Depression and Anxiety following a Traumatic Brain Injury

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ABSTRACT

Traumatic brain injuries (TBI) are one of the leading global causes of death and disability, creating a substantial public health and socio-economic burden. The personal consequences of a TBI can also be extensive, commonly encompassing functional, cognitive and psychological problems. These impairments can, in turn, affect relationships, employment status, leisure activities and independence. The present thesis focuses on two of the most common psychological outcomes following TBI: depression and anxiety. Both undermine an individual's quality of life, although their impact is not yet fully understood.

The prevalence of depression and anxiety varies widely in the existing literature, but our understanding of what might be contributing to this variability is limited. This makes it difficult to identify who is most at risk of developing depression and/or anxiety following a TBI and when they are most susceptible. Crucially, this constrains our capacity to understand the trajectory of psychological problems after a TBI which, in turn, hampers clinicians' ability to identify and implement targeted interventions for those who are most in need. The variability in rates likely reflects differences in how these problems are investigated, with data relating to the incidence, characteristics, risk factors and outcomes of TBIs collected in both epidemiological and clinical contexts. Adding to the problem is the fact that depression and anxiety are frequently measured using a variety of assessment methods and, moreover, there are often differences between the samples that are being examined, with studies evaluating individuals who have a variety of injury, and pre- and post-morbid characteristics. Thus, four studies were designed in order to examine these issues and comprehensively investigate whether, and to what extent, different methodologies and sample characteristics influence depression and anxiety after a TBI.

The first study (Chapter 3) assessed the prevalence of clinical diagnoses of major depressive disorder (MDD)/dysthymia and self-reported 'cases' of clinically significant levels of depression following adult TBI. Data from 99 studies were meta-analysed. Overall, depression

was found to be very common after a TBI, with 27% of people diagnosed with MDD/ dysthymia and 38% reporting clinically significant levels of depression.

Next, Chapter 4 built on these findings by comparing levels of self-reported depression in people with and without a TBI who were living in the general community. The sample was recruited as part of a large, longitudinal study - the Personality and Total Health (PATH) Through Life project - which measured the health and well-being of young (20-24 years), middle-aged (40-44) and older adults (60-64), on three occasions (waves), four years apart. Across the total sample, clinically significant levels of depression were more prevalent in those who had sustained a TBI, regardless of the length of time that had elapsed since their injury.

The next study (Chapter 5) focussed on anxiety, with data from 41 studies meta-analysed in order to examine the prevalence of generalized anxiety disorder (GAD) and self-reported 'cases' of clinically significant anxiety. Anxiety was also found to be common after TBI, with 11% of people formally diagnosed with GAD and 37% reporting clinically significant levels of anxiety on self-report questionnaires.

Lastly, data from the PATH study were analysed (Chapter 6) in order to compare the levels of self-reported anxiety in people with and without a TBI. In cross-sectional analyses, across the total sample, clinically significant levels of anxiety were more prevalent (at each wave) in people who had incurred a TBI, regardless of the time that had elapsed since the injury. Moreover, comorbid anxiety and depression in those with a TBI was common, reinforcing the need for clinicians to identify and treat both problems in order to minimise their cumulative burden. Importantly, this thesis highlights a broad range of variables that influence the prevalence of depression and anxiety and, thus, should be considered by researchers and clinicians alike.

DECLARATION

I, Amanda Osborn, certify that this work contains no material which has been accepted for the award of any other degree or diploma in my name, in any university or other tertiary institution and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text. In addition, I certify that no part of this work will, in the future, be used in a submission in my name, for any other degree or diploma in any university or other tertiary institution without the prior approval of the University of Adelaide and where applicable, any partner institution responsible for the joint-award of this degree.

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Amanda Osborn

Signed: _____ Date: _____

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ABBREVIATIONS

ACRM:	American Congress of Rehabilitation Medicine
AIS:	Abbreviated Injury Scale
APA:	American Psychiatric Association
APOE	Apolipoprotein E
AUDIT:	Alcohol Use Disorders Test
BAI:	Beck Anxiety Inventory
BDI:	Beck Depression Inventory
CDC:	Centers for Disease Prevention and Control
CES-D:	Center for Epidemiologic Scale – Depression
CI:	Confidence Interval
CIDI:	Composite International Diagnostic Interview
CIS:	Clinical Interview Schedule
CT:	Computed Tomography
DIS:	Diagnostic Interview Schedule
DSM:	Diagnostic and Statistical Manual
GAD:	Generalized Anxiety Disorder
GAS:	Goldberg Anxiety Scale
GCS:	Glasgow Coma Scale
GDS:	Goldberg Depression Scale
GEE:	Generalised Estimating Equations
HADS:	Hospital Anxiety and Depression Scale
HAM-D:	Hamilton Depression Rating Scale
ICD:	International Classification of Diseases
LOC:	Loss of Consciousness
Leeds:	The Leeds Scale for the Self-assessment of Anxiety and Depression
MADRS:	Montgomery Asberg Depression Rating Scale
MDD:	Major Depressive Disorder
MINI:	Mini-International Neuropsychiatric Interview
MOOSE:	Meta-Analysis of Observational Studies in Epidemiology

MRI:	Magnetic Resonance Imaging
N_{fs}:	Failsafe *N* statistic
NFI:	Neurobehavioral Functioning Inventory
OR:	Odds Ratio
PATH:	PATH Through Life Project
PHQ-9:	Patient Health Questionnaire -9
PSE:	Present State Examination
PTA:	Post-Traumatic Amnesia
PTSD:	Post-Traumatic Stress Disorder
SADS-L:	Schedule for Affective Disorders and Schizophrenia
SCAN:	Schedules for Clinical Assessment in Neuropsychiatry
SCID-1:	Structured Clinical Interview for DSM-IV Axis I Disorders
STAI:	State Trait Anxiety Inventory
TBI:	Traumatic Brain Injury
UK:	United Kingdom
US:	United States
W1:	Wave one PATH assessment
W2:	Wave two PATH assessment
W3:	Wave three PATH assessment
WHO:	World Health Organization
ZSDS:	Zung Self-rating Depression Scale

PREFACE

Context

Traumatic brain injuries (TBI) are one of the leading causes of death and disability, creating a substantial public health and socio-economic burden (World Health Organization [WHO], 2006). It is estimated that approximately 5.3 million people in the United States (US), and nearly 7.7 million people in Europe, are living with a permanent TBI-related disability (Rubiano, Carney, Chesnut, & Puyana, 2015). Moreover, the incidence of TBI (new TBIs per annum) is rising (Maas, 2016), with increasing motor vehicle use in low- to middle-income countries, more falls in older adults, and heightened public awareness about the importance of seeking medical attention, all contributing to higher rates (Faul & Coronado, 2015; Peeters et al., 2015; Roozenbeek, Maas, & Menon, 2013). These data suggest that epidemiological research that informs the prevention and treatment of TBIs needs to be intensified (Faul & Coronado, 2015; Maas, 2016; Roozenbeek et al., 2013).

The consequences of sustaining a TBI can be substantial. At an individual level, these commonly encompass functional, psychological and cognitive impairments (Andelic et al., 2009; Mathias & Alvaro, 2012; Rabinowitz & Levin, 2014; Whelan-Goodinson, Ponsford, Johnston, & Grant, 2009a). These impairments can, in turn, affect relationships, employment status, participation in sporting and leisure activities, and the ability to undertake 'normal' daily activities (e.g., travelling independently on public transport, driving) (Colantonio et al., 2004; Grauwmeijer, Heijenbrok-Kal, Haitsma, & Ribbers, 2012; Schwab, Gudmudsson, & Lew, 2015; Wise et al., 2010; Wood, Liossi, & Wood, 2005). Importantly, the aforementioned functional constraints further impact at a societal level, with substantial economic costs and loss of productivity resulting from full or partial disability (for a review see Humphreys, Wood, Phillips, & Macey, 2013). Although all TBI sequelae warrant attention, the current thesis will focus on two common outcomes: depression and anxiety. Both psychological problems are

known to considerably undermine an individual's quality of life, however, their impacts following TBI are not yet fully understood.

Motivation / problem statement

The prevalence of depression and anxiety (proportion of individuals experiencing these problems at any given time) varies widely in the extant literature, hampering clinicians' and researchers' understanding of the extent of these disorders within given populations. It is also difficult to identify who is most at risk of developing depression and/or anxiety following a TBI and when they are most susceptible. Crucially, this constrains our capacity to understand the trajectory of psychological problems following a TBI which, in turn, hampers clinicians' ability to identify and implement interventions for those who are most in need.

Currently, it is uncertain whether variability in the reported rates of depression and anxiety reflects different methodologies. For example, data relating to the incidence, prevalence, characteristics, risk factors and outcomes of TBIs are collected in a variety of epidemiological and clinical contexts; each of which has unique limitations. Whereas large-scale population studies are likely to encounter challenges in the accurate/consistent identification of TBI incidence data, clinical studies are hampered by recruitment and retention issues (Corrigan, Selassie, & Orman, 2010; Van Reekum, Cohen, & Wong, 2000). Adding to this is the fact that researchers have often examined samples that are heterogeneous in terms of their injury and pre- and post-morbid characteristics and, moreover, that depression and anxiety are frequently measured using a variety of assessment methods. These differences reduce the utility of findings by limiting the capacity to make direct comparisons and, thus, impact on the conclusions that can be drawn. Further, an estimated 30-40% of people who suffer a TBI do not seek medical attention, resulting in a large proportion of those who have sustained a TBI being overlooked (Setnik & Bazarian, 2007). Currently, clinicians and

researchers have little understanding of whether, and to what extent, these individuals suffer from depression and/or anxiety.

Aim and scope

The aim of this thesis was, therefore, to investigate depression and anxiety following TBI in order to advance our understanding of the frequency and severity of these outcomes, and to improve the clinical utility of this research. Although a wide range of neuropsychiatric conditions can occur after a TBI (e.g., social phobias, schizophrenia, obsessive-compulsive disorder), this thesis sought to improve our understanding of the two *most common* psychological problems, depression and anxiety, following TBI. Moreover, depression and anxiety are often comorbid, suggesting that both separate and joint consideration of these problems will contribute unique and crucial information.

Importantly, the present thesis focuses on civilian TBIs (i.e., excludes both veterans and those currently serving in the military) because combat environments expose military personnel to high levels of physical and emotional trauma, which increases their risk of psychological problems compared to civilians (Chapman & Diaz-Arrastia, 2014). Thus, military and civilian samples should be investigated independently. Individuals with penetrating TBIs (e.g., gunshot wounds) and acquired brain injuries that had a non-traumatic aetiology (e.g., stroke, tumour, meningitis) were also excluded because the causes, mechanisms, neuropathological damage and outcomes of these injuries differ from non-penetrating TBIs (e.g., blunt head trauma) (Coetzer, Daisley & Newby, 2013; Ylioja, Hanks, Baird, & Millis, 2010). Finally, adults, rather than children, were examined because differences in anatomical, physiological and behavioural development have the potential to influence TBI outcomes (McCrory, Collie, Anderson, & Davis, 2004).

Significance

This thesis was designed to augment our understanding of the long-term impact of a TBI on the depression and anxiety outcomes of adults who have sustained a TBI in a civilian/non-military setting (e.g., motor vehicle & sporting accidents, falls, assaults). Moreover, it will investigate depression and anxiety in both clinical and community-based (non-medical) settings. This enabled a comprehensive examination of these problems among those sustaining TBIs, regardless of whether they had contact with a healthcare system at the time of their injury; thus incorporating people who might otherwise be overlooked in the literature. In particular, this research is intended to assist clinicians by identifying those people who are most at risk of suffering from depression and anxiety after injury, thereby facilitating timely and effective treatment.

Overview of thesis structure

The findings from two meta-analyses and two longitudinal community-based studies are presented in four papers, reported here as separate chapters. Of these papers, three have been published, with the remaining paper in press:

(1) Osborn, A. J., Mathias J. L., & Fairweather-Schmidt A. K. (2014). Depression following adult, non-penetrating traumatic brain injury: A meta-analysis examining methodological variables and sample characteristics. *Neuroscience and Biobehavioral Reviews, 47*, 1-15. doi: 10.1016/j.neubiorev.2014.07.007

(2) Osborn, A. J., Mathias J. L., & Fairweather-Schmidt A. K. (2016) Prevalence of anxiety following adult traumatic brain injury: A meta-analysis comparing measures, samples and postinjury intervals. *Neuropsychology*, *30*(2), 247-261. doi: 10.1037/neu0000221

(3) Osborn, A. J., Mathias J. L., Fairweather-Schmidt A. K. & Anstey, K. J. (2016). Anxiety and comorbid depression following traumatic brain injury in a community-based sample of

young, middle-aged and older adults. *Journal of Affective Disorders*. Advance online publication. doi: 10.1016/j.jad.2016.09.045

(4) Osborn, A. J., Mathias J. L., Fairweather-Schmidt A. K. & Anstey, K. J. (in press). Traumatic brain injury in a community-based sample: a cohort study across the adult lifespan. *Journal of Head Trauma Rehabilitation*.

The thesis structure comprises seven chapters. Chapter 1 reviews the literature on TBI, with a particular emphasis on its epidemiology, risk factors, causes and potential functional, cognitive and psychological outcomes. Chapter 2 reviews methodological and sample characteristics that may impact on depression and anxiety outcomes after a TBI, after which the aims of the thesis are outlined.

The next four chapters contain four journal articles, constituting the empirical research components of this thesis; with each possessing a preamble detailing the study rationale and further contextualising it within the broader research goals. Specifically, Chapter 3 provides a meta-analysis examining depression following TBI, with the findings separately detailed according to various methodological (diagnostic criteria, interview schedule/self-report scale, method of administering self-report scales, type of control group) and sample (time post-injury, injury severity) characteristics. Chapter 4 augments these findings by comparing the depression outcomes of people, with and without a TBI, who were randomly selected from the general population within Australia. Thus, because this study was community-based, there was a greater likelihood of sampling people with mild TBIs who do not seek medical attention and whose outcomes are often overlooked in the existing literature.

Although depression is thought to be the most common psychological problem after a TBI, anxiety is also prevalent and often comorbid with depression, potentially magnifying the negative impact on quality of life. For this reason, Chapter 5 meta-analyses research examining anxiety after a TBI; again highlighting differences in the prevalence rates due to the

approach taken by researchers (i.e., clinical interview and diagnostic criteria employed, self-report questionnaires and their method of administration, time post-injury, injury severity). Following on from this, Chapter 6 examined participants from the general community; but investigated anxiety, and its comorbidity with depression, thereby adding to our understanding of how TBI impacts jointly on anxiety and depression.

Each of the articles was originally prepared to meet the requirements of the respective journals to which they were submitted: Neuroscience and Biobehavioral Reviews; Neuropsychology; the Journal of Head Trauma Rehabilitation and; the Journal of Affective Disorders. However, to ensure consistency, the bibliographic style of the American Psychological Association, Publication Manual (Sixth edition) (American Psychiatric Association, 2009) has been used, and American English spelling applied consistently across the thesis. Accordingly, the chapters may vary slightly from the published and/or submitted versions. A combined reference list for the entire thesis is provided at the end of the thesis, rather than references at the end of each chapter. Tables and figures are numbered consecutively and inserted at the appropriate place within each chapter, and online supplementary material referred to within a chapter is located at the end of that chapter in order to assist the reader.

Finally, Chapter 7 synthesises the findings of each of the studies and discusses the broader issue/conclusions. Limitations of the research are identified, as are the clinical implications of the findings. Suggestions for future research are also discussed.

CHAPTER 1: TRAUMATIC BRAIN INJURY

This chapter reviews the literature on TBI, including its definition, neuropathology, epidemiology, risk factors and causes, in addition to physical, cognitive, behavioural and psychological outcomes. Importantly, it underscores the methodological diversity of TBI research by discussing the different injury classification systems and methods of recording/collating TBI incidence data.

1.1 Definition, types and neuropathology of TBI

Definition

TBI is defined as an "alteration in brain function, or other evidence of brain pathology, caused by an external force" (Menon, Schwab, Wright, & Maas, 2010 p 1638). This consensus definition proposed several clinical signs that are used to identify an 'alteration in brain function', with at least one required in order to diagnose a TBI. Specifically, these signs involve a loss or decreased level of consciousness, an altered mental state (e.g., confusion, disorientation), an inability to remember events either before (retrograde amnesia) or after (post-traumatic amnesia) the injury, and/or neurological deficits, including weakness, loss of balance and changes in vision. Alternatively, there may be neuropathological indications of a TBI (e.g., positive findings on Magnetic Resonance Imaging [MRI]/Computed Tomography [CT]). Lastly, various aetiologies have been specified, including: a foreign body penetrating the brain; the head striking, or being struck by, an object; the brain undergoing an acceleration/deceleration movement without direct external trauma; blast-related injuries; and, other forces yet to be defined (Menon et al., 2010).

Types

The above definition encompasses the two main types of TBI, penetrating (open) and non-penetrating (closed) (Ylioja et al., 2010). Although this distinction is broad, it is important, because the acute clinical management and subsequent outcomes of each type differ (Hawryluk & Manley, 2015). Penetrating TBIs are caused by a moving projectile or sharp inanimate object (e.g., bullet) fracturing the skull, perforating the dura mater, and exposing the cranial vault to the external environment (Santiago, Oh, Dash, Holcomb, & Wade, 2012); and often result in high mortality rates (Ylioja et al., 2010). As penetrating TBIs constitute only a minority (< 10%) of head injuries and have differing aetiology and outcomes (Baguley, Slewa-Younan, Lazarus, & Green, 2000; WHO, 2006), they are not a focus of the present thesis and, thus, are not discussed further.

In contrast, non-penetrating TBIs can be caused by contact injuries, which result from the brain moving and coming into contact with the inner surface of the skull (McAllister, 2008). This type of injury can lead to bruising of the cortical tissue (cortical contusions) and haemorrhaging within the brain (McKee & Daneshvar, 2015). Bleeding can occur above or below the dura mater (epidural and subdural hematomas, respectively), within the cerebral tissue (intracerebral), and/or in the subarachnoid space (Nolan, 2005). Non-penetrating TBIs can also be caused by inertial forces generated during the rapid acceleration or deceleration of the brain (McAllister, 2011). These rotational (rapid rotations of the head) or linear (no head rotation) forces generate shear, tensile and compression forces throughout the brain, causing the brain to stretch and deform (Meaney & Smith, 2011; Santiago et al., 2012). This then affects both axons and blood vessels, resulting in diffuse axonal injury, tissue tears and intracerebral haematomas (McAllister, 2008).

An increasingly common form of non-penetrating TBI results from forces generated by the detonation of improvised explosive devices in combat zones (Ling et al., 2013). These explosions generate ‘blast-winds’, which are rapidly moving waves of over-heated, over-

pressurised air that are immediately followed by a reversal of pressure (low pressure trough) (McAllister, 2008; McKee & Daneshvar, 2015). Blast-winds are particularly damaging to fluid-filled organs (i.e., the brain) and, in conjunction with the risk of the head striking an object (e.g., ground, building structure) or being hit by fragments or debris from the explosion, blast-related TBIs can be particularly destructive to the brain (McAllister, 2011). This thesis focuses on civilian TBI thus, injuries sustained in combat zones are not discussed further.

Primary vs secondary damage

The neuropathological trajectory of a TBI is complex because damage can occur both at the time of injury (primary damage) and in the days and weeks following an injury (secondary damage) (Maas, Stocchetti, & Bullock, 2008). Primary injuries are the direct result of an external force damaging neurons, axons, dendrites, glia and blood vessels, and contrast with secondary damage, which results from a subsequent series of complex cellular, inflammatory, mitochondrial, neurochemical and metabolic alterations (McKee & Daneshvar, 2015). Once the injury has occurred, the immediate neuropathological damage is generally not modifiable. However, the secondary processes may be reversible, with acute post-injury triage intended to limit this subsequent wave of damage, thereby optimising the patient's long-term outcomes (Hawryluk & Manley, 2015; McKee & Daneshvar, 2015). Treatment may include the stabilisation and ongoing management of temperature, blood and intracranial pressure, as well as monitoring of ventilation techniques and oxygenation parameters (see Algattas & Huang, 2014 for a review).

Assessment of neuropathological damage

Although the damage that is sustained during a TBI can be assessed using neuroimaging techniques such as MRI/CT, people with milder injuries may not undergo imaging or, if they do, may not exhibit positive findings (Saatman et al., 2008). This may be due to a lack of damage or, alternatively, reflect the poor sensitivity of current neuroimaging

techniques, which limits the detection of small amounts of damage (Bigler, 2014). Abnormalities identified using neuroimaging can be classified using the Marshall CT classification system, which divides patients into six categories, according to the type and extent of neuropathological damage (Marshall et al., 1991). More recently, the Rotterdam score was developed to improve the prognostic value of the Marshall score (Maas, Hukkelhoven, Marshall, & Steyerberg, 2005); with both classification systems being used to determine injury severity and predict outcome (e.g., mortality) (Mata-Mbemba et al., 2014).

The precise pathophysiological mechanisms underpinning the clinical sequelae associated with TBIs is not yet clear, although both primary and secondary damage is thought to provide the neurological substrate for many of the cognitive and psychological changes that follow TBIs (Jorge & Starkstein, 2005; Sherin & Nemeroff, 2011). Specifically, diffuse axonal injury, microvascular changes, the breakdown of the blood-brain barrier, and a cascade of toxic metabolic processes that follow an injury (immunoexcitotoxicity) have all been implicated (Bailes, Dashnaw, Petraglia, & Turner, 2014).

1.2 TBI severity

A number of methods have been developed to classify the severity of a TBI, often relying on different aspects of patient functioning. Whereas some methods focus on a person's level of consciousness (e.g., Glasgow Coma Scale score [GCS]; Teasdale & Jennett, 1974), others focus on the observable structural properties of the brain (e.g., Abbreviated Injury Scale score; Committee on Medical Aspects of Automotive Safety, 1971). Moreover, alternative methods have been developed more recently in order to overcome some of the limitations of existing indices (e.g. , Full Outline of Unresponsiveness scale; Wijdicks, Bamlet, Maramattom, Manno, & McClelland, 2005). Each of these scales, in addition to other measures of injury severity, are discussed below.

Glasgow Coma Scale

GCS scores are the most widely used index of TBI injury severity because of their capacity to establish and monitor a patient's status during the early phases of recovery (Corrigan et al., 2014; Saatman et al., 2008). The GCS was initially introduced as a standardised graphical scale that was designed to provide a neurological assessment of patients in severe comas (>6 hours; Teasdale & Jennett, 1974) and was later adapted for use as an index of injury severity (Jennett, 2002; Rimel, Giordani, Barth, Boll, & Jane, 1981; Rimel, Jane, & Edlich, 1979). GCS scores range from 3 to 15 and are divided into three levels, with patients classified as having mild (13-15), moderate (9-12) or severe (3-8) TBI (Rimel, Giordani, Barth, & Jane, 1982). Mild TBIs are, on occasion, further categorised as 'complicated' if there is evidence of intracranial brain pathology, because this has been shown to result in more symptoms and disability, compared to individuals who have a GCS of 13-15, but no intracranial lesions (uncomplicated TBI) (Esselman & Uomoto, 1995; Williams, Levin, & Eisenberg, 1990).

The GCS has limitations, however, because it is susceptible to the confounding effects of sedation, alcohol intoxication and paralysis (Hawryluk & Manley, 2015). Moreover, its prognostic value is limited by its failure to consider extracranial injuries (e.g., organ system failure, facial injuries) and demographic information that is of prognostic importance (e.g., age) (Malec et al., 2007a; Povlishock, 2008; Saatman et al., 2008). Thus, the capacity of the GCS to discriminate between a patient's clinical course and prognosis has been widely debated, with some researchers advocating that the three injury categories (mild, moderate, severe) show distinct differences, while others are less convinced (for reviews see Hawryluk & Manley, 2015; McKee & Daneshvar, 2015).

Loss of consciousness

The period of unconsciousness immediately after a TBI (i.e., loss of consciousness [LOC]) is also used as an indicator of TBI severity, although this criterion is used much less frequently because most mild TBIs are not associated with LOC (Carroll, Cassidy, Holm, Kraus,

& Coronado, 2004). Thus, LOC is limited as an index of severity both by its inability to account for the full spectrum of TBIs and the fact that it can be difficult to get a reliable estimate. For example, witnesses may be unable to determine whether someone actually lost consciousness and patients may be unable to provide reliable information *because* of their injury (Lovell, Iverson, Collins, McKeag, & Maroon, 1999). Further, there is evidence that self-reported estimates of LOC are often unreliable, with one study reporting that most patients over-estimated LOC duration to such an extent that their injury severity classifications were changed, in some cases from mild to severe (Sherer et al., 2015). Nonetheless, a recent meta-analysis found that, overall, when LOC duration had been *medically verified*, LOC was an accurate predictor of cognitive impairment, both in the short- and long-term (Konigs, 2016).

Post-traumatic amnesia

Post-traumatic amnesia (PTA) refers to the state of confusion occurring immediately following a TBI (Russell & Smith, 1961) and is another commonly used measure of TBI severity. Specifically, PTA is measured as the length of time between the injury and when the individual is orientated and able to form new memories, and is used to guide clinical decision-making and determine prognostic outcomes (Langhorn, Sorensen, & Pedersen, 2010; Sherer, Struchen, Yablon, Wang, & Nick, 2008; Vos et al., 2012). The continued presence, or resolution, of PTA is used as a tool to monitor the recovery and early cognitive functioning (e.g., decision-making capability) of patients, plan the timing of their discharge from hospital, and determine rehabilitation requirements (Marshman, Jakabek, Hennessy, Quirk, & Guazzo, 2013). The duration of PTA also enables clinicians to estimate likely functional outcome, with many studies reporting that longer periods of PTA are associated with poor recovery (for a review see Ahmed, Bierley, Sheikh, & Date, 2000).

Abbreviated Injury Scale / Injury Severity Score

Also used in clinical and research environments, although less frequently, are injury severity indices which are based on structural or anatomical injury to the brain. For example, the Abbreviated Injury Scale (AIS) uses neuroradiologic or operative findings to rank anatomic injury to the head on a scale of 0 to 6 (from normal to lethal) (States, Fenner, & Flamboe, 1971). The Injury Severity Score, on the other hand, is a composite measure derived from the AIS score and is used in cases of multiple trauma and, thus, more severe injury (Baker, O'Neill, Haddon Jr, & Long, 1974). Both AIS and Injury Severity Scores have been shown to correlate more highly with functional outcome than GCS Scores (Foreman et al., 2007).

Barell matrix

Another index incorporating anatomical data is the Barell matrix, which was developed to standardise and simplify the process of classifying injuries using the International Classification of Diseases codes (9th edition, ICD-9) (Barell et al., 2002). There are three Barell types associated with TBI that combine both structural (recorded evidence of intracranial injury) and functional information, as reflected in length of LOC (none, <1 hour/unknown, moderate/prolonged) (Barell et al., 2002). Although numerous studies use the Barell matrix to classify both intra- and extra-cranial injuries (Eskridge et al., 2012; Han, Newmyer, & Qu, 2015; Tin Tin, Woodward, & Ameratunga, 2010; Wojcik, Stein, Bagg, Humphrey, & Orosco, 2010), few utilise this matrix to examine functional, cognitive or psychological outcomes following TBI (Corrigan et al., 2014; Horner, Selassie, Lineberry, Ferguson, & Labbate, 2008).

Mayo Classification System for TBI Severity

The Mayo Classification System for TBI Severity was developed to address problems arising from incomplete clinical information in patient files (e.g., missing GCS scores and neuroimaging findings) by using the *available* clinical evidence to determine injury severity (Malec et al., 2007a). TBIs are classified as moderate-severe (definite), mild (probable) or

symptomatic (possible), based on a combination of indicators ranging from death (definite TBI) to single symptoms, such as blurred vision, dazed, headache or nausea (possible TBI) (Malec et al., 2007a). A recent epidemiological study examining injury severity and outcomes in older adults attempted to use both the Mayo Classification System and Barell matrix to classify TBI injury severity (Scheetz, 2015). However, 22% of the sample was unable to be assigned a rating because the data could not be aligned between the two systems; thus highlighting the challenges involved in comparing and evaluating study outcomes when disparate methodologies have been used.

Full Outline of Unresponsiveness (FOUR) scale

The FOUR scale has been proposed as an injury severity rating scale that can provide *more* neurological detail than the GCS when a patient is in a coma and, additionally, is easy to use and can predict outcome. There are four testable components (eye and motor response, brainstem reflexes, respiration) with a maximal grade of four in each category, and higher scores indicating less severe TBI (Wijdicks et al., 2005). It is thought to overcome some of the limitations of the GCS, including the inability of the GCS to generate verbal scores in intubated patients and to test brainstem reflexes originating from pupil and corneal reflexes, in addition to eye response which is assessed by both the GCS and FOUR (Bordini, Luiz, Fernandes, Arruda, & Teive, 2010; Widjicks et al., 2005). Nevertheless, as yet, it is not frequently used (Hawryluk & Manley, 2015).

1.3 Incidence, causes and risk factors for TBI

Incidence

Recent research from the US has highlighted the dramatic annual increase in TBI-related emergency department visits from 1.2 million cases (1995) to 2.1 million cases (2009); equating to an increase in age-adjusted rates per 100,000 people from 434.1 to 686.0

(Coronado et al., 2012). Similarly, the number of TBI-related hospitalisations has risen from 253,280 to 300,667 per annum; although the rate per 100,000 people in the population remains stable (95.5 to 95.7) (Coronado, et al., 2012). In contrast, mortality rates display a different pattern: in the 1970s, they decreased dramatically as a result of modern neuroimaging techniques and improved therapeutic approaches, such as resuscitation in the field, aggressive respiratory and circulatory support, and better management of intracranial pressure (Gerber, Chiu, Carney, Härtl, & Ghajar, 2013; Stein, Georgoff, Meghan, Mizra, & Sonnad, 2010). However since then, mortality rates have remained relatively static, with 52,833 deaths in the U.S. in 1995, and 52,695 deaths in 2009 (Coronado et al., 2012). This stability is partly due to fewer motor-vehicle related deaths, more effective prehospital triage, and improved emergency and neurotrauma services in hospitals, each of which has served to *decrease* mortality rates. However, the population is also ageing, resulting in an associated *increase* in fall-related deaths; thereby negating decreases in mortality rates (Coronado et al., 2012; Roozenbeek et al., 2013).

The incidence estimates often cited for TBI do not include data from individuals who sought medical treatment from a hospital outpatient department or their general practitioner (Faul, Xu, Wald, & Coronado, 2010). These sources add a further 1.2 million people per annum (2007 – 2009) to commonly cited U.S. official estimates; an increase from 750,000 annually in 1995 – 1997 (Coronado et al., 2012). This increase may reflect the success of public awareness campaigns or updated sporting guidelines, which highlight the dangers of mild TBIs and encourage people to seek assistance following these injuries (Coronado et al., 2012). Nevertheless, many people do not seek any medical attention following a mild TBI (Corrigan et al., 2010; Roozenbeek et al., 2013; Setnik & Bazarian, 2007), resulting in a large sub-group of people who have sustained a TBI, but whose injuries and outcomes are not generally included in the literature.

Globally, the rates for the US are among the lowest, with a systematic review finding that the rates of hospital admissions per 100,000 people (incidence) were 103 for the US, 160 for India, 226 for Australia, 235 for Europe, and 344 for Asia (Tagliaferri, Compagnone, Korsic, Servadei, & Kraus, 2006). These TBI-related hospitalisation rates for the US are broadly consistent with data reported by Coronado et al. (2012), but variations in healthcare systems (e.g., case inclusion criteria, data collection procedures, hospital admission policies) and different methodologies (e.g., epidemiological versus clinical settings) all contribute to differences in these rates and highlight the difficulty in directly comparing rates across countries (Carroll et al., 2004; Corrigan et al., 2010; Maas et al., 2011; Menon et al., 2010; Peeters et al., 2015; Roozenbeek et al., 2013; WHO, 2006). A later review building on Tagliaferri et al.'s (2006) work, found the incidence of hospitalised TBIs in Europe had risen to 262 per 100,000 people (Peeters et al., 2015), consistent with US data.

Causes

The primary causes of TBI follow a tri-modal pattern, reflecting changes over the lifespan (Bruns & Hauser, 2003; Centers for Disease Control and Prevention [CDC], 2014; Roozenbeek et al., 2013). Falls are the most common cause of TBI in the early and late stages of life, when very young children and the elderly are most likely to experience issues with strength and stability (Faul & Coronado, 2015). In contrast, motor vehicle accidents are the most common cause among those aged 15 to 24 years (Faul & Coronado, 2015). Although improved road safety and in-vehicle protective measures – such as seat-belts and airbags – have decreased accident and injury rates in developed countries, motor vehicle accidents continue to be a leading cause of TBI-related mortality (CDC, 2014; Faul et al., 2010; Peeters et al., 2015; Roozenbeek et al., 2013). In lower-income countries, an increase in TBIs has predominantly been associated with the greater use of motor vehicles, resulting in a higher rate of TBIs in pedestrians, cyclists, motorcyclists, and motor vehicle occupants (Roozenbeek et al., 2013).

Risk factors

One of the primary risk factors for sustaining a TBI is sex, with males being, on average, 1.4 times more likely to sustain a TBI than females and, although this varies across the lifespan, TBI rates are higher for males than females at every age (Faul et al., 2010). The disparity is greatest (more than double) between boys and girls in adolescence (10-14 years old), but decreases by 75 years of age, by which time the rates are almost at parity (Faul & Coronado, 2015). In adolescence and early adulthood, males are more likely to engage in high-risk activities, behaviours and occupations, such as participation in contact sports, involvement in assaults and military employment; resulting in higher rates of TBI (Colantonio, 2016; Corrigan et al., 2010). In contrast, the high rates of fall-related TBIs experienced by the very young and elderly are, mostly, the result of stability problems that are less affected by a person's sex.

In addition, those who have already incurred a TBI are at an increased risk of experiencing another, regardless of the severity of their initial injury, with subsequent TBIs potentially having a cumulative impact on cognitive and behavioural impairments (Faden & Loane, 2015; Guskiewicz et al., 2007; Theadom et al., 2015). Moreover, people with pre-existing drug and alcohol problems (Graham & Cardon, 2008; Olson-Madden, Brenner, Corrigan, Emrick, & Britton, 2012) or who have consumed alcohol on the day-of-injury, are also more likely to sustain a TBI (Corrigan, 1995; Parry-Jones, Vaughan, & Miles Cox, 2006; Tagliaferri et al., 2006).

People with pre-existing psychological problems – including depression and anxiety disorders – are also more likely to sustain a TBI (Rao, Koliatsos, Ahmed, Lyketsos, & Kortte, 2015; Vassallo, Proctor-Weber, Lebowitz, Curtiss, & Vanderploeg, 2007). Few studies have examined the reasons for this increased risk, but the associated symptoms, such as decreased attention and concentration, physical difficulties (e.g., motor tension, shakiness and fatigue),

increased agitation and impulsivity, and impaired judgement and distractibility, have all been implicated (Fann et al., 2002). These symptoms have the potential to increase the likelihood of motor vehicle accidents (e.g., slower reaction times), contribute to lower levels of self-care, and increase risk-taking behaviours and carelessness; each of which may lead to a TBI (Fann et al., 2002).

Identifying those most at risk of incurring a TBI is important because, although primary prevention is the key strategy for reducing the burden of TBIs, preventing *all* TBIs is considered to be an impractical goal (CDC, 2014). Thus, if a TBI does occur, an improved understanding of the consequences is critical for mitigating a broad range of possible negative health and social effects (Binder, Corrigan, & Langlois, 2005). A review of a range of outcomes is provided below.

1.4 Outcomes following a TBI

TBIs are associated with a variety of physical, medical, cognitive, behavioural and emotional problems, which may substantially undermine a person's overall quality-of-life (Scholten et al., 2015). Moreover, some of these symptoms may have bidirectional influences on each other. For example, being depressed may lead to compromised cognitive functioning, potentially exacerbating TBI-related cognitive problems (Silver & Arciniegas, 2007). Importantly, the majority of research conducted on functional, cognitive, behavioural and psychological outcomes following a TBI is derived from samples recruited from hospitals and rehabilitation facilities (Bay & Donders, 2008; Bombardier et al., 2010; Brown, McCauley, Levin, Contant, & Boake, 2004; Bryant et al., 2010; Chiu et al., 2006). These individuals are more likely to be seriously injured and/or have been referred to support services for assistance with TBI sequelae; thus, they may be experiencing greater physical, cognitive and

psychological problems, than those not seen in these settings, potentially inflating reported symptom levels (Dworkin, 1992).

Physical and medical outcomes

The main physical consequences of TBIs include headaches (Lew et al., 2006), dizziness and impaired balance (Peterson & Greenwald, 2015), chronic pain (Lavigne, Khoury, Chauny, & Desautels, 2015), sleep difficulties (Mathias & Alvaro, 2012; Shekleton et al., 2010), physical fatigue (Englander, Bushnik, Oggins, & Katznelson, 2010), sexual dysfunction (Moreno, Arango Lasprilla, Gan, & McKerral, 2013), bladder and bowel incontinence (Safaz, Alaca, Yasar, Tok, & Yilmaz, 2008), and musculoskeletal dysfunction and gait abnormalities (Safaz et al., 2008; Williams, Morris, Schache, & McCrory, 2009). Moreover, in the long-term, individuals may also have an increased risk of developing a range of medical conditions, including epilepsy (Ferguson et al., 2010), stroke (Chen, Kang, & Lin, 2011), dementia (Wang et al., 2012), multiple sclerosis (Kang & Lin, 2012), chronic traumatic encephalopathy (Ling, Hardy, & Zetterberg, 2015), Parkinson's disease (Bower et al., 2003), autonomic dysregulation (Kanjwal, Karabin, Kanjwal, & Grubb, 2010), and pituitary dysfunction (Moon, Sutton, Wilson, Kirkham, & Davies, 2010).

Cognitive outcomes

Cognitive deficits are also a common consequence of TBI and can occur at all levels of injury severity (Rabinowitz & Levin, 2014). Indeed, the clinical signature of a TBI includes impaired consciousness, alterations in mental state and memory loss (Menon, et al., 2010). The cognitive domains that are most often affected by TBI include memory, attention, processing speed and executive functioning (Mathias & Wheaton, 2007; Rabinowitz & Levin, 2014). In addition, language and communication (McDonald et al., 2014), intellectual ability (Königs, Engenhorst, & Oosterlaan, 2016), judgement and decision-making (Cotrena et al., 2014), and planning abilities (Shum et al., 2009) may also be disturbed. All of these areas are

critically important to a person's quality-of-life; affecting their work performance, social relationships, and daily living (Rao et al., 2015).

Behavioural outcomes

Behavioural problems are also frequent consequences of TBI and may interfere with rehabilitation, in addition to professional, social and family reintegration (Arnould, Dromer, Rochat, Van der Linden, & Azouvi, 2016). Changes to behaviour range from minor exaggerations of pre-injury traits (e.g., increased irritability) to fundamental changes in the way a person responds (e.g., outright aggression) (Arciniegas & Wortzel, 2014; McAllister, 2008). Decreased levels of motivation and goal-directed activity (e.g., reduced productivity) are also common after a TBI (Starkstein & Pahissa, 2014), and can range from mildly diminished functioning to incapacitating levels of apathy (Silver & Arciniegas, 2007). Additionally, a TBI may lead to inappropriate verbal responses and/or behaviours due to increased levels of disinhibition, whereby an individual has a diminished, or significantly reduced, ability to appreciate social or cultural behavioural norms (Arciniegas & Wortzel, 2014); or impulsiveness, because they have failed to fully consider the implications of their words and/or actions (McAllister, 2008). Elevated levels of impulsivity have additionally been associated with a range of other problematic outcomes, such as irritability and poor decision-making (Arnould et al., 2016; Rochat, Beni, Annoni, Vuadens, & Van der Linden, 2013), highlighting the complexity of interactions between cognitive and behavioural disturbances.

Psychological outcomes

Lastly, a diverse range of psychological problems have been reported after a TBI (see Rao et al., 2015, for review). These include emotional dysregulation, such as affective lability, which refers to an exaggerated tendency to be easily overcome with intense emotions, and pathological laughing/crying, which manifests as brief, intense, and uncontrollable episodes of emotional expression (Arciniegas & Wortzel, 2014). Psychiatric disorders are also common,

including major depression (MDD) (Diaz et al., 2012; Gould, Ponsford, Johnston, & Schonberger, 2011a; Jorge et al., 2004; Mortensen, Mors, Frydenberg, & Ewald, 2003; Orlovska et al., 2014; Whelan-Goodinson et al., 2009a) and generalized anxiety disorder (GAD; Hiott & Labbate, 2002; Van Reekum et al., 2000); both of which are the focus of the present thesis and discussed in detail in Chapter 2.

Other anxiety disorders have also been diagnosed post-TBI, including social anxiety disorder, which is characterised as intense anxiety/fear in social situations and is primarily centred around a fear of negative evaluation from others (Bryant et al., 2010). Also prevalent is panic disorder, whereby an individual experiences abrupt surges of intense fear/discomfort combined with associated somatic symptoms (e.g., sweating, trembling), and agoraphobia, which develops as a result of marked anxiety/fear triggered by a real or anticipated exposure to specific situations (e.g., using public transport, being in open/enclosed spaces) (Bryant et al., 2010; Hibbard, Uysal, Kepler, Bogdany, and Silver, 1998). Post-traumatic stress disorder (PTSD) has also been frequently examined following TBI, especially in military settings (Combs et al., 2015; Gould et al., 2011a; Hoge et al., 2008). However, there has been a long-standing debate about whether PTSD is possible following moderate to severe TBI, due to the associated period of post-traumatic amnesia (for a review see Rogers & Read, 2007). Further, psychotic disorders (Fann et al., 2004; Molloy, Conroy, Cotter, & Cannon, 2011; Orlovska et al., 2014), substance abuse and dependence disorders (Bryant et al., 2010; Silver, Kramer, Greenwald, & Weissman, 2001), and suicidality (Anstey et al., 2004; Silver et al., 2001) have also been associated with TBI.

Impact on daily living

These multifaceted impairments have a substantial impact on many aspects of a person's life. General day-to-day functioning, such as driving, using public transport, meal preparation, household chores and child-care, may all be affected (Goverover, Genova, Smith,

Chiaravalloti, & Lengenfelder, 2016). Family relationships may become strained with partners, parents and children having to cope with changes in their relative and alterations in their family dynamics (Douglas & Spellacy, 1996; Ponsford & Schönberger, 2010). In particular, spouses of those incurring a TBI may lose their source of emotional support, companionship and sexual intimacy, while also needing to adjust to substantial changes in role expectations, such as increased parental and financial responsibilities (for reviews see Blais & Boisvert, 2005; Moreno et al., 2013). A person's employment status is often compromised after a TBI, applying additional challenges because returning to work is usually a primary goal and is considered to be a critical measure of successful rehabilitation (Levack, McPherson, & McNaughton, 2004; Saltychev, Eskola, Tenovuo, & Laimi, 2013). Meaningful employment, characterised by work that the individual perceives to be important, not only provides financial security, but has also been shown to contribute to psychological well-being (Coetzer, Carroll, & Ruddle, 2011; Grauwmeijer et al., 2012; Tsaousides, Ashman, & Seter, 2008).

After a TBI, people often report experiencing a reduction in the types of activities that they enjoy and tend to participate in them less frequently — or for shorter periods of time — while also often needing greater assistance from others (Wise et al., 2010). Moreover, the types of physical or leisure activities undertaken often change from outdoor (e.g., sports, fishing) to more sedentary, home-based activities (e.g., watching television, listening to music), leading to fewer opportunities for physical exercise and social engagement (Morton & Wehman, 1995). Limitations in mobility and reduced functional independence — in addition to cognitive problems affecting concentration, memory and motivation — may also contribute to reduced participation (Larsson, Björkdahl, Esbjörnsson, & Sunnerhagen, 2013; Wise et al., 2010). Thus, not surprisingly, studies consistently report that quality of life and life satisfaction are negatively impacted following a TBI (Andelic et al., 2009; Forslund, Roe, Sigurdardottir, & Andelic, 2013; Hawthorne, Gruen, & Kaye, 2009; Horneman, Folkesson, Sintonen, von Wendt, & Emanuelson, 2005; Pagulayan, Temkin, Machamer, & Dikmen, 2006;

Powell, Gilson, & Collin, 2012; Stålnacke, 2007; Van Der Horn, Spikman, Jacobs, & Van Der Naalt, 2013).

Despite the consistent finding that quality of life reportedly worsens after a TBI, there is a continuing debate in the literature about whether severely-injured individuals are able to perceive their impairments and limitations (see Bach & David, 2006, for review). This lack of awareness has been described as a multifaceted issue, which not only affects the ability of those who have sustained a TBI to recognise their impairments, but also leads to difficulties detecting day-to-day problems as they emerge, and a reduced understanding of the long-term consequences of their situation (Crosson et al., 1989). Moreover, a lack of insight can negatively impact on rehabilitation (e.g., return to work) and social interactions (e.g., family relationships) (Port, Willmott, & Charlton, 2002) and, additionally, may impact on assessments of outcome that are based on self-report questionnaires (Bach & David, 2006; Kreutzer, Seel, & Gourley, 2001).

Overview

In summary, TBIs are common and may result in substantial negative outcomes, affecting both the individual (physical, medical, cognitive, behavioural and psychological difficulties) and the broader society in which they live (e.g., economic costs, productivity loss). These impairments can impact on the individual's relationships and their ability to function independently, thereby reducing their overall quality of life. A variety of injury assessment methods (e.g., GCS, PTA, FOUR, Mayo Classification System for TBI Severity) have been developed in order to assist clinical decision making, but there is currently no agreement about the best approach for classifying injuries. Moreover, there are many potential negative outcomes following a TBI, but some of the most common and potentially debilitating (regardless of injury severity), are psychological problems. For this reason, the current thesis focused on depression and anxiety after a TBI.

CHAPTER 2: DEPRESSION AND ANXIETY AFTER A TBI

This chapter reviews research specifically relating to depression and anxiety after a TBI. In particular, it considers how differences in the conceptualisation and measurement of depression and anxiety, and in the samples that are assessed, may influence prevalence rates.

One of the difficulties associated with interpreting and comparing the existing literature is that the words *depression* and *anxiety* are terms used in both lay and clinical vernaculars. Clinically (the focus of the current thesis), they refer to psychological conditions characterised by a cluster of symptoms that are highly correlated with specific emotional states (Grohol, 2016). Depression and anxiety commonly encompass a constellation of symptoms that are grouped into three domains: physical (e.g., disturbed sleep and appetite, muscle tension), cognitive (e.g., depressed mood, fear, worry) and behavioural (e.g., reduced energy and libido, avoidance of situations). These symptoms may range in severity from mild sadness and apprehension (in the case of depression and anxiety, respectively) to extremely debilitating levels of distress (Rieger, 2008). The requisite number and type of symptoms (i.e., symptom cluster) can be indicative of either a clinically diagnosed psychiatric disorder (e.g., Major Depressive Disorder [MDD], Generalized Anxiety Disorder [GAD]) or can provide an assessment of symptom severity/level (e.g., clinical significance) using self-report scales. Both conceptualisations of depression and anxiety are discussed in further detail below. In terms of psychiatric disorders, the current thesis focuses only on MDD/dysthymia and GAD. Moreover, only self-reported — not informant-rated (e.g., parent, partner, caregiver) — symptoms of depression and anxiety are examined.

2.1 Depression and anxiety conceptualised as psychiatric disorders

Diagnoses of MDD and/or GAD are usually made using one of two sets of criteria, namely the Diagnostic and Statistical Manual of Mental Disorders (DSM-III, DSM-III-R, DSM-IV, DSM-5, American Psychiatric Association [APA]; 1980, 1987, 2001, 2013) and the International Classification of Diseases (ICD-9, ICD-10, World Health Organization [WHO]; 1977, 1992). The DSM criteria, rather than ICD, tends to be more frequently used in clinical settings (Andrews, Slade, & Peters, 1999). These diagnostic criteria are applied using structured interviews, such as the Structured Clinical Interview for DSM-IV - Axis 1 Disorders (SCID-1; First, Spitzer, Gibbon, & Williams, 1997), Schedules for Clinical Assessment in Neuropsychiatry (SCAN; Wing et al., 1990) and Composite International Diagnostic Interview (CIDI; Robins, Wing, Wittchen, & et al., 1988). For the purposes of this thesis, the term MDD is used to signify corresponding nomenclature across the different versions of the DSM and ICD criteria (e.g., major depressive episode, depressive episode, recurrent depressive episode).

Major depressive disorder (MDD): diagnostic criteria

MDD is characterised in the DSM-5 by the presence of at least five of nine depressive symptoms across a two week period: (1) depressed mood, (2) loss of interest or pleasure, (3) significant weight or appetite changes, (4) insomnia or hypersomnia, (5) frequent observable agitation (e.g., pacing) or retardation (e.g., slowed speech), (6) fatigue, (7) feelings of worthlessness or inappropriate guilt, (8) reduced concentration or decisiveness, and (9) recurrent thoughts of death or suicidal behaviour. Importantly, items (1) and (2) are cardinal (primary) symptoms and, hence, at least one must be present in order to diagnose MDD (APA, 2013). It is also imperative that symptoms represent a change from previous functioning, cause clinically significant distress or impairment in important areas of functioning (e.g., social, occupational settings), and not be attributable to another medical condition or mental disorder, or the physiological effects of a substance (e.g., medication) (APA, 2013).

Major depressive disorder: prevalence

The prevalence of clinically diagnosed depression (MDD/dysthymia) varies widely in the literature but, on closer examination, it appears that much of this variability may arise from differing methodologies and samples. Nevertheless, it appears that clinically diagnosed depression is considerably higher after a TBI, compared with the general population (12 month prevalence: 7%) (APA, 2013).

One of the earliest studies to examine MDD following TBI was conducted by Fedoroff, Starkstein, Forrester, and Geisler (1992) who reported that 27% of their mild-moderate-severe TBI sample were diagnosed with MDD one month after their injury. A similar rate (26%) was reported by Fann, Katon, Uomoto, and Esselman (1995) although, in their study, three years had elapsed between the TBI and the assessment of depression. The latter study also found that an *additional* 28% of their sample had experienced MDD after their TBI, which had resolved prior to the assessment. Thus, at some point over the three year post-TBI period, approximately 54% of their sample experienced MDD.

A similar rate was reported by Hibbard et al. (1998) who found that 61% of their sample had experienced MDD following a TBI. However, on closer examination, it can be seen that 17% of the sample, had MDD before the TBI (*pre-morbid* depression) and 48% of participants had *new* MDD diagnoses (onset post-TBI). Further, of the 48% who had developed MDD after their injury, only 18% were suffering from depression at the time of the assessment (*current* MDD), with MDD *resolving* in the remaining 30%. This highlights the difficulty in accurately comparing findings across studies.

In terms of *current* MDD, a number of studies have also reported prevalence rates between 16-18% (Bryant et al., 2010; Koponen, Taiminen, Hiekkanen, & Tenovuo, 2011; Rao et al., 2010; Rapoport, McCullagh, Streiner, & Feinstein, 2003a). Although a narrow range, these studies varied in terms of injury severity: two of the four studies incorporate mild-moderate-severe TBIs and assessed MDD at either 3 or 12 months post-injury, while the remaining two

studies assessed only mild TBI at one month post-injury. These methodological differences highlight the difficulty in drawing conclusions about who is most at risk of experiencing depression after a TBI and when they are most vulnerable.

Other studies have reported moderate (30-34%) (Diaz et al., 2012; Gould et al., 2011a; Jorge et al., 2004; Whelan-Goodinson et al., 2009a) to high (≥ 50%) (Al-Adawi et al., 2007; Alexander, 1992; Sebit, Siziya, Ndetei, & Sande, 1998; Van Reekum, Bolago, Finlayson, & Garner, 1996) rates of MDD after a TBI, suggesting that these studies may also have differed in terms of their samples and methodology. Indeed, the source of participants, method of assessment, post-injury interval, injury severity, age of participants, proportion of males/females, medication usage, history of TBIs and psychological problems all differed between them, thereby making it difficult to ascertain what factors may be contributing to the variable prevalence rates.

Generalized anxiety disorder (GAD): diagnostic criteria

The essential feature of GAD in the DSM-5 is excessive anxiety and worry (apprehensive expectation) about a number of events or activities (e.g., work or school performance), which the individual finds difficult to control, causing clinically significant distress (APA, 2013). This anxiety or worry must be associated with at least three of six symptoms: (1) restlessness or feeling on edge, (2) becoming easily fatigued, (3) difficulty concentrating, (4) irritability, (5) muscle tension, and (6) sleep disturbance. In addition, these symptoms must have occurred more days than not, for at least six months. As with MDD, the symptoms must not be attributable to the physiological effects of a substance, another medical condition, or mental disorder (APA, 2013).

Generalized anxiety disorder: prevalence

Although fewer studies have examined GAD than MDD, they too have used a variety of methodologies; making it challenging to summarise the findings. Again, consistent with

diagnoses of MDD, the percentage of individuals diagnosed with GAD following a TBI is generally higher than the estimated 12 month prevalence (3%) for the general population (APA, 2013). A number of studies have reported that GAD occurs in 9% to 15% of samples with mild (Bryant et al., 2010), severe (Diaz, et al., 2012), or mild-moderate-severe (Hibbard et al., 1998; Jorge, 1993c) TBI, with the average post-injury interval ranging from one month (Jorge, 1993c) to nearly eight years (Hibbard et al., 1998). Two studies report that approximately one quarter (24%, 28%) of their sample were diagnosed with GAD in the three to five years following mild to severe TBI (Fann et al., 1995; Van Reekum et al., 1996). However, despite DSM-III diagnostic criteria being used in both studies, different clinical interviews were administered and, moreover, the samples differed in terms of their history of psychiatric disorders. One study listed this factor as an exclusion criterion (Van Reekum et al., 1996), the other reported that 50% of their sample had a previous psychiatric diagnosis (Fann et al., 1995).

In contrast, two studies have reported *lower* rates of GAD (2%) in their TBI samples than seen in the general population (Deb, Lyons, Koutzoukis, Ali, and McCarthy, 1999b; Koponen et al., 2002). Interestingly, the average time since injury reported in these two studies varied enormously (1 and 30 years, respectively). Thus, given the range of post-injury intervals, in addition to other varying methodological factors, it is also difficult to determine the rates of GAD, thereby reducing the clinical usefulness of the research.

Comorbidity of MDD and GAD

Surprisingly few studies have examined comorbidity rates in TBI samples, despite the fact that MDD and GAD are well known to co-exist (Slade & Andrews, 2009). The two studies that have examined comorbid GAD and MDD found that *all* persons with GAD, had comorbid MDD (Jorge, 1993c; Van Reekum et al., 1996). Others have looked at depression/anxiety problems, more generally, with one finding that 69% of people who had an anxiety disorder

also had a mood disorder (Gould et al., 2011a) and others reporting that, of those with MDD, more than 70% had a comorbid anxiety disorder (Jorge et al., 2004; Whelan-Goodinson et al., 2010).

In the US general population, 58% of people with GAD have also been found to meet the criteria for MDD (Kessler, DuPont, Berglund, & Wittchen, 1999), with these high comorbidity rates leading to ongoing debate about the diagnostic validity of GAD. Some suggest that GAD is a prodrome (an early symptom predicting the onset) of MDD, while others argue that they are distinct disorders (Hunt, Slade, & Andrews, 2004; Kessler et al., 2008; Mathew, Pettit, Lewinsohn, Seeley, & Roberts, 2011; Wittchen, Carter, Pfister, Montgomery, & Kessler, 2000). Importantly, although MDD and GAD are both disabling, their impact is magnified when they occur together (Kessler et al., 1999). Specifically, comorbid conditions lead to greater symptom severity and disability (Hunt et al., 2004; Lecrubier, 2001), greater difficulty performing work and social roles (Kessler et al., 1999), higher rates of suicidal behaviour (Lewinsohn, Rohde, & Seeley, 1995), mental health treatment utilisation (Hämäläinen, Isometsä, Sihvo, Pirkola, & Kiviruusu, 2008) and medical costs (Marciniak et al., 2005).

2.2 Self-reported depression and anxiety

Self-report measures have also been used to identify clinically significant 'cases' of depression and anxiety using defined cut-offs (i.e., on a categorical scale) and, additionally, to identify the full spectrum of symptoms on a continuous scale (e.g., minimal to severe). These questionnaires are frequently used to screen for mental health problems and to examine both the prevalence and severity of depression and anxiety following TBI. Although the gold standard for psychological assessment is generally considered to be a structured interview and subsequent clinical diagnosis (see Section 2.1), psychological problems occur along a continuum (Clarke & Kuhl, 2014; Hyman, 2010). Thus, self-report questionnaires are valuable

for identifying individuals who have less serious psychological problems, but whose psychosocial functioning may still be affected (Mendlowicz & Stein, 2000).

Prevalence of clinically significant levels of depression and anxiety

Rates of clinically significant 'cases' of depression vary widely, with prevalence ranging between 18% (Van Der Horn et al., 2013), 26% (Weddell, 2010), 31% (Forslund et al., 2013), 36% (Dikmen, Bombardier, Machamer, Fann, & Temkin, 2004), 40% (Malec, Brown, Moessner, Stump, & Monahan, 2010), 54% (Evans, Sherer, Nick, Nakase-Richardson, & Yablon, 2005), 60% (Chen, Johnston, Petrides, & Ptito, 2008), and 72% (Alfano, 2006). Each of these studies varied in their methodology (e.g., the self-report scale selected, method of administration), in addition to having different sample characteristics (e.g., varying injury severity and time elapsed since the TBI), making it difficult to directly compare them and limiting the conclusions that can be drawn about the prevalence of clinically significant depression after a TBI.

Similarly, the rates of clinically significant 'cases' of self-reported anxiety range broadly between 9% (Al-Adawi et al., 2007), 22% (Van Der Horn et al., 2013), 28% (Powell, Heslin, & Greenwood, 2002), 36% (Schnieders, Willemsen, & De Boer, 2012), 43% (Wood & Williams, 2008), 57% (Ma et al., 2014), and 72% (de Almeida Lima, Filho, de Campos Vieira Abib, & Poli de Figueiredo, 2008). Once again, there is little understanding about what is contributing to this variation, particularly given the differing methodologies and samples that have been used.

Differences between self-report measures

The clinical utility of research that examines self-reported depression and anxiety (i.e., clinically significant 'cases' or levels) after a TBI is often hampered by a range of methodological issues. There are a number of self-report measures that have been used with TBI samples and, although the questionnaires are based around similar constructs, the specific set of symptoms vary between instruments. Table 2.1 highlights the differences between the items for the three most commonly-used depression scales: the Hospital Anxiety and

Depression Scale (HADS; Zigmond & Snaith, 1983), Beck Depression Inventory (BDI; Beck, Steer, & Brown, 1996), and the Center for Epidemiologic Studies Depression Scale (CES-D; Radloff, 1977). The items have been broadly grouped according to the DSM-5 diagnostic criteria for major depressive disorder: mood/affect, diminished interest/pleasure, somatic, worthlessness/guilt, cognitive and suicidality. Notably, this figure highlights the fact that there is a limited amount of overlap between the three measures in terms of the specific items or the way in which they are phrased (e.g., crying versus laughter).

Item differences are likely to have arisen because many self-report measures were not designed for use with TBI groups or in medical settings, which has the potential to impact on the accuracy of reported rates. For example, the CES-D was developed for use with the general population, consequently it may contain items that are influenced by the physical consequences of a TBI (e.g., poor sleep, fatigue, dizziness), potentially inflating the prevalence of depression in TBI samples. In contrast, the HADS was developed specifically to avoid using somatic symptoms that are common to both depression and physical illnesses (e.g., fatigue); focusing, instead, on the emotional aspects of depression (e.g., the extent to which people feel happy).

Table 2.1.

Comparison of the items used to assess depression: Beck Depression Inventory-II, Hospital Anxiety and Depression Scale (depression sub-scale) and Center for Epidemiologic Studies Depression Scale.

Questionnaire items	BDI-II	HADS	CES-D
MOOD/AFFECT			
Feel sad much of the time / I felt that I could not shake off the blues / I felt depressed / I felt sad	✓		✓ ✓ ✓
I cry more than I used to / I had crying spells	✓		✓
I can laugh and see the funny side of things		✓	
I feel cheerful / I was happy		✓	✓
I am not discouraged about my future / I felt hopeful about the future	✓		✓
I am much more irritable than usual	✓		
I was bothered by things that usually don't bother me			✓
I felt fearful			✓
I felt lonely			✓
LEVEL OF INTEREST / PLEASURE			
I am less interested in other people or things than before	✓		
I am much less interested in sex than I used to be	✓		
I don't enjoy things as much as I used to / I still enjoy the things I used to enjoy / I enjoyed life	✓	✓	✓
I have lost interest in my appearance		✓	
I look forward with enjoyment to things		✓	
I can enjoy a good book or radio or TV programme		✓	
I talked less than usual			✓
SOMATIC			
I feel more restless or wound up than usual	✓		
I have less energy than I used to have / I could not get going / I felt that everything I did was an effort	✓		✓ ✓
I sleep a lot more than usual / My sleep was restless	✓		✓
I get more tired or fatigued more easily than usual	✓		
My appetite is much less than before / I did not feel like eating, my appetite was poor	✓		✓
I feel as if I am slowed down		✓	
WORTHLESSNESS/GUILT			
I have failed more than I should have / I thought my life had been a failure	✓		✓
I feel guilty over many things I have done or should have done	✓		
I feel I may be punished	✓		
I have lost confidence and am disappointed in myself	✓		
I am more critical of myself than I used to be	✓		
I felt that I was just as good as other people			✓
I don't consider myself as worthwhile and useful as I used to	✓		
People were unfriendly			✓
I felt that people dislike me			✓
COGNITIVE			
I find it more difficult to make decisions than usual	✓		
I can't concentrate as well as usual / I had trouble keeping my mind on what I was doing	✓		✓
SUICIDALITY			
I have thoughts of killing myself	✓		

Note: BDI-II: Beck Depression Inventory, 2nd edition; HADS: Hospital Anxiety and Depression Scale; CES-D: Center for Epidemiologic Studies - Depression Scale. The above sub-categories are broad groupings representative of the diagnostic criteria for major depressive disorder (DSM-5).

Similarly, Table 2.2 compares the items used in the three most commonly-used measures of self-reported anxiety: the Beck Anxiety Inventory (BAI; Beck, Epstein, Brown, & Steer, 1988), HADS and the State-Trait Anxiety Inventory (STAI; Spielberger, 1970). The items are divided into 'anxiety/worry' and 'somatic' categories, which are broadly consistent with DSM-5 diagnostic criteria for GAD. The differences between measures is striking, with the BAI, which was developed for use with psychiatric patients, having many somatic items (e.g., dizziness, feeling hot, trembling, heart pounding). In contrast, the STAI and HADS have a larger proportion of items that reflect feelings of anxiety and/or worry. In those who have a sustained a TBI, the somatic nature of the BAI items may lead to inflated prevalence rates, however this has not yet been evaluated.

Table 2.2.

Comparison of the items used to assess anxiety: Beck Anxiety Inventory, Hospital Anxiety and Depression Scale (anxiety sub-scale) and State-Trait Anxiety Inventory (state anxiety).

Questionnaire items	BAI	HADS	STAI
ANXIETY / WORRY			
Fear of worst happening	✓		
Terrified or afraid / I get a sort of frightened feeling as if something bad is about to happen	✓	✓	
Nervous / I get a sort of frightened feeling like butterflies in the stomach / I feel anxious / I feel nervous	✓	✓	✓ ✓
Fear of losing control	✓		
Fear of dying	✓		
Scared	✓		
Worrying thoughts go through my mind / I am presently worrying over possible misfortunes / I am worried		✓	✓ ✓
I feel calm / I am at ease / I feel comfortable / I am relaxed / I am content			✓ ✓✓ ✓ ✓
I get sudden feelings of panic		✓	
I feel secure			✓
I am regretful			✓
I feel upset			✓
I feel self-confident			✓
I am jittery			✓
I feel “high-strung”			✓
I feel over-excited and “rattled”			✓
I feel joyful			✓
I feel pleasant			✓
SOMATIC			
Numbness or tingling	✓		
Feeling hot	✓		
Wobbliness in legs	✓		
Unable to relax / I feel tense or wound up / I feel restless and have to be on the move / I feel tense / I can sit at ease and feel relaxed	✓	✓ ✓✓	✓
Dizzy or lightheaded	✓		
Heart pounding/racing	✓		
Unsteady	✓		
Feeling of choking	✓		
Hands trembling	✓		
Shaky / unsteady	✓		
Difficulty in breathing	✓		
Indigestion	✓		
Faint / lightheaded	✓		
Face flushed	✓		
Hot/cold sweats	✓		
I feel rested			✓

Note: BAI: Beck Anxiety Inventory; HADS: Hospital Anxiety and Depression Scale; STAI: State Trait Anxiety Inventory (state anxiety). The above sub-categories are broad groupings representative of the diagnostic criteria for generalized anxiety disorder (DSM-5).

2.4 Biopsychosocial model

The preceding discussion highlights the fact that there is considerable variability in the prevalence rates reported for depression and anxiety. There are many different variables that may be contributing to this variability, thus, this thesis uses the prevailing biopsychosocial model of health in order to better understand some of the reasons for the varying prevalence rates. The biopsychosocial model emerged in response to the need for an 'holistic' approach to health care and contrasts with the traditional reductionist biomedical methodology used by clinicians (Engel, 1980). It posits that disease and illness/injury - and a person's vulnerability to them - are dynamic systems, just as people's systems dynamically adapt to changing situations over the course of their lives (Molina, 1983). The biopsychosocial model was developed to improve our understanding of the complex interaction between the biological, psychological and social factors that influence functioning (Engel, 1980). As such, it provides a useful conceptual framework by which to identify a range of factors that may be relevant to the development of depression and anxiety after a TBI. To this end, a variety of known risk factors for depression and anxiety, separated into the *biological*, *person* and *social* categories proposed by the biopsychosocial model, are discussed below.

2.4.1 *'Biological'* factors potentially associated with post-TBI depression and anxiety

Biological influences on the development of depression and anxiety following TBI are both varied and complex. For instance, age may impact on psychological problems after a TBI, but the relationship is complex because there is an increased risk of both formal diagnoses and 'cases' of depression after a TBI in both younger (Bombardier et al., 2010; Deb & Burns, 2007; Rapoport et al., 2003a) and older (Rao et al., 2010; Glenn, O'Neil-Pirozzi, Goldstein, Burke, & Jacob, 2001; Sigurdardottir, Andelic, Røe, & Schanke, 2013) adults. Similarly, studies that have examined age as a risk factor for anxiety after a TBI have found conflicting results. Some studies have reported an increased risk in adults less than 65 years of age, compared to older

adults (> 65 years; Deb & Burns, 2007; Horner et al., 2008). In contrast, others that have examined the full adult spectrum (18 – 75 years) report that older adults have a greater risk of psychological problems (Gould, Ponsford, Johnston, & Schonberger, 2011b; Whelan-Goodinson, Ponsford, Schonberger, & Johnston, 2010). In terms of the very young, childhood TBIs have been shown to lead to an elevated risk for psychological problems over the life-course (Rosema et al., 2014; Timonen et al., 2002). Moreover, the earlier a child's TBI, the greater their problems with depression and anxiety in adolescence and adulthood (Corrigan et al., 2013; Karver et al., 2012), possibly because their underlying neurodevelopmental processes have been compromised during a critical stage of development (Garcia, Hungerford, & Bagner, 2015).

Sex may also be an important variable because females are 1.5 to 3 times more likely to suffer from MDD, and twice as likely to be diagnosed with GAD, in the general community (APA, 2013). This imbalance in the number of cases of depression/anxiety appears to equalise post-TBI, but findings are inconsistent and may be influenced by the disproportionate number of males who sustain TBIs (Anstey et al., 2004). Moreover, some studies of clinical samples have found no differences between the sexes in terms of clinically significant depression (Seel & Kreutzer, 2003) or anxiety (Liossi & Wood, 2009), but others have reported higher levels of depression and anxiety both in females (Dischinger, Ryb, Kufera, & Auman, 2009; Hart et al., 2011; Iverson et al., 2011) and males (Burton & Volpe, 1988; Dikmen et al., 2004).

Genetic susceptibility is increasingly being considered important to the development of psychological problems. To this end, Apolipoprotein E (APOE) ∈4 allele status has frequently been researched; however, as with cognitive and functional outcomes (Mathias & Wheaton, 2015), APOE does not appear to be related to depression after a TBI (Chamelian, Reis, & Feinstein, 2004; Koponen et al., 2002); although it has been associated with mood and behaviour disturbances (Ariza et al., 2006). Genetic differences in the serotonergic system,

which influences vulnerability to depression, have also been examined (Beck, 2008). The serotonin transporter gene, 5-HTT, is thought to be associated with MDD in patients without TBI (Trivedi et al., 2006), however Chan et al. (2008) found no evidence of an association between 5-HTT and MDD in their TBI sample. Nonetheless, other research on the same gene variant demonstrated varying risk profiles according to the time post-injury (6 or 12 months) (Failla et al., 2013), suggesting that additional research examining the temporal association between 5-HTT, depression and TBI is needed. Moreover, an association between anxiety and polymorphisms of the *BMX* gene has been found in a general community sample, thereby identifying a potential predictor of post-TBI anxiety symptoms Wang et al. (2014).

The remaining *biological* risk factors in the biopsychosocial model relate to injury characteristics. Specifically, 'injury characteristics' subsume the impact of neuropathological damage (including lesion location), neurochemical changes, injury severity and the length of time that has elapsed since the injury.

A variety of complex and dynamic neuropathological changes occur following a TBI, each of which has the potential to provide a biological basis for the development of depression and anxiety. For example, the shear, tensile and compressive strains experienced during a TBI can lead to diffuse axonal injury in the frontal and temporal lobes, disrupting the neural circuitry between the prefrontal cortex (higher executive functions), amygdala (memory related to emotional events), hippocampus (formation of episodic or autobiographical memories), basal ganglia (includes volitional control of movement) and thalamus (relay between subcortical and cerebral cortex) (Jorge & Robinson, 2002; Kumar & Cook, 2002; Morris, 2010; Silver, McAllister, & Arciniegas, 2009). This neuronal damage and cell loss can occur for weeks to months after an injury, and may provide the neurological substrate for many of the cognitive and psychological changes that occur after a TBI (Jorge & Starkstein, 2005; Sherin & Nemeroff, 2011). Moreover, neuroendocrinal abnormalities, compromised hypothalamic-pituitary-adrenal axis function and neurochemical changes, such

as cholinergic and serotonergic deficits, also occur in the acute post-TBI period, potentially causing depression and anxiety (Jorge & Starkstein, 2005; Rosenthal, 1998).

Investigations into lesion site as a risk factor for psychological problems in adults with a TBI have proven challenging because the neuroanatomical basis of psychological functioning has not yet been identified (Bhalerao et al., 2013). Nonetheless, an injury that selectively affects prefrontal and anterior temporal structures, with corresponding widespread axonal damage, may increase the likelihood of psychological problems (Jorge, 2015; Koenigs et al., 2008). Consistent with this, Rao et al. (2012) found white-matter changes in fronto-temporal regions were associated with both the development of MDD and more self-reported depressive symptoms in the first year after a TBI. In terms of anxiety among veterans with a TBI, self-reported symptoms were associated with focal brain damage in the left cortical and limbic areas of the left hemisphere (Knutson et al., 2013).

The relationship between injury severity and psychological problems is similarly inconclusive, with limited evidence to support a dose-response relationship between increasing injury severity and higher levels of depression and anxiety (Rapoport, 2012; Seel et al., 2003). Rather, many studies report that injury severity and psychological functioning are inversely related, with milder injuries often leading to more psychological distress (Alexander, 1992; Dikmen et al., 2004; Findler, Cantor, Haddad, Gordon, & Ashman, 2001; Kurtz, Shealy, & Putnam, 2007; Youngjohn, Davis, & Wolf, 1997). This paradoxical relationship has been linked to involvement in litigation (e.g., worker's compensation or insurance claims), whereby individuals with mild TBIs are thought to exaggerate their symptoms in order to maximise financial compensation (Berry, Schipper, & Clark, 2012; Bianchini, Curtis, & Greve, 2006).

Finally, the length of time that has elapsed since a TBI was sustained (post-injury interval) has also been examined as a risk factor for depression and anxiety following a TBI. In the short-term, neurophysiological changes potentially contribute to psychological problems

(Bombardier et al., 2010) and, in the longer term, psychosocial problems (e.g., reduced social functioning, loss of independence) are commonly implicated (Jorge, 2015). Assessments conducted in the acute/post-acute stages after a TBI (i.e., < 3months) have revealed high rates of depression and anxiety (Dikmen et al., 2004; Evans et al., 2005; Goldstein, Levin, Goldman, Clark, & Altonen, 2001; Ma et al., 2014), as do those conducted more than 10 years post-TBI (Draper, Ponsford, & Schonberger, 2007; Koponen et al., 2002; Senathi-Raja, Ponsford, & Schonberger, 2010; Whalley Hammell, 1994). The continuing high levels of symptomology appear to suggest that the risk of experiencing depression and/or anxiety after a TBI does not abate over time.

2.4.2 *'Person'* characteristics potentially associated with post-TBI depression and anxiety

The second element in the biopsychosocial model is the *'person',* which incorporates individual experiences and behaviour that may contribute to depression and anxiety after a TBI. Having previously had a TBI (prior TBI) has been shown to increase the risk of depression and anxiety in sports (Guskiewicz et al., 2007; Kerr, Marshall, Harding, & Guskiewicz, 2012), clincial (Dams-O'Connor et al., 2013) and community-based samples (Anstey et al., 2004; Corrigan et al., 2013; Horner et al., 2008). This heightened vulnerability is thought to be associated with the cumulative damage that is caused by multiple TBIs (Bailes et. al., 2014).

Prior psychological problems have also been linked to an increased risk of depression and anxiety after a TBI (Alway, Gould, Johnston, McKenzie, & Ponsford, 2016; Barker-Collo et al., 2015; Bombardier et al., 2010; Deb et al., 1999b; Gould et al., 2011a; Hart et al., 2011; Horner et al., 2008; Wäljas et al., 2015; Whelan-Goodinson et al., 2010). However, given that MDD is recognised as a chronic illness with an 80% risk of repeated episodes (Judd, 1997), it is notable that some studies have failed to find a relationship between prior- and post-TBI depression (Dikmen et al., 2004; Rapoport, McCullagh, Streiner, & Feinstein, 2003b). These contrary findings may reflect differences in the exclusion criteria that were applied, with some

studies excluding people with 'any' (Al-Adawi et al., 2007) or 'major' pre-morbid psychiatric histories (McCauley, Boake, Levin, Contant, & Song, 2001), and others excluding specific psychiatric conditions, such as schizophrenia, bipolar disorder, dementia and major depressive disorder (Rapoport et al., 2003b), or schizophrenia, bipolar disorder and drug abuse (Rapoport, Kiss, & Feinstein, 2006). Other, less common exclusion criteria that have been used include: non-psychotic and no depression prior to the TBI, as determined by an examiner (Peleg, Barak, Harel, Rochberg, & Hoofien, 2009), not currently in psychotherapy (Ashman, Cantor, Gordon, Spielman, Flanagan, Ginsberg, Engmann, Egan, Ambrose & Greenwald, 2009), and no premorbid history of serious brain impairment (Kinsella, Moran, Ford, & Ponsford, 1988). These differing, and often unclear, criteria make it difficult to draw conclusions about whether pre-morbid psychological history has an impact on post-TBI depression and anxiety.

The existing evidence suggests that cumulative stressful life experiences may also elevate the risk of psychological problems after a TBI (Bay, Kirsch, & Gillespie, 2004). This is thought to result from a process known as allostasis, which refers to the body's ability, when challenged, to increase or decrease vital functions in order to achieve a new steady-state (McEwan & Stellar, 1998). Allostasis is critical for survival, but the strain on the body (allostatic load) caused by the increased wear and tear on organs and tissues is thought to heighten the risk of disease or illness (McEwan, 1993). It has also been suggested that genetic vulnerability, combined with these recurrent physiological responses to stress, may increase the risk of mental health problems (Taylor, 2010). In the case of adult TBI, childhood adversity (e.g., bullying, sexual abuse, domestic violence, negative parenting) is a major cause of chronic pre-injury stress that has been linked with adult depression in clinical TBI samples (Bay et al., 2004), but has not yet been investigated in TBI samples drawn from the broader community. Moreover, major stressful life events experienced after a TBI — such as financial problems and relationship breakdowns — are also strongly associated with depression (Bay et al., 2004).

High levels of alcohol consumption, both pre- and post-injury, are additionally known to affect levels of depression and anxiety (Bombardier et al., 2010; Dikmen et al., 2004; Jorge et al., 2005). A large proportion of those who sustain a TBI have chronic alcohol abuse problems pre-injury (Corrigan, Rust, & Lamb-Hart, 1995), but currently there is no consensus about whether this is a risk factor for developing depression/anxiety after a TBI, with some studies finding an association (Bombardier et al., 2010; Dikmen et al., 2004) and others not (De Guise et al., 2009; Lange et al., 2014). Reasons for the potential association between chronic alcohol abuse and depression after a TBI are not clear. Nevertheless, structural brain changes associated with long-term alcohol consumption, maladaptive personality traits (e.g., impulsivity, novelty-seeking), and the desire to self-medicate have each been implicated as factors that may increase psychological risk after a TBI (Horner et al., 2005; Jorge et al., 2005). Of particular note is that the biological mechanisms involved in addictive behaviours and the regulation of emotion and mood overlap (Jorge et al., 2005). For instance, alcohol dependence and depression may both be associated with alterations in some of the same neurotransmitter systems (e.g., serotonin), especially those in limbic-related brain structures (Markou, Kosten, & Koob, 1998).

An individual's psychological predisposition, including their capacity to adjust to cognitive, functional and behavioural changes resulting from the TBI, may also influence the development of depression and anxiety (Arlinghaus et al., 2005). For example, the strategy that a person uses to deal with new situations and serious life events (coping style) may undermine or, alternatively, strengthen their ability to regulate negative emotions and stress (Van Der Horn, Liemburg, Aleman, Spikman, & Van Der Naalt, 2016). After a TBI, coping strategies that deal directly with difficult situations by actively attempting to change them (i.e., adaptive, problem-focused coping) rather than passive, emotion-focused strategies, tend to be associated with lower levels of depression and anxiety after a TBI (Curran, Ponsford, & Crowe, 2000; Gould et al., 2011b; Maestas et al., 2014; Sasse et al., 2014; Van Der Horn et al.,

2016). Closely related to coping is the concept of resilience, which is the ability to maintain relatively stable, healthy levels of psychological and physical functioning in the face of major adversity, such as violent or life-threatening situations (Bonanno, 2004). Resilient individuals have more positive views of themselves, the world and the future, and are more likely to experience positive emotions even in stressful situations, such as a TBI (Losoi et al., 2015). Although there is limited research examining the impact of resilience on post-TBI psychological outcomes, low levels of resilience have been associated with both depression and anxiety in those with mild (Losoi et al., 2015; McCauley et al., 2013) and mild to severe TBI (Lukow et al., 2015). This relationship may be partly explained by the fact that traits that characterise resiliency, such as emotional stability, effective communication skills and insightful modification of behaviour, are often lacking in those who have suffered a TBI (Lukow et al., 2015).

2.4.3 *'Social'* factors associated with depression and anxiety post-TBI

Family, community and societal factors have the potential to heighten or attenuate a person's vulnerability to mental health problems after a TBI (Engel, 1980; Molina, 1983). For example, greater social support from family, friends, associates and health providers has been found to reduce levels of depression and anxiety, thereby reinforcing the importance of strong social networks after a TBI (Douglas & Spellacy, 2000; Horner et al., 2008). This support is critical because it helps those who have had a TBI to 'buffer' the stress brought about by their physical, cognitive and psychological impairments (Driver, 2005; Finset, Dyrnes, Krogstad, & Berstad, 1995). Importantly, though, the types and sources of support tend to change over time. Rehabilitation programs primarily focus on reducing physical and cognitive impairments soon after the injury, whereas the family meets the longer-term social needs (Morton & Wehman, 1995). Ironically, at a time when interactions with friends are of increased importance, those who have had a TBI commonly report a gradual decline in contact with friends over time. This deterioration in peer contact is likely to occur due to TBI-associated

changes in personality, behaviour and functional ability (Driver, 2005). A loss of friendships may also be compounded by an inability to form *new* social contacts (Rosenthal et al., 1998) and the rejection, experienced as a result of contracting social support, may contribute to feelings of low self-esteem and depression (Morton & Wehman, 1995).

Interpersonal problems within marital relationships (i.e., spouse, intimate partner) also frequently result from TBI-related motor impairments, communication and behavioural problems, and personality changes (Bay, Blow, & Yan, 2012a). Moreover, there may be a significant shift in roles and expectations within the marital relationship after a TBI, with the caregiving spouse potentially receiving less support to manage the home, finances and children, experiencing reduced intimacy, and the loss of emotional support and companionship (Blais & Boisvert, 2005). These factors can lead to relationship conflict, further adding to the burden and possibly explaining why marriage does not protect against the stressors that are being experienced (Bay et al., 2012a; Demakis, Hammond, & Knotts, 2010).

Employment provides people with established support networks as well as a sense of purpose, identity, independence and financial security, such that a return to work is a common goal of rehabilitation programs (McCrimmon & Oddy, 2006; Saltychev et al., 2013). When this reintegration does not occur, though, unemployment and any associated financial stressors increase the negative impact on psychological status (Franulic, Carbonell, Pinto, & Sepulveda, 2004; Tsaousides et al., 2008; Whelan-Goodinson et al., 2010). However, clarity about the role that depression and anxiety may play in poor employment outcomes after a TBI is still lacking. A bi-directional relationship may also exist, whereby psychological problems prevent successful return-to-work or, alternatively, a failure to resume work or gain employment may trigger depression and anxiety (Coetzer et al., 2011).

As physical activity has been shown to reduce depression and anxiety in the general population, it is likely that the social opportunities afforded by participation in exercise and leisure activities may be important post-TBI (Driver & Ede, 2009; Wegner et al., 2014). Aside

from improving mental and physical health, physical activity enhances interpersonal interactions, cognitive functioning and the ability to perform daily activities (Gordon et al., 1998; Pawlowski, Dixon-Ibarra, & Driver, 2013; Schwandt et al., 2012). Despite these benefits, the physical and cognitive problems resulting from TBIs frequently lead to a reduction in leisure and physical activities (Rosenthal et al., 1998); thereby indirectly increasing the risk of depression and anxiety.

2.5 Summary

The available evidence suggests that both depression and anxiety are common after a TBI, however the prevalence estimates for each vary widely. Thus, it is difficult to identify who is most at risk of developing depression and/or anxiety after a TBI and when individuals are most vulnerable. This then hampers clinicians' ability to identify and implement targeted interventions for those who are most in need. While it is not yet known whether, or to what extent, differences in methodology or sample characteristics may impact on psychological problems following a TBI, they do provide a potential explanation for the disparity in prevalence rates. Thus, these factors require further examination.

Importantly, differences in the way that depression and anxiety are conceptualised (i.e., diagnosed disorders vs self-reported symptoms) and the way that they are measured are likely to lead to disparate prevalence rates. MDD and GAD can be diagnosed using different diagnostic criteria and interview schedules and, similarly, a wide variety of self-report measures have been used to assess depression and anxiety. Moreover, most research has used samples that have been sourced from clinical settings to determine rates of depression and anxiety, but these individuals are more likely to be seriously injured and experience greater physical, cognitive and psychological problems; possibly leading to higher rates of depression and/or anxiety (Dworkin, 1992).

Differences across the samples that are being assessed may also affect reported prevalence rates, with a variety of demographic, health and lifestyle variables likely to be important in the development of depression and anxiety after a TBI. These include age, sex, genetic susceptibility, injury characteristics (e.g., lesion location, time post-injury, injury severity) and pre-morbid history of psychological problems or TBIs. Moreover, current lifestyle factors, such as the experience of stressful life events, and the extent to which someone undertakes physical activity, consumes alcohol, or has a strong social network to provide support, may also be relevant. Lastly, differences in a person's psychological predisposition (e.g., coping style, resilience levels) may influence the onset of mental health problems. Although the biopsychosocial model discussed in the preceding literature review identified a wide range of risk factors for psychological problems after a TBI, it is not possible to examine all of these variables in this thesis. An examination of genetic susceptibility, lesion site and psychological disposition are beyond the scope of the present thesis and, hence, they are not further discussed.

2.6 Aims of the thesis

The over-arching aim of this thesis was to examine depression and anxiety in adults who have sustained a non-penetrating TBI. To this end, four studies were completed. First, a comprehensive meta-analysis of research that has examined depression following TBI was completed in order to determine the prevalence of depression (clinically diagnosed MDD/dysthymia, self-reported clinically significant cases/levels). Importantly, the impact on depression of a variety of methodological variables (diagnostic criteria, interview schedule/self-report scale, method of administering self-report scales, type of control group) and sample characteristics (time post-injury, injury severity) were evaluated.

The second study augmented the findings from the meta-analysis by examining data from a large, longitudinal, Australian population-based sample. The aim was to determine the prevalence of both TBI and depression in the community and, moreover, compare the depression outcomes of people both with and without a TBI. In addition, the association of TBI and depression across the adult lifespan (young, middle-aged and older adults) was also evaluated. Importantly, known risk factors for psychological problems following TBI – age, sex, marital/employment status, comorbid medical conditions (cancer, arthritis, heart problems, diabetes), multiple TBIs, recent stressful life events, alcohol consumption, and levels of social support and physical activity – were also evaluated to identify whether they are related to self-reported clinically significant depression.

Next, anxiety following adult, non-penetrating TBI was examined. A meta-analysis of research examining the prevalence of formally diagnosed GAD or self-reported 'cases' of clinically significant anxiety was first undertaken, in order to determine the prevalence of each after a TBI. Further, this third study aimed to determine the impact of diagnostic criteria, the measure used (clinical interview, self-report questionnaire), the time that had elapsed since the injury and the severity of the injury on the prevalence of GAD or clinically significant levels of anxiety.

The aim of the final study was to compare the prevalence of clinically significant anxiety in people with and without a TBI. In addition, the comorbidity of 'cases' of anxiety and depression was examined, because comorbidity can alter the clinical course of both problems and, additionally, worsen overall outcomes. Lastly, the association between TBIs and clinically significant anxiety across the lifespan was investigated, again taking a broad variety of demographic, health, and lifestyle variables into account.

CHAPTER 3: META-ANALYSIS – DEPRESSION FOLLOWING TBI

3.1 Preamble

This Chapter consists of a manuscript entitled "Depression following adult, non-penetrating traumatic brain injury: A meta-analysis examining methodological variables and sample characteristics", which has been published in *Neuroscience and Biobehavioral Reviews* (2014).

The previous literature review highlighted the variability in the findings of studies that have examined TBI and depression, leading to difficulties in comparing the research and drawing conclusions. For this reason, the first study meta-analysed research that has investigated depression after adult TBI in order to identify which methodological variables impact on the prevalence of depression following a TBI and assist clinicians to select the most appropriate research outcomes applying to their patient's specific circumstances.

Tables and Figures are embedded within the text to make it easier for the reader. Supplementary information relating to this paper is included at the end of the current chapter (pages 76-81) and incorporates: the literature search strategy (Table S1); the depression measures that were eligible for analysis in the current study (Table S2); the flowchart for the meta-analysis review and selection process (Table S3); and the specific details for the studies that were included in the meta-analysis, as well as the corresponding list of references (Table S4). A complete list of all references for the thesis, including those for this paper, has been provided at the end of the thesis (pages 208-237); references marked with an asterisk (*) indicate studies included in this current paper's meta-analyses.

Chapter 3: Paper one

Depression following adult, non-penetrating traumatic brain injury:

A meta-analysis examining methodological variables and sample characteristics

Authors: A. J. Osborn, J. L. Mathias, A. K. Fairweather-Schmidt

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3.2 Statement of Authorship

Statement of Authorship

Title of Paper	Depression following adult, non-penetrating traumatic brain injury: A meta-analysis examining methodological variables and sample characteristics
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Name of Principal Author (Candidate)	Amanda Osborn
Contribution to the Paper	Conducted literatures searches, coded articles, analysed and interpreted data, wrote manuscript and acted as corresponding author.
Overall percentage (%)	85%
Certification:	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.
Signature	Date: 14/10/16

Co-Author Contributions

By signing the Statement of Authorship, each author certifies that:

i. the candidate's stated contribution to the publication is accurate (as detailed above);
ii. permission is granted for the candidate in include the publication in the thesis; and
iii. the sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

Name of Co-Author	Jane Mathias
Contribution to the Paper	Supervised and contributed to the study design, analysis and data interpretation, and manuscript preparation.
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Please cut and paste additional co-author panels here as required.

3.3 Paper one

Abstract

Background: Depression is one of the most frequently reported psychological problems following TBI, however prevalence estimates vary widely. Methodological and sampling differences may explain some of this variability, but it is not known to what extent.

Methods: Data from 99 studies examining the prevalence of clinically diagnosed depression (MDD/dysthymia) and self-reports of depression (clinically significant cases or depression scale scores) following adult, non-penetrating TBI were analysed, taking into consideration diagnostic criteria, measure, post-injury interval, and injury severity.

Results: Overall, 27% of people were diagnosed with MDD/dysthymia following TBI and 38% reported clinically significant levels of depression when assessed with self-report scales. Estimates of MDD/dysthymia varied according to diagnostic criteria (ICD-10: 14%; DSM-IV: 25%; DSM-III: 47%) and injury severity (mild: 16%; severe: 30%). When self-report measures were used, the prevalence of clinically significant cases of depression differed between scales (HADS: 32%; CES-D: 48%) method of administration (phone: 26%; mail 46%), post-injury interval (range: 33% to 42%), and injury severity (mild: 64%; severe: 39%).

Conclusion: Depression is very common after TBI and has the potential to impact on recovery and quality of life. However, the diagnostic criteria and measure, as well as time post-injury and injury severity, all impact on prevalence rates and must therefore be considered for benchmarking purposes.

Keywords

Traumatic brain injury, Major Depression, Dysthymia, Prevalence, Meta-analysis, Adult, Self-report measures, Injury severity, Post-injury interval

Introduction

Traumatic brain injuries (TBI) can cause a variety of changes in cognitive, physical, and psychological functioning, which may impact on all areas of a person's life. Cognitive changes include problems with memory and attention, poorer executive functioning and slowed information processing (Bay, Kalpakjian, & Giordani, 2012b; Belmont, Agar, & Azouvi, 2009; Konrad et al., 2011; Rochat, Ammann, Mayer, Annoni, & Van Der Linden, 2009), with the physical consequences including headaches, sleep problems and fatigue (Cantor et al., 2012; Chaput, Giguère, Chauny, Denis, & Lavigne, 2009; Mathias & Alvaro, 2012). Psychological problems are also very common following TBI (for a review see Kim et al., 2007), with the most widely recognised and researched of these being depression (Hart et al., 2012; Rapoport, 2012).

The prevailing biopsychosocial model of health provides one framework for understanding some of the variables that may contribute to the development of these problems - including depression - following TBI (Helmchen, 2013). Specifically, this model posits that illnesses are caused by a complex interaction between a range of biological, psychological and social factors, with a person's vulnerability to illness changing over time (Molina, 1983). In the context of TBI, there are a variety of neuroanatomical changes that may provide a biological basis for the development of depression. For example, the shear, tensile and compressive strains experienced during a TBI can lead to diffuse axonal injury in the frontal and temporal lobes, disrupting the neural circuitry between the prefrontal cortex, amygdala, hippocampus, basal ganglia and thalamus (Jorge & Robinson, 2002; Kumar & Cook, 2002; Morris, 2010; Silver et al., 2009). This neuronal damage and cell loss can occur for weeks to months after an injury, and may provide the neurological substrate for many of the cognitive and psychological changes that occur after a TBI (Jorge & Starkstein, 2005; Sherin & Nemeroff, 2011). Neurochemical changes, such as cholinergic and serotonergic deficits,

neuroendocrinal abnormalities and compromised hypothalamic-pituitary-adrenal axis function, also occur in the acute period post-TBI; potentially also causing depression (Jorge & Starkstein, 2005; Rosenthal et al., 1998). Psychological variables - such as a diminished tolerance to frustration, impaired self-awareness, low self-esteem, and poor coping strategies - may additionally lead to depression after a TBI (Kelley et al., 2012; Malec, Testa, Rush, Brown, & Moessner, 2007b; Molina, 1983). Lastly, a variety of social factors – including a lack of social support, the loss of personal relationships/friendships, unrealistic expectations and involvement in litigation – may independently contribute to the development of depression following TBI or exacerbate symptoms that arise from any of the aforementioned causes (Dikmen, Machamer, Powell, & Temkin, 2003; Gunstad & Suhr, 2001; Iverson, Lange, Brooks, & Rennison, 2010b; Wäljas et al., 2014). Thus, there are a large number of variables that may explain why depression is a common problem after TBI.

Estimates of the prevalence of depression following TBI vary considerably – ranging from 6% to 77% (Rutherford, Merrett, & McDonald, 1977; Varney, Martzke, & Roberts, 1987). This variability not only seriously limits the clinical utility of these findings, but also raises questions about its source. Differences in how depression is conceptualised (diagnosed disorder vs self-reported symptoms), the diagnostic criteria and/or measures that are used to assess depression and a number of patient characteristics (e.g., injury severity), may explain a significant amount of this variance; however, we do not currently know to what extent these variables impact on estimates of the prevalence of depression following TBI.

The two most commonly diagnosed depressive disorders following TBI are major depressive disorder (MDD) and dysthymia (Gomez-Hernandez et al., 1997; Hibbard et al., 1998; Meares et al., 2011; Whelan-Goodinson et al., 2009a), which are generally determined using one of two criteria, namely the Diagnostic and Statistical Manual of Mental Disorders (DSM-III, DSM-IV, DSM-5; APA; 1987, 2001, 2013) or the International Classification of

Diseases (ICD-9, ICD-10; WHO; 1977, 1992). These disorders have overlapping symptoms, including depressed mood, disturbed sleep, low energy and poor concentration. Whereas a diagnosis of MDD requires the presence of five or more symptoms during a two-week period, dysthymia (also known as persistent depressive disorder) requires the presence of two symptoms for a minimum of two years (APA; 2013).

MDD and dysthymia are frequently diagnosed using one of a number of structured clinical interviews to determine whether their patients meet DSM or ICD criteria (e.g., Structured Clinical Interview for DSM-IV Axis I Disorders [SCID-I]; First et al., 1997). However, these interviews examine symptoms over different time periods - ranging from the previous week (e.g., the Clinical Interview Schedule [CIS]; Lewis, Pelosi, Araya, & Dunn, 1992) to the previous month (e.g., Schedules for Clinical Assessment in Neuropsychiatry [SCAN]; Wing et al., 1990) or preceding 6 months/year (e.g., Composite International Diagnostic Interview [CIDI]; Robins et al., 1988); which may have a significant impact on the resulting prevalence rates. Not only can the symptoms vary between these time-frames, but memory and other cognitive problems following TBI may affect the accuracy of the information that is reported (Hilsabeck, Gouvier, & Bolter, 1998). Therefore, differences in the diagnostic criteria and/or interview schedules that are used may be impacting on estimates of the prevalence of MDD and dysthymia.

Prevalence rates may additionally be affected by a number of sample characteristics, including the time interval between the injury and when depression is assessed. Some studies have found that MDD is more prevalent in the early stages after an injury (Bombardier et al., 2010; Lin et al., 2010), possibly reflecting neuroanatomical abnormalities or the cascade of neurochemical changes that occur in the acute post-TBI period (Jorge et al., 1993a). Conversely, others have found MDD and/or dysthymia are more common in the long-term (Al-Adawi et al., 2007; Rao et al., 2010), which may be more indicative of the psychosocial

challenges faced by individuals as they adjust to their altered life circumstances (e.g., lack of social support, reduced social functioning) (Jorge et al., 1993a). Similarly, the severity of an injury can range from minor to severe, with some studies examining mixed samples (mild, moderate and severe), others targeting specific injuries (e.g., mild or severe), and still others examining less common categories, such as minor (Van Der Horn et al., 2013) or complicated mild TBI (Bombardier et al., 2010; Fann et al., 2005; Juengst, Skidmore, Arenth, Niyonkuru, & Raina, 2013).

In addition, control groups are often also recruited to examine the base-rates of depression because depression is not unique to TBI, but the samples chosen for this purpose can vary. Typically, medical patients (Brown et al., 2004; Jorge et al., 2004), people from the general community (Belmont et al., 2009; Konrad et al., 2011; Ponsford & Ziino, 2003), or family and friends of the TBI group (Perlesz, Kinsella, & Crowe, 2000; Ponsford, Olver, Ponsford, & Nelms, 2003) are used for this purpose. Each one attempts to control for the potential impact of different variables (e.g., illness-related stress) on the prevalence of depression and, therefore, the base-rates are likely to differ between these groups. Once again, it is not known whether or how the choice of control groups impacts on the conclusions that are drawn regarding post-TBI rates of depression when they are used for comparative purposes.

Also important is the distinction between clinical diagnoses of MDD/dysthymia and assessments that use self-report questionnaires (e.g., Beck Depression Inventory [BDI]; Beck et al., 1996) to assess depression on a continuous scale (minimal to severe); often with the additional ability to identify clinically-significant levels of depression ('cases') using designated cut-off scores (dichotomous scale). Self-report scales are frequently used in clinical settings to screen for depression, and in research settings to examine the prevalence and severity of depression following TBI. However, many of these scales were not specifically designed for

use in TBI or medical settings; instead being intended for use with the general population (e.g., Center for Epidemiologic Scale - Depression [CES-D]; Radloff, 1977) or psychiatric patients (e.g., Hamilton Depression Rating Scale [HAM-D]; Hamilton, 1960). Consequently, they may contain items that can be affected by the physical consequences of a TBI (e.g., poor sleep, fatigue), which may inflate the prevalence of depression.

Furthermore, the way that clinicians or researchers administer questionnaires may affect the depression scores obtained on self-report scales. Various administration methods have been used, with some participants completing them at the research site (Hudak et al., 2011; Konrad et al., 2011), in their own home (Bushnik, Englander, & Wright, 2008; King & Kirwilliam, 2011), over the phone (Bombardier et al., 2010; Hart et al., 2011) or by using a combination of these methods (Hawthorne et al., 2009; Smith, 1992). Specifically, certain situations may elicit socially-desirable responses, provide fewer opportunities to reflect on and revise answers (e.g., telephone interviews), or be subject to other unidentified influences (e.g., mailed: when completed and whether completed alone/with others). These variables are known to have an impact on people's responses (for a review see Richman, Weisband, Kiesler, & Drasgow, 1999) and, consequently, should be considered in the current context.

Any one or more of these variables has the capacity to influence estimates of the prevalence of depression and may help to explain why the aforementioned statistics vary so widely. However, as yet, their impact has not been assessed. A systematic analysis of the prevalence of depression following TBI is needed to evaluate the impact of these variables and to assist clinicians in selecting the most appropriate benchmark(s) for their particular circumstance. The current study therefore meta-analysed existing research that has examined: (1) the prevalence of clinical diagnoses of MDD and dysthymia following TBI or (2) used self-report scales to assess the prevalence of clinically significant symptoms and/or the severity of depression. To this end, the impact of diagnostic criteria, interview schedule, post-

injury interval and injury severity on the prevalence of MDD/dysthymia was evaluated, as was the type of control group. In addition, the impact of questionnaire, method of administration, post-injury interval, injury severity and type of control group on self-reported measures of depression was examined.

2. Methods

2.1. Literature search, inclusion and exclusion criteria

Comprehensive searches of the PsycINFO, Pubmed, Scopus, and ISI Web of Knowledge electronic databases, from January 1980 to June 2013, were undertaken to identify studies that examined depression following TBI using search terms that were tailored for each database (see Supplementary data: Table S1, page 76). In addition, the reference lists of all studies that were included in the final analysis were examined to identify any other relevant research.

For a study to be included in the current meta-analysis, it had to meet the following criteria: (1) it examined depression following non-penetrating TBI; (2) participants were 18 years or older (where age range was not provided: mean age minus 1 SD ≥ 18); (3) it reported the prevalence of current MDD or dysthymia, which was formally diagnosed using DSM or ICD criteria, and/or 'cases' (clinically significant levels of depression), or depression scale scores from a common self-report depression scale (excludes general quality of life and mood-state measures, and study-specific or modified scales) (see Supplementary data Table S2, page 78, for a list of eligible measures); (4) data were provided for a TBI sample (single-sample) or both a TBI and control group (independent samples); (5) the data (prevalence rates, cases or depression scores) were reported in a way that enabled the calculation of an effect size; (6) was published in a journal in English and contained original data (excludes reviews); and (7) the sample size was greater than 15 (excludes very small samples and case studies).

Studies were excluded if participants were drawn exclusively from very specific or at-risk TBI populations - such as war veterans, prison inmates, victims of large-scale trauma/terrorism, or psychiatric populations - as their exposure to other traumatic events/situations may have increased their vulnerability to depression, rendering them less comparable to the broader TBI population. In addition, control groups were excluded if the group was very specific (e.g., depressed controls), depression was not assessed, or different depression scales were administered to the TBI and control groups. Moreover, if a study examined the efficacy of some form of treatment, only the pre-treatment data were analysed.

The literature search initially identified 8,399 potentially relevant articles, 2,217 of which were duplicates. The titles and abstracts of the remaining 6,182 articles were screened by the first author (AJO) using the aforementioned inclusion and exclusion criteria, after which the full-text versions of 459 studies were retrieved for detailed screening. Re-application of the inclusion criteria to these papers reduced the number of eligible studies to 99 (see Supplementary data: Table S3, page 79, for an overview of the study review and selection process). In ambiguous cases, papers were independently assessed by AJO and JLM, and eligibility determined following discussion.

Data that are meta-analysed must be obtained from independent samples (Rosenthal, 1995); consequently all studies were checked to establish independence. Six samples were followed longitudinally (two articles each); the data from these articles were combined, resulting in six independent studies; further reducing the final number of eligible studies to 93. Moreover, the data for the control groups from five studies were unsuitable for present purposes: only the TBI data from these studies were extracted (Capizzano, Jorge, & Robinson, 2010; Hawthorne et al., 2009; Reza, Ikoma, Ito, Ogawa, & Mano, 2007; Schnabel & Kydd, 2012; Wood & Williams, 2008).

2.2. Data preparation

Some basic data preparation was needed in order to render it suitable for analysis. Specifically, where demographic details were reported for TBI subgroups that were not relevant to the current analyses (e.g., fatigued vs non-fatigued TBI patients), the data were combined. If median and range were reported (e.g., age), the mean and SD were estimated using the methods recommended by Hozo, Djulbegovic, and Hozo (2005). In addition, where necessary, standard errors were transformed to standard deviations and descriptive data transformed to a common scale of measurement (e.g., time-since-injury: months).

The post-injury interval for studies varied widely - ranging from a few days to over 30 years - necessitating the classification of these intervals into four broad groups: the first included studies that examined mean post-injury intervals of < 6 months (acute to post-acute period); the second included intervals of ≥ 6 months to < 2 years (short term); the third spanned ≥ 2 years to < 5 years (medium term); and the fourth ≥ 5 years (long-term). Unfortunately, very few studies reported separate prevalence rates for their mild, moderate and severe participants. Thus, the data from studies that examined mild-moderate and moderate-severe TBI samples were combined with those that assessed all three categories (mild, moderate & severe) for present purposes. Further, where studies assessed depression in a control group, the type of control was classified into one of three groups: 'medical controls' (spinal cord, orthopaedic or general trauma patients), 'general community', or 'significant other' (family/friends/caregivers).

2.3. Data collection and effect size calculation

Demographic and injury information (e.g., age, gender, time-since-injury, injury severity data), the method by which depression was assessed (e.g., clinical diagnosis of MDD/dysthymia or self-report measure), the criteria used to diagnose MDD/dysthymia (e.g., DSM-IV, ICD-10), the measure used (clinical diagnoses: SCID-I, SCAN etc., self-report: BDI,

Hospital Anxiety and Depression Scale [HADS] etc.), the method by which self-report scales were administered (research centre, phone, mail, or combination of methods), sample details (i.e., recruitment source, pre-injury history of mental health problems and TBIs, current medication use, type of control group [medical, community, significant other]), and statistical data necessary for the calculation of effect sizes were extracted from each study for analysis. This information was then entered into Comprehensive Meta-Analysis Software version 2 (CMA; ©2006, Biostat, Inc., Englewood, NJ, USA).

Three types of effect size were calculated in the current study. Firstly, proportions were used to summarize the prevalence of (1) clinically diagnosed cases of MDD and dysthymia, and (2) clinically significant levels of depression, based on self-report data ('cases'), in studies that used single (TBI) or independent (TBI and controls) samples designs. Weighted mean prevalence rates were calculated using sample size as the weighting variable. Secondly, odds ratios were calculated to measure any increase (OR >1) or decrease (OR <1) in the likelihood of experiencing depression following TBI for those studies that used self-report measures to identify clinically significant levels of depression (cases) in TBI and control groups. Thirdly, weighted standardised mean differences (Hedges *g*) were used to estimate the magnitude of the difference between the depression scale scores (means, SDs) of TBI and Control groups (independent samples study design). A positive Hedges *g* indicates that the TBI group reported higher levels of depression than the controls, with a small effect defined as ≥ .2, a moderate effect as ≥ .5, and a large effect as ≥ .8 (Cohen, 1992). As a guide, a Hedges *g* of .5 (medium effect) indicates that the means of the two groups differ by half of a pooled standard deviation.

The current study used a conservative random-effects model to calculate effect sizes, which assumes that effect sizes can vary due to sampling error and differences in study design. Importantly, when a study reported multiple scores that were eligible to be included in the

same analysis, a mean effect was calculated to ensure that each study only contributed one effect size to any given analysis (Lipsey & Wilson, 2001). Forest plots were generated to examine the effect size distributions and assist in identifying outliers (Boyles, Harris, Rooney, & Thayer, 2011), and ninety-five percent confidence intervals (95% CIs) were calculated to provide the upper and lower bounds within which we can be 95% confident that the actual population prevalence rate for depression following TBI lies. In the case of Hedges *g,* 95% CIs that do not include zero, indicate that there is a significant difference between the depression scores of the TBI and control groups.

One problem that meta-analyses face is that the research literature may be biased toward publishing studies that report significant findings (publication bias/file-drawer problem) and, consequently, the resultant analyses tend to exclude non-significant findings; thereby inflating the effect sizes (Rosenthal, 1979). Publication bias was assessed using Orwin's (1983) Fail-safe N statistic (N_{fs}), which estimates the number of unpublished studies that would be required to draw a finding into question. Orwin's formula requires three values to compute a N_{fs}: the number of studies contributing to a mean effect, the resulting weighted mean effect size, and an alternative mean effect size, below which a result would be considered inconsequential/of minor clinical significance. For current purposes, TBI prevalence rates of less than 7.5%, odds ratios of < 1.0, and Hedges *g* values of < 0.15 were deemed to be of minor clinical significance. These figures were chosen on the basis of (a) a population-based survey of the 12-month prevalence of depression in Australian adults (Australian Bureau of Statistics, 2008), (b) Hopkin's (2002) guidelines for a trivial effect when using odds ratios, and (c) Cohen's definition of a small standardised mean difference. The resulting N_{fs} indicates the number of unpublished studies, with non-significant findings, that would be required to render the current findings inconsequential. Therefore, the larger the N_{fs}, the more confidence we can have in a finding.

2.4. Statistical analyses

Consistent with recommendations made by the Meta-Analysis of Observational Studies in Epidemiology (MOOSE) group, the impact of a variety of methodological and sampling variables on findings were examined in order to address the fact that findings from different studies were heterogeneous. This approach is also suggested by Borenstein, Hedges, and Higgins (2009) who note that a random-effects model and subgroup analyses can be used to identify sources of variability in the data.

The overall prevalence of MDD and dysthymia was calculated on the basis of data extracted from studies that used a single-sample (TBI group) or independent samples (TBI + controls) design, after which the impact of a number of moderator variables on the prevalence of MDD and dysthymia was examined, namely the: diagnostic criteria (DSM-III, DSM-IV, ICD-10); clinical interview (SCID-I, SCAN etc); time post-injury (<6 mths, ≥6 mths to <2 yrs, ≥2 yrs to <5 yrs, ≥5yrs); and injury severity (i.e., mild, mild-moderate-severe, severe). In addition, the prevalence of MDD and dysthymia, relative to controls, was examined using ORs; both overall and based on the type of control group (medical, community, significant other).

Next, studies that used self-report scales to identify clinically significant levels of depression were examined. The overall prevalence of depression (cases) was calculated using data from single and independent samples designs, and the following moderator variables examined: the self-report scale (BDI, HADS etc); the method of administration (research centre, phone, mail, or combination of methods); time post-injury; and injury severity. The prevalence of clinically significant levels of depression (cases), relative to controls, was examined using ORs - both overall and by type of control group. Finally, the depression scale scores of TBI and control groups (level/severity of depression) were compared using Hedges *g* - both overall and by type of control group.

3. Results

3.1. Participant details

The 93 studies included in this meta-analysis provided data for a total of 11,926 participants. The background demographic and injury data for these studies are summarized in Table 1, where it can be seen that the majority of participants were young to middle-aged males.

Table 1

Summary demographic and injury characteristics for the studies (N = 93).

Variable	$N_{studies}$	$N_{participants}$	%	Mean	SD
Sample size	93	11,926		131	209
Age (years)	93	11,926		37.1	6.8
Gender (males)	93	8,176	68.6		
Time-since-injury (months)	92	11,898		33.7	51.7
Injury severity(GCS)	32	4,037		9.7	2.2
Injury severity					
Mild	12	1,134	9.5		
Mild, moderate	8	912	7.6		
Mild, moderate, severe	46	6,779	56.8		
Moderate, severe	17	2,569	21.5		
Severe	8	415	3.8		
Details not specified	2	117	0.9		
Recruitment source					
Outpatients	84	10,815	90.7		
Inpatients	6	936	7.8		
Both	3	175	1.5		
Pre-injury history of depression or anxiety					
Participants with history included	38	5,784	48.5		
Participants with history excluded	15	1,881	15.8		
Not specified	40	4,261	35.7		
Pre-injury history of TBI					
History of prior TBI	12	1,146	9.6		
No history of prior TBI	21	2,051	17.2		
Not specified	60	8,729	73.2		
Treatments					
Depression/anxiety medication	11	1,180	9.9		
Anti-epileptic medication	2	138	1.2		
Medication or counselling	1	100	0.8		
Participants excluded if using medication	2	73	0.6		
Medications used, no further detail	2	152	1.3		
Not specified	75	10,283	86.2		
	$N_{Studies}$	**N_{TBI}**	**%**	**$N_{Control}$**	**%**
Type of Control group					
Medical	11	1,077	42.5	1,067	44.6
General community	13	809	31.9	691	28.9
Significant others	7	647	25.5	633	26.5
TOTAL	31	2,533		2,391	

Note: $N_{studies}$ and $N_{participants}$ refer to the total number of studies and participants for which data were available.
One study used two different control groups: community and medical (Clarke, Genat, & Anderson, 2012).
GCS = Glasgow Coma Score

Most studies reported the mean time between injury and assessment ($N_{studies}$ = 92), with the average interval being just under three years (see Table 1). In contrast, only a limited number of studies reported mean Glasgow Coma scores (GCS) ($N_{studies}$ = 32), although most provided categorical information relating to injury severity. The majority of studies examined mixed samples of mild, moderate and severe ($N_{studies}$ = 46), however most did not report separate outcomes for these sub-groups.

Participants were largely recruited from outpatient settings ($N_{studies}$ = 84; see Table 1). Six studies recruited from inpatient settings, all of which examined depression 1 to 6 months after severe TBI. Thirty-eight studies included participants who had a pre-injury diagnosis of depression or anxiety (779 out of 5,784 participants), 15 excluded participants on this basis, and 40 did not specify. Although the majority of studies failed to report whether participants had previously sustained a TBI ($N_{studies}$ = 60) or excluded participants with such a history ($N_{studies}$ = 21), 12 studies reported that 167 of their 1,146 participants had previously sustained a TBI. Similarly, most studies ($N_{studies}$ = 75) failed to report medication use, however 11 reported that 314 (out of 1,180) participants were taking medications for depression or anxiety. Finally, 30 studies recruited one or more control groups (see Table 1), with the majority using medical ($N_{studies}$ = 11; primarily general trauma) or community ($N_{studies}$ = 13) controls, and a further seven recruiting significant others (family, friends, caregivers of the TBI group).

3.2 Prevalence of formally diagnosed depression following TBI

The data from all studies that reported the prevalence of MDD and/or dysthymia following TBI ($N_{studies}$ = 31, $N_{participants}$ = 5,678) were combined in order to calculate an overall prevalence rate. Figure 1a provides a forest plot of the prevalence rates for each of the individual studies (rank-ordered by size), together with the overall weighted mean, which indicates that, on average, 27% were diagnosed with MDD or dysthymia after a TBI. The associated N_{fs} was very large (N_{fs} = 81), suggesting publication bias is unlikely to be a problem.

Importantly, there was substantial variation in the prevalence estimates of individual studies (range: 9%-67%), highlighting the need to undertake additional analyses to examine some of the variables that may have contributed to this variability.

Studies were first partitioned according to the diagnostic criteria that were used and, as seen in Figure 1b, most used DSM criteria. The lowest prevalence rate (14%) was obtained using ICD-10 criteria and the highest (47%) using DSM III criteria. Moreover, the CIs for ICD-10, DSM-IV and DSM III prevalence rates did not overlap, indicating that they yielded significantly different rates.

As seen in Figure 1c, a total of 10 different interview schedules were used to diagnose MDD/dysthymia, with the SCID-I ($N_{studies}$ = 13) being the most commonly used, followed by the SCAN, Mini International Neuropsychiatric Interview (MINI; Sheehan et al., 1998), Present State Examination (PSE; Wing, Cooper, & Sartorius, 1974) and Patient Health Questionnaire (PHQ-9; Kroenke, Spitzer, & Williams, 2001), which were each used by three studies. The prevalence rates obtained using these measures varied between 16% and 33%; although, with the exception of the MINI and PSE, these differences were not significant. In contrast, the interviews used by single studies (e.g., CIDI, CIS, clinical diagnosis based on the Neurobehavioral Functioning Inventory [NFI]; Kreutzer, Seel, & Marwitz, 1999) yielded significantly higher prevalence rates (range: 42% - 54%) than the more commonly used measures (i.e., SCID-I, SCAN & MINI).

Next, post-injury interval was examined to determine whether this impacted on prevalence rates (see Figure 1d). The mean time intervals for the acute/post-acute, short, medium and long-term studies were 2.4 months (SD = 1.4), 11.5 months (SD = 5), 3.1 years (SD =0.8) and 10.5 years (SD = 6.5), respectively. Notably, the mean prevalence of MDD/dysthymia appears to increase in the first 5 years after a TBI (21% to 43%), after which it

declines to acute/post-acute levels (22%). Moreover, the medium-term prevalence rate was significantly higher than any other period.

Although injury severity may impact on the prevalence of depression after a TBI, only a coarse-grained analysis of this variable was possible because many studies used mixed samples (e.g., mild, moderate and severe) and only provided data for the whole sample. As seen in Figure 1e, mild TBI was associated with a significantly lower prevalence of MDD and dysthymia (16%), compared with the mixed sample category of mild, moderate and severe TBI (30%). Severe TBI was only examined by one small-scale study with a wide CI that overlapped with the other categories, indicating that it did not differ from them in terms of the prevalence of MDD/dysthymia.

Finally, data from five studies that compared the prevalence of MDD/dysthymia in TBI and control groups were examined ($N_{participants}$: TBI = 600; controls = 712) (see Figure 1f). Overall, there was a higher prevalence of MDD/dysthymia following TBI (23%) than in the controls (17%), with the associated OR indicating that a person is 1.66 times more likely than controls to develop MDD or dysthymia after a TBI. There was considerable variation in the ORs for individual studies (.67 to 7.69), some of which may have resulted from the choice of control groups. Of the five studies, four used medical controls and only one used community controls. Importantly, after sustaining a TBI, a person is nearly 8 times more likely to develop MDD or dysthymia (OR = 7.69) than someone from the general community but only one and a half times more likely than medical controls (OR = 1.55) (see Figure 1g).

Figure 1

Prevalence of formally diagnosed MDD and dysthymia: (a) overall, (b) diagnostic criteria, (c) interview schedule, (d) time post-injury, (e) injury severity, (f) overall, relative to controls, and (g) according to the type of control group

Figure 1a

Prevalence of MDD and Dysthymia following TBI - overall

	Nparticipants	*Prevalence*	*Lower CI*	*Upper CI*
Konrad, 2011	33	0.09	0.03	0.25
Meares, 2011	62	0.11	0.05	0.22
Chamelian, 2004	62	0.13	0.07	0.24
Deb, 1999	164	0.13	0.08	0.19
Ponsford, 2011	123	0.13	0.08	0.22
Huang, 2005	59	0.14	0.07	0.25
McCauley, 2005	340	0.15	0.12	0.19
Koponen, 2011	38	0.16	0.07	0.31
Rao, 2008 / 2010	54	0.16	0.08	0.29
Rapoport, 2003	210	0.17	0.12	0.22
Bryant, 2010	437	0.18	0.14	0.22
Hibbard, 1998	100	0.18	0.12	0.27
Bombardier, 2010	559	0.24	0.20	0.29
Capizzano, 2010	20	0.25	0.11	0.48
Koponen, 2002	60	0.27	0.17	0.39
Federoff, 1992 / Jorge 1993	66	0.27	0.17	0.41
Failla, 2013	109	0.29	0.21	0.39
Kennedy, 2005	78	0.29	0.20	0.40
Gould, 2011	102	0.30	0.22	0.40
Diaz, 2012	33	0.30	0.17	0.48
Jorge, 2004	91	0.33	0.24	0.43
Whelan-Goodinson, 2009	100	0.33	0.25	0.43
Gomez-Hernandaz, 1997	65	0.34	0.22	0.49
Fann, 1995	50	0.40	0.27	0.54
Kreutzer, 2001	722	0.42	0.38	0.46
Hart, 2011 / 2012	1,570	0.47	0.44	0.50
Hermann, 2009	200	0.48	0.41	0.55
Van Reekum, 1996	18	0.50	0.28	0.72
Al-Adawi, 2004 / 2007	80	0.52	0.40	0.63
Sebit, 1998	37	0.54	0.38	0.69
Alexander, 1992	36	0.67	0.50	0.80
OVERALL	5,678	0.27	0.22	0.32

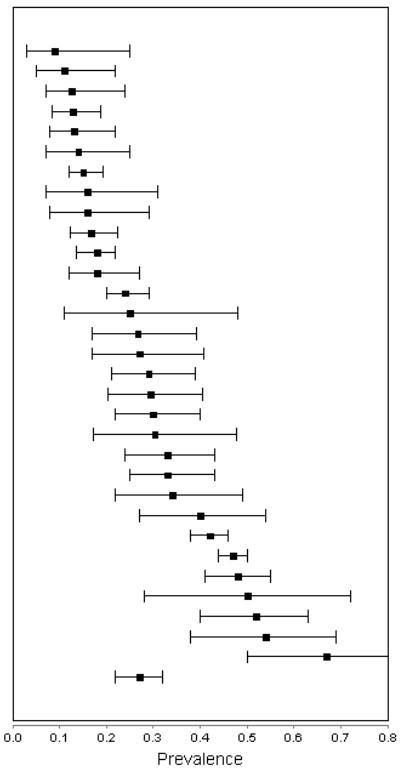


Figure 1b

Prevalence of MDD and Dysthymia following TBI - diagnostic criteria

	Nstudies	*Nparticipants*	*Prevalence*	*Lower CI*	*Upper CI*	*Nfs*
ICD-10	2	504	0.14	0.12	0.18	2
Both DSM-IV & ICD-10	3	579	0.24	0.08	0.51	7
DSM-IV	22	4,728	0.25	0.20	0.31	51
DSM III	5	207	0.47	0.33	0.61	26

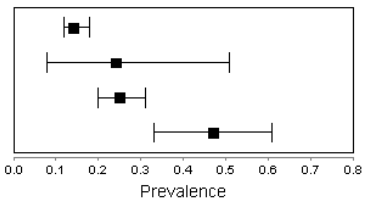


Figure 1c

Prevalence of MDD and Dysthymia following TBI - interview schedule

	Nstudies	*Nparticipants*	*Prevalence*	*Lower CI*	*Upper CI*	*Nfs*
MINI	3	622	0.16	0.12	0.20	3
SCAN	3	262	0.18	0.10	0.28	4
SCID	13	1,462	0.23	0.17	0.30	27
PSE	3	151	0.30	0.22	0.39	9
PHQ-9	3	2,238	0.33	0.19	0.51	10
DIS	1	50	0.40	0.23	0.54	4
NFI	1	722	0.42	0.38	0.46	5
SADS-L	1	18	0.50	0.28	0.72	6
CIDI	1	80	0.52	0.40	0.63	6
CIS	1	37	0.54	0.38	0.69	6
Not specified	1	36	0.67	0.50	0.80	8

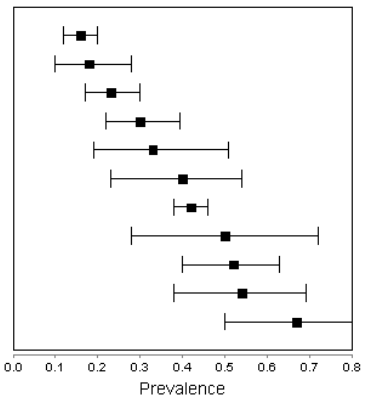


Figure 1d

Prevalence of MDD and Dysthymia following TBI - time post-injury

	Nstudies	Nparticipants	Prevalence	Lower CI	Upper CI	Nfs
Acute to post-acute (< 6 mths)	10	2,116	0.21	0.15	0.29	18
Short-term (≥ 6 mths - < 2 yrs)	16	3,526	0.27	0.20	0.35	42
Medium term (≥ 2 yrs - < 5 yrs)	7	2,516	0.43	0.38	0.49	33
Long term (≥ 5 yrs)	4	271	0.22	0.15	0.31	8

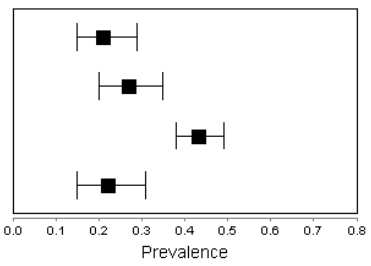


Figure 1e

Prevalence of MDD and Dysthymia following TBI - injury severity

	Nstudies	Nparticipants	Prevalence	Lower CI	Upper CI	Nfs
Mild	5	865	0.16	0.14	0.19	6
Mild, moderate, severe	25	4,780	0.30	0.25	0.36	75
Severe	1	33	0.30	0.17	0.48	3

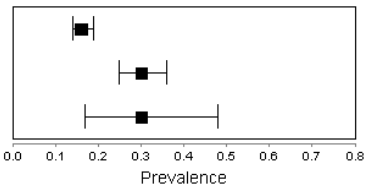


Figure 1f

Prevalence of MDD and Dysthymia following TBI - relative to Controls - overall

Study name	TBI prevalence	Control prevalence	Odds ratio	Lower CI	Upper CI
Meares, 2011	0.11	0.14	0.67	0.22	2.06
Bryant, 2010	0.18	0.17	1.12	0.87	1.44
Jorge, 2004	0.33	0.22	2.63	0.97	7.12
Sebit, 1998	0.54	0.26	3.41	1.30	8.97
Konrad, 2011	0.09	0.01	7.69	0.38	154.97
OVERALL	0.23	0.17	1.66	0.87	3.15

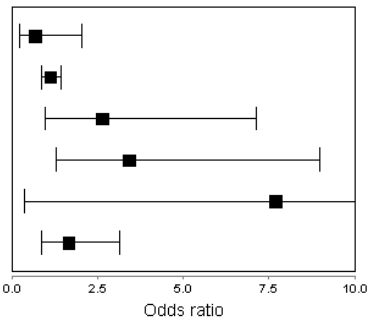
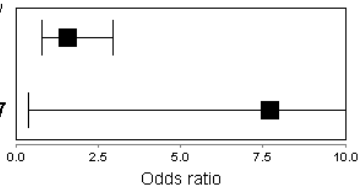


Figure 1g

Prevalence of MDD and Dysthymia following TBI - relative to Controls - by type of control group

	Nstudies	TBI prevalence	Control prevalence	Odds ratio	Lower CI	Upper CI
Medical	4	0.23	0.17	1.55	0.81	2.95
Community	1	0.09	0.01	7.69	0.38	154.97



Note: MDD = Major Depressive Disorder; CI = confidence interval; N_{fs} = Fail-safe N; ICD = International Classification of Diseases; DSM = Diagnostic & Statistical Manual; MINI = Mini-International Neuropsychiatric Interview; SCAN = Schedules Clinical Assessment in Neuropsychiatry; SCID = Structured Clinical Interview; PSE = Present State Examination; PHQ-9 = Patient Health Questionnaire -9; CIDI = Composite International Diagnostic Interview; SADS-L = Schedule for Affective Disorders & Schizophrenia (lifetime); DIS = Diagnostic Interview Schedule; NFI = Neurobehavioral Functioning Inventory; CIS = Clinical Interview Schedule; Refer Online Supplementary Data Table S4 for details of studies contributing to the summary analyses in Figure 1; Kreutzer & Seel, 2001 used the NFI to identify and quantify depressive symptoms of MDD as specified in the DSM-IV.

3.2.2 Prevalence of clinically significant levels of depression ('cases') following TBI

When the data from the 57 studies that used self-report scales to identify clinically significant cases of depression following TBI were combined, it was found that the overall prevalence was 38% (refer to Figure 2a). The associated N_{fs} statistic was very large (N_{fs} = 232), indicating that this is a very robust finding. As with diagnoses of MDD and dysthymia, there was considerable variability in the number of cases reported by individual studies (range: 2%-74%), again highlighting the importance of examining some of the variables that may impact on these findings.

In terms of methodology, the specific self-report scale may impact on the prevalence of clinically significant cases of depression (see Figure 2b). Indeed, there was considerable variability in the mean prevalence rates that were obtained using these different scales, ranging from 2% for the Montgomery-Asberg Depression Rating Scale (MADRS; Montgomery & Asberg, 1979) to 48% for the CES-D. However, as is evident from the CIs, the prevalence rates reported by studies using the same measure were also highly variable (e.g., BDI-II, Zung Self-rating Depression Scale [ZSDS]; Zung, 1965), so much so that after excluding the MADRS, which was only used by one small study, none of the other measures differed significantly; although the HADS and CES-D approached significance. Similarly, when studies were grouped on the basis of how they administered the self-report scale – by phone, in person (research centre), by mail or using a combination of methods - there was substantial variability in the number of cases of depression reported by studies using the same method. Interestingly, although only the 'combination' and 'mailed' groups differed significantly, there was a trend toward fewer cases when questionnaires were administered by phone, compared to mailed questionnaires (see Figure 2c).

Next, the prevalence of clinically significant cases of depression was found to steadily increase, albeit not significantly, as the post-injury interval increased (see Figure 2d), with

estimates ranging from 33% in the acute/post-acute period, 35% in the short-term, 41% in the medium term, and 42% in the longer term. Moreover, mild TBIs were associated with significantly more cases of depression (64%) than the mixed (mild/moderate/severe: 36%) and severe (39%) (see Figure 2e) TBI samples.

Finally, the data from the 16 studies that used self-report measures to identify cases of depression in TBI and control samples were examined ($N_{participants}$: TBI = 1,055; controls = 1,000) (see Figure 2f). The overall mean prevalence of depression following TBI (44%) was substantially higher than that of control groups (19%), with the associated OR of 3.41 indicating that a person is nearly three and a half times more likely to report clinically significant depression after a TBI, compared to controls. Once again, the ORs for individual studies varied substantially (range: 1-49), raising the possibility that the type of control group impacted on these findings. As seen in Figure 2g, controls from the general community reported the lowest rates of depression (9%), followed by significant others (23%) and medical controls (36%). This was reflected in the ORs, which indicated that, following a TBI, people are nearly six times more likely than those in the general community, three times more likely than their significant others (family, friends), and over twice as likely as those with other medical conditions to experience clinically significant levels of depression. Nevertheless, all CIs overlapped, indicating the aforementioned differences were not significant.

Figure 2

Prevalence of clinically significant levels of depression identified using self-report scales: (a) overall, (b) self-report scale, (c) method of administration, (d) time post-injury, (e) injury severity, (f) overall, relative to controls, and (g) according to the type of control group

Figure 2a

Prevalence of self-reported 'cases' of depression following TBI - overall

	Nparticipants	*Prevalence*	*Lower CI*	*Upper CI*
Belmont, 2009	27	0.02	0.00	0.23
Powell, 1996	35	0.09	0.03	0.23
Baumann, 2007 / Kempf, 2010	65	0.15	0.08	0.26
Skilbeck, 2013	214	0.17	0.12	0.22
Huang, 2005	59	0.17	0.08	0.29
van der Horn, 2013	242	0.18	0.14	0.24
Hudak, 2012	471	0.18	0.15	0.22
Al-Adawi, 2007	68	0.19	0.11	0.30
Hudak, 2011	25	0.20	0.09	0.40
Smith, 1992	19	0.20	0.08	0.43
Hawthorne, 2009	66	0.23	0.14	0.34
Gagnon, 2006	30	0.23	0.12	0.41
Chiu, 2006	199	0.24	0.19	0.31
Carroll, 2011	29	0.24	0.12	0.43
Rowland, 2005	51	0.25	0.15	0.39
Weddell, 2010	78	0.26	0.17	0.36
Bushnik, 2008	38	0.26	0.14	0.42
O'Carroll, 1991	36	0.28	0.16	0.44
Schnieders, 2012	90	0.30	0.21	0.40
Salmond, 2006	43	0.30	0.19	0.45
Forslund, 2013	91	0.31	0.22	0.41
Andelic, 2009	58	0.31	0.21	0.44
von Steinbuchel, 2010	795	0.32	0.29	0.35
Chalton, 2009	21	0.33	0.17	0.55
Kinsella, 1998	39	0.33	0.20	0.49
Williams, 1998	18	0.33	0.16	0.57
Goldstein, 2001	35	0.34	0.21	0.51
Powell, 2002	46	0.35	0.23	0.49
Ponsford, 2003	28	0.36	0.20	0.55
Dikmen, 2004	283	0.36	0.30	0.43
Senathi-Raja, 2010	112	0.37	0.28	0.46
Lin, 2010	168	0.37	0.30	0.45
Seel, 2003	172	0.38	0.31	0.45
Maleo, 2010	158	0.40	0.33	0.48
Wallace, 2000	50	0.40	0.27	0.54
Ponsford, 2010	301	0.44	0.39	0.50
Draper, 2007	53	0.45	0.33	0.59
Bryant, 2001	96	0.46	0.36	0.56
Bush, 2004	259	0.49	0.43	0.55
Anson, 2006	33	0.52	0.35	0.68
Whalley Hammell, 1994	15	0.53	0.29	0.76
Evans, 2005	96	0.54	0.44	0.64
Wood, 2008	89	0.55	0.45	0.65
Ponsford, 2003a	143	0.55	0.47	0.63
de Almeida Lima, 2008	36	0.56	0.39	0.71
Curran, 2000	88	0.56	0.45	0.66
Alfano, 1993	32	0.56	0.39	0.72
Glenn, 2001	41	0.59	0.43	0.72
Chen, 2008	40	0.60	0.44	0.74
Perlesz, 2000	62	0.60	0.47	0.71
Tyerman, 1984	25	0.60	0.40	0.77
Bay, 2007	75	0.64	0.53	0.74
King, 2011	24	0.65	0.44	0.82
Englander, 2010	119	0.70	0.61	0.78
Reza, 2007	31	0.71	0.53	0.84
Alfano, 2006	53	0.72	0.58	0.82
Peleg, 2009	65	0.74	0.62	0.83
OVERALL	5,719	0.38	0.34	0.43

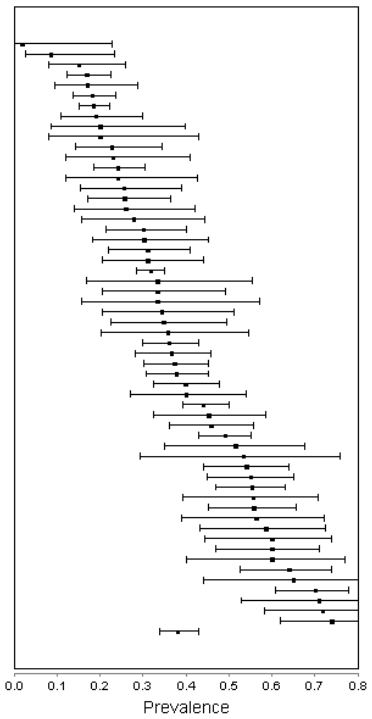


Figure 2b

Prevalence of self-reported 'cases' of depression following TBI - self-report scale

	Nstudies	*Nparticipants*	*Prevalence*	*Lower CI*	*Upper CI*	*Nfs*
MADRS	1	27	0.02	0.00	0.23	0
HADS	19	2,247	0.32	0.27	0.38	62
GDS	1	35	0.34	0.21	0.51	6
ZSDS	3	168	0.35	0.13	0.67	11
BDI-II	9	973	0.37	0.23	0.53	35
BDI-I	11	879	0.43	0.34	0.52	52
Leeds	6	542	0.46	0.36	0.55	31
CES-D	8	1,149	0.48	0.38	0.58	43

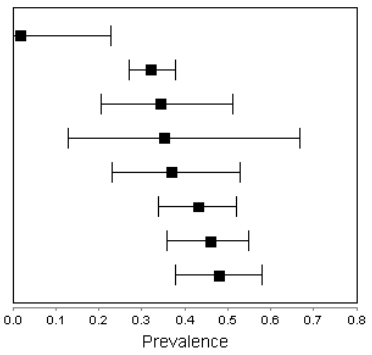


Figure 2c

Prevalence of self-reported 'cases' of depression following TBI - method of administration

	Nstudies	*Nparticipants*	*Prevalence*	*Lower CI*	*Upper CI*	*Nfs*
Phone	3	828	0.26	0.16	0.38	7
Combination	3	880	0.28	0.21	0.36	8
Research centre	43	3,558	0.39	0.34	0.44	181
Mailed	8	453	0.46	0.37	0.56	41

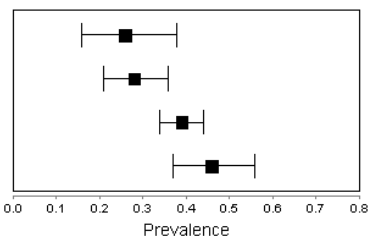


Figure 2d

Prevalence of self-reported 'cases' of depression following TBI - time post-injury

	Nstudies	Nparticipants	Prevalence	Lower CI	Upper CI	Nfs
Acute to post-acute (< 6 mths)	8	1,030	0.33	0.24	0.43	27
Short-term (≥ 6 mths - < 2 yrs)	25	2,422	0.35	0.28	0.43	92
Medium term (≥ 2 yrs - < 5 yrs)	19	2,225	0.41	0.35	0.48	85
Long term (≥ 5 yrs)	10	820	0.42	0.33	0.52	46

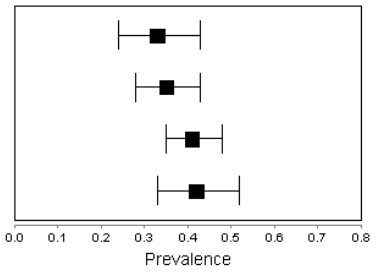


Figure 2e

Prevalence of self-reported 'cases' of depression following TBI - injury severity

	Nstudies	Nparticipants	Prevalence	Lower CI	Upper CI	Nfs
Mild	4	153	0.64	0.56	0.71	30
Mild, moderate, severe	44	5,161	0.36	0.32	0.41	167
Severe	9	405	0.39	0.28	0.50	38

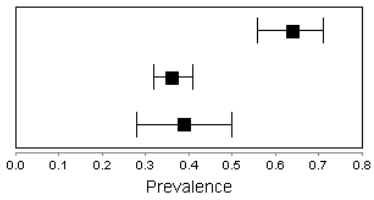


Figure 2f

Prevalence of self-reported 'cases' of depression following TBI - relative to Controls - overall

Study name	TBI prevalence	Control prevalence	Odds ratio	Lower CI	Upper CI
Belmont, 2009	0.02	0.02	1.00	1.00	1.00
Curran, 2000	0.56	0.55	1.03	0.48	2.18
Wallace, 2000	0.40	0.34	1.29	0.57	2.92
Whalley Hammell, 1994	0.53	0.33	2.29	0.52	10.01
Ponsford, 2010	0.44	0.23	2.63	2.04	3.40
Perlesz, 2000	0.60	0.30	3.48	1.86	6.52
Smith, 1992	0.20	0.06	4.00	0.40	39.83
Gagnon, 2006	0.23	0.07	4.26	0.81	22.53
Ponsford, 2003a	0.55	0.22	4.46	2.66	7.48
Senathi-Raja, 2010	0.37	0.11	4.81	2.36	9.80
Alfano, 1993	0.56	0.19	5.46	1.50	19.93
O'Carroll, 1991	0.28	0.06	6.15	0.72	52.72
Ponsford, 2003	0.36	0.07	7.22	1.41	36.96
de Almeida Lima, 2008	0.56	0.11	10.00	2.92	34.21
Goldstein, 2001	0.34	0.03	15.43	0.85	280.76
Chen, 2008	0.60	0.03	49.00	2.75	874.56
OVERALL	0.44	0.19	3.41	2.40	4.84

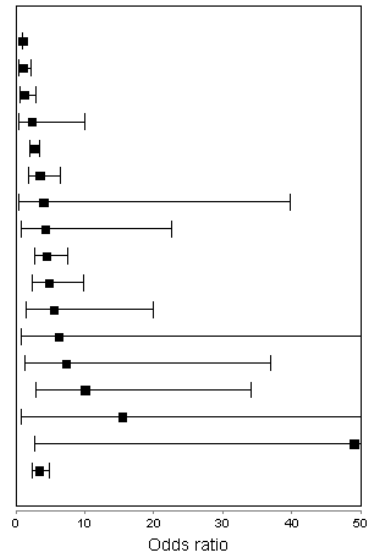
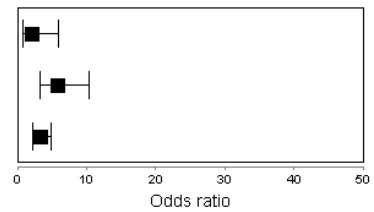


Figure 2g

Prevalence of self-reported 'cases' of depression following TBI - relative to Controls - by type of control group

	Nstudies	TBI prevalence	Control prevalence	Odds ratio	Lower CI	Upper CI
Medical	3	0.56	0.36	2.10	0.74	6.01
Community	6	0.35	0.09	5.75	3.21	10.30
Significant Other	7	0.46	0.23	3.25	2.20	4.81



Note: CI = confidence interval; N_{fs} = Fail-safe N; MADRS = Montgomery-Asberg Depression Rating Scale; HADS = Hospital Anxiety & Depression Scale; GDS = Geriatric Depression Scale; ZSDS = Zung Self-rating Depression Scale; BDI = Beck Depression Inventory; Leeds = The Leeds Scale for the Self-assessment of Anxiety and Depression; CES-D = Center for Epidemiologic Scale – Depression. Refer Online Supplementary Data Table S4 for details of studies contributing to the summary analyses in Figure 2.

3.3. Self-reported levels of depression: TBI versus controls

Twenty studies provided mean depression scale scores (continuous data) for TBI and Control groups, which were examined ($N_{participants}$: TBI = 1,563; controls = 4,017) using Hedges *g* (weighted standardised mean difference). Overall, there was a moderate and significant difference in the depression scores of the TBI and control groups (Hedges *g* = 0.63), together with a large N_{fs} statistic (N_{fs} = 43) (see Figure 3a). When these studies were grouped according to type of control group (medical/community/significant other), there was a large and significant difference between the depression scores of the TBI and community controls (see Figure 3b). Medical and 'significant other' controls also had significantly lower scores than the TBI group, but these differences equated to small to low-moderate effects.

Figure 3

Differences in the depression scores of TBI and Control groups, as assessed by self-report scales: (a) overall and (b) according to the type of control group

Figure 3a

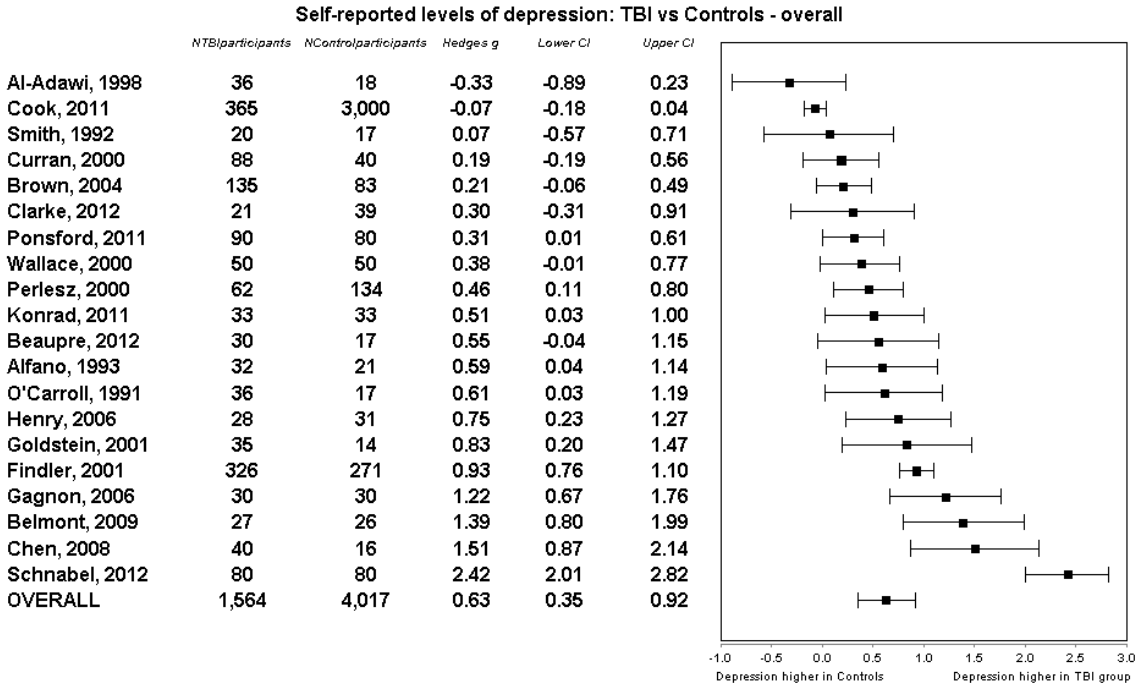
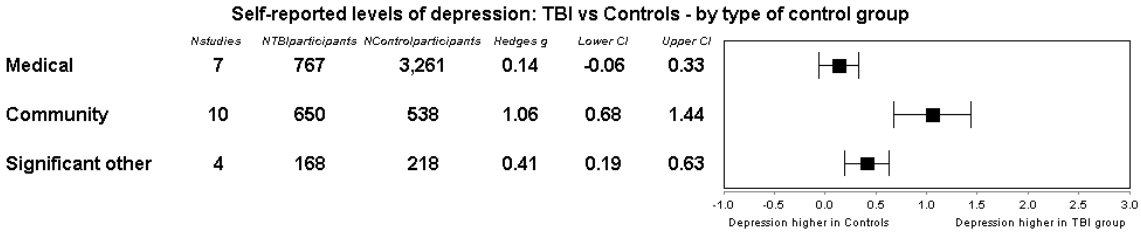


Figure 3b



Note: CI = confidence interval.

Discussion

Estimates of the prevalence of depression following TBI vary widely, limiting the clinical utility of this research. The present study analysed the data from research that has examined the prevalence of MDD/dysthymia or used self-report scales to assess the severity of depression following TBI. A variety of methodological (diagnostic criteria, interview schedule/self-report scale, method of administering self-report scales, control group) and patient (time post-injury, injury severity) variables were examined to determine whether, and to what extent, they impacted on the available findings.

Overall, the findings indicate that depression is extremely common after a TBI, with 27% of people receiving a formal diagnosis of MDD or dysthymia and 38% reporting clinically significant symptoms on self-report scales. The lower prevalence of clinical diagnoses is not surprising because, in addition to using more stringent criteria, they provide a detailed assessment of the aetiology and chronology of symptoms, and greater opportunities for clarification (APA; 2000). In contrast, self-report scales measure the presence and severity of symptoms, applying a threshold to identify clinically significant cases; and do not provide an opportunity to clarify whether symptoms are the result of pre-existing (e.g., prior psychiatric history) or comorbid conditions (e.g., physical/cognitive consequences of a TBI), which may inflate the prevalence rates (Green, Felmingham, Baguley, Slewa-Younan, & Simpson, 2001; Schwarzbold et al., 2008).

Moreover, people report more symptoms when prompted with specific questions than when asked to freely recall them (Iverson, Brooks, Ashton, & Lange, 2010a), also leading to higher prevalence rates. The cognitive changes associated with TBIs (e.g., poorer memory, impaired insight) can, however, lead to fewer reports of depression (Wallace & Bogner, 2000); the impact of which may be offset by using questionnaires. Regardless of the method of assessment, individuals may exaggerate their symptoms if they are seeking financial

compensation, highlighting the importance of assessing symptom validity when disingenuous performance may be an issue (Whiteside, Galbreath, Brown, & Turnbull, 2012). Once compensation claims have been settled, the motivation to exaggerate symptoms is likely to reduce, suggesting that longer-term prevalence rates are less likely to be affected by this.

Estimates of the prevalence of MDD and/or dysthymia differed when different diagnostic criteria were used, with the highest rates noted for the DSM III (47%) and DSM IV (25%) criteria, decreasing to 14% for the two studies that used ICD-10 criteria. These differences are surprising, given the overlap between these criteria and the fact that the DSM-IV revisions were relatively conservative (First, 2010). However, unlike the DSM, the ICD-10 categorises symptoms into two groups, each of which has a diagnostic threshold; potentially resulting in cases that meet one criterion, but not the other and leading to fewer diagnoses (First, 2009).

Prevalence rates were also affected by the specific interview that was used to diagnose MDD and dysthymia. The most commonly used schedule – the SCID-I – yielded a prevalence rate of 23% ($N_{studies}$ = 13), with the others ranging from 16% (MINI: $N_{studies}$ = 3) to 54% (CIS; $N_{studies}$ = 1). Some of this variability may result from the different time-frames that are assessed. Indeed, the CIS and Schedule for Affective Disorders and Schizophrenia (SADS; Endicott & Spitzer, 1978), which focus on the preceding week, had the highest rates (54% and 50%, respectively). Longer time frames (previous 2 weeks – month) yielded substantially lower rates (e.g., MINI = 16%; SCAN = 18%; SCID-I = 23%). Other scales allow clinicians to select the time-frame (e.g., Diagnostic Interview Schedule; Robins, Helzer, Croughan, & Ratcliff, 1981), but this was often not reported.

There was also considerable variability in the prevalence of clinically significant cases of depression, identified on the basis of self-report scales; with estimates ranging from 2% for the MADRS ($N_{studies}$ = 1) to 48% for the CES-D ($N_{studies}$ = 8). Notably, the CES-D was designed for

use in the general population and incorporates items that may be indicative of physical or cognitive TBI symptoms (e.g., sleep difficulties, fatigue, attentional problems), possibly inflating the number of 'cases'. Interestingly, the rate obtained from the most frequently used scale – the HADS ($N_{studies}$ = 19; 32%) – was substantially lower than the finding for the CES-D (48%). The HADS was specifically designed for use in medical settings and, consequently, does not include items that may reflect the physical, rather than psychological, consequences of a TBI (Zigmond & Snaith, 1983). This measure may therefore provide the best estimate of self-reported cases of depression.

The prevalence of self-reported 'cases' of depression also differed according to how the scale was administered. Specifically, more cases were identified when people completed questionnaires at home and returned them by mail (46%), than when completed by phone interview (26%). Phone administration may encourage people to respond in a socially-desirable manner, possibly causing them to down-play their symptoms and/or provide limited opportunity to reflect on and revise their answers (Aziz & Kenford, 2004; Fairweather-Schmidt & Anstey, 2012). However, at home, a person may be influenced by others, even when there are explicit instructions stating that all responses must be their own and/or no discussion with others is permitted (Alfano, Neilson, & Fink, 1993; O'Carroll, Woodrow, & Maroun, 1991).

In addition, prevalence rates varied according to the post-injury interval, with the prevalence of MDD/dysthymia steadily increasing in the first five years post-TBI (21% to 27% to 43%) and subsequently declining to a level similar to that seen in the early post-injury period (22%). In contrast, the number of 'cases' of depression identified using questionnaires steadily increased – although not significantly - from the acute/post-acute period until the medium-term (33% to 41%), when it plateaued. These findings highlight temporal changes to the risk of developing depression, possibly reflecting the changing influence of a number of different variables (e.g., neuronal/neurochemical, psychological, social). They also underscore

the importance of monitoring individuals over an extended period of time and providing ongoing access to mental health support services.

Unfortunately, injury severity could only be examined in a basic way, due to the limited availability of data. These analyses revealed that mild TBI was associated with the lowest prevalence of MDD and dysthymia (16%); a rate that was significantly lower than that seen in mixed samples (30%). Although lower than the rate for severe TBI (30%), this difference was not significant, possibly due to the small sample size. These findings contrasted with those from self-report measures, which revealed significantly more cases of depression following mild TBI (64%) (mixed samples = 36%; severe TBI = 39%). There are a number of factors that may contribute to the latter finding. For example, severe TBIs are more frequently associated with memory problems and impaired self-awareness (Evans et al., 2005), which may reduce the number of symptoms that are endorsed on questionnaires (Malec et al., 2007b). Alternatively, persons with mild TBI may be exaggerating their symptoms for financial gain (Kurtz et al., 2007). However, it is also possible that people do not receive adequate psycho-educational support following a mild TBI, which may increase their distress or, in the absence of significant physical injuries, they may focus on other problems (Malec et al., 2007b). Therefore, even following mild TBI, individuals should be monitored to ensure that these symptoms do not interfere with their recovery or quality of life.

Relative to others, people are more likely to be diagnosed with MDD/dysthymia (OR = 1.66), or experience clinically significant levels of depression (OR = 3.41) following a TBI. Even when contributing factors, such as pain and hospital/medical procedures, are taken into account, a TBI provides an additional, unique source of psychological distress. Similarly, TBI groups were nearly eight times more likely to be diagnosed with MDD/dysthymia, and over five times more likely to be classified as having clinically significant levels of depression, than members of the general community. Lastly, the family/friends/caregivers of those who have

sustained a TBI reported suffering from high levels of depression (23%), indicating that they are also at considerable risk of developing depression, and may require monitoring and treatment to optimise their outcomes (Ergh, Rapport, Coleman, & Hanks, 2002; Ponsford, Olver, Ponsford, & Schonberger, 2010).

Finally, when the full spectrum of self-reported depressive symptoms was examined - ranging from normal to severe depression – it was found that individuals experienced moderately higher levels of depression following a TBI than their peers. This finding was impacted by the source of the controls, with the largest difference associated with people residing in the community, followed by significant others and then medical controls. This highlights the importance of selecting the appropriate norms or controls, based on the clinical or research question, to enable depression to be examined independently of a range of confounding variables. Specifically, medical controls endeavour to control for pain, other injuries and hospital routines/procedures (Ponsford, Cameron, Fitzgerald, Grant, & Mikocka-Walus, 2011); significant others control for the increased levels of stress and emotional distress related to a family member's TBI (Ponsford & Schönberger, 2010); and community controls enable an assessment of depression relative to people who are residing in the general community (Wacholder, Silverman, McLaughlin, & Mandel, 1992).

Limitations and recommendations for future research

There are a number of limitations that warrant consideration. First, although prior TBIs and psychiatric history may contribute to the development of depression (Anstey et al., 2004; Fann et al., 2002), this data was often not reported, or in a form that could not be compared (e.g., no major psychiatric illness, no prior hospitalisation, not currently using medication); precluding an analysis of these variables. Second, data was often combined across different injury categories (mild, moderate, severe), which meant that it was only possible to undertake a coarse-grained examination of TBI severity. Third, it was not possible

to examine the impact of medications on the prevalence of depression because very few studies reported these data. Anti-depressant medications are likely to reduce symptoms and result in lower prevalence estimates, making this an important variable to consider. Fourth, it is possible that gender may have impacted on the prevalence of depression following TBI because females have a higher risk of developing depression (Kessler, McGonagle, Swartz, Blazer, & Nelson, 1993), although males are more likely to sustain a TBI (Anstey et al., 2004). Of the studies that reported the prevalence of MDD/dysthymia, only six provided gender-based data. While there was a trend for females to have higher rates of MDD/dysthymia in these studies (47% vs 34%), the difference was not significant.

It is recommended that researchers report participants' history of TBIs/psychiatric diagnoses and, ideally, provide subgroup data (mild/moderate/severe TBI; medicated vs unmedicated; males vs females), so that these variables can be examined in greater detail. Multivariate analyses of the data were not possible due to the variability in the research designs that have been used to examine the prevalence of depression following TBI. A large-scale study that evaluates the impact of these variables is now needed.

Conclusions

There is now a substantial body of research that has examined the prevalence of depression following TBI, but the estimates from individual studies vary widely. The challenges involved in interpreting these disparate findings are well-known, with researchers repeatedly noting that numerous methodological differences have made it difficult to compare findings and draw definitive conclusions (Koponen et al., 2011; Tsaousides, Ashman, & Gordon, 2013; Whelan-Goodinson, Ponsford, & Schönberger, 2009b).

Overall, the prevalence of formally diagnosed MDD and dysthymia was 27%, although this varied depending on whether ICD-10 (14%), DSM-IV (25%) or DSM III (47%) diagnostic

criteria were used. The different interview schedules also yielded variable prevalence rates, ranging from 16% to 54%. MDD/dysthymia was more prevalent between two and five years post-injury (43%), compared with the acute/post-acute period (< 6mths; 21%), short-term (≥ 6 months to < 2 years; 27%), and long-term (≥ 5 years; 22%). In addition, the prevalence of MDD/dysthymia was substantially higher following severe TBI (30%) than mild TBI (16%), although this difference was not significant. Moreover, MDD/dysthymia is more common following TBI than it is after other injuries (OR = 1.55) and in the general community (OR = 7.69).

The overall prevalence of clinically significant 'cases' of depression, assessed using questionnaires, was 38%; although this rate varied considerably depending on the measure that was used (2% to 48%) and the method of administration (phone: 26%; mail: 46%). Unlike MDD and dysthymia, self-reported depression continued to increase over time (from 33% to 42%) and injury severity had a paradoxical effect, with more cases of depression following mild TBI (64%, severe TBI = 39%). The odds of developing depression after a TBI are more than five, three and two times higher than those living in the general community, the family and friends of the person who sustained the TBI, and other medical patients, respectively.

3.4 Online Supplementary Data

Table S1: Search Strategy

PsycINFO - date limited to 1980 onwards, peer reviewed submissions

DE traumatic brain injury OR TI "traumatic brain injur*" OR AB "traumatic brain injur*" OR TI TBI OR AB TBI OR TI "head injur*" OR AB "head injur*" OR TI "brain injur*" OR AB "brain injur*" OR TI "brain damage" OR AB "brain damage" OR TI "head trauma" OR AB "head trauma" OR TI "craniocerebral trauma" OR AB "craniocerebral trauma" OR TI "cranio-cerebral trauma" OR AB "cranio-cerebral trauma" OR "cranio cerebral trauma" OR TI "cranio cerebral trauma" OR KW "traumatic brain injur*" OR KW TBI OR KW "head injur*" OR KW "brain injur*" OR KW "brain damage" OR KW "head trauma" OR KW "craniocerebral trauma" OR KW "cranio-cerebral trauma" OR KW "cranio cerebral trauma" AND DE anxiety disorders OR DE affective disorders OR DE Suicidal Ideation OR DE Suicide OR DE Suicidology OR DE Attempted Suicide OR TI "mood disorder" OR AB "mood disorder" OR TI depress* OR AB depress* OR TI "anxiety disorder" OR AB "anxiety disorder" OR TI "psychiatric diagnos*" OR AB "psychiatric diagnos*"OR TI "psychological sequelae" OR AB "psychological sequelae" OR TI "dysthymic disorder" OR AB "dysthymic disorder" OR TI "affective disorder" OR AB "affective disorder" OR TI psychosis OR AB psychosis OR TI psychoses OR AB psychoses OR TI psychotic OR AB psychotic OR TI suicid* OR AB suicid* OR KW "mood disorder" OR KW depress* OR KW "anxiety disorder" OR KW "psychiatric diagnos*" OR KW "psychological sequelae" OR KW "dysthymic disorder" OR KW "affective disorder" OR KW suicid* OR KW psychosis OR KW psychoses OR KW psychotic AND NOT (TI war OR AB war OR TI combat or AB combat)

PUBMED – MeSH categories

Brain injuries: Brain concussion, Brain hemorrhage, traumatic, Brain injury, chronic, Diffuse axonal injury
Coma, post head injury
Head injuries, closed: Brain concussion
Intracranial hemorrhage, traumatic: Brain hemorrhage, traumatic, Hematoma, epidural, cranial, Hematoma, subdural, Subarachnoid hemorrhage, traumatic
Skull fractures: Skull fracture, basilar, Skull fracture, depressed
Anxiety disorders
Agoraphobia
Obsessive-compulsive disorder
Panic disorder
Phobic disorders
Stress disorders, traumatic: Stress disorders, post-traumatic, Stress disorders, traumatic, acute
Mood disorders
Affective disorders, psychotic
Bipolar disorder
Depressive disorder: Depressive disorder, major, Dysthymic disorder, Seasonal affective disorder
Suicide: Suicidal ideation, Suicide, attempted

Table S1 cont.

PUBMED (thesaurus, title & abstract searching):

Brain concussion[mh] OR Brain hemorrhage, traumatic[mh] OR Brain injury, chronic[mh] OR Diffuse axonal injury[mh] OR Coma, post head injury[mh] OR Head injuries, closed[mh] OR Intracranial hemorrhage, traumatic[mh] OR Skull fractures[mh] OR traumatic brain injur* [tiab] OR TBI [tiab] OR head injur* [tiab] OR brain injur* [tiab] OR brain damage [tiab] OR head trauma [tiab] OR craniocerebral trauma [tiab] OR cranio-cerebral trauma [tiab] OR cranio cerebral trauma [tiab] AND Anxiety disorders[mh] OR Stress disorders, traumatic[mh] OR Mood disorders[mh] OR Affective disorders, psychotic[mh] OR Bipolar disorder[mh] OR Depressive disorder[mh] OR Suicide[mh] OR Mood disorder [tiab] OR Depress* [tiab] OR Anxiety disorder [tiab] OR Psychiatric diagnos* [tiab] OR Psychological sequelae [tiab] OR Dysthymic disorder [tiab] OR Affective disorder [tiab] OR Suicid* [tiab] OR Psychoses [tiab] OR psychotic [tiab] OR psychosis [tiab] AND english[lang] AND 1980/01:2013/6 [dp] NOT (TI war OR AB war OR TI combat or AB combat)

SCOPUS

("traumatic brain injur*" OR TBI OR "head injur*" OR "brain injur*" OR "brain damage" OR "head trauma" OR "craniocerebral trauma" OR "cranio-cerebral trauma" OR "cranio cerebral trauma") AND ("mood disorder" OR depress* OR "anxiety disorder" OR "psychiatric diagnos*" OR "psychological sequelae" OR "dysthymic disorder" OR "affective disorder" OR suicid* OR psychos* OR psychotic)

ISI Web of Science

Topic=(traumatic brain injur* OR TBI OR head injur* OR brain injur* OR brain damage OR head trauma OR craniocerebral trauma OR cranio-cerebral trauma OR cranio cerebral trauma) AND Topic=(mood disorder OR depress* OR anxiety disorder OR psychiatric diagnos* OR psychological sequelae OR dysthymic disorder OR affective disorder OR suicid* OR psychos* OR psychotic)

Refined by: Publication Years=(2009 OR 1992 OR 2010 OR 1991 OR 2008 OR 1990 OR 2007 OR 1989 OR 2013 OR 2006 OR 1986 OR 2005 OR 1988 OR 2004 OR 1987 OR 2003 OR 1983 OR 2002 OR 1984 OR 2000 OR 1985 OR 2001 OR 1981 OR 1999 OR 1980 OR 1998 OR 1982 OR 1997 OR 1994 OR 1995 OR 1993 OR 2011 OR 2012 OR 1996) AND Document Type=(ARTICLE)

Table S2: Depression measures eligible for analysis

Self-report scale name	Abbrev.	Author(s) / Year	Time frame
Beck Depression Inventory I	BDI-I	(Beck, Ward, Mendelson, Mock, & Erbaugh, 1961)	previous week
Beck Depression Inventory II	BDI-II	(Beck et al., 1996)	previous 2 weeks
Center for Epidemiologicl Scale – Depression	CES-D	(Radloff, 1977)	previous week
Geriatric Depression Scale	GDS	(Yesavage et al., 1983)	time interval determined by researcher
Hospital Anxiety and Depression Scale	HADS	(Zigmond & Snaith, 1983)	previous week
Leeds Scale for the Self-assessment of Anxiety & Depression	Leeds	(Snaith, Bridge, & Hamilton, 1976)	previous 1-2 days
Montgomery Asberg Depression Rating Scale	MADRS	(Montgomery & Asberg, 1979)	time interval determined by researcher
Zung Self-rating Depression Scale	ZSDS	(Zung, 1965)	previous several days

Clinical interview name	Abbrev.	Author(s) / Year	'Current' time frame
Clinical Interview Schedule -R	CIS	(Lewis et al., 1992)	previous week
Composite International Diagnostic Interview	CIDI	(Robins et al., 1988)	previous week, previous month, previous 6 months, previous year
Diagnostic Interview Schedule	DIS	(Robins et al., 1981)	previous week, previous month, previous 6 months, previous year
Mini International Neuropsychiatric Instrument	MINI	(Sheehan et al., 1998)	previous 2 weeks
Patient Health Questionnaire – 9	PHQ-9	(Kroenke et al., 2001)	previous 2 weeks
Present State Examination	PSE	(Wing et al., 1974)	previous month
Schedule for Affective Disorders and Schizophrenia - Lifetime	SADS-L	(Endicott & Spitzer, 1978)	previous week
Schedules for Clinical Assessment in Neuropsychiatry	SCAN	(Wing et al., 1990)	previous month
Structured Clinical Interview for DSM disorders	SCID	(First et al., 1997)	previous month

Table S3: Overview of study review and selection

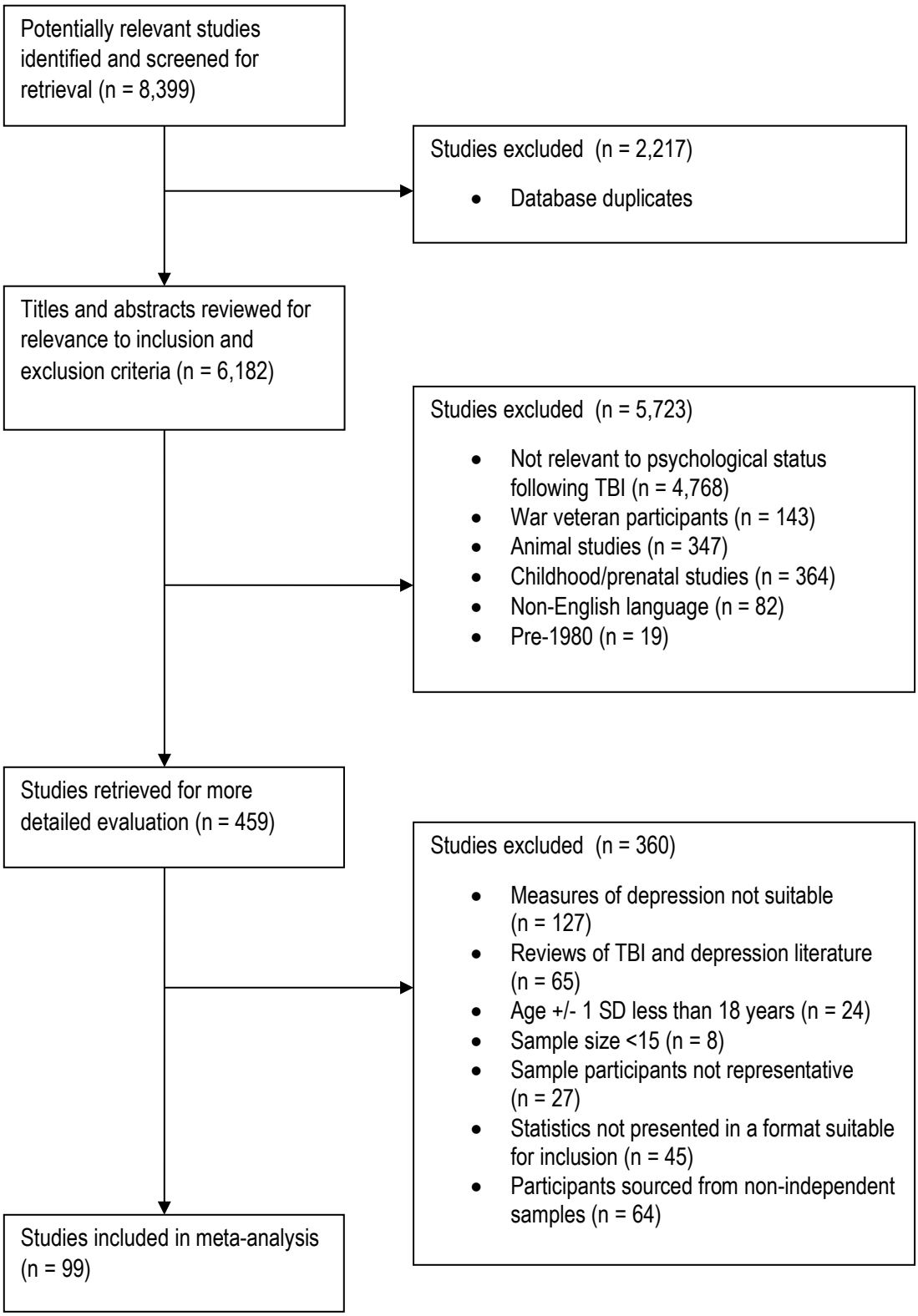


Table S4: Details of studies included in analyses

Figure	References
1a, 1b, 1c, 1d, 1e	1/2, 4, 13, 16, 19, 22, 28, 29, 34, 35, 36/53, 42, 43, 44/45, 48, 49, 50, 54, 56, 59, 60, 61, 62, 66, 67, 71, 77/78, 79, 85, 92, 97
1f, 1g	16, 54, 59, 67, 85
2a, 2b, 2c, 2d, 2e	1, 5, 6, 7, 8, 9/55, 10, 12, 15, 17, 18, 20, 21, 23, 24, 27, 63, 30, 31, 32, 33, 38, 39, 40, 41, 46, 50, 51, 52, 57, 58, 64, 65, 68, 69, 70, 72, 73, 74, 75, 76, 80, 81, 82, 84, 86, 87, 88, 89, 90, 91, 93, 94, 95, 96, 98, 99
2f, 2g	12, 27, 94, 96, 73, 70, 89, 39, 72, 87, 6, 68, 74, 63, 41, 23
3a, 3b	3, 26, 89, 27, 14, 25, 71, 94, 70, 59, 11, 6, 68, 47, 41, 37, 39, 12, 23, 83

1. (Al-Adawi et al., 2007)
2. (Al-Adawi et al., 2004)
3. (Al-Adawi, Powell, & Greenwood, 1998)
4. (Alexander, 1992)
5. (Alfano, 2006)
6. (Alfano et al., 1993)
7. (Andelic et al., 2009)
8. (Anson & Ponsford, 2006)
9. (Baumann, Werth, Stocker, Ludwig, & Bassetti, 2007)
10. (Bay, Hagerty, & Williams, 2007)
11. (Beaupre, De Guise, & McKerral, 2012)
12. (Belmont et al., 2009)
13. (Bombardier et al., 2010)
14. (Brown et al., 2004)
15. (Bryant, Marosszeky, Crooks, Baguley, & Gurka, 2001)
16. (Bryant et al., 2010)
17. (Bush, Novack, Schneider, & Madan, 2004)
18. (Bushnik et al., 2008)
19. (Capizzano et al., 2010)
20. (Carroll & Coetzer, 2011)
21. (Chalton & McMillan, 2009)
22. (Chamelian et al., 2004)
23. (Chen et al., 2008)
24. (Chiu et al., 2006)
25. (Clarke, Genat, & Anderson, 2012)
26. (Cook et al., 2011)
27. (Curran et al., 2000)
28. (Deb et al., 1999b)
29. (Diaz et al., 2012)
30. (Dikmen et al., 2004)
31. (Draper et al., 2007)
32. (Englander et al., 2010)
33. (Evans et al., 2005)
34. (Failla et al., 2013)
35. (Fann et al., 1995)
36. (Fedoroff et al., 1992)
37. (Findler et al., 2001)
38. (Forslund et al., 2013)
39. (Gagnon, Bouchard, Rainville, Lecours, & St-Amand, 2006)
40. (Glenn et al., 2001)
41. (Goldstein et al., 2001)
42. (Gomez-Hernandez et al., 1997)
43. (Gould et al., 2011a)
44. (Hart et al., 2011)
45. (Hart et al., 2012)
46. (Hawthorne et al., 2009)
47. (Henry, Phillips, Crawford, Theodorou, & Summers, 2006)
48. (Herrmann et al., 2009)

Table S4 cont.

49. (Hibbard et al., 1998)	75. (Powell et al., 2002)
50. (Huang, Spiga, & Koo, 2005)	76. (Powell, Collin, & Sutton, 1996)
51. (Hudak et al., 2011)	77. (Rao et al., 2010)
52. (Hudak, Hynan, Harper, & Diaz-Arrastia, 2012)	78. (Rao et al., 2008)
53. (Jorge et al., 1993b)	79. (Rapoport et al., 2003a)
54. (Jorge et al., 2004)	80. (Reza et al., 2007)
55. (Kempf, Werth, Kaiser, Bassetti, & Baumann, 2010)	81. (Rowland, Lam, & Leahy, 2005)
56. (Kennedy et al., 2005)	82. (Salmond, Menon, Chatfield, Pickard, & Sahakian, 2006)
57. (King & Kirwilliam, 2011)	83. (Schnabel & Kydd, 2012)
58. (Kinsella et al., 1988)	84. (Schnieders et al., 2012)
59. (Konrad et al., 2011)	85. (Sebit et al., 1998)
60. (Koponen et al., 2011)	86. (Seel & Kreutzer, 2003)
61. (Koponen et al., 2002)	87. (Senathi-Raja et al., 2010)
62. (Kreutzer et al., 2001)	88. (Skilbeck, Dean, Thomas, & Slatyer, 2013)
63. (de Almeida Lima et al., 2008)	89. (Smith, 1992)
64. (Lin et al., 2010)	90. (Tyerman & Humphrey, 1984)
65. (Malec et al., 2010)	91. (Van Der Horn et al., 2013)
66. (McCauley et al., 2005)	92. (Van Reekum et al., 1996)
67. (Meares et al., 2011)	93. (von Steinbuchel et al., 2010)
68. (O'Carroll et al., 1991)	94. (Wallace & Bogner, 2000)
69. (Peleg et al., 2009)	95. (Weddell, 2010)
70. (Perlesz et al., 2000)	96. (Whalley Hammell, 1994)
71. (Ponsford et al., 2011)	97. (Whelan-Goodinson et al., 2009a)
72. (Ponsford et al., 2003)	98. (Williams, Williams, & Ghadiali, 1998)
73. (Ponsford & Schönberger, 2010)	99. (Wood & Williams, 2008)
74. (Ponsford & Ziino, 2003)	

CHAPTER 4: TBI AND DEPRESSION IN A COMMUNITY-BASED SAMPLE

4.1 Preamble

This Chapter consists of a manuscript entitled "Traumatic brain injury and depression in a community-based sample: a cohort study across the adult lifespan", which is currently in press with the *Journal of Head Trauma Rehabilitation*.

The previous chapter focussed on existing research examining depression following a TBI. This meta-analysis demonstrated that, regardless of how depression is conceptualised (clinical diagnosis, self-reported symptoms), many people experience problems with depression after a TBI. Moreover, these difficulties often continue for many years. Crucially, it also revealed that depression was experienced more frequently and with greater severity, in people who had sustained a TBI, compared with those who have experienced other types of injuries (i.e., not involving injury to the brain), family and friends of the person with a TBI, and people from the general community.

Interestingly, all of the studies that met the eligibility criteria for this meta-analysis were sourced from clinical settings (e.g., hospitals, rehabilitation centres). Although clinical recruitment has dominated the field of TBI research, these individuals are likely to have experienced more severe injuries, and/or be receiving support for problems related to their TBI (e.g., functional, cognitive, psychological difficulties). Given that many people do not seek medical attention after a TBI, particularly mild TBIs (Demakis & Rimland, 2010), it is likely that they are currently not well-represented in the literature.

The second study therefore examined the prevalence of depression in a large community-based sample of people, both with and without a TBI. The sample was recruited as part of a longitudinal study – the Personality and Total Health (PATH) Through Life project - investigating the health and well-being of three Australian age-cohorts who, at baseline, were

young (20-24 years), middle-aged (40-44 years) or older (60-64 years) adults. Importantly, these data enabled a longitudinal and cross-sectional examination of depression following a TBI of all severities, regardless of whether a person had sought medical attention for their injury. Moreover, the present study examined whether sustaining a TBI is associated with a higher risk of clinically significant depression at different stages of the adult lifespan. Importantly, this chapter extends the previous study (depression meta-analysis) by looking at a broader population-based community sample.

Tables and Figures are provided throughout the chapter, in order to make it easier to read. Supplementary information relating to this paper is included at the end of the current chapter (pages 109-113) and incorporates: an overview of the full sample for the Personality and Total Health (PATH) Through Life study and participants in the current sample, (Table S1); a summary of the variables measured in the PATH study, and the TBI, depression and risk factor variables examined in the current study (Table S2); a comparison between PATH sample characteristics and population Census information (Table S3); and the univariate results for the risk factors analysed in the present study (Table S4). A complete list of all references for the thesis, including those for this paper, has been provided at the end of the thesis (pages 208-237).

Chapter 4: Paper two

Traumatic brain injury and depression in a community-based sample:

A cohort study across the adult lifespan

Authors: A. J. Osborn, J. L. Mathias, A. K. Fairweather-Schmidt, K. J. Anstey

This chapter consists of a manuscript in press with the Journal of Head Trauma Rehabilitation,

impact factor 3.23

Statement of authorship is on the following page.

4.2 Statement of Authorship

Statement of Authorship

Title of Paper	Traumatic brain injury and depression in a community-based sample: a cohort study across the adult lifespan
Publication Status	☐ Published ☑ Accepted for Publication ☐ Submitted for Publication ☐ Unpublished and Unsubmitted work written in manuscript style
Publication Details	Osborn, A. J., Mathias J. L., Fairweather-Schmidt, A. K., & Anstey K. J. (in press). Traumatic brain injury and depression in a community-based sample: a longitudinal study across the adult lifespan. *Journal of Head Trauma Rehabilitation*.

Principal Author

Name of Principal Author (Candidate)	Amanda Osborn
Contribution to the Paper	Study inception, design, methodology (including literature searches, statistical analysis and data interpretation), wrote manuscript and acted as corresponding author.
Overall percentage (%)	85%
Certification:	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.
Signature	Date: 18/1/17

Co-Author Contributions

By signing the Statement of Authorship, each author certifies that:

i. the candidate's stated contribution to the publication is accurate (as detailed above);
ii. permission is granted for the candidate in include the publication in the thesis; and
iii. the sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

Name of Co-Author	Jane Mathias
Contribution to the Paper	Supervised and contributed to the study design, analysis and data interpretation, and manuscript preparation.
Signature	Date: 18/1/17

Name of Co-Author	Kate Fairweather-Schmidt
Contribution to the Paper	Assisted in study design, data analysis and interpretation, and manuscript review.
Signature	Date: 20/01/17

Name of Co-Author	Kaarin Anstey
Contribution to the Paper	Is the leader of the PATH Project. Contributed to the overall design of the Personality and Total Health (PATH) Through Life study, including selecting measures, recruitment, and grant writing. For the current study, assisted in evaluating and editing the manuscript.
Signature	Date: 18/1/17

4.3 Paper two

Abstract

Objective: To determine whether self-reported traumatic brain injuries (TBIs) are associated with 'cases' of clinically significant depression in the general community. Interactions between variables previously linked to depression after a TBI were also examined.

Setting: Population-based community study (Canberra and Queanbeyan, Australia).

Participants and design: Three age cohorts: young, middle-aged and older adults (aged 20-24, 40-44, 60-64 years at baseline), randomly selected from the electoral roll and followed across three waves (four years apart). A total of 7,397, 6,621 and 6,042 people provided their TBI history in Waves 1-3.

Measures: Lifetime ($TBI_{lifetime}$: sustained at any time since birth), recent (TBI_{recent}: in the preceding four years) and multiple ($TBI_{multiple}$: more than one) TBIs, current depression, and known risk factors for depression (age, sex, marital/employment status, prior history of depression, medical conditions, recent life events, alcohol consumption, social support, physical activity).

Results: Generalized Estimating Equations demonstrated a significant association between sustaining a TBI and experiencing clinically significant depression (cases), even after controlling for multiple demographic and health/lifestyle factors.

Conclusion: There is a long-term association between depression and TBI, suggesting that, following a TBI, individuals should be monitored and supported in order to optimise their long-term psychological health.

Keywords

Traumatic brain injury, depression, community, population, longitudinal, multivariate

Introduction

Depression is common following a traumatic brain injury (TBI) (Osborn, Mathias, & Fairweather-Schmidt, 2014), but the complex interplay between demographic, health and psychosocial risk factors associated with its development remains unclear. A better understanding of how these risk factors work together is critical to improving clinicians' ability to identify and treat those who are most likely to develop depression after their injury (Kraemer, Stice, Kazdin, Offord, & Kupfer, 2001). Although considerable research has been undertaken, it has primarily examined a limited number of risk factors and/or used highly-selected clinical samples (Bombardier et al., 2010; Deb et al., 1999b; Horner et al., 2008; Whelan-Goodinson et al., 2010). A more multidimensional approach using community-based samples is now needed to identify which of these risk factors are associated with depression following a TBI. This research needs to be informed by the extant literature, which has identified a number of risk factors, including the following.

Specifically, older age has often been linked to higher levels of depression after TBI (Glenn et al., 2001; Sigurdardottir et al., 2013), although young adults may also be susceptible (Bombardier et al., 2010; Deb & Burns, 2007), suggesting that the relationship between age and depression following a TBI is complex. Moreover, although depression is more common in females in the general community (APA, 2013), this does not appear to be the case post-TBI (Dikmen et al., 2004; Hart et al., 2011; Koponen et al., 2002); possibly influenced by the disproportionate numbers of males who sustain these injuries (Anstey et al., 2004; Corrigan et al., 2010).

Injury-related factors, including lesion site, have also been examined as risk factors for depression in adults who have had a TBI, but this has proven challenging because the neuroanatomical basis for depression is not well understood (Jorge, 2015; Koenigs et al., 2008). Similarly, there does not appear to be a clear link between injury severity and

depression, with limited evidence supporting a dose-response relationship (Dikmen et al., 2004; Rapoport, 2012; Seel et al., 2003). Indeed, paradoxically, a recent meta-analysis found that clinically significant levels of depression were more common after mild than severe TBI (Osborn et al., 2014). In contrast, the time that has elapsed since the TBI appears less important, with high levels of depression found in both the short- (Dikmen et al., 2004) and longer-term (Draper et al., 2007). However, the basis for these symptoms may vary over time, with neurophysiological changes potentially making a greater contribution in the short-term (Bombardier et al., 2010) and psychosocial problems (e.g., reduced social functioning, loss of independence) being more important in the medium- and long-term (Jorge, 2015).

Pre-injury factors may additionally be related to a person's vulnerability to depression. For example, multiple TBIs appear to increase the risk of depression (Corrigan et al., 2013; Horner et al., 2008; Kerr et al., 2012), as do a variety of medical conditions (e.g., heart disease, diabetes, cancer)(Clarke & Currie, 2009). Similarly, previous episodes of depression may increase the risk of depression after a TBI (Bombardier et al., 2010; Whelan-Goodinson et al., 2010), although there are findings to the contrary (Dikmen et al., 2004; Rapoport et al., 2003b). Moreover, people with pre-existing psychological problems – such as depression and anxiety disorders – are more likely to sustain a TBI, suggesting a bidirectional relationship (Rao et al., 2015; Vassallo et al., 2007).

Stressful life-events following a TBI – including unemployment, financial problems and relationship breakdowns – are also consistently related to higher rates of depression (Coetzer et al., 2011; Dikmen et al., 2004; Seel et al., 2003; Seel, Macciocchi, Kreutzer, Kaelin, & Katz, 2011; Whelan-Goodinson et al., 2010). In contrast, social support may 'buffer' the stress caused both by the TBI and the associated physical, cognitive and psychological impairments (Driver, 2005), with greater support linked to lower levels of depression (Douglas & Spellacy, 2000; Horner et al., 2008).

Pre- and post-injury alcohol consumption have also been linked to depression. Not only does alcohol consumption increase the risk of sustaining a TBI (Corrigan et al., 1995), but it appears to be related to a variety of outcomes (e.g., mortality, cognitive/psychological problems) (Lange et al., 2014; Raj et al., 2015). Similarly, pre-injury alcohol abuse has been associated with an increased risk of depression after a TBI (Bombardier et al., 2010; Deb et al., 1999b; Dikmen et al., 2004), albeit not universally (Lange et al., 2014), and excessive post-injury alcohol consumption has consistently been associated with more symptoms of depression (Horner et al., 2005; Jorge et al., 2005).

Lastly, physical activity has been shown to reduce depression in both community (Wegner et al., 2014) and TBI (Driver & Ede, 2009) samples. Aside from improving mental and physical health, physical activity appears to enhance social engagement, cognitive functioning and the ability to perform daily activities (Gordon et al., 1998; Pawlowski et al., 2013; Schwandt et al., 2012). Despite these benefits, the physical and cognitive problems caused by TBIs frequently lead to a reduction in leisure and physical activities (Rosenthal et al., 1998); thereby indirectly increasing the risk of depression.

Thus, although a wide variety of risk factors for depression after a TBI have been investigated, neither their unique contribution nor their interaction is well understood (Bombardier et al., 2010; Carroll et al., 2004). What is clear, though, is that people have markedly different life-experiences, both before and after a TBI, which may impact on their mental health. However, it is often not feasible to measure a large number of variables in the clinical settings where most of this research has been conducted, and small samples, high attrition rates and referral bias may additionally limit the generalizability of the findings (Ashman, Cantor, Tsaousides, Spielman, & Gordon, 2014; Jorge, 2015). Moreover, many people who sustain a mild TBI – the most common level of injury, accounting for approximately 75% of all TBIs (Cassidy et al., 2004) – do not seek medical care (Voss, Connolly,

Schwab, & Scher, 2015) and may therefore be overlooked or under-represented in research that is based on clinical samples. In contrast, large-scale longitudinal community-based studies, which evaluate a variety of demographic/health/lifestyle variables, provide an opportunity to undertake a more comprehensive examination of risk factors for depression in people who have sustained a TBI.

With this in mind, the current study analysed prospectively collected data from a representative community-based cohort study - the Personality and Total Health (PATH) Through Life project – in order to determine whether TBIs are associated with depression across the adult lifespan (young, middle-aged and older adults). The prevalence of clinically significant 'cases' of depression was compared between samples who had never had a TBI (TBI_{no}) and those who had sustained a TBI sometime previously in their life ($TBI_{lifetime}$: sustained since birth) or in the recent few years (TBI_{recent}: preceding four years). These rates were compared at three intervals over an 8-year period: Wave one (W1), four years later (Wave two: W2), and a further four years later (Wave three: W3) to determine whether there was an association between TBI ($TBI_{lifetime}$/TBI_{recent}) and depression. Importantly, these longitudinal analyses controlled for the effect of known risk factors for depression following TBI (age, sex, marital/employment status, prior history of depression, medical condition, multiple TBIs, negative life events, alcohol consumption, social support, physical activity).

Method

Participants

PATH is an on-going prospective community-based study examining health and well-being across the adult lifespan. Participants were originally randomly selected from two electoral rolls (Canberra, Australian Capital Territory and Queanbeyan, New South Wales) which, because electoral enrolment is compulsory for Australian citizens aged ≥18 years (over

93% currently enrolled), capture a large proportion of the adult population. Census data indicate that Canberra and Queanbeyan had a population of approximately 300,000 and 27,500, respectively, when the study commenced. The PATH recruitment process originally targeted people in three age brackets: young (20-24 years: born 1975-1979), middle-aged (40-44 years: born 1956-1960) and older (60-64 years: born 1937-1941) adults, with participation rates in these age ranges being 59%, 65% and 58%, respectively. Data has been collected every four years since 1999 from these three age cohorts (W1: 1999-2002, W2: 2003-2006, W3: 2007-2010, and W4: 2011-ongoing). The number of participants lost to follow-up between W1 and W3 was low, with 90% completing W2 and 91% of those completing W3; equating to an 82% retention rate across the 8-years.

Data from 7,397, 6,621 and 6,042 participants who provided information relating to their TBI status in Waves 1, 2 and 3, respectively, were analysed in the current study. W4 data were not yet available for all cohorts, consequently it was excluded from the current analysis (see Table S1, Supplemental Digital Content for summary W1-W3 information). Additional details about the PATH participants and study methodology are provided in Anstey et al. (2012).

Measures

The PATH project used self-report measures to collect information about: socio-demographic details, general/physical/mental health, life stressors, social factors, cognitive functioning and personality. Not all measures were administered at every wave, consequently only those variables that were measured at all waves (W1-3) and have previously been found to be risk factors for TBI or depression – namely: age, sex, marital and employment status, prior history of depression and TBI, physical medical condition, negative life events, alcohol consumption, social support, physical activity – were analysed (refer to Supplemental Digital Content, Table S2, for summary details of the main PATH variables and those examined here).

TBI was defined by PATH as "a serious injury to the head that resulted in post-traumatic amnesia, loss of consciousness or brain haemorrhaging" and was determined by self-report (yes/no). At W1, participants were asked "have you ever had a serious head injury where you became unconscious for more than 15 minutes?" However, at W2, this item was modified to read "have you ever had a serious head injury, that interfered with your memory, made you lose consciousness or caused a blood clot in your brain?", thereby removing the minimum 15 minute loss of consciousness requirement. Importantly, the W2 item gathered information from birth, thereby enabling the data to be harmonized across W1 and W2, based on responses to questions about their age at the time of their first TBI, their most recent TBI, and the total number of TBIs experienced during their lifetime. The question relating to TBIs remained the same at W3, apart from the time-frame (since the last interview/wave). Thus, TBI status was determined at each wave in terms of the length of time that had elapsed since the injury: $TBI_{lifetime}/TBI_{no}$ (TBI sustained at any time previously in their life, yes/no); and TBI_{recent}/TBI_{no} (TBI sustained in the preceding four years, yes/no). An additional TBI variable was generated to indicate whether someone had sustained more than one TBI ($TBI_{multiple}$; yes/no). Participants were excluded from all analyses if TBI status could not be reliably determined (missing or contradictory data), which occurred in approximately 1-2% of cases (see Supplemental Digital Content, Table S1). Unfortunately, it was not possible to examine injury severity as a variable because the requisite data (e.g., Glasgow Coma Scale scores) were not available; thus all injury severities (mild, moderate and severe) were examined.

Depression was assessed at Waves 1-3 using the 9-item self-report Goldberg Depression Scale (GDS) (Goldberg, Bridges, Duncan-Jones, & Grayson, 1988), which measures the extent to which symptoms were experienced over the preceding month. As GDS data were skewed (therefore precluding the use of linear statistics) symptoms were summed and a binary variable (yes/no) generated. People who reported 6 to 9 depressive symptoms were

considered to have clinically significant levels of depression and are hereafter referred to as 'cases' ('no case' = 0-5 symptoms). A cut-off score of ≥6 (sensitivity 0.69, specificity 0.89) was used in the current study, although ≥4, ≥5, ≥6 and ≥7 symptoms have all been utilised elsewhere to identify 'cases' (Butterworth, Rodgers, & Windsor, 2009; e-hub Mental Health, 2015; Jacka, Cherbuin, Anstey, & Butterworth, 2014; Kiely & Butterworth, 2015). In addition, prior/lifetime history of depression ($depression_{lifetime}$), a risk factor for subsequent episodes of depression (Bombardier et al., 2010), was assessed at W1 via two questions about a person's previous experience of depression.

Finally, a number of risk factors for depression were extracted from the PATH dataset. Specifically, demographic characteristics encompassed age, sex, marital status (married/de facto; separated/divorced/widowed; never married), and employment status (employed full- or part-time; not in labour force; looking for more work). The presence of a comorbid medical condition was assessed according to whether the participant had been diagnosed with heart problems/cancer/arthritis/diabetes and a binary variable (yes/no) generated. The number of negative life events experienced in the previous six months (e.g., relationship, employment, financial problems) was assessed using the List of Threatening Experiences (12 items, total score range of 0-12, with higher scores indicating more stress (Brugha & Cragg, 1990). Levels of alcohol consumption, dependence and alcohol-related problems were assessed using the Alcohol Use Disorders Identification Test (AUDIT; total score range 0-40), with higher scores indicating more hazardous and harmful levels of drinking. Physical activity was measured in terms of the total time (hours/minutes) spent per week engaged in gardening, housework, golf/tennis, and swimming etc. Finally, social support was assessed using two scales measuring 'supportive interactions' with family and friends, which were averaged to provide a single measure (score range 0-6, higher scores indicate greater support).

Study procedure

Most PATH participants were interviewed in their home or at the Centre for Mental Health Research, Australian National University. Written consent was obtained immediately prior to conducting interviews, which assessed mental and physical health, personality, cognitive performance, medication and illicit substance use, social and family environment, life stressors and socio-demographic information. Trained interviewers administered the physical and cognitive tests, with participants completing the remaining measures on a laptop. The PATH study protocol was approved by the Human Research Ethics Committee at The Australian National University.

Statistical analysis

Pearson's χ^2 test (categorical variables) and *t*-tests (continuous variables) were used to compare the socio-demographic characteristics (age, education, sex, marital and employment status) of the TBI and non-TBI groups ($TBI_{lifetime}$ vs TBI_{no}) at W1. In addition, the prevalence of lifetime ($TBI_{lifetime}$), recent (TBI_{recent}), multiple ($TBI_{multiple}$) and no (TBI_{no}) TBIs were calculated at W1-W3; and depression 'cases' according to $TBI_{lifetime/recent}$ status were compared (Pearson's χ^2 test) to those without a TBI.

Generalized Estimating Equations (GEE) were then used to investigate (1) the relationship between 'cases' of depression (dependent variable; DV) and both $TBI_{lifetime}$ and TBI_{recent} (independent variables; IV) and (2) whether these relationships remained significant after taking into account specific risk factors. GEEs generated longitudinal analyses (total sample across all waves), which resulted in population-averaged effects (i.e., the aggregate response for the sample) between two groups with different risk factors (i.e., those with/without a TBI). GEEs are able to use all of the available data, even when participants fail to complete a wave/assessment, while also accounting for non-independent data (Twisk, 2004). Nonetheless, cases with any missing DV or IV data were excluded (for that wave only)

prior to analysis; thereby ensuring that data used in, and between, each GEE model were consistent. All GEE models used: an auto-regressive correlation structure to control for within-cluster bias (i.e., non-independence of repeated measures data); binomial distributions; logit-link functions; controlled for a lifetime history of depression ($depression_{lifetime}$); and excluded all cases with missing data (for the DV or IV). Two univariate GEE models (models 1 and 2) were initially generated in order to examine depression (DV) according to whether a participant had sustained a TBI (1) at any time in their life (IV: $TBI_{lifetime}$; model 1), and (2), in the preceding four years (IV: TBI_{recent}; model 2). Further univariate GEE models, using depression and TBI status ($TBI_{lifetime}$ and TBI_{recent}) as DVs, were then generated to determine which of the risk factors (IV: age, sex, marital and employment status, prior history of depression, physical medical condition, multiple TBIs, physical activity, life events, alcohol) had a significant, and potentially confounding, relationship with both depression and TBI status. Next, two multivariate GEE models (3 and 4) were generated, with the significant risk factors (covariates) identified in these univariate analyses, simultaneously entered. IBM® SPSS® Statistics (Version 22.0) was used for all analyses.

Results

Sample Representativeness.

Comparisons between the current study sample and the 2001 Australian Census are provided in the Supplemental Digital Content (Table S3). The Census data were provided by the Australian Bureau of Statistics and related to Australian citizens who were aged 20-24, 40-44, and 60-64, and residing in Canberra and Queanbeyan (Anstey et al., 2012). Weights for the PATH data were calculated independently for men and women in each of the three cohorts (6 separate calculations in all). Chi-square analyses demonstrated that there were no significant differences between the 2001 Australian Census and PATH participants, confirming that the sample was comparable to the referent population (Canberra and Queanbeyan).

Socio-demographic characteristics.

Summary demographic data at baseline (W1), stratified by age group and $TBI_{lifetime}$ status, are provided in Table 1. At W1, across the total sample, people who had sustained a TBI at any time in their life ($TBI_{lifetime}$) were slightly younger than those without TBIs (p <.05), but had comparable levels of education. Although the total sample was balanced for sex, more males sustained a TBI ($TBI_{lifetime}$); a pattern that was echoed across each age cohort (p <.05). Compared to those without a TBI, more TBI participants had never married and fewer were separated/divorced/widowed (total sample; p <.05) and, although employment rates were higher in those with a $TBI_{lifetime}$, more were also seeking additional work (p <.05). Therefore, other than sex, the demographic characteristics of $TBI_{lifetime}$ and TBI_{no} groups were generally comparable.

Table 1

Socio-demographic characteristics of participants at wave 1, grouped by age and lifetime TBI status.

	Young cohort (20+) n = 2,357					Middle-aged cohort (40+) n = 2,509					Older cohort (60+) n = 2,531					Total n = 7,397				
	Lifetime TBI		no TBI		*p*	Lifetime TBI		no TBI		*p*	Lifetime TBI		no TBI		*p*	Lifetime TBI		no TBI		*p*
	M	(SD)	M	(SD)		M	(SD)	M	(SD)		M	(SD)	M	(SD)		M	(SD)	M	(SD)	
Age (years)	22.6	(1.4)	22.6	(1.5)	.62	42.6	(1.4)	42.6	(1.5)	.86	62.5	(1.5)	62.5	(1.5)	.87	40.8	(15.9)	43.3	(16.3)	.00
Education (years)	14.4	(1.5)	14.6	(1.6)	.01	14.8	(2.3)	14.6	(2.3)	.12	14.0	(2.8)	13.8	(2.8)	.32	14.4	(2.2)	14.3	(2.4)	.22
	%	(n)	%	(n)	*p*	%	(n)	%	(n)	*p*	%	(n)	%	(n)	*p*	%	(n)	%	(n)	*p*
Sex					.00					.00					.00					.00
male	69.0	(203)	45.2	(933)		68.3	(200)	44.2	(979)		74.4	(166)	49.3	(1,138)		70.2	(569)	46.3	(3,050)	
female	31.0	(91)	54.8	(1,130)		31.7	(93)	55.8	(1,237)		25.6	(57)	50.7	(1,170)		29.8	(241)	53.7	(3,537)	
Marital status					.82					.07					.38					.00
married/de facto	23.1	(68)	23.6	(486)		77.1	(226)	79.8	(1,768)		81.6	(182)	77.7	(1,794)		58.8	(476)	61.5	(4,048)	
separated/divorced/widowed	0.7	(2)	1.1	(22)		11.6	(34)	12.8	(283)		16.6	(37)	19.5	(450)		9.0	(73)	11.5	(755)	
never married	75.9	(223)	75.4	(1,555)		11.3	(33)	7.4	(165)		1.8	(4)	2.7	(63)		32.1	(260)	27.1	(1,783)	
Employment status					.32					.95					.08					.00
employed (full, part-time)	79.6	(234)	80.4	(1,658)		88.4	(259)	88.9	(1,971)		42.6	(95)	40.4	(933)		72.6	(588)	69.3	(4,562)	
not in labour force	7.5	(22)	9.4	(193)		7.8	(23)	7.4	(163)		54.7	(122)	58.4	(1,349)		20.6	(167)	25.9	(1,705)	
looking for more work	12.6	(37)	10.3	(212)		3.8	(11)	3.7	(82)		2.7	(6)	1.1	(25)		6.7	(54)	4.8	(319)	

Differences between TBI, no TBI groups tested using Pearson's χ^2 (categorical variables) and independent-samples *t*-tests (continuous variables).

Prevalence of lifetime, recent and multiple TBIs.

The prevalence of lifetime (since birth; $TBI_{lifetime}$), recent (preceding four years; TBI_{recent}) and multiple (≥2; $TBI_{multiple}$) TBIs were calculated (see Table 2). Eleven per cent of the sample had sustained at least one $TBI_{lifetime}$ at W1, with this value increasing slightly at W2 and W3. The percentages of $TBI_{lifetime}$ were relatively similar across age groups, although young adults had consistently higher rates than middle-aged and older adults, and young adults also had slightly higher TBI_{recent} rates. Moreover, by W3, more than 30% of those with a $TBI_{lifetime}$ had sustained multiple TBIs.

Table 2

Prevalence of TBIs sustained since birth, with a post-injury interval < 4 years, and individuals with ≥ 2 TBIs, and no TBI; partitioned according to wave and age group.

	Lifetime TBI[a]		**Recent TBI[b]**		**Multiple TBIs[c]**				**No TBI[d]**		**Total sample[e]**
	%	(n)	%	(n)	%	(n)	M	(SD)	%	(n)	(n)
Wave 1											
young adults	12.5	(294)	4.3	(101)	29.9	(88)	2.7	(1.0)	87.5	(2,063)	(2,357)
middle-aged adults	11.7	(293)	1.0	(24)	28.7	(84)	3.0	(2.0)	88.3	(2,216)	(2,509)
older adults	8.8	(223)	0.5	(12)	19.7	(44)	3.4	(3.0)	91.2	(2,308)	(2,531)
total	11.0	(810)	1.9	(137)	26.7	(216)	2.9	(2.0)	89.0	(6,587)	(7,397)
Wave 2											
young adults	15.2	(319)	4.7	(98)	44.5	(142)	3.2	(2.4)	84.8	(1,774)	(2,093)
middle-aged adults	12.6	(294)	1.2	(28)	33.3	(98)	3.3	(2.8)	87.4	(2,031)	(2,325)
older adults	9.5	(209)	0.7	(16)	23.0	(48)	3.5	(2.9)	90.5	(1,994)	(2,203)
total	12.4	(822)	2.1	(142)	35.0	(288)	3.3	(2.6)	87.6	(5,799)	(6,621)
Wave 3											
young adults	16.3	(316)	1.9	(37)	42.7	(135)	3.4	(2.5)	83.7	(1,621)	(1,937)
middle-aged adults	13.2	(283)	0.9	(19)	34.3	(97)	3.2	(2.8)	86.8	(1,866)	(2,149)
older adults	10.0	(195)	0.9	(18)	24.1	(47)	3.4	(2.9)	90.0	(1,761)	(1,956)
total	13.1	(794)	1.2	(74)	35.1	(279)	3.3	(2.7)	86.9	(5,248)	(6,042)

a = TBI sustained since birth
b = TBI sustained in the previous four years
c = % (n) is the proportion of lifetime TBI participants who have had ≥ 2 TBIs; M (SD) is the average number of TBIs sustained by individuals with ≥ 2 TBIs
d = participant has never sustained a TBI
e = total sample is the number of participants who have sustained a lifetime TBI plus those without a TBI (i.e., a + d)

Lifetime and recent TBIs: clinically significant 'cases' of depression.

The prevalence of 'cases' (≥6 symptoms) of depression were then compared between groups with/without a $TBI_{lifetime}$ (see Table 3). The $TBI_{lifetime}$ group had significantly more 'cases' of depression than the TBI_{no} group, both in the total sample (W2, W3) and middle-aged adults (W3). Whereas there was a trend toward more 'cases' of depression in older adults with a $TBI_{lifetime}$, the rates were relatively similar in young adults, regardless of TBI status (except W2).

The rates of depression for samples with/without a TBI_{recent} were then compared to determine whether recent injuries were associated with higher levels of depression (see Table 3). Although there were more 'cases' of depression in the TBI_{recent} group (compared to TBI_{no}) at each wave in the full sample, these differences were only significant at W2. In terms of age-cohorts, the numbers of 'cases' of depression were comparable in young adults, with rates only differing significantly in middle-aged (W2) and older (W1) adults.

Table 3

Summary data for clinically significant 'cases' of depression in lifetime TBI ($TBI_{lifetime}$) and recent TBI (TBI_{recent}) and no TBI (TBI_{no}) groups, partitioned according to wave and age group.

	Wave 1					Wave 2					Wave 3				
	TBI		No TBI			TBI		No TBI			TBI		No TBI		
	%	(n)	%	(n)	*p*	%	(n)	%	(n)	*p*	%	(n)	%	(n)	*p*
Lifetime TBI															
young cohort	16.0	(47)	16.1	(331)		21.1	(67)	17.1	(302)		15.5	(49)	15.8	(256)	
middle-aged cohort	15.1	(44)	13.3	(293)		14.7	(43)	11.3	(228)		16.0	(45)	10.6	(196)	
older cohort	7.7	(17)	5.4	(125)		6.3	(13)	5.5	(109)		5.7	(11)	4.2	(73)	
total	13.4	(108)	11.4	(749)	.10	15.1	(123)	11.1	(639)	.00	13.3	(105)	10.1	(525)	.01
Recent TBI															
young cohort	14.9	(15)	16.1	(363)		19.6	(19)	17.5	(346)		18.9	(7)	16.0	(310)	
middle-aged cohort	12.5	(3)	13.5	(334)		28.6	(8)	11.4	(259)		15.8	(3)	11.5	(247)	
older cohort	25.0	(3)	5.5	(139)		6.3	(1)	5.6	(121)		0.0	(0)	4.5	(88)	
total	15.3	(21)	11.6	(836)	.18	19.9	(28)	11.3	(726)	.00	13.5	(10)	10.7	(645)	.44

Note: % of depression cases partitioned by TBI status – reported within each age group, and across all age groups; lifetime TBI = TBI sustained at any time prior to the reported wave; recent TBI = TBI sustained in the four years prior to the reported wave

Longitudinal relationship between lifetime/recent TBIs and depression.

Longitudinal analyses were performed using Generalized Estimating Equations (GEE) because the aim of the present study was to generate population-averaged effects between two groups with different risk factors (TBI status). Two univariate GEE models examined the relationship between depression 'cases' (DV) and TBI status (IV), controlling for prior history of depression, namely : (1) depression and $TBI_{lifetime}$ and, (2) depression and TBI_{recent} (see models 1 & 2), Table 4), which revealed that there was a 24% (p <.01) increase in the odds of clinically significant depression (a 'case') following a $TBI_{lifetime}$ when the data for all age groups were combined (total sample). Older adults who had recently sustained a TBI (<4 years) were the most vulnerable (OR = 1.72), although this result was not significant, possibly due to more variable outcomes or lack of statistical power (95% CIs: 0.76-3.88). Analyses for the remaining age-cohorts revealed small effects for the association between TBI ($TBI_{lifetime}$/TBI_{recent}) and depression, but none were significant.

Next, adjusted multivariate GEE models were generated to examine whether the significant relationship in the aforementioned univariate GEE analyses persisted after adjusting for covariates (risk factors identified as significant in additional GEE univariate analyses) (see Table 4). In terms of $TBI_{lifetime}$, after adjusting for these covariates (p <.05; age [total sample only], sex, marital status, employment status, and lifetime history of depression), the association with depression (model 3) remained significant in the full sample, with a 19% increase in the odds of depression 'cases' when a TBI had been sustained at some time in the person's life. For TBIs sustained recently (TBI_{recent}; model 4), the significant covariates entered into the multivariate model were: age (total sample only), sex, marital status, employment status, other medical conditions, multiple TBIs, physical activity, life events, alcohol and lifetime history of depression. Although the odds of experiencing clinically significant depression was higher (OR >1) for both the total and each age group (lower odds only in older adults), these results were not significant.

Table 4

Univariate & adjusted (multivariate) longitudinal analyses: odds ratios and 95% CIs for the association between depression and TBI status across waves 1, 2 and 3, partitioned according to age group.

	young cohort		**middle-aged cohort**		**older cohort**		**total^**	
	OR (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*
Univariate								
lifetime TBI (model 1)	1.07 (0.86 – 1.35)	.54	1.20 (0.92 – 1.56)	.17	1.20 (0.76 – 1.89)	.43	1.24 (1.05 – 1.45)	.01
recent TBI (model 2)	1.03 (0.73 – 1.46)	.87	1.10 (0.56 – 2.13)	.79	1.72 (0.76 – 3.88)	.19	1.29 (0.94 – 1.76)	.11
Multivariate								
lifetime TBI (model 3)	1.15 (0.91 – 1.45)	.23	1.24 (0.95 – 1.63)	.12	1.13 (0.71 – 1.80)	.60	1.19 (1.00 – 1.40)	.04
recent TBI (model 4)	1.19 (0.79 – 1.80)	.40	1.32 (0.65 – 2.69)	.44	0.70 (0.27 – 1.84)	.47	1.21 (0.87 – 1.69)	.26

Models controlled for:
1 = lifetime depression at W1
2 = lifetime depression at W1
3 = lifetime depression at W1, sex, marital status, employment status
4 = lifetime depression at W1, sex, marital status, employment status, physical medical condition, multiple TBIs, physical activity, life events, alcohol

^ = analyses using the total sample also controlled for age at W1, whereas analyses partitioned by age group did not control for age at W1

Discussion

The current study examined whether – in the general community – sustaining a TBI is associated with a higher risk of clinically significant depression ('case'). Importantly, it explored the association between demographic, health and lifestyle variables, which are known individual risk factors for depression following a TBI. The study findings are particularly useful because the prospective longitudinal data, unlike data collected from clinical samples, enables an examination of the association between TBI status and clinically significant depression in people who were randomly-selected from the general community. This difference in recruitment sources is critical because the available estimates suggest that 30%-40% of people do not seek medical attention after a mild TBI (Demakis & Rimland, 2010; Setnik & Bazarian, 2007) and, hence, are overlooked in much of the TBI literature. The present study also controlled for previous mental health problems– which may predispose someone to developing depression (Bombardier et al., 2010) – as well as a number of other risk factors.

Overall, approximately 13% of people had sustained a TBI by the final assessment, which is comparable to rates reported in a recent meta-analysis examining the prevalence of lifetime TBIs (12.1%) in Australasia/US/Canada (Frost, Farrer, Primosch, & Hedges, 2013). Somewhat surprisingly, we found that young adults had higher lifetime TBI rates than the older cohorts at each wave; a phenomenon that has also been documented in studies examining psychiatric disorders (Giuffra & Risch, 1994; Patten, 2003). Unfortunately, it was not possible to determine whether these paradoxical findings were attributable to cohort effects, whereby young adults may now be engaging in more risky activities than earlier generations, or the failure of older cohorts to recall previous TBIs (recall bias). In contrast, a seminal cross-sectional study, which also documented the prevalence of self-reported TBI and depression in a population-based sample reported a lower rate of TBIs (8.5%). However, as more than 50% of their sample was aged over 65 years, recall bias and/or cohort effects may

also have reduced their rates of self-reported TBI (Silver et al., 2001). At the other extreme, substantially higher rates of self-reported TBI (43%) have been found in a recent population-based study (Whiteneck, Cuthbert, Corrigan, & Bogner, 2016); although that study used a more comprehensive self-report measure to ascertain all lifetime injuries (including TBIs), which may have reduced recall bias. Young adults in the current study also sustained more recent TBIs than middle-aged/older adults at each of the three waves. This is probably not surprising because many participants had recently reached the minimum legal age for consuming alcohol (18 years) and driving (16 years), both of which are risk factors for TBI. Interestingly, the rate of recent TBIs in young adults more than halved by their late twenties/early thirties, suggesting they may have passed through the high-risk period for TBIs.

TBI is increasingly acknowledged as a chronic condition due to its long-term impact on outcomes (Corrigan & Hammond, 2013). Our results appear to support this notion because the risk of depression tended to be higher in people who had sustained their TBI at some time since birth (compared with TBIs sustained in the preceding 4 years); with those who had a lifetime TBI often reporting injuries that dated back to childhood. In these people ($TBI_{lifetime}$), the prevalence of clinically significant depression was slightly – although not markedly – higher (13% to 15%) than those in the community who had not sustained a TBI (10% to 11%). In comparison, Silver et al. reported greater differences in the lifetime prevalence of MDD/dysthymia between those with and without a TBI (16.6% vs 8.1%, respectively) however, in the absence of information about the temporal relationship between TBI and depression, it is possible that depression preceded the TBI. Further, studies using clinical TBI samples have also consistently reported higher rates of depression in those with a TBI, compared to people from the general community (Goldstein et al., 2001; Konrad et al., 2011; Ponsford & Ziino, 2003; Senathi-Raja et al., 2010). Moreover, even though the proportion of people married/in a de facto relationship and/or employed was comparable between people with and without a

TBI, depression was more prevalent in those with a TBI. This suggests that for the PATH sample, the availability of social contact/support did not impact on the frequency of depression.

In terms of age-cohorts, across W1-W2-W3, there were more 'cases' of depression in young adults (16%-21%-16%), than middle-aged (15%-15%-16%) and older (8%-6%-6%) adults. Interestingly, there were negligible differences in the rates of depression in young adults with and without a TBI, suggesting other factors were associated with clinically significant depression in this cohort.

When the longitudinal association between TBI and depression was evaluated, perhaps the most striking finding was the continued relationship between clinically significant 'cases' of depression and lifetime TBIs – even after controlling for age, sex, history of depression, marital and employment status, number of TBIs, physical activity, alcohol consumption, other medical conditions, social support, and recent life events. Thus, regardless of differences in a broad variety of demographic, health and lifestyle factors, people who had sustained a TBI – at any time since birth – were more likely to experience higher rates of depression than those who have never had a TBI. This finding is consistent with Silver et al. (2001) who also demonstrated that individuals with a head-injury were more likely to be diagnosed with MDD/dysthymia, even when age, sex, marital status, socio-economic status and level of alcohol abuse were taken into account. Of note, the strong association between depression and TBI was not apparent when the TBI had been sustained relatively recently (TBI_{recent} <4 years ago) because, although the odds ratios for $TBI_{lifetime}$/TBI_{recent} groups were comparable, the association between depression and TBI_{recent} was non-significant, possibly reflecting variability in individual outcomes or the smaller sample size.

Limitations

These findings should be contextualised in terms of the study limitations. First, the definition of a TBI was modified at W2 of the PATH study, which meant that all mild TBIs sustained since birth became eligible for inclusion. However, this change also removed the need for participants to make subjective (and potentially unreliable) judgements about the length of loss of consciousness (i.e., often mistaken for post-traumatic amnesia) (Menon et al., 2010). Moreover, data were harmonised across waves according to the age at which the TBI was sustained, providing a more comprehensive overview of the individual's TBI history. Second, the current study was not able to examine injury severity, although this has previously been found to have minimal impact on depression after a TBI (Bombardier et al., 2010; Rapoport, 2012). Additionally, TBIs were not medically confirmed, but being a community-based study, it is more likely to have included the 30-40% of people with mild TBIs who do not seek medical treatment and would otherwise be overlooked (Demakis & Rimland, 2010; Setnik & Bazarian, 2007). Hence, the present study is likely to better reflect population prevalence rates. Third, data collection for the PATH study is continuing and thus an assessment of the complete adult lifespan from 20 to 84 years of age, is not yet complete. Fourth, despite sampling from the general population, the communities of Canberra and Queanbeyan have relatively high levels of education, general good health and higher socio-economic status than the Australian average; potentially affecting the generalisability of the results (Anstey et al., 2012).

Fifth, it is possible that the prevalence of depression was under-estimated because the GDS was not necessarily completed proximal to the injury or at prescribed intervals after. Depression has a fluctuating time-course following TBI, hence more frequent assessments may have identified individuals who experienced depression between, but not at the time of, the assessments (Bombardier et al., 2010). Also, sample attrition resulted in more psychologically

healthier individuals being retained at each wave (retention bias), which may have influenced the accuracy of the data and under-estimated the prevalence of depression. Sixth, whereas a more comprehensive measure of depression would have been desirable, large community-based longitudinal studies are necessarily limited in the type and length of measures that can be administered. Moreover, the GDS does not specifically measure depressed mood (e.g., items assessing sadness or crying), which is one of two criteria for a diagnosis of MDD in the DSM-5, potentially affecting the prevalence of depression. However, a recent validation study (Kiely & Butterworth, 2015) found that 5 or more symptoms provided the optimal balance of sensitivity and specificity for the GDS, though they acknowledge that the best cut-points should depend on the context. Thus, the current study selected a higher cut-off of ≥6 symptoms to optimise specificity (number of 'non-cases' correctly classified). Finally, despite a selection of known risk factors for depression being examined, the importance of genetic vulnerability, acute injury-related factors (e.g., the neuroendocrine and neuroinflammatory alterations produced by the TBI), and personality traits (e.g., coping styles, mastery, rumination) all still need to be investigated (Jorge, 2015).

In conclusion, in community-dwelling adults, the occurrence of a TBI at any time in a person's life was associated with a greater risk of experiencing clinically significant levels of depression, however this association was not evident when the TBI had been sustained more recently (i.e., ≤ 4 years post-injury). The prevalence of depression was highest in young adults, but this was unrelated to whether or not someone had sustained a TBI, suggesting that early adulthood is a vulnerable time. Thus, health-care professionals need to be aware that people who have sustained a TBI may be at an increased risk of experiencing depression in the longer-term, and should therefore ensure that people are monitored and supported in order to optimise their health outcomes. Public health messages should also reinforce the importance of individuals seeking medical attention for all TBIs, regardless of severity.

4.4 Supplemental Digital Content

Table S1

Overview of the full sample in the Personality and Total Health (PATH) Through Life study, and participants in the current study sample, partitioned according to successive assessment

	Young cohort	Middle-aged cohort	Older cohort	Total
Wave 1				
age at assessment	20 – 24 years	40 – 44 years	60 – 64 years	
year of birth	1975 – 1979	1956 – 1960	1937 – 1941	
when assessed	1999 – 2000	2000 – 2001	2001 – 2002	
PATH participation rate (%)^	(58.6)	(64.6)	(58.3)	
PATH W1 full sample participants, n	2,404	2,530	2,551	7,485
TBI data missing, n (%)	47 (2.0)	21 (0.8)	20 (0.8)	88 (1.2)
current study W1 participants, n	2,357	2,509	2,531	7,397
Wave 2				
age at assessment	24 – 28 years	44 – 48 years	64 – 68 years	
when assessed	2003 – 2004	2004 – 2005	2005 – 2006	
lost to follow-up, n	265	176	329	770
PATH W2 full sample participants, n	2,139	2,354	2,222	6,715
PATH W2 participation rate (%)	(89.0)	(93.0)	(87.1)	(89.7)
TBI data missing, n (%)	46 (2.2)	29 (1.2)	19 (0.9)	94 (1.4)
current study W2 participants, n	2,093	2,325	2,203	6,621
Wave 3				
age at assessment	28 – 32 years	48 – 52 years	68 – 72 years	
when assessed	2007 – 2008	2008 – 2009	2009 – 2010	
lost to follow-up, n	161	172	249	582
PATH W3 full sample participants, n	1,978	2,182	1,973	6,133
PATH W3 participation rate (%)	(92.5)	(92.7)	(88.8)	(91.3)
TBI data missing, n (%)	41 (2.1)	33 (1.5)	17 (0.9)	91 (1.5)
current study W3 participants, n	1,937	2,149	1,956	6,042

Note: wave = assessment; 'TBI data not determined'= TBI item responses (missing, don't know, uncertain, refused) not clarified with data provided
at other assessments; participation rate = the percentage of PATH participants interviewed from the previous wave.

^ PATH participation rate at W1 based on eligible individuals identified from the Canberra and Queanbeyan electoral roll

Table S2

Summary of the variables measured in the full PATH sample; and the TBI, depression and risk factor variables examined in the current study.

Selected list of variables measured in the full PATH study	
Socio-demographic:	age, gender, marital & employment status, housing, income
Cognitive functioning:	memory, attention, executive functioning
General health:	TBI, medical conditions, medication, pregnancy, cigarette & alcohol consumption, illicit drug use
Mental health:	depression & anxiety, suicidality, self-harm, post-traumatic stress-disorder symptoms
Physical tests:	blood pressure, eye chart, lung function
Personality:	mastery, ruminative style, resilience
Life stressors:	financial & work stress, role strain, lifetime trauma, life events
Social factors:	social support, pet ownership, child-care, volunteering, care-giving

Variables analysed in the current study	
TBI	
Presence of a TBI	serious head injury (self-reported) that interfered with memory, caused loss of consciousness, or a blood clot in the brain
$TBI_{lifetime}$	TBI sustained at any time since birth
TBI_{recent}	TBI sustained in the 4 years preceding the W1, W2 or W3 assessment (participant may have experienced other TBIs)
$TBI_{multiple}$	2 or more TBIs sustained since birth
TBI_{no}	never sustained a TBI
Depression	
Presence of depression	Goldberg Depression Scale (GDS); self-report scale with 9 items (yes/no response), total score range 0 to 9, higher scores indicate more symptoms in the preceding month (Goldberg et al., 1988). Binary variable measuring 'cases' of clinically significant depression (6 – 9 symptoms), or no case (0 - 5 symptoms).
$depression_{lifetime}$	categorical variable: yes/no. A positive response to both (1) whether participants had ever been markedly depressed (felt sad, lost interest in things, lacked energy) for at least several weeks and (2) seen a doctor or counsellor for their depression at the time, indicated a prior history of depression.
Risk factors *(for depression)*	
age	participant's age
marital status	3 categories: married/de facto; separated/divorced/widowed; never married
employment status	3 categories: employed full- or part-time; not in labour force; looking for more work
medical conditions	binary variable (yes/no). Whether the participant had been diagnosed with: heart problems, cancer, arthritis, or diabetes.
negative life events	List of Threatening Experiences questionnaire; self-report scale measuring the number of negative life events experienced in the preceding six months (e.g., relationship, employment, financial problems); 12 items, score range 0 - 12, higher scores indicate more stress (Brugha & Cragg, 1990).
alcohol consumption	Alcohol Use Disorders Identification Test (AUDIT) assessed participants' levels of alcohol consumption, dependence & alcohol-related problems. Score range 0

	- 40, with higher scores indicating more hazardous and harmful levels of drinking (Saunders, Aasland, Babor, De la Fuente, & Grant, 1993).
social support	2 scales evaluating 'supportive interactions' with (1) family and (2) friends & relatives (e.g., whether family/friends/relatives make you feel cared for, express an interest in you). Scores for each scale ranged from 0-6, averaged to create a single measure of social support, higher scores indicate greater support (Schuster, Kessler, & Aseltine Jr, 1990).
physical activity	measured in terms of the total amount of time (hours/minutes) spent each week undertaking activities such as gardening, housework, playing golf/tennis, dancing and swimming.

Table S3

Comparison between PATH sample characteristics and population Census information (%)

Variable	PATH	Census
Marital status		
Married	46.03	42.94
De facto	9.81	8.87
Separated	2.71	2.65
Divorced	4.74	5.57
Widowed	1.68	1.57
Never married	35.04	38.40
Employment status		
Employment (full- or part-time)	79.06	74.59
Unemployed	3.49	4.21
Not in labour force	17.42	21.20
Education completed		
Post-school qualifications	66.22	53.17
Bachelor degree or above	32.09	31.59
Undertaking current study		
Full- or part-time study	25.64	21.27

Australian Bureau Statistics 2001 census

Data combined across age and gender; PATH percentages weighted for comparability to the census data

Table S4

Univariate GEE analyses: risk factors and (a) depression (b) lifetime TBI (c) recent TBI.

(a)

	Depression		
	OR	*95% CIs*	*p*
Age at baseline	0.97	0.97 - 0.97	.00
Gender	1.22	1.08 - 1.37	.00
Marital status = 2	1.77	1.56 - 1.99	.00
Marital status = 1	1.21	1.04 - 1.42	.02
Employment status = 2	2.18	1.78 - 2.67	.00
Employment status = 1	0.83	0.73 - 0.93	.00
Medical comorbidity	0.87	0.78 - 0.97	.01
Multiple TBIs	1.70	1.34 - 2.16	.00
Physical activity	0.99	0.99 - 1.00	.02
Positive social support	0.64	0.62 - 0.67	.00
Negative life events	1.37	1.33 - 1.40	.00
Alcohol	1.05	1.04 - 1.07	.00

(b)

	Lifetime TBI		
	OR	*95% CIs*	*p*
Age at baseline	0.99	0.98 - 0.99	.00
Gender	0.35	0.30 - 0.41	.00
Marital status = 2	0.92	0.86 - 0.98	.01
Marital status = 1	0.99	0.91 - 1.08	.84
Employment status = 2	1.01	0.96 - 1.07	.69
Employment status = 1	0.94	0.91 - 0.98	.01
Medical comorbidity	1.03	0.99 - 1.07	.10
Physical activity	1.00	1.00 - 1.00	.57
Positive social support	1.00	0.98 - 1.01	.58
Negative life events	1.00	0.99 - 1.01	.80
Alcohol	1.00	0.99 - 1.01	.61

(c)

	Recent TBI		
	OR	*CIs*	*p*
Age at baseline	0.95	0.94, 0.96	.00
Gender	0.41	0.32, 0.52	.00
Marital status = 2	3.01	2.36, 3.82	.00
Marital status = 1	1.12	0.75, 1.68	.57
Employment status = 2	1.49	0.92, 2.43	.11
Employment status = 1	0.36	0.26, 0.51	.00
Medical comorbidity	0.63	0.48, 0.83	.00
Multiple TBIs	35.63	28.36 – 44.75	.00
Physical activity	1.02	1.02, 1.03	.00
Positive social support	0.92	0.82, 1.04	.18
Negative life events	1.25	1.18, 1.32	.00
Alcohol	1.11	1.10, 1.13	.00

Note: significance levels of marital and employment status variables differ according to level, therefore results from the Tests of Model Effects Type III test were used to determine the variable's inclusion in the multivariate models. Each model controlled for lifetime history of depression. Lifetime and multiple TBI variables were highly correlated, therefore not included above, or in the multivariate analysis.

CHAPTER 5: META-ANALYSIS – ANXIETY FOLLOWING TBI

5.1 Preamble

This Chapter consists of a manuscript entitled "The prevalence of anxiety following adult traumatic brain injury: A meta-analysis comparing measures, samples and postinjury intervals", which has been published in *Neuropsychology* (2016).

An examination of anxiety problems following TBI is a natural progression for the present thesis given that anxiety is also common after a TBI and, moreover, that anxiety and depression are frequently comorbid in the general population. However, the clinical utility of research examining anxiety after a TBI is also limited because, as with depression, there is a large amount of variability between published studies. Thus, the third study meta-analysed research that has investigated anxiety after adult TBI in order to identify some of the variables that impact on the prevalence of anxiety following a TBI; thereby making an important contribution to the literature. In the absence of a meta-analysis, the existing research on anxiety following TBI is poorly consolidated and, as a result, less useful to clinicians and researchers alike.

Tables and Figures are provided within the text and supplementary information for this paper is included at the end of the chapter (pages 147-151): the literature search strategy (Table S1); the anxiety measures that were eligible for analysis in the current study (Table S2); the flowchart of the meta-analysis review and selection process (Table S3); and details of the papers that used overlapping samples, which were combined and treated as non-independent studies (Table S4). A complete list of references, including those for this paper, has been provided at the end of the thesis (pages 208-237); references marked with a cross ($^{+}$) indicate studies included in this current paper's meta-analyses.

Chapter 5: Paper three

Prevalence of anxiety following adult traumatic brain injury:

A meta-analysis comparing measures, samples and post-injury intervals

Authors: A. J. Osborn, J. L. Mathias, A. K. Fairweather-Schmidt

This chapter consists of a paper published in Neuropsychology,

impact factor 3.43

Statement of authorship is on the following page.

5.2 Statement of Authorship

Statement of Authorship

Title of Paper	Prevalence of anxiety following adult traumatic brain injury: A meta-analysis comparing measures, samples and postinjury intervals
Publication Status	☑ Published ☐ Accepted for Publication ☐ Submitted for Publication ☐ Unpublished and Unsubmitted w ork w ritten in manuscript style
Publication Details	Osborn, A. J., Mathias J. L., & Fairweather-Schmidt A. K. (2016). Prevalence of anxiety following adult traumatic brain injury: A meta-analysis comparing measures, samples and postinjury intervals. *Neuropsychology*, *30*(2), 247-261. doi: 10.1037/neu0000221

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Name of Principal Author (Candidate)	Amanda Osborn
Contribution to the Paper	Conducted literatures searches, coded articles, analysed and interpreted data, wrote manuscript and acted as corresponding author.
Overall percentage (%)	85%
Certification:	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.
Signature	Date: 14/10/16

Co-Author Contributions

By signing the Statement of Authorship, each author certifies that:

i. the candidate's stated contribution to the publication is accurate (as detailed above);
ii. permission is granted for the candidate in include the publication in the thesis; and
iii. the sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

Name of Co-Author	Jane Mathias
Contribution to the Paper	Supervised and contributed to the study design, analysis and data interpretation, and manuscript preparation.
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Signature	Date: 12/10/16.

Please cut and paste additional co-author panels here as required.

5.3 Paper three

Abstract

Objective: Anxiety following a traumatic brain injury (TBI) is a common problem, however disparate prevalence estimates limit the clinical utility of research. The purpose of the current study was to examine how differences in methodological variables and sample characteristics impact on the prevalence of anxiety.

Method: Data from 41 studies that examined either the prevalence of Generalized Anxiety Disorder (GAD) diagnoses or clinically significant 'cases' of self-reported anxiety following adult, non-penetrating TBI were analysed, and the impact of diagnostic criteria, measure, post-injury interval and injury severity was evaluated.

Results: Overall, 11% of people were diagnosed with GAD and 37% reported clinically significant levels of anxiety following TBI. Prevalence estimates varied for different diagnostic criteria (range: 2%-19%), interview schedules (range: 2%-28%) and self-report measures (range: 36%-50%). GAD and 'cases' of anxiety were most prevalent two to five years post-injury. The rates of GAD increased with injury severity (mild: 11%, severe 15%), but 'cases' decreased (mild: 53%, severe: 38%), although neither difference was significant.

Conclusions: Anxiety is common after a TBI, and ongoing monitoring and treatment should be provided. Methodological and sample characteristics should be clear and well-defined, as differences across studies (e.g., how anxiety is conceptualised, which measure is used, time since injury, injury severity) impact prevalence rates.

Keywords

Traumatic brain injury, anxiety, generalized anxiety disorder, prevalence, meta-analysis

Introduction

The neuroanatomical and neurochemical changes caused by traumatic brain injuries (TBI) can lead to a wide variety of cognitive (Dean & Sterr, 2013; Konrad et al., 2011), psychological (see Riggio, 2011 for review) and physical (Cantor et al., 2012; Mathias & Alvaro, 2012) problems. The functional consequences of these changes can be challenging (Gould, Ponsford, & Spitz, 2014), potentially restricting a person's employment, study and leisure activities and independence; which may, in turn, impact on life satisfaction (Powell et al., 2012; Stålnacke, 2007). Family relationships are also often affected, with partners, parents and children having to cope with changes in their relative and alterations in their family dynamics (Douglas & Spellacy, 1996; Ponsford & Schönberger, 2010).

Depression and anxiety are the most common psychological problems experienced following TBI (Bryant et al., 2010; Deb et al., 1999b; Koponen et al., 2002), with depression being the most frequently researched of the two (see Osborn et al., 2014 for review). However anxiety is also, arguably, equally important because it contributes to post-injury functional outcomes and quality of life (Franulic et al., 2004; Steadman-Pare, Colantonio, Ratcliff, Chase, & Vernich, 2001). Indeed, Bertisch et al. (2013) reported that anxiety has a greater impact than cognitive impairment on social and occupational functioning following brain injuries. Elevated levels of suicidality are additionally associated with anxiety following a TBI (Anstey et al., 2004; Tsaousides, Cantor, & Gordon, 2011), further highlighting its importance. In the community, general anxiety disorders are associated with relationship breakdowns, increased reliance on disability benefits, and lower annual incomes (Mendlowicz & Stein, 2000); findings that are likely to be mirrored in a TBI setting. Even sub-clinical levels of anxiety can cause suffering, impact on psychosocial and occupational functioning, and lead to increased benzodiazepine and health-care usage (see Haller, Cramer, Lauche, Gass, & Dobos, 2014 for review).

As with depression (Osborn et al., 2014), estimates of the prevalence of anxiety following TBI vary considerably; ranging from 2% (Koponen et al., 2002) to 83% (King & Kirwilliam, 2011). This variability undermines the clinical utility of these data, particularly because the reason(s) for these differences remains unknown. One explanation for the range in estimates is that the term 'anxiety' has both general and specific meanings. Used generally, anxiety refers to a range of distressing physical (e.g., muscle tension), cognitive (e.g., fear, worry) and behavioural (e.g., avoidance) symptoms (Rieger, 2008). These symptoms can range in severity from mild apprehension to extremely debilitating distress. Whereas mild levels of anxiety are experienced by most people and may be beneficial in certain situations, debilitating symptoms are experienced by many fewer people (Williams & Hill, 2012).

The term 'anxiety' is also used to refer to more severe disorders, for which there are accepted diagnostic criteria. Anxiety disorders seriously affect a person's quality of life and often require clinical assessment and treatment (Diaz et al., 2012), with Generalized Anxiety Disorder (GAD) and Post-traumatic Stress Disorder (PTSD) being common diagnoses following TBI (Gould et al., 2014). However, the most recent DSM (DSM-5; APA, 2013) has re-classified PTSD as a Trauma- and Stressor-Related Disorder, rather than an anxiety disorder, because the symptoms are not necessarily anxiety/fear-based. Moreover, there has been a long-standing debate about the status of PTSD following moderate to severe TBI due to the associated period of post-traumatic amnesia (for a review see Rogers & Read, 2007). In addition, there are concerns that TBIs sustained in psychologically traumatising circumstances (e.g., assaults) may impact outcomes, even when PTSD is not evident (Mathias, Harman-Smith, Bowden, Rosenfeld, & Bigler, 2014). The current study therefore only focused on GAD.

GAD diagnoses have predominantly been made using DSM criteria (DSM-III-R and IV, APA; 1987, 2001) (Fann et al., 1995; Whelan-Goodinson et al., 2009a), with many fewer people using ICD-10 criteria (World Health Organisation, 1992) (Deb, Lyons, & Koutzoukis, 1999a).

The DSM criteria for GAD emphasise the presence of excessive anxiety/worry and somatic symptoms, causing significant distress or impairment to the individual for at least six months (APA, 2013). This contrasts with ICD-10 criteria, which is less strict about duration, but requires a larger number of physical symptoms (Rickels et al., 2001). It is therefore possible that these differences may contribute to some of the variability in prevalence rates. No study has directly compared the two diagnostic criteria when assessing GAD following TBI, although the two systems have been found to yield comparable rates of PTSD (McCauley et al., 2005; Slade & Andrews, 2001).

Although not as stringently defined as GAD, clinically significant 'cases' of anxiety can also be identified using defined cut-offs for a number of self-report measures (e.g., Hospital Anxiety and Depression Scale [HADS]; Zigmond & Snaith, 1983). These questionnaires commonly assess a broad range of anxiety symptoms on a continuous scale (minimal to severe) and can be used to identify individuals with less serious problems whose psychosocial functioning may still be affected (Mendlowicz & Stein, 2000). However, it appears that the use of diagnostic criteria and self-report measures may yield disparate rates of anxiety, with minimal overlap between the 'cases' identified (Al-Adawi et al., 2007; Whelan-Goodinson et al., 2009b). This highlights the importance of distinguishing between the prevalence rates based on formal diagnoses of GAD and clinically significant 'cases' of anxiety.

The choice of interview schedule used to diagnose GAD also has the potential to impact prevalence rates. As yet, no study has directly compared the prevalence of GAD following TBI using different interview schedules (e.g., SCID-I; First et al., 1997; Schedules for Clinical Assessment in Neuropsychiatry [SCAN]; Wing et al., 1990) with the same sample. However, a recent meta-analysis examining this same issue in relation to major depression suggests that this variable warrants consideration (Osborn et al., 2014). Similarly, the choice of self-report measure may affect prevalence rates, as some were designed for use with non-

TBI samples (e.g., psychiatric outpatients) (Beck Anxiety Inventory [BAI]; Beck et al., 1988) and include items that may overlap with the somatic symptoms frequently experienced after a TBI (e.g., dizziness), potentially inflating scores.

Also important is the way in which self-report measures are administered (e.g., mailed, by phone), with a variety of methods having been used, including completion at a research centre or at home, over the phone, or via a combination of methods (Alfano et al., 1993; Hawthorne, Kaye, Gruen, Houseman, & Bauer, 2011; Kit, Mateer, & Graves, 2007; Skilbeck et al., 2013). Each of these situations may be affected by different variables, such as the desire to respond in a socially-acceptable way (research centre, phone), limited time to consider a response (phone), potential influence of others (at home), and/or degree of anonymity; all of which may impact prevalence rates (Fairweather-Schmidt & Anstey, 2012; Richman et al., 1999).

Anxiety is also related to different stages of recovery, making the time post-injury another important consideration (Koponen et al., 2002; Rao et al., 2008). Recovery from a TBI is a complex and dynamic process, and the time-frame for symptom resolution is variable, consequently differences in the timing of the assessment may impact both the number and severity of symptoms (Jorge et al., 1993a). In addition, the severity of an injury may be associated with anxiety, although the nature of this relationship remains unclear. For example, Van Reekum, Bolago, Finlayson and Garner (1996) reported that more severe injuries were associated with fewer anxiety problems, although others have failed to replicate this relationship (Hibbard et al., 1998; Jorge et al., 1993c). It is therefore possible that the timing of the assessment and severity of the injury may affect the prevalence of GAD or clinically significant 'cases' of anxiety following TBI, however it is not yet known to what extent.

In addition, some researchers have recruited control groups to compare the prevalence of anxiety post-TBI with persons suffering from other medical conditions (e.g.,

spinal injuries), significant others (family, friends and caregivers of the person with TBI) and people from the general community (Beaupre et al., 2012; Clarke et al., 2012; de Almeida Lima et al., 2008). Each group attempts to control for the impact of different confounding variables (e.g., pain), however it is not known whether, or how, the type of control group influences the findings.

In theory, any of the aforementioned variables may influence the prevalence of GAD or self-reported 'cases' of anxiety, potentially explaining why the reported rates vary so greatly. A detailed analysis is needed to assess their impact and to assist clinicians so that they are able select the most appropriate benchmark(s) for their particular circumstance. The current study therefore undertook a meta-analysis of research that has reported the prevalence of anxiety following TBI. The impact of different diagnostic criteria (DSM, ICD) and interview schedules (e.g., SCID-I, SCAN) on the prevalence of GAD; and the impact of questionnaire (e.g., HADS, BAI) and method of administration (e.g., mail, phone) on self-reported cases of anxiety were evaluated. In addition, the extent to which GAD diagnoses and 'cases' varied according to the time of assessment, injury severity and type of control group was examined.

Method

Literature search, inclusion and exclusion criteria

A comprehensive search of the literature, from January 1980 to May 2014, was undertaken using the PsycINFO, Pubmed, Scopus, and ISI Web of Knowledge electronic databases to identify studies that examined anxiety following adult TBI (see Table S1, page 147, Electronic Supplementary Material, for specific details). The reference lists of all studies that were meta-analysed were additionally examined for any other potentially relevant research.

For a study to be included in the current meta-analysis, it had to meet the following criteria: (1) it examined diagnoses of GAD or clinically significant anxiety following non-penetrating TBIs; (2) participants were adults, aged 18 years or older (in the absence of an age range: mean age minus 1 SD ≥ 18 years); (3) it reported the prevalence of current diagnoses of GAD and/or clinically significant 'cases' of anxiety assessed using a common and specific measure of anxiety (excludes quality of life and general function measures) (see Table S2, page 149, Electronic Supplementary Material, for eligible measures); (5) data were provided for a TBI sample (single sample) or both a TBI and control group (independent samples); (6) it was published in a journal in English and reported original data (excludes reviews); (7) the sample size was > 15 (excludes very small samples and case studies).

Studies were excluded if participants were drawn from highly specific or at-risk TBI populations, such as psychiatric patients, prison inmates, war veterans, or victims of large-scale trauma/terrorism, as these additional traumatic experiences/situations may increase an individual's propensity to develop psychological problems, making them less comparable to the general TBI population. Moreover, only pre-treatment data were analysed if a study examined treatment efficacy. Lastly, the current study focused on current/post-injury anxiety, rather than dispositional/trait anxiety; thus scores assessing the latter were excluded from analysis.

The literature search initially identified 5,991 potentially relevant articles; 1,146 of which were duplicates and many only broadly related to the current topic. The titles and abstracts of these articles were initially screened by the first author (AJO) using the aforementioned criteria, reducing this number to 552; for which full-text versions were sourced. Re-application of the inclusion criteria to these 552 papers narrowed the number of eligible studies to 62 (see Electronic Supplementary Material, Table S3, page 150, for a

summary of the review process). Papers were independently assessed by AJO and JLM if eligibility was unclear, after which a consensus decision was made.

All participants must be independent of those used in other eligible studies because the magnitude of an effect size may be distorted by the inclusion of non-independent samples (Rosenthal, 1995). There were 28 papers where the samples were not independent, either because the studies were longitudinal or reported different primary outcomes. The data from these papers were combined, resulting in seven independent studies (details provided in Table S4, page 151, Electronic Supplementary Material) and reducing the total number of studies from which data were analysed to 41. In addition, one of the studies that recruited a control group did not provide anxiety data for controls (Wood & Williams, 2008), hence the study was treated as a single-sample design.

Data preparation

Some simple transformations were needed to standardise the data before it could be analysed. First, when only a median and range were reported (e.g., age), means and standard deviations (SDs) were estimated using the methods recommended by Hozo, Djulbegovic and Hozo (2005). Secondly, data for post-injury interval were standardised (months) and, lastly, standard errors (SEs) were transformed into SDs where needed (Hedges, 1982).

Anxiety was assessed at different post-injury intervals, ranging from a few days to over 30 years, necessitating their classification into four broad intervals in order to sensibly analyse the data, these being: *early post-injury* (≤ 6 months after a TBI), *short-term* (> 6 months to ≤ 2 years), *medium-term* (> 2 years to ≤ 5 years), and *long-term* (> 5 years). Additionally, where studies assessed a control group, it was classified into one of three groups: 'medical controls' (general trauma, spinal cord injury patients), 'significant other' (family, friends and caregivers of the TBI participant) or 'general community' controls.

Data collection and effect size calculation

Demographic and injury information (e.g., age, gender, time-since-injury, Glasgow Coma Scale [GCS] score, injury severity: mild/moderate/severe), type of anxiety (GAD vs anxiety in broad sense of the term), method by which anxiety was assessed (e.g., interview schedule, self-report), GAD diagnostic criteria (DSM, ICD), specific measure (interview: SCID-I, SCAN etc.; self-report: BAI, HADS etc.), method by which self-report measures were administered (at research centre, by phone, mail or combination of methods), sample characteristics (recruitment source, prior TBIs and diagnosed mental health problems, current medications), type of control group (medical, significant other, community), and prevalence data were extracted from each study. This information was then entered into Comprehensive Meta-Analysis Software Version 2 for analysis (CMA; ©2006, Biostat, Inc., Englewood, NJ, USA).

The current study calculated two types of effect size: proportions and odds ratios (ORs). Proportions were used to summarize the prevalence of GAD (clinical diagnoses) and clinically significant cases of anxiety (self-reports), based on data extracted from studies that used either single (TBI) or independent (TBI + controls) sample(s). Weighted mean prevalence rates were calculated using sample size as the weighting variable. ORs were calculated from the prevalence data provided by studies that used self-report measures to assess clinically significant levels of anxiety ('cases') in TBI and Control groups (independent-samples) in order to evaluate any increase (OR >1) or decrease (OR <1) in the likelihood of experiencing serious anxiety following a TBI, relative to controls. As a guide, an OR of 2 means that the TBI group is twice as likely to experience clinically significant anxiety. According to the guidelines developed by Chen, Cohen and Chen (2010), ORs of 1.68, 3.47 and 6.71 are equivalent to small, medium, and large effects, respectively.

A conservative random-effects model was used to calculate all mean effect sizes. This model assumes that the effect sizes for individual studies vary as a result of sampling error and study design, and contrasts with that of a fixed-effects model, which assumes that sampling error is the only source of variability (Borenstein, Hedges, Higgins, & Rothstein, 2010). Importantly, where a study reported multiple scores (e.g., longitudinal studies) and these outcomes were eligible to be included in the same analysis, a mean effect was calculated to ensure that each study contributed only one effect size to any given analysis (Lipsey & Wilson, 2001). Forest plots were generated to examine the effect size distributions and to assist in identifying outliers (Boyles et al., 2011) and ninety-five percent confidence intervals (95% CIs) were calculated to provide the upper and lower bounds within which we can be 95% confident that the actual population prevalence rate for anxiety following TBI lies.

One problem facing meta-analyses is that the published literature is more likely to contain studies with significant findings, which may inflate the resulting effect sizes (Rosenthal, 1979). The potential impact of any such publication bias was assessed using Orwin's (1983) Fail-safe N statistic (N_{fs}), which estimates the number of unpublished studies that would be required to draw a finding into question. Three values are needed to compute the N_{fs}: the number of studies in an analysis, the resultant mean effect, and a hypothetical value that equates to a finding of minor importance/clinical significance. For current purposes, prevalence rates < 3% and ORs < 1.0 were deemed to be of minor clinical significance, based on: (1) the prevalence of anxiety in adults living in the general community (Wittchen & Hoyer, 2001) and (2) Hopkins' (2002) definition of a trivial OR. The resulting N_{fs} indicates the number of unpublished studies, with non-significant findings, that would need to exist in order to render a finding inconsequential. Thus, the larger the N_{fs}, the more confident we can be in a finding.

Statistical analyses

In accordance with guidelines provided by the Meta-Analysis of Observational Studies in Epidemiology (MOOSE) group, sub-group analyses were conducted in order to examine the impact of a variety of methodological and injury characteristics on the heterogeneous findings of studies that have examined anxiety following TBI (Stroup et al., 2000). This approach is also consistent with that of Borenstein, Hedges and Higgins (2009) who suggest that variability in the findings of different studies should be explored via sub-group analyses using a random-effects model.

The overall prevalence of GAD following TBI was examined using data extracted from studies that used either a single (TBI) or independent (TBI + controls) sample(s) design. Sub-group analyses were then conducted to assess the impact of a variety of methodological and injury characteristics on this prevalence rate. Specifically, these analyses examined: the criteria used to diagnose GAD (DSM, ICD), interview schedule (SCID-I, SCAN etc.), post-injury interval (i.e., ≤6 months, >6 months to ≤2 years, >2 to ≤5 years, >5 years), and severity of the TBI (i.e., mild, mild-moderate-severe, severe). Only one study examined GAD diagnoses in a TBI and Control group, limiting the analysis.

Following on from this, the prevalence of self-reported 'cases' of anxiety were evaluated using data from studies that examined TBI samples, with or without controls. A number of moderator variables were examined, namely: the questionnaire (HADS, BAI etc.), method of administration (research centre, phone, mail, combination), post-injury interval, and injury severity. In addition, ORs were used to examine the prevalence of self-reported 'cases', relative to controls; both overall and according to the type of control group (medical, significant other, community).

Results

Participant details

The 41 studies included in this meta-analysis provided data for a total of 4,210 participants. The background demographic and injury data for these studies are summarised in Table 1, where it can be seen that, on average, participants were young to middle-aged adult males. The average interval between the anxiety assessment and injury was four years, with seven studies assessing anxiety in the early stages (mean = 1.4 months, SD = 1.0), 14 in the short-term (mean = 13.8, SD = 4.7), 10 in the medium-term (mean = 40.7, SD = 12.2); and 10 in the long-term (mean = 137.9, SD = 86.6). Although relatively few studies provided a mean GCS score (12 studies), all provided categorical data relating to injury severity. The majority of studies examined mixed samples of mild, moderate and severe TBIs (25 studies), but did not provide separate subgroup data, leaving only 6 mild and 5 severe TBI studies that could be used to examine the impact of injury severity on anxiety.

Table 1

Summary demographic and injury characteristics for the studies (N = 41).

Variable	$N_{studies}$	$N_{participants}$	%	Mean	SD
Sample size	41	4,210		102.7	142.8
Age (years)	41	4,210		38.2	7.6
Gender (males)	41	2,904	70.0		
Time-since-injury (months)	41	4,210		48.5	67.5
Injury severity(GCS)	12	2,167		10.1	2.5
Injury severity					
Mild	6	692	16.4		
Mild, moderate, severe	25	2,923	69.4		
Mild, severe	1	214	5.1		
Moderate, severe	4	251	6.0		
Severe	5	130	3.1		
Recruitment source					
Outpatients	38	3,627	86.2		
Both inpatients & outpatients	3	583	13.8		
Pre-injury history of depression or anxiety					
Participants with history included	16	2,181	51.8		
Participants with history excluded	6	539	12.8		
Not specified	19	1,490	35.4		
Pre-injury history of TBI					
History of prior TBI	4	321	7.6		
No history of prior TBI	9	847	20.1		
Not specified	28	3042	72.3		
Medication					
Depression/anxiety medication	3	296			
Other medication (includes sedative, anti-epileptic, pain, hypnotic, and type not identified)	5	451			
Participants excluded if using medication	1	478			
Medications used, no further detail	2	264			
Not specified	33	3,038			
	$N_{Studies}$	N_{TBI}	%	$N_{Control}$	%
Type of Control group					
Medical	2	493	36.1	666	46.2
General community	4	666	48.8	519	36.0
Significant others	6	206	15.1	257	17.8
TOTAL		1,365		1,442	

Note: $N_{studies}$ and $N_{participants}$ refer to the total number of studies and participants for which data were available.
GCS = Glasgow Coma Scale. Three studies reported that participants were using both depression/anxiety medication and 'other' medications.
One study recruited controls from the person with TBIs significant others and the general community.

Most studies recruited participants from outpatient settings (38 studies; see Table 1), with the remaining few assessing a combination of outpatients and inpatients. Sixteen studies reported including participants who had experienced depression or anxiety prior to their TBI (equating to 4% of the sample), six excluded participants with a pre-injury psychiatric disorder, and 19 did not specify. The majority of studies failed to report whether participants had a prior TBI (28 studies) or excluded participants with such an injury (9 studies), but four reported including these participants (2.8% of the sample). Similarly, most studies (33 studies) failed to report medication use, although three indicated that 11% of their sample were taking depression or anxiety medication. Finally, there were 11 studies that assessed one or more control groups in addition to their TBI sample (see Table 1), with the majority recruiting significant others (6 studies) or people from the general community (4 studies) (one used both), and two recruiting medical controls (general trauma, spinal injuries).

Prevalence of Generalized Anxiety Disorder (GAD) following TBI

The data from studies that reported the prevalence of GAD following TBI (22 studies; 1,145 participants) were combined in order to calculate an overall estimate. Figure 1a provides a forest plot of the data for the individual studies (ordered by prevalence rate) and the weighted mean prevalence rate, which indicates that overall approximately 11% of people are diagnosed with GAD after a TBI. The N_{fs} statistic for this finding was large ($N_{fs} = 29$), suggesting that it is unlikely that there would be sufficient unpublished studies with non-significant findings in existence to draw this finding into question. However, there was substantial variation in the prevalence estimates of GAD across individual studies - ranging from 2% to 28% - highlighting the need to examine some of the variables that may be contributing to this.

As a first step, studies were grouped according to the GAD diagnostic criteria that they used, with the most common criteria being DSM-IV (6 studies), followed by DSM III-R (3

studies), ICD-10 (1 study), or a combination of DSM-IV/ICD-10 criteria (1 study). As seen in Figure 1b, the ICD-10 criteria were associated with a significantly lower prevalence rate (2%) than the other diagnostic classifications, although the associated N_{fs} undermined the reliability of this finding. The highest prevalence rate resulted from use of the DSM III-R criteria (19%), followed by the combined DSM-IV/ICD-10 criteria (11%) and DSM-IV criteria (9%), although none of these differences were significant (95% CIs overlapped).

GAD was diagnosed using one of six different interview schedules (see Figure 1c), with the SCID-I being used by five studies, the SCAN by two, and the others by one. The prevalence rates associated with each of these different measures ranged from 2% for the SCAN to 28% for the Schedule for Affective Disorders & Schizophrenia (SADS-L; Endicott & Spitzer, 1978); although the SCID-I, Mini-International Neuropsychiatric Interview (MINI; Sheehan et al., 1998) and Present State Examination (PSE; Wing et al., 1974) had equivalent rates (11%). Once again, although there were significant differences between the SCAN and all schedules except the PSE, the N_{fs} for the SCAN was low, indicating that the result is not robust. Moreover, the CIs for the remaining interview schedules overlapped, indicating that the prevalence rates did not deviate to a significant degree.

Next, post-injury interval was examined to determine whether it impacted the prevalence of GAD (see Figure 1d). Three studies measured participants in the early stages after their injury (≤ 6 mths; mean = 2 mths); four in the short-term (> 6mths to ≤ 2 yrs; mean = 1.1 years); four in the medium term (> 2 yrs to ≤ 5 yrs; mean = 3.2 yrs); and two in the long-term (> 5 yrs; mean = 19.5 yrs). Bryant et al. (2010) and papers included in 'Ponsford Group D' used a longitudinal design and consequently, contributed data in multiple categories. Although the mean rates for these different intervals varied between 5% and 17%, they did not differ significantly.

Although all studies provided categorical injury severity data, many used mixed samples (e.g., mild, moderate and severe) without reporting outcomes separately for each level, limiting the data that could be analysed (see Figure 1e). The data from studies that examined mixed samples - mild/severe (1 study), moderate/severe (4 studies), and mild/moderate/severe (25 studies) - were combined for this analysis and compared to those from single-category samples (mild, severe). GAD was found to be highest (and most variable) following severe TBIs (15%), followed by mild TBIs (11%) and mixed samples of mild/moderate/severe (10%), although these differences were not significant.

Lastly, only one study compared the prevalence of GAD following a TBI to that of a control group (TBI = 377; controls = 555). Although a reliable analysis was not possible, the findings from this study (Bryant et al., 2010) suggest that GAD is only slightly more prevalent following mild TBI than it is after general trauma at both 3 months (OR = 1.18) and 12 months post-injury (OR = 1.44).

Fig. 1

Prevalence of formally diagnosed GAD: (a) overall, (b) diagnostic criteria, (c) interview schedule, (d) time post-injury, (e) injury severity

Fig. 1a

Prevalence of GAD following TBI: overall

Study name	*Nparticipants*	*Prevalence*	*Lower CI*	*Upper CI*
Koponen (2002)	60	0.02	0.00	0.11
Deb (1999)	164	0.02	0.01	0.06
Ponsford Group D	123	0.04	0.01	0.12
Hibbard (1998)	100	0.09	0.05	0.16
Jorge (1993)	66	0.11	0.05	0.21
Bryant (2010)	377	0.11	0.07	0.18
Rao (2008)	54	0.11	0.05	0.23
Diaz (2012)	33	0.15	0.06	0.32
Ponsford Group C	100	0.17	0.11	0.26
Fann (1995)	50	0.24	0.14	0.38
Van Reekum (1996)	18	0.28	0.12	0.52
OVERALL	1,145	0.11	0.07	0.16

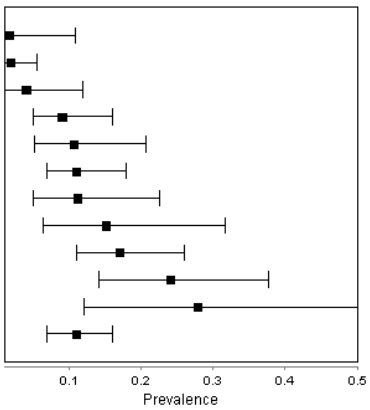


Fig. 1b

Prevalence of GAD following TBI: diagnostic criteria

	Nstudies	*Nparticipants*	*Prevalence*	*Lower CI*	*Upper CI*	*Nfs*
ICD-10	1	164	0.02	0.01	0.06	0
DSM-IV	6	470	0.09	0.07	0.16	12
Both DSM-IV & ICD-10	1	377	0.11	0.07	0.18	3
DSM III-R	3	134	0.19	0.11	0.33	16

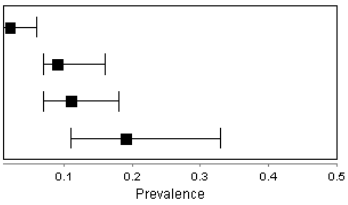


Fig. 1c

Prevalence of GAD following TBI: interview schedule

	Nstudies	*Nparticipants*	*Prevalence*	*Lower CI*	*Upper CI*	*Nfs*
SCAN	2	224	0.02	0.01	0.05	1
MINI	1	377	0.11	0.07	0.18	3
PSE	1	66	0.11	0.05	0.21	3
SCID-I	5	410	0.11	0.07	0.17	13
DIS	1	50	0.24	0.14	0.38	7
SADS-L	1	18	0.28	0.12	0.52	8

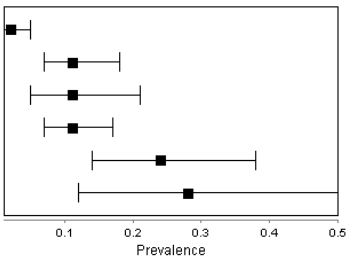


Fig. 1d

Prevalence of GAD following TBI: time post-injury

	Nstudies	*Nparticipants*	*Prevalence*	*Lower CI*	*Upper CI*	*Nfs*
Early (≤6 mths)	3	497	0.10	0.07	0.15	7
Short-term (>6 mths - ≤2 yrs)	4	697	0.06	0.02	0.16	4
Medium-term (>2 yrs - ≤5 yrs)	4	291	0.17	0.11	0.27	19
Long-term (>5 yrs)	2	160	0.05	0.01	0.19	1

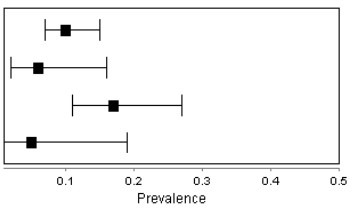
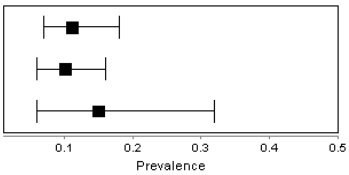


Fig. 1e

Prevalence of GAD following TBI: injury severity

	Nstudies	*Nparticipants*	*Prevalence*	*Lower CI*	*Upper CI*	*Nfs*
Mild	1	377	0.11	0.07	0.18	3
Mild, moderate, severe	9	735	0.10	0.06	0.16	21
Severe	1	33	0.15	0.06	0.32	4



Note: GAD = Generalized Anxiety Disorder; CI = confidence interval; N_{fs} = Fail-safe N; ICD = International Classification of Diseases; DSM = Diagnostic & Statistical Manual; MINI = Mini-International Neuropsychiatric Interview; SCAN = Schedules for Clinical Assessment in Neuropsychiatry; SCID-I = Structured Clinical Interview - Axis I Disorders; PSE = Present State Examination; SADS-L = Schedule for Affective Disorders & Schizophrenia (lifetime); DIS = Diagnostic Interview Schedule. Some studies included in more than one time post-injury category.

Prevalence of clinically significant cases of anxiety following TBI (self-report)

Next, the 32 studies (3,181 participants) that used self-report measures to assess clinically significant cases of anxiety following TBI were examined. This revealed that, overall, 37% of people reported experiencing clinically significant anxiety (see Figure 2a). The associated N_{fs} statistic was extremely large (N_{fs} = 363), indicating that this is a very robust finding. Once again, there was substantial variation in the rates reported by individual studies (range: 4% to 83%).

When these studies were grouped according to the measure that was used to identify 'cases' of anxiety, the most frequently used scale was found to be the HADS (23 studies), followed by the Leeds Scale for the Self-assessment of Anxiety and Depression (Leeds; Snaith et al., 1976), BAI and State Trait Anxiety Inventory (STAI; Spielberger, Gorsuch, & Luchene, 1970) (5, 4 and 1 study, respectively) (see Figure 2b). The prevalence of 'cases' ranged from 35% (Leeds) to 50% (STAI), although these differences were not significant.

When grouped according to how the self-report scales were administered (see Figure 2c), it was found that most studies (23 studies) had participants complete the measure at the research centre (hospital, university), five mailed their questionnaires, and four used a combination of methods (research centre, mail, phone). Mean prevalence rates were equivalent when scales were completed in a research environment or by mail (38%), but a lower (albeit non-significant) rate was observed when a combination of methods was used (29%). Moreover, there was greater variability (see 95% CIs) in the prevalence rates when questionnaires were completed at home and returned by mail, although this may be an artefact of the smaller sample.

Post-injury interval was also examined to determine whether this impacted the prevalence of anxiety (see Figure 2d). Four studies assessed 'caseness' in the early post-TBI period (≤ 6 mths; mean = 1.9 mths); 14 in the short-term (> 6mths to ≤ 2 yrs; mean = 1.1

years); 10 in the medium term (> 2 yrs to ≤ 5 yrs; mean = 3.5 yrs); and seven in the long-term (> 5 yrs; mean = 10.0 yrs). There was a non-significant increase in the number of cases of anxiety in the first five years (28%-37%-39%), after which the rates remained relatively stable (36%).

When studies that assessed mild, mild/moderate/severe or severe TBI were compared, it was found that mild TBI had the highest number of cases (53%), although there was considerable between-study variation (refer to Figure 2e). A lower, but still substantial, 38% of people in the severe TBI and 34% in the mixed injury groups reported clinically significant levels of anxiety.

Finally, the data from 10 studies (TBI = 884; controls = 943) that compared the number of 'cases' of anxiety in TBI and control groups were combined and an overall OR calculated. As seen in Figure 2f, the overall OR of 2.46 indicates individuals are two and a half times more likely to report experiencing clinically significant levels of anxiety after a TBI, when compared to controls. The ORs for individual studies varied between 0.88 (lower risk of anxiety following TBI) to a very high 13.81. When the type of control group was taken into account (see Figure 2g), it revealed that post TBI, individuals are in excess of three times more likely to develop anxiety problems than those in the general community, two and a half times more likely than those with a general medical condition, and nearly twice as likely as their significant others (family, friends, caregivers).

Fig. 2

Prevalence of clinically significant cases of anxiety: (a) overall, (b) self-report scale, (c) method of administration, (d) time post-injury, (e) injury severity, (f) overall, relative to controls, and (g) according to the type of control group

Fig. 2a

Prevalence of self-reported 'cases' of anxiety following TBI: overall

Study name	Nparticipants	Prevalence	Lower CI	Upper CI
Kempf (2010)	51	0.04	0.01	0.14
Al-Adawi (2007)	68	0.09	0.04	0.18
Smith (1992)	19	0.11	0.03	0.34
Andruszkow (2014)	76	0.16	0.09	0.26
Lannsjo (2013)	19	0.18	0.06	0.43
Ponsford Group D	172	0.21	0.14	0.32
van der Horn (2013)	242	0.22	0.17	0.28
Kinsella (1988)	39	0.26	0.14	0.41
Ponsford Group B	112	0.26	0.17	0.38
Powell (2002)	46	0.28	0.17	0.43
Powell (1996)	35	0.29	0.16	0.45
Skilbeck (2013)	214	0.29	0.23	0.35
Kreuter (1998)	92	0.30	0.22	0.41
Schnieders (2012)	90	0.36	0.26	0.46
Hawthorne (2011)	66	0.36	0.26	0.49
von Steinbuchel (2010)	795	0.37	0.34	0.41
Cantor (2005)	21	0.38	0.20	0.60
Whalley-Hammell (1994)	15	0.40	0.19	0.65
Wood (2008)	89	0.43	0.33	0.53
Ponsford Group C	153	0.43	0.30	0.56
Tyerman (1984)	25	0.44	0.26	0.63
O'Carroll (1991)	36	0.47	0.32	0.63
Ponsford Group A	301	0.49	0.42	0.57
Perlesz (2000)	62	0.50	0.38	0.62
Williams (1998)	18	0.50	0.28	0.72
Anson (2006)	33	0.52	0.35	0.68
Wallace (2000)	50	0.54	0.40	0.67
Ma (2014)	100	0.57	0.47	0.66
Chalton (2009)	21	0.57	0.36	0.76
Coetzer (2011)	62	0.66	0.54	0.77
de Almeida Lima (2008)	36	0.72	0.56	0.84
King (2011)	23	0.83	0.62	0.93
OVERALL	3,181	0.37	0.32	0.43

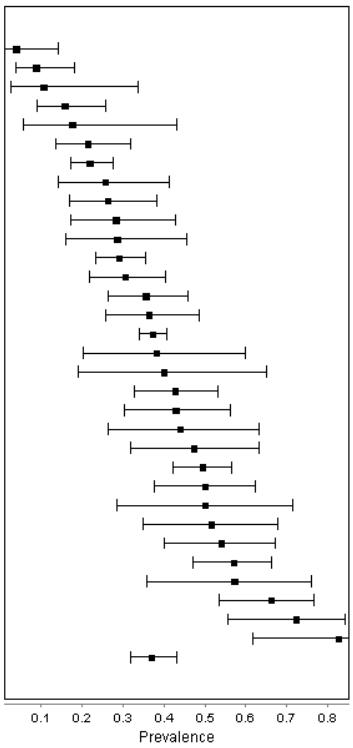


Fig. 2b

Prevalence of self-reported 'cases' of anxiety following TBI: self-report scale

	Nstudies	Nparticipants	Prevalence	Lower CI	Upper CI	Nfs
Leeds	5	241	0.35	0.23	0.49	77
HADS	23	2,761	0.36	0.30	0.43	299
BAI	4	260	0.49	0.41	0.58	61
STAI (state anxiety)	1	62	0.50	0.38	0.62	16

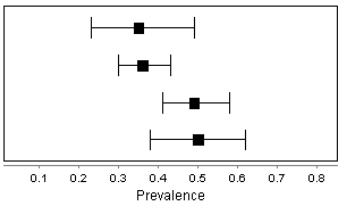


Fig. 2c

Prevalence of self-reported 'cases' of anxiety following TBI: method of administration

	Nstudies	Nparticipants	Prevalence	Lower CI	Upper CI	Nfs
Combination	4	1,052	0.29	0.20	0.40	35
Mailed	5	284	0.38	0.19	0.62	58
Research centre	23	1,845	0.38	0.32	0.45	288

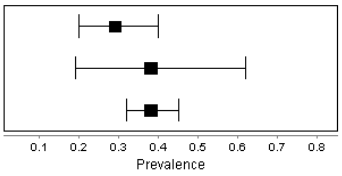


Fig. 2d

Prevalence of self-reported 'cases' of anxiety following TBI: time post-injury

	Nstudies	Nparticipants	Prevalence	Lower CI	Upper CI	Nfs
Early (≤ 6 mths)	4	326	0.28	0.10	0.56	33
Short-term (> 6 mths - ≤ 2 yrs)	14	1,492	0.37	0.28	0.47	159
Medium-term (> 2 yrs - ≤ 5 yrs)	10	1,597	0.39	0.32	0.47	120
Long-term (> 5 yrs)	7	411	0.36	0.24	0.49	77

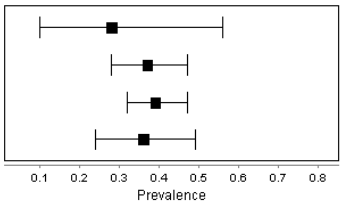


Fig. 2e

Prevalence of self-reported 'cases' of anxiety following TBI: injury severity

	Nstudies	Nparticipants	Prevalence	Lower CI	Upper CI	Nfs
Mild	5	213	0.53	0.32	0.73	83
Mild, moderate, severe	23	2,871	0.34	0.29	0.40	238
Severe	4	97	0.38	0.28	0.50	47

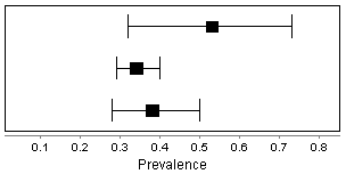


Fig. 2f

Prevalence of self-reported 'cases' of anxiety following TBI - relative to Controls: overall

Study name	TBI prevalence	Control prevalence	Odds ratio	Lower CI	Upper CI
Smith (1992)	0.11	0.12	0.88	0.11	7.06
Ponsford Group C	0.43	0.32	1.49	0.66	3.38
Wallace (2000)	0.54	0.40	1.76	0.80	3.89
Ponsford Group B	0.26	0.20	1.78	0.96	3.30
Perlesz (2000)	0.50	0.33	2.02	1.09	3.75
O'Carroll (1991)	0.47	0.29	2.15	0.63	7.36
Ponsford Group A	0.49	0.32	2.34	1.53	3.57
de Almeida Lima (2008)	0.72	0.50	2.60	0.98	6.92
Whalley-Hammell (1994)	0.40	0.20	2.67	0.52	13.66
Ma (2014)	0.57	0.09	13.81	6.77	28.15
OVERALL	0.47	0.27	2.46	1.57	3.86

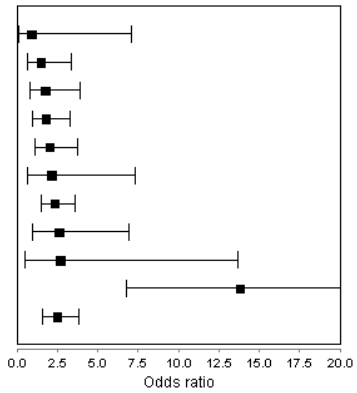
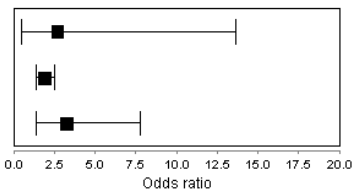


Fig. 2g

Prevalence of self-reported 'cases' of anxiety following TBI - relative to Controls: by type of control group

	Nstudies	TBI prevalence	Control prevalence	Odds ratio	Lower CI	Upper CI
Medical	1	0.40	0.20	2.67	0.52	13.66
Significant Other	6	0.50	0.36	1.89	1.42	2.51
Community	4	0.46	0.21	3.25	1.36	7.77



Note: Leeds = The Leeds Scale for the Self-assessment of Anxiety and Depression; HADS = Hospital Anxiety and Depression Scale; BAI = Beck Anxiety Inventory; STAI = State Trait Anxiety Inventory. Some studies included in more than one self-report scale, time post-injury, and by type of control group category.

Discussion

The clinical utility of research examining anxiety after a TBI has been limited by the wide variation in the prevalence rates and a poor understanding of what might be contributing to this variability. The current study was designed to determine whether, and to what extent, various methodological variables and sample characteristics impact on these estimates. To that end, it examined prevalence data in terms of formally diagnosed GAD and self-reported 'cases' of clinically significant anxiety, both overall and then in terms of specific variables. Specifically, diagnostic criteria and interview schedule were examined in the case of GAD; questionnaire and method of administration were evaluated for self-reported 'cases'; and post-injury interval and injury severity for both GAD and 'cases'. Lastly, the prevalence of anxiety following TBI was compared to that of controls.

GAD versus clinical 'cases' of anxiety

Overall, the prevalence of GAD (11%) was considerably lower than that of self-reported 'cases' of clinically significant anxiety (37%). Although not surprising, this finding highlights the importance of researchers clearly identifying when the term 'anxiety' is being used as a specific or generic term; something that has so far been lacking (Baxter et al., 2014). The discrepancy between the prevalence of GAD and anxiety 'cases' is likely to be caused by a number of factors. First, some self-report measures of anxiety include symptoms that may be attributable to a TBI (e.g., impaired concentration and memory, sleep disturbances); which may artificially inflate the scores on these questionnaires and, consequently, the number of cases of anxiety (Sumpter & McMillan, 2006). Clinical assessments, on the other hand, may better distinguish between TBI sequelae and the symptoms of anxiety. Second, people may report more symptoms when prompted with a checklist than when they respond to open-ended questions in a clinical interview (Iverson et al., 2010a), potentially increasing their scores on these scales and, consequently, the number of 'cases'. Third, whereas 'cases' are

identified purely on the basis of a cut-off/threshold, above which the severity and range of symptoms is considered to be of clinical importance, a diagnosis of GAD additionally requires the exclusion of other conditions (e.g., physical consequences of a TBI) that may explain the symptoms and artificially inflate the prevalence of anxiety.

Generalized Anxiety Disorder

When the data were analysed in terms of specific variables, the prevalence of GAD frequently differed, although many differences were not significant, possibly due to the small sample sizes. Specifically, estimates of the prevalence of GAD differed according to the diagnostic criteria, with the highest rates noted for the DSM III-R (19%), followed by the combined DSM-IV/ICD-10 criteria (11%), DSM-IV (9%) and ICD-10 (2%). These rates may reflect changes to the diagnostic criteria for GAD, particularly since 1987 when the DSM-III-R was published, and make comparisons between data based on different DSM editions problematic. Moreover, the DSM has shifted focus from somatic to psychological symptoms which, when combined with the more rigorous requirement of the DSM-IV that worry be "difficult to control", may help explain why the prevalence of GAD was lower when the DSM-III-R was in use (Rickels et al., 2001). Similarly, the ICD-10 captures symptoms that have a shorter duration (several months: > 2 months), compared with the DSM (6 months). However, the post-injury intervals of a number of studies suggest that this criteria was not always strictly adhered to, detracting from the accuracy of these data (Jorge et al., 1993c; Rao et al., 2008).

The prevalence rates for GAD also varied depending on the specific interview, with estimates ranging from 2% (SCAN) to 28% (SADS-L), although the MINI, PSE and SCID-I yielded equivalent rates (11%). The guidelines for the SCAN suggest clinicians be conservative when diagnosing GAD, which may explain the low rate for this measure (APA, 2000). Additionally, the interview procedures differ, with disparate formats and personnel potentially impacting prevalence rates. For example, the Diagnostic Interview Schedule (DIS; Robins et al., 1981)

uses closed-ended questions that may be administered by non-clinicians. In contrast, the SCID-I uses a semi-structured format requiring clinicians to use clinical expertise to flexibly explore the aetiology and severity of symptoms (Hasin & Grant, 1987). These differences may yield discrepant GAD rates.

Clinically significant 'cases' of anxiety

Similarly, there was considerable variability in prevalence rates associated with different self-report scales, ranging from 35%/36% for the Leeds and HADS to 49%/50% for the BAI and STAI. The HADS, in particular, was designed for use in medical settings and does not confound the physical and psychological consequences of a TBI (Zigmond & Snaith, 1983), possibly explaining the lower prevalence rate for this measure. In contrast, the BAI was developed for psychiatric settings and a large proportion (70%) of items assess physiological symptoms (Beck et al., 1988), which may inflate the prevalence of anxiety in TBI/medical samples. Some of the variability in rates may also be associated with differences in the interval covered by the questionnaires, which range from 'at this moment' (STAI) to the previous few days (Leeds) or week (HADS, BAI). As the number and severity of symptoms may change, particularly in the early stages post-injury, it is likely that prevalence rates may be impacted by these varying time-frames (Jorge et al., 1993a).

Prevalence rates also differed according to where/how the self-report measures were administered. More 'cases' of anxiety were evident when participants completed the questionnaires in the research setting (hospital, university) or at home (38%), compared to when a combination of methods were used (phone, mail, research centre; 29%). Unfortunately, with the exception of the Al-Adawi et al. (2007) study, where HADS items were read aloud to participants, information was not provided regarding how questionnaires were administered within research settings. Independently completed questionnaires are likely to minimise socially desirable responding (Aziz & Kenford, 2004) and differences have been

found when comparing pencil-and-paper and computerised versions (Fairweather-Schmidt & Anstey, 2012). In addition, verbal or phone administration provides limited opportunity for reflection and revision of responses (Aziz & Kenford, 2004) and, when completed at home, responses may be influenced by other people. Each of these methods are therefore vulnerable to different influences, which may impact reports of anxiety symptoms.

Post-injury interval and injury severity

The prevalence of anxiety was additionally affected by the length of time that had elapsed since the TBI. GAD diagnoses varied from 10% in the first 6 months after an injury, then decreased in the short-term (6%), increased in the medium-term (17%), before returning to a level similar to that seen in the short-term (5%). Although this suggests there was no consistent pattern between time since injury and the prevalence of GAD, some studies did not adhere to the minimum 6 month symptom duration requirement of the DSM, which may have inflated rates in the early post-injury period.

These results contrast with self-reported anxiety, where the number of clinically significant cases of anxiety steadily increased (28% to 37% to 39%) over time; although, as with GAD, the long term rates (> 5 years; 36%), more closely resembled those seen in the short-term. Interestingly, the prevalence of both GAD and self-reported anxiety peaked two to five years after an injury, suggesting that this may be a particularly vulnerable time for people. In addition, the ongoing presence of high anxiety levels post-injury reinforces the need to conceptualise TBI as a chronic health condition, with the capacity to negatively impact individuals for many years (Corrigan & Hammond, 2013; Masel & DeWitt, 2010). This underscores the need for longer-term monitoring of people after their TBI and the provision of mental health programs that will assist them to manage their anxiety (e.g., coping, resilience and functional communication).

Only a basic examination of the impact of injury severity on prevalence rates was possible because most studies examined mixed injuries. Although limited, these data revealed that GAD was marginally less common after mild (11%) than severe (15%) TBIs, which contrasted with self-reported anxiety, where 'cases' were substantially more frequent following mild (53%) than severe TBIs (38%). There are a number of potential explanations for the latter finding. First, individuals may not receive sufficient psycho-educational support following a mild TBI (e.g., post-injury information, ongoing access to support), increasing their anxiety levels. Second, in the absence of significant physical and cognitive sequelae - which are more commonly associated with severe than mild injuries - people may focus on other problems, such as anxiety (Malec et al., 2007b). Third, more severe injuries are often associated with a greater number of cognitive problems and reduced insight, possibly resulting in fewer reported symptoms or greater difficulty articulating problems in an interview environment, which is likely to impact prevalence rates (Iverson et al., 2010a; Wallace & Bogner, 2000). Finally, after a mild TBI, individuals may exaggerate their symptoms for the purposes of financial compensation (Kurtz et al., 2007). If this were the case, anxiety levels should reduce when legal matters have been resolved; however this does not appear to be the case, with the rates remaining high, even in the long-term.

Rates of anxiety, relative to other populations

The prevalence of anxiety was also compared to other groups. Unfortunately, only one study examined GAD relative to general trauma patients, with GAD being more frequent following TBI. When self-report scales were used, it was apparent that following a TBI, people were more than three times more likely to report severe anxiety than healthy adults living in the community, more than twice as likely as people with spinal injuries, and nearly double that of family, friends and caregivers. This suggests that sustaining a TBI provides an additional source of psychological distress, even when other factors, such as pain and hospital/medical procedures, are taken into account. Moreover, family and friends experienced high rates of

clinically significant anxiety (36%), compared to persons from the general community and those with spinal injuries (21% vs 20%). Thus, not only are individuals with a TBI at considerable risk of developing anxiety problems, so too are their family members. This may be the result of grief arising from changes to their relative's identity; frustration about changes to their family roles and responsibilities; altered sexual relationships; and uncertainty about the future (Downing, Stolwyk, & Ponsford, 2013; Landau & Hissett, 2008; Perlesz et al., 2000). Hence, ongoing support should be provided both to the person with a TBI and their close family in order to optimise their long-term outcomes. Greater consideration also needs to be given to the selection of appropriate control groups when undertaking TBI research (Mathias, Dennington, Bowden, & Bigler, 2013). Whereas medical/orthopaedic samples endeavour to control for the effects of pain and various injury-related stressors (Ponsford et al., 2011), family and friends ('significant others') control for the effects of increased stress and emotional distress (Ponsford & Schönberger, 2010), and community controls assess base-rates in the wider community (Wacholder et al., 1992).

Limitations and recommendations for future research

Anxiety following TBI is a complex area, incorporating diverse methodologies, resulting in a number of limitations that warrant consideration. First, a lack of suitable data often made specific and comprehensive comparisons difficult. For example, although psychiatric/TBI history and medications are likely to be important, many studies either did not provide these data or provided data that were not comparable (e.g., no prior depression/anxiety vs no prior significant psychiatric diagnosis). Limited data were also available to examine the relationship between injury severity and anxiety. Furthermore, although males are more likely to sustain a TBI (Anstey et al., 2004), females are more likely to develop an anxiety disorder (McLean, Asnaani, Litz, & Hofmann, 2011); making it important to consider sex. Unfortunately, too few studies reported this data, precluding such an analysis. Second, two studies used DSM criteria to diagnose GAD 1 to 2 months post-TBI, indicating that the diagnostic criteria – which require

a minimum of 6 months duration - were not strictly applied. Third, multivariate analyses were not possible due to the variability in the research designs that were used to examine the prevalence of anxiety following TBI, thereby limiting the opportunity to identify interactions between variables.

Importantly, this meta-analysis highlights the need for good quality research that examines anxiety using appropriate assessments. These include either formal interviews that incorporate a detailed assessment of the aetiology and chronology of symptoms, in the case of diagnosed anxiety disorders, or reliable self-report scales that are appropriate for use with TBI populations (i.e., items do not overlap with other TBI sequelae). This will help to ensure that the prevalence rates reported in the literature reflect genuine anxiety problems that are not inflated by other confounding factors (Green et al., 2001; Whelan-Goodinson et al., 2009b).

Furthermore, while the current study demonstrates that many individuals experience anxiety following a TBI, it was not possible to clearly determine which risk factors predispose an individual to mental health problems. Thus, a large-scale multi-factorial study that evaluates the impact of a range of injury and sample characteristics is now needed. Specific variables that warrant consideration include: the post-injury interval, injury severity, age at injury, sex, pre-morbid mental health problems, previous TBIs, as well as current psycho-social factors that may impact on anxiety levels (e.g., exercise, alcohol consumption, and availability of social support) (Hart et al., 2012; Horner et al., 2008; Wise, Hoffman, Powell, Bombardier, & Bell, 2012). In addition, researchers need to provide greater detail for some of the variables that may independently affect anxiety outcomes. Not only is it important that researchers report descriptive data for these variables - such as the gender composition of the sample and the number of people with a prior TBI or psychiatric history, and how many are undergoing treatment or receiving medication for their anxiety - but it would also be beneficial to provide

anxiety data for these subgroups. This will help to improve our understanding of the range of factors that predispose some individuals to develop anxiety problems following a TBI.

Conclusions

Although widely investigated, estimates of the prevalence of anxiety following TBI vary substantially. The challenge faced when attempting to interpret these disparate findings is well-documented, with researchers (Koponen et al., 2011; Tsaousides et al., 2011) suggesting that between-study variability in methodology and sampling makes comparisons and definitive conclusions difficult. This meta-analysis evaluated a range of variables which may impact on these rates, thereby improving our understanding of whether/how they impact on prevalence.

Overall, 11% of people were diagnosed with GAD, with rates varying, albeit non-significantly, according to the diagnostic criteria - DSM III-R (19%), DSM-IV (9%), and ICD-10 (2%) - and the interview schedule, which ranged between 2% (SCAN) and 28% (SADS-L). In addition, GAD was diagnosed more frequently between two and five years after an injury (17%), compared with the early post-injury period (≤6 months; 10%), the short-term (>6 months - ≤2 years (6%), and in the long-term (> 5 years; 5%). Mild TBIs were associated with a slightly lower prevalence (11%) of GAD than severe injuries (15%), indicating that even after a mild TBI, anxiety levels should be monitored; although these data were based on single studies. Lastly, although the evidence is very limited, GAD appears to be more prevalent after a TBI than following other medical conditions (i.e., general trauma patients).

Clinically significant levels of anxiety were commonly reported following a TBI, with 37% of people experiencing anxiety problems. This rate was affected by the measure that was used, ranging between 35% (Leeds) and 50% (STAI), and the method of administration (mailed: 38%, research centre: 38%; combination: 29%). Time since injury also affected rates, with the

number of ‘cases’ steadily increasing from 28% in the early period after a TBI to 39% in the two to five years post-injury; after which it declined slightly (36%). Unlike GAD, mild TBI was associated with higher rates (53%) of clinically significant anxiety than severe injuries (38%). Finally, a person with TBI is three times more likely to report high levels of anxiety than someone in the general community; more than two and a half times more likely than those with other medical conditions, and almost twice as likely as their close family and friends.

5.4 Electronic Supplementary Material

Table S1: Search Strategy

PSYCINFO

traumatic brain injur*.SH OR traumatic brain injur*.TI OR traumatic brain injur*.AB OR TBI.SH OR TBI.TI OR TBI.AB OR head injur*.SH OR head injur*.TI OR head injur*.AB OR brain injur*.SH OR brain injur*.TI OR brain injur*.AB OR head trauma.SH OR head trauma.TI OR head trauma.AB OR cranio?cerebral trauma.SH OR cranio?cerebral trauma.TI OR cranio?cerebral trauma.AB

AND

anxiety disorder.SH OR anxiety disorder.TI OR anxiety disorder.AB OR psychiatric diagnos*.SH OR psychiatric diagnos*.TI OR psychiatric diagnos*.AB OR psychological sequelae.SH OR psychological sequelae.TI OR psychological sequelae.AB OR affective disorder.SH OR affective disorder.TI OR affective disorder.AB OR anxiety.SH OR anxiety.TI OR anxiety.AB OR generali?ed anxiety disorder.SH OR generali?ed anxiety disorder.TI OR generali?ed anxiety disorder.AB OR social anxiety disorder.SH OR social anxiety disorder.TI OR social anxiety disorder.AB OR acute stress disorder.SH OR acute stress disorder.TI OR acute stress disorder.AB OR post traumatic stress disorder.SH OR post traumatic stress disorder.TI OR post traumatic stress disorder.AB OR post-traumatic stress disorder.SH OR post-traumatic stress disorder.TI OR post-traumatic stress disorder.AB OR posttraumatic stress disorder.SH OR posttraumatic stress disorder.TI OR posttraumatic stress disorder.AB OR social phobia.SH OR social phobia.TI OR social phobia.AB

PUBMED

Brain concussion[mh] OR Brain hemorrhage, traumatic[mh] OR Brain injury, chronic[mh] OR Diffuse axonal injury[mh] OR Coma, post head injury[mh] OR Head injuries, closed[mh] OR Intracranial hemorrhage, traumatic[mh] OR Skull fractures[mh] OR traumatic brain injur* [tiab] OR TBI [tiab] OR head injur* [tiab] OR brain injur* [tiab] OR brain damage [tiab] OR head trauma [tiab] OR craniocerebral trauma [tiab] OR cranio-cerebral trauma [tiab] OR cranio cerebral trauma [tiab]

AND

Anxiety disorders[mh] OR Stress disorders, traumatic[mh] OR Anxiety disorder [tiab] OR Psychiatric diagnos* [tiab] OR Psychological sequelae [tiab] Affective disorder [tiab] OR Anxiety [tiab] OR generalized anxiety disorder [tiab] OR generalised anxiety disorder [tiab] OR social anxiety disorder [tiab] acute stress disorder [tiab] post-traumatic stress disorder [tiab] posttraumatic stress disorder [tiab] OR post traumatic stress disorder [tiab] OR social phobia [tiab]

NOT

War [tiab] OR combat [tiab] OR military [tiab]

Table S1 cont.

SCOPUS

((traumatic brain injury) OR TBI OR (head injur*) OR (brain injur*) OR (brain damage) OR (head trauma) OR (craniocerebral trauma) OR (cranio-cerebral trauma) OR (cranio cerebral trauma)) AND (anxiety OR (anxiety disorder) OR (psychiatric diagnos*) OR (psychological sequelae) OR (affective disorder) OR (generalised anxiety disorder) OR (generalized anxiety disorder) OR (social anxiety disorder) OR (acute stress disorder) OR (post-traumatic stress disorder) OR (post traumatic stress disorder) OR (posttraumatic stress disorder)) OR PTSD AND NOT (combat OR war OR military OR veteran OR animal OR rat OR mice)

ISI Web of Science

Topic= (traumatic brain injur* OR TBI OR head injur* OR brain injur* OR brain damage OR head trauma OR craniocerebral trauma OR cranio-cerebral trauma OR cranio cerebral trauma)

AND

Topic= (anxiety OR anxiety disorder OR psychiatric diagnos* OR psychological sequelae OR affective disorder OR generalised anxiety disorder OR generalized anxiety disorder OR social anxiety disorder OR acute stress disorder OR post-traumatic stress disorder OR posttraumatic stress disorder OR post traumatic stress disorder OR PTSD)

NOT

Topic = (combat OR war OR military OR veteran OR animal OR rat OR mice)

Refined by: Publication Years AND Document Type=(ARTICLE)

Table S2: Anxiety measures eligible for analysis

Self-report scale name	**Abbrev.**	**Author(s) / Year**	**Time frame**
Beck Anxiety Inventory	BAI	(Beck et al., 1988)	previous week
Hospital Anxiety and Depression Scale	HADS	(Zigmond & Snaith, 1983)	previous week
Leeds Scale for the Self-assessment of Anxiety & Depression	Leeds	(Snaith et al., 1976)	previous 1-2 days
State Trait Anxiety Inventory	STAI	(Spielberger et al., 1970)	at this moment

Clinical interview name	***Abbrev.***	***Author(s) / Year***	***'Current' time frame***
Diagnostic Interview Schedule	DIS	(Robins et al., 1981)	previous week, previous month, previous 6 months, previous year
Mini International Neuropsychiatric Interview	MINI	(Sheehan et al., 1998)	previous 2 weeks
Present State Examination	PSE	(Wing et al., 1974)	previous month
Schedule for Affective Disorders and Schizophrenia - Lifetime	SADS-L	(Endicott & Spitzer, 1978)	previous week
Schedules for Clinical Assessment in Neuropsychiatry	SCAN	(Wing et al., 1990)	previous month
Structured Clinical Interview for DSM disorders	SCID	(First et al., 1997)	previous month

Table S3: Overview of study review and selection

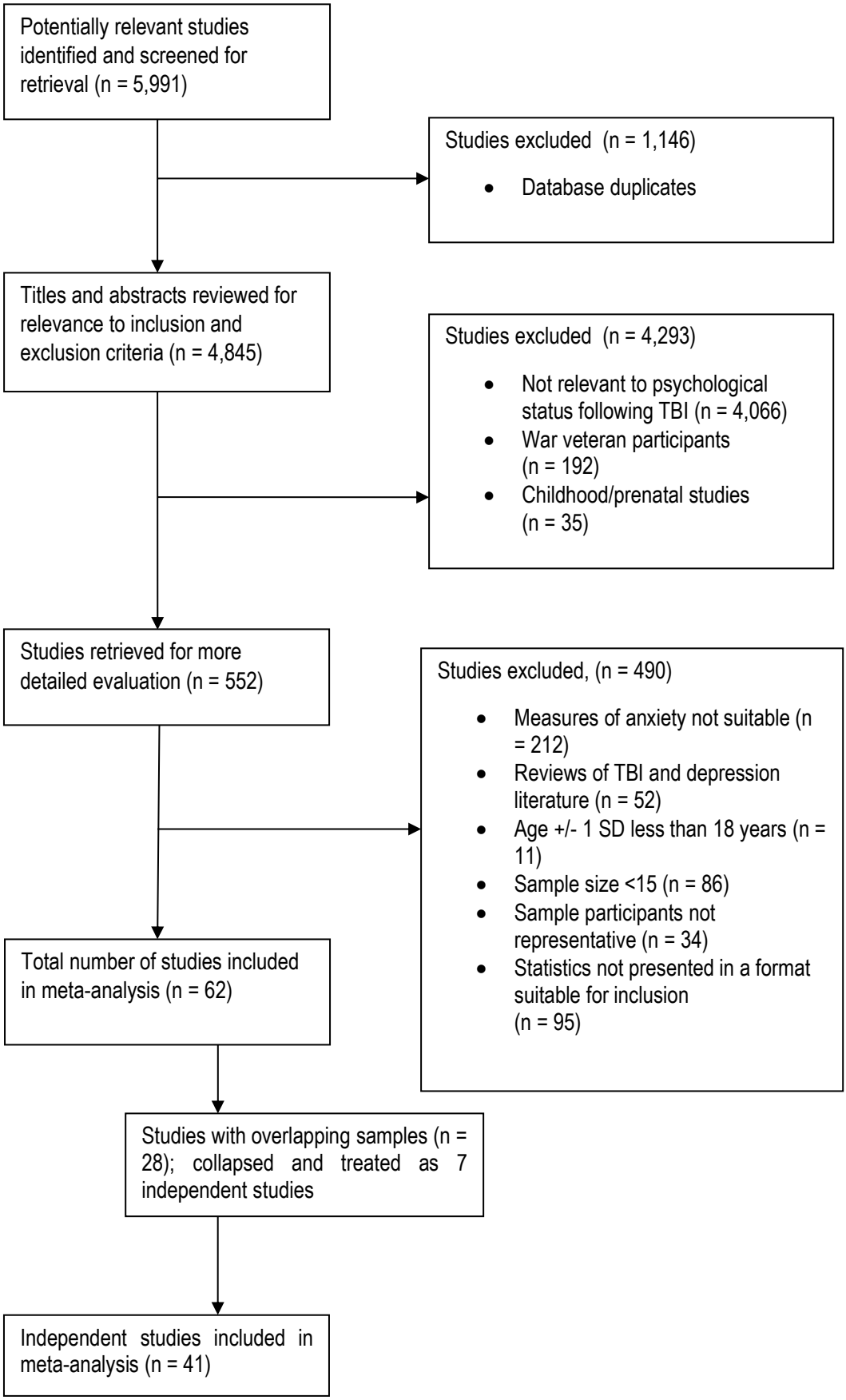


Table S4: Papers using overlapping samples - combined and treated as non-independent studies in the current meta-analysis

Study 'name' in meta-analysis	Papers with overlapping samples
Bryant 2010	(Bryant et al., 2010) (Meares et al., 2011)
Hawthorne 2011	(Hawthorne et al., 2009) (Hawthorne et al., 2011)
Koponen 2002	(Koponen et al., 2002) (Koponen et al., 2005)
Ponsford Group A	(Ponsford et al., 2003) (Ponsford, 2003)
Ponsford Group B	(Draper et al., 2007) (Draper & Ponsford, 2009) (Senathi-Raja et al., 2010)
Ponsford Group C	(Ponsford & Ziino, 2003) (Ziino & Ponsford, 2006) (Parcell, Ponsford, Rajaratnam, & Redman, 2006) (Whelan-Goodinson, Ponsford, & Schonberger, 2008) (Whelan-Goodinson et al., 2009b) (Whelan-Goodinson et al., 2009a) (Whelan-Goodinson et al., 2010) (Shekleton et al., 2010) (Ponsford, Parcell, Sinclair, Roper, & Rajaratnam, 2013)
Ponsford Group D	(Gould et al., 2014) (Gould et al., 2011a) (Dahm, Wong, & Ponsford, 2013) (Spitz, Schonberger, & Ponsford, 2013)

CHAPTER 6: TBI AND ANXIETY IN A COMMUNITY-BASED SAMPLE

6.1 Preamble

This Chapter consists of a manuscript entitled "Anxiety and comorbid depression following traumatic brain injury in a community-based sample of young, middle-aged and older adults", which has been published (advance online publication) in the *Journal of Affective Disorders*.

This study builds on the anxiety meta-analysis discussed in the previous chapter by examining the prevalence of clinically significant cases of anxiety in people living in the general community, both with and without a TBI. Moreover, this study also investigates co-morbidity rates of anxiety and depression, which is surprisingly under-researched.

Online supplementary information is included at the end of the current chapter (pages 179-183) and incorporates: an overview of the full sample in the Personality and Total Health (PATH) Through Life study, and participants in the current sample, partitioned according to successive assessment (Table S1); socio-demographic characteristics of participants at W2, grouped by age and lifetime TBI status (Table S2); socio-demographic characteristics of participants at W3, grouped by age and lifetime TBI status (Table S3); attrition analyses comparing socio-demographic and health characteristics at waves 2 and 3, partitioned according to participation status (Table S4); details on the prevalence of lifetime, recent, multiple and no TBI in the current sample (Table S5). A complete list of all references for the thesis, including those for this paper, has been provided at the end of the thesis (pages 208-237).

Chapter 6: Paper four

Traumatic brain injury, anxiety and comorbid depression in a population-based sample

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Statement of authorship is on the following page.

6.2 Statement of Authorship

Statement of Authorship

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Principal Author

Name of Principal Author (Candidate)	Amanda Osborn
Contribution to the Paper	Study inception, design, methodology (including literature searches, statistical analysis and data interpretation), wrote manuscript and acted as corresponding author.
Overall percentage (%)	85%
Certification:	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.
Signature	Date: 14/10/16

Co-Author Contributions

By signing the Statement of Authorship, each author certifies that:

i. the candidate's stated contribution to the publication is accurate (as detailed above);
ii. permission is granted for the candidate in include the publication in the thesis; and
iii. the sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

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6.3 Paper four

Abstract

Background: Anxiety is common following a traumatic brain injury (TBI), but who is most at risk, and to what extent, is not well understood.

Methods: Longitudinal data from a randomly-selected community sample (Wave 1: 7,397, Wave 2: 6,621 and Wave 3: 6,042) comprising three adult cohorts (young: 20-24 years of age, middle-aged: 40-44, older: 60-64), were analysed. The association between TBI history, anxiety and comorbid depression was assessed, controlling for age, sex, marital/employment status, medical conditions, recent life events, alcohol consumption, social support and physical activity.

Results: Thirteen percent of the sample had sustained a TBI by Wave 3, 35% of whom had sustained multiple TBIs. Cross-sectional analyses revealed that clinically-significant anxiety was more common in people who had sustained a TBI. Longitudinal analyses demonstrated an increased risk of anxiety post-TBI, even after controlling for potential demographic, health and psychosocial confounds. Anxiety was more common than depression, although 10% of those with a TBI experienced comorbid anxiety/depression.

Limitations: TBIs were not medically confirmed and anxiety and depression were only assessed every four years by self-report, rather than clinical interview. Sample attrition resulted in the retention of healthier individuals at each wave.

Conclusions: TBIs are associated with a lifelong increased risk of experiencing clinically-significant anxiety, highlighting the chronic nature of TBI sequelae. Positive lifestyle changes (e.g., increasing physical activity, reducing alcohol consumption) may decrease the risk of anxiety problems in the early years after a TBI. Comorbid anxiety and depression was common, indicating that both should be monitored and treated.

Keywords

Traumatic brain injury, anxiety, depression, community, population, longitudinal, multivariate

Introduction

Anxiety is common following a traumatic brain injury (TBI) (Mallya, Sutherland, Pongracic, Mainland, & Ornstein, 2015), with symptoms ranging from subtle changes (e.g., restlessness, irritability) to debilitating levels of tension, fear and worry, which can negatively impact on a person's quality-of-life and everyday functioning (APA, 2013). Although research has focussed on depression, self-report data indicate comparable rates of clinically-significant levels ('cases') of general anxiety (37%) and depression (38%) following TBI (Osborn et al., 2014; Osborn, Mathias, & Fairweather-Schmidt, 2016) and, indeed, that the average levels of anxiety may be higher than depression (King & Kirwilliam, 2011; Ortiz, Annoni, Trojan, Alberque, & Eytan, 2004; von Steinbuchel et al., 2010; Wood & Rutterford, 2006). In terms of clinical disorders, people are twice as likely to be diagnosed with an anxiety disorder (e.g., Generalized Anxiety Disorder [GAD], Post-traumatic Stress Disorder [PTSD]) after a TBI, compared to those without a TBI (Van Reekum et al., 2000). Together, these findings suggest that anxiety following TBI warrants greater attention.

Recent population-based longitudinal research data that controlled for a variety of injury, pre-injury and post-injury characteristics when analysing the data, demonstrated that individuals living in the community have a long-term increased risk of clinically significant depression if they had sustained a TBI at some time in their life (Osborn, Mathias, Fairweather-Schmidt, & Anstey, 2016). However, it is not yet clear if this heightened risk is also true for anxiety. Indeed, little is currently known about the complex interplay between a broad variety of demographic (e.g., age, sex), pre-injury (e.g., history of TBI and mental health problems such as depression), injury (e.g., injury severity, time since injury) and post-injury (e.g., stressful life-events, social support) variables that are potentially associated with anxiety (Vanderploeg, Curtiss, Luis, & Salazar, 2007; Whelan-Goodinson et al., 2010; Wood &

Rutterford, 2006). This makes it difficult to identify who is most at risk of experiencing problems with anxiety and, thus, implement targeted interventions.

Moreover, to date, most research into anxiety after a TBI has examined samples that are recruited from clinical settings (e.g., hospitals, rehabilitation centres), rather than sourcing individuals who are living in the community. Clinical samples are more likely to be seriously injured and experience greater physical, cognitive and psychological problems, which may lead to higher reported rates of anxiety and/or depression (Dworkin, 1992). Moreover, many people do not seek medical attention following a mild TBI (Corrigan et al., 2010; Setnik & Bazarian, 2007), resulting in a large sub-group who have sustained a TBI, but whose outcomes are often overlooked in the extant literature. Although a few studies have recruited from the general population and demonstrated an increased risk of developing neuropsychiatric problems after a TBI (Anstey, 2004; Silver, 2001), their data was cross-sectional rather than longitudinal. Thus, the relationship between a TBI and the anxiety levels of individuals living in the community over the long-term, is not yet known.

Notwithstanding the fact that anxiety and depression are often experienced, diagnosed, and commonly treated as independent conditions (APA, 2013), they are also frequently comorbid; both in the general population (Slade, Johnston, Oakley Browne, Andrews, & Whiteford, 2009) and following a TBI (Bombardier et al., 2010; Jorge et al., 2004; Whelan-Goodinson et al., 2010). In the case of TBI, comorbid anxiety and depression are frequently associated with greater disability, increased service-use and slower recovery (McEvoy, Grove, & Slade, 2011), suggesting that they should not be viewed in isolation. Indeed, some studies have reported that, after a TBI, *all* individuals diagnosed with GAD additionally met the criteria for major depression (Jorge et al., 1993c; Van Reekum et al., 1996). Similarly, many people who report experiencing clinically significant anxiety (using self-report scales), also report being depressed (Truelle et al., 2010; Van Der Horn et al., 2013).

However, research examining comorbid anxiety and depression following TBI is very limited, particularly in community-based samples; highlighting the need to examine comorbidity in a non-clinical sample.

The current study therefore used data from a randomly-selected community-based sample to address three aims relating to self-reported 'cases' of clinically-significant anxiety and depression. More specifically, it was designed to: (1) examine the prevalence of 'cases' of anxiety in individuals with a TBI, relative to those without a TBI; (2) investigate the prevalence of 'cases' of comorbid anxiety and depression in those with a TBI, and; (3) use longitudinal analyses to determine whether 'cases' of anxiety are related to having had a TBI, and whether these relationships are independent of potentially confounding demographic (age, sex, marital/employment status), health (depression history, comorbid medical conditions, multiple TBIs, alcohol consumption) and psychosocial (life-events, physical activity, social support) variables.

Method

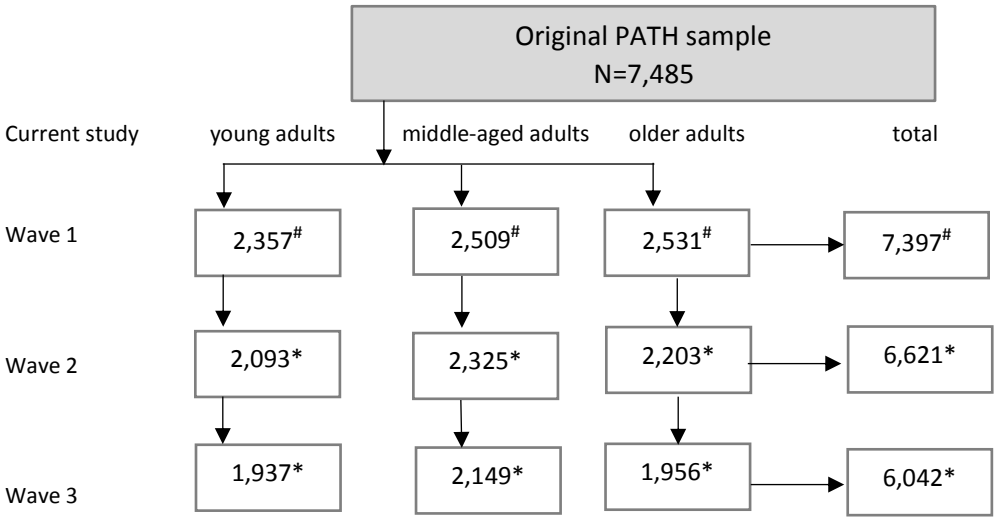
Participants and procedure

The PATH Through Life Project is an Australian population-based longitudinal study that is assessing adult life-span changes to physical (e.g., medical conditions, substance abuse) and mental (e.g., depression, anxiety) health, cognitive functioning (e.g., memory, attention), and social dynamics (e.g., support, networks). Three cohorts, originally aged 20-24, 40-44 and 60-64 years, were randomly selected from the Canberra and Queanbeyan (Australia) electoral rolls. Electoral registration is compulsory for Australian citizens aged ≥18 years (over 93% currently enrolled), with the final PATH sample being representative of the 2001 Australian Census data for the region (Anstey et al., 2012). Assessments were conducted every four years (Wave 1 [W1]: 1999-2002, Wave 2 [W2]: 2003-2006, Wave 3 [W3]: 2007-2010, Wave 4 [W4]: 2011-ongoing) in the participant's home or at the Centre for Mental Health Research,

Australian National University. After obtaining informed consent, trained interviewers administered the physical and cognitive tests, with the remaining measures completed on a laptop. The PATH project was approved by the Human Research Ethics Committee, Australian National University, and full details of the PATH sample and methodology are outlined in Anstey et al. (2012).

The current sample examined all individuals from the PATH study who reported whether or not they had ever sustained a TBI (W1: N=7,397, W2: N=6,621, and W3: N=6,042), but excluded those whose TBI status could not be determined (approximately 1-2%) because data were missing, or participants had responded 'don't know', 'uncertain' or 'refused'. W4 data were not yet available for all cohorts, consequently it was excluded from the current analysis. The number of participants lost to follow-up between W1 and W3 was low, with 90% of W1 completing W2 and 91% of W2 completing W3; equating to an 82% retention rate across the 8-years. Figure 1 provides summary details of the full W1 PATH sample (n = 7,485) and the samples examined in the current study at each successive wave. Additional summary details for these participants (W1-W3) are provided in the Electronic Supplementary Material, Table S1 (page 179).

Figure 1. Flow chart of participants, with and without a TBI sustained since birth, partitioned according to age-cohort and wave/successive assessment



excludes participants with missing TBI data;

* excludes participants with missing TBI data or who were lost to follow-up

Measures

The PATH project used a range of measures to collect information relating to a person's health and well-being, such as cognitive functioning, physical (e.g., blood pressure, lung function) and mental (e.g., anxiety, depression) health, drug and alcohol use, personality (e.g., ruminative style, resilience), and levels of pet ownership/volunteering. Variables used in the current study were:

Socio-demographics: age (assessment and TBI), education (total years), marital status (married/de-facto, separated/divorced/widowed, never married), and employment status (employed full- or part-time, not in labour force, looking for more work).

Traumatic brain injury: determined by the self-reported presence (yes/no) of "a serious injury to the head that interfered with memory, level of consciousness, or caused brain haemorrhaging" (see Osborn et al., 2016b for further details). TBI data were harmonised across assessments in order to determine, at each wave, whether a TBI had been sustained at

any time since birth ($TBI_{lifetime}$), in the preceding four years (TBI_{recent}), never (TBI_{no}), and more than once ($TBI_{multiple}$).

Anxiety and depression: the Goldberg Anxiety Scale (GAS) and Goldberg Depression Scale (GDS) (Goldberg et al., 1988) were used to assess anxiety and depression (respectively) at each wave (W1-W3). Each scale incorporates 9 items and has a total score range of 0-9, with higher scores indicating more symptoms in the preceding month. Clinically-significant 'cases' were identified using cut-offs of ≥7 (GAS) and ≥6 (GDS) (Kiely & Butterworth, 2015), creating a binary variable (yes/no). In addition, a lifetime history of depression (categorical variable yes/no) was assessed at W1 by two questions asking whether individuals had (1) ever been markedly depressed for several weeks (felt sad, lost interest in things, lacked energy) and (2) seen a doctor/counsellor for their depression at the time. A positive response to both questions was used to indicate the person had a history of depression.

Covariates: variables with the potential to influence post-TBI anxiety were additionally recorded and entered into regression analyses, namely: (1) *physical comorbidities (*diagnoses of heart problems/cancer/arthritis/diabetes; binary variable: yes/no), (2) number of *negative life events* within the preceding six months (e.g., relationship, employment, financial problems), assessed using the List of Threatening Experiences questionnaire (12 items, range 0-12, higher scores indicate more stress) (Brugha & Cragg, 1990), (3) *alcohol consumption and alcohol-related problems,* measured using the Alcohol Use Disorders Identification Test (AUDIT) (score range 0-40, higher scores indicate more hazardous/harmful drinking) (Saunders et al., 1993), (4) *physical activity,* measured in terms of the total time (hours/minutes) spent per week engaged in gardening, housework, sport etc., (5) *social support,* assessed using two scales measuring 'supportive interactions' with family and friends, which were averaged to provide a single measure (score range 0-6, higher scores indicate greater support) (Schuster et al., 1990).

Statistical analyses

Due to differences in the prevalence of TBI across the lifespan, the full sample was partitioned at each wave (W1, W2, W3), according to both TBI status and age-group, with cross-sectional analyses used to determine whether young/middle/older-aged adults were differentially impacted by their TBI history ($TBI_{lifetime}$, TBI_{recent}, $TBI_{multiple}$, TBI_{no}). Pearson's χ^2 test and t-tests first compared the socio-demographic characteristics (age, education, sex, marital/employment status) of the $TBI_{lifetime}$ and TBI_{no} groups at baseline (W1) in order to determine whether there were any significant differences. The proportion of people with clinically-significant 'cases' of (1) anxiety (with and without comorbid depression) and (2) depression only (no comorbid anxiety), were then compared between $TBI_{lifetime}$/TBI_{recent} and TBI_{no} groups (χ^2) at each wave (cross-sectional analyses) to determine whether sustaining a TBI impacted on the prevalence of anxiety/depression. Finally, three longitudinal logistic regression analyses (W1-W3) were performed, using Generalised Estimating Equations (GEE), to investigate the relationship between sustaining a TBI (independent variable: $TBI_{lifetime}$, TBI_{recent}, or TBI_{no}) and clinically significant 'cases' of anxiety (dependent variable). Prior to doing this, univariate analyses were conducted in order to identify potential confounds (i.e., age, sex, marital/employment status, multiple TBIs, physical activity, social support, alcohol consumption, lifetime history of depression, comorbid medical conditions, life-events), with all significant variables ($p < .05$) subsequently entered into the GEE analyses to determine whether the TBI-anxiety relationship was significantly impacted by these other variables. All GEEs used an auto-regressive correlation structure and were modelled with a binomial distribution and logit-link function.

Results

Socio-demographic characteristics

Summary demographic data for the $TBI_{lifetime}$ and TBI_{no} groups at W1, stratified by age-group, are provided in Table 1. The demographic data for the sample at W2 and W3 has been provided in the Electronic Supplementary Material (Tables S2 & S3, respectively, pages 180-181). For the total sample, people with a $TBI_{lifetime}$ had a slightly lower mean age (equating to a small effect), but had comparable levels of education. Although the total sample was balanced for sex, more males had sustained a TBI; a pattern echoed in all age-groups (p <.05). Compared to those without a TBI, more TBI participants had never married and fewer were separated/divorced/widowed (total sample; p <.05) and, although employment rates were higher in those with a $TBI_{lifetime}$, more were also seeking additional work (p <.05). Therefore, other than sex, the demographic characteristics of $TBI_{lifetime}$ and TBI_{no} groups were generally comparable.

Significantly more individuals with a $TBI_{lifetime}$, compared to those without (TBI_{no}), completed both the W1 and W2 assessments (p <.05), but not the third wave. Attrition analyses for waves 2 and 3 are provided in the Electronic Supplementary Material (Table S4, page 182). Individuals lost to follow-up at W2 were more depressed and anxious at W1 (p <.05), and individuals who were depressed at W2 were less likely to complete W3 (p <.05), indicating that healthier individuals were more likely to be retained in the sample.

Table 1

Socio-demographic characteristics of participants at baseline (Wave 1), partitioned by age group and lifetime TBI status.

	Young adults (20s+) n = 2,357					**Middle-aged adults (40s+)** n = 2,509					**Older adults (60s+)** n = 2,531					**Total** n = 7,397				
	Lifetime TBI n = 294		**no TBI** n = 2,063			**Lifetime TBI** n = 293		**no TBI** n = 2,216			**Lifetime TBI** n = 223		**no TBI** n = 2,308			**Lifetime TBI** n = 810		**no TBI** n = 6,587		
	M	(SD)	M	(SD)		M	(SD)	M	(SD)		M	(SD)	M	(SD)		M	(SD)	M	(SD)	
Age (years)	22.6	(1.4)	22.6	(1.5)		42.6	(1.4)	42.6	(1.5)		62.5	(1.5)	62.5	(1.5)		40.8	(15.9)	43.3	(16.3)	***
Education (years)	14.4	(1.5)	14.6	(1.6)	*	14.8	(2.3)	14.6	(2.3)		14.0	(2.8)	13.8	(2.8)		14.4	(2.2)	14.3	(2.4)	
	%	(n)	%	(n)	*p*	%	(n)	%	(n)	*p*	%	(n)	%	(n)	*p*	%	(n)	%	(n)	*p*
Sex					***					***					***					***
male	69.0	(203)	45.2	(933)	^	68.3	(200)	44.2	(979)	^	74.4	(166)	49.3	(1,138)	^	70.2	(569)	46.3	(3,050)	^
female	31.0	(91)	54.8	(1,130)	^	31.7	(93)	55.8	(1,237)	^	25.6	(57)	50.7	(1,170)	^	29.8	(241)	53.7	(3,537)	^
Marital status																				**
married/de facto	23.1	(68)	23.6	(486)		77.1	(226)	79.8	(1,768)		81.6	(182)	77.7	(1,794)		58.8	(476)	61.5	(4,048)	
separated/divorced/widowed	0.7	(2)	1.1	(22)		11.6	(34)	12.8	(283)		16.6	(37)	19.5	(450)		9.0	(73)	11.5	(755)	^
never married	75.9	(223)	75.4	(1,555)		11.3	(33)	7.4	(165)	^	1.8	(4)	2.7	(63)		32.1	(260)	27.1	(1,783)	^
Employment status																				**
employed (full, part-time)	79.6	(234)	80.4	(1,658)		88.4	(259)	88.9	(1,971)		42.6	(95)	40.4	(933)		72.6	(588)	69.3	(4,562)	^
not in labour force	7.5	(22)	9.4	(193)		7.8	(23)	7.4	(163)		54.7	(122)	58.4	(1,349)		20.6	(167)	25.9	(1,705)	^
looking for more work	12.6	(37)	10.3	(212)		3.8	(11)	3.7	(82)		2.7	(6)	1.1	(25)	^	6.7	(54)	4.8	(319)	^

lifetime TBI = TBI sustained at any time prior to W1
differences between TBI, no TBI groups tested using Pearson's χ^2 (categorical variables) and independent-samples *t*-tests (continuous variables).
χ^2 and t-tests * p <.05, ** p <.01, *** p <.0001
adjusted residuals > 2 or < -2 indicate that the difference between TBI and no TBI groups at that specific level of variable is significant, ^p <.05

Prevalence of TBIs

Overall, 11% of the sample had sustained at least one TBI ($TBI_{lifetime}$) prior to W1, increasing over time to 12.4% (W2) and 13.1% (W3). Approximately 1%-2% of people (W1: 1.9%, W2: 2.2%, W3: 1.2%) sustained a TBI in the preceding four years (TBI_{recent}) and by W3, 35% had sustained multiple TBIs. A breakdown of TBI prevalence ($TBI_{lifetime}$, TBI_{recent}, TBI_{no}, $TBI_{multiple}$), stratified by age-cohort and wave, is provided in the Electronic Supplementary Material (see Table S5, page 183).

Prevalence of clinically-significant anxiety ('cases') in people with lifetime and recent TBIs

Table 2 compares the number of anxiety 'cases' in the $TBI_{lifetime}$ and TBI_{recent} groups with the TBI_{no} group, stratified by age. Regardless of TBI status, there were consistently more 'cases' in younger adults, compared to both middle- and older-aged adults, indicating that early adulthood is a particularly vulnerable time. Anxiety 'cases' were also more common in the $TBI_{lifetime}$ than the TBI_{no} group across all waves and age-groups (except W3, where numbers were equivalent in young adults,). However, the statistical significance of individual findings varied, with 'cases' of anxiety significantly more prevalent (p <.05) in young (W2), middle-aged (W1) and older adults (W2 & W3). Thus, although younger adults experienced higher rates of clinically-significant anxiety in general (i.e., regardless of TBI status), sustaining a TBI appears to have differentially affected the anxiety levels of older adults to a greater extent. Middle-aged adults who sustained a TBI in the preceding four years (TBI_{recent}) experienced the highest rates of anxiety, with over 30% reaching the threshold for 'caseness' at W1 and W2; rates that differed significantly from their uninjured (TBI_{no}) counter-parts. Thus, people who have a TBI in mid-life appear to be more vulnerable to clinically significant levels of anxiety than people who do not sustain a TBI.

Table 2

Summary data for clinically significant 'cases' of anxiety in (1) lifetime TBI and no TBI groups, and (2) recent and no recent TBI groups: partitioned according to wave and age group.

	Wave 1					Wave 2					Wave 3				
	$TBI_{lifetime}$		No $TBI_{lifetime}$			$TBI_{lifetime}$		No $TBI_{lifetime}$			$TBI_{lifetime}$		No $TBI_{lifetime}$		
	%	(n)	%	(n)	*p*	%	(n)	%	(n)	*p*	%	(n)	%	(n)	*p*
Lifetime TBI															
young adults	24.6	(72)	19.9	(410)		22.6	(72)	18.0	(318)	^	18.4	(58)	18.4	(298)	
middle-aged adults	24.4	(71)	17.0	(375)	^	17.1	(50)	14.4	(291)		18.1	(51)	15.1	(281)	
older adults	9.5	(21)	6.4	(148)		11.1	(23)	5.3	(109)	^	8.3	(16)	4.5	(79)	^
total	20.3	(164)	14.2	(933)	^	17.7	(145)	12.4	(713)	^	15.8	(125)	12.6	(658)	^
	TBI_{recent}		No TBI_{recent}			TBI_{recent}		No TBI_{recent}			TBI_{recent}		No TBI_{recent}		
	%	(n)	%	(n)	*p*	%	(n)	%	(n)	*p*	%	(n)	%	(n)	*p*
Recent TBI															
young adults	24.8	(25)	20.3	(457)		24.7	(24)	18.3	(363)		16.2	(6)	18.7	(362)	
middle-aged adults	33.3	(8)	17.7	(437)	^	35.7	(10)	14.4	(327)	^	10.5	(2)	15.8	(338)	
older adults	16.7	(2)	6.6	(166)		12.5	(2)	5.8	(125)		5.6	(1)	5.0	(97)	
total	25.5	(35)	14.7	(1,060)	^	25.4	(36)	12.7	(815)	^	12.2	(9)	13.3	(797)	

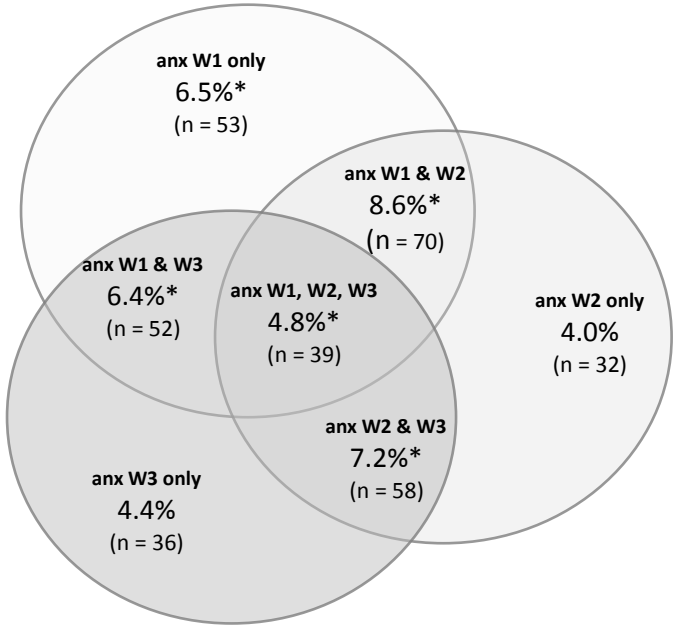
Note: lifetime TBI = TBI sustained at any time prior to the reported wave; recent TBI = TBI sustained in the four years prior to the reported wave.

a = % of each level of anxiety partitioned by TBI status – reported within each age group, and across all age groups;
b = % of anxiety cases partitioned by TBI status – reported within each age group, and across all age groups;
Significance levels: ^ = adjusted residuals >2 or <-2 indicates a significant difference between lifetime TBI and no TBI groups at $p < .05$

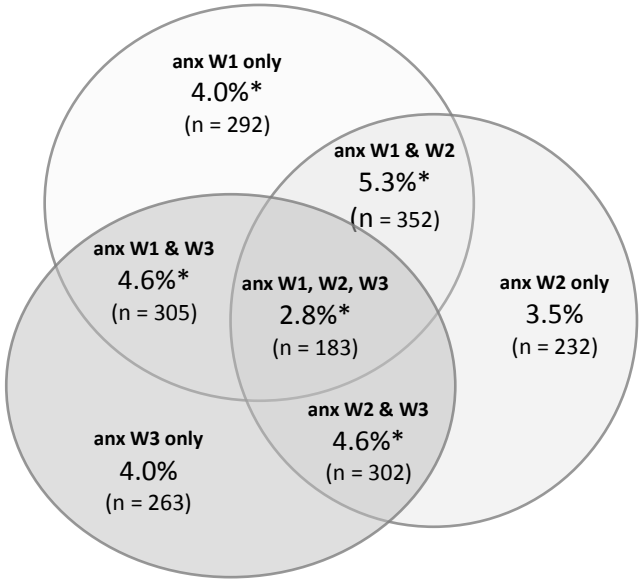
The prevalence of anxiety was then further examined in order to determine whether the chronicity of clinically significant anxiety ('case' ≥7 symptoms) differed between individuals who reported a lifetime TBI (see Figure 2a; $TBI_{lifetime}$; n = 810) or no TBI (see Figure 2b; TBI_{no}; n = 6,587) at W1 (baseline). This revealed that a higher proportion of individuals with a $TBI_{lifetime}$ had experienced clinically significant anxiety at a single wave/assessment only (W1, W2, W3), although the differences were only significant at W1. Further, and importantly, the $TBI_{lifetime}$ group was significantly more likely to have experienced anxiety at two assessments (W1+W2, W2+W3, W1+W3). These proportions were again significantly higher when examining all waves (W1+W2+W3), with just under 5% of the $TBI_{lifetime}$ and 3% of the TBI_{no} group experiencing high levels of anxiety ('case') at all three assessments. These results indicate that a TBI is associated with a greater risk of experiencing clinically-significant, and often chronic, anxiety.

Figure 2. The chronicity of clinically significant 'cases' of anxiety in participants who had (a) sustained a TBI before the W1 assessment ($TBI_{lifetime}$) and (b) had not sustained a TBI (before W1).

a) **TBI at W1** (baseline; n = 810)



b) **no TBI at W1** (baseline; n = 6,587)



Note: TBI = traumatic brain injury; anx = anxiety; W1 = wave one, W2 = wave two, W3 = wave three;

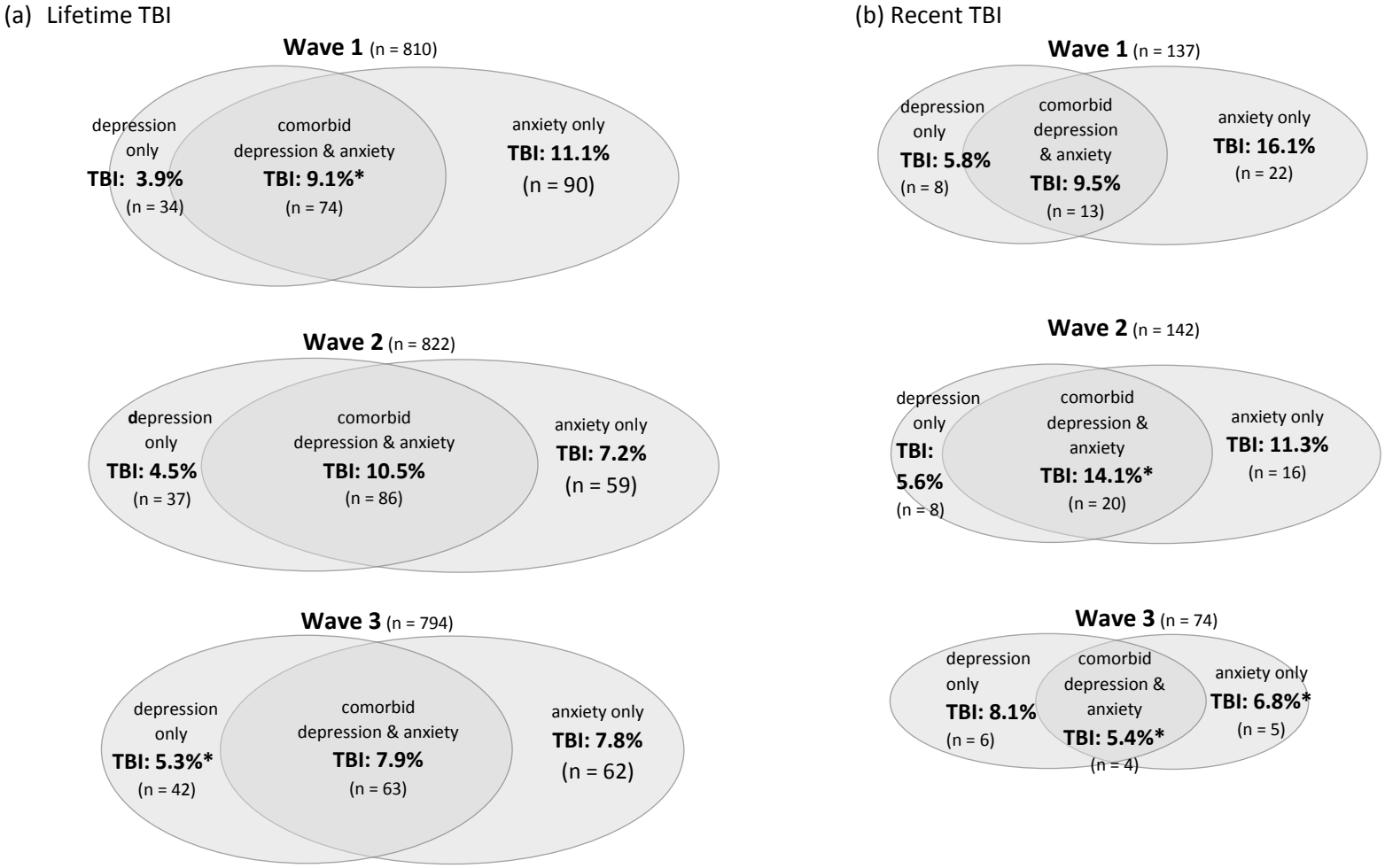
* = sig p <.05 difference between the $TBI_{lifetime}$ (above left) and TBI_{no} (above right) groups in the prevalence of clinically significant anxiety when evaluating comparable waves/assessments.

Anxiety, depression and comorbid anxiety/depression in those with a lifetime or recent TBI

Next, the proportion of people with a $TBI_{lifetime}$/TBI_{recent} who reported clinically-significant *anxiety, depression and comorbid* anxiety and depression were examined at each wave. In terms of $TBI_{lifetime}$, more people suffered from clinically-significant *anxiety* than *depression* at each wave, with *comorbid* anxiety/depression being present in approximately 10% of those with a $TBI_{lifetime}$ (W1-W3). However, when these rates were compared with those of the TBI_{no} group, only *comorbid* anxiety/depression (W1), and *depression* alone (W3) differed significantly (see Figure 3a).

Although there were fewer people who had sustained a TBI_{recent}, the proportion with clinically-significant *depression*, *anxiety* and *comorbid* anxiety/depression was greater than $TBI_{lifetime}$ (other than W3: *comorbidity* and *anxiety only*) (Figure 3b), suggesting that the risk of mental health problems is even greater within the first four years of an injury, compared to longer time post-injury periods.

Figure 3. Prevalence of clinically significant 'cases' of depression and anxiety in participants with a (a) lifetime and (b) recent TBI, partitioned according to wave.



Note: * = numbers of clinically significant 'cases' of depression/anxiety significantly higher (p <.05) than the no TBI group; TBI = traumatic brain injury

Longitudinal relationship between lifetime/recent TBIs and anxiety

Generalized Estimating Equations (GEE) generate population-averaged effects that account for repeated assessments of the same individual (Twisk, 2004), hence they were used to evaluate the relationship between $TBI_{lifetime}$ / TBI_{recent} (independent variables) and anxiety 'cases' (dependent variable) over time (W1-W3). Before doing so, univariate analyses (see Table 3) assessed the relationship between anxiety and (1) $TBI_{lifetime}$ (Model 1), and (2) TBI_{recent} (Model 2), while controlling for history of depression. Across the total sample, people with a $TBI_{lifetime}$ (Model 1) were 37% (OR = 1.37; p <.0001) more likely to experience clinically-significant anxiety. When stratified by age, all age-groups were at an increased risk of anxiety following a TBI, with older adults being particularly vulnerable (63%; p <.05), followed by middle-aged (29%; p <.05) and younger (13%, *ns*) adults, suggesting that a TBI, combined with increasing age, is associated with an increased vulnerability to anxiety. When a TBI had been sustained in the preceding four years (TBI_{recent}: Model 2), the risk of experiencing anxiety increased to 47% (total sample; p <.01), although the results were not significant for the different age cohorts; possibly reflecting the small number of 'cases', leading to wide confidence intervals and limited power.

Next, two multivariate GEE models (Model 3: $TBI_{lifetime}$; Model 4: TBI_{recent}; see Table 3) were generated to examine anxiety, adjusting for relevant significant covariates identified in univariate analyses. Model 3 found that the association between anxiety and $TBI_{lifetime}$ was significant in the full sample (39%) and each age-group (young: 29%; middle-aged: 39%; older: 76% adults), after controlling for covariates identified as significant in univariate analyses (i.e., lifetime history of depression and sex). Thus, even after controlling for sex-differences, older age was associated with an increased likelihood of anxiety problems after a TBI. In contrast, Model 4 shows that once significant covariates (i.e., lifetime history of depression, sex, marital/employment status, multiple TBIs, physical activity, stressful life events and alcohol consumption) were accounted for, the relationship between anxiety and TBI_{recent} was not

significant (total sample, all age-groups), suggesting that modifiable health/lifestyle/psychosocial variables impact on anxiety in the early years after a TBI.

Table 3

Unadjusted (univariate) and adjusted (multivariate) analyses: odds ratios and 95% CIs for the association between anxiety and TBI status across waves 1, 2 and 3, partitioned according to age group.

Clinically significant 'cases' of anxiety (≥ 7 symptoms)

	young adults		**middle-aged adults**		**older adults**		**Total^**	
	OR (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*
Univariate								
lifetime TBI (Model 1)	1.13 (0.91 – 1.40)		1.29 (1.02 – 1.63)	*	1.63 (1.12 – 2.38)	*	1.37 (1.18 – 1.58)	***
recent TBI (Model 2)	1.21 (0.91 – 1.63)		1.37 (0.78 – 2.40)		1.26 (0.44 – 3.67)		1.47 (1.13 – 1.92)	**
Multivariate								
lifetime TBI (Model 3)	1.29 (1.04 – 1.62)	*	1.39 (1.09 – 1.76)	**	1.76 (1.20 – 2.58)	**	1.39 (1.19 – 1.62)	***
recent TBI (Model 4)	0.99 (0.72 – 1.38)		0.85 (0.48 – 1.50)		0.98 (0.32 – 3.01)		0.99 (0.75 – 1.31)	

Notes:

* *p* <.05, ** p <.01, *** *p* <.0001

Univariate analyses (Models 1 and 2) controlled for lifetime depression at W1.

Multivariate analyses (Models 3 and 4) controlled for covariates identified as significant in preliminary univariate analyses. Covariates for each model were:

Model 3 = lifetime depression at W1 and sex

Model 4 = lifetime depression at W1, sex, marital status, employment status, multiple TBIs, physical activity, life events, alcohol

^ = multivariate analyses using the total sample also controlled for age at W1, whereas analyses examining age-groups did not control for age at W1

Discussion

The current study used rare, population-based longitudinal data to examine 'cases' of clinically-significant anxiety and comorbid depression in community-dwelling individuals. Young, middle-aged and older adults were assessed three times over a total of eight years, and anxiety outcomes compared between those who reported a TBI (sustained since birth or within the preceding four years) and those who had never suffered a TBI. In addition, the impact of a variety of demographic (i.e., age, sex, marital/employment status), health (i.e., depression history, comorbid medical conditions, multiple TBIs, alcohol consumption) and lifestyle (i.e., life-events, physical activity, social support) factors on anxiety after a TBI were evaluated. Importantly, the current study improves our understanding of the relationship between TBIs and anxiety over time. Anstey et al. (2004) and Butterworth, Anstey, Jorm, and Rodgers (2004) used PATH baseline data (W1) to investigate these constructs, however the current study extends their work by using a longitudinal methodology to incorporate two subsequent waves of data.

At the end of the eight-year study, 13% of people had reported having a TBI sometime in their life; a rate consistent with a recent meta-analysis (12%) (Frost et al., 2013). Conversely, the proportion of multiple TBIs (35%) was higher than previously reported (Corrigan et al., 2013; Whiteneck et al., 2004), possibly because self-reports were used and injuries of all severities included, thereby capturing the estimated 30-40% of untreated mild TBIs that may be missed by studies that recruit people in healthcare settings (Demakis & Rimland, 2010; Faul & Coronado, 2015). Hence, the present study probably better reflects population rates. Consistent with previous research (Bruns & Hauser, 2003; Butterworth et al., 2004; Cassidy et al., 2004; Eramudugolla et al., 2014; Maas et al., 2008), young adults were more at risk of sustaining a TBI than middle- and older-aged adults, possibly reflecting greater participation in activities known to be risk factors for TBI (e.g., excessive alcohol consumption,

driving, sports, assaults) (Mallya et al., 2015; Shahin & Robertson, 2012), or greater community awareness (e.g., in sport) of the negative consequences of TBI and, thus, increased rates of reporting (Butterworth et al., 2004).

A striking finding that was reinforced in both the cross-sectional (prevalence) and longitudinal (regression) analyses, was that individuals who had sustained a TBI at *any* time in their life were more likely to experience clinically significant (high) levels of anxiety than people without a TBI, even after taking into account a variety of demographic (age, education, marital and employment status), health (comorbid medical conditions, history of depression, multiple TBIs, excessive alcohol consumption) and lifestyle (stressful events, physical activity, social support) variables that could independently inflate these rates. This suggests that TBI is a chronic condition that requires psycho-education and ongoing support to optimise long-term outcomes (Corrigan & Hammond, 2013).

Consistent with prior research that has examined similar post-injury intervals and used comparable measures (Alway et al., 2012; Kinsella et al., 1988; Powell et al., 2002; Van Der Horn et al., 2013), anxiety problems were generally more prevalent (except W3) when a TBI had recently been sustained (≤4 years). These cross-sectional results were also reinforced in longitudinal analyses, whereby the risk of anxiety was greater after a recent TBI, even after controlling for prior episodes (history) of depression. However this relationship reduced after accounting for a variety of demographic, health and psychosocial variables, which highlights the importance of ensuring that patients have good social support and that they adopt healthy lifestyles (e.g., being physically active, limiting alcohol consumption).

The finding that the association between TBI and anxiety varied across age-cohorts was consistent with Eramudugolla et al. (2014) who demonstrated that cognitive decline in PATH participants with a TBI was differentially affected according to their age-group (young,

middle-aged, older adults). In the current study, young adults had a consistently higher prevalence of clinically-significant anxiety than middle- and older-aged adults, regardless of TBI status; highlighting the stressors associated with this time of life (e.g., establishing careers, relationships) (Arnett, 2000). TBI status only had a modest association with anxiety in this younger cohort, with both sexes at risk of experiencing anxiety following a lifetime TBI, indicating that although females suffer from anxiety more frequently (APA, 2013), it is critical that young males are also monitored for these symptoms after a TBI.

In contrast, having a TBI substantially impacted on middle-aged adults, with those in midlife reporting the highest prevalence of anxiety (TBI_{recent}: W1 and W2). Moreover, in longitudinal analyses, there was an association between having sustained a TBI at any time since birth and the likelihood of anxiety in this age-group, regardless of the person's sex and vulnerability to mental health problems. These results highlight the additional burden of TBIs in midlife – possibly because injury-related impairments lead to a perceived or actual inability to fulfil established career/family/social role commitments (Brzuzy & Speziale, 1997; McCabe, 2007) – and underscore the need to provide appropriate support to manage anxiety levels.

TBIs were reported infrequently in our older-adults (N<20 in the four years prior to each assessment). This would appear contrary to research demonstrating that TBI rates increase in the elderly, primarily as a result of falls (Faul & Coronado, 2015). However, none of the people in the older-adult cohort had reached the age (75 years) where the risk of falls has been shown to substantially increase (CDC, 2014). Moreover, even at this older-age when a person's TBI had often been sustained many years previously, anxiety levels were heightened, demonstrating the lifelong risk of increased anxiety after a TBI. In contrast, recent TBIs did not lead to an increased risk, possibly reflecting variability in individual outcomes, or a small and hence underpowered sample.

Anxiety was also found to be highly comorbid with depression, with approximately half the people who reported clinically-significant anxiety after a TBI, sustained at some time in their life, also being depressed. Surprisingly few studies have reported comorbidity rates in TBI samples, despite the fact that anxiety and depression are well known to frequently co-exist (Bombardier et al., 2010; Gould et al., 2011a; Jorge et al., 2004; Van Reekum et al., 1996). Further recognition of this issue by clinicians is crucial: comorbid depression alters the clinical course of anxiety and worsens outcomes by complicating recovery, increasing symptom levels and the risk of suicidality which, ultimately, imposes a greater burden on the individual and society (Lecrubier, 2001; Merikangas & Swanson, 2010; Sareen, et al., 2005). Given that anxiety and depression are both common after a TBI and can occur either independently or concurrently, clinicians are urged to screen for both types of problems separately in order to better assess an individual's mental health.

Although assessing a large community-based sample over a relatively long period, and controlling for a wide range of demographic/health/psychosocial variables, the current study faced a number of limitations. First, TBIs were not medically confirmed. Nonetheless, the fact that many TBIs do not receive any medical attention (Corrigan & Bogner, 2007) means that the present data is likely to better reflect population prevalence rates. Second, point estimates of anxiety were reported, which may lead to the under-estimation of the prevalence of anxiety as 'cases' in remission at the time of assessment are missed. Third, self-report scales were used to assess anxiety, providing a less comprehensive assessment than clinical diagnoses. However, using the current cut-points, the Goldberg Anxiety Scale has a specificity of 0.84 and sensitivity of 0.86 for diagnoses of GAD (Kiely & Butterworth, 2015). Fourth, sample attrition resulted in psychologically healthier individuals being retained at each wave (retention bias), potentially leading to a lower prevalence of anxiety problems.

In conclusion, the occurrence of a TBI at any time in a person's life was associated with a greater risk of developing anxiety, in both males and females. In contrast, the association between recent TBIs (≤4 years post-injury) and 'cases' of anxiety was less pronounced once a variety of demographic (i.e., age, sex, marital/employment status), health (i.e., depression history, comorbid medical conditions, multiple TBIs, alcohol consumption), and psychosocial (i.e., life-events, physical activity, social support) variables had been taken into account; suggesting that positive lifestyle changes may help to mitigate anxiety problems. Moreover, this increased lifelong risk of anxiety was found to be chronic, highlighting the need for ongoing monitoring after a TBI. Finally, comorbid anxiety and depression was also common, reinforcing the need for clinicians to identify and treat both conditions to reduce the cumulative burden imposed by dual conditions.

6.4 Electronic Supplementary Material

Table S1

Overview of the full sample in the Personality and Total Health (PATH) Through Life study, and participants in the current study sample, partitioned according to successive assessment

	Young adults	Middle-aged adults	Older adults	Total
Wave 1				
age at assessment	20 – 24 years	40 – 44 years	60 – 64 years	
year of birth	1975 – 1979	1956 – 1960	1937 – 1941	
when assessed	1999 – 2000	2000 – 2001	2001 – 2002	
PATH W1 full sample participants, n	2,404	2,530	2,551	7,485
TBI data missing, n (%)	47 (2.0)	21 (0.8)	20 (0.8)	88 (1.2)
current study W1 participants, n	2,357	2,509	2,531	7,397
Wave 2				
age at assessment	24 – 28 years	44 – 48 years	64 – 68 years	
when assessed	2003 – 2004	2004 – 2005	2005 – 2006	
lost to follow-up, n	265	176	329	770
PATH W2 full sample participants, n	2,139	2,354	2,222	6,715
PATH W2 participation rate (%)	(89.0)	(93.0)	(87.1)	(89.7)
TBI data missing, n (%)	46 (2.2)	29 (1.2)	19 (0.9)	94 (1.4)
current study W2 participants, n	2,093	2,325	2,203	6,621
Wave 3				
age at assessment	28 – 32 years	48 – 52 years	68 – 72 years	
when assessed	2007 – 2008	2008 – 2009	2009 – 2010	
lost to follow-up, n	161	172	249	582
PATH W3 full sample participants, n	1,978	2,182	1,973	6,133
PATH W3 participation rate (%)	(92.5)	(92.7)	(88.8)	(91.3)
TBI data missing, n (%)	41 (2.1)	33 (1.5)	17 (0.9)	91 (1.5)
current study W3 participants, n	1,937	2,149	1,956	6,042

Note: wave = assessment; 'TBI data not determined'= TBI item responses (missing, don't know, uncertain, refused) not clarified with data provided at other assessments; participation rate = the percentage of PATH participants interviewed from the previous wave.

Table S2

Socio-demographic characteristics of participants at wave 2, grouped by age and lifetime TBI status.

	Young adults (20+) n = 2,093					**Middle-aged adults (40+)** n = 2,325					**Older adults (60+)** n = 2,203					**Total** n = 6,621				
	Lifetime TBI n = 319		**no TBI** n = 1,774			**Lifetime TBI** n = 294		**no TBI** n = 2,031			**Lifetime TBI** n = 209		**no TBI** n = 1,994			**Lifetime TBI** n = 822		**no TBI** n = 5,799		
	M	(SD)	M	(SD)		M	(SD)	M	(SD)		M	(SD)	M	(SD)		M	(SD)	M	(SD)	
Age (years)	26.7	(1.5)	26.7	(1.5)		46.6	(1.4)	46.6	(1.5)		66.6	(1.5)	66.6	(1.5)		44.0	(15.9)	47.4	(16.1)	***
Education (years)	15.0	(1.6)	15.3	(1.7)	**	15.0	(2.2)	14.8	(2.2)		14.0	(3.0)	13.9	(2.7)		14.7	(2.3)	14.6	(2.3)	
	%	(n)	%	(n)	*p*	%	(n)	%	(n)	*p*	%	(n)	%	(n)	*p*	%	(n)	%	(n)	*p*
Sex					***					***					***					***
male	69.0	(220)	43.1	(765)	^	66.3	(195)	44.0	(893)	^	75.1	(157)	49.3	(983)	^	69.6	(572)	45.5	(2,641)	^
female	31.0	(99)	56.9	(1,009)	^	33.7	(99)	56.0	(1,138)	^	24.9	(52)	50.7	(1,011)	^	30.4	(250)	54.5	(3,158)	^
Marital status																				*
married/de facto	54.9	(175)	53.1	(942)		79.3	(233)	77.8	(1,581)		79.4	(166)	77.2	(1,540)		69.8	(574)	70.1	(4,063)	
separated/divorced/widowed	1.6	(5)	2.1	(38)		12.6	(37)	14.4	(293)		19.1	(40)	20.4	(407)		10.0	(82)	12.7	(738)	^
never married	43.6	(139)	44.8	(794)		8.2	(24)	7.7	(157)		1.4	(3)	2.4	(47)		20.2	(166)	17.2	(998)	^
Employment status																				***
employed (full, part-time)	88.1	(281)	86.8	(1,539)		87.1	(256)	88.7	(1,801)		29.2	(61)	25.9	(517)		72.7	(598)	66.5	(3,857)	^
not in labour force	6.3	(20)	8.4	(149)		8.5	(25)	8.0	(163)		70.8	(148)	73.8	(1,472)		23.5	(193)	30.8	(1,784)	^
looking for more work	5.6	(18)	4.8	(86)		4.4	(13)	3.2	(65)		0	(0)	0.3	(5)		3.8	(31)	2.7	(156)	

Differences between TBI, no TBI groups tested using Pearson's χ^2 (categorical variables) and independent-samples *t*-tests (continuous variables).
χ^2 and t-tests * p <.05, ** p <.01, *** p <.0001
Adjusted residuals > 2 or < -2 indicate that the difference between TBI and no TBI groups at that specific level of variable is significant, ^p <.05

Table S3

Socio-demographic characteristics of participants at wave 3, grouped by age and lifetime TBI status.

	Young adults (20+) n = 1,937					**Middle-aged adults (40+)** n = 2,149					**Older adults (60+)** n = 1,956					**Total** n = 6,042				
	Lifetime TBI n = 316		**no TBI** n = 1,621			**Lifetime TBI** n = 283		**no TBI** n = 1,866			**Lifetime TBI** n = 195		**no TBI** n = 1,761			**Lifetime TBI** n = 794		**no TBI** n = 5,248		
	M	(SD)	M	(SD)		M	(SD)	M	(SD)		M	(SD)	M	(SD)		M	(SD)	M	(SD)	
Age (years)	30.6	(1.5)	30.7	(1.5)		50.7	(1.4)	50.7	(1.5)		70.6	(1.5)	70.6	(1.5)		47.6	(15.8)	51.2	(16.1)	***
Education (years)	15.1	(1.6)	15.4	(1.7)	**	15.1	(2.2)	14.9	(2.2)		-		-			15.1	(2.0)	15.1	(1.9)	
	%	(n)	%	(n)	*p*	%	(n)	%	(n)	*p*	%	(n)	%	(n)	*p*	%	(n)	%	(n)	*p*
Sex					***					***					***					***
male	66.5	(210)	42.4	(688)	^	67.5	(191)	44.3	(827)	^	73.3	(143)	49.5	(871)	^	68.5	(544)	45.5	(2,386)	^
female	33.5	(106)	57.6	(933)	^	32.5	(92)	55.7	(1,039)	^	26.7	(52)	50.5	(890)	^	31.5	(250)	54.5	(2,862)	^
Marital status																				*
married/de facto	69.3	(219)	68.0	(1,103)		76.3	(216)	77.7	(1,449)		80.0	(156)	74.4	(1,310)		74.4	(591)	73.6	(3,862)	
separated/divorced/widowed	4.7	(15)	3.1	(50)		14.8	(42)	14.3	(267)		18.5	(36)	23.0	(405)		11.7	(93)	13.8	(722)	
never married	25.9	(82)	28.9	(468)		8.8	(25)	7.9	(148)		1.5	(3)	2.6	(46)		13.9	(110)	12.6	(662)	
Employment status																				***
employed (full, part-time)	91.1	(288)	89.3	(1,447)		91.9	(260)	91.0	(1,699)		14.4	(28)	16.7	(294)		72.5	(576)	65.5	(3,440)	^
not in labour force	5.1	(16)	8.3	(134)		6.4	(18)	6.6	(123)		83.6	(163)	82.5	(1,452)		24.8	(197)	32.6	(1,709)	^
looking for more work	3.8	(12)	2.5	(40)		1.8	(5)	2.4	(44)		2.1	(4)	0.9	(15)		2.6	(21)	1.9	(99)	

Differences between TBI, no TBI groups tested using Pearson's χ^2 (categorical variables) and independent-samples *t*-tests (continuous variables).
χ^2 and t-tests * p <.05, ** p <.01, *** p <.0001
Adjusted residuals > 2 or < -2 indicate that the difference between TBI and no TBI groups at that specific level of variable is significant, ^p <.05

Table S4

Attrition analysis: comparison of socio-demographic and health characteristics at waves 2 and 3, partitioned according to participation status.

	Wave 2 sample		**Wave 2 lost to follow-up**			**Wave 3 sample**		**Wave 3 lost to follow-up**		
	n = 6,621		n = 864			n = 5,943		n = 678		
	%	(n)	%	(n)	*p*	%	(n)	%	(n)	*p*
Sex					*					
male	48.5	(3,213)	53.1	(459)	^	48.4	(2,877)	49.6	(336)	
female	51.5	(3,408)	46.9	(405)	^	51.6	(3,066)	50.4	(342)	
Age group					***					**
young adults	31.6	(2,093)	36.0	(311)	^	31.6	(1,880)	31.4	(213)	
middle-aged adults	35.1	(2,325)	23.7	(205)	^	35.8	(2,125)	29.5	(200)	^
older adults	33.3	(2,203)	40.3	(348)	^	32.6	(1,938)	39.1	(265)	^
Marital status					***					
married/de facto	61.9	(4,091)	53.5	(461)	^	70.3	(4,180)	67.4	(457)	
separated/divorced/widowed	10.9	(719)	13.7	(118)	^	12.1	(722)	14.5	(98)	
never married	27.2	(1,794)	32.8	(282)	^	17.5	(1,041)	18.1	(123)	
Employment status					***					***
employed (full, part-time)	70.8	(4,685)	58.6	(504)	^	68.4	(4,063)	57.8	(392)	^
not in labour force	24.2	(1,600)	34.5	(297)	^	28.9	(1,715)	38.6	(262)	^
looking for more work	4.8	(319)	6.9	(59)	^	2.7	(163)	3.5	(24)	
Lifetime TBI status					**					
yes	11.3	(745)	8.1	(65)	^	12.4	(736)	12.7	(86)	
no	88.7	(5,849)	91.9	(738)	^	87.6	(5,207)	87.3	(592)	
Goldberg depression case					***					***
yes	17.9	(1,178)	23.0	(197)	^	16.8	(993)	22.2	(147)	^
no	82.1	(5,408)	77.0	(658)	^	83.2	(4,927)	77.8	(516)	^
Goldberg anxiety case					***					
yes	14.5	(953)	19.8	(169)	^	13.0	(768)	13.6	(90)	
no	85.5	(5,631)	80.2	(686)	^	87.0	(5,154)	86.4	(573)	

Note: figures are % (n) unless otherwise indicated; differences tested using Pearson's χ^2. Significance levels: χ^2 * p <.05, ** p <.01, *** p <.0001; adjusted residuals >2 or <-2 indicate a significant difference between W2/W3 sample and those lost to follow-up ^p <.05.

W2 lost to follow-up = completed W1, did not complete W2;
W3 lost to follow-up sample numbers lower than full W3 sample because:

(1) participants included in W3 attrition analyses were those with data at both W2 and W3

(2) participants not included were those who had data at W2, but did not complete the W3 assessment

(3) participants excluded from the analysis were those who (a) dropped out between W1 & W2 (b) had uncertain TBI responses (c) did not complete the W2 assessment, even though they completed the W3 assessment

Table S5

Prevalence of lifetime TBIs (since birth), no TBIs, recent TBIs (≤ 4 years post-injury), and multiple TBIs (≥ 2 TBIs); partitioned according to wave and age group.

	Lifetime TBI[a]		No TBI[b]		Total sample[c]	Recent TBI[d]		Multiple TBIs[e]		Average number of TBIs[f]	
	%	(n)	%	(n)	(n)	%	(n)	%	(n)	M	(SD)
Wave 1											
young adults	12.5	(294)	87.5	(2,063)	(2,357)	34.4	(101)	29.9	(88)	2.7	(1.0)
middle-aged adults	11.7	(293)	88.3	(2,216)	(2,509)	8.2	(24)	28.7	(84)	3.0	(2.0)
older adults	8.8	(223)	91.2	(2,308)	(2,531)	5.4	(12)	19.7	(44)	3.4	(3.0)
total	11.0	(810)	89.0	(6,587)	(7,397)	16.9	(137)	26.7	(216)	2.9	(2.0)
Wave 2											
young adults	15.2	(319)	84.8	(1,774)	(2,093)	30.7	(98)	44.5	(142)	3.2	(2.4)
middle-aged adults	12.6	(294)	87.4	(2,031)	(2,325)	9.5	(28)	33.3	(98)	3.3	(2.8)
older adults	9.5	(209)	90.5	(1,994)	(2,203)	7.7	(16)	23.0	(48)	3.5	(2.9)
total	12.4	(822)	87.6	(5,799)	(6,621)	17.3	(142)	35.0	(288)	3.3	(2.6)
Wave 3											
young adults	16.3	(316)	83.7	(1,621)	(1,937)	11.7	(37)	42.7	(135)	3.4	(2.5)
middle-aged adults	13.2	(283)	86.8	(1,866)	(2,149)	6.7	(19)	34.3	(97)	3.2	(2.8)
older adults	10.0	(195)	90.0	(1,761)	(1,956)	9.2	(18)	24.1	(47)	3.4	(2.9)
total	13.1	(794)	86.9	(5,248)	(6,042)	9.3	(74)	35.1	(279)	3.3	(2.7)

a = TBI sustained since birth
b = participant has never sustained a TBI
c = lifetime TBI plus no TBI
d = % (n) is the proportion of lifetime TBI participants who had sustained their injuries in the four years prior to an assessment (≤ 4 yrs post-injury interval)
e = % (n) is the proportion of lifetime TBI participants who have had ≥ 2 TBIs
f = M (SD) is the average number of TBIs sustained by individuals with ≥ 2 TBIs

CHAPTER 7: DISCUSSION

The overarching aim of the current thesis was to elucidate the relationship between TBI, depression and anxiety. Thus, two meta-analyses, which evaluated the existing literature, and two longitudinal population-based studies, which augmented these findings, were undertaken. The current discussion briefly outlines the findings from each study, then uses summative findings to discuss the research and clinical implications of the thesis. Lastly, thesis limitations are discussed, followed by suggestions for future research.

7.1 Summary of the findings from each study

Study 1: Depression meta-analysis

The first study (Chapter 3) assessed the prevalence of clinical diagnoses of MDD/dysthymia and self-reported depression (clinically significant cases), and severity of depression symptoms (self-report scale scores) after a TBI. Data from 99 studies were meta-analysed, with depression found to be extremely common after a TBI. Overall, 27% of people were diagnosed with MDD or dysthymia and 38% reported clinically significant levels of depression when completing questionnaires.

Some secondary findings were also notable. Specifically, estimates of the prevalence of MDD/dysthymia varied when different diagnostic criteria were used, with the highest rates noted for the DSM-III (47%) criteria, decreasing to 25% for the DSM-IV and then 14% for the ICD-10. The rates also differed according to the clinical interview that was used, with the most common — the SCID-I — yielding a prevalence rate of 23% and other schedules ranging between 16% (MINI) and 54% (CIS). Similarly, the choice of self-report measure impacted on findings, with 32% of those completing the HADS reporting clinically significant depression. The remaining scales were administered less frequently than the HADS, but revealed prevalence rates that ranged between 2% (MADRS) and 48% (CES-D). Moreover, the method

of administration also affected rates, with people reporting more symptoms when they were completing the questionnaires at home (46%), than by phone (26%).

The rates of MDD/dysthymia also differed over the various post-injury intervals, reaching a peak of 43% between 2 and 5 years after an injury. Although this rate decreased in the long term (> 5 years, 22%), it remained higher than that seen in the general population (7%; APA, 2013). In contrast, the rate of clinically significant depression identified using self-report questionnaires steadily increased from 33% in the first 6 months after an injury, to 35% between 6 months and 2 years after, with rates for longer post-injury intervals plateauing at over 40%.

Injury severity also impacted on the findings, with mild TBI being associated with fewer MDD/dysthymia diagnoses (16%) than samples that contained mixed injuries (e.g., mild/moderate, moderate/severe, mild to severe) or severe TBIs (both 30%). These findings contrasted with the rates obtained when people completed self-report measures, with more 'cases' of depression reported following mild TBI (64%) than either mild/moderate/severe or severe TBI (36% and 39%, respectively).

Finally, relative to people living in the general community, MDD/dysthymia (OR = 7.69) and clinically significant levels of self-reported depression (OR = 5.75) were more likely to be experienced following a TBI. Moreover, when the full spectrum of self-reported depressive symptoms was examined (ranging from no symptoms to severe depression), it was found that individuals experienced substantially higher (Hedge's g = 1.06) levels of depression following a TBI than their healthy peers. Similarly, those with a TBI had an increased risk of both MDD and clinically significant depression when compared to medical controls or their 'significant others'.

Study 2: PATH study of depression

Chapter 4 (Study 2) augmented these findings by evaluating the rates of TBI in a population-based community sample, and then comparing the prevalence and risk of clinically significant depression between people with and without a TBI. TBIs were found to be common, with approximately 13% of people sustaining at least one TBI in their lifetime and, of those, 35% incurring more than one. In the 4 years prior to each assessment, young adults sustained more TBIs than middle-aged or older adults, particularly in early adulthood when they were aged between 16 and 28 years (Waves 1 and 2).

The rates of clinically significant depression varied across the age-cohorts but, in terms of the full sample, cross-sectional analyses showed that depression was more prevalent in those who had sustained a TBI. Moreover, the findings supported the notion that TBIs have a long-term impact on the risk of experiencing depression, because this differential was observed regardless of the length of time that had elapsed since the injury. Longitudinal analyses demonstrated that there was a 19% increased risk of clinically significant depression if a TBI had been sustained at any time since birth. Importantly, this risk was evident even after taking into account a broad variety of demographic (age, sex, marital/employment status), health (prior history of depression or a TBI, physical comorbidities [cancer, heart problems, arthritis or diabetes]) and lifestyle (recent stressful life events, alcohol consumption, physical activities, and social support) factors.

Study 3: Anxiety meta-analysis

The impact of non-penetrating TBIs on the prevalence of GAD and clinically significant levels of self-reported anxiety in adults was assessed in the third study (Chapter 5). Data from 41 studies were meta-analysed and, overall, anxiety was also found to be common after a TBI, with 11% of people diagnosed with GAD and 37% reporting clinically significant levels of anxiety. As with MDD, the prevalence of GAD differed when various methodological and

participant characteristics were considered (i.e., diagnostic criteria, interview and self-report measure used, duration of post-injury interval, injury severity and type of control group).

In terms of diagnostic criteria, the highest rates of GAD were found when using the DSM-III-R (19%), followed by the combined DSM-IV/ICD-10 criteria (11%), DSM-IV (9%) and ICD-10 (2%). The rates also differed according to the specific clinical interview that was used, with estimates ranging from 2% (SCAN) to 28% (SADS-L), although the MINI, PSE and SCID-I yielded comparable rates (11%). Similarly, there was considerable variability in the prevalence of clinically significant 'cases' of anxiety when different self-report scales were used; ranging from 35%/36% for the Leeds and HADS, to 49%/50% for the BAI and STAI. Moreover, these rates also differed depending on where/how these measures were administered, with more 'cases' being identified when participants completed the questionnaires in a research setting or at home (38%), compared to when a combination of methods were used (phone, mail, research centre: 29%).

The prevalence of GAD and clinically significant anxiety was also affected by the length of time that had elapsed since the TBI. GAD diagnoses varied from 10% in the first six months after an injury, then decreased in the short-term (6%; > 6 mths to ≤ 2 yrs), increased in the medium-term (17%; > 2 to ≤ 5 yrs), before returning to a level similar to that seen in the short-term (5%; > 5 yrs). In contrast, self-reported clinically significant 'cases' of anxiety steadily increased over time (acute: 28%, short-term: 37%, medium-term: 39%), plateauing at 36% in the long-term (> 5 years). Injury severity could only be examined in a limited way because most studies examined samples with a range of different injury severities, however GAD was found to be slightly less common after mild (11%) than severe (15%) TBI. In contrast, 'cases' of self-reported anxiety were more frequent following mild (53%) than severe TBIs (38%). When mixed samples (mild-moderate-severe injuries) were used, GAD was diagnosed in 10%, and clinically significant anxiety identified in 34%, of people.

In terms of comparison groups, only one study examined GAD relative to controls (general trauma patients), with GAD being diagnosed more frequently following TBI (OR = 1.44). When self-report scales were used, people who had a TBI were more than three times as likely to report clinically significant anxiety than adults living in the community, more than twice as likely as people with spinal injuries, and nearly double that of family, friends and caregivers.

Study 4: PATH study of anxiety

The final study (Chapter 6) examined 'cases' of clinically significant anxiety and comorbid depression in data obtained from the same community-based sample as that used in Chapter 4. Overall, individuals living in the community experienced clinically significant anxiety more frequently than those without a TBI (except at the final assessment). Moreover, comorbidity was high after a TBI, because approximately half of those reporting clinically significant levels of anxiety, were also depressed. Notably, *more* individuals with a TBI were suffering from clinically significant anxiety, than depression, at each wave.

Longitudinal analyses demonstrated that people who had sustained a TBI at any time since birth were 39% more likely to experience clinically significant levels of anxiety than someone without a TBI; even after taking into account a broad range of demographic (age, sex, marital & employment status), health (depression history, comorbid medical conditions, multiple TBIs, alcohol consumption) and lifestyle (stressful life events, physical activity, social support) variables that could have independently predisposed them to psychological problems. Moreover, this increased risk was apparent across the adult lifespan, with young (29%), middle-aged (39%) and older (76%) adults all more vulnerable to anxiety after a TBI.

7.2 Summative findings from the four studies

Together, the findings from the four studies demonstrate that after a TBI, both depression and anxiety: are common, often persist for years, and occur more frequently in people who have sustained a TBI, relative to those who have not. This suggests a more contemporary conceptualisation of TBI as a long-term condition that goes beyond the initial event (Corrigan & Hammond, 2013; Masel & DeWitt, 2010). Moreover, findings clarify how different methodologies and sample characteristics influence study outcomes, information that is useful to researchers and clinicians alike. There were a number of themes that were observed across the studies and these collective findings are described below.

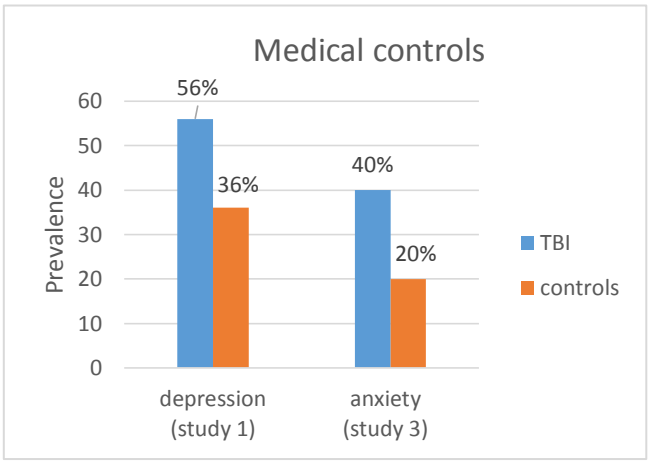
7.2.1 Increased risk of depression and anxiety relative to comparison groups

All four studies have highlighted the fact that depression and anxiety (MDD/GAD, self-reported 'cases') are more prevalent in people who have sustained a TBI, compared to those who have not. Figure 7.1 illustrates these differences by comparing rates for people with a TBI (shown in blue) with medical controls, their significant others, or people from the general community (all shown in red), highlighting the increased risk of psychological problems after a TBI. Moreover, this relationship was seen when the TBI samples were drawn from both clinical (Studies 1 & 3) and community (Studies 2 & 4) settings — an important finding because it demonstrates the increased psychological burden experienced after a TBI.

Also important is the fact that rates were consistently higher in those with a TBI, regardless of where the people used in the comparison groups were sourced from. This shows that even when trying to control for other factors that may impact on depression and anxiety, such as pain and hospital/medical procedures (medical controls), increased stress/distress in the family unit (significant others) (Ponsford et al., 2011; Ponsford & Schönberger, 2010) — in addition to comparing rates with those seen in the general community — the risk of psychological problems is still higher after a TBI. Notably, 'significant others' who are close to the person with a TBI (family, friends, caregivers; see Figure 7.1b) also report high levels of

depression and anxiety. Thus, both the person with a TBI and their partner/family should be provided with ongoing support in order to optimise outcomes.

(a)



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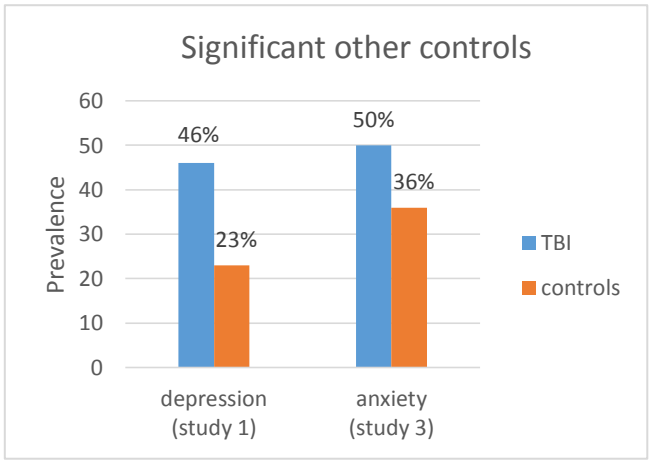

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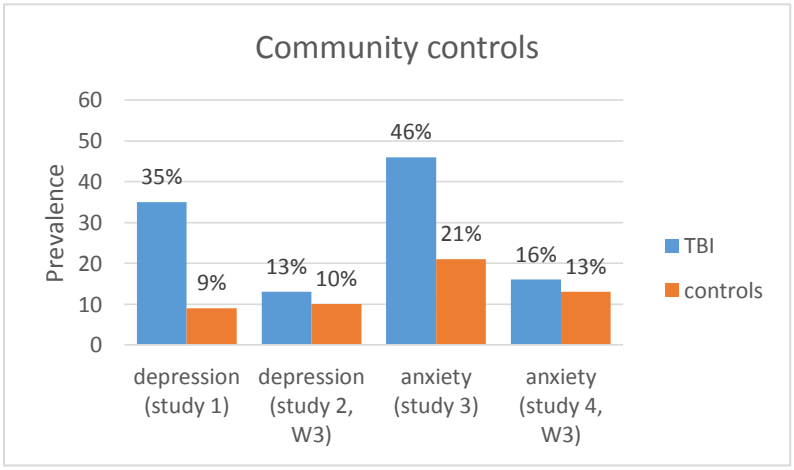


Figure 7.1. Prevalence of self-reported depression and anxiety in TBI and comparison groups (a) medical, (b) significant others (c) general community.

Note: TBI = traumatic brain injury, W3 = wave three; depression (Study 1) = depression meta-analysis; depression (Study 2) = PATH; anxiety (Study 3) = anxiety meta-analysis; anxiety (Study 4) = PATH anxiety

7.2.2 Clinical vs community samples

Importantly, the present thesis examined self-reported depression and anxiety both in clinical (Studies 1 & 3) and community-based (Studies 2 & 4) samples, with Figure 7.2 illustrating the prevalence of these problems, grouped by recruitment source. Unfortunately, it was not possible to compare rates of MDD/GAD, because the epidemiological nature of the PATH study precluded the use of more comprehensive depression and anxiety assessments (e.g., SCID-1, SCAN).

As can be seen from Figure 7.2, TBI samples sourced from clinical settings (meta-analyses) reported higher rates of depression (38%, shown in blue) and anxiety (37%, shown in red) than TBI samples sourced from the community (PATH, 13% and 16%, respectively). This may, in part, result from the fact that individuals in the healthcare system are still receiving support for their TBI-related sequelae, such as physical or cognitive problems, which may contribute to higher rates of depression and anxiety (Dworkin, 1992). Moreover, being community-based, the PATH studies capture the estimated 30-40% of mild TBIs that are not medically treated because the individual thinks their symptoms are insignificant, they found that the distance to medical care was prohibitive, or they did not have health insurance (Demakis & Rimland, 2010; Faul & Coronado, 2015; Roozenbeek et al., 2013). Similarly, epidemiological studies based on U.S. healthcare surveillance data exclude people who are treated by their local physician and in U.S. federal facilities, such as military/veteran's hospitals (Cassidy et al., 2004; Ruff et., 2009; Thurmond et al., 2010). For these reasons, the PATH community-based studies are likely to better reflect population rates for depression/anxiety following TBI.

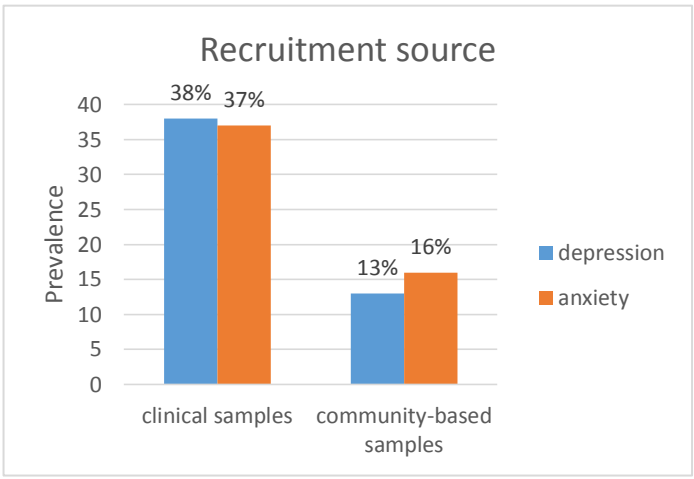


Figure 7.2. Prevalence of self-reported depression and anxiety, grouped by recruitment source.

Note: clinical samples = meta-analysis (Studies 1 & 3); community-based samples = Personality and Total Health Through Life study W3 (Studies 2 & 4).

It was not possible to examine comorbidity between anxiety and depression in clinical samples (Studies 1 & 3), however they were found to be highly comorbid in the community-based sample (PATH, Study 4), with approximately half of those experiencing problems with anxiety at each wave also being depressed (45%, 59%, 50% in Waves 1 to 3) following a TBI. Interestingly, *more* individuals with a TBI were suffering from clinically significant anxiety, than depression, at each assessment. Thus, given that anxiety and depression are both common after a TBI, and can occur either independently or concurrently, clinicians should ensure that they screen for both in order to better assess an individual's mental health.

7.2.3 Assessment instrument

The present thesis also highlighted the importance of considering how depression and anxiety are assessed (i.e., clinical diagnoses, self-report questionnaires) and what measure is used (e.g., SCID-I, HADS) when designing research or evaluating patients with TBI. Considerable differences in the prevalence of depression and anxiety were observed for the different diagnostic criteria, interview schedules, self-report measures, and methods of administration.

Formal diagnoses vs self-reported 'cases'

Whether depression and anxiety were formally diagnosed (MDD, GAD) or based on self-reported symptoms (clinically significant 'cases') affected prevalence rates, with Figure 7.3 illustrating these differences (Studies 1 & 3). Although comparable rates of depression and anxiety were found when symptoms were measured using self-report instruments (blue), clinically diagnosed rates of MDD and GAD were considerably lower (red). Moreover, the rates for depression (self-reported 38%, MDD 27%) were more closely aligned than those for anxiety (self-reported 37%, GAD 11%), with the larger differential in anxiety rates possibly a function of the diagnostic criteria for GAD, which require symptoms to be present for six months.

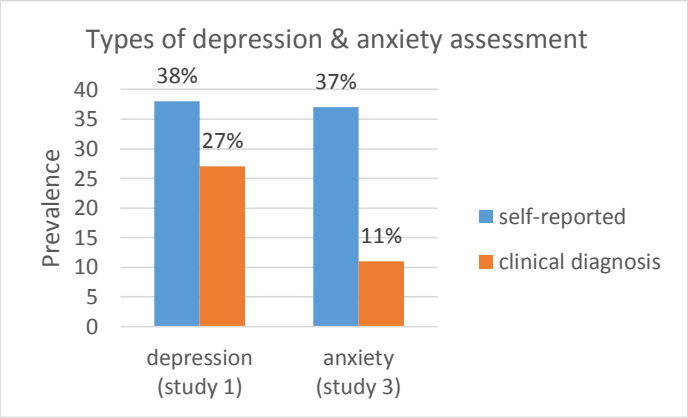


Figure 7.3. Overall prevalence of depression & anxiety partitioned according to self-reported symptoms and clinical diagnoses.

This disparity between self-reported and clinically diagnosed anxiety highlights the importance of using self-report measures in order to identify high levels of anxiety that may not meet strict diagnostic criteria, but are still potentially disabling. Importantly, research examining the general population has determined that subclinical GAD – where the number, or duration, of symptoms have failed to reach DSM or ICD thresholds – is common and often leads to comparable levels of distress and psychosocial impairment as GAD (Haller et al., 2014). Thus, the high rates of self-reported anxiety suggest that anxiety should be a clinical and research focus.

Diagnostic criteria

The use of different diagnostic criteria was found to impact on the prevalence of both MDD and GAD. This is illustrated in Figure 7.4 which shows the prevalence of MDD (Study 1) and GAD (Study 3), according to the diagnostic criteria used (i.e., DSM-III, DSM-IV, ICD-10). It can be seen that, although rates vary between the set that was used, a similar pattern occurs for both disorders: the highest rates came from studies that used DSM-III criteria, followed by DSM-IV and then ICD-10. These findings highlight the variability that can arise both from the use of different sets of diagnostic criteria (i.e., DSM, ICD) and also *different versions* of the same set (i.e., DSM-III, DSM-IV).

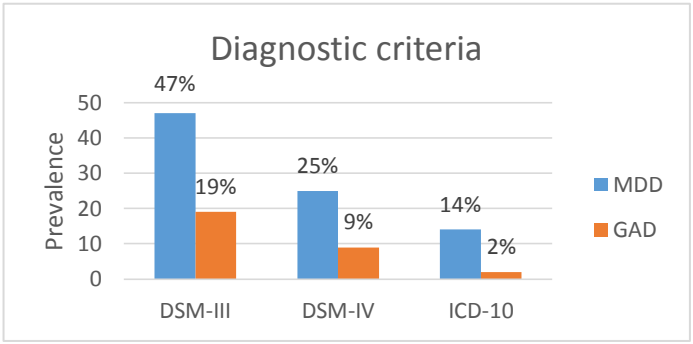


Figure 7.4. Prevalence of MDD and GAD according to the diagnostic criteria used.

Note: MDD = Major Depressive Disorder, GAD = Generalised Anxiety Disorder, DSM = Diagnostic and Statistical Manual, ICD = International Classification of Diseases.

These findings are consistent with other research that has shown that DSM-IV and ICD-10 criteria can lead to discrepant GAD diagnoses in the general population, largely due to differences in the endorsement of autonomic symptoms (e.g., trembling) and the presence of co-morbid disorders that, using the ICD-10, preclude a diagnosis of GAD (e.g., panic disorder) (Slade & Andrews, 2001). Further, later revisions of the DSM included stricter criteria, possibly explaining why there are fewer MDD and GAD diagnoses using the DSM-IV, compared to DSM-III. Specifically, for both MDD and GAD, the symptoms must lead to significant distress and impairment and — for GAD only — symptoms must be present for a minimum of six months (APA, 2001). These findings highlight the problem with comparing rates of MDD and GAD over time and/or rates obtained using different diagnostic criteria.

Interview schedule

Although clinical interviews are often considered to be the 'gold standard' for psychiatric evaluation (Starkstein & Lischinsky, 2002), the prevalence rates of MDD and GAD differed substantially depending on which interview schedule was used. Figure 7.5 shows the rates of MDD (Study 1, shown in blue) and GAD (Study 3, shown in red) grouped according to the clinical interview that was used to make the diagnosis, thereby highlighting the fact that the choice of interview can impact on prevalence.

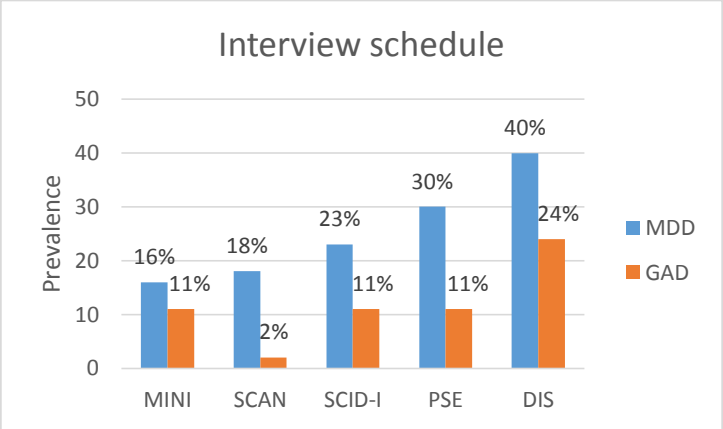


Figure 7.5. Prevalence of MDD and GAD according to the interview schedule used.

Note: MDD = Major Depressive Disorder, GAD = Generalised Anxiety Disorder, MINI = Mini International Neuropsychiatric Interview, SCAN = Schedules for Clinical Assessment in Neuropsychiatry, SCID–I = Structured Clinical Interview – Axis I Disorders, PSE = Present State Examination, DIS = Diagnostic Interview Schedule.

These measures range from complex interviews, which require clinical judgement and specialised training (e.g., SCAN), through to structured interviews that are designed for use by non-clinicians when conducting epidemiological research (e.g., DIS); potentially contributing to differences in the diagnosed rates. Moreover, they are also calibrated to different diagnostic criteria, with Table 7.1 highlighting the complexity of available interview options, depending on the interviewer's preferred format and/or level of expertise.

Table 7.1

Comparison of interview schedules according to (a) diagnostic criteria, (b) format, and (c) interviewer qualification requirements

Interview	Diagnostic criteria	Format	Administered by
SCID-I	DSM-III, DSM-IV	Semi-structured	Trained mental health professionals
SCAN	DSM-IV, ICD-10	Semi-structured	Trained mental health professionals
PSE-10	DSM-III & ICD-10	Semi-structured	Trained mental health professionals
MINI	DSM-IV & ICD-10	Semi-structured	Limited training
DIS	DSM-III, DSM-IV	Fully-structured	Non-clinical interviewers

Note: SCID-I = Structured Clinical Interview – Axis 1 disorders; SCAN = Schedules for Clinical Assessment Neuropsychiatry; PSE-10 = Present State Examination; MINI = Mini International Neuropsychiatric Interview; DIS = Diagnostic Interview Schedule; DSM = Diagnostic and Statistical Manual; ICD = International Classification of Diseases.

Interestingly, MDD and GAD were both diagnosed more often when using the PSE than the SCAN (see Figure 7.5); despite the PSE being a core component of the SCAN (Starkstein & Lischinsky, 2002). It is not clear whether the additional information obtained during a SCAN interview resulted in differential diagnoses or whether this disparity arose from other methodological or sample differences (e.g., the length of time since the injury).

The inter-rater agreement between lay interviewers (e.g., DIS) and clinicians (e.g., SCAN) has also been shown to be poor, possibly because clinicians have greater expertise, which enables them to use a more flexible interview format in order to explore symptomology (Eaton, Neufeld, Chen & Cai, 2000). Similarly, DIS and SCAN rates for both MDD and GAD (Studies 1 & 3) were also found to be disparate and, although the reason for this is unclear, the difference in rates may be due to varying symptom time-frames. For example, the SCAN usually examines symptoms experienced over the previous month, whereas the DIS can assess the previous week, month, 6 months or year. Moreover, many studies do not report which period is being assessed, making it difficult to directly compare findings. Not only are symptoms likely to vary across these timeframes (1 – 12 months) but, if memory has been impaired by a TBI, symptom recall may be more problematic over longer timeframes (Hilsabeck et al., 1998).

Self-report questionnaires

The two meta-analyses (Studies 1 & 3) revealed that the prevalence of depression and anxiety also varied according to the self-report scale that was used and how it was administered. The HADS was the most commonly used measure and identified 32% and 36% of people as having clinically significant depression and anxiety, respectively, after a TBI. In contrast, the PATH studies measured depression and anxiety with the GDS and GAS and, overall, 'cases' of depression and anxiety were surprisingly consistent over the three assessments spanning eight years (depression: 13%, 15%, 13% and anxiety: 20%, 18%, 16%) for those with a TBI. Notably, both the HADS (Studies 1 & 3) and the GDS/GAS (Studies 2 & 4) revealed that anxiety was more common than depression in those with a TBI.

Nevertheless, it is difficult to directly compare rates between the meta-analyses and PATH studies due to differences in where they were recruited (i.e., clinical versus community settings) and in the specific symptoms that are measured by the questionnaires that were used. To this end, Table 7.2 compares HADS and GDS/GAS items broadly grouped by the diagnostic criteria for MDD and GAD. This highlights the fact that when depression is assessed using the HADS, it mostly reflects a person's mood and reduced interest, whereas the majority of items in the GDS are somatic. Although the anxiety scales are more closely aligned, in that both the HADS/GAS comprise only somatic and anxiety/worry symptoms, the GAS again includes more somatic items. This may be problematic because TBI also results in somatic symptoms and, unfortunately, it is not known whether the high proportion of somatic items in the GDS and GAS served to increase prevalence rates in Studies 2 and 4. Some self-report questionnaires have also been modified over time, limiting direct comparisons between different versions of the *same* scale. For example, the original BDI contained questions about attractiveness and worry about physical problems, but these were excluded from the BDI-II. Moreover, the BDI-II also assesses symptoms over a longer time-frame (increased from the previous week to fortnight), which may have increased rates.

Table 7.2

Comparison of items used by questionnaires to assess depression (HADS, GDS) and anxiety (HADS, GAS).

Questionnaire items	Depression		Anxiety	
	HADS	GDS	HADS	GAS
MOOD/AFFECT				
I can laugh and see the funny side of things	✓			
I feel cheerful	✓			
LEVEL OF INTEREST / PLEASURE				
I still enjoy the things I used to enjoy	✓			
I have lost interest in my appearance	✓			
I look forward with enjoyment to things	✓			
I can enjoy a good book or radio or TV programme	✓			
Have you lost interest in things		✓		
SOMATIC				
I feel as if I am slowed down	✓			
Have you been lacking in energy		✓		
Have you lost weight (due to poor appetite)?		✓		
Have you been waking early?		✓		
Have you felt slowed up?		✓		
Have you tended to feel worse in the mornings?		✓		
I feel tense or 'wound up' / Have you felt keyed up or on edge?			✓	✓
I can sit at ease and feel relaxed / Have you had difficulty relaxing?			✓	✓
I feel restless as if I have to be on the move			✓	
Have you been irritable?				✓
Have you been sleeping poorly?				✓
Have you had headaches or neckaches?				✓
Have you had any of the following: trembling, tingling, dizzy spells, sweating, diarrhoea or needing to pass water more often?				✓
Have you had difficulty falling asleep?				✓
WORTHLESSNESS / GUILT				
Have you lost confidence in yourself		✓		
Have you felt hopeless		✓		
COGNITIVE				
Have you had difficulty concentrating		✓		
ANXIETY / WORRY				
I get sort of a frightened feeling as if something awful is about to happen			✓	
Worrying thoughts go through my head / Have you been worrying a lot?			✓	✓
I get sort of a frightened feeling like "butterflies" in the stomach			✓	
I get sudden feelings of panic			✓	
Have you been worried about your health?				✓

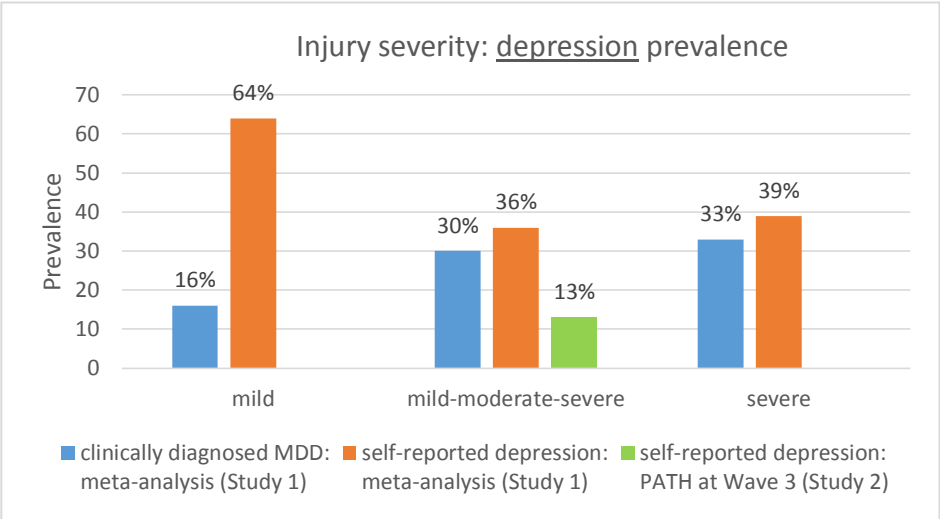
Note: HADS: Hospital Anxiety and Depression Scale; GDS: Goldberg Depression Scale; GAS: Goldberg Anxiety Scale. The above groupings are intended to be broadly representative of the diagnostic criteria for major depressive disorder and generalized anxiety disorder.

Lastly, the method of administering self-report questionnaires also affected prevalence rates, with each method (e.g., face to face, postal, phone) potentially influencing the way that a person responded (Richman, et al., 1999). For example, there may be interference from others, or other unknown influences, when surveys are mailed to people's homes for completion. Nevertheless, there was no consistent pattern discernible across the studies. Interestingly, some studies used a combination of approaches (e.g., face to face *and* phone), which may have affected findings *within* their study. Importantly, the PATH project (Studies 2 & 4) used computer-assisted self-interviewing (CASI) in order to overcome a variety of potential problems. For example, CASI ensured that items were administered in a standardised way and, moreover, minimised socially-desirable responding by providing participants with greater anonymity when they were completing items (Bowling, 2005; Fairweather-Schmidt & Anstey, 2012; Schuman & Presser, 1981).

7.2.4 Injury severity

Depression and anxiety outcomes were also affected by the severity of the TBI, although the relationship appears complicated. Figure 7.6 displays the prevalence rates for mild, mild-moderate-severe and severe TBIs, grouped according to how depression (Figure 7.6a) and anxiety (Figure 7.6b) were assessed (formal diagnosis or self-reports). This revealed a number of interesting relationships. Unfortunately, however, the data derived from the meta-analyses (Studies 1 & 3) and PATH (Studies 2 & 4) differed, which limited comparisons. Specifically, the PATH studies examined a mixed sample of mild, moderate and severe injuries because it was not possible to ascertain reliable estimates of severity. The meta-analyses also examined mixed samples but, additionally, looked at mild and severe injuries.

(a)



(b)

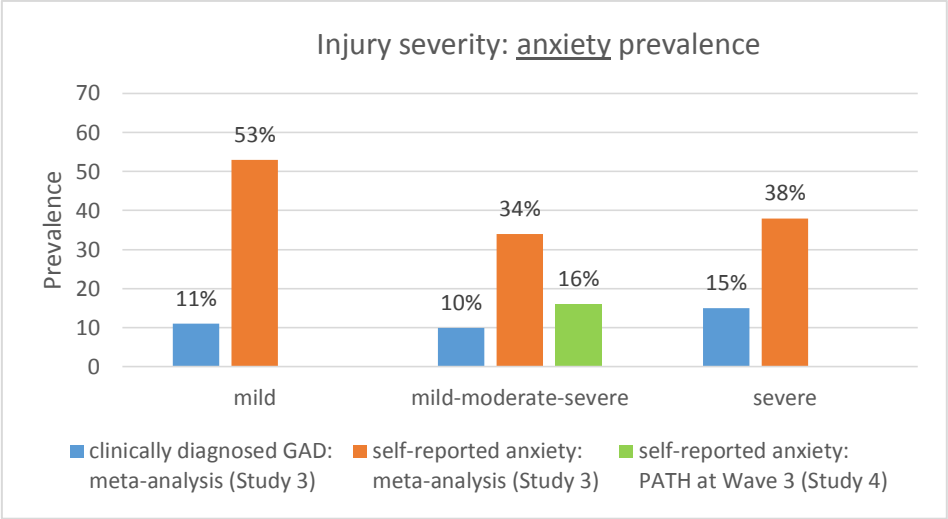


Figure 7.6. Prevalence of depression and anxiety grouped according to injury severity: (a) major depressive disorder (meta-analysis) and self-reported depression (meta-analysis and PATH), and (b) clinically diagnosed generalized anxiety disorder (meta-analysis) and self-reported anxiety (meta-analysis and PATH).

The findings for injury severity display an interesting pattern, depending on whether depression/anxiety was clinically diagnosed or the symptoms ascertained by self-report. After mild TBI, the prevalence of depression was considerably higher when symptoms were self-reported (red), compared to clinical diagnoses (blue), with this pattern replicated for anxiety. This pattern was also similar for severe TBIs, although the rates for MDD/GAD and self-reported symptoms were more closely aligned, particularly for depression.

Figure 7.6 also illustrates that, when using self-report measures, more individuals with a *mild* TBI reported problems with depression (64%) and anxiety (53%) than did people with a *severe* TBI (depression: 39%, anxiety: 38%). This paradoxical relationship has been observed elsewhere (Dikmen et al., 2004; Findler et al., 2001; Kurtz et al., 2007), with individuals often accused of exaggerating symptoms during litigation in order to maximise their financial compensation (Berry et al., 2012; Bianchini et al., 2006). However, there are a number of other potential explanations for the higher rates found in those with a mild TBI, including the stress arising from the legal proceedings (Hoffman, Scott, Emick, & Adams, 1999; Katz, Cohen, & Alexander, 2015), a lack of psychoeducational support which results in increased distress, or an absence of significant physical injuries which has encouraged them to focus on other problems (Malec et al., 2007b). In contrast, *lower* rates may be reported by those with a *severe* TBI due to cognitive difficulties, such as impaired memory and decreased self-awareness (Evans et al., 2005; Youngjohn et al., 1997).

Moreover, the way that injury severity has been categorised has evolved over time, adding to the problem of comparing findings across studies. For example, early TBI studies categorised TBIs with PTA lasting between 1 hour and 1 day as *moderate* (Russell & Smith, 1961; Jennett, 1976), whereas more recent studies use between 1 and 7 days (Forde, Karri, Young & Ogilvy, 2014; Voss et al., 2015). Unfortunately, it is not clear whether differences in how these injuries are categorised has impacted on the findings.

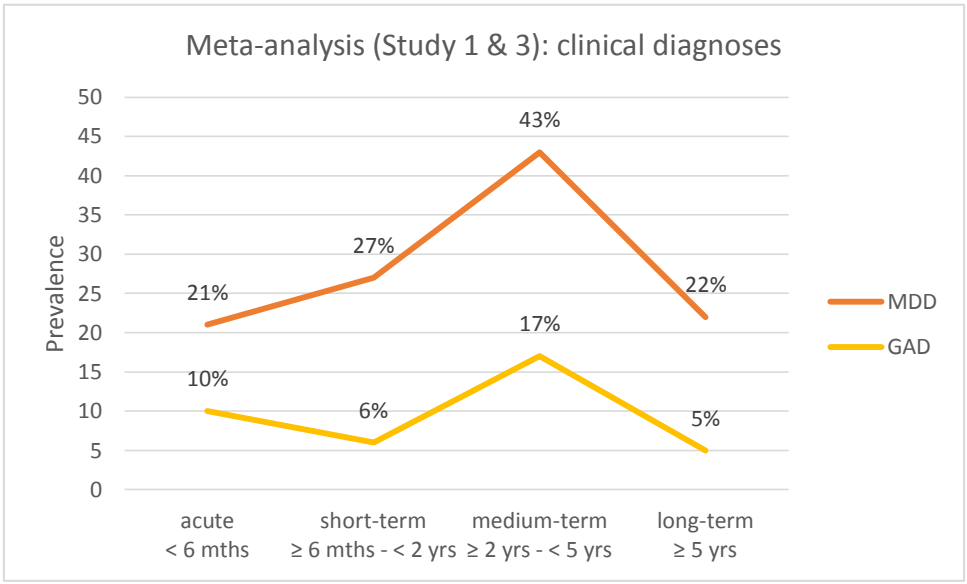
7.2.5 Time since injury

The time that has elapsed since the injury was sustained also impacted on the prevalence of depression and anxiety, with the impact of post-injury interval both on clinically diagnosed and self-reported depression and anxiety shown in Figure 7.7. Regrettably, it was not possible to directly compare the meta-analysis and PATH data because they used different time post-injury intervals.

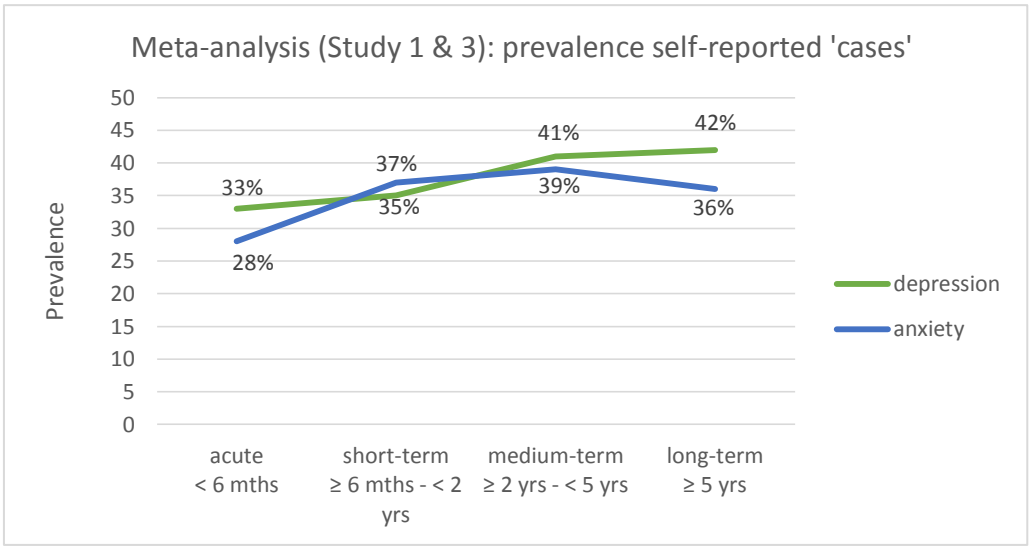
As can be seen, all four studies found high rates of depression and anxiety (formal diagnoses and self-reported) for many years after an injury. Moreover, regardless of how depression and anxiety were assessed, the trajectory of these problems was similar. Specifically, the prevalence of both MDD and GAD (Figure 7.7a) peaked two to five years after a TBI, then declined. However, even in the long-term, rates remained above those seen in the general population (MDD: 7%; GAD: 3%) (APA, 2013). Similarly, self-reported rates of depression and anxiety in people sourced from clinical settings increased steadily until the medium-term, although rates tended to plateau in the longer-term, rather than decrease, highlighting the potentially chronic nature of post-TBI psychological sequelae (Figure 7.7b). These results were supported by the self-report data from the PATH community-based studies, which showed that, following a TBI, rates were slightly lower in the long-term (> 4 years) compared with the short/medium-term (0 – 4 years). Nevertheless, rates remained high (and above others in their community without a TBI), regardless of the length of time that had elapsed since the injury; highlighting the lifelong risk of depression/anxiety after a TBI.

The high rates of depression and anxiety seen in the short-term (0 to 6 months) may reflect a variety of neuroanatomical (i.e., neuronal damage and cell loss) or neuropathological changes (e.g., cholinergic and serotonergic deficits) that provide the neurological substrate for depresson and anxiety (Jorge, 1993; Jorge & Starkstein, 2005; Sherin & Nemoroff, 2011). In contrast, depression and anxiety experienced in the long-term (Al-Adawi et al., 2007; Rao et al., 2010) may be more indicative of the psychosocial challenges faced by individuals as they adjust to their altered life circumstances (e.g., lack of social support, reduced social functioning) (Jorge et al., 1993a).

(a)



(b)



(c)

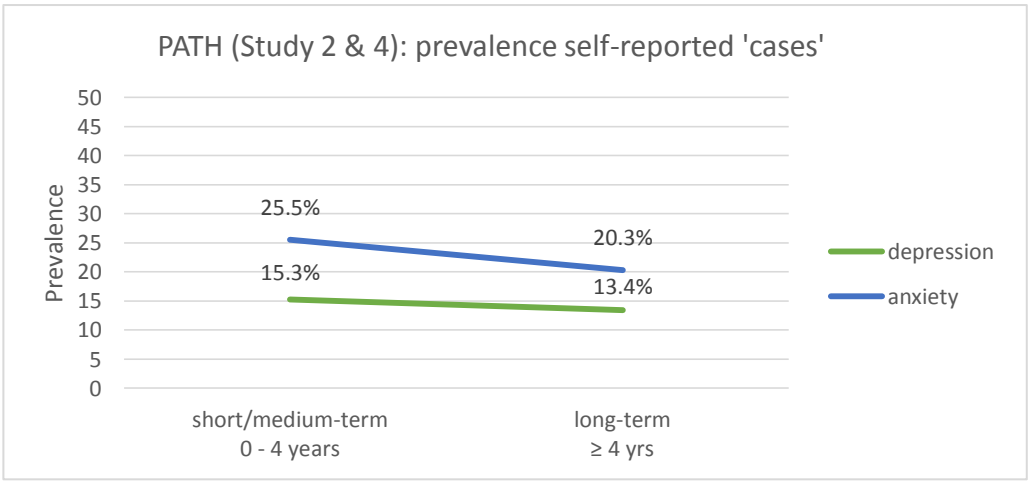


Figure 7.7. Prevalence of depression and anxiety following TBI according to the length of time that has elapsed since the TBI (a) clinical diagnoses (b) self-reported prevalence: meta-analyses (c) self-reported prevalence: PATH.

Note: MDD = major depressive disorder, GAD = generalised anxiety disorder.

7.3 Thesis limitations

The limitations associated with each of the individual studies were outlined in the relevant chapters (3, 4, 5 and 6). The following discussion therefore focuses on limitations of the overall thesis methodology and highlights potential areas for improvement.

With the benefit of hindsight, it would have been worthwhile to examine additional information in the meta-analyses. Specifically, research has used varying definitions of TBI, thus, an examination of their impact on psychological outcome may have been valuable. Although broadly similar, these definitions have often been developed for different purposes and although some are relevant to all TBI aetiologies (e.g., falls, motor vehicle accidents, etc), others are specific to sports-related concussions (McCrory et al., 2009) or military/combat settings (McCrea et al., 2008). Thus, the specific diagnostic criteria for TBI have differed between studies. TBI definitions have also been modified over time. For example, early definitions from the World Health Organization and Centers for Disease Control and Prevention permitted a diagnosis of TBI when only a skull fracture had been sustained (Thurman, Kraus, & Romer, 1995; Thurman, Sniezek, Johnson, Greenspan, & Smith, 1995). Although revised definitions have omitted this 'bone only' criterion, the validity of comparisons between studies that use earlier, versus later, versions of each is not known. Also problematic is the fact that many terms within TBI definitions are not operationally defined, with clinical signs — such as 'dazed' and 'disoriented' — being open to interpretation (Ruff, et al., 2009). The significance of these differing and often imprecise TBI definitions, and their potential impact on depression and anxiety outcomes, only became apparent after the meta-analyses were completed. Even so, many studies did not report this information or, if they did, the definitions did not align, which would have limited the possibility of such an examination had it been considered earlier.

Furthermore, studies often categorised mild, moderate and severe TBIs using different thresholds for the severity indices. For example, studies of mild TBI used varying GCS scores (13-15, 14-15, 15 only), duration of PTA (< 1 to 24 hours) and length of LOC (ranging from none to < 30 minutes) (Carroll et al., 2004), which made it difficult to align studies. Thus, when undertaking the meta-analyses, the description labels used by studies (i.e., mild, moderate, severe) were accepted. Nonetheless, given that each of these measures constitute continuous data that are being treated as categorical variables, the thresholds used to classify TBIs as mild, moderate or severe, are somewhat arbitrary (Fleminger, 2009).

It also may have been useful to examine depression and anxiety outcomes from generic quality of life/psychological distress measures in order to determine whether the use of these scales impacted on prevalence rates. However, these measures were deliberately excluded in order to maintain the quality and focus of the results, as many of these scales report emotional distress as a composite construct of both depression and anxiety (e.g., the Short Form 36 Health Survey and EQ-5D). Nevertheless, data from their depression and anxiety subscales could have been extracted and reported in sub-group analyses. Similarly, the Goldberg Depression Scale and Goldberg Anxiety Scale were not incorporated in the meta-analyses because neither scale is commonly used in TBI research. However, had the data been available, it would have enabled a direct comparison between meta-analysis and PATH results.

7.4 Future research

The present thesis has highlighted a number of areas that warrant additional research. Of fundamental importance is the continued effort to standardise the definition of TBI so that it can be uniformly applied across all health disciplines (e.g., neurology, neurosurgery, psychiatry, physical medicine and rehabilitation, and neuropsychology) and settings (e.g., hospitals, general population) in order to improve both clinical decision-making and future

research (Ruff et al., 2009). Similarly, the identification and use of standardised guidelines to rate injury severity would greatly facilitate the comparison of findings across research studies (Cappa et al., 2011; Sherer et al., 2008).

There are inherent difficulties associated with using TBI samples based only on medically confirmed cases of TBI, as not all TBIs receive medical treatment. Similarly, when using self-reported TBIs, problems also arise, such as the increased risk of recall bias as time post-injury increases. For these reasons, it is important to develop measures that can reliably determine a person's history of TBI retrospectively. For example, the Ohio State University TBI Identification Method provides a standardised, short, structured interview that comprehensively elicits information relating to lifetime history of TBI (Corrigan & Bogner, 2007). This should be adopted by researchers to improve the identification of self-reported TBIs and by clinicians when assessing patients for their TBI history.

Research on the risk factors for TBI is also required in order to ascertain who is most at risk of incurring a TBI and to identify modifiable risk factors (e.g., driving behaviour) that can be targeted in prevention programs. Additional large-scale population-based studies that are able to undertake an examination of a broad range of these potentially relevant risk factors are also needed in order to determine whether they have an impact on depression and anxiety after a TBI. Importantly, the high rates of multiple TBIs in the PATH studies show that having a TBI is associated with an increased risk for subsequent TBIs, indicating that educational awareness programs should be available in order to assist people manage their risk of another TBI. Furthermore, ongoing research efforts should focus on the long-term consequences of sustaining a TBI, particularly in terms of chronic, neurodegenerative outcomes, as the PATH studies demonstrated that the increased risk of psychological problems is evident for many years after a TBI.

Given that the PATH studies also revealed that the relationship between TBIs and depression and anxiety varies over the adult lifespan, continued efforts should be made to

identify specific risk factors affecting each life stage. For example, the incidence of mild TBIs, mainly due to falls, among the elderly is rising (Roozenbeek et al., 2013). Thus, research on the impact of mild TBIs on the elderly should be a priority (Carroll et al., 2004). Similarly, many of the TBIs reported in the PATH studies were incurred at a young age and were associated with an increased long-term psychological burden, indicating that research should also focus on strategies to prevent childhood TBI.

7.5 Conclusions

In conclusion, this thesis found that although depression and anxiety are common following a TBI, estimates of the prevalence of each varied widely, limiting the clinical utility of research. A range of differing methodological approaches (i.e., recruitment source, clinical diagnoses/self-reported symptoms, diagnostic criteria, interview schedule/self-report scale and the administration method for self-report scales) and sample characteristics (the length of time that had elapsed since the TBI, injury severity) were therefore assessed to determine their impact on depression and anxiety after a TBI. Importantly, each affected the prevalence of depression and anxiety to some extent, highlighting the fact that researchers should be cognisant of how these variables may impact on their study outcomes.

Regardless of the data source (clinical versus population), depression and anxiety continued to be problematic for many years after an injury. Moreover, this increased long-term risk was evident despite taking a comprehensive range of demographic, health and lifestyle variables that are known to impact on depression and anxiety into account. Thus, ongoing monitoring and support should be provided following a TBI in order to optimise an individual's long-term psychological health. Finally, comorbid anxiety and depression was also common, reinforcing the need for clinicians to identify and treat both problems in order to reduce the cumulative burden imposed by dual conditions.

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