Unravelling the biopsychosocial factors of fatigue and sleep problems after traumatic brain injury: Study protocol for a multicenter longitudinal cohort study

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Abstract

Background: Fatigue and sleep problems are common after traumatic brain injury (TBI) and are experienced as highly distressing symptoms, playing a significant role in the recovery trajectory and can drastically impact the quality of life and societal participation of the patient and their family and friends. However, the etiology and development of these symptoms is still uncertain.

Objective: The aim of this study is to examine the development of fatigue and sleep problems following moderate to severe TBI and explore the changes in underlying biological (pain, brain damage), psychological (emotional state) and social (support family, participation) factors across time.

Methods: Longitudinal multicenter observational cohort study with four measurement points (3, 6, 12 and 18 months post injury) including subjective questionnaires and cognitive tasks, preceded by 7 nights of actigraphy combined with a sleep diary. Recruitment of 137 moderate to severe TBI patients presenting at emergency and neurology departments or rehabilitation centers across the Netherlands is anticipated.

Results: The evolution of fatigue and sleep problems following TBI and their association with possible underlying biological (pain, brain damage), psychological (emotional state) and social (support family, participation) factors will be examined.

Conclusion: To the authors’ knowledge this study is the first study that examines the development of both post-TBI fatigue and sleep longitudinally within a biopsychosocial model in moderate to severe TBI using both subjective and objective measures. Identification of modifiable factors such as mood and psychosocial stressors may give direction to the development of interventions for fatigue and sleep problems post-TBI.

Trial Registration: Dutch Trial Register NTR7162; http://www.trialregister.nl/trialreg/admin/rctview.asp?TC=7162 (Archived by WebCite at http://www.webcitation.org/6z3mvNLuy)

Keywords: Traumatic brain injury; sleep; fatigue; biopsychosocial model.

Introduction
Traumatic brain injury (TBI) is one of the most serious, disabling neurological disorders, with ten million patients affected annually worldwide [1]. Consequently, societal costs are high and estimated to be around 33 billion in Europe [2]. TBIs appear on a spectrum of injury severity based on widely recognized injury characteristics. The more frequent mild TBI’s are considered as trivial and benign injuries as opposed to less prevalent moderate to severe injuries, which are associated with long-lasting consequences for the patients and their environment [3]. Due to the high individual and societal costs associated with extensive rehabilitation needs and chronic disability, moderate to severe TBI represents a critical public health issue [4], with fatigue and sleep problems playing significant roles in the recovery process [5, 6]. Between 30% to 70% of the patients experience fatigue [7] and a meta-analysis indicated that 53% experience sleep problems [8].

Study results concerning the presence of fatigue and type of sleep problems post-TBI are inconsistent, probably due to different study methodologies; patients are included in different time windows since their injuries, injury severity parameters differ across studies, measurement instruments are diverse and there is limited consensus on what variables at which moment in time should be measured [9]. In addition, most studies are cross-sectional and not longitudinal in terms of design. This makes it difficult to compare results across studies and to draw conclusions about sleep- and fatigue changes after TBI [10, 11]. Nevertheless, post-TBI sleep problems and fatigue are often consistently experienced as the most severe and distressing symptoms [5], interfering with recovery, rehabilitation treatment and negatively impacting the quality of life [12]. Furthermore, despite the magnitude and impact of these phenomena, the etiology is still debated and no efficacious treatments have been established [13].

Recovery from moderate to severe TBI is a time consuming and long term process and should therefore be explained in terms of a disease process. Accordingly, different factors may be involved in fatigue and sleep problems at different stages after the injury [14, 15]. By exploring underlying causes of fatigue and sleep problems and how these symptoms develop over time, key periods may be identified in which specific targeted interventions are needed. The outcome and prognosis following TBI are extremely variable across individuals regardless of the severity of the initial injury [9], which implies that outcome is not only influenced by biological factors, but should be studied in a biopsychosocial model in which physical, cognitive, affective and social factors interact with sleep-wake patterns and fatigue [9]. Previous research has already shown the involvement of biological factors (e.g. structural changes in the brain [16] and pain [17]), psychological (e.g. emotional distress [18, 19]) and social components (e.g. community integration and social support [20, 21]) to be involved in fatigue and sleep problems following TBI. However, no studies to the authors’ knowledge, have yet examined these biopsychosocial factors in a comprehensive model over time to determine the significant underlying factors that contribute to post-TBI fatigue and sleep problems. Understanding these complex interactions is crucial to establish, explain and treat fatigue and sleep problems associated with TBI. Therefore, this study proposes a biopsychosocial explanation of post-TBI fatigue and sleep problems.

The aim of the study is to examine the development of post-TBI fatigue and sleep problems longitudinally within a biopsychosocial model including several factors in moderate to severe TBI. The primary focus of the study will be on subjective fatigue and sleep problems post-TBI. We hypothesize that the associations between biopsychosocial factors and post-TBI fatigue and sleep problems change over time., i.e., that the associations with biological factors are strongest in the first six months and then decline, whereas the associations with psychological and social factors are initially weak, but slowly increase and become apparent between 12 and 18 months. Previous research has
shown a discrepancy between objective and subjective measures of fatigue and sleep in the TBI population [19, 22]. Therefore, the secondary aim of the study is to examine the development of post-TBI fatigue and sleep problems with objective measures within a biopsychosocial model. In this paper the design of the study will be presented.

Methods

Design
The present study is a multicenter observational prospective longitudinal cohort study in which participants are followed using five assessments during the first 1.5 years following moderate to severe TBI. The Medical Ethics Committee of University Hospital Maastricht/Maastricht University (NL60322.068.17) and all participating centers approved the study protocol. The study is registered in the Dutch Trial Register (NTR67162, registered on 10 April 2018).

Study population
Moderate to severe TBI patients are being recruited from emergency, neurology and rehabilitation departments in several hospitals and rehabilitation clinics across the Netherlands. Based on a linear mixed regression analysis with a medium effect size ($f^2=0.15$), seven significant predictors, a statistical power of 0.8, alpha level of 0.05 and a high test-retest reliability of at least 0.8 of the main study variables, the required sample is 103 TBI patients [23]. A drop-out of 25% during the 1.5 year follow-up is expected based on previous studies [24, 25]. Therefore, 137 patients will be recruited to lead to a total of 103 TBI patients being available for the analyses.

Inclusion and exclusion criteria
TBI patients are eligible to participate in this study if they have a clinically confirmed diagnose of a first moderate to severe, closed head TBI. Defined as Glasgow Coma Scale (GCS) score < 13 [26]; post-traumatic amnesia (PTA) > 24 hours; trauma related intracranial neuroimaging abnormalities or loss of consciousness (LOC) > 30 min [27]. In addition, participants must be between 21 and 70 years old, fluent in Dutch and provide informed consent.
Participants are excluded if they (1) had a prior moderate-severe TBI diagnosed by a neurologist or a mild concussion in the last half year; (2) have another condition which may interfere with the study outcome (e.g. pre-existing other neurological disorder (stroke, brain tumor etc.), sleep-wake disturbance or fatigue due to another medical condition than TBI, history of alcohol and/or drug abuse, prior mental disorder (for which treatment was necessary) or pregnancy); or (3) lack the ability to complete questionnaires based on clinical judgment (aphasia, severe cognitive impairment).
Participants meeting the following criteria are excluded during the study (1) participant wants to leave the study; (2) new incident of TBI, other neurological disease/injury or traumatic injury during the follow-up period.

Procedure
 Patients are informed about the study by their treating physician (e.g. neurologist, head nurse or rehabilitation specialist). If the patient is interested in participation a screening visit within the first six weeks after injury is made by the researcher, during which the informed consent is signed (if the
patient is eligible and decides to participate). During this visit demographics and pre-injury characteristics are collected.

The follow-up appointments take place at approximately three months (V1), six months (V2), one year (V3) and 1.5 years (V4) post injury. These visits consist of filling out questionnaires and performing cognitive tasks and can take place at Maastricht University, one of the participating clinical institutes or the home of the participant. The visit will be guided by the researcher or a research assistant and are always scheduled between 11:00 and 15:00 h to minimize effects of the circadian rhythm [28]. In the week before these visits the participant will wear an actigraph and fill out a sleep diary for 7 days at home (daily living).

**Measurements**

The main outcomes are fatigue and sleep. The primary focus of this study is on subjective level of fatigue and sleep problems, affecting the quality of sleep, to address the experience of these problems by TBI-patients. The relation over time between subjective fatigue and sleep and the biopsychosocial predictors will be examined. Secondly, the relation between objective fatigue and sleep measurements and the biopsychosocial predictors will be examined. An overview of all measurement instruments that are administered during the 1.5 year follow-up are shown in Table 1 (Table 1). The questionnaires are implemented in an online format, except for the demographic questionnaire which is in interview style. All questionnaires included in this study have good psychometric properties and have been used in the TBI population before.

Table 1. Overview of all measurement instruments for the TBI patients and the times of administration.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Instrument</th>
<th>Screenin</th>
<th>V1</th>
<th>V2</th>
<th>V3</th>
<th>V4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Follow-up moment</td>
<td></td>
<td>&lt; 6 w</td>
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<tr>
<td><strong>Main outcome parameters</strong></td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
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<tr>
<td>Subjective fatigue</td>
<td>Fatigue Severity Scale [29]</td>
<td></td>
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<tr>
<td>Subjective sleep quality</td>
<td>Pittsburg Sleep Quality Index [30]</td>
<td></td>
<td>X</td>
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<tr>
<td><strong>Predictors</strong></td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Pain (subjective)</td>
<td>Visual analogue scale pain [31]</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<td>X</td>
</tr>
<tr>
<td>Objective cognitive performance</td>
<td>Stroop, COWAT, digit span, SDMT</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Physical activity</td>
<td>7 days actigraphy [33]</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<tr>
<td>Emotional distress</td>
<td>Hospital anxiety and depression scale [34]</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<tr>
<td>Cognitive complaints</td>
<td>Dysexecutive Questionnaire Revised [35]</td>
<td>X</td>
<td>X</td>
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<tr>
<td>Participation</td>
<td>Utrecht Scale for Evaluation and Rehabilitation-Participation [36]</td>
<td>X</td>
<td>X</td>
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<tr>
<td>Social support</td>
<td>Multidimensional scale of perceived social support [37]</td>
<td>X</td>
<td>X</td>
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<tr>
<td><strong>Secondary outcome parameters</strong></td>
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<tr>
<td>Objective SWD</td>
<td>7-days actigraphy [38]</td>
<td>X</td>
<td>X</td>
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<tr>
<td>Objective fatigue</td>
<td>Psychomotor vigilance task [39]</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<td>X</td>
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</table>

**Group characteristics and monitor the participants**
**TBI characteristics**

- Injury severity such as structural imaging data, LOC, PTA, injury severity score; causes of injury; co-morbid (physical) injuries, seizures; drug or alcohol intoxication during injury from the hospital database.

**Demographics**

- Age, gender, education, marital status, work status

**Premorbid sleep**

- Premorbid question of PSQI [30]

**Premorbid participation**

- Premorbid frequency and satisfaction of the USER-P [36]

**Daytime sleepiness**

- Epworth Sleepiness Scale [40]

**Subjective fatigue**

- Dutch Multi-Factor Fatigue Scale [41]

**Subjective sleep-wake**

- 7 days Sleep Diary [42]

**Post-traumatic stress disorders**

- PTSD checklist for DSM-5 [43]

**Coping style**

- Proactive and passive coping scale of the Utrecht Coping List [44]

**Drugs/alcohol/medication use**

- Demographic questionnaire

**Sleepiness preceding the task**

- Karolinska sleepiness scale [45]

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**Primary outcome measures**

Subjective fatigue is measured with the Fatigue Severity Scale (FSS) [29]. The FSS is a widely used and measures the impact of fatigue on activities of daily life and distress caused by fatigue, it includes 9-items related to fatigue which are rated on a 7-point Likert scale. The mean score of the FSS is calculated and ranges from 1 to 7, where a higher score denotes more severe fatigue and a mean score of 4 or higher indicates severe fatigue [29]. The internal consistency is high [29], test-retest reliability is satisfactory and the FSS can distinguishes fatigue in brain-injured patients from that of controls [46].

Subjective sleep quality is assessed with the Pittsburg Sleep Quality Index (PSQI) [30]. The PSQI consists of 19 items and examines 7 components namely, overall sleep quality, sleep onset latency, total sleep time, sleep efficiency, sleep disturbances, use of sleep medication and daytime dysfunction. The global score is calculated by adding the 7 component scores and ranges from 0 to 21, where a lower score denotes better sleep quality. The questionnaire can discriminate between ‘good’ and ‘poor’ sleepers, with a global score of >5 indicating poor sleep quality [30]. The internal consistency and test-retest reliability of the PSQI are high and the PSQI has good concurrent validity with sleep diary data [30]. The Dutch version of the PSQI has been used to examine sleep quality in acquired brain injury patients [47].

**Predictors**

The development of sleep and fatigue is examined with a biopsychosocial model. Therefore, the factors taken into account as predictors can be divided in biological (e.g. structural changes in the...
brain and pain), psychological (e.g. emotional distress and the burden of cognitive impairments and social components (e.g. community integration and social support).

**Pain** The general level of pain is measured with a 100 mm Visual Analog Scale (VAS-P) [31]. The left end of the VAS represented ‘no pain’ and the right end ‘most severe pain imaginable’ with no intermediate divisions or descriptive terms [31]. The score ranges from 0 to 10 where a higher score indicates more severe pain. Pain intensity in the last 24 hours is measured. The VAS is widely used to measure pain in TBI patients [20] and is suggested as a valid and reliable measure [48].

**Cognition** A short test battery is used to assess cognitive performance. The extent in which cognitive functioning is affected is used as a proxy for the severity of the brain damage [49]. Cognitive tasks include measurements of speed, attention, interference and executive functioning. The following 4 tasks are included and the first three tasks are recommended as outcome measures in TBI research to measure neuropsychological impairments [32]:

- **Stroop task** measures response interference control, a cognitive form of inhibition/flexibility and selective attention [50]. Previous studies showed inhibition deficits following TBI and a slower response time [51]. The STROOP has good psychometric properties [32].

- **Controlled Oral Word Association Test (COWAT)** [52] is a verbal fluency test, which measures the spontaneous production of words belonging to a specific category or a designated letter. This test measures attentional control, working memory and other components of executive functioning. Focal frontal injuries following TBI show a strong association with performance on the COWAT [53]. COWAT is a reliable measure and is sensitive to TBI severity [54].

- **Digit Span** is a working memory task which assesses auditory attention. Both the forward and the backward order are used. The digit backward order is especially informative for working memory. This task has been used as a marker of cognitive deficit and recovery and has s high reliability [54].

- **Symbol Digit Modalities Test (SDMT)** is a cognitive test which measures attention and processing speed. The SDMT is sensitive to impairments of speed of information processing following TBI [55] and is a reliable measure [56].

**Physical activity** Daytime levels of physical activity are examined with actigraphy which is a non-invasive method to monitor the rest/activity cycle [33]. In addition, actigraphy is used for the secondary aim regarding objective measures of sleep. The actigraph is a wrist-watch-like device, worn on the non-dominant wrist, which allows the participant to continue normal routines in the natural environment. The actigraph (GENEAactiv, Activinsights Ltd., Cambridgeshire, UK) measures the movement/motor activity of the participant and thereby the time spent in sedentary behaviour, light intensity physical activity, moderate to vigorous physical activity and vigorous physical activity can be determined [33]. Participants will wear the actigraph for 1 week.

**Emotional distress** The level of emotional distress is examined with the Hospital Anxiety and Depression Scale (HADS) [34] which consists of 14 items. Each item is scored on a 4-point scale and the total score ranges from 0 to 42 where a higher score denotes more psychological distress. The HADS includes 2 subscales with each 7 items measuring anxiety and depression with scores ranging from 0 to 21. A subscale score of ≥8 is an indicator of depression or anxiety in patients with TBI,
which is in line with findings of the general population [57]. The HADS is a reliable measure and has been validated in the TBI population [58].

Cognitive complaints The Dysexecutive Questionnaire Revised (DEX-R) is used to assess cognitive complaints [35]. This questionnaire examines cognitive problems in daily life as experienced by the patient. The DEX-R assesses four-domain general types of dysexecutive problems (metacognition or social cognition, executive cognition, behavioral-emotional self-regulation, activation) and consists of 34 items. Each item is scored on a 5-point Likert scale how often certain difficulties related to cognition are experienced. The total score ranges from 0 to 136 where a higher score denotes more cognitive problems. The DEX-R is a reliable and valid measure [35, 59] and has been used in the TBI population [60].

Participation The Utrecht Scale for Evaluation and Rehabilitation-Participation (USER-P) [36] is used to assess participation. The questionnaire measures 3 aspects of participation: frequency of behaviors, experienced participation restrictions due to health condition, and satisfaction with participation. The USER-P consists of 31 items across the three subscales. Each sum score of a scale is converted to scores ranging from 0 to 100 where higher scores indicate good levels of participation (higher frequency, less restrictions, higher satisfaction). The USER-P is a valid and reliable measure in patients with brain injury and test-retest reliability and internal consistency of the USER-P are satisfactory [61].

Social support The Multidimensional scale of perceived social support (MSPSS) is used to assess social support [37]. The MSPSS consists of 12-items examining perceived social support from family, friends and significant other. Each item is rated on a 7-point Likert scale. The mean total score ranges from 1 to 7 where a higher score denotes more perceived social support. The MSPSS has shown good psychometric properties [37] and has been used in TBI patients [62].

Secondary outcome measures Previous research has shown a discrepancy between objective and subjective measures of fatigue and sleep in TBI population [19, 22]. Therefore, as the secondary aim objective measures of fatigue and sleep are included in this study.

Fatigue is measured objectively with the 10-minute Psychomotor vigilance task (PVT), which is a sustained-attention, reaction-time task, often used in sleep and fatigue research [39]. The PVT is a simple, reliable and sensitive task for measuring performance and attentional deficits due to fatigue [63]. When performing the PVT the response time to visual stimuli, occurring at random inter-stimulus intervals is measured. The task has good psychometric properties, has been validated and has been used in TBI patients [64].

Sleep problems are examined objectively with the actigraph described previously which measures sleep-wake patterns during 1 week. Actigraphy has shown to be a satisfactory objective estimate of sleep especially for global sleep parameters including total sleep time, sleep onset latency and sleep efficiency [38]. Multiple studies have included actigraphy to examine sleep in TBI patients [22, 65, 66] and shown that actigraphy is a reliable method for monitoring sleep in this population irrespectively of the injury severity [67].

Group characteristics and monitoring participants
Injury related characteristics Information regarding the injury such as time since injury, injury severity parameters (e.g., intracerebral abnormality on structural imaging data, LOC, PTA, injury severity score), causes of injury, co-morbid (physical) injuries, seizures and drug or alcohol intoxication during injury will be retrieved from the hospital database.

Demographics The demographic questionnaire asks about age, gender, education, marital status, level of occupational achievement, psychological and medical history. In addition this questionnaire assesses medication, drugs and alcohol use.

Daytime sleepiness The Epworth Sleepiness Scale (ESS) is used to examine daytime sleepiness [40]. The ESS measures general level of daytime sleepiness and sleep propensity with 8-items. Each item is scored on a 4-point scale indicating the chance of dozing off and the total score ranges from 0 to 24 where a higher score indicates more daytime sleepiness. A score of ≥11 indicates clinical significant subjective sleepiness [40]. The ESS is widely used in TBI research [68] and has a reasonably high reliability [69].

Subjective fatigue The Dutch Multi-Factor Fatigue Scale Fatigue (DMFS) is used to measure with fatigue. The DMFS examines several factors of fatigue following TBI [41], including impact of fatigue, mental fatigue, signs and direct consequences of fatigue, physical fatigue and coping with fatigue. The DMFS consist of 38 items rated on a 5 point scale Likert scale with higher scores on each subscale indicate more severe fatigue. This questionnaire is specifically developed to measure the multi facets of fatigue following acquired brain injury [41].

Subjective sleep-wake patterns The relevant questions of the consensus sleep diary, which is a standardized sleep diary (SD) developed by insomnia experts [42], are used to examine subjective sleep-wake patterns and for better interpretation of actigraphy data. The SD includes the core questions: (1) the time of getting into bed; (2) the time at which the individual attempted to fall asleep; (3) SOL; (4) duration of awakenings; (5) time of final awakening; (6) final rise time; (7) perceived sleep quality (rated via Likert scale) [42]. An additional question about napping/dozing is added. The diary is completed in the morning and is filled out for 7 consecutive days concurrent with the actigraphy. SD are a reliable and validated measure to examine sleep [70].

Post-traumatic stress disorder The presence of Post-traumatic stress disorder (PTSD) is determined with the PTSD Checklist for DSM-5 (PCL-5), a 20-item self-reported measure corresponding to the DSM-5 symptom criteria for PTSD [43]. Each item is rated on a 5-point scale Likert scale and the total score ranges from 0 to 80 where a higher score denotes more severe PTSD symptoms. A score of 33 or higher is suggested as indication of PTSD [43]. The PCL-5 is a reliable measure with strong validity [71]. PTSD occurs in 18-27% of the cases following severe TBI [72, 73]. To check whether PTSD is the underlying cause of elevated stress and since PTSD takes time to develop the PCL-5 is only assessed at visit 2 and 4.

Coping style Passive reaction coping style and active problem-solving coping style are examined with the Utrechts Coping Lijst (UCL), which will differentiate active approach vs passive approach [44]. Since this study only includes active and passive coping the questionnaire will consist of 14 items scored on a 4-point Likert scale. Scores for both subscales range from 7 to 28 where higher scores denote a higher preference for that coping style. Both subscales show fairly good internal consistency and reasonably high test-retest reliability in the Dutch population [74]. The UCL has been used in Dutch TBI patients before and showed limited variability over time therefore coping styles are only assessed at visit 1 and 4 [75].

Sleepiness preceding the task Sleepiness before the PVT is assessed with the Karolinska sleepiness scale (KSS) [45]. The KSS consist of 1 item on a 9-point Likert scale ranging from extremely
alert to very sleepy, great effort to keep awake, where a higher score denotes greater sleepiness. The subject indicates the sleepiness level of the preceding 5 min. The test-retest reliability and the construct validity of the KSS are high [76].

**Statistical analyses**

Descriptive statistics will be used to present mean scores and standard deviations at each time point of the outcome measures and predictive variables. Normality and assumptions will be checked. Next, two linear mixed regression analysis [77] will be performed to evaluate the associations between the predictive (independent) variables (pain, cognitive impairment, physical activity, emotional distress, cognitive complaints, social support, participation) and the primary endpoint (subjective sleep quality and fatigue) across time. For each of the two primary endpoints we will first determine whether these associations with predictors change across the four time points (i.e. time by predictor interactions). In case of a significant interaction, simple interaction contrasts comparing consecutive time points will be used to determine whether the association between predictor and primary endpoint decreases or increases. Bonferroni correction will be used to adjust for multiple testing.

For the secondary objectives, the temporal relation between objective fatigue, objective sleep and the predictive variables of the biopsychosocial model will be examined with the same linear mixed-effects regression analyses as used for the primary objectives.

**Results**

Recruitment of participants for this longitudinal cohort study started in October 2017 and enrolment of participants is ongoing. The first results are expected at the end of the year 2020.

**Discussion**

This paper describes the protocol of a longitudinal cohort study examining fatigue and sleep following moderate to severe TBI and the underlying predictors with a biopsychosocial model. There are several reasons why this cohort study is innovative. First, this study has a longitudinal design. To the authors knowledge there are only three longitudinal follow-up studies examining fatigue or sleep following moderate to severe TBI in the first 12-24 months post-TBI [20, 78, 79]. These studies had a much smaller sample size and focused on fatigue or sleep separately.

Secondly, even though fatigue and sleep are closely related they can be affected independently and problems with fatigue and sleep do not always co-occur [15]. Therefore, this study examines fatigue and sleep concurrently in a follow-up design to better understand their common and unique manifestations, as was also recommend by Cantor and colleagues (2012) [15].

Thirdly, this study uses a biopsychosocial explanation of post-TBI fatigue and sleep problems. [9]. Multiple researchers suggested integrated biopsychosocial approaches for future studies to best explain the outcome of TBI [80-83]. However, few studies have yet examined identified biopsychosocial factors in a comprehensive model over time to determine the significant underlying factors that contribute to post-TBI fatigue and sleep problems. Understanding these complex interactions is crucial to establish, explain and treat fatigue and sleep problems associated with TBI.

Lastly, this study uses both subjective and objective measures to examine fatigue and sleep. Previous research has shown discrepancies between objective and subjective measures of fatigue and sleep in the TBI population [19, 22]. Therefore, it is important to include both measures. However, most studies only include subjective or objective measures of fatigue and sleep.
A limitation of this study is that the extreme severe multi-trauma patients will not be included in the study, because they may not be recognized as TBI due to severe multiple physical injuries and may not be able to participate due to their injuries. This may jeopardize the generalizability of the results to all moderate-severe TBI patients.

To the authors knowledge this study will be the first that examines the development of both post-TBI fatigue and sleep longitudinally with a biopsychosocial model in moderate severe TBI and that will differentiate between fatigue and sleep using both subjective and objective measures. Identification of modifiable factors such as mood and psychosocial stressors may give direction to the development of interventions for fatigue and sleep problems post-TBI that subsequently lower the burden for the patient and may prevent development of secondary symptoms and complaints such as depression.

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**Conflicts of Interest:** none declared

**Abbreviations**
COWAT: controlled word association test  
DMFS: Dutch Multi-Factor Fatigue Scale  
DEX-R: Dysexecutive Questionnaire Revised  
ESS: Epworth Sleepiness Scale  
FSS: Fatigue Severity Scale  
HADS: Hospital Anxiety and Depression Scale  
KSS: Karolinska sleepiness scale  
LOC: Loss of consciousness  
MSPSS: Multidimensional Scale of Perceived Social Support  
PTSD: Posttraumatic stress disorder  
PCL-5: PTSD Checklist for DSM-5  
PSQI: Pittsburgh Sleep Quality Index  
PTA: Post-traumatic amnesia  
PVT: Psychomotor Vigilance Test  
USER-P: The Utrecht Scale for Evaluation of Rehabilitation-Participation (In Dutch: Utrechtse Schaal voor Evaluatie van Participatie)  
SD: Sleep diary  
SDMT: Symbol Digit Modality Test  
SE: Sleep efficiency  
SOL: Sleep onset latency  
TBI: Traumatic brain injury  
TST: Total sleep time  
UCL: Utrechtse Coping Lijst  
VAS-P: Visual Analog Scale Pain
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