Depression after Traumatic Brain Injury

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To my parents,

For encouraging their children into academic pursuits

Summary

Background

Depression is known to be common after traumatic brain injury (TBI) and associated with worse functional and psychosocial outcomes. However, there remains considerable uncertainty over the exact prevalence of the condition.

Aims

The aim of this study was to accurately assess the prevalence of post TBI depression and its changes over a period of one year. The associated demographic and injury features were also examined for possible association with risk of depression in the hope that those with higher susceptibility to depression may be identified.

Methods

The study population was a prospective cohort of TBI admissions to a teaching hospital emergency department over a two year period. Minimal exclusions were applied in order to recruit a representative TBI population who were then assessed in a specialist brain injury clinic at ten weeks and at one year post injury. Demographic and injury features were recorded to establish links with risk of depression which was recorded with a HADS (Hospital Anxiety and Depression Scale).

Results

Over a two year period, 774 individuals were recruited of whom 690 attended one year follow-up and 38 had died. Only 6% of the cohort was lost to follow-up after one year. The prevalence of depression at ten weeks was 56.3% [95% CI 52.8-59.8] and at one year 41.2% [95% CI 37.6-44.9]

A multivariable analysis identified the independent predictors of depression; at ten weeks these were TBI severity, abnormal CT scan, past psychiatric history, alcohol intoxication at the time of injury, female gender and non-white ethnicity. At one year the independent predictors were; abnormal CT scan, past psychiatric history, alcohol intoxication at the time of injury and female gender. TBI severity was no longer significant. Features such as injury aetiology, social isolation, age, length of stay and medical comorbidity were not associated with depression risk. All other outcome measures in the study, including psychosocial function, symptom severity and global overall outcome showed very high correlations with depression.

Discussion

The prevalence of depression is very high after TBI and associated with a number of injury features. While the prevalence drops over a year it still remains considerably elevated. There is also evidence that features related to the injury itself, such as TBI severity, become less significant in long term outcome compared to the initial period. It is possible that other psychosocial features such as personality and coping mechanisms are more important in determining long term outcome than injury features such as severity and aetiology. Some population features have been identified that may allow targeting of susceptible populations for intervention. The close correlations between all

outcome measures including depression suggest that they might be measuring a similar construct of emotional distress.

Future work will seek to reassess the prevalence of depression at three or five years as well as associated features, re-examining the relationship between various outcomes and use of interventions and treatments, especially in targeting at risk individuals.

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Abbreviations

95% CI	95% Confidence interval
ABC	Airway, Breathing, and Circulation
ACRM	American Congress of Rehabilitation Medicine
AIS	Abbreviated Injury Scale
AUC	Area Under Curve
BDI	Beck Depression Inventory
CASP	Critical Appraisal Skills Programme
CDC	Centers for Disease Control and Prevention
CES-D	Center for Epidemiologic Studies Depression Scale
CIRS	Cumulative Illness Rating Scale
CRASH	Corticosteroid Randomisation After Significant Head Injury
CT	Computed Tomography
DAI	Diffuse Axonal Injury
DASS	Depression Anxiety Stress Scales
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition
EBIQ	European Brain Injury Questionnaire
ED	Emergency Department
EDH	Extradural Haemorrhage
EQ5D	EuroQol-5 Dimension
FIM/FAM	Functional Independence & Assessment Measure
GCS	Glasgow Coma Scale
GOSE	Glasgow Outcome Scale- Extended
HADS	Hospital Anxiety and Depression Scale
HAM-D	Hamilton Rating Scale for Depression
HRQOL	Health Related Quality of Life
IAPT	Increased Access to Psychological Therapies
ICD-10	International Classification of Disease 10th revision
ICP	Intracranial Pressure
ICU	Intensive Care Unit
IMPACT	International Mission for Prognosis and Analysis of Clinical Trials in TBI
IQR	Interquartile Range
ISA	Impaired Self-Awareness
ISS	Injury Severity Score
JAMA	Journal of the American Medical Association
LOC	Loss of Consciousness
LOS	Length of Stay
MeSH	Medical Subject Heading
MMPI-2	Minnesota Multiphasic Personality Inventory version 2
N/A	Not Applicable
NFI	Neurobehavioral Functioning Index Depression Subscale
NHS	National Health Service

NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
NS-SEC	National Statistics Socio-economic Classification
ONS	Office for National Statistics
PCS	Post-Concussion Syndrome
PHQ-9	Patient Health Questionnaire-9
PICOS	Patient, Intervention, Comparator, Outcome, Study
PPV	Positive Predictive Value
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PTA	Post-Traumatic Amnesia
PTSD	Post-Traumatic Stress Disorder
QALYS	Quality Adjusted Life Year
QoL	Quality of Life
RCT	Randomised Controlled trial
RHFUQ	Rivermead Head Injury Follow-up Questionnaire
ROC	Receiver Operating Characteristic
RPCQ	Rivermead Post-Concussion Disorder Questionnaire
RTC	Road Traffic Collision
SAH	Subarachnoid Haemorrhage
SCAN	Schedules for Clinical Assessment in Neuropsychiatry
ScHARR	School of Health and Related Research
SCID	Structured Clinical Interview for DSM-IV
SCL 90	Symptom Checklist 90
SD	Standard Deviation
SDH	Subdural Haemorrhage
SE	Standard Error
SF-36	36-Item Short Form Survey Instrument
SPSS	Statistical Package for Social Sciences
STARD	Standards for Reporting of Diagnostic Accuracy
STH	Sheffield Teaching Hospitals
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
TARN	Trauma Audit and Research Network
TBI	Traumatic Brain Injury
UCLA	University of California, Los Angeles
UK	United Kingdom
USA	United States of America
UoS	University of Sheffield
VAS	Visual Analogue Scale
WHO	World Health Organization

CHAPTER 1: INTRODUCTION

1.1 Traumatic Brain Injury

Traumatic Brain Injury (TBI) is a leading cause of worldwide mortality and morbidity. In the United States alone, there are at least 1.4 million cases every year, of which an estimated 235,000 are admitted to hospitals and 50,000 are fatal [Thurman 1999, Langlois 2006a]. It is estimated that each year 80-90,000 individuals become disabled as a result of TBI and that approximately 5.3 million people in the USA suffer from long term disabilities as a direct result of TBI [Thurman 1999, Faul 2010]. Similar figures are found in Europe where pooled data from a number of countries yields an overall annual incidence of $235/10^5$ cases [Tagliaferri 2006]. The same authors estimate that 6.3 million people across Western Europe are alive with a significant level of disability, directly related to TBI. A more recent pooled calculation found a rate of $262/10^5$ [Peeters 2015] although higher estimates of up to $790/10^5$ also exist [Feigin 2013].

Despite this large societal impact of TBI, it is perhaps surprising how little public and medical attention has focused on the needs of individuals with TBI, which is often referred to as the "silent epidemic". This may be in large part, because such injuries are often invisible or because many patients are never hospitalised or seek medical advice. As a result, the public remain largely unaware of the extent and impact of TBIs. Even mild injuries can cause significant problems such as affecting an individual's ability to return to work [Schoenhuber 1988]. Often these individuals do not have obvious physical problems, leading to the existence of an "invisible disability" and there is often a lack of medical insurance among many health care providers [Langlois 2006b]. This may explain why there is such low general awareness of the impact of TBI and a lack of funding on its research [Roozenbeek 2013].

In recent years the awareness of TBI has been partially raised as a result of the wars in Afghanistan and Iraq. It is estimated that up to 20% of returning servicemen have suffered mild traumatic brain injury particularly as a result of blast and explosion injuries [Hoge 2008]. This has been labelled as

the “signature injury” of these conflicts and substantial numbers of veterans are experiencing long term impairments and disabilities as a result of these injuries [Warden 2006]. These victims are likely to require many years of medical input and suffer many years of disability and loss [Taylor 2012].

While TBI can affect all age groups, it is said to disproportionately affect children and young adults. As a result, TBI constitutes a significant worldwide public health problem due to the life expectancy of survivors who require varying levels of care for the rest of their lives. In turn, many carers suffer stress and loss of health [Douglas 2000]. For young lives affected by TBI, there is a significant impact on lifetime loss of earnings and careers foreshortened [Thornhill 2000, McMillan 2012]. The cost of this burden to society has been estimated at more than $60 billion every year [Binder 2005, Crooks 2007]. The bulk of this is indirect cost due to lost productivity, sick leave, carers and early retirement [Faul 2015].

Apart from this peak of incidence in this younger age group, there is also a secondary peak of TBI incidence in the elderly [Fletcher 2007]. This is mainly due to falls in a group that often have increasing frailty and medical conditions. In fact, falls has overtaken traffic accidents as the most common cause of TBI and the highest incidence of hospitalisation and mortality is now in the over 75s [Parekh 2010, Faul 2015]. Elderly patients with TBI have complex and demanding care needs. This has become an increasingly significant public health issue of its own as the population ages [Murray 1999, Koskinen 2008].

TBI remains the commonest cause of death in the under 45 age group. However it is notable that mortality rates have decreased steadily over a period of 150 years until recently [Silvestri 1997, Stein 2010]. This has been attributed to improved legislation and measures of road safety that prevent primary injury itself [Chiu 2000, CRASH-1 2008]. There is also a significant effect from improved standards of health care with standardised clinical guidelines, better provision of ED (Emergency Department) facilities, critical care, neurosurgical monitoring and interventions including intracranial pressure monitoring and more extensive use of radiological interventions, such as computerised tomography (CT scanning).

However, this steady improvement seems to have reached a plateau in recent times with no apparent reduction in crude mortality since 1990, albeit that case fatality has diminished [Stein 2010, Fuller 2011]. A meta-analysis of outcome studies confirms that long term outcomes remain unchanged from 1980 to 2011 [Rosenthal 2012]. This may be attributed to the ageing of the population and the shift of the population towards those with generally worse outcomes such as the elderly, balancing out any improvements that have occurred in quality of care.

While case fatality may have improved in TBI as a result of advances in acute care, this has not been reflected in similar improvements in rehabilitation after injury and many survivors suffer severe long-term psychosocial problems [Singh 2013]. In the long-term, up to 50% of TBI individuals suffer unemployment and 60% are socially isolated [Thornhill 2000, Hoofien 2001]. Marital break-up is common and the risk of suicide is increased [Simpson 2007, Wasserman 2008]. Recent studies have shown significant shortening of life expectancy and homelessness after TBI [Macmillan 2011, Ulfarsson 2014a]. The cost in terms of lost lives and quality of life is immense [Crooks 2007]. The challenge for clinicians is now to try and improve the quality of life for those who survive TBI and not simply the "quantity" of life.

1.2 Definitions of TBI

Providing a clear definition of what constitutes a TBI, is perhaps more difficult than one may expect. There are a number of formal definitions including the Centres for Disease Control (CDC), the World Health Organisation and the American Congress of Rehabilitation Medicine (ACRM) [ACRM 1993, Faul 2010, Carroll 2004]. Differences in these criteria have led to disparity in reported case incidence [Sherer 2007, Corrigan 2010]. As a result, an effort to unify diagnosis was made by an expert working group and resulted in a Common Data Elements definition [Menon 2010]. According to these criteria, TBI is best defined by the *"an alteration in brain function, or other evidence of brain pathology, caused by an external force".* Symptoms of altered brain function can include:-

- Any transient confusion, disorientation or impaired consciousness
- Dysfunction of memory at the time of injury
- Loss of consciousness
- Observed signs such as seizures, irritability, weakness, change in vision or sensory loss, lethargy or vomiting especially in infants
- Headache, dizziness, irritability, fatigue or poor concentration

Once the diagnosis has been made, TBI is further classified by severity or grade of injury. This has classically been divided into mild, moderate and severe injury as defined by three clinical parameters. These are Glasgow Coma Score (GCS), period of loss of consciousness and length of period of post-traumatic amnesia (PTA). A useful definition of PTA is the time that elapses from injury until an individual can demonstrate continuous memory. These are detailed in Table 1.1 which illustrates the cut-offs that are used to define the severity of injury. While there is general agreement and good correlation in using these measures, a small proportion of individuals with TBI can be classified into different severities depending on which clinical parameter is used. Therefore some misclassification or inconsistency can result [Boyd 1987, Corrigan 2010]. Most TBI literature uses GCS to grade severity as it tends to be the best documented parameter in clinical records and therefore the easiest to ascertain. GCS is commonly taken as the score on admission to ED if resuscitation took place at the accident scene or after resuscitation in the ED Department [Yates 2007].

Classification	Definition
Mild head injury	Defined as GCS 13-15 Coma less than 30 mins PTA less than 1day
Moderate head injury	Defined as GCS 9-12 Coma 30 mins-6 hrs PTA >1 day
Severe head injury	Defined as GCS less than 9 Coma more than 6 hrs PTA >7 days

Table 1.1: Classification of TBI Severity

Other classification systems for TBI have also been devised, using findings on CT scanning [Marshall 1991, Maas 2005, Lesko 2011]. These are particularly useful from a neurosurgical perspective for deciding on the timing of operative intervention rather than for use in predicting rehabilitation outcomes. Relatively little literature exists on the use of these classifications and association with long-term psychosocial outcomes; most research in TBI continues to utilise the classical indicators of severity as shown in Table 1.1.

1.3 Pathophysiology of TBI

A blow to the head applies an external force on the brain and surrounding tissues causing mechanical distortion. This may cause a skull fracture or the transmitted force can lead to both focal damage within the cerebral cortex as well as more diffuse or widespread damage, sometimes in

quite distant areas from the site of impact. The term *primary brain injury* is used to describe the results of the initial impact. *Secondary injury* is the effect of consequent complications such as hypotension, cerebral oedema, alterations of blood flow, raised intracranial pressure, hypoxia and infection.

Another description that is often used is *open* versus *closed* brain injury. The differentiating factor here is that in an open case, the environment communicates with the intracranial space and there is a risk of infection spreading into the brain and surrounding tissues.

The forces causing TBI will often result in intracranial lesions or pathology. These can usually be seen on CT scanning which is the investigation of choice after TBI. CT is effective at picking up the presence of acute bleeding and therefore most lesions seen on CT, have an element of blood present in them [Drevets 2000].

A brief discussion of some of these types of lesions after TBI is important in order to understand TBI pathology.

1.3.1 Cerebral contusions

These are small areas of bruised brain tissue with some evidence of cell damage or death. They are most commonly found at the surface of cortex where the relatively mobile brain impacts against the bony prominences of the skull, e.g. at inferior surface of the frontal and temporal lobes. These are usually small lesions and resolve spontaneously but larger contusions can coalesce and cause a mass effect, resulting in severe neurological deficits and at times surgical evacuation is required. These lesions are readily seen on CT scanning.

1.3.2 Diffuse axonal injury (DAI)

This injury usually involves a rapid acceleration or deceleration force resulting in small haemorrhagic lesions at grey/white matter interfaces. Common areas include the corpus callosum and cerebellar

peduncles. These lesions are often not seen on CT scanning and MRI is a far more effective means of demonstrating such injuries. In the absence of MRI scanning, the impact of DAI is often underestimated [Gennarelli 1997]. As it is more common in high velocity injuries, DAI constitutes a major cause of the morbidity associated with TBI.

1.3.3 Intracranial haematomas

Damage to small blood vessels within the brain or meningeal layers results in formation of a haematoma which expands according to the space it can occupy. This can lead to rapid rise in intracranial pressure and herniation of brain tissue. At other times blood can slowly accumulate over a matter of weeks.

Intracranial bleeding can be sub-divided further, depending on the exact location of blood relative to the meningeal layers and brain substance.

i. Extradural haematoma

This is a haemorrhage into the extradural space commonly caused by damage to the middle meningeal artery, which in turn is usually caused by a skull fracture crossing the path of this vessel. A smaller number of cases are caused by bleeding from a venous sinus. These lesions are significant as they can grow very rapidly and cause deterioration and death within minutes, if not recognised. However, prompt surgical evacuation can be lifesaving and recovery is often excellent. On CT scans, these lesions can often appear convex or lentiform in shape and hyperdense.

ii. Subdural haematoma

These lesions are usually caused by damage to a bridging vein that crosses the sub-arachnoid space into the dural sinus. They occur more commonly in elderly individuals where shrinking of brain tissue causes a stretch on these veins. Bilateral lesions are not uncommon and individuals can often present late. Indeed late presentation is often the hallmark of SDH especially in the elderly due to

the slow progression. Surgery is required if a significant mass effect exists. On CT scans, subdural lesions can often appear concave or crescent in shape.

iii. Intracerebral haemorrhage

This represents blood found within the cortical structures itself, most commonly in frontal or temporal lobes. Damage to small blood vessels within the brain parenchyma itself is often located quite deep within cortical structures and associated usually with severe trauma.

iv. Subarachnoid haemorrhage

This describes the presence of blood in the subarachnoid space that is found between the arachnoid and pia membranes. These can be spontaneous bleeds which occur after the rupture of a cerebral aneurysm or arterial venous malformation. In these sudden cases, the presentation can often be dramatic with sudden onset headache or collapse. However, the most common cause of SAH remains trauma.

1.3.4 Microscopic Changes

The gross macroscopic lesions described above are also accompanied at a microscopic or cellular level by a cascade of intra and extra-cellular processes. These are not fully elucidated but a number of neurotransmitters and secondary messenger systems are involved and the complexity of these pathways is beyond description here. However, in brief, stimulation by excitatory amino acids, release of intracellular calcium and magnesium as a result of injury, activation of calcium regulated protein complexes, free radical formation and mitochondrial damage are all part of this cytotoxic cascade and contribute to neuronal injury and death [Zetterberg 2013]. Studies after injury have shown increased release of many neurotransmitters including glutamate, dopamine, serotonin, acetylcholine and noradrenaline. While many of these levels return to normal within a few weeks, chronic deficits have also been identified particularly in cholinergic and serotonin systems. The loss of biogenic-amine containing neurons in frontal-subcortical circuits may affect brain function. Endocrine changes have also been noted with blunting of cortisol responses to stimulation by CRH.

These various processes modulate gene expression and protein regulation; they ultimately result either in cell death or attempts at cell repair but the exact mechanisms are poorly understood and await further research. Numerous attempts to intervene and modify these cascades have generally been disappointing, although considerable effort has gone into trying to modulate these errant pathways [Arciniegas 2014].

It is perhaps best to consider the pathophysiology of TBI as a result of a large number of biomechanical forces and resulting cytotoxic cascade and neurotransmitter disturbances rather than a single neurotransmitter disturbance. In this way TBI can cause damage to a wide area of brain tissue, often distant to the site of injury.

1.3.5 The "Normal" CT Scan

A number of individuals with TBI have a "normal" CT scan i.e. no lesion is seen on scan. This group have a disorder of brain function rather than an obvious structural deficit. While many patients with TBI recover quite quickly, a significant proportion, including those with normal scans, suffer poor psychosocial outcomes ("Miserable Minority") [Ruff 1996, Cassidy 2014]. The treatment and management of these individuals is complicated and involves considerable psychological interventions and behaviour management. It is important to appreciate that CT scans only look at gross anatomical structures and is no measure of cerebral function. The development of newer, more sophisticated scanning techniques, particularly functional scanning such as Positron Emission Tomography (PET) scans or Diffusion Tensor Imaging (DTI), may better unravel the exact functional problems that occur after TBI including those who can demonstrate physiological changes that take place in those with supposedly "normal" CT scans [Edlow 2012, Yuh 2013].

1.4 Causes of TBI

In the UK, a useful classification of TBI aetiology has been provided by the Trauma Audit and Research Network (TARN) [Lecky 2000]. The majority of TBIs are caused by falls with road traffic collisions closely behind. In a number of studies this order is reversed, perhaps because the researchers have focused on a younger population [Roozenbeek 2013]. In general, low and middle income countries suffer more RTC injuries; In contrast, in high income countries, the median age of TBI victims is increasing as a result of the ageing population. As a result, falls have now overtaken RTC as the most common cause of TBI [MRC-CRASH 2008]. Individuals over 75 now have the highest incidence of hospitalisation after TBI as well as the highest TBI–related mortality [Faul 2010, Korhonen 2013].

The third most common cause of TBI is assault. There are also miscellaneous injuries that include falls from height (>2metres), being struck by an object and workplace injuries. These are often combined as “other”.

In recent years, a number of studies have focused on war veterans suffering from bomb explosions causing TBI or the “signature injury” of recent Middle East conflicts [Taylor 2012]. There has also been considerable interest in the effects of sporting injuries on TBI. This has especially focused on repetitive brain injuries and risk of neurological deterioration in later life [Omalu 2010]. In the USA, the CDC includes a separate categorisation of sports injuries as this is a large enough group on its own. This does not exist in the TARN classification of aetiology outside of “other”.

These different aetiologies highlight the importance of clearly defining any study population and the group that has been examined. In a young population, road traffic collision (RTC) is more common than falls [MRC-CRASH 2008]. However in an ageing society, one may expect the proportion of injury caused by mechanical falls, to continue increasing [Fletcher 2007, Harvey 2012].

A criticism that can be made of the TBI literature is that the study populations often do not reflect the true community incidence or aetiologies of the injury, particularly the rising numbers of elderly patients. Much of the literature is made up of highly selected populations eg ITU admissions, surgical

patients, litigants or RTC victims. There are relatively few studies that truly reflect the community prevalence and constitution of TBI victims [Guillamendegui 2011, Rosenthal 1998].

1.5 Impairments and disability resulting from TBI

Survivors of TBI have a range of outcome from full recovery to severe disability. This disability encompasses a wide range of different deficits with varying degrees of severity. Usually, such deficits can be categorised into the following domains

a. Physical (e.g. headache, dizziness, pain, fatigue, poor sleep)
b. Cognitive (including communication impairment)
c. Behavioural/ Psychological.

Individuals are often most concerned by the physical disabilities immediately after injury but these tend to improve more rapidly than other deficits [Jorge 2002]. These include problems such as headache, dizziness, weakness, balance, sensory disturbance and pain.

Cognitive recovery in general, occurs at a slower rate than physical improvement over a considerable time period, usually 18 – 24 months [Grauwmeijer 2012]. However, improvement has been documented even later than this [McMillan 2004]. This domain includes features such as attention, memory and executive function.

By contrast psychological or behavioural deficits are often absent initially but may manifest later in the natural history of TBI. They are often the most disabling and limiting sequelae of TBI, manifesting in a broad range of emotional problems [Hibbard 2004, Warden 2006, Silver 2009, Singh 2014]. When these problems are manifested in sufficient intensity, they may be labelled as a distinct clinical psychiatric disorder. These should now be examined.

1.6 Neuropsychiatric disorders and TBI

The neuropsychiatric consequences resulting from TBI have been known for a long time. The classic case of Phineas Gage recorded dramatic personality changes after an iron bar was propelled through his skull after an explosion, damaging the frontal lobe. His doctor described how Gage's personality changed from being a responsible and well adapted individual into an "irresponsible, negligent and profane person unable to work or assume any responsibility" [Harlow 1848].

A case series of patients with behavioural disturbances after TBI was described at the start of the 20th century [Meyer 1920]. This included a description of "traumatic insanities" such as depression, psychosis and neurological symptoms.

A wide range of different psychiatric conditions can be found after TBI. Common diagnoses include depression, anxiety, post-traumatic stress disorder (PTSD), agitation or aggression and frank psychosis. Using strict clinical criteria, an incidence of 49% for all major psychiatric disorders was made in the first year after injury and many other studies have found similar high levels of a number of psychiatric conditions [Van Reekum 1996, Hibbard 1998, Koponen 2002, Fann 2004, Rapaport 2007, Singh 2014]. The most common of these is depression and this needs to be discussed in some general detail but also with particular regard to the context of TBI.

1.7 Depression

Depression is a disorder of mood characterised by persistent feelings of sadness, accompanied by several additional symptoms. These are problems with appetite or sleep, loss of interest in activities, fatigue, poor concentration, sense of hopelessness or suicidal thoughts.

First described in Western literature, by Hippocrates in 200BC as a syndrome of "melancholia", the word depression is thought to derive from the Latin verb *deprimere* which means to press down. In this regard it was thought that depression subjugated or brought ones spirits down.

The World Health Organisation recognises depression as a major health problem that affects individual functioning, work output and healthcare [Kroenke 2001]. It is the most common mental

health disorder across the world and is the fourth most common cause of disability adjusted life years (DALYs) [Collins 2011]. By 2020, it is projected to become the second most common cause [WHO 1993, Kessler 2003].

Studies show that depression causes greater loss of health than major chronic illnesses such as arthritis, ischaemic heart disease, diabetes and asthma [Wells 1989]. Combined with chronic physical health problems, depression worsens health compared with physical disease alone or combinations of other physical diseases [Moussavi 2007, Bornhofen 2008].

Worldwide estimates of the incidence or prevalence of depression varies considerably between studies. Most population estimates are between 4% and 10% depending on the criteria and tools used to assess and diagnose depression [Kessler 2004, Waraich 2004]. Point prevalence in the UK was 2.6% among 16-74 year olds. However this rose to 11.4% if the less specific category of "mixed depression and anxiety" was used [Singleton 2001].

Rates of depression are far higher in medical inpatients (up to 20% in some studies) or in individuals with co-existing chronic medical conditions [Crawford 2001, First 2002]. It is clear that there are certain groups of individuals who are more susceptible to developing depression than others and the presence of a chronic health condition increases this risk.

While a detailed review of the demographics and aetiologies of depression is not required here, it is important to note that a number of socioeconomic factors are commonly associated with the prevalence of depression. Women consistently show higher rates at between 1.5-2.5 times higher. Other studies find a link with middle age years, social isolation, lower education levels, divorce or deprivation. Others have found links with ethnicity [Singleton 2001, Wairich 2004, King 2006, Lindert 2008].

1.8 Diagnosis

In both the lay and research literature, depression can be a confusing term, meaning a number of different things to different people. Terms such as major depressive disorder (MDD), clinical

depression, major depression, depression with other features and unipolar depression are often interchangeably used. Hence some clarification of terminology is required.

Diagnostic criteria or methods of classifying depressive disorders have changed continuously over the years. While attempts to create firm operational diagnostic criteria can help to standardise practice, it is difficult if not impossible to try and classify such a heterogeneous disorder in such a rigid manner.

The two main systems for classification are the International Classification of Diseases, now in its 10th iteration [WHO-ICD 2010] and the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) which is currently in its 5th edition and published by the American Psychiatric Association [APA 2014]. While these both share very similar diagnostic features for a diagnosis of depression, they differ in the number of symptoms. ICD-10 requires four out of ten symptoms (including at least two of depressed mood, anhedonia and loss of energy) while DSM-5 requires five out of nine symptoms but must include either depressed mood or anhedonia. This means that different rates of depression can be found in the same population depending on the criteria that are set [Wittchen 2001, Andrews 2008]. Research literature in depression uses the DSM criteria far more than ICD and for this reason, it is better to focus on the background of this tool and its application to the diagnosis of depression.

DSM is the diagnostic “bible” of psychiatric disease [APA 1994]. It evolved initially from a system for collecting both census and psychiatric hospital statistics. Since its first publication in 1952, revisions have added considerably to the total number of mental disorders and it has been heavily criticised for over-medicalising human distress and creating disorders with very superficial symptoms and poorly validated criteria [Natl Inst Mental Health 2014].

DSM describes major depression as the most common form of depression. In addition a number of other disorders come under the general umbrella term of depression including bipolar depression, dysthymic disorders, adjustment disorder and depression secondary to medical illness.

The latest incarnation of DSM is the 5th edition, published in 2013 [APA 2014]. While there are a number of new diagnoses in this edition, there has been no significant change to the section on

depression and so for this study, the descriptions from DSM-IV are entirely valid. This is important as most studies have used older versions of DSM, particularly DSM-IV (1994) and DSM-III (1987). Many individuals studied in this thesis were recruited or evaluated prior to the publication of the newest edition.

The DSM describes nine symptoms of which five must be present for a period of no less than two weeks. In addition, one of the first two must be present as these are considered essential criteria for a diagnosis. The 9 criteria are:-

- Depressed mood
- Loss of interest or pleasure (anhedonia)
- Poor sleep pattern
- Psychomotor agitation or retardation
- Fatigue or loss of energy
- Feelings of worthlessness or guilt
- Diminished ability to think or concentrate
- Recurrent thoughts of death or dying
- Weight loss / weight gain

The diagnosis of depression can only be made by an individual's self-reported experiences. There is no single definitive laboratory test or clinical sign and therefore the diagnosis of depression is open to interpretation both by the individual and their reporting of symptoms as well as the clinician who evaluates the symptoms to make the diagnosis. As will be discussed later, this subjective evaluation can lead to widespread differences in reported incidence of the condition.

In this thesis the term "depression" is used as a term for major depressive disorder. Other disorders as defined by DSM will be described by their full name e.g. bipolar depression if they are mentioned in the text.

1.9 Difficulties with diagnosis and symptom overlap with TBI

1.9.1 Trans-diagnostic Symptoms

A major impediment to a better understanding and identification of depression after TBI, is the fact that many of the symptoms experienced after TBI are also key symptoms of depression. In other words symptoms such as appetite change, fatigue, decreased concentration and altered sleep occur in both conditions [Fleminger 2008]. These symptoms can be thought of as indicators of more than one diagnosis (trans-diagnostic symptoms). As will be discussed later, many of the clinical tools that are used to try and identify individuals with depression, have a high proportion of such somatic symptoms such as poor appetite, disturbed sleep, decreased libido, fatigue, poor concentration and inability to work.

It is possible to divide symptoms of depression into vegetative and psychological. Examples of "vegetative" or "somatic" symptoms include autonomic anxiety, weight loss, delayed sleep, fatigue and loss of libido. This is in contrast to those symptoms best described as "psychological" such as worrying, hopelessness, suicidal ideation and social withdrawal. After TBI, vegetative symptoms are common in this population and could be attributed as depressive symptoms. Therefore it is quite likely that depression could be over-diagnosed in a TBI population based on the presence of vegetative symptoms. For this reason, it has been suggested that psychological symptoms differentiate depressed from non-depressed individuals more consistently than vegetative symptoms and should be prioritised rather than vegetative symptoms [Jorge 1993].

1.9.2 Impaired Self-awareness (ISA)

Another problem that affects the ability to diagnose depression is the concept of *self-awareness*. Self-awareness can be described as "awareness of arousal, perceptual processes, expressive process and integration of both the self and its environment" [Prigatano 1991, Sherer 1998]. In other words

it can be said to encompass an awareness of oneself prior to the injury and afterwards. It implies an awareness of the long-term implications of that injury [Ownsworth 2011]. The more severe the extent of a brain injury, the more likely an individual will have a loss of self-awareness due to disruption of normal brain cognition and information processing [Prigatano 1997]. This may cause an individual to undermine the extent of the deficits or loss that they may be experiencing. An individual may deny depressive symptoms or distress even though they appear quite depressed to others, including their partner or family. Therefore, this is likely to confound the diagnosis of depression in such individuals. ISA may also explain the puzzling finding that in some studies, mild TBI has a higher incidence of depression than severe TBI [Kelley 2014, Robertson 2015]. It is possible that more severely injured individuals are less aware of their deficits and understate their symptoms, leading to fewer cases of diagnosed depression [Moldover 2004].

1.9.3 Identifying depression

A major area of debate in this field centres on the best means to diagnose depression. The purists may argue that the gold standard is considered to be a Structured Clinical Interview for DSM disorders (SCID). This must be administered by a trained neuropsychologist or psychiatrist and takes up to one hour to carry out [First 2002]. This clearly requires a great deal of resource allocation and professional time that is not available to most clinicians in everyday practice. Furthermore, many of the symptoms used in the DSM overlap with TBI symptoms as described above and may lead to over diagnosis of depression [Seel 2010].

By contrast, many clinicians and research studies use questionnaires, some of which are filled by the patient and some with the clinician. These usually ask for the presence of a number of symptoms and their severity using a Likert scale to classify severity of each symptom. These are usually then added up to give a score that describes the likelihood of depression. Cut offs can then be used to make the diagnosis e.g. score>8. The attraction of such methods are the speed with which they can be administered and the resource implications at a time where many face difficulties in expanding or

funding services. Compared to a one hour interview by a fully trained clinician, this has considerable resource advantages. Several studies have suggested that in TBI, these questionnaires yield similar results to more detailed interviews and are an effective and valid approach to diagnosis [Dyer 2006, Whelan-Goodinson 2008].

Some studies have even suggested that a single question e.g. “do you feel depressed?” can discriminate depression adequately [Whooley 1997, Turner-Stokes 2005, Sanchez-Villegas 2008].

Any study of depression must consider the means of making the diagnosis as this has ramifications for the resources needed and the burden placed on patients as well as staff.

1.10 TBI and Depression

1.10.1 Neuroanatomy

Given that TBI affects the organ that determines cognitive and affective symptoms of any psychiatric illness i.e. the brain, it would be reasonable to assume that a brain injury may affect some of the structures that regulate mood.

Several brain structures have been linked to the control of mood and behaviour. The regulation of emotion and mood is dependent on coordination and networking between these structures. Loss of control of these centres is thought to be central to this “anatomical” model [Finset 2000, Jorge 2005, Koenigs 2008]. The limbic system plays a major role in the generation of mood and is located in the frontal and medial temporal lobes of the brain. The limbic system also includes the hypothalamus that affects our emotional responses partly through control of endocrine systems. It also includes the amygdala, damage to which, often causes problems with aggressive behaviour and the hippocampus which plays a critical role in the formation and assimilation of memory. In turn, the limbic system has significant neural connections to the frontal lobes which play a vital role in monitoring and managing emotional output as well as inhibiting certain unwanted behaviours.

Unfortunately, the frontal lobes are especially susceptible to traumatic injury. As a result TBI is frequently associated with damage to the frontal lobes or the other brain structures mentioned above. This leads to changes in behaviour and mood and predisposes the individual to depression.

The central role of the brain as the primary organ of concern is apparent by the fact that trauma alone (without TBI) does not elevate depression [Jorge 2004]. However other neurological conditions that affect the brain such as Parkinson's Disease or Multiple Sclerosis are often reported to cause depression [Rickards 2005].

While the brains of individuals affected by TBI may show marked differences to those without TBI, the clinical features of depression in the TBI population show no difference to depression in the general population [Fleminger 2008]. The most common symptoms identified are low mood, poor concentration, frustration and fatigue in both groups.

1.10.2 Outcome and depression

It has been known for a long time that the psychological sequelae of TBI such as depression are a major determinant of overall long-term psychosocial outcomes [Thornhill 2000, Hoofien 2001]. Depression can worsen physical and cognitive function and slow the rate of any recovery [Brooks 1987, Thomsen 1984, Andersson 2002]. As function is probably already affected, the further impact of depression is therefore to worsen disability [Thomsen 1984, Bornhofen 2008]. Indeed, psychological deficits are a far more powerful predictor of overall adverse outcome than physical impairments and affect quality of life much more [Rogers 2007]. Depression has also been shown to negatively affect cognitive function although it is also known that poor cognition will also cause depression after TBI so there is an element of "chicken & egg" as to whether the cognitive impairment precedes depression or vice versa. Treatment of either depression or cognitive impairment leads to improvement in the other, reinforcing the link between them [Rapoport 2005, Himanen 2009].

A proper understanding of TBI-depression is imperative if we are to achieve successful rehabilitation goals and integration of an individual back into their home and family life and improve overall outcome. Therefore it is necessary to examine the features that are associated with depression and the susceptible populations which may increase or decrease risk of developing depression.

1.10.3 Previous literature

A large number of studies have examined the prevalence of depression after TBI but these rates vary considerably. This is discussed in more detail in the literature review (Chapter 3) but a very brief summary is relevant here. Reviews of many of these studies found a range between 11-77% [Rosenthal 1998, Rogers 2007, Guillamendegui 2011]. Such widely varying prevalence can in part be explained by the extensive differences between studies. They differ considerably in terms of the populations of TBI individuals studied, the time between injury and assessment, the type of clinical assessment made to diagnose depression and the quality of follow-up. The majority of studies are cross-sectional, short-term and subject to heavy attrition of follow-up.

However on review, it is clear that the majority of studies show a markedly increased rate of depression; a recent review calculated a mean rate across the studies of 31% [Guillamendegui 2011]. This compares to the rate in the general population of 4-8% [Cameron 2001, Kessler 2003, Crawford 2008].

While most studies have focussed on the first year after injury, increased prevalence is apparent even many years afterwards with studies showing elevated rates of depression up to 50 years after TBI [Holsinger 2002, Koponen 2002]. In other words, the risk of depression after TBI is markedly elevated and remains so for many years.

The different injury and demographic factors that may be associated with depression in the TBI population, is also discussed in the literature review (Chapter 3). However, in brief, a large number of different factors have been examined in relation to depression risk. These include age, ethnicity, gender, unemployment or low income, previous alcohol abuse, level of education and previous

history of psychiatric disorder. However there is little agreement between studies and reviews have concluded that there is no firm evidence for any single demographic or injury factor being linked to depression risk [Rosenthal 1998, Rogers 2007, Guillamendegui 2011]. Indeed, even the severity of TBI does not show a clear gradient for risk of depression across all studies and some studies have found an elevated risk in mild TBI as opposed to severe as was discussed previously.

It is reasonable to ask why there are such differences across studies and why it is difficult to form any consistent conclusion based on the substantial body of literature that has been published? Previous literature reviews conclude that it is not possible to identify any factors that generate or propagate depression [Guillamendegui 2011].

One of the reasons may lie in the nature of depression itself; the pathogenesis of depression is far from simple. A large number of theoretical models and concepts with varying evidence have been described in the literature and it is likely that individuals with depression comprise a heterogeneous group. It is possible that different groups of patients may manifest in the same way i.e. depression, but that they have very different aetiologies, predispositions and maintaining factors that produce the depression. While a detailed discussion of these theories of depression and the various models are beyond the scope of this thesis, a brief mention of some of the key concepts is relevant to our understanding of how depression and TBI interact and may help to explain why no clear picture emerges of the incidence or the risk features associated with it.

1.11 Models of depression in TBI

1.11.1 Introduction

While many different theories exist as to the development of depression, there are two main schools of thought. The first emphasises the importance of biological substrates and clear neuroanatomical lesions. Depression therefore directly results from neuroanatomical and physiological damage.

In contrast, others contend that the neuropathology is less important. After all, many individuals with extensive cerebral lesions show no change in mood and others with little abnormality visible on

CT scans, show extensive depression or behavioural change. This suggests that depression is caused by a maladaptive response to impairments caused by the injury. In this model the importance of premorbid psychosocial factors and susceptibility to depression is emphasised as well as post-injury behaviours and traits that prolong disability or a negative self-evaluation.

The older literature on depression often uses the terms “endogenous” and “reactive” as an early classification, although these terms have gone out of favour. Due to the lack of demographic and injury factors such as severity of TBI, to predict the likelihood of depression or the outcome, some authors suggest that the TBI is not related to the development of depression in these individuals and in this regard no different to any generalised trauma that an individual may undergo. This “reactive” model contends that depressive symptoms simply constitute a normal psychological response to a stressful event such as a trauma which negatively impacts upon that individual’s ability to adjust. In this regard some individuals are more predisposed to develop depression as a result of their premorbid personalities. There may also be a part played by lack of prompt medical attention or rehabilitation afterwards [Andelic 2012].

1.11.2 Biological substrates for depression

A number of studies have tried to correlate depression after TBI with neuro-anatomical findings and it is known that many of the areas associated with mood disturbance, are also damaged in TBI. A comprehensive study of this nature looked at 66 prospective admissions and examined the relationship between radiological findings and depression after injury [Federoff 1992]. They suggested that there was an increased early incidence of depression and left sided dorsolateral prefrontal cortex lesions and to a lesser extent, left sided basal ganglia lesions.

It has also been shown that after TBI there are volumetric changes in the left prefrontal cortex [Jorge 2005], in the orbitofrontal cortex bilaterally and the left anterior cingulate cortex [Hudak 2011]. Another recent study found marked asymmetry in frontal and parietal lobe volumes in depressed

individuals compared to non-depressed TBI [Koenigs 2008]. Areas of reduced neuron density are known to be rich in cholinergic innervation and interventions aimed at enhancing the cholinergic system have been shown to alter cognitive function [Salmond 2005]. Others have suggested that these lesions cause interruption and depletion of brain amines, particularly dopamine and serotonin and hence cause depression although a single neurotransmitter is unlikely to be the sole cause. It is also postulated that cerebral asymmetry in terms of the emotional processing may be caused by the left sided frontal lesions and altered activation or inhibition of a number of secondary brain centres then occurs [Schonberger 2011].

Studies show that over several weeks after TBI, cell damage and loss occurs in particularly vulnerable areas such as the prefrontal cortex, hippocampus, thalamus and amygdala [Raghupathi 2000, Grady 2003].

Many of these areas affected by TBI coincide with regions known to be important in regulating mood. The prefrontal cortex modulates a number of subcortical structures that evaluate aversive stimuli and their context [Finset 2000]. The orbitofrontal cortex is often affected by TBI and is important in regulating social behaviour [Fleminger 2008].

The regulation of mood is dependent on the coordination of neural networks within the cortex, limbic system and brain stem. Disruption of these neural circuits may constitute the substrate for cognitive and psychological impairments after TBI [Hariri 2003, Macgregor 2013] including depression [Jorge 2005].

Further development of such biological theories may be aided by newer and more sophisticated radiological techniques, particularly those that look at metabolic activity and brain function or which can more clearly define white matter tracts and lesions. Magnetic resonance spectroscopy has shown abnormalities of choline and N-acetyl aspartate in basal ganglia which are markers of neuronal integrity [Rao 2010]. Functional MRI scans (fMRI) and diffusion tensor imaging studies (DTI) show areas of heightened and decreased activity in areas of the cortex, particularly prefrontal [Matthews 2011]. DTI is particularly useful in identifying the integrity of white matter tracts and

SPECT (Single positron emission CT) is useful in studying areas of altered metabolic activity. New techniques may delineate and correlate brain function to specific cortical areas. This will allow better understanding of abnormalities such as mood and awaits wider availability of these techniques in clinical practice.

1.11.3 Psychosocial factors for depression

The neuroanatomical explanation for depression, described above, differs from the psychological theory. Many view the association between TBI and depression to be more likely to be mediated by psychological or psychosocial variables, particularly as time goes on. Indeed a later study by the same group that showed the early link with depression and left-sided lesions, found that the neuroanatomical lesions only correlated to presence of depression at an early phase, i.e. less than three months [Jorge 2005]. At a later date there was no link. They themselves suggest that psychosocial factors then become more significant in perpetuating depression than the anatomical substrates. Some individuals may have a pre-injury vulnerability to developing emotional difficulties and indeed pre-morbid psychiatric history prior to injury is often associated with a higher incidence of depression after TBI in the literature [Hart 2012]. Poor social circumstances after the injury such as lack of rehabilitation, poor family supports, ongoing substance or alcohol abuse may then perpetuate ongoing disabilities and the risk of depression [Helchem 2013]. Those individuals with fewer personal, social and financial resources, find themselves unable to resume their premorbid lifestyles and a consequence of this is poorer functional outcome and increased likelihood of depression. In this regard, depression can be considered a maladaptive psychological response to TBI and independent of the extent of injury or areas of brain affected [Hou 2012].

It follows that symptoms are more likely to be maintained in individuals with adverse psychological factors [Sawchyn 2000, Cassidy 2014]. A belief that recovery is unlikely and that any disability will be prolonged, may also contribute to the development of depression in such individuals.

1.11.4 Working model

It is clear that the theoretical model for depression is complex and it is probably unlikely that a specific brain lesion or a single psychological factor is responsible alone for producing depression. While neuroanatomical biological substrates such as localised lesions and disturbances in various neurotransmitters are significant, these are also linked with poor premorbid psychosocial functioning and ongoing psychological distress with a failure to socially reintegrate or find appropriate support [Demakis 2007]. The role of personality traits is also significant with regards to those with a "helpless" or attributional style of coping, along with an external locus of control [Curran 2000]. Poor insight and ongoing cognitive impairments may also contribute. No single model can explain the complex interplay of biological, developmental and psychosocial factors that determine an individual's susceptibility to depression after TBI. There is probably a heterogeneity of aetiologies [Busch 1998] with a variety of different factors but which ultimately end with a final common expression of psychological disturbance i.e. depression.

The combined theory postulates that the emotional disturbances in TBI can be attributed to complex networks of interaction between neurological impairment, pre-existing behaviours and maladaptive responses; in other words there are complex processes which implicate cerebral structures as well as the external psychosocial environment as involved in the manifestation of depression post-TBI.

1.12 Gaps in Knowledge

While previous reviews have clearly identified that TBI is associated with an increased risk of depression, our understanding as to the factors linked or associated with this depression are surprisingly limited. A need for a clearer understanding of these relationships is vital. With a better understanding of the causes and factors associated with depression, there would be more chance of formulating better means of both identifying and treating such disorders. This concern should be the overriding concern for clinicians in TBI because psychological and behavioural problems dominate long term outcome after TBI [Corrigan 2004, Silver 2009, Geraghty 2015].

A number of treatments for depression are available. A variety of pharmacological agents, cognitive behavioural therapies, exercise and group therapies can be used [Fann 2000, Gertler 2015]. The difficulty remains in our understanding and identification of individuals with depression. This leads to under-diagnosis and under-treatment. It is estimated that only 10% of depressed individuals after TBI receive any treatment at all [Bombardier 2010]. The effectiveness of treatments is also uncertain with systematic reviews suggesting that evidence is limited [Barker-Collo 2013].

It is therefore clear that a considerable gap exists in our knowledge of TBI and depression and our ability to even recognise it. There is a lack of consensus between studies on diagnosis and associations of this important patient group. A well-designed, prospective study that looks at the change in depression over a time period as well as the factors that may be associated with the development of depression, could clarify many controversies. The aim of this investigation is to conduct such a study. By understanding the trajectory of patients' symptoms and function as well as the features that may predict depression and outcome, clinicians may better be able to treat and design pathways to benefit patients. As TBI and depression constitute significant burden of disease worldwide, even a small difference in our management could have a significant effect on the health of many individuals. Improvement of health outcomes, based on firm clinical evidence, should be the aim of all clinicians, particularly in Rehabilitation Medicine [Playford 2010].

1.13 Brain Injury Services in Sheffield

1.13.1 Introduction

While the gaps in knowledge and the need for well-designed studies have been established, an understanding of the academic opportunities presented in Sheffield is necessary at this point. Sheffield benefits from an active academic Emergency Department with research dedicated to major

trauma and head injury. A considerable body of academic work is produced and in recent years closer links with TARN have extended this role.

1.13.2 Initial head injury care

Head injury is a non specific triage term indicating "any trauma to the head excluding superficial injuries to the face" [NICE 2014] where traumatic brain injury may be a consequence. Head injury patients are admitted through the Emergency Department (ED) Department at Sheffield Teaching Hospitals Foundation Trust. This Trust serves a population of approximately half a million people in South Yorkshire. The ED department is based at the Northern General Hospital, which is a large Teaching Hospital set in the north of Sheffield. During the course of the project, this hospital became a Major Trauma Centre (MTC) in 2014 after which many trauma patients from across South Yorkshire were also admitted through ED.

Initial identification and management of TBI patients is by the ED department based on the NICE head injury guidelines [NICE 2014]. This emphasises the importance of initial evaluation, particularly of neurological status using the Glasgow Coma Scale (GCS), management of airways, breathing and circulation as well as urgent management of other injuries including orthopaedic, major visceral organs and spinal cord. The NICE guidelines set out clear criteria for early CT imaging, admission and observation as well as identifying those individuals that can be discharged with appropriate advice. Many head injured patients who present to ED are discharged as they do not meet the NICE criteria for a period of admission and monitoring and are thought not to have a significant brain injury. Those who are admitted remain under the care of the ED department for a period of up to 48 hours where they are regularly reviewed. Other specialties are involved as appropriate and may include neurosurgery, maxillofacial surgeons, orthopaedics, spinal orthopaedics, ophthalmology, ENT and most recently Rehabilitation Medicine. A small number of patients may not enter this normal pathway, e.g. some of the most severe of injuries, likely to require surgical intervention, may be transferred to the Neurosurgery Department at the Royal Hallamshire Hospital. However this is less

than 1% of all admitted head injuries [Sosin 1996, Smits 2010]. Similarly, a small number of individuals may be transferred to the care of a more relevant specialty, such as orthopaedics or Care of the Elderly for the frail elderly patients. This is particularly important in the case of patients with dementia or significant comorbidities/frailty that would be better managed by a Care of the Elderly Team. Similarly, if the primary problem for an individual is the management of orthopaedic injury, then it is appropriate for that patient to be transferred to orthopaedic care. Otherwise, patients remain under ED.

All patients who require admission are assessed with a CT head scan as stated in NICE guidance. After admission to the ED ward, these individuals are monitored including neurological observations for as long as required or as long as they remain on the ward. The majority of these patients are discharged within 24 hours after they have stabilised and no longer require neurological observation.

1.13.3 Role of the Neurorehabilitation Service

For many years, there was a growing awareness that the follow-up and coordination of TBI care was poorly organised or non-existent with no involvement of Rehabilitation Medicine specialists. This is surprising as the long term care of neurological rehabilitation patients is led by this specialty. Furthermore, it has been shown that appropriate TBI follow-up through rehabilitation services can improve a wide range of outcomes and decrease frequency of TBI symptoms [Wade 1997, Paniak 1998, Paniak 2000]. This led to the development of a new brain injury rehabilitation service in 2009 to coordinate the management of post-acute brain injury.

This Head Injury Pathway was developed by Sheffield Teaching Hospitals under the auspices jointly of Emergency Department, Neurosciences and Rehabilitation Medicine. A Rehabilitation Medicine Physician was appointed to lead on the post-acute management and follow-up of brain injury patients and recognised the importance of follow-up after TBI under the rehabilitation pathway [Singh 2012]. This individual (the lead investigator) had an academic interest in TBI and mood

disorders but was employed as a clinician. However, close clinical links with an Academic ED Department and daily working alongside ED colleagues, offered the clear opportunity to study a TBI population at the same time as designing a *de novo* TBI rehabilitation service with the appropriate assessment tools, investigations and clinical examination.

1.13.4 Brain Injury Clinic

A key part of the new service was the creation of a new Brain Injury clinic to follow up individuals admitted through ED. This was designed to review patients 8-10 weeks after injury to assess if there were any on-going problems from the TBI. The clinic was led by the lead investigator but also had the presence of a nurse specialist and links to long-term neurorehabilitation services in the community for therapy involvement. This was a clinical service designed to meet the needs of patients and had to be designed to fulfil this need with relevant assessment, investigations and treatment options. Over a number of months, the lead investigator identified the best system of organising the clinic and the assessment tools that could best identify problems faced by patients.

While this service was set up as a clinical service in the NHS Trust, this new clinic also offered an academic opportunity to study the incidence and features of TBI prospectively. While this comes with certain drawbacks in terms of the time that can be allotted to assessments and the burden this places on patients and clinicians, there were also considerable advantages. The main advantage is the ability to follow-up patients extensively on a clinical basis and to chase up follow-up appointments in individuals who fail to attend. As the attrition rate in TBI studies is extremely high [Corrigan 1997, Corrigan 2003] with up to 70% of individuals being lost by six months, this presented a profound advantage over many other studies. The involvement of senior renowned academics from ED (including both Supervisors) in parts of the clinical pathway was also seen as a distinct advantage in devising both a clinical pathway and research projects. Indeed this combination may be unique and certainly presented an opportunity to produce results relevant to a clinician's standpoint.

1.14 Summary

TBI and depression are both very common conditions causing considerable morbidity and it is known that depression, as a consequence of TBI, is common. Yet the incidence of this depression after TBI is unclear and the associations with clinical and assessment measures is poorly characterised in the literature. The Lead Investigator had a key clinical role in devising a new pathway including a new head injury follow-up clinic. While this was aimed at delivering a clinical service for patients it was clear that considerable opportunities for research could also be generated with the appropriate academic guidance and supervision. It was hoped that the results of any research would also help to shape the clinic in years to come and improve the service, both locally and as an example for others. The first step to link the separate arms of clinical and academic work was to set appropriate aims and objectives for a study looking at depression after TBI.

CHAPTER 2: RATIONALE AND AIMS FOR STUDY

2.1 Introduction

Despite the extensive body of literature on TBI and depression, it is still clear that there are extensive gaps in our knowledge of depression after TBI.

As discussed previously, even the rate of depression varies considerably between different studies due to the heterogeneity of study designs, populations examined and tools used. The only firm assertion that can be made is that the incidence of depression is increased after TBI although the magnitude of such a change is uncertain [Guillamendegui 2011].

In addition, analysis of the various injury and demographic factors that may be linked to the development of depression, has found little agreement between studies. Indeed, in many instances, diametrically opposite findings are found e.g. role of injury severity. As a result, it is difficult to make any firm conclusions about such associations and predict who is more likely to develop depression.

It therefore follows that there is clear scope for a large, well-designed TBI study to examine both the prevalence of depression as well as the factors that are associated with this risk and how this changes over time. As the prevalence of both conditions is very high and both cause significant morbidity, even a small change in our understanding of depression after TBI may have significant impact for society if it can lead to better recognition and management of depression. The worst social outcomes after TBI are usually recorded in those with psychological and behavioural disability [Bryant 2010, Rogers 2007]. The incentive for a clinician to effect such a change is a powerful motivator.

2.2 Opportunities

The new Head Injury Clinic presented a unique opportunity to study this topic in depth. The Clinic was set up by the lead investigator to treat and support adult TBI patients and therefore presented an opportunity to capture a consecutive cohort of individuals with TBI, admitted to hospital. This

population constituted a “real life” population in that it sought to capture all admissions with TBI including elderly patients. Most of the previous literature tends to study a highly selected group, filtered through various referral processes or chosen for convenience. The lead investigator had a background interest in TBI, had published in the field and was responsible for the assessment of all patients seen at the clinic. The availability of this single investigator to devise and execute the project was a strength in that it reduced the risk of inter-observer variability for clinic assessments. Perhaps the single most significant advantage of this clinical set up was the ability to follow-up patients and to expedite attendance of individuals who failed to attend the clinic. Arguably the single biggest weakness in TBI studies is the loss of individuals to follow-up which can be as high as 70% at six months [Corrigan 1997]. The ability to counteract this with appropriate follow-up arrangements is essential if valid conclusions are to be made and this study presented such an opportunity.

To the best of our knowledge, no previous study has yet been designed with these strengths; the selection of a “real life TBI” population, avoidance of selection bias, size of the prospective cohort, length of follow-up and minimising loss of individuals to follow-up. Therefore this presented a unique opportunity.

2.3 PICO

Setting the appropriate aims and objectives of any project involves using an accepted and standardised framework for asking the correct questions for study. In this instance defining these aims used the PICO approach [Schwardt 2007] which identifies the population (P), intervention, prognostic factor or exposure(I), comparison or control(C) and outcome(O).

This approach allows the setting of appropriate aims and objectives based on these four parameters. The population(P) of study is a TBI population encompassing the full spectrum and various aetiologies of the condition to provide as representative a sample of this condition and the people who suffer it. While there is no intervention(I) in this study, the prognostic factors can be

considered as a number of different demographic and injury features which may alter the likelihood of developing depression. There is no control group (C) but comparison of the overall prevalence can be made with the background population rate as defined in a number of community studies [Blazer 1994, Kessler 2003].

Finally, the outcome(O) is the presence of depression. A number of other secondary outcomes can be considered, such as a global outcome of overall function, a participation/handicap score and a symptom score. In a clinical service, the measure of a few key outcomes such as these is important in order to show effectiveness.

Having identified these four questions, the aims and objectives of the project could be defined as follows:-

2.4 Aims

Based on the findings of the literature review and previously established research, it was possible to identify the gaps in our knowledge in this field. These include an accurate prevalence of depression and the key features that are associated with it.

1. To undertake a literature review of TBI and depression.
2. To undertake a prospective cohort study of individuals with TBI, followed up over a year and to calculate the prevalence of depression at 10 weeks and at 1 year
3. To identify the demographic and injury features that may predict an increased risk of depression, particularly severity of injury

2.5 Objectives

The means, by which these aims are achieved, constitute the objectives of the project. These are:-

1. To undertake a comprehensive literature review, identifying gaps in current knowledge and hence to guide the design of an appropriate study.
2. To recruit a consecutive cohort of patients with a range of TBI severity and aetiologies who are admitted to hospital after attendance at a large teaching hospital ED.
3. To follow-up this cohort of TBI patients for twelve months and calculate the prevalence of depression in the group using appropriate measures of depression and how this prevalence changes.
4. To document the demographic and injury features of the TBI at initial injury and follow-up using appropriate statistical approaches in order to identify predictors of subsequent new depression.

The next step in the project was to design and carry out a literature review with these aims and objectives in mind.

CHAPTER 3: LITERATURE REVIEW

3.1 Introduction

From background reading and personal research interests, it had already been established that the thesis would examine the prevalence of depression after TBI, particularly the changes and evolution within the first year after injury.

As discussed in the Introduction, it was known that there is already a substantial body of literature on the subject of depression after TBI, encompassing wide and varied aspects of both conditions. Some studies have looked at prevalence alone; others have included an examination of various demographic features associated with TBI. These features may include particular injury characteristics or specific social or psychological features of the individual e.g. social isolation, personality traits, treatment modalities, functional outcome after TBI or an evaluation of the diagnostic tools that may be used to measure depression itself. A further consideration is that there is considerable variation in the literature between study designs and the TBI populations that have been examined.

It was therefore clear that the design of this study would have to take full account of this body of previous work and to rectify the deficiencies of previous studies. In this way it was hoped to improve on much of the previous research and therefore provide new findings that would be relevant to clinicians working in the field of TBI.

The first step in this process involved conducting a literature review of the field. This chapter describes the methods used in conducting the literature search and review, with particular regards to the search terms that were used and the databases that were interrogated.

The relevant literature is also discussed briefly with regards to the state of knowledge to date and the implications for the aims and design of this study.

The original search was carried out in June 2012 and the papers then reviewed to assess if they were appropriate to the area under study.

In addition, search updates were set up to ensure that monthly alerts were forwarded by email and additional new papers were found. A further six studies were added in this way in years after 2012. The question that needed to be addressed by the literature review can be phrased as follows-

Q. *What is the prevalence of depression after TBI and how does this evolve over the first year after injury?*

In addition, it was also important to examine the patient or injury features that are associated with a risk of depression e.g. TBI severity, mechanism of injury, age, gender, previous illnesses including psychiatric history, social isolation, neuroanatomical location of brain lesions. It was known that the same key papers that examined prevalence would also have included a number of features such as any of the above. These associated factors often play a key role in the population that the researchers recruit into the study as well as the measurements and study design that is used. For example, studies looking at various psychiatric manifestations of TBI may use a war veterans group. The literature review needed to look at these details in order to decide on the features that should be examined in the study alongside depression.

From general reading around the topic during the course of the investigator's working life, a number of key papers were already well known as well as some of the key researchers across the globe. There were also monthly e-alerts from each of the major journals in which references were found in the initial search e.g. *Brain Injury, Journal of Head Trauma and Rehabilitation*. This allowed regular updates on relevant topics.

Attendance at national and international meetings brought the investigator into contact with other researchers who were working in either the area of TBI and psychiatric conditions or in TBI outcome. This led to further ideas around development of the research question particularly in terms of population selection and the study tools to be used.

3.2 Search Structure

3.2.1 Inclusion/exclusion Criteria

The inclusion criteria were geared towards capturing the papers related to answering the key question above. The aim was to capture all relevant papers and therefore the initial searches were designed with very wide criteria in order to capture as many papers as possible for later manual sifting. This “broad-brush” approach undoubtedly led to a very large number of initial papers being included. As there are so many publications pertaining to TBI and a large number of journals which may publish such articles, it was important to cast a wide net. The same is true of depression. This obviously required a great deal of results sifting afterwards. However this was considered to be the best way to ensure that all relevant papers would be found.

It was decided to look at all studies in adults over or including the age of 16. There is a considerable body of paediatric and adult literature that covers the needs and nature of TBI in children and adolescents. Much of this literature considers that the impact of TBI in a young and developing brain is quite different to that in adults and therefore sequelae such as depression may be very different. This study was aimed at an adult population with the aim of making suggestions relevant to that population only. For this reason, it was decided to exclude papers looking at non-adult populations. By contrast, there were no exclusions at the upper age group; it is well known that there is a peak of TBI incidence associated with the elderly population and many patients seen in everyday practice, constitute this population. It was therefore entirely reasonable to include all adults in the study. Indeed one criticism of much of the TBI literature is that it is heavily biased towards younger individuals and that the elderly are often excluded. It was important to reflect the population that increasingly sustain TBI and hence elderly patients were a particular interest in this study.

All countries of origin were included but papers had to be available in English in order to facilitate assessment of the study. It was felt that it was unlikely that there would be many papers that were

not written in English given the background knowledge of the field and the researchers who had a published track record.

Studies had to contain a clearly defined TBI population with a definition of how TBI was diagnosed. Given the difficulties with TBI definition, it was clear that the definition and classification used to identify TBI would have an impact on the prevalence of the condition. These differences in classification were discussed at length in the *Introduction*. Studies with well documented evidence of TBI using accepted criteria were clearly preferable. However in instances where individual self-report of TBI was used, this was made clear for evaluation of the quality of the studies (Table A1.2, appendix 1)

Similarly, studies also required a clear description and definition of how depression was recognised e.g. a validated diagnostic tool. There is considerable variation in the tools that may be used in the diagnosis of depression. This is considered in detail in the Methods chapter. For each study, the quality of the tools used to assess depression, were reflected in the evaluation of the study quality itself (Table A1.2, appendix 1)

Included study designs consisted of a wide range of study types including randomised controlled trials, cohort studies and case series. Case reports were excluded. There was no lower limit to study size although it was known that many of the early studies are quite small in numbers. It was felt that limiting study size, would exclude many studies. However larger studies would clearly rate more highly in evaluation of quality provided that their bias likelihood was low.

In terms of the date restrictions, the widest possible database selections were made. This meant that the earliest possible dates for each database was taken as the start point e.g. for MEDLINE, the earliest availability is 1946. Updates from the search strategies were then set up to ensure any further studies were picked up after the initial search.

The key inclusion/exclusion criteria used in the searches can be summarised-

- Any date of publication
- Human subjects only
- All article types
- English language only
- Adult subjects

3.2.2 Databases

The databases that were interrogated were MEDLINE/OVID, the PsychINFO database of psychological or psychiatric literature, Embase and the Cumulative Index of Nursing and Allied Health Literature (CINAHL).

3.2.3 Search Terms

There is some difference in the subject headings or descriptor terms (called MeSH or Medical Subject Headings) that are used between the different databases. It was possible to map the areas that we were examining i.e. depression and TBI to the appropriate MeSH headings in MEDLINE. However in some of the other databases, the subject headings are classed differently and had to be mapped onto different heading as appropriate e.g. TBI is subject mapped by MEDLINE to "Craniocerebral trauma" but to "TBI" in PsychINFO.

Similarly TBI is classed by some papers as "concussion" or "head injury" or "neurotrauma".

The same situation arises with defining depression. This can be described in a number of different ways apart from "depression" e.g. "mood disorders", "affective disorders" or "depressive illness".

It was therefore necessary to use text words for each database as well as truncated stems to incorporate plural terms e.g. injury/injuries.

Each search therefore had to be conducted carefully with assistance from ScHARR library staff to extract the maximum number of references although the database itself helps to map the terms that are searched for into the appropriate medical headings.

MEDLINE was interrogated from the earliest available collection (1946) up to the present day. PsychINFO was similarly interrogated with the largest data set from 1806 to present day. CINAHL has files from 1981 and has the added attraction of being able to exclude titles that are already found in MEDLINE.

3.2.4 Searches

The searches within the different databases are shown below-

3.2.4.1. Medline/OVID

1	brain injury.mp. or exp Brain Injuries/	61492
2	brain injur$.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] or neurotrauma.mp	57499
3	1 or 2	62818
4	head injury.mp. or exp Craniocerebral Trauma/	124274
5	3 or 4	136173
6	exp Depressive Disorders/ or sadness.mp.	177273
7	exp Depression/ or depression.mp.	261164
8	mood.mp. or exp Affect/	66985
9	mood disorders.mp. or exp Mood Disorders/	118646
10	6 or 7 or 8 or 9	458597
11	**5 and 10**	3749

3.2.4.2. PsychINFO

1	exp Head Injuries/ or exp Traumatic Brain Injury/	121688
2	exp Affective Disorders/	115722
3	Depressive.mp or sad.mp or hopeless.mp or sadness.mp/	85837
4	exp Depression Emotion/ or exp Hopelessness/ or exp Sadness/ or exp Suicidal Ideation/	119298
5	2 or 3 or 4	218641
6	**1 and 5**	1598

3.2.4.3. Embase

1	head injury/ or brain contusion/ or diffuse axonal injury/ or traumatic brain injury/ or ("craniocerebral trauma" or "brain trauma" or "head trauma" or TBI or "traumatic brain injury" or "traumatic brain injuries").ab. or ("craniocerebral trauma" or "brain trauma" or "head trauma" or TBI or "traumatic brain injury" or "traumatic head injury" or "traumatic brain injuries" or "traumatic head injuries").ti	12180
2	mental disease/ or mood disorder/ or depression/ or major depression/ or suicidal ideation/ or hopelessness/ or (depressive or sad or sadness or hopeless).ti. or (depressive or sad or sadness or hopeless).ab	92309
3	**1 and 2**	408

3.2.4.4. CINAHL

1	("traumatic brain injury") or (MH "Brain Injuries+") OR "neurotrauma" OR "brain injuries" OR "TBI" OR "concussion" OR "head injuries" OR "head injury" OR "head trauma" OR "brain trauma"	14041
2	((MH "Depression+") OR "depressive disorder" OR "sadness" OR "depressed" OR (MH "Suicide") or (MH "Suicide, Attempted") or (MH "Suicidal Ideation") OR "suicide" OR "hopelessness" or (MH "Hopelessness") OR "mood")	40193
3	**1 and 2**	421
4	**3 and Exclude Medline Records**	145

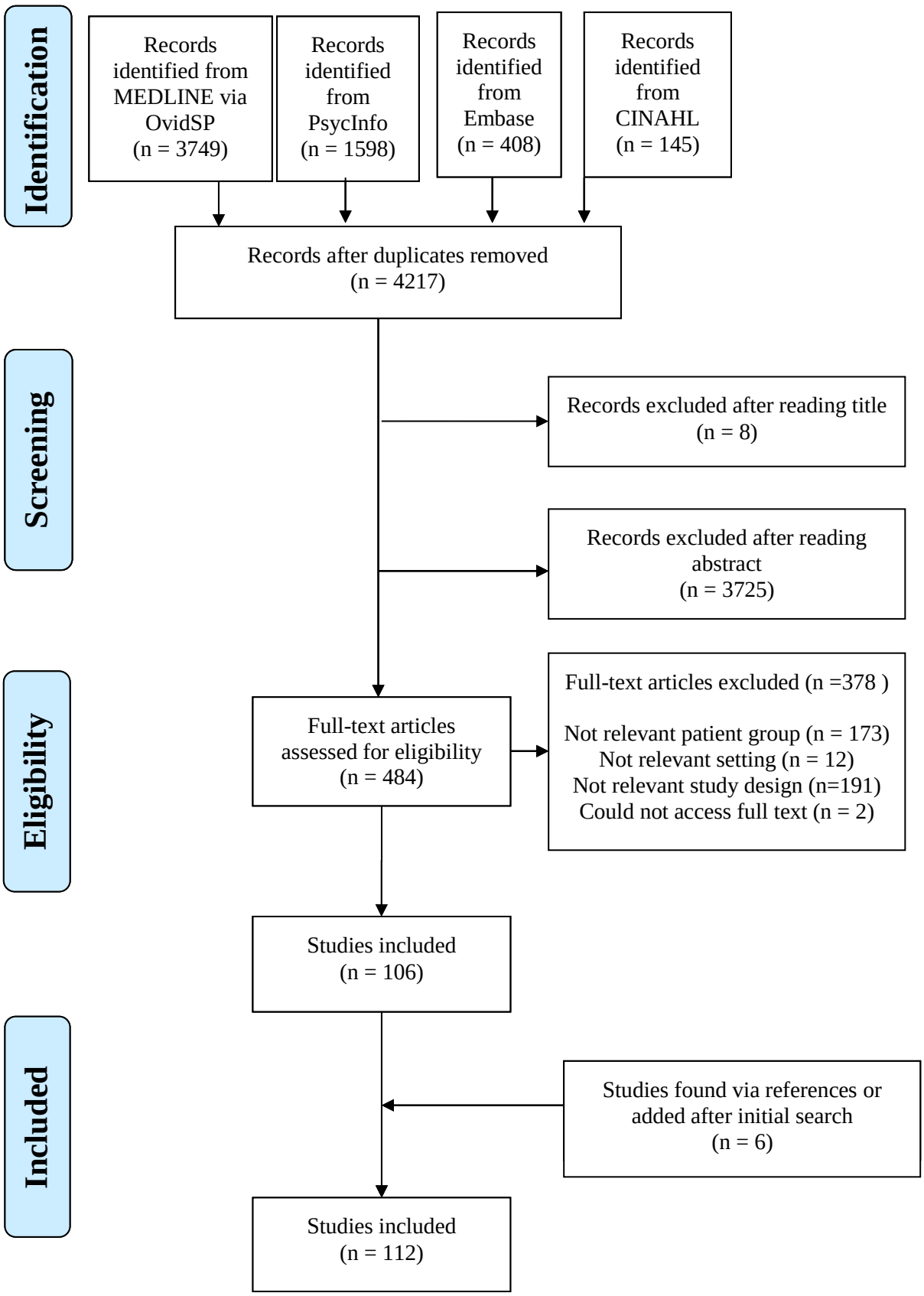
3.3 Results

3.3.1 Screening of search results

This search strategy elicited a very large number of papers as can be seen. The distribution of these is shown in the accompanying PRISMA diagram below (Figure 3.1). Over a period of several months, these abstracts were read by the author. Those with no abstract were judged by their title. Any papers considered to be of interest, were then requested or sought via electronic resources at the University of Sheffield. Most papers were not relevant and looked at areas not directly linked to the areas of study. Others had a cursory reference to the main search terms. From the initial 4217 abstracts that were found in the combined searches after removal of duplicates, 484 full text articles were then examined.

Only some of these papers specifically looked at the field of depression after TBI but many had interesting observations or had looked at predictive factors for TBI in general or the ways in which outcomes are measured or the tools used to measure depression. Some of these were therefore relevant to the study or for the discussion section and were kept but not as part of the formal literature review which had a clear goal in mind, namely the prevalence of depression and the features associated with it.

Figure 3.1: PRISMA chart for literature review



This strategy resulted in a total of 106 relevant studies being selected for the review i.e. studies which measured a prevalence of depression in a TBI population. A further six were then identified over the next two years from journal alerts as studies that were only published after the initial literature search of 2012. This resulted in a total of 112 studies in the literature review.
This is more than would usually be found in a literature review. The wide search terms that were used, combined with the very significant number of individuals who sustain either of these two diagnoses, always meant that it was likely that there would be many papers found. This was compounded by the decision to use wide ranging inclusion criteria such as self-report of TBI or self-assessment scales for depression diagnosis.

3.3.2 Summary of Studies

These papers are shown in table A1.1 in Appendix 1.
These are the most important papers for direct comparison with this study and the discussion of these studies should be made with reference to this Table. In very broad terms and at some risk of over-generalisation, many studies are quite old and limited in the number of subjects as well as unclear as to how the subjects were recruited. In recent years however, there have been a number of high-quality studies that are also discussed; the most important of these come from the TBI Model Systems in the USA and some recent Scandinavian studies (see appendix 1). This became apparent when studies were evaluated for quality.

3.4 Evaluation of Study Quality

Studies were assessed for quality based on the Critical Appraisal Skills Programme (CASP) checklist for evaluation [CASP 2013]. This appraisal tool is designed for evaluating descriptive or cross-sectional studies and was set up using JAMA criteria for evaluating research [Oxman 1994, Sackett 1996]. It comprises 11 key questions to guide quality assessment and each study is graded on these

criteria. From this, studies can be classified into 4 standards of quality, ranging from Poor to Very Good.

The quality of studies was 22 (19.6%) good, 60 (53.6%) average, and 28 (25%) poor. Only two were considered as very good, highlighting the difficulty of conducting a high quality study in this difficult field. Most of the literature is cross-sectional, the populations are often unclear and losses to follow-up are high in many of the studies. This is shown in Table A1.2 in appendix 1. The 11 key questions are also included in Appendix 2.

3.5 Discussion of literature

These 112 papers constitute a considerable number of studies of different sizes and design and have looked at different aspects of TBI or depression. After reading the papers in depth, it was possible to describe eight key areas in which the study findings and variations in study design can be discussed; these are listed below. This is not an evaluation of the *quality* of each study which was described in 3.4.

These areas are-

a. change in prevalence of depression over time
b. size of the study
c. definition of the group studied and how it was recruited
d. definition and severity of the condition (TBI) under study in the group
e. screening of cases/exclusions
f. measurement tools used to identify cases of depression
g. study design
h. time since injury
i. other aims of the study

3.5.1 Prevalence of depression

This was a key aim of the thesis. The prevalence of depression differed considerably between studies with a range of 11-77%. This is an extremely wide range that emphasises the difference in studies and which is not particularly helpful to clinicians, policy makers or TBI patients.

It is however possible to say with confidence, that after TBI, the prevalence of depression is elevated compared to the background population rate [Blazer 1994, Kessler 2003]. All but one study found an increased risk although the levels varied considerably. This was demonstrated in studies that used a control population either within the study or refer to the background rate of depression in the local population [Koponen 2006]. A number of other studies have used individuals with trauma but without head injury as a control group who would be similar to the TBI group in most other ways. In almost all of these, there was a lower rate of depression than the TBI group with two exceptions [Bryant 2010, Frenisy 2006].

The only study that found no increased risk was that of Koponen 2005 who reported a similar rate to the control population (5.8%). This is at odds with all the other studies; even their own study from the following year had an elevated rate of 24% post TBI depression [Koponen 2006]. It is unclear from their paper how they explain this finding and it is best to consider this an outlier study.

The average prevalence across the 112 studies was calculated. The mean was 36.7%(SD 15.0) and the median (range) was 35(11-77). A review of the topic which found a similar number of studies [Guillamendegui 2011] calculated a weighted average across all studies of 32% which is similar although this review seemed to give extra weight to studies that repeatedly measured depression over a number of time points. These figures give a sense of the size of effect that may be expected.

3.5.2 Time course

The time course of depression is unclear from the literature. Some studies show a very slight decrease in the rate of depression over time or maintenance at the same elevated level [Gomez 1997, Powell 2002]. However several studies have shown an increasing rate of depression with time after follow-up [Franulic 2004]. One study found high levels of depression some 30 years after TBI [Koponen 2006] and a study of World War 2 veterans, found that even 50 years after self-reported TBI, individuals carried a higher risk of depressive episodes than non-injured veterans [Holsinger 2002].

It was therefore a key aim of the study, to determine how the prevalence changed over a year. It was hoped that this may clarify some of the uncertainty around the temporal relationship of depression.

3.5.3 Size of study

Studies vary considerably in size from 18 to 1089 cases. The mean size was 148.3 (SD164.8) and median 91(range 18-1089, IQR104) It seems reasonable that larger studies are more likely to give statistically valid prevalence rates enabling more reliable conclusions to be drawn. At the same time, a well-designed but relatively small, representative prospective study can offer better value than a heterogeneous, cross-sectional convenience study with no clear definitions or vague assessment measures. In crude terms, the art of designing and recruiting a well-defined group to study and persevering with follow-up can often yield better results than a retrospective trawl through an extant database no matter how many cases one may acquire by this method.

Some of the studies are particularly noteworthy for their size including 1089 followed up by phone [Hart 2012] or 559 and 666 subjects [Bombardier 2006, Seel 2003]. However many other studies are extremely small; this is a particular problem for examining the features which may or may not be associated with depression, e.g. one study only has 14 individuals remaining at the end of the study

[McNiven 1993]. This makes it almost impossible to analyse any associated features on the depressed individuals with any sense of statistical confidence.

3.5.4 Recruitment

TBI constitutes a wide spectrum of severities and causes. It is therefore very important to consider the population of TBI individuals that is studied and how they were recruited to the study. In this regard, many studies poorly describe the TBI population that they have studied and how these individuals were recruited. In some instances the methods state that this was a "convenience" sample [Bay 2006, Peleg 2009]. Others describe "referrals from a variety of sources". [Mooney 2005, 2006] One paper [Ashman 2004] used volunteers from a brain injury support group and ran adverts in clinics in order to recruit. Others are even less forthcoming as to how patients were recruited e.g. which clinics or inpatient units made up the individuals and perhaps quite significantly, how individuals were excluded or omitted from studies. It is well established that TBI populations are difficult to follow-up and there is a very high rate of attrition in TBI studies; [Corrigan 2003, Ruttan 2008] there is a risk that the recruitment and follow-up of young, socially mobile individuals may be much harder and the population being studied is therefore not reflective of the true population or TBI rates. A number of studies give the differences in demographics between those who are successfully followed up and those who are lost to review. Often, this shows that the lost population is younger or has more psychiatric conditions or alcohol intake than may be expected. This emphasises the difficulty faced by TBI studies to attain representative populations and successful follow up.

Some studies examine a very specific population group of TBI. For example, three studies only used war veterans [Holsinger 2002, Hoge 2008, Mollica 2009]. The last of these was unique in that it looked at victims of torture in South Vietnam. Examining the methods of papers often reveals that a very select population has been recruited. Some studies have very high rates of RTC (Road Traffic Collision) e.g. 76% [Rao 2008] or previous psychiatric conditions at 52% [Rao 2009]. Another had

100% of recruits derived from tertiary referrals for psychiatric advice [Merskey 1972]. At the other extreme, some studies exclude all individuals with any previous psychiatric illness. This leads to significant difference between studied populations and makes comparison difficult. Another study contained many individuals with litigation cases while another specifically excluded all such cases for fear that it would affect the diagnosis of depression. It is clear that many differences exist across the studies.

Another reason for variation between studies is that the aims of the researchers vary considerably; this will affect the population that they recruit. Some studies were clearly designed to look at the prevalence of depression perhaps with some associated features as well, while others were part of studies looking at interventions with a drug, e.g. an antidepressant. Intervention studies may be more geared towards recruiting more severe cases in order to maximise the chance of finding intervention efficacy. Others were part of larger projects looking at other psychiatric conditions, such as PTSD [Bombardier 2010, Hoge 2008]. This is likely to lead to specific selection of a population that meets the aims of the specific project rather than representing TBI as a whole e.g. use of war veterans.

A particular cause for concern is that many studies seem to be quite biased with regard to older patients. The mean ages in several studies are young (<40 years) and the aetiology of injury is usually from RTC or assault. Some even specify that the recruitment is under a specified age. All of these will limit the number of older TBI patients that are studied. Given the ageing of the population and the high incidence of TBI in the elderly mainly caused by falls, this represents a significant gap in the literature.

This wide variation in the populations studied and recruited, has implications in terms of the conclusions that may be drawn and comparisons that can be made with the wider population e.g. findings in a population of TBI from RTC may not be relevant or at best, difficult to extrapolate to the wider group with TBI, particularly the elderly.

3.5.5 Defining condition and severity

TBI can be defined in a number of ways, much of which has been discussed in the *Introduction*. Many studies are very precise in how TBI was defined with particular regards to accepted definitions such as ACRM, WHO and CDC which are the main standards used across the literature. There is some variation in the definitions for MTBI and it is useful that many prospective studies clearly define the subjects. Other studies, particularly cross-sectional studies, many years after injury usually depend on self-report by the individual which is notoriously unreliable [Mollica 2009, Holsinger 2002]. In the Mollica study, individuals were simply asked if they had ever had a head injury and as they had all escaped war in South-east Asia, it is unclear how reliable such reporting is likely to be. The reliability of self-reported symptoms is known to diminish with time and it is therefore difficult to validate such self-reports that are more than 40 years after the event. In general the prospective studies define the condition of TBI more rigorously than the cross-sectional.

Some studies only included individuals with moderate or severe injuries; others only with mild TBI. A number of studies commented on the fact that MTBI constitutes at least 85% of all TBI and therefore they did not include such cases in their study population. Some studies only included MTBI with a positive CT scan which is often called Complicated MTBI and postulate that these cases are more significant than those with a normal CT scan. One study excluded individuals with all comorbidities [Ghaffar 2006]. This seems unusual given that so many elderly TBI individuals have significant comorbidities. It would be a reasonable aim to devise a study that incorporates such patients to at least some extent.

Some studies describe a very long length of stay in hospital e.g. 35 and 42 days. [Seel 2003, Whelan-Goodinson 2008]. This suggests that the study population was largely constituted of STBI. Many individuals at the milder end of the spectrum would stay overnight or indeed be discharged the same day. This actually constitutes the bulk of admissions with TBI and it would be helpful to include this group as well, rather than only STBI.

The problem with such selective populations is that it is difficult to extrapolate and make generalisations across the whole TBI population. This was particularly important in this study where it was hoped that the findings would be very relevant to daily medical practice and include all adult patients with TBI encompassing the whole range of severity and length of stay including overnight or 1-2 days, not just those with prolonged hospital spells.

3.5.6 Screening

A weakness in some studies is that many of them seem to have screened a very large number of cases, compared to the number that then emerge in the final study, e.g. one study screened 1477 individuals for an initial population of 437 [Bryant 2010]. Another screened 4618 down to 384 [Hoge 2008]. This again introduces a high degree of selection bias as individuals are excluded for one reason or another. In some cases, it is explained that some individuals declined to enter or were lost to follow-up but in some instances, there is no clear indication as to why some are included in the study and such large numbers filtered out. The suspicion remains that such extensive filtering results in a selected population who may be more likely to attend clinic, comply with the detailed assessments required and in general are more compliant for want of a better description. It is difficult to make generalisations from such select groups. To their credit, a few studies do report on the differences between those "screened out" compared to those in the study which shows an openness to scrutiny [Sigurdardottir 2013].

3.5.7 Measurement Tools Used

As with the definitions for TBI, there was considerable difference between studies as to how they identified cases of depression. This requires more extensive discussion in the chapter on Methods (Chapter 4).

Some of the papers compared more than one depression measurement tool and in general it is reassuring that similar rates seem to have been found. It would be a matter of some concern that different tools may yield very differing rates. On face value it is very reassuring that similar rates of depression were found with SCID (Structured Clinical interview for DSM) and CES (Center for Epidemiologic Studies) [Brown 2004] and for HADS and SCID [Al-Adawi 2007]. Another found that three different measures all yielded very similar rates [Bay 2008].

In general, it does not seem that the level of depression depends heavily on the assessment tool that is used. The widely accepted gold standard tool to assess depression is the SCID and some may be concerned that other tools may have a high level of false negatives. Yet this concern is not born out. The SCID was the tool used in both the lowest yielding study and the highest rate that was found suggesting that it is prone to a similar amount of variation.

A calculation was made to determine whether there was a difference between SCID based studies and other methods of diagnosis. The mean prevalence across SCID studies was 38.1(SD14.8) while all other methods resulted in a mean of 35.3(SD15.0). Furthermore the lowest and highest prevalence were both in SCID studies. It is clear that the prevalence does not seem to depend on the method of assessment and there is no evidence that self-report or questionnaires result in higher prevalence of depression.

The differences between these various assessment tools for depression will be discussed in the next chapter.

3.5.8 Study Design

Apart from the differences in the TBI recruited population, perhaps the biggest difference between studies is the nature of the study design. In general, prospective cohort studies are better regarded in science for the quality of the output rather than cross sectional studies that examine an incidence or condition at only one time point. Prospective studies usually have a better defined population, less prone to bias of sampling or recruitment. Many of the cross-sectional studies are unclear on the

details of patient recruitment or TBI severity as has been previously discussed. It is surprising that so many studies seem to omit quite significant information such as the severity of injury across the group or the time elapsed since injury. Some studies quote an average GCS score or average time since injury which is insufficient information to describe the cohort. Some describe the way in which the study group was recruited in very vague terms e.g. “a variety of sources” or a “convenience sample”. This is no substitute for a systematic recruitment such as consecutive admissions or referrals and there is considerable scope for bias in such methods. The prospective studies of Hart 2012, Bombardier 2010 and Bryant 2010 are all good examples of well-structured high quality studies using consecutive admissions rather than referrals. The largest of all the studies used a multi-centre design with 19 facilities contributing cases. Multi-centre studies are more highly regarded as they tend to dilute the potential bias that may arise from a single centre that has a skewed population for one reason or another e.g. near a university or factory.

Another study prospectively studied a large population group repeatedly over one year with multiple measures [Bombardier 2010]. This is an important study which shows that levels of depression are high and remain so over a year with repeated measurement. Over half of the group had depression at some point during this time period.

The problem with prospective studies however is the loss of individuals to follow-up. This is a particularly marked issue in TBI where it is well known that attrition rates can be up to 90% at one year [Corrigan 1997, Ruttan 2008]. Indeed, in some of the studies in the table, losses of up to 70% [Hawley 2008] were found. Some of the studies point out that the patients lost to follow-up are a different group when compared to the population who are successfully followed up. It is not surprising that problems such as substance abuse, prior psychiatric history, age and gender are often differently distributed in these two groups and it is to the credit of those studies that point out this difficulty in their papers.

Nevertheless, it is possible to manage effective follow-up. One study managed to follow up all 34 patients successfully although this is a very small study [Dunlop 1991].

3.5.9 Time since Injury

The studies differ considerably in terms of the time that has elapsed since the injury. In fact, some studies themselves have a very wide range with three months to eleven years in one study [Fann 1995, Dahm 2013]. This leads to further heterogeneity in the population that is being studied. There is a considerable body of literature which holds that the immediate aftermath of TBI is dominated by population, demographic and injury features whereas later problems are dominated by psychosocial features of that individual rather than injury characteristics. Many hold that the two time periods should be treated quite differently. This would be an argument for trying to confine the study group to a specified narrow time span since the time of injury in order to diminish this particular effect. Many of the studies have tried to study a group shortly after injury or within a specified time span since injury for precisely this reason. Most of the higher quality papers have recruited consecutive, new patients after TBI and followed them up, thus producing more systematic groups to draw conclusions from. It is difficult to do this when the time since injury can vary so much across one group.

The most common time course across those studies which study TBI from diagnosis, is 1-2 years of follow-up. A few long-term outcome studies exist but often with very variable times since injury, making the study groups, quite heterogeneous.

3.6 Associated Risk Factors for depression

The secondary aim of the study was to look at the injury or demographic features that may be related to the risk of depression in the TBI population. A large number of the studies in the final review, have also examined various demographic and injury features to assess higher risk of depression. These include variables such as age, gender, mechanism of injury, neuroanatomical areas of injury, previous illnesses and comorbidities. In general, it is difficult to discern any clear consistency of finding from this body of literature and reviews have made this same observation

[Rosenthal 1998]. However a brief discussion of this literature is relevant. This will also be examined in the *Discussion* with specific reference to the thesis findings so that comparisons can be made.

3.6.1 Severity of TBI

There is considerable difference between studies as to whether severity of injury affects the risk of depression. The review by Guillamondegui 2011 found that the overall prevalence of depression was 20.3% in those with mild or mild/moderate TBI compared to 32.5% in studies that enrolled or followed up populations of all severity. However this was a synthesis of all existing studies rather than a direct comparison.

Studies that found a difference between levels of TBI severity included Jorge 1993b, Lezak 1987, Homaifar 2009. Van Reekum 1996 found an inverse relationship with higher levels of depression in those with mild TBI. Others have also made similar findings [Hudak 2012, Homaifar 2009]. This may at first glance, seem counter-intuitive; it may be expected that more severe TBI with a wider range of impairments and disabilities, may lead to a higher risk of depression. It has been found that STBI is more likely to cause poor self-awareness of an individual's impairments when compared to those with milder injury [Ownsworth 2011]. This poor self-awareness may in turn, lead to less reporting of psychological distress [Moldover 2004]. It is postulated that as awareness of the problems that one faces, increases, the risk of developing depression also increases.

In contrast however, many studies have found no link to severity of TBI. Mollica assessed GCS scores, coma length, and duration of post-traumatic amnesia; none of these factors were associated with depression or its severity [Mollica 2009]. Similarly, others have found no link to TBI severity [Brooks 1983, O'Carroll 1991, Bowen 1999, Kreutzer 2001, Seel 2003, Dikmen 2004, Hoge 2008, Bombardier 2010, Malec 2010].

The Injury Severity Score also showed no association between severity and prevalence of depression [Bryant 2010].

In general the difficulty faced by many studies, is that they do not possess an adequate mix of TBI cases of all severities. Most studies have a focus on MTBI or on moderate-severe TBI and this limits their ability to draw such comparisons. There are too few studies with a sufficient mix of those with mild, moderate and/or severe injuries to make valid severity-based estimates of prevalence. Several studies concentrate on only severe or moderate injury. Other studies have excluded many patient groups such as normal CT findings. This seems evident in the level of patients that are screened out in several studies. Such limitations make it difficult to comment on the full range of TBI severity within any one study. It was hoped that in this study, it would be possible to recruit a large number of cases from across the spectrum of TBI and make valid comparisons between them.

3.6.2 Age

Age was reported in one of the largest cohort studies, to be an independent risk factor for depression among both those without prior depression and those with prior episodes [Bombardier 2010]. In this study, which reflected the full spectrum of severity of TBI, risk decreased with increasing age, such that those aged 60 and older were at lowest risk. Similarly others have reported an inverse relation to age [Dikmen 2004, Hart 2012]. All of these were large, significant studies and the authors speculate on the reasons why increased age may protect against depression.
Another study however found the opposite [Levin 2005]. They found that when age was grouped with other factors, the combination of older age at injury, CT scan with documented intracranial lesion, and higher 1-week CES-D scores, were sensitive (93%) though not specific (62%) for identifying those with mild TBI who were depressed by 3 months after their injury. Sigurdardottir also found an increased risk of depression with age while Seel found no link. In other words, three of the highest quality papers [Seel 2003, Hart 2012, Sigurdardottir 2013] have all found different associations between age and depression.

3.6.3 Gender

Women have been reported to have a higher risk of depression after TBI. Bombardier 2010 again reported a higher risk (relative risk [RR] = 1.27; 95% confidence interval [CI]: 1.07, 1.52) of new but not recurrent depression after TBI after adjusting for other risk factors. Other studies report a similar higher incidence in women [Whelan-Goodinson 2008, Levin 1978]

By contrast, one study reported a higher risk in men [Burton 1988].

Most studies however report no gender difference [Hart 2012]. In general most studies had fewer women than men in keeping with the population incidence affected by TBI.

3.6.4 Mechanism of Injury

TBI can be caused by a number of different mechanisms such as falls, road traffic collisions (RTC) or assault. It would seem intuitive that those subjected to a violent mechanism such as assault may be more prone to develop depression than those with a simple fall. However no studies have elicited such a link and some report that there is no association [Hudak 2012, Bombardier 2010]. Indeed, one study actually found a negative association with violent mechanism and depression [Glenn 2011].

A link between violence and PTSD has been noted [Bombardier 2010] and a number of studies report a high cross-over between those with both depression and PTSD. A number of studies have looked at depression as part of a study looking at other psychiatric conditions including PTSD or in psychiatric conditions in war veterans [Bombardier 2010, Hoge 2008].

3.6.5 Substance Misuse including Alcohol

A past history of alcohol and substance abuse increases risk according to a number of reports [Dunlop 1991, Holsinger 2002, Rapaport 2003, Dikmen 2004, Bombardier 2010, Hart 2012]. In some of these studies it was the single largest factor in risk of later depression. Several authors noted that

obtaining an accurate history of alcohol is difficult and can be inaccurate. It was also noted that there is a difference between chronic alcohol misuse and those individuals who may have drunk excessively at the time of the TBI only although many if not most of the latter group will also belong in the former. By contrast to other studies, Koponen 2011 reported a *lower* incidence of substance misuse in the depressed group after TBI.

3.6.6 Litigation, pain and fatigue

There is a very substantial body of literature that looks at the role of litigation and psychiatric morbidity. However in terms of the papers identified in this literature review, pain, involvement in litigation related to the injury, and perceived stress have all been reported as risk factors for depression in prospective cohorts [Shretein 2003, Iverson 2005, Bay 2008, Bryant 2010]

The presence of pain is also reflected in higher incidence of depression [Hibbard 2004, Mooney 2005, Bay 2008, Sullivan-Singh 2014].

Fatigue has been reported to not increase the risk of depression [Donders 2001, Oullet 2006].

3.6.7 Social Isolation

It is very difficult to measure the degree of social isolation and there are a wide range of questionnaires that assess a range of similar measures including social ties, loneliness and friendships. Very few studies have looked at the degree of psychosocial support available to individuals with TBI although considerable numbers of studies contain data from caregivers, partners, and family members. Out of those few models that incorporated social isolation items, one group reported that availability of a confidant reduced the risk of depression [Bryant 2010] and another that years married were inversely related to risk, while presence and degree of cognitive disability, motor disability, and social aggression elevated risk [Linn 1994] A study that used the

Friendship Scale, found an inverse link between friends and depression [Hawthorne 2009]. A much higher incidence of divorce was noted in the depressed group [Hoofien 2001].

A few of the studies also looked at the prevalence of depression in relatives which was reported as considerably elevated to the normal populations [Linn 1994, Lima 2008, O'Carroll 2011, Bombardier 2010] and in some cases even equivalent to that of the TBI group [Marsh 2006].

3.6.8 Personality Traits

None of these key 112 studies have examined concepts of personality or resilience; however scores on the Adult Hope Scale and the Life Orientation Test-Revised, a measure of dispositional optimism, have both been found to contribute independently to predicting depression and its severity [Peleg 2009].

The traditional role of learned helplessness in raising depression risk as well as the concept of loss of locus of control have been reported to increase depression risk by Seligman and Moore [1992].

Some studies have tried to look at the concept of stress after TBI and reported that those scoring highly on perceived stress have higher rates of depression [Ownsworth 2008, Bay 2008].

3.6.9 Previous psychiatric illness

A number of studies included information on the prevalence of previous psychiatric conditions [Jorge 1993, Fann 1995, Hibbard 2004, Jorge 2004, Whelan-Goodinson 2009, Bombardier 2010]. In most of these, a previous history of substance abuse, anxiety disorder, bipolar or psychotic illness, increased the risk of subsequent depression.

With regards to a previous episode of depression itself, a history of depression prior to TBI has been documented as a substantive risk for having depression at follow up (RR = 1.54; 95% CI: 1.31, 1.82), as was depression at the time of the injury (RR = 1.62; 95% CI: 1.37, 1.91)[Cicerone 1997, Bombardier 2010, Hart 2012].

Few studies seem to have looked at the role of alcohol related TBI and the risk of depression. Dikmen 2004 found a positive link to risk of later depression if there was intoxication at the time of injury.

3.6.10 Education Level/employment

A number of studies have reported an association between low education level and increased levels of depression [Holsinger 2002, Malec 2007, Hudak 2012] Again by way of contrast, an inverse effect on risk was reported with lower educational achievement [Dikmen 2004, Bombardier 2010]. Others have found no relationship to education level [Jorge 1993, 2004, Hart 2012, Sigurdardottir 2013]. There are reports of higher risk of depression in those who are unemployed at time of injury or who become unemployed afterwards [Oddy 1985, Hoofien 2001, Whelan-Goodinson 2008].

3.6.11 Neuroanatomical Areas

A number of reports focus on investigating whether information about the area of the brain affected by the injury helped identify those at highest risk. Imaging research about the areas of the brain injured and the relationship to depression risk has inconsistent results. In aggregate for all those with TBI, onset of major depression within 3 months of injury has been reported to be seven-fold as common (95% CI: 1.36 to 43.48) among those with abnormal CT scan results after injury compared with normal imaging [Levin 2005].

Jorge and colleagues have focused on locations of injury [Jorge 1993] and have replicated their findings in several CT-based studies. They have found that left anterior lesions involving the left dorsolateral frontal cortex and/or left basal ganglia are associated with increased risk of acute depression ($p = 0.006$) when injury location is assessed in multivariable regression models. They also note that frontal lesions, whether left, right, or bilateral, are associated with decreased risk of acute depression ($p = 0.04$). In contrast, delayed onset major depression was not associated with lesion

location. In a subanalysis of depression types, depression alone was related to left hemisphere injury ($p = 0.003$), while depression associated with anxiety was more common among those with right hemisphere injury ($p = 0.003$). A specific assessment of the presence or absence of contusions found that the type of injury was not predictive and that depression was somewhat more common among those with contusions (71%) than among those without (62%). Using MRI near the time of injury, the findings from CT studies are not supported and the only lesion type to emerge as a significant predictor was the protective effect of temporal lesions compared to other injury locations ($p=0.028$) [Koponen 2006].

In a study of political prisoners, up to 50 years after injury, TBI-associated cerebral cortical thinning in the left superior frontal and bilateral superior temporal cortex, as assessed by MRI, were associated with depression, and similar effects were not seen in prisoners without a history of TBI with respect to depression risk. This study however depended on patient recall many years after the event in order to diagnose TBI and the Hopkins Scale for depression which is a rarely used assessment tool [Mollica 2009].

Developments in new technologies such as DTI and PET scanning as well as the very small numbers in these studies, mean that this area of research is more exploratory than conclusive in beginning to understand the relationship between pathophysiology of brain injury and risk and timing of onset of depression. With time, a great deal more knowledge will emerge about the functional status of brain areas affected after TBI and the effect on depression.

3.7 Conclusions and Implications for Current Study

The literature review identified successfully, a large number of studies in depression after TBI. This should not be surprising in itself as both depression and TBI are among the most common of medical conditions and therefore the overlap is likely to be substantial.

However one may express some surprise at the lack of consistency in findings within this body of literature. There is no clear agreement around prevalence of depression post-TBI although it is

clearly raised. Furthermore there is no clear idea of the risk factors that are associated with depression after TBI. This is due to the large variation between studies in terms of inclusion criteria and study quality including sampling biases, variable success in follow-up and difference in measurement tools for depression.

There is therefore considerable scope for new studies to look at this prevalence, preferably in a large, well-designed, prospective study that includes all severity of TBI and the full spectrum of ages. There are some pointers that may help in this design from the body of previous work.

A major source of variation in depression levels is the difference in TBI severity that studies have looked at. Many took only severe or moderate injuries and those that looked at mild TBI often only considered those with abnormal CT scans or “complicated MTBI”. Some studies exclude individuals above a certain age e.g. 60 and many seem to have very young average ages within the group. For a study to truly reflect the general population with TBI, it is important to consider a population across all severities including normal CT scans and in all adult age groups. In this way a study may be considered to be a “real-life” study. There will still be many individuals who do not present with their TBI but these will be the mildest of cases and it is difficult to locate such cases unless they present to a health service.

Selection of patients within studies also varied considerably. The best studies do not use selected referrals or a “convenience sample” but rather use consecutive, unselected admissions to a service ideally via ED departments. Exclusion criteria need to be minimal to avoid selection bias and the best studies explain clearly the number of cases that are either screened out or are lost at follow-up. In this way it is possible to directly compare the “included” and “excluded” populations to determine any clear differences that affect conclusions from the study. Some studies excluded any individuals with previous psychiatric problems or any medical comorbidity.

Most studies are single centre. The use of multi-centre studies is often considered a better design as it will reduce the bias of a single centre that may have a skewed population for one reason or another. The TBI Model Systems in the USA is an excellent example of such studies and two high

quality publications used data from 17 and 19 centres. These projects benefit from considerable resources especially staff. In an ideal world, it would be possible to extend the number of cases, centres and assessments that could be done but there is always a balance to the funding and resource available for a piece of work. In this study there is one researcher responsible for all of the assessments along with some support to chase up clinic attendance. It is not possible therefore to have multiple centres but one may aspire to such resources in future.

The source of TBI cases is important to consider. Again there are studies that draw upon referrals to a neuropsychology service or only consider patients that spend considerable time in a neurorehabilitation service. One study contained 96% of cases caused by RTC and another 100% [Van Reekum 1996, Draper 2007]. This will limit the types of cases seen and not truly reflect the population of individuals that sustain TBI. Those studies that draw from the general population attending e.g. Trauma centres or ED, are much more likely to represent the population with TBI who present with the problem. A large ED with a Trauma Centre and serving a large population would seem ideal to draw a representative sample of adult TBI cases.

There is also considerable variation between studies in the timing of the assessments of outcomes such as depression. Some studies have looked at very long time spans since injury and are very revealing in their conclusions that depression is still elevated up to 50 years later. Some studies have taken repeated measures at time points e.g. over 2 years and they provide valuable insight as to how the levels of depression remain high for many years after TBI and in most cases, for life [Bombardier 2010]. However within individual studies, it is easier to draw conclusions if the majority of cases are at a similar time course in the evolution of their condition e.g. within the first year. In some studies, cases were between 3 months and 30 years elapsed since injury which makes it more difficult to make sense of results given the patient heterogeneity.

As we know that the history of TBI symptoms changes with time, it would be useful to try and design a study that takes cases along a set point in their evolution. This is most easily done in the first year since injury when cases can be picked up and then followed through. A longer elapsed time period

also affects the ability of an individual to recall events and medical records, if available, may be patchy as is described by some of the studies following up patients many years after the TBI.

It is well known that TBI studies in particular, suffer from high attrition rates when it comes to follow-up [Corrigan 2003]. In some of these studies, more than 70% of cases were lost by time of follow-up [Macniven 1993, Hawley 2008]. Even short term studies lost 45% of cases within 12 weeks [Levin 2005].

This presents us with a challenge to ensure high level of follow-up in any study and to organise a system to chase follow-up; in particular, those who miss an assessment would have to be quickly chased up to try and facilitate a replacement appointment quickly. Despite the high loss of cases in many prospective studies, it is refreshing to see that one study managed 100% follow up at 1 year and others of over 80% after similar times [Gould 2011, Sigurdardottir 2013]. This suggests that with enough time and persistence, it should be possible to organise high level of follow-up.

It still remains unclear from the literature, which associated demographic and injury characteristics are most linked to depression. Most studies have looked at a few features but it is difficult to draw any firm conclusions as there is little agreement e.g. there are studies that find no effect of TBI severity, some that find more depression in severe injury and some find more in mild injury. This is reflected in most other features too e.g. some studies find an association between previous psychiatric history and depression and others find an inverse relationship. For the purposes of this study, it would seem appropriate to measure those features that are more readily identifiable such as individual demographics as well as key injury features such as TBI severity, mechanism of injury, associated injuries or influence of comorbidities or alcohol intoxication. Most studies seem to have one key extra feature that they measure which can be a complex composite function requiring a detailed assessment of its own e.g. functional outcome score, social isolation, fatigue or any number of psychological and cognitive scores. Most of these take considerable time to assess and it is clear that incorporating any such feature would require considerable extra time to assess and document. Therefore care is needed in choosing the items to study. As discussed in methods, the study

recorded a key global outcome measure (the Extended Glasgow Outcome Score), a measure of participation restriction (Rivermead Head Injury Follow-up Questionnaire) and the Rivermead Postconcussion Score to evaluate symptom severity. Along with a number of key injury and individual characteristics, these formed the basis of the features studied for association with depression.

In summary, it is apparent that there is no consistency across studies with regards to the prevalence of depression and no agreement on the injury and population features that may be associated with risk of depression after TBI. There is therefore a clear niche for a large, well-designed, prospective study that is representative of all adult ages and severities of injury, ideally within the same time span since injury.

CHAPTER 4: METHODS, PROCEDURES AND DATA HANDLING

4.1 Introduction

This chapter describes the methods and procedures of the empirical study. This includes the standardised assessment tools that were used, the proforma design and the procedures carried out in the clinic whereby patients were recruited and data collected.

In chapter 1, the background to the head injury services within the organisation was described in some detail with particular regards to the head injury follow-up clinic. An understanding of how this NHS clinic was created is essential in order to appreciate the procedure for data collection and analysis as well as the specific assessment tools that were used.

4.2 Population / Subjects

The study design was a prospective observational cohort; there was no planned intervention to try and change the course of the condition. The subjects consisted of consecutive admissions with diagnosed traumatic brain injury from the ED from August 2013 to July 2015. All patients had a minimum period of overnight observation. Those requiring admission and observation on a ward were determined by the use of NICE guidelines [NICE 2014]. Children (<18years) were excluded as there is a separate hospital Trust in Sheffield for children.

Subjects had to be registered with a Sheffield general practitioner in order to attend follow up clinic and therefore, for entry to the study. This is part of the funding arrangements for hospital services. Patients admitted while on holiday or transferred to Sheffield as part of the Major Trauma Centre (MTC) after 2014 were therefore excluded. The GP of these patients were asked to refer to any local services in their own area.

There was no age restriction to recruitment and any young adults or teenagers admitted to ED were included. A key aim of the study was to examine a typical and representative group for the whole population and therefore all age groups were included. Individuals with severe dementia or extreme

frailty were excluded due to the difficulty of assessing history or primary outcome measures. In particular, it is difficult to assess how much of any given functional impairment can be attributed to the TBI and how much is due to other medical morbidity. For the same reason, any admissions with previous significant TBI who were treated in hospital were excluded.

Inclusion Criteria

- All admissions with TBI confirmed by lead investigator
- Overnight stay
- Head CT scan
- Able to attend follow-up (local GP)

Exclusion Criteria

- Children <18 (admitted to nearby children hospital)
- Non-local residents (unable to attend follow-up)
- Dementia or very frail elderly patients
- Previous significant TBI and disability
- TBI not admitted to hospital

4.3 Sample

Individuals were recruited the day after admission to the ED ward. There is a daily ward round carried out by the neurorehabilitation team except Sundays and bank holidays. Any admissions that were discharged before the team could attend them, were picked up by the ward register and notes examined for inclusion. The aim was to obtain a consecutive, non-selected, representative population with a mix of all head injury types.

It was acknowledged that the most minor of TBIs attending ED would be excluded as these individuals would not meet the criteria for admission and observation. A very small number of individuals with very severe TBI are transferred to neurosurgery at the nearby sister hospital in Sheffield for observation or surgery. These individuals were assessed on the neurosurgical ward by a liaison ward round for this purpose and then follow-up arranged as appropriate. Some admissions with severe TBI and other injuries may be admitted to the Intensive Care Unit. They were also picked up through the daily neurorehabilitation ward round and clinic follow-up arranged.

It was hoped that this systematic "scouring" of admissions for TBI patients would miss very few cases. Patients were brought back to the brain injury clinic created for this new head injury service. This was routinely planned at eight to ten weeks after injury. Individuals who remained as in-patients after this time were assessed on the ward but it was envisaged that this would be rare.

4.4 Design / Procedure

All patients were assessed by the lead investigator at the brain injury clinic. This was the case both for initial appointment as well as all follow-up appointments. The advantage of being seen by the same clinician at each interview is that it allows for consistency of approach and minimises inter-observer variation.

A clinic proforma was devised in order to provide a structured, consistent interview at the clinic. All forms and assessment tools used in the study are included in Appendix 3.

The clinic proforma was initially piloted when the clinic first started in 2010. After four months, a number of small changes were made based on the experience of using the form, e.g. addition of separate spaces to clearly document a number of parameters, including medication, GCS and length of PTA. A brief description of the outcomes to aid the classification was also inserted into the final form that was then used throughout the study and continues to the present day in the clinic.

The initial appointment was held eight to ten weeks after the brain injury. Each appointment was at the normal NHS clinic, held under Rehabilitation Medicine for the purposes of evaluating and

managing each individual's head injury and subsequent problems. The research study was based on the use of data collected at the clinic. It was therefore essential that there would be no extra burden placed on the individual for the purposes of research and therefore the plan was to gather routine data during the course of evaluating each individual. This burden exists in terms of the time taken to complete forms as well as emotional and cognitive load placed on individuals who have sustained a TBI. There was also a limit on the time available for the doctor to assess and gather such data.

This led to a highly "pragmatic" approach to data collection and the tools that would be used. As an example, there are head injury tools available that can take up to an hour or more to complete. These were considered inappropriate given the confines of the clinic as well as the patient burden as described above. The measures used for assessment are discussed a little later in this chapter and consisted of –

a. Semi-structured Interview Clinic Proforma

b. Rivermead Head Injury Follow-up Questionnaire (RHFUQ)

c. Rivermead Post Concussion Symptoms Questionnaire (RPCS)

d. Hospital Anxiety and Depression Scale (HADS)

e. Extended Glasgow Outcome Scale (GOSE)

These assessments were carried out at initial assessment and at one year. Many patients had clinic visits in between these times. Table 4.1 details the assessments that were completed at particular visits.

	Initial Assessment	Any intermediate visits	One year Follow up
Clinic Proforma	x	x	x
Clinical Examination	x	x	x
HADS	x		x
RHFUQ	x		x
RPCS	x	x	x
GOSE	x		x

Table 4.1: Assessments completed at clinic visits

The initial appointment took between 45 to 60 minutes based on the structured interview and proforma as well as the time to examine each patient. The investigator documented demographic details, including home and social circumstances, employment and return to work, gender and ethnicity. In addition, other important information was taken including alcohol intake and past medical history including a past psychiatric history.

4.4.1 Ethnicity

This was recorded using the standard categories documented in NHS notes. These are white, south Asian, Black, Oriental and Other. More complex groupings exist but this was considered sufficient for the purposes of this study and consistent with normal NHS practice.

4.4.2 Socioeconomic class

Socioeconomic class or status can be defined as a measure of an individual's work experience or their family's economic or social position relative to others. It is based on grouping of occupations by employment conditions and work relations rather than the skills for that job [Rose 2005].

It is known that socioeconomic status or income can explain large differences in health outcomes including mortality [Marmot 1997] and depression [Melzer 1995]. It was therefore important to attempt to measure socioeconomic class and the impact on the incidence of depression.

Until 2001 the Registrar General's social classification was the norm and was based purely on the occupation of the chief income earner of a family. It dates back to 1911 [Leete-Fox 1977, Rose 1995]. An extensive review for the Office for National Statistics led to the creation of a new socioeconomic classification based on employment relations and conditions and inclusive of all individuals in society, not just those who are working [Chandola 2000, Rose 2005]. The new system, the National Statistics Socioeconomic Classification [ONS 2005; ons.gov.uk] has been in use since the 2001 UK Census and was used in this study to classify each individual's socioeconomic status.

Table 4.2 describes the eight classes within the system. It is derived by asking a number of questions about the nature of employment, the size of employer, supervisor status at work and self-employment status. It covers all adults including students, the long term unemployed or those who have never worked. Each individual's previous occupation was used if they were currently unemployed.

A distinction is drawn between large scale employers (with more than 25 employees) as distinct from small employers or the self-employed. Employees are distinguished on the basis of their labour relationships, e.g. managers and professionals tend to have a higher degree of delegated authority from employers as well as perks such as salary increases, pension rights and job security. Other working class employees are often involved in more routine work and may have contracts based more on an hourly or time basis. Intermediate occupations fall somewhere in between these two.

While there is a shorter five category grouping of the NS-SEC, for this study the full eight class grouping was utilised. Familiarisation with the system to facilitate ease of classifying individuals took some considerable time and practice by the researcher in the months leading up to the start of the study but soon became easy to apply.

NS-SEC group	Examples	% in UK[1]
1.1 Employers and managers in larger organisation	Company directors, senior civil servants, senior police and armed forces	4.3
1.2 Higher professionals	Doctors, lawyers, clergy, teachers and social workers	6.8
2 Lower manager and professional	Nurses, journalists, actors, prison officers, lower ranks of police and armed forces	23.5
3 Intermediate occupations	Clerks, secretaries, computer operators	14.0
4 Small employers and own account workers	Publicans, farmers, taxi drivers, window cleaners, decorators	9.9
5 Lower supervisory, craft and related occupations	Printers, plumbers, train drivers, butchers	9.8
6 Semi-routine	Shop assistants, hairdressers, bus drivers, cooks	18.6
7 Routine	Cleaners, labourers, waiters, refuse collectors	12.7
8 Never had paid work and long-term unemployed		

Table 4.2: National Statistics Socioeconomic Classification (NS-SEC). [1]data from UK census 2011

4.4.3 Pre-injury employment status

Documentation of employment fell into three categories, those who were employed, unemployed and retired. The employed group included part-time work and full-time students. The unemployed group included those on long term disability benefits or unable to work through ill health.

4.4.4 Diagnosis of TBI

Details of the injury, its mechanism and history of subsequent events and symptoms were documented as in any normal history taking. It was imperative to confirm that the criteria to make a diagnosis of TBI were fulfilled. This was done using the standard American College of Rehabilitation Medicine (ACRM) criteria as described in Chapter 1 [Menon 2010]. This included the key feature of some form of neurological dysfunction, no matter how short in duration. The ACRM defines this as follows-

A traumatically induced physiological disruption of function with any of the following features

a. Any period of loss of consciousness
b. Any loss of memory for events immediately before or after the trauma
c. Any alteration of mental state e.g. dazed, disorientated or confused
d. Any focal neurological deficit

Any evidence of trauma induced intracranial abnormality on CT was also considered firm evidence of a TBI.

Accurate history taking is the key in establishing a diagnosis of TBI. It is important to establish the detailed history and whether any of the above features can be confirmed by patient or a witness. There are factors other than TBI that can affect mental state at time of an injury e.g. alcohol, pain, medication, traumatic shock. Therefore considerable time was spent at time of admission and at the initial interview, to take a detailed history.

4.4.5 Mechanism of TBI

The mechanism of injury was classified using the TARN classification [Lecky 2000]. This classifies mechanism of injury as falls, assault, road traffic collision (RTC) and other mechanisms, e.g. sports injury. In the case of RTC, it was further specified whether an individual was a driver, a passenger or a pedestrian for use in any subsequent sub-group analysis of outcome in this group.

4.4.6 Social History

Home circumstances were documented with particular regards to the amount of support an individual would have at home. The three item UCLA Loneliness Scale was used for this assessment [Hughes 2004]. It is included in the appendix. More detailed tools exist but these could not be justified as relevant in a clinical assessment and the three item version of this tool has been validated as an effective measure of degree of social isolation [Hughes 2004]. Any score above 4 (out of a maximum of 9) was considered to show significant isolation.

4.4.7 Previous psychiatric history

Previous psychiatric history was documented. This included any previous referral or assessment under a psychiatric team, including substance misuse, alcohol excess and depression. Any treatment for a psychiatric condition including depression was also considered as a positive history. These were ascertained by direct questioning at interview.

4.4.8 TBI Severity

Severity of brain injury was documented using the medical records and history at clinic. Glasgow Coma Score was documented as the score on arrival at hospital rather than at the scene of accident. Documentation of any period of loss of consciousness or post traumatic amnesia (PTA) was also undertaken at the clinic.

The GCS is an internationally recognised and well-used scoring system to measure conscious level devised by Teasdale and Jennett in 1974 [Teasdale 1974]. It consists of three domains, each with a subscore that is added to give a total score between 3-15. These domains are eye opening response, best motor response and best verbal response. While it was never intended to combine these three domain scores into an overall score, it is usually used in this way. Studies have confirmed that lower total GCS is associated with poor outcome [Helmy 2007].

The GCS was recorded as a score between 3 and 15 but was also used in a categorical measure to record injury as mild (GCS 13-15), moderate (GCS 9-12) or severe (GCS 3-8) TBI. Again, this is a well-recognised classification of brain injury severity and easier to use than assessment of LOC (loss of consciousness) or PTA [Sherer 2007]. These criteria for classification of TBI are shown in Table 1.1 in Chapter 1.

Length of inpatient stay was also documented for each patient as well as any ongoing difficulties during the course of inpatient stay, treatment of any specific complaints and any problems that developed after discharge.

4.4.9 CT Scan

TBI causes various types of intracranial pathology. These can be classified simply by traditional descriptive terms referring to the pathology e.g. subarachnoid haemorrhage (SAH), subdural haemorrhage (SDH), diffuse axonal injury, cerebral contusions etc. Alternatively, systems for classification such as the Abbreviated Injury Score (AIS) or Marshall Classification can be used [Marshall 1991, Gennarelli 2008]. These use the anatomical location of the pathology or the presence of raised intracranial pressure.

The initial plan was to use the Marshall Classification for CT scan in Table 4.3 [Marshall 1991]. However it readily became apparent that this was of limited use in this study. This is because the Marshall system is geared heavily towards the need for neurosurgical intervention. These are usually severe TBIs. It was not helpful in a mixed population of injury severity especially with a large number of mild and moderate injuries and few requiring surgery.

The AIS score could not be easily calculated and would have required extensive work by neuroradiology to estimate pathology volumes as well as required funding or further scans for patients [Gennarelli 2008, Lesko 2010].

Again it should be noted that this study was designed to minimise patient disruption and be as “real life” and pragmatic as possible.

It was decided to use an alternative means of CT classification called the “overall appearance” system [Wardlaw 2002]. This categorises CT findings based on the Neuroradiologist’s report and scans fall into the following groups (Table 4.4), normal appearance; mild focal lesion (in one area of the brain only with the rest of the scan normal); medium focal lesion (several contusions in one area or two immediately adjacent brain areas); severe or diffuse injury (several contusions, DAI or bleeds in several non-adjacent areas of the brain). Any individuals requiring neurosurgery are classed in the severe group.

This classification system has been validated and has been shown to predict functional outcome and survival [Wardlaw 2002]. It has also been used in large international studies of outcome after TBI [CRASH-2]. The extent of CT scan change has also been shown to be associated with functional outcome in large head injury studies such as IMPACT [Signorini 1999, Maas 2005].

All scans were reported by a Neuroradiologist and it was a simple matter to apply the grading system to attribute a category for each scan. Any queries on scans were clarified at the weekly neuroradiology meeting. This was an effective and simple classification system that was much more applicable to a mixed TBI population. Again as an acknowledgement of the pragmatic nature of the study, it was felt that a simple classification, using such readily available measures would be more useful than more complicated analysis that is not available to most clinicians. Assessments such as calculated volume of brain lesion (AIS) have also been shown to predict outcome but these are not available to most clinicians and hence non-applicable [Lesko 2010].

It was also documented whether the abnormalities on CT scans were bilateral or unilateral although this is a more simplified version of the “overall appearance” method again. It was felt intuitively, that individuals with bilateral hemisphere involvement would be more likely to have long-term problems including depression.

Category	Appearance
Diffuse injury I	No visible intracranial pathology seen on CT scan
Diffuse injury II	Cisterns are present with midline shift of 0-5 mm and/or lesions densities present; no high or mixed density lesion >25mls may include bone fragments and foreign bodies
Diffuse injury III (swelling)	Cisterns compressed or absent with midline shift of 0-5 mm; no high or mixed density lesion >25mls
Diffuse injury IV (shift)	Midline shift >5 mm; no high or mixed density lesion >25mls
Evacuated mass lesion V	Any lesion surgically evacuated
Non-evacuated lesion VI	High or mixed density lesion >25 mls; not surgically evacuated

Table 4.3 Marshall Classification of CT Abnormalities in TBI

Category	Example of appearance
Normal Scan	Normal scan
Mild Focal Injury	small lesion in one area of brain only
Medium Focal Injury	several lesions in one or two immediately adjacent areas of brain, or small EDH or small SDH
Moderate-Severe Diffuse Injury	Several small lesions or haematomas in several non-adjacent areas of the brain or neurosurgery

Table 4.4: The "overall appearance" of CT Scans for intracranial pathology

4.4.10 Medical Comorbidity

The World Health Organisation definition of comorbidity is "a chronic medical condition that requires ongoing management". It is known that medical comorbidities in individuals affect outcome adversely but assessing comorbidities can be difficult and a number of very detailed and complex tools exist for this. The most common or detailed measures are the Charlson Index [Charlson 1987] and Elixhauser Comorbidity Measure [Walraven 2009]. However these involve considerable resources including medical coding and time. Again because of the pragmatic nature of this study it was important to minimise the effort and burden on patients. The Cumulative Illness Rating Scale (CIRS) was devised as a reliable and brief tool for assessing medical comorbidity [Linn 1968]. The modified CIRS has been validated in a number of populations. A patient scores between 0 and 4 for each organ system that is affected by a significant medical illness depending on the severity of the condition. This is added up to provide a total score between 0 and 56. A cut off above 10 establishes a significant level of medical comorbidity and this has been shown to affect outcome

[Hudon 2005]. The CIRS is a reliable measure with good inter-rater variability and correlation coefficients between 0.55 and 0.91.

Individuals in the study were therefore classified as having significant comorbidity or not, using the cut-off.

4.4.11 Clinical Examination

All patients attending the clinic were neurologically examined by the lead investigator and a treatment plan made as appropriate. This included any medical interventions such as medication for pain or vestibular disturbance. Any relevant referrals e.g. to the Community Brain Injury Rehabilitation Team for individuals with ongoing symptoms, were made. Other specialty referrals were occasionally required, e.g. maxillofacial, ophthalmology or audiovestibular medicine. These were similar to any other standard NHS clinic.

4.5 Follow-up and compliance with clinic attendance

4.5.1 First clinic appointment

After initial appointment, subsequent follow-up was arranged as deemed appropriate for each patient. This could be a few weeks in the instance of individuals requiring considerable support with a high level of symptoms and problems. At the other extreme were individuals who it was felt had fully recovered even at the initial appointment and they were discharged with a one year appointment for the purposes of follow-up. It is well known that there is a high incidence of late symptoms after TBI and that follow-up in the first year has been shown to be effective in reducing the level of symptoms [Wade 1997, Paniak 1998]. It was on this basis that the head injury clinic was designed to follow-up up patients in this time period. As part of the normal hospital procedure

regarding clinic appointments, all individuals were sent a text message as well as a routine appointment letter.

In addition, any individuals who failed to attend were chased up by phone call, either by the lead investigator or the nurse specialist in order to rearrange an appointment. This phone call emphasised the importance of the clinic for the individual and their treatment. This was also the case for any follow-up appointments and was a key factor in the clinic protocol. It is known that failure to attend is common across most clinics but particularly so in TBI populations where up to 70% of individuals are lost within one year [Corrigan 2003, Ruttan 2008]. This limits the quality of many TBI studies. It was hoped that this would be reduced by facilitating communication with the patients and encouraging follow up compliance.

At each follow-up clinic the individuals were evaluated in the same way as any other normal clinic visit. Patients were asked about any ongoing problems that they may have and a treatment plan was set up if required or any further specialist referrals arranged. Any specific symptoms e.g. headache were treated as appropriate. This is a normal part of everyday clinical practice and this study was fitted in around the patient's complaints and needs at the clinic.

4.5.2 One Year Follow-up

At one year a proforma was again used to evaluate each individual in a structured, consistent interview. Clearly, the routine demographic details remained the same but any changes to living situation, employment, relationships, etc. were documented. All the assessments from the initial appointment were then repeated (Table 4.1).

The one year interview marked the end of the study for most individuals and they were discharged from the clinic. All patients were advised to contact the service or their GP in the event of any subsequent difficulties relevant to their TBI. A small number of patients who still had ongoing problems that required follow-up, continued to attend clinic as appropriate for those issues and for ongoing support.

4.6 Assessment of Depression

4.6.1 Introduction

It is important to consider the assessment of depression and the tools that may be used to make a diagnosis.

The diagnosis of depression after TBI presents a significant challenge to clinicians. No single test or single definitive symptom can make the diagnosis; nor can any laboratory or radiological test establish a diagnosis of depression [Williams 2002]. Therefore many investigators find it useful to combine a number of symptoms; if a number of these are present then the diagnosis becomes much more likely. A questionnaire lends itself to such an assessment and provides a low burden to both patient and clinician. It can be easily scored with clear cut-offs. Questionnaires provide a consistent and efficient means of measuring particular criteria across a sample and across time. However some purists argue that the diagnosis can only be made using a structured clinical interview (SCID) using the criteria set by the American Psychiatric Association as detailed previously [Gasquione 1992]. This can take up to 45 minutes and requires considerable resources which are unavailable to most clinical services. It is also important to consider the issue of “cognitive fatigue” [Bay 2007]. Many individuals are unable to complete the one hour interview for this, or other assessments that are sometimes used in clinical management. Up to 40% of individuals decline the completion of such questionnaires [Ghaffar 2006, Bay 2007, Wittkampf 2009].

Many of the symptoms from TBI sequelae, overlap with the symptoms of depression and hence complicate the diagnosis. Examples include poor concentration, loss of appetite, loss of energy and poor sleep [Seel 2010b]. The only symptoms that can be considered as different between the two conditions are subjective feelings of guilt, feeling worthless and thoughts of death and suicide [Cook 2011, Dyer 2016].

Another concern is that in severe cases of TBI, impaired self-awareness (ISA) may affect responses to questions and result in an under-appreciation of symptoms. This would affect the likelihood of a positive diagnosis of depression being made. [Babin 2003, Moldover 2004]

4.6.2 Structured Clinical Interview for DSM

The gold standard for diagnosis of depression is considered to be the DSM criteria, now in its fifth incarnation (Diagnostic and Statistical Manual of Mental Disorders, 5th edition) [First 2002, APA 2014]. An individual must have at least five out of nine key symptoms for depression; at least one of these must be one of the first two primary criteria as listed below:-

DSM-5 criteria

1. Depressed mood
2. Diminished interest or pleasure
3. Weight or appetite change
4. Sleep disturbance
5. Psychomotor agitation or retardation
6. Decreased energy
7. Feelings of worthlessness
8. Diminished thinking ability
9. Recurrent thoughts of death

Depressive symptoms should be present for most of the day for a period of at least two weeks prior to the diagnosis in order to meet the DSM criteria.

Unfortunately, many of these criteria are trans-diagnostic with TBI including loss of appetite, poor sleep, decreased energy and decreased thinking ability. Hence a major concern remains the ability of the DSM criteria to distinguish symptoms caused by depression from those due to the TBI itself.

It has also been suggested that anhedonia (one of the main criteria of DSM) is found in many other mental health disorders and that it poorly differentiates depressed and non-depressed in those with medical illness [Silverstone 1991, Parker 2001]. Reliance on anhedonia to make the diagnosis may lead to false positive errors.

The DSM specifies that the interview must be conducted by a suitably trained neuropsychologist or psychiatrist. Interviews typically take 45-60 minutes. Clinicians are instructed to consider whether symptoms may be caused by concurrent medical diagnosis such as is the case with TBI. Depending on the extent to which individuals are trained or aware of clinical conditions such as TBI, they will attribute varying levels of symptoms to the TBI or other medical condition. SCID has been shown to have poor inter-rater variability [Regier 2013]. This may explain in part, the wide range in prevalence of depression found in studies using these criteria if clinicians vary in the extent to which they are trained.

4.6.3 Self-report scales

An alternative to SCID is to use self-report scales or brief clinician administered interviews to detect cases of depression. Such measures offer an efficient tool for determining the incidence of depressive symptoms in large groups. They are easy to administer with a low respondent burden and are resource friendly to services that are often resource challenged. Such scales are usually easily administered and scored with accepted cut-off criteria. They can provide consistent measurement criteria across a sample and across time. Some can even be administered over the telephone [Hart 2012].

Strictly speaking such scales detect the presence of “depressive symptoms” rather than make a true diagnosis of clinical depression. In other words the diagnosis of clinical depression can only be made through DSM criteria if one takes the strictest possible clinical interpretation.

Yet the vast majority of individuals diagnosed with depression both in primary and secondary care are not diagnosed or treated on the basis of DSM criteria. Indeed the use of clinical judgement,

often aided by the use of screening tools remains the mainstay of the diagnosis and treatment of depression in the UK and worldwide. [NICE 2014, Kendrick 2009] Few clinical services have the resource allocation to spend an hour simply to make a diagnosis of depression, quite apart from any other assessments. Outside of psychiatric practice, the use of SCID remains largely an academic tool, no doubt of huge importance but limited in its clinical applications in a busy service.

There are many different clinical scales used and detailed review of all of these is neither possible nor desirable. There are methodological issues with all scales and all have their particular strengths and weaknesses. A number of studies have tried to compare tools both with SCID and with each another [Whelan-Goodinson 2008, Bay 2008, Dyer 2016]. The main problem with screening tools is that there are some somatic elements in many of the questionnaires [Rowland 2005]. This is particularly true of the Beck Depression Inventory (BDI), the SCL-90 and the Hamilton Depression Rating Scale (HAM-D). Other scales have not been validated in a TBI population, e.g. Zung Depression Scale. A tool that has found widespread use in recent years is the PHQ-9 which uses the nine diagnostic criteria on DSM as its questions. This scale has excellent psychometric properties, inter-rater variation and consistency. It is widely used in TBI and is one of the measures recommended by NICE guidance.

Another tool that has been widely tested with TBI as well as in many other conditions, is the HADS (Hospital Anxiety and Depression Scale). There are over 1000 published studies using the HADS in a wide range of medical settings including TBI [Hermann 1997, Bjelland 2002]. Devised by Zigmond and Snaith, primarily for use in patients with medical illness [Zigmond 1983], it has been shown to have excellent psychometric properties and correlation to other tests including the SCID [Whelan-Goodinson 2008, Schonberger 2010].

The HADS focuses on the presence of anhedonia or loss of pleasure. As this is regarded by many as the principle symptom for depression, this can be considered a strength. In doing so, it avoids questions that can be affected by medical illness, or so-called somatic symptoms of depression. It is easily self-administered by patients although occasionally requires carer or clinician help to read the

questions. Both the PHQ-9 and the HADS perform well in practice [Lowe 2004, Cameron 2008] and are responsive to treatment, showing improvement in scores. They perform considerably better than use of a clinician's own decision [Hermann 1997].

A concern over the use of self-report scales has been the risk of over-reporting of symptoms or a high false positive rate [Kendrick 2009]. It was therefore interesting to calculate the average rate of depression in studies that used the SCID/ DSM criteria versus self-report measures. Using the studies from the literature review, there were 112 studies in total of which 36 used DSM and the rest a variety of self-report scales. The SCID had a higher median depression of 39% versus 36% using self-report measures. Furthermore the lowest and highest reported incidences in the literature review were both in studies that used the SCID. While there are many reasons for variation across prevalence in different studies, one reason in studies using the SCID may be the different levels of training and experience of the clinicians in distinguishing the role of medical conditions in contributing to the diagnostic symptomatology. It is certainly clear that self-report scales are not finding a higher proportion of individuals with depression as may be expected if they result in increased false positives.

The time resource and training required to apply SCID for a diagnosis, is recognised in NICE guidance [NICE 2009]. The lack of adequate resources to deal with the number of patients, limits how useful such a strict approach to diagnosis can be. NICE recommends the use of two screening questions to determine whether individuals with possible depression, are then referred onwards to Increased Access to Psychological Therapies (IAPT)

The screening questions, often called Whooley questions [Whooley 1997, NICE 2009] are –

1. During the last month, have you been bothered by feeling down, depressed or hopeless?
2. During the last month, have you often been bothered by having little interest or pleasure in doing things?

The assessment of depression by IAPT relies on a basket of outcome measures and assessment scales which includes the PHQ-9 and HADS.

4.6.4 Conclusions

The literature review found that both the lowest and highest prevalence of TBI depression were in SCID studies and the overall prevalence of TBI was higher in SCID studies compared to questionnaires. Given that one of the criticisms of questionnaires is that they may be prone to a high level of false positives, this would seem to suggest otherwise. Studies that have compared SCID with questionnaire scores have shown similar levels of depression. If we consider depression as a syndrome with constellation of symptoms rather than one or two key criteria, then this may help our understanding of the condition. In this respect, the addition of a number of these symptoms in a self-report scale constitutes a measure of the accumulation of symptoms or disease burden. Combined with the time resource required for a SCID and the "pragmatic" nature of this clinic-based study, the decision to use a self-report scale was made.

The lead researcher has considerable previous experience in using this scale already with other disabled populations [Singh 2008]. This familiarity along with the ease of the use of this scale and its extensive validation across the TBI population, led to the choice of the HADS as the assessment tool to measure depression in this study.

4.7 Assessment Forms

Apart from the structured clinic proforma, a number of specific measurement tools were used in the study; each of these is included in the appendix but requires a description here. These were standardised instruments covering the domains of depression, symptoms of TBI, participation restriction (or handicap score) and overall TBI outcome.

4.7.1 HADS

As previously discussed, mood was assessed using the Hospital Anxiety and Depression Scale (HADS). The HADS is a 14 item questionnaire that documents common depressive and anxiety symptoms (7 items for each). The two scales are correlated but the two factor structure of the scales has been confirmed [Spinhoven 1997]. Each item is scored with a 4-point verbal rating scale and hence a maximum score for either anxiety or depressive symptoms is 21. Individuals are asked to fill the form so as to reflect their feelings over the previous week.

This assessment was designed specifically for individuals with medical illness and physical limitations by Zigmond and Snaith in 1983 [Zigmond 1983]. It avoids over-dependence on physical symptoms of depression and focuses on the psychological manifestations [Mykletun 2001]. It has been used extensively in many studies across different population and illness groups and been translated into several languages.

Although its name may suggest use within hospitals, in fact the HADS was designed with a view to use in community settings as well and has been validated in a large number of different population groups including many different conditions, such as cancer, heart failure and a number of neurological disorders. It has been used and validated in TBI [Dawkins 2006, Al-Adawi 2007, Whelan-Goodinson 2008]. Comprehensive reviews of the HADS are available [Hermann 1997, Bjellend 2002].

The form can be self-filled by an individual in a matter of a few minutes. A small number of patients may require some assistance by a relative or by the clinician to help e.g. patients unable to read or who require further explanation of the question items. A particular advantage of the HADS, apart from the short time taken to fill in is that it has been shown to be equally effective as more detailed or time-consuming tools in the diagnosis of depression [Whelan-Goodinson 2008]. It also minimises the confounding factor of somatic symptoms, many of which will overlap with the diagnosis of TBI, e.g. poor sleep, weight loss. Only one of the responses in the HADS (“I feel that I am slowed down”) would correspond to a somatic symptom or be common in individuals with a TBI alone, quite apart

from an added diagnosis of depression. A common problem with many of the other tools used to evaluate mood is that they have a high proportion of trans-diagnostic symptoms which make evaluation of mood over and above the presence of TBI very difficult. Other depression measures suffer from this "floor" effect as discussed in Chapter 1.

A number of different cut-offs have been used by studies but the original paper used a cut-off score above 8 [Zigmond 1983]. This has also been shown to have the best discriminant value and trade-off between specificity and sensitivity [Bjellend 2002, Hermann 1997]. Using this cut-off, Lowe found a sensitivity of 0.85 and specificity of 0.76 [Lowe 2004]. Some have used a higher level of cut-off (10/11) to define severe depression [Crawford 2001, Cameron 2008]. Use of this cut-off would undoubtedly improve specificity but has to be balanced against the lower sensitivity that would result. It is likely that many true cases would be missed at a higher cut-off.

The test can be easily repeated at intervals allowing monitoring of changes; this is particularly useful in assessing changes caused by intervention such as medication [Crawford 2008].

The internal consistency of the anxiety score varies from 0.8-0.93 and 0.81-0.9 for the depression score across a wide range of studies encompassing more than 60000 patients [Bjelland 2002].

The re-test value is very high and quoted as 0.91 after one month. This reduces with time but is probably due to changes in mood rather than the test reliability [Bjelland 2002, Lowe 2004].

A review of over 600 English publications found that the sensitivity and specificity were >0.8 for both. In TBI it was found that use of a cut-off at 8/9 results in a sensitivity of 0.66 and specificity of 0.88. For reference, this is comparable to the value of exercise ECG testing for the presence of coronary heart disease [Bjelland 2002]. The HADS has been noted to be better at diagnosing depression than non-psychiatrist physicians [Cosco 2012].

The accuracy of any test at diagnosing a condition depends on the presence of a "gold standard" test to compare against. The closest test in depression that approximates to this gold standard is the Structured Clinical Interview for DSM. In using this standard, Receiver Operated Characteristics curves indicated a best cut-off at 8/9 on the HADS for which the area under curve was 0.887 (95%

Confidence Intervals 0.84-0.91). The predictive power was 83% which compares very favourably to any other tests of depression [Herrero 1983].

The HADS has also been correlated positively to other measures of depression including PHQ-9 and BDI [Kroenke 2001, Cameron 2008, Revicki 2008].

There were two possible options for analysis of the HADS. Firstly, depression could be analysed as a linear outcome using the crude HADS scores (range 0-21). The advantage of such an analysis is that by preserving the whole score, analysis theoretically preserves the absolute scores allowing for better characterisation of the extent of depression an individual experiences. The alternative is to use a cut-off score to signify a case. For example, using a cut-off between 8 and 9, an individual with a HADS score of 9 would be considered depressed; at the same time an individual with a score of 17 would also be considered as depressed but presumably the much high score of the latter suggests that the extent of depression is much more significant. In a similar vein, a score of 8 would not be a case but the distinction between individuals with scores of 8 and 9 is likely to be small. Preserving the absolute scores would allow for this dimension of the data to be preserved in the analysis.

Nevertheless it was felt that the use of a binary method would be more realistic and akin to clinical practice. This was after all, the aim of the project. This is because in a clinical setting, the decision as to whether an individual is depressed or not, is essentially a binary one. Subsequent decisions to treat follow a yes or no pattern. This was the rationale for classing depression as a binary outcome.

4.7.2 Rivermead Head Injury Follow-up Questionnaire (RHFUQ)

This is a 10-item common measurement score for functional and social outcomes after TBI. It focuses on an individual's level of participation restriction (handicap) as opposed to symptom or impairment level in terms of work, relationships or social and domestic roles. Most patients fill this in themselves but occasional help from a clinician or relative is needed. Items are scored using the Likert method of grading with subjective scores from 0-4, resulting in a maximum overall score out of 40. The higher the score, the more significant is the level of handicap that the patient is experiencing. Items include activity such as "ability to participate in conversation with two or more people", "ability to maintain previous workload" and "performance of domestic duties". This tool was devised primarily for use with a TBI population and has been validated and studied several times. It is a very useful measure of the impact of TBI on an individual's lifestyle.

There is no cut off and the score is used as a linear outcome measure. Validity is difficult to assess as there is no gold standard for participation restriction/handicap measure after TBI but it correlates well with measures of symptoms after TBI [Crawford 1996]. In terms of reliability, there is excellent agreement between separate interviews both between self-administration and interview (K=0.61) and between self-administration on separate occasions (K=0.88).

Like many of the tests chosen for this study, the RHFUQ is sensitive enough to detect meaningful differences to an individual's lifestyle but short enough to be simple to administer in a busy clinical setting.

4.7.3 Rivermead Post Concussion Score (RPCS)

This is a commonly used check list consisting of sixteen common symptoms after a TBI. These are again scored in a Likert method of grading from 0-4 with 0 signifying a symptom never experienced and 4 signifying a severe level. This gives a maximum score of 64. This score provided a useful measure of the extent of an individual's symptoms after TBI as well as ongoing progress in terms of subsequent improvement in follow-up appointments. Comparison is made to the previous level of experience which is important as many of the symptoms are experienced within the normal population as part of life e.g. headache, fatigue. Others include forgetfulness, irritability and taking longer to think [Ryan 2003, Iverson 2003]. The tool was devised for use in TBI management and has been validated several times [King 1995].

Some groups have chosen to omit the *Headache* symptom because it is felt that this term does not measure the same underlying construct and others have suggested that 13 of the 16 symptoms should be grouped alone as the best item measures. This study chose to use the whole questionnaire and summate the total score rather than abridge a well-validated and frequently used measure.

There is good test-retest reliability with coefficient of 0.89 after 2 weeks separation and positive correlation (r=0.83) with measures of handicap/participation such as the Rivermead Head Injury Follow-up Questionnaire [Sawchyn 2000, Eyres 2005].

4.7.4 Extended Glasgow Outcome Scale (GOSE)

This is the most commonly used primary outcome measure after TBI [Wilson 1995]. The original version was formulated in 1975 by the same group that devised the GCS [Jennet/Bond 1975] and originally had five categories between Death and Good Recovery. Unfortunately this represented a relatively narrow range of options and did not allow for more detailed separation, sometimes between individuals with quite different outcomes. The Extended scale was developed with 8 categories(Table 4.5) and has been shown to improve the distinction between outcome groups allowing better differentiation between different outcomes e.g. ability to manage alone for 8 hrs or requiring constant supervision [Jennett 1981]. Previously these would both be classed as Severe Disability. The extended scale splits severe disability, moderate disability and good recovery into an upper and lower band for each. This allows a greater sensitivity to detect changes.

The extended version has been shown to correlate better with neuropsychological function, functional outcome and mood than the shorter version [Levin 2001].

The measure is best filled by use of a structured clinical interview [Wilson 1998] which has been shown to minimise misclassification [Lu 2010].

The form was completed by the lead investigator at each clinic appointment based on the individual's responses including items such as return to work or study, level of support required and level of social participation. It should be noted that this is a challenging scale to perform well in, e.g. to fall in the very best outcome group (good response/upper) one has to return to work in the same job to the same level and degree of difficulty and responsibility that existed prior to the accident. Even small changes to an individual's duties would imply that they have not made the best possible recovery e.g. working part-time or modification of pre-injury duties.

Despite these difficulties, the GOSE is the most commonly used outcome measure after TBI and in comparison to many of the other outcome measures it can be completed in considerably less time.

Numerous studies have evaluated the tool's psychometric properties and it is a valid and reliable scale.

Inter-rater variability can be high with untrained staff [Maas 1983, Brooks 1986] but this is minimised by use of the structured questionnaire. Using this method, inter-rater reliability is high (0.84-0.92) [Wilson 2000, Jennett 1981]. Inter-rater variability is further reduced in this study by use of a single investigator.

Test-retest reliability is very high, reported as K=0.98 and 0.92 [Wilson 2002, Pettigrew 2003].

There is excellent correlation of GOSE with functional outcomes, measures of injury severity and mood scales [Wilson 2002]. There is also excellent correlation with cognitive scores and neurological examination [Brooks 1986, Satz 1998]. Indeed there is also excellent correlation with GOSE at discharge and GOSE at 5-7 years after injury [Massagli 1996].

GOSE Level	Description
1	Dead
2	Vegetative state
3	Lower severe disability: completely dependent on others
4	Upper severe disability: dependent on others for some activities
5	Lower moderate disability: unable to return to work or participate in social activities
6	Upper moderate disability: return to work at reduced capacity, reduced participation in social activities
7	Lower good recovery: good recovery with minor social or mental deficit, no work alterations
8	Upper good recovery

Table 4.5: the Extended Glasgow Outcome Scale (GOSE)

4.8 Research Ethics

Research Ethics was obtained via the Integrated Research Application System, used for all healthcare research in the UK. This process, led by the lead investigator and the Sheffield Teaching Hospitals Research Department, took one year to complete. It was confirmed by the University of Sheffield that approval through the IRAS process via Sheffield Teaching Hospitals was satisfactory and that the project did not need separate University of Sheffield application (email correspondence, research approval forms and patient consent forms are in Appendix 2)

The Project reference number was STH16208.

The IRAS Project ID was 88821.

An important component of the study was to ensure no extra burden for the patients or extra follow-up appointments in order to fulfil purely research requirements. All the assessments, evaluations and questions were part of the normal clinical assessment for that individual and the structure of the clinic was designed to maximise the benefit for the patient rather than the research study. This included choosing shorter evaluation tools to minimise the clinic burden while avoiding loss of quality of data.

All patients were informed at their clinic appointment that data was being kept for their treatment and also for research purposes, although this would be anonymised and consent was taken on this basis. This was incorporated into the forms which patients signed.

4.9 Data collection

Clinic attendance and completed forms were kept in the individual's clinical medical notes. This included the clinic proforma. No extra copies were made of these forms and no paper copies were kept anywhere else.

A new database was created in ACCESS 2010 in association with STH audit and governance department. After the clinic, data from the proformas and assessment forms were entered into this database for later analysis. This data was later converted into an anonymised file for analysis in

SPSS. All data was stored on the hospital server and no data was transferred in any other form e.g. memory stick.

A key strength of the project was that data entry was carried out by the same investigator from the clinic and therefore any missing data was quickly identified and could usually be ascertained soon after each clinic appointment when the data was entered onto the database. This eliminated the problem of missing data variables being uncovered only at the end of the study. The investigator was able to check data at every clinic and was responsible for ensuring that all proforma questions were answered. If a data element was missing at time of entry, then the investigator was able to examine the medical records or flag up this gap on the database in order to ask the relevant question at the next clinical encounter.

4.10 Statistics and analysis

Statistical advice and assistance was taken from School of Health and Related Research (ScHARR) colleagues and from the University of Sheffield Statistics department. Initial population demographics were examined to look for potential patterns and identification of variable distribution. The key data was the clinic information at 10 weeks and follow-up at one year. Other clinical appointments in between were not examined for this study. Initial analysis used descriptive statistics including graphical representation. Subsequent univariable analysis for the key outcomes of depression and other factors of interest were carried out and comparisons made with the initial and one year data. For continuous data, a simple linear regression was used and for categorical data, a $\chi 2$-test or Fisher Exact test was used. This process included appropriate tests for assumptions of normality. Assessment of prevalence of depression (HADS Depression score>8) included calculation of 95% CI (Confidence intervals). This was conducted using the formula in standard textbooks of statistics.

A more detailed multivariable regression was then carried out with equations derived for each major outcome although with depression being the main outcome of interest.

A logistic regression for the binary outcome of depression was conducted with the same variables as used in the univariable analysis. This was repeated for the data at 1 year.

Individuals that were lost to follow-up were also compared in order to ascertain whether there were any differences with the study individuals. Comparison of the two groups was performed with t-test or χ^2-test.

4.10.1 Power Calculation

The primary outcome measure for the study was the incidence of depression in the TBI population. Calculation of sample size to show a statistically significant difference between this group and the background population requires knowledge of the likely difference in incidence between these groups.

From the literature review, the incidence of depression in the TBI group is estimated at 32% (range 11-77). The background rate of depression varies between population groups but large national studies estimate between 8-15% in the community. Hospital populations have an even higher rate of between 15-30% [Kessler 2005].

Therefore it is possible to estimate a difference between the two populations of about 15%. This would be a moderate size effect [Cohen 1992].

The sample size needed to show this difference was estimated using *Psychstat* website. For an effect size of 0.15, the sample size for 80% power at the 5% significance level is 380 patients.

One of the most difficult issues with TBI research is the high attrition rate to follow-up even at short timescales of a few weeks. Therefore even a 50% success at 1 year follow up would represent an optimistic view of the likelihood of attendance. On this basis, it was estimated that a population of at least 600 patients was required. This is clearly a very large study population. However it was still considered possible based on the fact that in previous years, approximately 1000 head injury patients are admitted at Sheffield ED. Over a period of two years, it was therefore likely that at least 600 patients could be recruited and about 300 would remain in the study by 1 year.

CHAPTER 5: RESULTS

5.01 Introduction

The Results constitute the major part of this thesis and the structure of this chapter is listed in the Contents; it will cover a description of the population recruited, its demographics, comparison with the individuals lost to follow-up, prevalence of depression and finally, more complex analyses of the features associated with depression. It is sometimes necessary to provide a little clarification around a particular finding. However efforts have been made to minimise this as much as possible and place the discussion of findings in the next chapter.

5.1 Study Recruitment and Follow-up

This section describes the total number of patients admitted, examined and recruited to the study over two years. It demonstrates how they were followed up over time and how many were lost to follow-up during the study duration (Figure 5.1).

5.1.1 Recruitment

There were 1289 admissions with an initial diagnosis of TBI over the 2 year period of this study from February 2013-Jan 2015. All of these cases were admitted via the Emergency Department with an initial diagnosis of TBI and spent at least one night in hospital. A small number of patients were transferred to neurosurgery and these were picked up by liaison visits by the head injury team to neurosurgery. It was not possible to calculate the exact number of these cases as this was not documented but it is estimated at fewer than 50. However it is also important to accept that a very small number of TBI cases may not have been traced and therefore could be lost to follow-up. Many

of the most severe injuries are admitted to ITU and may also be lost if not picked up by head injury services. However this is very unlikely due to the daily ward round carried out on ITU.

From the 1289 admissions, 173 were excluded as they had previous documented and treated TBI, dementia or could not be followed up locally. In 260 cases, the diagnosis of TBI could not be confirmed either from direct interview of the patient during admission or by examination of the medical records after the individual had been discharged. These decisions were all made after examination of patient, records or both by the author.

5.1.2 Initial appointments

The head injury service sent out appointments to the remaining 856 individuals over the time period of the study. The majority of appointments were made within 8-10 weeks and each individual was encouraged to attend the initial clinic by pre-clinic phone call and text message. Those who failed to attend were called again to emphasise the importance of attendance and a new appointment arranged. This process was also repeated at 1 year. This has undoubtedly improved the pick-up and follow-up rate of the study to establish a high quality cohort that has been followed up over the time period with minimal loss.

Over the study period, 803 attended for the initial follow-up with another 29 failing the criteria at the appointment (dementia, moved area, previous TBI, unable to meet the diagnostic criteria of TBI). The remaining 53 did not attend despite repeated attempts by letters, text messages and phone calls.

The net result was a total of 774 patients attending the initial assessment at 10 weeks and being included in the study (Figure 5.1).

5.1.3 One year appointments

Over a 1 year period, despite efforts to call patients and encourage re-attendance, a further 46 patients were lost to follow-up and 38 died. It is possible that some of the missing cases have also died but hospital and GP records were checked for each patient to try and minimise such errors. The IT systems for the hospital and community care are now integrated so that patient deaths will be recorded and such errors are unlikely.

This resulted in a total of 690 patients with both initial and 1 year follow up data. However for analysis using the global outcome measure (GOSE) it was possible to include the deaths in the cohort as these are an outcome. Therefore this number was 728 or 94% of the initial cohort.

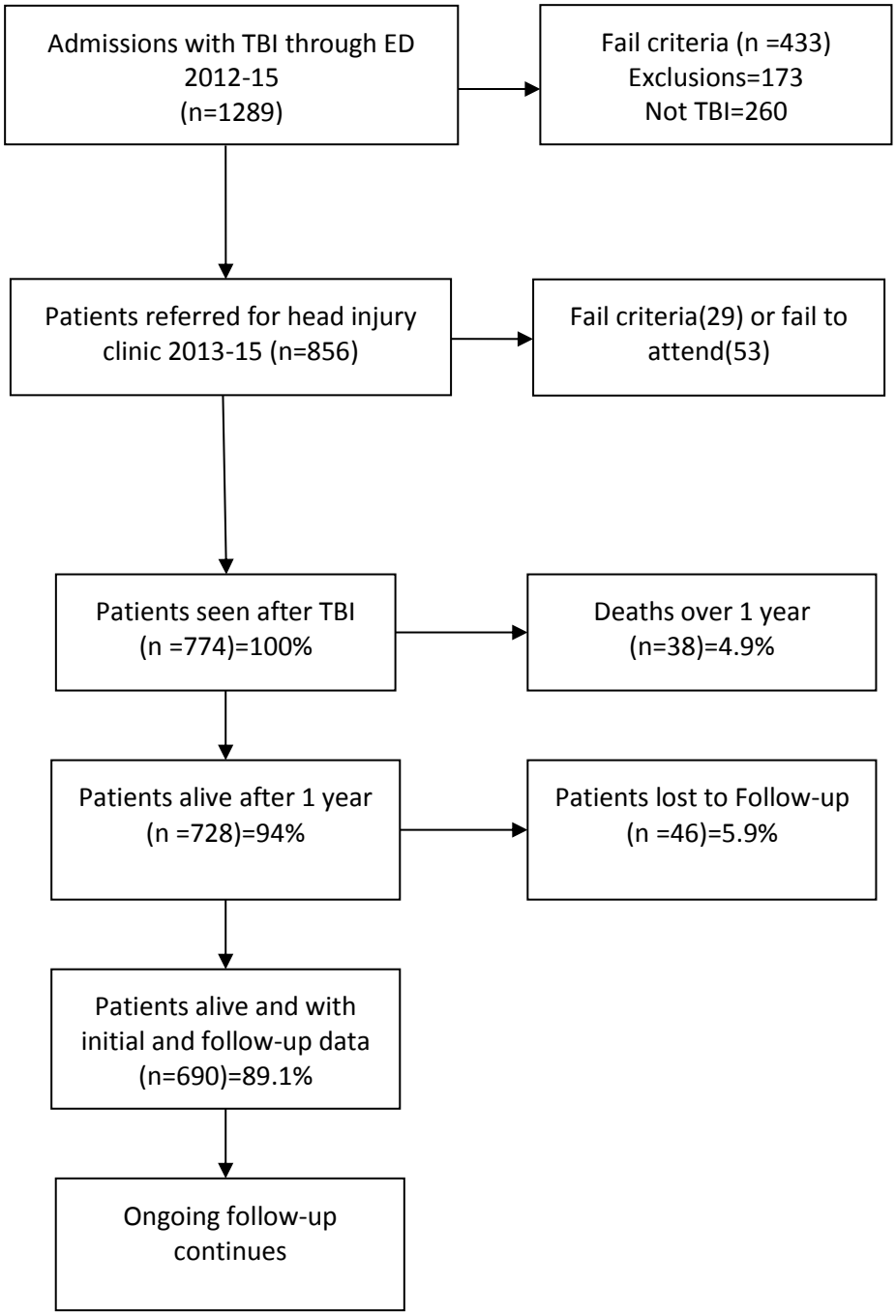


Figure 5.1: Study patients and follow-up numbers. Lost numbers and failed criteria explained in text

5.2 Comparison with patients lost to follow up at 1 year

5.2.1 Introduction

In any study, it is important to compare those who complete the study with those who drop out. This ascertains if there is any difference in the two groups. Often, many individuals are lost during the course of a study, particularly in TBI research. However in this study, the drop out group was very small indeed due to letters, text messages and phone-calls requesting attendance for appointments. In total there were 46 (5.9%) individuals who did not attend or could not be contacted after one year. This was one of the study's main strengths.

This section will compare the lost group to those with 1 year follow-up to highlight differences in any of the independent variables. There is also a group of individuals who were lost at the very start of the study (53 cases). There is limited data on this group as they were never entered into the study database and never had any assessments carried out. Therefore it is not possible to make any meaningful comparison to the patients who actually attend the clinic.

5.2.2 Continuous Variables

	Follow-up (728)	Lost (46)	t score	df	p-value
Age, mean (SD)	46.5(19.0)	53.2(21.5)	5.3	772	0.022*
Length of Stay (SD)	8.8(14.2)	7.2(12.1)	0.54	772	0.464
GCS (SD)	11.8(3.0)	12.3(2.9)	1.0	772	0.313
Anxiety Score (SD)	8.7(5.2)	6.6(5.7)	7.0	772	0.008*
Depression Score (SD)	8.2(5.1)	6.3(5.2)	6.2	772	0.013*
RHIFUQ (SD)	15.9(10.7)	11.8(9.7)	7.5	772	0.006*
RPCS (SD)	18.7(12.5)	13.6(10.4)	7.4	772	0.007*
GOSE (SD)	5.42 (1.32)	5.85 (1.48)	2.13	772	0.033*
Time to Appt	44.63 (19.8)	43.11 (18.1)	-0.508	772	0.612

Table 5.2.1: Differences in follow-up and lost groups for continuous variables

Individuals that were lost to follow-up are older by almost 7 years; this was not anticipated. In general most studies find that lost patients are younger and more likely to move address or be uncontactable.

Lost patients also had lower scores on their 10 week psychological questionnaires; this suggests that they have a better outcome early after injury. It may therefore be postulated that such individuals are less inclined to come to clinic after one year as their symptoms have resolved. In support of this view, is that these individuals have a tendency to milder brain injury (with a higher GCS) and a shorter LoS but these differences were not significant.

5.2.3 Categorical Variables

5.2.3.1 Demographic variables

Variable		Follow-up(728)	Lost (46)	χ^2-test	df	p-value
Gender						
	Male	507 (69.6)	28 (60.9)	1.56	1	0.212
	Female	221 (30.4)	18 (39.1)			
Aetiology						
	Fall	263 (36.1)	13 (28.3)	3.4	4	0.494
	RTC	191 (26.2)	15 (32.6)			
	Assault	137 (18.8)	6 (13.0)			
	Sport	48 (6.6)	4 (8.7)			
	Other	59 (8.2)	8 (17.4)			
Social Isolation						
	No	416 (57.1)	27 (58.7)	1.02	2	0.599
	Yes	296 (40.7)	17 (37.0)			
	Nursing Home	16 (2.2)	2 (4.3)			
Warfarin						
	No	667 (91.6)	41 (89.1)	0.344	1	0.558
	Yes	61 (8.4)	5 (10.9)			
Comorbidity						
	No	491 (67.4)	34 (73.9)	0.829	1	0.362
	Yes	237 (32.6)	12 (26.1)			
Past Psych History						
	No	568 (78.0)	37 (80.4)	0.148	1	0.701
	Yes	160 (22.0)	9 (19.6)			

Table 5.2.2: Differences in follow-up and lost groups for Demographic variables

There was no difference in any of these variables suggesting that patients lost to follow up are no different to those who are successfully found and re-attend. This is reassuring as regards these variables.

5.2.3.2 Ethnicity, Socioeconomic Class and Employment

Variable	Follow-up(728)	Lost (46)	Fisher Exact or χ^2-test	df	p-value
Ethnicity*					
White	678 (93.1)	44 (95.7)	2.116	4	0.714
South Asian	33 (4.5)	2 (4.3)			
Black	12 (1.6)	0 (0)			
Oriental	3 (0.4)	0 (0)			
Other	2 (0.3)	0 (0)			
(Non-white)	50 (6.9)	2 (4.3)	0.508	1	0.510
Social Class*					
Professional	41 (5.5)	2 (4.3)	24.27	8	0.002*
Lower managerial	111 (15.2)	12 (26.1)			
Intermediate	50 (6.9)	5 (10.9)			
Self-employed	58 (8.0)	11 (23.9)			
Lower supervisor	105 (14.4)	5 (10.9)			
Semi-routine	181 (24.9)	7 (15.2)			
Routine	101 (13.9)	1 (2.2)			
Never worked	42 (5.8)	1 (2.2)			
Students	39 (5.4)	2 (4.3)			
Employment					
Yes	492 (67.6)	26 (56.5)	5.22	2	0.074
No	99 (13.6)	5 (10.9)			
Retired	137 (18.8)	15 (32.6)			

*Comparison of ethnicity and socioeconomic class is with Fisher Exact test. Other variables examined with χ^2-test

Table 5.2.3: Differences in follow-up and lost groups for ethnic group, socioeconomic class and employment at time of injury. Comparison of ethnicity and socioeconomic class is with Fisher Exact test. Other variables examined with χ^2-test

There were no differences between the groups for ethnicity or for employment status at time of injury. However there was a difference in socioeconomic class; self-employed individuals were more

likely to be lost as were lower manager and intermediate professions. It is possible that self-employed patients are less likely to take time off to attend clinic as it will affect their work and pay but there is no way of testing this hypothesis with this data.

5.2.3.3 Brain Injury Variables

Variable		Follow-up(728)	Lost (46)	χ^2-test	df	p-value
Severity						
	Mild	326 (44.8)	26 (56.6)	2.44	2	0.295
	Moderate	290 (39.8)	14 (30.4)			
	Severe	112 (15.4)	6 (13.0)			
CT Findings						
	NAD	288 (39.6)	18 (39.1)	5.46	3	0.141
	Contusions	142 (19.5)	9 (19.6)			
	Bleed	231 (31.7)	18 (39.1)			
	DAI	67 (9.2)	1 (2.2)			
Hemisphere Involvement						
	NAD	288 (39.6)	18 (39.1)	2.89	2	0.236
	Unilateral	313 (43.0)	24 (52.2)			
	Bilateral	127 (17.4)	4 (8.7)			
Intoxicated						
	No	529 (72.7)	39 (84.8)	3.25	1	0.071
	Yes	199 (27.3)	7 (15.2)			

Table 5.2.4: Differences in follow-up and lost groups for Brain Injury variables

There were no significant differences between groups for these brain injury variables.

5.2.4 Psychological Measures/Work/Global Outcome

Variable		Follow-up(728)	Lost (46)	X^2-test	df	p-value
Depression Case 10 wks						
	No	312 (42.9)	26 (56.5)	3.28	1	0.070
	Yes	416 (57.1)	20 (43.5)			
Anxiety Case 10 wks						
	No	327 (44.9)	28 (60.9)	4.43	1	0.035*
	Yes	401 (55.1)	18 (39.1)			
Job at 10 wks						
	No	314 (43.1)	19 (41.3)	3.04	2	0.219
	Reduced	208 (28.6)	9 (19.6)			
	Yes (same)	206 (28.3)	18 (39.1)			
GOSE 10 wks						
	VS and Severe Lower	21 (2.8)	1 (2.2)	9.78	5	0.134
	Severe Upper	181 (24.9)	7 (15.3)			
	Moderate Lower	227 (31.2)	16 (34.8)			
	Moderate Upper	136 (18.7)	6 (13.0)			
	Good Lower	97 (13.3)	6 (13.0)			
	Good Upper	66 (9.1)	10 (21.7)			

Table 5.2.5: Differences in follow-up and lost groups for Psychological Measures/Work/Global Outcome at 10 week follow up

Those with anxiety or depression at 10 weeks were more likely to attend follow-up at 1 year although this was barely significant for the former and not significant for the latter. There was also a trend for those with fewer symptoms to attend at 1 year. Again this may be related to the hypothesis that those with symptoms or problems, are more likely to come to clinic for follow-up as they have problems to report. There was no difference in employment level or GOSE at 10 weeks between the two groups.

5.2.5 Summary

The number of patients lost to follow up at one year was very small and there does not seem to be any major difference in many of the demographic or injury features between those lost and those who attend one year follow-up except the presence of fewer symptoms including depression. It seems likely that those who have made a better recovery after injury are less motivated to attend clinic.

5.3 Basic Demographics of Study Population

5.3.1 Introduction

This section explores each of the variables that were measured in this study. This included demographic and injury features as well as scores on a number of questionnaires and the global outcome measure (GOSE). The distribution of each variable, either continuous or categorical, was examined. A concerted effort has been made to focus on the basic features of each variable rather than the possible interactions of variables with one another. However an understanding of some of these interactions is important in order to understand the study population e.g. gender and age or aetiology and injury severity. These relationships are described in more detail in Appendix 3 with a few tables that explore some of the key relationships between variables as well as graphs of each variable's distribution. However a concerted effort was made to avoid excessive over-examination of variables with one another.

Study variables can broadly be divided into two groups:

a. pre-injury features (Table 5.3.1)
b. injury features (Table 5.3.2)

For each group, the following tables depict mean values or numbers in each category.

	N or mean	% or SD
Age (yrs)	46.92	19.25
Gender		
Male	535	69.1
Female	239	30.9
Ethnicity		
White	722	93.3
South Asian	35	4.5
Black	12	1.5
Oriental	3	0.4
Other	2	0.3
(Non-white)	52	6.7
Social Class		
Professional	43	5.6
Lower managerial	123	15.9
Intermediate	55	7.1
Self-employed	69	8.9
Lower supervisor	110	14.2
Semi-routine	188	24.3
Routine	102	13.2
Never worked	43	5.6
Students	41	5.3
Employment		
Yes	518	67.0
No	104	13.4
Retired	152	19.6
Social Isolation		
No	443	57.2
Yes	313	40.4
Nursing Home	18	2.4

Table 5.3.1: Basic Demographics of Study Group; pre-injury factors

5.3.2 Pre-Injury Factors

The mean age of individuals was 46.92yrs (SD19.25). This is recorded as the age at time of injury. The distribution curve (Figure 5.3.1) shows a good approximation to a normal curve with a very slight positive skew which corresponds to the known peak of TBI in younger populations. The normal distribution satisfactorily reflects efforts to ensure a representative population especially inclusive of elderly patients.

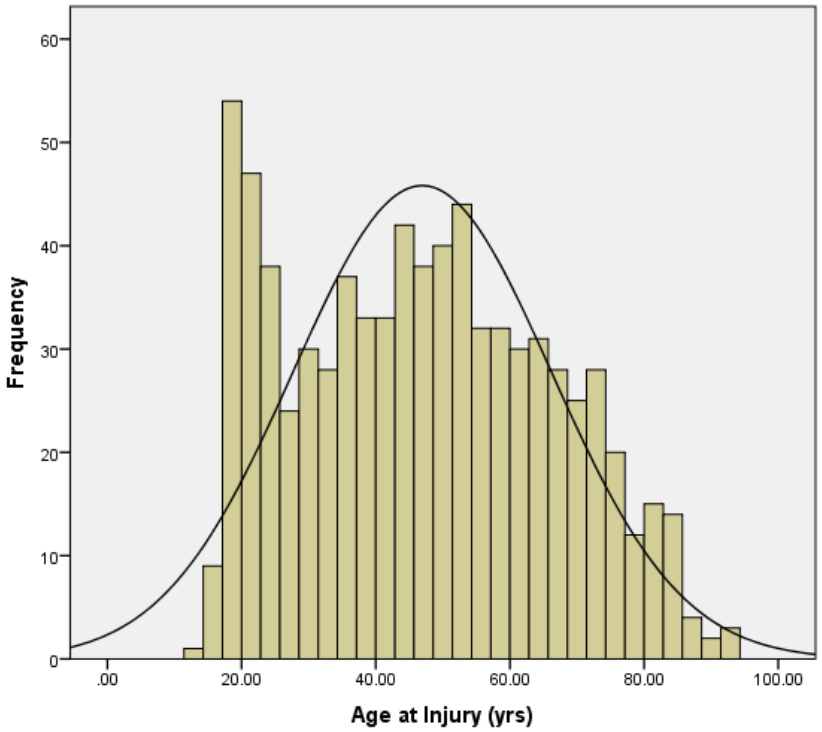


Figure 5.3.1: Distribution of Age at Injury

Males outnumbered females by more than 2 to 1. Furthermore males were 8 years younger than the female group (44.5 v 52.1) and also had more severe brain injury with lower GCS (11.67 v 12.39) reflecting the considerable differences between the male and female populations that experience TBI. More details are found in Appendix 3.

This study population did not truly seem to reflect a multi-ethnic society; only 6.7% of the population were non-white, using the classification system that is employed across NHS Trusts. Some ethnic groups were very poorly represented e.g. in the Oriental group, there were only 3 patients, all of whom were university students in Sheffield. Given the small numbers in some categories, ethnicity was reclassified as white and non-white. This new group was used in further analyses.

For socioeconomic class, this project utilised the classification system devised for use in the National Census, replacing the old Registrar-General classification of 1910. These numbers showed a fair distribution across all socioeconomic groups but compared to national averages, (ons.gov.uk) there were slightly fewer professional and slightly more long-term unemployed individuals in this group.

There was a relatively high unemployment rate in this group of 13.4%. This is considerably higher than the national average during the time of the study (6.2% at August 2014). In line with attempts to ensure that the elderly were not excluded, almost 20% of the population were retired.

A considerable proportion of the population were socially isolated with little or no family, friend or carer support. There was a relatively small number of cases from Nursing Homes (<3%).

	N or Mean	% or SD
Aetiology		
Fall	276	35.7
RTC	206	26.6
Assault	143	18.5
Sport	52	6.7
Other(work)	97	12.5
Warfarin	66	8.2
Comorbidity	249	32.3
Alcohol at injury	206	26.6
Psychiatric Hx	169	21.8
GCS	11.89	3.0
Severity		
Severe	118	15.2
Moderate	304	39.3
Mild	352	45.5
CT Scan Findings		
Nil	306	39.5
Mild	151	19.5
Moderate	250	32.3
Diffuse	67	8.7
Hemisphere Involved		
Nil on scan	306	39.5
Unilateral	334	43.2
Bilateral	134	17.3

Table 5.3.2: Basic Demographics of Study Group; injury factors

5.3.2 Injury factors

The majority of cases were caused by simple falls with road traffic collisions second, as demonstrated in Figure 5.3.2. This data seems representative of international large studies which show that the increasing proportion of falls is consistent with the ageing of the population [Tagliaferri 2006]. Given the large numbers recruited in the study, it was possible to identify a group that experience injuries through sporting activities; riding a mountain bike or a horse were the most common causes in this category. The category entitled “Other” predominantly constituted people injured at a place of employment or a fall from height greater than 2 metres. The age of those in the

categories of RTC or assault was younger and more likely to be male. Details of these differences are included in Appendix 3.

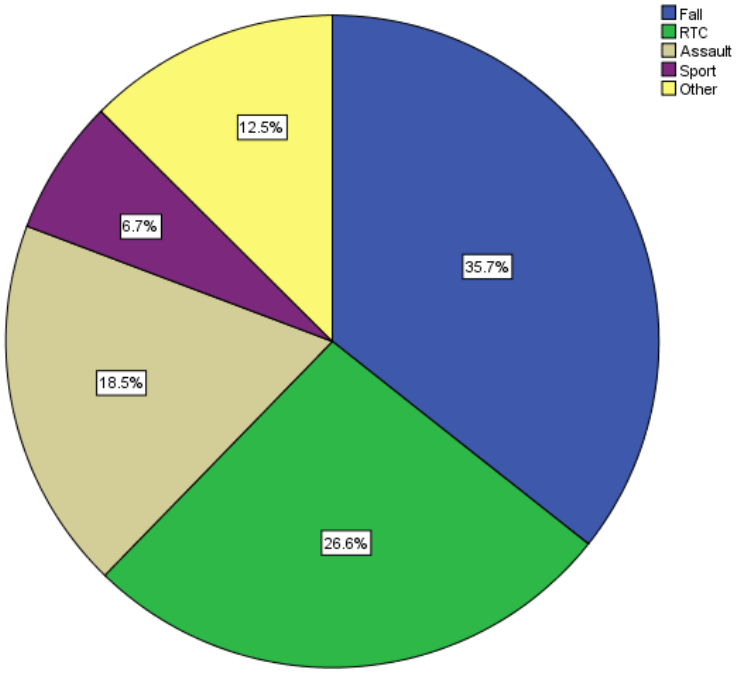


Figure 5.3.2: Aetiology of TBI cases

A high proportion of individuals (32.2%) had significant comorbidities. In a similar vein to results with warfarin, these patients were older (60.5 v 40.5 years). 60 individuals (8.2%) were on Warfarin. These individuals were older as may be expected because of the medical conditions that this group will have which require anticoagulation (70.3 v 44.7 years).

A high proportion of individuals (26.6%) were intoxicated at the time of admission. This figure seems quite high. Part of the explanation may be that assessment of such individuals is difficult and

often necessitates keeping them for longer observation. Therefore a higher proportion of intoxicated TBIs are detained in hospital.

Similarly, a high proportion of individuals (21.8%) also had a previous psychiatric history.

Brain injury severity can be classed in two ways, namely GCS or categories of mild, moderate and severe and both are shown in the table.

The distribution of GCS is represented in Figure 5.3.3 and shows a marked negative skew. Despite this skew, the mean GCS of 11.89 is similar to the median of 12. These averages suggest a tendency towards milder form of injury. This is confirmed by classification into mild, moderate and severe injury that shows almost half of individuals had a mild TBI. Division of TBI into categories often allows easier comparisons to be made. In this population, the gradient of severity of TBI was reflected in the length of stay for patients in each category as shown in Appendix 3 but there was no difference in age.

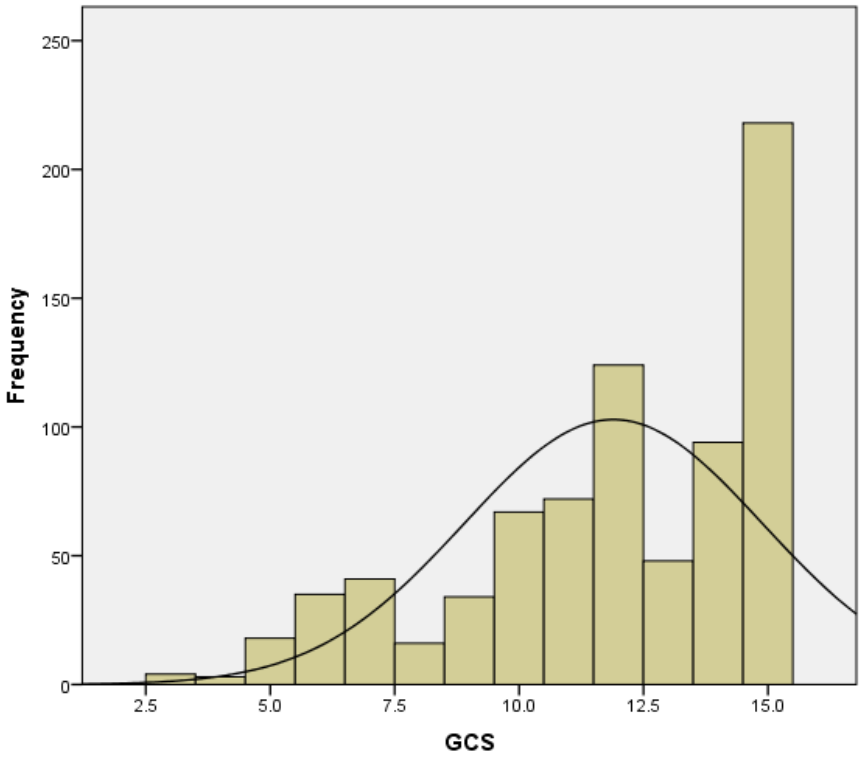


Figure 5.3.3: Distribution of Glasgow Coma Score

Classification of CT findings used the "overall appearance" method [Wardlaw 2002]. It was quite easy to apply in clinic and was very useful in this mixed TBI population. The largest group were those with a normal CT scan while those with diffuse abnormalities on scanning were relatively few (8.7%).

This hierarchy of CT severity seemed to be reflected in length of stay and GCS between the categories as shown in Appendix 3.

Similarly the majority of abnormal scans only involved one brain hemisphere with relative few affecting both sides of the brain. This information on hemisphere involvement did not offer any information over the findings of CT scans and was therefore not used in any further analysis.

The distribution of length of stay is shown in Figure 5.3.4. It is heavily skewed in a positive direction i.e. towards short lengths of stay; this is undoubtedly due to the preponderance of mild and moderate injuries which tend to have shorter inpatient stay. Compared to the mean of 8.68 days the median was only 3 days (range 1-83). In total, 494 (63.5%) of admissions were 3 days or less and only 123 (15.9%) were over 14 days. The latter were predominantly severe injuries.

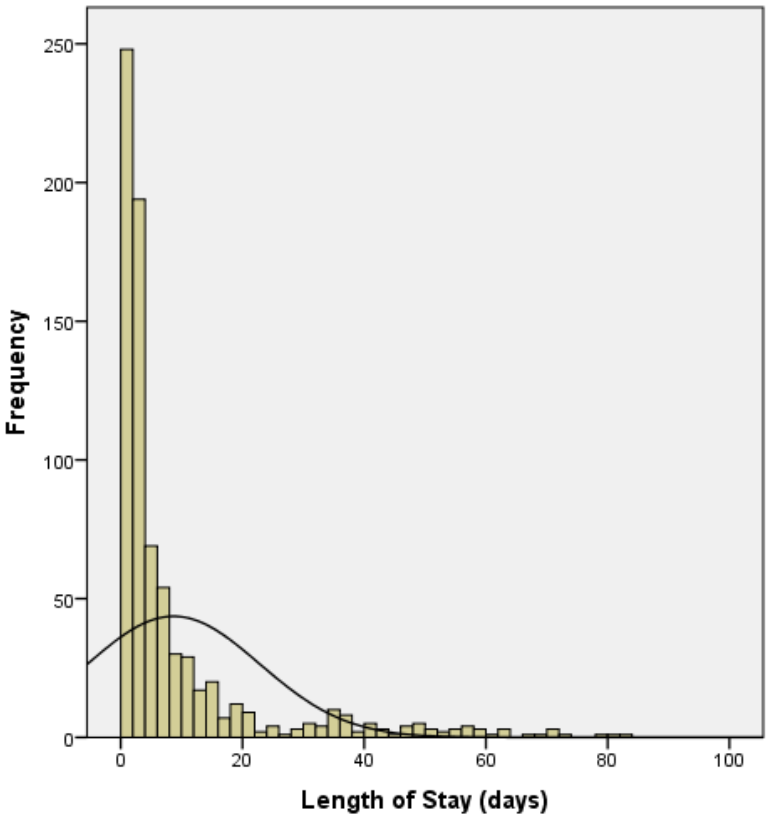


Figure 5.3.4: Distribution of Length of Stay (days)

5.4 Correlation Matrices of Study Variables

5.4.1 Introduction

This section examines the relationships between all of the study variables. These include the demographic features, injury features, psychological scores and outcome measures in the study. This has been demonstrated in three separate Tables as there are many variables to explore. The first examines demographic and injury features and the relationships between them (Table 5.4.1). The next table looks at the outcome measures and neuropsychological questionnaires (Table 5.4.2). The last table (Table 5.4.3) looks at a combination of these variables and compares the psychological/outcome measures (columns) with the demographic/injury features (rows). It is more detailed than the previous two tables and to allow it to be fitted into the page setting, each variable only appears once, on either the rows or columns. To include all variables in a full matrix, with each variable appearing in row and column, would have resulted in a table four times the size of the one presented here.

These analyses allow an evaluation as to which variables are closely related to one another and warrant closer examination. It also allows for an assessment of which variables are *very* closely correlated ($r>0.8$). Variables that are highly correlated, are likely to be measuring very similar constructs and care is required in including such variables in any model together. The output in a multivariable model is affected by such closely correlated scores.

5.4.2 Demographic and Injury Features

Most of the variables in this Table are binary measures. In general there did not seem to be high correlations between most of these features although injury severity (GCS) does relate to length of stay and CT scan findings. Treatment with warfarin and medical comorbidities were related to age as may be expected.

	Age	LoS	GCS	Gender	Social Isoln	White Ethnicity	Aetiol	Psych Hx	Intox	Warfarin	Comorb	CT Scan	Job at 1y	NS-SEC	Pre-inj job
Age	-														
Length Stay	0.051														
GCS (3-15)	0.028	-0.621													
Gender	0.181	-0.087	0.111												
Social Isoln	0.015	0.087	-0.091	-0.026											
White Ethnicity	0.170	0.039	-0.008	0.090	-0.037										
Aetiology	-0.305	0.036	-0.103	-0.105	0.056	-0.059									
Psych Hx	-0.017	0.040	-0.131	0.060	-0.003	-0.033	0.004								
Intox	-0.261	-0.087	-0.060	-0.194	-0.118	0.068	-0.049	0.156							
Warfarin	0.372	-0.026	0.114	0.056	-0.033	0.063	-0.183	-0.083	-0.132						
Comorbid	0.486	-0.008	0.025	0.126	-0.016	0.063	-0.220	0.145	-0.121	0.305					
CT Scan	0.080	0.376	0.577	-0.071	0.070	0.021	0.029	0.119	0.080	-0.052	0.091				
Job at 1yr	0.266	-0.167	0.134	0.055	0.056	0.023	-0.146	-0.131	-0.195	0.155	0.232	-0.055			
NS-SEC	-0.195	-0.046	-0.004	-0.037	-0.065	-0.107	0.004	0.038	0.114	-0.027	0.047	-0.012	0.040		
Pre-inj job	0.676	0.031	0.052	0.147	-0.008	0.067	-0.299	-0.004	-0.170	0.336	0.455	0.048	0.309	-0.014	-

Table 5.4.1. Correlation Matrix of Demographic and Injury features

Psych Hx is previous psychiatric history. Intox is alcohol intoxication at injury. NS-SEC is socioeconomic class. Pre-inj job is employment status prior to injury

5.4.3 Psychological and Outcome measures

There were some very high correlations in this analysis (Table 5.4.2). It was noted that scores tended to be highly correlated with other scores taken at the same time point rather than with the same measure taken at a different time. e.g. Dep2 is better correlated with all other measures at time2 (or one year) rather than with Dep1. This suggests that scores tend to be high or low at the same time. Nevertheless, all scores seemed to show high levels of correlation with one another irrespective of time.

It was also apparent that global outcome at 1 year (GOSE2) shows much less correlation to the questionnaire scores than GOSE1. This suggests that short-term outcome can be more easily predicted by a combination of injury features and questionnaire scores. However in the longer-term there must be other factors that influence outcome, making prediction considerably more difficult. In other words, short-term outcome is more predictable than long-term.

5.4.4 Population and psychological/outcome measures

There are a lot of variables in this analysis (Table 5.4.3). If each variable was placed in rows and columns, the table would be four times the size. Instead, the injury features and demographics have been placed in the rows and the questionnaires and outcomes in the columns.

There are considerable variations in these results but a few general comments can be made**.** In general, gender, social isolation, ethnicity, socioeconomic class, pre-injury employment, aetiology, warfarin and comorbidity have low correlations with the questionnaires and outcomes including depression.

Age seems to have an intermediate correlation to scores especially on GOSE2 and job

Injury severity(GCS), CT scan findings, previous psychiatric history and alcohol intoxication all have strong correlations with psychological scores/outcome. However while injury features such as severity and CT scan findings had high correlation with job and global outcome at 10 weeks, it was much weaker at 1 year. This suggests that global outcome at 1 year may be different to outcome at 10 weeks and that factors other than the injury features itself are at play in determining long term outcomes.

	GCS	Dep1	Dep2	Anx1	Anx2	FUQ1	FUQ2	PCS1	PCS2	GOSE1	GOSE2	Job1	Job2
GCS (3-15)	-												
Dep1 (3-21)	-0.389												
Dep2	-0.309	0.605											
Anx1(3-21)	-0.370	0.875	0.588										
Anx2	-0.298	0.561	0.897	0.569									
FUQ1(0-40)	-0.434	0.777	0.563	0.770	0.533								
FUQ2	-0.357	0.571	0.824	0.575	0.716	0.613							
PCS1(0-64)	-0.402	0.707	0.526	0.714	0.494	0.798	0.544						
PCS2	-0.336	0.557	0.782	0.560	0.767	0.571	0.857	0.585					
GOSE1 (3-8)	0.507	-0.747	-0.584	-0.734	-0.555	-0.742	-0.573	-0.688	-0.564				
GOSE2(3-8)	0.249	-0.331	-0.167	-0.336	-0.152	-0.301	-0.151	-0.296	-0.153	0.444			
Job1		-0.624	-0.512	-0.602	-0.476	-0.601	-0.492	-0.569	-0.491	0.779	0.354		
Job2	0.134	-0.169	-0.440	-0.154	-0.441	-0.195	-0.430	-0.173	-0.425	0.163	0.114	0.265	-

Table 5.4.2. Correlation Matrix of Psychological Questionnaires and Outcomes

Variables with a “1” are the 10 week scores and “2” are at one year. Anx and Dep are the level of anxiety and depression scores between 3-21; FUQ is the Rivermead Head Injury Follow-up questionnaire out of 40; PCS is the Post-Concussion symptom score out of 64; GOSE is the Glasgow Outcome Score (Global outcome) for the patient and scored from 1 (dead) to 8 (completely normal). Very strong correlations are shaded in yellow ($\rho>0.7$)

	Dep1 at 10 wks	Dep2 at 1yr	Anx1 at 10wks	Anx2 at 1yr	FUQ1 at 10wks	FUQ2 at 1yr	PCS1 at 10 wks	PCS2 at 1yr	Job at 10 wks	Job at 1yr	GOSE1 at 10 wks	GOSE2 at 1yr
Age	-0.063	-0.104	-0.112	-0.122	-0.052	-0.108	-0.118	-0.128	0.149	0.266	0.011	-0.224
Length Stay	0.209	0.211	0.200	0.214	0.292	0.258	0.265	0.230	-0.244	-0.167	-0.312	-0.130
GCS (3-15)	-0.389	-0.309	-0.370	-0.298	-0.434	-0.357	-0.402	-0.335	0.434	0.134	0.507	0.249
Gender	-0.010	0.017	-0.016	0.001	0.055	-0.025	-0.011	0.007	0.059	0.055	0.036	-0.043
Social Isoln	-0.034	-0.084	-0.037	-0.080	-0.003	-0.032	-0.028	-0.043	0.036	0.056	0.032	-0.027
White Ethnicity	-0.088	-0.030	-0.086	-0.040	-0.091	-0.039	-0.071	-0.036	0.029	0.023	0.008	-0.044
Aetiology	0.074	0.069	0.091	0.078	0.107	0.084	0.128	0.104	-0.125	-0.145	-0.078	0.015
Psych Hx	0.334	0.331	0.318	0.325	0.319	0.280	0.302	0.314	-0.292	-0.131	-0.353	-0.212
Intox	0.301	0.344	0.310	0.307	0.178	0.252	0.205	0.254	-0.280	-0.195	-0.258	-0.090
Warfarin	-0.075	-0.107	-0.091	-0.095	-0.071	-0.104	-0.116	-0.115	0.090	0.155	0.069	-0.061
Comorbid	-0.018	-0.021	-0.004	-0.046	-0.009	-0.057	-0.032	-0.082	0.056	0.232	-0.017	-0.139
CT Scan	0.299	0.245	0.311	0.259	0.339	0.279	0.334	0.255	-0.341	-0.055	-0.402	-0.265
Job at 1yr	-0.169	-0.512	-0.154	-0.476	-0.601	-0.492	-0.569	-0.491	0.265	1	0.729	0.354
NS-SEC	0.055	0.054	0.077	0.048	0.013	0.038	0.025	0.053	-0.071	0.040	-0.066	0.022
Pre-injury Job	-0.072	-0.114	-0.086	-0.129	-0.079	-0.117	-0.131	-0.156	0.161	0.309	0.029	-0.215

Table 5.4.3. Correlation Matrix of Population and injury features (rows) and psychological questionnaires and outcomes (columns)

Variables with "1" are the 10 week scores and "2" are at one year. Dep, Anx scores measure depression and anxiety level; FUQ is psychosocial score; PCS is head injury symptoms level; GOSE is global outcome score. Psych Hx is previous psychiatric history. Intox is alcohol intoxication at injury. NS-SEC is socioeconomic class. Pre-injury job is employment status prior to injury. Moderate correlations (0.3 to 0.5) are shaded peach and strong correlations (>0.5) are shaded yellow

5.5 Depression and other outcomes at 10 weeks

This section examines the point prevalence of depression and the other outcome measures at 10 weeks.

5.5.1 Depression and anxiety

The use of the HADS to assess depression involves using a cut off between 8 and 9 to distinguish cases [Bjelland 2002, Hermann 1997]. The exact distribution of scores on the HADS can be seen in Table 5.5.1 and Appendix 3 contains graphs of the depression and anxiety scores at 10 weeks and 1 year. The range of scores on the HADS is from 0-21.

From the results at ten weeks, those individuals with a score >8 was 436 or 56.3% which is a very high level of depression [95%CI 52.8-59.8]. Although 8/9 is the usual cut off described in the literature, some choose a second cut off above 11 to represent severe depression [Hermann 1997]. This would result in a total of 226 individuals or 29.2% being diagnosed with depression [95%CI 26.1-32.5].

HADS-D Score	Number (%)	Cumulative %
0	64 (8.3%)	8.3
1	44 (5.7%)	14.0
2	50 (6.5%)	20.4
3	43 (5.6%)	26.0
4	46 (5.9%)	31.9
5	19 (2.5%)	34.4
6	32 (4.1%)	38.5
7	26 (3.4%)	41.9
8	14 (1.8%)	43.7
9	62 (8.0%)	51.7
10	79 (10.2%)	61.9
11	69 (8.9%)	70.8
12	68 (8.8%)	79.6
13	47 (6.1%)	85.7
14	41 (5.3%)	91.0
15	24 (3.1%)	94.1
16	13 (1.7%)	95.7
17	19 (2.5%)	98.2
18	9 (1.2%)	99.4
19	2 (0.3%)	99.6
20	1 (0.1%)	99.7
21	2 (0.3%)	100

Table 5.5.1; distribution of HADS-D scores for initial depression

The HADS is also a measure of anxiety symptoms and a similar calculation for the anxiety scores can be carried out. The number of individuals who would be diagnosed with anxiety would be 419 (54.1%, 95%CI 50.6-57.6). Using the higher cut-off score >11, results in 272 or 35.1% of individuals [95%CI 31.9-38.6].

5.5.2 Other outcome measures at 10 weeks

Table 5.5.2 shows the other outcome measures in the project as well as the mean depression and anxiety scores. The RHFUQ (Rivermead Head Injury Follow-up Questionnaire), the RPCS (Rivermead Post-concussion Score) and GOSE (Extended Glasgow Outcome Score) were all administered at 10 weeks and again at 1 year. Levels of 18.42 (out of 64) and 15.94 (out of 40), represent high levels of TBI symptoms and participation limitation (handicap) respectively.

	N or mean	% or SD
Length of Stay (d)	8.68	14.15
HADS Anxiety score 1	8.56	5.27
HADS Depression score 1	8.14	5.10
RHFUQ 1	15.94	10.66
RPCS 1	18.42	12.41
GOSE 1	5.44	1.33
Time to 1st Appt (d)	62.94	18.16
Employment 1		
No	333	43.1
Partial	217	28.0
Full	224	28.9

Table 5.5.2: outcome measures at 10 week review

As a result of deaths (38) and individuals lost to follow-up (46), the 1 year group has 690 individuals compared to the 774 in the initial group. The 1 year results are shown in section 5.8

The mean GOSE corresponds to a level between moderate disability lower and upper (higher score is a better outcome). This is difficult to interpret but Table 5.5.3 shows the distribution of the group across the categories of GOSE. From this it can be seen that only 23% of individuals fall into the good outcome group and 27% had a severe disability outcome. This is a very poor extent of recovery although 10 weeks is early to judge overall outcome. Results should be compared to the 1 year outcome in 5.8.

GOSE Level	Number at 10 Weeks (774)
1 Death	0 (0)
2 VS	1 (0)
3 Severe Lower	21 (2.7)
4. Severe Upper	188 (24.3)
5. Moderate Lower	243 (31.4)
6. Moderate Upper	142 (18.3)
7. Good Lower	103 (13.3)
8. Good Upper	76 (9.8)

Table 5.5.3: GOSE at 10 weeks

5.6 Univariable tests on Initial depression and independent variables

5.6.1 Introduction

This section of results looks at the univariable relationships between all independent variables compared to initial depression as the dependent variable, using an appropriate statistical test. This was either a χ^2 test or Fisher Exact Test for categorical variables and a univariable regression for continuous variables.

The aim was to identify where relationships exist between study variables and depression. This would give a sense of the variables that are more likely to be significant in a full multivariable model which is the true test to determine independent predictors of depression.

As in previous sections it was helpful to consider variables in three groups. Firstly those that can be considered pre-injury factors such as socioeconomic class, ethnicity, gender and age (Table 5.6.1). The second group is injury factors such as aetiology, TBI severity or CT appearance (Table 5.6.2) and finally a third group of outcomes and questionnaires (Table 5.6.3). Most of the latter group are continuous variables.

	N(%) or mean(SD)	Depressed; N(%) or mean(SD)	Not Depressed; N(%)or mean(SD)	Regression or χ^2, p-value
Age (yrs)	46.92 (19.25)	45.6(18.10)	48.6(20.5)	2.15,df772, p=0.032*
Gender (M)	535 (69.1)	305 (57)	230 (43)	0.324,df1,
(F)	239 (30.9)	131 (54.8)	108 (45.2)	p=0.569
Ethnicity				
White	722 (93.3)	400 (55.4)	322 (44.6)	7.11, df4,
South Asian	35 (4.5)	27 (77.1)	8 (22.9)	p=0.130
Black	12 (1.5)	7 (58.3)	5 (41.7)	
Oriental	3 (0.4)	1 (33.3)	2 (66.7)	
Other	2 (0.3)	1 (50)	1 (50)	
(Non-white)	52 (6.7)	36 (69.2)	16 (30.8)	3.77,df1, 0.052
Social Class				
Professional	43 (5.6)	18 (41.9)	25 (58.1)	14.09, df8,
Lower managerial	123 (15.9)	67 (54.5)	56 (45.5)	p=0.082
Intermediate	55 (7.1)	34 (61.8)	21 (38.2)	
Self-employed	69 (8.9)	39 (56.5)	30 (43.5)	
Lower supervisor	110 (14.2)	56 (50.9)	54 (49.1)	
Semi-routine	188 (24.3)	113 (60.1)	75 (39.9)	
Routine	102 (13.2)	60 (58.8)	42 (41.2)	
Never worked	43 (5.6)	31 (72.1)	12 (27.9)	
Students	41 (5.3)	18 (43.9)	23 (56.1)	
Employment Status				
Yes	518 (67.0)	295 (56.9)	223 (43.1)	23.31, df2,
No	104 (13.4)	76 (73.1)	28 (26.9)	p<0.001*
Retired	152 (19.6)	65 (42.8)	87 (57.2)	
Social Isolation				
No	443 (57.2)	239 (54)	204 (46)	3.6, df2,
Yes	313 (40.4)	184 (58.8)	129 (41.2)	p=0.162
Nursing Home	18 (2.4)	13 (72.2)	5 (27.8)	

Table 5.6.1: Univariable analysis of initial depression and pre-injury factors *significant for p<0.05

5.6.2 Pre-injury factors

For age there was a three year difference between non-depressed and depressed individuals. This barely reached statistical significance (p=0.032). Gender and social isolation were not significant. Ethnicity was classified using the standard NHS classification system. As the population was overwhelmingly of white ethnicity (93.3%), a number of cell counts in several of the ethnic minority

groups were very small. Hence a χ^2 test could not be carried out and a Fisher Exact Test was used. This did not show any significance. All non-white ethnicities were therefore placed into one grouping in order to allow further analysis. Comparison of this group with white ethnicity found a difference with 69.2% of non-whites experiencing depression compared to 55.4% of white individuals; this just failed to reach statistical significance.

Socioeconomic class was not statistically different between the depressed and non-depressed groups. In spite of this, there were some interesting differences between groups e.g. 41.9% of professional class were depressed compared to 72.1% of those who had never worked.

Pre-injury employment status was significantly different between groups; 73.1% of the unemployed compared to 56.9% of the employed were depressed. Those who had retired seemed even less likely to be depressed at only 42.8%.

		N(%) or Mean (SD)	Depressed; N(%) or mean(SD)	Not Depressed; N(%)or mean(SD)	Regression or χ^2 , p-value
Aetiology					
Fall		276 (35.7)	138 (50)	138 (50)	21.3, df4, p<0.001*
RTC		206 (26.6)	112 (54.4)	94 (45.6)	
Assault		143 (18.5)	104 (72.7)	39 (27.3)	
Sport		52 (6.7)	26 (50)	26 (50)	
Other(work)		97 (12.5)	56 (57.7)	41 (42.3)	
Warfarin	N	708 (91.8)	405 (57.2)	303 (42.8)	2.570, df1, p=0.109
	Y	66 (8.2)	31 (47)	35 (53)	
Comorbidity	N	525 (67.8)	300 (57.1)	225 (42.9)	0.438, df1, p=0.508
	Y	249 (32.2)	136 (54.6)	113 (45.4)	
Alcohol at injury	N	568 (73.4)	265 (46.7)	303 (53.3)	81.2, df1, p<0.001*
	Y	206 (26.6)	171 (83)	35 (17)	
Psychiatric Hx	N	605 (78.2)	289 (47.8)	316 (52.2)	82.6, df1, p<0.001*
	Y	169 (21.8)	147 (87)	22 (13)	
GCS		11.89 (3.02)	10.91 (3.12)	13.11 (2.3)	10.86, df772, p<0.001
Severity					
Severe		118 (15.2)	99 (83.9)	19 (16.1)	66.7, df2, p<0.001*
Moderate		304 (39.3)	187 (61.5)	117 (38.5)	
Mild		352 (45.5)	150 (42.6)	202 (57.4)	
CT Scan Findings					
Nil		306 (39.5)	133 (43.5)	173 (56.5)	79.5, df3, p<0.001*
Mild		151 (19.5)	67 (44.4)	84 (55.6)	
Moderate		250 (32.3)	176 (70.4)	74 (29.6)	
Diffuse		67 (8.7)	60 (89.6)	7 (10.4)	
Hemisphere Involved					
Nil on scan		306 (39.5)	133 (43.5)	173 (56.5)	90.89, df2, p<0.001*
Unilateral		334 (43.2)	181 (54.2)	153 (45.8)	
Bilateral		134 (17.3)	121 (92.4)	10 (7.6)	

Table 5.6.2: Univariable analysis of initial depression and injury features

*significant for p<0.05

5.6.3 Injury features

The aetiology of the traumatic event showed differences between the two groups. This was largely due to the higher level of depression in those sustaining TBI after a physical assault (72.7%) compared to other aetiologies. It may reasonably be expected that the emotional effect of sustaining TBI from an assault on the person is more likely to induce depression than other, less violent aetiologies.

Injury severity can be represented either by GCS level or by categorising into mild, moderate and severe. In both these variables, severity was significantly different. Those with depression had more severe injury than those without depression (GCS 10.9 v 13.1). For severity in categorical format the incidence of depression dropped from 83.9% of STBI to 61.5% of moderate and 42.6% in mild.

The overall appearance of CT scan findings was also different between the two groups. With increasing severity of CT involvement, depression was far more likely. However those with a normal scan, seemed to have a similar level of depression to those with mild abnormalities on scan. These results were also reflected in the cerebral hemisphere involvement.

Those intoxicated at the time of injury or with a psychiatric history had almost double the risk of depression compared to those without these features.

	N(%) or mean (SD)	Depressed; N(%) or mean(SD)	Not Depressed; N(%) or mean(SD)	Regression or χ^2, p-value
Length of Stay (d)	8.68 (14.15)	10.94 (16.38)	5.76 (9.86)	-5.143, df772, p<0.001*
HADS Anxiety1	8.56 (5.27)	12.28 (3.27)	3.75 (2.94)	-37.62, df772, p<0.001*
RHFUQ 1	15.94 (10.66)	22.62 (8.0)	7.32 (6.76)	-28.204, df772, p<0.001*
RPCS 1	18.42 (12.41)	25.65 (10.47)	9.11 (7.55)	-24.52, df772, p<0.001*
GOSE 1	5.44 (1.33)	4.62 (0.76)	6.51 (1.13)	27.70 df772, p<0.001*
HADS Anxiety 2	6.03 (5.51)	8.62 (5.27)	2.68 (3.73)	-17.58, df772, p<0.001*
HADS Depression 2	5.57 (5.27)	8.16 (5.04)	2.22 (3.31)	-18.73, df772, p<0.001*
RHFUQ 2	11.36 (9.64)	16.24 (8.82)	4.94 (6.34)	-18.74, df772, p<0.001*
RPCS 2	13.13 (11.38)	18.80 (10.85)	5.67 (6.88)	-19.36, df772, p<0.001*
GOSE 2	5.85 (1.70)	4.85 (1.78)	6.65 (2.45)	9.86, df772, p<0.001*
Time to 1st Appt (d)	68.94 (18.16)	67.33(23.04)	69.92 (19.7)	0.597, df772, p=0.551
Time to 2nd Appt (d)	407.46 (28)	413.88 (53.90)	404.35 (62.41)	-0.923, df726, p=0.356
Employment 1				
No return	333 (43.1)	281 (84.4)	52 (15.6)	267.5, df2, p<0.001*
Partial	217 (28.0)	123 (56.7)	94 (43.3)	
Full return	224 (28.9)	32 (14.3)	192 (85.7)	
Employment 2				
No Return	198 (28.7)	165 (83.3)	33 (16.7)	213.5, df2, p<0.001*
Partial	187 (27.1)	148 (79.1)	39 (20.9)	
Full Return	305 (44.2)	79 (25.9)	226 (74.1)	

Time 1 refers to 10 week review and Time 2 refers to 1 year review. *significant at p<0.05

Table 5.6.3: Univariable analysis of initial depression and other outcome measures

5.6.4 Outcome measures / neuropsychological questionnaires

Most variables in this group were continuous variables, and therefore a univariable regression analysis was used.

Length of stay was longer by 5 days in depressed individuals; this was highly significant. Both neuropsychological questionnaires (the Rivermead Head Injury Follow-up Questionnaire and the Rivermead Post-Concussion Score) were considerably higher in those with depression, both at initial review and again at one year review. For both tests the overall mean scores had dropped considerably over 1 year as did anxiety score. As the HADS measures both anxiety and depression and both conditions denote a state of emotional disturbance, it would be expected that there would be considerable overlap between these two. Indeed out of 436 individuals who had initial depression, 396 (90.8%) also had a significant level of anxiety.

The global outcome measure (GOSE) was higher i.e. better, in non-depressed individuals than depressed (6.51 v 4.62) and again this was the case after one year. The overall GOSE improved from 5.44 to 5.85 but the latter score is heavily skewed by 38 individuals who died and therefore scored 0. If this group are excluded to only leave the 690 cases that completed questionnaires at the end of the year, then the mean GOSE rises to 6.01. This corresponds to the Moderate Upper category. Compared to the original level of outcome, this is not a very large improvement, indicating the limited improvement that many individuals make in returning to previous lifestyle.

For return to employment both at initial and one year follow-up, depression was much higher in those unable to return to work. There was a notable gradient from Full to Partial and No return. This was again apparent in the one year data. There appears to be a direct effect from the amount of return to work that an individual can manage.

5.6.5 Summary

In summary a large number of variables were shown to be significantly different between depressed and non-depressed groups. The exact nature of these univariable relationships needs to be tested in a multivariable model in the next section.

5.7 Multivariable regression analysis for depression at 10 weeks

After the initial univariable analysis of all the study variables with depression, a multivariable regression analysis was carried out using initial depression (Dep1) as the outcome measure. As this is a binary outcome, a logistic regression model was applied, entering the following factors of interest; ethnicity, socioeconomic class, pre-injury employment, gender, age, length of stay, social isolation, aetiology of injury, previous psychiatric history, comorbidity, warfarin treatment, alcohol intoxication, GCS, CT scan and return to work. In addition, socioeconomic class, social isolation, aetiology, CT scan and return to work had to be specified as categorical variables for this model as these had more than two possible categories.

A logistic regression with full entry method was applied.

The results are shown in Table 5.7.1.

	B	S.E.	df	Signif	OR	95% CI for OR Lower	Upper
Non-white Ethnicity	-1.267	0.467	1	**0.007***	3.546	1.420	8.851
Gender	0.497	0.237	1	**0.036***	1.643	1.032	2.616
Age at injury	0.014	0.009	1	0.124	1.014	0.996	1.032
Socioeconomic Class			8	0.752			
Professional	-						
Lower Manager	0.040	0.506	1	0.937	1.041	0.386	2.804
Intermediate	0.434	0.564	1	0.442	1.544	0.511	4.667
Small Employer	0.253	0.548	1	0.645	1.287	0.440	3.768
Lower Supervisory	-0.002	0.514	1	0.997	0.998	0.365	2.731
Semi-routine	-0.117	0.484	1	0.809	0.889	0.344	2.297
Routine	-0.384	0.519	1	0.460	0.681	0.246	1.885
Never Worked	0.406	0.697	1	0.560	1.501	0.383	5.887
Student	0.208	0.614	1	0.735	1.231	0.369	4.104
Pre-injury work			2	0.404			
Employed	-						
Unemployed	0.390	0.379	1	0.303	1.477	0.703	3.104
Retired	-0.214	0.384	1	0.577	0.807	0.380	1.713
Social Isolation			2	0.537			
Social Isolation- no	-						
Social Isolation- yes	-0.080	0.219	1	0.716	0.923	0.601	1.419
Soc Isol- Nurse home	-0.703	0.713	1	0.324	2.020	0.499	8.171
Aetiology			4	0.286			
Aetiology – fall	-						
Aetiology – assault	-0.012	0.311	1	0.968	0.988	0.537	1.816
Aetiology – RTC	0.672	0.365	1	0.065	1.959	0.958	4.003
Aetiology – sports	0.401	0.458	1	0.380	1.494	0.609	3.664
Aetiology – other	0.132	0.350	1	0.706	1.141	0.575	2.265
GCS	-0.217	0.052	1	**0.001***	0.806	0.718	0.905
Psychiatric Hx	1.441	0.303	1	**0.001***	4.224	2.332	7.653

Warfarin	0.437	0.389	1	0.261	1.548	0.722	3.318
Comorbidity	-0.238	0.276	1	0.389	0.788	0.459	1.354
Intoxicated	1.541	0.286	1	**0.001***	4.670	2.666	8.180
CT Scan			3	**0.007***			
CT Scan - NAD	-						
CT Scan – mild	-0.682	0.309	1	0.026*	0.506	0.277	0.928
CT Scan – moderate	0.096	0.294	1	0.744	1.101	0.618	1.961
CT Scan – severe	0.816	0.550	1	0.138	2.262	0.769	6.653
Return to Work			2	**0.001***			
No work	-						
Reduced return	-0.807	0.242	1	0.001*	0.447	0.277	0.720
Full return	-2.578	0.285	1	0.001*	0.076	0.043	0.133
Length of Stay	0.001	0.010	1	0.948	1.001	0.981	1.020
Constant	3.595	1.071	1	0.001	36.414		

Table 5.7.1: Logistic regression of Initial depression against study variables

Categories described in text

The table shows all the variables that were entered and highlights the significant results in this model.

The overall model was highly significant ($p<0.001$). Nagelkerke R^2 was 0.554. The model overall correctly classified 80.1% of cases compared to only 56.3% of cases in the model with no predictors. The Hosmer-Lemeshow Test for goodness of fit was highly significant ($\chi^2=6.339$, df8, $p=0.609$) and area under curve (AUC) was 0.890 (95% CI=0.868-0.912), $p<0.001$. This indicates an excellent fit.

From this table it can be seen that non-white ethnicity, female gender, previous psychiatric history, TBI severity, alcohol intoxication, CT scan findings and return to work were all significant variables.

Assumptions for the use of a logistic regression were tested and met. These were linear relationships between variables, normal distribution of residuals and independence of cases. Multicollinearity was also tested.

For CT scan appearance, on examining the inter-category probabilities, it can be seen that the risk of depression is higher with a normal CT scan compared to a mild abnormality. However this difference is not seen with comparison of normal scan with a moderate or a severe CT scan change. In other words, a normal scan carries a similar risk of depression to a scan with severe or moderate abnormalities and a higher risk than those with a mild abnormality. This is an unusual finding and the possible interpretation of this result is considered in the Discussion; but in brief, the normal scan group may be skewed by a higher level of somatising individuals with relatively minor head injuries who end up in this normal scan group.

In terms of return to work, the inter-category probabilities show that a partial or full return to work, carries a lesser risk of depression than the baseline of no return to work**.** In the case of those who had a partial return to work, the OR for depression compared to those who had not returned to work at all was 2.24(1.39-3.59). However those who had returned to full time previous employment had an even lower risk of depression with OR 13.15(2.51-23.26) showing a gradient effect of return to work.

Several variables that were initially significant on the univariable tests in 5.6, were no longer significant in this multivariable model. These were age, pre-injury employment status, length of stay and aetiology of injury. These variables dropped out of the model.

However, the variables of gender and ethnicity were *not* significant in the univariable analysis but became significant in the full multivariable model. This indicates why all study variables should be included in all the analyses carried out. Many studies discard variables that are not initially significant on univariable testing in any further modelling; this is discussed in 6.4.

It can therefore be stated that the independent predictors of initial depression at ten weeks are non-white ethnicity (OR 3.546, 95%CI 1.420-8.851), female gender (OR 1.643, 95%CI 1.032-2.616), previous psychiatric history (OR 4.224, 95%CI 2.332-7.653), alcohol intoxication (OR 4.670, 95%CI 2.666-8.180), injury severity (OR 0.806, 95%CI 0.718-0.905), CT Scan appearance and non-return to work after 10 weeks.

5.8 Depression and other outcome measures at 1 year

This section presents the depression scores at 1 year as well as the other outcome measures of the study. For comparison, the relevant scores at 10 weeks are also shown in this latter Table.

5.8.1 Depression at 1 year

The distribution of HADS scores for depression at one year follow up is shown in Table 5.8.1. For the 690 individuals who attended at this time, use of the usual cut off between 8 and 9, results in 284 or 41.2% [95%CI 37.6-44.9]having depression. If the stricter criteria of a score greater than 11 is utilised then the number is 117 or 17.0% [95%CI 14.3-19.9].

For the anxiety scores on the HADS at one year, a cut off of 8/9 resulted in 293 individuals having a significant level of anxiety symptoms or 42.3% [95%CI 38.8-46.2]. Using the higher cut off above 11 resulted in 149 or 21.6% [95%CI 18.7-24.8] of individuals having a significant level.

HADS-D Score	Number (%)	Cumulative %
0	119(17.2%)	17.2
1	65 (9.4%)	26.7
2	60 (8.7%)	35.4
3	46 (6.7%)	42.0
4	36 (5.2%)	47.2
5	20 (2.9%)	50.1
6	18 (2.6%)	52.8
7	27 (3.9%)	56.7
8	15 (2.2%)	58.8
9	41 (5.9%)	64.8
10	85 (12.3%)	77.1
11	41 (5.9%)	83.0
12	35 (5.1%)	88.1
13	19 (2.8%)	90.9
14	26 (3.8%)	94.6
15	10 (1.4%)	96.1
16	9 (1.3%)	97.4
17	6 (0.9%)	98.3
18	4 (0.6%)	98.8
19	6 (0.9%)	99.7
20	1 (0.1%)	99.9
21	1 (0.1%)	100

Table 5.8.1: distribution of HADS-D scores at 1 year

5.8.2 Comparing depression at 10 weeks and 1 year

Table 5.8.2 shows the overlap between those with initial and late depression. For this comparison, the 690 cases for which results at both times were available were used. Of those with initial depression, 64.8% also had late depression. Over one third however had resolved their depressive symptoms.

Out of the 298 without initial depression, the majority remained in this state (89.9%). However 30 individuals (10.1%) developed late depression.

Initial Depression	Number (%)	Late Depression	Number (%)
No	298 (43.2)	No	268 (89.9)
		Yes	30 (10.1)
Yes	392 (56.8)	No	138 (35.2)
		Yes	254 (64.8)

Table 5.8.2: Depression at 10 weeks and 1 year.

5.8.3 Overlap of depression and anxiety

Both depression and anxiety can be considered measures of emotional stress. It is therefore likely that they co-exist. The majority of individuals in this study either had both depression and anxiety or neither of the two. At 10 weeks, only 55 individuals (8.0%) had one but not the other condition. At 1 year there were only 47 (6.8%) individuals who only had one of the two conditions.

This high level of overlap means that anxiety and depression cannot be compared in the same multivariable model due to the high correlation between the two.

5.8.4 Other outcome measures at 1 year

Table 5.8.3 presents the different outcome measures and questionnaires that were administered. The RHFUQ (Rivermead Head Injury Follow-up Questionnaire), the RPCS (Rivermead Post-concussion Score) and GOSE (Extended Glasgow Outcome Score) were all administered at 10 weeks and again at 1 year. As a result of deaths (38) and individuals lost to follow-up (46), the 1 year group has 690 individuals compared to the 774 in the initial group.

	N or mean	% or SD
Length of Stay (d)	8.68	14.15
HADS Anxiety score 1	8.56	5.27
HADS Depression score 1	8.14	5.10
RHFUQ 1	15.94	10.66
RPCS 1	18.42	12.41
GOSE 1	5.44	1.33
HADS Anxiety score 2	6.03	5.51
HADS Depression score 2	5.57	5.27
RHFUQ 2	11.36	9.64
RPCS 2	13.13	11.38
GOSE 2 (728 patients)	5.85	1.80
Time to 1st Appt (d)	62.94	18.16
Time to 2nd Appt (d)	347.46	28.0
Employment 1		
No	333	43.1
Partial	217	28.0
Full	224	28.9
Employment 2		
No	198	28.7
Partial	187	27.1
Full	305	44.2

Table 5.8.3: study outcome measures. Time 1 refers to 10 week review and Time 2 refers to 1 year measure

In general, the scores across the questionnaires diminished considerably over a one year period. The HADS depression score dropped from 8.14 to 5.57, the HADS anxiety score from 8.56 to 6.03, the

RHFUQ from 15.94 to 11.36 and the RPCS from 18.42 to 13.13. This was expected as individuals improved over 1 year resulting in lower scores. Nevertheless these scores still show that a large number of individuals have a significant level of symptoms even at one year.

The GOSE also showed an improvement (higher score is a better outcome). The improvement would have been more marked if not for the individuals who died and therefore skewed the results somewhat. Excluding deaths, the one year GOSE for the 690 survivors would be 6.12 (SD1.43). Table 5.8.4 shows the change in GOSE over one year reflecting the shift of many individuals from a moderate or poor/severe outcome into the good outcome category. The proportion categorised with a good outcome had increased from 23% to 40%. While this is a large improvement, it still indicates that the majority of individuals after TBI, do not have a good outcome.

GOSE Level	Number at 10 Weeks (774)	Number at 1 yr (728)
1 Death	0 (0)	38 (5.2)
2 VS	1 (0)	0 (0)
3 Severe Lower	21 (2.7)	5 (0.7)
4. Severe Upper	188 (24.3)	91 (12.5)
5. Moderate Lower	243 (31.4)	190 (27.5)
6. Moderate Upper	142 (18.3)	110 (15.1)
7. Good Lower	103 (13.3)	121 (16.6)
8. Good Upper	76 (9.8)	173 (23.8)

Table 5.8.4: GOSE at 10 weeks and 1 year

5.8.5 Summary

The prevalence of depression is very high at 10 weeks (56%) and drops by 1 year to 41%. This remains a high level of morbidity. Anxiety shows a similar prevalence and most individuals with one of these conditions, also have the other, both at 10 weeks and 1 year. Only 10.1% of individuals have normal mood at 10 weeks but develop late depression at 1 year. Symptom and psychosocial function improve over a year but still represent considerable levels of distress after 1 year. Similarly, overall global outcome improves but only 40% of indivduals have a good outcome by 1 year.

5.9 Univariable tests of late depression (1yr)

5.9.1 Introduction

This is comparable to section 5.6 with univariable tests being carried out on all independent variables. However, instead of initial depression scores, the dependent variable this time was late or 1 year depression (DEP2). Again the appropriate statistical test was a $\chi 2$-squared test or Fisher exact test for categorical variables and a univariable regression for continuous variables.

Table 5.9.1 shows the pre-injury factors, Table 5.9.2 the injury factors and Table 5.9.3 the outcome measures and questionnaires.

At one year, there were 690 individuals in the dataset as compared to 774 at 10 week review.

	N(%) or mean(SD)	Depressed; N(%) or mean(SD)	Not Depressed; N(%)or mean(SD)	Regression or χ^2, p-value
Age (yrs)	45.08 (18.37)	44.89(16.46)	45.21(19.61)	0.220, df688, p=0.826
Gender (M)	484 (70.1)	194 (40.1)	290 (59.9)	0.776,df1,
(F)	206 (29.9)	90 (43.7)	116 (56.3)	p=0.378
Ethnicity				
White	641 (92.9)	263 (41)	378 (59)	5.07, df4,
South Asian	33 (4.8)	17 (51.5)	16 (48.5)	p=0.280
Black	11 (1.6)	4 (36.4)	7 (63.6)	
Oriental	3 (0.4)	0 (0)	3 (100)	
Other	2 (0.3)	0 (0)	2 (100)	
(Non-white)	49 (7.1)	21 (42.9)	28 (57.1)	0.063,df1, p=0.802
Social Class				
Professional	40 (5.8)	13 (32.5)	27 (67.5)	17.352, df8,
Lower managerial	108 (15.7)	42 (38.9)	66 (61.1)	p=0.027*
Intermediate	48 (6.9)	20 (41.7)	28 (58.3)	
Self-employed	55 (8.0)	21 (38.2)	34 (61.8)	
Lower supervisor	95 (13.8)	38 (40)	57 (60)	
Semi-routine	171 (24.8)	75 (43.9)	96 (56.1)	
Routine	98 (14.2)	44 (44.9)	54 (55.1)	
Never worked	36 (5.2)	23 (63.9)	13 (36.1)	
Students	39 (5.6)	8 (20.5)	31 (79.5)	
Employment Status				
Yes	488 (70.7)	194 (39.8)	294 (60.2)	22.94, df2,
No	96 (13.9)	59 (61.5)	37 (38.5)	p<0.001*
Retired	106 (15.4)	31 (29.2)	75 (70.8)	
Social Isolation				
No	399 (57.8)	151 (37.8)	248 (62.2)	4.432, df2,
Yes	281 (40.7)	129 (45.9)	152 (54.1)	p=0.109
Nursing Home	10 (1.5)	4 (40)	6 (60)	

Table 5.9.1: Univariable analysis of 1yr depression and pre-injury factors

*significant for p<0.05

5.9.2 Pre-injury Factors

The mean age of individuals at one year had decreased by two years compared to the initial analysis.

This is due to the 38 deaths that occurred in the group who may be expected to be older individuals.

Compared to the small statistical difference in age that existed at 10 weeks, there was no difference between depressed and non-depressed individuals at 1 year.

Gender, ethnicity and social isolation also showed no difference.

There was a small difference in socioeconomic class. This was due to a difference in the group who had never worked, 63.9% of whom showed depression compared to levels of between 30 and 40 in the other categories. While the result was statistically significant, it was a very small effect ($p=0.027$).

Pre-injury employment was again different between depressed and non-depressed individuals. Those who were working prior to injury showed less depression than those who were not working. Those who were retired seemed to be the least likely to develop depression.

		N(%) or Mean (SD)	Depressed; N(%) or mean(SD)	Not Depressed; N(%)/mean(SD)	Regression or χ^2, p-value
Aetiology					
Fall		233 (33.8)	90 (38.6)	143 (61.4)	7.048, df4, p=0.133
RTC		187 (27.1)	71 (38)	116 (62)	
Assault		137 (19.8)	69 (50.4)	68 (49.6)	
Sport		48 (7.0)	17 (35.4)	31 (64.6)	
Other(work)		85 (12.3)	37 (43.5)	48 (56.5)	
Warfarin	N	639 (92.6)	267 (41.8)	372 (58.2)	1.393, df1, p=0.238
	Y	51 (7.4)	17 (33.3)	34 (66.7)	
Comorbidity	N	486 (70.4)	194 (39.9)	292 (60.1)	1.047, df1, p=0.306
	Y	204 (29.6)	90 (44.1)	114 (55.9)	
Alcohol at injury	N	494 (71.6)	156 (31.6)	338 (68.4)	65.91, df1, p<0.001*
	Y	196 (28.4)	128 (65.3)	68 (34.7)	
Psychiatric Hx	N	538 (78.0)	169 (31.4)	369 (68.6)	95.80, df1, p<0.001*
	Y	152 (22.0)	115 (75.7)	37 (24.3)	
GCS		11.89 (3.02)	10.8 (3.19)	12.65 (2.68)	8.224, df688, p<0.001*
Severity					
Severe		108 (15.7)	66 (61.1)	42 (38.9)	29.91, df2, p<0.001*
Moderate		268 (38.8)	118 (44)	150 (56.0)	
Mild		314 (45.5)	100 (31.8)	214 (68.2)	
CT Scan Findings					
Nil		278 (40.3)	87 (31.3)	191 (68.7)	72.37, df3, p<0.001*
Mild		137 (19.9)	33 (24.1)	104 (75.9)	
Moderate		215 (31.1)	120 (55.8)	95 (44.2)	
Diffuse		60 (8.7)	44 (73.3)	16 (26.7)	
Hemisphere Involved					
Nil on scan		281 (40.7)	89 (31.7)	192 (68.3)	93.06, df2, p<0.001*
Unilateral		290 (42.1)	99 (34.1)	191 (65.9)	
Bilateral		119 (17.2)	96 (80.7)	23 (19.3)	
***significant for p<0.05**					

Table 5.9.2: Univariable analysis of late depression and injury features

*significant for p<0.05

5.9.3 Injury features

As before, alcohol intoxication and psychiatric history were very different between groups and TBI severity showed a gradient effect. This effect of severity was also seen if GCS was used as a continuous measure instead of categories of severity.

Similar results were seen with regards to CT scan appearance. However, it was interesting that those with a completely normal CT scan had a higher prevalence of depression (31.3%) than those with a mildly abnormal scan(24.1%). This had also been noted in the 10 week data. The possible reasons for this are described in the discussion.

	N(%) or mean (SD)	Depressed; N(%) or mean(SD)	Not Depressed; N(%) or mean(SD)	Regression or χ^2, p-value
Length of Stay (d)	8.98 (14.54) {Median 3(1-89)}	11.80 (17.06)	7.02 (12.12)	-4.301, df688, p<0.001*
HADS Anxiety 1	8.62 (5.23)	12.10 (3.89)	6.19 (4.63)	-17.58, df688, p<0.001*
HADS Depression 1	8.22 (5.13)	11.67 (3.51)	5.81 (4.69)	-17.84, df688, p<0.001*
RHFUQ 1	16.21 (10.74)	22.73 (8.40)	11.65 (9.81)	-15.48, df688, p<0.001*
RPCS 1	18.68 (12.48)	26.11 (10.82)	13.49 (10.83)	-15.06, df688, p<0.001*
GOSE 1	5.44 (1.33)	4.51 (0.81)	6.10 (1.20)	19.41 df688, p<0.001*
HADS Anxiety 2	6.76 (5.39)	12.10 (2.97)	3.03 (3.07)	-38.73, df688, p<0.001*
HADS Depression 2	6.24 (5.19)	11.70 (2.53)	2.42 (2.40)	-48.81, df688, p<0.001*
RHFUQ 2	11.36 (9.64)	19.62 (7.53)	5.58 (6.09)	-27.01, df688, p<0.001*
RPCS 2	13.13 (11.38)	22.74 (9.95)	6.41 (6.42)	-26.19, df688, p<0.001*
GOSE 2	6.12 (1.43)	4.82 (0.71)	7.02 (1.06)	30.67, df688, p<0.001*
Employment 1				
No return	300 (43.4)	204 (68)	96 (32)	186.51, df2, p<0.001*
Partial	195 (28.3)	66 (33.8)	129 (66.2)	
Full return	195 (28.3)	14 (7.2)	181 (92.8)	
Employment 2				
No Return	198 (28.7)	158 (79.8)	40 (20.2)	291.45, df2, p<0.001*
Partial	187 (27.1)	106 (56.7)	81 (43.3)	
Full Return	305 (44.2)	20 (6.6)	285 (93.4)	

Time 1 refers to 10 week review and Time 2 refers to 1 year review. *significant at p<0.05

Table 5.9.3: Univariable analysis of late depression and other outcome measures

5.9.4 Outcome measures

There was again a marked difference in scores between depressed and non-depressed individuals across all outcome questionnaires. These scores had decreased considerably over the course of a year but were still high, implying a high level of psychosocial problems, head injury symptoms, anxiety and depression, even at one year.

The effect of return to work was very large. Only 6.6% of those who had made a full return to work suffered depression compared to 79.8% of the non-working group. Those who had made a partial return had an intermediate level of depression (56.7%). Hence return to work shows a gradient effect for risk of depression.

All of these variables were analysed again in a multivariable model in section 5.10

5.10 Multivariable regression analysis for 1 year Depression

After the initial univariable analysis of all the study variables with depression, a multivariable regression analysis was carried out using 1 year depression (Dep2) as the outcome measure. As this is a binary outcome, a logistic regression model was applied, entering the following factors of interest; ethnicity, socioeconomic class, pre-injury employment, gender, age, length of stay, social isolation, aetiology of injury, previous psychiatric history, medical comorbidity, warfarin treatment, alcohol intoxication, GCS, CT scan and return to work status. In addition, socioeconomic class, social isolation, aetiology, CT scan and return to work status had to be specified as categorical variables for this model as these had more than two categories.

There were 690 cases with complete data at 1 year compared to the 774 at 10 weeks.

A logistic regression with full entry method was applied.

The results are shown in Table 5.10.1.

						95% CI for OR	
	B	**S.E.**	**df**	**Signif**	**OR**	**Lower**	**Upper**
Non-white Ethnicity	-0.515	0.467	1	0.271	0.598	0.239	1.494
Female Gender	0.737	0.279	1	**0.008***	2.089	1.210	3.606
Age at injury	0.007	0.010	1	0.489	1.007	0.988	1.026
Socioeconomic Class			8	0.996			
Professional-baseline	-			-			
Lower Manager	-0.291	0.564	1	0.606	0.747	0.247	2.259
Intermediate	-0.091	0.644	1	0.888	0.913	0.258	3.228
Small Employer	-0.035	0.626	1	0.955	0.965	0.283	3.294
Lower Supervisory	-0.297	0.579	1	0.608	0.743	0.239	2.312
Semi-routine	-0.279	0.537	1	0.604	0.757	0.264	2.168
Routine	-0.213	0.572	1	0.710	0.808	0.264	2.480
Never Worked	0.199	0.772	1	0.796	1.221	0.269	5.539
Student	-0.076	0.726	1	0.917	0.927	0.223	3.845
Pre-injury work			2	0.588			
Employed-baseline	-			-			
Unemployed	0.386	0.381	1	0.310	1.472	0.698	3.103
Retired	0.180	0.458	1	0.693	1.198	0.489	2.936
Social Isolation			2	0.189			
No- baseline	-			-			
Yes	-0.305	0.240	1	0.204	0.737	0.461	1.180
Nurse home	-1.361	0.910	1	0.135	0.256	0.043	1.527
Aetiology			4	0.693			
Fall - baseline	-			-			
Assault	-0.073	0.356	1	0.838	0.930	0.463	1.868
RTC	0.193	0.368	1	0.600	1.213	0.590	2.494
Sports	0.628	0.549	1	0.253	1.873	0.639	5.494
Other	0.193	0.408	1	0.636	1.213	0.545	2.696
GCS	-0.116	0.062	1	0.063	0.891	0.788	1.006

Psychiatric Hx	1.213	0.282	1	**0.001***	3.364	1.934	5.850
Warfarin	0.360	0.497	1	0.468	1.434	0.542	3.795
Comorbidity	-0.130	0.296	1	0.659	0.878	0.492	1.567
Intoxicated	1.068	0.285	1	**0.001***	2.909	1.664	5.087
CT Scan			3	**0.049***			
NAD-baseline	-			-			
Mild	-0.761	0.373	1	0.042*	0.467	0.225	0.972
Moderate	0.113	0.334	1	0.735	1.120	0.582	2.153
Severe	0.171	0.493	1	0.729	1.186	0.451	3.118
Return to Work				**0.001***			
No work-baseline	-			-			
Reduced return	-1.076	0.264	1	0.001*	0.341	0.203	0.572
Full return	-3.535	0.337	1	0.001*	0.029	0.015	0.056
Length of Stay	-0.006	0.010	1	0.546	0.994	0.976	1.013
Constant	2.284	1.258	1	0.069	9.814		

Table 5.10.1: Logistic regression of 1 yr depression against study variables. Categories described in text

The table shows the variables that were entered and highlights the significant results in this model.

The overall model was highly significant ($p<0.001$). Nagelkerke R^2 was 0.596. The model overall correctly classified 81.6% of cases compared to only 58.8% of cases in the model with no predictors. The Hosmer-Lemeshow Test for goodness of fit was highly significant ($\chi^2=2.516$, df8, $p=0.961$) and area under curve (AUC) was 0.901 (95% CI=0.879-0.924), $p<0.001$. This indicates an excellent fit.

Again, assumptions for the logistic regression test were checked and met.

This analysis yielded slightly different results to the analysis of depression at 10 weeks. At 1 year, variables of female gender, previous psychiatric history, alcohol intoxication, CT scan appearance and

return to work were all significant. Again, the finding for CT appearance showed a difference between those with a mild abnormality on scan compared to normal scan. There was no difference between normal scans and those with more severe findings on their CT scans. Again, a possible interpretation of this result may be that the population with a normal scan is skewed by a number of somatising individuals with minor head injuries in the normal scan group. This would elevate the level of perceived depression at baseline if these individuals are more likely to present with symptoms of emotional distress.

The model for year 1 data is different to that at 10 weeks in a few key regards. Injury severity (GCS) and non-white ethnicity have dropped out of this model although GCS tends towards significance (p=0.063). In other words, injury severity is more important at an early stage in the development of depression but not after 1 year. Similarly, non-white individuals seem more likely to develop depression shortly after injury but this difference has disappeared after 1 year.

The independent predictors of 1 year depression are therefore female gender (OR 2.089, 95%CI 1.210-3.606), previous psychiatric history (OR 3.364, 95%CI 1.934-5.850), alcohol intoxication (OR 2.909, 95%CI 1.664-5.087) and non-return to work after 1 year. In the case of the latter, those who had a partial return to work had less depression than those who had not returned to work at all but themselves had more depression than those who had returned to full time previous employment showing a gradient effect.

5.11 Multivariable regression analysis for 1 Year Depression in those with or without initial depression

5.11.1 Introduction

The incidence of depression at 1 year is likely to be influenced by the occurrence of initial depression. From section 5.4, it is known that the correlation between initial and late depression was 0.700 (Dep1 and Dep2). This is very high and therefore it is important to try and understand the effect of initial depression on the likelihood of later depression.

In order to evaluate this effect further it was necessary to split the original sample into two groups, namely those with and those without initial depression at 10 weeks; these two subgroups were then examined for the incidence of depression at 1 year so that comparisons could be made.

Initial(10wk) Depression	Number (%)	Late(1yr) Depression	Number (%)
No	298 (43.2)	No	268 (89.9)
		Yes	30 (10.1)
Yes	392 (56.8)	No	138 (35.2)
		Yes	254 (64.8)

Table 5.11.1: Depression at 1 year divided by initial (10 week) depression

From this table, the proportion of those with initial depression is 56.8%. This group of 690 individuals reflects those on whom we also have data at 1 year. This level of depression is comparable to the figure of 53.1% in the *whole* group of 774 individuals and suggests that the group is not affected by the loss of 84 individuals due to deaths or loss to follow-up.

It is also clear from this table, that the occurrence of depression at 1 year, is much higher in those who had initial depression as well compared to those who did not (64.8% v 10.1%)

The two groups were then analysed separately with the same factors of interest as previous analysis on the complete dataset (5.7 and 5.10).

This produced two separate results tables as shown below.

5.11.2 No initial depression group

This table shows the logistic regression for the 298 individuals without early depression. The outcome was 1 year depression and the same variables were entered as previously.

	B	S.E.	df	Signif	OR	95% CI for OR Lower	Upper
Non-white Ethnicity	-1.112	1.516	1	0.463	0.329	0.017	6.423
Female Gender	1.057	0.804	1	0.189	2.877	0.595	13.91
Age at injury	0.001	0.028	1	0.979	0.999	0.946	1.056
Socioeconomic Class			8	0.708			
Professional-baseline	-			-			
Lower Manager	-0.513	1.319	1	0.697	0.599	0.045	7.937
Intermediate	-1.859	1.824	1	0.308	0.156	0.004	5.559
Small Employer	0.180	1.488	1	0.903	1.198	0.065	22.11
Lower Supervisory	0.464	1.294	1	0.720	1.591	0.126	20.10
Semi-routine	-1.291	1.278	1	0.312	0.275	0.022	3.365
Routine	-0.705	1.315	1	0.592	0.494	0.037	6.506
Never Worked	-1.795	2.029	1	0.376	0.166	0.003	8.856
Student	0.738	1.678	1	0.660	2.092	0.078	56.06
Pre-Injury Work			2	0.775			
Employed-baseline	-			-			
Unemployed	0.664	1.263	1	0.599	1.943	0.163	23.09
Retired	0.746	1.175	1	0.526	2.109	0.211	21.10
Social Isolation			2	0.580			
No- baseline	-						
Yes	0.665	0.637	1	0.297	1.945	0.558	6.779
Nurse home	-23.69	17934	1	0.999	0.001	0.001	-
Aetiology			4	0.658			
Fall- baseline	-			-			
Assault	0.658	0.831	1	0.429	1.930	0.379	9.837
RTC	0.445	1.161	1	0.701	1.561	0.160	15.19
Sports	2.314	1.597	1	0.147	10.11	0.442	231.48
Other	-0.014	0.408	1	0.990	0.986	0.111	8.756
GCS	-0.167	0.204	1	0.413	0.846	0.568	1.262
Psychiatric Hx	3.312	1.204	1	**0.006***	27.44	2.589	290.79

Warfarin	0.401	1.203	1	0.739	1.493	0.141	15.769
Comorbidity	1.600	0.894	1	0.073	4.954	0.859	28.569
Intoxicated	0.298	0.799	1	0.709	1.348	0.282	6.449
CT Scan			3	0.550			
NAD- baseline	-			-			
Mild	0.284	0.912	1	0.756	1.328	0.222	7.942
Moderate	1.103	1.017	1	0.278	3.013	0.411	22.091
Severe	-0.997	1.649	1	0.545	0.369	0.015	9.341
Return to Work				**0.001***			
No work-baseline	-			-			
Reduced return	-1.224	0.687	1	0.075	0.294	0.076	1.131
Full return	-6.366	1.327	1	**0.001***	0.002	0.001	0.023
Length of Stay	-0.033	0.031	1	0.290	0.967	0.910	1.029
Constant	1.929	3.817	1	0.613	6.881		

Table 5.11.2: Logistic regression of 1 year depression in those without initial depression. Description of categories for each variable are described in text of methods. *significant for p<0.05

The overall model was highly significant (p<0.001). Nagelkerke R^2 was 0.599. The model correctly classified 93.6% of cases compared to 88.9% in the model with no predictors. The Hosmer-Lemeshow Test for goodness of fit was highly significant (χ^2=17.45, df8, p=0.026) and area under curve (AUC) was 0.943 (95% CI=0.848-0.987), p<0.001. This indicates an excellent fit.

From this table it can be seen that only previous psychiatric history (OR 27.4) and return to work were significant in the model. The variables of injury severity, gender, ethnicity, alcohol intoxication and CT appearance were no longer significant as they were in the previous analysis of the whole dataset.

5.11.3 Initial depression and late depression group

The results in 5.11.2 above need to be compared to the group that *did* have initial depression. This group was larger than those without initial depression (392 v 298) as shown in Table 5.11.1 and the logistic regression results are shown below in Table 5.11.3.

						95% CI for OR	
	B	**S.E.**	**df**	**Signif**	**OR**	**Lower**	**Upper**
Non-white Ethnicity	-0.519	0.528	1	0.326	0.595	0.211	1.677
Female Gender	0.852	0.350	1	**0.015***	2.345	1.182	4.652
Age at injury	0.010	0.011	1	0.358	1.010	0.988	1.033
Socioeconomic Class			8	0.972			
Professional-baseline	-			-			
Lower Manager	-0.560	0.760	1	0.461	0.571	0.129	2.532
Intermediate	-0.293	0.857	1	0.733	0.746	0.139	4.006
Small Employer	-0.602	0.825	1	0.466	0.548	0.109	2.759
Lower Supervisory	-0.837	0.785	1	0.286	0.433	0.093	2.016
Semi-routine	-0.489	0.731	1	0.504	0.613	0.146	2.570
Routine	-0.480	0.765	1	0.531	0.619	0.138	2.773
Never Worked	-0.024	0.973	1	0.980	0.976	0.145	6.576
Student	-0.767	0.933	1	0.411	0.464	0.075	2.889
Employment Status			2	0.953			
Employed-baseline	-			-			
Unemployed	0.127	0.431	1	0.769	1.135	0.488	2.641
Retired	-0.029	0.578	1	0.960	0.971	0.313	3.012
Social Isolation			2	0.087			
No- baseline	-			-			
Yes	-0.596	0.297	1	0.044	0.551	0.308	0.985
Nurse home	-1.292	1.023	1	0.207	0.275	0.037	2.042
Aetiology			4	0.956			
Fall-baseline	-			-			
Assault	-0.145	0.457	1	0.752	0.865	0.353	2.121
RTC	-0.016	0.436	1	0.972	0.985	0.419	2.315
Sports	0.175	0.671	1	0.794	1.192	0.320	4.439
Other	0.212	0.506	1	0.676	1.236	0.458	3.333

GCS	-0.077	0.072	1	0.287	0.926	0.803	1.067
Psychiatric Hx	0.654	0.308	1	**0.034***	1.923	1.052	3.513
Warfarin	0.361	0.658	1	0.583	1.435	0.395	5.210
Comorbidity	-0.333	0.353	1	0.346	0.717	0.359	1.433
Intoxicated	1.013	0.347	1	**0.003***	2.753	1.396	5.431
CT Scan			3	0.090			
NAD- baseline	-			-			
Mild	-0.986	0.454	1	0.030	0.373	0.153	0.908
Moderate	-0.165	0.414	1	0.691	0.848	0.377	1.911
Severe	-0.061	0.561	1	0.913	0.941	0.313	2.824
Return to Work				**0.001***			
No work-baseline	-			-			
Reduced return	-1.400	0.328	1	0.001*	0.247	0.130	0.470
Full return	-3.100	0.435	1	0.001*	0.045	0.019	0.106
Length of Stay	-0.007	0.011	1	0.553	0.993	0.972	1.015
Constant	3.203	1.522	1	0.035	24.61		

Table 5.11.3: Logistic regression of 1 year depression in those with initial depression
Description of the categories for each variable are described in text of methods. *significant for p<0.05

In this analysis, the variables of gender, past psychiatric history, alcohol intoxication and return to work, were all predictors of depression at 1 year.

The overall model was highly significant (p<0.001). Nagelkerke R^2 was 0.421. The model correctly classified 78.3% of cases compared to 64.8% in the baseline model. The Hosmer-Lemeshow Test for goodness of fit was highly significant (χ^2=3.03, df8, p=0.932) and area under curve (AUC) was 0.837 (95% CI=0.796-0.878), p<0.001. This indicates an excellent fit.

The contrast with the population of those *without* earlier depression is clear. In those *without* early depression, only psychiatric history and return to work were predictors. In those *with* early depression the features of gender and alcohol intoxication are also significant and CT scan findings were close to significance. This group shows more similarity to the overall analysis of the entire group.

A number of variables that were significant in the complete dataset (ethnicity and injury severity) were NOT significant in the smaller subgroups analysis.

CHAPTER 6: DISCUSSION

6.1 Summary of main findings

A literature review identified a large number of studies that have examined depression after TBI with a pooled median of 36%. While a number of demographic and injury features were associated with depression risk in individual studies, findings were inconsistent and no single feature can be said to affect the depression risk.

A large, well organised, prospective cohort of TBI cases was subsequently recruited from ED admissions over a 2 year period. At 10 weeks, 774 individuals were recruited and there were 690 complete cases at 1 year. The prevalence of depression using a clinically relevant, self-administered tool, was 56.3% at 10 weeks[95%CI 52.8-59.8] and 41.2% at 1 year [95%CI 37.6-44.9]. The depression rate in the background population is 2-8% [Kessler 2003, Blazer 1994].

There were very high correlations of depression with other measures of psychosocial outcome, TBI symptoms and global outcome measures ($r>0.7$). While each measure correlated with itself across both time points, there were even higher correlations with the other outcome measures taken at the same time point. This suggests that the different tools are measuring a similar construct of emotional distress at each given time point.

Initial univariable analysis of pre-injury and injury features found a number of significant associations with depression. However most of these became insignificant on a subsequent multivariable analysis that was carried out to identify the independent predictors of depression.

At 10 weeks, a logistic regression model found that features of non-white ethnicity, female gender, increasing TBI severity, overall CT scan appearance, previous psychiatric history, alcohol intoxication at time of injury and failed return to work were all significant risk factors for increased depression risk. With respect to CT scan appearance, those with mild abnormalities on scan, had least risk of depression

while those with normal scans or high abnormality of CT, had the highest risk. Return to work showed a gradient effect with those in a partial or full return to work, showing decreasing risk compared to those with no return. A logistic regression model with these features was highly significant with 82% of cases correctly classified, $p<0.001$ (AUC 0.9).

The logistic regression was repeated after one year. Increased risk of depression was associated with female gender, previous psychiatric history, alcohol intoxication at time of injury and failed return to work. This time, TBI severity was no longer significant and CT scan appearance barely significant ($p=0.049$). Again it was found that those with mild CT abnormalities, had the lowest risk of depression while those with a normal scan, had similar risk to those with more abnormal CT scans. The model was highly significant with 81% of cases correctly classified, $p<0.001$ (AUC 0.8).

Data were re-examined for those with early depression as distinct from late depression. There was some evidence for differences in the populations; it has been suggested that injury features are more significant in the development of early depression but that psychosocial and personality features are more significant in determining long-term outcome. Hence TBI severity or overall CT appearance change, were no longer or barely significant. Those with previous psychiatric histories and alcohol intoxication were at particular risk of depression at both time points.

It may be possible to target such susceptible individuals and this is an important implication for clinical practice. Future research needs to be directed at these areas and to recognise that the mechanisms of depression may vary between individuals. Further work on examining treatment modalities is also important in order to identify whether the immense burden of depression and TBI can be alleviated at least in part. Targeting those at highest risk of depression, is one way of achieving this.

6.2 Main findings and comparison with previous literature

6.2.1 Introduction

In this section, the results of the thesis will be discussed in some detail and comparisons made with previous literature. As outlined briefly in Chapter 1, a large number of studies have tried to measure the prevalence of depression but there is still a significant gap in our understanding and knowledge of the condition. Methodological differences in the way that studies are planned and populations recruited, have led to large differences in the reported incidence (11-77%). In addition, a large number of studies have examined the effects of demographic or injury features on depression but yield conflicting results and meaningful effects are often missing. As a result previous reviews have concluded that no association with any such factor can be made with depression, not even injury severity [Rosenthal 1998, Rogers 2007, Guilamendegui 2011]. It is important to place the findings of this thesis in context with the previous literature and that is done in this section. A detailed discussion of each previous study and the strengths and weakness of their findings is clearly beyond the remit of this thesis. However, it is important to point out that many studies are small, have potentially biased samples and are retrospective in design.

For each study variable, both the univariable and multivariable results are considered and any similarities or differences discussed. While univariable tests are useful in gaining an idea of the relationships that exist, the true test of significance is a multivariable regression to identify the independent predictors of outcome. Many variables found to be significant on initial univariable tests, turn out to be insignificant in a multivariable model. However it is also possible that some variables show no association to the outcome at univariable testing but do indeed have an independent association which may become apparent in the multivariable model (6.2.6).

Analyses were conducted on both 10 week and 1 year data. While these were broadly similar, a number of contrasting results were found. Due to losses to follow-up and deaths, the 1 year analysis was carried out on 690 cases with full data points.

6.2.2 Prevalence

The key aim of the study was to calculate the 10 week and 1 year prevalence of depression. Using a standard 8/9 cut off score on the HADS, the 10 week prevalence of depression was 56.3%. At 1 year this had dropped to 41.3% of the group. It has been suggested that a cut off between 11/12 can signify more severe depression [Hermann 1997, Crawford 2001]. Using this cut-off 29.2% of the 10 week cohort had severe depression and 17.0% of the 1 year group.

These levels are high, especially soon after TBI and are certainly at the higher end of the spectrum of previous studies (11-77%). While the prevalence dropped over the course of a year, it still represents a large proportion of the TBI population. For comparison, the weighted average across all previous studies is 31% [Guillamendegui 2011]

It is reassuring that the 1yr figure is broadly in line with previous large size studies. The only larger study [Hart 2012] cites 26% at one year, while Kreutzer [2001], 42% and Seel [2003], 27%.

Other studies that have used the HADS, quote 38% [Dahm 2013], 19.1% [Al-Adawi 2007], 46% [Draper 2007], 37.5% [Hawley 2008], 22.7% [Hawthorne 2009], 26% [Kreuter 1998], 55.2% [Lima 2008], 27% [O'Carroll 1991], 38% [Parcell 2006], 44% [Ponsford 2010], 18% [Sigurdardottir 2013], 25% [Wade 1998] and 34% [Whelan-Goodinson 2008].

The change in prevalence over one year and comparison between those with initial or later depression is very interesting and forms part of the next section. A very brief comment on the method of diagnosis of depression is important here although it was discussed at some length in the methods. The use of a questionnaire (HADS) to combine a number of key symptoms and use a threshold to diagnose

depression, seemed to be relatively straightforward and easy to administer. Individuals completed the form in two to three minutes although some needed the assistance of a family member or the lead investigator. By contrast the time that would be required for a structured clinic interview (SCID) would be extensive and beyond the capacity of almost any clinical TBI service. In addition studies that have compared SCID with questionnaire scores show similar levels of depression. In the literature review, studies utilising SCID found similar rates of depression to those which used questionnaires [Dyer 2016].

In addition, it is unlikely that many of the individuals attending the clinic would have been able to complete a 45 minute interview simply for the reasons of diagnosing depression. It is known that many TBI individuals suffer "cognitive fatigue" [Bay 2007] and up to 40% of individuals decline completion of long questionnaires including the SCID [Ghaffar 2006, Bay 2007, Wittkampf 2009, Gjerdingen 2011].

It is also known that the SCID is prone to clinician bias as the interviewer has to designate whether a symptom is primarily a psychiatric symptom or secondary to a medical condition, e.g. TBI. In this way it is highly susceptible to the clinician's bias or level of training and clinical background. SCID has been shown to have poor inter-rater variability [Regier 2013]. It may be for this reason that the literature review found that both the lowest and highest prevalence of TBI depression were in SCID studies and the overall prevalence of TBI in SCID studies is comparable to that in questionnaires and this has been reported by others [Dyer 2016]. In this regards, it seems that questionnaires produce similar results to SCID.

6.2.3 Time relationships

A key aim of the study was to assess the change in prevalence of depression over time. It was found that the prevalence dropped from 53% to 41%. This was the expected finding based on personal experience over many years of assessing TBI patients and in many of the studies in the literature review.

A comparison between those with initial and/or later depression is interesting. Out of all the individuals with depression at 10 weeks, 64.8% were still depressed at one year. In other words the state of depression tends to persist. Similarly, of those who were not depressed at ten weeks, only 10.1% developed late depression. This data suggests that most individuals will have early rather than late depression or will maintain their mood state. Depression is not a late phenomenon and tends to decrease with time.

Several other studies have also found that depression diminishes [Dikmen 2004, Ashman 2004, Jorge 2004]. A large population based study with long term follow-up similar to this project and using the HADS as an evaluation, found an initial elevated rate of depression that dropped after one year but then stabilised up to a 5 year period [Sigurdardottir 2013].

But this is in contrast to many studies where the prevalence of depression tends to rise with time [Lezak 1987, Franulic 2004, Gould 2011, Hart 2012]. In general, there seem to be more studies that have found an increasing or stable rate of depression.

Several studies show no relationship with time [Jorge 1993c, Bryant 2010, Hudak 2012, Seel 2013, Siponkoski 2013]. A study in war veterans found an elevated rate up to 50 years after self-reported TBI [Holsinger 2002] and a large population based register study from Denmark reported no change in depression risk 30 years after injury [Orlovska 2014]. Others report a prevalence of 27% after 30 years [Koponen 2006] and 31% after 10 years [Andelic 2009].

In an elegant study with repeated measurements over a period of one year, the prevalence over the first year remained the same [Bombardier 2010].

It is difficult to reconcile the significant discrepancy between studies. Indeed, this was the reason this project was initiated in the first place. Most sequelae of TBI improve over time. This includes in particular, the physical and cognitive impairments caused by TBI [Jorge 2005, Grauwmeijer 2012]. Intuitively it may be felt that the psychological sequelae might also improve. Furthermore, sequelae

such as depression are likely to be affected by improvements in physical and cognitive impairments [Hibbard 2004]. For this reason it would also seem logical to target individuals in the first year after TBI including those at risk of depression, at a time when rehabilitation interventions are most likely to produce positive results (See 6.6). It should be noted that our study is at odds with literature reviews which have concluded that no temporal pattern of depression can be discerned [Rogers 2007, Guillamendegui 2011]. However it is hoped that the high quality of this study, the repeated evaluation of depression, the representative TBI population and the excellent follow-up rate, indicates that these findings are robust. The evaluation of a cohort at the same time point in their post-injury course, is another key strength of this study compared to the many studies with patients assessed at varying times.

Future follow-up of this cohort will help to clarify whether the prevalence of depression continues to fall or stabilises or even rises. It is planned to try and follow-up patients at 5 years after injury.

A possible explanation for a temporal rise in the prevalence of depression in some studies could be the role of impaired self-awareness (ISA) which was briefly discussed in the introduction. ISA can be defined as "the awareness of arousal, perception, expression and integration in both the self and the environment" [Prigatano 1997, Moldover 2004]. Those with more severe injuries are likely to have decreased self-awareness of the extent of their deficits; whereas those who retain insight are more aware of the difficulties they face on their road to recovery and rehabilitation. It is often found that families report very differently on a TBI individual's performance suggesting that an individual may lack awareness [Robertson 2015]. Improvements in self-awareness have been shown to occur some six to eight months after injury and can be the focus of goal-setting [Prigatano 1997, Moldover 2004, Playford 2009]; this increasing self-awareness and a realisation of the effect of injury on an individual's abilities, is likely to result in an individual's reassessment of their own situation with a concomitant increase in the level of depression as the extent of impairment becomes more apparent to that individual [Sherer 1998,

Kelley 2014]. This could explain the increase in some studies especially with a higher proportion of severe TBI, in whom ISA is more common.

Another possible reason for such conflicting results is the heterogeneity of study populations and the means by which they are recruited. This has been mentioned in 6.2.2. Different studies may be recruiting very different individuals whose propensity for depression varies considerably [Strakowski 2013].

6.2.4 Age

There was a three year difference in age between depressed and non-depressed individuals and this was significant at 10 weeks although barely so (p=0.032) on univariable test. At 1 year, the difference was non-significant (NS).

In the multivariable analysis, age was NS at both timepoints.

Unfortunately many studies have excluded elderly patients. A systematic review to address this topic found only one paper that met the criteria for study! [Menzel 2008] This was an issue that was largely addressed in this study which sought to recruit elderly patients as much as any other group. It is well known that age is a very strong predictor of overall function and global outcome [Dagher 2013] but not necessarily known for depression.

Those studies that have examined age, have usually found that increasing age decreases the risk of depression [Deb 1999, Rapaport 2003, Bombardier 2010, Hart 2012]. Several have found no link [Seel 2003, Dikmen 2004, Jorge 2004]. A few studies have found the opposite i.e. with increasing age, the risk is slightly increased [Levin 2005, Sigurdardottir 2013]. Whelan-Goodinson[2008] has described a complex relationship between age and anxiety with an increase such that the highest level of symptoms and emotional distress are between 50 and 60 and postulated that middle age is the most stressful or vulnerable age group after TBI. This has been noted by others [Amstey 2004]. An examination of study

data also confirms that outcome scores such as the RPCS, RHFUQ and GOSE show highest abnormalities in middle age but this was not the aim of the thesis. It may be useful to analyse this data in future projects.

The increase in the proportion of older people in our society is significant and will affect our health care systems as well as home care needs. It is important that this population group is included in further studies [Koskinen 2008]. Given that overall outcome is often better [Anke 2015], it is important that this older cohort are not neglected.

6.2.5 Gender

Female gender showed no relationship with depression on univariable tests at 10 weeks or 1 year. However in the multivariable model it was highly significant at 10 weeks (OR 1.6) and at 1 year (OR 2.1). These results illustrate the importance of conducting a multivariable analysis, over and above simple univariable tests. It also highlights the importance of carrying all test variables forward into the multivariable analysis as significant relationships may become apparent in this way. Many studies in the literature seem to discard variables that are initially insignificant on univariable tests. In this study, it would have resulted in the loss of gender as a predictor of depression. When the effects of other factors were removed, it became clear that women have an increased risk of development of depression despite univariable tests suggesting that the risk was similar for both sexes. This fails to take into account the fact that men with TBI are younger and have more severe injuries as discussed in earlier sections (5.4). These factors increase the male risk when a univariable test is carried out. However, a multivariable analysis removes the effects of severity, age and other independent variables, thus allowing the increased risk for women to become apparent as it is in this study.

The reverse statistical phenomenon is much more common. In other words, variables that are significant on univariable testing, become insignificant on multivariable tests. As noted in 6.2.4, as an example, age

was insignificant in the multivariable model in contrast to its univariable probability. Several other variables in subsequent sections, will also be seen to be highly significant on univariable tests but then drop out of a multivariable model.

The finding that depression was more common in women, must take into consideration the known higher level of depression in women [Blazer 1994, Kessler 2003, Waraich 2004]. It is quite likely that this finding simply reflects the known population risk.

Several other studies have found a higher level of depression in women [Di Cesare 2004, Ashman 2004, Levin 2005, Glenn 2011, Hart 2012]. However a number of studies have also noted a higher risk in men [Burton 1988, Dikmen 2004, Sigurdardottir 2013]. Others have found no link to gender [Seel 2003, Jorge 2004]. By way of contrast, it is interesting that several studies looking at global outcome find that women tend to have a slightly better outcome than men. It has been suggested that progesterone plays a neuro-protective role and trials of progesterone are ongoing with some promising results [Bazarian 2010].

6.2.6 Medical Comorbidity

The cohort contained a high level of significant medical comorbidity (32.2%) including treatment with warfarin (8.2%). This is to be expected in a group with a large proportion of elderly patients. Medical comorbidity was evaluated with a validated tool rather than simply diagnosis or self-report [Hudon 2005]. This is more accurate and assesses the impact of any medical conditions on an individual's lifestyle and prognosis.

Comorbidity did not show any association with depression on univariable or multivariable tests at both timepoints.

This is contrast to the role of comorbidity and depression in the general population. It is known that medical illness is associated with increased risk of depression [Kessler 2003] However, studies in TBI are rare.

6.2.7 Previous Psychiatric history

A positive past psychiatric history showed one of the strongest associations with depression both on univariable tests and the regression model with an odds ratio of 4.2 at 10 weeks and 3.4 at 1 year.

It is therefore puzzling that many previous studies have excluded any individuals with a past history of depression or other psychiatric condition [Jorge 1993a, Forslund 2013, Kersel 2001]. This would seem to exclude a sizeable proportion of the population given that in this study, 21.8% had a positive history. It has been shown that up to 65% of individuals with TBI have a psychiatric diagnosis after five years [Whelan-Goodinson 2009] and that 10% of individuals in a large cohort of TBI required psychiatric referral although it is unclear on which criteria this was decided [Koning 2015].

In terms of previous literature several studies have found no link with past psychiatric history [Hibbard 2004, Dikmen 2004, Lezak 2004, Rappaport 2006, Vanderploeg 2007, Hermann 2009 Jorge 1993c].

Other studies have found an increased association similar to the finding in this study [Ashman 2004, Jorge 2004, Malec 2007, Bombardier 2010, Hart 2012]. Many of the latter group are high quality studies from the literature review.

Surprisingly one study reported that those without a positive psychiatric history, in fact, had a higher risk of depression but this study lost 71% of cases to follow-up [Fann 2005].

Unfortunately the study recorded all psychiatric morbidity as one entity and did not differentiate between past depression and other disorders. The majority were undoubtedly depression and it would be interesting to test the hypothesis that previous depression increases the risk of TBI perhaps by

increasing risky-taking behaviour. This would require a fresh study and detailed examination of the authenticity of past diagnoses.

The positive association in this study is one of the key findings and has implications for clinical practice and targeting of at risk individuals who are identified at clinic.

6.2.8 Ethnicity

Ethnicity and depression were not different between groups either at 10 weeks or at 1 year on a univariable test. Comparison with the white population approached, but did not reach a significant difference (p=0.052).

On multivariable testing however, non-white ethnicity became a risk factor (OR 3.5) for depression at 10 weeks but dropped out of the 1 year model. At 10 weeks, 69% of non-whites had depression compared to 55% of white individuals. This is similar to the way that gender had become significant only on multivariable tests. Again it is likely that other features such as injury severity or age may be affecting this relationship in a univariable test but is unmasked in the more complex analysis.

There is limited evidence that depression varies with ethnicity in the general population [Blazer 1994]. After TBI, the increased risk of depression in ethnic minorities has been previously noted [Seel 2003] but most studies have not examined this variable or found no relationship. The role of ethnicity is better investigated in a more diverse population than this one. Although there is a diverse population mix in South Yorkshire, the proportion of the study population that were an ethnic minority was surprisingly small (6.7%). By comparison, at the last Census, 16.3% of South Yorkshire was of non-white ethnicity [ons.gov.uk]. The possible reasons for fewer TBIs in an ethnic population are for another study.

6.2.9 Pre-injury work status

On univariable tests, pre-injury work status was highly significant at both times; those who were employed at the time of injury had a low risk of subsequent depression. Interestingly, those who were retired showed an even lower risk than workers. It is difficult to explain such a finding but it may be speculated that the expectations of a retired population are somewhat different to those who are working or expected to work and may have dependants. Anecdotally, many elderly patients in clinic reported lower expectations or consider that some element of disability and impairment is inevitable as one "ages". Many of the elderly seemed phlegmatic as regards an expectation of disability.

The unemployment rate in the TBI group (9% by self-report) was almost the same as the South Yorkshire unemployment rate in August 2014 (6.2%) suggesting this group are at similar risk of TBI to the working population.

When entered into the multivariable model, pre-injury work status dropped out and was insignificant indicating that depression after TBI was not associated with pre-injury work status. It is difficult to explain this finding; the general consensus is that depression is higher in the unemployed as far as the general population is concerned.

After TBI, others have noted the link between unemployment and depression [Seel 2003, Dikmen 2004, Franulic 2004, Van Horn 2013]. One study showed no link [Andelic 2009] and another found an inverse relationship so that the working individuals had higher depression [Sigurdardottir 2013]. This was explained in terms of the higher expectations of a working group which may not be achieved and is similar to another Scandinavian study showing those with lower education achievement, had less risk of depression (6.2.7).

6.2.10 Social Isolation

A surprisingly high proportion of individuals in this cohort had little or no social support network (40.3%) and a very small proportion of TBIs were in nursing home residents (2.4%). It is known that TBI can lead to relationship breakdown and many individuals end up living alone [Kim 2007]. However social isolation did not show any difference at either time point both on univariable and multivariable tests. This was slightly surprising as it had been postulated that a level of social and family support may protect against the development of depression.

A relationship to isolation has been noted in several previous studies although the means of assessment of isolation varies [Leavy 1983, Rosenthal 1998, Horner 2008]. Another showed a link to decreased personal friendships [Gomez-Hernandez 1997]. In a quality of life study, social support and community integration were the strongest predictors [Kalpakjian 2004]. There is also a link to global outcome [Forslund 2013].

6.2.11 Socioeconomic Class

There was a tendency for the higher socioeconomic classes to show less depression. It was clear that the group who had never worked or those in lower routine and semi-routine classes had higher depression risk compared to professional and managerial groups both at 10 weeks and 1 year (Table 5.6.1 and 5.8.1). This difference was insignificant (p=0.082) at 10 weeks but significant at 1 year albeit barely (p=0.027). On multivariable analysis, SEC was insignificant in both models.

It has long been known that SEC affects life expectancy and general health outcomes [Melzer 1995, Marmot 1997]. It was therefore postulated that there may be an effect on TBI outcomes and therefore it was documented at clinic.

To the best of our knowledge, no other TBI study has examined socioeconomic class using the National Census derived categories [Chandola 2000]. While the population was spread across all eight

socioeconomic classes, there were fewer individuals in higher professional or management grades compared to United Kingdom National Census data [ons.gov.uk]. This could be interpreted in two ways. Professional classes may be less likely to sustain TBI or alternatively, these classes constitute a smaller proportion of the Sheffield population [Labour Force Survey 2005].

Studies with socioeconomic status are rare. A few studies have used years of education or income level, rather than a validated system in order to classify groups. There is little discernible pattern and none of the studies identified in the literature review have examined SEC. Studies have shown more depression with lower education [Holsinger 2002, Dikmen 2004, Malec 2007, Hudak 2012] and lower income [Seel 2003]. Others show no link to education level [Jorge 1993b, Jorge 2004, Bombardier 2010]. In a study looking at life satisfaction rather than depression, lower education resulted in better satisfaction [Anke 2015]. This would seem unusual but was explained by the authors as those in higher professional roles or management, held higher expectations and therefore were less likely to achieve these after injury.

6.2.12 Aetiology

It was anticipated that some causes of TBI may be more likely to cause depression. In particular it may be expected that those suffering a violent mechanism of injury or with high energy impact with other associated injuries, would be more likely to experience depression.

Indeed this was the case with over 72% of assault TBIs experiencing initial depression. This was significantly different at 10 weeks, but was no longer the case at 1 year. In the multivariable analysis, aetiology was NS at both times.

The study population showed a good distribution across all TBI aetiologies. This may be expected with such a broadly selected group, designed to truly represent the TBI population. Falls were the most common cause of injury as has been noted in other large, Western epidemiological surveys [Tagliaferri 2006, Roozenbeek 2013, Feigin 2013]. In developing countries, RTC continues to be the most common

cause [CRASH-2, 2011]. American studies often include a proportion of gunshot victims which is rare in European studies. The large numbers in this study allowed us to include separate categories of sporting injury and a group predominantly made up of workplace injuries or struck by a falling object.

Other large, high quality studies have found no link with aetiology [Seel 2003, Bombardier 2010, Hudak 2012]. A study has shown a link to violent mechanisms of injury but this was in victims of torture [Mollica 2009]. Similarly victims of intentional injury such as assault also had a higher risk in one high quality study [Hart 2012]. Conversely, violence has been found to have an inverse link to depression [Glenn 2011].

6.2.13 Severity of TBI

The severity of TBI, described by presenting GCS, in this cohort showed a good distribution across the spectrum of severity, comparable to population estimates [Tagliaferri 2006]. While it is estimated that 80-85% of all TBI is mild [Busch 1998], many of these cases do not present for medical attention. The hospitalised population of TBI is very similar to the cohort recruited, as may be expected and is shown in Appendix 3. Unlike many other studies of depression, the cohort is not dominated by STBI or indeed by MTBI which often constitute the larger part of many studies. The study aim, of recruiting a clinically relevant population that is representative of real-life clinical practice seems to have been achieved.

Injury severity was associated with depression on univariable tests, whether measured by GCS or categorised into mild, moderate and severe. The gradation of depression risk with injury severity was quite striking, increasing from 42.6% in mild to 61.5% of moderate and 83.9% of severe TBI at 10 weeks. At 1 year the comparable figures were 32%, 44% and 61%.

For the multivariable model, TBI severity was entered as GCS. It was highly significant at 10 weeks (OR 0.8, 95%CI 0.72-0.91).

However it was fascinating that at one year, TBI severity was no longer a significant factor in predicting depression risk, although the p-value tended towards significance (p=0.06). Allied to this finding (see next section), was the fact that overall CT scan appearance at 1 year was barely significant (p=0.049). As has been previously noted, the extent of CT scan abnormality is highly correlated with TBI severity.

Taken together, these two findings suggest that the extent of injury severity in determining depression risk is more important at an early stage after TBI than it is at a later phase i.e. one year. No other study identified in the literature review has shown this change in the role of injury severity with time inpredicting depression, in a prospective cohort.

There is considerable literature on the importance of early and late factors in the risk of depression. It has been suggested that initial outcome after TBI may be more dependent on features of the injury itself such as severity or violent mechanism. However, these may become less significant as time passes and long term outcome is more dependent on an individual's psychological status and personality including coping mechanisms and predispositions for depression. This is discussed in some more detail in 6.2.21.

However it seems reasonable to postulate that the severity of injury is directly related to the amount of physiological disruption or neuronal and structural damage that occurs after TBI [Koenigs 2008]. In this regard it may be expected that the amount of tissue damage would correlate with the likelihood of depression, if depression is related to the amount of neuronal damage that occurs. This could be expected to be the case at an early stage after injury.

No other variable has been studied as much as the severity of TBI and relationship to outcomes including depression. Unfortunately there is little agreement on the nature of this relationship.

Several studies have found a positive relationship with severity [Satz 1998, Levin 2001, Holsinger 2002, Huang 2005].

However there are more studies that find an inverse relationship in so far as those with MTBI have a higher risk of depression [Alexander 1992, Linn 1994, Van-Reekum 2000, Rappaport 2002, Malec 2007, Hudak 2012, Siponkoski 2013].

Several studies have found no association with injury severity at all [O'Carroll 1991, Bowen 1998, Seel 2003, Jorge 2004, Van Horn 2008, Horner 2008, Hoge 2008, Hesdorffer 2009, Malec 2010].

It is clear that no pattern exists across the literature.

The findings in this paper are likely to be robust and reliable based on the quality of the mixed TBI population and the extent of follow-up. It is therefore of higher quality than many of the other studies and this lends credibility to the strength of the finding although it is a single centre study.

This possible inverse relationship between depression and injury severity in some studies, appears counterintuitive if the amount of brain damage is important. As discussed in 6.2.3, a possible reason for this is based on the concept of impaired self-awareness. This would explain why those with more severe injury, lacking relative insight into the extent and nature of their problems, are less likely to experience depression.

Another factor to explain this inverse relationship is that individuals with more severe injury often have a sense of "survivorship" and possibly an increased level of social support which may lead to decreased likelihood of depression [Jones 2011].

6.2.14 CT structure

The extent of abnormalities on CT scan after TBI shows a strong relationship with severity of TBI as noted in 5.4. It may be therefore expected that the relationship of depression with CT scan may show a similar relationship to TBI severity.

The overall CT appearance was significantly associated with depression both on univariable and multivariable tests. However at 1 year, it was barely significant ($p=0.049$) in the multivariable model. As

was discussed in 6.2.10, the difference between 10 weeks and 1 year was striking; TBI severity was no longer a significant variable in the model and CT scan was barely so. The theoretical differences between early and late depression features, is discussed in some detail in 6.2.21.

CT scan abnormalities are usually classified by the Marshall or Rotterdam systems [Marshall 1991, Maas 2008]. Unfortunately these were devised predominantly to guide neurosurgical intervention in the most abnormal or life threatening situation. In particular they focus on the state of the ventricular system and the evidence for raised intracranial pressure which often guides the need for surgery. These are very severe TBIs and they are not helpful in a general TBI population or a large population study such as this. Extensive gross changes have been shown to correlate to global outcome at three months [Signorini 1999, Yuh 2013] but have not been studied with respect to depression. In addition the nature of these scales means that they are only used in studies with the most severe of TBI.

The practical and large scale nature of this study necessitated the use of a simplified scheme that could be applied by a clinician. This study represents the first ever use of the "overall appearance" system for CT scan in a depression analysis. It has previously been used to measure global outcome and mortality after TBI [Wardlaw 2002, CRASH 2008]. The "overall appearance" system was devised some time ago but has not found its way into everyday use [Wardlaw, personal communication], although has been used in some large epidemiological studies. This was a relatively simple system to use and any uncertainties were clarified at the weekly neuro-radiological conference for specific cases. This cohort demonstrated a good distribution across the various categories of CT scan severity.

An interesting finding was that a large proportion of individuals with normal scans are admitted to hospital (39.5% of TBI admissions). This may be a surprising finding, as such individuals are often discharged if there are few clinical concerns in ED. Only 25% of ED attenders with TBI, are admitted [Sosin 1996]. Yet the implication from this finding is that despite a normal scan, there are enough clinical concerns over many individuals that warrant an overnight stay for caution e.g. alcohol intoxication.

Relatively few CT scans had diffuse or grossly abnormal findings (8.7%). This is important to note as many studies focus on the most severe of TBI who often require surgery or ITU. Yet this group make up relatively few cases when compared to the overall TBI population [Smits 2010].

Another surprising finding was the comparison between the different levels of abnormality seen on CT scan and risk of depression. This indicated that when compared to a normal CT scan as baseline, those with a mildly abnormal scan, had a lower risk of depression (OR 0.5). This occurred at both timepoints. Those with moderate and severe levels of abnormal CT scan shared a similar risk to those with a normal scan. This finding may appear to be somewhat unusual. If a true gradient of risk effect exists then it may be expected that those with increasingly abnormal scan, would exhibit a higher risk and those with normal scan exhibit the least risk.

It is important to try and explain such an unusual finding. A possible reason for this finding may be the presence of a confounding factor in those with normal scans. It is highly likely that a number of individuals in the "normal scan" group represent a sub-group of high somatisers or those with a propensity to present with symptoms. As the diagnosis of TBI is often dependent on the reporting of neurological dysfunction, it is quite possible that this sub-group are more likely to end up with a diagnosis of TBI compared to a less somatising group or individuals who downplay their symptoms and state that all is well. If this is indeed the case, then the "normal scan" group is likely to contain a significant number of individuals with a borderline diagnosis of TBI. These people are much more likely to present with depression or emotional upset at any time in their lives or to present with somatic complaints and this would skew the results of depression analysis [Ruff 1996, Iverson 2003]. It is difficult to postulate any other mechanism whereby those with a normal scan have a higher risk of depression than those with a mildly abnormal scan and a similar risk to those with much more severe abnormalities on CT imaging.

In general, CT scanning has been little studied with respect to depression. Some studies have looked at anatomical correlates in terms of the exact localisation of brain lesions. These have generally been small but highly detailed studies with a focus on the neuro-radiological evaluation. Such studies have often shown a relationship with left dorsolateral prefrontal cortical lesions or lesions in the anterior cingulate gyrus. [Fedoroff 1992, Robinson 1995. Jorge 2004]. In a follow-up study Fedoroff showed that this relationship was present at an early stage but not at one year. This is similar to the finding in this study with injury severity and the decreasing role of CT abnormality. Another study showed a link between depression and left sided dorsolateral prefrontal cortex lesions [Mollica 2009]. However this study consisted of victims of torture. The imbalance between left and right hemisphere as a result of TBI, has been suggested as a possible cause of depression [Schonberger 2011]

To the best of our knowledge no studies have looked at the extent of CT abnormalities with regards to the number of lobes or distribution of abnormalities. In general TBI affects a diffuse area of the brain by its very nature rather than distinct localised pathology as more commonly seen in conditions such as stroke.

A study with a small convenience sample, reported a similar finding to this study in that those with no abnormality on CT scan, had a higher risk than CT positive patients. They explained this by perceived stress and litigation in the CT Normal group [Bay 2008].

By contrast in a mild MTBI group, those with positive scans had a higher rate of depression than those with no abnormality [Levin 2005]. Others have reported a relationship to CT abnormality [Dikmen 2005] while others have shown no link [Lima 2008].

It has been suggested that CT scanning lacks the sensitivity to differentiate mild or moderate extent of abnormalities. This may explain why CT abnormalities show no relationship to overall global outcome [Dagher 2013]. It is perhaps more useful as a tool for monitoring severe TBI and the need for interventions. Certainly it is relatively insensitive to many of the changes seen in TBI such as DAI or

small contusions [Signorini 1999]. It is been shown that CT correlates to outcome at 3 months but not at one year again suggesting that long-term outcomes depend less on acute injury features [Sternberg 2013]. MRI may be better suited for this function particularly in later scanning and a mild effect on global outcome has been shown [Skandsen 2011, Yuh 2013].

It is likely that the development of more sophisticated techniques and their availability at clinical level such as volumetric methods or functional scanning, will allow better differentiation of the exact extent of brain involvement in the future.

6.2.15 Return to work

Depression and return to work were strongly associated with each other both at ten weeks and at one year on univariable and multivariable tests. In particular the association was graded such that those with no return had the highest risk of depression, those with a partial return to work carried an intermediate risk and full work return carried the lowest risk. The contrast in depression prevalence at 1 year between no return to work (79.8%), partial return (56.7%) and full return (6.6%) was stark. This "dose effect" is a new finding, previously unreported in the literature.

It was perturbing to note that even after one year, only 44% of individuals had returned to full employment. Over a quarter of individuals had no capacity for work whatsoever when compared to their previous job or capacity for work, including the elderly. In other words, this status was not affected by pre-injury unemployment which was only 9% by self-report.

Employment is an essential element of our daily life and wellbeing [Stocchetti 2016]. It affects social integration, health status and a number of financial and social benefits accrue from work. It is therefore likely that loss of employment would lead to psychological sequelae including depression [Franulic 2004, Tsaousides 2008]. A successful return to work should be a major goal of rehabilitation and employment plays an important role in self-esteem [Oddy 1985].

The link between employment and depression after TBI has previously been noted [Jorge 2005, Garrelfs 2015]. The role of an unstable work history with frequent job changes has also been linked to depression [Dikmen 2004]. Other studies have found only 44% return to work after two years in a moderate and severe TBI group [Forslund 2013], 58% in STBI after ten years [Andelic 2009], 66% in a mixed TBI group [Draper 2007] and 40% in another mixed group [Sander 1996]. Many of these were part-time jobs. The large TBIMS cohort reports 60% employment after two years either full or partial [Cuthbert 2015]. Manual and semi-skilled workers fare worse than professional classes [Ponsford 2015]. A systematic review encompassing most of these studies calculated a return to work of 40% at two years [Van Velzen 2009]

It is difficult to determine whether depression leads to unemployment or vice versa. Depression may delay recovery after injury and hence hinder return to work or education roles [Rogers 2007]. Alternatively the inability to return to work may be the primary problem and leads in turn to emotional distress and depression. This has yet to be addressed in a well-designed study although large studies have shown a worse overall outcome in the unemployed after TBI [Ulfarsson 2014b].

As TBI affects a young population, a disproportionate level of the burden of TBI will fall on young adults and parents at a time in their lives when paid employment is very important. This is clearly an area where rehabilitation efforts need to be focussed and where there is potential for making a marked difference.

6.2.16 Alcohol intoxication

Univariable associations between alcohol at time of injury and subsequent post-TBI depression were highly significant.

The multivariable model also showed a strong relationship to alcohol intoxication at time of sustaining TBI to depression at 10 weeks (OR 4.6) and at 1 year (OR 2.9). Along with psychiatric history, these are two of the strongest associations to predicting subsequent depression.

A very high number of individuals were intoxicated at the time of injury (26.6%) and these individuals were younger than non-intoxicated TBIs. This has been noted in other studies [Opreanu 2010, Chen 2012, Sternberg 2013]. Given that assessment of intoxicated individuals is difficult, it is likely that a higher proportion of such cases are admitted for observation overnight compared to non-intoxicated individuals [Harrison 2013]. The latter are more likely to have stable observations or allow full assessment, allowing for discharge home.

The risk of depression in those who were intoxicated at the time of admission was very high (83%) and was one of the strongest predictors of future depression risk. It is often difficult to assess an individual's weekly regular intake of alcohol and this can take considerable time. Furthermore the accuracy of such patient details is often questionable and it has been shown that patient estimate about alcohol intake is very inaccurate [Horner 2008, Schuckit 2009]. Therefore a pragmatic decision was taken not to try and document the amount individuals were drinking after their injury but from initial assessment in the ED it was possible to determine whether patients were intoxicated at the time they were admitted. As alcohol levels are not routinely done, individuals would have to be noticeably intoxicated or admit that they had been drinking in order for this to be documented and it is possible that a small number of individuals with a relatively low level of intoxication may not have been noted or recorded. The lead investigator always asked about alcohol intake during screening and at the initial interview so this variable should be accurate.

It is well recorded that a significant proportion of individuals sustaining TBI are intoxicated at the time with a range of 30%-50% noted [Dagher 2013 (also 3% had a positive drug screen), Tagliaferri 2006, Sternberg 2013, Andelic 2009, Corrigan 1995]. These are similar to our finding.

While some studies have noted an association similar to this study, [Dikmen 2004, Jorge 2005] many others have noticed no link [Rappaport 2006, Horner 2008, Cernich 2012]. Again as with all other variables it is clear that there is no concordance in the literature.

A point of particular interest is that a number of studies note that those with alcohol intoxication show more improvement both in overall function or other outcome measures [DeGuise 2009, Dagher 2013]. It has been suggested that this may be due to presence of binge drinkers who quickly recover and return to their normal lives with the binge being an aberration from normal behaviour. It has also been found that the biggest change in GCS within 24 hours occurs in those with alcohol intoxication [Shahin 2010]. It is therefore possible that individuals with intoxication are documented with an artificially low GCS that recovers as alcohol is metabolised. This may therefore over-estimate their injury severity and hence risk of poor outcomes including depression. There was no evidence for this in the present study although analysis of global outcome is yet to be done.

The finding in this study of greatly increased risk of depression was one of the key findings in this study and is of direct clinical relevance. It was noted that many of the individuals, intoxicated at injury, led chaotic life-styles and it is not surprising that this manifests in a higher prevalence of depression. Such individuals are known to underuse resources [Jourdan 2015]. Targeting such individuals may reap benefits.

6.2.17 Length of Stay

The vast majority of TBIs stayed in hospital for less than two days due to rapid recovery. 66.5% of admissions were <6 days and only 15.9% had a hospital stay>14 days. Others have also noted the short stay of most TBI admissions with 74%<3days [Kleiven 2003]. Again this contrasts with many studies focussing on STBI and individuals hospitalised for long periods upto 47 days on average [Malec 2007, Whelan-Goodinson 2008, Arango-Lasprilla 2010, Avesani 2012]

Length of stay showed a significant relationship with depression on univariable tests but not on the multivariable model. The relationship between length of stay and TBI severity has already been shown. It is therefore likely that individuals at high risk of depression require a longer period of stabilisation in hospital as they have more severe injury. In other words, length of stay is related to TBI severity rather than depression risk. Others have shown an association of length of stay with depression [Sander 1996]

6.2.18 Other variables

A number of other features have been investigated in other studies but not here.

Individuals who have substance misuse have frequently been shown in studies to have a higher risk of depression [Dikmen 2004, Willense 2007, Bryant 2010, Bombardier 2010, Hart 2012]. One study showed no link [Jorge 2004].

Fatigue and pain are commonly associated with depression but were not measured in this study. As these are relatively common symptoms in the general population as well as TBI it is a potential confounder. Both pain [Hibbard 2004, Mooney 2005, Sullivan-Singh 2014, Hoffman 2007] and fatigue [Kreutzer 2001, Ziino 2006] have been associated with risk of depression. Another study found a link to fatigue but not to pain [Sigurdardottir 2013].

No attempts were made to document cognitive changes in this cohort although of course individuals with particular problems were assessed for their clinical needs. Studies that have looked specifically at cognition have both found a positive link with poorer cognitive changes, especially executive function [Levin 2001, Andersson 2002, Jorge 2004, Chamelian 2006, Ghaffar 2006, Chaytor 2007]. No association with cognitive features has also been reported [Satz 1998].

Factors such as low education level [Hudak 2012], stress levels [Bay 2008], ongoing litigation [Mason 2006, Bay 2008] and genetic links with APOE4 gene [Jorge 2005] have all been linked to depression risk.

6.2.19 Other Outcomes measures

A number of other outcomes were measured in the study and a brief discussion of these and their relationship with depression is important.

6.2.19.1 Anxiety

As the HADS also measures the severity of anxiety symptoms, the use of this questionnaire also allowed an estimate of the presence of significant anxiety. This level was very similar to that of depression. At 10 weeks follow-up, only 8% of individuals had significant levels of either anxiety or depression but not the other. The corresponding figure at one year was only 6.8% emphasising that it is far more common to have both or neither condition.

The HADS has been criticised for being poor at differentiating anxiety and depression and that essentially the two scores measure the same or a similar construct of emotional distress [Clark 1991, Cosco 2012, Geraghty 2015]. Our findings would tend to support this theory.

The association between anxiety and depression has been shown in both the general population and also after brain injury [Kessler 2003]. Between 41% and 75% of TBI individuals have both conditions [Jorge 1993, Linn 1994, Piccinelli 1999, Sigurdardottir 2013, Whelan-Goodinson 2009, Seel 2010]. However a small study found that only 10% of depressed individuals after TBI also had anxiety and observed that depression was more common in those with MTBI as distinct to anxiety which was more common in those with STBI [Draper 2007]. There was no such finding here.

6.2.19.2 Rivermead Head Injury Follow-up Questionnaire/ Rivermead Post Concussion Score

Both of these scores were highly significant on univariable tests for association with depression. However the very high correlations between these scores, GOSE and depression meant that they could not be entered into the multivariable model (Section 5.5).

Over the course of a year, the scores for both of these questionnaires decreased, reflecting improvement in psychosocial outcome and head injury symptoms. A similar drop in these scores has been noted by others [King 1996, Fann 1995, Sigurdardottir 2013, Cassidy 2014]. Such an improvement is to be expected as individuals recover and improve over a year.

Nevertheless the scores were still remarkably high at one year showing falls from 15.9 to 11.4 for RHFUQ and 18.4 to 13.1 in RPCS. It seems that even in a population with predominantly MTBI and short inpatient stays, there is a high level of symptom and disability at one year caused by TBI. The high retention in this study implies that the result is not artificially inflated by attenders with ongoing problems while those who have recovered, decline to attend.

The scores were higher in those with depression which has also been noted by others [Jorge 1994, Fann 1995, Rappaport 2006a, Sigurdardottir 2009].

Interestingly in a study relating RPCS to life satisfaction, it was found that RPCS scores changed very slightly after one year and furthermore there was no evidence that symptoms were higher in those with more severe injury [Anke 2015]. This is in marked contrast to the finding here where TBI severity was highly correlated to outcome scores. It should be noted that a significant proportion of the normal population will score highly on the RPCS [King 1996, Sawchyn 2000, Ryan 2003, Iverson 2003] and that many of these symptoms are found in everyday life.

In a study that used many of the same outcomes in this study [Van Horn 2013], it was also noted that individuals scored highly on all self-report measures at the same time. It can be said that “the outcome measures, measure the same thing”. The dilemma of how to tease apart these separate scores is a vexing issue. Future work will look at statistical techniques that may allow a better understanding of these relationships and allow an examination of these outcomes together.

6.2.19.3 GOSE

GOSE and depression scores were highly associated on univariable tests. As explained in 6.2.18.2, the high correlations between all outcome measures meant that GOSE could not be entered into the multivariable model for depression.

While GOSE improved over the year, confirming that the population outcome had improved, the mean overall score was still in the moderate disability group. While there was a slight positive skew caused by the 38 deaths in the group (with GOSE=0), removing these from the analysis still left the overall outcome in moderate disability as reflected in Tables 5.23 and 5.24. The proportion of those in the Good outcome group, improved from 23.1% to 40.4% by one year indicating that many still have considerable disabilities.

The GOSE is an excellent "real life" outcome and the most commonly used measure in TBI studies [Wade 1992, Wilson 2002, Bagiella 2012]. It has an advantage over scores from neuropsychological tests which often fail to reflect everyday life functioning in activities of daily living and as a result are not a true reflection of global function [Roozenbeek 2013, Hellawell 2000]. It is important that results should illustrate social meaning and be relevant for patients [Pettigrew 1998, Wilson 2000].

Comparison to previous literature, confirms that there is a wide variation in outcome after TBI and considerable discrepancy. Those falling into good recovery after one year, range from 30% [Halley 2004], 36% [Sjoberg 2013], 33% [Godbolt 2015], 17% [Askainen 1998] and 49% [Hawthorne 2009]. Studies that only examine STBI may be expected to show worse overall outcome but Walker [2015] found 36% with good recovery at two years while the Paris-TBI Study only found 15.5% at one year fell into the good category [Jourdan 2013]. In another study only 1.3% of TBIs had a good outcome in a mixed group up to 15 years post-injury [Siponkoski 2013].

It is clear that there is considerable variation in TBI outcome, only part of which can be explained by study populations. Despite the use of structured questionnaires to assess the outcome [Wilson 1998], it

is clear to any clinician using the GOSE, that interpretation of the categories is open to interpretation and there is likely to be some inter-rater variability [Pettigrew 2003]. A significant advantage of this study is the use of a single observer which lends consistency to the evaluation of GOSE as well as other clinical parameters.

6.2.20 Early and Late depression

Further analysis of the cohort was carried out in order to better understand some of the difference between those with depression at an early stage compared to those with depression at 1 year. The 690 individuals, for whom one year data was available, divided quite evenly between those with or without initial depression (392 versus 298). However, these two groups differed considerably in how they were further divided into those with or without late depression. In the case of those with initial depression, the numbers who subsequently had late depression were 254 or 64.8% of this particular group, leaving 138 or 35.2% without late depression.

By contrast, those without initial depression behaved quite differently with only 30 (10.1%) of this cohort having late depression. This observation that late depression is unusual in those who do not initially have depression, is a key finding of this study. It contrasts with the number of previous studies that have found a stable or increasing rate of depression with time (6.2.3).

In an elegant study, [Hibbard 2004] it was found that the majority of individuals with early depression resolved these symptoms by one year follow-up. However 10% developed symptoms of late depression having previously been normal and 14% of individuals showed depressive symptoms at both times. These figures are similar to this study. They concluded that the four groups thus identified, represented very different populations within the TBI group (No depression, resolved, late depression and chronic).

Logistic regressions of the two groups were carried out with late depression as the outcome. The group with early depression showed more similarity to the overall model with all the study individuals in it.

Female gender, previous psychiatric history, alcohol intoxication at time of injury and failure of full return to work were all associated with an increased risk of depression. Again injury severity as GCS and overall CT scan appearance were not found to be significant. The group without early depression had fewer predictors of late depression; only past psychiatric history and no return to work were risk factors. These results in this latter analysis are intriguing but it is important not to over-interpret such preliminary results. But it is clear that early and late depression are different and associated with different risk factors.

A number of studies have found that acute depression is often associated with physiological and pathological processes caused by the initial brain injury [Silver 2009, Arciniegas 2014]. This is often associated with specific anatomical lesions, rich in neurotransmitters such as amines. It seems likely that the pathophysiological changes that occur shortly after injury, initiate depression in the acute phase. This relationship however resolves within a few months [Fedoroff 1992] and therefore other factors must assume more significance in the maintenance or development of late depression [Jorge 1993a].

It has been suggested that the maintenance of longer term depression is mediated by psychological predispositions or vulnerability, impaired self-awareness of disability, social loss and possibly secondary gain [Busch 1998, Babin 2003]. The use of maladaptive pre-learned strategies such as avoidant or emotion focussed behaviours in certain individuals, predisposes to a higher risk of depression [Helchem 2013]. This is in contrast to individuals with more problem-focussed coping styles and supportive environments including family and work. Good reviews of the topic are available [Prigatano 1997, Babin 2003, Moldover 2004]

Sigurdardottir [2014] examined the role of personality in determining outcome. The concept of resilience as a character trait, as typified by optimism and positive affect was important in determining the trajectory of recovery. However, it was not possible to predict which trajectory any individual may

follow although the strong effect of previous psychiatric history was also noted in this study. Others have discussed the concept of loss of "locus of control" [Just 1997]. The tendency to attribute outcomes to others and to the environment rather than maintaining an internal sense of direction, is also an important concept in distinguishing the role of such psychological factors [Tate 1989, Moore 1992]. Lower levels of self-esteem led to increased depression. Tate also noted the existence of a sub-set of "anxious complainers" whose level of symptoms seemed out of proportion to their seeming level of impairment or any measure of cognitive ability [Van Zomeren 1985, Tate 1989]. Others describe a "characterological problem" which predates the injury and affects the response to injury [Prigatano 1997].

It is therefore likely that the population experiencing TBI has a number of sub groups within it who have very different personal traits and responses to injury and subsequent trajectories of recovery [Mittenberg 1992, Moldover 2004].

The literature on coping mechanisms and personality types is extensive but unfortunately did not form any part of this study. The tools applied to identify and classify such different types of individuals are extensive, detailed and require extensive time and resource to apply and were considerably out with the means of a busy, time-pressured clinic based study such as this. However, a very small focussed, qualitative study may be possible in the future to look at differences in those with or without initial depression and how they respond after one year.

As many of the group had previous depression (see 6.2.15), it would be interesting to examine the likelihood of previous depression increasing the risk of TBI.

The study of other psychological factors or personality traits would be a fruitful area to consider in future research.

6.2.21 Summary

Prognosticating which factors are associated with increased depression risk is a challenging problem and is likely to involve multi-dimensional relationships with biological, psychological and social contributions. It is likely that acute depression is associated more commonly with injury features reflecting the biological mechanisms that are disrupted at an early stage. Long term depression is more likely to be modulated by psychological features such as pre-morbid coping behaviours, locus of control, and maladaptive behaviours. Social features such as family and employment support will also play a role. Differences in these characteristics may explain the variation in prevalence and associated features found in other studies which show no agreement or pattern of features that can be linked to depression risk.

6.3 Strengths and Weaknesses of the Study

6.3.1 Introduction

This study contains a number of strengths, both as a piece of research in its own right, but also in comparison to previous studies in the literature. Hence it adds to the existing knowledge of post-TBI depression in considerable measure. As with all studies, there are also a number of weaknesses that must be outlined as well. An attempt has been made to try and divide these into separate subheadings but some of these overlap e.g. a single observer has implications for consistency as well as data collection and follow-up.

6.3.2 Strengths

6.3.2.1 Clinic design

Considerable planning went into the design of the clinic and the measurement tools to be utilised for patient assessment. A compromise between the clinical needs of assessment and patient management had to be made against the desire to measure relevant outcomes that would be of interest in an academic context.

The creation of a rehabilitation based TBI service in 2009 presented a unique opportunity to study a TBI population prospectively and to develop a pathway for their rehabilitation management. While considerable changes in acute management of TBI has led to improvements in quality of care and overall mortality, there is still a considerable lack of rehabilitation provision and many gaps remain with particular regards to the post-acute management of sequelae. More than half of TBI admissions receive sub-optimal care and this is usually in their rehabilitation [Findlay 2007]. The primary objective of the new service was to set up a daily liaison service to review patients admitted with TBI and direct patients

to the appropriate services. Patients were also followed up at a new brain injury clinic by the lead investigator. The clinic aimed to support individuals and their families in the aftermath of TBI and to detect the development of any sequelae or complications after injury; this includes detecting cognitive, emotional or behavioural problems and referring to community services as required [Singh 2012].

Conducting daily ward rounds led to a systematic capture of all patients admitted with TBI and therefore a complete cohort unlike other studies. This population and the new clinic, allowed for a unique study.

The use of an NHS clinic to assess patients has distinct advantages and disadvantages. The need to compress history-taking, evaluation and treatment into 45 minutes is a challenge and also necessitated a pragmatic choice of tools that could be administered in a short time. Fortunately many of the tools can be self-filled while sat in the waiting room but an academic setting may have allowed for a more detailed assessment to be used for one specific area of interest e.g. some aspect of cognitive function. Given that some TBI tools take over an hour to complete, this would not be feasible in an NHS clinic [Hellawell 2000].

6.3.2.2 Study Design

The recruitment of a prospective cohort is a key strength of the study design. Administration of two follow-up assessments allows the evaluation of change, both in the prevalence of depression as well as the features that are related and is an additional advantage, particularly with the high follow-up ratio. TBI reviews have emphasised the need for long term follow-up and outcome data which is often lacking in the literature [Roozenbeek 2013, Guillamendegui 2011]. This cohort will hopefully generate some of this output.

Exclusion criteria were minimised (out of area residence, previous TBI requiring admission and dementia). Elderly patients were included. Many other studies suffer from selection bias or exclusion criteria, particularly of the elderly. Other studies exclude those with previous psychiatric conditions,

alcohol intoxication or lack of English or are purely convenience samples. Others are entirely or largely made up of a select group such as litigants or RTC victims. This study avoids such limitations.

The contemporaneous nature of the study assessments meant that patients were all evaluated at the same point after injury and in their recovery course. This is a key strength of the study and contrasts to the many studies which assess patients at varying times from injury.

6.3.2.3 Numbers

This study is the second largest study of depression after TBI. The only larger study was the TBIMS(TBI Model Systems) comprising nineteen of the most reputable Brain Injury Units in the USA which had 1089 cases [Hart 2012]. This model has extensive resources including staffing and finances available to it; yet even that group only used telephone follow-up. And even this high quality dataset is missing up to 20% of data [Dams-O'Connor 2015] such as GCS or CT scan findings. This highlights the concerted effort made in this study with face-to face interviews by a single observer and excellent data collection.

Other large studies include prospective studies of 559 [Bombardier 2010], 563 [Hawley 2008], 437 [Bryant 2010] and cross-sectional studies of 528 [Holsinger 2002], 666 [Seel 2003] and 722 [Kreutzer 2001]. None of the above approaches this study in terms of the extent of successful follow-up; some studies have lost as much as 80% of cases.

Taking all of the 112 studies identified in the literature review, the mean number of subjects in those studies was 149 (IQR 104) and the median was 91 (range 18-1089).

A further measure of the achievement in recruiting this cohort can be gained by considering the total population that will have suffered a TBI in total.

Over a 2 year period, the study successfully managed to recruit 803 patients. An even larger number of individuals (1289) were initially labelled with TBI by other clinicians.

The catchment area of the hospital is around 400,000. Over the two year period of the study, the 803 confirmed TBI patients would correspond to an incidence of $101/10^5$. If one takes the initial number of diagnosed TBI as 1289 cases, then this rises to $161.25/10^5$. The latter is probably a better comparison with previous epidemiological studies; it is likely that previous studies do not contain a TBI population, subject to such rigorous evaluation or screening by an experienced clinician as has been the case in this study.

This calculated incidence is comparable to other quoted incidences of TBI, from 150-229/105. [Tagliaferri 2006, Roozenbeek 2013, Peeters 2015] Most studies of incidence depend on self-report or ED based diagnosis rather than taking a detailed history at a later date. In addition, many of these estimates are of "all TBI", not just hospitalised cases, which may explain why the incidence in this study is at the lower end of the range. However, this calculation certainly suggests that the study has successfully identified and recruited the majority of TBI cases likely to have occurred in the entire region over a 2 year period and not just a select sample. This is an impressive feat.

By contrast, many other studies have struggled to recruit and retain subjects. We are not aware of any other study that has collected data on such a high proportion of the total TBI group; most populations are highly selected or vague as to the methods of recruitment and how many individuals are screened out. A similar head injury service in Cambridge only recruited 5% of all likely local cases based on predicted incidence [Seeley 2014]. By contrast, the numbers in this study constitute a very large and near complete, prospective cohort. This is an undoubted strength of the study.

6.3.2.4 Diagnosis of TBI

The diagnosis of TBI can be surprisingly difficult. Indeed the different criteria by which TBI is diagnosed has led to recent attempts to unify diagnostic criteria; it is these criteria that were used to confirm TBI in this study [Menon 2010]. Initial assessment and treatment of all patients was in ED by skilled clinicians.

Initially 1289 TBI cases were diagnosed. However 270 were ruled out of the study after interview by the lead investigator as TBI could not be confirmed by history. It was notable that in many cases of suspected TBI, the diagnosis simply could not be confirmed by history taking. In many instances, a patient history of feeling "dazed" or generally unwell was not sufficient to make a diagnosis in the lack of other corroborating evidence. Others were initially reported to have sustained a loss of consciousness but this could not be confirmed on close questioning.

The loss of almost a quarter of all "TBI" patients is illustrative of how difficult it is to correctly identify TBI victims even by experienced health professionals. However it also implies that the detailed history-taking will have removed many patients who probably do not have a TBI. Many other studies use self-report or another clinician's diagnosis for their population unlike the rigorous screening that this group have undergone. Hence this is likely to be a cohort with accurate diagnosis of TBI.

This difficulty in making a firm TBI diagnosis almost certainly contributes to wide differences in the quoted incidence of TBI [Roozenbeek 2013, Peeters 2015]. It will probably require the development and availability of better technologies e.g. fMRI, in order to improve the diagnostic accuracy of TBI.

6.3.2.5 Representative TBI Population

A key strength of the study is the recruitment of a truly representative and heterogeneous cohort of TBI cases. By capturing the overwhelming majority of hospital TBI cases that are likely to have occurred, the proportions of TBI severity and aetiology in the cohort should be comparable to the national picture. This makes the findings relevant to clinicians working in TBI everywhere. It is known that while MTBI constitutes up to 80% of all cases, only 30-50% of TBI admissions are mild [Bernstein 1999, Busch 1998] and that only 1 in 4 of MTBI are admitted [Sosin 1996, Rutland-Brown 2006]. The proportions in this group are equivalent to large epidemiological studies in the developed world [Tagliaferri 2006, CRASH-2]. By contrast, many other studies have heavily biased samples of severity or aetiology. Many studies

have used convenience samples [Bay 2007, Hawthorne 2009, Dahm 2012, Franulic 2012] or used adverts and volunteers from head injury groups [Ashman 2004]. Some studies have limited population to only STBI [Curran 2000] or MTBI [Bryant 2010] or only those with a positive CT scan [Bombardier 2010]. Some studies have drawn populations entirely from RTC [Draper 2007, Van Reekum 1996], TBI litigants [Sherman 2000, Gould 2011], political refugees [Mollica 2009] or only psychiatric cases referrals [Merskey 1972]. Others have chosen to exclude entire groups e.g. all patients with past psychiatric history [Kersel 2001, Forslund 2013] and most studies exclude the elderly at ages as low as 65 years [Mooney 2001, Ponsford 2010]. Such exclusions limit the ability of most studies to speak to the needs of the whole TBI population.

By contrast, the broad inclusion criteria, with minimal exclusions, allows this thesis to make relevant clinical observations that may have practical implications for treatment and identification of individuals at risk. The tendency for modern research to prefer randomised control trials is good for interventions but of less relevance in observational studies. The strict exclusion criteria often observed in RCTs leads to a marked selection bias and therefore less clinical relevance if we are to consider the strict population used in the trial.

In addition, the age distribution of the cohort confirmed a good dispersion across all ages and this approximated to a normal distribution. There was a slight positive skew towards younger individuals as is known to be the case in TBI populations [Roozenbeek 2013, Peeters 2015]. It was particularly reassuring to establish a cohort that included large numbers of elderly individuals, a group often excluded from TBI studies [Fletcher 2007]. With an aging population who possibly experience worse outcomes after head injury [Faul 2010], it is important that this group are shown due consideration in studies. The distribution of aetiologies of TBI also showed that falls (35.7%) were most common followed by RTC (26.6%). This reflects the known pattern of TBI in developed nations [Korhonen 2013,

Roozenbeek 2013] where RTC is no longer the most common cause. Again, this emphasises the importance of a study that incorporates the elderly population if it wishes to reflect real life.

6.3.2.6 Interview process

Face to face interviews by a single observer were a major strength of this study. The use of the lead investigator's training and extensive experience in TBI should lead to relevant and repeatable clinical observations. Many of the decisions made in clinic are a matter of opinion and having a single, skilled observer serves to standardise that observation and minimise inter-observer variation. Patients respond better to seeing the same clinician and understand the need for data collection within the context of a clinic appointment for their benefit rather than as part of a research exercise. Use of face to face interview is more accurate [Iverson 2010].

This contrasts with many studies that depend on the interrogation of an existing database gathered by busy clinicians or clerical staff in distant and disparate centres. The use of a single researcher in this regard is also the reason why the dataset is near complete with minimal loss of data.

It was important to limit the "patient burden" and therefore variables and questionnaires were selected on this basis. Many assessment or outcome tools have multiple items and require considerable time to fill which is not possible in a 45 minute interview. Cognitive fatigue after TBI is common and up to 40% of individuals refuse to fill questionnaires when asked [Ghaffar 2006, Bay 2007, Wittkampf 2009]. In a pragmatic study, the assessments had to be short but meaningful [Hellawell 2000].

6.3.2.7 Data

The quality of data collection is important in any study. The success in obtaining and documenting patient details has led to a high quality data set with very little missing data.

As the lead investigator was also the clinician for the service, there was a clear ownership of the project and data was avidly sought and completed at each clinic review. Extra efforts by the author were always made to fill any gaps in data, to ask the relevant questions at clinic and to document the findings accurately. Other studies are unlikely to have this same strength from a clinician's standpoint. Many studies are the interrogation of a large databank gathered by other people.

It can be very difficult to obtain high quality data in TBI cohorts. Many studies are missing considerable data; even the TBIMS cohort is missing GCS in 20% or CT results in 10% [Hart 2012]. In an in-patient study with a supposedly captive population, over 30% of cases were lost [Dagher 2013].

In real life, the dependence on busy clerical or junior medical staff to collate and submit data at a distant site, often with no sense of "ownership" of the study and its results, is very likely to affect the collection and quality of such data. At the same time, it should be acknowledged that such multi-centre studies are likely to recruit larger numbers and eliminate the potential bias in a single centre study such as this one (see next section).

6.3.2.8 Low Attrition rates

The other major strength of this study was the successful follow-up. Indeed at one year, once deaths are excluded (4.9%), the follow-up constituted 94.1% of all patients that were seen at the clinic; again, this is undoubtedly highly impressive. TBI studies are notorious for the loss of follow-up with as many as 70% of individuals lost by three months, let alone one year [Corrigan 1997, Corrigan 2003]. The high quality TBIMs study mentioned above, achieved 65% follow up at one year with considerable resources available to it. Many of the other studies lost up to 75% of cases within 6-12 months [MacNiven 1993,

Wade 1998, Jorge 2004, Fann 2005]. A large government funded study with considerable staff resource achieved only 50% follow up at one year [Bayen 2013] and over 30% of cases in an in-patient study were lost [Dagher 2013].

The achievement of such successful follow-up in this study, highlights the effective use of phone calls, text messages and letters to chase up individuals who forget to attend clinic. As this project stemmed from a clinic basis, it was important and appropriate to encourage clinic follow-up for patient benefit. This highlights an advantage of a clinician based study over an academic study. In the latter, ethical approval may have been difficult to obtain, in order to facilitate attendance for research purposes only. A clinic based study does not have such limitations.

While most of the studies listed in the literature review (Appendix 1), lose large proportions of their populations by time of follow-up, there have been some successful examples of good follow-up rates. A few, highly select, small studies, achieved 100% follow up [Dunlop 1991, McCauley 2001] while another managed 90% at 1 year and 75% after 5 years. [Sigurdardottir 2013]. While these were much smaller studies than this thesis, it would suggest that high follow-up can be achieved in an appropriate population, albeit rarely.

6.3.2.9 Population lost to follow-up

Although the numbers lost in this study were minimal, it is important to consider whether the individuals that were lost to follow-up, constitute a different group to those who were successfully followed up. Studies often find that the group lost to follow up or which is screened out, are very different to the actual study group.

Examination of the 46 (5.9%) cases that were lost, showed that there were minimal differences between the two groups; this is another strength of the study (Tables 5.4.1-5.4.5). Non-attenders had milder TBI although this was not statistically significant (Table 5.4.1). However lost patients were also 7 years older

than those who were followed up. This was a surprising finding as it is often thought that individuals with an erratic or haphazard lifestyle are more liable to be lost to follow-up; such individuals are likely to be younger [Schwarzbold 2008]. It is certainly the case that anecdotally, it was felt that the system of phone calls to facilitate follow-up of individuals, particularly those who fail to attend an appointment, seemed to have most impact on the younger population group which may have encouraged their attendance. However there is no way of testing this hypothesis.

The lost group also had milder level of head injury symptoms, disability scores and anxiety/depression scores. Interestingly, even at the ten week point, there was a significant difference between future non-attenders and other patients in terms of the global outcome scores. Non-attenders of the future, had a better early global outcome score (Table 5.4.5). It is likely that individuals choose not to attend clinic as they have improved to the point that they feel no need. It is difficult to envisage how their attendance could possibly be improved.

6.3.2.10 Statistical Strengths

A large, prospective study with near complete data collection and few lost cases, is likely to produce high quality and reliable results.

The high number of subjects also means that there is a high ratio of subjects to variables examined. This is often a weakness of other studies that over examine the number of independent variables relative to the number of subjects in the study.

Ideally a study should have 20 cases for each variable that is examined in order to minimise chance findings and avoid “overfitting”, although some studies quote a figure as low as 10 cases per variable [Peduzzi 1996]. On reflection, many of the studies in the literature review have “over-examined” the number of variables for the number of subjects.

However in a study of this size and extent of successful follow-up, it is statistically viable to examine a large number of variables. At the same time this was a pragmatic, clinic based study and therefore the extent of data collection had to be moderated by ethical considerations, namely patient time. Despite these considerations, it was possible to document a large number of demographic and injury variables. Given the strength of the data, it is possible to say with confidence that the findings are reliable.

A brief discussion of the multivariable models in this thesis is important. The overall models showed a very good fit both at ten weeks and one year. In a logistic regression model the statistic calculated is a pseudo-variance rather than a true variance. Nevertheless the model at ten weeks explained 54% of the pseudo-variance and the corresponding value at one year was 42%. By comparison other large models show lower levels of variance/pseudo-variance between 2.3% to 15% [Coral 2007, Anke 2015, Hart 2012]. Another study found a similarly high level of variance [Forslund 2013] but this was a more select group of only moderate and severe TBI. In general these low values indicate the extensive involvement of many other variables in long-term outcomes such as depression. Such outcomes are clearly multi-dimensional with several biological, psychosocial and environmental contributors to the eventual outcome. Most of the long-term outcome is likely to depend on psychosocial variables rather than injury features.

The AUC statistic in both models was excellent (0.89 and 0.90). In general it is considered that any model with AUC >0.75 is very good. Large multinational trials [CRASH, IMPACT] have found corresponding statistics of 0.77 and 0.80. Again this indicates the quality of the model calculated here.

A good model should have large numbers and reflect the true heterogeneity of the population and practice. This study has clearly achieved both of these goals. In addition, the high number of cases for each variable tested adds to the reliability of the model. In general the limited success of models to explain the outcome means that it is very difficult to predict who will or will not have a poor outcome. It is unlikely therefore that models will ever prove accurate enough to provide individual prognoses for

patients and families. It is more useful to consider the predictive power of individual variables as increasing or decreasing the relative risk of depression and this may allow the targeting of susceptible individuals.

6.3.2.11 Pathway of Clinical Care

The results of any study should have clinical implications and ideally should make a difference to patient care. The clinical nature of this study and the ongoing presence of the investigator in the clinic denotes that the relevant clinical findings can indeed be implemented into practice and further studies organised. The clinical recommendations will therefore find immediate clinical relevance for the TBI population and hopefully make a change to the assessment and ongoing management of such individuals. It is also planned to re-assess the outcomes at 5 and 10 years if possible. Integration of Rehabilitation Medicine into head injury pathways is increasingly recognised as important [Harradine 2004, Sorbo 2005, Singh 2013, Jourdan 2015].

6.3.3 Weaknesses

6.3.3.1 Observer

The use of a single observer at a single centre has been considered an advantage (6.3.2.6). In some ways it is also a disadvantage as it can introduce a systematic bias. Multi-centre data can overcome this potential bias that may exist with one observer. This should have been minimised by the use of an experienced clinician in TBI management

The observer was not blinded to patient observations and hence evaluations of outcome such as GOSE are unblinded. In a clinic where the investigator is also the lead clinician, it is quite possible that a bias exists in the documentation of outcome.

Cases were not matched and therefore it is impossible to state with certainty that the changes seen would not have happened in any other non-brain injury, e.g. major trauma without TBI. Ideally, the TBI cases could have been matched to a non-TBI inpatient population although it is highly unlikely that such a population would attend for assessment after 1 year. Very little of the existing literature has attempted to match case-controls.

6.3.3.2 Assessment Tools

As the study was based on a pragmatic clinic design, the tools for assessment and outcome had to be pragmatic and minimise patient effort. These tools were partly chosen for their brevity but also gave useful information. It would have been interesting to use some more detailed outcome tools. However it is likely that this would be at the cost of compliance as some tools can take over an hour to complete and more than one session [Williams 2002].

While the use of the HADS to assess depression was effective and has been reported by others, some purists may still feel that the SCID represents the only method of truly diagnosing depression. Apart from the time taken to perform, the literature review found that SCID studies had a similar average

depression rate to questionnaires and also a wider range. So it is unlikely that the HADS results in more false positive cases. With respect to use of the HADS, the use of a cut-off to distinguish case/non-case may be less effective than the use of the full linear range of scores, but it was considered to be more clinically relevant as decisions to treat are a yes/no outcome.

6.3.3.3 Study population

While this study was limited to hospital admissions using NICE guidance [NICE Clinical Guideline CG176 2014], it is known that many individuals do not present to hospital or are discharged from ED without admission. Those discharged directly from ED after assessment will represent a different and milder TBI population [Anstey 2004]. It is difficult to see how such a group could have been included or encouraged to attend clinics but findings are likely to have been different in this population.

The numbers lost in the study were remarkably small compared to other studies and this was a large strength. However there is always some uncertainty as to what would have happened to these individuals and what differences this would have made to the study if they could have been located and persuaded to come to follow-up. Compared to most other studies, differences in the groups was minimal.

Despite the high pick-up rate, it is likely that a very small number of individuals were rapidly triaged to neurosurgery or ITU. These individuals should have been picked up by liaison visits but it is possible, indeed likely, that a few individuals will have been missed. This would include those with very severe injuries who died shortly after admission although clearly they would not be part of a follow-up study. Survivors remain on the ward for some considerable time. Therefore the number of lost cases is likely to be very small because of almost daily liaison visits to neurointensive care or the neurosurgery unit.

6.3.3.4 Treatment of depression

The study did not look at treatment of depression and did not instigate treatment of any individuals. However a small number of individuals were referred back to their General Practitioner with a recommendation for monitoring or assessment and it is not known how many individuals will have received treatment with anti-depressants or counselling. This is a potential confounder. From the clinic documentation, less than 30 individuals were taking an antidepressant and it was not possible to look at whether this affected results. Future work may look at treatments and whether any modalities work in this group. Evidence suggests that treatment of depression after TBI can be effective but variable and is better for psychological intervention rather than medication [Weeks 2011, Barker-Collo 2013, Cooney 2013, Gertler 2015]

6.3.4 Summary

While there are some weaknesses to the study, the undoubted strengths of the study seem to outweigh these. Particular note of the size and prospective nature of the cohort, its reflection of the true TBI population including the elderly, the high follow up rate, complete data collection and the single observer to limit variation should be made. These considerations should make a valuable contribution to the existing literature.

6.4 Interpretation of Main Findings

In view of the previous discussion on strengths and weaknesses of the study, it is important to reassess the study's key findings. In particular it is important to consider the strength and validity of these findings in relation to previous studies that have been carried out.

While certain weaknesses exist as outlined in 6.3.3, they are outweighed by the considerable strengths that this study has enjoyed.

These include the validity of an inclusive study population with minimal exclusions, prospective follow-up at the same time interval post-injury, the validity of the test of depression, the rigorous assessment of individuals by a skilled clinician and clinic structure that facilitates face to face assessment and collection of data and finally the highly effective system of follow-up. Despite the extensive number of studies examined in the literature review, only two met the criteria for "excellent", indicating the difficulty in producing well designed, inclusive, follow-up studies in TBI. This study has met all of the above criteria and these strengths make this one of the highest quality studies in this entire area of literature.

It is therefore evident that the findings of this study are relevant to any clinician involved in the treatment of TBI and a number of the results are of particular relevance.

The finding that many individuals suffer depression is important and should be acknowledged. Clinicians should actively seek the presence of depressive symptoms that cannot be attributed to TBI. The finding that symptoms tend to improve over the course of the year but that 2/3 of initially depressed individuals show persistence indicates the long term nature of depression. The observation that depression is far more common in those who have a past history of psychiatric diagnosis or who were intoxicated at the time of injury is highly significant. This should allow such individuals to be targeted by clinicians for particularly close attention. The finding that depression was more common in women is also significant

although somewhat unclear. It is likely that this simply reflects the fact that depression is more common in women in the general population. Targeting a population based on gender would be much more difficult in terms of the number of individuals.

The finding that the features associated with early and late depression differed considerably is also important while a great deal more research is required to tease such features apart. There was evidence that injury related features such as TBI severity were more important at an early stage of depression whereas psychosocial features predominate late depression. The fact that late depression is not related to injury severity is very significant here. It is unclear whether targeting individuals based on injury severity at a late stage, is likely to be successful compared to depression at the initial stage.

6.5 Future work

There are several areas of work that could stem from this project and will hopefully do so over subsequent years. Continuing follow-up of this group to report on long-term outcomes after 5 and 10 years is planned. The lack of such long term studies has been noted in reviews [Rosenfeld 2012, Guillamendegui 2011] and is clearly important if we are to make the most of the undoubted improvements that have occurred in the acute management of TBI in recent years [Fuller 2011]. Most studies seem unable to generate long-term follow up numbers; the ability of this study to generate such data by facilitating follow-up is an advantage that should be repeated in further long-term studies.

It is planned to look at the role of rehabilitation pathways in the management of TBI and integrating previous work by the centre in this respect [Singh 2012]. Recent studies have shown that a carefully managed pathway can improve the outcomes but this is a difficult area to explore and does not lend itself to RCTs [Chesnut 1999, Cicerone 2011, Sveen 2016]. It is known that the majority of individuals do not receive rehabilitation care [Jourdan 2015] or suboptimal care even within a rehabilitation pathway [Sorbo 2005, Findlay 2007]. The challenge is to integrate acute TBI management into a long term pathway, including Rehabilitation Medicine, as has been successfully achieved in Sheffield [Singh 2012]. It would be ethically difficult to identify a population that does not receive the follow-up of the Brain Injury pathway and compare outcomes to the population in the clinic because this would be unfair to the population that are denied such contact. However future work could look at differences between those who attend the clinic readily and those who have to be chased up to keep their appointment. It may be reasoned that the “reluctant” group fare differently in outcome.

There was no quality of life measure recorded in this study. The HADS has been shown to be the best predictor of quality of life [Sjoberg 2013]. It is planned to introduce such a quality of life measure such as EQ-5D into the clinic and to explore the relationship with QOL and other outcomes such as depression.

The treatment of depression has not been a focus of this work. Clearly if a difference is to be made to patient outcomes then this needs to be examined. Unfortunately, the evidence for effectiveness of any treatment for depression is severely limited. Indeed reviews have failed to find any effect of medication and future trials of treatment are needed [Barker-Collo 2013, Gertler 2015].

This study did not systematically try and evaluate cognitive impairments caused by TBI. While such changes could be a confounding factor on depression, the exact relationship between the two is unclear and requires further study. For example, do cognitive impairments lead to depression or does the existence of a depressive state increase the likelihood of cognitive difficulties [Chamelian 2006]. This could be explored prospectively although time in each interview is at a premium and these assessments require considerable time.

Future work is required to evaluate the relationship between depression and other outcomes such as RHFUQ and GOSE. Statistical advice is needed to find the appropriate method for analysing variables that are very closely correlated with one another. Unfortunately, the high correlations between the various outcomes meant that they could not be entered into the same multivariable analyses. It is possible that such measures are so closely related, that only one needs to be measured rather than multiple assessments. This would have clear implications for clinicians and patients. The relationship to global overall outcome (GOSE) is of particular importance and will be analysed in future papers.

It is also likely that depression negatively affects an individual's participation in any rehabilitation programme and hence the overall outcome. It would be interesting to examine whether the depressed individuals participate in rehabilitation to the same extent as others.

A particular area of interest would be to assess whether there is a time relationship such that either depression or functional recovery precede one another or occur at the same time. It has been suggested that decreased functional outcome precedes the onset of depression i.e. that it is loss of

function that causes depression [Ownsworth 2011, Schonberger 2011a]. This could be explored with serial evaluations over time assuming that high follow-up rates can be maintained at the clinic.

6.6 Clinical Practice Recommendations

Depression is highly prevalent after TBI with over 50% of the admitted population displaying significant symptoms. While the prevalence drops over one year it remains significantly elevated at 41%. Although the relationship to time is unclear, it makes sense to target individuals in the first year after injury with most other studies showing the highest prevalence in the first year. Furthermore it is in this early stage that individuals may be most amenable to rehabilitation input and likely to show changes in physical and cognitive state. It is imperative that patients, who sustain TBI, are routinely assessed for mood symptoms and provided follow-up for ongoing assessment. It is important to educate individuals and their families after TBI about the risk or possibility of developing symptoms of emotional distress, inducing depression. Individuals at particular risk of depression should be targeted. The analysis of particular features in this study showed that those with alcohol intoxication at time of injury and previous psychiatric history were at considerable risk of depression. Women were also at higher risk although this may represent the known background risk of depression. Of equal importance is that several features were not related to depression risk, such as TBI severity at one year, age and aetiology of injury. Targeting individuals on the basis of these parameters may not prove fruitful.

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APPENDICES

Appendix 1: Table of Studies identified in Literature Review

The first appendix contains a summary table of the 112 studies identified for the literature review and lists the main details of each individual study, particularly to its main findings and strengths/weaknesses.

There is also a Table listing the quality assessment of each study with an overall grading of the paper using the CASP checklist.

Table A1.1: Studies identified in literature review and their key features

Table A1.2: Quality rating of studies

Author, Yr	N (N at follow up)	Depression measure	Time from injury	Study Type	Prevalence	Time of follow-up	Notes
Alexander 1992	36	SCID	6-60m	Cross-sectional	67	Between 1 and 5 yrs	Higher in MTBI
Ashman 2004	188 at 1yr 83 at 2 yrs	SCID	3m to 4yrs	Prospective	24 21	12 months 24 months	Recruited by adverts; levels remain high; link to previous psych hx
Andelic 2009	62	BDI	9-11 yrs	Cross-sectional	31 at 10yrs	10 yrs	Mod-sev and working age; no link to employment
Al-Adawi 2007	68	HADS	Not stated	Cross-sectional	19.1	18 months	No severity reported
Bay 2008	84	NFI	1-36 m	Cross-sectional	58.3	n/a	Mild Mod injury; assoc with stress, pain and litigation
Bay 2007	75	CES	9.57±6.3 m	Cross-sectional	64	n/a	Mild Mod injury; convenience sample
Brooks 1983	55	Single question	2-8 yrs	Cross-sectional	24%	n/a	Higher in relatives too (49%); no link to severity;own questionnaire
Bombardier 2006	211 (124 at 6m)	PHQ-9	<6 months	Prospective	21.8	6months	Abnormal scans only; mainly looking at PTSD (11.3%)
Bombardier 2010	559 (365 at 1 yr)	PHQ-9	Immediate	Prospective	24.5 20.8 23.3	3months 6 months 12 months	Abnormal scans only; phone calls; 53.1% had depression at any point and 41% had medication at any point

Bowen 1999	99 (77 at 1yr)	Wimbledon Self-report	<6 m	Prospective	39 (6m) 35 (1yr)	1 yr	Unselected cases; no link to severity
Brown 2004	135 (screened 399)	SCID CES-D	12±2 wks	Cross-sectional	16.3 (SCID) 21% (CES)	n/a	Mainly MTBI; all recent TBI; similar rates on two measures
Bryant 2001	96(161 screened)	BDI	Not stated	Cross-sectional	45.8	n/a	High rate of PTSD as well
Bryant 2010	437(321 at 1 yr; screened 1477)	MINI	Immediate	Prospective	18 17.5	3 months 12 months	MTBI; 54% depressed at both times; similar rate in non-TBI trauma group (16)
Burton 1988	33	MMPI	2-8 yrs	Cross-sectional	37	n/a	Men; focused on psychopathy and schizophrenia measures
Chamelian 2004	90	SCID, GHQ	Up to 6 months	Cross-sectional	18.2	n/a	Mild moderate; higher in APOE4+ group
Chaytor 2007	216	CESD	6 months	Cross-sectional	40	n/a	Mod-Sev; weak link to neuropsychological measures; large study on MgSO4
Curran 2000	88	BDI	1-5 yrs	Cross-sectional	57	n/a	Mainly STBI; 40% in Trauma group (no TBI)
Dahm 2012	123	HADS	434 days(64-9324)	Cross-sectional	38	n/a	Convenience sample; 37% also anxiety; 75% both
Deb 1999	164 (screened 346)	Behaviour checklist	< 1 yr	Cross-sectional	16.3 (Mild) 33.3(Mod/S)	n/a	Higher in S/Mod TBI but small group; own devised measure; higher in low education; 2.1% prevalence in general population
Di Cesare 1990	118	Hopkins symptoms	Not stated	Cross-sectional	36	n/a	Women higher

Dikmen 2004	283 (175 at 1 yr)	CESD	3-5 yrs	Prospective	46 (1 m) 30 (3-5yrs)	1 yr	CT +ve; no link to TBI severity or psych hx; link to low education and and job instability
Draper 2007	53	HADS	10 yrs (10-12)	Cross-sectional	46	n/a	96% RTC; more in MTBI; anx only 10%; depr best predictor of functional outcome
Dunlop 1991	34 (screened 193)	Modified symptom list	Not stated	Prospective	57	> 2 months	100% Follow –up achieved Measure not validated
Evans 2005	96	CES	Not stated	Cross-sectional	25% (Severe) 12 (Mod) 17 (Mild)	n/a	Unclear as to time since injury; similar rates for TBI severity
Fann 1995	50	SCID	1-128 months	Cross-sectional	54	n/a	50% had prior Psych hx; anxiety 55 %; wide range since injury; associated with decreased function
Fann 2005	478 (135 at end)	PHQ-9	Not stated	Prospective	22.5	12 months	No normal scans; 71% lost to FU
Fann 2009	145	PHQ-9	6.4±3.7 months	Cross-sectional	25.5	n/a	No normal scans; higher with psych hx; phone FU
Forslund 2013	160 (91 at end)	BDI	From diagnosis	Prospective	28 34	1 yr 2 yr	Working age mod-sev TBI; excl all psych hx; 50% of variance of outcome explained
Franulic 2004	71 (at 2 yrs) 58 (at 10 yrs)	Hamilton	2-10 yrs	Cross-sectional	42.3 59.3	n/a	Convenience sample; Mainly MTBI; high incidence at 2 and10 yrs; higher in unemployed
Frenisy 2006	25 (screened	SCL-90	1±0.4 yrs	Cross-sectional	76	n/a	STBI; same incidence in

	486)						trauma without TBI; highly selected group
Gagnon 2006	30 (screened 169)	BDI	3.3±3.2 yrs	Cross-sectional	43	n/a	Very selected group; matched controls only had 3.3%
Ghaffar 2006	122	GHQ	6 months	Cross-sectional	28.7	n/a	GCS 15; excluded all comorbidities and only<60 yrs; litigation associated but not previous TBI
Glenn 2001	41	BDI	Not stated	Cross-sectional	59	n/a	MTBI; less in assaults, female, older
Gomez-Hernandez 1997	65 (37 at 1 yr)	SCID	1 month	Prospective	36 38.1 27.0	3 months 6 months 12 months	Excluded most major trauma; TBI severity not clear; associated with fear of job loss
Gordon 1998	240	BDI	11.1 yrs mean	Cross-sectional	28	n/a	Part of exercise trial Severity not clear
Gould 2011	102	SCID	From admission	Prospective	26 26	1 yr 2 yr	Mainly Mod-Sev; Mainly RTC and litigation; Assoc to previous psych hx; 75% symptoms at both times
Hart 2012	1089 (1586 start)	PHQ9	<1 yr	Prospective	26	1 yr	Model Systems 19 centres; phone calls; Higher in women, young, psych hx; depression worsens functional outcome
Hawley 2008	563 (165 at 10 yrs)	HADS	4-30 months	Prospective	37.5(Mild) 25(Mod) 17.2(Sev)	10 yrs	62% STBI cases; 71% lost to FU; higher anxiety levels 25-33%; 52% had depression at any point
Hawthorne 2009	66 (screened	HADS	3-136 months	Cross-sectional	22.7	n/a	Convenience sample;

	203)						Matched controls only 3%; anxiety 36%
Hermann 2009	200	SCID	113±92 days	Cross-sectional	48	n/a	Mild Mod; no link to psych hx
Hibbard 2004	188	SCID	2.6±1.3 yrs	Prospective	55	1 yr	53% had another psychiatric condition at 1 yr; Divided into 4 gps; resolved depression group did better than late depression group; chronic depression group worst on outcomes; pre TBI psych hx not associated
Hibbard 1998	100 (431 screened)	SCID	7.6 yrs	Cross-sectional	61	n/a	50% had pre-existing psychiatry history; long FU
Himanen 2009	61 (screen 210)	BDI	Up to 31 yrs	Cross-sectional	52.5	n/a	Very wide range of time since injury; depr associated with slow process speeds and attention
Hoge 2008	384 (screened 4618)	PHQ-9	3-4 months	Cross-sectional	22.9	n/a	US infantry after combat duty; also 43.9% PTSD; not related to injury severity; self-report of TBI
Holsinger 2002	528 (screened 5444)	SCID	Up to 50 yrs (war veterans)	Cross-sectional	25.6	n/a	Lifetime risk of depression after TBI; OR 1.99 for STBI; 13.4% in non-TBI veterans; self-report of TBI
Homaifar 2009	52 (screen 107)	BDI	1-51 yrs; mean 23 yrs	Cross-sectional	44.2	n/a	Long time since injury; PTSD 35%; more in MTBI
Hoofien 2001	76 (screened	SCL-90	14.1±5.5 yrs	Cross-sectional	45.3	n/a	STBI; Long time since

	321)						injury; anxiety 43.8%; associated with unemployment/divorce
Huang 2005	59	Zung	1 yr	Cross-sectional	16.9	n/a	All cases in STBI(59% of STBI); none in mild/mod; biased to somatic symptoms
Hudak 2012	471(1279 screened)	BDI	6-8 months	Cross-sectional	19	n/a	Phone interview; link to functional status and low education; inverse link to TBI severity
Jorge 1993	66 (60 at 1 yr)	SCID Hamilton Rating	Not stated	Prospective	42 25.6	6 month 12 months	High level previous psychiatric hx; Lesion location; minor depression 3% but major 25.8%; good study with repeated, sequential measures
Jorge 2004	91 (74 at end)	SCID	Not stated	Prospective	50 33	initial 12 months	Substance abuse 6.7%; PTSD 43.2%; 33% on antidepressants
Kant 1998	83	BDI	Not stated	Cross-sectional	71.1	n/a	Highest incidence found
Kashluba 2006	110	PCL	12.1±5.8 days	Prospective	39 (40 at start)	3 months	MTBI; very recent TBI group; matched controls also 33% depression; anxiety 51%
Keiski 2007	53	Portland Inventory	Not stated	Cross-sectional	55.8	n/a	Mild/Mod only
Kersel 2001	123 (58 at 1yr)	BDI	153-277 days	Prospective	24 (initial) 24 (12 months)	12 months	STBI; high attrition; excluded all previous psych hx
Kennedy 2005	78	SCID	76±94	Cross-sectional	50	n/a	Very long time since injury

			months				
Koponen 2006	58 (screened 118)	SCID	31.5±4.5 yrs	Cross-sectional	24.1	n/a	Very long time since injury; less with contusions (17%)
Koponen 2005	54 (screen 210)	BDI	26-47 yrs	Cross-sectional	5.8	n/a	Very low prevalence; same in controls
Koponen 2011	45 (38 at one year)	SCID	From diagnosis	Prospective	21.1	1yr	6.5% in community rate; unselected A&E pts; high rate of other psych disorders; low substance abuse in depressed
Kreuter 1998	92	HADS	1-20 yrs; median 9yrs	Cross-sectional	26	n/a	Similar to level in spinal cord injury and higher than healthy volunteers
Kreutzer 2001	722	NFI	2.5±3.5 yrs	Cross-sectional	42	n/a	Large study; NFI scales grouped to DSM-IV domains but 105 items; 76% RTC; main symptoms were fatigue, frustration and poor concentration
Levin 2001	69	CES	3.2±1.4 months	Cross-sectional	17.4	n/a	87% MTBI; only 6% in general trauma group; poor functional recovery and high symptom levels
Levin 2005	239 (129 at end)	CES	Not stated	Prospective	11.6	12 weeks	MTBI; Higher with abnormal scan and age
Lezak 1987	42	Portland Inventory	< 1yr	Cross-sectional	38	n/a	Convenience sample; mainly STBI; Higher in 2nd 6 months
Lima 2008	39	HADS	>18 months	Cross-sectional	55.2	n/a	MTBI; 26% in relatives and 47% had anxiety; no link to CT+

Linn 1994	60	SCL-90	70.3±65.2 months	Cross-sectional	69.6	>12 months	Convenience sample; Highest in MTBI Also high level in spouses(73%)
MacNiven 1993	59 (14 at end)	MMPI	Not stated	Prospective	40 (initial) 42.9 (2 yrs)	1-2 yrs	Few patients at end;; high levels of hysteria and hypochondriasis
McCauley 2001	115	SCID, CES	31.4±8.1 days	Prospective	22	3 months	Short study; 100% FU; same in mild and mod TBI; lower in general trauma gp
McCauley 2006	340(screen 854)	SCID	86.4±17.4 days	Cross-sectional	35	n/a	Mild/mod; wide exclusions; much higher in PCS (47 vs 8%)
McCleary 1998	105(66 at end)	SCL-90	12 months	Prospective	41.9 36.3	6 months 12 months	Less in general trauma; 71% depressed at both times
Malec 2010	158	BDI	1-2 yrs	Cross-sectional	40	n/a	Depr linked to function; no link to severity; link to prev psych hx and low education
Marsh 2006	32 (123 screened)	HIBS	386±31 days	Cross-sectional	52	n/a	81% STBI; same prevalence in carers; 55% GR on GOSE, 24% SD
Merskey 1972	27	Own scale	6m-14 yrs	Cross-sectional	59	n/a	All psychiatric refs; MTBI; poor description of patients
Mobayed 1990	55	Leeds scale	11-13 months	Cross-sectional	29.1	n/a	Non-validated score in TBI; MTBI and all male
Mollica 2009	42(screen 337)	Hopkins Checklist	Not stated but decades at least	Cross-sectional	62.5 (12.5 in non-TBI)	n/a	Political refugees years after head injury; self reported TBI

Mooney 2001	80	SCID	24 weeks median	Cross-sectional	44	n/a	MTBI; young group (31 yrs); "variety of referral sources"
Mooney 2005	67	BDI	15 months median	Cross-sectional	61.2	n/a	MTBI; high previous TBI (25%) and previous depression (34%); mainly litigants with poor recovery
O'Carroll 1991	36 (122 screened)	HADS	4 yrs	Cross-sectional	22.9	n/a	25% anxiety; no link to TBI severity; also high in relatives
Ownsworth 2011	124 (96 at 3 mths)	DASS	From diagnosis	Prospective	24 27	discharge 3 mths	Working age group; decreased function precedes depr
Pagulayan 2008	379 (1035 screened)	CESD	From diagnosis	Prospective	44 29	1 mth 1yr	Mainly complicated MTBI; functional outcome associated with depression
Parcell 2006	63	HADS	230 days mean	Cross-sectional	38	n/a	Matched controls only 2%; 40% also had anxiety; GCS not correlated
Peleg 2009	65	BDI	2.9±2.3 yrs	Cross-sectional	73.9	n/a	61% STBI; 76% RTC
Ponsford 2010	301 266	HADS	2 yrs 5 yrs	Cross-sectional	45 44	n/a	Young group; mainly STBI; "no compensation"
Popovic 2004	67	Zung	3.8±0.7 yrs	Cross-sectional	46.3	n/a	Mod/sev;
Powell 2002	54 (48 at end)	HADS	4.0±4.9 yrs	Prospective	35	18-40 months	Varied FU length; 29% also anxiety; no change in scores HADS
Rao 2008	54(screened 1000)	SCID	0-3 months	Cross-sectional	13	n/a	Mainly MTBI; 52% RTC;
Rao 2009	67	SCID	<3 months	Cross-sectional	11.9	n/a	Very high previous psych hx (76%) or alcohol (52%)
Rapaport 2002	323(screened	NRS	78.0±21.8	Cross-sectional	38.3	n/a	Highest in STBI (48%); all

	870)		days				CT+
Rapaport 2003a	146	SCID	49.0±30 days	Cross-sectional	21.2	n/a	MTBI; less with age
Rapaport 2003b	170	SCID	48.4±33.6 days	Cross-sectional	15.3	n/a	MTBI; Poorer social function; excl all psych cases; more in car accidents
Rapaport 2006	77 (46 at end)	SCID	46.9±34 days	Prospective	15.6 55.6	discharge 1 yr	Mild Mod; over 50 yrs baseline 15.6% increasing to 55.6
Rapaport 2008	65(54 at end)	Hamilton	Not stated	Cross-sectional	83.1	10 weeks	Part of citalopram trial
Ruocco 2007	231	MCMI	Not stated	Cross-sectional	46.9	n/a	Anxiety common(57%); similar rates to psychiatry ward
Satz 1998	100	SCL	6 m- 1 yr	Cross-sectional	31	n/a	Mod-Sev; related to GOSE but not neuropsychological tests
Schoenburger 2011	54	SCID	2.2 yrs	Cross-sectional	24	n/a	Link to lest sided brain lesions; no link to frontal lesions
Schoenhuber 1988	35	Zung	5-17 mths	Cross-sectional	39	n/a	Select referrals and postal q; mainly MTBI; Control group had same anxiety but less depression
Seel 2003	666 (17 centres)	NFI mapped to DSM-IV	35.3±26.9 months	Cross-sectional	27	n/a	No link to time since injury; 17 centres; 7% suicidal thoughts; IP rehab 33.7±25.6 days so selected group
Sherer 2007	69(49 at end)	CES	82(23-938) days	Cross-sectional	31.9	n/a	Large range since injury; Higher if more “dependent” on therapist

Sherman 2000	175	MMPI	2.5±2.0 yrs	Cross-sectional	33	n/a	All litigation cases; similar for all TBI severities; depressed had worse cognition but mild loss
Sigurdardottir 2013	118 (89 at 5yrs and screened 270)	HADS	From diagnosis	Prospective	18 (3 month) 13 (1 yr) 18 (5 yrs)	5 yrs	Admissions only; wide exclusions; Age, anxiety, employment predict depression
Sjoberg 2013	162 (126 at end)	HADS	From diagnosis	Prospective	17.9	1 yr	Part of large QOL study; HADS best predictor of outcome; high follow up
Sliwinski 1998	100	BDI	7.6 yrs mean	Cross-sectional	23	n/a	BDI score elevated by hypersensitivity after TBI
Stalnacke 2007	163	BDI	3 yrs	Cross-sectional	40	n/a	MTBI;
Sullivan-Singh 2014	158 (116 at 1yr)	PHQ-9	1 yr	Prospective	31 (at start) 22 (1 yr)	1 yr	Phone calls; Mod-severe TBI; high pain levels
Tateno 2003	89	SCID	23.9±17.7 days	Cross-sectional	56.7	n/a	High previous psych hx;
Van Horn 2013	242	HADS	Within 1 yr	Cross-sectional	18	n/a	Similar level in all severities; assoc with return to work
Van Reekum 1996	18	SCID	Not stated	Cross-sectional	50	n/a	Convenience sample; 100% RTC
Varney 1987	120	SCID	3.4 yrs mean	Cross-sectional	76.7	n/a	TBI poorly defined; all neuropsychology referrals
Wade 1998	181(321 screened)	HADS	6 months	Cross-sectional	25	n/a	61% “significant” disability
Whelan-Goodinson 2008	100(720 screened)	HADS/ SCID	2.98±1.5 yrs	Cross-sectional	34	n/a	Long IP stay (mean 41days); HADS picked up most cases; depr best predictor of outcome; link

							to previous depr
Ziino 2006	46	HADS	Not stated	Cross-sectional	39.1	n/a	Mainly STBI; 45.7% also anxious

Quality Rating of each Study using CASP Cohort criteria

Citation	Size of study	TBI population	Depression diagnosis	Follow-up time from TBI	Loss to Follow-up	Design	Overall
Alexander 1992	1	2	3	2	n/a	3	average
Ashman 2004	2	1	3	3	2	1	average
Andelic 2009	1	2	2	3	n/a	2	average
Al-Adawi 2007	1	0/1	2	1	n/a	1	poor
Bay 2008	1	1	2	1	n/a	2	average
Bay 2007	1	1	2	1	n/a	2	average
Brooks 1983	1	1	1	1	n/a	2	average
Bombardier 2006	2	2	2	3	3	3	good
Bombardier 2010	3	2	2	3	3	3	good
Bowen 1999	1	3	1	2	3	2	average
Brown 2004	2	1	3	1	n/a	2	average
Bryant 2001	1	1	2	2	n/a	2	average
Bryant 2010	3	1	2	2	2	3	good
Burton 1988	1	1	2	1	n/a	1	poor
Dunlop 1991	1	1	1	1	3	2	average
Chamelian 2004	1	2	3	2	n/a	2	average

Chaytor 2007	2	2	2	2	n/a	2	average
Curran 2000	1	1	2	2	n/a	2	average
Dahm	2	1	2	2	n/a	2	average
Deb 1999	2	2	1	1	n/a	1	poor
Di Cesare 1990	1	2	1	1	n/a	1	poor
Dikmen 2004	2	3	2	3	2	3	good
Draper 2007	1	1	2	3	n/a	1	poor
Evans 2005	1	2	2	1	n/a	1	poor
Fann 1995	1	2	3	1	n/a	2	average
Fann 2005	3	2	2	2	1	2	average
Fann 2009	2	2	2	2	n/a	2	average
Forslund 2012	2	2	2	2	2	2	good
Franulic 2004	1	1	2	3	n/a	1	poor
Frenisy 2006	1	1	2	2	n/a	1	poor
Gagnon 2006	1	1	2	2	n/a	1	average
Ghaffar 2006	1	1	1	1	n/a	1	poor
Glenn 2001	1	1	2	2	n/a	2	average
Gomez-Hernandez 1997	1	2	3	2	1	2	good
Gordon 1998	2	1	2	3	n/a	1	poor

Gould 2011	1	2	3	3	2	3	good
Hart 2012	3	3	2	2	3	3	Very good
Hawley 2008	3	3	2	3	2	2	good
Hawthorne 2009	1	1	2	1	n/a	1	poor
Hermann 2009	2	2	3	1	n/a	2	average
Hibbard 2004	2	2	3	2	2	2	average
Hibbard 1998	1	2	3	3	n/a	2	average
Himanen 2009	1	2	2	3	n/a	1	average
Hoge 2008	3	2	2	2	n/a	2	average
Holsinger 2002	3	2	3	3	n/a	2	average
Homaifar 2009	1	2	2	3	n/a	2	average
Hoofien 2001	1	1	2	3	n/a	2	average
Huang 2005	1	2	2	2	n/a	2	average
Hudak 2012	3	2	2	2	n/a	2	average
Jorge 1993	1	2	3	2	2	2	average
Jorge 2004	1	2	3	2	2	2	average
Kant 1998	1	1	2	1	n/a	1	poor
Kashluba 2006	1	1	2	1	2	2	average
Keiski 2007	1	1	1	2	n/a	2	poor
Kersel 2001	1	1	2	2	1	2	average

Kennedy 2005	1	2	3	3	n/a	2	average
Koponen 2006	1	2	3	3	n/a	2	good
Koponen 2005	1	1	2	2	n/a	2	average
Koponen 2011	1	2	3	2	2	2	good
Kreuter 1998	1	1	2	2	n/a	1	poor
Kreutzer 2001	3	2	2	3	n/a	2	average
Levin 2001	1	1	2	2	n/a	2	average
Levin 2005	2	2	2	1	1	2	average
Lezak 1987	1	1	1	2	n/a	1	poor
Lima 2008	1	1	2	2	n/a	1	average
Linn 1994	1	2	2	3	n/a	2	average
MacNiven 1993	1	1	2	2	1	2	poor
McCauley 2001	1	3	3	1	3	2	average
McCauley 2005	3	2	3	2	n/a	2	average
McCleary 1998	1	2	2	2	1	2	average
Malec 2010	2	2	2	2	n/a	2	average
Marsh 2006	1	1	1	2	n/a	1	poor
Merskey 1972	1	1	1	2	n/a	1	poor
Mobayed 1990	1	1	1	2	n/a	2	poor
Mollica 2009	1	1	1	3	n/a	2	average

Mooney 2001	1	1	3	1	n/a	1	poor
Mooney 2005	1	1	2	2	n/a	2	average
O'Carroll 1991	1	2	2	1	n/a	2	average
Ownsworth 2011	1	2	2	1	2	2	average
Pagulayan 2008	2	2	2	2	2	2	good
Parcell 2006	1	2	2	2	n/a	2	good
Peleg 2009	1	1	2	2	n/a	2	average
Ponsford 2010	3	1	2	3	n/a	2	average
Popovic 2004	1	2	2	2	n/a	2	average
Powell 2002	1	2	2	2	3	2	good
Rao 2008	1	1	3	1	n/a	1	poor
Rao 2009	1	1	3	1	n/a	2	poor
Rapaport 2002	3	2	2	1	n/a	2	average
Rapaport 2003a	2	1	3	2	n/a	2	good
Rapaport 2003b	2	2	3	2	n/a	3	good
Rapaport 2006	1	2	3	2	2	2	good
Rapaport 2008	1	2	2	2	n/a	2	good
Ruocco 2007	2	2	1	1	n/a	1	poor
Satz 1998	1	2	2	2	n/a	2	average
Schonberger 2011	1	2	3	2	n/a	2	average

Schoenhuber 1988	1	1	2	2	n/a	1	poor
Seel 2003	3	2	2	2	n/a	2	good
Sherer 2007	1	1	2	2	2	2	average
Sherman 2000	2	2	2	2	n/a	2	average
Sigurdardottir 2013	2	3	2	3	3	3	Very good
Sjoberg 2013	2	2	2	2	2	2	good
Sliwinski 1998	1	1	2	2	n/a	1	poor
Stalnacke 2007	2	1	2	2	n/a	2	average
Sullivan-Singh 2014	2	2	2	2	2	2	good
Tateno 2003	1	1	3	1	n/a	2	average
Van Horn 2013	2	2	2	2	n/a	2	average
Van Reekum 1996	1	1	3	1	n/a	1	poor
Varney 1987	1	1	3	1	n/a	1	poor
Wade 1998	2	2	2	1	n/a	2	average
Whelan-Goodinson 2008	1	3	2	2	n/a	2	good
Ziino 2006	1	2	2	1	n/a	1	poor

Appendix 2: Assessment Tools

This short appendix lists the assessment tools that were used in the course of the thesis. Other classification systems such as the overall CT appearance and the socioeconomic classification (NS-SEC) are shown in the main text under Methods (Chapter 4)

It also includes details and email of the Ethics Committee approval and correspondence for the project.

Hospital Anxiety and Depression Scale (HADS)

D **I still enjoy the things I used to enjoy:** Definitely as much 0 Not quite so much 1 Only a little 2 Hardly at all 3	A **I feel tense or 'wound up':** Most of the time 3 A lot of the time 2 From time to time 1 Not at all 0
D **I can laugh and see the funny side of things:** As much as I always could 0 Not quite so much now 1 Definitely not so much now 2 Not at all 3	A **I get a sort of frightened feeling as if something awful is about to happen** Very definitely and quite badly 3 Yes, but not too badly 2 A little, but it doesn't worry me 1 Not at all 0
D **I feel cheerful:** Not at all 3 Not often 2 Sometimes 1 Most of the time 0	A **Worrying thoughts go through my mind:** A great deal of the time 3 A lot of the time 2 From time to time, but not often 1 Only occasionally 0
D **I feel as if I am slowed down:** Nearly all the time 3 Very often 2 Sometimes 1 Not at all 0	A **I can sit at ease and feel relaxed** Definitely 0 Usually 1 Not Often 2 Not at all 3
D **I have lost interest in my appearance** Definitely 3 I don't take as much care as I should 2 I may not take quite as much care 1 I take just as much care as ever 0	A **I get a sort of frightened feeling like 'butterflies' in the stomach** Not at all 0 Occasionally 1 Quite Often 2 Very Often 3
D **I look forward with enjoyment to things:** As much as I ever did 0 Rather less than I used to 1 Definitely less than I used to 2 Hardly at all 3	A **I feel restless as I have to be on the move:** Very much indeed 3 Quite a lot 2 Not very much 1 Not at all 0
D **I can enjoy a good book or radio or TV program:** Often 0 Sometimes 1 Not often 2 Very seldom 3	A **I get sudden feelings of panic:** Very often indeed 3 Quite often 2 Not very often 1 Not at all 0

I understand that this information may be used for my treatment or research by my rehab team

Signed:

RIVERMEAD HEAD INJURY FOLLOW UP QUESTIONNAIRE

SHEFFIELD HEAD INJURY SERVICE	
Date:	***Patient ID label***

After a head injury or accident some people experience problems which can cause worry or nuisance. We would like to know if you have difficulties with any of the activities listed below. We would like you to compare yourself **now** with before the accident/injury.

For each one please circle the number closest to your answer

0 = no change
1 = no change, but more difficult
2 = mild change
3 = moderate change
4 = a very marked change

Compared with before the accident/injury:- a) Has there been a change in your . . . ?

Ability to participate in conversation with one person	**0**	**1**	**2**	**3**	**4**
Ability to participate in conversation with 2 or more people	**0**	**1**	**2**	**3**	
Performance of routine domestic activities	**0**	**1**	**2**	**3**	**4**
Ability to participate in previous social activities	**0**	**1**	**2**	**3**	**4**
Ability to enjoy previous leisure activities	**0**	**1**	**2**	**3**	**4**
Ability to maintain your previous workload/standard	**0**	**1**	**2**	**3**	**4**
Finding work more tiring	**0**	**1**	**2**	**3**	**4**
Relationship with previous friends	**0**	**1**	**2**	**3**	**4**
Relationship with your partner	**0**	**1**	**2**	**3**	**4**
Ability to cope with family demands	**0**	**1**	**2**	**3**	**4**

I understand that this information may be used for my treatment or research by my rehab team Signed:

Sheffield Teaching Hospitals NHS
NHS Foundation Trust

HEAD INJURY CLINIC

STICKY			**DATE OF REVIEW:**	
			Referer:	
MARITAL STATUS SINGLE/MARRIED/DIVORCED			SUPPORTED AT HOME YES/NO	
EMPLOYMENT BEFORE	**AFTER** *(incl hours eg. ?less)*		**Prev Psych Hx incl substance use**	
DATE OF INJURY	**Days as Inpatient**		**Length PTA**	
HISTORY/MECHANISM OF INJURY				
ALCOHOL Y/N	**GCS-Admission**	**WARFARIN** **YES/NO**	**ANOSMIA?** **YES/NO/Partial**	
PRE INJURY PROBLEMS *(incl TBI,Headache)*		**INITIAL CT HEAD REPORT**		
Any Functional limitations Cognit/Phys/Emot/Behav				
CURRENT PROBLEMS	**DRUGS HX**			
PHYSICAL EXAMINATION				

Symptom Checklist	NEVER	NO MORE	MILD	MOD.	SEVERE

	0	1	2	3	4
Headaches					
Feelings of dizziness					
Nausea and/or vomiting					
Noise sensitivity					
Sleep disturbance					
Fatigue, tiring more easily					
Being irritable, easily angered					
Feeling depressed or tearful					
Feeling frustrated or impatient					
Forgetfulness, poor memory					
Poor concentration					
Taking longer to think					
Blurred vision					
Light sensitivity					
Double vision					
Restlessness					Max 64

Comments/ODP

Forward & Reverse Digit span; Backward months; Object recall

MANAGEMENT

TREATMENT

REFERRALS: SCBIRT/ENT….

SEVERITY OF INITIAL BRAIN INJURY

MILD MODERATE SEVERE

EXTENDED GLASGOW OUTCOME SCALE

SEVERE DISABILITY- LOWER
SEVERE DISABILITY- UPPER *(frequent help most times; can't travel/shop by self)*
MODERATE DISABILITY- LOWER *(daily disruption; rarely ppt in social :volunteer work only)*
MODERATE DISABILITY- UPPER *(reduced work; regular disruption; < half social ppt)*
GOOD RECOVERY- LOWER *(> half social ppt; any symptoms or problems)*
GOOD RECOVERY- UPPER *(completely normal)*

Extended- Glasgow Outcome Scale Assessment

The Glasgow Outcome Scale (GOS) is a global scale for functional outcome that rates patient status into one of five categories: Dead, Vegetative State, Severe Disability, Moderate Disability or Good Recovery. The Extended GOS (GOSE) provides more detailed categorization into eight categories by subdividing the categories of severe disability, moderate disability and good recovery into a lower and upper category:

Table 1: Extended Glasgow Outcome Scale (GOSE)

1	Death	D
2	Vegetative state	VS
3	Lower severe disability	SD -
4	Upper severe disability	SD +
5	Lower moderate disability	MD -
6	Upper moderate disability	MD +
7	Lower good recovery	GR -
8	Upper good recovery	GR +

Use of the structured interview is recommended to facilitate consistency in ratings.

STRUCTURED INTERVIEW FOR GOSE

Respondent: 0 = Patient alone 1 = Relative/friend/caretaker alone 2 = Patient plus relative/friend/caretaker

Consciousness:

1. Is the head-injured person able to obey simple commands or say any words?

Yes No (VS)

Note: anyone who shows the ability to obey even simple commands or utter any word or communicate specifically in any other way is no longer considered to be in vegetative state. Eye movements are not reliable evidence of meaningful responsiveness. Corroborate with nursing staff and/or other caretakers. Confirmation of VS requires full assessment.

Independence at home:

2a. Is the assistance of another person at home essential every day for some activities of daily living?

Yes No (VS) If no: go to 3

Note: for a NO answer they should be able to look after themselves at home for 24 hours if necessary, though they need not actually look after themselves. Independence includes the ability to plan for and carry out the following activities: getting washed, putting on clean clothes without prompting, preparing food for themselves, dealing with callers and handling minor domestic crises. The person should be able to carry out activities without needing prompting or reminding and should be capable of being left alone overnight.

2b. Do they need frequent help of someone to be around at home most of the time?

Yes (lower SD) No (upper SD)

Note: for a NO answer they should be able to look after themselves at home up to eight hours during the day if necessary, though they need not actually look after themselves

2c. Was the patient independent at home before the injury?

Yes No

Independence outside home:

3a. Are they able to shop without assistance?

Yes No (upper SD)

Note: this includes being able to plan what to buy, take care of money themselves and behave appropriately in public. They need not normally shop, but must be able to do so.

3b. Were they able to shop without assistance before?
Yes No

4a. Are they able to travel locally without assistance?
Yes No (upper SD)
Note: they may drive or use public transport to get around. Ability to use a taxi is sufficient, provided the person can phone for it themselves and instruct the driver.

4b. Were they able to travel locally without assistance before the injury?
Yes No

Work:
5a. Are they currently able to work (or look after others at home) to their previous capacity?
Yes If yes, go to 6 No

5b. How restricted are they?
a. Reduced work capacity? a. (Upper MD)

b. Able to work only in a sheltered workshop or non-competitive job or currently unable to work? b. (Lower MD)

5c. Does the level of restriction represent a change in respect to the pre-trauma situation?
Yes No

Social and Leisure activities:
6a. Are they able to resume regular social and leisure activities outside home?
Yes If yes, go to 7 No
Note: they need not have resumed all their previous leisure activities, but should not be prevented by physical or mental impairment. If they have stopped the majority of activities because of loss of interest or motivation, then this is also considered a disability.
6b. What is the extent of restriction on their social and leisure activities?
a. Participate a bit less: at least half as often as before injury a. (Lower GR)
b. Participate much less: less than half as often b. (Upper MD)
c. Unable to participate: rarely, if ever, take part c. (Lower MD)

6c. Does the extent of restriction in regular social and leisure activities outside home represent a change in respect or pre-trauma
Yes No

Family and friendships:
7a. Has there been family or friendship disruption due to psychological problems?
Yes No If no, go to 8

Note: typical post-traumatic personality changes are: quick temper, irritability, anxiety, insensitivity to others, mood swings, depression and unreasonable or childish behaviour.

7b. What has been the extent of disruption or strain?

a. Occasional - less than weekly (Lower GR)
b. Frequent - once a week or more, but not tolerable (Upper MD)
c. Constant - daily and intolerable (Lower MD)

7c. Does the level of disruption or strain represent a change in respect to pre-trauma situation?

Yes No

Note: if there were some problems before injury, but these have become markedly worse since the injury then answer yes to question

Return to normal life:

8a. Are there any other current problems relating to the injury which affect daily life?

Yes (Lower GR) No (Upper GR)

Note: other typical problems reported after head injury: headaches, dizziness, sensitivity to noise or light, slowness, memory failures and concentration problems.

8b. If similar problems were present before the injury, have these become markedly worse?

Yes No

9. What is the most important factor in outcome?

a. Effects of head injury
b. Effects of illness or injury to another part of the body
c. A mixture of these

Note: extended GOS grades are shown beside responses on the CRF. The overall rating is based on the lowest outcome category indicated.

Areas in which there has been no change with respect to the pre-trauma situation are ignored when the overall rating is made

Modified Cumulative Illness Rating Scale

Twin no. _____

Name: _____

Each system is rated as follows:

1 = NONE:	No impairment to that organ/system.
2 = MILD:	Impairment does not interfere with normal activity; treatment may not be required; prognosis is excellent (examples: skin lesions, hernias,
3 = MODERATE:	Impairment interferes with normal activity; treatment is needed; prognosis is good (examples: gallstones, diabetes, fractures)
4 = SEVERE:	Impairment is disabling; treatment is urgently needed; prognosis is guarded(examples: respectable carcinoma, pulmonary emphysema, congestive heart failure
5 = EXTREMELY SEVERE	Impairment is life threatening; treatment is urgent or of no avail; prognosis is grave (examples: myocardial infarction, cerebrovascular accident, gastrointestinal bleeding, embolus)

		Value 1-5
a.	Cardiac (heart only)	____
b.	Hypertension (rating is based on severity; affected systems are rated separately).	____
c.	Vascular (blood, blood vessels and cells, marrow, spleen, lymphatics).	____
d.	Respiratory (lungs, bronchi, trachea below the larynx).	____
e.	ENT (eye, ear, nose, throat, larynx).	____
f.	Upper GI (esophagus, stomach, duodenum, biliary and pancreatic trees; do no include diabetes).	____
g.	Lower GI (intestines, hernias).	____
h.	Hepatic (liver only).	____
i.	Renal (kidneys only).	____
j.	Other GU (ureters, bladder, urethra, prostate, genitals).	____
k.	Musculo-skeletal-integumentary (muscles, bone, skin)	____
l.	Neurological (brain, spinal cord, nerves; do not include dementia).	____
m.	Endocrine-Metabolic (includes diabetes, diffuse infections, infections, toxicity)	____
n.	Psychiatric/Behavioral (includes depression, anxiety, agitation, psychosis, not dementia).	____

R-UCLA Loneliness Scale

The next questions are about how you feel about different aspects of your life. For each one, tell me how often you feel that way.

Question	*Hardly Ever*	*Some of the Time*	*Often*
First, how often do you feel that you lack companionship: Hardly ever, some of the time, or often?	1	2	3
How often do you feel left out: Hardly ever, some of the time, or often?	1	2	3
How often do you feel isolated from others? (Is it hardly ever, some of the time, or often?)	1	2	3

Critical Appraisal Skills Programme (CASP) Cohort study check list

Questions

1) Did the study address a clearly focussed issue?
2) Was the cohort recruited in an acceptable way?
3) Was the exposure accurately measured to minimise bias?
4) Was the outcome accurately measured to minimise bias?
5) Have the authors identified all important confounding factors?
6) Was the follow-up of subjects complete and long enough?
7) What are the results of the study?
8) How precise are the results?
9) Can the results be applied to the local population?
10) Do the results of the study fit in with other available evidence?
11) What are the implications of this study for practice?

Critical Appraisal Skills Programme (2017). CASP Cohort Study Checklist. [online] Available at: http://www.casp-uk.net/checklists Accessed: June 2012.

Email Chain of Ethics Approval

From: Wallis, Erica (Research)
Sent: 21 February 2012 16:37
To: Keyworth, Jodie (Neurosciences); Singh, Rajiv (Rehabilitation Medicine)
Cc: Patel, Ramila (Research)
Subject: RE: Enquiry from NRES website

Hi Jodie

I can confirm that this study does not need to go to an NHS REC. It also does not need review by UoS ethics as the only issue of concern is that of confidentiality of patient identifiable data and this will be assessed by the data protection officer. Provided that no additional data is collected from patients for research purposes and only staff who are part of the clinical care team will access patient identifiable data and that the data will be analysed in an anonymised or pseudonymised form no patient consent is required and no ethical review is required. The study still needs R&D approval of course and part of that approval is review of an R&D form which needs to be completed in IRAS in the same way that a REC form would be completed. Ram and I will review this to check the study complies with the three points I have outlined here.

Best wishes,

Erica

Erica Wallis MBChB, Research Coordinator
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Please note: I am in the office on Tuesdays, Thursdays and Fridays only

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Have you visited our new website? www.sheffieldclinicalresearch.org

From: Keyworth, Jodie (Neurosciences)
Sent: 20 February 2012 15:17
To: Singh, Rajiv (Rehabilitation Medicine); Wallis, Erica (Research)
Cc: Patel, Ramila (Research)
Subject: RE: Enquiry from NRES website

Dear Dr Singh,

Many thanks for the clarification. Have you responded to the ISR comments raised by reviewer 2?

Dear Erica,

Can you confirm if in light of the below email UoS ethics will still need to be sought to ensure some ethical review of the project has been performed?

Please let me know if you require anything further in this regard.
Kind Regards, Jodie
Jodie Keyworth
Research Coordinator
Academic Directorate of Neurosciences
Working days Tuesday to Friday
N125d, N Floor
Direct line: 0114 22 65394
Fax: 0114 2713158
jodie.keyworth@sth.nhs.uk

From: Singh, Rajiv (Rehabilitation Medicine)
Sent: 20 February 2012 11:07
To: Keyworth, Jodie (Neurosciences); Wallis, Erica (Research)
Cc: Patel, Ramila (Research)
Subject: RE: Enquiry from NRES website

Hello,
I can confirm that we have added a line at the bottom of the forms to state that I consent that the data will be recorded on a database which is only accessible to the treating consultant.
Basil Sharrack and the IT governance lead suggested that this will cover it.
Basil confirmed in a long chat that there is no need for ethics consent for data that is already routinely collected.
Happy to answer any queries.

Rajiv

From: Keyworth, Jodie (Neurosciences)
Sent: 17 February 2012 15:53

To: Wallis, Erica (Research)
Cc: Singh, Rajiv (Rehabilitation Medicine); Patel, Ramila (Research)
Subject: FW: Enquiry from NRES website

Dear Erica,

I wondered if you may be able to advise me on one of our Neuro studies which may not need to be reviewed by NRES but for which I am unsure will require the UoS Ethics service.

I have attached a protocol for the study which is currently under 2nd review ISR and this states that all data collected from the patients is what is usually collected in clinic and will be totally anonymised. The PI Rajiv Singh (copied in) does not believe consent will need to be taken as patients will agree for their data to be collated for research on the normal clinic data collection forms. However one of the ISR reviewers has questioned the need for a PIS and ICF so I would need to await Dr Singh's response before confirming this.

We want to ensure we can move swiftly with the next stage of the study development once Dr Singh has responded to the ISR comments so your response is much appreciated.
Many Thanks

Jodie

ETHICS APPROVAL;EMAIL 2
From: NRES Queries Line [mailto:queries@nres.nhs.uk]
Sent: 16 February 2012 17:03
To: Keyworth, Jodie (Neurosciences)
Subject: RE: Enquiry from NRES website

ENQUIRY TO NRES

Dear Jodie,

Thank you for your enquiry seeking advice on whether your project should be classified as research requiring review by an NHS Research Ethics Committee (REC).Below, please see our standard advice on determining whether review by an NHS REC will be required. If you require further assistance with this, please send to us a summary of the propsed protocol (MSWord doc, <1000 words).

The new harmonised UK-wide edition of the Governance Arrangements for Research Ethics Committees (GAfREC) comes into effect on 01 September 2011. We have published detailed guidance on the NRES website on the changes in the harmonised GAfREC at: http://www.nres.nhs.uk/news-and-publications/news/nres-sops-version 5/.

Is your project research? / Ethical review requirements

i. The National Research Ethics Service (NRES) has produced a leaflet on "Defining Research", which will help you to distinguish between research, audit or service evaluation and public health surveillance.

ii. NRES has also developed an algorithm “Does my project require review by a Research Ethics Committee?” which is designed to assist researchers, sponsors and R&D offices in determining whether a project requires ethical review by a Research Ethics Committee under the UK Health Departments. It encompasses the requirements for ethical review under both the policy of the UK Health Departments and legislation applying to the UK as a whole or to particular countries of the UK. The Supplementary notes section, in particular, outlines the types of research that do not normally require review by a REC within the UK Health Departments’ Research Ethics Service. However, where the Research Governance Framework for Health and Social Care applies, the research will continue to require management permission from host care organisations (“R&D approval”). Within the Integrated Research Application System (IRAS), it is possible to indicate in the Filter that a research project requires review by

NHS R&D only. Where a project raises potential ethical concerns, NHS organisations may require ethical review and exceptionally NRES would be willing to undertake this review. For student research, most universities will require such a review as part of their normal institutional processes.
Further guidance on categorising projects is available from the NHS R&D Forum.
The responsibility for determining if an activity is research (and whether the research
requires review including ethics approval within the Research Governance Framework) sits ultimately with the sponsor and investigator. If your project will be taking place within the NHS, we would encourage you to seek the advice of your local R&D office in the first instance.If after seeking advice from your R&D office and/or supervisor you remain uncertain, further clarification can be obtained by the R&D office from the Chair of a REC or the NRES Queries line (queries@nres.npsa.nhs.uk). In seeking further advice, please email an A4 summary outlining your proposal (one side only, 1,000 words max). For ease of reference, please include your initial email request/response.
Regards
NRES Queries Line
Ref. 04/31

The NRES Queries Line is an email based service that provides advice from NRES senior management, including operations managers based in our regional offices throughout England. Providing your query in an email helps us to quickly direct your enquiry to the most appropriate member of our team who can provide you with an accurate written response. It also enables us to monitor the quality and timeliness of the advice given by NRES to ensure we can give you the best service possible, as well as use queries to continue to improve and to develop our processes.

Please note:

* If you have been asked to follow a particular course of action by a REC as part of a provisional or conditional opinion, then the REC requirements are mandatory to the opinion, unless specifically revised by that REC.
* Should you wish to query the REC requirements, this should either be through contacting the REC direct or, alternatively, the relevant local operational manager (details available from the NRES website NRES - NRES Office and Departmental Contact Details).

NRES Queries
National Research Ethics Service (NRES)
Health Research Authority

Skipton House, 80 London Road, London SE1 6LH
Email: queries@nres.nhs.uk Website: www.nres.nhs.uk
Streamline your research application process with IRAS (Integrated Research Application System):
www.myresearchproject.org.uk

From: Jodie.Keyworth@sth.nhs.uk [mailto:Jodie.Keyworth@sth.nhs.uk]
Sent: Thursday, February 16, 2012 10:46 AM
To: NRES Queries Line
Subject: Enquiry from NRES website

Dear All,

Please can you confirm if a study needs to be submitted to the REC for review? After reading the GAfREC I am still a little unsure of this.

The Investigator has recorded the following gin the protocol:
10. Ethics
Ethics Committee approval will not need to be sought due to the nature of data collection, which has been confirmed by the Clinical Research Office Sheffield. It is not planned to seek patient consent, as the HADS assessment is routinely done as part of the clinic assessment already and stored in the

notes. The only difference will be an anonymised database of scores kept on one STH computer, which will only be accessible to the investigator only and available for IT governance and research department monitoring. There is no intervention and patients are not being asked to do anything extra. The database is the only difference that this project will make. If required, a line can be inserted into the self-assessment forms agreeing for saving anonymised data for research

Your advice would be welcomed and more information can be provided if required
Kind Regards, Jodie
Jodie Keyworth
Research Coordinator
Academic Directorate of Neurosciences

Working days Tuesday to Friday

_____

STH NHS Foundation Trust
N125d, N Floor
Royal Hallamshire Hospital
Glossop Road
Sheffield
S10 2JF
? Direct line: 0114 22 65394
? Fax: 0114 2713158
? jodie.keyworth@sth.nhs.uk

From: Patel, Ramila (Research)
Sent: 06 June 2012 16:54
To: Singh, Rajiv (Rehabilitation Medicine)
Cc: Keyworth, Jodie (Neurosciences)
Subject: RE: STH16208_STH Research Governance authorisation
Attachments: Authorisation Letter Appendix v.2.2 24Feb08.doc; STH16208_Authorisation Letter_06Jun12.doc.pdf

Dear Dr Singh

RE: STH16208_Long term study of mood disorders after Brain Injury

Good news! The above study, STH16208, has been issued with STH Research Governance authorisation. Please find attached a scanned copy of the authorisation letter and a document detailing the conditions of authorisation.
Hard copies of these documents will be sent out to you.
Please let me know if you need any further information at this stage, and good luck!
Kind regards
Ram

Ram Patel, PhD
Research Co-ordinator, Clinical Research Office Sheffield
STH NHS Foundation Trust
STH Research Department
1st Floor, 11 Broomfield Rd
Sheffield, S10 2SE
? Direct line: +44 (0)114-2265942
? Fax: +44 (0)114 226 5937
? Ramila.patel@sth.nhs.uk

intelligence dr foster 2011 trust of the year (North)

Sheffield Teaching Hospitals NHS
NHS Foundation Trust

Ref: STH16208/RP

06 Jun 12

Dr Rajiv Singh
Consultant in Neuro-rehabilitation Medicine
Dept of Neurosciences
Northern General Hospital
Herries Road
Sheffield
S5 7AU

Dear Dr Singh

Authorisation of Project

STH ref: STH16208
Study title: Anxiety and Depressive disorders after acquired brain injury

Chief Investigator: Dr Rajiv Singh, Sheffield Teaching Hospitals NHS Foundation Trust
Principal Investigator: Dr Rajiv Singh, Sheffield Teaching Hospitals NHS Foundation Trust

Sponsor: Sheffield Teaching Hospitals NHS Foundation Trust
Funder: Unfunded

The Research Department has received the required documentation for the study as listed below:

1.	**Sponsorship IMP studies (non-commercial)**	N/A
	Sponsorship responsibilities between institutions	N/A
	Responsibilities of investigators	N/A
	Monitoring Arrangements	N/A
2.	**STH registration document: completed and signed**	NHS R&D Form, v3.3: D Patel, 08 May 12
3.	**Evidence of favourable scientific review**	STH R&D
4.	**Protocol – final version**	Version 2.0, 28 Feb 12
5.	**Participant Information sheet – final version**	N/A
6.	**Consent form – final version**	N/A
7.	**Signed letters of indemnity**	N/A
8.	**ARSAC / IRMER certificate**	N/A

Ref: STH16208/RP

9.	**Evidence of hosting approval from STH directorate**	STH Finance Form: N Leek, undated K M Mathew, 21 Mar 12
10.	**Evidence of approval from STH Data Protection Officer**	STH Finance Form: P Wilson, 31 May 12
11.	**Letter of approval from REC**	Email from Eric Wallis, STH R&D, confirming study does not need REC approval 21 Feb 12
12.	**Proof of locality approval**	STH R&D
13.	**Clinical Trial Authorisation from MHRA**	N/A
14.	**Honorary Contract**	N/A
15.	**Associated documents**	
	Sheffield head injury service follow up questionnaire HADS Questionnaire	Undated Undated
16.	**Signed financial agreement/contract**	STH Finance Form: L Fraser, 23 May 12

The project has been reviewed by the Research Department and authorised by the Director of R&D on behalf of STH NHS Foundation Trust to begin.

Yours sincerely

Professor S Heller
Director of R&D, Sheffield Teaching Hospitals NHS Foundation Trust
Telephone +44 (0) 114 2265934
Fax +44 (0) 114 2265937

Appendix 3: Demographics of study population

This appendix adds some detail to the chapter on basic demographics in the main body of text (5.2) Each of the variables that were measured in the study is explored in more detail including the distribution of the variable and a few key relationships between the variables are briefly inspected where this is important. As an example, differences in the distribution of gender is important with respect to age or injury severity as these are very different and in turn, therefore influence the effect of gender on depression.
There is always a risk that cross-examining several variables in this way may complicate or obscure the key project outcomes. To avoid excessive over examination of variables with one another, the focus in chapter 5.2 is kept to a minimum and more of the graphs and tables represented in this appendix. Comparison between variables e.g. age, GCS or length of stay is only carried out where it is essential in order to understand how these other measures are likely to affect another variable.

A3.1 Age
The mean age of individuals was 46.92 years**.** This was recorded as the age at time of injury. The standard deviation was 19.25 years and the distribution curve shows a good approximation to a normal curve although there is a slight positive skew to the younger ages. There is a known peak of TBI in younger populations.
Median age was 46.04(range 15.76-94.16) which is similar to the mean.
Age was not related to GCS (ρ=0.028) or LoS (ρ=0.051)

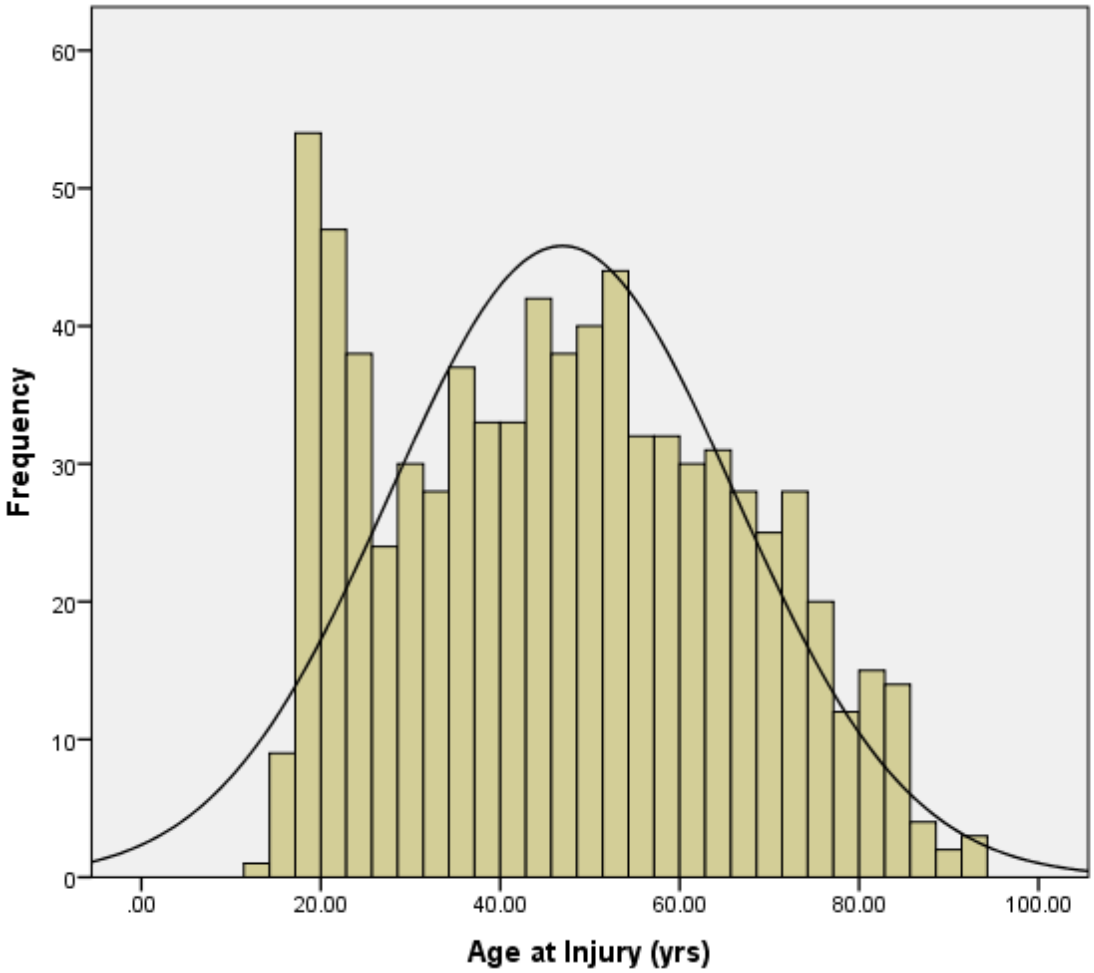

Figure A3.1: Distribution of Age at Injury

To further examine age the group were divided into age deciles as defined below-

Group	Age (years)
1	< 20
2	20.01 - 30
3	30.01 - 40
4	40.01 - 50
5	50.01 – 60
6	60.01 – 70
7	70.01 – 80
8	>80

Table A3.1; age categories (shown in Figure A3.2 below)

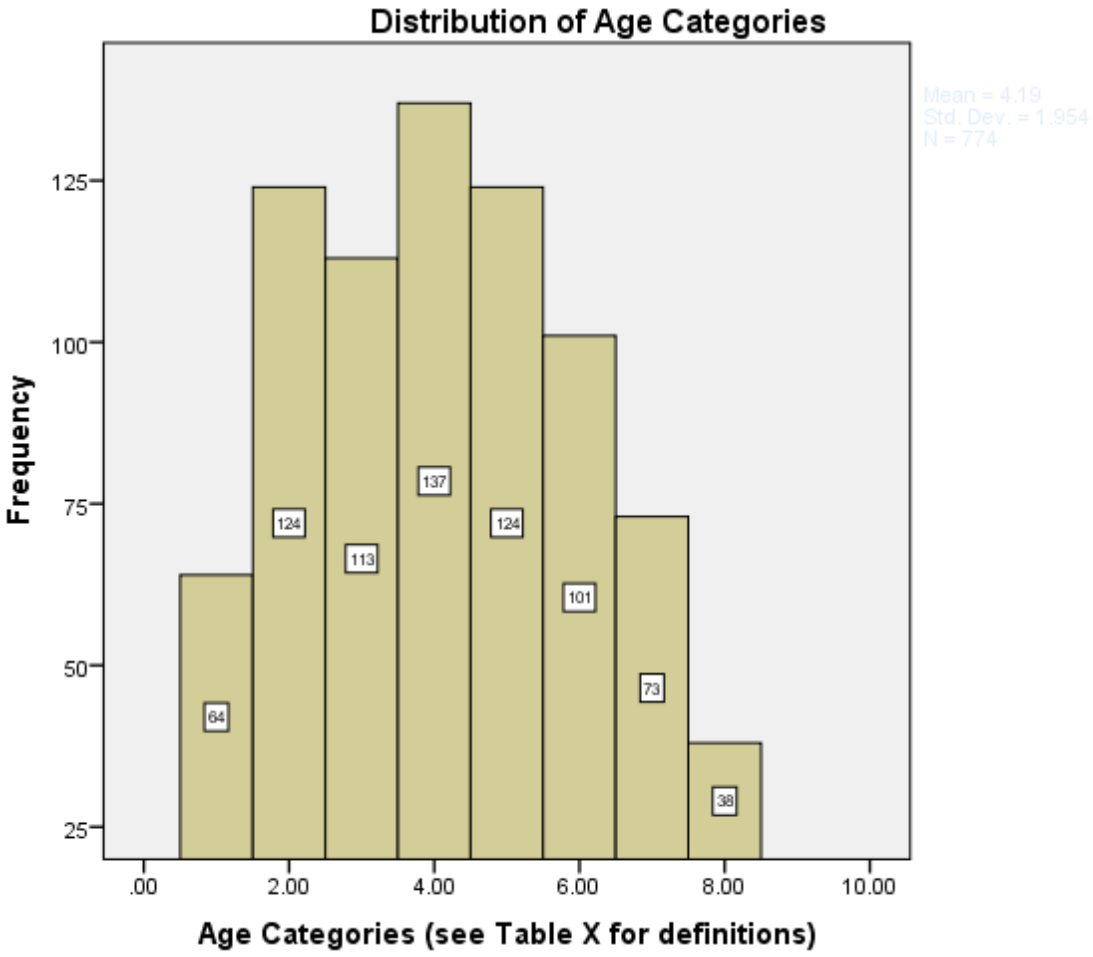

Figure A3.2: Distribution of ages in deciles

These categories showed no difference on a one-way ANOVA with regards to length of stay or GCS suggesting that age category is not related to these variables.

A3.2 Length of Stay

The distribution of LoS is heavily skewed in a positive direction i.e. towards short stay lengths (Figure 2.3). This is undoubtedly due to the preponderence of mild and moderate injuries who will tend to have shorter hospital stays compared to severe TBI. This skewed distribution results in very different mean and median length of stay. The mean was 8.68 days(SD14.15). The median was 3 days (range 1- 83). 494(63.5%) of admissions were 3 days or less and only 123(15.9%) were over 14 days.

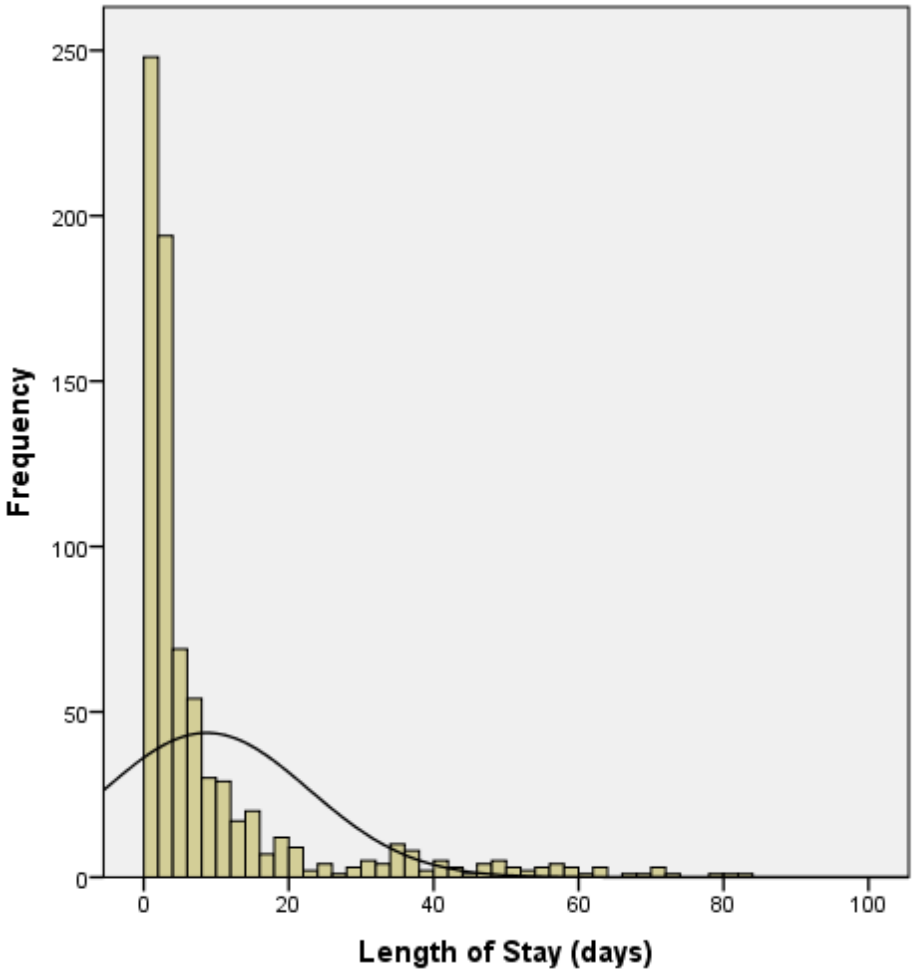

Figure A3.3: Distribution of Length of Stay (days)

A3.3 Glasgow Coma Score (GCS)

Brain Injury severity is usually measured using GCS. This can also be expressed in three categories of mild (GCS 13-15), moderate (GCS 9-12) and severe (GCS <9) which is examined later (A3.9).

The distribution of GCS is represented in Figure A3.4. Scores are between 3 and 15. There is a clear negative skew with many more scores of 13, 14 and 15 which constitute mild TBI. Mean GCS was 11.89 (SD 3.01) and median of 12(range 3-15)

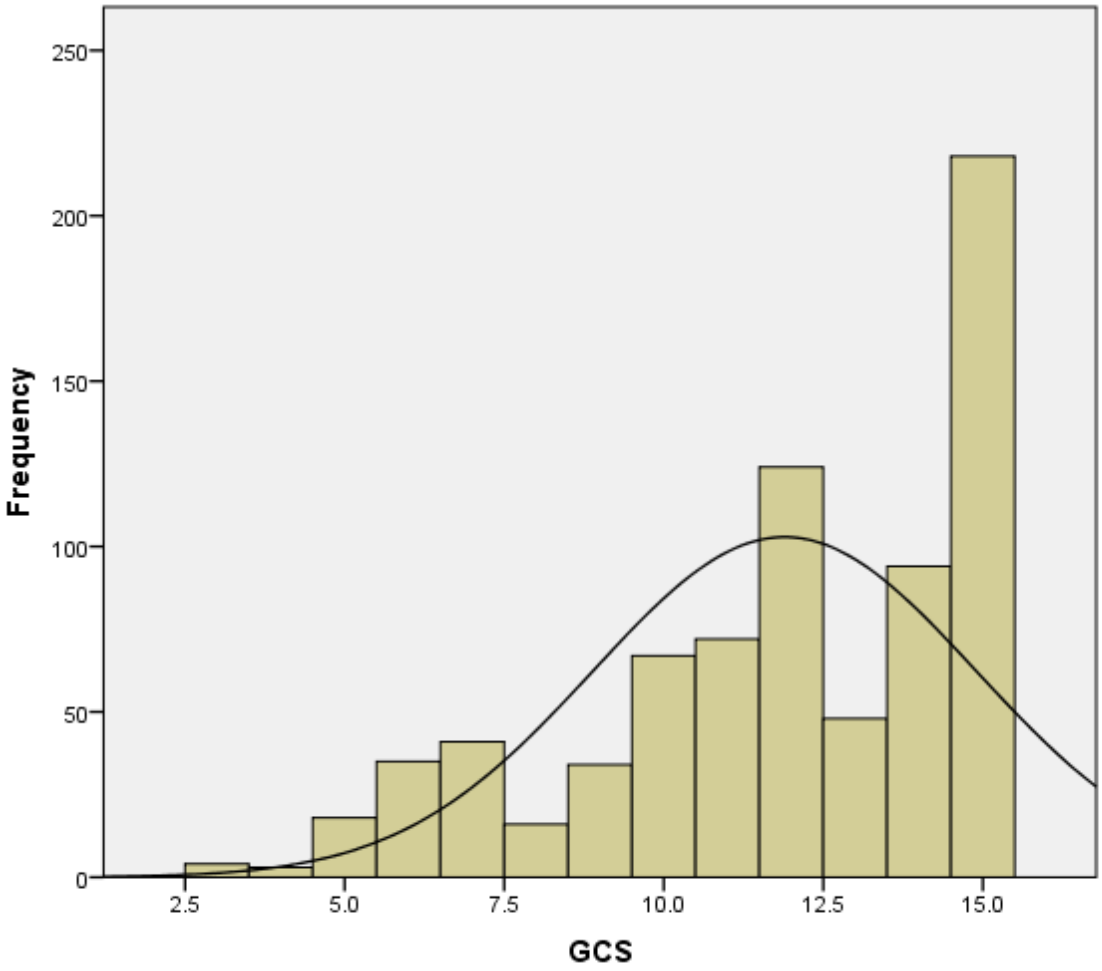

Figure A3.4: Distribution of Glasgow Coma Score

A3.4 Time from injury to first appointment

The incidence of depression or results of other questionnaires may change with time. It was therefore important to determine if there was wide variation in the time after injury patients were seen, both for the initial interview as well as after 1 year. The distributions for these are shown here and follow a clear normal distribution. The aim was to follow up within 10 weeks of injury and mean time was 62.94 days (SD 18.16) and median 64 days (range 1-104). There are a number of delayed appointments as patients do not attend and have to be contacted to arrange further appointments and expedite attendance.

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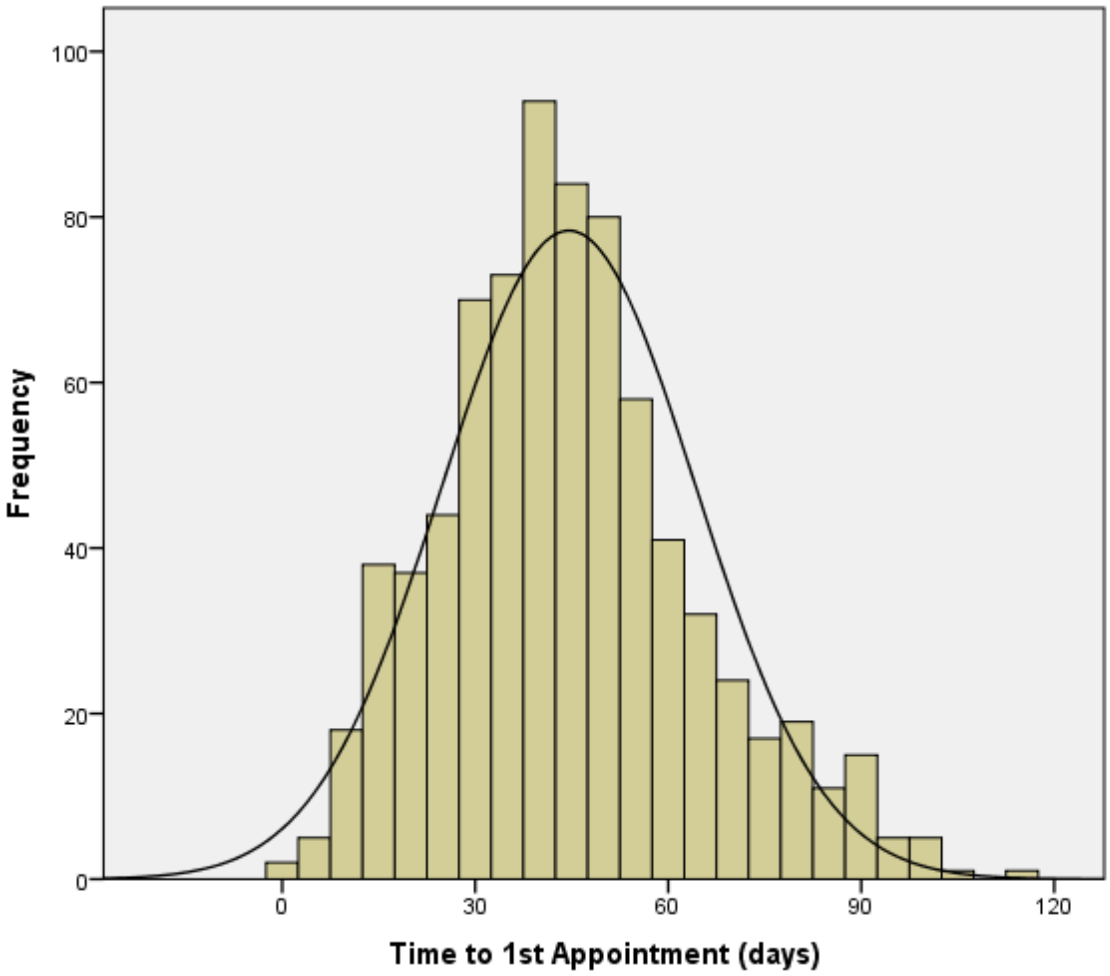

Figure A3.5: Time to 1st appointment

A3.5 Time to second appointment

The time to follow-up after initial appointment was 1 year and appointments were arranged for this time; again there was concern that variation in time to follow-up could affect the incidence of depression or the other questionnaire responses. The mean time between appointments was 347.46 days (SD28) with a median of 349 (range 116-413). This approximates well to the stated aim of one year follow-up. A range is always found as some patients will re-arrange their appointments for an earlier review if they have issues to discuss, or they may miss appointments and have to be chased by staff to re-arrange review dates.

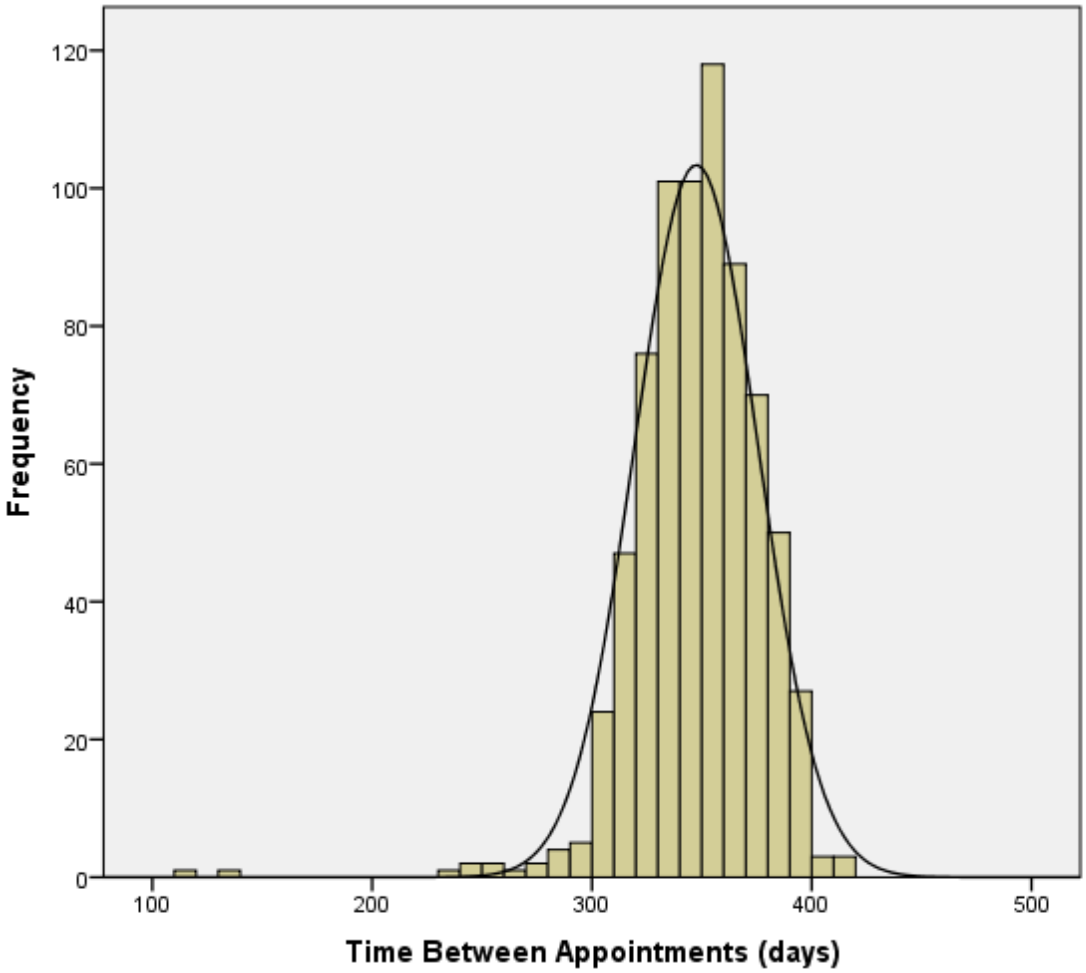

Figure A3.6: Time between appointments

A3.6 Gender

The majority of patients were male (535, 69.1%) shown in Table A3.2.

There was a significant difference between male and females for age and length of stay ($p<0.01$). Mean age was 44.59 (SD19.10) and 52.14 (SD 18.61) for women while LoS was 9.50 (15.21) days for men and 6.84 (11.23) for women. This is probably due to the increased frequency of falls in the female group which is associated with an older population. Similarly, the majority of RTC or assaults are in males and these tend to be more common in a younger population group.

A t-test found significant differences for age and LoS but not GCS between sex categories ($p<0.01$)

Gender		Age(yrs)	LoS (d)	GCS
male	Mean	44.59	9.50	11.67
	N (%)	535(69.1%)		
	SD	19.10	15.21	3.04
female	Mean	52.14	6.84	12.39
	N	239(30.9%)		
	SD	18.61	11.23	2.86

Table A3.2: Mean age, length of stay and GCS with gender

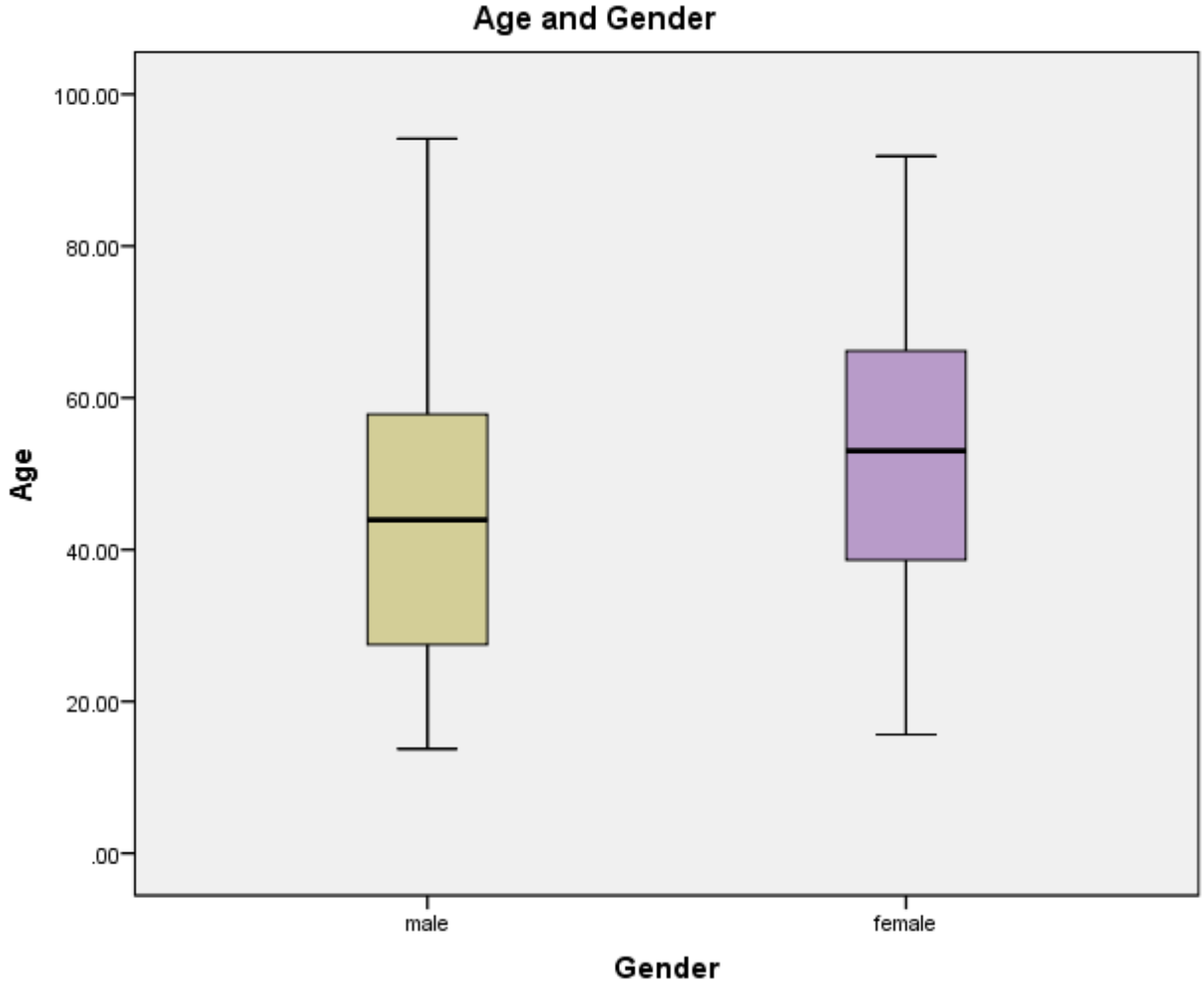

Figure A3.7: Boxplot of Age and gender

A3.7 Aetiology of Injury

The majority of cases were caused by simple falls with road traffic collision second. This is shown in Figure A3.8 below.

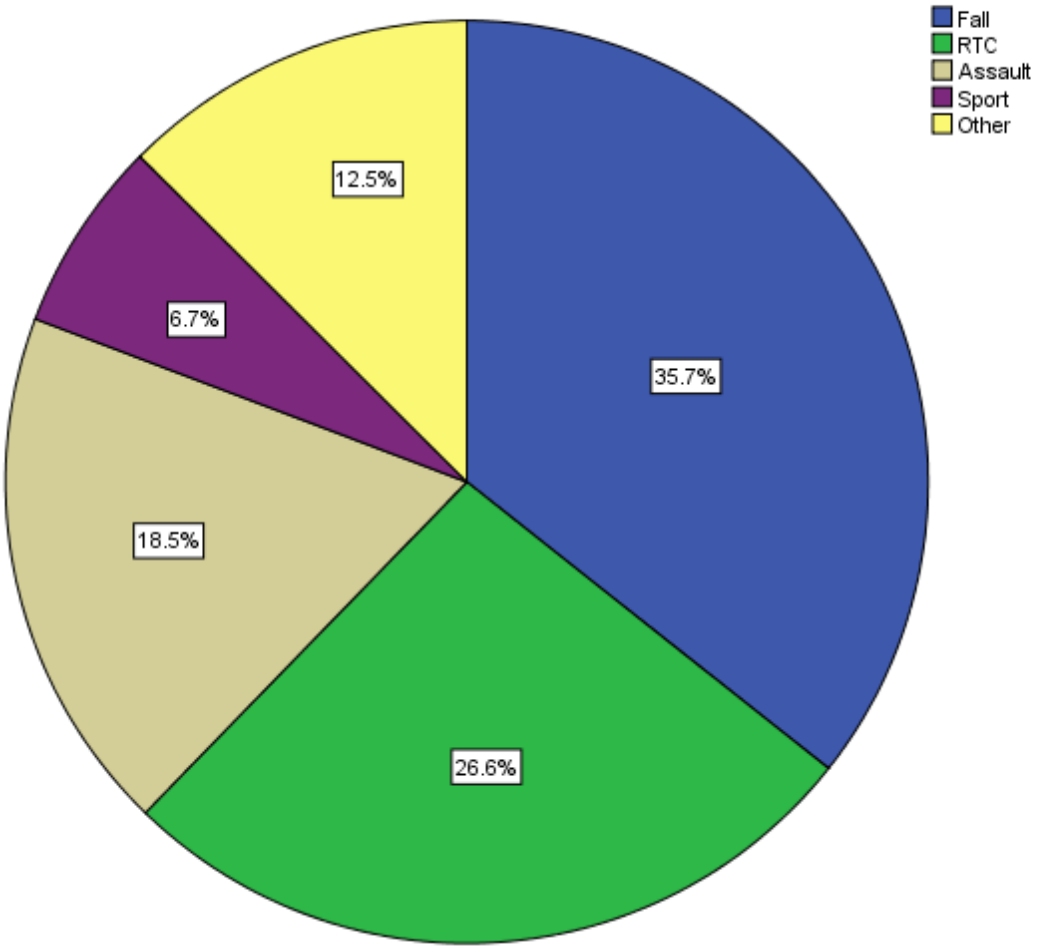

Figure A3.8: Aetiology of TBI cases

Numbers aside, there were considerable differences between the groups constituting aetiology of TBI as shown in table A3.3 below. Those suffering falls were older than those with RTC, assaults or sports injuries. Those with RTC or Other injury (high falls or work injury) mechanisms, had a longer length of stay compared to other groups but also had more severe injury in terms of GCS. These differences were statistically significant in a oneway-ANOVA ($p<0.01$)

Aetiology		Age(yr)	LoS(d)	GCS
Fall	Mean	59.76	7.55	12.40
	N (%)	276(35.7)		
	SD	17.08	11.57	2.52
RTC	Mean	41.04	12.33	11.33
	N (%)	206(26.6)		
	SD	17.78	18.21	3.59
Assault	Mean	33.77	3.96	12.19
	N (%)	143(18.5)		
	SD	12.47	5.84	2.52
Sport	Mean	34.69	5.13	12.42
	N (%)	52(6.7)		
	SD	14.00	10.49	2.59
Other	Mean	48.83	13.02	10.93
	N (%)	97(12.5)		
	SD	15.81	17.89	3.33

Table A3.3: Age, length of stay and GCS for Aetiology of TBI

A graphical representation of the differences in age are shown in Figure A3.9.

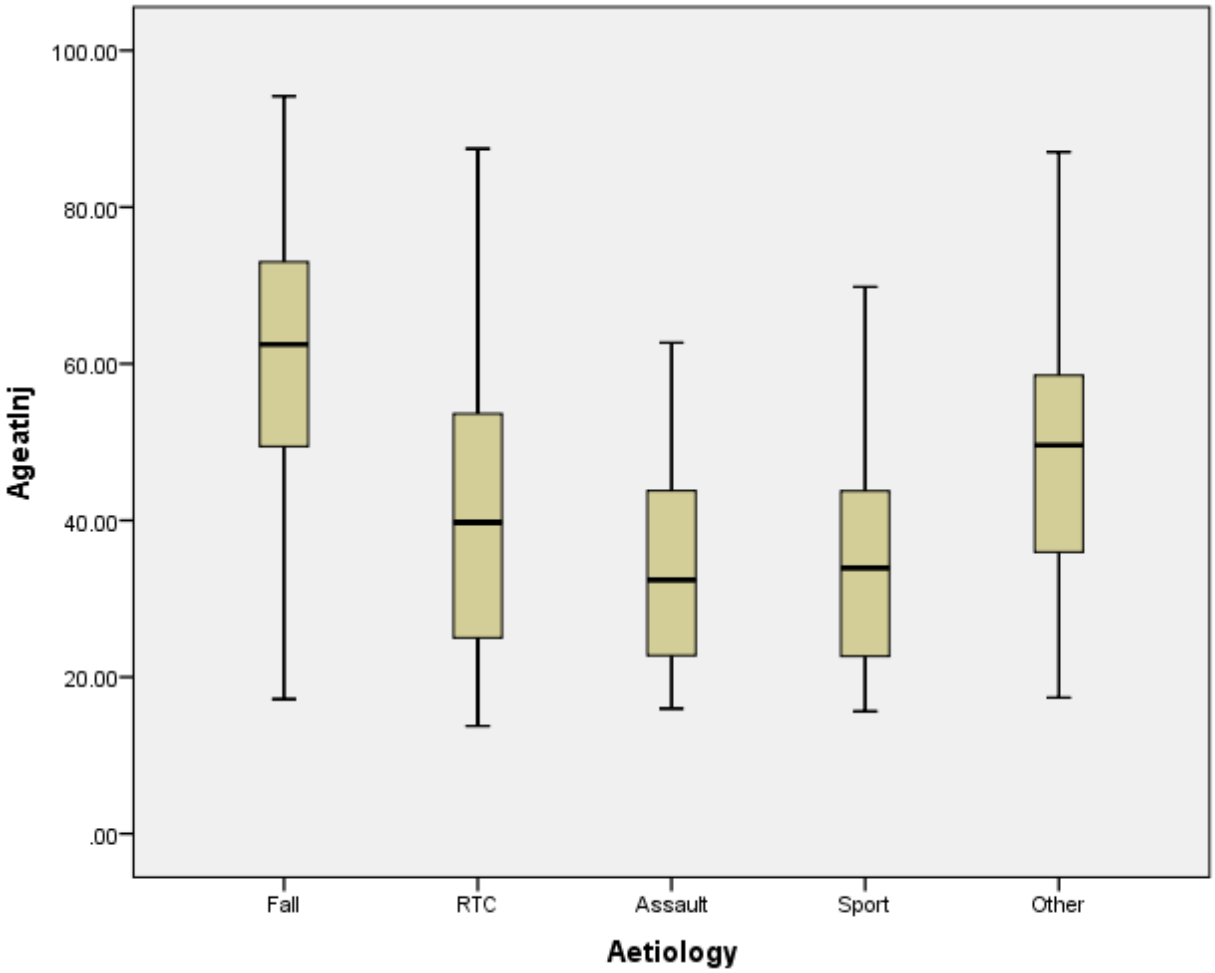

Figure A3.9: age and aetiology

A3.8 Ethnicity

Initial classification used the Trust's classification system which is used across most Hospitals in the UK. However it soon became apparent that there were very small numbers of non-white individuals in the cohort. This limits the ability to make any comparisons between groups with small sub-groups.

Ethnicity		Age	LoS
white	Mean	47.80	8.83
	N	722	722
	SD	19.25	14.34
south asian	Mean	34.13	6.37
	N	35	35
	SD	13.20	9.43
Black	Mean	40.44	8.33
	N	12	12
	SD	19.54	15.92
Oriental	Mean	22.01	1.00
	N	3	3
	SD	1.15	.00
other	Mean	30.26	9.50
	N	2	2
	SD	0.74	12.02

Table A3.4: Ethnicity

It was therefore decided to group all non-white ethnicity into one group to increase the group size. This resulted in 722 (93.3%) having white origin and 52 (6.7%) from other groups. Comparison between the white and non-white group is shown in Table 4.2.4 along with the initial ethnic groupings as well. The non-white group were younger with mean age 34.7 years compared to 47.8 in the white group ($p<0.001$). However the differences between LoS and GCS were not significant for the two groups.

A3.9 Socioeconomic Class

This was classified by the National Statistics Socio-Economic Classification (NS-SEC) with 9 possible groups and is shown in Table 4.2.2 in the main text. The distribution across the different groups showed that the largest groups were in semi-routine jobs (24.3%) and lower supervisory and lower management occupations (14.2% and 15.9% respectively).
Comparison to data from the National Census of 2001 on the proportions of individuals in each group in general, shows that our sample had higher numbers in the semi-routine (24.3 v 13%) and lower supervisor 14.2 v 9%). However there were fewer individuals in the highest two categories of higher management/professional and lower management in the sample (21.5 v 35%)
There was a similar level of long term unemployed or never worked (5.6 v 5%)
An overall summary of these findings would be that the TBI sample contains a smaller proportion of individuals from the higher social class categories and a corresponding higher proportion from lower supervisory and routine occupations.
Comparison across the group found no difference for severity or length of stay. For age, the student and unclassified group were younger (29.53 (SD21.33) years) than the other groups.

A3.10 Social Isolation

Social support was measured by the UCLA Loneliness Questionnaire; 313 (40.4%) had little or no support, 443 (57.2%) enjoyed good support and 18 (2.4%) came from nursing homes. Those from Nursing homes were more than 20 years older than the other groups($p<0.01$) but there were no other significant differences.

Social Isolation		Age(yrs)	LoS(d)	GCS
no support	Mean	46.91	7.21	12.23
	N (%)	313(40.4)		
	SD	19.94	12.50	2.79
support	Mean	46.02	9.62	11.67
	N (%)	443(57.2)		
	SD	18.37	15.09	3.14
Nursing Home	Mean	69.24	11.11	11.56
	N (%)	18 (2.3)		
	SD	15.33	15.57	2.81

Table A3.5: Social Isolation Level

The differences in the social groups for age are shown in Figure A3.10 below.

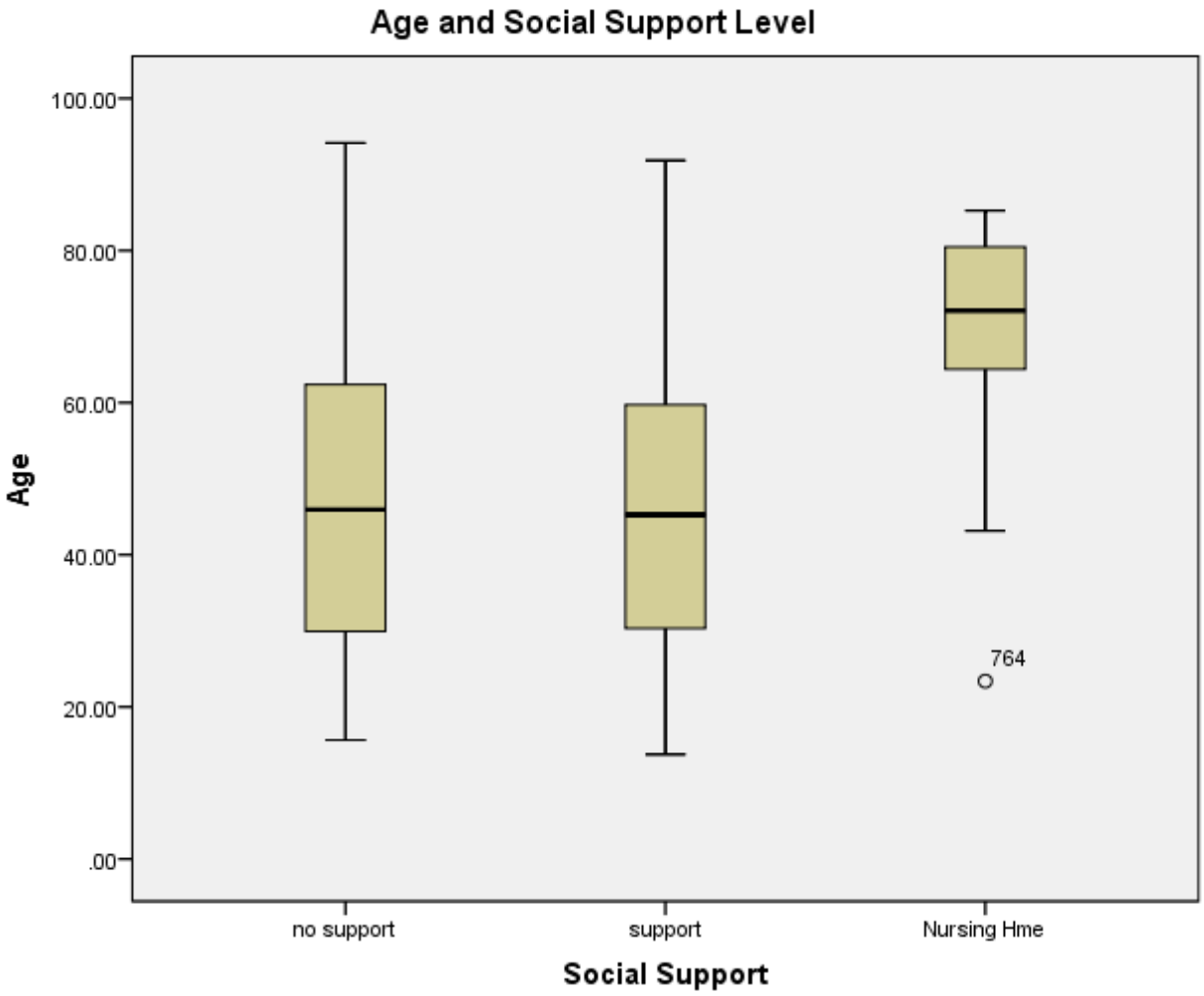

Figure A3.10: Social Isolation and age

A3.11 Employment status at time of injury

Each individual's job status was determined at the time of the injury. Full-time students were considered to be working while housewives were not. Part-time work is considered employed if it is paid but unpaid carers are not considered to be employed. Individuals taking early retirement on medical grounds were considered to be unemployed if under 60 but retired if over 60.

Table A3.6 shows that 13.4% of the population was unemployed, 19.6% was retired with the remaining 67% employed.

Length of stay or GCS did not differ between the three groups but age was 39.37, 44.60 and 74.24 year in the employed, unemployed and retired groups respectively and was significantly different between all three groups on one-way ANOVA ($p<0.01$)

A3.12 Traumatic Brain Injury Severity

Injury severity is usually divided into mild, moderate and severe TBI. This is distinct to the use of GCS in A3.4 where the absolute score between 3-15 was used. It is often useful to consider the distribution of the population in terms of the injury classification rather than simply a GCS score and many authors choose to categorise TBI severity in this way. This allows for better comparison across injury severity. The distribution across mild, moderate and severe injury was 45.5%, 39.3% and 15.2% respectively. Unsurprisingly, there was a large difference in length of stay for each category of injury severity with 3.03 days for mild, 6.62 for moderate and 30.81 for severe TBI which was significant on a oneway ANOVA ($p<0.01$). Age showed no difference.

Severity		Age	LoS
Mild	Mean	46.56	3.03
	N (%)	352(45.5)	
	SD	19.28	4.56
Moderate	Mean	48.33	6.62
	N (%)	304(39.3)	
	SD	19.75	8.51
Severe	Mean	44.39	30.81
	N (%)	118(15.2)	
	SD	17.68	21.70

Table A3.6: TBI Severity

A3.13 Past Psychiatric History

A total of 169 or 21.8% of the group had a significant past psychiatric history including appointments with a health professional or drug treatment. There was no difference between these individuals and others in terms of age, length of stay or GCS.

Past Psych History		Age (yrs)	LoS (d)	GCS
No	Mean	47.09	8.38	12.10
	N (%)	605 (78.2)		
	SD	20.26	13.81	2.92
Yes	Mean	46.32	9.75	11.15
	N (%)	169 (21.8)		
	SD	15.16	15.27	3.18

Table A3.7: Past Psychiatric History

A3.14 Extent of CT Scan Findings

The largest group is that with normal scan. This may be slightly surprising as it may be expected that this group would be less likely to be admitted using NICE guidance. There appears to be a clear gradient for lesions in terms of injury severity with GCS in the order of Normal scan, mild lesions, moderate lesions and diffuse changes. In other words, this proposed hierarchy of lesion extent, corresponds to increasing injury severity of TBI. This suggests that this suggested hierarchy of lesions, indeed follows a pattern of increasingly severe TBI. There is also a clear gradient in LoS, reflecting longer stay in those with more extensive CT findings. Age showed no difference across the groups.

CT lesion		Age(yr)	LoS(d)	GCS
Nil	Mean	45.59	2.83	14.24
	N (%)	306(39.5)		
	SD	18.67	4.53	1.23
Mild Lesion	Mean	43.45	8.30	11.51
	N (%)	151(19.5)		
	SD	20.14	11.98	2.41
Moderate Lesions	Mean	51.10	13.74	10.18
	N	250(32.3)		
	SD	18.91	17.52	2.73
Diffuse Lesions	Mean	45.23	17.37	8.42
	N (%)	67(8.7)		
	SD	18.85	20.78	2.82

Table A3.8: Extent of CT Scan Findings

A3.15 Unilateral/Bilateral brain Involvement

This is similar to the extent of CT lesion but focuses on whether abnormalities of imaging are seen on one or both hemispheres of the brain.

Again, there is a gradient seen from normal scan to unilateral and finally bilateral brain changes. The latter had the highest LoS (23.46 days) and lowest GCS (7.80) compared to no scan abnormality with Los of 3.02 days and GCS of 14.20. Age showed no difference across groups.

Hemisphere Involvement		Age	LoS	GCS
Nil	Mean	45.14	3.02	14.20
	N %	306(39.5)		
	SD	18.71	5.49	1.31
Unilateral	Mean	48.86	8.12	11.37
	N %	334(43.2)		
	SD	20.22	11.98	2.26
Bilateral	Mean	46.17	23.46	7.80
	N %	134(17.3)		
	SD	17.61	21.30	2.50

Table A3.9: Hemisphere Involvement

A3.16 Intoxicated at Injury

A large number of injuries (26.6%) are sustained while drinking. The intoxicated are younger (38.57 yrs versus 49.95) but had a shorter LoS (6.64 days versus 9.42). These were significantly different (p<0.001) while GCS was no different between groups.

Intoxicated		Age(yr)	LoS(d)	GCS
No	Mean	49.95	9.42	12.00
	N %	568(73.4)		
	SD	19.95	15.00	3.05
Intox	Mean	38.57	6.64	11.59
	N %	206(26.6)		
	SD	14.18	11.24	2.84

Table A3.10: Intoxicated at Time of Injury

A3.17 Warfarin at time of Injury

66 (8.2%) of individuals were on warfarin. These individuals were older with mean age of 70.39 compared to 44.74 years, (p<0.001) but surprisingly, had a shorter length of stay although this difference was not significant.

Warfarin		Age	LoS	GCS
No	Mean	44.74	8.79	11.79
	N %	708(91.8)		
	SD	18.39	14.33	3.03
Yes	Mean	70.39	7.45	13.02
	N %	66(8.2)		
	SD	10.96	11.97	2.44

Table A3.11: Warfarin Treatment at Time of Injury

A3.18 Medical Comorbidity

Medical comorbidity was graded on the Modified CIRS with a cut-off above 10 considered as significant medical comorbidity. A large number of individuals had significant comorbidity (32.2%) They were older (60.51 versus 40.48 years), p<0.001 but had similar length of stay and injury severity compared to those without comorbidity.

Comorbidity		Age	LoS	GCS
No	Mean	40.48	8.76	11.84
	N (%)	525(67.8)		
	SD	16.91	14.65	3.12
Yes	Mean	60.51	8.51	12.00
	N (%)	249(32.2)		
	SD	16.68	13.04	2.75

Table A3.12: Medical Comorbidity

A3.19 Initial Anxiety Score on HADS

The distribution of scores for the anxiety component of the HADS is shown in Figure A3.11. These scores range from 3-21 and show two peaks, one at low scores signifying low symptom levels and another at a higher level signifying a clinically significant level of symptoms. The mean score of 8.56 (SD 5.27) is different to the median score of 10(range 0-21) This suggests that the population does not follow a normal population distribution.

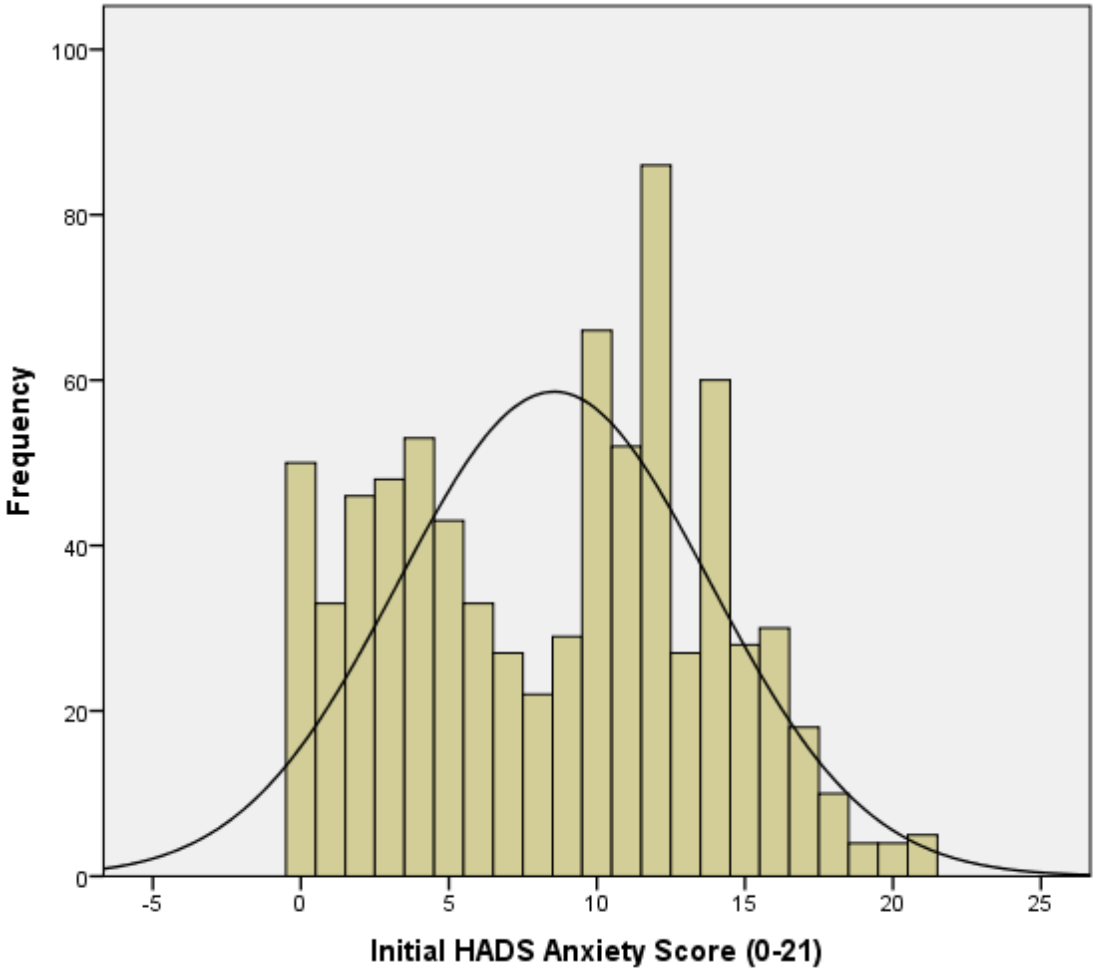

Figure A3.11: Initial Anxiety scores

A3.20 Initial Depression Scores in HADS

The distribution of scores for the depression component of the HADS is shown in Figure A3.12. As with anxiety, these scores range from 3-21. There are again two peaks of scores, one at zero score signifying no symptom level and another at a higher level around 11, signifying a clinically significant level of symptoms. The mean score of 8.14 (SD 5.10) is similar to the median score of 9 (range 0-21).

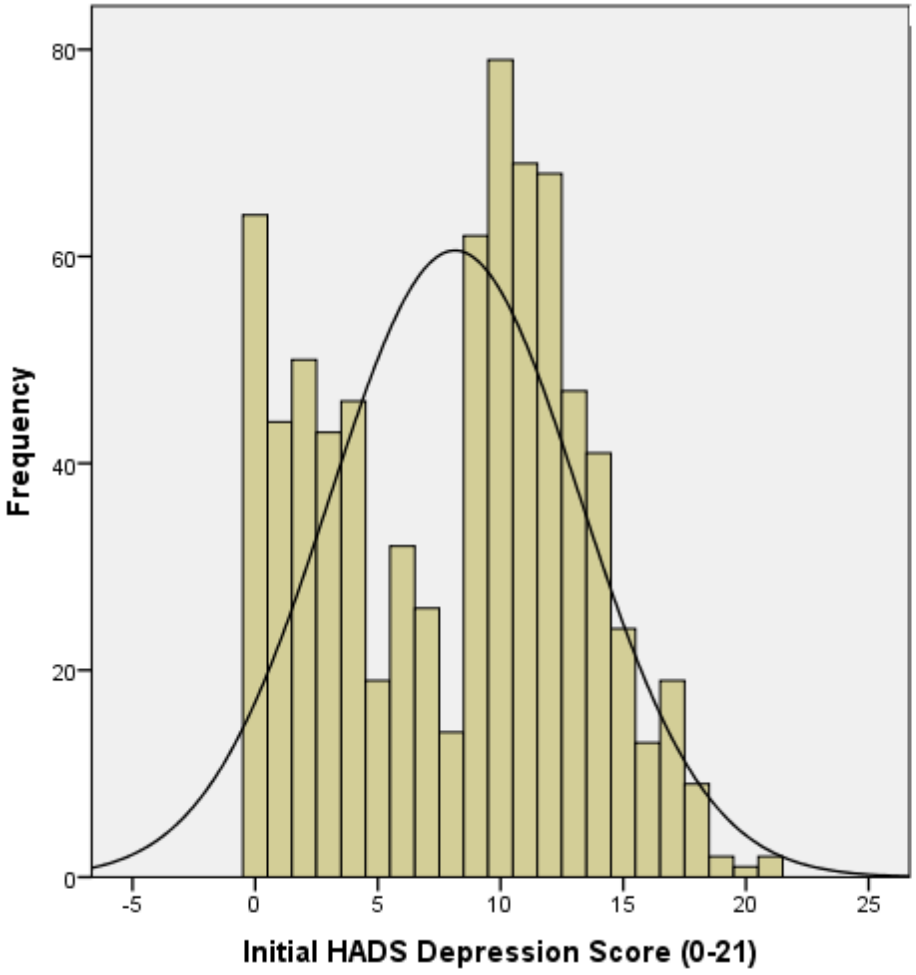

Figure A3.12: Initial Depression score on HADS

A3.21 Initial Rivermead Head Injury Questionnaire Score (RHFUQ)

This is a score for the level of psychosocial function of an individual. It measures the level of participation restriction (previously called handicap) and is scored between 0-40. There are a large number of individuals that score 0 which equates to no problems whatsoever. Otherwise the scores follow a normal distribution with very similar means (15.94, SD10.66) and median of 16 (range 0-40)

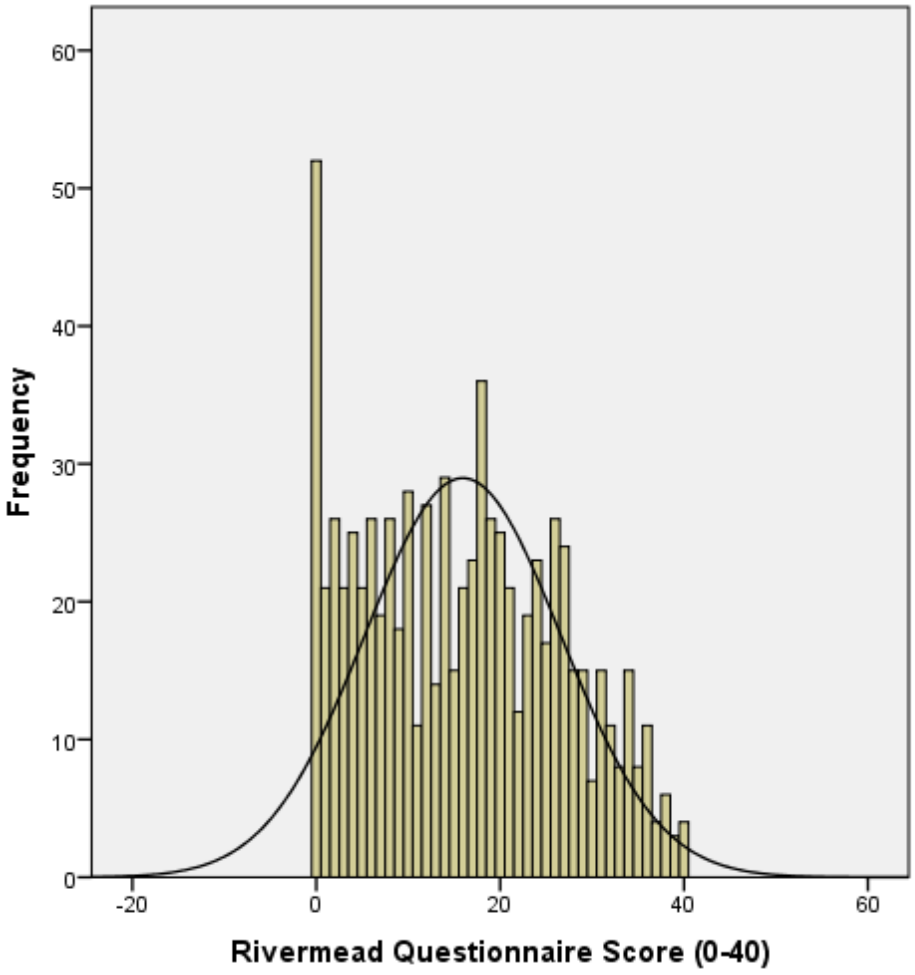

Figure A3.13: Initial Rivermead Questionnaire scores (psychosocial function)

A3.22 Initial Rivermead Post-concussion Score (RPCS)

This is a measure of the level of symptoms that an individual is experiencing after head injury which varies between 0 and 64. There is a positive skew towards lower scores but the distribution is similar to RHFUQ scores. These symptoms are often experienced by people in everyday e.g. headache, fatigue or dizziness and therefore many individuals would score a baseline level that is not 0. For each symptom that an individual experiences after TBI but at the same level at previous (i.e. no increased level) the score for that symptom would be 1. Therefore an individual could score a baseline of 16/64 without actually having any *increased* level of symptoms after TBI. This is different to the RHFUQ where a score of 0 implies no problem in that domain prior to the injury.
Despite this positive skew towards lower scores, the population has similar mean and median scores with mean of 18.42 (SD12.41) and median 17 (range 0-52)

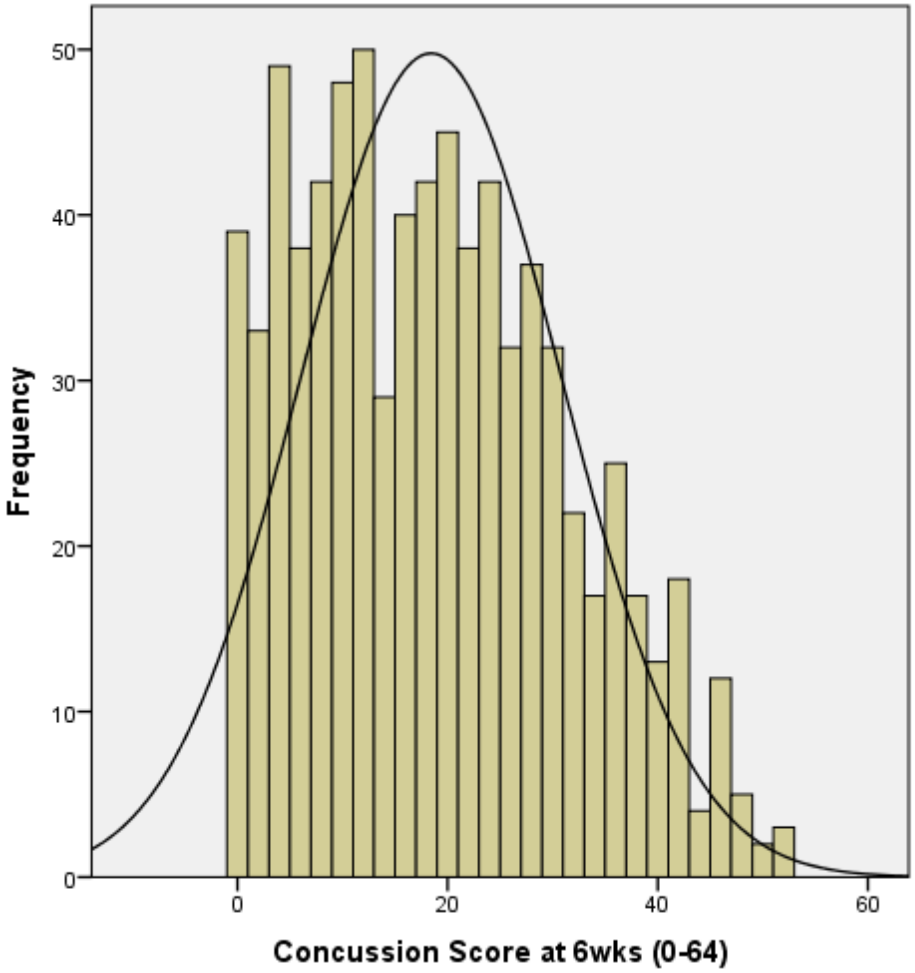

Figure A3.14: Initial Rivermead Post Concussion Score

A3.23 Initial Extended Glasgow Outcome Score (GOSE)

This is the measure of overall global outcome used in TBI. It is clear that most individuals cluster in the moderate level of outcome shortly after injury (GOSE 5-6) but even at this early stage of recovery, many individuals have made an excellent recovery into the good outcome bracket (GOSE 7-8).
This is compared to one-year outcome in Table A3.14 to show improvements over the year.

The mean GOSE1 score was 5.44 (SD1.33) with median of 5 which falls into Moderate Lower outcome.

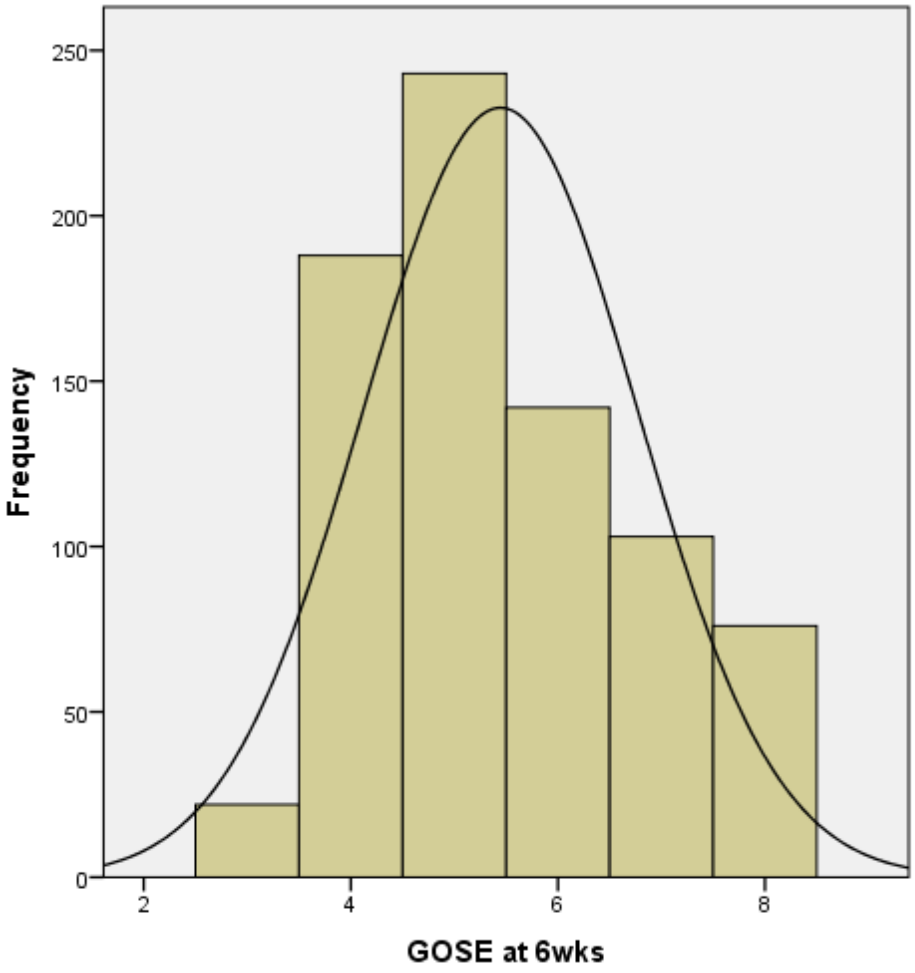

Figure A3.15: Initial Extended Glasgow Outcome Score

GOSE and Age

If the age of patients in each outcome category is considered, then there seems to be little difference in age which suggests that outcome category is not affected by age. There was only one patient in the VS category so that any statistical analysis was not possible. For any later analysis this patient was moved into the severe lower group.

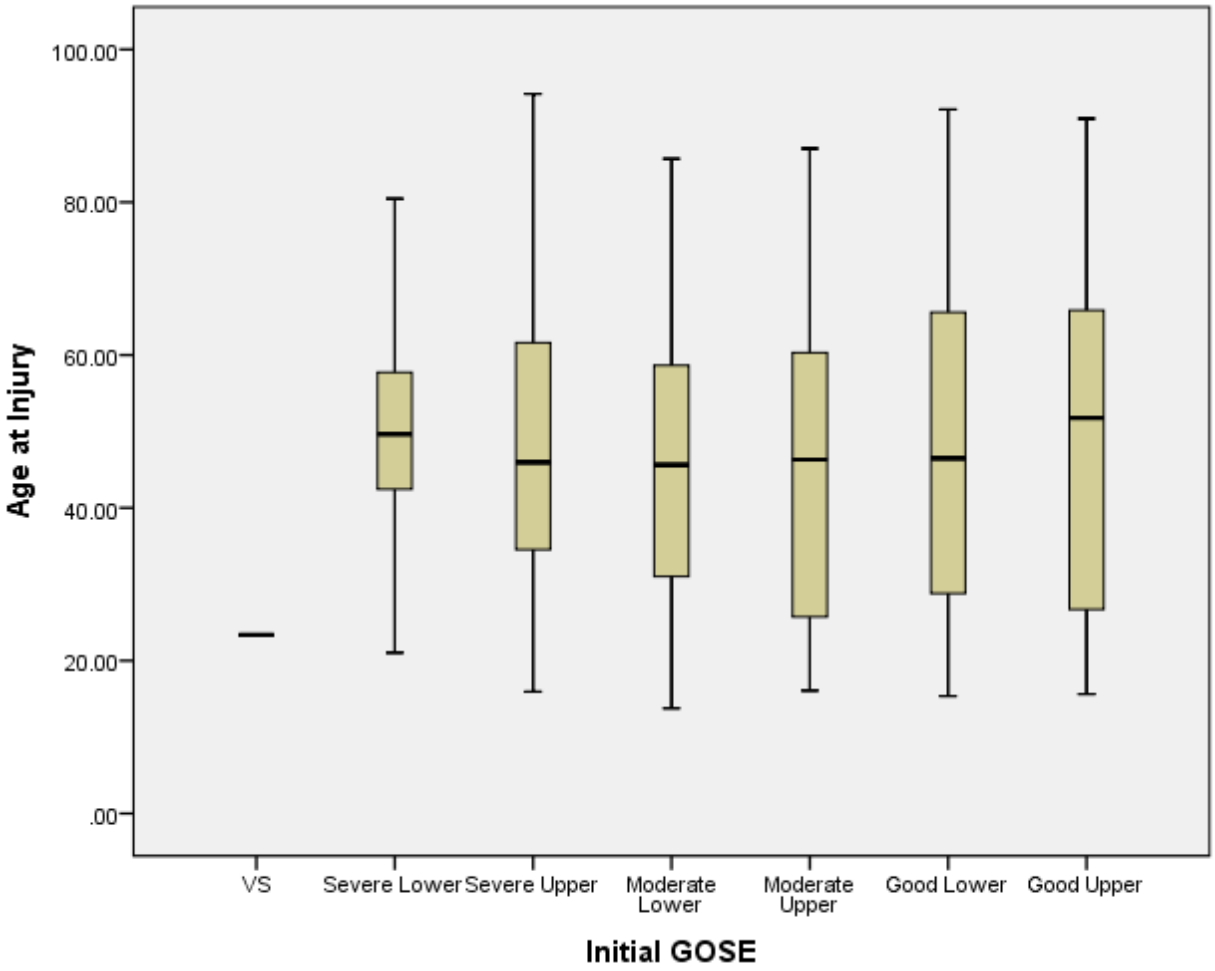

Figure A3.16: Age for Levels of Initial Extended Glasgow Outcome Score

GOSE and GCS

It is known that GOSE is affected by the severity of brain injury or GCS and comparison of this (Fig A3.17) shows a clear improvement of outcome with higher GCS (less severe injury). Intuitively this should make sense and a correlation coefficient between the two is 0.507

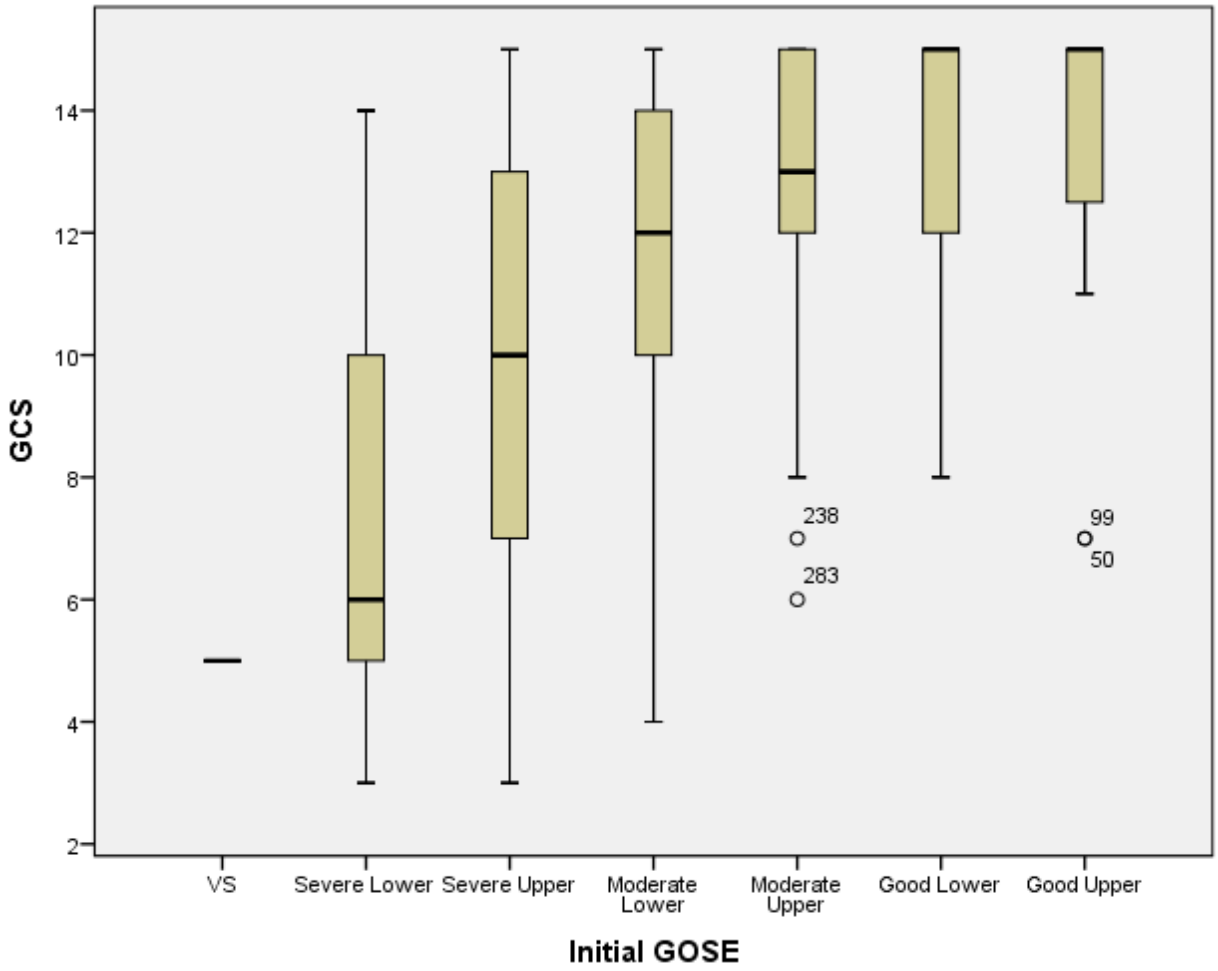

Figure A3.17: GCS and Initial Extended Glasgow Outcome Score

A3.24 GOSE and Depression Score

When initial GOSE and depression score on the HADS were compared, there seemed to be a clear relationship with better outcome and lower depression scores (Figure A3.18). Interestingly, the middle outcome categories showed much more variability of depression scores. This can be seen by the number of outliers in the column for moderate lower outcome which suggests that this outcome level is achieved by individuals with a wide range of depression scores, both high and low. Relatively fewer cases fall outside the confidence intervals in other outcome categories.

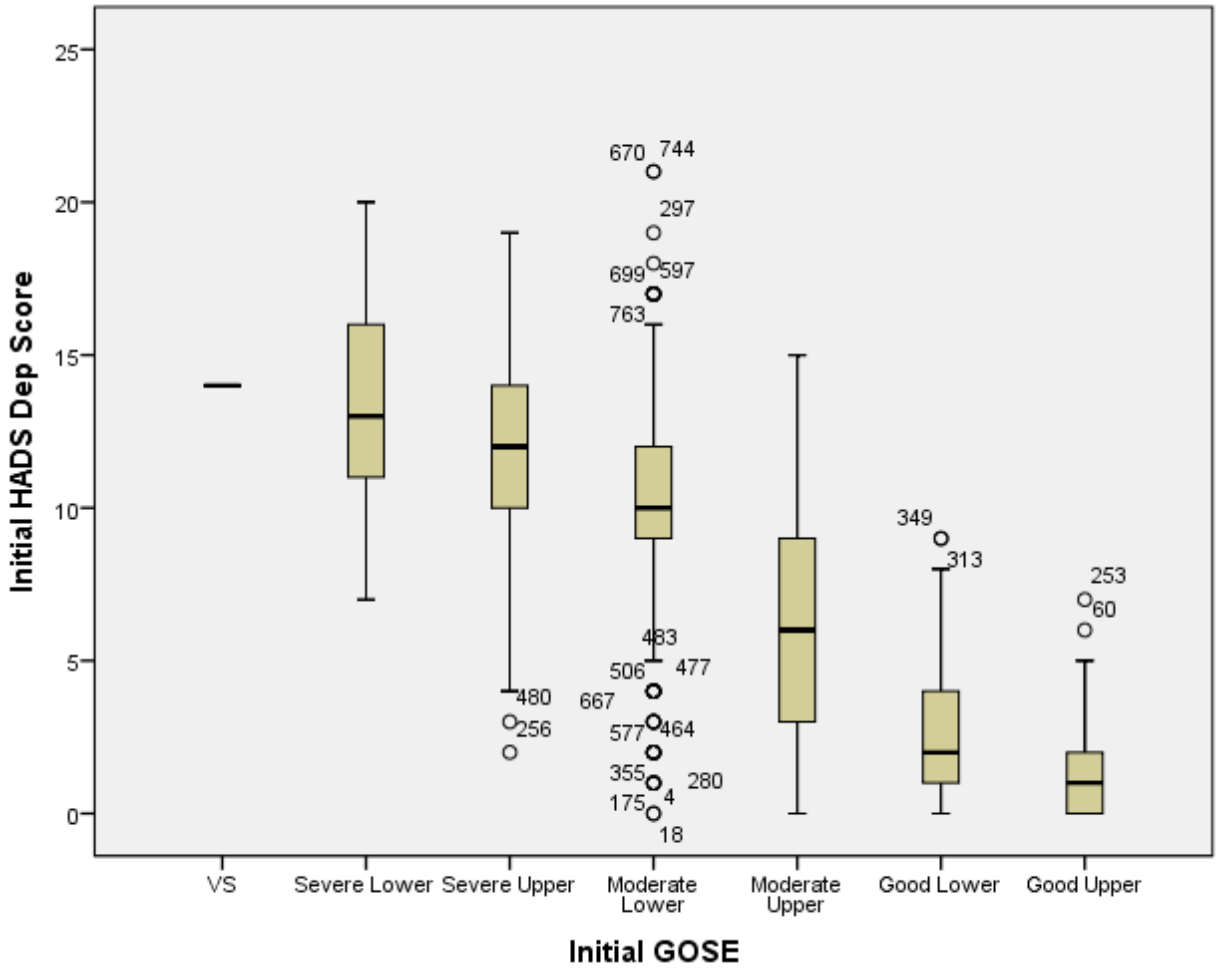

Figure A3.18 Initial GOSE and Depression score on HADS

This can also be presented in slightly different way. Rather than use the absolute HADS D score, if cases of depression are defined as HADS Score >8, then a plot of GOSE for both depressed and non-depressed individuals, shows the following.

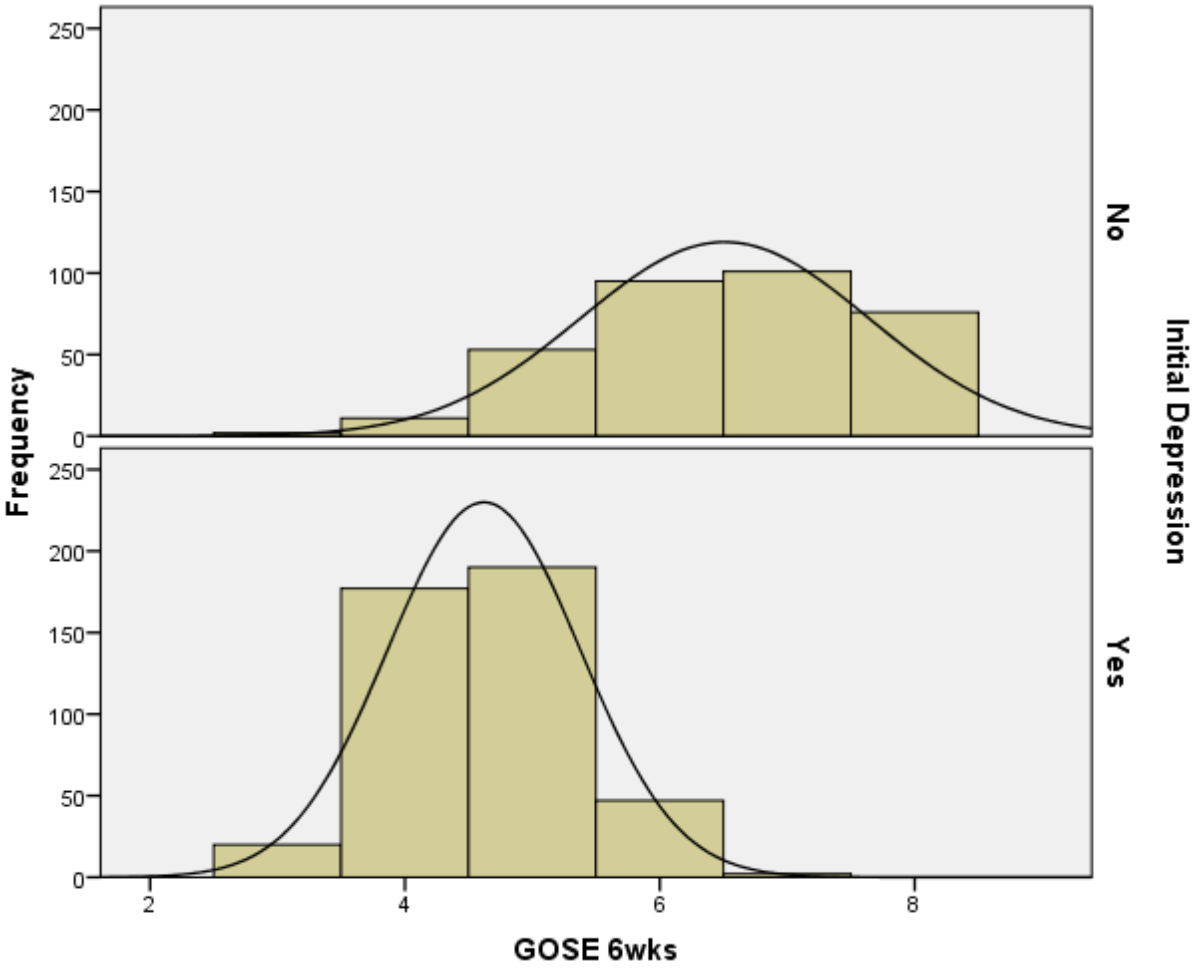

Figure A3.19 Initial GOSE for depressed and non-depressed cases (HADS D>8)

This clearly shows that depressed cases (Yes) have a distribution skewed towards worse GOSE score than those without depression (No).

Results at 1 year

A3.25 Anxiety Score at 1 yr

All one year data had to accommodate the loss of cases to death (38) and loss to follow-up (46) leaving a total of 690 cases who produced outcome assessments.
Individuals scored a HADS at a time as close to one year after the first appointment in clinic. The scores had reduced considerably (change in mean score from 8.56 to 6.03(SD5.51)) There was a very large number (83, 12%) of individuals who scored 0 at one year which means that they had no level of anxiety symptoms at all. The proportion with a clinically significant score >8 was 42.3%.

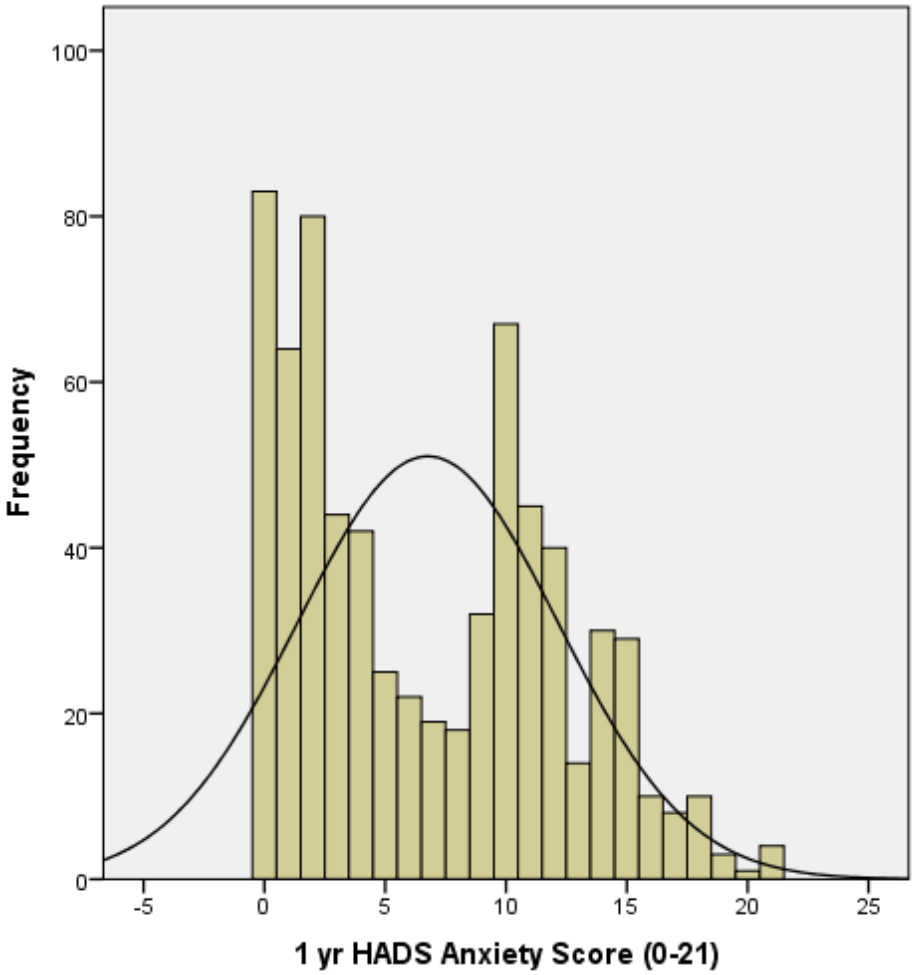

Figure A3.20: 1 year anxiety score on HADS

A3.26 Depression score at 1 yr

As with anxiety scores, the mean score for the depression component of the HADS reduced from 8.14 to 5.57. The median score at 1 year was 5. There were 119(17.2%) individuals with a score of 0 compared to 6 weeks when only 50(6.5%) had a zero score.

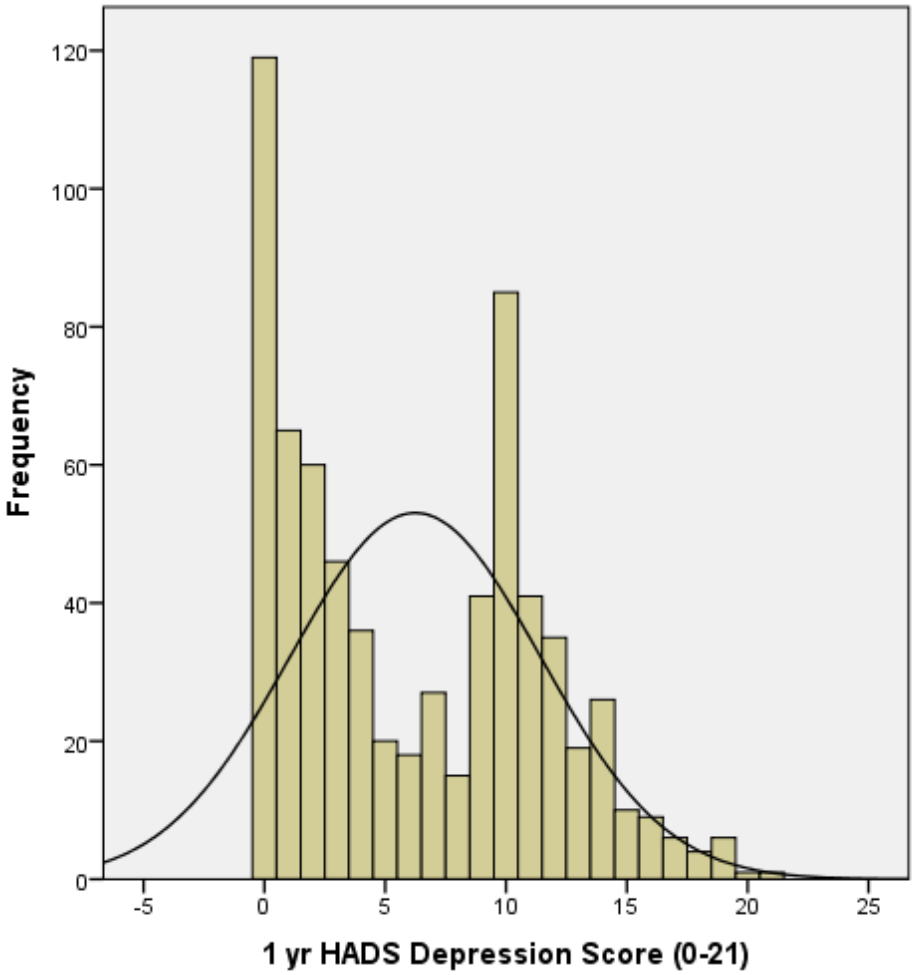

Figure A3.21: 1 year depression score on HADS

A3.27 Rivermead Head Injury Questionnaire Score at 1 yr (RHFUQ2)

There was a considerable reduction in the RHFUQ score from 6 weeks to one year. The mean score dropped from 15.94 (SD10.66), median 15, to 11.36 (SD9.64), median 9 after one year. There are no cut-offs used with this scale to signify levels of impaired psychosocial function and the measure can be considered a continuous scale. However, with personal experience of practice of many years, it is reasonable to consider that scores over 15 signify a high level of impaired function. Using this level, 395(51%) of individuals scored above 15 after 6 weeks which reduced to 219(31.7%) after one year. However this suggests that almost one third of individuals have significant problems with psychosocial function even after one year.

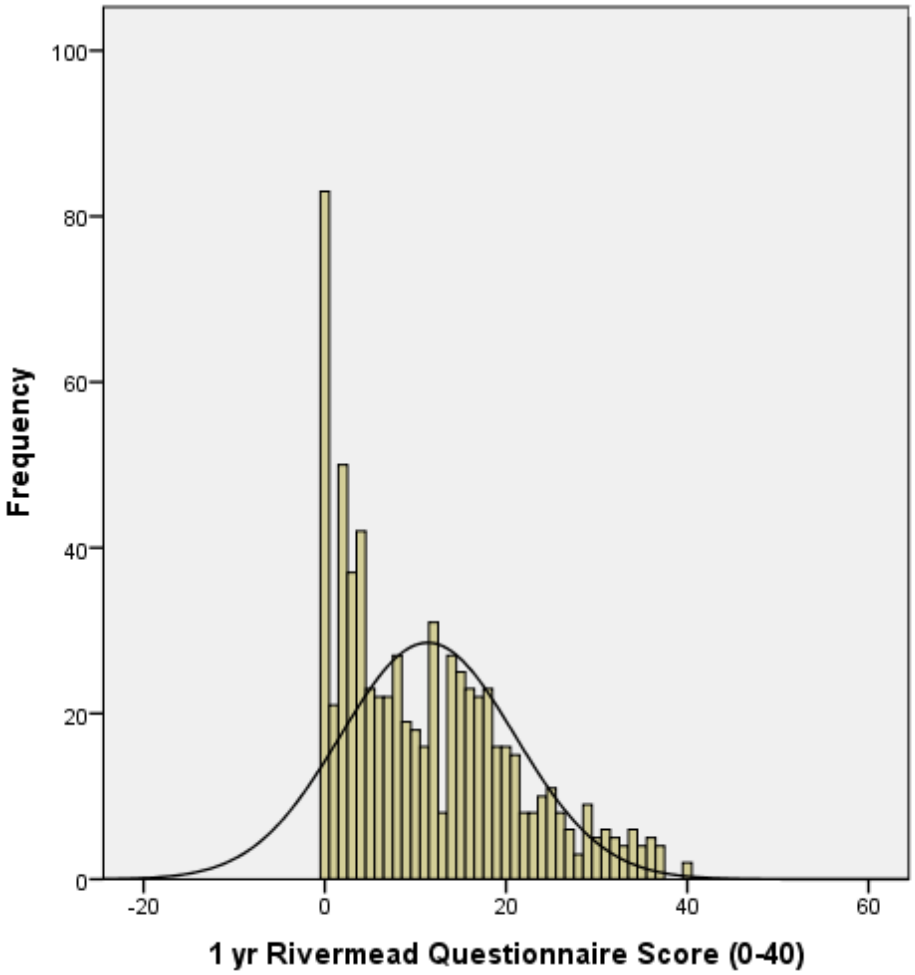

Figure A3.22: 1 year Rivermead Head Injury Follow-up questionnaire

A3.28 Rivermead Post Concussion Score at 1 yr (RPCS2)

As for other questionnaires, the mean score for the RPCS dropped considerably from a mean of 18.42 (SD12.41) median 17, to 13.13 (SD 11.38) median 10 after 1 year. The RPCS is difficult to interpret because many individuals experience some of the symptoms associated with head injury as explained in 4.2.18. However based on personal experience with this test over several years practice, a score over 20 would usually signify a significant level of symptoms. The number of individuals scoring above this level fell from 319(41.2%) initially to 155(22.5%) after one year. While this is a very large drop, it still implies that a large number of individuals are experiencing considerable symptoms even one year after TBI.

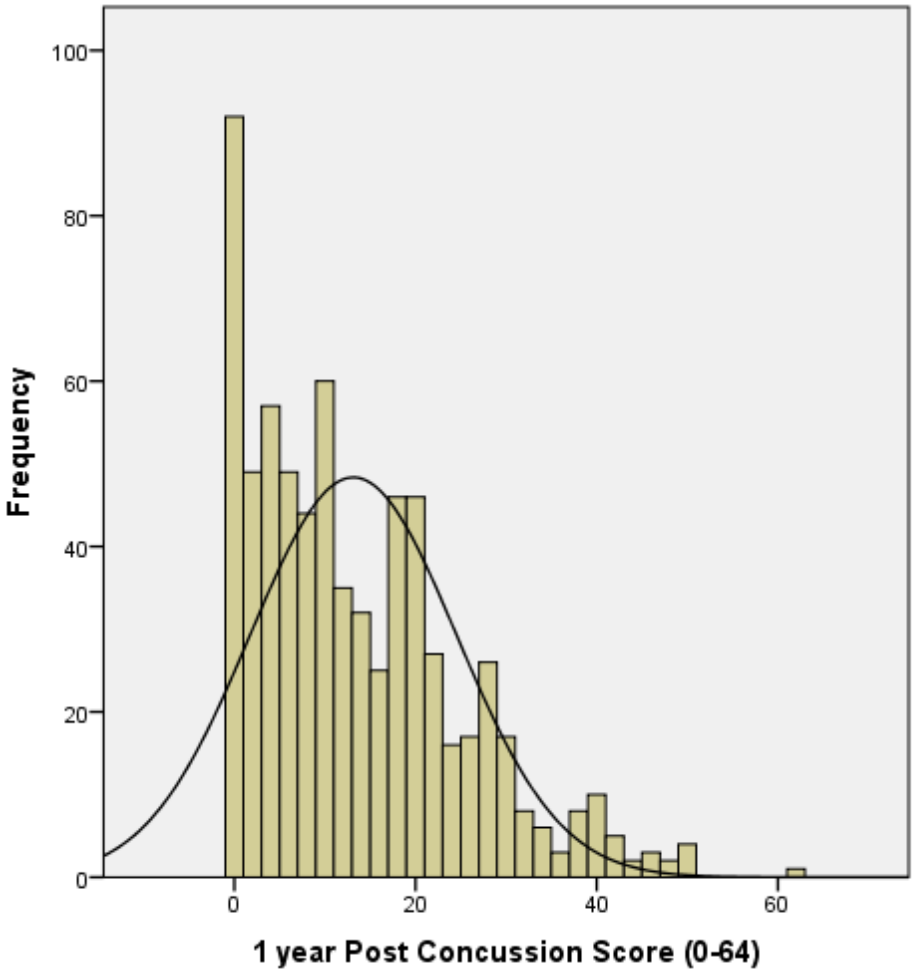

Fig A3.23: 1 year Rivermead Post Concussion Score

A3.29 Extended Glasgow Outcome Score at 1 yr (GOSE2)

The global outcome showed a trend to improvement in scores over one year with many individuals in the severe and moderately disabled groups at 6 weeks, moving into the Good outcome group. Compared to the previous distribution, there is now a small number of deaths recorded by one year (38) which is GOSE level 1. The Table below shows how the distribution of outcomes changed over one year with far more in the good outcome levels by one year, indicating that many individuals recover well after TBI.

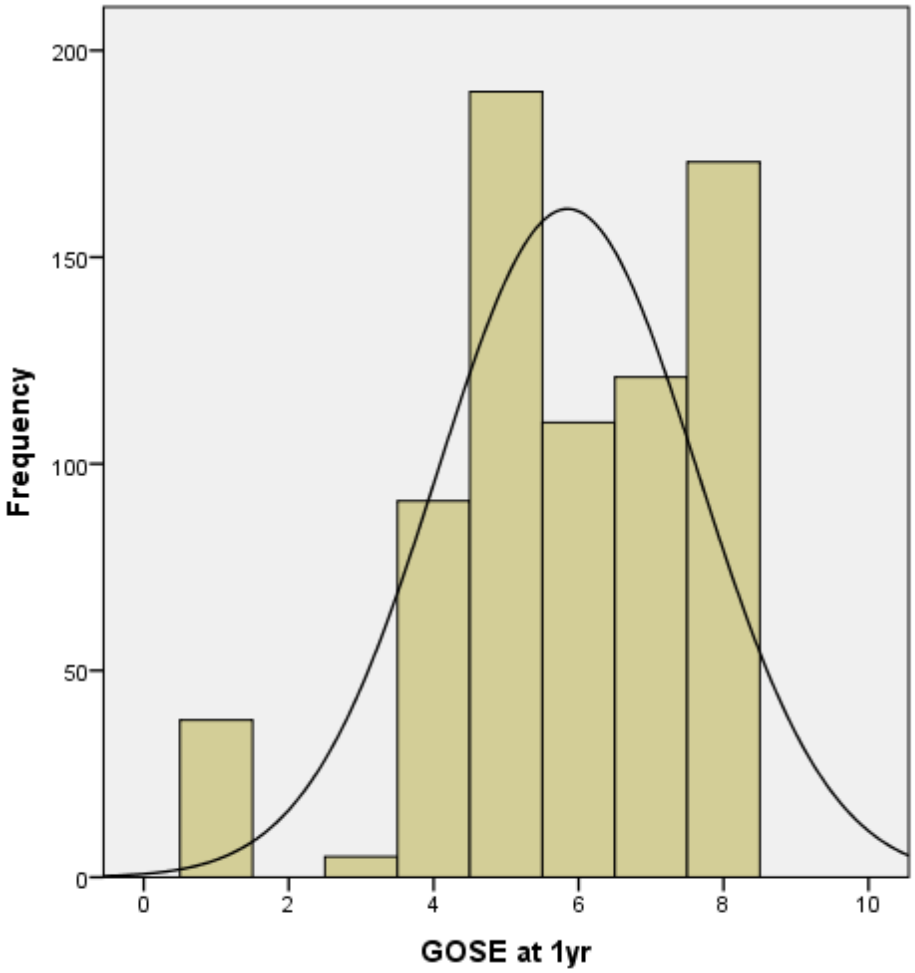

Figure A3.24: 1 year Extended Glasgow Outcome Score

This can also be shown in Table A3.13 which shows the distribution of individuals for outcome level at each time point.

GOSE Level	Number at 10 Weeks (774)	Number at 1 yr (728)
1 Deaths	0 (0)	38 (5.2)
2 VS	1 (0)	0 (0)
3 Severe Lower	21 (2.7)	5 (0.7)
4. Severe Upper	188 (24.3)	91 (12.5)
5. Moderate Lower	243 (31.4)	190 (27.5)
6. Moderate Upper	142 (18.3)	110 (15.1)
7. Good Lower	103 (13.3)	121 (16.6)
8. Good Upper	76 (9.8)	173 (23.8)

Table A3.13: GOSE1 and GOSE2 distribution

A3.30 GOSE and Depression score at 1 year

There was a again, a clear association between level of depression score on HADS with the outcome on GOSE after one year with lower depression scores resulting in better outcome (Fig A3.25). However there was still variability in the middle outcome levels where there were many outliers both with very low and very high levels of depression.

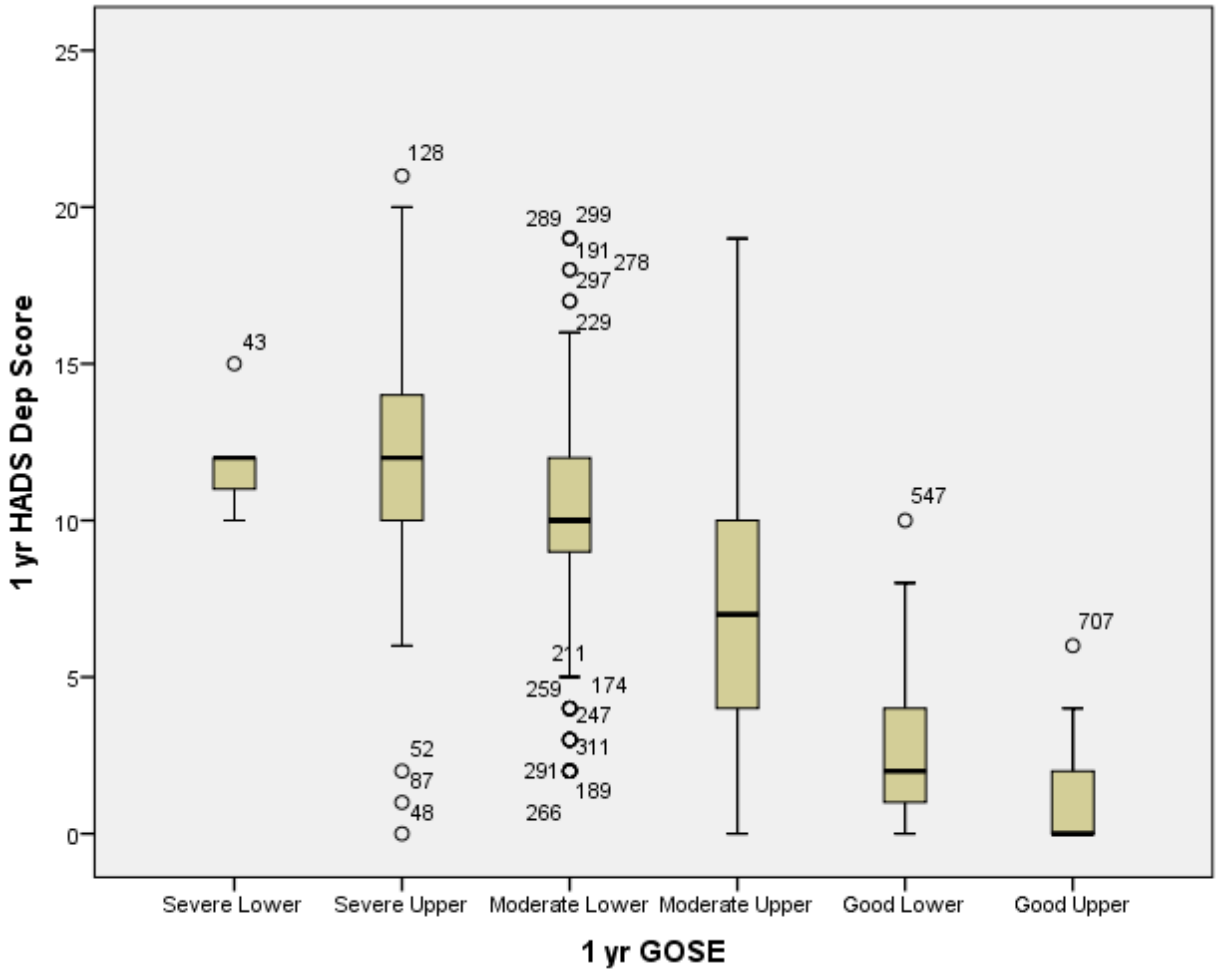

Figure A3.25 GOSE at 1 year with Depression score

This can again be considered by separating depression scores into cases and non-cases and plotting the GOSE (Fig A3.26) This shows that depressed individuals have outcome skewed towards worse scores

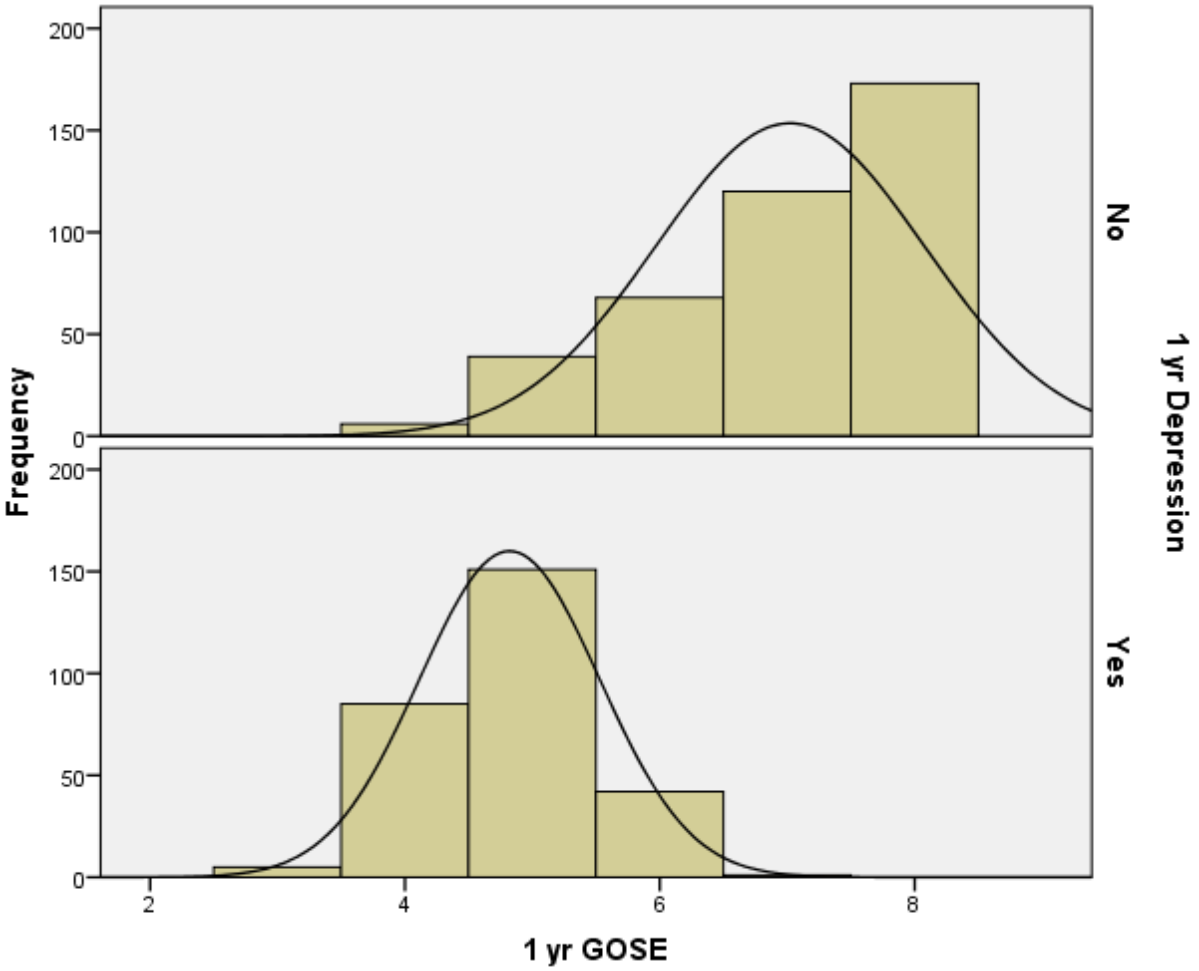

Figure A3.26: 1 year Extended Glasgow Outcome Score for depressed and non-depressed individuals

Appendix 4: Papers and Conference Presentations from the Thesis

Papers

R Singh J Kirkland, J Batterley. Clinical Pathways in Brain Injury; improving quality of care with early rehabilitation Disabil Rehab 2012; 34: 439-42

R Singh J Kirkland, J Batterley. Role of head injury teams in improving care with early rehabilitation. Arch Trauma Res 2013; 2: 103-7

R Singh, S Mason, F Lecky, J Dawson. High levels of Depression after TBI in a prospective cohort; the SHEFBIT study- submitted Brain Injury

R Singh, G Venkateshwara, S Mason, F Lecky. Outcomes in Traumatic Brain Injury; is mild really all that mild? submitted to Brain injury

R Singh, S Mason, F Lecky, J Dawson. Global outcome after TBI (SHEFBIT Study) – in preparation

R Singh, S Mason, F Lecky, J Dawson. Depression at 1 year after TBI – in preparation

Conference Abstracts

Early depression and risk factors after TBI – World Congress Neurorehabilitation 2016

Prevalence of depression after TBI; the SHEFBIT Cohort – ISPRM 2017

Anosmia and Traumatic Brain Injury; a Prospective Observational Study – ISPRM 2017

Disability & Rehabilitation, 2012; 34(5): 439–442

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REHABILITATION AND PRACTICE

Clinical pathways in head injury: improving the quality of care with early rehabilitation

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***Purpose*: To improve the management of all hospital admissions with head injuries, including mild and moderate by developing a clinical pathway and a head injury team. *Methods*: A head injury team was set up to take over the care of all admissions with head injury and to manage appropriate referrals and discharges. A key role was to facilitate communication between the different services involved in head injury care, arrange follow-up, support relatives and to educate healthcare staff. *Results*: In the first year, the team took over the care of 196 admissions of whom 128 attended for 3-month follow-up with 66% having a good outcome. Patients and relatives feedback was excellent with an average score of 4.8/5 on overall satisfaction rating. Other centers in the United Kingdom are aiming to set up similar pathways, and the team has presented on head injury pathways extensively. *Conclusions*: A clinical pathway can improve the quality of care for all admissions with head injury and enhance the role for rehabilitation at an early stage.**

Keywords: Brain injury, clinical pathways, quality, rehabilitation

Implications for Rehabilitation

- The care of head injury patients is often haphazard with several specialties involved and no coordination of care.
- Rehabilitation medicine is usually involved later on in head injury care.
- Setting up an acute head injury team can improve service outcomes and represents a development opportunity for rehabilitation medicine.

Introduction

The management of head injury is complex, demanding and requires a variety of specialist skills. Many individuals never seek medical advice or/are discharged from accident and emergency departments with no follow-up, and there is a high level of unmet need [1]. Those who are admitted may end up under a number of different specialties, and brain injury specialists in Rehabilitation Medicine (RM) are rarely involved at an early stage. There is no coordination of overall care needs, and the lack of responsibility leaves patients and families with an unsatisfactory service and hospitals with a clinical governance risk. This situation is common all over the United Kingdom. In order to change this unhappy state of play, we attempted to introduce an acute brain injury care pathway in Sheffield. The aim was to improve the quality of care for *all* brain injury admissions and not just those with a severe brain injury. Prior to the introduction of the pathway, head injuries were allocated to whichever element of hospital care met their immediate need on admission without due thought to an overall coordination of care and often not even for the brain injury itself. Patients could end up in general surgery, orthopedics, neurosurgery, ENT, Care of Elderly, A&E beds or be discharged.

Following admission there was no specialist input from a brain injury perspective unless specific neurorehabilitation referral was made and patients were often being discharged with little support or regard for social circumstances. Patients' families were, therefore, often put under great strain, and the lack of coordinated follow-up and inconsistencies in quality of care put the hospital at clinical governance risk.

The introduction of national policies and standards including the National Services Framework for Long-term Neurological Conditions (NSF) and National Institute for Clinical Excellence (NICE) Head Injury guidelines in 2005 [2–4] created an impetus to develop head injury services to meet the needs of patients. Several of the requirements of the NSF could be met by an appropriate head injury pathway to serve the needs of patients.

Clinical pathways have developed in many areas of medicine using a multidisciplinary approach to establish

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standards, facilitate decision-making and avoid inconsistencies of care [5–7]. Such pathways are attractive because they involve all staff, improve quality and safety for patients and hopefully improve outcomes [8,9]. However, a literature search using MEDLINE and EMBASE revealed little in the published literature as regard the use of pathways for head injury management. In severe brain injury, a pathway has been shown to improve some patient outcomes and reduce costs slightly [10]. Other studies have shown that a pathway reduced length of stay but other outcomes were unchanged [11–13]. However, our aim in Sheffield was to improve care of *all* admitted injuries and not just the most severe. There is an increasing awareness of the risks to even moderate and mild brain injury patients and head injury guidelines have led to many such patients being admitted for overnight observation and management [14,15]. The aims were to devise a pathway to reduce the variations in care quality for all admissions with traumatic brain injury (TBI), to assign overall responsibility for such admissions under a specialist in brain injury and to aid compliance with meeting national recommended requirements for head injury. Patient safety and clinical governance are of paramount importance and it was hoped that eventually it would be possible to show improved long-term patient outcomes.

Methods and development of pathway

The pathway was developed by a group of key stakeholders including local government, community health providers and voluntary sector organizations as well as hospital departments which routinely admitted head injury patients. All TBI patients were to be included in the pathway. Six beds were ring fenced as the Head Injury Observations Unit (HIOU). In order to support the running of these beds, the Acute Brain Injury Team (ABIT) was created under the Rehabilitation department. The team consists of a Brain Injury Specialist doctor, a Clinical Nurse Specialist and a Brain Injury Social Worker.

All patients admitted with head injury or suspected injury were admitted to the observation unit. Criteria for admission are extensive but include abnormal CT scans though not for surgical intervention, diminished Glasgow Coma Score or any unresolved clinical concerns that preclude discharge, e.g. alcohol intoxication. The Unit can also take step-down patients from ITU, while a management plan is made.

The pathway is not about specifying the exact treatment required in each specialty. For instance, it has not produced protocols for ITU or neurosurgical management; it is about coordinating care and taking responsibility for patients who do not fall clearly into specialties, such as neurosurgery. Those patients initially admitted to neurosurgery or ITU are again taken up by the Brain Injury team on discharge from those units.

Each day, the team joins the A&E ward round and takes over the care of any patients admitted the previous day. Referrals from other units, such as Care of Elderly, can be seen and patients either taken over or advice given. The ABIT is, therefore, a key link between the disparate elements of care services involved in brain injury, including neurosciences, surgery, ENT, general medicine and Care of Elderly as well as community services and it provides for smooth transitions between services as required and facilitates appropriate follow up or review by relevant specialists.

Therapy input comes from neurorehabilitation staff which ensures that staff has appropriate training for this patient group. The team manages patients' care needs on the observation unit and if longer term in-patient care is required for brain injury rehabilitation then patients can be transferred to the neurorehabilitation ward itself. This is useful in mobilizing patients or assessing any detailed cognitive problems and safety issues for discharge in those patients who require more than a short admission.

Relatives are often forgotten in acute settings [16] yet have to deal with ill patients on discharge and caregiver stress is a significant problem [17–19]. Considerable evidence is emerging that interventions directed at family support are effective [17,20]. The team is active in supporting families to fulfill their role. The social worker has a key role to play in the interface with relatives and can point to resources, such as local head injury groups, benefit agencies and several leaflets. On discharge, patients are given contact numbers for continuing support and a referral to community brain injury services is made, if needed.

Results and discussion

In order to support the smooth running of the pathway, a number of operational policies, referral and transfer criteria, discharge safety checklist and documentation proformas for head injury observation were devised. A Head Injury follow-up Clinic has been set up for all patients including those discharged by A&E within 24 hours. At the clinic, any ongoing problems are identified and appropriate assessments are undertaken and appropriate treatment or reassurance is provided. About 5% of even mild head injuries have significant symptoms at 1 year and it is known that appropriate management of mild TBI can reduce the incidence of symptoms [21,22].

A key benefit of the pathway has been to educate health staff as to the significance of head injury and its treatment. Intuitively, the training of staff and increased confidence in dealing with head injury should improve outcomes but this is difficult to show. A rolling program to train nursing staff the training of staff and increased confidence in dealing with head injury should improve outcomes but this is difficult to show. A rolling program to train nursing staff, junior doctors and therapists is in place, and the profile of head injury management has been raised across the region. Indeed and the profile of head injury management has been raised across the region. Indeed, the pathway has been highlighted nationally through the British Society of Rehabilitation Medicine and other professional bodies as a model of excellence. Other regional units are looking at the pathway in order to try and recreate similar systems elsewhere. The pathway has featured in the local press and the team has lectured on various aspects of brain injury extensively. The team acts as advocates for the importance of

brain injury services and hopefully will influence future service development.

For those of us who are interested in Brain Injury care and in RM as a specialty, the pathway has created an important niche for RM to show its value within a healthcare system. Traditionally the pathway has created an important niche for RM to show its value within a healthcare system. Traditionally, RM has been involved at a later stage after head injury. We now have an opportunity to make a difference to patients by introducing good rehabilitation principles right at the outset rather than wait for referrals from other colleagues at a late stage. In any case RM has been involved at a later stage after head injury. We now have an opportunity to make a difference to patients by introducing good rehabilitation principles right at the outset rather than wait for referrals from other colleagues at a late stage. In any case, many patients who are discharged from A&E or after overnight stay should be followed up by a specialist to reduce the incidence of future problems.

For the Hospital Trust, the thorny issue of overall patient responsibility has been solved. Patients are now under a specialist in brain injury who will coordinate appropriate referrals and care. Decisions are taken and clinical governance is much improved.

An important issue to address is the development of appropriate outcome data to show the impact of the team. Unfortunately head injury data are notoriously poorly coded [23] and we do not have appropriate pre-pathway data to compare parameters, such as length of stay or complications. In Table I, we present data from the first year of admissions. These are patients who returned to the head injury clinic at 3 months follow-up. In the first year, there were 196 admissions to the pathway. Of these, 128 attended clinic follow-up and were also available at 3 months for evaluation of outcome using the Extended Glasgow Outcome Score (E-GOS).

From Table I, it is clear that the majority of individuals had a mild or moderate injury, that a considerable number live alone and that depression is common. It is already well known that mood disorders are common after brain injury. Emotional difficulties are magnified in individuals with cognitive and physical impairments and our results highlight the need to address this. Use of reassurance, education and medication as well as early neuropsychological input is all beneficial.

The majority of individuals had a good outcome using E-GOS (66%). This compares favorably to landmark studies which range from 44% to 49% [15,24]. We hope to continue to follow up this group over time but head injury studies suffer from very high attrition rates and it will be difficult to show clear proof that the pathway has improved a hard outcome measure, such as E-GOS.

One important outcome for local services has been the improvement of clinical governance with pathway responsibility and care decisions being taken. This may be reflected in the patient and relatives feedback forms received from the same 128 patients in the cohort. A total of 76 patients and 62 relatives replied. Patients' ratings scored an average of 4.8/5 on overall satisfaction with the service and relatives rated the service at 4.7/5. Such data is not always the most reliable outcome measure but Patient Rated Outcome Measures (PROMS) are becoming increasingly important as a service outcome. Final proof of the utility of the pathway will only come if we can show improved hard outcome measures.

Table I. Clinical and demographic features of head injury admissions (based on 128 patients out of 196 who reattended at 3 months).

		N	%
Gender	Male	77	60
	Female	51	40
Severity of injury	Mild	55	43
	Moderate	59	46
	Severe	14	11
Ethnicity	White	116	90.6
	Other	12	9.4
Home support	Alone	73	57
	Supported	55	43
Alcohol excess	Yes	91	29
	No	37	71
Warfarin	Yes	9	7
	No	119	93
CT Scan findings	Nil	55	43
	Contusions	37	29
	Intracranial bleed	24	19
	DAI	12	9
Depressive symptoms	Yes	39	32
	No	87	68
Glasgow outcome score	1–4	4	3.1
	5. Moderate Lower	6	4.7
	6. Moderate Upper	33	25.8
	7. Good Lower	44	34.4
	8. Good Upper	41	32.0
Age in years; mean (SD)	42.8 (22.8)		
Length of Stay, days; mean (SD)	6.4 (6.2)		

We do not know of any other similar service under RM in the United Kingdom and other areas of the country are looking to develop similar programs. We suggest that this pathway may be a future model that RM professionals could look at to provide better care to individuals with brain injury and their families. It is also an opportunity for RM to enhance and extend its role in healthcare and improve clinical governance within NHS organizations. It would be interesting to know the experience of other healthcare professionals, particularly in other countries as to whether such pathways already exist and if they do, have outcomes been affected.

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Early Rehabilitation in Head Injury; Can We Improve the Outcomes?

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Background: The quality of care after head injury is still very variable with a little coordination between different specialties. Acute care dominates, often with little regard to rehabilitation needs.
Objectives: To improve the outcomes of all head injury admissions to hospital, including mild and moderate, by creating a head injury team to supervise a rehabilitation clinical pathway.
Patients and Methods: A head injury team was established to manage the care of all non-neurosurgical admissions with head injury to a large teaching hospital. Apart from inpatient care, the team coordinates various services involved in the care of head injuries, arranged suitable follow-ups, supported relatives and trained healthcare staff on general wards in the treatment of head injured patients. Follow-up clinics at 6 weeks and 6 months were arranged.
Results: In the first three years, the team managed the care of 812 admissions. Mean age was 44.3 years (SD = 24.8) and mean length of hospital stay was 6.1 days (SD=10.9). Of these individuals, 674 attended for 6 month follow-up with 52.2% having a good outcome on Extended Glasgow outcome score. Patients and their relatives' feedbacks were excellent with an average score of 4.7/5 on overall satisfaction rating. Following presentations at national meetings and elsewhere, other centers in the United Kingdom are now setting up similar pathways.
Conclusions: A dedicated clinical pathway and head injury team can improve the quality of care for all admissions with head injury and enhance the role for rehabilitation medicine input at an early stage.

Keywords: Craniocerebral Trauma; Critical Pathways; Healthcare Quality; Physical and Rehabilitation Medicine

1. Background

The management of head injury demands a wide variety of specialist skills and presents complex problems. Many individuals never seek medical advice or are discharged from accident and emergency departments with no follow-up and there is a high level of unmet need (1). Those with a severe injury are usually admitted to the neurosurgical or orthopaedic wards. But they are lucky if they receive neurological rehabilitation afterwards or ongoing referral for rehabilitation in the community. Furthermore, the management of those with mild or moderate injury is even more variable and patients can receive a wide range of care. Those who are admitted may end up under a number of different specialties; brain injury specialists in rehabilitation medicine are rarely involved at an early stage. There is no coordination of overall care needs and the lack of responsibility leaves patients and families with an unsatisfactory service and hospitals with a clinical governance risk. This situation is common all over the United Kingdom. In order to address this unhappy situation, we introduced an acute brain injury care pathway in Sheffield. The aim was to improve the caring quality for all brain injury admissions, not just those with a severe brain injury. Prior to the introduction of the pathway, head injuries in this region were admitted to different departments depending on their immediate need on admission without any thought to an overall coordination of care. Such specialties included general surgery, orthopaedics, neurosurgery, ENT, care of elderly, A&E beds or could be discharged the same day.

After admission there was no specialist input from a team specialized in brain injury. Patients were often being discharged with little support or regard for social circumstances. Their families were often put under great strain and the lack of coordinated follow up and inconsistencies in quality of care put the hospital at significant clinical governance risk.

The introduction of national policies and standards including the national services framework for long-term neurological conditions (NSF) and National Institute for Clinical Excellence (NICE) head injury guidelines in 2005 (2, 3) created a drive to develop head injury services. It was clear that many of the guideline requirements could be met by an appropriate head injury pathway, coordinated to meet the needs of patients. Since then, there

Implication for health policy/practice/research/medical education:
We can improve the outcomes of head injury care by using a clinical pathway under the control of a dedicated head injury team.

have been further initiatives to improve the quality of major trauma services nationally. This has added to the impetus to improve head injury care (4, 5).

In recent years, many different areas of medical practice have developed clinical pathways using a multidisciplinary team approach to set standards, assess quality of care, measure performance and avoid inconsistencies of care (6-8). Such pathways are attractive because they improve the quality of care and safety for patients and hopefully improve the outcomes (9, 10). However, a literature search using MEDLINE and EMBASE revealed little in the published literature as regards use of such pathways in head injury management. In severe brain injury, a pathway has been shown to improve some patient outcomes and reduce costs (11). A significant study by Fakhry et al. found that the outcomes could be improved but only included severe brain injuries (12). Other studies have shown that a pathway reduced the length of stay but other outcomes were unchanged (13, 14). However the aim in Sheffield was to improve the care of all admitted injuries not just the most severe injuries. There is a growing awareness of the significant risks to even those with moderate and mild brain injury (15) and the development of head injury guidelines has resulted in many such patients being admitted for overnight observation and management (16, 17). The aims of the pathway was to reduce the variations in quality of care for all admissions with TBI, to bring all admissions under a specialist in brain injury and to aid compliance with meeting national recommendations for head injury care. Clinical governance and patient safety are of vital importance and it was hoped that eventually it would be possible to show an improvement in long-term patient outcomes.

2. Objectives

To improve the outcomes of all head injury admissions to hospital, including mild and moderate, by creating a head injury team to supervise a rehabilitation clinical pathway.

3. Materials and Methods

A taskforce was set up by a group of key brain injury stakeholders. This included local government, community health providers and voluntary sector organisations as well as hospital departments which routinely admit head injury patients. It was important that all TBI patients were included in the pathway. Six beds were set up as the head injury observations unit (HIOU). An acute brain injury team (ABIT) was created based in the rehabilitation medicine department to have the responsibility for the care of patients admitted to these beds. The team consists of a brain injury specialist doctor, a clinical nurse specialist and a brain injury social worker.

All patients with head injury or suspected injuries are admitted to the observation unit. Criteria for admission are based on the NICE guidelines for head injury (3). These are extensive but include abnormal CT scans not admitted to neurosurgery, diminished Glasgow coma score or any unresolved clinical concerns that preclude discharge (e.g. alcohol intoxication). The unit can also take step-down patients from ITU while a management plan is made for ongoing care or management.

The pathway does not specify the exact treatment required in each the parent specialties involved in head injury care. For instance it has not produced protocols for ITU, ENT or neurosurgical management; these protocols remain the responsibility of the relevant departments. The pathway is about coordinating overall care and being responsible for patients who do not fall clearly into specialties such as neurosurgery. Those patients initially admitted to neurosurgery or ITU are again taken up by the brain injury team on discharge from those units.

Each day, the team joined the emergency ward rounds and take over the care of any patients admitted the previous day. Referrals from other units such as care of elderly can be seen and patients either taken over or advice given. The ABIT is therefore a key link between the varying elements of services that are involved in brain injury, including neurosciences, surgery, ENT, general medicine and care of elderly as well as community services. The team provides smooth transitions between services as required and facilitates appropriate follow ups or reviews by relevant specialists and ascribes to the use of a rehabilitation model at an early stage to improve patient service and outcome.

Patients received therapy input from neurorehabilitation staff who have the appropriate skill set and training for the head injury group. The team manages patients' care needs on the observation unit and if longer term in-patient care is required for brain injury rehabilitation then patients can be transferred to the main neurorehabilitation ward itself. This is useful for those with more severe injury who require a longer stay or for assessing detailed cognitive problems and safety issues for discharge.

Relatives are often forgotten the acute settings (18) have to deal with ill patients on discharge. Caregiver stress is recognized as a significant problem (19-21). Considerable evidence is emerging that interventions directed at family support can be effective (19, 22). The team was active in supporting families to fulfill their role. The social worker has a key role to play the interface with relatives and can point to the resources such as local head injury groups, benefit agencies and several leaflets developed by the group. On discharge, patients are given contact numbers for continuing support and a referral to community brain injury services is made if needed.

4. Results

To facilitate the new pathway, a number of operational policies, referral and transfer criteria, discharge checklist and documentation pro forma had to be devised for head injury observation. A head injury follow-up clinic has been set up for all patients including those discharged from emergency department within 24 hours. At the clinic, any on-going problem is identified and appropriate assessments undertaken. It is known that 5% of even mild head injuries have significant disabling symptoms at the first year and the appropriate management of mild TBI can reduce the incidence of these symptoms (23, 24). The aim of the clinic is to reassure patients and treat any persisting symptoms or complications.

A key benefit of the pathway was to educate other health staff as to the significance of head injury and its treatment. Intuitively, the training of staff and increased confidence in dealing with head injury should improve outcomes. However, this is difficult to show the use of appropriate objective outcome measures. A rolling program to train nursing staff, junior doctors and therapists is in place and the profile of head injury management has been raised across the region. Indeed the pathway has been highlighted nationally through the British society of rehabilitation medicine and other professional bodies as a model of excellence. Presentations on one year data at national and international meetings have highlighted the strengths of such a service and other regional units are looking at the pathway in order to try and recreate similar systems elsewhere. The pathway has featured in the local press and the team lectured on various aspects of brain injury extensively. The team acted as advocates for the importance of brain injury services and hopefully will influence future service development.

In the last year, the United Kingdom has followed models of trauma care in other countries, most notably the United States and has set up regional major trauma centers (4, 5). An important part in caring such individuals is the rehabilitation that they receive (25). The resulting development of trauma rehabilitation in the United Kingdom has acted as a fresh impetus to the role of rehabilitation medicine specialists in the acute stages of traumatic injury and the brain injury team has been pivotal in the development of national as well as the local trauma rehabilitation systems.

For those of us who are interested in rehabilitation medicine (RM) as a specialty, the development of head injury and trauma rehabilitation pathways has presented an opportunity for RM to show its value within acute healthcare systems. Traditionally RM is involved at a later stage after injury if indeed at all. We now have an opportunity to make a difference to patients by introducing good rehabilitation principles at the outset of care rather than waiting for referrals from other colleagues at a later stage. We believe strongly that all head injury patients who are discharged from A&E or after overnight stay, should be followed up by a specialist to reduce the incidence of future problems.

For the hospital trust, the problem of overall patient responsibility has been solved. Patients are now under a specialist in brain injury who will coordinate appropriate referrals and care. Decisions are taken and clinical governance is much improved.

The ultimate measure of success would be to show a change in objective outcomes after head injury. Unfortunately there was no previous record of head injury outcome measurement in our hospital until the team was set up and started to collect such data. It is therefore impossible to show a definitive improvement in any such outcome measurments. Furthermore, it is known that head injury data is notoriously poorly coded (26) and there is considerable variation in the measures that different units use (27). The most common measure that is used is the extended Glasgow outcome score (E-GOS) (28). Compared to most other measures, it is relatively quick to administer and has less room for subjective reporting. This is the key outcome that we decided to report. We have reported previously on one year data but numbers were understandably insufficient and many people took time to become aware of the new service (29).

In Table 1 we present data from the first three years of admissions under the pathway. These are patients who returned to the head injury clinic at 6 months follow-up. In this period, there were 812 admissions to the pathway. Of these, 674 attended both the initial clinic and then follow-up at 6 months for evaluation of outcome using the extended Glasgow outcome score (E-GOS).

From Table 1, it is clear that the majority of individuals had a mild or moderate injury while only 21% having a severe TBI. We also found that a considerable number of patients live alone and that depression was common with 32% showing significant depressive symptoms. It is already well known that mood disorders are common after brain injury (30 , 31). Emotional difficulties magnified in individuals with cognitive and physical impairments and our results highlighted the need to address this issue. The role of the social worker in facilitating further input, discussion and referral to appropriate support groups has been invaluable. The early use of education, medication and neuropsychological input has all been beneficial.

The majority of individuals had a good outcome using E-GOS (52%). This compares favorably to landmark studies which range from 44 - 49% (17, 32, 33).

Table 1. Clinical and Demographic Features of Head Injury Admissions (based on 674 patients out of 812 who reattended at 6 months)

Characteristic	No. (%)	Mean (SD)
Gender		
Male	460 (68.3)	
Female	214 (31.7)	
Severity of injury		
Mild	239 (35.5)	
Moderate	293 (43.5)	
Severe	142 (21.0)	
Etiology		
Assault	114 (16.9)	
Fall	336 (49.9)	
Road Traffic Accident	170 (25.2)	
Work accident	45 (6.7)	
Fits	9 (1.3)	
Ethnicity		
White	635 (94.2)	
Other	39 (5.8)	
Home support		
Alone	354 (52.5)	
Supported	320 (47.5)	
Alcohol excess		
Yes	182 (27.0)	
No	492 (73.0)	
Warfarin		
Yes	51 (7.6)	
No	623 (92.4)	
CT scan findings		
Nil	246 (36.4)	
Contusions	191 (28.4)	
Intracranial bleed	164 (24.3)	
DAI	73 (10.9)	
Depressive symptoms		
Yes	219 (32.4)	
No	455 (67.6)	
Glasgow outcome score		
1- 4	36 (5.4)	
5. Moderate Lower	120 (17.8)	
6. Moderate Upper	166 (24.6)	
7. Good Lower	203 (30.1)	
8. Good Upper	149 (22.1)	
Age , mean (SD), y		44.3 (24.8)
Length of stay, mean (SD), d		6.1 (10.9)

5. Disscusion

Clearly these studies were carried out in different populations but we would not expect there to be much difference in baseline demographics. These results certainly encourage us that the pathway is an effective way of treating head injury patients. We hope to continue to follow up this group over time but head injury studies suffer from very high attrition rates and it will be difficult to show clear proof that the pathway has improved a hard outcome measure such as E-GOS.

One important outcome for local services has been the improvement of clinical governance with pathway responsibility and care decisions. This may be reflected in the patient and family feedback forms given to 125 patients and 125 relatives in the cohort. Replies were received from 104 patients and 97 relatives. Patients' ratings scored an average of 4.8/5 on overall satisfaction with the service and relatives rated the service at 4.7/5. Such data is not always the most reliable outcome measurements but these patient rated outcome measures (PROMS) are becoming increasingly important as a service outcome (34).

To the best of our knowledge, we do not know of any similar RM service in the United Kingdom up to date but we know that other units are now looking to develop similar programs after discussion with us. We suggest that this pathway may be a future model that RM professionals could see to provide better care to individuals with brain injury and their families. It is also an opportunity for RM to enhance and extend its role in healthcare and improve clinical governance within health organizations. It would be interesting to know the experience of other healthcare professionals, particularly in other countries as to whether such pathways already exist and if they do, have outcomes been affected.

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Authors' Contribution

Rajiv Singh is the guarantor and lead writer. Julie Batterley and Sarah Bruce helped with redrafts and wrote the protocols. Prasad helped with data collection and analysis.

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