 2 participants. GOSE data were available for 76 of these participants. 17/18 without complications and 26/58 with complications had a good outcome (Fisher's exact test, $p<0.001$).

The results of logistic regression analyses show odds ratios and confidence intervals for adjusted and unadjusted values of these factors on outcome (dichotomised GOSE) at one year (table 5).

In summary, the logistic regression model demonstrated that LOSIC, length of time between intensive care and rehabilitation admission and the presence of post-acute complications contributed significantly to the variation in outcome, and together explained 54% of the variation in the model. Further, a Mann-Whitney test found that time between intensive care and rehabilitation admission was not significantly different for participants with and without complications at 3 weeks ($p=0.11$).

Data on co-existing medical problems at the time of injury were available for 85/89 participants alive and followed up at one year. 39 participants had no co-existing medical problems, (21 with a good outcome,18 a bad outcome). 46 participants had co-existing medical problems, (28 good outcome,18 bad outcome), difference between groups not significant, $p=0.4$ chi-squared. The variable was therefore not included in the logistic regression model.

Table 5. Stepwise logistic regression analysis with odds ratio for good outcome one year after injury (GOSE >4).

	Unadjusted					Adjusted				
	n (missing)	Odds Ratio	95% CI	p-value	Variation explained**	n (missing)	Odds Ratio	95% CI	p-value	Variation explained**
Acute injury severity* (% risk of unfavorable outcome)	75 (6)	0.98	0.95 - 1.01	0.16	3.5%	Excluded from model as not significant				
Pre-existing medical conditions	77 (4)	0.79	0.32 – 1.94	0.60	0.5%					
Length of stay, intensive care (days)	77 (4)	0.89	0.83 – 0.96	0.001	28%	73 (8)	0.92	0.86 – 0.98	0.015	54%
Time between discharge from intensive care and admission to inpatient rehabilitation (days)	77 (4)	0.96	0.93 – 0.99	0.004	24%		0.94	0.91 – 0.98	0.006	
Complications at 3 weeks (yes/no)	76 (5)	0,05	0,006 – 0,38	0,004	26%		0.11	0.01 – 0.98	0,048	

Analysis of surviving patients followed up to one year who received inpatient rehabilitation (n=81).
CI = confidence interval.
*Evaluated using the ”CRASH model” (see text).
**Variation explained = Amount of variation explained by the model. (Model summary, Nagelkerke R square.

Length of stay – Inpatient rehabilitation

Length of inpatient rehabilitation stay (LORS) was significantly inversely related to outcome, a bad outcome being associated with a longer LORS (Mann-Whitney test p=0.001). Median LORS was 34 days (range 3 -127) for participants with a good outcome and 64 days (range 2 – 315) for participants with a bad outcome. This variable was not incorporated into the regression model due to the high likelihood of confounding: within a healthcare system where there are no formal restrictions on length of stay, patients with persistent severe deficits leading eventually to worse outcome are likely to be the subject of more prolonged attempts at rehabilitation.

Study IV

Participants' characteristics

The median age among the 166 participants with severe TBI, by the time of admission to NICU, Sahlgrenska was 45.1 years, and 25.9% were women. The median age among the controls was 45.5 years, and 26.0% were women (table 6).

Table 6. Age at the start of follow-up (admission to NICU).

Group	n	Age (years)		
		Median	Range	Mean ± SD
Cases				
Male	123	45.1	6.5–81.3	43.3 ± 20.4
Female	43	46.7	6.6–81.9	43.3 ± 21.5
Controls				
Male	599	45.1	6.5–81.3	43.3 ± 20.5
Female	210	46.7	6.6–81.9	43.7 ± 20.9

10 year all cause mortality pattern

In the severe TBI injury group 56/166 (33.7%) people had died within 10 years of injury. The proportion of deaths was higher in the severe TBI than in the community control group (80/809; 9.9%). This remained the case beyond the early period in year one where mortality was particularly high.

Death hazard function was estimated by Poisson regression analysis (paper IV, appendix). By use of the estimated hazard function and the general relationship between hazard and survival function the probability of death was calculated for a follow-up period of 1 year, 5 years and 10 years (table 7 and 8).

Table 7. Probability of death in men at 1, 5, and 10 years of follow-up

Age at start of follow-up (years)	1 year		5 years		10 years	
	Cases	Controls	Cases	Controls	Cases	Controls
20	0.024	0.001	0.037	0.005	0.057	0.012
40	0.066	0.003	0.101	0.015	0.153	0.033
60	0.175	0.008	0.273	0.047	0.437	0.122
80	0.807	0.064	0.935	0.336	0.993	0.670

Table 8. Probability of death in women at 1, 5, and 10 years of follow-up

Age at start of follow up (years)	1 year		5 years		10 years	
	Cases	Controls	Cases	Controls	Cases	Controls
20	0.022	0.001	0.035	0.003	0.054	0.007
40	0.061	0.002	0.094	0.009	0.143	0.019
60	0.164	0.004	0.257	0.027	0.414	0.073
80	0.784	0.038	0.921	0.212	0.990	0.475

The excess mortality was very large in the severe TBI group in the beginning of the follow-up, increasing with a higher age (figure 6). The excess mortality for the severe TBI group remains several years after the start of follow-up (figure 7). The estimated difference between the sexes is more pronounced for the controls than for the severe TBI group (figure 7).

The hazard of death was much higher in the severe TBI group compared to the controls over a 10-year period, and it was higher for the head injured women than the men, when compared to the controls (table 9). The hazard of death was extremely high in the severe TBI group in the first weeks from the start of follow-up, and although gradually decreasing thereafter, it was still 3 - 5 times higher than for the controls at the end of the first year. The hazard of death then increased gradually among the one-year severe TBI survivors and was 5 - 8 times higher at 10 years from the start of follow-up, compared to the controls (table 9).

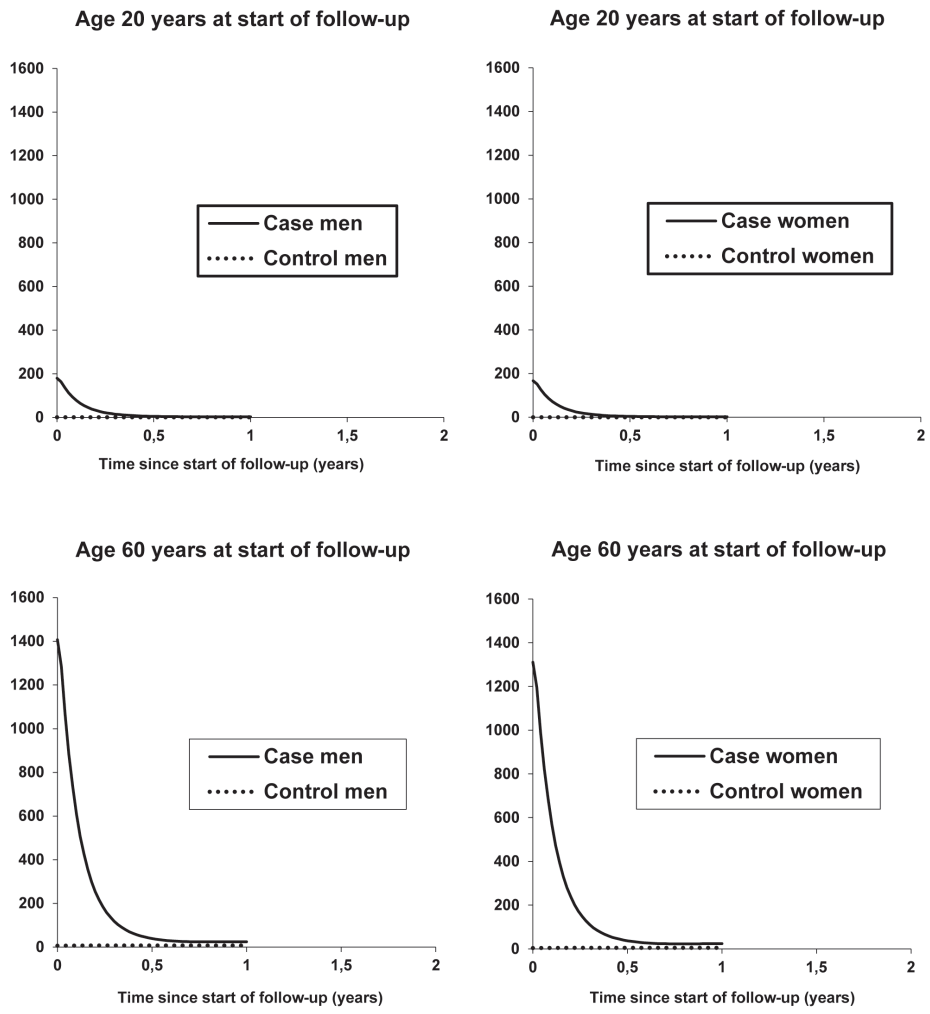

Figure 6. Incidence of death per 1000 person years from admission to NICU to 1 year of follow-up.

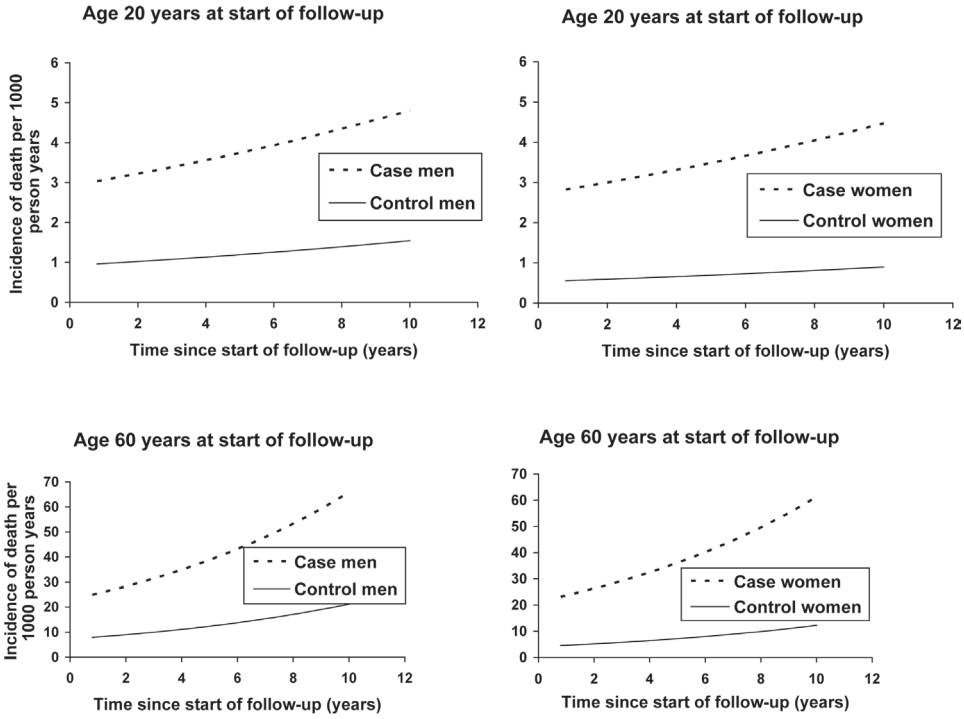

Figure 7. Incidence of death from 1–10 years of follow-up

Table 9. The hazard ratio, cases versus controls, and 95% CI at different times over 10 years of follow-up

Years of follow-up	Men		Women	
	HR	95% CI	HR	95% CI
0.00	211.65	109.13–410.51	339.07	136.05–845.09
0.20	34.79	15.45–78.37	55.74	19.75–157.34
0.40	8.57	4.53–16.21	13.73	5.54–34.04
0.60	3.90	1.85–8.23	6.25	2.33–16.76
0.80	3.29	1.50–7.24	5.27	1.91–14.59
1.00	3.32	1.54–7.15	5.33	1.96–14.49
1.20	3.36	1.59–7.08	5.38	2.01–14.39
2.00	3.49	1.79–6.81	5.60	2.22–14.09
5.00	4.06	2.47–6.67	6.50	2.93–14.44
10.00	5.21	2.27–11.93	8.35	3.00–23.23

HR, hazard ratio; CI, confidence interval

Mortality patterns for specific causes of death

In the severe TBI group, the death rate from external causes was particularly high early after injury (table 10). The distribution of the causes of deaths differed between the severe TBI group and the controls in the 10 years (baseline to 10 years: chi-square: = 25.31, 6 degrees of freedom, p=0.0003; baseline to 1 year: chi-square=14.25, 4 degrees of freedom, p=0.0065). However, the causes of death did not differ between the 1-year survivors and controls (1–10 years: chi-square=3.94, 6 degrees of freedom, p=0.6850).

The six primary causes of death in Sweden accounted for 88– 97% of deaths in each group (table 10) (168). Other primary causes of death were registered in 4 cases (epilepsy, hepatitis, anoxic brain injury, renal failure) and 6 controls (diabetes (4), dementia, unclear).

Table 10. Frequency of the most common primary causes of death in the severe TBI group and controls

Cause of death	Controls (n=80)			Cases (n=56)		
	0–10 years	0–1 year	1–10 years	0–10 years	0–1 year	1–10 years
Circulatory	27 (34%)	3 (43%)	24 (33%)	11 (20%)	4 (13%)	7 (28%)
Neoplasms	27 (34%)	3 (43%)	24 (33%)	5 (9%)	1 (3%)	4 (16%)
Respiratory	9 (11%)	1 (14%)	8 (11%)	6 (11%)	1 (3%)	5 (20%)
Digestive	3 (3%)	-	3 (4%)	2 (3%)	-	2 (8%)
Mental	3 (4%)	-	3 (4%)	-	-	-
External	5 (6%)		5 (7%)	28 (50%)	24 (78%)	4 (16%)
Fall	1	-	1	10	9	1
Traffic	-	-	-	7	6	1
Iatrogenic	1	-	1	2	-	2
Unclear	-	-	-	4	3	1
Violence	-	-	-	4	4	-
Suicide	3	-	3	1	1	-
Other	6 (8%)	-	6 (8%)	4 (7%)	1 (3%)	3 (12%)
All causes	80	7	73	56	31	25

0 = baseline

DISCUSSION

Main findings

This thesis describes long-term global outcome in individuals with severe TBI who received acute care at a modern NICU in Sweden and in Iceland. The participants reported low HRQL and lasting disability, with a high rate of symptom reporting and a complex range of physical, cognitive, behavioral and emotional disturbance many years after the injury.

The results indicate that individuals with severe TBI, compared to community controls have increased risk of death from a variety of causes for at least 10 years after the head injury. The distribution of the causes of deaths was shown to differ between the severe TBI group and the controls in the first year from the start to follow-up, but not between the one-year survivors and the controls.

Further, the studies found evidence that pre-morbid labor force participation influences long-term functioning and HRQL in these patients, and that a delay between discharge from intensive care and admission to a rehabilitation unit impacts negatively on global outcome one year after severe TBI. The findings revealed that patients with PTHP were more often overweight at follow-up; the higher body mass index was partially explained by PTHP, especially GH-deficiency. Otherwise, the findings did not support the hypothesis that PTHP causes disability and decreased quality of life in individuals with severe TBI.

Comparison with other studies

The pattern of symptom reporting in the severe TBI participants is quite consistent with other studies, a fact that strengthens our findings (62, 65, 169-171). A newly published Australian longitudinal follow-up study of functional outcome over 10 years in a sample across the spectrum of moderate to severe TBI, highlighted a number of the key problems associated with severe TBI that continue to be prominent over 10 years after the injury (62). The study showed a very similar rate of participants working (40%) and participants independent in domestic activities (65%) as reported in this thesis. As in our sample, cognitive and emotional problems were more common than physical problems, particularly in the domains of memory, attention and cognitive fatigue. Similarly, irritability was a common and persistent problem as well as word-findings difficulties. As in our sample, almost half the patients felt anxious and/or depressed, a frequency consistent with rates of anxiety and depression reported over the long-term on the basis of symptom rating scales or diagnostic interviews in other studies (67-70).

The severe TBI group showed significantly lower HRQL for SF-36 physical and mental composite scores compared to the general Swedish population that has a mean reference of 50 points for the component summary scores (95% CI=49.8-50.2) (159). The HRQL was lower for all SF-36 domains compared with the general population of Sweden, except for bodily pain where no statistical difference was found (159). The HRQL reported in this thesis is similar to newly published Norwegian prospective studies, and an American SF-36 validation study, further strengthening our findings (172-174).

Study I

About one forth of the participants in study I had PTHP, most commonly deficiencies of GH and gonadotrophins, which is in accordance with the prevalence published in previous studies (105, 118).

The findings did not support the hypothesis that PTHP causes disability and decreased quality of life in individuals with severe TBI. There are discrepancies in the limited data on PTHP and outcome. Several studies have described worse outcomes in patients with PTHP (120, 122-128, 130, 131), but these findings were not confirmed in others (119, 121, 129). Although associations are interesting, they do not prove causality and there may well be common risk factors for both PTHP and disability.

Few studies used a similar approach to ours, examining the relative contribution of the injury severity and PTHP to outcome. One of them, relating neuropsychological complaints to pituitary function and to CT-scan findings at the time of injury, showed no significant difference in neuropsychological complaints and HRQL between patients with PTHP or not, measured with patient-reported questionnaires (119). The other studies described worse global and functional outcome and HRQL in patients with PTHP compared to those with normal pituitary function (124, 128, 131).

GHD is associated with a reduced HRQL (175-177). However, it is unclear whether pituitary dysfunction influences HRQL in TBI patients. A few studies have reported a worse HRQL in patients with PTHP, with poorer sleep and energy levels and an increased sense of social isolation (120, 125). Both prospective studies and cross-sectional studies have described poorer HRQL in TBI patients with GHD (125, 131) (120, 127). All of these studies evaluated patients up to one year after the injury.

Studies have now related PTHP to cognition and functional outcome in TBI patients tested within 1 year or up to 2 years after injury (123, 130). TBI patients with GHD have been reported to experience greater deficits in attention, executive functioning, memory, and emotion than GH sufficient TBI patients (123, 124, 130).

Hypopituitarism is associated with an unfavorable body composition and lipid profile, features that tend to improve when relevant insufficiencies are treated (178-181). Studies of body composition reported that BMI, total abdominal fat mass, and LDL cholesterol and triglycerides were higher in TBI patients with PTHP (122, 125, 131, 182). Similarly, our findings suggest that pituitary function partially explains a high BMI in patients with severe TBI, even though the fraction of variance explained is small. Furthermore the patients with PTHP in our study were more often overweight at the time of follow-up. Many factors may act as confounders and contribute to these findings, including physical activity, appetite and food intake, medications, and common comorbidities of TBI such as epilepsy, alcoholism, and drug abuse, partly controlled for in the current study. In addition, it has been established that spontaneous and stimulated secretion of GH is lower in obese relative to normal weight individuals, and even though specific BMI-related cut-off limits were assumed in our study, the patients with a high BMI might have a higher risk of a false positive test for PTHP caused by metabolic changes (183-185).

The TBI patients with GHD in our study were older than those with normal GH secretions. This is an interesting finding, which indicates a possible predisposing factor for the

development of GHD after TBI. Discrepancies in published data on the association between age and PTHP suggest that this issue needs to be studied more extensively (125, 131). Hypopituitarism increases the risk of premature death, mainly due to an increased prevalence of cardiovascular disease (115, 117). GHD is the most likely explanation for this finding (186-188). An important finding in our study was that the TBI patients suffering from PTHP and especially those with GHD more often had cardiovascular disease and/or diabetes mellitus. These findings linking PTHP to important health issues that might cause functional impairments and premature death suggest that even though the study did not support its effects on functional outcome and quality of life as measured here, a longer follow-up time would be needed to measure the effects of these health issues.

Study II

The few studies that have addressed the long-term consequences of pre-morbid factors in adults with severe TBI have yielded conflicting results, and meaningful effects of pre-morbid factors have not always been noted (132, 136, 137). Our findings show that being unemployed or on sick leave before the injury predicted worse HRQL and more disabilities, measured as perceived problems with routine activities of daily living. Additionally, being unemployed or on sick leave for 12 months or more before severe TBI predicts a worse long-term global outcome, measured by GOSE. Patients with a history of unemployment or sick leave more often reported depression and less participation in work at follow up. The findings also link a history of unemployment to substance abuse in patients with severe TBI.

In Sweden, sickness allowance and unemployment benefits are central to the welfare of people who are ill or unemployed. In the current studies, 19 participants (37%) were either unemployed or on sick leave before the trauma. By contrast, during the period of the study, only 25% of the general Swedish population age 16–65 years were unemployed or not in the labor force (students included) (189). The finding that being unemployed or on sick leave for 12 months or more before severe TBI predicted a worse global outcome suggests that the longer the duration of sick leave or unemployment before the injury, the more likely it will have a negative effect on the long-term outcome. The study shows a high prevalence of alcohol and drug abuse in the TBI patients, especially among those who where unemployed before the injury, compared to the general Swedish population (190). Previous studies have also reported a high prevalence of substance abuse among individuals who incur TBI, and, as would be expected, generally found poorer outcomes in TBI patients with substance abuse (137).

Study III

Study III found further evidence that a delay between discharge from intensive care and admission to a rehabilitation unit impacts negatively on outcome a year after injury (150). From our data it is not possible to determine whether short periods of a day or two between discharge from intensive care and admission to rehabilitation have a negative effect on outcome. Indeed, establishing that the patient is indeed medically stable enough for transfer to rehabilitation seems a clinically reasonable strategy. However the delays identified in this study were not short, with nearly as many patients waiting longer than a month (n=22) as being transferred direct (n=23). During the period between intensive care and inpatient rehabilitation, nearly a third of patients received care on units that would not be expected to

have specific knowledge of recovery after traumatic brain injury, for example medical, geriatric, and general surgical wards. Some patients even received a short period of care in short stay nursing homes, before the initial rehabilitation stay.

Several pre-morbid and injury related factors may impact on the likelihood of well-timed transfer to rehabilitation, and are possible confounders when considering relationship between delay in rehabilitation and outcome: co-existing medical problems, extracranial injuries and post-acute complications. Our findings did add support for the role of post-acute complications in contributing to poorer outcome. The impact of time to rehabilitation admission on outcome remained however significant even when complications were accounted for, as demonstrated by the logistic regression model. Interestingly, participants with complications did not have a significantly longer time between intensive care discharge and rehabilitation admission.

Experience suggests that bottlenecks at certain stages, specifically delays in discharge from rehabilitation to appropriate social care, hinder and prevent timely transfer of patients to inpatient rehabilitation. These delays may be undocumented and as such hidden, especially within a health care system where length of stay is not directly influenced by external funders: Rehabilitation professionals informally have an understanding that available post-rehabilitation care is in some cases suboptimal, and the length of rehabilitation stay may therefore be extended on a case-to-case basis in an attempt to avoid negative effects from this. For some patients, a degree of continued medical instability (not requiring intensive care but exceeding that which can be safely managed in existing rehabilitation facilities) may be another contributing factor. A willingness to work across organisational boundaries (both within health care services and also between health and social care), and to introduce central standards within fragmented health and social care systems, are also essential in order to be able to counter such delays.

Given the evidence for effectiveness of rehabilitation (44, 191), it is positive that the majority of patients did eventually receive inpatient brain injury rehabilitation. A previous retrospective study of a comparable group of patients with severe TBI receiving care in 2003-2004 at three neurosurgical centres in Sweden, found that 17% were never admitted to rehabilitation (192). It is reassuring that only 7% of the participants in study III did not receive inpatient rehabilitation.

The relationship between longer LOSIC and worse outcome can be understood by considering LOSIC as a proxy for the contribution of post-acute complications and secondary brain injury during the post-acute phase after severe TBI. A recent French study also found LOSIC to be an independent predictor of outcome at one year (193). LOSIC is somewhat susceptible to local variations in policy regarding discharge from intensive care. However pressure on intensive care beds is extremely high in all centres, leading to discharge as soon as the patient is clinically stable.

It was unexpected that the CRASH composite was not significantly related to actual outcome for the participants in study III. Several factors may explain this apparent paradox. Assessment of outcome was at 6 months in the CRASH model but at one year in study III. The CRASH model may therefore be missing changes that have an important long- term impact on individuals functioning (194). Another factor is that CRASH included patients who died in the group with unfavourable outcome, and as study III evaluated the impact of

rehabilitation care pathways it was not meaningful to include patients who died before any rehabilitation was received. Additionally, the CRASH study omitted any consideration of rehabilitation interventions when considering outcome, and it is unknown what proportion of CRASH patients received any rehabilitation. If the proportion was low, then the CRASH findings may not be generalizable to patients who do receive well-timed rehabilitation. Timing of assessment of acute GCS for inclusion in the CRASH model is not specified, other than that an inclusion criteria was GCS 3-14 within the first 8 hours after injury. In study III patients with a lowest unsedated GCS of 3-8 within the first 24 hours were included, i.e. over a somewhat longer time window, which could also lead to discrepancies. The CRASH model has also recently been shown to overestimate rates of unfavourable outcome in patients receiving intracerebral pressure targeted neurosurgical treatment(195) (according to the Lund concept, which is common in Sweden (196)).

The finding that the number of intervening care units between intensive care and inpatient rehabilitation did not impact on outcome was also unexpected. A high number of transfers could however have negative effects for both patients and relatives, due to lack of continuity, even if these could not be detected in terms of outcome.

The association between longer rehabilitation stay and worse outcome was expected. Reverse causality is likely in a health care system where the length of stay is determined by individual clinicians. This may be due to both a real need for a longer period of rehabilitation (due to more severe deficits and slower improvement in patients with more severe injuries), and to the difficulty to arrange another medium to long term discharge placement for these patients, due to persistent deficits and need for supervision, nursing care, and personal care.

Study IV

Our results indicate that individuals with severe TBI, compared to community controls have an increased risk of death from a variety of causes for at least 10 years after the head injury. The results are consistent with a recent prospective 13-year outcome study that similarly used case matched controls, matching by age, gender and postcode area at the time of the injury (83).

The finding that mortality after head injury is high during hospital admission and for up to a year after injury is not surprising and has been observed before (14, 92, 197).

Similar to prior studies, those of older age were found to be at greater risk for death (53, 78, 83). This is also true for the control population; however, probability of death by age provides an important insight. At all ages, individuals with severe TBI were at greater risk of death than the control population, and the relative risk (ratio between probabilities) was at least as high in the younger age group.

Males at all ages had elevated mortality rates compared with females. However, the estimated difference between the sexes was more pronounced for the controls than for the cases and the hazard of death was therefore considerable higher for the head injured women compared to the controls. It may be that the higher hazard ratio in women simply reflects that the severe TBI removes the natural survival advantage that women have over men in the general population. In the literature there is no consensus regarding risk of death after TBI associated with gender (78, 83, 90, 198-201).

The main causes of death after head injury were similar to those found in the general population (168). Others also report high rates of death from respiratory, digestive and circulatory causes (53, 78, 83, 85, 202). The particularly high death rate from external causes is partly due to deaths early after injury, and could also partly be due to drug and alcohol related deaths. Relationships between head injury and deaths from suicide or seizures are not possible to deduce from the present study due to the low frequency of these causes in the study cohort.

Strengths and limitations

All the head injured participants had a severe TBI and received similar acute care in a modern NICU at a university hospital. For this relatively homogenous group of patients we were able to use the validated and generalizable CRASH model. This approach made it possible to adjust for injury severity while estimating the impact of PTHP, pre-injury sick leave/unemployment and care pathways on long-term outcome.

In study IV, exclusions were not made on the basis of age. In this way the cohort selected for follow-up included all but four hospital admissions with severe TBI over a 4-year period. Further, we were able to compare the occurrence of deaths for 10 years after head injury with the death rate expected in the demographic population from which the head injured came from, matched by age and sex.

The studies have a number of limitations. The incidence of severe TBI is low compared to the incidence of the milder forms of TBI and many individuals are lost to follow-up so many years after the trauma, which made it difficult to include a large sample in a geographic area of Västra Götaland, with a small population size. The relatively small sample size, in addition to the fact that the findings in studies I and II are subject to multiple testing, resulted in a poor ratio of subjects to variables and p-values of results with respect to specific symptoms signs and diseases are less reliable. One implication of this is that gender, PTHP and sick leave/unemployment are not totally separable.

Further, since participants in studies I and II were evaluated 2–11 years after the injury, it was not possible to predict whether important determinants of global outcome, premature death, substance abuse, and serious illness that would hinder participation might be more common in individuals with PTHP or a history of sick leave/ unemployment. Research has shown that loss to follow is often high when performing a longitudinal study of individuals with TBI, especially in socially disadvantaged individuals, such as those that are unemployed and with substance abuse (203, 204).

Additional weakness is the unknown psychometric properties of the specifically designed questionnaire.

Although the prospective multicentre design in study III, independent of care pathways, guards against selection bias, some eligible participants may have been missed if they were admitted to and discharged from intensive care between the authors' weekly contacts. This would likely impact primarily on recruitment of less severely injured patients. Completeness of follow up (a total of 84%, 78% alive, 6% dead) is acceptable, especially given the necessity of obtaining consent from relative at study start, due to injury induced lack of capacity.

Clinicians who assessed outcome at one year in study III were not systematically blinded to acute data, which is a source of potential bias and thus a study limitation. This type of study has many inherent logistical difficulties, due to the follow up of patients over a very wide geographical area and over a period of time in order to minimise other sources of bias. Within reasonable study resources it was not possible to arrange blinded follow-up at all locations and at the same time protect completeness of follow up and inter-rater reliability, thus minimizing other possible biases. The time interval between the assessments at 3 months and 1 year can reasonably be expected to go some way to protect against this bias, as the relatively long time would make it unlikely that examiners would remember data from the acute phase at the time of follow up. We acknowledge this limitation.

Matched traumatic non-head injury controls were not used in our studies. The findings could therefore be true of any new major injury or illness and need to be studied more extensively in different group of patients (e.g. non-head injury, stroke, etc.).

Two recently published studies used matched community controls as in study IV to investigate mortality over more than 10 years after TBI, and additionally matched the individuals with TBI with individuals who experienced traumatic non-head injuries (79, 83). Both these studies indicate that the risk of death remained high for the individuals with TBI during the whole follow-up period. However, admission for non-head injury was also associated with a greater late risk of mortality, implying that factors associated with risk of traumatic injury in general or the consequences of the injury are related to longevity and emphasizes the importance of comparison groups in studies of this kind.

Study IV was further limited by the lack of qualitative information in the study groups, whose data were obtained retrospectively, and by reliance on SoS cause of death information solely. The SoS register has had a gradual decline in the autopsy rate for many years, to about 12 % in 2011 (168).

CONCLUSION

This thesis describes long-term global outcome in individuals with severe TBI who received acute care at modern NICUs in Sweden and in Iceland.

- The participants reported lasting disability, and low HRQL, with a complex range of physical, cognitive, behavioral and emotional disturbance 2-11 years after severe TBI.
- A higher body mass index and overweight was partially explained by PTHP, especially GH-deficiency. Otherwise no significant correlation was found between PTHP, functioning and HRQL.
- A history of sick leave or unemployment before injury was found to predict worse global outcome, more problems with activities of daily living and reduced HRQL.
- A delay of discharge from intensive care and admission to a rehabilitation unit was associated with worse global outcome one year after injury.
- The risk of death was increased from a variety of causes for at least 10 years after injury.

These findings highlight the increasingly recognized concept, that TBI is a chronic medical condition (62, 205, 206), which should be considered when refining long-term outcome predictions and optimizing rehabilitation interventions and care pathways for individuals with severe TBI.

FUTURE CONSIDERATIONS

Some further considerations that have emerged during the progress of this work are listed here:

- The results indicate that screening for PTHP might be warranted to specific subgroups such as overweight patients. The fact that most of the individuals with PTHP were overweight suggests that BMI should be monitored more closely, and greater effort should be made to help individuals with TBI to loose weight. GH replacement therapy could be an important supplement to other interventions to reduce weight, e.g. lifestyle changes, a healthier diet, and increased physical training.

- The high prevalence of alcohol and drug abuse, and of a history of unemployment/sick leave, predicting worse global outcome in the participants, further highlights the importance of underlying multifactorial and bio-psychosocial vulnerability in individuals with severe TBI. A challenge for future development of an optimal chain of care for these individuals is to develop smoother bridges between health and social care, e.g. for vocational rehabilitation and intervention for alcohol and drug abuse.

- Well –timed admission to rehabilitation after severe TBI should be considered in itself as evidence based treatment intervention that improves outcome, and strategies to ensure delivery of this intervention should be prioritized, in a similar way to other effective treatment interventions.

- Health-economic studies to study possible additional costs of delay to rehabilitation admission would be of interest, both during the initial period of hospitalization, and in terms of longer-term care requirements.

- Examining patient characteristics by cause of death may shed further light on how, for a number of TBI-associated disorders, prevention, surveillance, and treatment may need to improve. Elsewhere it has been reported that mortality after TBI is related to unemployment and alcoholism (88, 140). Further, it is of high importance to remember that untreated hypopituitarism is related to increased mortality, and although PTHP might not be evident, it could be an indirect cause of death, especially from respiratory and circulatory causes(116, 117).

- Health-economic studies to study costs of reduced life expectancy would be of interest.

- Finally, further research will be required to determine whether systematic rehabilitation programs offer any advantage in terms of lowering the late mortality of survivors of severe TBI.

SAMMANFATTNING PÅ SVENSKA
(SUMMARY IN SWEDISH)

Det kliniska förloppet efter en svår traumatisk hjärnskada (engelska; traumatic brain injury, TBI) varierar mycket och möjligheterna att tidigt förutsäga det långsiktiga förloppet är fortfarande begränsade. Det övergripande syftet med denna avhandling var att belysa betydelsen av hypofyssvikt efter svår traumatisk hjärnskada, av sjukfrånvaro/arbetslöshet innan skada och betydelsen av vårdkedjan för personer med svår TBI, för det långsiktiga utfallet. Vidare var syftet att studera kort- och långtidsöverlevnad hos denna patientgrupp.

Totalt inkluderades 280 personer med svår traumatisk hjärnskada. I studie I och II deltog 51 personer, 16-65 år som ådragit sig svår traumatisk hjärnskada och som behandlats på Sahlgrenska Universitetssjukhuset. Betydelsen av hypofyssvikt och sjukfrånvaro/arbetslöshet för funktions- och aktivitetsförmåga, delaktighet, samt hälsorelaterad livskvalitet granskades. Validerad och generaliserbar prognostisk traumamodell användes i syfte att kontrollera för skadans svårighetsgrad genom att kombinera det prediktiva värdet av akuta datortomografi-fynd samt av några kliniska parametrar. Uppföljning gjordes 2-11 år efter skadan och inkluderade utvärdering av hypofysfunktion, mätning med frågeformulär som framtagits särskilt för denna studie (se bilaga), SF-36 hälsoenkät samt Glasgow Outcome Scale–Extended. Data från Försäkringskassan angående sjukskrivning och arbetslöshet hämtades in. I studie III deltog 114 personer, 18-65 år med svår TBI från 6 neurointensivvårdsavdelningar (NIVA) i Sverige och på Island, med uppföljning ett år efter skadan. Sambandet mellan vårdkedja (tid från NIVA till rehabiliteringsmedicinsk enhet) och det globala utfallet mättes. Skadans svårighetsgrad kontrollerades med prognostisk traumamodell. I studie IV inkluderades 166 personer, 6-82 år som vårdads på Sahlgrenska med svår TBI. Tio-års överlevnad och dödsorsaker hos denna grupp jämfördes med ålders- och könsmatchad kontrollgrupp från samma bostadsområde vid skadan. Data hämtades från Socialstyrelsens dödsorsaksregister.

Resultaten visar att sjukfrånvaro eller arbetslöshet före skadan ger sämre funktions- och aktivitetsförmåga samt sämre hälsorelaterad livskvalitet, flera år efter skadan. Vidare visar fynden att hypofyssvikt efter skadan ger övervikt hos patienterna. Samband fanns mellan länge vård på NIVA samt längre tid innan patienten flyttades från NIVA till rehabiliteringsmedicinsk enhet och sämre utfall globalt ett år efter skadan. Slutligen visar resultaten att svår TBI ökar risken för död av olika orsaker i minst 10 år efter skada.

Följande slutsatser kan dras från avhandlingen:

Personer med svår TBI rapporterade att de har kvarstående problem efter sin hjärnskada, med låg hälsorelaterad livskvalitet och en rad komplexa psykiska och fysiska besvär som kan orsaka sjuklighet och förklara den ökade dödsrisken flera år efter skadan. Resultaten har betydelse för planering av vårdkedjan och resursanvändning i denna, för personer med svår TBI. Fynden ger värdefull information för att kunna utvärdera behandlingseffekter, förfina prognoser och optimera rehabiliteringsinsatser för denna patientgrupp. Resultaten understryker behovet av specifika interventioner för arbetslösa eller sjukskrivna personer som drabbas av svår TBI och att screening för hypofyssvikt är indikerad hos individer med övervikt och svår TBI. Åtgärder för att etablera inskrivning vid rätt tidpunkt till rehabiliteringsmedicinsk enhet kan förbättra utfallet efter svår TBI.

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APPENDIX

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Rehabiliteringsmedicin
Box 30110
400 43 Göteborg

FRÅGEFORMULÄR – TRAUMATISK HJÄRNSKADA

Datum för ifyllande:……

Personuppgifter:
Förnamn: ..... Efternamn: .....

Personnummer: ..... Kön: □ Kvinna □ Man

Adress:..... Postnr: .....

Telefon bostad: ..... Telefon arbete: .....

Mobil: .....

Civilstånd:
□ Gift
□ Ensamstående
□ Sambo
□ Särbo

Barn:
□ Ja □ Nej Hemmavårdade barn: □ Ja □ Nej

Skadeuppgift:
Vilket år fick **Du** din hjärnskada? ……..
Vad orsakade **Din** hjärnskada?
□Fall □Trafikolycka □Misshandel □Annat,nämligen:…….

Arbete/Försörjning:
Vilken typ av försörjning har **Du** ?

Lön?	□ Ja	□ Nej
Studiemedel/utbildningsbidrag?	□ Ja	□ Nej
Sjukpenning/tidsbegränsat sjukersättning?	□ Ja	□ Nej
Aktivitetsstöd/rehabiliteringsersättning?	□ Ja	□ Nej
Förtidspension/långvarig sjukersättning?	□ Ja	□ Nej
Ålderspension?	□ Ja	□ Nej

Annat, nämligen: .....

Vilket är **Ditt** nuvarande arbete/studier? ……
Om **Du** arbetar eller studerar gör **Du** det till ☐100% ☐75% ☐50% ☐25% ☐Inte alls

Vad gör **Du** på fritid idag?.....
.....
Vad gjorde **Du** på fritid förre hjärnskadan? ……
.....
.

Röker **Du**?	□ Ja	□ Nej
Har **Du** problem med alkohol?	□ Ja	□ Nej
Har **Du** haft problem med alkohol?	□ Ja	□ Nej
Använder **Du** hasch/andra droger?	□ Ja	□ Nej
Använde **Du** hasch/andra droger tidigare?	□ Ja	□ Nej

Fysiska/psykiska funktioner:
Har **Du** problem med något av följande i dag?
Svarar **Du** ja på en fråga vänlig besvara följdfrågan.

Rörlighet/svaghet i arm?	□Ja	□Nej	Debut:……
Rörlighet/svaghet i ben?	□Ja	□Nej	Debut:……
Rörlighet/svaghet i bålen?	□Ja	□Nej	Debut:……
Sväljningsfunktion?	□Ja	□Nej	Debut:……
Talfunktion?	□Ja	□Nej	Debut:……
Viktminskning?	□Ja	□Nej	Hur många kg efter hjärnskadan? ……..
Viktökning?	□Ja	□Nej	Hur många kg efter hjärnskadan? ……..
Ökat törst?	□Ja	□Nej	Debut:……
Stora urinmängder?	□Ja	□Nej	Debut:…….
Vattenkastningsbesvär?	□Ja	□Nej	Debut:…….
Allmän trötthet?	□Ja	□Nej	Debut:……
Koncentrationssvårigheter?	□Ja	□Nej	Debut:……
Minnessvårigheter	□Ja	□Nej	Debut:……
Språksvårigheter?	□Ja	□Nej	Debut:……
Nedstämdhet?	□Ja	□Nej	Debut:……
Irritabilitet?	□Ja	□Nej	Debut:……
Ängslan?	□Ja	□Nej	Debut:……
Sömnsvårigheter?	□Ja	□Nej	Debut:……
Nedsatt sexuell förmåga?	□Ja	□Nej	Debut:……
Nedsatt sexuell lust?	□Ja	□Nej	Debut:……
Nedsatt hörsel?	□Ja	□Nej	Debut:……
Synstörning?	□Ja	□Nej	Debut:……
Nedsatt lukt?	□Ja	□Nej	Debut:…….
Yrsel?	□Ja	□Nej	Debut:……
Känselstörning?	□Ja	□Nej	Debut:……
Huvudvärk som kräver regelbunden behandling?	□Ja	□Nej	Debut:……
Övriga smärtproblem?	□Ja	□Nej	Debut:……

Vilka övriga smärtproblem? ……

Aktiviteter:
Har **Du** problem med något av följande nu?

Gå på slät mark?	□ Ja	□ Nej	□ Kan ej
Gå i trappor?	□ Ja	□ Nej	□ Kan ej
Av- och påklädning?	□ Ja	□ Nej	□ Kan ej
Bada/duscha?	□ Ja	□ Nej	□ Kan ej
Toalettbesök?	□ Ja	□ Nej	□ Kan ej
Läsa tidning?	□ Ja	□ Nej	□ Kan ej
Se långfilm på tv?	□ Ja	□ Nej	□ Kan ej
Praktiska hemsysslor?	□ Ja	□ Nej	□ Kan ej
Sköta hushållsekonomin?	□ Ja	□ Nej	□ Kan ej
Deltaga i fritidsintressen	□ Ja	□ Nej	□ Kan ej
Använda allmänna transportmedel?	□ Ja	□ Nej	□ Kan ej
Bilkörning?	□ Ja	□ Nej	□ Kan ej

Stödinsatser:
Använder **Du** något av följande hjälpmedel?

□ Rullator □ Manuell rullstol
□ Käpp □ Elektrisk rullstol
□ Kryckor
□ Bilstöd för handikappade □ Innehar färdtjänst
□ P-tillstånd för handikappade
□ Övrigt hjälpmedel, nämligen.....

Har **Du** i dag hjälp av…

Hemtjänst?	□ Ja	□ Nej	□ Flera gånger om dagen	□ Varje dag	□ Varje vecka
Ledsagare?	□ Ja	□ Nej	□ Flera gånger om dagen	□ Varje dag	□ Varje vecka
Familjemedlem?	□ Ja	□ Nej	□ Flera gånger om dagen	□ Varje dag	□ Varje vecka
Personlig assistent?	□ Ja	□ Nej	□ Flera gånger om dagen	□ Varje dag	□ Varje vecka
Annan assistans?	□ Ja	□ Nej	□ Flera gånger om dagen	□ Varje dag	□ Varje vecka

Vem är **Din** ordinarie läkare? ……

På vilken mottagning/klinik? …….

Aktuella läkemedel?.....

Andra sjukdomar:
Har eller har **Du** haft någon/några av följande sjukdomar?

□ Diabetes	Debut:.....	□ Hjärtsjukdom	Debut:.....
□ Högt blodtryck	Debut:.....	□ Slaganfall	Debut:.....
□ Sköldkörtelsjukdom	Debut:.....	□ Cancer	Debut:.....
□ Andningssjukdom	Debut:.....	□ Epilepsi	Debut:.....
□ Mag-tarmsjukdom	Debut:.....	□ Njursjukdom	Debut:.....
□ Ledsjukdom	Debut:.....	□ Olycksfall som krävd sjukvård	Debut:.....
□ Nedsatt cirkulation	Debut:.....		

Annan sjukdom eller kroppsskada:.....
Andra viktiga händelser som kan ha påverkat **Ditt** hälsotillstånd:……..
Har **Du** fyllt i formuläret själv? □ Ja □ Nej □ Delvis