Assessment and outcomes in mild traumatic brain injury in the Emergency Department

A thesis submitted in partial fulfilment
of the requirements of the
Degree of Doctor of Philosophy

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Declaration

I, Benjamin Bloom, confirm that the research included within this thesis is my own work or that where it has been carried out in collaboration with, or supported by others, that this is duly acknowledged below, and my contribution indicated. Previously published material is also acknowledged below.

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Short Abstract

Objective

The objectives of this thesis are to ascertain how long it takes for patients with a mild traumatic brain injury to return to work or other usual activities; to identify the short-term effects on neurocognition and symptoms in patients with a mild traumatic brain injury; to determine the proportion of patients, out of all that attend the Emergency Department with a seizure, that attend as a consequence of traumatic brain injury; and to assess the value of the biomarkers S100B and copeptin in predicting outcomes in patients that attend the Emergency Department following a seizure.

Methods

This thesis comprises three studies in which I investigated the short and long-term effects of mild traumatic brain injury (TBI) and prognostication in seizure. In study one, I undertook a systematic review and meta-analysis to determine return to work times for adults with mild TBI. A narrative synthesis and a random-effects meta-analysis was performed. The second study was a prospective observational cohort study of adults with mild TBI and non-head injured controls. The outcomes of interest were neurocognitive function and concussion symptom severity at baseline and 72 hours. The third study was a prospective observational cohort study of adults attending the Emergency Department with seizure. The proportion of patients that attended with seizure as a consequence of TBI was recorded. The biomarkers S100B and

copeptin were measured to predict a composite primary outcome of seizure recurrence, death, hospitalisation, rehospitalisation or re-attendance at Emergency Department by seven days.

Results

In the systematic review and meta-analysis, the pooled proportion of people returned to work at one month was 56%, at six months 83%, and at 12 months 89%.

In the study of short-term effects of mild TBI, I enrolled 240 patients. Patients with TBI had marked cognitive impairment which persisted at 72 hours, and persistently high numbers of symptoms and high symptom severity. Patients with TBI had worse neurocognitive function, higher overall symptom severity, and a higher total number of symptoms compared with controls.

In the third study of patients with seizures, 97 patients were recruited. No patients attended with a seizure as a consequence of TBI. 52% met the primary endpoint. S100B and copeptin were significantly higher in patients with compared to without the composite primary endpoint, but the biomarkers had poor prognostic value for predicting the primary outcome.

Conclusions

In this body of work, I have shown that mild TBI results in a neurocognitive deficit and a significant symptom burden, which persists for several days. Furthermore, although most patients have returned to usual activities, including work, by three months after injury, some are still unable to work a

year after injury. A third of patients that have a seizure for any reason go on to have another seizure within a week. S100B and copeptin do not add value in predicting which patients have recurrence of seizure and very few patients attend the Emergency Department with seizure secondary to TBI.

Scientific Abstract

Background

Traumatic brain injury (TBI) is common, affecting up to 600/100,000 people. Mild TBI accounts for up to 90% of all TBI. The Emergency Department attendance rate for head injuries is as high as 1800/100,000 population, and 15-20% of those attendances result in hospital admission. Mild TBI causes symptoms such as headaches, dizziness, disordered balance, cognitive dysfunction and depression which in turn impact on quality of life. Accurate risk assessment and prognostication of patients with acute neurological conditions in the Emergency Department is essential. This PhD consists of a systematic review that examines the hard outcome of 'return to work' following a mild TBI; a prospective observational cohort study that reports the difference in neurocognitive function and symptoms that patients experience at baseline and three days after mild TBI; and a prospective observational cohort study that reports the number of patients that attend the Emergency Department with seizure secondary to TBI, and the value of two biomarkers in predicting the recurrence of seizures in patients that attend the Emergency Department having had a seizure.

Methods

This thesis comprises three studies in which I investigated the short and long-term effects of mild traumatic brain injury (TBI) and prognostication in seizure. In study one, I undertook a systematic review and meta-analysis to

determine return to work times for adults with mild TBI. The primary objective was to determine the time taken to return to work following a mild TBI. Articles were included if they reported on adults with mild TBI and recorded the outcome return to work. Six electronic databases and eight clinical trial registries were searched. A narrative synthesis and a random-effects meta-analysis was performed. Bias was assessed using a modified version of the Newcastle Ottawa quality assessment tool.

The second study was a prospective observational cohort study of adults with mild TBI and a comparison group of Emergency Department patients without brain injury. The primary outcomes were neurocognitive function and concussion symptom severity at baseline and 72 hours. Adult patients with mild TBI within the last 24 hours were included in the mild TBI group, and adults that attended the Emergency Department with trauma beneath the clavicle, or with a non-neurological medical condition, were included in the comparison group. Outcomes were measured on the Standardized Assessment of Concussion (SCA) and the Concussion Symptom Inventory (CSI) at baseline in the Emergency Department and at follow up at 72 hours. Comparisons were made between baseline and follow up, and between groups at single time points.

The third study was a prospective observational cohort study designed to assess the prognostic value of the biomarkers S100B and copeptin in patients with seizure. Adult patients attending the Emergency Department with seizure of any cause were included. The primary outcome was a composite of seizure recurrence, death, hospitalisation, rehospitalisation or re-attendance at the Emergency Department at seven days. S100B and copeptin were measured in

the Emergency Department. Statistical comparison of the two groups was performed, optimum thresholds of the biomarkers for diagnosing the endpoint were derived, diagnostic test characteristics were calculated, and logistic regression modelling was performed to identify variables most closely associated with the outcome. The aetiology of the seizure was identified and the proportion that had a seizure secondary to TBI was recorded.

Results

In the systematic review and meta-analysis, 14 studies were included. Three reported the average time taken to return to work, and 12 reported the proportion of patients that have returned to work by a pre-specified time point. The pooled proportion of people returned to work at one, three, six and 12 months was 56%, 75%, 83%, and 89% respectively.

In the study of short-term effects of mild TBI, 240 patients were included, of which 189 had mild TBI and 51 comprised the non-brain injured comparison group. Patients with mild TBI had marked neurocognitive impairment (SAC at baseline 25 [23-27], difference in SAC score between brain injured and non-brain injured 1, p=0.02, [95% confidence interval [CI] -1.4 to -2.4]), worse symptom severity (CSI at baseline 9 [4-21], difference in CSI between brain injured and non-brain injured 9, p<0.001 [95% CI 8.4 to 13.7]), and high numbers of symptoms (number of symptoms at baseline 4 [2-8], difference between brain injured and non-brain injured 4, p<0.001 [95% CI 2.6 to 4.4]), all of which persisted at 72 hours.

In the study of patients with seizures, 97 patients were recruited, of which 52% met the composite primary endpoint. No patients attended with a seizure as a consequence of TBI. S100B and copeptin were significantly higher in patients with compared to without the composite primary endpoint: 0.22 μg/L (95% CI 0.14 to 0.31) vs 0.11 μg/L (95% CI 0.08 to 0.14) (difference 0.02 μg/L, p = 0.01, 95% CI 0.02 to 0.2) for S100B; and 77.0 pmol/L (95% CI 44.3 to 109.7) vs 27.0 (95% CI 18.2 to 35.9) (difference 50 pmol/L, p = 0.004, 95% CI 16.2 to 83.8) for copeptin. Thresholds of 0.088 μg/L and 6.26 pmol/L were identified for S100B and copeptin respectively. At those thresholds, S100B sensitivity and specificity was 58% (95% CI 43-72) and 60% (95% CI 44-74); and copeptin sensitivity and specificity was 80% (95% CI 66-90) and 21% (95% CI 11-36). Epilepsy, complex partial seizure, provoked/acute symptomatic seizure, and pyrexia were identified as factors independently associated with the primary outcome but there was no additional value when the biomarkers were included in the model.

Conclusions

In this body of work, I have shown that patients with mild traumatic brain injury have impaired neurocognitive function and a significant symptom burden that persists for several days, and in some patients is likely to persist for many months. Although most patients return to normal activities, including working, by three months after a mild traumatic brain injury, up to a tenth of patients are still unable to return to work at one year after the injury. Around half of patients that attend an Emergency Department with a seizure go on to be admitted or have another seizure by one week, but the biomarkers

S100B and copeptin add no extra value to current prediction tools in identifying who will have a recurrent seizure, and few patients have a seizure secondary to TBI.

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List of Abbreviations

µg	Microgram
AUC	Area under the curve
CI	Confidence interval
CSI	Concussion Symptom Inventory
CT	Computed tomography
DTI	Diffusion tensor image
ECDS	Emergency Care Data Set
EEG	Electro-encephalogram
GCS	Glasgow Coma Scale
ICU	Intensive Care Unit
IQR	Interquartile range
kDa	Kilodalton
L	Litre
mg	Milligram
mEq	Milliequivalent
mmHg	Millimetres of mercury
MRI	Magnetic Resonance Imaging
NHS	National Health Service
NPV	Negative predictive value
OR	Odds ratio
pmol	Picomole
ROC	Receiver operating characteristic
SAC	Standardized Assessment of Concussion
SD	Standard deviation
TBI	Traumatic brain injury
UK	United Kingdom
US	United States

Chapter 1 Introduction

Acquired brain injury

A brain injury can occur because of a physical or traumatic mechanical force applied to a person's head, or as a product of an electrophysiological, metabolic, hypoxic, or other pathological insult. The consequences of an acquired brain injury range from very transient symptoms to full dependence and death. Acquired brain injury is one of the most common reasons for patients to attend Emergency Departments and has a rate of admission into hospital of 566/100,000 people.[1] Traumatic brain injury (TBI) is grouped into mild, moderate and severe categories based on the first measured Glasgow Coma Scale (GCS).[2] Traumatic brain injury is termed mild, moderate or severe if the initial GCS is 13-15, 9-12, or 3-8 respectively.[3,4] However, mild TBI is conceptually a condition that results from some form of physical trauma to the head and which may involve loss of consciousness and memory dysfunction around the time of the injury and be followed by symptoms including headache and difficulty thinking. Since there are rarely abnormalities seen on routine imaging studies, mild TBI is primarily a functional condition.[5] Mild TBI can be thought of as possessing features occurring at the time of injury, specifically the presence of loss of consciousness or amnesia, and features occurring after the injury. There are many features that may follow, and these may occur immediately after the injury, or within minutes, hours or sometimes days (Table 1.1 and Figure 1.1). There are four definitions of mild TBI frequently described in the medical literature; those developed by the American Congress of Rehabilitation Medicine, the Centers for Disease Control and Prevention,

the World Health Organisation collaborating Centre for Neurotrauma Task Force on mild TBI, and the European Federation of Neurological Societies (Table 1.2 and Appendix 1).[6-9]

Reference	Ruther-ford[10]	Rimel[3]	Kraus[11]	Pons-ford[12]	Cunning ham[13]	Lange[14]
Number of patients	145	538	687	123	94	37
Follow up	6 weeks	3 months	3 months	3 months	1 month	<8 months
No complaints	49%	16%	---	---	37%	---
Headache	25%	79%	22%	26%	42%	70%
Memory problems	8%	59%	22%	16%	28%	57%
Anxiety	19%	---	---	14%	---	27%
Sleep disturbance	15%	---	23%	23%	22%	60%
Dizziness	15%	---	14%	8%	29%	60%
Irritability	9%	---	18%	24%	26%	51%
Fatigue	9%	---	26%	37%	28%	65%
Loss of concentration	8%	---	19%	14%	28%	57%
Taking longer to think	---	---	20%	---	29%	---
Frustration/Impatience	---	---	21%	---	27%	24%
Depression	6%	---	14%	16%	22%	---
Hyperacusis	---	---	9%	---	21%	51%
Light sensitivity	---	---	9%	5%	17%	---
Nausea	---	---	7%	3%	16%	30%

Table 1.1 Proportions of patients with symptoms after mild TBI

Figure 1.1 Proportions of patients with symptoms after mild TBI

When reporting in the scientific literature, symptoms of mild TBI are recorded in checklists. Two of the commonest are the Rivermead Post Concussion Symptoms Questionnaire and the Concussion Symptom Inventory (Appendix 2), which contain 16 and 12 symptoms respectively (Table 1.4).[15,16] Mild TBI and concussion are terms that are often used interchangeably, and the difference between the two conditions is not well defined.[5] It is unknown whether concussion is part of a TBI spectrum with less structural change than seen in more severe grades of TBI, or whether the functional brain injury associated with concussion is simply the result of reversible physiological changes. The term concussion is used commonly in sports and the most comprehensive definition of concussion is derived from sports related

concussion. Sports related concussion is defined as a TBI induced by biomechanical forces, with several common features that may be present including transient impairment of neurological function, functional acute clinical signs and symptoms (no abnormalities on commonly utilised scans) and involving a range of clinical signs and symptoms that may or may not involve loss of consciousness.[5] Despite symptoms of mild TBI routinely being measured on scores with the word 'concussion' in their title, a comparison of the most recent definition of concussion with the most commonly used definitions of mild TBI shows that the symptoms and signs used to describe mild TBI are more severe than those used to describe concussion (Table 1.2).

	ACRM (1993) Mild TBI	CDC (2003) Mild TBI	WHO (2004) Mild TBI	EFNS category (2002) Mild TBI	CISG (2017) Concussion
Mechanical injury description	Traumatically induced	An injury to the head as a result of blunt trauma or acceleration or deceleration forces	Mechanical energy to the head from external physical forces	Blunt (non-penetrating) impact with rapid acceleration, deceleration or rotation force to the head	Biomechanical forces; direct blow to the head, face, neck or elsewhere on the body with an impulsive force transmitted to the head
Brain injury description	Disruption of brain function	Not included	Acute brain injury	Cat. 0: Head injury with no TBI Cat. 1-3: Not explicit	Traumatic brain injury
GCS incorporated	Yes	No	Yes	Yes	No
GCS details	GCS 13-15 after 30 min	---	GCS 13-15 after 30 min, or later upon presentation for healthcare.	Cat. 0-2: GCS 15 Cat. 3: GCS 13-14	---
LOC incorporated	Yes	Yes	Yes	Cat. 0,1,3: Yes Cat. 2: No	Yes - states may or may not be present
Duration LOC	<30 min	<30 min	<30 min	Cat. 0: 0 min Cat. 1,3: <30 min Cat. 2: not specified	Not defined
Amnesia incorporated	Yes	Yes	Yes	Cat. 0,1,3: Yes Cat. 2: No	No
Amnesia type	Immediately before or after injury	Immediately before, during, or after the injury	PTA	Cat. 0,1,3: PTA Cat: not specified	---
Amnesia duration	PTA <24 hrs	PTA <24 hrs	PTA <24 hrs	No PTA	---

Altered mental state incorporated	Yes	Yes	Yes	No	Yes
Which altered mental state symptoms/signs	Any, e.g. feeling dazed, disoriented, confused	Transient confusion, disorientation, impaired consciousness	Confusion or disorientation	---	Rapid onset (can be min-hrs) of short-lived impairment of neurological function, resolves spont.
Focal neurological deficit incorporated	Yes	Yes	Yes	Cat. 0,1: No Cat. 2,3: Yes	No
Duration of focal neurological deficit	May or may not be transient	Not specified	Transient	Cat. 0,1: No Cat. 2,3: Not specified	---
Seizures incorporated	Not specified	Yes	Yes	Cat. 0,1: No Cat. 2,3: Yes	No
Other	---	Irritability, lethargy, vomiting (infants/ young children). Headache, dizziness, irritability, fatigue, poor concentration, if assoc. with LOC or altered consciousness (adults/older children)	Intracranial lesion not requiring surgery	Cat. 0,1: No risk factors present Cat. 2,3: With risk factors.	---

Table 1.2 Comparison of definitions of mild TBI.
ACRM, American Congress of Rehabilitation Medicine; CDC, Centers for Disease Control and Prevention; WHO, World Health Organisation collaborating task force; EFNS, European Federation of Neurological Societies; CISG, Concussion in Sports Group; GCS, Glasgow Coma Scale; Cat, EFNS category of mild TBI; LOC, loss of consciousness; PTA, post-traumatic amnesia; RGA, retrograde amnesia. Risk factors used in EFNS definition: unclear or ambiguous history, continued PTA, RGA > 30 min, trauma above the clavicles, signs of base of or depressed skull fracture, severe headache, vomiting, focal neurological deficit, seizure, age < 2, age > 60, coagulation disorders, high-energy accident, intoxication with alcohol/drugs

An epileptic seizure is defined as a transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain.[17] Seizures are a rare consequence of mild TBI but a common reason for patients to attend the Emergency Department. Seizures account for 1% of all Emergency Department attendances in the US, and 1.4% of all medical admissions into hospital in the UK.[18,19] Although 11% of the population will have a seizure in their lifetime, most are not due to epilepsy.[20] Furthermore, seizures in patients that present to the Emergency Department are usually acute symptomatic, that is, secondary to another diagnosis, and not caused by epilepsy.[18] The most frequently associated diagnoses in adults are alcohol-related.[18,21] In Emergency Department patients that present with a seizure and are investigated with neuroimaging, head injury is the second most common reason for scan, after alcohol-related seizure.[22] The potential consequences of a seizure include physical injury, time off from working, degeneration into status epilepticus, hypoxic brain damage and death.[23-25] In one study, 1.2% of Emergency Department attendances for seizure resulted in death, and injury or death was associated with 15% of seizure attendances.[26] By far the most common injury was a head injury at 67%, followed by fractures, dislocations and sprains (14%). In a study of patients with epilepsy, which is a smaller group than patients that attend the Emergency Department with seizures, 12.5% were unable to work due to epilepsy.[23] Estimates of numbers of patients with status epilepticus vary from 6 - 7% with an associated mortality rate of up to 26% in adults.[27-29] This can partly be explained by the diagnoses associated with status epilepticus. Hypoxia and anoxia carry the highest mortality rates, followed by stroke, tumour, metabolic derangement, drug overdose and

traumatic brain injury.[25] The ability therefore to identify patients likely to have a poor outcome or recurrent seizure is important.

The risk of recurrence following a first unprovoked seizure is high with estimates ranging from 23% to 71% at two years.[30] For patients treated with an anti-epileptic drug as soon as possible after a seizure, the recurrence rate was 37% at two years, and the number of seizures prior to starting the drug, an abnormal EEG, and the presence of a neurological disorder were associated with increased risk of recurrence.[31,32] The overall likelihood of seizure recurrence at one year is 43% but was 48% for unprovoked first seizures and 29% for provoked first seizures, with the lower rate of recurrence in provoked first seizures because the provoking cause is subsequently treated.[33]

Epidemiology

Traumatic brain injuries can result in significant morbidity and mortality, and consequently create a burden carried by patients, the healthcare system and society. To understand the burden, it is essential to understand the size of the problem. Patients may experience a head injury. A head injury is distinct from a brain injury, because it is possible to sustain a head injury without a brain injury. Although rare, it is also possible to sustain a TBI without a head injury. The mechanism for this is a rapid acceleration-deceleration injury without a strike to the head, for instance during a motor vehicle collision. Patients or their associates may choose to attend an Emergency Department because they sustained a head injury. Within the Emergency Department they may be diagnosed with a brain injury. They may be admitted into the hospital or they may be discharged home. Epidemiological studies report all these rates, i.e. Emergency Department attendance rate, hospital admission rate, head injury rate and brain injury rate (Table 1.3). In the UK, a common source of data reported in epidemiological studies is Hospital Episode Statistics.[34] Hospital Episode Statistics is a database containing details of all admissions and Emergency Department attendances at NHS hospitals in England. Each Hospital Episode Statistics record contains clinical information including diagnoses, operations, and patient, geographic and administrative information. The key studies from the UK that describe head or brain injury, report Emergency Department or hospital episodes from 1974, 1986 and 2001-2003.[35] Several more reports from Europe and the USA utilise equivalent national databases or local hospital records as data sources. The majority of

studies use definitions of brain injury from the International Classification of Diseases systems (Table 6.1).[36]

United Kingdom

Traumatic brain injury represents an ongoing epidemic. Evidence on head and brain injuries has been collected in different regions in the UK since the 1970s. In a landmark study, information was abstracted from national, hospital admission and Emergency Department attendance data sets for the years 1971-1976.[35] Head injuries accounted for 9/100,000 deaths overall (less than 1%) but 15% of all deaths in the 15-24 years age group and up to 49% of all deaths were associated with motor vehicle collisions. This study, which describes data from 1974, reported hospital admission rates of 270/100,000 patients for head injuries. This rate was based on analysis of International Classification of Diseases codes assigned to patients in a four-week period. There was an overall Emergency Department attendance rate of 1778/100,000 attendances with higher attendance rates in younger age ranges and in males compared with females.

In 1986, the north west of England was home to four million people. At that time, the hospital admission rate, distinct from Emergency Department attendance rate, for head injuries was 297/100,000.[37] There was significant variation in rates across the region, from 88 to 886/100,000. In a nationwide analysis of Hospital Episode Statistics from 2001-3, compared with 1974, there was a reduction of 229/100,000 and an absolute number of admissions in England of 112,718 patients.[38] The variation between local districts was seen again, from 91 to 419/100,000. The admission rate in the 0-15 and 75+ age ranges was much higher than in the 16-74 age group. A regression analysis

performed on this data found that unemployment, long term sickness and lone parent families increased the hospital admission rate. In contrast, the use of public transport to get to work reduced the hospital admission rate.

In Scotland, an analysis of the Scottish Morbidity Record data set, which includes all in-patient episodes, from 1998 to 2009, identified a rate of admission for TBI in males of 446/100,00 and females of 195/100,000.[39] Over the 11 years of the study, the authors noted two periods at which the trend in admission rate reduced. This was in 2002 and 2005 for men, and 2001 and 2004 for women. This decrease in admissions was seen chiefly in the younger age group, while there was an increase in admission trends in 2004 in older women, which was caused primarily by falls. This is seen again in a simple analysis of numbers of patients admitted for TBI in England from 1998 to 2010.[40] This study showed a near doubling in absolute admissions, from 13,800 admitted in 1998 to 25,200 in 2010. When grouped by age, there was a small decrease in admissions in children, and a large increase in admissions in over 60s, from 3350 in 1998 to 12,800 in 2010.

Emergency Department attendance rates for head injury are higher than hospital admission rates as many head injuries do not result in a brain injury significant enough to warrant admission. An analysis of the database of a UK Emergency Department treating rural and urban populations and covering 1997 to 2003, found that head injuries accounted for 3.4% of all Emergency Department attendances with an attendance rate of 453/100,000.[41] Urban rates were almost four times as high as rural and 10.9% of attendances were moderate or severe.

Europe

Evidence of head injury rates in Europe comes from a range of geographic locations including urban and very rural regions. Because the populations are so distinct, and the type of rate reported (head injury, brain injury, Emergency Department attendance, hospital admission) are different, it is difficult to generalise or make assumptions about one population based on reports from another. In central Norway from 1979 to 1980, the incidence of head injury due to motor vehicle collision and requiring admission to hospital was 89/100,000.[42] In north Norway the rate for all cause TBI was estimated at 229/100,000.[43] The primary cause was falls (62%) followed by motor vehicle collisions (21%) and assault (7%). The two rates are different (head injury and TBI), and the head injury rate, reported in north Norway, is due to motor vehicle collision only. To compare central with north Norway, the rate of TBI due to motor vehicle collision must be calculated from the all cause rate, i.e. 21% of 229/100,000, which is 48/100,000. Therefore, the rate of TBI due to motor vehicle collision in central Norway is almost half the rate of head injury due to motor vehicle collision in norther Norway.

An analysis of nationally collected data in Norway, Sweden, Denmark and Finland between 1987 and 2001 found that the death rate from TBI was around 10% in the former three countries and just over 20% for Finland, with males three times more likely to die than females in all four countries.[44] The higher mortality rate in Finland was thought to be associated with alcohol consumption patterns, suicide and homicide. In Denmark, TBI-related Emergency Department attendances and hospital admissions both increased from 1998 to 2012.[45] In patients aged ≥65, TBI related attendances rose

substantially more than age <65 by 9% vs 3% per year. TBI related admissions also rose in the older group from 17% to 28% of all TBI related admissions. As a mechanism of injury, falls rose, and motor vehicle collisions reduced over the study period. In Hanover and Munster, Germany, all Emergency Department attendances for head injury with either symptoms of TBI or an ICD-10 code for TBI were analysed (Appendix 3). The incidence of Emergency Department attendance for TBI was 332/100,000, and 73% were admitted into hospital. The proportion of mild TBI was 90.2%, moderate 3.9%, and severe 5.2%.[46] There was a 1% mortality rate, and the primary cause was falls (52.5%), followed by motor vehicle collisions (26.3%).

USA

Prior to the 1990s in the USA, data on TBI incidence were reported based primarily on hospital discharge codes and at hospital, city or county level. Emergency Department attendance rates were rarely reported, and the data sources were often small (Table 1.3). This began to change in the 1990s, with an analysis of the 1991 National Health Interview Survey. This US-wide survey collected data on mild or moderate TBI only, which were defined as head injuries resulting in loss of consciousness but not death or long-term disability. The authors reported that there was a TBI rate of 618/100,000, which is higher than other reports, but includes patients that did not receive any medical care, or that received primary care only. Among this group, 25% did not receive medical care, 14% were treated as out-patients, 35% attended Emergency Departments and were discharged, and 25% were admitted to hospital.[47]

The National Hospital Ambulatory Medical Care Survey is a large database in the US designed to estimate utilisation and provision of Emergency

Department and outpatient care. An analysis of the 1992-1994 dataset was performed to describe the characteristics of patients with TBI that present to the Emergency Department.[48] There were an estimated 1,144,807 new Emergency Department attendances with TBI per year, with an Emergency Department attendance rate of 444/100,000, accounting for 1.3% of all Emergency Department visits. The greatest attendance rate was amongst the less than five age group at 1,091/100,000, followed by the greater than 85 age group at 1,026/100,000. The male to female ratio was 1.6 and female attendances were only greater than male attendances in the over 65 age groups. The primary cause was falls (39%) followed by motor vehicle collisions (23%) and assault (23%).

The National Hospital Ambulatory Medical Care Survey dataset was also used to identify Emergency Department attendances for mild TBI during the years 1998-2000.[49] The authors found that for mild TBI there were 1.4 million Emergency Department attendances per year, which represented an Emergency Department attendance rate of 503/100,000. The highest attendance rates were in males (781/100,000) and in children under five (1115/100,000). The most common mechanism varied with age, with falls being most common in the extremes of age, and motor vehicle collisions in the middle age groups. When this data was analysed for isolated mild TBI, i.e. mild TBI with no other concomitant Emergency Department diagnosis, the Emergency Department attendance rate was 56/100,000, which equated to 153,300 Emergency Department attendances annually.[50] A further analysis of the National Hospital Ambulatory Medical Care Survey for Emergency Department visits, along with National Hospital Discharge Survey for in-

patient episodes, and the National Center for Health Statistics for mortality data, was performed for 2003.[51] This study reported 1.6 million TBIs, which was made up of 1.2 million Emergency Department attendances, 290,000 hospital admissions, and 51,000 deaths. The highest Emergency Department attendance rate was seen in the youngest age group, and the highest hospital admission rate was seen in the oldest age group. The most common mechanism was falls (32%), followed by motor vehicle collision (19%), struck by/against (18%) and assault (10%).

The US Department of Health and Human Services, Centers for Disease Control and Prevention published a landmark study in 2010, which observed and calculated TBI rates from 2002 to 2006.[52] This study also utilised data from the National Hospital Ambulatory Medical Care Survey and National Center for Health Statistics. The annual incidence of TBI in the US was 1.7 million, of which 1.4 million (80%) attended the Emergency Department and were discharged, 275,000 (16%) were admitted into hospital, and 52,000 (3%) patients died. The age groups with highest rates of TBI-related Emergency Department visits were 0-4, and 15-19 years, although patients aged greater than 75 had the highest rates of admission and death. Males had a higher incidence than females in all age groups. Falls were the leading cause of TBI, and motor vehicle collisions were the most common cause of TBI-related death. Emergency Department attendances rose from 14.4% to 19.5% over the five years. Injuries comprised 30% of all Emergency Department attendances and 5% of all admissions, and TBI comprised 1.4% of all attendances (5% of all injuries), 0.7% of all admissions and 2% of all deaths.

In North Carolina in 2010-2011, there were more than 140,000 Emergency Department attendances with TBI, equating to 7.3 Emergency Department visits per 1000 person-years.[53] Emergency Department attendance rates were highest in the 0-4, 15-19 and >75 years age groups. The primary cause of TBI was falls (39.0%), followed by being struck by an object (17.6%) or motor vehicle collisions (14.1%).

In addition to Emergency Department and in-patient healthcare usage, patients with head injuries also attend primary care and clinic-based services. In the US, over the five years from 2005 to 2009, for mild TBI, there were 3.8 million primary care attendances, 380,000 outpatient attendances, and six million Emergency Department attendances with mild TBI (data also from the National Hospital Ambulatory Medical Care Survey and the National Center for Health Statistics).[54]

These findings are consistent with estimates of 1.6 million, 1.7 million and 2.1 million Emergency Department attendances for TBI in 2006, 2007, and 2008 respectively.[55] Around 15% were patients aged greater than 65 years, and of those, 61% were female and the older group also had higher acuity levels (represented as being assigned higher priority codes). A further US study, using the same methodology, and looking at US Emergency Department attendances in 2009 and 2010, estimated TBI diagnosed in the Emergency Department at 2.5 million cases a year.[56] Falls (49%), followed by motor vehicle collisions (20%), struck by/against (11%), and assault (8%) were the commonest mechanisms. Using a different methodology, the Centers for Disease Control and Prevention published a national estimate for TBI related Emergency Department attendance, hospitalisation and death for 2007 and

2013.[57] They found that attendances were rising, from 1.6 million in 2007 to 2.5 million 2013. This rise was chiefly accounted for by patients aged 0-4, 15-24 and ≥75 years. Admissions into hospital also rose, and this was accounted for by the older age group. Overall, the most common mechanisms of injury were falls, followed by struck by/against an object and motor vehicles collisions. However, when stratified by age, in the older and youngest groups, falls accounted for most of the injury mechanisms, whereas in other age groups other mechanisms were more common. The methodology used in national studies in the US of Emergency Department attendances per year results in estimates from survey data. From these there is a clear rise in attendances per year (Figure 1.2).

In Ontario, Canada in 2001, the incidence of mild TBI, calculated from Emergency Department and Family Physician health records, was 426/100,000.[58] Further data from Ontario, from 2002 to 2009, showed that Emergency Department attendance rates remained broadly stable at around 1000/100,000 and similar patterns of sex, age and mechanism were seen.[59] In British Columbia, Canada the rate of hospital admission for head injury in 2000 was 255/100,000, and of those admissions, concussion accounted for 34.9% of diagnoses.[60] Across all of Canada the rate of concussion was estimated at 110/100,000.[61]

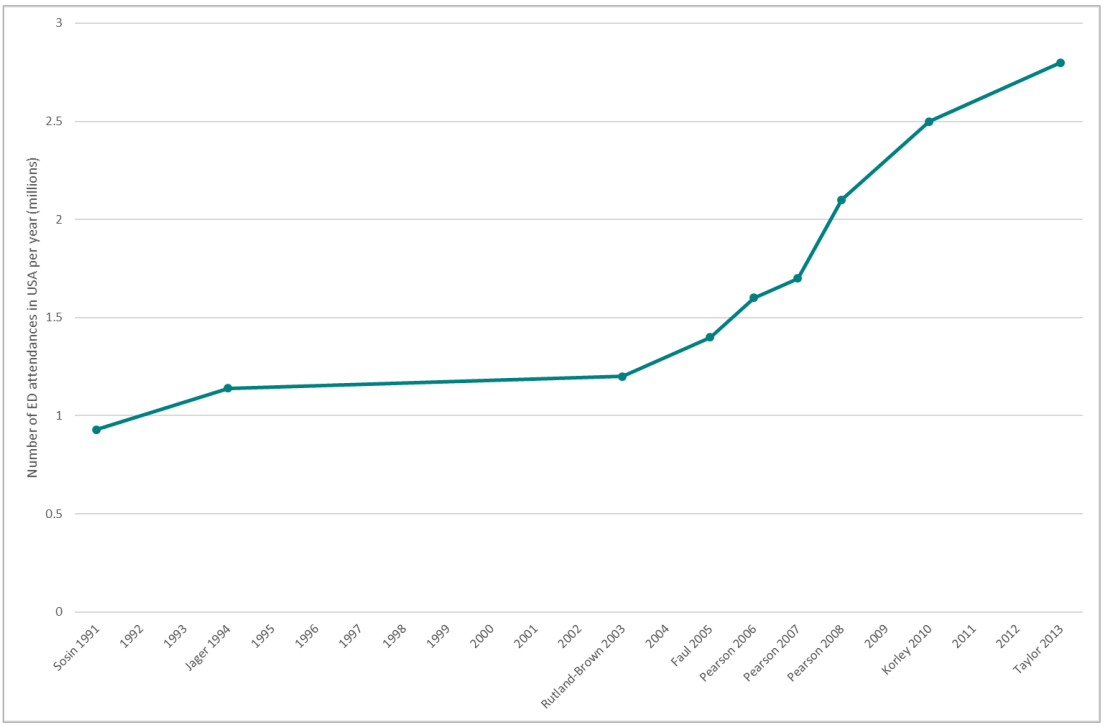

Figure 1.2 US Emergency Department attendances with head injury
Methodology used in each paper: Sosin, National Health Interview Survey; Jager, National Hospital Ambulatory Medical Care Survey (NHAMCS); Rutland-Brow, NHAMCS; Faul, NHAMCS; Pearson National Hospital Ambulatory Medical Care Survey Emergency Department (NHAMCS-ED); Korley, NHAMCS; Taylor, Healthcare Cost and Utilization Project, Nationwide Emergency Department Sample, National Inpatient Sample, National Vital Statistics System.

Reference	Year(s) from which data sourced	Country/region	Source	Total ED attendances /year	ED attendance rate /100,000	Hospital admission rate /100,000	Head injury rate /100,000	Brain injury rate /100,000	Code set used
Jennet[35]	1974	England, Scotland, Wales	HES equivalent England, Scotland, Wales	---	1778	270	---	---	ICD-9
Klauber[62]	1978	San Diego County, California	Hospital discharge data	---	---	---	295	---	ICD-A
Jagger[63]	1978	North central Virginia	Hospital admission data	---	---	208	---	---	---
Fife[64]	1979	Rhode Island	Hospital discharge data			---	---	---	ICD-9-CM
Edna[42]	1979-1980	Trøndelag, central Norway	Hospital admission records	---	---	89	----	---	N/A
Whitman[65]	1980	Chicago, Illinois	Hospital discharge data	---	---	403	---	---	ICD-9-CM
Cooper[66]	1980	The Bronx, New York City	ED attendance data Hospital admission data Hospital discharge data	---	---	249	---	---	ICD-9-CM
Kraus[67]	1981	San Diego County, California	ED records, coroners' cases, death certificates, and nursing home records	---	---	---	---	180	ICD
Servadei[68]	1981-1982	San Marino	ED and hospital records	---	694	468	---	---	NA
Tennant[37]	1986	North West England	HES NWRHA	---	---	297	---	---	ICD-9
Leibson[69]	1987-1999	Olmsted County, Minnesota	Local hospital diagnostic coding system and manual case examination	---	---	---	---	558 (REPR) 341 (ICD-9-CM)	REPR ICD-9-CM
Tate[70]	1988	North Coast Health Region, New South Wales, Australia	Hospital discharge data & manual case examination	---	---	106	---	---	ICD

Sosin[47]*	1991	USA	NHIS	935,000	---	158	---	618	ICD
Phillips[60]	1991-2001	British Columbia, Canada	CIHI & Health Insurance Records (in patients only)	---	---	255 (1991) 128 (2000)	---	---	ICD-9
Jager[48]	1992-1994	USA	NHAMCS	1,144,807	444	---	---	---	ICD-9-CM
Ingebrigtsen[43]	1993	Tromsø, Northern Norway	Hospital admission records	---	---	---	229	---	N/A
Gordon[61]	1996-1997	Canada	NPHS	---	---	---	---	110*	N/A
Yates[41]	1997-2003	Single ED in Devon, UK	Hospital database	---	453	---	---	---	NHS Centre for Clinical Coding and Classification, based on ICD-10
Servadei[71]	1998	Romagna and Trentino, Italy	Hospital admission records	---	---	297 (Romagna) 332 (Trentino)	---	---	ICD-9
Shivaji[39]	1998-2009	Scotland	SMR01	---	---	Male 446 Female 195	---	---	ICD-10
Van den Brand[45]	1998-2012	Denmark	Dutch Injury Surveillance System	---	153 (1998) 267 (2012)	64 (1998) 125 (2012)	---	---	ICD-9-CM
Rickels[46]	2000-2001	Hanover and Münster, Germany	ED and hospital records	6783	332	242	---	---	ICD-10
Ryu[58]	2001	Ontario, Canada	ED and GP records	---	---	---	---	426	ICD-9
Tennant[38]	2001-2003	England	HES	---	---	229	---	---	ICD-9
Fu[59]	2002-2010	Ontario, Canada	NACRS	---	1014 (2002) 979 (2009)	---	---	---	ICD-10
Faul[52]	2002-2006	USA	NHAMCS	1.4m	468	94	---	---	ICD-9-CM

Rutland-Brown[51]	2003	USA	NHAMCS (for ED attendance) NHDS (for in-patient episodes) NCHS (for mortality data)	1.2m	420	99	---	---	ICD-9-CM
Pearson[55]	2006-2008	USA	NHAMCS-ED	1.6m (2006) 1.7m (2007) 2.1m (2008)	---	---	---	---	ICD-9-CM
Taylor[57]	2007 & 2013	USA	HCUP NEDS, HCUP NIS & NVSS	2.8m (2013)	534 (2007) 787 (2013)	88 (2007) 85 (2013)	---	---	ICD-9-CM (ED attendance, admission) ICD-10 (TBI related death)
Korley[56]	2009-2010	USA	NHAMCS	2.5m	---	---	---	---	ICD-9-CM

Table 1.3 Emergency department attendance and hospital admission rates for head and traumatic brain injury
ED, Emergency Department; HES, Hospital Episode Statistics; ICD-9, International Classification of Diseases, 9th Revision; ICD-A, International Classification of Diseases Adapted; REPR, Rochester Epidemiology
Project Records; NWRHA, North West Regional Health Authority; NHS, National Health Service; NHIS, National Health Interview Survey; SMR01, Scottish Morbidity Record; ICD-10, International Classification of Diseases, 10th Revision; NHAMCS, National Hospital Ambulatory Medical Care Survey; NHAMCS-ED, National Hospital Ambulatory Medical Care Survey– Emergency Department; ICD-9-CM, International Classification of Diseases, 9th Revision Clinical Modification; NHDS, National Hospital Discharge Survey; NCHS, National Center for Health Statistics; NACRS, National Ambulatory Care Resource System; HCUP, Healthcare Cost and Utilization Project; NEDS, Nationwide Emergency Department Sample; NIS, National Inpatient Sample; NVSS, National Vital Statistics System; CIHI, Canadian Institute of Health Information; NPHS, National Population Health Survey. * mild and moderate TBI only

Outcomes following head injury

Mild TBI results in a constellation of symptoms including headaches, cognitive dysfunction and emotional lability (Table 1.4). Although there are many validated tools available to measure such symptoms, application of the tools can sometimes only be performed by a neuropsychologist and may take several days to complete. Interpretation of the results may also only be done by a specialist, making the results difficult to utilise by wider healthcare professionals. Patient centred outcomes represent a more practical measure and are easy to understand for patients and physicians.

CSI	RPQ	Common to both
Headache	Headaches	Yes
Nausea	Nausea	Yes
Balance problems/Dizziness	Feelings of dizziness	Yes
Fatigue	Fatigue	Yes
Drowsiness		No
Feeling like “in a fog”		No
Difficulty concentrating	Poor concentration	Yes
Difficulty remembering	Forgetfulness	Yes
Sensitivity to light	Light sensitivity	Yes
Sensitivity to noise	Noise sensitivity	Yes
Blurred vision	Blurred vision	Yes
Feeling slowed down	Taking longer to think	Yes
	Being irritable	No
	Double vision	No
	Feeling depressed	No
	Feeling frustrated	No
	Restlessness	No
	Sleep disturbance	No

Table 1.4 Comparison of two commonly used checklists of symptoms of mild TBI

CSI, Concussions Symptom Inventory; RPQ, Rivermead Post-Concussions Questionnaire.

Return to work

Return to work is a key outcome measure following mild TBI. Being unable to work impacts negatively on an individual's wellbeing and on the greater economy.[72] Mild traumatic brain injury has a significant impact on when and whether patients return to work. Some researchers estimate a third of patients with mild TBI that were previously employed were unemployed at three months follow up.[3] On top of sustaining mild TBI, if the patient sustains further extra-cranial injuries, they are at risk of increased limitation in function and resume work less frequently than those without extra-cranial injuries.[73] The main barriers to returning to work following mild TBI are headaches, visual deficits, pain syndromes, dizziness, and postural instability, but return to work is also affected by age, multiple injuries, intracranial haemorrhage, and fatigue ratings.[74,75] The indirect costs, i.e. cost of resources lost owing to illness, associated with TBI in Europe is estimated at around €20 billion a year.[76] Return to work is a pragmatic real-world outcome with direct relevance to patients and quality of life, and thus a clear understanding of the numbers of patients that return to work is essential.[77-79] As an outcome it has some limitations, including variation in how it is defined. For instance, when a patient returns to work after mild TBI, they may not return full time or to the same physical or mental activities that they performed prior to the injury. Furthermore, in its purest sense, that is, when defined in terms of employed work, it only applies to people that were in employed work prior to injury. However, the definition is often extended to include studying, and extended further to include usual daily activities. The extension of the definition has worth in that it includes more patients, but at the expense of precision, as definitions of usual activities or activities whilst studying are not possible to

apply consistently. Nevertheless, as an indicator of improvement, return to work is a valuable outcome measure following mild TBI.

Mortality

Although trauma is the leading cause of death in males below the age of 65, mild TBI rarely results in death. Deaths attributable to head injury are ascertained from International Classification of Diseases codes, although there are inherent problems with this classification system, such as the large number of codes that cover head injury or TBI. They are not mutually exclusive and provide no clinical data and no data on injury severity. Deaths attributable to injury vary widely between countries. In the mid-1980s, France had the greatest death rate due to injury out of eight developed countries at 7% and England the lowest at 2%.[80] From 1979 to 1992, an average of 52,000 US residents died each year due to TBI, although the rate declined over this period from 25 to 19/100,000 population over this time.[81] The mechanism of injury also changed over this period with an increase of 13% in firearm related injuries and a decrease of 25% in motor vehicle related injury. Of almost 3000 patients admitted to hospital with TBI in Glasgow, 90% had mild TBI. At one year follow up, increased severity of injury at admission was associated with increased rate of death and vegetative state, and decreased rate of good outcome.[82] However, initial TBI classification was not associated with rates of severe or moderate disability which, when combined was similar in each group (47% in mild TBI, 45% in moderate TBI, 48% in severe TBI). These results are striking in that they imply that at one year after injury, patients that had even a mild TBI still had high rates of disability, comparable to patients with moderate or severe TBI. This is in contrast to the results of a systematic review in which significant neurological outcomes such as

unprovoked seizures, Parkinson's disease, and dementia were associated with moderate and severe TBI but not with mild TBI.[83] The finding that seizures are rarely associated with mild TBI was reproduced in a study of 2005 patients with mild TBI, of which only two patients (0.1%) developed seizures.[84]

Pathophysiology of mild traumatic brain injury

Biomechanics

When the head sustains an impact, it rapidly accelerates then decelerates. There is relative motion between the brain and the skull which causes tension and pressure gradients within brain tissue. If limits of toleration are exceeded, injury can occur. In human cadaveric heads to which concussive impacts were administered, there can be a brain-skull displacement of up to 7 mm.[85,86] Two types of accelerations, linear and rotational, are thought to be related to brain injury. Furthermore, they are thought to result in different injuries.[87] Linear acceleration is thought to result in pressure gradient changes and focal injuries, whilst rotational acceleration causes shear forces at the skull-brain interface and results in more diffuse injury.[88] In reality, both linear and rotational forces are applied to individuals as they suffer a head injury, and both types of force will contribute to mild TBI.[89] The point on the head on which the impact is sustained is also important. Lateral and rear impacts create rotational accelerations that are up to 30% higher than frontal impacts.[90] Lateral impacts cause high strain in the corpus callosum, whereas frontal impacts of the same energy results in high strain in the midbrain.[90] In addition to whether the impact creates linear or rotational movement, the duration of the acceleration-deceleration, and whether the direction in which the head moves is coronal or sagittal is also critical.[91,92] Sustained acceleration-deceleration causes displacement of the cytoplasm leading to intra-axonal damage to the neurofilament subunits, failure of the axonal cystoskeleton, and diffuse axonal injury.[93] Current understanding of biomechanical thresholds for injury comes from sports in which athletes wear helmets with impact measurement devices such as the Riddell Head Impact

Telemetry System sensor device or the six-degree-of-freedom system are the two most commonly used research systems.[94] A mean peak linear acceleration of 100g, and rotational acceleration of 5776 rad/s^2 have been identified as theoretical thresholds for injury.[95,96] However, a definitive concussion threshold is probably not possible to determine as levels of acceleration greater than 200g have been recorded in elite athletes with no reported concussion.[97]

Cellular changes

A mild TBI is the result of energy, in the form of a physical strike, imparted either directly to the head, described as contact forces, or to another part of the body, with the energy transmitted through the body to the brain, described as inertial forces.[98] There are multiple mechanisms occurring at a cellular level that result in altered neuronal function (Figure 1.3). Damage to deep white matter tracts, which result in diffuse axonal injury, are a consequence of rotational forces around a fixed fulcrum, thought to be the brainstem.[92] The energy transmitted through the brain causes damage to the axolemma, the plasma membrane of the axon, resulting in microscopic pores which in turn alter the permeability of the axolemma.[99-101] Unchecked ionic fluxes and a simultaneous indiscriminate release of neurotransmitters occurs.[102] Potassium then moves extracellularly, and calcium and sodium intracellularly.[103] During this early period (up to about 20 minutes after injury), extracellular potassium levels continue to increase.[104] Under normal circumstances, the potassium would be absorbed by surrounding glial cells, but in the context of TBI this does not happen.[105] Simultaneously, non-specific depolarisation results in glutamate (an excitatory amino acid) release which in turn increases the potassium efflux from the cells by activating multiple neurotransmitter receptors.[104] In the acute

phase, in response to altered membrane potential as a consequence of the ion shifts, axolemmal energy-dependent voltage and ligand gated ion channels, such as sodium-potassium pumps, increase work, thereby increasing the demand for adenosine triphosphate, with consequent increased glycolysis.[106] This hypermetabolic state lasts about half an hour after mild injury and up to four hours following severe injury.[107]

Energy applied to the brain during the instant of impact results in damage to microstructural components of the brain, including axons, dendrites, dendritic connections, and astrocytic processes.[107] The elevated intra-axonal calcium concentration results in neurofilament phosphorylation and collapse of axonal structure.[100] Points on the axonal cell membrane at which intracellular microtubules anchor are mediated by integrins and other proteins, and may be a specific point of molecular damage following injury.[108,109] These physical, neurotransmitter and neurometabolic changes lead to axonal dysfunction, disconnection and death.[99] In addition, an inflammatory response occurs after mild TBI as a result of upregulation of inflammatory and cytokine genes, leading to oxidative stress and potentially to cellular injury, described as 'immunoexcitotoxicity'.[110]

These pathophysiological changes have been postulated to be correlated with clinical symptoms. Migraines, headaches, photophobia and phonophobia are thought to be associated with ionic flux; axonal injury and altered neurotransmission with impaired cognition and slowing of reaction times; and altered cytoskeletal proteins and cell death with chronic or persistent impairments.[107]

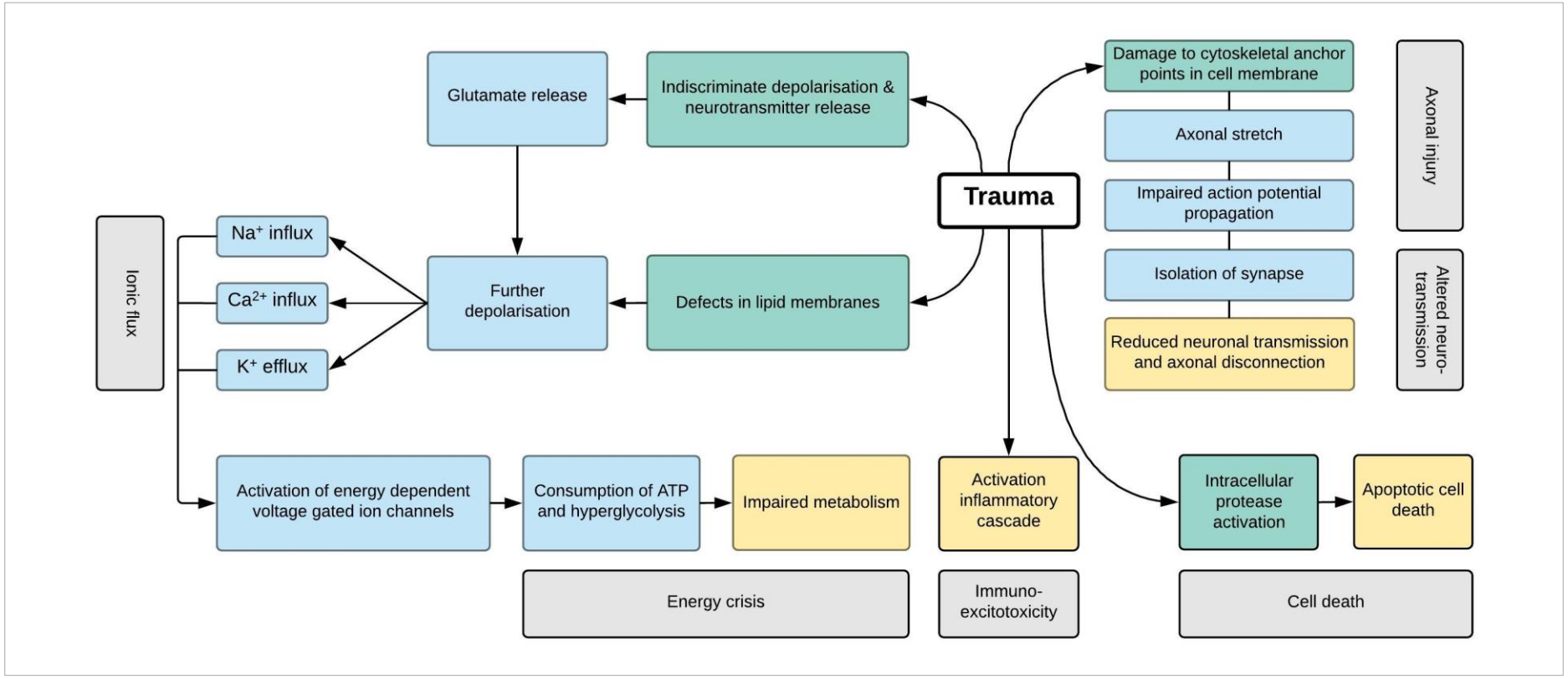

Figure 1.3 Neurometabolic changes in traumatic brain injury

Cerebral autoregulation

Traumatic brain injury affects cerebral vascular autoregulation. Cerebral autoregulation is often described in the form of the cerebral autoregulation index. This is a function of cerebral vascular resistance and mean arterial blood pressure. Cerebral vascular resistance is in turn a function of middle cerebral artery flow velocity and is usually measured using transcranial Doppler ultrasound. The cerebral autoregulation index ranges from one (perfect autoregulation) to zero (absent autoregulation).[111] Cerebral autoregulation was profoundly affected in a patient that was hit by a car and suffered a brief concussion.[111] Six days after the injury, during elective anaesthesia for a knee operation, there was no change middle cerebral artery flow velocity in response to inducing a rise in mean arterial blood pressure by infusing phenylephrine. A normal response would have been to see maintenance of constant middle cerebral artery flow velocity but in this case, there was a rise in flow velocity which matched the rise in mean arterial blood pressure, and a calculated cerebral autoregulation index of zero, indicating absent cerebral autoregulation.

In 29 patients with mild TBI and 29 age matched controls, transcranial Doppler ultrasonography of the middle cerebral arteries was performed within 48 hours injury.[112] A blood pressure cuff on each leg was inflated to levels higher than systolic pressure, then rapidly deflated, triggering a sudden drop in systemic BP. The normal response to this would be to reduce overall cerebrovascular resistance which would in turn restore cerebral blood flow to normal resting level. The changes in blood pressure and cerebral blood flow in the proximal middle cerebral arteries immediately before and after the cuff release were used to calculate the cerebral autoregulation index. Eight of the 29 patients with mild

TBI (but none of the 29 controls) had poorly functioning or absent cerebral autoregulation. Poor autoregulation was correlated with low blood pressure but not with any peri- or post-injury factors. Furthermore, disrupted cerebral autoregulation has been described in concussed athletes 72 hours after injury.[113] In this group reduced cerebral autoregulation also appeared to be associated with symptoms. The theory that altered cerebral autoregulation is associated with symptoms is supported by the finding that in adolescents with mild TBI, cerebral autoregulation was initially reduced and gradually improved as symptoms resolved, such that autoregulation was normal and symptoms completely resolved by 12 weeks.[114] Cerebral autoregulation abnormalities also may persist beyond perceptible clinical recovery. In 18 athletes that sustained a concussion, there was impaired autoregulation that persisted at 14 days but had resolved by a month, and in whom all were cleared to return to play by 14 days.[115] However not all patients with mild TBI have reduced middle cerebral artery flow velocity. In a small study of six adolescent patients with sports related TBI, flow velocity was measured and a change in mean arterial blood pressure was triggered by a change in position from supine to upright.[116] Middle cerebral artery flow velocity was reduced in three patients, elevated in two patients.

Abnormalities detectable on magnetic resonance imaging

Magnetic resonance imaging techniques

Diffusion tensor imaging (DTI), also known as diffusion weighted magnetic resonance imaging (MRI), is an MRI technique in which multi-directional magnetic field gradients are used to describe the movement of water molecules in tissue. In cerebrospinal fluid water molecule movement is essentially unrestricted, since it can occur in any direction. This is termed isotropic diffusion. In axonal tracts, because the cell membrane and myelin sheath represent a relatively impermeable barrier to water, movement is restricted to the direction of the tract. This 'unequal' movement is termed anisotropic. As water moves along the directions of the magnetic field gradients, the MR signal of diffusing hydrogen protons is attenuated in proportion to the movement along the gradient. Diffusion can then be modelled in three dimensions in an ellipsoid (also known as a tensor).[117,118] There are several metrics used to describe anisotropy. Fractional anisotropy is a quantification of the degree of anisotropy, that is, the degree to which water molecules travel along the main axis of the ellipsoid. Fractional anisotropy ranges from zero to one, with one meaning movement in a single direction (along the axis of the ellipsoid), and zero meaning wholly isotropic movement, i.e. movement in any direction in a perfect sphere. Other commonly used DTI variables include mean diffusivity (average amount of diffusion irrespective of direction), axial diffusivity (diffusion along the main axis of the ellipsoid), radial diffusivity (average of diffusion in the two other axes), and the apparent diffusion coefficient, which is a measure of the impedance of water molecule diffusion. Fractional anisotropy is a commonly reported measure in mild TBI but is limited by the requirement that fractional anisotropy measurements are extracted from pre-defined white

matter tracts or anatomical regions of interest. If a lesion exists outside of the region of interest it will not be apparent in the fractional anisotropy analysis.[118] To circumvent this limitation, the entire brain volume can be assessed using a voxel-by-voxel (also known as voxelwise) approach. A voxel is a pixel volume in the three-dimensional space of the MR image. A limitation to the voxelwise approach is that it requires standard registration algorithms for analysis. This method does not easily allow alignment of multiple subjects' fractional anisotropy images in a way that allows valid conclusions to be drawn from the subsequent voxelwise analysis. A solution to this is a technique called Tract Based Spatial Statistics, which aims to improve the sensitivity, objectivity and interpretability of analysis of multi-subject diffusion imaging studies.[119] Graphical model based multivariate analysis is sometimes used as a complement to the tract based spatial statistics approach of identifying neuronal tract abnormalities. Graphical model based multivariate analysis is a Bayesian multivariate technique that can identify voxels that are predictive of group, for instance mild TBI or control, at an individual patient level rather than at a group level.[120-122]

Different white or grey matter tracts have different normal fractional anisotropy ranges. An abnormal fractional anisotropy can be higher or lower than the normal range. An elevated fractional anisotropy, that is, more unidirectional water movement than would be expected, might reflect inflammatory changes such as axonal swelling or cytotoxic oedema.[123,124] A lower than normal fractional anisotropy, representing more multi-directional water movement, might reflect axonal degradation, axonal discontinuity, or increased water in the interstitial space.[125]

Susceptibility weighted imaging is an MR technique that is especially sensitive to changes in the local magnetic field. This makes it particularly useful in detecting microhaemorrhages in mild TBI.

Arterial spin labelling is an MR technique that provides a measure of blood flow without using intravenous contrast. To obtain the measure of cerebral blood flow, a conventional MR sequence is first performed. Following conventional imaging, blood water protons, which are outside of the region of interest that is being imaged, are saturated or have their magnetisation inverted. This gives them a magnetic label. Images are then acquired after enough time has passed to allow the labelled protons within blood water to flow into the region that is being imaged. When the two images are subtracted, cerebral perfusion can be demonstrated, which in turn can be associated with cerebral blood flow.[118]

Neuronal tract abnormalities

A PubMed search using the terms ((((tract abnormality[Title/Abstract]) OR diffusion tensor imag*[Title/Abstract]) OR dti[Title])) AND ((((mtbi[Title/Abstract]) OR mild tbi[Title/Abstract]) OR mild traumatic brain injury[Title/Abstract]) OR concussion[Title/Abstract]) identified 361 articles, of which 23 were identified as relevant to describing neuronal tract abnormalities in mild TBI (Table 1.5). All studies included a comparator group acting as a control, some of which were healthy volunteers and some of which were patients with musculoskeletal injuries, often described as orthopaedic controls. The number of patients with mild TBI enrolled in each study ranged from eight to 102, with a median of 33 patients included. More recently published studies tended to include more patients. Two studies reported the results of MRI performed on the day of injury, eight within a week of injury, five

within one and two weeks of injury, four within two and four weeks of injury, one within one and six months of injury, one more than a year after injury and two did not specify when the scan was done (Figure 1.4).

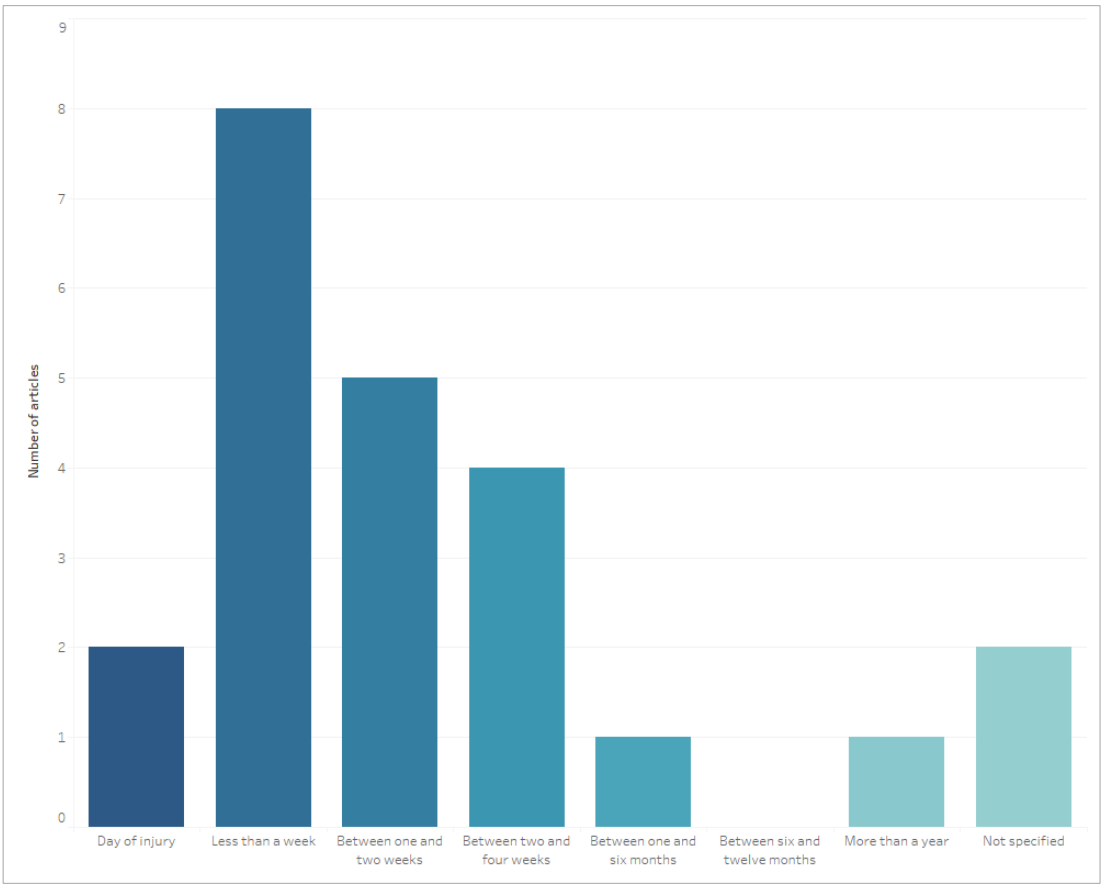

Figure 1.4 Number of studies by time of MRI

Eighteen of the 23 studies reported changes in fractional anisotropy. Nine of those 18 reported increased fractional anisotropy. The specific white matter tracts affected that displayed increased fractional anisotropy were frequently in the corpus callosum and particularly in the genu and splenium of the corpus callosum, the corona radiatae bilaterally, uncinate fasciculus, the frontal lobes, and the middle cerebellar peduncles and pontine crossing tract (Figure 1.5 and Figure 1.6).[126-133] Twelve of the 17 studies reported decreased fractional anisotropy. As in studies that described increased fractional anisotropy,

decreased fractional anisotropy was also noted in the corpus callosum, corona radiatae bilaterally, the uncinate fasciculus, and the frontal lobes. In addition, decreased fractional anisotropy was also noted in the left superior temporal gyrus, internal and external capsules, and the inferior longitudinal and inferior fronto-occipital fasciculi.[125-128,134-141] Three studies reported both increased and decreased fractional anisotropy in different regions of the brain.[126-128]

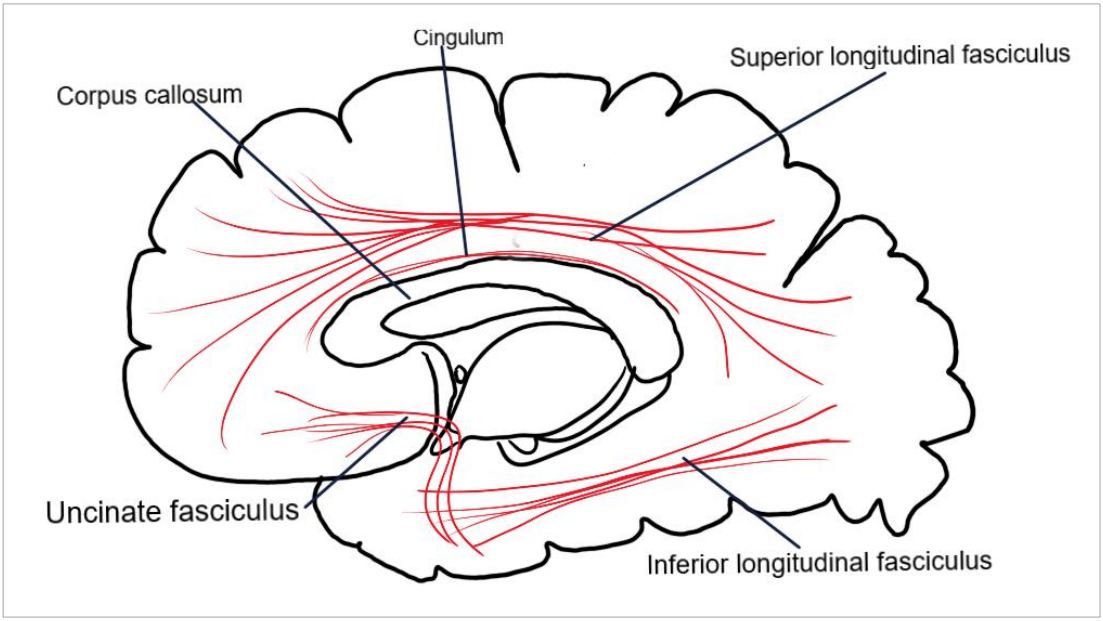

Figure 1.5 Sagittal view of brain showing fasciculi

Two studies reported increased mean diffusivity, and this was noted in the right uncinate fasciculus, posterior limb of the internal capsule, optic radiation & splenium (Figure 1.6 and Figure 1.7).[139,142] One study reported decreased mean diffusivity, and this was in the frontal lobe.[125] Three studies reported increased radial diffusivity, and this was in the corpus callosum, the corona radiatae, and the internal external capsules.[136,141,143] In one of these studies an increase in radial diffusivity was only seen in complex mild TBI compared with controls.[141] One study reported reduced radial diffusivity, and this was seen in the genu, left corona radiata & left uncinate fasciculus.[131]

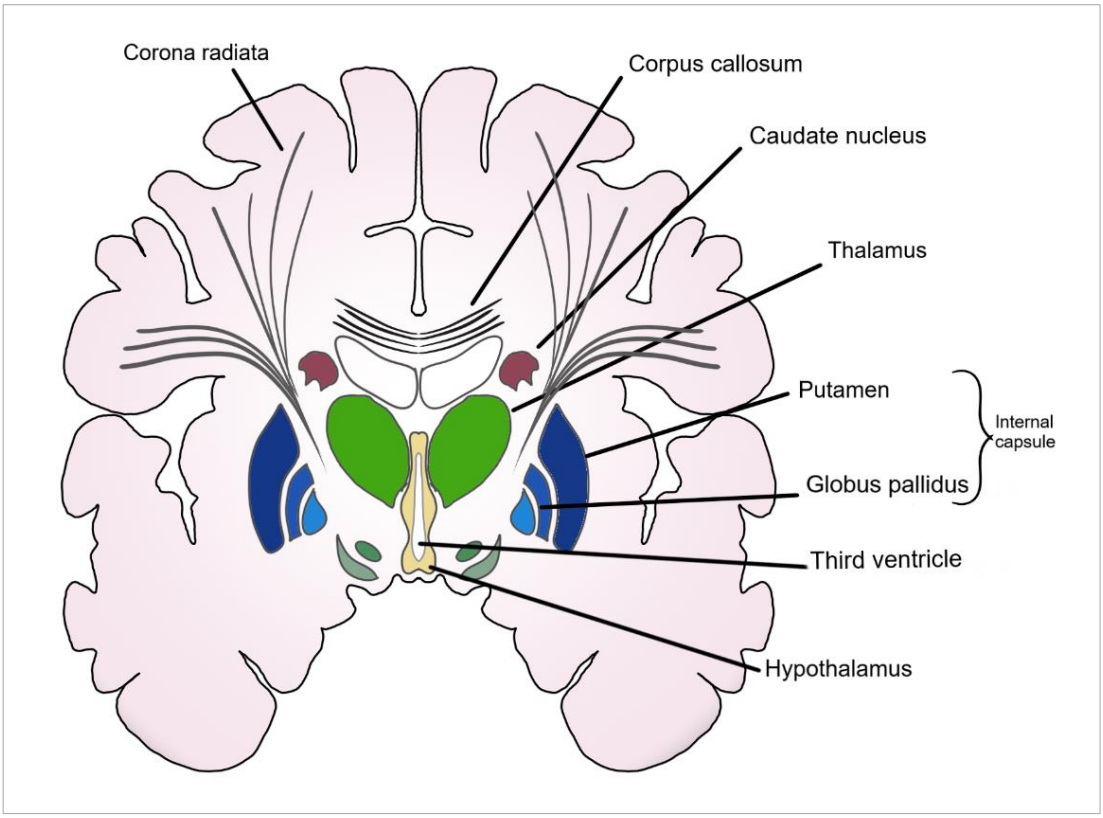

Figure 1.6. Coronal section through basal ganglia

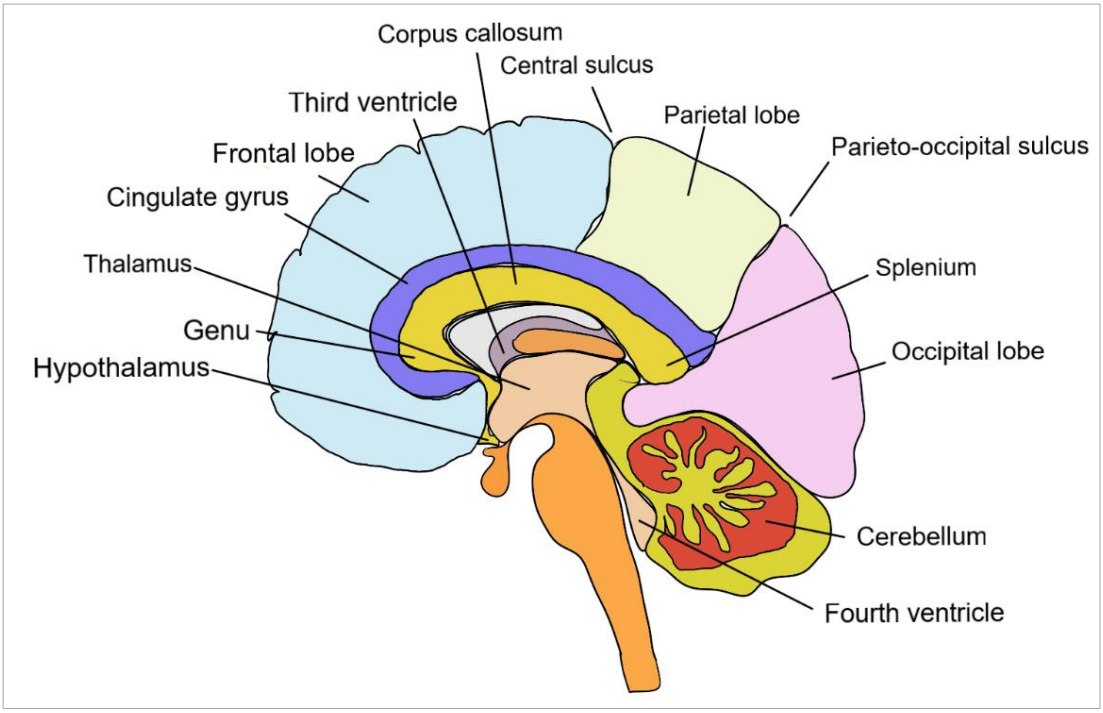

Figure 1.7. Sagittal section through midline

Although there is little consistency in whether the measures of diffusion are increased or decreased, there is some consistency in the region of the brain affected, with the corpus callosum most frequently affected (Figure 1.6). Furthermore, any change in diffusivity indicates injury, with an increase in diffusivity potentially indicating oedema and a decrease potentially indicating tract disruption or axonal discontinuity. This suggests that in mild TBI the corpus callosum is most frequently affected and this could either be by developing oedema after injury, or by individual neurones becoming disrupted. That this deep structure of the brain is commonly affected is consistent with biomechanical models of brain injury, in which deep structures such as the corpus callosum are subject to the highest strain forces as a result of lateral impacts.[90] In contrast, in a study that included moderate as well as mild TBI, lower fractional anisotropy was noted in the corpus callosum, particularly in the more severely injured patients.[135] This was explained by the falx being elongated at the posterior portion of the corpus callosum, limiting posterior movement of the corpus callosum and consequently making it more susceptible to strain. The reduction in fractional anisotropy noted in this study, indicating increased multidirectional water movement, may be a consequence of callosal oedema.

Eight studies reported correlations or associations between neuronal tract abnormalities and neurocognitive test results. In 20 patients with mild TBI, executive function was inversely related to lower fractional anisotropy in the frontal lobes, whilst in 22 patients with mild TBI, elevated fractional anisotropy in the right hemisphere was positively associated with attentional deficits.[125,131] In this last study, there were no structural lesions identified on conventional MRI sequences. The elevated fractional anisotropy was postulated to be due to

cytotoxic oedema or changes in water content within the myelin sheath. This implies that subtle white matter tract lesions, in the absence of structural abnormalities seen on conventional imaging, account for persistent symptoms and signs observed in patients with mild TBI. The authors repeated their study and found only elevated fractional anisotropy in the genu to be consistently replicated.[130] When assessed at four months, there was recovery of several lesions, which correlated with a reduction in self-reported symptoms. Increased fractional anisotropy in white matter was also negatively correlated with cognitive function in 11 patients with mild TBI compared with controls, and with DTI lesion load in nine patients with mild TBI.[126,128] Lower fractional anisotropy in several regions including the corona radiata, superior longitudinal fasciculus and corpus callosum was positively correlated with deficits in attention, whilst lesions in the optic radiation were associated with deficits in spatial awareness.[139] Lower fractional anisotropy in the internal capsule was also associated with reduced cognitive processing speed in 33 patients with mild TBI.[140]

Reference	Number/condition	MRI technique & regions of interest scanned	Timing of MRI	Findings (change compared with control)	Regions affected & clinical correlates
Lipton[125] *2009*	40 20 (mild TBI) 20 (Control)	T1, T2 & voxelwise DTI None prespecified*	< 2 weeks after injury	FA reduced MD reduced	15 regions, 5 in frontal lobe Mild TBI patients had poorer neurocognitive test results than controls. Frontal lobe deficit correlated with executive function impairment.
Mayer[131] *2010*	76 22 (mild TBI) 21 (matched control) 32 (unmatched control)	T1, T2 & DTI Bilateral genu, splenium, and body of the corpus callosum, superior longitudinal fasciculus, corona radiata, superior corona radiata, uncinate fasciculus, internal capsule	Mean 13 days after injury 3-5 month follow up	FA increased RD reduced Normalisation at 3 months follow up of DTI measures.	FA increased in genu, left superior corona radiata, left corona radiata, & left uncinate fasciculus. RD reduced in genu, left corona radiata & left uncinate fasciculus. FA levels in the right hemisphere predicted variance in attentional deficits (positive relationship) for the mTBI group.
Matsushita[135] *2011*	47 20 (mild to moderate TBI) 27 matched control	T1, T2 & DTI genu, stem, and splenium of the corpus callosum, corona radiata, anterior & posterior limbs of internal capsule, frontal & occipital white matter	Median 3.5 days after injury	FA reduced	Reduced FA values in the genu, stem and splenium of the corpus callosum. FA in splenium associated with IQ at one year.
Ling[130] *2012*	58 29 (mild TBI) 29 (control)	T1, T2 & DTI Voxelwise analyses Bilateral genu, splenium, and body of the corpus callosum, superior longitudinal fasciculus, corona radiata, superior corona radiata, uncinate fasciculus, internal capsule	Mean 16 days after injury	FA increased	Genu of corpus callosum
Rao[137] *2012*	14 (mild TBI)	Voxelwise 31 areas of the brain	< 1 month after injury	FA reduced	Left superior temporal gyrus. Lower baseline FA in the superior and middle temporal gyri were predictive of depression over time. Higher MD scores in the right superior longitudinal fasciculus, inferior frontal & superior temporal white matter were predictive of depression over time.

Wilde[133] *2012*	8 (uncomplicated mild TBI)	T1, GRE, FLAIR & DTI Multiple ROI	MRI performed 4 times for each patient within 8 days after injury	FA increased	Not specified Impaired memory correlated with white matter tract abnormalities in some cases
Bouix[126] *2013*	22 11 (mild TBI with persistent PCS) 11 (control)	DTI Multiple ROI	62 ± 46 months	FA increased & decreased	Increased FA in grey matter Reduced FA in white matter Significant negative correlation between the digit symbol test (indicator of neurological dysfunction) & both FA severity & FA load. High PCS scores correlated with DTI findings
Kou[128] *2013*	9 (mild TBI)	T1, T2, GRE, FLAIR, SWI, DTI, fMRI Voxelwise	In ED	FA increased & decreased	Multiple regions. SAC scores were found to be inversely correlated with DTI lesion load.
Ling[129] *2013*	102 51 (mild TBI) 51 (control)	T1, T2, DTI, SWI Examined 12 frontotemporal cortical (grey matter) regions, & 2 white matter regions (thalami and hippocampi). Voxelwise	Mean 14 days after injury	FA increased	Bilateral superior frontal cortices on voxelwise but no difference in ROI analyses. TBI patients had increased cognitive, somatic, & emotional complaints but there was no association with the MRI abnormalities.
Siman[138] *2013*	38 17 (mild TBI) 13 (orthopaedic injury control) 8 (healthy volunteer control)	DTI ROI: corpus callosum, right and left uncinate fasciculi, and right and left frontal lobes	<4 days for 28/38 of participants	FA reduced ADC increased	FA reduced in corpus callosum & right uncinate fasciculus, and ADC increased in right uncinate fasciculus. SNTF serum biomarker. SNTF+ patients exhibited DTI findings.
Ilvesmaki[144] *2014*	115 75 (mild TBI) 40 (ankle injury controls)	T1, T2, FLAIR, SWI, DTI Voxelwise	<14 days (mean 5.8)	No differences	No association between MRI findings and clinical outcomes of amnesia or symptoms
Liu[145] *2014*	67 39 (mild TBI) 28 (control)	DTI, TBSS, GAMMA	< 7 days		GAMMA detected abnormalities in the right and left frontal lobes

Yuh[141] *2014*	126 76 (mild TBI) 32 (CT+ mild TBI) 44 (CT- mild TBI) 50 (control)	T1, T2, DTI Voxelwise & ROI	11.2 ± 3.3 days	FA reduced RD increased	Mild TBI: right internal and external capsules, genu of the corpus callosum, and uncinate fasciculi and anterior corona radiata bilaterally. Complex mild TBI: genu and body of the corpus callosum, the external capsules, uncinate fasciculi, and anterior corona radiata bilaterally, the right internal capsule, and the right inferior longitudinal and inferior fronto-occipital fasciculi. Increased RD in complex TBI compared with controls.
Alhilali[134] *2015*	74 mild TBI 45 (neuropsychiatric symptoms) 29 (no neuropsychiatric symptoms)	T1, T2, DTI TBSS & ROI	Not described	FA reduced	Depression: right nucleus accumbens, anterior limb of the internal capsule, and superior longitudinal fasciculus. Anxiety: cerebellar vermis.
Lange[143] *2015*	108 72 (mild TBI) 36 (trauma control)	DTI TBSS & multiple ROI	6-8 weeks after injury	RD Increased in PCS+ patients	Increased RD in genu, body, & splenium of the corpus callosum; bilateral anterior, superior, & posterior corona radiata; bilateral superior longitudinal fasciculus; bilateral cingulum; bilateral posterior thalamic radiations; bilateral anterior limb of the internal capsule; & bilateral external capsule. Increased MD in genu & body of the corpus callosum, bilateral superior corona radiata, right anterior corona radiata, right anterior & posterior limb of the internal capsule, & the right superior longitudinal fasciculus. Three groups – PCS+ mild TBI, PCS- mild TBI, & control. No difference in neurocognitive test results across groups. No difference in DTI measures between the two mild TBI groups.

Veeramuthu[139] *2015*	80 61 (mild TBI) 19 (healthy control)	DTI TBSS & ROI	Mean 10 hours & 6 months after injury follow up	FA reduced MD increased	FA reduced in splenium. MD increased in posterior limb of internal capsule, optic radiation & splenium in mild TBI compared to control. FA on day of injury in corona radiata, superior longitudinal fasciculus & genu negatively correlated with attention and language, RD in corona radiata & superior longitudinal fasciculus positively correlated with attention, optic radiation negatively correlated with spatial measures in neurocognitive tests.
Ghodadra[127] *2016*	64 40 (mild TBI with headache) 24 (mild TBI without headache)	DTI	Not described	FA increased & decreased	Mild TBI and post-traumatic headache: reduced FA in splenium and increased FA in genu of corpus callosum.
Wang[120] *2016*	84 47 (mild TBI) 37 (control)	DTI TBSS & ROI designed to identify cerebellar white matter tract injury GAMMA	< 7 days after injury	FA increased	TBSS analysis: higher FA in the middle cerebellar peduncle. ROI-based analysis: FA higher in middle cerebellar peduncle & pontine crossing tract. GAMMA analysis: abnormalities in middle cerebellar peduncle, pontine crossing tract, right & left inferior & superior cerebellar peduncles.
Wilde[142] *2016*	143 79 (CT- mild TBI) 64 (orthopaedic injured control)	DTI, SWI ROI including bilateral right uncinate fasciculi, bilateral inferior frontal occipital fasciculi, & the genu of the corpus callosum.	Mean 25.9 hours & 3 months after injury follow up	MD increased	Left uncinate fasciculus, right inferior frontal occipital fasciculus, and genu. MD higher in LOC+ than LOC- TBI patients in right uncinate fasciculus. No differences at 3 months, and orthopaedic controls improved, indicating resolution of tract abnormality by 3 months.
Mohammadian[136] *2017*	132 102 mild TBI 30 control	DTI Voxelwise	Mean 21 days	FA reduced RD increased	Not specified

Thomas[146] *2017*	36 20 (mild TBI) 16 (control)	DTI TBSS & ROIs including the splenium, body and genu of the corpus callosum, bilateral posterior limbs of the internal capsule, uncinate fasciculus, corona radiata & corticospinal tract.	<72 hours and 7-10 days follow up	FA increased	Splenium of corpus callosum.
Chung[147] *2018*	53 32 (mild TBI) 21 (controls)	DTI TBSS & compartment specific WMTI** metrics	Mean 17 days	Reduced intra-axonal diffusivity	Splenium of corpus callosum.
Yin[140] *2019*	64 33 (mild TBI) 31 (control)	DTI TBSS & ROI	<7 days and 1-3 months follow up	Reduced FA	Left anterior limb of the internal capsule and the right inferior fronto-occipital fasciculus, which improved by follow up. Test of cognitive information processing speed at baseline predicted recovery of structural integrity of left anterior limb of internal capsule & right inferior fronto-occipital fasciculus at follow up.

Table 1.5. Studies of neuronal tract abnormalities in mild TBI

MRI, magnetic resonance imaging; TBI, traumatic brain injury; Control, control; ASL, arterial spin labelling; CBF, cerebral blood flow; DTI, diffusion tensor imaging; FA, fractional anisotropy; MD, mean diffusivity; GRE, gradient recalled echo; FLAIR fluid attenuated inversion recovery; ROI, regions of interest; PCS, post-concussion symptoms; SWI, susceptibility weighted imaging; SAC, Standardised Assessment of Concussion; SNTF, calpain-cleaved αII-spectrin N-terminal fragment; ADC, apparent diffusion coefficient; TBSS, Tract-Based Spatial Statistics; GAMMA, Graphical-model-based Multivariate Analysis; LOC+, loss of consciousness at time of injury; LOC-, no loss of consciousness at time of injury; WMTI, white matter tract integrity.

*Voxelwise analysis allows identification of abnormal regions without pre-specifying the region.

**Compartment specific white matter tract integrity metrics include measures of microstructural characteristics in intra- and extra-axonal environments of white matter including the axonal water fraction; intra-axonal diffusivity along axons; extra-axonal AD; extra-axonal RD; and the derived tortuosity of the extra-axonal space.

Cerebral perfusion

A possible objective and reproducible abnormality detectable in patients with mild TBI could be alterations in cerebral blood flow. There is evidence from animal models that after a traumatic brain injury there are regional ischaemic areas and regions of reduced blood flow.[148,149] This is supported by the finding that in 21 patients with mild TBI, there was significantly lower cerebral blood flow to the thalamus compared with controls (Table 1.6).[150] The thalamus is a complex deep grey matter structure consisting of multiple groups of nuclei and white matter tracts. It acts as a relay station for transmitting information around the brain and is particularly vulnerable to acceleration-deceleration injury.[150] However this study was performed on average more than two years after injury. Lower cerebral blood flow was also seen in the cerebellum, cuneus, anterior and middle cingulate and middle temporal gyri in patients with mild TBI on average four months after injury.[151] In patients with mild TBI assessed on the day of injury, low cerebral blood flow was also described, as was low cerebral blood volume and increased blood mean transit time, in the frontal and frontotemporal regions.[152] Similarly in 18 concussed American football players, there was reduced cerebral blood flow in the supplementary and pre-supplementary motor areas on the day of injury.[132] Furthermore, when assessed eight days after injury there was reduced cerebral blood flow in multiple cortical regions and the hypothalamus. Several other studies also report reduced cerebral blood flow in patients with mild TBI, in deep structures including the insula and thalamus, and in cortical regions including frontal, temporal, parietal and occipital lobes.[132,153-155]

Although most studies describing cerebral blood flow in patients with mild TBI report it to be reduced, some report increased cerebral blood flow, and this discrepancy does not seem to be related to time from injury to scan. In 14 patients with mild TBI who were scanned on average 31 hours after injury, cerebral blood flow was increased in the left striatum, and particularly in the caudate, putamen, and pallidum.[156] The authors postulated that the unexpected increase in cerebral blood flow could be an early change in physiology associated with mild TBI since the patients were scanned so early. This theory is not supported by prior or subsequent evidence. Only one other study reported increased cerebral blood flow, and this was in athletes from several sports that had suffered a concussion. In this study, increased cerebral blood flow was found in posterior brain structures, including the cerebellum and occipital lobe.[157]

Few studies describe an association between clinical outcomes and changes to cerebral blood flow. Reduced cerebral blood flow in the frontal and occipital lobes correlated with increased nausea and dizziness at 12 days after injury.[153] Conversely in concussed athletes, increased posterior cerebral blood flow was associated with higher symptom scores.[157] Low cerebral blood flow in the frontal and frontotemporal regions was associated with lower executive function and lower social cognitive function.[152]

Reference	Number/condition	Imaging technique & Regions of interest scanned	Timing of MRI	Findings (change compared with control)	Regions affected & clinical correlates
Ge[150] *2009*	41 21 (mild TBI) 20 (control)	Conventional & ASL Bilateral thalamus, putamen, heads of caudate nuclei, frontal grey matter & white matter	24.6 months	Reduced CBF	Left & right thalamus. Reduced thalamic CBF significantly correlated with several neurocognitive measures.
Liu[151] *2013*	38 27 (mild TBI) 11 (control)	T1, T2, fMRI, DTI, SWI, spectroscopic and DSC perfusion imaging. DSC images acquired using gadolinium & manually & automatic arterial input function calculation.	113 ± 74 days	Reduced CBF	Left cerebellum, left cuneus, right anterior cingulate, right middle cingulate and left middle temporal gyrus.
Metting[152] *2014*	18 (mild TBI)	Perfusion CT	Mean 3.8 hours	Reduced CBF Reduced CBV Increased MTT	Patients with lower executive function had lower perfusion (lower CBV) in the right frontal white matter, & right and left frontotemporal white matter. Patients with poorer social cognitive function had lower perfusion (higher MTT) in bilateral frontal white matter, and (lower CBF) in left parieto-temporal grey matter.
Doshi[156] *2015*	32 14 (mild TBI) 18 (control)	SWIM, ASL	Median 31 hours Range 3 hours to 10 days	Increased CBF Increased blood oxygenation	Increased blood oxygenation in left thalamostriate vein & right basal vein of Rosenthal. Increased CBF in the left striatum, particularly the caudate, putamen, and pallidum.
Meier[154] *2015*	44 17 (concussed athletes) 27 (athletes without concussion)	ASL Voxelwise	Mean 1.4 days, 8.7 days, & 31.5 days.	Reduced CBF	Right dorsal mid-insular cortex and right superior temporal cortex at first time point compared to follow up and compared to non-concussed athletes. No association with clinical correlates.
Lin[153] *2016*	45 23 (mild TBI) 22 (control)	ASL ROI in bilateral frontal, parietal, temporal, & occipital lobes, bilateral anterior, middle & posterior cerebral artery & posterior cerebellar artery territories.	Mean 12 days.	Reduced CBF	Bilateral frontal cortices and left occipital cortex. Left frontal lobe CBF correlated with dizziness & nausea. Right frontal lobe & left occipital lobe CBF correlated with nausea.

Wang[132] *2016*	37 18 (American footballers with concussion) 19 (American footballers without concussion)	ASL	<24 hours and 8 days	Reduced CBF	Right supplementary motor area and pre-supplementary motor area regions at 24 hours. Cortical grey matter, in bilateral prefrontal regions, temporal lobes, parietal regions, & thalamus at 8 days CBF reduced further from baseline to follow up in TBI patients.
Churchill[157] *2017*	70 35 (athletes with concussion) 35 (athletes without concussion)	ASL	1 to 7 days	Increased CBF	Superior cerebellum, occipital lobe and cuneus. Higher symptom scores associated with increased posterior CBF.
Wang[155] *2018*	48 24 (athletes with concussion) 324 (athletes without concussion)	ASL	24-48 hours	Reduced CBF	Left inferior parietal lobule, right supramarginal gyrus, right middle frontal gyrus, posterior cingulate cortex, left occipital gyrus, and thalamus.

Table 1.6. Studies reporting cerebral blood flow in mild TBI

MRI, magnetic resonance image; TBI, traumatic brain injury; ASL, arterial spin labelling; CBF, cerebral blood flow; fMRI, functional magnetic resonance image; SWI, susceptibility weighted imaging; DSC, Dynamic susceptibility contrast; CT, computed tomography; CBV, cerebral blood volume; MTT mean transit time; SWIM, susceptibility weighted imaging and mapping; ROI, region of interest.

Functional neural network injury

Resting state functional MRI can be used to describe interactions between networks of neural regions. These interactions can be described using neurophysiological indices which correlate when measured at the same time in different brain areas.[158] The interaction is calculated by determining functional connectivity, defined as "The temporal correlation of a neurophysiological index measured in different brain areas".[159] One resting state network is the Default Mode Network and another the Task Positive Network, also known as the executive network. The default mode network consists of several regions including the anterior and posterior cingulate cortices, lateral parietal cortex, and the medial prefrontal cortex.[160,161] These are active during resting state conditions but consistently deactivated during task-based activity.[162] In contrast to the default mode network, the task positive network includes the dorsolateral prefrontal cortex and posterior parietal cortex and is operative during externally directed activity.[163] In patients with mild TBI, the default mode network is not affected in the acute phase, but in the chronic phase there is increased resting-state functional connectivity.[158] Consistent with this, in patients with ongoing post-traumatic complaints, there is higher functional connectivity between the anterior and posterior elements of the default mode network, which was associated with a higher number of post-traumatic complaints at three months.[164] The authors speculated that relatively higher functional connectivity in the default mode network in patients with mild TBI could reflect ongoing internally focused mental activity including thoughts about the injury and recovery. Furthermore, since the default mode network is associated with spontaneous thought processes like daydreaming and envisioning past and

future events, activation of the default mode network may present a barrier to recovery or response to therapy in patients with mild TBI.[164-166]

In summary, diffusion tensor imaging and arterial spin labelling, two relatively recent imaging techniques, hold promise for developing an objective and consistent measure of mild TBI. Based on these techniques, deep brain structures appear to be injured more frequently than superficial structures. Furthermore, tests of cerebral autoregulation, which are relatively cheap and non-invasive, may also be correlated with symptoms and predictive of outcomes. Association and correlation with clinical outcomes have been inconsistently described in several mild TBI populations including patients identified in the Emergency Department and individuals that have experienced sports related concussion. Further development of these procedures may result in a test for mild TBI.

Neurocognition in mild traumatic brain injury

Symptoms following mild TBI

The burden of symptoms that patients experience following a mild TBI cause the most significant impact on quality of life. The constellation of symptoms is complex and includes pain and cognitive dysfunction. In 538 patients with mild TBI, persistent headaches were the most common symptom (79%), followed by memory problems (59%).[3] In 145 patients with concussion, 51% had one or more symptoms six weeks later, the most common of which was headache (24%), followed by anxiety (19%), insomnia (15%) and dizziness (14%).[10] Patients with mild TBI also have more disturbed sleep than patients with severe TBI.[167] In 689 patients with mild TBI, more than half had one or more symptoms at three months after injury, and the most common symptoms were fatigue, sleep disturbance and headaches.[11] In 123 patients with mild TBI, at one week the most common symptom was also fatigue, followed by headache.[12] In 94 patients with mild TBI, headache, followed by fatigue, dizziness, and taking longer to think, were the most common symptoms both in the Emergency Department and at one month follow-up.[13] Loss of consciousness at the time of injury, and post-traumatic amnesia following injury, are both associated with recovery times following mild TBI of over one week.[168]

Cognitive difficulties following mild TBI

Mild TBI causes difficulty in thinking. Broadly there are two ways of objectively assessing subjective cognitive deficits; using self-report scores, and specific tests of neurocognitive function. The domains which these assessments occupy are numerous, and include assessments of fatigue,[169] stress,[169] depression,[74]

symptoms,[170] intelligence,[171] memory,[172] learning,[173] attention and executive function,[173] processing speed,[174] and reasoning.[172]

In 57 patients with minor head injury, memory and information-processing was reduced at baseline but improved to the same level as a control group by three months.[175] In 62 patients with concussion, attention, measured three times in the Emergency Department, was persistently reduced compared to normal levels.[176] In 25 Emergency Department patients with mild TBI, visual motor speed and reaction times were low compared with controls, but there was no difference in the other two assessment domains, verbal and visual memory.[177] In an assessment of patients with severe burns injuries, grouped into those with mild TBI and those without, the mild TBI group had significantly worse processing speed.[178] In 123 patients with mild TBI, visual memory was significantly worse in the Emergency Department at one week, and at three months, compared with non-head injured controls.[12] In 29 patients with mild TBI, immediate and delayed memory was worse than non-head injured controls, and head injured patients also had significantly worse symptoms scores.[179] Even when symptoms resolve however, neurocognitive dysfunction may persist. In athletes with mild TBI, the mean time to become asymptomatic for concussion was 6 days, but 38% of asymptomatic athletes had ongoing neurocognitive deficits.[180]

The time taken for resolution of neurocognitive deficits is unclear and reports vary from just over a week to six months or more. In 28 athletes with concussion, neurocognitive function resolved by day eight following injury, and in 400 athletes with a history of concussion but no concussion within six months preceding assessment, there was no measurable neurocognitive deficit,

implying that the neurocognitive deficit completely resolves by six months.[181,182] In contrast, in 94 Emergency Department patients with mild TBI, 63% still had concussive symptoms at follow up a month later, and in a separate cohort of 795 Emergency Department patients with mild TBI, most had concentration and memory disorders six months later.[13,183] In a large literature review that included 120 articles, cognitive defects and post-concussion symptoms had resolved in the majority by three to twelve months.[184] Furthermore, in those patients in which resolution had not occurred, only litigation was identified as a factor associated with ongoing symptoms.

Age as a factor in predicting severity of outcome following mild TBI remains controversial. In 190 patients with TBI there was no difference in neurocognitive function of mild TBI cases of greater and lesser age, indicating that age may not be an important predictor of neurocognitive function following mild TBI.[185] However, in a separate cohort recruited from the Emergency Department older and younger patients did have greater symptom severity and number than a middle group aged 35-54 years at three month follow up.[11] TBI can also increase the risk of developing psychiatric sequelae. Having a history of three or more concussions is associated with a three times increased chance of being diagnosed with depression than having a history of no concussions.[186] In a comparison of patients with dementia that had and had not sustained a TBI there was an increased risk of dementia in the group that had previous TBI.[187] Mild TBI following motor vehicle collision predisposed to a range of psychiatric disorders including personality disorder, persistent altered consciousness, post-traumatic stress and psychodynamic reactions to impairment.[188]

There is also an association between having post-concussion symptoms and having a neurocognitive deficit. Following a mild TBI, patients with symptoms perform more poorly on neurocognitive testing than patients without, although patients without symptoms may still perform more poorly than controls.[189] Athletes with mild TBI that take more than ten days to become asymptomatic also have poorer neurocognitive function compared with athletes with mild TBI that recover within ten days.[190] Conversely, the absence of premorbid physical problems, low levels of post-concussion symptoms, and no post-traumatic stress early after injury are associated with low levels of late post-concussion symptoms.[169] Similarly, having been educated for 11 years or more, the absence of nausea or vomiting, no additional extra-cranial injuries and low levels of pain early after injury are associated with a 90% chance of full return to work.[169]

Assessment of cognitive function and symptoms in the acute phase

In 1997, the American Academy of Neurology published guidelines on the management of concussion in sports and within it was a call for a standardised assessment of concussion.[191] In response, an examination containing assessments of orientation, immediate memory, concentration and delayed recall was devised, and termed the Standardized Assessment of Concussion (Appendix 2).[192] This is a 30 point tool with higher scores indicating better neurocognitive function (Table 1.7). An initial evaluation found differences between American football players with concussion and those without of 4.2 points, with most of the difference being in the immediate memory domain.[192] Validation usually takes the form of a larger set of baseline SAC scores, performed on all players, and a smaller set of post-concussion scores, taken only from head injured players. The tool was validated in several studies that

included concussed and non-concussed athletes. There were differences between concussed and non-concussed players of 3.7 points, and all domains were significantly different between the two groups.[193-200] Importantly, a decrease of 1.7 points was calculated to be sufficiently sensitive and specific to discriminate between concussed and non-concussed groups. Since this is an aggregate score, and an individual cannot score a fraction of a point, a change of 2 points can be taken as being clinically significant. This was confirmed in a review that concluded a change of two to four points was the most common change seen before and after injury.[201] The first validation in patients rather than athletes was from a mild TBI clinic associated with the US military.[202] Crucially, the assessment was not performed at the time of the head injury, but, on average 100 to 135 hours after injury. SAC scores were lower by 2.65 points in patients that had post-traumatic amnesia compared to those that hadn't, but absolute scores were not reported. The first investigation of the SAC in the Emergency Department was on 62 patients with concussion and negative CT head scan (Table 1.7).[176] Measurements were made at arrival then at three and six hours, and cognitive function improved from 21.0 to 23.5 points over six hours. In a second study of Emergency Department patients, the SAC was performed a median of 30 hours after injury and at one month follow up. Included patients had mild TBI (WHO definition) and orthopaedic injuries, the latter recruited as a non-head injured comparison group. At baseline, the SAC in the mild TBI group was 25.3, which improved by 1.4 at follow-up one month after injury.[203] These patients also differed from the comparison group, which had an average initial SAC score 2.4 points higher that mild TBI patients, at 27.3 points. These results were partly replicated in a small study of 26 Emergency Department patients with mild TBI and 33 patients with ankle injury, recruited

as a comparison group. [204] In this study, the SAC was measured only once. However, the time of measurement was different in the two groups; in the mild TBI group the SAC was measured in the Emergency Department, but in the ankle injury group it was measured 1-2 years after the injury. The mild TBI and ankle injury groups had average SAC scores of 26.00 and 27.7 respectively. In the first assessment the SAC in mild TBI patients grouped by CT scan 262 patients were recruited into four groups; CT positive (acute trauma related pathology visible on CT), CT negative (no acute abnormality on CT), healthy non-injured group comparator, and a comparison group that had sustained musculoskeletal injuries.[205] A single measurement was taken in the Emergency Department. The CT positive, CT negative, musculoskeletal injury, and healthy controls scored 21.4, 22, 24.3, and 26 respectively. In this study the key eligibility criterion for the head injured groups was that the patient warranted a CT scan. This excludes patients with head injuries and potentially mild TBI, that are less injured, and therefore the results may be biased. They are also similar to those noted above in which only patients with negative CT were included.[176] A study was therefore performed to determine whether positive findings on a CT will always reduce the SAC, and only patients with positive CT scans were recruited.[206] The average SAC score was 22.6 but when the cohort was split into a group with the SAC ≥25 and <25, the average scores were 26.1 and 20.2 respectively, indicating that the SAC alone cannot discriminate between a positive or negative head scan. This finding was replicated in an almost identical study in which only patients with positive CT scans were recruited.[207] In this study, the mean SAC score was 20.8 and when the patients were split into SAC ≥25 and <25 groups, the respective scores were 26.4 and 19.0. The scores in this study are worse than in the previous study of CT positive patients, and this may

be because the proportion of patients with more severe intracranial haemorrhages was higher in the study with worse scores. The interpretation of these studies is that the SAC can be used in an Emergency Department population, and that it does not in isolation identify structural injury seen on CT scans.

Reference	Setting	Number mild TBI (%)	Number uninjured	Baseline	Post-injury	Difference
McCrea[192] *1997*	High school American football	6 (4)	141	25.6	21.5 (sideline)	4.1
McCrea[193] *1998*	High school and college American football	33 (6)	568	26.6	22.9 (sideline)	3.7
Daniel[195] *2002*	US Navy American football	21 (7)	298	27.9	24.5 (sideline)	3.4
McCrea[197] *2003*	College American football	94 (6)	1631	27.6	24.7 (sideline)	2.9
Naunheim[176] *2008*	ED patients with concussion & CT-ve	62	---	---	21.0 (arrival) 22.7 (3 hrs) 23.5 (6 hrs)	1.7 (0-3 hrs) 2.5 (0-6 hrs)
Luoto[203] *2014*	ED patients with mild TBI	49	---	---	25.3 (0-120 hrs) 26.7 (1 month)	1.4
Silverberg[204] *2014*	ED patients with mild TBI	26	---	---	26.0 (in ED)	---
O'Neil[206] *2014*	ED patients with head injury, GCS > 8 & CT performed	66 25 (SAC ≥25) 41 (SAC <25)	---	---	22.6 (in ED) 26.1 (SAC ≥25) 22.2 (SAC <25)	---
Bin Zahid[205] *2018*	ED patients with head injury (LOC, signs trauma, & CT performed)	31 (CT+) 87 (CT-) 46 (OI) 98 (NI)	---	---	21.4 (CT+) 22 (CT-) 24.3 (OI) 26 (NI) All in ED	---
Curley[207] *2018*	ED patients with mild TBI & CT+	191 46 (SAC ≥25) 145 (SAC <25)	---	---	20.8 26.4 (SAC ≥25) 19.0 (SAC <25) <72 hrs after injury	---

Table 1.7 Derivation and validation studies of the Standardised Assessment of Concussion (SAC)
Hrs, hours; CT, computed tomography; CT-ve, no acute haemorrhage on CT; CT+ve, acute haemorrhage on CT; ED, Emergency Department; GCS, Glasgow Coma Scale; LOC, loss of consciousness; OI, orthopaedic injury (non-head injured); NI, no injury.

Differences between females and males

Females seem to have poorer neurocognitive and symptom outcomes following mild TBI. Among 155 athletes with mild TBI, females had significantly worse reaction times, were more cognitively impaired and reported more post-concussion symptoms than males.[208] In another study of athletes with mild TBI, females had higher numbers of symptoms and poorer visual memory, but better verbal memory than males.[209,210] In Association football players with concussion, females also had a significantly greater neurocognitive deficit than males.[211] The trend for more symptoms in female patients than males is also seen in injuries not related to sports. In Emergency Department patients with mild TBI, females were three times more likely than males to develop acute post-concussion syndrome, and in another study in the Emergency Department females had greater symptom severity than males.[11,212] In 1425 patients with mild TBI, females had greater odds than males of having post-concussion symptoms.[213] In another study females with mild TBI performed worse in visual memory but equally in four other neurocognitive domains.[214] Of note, phase of menstrual cycle has not been shown to have influence on neurocognitive function.[215] However, in athletes with more than one prior concussion, females had better verbal and visual memory, and were better overall on processing speed and reaction times compared with males, suggesting that the apparent poorer outcomes in females may be reversed when there is a history of prior concussion.[216]

Importance of repeated head injuries

A mild TBI in a patient with a history of prior concussion results in poorer neurocognitive performance than in a patient that has never had a concussion.

Occasionally the consequences of a repeat injury can include cerebral oedema and be devastating. This is often called 'second impact syndrome' and was first described in 1984.[217] However, the existence of second impact syndrome is controversial.[218] It is undisputed that a head injury can result in brain swelling.[219] It is not clear that a second concussive head injury is a risk factor for this. The evidence for second impact syndrome is based on anecdotal case reports. The case reports are dependent on team mates recalling whether players had previously sustained a concussion, and are therefore subject to recall bias.[220] In a structured review of potential cases of second impact syndrome, 17 published cases were assessed and none were found to be 'definitely second impact syndrome'. Five were 'probable' and 12 were not second impact syndrome.[220] Whilst catastrophic cerebral oedema may not be a direct consequence of a second concussion, athletes with a history of two or more mild TBIs that sustained a further mild TBI have had recorded poorer memory and reaction times at day five, compared with those that had no history of previous mild TBI.[221] Complete resolution of symptoms and neurocognitive deficit may also be prevented by repeated concussions, which also can increase the risk of mild cognitive impairment in later life. In a study of retired American football players, compared to players with no prior concussions, players with a history of three or more concussions had a five times higher prevalence of mild cognitive impairment and three times greater prevalence of significant memory problems.[222] Having a history of three or more concussions is also associated with a three times increased chance of being diagnosed with depression.[186] Having prior concussions even increases the risk of sustaining a further concussion. American football players with previous mild TBI are three times as likely to sustain a further mild TBI than

those with no history of previous concussion.[223] Second impact syndrome is also described in resources provided for England Rugby Football Union players, including children and coaches, and the recent rule change that mandates two weeks off play and graduated return to play following concussion is in part based on poorer outcomes associated with repeated concussions.

Importance of intracranial haemorrhage

Mild TBI with acute intracranial abnormalities on CT scan, namely extra-dural haemorrhage, sub-dural haemorrhage, contusion, intra-parenchymal haemorrhage or intra-ventricular haemorrhage, is termed 'complicated mild TBI'. Complicated mild TBI is associated with increased risk of poorer outcome. In 150 patients with mild TBI, those with complicated mild TBI had worse neurocognitive outcomes in three domains including information processing and memory at one to three months following injury, compared with uncomplicated mild TBI.[224] Complicated mild TBI is also associated with longer times to return to pre-injury employment levels compared with uncomplicated mild TBI, and is the primary predictor of memory and emotional complaints.[171,225] However, having an acutely abnormal CT scan does not necessarily result in poor neurocognitive function. In 191 patients with mild TBI and acute haemorrhage on CT, 25% had normal neurocognitive function and were GCS 15.[207] Some studies have found that neurocognitive outcomes in complicated mild TBI and moderate TBI are so similar that there is a call to consider the two entities as the same, whereas others report poorer neurocognitive function in patients with complicated mild TBI in the acute

phase but slower improvement in patients with uncomplicated mild TBI over time.[226,227]

Sports related concussion

The Professional Rugby Injury Surveillance Project is an ongoing project running within the English Rugby Football Union. It has found that the likelihood of a player sustaining any injury is 62/1000 player-hours. The most common injury is concussion with a rate of 15.8/1000 player-hours, which resulted in a mean time off play of 13 days. Head high tackles account for a large number of concussions.[228] The Rugby Football Union has changed the rules surrounding play following a head injury for both adults and children, which now state that after a concussion, players can only return to play after two weeks following the injury and only if they are symptom free. At that point their return to play must be graduated, both in time and activity.[229] Concussions sustained playing rugby football most commonly involve amnesia, headache and unsteadiness but rarely loss of consciousness. Players also exhibit poorer memory and poor attentional task function, compared with themselves pre-injury, and compared with controls.[230]

In Association football players that 'head' the ball, those that had the highest heading frequency and that had headed the ball within the last seven days exhibited the poorest neurocognitive function.[231] However, in players divided into 'low exposure headers', 'intermediate exposure headers', and 'high exposure headers' groups, there were no differences in neurocognitive function.[232]

In a landmark study, the prevalence of concussion in American football players was found to be 6.3%.[223] The most common symptom players experienced was

headache, and the mean symptom duration was three days. In another study, neurocognitive function had returned to normal by three days, and balance control by five days.[197] By seven days, 91% of concussed athletes were symptom free. In players that required seven or more days out of play following concussion, the most common signs and symptoms were disorientation to time, retrograde amnesia, and cognitive defects.[233] American footballers that have had a concussion in the past also have a high risk of sustaining a repeat concussion; 16.5% in players with previous concussion versus 2.9% with no previous concussion in one study, and of the 5.1% of players that sustain a concussion, 15% sustained a repeat in another study.[234,235] Neurocognitive function is significantly worse in players that have sustained a concussion compared to those that haven't.[192] In this study, neurocognitive function was measured on the SAC, and there was a 4.1 point difference between controls (25.6 points) and concussed players (21.5 points). Most affected were the immediate and delayed recall elements of the memory domain. In a separate group of American football players, there was again a significant difference in neurocognitive function measured on SAC between non-concussed (26.6 points) and concussed players (22.9 points).[193] There was also a significant drop between pre-injury baseline score (26.3 points) and immediate post-injury testing (22.8 points) within the concussed group, however scores returned to normal within 48 hours of injury. In this study no single domain was responsible for the deficit and all four contributed.

Biomarkers in acquired brain injury

Patients that have sustained a head injury are at risk of a TBI. Outcomes following TBI are varied and include persistent symptoms, reduced capacity to perform tasks that they could previously perform, and new mental health diagnoses. Being able to stratify patients on the day of injury to high and low risk groups for various outcomes is of critical importance. An established way of stratifying patients is to perform a non-contrast CT head scan. If a patient fulfils criteria for mild TBI and has acute abnormalities on CT, then they may have poorer outcomes in the future. However, performing CT scans is expensive, time and resource consuming, and delivers radiation to patients with a cumulative increased lifetime risk of malignancy.[236] An alternative to an initial diagnostic or prognostic step of doing a CT scan is to stratify patients based on blood-based biomarkers, which may be elevated in physiological states or clinical conditions. A commonly utilised diagnostic strategy is to treat the biomarker as a screen. In this strategy, biomarker levels are dichotomised into a positive or negative category, and the disease 'ruled out' based on a negative biomarker result. However, in this strategy, the disease is not 'ruled in' based on a positive biomarker result. Instead, a second diagnostic test is then used, usually a CT scan. In mild TBI research the disease that is screened for may be present on the day of the injury, for instance a positive result on the CT, or simply having mild TBI. In those disease cases the converse must be possible too. Consequently, if the research is investigating CT positives for 'disease present' then there must be a population who are CT negative. Similarly, if the research is investigating whether biomarkers can identify mild TBI, then there must be a population without mild TBI. In mild TBI research

these groups are usually either healthy volunteers or patients with musculoskeletal injuries below the clavicle. These groups act as controls. The disease of interest may however only be definable some months after the injury. An example of this is post-concussion syndrome, which is defined as being present three months after injury. Another example is simply a 'good' versus 'not good', or 'poor' versus 'not poor' outcome, defined by a dichotomised Glasgow Outcome Scale-Extended score.

Biomarkers in mild TBI reflect pathophysiological areas of the brain micro-architecture from which the biomarker molecules derive. These include axons, dendrites, neuronal cell bodies, myelin sheaths, synapses, astroglia and microglia (Figure 1.8).[237-239] Biomarkers can also be isolated from serum, cerebrospinal fluid and saliva. In clinical practice, cerebrospinal fluid biomarkers are measured in patients with severe TBI who are cared for on a critical care unit and who have an extra-ventricular drain placed. Salivary biomarkers are researched but not used in clinical practice.[240] I have therefore limited this review to serum biomarkers.

A search of the PubMed database using the terms ((((((((((biomarker[Title/Abstract]) OR S100B[Title/Abstract]) OR Ubiquitin C-terminal hydrolase-L1[Title/Abstract]) OR UCH-L1[Title/Abstract]) OR Neurone specific enolase[Title/Abstract]) OR NSE[Title/Abstract]) OR neurofilament[Title/Abstract]) OR Glial fibrillary acidic protein[Title/Abstract]) OR GFAP[Title/Abstract]) OR spectrin breakdown product*[Title/Abstract]) OR tau protein[Title/Abstract])) AND ((((((mtbi[Title/Abstract]) OR mild tbi[Title/Abstract]) OR mild traumatic brain injury[Title/Abstract]) OR concussion[Title/Abstract])))) was performed

for this narrative review and identified 454 articles. Relevant references of included articles were also included.

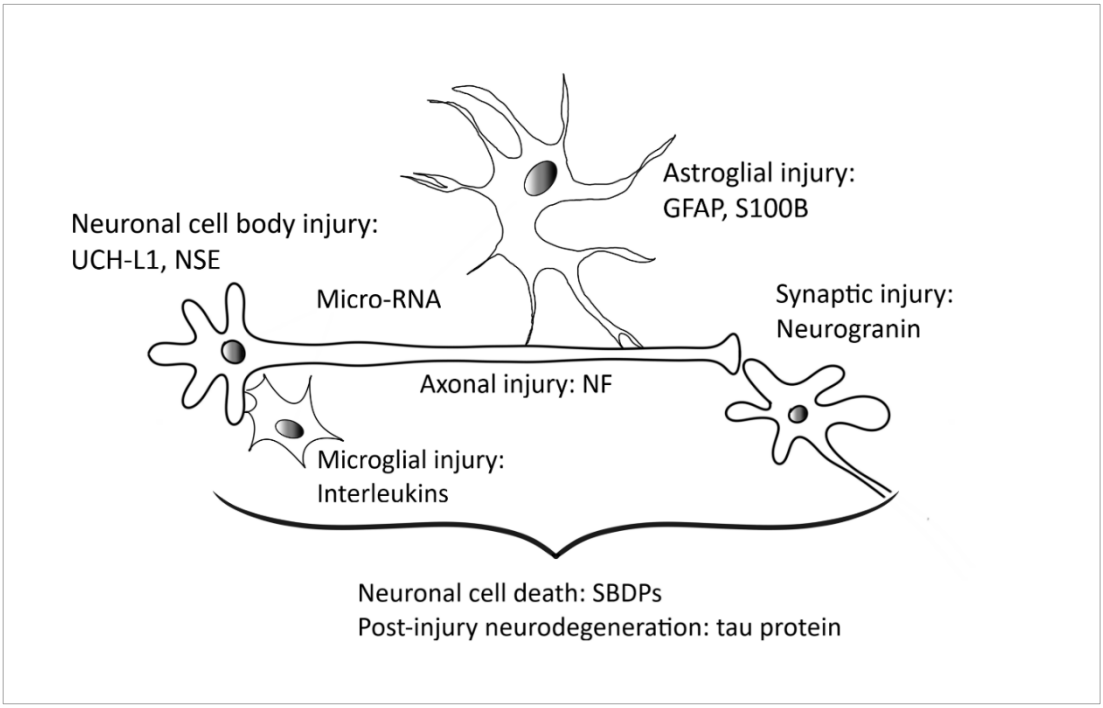

Figure 1.8. Sites of biomarker source
UCH-L1, ubiquitin C-terminal hydrolase L1; NSE, neurone specific enolase; GFAP, glial fibrillary acidic protein; NF, neurofilament; SBDPs, spectrin breakdown products.

Neuronal cell body injury

Ubiquitin C-terminal hydrolase-L1 (UCH-L1)

Ubiquitin is a protein that combines singly or as chains to target proteins, thereby altering their function.[241] Ubiquitin is essential for almost all processes in cells.[242] The process of removing a ubiquitin from a substrate protein is mediated by a group of enzymes called deubiquitinases, of which UCH-L1 is a member. UCH-L1 is found predominantly in the brain where it makes up as much as 5% of all neuronal protein, but is also present in the gonads and weakly present in fibroblasts that are active in wound healing.[243] UCH-L1 has

been investigated as a biomarker of potential use in mild TBI since 2012 and has shown promise in discriminating between patients with and without intracranial abnormality on CT (Table 1.8).

In 206 Emergency Department patients with predominantly mild TBI, UCH-L1 was higher in patients with moderate or severe TBI compared to those with mild TBI, and was higher in patients with mild TBI with acute intracranial abnormality on CT compared to those without.[244] UCH-L1 had only moderate ability to discriminate between CT positive and negative patients (AUC 0.67), poor ability to discriminate between complete and incomplete recovery (GOSE-E 8 vs < 8) at three months (AUC 0.59), but good ability to discriminate between poor and not poor outcome (GOSE-E ≤ 4 vs > 4) (AUC 0.8). When UCH-L1 and GFAP were taken together, there was improved discrimination with the combined biomarker panel (compared to either one alone) in discriminating between healthy volunteers and TBI patients, and at discriminating between poor and not poor outcomes at three and six months. However, since the cohort studied included all grades of TBI, it is not possible to extrapolate based on this study alone that UCH-L1 or even UCH-L1 and GFAP is predictive in a mild TBI cohort. In a study of 96 Emergency Department patients, UCH-L1 was significantly higher in mild to moderate TBI compared with 176 healthy volunteers and 23 'control' Emergency Department patients.[245] Within the TBI group, UCH-L1 was also significantly higher in patients that had an acute intracranial abnormality on CT scan. At a threshold of 0.09 μg/L, UCH-L1 had a sensitivity of 100% and specificity of 21% for an abnormality on CT. In a further study of 247 Emergency Department patients with head injury, UCH-L1 was significantly different in

the three groups of no TBI, CT negative mild TBI, and CT positive mild TBI.[246] However, the AUC to discriminate between groups was moderate at 0.65 for mild TBI versus no TBI and 0.60 for uncomplicated mild TBI versus no TBI.

In a landmark study that included 584 trauma patients, 325 had mild to moderate TBI, and 259 were classified as "trauma controls" (and had no TBI).[247] This study is important because the investigators describe serum concentration with time; UCH-L1 and GFAP were measured at 19 time points after injury, from the first one at less than four hours from injury to the last at 180 hours after injury. In TBI patients, UCH-L1 peaked at enrolment and was significantly higher than trauma control patients until 16 hours after injury. At enrolment, UCH-L1 discriminated well between patients with and without acute intracranial abnormality on CT (AUC 0.77), and moderately between patients with TBI and controls (AUC 0.66).

In a second landmark study, UCH-L1 and GFAP were measured in 1959 patients with mild or moderate TBI (<1% had moderate TBI), of whom 125 (6%) had an acute intracranial abnormality on CT scan.[248] Prespecified thresholds for 'positivity' were determined as 0.327 μg/L for UCH-L1 and 0.022 μg/L for GFAP. Together the sensitivity for an intracranial abnormality was 97% and the negative predictive value (NPV) was 100%. UCH-L1 alone had a sensitivity of 70% and NPV of 97%. There were three false negatives (patients whose blood tests were negative, but scans were positive), all of whom presented with a GCS of 15, and none of whom underwent neurosurgery. These data were the first considered to be of genuine clinical value and sufficiently so that the US Food and Drug Administration (FDA) authorised marketing of the platform used to assay UCH-L1 and GFAP in this

trial.[249] In 166 patients 73 of whom had musculoskeletal injuries and 93 of whom had mild TBI, there was no difference in UCH-L1 levels on the day of injury (0.40 μg/L and 0.41 μg/L respectively).[250]

UCH-L1 has been shown to have some value in sports concussion. In 34 concussed high school and college American football players, UCH-L1 was significantly higher within six hours of injury (0.204 μg/L) compared to preseason baseline (0.139 μg/L) and to non-concussed players (0.101 μg/L), with an AUC of 0.74 to discriminate between concussed and non-concussed players.[251] After the six hour measurement, UCH-L1 then trended down such that at 48 hours after the concussion, it was lower (0.097 μg/L) than measured before the sports season had started. Similarly, in six American football players that sustained a high impact head injury, defined as a linear acceleration of > 95g and a rotational acceleration > 3760 rad/s^2 as measured by helmet-based accelerometers, UCH-L1 had increased more than five times than the pre-game level baseline (0.18 μg/L to 0.94 μg/L).[252] In players that had low impact or no head injury UCH-L1 increased too, but significantly less (less than three times, from 0.23 μg/L to 0.69 μg/L). The rise in the exercised non-head injured players is mirrored in a group with musculoskeletal injuries but no head injury.

Reference	Number/ Condition	Age (mean)	Sex (%m)	LOD, ROD, predetermined threshold	Objective/outcome	Result
Papa[245] 2012	295 96 (mild & moderate TBI) 176 (Ctrl) 23 (MVC)	38	62	LLOD 0.03 µg/L	UCH-L1 in TBI vs non-injured controls vs non-head injured patient controls. UCH-L1 in CT+ vs CT- TBI patients.	UCH-L1 higher in TBI (0.96 µg/L) vs all controls (0.08 µg/L) UCH-L1 higher in CT+ (1.6 µg/L) vs CT- (0.6 µg/L) AUC 0.87 for TBI vs controls AUC 0.73 for CT+ vs CT- TBI patients
Diaz-Arrastia[244] 2014 a	206 171 (mild TBI) 8 (moderate TBI) 27 (severe TBI)	42	73	LLOD 0.03 µg/L	UCH-L1 in moderate & severe TBI vs mild. UCH-L1 in CT+ mild TBI vs CT-. UCH-L1 to predict GOS-E at 3 months.	43% of mild TBI patient CT+ UCH-L1 higher in moderate/severe TBI (0.5 µg/L) vs mild TBI UCH-L1 higher in CT+ mild TBI (0.23 µg/L) vs CT- mild TBI (0.18 µg/L) AUC 0.67 for CT+ vs CT- AUC 0.57 for GOS-E 8 vs < 8 (complete recovery) AUC 0.80 for GOS-E ≤ 4 vs > 4 (poor outcome)
Puvenna[253] 2014 a	871 406 (mild TBI) 465 (Ctrl)	NS	NS	ROD 0.056 to 10 µg/L	UCH-L1 & S100B in subconcussive head impact in American Football players. Compare with ED based mild TBI & healthy controls.	No difference in UCH-L1 between mild TBI (0.09 µg/L) vs ctrls (0.09 µg/L No difference in UCH-L1 between mild TBI CT+ (n=21, 0.10 µg/L) vs CT- (n=385, 0.08 µg/L)
Papa[247] 2016 a	584 325 (mild & moderate TBI) 259 (trauma, no TBI)	40	62	LLOD 0.045 µg/L	UCH-L1, GFAP & both to discriminate between CT+ & CT- at 19 time points after injury.	UCH-L1 peaked at initial sample (mean 3 hours after injury) UCH-L1 higher in TBI (0.26 µg/L) vs controls (0.17 g/L) Highest AUC at initial sample 0.66 for TBI vs no TBI
Dey[254] 2017 a	40 20 (mild TBI) 20 (Ctrl)	30.5	90	ROD 0.2 to 30 µg/L	UCH-L1 & S100B in mild TBI vs healthy volunteer controls. UCH-L1 & S100B to predict cognitive deficits at 3 months.	No difference in UCH-L1 between mild TBI (4.43 µg/L) vs ctrls (4.65 µg/L) Weakly positive correlation between UCH-L1 & 1 of 12 neuropsychological tests at 3 months

Lewis[246] 2017	247 154 (CT- mild TBI) 34 (CT+ mild TBI) 59 (HI no TBI)	46	60	LOD 0.01 µg/L	UCH-L1 to discriminate between head injured patients with & without mild TBI UCH-L1 to discriminate between mild TBI CT+ & CT-	UCH-L1 higher in CT+ (0.132 µg/L) vs CT- (0.064 µg/L) vs HI no TBI (0.043 µg/L) AUC 0.65 for mild TBI vs no mild TBI
Posti[250] 2017 a, b	166 93 (CT- mild TBI) 73 (extracranial musculoskeletal injuries)	44	55	Limits of quantification: 0.3-50 µg/L	UCH-L1 & GFAP to discriminate between mild TBI CT- & no TBI extracranial musculoskeletal injuries.	No difference between UCH-L1 in mild TBI CT- (0.40 µg/L) & patients with extracranial musculoskeletal injuries (0.41 µg/L).
Bazarian[248] 2018	1959 1834 (CT- mild & mod. TBI) 125 (CT+ mild & mod. TBI)	49	57	ROD 0.08-2.56 µg/L	Determine NPV & sensitivity of UCH-L1 & GFAP for CT+.	UCH-L1 higher in CT+ (0.60 µg/L) vs CT- (0.26 µg/L) Using a threshold of 0.327 µg/L: UCH-L1 alone; sensitivity 70% & NPV 97% UCH-L1 & GFAP together; sensitivity 98%, NPV 100%

Table 1.8 Characteristics of ubiquitin C-terminal hydrolase L1 studies

a = absolute values of UCH-L1 calculated from graph in source paper using plot digitizer; *b* = overall mean age and % male calculated from more than one group reported in source paper. % M, percentage male; LOD, limit of detection; ROD, range of detection; Ctrl, control; MVC, motor vehicle collision; TBI, traumatic brain injury; LLOD, lower limit of detection; UCH-L1, ubiquitin C-terminal hydrolase L1; CT, computed tomography; CT+, acute intracranial abnormality on CT; CT-, no acute intracranial abnormality on CT; AUC, area under the (receiver operating characteristic) curve; GOS-E, Glasgow Outcome Scale – Extended; GFAP, glial fibrillary acidic protein; HI, head injury.

Neurone specific enolase

Enolase is a metalloenzyme active in glycolysis. It catalyses the conversion of phosphoglycerate to phosphoenol pyruvate, which is the ninth and penultimate step in glycolysis. Neuron-specific enolase (NSE) is present in mature neurons, neuroendocrine cells and amine precursor uptake and decarboxylation cells. NSE been investigated for value in mild TBI and characteristics of NSE studies are reported in Table 1.9.

In a study of 141 Emergency Department patients with mild TBI, 65% of patients had elevated NSE.[255] The investigators measured the Galveston Orientation and Amnesia Test in the ED, the Rivermead Post Concussion Symptom Questionnaire at three days, and the Rivermead Post Concussion Symptom Questionnaire, the Balance Error Scoring System and other neuropsychological tests at one and six weeks.[15,256,257] At each time point patients were classified as normal or abnormal based on an assessment by the treating clinician. NSE had an odds ratio of 5.32 for poor outcome at six weeks. In another study of 154 Emergency Department patients with mild to moderate TBI and 30 matched healthy volunteers, NSE was taken in the Emergency Department and at two to seven days after injury.[258] NSE was twice as high in mild TBI patients than controls at both time points. Of note, if the threshold for 'abnormal' used in the previously described study (>12 μg/L), was used in this study, all patients, including the healthy volunteers, would be classified as abnormal. This discrepancy is because two different methods of analysis were used.

In 334 Emergency Department patients with mild TBI, NSE was significantly higher than in a control group of 328 healthy volunteers.[259] NSE increased

with age in the control group, but this change was not seen in patients with mild TBI. NSE had an AUC of 0.85 to discriminate between patients with mild TBI and healthy volunteers. In contrast, in 104 patients with mild TBI and 91 controls, was no difference in NSE levels although there was a difference when corrected for age and sex.[260] Furthermore, in a study of 107 Emergency Department patients with mild TBI, of whom 25% were CT positive, NSE had an AUC of 0.65 to discriminate between patients that were CT positive and negative.[261]

Three studies have investigated NSE in sports concussion. In 27 ice-hockey players that sustained a concussion, NSE was not elevated from before the season started to an hour after the concussion (6.1 μg/L and 6.5 μg/L, p = 0.20).[262] Similarly, in 12 College American Football players that sustained a concussion, there was no difference between baseline and post-concussion NSE levels (8.5 μg/L and 9.1 μg/L respectively).[263] In contrast, in 18 boxers compared to 17 healthy volunteers, NSE was significantly elevated between before and after a boxing match (1.3 μg/L and 1.7 μg/L respectively) and the pre-match levels in boxers were significantly elevated compared with healthy volunteers (0.2 μg/L).[264] In this small study, participating professional boxers had been boxing for three years, 5% of them had sustained previous concussions and during the boxing match sustained an average of 47 blows to the head. Furthermore, the control group is not described in any detail. The clear difference between boxers and Emergency Department patients with mild TBI, and the absence of any description of the control group, makes clinical interpretation of these data difficult.

Reference	Number/condition	Age (mean)	Sex (%m)	LOD, ROD, predetermined threshold	Objective/outcome	Result
De Kruijk[260] 2001	195 104 (mild TBI) 91 (Ctrl)	36 (TBI) 40 (Ctrl)	57 (TBI) 86 (Ctrl)	NS	NSE & S100B in mild TBI vs controls	No difference between mild TBI (10.2 µg/L) patients vs controls (9.6 µg/L)
Topolovec-Vranic[255] 2011	141 (mild TBI)	39	89	12 µg/L	NSE to predict GOAT in ED; NSE to predict RPQ at 3 days; NSE to predict RPQ, BESS & other neuropsychological tests at 1 & 6 weeks	NSE ≥ 14.6 µg/L had OR 5.32 for poor outcome at 6 weeks
Wolf[261] 2013	107 (mild TBI)	59	56	16.4 µg/L	Logistic regression model including NSE & S100B to discriminate CT+ from CT-	25% were CT+ NSE higher in CT+ (22.5 µg/L) vs CT- (15.2 µg/L) AUC 0.88 for CT+ vs CT- (using NSE, S100B, nausea, amnesia, unconsciousness, & patient age > 60 years)
Buonora[258] 2015	184 154 (mild to mod. TBI) 30 (Ctrl)	47 (TBI) 25 (Ctrl)	67 (TBI) 50 (Ctrl)	NS	Fold change discrimination index between TBI & controls	NSE 30 µg/L (Ctrl) NSE 55.5 µg/L (baseline TBI) NSE 67.3 µg/L (2-7 days after TBI) For each fold-change in NSE, AUC 0.89
Peacock[259] 2017	507 179 (mild TBI) 328 (Ctrl)	43 (TBI) 39 (Ctrl)	66 (TBI) 43 (Ctrl)	NS	Logistic regression model including NSE, NRGN & MT3 to discriminate between mild TBI & controls	NSE higher in mild TBI (12.2 µg/L0 vs controls (3.48 µg/L) Model with NSE alone AUC 0.85 Model with all 3 biomarkers AUC 0.88

Table 1.9. Characteristics of neuron-specific enolase studies
% M, percentage male; LOD, limit of detection; ROD, range of detection; TBI, traumatic brain injury; LLOD, lower limit of detection; NSE, neuron-specific enolase; GOAT, Galveston Orientation & Amnesia Test; RPQ, Rivermead Post-concussion Questionnaire; BESS, Balance Error Scoring System; OR, odds ratio CT, computed tomography; CT+, acute intracranial abnormality on CT; CT-, no acute intracranial abnormality on CT; AUC, area under the (receiver operating characteristic) curve; NRGN, neurogranin; MT3, metallothionein 3.

Axonal injury

Neurofilament proteins

Neurofilaments have a diameter of 10 nm, similar to that of neurones. They are particularly plentiful in axons and are essential for the radial growth of axons during development, and maintenance of axon diameter.[265,266] They are composed of four subunits; neurofilament heavy, medium and light (NFH, NFM, NFL), and α-internexin.[267] There is limited evidence that neurofilament is useful for assessing patients with mild TBI. In 34 patients with mild TBI, half of whom were CT positive, NFH was higher than in patients in a healthy volunteer group, and higher in patients that were CT positive compared to CT negative.[268] In a separate study, in 107 patients with mild TBI, NFL was significantly higher in patients with a Glasgow Outcome Scale-Extended score of < 8 (i.e. not complete recovery) at six to 12 months but there was no difference in NFL between patients that were CT positive and CT negative.[269] This is consistent with the relatively low AUC of 0.676 for NFL to discriminate between CT positive and negative in a group of 93 patients with mild TBI.[270] NFL may be further limited in clinical use by the confounder that it is associated with several chronic neurological conditions, and has been found to be correlated with age and pre-existing neurological diagnoses in patients with mild TBI.[271] NFL has been more extensively investigated in sports concussion, and may have some utility in identifying concussion and sub-concussion in boxing, American football, hockey, and soccer headers.[272-276]

Astroglial cell injury

Glial fibrillary acidic protein

Glial fibrillary acidic protein (GFAP) is a type III intermediate filament. Intermediate filaments are strong yet flexible protein polymers 10nm in diameter, and consequently intermediate to microfilaments (smaller) and microtubules (also known as myosin thick filaments, and larger than intermediate filaments).[277] GFAP is thought only to be found in the central nervous system and makes up the cytoskeletal structure of astrocytes.[278] Characteristics of studies of GFAP are reported in Table 1.10.

Several studies have investigated the value of GFAP in predicting severity and outcomes following severe TBI.[279-282] In 92 patients with severe TBI, mortality and the Glasgow Outcome Scale was measured at three months after injury[283]. GFAP was significantly higher in non-survivors (4.8 μg/L) than in survivors (0.5 μg/L) (abstracted from bar chart using Plot Digitiser), and the AUC for mortality at three months was 0.84. Furthermore, GFAP was higher in severely brain injured patients than in multiply injured but not brain injured patients.[284]

In one of the first investigations into GFAP in patients with mild TBI, GFAP was significantly higher in CT positive patients compared to CT negative, and in patients that had not fully returned to work at six months compared to those that had.[285] However the diagnostic test characteristics were poor for diagnosing abnormalities on MRI, the Extended Glasgow Outcome Scale, or return to work (although the cut-off for dichotomisation was not reported). In contrast, in a study published in the same year, GFAP breakdown product (GFAP-BDP) demonstrated better diagnostic characteristics.[286] In this study

of 108 patients with mild to moderate TBI, GFAP-BDP levels were significantly higher in lower GCS groups. This was the case whether the dichotomisation was set at the conventional definitions of mild and moderate TBI of GCS 13-15 versus 9-12, or GCS 14-15 versus 9-13. GFAP-BDP was also higher in a low acuity TBI group, that is a group with GCS 15, when compared to non-head injured trauma patients with musculoskeletal injuries. Furthermore, GFAP-BDP was higher in CT positive than CT negative patients. The discriminatory ability of GFAP-BDP was also good with an AUC of 0.9 for TBI versus controls, 0.88 for GCS 15 versus healthy volunteers with no injury, and 0.79 for CT positive versus CT negative TBI patients. A further study that included nearly 400 patients also reported significantly higher GFAP levels in CT positive patients with mild to moderate TBI compared to CT negative patients, and also higher levels in CT negative patients compared to patients with musculoskeletal injuries but no head injuries.[287] GFAP had good capacity to discriminate between CT positive and CT negative patients, with an AUC of 0.84. In 215 patients with TBI, of which 83% were mild, GFAP-BDP also performed well at discriminating between CT positive and CT negative patients.[288] The AUC was 0.88, and when adjusted for age, pupillary exam, GCS, and injury severity score, the AUC was 0.96. Using a threshold of 1.66 µg/L, the specificity was 99% and sensitivity 45%. Using decision curve analysis, a net benefit of scanning only when the GFAP-BDP was positive would have resulted in 12% fewer scans being performed than if the decision to scan had been based on a clinical screen. In a paper by the same authors, 584 patients recruited in the ED, 56% of whom had mild or moderate TBI and 44% of which had trauma but no TBI, GFAP (and UCH-L1) was measured at 19 points in time from arrival (median 3 hours from injury) until a week

later.[247] GFAP was significantly higher in the TBI group compared with the no TBI group, and in CT positive compared with CT negative patients. The AUC to discriminate CT positive from CT negative for GFAP alone was highest at 36 hours at 0.97 and was 0.86 at initial assessment. When GFAP and UCH-L1 were assessed together, the highest AUC was also at 36 hours at 0.97. The great value of this study compared with studies previously published is that a clear description is provided of the trend of GFAP and UCH-L1 over 19 points in time across a week. GFAP peaked at 20 hours after injury, and UCH-L1 peaked at the initial measurement. However, as described above, in a recent key publication, a panel consisting of GFAP and UCH-L1 was 98% sensitive and had a NPV of 99.6% for an acute abnormality on CT.[248] Because not all patients in the study had results from both assays within the panel, a sensitivity analysis was performed which showed that compared to GFAP alone the combined biomarker test had neither superior sensitivity nor NPV. However, compared to UCH-L1, the combined biomarker test had both higher sensitivity and NPV. This is surprising because in the report by Papa and colleagues, GFAP peaked at 20 hours after injury.[247] Nevertheless, the results were compelling enough to be fundamental to the decision by the US Food and Drug Administration (FDA) to endorse the panel as the first for use in US EDs.[249]

One issue with using biomarkers in a clinical setting is the potential for leakage from non-brain tissue, which would produce false-positive results. This has been reported with S100B but seems not to be an issue with GFAP. When CT negative TBI patients were compared with patients with extracranial bony injuries, GFAP was lower in TBI patients on the day of injury, but there were no differences between groups on subsequent days.[250] Furthermore, in

another study comparing patients with TBI to patients with extracranial injuries and with fractures, there was no difference in GFAP between patients with fractures and those without (regardless of whether those patients had a TBI or not).[287]

Reference	Number/condition	Age (mean)	Sex (% male)	Lod, rod, predetermined threshold	Objective/outcome	Result
Metting[285] *2012*	94 (mild TBI)	34		LLOD 0.045 µg/L	GFAP in CT+ vs CT- GFAP in MRI diagnosed axonal injury vs no axonal injury GFAP in complete vs incomplete return to work at 6 months.	GFAP higher in CT+ (1.2 µg/L) vs CT- (0.05 µg/L). GFAP higher in patients with axonal injury on MRI at 3 months (0.65 µg/L) vs those without (0.07 µg/L) GFAP higher in incomplete return to work (0.69 µg/L) at six months vs complete return to work (0.12 µg/L)
Papa[286] *2012 b*	307 97 (mild TBI) 11 (moderate TBI) 23 (non-head injured musculoskeletal injured control) 176 (healthy volunteer ctrl)	38	58	LLOD 0.02 µg/L	GFAP-BDP to discriminate between mild to moderate TBI vs non-head injured controls GFAP-BDP to discriminate between injury severity levels including mild vs moderate TBI, & CT+ vs CT-	GFAP-BDP significantly higher in TBI (0.32 µg/L) than controls (0.01 µg/L) AUC 0.9 for TBI vs. controls AUC 0.88 for mild TBI GCS 15 vs healthy volunteers with no injury AUC 0.79 for CT+ vs CT-
Diaz-Arrastia[244] *2014 a*	206 171 (mild TBI) 8 (moderate TBI) 27 (severe TBI)	42	73	LLOD: 0.1 µg/L	Combined GFAP & GFAP-BDP to discriminate between patients with TBI vs healthy volunteers	AUC 0.91 for TBI vs healthy volunteers
Papa[287] *2014 a*	397 209 (mild to moderate TBI) 188 (trauma without TBI)	40	59	LLOD 0.008 µg/L	GFAP to discriminate between CT+ vs CT- GFAP to discriminate between patients with TBI vs patients with fractures.	GFAP higher in CT+ (0.74 µg/L) vs CT- (0.04 µg/L) GFAP higher in CT- vs no TBI (0.01 µg/L). AUC 0.84 for CT+ vs CT-
Mcmahon[288] *2015*	215 179 (mild TBI) 9 (moderate TBI) 27 (severe TBI)	42	73	LLOD ~0.01 µg/L	GFAP-BDP to discriminate between CT+ vs CT-	GFAP higher in CT+ (2.86 µg/L) vs CT- (0.26 µg/L) AUC 0.88 for CT+ vs CT-
Papa[247] *2016 a*	584 325 (mild & moderate TBI) 259 (trauma, no TBI)	40	62	LLOD: 0.008 µg/L	UCH-L1, GFAP & both to discriminate between CT+ vs CT- at 19 time points after injury	Peak GFAP at 20hrs. GFAP higher in TBI (0.112 µg/L) vs controls (0.008 µg/L)

Bogoslovsky [289]	103 34 (TBI) 69 (healthy volunteer)	39	85	LLOD: 0.0008 µg/L	Determine whether: GFAP higher in TBI vs controls GFAP reduces over weeks following injury GFAP is associated with 6-month outcomes	GFAP higher on day of injury (0.0176 µg/L), at 30 days (0.00133 µg/L) & at 90 days 0.00135 µg/L) compared with controls (0.0008 µg/L). GFAP by day 30 but no further after day 30. No relationship between GFAP & GOSE.
Lewis[246] 2017	247 154 (CT- mild TBI) 34 (CT+ mild TBI) 59 (HI no TBI)	46	60	LOD 0.02 µg/L	GFAP to discriminate between head injured patients with & without mild TBI GFAP to discriminate between mild TBI CT+ vs CT-	GFAP higher in CT+ (0.12 µg/L) than either (CT- 0.02 µg/L) or head injury no TBI (0.02 µg/L). AUC 0.7 for mild TBI vs no mild TBI.
Posti[250] 2017 a, b	166 93 (mild TBI) 73 (musculoskeletal injuries, no TBI)	44	55	Limits of quantification 0.16-100 µg/L	GFAP & UCH-L1 to discriminate between patients with mild TBI CT- & patients with extracranial musculoskeletal injuries & no TBI.	Samples taken on arrival in ED & at days 1, 2, 3 & 7. GFAP *lower* in TBI (0.19 µg/L) than musculoskeletal controls (0.23 µg/L) on day of arrival & no difference subsequently.
Bazarian[248] 2018	1959 1834 (CT- mild & mod. TBI) 125 (CT+ mild & mod. TBI)	49	57	ROD 0.08-2.56 µg/L	GFAP and UCH-1 NPV & sensitivity for CT+	GFAP higher in CT+ (0.135 µg/L) vs CT- (0.0222 µg/L) Using a threshold of 0.022 µg/L: GFAP alone; sensitivity 96% & NPV 99% UCH-L1 & GFAP together; sensitivity 98%, NPV 100%

Table 1.10. Characteristics of glial fibrillary acidic protein studies
a = absolute values of UCH-L1 calculated from graph in source paper using plot digitizer; *b* = overall mean age and % male calculated from more than one group reported in source paper. % M, percentage male; LOD, limit of detection; ROD, range of detection; LLOD, lower limit of detection; GFAP, glial fibrillary acidic protein studies; TBI, traumatic brain injury; CT, computed tomography; CT+, acute intracranial abnormality on CT; CT-, no acute intracranial abnormality on CT; BDP, breakdown products; AUC, area under the (receiver operating characteristic) curve; HI, head injury.

S100B

The S100 family of proteins are predominantly intracellular calcium-modulated proteins. There are 16 members, of which S100B is one of the original two to have been discovered in the 1960s.[290] S100B is a 21-kDa calcium-binding glial-specific protein mainly expressed by astrocytes and has mitogenic and glial cell proliferative functions.[291] S100B is estimated to have a half-life of 97 minutes in mild TBI patients.[292] Characteristics of S100B studies in mild TBI are reported in Table 1.11.

The half-life of S100B has been estimated to be from 25 to 120 minutes in head injured and cardiac surgical patients.[292-294] This is relatively short for practical purposes, as during the time taken to transport a patient to hospital and within an Emergency Department prior to blood sampling, a significant proportion of circulating S100B will be metabolised. This may confound its use in decision rules, and although there is ample evidence that elevated S100B is sensitive for brain injury, there is no evidence that it adds value to clinical guidance.[292,295]

S100B has also been investigated as a tool to predict outcome following cardiac arrest. Several studies have reported associations between higher levels of S100B and lower rates of survival to admission, the presence of brain damage, and poorer functional outcomes.[296,297]

S100B to discriminate between CT positive and CT negative

In 182 patients with mild TBI, S100B was detectable (>0.2 μg/L and defined as elevated at this level) in 38%.[298] S100B was 90% sensitive with a NPV of 99% for CT positive patients. The optimum threshold for abnormality was investigated using a definition of the 95th percentile in a healthy volunteer.[299]

In this study, 1309 patients with mild TBI, 55 with moderate or severe TBI and 540 healthy volunteers were included, and the threshold was found to be 0.1 μg/L. Of the 1308 mild TBI patients, 7% were CT positive, and of the 55 moderate to severe TBI patients, 42% were CT positive. S100B was 99% sensitive, 30% specific, had a NPV of 100%, a PPV of 10%, and an AUC of 0.80 to discriminate between CT positive and negative patients.

In 2007 S100B was introduced into local practice in some Scandinavian Emergency Departments to fit within an existing Scandinavian Neurotrauma Committee guideline on the management of head injured patients.[299,300] Patients with GCS 14-15, and loss of consciousness or amnesia were eligible for S100B testing prior to CT scan if the test was performed within 3 hours. If the S100B was < 0.1 μg/L, then the patient could be discharged home without CT. When validated, out of 512 patients, 27% were below the S100B threshold for CT.[301] 32% of those were 'over-triaged', that is either investigated with a CT (all of which were negative) or admitted. 73% were above the threshold, and of those 7% were 'under-triaged', that is not investigated with a CT, none of whom were found subsequently to have had intracranial abnormalities. Overall, S100B had a sensitivity and NPV of 100% for intracranial injury, and a specificity of 28%.

In 1560 patients with minor head injury, of which 7% were CT positive S100B had an AUC of 0.76 to discriminate between CT positive and negative patients.[302] At a threshold of 0.1 μg/L, the sensitivity and NPV were both 99%, and the likelihood ratio for a negative test (LR-) was 0.07. At a slightly higher threshold of 0.14, the sensitivity was 97%, NPV 99% and LR- was 0.06. Had S100B been part of the diagnostic algorithm, 12 or 25 CT scans would have

been avoided at thresholds of 0.10 μg/L and 0.14 μg/L respectively. These findings contributed to the addition of S100B to the Scandinavian guidelines for initial management of minimal, mild and moderate head injuries in adults, which was one of the first head injury guidelines to include S100B.[303] In separate large study that included 787 patients with mild TBI and 467 healthy volunteers, S100B was higher in patients with mild TBI compared to controls.[304] S100B was also higher in mild TBI patients with a positive CT scan compared to those with a negative CT. The authors tested the diagnostic characteristics using several thresholds, including a threshold defined by the healthy volunteer group, a conventional threshold of 0.1 μg/L, and thresholds allowing 98% and 90% sensitivity, and 98% and 90% specificity. The intention was to balance CT usage against missing intracranial injuries. In this study, at a threshold allowing 90% sensitivity (0.097 μg/L), 31% of CT scans could have been avoided, but six CT positive mild TBI patients would have been missed. By reducing the threshold to allow 98% sensitivity (0.060 μg/L), 23% of CT scans could have been avoided and one patient with an abnormal CT scan (a small contusion) would have been missed.

S100B in intoxicated patients

A significant proportion of patients with head injuries and potential TBI that present to the Emergency Department are intoxicated with alcohol, and consequently it is important to determine whether alcohol affects biomarker levels. In 160 patients that presented to an Emergency Department in Canada, four groups were defined: medical controls (non-traumatic medical complaints), trauma controls (physical injuries not involving the head), mild TBI, and moderate or severe TBI.[305] Each of these were separated into those

that were and were not intoxicated with alcohol. S100B was significantly lower in the intoxicated compared with sober moderate or severe TBI groups, and trended to be lower in the intoxicated compared with sober mild TBI group. S100B was higher in the TBI groups compared with the non-TBI groups regardless of alcohol. The authors of this study replicated the methodology in a second cohort of patients who were categorised into identical groups and subcategorised by alcohol intoxication or sobriety.[306] In this study similar findings were reported with higher S100B levels seen in patients with TBI compared with those without, but in contrast to the previous study there was no difference between intoxicated and sober patients in any group. The authors suggested this discrepancy may be due to tighter inclusion criteria in the second study but concluded that alcohol does not affect S100B levels.

S100B to predict longer term outcomes after mild TBI

S100B has been shown to have moderate value as a predictor of post-concussion symptoms, and in mild TBI, at a cut off of 0.5 μg/L, had a sensitivity of 93% and an area under the receiver operating characteristic (AUC) curve of 0.70 for post-concussion syndrome at one month.[307] In 182 patients with mild TBI, patients with elevated S100B had significantly more symptoms than those with low S100B but there was no analysis reported for S100B predicting post-concussion syndrome.[298] In a separate study, at a threshold of 0.5 μg/L, S100B had an AUC of 0.7 to predict post-concussion symptoms, and at a threshold of >0.13 μg/L, had an OR of 10.4 to predict post-concussion symptoms. As a predictor of functional outcome in patients with all types of TBI, at a threshold of 0.32 μg/L, S100B had a sensitivity of 93% and an AUC of 0.9 for severe disability.[308] In the same study, in a subset of

patients with mild TBI for moderate disability, a threshold of 0.48 μg/L had a negative predictive value of 99%. S100B has also been reported to predict failure to return to work; in patients with mild TBI, 38% of patients with abnormal S100B (≥0.15μg/L) compared with 5% of patients with normal S100B were unable to return to work at one week following injury.[309] In another study, elevated S100B had a sensitivity of 80% and a PPV of 38% for inability to return to work (or usual activities) at one week.[310] In this study, of the patients with elevated S100B, 38% had not returned to work at one week, compared with only 5% of the patients with normal S100B. Elevated S100B has also been associated with post-traumatic stress at a year.[311]

In contrast, there was no difference in S100B measured in 94 patients with mild TBI that were categorised by GCS, CT, MRI at three months, Extended Glasgow Outcome Scale at six months, or return to work at six months after injury.[285] Although it may be expected that S100B might not predict longer term outcomes, it might be expected that S100B would predict acute outcomes, particularly whether patients were CT positive or negative. The authors suggest this may be because there is a high prevalence of CT positive patients in this study (20%) which would reduce the NPV, and indeed the mean S100B across all patients is 0.54 μg/L. In another study, there was no association between elevated S100B (> 0.1 μg/L) and return to work, or post-concussive symptoms at three, six and nine months.[312]

Limitations of S100B

S100B has poor specificity both for diagnosing mild TBI and for discriminating between mild TBI patients with and without CT abnormalities. This means that S100B is frequently elevated in patients that either do not have mild TBI,

or do not have an intracranial abnormality (false positives). One potential reason for this may be because S100B is present in adipocytes and melanocytes. Consequently, normal S100B levels may be naturally higher in people with more pigmented skin. In one study, the average S100B level in black people was twice that of Caucasian people.[313]

Another reason for poor specificity may be due to extra-cerebral expression or release of S100B. In 397 patients with extracranial injuries, half of which had TBI, S100B was significantly higher in patients with fractures compared to those without, regardless of whether patients had TBI or not.[287] Furthermore, in a study comparing patients with polytrauma and no head injury and healthy volunteers, S100B was highest in trauma patients with fractures.[314] This suggests that there may be S100B false positives in patients with head injuries and fractures.

Reference	Number/condition	Age (mean)	Sex (% male)	LOD, ROD, predetermined threshold	Objective/outcome	Result
Ingebrigtsen [298] 2000	Mild TBI (182)	33	61	LOD 0.2 µg/L Threshold 0.2 µg/L	S100B to discriminate between CT+ vs CT-	Of all patients, 38% elevated S100B, 5% CT+ Of CT+ patients, S100B elevated in 90% S100B 90% sensitive, 65% specific, NPV 99%, PPV 13% for CT+
Romner[315] 2000	TBI (278) Mild TBI (254) Moderate TBI (16) Severe TBI (8)	32	63	LOD 0.2 µg/L Threshold 0.2 µg/L	S100B to discriminate between CT+ vs CT-	Of all patients, 39% elevated S100B, 9% CT+ Of CT+ patients, S100B positive in 92% S100B 92% sensitive,66% specific, NPV 99%, PPV 23% CT+
Biberthaler[316] a	Mild TBI (52) GCS < 8 (NS) Healthy volunteer (20)	NS	73	Threshold 0.1 µg/L	Evaluate diagnostic value of S100B for screening patients at high risk after mild TBI	Of mild TBI patients, 71% elevated S100B, 21% CT+ S100B 0.04 µg/L (CT-), 0.63 (CT+) in mild TBI S100B 0.05 µg/L, 0.47 µg/L, 7.16 µg/L in healthy volunteers, mild TBI, & low GCS groups respectively Sensitivity 100%, specificity 40%, NPV 100%, PPV 40.5 for CT+
Biberthaler[317] 2001	Alcohol intoxicated mild TBI (20) Sober mild TBI (29) Moderately intoxicated healthy volunteers (20) Severely intoxicated patients without TBI (20)	43	NS	LOD 0.02 µg/L	Determine the influence of alcohol on S100B levels in patients with mild TBI & patients without mild TBI	S100B higher in mild TBI vs no TBI S100B higher in mild TBI CT+ vs CT- patients, regardless of alcohol intake. Alcohol did not elevate S100B independently.
De Kruijk[260] 2001	Mild TBI (104) Healthy controls (92)	40	70	LOD 0.03 µg/L	Determine whether S100B (& NSE) higher in patients with mild TBI compared to healthy volunteer control.	S100B higher in mild TBI (0.25 µg/L) vs controls (0.02 µg/L)
Mussack[318] 2002	Intoxicated mild TBI (139) Healthy volunteers (20)	36	76	LOD 0.02 µg/L	S100B to discriminate between CT+ vs CT- in intoxicated patients	14% CT+ S100B higher in CT+ (0.94 µg/L) vs CT- (0.22 µg/L) AUC 0.86 for CT+ vs CT- At threshold 0.21 µg/L, sensitivity 100%, specificity 50%, PPV 24%, NPV 100%.

Savola[307] 2003	Mild head injury (172) PCS at one month (37) No PCS at 1 month (135)	31	75	LOD 0.02 µg/L Threshold 0.5 µg/L	Determine if S100B (& other factors) predict post-concussion symptoms at one month after mild TBI.	Elevated S100B had OR 5.5 for PCS at 1 month AUC 0.7 for PCS at 1 month Sensitivity 27%, specificity 93%
Stranjalis[310] 2004	Mild head injury (100)	33	52	Threshold 0.15 µg/L	Determine the association between S100B & return to work or usual activities at one week.	32% had elevated S100B. 37% of elevated S100B patients had not returned to work at one week compared with 5% of patients with normal S100B
Biberthaler[299] 2006	Mild head injury (1309) Moderate-severe TBI (55) Healthy volunteers (540)	47	65	ROD 0.005-39 µg/L	Determine a threshold set pre-hoc at 95th percentile to define S100B positive & negative in healthy volunteers. Calculate diagnostic test characteristics for S100B in mild TBI patients.	95th percentile identified as 0.1 µg/L. AUC 0.80 for mild TBI vs no TBI Sensitivity 99%, NPV 100%
Poli-De-Figueiredo[319] 2006	Mild TBI (50) Healthy volunteers (21)	NS	66	Threshold 0.1 µg/L	S100B to discriminate between CT+ vs CT-	Of mild TBI patients, 82% elevated S100B, 21% CT+ S100B higher in CT+ (0.75 µg/L) vs CT- (0.26 µg/L) AUC 0.82 for CT+ vs CT- Sensitivity 100%, specificity 20%, PPV 15%, NPV 100%
Muller[320] 2007	Mild TBI (226)	39	74	LOD 0.013 µg/L	S100B to discriminate between CT+ vs CT-	9% CT+ S100B higher in CT+ (0.36 µg/L) vs CT- (0.18 µg/L) AUC 0.73 for CT+ vs CT- At threshold 0.1 µg/L, sensitivity 95%, specificity 31%, PPV 12%, NPV 98%
Morochovič[321] 2009	Mild TBI (102)	42	70	LOD 0.005 µg/L Threshold 0.1 µg/L	S100B to discriminate between CT+ vs CT-	73% had elevated S100B, 18% CT+ Sensitivity 83%, specificity 30%, PPV 20%, NPV 89%
Muller[322] 2011	Mild TBI (233)	48	61	Threshold 0.105 µg/L	S100B to discriminate between CT+ vs CT-	72% had elevated S100B, 9% CT+ Sensitivity 86%, specificity 12%, PPV 13%, NPV 86%
Topolovec-Vranic[255] 2011	Mild TBI (141)	39	89	LOD 0.005 µg/L Threshold 0.1 µg/L	Determine whether S100B (& NSE) was predictive of: GOAT in ED; RPQ at 3 days; RPQ, BESS & other neuropsychological tests at 1 & 6 weeks	Elevated S100B had OR 3.9 for abnormal status according to a physician's evaluation at 1 week, but not predictive for outcome at 6 weeks

Calcagnile[301] 2012	Mild TBI (512)	42	62	ROD 0.005-39 µg/L Threshold 0.1 µg/L	Determine whether including S100B in CT decision rule is safe	S100B had sensitivity & NPV of 100% for intracranial injury Specificity 28%, PPV 6%
Cervellin[323] 2012	Mild TBI (60)	58	68	ROD 0.02-30 µg/L	S100B to discriminate between CT+ vs CT-	33% CT+ S100B higher in CT+ (1.35 µg/L) vs CT- (0.48 µg/L) AUC 0.80 for CT+ vs CT- At a threshold of 0.38 µg/L, sensitivity 100%, specificity 58%, PPV 54%, NPV 100%
Egea-Guerrero[324] 2012	Mild TBI GCS 15 (143)	49	62	ROD 0.005-36 µg/L Threshold 0.105 µg/L	S100B to discriminate between CT+ vs CT- in patients with mild TBI & no reduction in consciousness	11% CT+ S100B higher in CT+ (0.585 µg/L) vs CT- (0.369 µg/L) AUC 0.73 for CT+ vs CT- Sensitivity 100%, specificity 27%, PPV 14%, NPV 100%
Metting[285] 2012	Mild TBI (94)	34	NS	LOD 0.005-µg/L	Determine whether S100B (& GFAB) can predict initial GCS, initial CT, MRI 3 months postinjury, GOS-E (dichotomised to good or poor outcome) & RTW 6 months after injury	Mean S100B 0.54 µg/L No difference in S100B in patients with GCS 13, 14 or 15; nor between groups in any of the other four categories
Zongo[302] 2012	Mild TBI (1646)	57	56	NS	Determine the NPV & LR- for S100B for CT+. Determine threshold most effective to keep NPV near 100%	S100B higher in CT+ (0.46 µg/L) vs CT- (0.22 µg/L) At thresholds of 0.1, 0.12, & 0.14 NPV was 99% & LR- was 0.07, 0.04, & 0.06 AUC 0.76 for CT+ vs CT-
Bazarian[304] 2013	Mild TBI (787) Healthy volunteers (467)	38	63	ROD 0.005-39 µg/L	Determine whether S100B (& apoA-I) discriminate between patients with & without mild TBI, & between mild TBI patients with & without intracranial pathology	S100B higher in CT+ (0.292 µg/L) vs CT- (0.144 µg/L) AUC 0.69 for CT+ vs CT- At threshold of 0.1 µg/L, sensitivity 87%, specificity 36%. S100B higher in mild TBI (0.149 µg/L) vs healthy volunteers (0.071 µg/L) AUC 0.71 for mild TBI vs controls

Wolf[261] *2013*	Mild TBI (107)	59	56	NS	Determine whether the combination of an increase of S100B (& NSE) is associated with CT+	S100B higher in CT+ (0.21 g/L) vs CT- (0.7 µg/L) AUC for S100B alone 0.63 for CT+ vs CT- Regression model including S100B, NSE, nausea, amnesia, vomiting, & loss of consciousness had AUC 0.88
Laribi[325] *2014*	Mild TBI (431)	36	65	ROD 0.005-39 µg/L Threshold 0.1 µg/L	S100B to discriminate between CT+ vs CT-	6% CT+ S100B higher in CT+ (0.21 µg/L) vs CT- (0.11 µg/L). AUC 0.69 for CT+ vs CT- Sensitivity 100%, specificity 38%, PPV 10%, NPV 100%.
Thaler[326] *2015*	Mild TBI (782)	83	31	ROD 0.005-39 µg/L Threshold 0.105 µg/L	Determine NPV for S100B for intracranial pathology in patients with mild TBI who are either on anti-platelet medication or aged >65	6% CT+ Sensitivity 98%, specificity 35, PPV 9%, NPV 100%
Asadollahi[327] *2016*	Mild TBI (158)	35	52	ROD 0.02-30 µg/L Threshold 0.11 µg/L	Determine predictors for intracranial abnormality in patients with mild TBI including S100B & clinical variables	50% CT+ S100B higher in CT+ (0.68 µg/L) vs CT- (0.10 µg/L) AUC 0.7 for S100B alone to discriminate between CT+ & CT- LOC & PTV associated with CT+
Welch[328] *2016*	Mild to moderate TBI (251)	46	60	NS	Compare GFAP & UCH-L1 with S100B to discriminate between CT+ vs CT-	14% CT+ AUC 0.75 for S100B to discriminate between TC positive & CT-

Table 1.11. Characteristics of S100B studies

a = absolute values of UCH-L1 calculated from graph in source paper using plot digitizer. % M, percentage male; LOD, limit of detection; ROD, range of detection; NPV, negative predictive value; PPV, positive predictive value; Ctrl, control; MVC, motor vehicle collision; TBI, traumatic brain injury; LLOD, lower limit of detection; CT, computed tomography; CT+, acute intracranial abnormality on CT; CT-, no acute intracranial abnormality on CT; AUC, area under the (receiver operating characteristic) curve; PCS, post-concussion syndrome; NSE, neuron specific enolase; GOS-E, Glasgow Outcome Scale – Extended; MRI, magnetic resonance imaging; LR-, likelihood ratio for a negative test; GOAT, Galveston Orientation and Amnesia Test; RPQ; Rivermead Post-concussion Symptom Questionnaire; ED, Emergency Department; GFAP, glial fibrillary acidic protein; UCH-L1, ubiquitin C-terminal hydrolase L1; apoA-I, apolipoprotein AI; HI, head injury; LOC, loss of consciousness; PTV, post traumatic vomiting.

Neuronal cell death

Spectrin breakdown products

The spectrin family of proteins are molecules associated with the cell membrane of various tissues.[329] Their functions include the maintenance of the cell membrane-cytoskeleton interface.[330,331] Spectrin is composed of an alpha subunit, of which there are two, αI and αII, and a beta subunit, of which there are five.[332] In the event of neuronal stress such as following a TBI, damage to the neuronal cell membrane leads to catabolism of membrane and cytoskeletal elements. This in turn leads to catabolism of spectrin by calpain or caspase-3 to signature breakdown products, which are described in terms of the catabolic agent and the molecular weight in kilodaltons.[329,333] In patients with severe TBI, alpha-II spectrin breakdown products (αII-SBDP) are detectable in CSF, are higher in TBI patients than controls, are associated with severity of injury, and correlate with survival.[333-335] Although there is limited evidence to support the clinical use of spectrin breakdown products in mild TBI, an αII-spectrin breakdown product called calpain-cleaved αII-spectrin N-terminal fragment (SNTF) was measured in 38 Emergency Department patients who had either mild TBI or musculoskeletal injuries, or were healthy volunteers.[138] SNTF was elevated in seven of 17 mild TBI patients and three of 13 patients with musculoskeletal injuries, but in none of the healthy volunteers. SNTF also correlated with cognitive impairment at three months. SNTF was also elevated in concussed ice hockey players and exhibited diagnostic accuracy for concussion, particularly in players that had delayed return to play.[336]

Post-injury neurodegeneration

Tau protein

Tau proteins bind and stabilise microtubules, predominantly in cells of the central nervous system.[337] How effective they are at binding microtubules depends on their phosphorylation status. Non-phosphorylated tau proteins are more effective than phosphorylated tau at binding and polymerising microtubules.[338] Tau aggregates with ubiquitin (above) to form intracellular neurofibrillary tangles, which are the hallmark neuropathological changes found in Alzheimer's Disease. Although Tau has been investigated as a biomarker in mild TBI, it is most commonly referred to as a diagnostic requirement in chronic traumatic encephalopathy. In a study of 36 patients with mild TBI, tau was not correlated with three month post-concussion symptoms, and had poor prognostic ability with an AUC of 0.6.[339] A separate study looking at three month symptom outcomes also found no difference in tau levels in patients with and without post-concussion symptoms.[340] The previously noted studies recorded tau levels on the day of injury. When measured at the time of outcome measurement, for instance at three months, and when measured on a novel ultrasensitive single molecule array (SIMOA) assay, a number of studies have identified elevated tau. Compared with healthy volunteers, tau was elevated in 70 US soldiers that sustained repeated mild TBI during deployment many months or years prior to tau measurement.[341] In a study recruiting all types of TBI, tau was elevated (compared with healthy volunteers) at days 0, 30 and 90, and most maximally at day zero.[289] In 217 patients with TBI, phosphorylated tau and the total-tau-phosphorylated-tau ratio, when measured on a SIMOA assay, performed highly at discriminating between CT positive and CT negative TBI patients, with AUCs of more than 0.9 for both.[342] Total tau

discriminated more poorly with an AUC of 0.6. Phosphorylated tau and total-tau-phosphorylated-tau ratio both discriminated weakly between patients with poor and not poor outcomes (GOS-E ≤ 4 vs >4) (AUC 0.66 and 0.66 respectively), and good and not good outcomes (GOS-E ≥ 7 vs < 7) (AUC 0.77 and 0.78 respectively) at six months. In 60 patients with mild TBI compared with 20 healthy volunteers, there was no difference between mean tau levels in each group, nor between mild TBI patients with and without acute intracranial abnormality on CT.[343]

Future biomarkers: micro-RNA and interleukins

Micro-RNAs are small non-protein-coding RNA sequences that are implicated in post-transcription protein regulation.[344] Micro-RNAs play a role in regulating protein synthesis, and are implicated in cellular elements of nervous system injury and repair.[345,346] In a study attempting to identify potential micro-RNAs that can discriminate between mild and severe TBI, miR-21 and miR-335 were significantly upregulated, and miR-425-5p and miR-502 were significantly downregulated.[345] In another study, some micro-RNAs, including miR-21, miR-16 and let-7i were found to discriminate between mild and severe TBI.[347] The micro-RNAs miR-153-3p, miR-223-3p, and miR-let-7a-5p have been shown to be significantly higher in athletes with sports related concussion compared to pre-concussion baseline levels.[344]

Interleukins are cytokines; inflammatory mediators released in response to insult or injury. In a study involving a series of validations, out of an initial panel of 92 biomarkers, IL-10 was identified as one of three biomarkers that were sufficiently specific at a sensitivity of 100% to show promise in discriminating between CT positive and negative patients with mild TBI.[348] However, although

IL-10 was significantly higher in CT positive compared to CT negative patients, at 100% sensitivity, the specificity was 31%, and neither the area under the receiver operating characteristic curve, nor the negative predictive value were reported.

Copeptin

Vasopressin, also known as arginine vasopressin or anti-diuretic hormone, is a nonapeptide produced by the hypothalamus.[349] Circulating vasopressin is increased when a patient has an infection associated with physiological stress, including hypotension, hypoxia, and hyperosmolar states.[350-352] Vasopressin has been used as a biomarker and pro-contractility agent in critical illness and septic vasodilatory shock, however its instability makes it difficult to use in routine clinical care.[353-356] Arginine vasopressin is derived from a larger precursor peptide (pre-provasopressin) along with two other peptides, copeptin and neurophysin II.[357] Copeptin is a 39 amino-acid glycopeptide, the C-terminal of pre-provasopressin, and is stable for days after blood withdrawal therefore accurately reflecting acute levels of vasopressin.[357] In a study of patients with acute exacerbation of chronic obstructive pulmonary disease, using an assay with a threshold of normal of 2.25 pmol/L the average copeptin level was 12.4 pmol/L, which was significantly associated with prolonged hospital stay and long term treatment failure.[358] In patients with ischaemic stroke, copeptin levels increased with increasing severity of stroke, and were higher in patients with poorer outcomes both in the short and long terms.[359-361] Similar findings were reported in patients with haemorrhagic stroke, with copeptin levels higher in patients that died or had poorer functional outcomes.[362,363] Elevated copeptin levels have also been found to be associated with increased risk of all cause and

cardiovascular mortality in primary care patients with heart failure.[364] An association between abnormal levels of copeptin and severity of brain injury in TBI patients has been described, and in severe TBI patients elevated copeptin was significantly associated with short and long term mortality.[365-367] Mild TBI may also be associated with upregulation of proinflammatory mediators such as copeptin, but has not been extensively investigated in this patient group.[368,369] In the only study investigating copeptin in mild TBI, copeptin rose by 3.4 times in the acute phase after injury, and had an AUC of 0.9 to discriminate between patients with mild TBI and healthy controls.[370]

Summary

Acquired brain injury is a common reason for patients to attend Emergency Departments, and mild TBI is a commonly made diagnosis after a head injury. How mild TBI is diagnosed is contentious because some of the elements that make up the diagnostic criteria occur before the patient arrives at the Emergency Department and are elements that the patient often cannot remember. Hence a greater reliance is placed on witnesses, which are often unreliable. Assessment of the severity of mild TBI is important because it predicts outcomes, however, the best method of assessment is also controversial. There are multiple symptoms that may follow a mild TBI but the exact clinical course that a patient may take is not known. The consequences of mild TBI include post-concussion symptoms and cognitive dysfunction. These symptoms and signs are commonly assessed using specialist neuropsychological tests, which can take days to apply, and require specialist interpretation. There is a requirement for an accurate neuropsychological test that can identify the degree of cognitive impairment or function that a patient has and that can be applied after minimal training by clinicians in an Emergency Department. Of great value would be to have the capability to apply the test and be able to advise a patient with mild TBI how the test results might change over time, and how that might make them feel. The Standardized Assessment of Concussion and the Concussion Symptom Inventory are two tests that could provide that function. In addition to the symptoms and signs a patient may experience immediately after a mild TBI, the injury may subsequently affect that patient's ability to remain in employment. Patient centred outcomes are particularly relevant when discussing consequences of injuries with patients in an Emergency Department

setting. This may be the only opportunity to explain to a patient what has happened to them and what they can expect to experience. The capacity to be able to prognosticate, that is, to describe to a patient the chance of an outcome occurring, is of great value both to the patient and to the physician. A pragmatic real-world outcome that can be readily measured is whether or when a patient returns to work after an injury.

S100B is the most established biomarker for mild TBI and is associated with compelling evidence for its use in discriminating patients with acute abnormality on CT from those without. The evidence that it discriminates between patients that will go on to have longer term sequelae and those that will not, is not as compelling. Nevertheless, S100B is incorporated into the head injury assessment guidance of several European countries. An important consequence of mild TBI is seizure, which can occur at the time of injury, soon after or persist to become post-traumatic epilepsy. Seizure is also a common reason for patients to attend the Emergency Department. Seizures carry a significant morbidity in themselves and can result in poor outcomes such as physical injury, time off from working, degeneration into status epilepticus and hypoxic brain damage and death. Identifying the proportion of patients with seizure that attend the Emergency Department following a mild TBI, and the risk of recurrence after seizure of any kind, is important because an intervention could be made to reduce the risk of recurrence and consequent potential poor outcomes.

Research Aims

1. To investigate the relationship between mild traumatic brain injury and the time it takes for a patient to return to work after the injury.
2. To investigate the short-term changes in neurocognitive function and symptom burden following mild traumatic brain injury.
3. To determine the number of patients with traumatic brain injury that attend the Emergency Department with a seizure and investigate the value of the biomarkers S100B and copeptin in predicting outcomes following seizure.

Chapter 2 A Systematic Review and Meta-analysis of Return to Work after Mild Traumatic Brain Injury

Introduction

There are many outcomes reported following mild TBI and their pragmatic relevance can be difficult to apply or communicate to patients immediately after injury. Mild TBI outcomes include assessments for symptoms, functional outcomes, fatigue, pain, insomnia, depression, resilience and neuropsychological test scores.[371-373] Persistent symptoms or cognitive deficits can impact on a patient's ability to work.[371,374-377] Some researchers estimate up to a third of patients have persistent problems with employment at six months.[378] This variation in rates of return to work may be due to differences in the definition of mild TBI, geography, classification of occupation, or payment systems.[74,174,379-381] The indirect costs, i.e. cost of resources lost owing to illness, associated with TBI in Europe, is estimated at around €20 billion a year.[76] Return to work is a pragmatic real-world outcome with direct relevance to patients and quality of life, and thus a clear understanding of the numbers of patients that return to work is essential.[77-79] This review aims to determine the time taken for an adult to return to work or usual activities after they sustain a mild TBI.

Methods

Primary objective

The primary objective for this study was to determine how long it takes adults that have sustained a mild TBI to return to work following the injury.

Outcomes

Primary outcome

The primary outcome was return to work. This could be reported either as an average (mean or median) time from injury to return to work, as the number of sick days taken, or whether the patient had returned to work at or by a pre-defined point in time after injury. Return to work was defined as any return to work regardless of level of duty. The aggregation of all levels of return to work was taken for pragmatic reasons as the expectation was that the degree of heterogeneity associated with including levels of return to work would preclude analysis.

Secondary outcome

The secondary outcome was the degree of return to work, which was defined as either to the same duties as prior to injury, or to modified duties. Modified duties were defined as reduced time at work or less physically or mentally demanding duties at work.

Eligibility

Inclusion criteria

Articles were included if they met the following criteria:

Population

- Adults (16 years or above) with mild TBI. Articles were accepted if mild TBI was defined by the authors, but definitions of mild TBI were expected to be those derived by the American Congress of Rehabilitation Medicine, the American Academy of Neurology, the World Health Organisation Collaborating Task Force on MTBI, or the Center for Disease Control and Prevention (Appendix 1).[6,8,382] Studies including patients with moderate or severe TBI were included if a mild TBI subgroup was reported separately.

Setting

- Patients were identified or recruited from any area so long as they fulfilled the inclusion criteria. This could have been from the Emergency Department, an in-patient ward, or an out-patient clinic.

Study design/publication type

- Controlled trial or observational cohort study (retrospective or prospective, i.e. case-control, cohort, or cross-sectional) reporting 30 or more patients with mild TBI.

Language

- English or translation into English available.

Exclusion criteria

- Studies that recorded the final measurement of return to work at less than one month, or the first measurement at more than one year were excluded. This excluded papers that measured return to work only over a very short time after injury or only following a very long time after injury.
- Studies that recorded only moderate or severe TBI or studies from which it was not possible to isolate a mild TBI subgroup were excluded. This excluded papers that did not include analysable patients with mild TBI.

Study design

This was a systematic review and meta-analysis of return to work following mild TBI. The protocol for this study was written according to guidance set out in the Preferred Reporting Items for Systematic review and Meta-Analysis Protocols (PRISMA-P) 2015 statement.[383,384] The methods described below were designed in accordance with the Preferred Reporting Items for Systematic review and Meta-Analysis (PRISMA) statement (Appendix 4Appendix).[385] The protocol was registered with PROSPERO (reference CRD42018086349).[386]

Information sources

The following electronic databases were searched: Embase, Medline, PsycINFO, PubMed, the Cochrane Central Register of Controlled Trials, the Trip database, Clinicaltrials.gov, the European Clinical Trials Registry, the International Standard Randomised Controlled Trials registry (ISRCTN), the Australia and New Zealand Clinical Trials Registry, the Clinical Trials Registry of India, the China Clinical Trials Registry, the Brazilian Clinical Trials Registry, and the Pan-African Clinical Trials Registry.

Search strategy

Medline was searched using the following terms: (((tbi).ti,ab OR (mtbi).ti,ab OR (mild tbi).ti,ab OR ("mild tbi").ti,ab OR (minor tbi).ti,ab OR ("minor tbi").ti,ab OR (mild traumatic brain injury).ti,ab OR ("mild traumatic brain injury").ti,ab OR (minor traumatic brain injury).ti,ab OR ("minor traumatic brain injury").ti,ab OR (mild head injury).ti,ab OR ("mild head injury").ti,ab OR (minor head injury).ti,ab OR ("minor head injury").ti,ab OR (mild head trauma).ti,ab OR ("mild head trauma").ti,ab OR (minor head trauma).ti,ab OR ("minor head trauma").ti,ab OR (minor brain trauma).ti,ab OR ("minor brain trauma").ti,ab OR (concussion).ti,ab OR (concus*).ti,ab) AND (("return to work").ti,ab))) OR (((exp "BRAIN CONCUSSION"/) OR (exp "BRAIN INJURIES"/ OR exp "CRANIOCEREBRAL TRAUMA"/)) AND (exp "RETURN TO WORK"/)). The full search strategy for all databases is available in Appendix 5Appendix .

Study records

Data management

Articles were downloaded from the searched databases as a Research Information Systems (RIS) file into Endnote X8.0.1 (Clarivate Analytics, Philadelphia, PA, USA). From Endnote, all articles were uploaded into Rayyan, an online platform designed to assist in collaborative systematic reviews.[387]

Selection process

I performed an initial screen of identified articles by applying inclusion criteria, based on the titles and abstracts. Full text copies of the articles that met inclusion criteria, based on the title and abstract, were obtained and then reviewed as part of a second round of selection. During the second round, I and

another reviewer (JA) independently re-applied inclusion criteria and applied exclusion criteria applied. In cases of non-agreement, a third reviewer (RW) adjudicated.

Data collection process

Once all eligible articles were identified, data were abstracted from the full text article into a Microsoft Excel file. In cases in which data were not present in the published article but it seemed likely that relevant data existed but was unpublished, I contacted the authors of the relevant articles.

Risk of bias in individual studies

Newcastle Ottawa Quality Assessment Scale

Multiple tools for assessing bias have been developed, with no single tool being globally accepted.[388] The most important domains of a tool are appropriate selection of participants, appropriate measurement of variables and appropriate control of confounding.[388] In this review, I used a modified version of the Newcastle Ottawa quality assessment scale.[389] The Newcastle Ottawa quality assessment scale comprises three domains: patient selection, patient group comparison, and whether the patient actually had the outcome purported to be measured. The scale categorises studies according to quality within each domain. Assessment of bias resulting from confounding factors, or patient group comparison, was less relevant to this review, because the focus was on a single patient group with a single outcome. Therefore, a modified version of the Newcastle Ottawa scale was used, which did not include an assessment of a non-exposed cohort or comparability of cohorts. Disagreements between the abstractors over the risk of bias in specific studies were resolved by adjudication by a third abstractor. Within each of the domains of Selection and Outcome are

three questions, and each question has a categorical answer, as below. Each study was subjected to six questions; three that assess selection bias and three that assess outcome bias.

Assessment of selection bias

A. Representativeness of the exposed cohort
    1. Truly representative of the average mild TBI
    2. Somewhat representative of the average mild TBI
    3. Selected group of users e.g. Nurses, volunteers
    4. No description of the derivation of the cohort
B. Ascertainment of exposure
    1. Secure record (e.g. clinical record)
    2. Structured interview
    3. Written self-report
    4. No description
C. Demonstration that outcome of interest was not present at start of study (Ascertainment of pre-injury employment status)
    1. All patients employed
    2. Patients were employed, including student/homemaker/other activity
    3. Pre-injury employment status unclear
    4. Pre-injury employment status not described

Assessment of outcome bias

A. Assessment of outcome
    1. Independent blind assessment
    2. Record linkage
    3. Self-report
    4. No description
B. Was follow-up long enough for outcomes to occur
    1. Yes (at least one month)
    2. No
C. Adequacy of follow up of cohorts
    1. Complete follow up - all subjects accounted for
    2. Subjects lost to follow up unlikely to introduce bias - lost <20% follow up, or description provided of those lost)
    3. Subjects lost to follow up likely to introduce bias - >20% loss to follow up
    4. No statement

Data items

See Appendix 2 for the data abstraction sheet. The following data items were abstracted from included studies.

1. Author
2. Journal
3. Year
4. Study or trial
5. Prospective or retrospective
6. Return to work reported as average or as proportion at pre-defined time

7. Number of patients in study
8. Number of patients followed up
9. Percentage followed up out of included
10. Number of patients in groups
11. Name(s) of group(s)
12. Setting
13. Age
14. Sex
15. Education
16. Definition of mild TBI
17. Post traumatic amnesia
18. Loss of consciousness
19. Whether patients had intracranial haemorrhage
20. Return to work level of duty
21. Average time to return to work
22. Pre-defined time point(s) at which proportion returned to work was measured
23. Proportion of patients that returned to work by time point(s)
24. Excluded patients if they had mental health problems, drugs/alcohol, previous TBI
25. Assessment of bias measures in accordance with modified Newcastle Ottawa Quality Assessment Scale

Statistical analysis

Data handling and descriptive analysis approaches

Data were obtained in a systematic fashion as described above. Excel data were then imported in Stata for analysis (version 15MP, StataCorp, College Station TX, USA). All analyses were executed with Stata, using commands that are not actually included in the off-the-shelf versions of the software but are instead user written. Despite the "non-official" nature of the commands, they are quite well-documented (e.g. in the *Stata Journal*) and the meta-analysis command sets are broadly accepted.

Some of the aggregate studies' data were reported in descriptive fashion. For such reporting of continuous data, normality testing was first executed using the Shapiro-Wilk test. The Shapiro-Wilk tests the hypothesis that the data is not normally distributed, and therefore the null hypothesis that the data is normally distributed. A significant p value, which corresponds to rejection of the null hypothesis of normality, means that the data is not normally distributed. The central tendencies of non-normally distributed data were reported as medians with interquartile range (IQR), and that of normally distributed data as means ± standard deviation (SD). Central tendencies were only calculated for data with at least six observations.

Model formulation

Fixed-effect vs. random-effects

The fixed-effect assumption is that the published articles being assessed are all estimating a single effect-size "truth" that is theoretically shared in all of the studies. Whatever selection and other biases may exist in the study set; the judgment of an investigator is that the underlying "truth" is the same. In a fixed-

effect paradigm, the effect that is observed is denoted T_i and this is a function of the true population effect mean (μ) and an error term ε. The fixed-effect means that there are no other sources of deviation of T_i besides the within-studies error. The weighting of the meta-analysis thus follows a simple inverse-variance formula, weighting studies on the amount of information within those studies, so each study (i) has a weight equal to $1/v_i$.

In the random-effects model, each study is said to estimate a different parameter (e.g. return to work in patients who are somehow different in one study as compared to another). The random-effects model postulates that differences in varying studies' results are not simply a function of sampling.

The random-effects model approach allows for differences in patients, study design, or any other factor(s) that could contribute to identification of different point estimates for return to work across the included analyses. In most cases the random-effects model is more conservative. The random-effects model calculates a variance parameter, which represents the heterogeneity across studies. When the variance parameter is estimated at zero the random-effects model essentially reduces to a fixed-effects model.

In this study, a random-effects meta-analysis was preferentially used to pool the mean proportion of patients that had returned to work by a specific time point. The random effects rather than fixed effect method was selected because the sample populations were expected to be sufficiently varied to assume that any variation in return to work between studies would not have been due to chance. Specifically, patients were expected to have been recruited from different settings or to have different injury characteristics (proportions with complicated

mild TBI, lengths or proportions of post-traumatic amnesia and loss of consciousness).

Estimated parameter in this meta-analysis: Stata commands and associated statistical approach

The study employed Stata's *metaprop* command set, which is an extension of Stata's *metan* suite of commands.[390,391] The *metaprop* command suite includes reporting of I^2 and also a reporting of a p value assessing for heterogeneity. Based on the work by Higgins et al the preferred measure of heterogeneity is the I^2.[392] This runs from 0%, meaning that all inter-study variation is due to chance, to 100%, meaning that all inter-study variation is due to heterogeneity between studies. I^2 interpretation guidelines are not rigidly set. The suggested specific adjective wording for interpreting I^2 is follows: ≤25% = low, 25-50% = moderate, and ≥75% = high heterogeneity. An alternative measure of heterogeneity is Cochrane's Q, calculated as a weighted sum of squared differences between the individual effect and the pooled effect. It is distributed as a χ^2 statistic. The hypothesis tested by the Cochran's Q test is that the variables analysed are different, and therefore the null hypothesis is that there is no difference between the variables. If the p value is significant, then the null hypothesis is rejected. The conclusion therefore is that the proportions in at least two of the variables are significantly different to each other, i.e. that there is heterogeneity. The magnitude of variance between studies was measured with the τ^2 statistic.[393] The τ^2 statistic is the estimate of the variance of the true effect size between studies, with the assumption that the effect is randomly, normally distributed between studies.

Ninety-five percent confidence intervals and two-sided p-values were calculated for the summary effect sizes. Assessment of any sources of heterogeneity was performed using meta-regression. Publication bias is commonly reported in systematic reviews and meta-analyses investigating efficacy studies, however funnel plots have been found to be an inaccurate measure of reporting bias in studies of proportion and consequently were not be performed as part of this analysis.[394]

Results

Baseline data

Six databases and six clinical trial registries returned a total of 978 unique titles. Following application of the inclusion criteria to the titles and abstracts, and then reapplication of the inclusion and application of the exclusion criteria to full text copies, fourteen studies were identified for the final data abstraction (Figure 2.1).

Two studies reported the outcome as the average time taken for patients to return to work (Reynolds et al, Iverson et al[171,395]), 11 reported the outcome as the proportion of patients that returned to work at pre-specified time points,[74,169,174,312,376,396-401] and one reported both[371] (Table 2.1 and Table 2.2). All studies except one reported mean age, which ranged from 28 to 46.5 years.[376] Five studies reported an age range, which was from 16 to 65 years.[171,174,376,395,398] The lower age was 16 in four studies and 19 in a fifth, and the upper age ranged from 46 to 65. The proportion of male sex ranged from 45% to 77% in the 14 studies (Table 2.1 and Table 2.2).

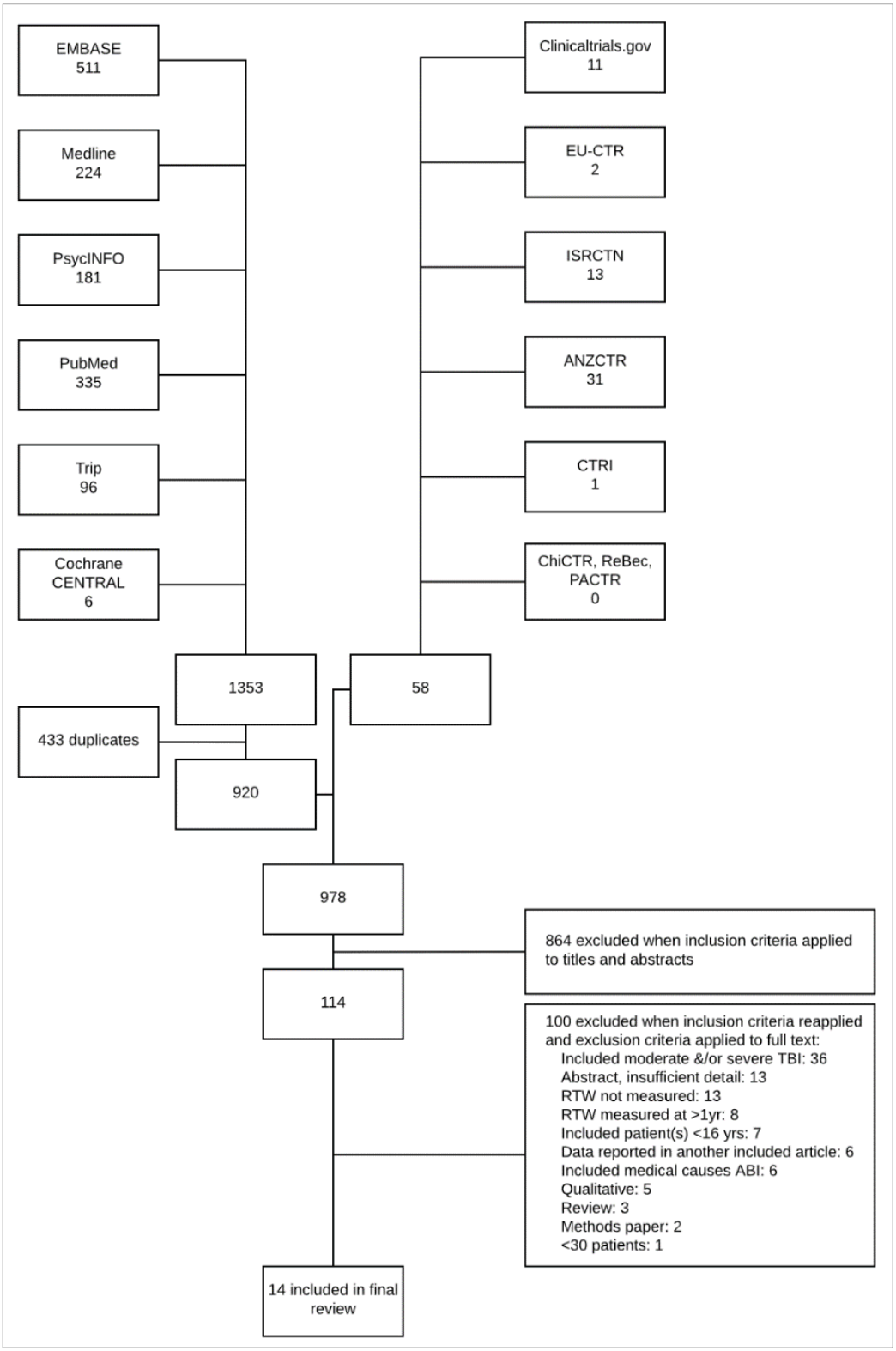

Figure 2.1 Article inclusion flow chart

CENTRAL, Cochrane Central Register of Controlled Trials; EU-CTR, European Union Clinical Trials Registry; ISRCTN, International Standard Randomised Controlled Trials Number; ANZCTR, Australia and New Zealand Clinical Trials Registry; CTRI, Clinical Trials Registry of India; ChiCTR, Chinese Clinical Trial Registry; ReBec, Brazilian Clinical Trials Registry; PACTR, Pan-African Clinical Trials Registry; TBI, traumatic brain injury; RTW, return to work.

Studies reporting average time to return to work

Three studies reported average time to return to work (Table 2.1).[171,371,395] Of the studies reporting average time to return to work, the largest, by Reynolds et al (n=118), reported a group with the shortest average time to return to work.[395] This study grouped patients into those not seeking compensation for their injury (non-seekers), those seeking social benefits, those in litigation, and both. For non-seekers (n=62), the median time to return to work was four days, but mean was 72 (SD 139). Those seeking social support (n=14) or in litigation (n=15) were similar to each other with median time to return to work 43 and 40 days (mean 114 [SD 137] and 100 [SD 136]) respectively. Only six patients sought both, and their return to work times were longest; median 304 days (mean 245 [SD 175]). Iverson et al reported return to work in patients with uncomplicated and complicated mild TBI. In patients with uncomplicated mild TBI the median time to return to work was 6 days (IQR 1-15, mean 13 [19]), compared to 36 days (IQR 14-53, mean 58 [84]) in patients with complicated mild TBI.[171] There was a significant difference in return to work times between the two groups, but the differences between the mean and median, the large SD and IQR, and the small numbers in the groups, indicate significant variation. This variation was seen in all three studies that report average time to return to work. Iverson et al and Losoi et al reported the proportion of patients with complicated mild TBI (28% of 47 patients and 10% of 115 patients).[171,371] Those same two studies report post-traumatic amnesia, but the results are very different; 333-366 minutes in the study by Iverson et al, containing 47 patients, and 156 minutes in the study by Losoi et al, containing 115 patients. Losoi et al reported loss of consciousness and all three reported years of education, which were from 13 to 14 years (Table 2.1). Reynolds et al did not report mechanism of injury, Iverson et al reported

only the proportion of patients involved in an MVA (44%), and Losoi et al reported mechanism in all patients.[171,371,395]

Reference, setting and mechanism	Definition	N	FU	Excl.	Age (mean [SD])	% Male	Education (years)	Severity: % with abnl CT	LOC: % with LOC	PTA: Time, % with PTA	Return to work in days Mean (SD) or median (IQR)
Reynolds, S, 2003[395] *Identified from hospital emergency wards, invited to enrol by telephone/ letter, recruited mean 12 days from injury. Mechanism not reported but these patients were classified according to their status of seeking compensation for their injury: 64% not seeking, 14% seeking administrative compensation, 16% in litigation, 6% both.*	ACRM	118	88%	Yes	33 (12)	45%	14 years	---	---	---	93 (140) *
Iverson, GL, 2012[171] *Identified in and recruited from ED of Tampere, University Hospital, Finland. 44% MVA. Divided patients into those with UC & C mTBI.*	WHO	47: UC. 34 C. 13	100%	No	30 (9)	51%	13 years	28%	---	UC. 333 C. 366	*Overall:* Mean 25 (50) * *Uncomplicated:* Mean 13 (19), Median 6 (1-15) *Complicated:* Mean 58 (84), Median 36 (14-53)
Losoi, H, 2016[371] *Identified in and recruited from ED of Tampere, University Hospital, Finland. Sports 18%, falls from height 16%, car accidents 16%, bicycle accidents 15%, ground-level falls 14%, motorcycle accidents 7%, violence related injuries 5%, other 10%.*	WHO	115	87%	Yes	37 (12)	61%	14 years	10%	37%	156 min 92%	Mean 55 (139) Median 16 (5-42)

Table 2.1 Studies that report an average number of days taken to return to work

N, number included in study; % FU, percentage of sample followed up for return to work outcome at first follow-up time point; Excl., patients excluded if they had a history of mental health problems, drugs, alcohol or previous TBI; SD, standard deviation, where not reported, not available; IQR, inter-quartile range; ED, Emergency Department; definition is the definition of mild TBI used in the source article; LOC, loss of consciousness; PTA, post traumatic amnesia; ACRM, American Congress of Rehabilitation Medicine; ---, not available/reported; MVA, motor vehicle accident; UC, uncomplicated mild TBI (no acute abnormality on computed tomography [CT] head); C, complicated mild TBI (acute intracranial abnormality on CT head); WHO, World Health Organisation Collaborating Task Force on MTBI. *Overall mean (SD) calculated by authors.

Reference, setting and mechanism	Definition	N	FU	Excl.	Age: mean (SD)	Sex/ % M	Education average years or % to second-ary	Severity: % with abnorm al CT	LOC: average time, % with LOC	PTA: average time, % with PTA	RTW time point 1, % RTW	RTW time point 2, % RTW	RTW time point 3, % RTW	RTW time point 4, % RTW
Dikmen, SS, 1994[396] *Identified in & recruited on wards at Shock Trauma Units in MA, USA, followed up in clinic. Sample reported included patients with moderate and severe TBI. Data on mTBI extracted for this review. Mechanism not reported.*	Head injury and GCS 13-15	213	---	Yes	30 (11)	77%	12 years	---	---	---	1 month 25% RTW	6 months 63%	12 months 80%	24 months 83%
Ruffolo, CF, 1999[174] *Identified as in-patients at large tertiary care centre in Toronto, Canada, recruited average 13 (SD 7) days post injury. All patients had MVA.*	ACRM	63	79%	Yes	31 (10)	62%	---	---	---	---	6-9 months (mean 7.4) 42% RTW	---	---	---
Haboubi, NHJ, 2001[399] *Identified from ED or <48hrs hospital admission in North Staffs, UK. Recruited in 1st assessment in head injury clinic 2 weeks post injury. MVA 31%, other 28%, assault 27%, sport 8%, industrial 6%.*	Clinical diagnosis	391	38%	No	33	80%	---	---	70%	---	2 weeks 44% RTW	6 weeks 73% RTW	---	---
McCullagh, S, 2001[397] *A consecutive sample of mild TBI patients receiving follow-up care at a tertiary TBI referral clinic in Toronto, Canada. Recruited ~6 months post injury. MVA 74%, sports 9%, falls 8%, assaults 2%, other 7%.*	ACRM	57	100%	No	35 (14)	56%	38% to secondary	---	---	---	Mean 159 (SD 67) days 52%	---	---	---

Hughes, DG, 2004[401] *Identified in and recruited from ED in Salford, UK. Assaults 60%, falls 30%, MVA 9%, 1%.*	ACRM	73	49%	Yes	31	73%	---	6%	53%	39%	6 months 81%	---	---	---
Stulemeijer, M, 2008[169] *Identified in and recruited from ED in a level I trauma centre in Nijmegen, Netherlands. MVA 55%, falls 20%, sports 10%, other 15%.*	EFNS	280	72%	Yes	36 (12)	61%	59% to secondary	20%	36%	61%	6 months 76%	---	---	---
Ryb, GE, 2014[312] *Identified in and recruited from Shock Trauma Center, MA, USA. Excluded complicated mTBI. 55% MVA.*	WHO	180	61%	Yes	35 (13)	64%	34% to secondary	0%	---	---	3 months 66%	6 months 90%	12 months 89%	---
Vikane, E, 2014[398] *Identified during admission to Department of Neurosurgery in Level 1 Trauma Centre, Bergen, Norway, recruited in clinic ~2 months post injury. RTW ascertained from national database. Falls 46%, MVA 20%, assault 24%, sports && other 11%. 10% were injured at work.*	WHO & ACRM	241	100%	Yes	28	65%	56% to secondary	15%	---	8% PTA > 1hr	2 months 80%	12 months 88%	---	---
Waljas, M, 2014[74]*** *Identified in and recruited from ED in Tampere, Finland. Mechanism not reported.*	WHO & ACRM	112	97%	No	37 (13)	48%	13 years	15%	---	---	7 days 47%	14 days 60%	21 days 67%	1 month 75%

Vikane, E, 2016[376] *Identified during admission to Department of Neurosurgery in Level 1 Trauma Centre, Bergen, Norway. Recruited from clinic ~2 months post injury if sick-listed or at risk of being sick-listed with persistent post-concussion symptoms. MVA 55%, falls 20%, sports 10%, other 15%.*	WHO & ACRM	151	100%	Yes	32 (median)	61%	43% to secondary	27%	---	27% PTA > 1 hr	2 months 44%	12 months 76%	---	---
Losoi, H, 2016[371] *Recruited from ED of Tampere, University Hospital, Finland. Sports 18%, falls from height 16%, car accidents 16%, bicycle accidents 15%, ground-level falls 14%, motorcycle accidents 7%, violence related injuries 5%, other 10%.*	WHO	115	87%	Yes	37 (12)	61%	14 years	10%	37%	92% 156 min	1 month 68%	6 months 93%	12 months 96%	---
de Koning, ME, 2017[400] *Identified in and recruited from EDs of three Level 1 Trauma Centres in the Netherlands. MVA 17%, bicycle 32%, pedestrian 3%, fall 38%, violence 5%, sports 2%, other 3%.*	WHO	319	92%	Yes	47 (19)	62%	---	15%	---	---	2 weeks 49%	3 months 79%	6 months 84%	12 months 88%

Table 2.2 Studies that report the proportion of patients that have returned to work at a pre-specified time point
Def. definition of mild TBI used; N, number included in study; FU, percentage of sample followed up for RTW outcome at first follow-up time point; Excl, patients excluded if they had a history of mental health problems, drugs, alcohol or previous TBI; ED, Emergency Department; SD, standard deviation, where not reported, not available; %M, percentage of population that were male; LOC, loss of consciousness; PTA, post traumatic amnesia; RTW, return to work; ED, Emergency Department; ACRM, American Congress of Rehabilitation Medicine; ---, not available/reported; MVA, motor vehicle accident; ED, emergency department; EFNS, European Federation of Neurological Societies; WHO, World Health Organisation Collaborating Task Force on MTBI; IQR, interquartile range. *This article reports a further two time-points: at 2 months 92% had RTW and at 12 months 97% had RTW.

Studies reporting the proportion of patients returned to work by a pre-specified time point

In the 12 studies that described return to work as a proportion, the time points at which patients were most frequently assessed were 12 months (seven studies), six months (six studies), and two months, one month, and two weeks (three studies each) (Figure 2.2). The number of time points at which return to work was assessed in each study varied from one to six (Figure 2.3).

Table 2.3 shows all time points with return to work proportions. Ten studies excluded patients with mental health problems, alcohol or drug use, and previous TBI, nine reported acute abnormalities on CT, five reported loss of consciousness, and six reported post-traumatic amnesia. Two did not report mechanism of injury, and one reported only the proportion involved in a motor vehicle accident. Five recruited patients in the Emergency Department, five as in-patients, and two in clinic. Recruitment times varied from <24 hours from mild TBI to six months (Table 2.1 and Table 2.2).

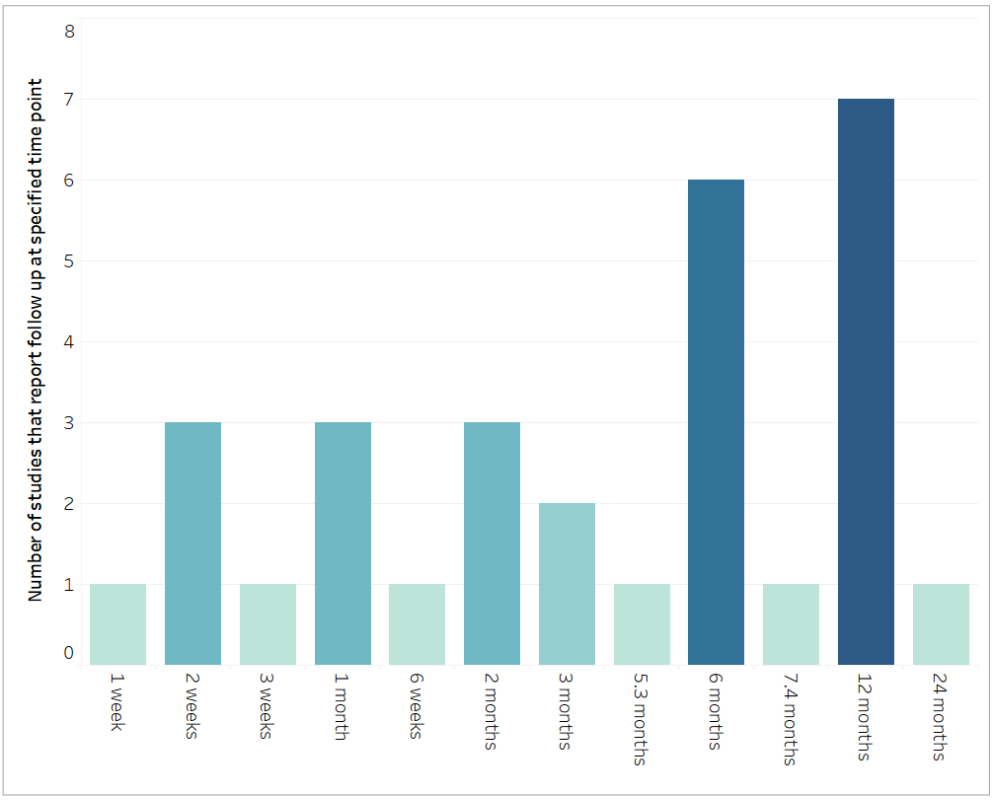

Figure 2.2 Frequency of follow up time points reported

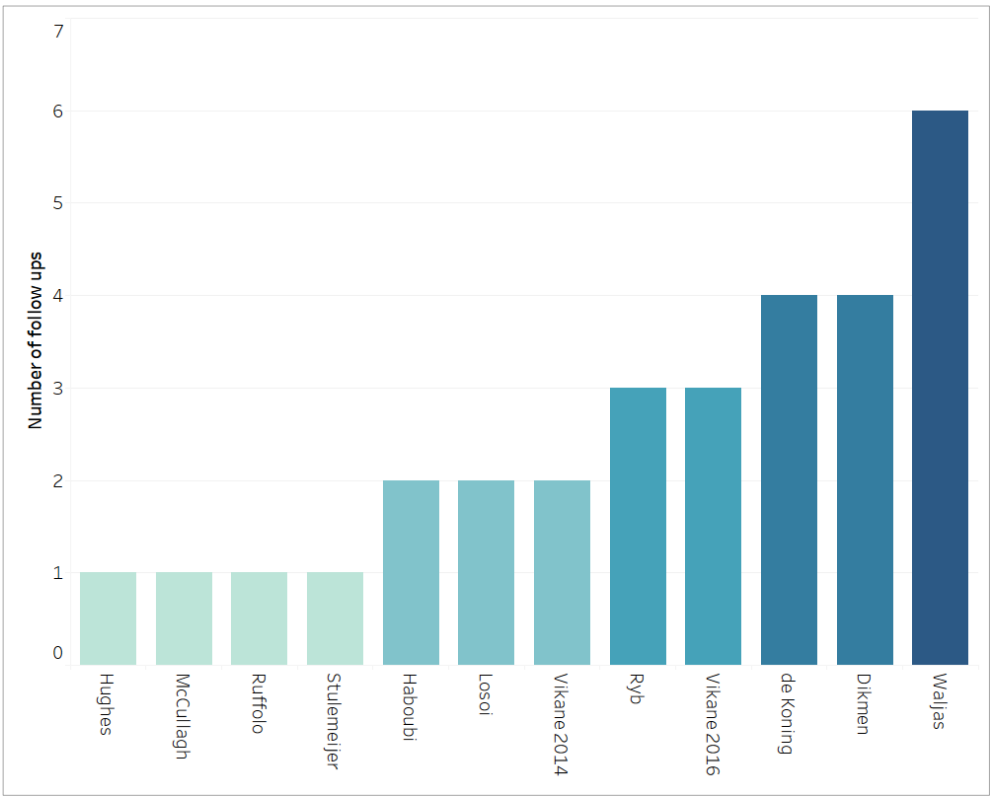

Figure 2.3 Number of follow ups by article

Table 2.4 and Figure 2.4, Figure 2.5, Figure 2.6, and Figure 2.7 show pooled proportions of return to work at pre-specified time points. In the two studies that report return to work at one week after mild TBI, almost half of patients had returned to work.[74,400] Both of those studies recruited patients from the ED, i.e. patients were not deemed sufficiently unwell by treating physicians to warrant admission into hospital.

Three studies reported return to work at one month with rates of 25%, 68% and 75%.[74,371,396] The pooled proportion of patients having returned to work at one month was 56% (95% CI 30-79%). Dikmen et al reported 25% having returned to work at one month, but the results reported in this study are outliers for all time points at which return to work was recorded.[396] This study is more than 20 years old, reported all severities including severe TBI, and patients were drawn from three prospective longitudinal studies. I extracted data on the mild TBI subgroup for this review, and although all patients were unwell enough to warrant admission to hospital, further detail regarding injury severity for the mild TBI subgroup was not available.

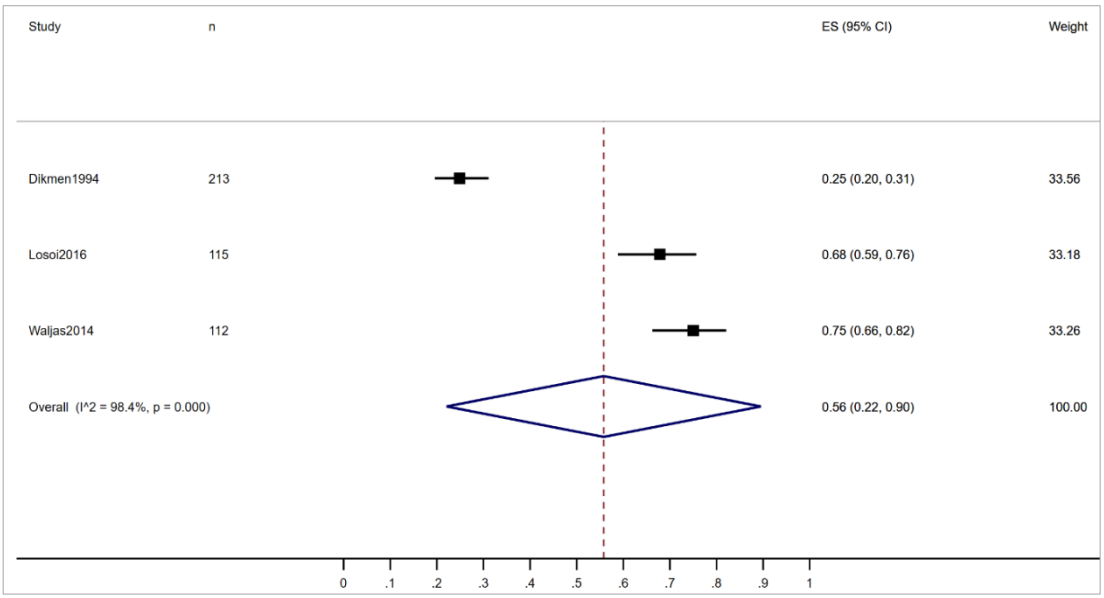

Figure 2.4 Forest plot of proportion of patients returned to work by one month

Three studies reported return to work at two months with rates of 44%, 80%, and 92%.[376,398,400] The pooled proportion of patients that had returned to work by two months was 72% (95% CI 48-96%). Vikane et al reported a substantially lower return to work rate of 44%.[376] The patients in this study were identified whilst admitted acutely to a neurosurgical department and then selectively recruited around two months post injury if they were taking sick leave, or had sufficient persistent post-concussion symptoms that they were deemed at risk of taking sick leave. Therefore, patients with mild TBI without persistent symptoms were excluded from this study. In an adjusted logistic regression model, the authors found one pre-injury variable and three post-injury variables that predicted failure to return to work at 12 months, namely having taken sick leave the year before injury, having anxiety or depression, poorer scores on the Glasgow Outcome Scale Extended or taking sick leave at two months after injury. This study also included patients with the highest proportion of complicated mild TBI at 27%, and although this was not found to be predictive

of return to work at 12 months, the authors did not analyse for return to work at two months.

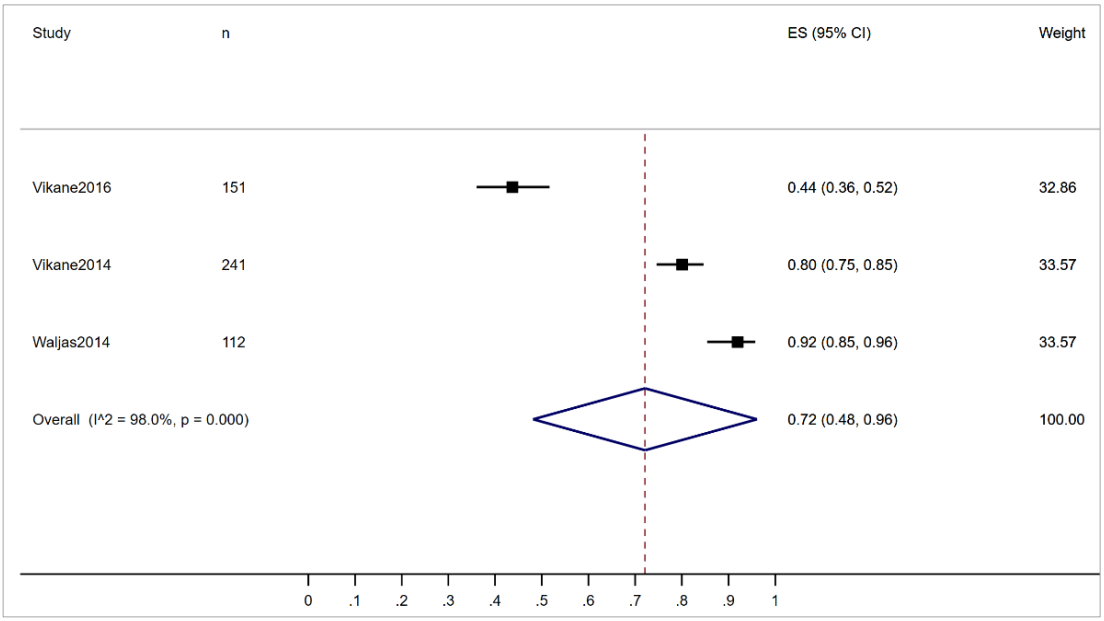

Figure 2.5 Forest plot of proportion of patients returned to work by two months.

At six months, most patients had returned to work in all studies. The pooled proportion of patients that returned to work by six months was 81% (95% CI 73-89%). The lowest rates of return to work were 63%, reported in the study by Dikmen et al, and 76% in the study by Stulemeijer et al of 280 patients with mild TBI identified and recruited from an Emergency Department in the Netherlands.[169,396] The patients in this latter study included one of the highest proportions of patients with complicated mild TBI. This is despite the sample having been recruited from the Emergency Department, and therefore potentially having included patients that were discharged and not admitted into hospital.

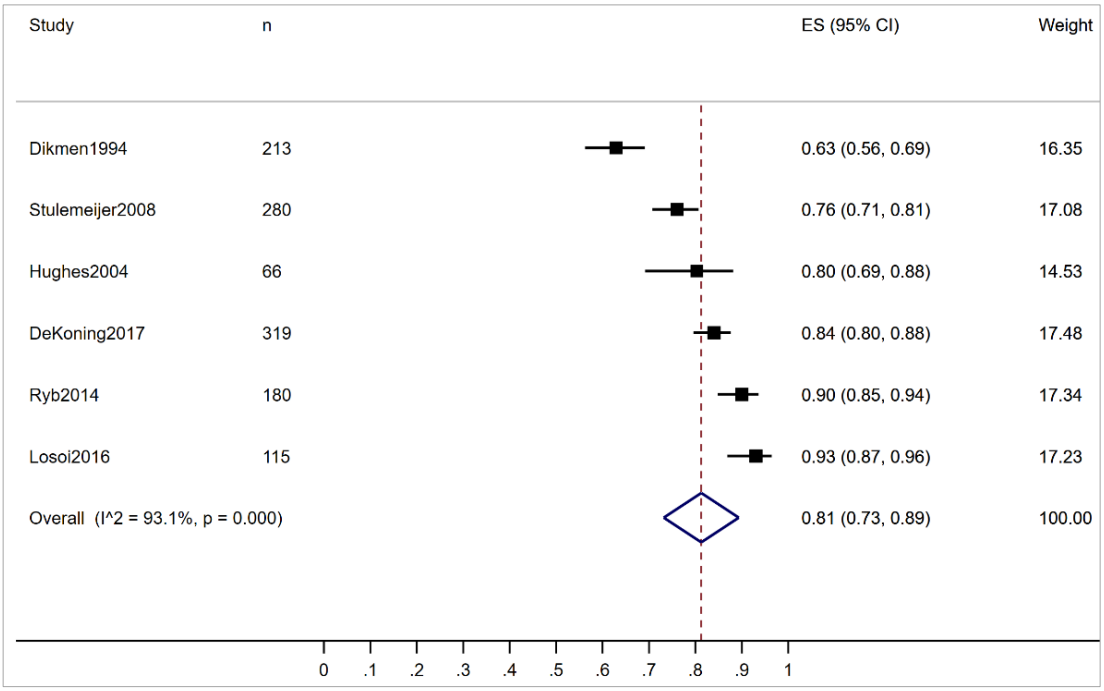

Figure 2.6 Forest plot of proportion of patients returned to work by six months.

At 12 months, the great majority of patients had returned to work, with two studies reporting more than 90% of patients returned to work, four studies reporting 80-90% of patients returned to work, and one study reporting 76% returned to work (Table 2.3). The pooled proportion of patients that returned to work by 12 months was 88% (95% CI 83-93%). The lowest proportion of patients having returned to work at 12 months was 76%, reported in the study noted above for having selectively recruited patients that were both 'sick-listed' or 'at risk of being sick-listed' with persistent post-concussion symptoms.[376]

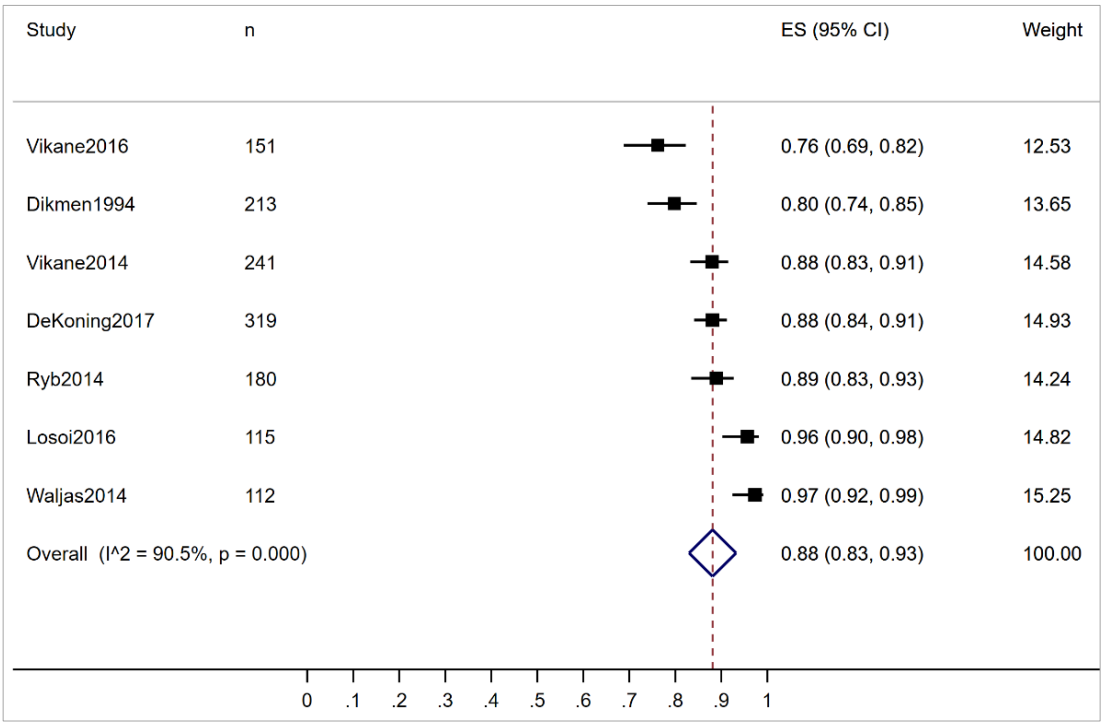

Figure 2.7 Forest plot of proportion of patients returned to work by one year.

For the purposes of this review, I dichotomised any description of levels of return to work as either return to work in any capacity, or not returning to work. The category of 'return to work in any capacity' was an aggregate of 'full' (same duties as prior to injury) and 'partial' return to work (fewer hours and/or lighter duties). Two studies described partial return to work.[174,400] In 42% of 63 in-patients that returned to work at six to nine months, 12% had returned to work at pre-injury levels, and 30% had partial return to work.[174] In 319 Emergency Department patients, the proportion of partial return to work remained broadly consistent at 16-17% at two weeks, three months, and six months but at 12 months was reduced to 10%. In contrast, no return to work gradually dropped from 51% at two weeks to 12% at 12 months, and full return to work gradually rose from 33% at two weeks to 78% at 12 months.[400]

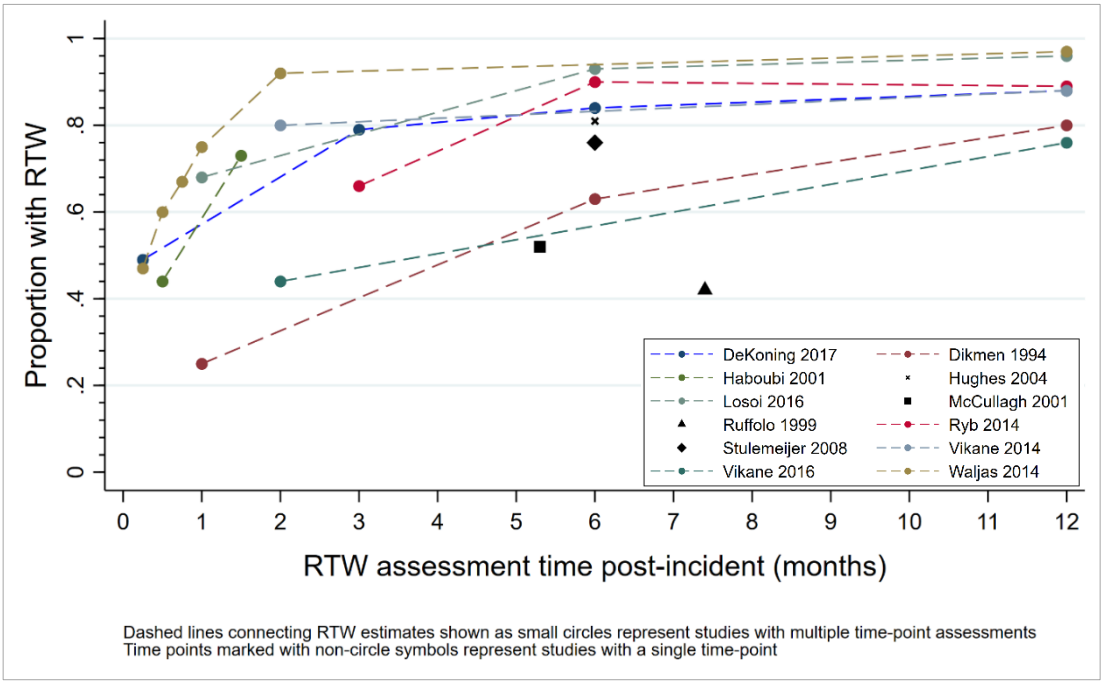

Figure 2.8 Return to work proportions at time points by study. RTW, return to work

Reference	1 week	2 weeks	3 weeks	1 month	6 weeks	2 months	3 months	5 months	6 months	7.4 months	12 months	24 months
Dikmen[396]				25%					63%		80%	83%
Ruffolo[174]										42%		
Haboubi[399]		44%			73%							
McCullagh[397]								52%				
Hughes[401]									81%			
Stulemeijer[169]									76%			
Ryb[312]							66%		90%		89%	
Vikane[398]						80%					88%	
Waljas[74]	47%	60%	67%	75%		92%					97%	
Losoi[371]				68%					93%		96%	
Vikane[376]						44%					76%	
De Koning[400]	49%						79%		84%		88%	

Table 2.3 Percentage of patients returned to work by each pre-specified time point in each article

Study	Proportion RTW	95% CI
One week		
Waljas 2014	0.47	0.38 - 0.57
De Koning 2017	0.49	0.43 - 0.55
Random pooled ES	0.48	0.44 - 0.57
Two weeks		
Haboubi 2001	0.44	0.39 - 0.49
Waljas 2014	0.60	0.51 - 0.68
Random pooled ES	0.48	0.43 - 0.52
One month		
Dikmen 1994	0.25	0.20 - 0.31
Waljas 2014	0.75	0.66 - 0.82
Losoi 2016	0.68	0.59 - 0.76
Random pooled ES	0.56	0.30 - 0.79
$\chi^2 = 125.16$, $p < 0.01$; $I^2 = 98.4\%$, $\tau^2 = 0.09$		
Two months		
Vikane 2014	0.80	0.75 - 0.85
Waljas 2014	0.92	0.85 – 0.96
Vikane 2016	0.44	0.36 - 0.52
Random pooled ES	0.72	0.48 - 0.96
$\chi^2 = 102.08$, $p < 0.01$, $I^2 = 98.0\%$, $\tau^2 = 0.04$		
Three months		
Ryb 2014	0.66	0.59 - 0.73
De Koning 2017	0.79	0.74 - 0.83
Random pooled ES	0.75	0.71 - 0.79
Six months		
Dikmen 1994	0.63	0.56 - 0.69
Hughes 2004	0.80	0.69 - 0.88
Stulemeijer2008	0.76	0.71 - 0.81
Ryb 2014	0.90	0.85 - 0.94
Losoi 2016	0.93	0.87 - 0.96
De Koning 2017	0.84	0.80 - 0.88
Random pooled ES	0.81	0.73 - 0.89
$\chi^2 = 72.31$ (df = 4), $p < 0.01$, $I^2 = 93.1\%$, $\tau^2 = 0.01$		
Test of ES=0: z = 5.67, p = 0.00		
12 months		
Dikmen 1994	0.80	0.74 - 0.85
Ryb 2014	0.89	0.83 - 0.93
Vikane 2014	0.88	0.83 - 0.91
Waljas 2014	0.97	0.92 - 0.99
Losoi 2016	0.96	0.90 - 0.98
Vikane 2016	0.76	0.69 - 0.82
De Koning 2017	0.88	0.84 - 0.91
Random pooled ES	0.88	0.83 - 0.93
$\chi^2 = 63.23$, $p < 0.01$, $I^2 = 90.5\%$, $\tau 2 = 0.00$		
Test of ES=0: z = 1.63, p = 0.10		

Table 2.4 Pooled return to work proportions by time point.
RTW, return to work; ES, effect size

Assessment of bias

Selection bias

Five of 14 studies were assessed to include patients truly representative of mild TBI. This assessment was based on those studies recruiting patients from the Emergency Department, and hence likely to include patients with a range of acuities within the category of mild TBI, including those eligible for discharge and those that needed admission.[74,169,371,400,401] Five studies were assessed to be somewhat representative of patients with mild TBI. One of these included patients that were invited to attend by post, and hence were self-selected,[399] three recruited patients from an in-patient ward, and therefore excluded those that were discharged from the Emergency Department and consequently may have biased results to select a group with higher acuity,[74,395,398] and one was from a larger study whose methods were not clearly described but the patients did present to the Emergency Department.[171] Four studies included patients that were highly selected: one included only patients that sustained a mild TBI after a motor vehicle collision, one included patients with moderate and severe TBI, and one recruited only in-patients but excluded patients with complicated mild TBI.[174,396,397]

Ascertainment bias: pre-injury employment

Of the 14 included studies, two only included patients that were exclusively in paid employment prior to injury.[396,400] Four studies included patients with mild TBI that were either in paid employment or otherwise occupied i.e. either students, home-makers, or carried out other daily activities, but not unemployed for reasons of sickness.[74,174,371,395] The proportion of patients that were in paid employment, students, home-makers, or other were not reported. Seven studies reported rates of return to work but the number of patients that

were working prior to injury was not reported in the articles,[171,312,376,397-399,401] however three of those studies explicitly excluded patients that were either retired or on sick leave prior to injury, thereby increasing the internal validity of the findings reported.[376,397,401] One study did not include any description of employment status prior to injury.[169]

Ascertainment bias: return to work after injury

Six studies reported follow up in more than 90% of recruited patients (Table 2.1 and Table 2.2).[74,171,376,397,398,400] The outcome return to work was ascertained by self-report in 12 studies,[74,169,171,174,312,371,395-397,399-401] and by data linkage from national databases in two studies.[376,398]

Study	Representativeness of the exposed cohort	Ascertain-ment of exposure	Ascertainment of pre-injury employment status	Assess-ment of outcome	Was follow-up long enough for outcomes to occur?	Adequacy of follow up of cohorts	*Total score*
Dikmen 1994	3 Drawn from three studies that included moderates and severe, and inclusion criteria not clear - published across four separate articles.	1	1 All patients were 'workers' - defined as major pre-injury activity to be work not school/homemaking/retirement	3 Self-report	1	4 Proportion or patients followed up not described	13
Ruffolo 1999	3 All patients had motor vehicle collisions so excludes other mechanisms of injury	1	2 Patients were working before the accident in paid or unpaid employment (e.g., as a student, homemaker, or volunteer worker).	3 Self-report	1	3 79% followed up	13
Haboubi 2001	2 Self-selected as invited to participate by post - 1255 invited, 639 responded	1	3 Unclear exactly how the authors calculated RTW, but text implies that only patients that were employed pre-injury were followed up for RTW.	3 Self-report	1	3 38% followed up	13

McCullagh 2001	*3* *Recruited from TBI clinic so excludes those not followed up in clinic*	*1*	*3* *90% of patients were employed prior to injury and RTW was defined as return to previous work or studies. Patients that were retired prior to injury, and those who remained off work for reasons other than their TBI, such as persisting orthopaedic injuries, were excluded.*	*3* *Self-report*	*1*	*1* *100% followed up*	*12*
Reynolds 2003	2 Recruited as in-patient so excludes those discharged from ED	1	2 Patients reported their pre-injury occupational status as working, student, homemaking, or other regular daily activities	3 Self-report	1	2 88% followed up	11
Hughes 2004	1 Recruited from ED	1	3 Describes RTW rates and excludes patients that were 'not applicable', therefore implying that patients unemployed prior to injury were excluded.	3 Self-report	1	3 49% followed up	12
Stulemeijer 2008	1 Recruited from ED	1	4 Patients pre-injury occupational status not described	3 Self-report	1	3 72% followed up	13

Iverson 2012	*2* *Sample is from a larger study but no reference to methodology for recruiting to it*	*1*	*3* *A 'known duration of time off work' is reported, therefore implying but not explicit that all patients were working prior to injury.*	*3* *Self-report*	*1*	*1* *100% followed up*	*11*
Ryb 2014	3 Recruited as in-patient so excludes those discharged from ED, and excluded complicated mTBI	1	3 90% of patients were employed prior to injury. RTW rates not explicitly calculated on this majority sub-group.	3 Self-report	1	3 61% followed up	14
Vikane 2014	2 Recruited as in-patient so excludes those discharged from ED	1	3 Included patients that could have been employed prior to injury but didn't report which were employed. Excluded those on sick leave for a year prior to injury.	2 RTW outcome derived from national database	1	1	10
Waljas 2014	1 Recruited from ED	1	2 All patients were working or students at the time of injury	3 Self-report	1	2 97% followed up	10
Losoi 2016	1 Recruited from ED	1	2 Included patients that were employed, students, or unemployed prior to injury. If students or unemployed, return to work was defined as returning to normal activities.	3 Self-report	1	2 87% followed up	10

Vikane 2016	*2* *Recruited as in-patient so excludes those discharged from ED*	*1*	*3* *RTW defined as not sick listed on Norwegian Welfare Registry. Included patients that were employed and unemployed and defined return to work as 'not on sick leave', therefore patients that were unemployed but not on sick leave after injury were analysed along with those that were employed.*	*2* *RTW outcome derived from national database*	*1*	*1* *100% followed up*	*10*
de Koning 2017	1 Recruited from ED	1	1 Recruited patients that were employed prior to injury.	3 Self-report	1	2 92% followed up	9

Table 2.5 Results of Newcastle Ottawa Score for the assessment of bias

Representativeness of the exposed cohort (1=truly representative of the average mild TBI; 2=somewhat representative of the average mild TBI; 3=selected group of users e.g. nurses, volunteers; 4=no description of the derivation of the cohort). Ascertainment of exposure (1=secure record (e.g. surgical records); 2=structured interview; 3=written self-report; 4=no description). Demonstration that outcome of interest was not present at start of study. (1=yes; 2=no). Assessment of outcome. (1=independent blind assessment; 2=record linkage; 3=self-report; 4=no description). Was follow-up long enough for outcomes to occur (1=yes; 2=no). Adequacy of follow up of cohorts (1=complete follow up - all subjects accounted for; 2=subjects lost to follow up unlikely to introduce bias - lost <20% follow up, or description provided of those lost); 3=follow up rate <50% and no description of those lost; 4=no statement)

Discussion

This systematic review is to my knowledge the most comprehensive review published that specifically and exclusively included mild TBI patients in whom return to work or usual activities was measured. It is also the most methodically performed and presented review with respect to mechanism of injury, injury characteristics (loss of consciousness and post-traumatic amnesia), exclusion criteria (e.g. psychiatric history or previous TBI), and years in education.

The principal finding of this study was that by one month only 50% and by six months 80% of patients with mild TBI have returned to work. Fourteen studies were identified of which three reported return to work after mild TBI as an average, 12 reported return to work as a proportion at a pre-specified time point (one reported both). Average return to work times varied from mean 25 to 93 days, but interpretation of these times is limited by the small number of studies, which include small numbers of patients, with wide variability and skewed distributions. Proportions of patients returning to work gradually increased as time passed from just under 50% at one and two weeks to the great majority by six months. There was significant heterogeneity at all time points. Study quality was poor, with only six studies reporting >90% follow up rates, and only five enrolling a representative sample of patients with mild TBI. i.e. enrolled patients with mild TBI from the Emergency Department prior to decision to admit or discharge. Only the study by De Koning et al recruited patients in paid employment prior to injury, and with only mild TBI, from the Emergency Department, and followed up more than 90% of them.

There have been several previous reviews of return to work after TBI, but few included only studies of patients with mild TBI. This is also the first review that includes a meta-analysis of return to work in patients with only mild TBI. Van Velzen et al reported a review of return to work after acquired brain injury, which included traumatic and non-traumatic causes of brain injury.[402] Forty-nine studies were included and return to work rates in traumatic and non-traumatic brain injury, at one and at two years, were very similar at around 40%. The patients included in this review were very heterogenous and included patients with stroke, sub-arachnoid haemorrhage and all types of TBI. Another review of return to work in patients with all types of TBI, by Saltychev et al, identified 12 controlled and 68 uncontrolled studies of rehabilitation or other treatment measures.[403] They found that studies were very poorly designed but showed no strong evidence that vocational outcomes could be predicted or improved. In a 2014 systematic review of return to work after mild TBI, four studies were included, of which only one, by Stulemeijer et al, met eligibility criteria for my review.[169,379] The authors concluded that up to 20% of patients with mild TBI may experience symptoms that persist for longer than six months. In this review I found that return to work rates are around 75% at three months and around 80% at six months. In line with several other reviews of recovery after TBI, most patients had returned to work by six months. This is broadly similar to patients with an ankle fracture requiring surgery, but patients that have surgery for an ankle fracture may undergo extensive physiotherapy.[404] In contrast, in the US, 38% of all annual mild TBI Emergency Department attendances, accounting for more than two million patients, are discharged from the Emergency Department with no follow-up.[50,54]

For return to work to be a meaningful outcome, the population studied should be working prior to injury. In January to March 2018, out of an estimated total UK population of 63.2 million people, 67% (41.2m) were of working age (16 to 64).[405] Data from the UK Labour Force Survey revealed that 76% (32.4m) of people of working age were employed and 3% (1.4m) were unemployed but seeking or available to work (these two categories being collectively described as 'economically active'), whilst 20% (8.7m) people were without a job and not seeking to find one (described as 'economically inactive').[406] The economically inactive group includes students, home-makers, and those unable to work for reasons of disability. However, not all people with disabilities are economically inactive. Using a definition of disability consistent with the 2010 Equalities Act, in January to March 2018, there were 7.4 million people with a disability aged 16-65 in the UK.[407,408] Less than half of those (3.3m, 44% of people with disabilities, 8% of the whole population) were economically inactive. However, the reason for the economic inactivity is not necessarily their disability. When asked to self-report whether they had a condition that affected the amount or type of work they could do, 6.3 million people answered 'yes'. Nevertheless, 51% (3.2m) of those were economically active: 2.9m (46%) were employed and 0.3m (1%) were unemployed; only 3m (49%) were economically inactive. This means that 3m people reported that they had both a condition that affected their work and were neither employed nor looking for employment. However, since half of people that have a condition that affects their work are nevertheless employed, it is not possible to infer that the medical condition is the reason for the economic inactivity in people who are economically inactive and have a condition that affects their work. Consequently, although return to work as an outcome is most relevant in employed people, more than three quarters of the

UK population aged 16-65 are employed. Furthermore, paradoxically, having a condition that affects a person's capacity to work, doesn't necessarily affect whether they are employed or not.

All studies included in this review investigated patients of working age, but only two studies included exclusively employed patients at the time of injury. Seven studies did not include a description of the pre-injury employment status of the study population or did not include an analysis of the patients that were working prior to injury. Of those seven, two report pre-injury employment rates of 90% but do not include an analysis of return to work in that subgroup. At 12 months, 10% overall have not returned to work. This group may represent patients that do not have work to return to for various reasons, including disability, mental health or substance misuse problems or homelessness. Ten of the included studies tackle this by excluding patients with the above diagnoses (Table 2.1 and Table 2.2).

Complicated mild TBI has been reported to be associated with poorer neuropsychological test performances and extended return to work times compared with uncomplicated mild TBI.[171,227,409-411] Seven studies reported CT findings. In a study of 47 patients, 34 (72%) had uncomplicated and 13 (28%) complicated mild TBI. There was a significant difference in return to work times between the two groups (median 6 [11-15] vs 36 [14-53] days), but the differences between the mean and median, the large SD and IQR, and the small numbers in the groups, indicate substantial variation.[171] In contrast, in the two studies that included such an analysis, having complicated mild TBI was not a predictor for persistent post-concussion symptoms or return to work.[169,376] This is consistent with recent calls to discredit the concept of complicated mild TBI,

at least based on CT findings.[412] This is because many patients with complicated mild TBI have favourable outcomes. Furthermore, although the commonest imaging modality in the acute phase after brain injury is CT scan, it is usually normal in patients with mild TBI, and many of those patients with a normal scan have persistent symptoms.[413] Localised inflammatory reactions in the brain microvasculature, traumatic axonal injury and microhaemorrhages resulting in haemosiderin deposits can be identified on MR imaging, and particularly susceptibility-weighted imaging, in patients that have normal CT scans on the day of injury. These may result in chronic structural abnormalities and could be a more accurate model for complicated mild TBI.[412,414]

The strengths of this meta-analysis are that it was written in accordance with international guidance, and adhered to a robust, prospectively written search strategy and analysis plan. Studies were rigorously assessed for strict adherence to eligibility criteria. It is also, to my knowledge, the first systematic review and meta-analysis examining return to work exclusively in mild TBI patients. The main limitation presented by this review is the high level of heterogeneity found in the included articles. This heterogeneity may exist because there is little standardisation of outcomes in mild TBI research. There were few commonly recorded outcomes across 14 studies. Return to work was the primary outcome in 10 studies, and not even all studies reported the overall age of the sample. Other variables that were reported inconsistently were mechanism of injury, definition of mild TBI used, education, severity based on day of injury CT (or whether CT was performed), and injury characteristics including post traumatic amnesia and loss of consciousness. This variation may have accounted for the heterogeneity found in the meta-analysis and makes drawing further

conclusions difficult. The Core Outcome Measures in Effectiveness Trials (COMET) initiative designs outcome sets that are disease based and although not designed to be restrictive or exclusive, are expected to be collected and reported to allow studies to be compared.[415] Mild traumatic brain injury research would benefit greatly by standardisation.

Conclusion

Around half of patients with mild TBI have returned to work by one month after injury, and most by six months. Most studies had poor internal validity. Reporting of outcomes in mild TBI was variable, which means that it is difficult to draw conclusions regarding the importance of factors that predated the injury such as education, or factors that were associated with the injury such as the presence of loss of consciousness or amnesia. This variability accounted for some of the heterogeneity found in this review.

Chapter 3 Short term neurocognitive and symptomatic outcomes following mild traumatic brain injury

Introduction

Mild TBI is an acute condition characterised by transient altered mental status and disorders of memory.[9] There is therefore a cognitive dysfunction associated with mild TBI. The evolution of neurocognitive dysfunction in the early phase of mild TBI is poorly understood. Several small studies report an immediate neurocognitive deficit, however most of these enrolled fewer than fifty patients with TBI and all were single centre studies.[177,203,204,416] In a population of more than a million patients in the US alone, many of whom are of working age, the consequences of failure to understand how neurocognitive dysfunction develops are enormous. Mild TBI has been called the silent epidemic because neurocognitive deficits that are not immediately apparent may persist.[417] There remains a need to understand how neurocognitive function deficits develop over the early period following injury. How neurocognitive function is affected in patients that attend the Emergency Department for non-neurological or non-neurotraumatic reasons is completely unknown. There may be a cognitive deficit associated with Emergency Department attendance for any reason.

The objective of this study was to study the cognitive function, symptom severity and number of symptoms in patients with mild TBI at baseline in the Emergency Department, and to re-evaluate them at 72 hours. The secondary

objective of this study was to compare cognitive function, symptom severity and number of symptoms at both time points between patients with and without mild TBI. I hypothesised that there would be an improvement in cognition, symptom severity and number of symptoms between baseline and 72 hours, and a difference between patients with and without mild TBI.

Methods

Objective

The primary objective of this study was to evaluate the short-term impact that mild TBI has on neurocognitive function and concussion symptoms in Emergency Department patients, and to compare that with comparable non-head injured patients.

Outcomes

Primary outcome

The primary outcomes were neurocognitive function, concussion symptom severity, and number of concussion symptoms. The outcomes were measured at baseline in the Emergency Department, and at follow up 72 hours later.

Secondary outcomes

Patients with previous head injuries, and patients with varying acuity of mild TBI were identified as subgroups of particular interest. Mild TBI was split into low and high acuity groups based on the presence of acute intracranial haemorrhage on CT, described as the CT positive group, or no acute haemorrhage on CT or CT not done, described as the CT negative group. Further subgroups of low acuity patients were defined as GCS 14-15 and CT done and negative, and GCS 14-15 and CT not done. Those patients that had a CT scan of the head performed, had one done so in line with national guidance.[418]

Eligibility

Inclusion criteria

Patients were included in the mild TBI group if they met the following criteria:

- Aged 18 to 80 years
- Attended the Emergency Department
- Suspected of an acute traumatically induced structural brain injury and/or clinical manifestations of functional brain injury, because of an insult to the head from an external force, including acceleration or deceleration movements without direct external trauma to the head
- Initial GCS 9-15

Exclusion criteria

Patients were excluded if they had any one of the following criteria:

- Chronic neurological, psychiatric or cognitive conditions
- Temperature ≥37.7°C
- Critical illness
- Open head injury/forehead abnormality
- Received procedural sedation or were mechanically ventilated
- Receiving dialysis or in stage four chronic kidney disease
- Pregnant

Patients were eligible to be in the comparable non-head injured group if they attended the emergency department with any condition excluding:

- An injury with any trauma above the clavicle

- Attending the Emergency Department because of a road traffic collision (because they may have a brain injury without a head injury due to acceleration-deceleration)
- Having sustained a TBI within the past year
- A primary acute neurological complaint or complaint of syncope.

Study design and Setting

This was a prospective observational cohort study conducted over the course of six months in the Emergency Departments of the Royal London Hospital and Salford Royal Hospital. Both hospitals are large university hospitals and designated Major Trauma Centres, which is equivalent to level one trauma centres. The annual Emergency Department patient attendance rates are 130,000 and 85,000 respectively. The study was approved by the National Research Ethics Service, North West 6 Research Ethics Committee, Greater Manchester South (reference 11/H1003/6). I performed most of the screening and recruitment at Royal London, and a small proportion was done by research nursing staff. Screening and recruitment was done Monday to Saturday, from 0800hrs and 0000hrs. Sources of bias were minimised by measures taken to obtain a complete dataset, including data abstraction from medical and pre-hospital emergency services records; and discussion with medical and emergency medical service personnel. Written informed consent was obtained from the patient, and in instances where the patient was unable to provide consent, consultee declaration to participate was obtained from a family member or the primary treating physician.

Data items

Neurocognitive function was measured using the Standardized Assessment of Concussion (SAC) (Appendix 2). The SAC provides an objective, reproducible and standardised report of the consequences of concussion.[192] The SAC is a paper-and-pencil assessment consisting of four domains (orientation, immediate memory, concentration, and delayed recall). It has a maximum score of 30, with higher scores indicating better neurocognitive function. It takes between five and ten minutes to complete. The SAC has been extensively validated for use in sport related concussion and has been reported as sensitive to sports concussion if administered within the first 48 hours.[193,194,197,199]

Symptom severity and number of symptoms was measured using the Concussion Symptom Inventory (CSI) (Appendix 2). The CSI is a list of 12 symptoms that are graded in severity by the patient on a seven point Likert scale.[16] The symptoms recorded are: headache; nausea; balance problems/dizziness; fatigue; drowsiness; feeling like "in a fog"; difficulty concentrating; difficulty remembering; sensitivity to light; sensitivity to noise; blurred vision; feeling slowed down. It has a maximum severity score of 72 with lower scores indicating lower severity, and a maximum of 12 symptoms. The total number of symptoms reported on the CSI, i.e. any symptom that did not have a score of 0, was calculated. Within group (baseline vs follow up) and between group (patients with and without mild TBI) comparisons were calculated. The comparison of numbers of concussion symptoms between groups was calculated because the sensitivity of the diagnosis of post-concussion syndrome is not limited to patients that have sustained a

concussion, and consequently it is possible that symptoms of acute concussion are not limited to head injured Emergency Department patients.[419]

Clinical variables collected were assessed by the treating physician or research personnel, and utilised information from the patient, the prehospital medical record, and witness reports. Loss of consciousness and amnesia were dependent on collateral reports. Altered mental state was assessed by the treating physician. Previous TBI was determined as remembered by the patient and defined as 'head injury' with or without loss of consciousness.

Neurocognitive function, symptom severity and number were collected at baseline in the Emergency Department and at follow up at 72 hours. Data at follow up were collected either face to face if the participant was an in-patient, or via telephone. Seventy-two hours was chosen as an appropriate follow-up time because it is a suitable time point to determine resolution of signs, duration of symptoms, and repeat CT scans, and also because there is little evidence on short term neurocognitive follow up in Emergency Department patients with mild TBI.[176,203,204] Demographic and clinical variables, mechanisms of injury and details of the TBI (loss of consciousness, amnesia) were obtained. A predefined subgroup of participants with acute intracranial haemorrhage on CT head scan was analysed. This was done to assess the cognitive changes in complicated mild TBI, in which patients have a GCS of 13 or more but an acute intra-cranial haemorrhage on CT scan.[420]

Statistical analysis

The central tendencies of non-normally distributed data were reported as medians with interquartile range (IQR), and that of normally distributed data as means ± standard deviation (SD). Central tendencies were only calculated

for data with at least six observations. Categorical data were represented as number (percentage). Normality was tested using the Shapiro-Wilk test and by visually assessing the frequency distribution. The Shapiro-Wilk tests the hypothesis that the data is not normally distributed, and therefore the null hypothesis that the data is normally distributed. A significant *p* value, which corresponds to rejection of the null hypothesis of normality, means that the data is not normally distributed.

Continuous data were compared using the paired or unpaired t-test, the related samples Wilcoxon Signed Rank test, or the independent sample Mann-Whitney U test as appropriate. 95% confidence intervals (CI) were calculated for differences between means. Categorical data were compared using the chi-squared test. Analyses were performed using the R Project for Statistical Computing.[421] Significance was set at $p < 0.05$. There was no imputation of missing data. Loss to follow up was managed with a whole group and longitudinal analysis.

Data representation

In this chapter I present three variables (neurocognitive function, symptom severity, and total number of symptoms), measured at two points in time (baseline and follow up), and in two groups (mild TBI and non-head injured). These several measurements are in effect all variations of paired data, i.e. an outcome measured from a single patient twice. There are several ways to represent paired data, including using measures of central tendency (e.g. mean or median of the baseline and follow up measurements) and variation range (standard deviation, interquartile ranges, or other centiles of the baseline and follow up measurements).[422] A common method of graphically representing

before and after measurements is to use box and whisker plots.[423] These are graphs that represent the median as a horizontal line, within a box whose upper and lower margins represent the upper and lower limits of the inter-quartile range. The original description of box and whisker plots was by J W Tukey, who described lines (whiskers) projecting above and below the box and representing 1.5 times the interquartile range. Individual outliers are plotted beyond these whiskers.[423] One limitation of these plots in isolation is that the interpretation of the results of paired data studies can also be affected by incomplete data, for instance due to lost to follow up rates. This is particularly relevant when using measures of central tendency. For example, if many patients have poor neurocognitive function at baseline, and then those that persist in having poor neurocognitive function at follow up are lost to follow up, the addition of this bias may result in the median neurocognitive function at follow up appearing erroneously improved. A further limitation of summary statistics alone is that they provide little information about the distribution of the data, particularly if it is bimodal.[424] This means that there can be several competing interpretations of the data.[422] To demonstrate the change from baseline to follow up at a per patient level, and simultaneously to represent the summary statistic, I have utilised two types of plot. For representation of the primary results, I have used a hybrid parallel line plot, also known as a waterfall or lollipop plot.[422] These depict each patient as a vertical line. The start of the line is the baseline score, and the direction and colour of the line represents whether the patient has clinically improved or deteriorated between measurements. The lines are ordered by patient from the worst to the best baseline score. The hybrid element refers to the inclusion of box and whisker plots of the before and after measurements on the left. The value of

the hybrid parallel line plot is that the reader can see the distribution of scores, and how they change over time. To emphasise this, and to compare changes rather than simply scores, I have also created parallel line plots of the absolute difference in outcome, also known as bow-tie plots, ordered from most improved to most deteriorated, with each patient's line starting at zero, and with the box and whisker plot of the difference to the left and using the same scale. These are useful in depicting proportions of improved or deteriorated patients and display this more clearly than the hybrid parallel lines plots. The limitation to these latter graphs is that a reader cannot tell how the baseline measure is associated with change in measure over time. These are seen in Figure 3.3 to Figure 3.8 and Figure 3.11 to Figure 3.22.

Results

Baseline data

A total of 240 patients were enrolled. Of these, 189 patients had TBI and 51 patients were patients without TBI (Figure 3.1 and Figure 3.2). The mean age was 43 (16) years and 169 (70%) of participants were male. Demographic and clinical details of patients with and without TBI are given in Table 3.1, Table 3.2 and Table 3.3. At Royal London Hospital 414 patients were screened of which 153 (37%) were recruited, and at Salford Royal Infirmary 253 patients were screened of which 87 (34%) were recruited. Further detail regarding screening and exclusion is given in Table 3.4. It was not possible to complete the 72 hours assessment in 110 cases (46%), which comprised 90 (48%) in patients with TBI group and 20 (39%) patients without TBI (Figure 3.2). Of the 189 patients with TBI, 174 (92%) provided consent themselves on initial recruitment, 15 (8%) were recruited via consultee declaration and 7 (4%) of those were able to provide retrospective consent. No patients withdrew.

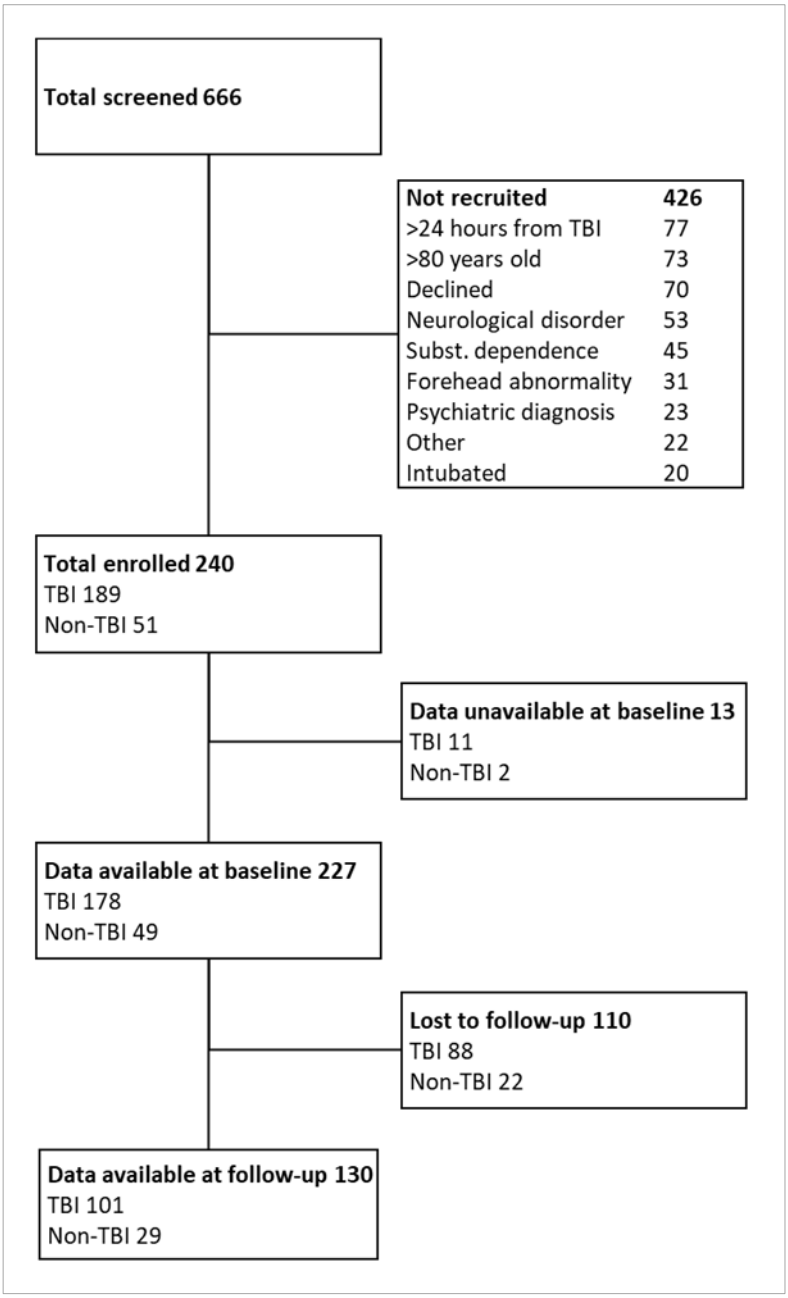

Figure 3.1 Patient inclusion diagram

	TBI	Non-TBI	p-value (95% CI)
Demographics			
Number	189 (79)	51 (21)	
Age	43 (16)	40 (15)	0.20 (-1.6 to 7.7)
Male Sex	133 (70)	36 (71)	0.98 (-0.1 to 0.1)
Years in education	16 (4)	17 (5)	0.12 (-2.5 to 0.3)
Disposition			
Discharge home from ED	95 (50)	23 (45)	0.97 (-0.1 to 0.1)
Admission to CDU	37 (20)	15 (29)	0.13 (-0.04 to 0.2)
Admission to hospital	57 (30)	13 (26)	0.52 (-0.1 to 0.07)
Neurosurgery performed	1 (0.5)	N/A	
Previous head injury			
Total	62 (33)	10 (20)	0.016 (0.014 to 0.018)
One	39 (21)	6 (12)	0.13 (-0.2 to 0.13)
Greater than one	23 (12)	4 (8)	0.4 (-0.2 to 0.07)

Table 3.1 Baseline data common to TBI and non-TBI groups
TBI, traumatic brain injury; non-TBI, patients without TBI; CI, confidence interval; ED, emergency department; CDU, clinical decision unit; N/A, not applicable. Data are reported as number (%) or mean (standard deviation).

Mechanism of TBI	Number (%)
Fall	55 (28)
Other	41 (21)
Assault	31 (16)
Struck by vehicle	22 (11)
Bicycle	15 (8)
RTC	13 (7)
Motorcycle	9 (5)
Fall due to syncope	7 (4)
Sports	2 (1)
Fall due to seizure	1 (1)
TBI characteristics	
GCS 14-15	183 (97)
GCS 13	3 (1.5)
GCS 9-12	3 (1.5)
LOC	72 (38)
Seizure	3 (1)
PTA	64 (34)
RGA	34 (18)
AMS	90 (48)
Radiological characteristics	
CT performed	102 (54)
Of TBI group, CT positive	25 (13)
Diagnosis within CT positive group	
EDH	5 (21)
SDH	6 (25)
SAH	3 (13)
Contusion and IPH	9 (38)
IVH	0 (0)
Mixed	1 (4)

Table 3.2 Baseline data specific to TBI group
TBI, traumatic brain injury; RTC, road traffic collision; GCS, Glasgow Coma Score; LOC, loss of consciousness; PTA, post traumatic amnesia; RGA, retrograde amnesia; AMS, altered mental status; CT, computed tomography; EDH, extra-dural haematoma; SDH, sub-dural haematoma; SAH, sub-arachnoid haemorrhage; IPH, intra-parenchymal haematoma; IVH, intraventricular haematoma. Data are reported as number (%).

Presenting complaint inpatients without TBI	
Abdominal pain	12 (24)
Fracture/sprain/dislocation	11 (22)
Back/limb pain	10 (20)
Other	10 (20)
Chest pain	6 (10)
Laceration	3 (6)

Table 3.3 Presenting complaints of patients without TBI
Data are reported as number (%) or number (standard deviation)

Reason	Royal London	Salford Royal
Total	261	166
>24 hrs since head injury	51 (19.5)	26 (15.8)
Other	48 (18.4)	37 (22.4)
>80 years old	39 (14.9)	34 (20.6)
Substance dependence	30 (11.5)	15 (9.1)
Advanced airway management	20 (7.7)	0 (0)
Psychiatric medications	14 (5.4)	9 (5.5)
Neurological disorder	14 (5.4)	25 (15.2)
<18 years old	11 (4.2)	1 (0.6)
CVA/TIA < 1yr	4 (1.5)	1 (0.6)
History of brain surgery	4 (1.5)	0 (0)
Prisoner	2 (0.8)	1 (0.6)
Procedural sedation medications	2 (0.8)	0 (0)
Headache	1 (0.4)	1 (0.6)
Pregnant	1 (0.4)	0 (0)
Syncope	1 (0.4)	2 (1.2)
Dialysis	0 (0)	1 (0.6)

Table 3.4 Screened and excluded patients with reasons for exclusion, by recruitment site.
Data are reported as number (%). CVA/TIA cerebrovascular accident/transient ischaemic attack.

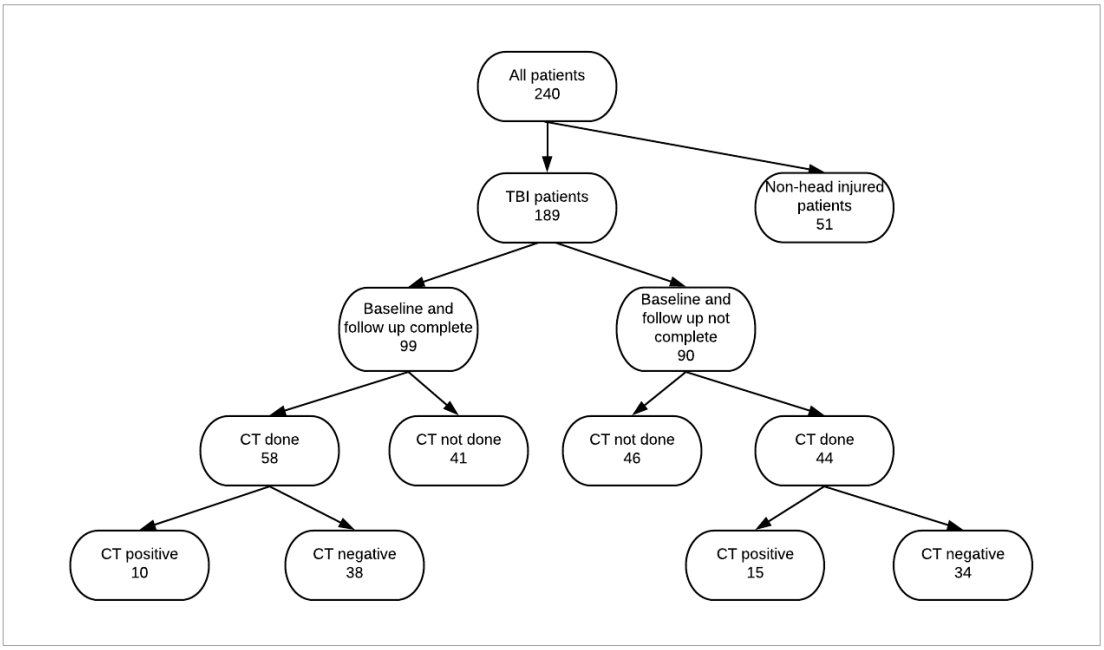

Figure 3.2 Patient follow up and CT outcomes

Primary results

Neurocognitive and symptom data are presented in Table 3.5, Figure 3.3, Figure 3.4, Figure 3.5, Figure 3.6, Figure 3.7, and Figure 3.8. Patients with TBI presented with marked neurocognitive impairment. Patients with TBI had poorer neurocognitive function than those without TBI at baseline (difference in SAC score 1, p=0.02, 95% CI -1.4 to -2.4), and at follow up at 72 hours (difference in SAC score 2, p=0.04, 95% CI -3.0 to 0.0). The hybrid parallel line plots show that although most patients with very poor neurocognitive function at baseline tended to improve, most patients whose baseline SAC score was 23 or above tended to deteriorate by follow up (Figure 3.3 and Figure 3.6). This is seen in the box plots which show no improvement overall and greater variation with longer whiskers at follow up. The absolute change plots show that regardless of group, the majority of patients' neurocognitive function had deteriorated by follow up (Figure 3.6). Neurocognitive function was measured on the SAC, which is a score from 0-30 and composed of four domains: orientation (0-5), immediate memory (0-15), concentration (0-5), and delayed recall (0-5). Because immediate memory makes up a potential half of the points available, when the SAC is broken into its components, immediate memory accounts for the greatest proportion of the median SAC at baseline and follow up. However, when the SAC is represented in its component parts as proportions of potential score, i.e. by percentage, there is a more even spread of score attributable to individual components (Figure 3.9). Delayed recall makes up the greatest proportion (32%), then concentration (30%), with immediate memory and orientation contributing equally (19% each). There is no difference in the degree to which the SAC components contribute to the overall score between baseline and follow up.

Patients with TBI also reported notably higher symptom severity than those without TBI. Patients with mild TBI's symptom severity reduced significantly between baseline and 72 hours but was greater than that reported by patients without TBI at both time points (difference between TBI and non-TBIs in CSI score at baseline 9, $p<0.001$, 95% CI 8.4 to 13.7; and at 72 hours 5, $p<0.001$, 95% CI 5.7 to 11.6) (Figure 3.4 and Figure 3.7). This shows an overall reduction in symptom severity regardless of baseline severity, except for 10 patients with very low baseline symptom severity whose scores deteriorated by follow up.

Patients with TBI also had higher total numbers of symptoms than those without TBI at both time points (difference in total number of symptoms between TBI and non-TBIs at baseline 4, $p<0.001$, 95% CI 2.6 to 4.4; and 72 hours 4, $p=0.001$, 95% CI 1.9 to 4.1). The hybrid parallel line plot shows an overall reduction in the number of symptoms experienced by follow up (Figure 3.5 and Figure 3.8). In contrast to neurocognitive function, most patients had lower symptom severity and fewer symptoms, i.e. improved from a symptoms perspective, by follow up. The most frequently occurring symptoms at baseline, which were experienced by more than 50% of TBI patients were headache, fatigue, feeling slowed down and drowsiness (Figure 3.10).

	Baseline	72 hours	Difference	p-value (95% CI)
Patients with mild TBI (n=189)				
SAC	25 (23-27)	25 (22-27)	0	0.1 (-0.4 to 1.2)
CSI	9 (4-21)	5 (1-18)	4	0.002 (1.2 to 6.3)
No. symptoms	4 (2-8)	4 (1-6)	0	0.051 (-1.5 to 0)
Patients without mild TBI (n=51)				
SAC	26 (24-28)	27 (24-29)	1	0.5 (-0.6 to 1.7)
CSI	0 (0-2)	0 (0-2)	0	0.3 (-0.5 to 3.4)
No. symptoms	0 (0-2)	0 (0-1)	0	0.15 (-0.1 to 0.9)

Table 3.5 Neurocognitive function, symptom severity, and total number of concussive symptoms
Measured on the standardised assessment of concussion (0-30, best = 30), the concussion symptom inventory (0-72, best =0), in TBI and non-TBI groups, at baseline and 72 hours.

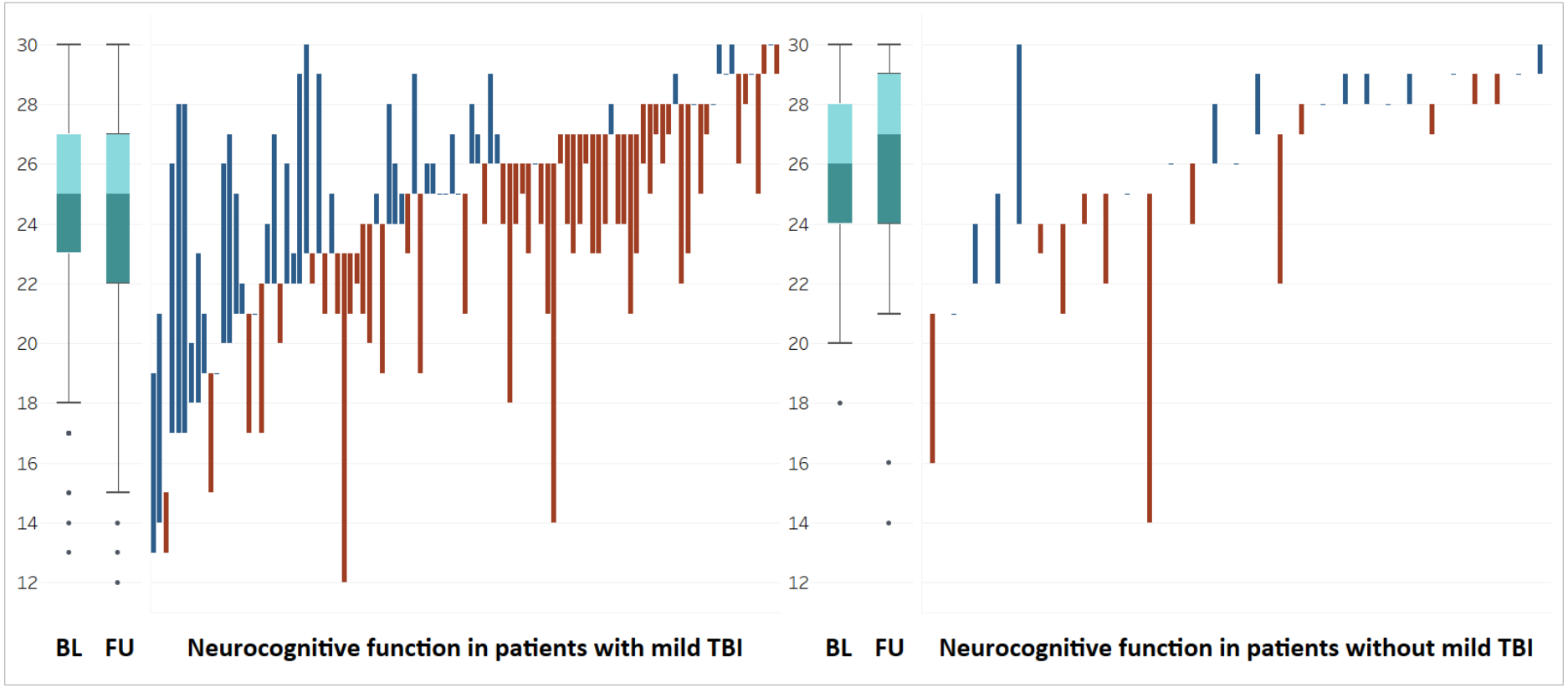

Figure 3.3 Hybrid parallel line plots representing change in neurocognitive function in patients with and without mild TBI.

Box plots with Tukey's hinges of neurocognitive function scores at baseline and follow up are displayed to the left of each chart. Neurocognitive function is measured on the standardised assessment of concussion (best = 30, worst = 0) and represented on the y-axis. Individual patients are represented on the x-axis, are ordered from worst to best baseline score, and each vertical line represents a single patient. Blue indicates an upwards deflection and clinical improvement, and red indicates a downwards deflection and clinical deterioration. Flat horizontal lines indicate no change. BL, baseline; FU, follow up; TBI, traumatic brain injury.

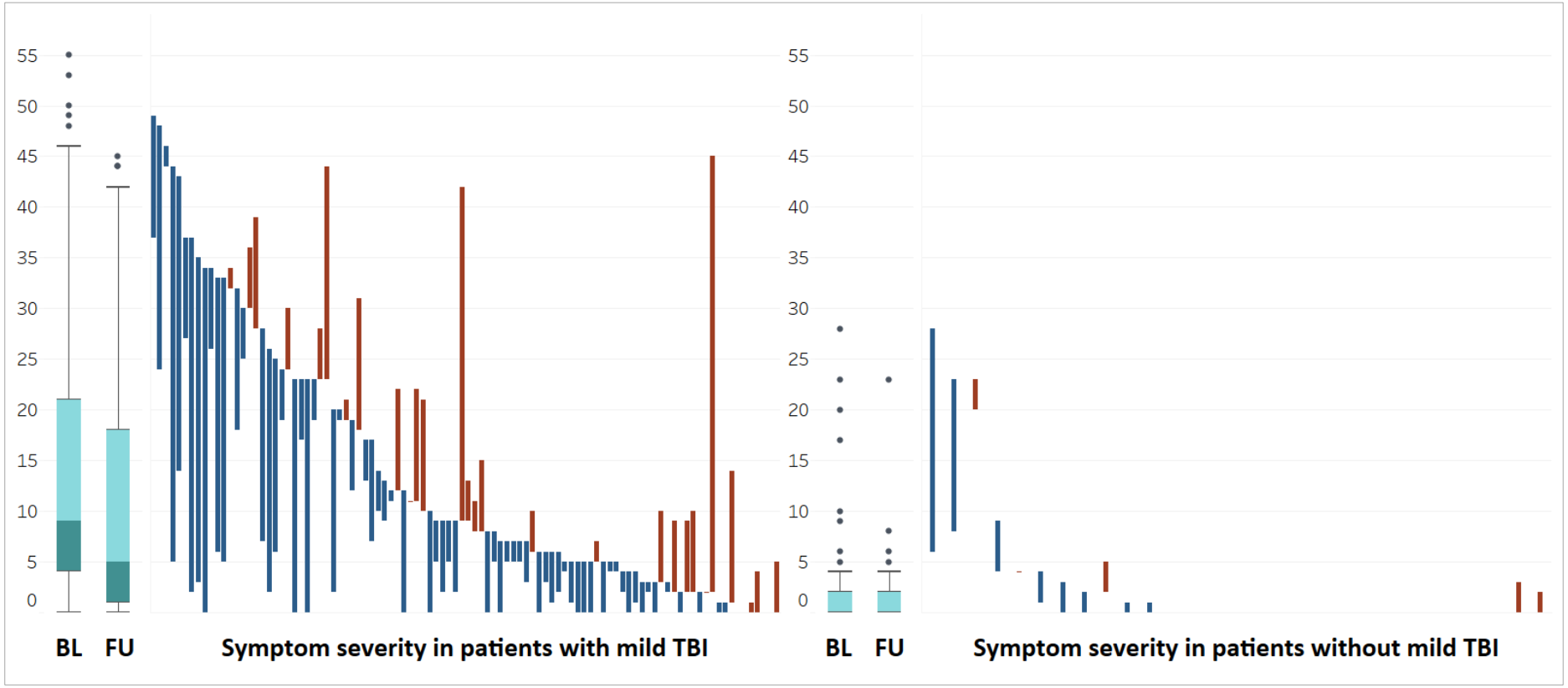

Figure 3.4 Hybrid parallel line plots representing change in symptom severity in patients with and without mild TBI.

Box plots with Tukey's hinges of symptom severity scores at baseline and follow up are displayed to the left of each chart. Symptom severity is measured on the concussion symptom inventory (best = 0, worst = 72) and represented on the y-axis. Individual patients are represented on the x-axis, are ordered from worst to best baseline score, and each vertical line represents a single patient. Blue indicates a downwards deflection and clinical improvement, and red indicates an upwards deflection and clinical deterioration. Flat horizontal lines indicate no change. BL, baseline; FU, follow up; TBI, traumatic brain injury.

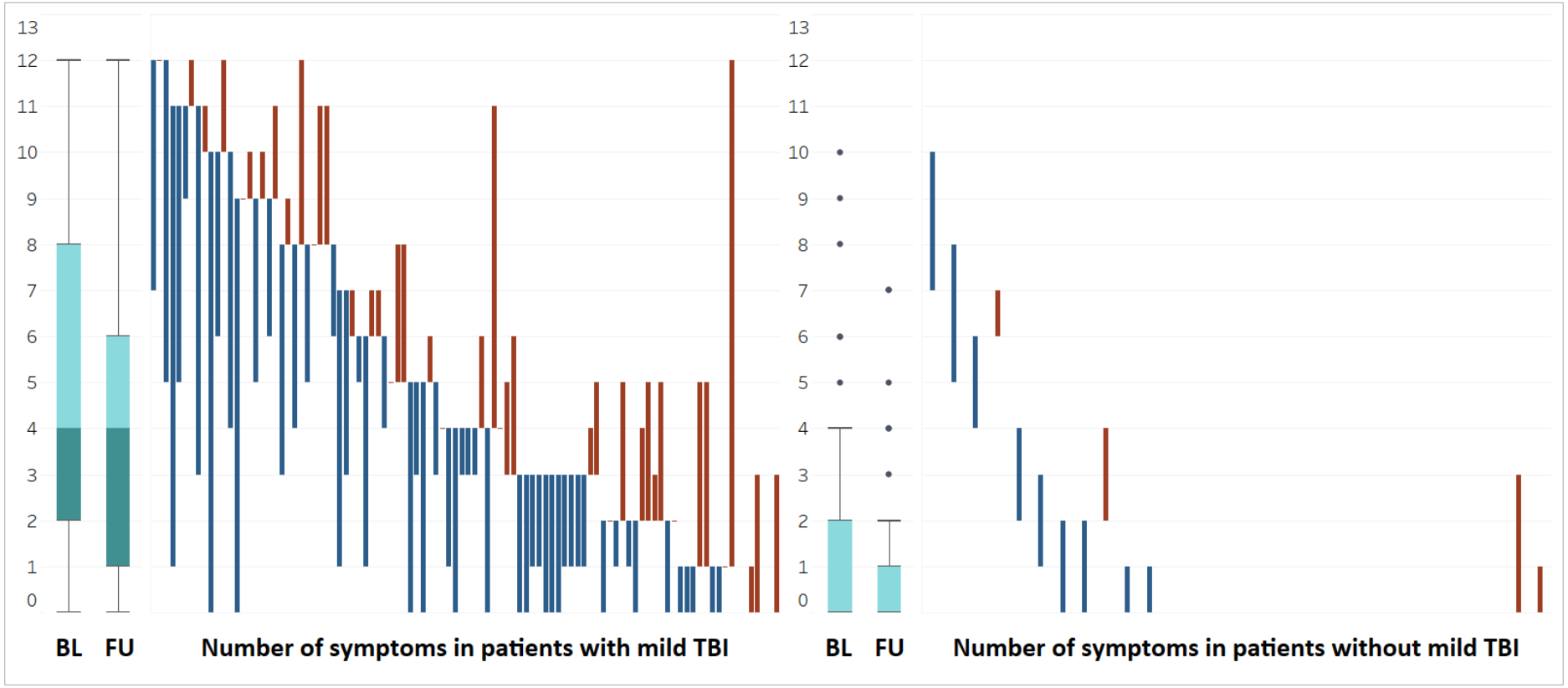

Figure 3.5 Hybrid parallel line plots representing change in number of symptoms in patients with and without mild TBI.

Box plots with Tukey's hinges of the number of symptoms at baseline and follow up are displayed to the left of each chart. The number of symptoms is represented on the y-axis (fewest = 0, most = 12). Individual patients are represented on the x-axis, are ordered from most to fewest symptoms at baseline, and each vertical line represents a single patient. Blue indicates a downwards deflection and clinical improvement, and red indicates an upwards deflection and clinical deterioration. Flat horizontal lines indicate no change. BL, baseline; FU, follow up; TBI, traumatic brain injury.

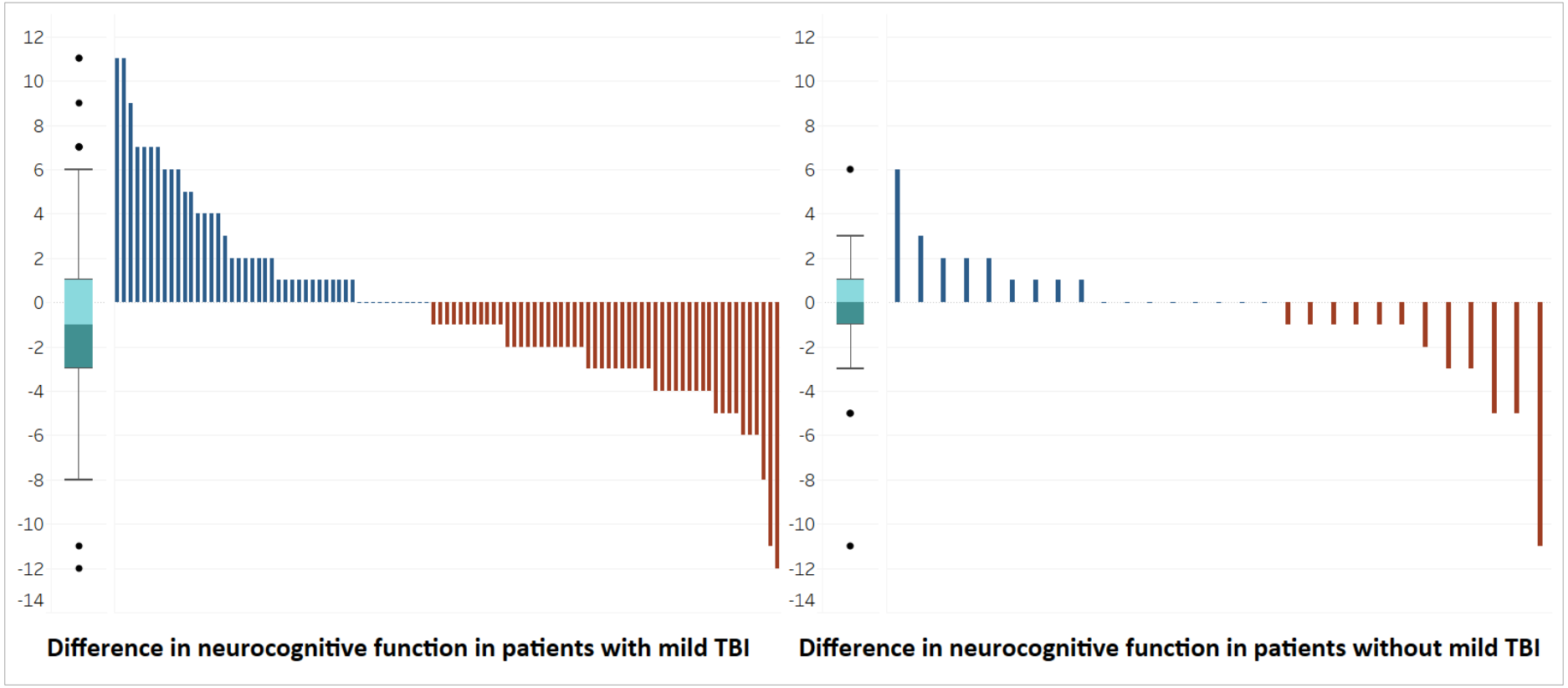

Figure 3.6 Absolute difference in neurocognitive function in patients with and without mild TBI.
A box plot with Tukey's hinges of the difference in neurocognitive function scores between baseline and follow up is displayed to the left of each chart. Neurocognitive function is measured on the standardised assessment of concussion (best = 30, worst = 0) and the difference from baseline to follow up is represented on the y-axis. Individual patients are represented on the x-axis, are ordered from most improved to most deteriorated and each vertical line represents a single patient. Blue indicates an upwards deflection and clinical improvement, and red indicates a downwards deflection and clinical deterioration. TBI, traumatic brain injury.

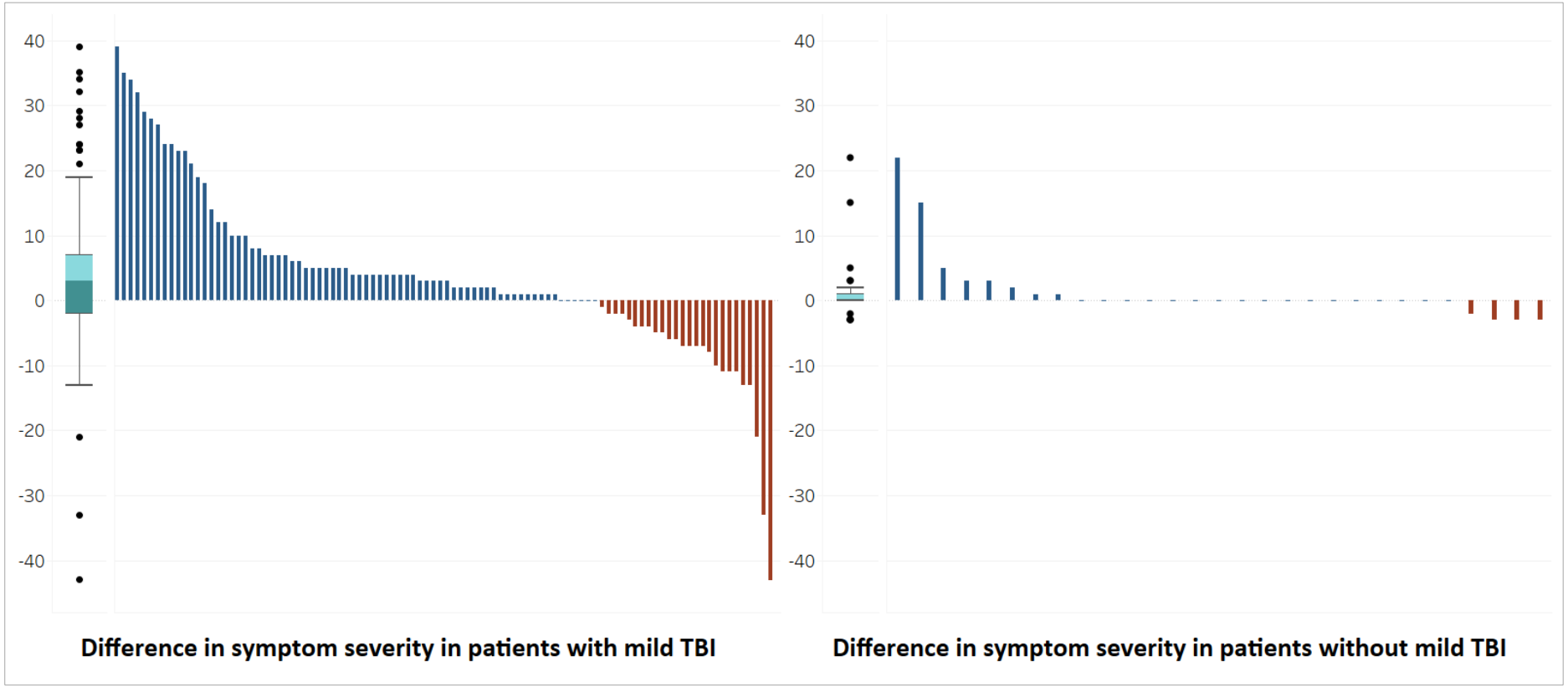

Figure 3.7 Absolute difference in symptom severity in patients with and without mild TBI.
A box plot with Tukey's hinges of the difference in symptom severity scores between baseline and follow up is displayed to the left of each chart. Symptom severity is measured on the concussion symptom inventory (best = 0, worst = 72) and the difference from baseline to follow up is represented on the y-axis. Individual patients are represented on the x-axis, are ordered from most improved to most deteriorated and each vertical line represents a single patient. Blue indicates an upwards deflection and clinical improvement, and red indicates a downwards deflection and clinical deterioration. TBI, traumatic brain injury.

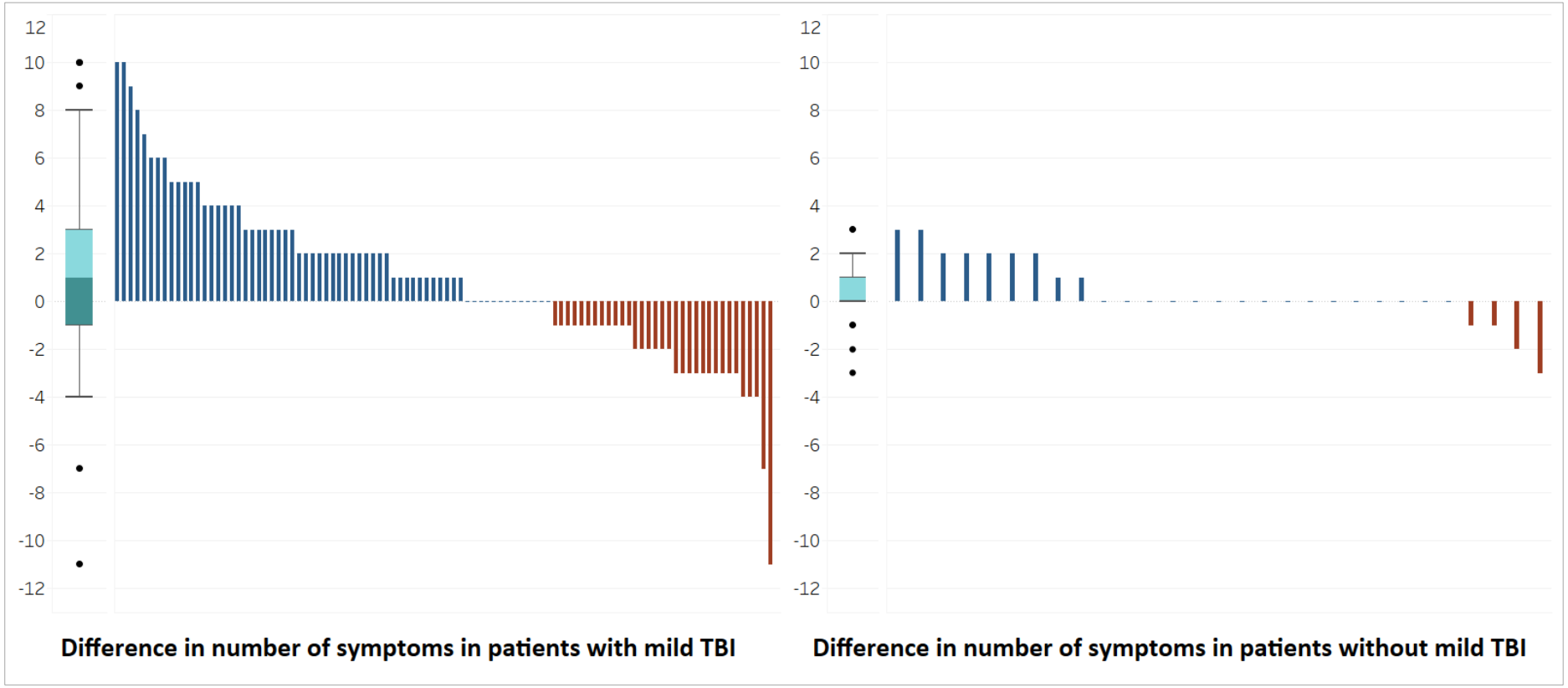

Figure 3.8 Absolute difference in number of symptoms in patients with and without mild TBI.
A box plot with Tukey's hinges of the difference in number of symptoms between baseline and follow up is displayed to the left of each chart. The difference in the number of symptoms from baseline to follow up is represented on the y-axis (fewest = 0, most = 12). Individual patients are represented on the x-axis, are ordered from most improved to most deteriorated and each vertical line represents a single patient. Blue indicates an upwards deflection and clinical improvement, and red indicates a downwards deflection and clinical deterioration. TBI, traumatic brain injury.

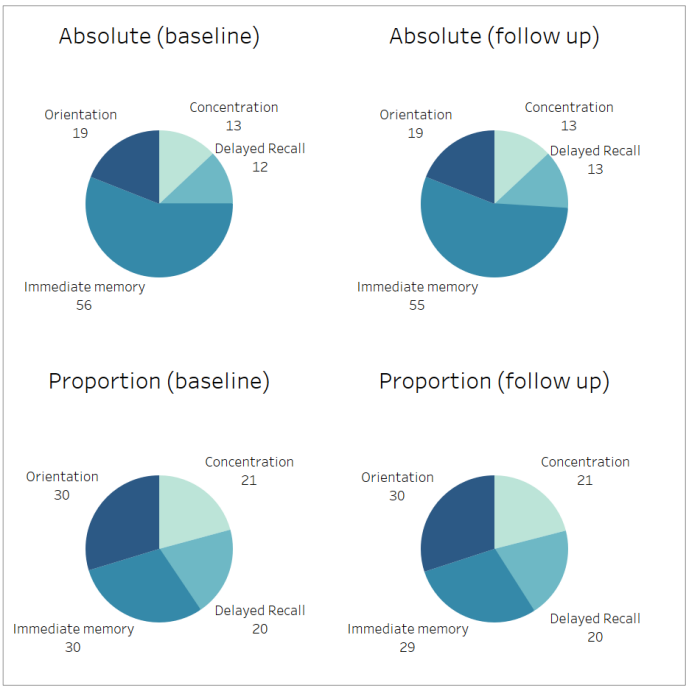

Figure 3.9 Components of the SAC score
Percentages mean absolute value and by proportion at baseline and follow up in TBI group

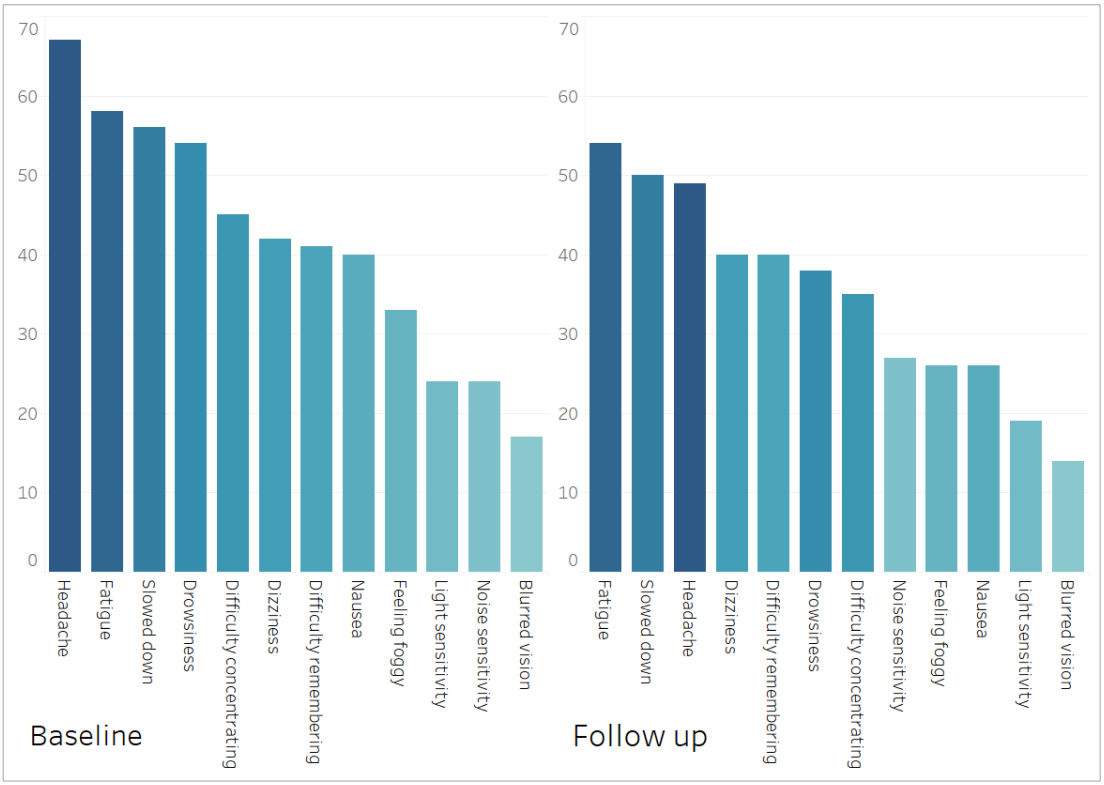

Figure 3.10 Symptom frequency
The percentage of patients with mild TBI group that experienced each symptom at baseline and follow up.

Post hoc power calculations

I performed no power calculations in the design phase of this study. Of the three primary outcomes (neurocognitive function, concussion symptom severity, and number of concussion symptoms), there was no statistically significant difference between baseline and follow up measures of neurocognitive function, nor of total number of symptoms. In order to determine whether a larger study would have detected a statistically significant difference, post hoc power calculations were performed. Firstly, the data for neurocognitive function and total number of symptoms were demonstrated to be non-parametric. This was done by performing the Shapiro-Francia test for normality, which tests the null hypothesis that the data is normally distributed. The test was performed for the baseline and follow up values for both outcomes and produced p-values less than 0.05 for all four variables (Appendix 7, Table 6.5). Assessment of the source of the non-normality was then done, and were statistically significant for both skewness and kurtosis in all four variables (Appendix 7 Table 6.6). Sometimes even when the raw data is not normally distributed, the differences between before-and-after data can be normally distributed. The differences between baseline and follow up for neurocognitive function and number of symptoms were tested for normality, skewness and kurtosis in the same way as described above (Appendix 7, Table 6.7 and Table 6.8). There was borderline statistical significance for the assessment of normality in the difference in the total number of symptoms. In order to be maximally conservative, this borderline p value (of 0.058) was judged to warrant treatment of these data as non-parametric.

Standard power calculations were then performed, using the *sampsi* Stata command. The *sampsi* requires entry of alpha, mean and standard deviation for each group, and specification of the number of assessments. The alpha was set at 0.05, and the mean and standard deviation for each group was calculated from the raw data. Stata also requires a set correlation between baseline and follow-up. However, the overall calculated power did not change regardless as to where that correlation was set. Regardless of whether it was set at 0.0 or either extremes of possible values (-0.9 to 0.9), the output was unaffected. This is because with the two means being equal it is extraordinarily difficult to project a study power to identify them as different.

The calculated power of the study to detect a difference between baseline and follow up neurocognitive function was 0.05. The power to detect a difference between baseline and follow up total number of symptoms was also 0.05.

Power is 1-beta. Beta is the (set) probability of the study having a type 2 error, that is not finding a difference when one does actually exist, and is conventionally set at either 0.2 or 0.1, so that power is usually 0.8 or 0.9. Technically this means that this study has only a 5% chance that a type 2 error doesn't exist. However these results are a reflection on the fact that the means for baseline and follow up neurocognitive function are the same, as are the means for baseline and follow up total number of symptoms (Table 3.5), and consequently low power is expected when using this approach.

Since there is expected low power provided by traditional calculations, when those calculations are used to determine the power of a study to find a statistically significant difference between two groups with the same mean, an

alternative approach was adopted. There have been arguments for increasing emphasis on the employment of confidence intervals for conveying information about a study's precision and overall results interpretation, rather than relying alone on a test of statistical significance.[425] Therefore, confidence intervals about the median differences between baseline and follow up for the two variables were calculated. Confidence intervals about medians rather than means were calculated because the data was demonstrated to be non-normally distributed, and because this was thought to be a more conservative approach that made relatively few assumptions about the data. The Stata procedure utilised was *cendif*.[426]

The median change in neurocognitive function from baseline to follow up was 0, with a 95% confidence interval calculated as 0 to 1. A 99% confidence interval was also calculated and was also 0 to 1. The minimum significant clinical difference in neurocognitive function (as measured on the SAC) is 2.[201] Consequently, there is very little chance (<1% given the 99% CI results) that a larger study would identify a significant difference in neurocognitive function. The median change in total number of symptoms from baseline to follow up was 0, with a 95% confidence interval calculated as 0 to 1. A 99% confidence interval was also calculated and was also 0 to 1. Just as with neurocognitive function, this implies that the chances of a larger study identifying a significant change in number of symptoms from baseline to follow up is very low. Together this constitutes compelling evidence that although the post hoc power calculation is low, that is a factor of there being no change from baseline to follow up, and that the 95% and 99% confidence intervals suggest that the

result of this study can be relied upon to represent truth, and that it is unlikely that the study contains a type 2 error.

Patients with acute haemorrhage on CT brain

Table 3.6 contains neurocognitive and symptom data for the subgroups with (CT positive) and without (CT negative) acute intracranial haemorrhage. Patients that did not have a positive CT scan were defined as CT negative, however, some patients within that group did not have a CT at all. Because this group may have had acute abnormalities on CT were a CT to have been performed, data for the subgroups of CT negative patients are also presented. Of the 189 TBI participants, there were 25 (13%) CT positive and 154 (87%) CT negative patients. Neurocognitive function was considerably worse in CT positive compared to CT negative patients at both time points (difference in SAC score between CT positive and negative at baseline 3, p=0.009, 95% CI -1.0 to -3.0, and at 72 hours 3, p=0.009, 95% CI -1.0 to -5.0). Figure 3.11 shows the difference in baseline neurocognitive function between CT positive and CT negative patients, and shows the variation within the groups, specifically, that most CT positive patients deteriorated. Figure 3.14 shows that the degree of deterioration is substantial: the greatest deterioration is 5 points on the SAC score. Both CT negative and CT positive patients show a tendency to deteriorate by follow up if the baseline score is at the higher function end of the scale. Most patients had worse neurocognitive function by follow up compared to baseline (Figure 3.14). The differences from baseline function, whether an improvement or a deterioration, are less marked in CT positive patients than CT negative patients. Figure 3.11 shows that one of the two patients with the lowest baseline scores (13) is in the CT positive group and

one in the CT negative group. Because the CT positive group is small, it is not possible to determine whether the smaller difference from baseline to follow up in that group is dependent on a lower baseline score. CT positive patients also had worse symptom severity than CT negative patients at baseline (difference in CSI 11, p = 0.01, 95% CI -15.0 to -2.0) and at 72 hours (difference in CSI 10, p = 0.06, 95% CI -13.0 to 0.0) (Figure 3.12). CT positive patients also had greater numbers of symptoms compared with CT negative patients at both time points (difference in total number of symptoms 4, p=0.027, 95% CI -4.0 to 0.0; and 3, p=0.038, 95% CI -5.0 to 0.0 at baseline and follow up respectively) (Figure 3.13). However, in contrast to neurocognitive function, more patients experienced an improvement in symptom severity and number of symptoms from baseline to follow up (Figure 3.15 and Figure 3.16). In case the group that were not scanned were more unwell than thought at clinical assessment, which would constitute a selection bias, a sensitivity analysis separating the CT negative group into those that had a CT which was negative and those that didn't have a CT was performed. Three TBI subgroups consisting of CT not done, CT with no intracranial haemorrhage and CT with intracranial haemorrhage were analysed. There is a trend towards improved cognitive function and lighter symptom burden from intracranial haemorrhage to no CT performed (Table 3.6). Further sensitivity analyses designed to apply the outcome measures in the lowest acuity patients were performed. In patients with GCS 14-15 that had a negative CT scan, or no CT scan performed (n=162), there was no improvement in cognitive function or symptom burden between baseline and follow up (Table 3.6). This suggests that patients that qualify for a CT, even if their scan is normal, may have neurocognitive dysfunction and a symptom burden that persists. In patients

with GCS 14-15 that had a scan which was negative (n=71), not only overall cognitive function, but also overall symptom severity and total number of symptoms remained unchanged between baseline and follow up.

	Baseline	72 hours	Difference	p-value (95% CI)
CT positive (n=25)				
SAC	23 (22-26)	22 (19-24)	1	0.5 (-0.6 to 1.7)
CSI	20 (11-30)	15 (6-21)	5	0.3 (-0.5 to 3.4)
No. symptoms	8 (4-9)	6 (5-9)	2	0.14 (-0.1 to 0.9)
CT negative (all patients that are not CT positive), n=164				
SAC	26 (23-28)	25 (22-27)	1	0.2 (-0.6 to 1.2)
CSI	9 (4-19)	5 (1-15)	4	0.006 (0.7 to 6.2)
No. symptoms	4 (2-7)	3 (1-6)	1	0.01 (0.2 to 1.7)
CT done and negative (n=78)				
SAC	25 (22-26)	25 (22-28)	0	0.80 (-1.5 to 1.4)
CSI	13 (7-32)	13 (5-27)	0	0.16 (-1.5 to 9)
No. symptoms	6 (3-10)	5 (3-8)	1	0.34 (-0.7 to 1.9)
CT not done (n=86)				
SAC	26 (25-28)	26 (23-27)	0	0.11 (-0.3 to 1.8)
CSI	6 (3-11)	2 (0-5)	4	0.002 (1.2 to 5.7)
No. symptoms	3 (1-5)	1 (0-4)	2	0.005 (0.4 to 2.1)

Table 3.6 Neurocognitive and symptom outcomes for TBI patients with and without intracranial haemorrhage
Measured on the concussion symptom inventory, in TBI patients with and without intracranial haemorrhage, at baseline and at 72 hours.

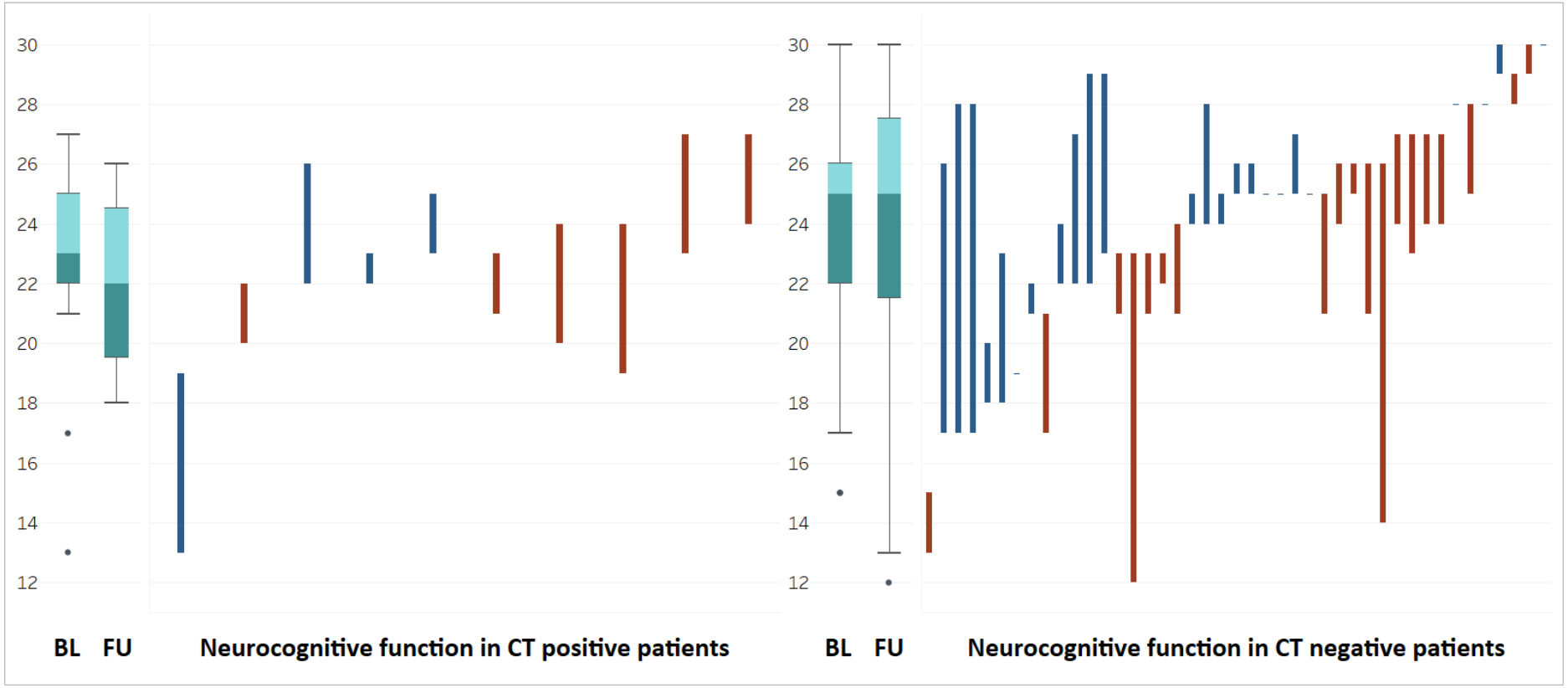

Figure 3.11 Hybrid parallel line plots representing change in neurocognitive function in CT positive and CT negative mild TBI patients.

Box plots with Tukey's hinges of neurocognitive function scores at baseline and follow up are displayed to the left of each chart. Neurocognitive function is measured on the standardised assessment of concussion (best = 30, worst = 0) and represented on the y-axis. Individual patients are represented on the x-axis, are ordered from worst to best baseline score, and each vertical line represents a single patient. Blue indicates an upwards deflection and clinical improvement, and red indicates a downwards deflection and clinical deterioration. Flat horizontal lines indicate no change. BL, baseline; FU, follow up; CT, computed tomography.

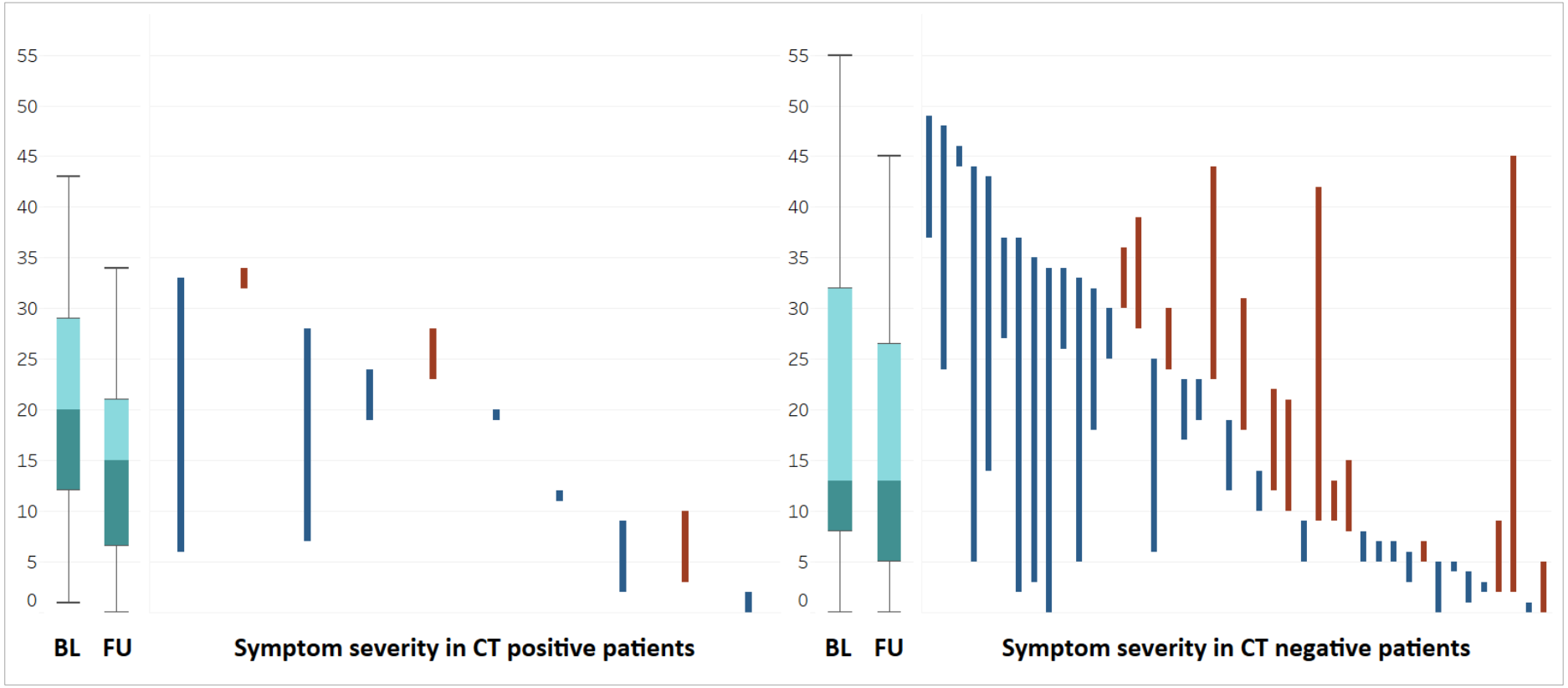

Figure 3.12 Hybrid parallel line plots representing change in symptom severity in CT positive and CT negative mild TBI patients.

Box plots with Tukey's hinges of symptom severity scores at baseline and follow up are displayed to the left of each chart. Symptom severity is measured on the concussion symptom inventory (best = 0, worst = 72) and represented on the y-axis. Individual patients are represented on the x-axis, are ordered from worst to best baseline score, and each vertical line represents a single patient. Blue indicates a downwards deflection and clinical improvement, and red indicates an upwards deflection and clinical deterioration. Flat horizontal lines indicate no change. BL, baseline; FU, follow up; TBI, traumatic brain injury.

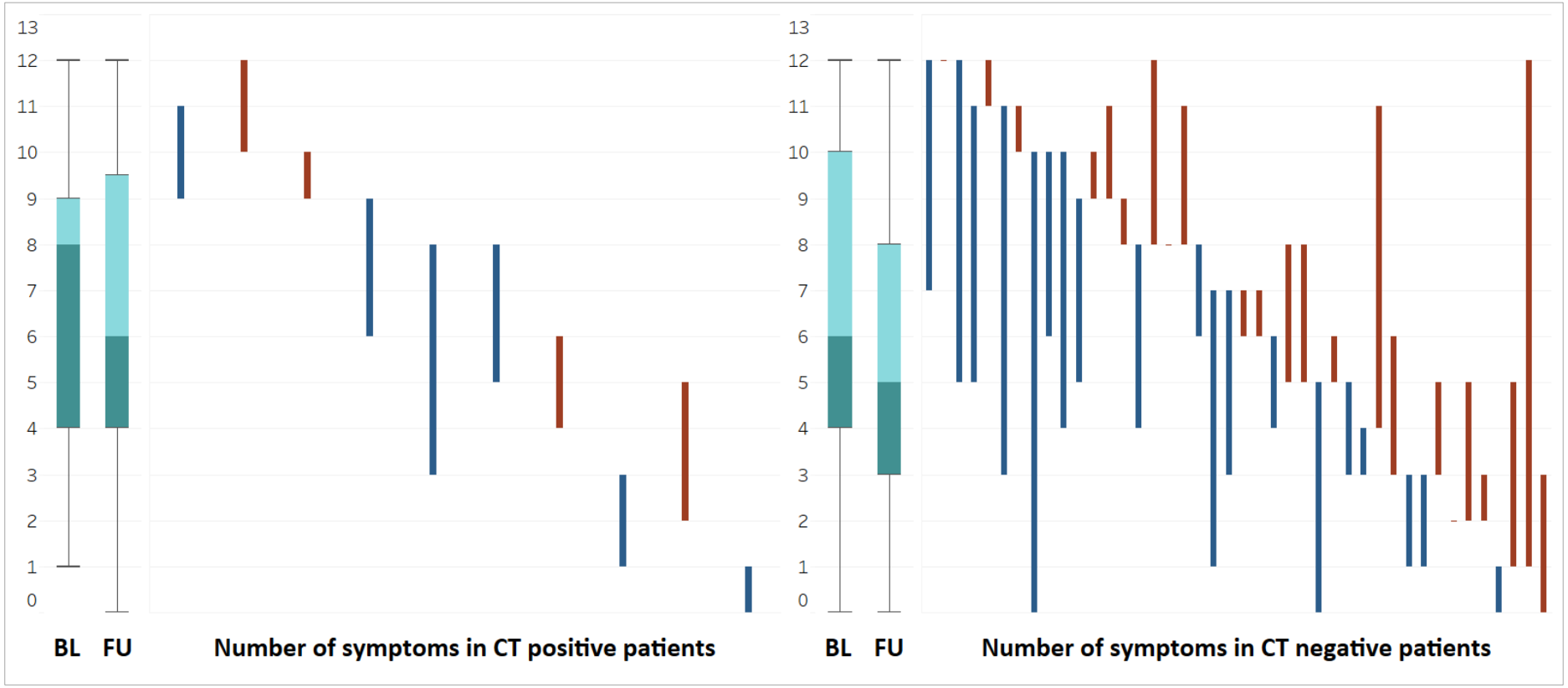

Figure 3.13 Hybrid parallel line plots representing change in number of symptoms in CT positive and CT negative mild TBI patients.

Box plots with Tukey's hinges of the number of symptoms at baseline and follow up are displayed to the left of each chart. The number of symptoms is represented on the y-axis (fewest = 0, most = 12). Individual patients are represented on the x-axis, are ordered from most to fewest symptoms at baseline, and each vertical line represents a single patient. Blue indicates a downwards deflection and clinical improvement, and red indicates an upwards deflection and clinical deterioration. Flat horizontal lines indicate no change. BL, baseline; FU, follow up.

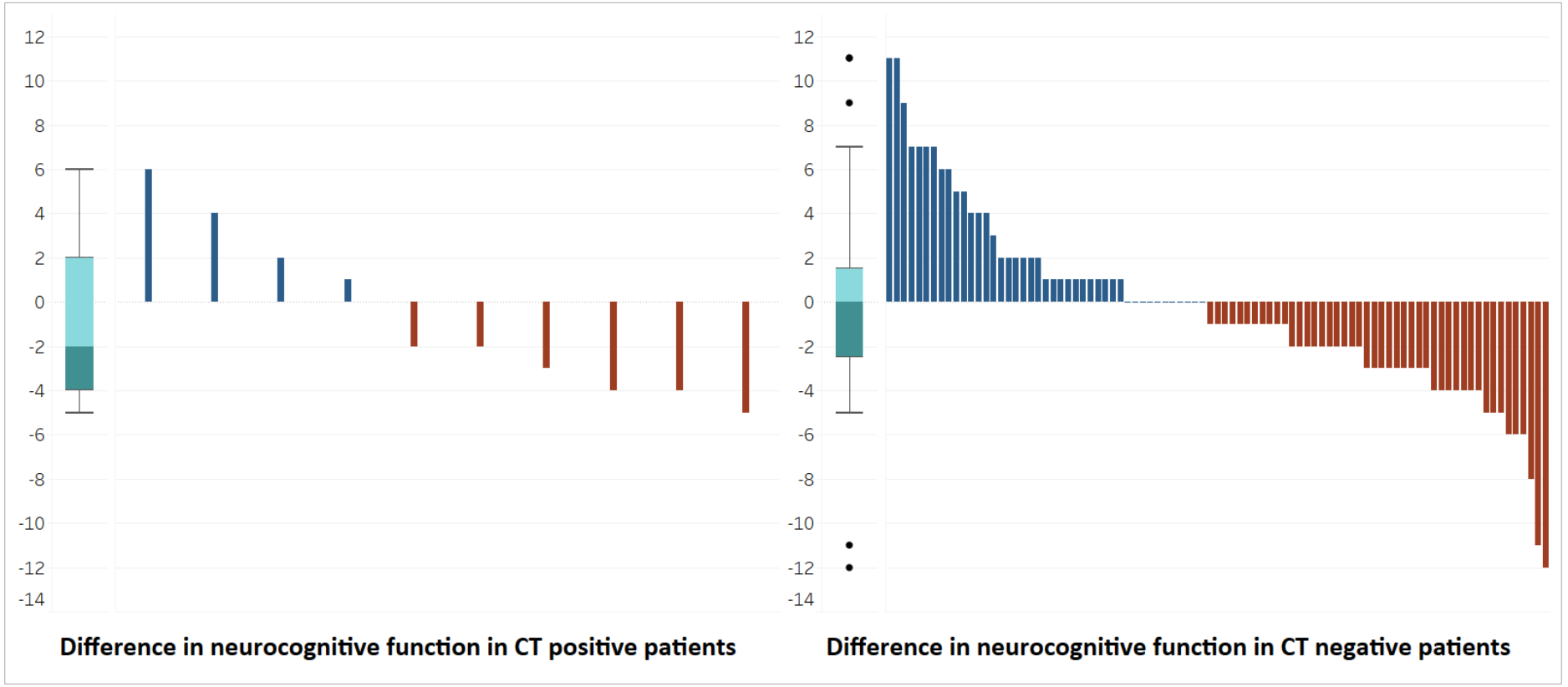

Figure 3.14 Absolute difference in neurocognitive function in CT positive and CT negative mild TBI patients.
A box plot with Tukey's hinges of the difference in neurocognitive function scores between baseline and follow up is displayed to the left of each chart. Neurocognitive function is measured on the standardised assessment of concussion (best = 30, worst = 0) and the difference from baseline to follow up is represented on the y-axis. Individual patients are represented on the x-axis, are ordered from most improved to most deteriorated and each vertical line represents a single patient. Blue indicates an upwards deflection and clinical improvement, and red indicates a downwards deflection and clinical deterioration. TBI, traumatic brain injury.

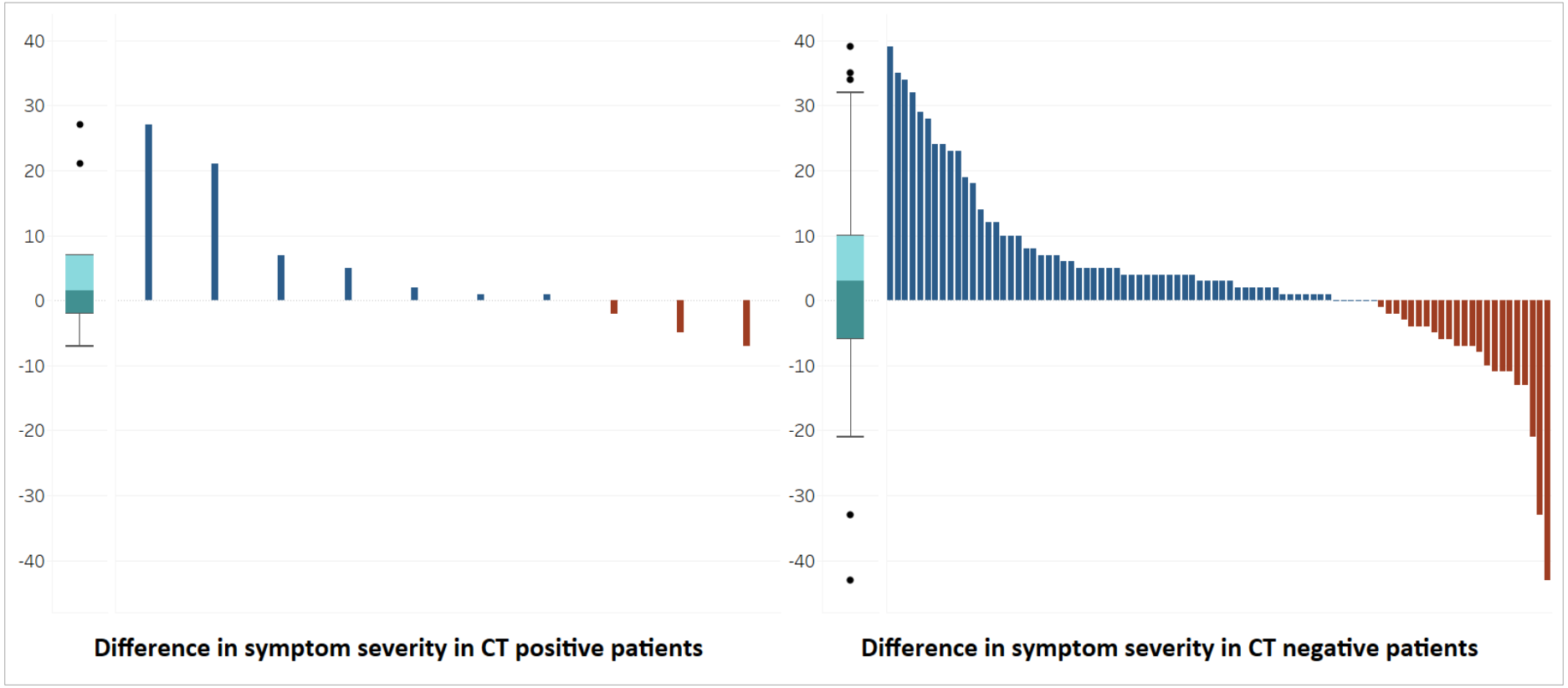

Figure 3.15 Absolute difference in symptom severity in CT positive and CT negative mild TBI patients.
A box plot with Tukey's hinges of the difference in symptom severity scores between baseline and follow up is displayed to the left of each chart. Symptom severity is measured on the concussion symptom inventory (best = 0, worst = 72) and the difference from baseline to follow up is represented on the y-axis. Individual patients are represented on the x-axis, are ordered from most improved to most deteriorated and each vertical line represents a single patient. Blue indicates an upwards deflection and clinical improvement, and red indicates a downwards deflection and clinical deterioration. TBI, traumatic brain injury.

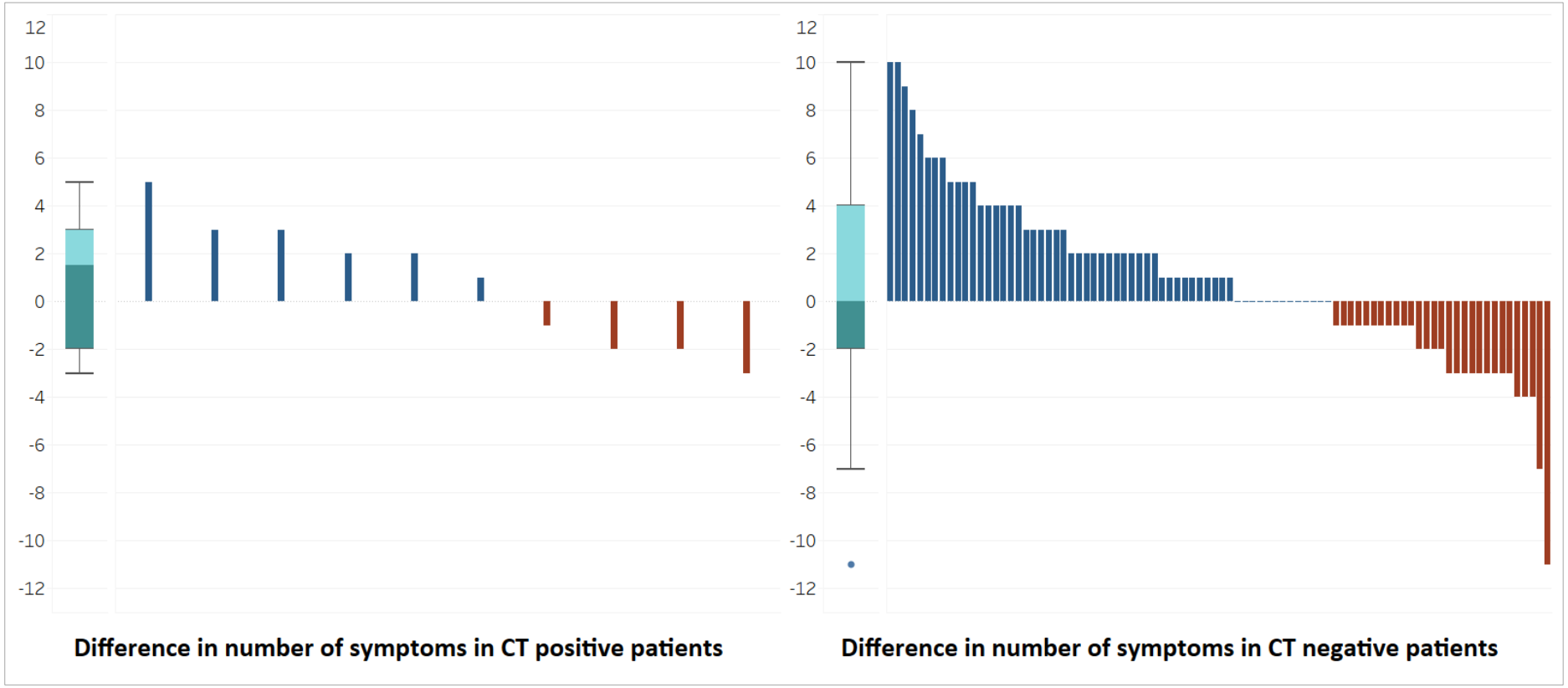

Figure 3.16 Absolute difference in number of symptoms in CT positive and CT negative mild TBI patients.
A box plot with Tukey's hinges of the difference in number of symptoms between baseline and follow up is displayed to the left of each chart. The difference in the number of symptoms from baseline to follow up is represented on the y-axis (fewest = 0, most = 12). Individual patients are represented on the x-axis, are ordered from most improved to most deteriorated and each vertical line represents a single patient. Blue indicates an upwards deflection and clinical improvement, and red indicates a downwards deflection and clinical deterioration. TBI, traumatic brain injury.

Patients with previous head injuries

In a subgroup of patients with mild TBI that had sustained one or more previous head injuries (n=63) there was no change in cognitive function or symptom burden between baseline and follow up (Table 3.7, Figure 3.17, Figure 3.18, Figure 3.19, Figure 3.20, Figure 3.21 and Figure 3.22). This contrasts with a subgroup of patients with TBI that had never had a previous head injury (n=111), where neurocognitive dysfunction persisted to follow up, but symptom burden improved. Figure 3.17 shows that more patients experience poorer rather than improved neurocognitive function at follow up in both the previous and no previous head injury groups and that the degree of deterioration may be worse in the group that has not had a previous head injury.

	Baseline	72 hours	Difference	p-value (95% CI)
Previous head injury (n=63)				
SAC	25 (23-28)	25 (22-28)	0	0.43 (-1.4 to 1.3)
CSI	11 (5-24)	5 (2-13)	6	0.25 (-1.8 to 7.8)
No. symptoms	5 (2-8)	3 (1-6)	2	0.8 (-0.8 to 1.7)
No previous head injury (n=111)				
SAC	26 (23-27)	24 (22-27)	2	0.21 (-0.4 to 1.7)
CSI	9 (4-19)	5 (0-19)	4	0.001 (1.3 to 7.3)
No. symptoms	4 (2-8)	4 (0-6)	0	0.002 (0.4 to 2.0)

Table 3.7 Neurocognitive and symptom outcomes for TBI patients that had had one or more previous head injuries compared to those that had had no previous head injuries

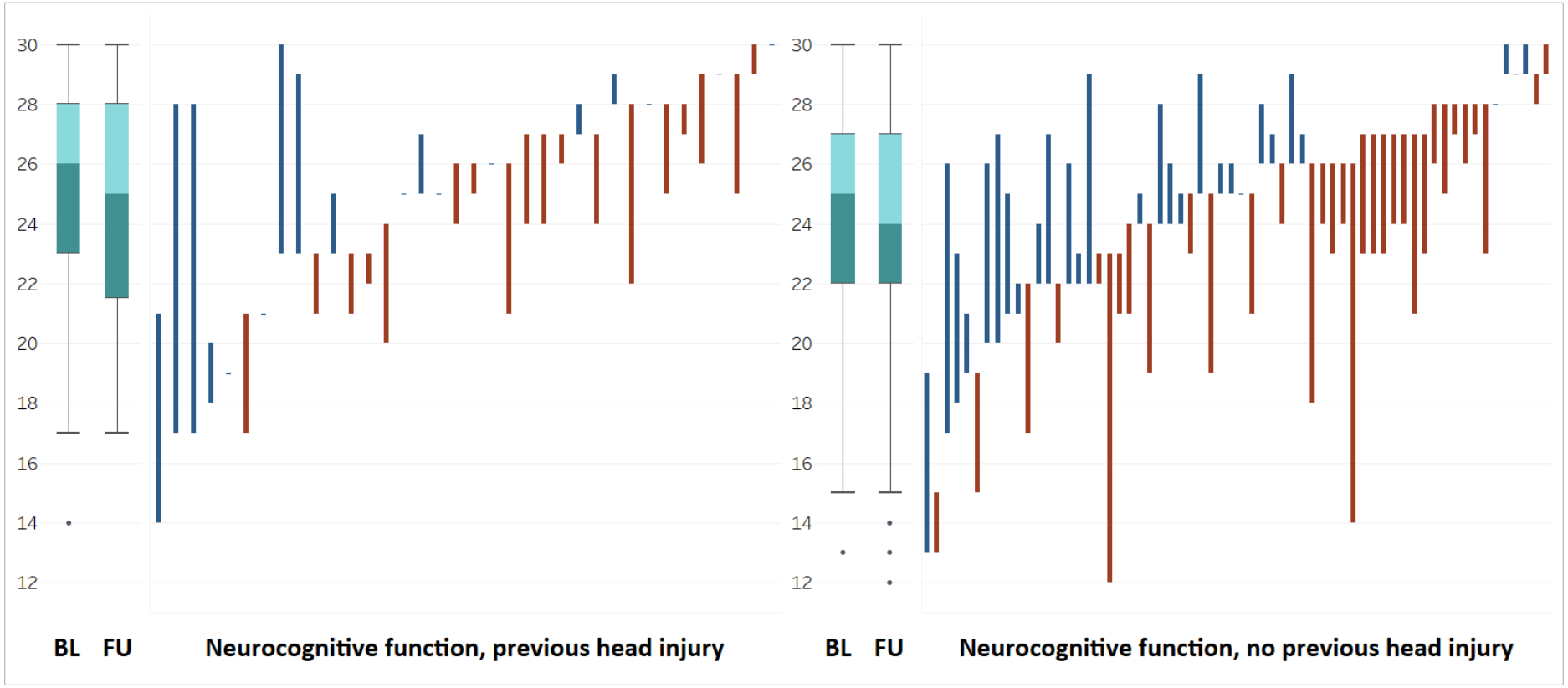

Figure 3.17 Hybrid parallel line plots representing change in neurocognitive function in mild TBI patients with and without previous head injury.

Box plots with Tukey's hinges of neurocognitive function scores at baseline and follow up are displayed to the left of each chart. Neurocognitive function is measured on the standardised assessment of concussion (best = 30, worst = 0) and represented on the y-axis. Individual patients are represented on the x-axis, are ordered from worst to best baseline score, and each vertical line represents a single patient. Blue indicates an upwards deflection and clinical improvement, and red indicates a downwards deflection and clinical deterioration. Flat horizontal lines indicate no change. BL, baseline; FU, follow up.

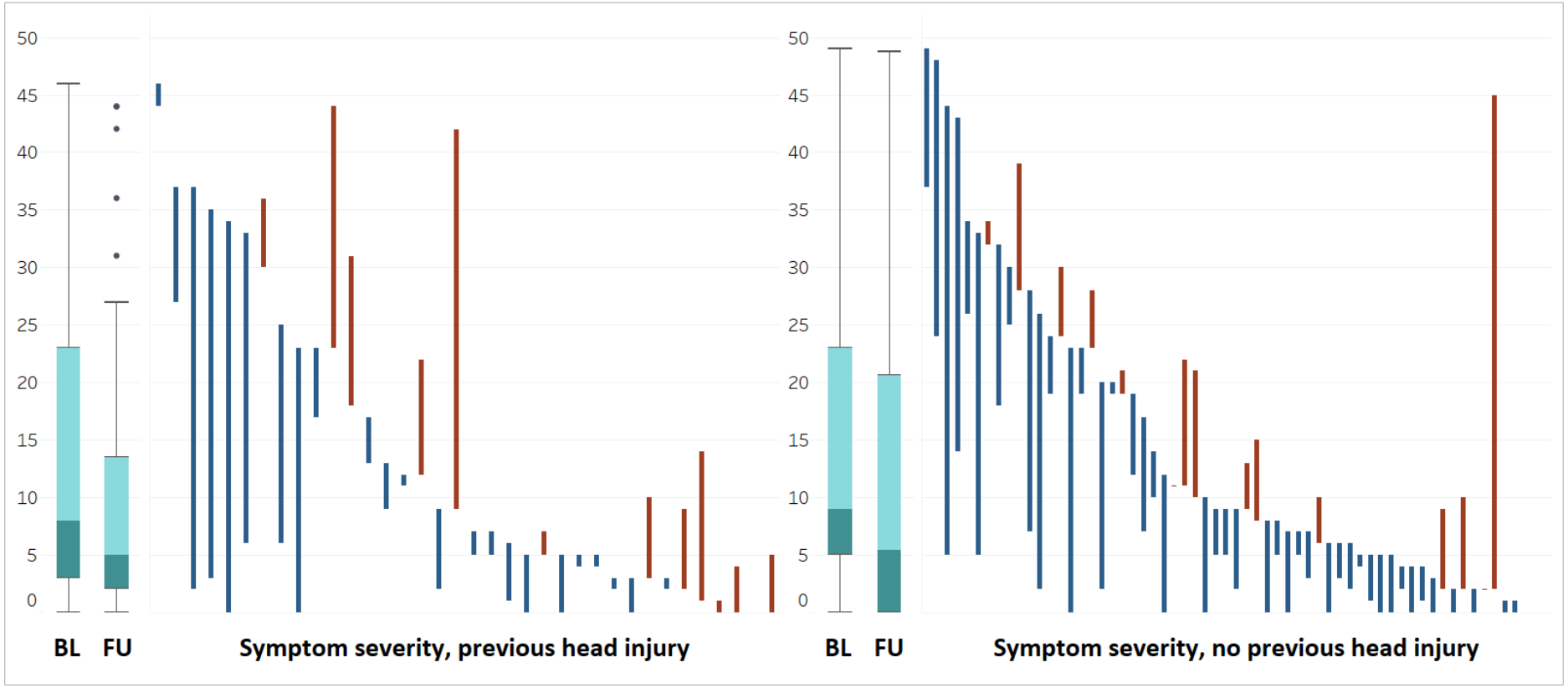

Figure 3.18 Hybrid parallel line plots representing change in symptom severity in mild TBI patients with and without previous head injury.

Box plots with Tukey's hinges of symptom severity scores at baseline and follow up are displayed to the left of each chart. Symptom severity is measured on the concussion symptom inventory (best = 0, worst = 72) and represented on the y-axis. Individual patients are represented on the x-axis, are ordered from worst to best baseline score, and each vertical line represents a single patient. Blue indicates a downwards deflection and clinical improvement, and red indicates an upwards deflection and clinical deterioration. Flat horizontal lines indicate no change. BL, baseline; FU, follow up.

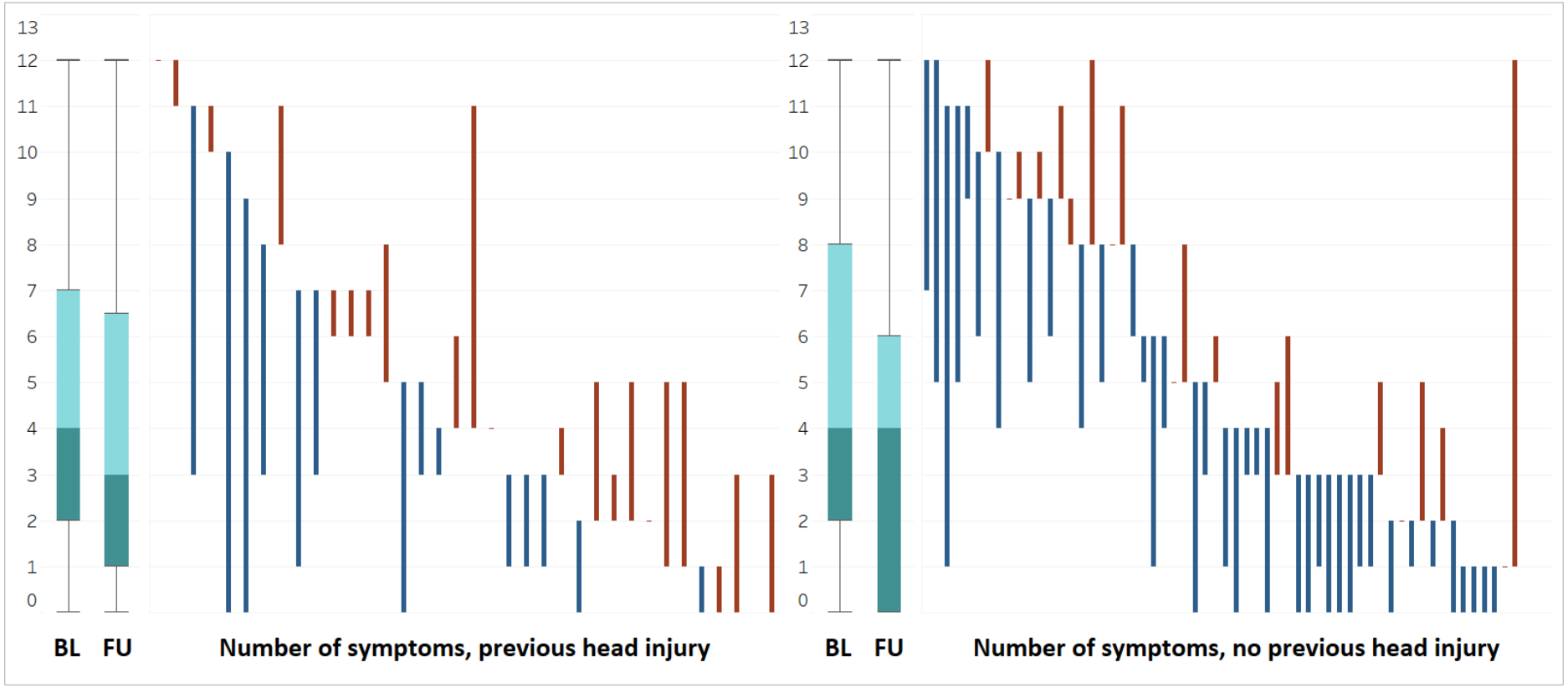

Figure 3.19 Hybrid parallel line plots representing change in number of symptoms in mild TBI patients with and without previous head injury.

Box plots with Tukey's hinges of the number of symptoms at baseline and follow up are displayed to the left of each chart. The number of symptoms is represented on the y-axis (fewest = 0, most = 12). Individual patients are represented on the x-axis, are ordered from most to fewest symptoms at baseline, and each vertical line represents a single patient. Blue indicates a downwards deflection and clinical improvement, and red indicates an upwards deflection and clinical deterioration. Flat horizontal lines indicate no change. BL, baseline; FU, follow up.

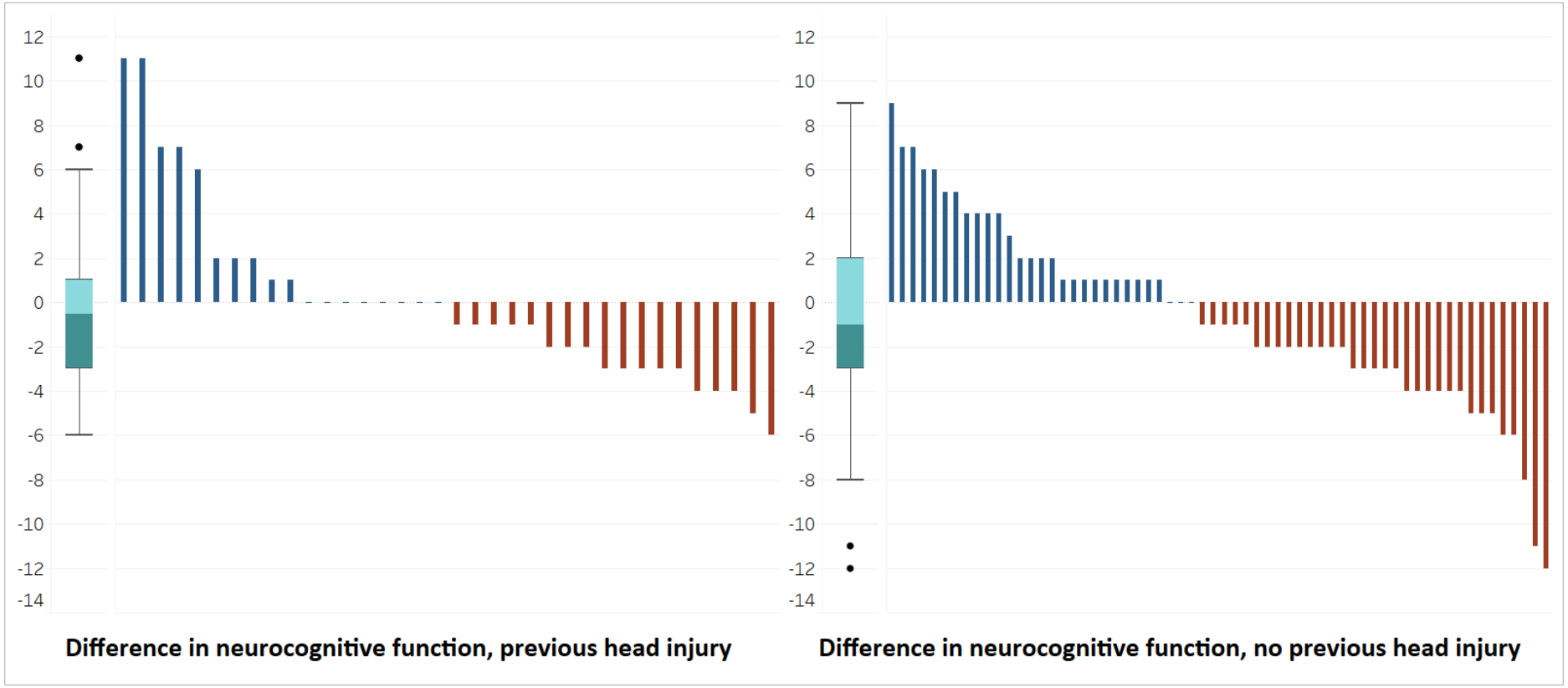

Figure 3.20 Absolute difference in neurocognitive function in mild TBI patients with and without previous head injury.

A box plot with Tukey's hinges of the difference in neurocognitive function scores between baseline and follow up is displayed to the left of each chart. Neurocognitive function is measured on the standardised assessment of concussion (best = 30, worst = 0) and the difference from baseline to follow up is represented on the y-axis. Individual patients are represented on the x-axis, are ordered from most improved to most deteriorated and each vertical line represents a single patient. Blue indicates an upwards deflection and clinical improvement, and red indicates a downwards deflection and clinical deterioration. TBI, traumatic brain injury.

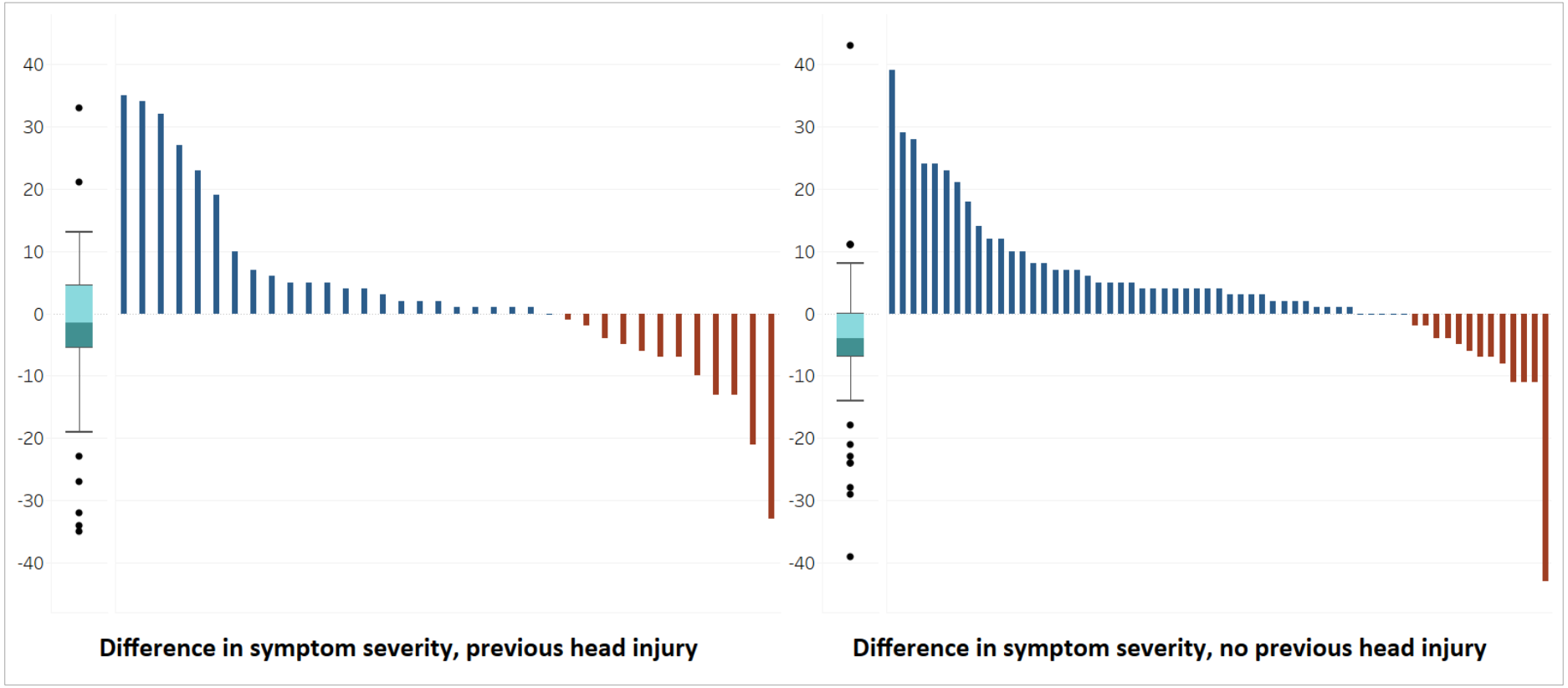

Figure 3.21 Absolute difference in symptom severity in mild TBI patients with and without previous head injury. A box plot with Tukey's hinges of the difference in symptom severity scores between baseline and follow up is displayed to the left of each chart. Symptom severity is measured on the concussion symptom inventory (best = 0, worst = 72) and the difference from baseline to follow up is represented on the y-axis. Individual patients are represented on the x-axis, are ordered from most improved to most deteriorated and each vertical line represents a single patient. Blue indicates an upwards deflection and clinical improvement, and red indicates a downwards deflection and clinical deterioration. TBI, traumatic brain injury.

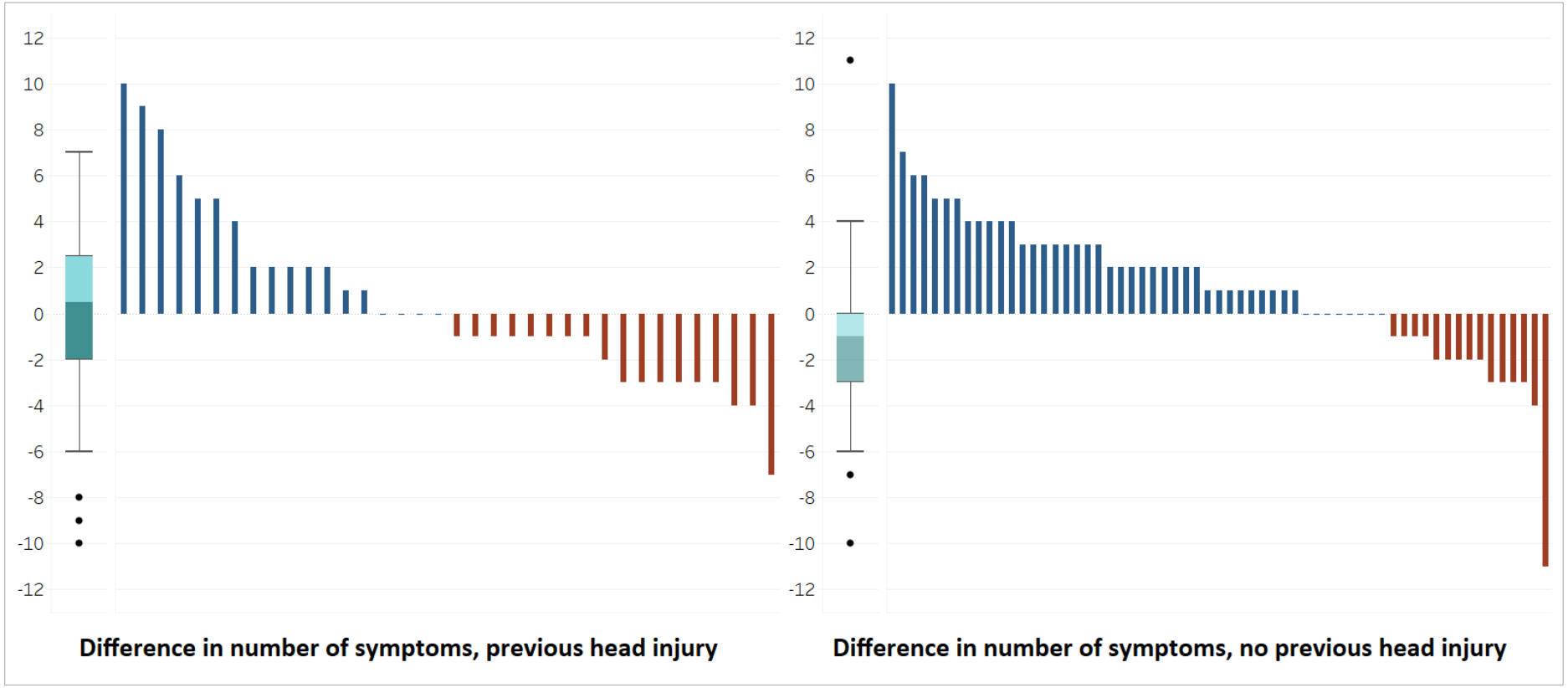

Figure 3.22 Absolute difference in number of symptoms in mild TBI patients with and without previous head injury.

A box plot with Tukey's hinges of the difference in number of symptoms between baseline and follow up is displayed to the left of each chart. The difference in the number of symptoms from baseline to follow up is represented on the y-axis (fewest = 0, most = 12). Individual patients are represented on the x-axis, are ordered from most improved to most deteriorated and each vertical line represents a single patient. Blue indicates an upwards deflection and clinical improvement, and red indicates a downwards deflection and clinical deterioration. TBI, traumatic brain injury.

Discussion

The principal finding of this study was that patients with mild TBI have a clinically relevant neurocognitive deficit immediately after the injury that persists to at least 72 hours. More patients had deteriorated than improved neurocognitive function by follow up. Patients with mild TBI also have persistently greater severity of symptoms and more concussive symptoms than patients without TBI, both of which also persist to 72 hours. Patients with TBI with acute haemorrhage on their CT scan had poorer neurocognitive function than those without.

To my knowledge, this study is the largest that enrolled patients with mild TBI and followed them over the short term. It is also the only multi-centre study that focuses on the neurocognitive effects of mild TBI in patients presenting to the Emergency Department. Neurocognitive function is usually measured either by psychological test that requires administration by a trained psychologist; by standardised paper and pencil tests such as the SAC; or by computer administered tests such as ImPACT.[427] In this study, patients with mild TBI had clinically poorer neurocognitive function than non-head injured patients at follow up. A difference in SAC of two or more points is thought to be clinically relevant, although the SAC is not sensitive enough to pick up subtle changes in neurocognitive function, and there is a ceiling effect associated with its application.[201,428] These findings of a neurocognitive deficit immediately following mild TBI are consistent with those in previously published studies, however a deficit persisting at 72 hours has not been reported before in this patient group.

When measured using paper and pencil tests, in studies enrolling 100 and 246 patients with TBI, there was a significant difference in neurocognitive function at baseline, but no follow up was performed.[416] In further studies of 29 and 49 patients with TBI, neurocognitive function had significantly improved by one month.[203] In a study of 62 patients presenting to the Emergency Department with concussion, cognitive function measured on the SAC improved between baseline and six hours later (from 21 to 24).[429] The results reported in this latter study present poorer baseline neurocognitive function than I report. This may be because the composition of the patients included in that study's population comprised a greater proportion of patients that reported loss of consciousness and post traumatic amnesia compared with my sample, both of which have been associated with poorer SAC scores.[196] A study of 29 patients with TBI found a significant deficit compared with patients without TBI at around 31 hours post injury.[204] The same authors measured SAC at baseline post injury and a month later and reported significant improvement.[203] I report no improvement by 72 hours, however the authors' studies measured cognitive function at different time points to ours: a single observation at 31 hours; and follow up at one month. The results of my study taken with previous work implies a continuum of recovery, during which there is a neurocognitive deficit present up to and beyond 72 hours, but which may resolve at some point before one month. This theory is backed up by the results of neurocognitive function testing by the computerised ImPACT programme, which showed gradual improvement in function measured at 24 hours, one week and three months post injury.[430]

Normal values for SAC scores are primarily derived from athletes that completed the SAC prior to a sports season and therefore prior to any injury. A normal SAC varies from 27 to 28.[193,194,197] Patients with TBI in my study had baseline and 72 hours SAC scores 2-3 points lower than this, and although the two populations are different, this represents a clinically relevant deficit. Patients without TBI reported in this thesis also had lower than normal SAC scores at baseline. However, they increased by one point, which was not a statistically significant increase, to 27, which seems to be the lower end of normal. I also report that there were significant differences in overall symptom severity as measured on the CSI, and total numbers of symptoms, between baseline and 72 hours, and between patients with and without TBI. These findings are in line with previously published work on symptom pattern post mild TBI, which suggests that both overall symptom severity and total number of symptoms may discriminate between patients with and without mild TBI.[431] However, these findings are important because I have reported the persistence of a neurocognitive deficit in the largest group of hospital Emergency Department patients thus far described. In addition, I report two subgroup analyses which suggest that cognitive deficit persists regardless of whether the patient has a GCS of 13, 14, or 15; or whether the patient is in a presumed low acuity group (i.e. did not require or did not have a CT scan); or whether they had a history of previous head injuries or not. Finally, I report that patients with mild TBI and intracranial haemorrhage have poorer neurocognitive function than those without intracranial haemorrhage. This adds weight to the concept of complicated mild TBI and emphasises the importance of this group of patients.[420]

This study has strengths and weaknesses. It is one of the largest studies and the only multicentre study examining short term change in neurocognitive function following mild TBI. Although convenience sampling was necessitated based on resources, selection bias was minimised by approaching potential participants that had been admitted to hospital but were still within 24 hours of their TBI as well as by approaching all potential participants in real time. It was not possible to eliminate bias in the form of drop-outs or lost-to-follow-up, and consequently bias was quantified and is reported in Figure 3.1 and Figure 3.2. The lost-to-follow-up rate is high; 46% in the TBI group and 43% in patients without TBI. The narrow follow-up window was defined by protocol. It was required because a patient's cognitive function after a mild TBI can change day to day. Consequently, collecting cognitive data across a range of days in the short term following a mild TBI, for instance at day two for one patient and at day seven for another, would not produce a set of comparable data. This narrow window did however present significant difficulties in contacting participants. Another limitation is could be that the exclusion criteria could be said to be unnecessarily narrow. They are, however, in line with other similar studies.[203] For many participants, follow-up was by telephone. Telephone based cognitive assessments are employed in cognitive research, particularly in screening for cognitive defects and dementia, however the SAC is not validated for use over the telephone. The proportion of follow ups completed by telephone was not recorded and so any difference between telephone and face-to-face follow groups is not known. There may be an element of learning that is dependent in part on visual stimulus, which clearly is missing during a telephone follow up. The theory that learning for the SAC memory recall may be partly dependent on visual stimulus is enforced by the

observation that the domain that represented the greatest decrease in SAC between initial attendance and 72 hours in patients without TBI was the delayed recall domain. This may explain the results seen in patients without TBI, who had a wider SD between baseline and 72 hours. There were many more patients enrolled with than without TBI, which may introduce bias in comparisons between those with and without TBI. This was partly because the primary outcome was the difference between baseline and follow up within the head injured group, and partly because of the nature of convenience sampling. Whilst recognising this as a limitation, I do not believe that this is an insurmountable flaw in the methodology. Finally, because this was an analysis of data from a separate study, there was no specific sample size calculation associated with either TBI or non-TBI based endpoints.

Methods for assessing and managing acute mild TBI in the Emergency Department are varied. This reflects the uncertainty surrounding optimal management strategies. Decision making tools that help determine whether or not a patient should have a CT scan of the head are based on studies that were designed to assess whether a patient has an intracranial haemorrhage, not whether or not they have concussion.[418] I report that neurocognitive dysfunction is associated with mild TBI but the speed of recovery and the repercussions on patients' work and home lives is still unknown. The clinical follow up for these patients is important. Leaflets explaining the likely clinical course and provision of access to TBI clinics may well contribute to an improvement in clinical variables.[399]

Conclusion

Emergency Department patients with mild TBI experience a neurocognitive deficit and concussive symptoms that persist to at least 72 hours. This has significant implications on the management of mild TBI, including the potential for early treatment, and explicit explanations to patients on what they can expect following 'normal' scan results. Further work evaluating the pattern of neurocognitive recovery, repercussions on home and work life, and management strategies is warranted.

Chapter 4 Seizure after mild TBI and biomarkers to predict outcomes

Seizure as a consequence of traumatic brain injury

Mild TBI is characterised based on peri- or post-injury features. These include many of the elements in the definitions of mild TBI, and include seizure (Table 1.2 and Appendix 1). Seizure can occur at the time of injury, or in the minutes to hours following. When seizures occur more than a week after injury, they are considered evidence of post-traumatic epilepsy.[432,433] Seizure is thought to be an important acute clinical manifestation of TBI as it reflects a structural abnormality that results in disordered electrical activity. The rate of seizure at the time or soon after injury is from 1-5%. In a landmark study from the US of 520 patients with minor head injury, 5% (24) had a seizure, and four of those had positive CT findings.[434] In a Canadian cohort of 3121 head injured patients, the rate of seizure in the Emergency Department was 0.1% (4) and one of those four patients had an acute CT abnormality.[435] The same authors went on to recruit another large cohort of 1822 patients with minor head injury from mostly the same EDs, and found the rate of seizure to be 2.0% overall (37), with a rate of 4.3% in CT positive patients and 1.9% in CT negative patients.[436] The low rate of seizure of 0.1% in the first Canadian study is likely due to the criterion that the seizure happened in the Emergency Department rather than at any time after injury.

The 4.3% rate of head injury induced seizure in CT positive patients noted above contrasts with a study of patients with mild TBI and isolated subdural haematoma, in which the rate of seizure occurring during the in-patient

episode, not just during the Emergency Department episode, was reported as 2.2%.[437] In a more recent study of 453 patients with head injury and GCS 15, 4.4% had seizure.[438] This study was conducted in level one neurotrauma centre in Karnataka, India, and 43% were CT positive. This is an unusually high proportion of CT positive patients, particularly in the context of patients exclusively with GCS 15. This could in part be accounted for by the authors' decision to include skull fractures within their definition of abnormality on CT, and possibly in part by the rural and lower middle-income nature of the catchment area from which patients were admitted to the hospital.

After TBI, the rate of post-traumatic epilepsy ranges from 2-5% and the rate of seizures without a diagnosis of epilepsy may be even higher.[439-444]. Out of 305 patients seen in a head injury clinic in the UK, 97% had never had a seizure prior to TBI, and 7% (24) had had seizures by the time they were seen in clinic.[445] Of those patients with seizures, 80% had moderate or severe TBI. Furthermore, post-traumatic epilepsy is also more common in patients with more severe TBI. In Sweden, eight of 109 patients had had a seizure within 24 hours of injury, and 12 of 109 were diagnosed with epilepsy within 10 years. Compared to a TBI cohort that did not develop epilepsy, there was a greater proportion of patients with moderate and severe TBI in the epilepsy group.[446] Less is known about the rate of sports related concussion convulsions, which is estimated to be 1 in 70 or less, and with very few patients going on to be diagnosed with post-traumatic epilepsy.[447] In one systematic review, of those that did develop epilepsy, all were boxers.[447]

Patients with seizures account for 1% of all Emergency Department attendances (250,000 patients in the UK), and 1.4% of all medical

admissions.[18,19,21,27,28,448] Previous studies have shown that 5 to 10% of the general population will suffer from a seizure in their lifetime.[20,449-451] Among these patients, only a proportion is diagnosed with epilepsy. When managing a patient presenting with seizure activity a physician must consider several parameters to assess the risk of early recurrence and of complications. If there is a clear precipitant such as trauma, then that must be managed in addition to managing the seizure. However, important prognostic factors, such as predictors of seizure recurrence, the need for emergent therapy and consequently the requirement for hospital admission are not well studied. There is therefore a chance of admitting patients that may not require emergency therapy, and consequently utilising resources unnecessarily, or conversely, discharging patients that may require inpatient care. Thus, in emergency medicine when managing these patients, evaluation of the risk of short-term recurrence is essential for the physician to decide whether discharge is possible or not.

Seizure recurrence

After a first seizure, recurrence rates are around 20% during the following month, up to 50% at three years, and about 70% after more than one seizure.[30,31,452,453] There is little evidence to inform whether patients that have a seizure at the time of a mild TBI are more or less likely to go on to have recurrent seizures compared to patients that have seizures for any other reason. Patients with a first seizure that attend the Emergency Department have a recurrence rate of 18.5% at 24 hours, and up to 40% of these patients chronically abuse alcohol.[21,454] Chronic alcohol abuse increases the risk of seizure recurrence with an odds ratio of 1.7 for early seizure recurrence.[454]

These data and other associated factors are used to evaluate the need for long term anti-epileptic treatment. Factors associated with long term recurrence were analysed in a large multi-centre European study: The Multicentre trial for Early Epilepsy and Single Seizures.[31] This trial also evaluated the benefit of immediate antiepileptic drug introduction. In an ancillary study, the authors developed a model to predict the risk of long-term recurrence. The model included the number of seizures before presentation, the presence of a neurological disorder and EEG findings. Patients were stratified as having low, medium or high risk of recurrence at one, three and five years.[32] However, Kho et al. found different results, with the number of seizures and type of epilepsy not being associated with increased recurrence of risk. The only independent factor identified in this study was the type of seizure: remote symptomatic seizure, versus provoked or idiopathic seizure (odds ratio 2.2).[455]

Few studies have attempted to link clinical and biological parameters on admission with short-term seizure recurrence. One prospective observational study evaluated predictors of early rather than late seizure recurrence.[454] In this study, alcoholism, low plasma glucose, and a low GCS were associated with a higher risk of early seizure recurrence, but this single study has not been replicated. There is conflicting evidence that the number of seizures before presentation, the presence of a neurological disorder and the EEG findings, or the type of seizure, predicts long term recurrence.[32,455] There is therefore a deficiency of information available to clinicians when assigning a risk of early seizure recurrence in Emergency Department patients.

The potential consequences of a seizure include physical injury, time off from work, degeneration into status epilepticus and hypoxic brain damage and

death.[23-25] In one study, 1.2% of Emergency Department attendances for seizure resulted in death, and injury or death was associated with 15% of seizure attendances.[26] Recurrent seizures also result in altered functional brain connectivity, with patients that have frequent seizures exhibiting widespread areas of poor brain connectivity compared with epileptic patients that seize less frequently.[456] Physicians must also evaluate whether the patient has any underlying illness that may have precipitated the seizure (for instance meningitis, intracranial haemorrhage or stroke) and complications resulting from it (for example brain injury or aspiration). A primary goal of the emergency physician is to identify underlying critical illness, institute appropriate treatment and identify those patients that need to be hospitalised and those that can be safely discharged.

Biomarkers

S100B is a glial-specific protein expressed by astrocytes and is a specific marker of cerebral injury.[291] S100B has been extensively evaluated as a biomarker of immediate and long term outcomes in TBI (Table 1.11) as well as other neurological conditions such as cardiac arrest.[317] Seizures can be associated with poor outcomes, particularly if they are prolonged, but many are not. S100B concentration is normal following febrile seizure in children, and that febrile seizures are considered to be relatively harmless contributes to the hypothesis that elevated S100B might predict adverse neurological outcomes.[457] Copeptin, the C-terminal of pre-provasopressin, is a biomarker of endogenous stress. Recently it has been described as a good prognostic marker in neurological disorders, such as traumatic brain injury, intracerebral haemorrhage, and stroke.[359,362,366]

Methods

Objectives

Primary objective

The primary objective of this study was to test the hypothesis that the use of two biomarkers, a specific neurologic biomarker (protein S100B) and a biomarker of endogenous stress (copeptin), would improve the prediction of adverse events following seizures.

Secondary objectives

- To determine the rate of TBI-induced seizure attending the Emergency Department.
- To evaluate the diagnostic performances and the area under the curve (AUC) for a predictive model based on clinical parameters alone and a model based on clinical parameters with the biomarkers for the prediction of the secondary endpoints.

Outcomes

Primary endpoint

The primary outcome was a composite of seizure recurrence, death, hospital admission, and hospital re-admission by day seven.

Secondary endpoints

The secondary endpoints were:

- Recurrence of convulsive seizure within seven days.
- Hospital admission for more than 24 hours.
- A composite of severe outcomes including ICU admission, neurosurgical procedure or death by 28 days.

Eligibility

Inclusion

Patients were eligible if they met either one of the following criteria:

- Attending the Emergency Department with one or more documented seizure before arrival
- Patients having a convulsive seizure in the Emergency Department

Exclusion

Patients were excluded if they had any one of the following criteria:

- Age less than 18 years
- Pregnancy
- Prisoners

Study design and setting

This was the UK arm of an international multicentre prospective observational cohort study designed to assess the incremental added value of serum S100B and copeptin measurements together with usual clinical and biological data to predict adverse outcomes following seizure related Emergency Department visits. I screened and recruited patients from the Royal London and Whipps Cross University Hospitals during a one-year period. The study was approved by the National Research Ethics Service Committee London, Camberwell St Giles (reference 12/LO/1783). The project followed the Standards for Reporting of Diagnostic Accuracy (STARD) recommendations for diagnostic studies.[458]

Consent process

Potential participants were screened on admission to the Emergency Department by local investigators, nurses and medical staff. There were no financial payments offered to subjects or volunteers. Written informed consent was sought prior to enrolment. Consent was always obtained prior to blood collection. The consent process included an explanation of the aims, methods and potential benefits of the study, as well as of the potential hazards. The physician or the nurse explained to all patients that they were free to refuse to enter the study, or to withdraw at any time during the study for any reason. Patients were approached as soon as their level of consciousness allowed them to understand the explanations given. Printed patient information sheets were left for the subjects to read, and the principal investigator was contactable by telephone and email to address further queries.

The processes involved in obtaining and documenting informed consent were adherent to standards described in Good Clinical Practice and the Declaration of Helsinki. Prior to any study-related activity, the patient (and/or the patient's legally acceptable representative) received oral and written information about the study in a form that the subject could read and understand. A voluntary signed and dated Informed Consent Form was obtained from the patient prior to any study-related activity.

Inability to consent

Many eligible subjects were likely to present with impaired cognitive ability, for instance due to being in a post-ictal phase, cognitive impairment, coma, or alcohol intake. In such situations an appropriate partner, relative or friend was

sought to give assent. When a patient was enrolled through partner, relative or friend's assent, the patient's consent was sought in retrospect once capacity was regained. When a patient refused to grant retrospective consent, further contact with the patient ceased and they were withdrawn from the study. In those situations, data that had already been gathered was included in the final analysis unless the subject requested that it be withdrawn, in which case it was destroyed.

If a suitable friend or relative could not be identified, or if none were available, the Consultant in charge of the Emergency Department was approached to give assent for the patient to be enrolled into the study. The Consultant concerned was not in a position which could be considered subordinate to any member of the study team and was wholly independent of the research team. The process was the same as the process of partner, relative or friend's assent, involving provision of an information sheet and an opportunity to discuss the study and ask questions. When a patient was enrolled through Consultant assent, the patient's consent was sought in retrospect once capacity was regained. If a subject refused to grant retrospective consent, the process was the same as if a relative had provided assent and the subject retrospectively wished to withdraw.

Data items

The following data was collected:

Demographic data

Age, sex.

Medical history

Past episode of seizure, known epileptic disorder, stroke with persistent neurological deficit, degenerative neurological disorder, brain tumour, meningitis/encephalitis, chronic alcohol abuse, other toxic abuse, chronic treatment.

Seizure type

Unwitnessed, simple partial, complex partial, generalised tonic-clonic, secondary generalised tonic-clonic, absence, status epilepticus, other.

Provoked, idiopathic, or remote symptomatic.

Time from seizure to presentation in Emergency Department.

Number of seizures in the last month.

Physiological and clinical data

Heart rate, blood pressure, temperature, GCS with component breakdown, peripheral saturations of oxygen.

Neurological deficit on examination.

Headache, photophobia/phonophobia, neck stiffness.

Main suspected cause (chronic epileptic disorder, recent alcohol intake, alcohol withdrawal, stroke, intracerebral haemorrhage, head injury, sepsis, cerebral neoplasia, metabolic disturbances).

Laboratory values

Serum glucose, white blood cell count, serum sodium, serum venous lactate, EEG.

Outcomes

Death at seven days and 30 days, seizure recurrence at 24 hours and seven days, length of hospitalisation, hospitalisation subsequent to first Emergency Department visit within one month, ICU admission, length of ICU admission.

A retrospective analysis of the medical record was performed after the study closed to identify the cause of seizure in order to determine the proportion of patients that had a seizure as a consequence of TBI.

Biochemical analysis

Copeptin and Protein S100B were collected on the arrival of the patient in the Emergency Department, and no later than 24 hours following the seizure. The volumes were 5ml for S100B and 5ml for copeptin. The blood was collected in heparinised red topped sample tubes and allowed to stand from 30 minutes to four hours. The sample was then centrifuged at 2640g for 20 minutes followed by 3010g for 10 minutes. A volume of 0.75-1ml of serum was then pipetted into an Eppendorf and the sample frozen and stored at -80°C at Barts Health NHS Trust. S100B samples were analysed on an Elecsys® analyser (Roche Diagnostics). This method is based on the sandwich principle, in which a biotinylated S100B-specific antibody and an S100B-specific antibody labelled with a ruthenium complex react to form a sandwich complex. The complex is then bound to a streptin-biotin-paramagnetic bead complex and magnetically captured onto the surface of an electrode. Application of a current across the electrode induces a measurable electrochemiluminescent emission.[459] Copeptin samples were stored until the end of the study and transported together to Central Biological Ressource laboratoire (CRB) in Pitie-Salpetriere Hospital, Paris, France for batched immuno-analysis using the KRYPTOR® method, ThermoFisher BRAHMS. The KRYPTOR® method employs time resolved amplified cryptate emission technology in which europium cryptate and fluorophores bind with an immune complex to the copeptin molecule and emit light waves of predictable wavelength, which are detected and resolved as a concentration of copeptin.[460]

Follow up

Discharged patients were followed up with a phone call at seven and thirty days after recruitment. Recurrence of convulsive seizure, re-consultation, rehospitalisation, ICU admission and the presence of an abnormality on EEG was recorded.

Statistical Analysis

The central tendencies of non-normally distributed data were reported as medians with interquartile range (IQR), and that of normally distributed data as means ± standard deviation (SD). Central tendencies were only calculated for data with at least six observations. Categorical data were represented as number (percentage). Normality was tested using the Shapiro-Wilk test and by visually assessing the frequency distribution. The Shapiro-Wilk tests the hypothesis that the data is not normally distributed, and therefore the null hypothesis that the data is normally distributed. A significant *p* value, which corresponds to rejection of the null hypothesis of normality, means that the data is not normally distributed. Sensitivities and negative predictive values of the combination of copeptin and S100B for the primary outcome were calculated.

Comparison of the two groups was performed using the Student t test, the Mann-Whitney U test, and Fisher's exact method when appropriate. Multiple backward logistic regression was performed to assess variables associated with the severity of the seizure, and odds ratios with 95% confidence intervals were calculated. Severe outcome probability was tested initially using a score derived from the logistic regression model without the two biomarkers, then including the biomarkers. To avoid overestimation, a conservative approach

was used and only significant variables in the univariate analysis were included. Calibration of the model was estimated with Hosmer-Lemeshow test, and discrimination with the c-index.

Pre-existing literature suggests a low correlation between standard clinical and biological data with the primary outcome. A receiver operating characteristics (ROC) curve with predictive probability for the primary endpoint was calculated using clinical data alone, then a second one calculated using the addition of the one biomarker; then a third calculated with the addition of the second biomarker. The threshold was that which minimised the distance to the ideal point (1 = sensitivity = specificity).

Diagnostic data (sensitivity, specificity, negative predictive value [NPV], positive predictive value [PPV]) with their 95% confidence intervals were calculated. A NPV greater than 98% is required for an acceptable diagnostic test, which corresponds to a rate of errors related to discharge of less than 2%.

A sub-group analysis was conducted to establish the rate of the primary endpoint and seizure recurrence by day seven in epileptic patients because the incidence of the primary endpoint may differ in epilepsy.[454] Epileptic patients were defined as those prescribed anti-epileptic drugs. A further sub-group analysis was conducted to determine the rate of seizure recurrence by day seven in the group that was initially discharged from the Emergency Department. This was conducted because the composite primary endpoint might have led to a higher rate of endpoint than expected.

Results

Baseline data

The UK arm recruited 97 patients out of a total of 443 internationally (Figure 4.1). Baseline data is shown in Table 4.1 and comparisons between UK and French baseline data is shown in Appendix 8. Fifty (52%) patients met the composite primary endpoint of seizure recurrence, death, hospital admission, or hospital re-admission by day seven. Of those, 31 (32%) had seizure recurrence, 33 (34%) were admitted (28 under acute medicine, four under critical care, two under neurosurgery), and 8 (8%) were readmitted by day 7 (Table 4.3). No patients died. Some patients had more than one element of the composite endpoint (Figure 4.2). The most common cause for a seizure was epilepsy (47%), followed by alcohol associated seizures (21%) (Table 4.2). Alcohol associated seizures could have been associated with abuse of alcohol or withdrawal from alcohol use. First fits accounted for 11% of all patients and convulsive syncope for 8%.

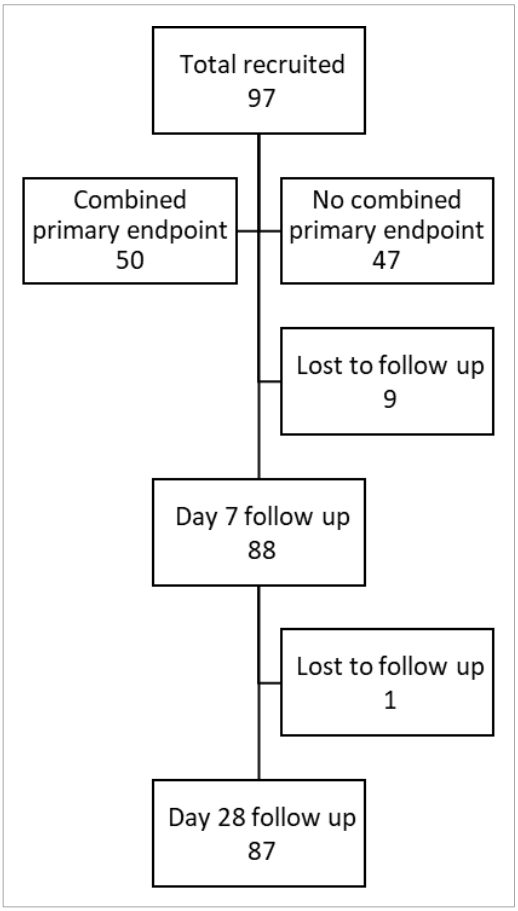

Figure 4.1 Participation inclusion diagram

Variable	Overall	Primary outcome N=50 (52%)	No primary outcome N=47 (48%)
Eligibility			
Seizure prior to ED arrival	91 (94%)	46 (92%)	45 (96%)
Seizure in ED	19 (20%)	18 (36%)	1 (2%)
Male Sex	59 (61%)	28 (56%)	31 (66%)
Age	41 (15)	43 (14)	36 (14)
Previous seizures	91 (94%)	46 (92%)	45 (96%)
Previous diagnoses			
Epilepsy	39 (40%)	21 (42%)	18 (38%)
Alcohol abuse	25 (26%)	16 (32%)	9 (19%)
Stroke	12 (12%)	5 (10%)	7 (15%)
Other neurological path.	7 (7%)	6 (12%)	1 (2%)
Substance abuse	6 (6%)	4 (8%)	2 (4%)
Meningitis	4 (4%)	3 (6%)	1 (2%)
Regular prescriptions			
Anti-epileptic drugs	31 (32%)	15 (30%)	16 (34%)
Benzodiazepines	5 (5%)	2 (4%)	3 (6%)
Symptoms in ED			
Headache	28 (29%)	14 (28%)	14 (30%)
Confusion	16 (16%)	13 (26%)	3 (6%)
Photophobia	6 (6%)	4 (8%)	2 (4%)
Meningism	6 (6%)	4 (8%)	2 (4%)
Focal neurol. deficit	5 (5%)	5 (10%)	0 (0%)
Seizure characteristics			
Generalized Tonic-clonic	82 (85%)	39 (78%)	43 (91%)
Complex Partial	9 (9%)	8 (16%)	1 (2%)
Absence	1 (1%)	1 (2%)	0 (0%)
Other seizure	3 (3%)	1 (2%)	2 (4%)
Simple Partial	2 (2%)	1 (2%)	1 (2%)
Provoked/Acute sympt.	31 (32%)	22 (44%)	9 (19%)
Witnessed?	73 (75%)	42 (84%)	31 (66%)
Physiological			
Heart rate (bpm)	92 (20)	98 (24)	85 (18)
SBP (mmHg)	129 (23)	131 (33)	125 (18)
DBP (mmHg)	76 (15)	80 (17)	74 (13)
Temperature (°C)	36.5 (0.7)	36.6 (0.8)	36.3 (0.7)
SpO_2 (%)	97 (2)	97 (2)	97 (2)
GCS 13-15	85 (88%)	42 (84%)	43 (91%)
GCS 9-12	5 (5%)	4 (8%)	1 (2%)

GCS 3-8	7 (7%)	4 (8%)	3 (6%)
Laboratory			
White blood cell count ($x10^3$)	8.7 (6.4 to 12.4)	9.1 (7.0 to 14.2)	8.7 (5.8 to 11.2)
Glucose (mmol/L)	6.1 (5.2 to 7.7)	6.7 (5.3 to 8.0)	6.1 (5.1 to 7.7)
Sodium (mEq/L)	140 (138 to 142)	140 (137 to 141)	141 (139 to 143)
Calcium (mmol/L)	1.23 (1.20 to 1.28)	1.23 (1.19 to 1.29)	1.23 (1.22 to 1.27)
Lactate (mmol/L)	2.5 (1.4 to 4.4)	2.9 (1.8 to 6.9)	2.2 (1.5 to 3.9)
S100B (µg/L)	0.09 (0.06 to 0.18)	0.1 (0.07 to 0.21)	0.08 (0.06 to 0.12)
Copeptin (pmol/L)	22.0 (7.7 to 48.4)	25.1 (9.3 to 93.5)	19.4 (6.6 to 38.7)

Table 4.1 Baseline data
Categorical data are reported as number (%), continuous data as mean (SD), or median (IQR). ED, Emergency Department; SBP, systolic blood pressure; mmHg, millimetres of mercury; DBP, diastolic blood pressure; SpO2, peripheral saturation of oxygen; GCS Glasgow Coma Score; mmol/L, millimoles per litre; mEq/L, milliequivalents per litre; µg/L, micrograms per litre; pmol/L, picomoles per litre.

Cause of seizure	Number	Percentage
Epilepsy	46	47%
Alcohol	21	21%
First fit	11	11%
Convulsive vasovagal syncope	8	8%
Stroke	3	3%
Other	9	9%

Table 4.2 Cause of seizure
Alcohol, any seizure presumed to be precipitated by alcohol use, which could be abuse or withdrawal. Other causes were recreational drug overdose, sertraline & diphenhydramine overdose, venlafaxine overdose, neurosarcoid, hydrocephalus due to cerebral abscess, hypoglycaemia, cerebral neoplasm, & encephalitis.

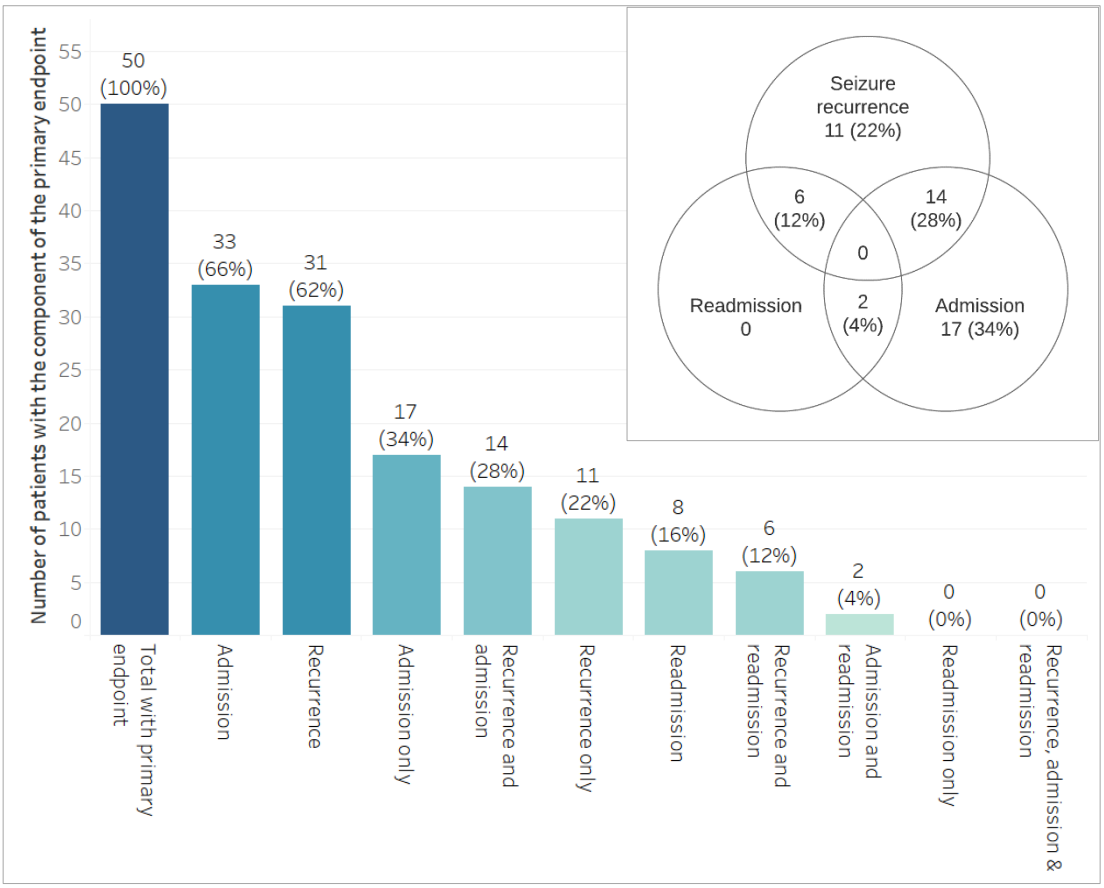

Figure 4.2 Composition of the primary endpoint of recurrence, admission, readmission and death

Thirty-one (32%) patients fulfilled the secondary endpoint of a recurrence of seizure by day seven, 31 (32%) patients were admitted into hospital for more than 24 hours, and five (5%) patients had the composite severe secondary outcome of ICU admission, a neurosurgical procedure or death by 28 days. Of those five, all achieved the endpoint by being admitted to ICU, and one of those also had a neurosurgical procedure and died of a brain tumour (Table 4.3).

Outcome	UK N=97 (22%)	France N=346 (78%)	Overall N=443 (100%)
Composite primary outcome	50 (52%)	81 (23%)	131 (30%)
Secondary outcomes			
Severe composite secondary outcome	5 (5%)	32 (9%)	38 (9%)
Length of stay > 24 hours	31 (32%)	76 (22%)	107 (24%)
Recurrence of seizure by day 7	31 (32%)	29 (8%)	60 (14%)
Discharge destination from ED			
Discharge home	52 (54%)	238 (69%)	290 (65%)
Admission any service (not obs. unit)	33 (34%)	62 (18%)	95 (21%)
Admission observation unit	11 (11%)	95 (27%)	106 (24%)
Admission under medicine	28 (29%)	44 (13%)	71 (16%)
Admission under critical care	4 (4%)	6 (2%)	10 (2%)
Admission under neurosurgery	2 (2%)	12 (3%)	14 (3%)
Death	0 (0%)	2 (1%)	2 (1%)
Day 7 follow up			
Re-admitted into hospital by day 7	8 (8%)	10 (3%)	18 (4%)
Death between admission and day 7	0 (0%)	5 (1%)	5 (1%)
Readmitted to critical care by day 7	4 (4%)	3 (1%)	7 (2%)
Neurosurgical intervention by day 7	1 (1%)	2 (1%)	3 (1%)
Day 28 follow up			
Seizure recurrence	38 (39%)	48 (14%)	86 (19%)
Readmission into hospital	9 (9%)	21 (6%)	30 (7%)
Readmission under critical care	3 (3%)	1 (0%)	4 (1%)
Readmission under neurosurgery	1 (1%)	5 (1%)	6 (1%)
Death by day 28	1 (1%)	3 (1%)	4 (1%)

Table 4.3 Outcomes in the UK and France

Biomarker data

The median S100B and copeptin levels were 0.09 µg/L (IQR 0.06-0.18) and 22.0 pmol/L (IQR 7.7-48.4) respectively. S100B and copeptin were significantly higher in patients with compared to without the composite primary endpoint: 0.22 µg/L (95% CI 0.14 to 0.31) vs 0.11 µg/L (95% CI 0.08 to 0.14) (p = 0.01, 95% CI 0.02 to 0.2) for S100B; and 77.0 pmol/L (95% CI 44.3 to 109.7) vs 27.0 (95% CI 18.2 to 35.9) (p = 0.004, 95% CI 16.2 to 83.8) for copeptin (Figure 4.3).

No power calculation was performed in the design phase of this study. However, S100B and copeptin in patients with the composite primary endpoint were both significantly higher than in those without the endpoint. Therefore, there is no type 2 error and consequently, no post-hoc power calculation is necessary.

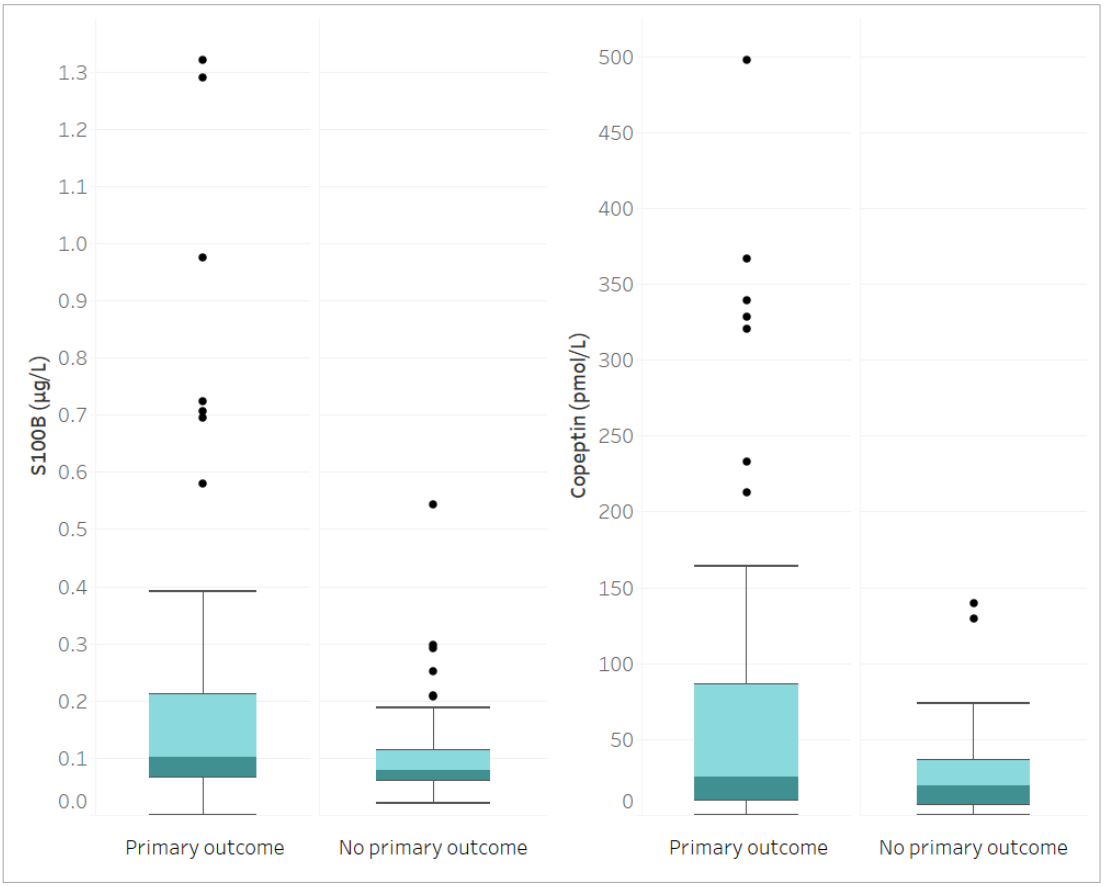

Figure 4.3 S100B and Copeptin levels by group
Outcome is the composite primary endpoint of recurrence, admission, readmission and death. Box plot shows median, 25th centile, 75th centile, Tukey's hinges, and outliers.

Diagnostic test characteristics

The area under the receiver operating characteristic curves (AUC) for the composite primary endpoint were 0.6 (95% CI 0.5 to 0.7) and 0.6 (95% CI 0.5 to 0.7) for S100B and copeptin respectively (Figure 4.4). The AUC for recurrence of seizure by seven days were 0.5 (95% CI 0.4 to 0.7) and 0.5 (95% CI 0.4 to 0.7) for S100B and copeptin respectively (Figure 4.5).

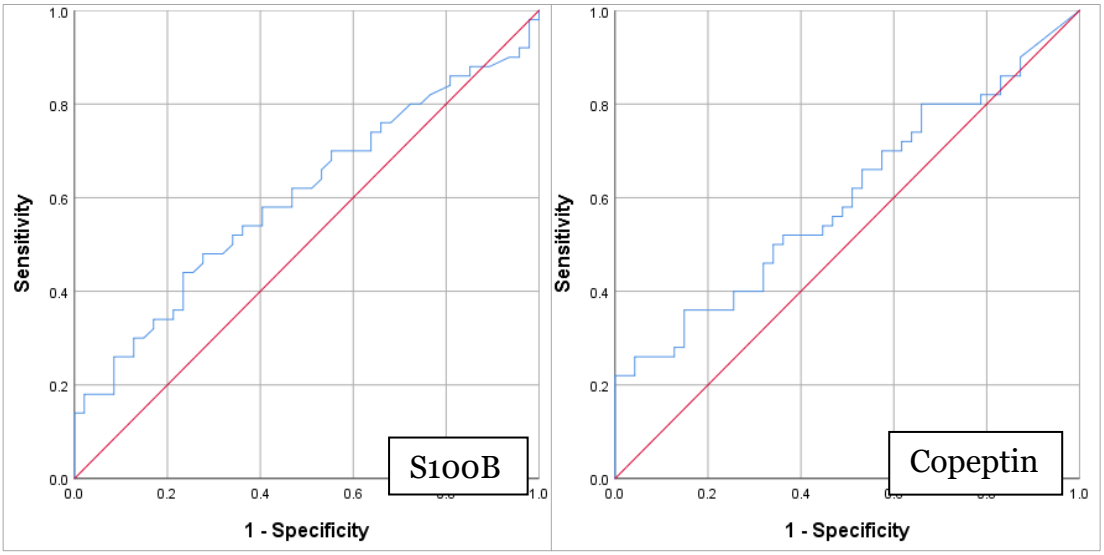

Figure 4.4 Receiver operating characteristic curve for S100B and copeptin to diagnose the composite primary endpoint

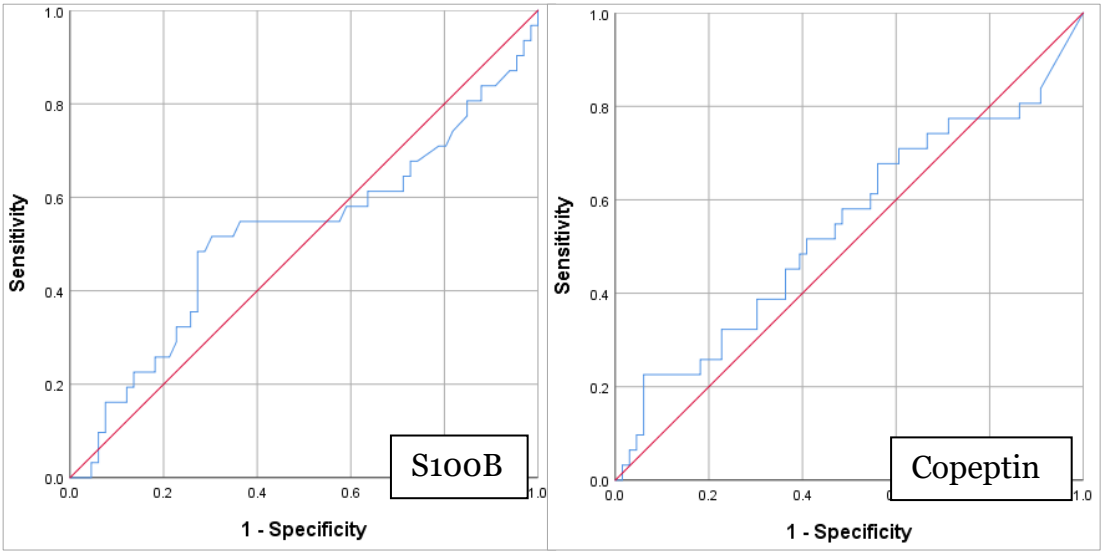

Figure 4.5 Receiver operating characteristic curves for S100B and copeptin to diagnose seizure recurrence by day seven.

Using Youden's method, a threshold of 0.088 μg/L and 6.26 pmol/L was identified for S100B and copeptin respectively. This threshold was selected as closest to the ideal point (where sensitivity and specificity are 100%). However, as the capacity to rule in rather than rule out a diagnosis is often of greater value to physicians when the diagnosis has a high morbidity, further thresholds were identified to maximise the specificity. The diagnostic performances for these thresholds are shown in Table 4.4.

Biomarker & threshold	Sensitivity	Specificity	PPV	NPV	LR+	LR-
S100B>0.09	58% (43-72)	60% (44-74)	60% (50-70)	57% (47-67)	1.44 (0.94-2.18)	0.71 (0.47-1.05)
S100B>0.1	52% (37-66)	66% (51-79)	62% (50-72)	56% (48-65)	1.53 (0.95-2.47)	0.73 (0.51-1.04)
S100B>0.2	26% (15-40)	87% (74-95)	68% (47-84)	53% (48-57)	2.04 (0.84-4.92)	0.85 (0.7-1.03)
S100B>0.5	14% (6-27)	98% (89-100)	88% (47-98)	52% (49-55)	6.58 (0.84-51.48)	0.88 (0.78-0.99)
Copeptin >6.2	80% (66-90)	21% (11-36)	52% (47-57)	50% (31-69)	1.02 (0.83-1.25)	0.94 (0.43-2.05)
Copeptin>15	68% (53-80)	43% (28-58)	56% (48-63)	56% (43-68)	1.18 (0.87-1.62)	0.75 (0.45-1.27)
Copeptin>50	30% (18-45)	85% (72-94)	68% (49-83)	53% (48-59)	2.01 (0.9-4.5)	0.82 (0.66-1.02)
Copeptin>100	24% (13-38)	96% (85-99)	86% (59-96)	54% (50-58)	5.64 (1.33-23.88)	0.79 (0.67-0.94)

Table 4.4 Diagnostic performances of S100B copeptin at various thresholds
PPV, positive predictive value; NPV, negative predictive value; LR+, likelihood ratio for a positive test; LR-, likelihood ratio for a negative test; S100B (µg/L), copeptin (pmol/L), numbers in brackets 95% confidence intervals**.**

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Logistic regression model

A multivariate logistic regression was performed with pre-specified variables. After assessment for collinearity, the variable 'provoked/acute symptomatic seizure' was found to be correlated with 'alcohol dependence', and 'epilepsy' was found to be correlated with 'previous seizures'. Alcohol dependence and previous seizures were removed from the model for statistical rather than clinical reasons (because they had a lower pseudo R^2 than the variables they were correlated with), and focal neurology was removed as there were no events in patients with focal neurology. Two models were derived, the first not including, and the second including the biomarkers. In the first model, independent risk factors for the composite primary outcome were a diagnosis of epilepsy, complex partial seizure, provoked/acute symptomatic seizure, and pyrexia. Discrimination of the model was good, with a C-statistic of 0.75, and the Hosmer-Lemeshow goodness of fit test had a p value of 0.70 (Table 4.5). Adding the two biomarkers did not change the model and neither of the biomarkers were independently associated with the outcome (C-statistic 0.79, Hosmer-Lemeshow goodness of fit p = 0.27).

	Clinical model alone		Clinical model with biomarkers	
Variable	Adjusted OR	P value (95% CI)	Adjusted OR	P value (95% CI)
Epilepsy	3.1	0.044 (1.0 – 9.0)	4.2	0.020 (1.3 – 14.3)
Complex Partial	13.7	0.021 (1.5 – 127.9)	17.5	0.015 (1.8 – 173.6)
Provoked	7.0	0.001 (2.2 – 22.5)	8.4	0.001 (2.3 – 29.7)
Pyrexia	10.4	0.050 (1.0 – 108.3)	12.4	0.058 (0.9 – 167.8)
Copeptin			1.0	0.058 (1.0 – 1.0)
S100B			11.9	0.246 (0.2 – 771.6)
	Hosmer-Lemeshow p=0.70		Hosmer-Lemeshow p=0.27	
	C-statistic 0.75		C-statistic 0.79	

Table 4.5 Adjusted odds ratios of independent predictors of the primary outcome

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Subgroup analysis

Two subgroup analyses were performed to investigate the rate of the primary outcome and early seizure recurrence in patients with epilepsy, and to determine the rate of early seizure recurrence in patients discharged home. Out of 97 patients in total, 39 (40%) patients had a pre-existing diagnosis of epilepsy. Of those, 21 (54%) experienced the composite primary outcome of admission, readmission, or early seizure recurrence, and 18 (46%) experienced an early recurrence of seizure. The median S100B was 0.08 μg/L (IQR 0.06 to 0.13) and 0.09 (IQR 0.06 to 0.14), and median copeptin was 18.0 pmol/L (IQR 5.4 to 49.7) and 10.9 (IQR 1.5 to 23) in epileptic patients that did and didn't have the primary endpoint respectively. There was no significant difference in S100B ($p = 0.8$, 95% CI -0.8 to 0.06), or copeptin ($p = 0.06$, 95% CI -2.4 to 103) in epileptic patients that did and didn't have the primary endpoint.

Fifty-two (54%) patients were discharged home from the Emergency Department, and of those 15 (29%) experienced the primary endpoint and 15 (29%) had early seizure recurrence. Medians for S100B were 0.07 μg/L (IQR 0.05 to 0.15) and 0.08 (0.06 to 0.10), and copeptin 21.1 pmol/L (IQR 5.4 to 35.9) and 15.8 (IQR 6.4 to 39.4) in discharged patients with and without early seizure recurrence respectively. There was no difference in S100B ($p = 0.4$, 95% CI -0.04 to 0.10) or copeptin ($p = 0.5$, 95% CI -16.4 to 33.4) in patients that were discharged home from the Emergency Department that did and did not have the primary outcome.

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Discussion

The principle findings of this study are that in adult patients presenting to the Emergency Department with a seizure, the biomarkers S100B and copeptin were both significantly higher in patients that had a composite primary endpoint of recurrence of seizure, admission or readmission by day seven, compared to those that didn't (0.22 vs 0.11 μg/L and 77.0 vs 27.0 pmol/L for S100B and copeptin respectively). However, the predictive power of each biomarker was poor, with areas under the receiver operating characteristic curve of 0.6 and 0.6 respectively, and in a logistic regression analysis, neither biomarker was independently associated with the outcome. Furthermore, no patient presented with a seizure as a consequence of TBI. The most common reason for having a seizure was a pre-existing diagnosis of epilepsy, followed by alcohol associated seizure and first fit. Of the 97 patients recruited from a UK Emergency Department, 50 (52%) had the composite primary endpoint of seizure recurrence, admission or readmission into hospital by day seven; five (5%) had the composite severe secondary endpoint of death, critical care admission or neurosurgical intervention by day 28; 31 (32%) had the secondary endpoint of seizure recurrence by day seven; and 31 (32%) had the secondary endpoint of admission for more than 24 hours by day seven. This was the UK arm of an international study that recruited patients from the Royal London Hospital in London and three hospitals in France.[461] Although the principle findings in the overall study are the same as in the UK arm, there are some differences noted between the UK and French populations. The main difference between the UK and the French populations are the rates of the primary outcome: 52% vs 23% in UK and France respectively. This difference

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is due to higher rates in the UK of all components of the primary outcome except death: seizure recurrence 32% vs 8%, admission 29% vs 13%, readmission 8% vs 3%. In the UK no patients died by day seven in contrast to France in which five patients died. This difference may indicate a UK population that has an overall lower seizure threshold, and this hypothesis is supported by the higher numbers of pre-morbid conditions, specifically alcohol dependence, substance misuse and stroke, seen the UK population. This pre-morbid burden may be attributable to the population that the Royal London Hospital serves, which is central and urban, with higher than average alcohol associated attendances, both for chronic and acute alcohol abuse. In addition, the emergency care systems of the two countries are different. In the French system patients with low acuity are seen in the Emergency Department whereas in the UK they are not. This could mean that low acuity patients with a lower risk of achieving the primary endpoint were recruited in France but could not have been in the UK.

In recent years S100B has been reported to have a very high specificity for death (95% to 98%) and unfavourable neurological outcomes (85 to 98%), and a very high sensitivity for the diagnosis of brain lesions (99 to 100%) in traumatic brain injury (Table 1.11).[302,462,463] In the context of seizure, the diagnostic performance of S100B is poor, with failure to obtain thresholds that would allow greater sensitivity with acceptable specificity, or vice versa. At thresholds of 0.1 and 0.2 μg/L the rate of false positives (S100B greater than the threshold but the patient not having the outcome) was high at 34% and 13% respectively, i.e. S100B was raised in many cases that did not meet the primary endpoint. This suggests that there is an increase in blood

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concentration of S100B after a seizure, regardless of whether that patient will go on to develop the primary endpoint or not. Similarly, there was no added value of copeptin in the setting of seizure. No threshold was determined for S100B or copeptin that could help clinicians either to rule in or rule out the occurrence of adverse events.

The high frequency of the primary endpoint contrasts with previously published work. This could be explained by the fact that the endpoint is a composite whereas previous studies report singular primary endpoints such as seizure recurrence. One study reported an early seizure recurrence rate of 19% (within 24 hours), whilst another suggested that a rate of at least 28% of patients not initially admitted experienced the endpoint within six weeks.[454,464] In my study, nearly 30% of patients that were initially discharged home had early seizure recurrence.

S100B and copeptin have not previously been tested in Emergency Department patients with seizure, however the difference in biomarker levels seen in the groups that had and didn't have the primary outcome is consistent with studies of S100B in mild head trauma and in alcohol associated admissions.[317,465] The median S100B was 0.1 μg/L and 0.08 μg/L in the groups with and without the primary endpoint respectively. In a study of 1560 patients with minor head injury, those with intracranial lesions on CT scan had a median S100B of 0.46 μg/L compared with 0.22 μg/L in those with no lesion on CT.[302] The S100B analyser in this study was the same type as used in the study reported in this thesis, namely an Elecsys (Roche Diagnostics), and the results may therefore be comparable. The medians reported here are more than twice as low as in the study of patients with minor head injuries,

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particularly when comparing the seizure group with no outcome with the head injury group with no intracranial injury. In another study of patients with mild head injury, the median S100B, measured on an immuno-luminometric assay kit (LIA-mat, AB Santec, Sweden), was 0.11 μg/L (IQR 0.08 to 0.18), which is comparable with the results presented here.[309] There was a predefined threshold of 0.15 μg/L and an outcome of return to work, with a sensitivity and specificity of 80% and 74% respectively. In patients with out of hospital cardiac arrest and return of spontaneous circulation within 20 minutes, the mean S100B was 3.68 μg/L (measured on the Roche Elecsys), more than thirty times higher than the median S100B in the seizure population with the primary outcome.[296] The degree of cerebral and other organ injury consequent to cardiac arrest is significantly higher than that following a seizure, and so the differences in S100B levels in these two groups is not unexpected. Furthermore, on retrospective analysis of the medical record, 8% of patients were subsequently diagnosed with convulsive syncope rather than seizure, so did not experience the same disordered electrophysiological state that occurs in a true seizure, and consequently S100B release may be reduced even further in this subgroup.

In a study comparing patients with acute spontaneous intracerebral haemorrhage with healthy controls, mean copeptin levels were 622.5 pmol/L and 96.8 pmol/L respectively.[466] The analyser in this study was by enzyme-linked immunosorbent assay using commercial kits (Phoenix Pharmaceuticals, Burlingame, CA, USA), and is reported in pg/ml and converted using the formula 1 pg/ml copeptin = 0.249 pmol/L. A further study comparing survivors and non-survivors with acute spontaneous intracerebral

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haemorrhage reported copeptin levels of 847 and 1237 pmol/L respectively (analyser also enzyme-linked immunosorbent assay by Phoenix Pharmaceuticals).[467] In another study comparing survivors and non-survivors of acute spontaneous intracranial haemorrhage, copeptin levels were 18.5 pmol/L and 31.9 pmol/L. In patients with ruptured aneurysmal subarachnoid haemorrhage the mean copeptin was 21.2 pmol/L.[468] The analysis technique in this case was an enzyme-linked immunosorbent assay (Cusabio Biotech Co. Ltd, Wuhan, Hubei Province, China). In 94 patients with severe TBI, mean copeptin was 103 pmol/L, and 141 vs 89 pmol/L in non-survivors vs survivors (analysis technique also enzyme-linked immunosorbent assay by Cusabio Biotech Co. Ltd).[366] In this series, a threshold of 112 pmol/L had an AUC of 0.87, which was far in excess of the discrimination achieved by copeptin in patients with seizures. In non-acute patients with heart failure, baseline copeptin was 31 and 55 pmol/L in the lowest and highest quartiles for cardiovascular mortality over 13 years respectively, and 45 and 82 in the lowest and highest quartiles for all-cause mortality respectively (analyser same as in this thesis, Kryptor Compact platform, BRAHMS, Hennigsdorf, Germany).[364] In patients with stroke, copeptin levels ranged from 8.6 pmol/L to 30.1 pmol/L in patients with low to high National Institute of Health Stroke Scale scores.[359] The analyser in this study was the similar to that used in this thesis, namely a commercial sandwich immunoluminometric assay (BRAHMS LUMItest CT-proAVP, Hennigsdorf/Berlin, Germany).[357] The range of copeptin levels seen in these studies that included patients with spontaneous intracranial haemorrhage, severe TBI, occlusive stroke and non-acute heart failure, is wide. Higher levels are seen with more severe pathology and the results reported in this thesis are amongst the lower levels reported. This indicates that although

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there may be a rise in copeptin following a seizure, the rise is not predictive of severe outcomes following seizure. The outcomes reported in this thesis are also not directly comparable to those reported in previous work as, in contrast to previously published work, there were no deaths and long-term disability was not measured. A further reason for variation in copeptin levels seen in the studies may be accounted for not only by acuity but also by analyser, of which two main methods are utilised; enzyme-linked immunosorbent assay and sandwich immunoluminometry.

This study presents strengths and weaknesses. It is the first to assess the value of the biomarkers S100B and copeptin in the setting of patients presenting to the Emergency Department with a seizure. One limitation was the choice of the composite endpoint of admission, readmission, seizure recurrence and death. The decision to admit (or readmit) a patient that has had a seizure is subject to the idiosyncrasies of an individual doctor, and dependent on the values of the healthcare system to which the patient presents. In the UK, there were significantly more patients that had the primary endpoint, and the difference was made up of all components of the primary endpoint except mortality. This difference and the subjective nature of the endpoint components admission and readmission make the results difficult to generalise. There may also be an element of inclusion bias because the diagnosis of seizure may be uncertain in the Emergency Department, and consequently some patients that did not have a true electrophysiological seizure but instead may have had a pseudo-epileptic seizure or convulsive syncope could have been included. Indeed, on retrospective analysis of the medical record, 8 (8%) of recruited patients were subsequently diagnosed with

convulsive syncope. This limitation is inherent to the design and reflects the day to day work of an emergency physician, in which it is sometimes impossible to fully confirm than an epileptic seizure has occurred. In the same way, information on the type of seizure was retrieved from the history of patients and witnesses and are consequently also subject to bias. This again mirrors the real-life information to which a clinician has access.

The biomarkers S100B and copeptin have shown promise in predicting poor outcomes in mild TBI as well as several other modes of acquired brain injury, but the subjective nature of much of the combined primary endpoint in this study make their specific value in Emergency Department patients with seizures of any cause hard to establish. Further work in patients with mild TBI and seizures looking at purely clinical and patient centred outcomes such as seizure recurrence should be performed with sufficient numbers of patients in subgroups including alcohol dependence, drug dependence and epilepsy.

Conclusion

Although levels of S100B and copeptin were higher in patients with seizure and poor outcomes, no patient had a seizure as a consequence of mild TBI, and the biomarkers did not improve the prediction of poor outcomes more than routinely collected clinical and physiological data.

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Chapter 5 Conclusions

Summary of findings

In this thesis I investigated outcomes in patients with mild acquired brain injuries after attendance at an Emergency Department. I investigated the effect that a mild traumatic brain injury has on how long it takes for a patient to return to work following injury. I used a structured methodology to identify the academic literature containing data on patients with mild TBI and in which return to work was measured. Out of more than 900 articles reviewed, 14 fit the inclusion criteria for the study. I devised a tool that allowed me to abstract data reproducibly and categorically so that it was in an analysable form, then applied the tool to the 14 articles. I collated the data to create summary findings on baseline characteristics reported in the 14 articles. I then pooled the data to create a meta-analysed estimate of proportions of patients that have returned to work by a pre-set time after the injury. I applied a previously validated tool to assess for bias.[389] The average time taken to return to work was only reported in three studies and ranged from six to 16 days but was highly skewed. By one month 56%, by three months 75%, by six months 81%, and by one year 88% of patients had returned to work.

I then investigated the short-term effects that a mild TBI has on patients' capacity to think, and the symptoms they experience. I recruited 240 patients, of whom 189 had mild TBI and 51 were non-head injured comparators. I found that in patients with mild TBI, there is no statistical difference in neurocognitive function between baseline and follow up three days later, but

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patients with mild TBI have marked neurocognitive impairment compared to patients without TBI. Furthermore, more patients with mild TBI deteriorated than improved by follow up. In contrast, in patients with mild TBI, the severity of symptoms improved from baseline to follow up, but were worse than patients without TBI both at baseline and at follow up. The number of symptoms patients with mild TBI experienced remained the same at baseline and follow up. Patients with acute haemorrhage on CT had considerably worse neurocognitive function, symptom severity, and number of symptoms than those without. Neurocognitive function remained poor at follow up, but symptom severity and number of symptoms improved. When comparing patients that had had previous head injuries and those that hadn't, there was no difference in neurocognitive function from baseline to follow up in either group, nor was there a difference between the groups at either time point. There was also no improvement in symptom severity nor number of symptoms in patients with previous head injuries, but there was improvement in those outcomes in patients without previous head injuries.

I then assessed the value of two novel biomarkers in predicting poor outcomes after seizure of any cause. Both S100B and copeptin showed promise in previous work in predicting poor outcomes following brain injury. I recruited 97 patients that had had a seizure and presented to the Emergency Department, and measured a composite endpoint of seizure recurrence, death, hospital admission, and hospital re-admission by day seven. The secondary endpoints were seizure recurrence by day seven, admission into hospital for more than 24 hours, and a composite severe outcome of ICU admission, neurosurgical procedure or death by 28 days. More than half of patients (52%)

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met the primary endpoint, 32% had seizure recurrence, 32% were admitted for more than 24 hours, and five patients experienced the composite severe outcome ICU admission, neurosurgical procedure or death by 28 days. S100B and copeptin were both significantly higher in patients that experienced the primary endpoint, but the prognostic value of each biomarker for each outcome (primary and secondaries) was low. A multivariate logistic regression model using clinical variables only had good discrimination. Adding the biomarkers to the model neither improved the discrimination nor were either biomarker independently associated with the outcomes.

Strengths and weaknesses of this work

The systematic review and meta-analysis was conducted in line with international guidelines, and according to a methodologically robust protocol, which was prospectively registered with a globally recognised registry of reviews. To my knowledge it is the only systematic review and meta-analysis published on return to work following mild TBI. It is also the most comprehensive review in this group with this outcome. In it I have collated and presented not only the raw data of how long it takes for patients to return to work following mild TBI, but also the significant variation in outcome reporting. This constitutes strong evidence that a consensus in outcome reporting amongst researchers of mild TBI is needed. The main limitation of the methodology of the review was the choice of using an outcome as an inclusion criterion, rather than a characteristic of the patient at the time of injury. Specifically, I chose to include studies based on whether they reported the outcome return to work, not based on whether patients were working at

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the time of injury. This was because I wanted to be as inclusive as possible to answer the question of how long it takes to return to work after injury. I accepted that this might be at the expense of introducing bias, in the form of including patients in the pooled analysis that were reported as having returned to work or usual activities, rather than exclusively as returned to work. I quantified the bias as far as possible given the heterogeneity of reporting in the source studies. I found that only two out of 14 studies exclusively included patients that were in paid employment prior to injury, and only one of those reported the follow-up rate. Another important limitation of the review was the heterogeneity of the included studies. The variables I abstracted included years in education, CT findings, presence of loss of consciousness, and presence of post-traumatic amnesia, and I found that there was significant variation in reporting these characteristics. If different researchers are reporting different outcomes, the variation in outcome reporting presents specific challenges in studying mild TBI and its effect on patients. In addition to the variation in outcome reporting noted in the included studies, there is also a problem with selection bias in studies on mild TBI.[469] In order to reduce the effect of confounding factors in observational studies, multiple exclusion criteria are applied. The consequence of the introduction of exclusion criteria such as previous TBI, psychiatric comorbidities, or previous neurosurgery, is that they can reduce the proportion of eligible patients to as low as 5% of all patients with mild TBI.[469] The reverse perspective of this is that patients that sustain a mild TBI are a profoundly heterogenous group. Although studying selected samples may be necessary, the outcomes can't be generalised to the greater population, and outcomes in excluded groups cannot be known unless they are explicitly studied. Another limitation was the intention to pool the

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average time it takes to return to work (in contrast to the proportion returned by a specific time-point). Only three studies reported average times to return to work, and the way they were reported was different in each study. Reynolds et al reported central tendencies (median, mean, and standard deviation) in four sub-groups but not overall and complete measures of central tendency.[395] Iverson et al reported measures of central tendency (mean, median, standard deviation, interquartile range, minimum and maximum) in two sub-groups but not an overall measure; whilst Losoi et al reported overall central tendencies.[171,371] Where means and medians were reported, they were very different, indicating the distribution of the return to work outcome to be non-parametric. With so few studies, and such variation within the data, pooling was not a suitable statistical approach.

The study of short-term outcomes following mild TBI demonstrated an ongoing and potential deterioration in cognition. This was particularly seen in patients with acute haemorrhage on CT. The main limitation in this study was the high rate of loss to follow up; 46% in patients with mild TBI group and 43% in patients without mild TBI. This is mitigated against by quantifying the bias, and most clearly seen in the hybrid parallel line plots of change and difference in outcomes (Figure 3.3 to Figure 3.8). The other limitation may be that follow up was at times over the telephone, which could have impacted on a patient's capacity to perform the delayed recall domain of the neurocognitive assessment. There is no direct evidence to support this hypothesis, but it may be a possibility.

The study of S100B and copeptin to predict outcomes following seizure remains the only study utilising those biomarkers and that outcome. Although

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serum levels of both biomarkers were elevated in patients with the outcome compared to those without, there was no prognostic value associated with the biomarkers. The main limitation in this study was the choice of the composite endpoint of admission, readmission, seizure recurrence and death. The only entirely objective element to that endpoint is death, which occurred in only one patient, who died of a brain tumour. Admission into hospital is fundamentally a subjective outcome and dependent on the treating physician and the norms of the healthcare system. Even the diagnosis of seizure can be inaccurate because patients can commonly have a convulsive syncope which is cardiac in nature, with no deranged electrophysiological activity consistent with an epileptic seizure. However, this last potential source of bias is pragmatic and reflects routine diagnostic challenges faced in the Emergency Department, where accurate descriptions of convulsive episodes may not be available. Because the endpoint was so broad, the outcome was experienced by half of the study population. This influences the discrimination of the test under investigation – at higher prevalence a test will have a higher positive predictive value and lower negative predictive value, and vice versa. Regardless of prevalence, neither biomarker showed promise for discriminating between patients that did or did not have either the primary or the secondary outcomes.

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Comparison to previous work

I found that half of patients with mild TBI have returned to work by one month and three quarters by three months. This is similar to that found in the only previously published systematic review of return to work exclusively in patients with mild TBI, in which the authors concluded that that most workers return to work three to six months after injury.[379,470] In that review, four studies were included, compared to 14 in my review. I was able to include more studies in my review because the eligibility criteria I used incorporated all four definitions of mild TBI, compared to only two in the previously published review. In addition, in the previously published review, studies were only eligible for inclusion providing both functional recovery (such as return to work) was measured and an examination of modifiable prognostic factors was performed. The focus of my review was not to identify prognostic factors and consequently of the four included studies in the previously published review, only one was included in my review.[169] Of the three that they included and I did not, one reported data that was also reported in another study that I did include, one included patients with severe TBI, and one did not report return to work outcomes.[174,471,472] Despite the differences in included studies, the findings were similar, adding strength to the conclusion that most patients with mild TBI have returned to work by three months.

My study of neurocognition following mild TBI was the largest performed in an Emergency Department population using the SAC, and the first to be conducted in more than one hospital. I found that patients with mild TBI had worse neurocognitive function than patients without TBI, and that their cognitive dysfunction had not improved by follow up three days later.

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Compared to another study of Emergency Department patients with mild TBI, the patients I recruited had better initial neurocognitive function (25 vs 21 points on SAC).[176] This may be because in the comparison study, the population had almost twice the proportion of patients that sustained a loss of consciousness or post-traumatic amnesia, indicating that possibly the degree of mild TBI was more severe. In addition, the average first cognitive assessment was very soon after injury (less than four hours), allowing less time for recovery in the very early stages after injury, which could also explain the difference. One other study reports such poor neurocognitive function in mild TBI patients in the Emergency Department.[205] In this study of 118 patients with mild TBI, the neurocognitive function measured in the Emergency Department was 21.5 to 23 SAC points, in CT positive and negative groups respectively. Unfortunately, no information regarding injury characteristics was reported so postulating reasons for the relatively low scores is not possible. In contrast, in two smaller studies, neurocognitive function was higher at baseline at 25 and 26 SAC points.[203,204] These studies included 49 and 26 Emergency Department patients with mild TBI. The higher neurocognitive function could be explained by the patients being younger, and that a third were involved in sports injuries, compared with only 1% in the patients reported in this thesis.

The astroglial protein S100B has proved to have diagnostic value in predicting the presence of traumatic intracranial haemorrhage. There has been particular interest in the value of S100B in paediatric populations because radiation exposure from CT scanning in childhood may be associated with a higher risk of cancer in later life.[236,473,474] The sensitivity of S100B for intracranial

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haemorrhage has been reported as greater than 90% in several studies (although specificities are universally poor).[475-480] In a meta-analysis the pooled sensitivity and specificity was 100% and 34% respectively.[481] S100B has also been reported to have a negative predictive value of 99-100% to exclude intracranial haemorrhage in adults with head injury.[301,302,482] My findings are very different to these. I found that the highest negative predictive value for excluding the composite primary outcome in patients with seizure was 58%. This is likely in part to be a function of the high prevalence of patients with the primary outcome (52%). Sensitivity and specificity are not affected by disease prevalence, but negative and positive predictive value are. Consequently, if around half of patients have the disease (have the composite primary endpoint) the predictive values of a diagnostic test will not be useful.

In studies of S100B in TBI, the diagnostic thresholds range from 0.006μg/L to 0.2 μg/L.[479,483] I identified the optimum threshold of S100B for predicting the composite outcome as 0.088 μg/L and then derived the diagnostic test characteristics at thresholds of 0.09, 0.1, 0.2 and 0.5 μg/L. The highest sensitivity was 58% at a threshold of 0.09 μg/L. This is well below an acceptable level and below the level that S100B performs at in patients with TBI, although similar to that found in patients in coma after recovery of spontaneous circulation following a cardiac arrest. In this situation, S100B has sensitivities ranging from 42% to 88% for diagnosing poor neurological outcome.[484] In these studies, the threshold ranged from 0.12 to 0.76 μg/L, which is higher than the threshold in which S100B performed best in patients with seizure.[485,486] At a higher threshold, fewer patients are 'positive' for the test, which increases the specificity (true negative rate). This is seen in the

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assessment of different thresholds for seizure patients, with a specificity of 98% at a threshold of 0.5 μg/L.

Why is a negative S100B effective for excluding intracranial haemorrhage in TBI patients, but not for excluding poor neurological outcomes in comatose post cardiac arrest patients, nor for the composite primary outcome in patients that had a seizure? Patients that are comatose after a cardiac arrest are likely to have sustained a hypoxic brain injury. However, in these patients, S100B was sometimes measured days after the cardiac arrest, and if the injury to the brain is no longer occurring, there may be no ongoing leak of S100B into the plasma, and previously elevated levels of S100B may have reduced. In contrast, the insult to the brain because of a seizure, in the absence of a concurrent injury, may be so minimal as not to elevate the S100B sufficiently. But, S100B levels were significantly higher in patients with the composite primary endpoint compared to without (0.22 vs 0.11 μg/L, Figure 4.3). The levels I report are comparable to the thresholds utilised in TBI studies (although not in post cardiac arrest studies), yet S100B had little prognostic value. The conclusion is therefore that elevated S100B has little association with the composite primary endpoint of seizure recurrence, admission, readmission and death.

Copeptin, which occurs in identical quantities as vasopressin in the plasma, but is more stable, has also shown promise in predicting poor neurological outcomes. In patients with acute ischaemic stroke, copeptin is significantly different in survivors and non-survivors, and in patients with good and poor neurological outcomes.[359,487-490] Copeptin levels were 8 to 10 and 19 to 32 pmol/L in patients with good and poor neurological outcomes respectively,

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and 10 to 15 and 29 to 60 pmol/L in survivors and patients that died respectively. In patients with spontaneous basal ganglia haemorrhage and healthy controls, copeptin levels were 24 and 5 pmol/L respectively.[491] Furthermore, in patients with basal ganglia haemorrhage, copeptin has a sensitivity of 82% for one year mortality. In another study comparing patients that survived or died after spontaneous intracranial haemorrhage, copeptin was 13 pmol/L and 178 pmol/L respectively, with an AUC of 0.88 for 30-day mortality. I found that copeptin was significantly different in patients with seizure that did and did not meet the composite primary endpoint, at 77.0 pmol/L and 27.0 pmol/L respectively (Figure 4.3). The thresholds used in studies of copeptin in ischaemic or haemorrhagic stroke are not reported. I derived the optimum threshold to maximise the test characteristics, and found it to be 6.26 pmol/L. Using thresholds of 6.2, 15, 50, and 100 I calculated test characteristics. The sensitivity for the combined endpoint was 80% at a threshold of 6.2 pmol/L, with a low specificity, and as the threshold is set higher, sensitivity reduces, and specificity rises. As seen with S100B, the negative predictive value is around 50% regardless of the threshold, because the prevalence of patients with the outcome is so high. Copeptin had no prognostic value for predicting the primary endpoint. This may be because of the four elements that composed the primary endpoint, only two were physiological processes that could conceivably elevate a biomarker. One was seizure, which is a physiological process, the other death, which is also a physiological process but only occurred in one patient. The other two components are process measures, proxy for a disease state (admission or readmission).

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Recommendations for further research

This thesis has shown that although most patients return to normal functional activities relatively quickly, most have short term ongoing symptoms and a proportion have poor outcomes at one year. The reasons for ongoing disability are not clear but could be influenced by pre-injury factors such as previous injuries, years in education or previous mental health diagnoses; factors associated with the injury, such as the force absorbed by the body; or factors occurring after the injury such as follow up care. The resolution of normal function may be predicted by clinical signs such as the presence of loss of consciousness or amnesia, or by the results of tests such as neurocognitive tests. The degree of heterogeneity in reporting these factors is large, with mostly small studies that report many different outcomes, making analysis of multiple studies challenging.

Outcomes after traumatic brain injury

A consensus on the most useful patient-centred outcomes would enable high quality research to be performed that would also lend itself to comparison between research groups. Initiatives such as the Core Outcome Measures in Effectiveness Trials (COMET) and the International Consortium for Health Outcomes Measurement (ICHOM) create core outcome sets that if used in research or clinical practice represent value-based healthcare and a standardised system for measuring endpoints in research.[415,492] Common data elements for TBI research have in fact been recommended in two different publications, and include the global outcome measure the Extended Glasgow Outcome Scale (GOSE-E), as well as specific outcome measures for several functional domains including psychological status, symptoms, behavioural

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symptoms and cognition.[493,494] However, many of the recommended outcomes are difficult to interpret and communicate to patients. Further research should be undertaken, with patient liaison involvement, to determine outcomes that if they were improved after a mild TBI, would most positively impact on patients' lives. A large-scale observational study measuring mild TBI core outcome sets could then be undertaken. Identification of interventions that might improve core outcomes in mild TBI is essential and these may be pharmaceutical, psychotherapeutic, educational or simply be the act of seeing a patient in clinic after the injury.

Epidemiology of traumatic brain injury

In the UK a new commissioning dataset for emergency care (the Emergency Care Data Set [ECDS]) was introduced, with the first of 200 English Emergency Departments submitting data centrally in September 2017. One of the key premises of the ECDS is that accurate presenting complaint, mechanism of injury and diagnostic data are recorded at a national level. This is the first time in the world that such a clean and lean set of categorical data is legally required to be submitted nationally. This gives researchers in the UK a unique opportunity to identify people with head injuries, understand how the head injury was sustained, and know the associated diagnosis. The current most up to date and accurate assessment of TBI epidemiology comes from the US and is derived from survey data, most commonly the National Hospital Ambulatory Medical Care Survey – Emergency Department (Figure 1.2). By definition this is an estimate. The Emergency Care Data Set gives UK researchers the opportunity to know the exact number of patients that attend Emergency Departments with a head injury, and the correct diagnoses. Two

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SNOMED-CT (Systematized Nomenclature of Medicine – Clinical Terms) coded chief complaints and 14 diagnoses would be required to identify patients (Table 5.1). The Emergency Care Data Set also has a detailed section on injury, including injury mechanism, whether the injury was sustained as a result of an apparent assault, and whether the injury was associated with alcohol or drugs. This would be of enormous importance in planning resource allocation from a healthcare, social and Policing perspective. Furthermore, outcomes in terms of use of health care, such as admission into hospital, surgery, or discharge and subsequent primary care access, could be measured. Analysis of this national data set would be an extremely cost-effective way of understanding how head injuries relate to brain injuries at a country level and would be unparalleled. Regionally this would also be invaluable in helping to plan resources required for head injury clinics, which in turn would contribute to improved outcomes for patients with TBI.

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SNOMED-CT code	SNOMED-CT term
Chief complaint	
82271004	Injury of head (disorder)
417746004	Traumatic injury (disorder)
Diagnosis	
371162008	Closed fracture of skull (disorder)
371161001	Open fracture of skull (disorder)
127302008	Minor traumatic brain injury : no LOC
127299008	Minor traumatic brain injury : LOC less than 30s
127300000	Minor traumatic brain injury : LOC more than 30s
40425004	Post-concussion syndrome (more than 1 day post incident)
262952002	Subdural hematoma
262949005	Extradural haematoma
262955000	Traumatic subarachnoid haemorrhage
450418003	Traumatic intracerebral haemorrhage
262693007	Diffuse axonal injury
34663006	Contusion of brain
314661000	Moderate traumatic brain injury (GCS less than 13)
314662007	Severe traumatic brain injury (GCS less than 9)

Table 5.1 SNOMED-CT codes and terms for traumatic brain injury
SNOMED-CT; Systematized Nomenclature of Medicine -- Clinical Terms; LOC, loss of consciousness; GCS, Glasgow Coma Scale.

Treatments for traumatic brain injury

Treatments for TBI can be broadly classified as pharmaceutical, therapeutic (including cognitive behavioural therapy and other psychological therapies), information giving and education, generic follow up, and rest or exercise. Pharmaceutical interventions target multiple proposed pathophysiological pathways implicated in symptoms following mild TBI. Cholinergic agents, specifically donepezil, rivastigmine, and galantamine, which are acetylcholinesterase inhibitors, are licensed in the UK to treat Alzheimer's Disease. There are some parallels between Alzheimer's Disease and TBI, particularly similarities in deficiencies in cognitive domains and in cellular processes. Evidence from several sources suggest that TBI alters cholinergic

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function in the brain, with an initial period of hypercholinergic activity, followed by more sustained hypocholinergic activity.[495,496] TBI frequently causes damage to deep structures, and particularly the hippocampal region, which is both high in levels of acetylcholine and responsible for short term memory formation.[497-499] Patients with TBI can have problems laying down new memories, which implicates the hippocampus both as a region critical for forming memories and for having high concentrations of acetylcholine.[500] However in the single PubMed listed trial of donepezil in TBI, only ten patients were included.[501] Eight of ten patients completed treatment and there was no improvement in memory, although clinical global improvement ratings did increase.

Cerebrolysin is another compound shown to be of benefit in Alzheimer's Disease, and also in stroke, and is consequently proposed for mild TBI. Cerebrolysin is thought to improve neuronal oxygen utilisation, reduce cerebral lactic acid concentration, and decrease oxygen free radical concentration.[502] In a double-blind randomised controlled trial of conscious patients with TBI and intracranial haemorrhage, cerebrolysin or placebo was administered within 24 hours of injury.[502] At 12 weeks, the cerebrolysin group had significantly improved overall cognitive ability and specifically drawing and long term memory abilities, compared to the placebo group.

Another proposed mechanism of disease in mild TBI is disruption to catecholamine action in the brain.[503] As noted above, patients with mild TBI commonly have deficits in memory, and specifically in working memory. Despite this, patients with mild TBI can score as highly in tests of working memory as healthy controls. However, functional MRI demonstrates

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significantly greater cerebral activation in patients with mild TBI being given working memory tasks compared with healthy controls.[504] This indicates that patients with mild TBI have to 'work harder' to achieve the same scores as control subjects. A potential mechanism for this is disruption to catecholamine pathways. This was tested indirectly by trialling bromocriptine, a dopamine D_2-receptor agonist, and placebo, both in patients with mild TBI and controls, i.e. in four groups.[504] Prolactin and functional MRI were measured. Dopamine inhibits prolactin secretion, therefore a patient with an altered catecholamine pathway might be expected not to respond to bromocriptine in the same way as that of a healthy control patient. There were significant differences in prolactin between bromocriptine and placebo in both mild TBI patients and controls, but no difference between mild TBI and controls when grouped by bromocriptine and placebo. During tests of working memory, on placebo, control patients showed increased cerebral activation compared with patients with mild TBI. On bromocriptine, a similar pattern was seen, but in addition, patients with mild TBI displayed activation in regions outside of normal working memory circuitry, including the bilateral post-central and superior temporal gyri. This indicates that patients with mild TBI do have a subtle dysregulation of dopaminergic systems in the first four to six weeks after injury but that treatment with a dopamine agonist may not improve cognitive functioning. An alternate pathway within the catecholamine system is based on evidence that experimental alpha-2A antagonism produces spatial working memory impairment, whereas alpha-1 and beta receptor antagonism do not. Conversely alpha-1A *agonism* leads to impaired working memory. The same authors that conducted the study of bromocriptine also investigated guanfacine, an alpha-2A agonist.[505] If alpha-2A antagonism leads to deficiency

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in working memory, then alpha-2A agonism should improve it. In this study, guanfacine was associated with increased cerebral activation in a region specific to working memory in the mild TBI group, indicating that guanfacine may be a potential pharmaceutical intervention of value in patients with mild TBI and deficiencies in working memory.

N-acetyl cysteine has been shown to be neuroprotective in animal models of stroke and TBI.[506,507] The neuroprotective effects of N-acetyl cysteine are thought to be mediated through anti-oxidant and anti-inflammatory effects.[508] In a single randomised controlled trial of N-acetyl cysteine versus placebo, administered intravenously for a week from day of injury in blast-injured US military personnel, patients that received N-acetyl cysteine had higher rates of complete resolution of symptoms by day seven, and a better chance of symptom resolution.[509]

Several studies have reported hyperbaric oxygen therapy for the treatment of mild TBI. One theory behind using hyperbaric oxygen therapy for mild TBI is that supraphysiological levels of oxygen will reactivate metabolic or electrophysiological pathways in functionally retrievable neurons that are adjacent to dead or severely damaged neurones.[510] Other mechanisms of action proposed include stem cell mobilization to sites of injury, immune modulation, and impact on fundamental neurotransmitters such as nitric oxide.[510] However, in a randomised controlled trial there was no difference between 30 sessions hyperbaric oxygen and sham compression (placebo) in symptoms, cognitive measures or post-traumatic disorder measures in US military service members with mild TBI.[510] In contrast, in 56 patients with symptoms of mild TBI for greater than one year, in a randomised crossover

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trial of 40 sessions of hyperbaric oxygen versus placebo, there was improvement in the cognitive function and quality of life in the treatment group.[511] Improvements in multiple domains of neurocognitive function were also seen in a preliminary study of hyperbaric oxygen, with earlier administration after injury, younger age, military status, and increased number of hyperbaric oxygen administrations being associated with improved outcomes.[512] However, hyperbaric oxygen therapy is expensive, is contra-indicated in some patients and represents a significant logistical challenge to deliver. As such, implementing a hyperbaric oxygen therapy service for patients with mild TBI would have to include a careful selection procedure that would take into account which patients are most likely to benefit.

Other pharmaceutical interventions have been trialled in moderate to severe TBI. A monoaminergic stabiliser called OSU6162 has effect on dopamine D_2 and D_3 receptors, and 5-HT_{2A} receptors. In patients with moderate to severe TBI, there was increased fMRI signs of blood oxygen level dependent signal changes (relative to placebo) in the right occipitotemporal cortex, the right brain-stem, and the right orbitofrontal cortex, but no difference in clinical measures.[513] In a different study, succinate was infused via a microdialysis catheter directly into brain tissue in sedated patients with severe TBI.[514] This resulted in a decreased lactate/pyruvate ratio which suggested better redox status, indicating better mitochondrial function, and lower glucose, indicating improved glucose utilisation. The authors concluded that direct tricarboxylic acid cycle supplementation with 2,3-$^{13}C_2$ succinate improved human traumatic brain injury brain chemistry. Minocycline, a semi-synthetic tetracycline which has been shown to have neuroprotective properties in rats, has been tested for

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safety and feasibility but not efficacy in patients with severe TBI.[515] Amantadine, an antiviral drug also used in Parkinson's disease, administered for six weeks, had no benefit compared with placebo at six months in patients with severe TBI. Another promising pathway may be that of mast cells. Mast cells have been shown to play a role in blood brain barrier disruption, neuroinflammation and neurodegeneration. Multiple mast cell antagonists including hydrogen, ketotifen, palmitoylethanolamide, luteolin, masitinib, and intravenous immunoglobulin may be of value in attenuating the effect of mast cells and providing some neuroprotective function but no clinical trials in TBI exist at this point.[516]

A final intervention in mild TBI, which although not pharmaceutical is a physical intervention, is selective brain cooling. This is achieved by placing a cooling helmet and neck piece on the patient, and can apply temperatures ranging from -20˚C to 54˚C. In 12 patients with sports related concussion, symptoms were reduced compared to controls whilst they were receiving the cooling, but recurred immediately after.[517] Arterial spin labelling MRI revealed reduced cerebral blood flow immediately before cooling but increased cerebral blood flow after cooling. The authors postulated that this was a consequence of compromised neurovascular coupling in the acute phase of injury possibly being temporarily restored by cooling to match cerebral blood flow with surges in metabolic demands of the brain.

Several studies have investigated psychological therapies as an intervention for mild TBI. Two studies investigate cognitive behavioural therapy. In one, cognitive behavioural therapy was compared with a telephone counselling service, initiated from four to six weeks of injury in an 'at-risk' population,

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defined as patients with mild TBI and high numbers of early complaints.[518] At three and 12 months, patients that received telephone counselling reported fewer complaints. Furthermore, more patients that received telephone counselling had complete resolution of symptoms at a year than those that had cognitive behavioural therapy. This suggests that early follow up in at risk patients is effective, and that the less resource intensive intervention of telephone counselling may be better than cognitive behavioural therapy. However, cognitive behavioural therapy was beneficial in adolescents with mild TBI and high numbers of symptoms and sleep disruption.[519] Patients that received cognitive behavioural therapy reported large and clinically significant improvements in insomnia ratings immediately after treatment, which were maintained at four weeks. They also reported improved sleep quality and fewer dysfunctional beliefs. Cognitive therapy was also beneficial in patients with chronic post-concussive symptoms after mild TBI compared with usual care.[520] Those receiving cognitive therapy reported fewer cognitive and memory difficulties, greater use of cognitive strategies, and improved attention, learning and executive function. In addition to cognitive therapy, other reported interventions include multidisciplinary assessment and therapy, which resulted in no difference in symptoms or psychosocial functioning; a telephone delivered problem solving treatment which did result in reduced psychological distress but no difference in symptoms; and individual and group-based neuropsychological treatment with exercise therapy and physiotherapeutic coaching which resulted in reductions in symptoms and mental fatigue, and improved social functioning.[521-523]

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Conventionally, the advice given to patients with mild TBI was to 'rest'. This could mean a break from physical activity, or cognitive rest. However, recent studies have shown consistently that rest, in the form of bedrest or sick leave (i.e. cognitive rest) does not result in improved short term or medium term symptoms or cognition, and may result in poorer outcomes.[374,524-526] Conversely, exercise in the form of sub-symptom threshold aerobic training or simple exercise therapy results in reduced symptoms and a shorter time to become symptom free.[523,527,528]

Giving information regarding the nature of mild TBI or concussion, and what to expect over the coming days and weeks, reduces anxiety and stress in adult and parent-child populations.[529,530] Furthermore, a single education session may not be inferior to a more resource-intensive and extensive assessment, education, and treatment-as-needed.[531] A mobile phone app symptom diary with a video game theme for children with mild TBI resulted in improved post-concussion symptoms and optimism compared with a control group.[532] Follow up has inconsistent outcomes, with two studies finding no difference in symptoms or limitations in activity, and one study reporting longer time to return to work in a multi-disciplinary out-patient follow up compared with general practitioner follow up.[533-535] However, a recently proposed structured approach to a clinic based assessment of patients with mild TBI, which includes a history, clinical exam, symptom inventory, neurocognitive tests, vestibular and oculomotor assessment, exertion assessment and psychological assessment, has yet to be tested.[536]

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Conclusion

In conclusion, mild traumatic brain injury represents a significant disease burden to individual patients and to the population. Many patients with mild traumatic brain injury experience both persistent deficiencies in cognition and persistent symptoms, which impact on their ability to perform usual activities including maintaining employment. Lack of standardisation of outcome measurement and variation in reporting in mild traumatic brain injury research may give rise to results that are difficult to generalise and so reduce the impact of any potential intervention. Few patients with traumatic brain injury attend the Emergency Department with a seizure. Being able to predict outcomes following TBI is important for information and health care planning, but the biomarkers S100B and copeptin add no extra value to current prediction tools in identifying who will go on to have a further seizure. Since traumatic brain injury is extremely common and as much as 90% of all traumatic brain injury is mild, the consequences of any minor improvement in outcomes for this disease would translate into sizeable societal health gains. Several pharmaceutical and psychological therapeutic interventions show promise in improving outcomes after mild TBI, but studies are small and rarely repeated. Large randomised controlled trials of pharmaceutical and cognitive therapies in patients with mild TBI should be performed.

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Chapter 6 Appendices

Appendix 1

Definitions of mild traumatic brain injury

American Congress of Rehabilitation Medicine (1993)[6]

A traumatically induced disruption of brain function manifesting with at least one of the following criteria:

1. Any loss of consciousness
2. Any loss of memory of the event immediately before or after the accident;
3. Any alteration in mental state at the time of the accident (e.g., feeling dazed, disoriented, or confused);
4. Focal neurological deficit that may or may not be transient.

But where the severity of the injury does not exceed the following

- Loss of consciousness of 30 minutes or less;
- After 30 minutes an initial GCS of 13-15;
- Post-traumatic amnesia not greater than 24 hours

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European Federation of Neurological Societies (2002)[7]

The EFNS definition subclassifies mild TBI into four categories, based on which decisions on admission and investigation can be made. All mild TBI in the EFNS definition have traumatic head injury or rapid acceleration, deceleration or shear force to the head, with GCS 13 to 15. They are categorised as follows:

1. Category 0
    - GCS 15, no loss of consciousness, no post-traumatic amnesia, no risk factors
        - Can be considered a head injury with no TBI
        - Can be discharged home
2. Category 1
    - GCS 15, loss of consciousness < 30 minutes, post-traumatic amnesia < 1 hour, no risk factors
    - CT recommended
3. Category 2
    - GCS 15, and risk factors present
    - CT mandatory
4. Category 3
    - GCS 13–14, loss of consciousness < 30 minutes, post-traumatic amnesia < 1 hour, no risk factors, with or without risk factors present

Risk factors are defined as: unclear or ambiguous accident history, continued post-traumatic amnesia, retrograde amnesia longer than 30 min, trauma above the clavicles including clinical signs of skull fracture (skull base or depressed skull fracture), severe headache, vomiting, focal neurological deficit, seizure, age < 2 years, age > 60, coagulation disorders, high-energy accident, intoxication with alcohol/drugs.

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Centers for Disease Control and Prevention (2003)[8]

An injury to the head as a result of blunt trauma or acceleration or deceleration forces that result in one or more of the following conditions:

- Any period of observed or self-reported:
    - Transient confusion, disorientation, or impaired consciousness
    - Dysfunction of memory around the time of injury
    - Loss of consciousness lasting less than 30 minutes.
- Observed signs of neurological or neuropsychological dysfunction, such as:
    - Seizures acutely following injury to the head
    - Among infants and very young children: irritability, lethargy, or vomiting following head injury
    - Symptoms among older children and adults such as headache, dizziness, irritability, fatigue or poor concentration, when identified soon after injury, can be used to support the diagnosis of mild TBI, but cannot be used to make the diagnosis in the absence of loss of consciousness or altered consciousness. Research may provide additional guidance in this area.

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World Health Organisation collaborating task force (2004)[9,537]

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

1. One or more of the following:
    a. confusion or disorientation
    b. loss of consciousness for 30 minutes or less
    c. post-traumatic amnesia for less than 24 hours
    d. and/or other transient neurological abnormalities such as focal signs, seizure, and intracranial lesion not requiring surgery; and
2. Glasgow Coma Scale score of 13 to 15 after 30 minutes post-injury or later upon presentation for healthcare.

These manifestations of mild TBI must not be due to drugs, alcohol, medications, caused by other injuries or treatment for other injuries (e.g. systemic injuries, facial injuries or intubation), caused by other problems (e.g. psychological trauma, language barrier or coexisting medical conditions) or caused by penetrating craniocerebral injury

Appendix 2

Neurocognitive and symptom assessment tools

Standardized Assessment of Concussion

Orientation

What month is it?	0/1
What's the date today?	0/1
What's the day of the week?	0/1
What year is it?	0/1
What time is it right now (within 1 hour)?	0/1
Orientation test score:	_/5

Immediate memory

I am going to test your memory. I will read you a list of words and when I am done, repeat back as many words as you can remember, in any order.

List	*Trial 1*	*Trial 2*	*Trial 3*
Elbow	0/1	0/1	0/1
Apple	0/1	0/1	0/1
Carpet	0/1	0/1	0/1
Saddle	0/1	0/1	0/1
Bubble	0/1	0/1	0/1
Total	/5	/5	/5

Trials 2 and 3: I am going to repeat that list again. Repeat back as many words as you can remember in any order, even if you said the word before.

Complete all trials regardless of score on trials 1 and 2. 1 point for each correct response. Total score equals sum across all 3 trials.

Immediate memory test score: _/15

Concentration

Digits backwards: I am going to read you a string of numbers and when I am done, you repeat them back to me backwards, in reverse order of how I said them to you. For example, if I say 7-1-9 you would say 9-1-7.

If correct go to next string length. If incorrect, read trial 2. 1 point possible for each string length. Stop after incorrect on both trials.

4-9-3	6-2-9	0/1
3-8-1-4	3-2-7-9	0/1
6-2-9-7-1	1-5-2-8-6	0/1
7-1-8-4-6-2	5-3-9-1-4-8	0/1

Months in reverse order: Now tell me the months of the year in reverse order. Start with the last month and go backwards. So, you'll say December, November…go ahead.

1 point for entire sequence correct.

Dec-Nov-Oct-Sept-Aug-Jul-Jun-May-Apr-Mar-Feb-Jan	0/1
Concentration total score	_/5

Delayed recall

Do you remember that list of words I read a few times earlier? Tell me as many words from the list as you can remember in any order.

Circle each word correctly recalled. Total score equals number of words recalled.

Elbow Apple Carpet Saddle Bubble

Delayed recall total score: /5

SAC scoring summary

Orientation	/5
Immediate memory	/15
Concentration	/5
Delayed recall	/5
SAC total score	/30

Concussion Symptom Inventory

The following symptoms graded 0-6 (0 = absent, 1 = mild, 6 = severe)

1. Headache
2. Nausea
3. Balance problems/Dizziness
4. Fatigue
5. Drowsiness
6. Feeling like "in a fog"
7. Difficulty concentrating
8. Difficulty remembering
9. Sensitivity to light
10. Sensitivity to noise
11. Blurred vision
12. Feeling slowed down

Appendix 3

International classification of disease codes used for identifying head or brain injured patients in epidemiological studies

ICD-9 codes:

800-80	Fracture of Skull
800	Fracture of vault of skull
801	Fracture of base of skull
802	Fracture of face bones
803	Other and unqualified skull fractures
804	Multiple fractures involving skull or face with other bones
850-854	Intracranial Injury, Excluding Those With Skull Fracture
850	Concussion
851	Cerebral laceration and contusion
852	Subarachnoid subdural and extradural hemorrhage following injury
853	Other and unspecified intracranial hemorrhage following injury
854	Intracranial injury of other and unspecified nature

ICD-10-CM heading codes

S00	Superficial injury of head
S01	Open wound of head
S02	Fracture of skull and facial bones
S03	Dislocation, sprain and strain of joints and ligaments of head
S04	Injury of cranial nerves
S05	Injury of eye and orbit
S06	Intracranial injury
S06.1	Traumatic cerebral oedema
S06.2	Diffuse brain injury
S06.3	Focal brain injury
S06.4	Epidural haemorrhage
S06.5	Traumatic subdural haemorrhage
S06.6	Traumatic subarachnoid haemorrhage
S06.7	Intracranial injury with prolonged coma
S06.8	Other intracranial injuries
S06.9	Intracranial injury, unspecified
S07	Crushing injury of head
S08	Traumatic amputation of part of head
S09	Other and unspecified injuries of head
T00	Superficial injuries involving multiple body regions
T01	Open wounds involving multiple body regions
T02	Fractures involving multiple body regions
T03	Dislocations, sprains and strains involving multiple body regions
T04	Crushing injuries involving multiple body regions
T05	Traumatic amputations involving multiple body regions
T06	Other injuries involving multiple body regions, not elsewhere classified
T07	Unspecified multiple injuries
T90	Sequelae of injuries of head

National Health Service Centre for Clinical Coding and Classification, based on ICD-10

18	minor HI
19	moderate to severe HI

Table 6.1 Diagnostic codes used in epidemiological studies of head or brain injury

Appendix 4

PRISMA 2009 Checklist

			Page
Title			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	122
Abstract			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	N/A
Introduction			
Rationale	3	Describe the rationale for the review in the context of what is already known.	122
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	123
Methods			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	124
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	124

Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	125
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	126, 313
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	126
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	127
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	127
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	127
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	131
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	131

Table 6.2 PRISMA 2009 Checklist

Appendix 5

Search strategy for systematic review and meta-analysis of return to work after mild traumatic brain injury

Search date – 09/10/2017

#	Database	Search Platform	Search term
1	Medline	HDAS	(tbi).ti,ab
2	Medline	HDAS	(mtbi).ti,ab
3	Medline	HDAS	(mild tbi).ti,ab
4	Medline	HDAS	("mild tbi").ti,ab
5	Medline	HDAS	(minor tbi).ti,ab
6	Medline	HDAS	("minor tbi").ti,ab
7	Medline	HDAS	(mild traumatic brain injury).ti,ab
8	Medline	HDAS	("mild traumatic brain injury").ti,ab
9	Medline	HDAS	(minor traumatic brain injury).ti,ab
10	Medline	HDAS	("minor traumatic brain injury").ti,ab
11	Medline	HDAS	(mild head injury).ti,ab
12	Medline	HDAS	("mild head injury").ti,ab
13	Medline	HDAS	(minor head injury).ti,ab
14	Medline	HDAS	("minor head injury").ti,ab
15	Medline	HDAS	(mild head trauma).ti,ab
16	Medline	HDAS	("mild head trauma").ti,ab
17	Medline	HDAS	(minor head trauma).ti,ab
18	Medline	HDAS	("minor head trauma").ti,ab
19	Medline	HDAS	(minor brain trauma).ti,ab
20	Medline	HDAS	("minor brain trauma").ti,ab
21	Medline	HDAS	(concussion).ti,ab
22	Medline	HDAS	(concus*).ti,ab
23	Medline	HDAS	exp "BRAIN CONCUSSION"/
24	Medline	HDAS	exp "BRAIN INJURIES"/ OR exp "CRANIOCEREBRAL TRAUMA"/
25	Medline	HDAS	(1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12 OR 13 OR 14 OR 15 OR 16 OR 17 OR 18 OR 19 OR 20 OR 21 OR 22)
26	Medline	HDAS	(23 OR 24)

27	Medline	HDAS	exp "RETURN TO WORK"/
28	Medline	HDAS	("return to work").ti,ab
29	Medline	HDAS	(27 OR 28)
30	Medline	HDAS	(25 AND 28)
31	Medline	HDAS	(26 AND 27)
32	Medline	HDAS	(30 OR 31)
33	EMBASE	HDAS	(tbi).ti,ab
34	EMBASE	HDAS	(mtbi).ti,ab
35	EMBASE	HDAS	(mild tbi).ti,ab
36	EMBASE	HDAS	("mild tbi").ti,ab
37	EMBASE	HDAS	(minor tbi).ti,ab
38	EMBASE	HDAS	("minor tbi").ti,ab
39	EMBASE	HDAS	(mild traumatic brain injury).ti,ab
40	EMBASE	HDAS	("mild traumatic brain injury").ti,ab
41	EMBASE	HDAS	(minor traumatic brain injury).ti,ab
42	EMBASE	HDAS	("minor traumatic brain injury").ti,ab
43	EMBASE	HDAS	(mild head injury).ti,ab
44	EMBASE	HDAS	("mild head injury").ti,ab
45	EMBASE	HDAS	(minor head injury).ti,ab
46	EMBASE	HDAS	("minor head injury").ti,ab
47	EMBASE	HDAS	(mild head trauma).ti,ab
48	EMBASE	HDAS	("mild head trauma").ti,ab
49	EMBASE	HDAS	(minor head trauma).ti,ab
50	EMBASE	HDAS	("minor head trauma").ti,ab
51	EMBASE	HDAS	(minor brain trauma).ti,ab
52	EMBASE	HDAS	("minor brain trauma").ti,ab
53	EMBASE	HDAS	(concussion).ti,ab
54	EMBASE	HDAS	(concus*).ti,ab
64	EMBASE	HDAS	(33 OR 34 OR 35 OR 36 OR 37 OR 38 OR 39 OR 40 OR 41 OR 42 OR 43 OR 44 OR 45 OR 46 OR 47 OR 48 OR 49 OR 50 OR 51 OR 52 OR 53 OR 54)
55	EMBASE	HDAS	exp "BRAIN INJURY"/ OR exp "BRAIN CONCUSSION"/
56	EMBASE	HDAS	exp "TRAUMATIC BRAIN INJURY"/
57	EMBASE	HDAS	exp "POSTCONCUSSION SYNDROME"/
58	EMBASE	HDAS	(55 OR 56 OR 57)
59	EMBASE	HDAS	exp "RETURN TO WORK"/

60	EMBASE	HDAS	exp "WORK RESUMPTION"/
61	EMBASE	HDAS	("return to work").ti,ab
62	EMBASE	HDAS	(59 OR 60)
63	EMBASE	HDAS	(58 AND 62)
65	EMBASE	HDAS	(61 AND 64)
66	PsycINFO	HDAS	(tbi).ti,ab
67	PsycINFO	HDAS	(mtbi).ti,ab
68	PsycINFO	HDAS	(mild tbi).ti,ab
69	PsycINFO	HDAS	("mild tbi").ti,ab
70	PsycINFO	HDAS	(minor tbi).ti,ab
71	PsycINFO	HDAS	("minor tbi").ti,ab
72	PsycINFO	HDAS	(mild traumatic brain injury).ti,ab
73	PsycINFO	HDAS	("mild traumatic brain injury").ti,ab
74	PsycINFO	HDAS	(minor traumatic brain injury).ti,ab
75	PsycINFO	HDAS	("minor traumatic brain injury").ti,ab
76	PsycINFO	HDAS	(mild head injury).ti,ab
77	PsycINFO	HDAS	("mild head injury").ti,ab
78	PsycINFO	HDAS	(minor head injury).ti,ab
79	PsycINFO	HDAS	("minor head injury").ti,ab
80	PsycINFO	HDAS	(mild head trauma).ti,ab
81	PsycINFO	HDAS	("mild head trauma").ti,ab
82	PsycINFO	HDAS	(minor head trauma).ti,ab
83	PsycINFO	HDAS	("minor head trauma").ti,ab
84	PsycINFO	HDAS	(minor brain trauma).ti,ab
85	PsycINFO	HDAS	("minor brain trauma").ti,ab
86	PsycINFO	HDAS	(concussion).ti,ab
87	PsycINFO	HDAS	(concus*).ti,ab
91	PsycINFO	HDAS	(66 OR 67 OR 68 OR 69 OR 70 OR 71 OR 72 OR 73 OR 74 OR 75 OR 76 OR 77 OR 78 OR 79 OR 80 OR 81 OR 82 OR 83 OR 84 OR 85 OR 86 OR 87)
88	PsycINFO	HDAS	exp "BRAIN CONCUSSION"/ OR exp "TRAUMATIC BRAIN INJURY"/ OR exp "HEAD INJURIES"/
89	PsycINFO	HDAS	exp REEMPLOYMENT/
90	PsycINFO	HDAS	("return to work").ti,ab
92	PsycINFO	HDAS	(88 AND 89)
93	PsycINFO	HDAS	(91 AND 90)

94	PubMed	HDAS	(tbi).ti,ab
95	PubMed	HDAS	(mtbi).ti,ab
96	PubMed	HDAS	(mild tbi).ti,ab
97	PubMed	HDAS	("mild tbi").ti,ab
98	PubMed	HDAS	(minor tbi).ti,ab
99	PubMed	HDAS	("minor tbi").ti,ab
100	PubMed	HDAS	(mild traumatic brain injury).ti,ab
101	PubMed	HDAS	("mild traumatic brain injury").ti,ab
102	PubMed	HDAS	(minor traumatic brain injury).ti,ab
103	PubMed	HDAS	("minor traumatic brain injury").ti,ab
104	PubMed	HDAS	(mild head injury).ti,ab
105	PubMed	HDAS	("mild head injury").ti,ab
106	PubMed	HDAS	(minor head injury).ti,ab
107	PubMed	HDAS	("minor head injury").ti,ab
108	PubMed	HDAS	(mild head trauma).ti,ab
109	PubMed	HDAS	("mild head trauma").ti,ab
110	PubMed	HDAS	(minor head trauma).ti,ab
111	PubMed	HDAS	("minor head trauma").ti,ab
112	PubMed	HDAS	(minor brain trauma).ti,ab
113	PubMed	HDAS	("minor brain trauma").ti,ab
114	PubMed	HDAS	(concussion).ti,ab
115	PubMed	HDAS	(concus*).ti,ab
116	PubMed	HDAS	("return to work").ti,ab
117	PubMed	HDAS	(94 OR 95 OR 96 OR 97 OR 98 OR 99 OR 100 OR 101 OR 102 OR 103 OR 104 OR 105 OR 106 OR 107 OR 108 OR 109 OR 110 OR 111 OR 112 OR 113 OR 114 OR 115)
118	PubMed	HDAS	(116 AND 117)
1	PubMed	PubMed	concussion[MeSH Terms]
2	PubMed	PubMed	mild traumatic brain injury[MeSH Terms]
3	PubMed	PubMed	("Brain Concussion"[Mesh]) AND "Return to Work"[Mesh Terms]
#1	Cochrane library	Cochrane database of systematic reviews	tbi
#2	Cochrane library	Cochrane database	mtbi

		of systematic reviews	
#3	Cochrane library	Cochrane database of systematic reviews	mild tbi
#4	Cochrane library	Cochrane database of systematic reviews	"mild tbi"
#5	Cochrane library	Cochrane database of systematic reviews	minor tbi
#6	Cochrane library	Cochrane database of systematic reviews	"minor tbi"
#7	Cochrane library	Cochrane database of systematic reviews	mild traumatic brain injury
#8	Cochrane library	Cochrane database of systematic reviews	"mild traumatic brain injury"
#9	Cochrane library	Cochrane database of systematic reviews	minor traumatic brain injury
#10	Cochrane library	Cochrane database of systematic reviews	"minor traumatic brain injury"
#11	Cochrane library	Cochrane database of systematic reviews	mild head injury
#12	Cochrane library	Cochrane database of	"mild head injury"

		systematic reviews	
#13	Cochrane library	Cochrane database of systematic reviews	minor head injury
#14	Cochrane library	Cochrane database of systematic reviews	"minor head injury"
#15	Cochrane library	Cochrane database of systematic reviews	mild head trauma
#16	Cochrane library	Cochrane database of systematic reviews	"mild head trauma"
#17	Cochrane library	Cochrane database of systematic reviews	minor head trauma
#18	Cochrane library	Cochrane database of systematic reviews	"minor head trauma"
#19	Cochrane library	Cochrane database of systematic reviews	minor brain trauma
#20	Cochrane library	Cochrane database of systematic reviews	"minor brain trauma"
#21	Cochrane library	Cochrane database of systematic reviews	concussion
#22	Cochrane library	Cochrane database of	concus*

		systematic reviews	
#23	Cochrane library	Cochrane database of systematic reviews	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22
#24	Cochrane library	Cochrane database of systematic reviews	MeSH descriptor: [Brain Concussion] explode all trees
#25	Cochrane library	Cochrane database of systematic reviews	MeSH descriptor: [Brain Injuries] explode all trees
#26	Cochrane library	Cochrane database of systematic reviews	#24 or #25
#27	Cochrane library	Cochrane database of systematic reviews	#23 or #26
#28	Cochrane library	Cochrane database of systematic reviews	"return to work"
#29	Cochrane library	Cochrane database of systematic reviews	return to work
#30	Cochrane library	Cochrane database of systematic reviews	MeSH descriptor: [Return to Work] explode all trees
#31	Cochrane library	Cochrane database of systematic reviews	#28 or #29 or #30
#32	Cochrane library	Cochrane database of	#27 and #31

	systematic reviews	
1	Trip database	((("mild traumatic brain injury") OR (concussion)) AND ("return to work"))
1	Clinicaltrials.gov	Mild traumatic brain injury
2	Clinicaltrials.gov	Return to work
1	European Clinical Trials Registry (EU-CTR)	Mild traumatic brain injury
2	European Clinical Trials Registry (EU-CTR)	Concussion
3	European Clinical Trials Registry (EU-CTR)	Return to work
1	ISRCTN	Condition: mild traumatic brain injury
2	ISRCTN	Condition: concussion
1	Australia and New Zealand Clinical Trials Registry (ANZCTR)	Mild traumatic brain injury
2	Australia and New Zealand Clinical Trials Registry (ANZCTR)	Concussion
1	Clinical Trials Registry of India (CTRI)	Mild traumatic brain injury
2	Clinical Trials Registry of India (CTRI)	Concussion
1	China Clinical Trials Registry (ChiCTR)	Mild traumatic brain injury
2	China Clinical Trials Registry (ChiCTR)	Concussion
1	Brazilian Clinical Trials Registry (ReBec)	Mild traumatic brain injury
2	Brazilian Clinical Trials Registry (ReBec)	Concussion
1	Pan-African Clinical Trials Registry (PACTR)	Mild traumatic brain injury
2	Pan-African Clinical Trials Registry (PACTR)	Concussion

Table 6.3 Search strategy for systematic review and meta-analysis of return to work after mild traumatic brain injury

Appendix 6

Data abstraction dictionary for systematic review and meta-analysis of return to work following mild traumatic brain injury

Name of data point	Description of data point	Data points
UI	Unique identifier for this review	numerical
Au_F	First Author	text
Journal	Journal	text
Year	Year	numerical
St_tr	Study or trial	1=study, 2=trial
Pr_Rt	Prospective or retrospective	1=prospective, 2=retrospective
RTW_ave/prop	RTW is reported as average or as proportion at pre-defined time point	1=average, 2=proportion
No_pt	Number of patients in study	numerical
No_F/U	Number of patients followed up	numerical
Prop_F/U	Percentage followed up out of included	numerical
No_gp_1	Number of patients in group 1 (if applicable)	numerical
No_gp_2	Number of patients in group 2 (if applicable)	numerical
No_gp_3	Number of patients in group 3 (if applicable)	numerical
No_gp_4	Number of patients in group 4 (if applicable)	numerical
Nm_gp_1	Name of group 1	text
Nm_gp_2	Name of group 2	text
Nm_gp_3	Name of group 3	text
Nm_gp_4	Name of group 4	text
Setting	Setting	text
Mean_age	Mean age	numerical
Age_SD	Standard deviation of age	numerical
Med_age	Median age if reported	numerical
Age_IQR	Interquartile range of age	numerical
Age_youngest	Youngest included	numerical
Age_oldest	Oldest included	numerical
Sex_male	Sex – proportion male	numerical
Ed_secondary	Proportion up to secondary	numerical
Ed_years	Mean years education	numerical
Def_mTBI	Definition of mild TBI	1=American Academy of Neurology; 2=World Health Organisation Collaborating Task

		Force on MTBI; 3=Center for Disease Control and Prevention; 4=American Congress of Rehabilitation Medicine; 5=European Federation of Neurological Societies; 6=clinical diagnosis
PTA_pr	Proportion post traumatic amnesia	numerical
PTA_dur	Duration post traumatic amnesia (hours usually)	numerical
LOC_pr	Loss of consciousness proportion	numerical
Inj_sev_pr	Injury Severity (blood on CT) proportion	numerical
RTW_duties	Narrative description of level of duties patients RTW to work at, if reported	text
RTW_mean_time	Mean time to RTW (if reported)	numerical
RTW_median_time	Median time to RTW (if reported)	numerical
Pre_d_t_1	Pre-defined time point 1	text
Pre_d_t_2	Pre-defined time point 2	text
Pre_d_t_3	Pre-defined time point 3	text
Pre_d_t_4	Pre-defined time point 4	text
Prop_RTW_t_1	Proportion of cohort that RTW at time point 1	numerical
Prop_RTW_t_2	Proportion of cohort that RTW at time point 2	numerical
Prop_RTW_t_3	Proportion of cohort that RTW at time point 3	numerical
Prop_RTW_t_4	Proportion of cohort that RTW at time point 4	numerical
Pred_v	Predictor/independent variable(s) if study, intervention if trial	text
Outcome_v	Outcome/dependent variable(s) if study, control if trial	text
Effect_est	Effect estimates (RR/OR)	1=RR, 2=OR
Selection_MH_drugs_TBI	Excluded patients if MH, drugs/alcohol, prev TBI	1=Y, 2=N
Selection_rep	Representativeness of the exposed cohort	1=truly representative of the average mild TBI* ; 2=somewhat representative of the average mild TBI*; 3=selected group of users e.g. nurses, volunteers; 4=no description of the derivation of the cohort

Selection_sel	Selection of the non-exposed cohort	1=drawn from the same community as the exposed cohort*; 2=drawn from a different source; 3=no description of the derivation of the non-exposed cohort
Selection_asc	Ascertainment of exposure	1=secure record (e.g. surgical records)*; 2=structured interview*; 3=written self-report; 4=no description
Selection_dem	Demonstration that outcome of interest was not present at start of study	1=yes*; 2=no
Comparability_com	Comparability of cohorts based on the design or analysis	1=study controls for mild TBI*, 2=study controls for any additional factor* (this criterion could be modified to indicate specific control for a second important factor)
Outcome_ass	Assessment of outcome	1=independent blind assessment*; 2=record linkage*; 3=self-report; 4=no description
Outcome_f/u_t	Was follow-up long enough for outcomes to occur	1=yes*; 2=no
Outcome_f/u_adeq	Adequacy of follow up of cohorts	1=complete follow up - all subjects accounted for*; 2=subjects lost to follow up unlikely to introduce bias - lost <20% follow up, or description provided of those lost)*; 3=follow up rate <50% and no description of those lost; 4=no statement
Pop_empl_pre-mTBI	Was the sample population employed prior to the injury?	1=all workers, 2=employed including student/homemaker/other activity, 3=unclear, 4=not described
Pop_employed_pre-mTBI_notes	Description of pre-injury employment status	text

Table 6.4 Data abstraction dictionary for systematic review and meta-analysis of return to work following mild traumatic brain injury

Appendix 7

Post hoc power calculation data

Variable	Obs.	*W'*	*V'*	*z*	*p*
Baseline NC function	178	0.91774	12.129	5.121	0.00001
Follow up NC function	101	0.96211	3.476	2.464	0.00687
Baseline #Sx	178	0.96909	4.557	3.112	0.00093
Follow up #Sx	101	0.96782	2.953	2.141	0.01612

Table 6.5 Normality of neurocognitive and total number of symptoms data

Tested using the Shapiro-Francia test for normality in which the null hypothesis is that the data is normally distributed. NC, neurocognitive; #Sx, number of symptoms, Obs, number of observations; W', Shapiro-Francia test result, V', index of departure from normality in which a median value of V' is 1 for samples from normal populations; z, z-statistic, estimate divided by its standard error.

Variable	Obs.	*p (*skewness)	*p (*kurtosis)	*Chi²*	*p (Chi²)*
Baseline NC function	178	0.0000	0.0001	37.28	0.0000
Follow up NC function	101	0.0015	0.1892	10.14	0.0063
Baseline #Sx	178	0.0178	0.0000	19.35	0.0001
Follow up #Sx	101	0.0114	0.0489	8.99	0.0112

Table 6.6 Skewness/kurtosis tests for normality of neurocognitive and total number of symptoms data

Significant p values indicate the source of non-normality. The Chi² and associated p values is also a test of normality, testing the null hypothesis that the data is normally distributed, but is less favoured than the Shapiro-Francia test.

Variable	Obs.	*W'*	*V'*	*z*	*p*
Change in NC function	99	0.96843	2.849	2.068	0.01931
Change in #Sx	98	0.97531	2.209	1.565	0.05883

Table 6.7 Normality of change in neurocognitive and total number of symptoms data

Tested using the Shapiro-Francia test for normality in which the null hypothesis is that the data is normally distributed. NC, neurocognitive; #Sx, number of symptoms, Obs, number of observations; W', Shapiro-Francia test result, V', index of departure from normality in which a median value of V' is 1 for samples from normal populations; z, z-statistic, estimate divided by its standard error.

Variable	Obs.	*p (*skewness)	*p (*kurtosis)	*Chi²*	*p (Chi²)*
Change in NC function	99	0.1510	0.0644	5.35	0.0689
Change in #Sx	98	0.8094	0.0303	4.77	0.0922

Table 6.8 Skewness/kurtosis tests for normality of change in neurocognitive and total number of symptoms data

Significant p values indicate the source of non-normality. The Chi² and associated p values is also a test of normality, testing the null hypothesis that the data is normally distributed, but is less favoured than the Shapiro-Francia test.

Appendix 8

Baseline data in UK and French groups

Variable	UK	France	Overall
Total	97 (22%)	346 (78%)	443
Eligibility			
Seizure prior to arrival in ED	91 (83%)	327 (84%)	418 (94%)
Seizure in ED	19 (17%)	61 (16%)	79 (18%)
Male Sex	59 (61%)	188 (54%)	247 (56%)
Age	40.5 (14.9)	45.9 (19.2)	44.7 (18.5)
Previous seizures	66 (68%)	200 (58%)	266 (60%)
Previous diagnoses			
Epilepsy	39 (40%)	201 (58%)	240 (54%)
Alcohol abuse	25 (26%)	39 (11%)	64 (14%)
Stroke	12 (12%)	26 (8%)	38 (9%)
Other neurological path.	7 (7%)	16 (5%)	23 (5%)
Substance misuse	6 (6%)	11 (3%)	17 (4%)
Meningitis	4 (4%)	10 (3%)	14 (3%)
Regular prescriptions			
Anti-epileptic drugs	31 (32%)	167 (48%)	198 (45%)
Benzodiazepines	5 (5%)	64 (18%)	69 (16%)
Symptoms in ED			
Headache	28 (29%)	86 (25%)	114 (26%)
Confusion	16 (16%)	29 (8%)	45 (10%)
Photophobia	6 (6%)	10 (3%)	16 (4%)
Meningism	6 (6%)	1 (0%)	7 (2%)
Focal neurological deficit	5 (5%)	9 (3%)	14 (3%)
Seizure characteristics			
Generalized Tonic-clonic	82 (85%)	252 (73%)	334 (75%)
Complex Partial	9 (9%)	36 (10%)	45 (10%)
Absence	3 (3%)	31 (9%)	34 (8%)
Other seizure	2 (2%)	29 (8%)	31 (7%)
Simple Partial	1 (1%)	28 (8%)	29 (7%)
Provoked/ Acute sympt.	31 (32%)	125 (36%)	156 (35%)
Witnessed	73 (75%)	242 (70%)	315 (71%)
Therapy in ED			
Benzodiazepine	8 (8%)	241 (70%)	249 (56%)
Antiepileptic drug	3 (3%)	123 (36%)	126 (28%)
Physiological			
Heart rate (beats per minute)	92 (20)	89 (18)	90 (19)
Systolic blood pressure (mmHg)	129 (23)	130 (20)	129 (21)
Diastolic blood pressure (mmHg)	76 (15)	78 (14)	78 (15)

Temperature (°C)	36.5 (0.7)	36.7 (0.5)	36.7 (0.6)
Peripheral saturation oxygen	97 (2)	97.2 (2.3)	97 (2)
GCS 13-15	85 (87.6%)	329 (95.1%)	414 (93.2%)
GCS 9-12	5 (5.2%)	6 (1.7%)	11 (2.5%)
GCS 3-8	3 (3.1%)	3 (0.9%)	6 (1.4%)
Laboratory			
White blood cell count (x10^3)	8.7 (6.5 to 12.3)	10.3 (7.3 to 14.5)	9.7 (12 to 6.7)
Glucose (mmol/L)	6.6 (5.2 to 8)	6.2 (5.2 to 7.1)	6 (8.1 to 5.2)
Sodium (mEq/L)	140 (138 to 142)	138 (136 to 140)	139 (138 to 137)
Calcium (mmol/L)	1.2 (1.2 to 1.3)	2.4 (2.3 to 2.5)	2.3 (2.2 to 1.3)
Lactate (mmol/L)	2.5 (1.6 to 4.7)	1.6 (1.1 to 2.7)	1.8 (3.3 to 1.2)
S100B (µg/L)	0.08 (0.06 to 0.19)	0.08 (0.06 to 0.16)	0.09 (0.17 to 0.07)
Copeptin (pmol/L)	27.3 (9.1 to 60.3)	26.1 (9.5 to 70.8)	19.8 (54.6 to 8.7)

Table 6.9 Baseline date in UK and French groups