Gender Differences in Depression and Anxiety Symptoms Eight Years After Mild Traumatic Brain Injury

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Abstract

The majority of all treated cases of traumatic brain injury are classified as being in the mild severity range (MTBI) but many symptoms are far from mild and can result in difficulties that persist for years after the initial injury, severely affecting quality of life. Chronic depression and anxiety symptoms can be masked by acute post-concussion symptoms and can affect males and females differently in the long-term but little research has been undertaken in this area. The aims of this study were to investigate the gender differences in depression and anxiety over 1-month, 12-months and 8-years following a mild traumatic brain injury and to investigate gender differences in depression and anxiety between a group of MTBI subjects (8-years post-injury), and a group of participants who were TBI-free, by comparing Hospital Anxiety and Depression Scale (HADS) scores and self-reported symptoms. A MTBI cohort consisting of a population-based sample of 151 adults who sustained a mild TBI between 2010 and 2011 was identified from an earlier longitudinal study: Brain Injury Incidence and Outcomes New Zealand In the Community Study (BIONIC). Additionally, 213 participants with no history of head injury were recruited for comparison. Both groups answered questions about current anxiety and depression symptoms using the HADS.

Overall, results suggest that males and females with MTBI have the same overall course of recovery in relation to depression and anxiety symptoms over the 8-years following injury but that females consistently report significantly increased symptoms than males over time, as reflected in the general population. Depression and anxiety scores fluctuate over the 8-years post-MTBI but, overall, depression increases, anxiety decreases and symptom levels are below clinical severity. Females with MTBI are significantly more likely than males to experience anxiety in the clinical range at 12-months post-injury.

There were no significant gender differences in depression or anxiety levels between the MTBI and comparison groups, and average HADS scores were not significantly different between groups. However, individual symptom analysis showed that females who were 8-years post-MTBI experienced increased panic symptoms than females with no TBI and that both males and females with MTBI reported increased anhedonia and "restlessness' symptoms than those without MTBI. Overall, females reported significantly higher severity symptoms related to nervousness and feeling slowed down than males.

The clinical implications of this study suggest a focus on the longer-term impacts of MTBI as patients may experience later onset depression or anxiety that may not be present in the acute phase. Evaluating individual symptoms as well as overall scores on measures can identify important clinical effects at symptom level that are masked by total score analysis.

Practitioners should consider gender differences in how patients respond to self-report symptom measures to ensure accurate clinical assessment of both males and females, particularly in relation to MTBI which has a higher male prevalence. Future research into MTBI outcomes that includes a broader range of measures, in addition to self-report, will ensure comprehensive clinical data is obtained about individual symptoms and risk factors.

This study uniquely contributes to current research into gender outcomes post-MTBI and may guide clinical practice to develop effective, timely and targeted assessment and treatment interventions for depression and anxiety symptoms experienced by both males and females after mild traumatic brain injury.

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Introduction

Traumatic Brain Injury (TBI) is a leading cause of injury-related death and disability worldwide and is projected to become the third largest cause of disease burden by 2020 due to its lasting effects and high cost of treatment and rehabilitation (Cassidy et al., 2004). Road traffic accidents, falls, personal assault and exposure to mechanical forces often lead to head injury causing trauma to the prefrontal and anterior temporal structures of the brain which can produce a spectrum of damage ranging from focal lesions to extensive axonal injury resulting in contusions and extracerebral haemorrhages. This damage and cell loss, which may go undetected in mild trauma, may lead to long-term difficulties with physical, cognitive, behavioural, emotional and psychosocial functioning (Jorge et al., 2004). This can make activities of daily living and community reintegration problematic for TBI patients and their caregivers and can significantly affect their quality of life in the longer-term (Fann, 1997).

The social and economic impact of TBI can be significant with increased unemployment rates, work limitations and long-term productivity losses (Theadom et al., 2018). TBI incurs significant economic burden and in New Zealand in 2010 the lifetime cost of all TBI survivors was estimated to be US$146.5 million, and expected to rise to US$177 million in 2020 (Te Ao et. al., 2014). With the substantial effects on public health and significant economic burden, exploring outcomes of TBI in the population is an important part of finding and delivering the most effective prevention and intervention strategies post-injury. Longitudinal studies are useful in tracking outcomes over time and the current study was based upon an eight year follow up of novel findings from the original participants from the Brain Injury Incidence and Outcomes New Zealand in the Community (BIONIC) study, a large population-based study carried out between 2010-11 that examined the incidence and outcomes (up to 12-months) of TBI across all age groups (Feigin et. al., 2013).

Definition of TBI and Injury Severity

The World Health Organisation (WHO) defines TBI as "an acute brain injury resulting from mechanical injury to the head from external physical forces" (Carroll, Cassidy, Holm, Kraus & Coronado, 2004, p. 115). This may include one or more of the following effects: confusion or disorientation; loss of consciousness; post-traumatic amnesia; other neurological abnormalities, such as focal neurological signs, seizure and/or intracranial lesion (and not due to drugs, alcohol or medications, other injuries or treatment for other injuries (e.g. systemic injuries, facial injuries or intubation), or other problems (for example, psychological trauma, language barrier, co-existing medical conditions). TBI severity was classified in the current study using the widely-used Glasgow Coma Scale (GCS, Teasdale & Jennett, 1974) and based on suggested criteria for population-based studies of incidence in TBI by Barker-Collo & Feigin, (2008). The GCS classifies TBI into one of three categories: mild, moderate or severe. This measures motor responses, eye opening and verbal performance following injury to assess the depth and duration of impaired consciousness and coma. Mild TBI is defined as a GCS of 13-15 or post traumatic amnesia (PTA) within 24 hours of injury; moderate TBI is defined as GCS 9-12 or PTA within 1-6 days of injury; and severe TBI is defined as GCS 8 or lower or a PTA of 7 or more days from injury.

Epidemiology

The global epidemiology of Traumatic Brain Injury (TBI) is not well documented in the current literature due to the challenges of nonstandardised and heterogenous reporting among epidemiological studies both nationally and internationally. A meta-analysis, conducted of pooled studies in North America in 2016, reported an incidence of 331 per 100,000 people and in Europe 228 per 100,000 but these figures were obtained from TBI diagnosed via hospital records and did not capture incidences of mild TBI that did not present

to hospital. The BIONIC study incidence rate for TBI in New Zealand was found to be 790 per 100 000 people per year (95% CI 749-832), (Feigin, et al., 2013). This is high compared to a range of between 47 cases and 618 cases per 100,000 person-years within other high-income countries in Europe and North America (Andelic, 2013). Andelic posits that the incidence of TBI in New Zealand, and particularly mild TBI, exceeds those estimated by previous studies undertaken due to variations in the diagnostic criteria and methods used between the different studies. Feigin et al., (2013) utilised the case ascertainment method at a population level and included individuals with mild TBI who were not admitted to hospital (people who are often overlooked in hospital-based TBI studies, Setnik & Bazarian, 2007), and this may be more representative of actual prevalence of TBI in New Zealand. In fact, according to Feigin et al., (2013), 749 cases per 100,000 person-years are classified as MTBI (95% CI 709-790 for MTBI and 95% CI 31-51 for moderate to severe TBI). For this study, the majority of cases were MTBI and my research specifically focuses on outcomes in adults after MTBI.

Mechanism of Injury

In New Zealand, 38% of TBI cases were due to falls (516 of 1369), 21% were due to mechanical forces (288 of 1369) and 20% were due to transport accidents (277 of 1369). Falls caused 82% of TBI in adults older than 65 years and exposure to mechanical forces was to blame for 48% of TBI in adolescents and young adults (Feigin et al., 2013).

Mild Traumatic Brain Injury (MTBI)

The majority of all treated cases of TBI (95%) are classified as being in the mild severity range (Feigin et al., 2013). The risk of sustaining a MTBI is more than 18 times greater than the risk of sustaining a moderate to severe TBI and nearly a third of people will experience a MTBI by the time they are 25 years of age (Feigin et al., 2013). By virtue of

their mild presentation, the deleterious effects of MTBI's are often undetected and are therefore left untreated rendering the full burden of MTBI unknown. Wood, 2004 described the undetected effects of MTBI as a "silent epidemic" (p.1149) as MTBI is one of the most common neurological conditions experienced by people overall. MTBI, which includes 'concussion' and defined as a GCS score of 13-15 and PTA within 24 hours of injury, has been recognised by the World Health Organisation (WHO) as a public-health concern (Cassidy et al., 2004) as it can lead to substantial disruptions in education and working life (Khan, Baguley & Cameron, 2003). Although injury severity is the most reliable predictor of outcomes after moderate and severe TBI, the impact of mild TBI is not so clear cut and there is evidence that socio-demographic and contextual factors, as well as the nature of the MTBI injury, may also determine longer term outcomes (Theadom et al., 2018), even though it was previously thought that people made a good recovery from MTBI within the first few months post-injury (Ruff, 2005). A significant proportion of those sustaining a MTBI continue to report problems far beyond the typical 1-3 month recovery period (Mcmahon, et al., 2014) and there is now accruing evidence that nearly half of those affected by even mild traumatic brain injury (MTBI) go on to experience on-going difficulties such as cognitive and emotional impairments that can significantly disturb daily functioning in the long-term (Theadom et al., 2016).

Mild TBI affects boys and men at a greater rate than women and girls (RR 1.73, 95% CI 1.54-1.93, Feigin et al., 2013) and this may be due to lifestyle differences such as levels of risk-taking activities, exposure to work-related hazards and violent assault-related injuries. In terms of gender differences of MTBI, despite males being more likely to sustain a MTBI, female gender was associated with poorer outcomes at 12-months post-injury (Theadom et al., 2016).

Regarding the physiological effects of MTBI, Busch and Alpern, 1998, suggested that the mechanism of injury is inertial forces as opposed to impact, which stretch and fracture axons, disrupt cell bodies, tear blood vessels and interrupt blood flow (diffuse axonal injury or DAI) which can be extensive, even in MTBI. Whilst most MTBI patients do not have access to or opportunity for brain imaging measures to identify DAI, neuro-radiological and neuro-pathological investigations have found diffuse brain damage in the frontal and temporal lobe, corpus callosum and fornices in those with MTBI which are linked with information processing deficits. DAI has also been associated with deficits in executive functioning due to the profusion of white matter (Barker-Collo, 2015). Advances in neuroimaging during the past 15 years have required researchers, clinicians, and policy makers to revise their views about MTBI as a fully reversible injury that can be repeated without consequences as more recent studies suggest that the life-long effects of MTBI, especially when repetitive, may be more severe than initially believed. This is due to a marked increase in the diagnoses of chronic traumatic encephalopathy (CTE) amongst recently deceased athletes (McKee et al., 2013) and in neuroimaging studies of MTBI which have found that neuronal pathology may be present long after post-concussion assessment outcomes have returned to pre-morbid levels of functioning (Bigler, 2013). As a result of this new research, it has been suggested that a single concussion can result in lifetime impairment for some individuals.

MTBI is estimated to cost 40% of the total annual cost of TBI in the USA ($60 billion U.S. Dollars) (Finkelstein, Corso & Miller, 2006). As well as the financial cost of treatment, many people experience a reduced quality of life due to the effects of MTBI. Although, for many people, functional recovery usually improves over 3 months, patients with MTBI frequently take one month or longer to return to work, and unemployment at 3 months could be as high as a third of patients (Bloom et al., 2018). When returning to work, patients with

MTBI have reported that they expend greater effort and become more fatigued relative to pre-injury suggesting persistent post-injury effects of MTBI.

The burden of MTBI is not just experienced by the patient and the challenge for families of those who have sustained a MTBI is recognising, acknowledging and understanding the persistence of their loved-ones often 'invisible' symptoms (Saban, Hogan, Hogan, & Pape, 2015).

Symptoms and outcomes of MTBI.

The range of post-MTBI complaints, collectively known as post-concussive symptoms (PCS), can include physical symptoms, such as headache, visual disturbances, sensitivity to noise, dizziness and fatigue, affective disturbances, such as emotional lability, irritability, anxiety and depression, and cognitive problems, such as difficulty concentrating, mental slowness, difficulty in dividing attention, and memory deficits (Ponsford et al., 2012; Emanuelson et al., 2003; Theadom et al., 2016).

Of the persistent complaints reported, cognitive difficulties are most common and the most substantial contributors to long-term disability after MTBI (Clarke, Genat & Anderson, 2012). Emotional processing following MTBI has not been as widely examined as cognitive difficulties but depressive and anxiety symptoms with similar characteristics might be observed as part of the PCS in both the short and long-term and, indeed, cognitive complaints may reflect underlying depression and anxiety and not just cognitive impairment, (Stulemeijer, Vos, Bleijenberg, & Van der Werf, 2007).

Factors that affect outcomes.

Many variables can affect the outcomes of a MTBI including time post-injury, pre-morbid status, recurrent injury, sociocultural and gender differences.

Time post-injury.

The typical clinical course of MTBI is the clearing of confusion within 24 hours, some initial impairment of memory and information processing, and executive dysfunction within the first 2 weeks and up to one month after injury (as detected by neuropsychological tests, Levin & Diaz-Arrastia, 2015; Theadom et al., 2016). In most patients, symptoms gradually resolve during the following 12 weeks (Podell, Gifford, Bougakov & Goldberg, 2010; Ruff, 2005) with 80-85% of patients with an isolated MTBI having a favourable recovery within 3-6 months (Gentilini Nichelli, Schoenhuber et al., 1985). There is evidence however that long-term physical, cognitive and affective deficits can occur in some individuals with MTBI (Clarke, Genat & Anderson, 2012).

A prospective, longitudinal study found that 30% of patients with mild TBI had new onset or intensification of at least one post-concussion symptom 3 months after injury (Meares et al., 2011). This is consistent with previous research by Lannsjö et al., (2009), a population-based large study (n = 2602) based on non-hospitalized mild TBI cases, which indicated the presence of one or more post-traumatic symptoms (as measured by the Rivermead Post-Concussion Symptoms Questionnaire - RPQ) at three months after injury in 44% of the cases and three or more symptoms in 24% of the cases. Unfortunately, this study did not use a control group to compare with TBI-free participants and it is possible that post-concussive-type symptoms are commonly experienced by the general population overall.

The BIONIC study found a longer-term trajectory for cognitive effects with over 20% of people still experiencing difficulties with complex attention and memory at 12-months post-injury (Barker-Collo et. al., 2015). Between 27.3% and 47.9% of their longitudinal study participants experienced four or more mild to severe PCS at 12-months post-injury.

A substantial amount of research looking at outcomes from MTBI has focused on concussion which is one type of MTBI that is often sustained by athletes. Athletes with concussion appear to have a more rapid recovery than those in the general population (McCrory, Meeuwisse, Aubry, Cantu & Dvorak, 2013) . In concussion, there are differences in the loss of consciousness, comorbidities, and pre-injury disorders. Many sports clinicians now use comprehensive TBI assessments such as the Sports Concussion Assessment Tool which includes a cognitive assessment, assessment of symptoms, loss of consciousness, GCS and a balance, neck and co-ordination examination. (Theadom et al., 2018). These more complex assessments are too time-intensive for Emergency Departments and are not designed for the general public. Head injuries sustained during sporting activity are therefore often more effectively identified in the acute phase than those sustained by the general public. In comparison with patients with MTBI presenting to emergency rooms, post-concussion symptoms in 80–90% of adult athletes typically resolve within 7–10 days after their first concussion (McCrory, Meeuwisse, Aubry, Cantu & Dvorak, 2013). The more mild effects of concussion could be due to the specialist medical attention and support that those who sustain a sports concussion commonly receive at the side-line at the time of injury whereas in the general population once a MTBI is sustained there is usually waiting time before medical assistance is received.

The timeline for symptom resolution after MTBI is therefore not a linear process with wide heterogeneity in terms of recovery even with similar injury profiles (Theadom et al., 2016). The impact of MTBI on an individual's ability to adapt to life changes will fluctuate and, in relation to affect changes for example, it cannot be assumed that someone who initially presents without depression or anxiety for example will remain free of these in the long-term as they continue to acclimatise to life after injury (Barker-Collo, et al 2018).

Pre-morbidity.

Levin et al., (1987) concluded that a single uncomplicated minor head injury produces no permanent neurobehavioural difficulties in the majority of patients without pre-existing psychiatric disorder or substance abuse. Levin's conclusions are supported by Ponsford et al., (2012) who compared post-concussion symptoms of 123 patients with MTBI and 100 trauma patient controls, both groups recruited from the emergency department, and found that, at 3 months post-injury, premorbid physical or psychiatric problems, but not MTBI, most strongly predicted continuing symptoms. This concurs with Clarke et al. (2012) who concluded that 3-12-month post-concussive symptoms (physical, affective and cognitive) were principally characteristics of psychological symptoms (depression, anxiety and neuroticism) and not of brain damage. Another prospective, longitudinal study (Ponsford, Cameron, Fitzgerald, Grant & Mikocka-Walus, 2011) indicated that a pre-injury neuropsychiatric disorder is strongly related to persistence of symptoms for 3 months or longer after MTBI.

Recurrent TBI.

There have been limited studies on the frequency or impact of recurrent TBI within the general population. Although a meta-analysis by Belanger, Spiegel & Vanderploeg (2010) highlighted inconsistent findings overall about the impact of recurrent TBI, their follow-up analysis revealed poorer outcomes from multiple MTBI. A more recent population-based study on recurrent TBI incidence and outcomes over a one year period (Theadom et al., 2015) identified participants from the original BIONIC study, which was carried out between 2010-11 and that examined the incidence and outcomes (up to 12-months) of TBI across all age groups (Feigin et al., 2013). Those who had sustained a recurrent brain injury within one year following their initial index injury were matched to a comparison group from within the study, based on age ($\pm$ 2 years) and gender, who had only

sustained the one index injury. A high proportion of these recurrent TBI's were classified as mild. Outcomes measured were post-concussion symptoms, cognitive impairment and disability. Theadom and colleagues found that 9.9% of their study participants (n=72) had experienced recurrent TBI, higher than previous empirical estimates of 7-9% over a 6-7 year period (Theadom et al., 2015). Recurrent TBI cases reported significantly increased frequency and severity of PCS at 1 year, compared to the matched controls sustaining one TBI. There was no difference in overall cognitive ability and disability between the two groups (Theadom et al., 2015).

Sociocultural factors.

Ethnic minorities may be at higher risk of TBI. In New Zealand the total incidence of TBI within Māori populations was found to be significantly higher compared to all other ethnic groups (1206/100,000 compared to 887/100,000 for Europeans, Feigin et al., 2013). This was mainly due to a higher TBI incidence in Māori people older than 35 years compared to those in the same age range of other ethnicities. Compared with Europeans, Māori people had a greater risk of MTBI (RR 1.23, CI 1.08-1.39) and poorer cognitive outcomes which were related to social and socio-economic factors, lower educational levels, emotional distress (such as depression) and poorer physical functioning 6-months post-MTBI (Barker-Collo et al., 2015). Non-white ethnic group was associated with poorer outcomes at 12-months post-injury (Theadom et al., 2016).

The majority of TBI's are mild and although symptoms and outcomes can be difficult to detect, they can be persistent and debilitating. Many factors can affect the recovery trajectory of MTBI, including time post-injury, pre-morbid functioning, recurrent injury and sociocultural factors. Gender may also influence the outcome of a MTBI but this relationship has not been well studied outside of the sports athlete domain which does suggest some gender differences.

Gender differences in outcomes of MTBI.

In a literature review investigating sex, gender and intersecting vulnerabilities in relation to TBI in general, Mollayeva, Mollayeva & Colantonio, (2018), concluded that many interacting factors, including sex and gender, can modify the structural and functional outcomes of TBI. The authors found that males and females exhibited biological differences that could affect injury perception, communication, motivation, memory and aggressive behaviour. Additionally, they discovered a complex array of factors, linked to gender inequalities, such as access to health services, economic opportunities, relationships, gender roles and capacity for personal development that could determine gender differences in TBI outcomes.

It has been observed that in 40% of those admitted to hospital and undergoing a CT scan within 24 hours of sustaining a TBI, changes take place in the brain that may make the patient prone to developing hormone deficiencies and this may explain gender differences in outcomes from MTBI. However, a study by McCauley, Boake, Levin, Contant & Song, (2001) found no significant gender differences in post-injury symptoms (as per DSM-IV post-concussional disorder symptoms which include tiring easily, disordered sleep, headaches, vertigo/ dizziness, irritability, anxiety/ depression/ affective lability, changes in personality, or apathy) between a general trauma group (TBI-free) and a group 3 months post-MTBI.

A systematic review of sex differences in sports-related concussion by Solomito, Reuman & Wang, (2019) identified differences in brain structure between sexes with the corpus callosum in males to be larger, more fibrous compared to females and concluded that males tend to use one hemisphere of their brains for most tasks whereas females utilise both hemispheres. Their final analysis was that, because of these differences, strain injury of the

corpus callosum may affect females to a greater degree than males as their ability to process information may become more disrupted following MTBI.

Mild TBI often goes unreported to the medical profession as its felt effects can be minimal in the acute phase and the reporting of symptoms is the first step in identifying the outcomes and course of MTBI. As such, there may also be gender differences in the level of symptom-reporting following a MTBI, due to both the degree of knowledge and awareness around injury-relevant symptoms and the associated risks, and also to gender-related reasons for not reporting symptoms to a medical professional or authoritative figure. Miyashita, Diakogeorgiou & Vandervegt, (2016), found gender differences in concussion reporting among high school athletes with female athletes significantly more likely to report a concussion than their male colleagues. These results raise the issue of possible under-reporting by men, either due to different norms and expectations in their sports, or due to issues related to their gender identity. This is also of concern as males have an increased risk of TBI at all ages compared to females (Saunders, et al., 2009).

Wallance, Covassin & Beidler, (2017) conducted a cross-sectional survey of 288 high-school athletes' knowledge of sport-related concussion symptoms and their reasons for not reporting them. The researchers found that males and females had similar symptom knowledge but that females were more likely to report their concussive symptoms to an authoritative figure. Chi-square tests identified significant relationships between sex and eight reasons for not reporting a concussion. Males were less likely to report their symptoms due to thoughts that their coach would get mad, their teammates and coach would think they were weak, their parents would be upset or because it was the end of the season and they did not want to miss a game or lose playing time and they did not want to let their team down. These reasons for not reporting a concussion reflect a focus from the individuals on the reactions and perceptions of others rather than on internal factors and may indicate a fear of

being stigmatised for seeking help and therefore more concerned than females about their image and their reputation on the team. Males were 4 to 10 times more likely not to report concussion symptoms because they did not want to lose playing time and this could support stereotypical male gender norms of "sucking it up" or playing through the pain due to pressures to win games.

This is consistent with research by Gaudet et al., (2018) which found that, based on self-reported and objective outcomes, females' usual daily activities were more affected by MTBI and post-concussion symptoms than men. Studies have also found that male and female athletes exhibit differences on baseline (pre-concussion) neuropsychological test performance and concussion symptoms and that they may also demonstrate sex differences on post-concussion test scores and symptom reporting. Female athletes reported higher symptoms prior to concussion than males, and females were more likely than males to endorse mild degrees of headache, fatigue, irritability, sadness, nervousness, feeling more emotional, feeling slowed down and difficulties with sleep and concentration at pre-injury (Iverson and Stearne, 2006). These findings had small-to-medium effect sizes.

Whilst there are an array of symptoms that can present following MTBI, a lesser-researched area of symptomatology after MTBI is in relation to gender differences in longer-term depression and anxiety outcomes and this is the focus of my study. A definition of depression and anxiety and their epidemiological factors in the general population is provided followed by a more detailed literature review of the trajectory of depression and anxiety following MTBI and associated gender differences. Depression will be documented first, followed by anxiety.

Depression

Worldwide projections by the World Health Organization for the year 2030 identify unipolar major depression as the leading cause of disease burden. Depressive disorders are characterised by the presence of sadness, emptiness, hopelessness and irritability, accompanied by somatic and cognitive changes that significantly affect the individual's ability to function, such as concentration problems, fatigue, loss of interest in previously enjoyed activities, disturbances in appetite, weight and/or sleep and often recurrent thoughts about death or suicidal ideation (American Psychiatric Association, 2013). The mortality risk for suicide in depressed patients is more than 20-fold greater than in the general population with over half of all suicides occurring within the context of a mood disorder (Guillamondegui et al., 2011). The manifestations of depression may differ in duration, timing, or aetiology and can range from mild to full impairment, such as the incapacity for basic self-care. Major depressive disorder is characterised by discrete episodes of at least 2 weeks' duration involving clear changes in affect, cognition, autonomic nervous system function and inter-episode remissions. Diagnostic criteria include five, or more, symptoms present for at least 2 weeks and including depressed mood or loss of interest or pleasure. A more chronic form of depression, persistent depressive disorder, can be diagnosed when the mood disturbance continues for at least 2 years in adults and includes the presence of poor appetite or overeating, insomnia or hypersomnia, low energy or fatigue, low self-esteem, poor concentration or difficulty making decisions and feelings of hopelessness.

In the New Zealand Mental Health Survey (2006) the lifetime prevalence of depression has been reported as 20.2% (CI 95% 19.3 – 21.1). The 12-month prevalence of mood disorder was 7.9% (CI 95% 7.3-8.7) for the total New Zealand population, with decreasing prevalence with increasing age, and higher prevalence in females (8.1% versus 4.9% in males) (Scott, Oakley Browne & Wells, 2010). Depressive disorders, as defined by

the World Health Organisation, have a 12-month prevalence which varies from 3% in Japan to over 9% in the United States (Demyttenaere et al., 2004). Greater severity of depressive symptoms has been found to be associated with significantly higher risk of all-cause mortality including cardiovascular death and stroke as well as with diabetes and obesity.

Depression can disturb many life domains, including physical, emotional, social wellbeing and professional competence. It is also is also a huge burden for both the family of the depressed patient and for society at large. Depression increases the risk of diminished workplace productivity and has been estimated to result in a loss of $36.6 billion per year in the United States of America ($USD). Depression is often a chronic and relapsing condition (Oquendo et al., 2013).

Heritability estimates of major depression of 40% suggest that environmental experiences are the major contributor to risk (Sullivan, Neale & Kendler, 2000) and these risk factors may include experiencing adverse events during childhood such as emotional, physical and/or sexual abuse (American Psychiatric Association, 2013). The somatic consequences of depression could partly be due to metabolic, immuno-inflammatory, autonomic and hypothalamic-pituitary-adrenal (HPA)-axis dysregulations which have been consistently observed among depressed patients (Penninx, Milaneschi, Lamers & Vogelzangs, 2013).

Sociocultural differences in depression.

There are documented cultural/ethnic differences in the rates and symptom expression of depression. Dunlop et al., (2003) found that higher depression rates among minority individuals were largely associated with greater health burdens and lack of health insurance. Dreher et al., (2017) discovered differences in the cultural dynamics of symptom presentation in people with depression; for example, Vietnamese patients presented with more somatic

symptoms than German patients. Kwon, Yoon, Joormann & Kwon (2013) found cultural differences in the depression-associated emotional regulation strategies used by American and Korean adults.

Gender differences in depression.

In the general population, females are 70% more likely to experience depression than males (National Alliance on Mental Illness, 2016), particularly during the reproductive years, and women can often present differently to males with depression. Explanations for this higher prevalence are inconclusive but include psychological, neurochemical, anatomical, hormonal, genetic and personality factors (Bremner et al., 2002; Grigoriadis & Robinson, 2007). One theory is that females are more prone to the effects of stress and there is a strong positive relationship between stress and depression (Davidson et al., 2002; Nemeroff & Vale, 2005) and depression is a common response to stress (Kendler & Gardner, 2000). Stressors can cause long-term dysregulation of the HPA axis (Heim & Nemeroff, 2001) which has also been observed by Penninx et al., (2013). There is also a view by some researchers that the DSM-5 (American Psychiatric Association (APA), 2013) used to diagnose psychiatric conditions, includes depressive symptoms that are more easily observed in female-specific depression (Lavoie et al., 2017). Women are also at greater risk for relapse as compared to men (Oquendo et al., (2013) within a two year period.

Women with depression report more somatic symptoms, including pain, than do men (Silverstein et al., 2013). Iverson and Stearne, (2006) found in a study of college athletes that female athletes reported higher symptoms at baseline than males and that females were more likely than males to endorse mild emotional symptoms such as irritability and sadness, at baseline neuropsychological assessment. Although not conclusive, these data may suggest a stronger likelihood for females to endorse greater depression symptomology than males at

baseline. Males may be under-reporting and females may be accurately reporting or perhaps females are more willing to report affect symptoms than males in general.

Anxiety

Anxiety disorders are characterised by excessive fear and anxiety and related behavioural disturbances. Fear is the emotional response to real or perceived imminent threat, whereas anxiety is anticipation of future threat. Fear is more often associated with surges of autonomic arousal necessary for flight or flight, thoughts of immediate danger and escape behaviours, and anxiety is more often associated with muscle tension and vigilance in preparation for future danger and cautious or avoidance behaviours. Whilst anxiety is a normal physiological state, an anxiety disorder develops when the fear or anxiety becomes excessive or persisting, typically, for 6 months or more and causes clinically significant distress or impairment in social, academic, occupational or other important areas of functioning (APA, 2013). Anxiety disorders featured in the DSM-5 include social anxiety disorder, panic disorder and generalised anxiety disorder. The New Zealand Mental Health Survey (Wells et al., 2006) has reported the lifetime prevalence of anxiety (all types) to be 24.9% (CI 95% 23.6 – 26.2) and the 12-month prevalence to be 14.8% (CI 95% 13.9 – 15.7). Prevalence estimates for anxiety disorders vary across countries, with 12-month prevalence ranging from 2·4% (Italy) to 29·8% (Mexico) and prevalence in the U.S.A and European countries tends to be higher than in the rest of the world, (Craske & Stein, 2016).

Anxiety disorders are often co-morbid with major depression and if left untreated can become chronic. Impairment and disability associated with anxiety disorders might be greater for women than for men and adverse childhood experiences (e.g., childhood abuse), parents with a history of mental disorders, low socioeconomic status, and an overprotective

or overly harsh parenting style are also risk factors for anxiety disorders (Craske & Stein, 2016).

The heritability of anxiety disorders is estimated to be in the range of 30-50% (Shimada-Sugimoto, Otowa & Hettema, 2015). The pathophysiology of anxiety disorders is poorly understood but accepted hypotheses include overgeneralisation of conditioned fear and deficits in the extinction of conditioned fear (Craske & Stein, 2016). Brain imaging, including functional Magnetic Resonance Imaging (MRI), suggest that anxiety is characterised by limbic region overactivity during emotional stimulation and deficits in functional connectivity in this and other regions of the brain (Fonzo et al., 2015).

Sociocultural differences in anxiety.

Differences have been found in the prevalence and severity of anxiety in African Americans and European Americans, (Hopkins & Shook, 2017). A number of sociocultural risk and protective factors have been suggested to contribute to these group differences in anxiety including ethnic identity and stigma toward mental illness which consistently differed by racial group and were associated with anxiety in African Americans. Ethnic identity may buffer against the negative consequences of anxiety, reducing prevalence rates in African Americans or stigma toward mental illness may decrease African Americans' willingness to report anxiety symptoms, reducing overall prevalence rates but increasing the severity of treated cases, (Hopkins & Shook, 2017).

In a study of Latino participants, results indicated that the interaction between anxiety sensitivity and subjective social status was significantly associated with the number of mood and anxiety disorders, panic, social anxiety, and depressive symptoms, (Zvolensky et al., 2015).

Gender differences in anxiety.

Females have a higher, (approximately doubled), prevalence of anxiety symptoms and anxiety disorders compared to males and the causal mechanisms for this remain inconclusive (Faravelli, Scarpato, Castellini & Lo Sauro, 2013). This greater female prevalence of anxiety disorders could be due to differences in gender socialisation and mastery learning experiences, where the indirect effects of gender on anxiety via instrumentality and mastery were both significant in a cross-sectional, not causal, study of 398 undergraduate students (Zalta & Chambless, 2012). These findings were consistent with theories that gender differences in anxiety are associated with socially-constructed and reinforced gender roles and learning experiences for men and women, including perceived societal norms such as rewarding boys for assertiveness, more controlling parenting styles for girls, higher expectations of boys and different tolerance levels of specific emotions between the sexes. Males and females may also show different environmental risk factors such as childhood trauma, psychosocial and economic factors (Oldehinkel & Bouma, 2011). The higher prevalence of anxiety in females is a trend that persists until middle age (mid-fifties) and then declines once post-menopausal (Cairney & Wade, 2002; Leach, Christensen, Mackinnon, Windsor & Butterworth, 2008; Bijl, De Graaf, Ravelli, Smit & Vollebergh, 2002). This could suggest that hormones are a factor in the prevalence of anxiety in females and in support of this hypothesis, Faravelli et al., (2013) found that the risk of the onset of anxiety after menopause was similar in both genders.

Gender differences in DSM-IV anxiety disorders were examined in a large sample of adults (N = 20,013) in the United States of America using data from the Collaborative Psychiatric Epidemiology Studies (CPES). Women had higher rates of lifetime diagnosis for each of the anxiety disorders examined which were also associated with a greater illness burden in women than in men, particularly among European American and Hispanic women.

These results suggest that anxiety disorders are not only more prevalent but also more disabling in women than in men. (Mclean, Asnaani, Litz, & Hofmann, 2011).

There is some evidence to indicate that men tend to underreport anxiety symptoms (Pierce & Kirkpatrick, 1992 in Zalta & Chambless, 2012). Iverson and Stearne, (2006) found in a study of college athletes that female athletes reported higher symptoms at baseline than males and that females were more likely than males to endorse mild emotional symptoms such as nervousness at baseline neuropsychological assessment. Further studies have concluded that other (sociocultural) factors and not just reporting biases account for gender differences in anxiety (Mclean & Hope, 2010). However, it cannot be ruled out that the observed differences between men and women are somewhat influenced by gender-related differences in the conceptualization and reporting of symptoms (Mclean et al., 2011).

Co-morbid Depression and Anxiety

There is a high level of co-morbidity between depression and anxiety and a co-morbid presentation increases the risk of a poorer outcome in terms of prognosis (Bruce et al., 2008 & Merikangas et al., 2003). The National Comorbidity Survey Replication (2012) projected that between 5% and 9% of the adult population in a 12-month period would have co-morbid depression and anxiety (Gadermann, Alonso, Vilagut, Zaslavsky & Kessler, 2012).

Penninx et al., (2011) compared the 2-year course of depressive and anxiety disorders within the same study design and with the same instruments, namely the DSM-IV based Composite Interview Diagnostic Instrument and Life Chart Interview (n = 2981). The prevalence of co-morbid depression and anxiety was 37.6% and the index episodes of this group were more severe and chronic with an earlier age of onset and with a more frequent treatment regime. Penninx et al., (2011) found that depression and anxiety have a different naturalistic course trajectory in terms of recovery and duration (with worse outcomes for

anxiety) and concluded that separate consideration should be given to each disorder in clinical practice to achieve optimum outcomes.

The majority of TBI are mild and, to date, long-term outcomes of MTBI have not been adequately documented and this restricts the effective and efficient provision of healthcare to this population. It is known that depression and anxiety are commonly experienced following a TBI (Barker-Collo et. al., 2015) but the full burden of these disorders, and the interaction with gender, is undetermined.

MTBI and Depression

There is much variability in reports of the prevalence of depression after MTBI and it ranges from 12% to 44% in the first 3 months (Waljas et al., 2015; Mooney & Speed, 2001; Levin & Diaz-Arrastia, 2005) to between 8% to 70.1% in the first year post-MTBI (Barker-Collo et al., 2015; Scholten et al., 2016; Wood, 2004; Rapoport, McCullagh, Streiner & Feinstein, 2003 and Bombardier, Hoekstra, Dikmen & Fann, 2016). This variability was highlighted by Kreutzer, Seel and Gourley, (2001): who stated '…despite researchers best efforts, the brain injury rehabilitation community has been provided with disparate, incomplete and inconsistent information about depression' (p. 563). The average prevalence of depression after MTBI of 31.7% was calculated from over 100 studies by Guillamondegui, et al., 2011. This extensively-reported variability in depression prevalence following MTBI is due to methodological differences between studies, including variances in sample populations and measures of depression. There is also variability in the exact direction in which depression changes after MTBI: many studies report a drop in depression, a stable rate over time and some propose an increase (Wood, 2004). Others suggest a variable and non-linear direction (Barker-Collo et al., 2018). Compared to a lifetime prevalence of depression in New Zealand of 20.2% and a 12-month prevalence of mood disorder in New Zealand of

7.9% (CI 95% 7.3-8.7), empirical findings may suggest that there is an increased risk of developing mood disorders after MTBI.

Kontos, Covassin, Elbin & Parker, (2012) concluded that, although not clinically significant, athletes experienced statistically significant increased depression scores on the Beck Depression Inventory-II (BDI-II) up to 14 days after concussion injury (measures at baseline, 2 days and 7 days). Depression was found to be related to post-concussion symptoms at both one month and one year following MTBI in 126 adult participants, recruited from an emergency department in Finland and compared with an age- and sex-matched control group with no history of head injury or psychiatric disorders, (Waljas, et al., 2015. The scales used by Waljas et al., 2015 to measure depression were the BDI-II (a more somatic measure of depression than the HADS) which was adjusted to ensure specific differentiation between depressive and post-concussive symptoms. The researchers found that the MTBI participant group reported more depressive symptoms at one month post-injury compared with controls but this was not statistically significant and the groups did not differ in depressive symptom reporting at the one year point. They found a sub-group of MTBI patients who had endorsed an extremely high number of post-concussion symptoms (>11 on the RPQ) at 1-month and 1-year post-injury but none of the control participants did so and this could suggest that some MTBI patients have persistent post-injury issues.

As part of the BIONIC study of depression after 1-, 6- and 12- months after MTBI, Barker-Collo et al., (2015) found that, although depression symptoms did commonly occur, the average total depression scores on Hospital Anxiety Depression Scale (HADS) depression items for their sample (n=315) were quite low at each assessment (subclinical) and they significantly decreased over time. The most commonly-reported depression-related symptom was a “feeling of being slowed down” (which is also a common sequelae of PCS). The authors found that the levels of depression throughout the same timepoints were comparable

with the general population. Within 2 weeks (baseline) of injury 21% of their sample met criteria for depression (HADS >8) but by one month following injury this had reduced to 17.1% and this downward trajectory continued at 6 months (15.7%) and 12-months (12.4%) post-injury. The HADS total depression mean scores followed the same pattern: 4.73 at baseline and significantly decreasing to 3.48 at 12-months post-injury. Of the individuals who met HADS criteria for depression at baseline, 35.7% continued to meet criteria at 12-months. Of those not presenting with depression at baseline (n=122), 3.2% met criteria for depression at 12-month follow-up.

The SHEFBIT study (Sheffield Brain Injury after Trauma) by Singh, Mason, Lecky & Dawson (2019), studied 774 individuals with TBI, which included a high proportion of MTBI participants (44.8%). They reported a prevalence for depression at 10 weeks of 56.3% [95% CI 52.8-59.8] using a HADS cut-off of >8 which reduced at 12-months to 41.2% [95% CI 37.6-44.9]. In the same study, at the higher cut-off of HADS >11, depression was 17% at 12-months post-TBI and had reduced from 29.2% at 10 weeks post-injury. Many of the participants with initial depression at 10 weeks had it resolved by 12-months (35.2%) but 89% of those with depression at 12-months had also been depressed at 10 weeks. A small number (10.9%) of those with depression at 12-months had not shown depression symptoms at 10 weeks. This shows some fluctuation of depression over time.

Utilising the Structured Clinical Interview for DSM (SCID), the Centre for Epidemiological Studies – Depression Scale (CES-D) and the Visual Analogue Scale For Depression (VASFD), McCauley et al., 2001 found different prevalence levels of major depression disorder (MDD) between a general trauma (TBI-free) group and a MTBI group 3-months' post-injury: 16.5% compared to 21.4% for the MTBI group. Schoenhuber and Gentilini (1988) examined 35 MTBI patients from 5 to 17 months post-injury and compared them to a control group (TBI-free) on the Self-Rating Depression Scale and the State-Trait

Anxiety Inventory. Those with MTBI were at greater risk of developing depression (p = 0.003*)* and 39% of the MTBI patients reported depression symptoms at 1 year post-TBI.

To study even longer-term effects of MTBI on depression, Barker-Collo et al., (2018) extended the authors' previous 2015 study to 48 months using the same population sample (n = 341). Total mean scores on the HADS depression scale significantly decreased from baseline (2 weeks) over the 48-month follow-up periods. However, the proportion of their population sample meeting HADS (>7) criteria for depression increased to 7.7% at 48 months compared to 2.2% at 12-months post-injury suggesting that the level of depression increases for some people in the longer-term.

Scholten et al., 2016 examined pre- and post-injury prevalence of SCID diagnosed depressive disorders after all severities of TBI. Their systematic literature search included a total of 34 studies: pooled prevalence estimates of depressive disorders increased over time and indicated high long-term prevalence of 43% for depression (after average follow-up periods of between 1.5 – 5 years). Long-term prevalence rates were almost all greater than (or equal to) the rates before TBI in all studies that measured both pre-injury and long-term prevalence.

Konrad et al., (2011) studied 33 participants who had sustained MTBI on average 6 years prior and matched these to healthy controls by age, gender and education. The researchers assessed psychiatric symptoms via a structured clinical interview for DSM-IV (SCID-1) and the Beck Depression Inventory (BDI). The BDI scores were significantly higher in the patient group, and three patients fulfilled DSM-IV criteria for a mild episode of major depression. They concluded that long-term emotional sequelae continue even after 6 years post-injury.

In summary, in the acute phase of MTBI, mean scores for depression have been reported to significantly increase in the first 14 days (Kontos et al., 2012) and then to significantly decline to 48 months post-injury (Barker-Collo et al., 2018), although these scores were not within clinical ranges. In some studies the prevalence of depression is higher and decreases over time (from 56.3% to 41.2% and from 21% to 12.4% from baseline to 12-months post-injury) and in others the prevalence is lower and increases over time (2.8% to 7.7% at 48 months). Long-term prevalence for depression has been reported as between 9% and 43% for on average 1.5 – 6 years post-injury. However, Barker-Collo et al., (2015) found that the levels of depression throughout 1, 6 and 12-month timepoints were comparable with the general population.

MTBI and Anxiety

A literature review by Moore, Terryberry-Spohr & Hope, 2006 noted significant evidence that MTBI can give rise to the manifestation of anxiety and that anxiety symptoms may severely impact the prognosis and recovery course from MTBI. This contrasts with other research that demonstrated no differences between HADS anxiety scores between MTBI patients and 100 trauma controls at acute assessment, 1 week and 3 months post-injury (Ponsford et al., 2012). Research by Singh, Mason, Lecky & Dawson, 2019 who studied all severities of TBI (with nearly 45% MTBI), showed a reduction from 63% to 42.3% of participants on measures of anxiety (HADS >8) between the 10 week and one year post-injury follow-up. At the higher cut-off of HADS >11, anxiety was reported in 21.6% of participants at 1 year post MTBI. Barker-Collo et al., (2015) found that anxiety, as measured by the HADS (cut-off >8), was experienced by 42.2% of participants at baseline and decreased to 30% by 1-month post-MTBI. At 6 months post-MTBI the prevalence of anxiety increased slightly to 33.2% and decreased slightly at 12-months to 29.3%. The mean

anxiety scores on the HADS (cut-off >8) increased significantly from baseline to 1-month and overall from baseline to 12-months with a significant change reflected in the decrease in anxiety scores from 6 to 12-months. The mean level of anxiety peaked at 6 months post-MTBI, suggesting that anxiety difficulties are more prominent within the first 6 months post-injury. Barker-Collo et al., (2015) concluded that levels of anxiety found post-TBI across the follow-up periods were comparable to the general population.

Schoenhuber and Gentilini (1988) examined 35 MTBI patients from 5 to 17 months post-injury and compared them to a control group (TBI-free) on the Self-Rating Depression Scale and the State-Trait Anxiety Inventory. Those with MTBI were at no greater risk of developing anxiety than the control group and 26% of MTBI patients reported anxiety after 1 year.

In terms of the longer-term trajectory for anxiety following MTBI, Scholten et al., 2016, in their literature search of all-severity TBI, indicated high long-term prevalence of 36% for anxiety (after average follow-up periods of between 1.5 – 5 years). The authors found that long-term prevalence rates were almost all greater than (or equal to) the rates before TBI in all studies that measured both pre-injury and long-term prevalence. In contrast, with a focus on MTBI, Barker-Collo et al., (2018) found in the BIONIC study that total scores on the HADS anxiety scale decreased significantly over the 48-month follow-up periods. At baseline, the prevalence for anxiety, using a HADS clinical cut-off score of 7, was at its highest with 29.5% of the sample, dropping to 13.6% at 48 months.

Compared to the New Zealand Mental Health Survey (Wells et al., 2006) figure for the 12-month prevalence of anxiety disorder of 14.8% (CI 95%, 13.9-15.7), Barker-Collo et al., (2018) showed a variable post-TBI anxiety prevalence of between 3.7-29.5% suggesting that the presence of TBI may increase the risk of anxiety.

MTBI and Comorbid Depression and Anxiety

Depression and anxiety have an extremely high comorbidity rate (Alway, Gould, Johnston, McKenzie & Ponsford, 2016) and Singh, Mason, Lecky & Dawson, (2019) found that over 90% of their study sample population who classified as having depression (HADS >8) also had comorbid anxiety at 10 weeks post-TBI. At 1 year this prevalence decreased to 42.3% and at the higher cut-off of >11 on the HADS, comorbid anxiety was at 21.6% at 1 year. Penninx et al., (2011) found a 37.6% 2 year prevalence of comorbid depression and anxiety as measured by DSM-IV. This has been supported by Barker-Collo et al., 2018 findings that anxiety or a combination of anxiety and depression was much more common than depression alone after MTBI injury across timelines (2 weeks, 6, 12 and 48 months) with comorbidity rates ranging from 10.2% to 20.7% over the first year post-injury. At baseline co-morbid prevalence was 20.7%, decreasing across the 6-month and 12-month timepoints to 15.7% and 10.2% respectively and remaining at 11.8% at 4 years post-injury, higher than that of between 5% and 9% of the adult population in a 12-month period which has been projected by The National Comorbidity Survey Replication (Gadermann et al., 2012).

Predictors of Depression and Anxiety post-MTBI

As with other post-concussion symptoms, the cause of persistent mood symptoms following MTBI is diverse, multifactorial and individualised, and a biopsychosocial perspective in understanding the cause of these symptoms is useful. With regard to injury and demographic features which may predict depression risk at 1 year, literature reviews have not found one consistent feature that is associated with this risk (Singh, Mason, Lecky & Dawson, 2019). Chronic depression and anxiety symptoms can arise from both the physiological effects of trauma to the brain and as a result of psychological distress

associated with altered functional ability and changes in quality of life. An accepted hypothesis is that prefrontal dysfunction affects emotional regulation and high levels of amygdala activation may be associated with an increase in anxiety symptoms and negative affect (Davidson, Pizzagalli & Nitschke, 2002), which together with the distress of sustaining a TBI, may explain persistent symptoms (Vasterling & Dikmen, 2012). Theories suggested by Silverberg & Iverson (2011) and Moldover, Goldberg & Prout (2004) posit that longer-term depression and anxiety symptoms, are impacted by pre-morbid personality traits, coping mechanisms, post-injury support mechanisms and other psychosocial features.

In terms of pre-morbid psychiatric difficulties as a risk factor for depression and anxiety post-MTBI, Barker-Collo et al., (2015) found that there was a significant correlation between those who met criteria for depression at 12-months post-injury and a self-reported pre-morbid history of depression (35.9% of depressed subjects vs. 18.8% of non-depressed subjects), a history of anxiety and greater age at the time of injury. Whilst those with a pre-injury history of mental health difficulties were more likely to have post-concussion symptoms at one month, but not at one year, post-concussion symptoms were significantly correlated with depression symptoms at both one month and one year following injury (Waljas, et al., 2015). Singh et al., (2019) analysed pre-morbid self-reports of a history of depression and found that predictors of 1-year depression were an abnormal CT scan, past psychiatric history, alcohol intoxication and female gender. However, Scholten et al., (2016) found that 35.8% of those with a pre-injury mood disorder presented post-injury with an additional novel diagnostic class of mood or anxiety disorder and findings of mood and anxiety post-injury often presented without a pre-injury disorder (35.8% depression, 31.8% anxiety).

With regard to injury severity as a predictor of depression, Singh et al., (2019) found that at 1-year post-injury, TBI severity, age, aetiology and medical comorbidity were not

significant predictors whereas at 10 weeks post-injury, increased severity and CT findings were highly significant. In Barker-Collo et al., (2015) levels of injury severity, impairment and functioning did not appear to be related to developing major depression at 1-year (Barker-Collo et al., 2015 and Seel & Kreutzer, 2003) and nor did the type of injury (e.g., close, penetrating, diffuse or focal injury, Rapoport et al., 2003; Jorge 2004).

Other predictor factors of mood disorder post-MTBI include being female and being without employment (Scholten et al., 2016; Singh et al., 2019). However, Theadom et al., (2016) found that, whilst being female was a significant predictor of a poorer outcome on post-concussion symptom measures including HADS, levels of anxiety and depression were comparable with the general population.

The predictors of depression and anxiety after MTBI are not conclusive as research findings are mixed and many different individualised factors can make a person more vulnerable after injury, including the physiological effects to the brain, adapting to lifestyle changes, personality, premorbidity and significant life events. Female gender has also been found to be a common predictor of depression among MTBI patients but this is no different to the general population where more females than men overall tend to report depression symptoms.

Gender Differences in Depression and Anxiety post-MTBI

Understanding the relationship between gender and depression and anxiety symptoms following MTBI is important in planning rehabilitation and intervention strategies in the long-term, but relative to the literature available on traumatic brain injury outcomes, there is a dearth of research about this area in clinical populations, and the various conclusions are mostly based on findings from the sports-concussion literature utilising a number of varied measures for depression and anxiety symptoms.

Kontos et al., (2012) examined depression symptoms (using the Beck Depression Inventory II) at 2-, 7- and 14-days following sports concussion and found that sex did not influence post-MTBI depression levels. In concurrence with these findings, a study of a university student population, by Hurtubise, Hughes, Sergio & Macpherson (2018), did not find any clinically significant differences between genders in SCAT3 scores (Sport Concussion Assessment Tool 3) which includes measures of affect, taken within 48 hours of injury. Sex differences were found in post-concussion symptoms in college athletes in the 7-10 days post-injury in that concussed men were significantly more likely than concussed women to report sadness on the Immediate Post-concussion Assessment and Cognitive Test (ImPACT) ($p = 0.017$), (Covassin, Schatz & Swanik, 2007). In contrast, Baker et al., 2015 found, from a sample of 147 student athletes with sports concussion, aged 13 to 19 years, that females reported significantly higher scores for seven depression symptoms, up to 3 months post-injury, which included affective symptoms such as feeling slowed down ($p < .03$), more emotional ($p < .002$), irritability ($p < .03$), and sadness ($p < .04$). In concurrence, the study of 690 emergency department admissions (of all TBI severities and ages), demonstrated that female gender was an independent predictor of depression at 10 weeks and at 1 year following a TBI, using the HADS (>8), (Singh et al., 2019).

In terms of longer-term analysis of gender differences, there is some evidence that females have a higher prevalence of depression and anxiety symptoms post-MTBI. Farace & Alves (2000) conducted a metanalyses of sex differences in TBI outcomes which focused on all severity levels from 6-months to 6-years after TBI, and included eight studies. The authors demonstrated a significant difference, (effect size = 0.15), between genders and found that women demonstrated a worse outcome than men in 85% of the variables evaluated, including somatic/post concussive complaints, return to work, and new psychiatric symptoms including depression and anxiety. In their systematic review of 37 MTBI studies ranging

from baseline to 11 years post-injury, Merritt, Padgett & Jack, (2019) found that females reported greater overall symptoms than males in psychiatric domains including fatigue, sleep difficulties, irritability, sadness, nervousness, feeling more emotional, feeling slowed down, difficulty concentrating, and difficulty remembering.

In a prospective cross-sectional cohort study including 172 MTBI patients (out of 242 TBI patients overall), after 6 months post-injury a higher percentage of women (45% vs. 13%, $p = 0.01$) with MTBI were depressed compared with men (HADS $\geq$7). A higher percentage of women also had an incomplete return to work compared to men (50% vs 18%, $p = 0.05$) at 6 months' post- MTBI (van der Horn, Spikman, Jacobs & van der Naalt, 2013).

A study by Bay, Sikorskii, & Saint-Arnault, (2009), of 159 outpatients in rehabilitation after mild to moderate TBI, found a higher frequency of depressive symptoms in women than in men during the first 6-months post-injury (measured by the CES-D). The authors proposed that women were more at risk of depressive symptoms after TBI and cited post-injury chronic stress as a major explanatory factor for this as it was measured at a higher rate relative to men. The BIONIC study, (2018), found that across the baseline and 6 month timepoints of their 48-month longitudinal study, women produced significantly higher scores for anxiety and depression on the HADS scale than men and that at 12- and 48-month follow-up women's scores for anxiety were significantly higher than the men's scores. Rates at each time point were not provided in the study.

King, (2014) highlighted, from his literature review of 77 studies, four studies which reported correlation data on gender and outcome after MTBI. Post-concussive symptoms in general were reviewed which included subjective physical complaints, cognitive, emotional and behavioural changes which could be chronic, permanent or late emerging (but not specifically depression and anxiety). Three of the studies reported a positive correlation

between female gender and poorer symptomatic outcome relative to males 12-18 months post-injury and the smallest study found no correlation. Scholten et. al., 2016 found that females were at higher risk for anxiety and depressive disorders after TBI (1.5 – 5 years post-injury). Correlational studies reviewed by King (2014) at 3-6 years post-MTBI, found that in two out of the four studies females were at higher risk for 'permanent' post-concussive symptoms. One study, found that women had a significantly higher prevalence of anxiety than men after 3-5 years post-TBI, but the effect size was small (0.17), (Edna & Cappelen, 1987).

The evidence regarding gender differences is mostly based on findings from the sports-concussion research which involves measures at the early phase (up to 3 months) after MTBI and is to date inconclusive. Longer-term studies do suggest a higher female prevalence and severity of depression and anxiety symptoms post-MTBI but no higher than that in the general population.

Summary and Aims

Many studies to date that have investigated long-term outcomes of mild TBI have used hospital and clinic-based samples which may bias the research towards moderate-severe TBIs and exclude cases of MTBI, which approximate 95% of all TBI cases in New Zealand. In terms of outcomes from MTBI, very few studies have investigated the gender differences in depression and anxiety disorders over time and findings are variable and inconclusive. Furthermore, there are limited studies which involve comparisons with the general population. Overall, much of the research presented suggests that depression and anxiety are common sequelae of MTBI, particularly in the first year following injury and that these symptoms have a detrimental effect on rehabilitation from MTBI. Additionally, post-concussion symptom assessment within the first 3-6 months of TBI may mask the

identification of the long-term effects and course of depression and anxiety disorders post-injury and this warrants further analysis of symptoms over time.

In the acute phase, mean scores for depression have been reported to significantly increase in the first 14 days and then to significantly decline to 48 months post-injury, although these scores are not in the clinical range. In some studies the prevalence of depression is higher and decreases over time and in others the prevalence is lower and increases over time. Long-term prevalence for depression has been reported as between 9% and 43% , on average 1.5 – 6 years post-injury, but studies that have used control or comparison groups to test differences in depression levels between post-MTBI and TBI-free participants have been limited, particularly longer-term longitudinal studies. Theadom et. al., (2016) proposed that the levels of depression found in the authors' prevalence studies were comparable with the general population.

Research suggests that anxiety levels increase during the acute phase post-injury, peak at 6-months and decrease significantly over 48-months but again are comparable with the general population. Experimental studies using a control or comparison group to test differences in anxiety levels between post-MTBI and TBI-free participants have been limited, particularly longer-term studies, and have shown mixed results.

With regard to gender differences, there is some evidence that overall females have higher post-MTBI depression and anxiety scores and in general worse outcomes than males after MTBI. There is also some evidence suggesting that being female is a predictor of depression and anxiety following MTBI. However, with a lack of control group comparisons, there is limited evidence that these findings are not purely a reflection of the fact that women experience more depression and anxiety than men in the general population (APA, 2013).

As Barker-Collo et. al., (2018) concluded, there are multiple trajectories of depression and anxiety after MTBI and no studies have yet been done on the gender differences in the longer-term trajectory of post-MTBI depression and anxiety disorders after 8-years compared with the general population. In order to guide research and clinical practice with regard to effective evidence-based interventions for prevention and treatment of MTBI-related depression and anxiety disorders, my study investigated gender differences in the longer-term course of depression and anxiety symptoms 8-years following MTBI by conducting a longitudinal analysis of symptoms. This overall aim was two-fold: the first was to identify gender differences in the recovery trajectory of depression and anxiety over 1-month, 12-month and 8-year timepoints post-injury. The second was to investigate the gender differences in depression and anxiety scores between a group of MTBI subjects (8-years post-injury) and a group of participants who were TBI-free by comparing Hospital Anxiety and Depression Scale (HADS) scores and self-reported symptoms.

Method

Study Context

Participants for the MTBI group were initially recruited via the Brain Injury Incidence and Outcomes New Zealand in the Community (BIONIC) study. This was a large population-based epidemiological study carried out between 2010-11 that examined the incidence and outcomes (up to 12-months) of TBI across all age groups (Feigin et al., 2013). The aim of the current Brain Injury Outcomes New Zealand In The Community 8-years Later (BIONIC8) study was to explore outcomes of MTBI at 8-years post-injury and this thesis focuses on gender differences in depression and anxiety over time following a MTBI, using the Hospital Anxiety and Depression Scale. The first objective was to identify gender differences in the recovery trajectory of depression and anxiety over 1-month, 12-month and 8-year timepoints post-injury. The second was to investigate the gender differences in depression and anxiety scores between a group of MTBI subjects (8-years post-injury) and a group of participants who were TBI-free by comparing Hospital Anxiety and Depression Scale (HADS) scores and self-reported symptoms.

The definition of TBI used by the BIONIC studies was based on the World Health Organisation (WHO) definition of "an acute brain injury resulting from mechanical energy to the head from external physical forces" (Carroll et. al., 2004, p. 115) and not due to drugs, alcohol, medications, other injuries or treatment for other injuries, or other problems, such as psychological trauma. To meet the requirements for having sustained a TBI, as well as evidence of a TBI as defined by WHO, the participant also had to report at least one of the following symptoms following their head injury: 1) dazed, confused or had 'seen stars' at the time of injury; 2) loss of consciousness; 3) post-traumatic amnesia or any post-injury memory

loss; or 4) other neurological abnormalities such as focal neurological signs, seizure and/or intracranial lesions.

The TBI severity for each participant's primary injury was classified according to the Glasgow Coma Scale (GCS) which assesses the level of consciousness of patients with an acute brain injury, with the scores as follows: mild (GCS score of 13-15 and Post Traumatic Amnesia (PTA) of less than 24 hours), moderate (GCS score of 9-12 and 1-6 days of PTA) or severe (GCS score of 3-8 and 7 or more days of PTA) (Teasdale & Jennett, 1974). Scores for the GCS were recorded from medical records where available. Where participants did not have a GCS or PTA score recorded in their medical notes their TBI was classified as mild (GCS score of 15), as moderate or severe TBI's would have necessitated immediate medical assistance by the ambulance service or a primary or secondary health care service where GCS is routinely recorded.

Participants were recruited for the BIONIC study if they had experienced a TBI between the period of March 1st, 2010 and February 28th, 2011. Inclusion criteria involved living in Hamilton City (urban), or in the Waikato District (rural), of New Zealand. This geographical area was selected for the study as the demographic and social characteristics of this population reflected the overall population of New Zealand (Statistics New Zealand, 2006). Participants were also required to have lived within this designated area for at least 12-months prior to their head injury. No other exclusion criteria were employed for the TBI group. Those participants that consented to be part of the original BIONIC study were followed up with in-person assessments over the 12-months following their TBI and then at 4-years post-injury to assess the longer-term impacts of TBI via an extended Health Research Council (HRC) funded study called BIONIC4you (Brain Injury Outcomes New Zealand in the Community: 4 Year Outcomes). Further details of the methodology used in the original

BIONIC study and BIONIC4you study can be found in Theadom et al., (2012) and Barker-Collo et al., (2018) respectively and in Feigin et al., (2013).

During the 12-month and 4-year post-injury assessment participants were asked for their permission to be contacted regarding any related future studies including this current study known as the Brain Injury Outcomes New Zealand In The Community 8-years Later (BIONIC8) study, funded by Waikato Medical Research Foundation. This study was an extension of the BIONIC and BIONIC4you studies, and investigated the outcomes of TBI on adults (aged 16 and over) at 8-years post-injury compared with an age and gender matched comparison group. The purpose of this study was to characterise the most persistent difficulties experienced by participants after their TBI, to identify those at high risk of poor long-term outcomes and to identify the factors that influence recovery. My particular research focused on the pattern of recovery after MTBI in relation to depression and anxiety and associated gender differences.

The BIONIC8 study was co-ordinated by the School of Psychology, University of Waikato, Hamilton, New Zealand, in collaboration with the National Institute for Stroke and Applied neurosciences at AUT University, Auckland. The study received approval from the Southern Health and Disability Ethics Committee (17/STH/247/AM01).

Participants

TBI group.

Participants of the BIONIC and BIONIC4You studies, currently aged 16 years and over, who had given permission to be contacted (n=467) were invited to complete a study questionnaire. The recruitment of participants from the BIONIC study into the current study is shown as a flowchart in figure 1.

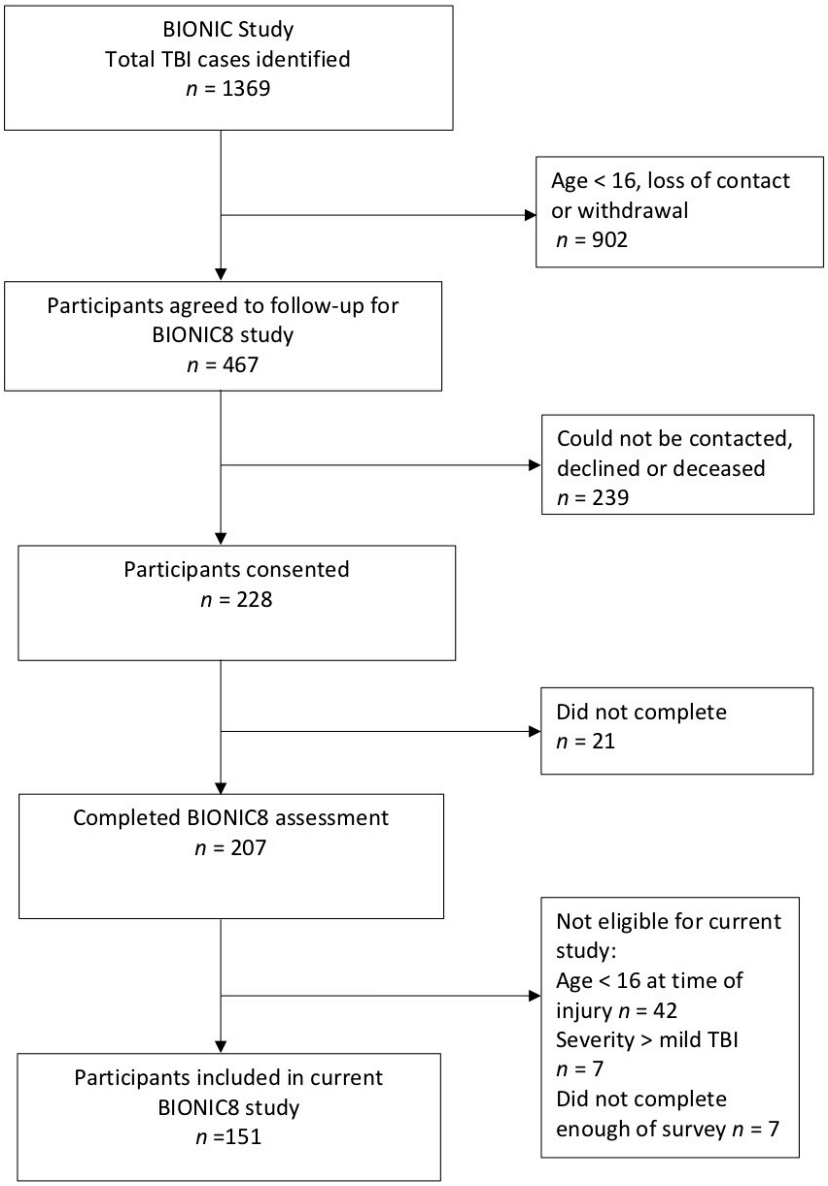

Figure 1. Flowchart for Recruitment of BIONIC8 MTBI Group

Of the 467 participants invited, 228 consented to participate in the current study and the final sample consisted of 151 people, with an equal proportion of genders: 77 males (51%) and 74 females (49%). In terms of ethnicity, there were 115 European (76.2%), and 30 Māori (19.9%) participants. Nearly 60% of participants had experienced multiple TBI (two or more injuries), and over 33% of these people had experienced four or more injuries in 8-years. The remainder of participants (40.4%) had sustained only one TBI at the eight year assessment. Most injuries were caused by falls (32.5%) followed by traffic/motor vehicle accidents (25.8%). Characteristics of the MTBI group who completed the 8 year assessment are shown in Table 1.

Table 1

MTBI group characteristics

	Male (%)	Female (%)	Total n (%)
	77 (51)	74 (49)	151
Age at eight year assessment *M (SD)*	43.2 (16.1)	47.7 (17.8)	45.4 (17.1)
Age range 24-90			
Mechanism of injury, *n* (%)			
Fall	21 (27.3)	28 (37.8)	49 (32.5)
Traffic/motor vehicle accident	23 (29.9)	16 (21.6)	39 (25.8)
Exposure to mechanical force	15 (19.5)	15 (20.3)	30 (19.9)
Assault	17 (22.1)	13 (17.6)	30 (19.9)
Unknown	0	1 (1.4)	1 (0.7)
Number of TBI at eight year assessment, *n* (%)			
One	24 (31.2)	37 (50)	61 (40.4)
Two	23 (29.9)	18 (24.3)	41 (27.2)
Three	9 (11.7)	6 (8.1)	15 (9.9)
Four or more	18 (23.4)	12 (16.2)	30 (19.9)
Unknown	3 (3.9)	1 (1.4)	4 (2.6)
Ethnicity			
European	62 (80.5)	53 (71.6)	115 (76.2)
Māori	14 (18.2)	16 (21.6)	30 (19.9)
Other	1 (1.3)	5 (6.8)	6 (4.0)

Comparison group.

Comparison participants were recruited to match the age and gender of the TBI participants at their 8-year post-injury assessment. Participants were required to be aged 16 or over and TBI-free over their lifetime.

Participants for the comparison group were recruited via local advertisement through posters and social media and contacted the study by email if they were interested in taking part. Comparison group participants were also recruited via ResearchNow (a company hosting a New Zealand based panel of participants) as this method proved feasible in the BIONIC4You study. A study information sheet describing the study was emailed to potential participants. Exclusion criteria for the comparison group included any participant that had previously experienced a TBI in their lifetime. A series of exclusion questions were asked based on the Ohio State University TBI Identification Method (Corrigan & Bogner, 2007), which was used as an eligibility screen. Participants were asked five probe questions, such as '*have you ever injured your head or neck in a fall or from being hit by something (for example falling from a bike or horse, rollerblading, falling on ice, being hit by a rock), or by playing sports or on the playground.*' Each positive response was followed by two additional questions: '*did you lose consciousness*' and '*did you feel dazed or have a gap in your memory*'. If participants in the Comparison group indicated loss of consciousness or feeling dazed or confused after any incident, they were deemed ineligible and did not complete the study specific questionnaire.

Sample Characteristics.

The demographic characteristics of the TBI and Comparison groups are summarised in Table 2. The two groups were compared across four variables using a chi square for frequency counts and a t-test (or non-parametric equivalent). There were no significant

differences between the MTBI and Comparison group for age or gender. The age of those in the MTBI group ranged from 24-90 years, with a range of 24-71 years for the Comparison group. There was a significant difference in ethnicity between groups; both MTBI and Comparison groups were predominantly European (76.2% and 63.8%, respectively). The difference in ethnicity between the groups is due to the greater proportion of those in the Comparison group self- identifying as other ethnicities (31.9s%); additionally, Māori were less represented in the Comparison group (4.3%) than the MTBI group (19.9%).

As an indication of socioeconomic stats (SES), the occupation of the participant at the time of assessment was coded into major groups from Australian and New Zealand Standard Classification of Occupations (ANZSCO); professional (including managerial/technical), skilled (including non-manual, skilled manual, partly skilled) and other (including armed forces, unemployed/retired/student). Pearson's chi-squared test revealed no significant association between groups (MTBI or control) and ANZSCO group, suggesting the two groups were not significantly different in terms of SES, ($\chi^2(2) = .710$, $p = .701$).

Table 2

Participant characteristics

Demographic	Group		Significance of difference
	MTBI (*n*=151)	Comparison (*n*=211)	χ^2 or *t*
Age at eight year assessment, *M (SD)*	45 (17.1)	45 (15.2)	$t(360) = .286$, $p = .775$
Male gender *n* (%)	77 (51.0)	104 (49.2)	$\chi^2(1) = .102$, $p = .749$
Classified Ethnicity, *n* (%)			$\chi^2(2) = 55.572$, $p = .000$
European	115 (76.2)	134 (63.8)	
Māori	30 (19.9)	9 (4.3)	
Other	6 (4.0)	67 (31.9)	
ANZSCO major group *n* (%)			$\chi^2(2) = .710$, $p = .701$
Professional	47 (32.2)	77 (36.5)	
Skilled	30 (20.5)	40 (19.0)	
Other	69 (47.3)	94 (44.5)	

Materials and Standardised Measures

Participants completed a questionnaire about their current health, including subsequent TBIs and hospitalisations since their initial assessment. They were asked about any psychological or mood disturbance (Hospital Anxiety and Depression Scale – HADS and Post-traumatic Stress Disorder Checklist – PCL-C), cognitive functioning (Cognitive Complaint After Closed Head Injury – CCACHI), post-concussive symptoms (Rivermead Post Concussion Symptoms Questionnaire – RPQ), living and work arrangements, work limitations, substance use, current medications and community participation (The

Participation Assessment with Recombined Tools – Objective – Part O). The questionnaire utilised a set of standardised measures and a study-specific subset of the questionnaire assessments retained from the BIONIC and BIONIC4you studies to enable observation of recovery trajectories following injury after 8-years. To maximise participation, questionnaires could be completed online, via the Qualtrics platform, or during a face-to-face interview at the participant's home or other suitable location. The measures I used in my thesis are described below.

Study specific questionnaire.

Demographic and background information.

Participants were asked to report their age, gender, ethnicity, occupation of the main income earner in the household, living and financial situation, educational attainment, employment, their marital status and ethnicity.

TBI participants were also asked to report all hospital admissions during the study period (8-years), whether or not these were related to the TBI. The Ohio State University TBI Identification Method (Corrigan & Bogner, 2007) was used to identify recurrent TBI in the TBI group and as an eligibility screen for the comparison group.

*Ethnicity***.**

Each participant was provided with a list of different ethnicities from which they were asked to select one or more as appropriate. In line with the initial BIONIC study methodology (Feigin et al., 2013), in instances where several ethnicities were chosen a prioritisation system was used to obtain a single ethnicity and priority was given to Māori, Pacific peoples, Asian, Middle Eastern/Latin American/African, Other ethnicity and European. Standard procedures described by the Ministry of Health's Ethnicity Data

Protocols were used. These protocols are consistent with Statistics New Zealand's Statistical Standard for Ethnicity and identify the minimum standards that apply across the health and disability sector (Ministry of Health, 2017).

For the current study, participants were classified as European, Māori, or other. The category of 'other' was a heterogeneous group, with all other ethnicities aggregated due to the small number of individuals in the remaining ethnic categories.

Recurrent TBI.

The study questionnaire asked TBI group participants to recall any subsequent TBIs, and, to be consistent with the original BIONIC studies, TBI was defined using the WHO TBI definition criteria of "an acute brain injury resulting from mechanical energy to the head from external physical forces" (Carroll et al., 2004). Operational criteria for recurrent TBI included the presence of one or more of the following: (1) confusion or disorientation; (2) loss of consciousness; (3) post-traumatic amnesia; (4) other neurological abnormalities (e.g., seizure) as a result of an injury to the head. TBI recall was facilitated by the Ohio State University Traumatic Brain Injury Identification Method – OSU-TBI-ID (Corrigan & Bogner, 2007) which used eligibility screening questions designed to facilitate recollection of injuries or events that could result in a TBI or concussion, and has demonstrated predictive validity and reliability in self-report recall of lifetime TBI (Gardner, Langa, & Yaffe, 2017). Participants were asked five probe questions, such as '*have you ever injured your head or neck in a fall or from being hit by something (for example falling from a bike or horse, rollerblading, falling on ice, being hit by a rock), or by playing sports or on the playground.*' Each positive response was followed by two additional questions: '*did you lose consciousness'* and '*did you feel dazed or have a gap in your memory'*. This information was used to determine the number of recurrent injuries in the MTBI group and positive responses

were followed up with a phone interview by a member of the research team to collect further information about each incident, including the date and cause of injury.

A more detailed description of the psychological and mood disturbance measure used in this thesis, the Hospital Anxiety and Depression Scale, is provided below:

Hospital Anxiety and Depression Scale (HADS).

The Hospital Anxiety and Depression Scale (HADS) was completed by participants to assess their levels of depression and anxiety. The HADS is a brief (2-5 minute) 14 item self-report questionnaire, developed by Zigmond and Snaith (1983) to examine levels of depression and anxiety in non-psychiatric populations. It consists of an Anxiety subscale and a Depression subscale, with seven items related to each subscale (see Appendix A).

The Anxiety subscale assesses the participant's worries and fears with statements such as "I get sudden feelings of panic" and "I can sit at ease and feel relaxed". The depression subscale predominantly examines the participant's ability to feel pleasure (anhedonia) with statements such as "I look forward with enjoyment to things" and "I have lost interest in my appearance." Both the HADS Depression and Anxiety subscales were used in this current study, as an indication of the current mental health status of the participants.

The HADS responses are on a 4-point Likert scale, and scores range from 0 to 3 for each question. Respondents are asked to select the response that best described the extent to which each symptom had applied to them over the previous week, (for example, 'yes, definitely', 'yes, sometimes', 'no, not very much' and 'no, not at all'). The minimum score for each subscale is 0 and the maximum score is 21. Higher scores on both subtests suggest greater difficulty with symptoms of depression or anxiety. In the current study a cut-off of 11 for each subscale was used, as a score above 11 on either subscale is considered to indicate a

moderate to high presence of that particular mood disorder (Snaith, 2003). A score between 0 -7 on either subscale is considered to be within the normal range, while a score of 8 - 10 indicates the possibility of the respective mood disorder. The HADS has been widely used with TBI populations (Anson & Ponsford, 2006, Hawley, 2003) and is considered to perform well in screening for the presence of depression and anxiety disorders within the general population, (Bjelland, Dahl, Haug, & Neckelmann, 2002). The HADS has high internal consistency and sensitivity to change with good concurrent validity and correlations between the HADS and other commonly used questionnaires for depression and anxiety ranging from 0.60 and 0.80 (such as the State-Trait Anxiety Inventory, Beck Depression Inventory and the Symptom Checklist 90 Scale (Bjelland et al., 2002).

The responses to the individual items of the measure as well as total scores for anxiety and depression were used in the analyses.

Procedure

TBI group.

Contact information for TBI group participants (aged 16 or over and who had given permission to be contacted regarding future studies) was extracted from the BIONIC and BIONIC4you study databases. I was one of three Research Assistants collecting participant data for the BIONIC8 study and participants were contacted by telephone to assess their interest in the current study. I was assigned to contact 153 participants in total. A Patient Consent Form and Information Sheet was posted, emailed or faxed to those who expressed an interest (Appendix B). If willing to take part, participants were asked to print, sign, scan and email (or post/fax) their written consent form back to the research assistant or to provide verbal consent over the telephone (which was recorded). During the study we received approval to obtain consent online, and this method was used if preferred by the participant.

In these cases, a link to the online consent was emailed to the participant and once completed consents were submitted online direct to the Research Assistant. Once informed consent was obtained, participants were emailed a link to complete the study assessment questionnaire online (via the Qualtrics platform), or if preferred, a time was arranged to complete the assessment face-to-face at the participant's home or other suitable location. Participants were invited to ask questions about the study at any stage of the recruitment process. The timeline for contact to be made with the participant and for submission of the completed study questionnaire was within two months either side of the participant's initial TBI anniversary date.

If a participant could not be contacted, the researcher attempted to telephone at different times and days and contacted any alternative contact numbers available for the participant. If contact was still unable to be made, a letter (contact slip) was sent to the address provided asking the participant to contact the BIONIC8 team. If there was no response from this letter, the researcher checked the New Zealand telephone directory (White Pages) for listings that met the participant's criteria. Any potential listings were contacted and asked if they knew the participant in question. If this failed to locate the participant, the electoral roll was checked for that participant and contact slips were sent to all addresses found featuring the participant's name. If no listing met the participant's criteria from the electoral roll, the GP was contacted (if GP details were known). Finally, if this failed to enable contact with the participant, the participant's NHI number was checked for contact details by a research assistant based at the local hospital (Waikato). If contact was not made within two months of the anniversary date of the initial TBI, the participant was deemed to be un-contactable and further attempts to locate them ceased.

On completion of the questionnaire, participants were contacted again if they had indicated that they had experienced a recurrent head injury since the primary injury in

2010/11, or if they had been hospitalised at all during that time. Participants who scored in the abnormal range (>11) for the Hospital Anxiety and Depression Scale (HADS) were also contacted, informed and encouraged to seek medical advice. If they consented, this information was also passed to their General Practitioner for follow-up.

Comparison group.

Participants for the comparison group, recruited via advertising or through ResearchNow, were provided with a study information sheet via email and a link to the online consent form and questionnaire.

On completion of the questionnaire assessment, the TBI group participants received a $10 Warehouse store voucher as a 'thank-you' compensation. The comparison group participants recruited via ResearchNow were reimbursed at the standard rate of $7.50 for a completed questionnaire.

Statistical Analysis

Quantitative data analyses were undertaken using SPSS (version 25). There were no extreme outliers as identified by boxplot; however, a z-score analysis (standard deviations from the mean of > $\pm$3.29) identified 6 outliers in total, one of which was an outlier on two variables. These outliers were excluded from the analyses.

The first stage of data analysis examined the prevalence of depression and anxiety symptoms by gender within the TBI sample at each post-injury assessment (at 1-month, 12-months using existing data and 8-years). This included examining the total HADS scores for anxiety and depression subscales and identifying those scores that met the current study clinical cut-off score for depression and anxiety (>11). Within-subject repeated measures two-way ANOVA and post-hoc tests were conducted to determine if there were significant

changes in depression and anxiety mean scores over time in males and females for the MTBI group. To test for an association between gender and a score exceeding the clinical cut-off score for depression and anxiety across time, a chi-squared test was carried out with Fisher's Exact test reported as cell sizes were small. For each of these tests, only individuals with data on the scale of interest at all assessment points were included.

The second stage of data analysis involved evaluating between-group differences for depression and anxiety symptoms after 8-years by gender and this was examined using parametric tests (2 x 2 between group ANOVA) and non-parametric techniques (chi-squared test) when the data was categorical. Effect sizes were calculated using Cohen's 'd' for continuous variables where .2 is a small effect size, .5 medium and .8 large (Cohen, 1988). Results were summarised using means (95% confidence intervals [CI]) and standard deviations.

Bonferroni correction was used to account for the multiplicity of tests of a given outcome. Inferences were based on a 5% significance level and two-sided alternative $\alpha = .05$.

Results

The results are presented in two parts. Firstly, recovery trajectories and clinical (or abnormal) ratings of depression and anxiety symptomology (based on the HADS measurement tool) were examined in males and females at 1-month, 12-months and 8-years post-MTBI (Aim 1). Secondly, gender differences in depression and anxiety outcomes for adults eight years after experiencing MTBI were investigated and compared to the TBI-free group (Aim 2). For each section, depression symptoms are considered first, followed by anxiety symptoms.

Recovery Trajectories in Males and Females post-MTBI (Aim1)

Depression.

In order to track changes in depression scores over time, the first stage of the data analysis examined the total score of depression symptoms by gender within the TBI sample at each assessment (at 1-month, 12-months and 8-year follow-up).

Figure 2 shows that the pattern of scores in men and women was similar over time and that the females had higher scores at each time point. For both men and women the depression scores decreased at a similar rate between 1-month and 12-months post-injury. These scores then increased, again at a similar rate, between 12-months and 8-years. The mean scores at each time point were within the normal range (< 8) and below the cut-off score for clinically significant symptoms (>11).

The sample for repeated measures analysis consisted of 90 people (48 male, 42 female) as all other participants had missing data at one or more time points.

A repeated-measure two-way ANOVA was conducted to examine the changes in depression scores over time in males and females. The interaction between time and gender was not statistically significant $F(2,176) = .823$, $p = .441$, $\eta^2 = .009$.

The main effect of time, however, showed that there was a statistically significant difference in depression scores across time points, $F(2, 176) = 5.487$, $p = .005$, partial $\eta^2 = .059$. Bonferroni corrected post-hoc test revealed that the increase in scores between 12-months and 8-years was statistically significant ($p = .002$). The decrease in scores between 1-month and 12-months was not statistically significant ($p = .054$) and neither was the change in scores between 1-month and 8-years ($p = 1.000$).

The main effect of gender showed a statistically significant difference in mean depression scores between males and females, $F(1,88) = 4.050$ $p = .047$, partial $\eta^2 = .044$ with females having the highest scores.

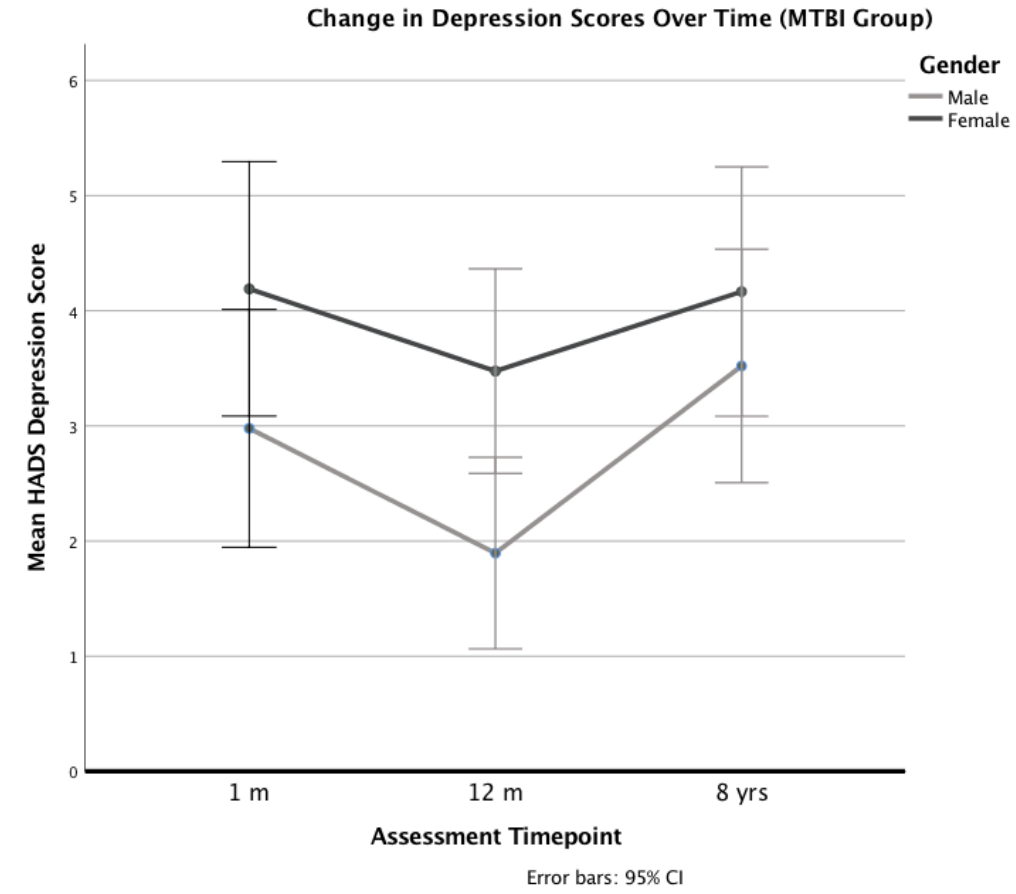

Figure 2. Mean HADS Depression Scores over time by gender

Anxiety.

In order to track changes in anxiety scores over time, examination of the prevalence of anxiety symptoms by gender within the TBI sample at each assessment (at 1-month, 12-months and 8-year follow-up) showed that the scores for both genders followed the same pattern across the three time points (Figure 3). The females had higher scores at each time point. For both men and women the anxiety scores decreased from 1-month, where the gender difference was least pronounced, to 12-months post-injury, and with a slightly greater rate of decline in scores for men. The gender difference was most pronounced at 12-months, at which point anxiety scores stabilised up to the 8 year point for both genders with a slight

decline for women's scores at the 8 year point. The mean scores at each time point, which were higher overall than the mean scores for depression, were within the normal range (< 8) and below the cut-off score for clinically significant symptoms (>11).

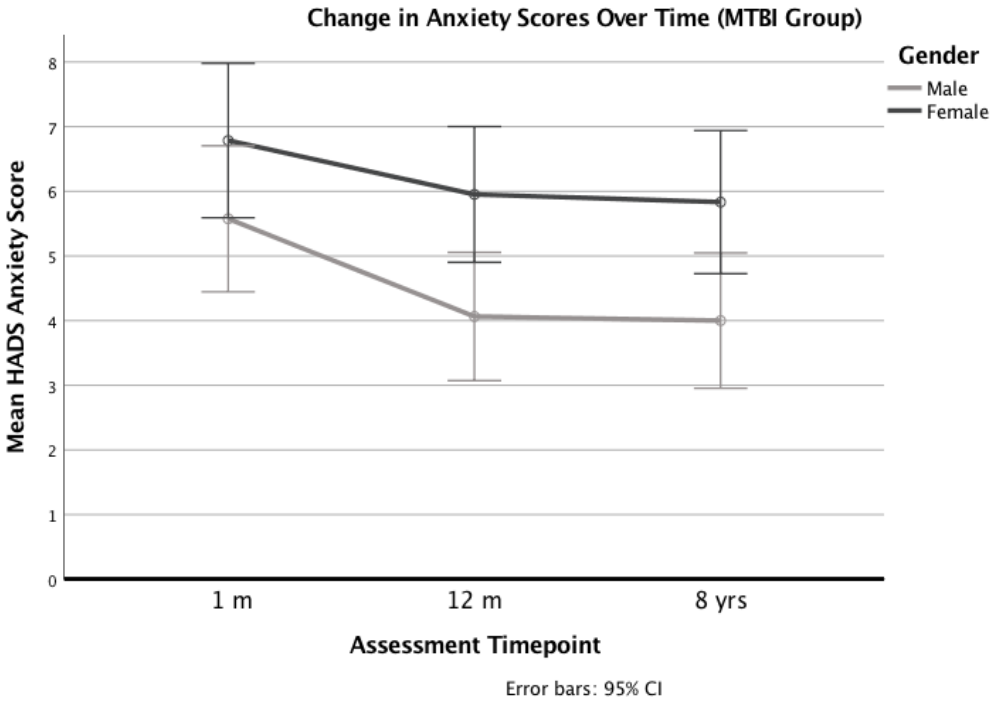

Figure 3. Mean HADS Anxiety Scores over time by gender

The sample for repeated measures analysis consisted of 89 people (47 male and 42 female) as all other participants had missing data at one or more time points. A two-way repeated measure ANOVA was conducted to examine changes in anxiety scores over time in males and females. The interaction between time and gender was not statistically significant, $F(2,174) = .447$, $p = .640$, $\eta^2 = .005$.

The main effect of time, however, showed a statistically significant change in mean anxiety scores across the three time points, $F(2, 174) = 6.280$, $p = .002$, partial $\eta^2 = .067$. Bonferroni corrected post-hoc tests found that the decrease in mean anxiety scores between 1-month and 12-month and between 1-month and 8-years' post-injury was statistically

significant (p = .022 and p = .006, respectively). The very slight decrease in anxiety scores between the 12-month and 8 year point was not statistically significant (p = 1.000).

The main effect of gender showed that there was a statistically significant difference in mean anxiety scores between males and females $F(1,87) = 6.948$, p = .010, partial η^2 = .074 with females having the highest anxiety scores.

Clinical Range Scores.

Mean score analysis can mask the number of people who have scores within the clinical range for depression and anxiety which indicates a higher degree of symptom-reporting. Therefore, to ascertain the number of people whose scores met the clinical cut-off for depression and anxiety across time, the frequencies, and then association with gender, were explored.

The number of participants exceeding the clinical cut-off score for depression (>11 on the HADS) at each of the three assessment periods was calculated. Figure 4 shows that the percentage of total TBI participants that exceeded the clinical cut-off score for HADS depression (>11) was greatest at the one month and 8 year assessment points (5.8% and 6.1% respectively). The percentage of TBI group males and females exceeding cut-off score at one month was equal (2.9%) and at 12-months and 8-years there was a greater percentage of females exceeding cut-off score for depression (2.5% of females vs 0.8% of males and 4.1% of females vs 2% of males, respectively). The 8 year point saw the highest percentage of females exceeding cut-off score and the percentage of men exceeding cut-off score was highest at the one-month point. The lowest percentage of both males and females exceeding cut-off score was at the 12-month point.

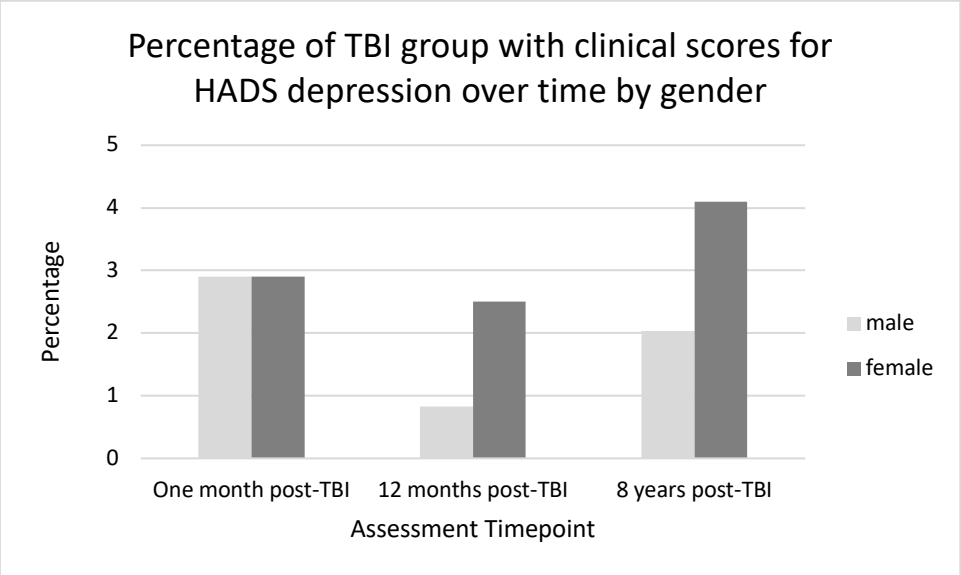

Figure 4. Percentage of TBI group with scores in the clinical range for HADS depression over time by gender.

To determine if the same people exceeded cut-off score across timepoints, all participant scores were reviewed. An analysis of TBI participants' depression scores over time showed that 11% of participants (10 out of a total of 90) had one or two reports of a clinical score for depression across the 8 year assessment timeframe. Eight participants had one report (four of these were reported at 1-month, two cases at 12-months and two cases at 8-years) and two participants (20% of those reporting a clinical score) had two reports of clinical scores for depression (two cases at 1-month, one case at 12-months and one case at 8-years). No participants reported depression scores above the clinical cut-off at all three timepoints.

To test for an association between gender and exceeding the clinical cut-off score for depression at the one month, 12-month and 8-year assessment dates, a chi-squared test was carried out with Fisher's Exact test reported, given the small cell sizes. There was no statistically significant association between gender and exceeding clinical cut-off scores for

depression over time: one month, $\chi^2(1) = .059$, $p = 1.000$; 12-months, $\chi^2(1) = 1.069$, $p = .365$ or 8-years, $\chi^2(1) = 1.245$, $p = .318$.

The number of participants exceeding the clinical cut-off for anxiety (>11 on the HADS) at each of the three assessment periods was identified. Figure 5 shows that the percentage of total participants exceeding HADS anxiety clinical cut-off scores was greatest at the one month (6.73% female, 3.85% male) and 12-month assessment points (6.61% female, 0.83% male) and at 8-years the proportion was 4.11% female and 1.37% male. At each time point, there was a greater percentage of females than males exceeding the cut-off score. The percentage of males was highest at one month post-TBI, lowest at 12-months and increased slightly at 8-years. The percentage of females was greatest at one month and then declined at both 12-months and, more substantially, at 8-years.

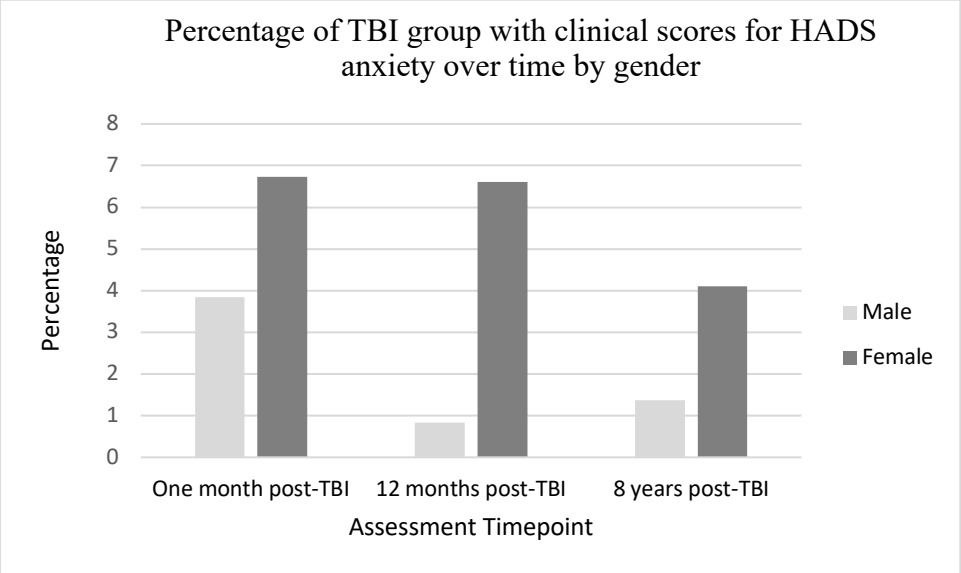

Figure 5. Percentage of TBI group with scores in the clinical range for HADS anxiety over time by gender.

An analysis of TBI participants' anxiety scores over time showed that over 15% of participants (14 out of a total of 89) had one or two reports of a score in the clinical range for

anxiety across the 8 year assessment timeframe. Ten participants had just one report (eight cases at 1-month, one at 12-months and one at 8-years) and four participants (29% of those reporting a clinical score) had two reports of anxiety scores within the clinical range up to the 8 year assessment point (three cases at 1-month, three cases at 12-months and two cases at 8-years). No participants had scores in the clinical range for anxiety across all three timepoints.

To test for an association between gender and a score which exceeded the clinical cut-off score for anxiety at the one month, 12-month and 8 year assessment dates, a chi-squared test was conducted with Fisher's Exact test reported, given the small cell sizes.

There was no statistically significant association between gender and the proportion of participants exceeding the clinical cut-off for anxiety at the one month or 8-year assessment points, $\chi^2(1) = 1.689$, $p = .217$ and $\chi^2(1) = 2.356$, $p = .158$ but there was a statistically significant association between gender and proportion exceeding the clinical cut-off at 12-months, $\chi^2(1) = 6.008$, $p = .017$, $\varphi = .223$, $p = .014$, with a much higher proportion of females reporting scores within the clinical range for anxiety.

Co-morbid depression and anxiety.

At the 1-month assessment, four participants had a score in the clinical range for both depression and anxiety; at the 12-month assessment, one participant had a score in the clinical range for both and at the 8 year assessment, two participants had a score in the clinical range for both.

Summary

There was a statistically significant increase in depression scores from 12-months to 8-years and a statistically significant decrease in scores for anxiety from 1- to 12-months and from 1-month to 8-years. Females scored significantly higher than males for both depression

and anxiety overall. There were no significant gender differences in the changes in mean HADS scores for depression or anxiety over time.

The number of people whose scores exceeded the clinical cut-off score (>11) for depression and anxiety across time followed the same pattern as the mean scores for males and females. Females generally had a much higher percentage of scores in the clinical range for depression and anxiety. There was no significant association between gender and the percentage of participants who exceeded the clinical cut-off score, except for anxiety at the 12-month point, with a much higher percentage of females scoring in the clinical range. However, the strength of this association was low. Most cases which exceeded the clinical cut-off scores for depression or anxiety were single cases over the whole assessment period and no participants reported a clinical range score at each assessment timepoint.

Gender Differences in HADS Scores for Depression and Anxiety between MTBI and Comparison Groups (Aim 2)

Depression. Figure 6 shows that, overall, the TBI group had higher scores for depression than the comparison group at the 8 year post-injury point. Males in the TBI group had higher depression scores than males in the comparison group. Females in the TBI group had higher depression scores than females in the comparison group. In both groups, females had higher depression scores than males overall.

A 2 x 2 between-group ANOVA was carried out to analyse the differences in HADS depression scores at 8 yrs post-injury, by group (TBI and Comparison) and gender.

There was no statistically significant interaction between the group membership and gender on the HADS scores for depression $F(1,352) = .059$, $p = .809$, $\eta^2 = .003$. There was no statistically significant main effect of gender on the HADS score for depression, $F(1,352)$

= 2.010, p = .157, η^2=.001 nor was there a statistically significant main effect of group on the HADS score for depression, $F(1,352) = 3.306$, $p = .070$, η^2=.005.

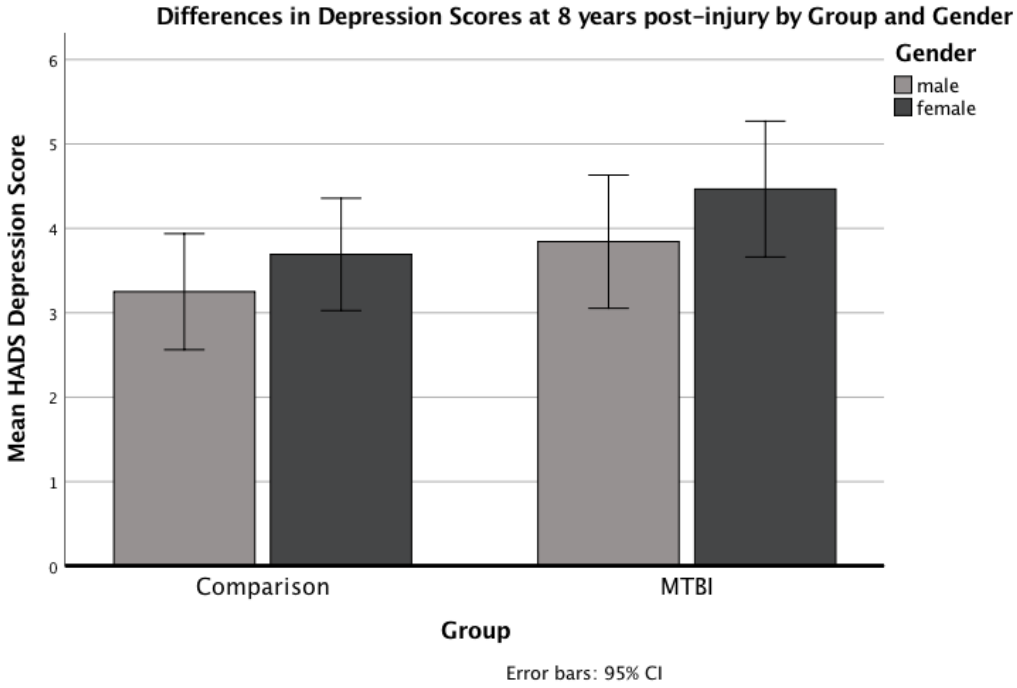

Figure 6. Graph of the interaction of gender and group for HADS Depression Scores

Anxiety.

Figure 7 shows that, overall, the comparison group had higher scores for anxiety than the TBI group at the 8 year post-injury point. Males in the comparison group had higher anxiety scores than males in the TBI group. Females in the TBI group had slightly higher anxiety scores than females in the comparison group. In both groups, females had higher anxiety scores than males overall.

A 2 x 2 between-group ANOVA was carried out to analyse the differences in anxiety scores at 8 yrs post-injury, by group (TBI and Comparison) and gender.

There was no statistically significant interaction between the group membership and gender on the HADS scores for anxiety $F(1,350) = .505$, $p = .478$, η^2=.001, nor a significant

main effect of group , F(1,350) = .089, p = .766, η^2=.000. There was, however, a statistically significant main effect of gender for the HADS score for anxiety after 8-years, F(1,350) = 8.725, p = .003, η^2=.024 showing a statistically significant difference in anxiety scores between genders. In both groups, females had higher anxiety scores than males overall.

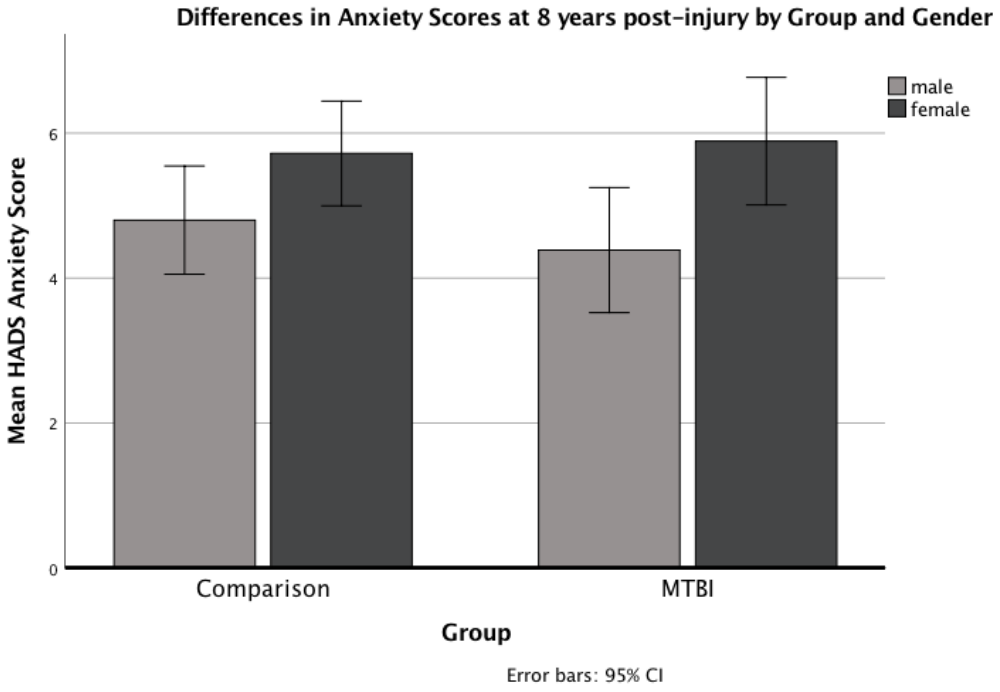

Figure 7. Graph of the interaction of gender and group for HADS Anxiety Score

Clinical Range Scores.

To investigate relationships between group (MTBI or Comparison), gender and clinical range HADS scores for anxiety and depression, participants who exceeded the clinical cut-off score for depression or anxiety (>11) were identified.

As shown in figure 8, the percentage of the comparison group with HADS depression scores in the clinical range was lower than that of the MTBI group overall with a much

greater proportion of females than males, in both groups, with scores in the clinical range at assessment.

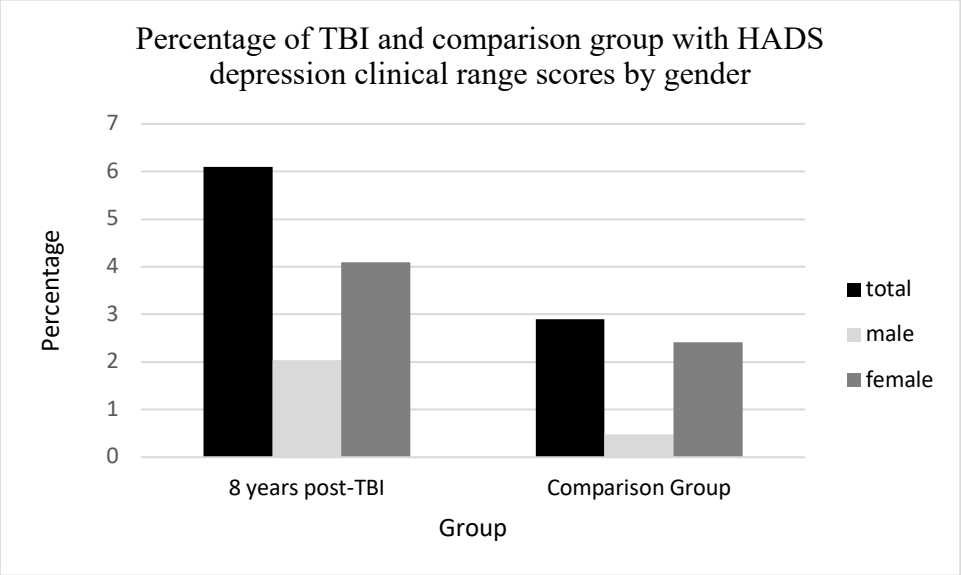

Figure 8. The percentage of TBI and comparison group with scores in the clinical range for depression, by gender

As shown by Figure 8, within the MTBI group, 6% of participants had scores within the clinical range for depression at 8-years, compared to 2.9% of the comparison group.

A chi-squared test for association was conducted between group and scores within the clinical range for depression. All expected cell frequencies were greater than five. There was no statistically significant association between group and scores within the clinical range for depression, $\chi^2(1) = 2.119$, $p = .145$. The same test was used to identify associations between gender and scores within the clinical range for depression. There was no statistically significant association between gender and scores within the clinical range for depression, $\chi^2(1) = 3.249$, $p = .071$.

As shown in figure 9, the percentage of the comparison group with HADS anxiety scores in the clinical range had a similar pattern to that of the MTBI group, but was slightly

less overall. The comparison group had a greater proportion of females than males with scores in the clinical range at assessment as did the MTBI group.

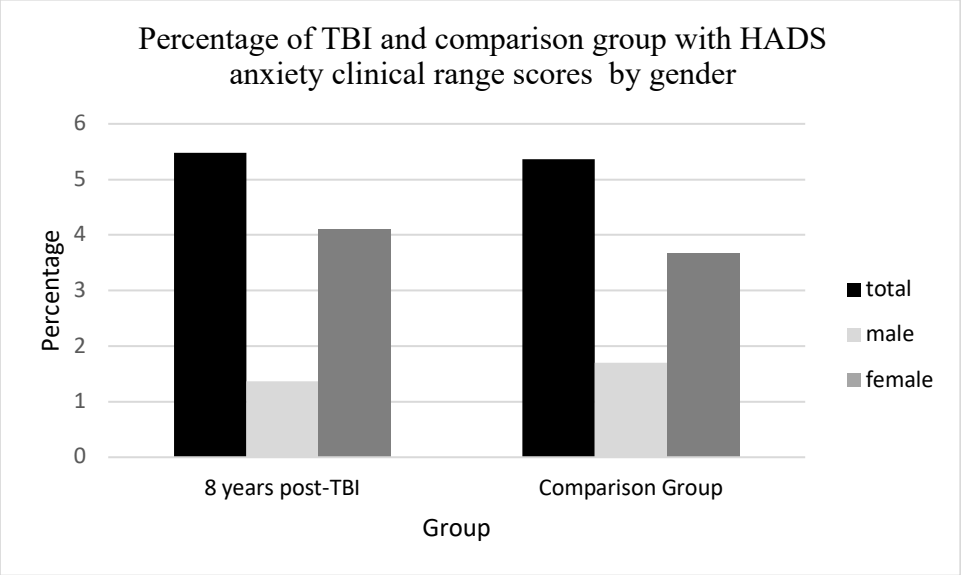

Figure 9. The percentage of TBI and comparison group with scores in the clinical range for anxiety, by gender

As shown by figure 9, within the MBTI group, 5.4% of participants had scores in the clinical range for anxiety, compared to 5.3% of the comparison group.

A chi-square test for association was conducted between group and scores in the clinical range for anxiety. All expected cell frequencies were greater than five. There was no statistically significant association between group and scores in the clinical range for anxiety, $\chi^2(1) = .003$, $p = .958$. The same test was used to identify associations between gender and scores in the clinical range for anxiety. All expected cell frequencies were greater than five. There was no statistically significant association between gender and scores in the clinical range for anxiety, $\chi^2(1) = 2.561$, $p = .110$.

Group and Gender Differences in Symptom Reporting at HADS Item Level

The current analysis has focused on total HADS scores for both depression and anxiety subscales. To determine whether different depression and anxiety symptoms were endorsed by each group and by which gender, analysis of the number of endorsements for each symptom of at least moderate severity, was carried out on the 8-year assessment data.

Figure 10 depicts the percentage of participants in each group (8-years post-MTBI and comparison group), by gender endorsing each depression symptom, to at least a moderate severity. The most notable gender differences were in relation to items "I still enjoy the things I used to enjoy" with almost twice the number of males in the MTBI group reporting moderate to severe symptoms than males in the comparison group. With the item " I feel as if I am slowed down" both groups had a much higher proportion of females than males who indicated moderate to severe symptoms and the MTBI group had the highest proportion overall and there were twice as many females than males reporting moderate-severe symptoms for this item in the comparison group (22 females vs.11 males). The MTBI group had almost twice the number of people, and more than twice the number of males, scoring in the moderate to severe range for the item "I look forward with enjoyment to things" than in the comparison group. The number of participants scoring depression items to a moderate-severe level are displayed in Table C1 in the Appendix C.

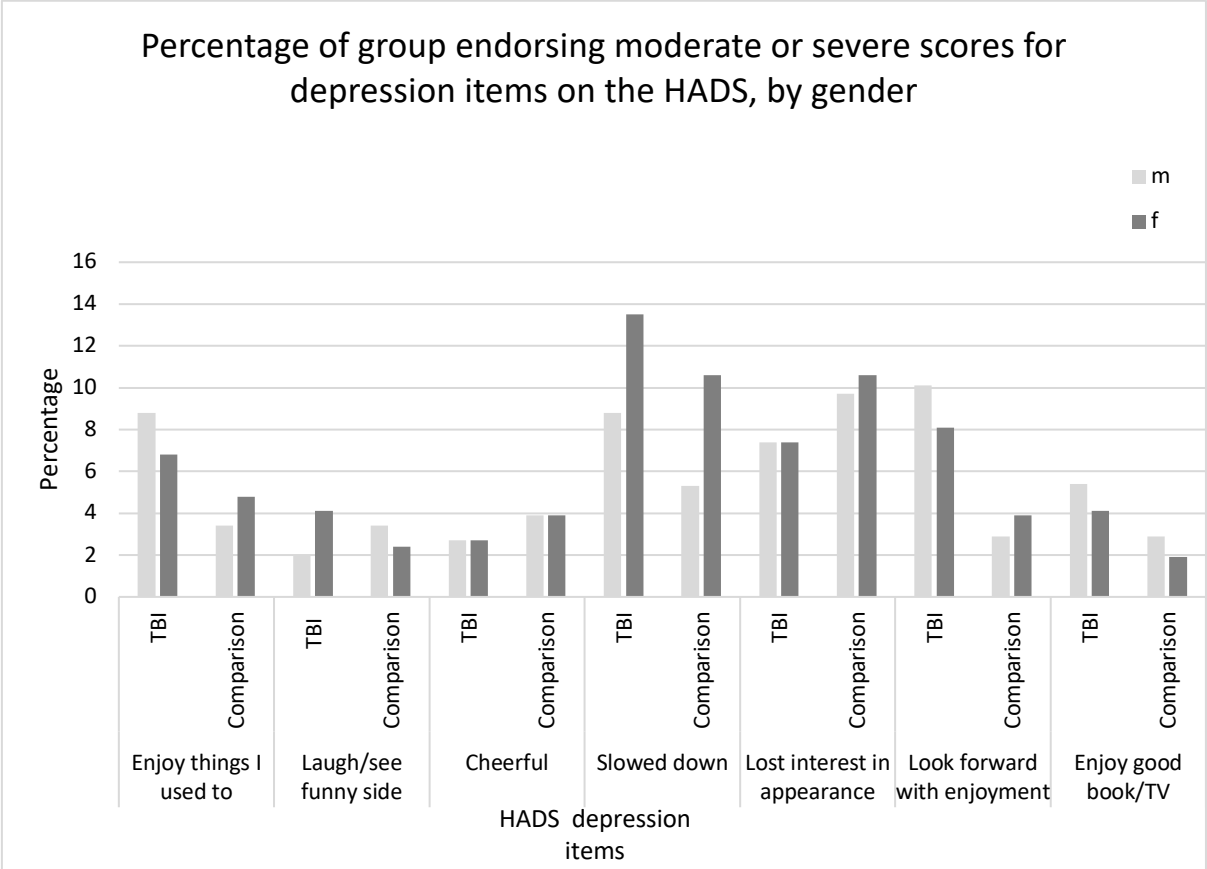

Figure 10. The percentage of TBI and comparison group endorsing moderate to severe depression items, by gender

Mean scores for questions on the HADS depression subscale by group and gender– 8 year assessment.

Figure 11 shows the mean scores of depression subscale items endorsed by TBI and comparison groups, by gender. The majority of depression items followed the same pattern of scores with the TBI group having higher mean scores for each item than the comparison group (the exception was the item "I have lost interest in my appearance" which was scored slightly higher by the comparison group, especially by males). Females had higher scores than males in both groups for most items, except for the items "I still enjoy the things that I used to" and "I can enjoy a good book or radio/TV program" where males in the MTBI group

scored slightly higher than females in the MTBI group and higher than the males in the comparison group.

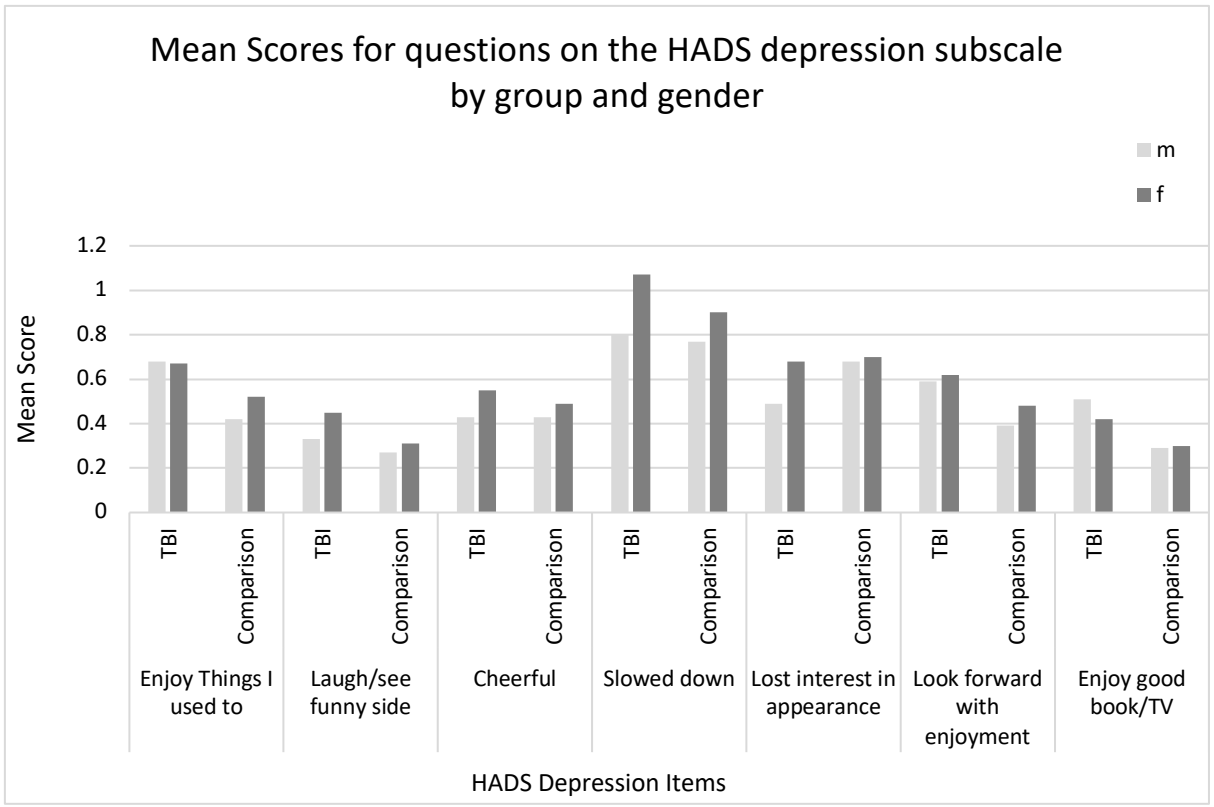

Figure 11. Mean scores of depression subscale items endorsed by TBI and comparison groups, by gender.

A 2 x 2 between-group univariate analysis (ANOVA) was carried out to analyse the gender and group differences in mean scores between the 8-year post-TBI and comparison groups for each depression subscale item. A summary of the results can be found in Table 3 for depression and Table 4 for anxiety. The F-values are included in Appendix D. There was no statistically significant group/gender interaction for depression item mean scores. There were no main effects for scores on items "I can laugh and see the funny side of things", "I feel cheerful", or "I have lost interest in my appearance" (see Table D1 in Appendix D).

There was a significant main effect of group on the items "I still enjoy the things I used to enjoy", $F(1,352) = 6.355$, $p = .012$, $\eta^2 = .018$, "I look forward with enjoyment to things", $F(1,352) = 4.451$, $p = .036$, $\eta^2 = .012$, and on the item "I can enjoy a good book or radio or TV program", $F(1,352) = 5.797$, $p = .017$, $\eta^2 = .016$, with significantly higher scores on these items from the TBI group. There was a significant main effect of gender on the item "I feel as if I am slowed down", $F(1,352) = 5.295$, $p = .022$, $\eta^2 = .015$, with significantly higher scores on this item from females in both groups.

Table 3

Summary of gender and group differences in mean scores for HADS depression subscale items

	TBI (8-years)				Comparison				F Statistic		
Item	M	SD	F	SD	M	SD	F	SD	Group * gender	Group	Gender
Enjoy things I used to	.68	.852	.67	.783	.42	.654	.52	.769		√	
Laugh/see funny side	.33	.681	.45	.646	.27	.617	.31	.650			
I feel cheerful	.43	.596	.55	.602	.43	.671	.49	.635			
Feel slowed down	.80	.880	1.07	.839	.77	.694	.90	.788			√
Lost interest in appearance	.49	.872	.68	.864	.68	.863	.70	.838			
Look forward/enjoyment	.59	.867	.62	.793	.39	.665	.48	.718		√	
Enjoy good book/TV	.51	.757	.42	.725	.29	.608	.30	.633		√	

Figure 12 depicts the percentage of participants reporting moderate or severe anxiety symptoms 8-years after mTBI, expressed as percentages of the group, by gender. A similar pattern is followed by both genders in the MTBI and comparison groups. In the MTBI group the item "sudden panic" shows a much higher frequency of females reporting this symptom than males, compared to the comparison group. Predominantly more females than males report moderate to severe symptoms overall in both groups and the pattern of frequency is similar to that of the mean scores except for "sit at ease/relax" and "butterflies" which have a low frequency of scores from males compared to females but the mean scores are more comparable between males and females in both groups. The number of participants scoring anxiety items to a moderate-severe level are displayed in Table C2 in Appendix C.

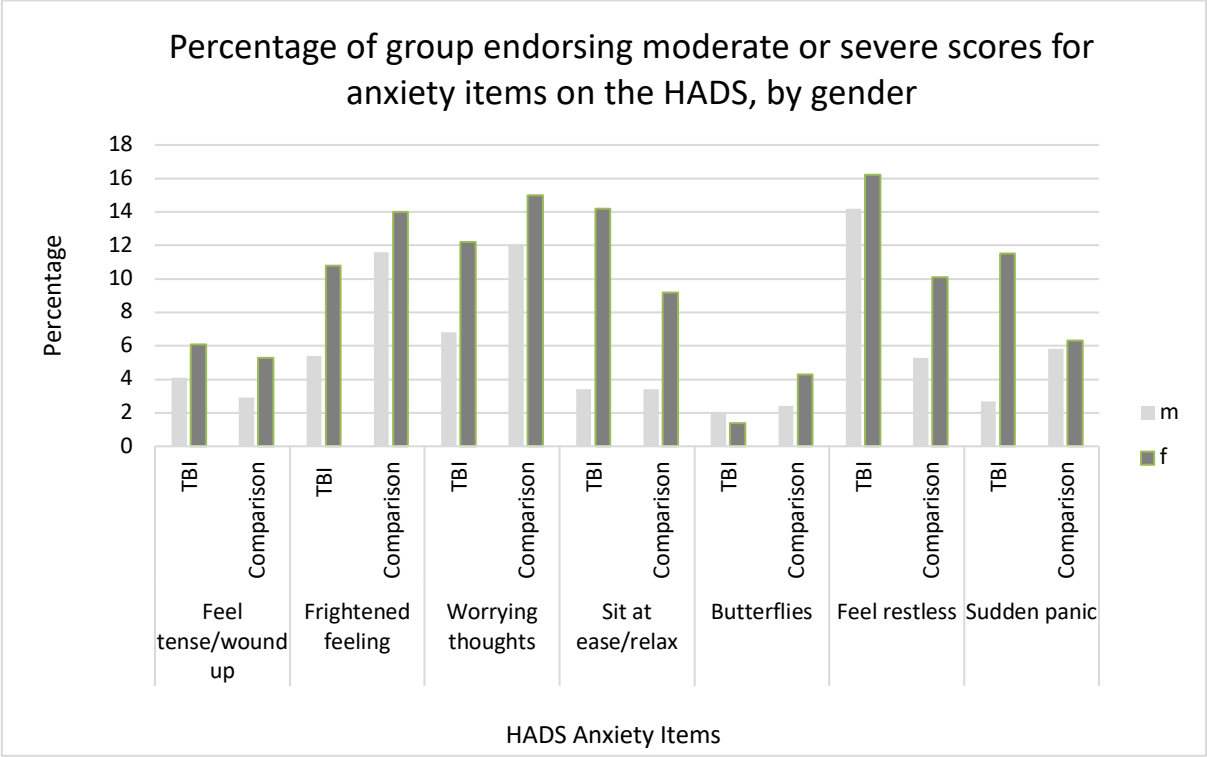

Figure 12. The percentage of TBI and comparison group endorsing moderate to severe anxiety items, by gender.

Mean scores for questions on the HADS anxiety subscale by group and gender– 8 year assessment.

As can be seen in figure 13, most of the total mean scores for items on the HADS anxiety subscale were higher in the comparison group than the MTBI group except for three items – "I can sit at ease and feel relaxed", " I feel restless as if I have to be on the move" and "sudden panic". For all items, females scored higher than males in both groups.

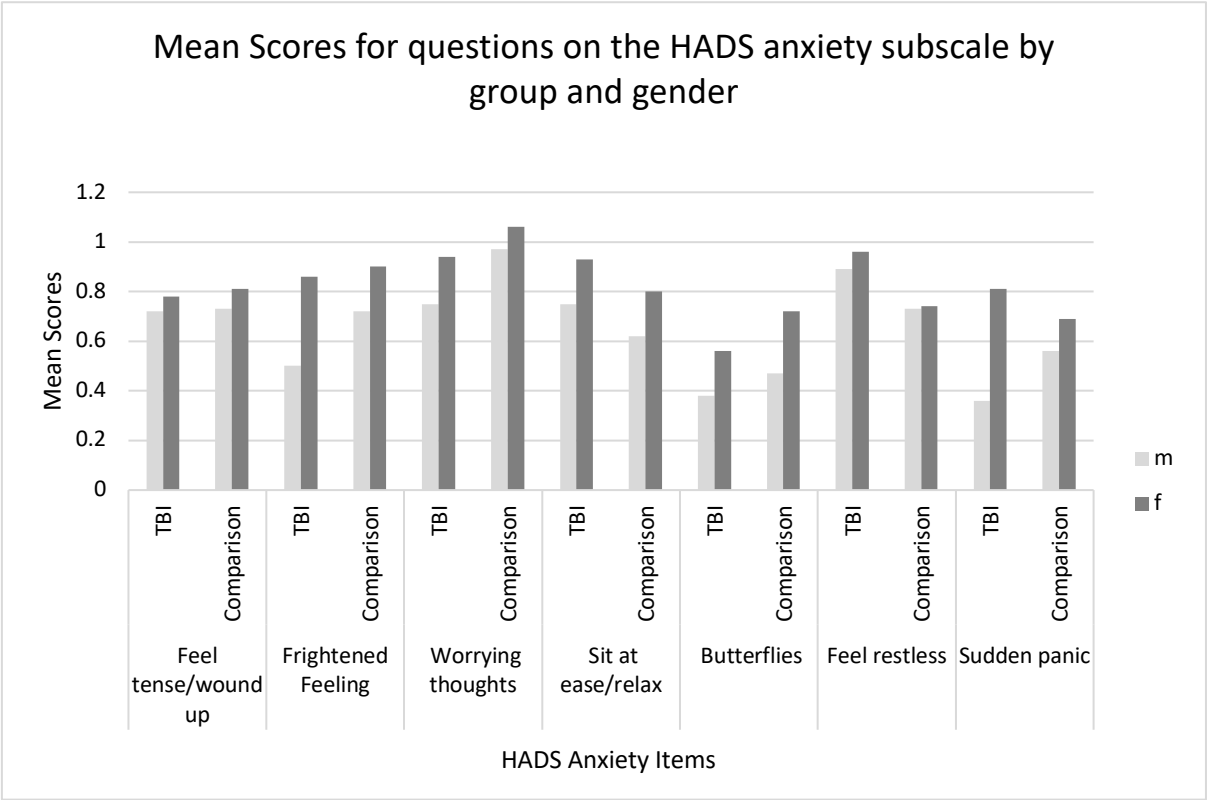

Figure 13. Mean scores of anxiety subscale items endorsed by TBI and Comparison groups, by gender.

A 2 x 2 between-group univariate analysis (ANOVA) was carried out to analyse the gender and group differences in mean scores between the TBI and comparison groups for each anxiety subscale item (8-years post-injury). The results can be seen in Table 4.

There was no statistically significant interaction or main effects for scores on items "I feel tense or wound up" or "Worrying thoughts go through my mind" (see Table D2 in

Appendix D). There was a statistically significant interaction between the group membership and gender on the mean score for the item "I get sudden feelings of panic", $F(1,352) = 4.094$, $p = .044$, $\eta^2 = .011$, with females in the MTBI group scoring significantly higher and males scoring significantly lower than those in the comparison group. There was significant main effect of group on the item "I feel restless as if I have to be on the move", $F(1,352) = 5.132$, $p = .024$, $\eta^2 = .014$, with significantly higher scores on this item from the MTBI group. There was a significant main effect of gender on the items "I get a sort of frightened feeling as if something awful is about to happen", $F(1,352) = 8.765$, $p = .003$, $\eta^2 = .024$, "I can sit at ease and feel relaxed", $F(1,352) = 5.796$, $p = .017$, $\eta^2 = .016$, "I get a sort of frightened feeling like butterflies in the stomach", $F(1,352) = .263$, $p = .002$, $\eta^2 = .028$, and "I get sudden feelings of panic", $F(1,352) = 13.545$, $p = .000$, $\eta^2 = .037$, with significantly higher scores on these items from females in both groups.

Table 4

Summary of gender and group differences in mean scores for HADS anxiety subscale items

	TBI (8-years)				Comparison				*F* Statistic		
Item	M	SD	F	SD	M	SD	F	SD	Group * gender	Group	Gender
Feel tense/wound up	.72	.685	.78	.692	.73	.566	.81	.661			
Frightened feeling	.50	.683	.86	.871	.72	.877	.90	.910			√
Worrying thoughts	.75	.790	.94	.918	.97	.948	1.06	.867			
Sit at ease/relax	.75	.569	.93	.805	.62	.648	.80	.770			√
Butterflies	.38	.610	.56	.645	.47	.594	.72	.670			√
Feel restless	.89	.842	.96	.904	.73	.679	.74	.769		√	
Sudden panic	.36	.667	.81	.861	.56	.756	.69	.679	√		√

Summary.

For depression, the MTBI group had higher scores than the comparison group overall and, within both groups, females scored higher than males. However, there were no statistically significant differences in mean HADS scores between groups or genders for depression at the 8-year point post-MTBI.

In contrast, for anxiety scores, the comparison group had higher scores than the TBI group overall and, within both groups, females scored higher than males. There were no statistically significant differences in mean HADS scores between groups for anxiety at the 8

year point post-MTBI. Female anxiety scores from both groups were significantly higher than males.

In terms of HADS scores which exceeded the clinical cut-off score for depression, more TBI participants scored within the clinical range than those from the comparison group (6% compared to 2.9%). Over 73% of those participants exceeding the clinical cut-off score were female. There was no association between group membership and exceeding clinical cut-off score and there was no association between gender and exceeding clinical cut-off score for depression.

For anxiety, the proportion of participants exceeding clinical cut-off was similar for both the TBI and comparison groups (5.4% compared to 5.3% respectively). Of those within the clinical range for anxiety, over 68% were female. There was no association between group membership and exceeding clinical cut-off score for anxiety and there was no association between gender and exceeding clinical cut-off score for anxiety.

With regard to depression symptom items, there were no significant gender differences in item scores between groups. Mean scores for the items “I still enjoy the things I used to enjoy”, “I look forward with enjoyment to things” and “I can enjoy a good book or radio or TV program” were significantly higher in the MTBI group but with no differences between genders. For both groups females scored significantly higher than men on the item “I feel as if I am slowed down”.

For anxiety items, there was a significant gender difference between groups for the score for the item “I get sudden feelings of panic” in that females in the MTBI group had significantly higher mean scores than males. However, the effect size, or proportion of variance attributed to group and gender was small. For the item “ I feel restless as if I have to be on the move”, the MTBI group scored significantly higher than the comparison group.

For the items “ I get a sort of frightened feeling as if something awful is about to happen”; “I can sit at ease and feel relaxed”, “ I get a sort of frightened feeling like ‘butterflies’ in the stomach” and “I get sudden feelings of panic”, females scored significantly higher than males, regardless of group membership.

Discussion

This thesis investigated the gender differences in depression and anxiety over time following a mild traumatic brain injury, using the Hospital Anxiety and Depression Scale. This overall aim was two-fold: the first was to identify gender differences in the recovery trajectory of depression and anxiety over 1-month, 12-month and 8-year timepoints post-injury. The second was to investigate the gender differences in depression and anxiety scores between a group of MTBI subjects (8-years post-injury) and a group of participants who were TBI-free, by comparing Hospital Anxiety and Depression Scale (HADS) scores and self-reported symptoms.

Among the MTBI participants in the current study, female depression and anxiety scores were significantly higher than males across the assessment periods. For both males and females, depression scores significantly increased between 12-months and 8-years and, conversely, anxiety scores decreased significantly between 1-month and 12-months and between 1-month and 8-years post-injury. For both depression and anxiety the mean scores at each time point fell within the normal (non-clinical) range, and the average recovery trajectory did not differ between males and females over time. Within the MTBI group the number of people scoring within the clinical range for depression followed the same pattern as the mean scores. For depression, males and females were equally as likely to obtain clinical range scores across all assessment timepoints. Similarly, for anxiety, at the 1-month and 8-year follow-up males and females were equally as likely to obtain a clinical range score; however, at 12-months post-injury, females were more likely than males to experience anxiety at the clinical severity level. However, this was not apparent in the total mean score analysis. Most people who met clinical levels for depression or anxiety only did so on one occasion across the whole assessment period.

The group comparisons at 8-years post-injury between the MTBI and TBI-free groups found no significant differences in average scores for depression and anxiety and no gender differences between groups. In addition, there was no significant relationship found between group or gender and obtaining a clinical-range score which means that females in either group were no more likely than males to report clinical severity symptoms for depression or anxiety. However, females overall in both groups had significantly higher mean anxiety scores than males at 8-year follow-up though these average scores were not within the clinical range.

When evaluating individual symptom items there were no gender differences in depression item scores between groups. The MTBI group scored significantly higher scores than the TBI-free group on the depression items: “I still enjoy the things I used to enjoy”, “I look forward with enjoyment to things“ and I can enjoy a good book or radio or TV program”. In both groups, females had significantly higher scores on the item “I feel as if I am slowed down” than males.

With regard to anxiety items, there was a significant, but small, difference between how females and males in the MTBI group scored for the item “I get sudden feelings of panic” compared to the TBI-free group. Females in the MTBI group scored significantly higher and males scored significantly lower. Overall in both groups, females scored significantly higher than males on this item but the difference in scores between genders was particularly marked in the MTBI group. The MTBI group had significantly higher scores on the anxiety item “I feel restless as if I have to be on the move” than the TBI-free group. In both groups, females also scored significantly higher than males on the items “I get a sort of frightened feeling as if something awful is about to happen, “I can sit at ease and feel relaxed”, I get a sort of frightened feeling like butterflies in my stomach”.

Gender Differences in Depression and Anxiety over Time – MTBI group

The results of the current study found no difference between males and females in the course of depression and anxiety up to 8-years' post-injury although females experienced increased depression and anxiety compared to males across the three follow-up assessment periods. This is consistent with previous research that has found that, overall, females have higher levels of post-MTBI depression and anxiety than males (Barker-Collo et. al., 2018; Farace & Alves, 2000; Merritt, Padgett & Jack, 2019; Scholten et al., 2016) and that female gender is an independent predictor of depression at 10 weeks and 1 year following a TBI (Singh et al., 2019). The pattern observed in other shorter follow-up studies remains consistent in the current study up to eight years after injury: in Barker-Collo et al., (2018), for example, females produced significantly higher scores for both anxiety and depression at baseline and 6-months post-MTBI and for anxiety at 12 and 48-months post-injury. These reports are also consistent with the finding that in the general population females have a higher prevalence of both depression and anxiety than males (National Alliance on Mental Illness, 2016; Faravelli et al., 2013).

In terms of whether more females or males scored in the clinical range for depression and anxiety across timepoints, the current study found that for depression males and females were equally as likely to report more severe symptoms across the timepoints. For anxiety, after 1-month and 8-years females with MTBI were equally as likely as males to obtain clinical range scores but at 12-months' post-injury females were more likely than males to score in the clinical range. This could be due to females having increased expectations of recovery or greater demands after one year has passed, or due to under-reporting by males as suggested by Miyashita et al., (2016). This result indicates that females may experience anxiety difficulties in greater severity than males at 12-months post-injury which could signify a peak for women at this point. Although this was not evident in the total scores

analysis it was also reflected in the proportion of women who reported increased levels of anxiety at 12-months post-injury.

Recovery Trajectory – Depression.

Results show that, overall, for both males and females, average depression scores in the MTBI group remained low but significantly increased from 12-months to 8-years, as did the proportion of people who scored within the clinical range for depression. This could indicate that depression may worsen in the longer-term following a MTBI, particularly after 12-months post-injury. The current study findings do not concur with the downward trajectory found by Barker-Collo et al., (2015 and 2018) that showed depression scores significantly decreased from baseline to 48 months post-injury. However, their 48-month outcome study (2018) showed that the proportion of those with depression scores in the clinical range (HADS >7) increased from 2.2% at 12-months post-injury to 7.7% at 48-months post-injury. This could suggest a longer-term trajectory of increased depression for some people following MTBI in concurrence with Konrad et al., (2011) who found that after 6-years post-MTBI, emotional sequelae continued to be experienced by participants. My findings show that the proportion of the MTBI group with depression scores in the clinical range (>11) at 8-years was 6.1% which is comparable with the 12-month population prevalence of depression of 7.9% (Scott et al., 2010), suggesting that there is no higher risk of depression for those with MTBI in the long-term. This is in accordance with my findings that at 8-years post-MTBI there were no differences in depression levels between the MTBI and comparison (TBI-free) group. It is also consistent with other research findings that depressive symptom reporting did not differ between MTBI and control groups at 12-months post-injury (Waljas et. al., 2015) and that at 12-months post-injury, levels of depression were comparable with the general population (Theadom et. al., 2016).

Overall, although depression may be quite common in patients with MTBI, particularly in women, and may seem to increase over time, it is not necessarily more common than in people in the general population, contrary to the view held by Kessler et al., (2003), Konrad et al., (2011) and other prevalence studies (e.g., Scholten et al., 2016).

Most people who scored in the clinical range for depression were single cases over the whole assessment period and no participants obtained a clinical range score at every assessment point. This suggests that the intensity of these symptoms fluctuate, rather than persist, over time and could therefore be due to other non-TBI related biopsychosocial factors, such as heritability and other environmental risk factors, (Sullivan et al., 2000; Singh et al., 2019). This fluctuation is consistent with studies showing that many of those with initial depression at 10 weeks had it resolved by 12-months and some people with depression at 12-months had not shown depression symptoms at 10 weeks (Barker-Collo et al., 2015; Singh et al., 2019).

Recovery Trajectory – Anxiety.

My findings showed that most people obtained scores in the clinical range for anxiety at 1-month (3.85% male, 6.73% female) before it decreased at 1-year (0.83% male, 6.61% female) and decreased again at 8-years (1.37% male, 4.11% female), consistent with the decline in total mean scores and with findings by Singh et. al., (2019) that the majority of (HADS >8) clinical range scores were at 10 weeks post-injury and reduced by 1-year. My findings continue the downward trajectory found by Barker-Collo et. al., (2018) that showed a reduction in anxiety from baseline to 48 months post-injury. However their study also showed that the proportion of those with anxiety scores in the clinical range (>7) fluctuated across the timepoints, decreasing from 29.5% to 3.7% baseline to 6 months and then increasing to 25.5% at 12-months before decreasing to 13.6% at 48-months post-injury. This

could suggest that whilst the number of those experiencing clinical range levels of anxiety post-MTBI reduces over time, the direction is not linear due to a range of other influencing factors not related to TBI.

In contrast to depression, current research could indicate that anxiety may be at its worst in the acute phase after MTBI. However, my study's prevalence rate of 10.6% at one month was lower than the general 12-month prevalence rate of anxiety in New Zealand of 14.8%. The percentage of MTBI participants with scores in the clinical range at the 8-year follow-up was almost the same as the comparison group (5.4% vs. 5.3%) and the MTBI 8-year follow-up scores were not significantly different to the comparison group in my study. This suggests that although anxiety is experienced by people after a MTBI, it appears to decrease in the longer term, and is no more common than in the general population (Theadom et al., 2016). Most people who scored within the clinical range for anxiety did so on only one occasion over the whole assessment period and no person reported a clinical range score at every assessment point. As with depression, this suggests that the intensity of these symptoms fluctuate, rather than persist, over time and could therefore be due to other non-TBI related biopsychosocial factors (Moldover et al., 2004).

Gender Differences in Depression and Anxiety between MTBI and Comparison Groups

My findings show that there were no gender differences between the MTBI and TBI-free groups in average levels of depression and anxiety experienced and that there was no elevated risk of experiencing depression or anxiety for those people who were 8-years' post-MTBI compared to those who were TBI-free. This indicates that after 8-years post-MTBI any onset of depression or anxiety is not related to the head injury. Females in both groups reported increased anxiety symptoms compared to males overall, which again may support

current evidence that there is a higher female prevalence of anxiety in the general population (Faravelli et al., 2013).

In terms of individual symptom reporting, the finding that people in the MTBI group reported greater severity symptoms for the depression items “I still enjoy the things I used to enjoy, “I look forward with enjoyment to things” and “I can enjoy a good book/radio/TV programme” suggests a statistically significant higher level of anhedonia within the TBI group, which is a major flagship symptom of depression. Indeed, research on the association between HADS items and 12-month post-injury diagnosis of anxiety and depression, found that the item “I still enjoy the things I used to enjoy” was highly associated with a 12-month post-injury psychiatric SCID diagnosis (Structured Clinical Interview for DSM-IV) (McKenzie, Downing and Ponsford, 2018). This is of clinical relevance as it emphasises the importance of looking at individual symptom scores of measures, in particular the HADS, and not solely at total subscale scores. The MBTI group scores for the item “I feel restless as if I have to be on the move” were significantly higher than the comparison group and this could indicate latent post-concussional syndrome which commonly includes irritability and attention problems and which can overlap with depression and anxiety symptoms (Waljas et al., 2015).

Although this current study did not find significant gender differences in levels of depression and anxiety experienced between those in the MTBI group and those in the comparison group, there was some evidence of gender differences in symptom reporting/endorsement overall.

For the item “I feel as if I am slowed down” the scores from female participants in both groups were statistically significantly higher than males indicating that females may experience higher levels of this symptom than males in the general population. This is

consistent with Iverson and Stearne, (2006) who found that, prior to concussion, their female participants reported higher post-concussive symptoms overall and that they were more likely to report mild emotional symptoms including “feeling slowed down” than were males. It is possible therefore that females are more likely to endorse greater depression symptoms than males even prior to a head injury which again supports the evidence that there is a higher population prevalence of depression in females. It is also worth noting that ‘feeling slowed down’ is also a commonly reported TBI post-concussive syndrome sequelae (Barker et al., 2015).

The finding that females in the MTBI group experienced the symptom “I get sudden feelings of panic” more greatly than females in the comparison group could indicate that, after 8-years post-injury, females are more vulnerable to increased anxious symptoms. This is in line with research suggesting that injury to the brain can affect stress hormones, particularly in women (Mollayeva et al., 2018; Faravelli et al., 2013). However, the effect size was small for the group difference. Females across both groups scored significantly higher than males for this symptom but this gender difference was significantly greater in the MTBI group.

In terms of gender overall, across both groups, females also scored significantly higher on the items “I get a sort of frightened feeling as if something awful is about to happen, “I can sit at ease and feel relaxed” and “I get a sort of frightened feeling like 'butterflies' in the stomach. These symptom analysis results could reflect gender differences in how symptoms are reported by females as compared to males. These items can be compared to those areas suffered more greatly by females in the general population as reported in the study by Angst et al., (2007), including work impairment (which may relate to feeling slowed down), social impairment and distress and feeling fearful with muscle tension which may relate to items endorsing a ‘frightened feeling’, ‘sudden panic’ and ‘butterflies’.

Strengths & Limitations

This study investigated long-term outcomes of a population-based sample of adults in the community who had sustained a mild traumatic brain injury and this reduced potential severity bias which may have occurred from studies using samples from hospital admissions only. The MTBI sample was large and included a broad range of participants for more comprehensive results. This research is a unique contribution to current research in that it extends the timepoint over which previous studies have measured MTBI outcomes in the longer-term, to 8-years and specifically relates to gender. It also allows for post-injury comparisons to be made to the general population as well as appraising the recovery trajectory over time. Given the heterogenous nature of post-injury depression and anxiety outcomes over time, longitudinal studies are important to inform clinical practice of specific risk and protective factors salient to depression and anxiety following MTBI, so that people affected can access timely interventions as needed. A limitation of this study was the variability of the sample over time in that the follow-up assessments did not include all of the cases identified in the original study and therefore the current sample may have been biased.

Use of a single measure (HADS) is a strength as it enables direct comparisons to be made over time. However, it is also a weakness, and additional measures, for example the structured clinical interview for DSM (SCID), may have made assessment of depression and anxiety more accurate rather than relying on self-report which has its limitations (Uher et al., 2012). Self-reported measurements may be unreliable in a TBI population because of the overlap between mood symptoms and PCS (for example irritability, fatigue, memory deficits, low self-awareness, attention problems) and evidence that TBI patients tend to underestimate their problems (Cnossen et al., 2017). The SCID may be advantageous as it distinguishes between psychopathology symptoms and TBI symptoms and structured interviews are less influenced by TBI related problems such as memory deficits. There may also be cultural, as

well as gender-based, variances in how participants respond to the HADS questions in terms of interpretation of meaning or presence of any stigma regarding mental illness symptoms, and so a broader range of measures would mitigate this risk, as well as identify additional individual environment risk factors for depression and anxiety.

In terms of identifying the clinical range at which depression and anxiety is diagnosed, this can vary greatly based on what measurement criteria are used (e.g., HADS, DSM, ICD-10) and the clinical range cut-off that is used. As the current study used a HADS definition (>11), it is more useful to make comparisons with other studies using this measure which may then limit the scope of evaluation.

This study examined group rather than individual level outcomes which excludes many other variables contributing to the multiple trajectories of depression and anxiety over time, such as pre-morbidity, co-morbidity, recurrent TBI, and biopsychosocial factors that were not controlled for in this study and so the level of influence these factors have had on the degree of depression and anxiety experienced over 8-years by the study's MTBI participant group is unknown.

Recommendations for future research

Based on the results of my study, there are several recommendations for future research. As my findings show the trajectory of depression and anxiety post-MTBI up to 8-years after injury, further follow-up studies beyond this period could determine the longer-term course of depression and anxiety after MTBI and whether depression does continue to increase further compared to levels within the general population.

Some of the limitations outlined in this study may be minimised by incorporating additional measures of depression and anxiety to gain a more comprehensive account of the

symptoms experienced by the study participants. Additionally, to control for other demographic/biopsychosocial factors that might influence the reporting of depression and anxiety apart from the MTBI. A measure such as the Life Events Checklist may assist with controlling for these variables over the long-term analysis. Similarly, as MTBI may be a separate diagnosis to moderate-severe TBI with different risk factors, outcome trajectories, and gender effects with regard to the expression of depression and anxiety, future research could identify how these factors can, and not in association with head injury, account for persistent post-concussive symptoms (Suhr & Gunstad, 2002). Additionally, as we know that females report higher levels of depression and anxiety than males in the general population, further research on how the expression of these symptoms manifest in, and are reported by, men may help to understand these differences and target assessment and treatments effectively and gender-sensitively, particularly as males have an increased risk of TBI compared to females (Saunders et. al., 2009).

A high co-morbidity rate of depression and anxiety has been found in the MTBI population, though not in my study sample, and further analysis to determine if those with a co-morbid diagnosis are at greater risk of poor outcomes or persistent symptoms following MTBI would also contribute to the identification and prioritisation of effective treatment interventions. Given that depression and anxiety appear to have a different prognostic and recovery course trajectory in this study, and as suggested by Penninx et. al., (2011), it could be clinically beneficial to assess and treat these two disorders differently as part of the assessment and treatment process following MTBI.

In addition, as we know that PCS symptoms can overlap with depression (Waljas et al., 2015), in order to predict long-term depression and anxiety symptoms from acute PCS assessment, future research could include identifying a specific measure or heuristic for

identifying depression and anxiety in the acute phase of MTBI that may detect long-term outcomes in males and females.

Conclusion

Understanding the relationship between gender and depression and anxiety symptoms following MTBI is important in planning the most effective treatment and rehabilitation post-injury. This is the first study to assess gender differences in the levels of depression and anxiety 8-years after sustaining a MTBI and as compared to a general population comparison group. Overall, results suggest that males and females with MTBI have the same overall and fluctuating course of recovery in relation to depression and anxiety symptoms over the 8-years following injury, but that females consistently report higher levels of depression and anxiety than males over this time. Whilst this is consistent with the female prevalence of depression and anxiety in the general population, these symptoms can impede recovery and quality of life after a MTBI.

In comparisons between the MTBI and TBI-free groups, results showed that there were no gender differences in depression or anxiety between these groups and females in both groups reported increased anxiety compared to men, which again reflects the trend in the general population. Individual symptom differences were found between groups and genders: both males and females with MTBI showed increased anhedonia and restlessness, and females with head injury experienced more elevated panic symptoms than females with no head injury. Females in general experienced more severe nervousness and feeling slowed down symptoms than males which points to specific characteristics of the expression of depression and anxiety in females.

Whilst longitudinal studies are extremely valuable to track recovery over time in a participant group, my study demonstrates that a control group comparison gives meaning to

this information across the general population and that individual item analysis can provide a greater understanding of gender and group differences in self-reported symptoms not revealed by total score analysis. The fact that there is a significant difference between males and females in the general population with regard to depression and anxiety may reflect actual gender differences in how these problems manifest and/or it could reflect the different attitudes towards reporting symptoms which can bias data collected from measures like the HADS. From a clinical perspective being cognisant of this, and the fact that males may under-report depression and anxiety symptoms, is important in the differentiation of effective assessment and treatment in both males and females. Other clinical implications of this study suggest a focus on the longer-term impacts of MTBI and that even if a patient does not present with depression or anxiety symptoms at the acute phase following injury, it may not exclude onset later on. Providing awareness of this possibility to the patient as well as regular assessment of individual symptoms over time may therefore be needed, particularly as depression and anxiety are discrete disorders with different recovery trajectories and treatment pathways.

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Appendix A

Hospital Anxiety and Depression Scale (HADS)

Tick the box beside the reply that is closest to how you have been feeling in the past week.
Don't take too long over you replies: your immediate is best.

D	A		D	A	
		I feel tense or 'wound up':			**I feel as if I am slowed down:**
	3	Most of the time	3		Nearly all the time
	2	A lot of the time	2		Very often
	1	From time to time, occasionally	1		Sometimes
	0	Not at all	0		Not at all
		I still enjoy the things I used to enjoy:			**I get a sort of frightened feeling like 'butterflies' in the stomach:**
0		Definitely as much		0	Not at all
1		Not quite so much		1	Occasionally
2		Only a little		2	Quite Often
3		Hardly at all		3	Very Often
		I get a sort of frightened feeling as if something awful is about to happen:			**I have lost interest in my appearance:**
	3	Very definitely and quite badly	3		Definitely
	2	Yes, but not too badly	2		I don't take as much care as I should
	1	A little, but it doesn't worry me	1		I may not take quite as much care
	0	Not at all	0		I take just as much care as ever
		I can laugh and see the funny side of things:			**I feel restless as I have to be on the move:**
0		As much as I always could		3	Very much indeed
1		Not quite so much now		2	Quite a lot
2		Definitely not so much now		1	Not very much
3		Not at all		0	Not at all
		Worrying thoughts go through my mind:			**I look forward with enjoyment to things:**
	3	A great deal of the time	0		As much as I ever did
	2	A lot of the time	1		Rather less than I used to
	1	From time to time, but not too often	2		Definitely less than I used to
	0	Only occasionally	3		Hardly at all
		I feel cheerful:			**I get sudden feelings of panic:**
3		Not at all		3	Very often indeed
2		Not often		2	Quite often
1		Sometimes		1	Not very often
0		Most of the time		0	Not at all
		I can sit at ease and feel relaxed:			**I can enjoy a good book or radio or TV program:**
	0	Definitely	0		Often
	1	Usually	1		Sometimes
	2	Not Often	2		Not often
	3	Not at all	3		Very seldom

Please check you have answered all the questions

Scoring:
Total score: Depression (D) _____ Anxiety (A) _____
0-7 = Normal
8-10 = Borderline abnormal (borderline case)
11-21 = Abnormal (case)

Appendix B

Brain Injury Outcomes in the Community 8 years later - BIONIC8

Adult Participant Information Sheet (16 years of age and above)

Who are we?

We are a team of people who work in universities and health care services in New Zealand. We would like to help adults who have had a head injury and to find out information that will make treatment better. For us to find out how head injury affects adults, we need to talk to those who have had a head injury and to those who haven't.

An invitation

The aim of this study is to examine the long-term effects of head injury in adults. You are being invited to take part in this research study because:

1) you had a head injury (brain injury) between March 2010 and February 2011,

OR

2) you are interested in being part of the non-injured comparison group.

This study is coordinated by the School of Psychology, University of Waikato, Hamilton, in collaboration with the National Institute for Stroke and Applied Neurosciences, AUT University, Auckland.

Your participation is entirely voluntary (your choice). You do not have to take part in this study. If you choose not to take part, any care or treatment that you are currently receiving will not be affected. If you do agree to take part, you are free to withdraw from the study at any time, without having to give a reason. Withdrawing at any time will in no way affect your future health care. To help you make your decision please read this information brochure. You may take as much time as you like to decide whether to take part or not.

If you agree to take part in this study, you will be asked to complete the Consent Form on the last page of this document. You will be given a copy of both the Participant Information Sheet and the Consent Form to keep.

What are the aims of this study?

The main aim of the study is to find out about the long-term effects of head injury. We will be looking at how adults recover, 1, 4 and 8 years after their injury, and comparing them to adults of a similar age who have not had a head injury.

The study aims to find out what the effects of the head injury (if any) are on:

- Health
- Social behaviour
- Work
- Mood and feelings

We hope this study will be of long-term benefit to New Zealanders in identifying the effects of head injury, and we hope it will eventually lead to improved care and help for those with head injury.

Who can take part in the study?

We need two groups of people to take part in this study. You can participate in this study if:

a) You took part in the BIONIC (Brain Injury Outcomes New Zealand in the Community) study and are currently 16 years of age or older. This means you had a head injury between 1st March 2010 and 28th February 2011.

OR

b) You are 16 years of age, have not had a head injury in your lifetime and would be willing to be part of the comparison group.

How many people will be in the study?

We estimate about 518 people will be involved in this study.

What happens if I do decide to take part?

If you decide you would like to take part, your involvement would be for a one-off assessment only. Each assessment will take approximately 30 minutes each.

The researcher will ring you and you will be given the option of completing the study questionnaire over the phone, online or we can arrange a time to meet with you face-to-face to complete the assessment. This meeting can be at your home, at the University or other suitable place.

We will ask you some questions about any illnesses or injuries you may have had, how you have been feeling, and about your health generally. You can take a break when needed and the assessment can be finished over more sessions if you would prefer.

You are free to stop the interview at any time, or withdraw your data before the study and data analysis is complete (May 2019).

What is the time-span for the study?

The study is expected to start 1st January 2018 and will continue until 31st December 2019.

How will the study affect me?

Taking part in this study will take some of your time and you will answer a series of questions. There are no known risks caused by this study. If you are receiving medical care, it will not be affected in any way by participating in the study, or by declining to participate or withdrawing from the study at any stage. Your participation in this study will be stopped should any harmful effects appear or if the doctor feels it is not in your best interests to continue. Similarly, your doctor may at any time provide you with any other treatment he/she considers necessary.

If the questions we ask raise issues that are distressing to you we will provide you with information on relevant local support services. This may include encouraging you / helping you to contact your GP or other health care professionals.

This study will be of benefit to the wider population. There is no assurance that you will benefit directly from being involved in this study. However, if you have had a head injury, you will be given an opportunity to discuss your injury with a researcher. The results gained from your involvement may help others with this condition in the future.

Compensation

A $10 food/fuel voucher will be provided to you after you complete the assessment.

Confidentiality

The study files and all other information that you provide will remain strictly confidential, unless there is an immediate risk of serious harm to yourselves or others. No material that could personally identify you will be used in any reports on this study. Upon completion of the study your records will be stored for at least 5 years in a secure place at the University of Waikato. All computer records will be password protected. All future use of the information collected will be strictly controlled in accordance with the Privacy Act.

Your rights

If you have any questions or concerns regarding your rights as a participant in this study, you may wish to contact an independent Health and Disability Advocate. This is a free service provided under the Health and Disability Commissioner Act:

Free phone: 0800 555 050
Free fax: 0800 2787 7678 (0800 2 SUPPORT)
Email: advocacy@hdc.org.nz

Or
Te Puna Oranga (Waikato DHB Maori Health Unit), Hockin Building, Level 1, Pembroke St, P.O. Box 934, Hamilton. Ph: (07) 834 3644. Fax: (07) 834 3619.

You can also contact the health and disability ethics committee (HDEC) that approved this study on:

Phone: 0800 4 ETHICS
Email: hdecs@moh.govt.nz

Finally

This study has received approval from the Southern Health and Disability Ethics Committee (Reference number 17/STH/247).

If you would like more information about the study please feel free to contact the principle investigator:
Dr. Nicola Starkey, Professor, School of Psychology, University of Waikato, Hamilton, on 07 8384466 ext 6472 or email: nstarkey@waikato.ac.nz

Study Investigators

The principal investigator for this study is: **Dr Nicola Starkey** Tel: (07) 8379230
School of Psychology, University of Waikato, Knighton Road, Hamilton

Please keep this brochure for your information.
Thank you for reading about this study

Brain Injury Outcomes in the Community 8 years later - BIONIC8

ADULT CONSENT FORM

Please tick to indicate you consent to the following

I have read, or have had read to me in my first language, and I understand the Participant Information Sheet.	Yes ☐	
I have been given sufficient time to consider whether or not to participate in this study.	Yes ☐	
I have had the opportunity to use a legal representative, whānau/ family support or a friend to help me ask questions and understand the study.	Yes ☐	
I am satisfied with the answers I have been given regarding the study and I have a copy of this consent form and information sheet.	Yes ☐	
I understand that taking part in this study is voluntary (my choice) and that I may withdraw from the study at any time without this affecting my medical care.	Yes ☐	
I consent to the research staff collecting and processing my information, including information about my health.	Yes ☐	
If I decide to withdraw from the study, I agree that the information collected about me up to the point when I withdraw may continue to be processed.	Yes ☐	No ☐
My GP or current provider may be informed about my participation in the study and of any significant abnormal results obtained during the study. (We will ring to obtain your permission first).	Yes ☐	No ☐
I agree to an approved auditor appointed by the New Zealand Health and Disability Ethic Committees, or any relevant regulatory authority or their approved representative reviewing my relevant medical records for the sole purpose of checking the accuracy of the information recorded for the study.	Yes ☐	No ☐
I understand that my participation in this study is confidential and that no material, which could identify me personally, will be used in any reports on this study.	Yes ☐	No ☐
I know who to contact if I have any questions about the study in general.	Yes ☐	No ☐
I understand my responsibilities as a study participant.	Yes ☐	No ☐
I wish to receive a summary of the results from the study.	Yes ☐	No ☐

Declaration by participant:
I hereby consent to take part in this study.

Participant's name: _____

Signature: _____ Date: _____

Declaration by member of research team:

I have given a verbal explanation of the research project to the participant, and have answered the participant's questions about it.

I believe that the participant understands the study and has given informed consent to participate.

Researcher's name: _____

Signature: _____ Date: _____

Appendix C

Table C1

The number and percentage of group scoring depression items to a moderate-severe level, by gender

	MTBI N=148				Comparison N=207			
	Male		Female		Male		Female	
Item	N	%	N	%	N	%	N	%
Enjoy things I used to	13	8.8	10	6.8	7	3.4	10	4.8
Laugh/see funny side	3	2.0	6	4.1	7	3.4	5	2.4
Cheerful	4	2.7	4	2.7	8	3.9	8	3.9
Slowed Down	13	8.8	20	13.5	11	5.3	22	10.6
Lost interest in appearance	11	7.4	11	7.4	20	9.7	22	11.0
Look forward with enjoyment	15	10.1	12	8.1	6	2.9	8	3.9
Enjoy good book/TV	8	5.4	6	4.1	6	2.9	4	1.9

Table C2

The number and percentage of group scoring anxiety items to a moderate-severe level, by gender

	MTBI N=148				Comparison N=207			
	Male		Female		Male		Female	
Item	N	%	N	%	N	%	N	%
Feel tense/wound up	6	4.1	9	6.1	6	2.9	11	5.3
Frightened feeling	8	5.4	16	10.8	24	11.6	29	14.0
Worrying thoughts	10	6.8	18	12.2	25	12.1	31	15.0
Sit at ease/relax	5	3.4	21	14.2	7	3.4	19	9.2
Butterflies	3	2.0	2	1.4	5	2.4	9	4.3
Feel restless	21	14.2	24	16.2	11	5.3	21	10.1
Sudden panic	4	2.7	17	11.5	12	5.8	13	6.3

Appendix D

Table D1
Gender and group differences in mean scores for HADS depression subscale items

	MTBI (8 years)				Comparison				*F* Statistic		
Item	M	SD	F	SD	M	SD	F	SD	group * gender	group	gender
Enjoy things I used to	.68	.852	.67	.783	.42	.654	.52	.769	$F(1,352) = .507$, $p = .477$, $\eta^2 = .001$	$F(1,352) = 6.355$, $p = .012$, $\eta^2 = .018$	$F(1,352) = .306$, $p = .581$, $\eta^2 = .001$
Laugh/see funny side	.33	.681	.45	.646	.27	.617	.31	.650	$F(1,352) = .371$, $p = .543$, $\eta^2 = .001$	$F(1,352) = 2.122$, $p = .146$, $\eta^2 = .006$	$F(1,352) = 1.349$, $p = .246$, $\eta^2 = .004$
I feel cheerful	.43	.596	.55	.602	.43	.671	.49	.635	$F(1,352) = .182$, $p = .670$, $\eta^2 = .001$	$F(1,352) = .238$, $p = .626$, $\eta^2 = .001$	$F(1,352) = 1.568$, $p = .211$, $\eta^2 = .004$
Feel slowed down	.80	.880	1.07	.839	.77	.694	.90	.788	$F(1,352) = .659$, $p = .417$, $\eta^2 = .002$	$F(1,352) = 1.425$, $p = .233$, $\eta^2 = .004$	$F(1,352) = 5.295$, $p = .022$, $\eta^2 = .015$
Lost interest in appearance	.49	.872	.68	.864	.68	.863	.70	.838	$F(1,352) = .923$, $p = .337$, $\eta^2 = .003$	$F(1,352) = 1.287$, $p = .257$, $\eta^2 = .004$	$F(1,352) = 1.411$, $p = .236$, $\eta^2 = .004$
Look forward/enjoyment	.59	.867	.62	.793	.39	.665	.48	.718	$F(1,352) = .148$, $p = .701$, $\eta^2 = .000$	$F(1,352) = 4.451$, $p = .036$, $\eta^2 = .012$	$F(1,352) = .469$, $p = .494$, $\eta^2 = .001$
Enjoy good book	.51	.757	.42	.725	.29	.608	.30	.633	$F(1,352) = .454$, $p = .501$, $\eta^2 = .001$	$F(1,352) = .5.797$, $p = .017$, $\eta^2 = .016$	$F(1,352) = .301$, $p = .584$, $\eta^2 = .001$

Table D2
Gender and group differences in mean scores for HADS anxiety subscale items

	MTBI (8 years)				**Comparison**				***F* Statistic**		
Item	M	SD	F	SD	M	SD	F	SD	group * gender	group	gender
Feel tense/wound up	.72	.685	.78	.692	.73	.566	.81	.661	$F(1,352) = .035$, $p = .852$, $\eta^2 = .000$	$F(1,352) = .077$, $p = .782$, $\eta^2 = .000$	$F(1,352) = 1.014$, $p = .315$, $\eta^2 = .000$
Frightened feeling	.50	.683	.86	.871	.72	.877	.90	.910	$F(1,352) = 1.037$, $p = .309$, $\eta^2 = .003$	$F(1,352) = 1.941$, $p = .164$, $\eta^2 = .005$	$F(1,352) = 8.765$, $p = .003$, $\eta^2 = .024$
Worrying thoughts	.75	.790	.94	.918	.97	.948	1.06	.867	$F(1,350) = .342$, $p = .559$, $\eta^2 = .001$	$F(1,350) = 3.072$, $p = .081$, $\eta^2 = .009$	$F(1,350) = 2.206$, $p = .138$, $\eta^2 = .006$
Sit at ease/relax	.75	.569	.93	.805	.62	.648	.80	.770	$F(1,352) = .000$, $p = .988$, $\eta^2 = .000$	$F(1,352) = 2.887$, $p = .090$, $\eta^2 = .018$	$F(1,352) = 5.796$, $p = .017$, $\eta^2 = .016$
Butterflies	.38	.610	.56	.645	.47	.594	.72	.670	$F(1,352) = .263$, $p = .609$, $\eta^2 = .001$	$F(1,352) = 3.294$ $p = .070$, $\eta^2 = .009$	$F(1,352) = .263$, $p = .002$, $\eta^2 = .028$
Feel restless	.89	.842	.96	.904	.73	.679	.74	.769	$F(1,352) = .108$, $p = .743$, $\eta^2 = .000$	$F(1,352) = 5.132$, $p = .024$, $\eta^2 = .014$	$F(1,352) = .182$, $p = .670$, $\eta^2 = .001$
Sudden panic	.36	.667	.81	.861	.56	.756	.69	.679	$F(1,352) = 4.094$, $p = .044$, $\eta^2 = .011$	$F(1,352) = .308$, $p = .579$, $\eta^2 = .001$	$F(1,352) = 13.545$, $p = .000$, $\eta^2 = .037$