Subjective Cognitive Complaints 8-Years after Mild Traumatic Brain Injury

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Abstract

Mild traumatic brain injury (TBI) is common and can result in symptoms that persist for years after the initial injury. The symptoms following TBI are dynamic, and can result in cognitive, emotional, behavioural and physical symptoms, often collectively referred to as post-concussion symptoms. Persistent post-concussion symptoms impact education, employment, relationships and quality of life. The first aim of this study was to evaluate the long-term symptoms of adults eight-years after a mild TBI compared to a TBI-free group. The second aim of this study was to compare the prevalence and severity of post-concussion symptoms that were reported at 1-month post-injury, 12-months post-injury, and the symptoms reported now, at 8 years post-injury. Finally, the factors contributing to subjective cognitive complaints at 8-years post-injury were explored.

A population-based sample of 151 adults who sustained a mild TBI (mTBI) between 2010 and 2011 participated in this study. Additionally, 213 participants with no history of head injury took part. Both groups answered questions about current post-concussion symptoms using the Rivermead Post-Concussion Symptom Questionnaire (RPQ).

The results of this study revealed the prevalence and severity of post-concussion symptoms was significantly greater in participants with mTBI at 8-years post-injury. Differences in cognitive symptoms were most prominent between groups, with the mTBI participants reporting significantly more cognitive complaints. When evaluating symptom-severity over time, we found no significant change in post-concussion symptoms from 12-months post-injury to 8-years. Older age at injury and increased symptoms of depression were associated with increased cognitive complaints at 8-years post-injury. These results confirm post-concussion symptoms persist long-term, and may not improve beyond the levels reported at 12-months post-injury. Further research is needed to explore the impact that treatment of mood symptoms early post-injury may have on recovery.

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Table of Contents

List of Tables

List of Figures

Introduction

Overview

A traumatic brain injury (TBI) is the result of a sudden force to the head or body, which causes the brain to move abruptly within the skull. TBI is a serious public health problem and leading cause of death and disability worldwide (Hyder, Wunderlich, Puvanachandra, Cururaj, & Kobusingye, 2007; Johnson & Griswold, 2017). According to the Centres for Disease Control (CDC), the number of TBI-related cases resulting in emergency department visits, hospitalizations, and deaths increased by 53% from 2006-2014 in the United States (CDC, 2019). In New Zealand, the Accident Compensation Corporation (ACC) reported over half of serious injury claims filed related to TBI, costing $83.5 million in 2015 (ACC, 2017). The cost of TBI is substantial both economically and socially, as survivors of TBI can be affected for the rest of their lives with impairments in cognitive, physical and emotional function (CDC, 2003). Until recently research has focused on prognosis following moderate and severe injuries, as these typically have the worst outcomes; however, injuries from sports and combat have increased the awareness of the prevalence and consequences of mild injuries (Donovan, Cancelliere, & Cassidy, 2014). It is estimated that more than 10 million people experience a traumatic brain injury each year, with 70-95% of these being classified as mild (Cassidy et al., 2004; Feigin et al., 2013).

Injury Severity

The severity of a traumatic brain injury depends on several factors, including the directionality and force of the movement, and ultimately the resulting impact on the brain (Bigler, 2008). There are two types of TBI, *closed* (no penetration to the head) or *open* (where an object penetrates the skull). In general, penetrating TBI is considered more severe and results in a more localized injury; however, closed head injuries are more common and the acceleration/deceleration forces from these

injuries result in more diffuse cerebral damage. Additionally, TBI is classified as mild, moderate or severe depending on factors such as loss of consciousness (LOC) and post-traumatic amnesia (PTA) and severity is most commonly assessed using the Glasgow Coma Scale (GCS) (Teasdale, 2014; Teasdale & Jennett, 1974). The GCS measures level of consciousness following a TBI by assessing motor responsiveness, verbal response and eye opening. Total scores range from 3 to 15 with lower scores reflecting greater injury severity: GCS 3-8 Severe, 9-12 Moderate, and 13-15 Mild TBI. Mild TBI can also be referred to as *complicated* or *uncomplicated,* referring to the presence or absence of abnormalities on computed tomography (CT) scans.

Incidence of Mild TBI

Over the past decade, mild traumatic brain injury (mTBI) has become a prominent public health concern and a leading cause of death and disability worldwide (CDC, 2003; Donovan et al., 2014; Hyder et al., 2007). In 2004, the literature reviewed by a World Health Organisation (WHO) Task Force revealed an incidence of 100-300/100,000 population (Cassidy et al., 2004), however more recent estimates suggest the annual incidence likely exceeds 600 per 100,000 person-years (Donovan et al., 2014). In a New Zealand population-based study, Feigin et al. (2013) identified the prevalence of mild TBI as 749 cases per 100,000 person-years. This higher rate reflects the inclusion of TBI cases from all sources, including self-referrals; in this sample, 36% of those identified did not attend hospital for treatment and were identified through consultation with community health services (Feigin et al., 2013), further reinforcing the probability that the actual incidence of mild TBI in the general population is much higher than previously estimated. Efforts to quantify the true incidence and consequences of mild traumatic brain injury are hindered by the limited number of people who seek immediate medical attention and the diverse presentations of symptoms following the injury, many of which may not be apparent until days later.

Impact of Mild TBI

Symptoms from a traumatic brain injury can vary significantly, even within injuries classified as mild. The symptom profile is dynamic and includes physical, sensory, emotional and cognitive symptoms. The rate of recovery is variable, and depends on the type and severity of the injury and which part of the brain is injured. Even with mild injuries, TBI can have long-term consequences (Cole & Bailie, 2016; Polinder et al., 2018).

Acute Symptoms

Impaired consciousness and post-traumatic amnesia (PTA), being confused or unsure of what happened, are neurobehavioral hallmarks of acute TBI (Rabinowitz & Levin, 2014). Typical symptoms include headache, dizziness, blurry vision, nausea, fatigue, drowsiness, difficulties sleeping and hypersomnia. Physical complaints such as drowsiness, headaches, dizziness and nausea are the most common symptoms at the acute stage; additional physical, cognitive and emotional/behavioural symptoms, such as fatigue, irritability and memory problems, continue to develop in the days and weeks following injury (Eyres, Carey, Gilworth, Neumann, & Tennant, 2005). At 2-weeks post injury, van der Naalt reported 84% of patients had one or more post-traumatic complaints, with the most common being headache (51% of patients), dizziness (55% of patients), and fatigue (56% of patients). Psychological complaints were also common, with patients reporting clinically significant levels of anxiety (18%), depression (16%) and post-traumatic stress (39%) (van der Naalt et al., 2017).

Recovery and Persistent Symptoms

Cognitive, emotional, behavioural and physical symptoms are common after traumatic brain injury. The majority of people who sustain a mild TBI see full resolution of these symptoms within three months of their initial injury; however, long-term physical, cognitive, behavioural and emotional consequences are not uncommon following these injuries (Arciniegas, Anderson, Topkoff, & McAllister, 2005; Carroll, Cassidy, Peloso, et al., 2004; Langlois, Rutland-Brown, & Wald, 2006; McInnes, Friesen, MacKenzie, Westwood, & Boe, 2017). Additionally, it is becoming increasingly clear that recurrent injuries may result in cumulative damage, as subsequent TBIs are often associated with increasingly severe symptoms (Cole & Bailie, 2016; Karr, Areshenkoff, & Garcia-Barrera, 2014; Polinder et al., 2018).

Post-Concussion Syndrome

When the symptoms of concussion persist long-term, they can lead to a diagnosis of post-concussion syndrome or post-concussion disorder. This diagnosis is based on criteria from either the International Classification of Diseases [ICD-10; (World Health Organization, 1993)] or the Diagnostic and Statistical Manual of Mental Disorders [DSM-IV; (American Psychiatric Association, 2000)]. There are clear differences between them regarding the nomenclature and criteria for the diagnosis; the diagnostic criteria for both classifications are summarized in Table 1.

Both the ICD-10 and the DSM-IV require symptoms in three or more categories to be present; the symptom lists are similar, however the ICD-10 lists 16 symptoms in six categories whereas the DSM-IV lists 13 symptoms in eight categories; timing of symptom onset also differs between the two classifications. These differences have a significant impact on the symptom profile that can constitute the diagnosis. Another key difference is the ICD-10 requires loss of consciousness (LOC), which is not a criterion in the DSM-IV.

Table 1:

Diagnostic Criteria for Post-Concussion Syndrome & Post-Concussion Disorder

Diagnostic Criteria for Post-Concussion Syndrome **(ICD-10)**	Diagnostic Criteria for Post-Concussion Disorder **(DSM-IV)**
A. History of head trauma with LOC preceding symptom onset by maximum of 4 weeks	**A.** History of head trauma that has caused significant cerebral concussion (manifestations include LOC and PTA) **B.** Evidence from neuropsychological testing or quantified cognitive assessment of difficulty in attention or memory
B. Symptoms in 3 or more of the following categories: • Headache, dizziness, malaise, fatigue, noise tolerance • Irritability, depression, anxiety, emotional lability • Subjective concentration, memory or intellectual difficulties without neuropsychological evidence of marked impairment • Insomnia • Reduced alcohol tolerance • Preoccupation with above symptoms and fear of brain damage with hypochondriacal concern and adoption of sick role	**C.** Three (or more) of the following occur shortly after the trauma and last at least 3 months: • Becoming fatigued easily • Disordered sleep • Headache • Vertigo or dizziness • Irritability or aggression on little to no provocation • Anxiety, depression, or affective instability • Changes in personality (e.g. social or sexual inappropriateness) • Apathy or lack of spontaneity
	D. The symptoms in criteria B and C have their onset following head trauma or represent a substantial worsening of pre-existing symptoms
	E. The disturbance causes significant impairment in social or occupational functioning and represents significant decline from previous level of functioning
	F. The symptoms do not meet the criteria for Dementia Due to Head Trauma and are not better accounted for by another mental disorder (e.g. Amnestic Disorder Due to Head Trauma, Personality Change Due to Head Trauma)

Adapted from International Classification of Diseases (ICD-10) and Diagnostic and Statistical Manual of Mental Disorders (DSM-IV)

Additionally, the DSM-IV requires an objective neuropsychological assessment or cognitive evaluation, which is explicitly precluded in the ICD-10 criteria. These differences make the diagnostic label of Post-Concussion Syndrome (ICD-10) or Post-Concussion Disorder (DSM-IV) relatively meaningless as a general classification of persistent problems post-TBI for both clinical and research purposes.

Prevalence of Post-Concussion Syndrome

In a recent review, ICD-10 prevalence rates of Post-Concussion Syndrome at 3-months post-injury vary between 6-64%, whereas the DSM-IV criteria often result in lower estimates (Polinder et al., 2018). For example, when comparing the diagnostic specificity of the ICD-10 and DSM-IV criteria in TBI patients and those with extracranial trauma, Boake et al. reported a higher prevalence of Post-Concussion Syndrome in both groups using the ICD-10 criteria (64%) compared with the DSM-IV criteria (11%) (Boake et al., 2005).

The appropriateness of the diagnostic term 'Post-Concussion Syndrome' has also been challenged, as these symptoms are not necessarily specific to TBI and have been found in other populations following traumatic injury. In a hospital-based sample, Meares et al. examined the frequency of Post-Concussion Syndrome in patients with mild TBI and non-brain injured trauma controls at the acute phase (within 14 days) of injury using the Post-Concussion Syndrome Checklist (PCSC), which assesses symptom complaints based on the ICD-10 diagnostic criteria. In this sample, a diagnosis of Post-Concussion Syndrome was reported for 43.3% of patients with mild TBI and 43.5% of non-brain injured trauma controls (Meares et al., 2008). This result is consistent with other research reporting no significant differences between mild TBI and trauma control groups on the frequency, intensity or duration subscales of the PCSC at 4.5 days post-injury (Landre, Poppe, Davis, Schmaus, & Hobbs, 2006). These results, among others, indicate the possibility that the current diagnostic criteria are not sufficiently distinctive to discriminate

symptom profiles between TBI patients and other trauma patients at the acute stage post-injury.

To a varying degree, mild TBI patients tend to endorse different post-concussion symptoms than other populations that meet diagnostic criteria for Post-Concussion Syndrome. For example, when compared with other trauma patients at one-month and one-year post-injury, TBI groups reported significantly more symptoms than trauma controls at both time points, and the clustering of these symptoms also differed with cognitive symptoms more frequently endorsed by the TBI group (Dikmen, Machamer, & Temkin, 2017). Similar outcomes were reported when investigating self-reported symptoms at 5-10-years post-injury in patients with prior TBI, traumatic orthopaedic injury (TOI) and uninjured controls (Dahm & Ponsford, 2015). These results suggest that persistent symptoms observed post-TBI may not be unique to head injury *per se*, but instead may come to resolution more effectively after other traumatic injuries. Alternatively, the development of post-concussion symptoms specific to a head injury may develop over weeks to months following the initial injury, as a result of blunt or shearing injuries sustained during the trauma.

In a community sample of mild TBI and control participants, Dean et al. evaluated the prevalence of Post-Concussion Syndrome using both the ICD-10 and modified DSM-IV criteria and reported a 'notable incidence rate of post-concussion-like symptoms' in the non-clinical population (Dean, O'Neill, & Sterr, 2012). Several studies have demonstrated that factors such as depression, anxiety, PTSD and involvement in litigation influence levels of reported post-concussion symptoms in populations both with and without a history of TBI (Dean et al., 2012; Polinder et al., 2018; Ponsford et al., 2012).

In summary, the symptoms that comprise Post-Concussion Syndrome are non-specific, overlap with other disorders, and are found to some extent in the general population. Following an extensive literature review, the WHO has

suggested the diagnostic label of "Post-Concussion Syndrome" is not a useful construct, and recommends referring to such ongoing sequelae as "post-traumatic symptoms" (Donovan et al., 2014). Ultimately, the validity or appropriateness of the diagnostic term Post-Concussion Syndrome does not alter the outcome for what has been referred to as the 'miserable minority' of patients who continue to suffer from persistent symptoms post-TBI (Ruff, Camenzuli, & Mueller, 1996).

Persistent Symptoms Post-TBI

The majority of mild TBI patients are expected to recover within three months post-injury, however there is evidence that 46-65% of patients report persistent symptoms at 6 months (de Koning et al., 2017; Theadom et al., 2016; van der Naalt et al., 2017), and 10-25% of patients continue to experience persistent symptoms up to and beyond 1 year post-injury (Cassidy et al., 2014; Hou et al., 2012; McInnes et al., 2017). Although it is commonly acknowledged that mild TBI can result in long-term sequelae for some patients, the aetiology is still unknown; persistent symptoms following these injuries have been attributed to neural damage, neurobiological dysfunction, pre- and post-injury factors, somatization and malingering (Arciniegas et al., 2005).

Persistent post-concussive complaints, defined as those that persist beyond three-months post-injury, include headache, fatigue, dizziness, depression, anxiety, irritability, difficulty concentrating and memory impairments. Those reporting more acute symptoms and more emotional stress are at increased risk for developing persistent symptoms (Cassidy et al., 2014). Psychological factors have been consistently associated with persistent symptoms and poor outcomes; when looking at predictors of post-concussive symptoms at 1-week post-injury in participants with mild TBI and trauma controls, Ponsford et al. identified presence of mild TBI, female gender, premorbid psychiatric history and elevated anxiety symptoms as predictive of persistent symptoms. However, when followed up at 3-months post-injury, mild

TBI was no longer a strong predictor and preinjury psychiatric problems, anxiety and PTSD symptoms were most predictive of post-concussive symptoms (Ponsford et al., 2012). Factors such as gender, age at injury, previous TBI, education level, socioeconomic status, involvement in litigation, pre-injury psychiatric history and psychosocial factors have been linked to persistent symptoms following mild TBI (Dikmen, Machamer, Fann, & Temkin, 2010; Donovan et al., 2014; McCauley et al., 2013; Silverberg et al., 2015).

Post-concussion symptoms are commonly assessed using self-report measures, such as the Rivermead Post-Concussion Questionnaire [RPQ; (King, Crawford, Wenden, Moss, & Wade, 1995)]. The RPQ is designed to assess the prevalence and severity of common complaints that occur after a head injury, such as sleep, somatic, affective, and cognitive symptoms. Generally symptoms reported at the acute or sub-acute stage are those most frequently reported as problematic at longer-term follow up (Røe, Sveen, Alvsåker, & Bautz-Holter, 2009), although the development and recovery of persistent symptoms is unpredictable and there is significant variability between patients. For example, when evaluated at 1-month and 1-year post-injury, Dikmen et al. reported a general decline in symptoms, although up to 18% of TBI patients endorsed a symptom at 1 year that they had not endorsed at 1-month post-injury (Dikmen et al., 2010). However, another study found that 82% of patients experiencing post-concussion symptoms 1-year post-injury had reported those symptoms at 1-month post-injury (Waljas et al., 2015).

Sleep & Somatic Symptoms

Physical symptoms are most common in the acute and sub-acute phase post-injury, and include headache, dizziness, pain, and fatigue. The development of chronic somatic symptoms, defined as those that persist after physical healing has occurred, is poorly characterized, subjective in nature, and common in mild TBI patients with delayed recovery (Mollayeva, Cassidy, Shapiro, Mollayeva, & Colantonio, 2017; Polinder et al., 2018). The mechanism of persistent physical symptoms is unclear,

and may be attributed to the neurological consequences of traumatic injury on brainstem structures, or as a problem mediated by other factors such as post-traumatic stress (Mollayeva et al., 2017).

Factors such as involvement in litigation or compensation claims have been highlighted as a risk factor for persistent physical symptoms, however age at injury, mechanism of injury and gender also seem to play a role. The underlying cause and risk factors for persistent somatic symptoms following mild TBI has been shown to differ between males and females, and is influenced by socio-demographic, clinical and injury-related characteristics (Mollayeva et al., 2017). Additionally, factors such as age at injury may impact the clustering of persistent symptoms following mild TBI, with older adults more likely to experience persistent physical symptoms (Theadom et al., 2016).

Physical complaints at 1- and 2-weeks post-injury have been reported as significantly more common in patients that went on to experience persistent post-concussion symptoms (PPCS), defined as those persisting beyond 3-months post-injury (Yang, Hua, Tu, & Huang, 2009). Additionally, sleep difficulties and poor sleep quality as assessed at 2-weeks post-injury have been linked to more severe post-concussive symptoms 1-year post-injury (Theadom et al., 2015). In a longitudinal study, McMahon et al. evaluated the evolution of post-concussive symptoms using the Rivermead Post-Concussion Questionnaire at 3-months, 6-months, and 12-months post-TBI. At 6-months post-injury 71.8% of patients reported more than one physical symptom (compared to 67% at 3 months and 69.4% at 12 months) and 60.3% more than one sleep symptom (compared to 50.2% at 3 months and 53.5% at 12 months) (McMahon et al., 2014).

Identifying persistent complaints and providing adequate treatment is essential to limit the impact of these symptoms on the recovery process. Both emotional and environmental factors have been shown to correlate with insomnia and chronic fatigue, and may be beneficial targets for treatment leading to

improved outcomes for patients experiencing delayed recovery (Mollayeva, Mollayeva, Shapiro, Cassidy, & Colantonio, 2016). Sleep difficulties, fatigue and chronic pain can be a significant impairment to full recovery, including community participation and return to work, factors that are associated with favourable outcomes following mild TBI (Mollayeva et al., 2014; Polinder, Haagsma, van Klaveren, Steyerberg, & van Beeck, 2015). Furthermore, somatic symptoms such as post-traumatic headaches and fatigue can compound psychological symptoms and confound assessments of other post-concussive symptoms, particularly post-traumatic cognitive impairments (Arciniegas et al., 2005; Silver, McAlister, & Arciniegas, 2009).

Affective Symptoms

Traumatic brain injury can result in affective symptoms that persist past the acute stage post-injury. Traditionally, psychiatric symptoms occurring post-injury have been viewed as a reaction to persistent symptoms, such that changes in functional ability and necessary life changes contribute to psychological distress (Cole & Bailie, 2016). More recently, biopsychosocial approaches have highlighted the co-occurrence of physiological disruption and psychological distress from the injury as a plausible framework to explain persistent symptoms (Vasterling & Dikmen, 2012). Neuroscience research provides additional evidence for the role of physiological insult as the basis for emerging and persistent symptoms. Neuroimaging studies have identified several areas of the brain that are particularly vulnerable to traumatic forces, including the hypothalamic-pituitary-adrenal (HPA) axis which, if disrupted, would result in dysregulated biological responses to stress (Bigler, 2008). However, the behaviour-based literature reports that persistent psychological symptoms may develop independently from the physiological insult of the injury, and such symptoms, as well as favourable outcomes, are better predicted by psychosocial factors and pre-morbid psychiatric history than the insult to the brain specifically (Cassidy et al., 2014; Donovan et al., 2014).

Mood Disorders Post-TBI

Individuals sustaining a TBI are at risk for developing clinically significant psychological distress, most commonly depression, anxiety, and post-traumatic stress disorder (PTSD) (Cole & Bailie, 2016; Rapp et al., 2013). Clinically, it can be difficult to disentangle a diagnosis of PTSD from other combinations of symptoms that may result from a TBI. Many post-concussion symptoms (e.g., sleep difficulties, irritability and concentration problems) are similar to symptoms of the hyperarousal dimension of PTSD (Polinder et al., 2018). This makes it difficult to attribute these symptoms to a specific neurological insult, particularly if there is emotional distress in response to the trauma that caused the injury (Lagarde et al., 2014). Recent estimates suggest that there is a prevalence rate of approximately 13.8% following TBI of any severity (Polinder et al., 2018), although the nature and prevalence of PTSD following TBI has been controversial due to ''the apparent paradox of suffering PTSD with impaired memory for the traumatic event'' (Bryant et al., 2009). The increased rates of PTSD after mild compared to more severe head injuries suggests that PTA and LOC may be protective factors against intrusive memories and emotional distress (Bombardier et al., 2006; Bryant et al., 2009).

Depression is a common consequence of TBI and has been reported in 10-77% of TBI patients in the first year following injury (Arciniegas et al., 2005; Dikmen, Bombardier, Machamer, Fann, & Temkin, 2004; Silver et al., 2009). The functional impairment associated with depression can further impede improvement and recovery of individuals post-TBI, and is associated with self-reported increases in the number and perceived severity of other post-concussive symptoms and cognitive complaints (Silver et al., 2009). Dikmen at al. evaluated the prevalence and risk factors for depression in patients following all severities of TBI, and reported only preinjury psychosocial factors, not injury severity, as predictive of depressive symptoms; in fact, milder injuries were associated with greater depressive symptoms at one month post-injury (Dikmen et al., 2004). A population-based longitudinal study suggests that prevalence of depressive symptoms are common

after mild TBI, but show improvement over time with baseline levels of depression decreasing from 21% to 12.4% using HADS diagnostic criteria, and 49.1% to 34.1% using DSM-IV criteria (Barker-Collo et al., 2015). In the same study, the most commonly reported symptom was 'feeling slowed down,' which is associated with cognitive complaints relating to attention (Rabinowitz & Levin, 2014). Additionally, sleep dysfunction is a commonly observed in depression, and depression often results in poor sleep (Mollayeva et al., 2017), further highlighting the interdependence of sleep, affective and cognitive symptoms post-TBI.

Both depression and anxiety are risk factors for the persistence of post-concussion symptoms, in particular patients who have had previous psychiatric diagnoses are more likely to exhibit PCS longer post-injury (Donovan et al., 2014; van der Naalt et al., 2017). Although anxiety and depression have shown promise as predictors for patients who may continue to experience long-term difficulties following mild TBI, not all of the literature supports this. For example, Hou et al. reports negative injury perceptions and all-or-nothing behaviour as the strongest predictors of outcome at 3- and 6-months post-injury, with anxiety and depression being insignificant contributors to their final prediction model (Hou et al., 2012).

Considering the psychological impact of traumatic injury, it is not unexpected that emotional distress is common in a significant number of patients in the weeks and months following traumatic injury. In a sample of 363 consecutively admitted trauma patients, O'Donnell et al. reported 20% of the group met criteria for at least one psychiatric diagnosis 12 months after their injury. PTSD and major depressive disorder were the most frequent, with 10% of participants meeting diagnostic criteria for each disorder at 12 months (O'Donnell, Creamer, Pattison, & Atkin, 2004). The prevalence of psychiatric disorders in those who have experienced trauma along with the significant overlap of post-concussive symptoms with other psychiatric diagnoses make it difficult to determine which aspects of post-traumatic

complaints are specific to the neurological insult of traumatic brain injury (Bigler, 2008).

Neuropsychological & Cognitive Symptoms

Neuropsychological and cognitive functions commonly affected by TBI include memory, attention, motivation and impulsivity. Somatic and affective symptoms, such as headache, depression and sleep-related symptoms, can confound assessment of cognitive sequelae after a TBI (Prince & Bruhns, 2017). It is increasingly recognized that cognitive and emotional control are innately linked, relying on overlapping functional networks and cortical structures (Okon-Singer, Hendler, Pessoa, & Shackman, 2015), many of which have been identified as particularly vulnerable in TBI. The anterior and inferior frontal and temporal areas of the brain are those most commonly and most severely affected by impact forces (Bigler, 2008). These regions are particularly important for tasks involving executive functions, including working memory and attention. Deficits in attention regulation affect multi-tasking and distractibility, which are among the most common features of post-concussive symptoms (Prince & Bruhns, 2017). Furthermore, attention regulation has been implicated in neuropsychiatric disorders such as anxiety (Okon-Singer et al., 2015), highlighting the dynamic interactions between affective and cognitive symptoms.

Executive Function

The term 'executive function' describes a variety of high order cognitive abilities, which include planning, prioritizing, and problem solving. Executive functions are essential for success and adaptation to changing environments, as these higher-order cognitive abilities affect and influence more basic aspects of functioning such as attention, memory and behaviour. Deficits in executive functions are common following all severities of TBI and have broad impacts on the awareness, monitoring and regulation of thoughts, feelings and behaviours (Prince & Bruhns, 2017; Rabinowitz & Levin, 2014). Executive function impairment after mild TBI likely

reflects frontal lobe injury, specifically the dorsolateral prefrontal cortex (DLPFC), which is essential for normal executive function, and may be particularly vulnerable to multiple recurrent injuries (Belanger, Spiegel, & Vanderploeg, 2010).

Cognitive Complaints

Moderate and severe TBI are clearly associated with persistent cognitive deficits, which often involve aspects of cognitive functioning that remain preserved following a mild injury (Rabinowitz & Levin, 2014). Deficits resulting from mild TBI typically affect working memory and are more subtle, less often recognized, and may, in some patients, continue to persist beyond the expected recovery period (Arciniegas et al., 2005; Dikmen, Machamer, & Temkin, 2001). Although there is still considerable debate regarding the extent and persistence of cognitive deficits following mild TBI, there is evidence that traumatic brain injury can result in persistent cognitive impairment, regardless of the severity of the initial injury (Carroll, Cassidy, Peloso, et al., 2004; Karr et al., 2014; Sharp, 2008).

Assessing Cognitive Impairment

The cognitive domains that are most often affected by mild TBI include memory, attention and processing speed (McInnes et al., 2017). Traditional neuropsychological assessments have been useful diagnostic tools for patients with more severe TBI, however many of these assessments are unable to detect neuropsychological dysfunction in patients with mild injuries, even those who report ongoing cognitive complaints (Rabinowitz & Levin, 2014). Few studies have reported performance-based mild neuropsychological impairment in patients with mild TBI, most commonly in fluency and memory recall; however, the deficits identified in these studies were generally not maintained beyond 3 months post-injury (Belanger, Curtiss, Demery, Lebowitz, & Vanderploeg, 2005), however there are reports of subtle changes being detected up 6 to 8-years post-injury (Konrad et al., 2011; Vanderploeg, Curtiss, & Belanger, 2005). This may be attributed to the limited ecological validity of these tests, or their lack of sensitivity to the subtle and diffuse

damage that results from a mild injury. As a result of these limitations, cognitive impairment may persist undiagnosed in this population. Considering the anatomy of a TBI, tests that specifically screen for frontally-mediated cognitive functions may be more sensitive to the resulting deficits and improve detection of cognitive impairment (Arciniegas et al., 2005; Prince & Bruhns, 2017). The disproportionate cognitive effort required to perform daily tasks may instead be reflected in complaints of other symptoms, such as fatigue.

Studies using functional magnetic resonance imaging (fMRI) during working memory tasks have demonstrated abnormal activation in functional circuitry under increased working memory loads in patients after mild TBI, even when their task performance remains comparable to normal controls (Chao et al., 2015; Chen et al., 2012; Sinopoli et al., 2014). Recruitment of additional brain regions and alterations in blood oxygen levels has been interpreted as a compensatory response to microstructural injury, and there is some evidence that activation patterns are associated with severity of post-concussion symptoms (Smits et al., 2009). Although there is some variability in reporting of increased and decreased blood oxygen levels, there is evidence that these activation patterns return to normal when assessed at multiple time points post-injury (Chen et al., 2012; Karr et al., 2014).

Neuroimaging methods evaluating white matter integrity also support the idea that neurological abnormalities are associated with cognitive symptoms after mild TBI. In a study evaluating fractional anisotropy (FA), a measure of diffusion along axons, lower FA in the dorsolateral prefrontal cortex (DLPFC) was predictive of impaired executive function in acute mild TBI (Lipton et al., 2009). In summary, although the majority of mild TBI patients do not show abnormalities on CT scans, microstructural damage and shearing injuries may explain ongoing cognitive sequelae in some mild TBI patients (Smits et al., 2009).

Subjective Cognitive Complaints

Self-reported assessments are commonly used to collect information about difficulties in cognitive function following TBI, however, particularly in mild injuries, self-reported cognitive functioning has not been consistent with objective assessments of cognitive functioning (Schiehser et al., 2011; Spencer, Drag, Walker, & Bieliauskas, 2010). Self-reported cognitive complaints have been linked to premorbid characteristics, such as education level, as well as physical symptoms such as fatigue (Oldenburg, Lundin, Edman, Nygren-de Boussard, & Bartfai, 2016; Stulemeijer, Vos, Bleijenberg, & van der Werf, 2007). Memory difficulties are commonly reported after mild TBI, and as described above, are not often identified as clinically significant using standard neuropsychological measures (Rabinowitz & Levin, 2014). Memory, working memory and attention are highly interdependent, and it has been proposed that self-reported memory deficits are representative of attentional and executive functioning deficits, which impact the acquisition and retrieval of memories (Prince & Bruhns, 2017).

Subjective cognitive complaints are also associated with emotional symptoms such as depression and anxiety (Chamelian & Feinstein, 2006). These symptoms are also known to impact cognitive processing and perceived effort, which has been associated with evaluation of task difficulty. Consequently, treatment of affective symptoms may, in some patients, reduce the burden of cognitive impairment (Silver et al., 2009; Spencer et al., 2010). Neuroimaging evidence supports this, showing functional connectivity is associated with self-reported effort and fatigue during cognitively demanding tasks (Ramage, Tate, New, Lewis, & Robin, 2019).

Outcomes and Prognosis

The impact of moderate to severe traumatic brain injuries on cognitive, emotional and behavioural function is well documented, but there is still considerable debate about the long-term consequences and recovery from mild injuries (Arciniegas et al., 2005; Dikmen et al., 2009).

Long Term Outcomes

Long-term cognitive and behavioural changes following TBI include difficulties with attention, memory and executive functioning, fatigue and irritability. Draper & Ponsford investigated cognitive impairments and their association with injury severity 10-years post-TBI. As expected, greater injury severity within the TBI group was associated with worse performance; however, while some patients did score within the normal range, the TBI group exhibited more attentional, memory and executive problems than healthy controls even 10-years post-injury (Draper & Ponsford, 2008). When comparing outcomes 5 to 10-years post-injury between TBI, traumatic orthopaedic injury (TOI) and uninjured controls, individuals with TBI reported greater cognitive difficulties and anxiety compared to an uninjured control group, and greater anxiety, psychological distress and psychosocial difficulties than those who had sustained a traumatic orthopaedic injury 10 years ago (Dahm & Ponsford, 2015).

In an evaluation of cognitive and emotional sequelae 6-years post-injury, Konrad et al. reported that individuals with mTBI displayed significant cognitive impairments when administered a neuropsychological test battery compared with healthy control subjects, and that these deficits were not accounted for by negative self-perceptions or involvement in compensation claims (Konrad et al., 2011). Additionally, the high rates of mood disorders such as depression, anxiety and posttraumatic stress disorder often reported following TBI have been documented decades post-injury. In a 30-year follow-up study, almost half (n = 29; 48.3%) of

participants were diagnosed with an axis 1 disorder that began after their injury (Koponen et al., 2002).

Long term follow-up studies have provided mixed results regarding the predictive power of injury-related and patient characteristics associated with poor outcomes. However, the characteristics of favourable outcome vary significantly between studies, and, as such, it would be expected that the factors reported as associated with good and poor outcomes would also vary. For example, reports of functional outcome may emphasize psychosocial components such as current relationships and employment status as indicative of recovery. When investigating characteristics associated with functional outcome 10-years post-injury, longer post-traumatic amnesia and lower preinjury education have been linked to poorer outcomes (Ponsford, Draper, & Schonberger, 2008). Other studies may evaluate cognitive performance, prevalence of post-concussion symptoms, or presence of mood disorders as indicative of outcome. Factors such as gender, age at injury, ethnicity, education and socioeconomic status have been linked to outcomes and persistent symptoms following mild TBI (Donovan et al., 2014; McCauley et al., 2013; Silverberg et al., 2015). Scores on the RPQ-13, which measures severity of common post-concussion symptoms, are associated with greater impact on lifestyle beyond the acute phase post-injury (Eyres et al., 2005). The presence of post-concussion and mood symptoms, when severe enough to impact activities of daily living, impact overall wellbeing and associated functional outcome (Ponsford et al., 2008; Silver et al., 2009). The interaction between symptom profiles, measures of outcome, and risk factors for delayed recovery further reinforces the complications associated with quantifying, classifying, and treating persistent symptoms post-TBI.

Due to the heterogeneous symptom profiles and variable recovery rates within mild TBI patients, assessments focusing on long term recovery may not be statistically sensitive enough to identify, or group sizes may mask variations in, the residual symptom profiles (Dikmen et al., 2017; Iverson, 2010; Rabinowitz & Levin,

2014). Additionally, the evolution of persistent symptoms following mild TBI is often reported using group level analysis, which can obscure the prognosis for individual patients at risk for persistent symptoms and distort reported rates of recovery, as changes in symptom prevalence at the group level is not necessarily indicative of symptom progression for an individual patient (Iverson, 2010; Røe et al., 2009). Differences in methodology and patient populations in existing longitudinal studies make it difficult to draw firm conclusions; ultimately, these studies lack a consensus regarding chronic symptoms, at-risk populations, reliable risk factors and the time-frame to resolution of post-traumatic sequelae. Early identification of patients at risk for delayed recovery, and providing them with education and appropriate interventions, could prevent long-term sequelae and improve outcomes following mild TBI (Dikmen et al., 2017). Reliable diagnostic strategies and early identification for those at risk for delayed recovery is essential to the development of successful treatment and efficient allocation of resources (Cassidy et al., 2014).

Predictors of Long Term Outcome

For over 25 years, mild TBI has been termed a 'silent epidemic', a reference to the nature of the symptoms, such as impairments in memory or cognition, which are often overlooked (Hyder et al., 2007). The substantial psychosocial impact of TBI and the increasing number of people sustaining traumatic brain injuries each year makes identifying those at risk for long-term sequelae increasingly important. Specifically, it has been suggested that identification of modifiable risk factors take priority (Donovan et al., 2014). Although poor recovery after mild TBI has been associated with poorer premorbid mental and physical health status, and with more injury-related stress (Cassidy et al., 2014), the lack of consistency in the literature regarding sample selection criteria, definition of mild TBI, type of outcome measures used, type of comparison group used and timing of outcome assessments, makes it difficult to draw firm conclusions (Carroll, Cassidy, Holm, Kraus, & Coronado, 2004; Dikmen et al., 2001, 2017; Donovan et al., 2014; Mena et al., 2011).

A crucial limitation in the evaluation of long-term outcomes following TBI is the use of hospital and clinic-based samples. Furthermore, there are limited studies on long-term outcomes post-TBI (> 5 years), and those that do exist tend to focus on more severe injuries, or evaluates outcomes across all injury severities. The use of hospital or clinic-based samples for recruitment and follow-up of those sustaining mild TBI may provide bias samples, as most people who sustain mild injuries do not seek treatment (Feigin et al., 2013). The long-term follow-up of a population-based sample of individuals sustaining a mild TBI will provide critical insight into the prevalence of persistent post-concussion symptoms and outcomes following mild injuries. The current study seeks to contribute to the literature by following up a population-based sample of adults who had sustained a mild TBI eight-years prior (Feigin et al., 2013). During their initial assessment, study participants were administered neuropsychological and health assessments at baseline (within two weeks of injury), one-month, six-months and 12-months post-injury (Feigin et al., 2013; Theadom et al., 2012). Similar measures have been employed in the current investigation for comparative purposes.

This thesis seeks to evaluate current PCS and mood symptoms in individuals $\geq$ 16 years of age at injury who sustained a mild TBI 8-years prior. The symptoms reported will be compared with those reported from an age and gender-matched comparison group. It is hypothesized that the mild TBI group will report more severe PCS, and that cognitive complaints will be specific to the mild TBI group. Additionally, the evolution of symptoms over time will be evaluated using information collected from assessments at 1-month, 12-months and now 8-years post-injury. The use of consistent outcome measures will allow comparison of self-reported symptoms across acute, sub-acute and long-term time phases post-injury. It is hypothesized that symptoms reported at 1-month post-injury will be the most severe, and that there will be a significant decrease in symptoms by 12-month post-injury; however, reported symptoms at 12-months will see only minor improvement to 8-years. Finally, the presence of mood symptoms at 1-month post-injury will be

evaluated as predictors of subjective cognitive complaints at eight-years post-injury. In addition to age at injury, history of previous TBI and gender, it is hypothesised that more severe symptoms of anxiety and depression at the acute stage post-injury will be associated with greater cognitive complaints at 8-years post-injury.

Methods

Design and Sample

Brain Injury Incidence and Outcomes New Zealand in the Community (BIONIC)

Participants in the mTBI group were initially recruited through the Brain Injury Incidence and Outcomes New Zealand in the Community (BIONIC) study. This population-based incidence study aimed to register all cases of TBI that occurred in Hamilton and Waikato New Zealand over a one-year period, between 1 March 2010 and 28 February 2011 (Feigin et al., 2013). The study population was identified through hospital admissions, general practitioner and medical centres, key word searches in databases and discharge registers, rehabilitation centres, community health services, sports centres, and self-referrals. The protocol for this study is described in detail elsewhere (Theadom et al., 2012).

Traumatic brain injury was defined according to the World Health Organisation (WHO) definition of TBI, as "an acute brain injury resulting from mechanical energy to the head from external physical forces" (Carroll, Cassidy, Holm, et al., 2004, p. 115). Operational criteria for clinical identification of TBI included the presence of one or more of the following: confusion or disorientation; loss of consciousness; post-traumatic amnesia; other neurological abnormalities (e.g. focal neurological signs, lesions or seizure); and must not be due to drugs, alcohol, medications or caused by other problems or injuries (Carroll, Cassidy, Holm, et al., 2004; Feigin et al., 2013). This investigation identified 1,369 confirmed cases of TBI in the study region, the majority (95%) of which were classified as mild (Feigin et al., 2013).

Within BIONIC, neuropsychological and health assessments were administered at baseline (within two weeks of injury), one-month, six-months and

12-months post-injury. Participants were asked at their 12-month assessment if they consented to being contacted for future studies.

The protocol used in this thesis is part of a longitudinal prospective study of the same cohort eight-years post-index TBI who were previously assessed as part of the original BIONIC cohort and consented to follow-up (N=467; $n = 363 \geq 16$ years at injury). The data reported here was collected as part of the eight-year follow-up of the BIONIC participants; *Eight Years Later: Long-Term Outcomes from Traumatic Brain Injury in Adults*, funded by the Waikato Medical Research Foundation (WMRF #289). Ethical approval of the study protocol was obtained from the Health and Disability Ethics Committee (HDEC; 17/STH/247) and the University of Waikato Health Research Ethics Committee.

Participants

mTBI Group

Adults (≥16 years at injury) who were identified in the original BIONIC study and consented to follow-up were contacted to participate in this study. These participants had sustained a mild TBI between 1 March 2010 and 28 February 2011. Mild TBI severity was defined using the Glasgow Coma Scale (GCS; 13-15) and/or post-traumatic amnesia (<24 hours).

Comparison Group

An age and gender matched cohort (n=213), free from TBI in their lifetime, was recruited for comparison purposes. Participants in this group were recruited from a panel maintained by ResearchNow, an online data collection company. Participants in the comparison group were screened for previous TBI, or injuries that likely result in a TBI, prior to completing the questionnaire.

Sample Characteristics

Sample characteristics for both groups are presented in Table 2. 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. Difference in ethnicity between groups was significant; however, both the TBI and Comparison groups were predominantly European (76.2% and 63.7%, respectively). The difference in ethnicity between the groups is driven by the greater proportion of those in the Comparison group self-identifying as other ethnicities (17%); additionally, Maori were less represented in the Comparison group (4.2%) than the TBI group (19.9%). Education level also significantly differed between groups; the majority of participants in the Comparison group completed a degree, whereas a diploma or certificate was the most common qualification in the mTBI group. The difference in education level was not reflected in occupation, which was not significantly different between groups (p = .684). Occupation was broadly categorized as professional (including managerial), skilled (including partially-skilled) and other (which included students, armed forces and retired).

Outcome Measures and Assessments

The outcome measures included in the study protocol were selected based on their applicability and proven utility in TBI (Wilde et al., 2010). Additionally, a subset of the assessments from the original BIONIC study have been retained to allow for comparative analyses. Participants were asked questions about their mood, employment, community participation, general health and wellbeing and subsequent TBIs. All assessments were made available online through Qualtrics software (www.qualtrics.com).

For the purposes of this thesis, the following assessments have been used in the analysis: *Rivermead Post-Concussion Questionnaire* (RPQ) and *Hospital Anxiety and*

Depression Scale (HADS). *The Ohio State University Traumatic Brain Injury Identification Method* (OSU-TBI-ID) was used to screen for additional head injuries.

Table 2

Sample characteristics of participants at 8-year assessment

		Group		**Test of Difference**
		TBI (*n* = 151)	**Comparison** (*n* = 213)	TBI vs Comparison
		M (SD)	M (SD)	
Age		45.42 (17.05)	45 (15.2)	t (362) = -.245, p = .806
		n (%)	*n* (%)	
Gender				X^2 (2) = 1.5, p = .466
	Male	77 (51%)	104 (48.8%)	
	Female	74 (49%)	107 (50.2%)	
	Other	0	2 (0.9%)	
Ethnicity				X^2 (4) = 58.9, p < .001
	Asian	3 (2%)	24 (11.3%)	
	European	115 (76.2%)	135 (63.7%)	
	Maori	30 (19.9%)	9 (4.2%)	
	Pacific	3 (2%)	8 (3.8%)	
	Other	0	36 (17%)	
Education				X^2 (3) = 14.65, p = .002
	Degree	40 (26.5%)	87 (40.8%)	
	Diploma /Certificate	54 (35.8%)	41 (19.2%)	
	Trade /Technical	27 (17.9%)	38 (17.8%)	
	Other	30 (19.9%)	47 (22.1%)	
Occupation				X^2 (2) = .76, p = .684
	Professional	47 (32.2%)	78 (36.6%)	
	Skilled	30 (20.5%)	40 (18.8%)	
	Other	69 (47.3%)	95 (44.6%)	
Mechanism of Injury				
	Fall	49 (32.5%)		
	Traffic/MVA	39 (25.8%)		
	Mechanical Force	30 (19.9%)		
	Assault	30 (19.9%)		
	Other	3 (2%)		

General Questions

Demographics, Employment and Education

Basic demographic information was collected for all participants in the Comparison group, and updated information gathered for the mTBI group. Participants were asked about their current employment status and occupation, how many hours per week they worked, and if they were the main income earner in their household. Additionally, the mTBI group was asked to compare their current employment to their employment pre-injury.

Comorbidities & Current Symptoms

Participants were asked to list diagnosed medical conditions and any current medications. Additionally, the mTBI group was asked if they felt they were still affected by the brain injury they sustained eight years ago. If the participant indicated yes, they were asked to identify the area of their life (e.g. work, socializing) that was affected the most, and the most disabling issue (e.g. physical, cognitive or emotional) they attributed to their brain injury.

Recurrent Injuries & Identification of TBI

Ohio State University Traumatic Brain Injury Identification Method (OSU-TBI-ID)

To assist with recall of TBI, we used the Ohio State University TBI Identification Method (OSU TBI-ID). The OSU TBI-ID is a standardized procedure designed to improve accurate recall of a person's lifetime history of TBI (Corrigan & Bogner, 2007). This brief assessment asks targeted questions designed to facilitate recollection of injuries or events that could result in a TBI or concussion, and has demonstrated predicative 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 their memory'. This information was used to determine the number of recurrent injuries in the mTBI group, and was used as a screen for eligibility for the comparison group. If participants in the Comparison group indicated LOC or feeling dazed or confused after any incident, they were deemed ineligible and did not complete the questionnaire. For the mTBI group, 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. This information was used to determine the number of recurrent injuries in the mTBI group.

Post Concussive Symptoms

The Rivermead Post Concussive Symptoms Questionnaire (RPQ)
The Rivermead Post Concussive Symptoms Questionnaire (RPQ) is a 16-item self-report questionnaire designed to assess common symptoms that occur after a head injury (King et al., 1995). Traditionally, respondents are given the instruction, 'compared with before the accident, do you now (i.e., over the last 24 hours) suffer from' the items listed. Each item is rated between 'not experienced' to 'severe problem' on a five-point scale, with higher scores indicative of greater severity. Due to the longitudinal nature of this study, participants were not asked to compare their current symptoms with those prior to their TBI 8 years ago. Instead, they were given the instruction, 'do you now (i.e., over the last 24 hours)' and presented with four response choices: 0, not experienced; 2, mild problem; 3, moderate problem; 4, severe problem. Because there was no comparison time point, the response option 1 (no more of a problem) was not included in this questionnaire for either the mTBI or the Comparison group.

The RPQ has two subscales, the RPQ-3 and the RPQ-13, with good test-retest reliability (0.83 and 0.72) and adequate external construct validity (Eyres et al., 2005). The first three items on the RPQ assess symptoms common at the acute stage of TBI (headache, dizziness and nausea/vomiting), and form the RPQ-3. The total

RPQ-3 score was calculated for all participants. The RPQ-13 is composed of the remaining 13 questions, which focus on cognitive, emotional and somatic symptoms commonly experienced after a TBI. The total RPQ-13 score was calculated for all participants.

PCS severity was evaluated using symptom-severity criteria for identification of symptomatic responses. For each individual question, a score of 2 or higher indicates that the symptom is a problem in daily life. A score of 2 or more on four items was used to identify participants reporting symptoms that may be indicative of a clinical diagnosis of PCS. The value '2' on the RPQ is labelled as 'a mild problem,' and so those meeting criteria for PCS using this threshold were identified as 'mild PCS'. The value '3' on the RPQ is labelled as 'a moderate problem' and a score of 3 or more on four items was used to identify participants reporting more severe symptoms indicative of PCD; those meeting this threshold were identified as 'moderate PCS'.

Additionally, subscales for cognitive, emotional and somatic symptoms were calculated using values of responses specific to each domain (Potter, Leigh, Wade, & Fleminger, 2006). The cognitive subscale is made up of three items: forgetfulness, poor memory; poor concentration; taking longer to think. The minimum score is 0 and the maximum score is 12. The emotional subscale is made up of four items: being irritable, easily angered; feeling depressed or tearful; feeling frustrated or impatient; restlessness. The minimum score is 0 and the maximum score is 16. The somatic subscale is more diverse and consists of 11 items, including all items on the RPQ-3 with the remaining 8 from the RPQ-13.

To identify change over time for the mTBI group, and compare the mTBI and Comparison group, the total scores for the RPQ-3 and RPQ-13 were used in the analysis; additionally, the cognitive subscale was calculated to evaluate subjective cognitive functioning. The symptom-severity criteria, as outlined above, was used to identify those with mild and moderate PCS.

Psychological and Mood Disturbance

Hospital Anxiety and Depression Scale (HADS)

The Hospital Anxiety and Depression Scale (HADS) is a fourteen item self-report questionnaire designed to measure levels of anxiety and depression (Zigmond & Snaith, 1983). It has proven utility in both psychiatric and general populations, demonstrated high internal consistency, sensitivity to change and has been extensively used with TBI populations (Bjelland, Dahl, Haug, & Necklemann, 2002; McKenzie, Downing, & Ponsford, 2018; Schonberger & Ponsford, 2010; Whelan-Goodinson, Ponsford, & Schonberger, 2009). The HADS is comprised of two subscales consisting of seven items each, which allows for independent evaluation of Anxiety and Depressive symptoms. For each item, respondents are asked to indicate the extent to which each statement applied to them over the past week. Responses are scored on a 4-point Likert scale, with scores ranging from 0 to 3 for each question. The minimum score for each subscale is 0 and the maximum score is 21, with higher scores indicating greater symptom severity.

Scores between 0-7 on either subscale are considered to be within the normal range, while scores above 8 are suggestive of clinical levels of depressive or anxiety symptoms. In this thesis, the Anxiety and Depression subscale total scores were used to evaluate the presence and severity of mood symptoms in both the TBI and Control groups. Additionally, case-ness for both scales (i.e. scores > 8) was calculated to identify the number of participants reporting clinically significant symptoms; this cut-off has been previously identified in the literature with a specificity and sensitivity for depression of 0.79 and 0.83, and for anxiety 0.78 and 0.90. (Bjelland et al., 2002).

Procedure

TBI Group

Contact information for eligible participants was extracted from the BIONIC database. Participants were contacted by phone and given information about the current study. If we were unable to reach the participant with the contact information on file, family members, next of kin, and health care providers were contacted for updated information. If that was unsuccessful, we searched the electoral roll and sent an attempt to contact slip to listed addresses for individuals with a matching name. This was our final attempt to contact participants; if this was unsuccessful, they were deemed uncontactable.

Contact with participants was initiated within two months of the eight-year anniversary of their index injury, and they were deemed eligible for follow-up through two-months past their eight-year injury date. If participants were unable to be contacted prior to this cut-off, follow-up was abandon. Once contacted, participants were given information about the study over the phone, and an electronic copy of the participant information sheet and consent form was provided to them.

Where possible participants were encouraged to complete the measures online, however they were given the option of an in-person assessment. For those who preferred to complete the questionnaire electronically, they were emailed a link to the online consent form. Once consent was received, a separate link coded with a unique participant identifier was sent for them to complete the online questionnaire. The questionnaire asked about their current health, subsequent TBIs, mood, cognitive functioning, post-concussive symptoms, social participation and employment eight years after their index injury.

Indication of recent hospitalizations and any positive response on the OSU-TBI screen was followed up with a phone call by the study team to collect information about the incident. Additionally, participants endorsing significant

symptoms of anxiety or depression, as identified by a total score > 11 on the HADS, were contacted to ensure they were receiving adequate support. Once the survey was completed, participants had the opportunity to request information about the study findings. All participants completing the questionnaire were sent a $10 gift voucher.

Comparison Group

Participants in the comparison group were recruited through ResearchNow, who contacted their panellists with the opportunity to participate in this research study. Those interested in completing the survey were screened for previous head injuries using the OSU-TBI questionnaire. Those reporting any prior head injury were ineligible. Those meeting eligibility criteria (i.e. no history of head injury) completed the same questionnaire as the mTBI group. The participants in this group were not followed up individually, however resources for emotional and social support were provided at the end of the questionnaire as required (i.e. HADS total scores $\geq$ 11).

Statistical Analysis

Data were analysed using IBM SPSS version 25. Collected data was checked for completeness, with any participants completing less than 80% of the questionnaire excluded from the final analysis. Tests for outliers and distribution of data was completed prior to beginning the analysis. To investigate whether the mTBI group endorsed different symptoms than the Comparison group, we carried out tests of Analysis of Variance (ANOVA). One-way between-group ANOVA was used to compare scores on the Rivermead Post-Concussion Symptoms Questionnaire (RPQ) and the Hospital Anxiety and Depression Scale (HADS). The total scores for the RPQ-3 and RPQ-13 and HADS Anxiety and Depression subscales were compared. Scores on RPQ-Cognitive, -Emotional and -Somatic subscales were also compared. Additionally, the frequency of individuals meeting symptom-severity criteria for mild

and moderate PCS in both groups are presented; the proportion meeting symptom-severity PCS was compared, differences are reported with chi-squared.

Next, repeated measures ANOVA was used to examine changes in scores over time for the mTBI group. Means and standard deviations are presented for the RPQ subscales (RPQ-3, RPQ-13, and RPQ-Cognitive, -Emotional and -Somatic subscales) and HADS Anxiety and Depression scores using data from the 1-month, 12-month and 8-year assessment. T-tests were used to compare differences between participants included in the repeated measures analysis and those that did not have data at all time points to identify any significant differences. Additionally, the number of individuals meeting symptom-severity criteria for PCS at each time point is presented. Perceptions of recovery were summarized using responses to the question 'do you still feel affected by the brain injury you sustained 8 years ago.'

Finally, linear regression analysis was performed to evaluate the factors influencing self-reported cognitive symptoms. Predictors previously shown to influence outcome post-TBI (age at injury, gender, previous TBI) and mood symptoms at 1-month post-injury were evaluated.

Results

Comparison of Post-Concussion Symptoms

The mTBI group scored higher than the Comparison group on both the RPQ-3 and RPQ-13; the mean scores for both groups are presented in Table 3. Between groups ANOVA confirmed the difference in scores between groups on the RPQ-3 was statistically significant (p < .001). The most reported symptom on the RPQ-3 for all participants was headaches, with 55% of the mTBI group and 38% of the Comparison group reporting this symptom as at least a mild problem (RPQ score 2 or higher), followed by dizziness, (mTBI 35%; Comparison 21%) and nausea/vomiting (mTBI 23%; Comparison 10%).

The mTBI group also reported more PCS symptoms on the RPQ-13; between groups ANOVA confirmed the difference in total scores between groups was statistically significant ($p < .001$). The least reported symptom for both groups was double vision (mTBI 15%; Comparison 7%), followed by blurred vision (mTBI 33%; Comparison 17%) and light sensitivity (mTBI 33%; Comparison 17%). The most prevalent symptom in the mTBI group was forgetfulness/poor memory (60%), followed by fatigue (59%), sleep disturbance (53%) and taking longer to think (50%). For the Comparison group, sleep disturbance (52%) and fatigue/tiring easily (50%) were the most reported symptoms.

Table 3

RPQ-3 and RPQ-13 scores

	Group				
	mTBI		Comparison		Test of Difference
	(*n* = 151)		(*n* = 213)		
	M (SD)	95% CI	*M* (SD)	95% CI	mTBI vs Comparison
RPQ-3	2.7 (2.86)	2.28 - 3.21	1.64 (2.42)	1.29 - 1.99	F (1, 362) = 14.64, ***p* < .001**, ηp2 =0.039
RPQ-13	14.5 (12.8)	12.73 -16.28	9.08 (9.73)	7.59 -10.58	F (1, 362) = 21.04, ***p* < .001**, ηp2 =0.055

Symptomatic Responses

Symptom-severity cut-offs scores were used to identify symptomatic responses and determine the prevalence of symptom levels indicative of post-concussion disorder (PCD). Participants endorsing 4 or more symptoms as at least a 'mild problem' (≥ 2) met the symptom-severity criteria for mild PCS, and participants endorsing 4 or more symptoms as at least a 'moderate problem' (≥ 3) met the symptom-severity criteria for moderate PCS. Using this classification method, Figure 1 shows the percent of participants per group meeting symptom-severity criteria for Mild and Moderate PCS.

Figure 1
Prevalence of PCS Symptom-Severity in the mTBI and Comparison group
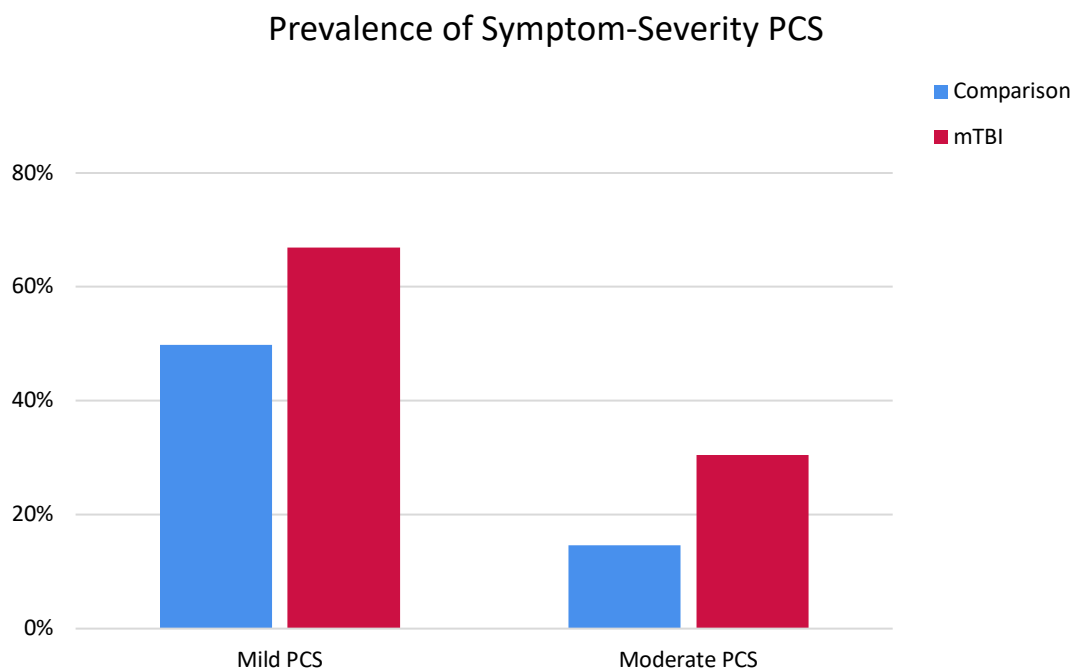
When using scores ≥ 2 as a cut-off for symptomatic responses, two-thirds of participants in the mTBI group (66.9%; *n*=101) and half (49.8%; *n*=106) of participants in the Comparison group met symptom-related criteria for Mild PCS. Analysis revealed the proportion of participants meeting criteria for Mild PCS was significantly higher in the mTBI group then the comparison group (x^2 (1, N=364) =

10.56, p = .001). Using scores ≥ 3 as a cut-off for symptomatic responses, the number of participants in both groups meeting criteria decreased considerably. However, 30.5% of participants in the mTBI group still met criteria for Moderate PCS (n = 46). In the Comparison group this number dropped to 14.6% (n = 31). Analysis revealed the proportion of participants meeting criteria for moderate PCS was significantly higher in the mTBI group (x^2 (1, N=364) = 13.41, p < .001).

**RPQ Subscales: Cognitive, Emotional, Somatic**

The total scores of the cognitive, emotional and somatic subscales of the RPQ were also compared between groups. The mTBI group reported higher scores on all three subscales as shown in Figure 2. Scores on the cognitive subscale revealed the greatest difference between groups (F (1, 362) = 30.26, p < .001, η_p^2 =0.077), with mTBI participants reporting a mean score nearly two-times greater than the Comparison group. Emotional subscale scores were significantly different between groups (F (1, 362) = 11.88, p = .001, η_p^2 =0.032), with the mean score for mTBI participants nearly one and a half times greater than the Comparison group. Scores on the somatic subscale were most similar between groups, although the mTBI group reported slightly more severe symptoms than the Comparison group, the difference did not reach statistical significance (F (1, 362) = 0.45, p = .504, η_p^2 =0.001).

To determine the severity of specific symptoms on the cognitive subscale, individual items were also analysed separately. Of the three items, forgetfulness/poor memory was the most pervasive symptom in the mTBI group, with 59.6% reporting this as at least a mild problem (≥ 2). This was followed by taking longer to think (49.7% ≥2) and poor concentration (48.3% ≥2). Forgetfulness/poor memory was also the most pervasive symptom in the Comparison group (32.4% ≥2), followed by poor concentration (30.5% ≥2) and taking longer to think (29.6% ≥2). The mean symptom severity rating for all items on the

cognitive subscale was significantly different between groups (p < .001); summary statistics for these items are reported in Table 4.

Figure 2

Scores on the RPQ-Subscales for the mTBI and Comparison group (error bars represent 95% CI; **p $<$ and = .001)
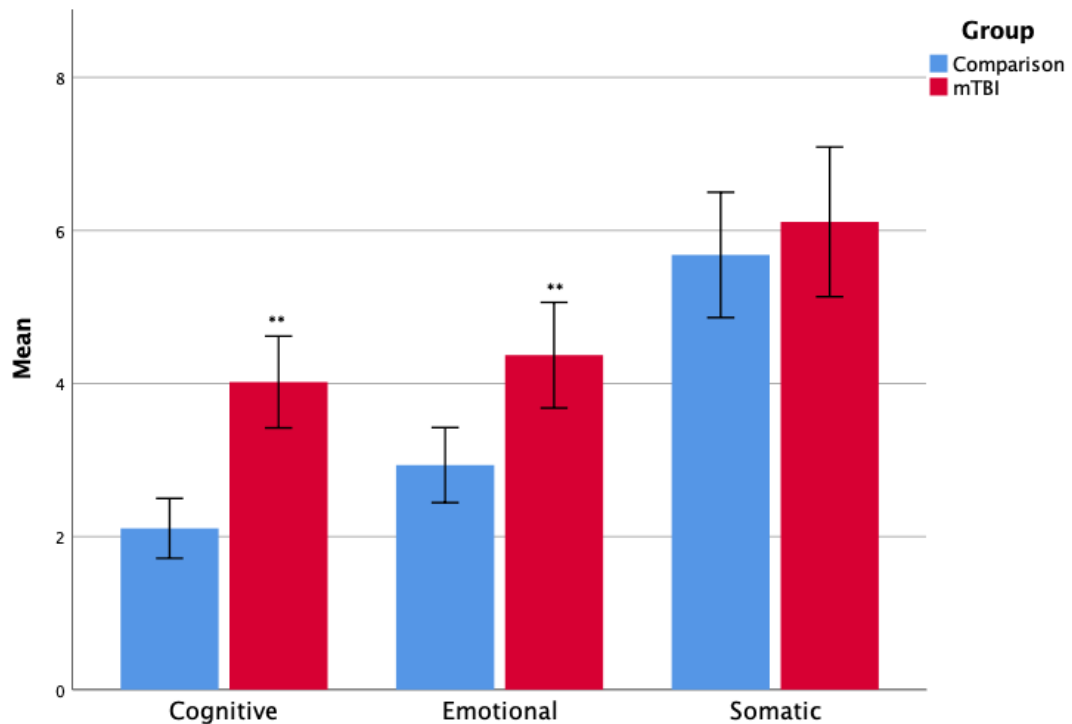
Table 4

Symptom scores on the RPQ-Cognitive subscale for the mTBI and Comparison group (all items p < .001)

	Group				
	mTBI		Comparison		Test of Difference
	(n = 151)		(n = 213)		mTBI vs Comparison
RPQ Cognitive	*M*	*SD*	*M*	*SD*	
Forgetfulness	1.6	1.45	.75	1.13	$F (1, 362) = 38.95, p < .001, \eta_p^2 = 0.097$
Poor Concentration	1.19	1.31	.71	1.12	$F (1, 362) = 13.53, p < .001, \eta_p^2 = 0.036$
Taking Longer to Think	1.24	1.34	.64	1.03	$F (1, 362) = 23.11, p < .001, \eta_p^2 = 0.060$

HADS: Anxiety and Depression

Symptoms of anxiety and depression have been linked to increased reporting of subjective cognitive complaints and outcomes following TBI. To identify differences in mood symptoms between groups, total scores on the HADS Anxiety and Depression subscales were compared. Similar levels of anxiety and depression symptoms were reported in both groups, with mean anxiety scores slightly higher in the Comparison group and higher mean depression in the mTBI group. These differences did not reach statistical significance; a summary of means, standard deviations and comparisons between groups are presented in Table 5. To determine if mood influenced reporting of symptoms on the RPQ, the ANOVAs comparing the mTBI and Comparison group were carried out again using the HADS score as a covariate. The inclusion of the covariate did not change the outcome analyses, and the difference in RPQ scores between groups remained significant.

Table 5

HADS Anxiety and Depression scores for the mTBI and Comparison group

	Group				
	TBI		Comparison		Test of Difference
	(n = 149, Anxiety) (n = 151, Depression)		(*n* = 213)		TBI vs Comparison
HADS	*M*	*SD*	*M*	*SD*	
Anxiety	5.3	4.1	5.46	3.96	F (1, 360) = .16, p = .693, ηp^2 = .000
Depression	4.3	4.01	3.83	3.89	F (1, 362) = 1.27, p = .261, ηp^2 = .003

Evaluation of Symptom Prevalence & Severity

Within-subjects repeated measures ANOVA was used to determine if there were significant changes in symptom reporting over time. Separate repeated measures analysis of scores was conducted for the RPQ and HADS at 1-month, 12-months and 8-years post-injury. This included examining the subscale total scores for both questionnaires at each time point. Only individuals with data on the items of interest

at all assessment time points were included in each analysis. A separate analysis was conducted to identify any differences between individuals included in the repeated measures and those not included (to assess for bias); there were no significant differences in current age, age at injury, ethnicity, history of previous TBI, mechanism of injury or mild TBI severity between those included and excluded from the analyses (p > .05).

Rivermead Post-Concussion Symptoms

A total of 88 participants had data at all time points for the RPQ-3, and 87 participants had data at all time points for the RPQ-13. For both the RPQ-3 and RPQ-13, scores were highest at 1-month, decreased at 12-months, and increased slightly at 8-years. Summary statistics are presented in Table 6. As shown in the Table, the overall change in scores over time was significant for both the RPQ-3 and the RPQ-13. Post-hoc analysis (Bonferroni corrected) revealed that the decrease in scores from 1-month to 12-months reached statistical significance for both the RPQ-3 (p = .004) and RPQ-13 (p < .001).

Table 6
Change in post-concussion symptoms over 1-month, 12-months and 8-years post-injury

| | mTBI | | | | | | |
| | Time Since Injury | | | Test of Difference | Significance of Change | | |
RPQ	1 Month	12 Months	8 Years		1mth-12mth	12mth-8yrs	1mth-8yrs
RPQ-3	3.2 (2.57)	2.27 (2.39)	2.65 (2.74)	$F(2, 174) =$ 5.21, **p = .006,** $\eta p2 = 0.057$	p = .004	p =.580	p = .215
RPQ-13	17.05 (11.63)	12.47 (11)	14.47 (12.18)	$F(2, 172) =$ 8.23, **p < .001,** $\eta p2 = 0.087$	p < .001	p = .303	p = .109

Self-Reported Cognitive Complaints

The RPQ-Cognitive subscale score was used to quantify self-reported cognitive complaints. A total of 88 participants had recorded data at all time points. The

subscale consists of 3 items (forgetfulness/poor memory; poor concentration; taking longer to think. Following the same pattern as the RPQ-3 and RPQ-13, the cognitive subscale scores were highest at 1-month, decreased at 12-months and increased slightly at 8-years. As shown in Table 7, the overall change in scores over time was significant. Post-hoc analysis (Bonferroni corrected) revealed the decrease in scores from 1-month to 12-months ($p < .001$) and the decrease from 1-month to 8-years ($p = .002$) reached significance.

Table 7
Change in RPQ-Cognitive subscale scores over 1-month, 12-months and 8-years post-injury

	Time Since Injury			Test of Difference
RPQ-Cognitive	1 Month	12 Months	8 Years	
RPQ-Cog Total	5.32 (3.56)	3.55 (3.32)	3.98 (3.75)	*F* (2, 174) = 12.29, *p* < .001, ηp2 =0.124
Cognitive Component				
Forgetfulness	1.86 (1.28)	1.2 (1.21)	1.65 (1.46)	*F* (2, 174) = 10.37, *p* < .001, ηp2 =0.106
Poor concentration	1.74 (1.25)	1.17 (1.22)	1.12 (1.33)	*F* (2, 174) = 11.09, *p* < .001, ηp2 =0.113
Taking longer to think	1.72 (1.29)	1.17 (1.22)	1.2 (1.35)	*F* (2, 174) = 9.43, *p* < .001, ηp2 =0.098

In addition to the RPQ-Cognitive total score, the mean severity rating for the three components were also analysed separately. For the first symptom on the cognitive subscale, **forgetfulness/poor memory,** scores were highest at 1-month, decreasing at 12-months and then increasing at 8-years. For this symptom, post-hoc analysis revealed the decrease in scores from 1-month to 12-months reached significance (p < .001), as did the increase from 12-months to 8-years (*p* = .018). The second symptom**, poor concentration**, was most severe at 1-month, and then remained relatively stable from 12-months to 8-years. Post-hoc analysis revealed the decrease from 1-month to 12-months and 1-month to 8-years reached significance at (*p* < .001). For the final symptom on the cognitive subscale, **taking**
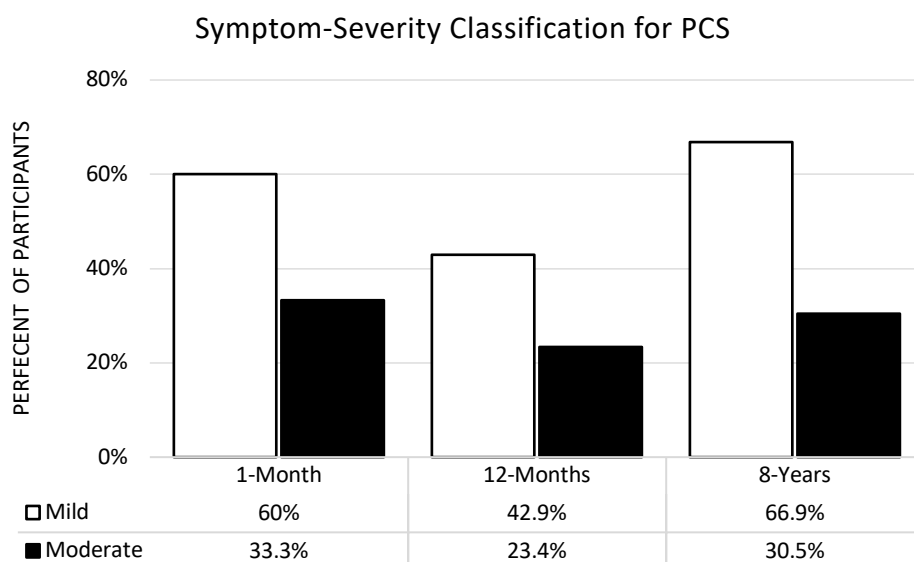
longer to think, scores were highest at 1-month, and then remained relatively stable from 12-months to 8-years. Post-hoc analysis revealed the decrease from 1-month to 12-months reached significance ($p < .001$), as did the decrease from 1-month to 8-years ($p = .002$).

Symptom Severity

Symptom severity on the RPQ was used to identify participants meeting symptom-related criteria indicative of PCD. As described above, participants were considered to have Mild PCS if 4 or more symptoms were rated ≥ 2 on the RPQ, and Moderate PCS if 4 or more symptoms scored ≥ 3. At 1-month post-injury, RPQ scores were available for 105 participants; at 12-months post-injury, RPQ scores were available for 124 participants; at 8-years post-injury, RPQ scores were available for 151 participants. Mild PCS was most prevalent 8-years post-injury, and Moderate PCS was most prevalent at 1-month post-injury. The percentage of participants meeting symptom-severity classification for mild and moderate PCS at 1-month, 12-months and 8-years post-injury is shown in Figure 3.

Figure 3

Change in Post-Concussion Symptom-Severity Classification for the mTBI group at 1-month, 12-months and 8-years post-injury

Symptom-Severity Classification for PCS

	1-Month	12-Months	8-Years
Mild	60%	42.9%	66.9%
Moderate	33.3%	23.4%	30.5%

HADS Anxiety and Depression

To evaluate the change of mood symptoms over time, and identify the influence mood symptoms had on PCS, total scores on both HADS subscales Anxiety and Depression were analysed separately using repeated measures ANOVA (Table 8). Anxiety scores were highest at 1-month, and then remained relatively stable 12-months to 8-years. Analysis revealed the decrease from 1-month to 12-months was significant (p = .020), as was change from 1-month to 8-years (p= .012). Conversely, depression scores were highest at 8-years. Depression scores decreased from 1-month to 12-months, however this change was not statistically significant (p = 0.61). Analysis revealed the increase in depression scores from 12-months to 8-years was statistically significant (p = .001), however the increase from 1-month to 8-years was not (p = .825).

Table 8
Change in HADS Anxiety and Depression subscale scores over 1-month, 12-months and 8-years post-injury

	Time Since Injury			Test of Difference
HADS	1 Month	12 Months	8 Years	
Anxiety	6.32 (1.07)	5.14 (3.88)	5.15 (4.15)	$F (2, 180) = 5.74, p = .004, \eta p2 = 0.060$
Depression	3.63 (3.64)	2.76 (3.15)	4.08 (3.92)	$F (2, 182) = 6.25, p = .002, \eta p2 = 0.064$

Perceptions of Recovery

The response to the question 'do you still feel affected by your brain injury 8 years ago' was used to assess individual perceptions of recovery. Answers to this question were coded as cognitive, emotional, physical, or multiple if more than one type of complaint was indicated. Of the 150 participants that responded to this question, 64% stated they no longer felt affected by the brain injury they sustained 8 years ago. However, 36% of participants reported that they still felt affected by their injury. A summary of responses is provided in Table 9.

Table 9

Perceptions of recovery at 8-years post-injury

| No | Yes | Area Affected | Still affected by brain injury 8 years ago? | | |
| | | | Number Affected | % Affected (n = 54) | % Total (N = 150) |
n (%)	*n* (%)				
96 (64%)	54 (36%)	**Cognitive**	22	40.7%	14.7%
		Multiple	13	24.1%	8.7%
		Physical	11	20.4%	7.3%
		Emotional	8	14.8%	5.3%

For those indicating they still felt affected by their injury 8-years ago, cognitive complaints were the most reported disabling issue. The most common cognitive complaints were difficulty remembering things, cognitive fatigue and feeling slowed down. Additionally, almost one quarter of those still feeling affected reported more than one disabling issue, most commonly a combination of physical and cognitive or physical and emotional complaints. Those reporting disabling physical symptoms endorsed fatigue, headaches and dizziness as the most problematic. Emotional symptoms were also highlighted as an issue, affecting social commitments and relationships in those with the complaint; additionally, more than half of participants indicating more than one disabling issue highlighted affective complaints as a significant barrier to recovery.

Predictors of Cognitive Complaints

Bivariate correlations were generated between reported symptoms on the RPQ-Cognitive subscale at 8-years and baseline characteristics linked to outcomes in mTBI [age at injury, gender, ethnicity and prior TBI]. Total scores for HADS Anxiety and Depression subscales from 1-month post-injury were also included in the covariate matrix to determine any interactions between the baseline characteristics and potential predictors in the final regression model.

Age at injury was significantly correlated with RPQ-Cognitive subscale total score such that older age at injury was associated with more cognitive complaints at 8-years (r = .277, p = .001) and was included in the final regression model. Gender was not significantly correlated with RPQ-Cognitive subscale total score at 8-years post-injury (r = .134, p = .102). Due to consistent reports in the literature regarding gender and outcomes following mTBI, and the correlation between gender and prior TBI reaching significance (r = .165, p = .046), gender was included in the final regression model. Ethnicity was not significantly correlated with RPQ-Cognitive subscale total score at 8-years post-injury (r = .148, p = .069), and therefore was not included in the final regression model. Presence of prior mTBI was coded numerically, with values 0-3 representing the corresponding number of previous injuries, and value of 4 representing 4 or more prior head injuries. Prior TBI was significantly correlated with RPQ-Cognitive subscale total score; previous head injury, as reported at 1-month post-injury, was associated with more cognitive complaints at 8-years (r= .202, p = 0.14). Mood symptoms have been highlighted as a predictor of outcomes in other studies, and have been shown to affect cognitive complaints. Therefore, it was pertinent to examine the relationship between RPQ-Cognitive scores and mood symptoms. Bivariate correlations were generated for HADS Anxiety and Depression scores at 1-month post-injury and total RPQ-Cognitive scores at 8-years post-injury. This relationship was significant for both Anxiety (r = .348, p < .001) and Depression (r = .428, p < .001), such that higher scores for both symptom subscales at 1-month post-injury were associated with more cognitive complaints at 8-years.

Subjective cognitive complaints were based on the RPQ-Cognitive subscale total score. The final predictors included in the model were chosen based on PCS outcomes reported in the literature, and informed by correlations conducted on the current sample as reported above. The regression was compiled in two blocks, with participant characteristics in the first block (age at injury, previous TBI, gender) and mood symptoms in the second block (HADS Anxiety and Depression scores at the 1-

month assessment). The overall model was significant and explained 32.1% of the variance; summary statistics are provided in Table 10.

The first block was based on participant characteristics, and included age at injury, previous TBI and gender. These characteristics made a statistically significant contribution to the model and explained 19.5% of the variance ($F_{(3, 103)}$ = 8.16, p < .001). Age at injury and previous TBI made the greatest contribution, both of which were statistically significant. The inclusion of mood symptoms at 1-month post-injury created a model that explained 32.1% of the variance ($F_{(5, 99)}$ = 9.37, p < .001). In the final model, age at injury and HADS Depression made the greatest contribution, and were the only components making a statistically significant contribution. With the inclusion of mood symptoms, prior TBI was no longer a significant predictor, and gender remained an insignificant contributor to the final model.

Table 10
The final regression model predicting RPQ-Cognitive scores at 8-years post-injury, including standard errors and significance of the predictors (*n* = 105)

	b	95% CI	SE B	β	*t*	*p*
Step 1						
Constant	-1.08	(-3.23, 1.06)	1.08		-1	p = .319
Age at Injury	0.08	(0.04, 0.12)	0.2	.35	3.93	p < .001
Prior TBI	0.81	(0.19, 1.42)	0.31	.24	2.6	p = .011
Gender	0.9	(-0.46, 2.26)	0.69	.12	0.12	p = .191
Step 2						
Constant	-1.99	(-4.15, 0.17)	1.09		-1.82	p = .071
Age at Injury	0.08	(0.04, 0.12)	0.02	.34	4.02	p < .001
Prior TBI	0.52	(-.08, 1.12)	0.3	.15	1.72	p = .089
Gender	0.21	(-1.09, 1.51)	0.66	.03	0.32	p = .751
HADS-D	0.27	(0.04, 0.5)	0.11	.26	2.36	p = .020
HADS-A	0.14	(-.08, 0.34)	0.11	.15	1.29	p = .201

Note: R^2 = .195 for Step 1 (*p* <.001) ; ΔR^2 = .126 for Step 2 (*p* < .001)

Summary of Results

Group differences. In summary, the mTBI group scored higher on all RPQ subscales than the Comparison group. Additionally, a greater number of participants in the mTBI group met symptom-severity criteria for Mild and Moderate PCS.

Evaluating change over time. The severity of PCS (RPQ-3 and RPQ-13 scores) was greatest at 1-month post-injury and showed a significant decrease by 12-months post-injury. The scores showed a slight increase from 12-months to 8-years, however this did not reach statistical significance. The cognitive subscale showed the same trend, however one symptom (forgetfulness/poor memory) showed a statistically significant decrease from 1-month to 12-months and subsequently a statistically significant increase from 12-months to 8-years. Anxiety scores were highest at 1-month, showing a statistically significant decrease from 1-months to 12-months, and then remained stable from 12-months to 8-years. Depression scores decreased from 1-month to 12-months post-injury, however this decrease was not statistically significant. Unlike anxiety scores, depression scores were highest at 8-years post-injury. The increase in score from 12-months to 8-years was statistically significant.

Predicting cognitive complaints. The final regression model included participant characteristics and mood symptoms from 1-month post-injury. The resulting model showed older age at injury and higher depression scores at 1-month post-injury as making the only statistically significant contribution to the final model.

Discussion

This thesis investigated the presence and severity of post-concussion symptoms in a previously identified community-based sample of adults 8-years post-mTBI. Additionally, the change in symptoms over time was evaluated by comparing previous reports of PCS from 1-month, 12-months and now, 8-years post-injury. The final aim of this thesis was to evaluate the predictive value of individual and injury-related characteristics to cognitive complaints 8-years post-injury.

At 8-years post-injury, it was hypothesised that the mTBI group would report more post-concussion symptoms than the Comparison group. As expected, the difference in mean scores between groups was statistically significant, with the mTBI group reporting more severe PCS than the Comparison group on the RPQ-3 and RPQ-13. Additionally, a higher proportion of individuals in the mTBI group met the symptom-severity criteria for both mild and moderate PCS. In our sample, two-thirds of participants reported four or more post-concussion symptoms as at least a mild problem at 8-years post-injury. Even when the symptom-severity threshold was increased, over 30% of participants in the mTBI group still met symptom-severity criteria for PCS, reporting four or more symptoms as either a moderate or severe problem. The indication that considerable symptoms are still present 8-years post-injury is inconsistent with the literature expecting recovery within 3 to 6-months post-TBI, however our result is consistent with the high levels of moderate PCS reported in a long-term follow-up study by King & Kirwilliam (2011). In their sample of 24 individuals 7-years post-mild TBI, the mean RPQ score for the group reflected rates of at least 12 symptoms as a moderate problem on average (King & Kirwilliam, 2011).

In addition to the prevalence of PCS, it was hypothesized that participants in the mTBI group would have more cognitive complaints than the Comparison group. As predicted, the difference in RPQ-Cognitive scores were statistically significant,

with the mTBI group reporting higher scores than the Comparison group. This is in line with previous reports of increased self-reported cognitive symptoms four-years post-injury compared to a control sample (Theadom et al., 2018). Increased cognitive symptoms have also been reported in populations with prior TBI 5 to 10-years post-injury compared to control groups and individuals with history of traumatic orthopaedic injury (Dahm & Ponsford, 2015). In addition to increased cognitive difficulties, Dahm & Ponsford also reported levels of psychological distress and symptoms of anxiety were more prevalent in participants with TBI. Similarly, we found scores on the RPQ-Emotional subscale were significantly higher in the mTBI group. Interestingly, this difference in affective symptoms was not reflected in HADS Anxiety or Depression subscale scores, which were similar in each group. In contrast to cognitive and emotional symptoms, scores on the RPQ-Somatic subscale were similar between groups. This suggests that these symptoms are less specific to long-term outcomes from TBI, which may be attributed to the diversity of symptoms assessed in this subscale, as the questions include sleep difficulties (sleep disturbance, fatigue), perceptual disturbances (blurred vision, double vision, light sensitivity, noise sensitivity), and physical symptoms (headache, nausea, dizziness).

In addition to collecting new information, this study also examined symptom reporting over time. It was hypothesised that post-concussion symptoms would be most severe at 1-month post-injury. Symptom reporting was expected to decrease by 12-months post-injury, and would see only minor improvement at the 8-year assessment. As expected, the severity of PCS was highest at the 1-month assessment, with total scores on both the RPQ-3 and RPQ-13 showing a statistically significant decrease from 1-month to 12-months post-injury. Additionally, symptom-severity criteria for classification of PCS was used to identify participants experiencing post-concussion symptoms that may be clinically significant. The percentage of participants meeting symptom-related criteria for mild levels of PCS was highest at 8-years post-injury, however the prevalence of moderate PCS remained below 1-month levels. Using our classification criteria, this suggests that

the symptoms reported at 8-years have decreased in severity. The higher levels of mild PCS reported at 8-years may reflect an increase in symptom prevalence, with a more dynamic symptom profile of less severity. It has been suggested that symptoms sustained in persistent PCS do not develop until weeks to months after the injury (Eyres et al., 2005), and so the symptom profile at 1-month post-injury and 8-years post-injury may be considerably different. In fact, the symptoms commonly reported in the literature as problematic at the acute stage post-TBI (headache, dizziness, nausea/vomiting) were some of the least endorsed symptoms at the 8-year assessment.

In a study evaluating the variation in PCS within the first year after mild TBI, Roe et al. noted a decrease in participants meeting PCS criteria from 3-months to 6-months, but no further improvement from 6- to 12-months post-injury (Røe et al., 2009). When evaluating symptom prevalence, McMahon et al. reported an increase in symptoms from 3- to 6- and 3- to 12-months post-injury, with a considerable proportion of patients still endorsing symptoms at 12-months post-injury (McMahon et al., 2014). The improvement from 1-month to 12-months post-injury in our sample is consistent with the literature on recovery from TBI (Cassidy et al., 2014; Donovan et al., 2014), however, the lack of continued improvement from 12-months to 8-years suggests that the prevalence of symptoms may not decrease considerably after 12-months post-injury.

Scores on the RPQ-Cognitive subscale were highest at 1-month post-injury, decreasing from 1-month to 12-months and showing no statistically significant change at 8-years. Despite this result, 36% of participants reported still feeling affected by their head injury, with cognitive complaints being the most common. However, there was an anomaly to the trend of overall improvement. The symptom 'forgetfulness/poor memory' was highest at 1-month and did decrease in reported severity from 1-month to 12-months ($p < .001$); however, the overall change, from 1-month to 8-years was not statistically significant ($p = .449$), suggesting that the

severity of this symptom has not decreased significantly from 1-month post-injury to the 8-year follow-up, despite the statistically significant decrease in severity reported at the 12-month assessment. In a follow-up study 6-years post-mild TBI, Konrad et al. found significant impairments in working memory and attention (Konrad et al., 2011). Additionally, Vanderploeg et al. reported long-term, subtle deficits in complex attention and working memory 8-years post-mild TBI (Vanderploeg et al., 2005). Subjective cognitive complaints post-TBI have not consistently been linked to objective neuropsychological assessments; however, cognitive complaints are common following head injuries and are often the most reported post-concussive symptoms (Røe et al., 2009).

Cognitive complaints post-TBI have also been attributed to emotional symptoms, such as anxiety and depression. In the current study, symptoms of anxiety were highest at 1-month, and showed a statistically significant decrease which was maintained at the 8-year assessment. In contrast to the change in anxiety scores, which improved over time, symptoms of depression were highest at 8-years post-injury. To investigate the relationship of acute mood symptoms to long-term cognitive complaints we evaluated the relationship between HADS Anxiety and Depression scores at 1-month post-injury and scores on the cognitive subscale of the RPQ at 8-years post-injury. It was hypothesised that higher levels of mood symptoms at the 1-month assessment would be associated with increased cognitive complaints at 8-years post-injury. Participant characteristics known to be associated with outcomes post-TBI include age at injury, gender and previous head injury. We found age at injury and history of previous head injury were the most predictive injury-related characteristics to total scores. The inclusion of HADS Anxiety and Depression scores from 1-month post-injury resulted in a model that explained 32.1% of the variance in RPQ-Cog scores at 8-years. This contribution was significant, which suggests that levels of mood symptoms at the acute stage post-TBI may be a risk factor for persistent cognitive symptoms/complaints at 8-years post-injury. This finding is consistent with other studies reporting higher levels of emotional distress

with persistent symptoms (van der Naalt et al., 2017). Unlike many studies reporting predictors of outcomes, we did not find a significant relationship of gender or ethnicity to mood or cognitive outcomes; age at injury and symptoms of depression were the only significant contributors in the final model.

Strengths & Limitations

This study investigated long-term outcomes of a population-based sample of adults sustaining a mild TBI in the study region. This limits potential severity bias, which may be present studies that use hospital-based samples. Additionally, the identification of participants with mild TBI from a wide range of sources results in a comprehensive sample of individuals sustaining head injuries. Due to the limited number of individuals sustaining mild TBI that seek medical attention, the results of this study may be more generalisable to the population and individuals sustaining mild TBI in the future. Additionally, the number of follow-up assessments and availability of injury-related information is a unique and valuable contribution to the literature on outcomes post-TBI. Maintaining the use of measures throughout multiple time-points post-injury allows for comparative analysis and evaluation of recovery over multiple assessments spanning the acute- post-acute and long-term outcomes. Finally, the number of studies evaluating outcome of mTBI beyond 24-months post-injury are limited, but given the prevalence of persistent post-concussion symptoms exceeding the 12-month recovery period, longitudinal studies are necessary to determine the fate of the 'miserable minority.' Identification of risk and protective factors, as well as characteristic acute symptom profiles of those who continue to experience post-concussion symptoms long-term, will be essential to inform clinical practice and treatment of the diverse and dynamic symptom profile of those with delayed recovery.

The use of a single outcome measure is both a strength and a limitation of the analysis and conclusions used in this thesis. The ability to compare recovery and

symptoms over time is valuable, however the RPQ has been developed to assess more acute symptoms post-TBI. Use of an outcome measure designed to identify PCS longer-term post-injury may have provided better insight into current symptoms. Additionally, elimination of the response option for 'no more of a problem' on the RPQ may have contributed to increases in mild symptom reporting. However, the Comparison group had the same response options and RPQ scores were significantly higher in participants post-mTBI, suggesting that even 8-years post-injury mild TBI is associated with greater PCS than rates in the general population. As with any longitudinal study, the attrition of participants over the course of the study may result in selection-bias. However, because the origin of the sample is population-based, there is less bias than would be expected in a hospital-based sample. Finally, changes and trends were only examined at the group level, which may mask individual variations in recovery trajectory, symptom severity and protective factors for favourable outcomes. Further research and evaluation of outcomes at an individual patient level is necessary to determine the specific relationship and predictive value the characteristics identified in this study contribute to cognitive outcomes 8-years post-TBI. Additionally, further investigation into the prevalence of emotional symptoms as reported on the HADS and RPQ-Emotional subscale may provide valuable insight into the interplay of affective disorders, mood symptoms and subjective cognitive complaints and identification of affective symptoms adversely impacting long-term recovery.

Conclusions

The results of this study confirm that post-concussion symptoms are still prevalent 8-years post-mild TBI. Symptom severity was highest at 1-month post-injury, and significantly decreased by 12-months post-injury. However, there was no additional improvement from 12-months to 8-years. In fact, 36% of participants reported they still feel affected by the brain injury they sustained 8-years ago. The prevalence of post-concussion symptoms was still quite high in the sample at 8-years with two thirds of participants still reporting at least four post-concussion symptoms.

Cognitive difficulties were the most reported PCS, suggesting cognitive symptoms may persist longer and be more severe than other symptoms. In our sample, subjective cognitive impairment and symptoms of depression were the most prevalent complaints. This finding is consistent with the increased levels of depression reported in patients post-TBI, and the relationship between depression and cognitive symptoms (Rapp et al., 2013; Silver et al., 2009). These findings suggest prevalence of depression and older age at injury may be risk factors for persistent cognitive complaints long-term. Clinical importance should be placed on evaluating the presence of mood symptoms early post-injury.

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