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Mild traumatic brain injury and fatigue: A prospective longitudinal study

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Abstract

Primary objective: To examine fatigue prevalence, severity, predictors and co-variates over 6 months post-mild traumatic brain injury (MTBI).

Research design: Longitudinal prospective study including 263 adults with MTBI.

Procedures: Participants completed the Fatigue Severity Scale (FSS), Rivermead Post-concussion Symptoms Questionnaire (RPSQ), Hospital Anxiety and Depression Scale (HADS) and the Short Form 36 Health Survey-Version 2 (SF-36v2). Complete data were available for 159 participants. Key measures; prevalence—RPSQ Item 6: severity—FSS. The effect of time on fatigue prevalence and severity was examined using ANOVA. Multiple regression analysis identified statistically significant covariates.

Main outcomes and results: Post-MTBI fatigue prevalence was 68%, 38% and 34% at 1 week, 3 and 6 months, respectively. There was a strong effect for time over the first 3 months and moderate-to-high correlations between fatigue prevalence and severity. Early fatigue strongly predicted later fatigue; depression, but not anxiety was a predictor. Fatigue was seen as laziness by family or friends in 30% of cases.

Conclusions: Post-MTBI fatigue is a persistent post-concussion symptom, exacerbated by depression but not anxiety. It diminishes in the first 3 months and then becomes relatively stable, suggesting the optimum intervention placement is at 3 months or more post-MTBI.

Keywords: *Fatigue, mild traumatic brain injury, concussion, depression, anxiety, FSS, FAS, RPSQ, HADS, SF-36v2*

Introduction

Fatigue is one of the three most common symptoms of mild traumatic brain injury (MTBI) interfering with participation in work, home and social activities and, thereby, reducing quality of life [1–5]. Reviews report persistent post-MTBI fatigue prevalence rates of 22–59% at 3 months and longitudinal studies have listed post-TBI fatigue among the symptoms lingering for months and years [6–9].

Earlier studies demonstrated an association between post-TBI fatigue and factors such as acute symptoms, mechanism of injury, time since injury and higher education levels [5, 10]. Litigation is frequently cited as a predictor of persistent post-concussion syndrome (PCS) which includes fatigue [11, 12]. On the other hand, factors such as injury severity and mood (depression) have not been found to be significantly associated with post-TBI fatigue. As fatigue and low energy are among criteria for the diagnosis of depression [13, 14], the current study sought to clarify the relationship between depression and post-MTBI fatigue. The terms MTBI, mild

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head trauma and mild head injury are not synonymous as only MTBI implies brain injury; the others can refer to superficial injuries with no brain damage. However, in the course of the literature review it was noted that the three terms are used interchangeably. As the context of the articles clearly indicated that authors were referring to MTBI rather than superficial injuries, the authors have chosen to report these terms as they were used in articles cited.

A 2009 study [15] found fatigue severity 12 months after mild head injury was associated with characteristics (fatigue, medical disability, marital status and litigation) present in the month preceding the injury but not with the MHI directly. However, while pre-morbid characteristics are relevant to recovery, the data collection was part of a larger study and there was no opportunity to investigate participants' pre-morbid characteristics in depth. This study also sought to describe the temporal profile of post-MTBI fatigue with a view to guiding timing of an intervention and to study fatigue in a litigation-free population with mild TBI. Psychosocial issues play a part in recovery from MTBI and the reaction of professionals, family members, friends and colleagues impacts on recovery progress [16]. The family's perception of post-MTBI fatigue in their injured relative is not well researched. Seeing the fatigued person as 'lazy' is likely to result in unsupportive interactions, exacerbate any pre-existing psychological conditions and generally undermine recovery. This study aimed to provide data on the prevalence of post-MTBI fatigue being perceived as 'laziness' by family and friends of the person with post-MTBI fatigue.

Fatigue as experienced in the general population may be defined as a sense of tiredness or exhaustion following extended effort accompanied by reduced power and motivation to engage in effortful activity, independent of mood. This definition implies depleted energy resources which can be replenished by rest and sustenance. It is a relatively common problem within the general population and epidemiological studies report an incidence of between 5–41.2% incidence of prolonged fatigue, i.e. greater than 1 month [17–22]. An epidemiological study with a very large sample ($n = 15\,283$) found fatigue complained of by 18.3% of a general practice population [23].

Pathological fatigue, such as that associated with MTBI, occurs when the amount of effort required to induce the sense of tiredness or exhaustion, reduced power and motivation is considerably smaller than expected in a healthy individual. Energy resources are depleted more quickly and more extensively than normally expected and pathological fatigue is not as responsive to rest and sleep.

Comparative studies of post-concussion symptoms in both MTBI and healthy samples have shown fatigue is more prevalent within the MTBI population than in the healthy controls [10, 24, 25]. Several studies of fatigue in the community [20, 23, 26–28] drew their samples from primary care populations. The base rates of fatigue reported in these studies may be inflated by post-(M)TBI fatigue and other neurological-based fatigue conditions that were not screened out.

Severity of injury is another confounding factor in considering fatigue after TBI [5, 29]. Reporting findings for a mixed TBI severity group is likely to mask the 'real' picture for both the mild and the more severe injuries where disability is very often permanent and profound. Since 80% of TBI are mild [30], it is important to consider this group separately. This study focused on a large sample including only participants with MTBI. Additionally, severity ratings, rather than frequency, were found to distinguish 'normal subjects' from those who had a MTBI [31]. The current study sought to examine both severity and frequency of post-MTBI fatigue and how each of these changed over time.

Regardless of whether fatigue is normal or pathological, psychological factors such as depression and anxiety have been closely linked with fatigue, e.g. in the formal diagnostic criteria for depression such as in the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) [13] and the International Classification of Diseases and Related Health Problems, 10th Edition (ICD-10) [14]. Depression has a potential role in producing, exacerbating and maintaining PCS-like symptoms. After comparing normal, currently depressed and mild head injury (MHI, 12 months post-injury) groups, significant, large correlations were found between post-concussion symptoms (including fatigue) and both depression ($r = 0.68$) and anxiety ($r = 0.64$) [32]. While the MHI group scores more closely resembled the normal group scores, there were significant differences between the three groups for frequency and severity of fatigue and depression symptoms. Another study [33] found a positive relationship, which strengthened over time, between perceived stress and intensity of post-concussion symptoms. Treatment of depression in MTBI patients resulted in improvement of global and psychosocial functioning, post-concussive symptoms and neurobehavioural difficulties.

These studies used relatively small MTBI samples, whereas this study had a much larger MTBI sample within which to examine the relationship between post-MTBI fatigue, anxiety and depression. A significant relationship between depression and post-MTBI fatigue was expected for several reasons.

First, depression is a persistent symptom following MTBI [34]. Secondly, a current, oft quoted, neuroscience theory attributes post-TBI fatigue to injury in the Hypothalamic-Pituitary-Adrenal axis [35] and consequent interruption of the neurotransmitter (Serotonin, Dopamine, Norepinephrine, Acetylcholine) pathways associated with depression and euphoria [34]. Thirdly, the distress caused by ongoing excessive post-MTBI fatigue is likely to manifest as depression. For similar reasons, anxiety was also expected to have a significant relationship with post-MTBI fatigue prevalence and severity. This was particularly expected among the 'Miserable Minority' [31, 36, 37], those MTBI patients who are high achievers; anxious when they under-perform and when they can not resume their pre-accident participation as quickly as they would like.

Recovery from MTBI can be complicated by a combination of symptoms such as a new mental health condition (e.g. depression) and pain [38]. Sleep dysfunction and pain have been linked to fatigue in an investigation of post-concussive symptoms in a chronic pain sample [39], although Mooney et al. [38] and Rao et al. [4] pointed out that fatigue and sleep dysfunction can also be mediated by psychiatric symptoms.

While major sources of pain such as orthopaedic injuries were an exclusion criterion in this study, the link between fatigue and single item measures of headache and sleep dysfunction as well a general pain perception were examined as part of the symptom evaluation in anticipation of an association between pain and fatigue in people with MTBI.

Another relevant issue in the context of MTBI is the role of litigation. New Zealand has a unique system where all accident-related rehabilitation is covered by a 24-hour no-fault personal accident insurance cover funded primarily by the New Zealand government. Hence, the issue of litigation as a predictor of persistent symptoms such as post-MTBI fatigue [40–42] was minimized.

At the time this study was conducted the literature indicated that post-MTBI fatigue was significantly related to factors such as acute symptoms, mechanism of injury, time since injury and higher education levels. Less clarity existed around the relationship with factors such as injury severity, anxiety and depression and the temporal profile of post-MTBI fatigue. Also, litigation is frequently cited as a predictor of persistent post-concussion syndrome (PCS). This study used a prospective longitudinal design, in a MTBI population, to address these factors and aimed to investigate the prevalence of post-MTBI fatigue and to track its temporal profile over the first 6 months post-injury.

Another important aspect of the present study was the examination of factors predicting persistent fatigue at an early stage post-injury. In a concussion clinic setting, a screen that predicted, early on, which individuals are at risk of developing pathological fatigue would be useful as it would identify individuals in need of intervention as early as possible. The current study employed several measures of fatigue prevalence and/or severity. These varied from a single item through scales of four and nine items to allow comparison to test whether a single item, the most parsimonious solution, could effectively identify an early predictor of persistent post-MTBI fatigue.

The study also examined the association of psychological factors such as depression, anxiety, emotionality and mental health to post-MTBI fatigue. Previous studies noted the likely association between psychosocial issues, mood and persistent PCS [43, 44]; however, this study sought to clarify the relationship with one PCS symptom, fatigue.

An understanding, well-informed social support network facilitates rehabilitation [45], while critical non-supportive beliefs among family and friends could potentially slow a person's recovery from post-MTBI fatigue and exacerbate psychological reactions such as depression, anxiety or personality disorders [16]. The opportunity was taken, during this study, to explore the prevalence of post-MTBI fatigue sufferers being considered 'lazy' by their significant others. Such a perspective could impact both on the type of support received and the emotional health of the post-MTBI fatigue sufferer.

This investigation into post-MTBI fatigue was carried out in conjunction with a larger prospective, longitudinal study [46] investigating outcome prediction after mild closed head injury.

Method

Participants

Participants were recruited from the body of patients presenting with mild closed head injury [47] to Christchurch Hospital (the main hospital for a population pool of >400 000 in the South Island of New Zealand). Patients had to have a Glasgow Coma Scale (GCS) score of between 13–15 on first assessment, without falling below 13 at any consecutive assessment at the hospital. Patients whose first GCS score was taken more than 1-hour post-injury but whose case history and injury mechanism was considered consistent with mild head trauma were eligible for the study if all subsequent GCS scores were above 13. Post-injury loss of consciousness (LOC) had to be less than 20 minutes and duration of post-traumatic amnesia (PTA) less than 24 hours. Duration of LOC was established based on available patient records or witness reports. Estimated PTA

duration was established retrospectively at the time of study assessment following an iterative protocol applied in previous studies [48, 49]. Potential participants were excluded if there was an abnormal CT scan, evidence of regular intake of psychoactive drugs or history of drug abuse, central neurological disorder or psychiatric condition, evidence of skull or facial fractures or presence of multiple trauma or significant trauma to other parts of the body (e.g. broken limbs or ribs, spinal injuries, soft tissue injury requiring plastic surgery). All participants were made aware that their future healthcare, including access to free public healthcare, would not be affected by their decision whether or not to take part in the study. Participants were offered compensation for travel costs to attend the study assessment but received no other payment. Several attempts were made to contact participants by phone and mail in order to improve the response return rate at follow-up. The project was approved by the Canterbury Ethics Committee/Upper South A Regional Ethics Committee, CTB/04/04/044, and this was endorsed by the Massey University Human Ethics Committee. Written consent was obtained from all participants.

Measures

The Fatigue Severity Scale (FSS) and a fatigue-related item from the Rivermead Post-concussion Symptoms Questionnaire were used to examine fatigue severity and prevalence, respectively. As fatigue is consistent with low energy, the Vitality Scale of the Short Form 36 Health Survey Version 2 (SF-36v2) [50, 51] enabled comparison between fatigue and energy within the sample. All three measures have been used extensively in fatigue research.

Fatigue Severity Scale (FSS) [52]. This has nine items. FSS items are rated on a 7-point Likert scale ranging from strongly disagree to strongly agree and the score is the average of the nine items. Krupp et al. [52], developers of the FSS, reported good internal consistency ($\alpha = 0.88$) and both test–re-test reliability and sensitivity to change consistent with predictions. Kleinman et al.'s [53] international study ($n = 1223$) reported as good internal consistency ($\alpha = 0.94$) and test–re-test reliability (intra-class correlation coefficient $= 0.82$). FSS means in normal, healthy samples were 3.35 (1.11) [5], 2.3 (0.7) [52] and 2.53 (1.18) [54]. Krupp [55] stated a score ≥ 4 was indicative of severe fatigue. In this study the cut-off for post-MTBI fatigue caseness was set at 3.7, that is, 1 SD above the mean for normal controls [54].

One item 'When I am tired my family, or partner, thinks I am being lazy' was added to the end of the FSS to assess significant other's attitude towards fatigue.

Rivermead Post-concussion Symptoms Questionnaire (RPSQ) [56]. On the RPSQ the participants rated the presence and problem-status of 16 possible post-concussional symptoms, including fatigue, on a scale from 0–4, comparing the presence and problem-status of each symptom with its pre-morbid status ($0 =$ not experienced at all after the injury, $1 =$ experienced but no more of a problem compared to before the injury, $2 =$ a mild problem, $3 =$ a moderate problem and $4 =$ a severe problem). For the initial assessment at ~1 week post-injury, the assessment period for answers on the RPSQ was extended from 'the previous 24 hours' to 'the time post-injury'. For the follow-up assessments at 3 and 6 months post-injury, the assessment period was 'the previous 2 weeks' in keeping with the time frame for the fatigue assessment. Fatigue prevalence was the frequency with which RPSQ-Item 6 was rated ≥ 2.

Vitality scale of the Short Form 36 Health Survey–Version 2 (SF-36v2) [51]. The SF-36v2 is a multi-purpose, short-form, 36 item, health survey with eight sub-scales, Physical Functioning, Role Physical, Bodily Pain, General Health, Vitality, Social Function, Role Emotional and Mental Health [51]. The Vitality sub-scale is a measure of both fatigue and energy with good internal consistency (alpha > 0.70) and test–re-test reliability across a wide range of illness conditions [57–60]. A high score on the vitality sub-scale indicates low fatigue. The correlation between the vitality scale and the FSS was $r = -0.76$) [53]. Vitality sub-scale internal consistency for an MTBI group ranged from 0.83–0.91 across the SF-36v2 sub-scales [61], indicating the Vitality sub-scale had good reliability within a MTBI sample. At the first assessment participants were asked to refer only to the time period since injury when answering the questionnaire items. At follow-up participants were asked to use the standard, preceding 4-week time period, when responding to the measure. The key measure for each scale was the 'Transformed Scale Score' with a best score of 100.

Psychological factors were measured using the Hospital Anxiety and Depression Scale [62] which has been extensively used in health research.

Hospital Anxiety and Depression Scale (HADS) [62]. The HADS is a 14 item measure of generalized anxiety and depression. Items are rated 0–3.

Two scales; anxiety and depression. Both clinically and in research it is a widely used instrument found to be reliable and valid [63]. Cronbach alphas ranged from 0.68–0.93 (mean = 0.83) for anxiety and from 0.67–0.90 (mean = 0.82) for depression. An updated literature review [64] reported the HADS cut-off score of ≥ 8 gave a sensitivity range of 0.90–0.66 and a specificity range of 0.78–0.83 across medical samples. A study of a small MTBI sample [65] found, with a cut-off score of ≥ 8, the HADS-Anxiety scale had 0.75 sensitivity and 0.69 specificity and the HADS-Depression scale had 62% sensitivity and 92% specificity. This study found the HADS to be a reliable measure of emotional distress but cautioned against using it as the sole diagnostic tool for depression or anxiety. Internal consistency of the English version is acceptable as is 2-week re-test reliability ($r > 0.8$). Over time the test–re-test reliability reduces suggesting HADS is a suitable measure of change. The two factors, anxiety and depression, explain 50% of the variance, remain stable across sub-groups, correlate highly with the corresponding sub-scales ($r > 0.9$) [63]. One major advantage of the HADS is that it excludes somatic symptoms such as insomnia, anergia and fatigue [66], making it a suitable instrument to use while exploring fatigue in an MTBI population.

Procedure

Consenting participants recruited from the Emergency Department of Christchurch Hospital between July 2006 and August 2008 were assessed as soon as possible but not later than 10 days post-injury. Participants completed a set of questionnaires including the SF-36v2, RPSQ, HADS and the FSS. Questionnaires were mailed out with freepost return envelopes for follow-up at 3 and 6 months post-injury. Participants who did not return their questionnaires within 3 weeks of mailing the follow-up letter were reminded via email and/or phone as required. Participants who failed to return their follow-up questionnaires after two reminder contacts were not further contacted.

Statistical analyses

The Statistical Package for the Social Sciences (SPSS) was used for statistical analysis. Only participants for whom there was fatigue follow-up data at each time period and who had not reported confounding temporary illness during the project ($n = 159$) were retained for the primary analyses. Results were considered significant at $p < 0.05$. Prevalence of fatigue was based on RPSQ Item 6 and severity on the Fatigue Severity Scale (FSS). Pearson correlation coefficients were calculated to examine the relationship between the primary dependent variables, fatigue prevalence and severity, energy, depression and anxiety for each time period and across time periods. A one-way analysis of variance was carried out to explore how fatigue prevalence and severity and energy changed over time. An hierarchical regression analysis was carried out to examine the relationship between the dependent variable 6 month fatigue severity and independent variables 3 month fatigue severity, depression and anxiety. The Receiver Operating Characteristic (ROC) curve [67] was used to calculate sensitivity and specificity of the RPSQ fatigue item in discriminating individuals who exhibited pathological fatigue (FSS) at 6 months from those who did not.

Results

Of the 263 recruited participants, full fatigue-related follow-up data was available for 180, but 21 of these had to be withdrawn because they had another accident or illness which would have distorted the fatigue analysis. Comparison between the group with fatigue data at all three data points ($n = 180$) and the remainder of the initial sample ($n = 83$) showed a small ($\cong 0.02$) significant group effect for GCS score at 1 hour post-injury, time since injury and anxiety, vitality and prevalence of sleep difficulties at 1 week. Of the 159 participants on whom most of the analysis was based, 57 were female and 102 male, aged between 16–70, mean 35.92, SD 15.63 years. Thirty-seven per cent were ≤ 25 years old and 41.5% were ≥ 40 years, the age after which MTBI recovery takes longer [68]. First GCS scores were available for 158 participants, mean 14.8, SD 0.49. Of the 86 for whom PTA information was available, 80% had PTA ≤ 60 minutes. Mean years of education was 14.64, SD 2.8. Sixty-five participants reported LOC with a mean duration of 2.82 minutes and standard deviation of 3.98 minutes. Almost 35% had sustained a previous TBI.

While only 159 of the 263 recruited participants had full follow-up fatigue data, it was available for 228 (86.7%) at 3 months and 202 (76.8%) at 6 months. The majority of participants reported post-MTBI fatigue in the immediate weeks after their injury and this number reduced to just over a quarter of the population at 6 months. Approximately 50% reported fatigue 1 SD above the norm [55] in the early period (1 week) and over 30% still reported this severity of fatigue at 3 and 6 months post-injury (Table I).

It has been argued [68] that findings of problems with fatigue can be distorted due to a greater likelihood that those with pathological fatigue would remain participants of the project. To address this argument, the fatigue percentages for those for

Table I. Prevalence and severity of post-MTBI fatigue at 1 week, 3 and 6 months for all participants.

	Prevalence[a] (*n*)	Severity[b] (*n*)
1 week	68.1% (263)	54.9% (255)
3 months	31.4% (226)	37.6% (218)
6 months	28.2% (202)	34.4% (195)

[a]Rivermead Post-concussion Symptom Questionnaire Item 6 $\geq$ 2;
[b]Fatigue Severity Scale $\geq$3.7.

Table II. Prevalence and severity of post-MTBI fatigue at each interval for population with data available at all three intervals.

	Prevalence[a]	Severity[b]
1 week	67.3%	54.1%
3 months	29.6%	35.8.4%
6 months	26.4%	34.0%

$n = 159$.
[a]Rivermead Post-concussion Symptom Questionnaire Item 6 $\geq$ 2;
[b]Fatigue Severity Scale $\geq$3.7.

whom data was available at each measurement point ($n = 180$) less those reporting a health condition are reported in Table II ($n = 159$).

There were moderate-to-high correlations ($p < 0.000$) between FSS (severity), RPSQ Item 6 (prevalence) and the Vitality sub-scale (energy) at most time periods (Table III). These findings suggest convergent validity between the two fatigue measures, but the relationship with the vitality measure is less clear. At 1 week, the relationship between Vitality and the fatigue measures was not significant, however, at 3 and 6 months there were moderate-to-high correlations with the other fatigue measures ($p < 0.000$). Moderate-to-high correlations were found between depression and post-MTBI fatigue severity and most of the correlations between anxiety and fatigue severity were moderate. Table III also shows that depression and anxiety were strongly correlated within each stage, 1 week, 3 and 6 months, but across stages correlations for these two factors were in the moderate range.

Given the strong relationship between depression and anxiety at each interval a hierarchical regression analysis was carried out and both depression and anxiety were independently found to make significant unique contributions to fatigue. However, when depression, which had a stronger correlation with fatigue, was held constant, anxiety did not make a significant unique contribution to fatigue. Depression regression coefficients ranged from $\beta = 0.34$–0.66 for fatigue at each interval and from $\beta = -0.49$ to -0.66 for vitality at 3 and 6 months ($p < 0.0005$). There were no significant regression coefficients for anxiety (all *p*'s >0.05).

Pain and sleep dysfunction

A combination of pain, anxiety, depression and sleep difficulties predicts post-MTBI fatigue severity accounting for 37.7%, 28.4% and 47.6% of the variance at each data point, respectively. However, when fatigue prevalence and depression are held constant stepwise then the other symptoms (pain, sleep difficulties and anxiety) add very little to the variance (<1–3%) across the data points.

Fatigue over time

Table IV shows the means and standard deviations for fatigue prevalence and severity and for energy (vitality). Each of the measures shows a larger reduction between 1 week and 3 months than between 3 and 6 months.

To determine whether these changes were significant over time, each of the dependent variables, prevalence (RPSQ), severity (FSS) and energy (SF-36v2 Vitality) was analysed using a one-way repeated measures ANOVA. There was a large effect of time, over the 6 months post injury, for all three measures (Table V). Post-hoc analysis (paired-samples *t*-test) indicated that while significant change occurred for all three measures over the first 3 months, there was no further significant change over the second 3 months, suggesting a recovery plateau and/or fatigue and low energy becoming persistent post-concussion symptoms.

The relationship between duration of loss of consciousness (LOC) and FSS at 3 months was significant ($r = 0.3$, $p < 0.05$). The Glasgow Coma Scale score, length of PTA, gender, years of education, occupation and alcohol at time of accident were not significantly correlated with FSS.

In the sample for whom full data was available ($n = 159$), early fatigue severity (FSS at 1 week) predicted later fatigue severity at 3 ($r = 0.53$, $p < 0.000$) and 6 months ($r = 0.49$, $p < 0.000$) and accounted for 28% and 24% of the variance, respectively. Fatigue severity at 3 months accounted for 56.7% of the variance and was a stronger predictor of fatigue at 6 months ($r = 0.76$, $p < 0.000$) than fatigue at 1 week. Indeed, in the whole sample ($n = 263$) fatigue severity at 1 week ($r = 0.40$, $p < 0.000$) and 3 months ($r = 0.53$, $p < 0.000$) predicted persistent PCS (RPSQ total) at 6 months.

As neuropsychological function is frequently found to be restored in the early weeks post-MTBI [68] many attribute persistent post-concussion symptoms to psychological factors rather than to the effects of the injury itself [69]. Moderate-to-strong relationships were found between measures of fatigue and psychological factors such as depression and anxiety (Table III) which seemed to support the

Table III. Comparison of the single item measure of fatigue (RPSQ item 6), the nine item FSS, the four item SF36v2 Vitality sub-scale, depression and anxiety over time and within the measures ($n = 159$).

	FSS1	FSS3	FSS6	RPSQ1	RPSQ3	RPSQ6	Vit1	Vit3	Vit6	Dep1	Dep3	Dep6	Anx1	Anx3	Anx6
FSS1	1														
FSS3	0.53**	1													
FSS6	0.49**	0.76**	1												
RPSQ1	0.57**	0.16*	0.20*	1											
RPSQ3	0.30**	0.45**	0.40**	0.24**	1										
RPSQ6	0.38**	0.50**	0.62**	0.34**	0.60**	1									
Vit1	ns	ns	ns	ns	ns	ns	1								
Vit3	0.42**	0.66**	0.56**	−0.20*	−0.57**	−0.52**	ns	1							
Vit6	0.40**	0.39**	0.59**	−0.20*	−0.51**	−0.70**	ns	0.69**	1						
Dep1	0.52**	0.34**	0.34**	0.52**	0.31**	0.37**	ns	−0.35**	−0.36**	1					
Dep3	0.30**	0.44**	0.50**	ns	0.45**	0.44**	ns	−0.54**	−0.57**	0.37**	1				
Dep6	0.32**	0.54**	0.65**	ns	0.44**	0.65**	ns	−0.49**	−0.75**	0.46**	0.61**	1			
Anx1	0.37**	0.40**	0.28**	0.34**	0.29**	0.28**	ns	−0.35**	−0.28**	0.67**	0.31**	0.40**	1		
Anx3	0.26**	0.32**	0.32**	0.16*	0.39**	0.40**	−0.18*	−0.38**	−0.36**	0.29**	0.63**	0.38**	0.31**	1	
Anx6	0.26**	0.48**	0.51**	ns	0.38**	0.51**	ns	−0.43**	−0.62**	0.35**	0.45**	0.75**	0.44**	0.45**	1

FSS = Fatigue Severity Scale; RPSQ = Item 6 of Rivermead Post-concussion Symptoms Questionnaire; Vit = SF36v2 Vitality sub-scale where high values are equivalent to low fatigue; Dep = HADS Depression; Anx = HADS Anxiety. *$p \leq 0.05$; **$p \leq 0.000$.

Table IV. Descriptive statistics for fatigue and energy for 1 week, 3 and 6 months post-injury.

Time period	M	SD
RPSQ		
1 week	2.09	1.24
3 months	1.03	1.05
6 months	0.96	1.05
FSS		
1 week	3.99	1.53
3 months	3.29	1.44
6 months	3.20	1.39
SF36v2 Vitality		
1 week	46.57	24.72
3 months	60.21	19.68
6 months	62.11	20.18

$n = 159$.
RPSQ = Item 6 of Rivermead Post-concussion Symptoms Questionnaire; FSS = Fatigue Severity Scale; SF36v2 = Short Form 36 Health Survey–Version 2.

Table V. ANOVA summary of the within-subjects effects for fatigue prevalence and severity and energy over the first 6 months post-MTBI.

	df	F	partial η^2
Fatigue prevalence (RPSQ)	2,157	60.556**	0.44
Fatigue severity (FSS)	2,157	23.60**	0.23
Energy (SF36v2-Vitality)	2,157	17.573**	0.18

$n = 159$.
**$p < 0.0005$, RPSQ = Item 6 of Rivermead Post-concussion Symptoms Questionnaire, FSS = Fatigue Severity Scale, SF36v2 = Short Form 36 Health Survey–Version 2.

argument for psychological factors being a strong predictor of ongoing post-MTBI fatigue. Multiple regression analysis showed fatigue severity, depression and anxiety at 3 months together accounted for 59.6% (adjusted R-square) of the variance in fatigue severity at 6 months. The beta values in Table VI demonstrate that, of the three independent variables included, fatigue severity at 3 months is the strongest significant predictor of fatigue severity at 6 months and depression at 3 months is also a significant predictor but anxiety at 3 months is not.

The RPSQ fatigue item served as a quick screen to identify the presence of post-MTBI fatigue and accounted for ∼32.6%, 20.1% and 37.4% of the variance in fatigue severity at each interval, respectively ($n = 159$, $p < 0.0005$). Hierarchical regression analysis showed that when fatigue severity was held constant for any particular time period then the RPSQ fatigue item at that time period added little to the variance of fatigue severity in the next time period. For instance fatigue severity at 1 week (FSS1) accounted for 28% of the variance of fatigue severity at 3 months (FSS3) and fatigue prevalence at 1 week (RPSQ1) added just 3.1% to the variance of fatigue severity at 3 months. The sensitivity and specificity of Item 6 within the first 10 days after injury to correctly identify pathological fatigue at 6 months (FSS6) was 0.74 and 0.63, respectively. Both Type one and two errors became increasingly more likely when Item 6 was used to predict persistent fatigue severity at 3 or 6 months post-injury (Table VII).

A potentially unsupportive interpretation of fatigue-related behaviours as 'laziness' by family members was reported by up to 30% of all

Table VI. Summary of hierarchical regression analysis with fatigue severity, depression and anxiety, at 3 months, as predictors of fatigue severity at 6 months post-MTBI ($n = 159$).

Variable	B	SE B	β	Semi-partial correlation	Sig.
Constant	0.92	0.18			0.000
FSS3	0.64	0.05	0.69	0.69	0.000
Depression3	0.12	0.04	0.25	0.25	0.000
Anxiety3	−0.01	0.03	−0.04	−0.04	0.610

FSS = Fatigue Severity Scale.

Table VII. Sensitivity and specificity of RPSQ Item 6 (fatigue) ≥ 1.5 in discriminating pathological fatigue at 6 months (FSS6 $\geq$ 3.7) ($n = 192$).

	Sensitivity	1 – Specificity
RPSQ 1 week	0.74	0.63
RPSQ 3 months	0.42	0.24
RPSQ 6 months	0.55	0.12

RPSQ = Item 6 of Rivermead Post-concussion Symptoms Questionnaire.

participants at each interval. The correlation between post-MTBI fatigue severity and being thought lazy increased from time 1 ($r = 0.21$, $p < 0.01$) to time 2 ($r = 0.51$, $p < 0.0005$) then remained stable over the next 3 months, suggesting a less supportive environment for rehabilitation.

Discussion

This study examined fatigue in the first 6 months after MTBI using a prospective longitudinal design whilst excluding known confounding factors such as litigation, presence of psychological or neurological disorders and substance abuse. Importantly the study focused on a participant sample including only MTBI, thus providing specific evidence on the role of fatigue after mild head trauma not easily identifiable in previous studies that used mixed severity samples.

The results show that over half of the participants reported pathological fatigue, immediately after injury and that a third to a quarter of the sample continued to report pathological fatigue 3 and 6 months later, respectively. For those reporting fatigue problems at 3 months, there was a strong likelihood they would report fatigue at 6 months post-MTBI. Clinically this is an important finding of the study as post-MTBI fatigue appears to move into the realm of persistent post-concussion symptoms at ~3 months post-MTBI. The implication of this

finding is that a sizeable proportion of the MTBI population are likely to be in need of an intervention to reduce fatigue, build energy levels and return to a pre-injury participation level.

Epidemiological studies of persistent fatigue in the general population reported rates of between 5–41.2% [17–22, 70], with most studies reporting at the lower end of this range. These studies typically drew their samples from general medical practices whose patient bases could be expected to include some who had a recent MTBI and therefore were likely to report fatigue. Those few studies which drew samples from the healthy general population found fatigue prevalence was less than 20% [18]. Hence the finding of 31.4% fatigue prevalence and 37.6% mild-to-severe post-MTBI fatigue at 3 months suggests that fatigue is at least as common after MTBI as base rates within the population presenting for treatment to a primary care situation and more common than base rates within the normal healthy population.

The prevalence and severity of post-MTBI fatigue in this study was consistent with previous evidence, e.g. [4] showing that 29–59% of patients experience problems with fatigue at 3 months post-injury. Importantly, there were no differences for these measures between the entire study sample and the sub-group of participants for whom data was available at all time points. There was a small significant group effect for time since injury, GCS at 1 hour, anxiety, vitality and prevalence of sleep difficulties at 1 week, between those who were included in the study and those who were not because of incomplete data. Given that those whose data was incomplete or not present had higher scores on all these measures there is a likelihood that the findings under-estimate the prevalence and severity of post-MTBI fatigue in the long-term.

There was no significant change in the percentage of individuals with MTBI reporting fatigue prevalence (RPSQ) or severity (FSS) between 3–6 months. However, there was a significant increase in the percentage of those reporting depression and/or anxiety above the cut-off for mild problems at 6 months compared with reports at 3 months. This increase coincides with a levelling-off of the fatigue percentages within the sample population. A strengthening positive relationship has been found between perceived stress and intensity of post-concussion symptoms over time [33]. This study examined this relationship in more detail, with respect to fatigue, anxiety and depression, and found a pattern which suggests persistent symptoms are associated with increased distress, as illustrated by enduring elevated fatigue, anxiety and depression scores. Also, contrary to Ziino and Ponsford [5], this study found depression (but not anxiety) *was* a

significant predictor of post-MTBI fatigue. It was also found that when depression was held constant other factors such as pain and poor sleep did not contribute significantly to post-MTBI fatigue. The clinical implications of these findings are that both fatigue and psychological factors require treatment early to prevent symptoms worsening. However, whether the increased psychological symptoms are related to fatigue, to neurological sequelae (neurotransmitter disruption within the HPA pathway) or to pre-morbid psychological conditions remains unclear and could not be determined from this study.

The search for a parsimonious 'one-item-screen' to predict persistent post-MTBI fatigue is unlikely to be satisfied by using RPSQ item 6. Within the sample for which there was data at each time point, the initial RPSQ response accounts for ~12% of fatigue prevalence and 4% of fatigue severity at 6 months.

It was hypothesized that as fatigue symptoms persisted significant others would become less sympathetic towards the person with post-MTBI fatigue. The findings that 28% of participants with MTBI faced this type of attitude gives impetus to including family in interventions promoting recovery from post-MTBI fatigue.

There are several limitations of this study. The HADS is widely used in research but, despite this, it is not a diagnostic tool for anxiety and depression. It indicates the possibility of depression and anxiety, but a follow-up psychiatric or psychological assessment is required to determine whether there is a clinical level of anxiety or depression difficulties [71]. The HADS was originally developed to look for symptoms in non-psychiatric inpatients and, while Bjelland et al. [64] reviewed 747 studies involving the HADS there is minimal research on its validity and reliability following MTBI. A general problem with assessing depression and anxiety in patients who have a brain injury, acquired or traumatic, is the cross-over of symptoms between psychological conditions and the sequelae of MTBI. This is particularly true of HADS items such as Item 8 'I feel as if I am slowed down' which can refer to brain injury-related slowed information processing or to depression-related low motivation and lassitude. Hence, the HADS scales must be interpreted with caution [71, 72].

Another limitation was that there was no systematic attempt to measure pre-injury fatigue status. However, many clinicians and researchers are of the belief that the individual's perception of their pre-injury status is not reliable. It is likely to be coloured by their post-injury status and other issues such as personal resilience and secondary gain factors such as financial or emotional support [73].

A further limitation was that the terms MTBI, mild head trauma and mild head injury are used interchangeably across studies. This causes confusion, as MTBI refers to brain injury whereas head trauma/injury can refer to superficial wounds, such as lacerations or contusions with or without actual brain injury. The authors have chosen to use the terms employed by the authors cited. de Leon et al. [15], reviewing predictors of fatigue following mild head injury, found a dose–response effect for fatigue when severity of injury was considered. However the 'time to follow commands' [74, 75] measure of severity was not available as the protocol for recruiting participants approved by the ethics committee did not allow collection of this type of information. Additionally, the protocol in the Emergency Department for triage of patients presenting with head injury did not include automatic assessment of post-traumatic amnesia such as 'time to follow commands'.

The primary purpose of the larger 'mother-study', under which the present investigation into post-MTBI fatigue was conducted, was the examination of eye movement control and the relationship of oculomotor control with health recovery after MTBI. As a result, no explicit record was kept of participants' medications, other than those referred to in the exclusions (e.g. psychoactive medication). Medications which might have caused fatigue could potentially inflate the numbers reporting fatigue during their recovery period and this potential inflation constitutes another limitation.

In conclusion this study examined post-MTBI fatigue in a non-litigious population and found that not only does it persist for at least 6 months post-injury but also that it does not improve significantly after ~3 months. As the fatigue becomes more persistent, psychological factors such as anxiety and depression tend to worsen. These findings are useful in guiding interventions for post-MTBI fatigue and have helped to inform the design of a post-MTBI fatigue treatment programme developed by the lead author.

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