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Review

A systematic review of fatigue in patients with traumatic brain injury: The course, predictors and consequences

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ABSTRACT

Background: Fatigue is common after traumatic brain injury (TBI). Its risk factors, natural history and consequences are uncertain. Best-evidence synthesis was used to address the gaps.
Methods: Five databases were searched for relevant peer-reviewed studies. Of the 33 articles appraised, 22 longitudinal studies were selected. Results were reported separately based on their timing of baseline assessment.
Results: All studies document changes in fatigue frequency and severity with time, irrespective of setting or TBI severity. There is limited evidence for certain clinical and psychosocial variables as predictors of fatigue severity at follow-up. Early fatigue severity predicted persistent post-concussive symptoms and Glasgow outcome score at follow-up.
Conclusions: Fatigue is present before and immediately following injury, and can persist long term. The variation in findings supports the idea of fatigue in TBI as a nonhomogeneous entity, with different factors influencing the course of new onset or chronic fatigue. To decrease the heterogeneity, we emphasize the need for agreement on a core set of relevant fatigue predictors, definitions and outcome criteria.
PROSPERO registry number: CRD42013004262.

Abbreviations: APOE-ε4, apolipoprotein-ε4; BDI, Beck depression inventory; BFS, Barosso fatigue scale; CHART, Craig handicap assessment and reporting technique; CNS, central nervous system; DRS, disability rating scale; FSS, fatigue severity scale; GCS, Glasgow coma scale; GOSE, Glasgow outcome scale-extended; GFI, global fatigue inventory; HADS, hospital anxiety and depression scale; MFIS, modified fatigue impact scale; MFI, multidimentional fatigue inventory; mTBI, mild traumatic brain injury; PRISMA, preferred reporting items for systematic reviews and meta-analyses; PCSC, post-concussion syndrome checklist; POMS, profile of moods scale; RCT, randomized controlled trial; RPQ, Rivermead post-concussive questionnaire; SIGN, Scottish intercollegiate guidelines network; SF-36, 36-item short form health survey (from medical outcomes study); TBI, traumatic brain injury; VAS, visual analog scale.

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Contents

1. Background

Traumatic brain injury (TBI), defined as "an alteration in brain function, or other evidence of brain pathology, caused by an external force" (Brain Injury Association of America, 2013), is among the most serious, disabling neurological disorders in all societies and expected to rank as the major cause of death and disability by the year 2020 (World Health Organization, 2002). Over the past decades, evidence has emerged citing fatigue as a common, long-lasting problem after TBI (Belmont et al., 2006; Ponsford et al., 2011; Middleboe et al., 1992). It is burdensome to patients, and is associated with poor outcomes (Belmont et al., 2006; Ponsford et al., 2011). In a number of studies, over half of the patients making up the TBI samples reported fatigue's negative effect on social, physical and cognitive functioning (Ziino and Ponsford, 2006) and participation in everyday activities (Cantor et al., 2008), and role in increased work-related and other disabilities (McCrimmon and Oddy, 2006). Estimates of the incidence of fatigue after TBI vary from 21% to 73%, depending on the characteristics of the studied population (e.g. severity of injury, time since injury, sampling of patients, etc.) and the method used to identify fatigue (e.g. single item or fatigue scales) (Belmont et al., 2006; Ponsford et al., 2011; Middleboe et al., 1992; Borgaro et al., 2005; Lidvall et al., 1974).

The term "fatigue" has several meanings. It is recognized when performance of an activity results in diminished capacity for carrying out a function (Chaudhuri and Behan, 2004). Within this, 'physiological fatigue' refers to the state of general tiredness due to physical or mental exertion, which can be ameliorated by rest (Schillings et al., 2007). A state that refers to a weariness unrelated to previous exertion level, and not ameliorated by rest, is termed 'pathological fatigue' (Jason et al., 2010). Despite such characterization, fatigue in the TBI population is difficult to elucidate. This is partly due to the numerous plausible biological causes of fatigue (i.e. neuroanatomical, functional, psychological/psychiatric, biochemical, endocrine, sleep-related), independently or combined, through which this symptom can evolve after brain injury (Fig. 1) (Prins et al., 2006). To date, several narrative reviews have been published to provide insight into the topic of post-traumatic fatigue (PTF) (Belmont et al., 2006; Borgaro et al., 2005; Ponsford et al., 2012; Levine and Greenwald, 2009). Nevertheless, there is still little known about which specific clinical, behavioral and physiological factors are associated with its occurrence after brain injury; nor whether fatigue remains the same in its frequency/intensity, or changes over time. Finally, the overall health burden of this symptom in the TBI population remains uncertain. Understanding the facets of fatigue in TBI can guide in differential diagnosis

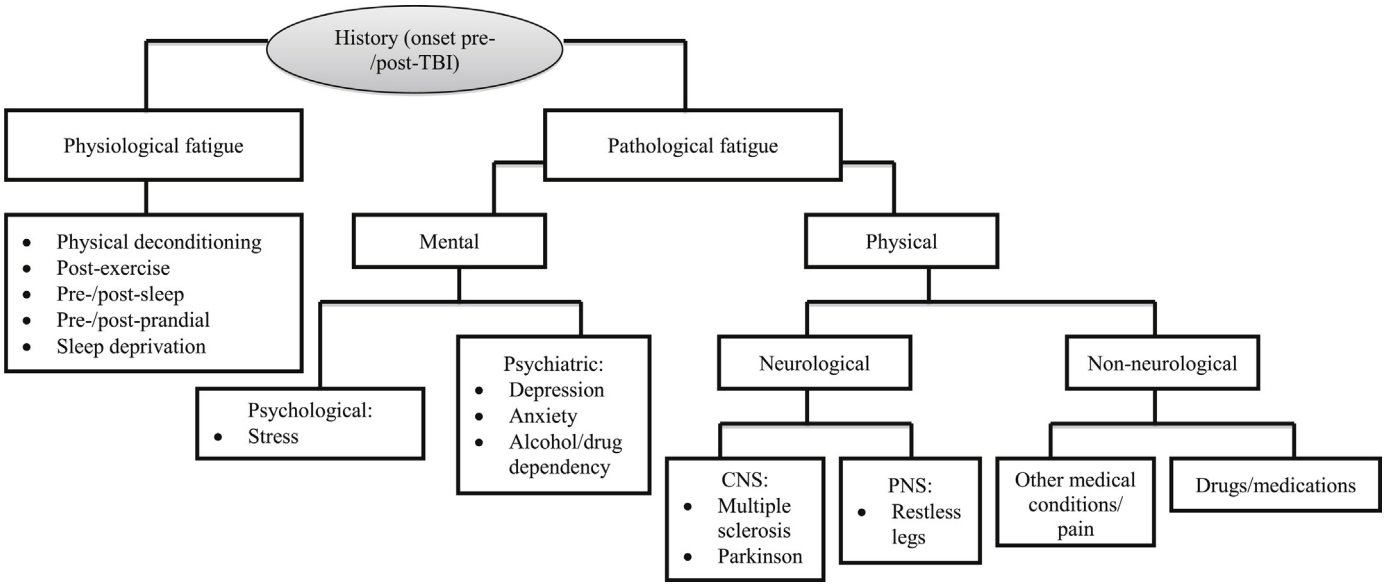

Fig. 1. Pathways to fatigue in traumatic brain injury.
Modified from Chaudhuri and Behan (2004), Finsterer and Mahjoub (2013) and Kluger et al. (2013).

and follow-up treatments. Moreover, identifying the most important contributors to PTF can change the view on the interventions necessary to deal with this significant symptom. This systematic review was performed with the following goals, all with respect to patients with TBI: (1) to determine the prognostic factors associated with fatigue onset; (2) to describe the course of fatigue; and (3) to describe the health consequences of fatigue.

2. Methods/design

2.1. Data sources and searches

This review was conducted and reported in compliance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Moher et al., 2009). The systematic review protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO) (Mollayeva et al., 2013a) on April 25, 2013 (registration number CRD42013004262).

In collaboration with disease experts and a medical information specialist, we developed a comprehensive search strategy for studying fatigue in TBI (Mollayeva et al., 2013a). All English language peer-reviewed studies with prospective or retrospective data collection and a longitudinal design, found through PsycINFO, MEDLINE, EMBASE and CINAHL, published since 1806, 1946, 1974 and 1980, respectively, were eligible. Cochrane Database of Systematic Reviews was also searched for studies published between 2005 and early April 2013. Publications identified from bibliographies of identified articles and reviews were considered eligible. The basic search can be found in Supplementary File 1. For the complete search strategy, we refer the reader to the published protocol (Mollayeva et al., 2013a).

2.2. Inclusion criteria

Peer-reviewed, English language studies that investigated fatigue in adult patients with a diagnosis of TBI and followed them for any period were included. Studies that focused on a different but parallel topic to fatigue (e.g. sleepiness, impaired alertness, or vigilance) and studies about fatigue after brain injury due to secondary pathological processes (e.g. edema, intracranial hemorrhages, ischemia/infarction, and systemic intracranial conditions) were excluded. Further, case reports, pediatric studies, dissertations, and articles with no primary data were excluded. For more information, we refer the reader to the protocol (Mollayeva et al., 2013a).

2.3. Study design

All experimental intervention and effectiveness studies of longitudinal design and observational cohort- and case control-designed studies were considered for this review.

2.4. Study review

In the first stage of screening, two reviewers (TM and TK or TM and SM) assessed study titles and abstracts for possible agreement with the inclusion criteria. In the second stage, each reviewer individually assessed the full text of articles selected in the first stage to determine whether they met inclusion criteria. Differences of opinion were resolved by discussion between reviewers, or by seeking advice from other experts (AC, CS, and JDC). Studies failing to meet the inclusion criteria were excluded, with reasons listed in Supplementary file 2.

2.5. Data extraction and quality assessment

The abstracted data included: (1) study characteristics (i.e. author names, publication year, country, setting, design, sample size, methods of measuring fatigue, and other variables [e.g. factors], number of participants assessed at each time point, time between assessments, and time from injury to follow-up); (2) participant characteristics (i.e. mean age, sex, definition of TBI, localization of injury, and injury severity); (3) medications used by or administered to participants; and (4) results (i.e. reported frequencies of fatigue and other factors, and reported associations between fatigue and other variables) (Tables 1–3).

For studies that fulfilled the inclusion criteria, two reviewers (TM and TK) independently extracted data into data collection forms grouped according to study design. The observational studies' data were used to address the three research objectives (i.e. prognostic factors, course of fatigue, and consequences). Randomized control trials (RCTs) were treated as cohorts, and the control

Table 1
Summary of study characteristics, including details on study sample, design, methods and results pertaining to fatigue.

Reference Country Sample by	Objective Design Follow-up (F/U) Inclusion/exclusion criteria (IC/EC)	Sample size Attrition Age, sex (% M) Time since injury (TSI) Injury severity (IS) Assessment time points/N assessed (AT: t_1, t_2, etc.)	Statistical method	Medications	Results	
					Fatigue definition Frequencies, scores	Score differences over time Notes
Bushnik et al. (2008a) US Medical center inpatient rehabilitation	Preliminary findings from study of fatigue in individuals with mod-sev TBI 2 yrs post-injury; document change in nature of fatigue over time, assess contributing factors Prospective longitudinal F/U: 6, 12, 18–24 mos post-injury IC: inpatient rehabilitation; TBI; ≥18 yrs at injury; speak/write/read English; informed consent EC: conditions associated with fatigue	$n = 51$ Attrition: 0 Age: 31 ± 13 Sex: 76% M TSI: discharge – 6 mos post-injury IS: GCS motor; PTA length; degree cranial midline shift: mod-sev AT: baseline t_1: 2.6 ± 1.8 mos t_2: 12.6 ± 1.2 mos t_3: 23.2 ± 3.4 mos	rmANOVA: change over time Post hoc pairwise *t* tests: significant variables *p*-value = .01	NR* *Study #2, same population: at year 1 – 11% illicit drug users, 19% classified as problem substance users; at year 2 – 29% classified as problem substance users	BFS: synthesis of items from other scales: MAF, FSS, FAI, FIS, GFS BFS: higher scores = greater fatigue From BFS: scores for Global Fatigue Index (GFI) of MAF and FSS: higher scores = greater fatigue Scores: t_1, t_2, t_3: BFS subscales ($n = 46$*): Intensity: 36 ± 17; 30 ± 19; 33 ± 18 Activities of daily living: 33 ± 18; 28 ± 18; 32 ± 21.5 Socialization: 24 ± 14; 20 ± 13; 22 ± 15 Mental functioning: 25 ± 12; 20 ± 12; 21 ± 12 General impact: 11 ± 7; 9 ± 6; 10 ± 6 Relieving factors: 16 ± 8; 15 ± 8; 18 ± 6 Aggravating factors: 21 ± 14; 18 ± 11; 21 ± 10 GFI ($n = 43$*): 23 ± 10; 17 ± 11; 20 ± 11 FSS ($n = 45$*): 3.4 ± 1.5; 2.9 ± 1.6; 3.2 ± 1.8 *Missing data, unanswered questions	Score changes: BFS subscales: NS GFI: significant decrease $t_1 - ct_2$ ($t_{42} = 5.4$; $p = .0018$; effect size = .58) FSS: NS *Notes*: Fatigue total scores had same pattern of change: highest at t_1, lowest at t_2, slight increase at t_3 GFI at t_1: only score comparable to other populations with significant fatigue BFS subscales: low-mod fatigue; avg scores below 50% of max score for each subscale (exception: relieving factors) Associations: Increased fatigue $t_1 - t_2$, more sleep problems (PSQI) decreased and stable fatigue scores, decreased PSQI Increased fatigue, decreased cognitive functioning; decreased fatigue-increased cognitive functioning; similar for general functioning, motor symptoms

Table 1 (*Continued*)

Reference Country Sample by	Objective Design Follow-up (F/U) Inclusion/exclusion criteria (IC/EC)	Sample size Attrition Age, sex (% M) Time since injury (TSI) Injury severity (IS) Assessment time points/N assessed (AT: t_1, t_2, etc.)	Statistical method	Medications	Results Fatigue definition Frequencies, scores	Score differences over time Notes
De Leon et al. (2009) US Level II community hospital ED	Compare fatigue reports of participants 12 mos post-MHI with those with other injury by mild trauma; injury, BL predictors of fatigue Inception, cohort F/U: 12 mos IC: presented directly to ED w/I 24 h of injury; ≥18 yoa; GCS ≥ 13; did not meet criteria for activation of adult trauma team; discharged directly from ED; competency for informed consent; mini-mental state examination ≥18; able to describe essential elements of study EC: transfer from other hospital; non-English speaking; being incarcerated; medical evaluation resulting in admission; state of PTA at recruitment; LOC ≥ 30 min; LOC not attributable to trauma	n = 359 (w/ 12 mos data) 3 groups: 1: HI w/ PTA &/OR LOC; 2: HI only; 3: other injury (n_1, n_2, n_3) n_1 = 58, n_2 = 173, n_3 = 128 * No medical info wrt occurrence of brain injury Attrition: 31.9% Age: NR Sex: 1: 44.8% M 2: 41% M 3: 43.7% M TSI: 12 mos IS: mild AT: BL/n = 504 t_1: 1 mos (NR) t_2: 3 mos (NR) t_3: 12 mos/n = 359	2-tailed tests of significance, α = .05 Chi-square: group differences (categorical) Univariate ANOVA: group differences (continuous) Hierarchical linear regression: variable associations	NR	MOS SF-36 Vitality subscale Low scores on vitality subscale indicate more fatigue Mean SF-36 vitality subscale scores at BL: 1: 52.8 ± 9.5 2: 50.4 ± 10.5 3: 53.4 ± 8.6 *HI only group (2): greater fatigue severity (p = .026) t_3: 1: 52.3 ± 12.2 2: 49.6 ± 11.8 3: 53.0 ± 10.4 *Significant differences between groups ($F_{2,356}$ = 3.77, p = .024, partial η^2 = .02)	Pair-wise comparisons: 1: Lower mean score at 12 mos than other injury group (p = .027) 2: Comparison NS
Driver and Ede (2009) US Community	Changes in mood in response to 8 wk physical activity (PA) intervention Stratified random sampling F/U: 8 wks IC: >level 6 Ranchos Los Amigos Scale of Cognitive Functioning; TBI > 1 yr prior; outpatients at rehabilitation center EC: NR	n = 18 TBI 2 groups: 1: PA; 2: control Attrition: 0 Age: 37.7 ± 2.3 Sex: NR TSI: 1:40.8 ± 14.7 mos 2:36.3 ± 14.2 mos IS: Each group: 6 w/ left-sided lesion proximity to frontal pole; 1: 2 w/ damage to left basal ganglia; 2: 2 w/damage to right parietal occipital lobe AT: BL t_1: 8 wks	ANOVA: between, within group differences Effect size: total variance accounted for by independent variable	1: 5 taking SSRIs for duration of program* 2: 6 taking SSRIs for duration of program* *Not as part of study	Fatigue definition: NR POMS fatigue-inertia subscale Mean fatigue subscale scores at BL: 1: 1.4 ± 1.1 2: 1.2 ± .6 Mean fatigue subscale scores at t_1: 1: .5 ± .6 2: 1.3 ± .6 Effect size: 1: 1.00 2: .08	Within group differences (BL – t_1): 1: significant (F = 4.7, p < .05) 2: NS Between group differences: Fatigue NR; significant wrt total POMS score (F = 5.7, p < .05)

Gemmell and Leathem (2006) NZ Psychology clinic, head injury society	Whether Tai Chi would have immediate effect on mood states in TBI group; improvement of perceived physical, emotional functions, self-esteem, social functioning, health over time Within-group, between-group with control F/U: 6 wks IC: mild, mod, severe TBI on basis of retrograde/anterograde amnesia, PTA, and/or LOC with associated outcomes EC: NR	$n = 18$ 2 groups: 1: Tai Chi (9); 2: control, waiting list for Tai Chi (9) Attrition: 0 Age: F: 40.2 ± 12.5, M: 51.2 ± 8.7, Sex: 50% M TSI: mean = 8.7 yrs IS: NR AT: Before t_1: After (6 wks)	*t*-tests: within, between group differences at time points ANOVA: within, between group differences over time periods	NR	Fatigue definition: NR MOS SF-36 Vitality subscale VAMS Tired mood state scale (Tai Chi group only) SF-36 Vitality: Before: 1: 47.1 ± 18.2 2: 47.5 ± 20.2 After: 1: 40.7 ± 22.3 2: 38.8 ± 4.4 VAMS Tired: Before: 1: 54.4 ± 6.0 After: 1: 52.5 ± 5.8	SF-36 Vitality: Before: 1 vs. 2: NS ($t = -0.04$) After: 1 vs. 2: NS ($t = 0.25$) VAMS: 1: Fatigue NS ($t = 1.10$)
Hou et al. (2012) UK ED	Optimal early predictors for post-concussional syndrome (PCS) following mild TBI (mTBI); cognitive, emotional, behavioral, social perpetuating factors in development of PCS Prospective cohort F/U: 3, 6 mos IC: 18–60 yoa, mTBI EC: multi-trauma requiring hospitalization, major neurological/psychiatric disorders	$n = 126$ Attrition: 25% Age: 38.3 ± 14.1 Sex: 63% M TSI: $\leq$2 wks IS: GCS: mild AT: BL: $\leq$2 wks post-injury/$n = 126$ t_1: 3 mos/$n = 107$ t_2: 6 mos/$n = 107$	*t*-tests, chi-square: demographic, clinical characteristics Individual regression analyses: cognitive, emotional, behavioral variables as covariates with gender/age, PCS outcome as dependent variable Logistic regressions (LR): for significant variables from individual regression analyses Stepwise backward LR: derive models for 3, 6 mos Hosmer–Lemeshow 'goodness of fit statistic': fit of model assessment	NR	Fatigue definition: NR RPQ (including fatigue, sleep disturbance items) RPQ: fatigue, sleep disturbance – most commonly reported symptoms are 3 and 6 mos port-mTBI Fatigue frequencies: NR From bar graph: Fatigue at 3 mos $\approx$33%, at 6 mos $\approx$28% Sleep disturbance at 3 mos $\approx$27%, at 6 mos $\approx$24%	NR

Table 1 (*Continued*)

Reference Country Sample by	Objective Design Follow-up (F/U) Inclusion/exclusion criteria (IC/EC)	Sample size Attrition Age, sex (% M) Time since injury (TSI) Injury severity (IS) Assessment time points/N assessed (AT: t_1, t_2, etc.)	Statistical method	Medications	Results	
					Fatigue definition Frequencies, scores	Score differences over time Notes
Hutchinson et al. (2009) CA University sports	Determine whether athletes with concussion and those with musculoskeletal injuries (MSI) differed in emotional responses post-injury; differences in BL emotional status in 3 groups: mTBI, MSI, active control (CTL) (control for premorbid emotional disturbance) Prospective longitudinal cohort F/U: 1,2,3 d IC: university athletes in sport with risk of concussion EC: self-reported at neuropsychological assessment: >5 concussions; learning disability; psychiatric disorder	$n = 53$ 3 groups: 1: mTBI (20); 2: MSI (14); 3: CTL (19) Attrition: 0 Age: 1: 20.1 ± 1.8 2: 19.2 ± 2.3 3: 21.6 ± 1.6 Sex: 1: 60% M 2: 86% M 3: 47% M TSI: 1: $\leq$96 hrs IS: 1: concussion (mTBI) by team physicians, therapists AT: BL t_1, t_2, t_3: 3 d* *Nonconsecutive over 2 wks	Descriptive: demographic variables, mood scales Cronbach alpha: scale reliability ANOVA: group differences on POMS subscales at BL; physical characteristics Student–Newman–Keuls multiple-range test (.05): F/U means Tukey–Kramer correction for type I error	NR	Fatigue definition: NR POMS fatigue subscale: Reliability: .863 Scores: Main effects: NS Significant interacting effect for fatigue ($F(6, 150)$, 10.11; $p < .001$) Difference at t_1: significant for 1 (increase) vs. 2, 3	POMS fatigue subscale: Difference BL – t_1: significant for 1 *Notes*: 1: significantly greater fatigue, lack of energy (POMS vigor subscale) post-injury

Jha et al. (2008) US Hospital	Efficacy of modafinil for treating fatigue, excessive daytime sleepiness (EDS) in persons with TBI; hypothesis: modafinil more efficacious than placebo; outcomes wrt cognitive function, health related quality of life Single-center randomized blinded, placebo-controlled cross-over F/U: 4, 10 wks IC: 1-year post-TBI; 18–65 yoa; received inpatient rehabilitation at single model system of care EC: presence of neurologic/neuropsychiatric diagnosis; diagnosis by history of other likely causes of EDS; concurrent medication use and/or clinically significant systemic disease that might cause fatigue/diminished arousal; epilepsy; cardiovascular disease/hypertension requiring medical tx; history of severe renal/hepatic impairment; significant psychiatric/behavioral disturbance; non-English speaking; pregnant females/of childbearing potential	$n = 51$ (46*) 2 groups: 1: modafinil first (27 (22*)); 2: placebo first (24) *5 participants in group 1 withdrew Demographic/clinical characteristics reported for $n = 51$** **NS imbalances to affect trial results Attrition: 0 Age: 38.3 ± 12.2 Sex: 69% M TSI: 5.8 ± 5.0 yrs IS: GCS: mild (25.5%), mod (23.5%), sev (51%) AT ($n = 46$): BL t_1: wk 4 t_2: wk 10	*t*-tests, chi-square: continuous and categorical, respectively: BL differences in demographic/clinical characteristics between groups Paired *t*-test: crude tx effects 2-sample *t*-tests: within group tx effects Linear mixed-effects regression: 4-wk change in each of 2 periods for all participants Secondary analyses: tx effects on secondary end-points and at 10 wks	Modafinil (≥400 mg) Concurrent medication use in exclusion criteria	MFIS FSS SF-12 (fatigue item)* *Fatigue NR separately FSS, MFIS high scores Scores: BL; t_1; t_2: FSS: 1: 45.2 ± 11.8; 39.4 ± 15.6; 37.13 ± 18.33 2: 44.46 ± 12.17; 37.7 ± 12.55; 36.91 ± 14.08 MFIS: 1: 46.56 ± 19.28; 38.65 ± 16.09; 35.63 ± 20 2: 47.17 ± 15.53; 36.45 ± 15.03; 33.55 ± 18.16 Group medication switch – modafinil to placebo, vice versa: FSS: 1 (placebo): 35.92 ± 16.82; 33.74 ± 16.16; 30.95 ± 16.25 2 (modafinil): 38.17 ± 15.23; 31.38 ± 10.66; 28.90 ± 14.03 MFIS: 1: 36.27 ± 17.67; 37.74 ± 17.51; 31.20 ± 19.44 2: 39.73 ± 20.82; 28.91 ± 19.06; 28.27 ± 16.06	1 vs. 2: modafinil-placebo scores: Change wk 4-BL (*p* value): FSS: 2.33 ± 12.96 (.54) MFIS: 5.68 ± 14.79 (.21) Wk 10-BL: FSS: .44 ± 15.31 (.92) MFIS: 4.03 ± 16.93 (.43) Group medication switch – modafinil to placebo, vice versa: Wk 4-BL: FSS: −2.55 ± 11.07 (.45) MFIS: −10.9 ± 15.93 (.03) Wk 10-BL: FSS: −3.70 ± 14.60 (.43) MFIS: −8.07 ± 16.61 (.14) *Notes*: Participants suggested fatigue measures used in study do not accurately reflect fatigue experienced by persons with TBI

Table 1 (*Continued*)

Reference Country Sample by	Objective Design Follow-up (F/U) Inclusion/exclusion criteria (IC/EC)	Sample size Attrition Age, sex (% M) Time since injury (TSI) Injury severity (IS) Assessment time points/N assessed (AT: t_1, t_2, etc.)	Statistical method	Medications	Results Fatigue definition Frequencies, scores	Results Score differences over time Notes
Kaiser et al. (2010) CH Hospital neurology department	Effect of modafinil on posttraumatic EDS and fatigue Prospective, double-blind, randomized, placebo-controlled, pilot F/U: 6 wks IC*: presence of fatigue/EDS/both since injury * Patients from earlier study (Baumann et al., 2007) admitted for closed mild-sev TBI to surgical intensive care unit EC: patients with neurologic, psychiatric, other disorders, medications that may cause SWD; significant SWD other than posttraumatic vigilance impairment at BL; chronic sleep deprivation	$n = 20$ 2 groups: 1: modafinil (10); 2: placebo (10) Attrition: 0 Age: 1: 37 ± 9 2: 43 ± 19 Sex: 1: 80% M 2: 90% M TSI: 1: $1.8 \pm .9$ yrs 2: 2 ± 1.2 yrs IS: GCS: mild-sev AT: BL t_1: 6 wks	Pearson, Spearman correlation analyses; two-tailed *t*-tests; Mann–Whitney *U* tests; multivariate regression analyses	Modafinil (100–200 mg) Interfering medication use as part of exclusion criteria; caffeine, other drugs not allowed during course of study	FSS > 4 BL: frequency of fatigue diagnosis: 1: .8 2: .8 BL: FSS 1: 5 ± 1.4 2: $4.6 \pm .8$	t_1 ($p = 0.07$): 1: $-.8 \pm 1$ 2: $.0 \pm .6$ *Notes*: Overall subjective estimation of vigilance impairment amelioration: 1: much better (0%); better (30%); somewhat better (30%); unchanged (30%); worse (10%) 2: much better (10%); better (10%); somewhat better (10%); unchanged (70%); worse (0%)
Kempf et al. (2010) CH University neurology department	Prevalence, characteristics of post-traumatic sleep-wake disorders (SWD) Prospective, longitudinal, clinical F/U: 3 yrs IC: acute, first TBI; no SWD, psychiatric/neurological disorders prior; admitted immediately after injury EC: NR	$n = 51$ *Studied at 6 mos wrt SWD ($n = 65$, Baumann et al., 2007) Attrition: 21.5% Age: 40 ± 16 Sex: 84% M TSI: 3 yrs IS: GCS: mild (42%), mod (22%), sev (38%) AT: t_1: 6 mos/$n = 65$ (Baumann et al., 2007) t_2: 3 yrs/$n = 51$ (this study)	Correlation analyses *t*-tests: parametric Mann–Whitney *U* tests: non-parametric One-way ANOVA: group differences McNemar test: Δ repeated dichotomous measures	3 (antiepileptic drugs), 1 (zopidem for sleep)	Fatigue Severity Scale (FSS) FSS ≥ 4 t_1: 17% t_2: 35% 51%: fatigue associated symptoms (daytime tiredness, lack of energy, exhaustion) since injury	NR

Khateb et al. (2005) CH University hospital neurology clinic	Whether patients with cognitive/behavioral impairment after brain injury would benefit from donepezil; improvement would concern one cognitive domain more than others Intervention F/U: 3 mos IC: outpatients of neurology clinic; informed consent; history of mod-sev TBI for ≤6 mos EC: history of previous CNS injury/disease; ongoing drug/alcohol abuse; severe speech/language disorders; unstable psychiatric disorders; compliance difficulties; use of AchE inhibitors	$n = 10$ Attrition: 33.3% Age: 43 ± 8 Sex: 60% M TSI: 42 ± 33 mos IS: PTA: 8 ± 10 d AT: BL t_1: 3 mos	Non-parametric Wilcoxon: statistical significance of changes by donepezil therapy	Donepezil (5–10 mg) Ongoing alcohol/drug abuse, current use of acetylcholine AchE inhibitors as part of exclusion criteria	Fatigue disability measured by 29-item fatigue scale: severity, specificity, psychological consequences, effects of sleep/rest on fatigue Fatigue scale high score – severe symptoms BL: mean score: 132.6 ± 27.3	t_1: mean score: 126.1 ± 32.3 ($p = .92$, $Z = .10$) *Notes*: Subjects' self-report post-tx: 80% reported medication-related improvement in ≥1 cognitive/affective-behavioral domain – 40% wrt fatigue – dominating improvement Subjective fatigue improvement did not correlated with decrease in fatigue score – only 2 patients showed notable decrease in score 2 patients that did not report subjective improvement had notable decrease in fatigue score Discrepancies may be result of varying definitions of fatigue

Table 1 (*Continued*)

Reference Country Sample by	Objective Design Follow-up (F/U) Inclusion/exclusion criteria (IC/EC)	Sample size Attrition Age, sex (% M) Time since injury (TSI) Injury severity (IS) Assessment time points/N assessed (AT: t_1, t_2, etc.)	Statistical method	Medications	Results	
					Fatigue definition Frequencies, scores	Score differences over time Notes
Lidvall et al. (1974) SE EDs	Establish whether PCS were experienced only after injury, or whether the patient was already suffering them before the trauma; explore the etiology of the PCS Prospective longitudinal cohort F/U: 2, 6, 14, 30, 90 d post-injury IC: cerebral concussion (CC); PTA; hospital emergency admission ≤24 and examination on the second d after injury; ≤15; able to cooperate; not required surgical tx; good knowledge of Swedish EC: with mental or comatic illness; alcoholics and drug addicts	*n* = 100 CC Attrition: 0 Stats: PTA (min): <1: 17%; 1–5: 34%; 6–45: 29%; >45: 20% Age: 33 y (av) Sex: 69% M TSI: <24 h IS: PTA: mild-sev AT: post-injury: t_1: 2 d t_2: 6 d t_3: 14 d t_4: 30 d t_5: 90 d	Descriptive: summary of all variables Chi-square: discrete variable differences between PCS- and C-groups Phi coefficients for symptoms clustering	NR	PCS-symptom questionnaire Fatigue frequencies by PCS list: t_1: 7% t_2: 5% t_3: 10% t_4: 8% t_5: 10% Fatigue frequency at any given time point – 12%	Clusters unstable, varying in extent and character across time points: t_1: 1: headaches, dizziness, fatigue, concentration impairment (largest) 2: memory impairment, sensitivity to light t_2: 1: headaches, dizziness 2: headaches, fatigue 3: dizziness, fatigue t_3: 1: headaches, fatigue, dizziness 2: anxiety, concentration impairment t_4: 1: anxiety, fatigue, headaches t_5: 1: headaches, anxiety 2: dizziness, concentration impairment 3: fatigue, anxiety 4: fatigue, headaches
Lundin et al. (2006) SE EDs	Report character, frequency, course of persisting symptoms and their relation to disability through effects on daily activities in mTBI patients Prospective cohort F/U: 1, 7, 14 d, 3 mos post-injury IC: blunt head trauma; LOC and/or PTA; hospital admission ≤24 h post-injury; GCS 14–15 at ED assessment; 15–65 yrs EC: LOC ≥ 30 min; PTA ≥ 24 h; other significant physical injury/major neurological disorder	*n* = 102 mTBI; 35 controls Attrition: 16.4% Stats for TBI: Age: 37.3 Sex: 58% M TSI: 24 h IS: GCS: mild AT: post-injury: t_1: 1 d t_2: 7 d t_3: 14 d t_4: 3 mos	Mann–Whitney *U* tests: non-normal continuous data Chi-square/Fisher's exact tests: categorical data Bonferroni adjustment: multiple comparisons $p = .05$ Multilevel logistic regression: relationship between stable patient characteristics and multiple measurements	NR	Rivermead Post-Concussional Questionnaire (RPQ); Rivermead Head Injury F/U Questionnaire (RHFUQ*): both feature fatigue item *Administered only at t_4 RPQ score classification: symptom resolution (1); mild (2); moderate (3); severe (4) RPQ fatigue frequencies: t_1: mTBI: 66.8% (calculated from symptom load bar graph) t_4: mTBI: 21% Control: 11%	t_1–t_4: significant decrease

McLean et al. (1993) US Medical Center	Investigate type of psychosocial difficulties associated with head injury (HI) at 1mos and 12 mos post-injury; whether degree of psychosocial impairment relate to HI severity Prospective cohort F/U: 1 mo, 12 mos post-injury IC: HI; LOC and PTA > 1 h, or obj evidence of cerebral trauma; trauma required hospital admission; 15–60 yrs EC: previous CNS insult or involvement (e.g. epilepsy, HI, alcoholism, mental retardation); psychiatric disorder	n = 102 HI; 102 controls Attrition: 0 Stats for HI: Age: 26.33 Sex: *primarily single M TSI: 24 h IS: GCS: mild – 58%; mod – 11%; sev – 28% AT: post-injury: t_1: 1 mos t_2: 12 mos	2 by 2 Chi-square tests Mann–Whitney U tests comparison of change with time Kruskal–Wallis distribution-free analysis of variance; post hoc comparison according to Tukey's method for unequal-sized groups	NR Prior history of epilepsy, alcoholism, mental retardation as part of exclusion criteria	The Head Injury Symptom Checklist Frequencies: t_1: 74% t_2: 47%	A significant reduction in the number of fatigue endorsed from 1 mo to 12 mos post-injury ($p < .001$) Significant difference between cases and controls at 1 mo but not at 12 mos post-injury
Meares et al. (2011) AU Level 1 trauma hospital	Investigate course of PCS, PCS-like symptoms; relationship pre-injury, injury-related, post-injury factors to PCS development Prospective F/U: 3 mos since hospitalized IC: trauma center patient; traumatic nonbrain injury/mTBI; hospital admission ≤24 h post-injury; first assessment ≤14 d post-injury; 18–65 yrs; IQ ≥ 70; adequate understanding of English EC: mod-sev TBI/intracranial lesion; self-harm physical injury; psychotic; history of cognitive impairment; medically unstable; interstate/overseas visitor; pregnant EC at 3 mos: >5 mos post-injury at F/U; inadequate effort on testing by failure on memory test	n = 62 mTBI; 58 TC Attrition: 0 Stats for TBI: Age: 35.7 ± 14.5 Sex: 67.7% M TSI: 4.8 ± 3.1 d IS: GCS: mild AT: post-injury: t_1: ≤14 d t_2: 3 mos	Mann–Whitney U tests: non-normal continuous data Chi-square/Fisher's exact tests: categorical data Bonferroni adjustment: multiple comparisons p = .05 Multilevel logistic regression: relationship between stable patient characteristics and multiple measurements	Opiate administration at t_1/t_2 (n): mTBI (37/62) Control (37/58) Marijuana use: mTBI: 24.4% Control: 19% AUDIT alcohol screen – mTBI = 6.4 ± 6.8; ≥8 – hazardous alcohol use indicator At least 1 subs use disorder: 12.5%	PCSC: adapted version including fatigue symptom PCSC symptoms: 5-point scale; clinically significant if scored as ≥3, indicating "often" for frequency Fatigue symptom frequencies (≥3 on PCSC): None: mTBI: 40.3% Control: 20.7% Present at t_1 and t_2: mTBI: 21% Control: 32.8% Present at t_2 only: mTBI: 14.5% Control: 15.5%	Fatigue symptom frequencies (≥3 on PCSC): Absent at t_2: mTBI: 24.2% Control: 31% Difference in frequency between mTBI and controls in presence/absence at t_1/t_2 of fatigue: NS

Table 1 (*Continued*)

Reference Country Sample by	Objective Design Follow-up (F/U) Inclusion/exclusion criteria (IC/EC)	Sample size Attrition Age, sex (% M) Time since injury (TSI) Injury severity (IS) Assessment time points/N assessed (AT: t_1, t_2, etc.)	Statistical method	Medications	Results	
					Fatigue definition Frequencies, scores	Score differences over time Notes
Mickeviciene et al. (2004) LT Hospital emergency ward	Investigate PCS symptoms, effects of sociodemographic factors and expectations on symptoms Prospective controlled cohort F/U: 3 mos, 1 yr post-injury IC: admitted for head trauma (w/ LOC) evaluation/tx; LOC ≤15 min EC: history of drug/alcohol abuse, epilepsy, significant psychiatric/neurological disorder; previous concussion; concussion-related seizures; focal neurological signs, abnormal neurological status at admission; other major injury leading to hospitalization; hospital stay >1 wk	*n* = 217 concussion; 221 minor injury controls Attrition: 7.8%; 4% Stats for concussion group: Age: M: 33 ± 13 F: 38 ± 14 Sex: 66% M TSI: 7–14 d IS: NR AT: post-injury BL/*n* = 217 t_1: 3 mos/*n* = 200 t_2: 1 yr/*n* = 192	Chi-square w/ Yates' correction: between-group symptom comparison 2-Sided *t* test: VAS score comparison Multiple regression: headache, cognitive dysfunction VAS scores as dependent, demographic characteristics as independent	NR Prior history of alcohol abuse, drug abuse as part of exclusion criteria Alcohol intolerance 31% at 3 mos post-injury, 31% at 1 yr post-injury	VAS fatigue item Fatigue: score ≥50 on VAS VAS fatigue scores: BL: between-group differences NS t_1 (p = .002): Concussion: 50 ± 28 Control: 41 ± 29 t_2 (p = .08): Concussion: 50 ± 30 Control: 44 ± 28 VAS fatigue scores in participants: Married 1 yr (p = .17): Concussion: 51 ± 30 Control: 45 ± 27 Unmarried 1 yr (p = .11): Concussion: 49 ± 30 Control: 42 ± 29 With 1 yr high education (p = .01): Concussion: 52 ± 30 Control: 42 ± 27 With 1 yr low education (p = .72): Concussion: 47 ± 30 Control: 45 ± 29	NR

Norrie et al. (2010) NZ Hospital	Prevalence, severity, predictors, covariates of fatigue in persons with mTBI Longitudinal prospective F/U: 3, 6 mos post-injury IC: patients presenting to hospital with mild closed head injury; GCS 13–15; LOC < 20 min; PTA < 24 h EC: abnormal CT scan; regular admission of psychoactive drugs/history drug abuse; central neurological disorder/psychiatric condition; skull/facial fractures/multiple trauma/other major trauma	$n = 159$ Attrition: 14.1%; 10.6% Age: 35.9 ± 15.6 Sex: 64% M TSI: 1 wk; ≤10 d IS: GCS: mild AT: post-injury BL/$n = 263$ t_1: 3 mos/$n = 159$ t_2: 6 mos/$n = 159$	Pearson correlation coefficients: primary dependent variables, fatigue prevalence, severity, energy, depression, anxiety associations One-way ANOVA: fatigue prevalence, severity, energy change Hierarchical regression: t_2 fatigue severity with t_1 fatigue severity, depression, anxiety Receiver operating characteristic curve: sensitivity, specificity of fatigue item on RPQ in distinguishing those w/ and w/o pathological fatigue by FSS at t_2	NR Regular intake of psychoactive drugs, history of drug abuse as part of exclusion criteria	FSS (severity) RPQ fatigue item (prevalence) SF-36v2 Vitality Subcale FSS cut-off = 3.7 RPQ fatigue prevalence – frequency of item rating ≥2 (max 4) SF-36v2 Vitality high score = low fatigue (max 100) Frequencies: BL: FSS: 54.1% RPQ: 67.3% t_1: FSS: 35.8% RPQ: 29.6% t_2: FSS: 34% RPQ: 26.4% Scores: BL: FSS: 3.99 ± 1.53 RPQ: 2.09 ± 1.24 SF-36v2 Vitality: 46.57 ± 24.72 t_1: FSS: 3.3 ± 1.4 RPQ: 1.0 ± 1.1 SF-36v2 Vitality: 60.2 ± 19.7 t_2: FSS: 3.2 ± 1.4 RPQ: .96 ± 1.1 SF-36v2 Vitality: 62.1 ± 20.2 Correlations between measures at time points ($p \leq .000$, unless otherwise indicated): FSS BL w/: FSS t_1: .53; FSS t_2: .49; RPQ BL: .57; RPQ t_1: .30; RPQ t_2: .38; SF-36v2 BL: NS; SF-36v2 t_1: .42; SF-36v2 t_2: .4 FSS t_1 w/: FSS t_2: .76; RPQ BL: .16 ($p \leq .05$); RPQ t_1: .45; RPQ t_2: .5; SF-36v2 BL: NS; SF-36v2 t_1: .66; SF-36v2 t_2: .39 FSS t_2 w/: RPQ BL: .2 ($p \leq .05$); RPQ t_1: .4; RPQ t_2: .62; SF-36v2 BL: NS; SF-36v2 t_1: .56; SF-36v2 t_2: .59	Within-subject effects BL-t_2 ($p < .0005$): FSS: $F_{2,157} = 23.60$; $\eta^2 = .23$ RPQ: $F_{2,157} = 60.556$; $\eta^2 = .44$ SF-36v2 Vitality: $F_{2,157} = 17.573$; $\eta^2 = .18$ *Notes*: RPQ fatigue item – unsatisfactory for prediction of pathological fatigue post-mTBI

Table 1 (*Continued*)

Reference Country Sample by	Objective Design Follow-up (F/U) Inclusion/exclusion criteria (IC/EC)	Sample size Attrition Age, sex (% M) Time since injury (TSI) Injury severity (IS) Assessment time points/N assessed (AT: t_1, t_2, etc.)	Statistical method	Medications	Results	
					Fatigue definition Frequencies, scores	Score differences over time Notes
					RPQ BL w/: RPQ t_1: .24; RPQ t_2: .34; SF-36v2 BL: NS; SF-36v2 t_1: −.2 ($p \leq .05$); SF-36v2 t_2: −.2 ($p \leq .05$) RPQ t_1 w/: RPQ t_2: .6; SF-36v2 BL: NS; SF-36v2 t_1; −.57; SF-36v2 t_2: −.51 RPQ t_2 w/: SF-36v2 BL: NS; SF-36v2 t_1: −.52; SF-36v2 t_2: −.7 SF-36v2 BL w/: SF-36 t_1/t_2: NS SF-36v2 t_1 w/: SFv2 t_2: .69 Sensitivity/specificity of RPQ fatigue item (i.e. discriminating symptom at t_2 on FSS): BL, t_1, t_2: sensitivity = .74, .42, .55; specificity = .63, .24, .12	
Ponsford et al. (2012) AU Emergency and trauma center	Report on post-concussive symptoms and associated cognitive, psychological, functional outcomes in persons with uncomplicated mTBI Prospective F/U: 1 wk, 3 mos post-injury IC: admitted to emergency and trauma center; trauma/acceleration-deceleration movement to head w/ LOC < 30 min, PTA < 24 h, GCS 13–15 in last 24 h; ≥18 yrs; English-speaking EC: general anesthesia after injury; breath alcohol >.05 mg/L at recruitment; under influence of illicit drug at injury; focal neurological signs/seizures and/or intracerebral abrnormalities based on CT; dominant upper limb injury disabling from use of computer mouse; spinal precautions, cannot sit upright; previous cognitive impairment, neurological illness, major alcohol/drug abuse, other psychiatric impairment affecting daily functioning; not available for F/U	n = 123 (90 analyzed), 100 TC (TC) (80 analyzed) Attrition: 9.8%; 18.9% Stats for mTBI: Age: 35.0 ± 13.1 Sex: 74% M TSI: ≤24 hrs at BL IS: GCS: mild; PTA: 103 ± 191 min (n = 118); LOC: 61.4 ± 110 s (n = 111) AT: BL: ED/n = 123 t_1: 1 wk/n = 90 t_2: 3 mos/n = 90	qq, box plots; Kolmogorov–Smirnov; Shapiro–Wilk: distribution normality Univariate; multivariate; repeated-measures: between-group score comparison Chi-square: categorical variables, not normally distributed Mann–Whitney U: continuous variables, not normally distributed Wilcoxon Signed Ranks; Friedman: within-subject changes over time p = .05	Narcotic analgesics by self-report: BL: 62.6% mTBI, 44% TC t_1: 18.2% mTBI, 21.1% TC t_2: 2.2% mTBI, 2.5% TC	PCS – post-concussive symptoms checklist with fatigue item SF-36 Vitality (scores NR separately) Fatigue frequencies by PCS: BL (p < .001): mTBI: 73.3% TC: 47.5% t_1 (p = .019): mTBI: 61.1% TC: 42.5% t_2 (p = .424): mTBI: 37.1% TC: 22.5% SF-36 Vitality: TC significantly higher median pre-injury, t_1 score (z = −3.11, p = .002; z = −2.96, p = .007) t_2: mTBI had lower mean score vs. TC (z = −2.33, p = .020)	NA

Schoenberger et al. (2001) US Tx seekers/patients of neurologists/rehabilitation clinics	Preliminary study of efficacy of FNS in persons with TBI Preliminary experimental randomized F/U: post-tx: 3 mos IC: mild-mod sev closed head injury; informed consent EC: penetrating head injury; substance abuse/psychotic diagnosis pre-injury; seizure pre-/post-injury; pregnant/trying to get pregnant	$n = 12$; 2 groups: 1: immediate tx; 2: waitlist control Attrition: 0 Age: 21–53 Sex: 16.7% M TSI: 36 mos–21 yrs; mean: 7.7 yrs IS: mild (75%); mod sev (25%); PTA (self-report): 41.7%; LOC: 1–27 d AT: t_1: 1: pre-tx; 2: BL t_2: 1: post-tx; 2: pre-tx t_3: 1: 3 mos post-tx; 2: post-tx t_4: 1: NA; 2: 3 mos post-tx	ANCOVAs: between-group ANOVAs: within-group; changes over time $p = .05$ (not adjusted for multiple tests)	Change in medication with tx: NA (33.3%); eliminated (25%); decreased (16.7%); no change (25%)	MFI – general fatigue, physical fatigue, mental fatigue, reduced motivation, reduced activity Fatigue by MFI: 5-point severity scale/item; subscale scores 4–20 – higher score, greater severity Stratified MFI scores by group and time point: 1: t_1, t_2: total (74.8 ± 20.4, 48.5 ± 20.9); general (17.2 ± 4.0, 9.8 ± 4.8); physical (16 ± 6.2, 10 ± 3.5); mental (17.2 ± 3.3, 10.3 ± 6.3); reduced activity (14.3 ± 5.6, 11.3 ± 5.4); reduced motivation (10.2 ± 4.8, 7 ± 2.8) 2: t_1, t_2: total (61.5 ± 18.9, 61.3 ± 20.6); general (14.8 ± 4.2, 14 ± 4.6); physical (10.5 ± 4.5, 10.8 ± 5.3); mental (15.5 ± 3.8, 15.7 ± 3.5); reduced activity (10.7 ± 4.7, 10.8 ± 5.3); reduced motivation (10 ± 3.9, 10 ± 4.9) Stratified MFI scores by time-point: Pre-tx: total (68.1 ± 20.8); general (15.6 ± 4.4); physical (13.4 ± 6.2); mental (16.4 ± 3.3); reduced activity (12.6 ± 5.4); reduced motivation (10.1 ± 4.6) Post-tx: total (50.1 ± 19.0); general (11.2 ± 4.8); physical (9.8 ± 3.3); mental (11 ± 4.9); reduced activity (10.1 ± 4.8); reduced motivation (8 ± 3.6) F/U: total (47.3 ± 20.0); general (10.5 ± 5.1); physical (9.3 ± 5.0); mental (10.7 ± 4.4); reduced activity (8 ± 4.2); reduced motivation (7.7 ± 4.4)	Between-group comparison of MFI scores: total ($F = 3.68$, $p < .1$); general ($F = 8.04$, $p < .05$); physical ($F = 2.88$); mental ($F = 9.10$, $p < .05$); reduced activity ($F = .24$); reduced motivation ($F = 1.99$) Changes in MFI scores: total ($F = 8.43$, $p < .01$); general ($F = 6.5$, $p < .01$); physical ($F = 4.02$, $p < .05$); mental ($F = 14.68$, $p < .001$); reduced activity ($F = 3.48$, $p < .1$); reduced motivation ($F = 2.72$, $p < .1$) Significant differences ($p < .05$): Pre-post, F/U: total, general, mental

Table 1 (*Continued*)

Reference Country Sample by	Objective Design Follow-up (F/U) Inclusion/exclusion criteria (IC/EC)	Sample size Attrition Age, sex (% M) Time since injury (TSI) Injury severity (IS) Assessment time points/N assessed (AT: t_1, t_2, etc.)	Statistical method	Medications	Results	
					Fatigue definition Frequencies, scores	Score differences over time Notes
Sigurdardottir et al. (2009) NO Level I trauma center	Study cognitive recovery 3–12 mos post-TBI; use of neuropsychological tests to predict functional outcome Prospective F/U: post-injury: 3, 12 mos IC: admission to trauma center with acute TBI; 16–55 yrs; ≤24 h post-injury; fluency in Norwegian EC: earlier neurological disorder; spinal cord injuries w/ current TBI; severe psychiatric disorders/substance abuse	$n = 115$; mild $n = 40$; mod $n = 34$; sev $n = 41$ Attrition: 7.8% Age (at injury): mild: 35.9 ± 11.4; mod: 33.5 ± 10.8; sev: 28.5 ± 10.4 Sex: mild: 63% M; mod: 74% M; sev: 71% M TSI: ≤24 h (at recruitment) IS: Mild: GCS ($14.7 \pm .6$); PTA (.08 (range 0–1) d); $AIS_{head} \geq 3$ (23%); ISS ≥ 15 (15%); intracranial pathology by CT/MRI (28%) Mod: GCS (10.8 ± 1.3); PTA (5.25 (range 0–30) d); $AIS_{head} \geq 3$ (79%); ISS ≥ 15 (68%); intracranial pathology by CT/MRI (85%) Sev: GCS (5.5 ± 1.8); PTA (35.83 (range 0–128) d); $AIS_{head} \geq 3$ (100%); ISS ≥ 15 (98%); intracranial pathology by CT/MRI (100%) AT: post-injury t_1: 3 mos/$n = 115$ t_2: 12 mos/$n = 106$	Parametric statistics (Pearson) chi square: categorical variables ANOVA: between-severity group comparison Multiple regression: demographic, IS predictors Principal components analysis w/ varimax rotation: neuropsychological variable assessment at t_2 (to reduce predictors in multiple regression) Bonferroni corrections: significant tests w/ multiple comparisons Post hoc: cognitive functioning in mild TBI $p < .05$ (2-tailed)	At t_2, drug/alcohol use by Alcohol use disorders identification test Alcohol >once/mo (chi(8) = 24.1, $p < .01$): mild, mod (48%); sev (27%) $n = 106$ Alcohol and/or drugs 2–3×/wk: 13%; ≥4×/wk: 7%	FSS: avg 1–7 across 9 items – total 0–7 (higher score, more fatigue) t_2, between-severity groups: NS; mean score: 4 ± 1.8 At t_1, fatigue (along w/ 2/3 cognitive components, PTA, intracranial pathology) as a predictor of Glasgow Outcome Scale-Extended (GOSE) at t_2: significant ($R^2 = .61$, $p < .001$) Fatigue, by FSS, as predictor of GOSE at t_2: $B = -.13$; SE = .04; $\beta = -.25$ ($p < .001$) Significant correlations at t_2: fatigue w/ ($n = 96$): Memory/speed: −.38 ($p < .001$) Verbal/reasoning: −.2 ($p < .01$) GOSE: −.39 ($p < .001$)	NR *Notes*: Less fatigue predicts better outcome No effects of sex, education, TBI severity on fatigue at t_2

Sundstrom et al. (2007) SE Longitudinal prospective cohort study sample	Study self-reported fatigue incidence pre- and post-mTBI; compare incidences at time points to controls; examine association between fatigue and APOE ε4 genotype Longitudinal population-based F/U: post-injury IC: in subset of previous longitudinal study (previously tested); participated in $\geq$2 evaluations in previous study EC: missing data; mini-mental state examination score <23; not genotyped; dementia at 1st/2nd/3rd evaluation in previous study	n = 31 mTBI; 62 controls Attrition: 0 Stats for mTBI: Age (at entry): 55.2 $\pm$ 13.6 Sex: 58.1% M TSI (n = 18): (injury-post-seccion): 19.7 $\pm$ 14.5 mos IS (self-report, confirmed w/ criteria): mild AT: BL: pre-injury (previous study) F/U: post-injury Controls: 1st, 2nd assessments from previous study	McNemar's test: differences pre- to post-injury; for controls, differences 1st to 2nd assessment Fisher's exact test: between-group comparison (i.e. mTBI vs. controls)	NR	Yes/no questions about presence of fatigue Fatigue presence: Yes to "Do you often feel fatigued?" Fatigue frequencies: Pre-injury/1st assessment: mTBI: 16.1% Control: 25.8% Post-injury/2nd assessment (p < .05): mTBI: 41.9% Control: 19.4% Post-injury fatigue in mTBI w/ APOE ε4: 58%; w/o APOE ε4: 32% 2nd assessment fatigue in controls w/ APOE ε4: 17%; w/o APOE ε4: 21% mTBI w/ APOE ε4 vs. control w/ APOE ε4: significant (p = .02) mTBI w/o APOE ε4 vs. control w/o APOE ε4: NS (.52)	Fatigue frequency within-group change: mTBI: significant (p < .05) Control: NS
van der Naalt et al. (1999) NL Hospital	Report long-term outcomes in persons w/ mild-mod head injury, GCS 9–14, irrespective of length of hospital stay and CT abnormalities; examination of complaints, return to work; whether GCS scores at admission and length of PTA is predictive of outcome Prospective F/U: post-injury: 1, 3, 6, 12 mos IC: 15–65 yrs; GCS 9–14 at hospital admission; PTA $\geq$ 1 h EC: earlier admission for head injury; history of drug/alcohol abuse; psychiatric disorder/mental retardation diagnosis; severe aphasia interfering w/ report of PTA; PTA $\geq$ 28 d	n = 67 Attrition: 0 Age: 33.2 $\pm$ 14.7 Sex: 64.2% M TSI: 1–2 h post-injury at hospital admission IS: GCS mean: 12.6 (range 9–14); PTA mean: 7.8 $\pm$ 7.3; range 1–30 d) Mild: 64.2% Mod: 35.8% AT: post-injury: t_1: 1 mos t_2: 3 mos t_3: 6 mos t_4: 12 mos	Student's t/Mann–Whitney U tests: where appropriate Pearson's correlation coefficients: independent measure associations κ analysis: interobserver scoring Chi-square w/ correction for continuity: frequencies Multivariate regression by stepwise backward method Outcome variables distribution: normal for scales w/ $\geq$4 points; all else categorical	NR History of addiction to alcohol or drugs as part of exclusion criteria Alcohol intolerance at 1, 3, 6 mos and 1 year = 6, 11, 17 and 20%, respectively	Fatigue as complaint on symptoms checklist Fatigue frequencies at time points: t_1: 57% t_2: 61% t_3: 45% t_4: 45% At all time points, features as 1/6 most frequent complaints No correlation between injury characteristics and complaints at all time points	NR

Table 1 (*Continued*)

Reference Country Sample by	Objective Design Follow-up (F/U) Inclusion/exclusion criteria (IC/EC)	Sample size Attrition Age, sex (% M) Time since injury (TSI) Injury severity (IS) Assessment time points/N assessed (AT: t_1, t_2, etc.)	Statistical method	Medications	Results	
					Fatigue definition Frequencies, scores	Score differences over time Notes
Yang et al. (2009) TW Level I trauma center	Study early clinical predictors, PCS in mTBI persons with persistent symptoms 2 mos post-injury; study w/i a study Prospective F/U: post-injury: 1, 2, 8 wks IC: mTBI patients from other prospective study EC: could not be reached for F/U	$n = 180$; 2 mTBI groups: 1: persistent PCS (PPCS) $n = 17$; non-PPCS $n = 163$; control group $n = 40$ Attrition: 0 Age: 1: 37.2 ± 14.2 2: 35.7 ± 16.4 Sex: 1: 41% M 2: 48% M TSI: recruitment at ED IS: GCS mean: 1: 14.9 ± .3 2: 14.9 ± .3 Intracranial lesions: 1: 53% 2: 15% AT: post-injury: t_1: 1 wk t_2: 2 wks t_3: 8 wks	Chi-square: associations of PCS items in groups 1 and 2 Logistic regression: predictors of mTBI w/ PPCS $p < .05$	NR	Checklist of PCS (CPCS) featuring fatigue item Fatigue frequencies by CPCS: mTBI: t_1: 23% t_2: 11% t_3: 3% Fatigue frequency within 2 mos (previous study): Control ($n = 40$): 8% Fatigue frequencies by CPCS by group: 1: t_1: 24%; t_2: 35% 2: t_1: 23%; t_2: 9% t_1: OR = .02 t_2: OR = 2.76 Fatigue as one of most common PCS in group 1 Fatigue strongly associated with PPCS incidence at t_2: $\chi^2 = 11.12$, $p < .01$	NR

APOE ε4 apolipoprotein-ε4; BDI, Beck depression inventory; BFS, Barroso fatigue scale; BL, baseline; CNS, central nervous system; CPCS, checklist for post-concussion syndrome; CT, computed tomography; d, day; ED, emergency department; IC/EC, inclusion/exclusion criteria; IS, injury severity; ISS, injury severity score; FSS, fatigue severity scale; FNS, flexyx neurotherapy system; F/U, follow-up; GCS, Glasgow coma scale; GOSE, Glasgow outcome scale-extended; GFI, global fatigue inventory; LOC, loss of consciousness; MFIS, modified fatigue impact scale; MRI, magnetic resonance imaging; MHI, mild head injury; mTBI, mild traumatic brain injury; mos, months; NR, not reported; NS, not significant; PCS, post-concussion syndrome; PCSC, post-concussion syndrome checklist; POMS, profile of moods scale; PPCS, persistent post concussive syndrome; PTA, post traumatic amnesia; RPQ, Rivermead post-concussive questionnaire; PSQI, Pittsburgh sleep quality index; SF-36, 36-item short form health survey (from medical outcomes study); TC, trauma controls; TBI, traumatic brain injury; tx, treatment; TSI, time since injury; SSRI, selective serotonin reuptake inhibitor; VAS, visual analog scale; wks, weeks; yrs, years.

Table 2
Summary of reported predictors of fatigue.

Study	Measure and purpose in study	Results: predictors of fatigue
De Leon et al. (2009)	**MOS SF-36 Vitality subscale** • Severity measure (i.e. low score indicates more fatigue)	**Predictors of severity at 12 months** • Baseline fatigue ($p = .000$) • Counseling for mental health ($p = .016$) • Medical disability ($p = .012$) • Marital status ($p = .006$) • Litigation involvement ($p = .044$) **NS** • Sex ($p = .762$) • Age ($p = .507$) Education ($p = .77$) Prior drug/alcohol treatment ($p = .382$) Motor vehicle crash ($p = .444$) Injury type ($p = .792$, $p = .427$)
Norrie et al. (2010)	**FSS** • Frequency measure (i.e. score ≥3.7 indicates fatigue) RPQ fatigue item • Frequency measure (i.e. symptom rating ≥2 indicates fatigue) **MOS SF-36v2 Vitality subscale** • Severity measure (i.e. low score indicates more fatigue)	**Predictor of severity at 3 mos** • Severity at wk 1 (FSS) ($R = 0.53$; $p < .000$) **Predictor of severity at 6 mos** • Severity at wk 1 ($R = 0.49$; $p < .000$) • Severity at 3 mos ($R = 0.76$; $p < .000$) • Depression at 3 mos ($B = .12$; SE = .04; $\beta = .25$; $p < .0000$) • Anxiety at 3 mos ($B = -.01$; SE = .03; $\beta = -.04$; $p = .610$)
Sundstrom et al. (2007)	**Fatigue question** • Frequency measure (i.e. answer "yes" to question "Do you often feel fatigued?" indicates fatigue)	**Predictor of frequency post-injury** • APOE ε4 genotype ($p = .02$)

APOE ε4, apolipoprotein-ε4; MOS SF-36v2 NS, not significant – 36-item short form health survey vitality subscale (from medical outcomes study); FSS, fatigue severity scale; RPQ, Rivermead post-concussive questionnaire; wk, week.

(i.e. untreated group) data and no effect data (i.e. intervention has not effect) were utilized to address the second research objective (i.e. to determine the course of fatigue) in patients with TBI.

Study quality was independently assessed by two reviewers (TM and TK), using guidelines developed by Hayden et al. (2006) for assessment of prognostic studies (Table 4). The appraisal was performed in two steps. First, the items related to six potential sources of bias (i.e. study participation and attrition, associated factors and outcome measurements, confounding measurement, and analyses) were assessed, then presence of potential biases was judged "Yes", "Partly", "No", or "Unsure". To summarize the level of evidence, we used a system similar to the Scottish Intercollegiate Guidelines Network (SIGN) methodology (SIGNPG, 2013): (i) "+++" when all or most of the quality criteria proposed by Hayden et al. were fulfilled (i.e. allowing one "Partly" while appraising all potential sources of bias); (ii) "++" when the majority of criteria were fulfilled; (iii) "+" when few criteria were fulfilled (i.e. at least one "Yes"). Additionally, as proposed by SIGN, studies with retrospective data collection did not receive a "++" rating, as this design is weaker than prospective data collection. We refer to group (i) as 'high quality studies'; group (ii) as 'good quality studies'; and group (iii) as 'fair quality studies'.

2.6. Data synthesis

A best-evidence synthesis approach was applied, synthesizing findings from studies with sufficient quality through tabulation and qualitative description (Slavin, 1995; Carroll et al., 2004a).

Results were grouped into three main categories: prognostic factors of fatigue, course of the fatigue, and consequences of fatigue (Tables 1–3). For studies utilizing measures of fatigue prevalence, sample size-weighted mean frequencies were reported. Fatigue severity measures used in the studies were reported with their corresponding sample mean scores. To determine the course of fatigue, matching assessment times (i.e. time post-injury that fatigue was measured) were grouped, with their corresponding fatigue frequencies, and a sample size-weighted mean frequency value was calculated for time points with more than one contributing frequency value (i.e. more than one study reporting fatigue at that time point). Fatigue resolution/exacerbation/no change designations were reported.

Prognostic factors associated with fatigue were extracted for all cohorts and untreated/no effect RCTs. All factors influencing the course of fatigue, as reported by authors, were considered associated with fatigue and not necessarily causal factors. To address our third research objective (i.e. health consequences of fatigue in TBI), we evaluated reports of poor health outcomes associated with fatigue after TBI.

2.7. Zero-time

The nature of our research questions related to fatigue in the TBI population (i.e. prognostic factors, course, and consequences) raises the issue of zero-time bias. In prognostic studies, testing should start at a defined point, called zero time (Giobbie-Hurder et al., 2013; van Rein et al., 2014). Designated zero times (i.e. baseline or first assessment) varied between studies included in this review. For this reason and to best address our research questions, studies were grouped based on whether baseline assessments were conducted before or after the one-month post-injury mark. This point was arbitrarily set.

2.8. Missing data

Primary authors were contacted in the case of missing data. In the case of duplicate publications and companion papers of a primary study, we attempted to maximize the yield of information by the simultaneous evaluation of all available data (i.e. all data necessary to address the three objectives of research, see Section 2.5). Original publications took priority.

3. Results

3.1. Literature search and quality assessment

Of 2745 articles identified, 33 were selected for full-text review (Lidvall et al., 1974; Ponsford et al., 2012; De Leon et al., 2009; Lundin et al., 2006; Meares et al., 2011; Mickeviciene et al., 2004;

Table 3
Summary of reported consequences of fatigue.

Study	Measure and purpose in study	Results: consequences of fatigue
Norrie et al. (2010)	**FSS** • Frequency measure (i.e. score ≥3.7 indicates fatigue) **RPCQ fatigue item** • Frequency measure (i.e. symptom rating ≥2 indicates fatigue) **RPSQ** • Presence/problem status of 16 post-concussional symptoms	**Predictors of persistent PCS (RPSQ total) at 6 mos** • Fatigue severity at wk 1($R = 0.40$; $p < .000$) • Fatigue severity at 3 mos ($R = 0.53$; $p < .000$)
Sigurdardottir et al. (2009)	**FSS** • Severity measure (i.e. higher score indicates more fatigue)	**Full sample** *Predictor of GOSE* • Fatigue severity at 3 mos ($R^2 = .61$, $p < .001$) *Predictor of GOSE at 12 mos* • Fatigue severity by FSS ($B = -.13$; SE = .04; $\beta = -.25$; $p < .001$) **mTBI** *Predictor of GOSE at 12 mos* • Fatigue severity by FSS ($R^2 = .47$, $p < .01$) *Moderate/severe TBI* • Fatigue severity by FSS ($R^2 = .58$, $p < .001$)

FSS, fatigue severity scale; GOSE, Glasgow Outcome Scale-Extended; mTBI, mild traumatic brain injury; mos, months; PCS, post-concussion syndrome; RPCSQ, Rivermead post-concussion symptom questionnaire; wk, week.

Norrie et al., 2010; van der Naalt et al., 1999; Yang et al., 2009; McLean et al., 1993; Sundstrom et al., 2007; Hutchinson et al., 2009; Sigurdardottir et al., 2009; Kempf et al., 2010; Driver and Ede, 2009; Gemmell and Leathem, 2006; Bushnik et al., 2008a; Jha et al., 2008; Kaiser et al., 2010; Khateb et al., 2005; Schoenberger et al., 2001; Hou et al., 2012; Bhambhani et al., 2008; Bateman et al., 2001; Bushnik et al., 2008b; Cooper et al., 2009; Hillier et al., 1997; Wiart et al., 2012; Kim et al., 1999; Haboubi et al., 2001; Olver et al., 1996; Rees and Bellon, 2007) and 22 were included in the final review (Fig. 2) (Lidvall et al., 1974; Ponsford et al., 2012; De Leon et al., 2009; Lundin et al., 2006; Meares et al., 2011; Mickeviciene et al., 2004; Norrie et al., 2010; van der Naalt et al., 1999; Yang et al., 2009; McLean et al., 1993; Sundstrom et al., 2007; Hutchinson et al., 2009; Sigurdardottir et al., 2009; Kempf et al., 2010; Driver and Ede, 2009; Gemmell and Leathem, 2006; Bushnik et al., 2008a; Jha et al., 2008; Kaiser et al., 2010; Khateb et al., 2005; Schoenberger et al., 2001; Hou et al., 2012). Supplementary Table 2 reports reasons for exclusion of 11 studies (Bhambhani et al., 2008; Bateman et al., 2001;

Table 4
Quality assessment of studies using guidelines developed by Hayden et al. (2006).

Study	Study participation	Time-zero	Study attrition	Prognostic factor	Outcome	Confounding measurement and account	Analysis	Reason for exclusion	Overall assessment
Bushnik et al. (2008a)	No	Yes[i]	Yes[d]	NA	No	No	No	–	+
De Leon et al. (2009)	No	No	Partly[a]	No	No	No	No	–	+++
Driver and Ede (2009)	Partly[e]	Yes[i]	No	NA	No	Not sure	No	–	+
Gemmell and Leathem (2006)	Partly[e]	Yes[i]	Not sure	NA	No	No	Partly[c]	–	+
Hou et al. (2012)	No	Yes[i]	No	No	No	Partly[h]	No	–	+
Hutchinson et al. (2009)	Partly[e]	No	Not sure	NA	No	Yes[b]	No	–	+
Jha et al. (2008)	No	Yes[i]	No	Partly[g]	No	No	No	–	+
Kaiser et al. (2010)	Partly[e]	Yes[i]	No	Not sure	No	No	No	–	+
Kempf et al. (2010)	No	Yes[i]	No	NA	No	No	Partly[c]	–	+
Khateb et al. (2005)	Partly[e]	Yes[i]	Partly[a]	NA	Partly[f]	Partly[h]	Partly[c]	–	+
Lidvall et al. (1974)	No	No	No	NA	Partly[f]	Partly[h]	Partly[c]	–	++
Lundin et al. (2006)	No	No	No	NA	Partly[f]	Partly[h]	No	–	++
McLean et al. (1993)	No	No	No	NA	Partly[f]	No	Partly[c]	–	++
Meares et al. (2011)	No	No	Partly[a]	No	No	Partly[h]	No	–	++
Mickeviciene et al. (2004)	No	No	No	NA	No	No	Partly[c]	–	+++
Norrie et al. (2010)	No	No	Partly[a]	No	No	Partly[h]	No	–	++
Ponsford et al. (2012)	No	No	Partly[a]	NA	No	Partly[h]	Partly[c]	–	+
Schoenberger et al. (2001)	Partly[e]	Yes[i]	Not sure	NA	No	No	Partly[c]	–	+
Sigurdardottir et al. (2009)	No	Yes[i]	No	No	No	Partly	No	–	+
Sundstrom et al. (2007)	No	No	No sure	No	Partly[f]	No	No	–	++
van der Naalt et al. (1999)	No	No	No	NA	Partly[f]	Partly[h]	No	–	++
Yang et al. (2009)	No	No	Partly[a]	No	Partly[f]	Partly[h]	No	–	+

Yes – yes, sources of potential bias are presented; No – no potential bias; Not sure – not enough details were reported to make a decision (in some cases authors were contacted); NA – not applicable according to the study design or type of analyses used.

[a] Not all required information about study attrition was provided.
[b] A study does not address the possibility of confounding.
[c] Some errors in analyses performed were observed: e.g. limited details about analyses.
[d] Completeness of follow-up was not adequate.
[e] Small sample size.
[f] Detail information about measure used was not provided or used measure was not validated.
[g] Analyses performed were not adequate.
[h] Not all important covariates were included or exclusion criteria are not completed.
[i] Baseline assessment performed after 1 month post-injury.

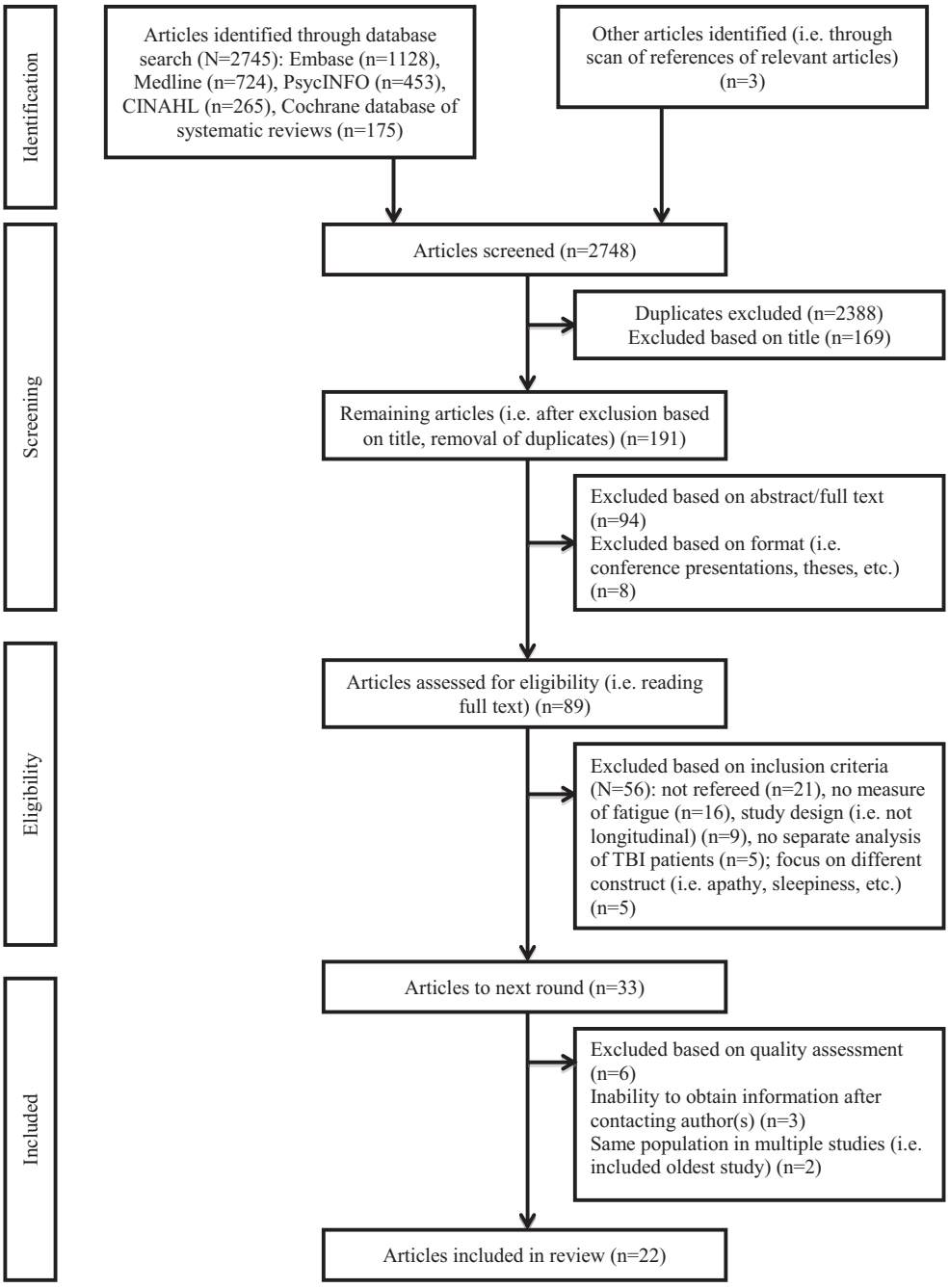

Fig. 2. Flow chart documenting process of article selection for review. Embase (1974-4/11/2013); Medline (1946-4/14/2013); PsycINFO (1806-4/7/2013); CINAHL (1980-4/18/2013); Cochrane (2005-3/2013).

Bushnik et al., 2008b; Cooper et al., 2009; Hillier et al., 1997; Wiart et al., 2012; Kim et al., 1999; Haboubi et al., 2001; Olver et al., 1996; Rees and Bellon, 2007; Meares et al., 2011). Main analyses featured 11 inception cohort studies with baseline assessment performed within one-month post-injury (Lidvall et al., 1974; Ponsford et al., 2012; De Leon et al., 2009; Lundin et al., 2006; Meares et al., 2011; Mickeviciene et al., 2004; Norrie et al., 2010; van der Naalt et al., 1999; Yang et al., 2009; McLean et al., 1993; Hutchinson et al., 2009). Separate analyses of studies with baseline assessment after one month included 11 studies (McLean et al., 1993; Sundstrom et al., 2007; Sigurdardottir et al., 2009; Kempf et al., 2010; Driver and Ede, 2009; Gemmell and Leathem, 2006; Bushnik et al., 2008a; Jha et al., 2008; Kaiser et al., 2010; Khateb et al., 2005; Schoenberger et al., 2001; Hou et al., 2012), among them six RCTs (Driver and Ede, 2009; Gemmell and Leathem, 2006; Jha et al., 2008; Kaiser et al., 2010; Khateb et al., 2005; Schoenberger et al., 2001).

All 22 studies (Lidvall et al., 1974; Ponsford et al., 2012; De Leon et al., 2009; Lundin et al., 2006; Meares et al., 2011; Mickeviciene et al., 2004; Norrie et al., 2010; van der Naalt et al., 1999; Yang et al., 2009; McLean et al., 1993; Sundstrom et al., 2007; Hutchinson et al., 2009; Sigurdardottir et al., 2009; Kempf et al., 2010; Driver and Ede, 2009; Gemmell and Leathem, 2006; Bushnik et al., 2008a; Jha et al., 2008; Kaiser et al., 2010; Khateb et al., 2005; Schoenberger et al., 2001; Hou et al., 2012) were assessed as having "Partly" or "No" on all bias criteria. Two studies (De Leon et al., 2009; Mickeviciene et al., 2004) were of high quality ("+++"), six (Lidvall et al., 1974; Lundin et al., 2006; Norrie et al., 2010; van der Naalt et al., 1999; McLean et al., 1993; Sundstrom et al., 2007) were of good

quality ("++") and the remaining 14 (Ponsford et al., 2012; Yang et al., 2009; Hutchinson et al., 2009; Sigurdardottir et al., 2009; Kempf et al., 2010; Driver and Ede, 2009; Gemmell and Leathem, 2006; Jha et al., 2008; Kaiser et al., 2010; Khateb et al., 2005; Schoenberger et al., 2001; Bushnik et al., 2008b) were of fair quality ("+"). The latter group were penalized by the SIGN criteria (SIGNPG, 2013) for incomplete statistical analysis, potential confounders, selection bias due to study attrition, and/or zero-time bias (Table 4).

3.2. Study characteristics

Tables 2–4 summarize the study characteristics pertinent to our research questions: population characteristics, definitions of TBI, definitions of fatigue, follow-up time, statistical analysis methods, and study results. Means were calculated for the reviewed studies' sample data.

3.3. Studies with baseline assessment up to one month post-injury

Eleven studies featured a total of 1366 participants with TBI. Nine studies performed recruitment at emergency departments, hospitals, or trauma centers, making up 91% of the total group ($n = 1244$) (Lidvall et al., 1974; Ponsford et al., 2012; De Leon et al., 2009; Lundin et al., 2006; Meares et al., 2011; Mickeviciene et al., 2004; Norrie et al., 2010; van der Naalt et al., 1999; Yang et al., 2009). One study recruited participants from the community (7.5% of the sample, or $n = 102$) (McLean et al., 1993). One study featured university athletes within four days of concussion, making up 1.5% of the sample ($n = 20$) (Hutchinson et al., 2009).

Nine studies featured strictly participants with mild TBI (Lidvall et al., 1974; Ponsford et al., 2012; De Leon et al., 2009; Lundin et al., 2006; Meares et al., 2011; Mickeviciene et al., 2004; Norrie et al., 2010; Yang et al., 2009), one examined mild to moderate TBI (van der Naalt et al., 1999), and one included all TBI severities (McLean et al., 1993).

The study samples comprised males in a range between 42% (De Leon et al., 2009) and 69% (Lidvall et al., 1974), with a mean $62.1 \pm 9.5\%$ across studies. One study did not report a sex ratio, stating the sample consisted mainly of single males, and was included in the mean calculation as 75% male (McLean et al., 1993). The mean age ranged between 20.1 (Hutchinson et al., 2009) and 41.2 years of age (De Leon et al., 2009), with a mean 33.5 ± 5.6 years across studies. Mean time since injury (TSI) to baseline assessment ranged from one day (Lundin et al., 2006) to one month (Mickeviciene et al., 2004), and the mean TSI across all studies was 0.34 ± 0.38 months, or 10.2 ± 11.4 days.

3.4. Studies with baseline assessment after one month post-injury

Eleven studies (Sundstrom et al., 2007; Sigurdardottir et al., 2009; Kempf et al., 2010; Driver and Ede, 2009; Gemmell and Leathem, 2006; Bushnik et al., 2008a; Jha et al., 2008; Kaiser et al., 2010; Khateb et al., 2005; Schoenberger et al., 2001; Hou et al., 2012) featured a total 482 participants. Eight of these studies recruited from the community, making up 43.4% of the total group (i.e. $n = 209$) (Sundstrom et al., 2007; Sigurdardottir et al., 2009; Kempf et al., 2010; Driver and Ede, 2009; Gemmell and Leathem, 2006; Bushnik et al., 2008a; Kaiser et al., 2010; Schoenberger et al., 2001). Bushnik et al. (2008a) ($n = 51$) and Sigurdardottir et al. (2009) ($n = 115$) recruited from an inpatient rehabilitation center and a level 1 trauma center, respectively. Hou et al. (2012) recruited from the emergency department ($n = 107$), with baseline assessment performed at a laboratory at a later time.

Seven studies featured participants with all severities of TBI (Sigurdardottir et al., 2009; Kempf et al., 2010; Driver and Ede, 2009; Gemmell and Leathem, 2006; Jha et al., 2008; Kaiser et al., 2010; Schoenberger et al., 2001), two comprised patients with moderate to severe TBI (Bushnik et al., 2008a; Khateb et al., 2005), and two with mild TBI (Sundstrom et al., 2007; Hou et al., 2012).

The percentage of males ranged between 17%(Schoenberger et al., 2001) and 85% (Kaiser et al., 2010), with a mean $62 \pm 19.2\%$ across samples. The mean age ranged from 31 years (Bushnik et al., 2008a) to 55.2 years of age (Sundstrom et al., 2007), with a mean 39.9 ± 6.6 years across studies. Mean TSI, across the ten studies, was 39.5 ± 35.5 months (i.e. 1185 ± 1065 days) and baseline assessment times ranged from 2.6 months (Bushnik et al., 2008a) to 8.6 years post-injury (Gemmell and Leathem, 2006).

3.5. Assessment of TBI

Considerable between-study variation was observed in TBI diagnostic criteria and definitions, irrespective of TSI at baseline assessment (Tables 1–3). Most studies (17/22) used a combinatorial approach to confirm and assess TBI, using tools such as the Glasgow Coma Scale (GCS), duration of posttraumatic amnesia (PTA) and loss of consciousness (LOC), and clinical evaluation (Lidvall et al., 1974; Ponsford et al., 2012; De Leon et al., 2009; Lundin et al., 2006; Meares et al., 2011; Mickeviciene et al., 2004; Norrie et al., 2010; van der Naalt et al., 1999; Yang et al., 2009; McLean et al., 1993; Hutchinson et al., 2009; Sigurdardottir et al., 2009; Gemmell and Leathem, 2006; Bushnik et al., 2008a; Jha et al., 2008; Khateb et al., 2005; Hou et al., 2012). Three studies (Sundstrom et al., 2007; Driver and Ede, 2009; Schoenberger et al., 2001) used other methods, including patient report, description of damage and/or lesions based on medical records, and diagnoses of referring professionals. Two studies used GCS scores alone (Kempf et al., 2010; Kaiser et al., 2010).

3.6. Methods used for assessing fatigue

Measures used to assess fatigue in the TBI population varied depending on the study objectives. Studies where fatigue was not a main focus most commonly used a single item for the symptom within a checklist with broad symptom coverage (9/22) (e.g. Rivermead post-concussion questionnaire (RPQ) and the post-concussion syndrome checklist (PCSC)) (Tables 2 and 3). If fatigue was studied more extensively, standardized measures looking at different aspects of the symptom, such as momentary perception, chronic characteristics, impact of fatigue on function, rating/rank of fatigue intensity/severity and dimensions of fatigue (i.e. cognitive, physical) were utilized. Four of the 22 studies used more than one measure to assess fatigue. All fatigue scales were designed for other populations, with some having psychometric properties described in the TBI population (Supplementary file 3).

3.6.1. Multi-item scales

Most studies (14/22) assessed fatigue based on standardized self-report measures – four used the fatigue severity scale (FSS) (Sigurdardottir et al., 2009; Kempf et al., 2010; Jha et al., 2008; Kaiser et al., 2010); four – the short-form health survey-36 (SF-36) vitality subscale (Ponsford et al., 2012; De Leon et al., 2009; Norrie et al., 2010; Gemmell and Leathem, 2006); two – a visual analog scale (VAS) for fatigue (Mickeviciene et al., 2004; Gemmell and Leathem, 2006), and two – the profile of mood states (POMS) fatigue-inertia scale (Hutchinson et al., 2009; Driver and Ede, 2009). One study assessed fatigue with the Barroso fatigue scale (BFS), a synthesis of five independent scales, with additions (Bushnik et al., 2008a). The BFS yields FSS and global fatigue index (GFI) scores. One study utilized the modified fatigue impact scale (MFIS) (Jha et al., 2008), one used the fatigue assessment inventory (Khateb et al., 2005), and one again used the multidimensional fatigue inventory

(Schoenberger et al., 2001). We refer the reader to Supplementary file 3 for descriptions of measures.

On the FSS, participants rate their level of agreement with respect to nine statements about the severity of fatigue and its impact on everyday activities (Krupp et al., 1989). The total score is the mean, and higher scores indicate greater fatigue. In some cases, studies reported frequency of fatigue by the FSS, defining presence of the symptom as a total score ≥4 (Kempf et al., 2010; Kaiser et al., 2010), or ≥3.7 (Norrie et al., 2010). Others used FSS scores as indicators of fatigue severity (Sigurdardottir et al., 2009; Bushnik et al., 2008a; Jha et al., 2008).

On the four-item SF-36 vitality subscale, participants choose, on a six-point scale, the frequency of events related to fatigue and energy (Ware, 1992). Fatigue item means are combined with reverse-scored energy means to yield a total score. Two studies utilized two different versions of the measure (i.e. SF-36 and SF-36 version 2). SF-36 and the updated SF-36 version 2 are comparable in terms of scores.

3.6.2. Single item assessment of fatigue

Nine papers used a single item or question to assess fatigue (Lidvall et al., 1974; Ponsford et al., 2012; Lundin et al., 2006; Meares et al., 2011; van der Naalt et al., 1999; Yang et al., 2009; McLean et al., 1993; Sundstrom et al., 2007; Hou et al., 2012), presenting TBI patients with a list of symptoms (e.g. Rivermead PCSQ, PCS checklist, etc.), including fatigue. One study determined presence of fatigue by participants' 'Yes' responses to the question, "Do you often feel fatigued?" (Sundstrom et al., 2007).

3.6.3. Multiple measures of fatigue

Four studies used more than one measure to assess fatigue (Ponsford et al., 2012; Norrie et al., 2010; Gemmell and Leathem, 2006; Jha et al., 2008). Gemmell and Leathem (2006) utilized the SF-36 vitality subscale with the VAS for fatigue, for a measure of fatigue severity. Jha et al. (2008) worked with the FSS and MFIS and reported change in severity of fatigue with use of medications. Norrie et al. (2010) utilized the SF-36 vitality subscale with the RPQ for severity and frequency values. The SF-36 vitality subscale was used again by Ponsford et al. (2012) together with a single item from the PCS checklist, to report frequency and severity of fatigue across time.

3.7. Overall predictors of fatigue

Only studies with baseline assessment prior to one month post-injury investigated predictors of fatigue. All statistically significant predictors of fatigue identified are reported in Table 2. Three studies, one of high quality and two of moderate quality (De Leon et al., 2009; Norrie et al., 2010; Sundstrom et al., 2007) identified eight factors significantly associated with fatigue in TBI patients (Table 3). The factors comprised earlier fatigue severity, significant in two studies (De Leon et al., 2009; Norrie et al., 2010), carriage of the apolipoprotein E ε4 allele, significant in one study (Sundstrom et al., 2007), having seen a counselor for a mental health issue, medical disability, marital status (i.e. widowed, divorced, or separated) and litigation involvement, all significant in one study (De Leon et al., 2009), and depression, also significant in one study (Norrie et al., 2010). One moderate quality study did not find a significant effect of sex, education, or TBI type/severity on fatigue in a fully adjusted model (Norrie et al., 2010). In that same study, anxiety at three months was not a predictor of fatigue at six months (Norrie et al., 2010).

3.8. The course of fatigue

Mean frequencies of fatigue at time points with more than one reported value (i.e. two or more studies reported frequency at the same time post-injury) were weighted based on sample size. For studies where baseline assessment was conducted prior to or at one month post-injury, mean weighted frequencies were 46.6% (SD = 32.7, n = 206) (Lidvall et al., 1974; Ponsford et al., 2012), 45.9% (SD = 24.8, n = 637) (Lidvall et al., 1974; Ponsford et al., 2012; Norrie et al., 2010; Yang et al., 2009), 17.3% (SD = 13.6, n = 325) (Lidvall et al., 1974; Meares et al., 2011; Yang et al., 2009), 45.2% (SD = 29, n = 230) (Lidvall et al., 1974; van der Naalt et al., 1999; McLean et al., 1993), 30.5% (SD = 11.7, n = 830) (Lidvall et al., 1974; Lundin et al., 2006; Mickeviciene et al., 2004; Norrie et al., 2010), 32.4% (SD = 7.3, n = 269) (Norrie et al., 2010; van der Naalt et al., 1999) and 37.4% (SD = 8.1, n = 354) (Mickeviciene et al., 2004; van der Naalt et al., 1999; McLean et al., 1993) for two days, six days-one week, two weeks, one month, three months, six months and one year post-injury, respectively. The number of studies contributing to the mean for a particular time point ranged from two studies for two days and six months post-injury to seven studies for three months post-injury (Fig. 3a).

For studies with baseline assessment after one-month post-injury, just one mean weighted frequency value was obtained for one time point, 22.8% (SD = 5.4, n = 172) (Kempf et al., 2010; Hou et al., 2012) at six months post-injury. Two studies contributed values for calculation of this mean. The remaining time points comprised single studies and therefore one frequency value (Fig. 3b).

3.9. The course of fatigue, by injury severity

When fatigue frequency calculations were stratified by injury severity, mean weighted frequencies could only be obtained for the mild TBI group with baseline assessments conducted less than or at one month after injury. The frequencies of fatigue were 46.6% (SD = 32.7, n = 206) (Lidvall et al., 1974; Ponsford et al., 2012), 45.9% (SD = 24.8, n = 637) (Lidvall et al., 1974; Ponsford et al., 2012; Norrie et al., 2010; Yang et al., 2009), 17.3% (SD = 13.6, n = 325) (Lidvall et al., 1974; Meares et al., 2011; Yang et al., 2009) and 27.8% (SD = 7.8, n = 763) (Lidvall et al., 1974; Ponsford et al., 2012; Lundin et al., 2006; Meares et al., 2011; Mickeviciene et al., 2004) for two days, six days-one week, two weeks and three months post-injury, respectively. The number of studies contributing to the means ranged from two studies for two days post-injury to six studies for three months. The mild TBI group with baseline assessments performed after one-month post-injury and mild to moderate and mixed groups all had one contributing study each. The studies featuring moderate to severe TBI did not report fatigue frequencies.

For the purpose of comparison of fatigue frequencies between mild TBI and other severities, studies reporting frequencies in samples of mild to moderate and mixed severities of TBI were grouped. Mean frequencies were 66.3% (SD = 8.5, n = 147) (van der Naalt et al., 1999; McLean et al., 1993) and 46.2% (SD = 1, n = 162) (van der Naalt et al., 1999; McLean et al., 1993) for one month and one-year post TBI, respectively. The two contributing studies had baseline assessment performed within the first month post-injury.

3.10. Fatigue severity

In two studies using the FSS, the sample mean scores at 12 months were 3.20 ± 1.39 (Norrie et al., 2010) and 2.9 ± 1.6 (Bushnik et al., 2008a). One study, using an alternate FSS scoring system (Jha et al., 2008), reported similar fatigue severity. In the two studies that utilized the SF-36 vitality subscale and the SF-36 vitality subscale version 2, the mean scores at one year post-injury were 62.11 ± 20.18 (Norrie et al., 2010) and 49.6 ± 11.83 and 52.3 ± 12.22

Table 5
Fatigue measures and their corresponding scores at assessment.

Study	Injury type/severity	Assessment	Measure	Sev(BL)	Sev(t_1)	Sev(t_2)	Sev(t_3)
Bushnik et al. (2008b)	TBI/mod-sev	t_1: 2.6 ± 1.8 mos t_2: 12.6 ± 1.2 mos t_3: 23.2 ± 3.4 mos	GFI	NR	23 ± 10	17 ± 11	20 ± 11
			FSS		3.4 ± 1.5	2.9 ± 1.6	3.2 ± 1.8
De Leon et al. (2009)	1: HI w/ PTA and/or LOC/mild 2: HI only/mild	BL: ED t_1: 1 mo t_2: 3 mos t_3: 12 mos	SF-36v	1: 52.8 ± 9.53 2: 50.4 ± 10.48	NR	NR	1: 52.3 ± 12.22 2: 49.6 ± 11.83
Driver and Ede (2009)	TBI control/NR	BL: before start t_1: 8 wks later	POMS fatigue-inertia subscale	1.24 ± .61	1.29 ± .57	NA	NA
Gemmell and Leathem (2006)	TBI control/NR	BL: before start t_1: 6 wks later	SF-36v	47.50 ± 20.18	38.75 ± 4.43	NA	NA
Hutchinson et al. (2009)	TBI/mild	BL: ≤96 h post-injury t_1, t_2, t_3: 3 non-consecutive d over 2 wks	POMS fatigue-inertia subscale	≈4.3	≈8	≈6.8	≈4.4
Jha et al. (2008)	1: TBI/mild-sev modafinil first 2: TBI/mild-sev placebo first	BL: before start t_1: 4 wks t_2: 10 wks	MFIS	1: 46.56 ± 19.28 2: 47.17 ± 15.53	1: 38.65 ± 16.09 2: 36.45 ± 15.03	1: 35.63 ± 20 2: 33.55 ± 18.16	NA
			FSS	1: 45.22 ± 11.82 2: 44.46 ± 12.17	1: 39.36 ± 15.61 2: 37.7 ± 12.55	1: 37.13 ± 18.33 2: 36.91 ± 14.08	NA
Khateb et al. (2005)	Brain injury/PTA 8 ± 10 d	BL: before start t_1: 3 mos	29-item fatigue scale	132.6 ± 27.3	126.1 ± 32.3	NA	NA
Mickeviciene et al. (2004)	Concussion/NR	BL: ED t_1: 3 mos t_2: 1 y	VAS fatigue item	NR	50 ± 28	50 ± 30	NA
Norrie et al. (2010)	TBI/mild	t_1: 1 mo t_2: 3 mos t_3: 12 mos	SF-36 Vitality	NR	46.57 ± 24.72	60.21 ± 19.68	62.11 ± 20.18
			FSS	NR	3.99 ± 1.53	3.29 ± 1.44	3.20 ± 1.39
Ponsford et al. (2012)	TBI/mild	BL: ED post-injury t_1: 1 wk t_2: 3 mos	PCSC Checklist	NR	≈2.8	≈2.2	NA
Schoenberger et al. (2001)	Closed HI/mod-sev	BL: before start t_1: 6–8 wks later	MFI: Gen MFI: Phys MFI: Men	14.83 ± 4.17 10.50 ± 4.51 15.50 ± 3.83	14.00 ± 4.56 10.83 ± 5.34 15.67 ± 3.50	NA	NA
Sigurdardottir et al. (2009)	TBI/mild-sev	BL: ED t_1: 3 mos t_2: 12 mos	FSS	NR	NR	4.0 ± 1.8	NA

BL, baseline; ED, emergency department; FSS, fatigue severity scale; GFI, global fatigue inventory; LOC, loss of consciousness; MFIS, modified fatigue impact scale; MFI, multidimensional fatigue inventory; HI, head injury; TBI, traumatic brain injury; mos, months; NR, not reported; NA, not applicable; PCSC, post-concussion syndrome checklist; POMS, profile of moods scale; PTA, post-traumatic amnesia; sev, severity; SF-36 V, 36-item short form health survey vitality subscale (from medical outcomes study); TBI, traumatic brain injury; VAS, visual analogue scale; wks, weeks; y, year.

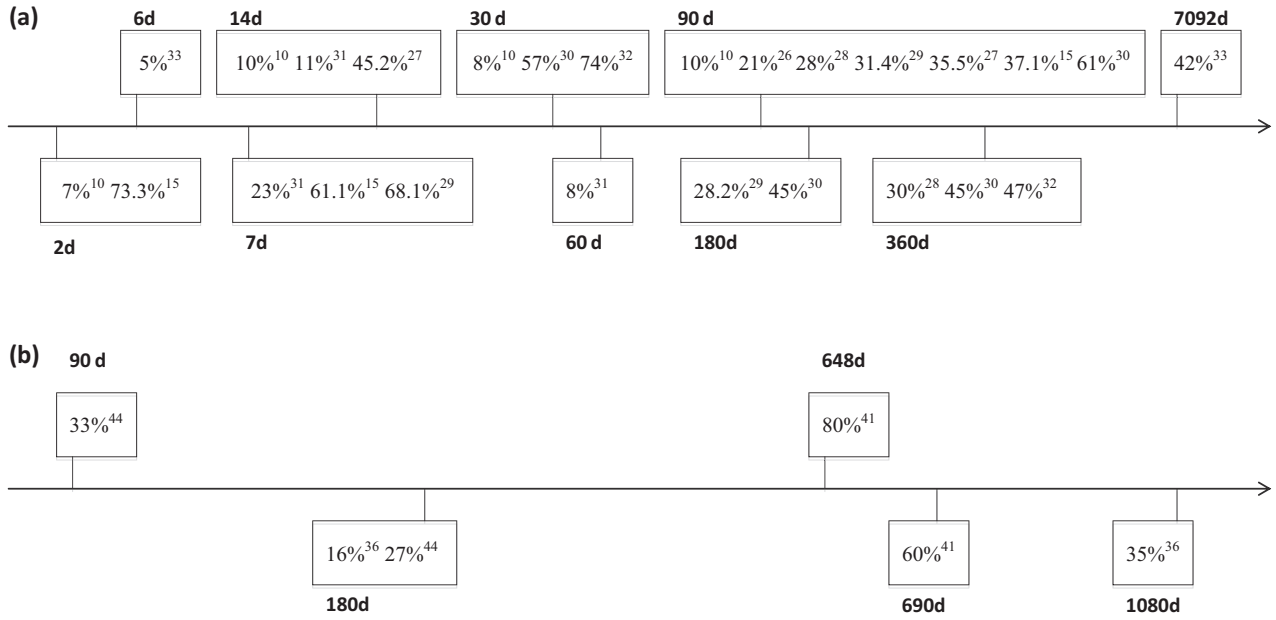

Fig. 3. (a) Reported frequencies of fatigue for studies with time zero ≤1-month post-injury. (b) Reported frequencies of fatigue for studies with time zero >1-month post-injury.

for two TBI subgroups (De Leon et al., 2009). Other researchers who utilized the same standardized scales could not be compared on the basis of their measurement of fatigue at different time points, or missing data on scores (Table 5).

3.11. Impact of fatigue after TBI

One study where baseline assessment took place prior to one month post-injury and one with baseline assessment at three months post-injury investigated consequences of fatigue.

Table 4 shows lists the consequences significantly associated with fatigue. One study of moderate quality looked at the relationship of fatigue with persistent post-concussive symptoms (Norrie et al., 2010), and one of fair quality looked at its association with the Glasgow outcome scale-extended (GOSE) total score (Sigurdardottir et al., 2009).

Persistent post-concussive symptoms: Fatigue severity at one week and three months predicted persistent post-concussive symptoms at three months and six months, respectively, controlling for litigation, psychological/neurological disorders, and substance abuse (Table 4) (Norrie et al., 2010).

GOSE total score: An association with the GOSE score was found in Sigurdardottir et al.'s study controlling for education, PTA, intracranial pathology and relevant psychological tests in multivariate regression analysis models. In the mild TBI group, the FSS total score was a significant predictor of GOSE score ($R^2 = 0.47$; $p < .001$), explaining 23% of the total variance in GOSE score at one year post-injury. Similar results were obtained for the moderate to severe TBI group ($R^2 = 0.58$; $p < .001$) (Table 4).

3.12. Associations of fatigue with other clinically important variables

3.12.1. Studies with baseline assessment up to one month post-injury

Lundin et al. (2006) found poor memory, sleep disturbance and fatigue to be most commonly reported within their sample, with early symptom overlap correlated with later results. Similarly, Meares et al. (2011) found symptom overlap of fatigue, insomnia, and irritability at five days and three months post-injury, with some participants recovering from and others developing the symptoms as time went on.

Norrie et al. found a significant increase in the percentage of those with fatigue reporting depression and/or anxiety, both symptoms over the cut off indicating mild severity, at six months after injury, compared with reports at three months. This increase coincides with a leveling off of fatigue percentages. As fatigue becomes persistent, psychological factors such as anxiety and depression tend to worsen (Norrie et al., 2010).

Ponsford et al.'s mTBI group reported significantly poorer general health, vitality, and mental health, as demonstrated by their scores in the corresponding subscales of the SF-36, compared to trauma controls; however, a similar pattern was observed when participants completed the same scales but with regard to their pre-injury status. The authors highlighted the importance of documenting pre-injury status in TBI studies.

3.12.2. Studies with baseline assessment after one month post-injury

Bushnik et al., investigating changes in fatigue from 6 to 12 months post-injury, reported a significant change in the Pittsburgh sleep quality index (PSQI) scores: where fatigue increased, PSQI scores were higher compared to cases where there was no change or decreased fatigue. There were no other significant group differences on the pain VAS, disability rating scale, neurobehavioral functioning inventory motor subscale, the Craig handicap assessment and reporting technique (CHART) cognitive independence, and CHART occupation (Bushnik et al., 2008a). The authors suggested that, for TBI individuals who complain of fatigue, assessing sleep quality would be a high-yield correlate and possibly treatable with behavioral and/or medication interventions.

Kempf et al. reported no associations between fatigue parameters and TBI severity, alcohol intake at time of injury, nor with sleep duration, education, age or gender. They did, however, find a moderate correlation between FSS and depression symptoms assessed with the Beck depression inventory (BDI) ($r = 0.46$, $p = 0.001$), and with anxiety symptoms assessed with the Hospital anxiety and depression scale (HADS) ($r = 0.37$, $p = 0.007$). They also reported coincidence of fatigue and excessive daytime sleepiness (Kempf et al., 2010).

3.13. Medications, drugs and alcohol

Seven of the 22 studies listed regular intake of psychoactive drugs and/or history of drug or substance abuse prior to TBI in study exclusion criteria (Mickeviciene et al., 2004; Norrie et al., 2010; McLean et al., 1993; Jha et al., 2008; Kaiser et al., 2010; Khateb et al., 2005; Schoenberger et al., 2001). One study excluded persons taking medications that cause sleep/wake disturbances, however, details were not provided (Kaiser et al., 2010). Eight of the 22 studies did not report on use of medications/illicit drugs/alcohol by participants prior to or over the course of the study (Lidvall et al., 1974; De Leon et al., 2009; Lundin et al., 2006; Yang et al., 2009; Sundstrom et al., 2007; Hutchinson et al., 2009; Gemmell and Leathem, 2006; Hou et al., 2012). Nine studies reported a variation of data. Bushnik et al. (2008a) reported use of alcohol by 62% prior to the first assessment, with 19% identified as drug users and heavy and/or binge drinkers. Sigurdardottir et al. (2009) described, at the second assessment, use of alcohol more than once per month in 48% of mild to moderate injured persons and in 27% of the severely injured. Use of alcohol and/or drugs more than two or three times per week was reported by 17%, and more than four times per week by 7% of participants (Sigurdardottir et al., 2009). Ponsford et al. (2012) included breath alcohol levels at recruitment exceeding 0.05 mg/L of alcohol, influence of illicit drugs at injury, history of significant drug/alcohol abuse affecting daily functioning in their exclusion criteria. Those reporting alcohol or cannabis use, and who did not have cognitive difficulties pre-injury were not excluded. The study reported frequency of lifetime substance abuse to be 31.3% in the mTBI sample and frequency of substance abuse in the previous three months to be 6.7% (Ponsford et al., 2012). Meares et al. (2011) reported use of opioids/opiates by 59.7% across the first and second assessments, and use of marijuana was reported in 24.4% of mTBI cases. In Driver and Ede's study, 61.1% reported intake of selective serotonin reuptake inhibitors (SSRIs). One study indicated changes in medication regimes of participants with flexyx neurotherapy system treatment, but did not clarify the nature of the changes (Schoenberger et al., 2001).

4. Discussion

4.1. Factors associated with fatigue

When we sought evidence of a temporal relationship between clinically important factors and fatigue we focused on: (1) TBI population characteristics (e.g. time since injury, severity of injury, comorbid conditions, etc.) and (2) our outcome of interest (i.e. fatigue) – its frequency, severity, and definition, with the goal of obtaining a set of risk factors that can be used for prognosis. Table 4 presents a descriptive summary of the available evidence. In summary, several potential risk factors for fatigue in TBI have been investigated, including those related to demographics and socioeconomic status, injury severity, medical comorbidities, baseline fatigue levels, genetic makeup, and physical and cognitive independence.

Fatigue at baseline, occurring at any time from injury through the acute care course, was found to be a primary predictor of symptom chronicity in TBI of varying severities (Norrie et al., 2010). Baseline fatigue was found to be one of the most powerful predictors of fatigue at follow-up (De Leon et al., 2009; Norrie et al., 2010). Other studies on chronic fatigue syndrome show similar associations between long-lasting fatigue and fatigue at baseline (Cairns and Hotopf, 1997; Nisenbaum et al., 2003; Kato et al., 2006), concurrent with the results of another study, where pre-stroke fatigue was reported to be related to fatigue in the acute phase after stroke (Lerdal et al., 2011). Despite reports of an impact of baseline fatigue on outcome at follow-up, the clinically important "critical values" of fatigue severity and duration following brain injury are not established. Future research should record frequent and specific data in investigation of the etiology of pre-morbid and baseline fatigue, and control for multiple factor interactions, in addition to the magnitude of effect attributable to individual factors in analyses. More attention needs to be paid to patients with intensive fatigue at baseline, as it is related to prognosis.

Female sex, education, GCS score, and alcohol use at the time of injury were reported to have no associative value for fatigue severity in a study of mild TBI (Kempf et al., 2010). Differences in severity and frequency of fatigue between men and women have been observed after stroke (Lerdal et al., 2011), depression (Khan et al., 2002), obstructive sleep apnea (Chervin, 2002), heart disease (Ekman and Ehrenberg, 2002), and cancer (Miaskowsky, 2004), with females more often reporting fatigue than their male counterparts. Sex-related differences in fatigue were investigated in just one reviewed study, and further research is warranted. Other factors associated with fatigue frequency and severity at follow-up, reported reviewed studies, included carriage of the APOE $\varepsilon 4$ allele (Sundstrom et al., 2007), counseling for mental health, medical disability, specific marital status (i.e. widowed, divorced, or separated), and involvement in litigation (De Leon et al., 2009). The APOE $\varepsilon 4$ allele in persons with TBI was previously reported to be linked to an increased risk of Alzheimer's disease (Jellinger et al., 2001). In a study of the general population (O'Hara et al., 2005), a relationship between sleep apnea (SA) and dementia through the APOE $\varepsilon 4$ allele was observed. Sleep apnea, highly prevalent in the TBI population (Mollayeva et al., 2013b), may explain the link between the APOE $\varepsilon 4$ allele and fatigue and dementia. While studies to date have outlined the separate relationships between TBI, SA, fatigue, the APOE $\varepsilon 4$ allele, and dementia, their complex interaction requires rigorous study.

4.2. Frequency, severity and course of fatigue in TBI

This systematic review underlines the variation in frequency of fatigue that exists after TBI, regardless of studies' set time zeros (Fig. 3a and b). Changes in the proportion of participants reporting fatigue from the start of the study to its completion also varied, some reporting gradual or abrupt increases or decreases, and others reporting frequency fluctuation over the course of study. A steep drop in frequency was observed at two weeks post-injury, with most of the contributing studies featuring mTBI patients. This drop might be explained by the current clinical management of mTBI, including the prescription of a rest period of at least two weeks after injury. As fatigue is influenced by the degree of physical and/or cognitive exertion, as well as the amount of rest one has received, it is possible that a mildly injured person, after completing a course of rest, would not perceive fatigue; however, their fatigue could resume when they return to regular duties and responsibilities. Unchanged frequencies were commonly associated with RCTs with close follow-up times (e.g. 1–3 months). The observed variation in the natural history of fatigue post TBI may be related to the tools utilized by the different researchers, and the constructs those tools measured. Respondents' interpretations of the construct of fatigue, as well as its complex underlying pathogenesis with different mechanisms inter-related at different time points, are expected to influence the results obtained.

The dimensions assessed in the studies utilizing fatigue scales or single items included momentary perception, chronic perception, the impact of fatigue on function, rating of tiredness, dimensions of fatigue (i.e. mental, physical), or severity of the fatigue (Supplementary file 3). The various measures also attach different weights to different aspects of fatigue, depending on the conceptualization of fatigue by the developer (Chaudhuri and Behan, 2004). In some

studies, fatigue was conceptualized as a one-dimensional entity in which persons are deemed either fatigued or not fatigued based solely on their perception of the experience at the time of completion.

Interpretation of scale items by the respondent can be significantly confounded by the association of fatigue with other symptoms, particularly apathy, excessive sleepiness, depression, lack of motivation, anxiety, litigation and cognitive dysfunction. In TBI patients, fatigue was reported to be associated with depression; moreover, in the regression analyses in one reviewed study (Norrie et al., 2010), the severity of fatigue was predicted by depression. Kempf et al. (2010) reported that fatigue and excessive daytime sleepiness coincided in their sample. Excessive daytime sleepiness may be an indicator of central nervous system (CNS) pathology due to brain injury (i.e. hypocretin/orexin deficiency), as well as related to quantity and quality of sleep (Mollayeva et al., 2013b; Baumann, 2012; Nardone et al., 2011; Mathias and Alvaro, 2012; Siebern and Guilleminault, 2012). While Kempf et al. (2010) studied and did not uncover a relationship between fatigue and sleep duration, quality of sleep was not investigated. A number of sleep disorders (i.e. sleep-related breathing disorder, periodic leg movement disorder, etc.) highly prevalent post-TBI (Nardone et al., 2011; Mollayeva et al., 2013c) are characterized by frequent arousals, which generally result in fragmented sleep, which can produce daytime sleepiness (Stepanski, 2002). Bushnik et al. (2008a) suggests assessment of sleep quality as a valuable measure when studying TBI patients with fatigue complaints.

Symptoms of fatigue and cognitive dysfunction have been reported to overlap in persons with TBI (Johansson et al., 2009; Zaben et al., 2013). This can potentially influence accuracy of self-report, as a person with cognitive dysfunction may not be able to fully grasp the changes in fatigue since their injury, as well as its impact on daily functioning, as required in completion of certain self-report measures. Bushnik et al. (2008a) reported that a subset of individuals who experienced significant increase in fatigue over the first two years post-injury demonstrated poorer outcomes in cognition, motor symptoms, and general functioning compared to those with decreased or stable fatigue (Bushnik et al., 2008a). A separate study had similar findings – subjective mental fatigue following brain injury was correlated with objectively measured information processing speed (Johansson et al., 2009). In other literature again, post-traumatic conditions such as hypopituitarism have been reported to have a wide range of manifestations, including fatigue, myopathy, cognitive difficulties, depression, and behavioral changes (Zaben et al., 2013). The same degree of fatigue, therefore, will not be perceived with equal intensity by persons with different comorbid conditions or fatigue etiology. Moreover, fatigue manifestation is thought to be differentially modulated by a variety of factors within and between TBI persons with time. Distinguishing fatigue as a result of TBI from fatigue associated with comorbid conditions (i.e. depression, pain, anxiety, apathy, sleep dysfunction, medication effect, etc.) is a complicated task. As such, future research should consider use of additional measures for common comorbidities when assessing PTF.

Fatigue severity (i.e. mean FSS scores) was higher in persons with TBI than previously reported for healthy adults (2.3 ± 0.7) (Krupp et al., 1989), but lower than those in patients with systemic lupus erythematosus (SLE) (4.7 ± 1.5) (LaChapelle and Finlayson, 1998), rheumatoid arthritis (4.2 ± 1.2) (Krupp et al., 1989) and psoriatic arthritis (6.9 ± 2.4) (Cella et al., 2005). Bushnik et al. (2008a) reported FSS scores obtained at 6, 12, and 18–24 months post-injury, all falling within the score range for non-fatigued control subjects (Table 5).

Studies differed in reports of fatigue severity over time, with some noting changes with and others stability. It is plausible that time since injury is a determinant of effectiveness of coping strategies and thereby perception of symptom severity. A study of persons with chronic fatigue syndrome (Brown et al., 2010) reported better adaptive coping strategies with longer disease duration. Alternatively, spinal cord injury patients showed no changes in coping styles over time (Craig et al., 1994). Future longitudinal studies of coping by persons who sustained a TBI may provide greater insight. Age differences between samples should also be considered. In a study of fatigue in the general population, Cella et al. (2002) reported that people older than 50 years in the described more severe fatigue than the younger population. The mean age in samples of reviewed studies reporting fatigue severity ranged from 20.1 ± 1.8 (Hutchinson et al., 2009) to 45.7 ± 10.8 (Gemmell and Leathem, 2006). We did not observe relationship between age and severity of reported fatigue, however (Table 5).

Other factors related to the discussion of fatigue severity have to do with the impact of brain injury on a person's ability to perform pre-morbid duties and manage responsibilities. Diminished activity due to changes in lifestyle, with subsequent loss of muscle tone and weakness, or muscle weakness due to neurological impairment, can result in greater fatigue perception associated with mild activity (Chaudhuri and Behan, 2004).

4.3. Consequences of fatigue in TBI

Possible consequences of fatigue emerged in the studies reviewed. Fatigue severity one week post-injury was associated with persistent post-concussive symptoms at three months (Norrie et al., 2010), and the FSS total score was significantly associated with the GOSE score for all severities of TBI (Sigurdardottir et al., 2009). Post-concussion syndrome (PCS) itself refers to a group of symptoms, including headache, dizziness, fatigue, and affective and cognitive changes, that may be reported by patients after TBI (McAllister, 1994). Thus, it is possible that severe post-concussive symptoms that are not resolved over a short period (i.e. three months), influence fatigue outcomes. The fact that the GOSE, the "gold standard" for assessing patient outcomes after TBI (Shukka and Devi, 2011), was affected by baseline fatigue severity across all injury severities at one year post-injury is significant, as it suggests that fatigue can be long lasting, with a low likelihood of resolution. Consequently, diagnostic efforts that consider diverse factors and comorbid conditions (Figs. 1 and 2) should be implemented in the very early stages post-injury.

4.4. Medication effects

CNS depressants can cause or increase fatigue (Liska, 2008). In the reviewed studies, just seven included their use in the exclusion criteria. Nine studies provided some information on the use of medications/illicit drugs/alcohol by participants prior to or over the course of the study. None, however, considered the potential confounders in this relationship. Reported use of alcohol by 62% of participants in the period before the first assessment, with 19% identified as drug users, heavy and/or binge drinkers is striking (Sigurdardottir et al., 2009). Ethyl alcohol is a CNS depressant, and the injured brain is particularly sensitive to its effects at the highest centers (i.e. speech, thought, cognition) and lower brain functions (i.e. spinal cord reflexes, respiration), as the dosage increases (Liska, 2008). Norrie et al. (2010) reported that alcohol intake prior to the injury was not correlated with fatigue severity at three months after injury, as measured by FSS, however, the researchers did not report alcohol intake of participants throughout the course of the study. This is significant, as studies in the general population have reported fatigue to be the most severe hangover symptom (Penning et al., 2012; Rohsenow et al., 2007).

Intake of SSRIs was reported by 61.1% of the participants in Driver and Ede's study. While this class of medications is a first

line of treatment for depression following TBI (World Health Organization, 2002), some drugs within this class (i.e. fluoxetine and paroxetine) may be problematic due to their adverse effects, including those related to fatigue and cognitive function (Schmitt et al., 2001). Another reviewed study reported use of opioids/opiates by 59.7% of participants (Meares et al., 2011). Opium alkaloids are narcotic analgesics and narcosis is defined by depression of the CNS leading to analgesia, drowsiness, changes in mood, mental clouding, lethargy, apathy and subsequent unconsciousness (Shukka and Devi, 2011). While currently there is no strong evidence directly relating physical and mental fatigue in TBI to side effects of opiates and opiods (Chapman, 2002; Leong and Royal, 2004), data on its safety for chronic use is also lacking (Rhodes, 2012). While our discussion of medication effects and fatigue in TBI is limited, given the complexity of the fatigue symptom and incomplete data available, future research should consider such effects, as the potential of medications to cross the blood–brain barrier and mimic neurological deficits and cause or exacerbate PTF, is real (Daneman, 2012; Maher et al., 2011).

To complete our discussion, we follow with recommendations for future research in the field of fatigue and TBI. As mentioned, along with the confounding effects and selection bias, the method by which fatigue was measured contributed significantly to the variation observed in results. The words that one uses to define fatigue can be vague, especially if the reporter (i.e. patient with TBI) has additional complaints related to constructs such as excessive sleepiness and impaired alertness. As such, separate assessment of each construct is preferable. When featured as one item within a self-report measure, even when spontaneously endorsed and ranked as the most important symptom, patients may rank their fatigue experience understanding it as being exhausted, tired, weak, while others may feel physically exhausted but mentally alert. As such, a single question hampers interpretation of the score. While it is not always the case that multi-item instruments are more valid than a single item, especially if the global opinion of the patient is of interest, adding one global item about the construct to a multi-item symptom measure in the future can help in the interpretation and validation of the instrument in the population of interest. This is particularly relevant to the study fatigue in the TBI population as, despite the number of multi-item standardized measures that have been utilized, only the FSS, the MFIS and the SF-36 have been partially validated against other fatigue measures in a TBI sample. Moreover, there are no psychometric data on the responsiveness of these measures, implying limited understanding of how much error exists when measuring changes in fatigue over time. Currently, the field of TBI requires further testing of existing self-report measures whose psychometric properties were described in other target populations, focusing on measures pertaining to the multidimensional etiology and state of PTF.

None of the studies reviewed applied technologies (i.e. electroencephalography, functional magnetic resonance imaging, magnetic resonance spectroscopy, regional brain volumes, motor evoked potential, etc.) or markers of physiological processes (i.e. function of hypothalamic–pituitary–adrenal axis, autonomic nervous system response, metabolic processes, immune system response, etc.) to study the fatigue experienced by individuals with TBI. The latter is important, as research has shown that the resting pulmonary and cardiorespiratory function in patients with TBI is compromised (Jankowski and Sullivan, 1990). This can be related to deconditioning as a result of a more sedentary lifestyle (Giordon et al., 1998). In a study of maximal physiologic responses during exercise in patients with moderate to severe TBI at 17.2 ± 17 months after injury, several weeks of an exercise training program reduced physiologic fatigue (Bhambhani et al., 2005). Others reported that aerobic fitness in individuals with TBI enhanced cognition and improved mood (Carroll et al., 2004b; Cassidy et al., 2014). This is extremely important as fatigue perception ratings were found to be higher in patients with depression (Norrie et al., 2010). Again another study (Jankowski and Sullivan, 1990) reported that a 16-week circuit training program of moderate intensity and prolonged duration increased TBI patients' oxidative capacity and muscular endurance and the index of physiologic fatigability was shown to be useful for the assessment and evaluation of individuals with TBI. Similarly, in a reviewed study by Driver and Ede (2009) fatigue elimination was reported after an eight-week group aquatic program, with no changes in fatigue in the control group. Thus, further study that accounts for the physiologic, objective performance, and/or homeostatic changes with regard to increased perception/manifestation of fatigue after brain injury is within the top priorities for future research.

4.5. Limitations

We acknowledge heterogeneity in the primary studies with respect to sample characteristics (i.e. age, injury/localization of injury, time since injury) and fatigue definitions. Another concern related to the reviewed studies, largely of "moderate" quality, is that severe TBI is underrepresented in the inception cohorts and the evidence for the second and third research questions of this review was based largely on mild TBI cohorts. Additionally, the majority of the patients in the studies were men, which limits the precision of estimates of predictors and consequences for fatigue in severe TBI, especially for women (Table 2).

Most studies focused largely on the fatigue symptom; the strength and significance of associations with other factors (e.g. sleep, other medical conditions, medication use or clinically important symptoms such as alertness, sleepiness) were often not reported. Thus, the roles of other factors could be underestimated in this review.

The focus of this review was the natural history of fatigue in patients with TBI. To be consistent with our protocol (Mollayeva et al., 2013a), results from all selected longitudinal studies were used to address the first research question (i.e. natural history of fatigue). Since baseline fatigue assessment was performed at different times since injury, we attempted to mitigate zero-time effect by reporting results with baseline assessments up to one month post-injury and after one month, separately. Nevertheless, generalizability of results remains unclear due to inadequate reporting of selection criteria, poor control of confounding effects, and attrition.

There are limitations to the presented data on fatigue measures used in the reviewed studies (Supplementary file 3). For conciseness, properties of the measures, specifically those related to psychometrics, were not reported in great detail. Despite attempts to include all relevant articles for their use in the TBI population, it is possible studies were missed.

All articles included in this review are peer-reviewed. As such, there is possibility for publication bias. Finally, the inclusion of only English language articles could affect the generalizability of our findings.

4.6. Pitfalls and controversies

Despite the existence of clinical criteria for the diagnosis of PCS, the self-reported nature of nonspecific symptoms such as fatigue can be confounded by other factors (i.e. psychological distress, pain, depression, etc.). This may be particularly apparent in patients with insurance claims that are being disputed. Their need to provide proof of disability may magnify fatigue symptoms and result in controversy about whether symptoms are indicators of brain injury or are of behavioral origin (Carroll et al., 2004b; Cassidy et al., 2014). Also, fatigue as a symptom is nonspecific to TBI. Fatigue appears with other diagnostic labels in other clinical specialities

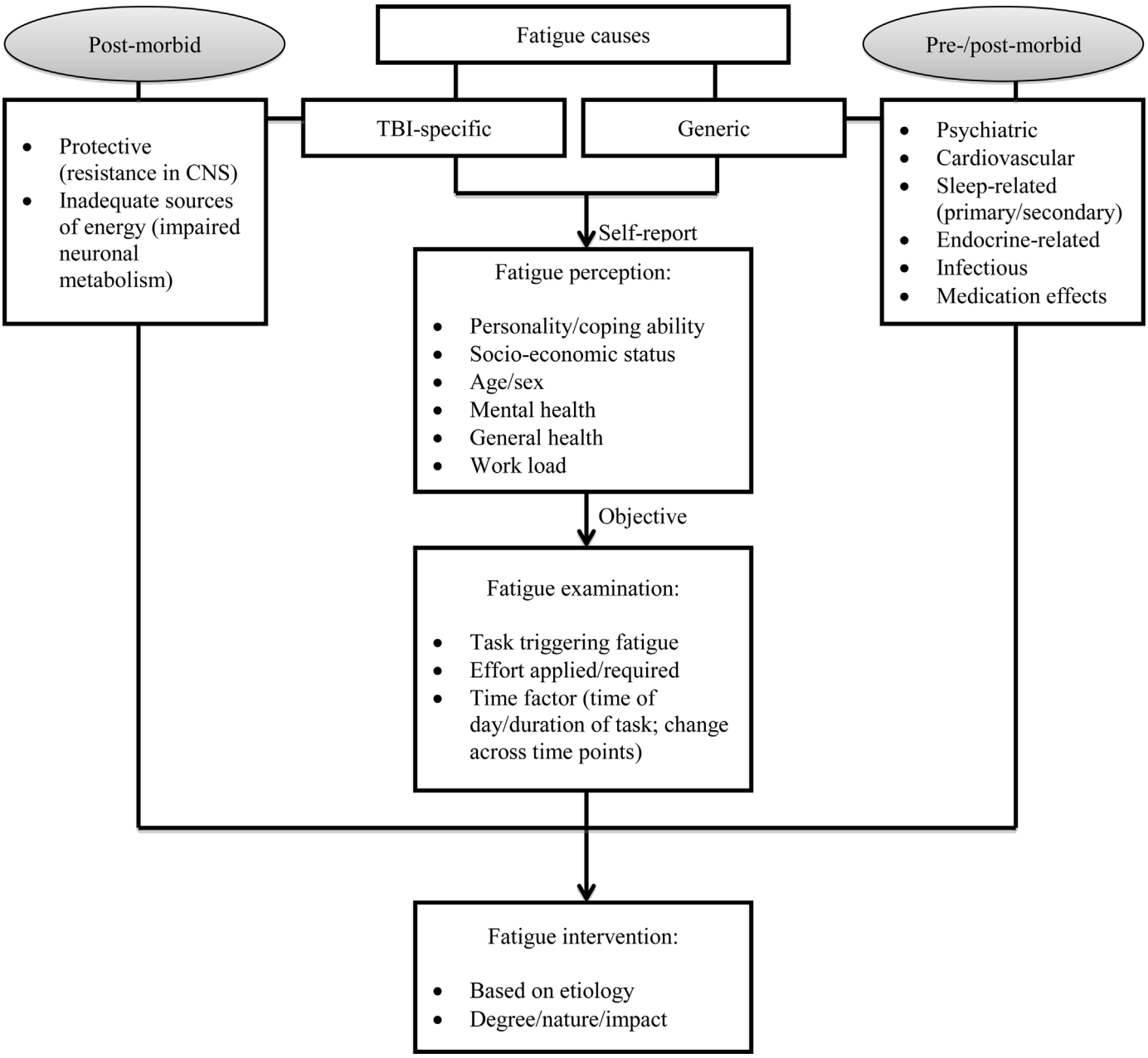

Fig. 4. Model for studying fatigue symptoms in patients with traumatic brain injury.

– for example fibromyalgia, chronic fatigue syndrome, endocrine disorders, and patients with psychiatric illness (Norrie et al., 2010; Cairns and Hotopf, 1997; Nisenbaum et al., 2003; Kato et al., 2006; Lerdal et al., 2011; Cassidy et al., 2014). Previous systematic reviews on the epidemiology, diagnosis, prognosis, treatment and costs of mTBI raised the issue of specificity of self-reported symptoms such as headache, fatigue, cognitive deficits to mild TBI (Carroll et al., 2004b; Cassidy et al., 2014), with the recommendation to replace the term *post-concussion syndrome* with the term *post-traumatic symptoms*.

The reviewed studies allowed comparison of fatigue severity only between mild TBI participants and controls, limiting our discussion to a single severity of injury. While concussed athletes had more fatigue compared to healthy controls at one week post-injury, that was not the case at two weeks (Hutchinson et al., 2009). Similarly, fatigue was greater in the mild TBI group compared to controls shortly after the injury, but not at three months post-injury in Lundin et al.'s and Meares et al.'s samples. De Leon et al. (2009) found that fatigue severity at the one year follow-up was not associated with the type of injury (i.e. mild TBI vs. non-head injury) in a fully adjusted model. Pair-wise comparisons showed lower fatigue scores in the mild TBI group at 12 months compared to the other injury group. Contrariwise, Sundstrom et al. (2007) reported that their mild TBI group had less fatigue pre-injury and more post-injury compared to age-, sex-, and education-matched controls.

Given this lack of specificity of the fatigue symptom, this topic is perplexing and time consuming. An accurate investigation of fatigue in TBI must begin with a clear definition of the most common symptomatic descriptor, "feeling fatigued". Next, the cause of fatigue must be determined and a diagnosis established. Although the pathophysiology of fatigue after TBI is still poorly understood, the goal is to determine whether the fatigue is caused by a correctable factor (i.e. depression, endocrine dysfunction,

deconditioning, poor sleep, etc.) so that interventions are applied appropriately. Fig. 4 illustrates the proposed algorithm for study of PTF.

5. Conclusions

Fatigue is a common symptom post TBI. Its frequency may change over time, but fatigue can persist years after the injury. This may be related to pre-morbid/early fatigue, mental health issues, other medical conditions, and ongoing societal stressors. Clinicians seeing patients with TBI at the acute stages post-injury with high early fatigue intensity, mental health issues, and litigation involvement should be aware that these may be associated with the development of persistent post-concussive symptoms. The available evidence on the associative value of these factors, as well as the consequences of fatigue, is currently not very strong, as we found just three cohort studies addressing these issues. More research is needed to establish associations between fatigue and other clinically important pre- and post-morbid variables (i.e. sleep dysfunction, depression, physical and cognitive impairments, other medical/neurological disorders), and their impact on outcomes post-injury. Medication effects, personal factors such as coping ability, physical deconditioning, stress level, and time factors should also be investigated. This is particularly important for translation of research into clinical practice, in order to address risk factors and course of condition. An international consensus, similar to the *National Institutes of Health and* developed for rehabilitation in TBI in 1999 (Consensus Conference, 1999) advising on how best to study clinically important symptoms such as fatigue in TBI, is of utmost importance. In particular, there needs to be a consensus on the definition of pathological PTF, set times for baseline assessment, recognizing the challenges in studying the symptom in moderate-severe brain injury at time zero, clinically relevant period of follow-up, acceptable attrition rates to ensure representative samples, and validated measures of outcome, all of which can reduce heterogeneity of results. What will be left to focus on then is the variety of lesions from TBI (i.e. white or gray matter, specific tract damage, lesion volume, localization of injury, etc.) and inter-individual variability in perception and multifactorial fatigue etiology, which may find study of individual patients best. A caveat to this point is that case-reports of patients whose symptoms and clinical course do not fit the typical picture, may lead to scientific progress in the understanding of and appreciation for the complexity of the fatigue symptom post TBI (Yennurajalingam and Bruera, 2007).

Authors' contributions

Tatyana Mollayeva had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Tatyana Mollayeva, Colin M Shapiro, Angela Colantonio, J David Cassidy. Acquisition of data: Tatyana Mollayeva, Tetyana Kendzerska, Shirin Mollayeva. Analysis and interpretation of data: All authors. Drafting of the manuscript: Tatyana Mollayeva. Critical revision of the manuscript for important intellectual content: All authors. Statistical analysis: Tatyana Mollayeva, Shirin Mollayeva. Administrative, technical, and material support: Shirin Mollayeva. Study supervision: Angela Colantonio, Colin M Shapiro, J David Cassidy.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.neubiorev.2014.10.024.

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