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# Sleep and mild traumatic brain injury

Doctoral thesis

NTNU
Norwegian University of Science and Technology
Thesis for the Degree of
Philosophiae Doctor
Faculty of Social and Educational Sciences
Department of Psychology

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Trondheim, May 2021

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**Søvn og lette hodeskader**

**Bakgrunn**

Mange som får lette hodeskader (mild TBI) opplever søvn-våkenhetsvansker i tiden etter skaden. Det er imidlertid ukjent akkurat hvor vanlig det er og hvor lenge de varer og om personer med mild TBI er mer utsatt for å få vedvarende søvn-våkenhetsvansker enn andre personer. I tillegg er det nødvendig med mer kunnskap om konsekvensene av søvn-våkenhetsvansker, både etter lette hodeskader og hos mennesker som ikke har hatt en hodeskade.

**Formål**

I denne avhandlingen var målet å undersøke klinisk forløp av søvn-våkehetsvansker etter mild TBI, og konsekvenser av slike plager etter mild TBI sammenlignet med personer uten skader og personer med ortopediske skader.

**Metode**

Trondheim MTBI follow-up study er en populasjonsbasert longitudinell studie, hvor 378 pasienter med mild TBI, 82 pasienter med lette ortopediske skader og 81 personer uten noen skader ble inkludert. Alle deltagerne var mellom 16 og 60 år. Deltagerne ble fulgt over ett år og søvn-våkenhetsvansker, kognitiv og emosjonell fungering ble målt 2 uker, 3 måneder og 12 måneder etter skade.

I «sleep, individual differences and cognitive functioning" (SLEEPIC) studien ble 59 unge voksne (18-35) inkludert til en prospektiv søvnstudie. I studien fikk deltagerne beskjed om å sove som normalt i sju dager. Etter disse sju dagene ble de bedt om å sove 2 timer kortere enn gjennomsnittet av de første sju nettene (delvis søvndeprivasjon) i tre netter på rad. Deltagerne ble testet i kognitiv fungering og rapporterte hvordan de følte seg tre ganger før søvndeprivasjonen og to ganger mens de var søvndepriverte.

I den første studien i avhandlingen undersøkte vi forekomsten og stabiliteten av søvn-våkenhetsvansker etter lette hodeskader, sammenlignet med personer med lette ortopediske skader og personer uten noen skader. I den andre studien i avhandlingen undersøkte vi hvilke konsekvenser det å sove 2 timer mindre enn vanlig har på kognitiv og emosjonell fungering for friske unge voksne. I den tredje studien i avhandlingen undersøkte konsekvensene av søvnvansker for kognitiv og emosjonell fungering for pasienter med lette hodeskader, sammenlignet med pasienter med ortopediske skader.

**Resultater**

Pasienter med lette hodeskader hadde en signifikant høyere forekomst og varighet av vedvarende søvn-våkenhetsvansker sammenlignet med pasienter med ortopediske skader og personer uten noen skader. Pasientene med mild TBI som hadde intrakranielle funn på hjerneavbildning (CT og/eller MR) hadde høyere forekomst av fatigue sammenlignet med pasientene uten funn på hjerneavbilding (Studie I).

Det å sove to timer mindre enn vanlig (delvis søvndeprivasjon) over tre netter på rad for unge voksne førte til mer impulsive responser på en kognitiv test. Etter delvis søvndeprivasjon rapporterte deltagerne å ilegge større innsats i testen, men følte likevel at prestasjonen ble dårligere. Delvis søvndeprivasjon var også assosiert med lavere positiv affekt som for eksempel innebærer mindre glede og lavere entusiasme (Studie II).

Søvnvansker var assosiert med større negative konsekvenser for kognitiv og emosjonell fungering etter mild TBI, sammenlignet med etter ortopediske skader. For både pasienter med mild TBI og pasienter med ortopediske skader var søvnvansker assosiert med mindre nøyaktige responser på kognitive tester (Studie III).

**Konklusjon**

Det å få en hodeskade ser ut til å føre til flere og vedvarende søvnvansker, som i seg selv kan føre til kognitive og emosjonelle problem. Disse funnene kan tyde på at det er noen spesifikke mekanismer knyttet til å få en hodeskade som fører til søvnvansker, som kan ha negative konsekvenser i lengre tid etter skaden. Endringer i søvn kan i seg selv påvirke kognitive prestasjoner og positive følelser. Pasienter med lette hodeskader ser ut til å være spesielt sårbare for de negative konsekvensene søvnvansker har på kognitiv og emosjonell fungering etter skaden.

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## Summary

### Background

After a mild traumatic brain injury (mild TBI) individuals often experience sleep-wake disturbances. It is unknown whether individuals with mild TBI have a higher risk for persistent sleep-wake disturbances compared to other individuals. There is also a need to identify the consequences of sleep-wake disturbances, both after mild TBI, but also for individuals without head injuries.

### Aims

The aim of the present thesis was to evaluate the clinical course and consequences of sleep-wake disturbances for patients with mild TBI as compared to individuals in the general population and patients with orthopedic injuries.

### Methods

The Trondheim MTBI follow-up study is a population-based longitudinal study of individuals where 378 patients with mild TBI, 82 patients with orthopedic injuries and 81 individuals without any injury were included. All participants were between 16 and 60 years of age. Sleep-wake disturbances, neurocognitive and emotional functioning were assessed at 2 weeks, 3 months and 12 months after injury.

In the "sleep, individual differences and cognitive functioning" (SLEEPIC) study a total of 59 young adults (age 18-35) were included in a prospective sleep study. In the study the participants were asked to sleep normally for seven days. After the first seven days, we asked the participants to sleep 2 hours shorter than their mean total sleep time the first seven days (partial sleep deprivation), for the last three days of the study. Neuroognitive performance and affect were assessed three times before sleep deprivation and two times when the participants were sleep deprived.

In the first paper we investigated the prevalence and stability of sleep-wake disturbances after mild TBI, compared to patients with orthopedic injury and individuals without any injury. In paper II we investigated the consequences of partial sleep deprivation on neurocognitive performance and affective functioning in healthy young adults. In paper III we investigated the consequences of poor sleep quality on neurocognitive and psychological functioning after mild TBI, compared to patients with orthopedic injury.

**Results**

Patients with mild TBI had a significantly higher prevalence and stability of sleep-wake disturbances and fatigue compared to patients with orthopedic injury and individuals without any injury. We observed a higher prevalence of fatigue in patients with mild TBI who had intracranial findings on brain imaging (CT and/or MRI) compared to those without intracranial findings on brain imaging (Paper I).

Partial sleep deprivation for three nights in a row was associated with faster reaction time and higher amounts of errors on a continuous performance test. The participants reported to put more effort into the test after sleep deprivation, but still reported that they performed worse after sleep deprivation. Partial sleep deprivation was also associated with lower positive affect, such as feelings of joy and enthusiasm (Paper II).

Poor sleep quality was associated with greater negative consequences for neurocognitive and psychological health after mild TBI than after orthopedic injury. For both patients with mild TBI and patients with orthopedic injury poor sleep quality was associated with less accurate responses on continuous performance tests (Paper III).

**Conclusions**

Sustaining a mild TBI is associated with the development and maintenance of sleep-wake disturbances that by themselves can lead to neurocognitive and psychological problems. These findings indicate that mechanisms specific to the mild traumatic brain injury is associated with the development of sleep-wake disturbances, which in turn can have negative consequences long-term after injury. Sleep changes can by itself influence cognitive and psychological functioning. Poor sleep quality may be particularly detrimental to cognitive and psychological functioning after mild TBI.

## Acknowledgements

First and foremost I would like to thank the many patients and other participants who have given of their valuable time in the two studies the present thesis capitalizes on. The accumulated work presented in the present thesis could not have been done by one single person and there are several people deserving recognition. I want to thank my main supervisor **Alexander Olsen** for sharing expert knowledge and being available around the clock, just be careful you get enough sleep. Thank you **Toril Skandsen** for everything you have thought me since I started working on the mTBI-project in 2013. **Håvard Kallestad** thank you for guidance in the growing sleep field, for including me in the research community at Østmarka. I do not think one could get a better team of supervisors, and you should consider supervising together again.

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Finally, thank you Edona for your existence, I genuinely could not have done this without you.

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## List of papers

Paper I:

**The prevalence and stability of sleep-wake disturbances and fatigue throughout the first year after mild traumatic brain injury**

Simen Berg Saksvik, Migle Karaliute, Håvard Kallestad, Turid Follestad, Robert Asarnow, Anne Vik, Asta Kristine Håberg, Toril Skandsen, Alexander Olsen.
*Journal of Neurotrauma, 2020.* https://doi.org/10.1089/neu.2019.6898

Paper II:

**Mild to moderate partial sleep deprivation is associated with increased impulsivity and decreased positive affect in young adults**

Ingvild Saksvik-Lehouillier, Simen Berg Saksvik, Johanna Dahlberg, Tiril K Tanum, Heidi Ringen, Håvard Rudi Karlsen, Trine Smedbøl, Torhild Anita Sørengaard, Mailen Stolpe, Håvard Kallestad, Alexander Olsen
*Sleep, 2020*. https://doi.org/10.1093/sleep/zsaa078

Paper III:

**Poor sleep quality is associated with greater negative consequences for neurocognitive and psychological health after mild traumatic brain injury than after orthopedic injury**

Simen Berg Saksvik, Hanne Smevik, Jonas Stenberg, Turid Follestad, Anne Vik, Asta Kristine Håberg, Robert F. Asarnow, Håvard Kallestad, Toril Skandsen, Alexander Olsen
*Submitted manuscript. Preprint in PsyArXiv, 2020.* 10.31234/osf.io/hc8jz

## Abbreviations and acronyms

| | |
|---|---|
| AST | Attention Switching Task |
| BSI-18 | Brief Symptom Inventory 18 |
| CANTAB | Cambridge Neuropsychological Test Automated Battery |
| CBT-I | Cognitive Behavioral Therapy for Insomnia |
| CCPT | Conners' Continuous Performance Test |
| CI | Confidence Interval |
| CT | Computerized Tomography |
| DSM | The Diagnostic and Statistical Manual of Mental Disorders |
| DWI | Diffusion Weighted Imaging |
| EEG | Electroencephalogram |
| ESS | Epworth Sleepiness Scale |
| FLAIR | Fluid-Attenuated Inversion Recovery |
| FSS | Fatigue Severity Scale |
| GCS | Glasgow Coma Scale |
| HADS | Hospital Anxiety and Depression Scale |
| ICD-10 | International Classification of Diseases-10 |
| ISI | Insomnia Severity Index |
| LOC | Loss Of Consciousness |
| MRI | Magnetic Resonance Imaging |
| nREM | non-Rapid Eye Movement |
| OR | Odds Ratio |
| PANAS | Positive and Negative Affect Schedule |
| PSG | Polysomnography |
| PSQI | Pittsburgh Sleep Quality Index |
| PTA | Post Traumatic Amnesia |
| GP | General Practitioner |
| PSG | Polysomnography |
| REM | Rapid Eye Movement |
| REK | Regional Committee for Research Ethics in Norway |
| rmANOVA | Repeated Measures Analysis Of Variance |
| RTI | Reaction Time |
| RVP | Rapid Visual Information Processing |
| RTI | Reaction Time |
| SLEEPIC | Sleep, Individual Differences and Cognitive Functioning |
| SWI | Susceptibility Weighted Imaging |
| TBI | Traumatic Brain Injury |

Table of contents

# 1 Introduction

## 1.1 Sleep and sleep-wake disturbances

Sleep is a highly conserved biological phenomenon (Van Someren et al., 2015), characterized by naturally reoccurring alteration of consciousness, that follows a circadian rhythm (Deboer, 2018), and serves multiple vital functions (Assefa et al., 2015; Irwin, 2019). The function of sleep is a controversial scientific topic that have bewildered scientist over the last 100 years (Krueger et al., 2016). Much of what we know about the function of sleep has been learned by experimentally manipulating sleep and wakefulness and observing its consequences (Van Someren et al., 2015). Such interference and manipulations have indicated that sleep is important for energy conservation and storage, immune function, glymphatic function, optimization of performance and brain connectivity (Krueger et al., 2016).

Sleep is influenced by homeostatic and circadian factors, and these factors interact with each other in a complex manner (Deboer, 2018). The homeostatic factor regulates sleep need accumulated from spending time awake. During wakefulness, adenosine and other sleep promoting substances accumulates and is thought to reduce activity in wake-promoting brain regions and increase the activity in sleep-promoting brain regions. The circadian factor regulates the rhythm of sleep and wake propensity according to a cycle of approximately 24 hours (Borbély et al., 1989; Deboer, 2018). Human circadian rhythms are evolved to be synchronized with the pattern of night and day. Each cell in the body have a 24-hour circadian rhythm ordered in a hierarchical oscillating system that is regulated by the suprachiasmatic nucleus, located in the anterior hypothalamus (Honma, 2018). If individuals stay awake when he or she should be sleeping, this can lead to desynchronization of circadian rhythms (Reinberg et al., 2007). This pose a problem during the hours following awakening, if the circadian and the homeostatic curve do not meet at the right time to promote awakening.

The overall electrical activity in the brain changes during sleep and can be categorized into two major phases: rapid eye movement (REM) sleep and non-rapid eye movement (nREM) sleep (Kandel et al., 2012). NREM sleep can be further divided into stages of increasing sleep depth; N1, N2 and N3. N3 is characterized by low frequency, high

amplitude slow-wave sleep defined by the electroencephalogram (EEG) (Irwin, 2019). Slow-wave activity on EEG, reflects synchronous neuronal firing and inactivity and higher frequency EEG, reflects desynchronized neuronal firing (Lee & Dan, 2012). Both the slow-wave nREM sleep and high frequency REM sleep have important shared and distinct functions important for overall brain health (Assefa et al., 2015).

The transition from wakefulness to sleep, and sleep to wakefulness involves intricate mutually inhibitory interactions between wake promoting neurons and sleep promoting neurons (Brown et al., 2012). Sleep-wake regulating networks are widespread in the brain and originate in the brain stem, basal forebrain and the hypothalamus and have extensive projections to the cortex (Sandsmark et al., 2017). Disruptions to sleep-wake regulating networks may at the one hand cause interruptions in the promotion of wakefulness, causing an increase in sleep (Elliott et al., 2018; M. M. Lim et al., 2013). On the other hand may disruptions in the inhibitory interactions in the sleep-wake networks lead to an inability to disengage from arousal, interfering with the ability fall or stay asleep (Van Someren, 2020).

During sleep, the Glymphatic system regulates protective immunity in the brain by clearing waste and returning proteins and fluids form the interstitial space to the general circulation (Jessen et al., 2015). During sleep (particularly during slow-wave sleep) the interstitial space is increased which leads to an increased convection of cerebrospinal fluid and interstitial fluid through brain tissue (i.e. neurons and glial cells). This promotes removal of waste products that accumulates during wakefulness (Xie et al., 2013).

Because of all these reasons it is clear that sleep plays several and vital functions important in the regulation of normal brain health. Given the complexities of the mechanisms underlying sleep, there are several different ways an individual can experience disruptions in sleep (**Figure 1**). It is also likely several factors that contribute in a synergistic manner in the development of sleep-wake disturbances.

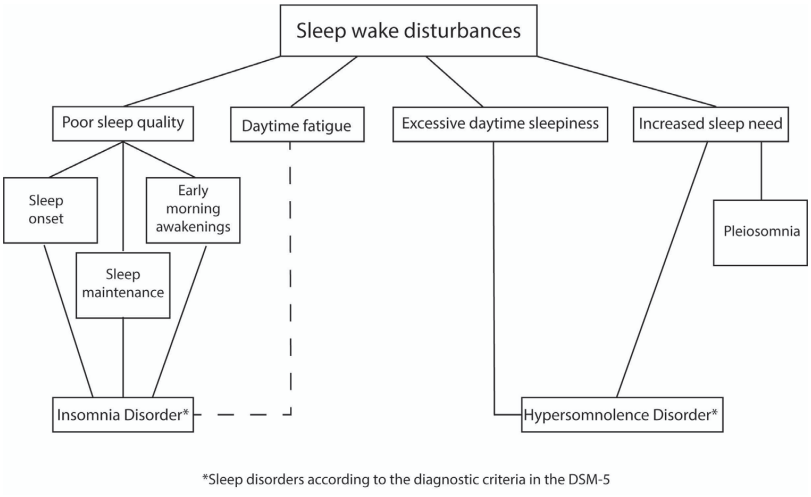


**Figure 1: Sleep-wake disturbances and sleep-wake disorders**. *An overview of different sleep-wake disturbances and how they correspond to the sleep.wake disorders insomnia disorder and hypersomnolence disorder in the Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5)* (American Psychiatric Association, 2013)

Disruption of sleep is comorbid to all major psychiatric (Kallestad et al., 2011) and neurologic disorders, including depression (Otte et al., 2016), anxiety (Baglioni et al., 2016; Cox & Olatunji, 2016), schizophrenia (Baglioni et al., 2016), addiction disorders (Brower & Perron, 2010), Alzheimer's disease (Zhao et al., 2016), stroke (Fulk et al., 2020) and traumatic brain injury (J. Mathias & Alvaro, 2012). An increasing body of research indicates that sleep-wake disturbances are important contributors to the development and maintenance of such disorders (Freeman et al., 2020; Hertenstein et al., 2019; Irwin, 2019; Lucey et al., 2019). Sleep-wake disturbances such as poor sleep quality, excessive daytime sleepiness, increased sleep need, short sleep and fatigue are increasing in the general population in the modern society (Bin et al., 2013; Engberg et al., 2017; Ferrara & De Gennaro, 2001; Pallesen et al., 2007, 2014; Sheehan et al., 2019). Sleep-wake disturbances are among the leading causes for work absenteeism and reduced work productivity (Daley et al., 2009) traffic-, work- and home- related accidents (Leger et al., 2014; Melamed & Oksenberg, 2002; Powell et al., 2002; Prats-Uribe et al., 2018) and cause monumental personal and societal costs (Wilson et al.,

2019). Sleep-wake disturbances are therefore major contributors to disability in the modern world and require increased attention from scientists and health professionals.

Most people have experienced transient difficulties with sleep such as problems falling asleep or experienced an increased need for sleep, sleepiness and fatigue for example after a mild illness or injury. Such difficulties are in most circumstances harmless and have no adverse long-term consequences. When a sleep-wake disturbance is severe and persistent it can be categorized as a sleep-wake disorder. Insomnia disorder and hypersomnolence disorder are among the most common sleep-wake disorders and are particularly relevant for the present thesis (**Figure 2**).

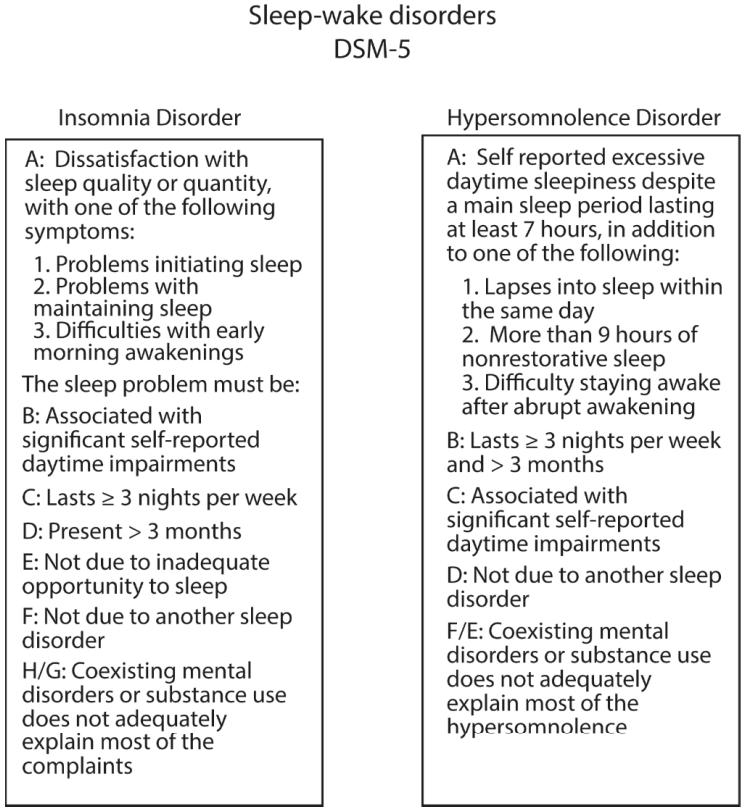


**Figure 2: Sleep-wake disorders**. *Diagnostic criteria for insomnia disorder and hypersomnolence disorder*

## 1.2 Causes of sleep-wake disturbances

Behavior and sleep habits are strongly associated with the development and maintenance of sleep-wake disturbances (Carskadon, 2011). There is for example a large discrepancy between sleep time in the weekend and weekdays in the general population in Norway, which may lead to problems with sleep (Sivertsen et al., 2011). Work demands, shift work, night work and environmental stimuli may also dysregulate circadian and homeostatic factors, leading to sleep-wake disturbances (Pallesen et al., 2014). Additionally may medication use (Buysse et al., 2006), substance misuse (Roane & Taylor, 2008), pain (Wylde et al., 2011), traumatic experiences (Crofford, 2007; Sinha, 2016), stress (Lund et al., 2010), nighttime rumination or worry (Thomsen et al., 2003) and psychological distress (Freeman et al., 2020) interfere with both homeostatic factors and circadian factors and therefore be involved in the development and maintenance of sleep-wake disturbances.

There is a well-established connection between sleep and the immune system (Irwin, 2019). During an infection, after a disease or injury, humans and other animals typically experience an increased propensity for sleep in the form of increased sleep need, daytime sleepiness and fatigue, which have been labeled 'sickness behavior' (Dantzer & Kelley, 2007; Hart, 1988). An activated immune system releases inflammatory cytokines, which promote increased sleep duration, sleep depth and sleep efficiency (Imeri & Opp, 2009). When sleep is disrupted the important connection between sleep and immune function may be dysregulated; low levels of inflammation is associated with increased sleep need (Imeri & Opp, 2009), whereas higher levels of inflammation is associated with sleep fragmentation and shorter sleep duration (Irwin & Opp, 2017; Irwin, 2019).

The factors mentioned might all contribute to the development of sleep-wake disturbances also after acquired brain injuries, such as stroke or traumatic brain injury. However, sleep-wake disturbances after acquired brain injuries may also result from direct consequences of the brain injury itself. Direct damage to sleep-wake promoting neurons and networks in the brain may result in sleep-wake disturbances (Grima et al., 2017). Consequences of brain injury, such as impaired axonal conduction, synaptic

transmission and/or damage to brain networks may also lead to neurocognitive deficits (Churchill et al., 2020), neuro-inflammation (Tapp et al., 2020), fatigue (Ponsford et al., 2015) and psychiatric problems (Mollayeva et al., 2017) which may exacerbate sleep-wake disturbances. Additionally, may coping strategies, other cognitive changes and mental health in general influence the development and maintenance of sleep-wake disturbances after acquired brain injuries (Beaulieu-Bonneau et al., 2017; Grima et al., 2017).

Because of the vital function of sleep for normal brain function, are sleep-wake disturbances after acquired brain injuries likely to be associated with additional functional impairment, and can impede recovery processes.

## 1.3 Traumatic brain injury

Traumatic brain injury (TBI) is defined as "*an alteration in brain function, or other evidence of brain pathology, caused by an external force"* (Menon et al., 2010, page 2). Approximately 50 million individuals experience a TBI each year worldwide, and the vast majority of the cases are mild (Maas et al., 2017). The incidence of mild TBI has been reported to be as high as 749 per 100 000 in a population-based study, including all cases of TBI, those admitted to the hospital and those not admitted (Feigin et al., 2013).

Typical external causes of a mild TBI is non-penetrating forces where the head is being struck by an object or the head strikes an object. Central causes for brain injury after mild TBI are acceleration and deceleration forces that impact the brain after the external cause (Blennow et al., 2016; Menon et al., 2010). The most common causes of mild TBI in Trondheim, Norway are falls, violence, bicycle accidents, and motor vehicle accidents (Skandsen et al., 2018).

### 1.3.1 *TBI severity*

The TBI spectrum ranges from mild to severe based on the Glasgow Coma Scale (GCS) (Teasdale & Jennett, 1974). The GCS is a measure of consciousness or awareness in patients and ranges from a score of 15, which is a fully alert and oriented individual, to 3 which is a non-responsive individual. The scores are based on verbal responses, motor response and eye opening. A patient with TBI is categorized into having a severe TBI if

he or she have a GCS score of 3-8, a moderate 9-12 and a mild 13-15. There is some discussion whether a GCS score of 13 should be considered a moderate or mild TBI (Fabbri et al., 2008; Maas et al., 2008). The GCS score has good prognostic value, but the scoring is complicated by intoxication, intubation and medical sedation (Teasdale et al., 2014). Especially intoxication is relevant in mild TBI because many individuals are injured at night time under the influence of alcohol (Skandsen et al., 2018).

In 2004 the World Health Organizations (WHO) task force on mild TBI (Carroll et al., 2004) aimed to reach unified criteria for a mild TBI. The task force recommended the following clinical identifications for mild TBI: One of the following must be present for a mild TBI diagnosis: A GCS score between 13 and 15, post traumatic amnesia or confusion less than 24 hours, a witnessed loss of consciousness, confusion or disorientation no longer than 30 minutes or other transient signs of neurological abnormalities such as intracranial lesion, seizure or focal signs. In the present thesis a mild TBI is defined according the WHO criteria.

### 1.3.2 *Pathophysiology*

Most patients with mild TBI have an uncomplicated mild TBI, indicating no evident hemorrhage or other structural abnormalities on clinical Computed Tomograhpy (CT) scans or Magnetic Resonance Imaging (MRI). The hallmark of a mild TBI is neurological signs and symptoms, but an absence of macroscopic neuronal damage (Giza & Hovda, 2014). It is still possible that patients have subtle brain changes due to the trauma that are detectable with more sensitive MRI techniques (Shenton et al., 2012), i.e. microstructural injury. The absence of clinical findings on brain imaging, even newer more sensitive ones, does not rule out brain changes after mild TBI. The mechanical force leading to a mild TBI causes a complex neurometabolic and neurochemical cascade of events in the brain (Giza & Hovda, 2014). Animal models have elucidated the changes in neurobiology after a mild TBI, and these findings have been substantiated in human studies over the last years (Romeu-Mejia et al., 2019).

Immediately after the mechanical force to the brain, axons get stretched and sheared which in turn leads to a perturbation of cell membranes and diffuse depolarization of neurons (Giza & Hovda, 2014). This depolarization causes a dysregulation of ion

channels and efflux of ions and excitatory neurotransmitters (e.g. glutamate). Dysregulated ion efflux may cause a feedback loop of hyperexcitability and further depolarization. This dysregulation typically normalizes within the first hours of injury. However, the released excitatory neurotransmitters leads to accumulation of calcium and sodium within the cell, which may cause cell damage, mitochondrial damage and further deformation of axonal structures (Romeu-Mejia et al., 2019). Additionally, the hyperexcitability causes an uncoupling between energy supply and demand, leading to an energy crisis (Giza & Hovda, 2014). The following anaerobic metabolism may result in an acidic microenvironment (Romeu-Mejia et al., 2019). The hypermetabolism is followed by hypomatabolism that can last up to 10 days after injury (Giza & Hovda, 2014; Romeu-Mejia et al., 2019). This cascade of events may result in deformation and damage to axons, some reversible, but not all. These acute factors may cause ripple effects in the brain, which may result in long term axonal injury, impaired synaptic plasticity, neuroinflammation, in some rare cases, cell death (Romeu-Mejia et al., 2019).

The acute neurobiological changes in the brain are associated with slowed reaction time, blurred vision and balance problems (Guskiewicz & Mihalik, 2011; Niogi et al., 2008). It is also likely that specific symptomatology, and behavior in the acute phase may exacerbate the neurobiological changes after injury.

### 1.3.3 *Prolonged post-concussion symptoms*

Early after a mild TBI it is common to experience headache, blurred vision, cognitive and emotional problems, dizziness, sleep-wake disturbances and fatigue (Cassidy et al., 2014). Some patients with mild TBI experience persistent symptoms that can last for months (Oldenburg et al., 2016) or even years after injury (Hiploylee et al., 2017). It is unknown why these individuals develop lasting symptoms, but an interaction between structural and functional brain abnormalities, pre- and post-injury physiological, psychological and social factors are likely involved (Iverson, 2019). Persistent post-concussion symptoms, that last >3months, are categorized as postconcussional disorder in the *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition (DSM-IV) and as postconcussional syndrome in the *International Classification of Diseases-10* (ICD-10). However, prolonged post-concussion symptoms are not specific to mild TBI and is also present in the general population and after injuries not involving the head

(Ettenhofer & Barry, 2012). Accordingly, the WHO Collaborating Centre Task Force recommended in 2014 to replace the term postconcussion syndrome with posttraumatic symptoms (Cassidy et al., 2014) and the DSM-5 no longer includes the diagnostic category postconcussional disorder.

### 1.4 Sleep-wake disturbances after Mild Traumatic Brain Injury

Sleep-wake disturbances affect approximately half of patients sustaining a TBI, and one third have a diagnosed sleep-wake disorder (J. Mathias & Alvaro, 2012). The prevalence of sleep-wake disturbances may be higher because these symptoms are often underreported by patients and underrecognized by clinicians (Sandsmark et al., 2017). Insomnia disorder and hypersomnolence disorder are the two most commonly diagnosed sleep-wake disorders after TBI (J. Mathias & Alvaro, 2012; Sandsmark et al., 2017). Sleep-wake disturbances are common across TBI severity (J. Mathias & Alvaro, 2012), and are associated with long-term symptomatology, also after mild TBI (Theadom et al., 2015). Normal sleep may be important for recovery after mild TBI (Wickwire et al., 2016), making sleep-wake disturbances a particularly troublesome symptom after injury (Kalmbach et al., 2018).

Few prior studies have included control groups in their evaluation of sleep-wake disturbances after mild TBI. The controlled longitudinal studies that exist are typically on selected subsamples of patients with mild TBI (Losoi et al., 2015, 2016; Ponsford et al., 2011; Sullivan et al., 2015) or on samples of mixed severity TBI (i.e also moderate or severe TBI) (Imbach et al., 2015, 2016) and therefore not representative for the highly heterogenic mild TBI population (Luoto et al., 2013). Sleep-wake disturbances are prevalent also after injuries not involving the head (Shulman et al., 2015) and in the general population (Pallesen et al., 2007, 2014). Inclusion of control groups are therefore essential for studies aiming to determine whether sustaining a mild TBI is associated with the development and maintenance of sleep-wake disturbances (Wickwire et al., 2016). Additionally, the vast majority of patients with mTBI that do not seek medical assistance, or are treated outside of hospitals, have typically not been included in prior studies. There is therefore a need to investigate sleep-wake

disturbances after mild TBI in controlled population-based longitudinal studies with well characterized samples.

### 1.4.1 *Measuring sleep wake disturbances after mild TBI*

Sleep can be assessed with objective and subjective measures. Polysomnography (PSG) is the gold standard for objective laboratory based measure of sleep (Baglioni et al., 2016; Van Someren, 2020). There are however some disadvantages with measuring sleep with PSG. Most PSG recordings are restricted to laboratory sleep schedules (Grima, Ponsford, Rajaratnam, et al., 2016), that does not always correspond with the natural sleep schedule of the individual (Imbach et al., 2015). Additionally, PGS may in itself cause a disturbance of sleep, especially in the first night of recording (e.g. because of discomfort due to the equipment or sleeping in an unfamiliar environment). This effect may be particularly prominent in patient populations, and is present even when the PSG is used at home and not in the laboratory (Blackwell et al., 2017).

Sleep can also be measured objectively with simpler means, by the use of actigraphy (Van Someren, 2020). Actigraphy is limb-worn accelerometers that record movement where rest/activity cycles can be collected continuously both day and night, over several days and may be used at home (Ancoli-Israel et al., 2003). Overall effects of changes in sleep does not seem to differ when investigated with PSG or actigrapy. Because of the disadvantages with PSG recordings, are future studies recommended to measure sleep in more naturalistic settings using ecological valid measures (Lowe et al., 2017).

Self-reported measures of sleep can be obtained through sleep diaries, questionnaires and interviews (including structured diagnostic interviews). There is generally a low correspondence between subjective and objective measures of sleep both in the general population and clinical populations (Van Someren, 2020), including mild TBI (Raikes et al., 2019). This does not indicate that objective measures are better at capturing specific sleep outcomes, but it is possible that objective and subjective sleep measures capture different aspects of sleep, and that both may be important in measuring actual sleep (Berger et al., 2017; Raikes et al., 2019). The diagnosis of both Insomnia disorder and Hypersomnolence disorder in the DSM-5 are strictly based on self-report, and

objective measures are not required for diagnosis (American Psychiatric Association, 2013).

### 1.4.2 *Subtypes of sleep-wake disturbances after mild TBI*

There is a lack of consensus regarding precisely how sleep is affected after mild TBI. Poor sleep quality (i.e. difficulties initiating and maintaining sleep and problems with early morning awakenings) is the most frequently investigated sleep-wake disturbance after mild TBI (Sullivan et al., 2015). A meta-analysis combining scores from prior objective and subjective sleep studies in TBI samples concluded that patients with TBI across severity seems to have an overall shorter nocturnal total sleep time compared to controls (Grima, Ponsford, Rajaratnam, et al., 2016). However, the studies included in the meta-analysis restricted bedtimes to 8 or 9 hours, due to restrictions in laboratory PSG recordings. This is relevant for patients with TBI who experience an increased need for sleep that normally would require longer sleep than 8 or 9 hours. If total sleep time is measured over 24 hours, patients with TBI across severity seems to have significantly longer total sleep time (>8 hours) compared to controls (Imbach et al., 2015, 2016; Sommerauer et al., 2013). Post traumatic *"pleiosomnia*" has been introduced as a term for increased sleep need after TBI that does not necessarily co-exists with excessive daytime sleepiness (Sommerauer et al., 2013).

It is likely that there exist several different sleep profiles after mild TBI, where some experience longer total sleep time and others shorter total sleep time, some experience longer sleep onset latency whereas other have shorter sleep onset latency (Raikes et al., 2019). Concertedly, prior findings show that sleep may be affected in several different ways after mild TBI, and a mild TBI may give rise to several different sleep phenotypes (Sandsmark et al., 2017) or sleep profiles (Raikes et al., 2019). In order to understand the different phenotypes of sleep after mTBI, there is a need for studies investigating different types of sleep-wake disturbances after mild TBI over time in the same study and in large samples.

### 1.4.3 *Fatigue and daytime functioning*

Sleep-wake disturbances are often associated with fatigue (Sandsmark et al., 2017) and one of the key criteria for both insomnia and hypersomnolence disorder is daytime impairments often in the form of fatigue (American Psychiatric Association, 2013).

Fatigue is a feeling of weariness or exhaustion that is distinguishable from similar symptoms such as somnolence (i.e. increased sleep need), sleepiness and depression, and can arise from psychological factors and homeostatic factors (Kluger et al., 2013). Most individuals experience non-pathological feelings of fatigue after prolonged extensive mental activity (Kluger et al., 2013). However, clinically significant fatigue can be a primary symptom after neurologic illness, that give rise to later developing symptoms (Ponsford et al., 2015; Schönberger et al., 2014). Fatigue and especially the interplay between sleep-wake disturbances and fatigue are important factors to consider when evaluating disease, illness and injury etiology.

The reported prevalence of fatigue after mild TBI ranges from 17% to 47% in prior studies (Mollayeva et al., 2014). The nature of sleep and fatigue following TBI has, despite some recent advancements (Beaulieu-Bonneau & Ouellet, 2017), traditionally been poorly characterized. There may be considerable overlap between sleep-wake disturbances and fatigue, but there is need for a better characterization and distinction between different sleep-wake disturbances and fatigue in future studies (Sullivan et al., 2018).

## 1.5 Causal factors of sleep-wake disturbances after mild TBI

Sleep-wake disturbances, both in general and after mild TBI, are likely caused by a range of interacting factors. Sleep wake disturbances can result as a direct consequence of the mild TBI (e.g. due to axonal injury), due to neurocognitive and psychological problems that subsequently influences sleep (Grima et al., 2017) or due to other daytime behaviors and activity levels where they perpetuate and aggravate each other. Some individuals may also have some predisposing factors that makes them particularly vulnerable to develop sleep-wake disturbances after injury (Ouellet et al., 2015). Importantly, sleep-wake disturbances prior to injury may also be maintained and

exacerbated after mild TBI and are important to consider in research and clinical evaluations (Wickwire et al., 2016).

### 1.5.1 *Pre-injury factors*

Pre-injury factors are also associated with the development and maintenance of sleep-wake disturbances after TBI, indicating that some individuals are at higher risk of developing such problems after sustaining a mild TBI (Wickwire et al., 2018). Older age (Rabinowitz et al., 2015; Theadom et al., 2015) and female sex (Kalmbach et al., 2018; Rabinowitz et al., 2015) seems to be risk factors for developing sleep-wake disturbances and for poorer general recovery after mild TBI. Having a prior mild TBI is a risk factor for developing subsequent mild TBI (Rabinowitz et al., 2015), and repeated mild TBI have a more severe impact on sleep-wake disturbances after injury (Oyegbile et al., 2019). Additionally, psychiatric disorders, personality factors and cognitive functioning prior to injury may influence the outcome after mild TBI, including sleep-wake disturbances (Cassidy et al., 2014). Importantly, sleep-wake disturbances may in itself be a risk factor for mild TBI (Wickwire et al., 2016), and sleep-wake disturbances prior to mild TBI is likely to persist and may also be worsened after injury. It is also likely that other factors such as genetics, neuroanatomy, medication interactions and sleep patterns before the injury are involved in the development of chronic sleep-wake disturbances after mild TBI (Wickwire et al., 2018).

### 1.5.2 *Post injury symptomatology*

The post injury symptomatology after mild TBI is also associated with the development and maintenance of sleep-wake disturbances (Grima et al., 2017). Psychological distress is generally associated with poor sleep quality, and patients with depression often experience an increased need for sleep (Freeman et al., 2020). Other injury related factors such as post-traumatic stress (Germain, 2013), pain (J. L. Mathias et al., 2013), headache (Kim et al., 2020), medication use (Mollayeva et al., 2013), neurocognitive function (Theadom et al., 2015) and changes in work and social life (Kalmbach et al., 2018) may all be influenced by and contribute to the development of sleep-wake disturbances.

In summary, there is a host of reasons for why individuals may experience sleep-wake disturbances after mild TBI. It is likely that neurobiological, neurocognitive and psychological mechanisms as well as pre-injury factors interact in the development and maintenance of sleep-wake disturbances after mild TBI.

## 1.6 The short- and long-term consequences of sleep-wake disturbances

There is a lack of information regarding the short- and long-term consequences of sleep-wake disturbances after mild TBI (Wickwire et al., 2018). If the hypothesized association between a mild TBI and the development of acute, subacute or long-term sleep-wake disturbances (Wickwire et al., 2016, 2018) holds true, this would lead to rather abrupt changes to the sleep pattern after injury. One way of observing the consequences of such sudden changes in sleep is by experimentally manipulating the sleep (Van Someren et al., 2015). In order to explore the direct consequences of sleep-wake disturbances, it may be informative to first explore how sleep changes interferes with function in uninjured individuals. Prior studies have shown that total sleep deprivation in healthy individuals have marked effects on cognitive control function and psychological health (Killgore, 2010; J. Lim & Dinges, 2010; Lowe et al., 2017).

However, naturally occurring changes to sleep both in the general population and following mild TBI is most often more subtle than a total sleep deprivation. Studies focusing on partial sleep deprivation have typically been performed in the laboratory setting, which in itself may interfere with the sleep (Blackwell et al., 2017). It is therefore likely that studies investigating subtle and acute changes to sleep in more naturalistic settings (e.g. by the use of actigrapy) can provide more ecologically valid outcomes (Lowe et al., 2017). Such studies may also contribute to better the understanding of the consequences of abrupt changes to the sleep after mild TBI.

### 1.6.1 *Sleep, cognitive control function and psychological health*

Cognitive control function (Power & Petersen, 2013) is the goal directed control over thoughts, actions and emotions. Neural correlates of cognitive control functions are widely distributed in the brain and rely on rapid communications between key brain areas (Olsen et al., 2013). Sleep seems vital for regulating normal brain health (Goldstein & Walker, 2014; van der Helm & Walker, 2009) and even small

manipulations of sleep may have severe consequences for cognitive control function (Krause et al., 2017).

Neurocognitive tests assessing cognitive control functions such as the ability to sustain attention over time (i.e sustained attention), seems to be most affected by partial sleep deprivation (Lowe et al., 2017). Sleep loss may lead to a disruption of the communication between key functional brain networks, which can lead to unstable task performance and changes in performance speed and accuracy (Krause et al., 2017; J. Lim & Dinges, 2008). Specifically, partial sleep deprivation seems to be associated with increased response times and lapses of attention leading to lower accuracy on tasks requiring sustained attention (Alhola & Polo-Kantola, 2007; Belenky et al., 2003; Dinges et al., 1997; J. Lim & Dinges, 2008). However, a recent study failed to find any significant effects of partial sleep deprivation on sustained attention (Santisteban et al., 2019). In this study the participants were instructed to sleep one hour less than normal. It is therefore possible a sleep restriction of more than 1 hour is needed in order to have marked effects on sustained attention and cognitive control function.

Both sleep deprivation and subjective poor sleep quality in insomnia disorder may interfere with an individual's ability to regulate emotions (van der Helm & Walker, 2009; Van Someren, 2020). Sleep loss and poor sleep quality have been associated with disruptions in core networks involved cognitive control and emotion regulation (Goldstein & Walker, 2014; Van Someren, 2020). Prior studies have shown that restricting the sleep to 2 hours for one night, in the laboratory, may decrease positive affect (i.e. feelings of joy, enthusiasm and alertness) in adolescents and young adults (Talbot et al., 2010). The consequences of partial sleep deprivation on negative affect (i.e. feelings of shame, frustration and stress) is mixed, where some studies find that partial sleep deprivation leads to more negative affect (Mastin et al., 2005; Short & Louca, 2015) whereas other studies report that negative affect are unchanged after partial sleep deprivation (Dagys et al., 2012; Talbot et al., 2010). Some studies show that sleep deprived individuals are more sensitive to experiencing negative affect, relative to non-sleep deprived individuals (Minkel et al., 2012; Zohar et al., 2005). These findings may indicate that loss of sleep interacts with cognitive control functions, such that the threshold for experiencing psychological distress is lowered after sleep

deprivation (Minkel et al., 2012). In order to explore these relationships further, there is therefore a need for studies investigating both cognitive control function and affect after partial sleep deprivation in the same study.

### 1.6.2 *Sleep, neurocognitive performance and psychological distress after mild TBI*

Sleep-wake disturbances and mild TBI is by themselves associated with neurocognitive and psychological problems (Cassidy et al., 2014; Krause et al., 2017; Van Someren, 2020). It is therefore difficult to establish whether the problems associated with sleep-wake disturbances after mild TBI (Kalmbach et al., 2018; Theadom et al., 2015) are better explained by the sleep-wake disturbances by themselves, or by potential interactions between the mild TBI and the sleep-wake disturbances.

Animal studies have indicated a link between normal sleep and good recovery and outcome after TBI (Wickwire et al., 2016). For example, one animal study showed that sleep disruption after TBI was associated with an exacerbation and prolongation of neuroinflammation (Tapp et al., 2020). It is therefore possible that individuals experiencing poor sleep quality after mild TBI are deprived of the beneficial effects of sleep. Indeed, prior studies have indicated that there is an association between poor sleep quality and worse neurocognitive performance and psychological distress after mild TBI (Dean & Sterr, 2013; Kalmbach et al., 2018; Landry-Roy et al., 2018; Theadom et al., 2015, 2016). Particularly neurocognitive tests requiring continuous performance and both fast and accurate responses seems sensitive to the effects of mild TBI and poor sleep quality (Dean & Sterr, 2013). However, there are generally few studies investigating neurocognitive and psychological consequences of poor sleep quality both early (Ludwig, D'Silva, et al., 2020) and in the longer term after mild TBI (Ludwig, Nelson, et al., 2020). A general lack of relevant control groups in prior studies have precluded clear conclusions regarding the combined effect of mild TBI and poor sleep quality. Including a control group with orthopedic injuries allow for a control of general injury related factors, such that factors specific to the mild TBI may be explored (Ludwig, D'Silva, et al., 2020). There is therefore a need for controlled longitudinal studies investigating the consequences of having sleep-wake disturbances after mild TBI as compared to relevant control groups.

# 2 Aim of the thesis

The overall goal of this thesis was to evaluate the clinical course of sleep-wake disturbances after mild TBI and to investigate the neurocognitive and psychological consequences of sleep-wake disturbances after mild TBI as compared to patients with orthopedic injury and individuals without any injury. This goal was operationalized in three papers:

## 2.1 Paper I

To evaluate the clinical course of sleep-wake disturbances after mild TBI we investigated the prevalence and stability of sleep-wake disturbances and fatigue after mild TBI compared to trauma controls with orthopedic injury and community controls without any injury. We also aimed to evaluate the overlap between different sleep-wake disturbances and fatigue. Finally, in order to explore the potential brain injury specific mechanisms, we investigated the impact of intracranial findings on CT or MRI on sleep-wake disturbances and fatigue after mild TBI.

## 2.2 Paper II

In the second paper we investigated the effect of sleeping less than two hours than normal on neurocognitive performance and psychological functioning in healthy young adults. In this way, we were able to explore the short-term consequences of relatively mild to moderate and abrupt changes to the sleep, which may further elucidate how sleep-wake disturbances may influence neurocognitive and psychological health also after mild TBI. The study was designed such that participants' sleep could be observed in their naturalistic home environment. The protocol for sleep deprivation was also individually adjusted.

## 2.3 Paper III

In the final paper we further investigated the impact of poor sleep quality on neurocognitive and psychological functioning after mild TBI. Poor sleep quality may be particularly detrimental to long-term outcome after mild TBI, relative to individuals without mild TBI. We therefore investigated whether poor sleep quality had a greater negative impact on neurocognitive and psychological health for patients with mild TBI than patients with orthopedic injury.

# 3 Methods

The present thesis is made up of three studies. The first paper and third paper capitalized on the Trondheim MTBI follow-up study, and paper II was based on the sleep, individual differences and cognitive functioning (SLEEPIC) study.

## 3.1 Study designs

### 3.1.1 *Paper I and III*

The Trondheim MTBI-follow up study is a prospective longitudinal cohort study. Three groups (cohorts) were included in the study; one group of patients with mild TBI, one trauma control group with orthopedic injuries and one community control group.

### 3.1.2 *Paper II*

The SLEEPIC study was conducted with a within group multiple-baseline experimental design. The study group consisted of healthy young adults.

## 3.2 Study populations

### 3.2.1 *The Trondheim MTBI follow-up study (Paper I and III)*

In the Trondheim MTBI follow-up study, patients with mTBI (age 16-60) were prospectively recruited from the Trondheim municipal emergency clinic (outpatients) and from the trauma center at St.Olavs Hospital. These two emergency departments have a main catchment area of 230 000 inhabitants in Trondheim and surrounding regions. Patients with orthopedic injuries were recruited as trauma controls from the same two emergency departments as patients with mild TBI. The community control group was required within the same catchment area as patients with mTBI and trauma controls. Both control groups were matched to patients with mild TBI in terms of age and sex. The community control group was also matched to the patients with mTBI in terms of years of completed education.

### 3.2.2 *Sleep, individual differences and cognitive functioning (SLEEPIC) (Paper II)*

In the SLEEPIC study young adults (age 18-35) were recruited in a convenience sampling procedure using ads at the university campus, lectures and in social media.

## 3.3 Recruitment and participants

### 3.3.1 *Inclusion of participants in the Trondheim MTBI-follow-up study (Paper I and III)*

Patients with mild TBI were recruited between April 2014 and December 2015. The patients with mild TBI were included if they had sustained a mild TBI according to the WHO criteria (Carroll et al., 2004) and were between 16 and 60 years of age. According to the TBI definition (Menon et al., 2010), patients were evaluated for inclusion if they had sustained a physical trauma to the head or high energy trauma that resulted in either witnessed loss of consciousness (LOC), pre-injury or post injury amnesia (PTA) and/or traumatic lesions visible on CT. For the TBI to be categorized as mild the patients needed to have a LOC < 30 minutes, a PTA <24 hours and a GCS score 13-15 at presentation to the emergency department (Carroll et al., 2004).

The exclusion criteria for the Trondheim MTBI-follow-up study was as follows: I) Non-fluency in Norwegian, II) any severe somatic or neurologic condition prior to injury, III) any prior moderate, severe or complicated mild TBI, IV) any prior psychiatric disorders or substance abuse that could complicate follow-up.

Community controls were recruited between April 2014 and December 2015 and trauma controls were recruited between April 2015 and December 2017. Community controls were recruited from students and employees at the university hospital as well as from friends and family of employees and patients. Trauma controls were included if they had sustained an orthopedic injury and did not have any evidence for head or neck injury, injury to their dominant upper extremity or polytrauma. We applied the same exclusion criteria for the control groups as for patients with mTBI, with the additional criteria that the community controls did not receive ongoing treatment for a psychiatric disorder.

The recruitment of patients with mild TBI and control participants were distributed evenly throughout the year. In Trondheim, Norway the sunrise varies between 10.00 am in December to 03.00 am in June, the sunset varies between 02.30 pm in December and 11.30 pm in June.

### 3.3.2 *Inclusion of participants in the SLEEPIC study (Paper II)*

Participants for the SLEEPIC study were included in groups of 3-15 at a time. They were included in March, April or May 2017 or in February or March 2018 when sunrise varied from 04.58 am to 06.54 am and sunset varied from 06.04 pm to 09.34 pm.

We applied the following exclusion criteria: Any psychiatric, neurological or medical condition.

## 3.4 Data collection in the Trondheim MTBI-follow-up study (Paper I and III)

Data in the Trondheim MTBI-follow-up study were collected at four time points: within 72 hours of injury, at 2 weeks, at 3 months and at 12 months after injury. Within 72 hours of injury the participants completed MRI and a structural interview. At 2 weeks and 3 months after injury the participants completed questionnaires, a structural interview and neurocognitive testing. Finally, at 12 months, the participants completed questionnaires and structural interviews. A subgroup of the patients answered interviews and questionnaires, but did not participate in the part of the study including MRI and cognitive testing. The participants were allocated to this subgroup if they were not eligible for MRI, if MRI was not available within 72 hours of injury or if they merely preferred this simplified participation (e.g. for those not living in close proximity to the hospital).

### 3.4.1 *Structural interview*

The baseline interview performed within 72 hours of injury included questions about demographic information, prior illness or injuries and questions about the injury itself (e.g. GCS score, PTA and LOC). Subsequent interviews were performed in person for those meeting at the hospital for cognitive testing and MRI, and over telephone for those not meeting in person at the hospital.

Poor sleep quality was assessed in the structural interview within 72 hours (retrospectively assessed poor sleep quality the 2 weeks prior to the injury), at 2 weeks, 3 months and 12 months after injury. The assessment consisted of three selected items from the Insomnia Severity Index (Bastien et al., 2001). These three items mirrors the key criteria for insomnia disorder in the DSM-5, namely trouble falling asleep, trouble

staying asleep and trouble with early morning awakenings (**Figure 2**) (American Psychiatric Association, 2013). The participants were asked to rate how much of a problem these three items had been in the last two weeks on a five-point Likert-scale, ranging from 0 – no problem to 4 – very severe problem.

Patients with mild TBI and trauma controls answered these questions at all time points whereas community controls were asked about poor sleep quality only at the first meeting at the hospital. In paper I the participants were categorized into having poor sleep quality if they rated at least a 3 – severe problems on either of the three items. In paper III we combined these items into a total score. Higher scores indicated worse problems with poor sleep quality.

In the interviews at 2 weeks and 3 months after injury, patients with mild TBI and trauma controls were asked if they had experienced any increased sleep need after the injury (yes/no). They were also asked for how many hours they usually slept a day (24 hours) before their injury. Those who experienced increased sleep need were further asked for how many days they experienced increased sleep need, and for how many hours a day (24 hours) they slept in this period. In paper I, we categorized the participants who experienced increased sleep need *and* who slept more than one hour longer than before their injury as having increased sleep need. This categorization reflect the criteria for pleiosomnia in TBI (Imbach et al., 2015; Sommerauer et al., 2013)

### 3.4.2 *Questionnaires*

Questionnaires were assessed 2 weeks, 3 months and 12 months after injury. In paper I we used the Epworth Sleepiness Scale (ESS) (Johns, 1991) to measure levels of excessive daytime sleepiness and the Fatigue Severity Scale (FSS) (Krupp et al., 1989) to measure levels of fatigue. In the ESS we categorized the participants into having excessive daytime sleepiness if they had a ESS total score equal to or greater than 13 (Aurora et al., 2011). In the FSS we categorized the participants into having fatigue if they had a FSS total mean score equal to or greater than 5 (Lerdal et al., 2005).

In paper III we used the Brief Symptom Inventory-18 (BSI-18) to measure levels of psychological distress (Derogatis, 2000). The BSI-18 consist of questions assessing symptoms of depression, anxiety and somatization and is a shorter version of the Brief Symptom Inventory which is a shorter version of the Symptom Checklist 90 Revised. The items in the BSI-18 can be combined into a general severity index measuring general psychological distress. A higher general severity index score indicate higher levels of psychological distress.

### 3.4.3 *Neuroimaging*

Patients presenting to the emergency departments are routinely scheduled for non-contrast head CT scans as a part of the initial clinical assessment. The CT-examination at the emergency departments in Trondheim are performed on a Siemens Somatom Sensation 64-row scanner. MRI was performed within 72 hours of injury on a 3 Tesla Siemens Skyra System (32-channel head coil) with the following sequences 3D, T1, T2, Fluid-Attenuated Inversion Recovery (FLAIR), Susceptibility Weighted Imaging (SWI) and Diffusion Weighted Imaging (DWI). An experienced radiologist inspected both the CT and MRI scans (Einarsen et al., 2019).

### 3.4.4 *Neurocognitive testing*

The neurocognitive test battery in the Trondheim MTBI follow-up study is comprehensive and includes the computerized test battery Cambridge Neuropsychological Test Automated Battery (CANTAB) and the following paper and pencil tests: Verbal fluency, Rey Auditory Verbal Learning Test, Trail Making Test A and B and the Coding and Symbols subtests from the Wechsler Adult Intelligence Scale-Fourth Edition. At the first visit (2 weeks after injury) the participants also completed the vocabulary and matrices subtest from the Wechsler Abbreviated Scale of Intelligence. The full neurocognitive test battery took approximately 2.5 hours at the first visit and 2 hours at the second visit.

Our primary focus in paper III was to investigate response speed (measured in milliseconds) and accuracy (measured in number of errors), we therefore selected tests from the CANTAB where the participants were instructed to react as fast and accurate as possible. The following subtests from the CANTAB were selected: Reaction time

(RTI), rapid visual information processing (RVP) and the attention switching task (AST). In addition to requiring fast and accurate responses, these tests lasts for several minutes and requires the utilization of cognitive control resources to maintain attention over time.

The outcome measures simple reaction time and five choice reaction time from the RTI test, reaction latency from the RVP test and reaction latency from the AST were used as measures of response speed. The outcome measures number of false alarms and number of misses on the RVP test and commission errors, omission errors and incorrect responses were used as measures of response accuracy.

First, we used a log-transform on each raw score because the raw scores were positively skewed and not normally distributed. We transformed each outcome measure into Z-scores with the formula $z= (x – \mu)/\sigma$, where x is each of the outcome measures, $\mu$ is the mean score for each outcome measure across the two time points for the whole sample (patients with mild TBI and trauma controls with cognitive testing), and $\sigma$ is the standard deviation across the two time points of the whole sample. We created one response speed composite score by averaging the response speed Z-scores and one response accuracy composite score by averaging the response accuracy Z-scores. Higher speed Z-score indicated longer (slower) responses, and higher accuracy Z-scores indicated a higher amount of errors (less accurate responses).

### 3.5 Data collection in the SLEEPIC study (Paper II)

In the SLEEPIC study the participants were asked to meet at the university at five times. The day of the meeting was the same weekday for each participant. After the first baseline meeting (visit 1, Monday) the participants met at day 4 (visit 2, Thursday), at day 7 (visit 3, Monday), at day 8 (visit 4 Tuesday) and at day 11 (visit 5, Thursday). All tests were in the morning at 9 am +/- 90 minutes. The participants were asked to not consume any caffeinated substances prior to testing.

At visit 7 the participants mean total sleep time was calculated based on the sleep data collected in the first week of the study (habitual sleep period). The participants were asked to sleep 2 hours less than their mean total sleep time for the remaining three

nights in the study period (sleep deprivation period). At each visit the participants completed questionnaires and a cognitive test.

### 3.5.1 *Sleep measures*

Total sleep time in the habitual sleep period and the sleep deprived period was assessed with actigraphy and sleep diaries.

All participants were asked to wear actiwatch (Actiwatch Spectrum Pro) around their wrist on their non-dominant hand for 11 consecutive days 24 hours a day. The actiwatch contains a piezoelectric accelerometer that record the intensity, duration and amount of movement in all directions. The Actiwatch Spectrum Pro also contains illuminance markers, an event marker and a display showing the time of day. The built-in algorithm in the software (Philips Actiware 6.0.0) was used for the actigraphy analyses to assess total sleep time, sleep efficiency, bed time and time of awakening based on the activity of the participant. The 24-hour activity in the habitual and sleep deprived period of each participant was inspected in an actogram (a visual display of the activity in the Actiware software). The participants sleep windows were systematically cross checked with the sleep diary data, illuminance markers and event markers in accordance with prior research (Grønli et al., 2017; Solheim et al., 2018). The scheduled sleep time during the sleep deprived period was calculated on site during visit 7 when the participants completed their cognitive testing and questionnaires. Based on this calculation the participants were asked to go to bed two hours later than in their habitual sleep period, for the remaining three nights of the study period.

The participants were also asked to complete sleep diaries every day of the habitual and sleep deprived period. In the sleep diary (Carney et al., 2012) the participants were instructed to write down the time they went to bed, fell asleep, awakened and got out of bed in addition to the number and duration of awakenings during the night and their overall sleep quality. These data were used to calculate the participants subjective sleep efficiency and sleep duration. The participants were also asked to write down the number and duration of naps during the day, dosage and units of sleep medicine and alcohol.

### 3.5.2 *Baseline questionnaire*

At the first meeting the participants completed a comprehensive baseline questionnaire assessing demographic information, sleep, psychological functioning, cognitive functioning and personality traits. The insomnia severity index (Bastien et al., 2001) and the Pittsburgh sleep quality index (Buysse et al., 1989) was used to assess symptoms of insomnia (i.e. poor sleep quality). The Diurnal Scale (Torsvall & Åkerstedt, 1980) was used to assess morningness/eveningness. The Hospital Anxiety and Depression Scale (HADS) (Crawford et al., 2001) was used to assess symptoms of anxiety and depression. The Fatigue Severity Scale (Krupp et al., 1989) was used to assess levels of fatigue.

### 3.5.3 *Follow-up questionnaire*

At each of the five visits the participants completed the Positive and Negative Affect Schedule (PANAS) (Watson et al., 1988). The PANAS assesses self-reported positive and negative affect on 20 item scale. 10 of the items assesses positive affect and 10 assesses negative affect. Positive affect items can be combined into a positive affect total score, and negative affect items can be combined into a negative affect total score. Higher scores indicate higher levels of positive/negative affect.

### 3.5.4 *Cognitive testing*

The Conners´ Continuous performance test -3 (CCPT-3) (Conners et al., 2003) was used to assess performance based cognitive control function at each of the five visits. In the CCPT-3 the participants are instructed to press the space bar on the computer when the letters A-Z appears on the screen, but they are instructed to withhold their response when the letter X appears. There are 360 trials and the letters are presented in a pseudo-random fashion and the test last for 14 minutes. The participants were instructed to respond as fast and accurate as possible. The test requires cognitive control in order to maintain attention to react fast and accurate over time. We used the outcome measures hit reaction time, commission errors and omission errors as measures of speed and accuracy.

Immediately after the test the participants were asked how much exertion they felt they put into the test and how well they felt they performed on a 10-point Likert scale from 0 – no exertion/bad performance to 10 – very much exertion/very good performance).

## 3.6 Statistical analyses

### 3.6.1 *Paper I*

In Paper I we used chi-square tests, independent samples t-tests, Mann-Whitney U tests and Kruskal-Wallis tests to investigate whether there were any statistically significant differences between patients with mild TBI, community controls and trauma controls in age, sex, length of education and other key demographic variables. We also used chi-square tests and independent samples t-test to investigate whether there were any statistically significant differences on demographic variables between participants with missing data and those with complete data.

We used linear mixed logistic regression models to investigate whether patients with mTBI had significantly higher prevalence of increased sleep need, poor sleep quality, excessive daytime sleepiness and fatigue compared to the trauma control group and the community control group. The models included the fixed factors time, group, age, sex and prior psychiatric disorders and a random intercept on a logit-scale. We also included and examined the interactions between group and time, and between prior psychiatric disorders and group. Community controls did not have available data for all outcome measures at all time points. We therefore performed separate linear mixed logistic regression models and a logistic regression model including time points were community controls had available data. These models included the same dependent and independent variables as the first logistic regression models.

In order to investigate whether patients with complicated mild TBI (intracranial findings on CT or MRI) had higher prevalence of increased sleep need, poor sleep quality, excessive daytime sleepiness and fatigue compared to patients with uncomplicated mild TBI and trauma controls. These models also included the fixed factors time, group, age, sex, prior psychiatric disorders and the interaction between group and time.

We investigated the overlap between the different sleep-wake disturbance and fatigue problems with a frequency count that were visualized with overlap-figures for each time point.

For all analyses we set an alpha level of 0.05. A 95% interval is described for all Confidence Intervals (CI). Data handling and preliminary analyses were performed in SPSS (version 25). All linear mixed logistic and logistic regression models were performed in STATA (version 15).

### 3.6.2 *Paper II*

In paper II we used paired samples t-test to investigate differences in sleep measures measured with actigraphy and the sleep diary as well as differences in sleep measures in the habitual sleep period compared to the sleep deprived period.

We performed three repeated measures analysis of variance (rmANOVA). Hit reaction time, commission errors and omission errors from the CCPT-3 were included as measures of cognitive function in the first model. Our questions about exertion and performance after the CCPT-3 were included as self-reported measures in the second model. Positive and negative affect from the PANAS were included as measures of affect in the third model. The first model was run as a 3×5 rmANOVA with cognitive function as the dependent variable and time (the five visits) as a fixed factor. In the second model, we performed a a 2×5 rmANOVA with self-reported measures as the dependent variable and time as a fixed factor. In the third model we performed a 2×5 rmANOVA with affect as the dependent variable and time as a fixed factor.

The assumption of sphericity in the rmAVONAs were investigated with Mauchley's test. For models for which the assumption was violated we used the Greenhouse–Geisser (ε) method to correct the F test (Greenhouse & Geisser, 1959).

For all analyses we set an alpha level of 0.05. A 95% interval is described for all CIs. The analyses were performed in SPSS (version 25).

### 3.6.3 *Paper III*

As in paper I, we used chi-square tests, independent samples t-tests to investigate whether there were any differences between patients with mTBI and trauma controls on key demographic variables, as well as to investigate differences between participants with and without missing data.

In order to investigate whether poor sleep quality had a significantly stronger negative effect on cognitive performance and psychological distress we performed three linear mixed models: a) one model with response speed as the dependent variable, b) one model with response accuracy as the dependent variable and c) one model with psychological distress as the dependent variable. Age, sex, group and time were included as fixed factors in all three models. The model also included a random intercept in order to account for within subject dependencies. To test out main hypothesis that poor sleep quality had a significantly stronger effect on cognitive and emotional functioning we included the three-way interaction poor sleep quality×group×time and the two-way interaction poor sleep quality×group. In order to explore whether there were any differences in the dependent variables over time between the groups we included and examined the interaction between group and time. In order to investigate whether the poor sleep quality had a statistically significant effect between the two time points, we included and examined the interaction between poor sleep quality and time.

We used an alpha level of 0.05 as a cut-off for statistical significance. A 95% interval is described for all Cis. All analyses were performed in STATA (version 16).

## Ethics

In both the MTBI-follow up study and the SLEEPIC study all participants 18-60 years of age gave informed written consent. In the Trondheim MTBI-follow up study parents of participants in the age 16-17 gave informed written consent. Both studies were approved by the Regional Committee for Research Ethics in Norway (REK 2013/754 and REK 2017/85) and performed in accordance with the Helsinki declaration.

# 4 Results

## 4.1 Included participants in the Trondheim MTBI follow-up study

In the Trondheim MTBI follow-up study, we included 378 patients with mild TBI, 82 trauma controls and 83 community controls (**Figure 3**).

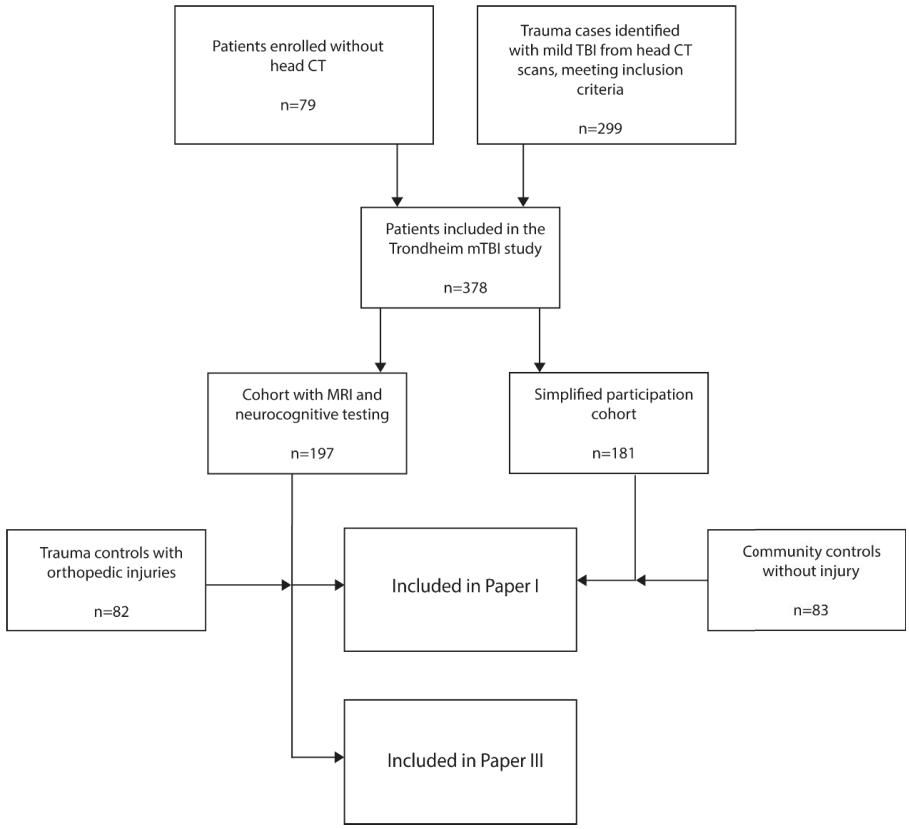


***Figure 3: Flow-chart of inclusion in Paper I and III***

## 4.2 Paper I

Of the patients with mild TBI in paper I were 65.3% male, the mean age was 31.2 years and the mean length of education was 13.6. We observed no statistically significant differences in age, sex and length of education between patients with mild TBI and the two control groups. Additionally, we observed no significant differences between

patients with mild TBI and the trauma control group on total sleep time and occupational status before injury or on pain levels and return to work after injury. Patients with mild TBI were most often injured due to falls (35.7%), violence (17.2%) and bicycle accidents (15.3%) whereas the trauma controls were most often injured due to sports accidents (36.6%), falls (31.7%) and other injuries including sharp injuries such as cuts (11.0%). Among the patients with mild TBI who had brain imaging after injury (n=332), 9% had intracranial lesions on MRI or CT, indicating a complicated mild TBI. Participants with missing data did not seem to differ significantly from participants with complete data on key demographic variables, we concluded that the data was missing at random (Enders, 2017).

Our main results in paper I showed that patients with mild TBI had a significantly higher prevalence of increased sleep need (OR: 4.7, CI: 1.7-12.8, p=0.002), poor sleep quality (OR: 2.96, CI: 1.1-8.1, p=0.034), excessive daytime sleepiness (OR: 4.26, CI: 1.01-18.07, p=0.049) and fatigue (OR: 7.4, CI: 2.1-26.1, p=0.002) compared with trauma controls. Compared to community controls, patients with mild TBI also had significantly higher levels of poor sleep quality (OR: 7.3, CI: 17-38.8, p=0.007) and fatigue (OR: 7.2, CI: 1.9-27.4, p=0.004), but not excessive daytime sleepiness (OR: 2.5, CI: 0.6-9.9, p=0.205). The prevalence of the sleep-wake disturbances and fatigue decreased over time. The reduction was statistically significant for increased sleep need from 2 weeks to 3 months after injury (OR: 0.22, CI: 0.12-0.40, p<0.001), and for fatigue between 2 weeks and 12 months after injury (OR:0.45, CI: 0.23-0.88, p=0.020). Patients with mild TBI had significantly higher levels of sleep-wake disturbances and fatigue early after injury compared to trauma controls, this group difference continued throughout the first year after injury. Approximately half (53%) of the patients with mild TBI who had at least one sleep-wake disturbance or fatigue after injury had problems that lasted longer than 3 months (i.e. stable symptoms), whereas 35% of the trauma controls had stable problems lasing longer than 3 months.

We also observed that patients with complicated mild TBI had higher levels of fatigue compared to patients with uncomplicated mild TBI (OR: 3.6, CI: 1.0-12.3, p=0.045) and trauma controls (OR: 22.8. CI:4.2-124.2, p<0.001). Patients with complicated mild TBI had significantly higher levels of increased sleep need compared to trauma controls

(OR:7.2, CI:1.9-27.4, p=0.004), but not compared to patients with uncomplicated mild TBI. We observed no significant differences between patients with complicated mild TBI and trauma controls with regards to poor sleep quality and excessive daytime sleepiness. Patients with uncomplicated mild TBI had significantly higher prevalence of all sleep-wake disturbances and fatigue compared to the trauma controls.

We observed a limited overlap between increased sleep need, poor sleep quality, excessive daytime sleepiness and fatigue across the three time points in the study. For the patients with mild TBI who reported sleep-wake disturbances and fatigue it was more common to experience one sleep wake disturbance or fatigue, rather than having more than one problem at each time point. The percentage of the patients with mild TBI reporting symptoms who reported only one sleep wake disturbances or fatigue, increased over time: from 61% at 2 weeks, to 75% at 3 months and 79% at 12 months.

### 4.3 Paper II

In the SLEEPIC study we included a total of 52 individuals. The majority of these were female (78.8%) with a mean age of 22.57 years. When compared to similar age groups in the general population in the UK and US (Crawford et al., 2001; Taylor et al., 2013), our sample seemed to consist of relatively healthy individuals with low baseline levels of anxiety (mean=5.56 on the HADS), depression (mean=2.82 on the HADS), fatigue (mean=3.9 on the FSS), symptoms of insomnia (mean=5.77 on the ISI) and an overall good sleep quality (mean=3.25 on the PSQI).

In the rmANOVAs the assumption of sphericity was violated for commission errors, omission errors, self-reported exertion and negative affect. The F-test was therefore corrected with the Greenhouse-Geisser method for these variables.

In our first model we observed a significant main effect of cognitive function ($F$ (1, 61) = 28.35, $p < .001$, $\eta p^2 = .376$.). This effect was driven by a significant effect of Hit reaction time ($F$ (4, 188) = 10.05, $p < .001$, $\eta p^2 = .18$) and commission errors, ($F$ (3, 152) = 7.12, $p < .001$, $\eta p^2 = .13$.), but we observed no significant effect of omission errors. Hit reaction time decreased linear throughout the five visits in the study. Commission errors seemed to have a quadratic change between the visits in the study,

this means that the number of commission errors first decreased, but increased again after visit 3 when the participants were sleep deprived. We observed a significant interaction effect between Hit reaction time and commission errors.

Additionally, we observed significant linear interactions between hit reaction time and commission errors ($F$ (1, 47) = 13.52, $p$ = .001, $\eta p^2$ = .221), and hit reaction time and omission errors ($F$ (1, 47) = 5.69, $p$ = .021, $\eta p^2$ = .108). This means that as the reaction time decreases throughout the visits in the study, the number of errors increases, such that the relative difference between hit reaction time and the number of errors was largest after three nights of partial sleep deprivation (**Figure 4**).

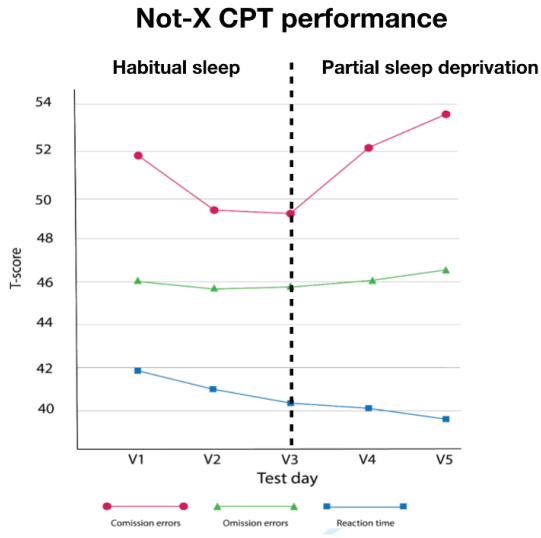


***Figure 4 (Paper II): Speed and accuracy measures on the CCPT-3****: Hit reaction time (blue line) decreased linearly from visit 1 to visit 5. Before partial sleep deprivation the number of commission errors (red line) decreased, but after partial sleep deprivation the number of commission errors increased. After three nights of partial sleep deprivation (visit 5) we observed the largest relative difference between hit reaction time and number of errors.*

In our second model, we observed a significant main effect of self-reported measures ($F$ (1, 47) = 45.05, $p$ < .001, $\eta p^2$ = .489). This effect was driven by a linear decrease in self-reported performance ($F$ (4, 188) = 7.08, $p$ < .001, $\eta p^2$ = .131) and a quadratic change in exertion ($F$ (3, 135) = 3.79, $p$ = .013, $\eta p^2$ = .075). We observed a significant quadratic

interaction between self-reported performance and exertion ($F$ (1, 47) = 23.71, $p$ < .001,$\eta p^2$ = .335). This means that, before partial sleep deprivation, from visit 1 to visit 3 the participants reported a decrease in exertion, but an increase in performance. However, in the sleep deprived period, between visit 3 and 5, the participants reported an increase in exertion, but a decrease in performance.

In our third model, we observed a significant main effect of affect ($F$ (1, 48) = 122.99, $p$ < .001, $\eta p^2$ = .719), this effect was driven by a linear decrease in positive affect across the visits in the study ($F$ (4, 192) = 26.37, $p$ < .001, $\eta p^2$ = .355), but we observed no significant change in negative affect across the visits in the study. We observed a significant interaction effect between positive and negative affect ($F$ (1, 48) = 52.70, $p$ < .001, $\eta p^2$ = .523). This means that positive affect decreased linearly from visit 1 to visit 5, relative to negative affect.

### 4.4 Paper III

In the Trondheim MTBI-follow-up study, 197 patients with mild TBI and all the 82 trauma controls were scheduled for neuropsychological testing and included in the study sample in Paper III. We observed no significant differences in key demographic variables between the two groups or between those with and without neuropsychological testing. A total of 164 patients with mild TBI had complete neuropsychological data at 2 weeks and 3 months, whereas 182 patients with mild TBI had complete neuropsychological data at 2 weeks or 3 months. A total of 75 trauma control had complete neuropsychological data at 2 weeks and 3 months, whereas 79 trauma controls had complete neuropsychological data at 2 weeks or 3 months. Of the participants scheduled for neuropsychological testing, 15 patients with mild TBI and 3 trauma controls did not complete either the 2 week testing or the 3 month testing.

In paper III we showed that poor sleep quality had a significantly stronger negative effect on response speed (b=-0.050, CI: -0.095 to -0.005, p=0.028) and psychological distress (b=-0.843, CI: -1.336 to -0.350, p=0.001), but not response accuracy for patients with mild TBI relative to the trauma controls. This effect was independent of time. Poorer sleep quality was associated with an increase in response speed (slower responses) (b=0.055, CI: 0.029 to 0.081, p<0.001) less accurate responses (more errors)

(b=0.036, CI: 0.013 to 0.058, p=0.002) and higher levels of psychological distress (b=1.138, CI: 0.897 to 1.379, p<0.001) for patients with mild TBI. For trauma controls poorer sleep quality was associated with less accurate responses (more errors) (b=0.040, 95% CI: 0.005 to 0.075, p=0.025), but we observed no statistically significant association between poor sleep quality and response speed or psychological distress for the trauma controls.

# 5 Discussion

The results in in the present thesis showed that sleep-wake disturbances were more common and persistent after mild TBI, relative to control groups and that even small changes to sleep was associated with specific alterations in neurocognitive and psychological functioning. There are three specifically important implications of the findings in the present thesis. First, the results indicate that a mild TBI is associated with a heightened prevalence and stability of sleep-wake disturbances. Second, a partial sleep deprivation of 2 hours in healthy individuals was associated with poorer neurocognitive function and decreased positive affect. This indicates that sleep-wake disturbances may have significant short-term consequences. Finally, we evaluated the consequences of having poor sleep quality after mild TBI relative to other types of injuries, not involving the head. This investigation showed that poorer sleep quality was associated with greater negative consequences for neurocognitive and psychological health after mild TBI than after orthopedic injury. Taken together, the findings in the present thesis confirms that sleep-wake disturbances are commonly persistent problems after mild TBI and that such problems may have both transient and long-lasting consequences for neurocognitive and psychological health after injury. From the results in the present thesis it is clear that sleep-wake disturbances require increased attention from scientists and health professionals, particularly after mild TBI.

## 5.1 The clinical course of sleep-wake disturbances following mild TBI

One of the main aims of this PhD project was to increase the understanding of the natural clinical course of sleep-wake disturbances after mild TBI. This has been raised as one of six domains that requires increased understanding in mild TBI and sleep research (Wickwire et al., 2018). In paper I we showed that increased sleep need, poor sleep quality, excessive daytime sleepiness and fatigue was significantly more prevalent and persistent after mild TBI compared to after orthopedic injury and community controls. Patients with mild TBI reported a higher prevalence of these problems early after injury relative to the control groups. The prevalence of the sleep-wake disturbances decreased between 2 weeks and 3 months after injury for both trauma groups. Between 3 months and 12 months the prevalence of the sleep-wake disturbances seemed to stabilize. The group differences between patients with mild TBI and the

control groups remained similar across time. The trauma controls returned to pre-injury levels of sleep-wake disturbances and had a similar prevalence of sleep-wake disturbances as the community controls by 3 months after injury. Patients with mild TBI, on the other hand, had persistent heightened prevalence of sleep-wake disturbances also 12 months after injury, relative to both control groups. Many of the patients with mild TBI recovered from their sleep-wake disturbance, but a substantial proportion had sleep-wake disturbances that lasted 3 months or longer. Our findings therefore indicate that sleep-wake disturbances are more common and persistent problems after mild TBI than after orthopedic injuries and in the general community.

The different sleep-wake disturbances and fatigue presented in paper I, seemed to have a similar clinical course over time, but our results also indicated that different sleep-wake disturbances affected different individuals after mild TBI. We showed that it was more common to experience *one* sleep-wake disturbance or fatigue (e.g. poor sleep quality, but not increased sleep need), rather than experiencing more than one sleep-wake disturbance at the same time. These findings further consolidate the prior findings that sleep-wake disturbances can have varied manifestations after mild TBI in the form of different sleep phenotypes or sleep profiles (Raikes et al., 2019; Sandsmark et al., 2017).

The limited overlap between the different sleep-wake disturbances in Paper I was accompanied with a relatively high prevalence of having at least one sleep-wake disturbances or fatigue at the different time points after injury. In total 36% (n=136) of the patients with mild TBI had at least one sleep-wake disturbance or fatigue 2 weeks after injury. Around half of these patients (55%) had stable symptoms lasting more than 3 months. Compared to prior studies (Norrie et al., 2010; Theadom et al., 2015) we applied relatively strict cut-off levels for having a sleep-wake disturbance or fatigue in paper I. Clinically significant sleep-wake disturbances that lasts longer than 3 months reflect the diagnostic criteria for insomnia and hypersomnoloence disorder (American Psychiatric Association, 2013). Our findings therefore extends the findings in a prior meta-analysis (J. Mathias & Alvaro, 2012), by indicating that a substantial number of patients also with *mild* TBI may experience sleep-wake disturbances that could meet the criteria for a diagnosable sleep-wake disorder. Still, there are important diagnostic

criteria that we did not assess in paper I (**Figure 2**), it is therefore not possible to directly conclude that the patients with mild TBI have developed a sleep-wake disorder after injury. It is also important to note that 45% of the patients with sleep-wake disturbances at 2 weeks after injury seemed to recover from their problems. In future studies, it is therefore important to investigate the early risk factors for prolonged sleep-wake disturbances after mild TBI, but also to investigate protective factors associated with recovery.

Taken together, the findings in paper I support the hypothesis that there is an association between a mild TBI and the development of acute, subacute and long-term sleep-wake disturbances.

## 5.2 Consequences of sleep-wake disturbances

After establishing that sleep-wake disturbances were common and persistent problems after mild TBI, we sought to elucidate some of the consequences of such problems in paper II and III. Specifically, we investigated the neurocognitive and psychological consequences that are associated with sleep loss in healthy individuals in paper II and poor sleep quality in patients with mild TBI as compared to patients with orthopedic injury in paper III.

Our findings in paper I indicate that mild TBI may be associated with rather abrupt changes in the sleep-wake cycle. One way of exploring such abrupt changes is by experimentally manipulating sleep and observing the consequences (Van Someren et al., 2015). To delineate how sleep changes in itself interferes with neurocognitive performance and psychological health we explored the consequences of mild to moderate partial sleep deprivation in healthy individuals in paper II.

### 5.2.1 *Sleep, cognitive control and psychological function after partial sleep deprivation*

In paper II we showed that sleeping 1.5 to 2 hours less than normal was associated with poorer neurocognitive performance on a test of continuous performance (CCPT-3) and reduced positive affect in healthy young individuals. These findings show that even subtle manipulations of sleep are associated with poorer cognitive control functions and psychological health. Our findings corroborate prior studies showing marked effects of total and partial sleep deprivation on neurocognitive and psychological functioning

(Killgore, 2010; J. Lim & Dinges, 2010; Lowe et al., 2017). Specifically, we showed that partial sleep deprivation was associated with shorter hit reaction times (faster responses), but more errors (lower accuracy) on the CCPT-3.

Faster and less accurate response styles indicate impulsive responses (Conners, 2014). These findings show that after partial sleep deprivation, the participants traded faster responses for less accurate responses, reflecting a more careless response style. This is also supported by the general decrease in positive affect, which indicate more blunted affect after partial sleep deprivation, compared to the habitual sleep period. At the same time, the participants reported that they performed worse on the CCPT-3 after partial sleep deprivation than in the habitual sleep period. Still, the participants reported that they put more exertion (effort) into the test after sleep deprivation, compared to the habitual sleep period. This increase in effort indicate that the participants tried to compensate for the effects of partial sleep deprivation. However, the faster responses were associated with less accurate responses on the CCPT-3 and this may indicate a maladaptive compensation strategy. These findings indicate that the participants were aware of their reduced performance, but were still unable to adaptably compensate for the poorer neurocognitive functioning.

Our findings therefore indicate that relatively mild to moderate changes to sleep have adverse consequences for neurocognitive and psychological health the following day. Specifically, healthy young individuals were more impulsive, tired and reported blunted affect after partial sleep deprivation. These effects were greater after three days of sleep deprivation, than after one night, indicating a dose-dependent relationship. Sleep loss may have further severe consequence for daily life by increasing the risk of traffic and work-related accidents (Powell et al., 2002; Prats-Uribe et al., 2018). Interestingly, our results partially support the hypothesis that sleep loss can interfere with neurocognitive functioning and are therefore likely to increase the risk of sustaining a TBI via an increased accident risk (Wickwire et al., 2016).

### 5.2.2 *Sleep, cognitive control and psychological function after mild TBI*

In paper III we built on the findings in paper II and explored the consequences of sleep-wake disturbances on cognitive control and psychological functioning after mild TBI.

Prior studies have indicated that poor sleep quality after mild TBI is associated with neurocognitive performance and psychological distress after injury (Dean & Sterr, 2013; Kalmbach et al., 2018; Theadom et al., 2015). There is, however, a lack of studies investigating consequences of poor sleep quality, both in the acute stage (Ludwig, D'Silva, et al., 2020) and the chronic stage after mild TBI (Ludwig, Nelson, et al., 2020). We aimed to extend these prior findings by comparing the consequences of poor sleep quality in the acute and chronic stage of mild TBI as compared to a control group with orthopedic injuries. Inclusion of a control group allows for a control of pre-injury and general injury related factors, such that mechanisms specific for the mild TBI may be explored (Ludwig, D'Silva, et al., 2020).

Extending our findings in paper II, we showed in paper III that poor sleep quality was associated with greater negative effects on neurocognitive performance and psychological distress after mild TBI, relative to trauma controls. Prior studies have indicated that there is an overlap in the symptoms experienced by patients with mild TBI and by patients with insomnia disorder where both patient groups typically report reduced neurocognitive function, fatigue, behavioral problems and mood disturbances (Cassidy et al., 2014; Van Someren, 2020). Our results in paper III indicate that the combination of a mild TBI and concurrent poor sleep quality may have a combined negative effect for neurocognitive and psychological outcome. Specifically, we showed that poor sleep quality was associated with *slower* response speed, less accurate responses and higher levels of psychological distress for patients with mild TBI. Poor sleep quality was also associated with lower response accuracy for the trauma control group, but poor sleep quality had a stronger negative effect on response speed and levels of psychological distress for patients with mild TBI. These findings show that patients with mild TBI may be particularly vulnerable to the negative effects of poor sleep quality.

### 5.2.3 *Neurocognitive and psychological consequences of partial sleep deprivation vs poor sleep quality*

Our findings in paper II and III indicate that mild to moderate partial sleep deprivation in healthy individuals and poor sleep quality after mild TBI have significant effects on cognitive control function and the ability to sustain attention over time. Prior studies

have shown that there are distinct differences in neurocognitive performance between sleep deprived individuals and patients with insomnia disorder (Van Someren, 2020). Both sleep deprived individuals and patients with insomnia *report* neurocognitive problems. Still, compared to sleep deprived individuals (Krause et al., 2017), patients with insomnia disorder seems to have remarkably intact neurocognitive functions when measured with neurocognitive tests assessing reasoning, short reaction time, short term -, visual- and prospective- memory (Kyle et al., 2017). On rather simple and short reaction time tests, individuals with insomnia symptoms have faster reaction times, compared to normal sleepers (Altena et al., 2008; Kyle et al., 2017). Conversely, some studies show that individuals with insomnia have slower response times, compared to normal sleepers, when response times are measured over several minutes in continuous performance tests where participants are instructed to react as fast and accurate as possible (Altena et al., 2008; Edinger et al., 1997). This is also a common finding in studies of total sleep deprivation (J. Lim & Dinges, 2010). Our findings support these findings by showing that continuous performance tasks requiring both fast and accurate responses are sensitive to the effects of partial sleep deprivation and the combined effect of mild TBI and poor sleep quality.

Both partial sleep deprivation in healthy individuals (paper II) and poor sleep quality in patients with mild TBI (paper III) was associated with psychological health. One important difference between these two studies is that we in paper II investigated both positive and negative affect with the PANAS, whereas in paper III investigated psychological distress with the BSI-18. The PANAS assesses state affect and the participants were asked to rate how they feel 'right now' (Watson et al., 1988). The BSI-18 assesses psychological distress and the participants were asked to rate how their level of distress had been the 'the last seven days' (Derogatis, 2000). These two inventories assess different constructs, our results in paper II and paper III indicate that partial sleep deprivation and poor sleep quality after mild TBI have a significant impact on different aspects of psychological health.

### 5.2.4 *The speed accuracy trade-off*

Our findings in paper II and paper III show that partially sleep deprived healthy individuals and patients with mild TBI and concurrent poor sleep quality displayed

different response styles on neurocognitive tests of continuous performance. Faster responses on continuous performance tests will typically bias an individual towards less accurate responses, whereas an individual who prioritizes more accurate responses typically needs to slow down their response speed (i.e a speed-accuracy tradeoff) (Heitz, 2014).

In this context, it is interesting that partial sleep deprivation was associated with faster and less accurate responses in paper II, whereas mild TBI and poor sleep quality was associated with slower and less accurate responses on continuous performance tests in paper III. In paper II, the participants reported to increase their effort after partial sleep deprivation which may indicate that they tried to compensate for the effects of sleep deprivation by trading accuracy for speed. On the other hand, our results in paper III may indicate that patients with mild TBI and poor sleep quality were unable to recruit the necessary cognitive control functions in order to maintain optimal performance that resulted in slower *and* less accurate responses. Although speculative, the combination of findings in paper II and III indicate a dose-dependent relationship, where relatively mild effects on cognitive control function leads to a speed accuracy trade-off, whereas stronger effects (e.g. a mild TBI *and* poor sleep quality) leads to both slow and inaccurate responses. It is important to point out that there are distinct differences between the two studies in paper II and III (e.g. experimental vs observational, patients with mild TBI vs. healthy volunteers). Therefore, the existence of a dose-dependent relationship of the speed-accuracy trade-off requires further investigation.

### 5.2.5 *Habitual sleep and increased sleep need*

We showed in paper I that some patients with mild TBI have an increased amount of sleep after injury. However, because of work or social demands it may be difficult for individuals with mild TBI to adhere to this new need for longer sleep. This could therefore lead to an, in practice, partial sleep deprivation for these individuals. Prior studies have shown that not only poor sleep quality, but also shorter amounts of sleep is associated with worse long-term outcome after mild TBI (Kalmbach et al., 2018). Our sleep deprivation protocol in paper II differed from prior sleep deprivation studies, providing *individually adjusted* sleep windows. This means that we asked the participants to sleep two hours less than their normal sleep, as opposed to asking them

to sleep a given sleep-window of e.g. 4-5 hours. In this way, we could show that deviating from habitual sleep may have marked consequences for neurocognitive and psychological health. Our findings in paper I suggest that a mild TBI may lead to an increased sleep need (>1 hour longer total sleep time), such that the patients have a longer habitual sleep after injury, relative to before their injury. It may be important to adhere to the increased sleep need in order to ensure optimal recovery after mild TBI, but increased sleep need was assessed only with self-report in paper I. Based on our findings it is not possible to conclude that the increased sleep need have beneficial properties after mild TBI. Still, prior findings suggest that increased sleep need, particularly increased slow-wave sleep (Shekleton et al., 2010; Sommerauer et al., 2013), may play an important role in recovery from mild TBI (Wickwire et al., 2016). Although our studies do not provide direct evidence, it is possible that deviating from the increased sleep need after mild TBI may have marked negative consequences for neurocognitive performance, psychological functioning and impede recovery processes.

We also showed in paper I that a significant amount of the patients with mild TBI recovered from increased sleep need to normal sleep between 2 weeks and 3 months after injury. For some individuals, these changes in habitual sleep may be rather abrupt which can influence long-term sleep-wake pattern. It is for example possible that some individuals still attempt to sleep longer after they have recovered from their increased sleep need. A consequence of this may be that they spend more time in bed without sleeping, which in the long-run can weaken the sleep drive and lead to chronic poor sleep quality (Dietch & Furst, 2020).

Finally, changes to the sleep-wake cycle, and frequent daytime napping can interfere with circadian rhythms (Beaulieu-Bonneau & Morin, 2012). Ultimately, prolonged increased sleep need and excessive daytime sleepiness may therefore increase the risk of developing a circadian rhythm sleep-wake disorder (American Psychiatric Association, 2013). Indeed, prior studies have reported that a TBI is also associated with disrupted circadian rhythms (Grima, Ponsford, St. Hilaire, et al., 2016; Wickwire et al., 2018).

### 5.2.6 *Future perspectives and research area: Neurobiological mechanisms of sleep after mild TBI*

In paper I, we observed a significantly higher prevalence of sleep wake disturbances and fatigue in patients with mild TBI compared to two control groups without injury to the head. In paper III, patients with mild TBI seemed to be more vulnerable to the negative impact of poor sleep quality on neurocognitive and psychological health than trauma controls. These findings indicate that persistent sleep-wake disturbances after mild TBI may be associated with brain injury specific factors. Symptoms after mild TBI may be linked to structural disruptions in brain networks, such as axonal injury (Smith & Stewart, 2020). We did not identify any statistical significant differences in sleep-wake disturbances between patients with complicated mild TBI (intracranial findings on CT or MRI) and patients with uncomplicated mild TBI. These null-findings must be interpreted with caution given that relative few patients had complicated mild TBI compared to uncomplicated mild TBI. The prognostic value of early CT or MRI for long-term outcome is uncertain (Polinder et al., 2018), but it is possible that more sensitive MRI techniques, such as diffusion tensor imaging, may be a better prognostic marker after mild TBI (Smith & Stewart, 2020). Prior studies have linked sleep-wake disturbances to axonal injury after mild TBI (Jang et al., 2016; Raikes et al., 2018; Zhou, 2017), but more studies with larger samples are required in order to clearly conclude on this association. Early identification of individuals at risk of developing long-term problems after mild TBI is important to ensure optimal follow-up. It is possible that such identification is achievable with newer objective biomarkers in the near future (Smith & Stewart, 2020).

One possible explanation for why individuals with mild TBI may be particularly vulnerable to the consequences of poor sleep quality for neurocognitive and psychological functioning may be because of interactions between initial brain injury, poor sleep quality and neuroinflammation (**Figure 4**). First, the mild TBI may cause stretching and shearing of axons and initiate an acute neurometabolical cascade in the brain (Giza & Hovda, 2014; Romeu-Mejia et al., 2019). In this acute period sleep may be important, and potentially moderate neuronal recovery (Wickwire et al., 2016). The heightened prevalence of increased sleep need we observed in paper I may reflect such recovery processes. However, sleep disruption and poor sleep quality are also associated

with structural cortical changes (Elvsåshagen et al., 2017; Sexton et al., 2014). Poor sleep quality after mild TBI may therefore exacerbate the structural cortical injury after mild TBI (Raikes et al., 2018). Aggravating the matters further, both mild TBI (Chaban et al., 2020; Vedantam et al., 2020) and poor sleep quality (Irwin & Opp, 2017; Irwin, 2019) are associated with elevated systemic neuroinflammation. The initial neuroinflammatory response to mild TBI may therefore be exacerbated and prolonged by sleep disruption or poor sleep quality (Green et al., 2020; Tapp et al., 2020). Finally, neuroinflammation and recovery after mild TBI relies heavily on the glymphatic system (Sullan et al., 2017). The glymphatic functions of the brain are upregulated during sleep, and particularly during slow-wave sleep (Jessen et al., 2015). The glymphatic system may be compromised directly due to the mild TBI, or indirectly through sleep loss, or poor sleep quality. The combination of a mild TBI and poor sleep quality may therefore lead to a self-reinforcing cascade in the brain. These brain mechanisms may in turn interfere with neurocognitive performance and psychological functioning that we observed in paper III in the present thesis.

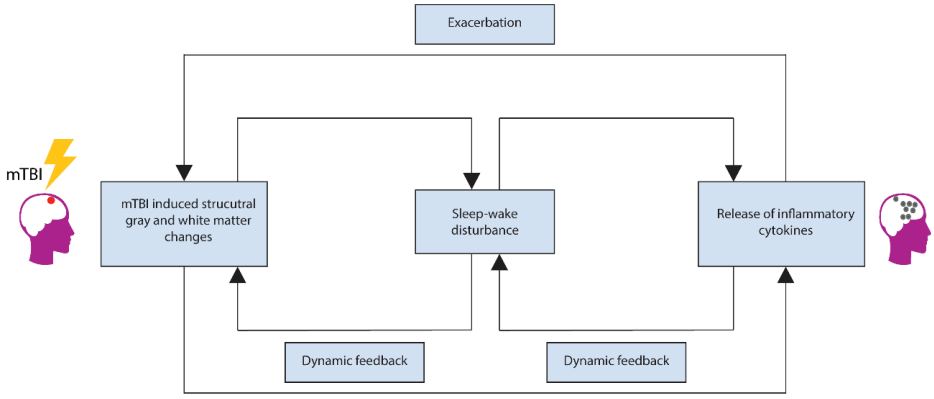


***Figure 4: Key candidate neurobiological mechanisms of sleep-wake disturbances after mTBI****: MTBI can cause structural brain changes, these brain changes can in turn cause an inflammatory response that feedback and exacerbate the brain changes. MTBI can also cause sleep-wake disturbances that is bi-directionally associated with both structural changes in the brain and neuroinflammatory processes.*

## 5.3 Implications

### 5.3.1 *Clinical assessment*

It is demonstrably clear from the findings in the present thesis that individuals with sleep-wake disturbances after mild TBI require increased attention from health professionals. Sleep-wake disturbances have traditionally been regarded as secondary symptoms to a primary disorder, e.g. a mental disorder such as depression. Insomnia was for example previously categorized as *secondary* insomnia in the diagnostic manuals. This has changed, and patients meeting the criteria now gets an additional diagnosis of "insomnia disorder", even if they also meet the criteria for other mental disorders (American Psychiatric Association, 2013). The lack of diagnostic specificity after mild TBI is likely to cause a substantial part of sleep-wake disturbances after mild TBI to go unnoticed. The assessment of sleep-wake disturbances and other symptoms in paper I, II and III in the present thesis does not constitute any formal diagnosis. It is still important to also evaluate subclinical symptoms after mild TBI. It may be important to provide more specific characterization of the specific sleep-wake disturbances after mild TBI, especially given that sleep-wake disturbances after mild TBI are underrecognized by clinicians (Sandsmark et al., 2017).

The present thesis has a particular focus on the sleep-wake disturbances increased sleep need and excessive daytime sleepiness, poor sleep quality as well as fatigue. These sleep-wake disturbances quality may all also be associated with circadian rhythm sleep-wake disturbances. Circadian rhythm sleep-wake disorders are characterized by sleep disruption caused by changes in the circadian rhythm or a misalignment between the circadian rhythm and the sleep-wake cycle. Diagnosis also requires that the sleep disruption is associated with significant sleepiness, poor sleep quality or both (American Psychiatric Association, 2013). Insomnia and hypersomnolence disorder therefore have a considerable overlap in symptomatology with circadian rhythm sleep-wake disorders, which is important to consider in differential diagnostics. In the context of the findings in the present thesis, it cannot be ruled out that the observed sleep-wake disturbances are associated with circadian-related sleep problems. Light therapy is specifically developed to modify the circadian rhythm and treat circadian related sleep problems and can be an effective treatment for patients with mild TBI (Raikes &

Killgore, 2018). Indeed, blue-light therapy, in the morning, was recently shown effective in improving subjective and objective sleep measures, cognitive functioning, gray matter volume and axonal integrity for patients with mild TBI, relative to a placebo group (amber light) (Killgore et al., 2020). However, patients with mild TBI commonly report sensitivity to light as one of their problems (Cassidy et al., 2014). It may therefore be difficult for these individuals to complete a full treatment plan incorporating blue-light therapy.

### 5.3.2 *Treatment*

The results in the present thesis corroborate the findings in a recent systematic review that concluded that there is a need for more targeted treatment strategies after mild TBI (Sullivan et al., 2018). Our findings indicate that increased sleep need, poor sleep quality, excessive daytime sleepiness and fatigue have distinct etiologies after mild TBI and may require different treatment approaches to ensure optimal long-term outcome after injury. Hypersomnolence disorder and associated symptoms (e.g. excessive daytime sleepiness) are frequently treated with off label prescribed stimulants (Wickwire et al., 2016). In fact, prescription and over-the counter medication are the most common treatment across sleep-wake disturbances after TBI (Orff et al., 2009; Sullivan et al., 2018). However, there is a paucity of large scale treatment studies investigating the effectiveness and safety of pharmacological treatments for sleep-wake disturbances in patients with mild TBI (Wickwire et al., 2016). It is therefore important to provide a better understanding of the underlying biological mechanism of sleep-wake disturbances after mild TBI in order to provide more effective, targeted and safe pharmacological treatments. Psychological treatment is the recommended first-line treatment for most sleep-wake disturbances after TBI (Sullivan et al., 2018). For individuals with insomnia are cognitive behavioral therapy for insomnia (CBT-I) the recommended first line treatment (Riemann et al., 2017). However, one major problem has been the dissemination of the research findings into the clinics. In Norway psychological treatments specifically targeting sleep-wake disturbances have been underutilized in the specialist health care, including clinics specializing in acquired brain injuries.

The participants in paper II reported better sleep quality in the sleep deprived period compared to the habitual sleep period. This finding is in line with prior studies also showing an improvement in sleep quality after sleep deprivation (Elmenhorst et al., 2008). One possible explanation of this finding is that the sleep drive is increased after sleep deprivation. We included healthy individuals without sleep problems in paper II, but there are some similarities between our findings in paper II and sleep restriction used in CBT-I (Mansel & Carey, 2014). Sleep restriction is effective in improving sleep quality, because a larger part of the time spent in bed is spent actually sleeping (Elmenhorst et al., 2008; Morin et al., 2006). There may be some adverse, but likely transient, effects of sleep restriction (Maurer et al., 2020). It may therefore be difficult for individuals to adhere to the sleep restriction protocol in CBT-I. Despite potential adverse effects, it seems important to investigate the long-term effects of sleep restriction and CBT-I after mild TBI. There are promising preliminary findings of CBT-I in mild TBI samples (Lu et al., 2016; Nguyen et al., 2017; Ouellet & Morin, 2007), but there is a general need to investigate the effect, benefits and limitations of CBT-I in this patient population (Dietch & Furst, 2020).

We also showed in paper I that a substantial number of patients with mild TBI experience increased sleep need after injury. This increased amount of sleep may be important after injury (Wickwire et al., 2016), but it is unknown how these patients may respond to sleep restriction. It is highly important to determine the biological and psychological underpinnings of long-lasting increased sleep need after mild TBI. A better understanding of the mechanisms underlying sleep-wake disturbances after mild TBI may help determining optimal timing of sleep interventions following mild TBI.

## 5.4 Methodological considerations

### 5.4.1 *Validity*

Some individuals are at higher risk of sustaining a mild TBI than others. Young men with low socioeconomic status have a disproportionately high prevalence of mild TBI (Nordström et al., 2013), and if one individual sustain one mild TBI the risk of sustaining a new TBI likely increases (Wickwire et al., 2016). Females seems to be more vulnerable to develop persistent symptoms after mild TBI and older age is associated with worse outcome after injury (Rabinowitz et al., 2015). Prior studies have

applied strict exclusion criteria such that most patients filling the criteria for mild TBI have been excluded. This selection bias may lead to study samples that are not representative to the mild TBI population and therefore lead to erroneous conclusions (Luoto et al., 2013). The Trondheim MTBI-follow up study had a population-based design, with an overall goal of including as may patients with mild TBI as possible by not having to strict exclusion criteria (Skandsen et al., 2018). The results in paper I and III in the present thesis may therefore be more representative for the mild TBI population at large, compared to prior non-population based studies.

Paper I and Paper III in the present thesis was the first studies investigating sleep-wake disturbances with a population-based sample that also included control groups. The control groups were matched to the patients with mild TBI, in terms of age and sex. Community controls were also matched in terms of length of education. The inclusion of matched control groups ensured that general injury related factors and pre-injury factors could be sufficiently controlled for (Ludwig, D'Silva, et al., 2020). Because the control groups were selected to be matched to the mild TBI group, they may not be representative to their respective sample population, individuals in the community and patients with orthopedic injuries.

The sample size of 378 patients with mild TBI is similar to two prior longitudinal studies (Chan & Feinstein, 2015; Theadom et al., 2015) and is larger than most prior studies investigating sleep-wake disturbances after mild TBI (Imbach et al., 2015, 2016; Kalmbach et al., 2018; Losoi et al., 2015, 2016; Ponsford et al., 2011; Suzuki et al., 2017). The relatively large sample size provided enough statistical power to investigate several sleep-wake disturbances as well as fatigue in paper I. Prior studies have typically focused on one sleep-wake disturbance in each study (Sullivan et al., 2015). The sample size of the two control groups were however smaller than the sample size for the patients with mild TBI. Still, the sample size of the two control groups was similar to (Ponsford et al., 2011) or larger than those included in prior studies (Imbach et al., 2015, 2016; Losoi et al., 2015, 2016).

In paper III we included a subsample of the patients with mTBI included in Trondheim MTBI-follow-up study. It was planned a priori in the Trondheim MTBI follow-up study

to include one cohort of patients for neuropsychological testing, blood sampling and MRI and one simplified participation cohort. Patients with mild TBI were allocated to the simplified cohort if they were ineligible for MRI or had problems attending the hospital for testing (e.g. due to long travel). We observed no significant differences between patients in these two cohorts on key demographic variables. Even though the sample size in paper III was smaller than in paper I, few prior studies have included larger samples when investigating neurocognitive performance after mild TBI.

In the SLEEPIC study we included 59 young adults in a convenience sample consisting mostly of students at the university. These individuals were rather high functioning, and may not be representative neither for the general population nor for individuals at risk of sustaining a mild TBI. There was an overrepresentation of women in the sample. Female sex have been associated with increased risk of experiencing sleep-wake disturbances (Reyner & Horne, 1995; Van Someren, 2020). It is possible that a more evenly distributed sample with regards to sex may have led to different conclusions in paper II.

Patients with mild TBI were prospectively included over the course of 20 months. In Trondheim, Norway, there is a large variability in daylight over the course of one year. The variability in daylight is also associated with a variability in mood, which is associated with the DSM-5 disorder seasonal affective disorder (American Psychiatric Association, 2013). It is possible that the findings in paper I and III is influenced by seasonal variations in daylight. In order to provide some control for such seasonal effects, control participants were also prospectively included during the same time of the year as patients with mild TBI. In the SLEEPIC study all participants were included during the time of the year with similar light conditions, and not during the longest or shortest days during summer and winter.

Sleep-wake disturbances was assessed at 2 weeks, 3 months and 12 months in the Trondhiem MTBI-follow-up study. There may be significant daily or weekly variability in sleep-wake disturbances also in the samples included in paper I and III, but we did not assess such variability in these studies. Prior studies have included control groups matched to patients with TBI in daily variations in sleep in order to control for

weekend/weekdays effects (Imbach et al., 2015, 2016). Other studies have shown that patients with mild TBI seems to have a greater day to day variability in sleep-wake disturbances early after injury, compared to non-injured controls (Hoffman et al., 2018). Due to the large sample size and the population-based design in the Trondheim MTBI-follow up study it may have been unrealistic to provide the same level of control over these variables as prior studies (Imbach et al., 2015, 2016).

We used a multiple baseline design in the SLEEPIC study (paper II) (Hawkins et al., 2007). The participants were tested three times before the sleep deprivation and in this way could serve as their own control. We identified for example a significant decrease in self-reported exertion and an increase in self-reported performance before partial sleep deprivation in the study. This relationship was reversed after partial sleep deprivation such that self-reported exertion decreased and self-reported performance increased. We also identified a significant interaction effect between reaction time and commission errors. This interaction was driven by a significant decrease in hit reaction time (faster responses) that was accompanied by an increase in commission errors (less accuracy). With three baseline tests we were able to provide better control over potential practice effects, which could have masked findings in prior studies with only one baseline test (Santisteban et al., 2019). We observed a linear decrease in positive affect throughout the study period, also before partial sleep deprivation. It is possible that the observed reduction in positive affect could be due to the mere participation in the study (e.g. because of boredom due to repeated testing). It is possible that we could have had better control over this reduction in positive affect by including more baseline tests before partial sleep deprivation and allow the reduction in positive affect to stabilize before introducing the intervention. Based on the present findings it is not possible to firmly conclude on the main contributor to the reduction in positive affect observed in paper II.

### 5.4.2 *Sleep measurements*

In paper I and III we relied solely on subjective measures of sleep-wake disturbances. This is clinically relevant because insomnia disorder and hypersomnolence disorder is based strictly on self-report (American Psychiatric Association, 2013). Increased sleep need and poor sleep quality was assessed in a structural interview whereas excessive

daytime sleepiness and fatigue was assessed trough well-validated questionnaires (Johns, 1991; Krupp et al., 1989). There are important differences between interviews and questionnaires, where questionnaires generally are less precise compared to structured interviews (American Psychiatric Association, 2013).

In paper I and III we used three selected items from the Insomnia Severity Index (ISI) as a measure of poor sleep quality. These items measure the key criteria for insomnia disorder, problems initiating sleep, problems maintaining sleep and difficulties with early morning awakenings (criterion A, **Figure 2**). In addition to the items included, the full ISI also assesses how the sleep disturbance interferes with daytime functioning which is an important criteria in insomnia disorder (American Psychiatric Association, 2013). Our poor sleep measure may therefore be less clinically relevant and less comparable to prior studies who have used the full ISI. The included items were a part of a comprehensive interview in the Trondheim MTBI-follow-up study, in which we also assessed other information. The decision to leave out the remaining items from the Insomnia Severity Index was partly motivated by a general need for limiting the total load on the participants. Prior studies have also used criterion A in the DSM-5 as a measure of poor sleep quality (Bragantini et al., 2019; Uhlig et al., 2014) and such a categorization of poor sleep quality have been found to have acceptable agreement with a clinical interview (Engstrøm et al., 2011). Still, the full ISI (cut off 12) have good agreement with a definite interview diagnosis (Filosa et al., 2020) and are likely better at capturing clinically significant poor sleep quality than the measure used in the present thesis. Our results in paper I and III must therefore be interpreted with this in mind.

Fatigue was assessed with the FSS in paper I. The FSS is the recommended measure of fatigue in research assessing insomnia (Buysse et al., 2006). The Norwegian version of the FSS have satisfactory psychometric properties (Lerdal et al., 2005). However, one potential bias when assessing fatigue in Norwegian samples is that there does not exist a word in Norwegian that can be directly translated from the word fatigue. The two words used to define fatigue in the Norwegian version of the FSS is back translated to English as “tired and weary”. It is therefore possible that the Norwegian version of the FSS may capture different aspects than studies using the original version.

We used relatively conservative cut-offs for identifying clinically significant excessive daytime sleepiness and fatigue in paper I, compared to the originally defined cut-offs (Johns, 1991; Krupp et al., 1989). This may have reduced the comparability with prior studies. The cut-off values were chosen based on validation studies and studies comparing objective and subjective measures (Aurora et al., 2011; Lerdal et al., 2005). The use of this cut-off was motivated by need to avoid an overestimation of the prevalence of excessive daytime sleepiness and fatigue in paper I.

Prior studies have indicated that objective and subjective measures of sleep may capture different aspects of sleep (Berger et al., 2017; Raikes et al., 2019). It may therefore be important for future studies to include both objective and subjective measures of sleep. In paper I, we defined 'increased sleep need' as an increased sleep need and a total sleep time of > 1 hour, according to the criteria for pleiosomnia defined in prior studies (Imbach et al., 2015, 2016; Sommerauer et al., 2013). It is important to note that these prior studies defined pleiosomnia with objective measures, and the same studies showed that there are marked differences in subjective and objective measures of pleiosomnia and excessive daytime sleepiness. Specifically, when patients were asked to rate their sleepiness with the ESS, they underreported their sleepiness as compared to objective sleepiness (the multiple sleep latency test) (Imbach et al., 2015, 2016). We used the ESS to measure excessive daytime sleepiness in paper I, and we cannot rule out that we would have shown a higher prevalence of excessive daytime sleepiness and pleiosomnia using objective measures. The Trondheim MTBI follow-up study included a range of different measures, and the participants provided data from interviews, questionnaires, MRI, neurocognitive testing and blood-samples. It was not planned, and it may have been considered unfeasible to include objective measures of sleep in this large longitudinal cohort study. Importantly, the cut-off used for defining excessive daytime sleepiness in paper I are more comparable to objective excessive daytime sleepiness than the originally defined cut-off (Aurora et al., 2011).

In the SLEEPIC study we provided both subjective questionnaire data and objective measures of sleep. In order to measure more naturalistic objective sleep in a home environment we used actigraphy in this study. The gold standard for objective sleep measurement, the PSG, may in itself interfere with sleep, and PSG sleep recordings are

traditionally performed in the laboratory (Blackwell et al., 2017). Actigraphy may provide more *ecologically* valid data compared to laboratory recordings and is a recommended valid measure of sleep (Ancoli-Israel et al., 2003; Lowe et al., 2017). In paper II we also applied individually adjusted mild to moderate sleep restriction protocol, and most prior studies have sleep restrictions of 4-5 hours (Lowe et al., 2017). Small deviations from habitual sleep is common (Sivertsen et al., 2011). Our findings in paper II therefore provide ecologically valid and objectively measured sleep data.

### 5.4.3 *Neurocognitive assessment*

The test battery utilized in the Trondheim MTBI follow-up study, the CANTAB, constructed to measure planning, decision making, response control, social cognition, attention, executive function, visual memory and working memory (Cambridge Cognition, 2014). However, studies indicate that these neurocognitive subtest do not measure the neurocognitive domains they are designed to measure (Robbins et al., 1994, 1998).

Neurocognitive tests requiring continuous performance seems sensitive to the effects of sleep deprivation (Massar et al., 2019), poor sleep quality (Altena et al., 2008; Edinger et al., 1997) and mild TBI (Rabinowitz et al., 2015). One such test is the well-validated Conners Continous Performance Test- 3 (CCPT-3) (Conners, 2014), we used in paper II. The CCPT-3 lasts for 14 minutes and requires sustained attention over time to maintain performance. One advantage of the CCPT is that this test calculates response times based on hundreds of trials, providing more robust measures of response times, compared to other commonly used tests, such as the Psychomotor Vigilance Task. In paper III we included subtest from the CANTAB that required continuous performance and just like in the CCPT the participants were asked to respond as fast and accurate as possible, and therefore required a balance of speed and accuracy (Heitz, 2014). None of the sub-tests included in paper III, last for as long as the CCPT-3 (the longest test, the Rapid Visual Information Processing task lasts for 6.5 minutes). The selected sub-tests in the CANTAB used in paper III and the CCPT-3 used in paper III have not been directly compared in prior research. It is, however, possible that the CCPT-3, is more sensitive to measure the consequences of sleep deprivation, and sleep-wake

disturbances after mild TBI. In our future studies we will continue to investigate neurocognitive performance with the CCPT.

Neurocognitive test performance is also highly dependent on effort and motivation (Botvinick & Braver, 2015). In paper II we showed that participants had an initial drop in effort, as they felt they got better on the continuous performance test between the first visits. After sleep deprivation, the participants felt they performed worse and therefore tried to compensate with increased effort. There was no measure of effort or motivation included in paper III. We considered it unlikely that there would be any group differences in motivation or effort between patients with mild TBI and trauma controls in this study.

In paper II we demonstrated that the participants had a significant improvement in neurocognitive performance between visit 1 and visit 3 in the habitual sleep period. This change in performance may reflect a practice effect on the CCPT-3. One night of partial sleep deprivation seemed to erase this practice effect, and we observed a further worsening of performance after three nights of partial sleep deprivation. This may not have been possible to observe if we only included two or three assessment points. The CCPT-2 have been shown to have adequate test-retest reliability (Shaked et al., 2020), but no studies have investigated the test-retest reliability of the CCPT-3 yet. In paper III we only had two test points, and we observed a significant improvement in performance between 2 weeks and 3 months after injury (faster and more accurate responses). We have previously shown that the subtests Attention Switching Task and the Rapid Visual Information Processing task included in paper II have adequate test-retest reliability, whereas the Reaction Time task had inadequate test-retest reliability (Karlsen et al., 2020).

### 5.4.4 *Statistical analyses*

In paper I we used mixed logistic regression models and in paper III we used linear mixed regression models. Both these methods utilize maximum likelihood estimation, and is robust to missing data, when the data is missing at random (Rabe-Hesketh & Skrondal, 2008). The data is not missing at random if the outcome variable that is missing is lost because of the outcome variable (Enders, 2017). For example, if we are

measuring poor sleep quality, and the poor sleep quality is the direct cause of why the data is missing, the data is not missing at random. Because we are not able to measure data that is missing, we are not able to directly prove that the data is missing at random or not. In paper I and III we therefore investigated differences between participants with missing data and not missing data on variables that were not missing, such as age, sex and total years of education. We did not observe any significant differences considered the data to be missing at random.

In paper II we had complete data on all time points. We used repeated measures ANOVA (rmANOVA) in paper II in order to investigate potential interaction effects between speed and accuracy, self-reported measures and between positive and negative affect. This analysis also allowed for an exploration of polynomial and linear trends in the data. We used a multiple baseline design to investigate within group repeated measures. Such repeated measures can be assessed with the rmANOVA, which also provides a reasonable control over multiple comparisons.

Another important aspect of the analyses used in the present thesis is that they are robust when the assumption of normality is violated (Rabe-Hesketh & Skrondal, 2008). We used measures of response speed in both paper II and III, such measures are typically not normally distributed and have a positive skew in their distribution (Lo & Andrews, 2015). In paper III we therefore chose to log-transform the neurocognitive data to have data that was normally distributed. This transformation was partially done because the different outcome measures were combined into a composite score. If the raw scores in each outcome measures had different distribution (some more skewed than others) this could have caused some of the scores to have a much larger contribution to the composite score than others. The log-transformation ensured similar distribution and that each outcome measure had a more or less equal contribution to the composite score. We performed no normality transformation of the neurocognitive data in paper II, but used age and sex adjusted T-scores for hit reaction time, commission errors and omission errors in our analyses. In both in rmANOVA (paper II) and linear mixed models (paper III) the assumption of normality applies to the *residuals* in the model. Although the raw-data in the analyses were not normally distributed in paper II

and III, the residuals looked approximately normally distributed when examining normal QQ-plots and histograms.

# 6 Conclusion and future perspectives

The collection of papers included in the present thesis demonstrates that sleep-wake disturbances are common and persistent after mild TBI, that such problems may in themselves have adverse short-term consequences and that the consequences may be particularly adverse after mild TBI relative to other types of injuries. There are three main areas of research that should be a primary focus in future studies based on the findings in the present thesis.

First, future studies should delineate the risk factors for developing sleep-wake disturbances after mild TBI as well as protective factors that may be important for recovery. A further investigation of such factors may improve clinical care and lead to better follow-up of patients with mild TBI in the future.

Second, there is a need for a further investigation of the neurobiological mechanisms of sleep-wake disturbances. The findings in the present thesis indicate that partial sleep deprivation and mild TBI may be interesting models for a further exploration of these mechanisms. The present thesis has suggested a path forward for future studies that includes an investigation of the interaction between mild TBI, poor sleep quality and neuroinflammation. In the Trondheim MTBI-follow-up study we have available MRI and blood samples which may allow for a direct investigation of this relationship.

Finally, the findings in the present thesis show that there is a marked need for a further investigation of the personalized and targeted treatment options after mild TBI. Self-guided digital treatment options are promising treatment plans that should be investigated in future studies. This type of treatment does not require trained therapist and may therefore be more cost-effective and more easily implemented in the specialist health care and in public health at large.

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# PAPER I

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# The Prevalence and Stability of Sleep-Wake Disturbance and Fatigue throughout the First Year after Mild Traumatic Brain Injury

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## Abstract

In this prospective, longitudinal study, we aimed to determine the prevalence and stability of sleep-wake disturbance (SWD) and fatigue in a large representative sample of patients (Trondheim mild traumatic brain injury [mTBI] follow-up study). We included 378 patients with mTBI (age 16–60), 82 matched trauma controls with orthopedic injuries, and 83 matched community controls. Increased sleep need, poor sleep quality, excessive daytime sleepiness, and fatigue were assessed at 2 weeks, 3 months, and 12 months after injury. Mixed logistic regression models were used to evaluate clinically relevant group differences longitudinally. Prevalence of increased sleep need, poor sleep quality, and fatigue was significantly higher in patients with mTBI than in both trauma controls and community controls at all time points. More patients with mTBI reported problems with excessive daytime sleepiness compared to trauma controls, but not community controls, at all time points. Patients with complicated mTBI (intracranial findings on computed tomography or magnetic resonance imaging) had more fatigue problems compared to those with uncomplicated mTBI, at all three time points. In patients with mTBI who experienced SWDs and fatigue 2 weeks after injury, around half *still* had problems at 3 months and approximately one third at 12 months. Interestingly, we observed limited overlap between the different symptom measures; a large number of patients reported one specific problem with SWD or fatigue rather than several problems. In conclusion, our results provide strong evidence that mTBI contributes significantly to the development and maintenance of SWDs and fatigue.

**Keywords:** fatigue; hypersomnia; insomnia; mild traumatic brain injury; sleep-wake disturbances

## Introduction

Sleep-wake disturbance (SWD) and fatigue are common after mild (mTBI) traumatic brain injury (TBI) and have been linked to a range of adverse consequences, including reduced cognitive functioning,[1,2] emotional distress,[1,3] and reduced quality of life.[4] Insomnia and hypersomnolence disorder are the most common SWDs after TBI of all severities.[5] In the *Diagnostic and Statistical Manual of Mental Disorders*, fifth edition (DSM-5), insomnia disorder is characterized by poor sleep quality, and hypersomnolence disorder by excessive sleep quantity and daytime sleepiness.[6] In a meta-analysis, 50% of TBI patients across all severities experienced some form of SWD after injury.[7] Both insomnia and hypersomnolence disorder are accompanied by daytime distress, often in the form of fatigue.[6]

A recent systematic literature review indicates that between 17% and 47% of patients with mTBI may experience fatigue during the first 3 months after injury.[8] Problems with increased sleep need, poor sleep quality, excessive daytime sleepiness, and fatigue appear to decrease during the first month,[1,9,10] but stabilize at higher levels than before the injury between 3 and 6 months after mTBI.[1,10] Because SWD and fatigue are prevalent in the

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general population[11–13] and after traumatic injuries not involving the head,[14] it is important to carefully consider the choice of comparison groups included in studies investigating such problems after mTBI.[15,16]

Factors specific to mTBI that can be involved in the development or maintenance of SWD and fatigue include primary damage to the brain as a direct consequence of the injury or secondary to, for example, mood or lifestyle changes after mTBI.[17] Pre-injury factors, such as personality factors or a history of psychiatric problems, may also affect SWD and fatigue after mTBI.[18] General injury-related factors,[14,19] such as medication use[20] and injury-related pain or stress,[21,22] might lead to SWD and fatigue, but are also present after injuries not involving the head (e.g., orthopedic injuries). Moreover, SWD has increased in the general population, likely because of higher work demands, increased shift and night work, and more excessive environmental stimuli (e.g., computer/cell-phone screen time).[11]

In previous longitudinal studies with control groups, patients with mTBI and previous psychiatric problems have been excluded,[23–25] which might have biased these studies toward more homogeneous mTBI samples, not generalizable to the heterogenetic mTBI population.[26] An additional source of bias is that the majority of patients with mTBI who are treated outside of hospitals[27] have not been included in most previous studies.[28] Only one population-based study investigating SWD after mTBI has recruited patients in the primary healthcare setting, but this study did not include any control groups.[1] Earlier studies have also typically aggregated SWD and fatigue-related findings across all TBI severities. Studies focusing on well-characterized mTBI patients are therefore needed.[29]

Most studies investigating SWD after mTBI have assessed only one facet of sleep, with poor sleep quality being the most frequently investigated symptom.[30] Information about how increased sleep need, poor sleep quality, excessive daytime sleepiness, and fatigue coexist is important for understanding potentially shared and distinct etiology,[31] as well as different phenotypes[5] after mTBI.

Here, we investigated a broad range of SWDs and fatigue in a large representative sample of patients with mTBI.[32] Our main aim was to evaluate the prevalence and stability of SWD and fatigue throughout the first year after mTBI. To extend and substantiate earlier studies, we compared patients with mTBI to two control groups (patients with orthopedic injuries and community controls) throughout the first year after injury on measures of increased sleep need, poor sleep quality, excessive daytime sleepiness, and fatigue. To substantiate our findings, we evaluated the overlap between different types of SWD and fatigue problems. Finally, to further evaluate possible associations with brain-injury–specific factors, we investigated whether there were any differences between patients with complicated mTBI (intracranial findings on computed tomography [CT] or magnetic resonance imaging [MRI]) and patients with uncomplicated mTBI.

## Methods

### Participants

In this longitudinal cohort study,[32] we recruited patients with mTBI prospectively from two emergency departments (EDs); the level 1 trauma center at St. Olavs Hospital and the general-practitioner–run Trondheim municipal clinic. These two EDs evaluate the vast majority of acute mTBI in Trondheim and adjacent regions. Both EDs are part of the public healthcare system in Norway, located at the university hospital campus, and use the same CT service. These two EDs serve ~230,000 residents in Trondheim and adjacent regions in addition to ~18,000 students (who are officially registered as residents in other parts of the country). The inclusion period was between April 1, 2014 and December 5, 2015.

Participants were included if they were between 16 and 60 years of age and had sustained an mTBI according to the World Health Organization criteria.[33] Patients had to have a witnessed loss of consciousness (LOC) <30 min, post-traumatic amnesia (PTA) <24 h, or evident lesions on CT, in addition to a Glasgow Coma Scale (GCS) score between 13 and 15. Exclusion criteria were: 1) non-fluency in Norwegian or residence in another country; 2) any *severe* ongoing alcohol/drug abuse, psychiatric or somatic disease, or condition that would complicate follow-up; 3) any previous complicated mild, moderate, or severe TBI, stroke, or other acquired brain injuries; 4) severe concurrent multi-trauma, such as spinal cord injury, internal bleeding, or severe fractures; and 5) presentation to the ED >72 h of injury. A main aim of the overarching cohort study was to evaluate neuroimaging findings from CT and MRI.[32] Patients with previous *complicated* mTBI were excluded to reduce the likelihood of including patients with *pre-existing* gross brain pathology. Apart from this, we aimed to be as inclusive as possible to optimize the clinical representativeness in the sample.

Trauma controls with orthopedic injuries (e.g., sprains or fractures) were included between April 1, 2015 and December 1, 2017 from the same two clinics as the patients with mTBI. Trauma controls were identified by screening patient lists at the ED at the municipal clinic and lists of referrals to the hospital. They were evaluated for inclusion if they were between 16 and 60 years of age and had sustained an orthopedic injury. They could not have any evidence of head or neck trauma, polytrauma, or injury to their dominant upper extremity. Other exclusion criteria were identical to those applied for the mTBI group.

Community controls, between 16 and 60 years of age, were included from a convenience sample recruited from employees and students at the university hospital as well as from friends and family of the patients with mTBI, or from employees and students at the university hospital. Exclusion criteria were the same as for the patients with mTBI, with the additional criteria that the community controls did not receive any ongoing treatment for psychiatric disorders. Participants in the community control group were matched at group level to the mTBI group in terms of age, sex, and length of education in years, whereas participants in the trauma control group were matched at group level to the mTBI patients in terms of age and sex.

### Procedure

Detailed procedures for recruitment to the study have been described elsewhere.[32] Patients with mTBI were assessed at four time points (Fig. 1). Within 72 h of their injury, the patients with mTBI completed a structured interview containing questions related to injury characteristics, demographics, and premorbid health problems. Clinical MRI (3 Tesla) was performed within 72 h of injury. At 2 weeks, 3 months, and 12 months after injury, patients with mTBI completed a structured interview and questionnaires. Trauma controls underwent the same procedures as patients with mTBI, except MRI. Community controls also underwent the same procedures as patients with mTBI, excluding the first visit (within 72 h of injury).

A subgroup of patients with mTBI did not meet at the hospital, but answered interviews over the telephone and sent completed questionnaires by mail. Participants who met at the hospital for

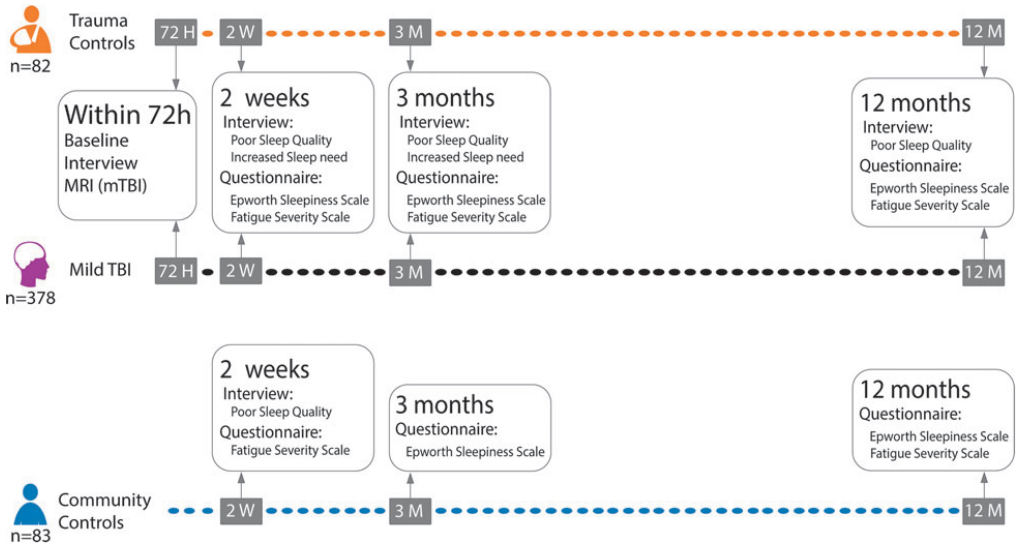


**FIG. 1.** Timeline of follow-up. MRI, magnetic resonance imaging; mTBI, mild traumatic brain injury; TBI, traumatic brain injury.

their assessments received a gift certificate (~EUR 54) for each attendance. All participants gave their informed consent. The project was performed according to the Helsinki Declaration and was approved by the Regional Committee for Medical and Health Research Ethics (REK) in Norway (REK 2013/754).

### *Measures*

Brain imaging. Non-contrast head CT was performed on a Siemens Somatom Sensation 64-row scanner (Siemens Healthineers, Erlangen, Germany) in 299 of the patients as a part of routine clinical assessment. In addition, brain MRI scans were acquired on a 3 Tesla Siemens Skyra System (32-channel head coil; Siemens Healthineers) within 72 h of injury for 198 patients with mTBI. The following sequences were included: three-dimensional $T_1$, $T_2$, susceptibility-weighted imaging, diffusion-weighted imaging (DWI), and fluid-attenuated inversion recovery. All CT and MRI scans were read by experienced radiologists,[34] and patients with mTBI and intracranial traumatic findings on CT and/or MRI were considered to have complicated mTBI.

Structured interviews. In the first interview, completed within 72 h of injury, participants were asked to provide information about cause of injury, LOC, PTA, pre- and post-injury medication use, pain, previous health problems, and previous uncomplicated mTBI. Information about previous uncomplicated mTBI was based on self-report as recommended in other studies.[35] Three subsequent interviews were performed at 2 weeks, 3 months, and 12 months after injury to assess post-injury problems and functioning.

*Pre-injury psychiatric disorders.* A structured interview during the first study visit was performed to assess previous psychiatric history. Participants were asked to report and describe any previous psychiatric disorders. Participants that reported psychiatric disorders were further asked to describe the onset and duration (if relevant) of the disorder and to what degree the disorder affected their daily life. Based on information from the structured interview, patients were categorized as having a pre-injury psychiatric disorder or not.

*Increased sleep need.* Participants were asked to report their average total sleep time during the 2 weeks before inclusion in the study (i.e., before the injury for the patient groups). Second, participants were asked whether they experienced any increased sleep need after injury. Participants who answered *yes* to this question were further asked to report the duration (in days) of this increased sleep. Finally, participants were asked to report their average total sleep time in the period they experienced this increased sleep need. Increased total sleep time of >1 h is commonly used as a measure of increased sleep need in TBI research.[36–38] We therefore classified patients with mTBI into an increased sleep need group that reported to sleep >1 h longer after injury than their average total sleep time before the injury and a group that did not experience increased sleep need. We applied the same dichotomization for trauma controls.

*Poor sleep quality.* Three items from the Insomnia Severity Index[39] were included to investigate symptoms of insomnia. These items were selected based on being direct measures of insomnia according to the diagnostic manual DSM-5,[6] namely subjective difficulties falling asleep (sleep onset insomnia), difficulties staying asleep (maintenance insomnia), and unwanted early morning awakenings (terminal insomnia). Participants were asked to rate how much of a problem each item had been during the last 2 weeks using a 5-point Likert-type scale, 0 to 4 (0 = No problem, 1 = A mild problem, 2 = A moderate problem, 3 = A severe problem, and 4 = A very severe problem). Participants were classified as poor sleepers if they reported at least severe difficulties on one of these three items, which is in line with criterion A of Insomnia Disorder in DSM-5.[6]

### Questionnaires

*Pain map with Numeric Rating Scale.* Participants were asked whether they experienced any pain beyond that of everyday mundane pain after their injury. They were then asked to rate the pain intensity, using an 11-point Numeric Rating Scale (NRS) from 0 to 10, and to indicate the location of their pain using a body map.

*Excessive daytime sleepiness: Epworth Sleepiness Scale.* The Epworth Sleepiness Scale (ESS) consists of eight items measuring self-reported excessive daytime sleepiness.[40] The eight items represent real-life situations where the participants must rate their chance of dozing off using a 4-point scale from 0 to 3. Higher scores indicate higher chance of dozing off. Total score indicates the extent of self-reported sleep propensity. The Norwegian version of the ESS has high validity[12] and high reliability.[41] According to studies comparing the ESS to objectively measured sleepiness,[42] we applied a cutoff of 13 and above.

*Fatigue: Fatigue Severity Scale.* The Fatigue Severity Scale (FSS) measures feelings of fatigue, with nine items rated on a 7-point scale from 1 to 7.[43] Higher total scores indicate higher levels of fatigue. A total mean score of 4 was originally defined as clinically significant fatigue.[43] The Norwegian version of FSS has been shown to have satisfactory psychometric properties.[44] According to a validation study in a Norwegian sample, we applied a cutoff of 5 and above.[44]

Patients with mild TBI and trauma controls completed all the interviews and questionnaires at all time points. Community controls did not answer the questions about increased sleep need, but answered poor sleep quality questions at the 2 weeks after injury time point, excessive daytime sleepiness at the 3 and 12 months after injury time points, and fatigue at the 2 weeks and 12 months after injury time points.

### Statistical analysis

We performed attrition analyses and investigated differences between participants with missing data and participants with complete data on demographic variables, using chi-square tests and independent-sample *t*-tests to evaluate the pattern of missing data. Based on these attrition analyses, a missing at random, but not missing *completely* at random, assumption was most reasonable.[45]

Chi-square tests and independent-sample *t*-tests were used to investigate whether the control groups were successfully matched on a group level with the mTBI group on variables of sex, age, and total years of completed education. We also performed chi-square tests, independent-sample *t*-tests, Mann-Whitney U tests, and Kruskal-Wallis tests to evaluate other group differences on key demographic- and injury-related variables.

We used mixed logistic regression, a generalized linear mixed model for binary outcomes, to investigate differences in increased sleep need, poor sleep quality, excessive daytime sleepiness, and fatigue over time between patients with mTBI and trauma controls. The models included the fixed factors time, group, and their interaction and a random intercept on logit scale to account for within-subject dependencies. Additional mixed logistic regression models, based on data from time points where community controls had available data, were used to compare patients with mTBI to trauma controls as well as community controls. Data for community controls were available for fatigue at 2 weeks and 12 months after injury and excessive daytime sleepiness at 3 and 12 months after injury. A logistic regression model was used to compare patients with mTBI to trauma controls and community controls on poor sleep quality 2 weeks after injury (the time point at which community controls had available data). For all analyses performed, $p$ values $<0.05$ were considered statistically significant.

To investigate the effects of complicated mTBI (intracranial lesions visible on MRI or CT) on SWD and fatigue, we performed mixed logistic regression models to investigate differences in SWD and fatigue between patients with complicated mTBI, uncomplicated mTBI, and trauma controls. Community controls were not included in the models comparing patients with complicated and uncomplicated mTBI because they did not have data on all time points. We controlled for age, sex, and pre-injury psychiatric disorders in all models.

To investigate the overlap between increased sleep need, poor sleep quality, excessive daytime sleepiness, and fatigue, we performed a frequency count to investigate the degree of overlap between these four problems at the respective time points.

The data handling, attrition analyses, and investigation of whether the groups were successfully matched were performed in SPSS software (version 25; SPSS, Inc., Chicago, IL). The mixed logistic regression analyses as well as logistic regression analysis were performed in STATA software (version 15; StataCorp LP, College Station, TX), and overlap figures were created with the R package, eulerr (R Foundation for Statistical Computing, Vienna, Austria).[46]

## Results

We identified a total of 624 mTBI cases from screening lists of CT referrals (Fig. 1). Of these, a total of 299 patients with mTBI met the inclusion criteria and agreed to participate in the study. An additional 79 patients with mTBI without CT scans were recruited from the EDs, by screening patient lists. Accordingly, a total of 378 patients with mTBI, 82 trauma controls, and 83 community controls were included in the study (Fig. 1). Key demographic and clinical variables are presented in Table 1. Patients with mTBI, trauma controls, and community controls were successfully matched and did not differ significantly on the variables age, sex, and years of completed education. Patients with mTBI who completed their assessments at the hospital and those who completed these at home did not differ significantly on the variables age (mean [M] = 32.5, standard deviation [SD] = 13,1 vs. M = 29.9, SD = 12.7, $p = 0.054$), sex ($\chi^2_{(1)} = 1.04$, $p = 0.306$) and years of completed education (M = 13.9, SD = 2.50 vs. M = 13.4, SD = 2.4, $p = 0.053$).

The majority of patients with mTBI had a PTA duration <1 h (72%), LOC duration <5 min (42%), and a GCS score of 15 (73%). Sixty-five percent of patients with mTBI were men. Most of the sample was employed (58%) or students (36%). Most patients with mTBI had sustained their first-ever mTBI (77%). In total, 332 patients with mTBI had a head CT scan, brain MRI scan, or both CT and MRI; of these, 9% ($n = 31$) had complicated mTBI (intracranial pathology on CT or MRI). Proportions of different causes of injury were significantly different between patients with mTBI and trauma controls ($p < 0.001$; Table 1). Falls were the most common cause of injury for both patients with mTBI (36%) and trauma controls (32%). More patients with mTBI than trauma controls were injured because of violence (17% vs. 1%) and motor vehicle accidents (11% vs. 4%), but trauma controls were more often injured because of sports accidents than patients with mTBI (37% vs. 14%). There were no statistically significant differences between patients with mTBI and the two control groups in occupational

Table 1. Participant Characteristics

| *Variable* | *Mild TBI patients* n = *378* | *Trauma controls* n = *82* | *Community controls* n = *83* |
|---|---|---|---|
| Sex | | | |
| Men | 247 (65.3%) | 51 (62.2%) | 50 (60.2%) |
| Women | 131 (34.7%) | 31(37.8%) | 33 (39.8%) |
| Age | | | |
| Mean (SD) | 31.2 (12.9) | 32.6 (13.0) | 33.1 (13.0) |
| Education, years | | | |
| Mean (SD) | 13.6 (2.5) | 14.3 (2.6) | 14,0 (2.4) |
| Employment status | | | |
| Employed | 215 (56.9%) | 48 (58.5%) | 52 (62.7%) |
| Unemployed | 24 (6.3%) | 2 (2.4%) | 2 (2.4%) |
| Student | 138 (36.5%) | 31 (37.8%) | 27 (32.5%) |
| Missing | 1 (0.3%) | 1 (1.2%) | 2 (2.4%) |
| GCS score | | | |
| 13 | 5 (1.3%) | NA | NA |
| 14 | 57 (15.1%) | NA | NA |
| 15 | 277 (73.3%) | NA | NA |
| Unknown | 39 (10.3%) | NA | NA |
| PTA duration | | | |
| < 1 hour | 271 (71.7%) | NA | NA |
| 1 hour–24 hours | 107 (28.3%) | NA | NA |
| LOC duration | | | |
| No LOC | 67 (17.7%) | NA | NA |
| < 5 min | 157 (41.5%) | NA | NA |
| 5–15 min | 15 (4.0%) | NA | NA |
| 15–30 min | 1 (0.3%) | NA | NA |
| Difficult to assess | 6 (1.6%) | NA | NA |
| Unknown | 132 (34.9%) | NA | NA |
| Injury mechanism | | | |
| Fall | 135 (35.7%) | 26 (31.7%) | NA |
| Motor Vehicle accident | 43 (11.4%) | 3 (3.7%) | NA |
| Bicycle accident | 58 (15.3%) | 7 (8.5%) | NA |
| Violence | 65 (17.2%) | 1 (1.2%) | NA |
| Sports accident | 54 (14.3%) | 30 (36.6%) | NA |
| Hit object | 17 (4.5%) | 6 (7.3%) | NA |
| Other* | 3 (0.8%) | 9 (11.0%) | NA |
| Unknown | 3 (0.8%) | 0 (0%) | NA |
| Surgery (TC) (%yes/no) | NA | 25/75 | NA |
| Prior Uncomplicated mild TBI | | | |
| No prior mTBI | 292 (77.2%) | 75 (91.5%) | 73 (88.0%) |
| 1 | 65 (17.2%) | 4 (4.9%) | 8 (9.6%) |
| 2 | 15 (4.0%) | 2 (2.4%) | 0 |
| 3 | 1 (0,3%% | 0 | 0 |
| 4 | 1 (0,3%) | 0 | 0 |
| Missing | 4 (1.1) | 1 (1.2%) | 2 (2.4) |
| Mean years since last prior mTBI (SD) | 12.2 (10.3) | 14.6 (9.22) | 23.5(13.6) |
| CT | | | |
| Normal | 252 (66.7%) | NA | NA |
| No CT | 79 (20.9%) | NA | NA |
| Facial Fracture | 18 (4.8%) | NA | NA |
| Cranial Fracture | 5 (1.3%) | NA | NA |
| Intracranial lesions | 11 (2.9%) | NA | NA |
| Fracture and intracranial lesions | 11 (2.9%) | NA | NA |
| Other | 2 (0.5%) | NA | NA |
| MRI (within 72h of injury) | | | |
| Normal | 172 (45.5%) | NA | NA |
| Extracranial findings | 3 (0.8%) | NA | NA |
| Intracranial findings | 23 (6.1%) | NA | NA |
| Not performed | 180 (47.6%) | NA | NA |
| Prescribed psychotropic medication before injury/study inclusion | | | |
| Yes | 25 (6.6%) | 7 (8.5%) | 2 (2.4%) |
| No/No answer | 353 (93.4%) | 75 (91.5%) | 81 (97.6%) |
| Prescribed medication after injury | | | |
| Yes | 39 (10%) | 22 (27%) | NA |
| No/No answer | 339 (90%) | 60 (73%) | NA |
| Average total sleep time the two weeks before injury/ study inclusion | | | |
| Mean (SD) | 7.09 (1.11) | 7.18 (1.03) | 6.90 (0.92) |
| Poor sleep quality the two weeks before injury/study inclusion | | | |
| Yes | 25 (6.6%) | 5 (6.1%) | 2 (2.4%) |
| No | 346 (91.5%) | 76 (92.7%) | 78 (94.0%) |
| Missing | 7 (1.9%) | 1 (1.2%) | 3 (3.6%) |
| Prior Psychiatric Disorders | | | |
| No psychiatric history | 316 (83.6%) | 72 (87.8%) | 69 (83.1%) |
| Depression | 22 (5.8%) | 6 (7.3%) | 4 (4.8%) |
| Anxiety | 17 (4.5%) | 2 (2.4%) | 1 (1.2%) |
| Other** | 16 (4.2%) | 0 (0%) | 1 (1.2%) |
| Missing | 7 (1.8%) | 2 (2.4%) | 8 (9.6%) |

*Other injuries in the trauma control group include sharp injuries, such as cuts.

**Other psychiatric disorders include disorders that few individuals reported such as eating disorders

GCS: Glasgow Coma Scale, PTA: Post Traumatic Amnesia, LOC: Loss of consciousness, CT: Computed Tomography, MRI: Magnetic Resonance Imaging, OCD: Obsessive Compulsive Disorder; NA, not applicable.

status ($p = 0.379$; Table 1), or between patients with mTBI and trauma controls in time to return to work at any of the time points after injury (Table 2).

We observed no significant differences between patients with mTBI and the two control groups in self-reported total sleep time the 2 weeks before study inclusion ($p = 0.160$; Table 1). At 2 weeks, the time point where community controls had available data, both patients with mTBI and trauma controls reported significantly higher pain levels than community controls (Table 2). Patients with mTBI and trauma controls did not differ significantly in levels of pain intensity at 2 weeks, 3 months, or 12 months. Throughout all time points, most patients with mTBI who reported pain had pain in their head, face, or neck region, whereas most trauma controls and community controls who reported pain had pain in other parts of the body (Table 2).

Of the 378 included patients with mTBI, 333 (88%) completed the 3-month interview, and 321 (85%) completed the 12-month interview. The 3-month questionnaire was completed by 235 patients (62%) and the 12-month questionnaire by 239 patients (63%). Most patients had more than one follow-up time point with interview data ($n = 363$; 96%) and questionnaire data ($n = 298$; 78%). In total, 365 patients with mTBI (97%; Fig. 2), 79 trauma controls (96%), and 77 community controls (93%) had at least one follow-

Table 2. Time Related Variables

| *Variable* | *Mild TBI patients* n=*378* | *Trauma controls* n=*82* | *Community controls* n=*83* | *p-value* |
|---|---|---|---|---|
| | n (%) | n (%) | n (%) | |
| Return to work/studies at 2 weeks | | | | |
| No sick leave | 147 (38.8%) | 32 (39.0%) | NA | p=0.122 |
| Returned to work/studies | 93 (24.6%) | 14 (17.1%) | NA | |
| Not returned to work/studies | 91 (24.1%) | 27 (32.9%) | NA | |
| Returned part-time | 11 (2.9%) | 5 (6.1%) | NA | |
| Unemployed before injury | 24 (6.3%) | 2 (2.4%) | NA | |
| Missing | 12 (3.2%) | 2 (2.4%) | NA | |
| Return to work/studies at 3 months | | | | |
| No sick leave | 126 (33.3%) | 29 (35.4%) | NA | p=0.601 |
| Returned to work/studies | 165 (43.6%) | 33 (40.2%) | NA | |
| Not returned to work/studies | 26 (6.9%) | 8 (9.8%) | NA | |
| Returned part-time | 15 (4.0%) | 3 (3.7%) | NA | |
| Unemployed before injury | 24 (6.4%) | 2 (2.4%) | NA | |
| Missing | 22 (5.8%) | 7 (8.5%) | NA | |
| Return to work/studies at 12 months | | | | |
| No sick leave | 93 (24.6%) | 27 (32.9%) | NA | p=0.202 |
| Returned to work/studies | 159 (42.1%) | 39 (47.6%) | NA | |
| Not returned to work/studies | 23 (6.1%) | 3 (3.7%) | NA | |
| Returned part-time | 5 (1.3%) | 0 (0%) | NA | |
| Unemployed before injury | 24 (6.3%) | 2 (2.4%) | NA | |
| Missing | 74 (19.6%) | 11 (13.4%) | NA | |
| Pain location 2 weeks | | | | |
| Head, Neck or face | 105 (39.2%) | 8 (10.7%) | 6 (8%) | p<0.001 |
| Other parts of the body | 33 (12.3%) | 41 (54.7%) | 15 (20%) | |
| No pain | 130 (48.5%) | 26 (34.7%) | 55 (72%) | |
| Pain location at 3 months | | | | |
| Head, Neck or face | 53 (22.6%) | 6 (8.0%) | NA | p<0.001 |
| Other parts of the body | 25 (10.7%) | 24 (32.0%) | NA | |
| No pain | 156 (66.7%) | 45 (60.0%) | NA | |
| Pain location at 12 months | | | | |
| Head, Neck or face | 48 (20.1%) | 4 (6.1%) | NA | p<0.001 |
| Other parts of the body | 20 (8.4%) | 18 (27.3%) | NA | |
| No pain | 171 (71.5%) | 44 (66.7%) | NA | |
| | Median (range) | Median (range) | Median (range) | |
| Pain intensity (NRS 0–11) at 2 weeks | 1 (10) | 2 (9) | 0 (6) | p<0.001 |
| Pain intensity (NRS 0–11) at 3 months | 0 (8) | 0 (7) | NA | p=0.375 |
| Pain intensity (NRS 0–11) at 12 months | 0 (10) | 0 (8) | NA | p=0.745 |

Chi squre tests were used to investigate group differences in return to work and pain location 2 weeks, 3 months and 12 months after injury. Kruskal-Wallis test was used to investigate group differences in pain intensity at 2 weeks. Mann-Whitney U tests were performed to investigate which groups were statistically significant from one another in pain intensity at 2 weeks. These tests showed that patients with mTBI (U=7211, p<0.001, r=0.22) and trauma controls (U=1589, p<0.001, r=0.61) had significantly higher pain intensity compared to community controls. Patients with mTBI did not differ significantly from trauma controls in pain intensity 2 weeks after injury (U=8821, p=0.090, r=.0.09. Mann-Whitney U tests were also used to investigate differences between patients with mTBI and trauma controls in pain intensity 3 months and 12 months after injury.

NRS, Numeric Rating Scale.

up time point after baseline. In total, 56 patients with mTBI (15%), 11 trauma controls (13%), and 15 community controls (18%) were lost to follow-up.

### *The prevalence of sleep-wake disturbance and fatigue*

Patients with mTBI consistently reported higher rates of having problems with sleep need, poor sleep quality, excessive daytime sleepiness, and fatigue than both control groups. Results from mixed logistic regression models are presented in Table 3 and Figure 3. There were no statistically significant interaction effects between time after injury and group affiliations for any of the models. This means there were no significant differences in the degree of worsening or recovery from SWD or fatigue between the groups (mTBI, community controls, or trauma controls). In addition, there were no significant interaction effects between previous psychiatric disorders and group affiliation for any of the models. This means there were no differences in the effect of previous psychiatric disorders on SWD and fatigue between the groups (mTBI, community controls, or trauma controls). Therefore, the models were run without interaction effects. Age, sex, and previous history of psychiatric disorders were controlled for in all models. Across the groups, female sex was associated with increased sleep need ($p=0.014$), poor sleep quality ($p=0.048$), excessive daytime sleepiness ($p=0.013$), and fatigue ($p=0.013$). Older age was associated with fatigue ($p=0.048$), and reporting a previous psychiatric disorder was associated with poor sleep quality ($p<0.001$) and fatigue ($p=0.017$).

In the models, throughout the first year after injury, patients with mTBI had a significantly higher prevalence of problems with

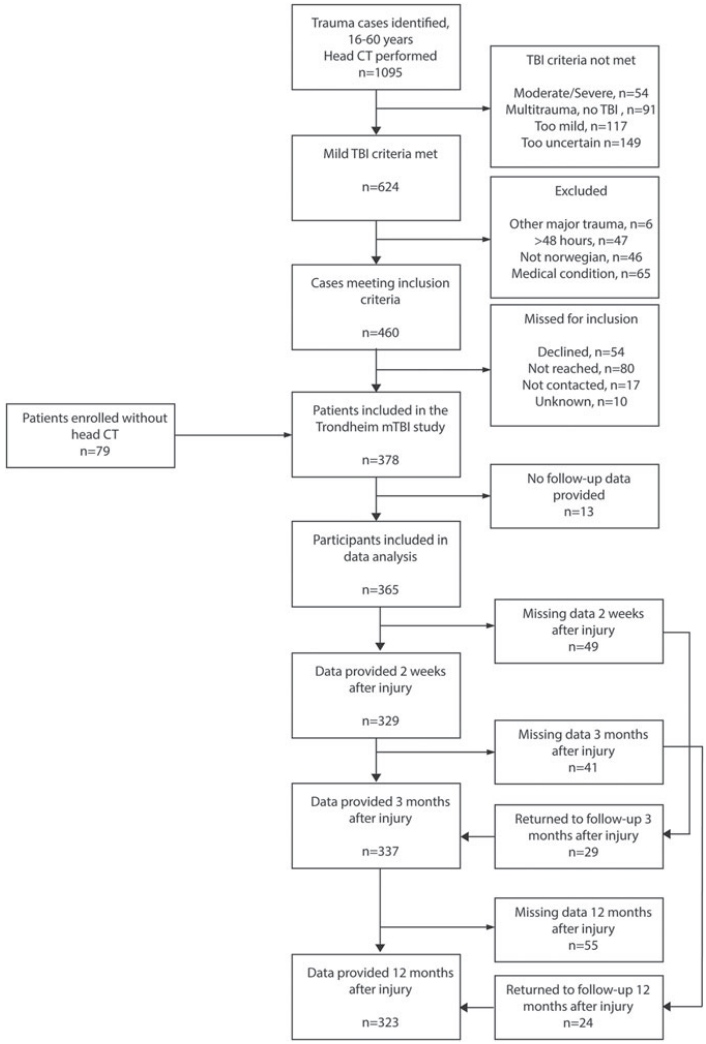


**FIG. 2.** Flowchart of follow-up, patients with mTBI. CT, computed tomography; mTBI, mild traumatic brain injury; TBI, traumatic brain injury.

increased sleep need (odds ratio [OR], 4.7; confidence interval [CI], 1.7–12.8; $p = 0.002$), poor sleep quality (OR, 2.96; CI, 1.1–8.1; $p = 0.034$), excessive daytime sleepiness (OR, 4.26; CI, 1.01–18.07; $p = 0.049$), and fatigue (OR, 7.4; CI, 2.1–26.1; $p = 0.002$) compared to trauma controls.

Patients with mTBI also had a significantly higher prevalence than community controls with regard to poor sleep quality (OR, 7.3; CI, 17.0-38.8; $p = 0.007$) and fatigue (OR, 7.2; CI, 1.9–27.4; $p = 0.004$), but not excessive daytime sleepiness (OR, 2.5; CI, 0.6–9.9; $p = 0.205$). Trauma controls did not report significantly higher prevalence than community controls on problems with poor sleep quality (OR, 4.71; CI, 0.9–22.7; $p = 0.054$), excessive daytime sleepiness (OR, 0.81; CI, 0.13–4.90; $p = 0.811$), or fatigue (OR, 1.45; CI, 0.3–7.3; $p = 0.650$).

### *The stability of poor sleep quality, excessive daytime sleepiness, and fatigue in mild traumatic brain injury and trauma controls*

Fifty-two percent of patients with mTBI and 30% of trauma controls reported SWD or fatigue at least one time point after injury. Table 3 shows that there was a decrease (estimated decrease in odds) in prevalence of SWD and fatigue throughout the first year after injury, but significantly so only for increased sleep need between 2 weeks and 3 months (OR, 0.22; CI, 0.12–0.40; $p < 0.001$) and for fatigue between 2 weeks and 12 months after injury (OR, 0.45; CI, 0.23–0.88; $p = 0.020$). Poor sleep quality and excessive daytime sleepiness did not have a significant change in prevalence over time. Trauma controls did not display significantly different

TABLE 3. MIXED LOGISITC REGRESSION MODELS COMPARING PATIENTS WITH MTBI TO TRAUMA CONTROLS AND COMMUNITY CONTROLS

| *Variables* | *Group difference mTBI vs. TC OR (95%CI)* | p-*value* | *Group difference mTBI vs. CC OR (95%CI)* | p-*value* | *Group difference TC vs. CC OR (95%CI)* | p-*value* | *Change over time OR (95%CI)* | p-*value* |
|---|---|---|---|---|---|---|---|---|
| Increased sleep need | 4.70 (1.73–12.76) | p=**0.002** | - | - | - | - | | |
| 2 weeks – 3 months | | | | | | | 0.22 (0.12–0.40) | p**<0.001** |
| Poor Sleep Quality | 2.96 (1.08–8.06) | p=**0.034** | 7.30 (1.73–30.80) | p=**0.007** | 4.71 (0.98–22.70) | p=0.054 | | |
| 2 weeks – 3 months | | | | | | | 0.72 ( 0.43–1.21) | p=0.217 |
| 2 weeks – 12 months | | | | | | | 0.65 (0.38–1.10) | p=0.109 |
| Excessive Daytime Sleepiness | 4.26 (1.01–18.07) | p=**0.049** | 2.46 (0.61–9.92) | p=0.205 | 0.81 (0.13–4.94) | p=0.811 | | |
| 2 weeks – 3 months | | | | | | | 0.45 (0.20–1.06) | p=0.054 |
| 2 weeks – 12 months | | | | | | | 0.56 (0.25–1.22) | p=0.144 |
| Fatigue | 7.38 (2.08–26.09) | p=**0.002** | 7.22 (1.91–27.36) | p=**0.004** | 1.45 (0.29–7.28) | p=0.650 | | |
| 2 weeks – 3 months | | | | | | | 0.57 (0.30–1.08) | p=0.086 |
| 2 weeks – 12 months | | | | | | | 0.45 (0.23–0.88) | p=**0.020** |

Mixed logisitc regression models without interaction between time x group affiliation and group x psychiatric history are presented. ORs in the models represents the increase in odds for having the symptoms depending on whether the participants belongs to the mTBI, TC or CC group. ORs over time represents the change in odds over time, and respective p-values indicate whether this change is statistically significant. A separate logistic regression model were completed, comparing patients with mild TBI, TC and CCs on poor sleep quality 2 weeks after injury, because this was the only time point were CCs had available data. Age, sex and prior psychiatric disorders were controlled for in all models.

mTBI: Mild Traumatic Brain Injury, TC: Trauma Controls, CC: Community Controls, OR: Odds Ratio. CI: 95% Confidence Interval. Bold p-values are significant at the 0.05 alpha level.

changes in SWD and fatigue over time compared to patients with mTBI. Given that patients with mTBI had higher levels of SWD and fatigue early after injury, this difference therefore remained similar across time points the first year after injury (Fig. 3).

In total, of the mTBI patients experiencing SWD and fatigue 2 weeks after injury ($n=136$), approximately half ($n=72$, 53%) continued to experience these problems for 3 months or longer. Of the trauma controls experiencing SWD and fatigue 2 weeks after injury ($n=20$), 35% ($n=7$) continued to experience these problems 3 months or longer.

### *Prevalence of sleep-wake disturbance and fatigue after complicated mild traumatic brain injury*

When comparing patients with complicated mTBI, patients with uncomplicated mTBI, and trauma controls, there were no significant interaction effects (group affiliation × time since injury or group affiliation × previous history of psychiatric disorders). The models were therefore run without interaction effects. Age, sex, and previous psychiatric disorders were controlled for in the models. Patients with complicated mTBI had statistically significant higher prevalence of problems with fatigue compared to patients with uncomplicated mTBI (OR, 3.6; CI, 1.0–12.3; $p=0.045$). There were no statistically significant differences between patients with complicated and uncomplicated mTBI regarding levels of increased sleep need, poor sleep quality, or excessive daytime sleepiness (Table 4).

Patients with complicated mTBI had significantly higher prevalence of increased sleep need (OR, 7.2; CI, 1.9–27.4; $p=0.004$) and fatigue (OR, 22.8; CI, 4.2–124.2; $p<0.001$) compared to trauma controls. No significant differences were observed between patients with complicated mTBI and trauma controls in regard to poor sleep quality or excessive daytime sleepiness.

Patients with uncomplicated mTBI had significantly higher prevalence of increased sleep need (OR, 4.4; CI, 1.7–11.9; $p=0.003$), poor sleep quality (OR, 2.7; CI, 1.0–7.4; $p=0.047$), excessive daytime sleepiness (OR, 5.2; CI, 1.2–22.1; $p=0.024$), and fatigue (OR; 6.4; CI, 1.8–22.4; $p=0.004$) compared to trauma controls.

### *Overlap of symptoms*

We examined the overlap between increased sleep need, poor sleep quality, excessive daytime sleepiness and fatigue. A considerably large proportion of patients with mTBI reported only one specific problem, rather than a combination of more problems at the same time point (Fig. 4). In total, 61%, 75%, and 79% of the patients with mTBI that reported problems at 2 weeks, 3 months, and 12 months, resepectively, reported one problem. Compared to SWDs, fewer patients reported fatigue as their only problem. Two weeks after injury, 29% of patients with mTBI reporting fatigue had fatigue as their only problem, whereas 45% reported increased sleep need, 46% reported poor sleep quality, and 41% reported excessive daytime sleepiness as their only problem. The proportion of patients with mTBI experiencing one problem rather than several problems increased over time. Three months after injury, 48% reported increased sleep need, 68% reported poor sleep quality, 57% reported excessive daytime sleepiness, and 43% reported fatigue as their only problem. By 12 months after injury, 71% reported poor sleep quality, 69% reported excessive daytime sleepiness, and 58% fatigue as their only problem (increased sleep need not included).

## Discussion

This study shows that SWD and fatigue are considerably more common throughout the first year after mTBI than after orthopedic trauma and in community controls. Our findings extend and

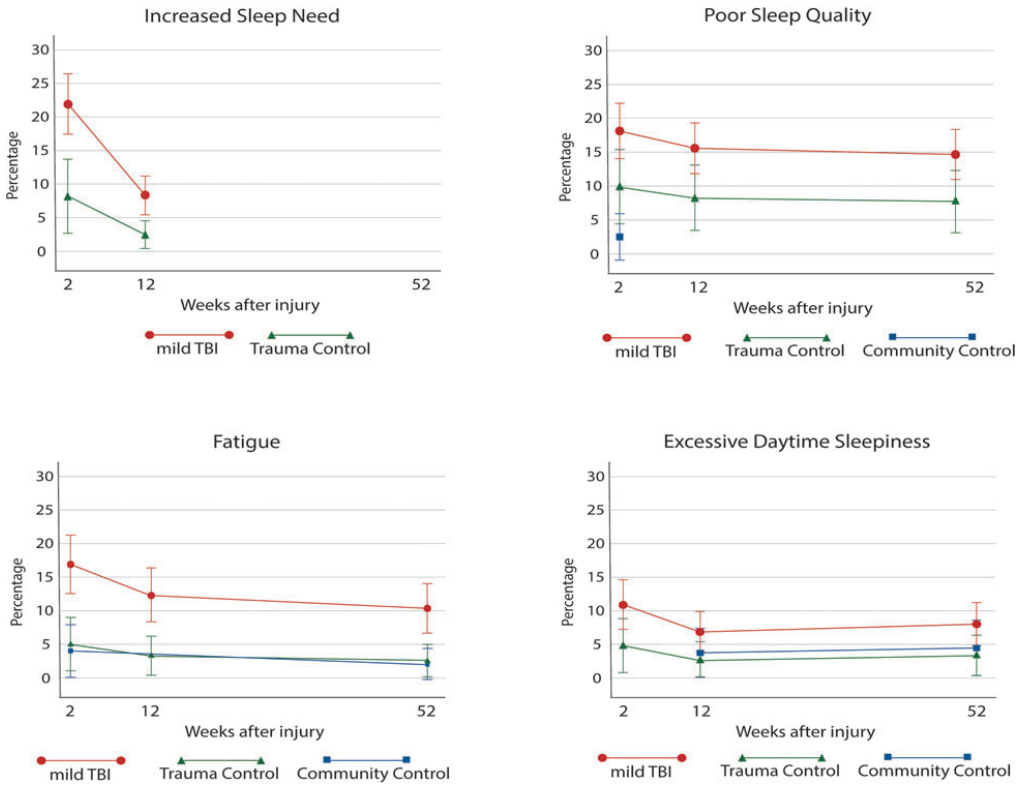


**FIG. 3.** Estimated proportion of patients with mTBI, trauma controls, community controls with sleep-wake disturbances, and fatigue over the course of 1 year after injury. mTBI, mild traumatic brain injury.

substantiate previous studies by showing that *both trauma groups* (mTBI and orthopedic trauma controls) have a reduction of SWD and fatigue problems during the first year after injury; but whereas trauma controls return to levels similar to community controls 3 months after injury, a considerable proportion of patients with mTBI do not recover fully by 12 months after injury. In fact, as many as 53% of mTBI patients who experienced SWD or fatigue at 2 weeks after injury in the present study had persisting problems that lasted 3 months or longer. Stable symptoms lasting >3 months is a key criterion for insomnia and hypersomnolence disorder in the diagnostic manual DSM-5.[6]

These findings indicate that an mTBI is involved in onset and maintenance of SWD and fatigue, even when compared to other types of injuries, and when age, sex, and history of previous psychiatric disorders are controlled for. Patients with complicated mTBI had higher levels of fatigue than those with uncomplicated mTBI, which further suggests a dose-response relationship between brain injury severity and fatigue. Moreover, a few of the patients with mTBI had more than one problem with SWD and fatigue at once, indicated by the limited overlap between the individual measures of SWD and fatigue. This suggests that these different problems may be linked to different underlying mechanisms, and that personalized symptom-targeted strategies may be effective in the treatment of SWD and fatigue after mTBI.

Higher proportions of patients with mTBI had increased sleep need, poor sleep quality, excessive daytime sleepiness, and fatigue compared to trauma controls throughout the first year after injury. Compared to community controls, a larger proportion of patients with mTBI reported poor sleep quality and fatigue, whereas there was no statistically significant difference in excessive daytime sleepiness. Previous cross-sectional studies have indicated that both SWD and fatigue are more prevalent within the first month after mTBI, compared to trauma controls[47] and community controls.[30,48–50] Other longitudinal studies with control groups have also shown that SWD and fatigue are more common the first month after injury in patients with mTBI than in trauma controls[24,25,51] and community controls.[51] However, in these studies, patients with mTBI have typically recovered to similar levels of SWD and fatigue as trauma-[23–25] and community controls[51] 1–3 months after injury.

Previous findings therefore imply that patients with mTBI recover more rapidly than trauma controls. In contrast, we did not observe any statistically significant interaction effects between group (mTBI vs. trauma controls) and time in our study. This means that the two injury groups did not differ in rate of recovery from SWD or fatigue. In fact, the present study and longitudinal studies without control groups[1,10] show that a substantial number of patients with mTBI report SWD and fatigue also >3 months after injury. We also observed that trauma controls had recovered to similar levels of SWD and fatigue as community controls at 3 months after injury. Earlier longitudinal studies also report higher rates of SWD at 6, 12, and 18 months after mTBI[1] compared to

TABLE 4. MIXED LOGISTIC REGRESSION MODELS COMPARING PATIENTS WITH COMPLICATED MTBI, UNCOMPLICATED MTBI AND TRAUMA CONTROLS

| *Variables* | *Group difference cmTBI vs. umTBI OR (95%CI)* | *p-value* | *Group difference cmTBI vs. TC OR (95%CI)* | *p-value* | *Group difference umTBI vs. TC OR (95%CI)* | *p-value* | *Change over time OR (95%CI)* | *p-value* |
|---|---|---|---|---|---|---|---|---|
| Increased sleep need | 1.62 (0.59–4.40) | p = 0.347 | 7.20 (1.89–27.41) | p = **0.004** | 4.45 (1.67–11.88) | p = **0.003** | | |
| 2 weeks – 3 months | | | | | | | 0.24 (0.14–0.44) | p<**0.001** |
| Poor Sleep Quality | 1.52 (0.45–5.18) | p = 0.500 | 4.17 (0.95–18.30) | p = 0.058 | 2.73 (1.01–7.41) | p = **0.047** | | |
| 2 weeks – 3 months | | | | | | | 0.73 (0.43–1.24) | p = 0.248 |
| 2 weeks – 12 months | | | | | | | 0.58 (0.33–1.02) | p = 0.058 |
| Excessive Daytime Sleepiness | 0.28 (0.37–2.07) | p = 0.211 | 1.46 (0.15–14.55) | p = 0.749 | 5.23 (1.24–22.08) | p = **0.024** | | |
| 2 weeks – 3 months | | | | | | | 0.44 (0.19–0.99) | p = **0.048** |
| 2 weeks – 12 months | | | | | | | 0.60 (0.27–1.32) | p = 0.207 |
| Fatigue | 3.56 (1.03–12.29) | p = **0.045** | 22.78 (4.17–124.20) | p<**0.001** | 6.40 (1.82–22.42) | p = **0.004** | | |
| 2 weeks – 3 months | | | | | | | 0.60 (0.32–1.15) | p = 0.123 |
| 2 weeks – 12 months | | | | | | | 0.50 (0.25–0.97) | p = **0.041** |

Mixed logistic regression models without interaction between time x group affiliation and psychiatric history x group affiliation are presented. ORs in the models represents the increase in odds for having the SWDs and fatigue depending on whether the participants belong to the complicated mTBI, uncomplicated mTBI or TC group. ORs over time represents the change in odds over time, and respective p-values indicate whether the change is statistically significant. Age, sex and prior psychiatric disorders were controlled for in all the models.

Bold p-values indicate significant p-values at the 0.05 alpha level.

cmTBI: Complicated Mild Traumatic Brain Injury, umTBI: Uncomplicated mTBI, TC: Trauma Controls, OR: Odds Ratio, CI: 95% Confidence Interval.




**FIG. 4.** Overlap of increased sleep need, poor sleep quality, excessive daytime sleepiness, and fatigue 2 weeks to 12 months after injury for patients with mTBI. mTBI, mild traumatic brain injury; SWD, sleep-wake disturbance.

control groups[37,38] and the general population.[52] In the context of the present results, these findings support the hypothesis that the brain injury itself may be involved in onset of SWD and fatigue.

We did not have direct information about shift work, social jet lag, sleep satiation, or rhythms, which may also impact sleep-wake outcomes.[53,54] However, the groups included in our study did not

differ much in the distribution of occupational status or in their self-reported average total sleep time the last 2 weeks before inclusion to the study (i.e., before the injury for the patient groups). Neither was there any evidence of a difference between patients with mTBI and trauma controls regarding return to work/school after injury. Although not providing the same stringent level of control as in other studies,[37,38] there were therefore no obvious contextual factors indicating that there should be any substantial differences in sleep habits or rhythms across the groups.

The proportion of patients that was injured because of violence was higher in the mTBI group than in the trauma control group. Earlier studies on mTBI have found that injuries caused by violence are associated with more time away from work,[55] post-traumatic stress, and depression.[56] More generally, violence is often associated with stress-related symptoms, including problems with SWD and fatigue.[57] Consequently, we cannot completely rule out that differences in injury mechanisms may have contributed to the differences in SWD and fatigue between patients with mTBI and trauma controls.

Pain can be associated with SWD and fatigue after any kind of trauma.[22] In our study, both patient groups reported higher levels of pain intensity than community controls, as well as considerably higher levels of pain intensity at 2 weeks than at 3 and 12 months after injury. As expected, the mTBI group mainly reported pain in their head, face, or neck region, whereas trauma controls and community controls predominantly reported pain in other parts of their body. Despite this difference in pain topography, level of pain intensity did not differ between the mTBI group and trauma controls at any time point. It is therefore unlikely that the differences in SWD between these groups can be explained by differences in pain intensity.

In the present study design,[32] we applied more liberal inclusion criteria compared to previous longitudinal studies comparing mTBI patients with control groups on SWD and fatigue measures.[23–25] Differences in exclusion criteria may explain the aforementioned discrepancies between the present study and earlier controlled longitudinal studies investigating SWD and fatigue after mTBI.[23–25] These earlier studies excluded many patients, such as patients with complicated mTBI,[25] or patients with pre-existing conditions, such as psychiatric problems[23,24] or previous mTBI.[23,24] Only patients with *previous complicated*, but not *uncomplicated*, mTBI were excluded from participation in our study. Patients with *current* complicated mTBI were included in our study, albeit these patients accounted for a small fraction of the total sample (9% with intracranial findings on CT or MRI). Regarding previous psychiatric problems, only patients with mTBI and *severe* ongoing psychiatric disorders that would complicate follow-up were excluded in the present study. Reporting a previous psychiatric disorder was generally associated with poor sleep quality and fatigue across groups, but there was no evidence that this relationship differed between patients with mTBI and the control groups.

Importantly, even when controlling for previous psychiatric disorders in our analyses, we obtained different results than other studies.[23–25] Two of the aforementioned studies[23,24] stated that the aim of their study was to have a more homogeneous sample, whereas the present study aimed for a representative (and, as a consequence, more heterogeneous) mTBI sample. Another difference between the present study and earlier controlled longitudinal studies is that we also included patients from the primary healthcare setting, persons who are not often included in mTBI research. A recent population-based longitudinal study that applied similar exclusion procedures as the present study, and also included patients in a primary healthcare system, similarly found SWD to remain a significant long-term problem after mTBI.[1] Altogether, these findings show that when including patients with mTBI who are often not included in mTBI research, SWD and fatigue appear to be considerable long-term problems after mTBI.

Prevalence of fatigue problems was statistically significantly higher in the subgroup of patients with complicated mTBI compared to the group considered to have uncomplicated mTBI. Although patients with uncomplicated mTBI still had significantly higher prevalence of fatigue compared to trauma controls, this further supports a link between visible brain pathology and fatigue. We failed to demonstrate any statistically significant differences in SWD between the complicated and uncomplicated mTBI groups; however, the results from the subgroup analyses should be interpreted with caution considering the modest sample size and relatively large confidence intervals in these analyses. Earlier studies have shown that complicated mTBI may be associated with worse outcomes and higher levels of symptoms.[58–60] There are, however, only a few existing large-scale longitudinal studies, and these show small to no effects of findings on early MRI and CT.[61] Consequently, no consensus has been reached regarding the predictive value of complicated mTBI on symptom development post-mTBI.[62]

The present study is the first study to show a relationship between complicated mTBI and fatigue after adult mTBI. These findings indicate that the effects of the brain injury itself may be involved in the onset of fatigue, which has previously been demonstrated only after moderate and severe TBI.[63] The imaging protocol used in the present study was comprehensive and state-of-the-art from a clinical perspective. It is possible that some patients with mTBI in our sample have poor white matter organization attributable to their mTBI, which is only detectable with potentially more-sensitive MRI techniques, such as diffusion tensor imaging (DTI).[64] Earlier studies using DTI and DWI have indicated a link between disrupted white matter organization and SWD and fatigue after mTBI, but with small to modest sample sizes and varying time after injury.[65–67] Our future work will further investigate *longitudinal* associations between white matter organization and the development of SWD after mTBI using advanced MRI techniques, including DTI, DWI, and structural morphological measures.

It is important to note that most mTBI patients (55%) and trauma controls (77%) did not report any SWD or fatigue during the first year after injury. We also observed a decrease in prevalence of SWD and fatigue throughout the first year after injury, statistically significant so for increased sleep need and fatigue. Still, 55% of patients with mTBI who had SWD and fatigue 2 weeks after injury had problems that lasted 3 months or longer. Detection of SWD and fatigue is crucial for optimal recovery in patients with mTBI, because such problems are related to a range of negative consequences, including impeded long-term recovery,[68] reduced cognitive functioning,[1,69] social and functional outcome,[1,70] emotional processing,[71] and other post-concussive symptoms.[1] Screening for SWD and fatigue in an early phase can therefore be beneficial for these patients because interventions and advice about sleep hygiene can be effective and improve overall outcome.[5] On the other hand, given that approximately half of patients with SWD and fatigue recovered, future work should also focus on more detailed delineation of risk factors for prolonged SWD and fatigue as well as protective factors for recovery.

We observed limited overlap between individual symptom measures of SWD and fatigue across all time points in this study (Fig. 4). For patients with mTBI who reported SWD or fatigue, 61%, 75%, and 79% reported experiencing one problem rather than two or more problems at 2 weeks, 3 months, and 12 months, respectively. That relatively few patients with mTBI reported fatigue as their only problem 2 weeks after injury is somewhat mirroring the diagnostic criteria for insomnia and hypersomnolence disorder, in which these

disorders often are accompanied by daytime distress in the form of fatigue.[6] All SWDs and fatigue decreased over time, resulting in reduced overlap, but the number of patients with mTBI experiencing one problem remained stable, resulting in an increasing proportion of patients with mTBI experiencing one problem with time.

The present study therefore indicates that it is important to include several measures to capture the full extent of SWD and fatigue after mTBI. Moreover, limited overlap between increased sleep need, poor sleep quality, excessive daytime sleepiness, and fatigue suggests that these problems may have different underlying mechanisms.[31] If these problems have distinct underlying mechanisms, personalized[72] and symptom-targeted treatment strategies may be more viable than a generic approach aimed at post-concussive problems in general.[73]

Altogether, findings from the present study show that persons with mTBI can have different paths to the development and maintenance or recovery from SWD and fatigue. Clinical decision making is challenging after mTBI, but sleep is a modifiable factor.[73] Targeted SWD interventions have been shown to be effective in reducing the symptom burden of comorbid symptoms in other patient populations,[74] and preliminary findings are also promising for patients with mTBI.[75]

### *Limitations*

Our results rely on self-reported data collected through structured interviews and questionnaires. It is important to capture the person's own perceived state,[7] but questionnaires may not be as precise in capturing clinically relevant problems as clinical diagnostic interviews.[6] Objective measures, such as polysomnography and actigraphy, may also be effective in measuring total sleep time or sleep efficiency.[38,76] Insomnia is based on the subjective assessment of having disturbed sleep,[6] whereas pleiosomnia is based on objective assessments of sleep quantity and/or daytime sleepiness.[36–38] This distinction is important given that earlier studies have revealed important differences between objective and subjective sleep measures in TBI. Both subjective sleep duration and subjective sleepiness may be underestimated relative to objective assessments of sleep duration and sleepiness in TBI.[37,38] Consequently, our finding that subjective sleepiness was not more prevalent after mTBI than in community controls should be interpreted with caution given that there may be differences in objective sleepiness.

We had a high success rate in contacting participants for interviews, but less success in receiving complete questionnaires from our participants. Based on our attrition analyses, we found treating the data as missing at random to be reasonable, and our primary analysis is robust to missing data under the missing at random assumption.[77] Therefore, the missing data are not expected to have a large impact on our results. We did not investigate other SWDs, such as circadian rhythm sleep disorder[78] or obstructive sleep apnea,[79] which can affect increased sleep need, sleep quality, excessive daytime sleepiness, or fatigue.[17]

We applied relatively conservative cut-off scores for determining SWD and fatigue problems, also compared to earlier similar studies.[1,10] Currently, there is no consensus in the literature on whether to use originally defined cutoffs[1] or study-specific cutoffs.[10] The use of different cut-off values limits direct comparisons between studies. However, a strength in our approach was that our cut-off values were based on recommendations from earlier validation studies[44] and studies comparing subjective and objective measures.[42] Using strict cut-off values increased the chance of false negative findings, but in the context of our study, we are at least confident that we have avoided an overestimation of significant problems with SWD and fatigue.[44]

Fatigue, as measured with the FSS, may overlap with conditions such as depression and apathy.[80] We adjusted for previous psychiatric disorders in our analyses, but we cannot rule out that the levels of fatigue measured in our study may be overlapping or interacting with other post-injury symptomatology that was not included in our analyses.

There is a substantial pre-clinical and clinical body of evidence that repeated mTBI has a more severe effect on SWD than a single mTBI.[81–84] Our data on previous uncomplicated mTBI was based on self-report and obtained according to procedures used in other studies.[35] However, considering the uncertainty of such data,[85] and the considerable variance in time after injury (Table 1), we did not consider our data to have sufficient quality for being included in formal analyses.

The findings in the present study were limited in the comparison of patients with mTBI to community controls because community controls did not provide data at all the time points. We did not observe much change in scores for community controls on SWD and fatigue measures that were available for two time points. It is therefore not likely that this lack of data has significant impact on the main conclusions in this study.

One strength of the present study was the inclusion of both trauma controls and community controls. The sample size in the control groups was lower than in the mTBI group because of the lower expected variance in symptoms in the former groups. No formal *a priori* power estimation was performed for determining the sample size for the specific analyses included this study, but the sample size of control groups are comparable to,[25] or larger than,[23,24,37,38] in other studies reporting effects on SWD and fatigue after mTBI.

## Conclusions

The findings in this study demonstrate that mTBI is associated with the presence and maintenance of SWD and fatigue over time. Problems with SWD and fatigue resolve for most, but persist and become chronic for a considerable subgroup of patients with mTBI. It was more common for patients with mTBI to experience one problem with SWD or fatigue, rather than several problems. Moreover, patients with complicated mTBI had higher prevalence of fatigue than did patients with uncomplicated mTBI. Different SWDs and fatigue may therefore have different origins and underlying mechanisms after mTBI. These results therefore indicate that patients with mTBI may benefit from personalized and targeted treatment strategies aimed at the patient's specific symptom burden.

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# PAPER II

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ORIGINAL ARTICLE

# Mild to moderate partial sleep deprivation is associated with increased impulsivity and decreased positive affect in young adults

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## Abstract

The effects of mild–moderate partial sleep deprivation on affective and cognitive functioning were evaluated in a naturalistic home environment, mimicking short sleep typically caused by demands from work or society. A total of 52 healthy individuals aged 18–35 was included in an 11-day study protocol. Participants slept at home, and sleep patterns were observed using actigraphs and sleep diaries. After maintaining habitual sleep for 7 days, the participants were asked to sleep 2 hours less than their average sleep duration for the last three nights of the study protocol. A not-X continuous performance test was administered at 9 am (± 90 minutes) on days 1, 4, 8 (habitual sleep), 9 and 11 (sleep deprivation). Performance-based measures included response accuracy and speed. Participant-reported measures included how well the participants felt they performed and how exhausted they were from taking the test, as well as positive and negative affect. There was a significant change in reaction time, number of commission errors, subjective performance, subjective exertion, and positive affect across the visits. Specifically, there was a linear decrease in reaction time, performance, and positive affect throughout the study, and a significant quadratic trend for commissions and exertion (first decreasing, then increasing after sleep deprivation). The univariate tests for omissions and negative affect were not significant. We conclude that sleeping 1.5–2 hours less than usual leads to faster response speed, but more commission errors and decreased positive affect. This indicates that individuals become more impulsive and experience less positive affect after a period of short sleep.

### Statement of Significance

In this study, we asked participants to sleep 1.5–2 hours less than they usually do for three consecutive nights in their own home. We found that this individually calculated mild to moderate sleep deprivation changed several cognitive and affective processes, indicating that the subjects became more impulsive and experienced reduced positive affect in the morning after the sleep deprivation compared with normal sleep. With these findings, we show that the sleep loss many individuals experience during a normal week significantly affects morning cognitive and emotional functioning, which may increase the risk of mistakes and accidents in everyday life. This could limit the capacity to manage negative life events and stress. Future studies need to investigate individual differences in this change in cognition and affect.

**Key words:** speed-accuracy trade-off; sleep restriction; short sleep; sleep deprivation; affect; cognitive control function; executive function

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## Introduction

Lack of sufficient sleep is associated with cognitive and emotional problems [1, 2] and an increased risk of accidents [3]. Despite the known negative effects of insufficient sleep, shorter sleep has become more common in the last 5 years among adults [4]. Seven to 9 hours of sleep is recommended for young adults and 7–8 hours for older adults [5]. Still, 29.2% of all adults in the 2012 US National Health Survey reported that they sleep less than 6 hours per night [6]. Prior studies have examined how partial sleep deprivation influences cognition and affect, but few have investigated mild–moderate partial sleep deprivation in a naturalistic setting [7]. Also, extant studies have not simultaneously assessed how sleep deprivation may influence both performance-based and participant-reported measures. Accordingly, we lack a broad picture of the effect of mild–moderate sleep deprivation on cognitive and affective processes.

Most research focuses on the effects of total sleep deprivation, while partial sleep deprivation is more common in everyday life [8]. Being deprived of sleep leads to several changes in brain function [9], and short-term total sleep deprivation typically shows negative effects across several cognitive domains [10]. Both total and partial sleep deprivation markedly affect an individual's capacity to sustain attention and maintain vigilance [8, 11], especially for attention tasks with relatively simple task demands [10, 12]. Moreover, partial sleep deprivation, by restricting sleep to 5 hours per night, increases the number of lapses of attention and increases response speed after only two to three nights [13, 14]. A recent meta-analytical review shows that partial sleep deprivation can have negative effects on several cognitive domains, especially sustained attention and executive function [15]. Still, sleeping only 1 hour less than normal does not seem to influence sustained attention and response inhibition [7]. Thus, the critical limit for mild–moderate sleep deprivation remains to be determined.

Sleep loss and poor sleep quality negatively affect how the brain process emotions after a night of poor sleep [16]. Both the ability to express and regulate emotions are affected by lack of sleep [17]. Partial sleep deprivation measured in laboratory settings seems to be associated with decreased positive affect in adolescents and adults [18]. Some studies find no change in negative affect following sleep deprivation [18, 19], whereas others show that partial sleep deprivation may lead to worsening in mood or increase in negative affect [20, 21]. This indicates that sleep deprivation may lower the psychological threshold for experiencing stress and negative affect (i.e. lower cognitive control) in contexts with higher cognitive demands [22, 23]. However, the exact mechanisms of such alterations remain largely unknown, and there is a need for studies investigating both cognition and affect in a naturalistic context of mild–moderate sleep deprivation.

Studies investigating effects of partial sleep deprivation have typically been performed in a laboratory setting, but naturalistic actigraphy studies are recommended when investigating the effects of partial sleep deprivation on cognition to provide more naturalistic and ecologically valid effects [15]. Recently, some studies using this approach have been performed [7, 24], but a challenge with these studies is a lack of control over prior sleep and/or a too-short study period. Although naturalistic and ecologically valid studies are called for, it is still necessary to maintain as much control over the experimental setting as possible. It is therefore necessary for future research to perform naturalistic actigraphy studies of partial sleep deprivation with a higher level of control than what has been the case for previous studies. This should be done by controlling for sleep prior to the sleep deprivation with actigraphy and sleep diary, measuring partial sleep deprivation across several nights, and including more than one baseline test to control for practice effects. It is critical that most previous research performed on partial sleep deprivation has investigated the effects of sleeping a given number of hours, typically 4–5 hours, without considering individual sleep needs. This may lead to a more extensive sleep deprivation than people typically experience in daily life. Thus, the results may not be generalizable to the everyday mild–moderate sleep deprivation many people experience in today's society.

The aim of this study was to incorporate a multiparametric perspective to investigate the effect of mild–moderate partial sleep deprivation on cognitive and affective processes experienced in the morning. To mimic naturalistic short sleep caused by demands from work or society in general, healthy young participants were observed in a naturalistic home environment, and the sleep deprivation protocol was adjusted for individual sleep needs. We hypothesized that mild–moderate partial sleep deprivation in a naturalistic setting would have negative impacts across several cognitive and affective domains measured in the morning.

## Methods

### Sample

A total of 59 healthy individuals aged 18–35 participated in this study. Inclusion criteria were 18–35 years of age and fluency in the Norwegian language. Exclusion criteria were any self-reported severe psychiatric, neurological, or medical conditions. Apart from this, the participants prior sleep habits and sleep quality were not considered in the inclusion or exclusion criteria. Participants were recruited through ads at different university campuses and, nearby, through social media and in lectures. Figure 1 shows a flow chart of the recruitment process. Because we were interested in testing mild–moderate partial sleep deprivation (in line with ref. [15]), we decided to include all participants who successfully complied with the sleep restriction protocol by reducing their sleep for at least 90 minutes or more on all 3 days of the sleep deprivation condition. Seven participants were excluded from the final analyses because of

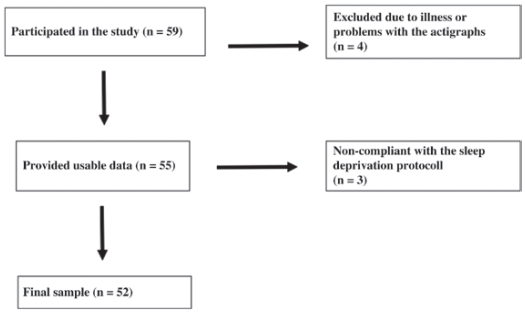


**Figure 1.** Flow chart of participants.

illness during the study or problems with the actigraphs ($n$ = 4) or because they could not comply with the sleep deprivation protocol ($n$ = 3). The final sample included in the analyses comprised 52 individuals, 41 (78.8%) of these were women, and the mean age was 22.57 ($SD$ = 3.09) years.

## Ethics

The study protocol was approved by the Regional Committee for Medical and Health Research Ethics in Central Norway (REK number 2017/85) and was in accordance with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Written informed consent was obtained from all participants.

## Study design

A within-group multiple baseline experimental design was applied (see flow chart in Figure 2).

## Procedure

The participants took part in an 11-day study protocol with partial sleep deprivation applied during the last 3 days of the study (Figure 1). In the mild–moderate [25] partial sleep deprivation protocol, participants were asked to sleep 2 hours less than their average sleep duration in the habitual sleep period (first seven nights). The participants were asked to go to bed 2 hours later than usual and get up at the same time in the morning as in the habitual sleep period. Cognitive and emotional function was assessed at five time points; three times during the habitual sleep period: visit 1 (V1), visit 2 (V2) and visit 3 (V3), and two times during the sleep-deprived condition: visit 4 (V4) and visit 5 (V5).

The participants were tested in groups of 3–15 individuals at different times of the year when the light conditions varied from sunrise at 04.58 am to 06.54 am and from sunset at 6.04 pm to 9.34 pm. Every data collection period started on the same day of the week (Monday). All participants had to meet for five visits on five different days (Monday week 1, Thursday week 1, Monday week 2, Tuesday week 2, and Thursday week 2), every time in the same time slot (see flow chart). Participants were tested at 09.00 in the morning, ± 90 minutes, in line with other experimental sleep deprivation studies [26]. All participants were asked to not consume any caffeinated drinks between awakening and testing.

## Instruments

All participants completed a baseline questionnaire, including demographic information and a range of established and validated instruments measuring sleep, emotional functioning, fatigue, pain, cognitive functioning, and individual differences. The following instruments assessed sleep and sleepiness: Insomnia Severity Index [25], Pittsburgh Sleep Quality Index [27], and Epworth Sleepiness Scale [28], in addition to single questions used in epidemiological studies on sleep duration. The Hospital Anxiety and Depression Scale was included to measure anxiety and depression [29].We used the Fatigue Severity Scale to measure fatigue [30] and the Diurnal Scale to measure morningness/eveningness [31].

All participants were asked to complete a sleep diary every morning during the study. The sleep diary was a modified version of the diary published by Morin [32] and included questions about bedtimes, rise times, sleep latency, and wake periods in the night, enabling us to calculate the participants' subjective sleep duration and sleep efficiency. In addition, the sleep diary included questions about naps, daytime sleepiness, and subjective sleep quality. Subjective sleep quality was measured with one question asking the participants to rate the quality of sleep on a scale from 1 (= very light) to 5 (=very deep) for each day.

### *Actigraphy*

Participants were asked to wear a wrist-worn actigraph device for the whole study period (Actiwatch Spectrum Pro, Philips Respironics, USA). In addition to activity measures based on an accelerometer, this device recorded time and date indicators, event markers, and illuminance monitoring. The actigraphs collected data in 15-second epochs. The actigraphs were used to assess the participants' total sleep time, sleep efficiency, and time of bedtime and rise time (including midpoint of sleep). We used the actigraphy data collected during the habitual sleep period to calculate the participants' individual total sleep time in the sleep-deprived condition and manually cross-checked and adjusted bed time and rise time based on sleep diary data [33], as well as systematic inspection of the automatically coded rest periods in the actograms based on activity, light conditions, and event markers [34]. The participant´s mean total sleep time in

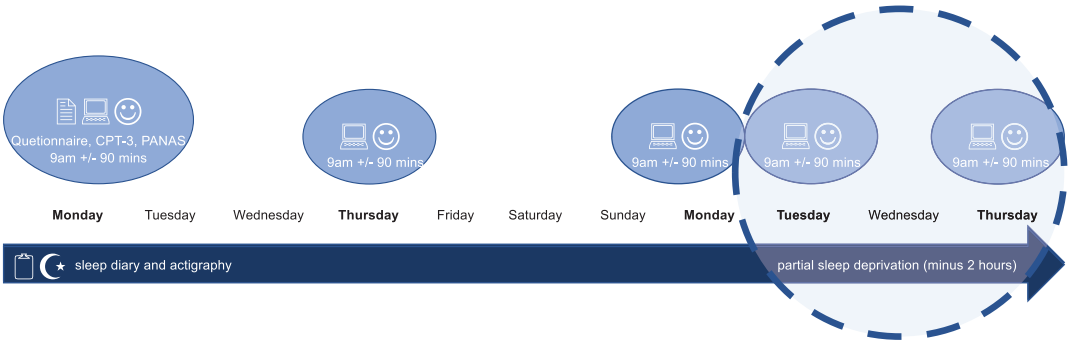


**Figure 2.** Flow chart of the procedure.

**Table 1.** Baseline measures of cognition, affect, sleep, mental health, diurnal preference, and demographic characteristics of the sample measured at visit 1 ($n$ = 47–52)

| | Mean (*SD*) |
|---|---|
| Gender | 41 (78.8%), females |
| Age | 22.58 (3.06) |
| Commissions | 52.00 (8.87) |
| Omissions | 46.15 (2.50) |
| Reaction time | 41.67 (5.04) |
| Negative affect | 13.86 (3.75) |
| Positive affect | 26.82 (5.81) |
| Performance | 4.71 (1.31) |
| Exertion | 4.83 (1.92) |
| Insomnia[a] | 5.77 (3.65) |
| Sleep quality[b] | 3.25 (2.05) |
| Sleepiness[c] | 7.51 (4.48) |
| Anxiety[d] | 5.56 (3.38) |
| Depression[d] | 2.82 (2.42) |
| Fatigue[e] | 3.9 (1.01) |
| Diurnal preference[f] | 17.38 (4.37) |

[a]Measured with Insomnia Severity Index.
[b]Measured with Pittsburgh Sleep Quality Index, where low score indicates good sleep quality.
[c]Measured with Epworth Sleepiness Scale.
[d]Measued with Hospital Anxiety and Depression Scale.
[e]Measured with Fatigue Severity Scale.
[f]Measured with Diurnal Scale.

the habitual sleep period was assessed in the actigraphy software on site (Philips Actiware 6.0.0), and the shortened sleep time was conveyed to the participants verbally and in writing. Actigraphy total sleep time minimum, maximum, mean and standard deviations can be seen in Table 1.

#### *Conners' Continuous Performance Test-3*

The Conners' Continuous Performance Test (CCPT) [35] is an extensively used and well-validated not-X continuous performance test that was used to assess performance-based cognitive control function. Letters A–Z are consecutively presented on the screen in a pseudorandom fashion for 360 trials with a duration of 14 minutes. The participants were instructed to press a button each time a letter is presented on the screen, except for the letter X. Both response speed (hit reaction time, the mean response speed, measured in milliseconds, for all correct responses to target made during the test) and accuracy (omission errors and commission errors) were extracted and used in analyses. Immediately after the test, participants were asked to rate their perceived *performance* and *exertion* on a scale from 1 to 10 (very bad—very good performance; no exertion at all—very much exertion).

#### *The Positive and Negative Affect Schedule*

The Positive and Negative Affect Schedule (PANAS) was used as a self-report measure of positive and negative affect. Positive affect and negative affect reflect independent (orthogonal) affective state dimensions [36]. The scale consists of 20 items (descriptors) describing various feelings and emotions. Respectively, 10 scale items correspond to positive affect (e.g. excited, determined, alert) and 10 items to negative affect (e.g. fear, guilt, nervousness). Cronbach's alpha for positive affect and negative affect at baseline was acceptable at .77 and .75.

### Statistical analysis

Paired-sample *t*-tests were used to evaluate differences in sleep duration and sleep efficiency/quality measured with actigraphy and the sleep diary, midpoint of sleep measured with actigraphy, as well as differences between the habitual sleep period and the sleep-deprived condition. We considered cognitive function, affect, and self-reported performance and exertion to represent three a priori different domains to be evaluated. Separate repeated-measures analyses of variance (rmANOVAs) were therefore performed to investigate the effects of cognitive function, affect, and self-reported measures of performance and exertion throughout the study. Each domain had two or more submeasures and we therefore chose to test these in the same models. Our data analysis strategy was mainly motivated by three important features of the rmANOVA in the context of complete data from all time points: (1) the opportunity of evaluating polynomial trends potentially associated with learning effects, and/or dose–response relationships; (2) the opportunity of delineating interaction effects (e.g. speed-accuracy trade-off, positive-negative affect interaction, etc.); and (3) the powerful but reasonable control for multiple comparisons provided by the ANOVA. To investigate cognitive functioning across the different time points, we performed a 3 × 5 rmANOVA with cognitive functioning (hit reaction time, commission errors, and omission errors) as the dependent variable and time (V1, V2, V3, V4, and V5) as a fixed factor. To investigate self-reported measures across the different time points (self-reported *exertion* and *performance* on the Conners' Continuous Performance Test-3 [CCPT-3] test), we performed a 2 × 5 rANOVA with self-reported measures (*performance* and *exertion*) as the dependent variable, and time (V1, V2, V3, V4, and V5) as a fixed factor. To investigate affect across the different time points, we performed a 2 × 5 rANOVA with affect (*positive* and *negative affect*) as the dependent variable and time as a fixed factor. For all rANOVAs, we tested the assumption of sphericity using Mauchley's test. If the assumption was violated, the following *F* tests were corrected using the Greenhouse–Geisser ($\varepsilon$) method [37]. In case of significant main or interaction effects, we performed univariate analyses and polynomial trend analyses to further break down the specific effects. *P*-values < .05 were considered statistically significant. Partial eta squared ($\eta_p^2$) was used as a measure of effect size. All analyses were performed in SPSS v.25.

## Results

In Table 1, we report baseline means and standard deviations for demographics, sleep, and health information of the participants. The means indicate that the group was relatively healthy, as illustrated in, for example, the mean scores of anxiety and depression, which were lower than a normative sample of the general UK population [29]. Moreover, the scores for sleep quality were better; scores for fatigue were lower, and scores for insomnia were similar to the means of a US college student sample reported in an epidemiological study of sleep among students [38].

Table 2 shows sleep duration, sleep efficiency, midpoint of sleep, and subjective sleep quality for all participants represented in mean scores across the habitual sleep period and across the three days of partial sleep deprivation. Sleep duration was statistically significantly shorter in the sleep-deprived condition compared to the habitual sleep period ($t$ = 34.21, $p$ < .001).

**Table 2.** Means and *SD* for sleep measures during the 7 days of habitual sleep period and during the 3 days of partial sleep deprivation ($n$ = 49–52)

| | Habitual sleep period | | | Sleep deprived | | | | |
|---|---|---|---|---|---|---|---|---|
| | Min | Max | Mean (*SD*) | Min | Max | Mean (*SD*) | *t* | *p* |
| Sleep duration actigraphy (min) | 327 | 517 | 435 (41) | 214 | 382 | 301 (43) | 38.09 | .000 |
| Sleep duration sleep diary (min) | 360 | 553 | 452 (42) | 217 | 392 | 312 (43) | 34.21 | .000 |
| Sleep efficiency actigraphy (%) | 76.3 | 93.5 | 86.9 (3.7) | 68.5 | 97.1 | 86.9 (5.3) | −0.12 | .906 |
| Midpoint of sleep actigraphy (time) | 2.57 am | 6.21 am | 4.22 am (00:49 min) | 3.01 am | 6.53 am | 4.26 am (00:51 min) | −1.43 | .159 |
| Subjective sleep quality (1–5) | 2.3 | 4.7 | 3.5 (0.6) | 2.7 | 5.0 | 4.1 (0.7) | −6.26 | .000 |

**Table 3.** *F* values with corresponding degrees of freedom for analyses of changes in cognition, self-reported measures, and affect at the five visits, interaction effects of time and the different outcomes, as well as means and *SD* for all outcome variables

| Outcome | Time | Time × outcome[a] | Mean (*SD*) V1 | | Mean (*SD*) V2 | | Mean (*SD*) V3 | | Mean (*SD*) V4 | | Mean (*SD*) V5 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Cognition | 28.35** (1,6) | 3.82* (4,185) | | | | | | | | | | |
| Reaction time | 10.05** (4,188) | | 41.73 | (4.84) | 40.73 | (5.15) | 40.19 | (5.43) | 39.94 | (5.37) | 39.25 | (5.30) |
| Commission errors | 7.12* (3,152) | | 52.02 | (9.05) | 49.58 | (9.47) | 49.46 | (10.58) | 52.15 | (10.82) | 53.35 | (11.98) |
| Omission errors | 1.29 (2,79) | | 46.12 | (2.47) | 45.38 | (1.47) | 45.46 | (1.71) | 46.15 | (6.58) | 47.29 | (8.79) |
| Self-reported measures | 45.05** (1,47) | 8.41** (4,188) | | | | | | | | | | |
| Performance | 7.08** (4,188) | | 4.67 | (1.26) | 5.13 | (1.71) | 5.00 | (1.90) | 4.06 | (1.60) | 4.00 | (1.74) |
| Exertion | 3.79* (3,135) | | 7.00 | (1.74) | 6.27 | (2.34) | 6.08 | (2.04) | 6.50 | (2.06) | 6.60 | (2.21) |
| Affect | 122.99** (1,48) | 14.14** (3,162) | | | | | | | | | | |
| Negative affect | 0.55 (3,141) | | 14.16 | (3.85) | 13.61 | (3.63) | 13.88 | (4.15) | 14.06 | (4.05) | 13.59 | (2.96) |
| Positive affect | 26.37** (4,192) | | 26.84 | (5.92) | 24.45 | (7.50) | 22.57 | (6.01) | 20.14 | (6.04) | 18.90 | (6.03) |

V1–V3 = baseline, V4–V5 = sleep deprived.
[a]Outcome is cognition, affect, or self-reported measures.
*$P$ < .05; **$p$ < .001.

The participants slept for an average of 124 minutes (slightly over 2 hours) less during the sleep deprived condition compared with the habitual sleep period. Sleep efficiency was higher during the habitual sleep period compared with the partial sleep deprivation period. There were no statistical differences in the midpoint of sleep in the two conditions. Subjective sleep quality was higher during sleep-deprived condition compared with the habitual sleep period.

## Cognitive function, self-reported measures, and affect in habitual sleep and partial sleep deprivation

Table 3 shows the mean scores at all five measure points on commissions, omissions, hit reaction time, subjective performance, subjective exertion, negative and positive affect, as well as the results from the analyses. The mean differences are also illustrated in Figure 3A–C.

The assumption of sphericity was violated for *cognition*, *commission errors*, *omission errors*, self-reported *exertion*, and *negative affect*. For these variables, the *F* tests were therefore corrected with the Greenhouse-Geisser (ε) method for the main effect of cognition ε = .65, commission errors ε = .81, omission errors ε = .42, self-reported exertion ε = .72, and negative affect ε = .738.

## Changes in cognition after partial sleep deprivation

There was a statistically significant main effect of cognition $F$ (1, 61) = 28.35, $p$ < .001, $\eta_p^2$ = .376. Univariate tests showed a significant effect for hit reaction time, $F$ (4, 188) = 10.05, $p$ < .001, $\eta_p^2$ = .18 and commission errors, $F$ (3, 152) = 7.12, $p$ < .001, $\eta_p^2$ = .13. There was no significant effect for omission errors $F$ (2, 79) = 1.29, $p$ = .227, $\eta_p^2$ = .027. A polynomial trend analysis revealed that hit reaction time decreased linearly throughout the five study visits ($p$ < .001, $\eta_p^2$ = .341 (see Figure 3A, blue line), including both the habitual sleep period and the sleep-deprived condition. Commission errors showed a significant quadratic trend between visits, $p$ < .001, $\eta_p^2$ = .238 (see Figure 3A, red line). As illustrated in Figure 3A, the quadratic trend implies that the changes in commission first decrease and then increase, and the change from decrease to increase occurs after visit #3 when the sleep deprivation is implemented.

Moreover, there was a significant interaction effect between the dependent variable cognition and the fixed factor time $F$ (4, 185) = 3.82, $p$ = .005, $\eta_p^2$ = .075. The contrast showed a significant linear interaction effect between hit reaction time and commission errors $F$ (1, 47) = 13.52, $p$ = .001, $\eta_p^2$ = .221, as well as a significant linear interaction effect between hit reaction time and omission errors $F$ (1, 47) = 5.69, $p$ = .021, $\eta_p^2$ = .108. Figure 3A shows that as the hit reaction time decreased, the number of omission errors and commission errors increased relative to the changes in hit reaction time. There was no significant interaction effect between commission and omission errors.

## Changes in self-reported measures after partial sleep deprivation

Results from the 2 × 5 rANOVA showed a main effect of *self-reported measures*, $F$ (1, 47) = 45.05, $p$ < .001, $\eta_p^2$ = .489. Univariate tests showed significant effects for self-reported performance, $F$ (4, 188) = 7.08, $p$ < .001, $\eta_p^2$ = .131 and self-reported exertion between visits, $F$ (3, 135) = 3.79, $p$ = .013, $\eta_p^2$ = .075. Self-reported performance decreased linearly across visits ($p$ = .001, $\eta_p^2$ = .235)

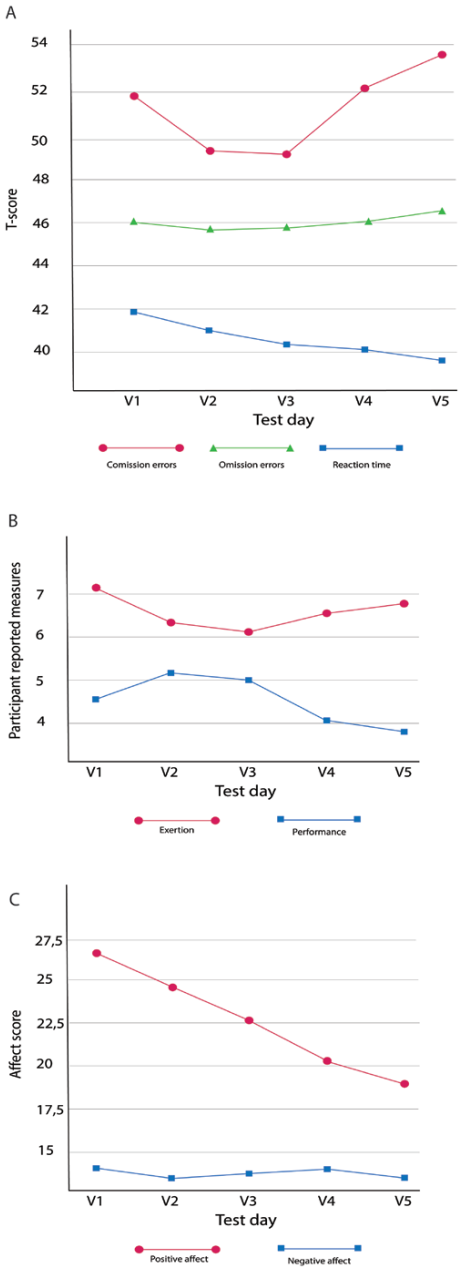


**Figure 3.** Change in cognition (A), self-reported measures (B), and affect (C) over time.

(see Figure 3C, blue line). Self-reported exertion first decreased during the habitual sleep period (three first visits) of the study and then increased throughout the partial sleep deprivation period, creating a quadratic curve, $p < .001$, $\eta_p^2 = .24$ (see Figure 3C, red line).

There was also a significant interaction effect between the dependent variable self-reported measures and the fixed factor time, $F$ (4, 188) = 8,41, $p < .001$, $\eta_p^2 = .152$. The contrast showed a significant quadratic interaction effect between self-reported performance and self-reported exertion, $F$ (1, 47) = 23.71, $p < .001$, $\eta_p^2 = .335$. This quadratic interaction demonstrates that compared with self-reported exertion, self-reported performance increased during the first visits of the study and then decreased, while the opposite trend was seen for self-reported exertion (Figure 3C).

### Changes in affect after partial sleep deprivation

The 2 × 5 rANOVA showed a main effect of the dependent variable affect, $F$ (1, 48) = 122.99, $p < .001$, $\eta_p^2 = .719$. Univariate tests showed significant changes in positive affect across the different visits, $F$ (4, 192) = 26.37, $p < .001$, $\eta_p^2 = .355$ (see Figure 3B, red line). Negative affect did not differ significantly between the visits, $F$ (3, 141) = 0.55, $p = .648$, $\eta_p^2 = .011$. Positive affect decreased linearly across the five visits, $p < .001$, $\eta_p^2 = .680$.

Lastly, the analyses showed a significant interaction effect between the dependent variable affect and the fixed factor time, $F$ (3, 162) = 14.14, $p < .001$, $\eta_p^2 = .228$, and the contrast showed a significant linear interaction effect between positive and negative affect over time, $F$ (1, 48) = 52.70, $p < .001$, $\eta_p^2 = .523$. This indicates that relative to negative affect, positive affect decreased linearly during the study period.

## Discussion

The present study demonstrates that sleeping 1.5–2 hours less than usual per night for 1–3 days in a home environment is associated with poorer cognitive control function in the morning, as reflected by increased impulsivity (faster hit reaction time but more commission errors), more exertion, poorer subjective performance, and decreased positive affect. This indicates that individuals become more impulsive, tired, and emotionally blunted after a period of short sleep. These effects were already present after 1 day of partial sleep deprivation and were further amplified throughout the next 2 days, indicating a dose–response relationship. These findings show that the sleep loss many adults experience in everyday life [6] may have detrimental effects on self-reported and performance-based cognitive performance and affect, which may have important implications for their health, productivity, and accident risk. Especially these effects may have severe consequences in the morning, on the way to work and in the beginning of the work day, possibly caused by sleep inertia [39].

### Increased impulsivity and exertion, poorer subjective performance, and decreased positive affect

Overall, our findings support studies indicating that mild–moderate partial sleep deprivation limits access to affective and cognitive resources [40]. We found that even though the participants reported putting more effort (exertion) into the CCPT-3 after sleep deprivation, they also reported performing worse compared with the baseline measures. This indicates that the participants tried to compensate for the effects of sleep loss with an increase in exertion [40]. Despite this

increase in exertion, the participants had a decrease in both subjective and objective performance, as well as in positive affect. Thus, the participants in our study were aware of their reduced performance level. Compensatory exertion associated with only partial recovery of performance has also been observed in a number of studies on total sleep deprivation [9]. Our study indicates that these compensatory efforts also occur after partial sleep deprivation. Importantly, previous studies have shown that chronic sleep restriction is associated with less awareness of the effects following sleep deprivation, when objective measures are used [41]. This might indicate that the awareness of ones' performance may be reduced upon repeated nights of sleep deprivation. These findings may have important implications for everyday factors (such as work–life, driving, and social interactions) because the effects of sleep loss might not be reversed or withheld with increased exertion. Conversely, it is also possible that reduced positive affect (emotional blunting) leads to the observed impulsive behavior (faster hit reaction time and more errors) on the CCPT-3, as well as the reduced subjective performance and increased exertion after sleep deprivation. Reduced positive affect may lead to an increased feeling of poor performance and exertion performance on the test. It is possible that such reduced access to cognitive and affective recourses due to lack of sleep could lead to increased vulnerability for developing mental disorders. It is well-known that sleep problems are an important mechanism causing and maintaining several mental disorders [42].

Subjective sleep quality measured with sleep diary was higher during the sleep deprivation period compared with the habitual sleep period. Thus, despite the negative effects of sleep deprivation on subjective and objective measures of cognitive control and affect, the participants still reported sleeping better when sleep deprived than when they had normal sleep. This is in line with previous studies reporting that partial sleep deprivation increases subjective sleep quality [43]. During the sleep deprivation phase, participants were awake for longer during the evening and therefore had a possibility of longer exposure to light which may cause an underlying phase delay in the circadian rhythm relative to being in darkness [44]. However, there is also evidence that a high homeostatic sleep drive may reduce the phase-shifting capacity of light [45]. We did not include measures of circadian rhythm such as Dim Light Melatonin Onset in this trial. However, the sleep midpoint did not differ in habitual sleep compared with sleep deprivation, indicating that there was no major shift in the timing of the sleep–wake phase.

In our study, the tests were performed in the morning between 7.30 and 10.30 am. Laboratory studies have reported that cognitive performance is severely affected by sleep loss, especially in the morning [39], that sleep deprivation increase sleep inertia [46], and that sleep inertia can last up to four hours for some individuals [47]. Moreover, naturalistic studies have shown that sleep inertia can be present up to 2 hours after awakening from normal sleep length in a home environment [48]. Our participants were healthy young adults who had to travel to the university campus before testing, and hence, even though the partial sleep deprivation may have increased their sleep inertia, it is not likely that the participants still was in a state of sleep inertia at the time of testing.

### Cognitive control functioning

Our findings that partial sleep deprivation influences the number of errors and hit reaction time is in line with previous studies on sleep restriction [14], and total sleep deprivation [10], and the conclusions from a recent meta-analysis of a large amount of research in this topic [15]. However, some previous studies report an increase in response time following sleep deprivation [11, 14] and not a reduction as we found. The task in this research was the Psychomotor Vigilance Task (PVT). The PVT is one of the most-used cognitive tasks in sleep deprivation research and has provided valuable information for the field. However, one limitation with this test is that participants are asked to respond to relatively few and infrequent stimuli (targets). Although this has some advantages for detecting attentional lapses (omissions), this task, by design, provides rather unreliable response time estimates. In contrast, the CCPT-3 provides robust response time measures based on calculations including several hundred trials.

By indicating faster performance in speed and a decline in accuracy, our results support a speed-accuracy trade-off in line with what has previously been suggested by Lim and Dinges [10]. That is, faster responses may lead to a decline in accuracy, and vice versa.

We found that the number of errors and hit reaction time measured with CCPT-3 decreased at the three baseline measures, but the changes in hit reaction time and errors from the habitual sleep period to the sleep-deprived condition interacted. This shows that, in the sleep-deprived condition, as hit reaction time decreases, the number of errors increases. This is in line with prior findings of improved CCPT-3 performance in nonsleep-deprived participants [7]. Notably, however, in this study there were no changes in CCPT-3 performance after mild (1 hour) partial sleep deprivation over six consecutive days. Considering this finding, our results indicate that the negative effects of partial sleep deprivation on cognition may commence after sleep deprivation after close to 2 hours of deprivation. The effects of sleep deprivation in the study by Santisteban et al. [7] might also be masked by practice effects, as they only included one baseline measure and one sleep-deprived measure. It should also be noted that the participants in our study were rather high functioning, as they performed average or above average on all cognitive control variables at baseline. For example, at visit 3 (before sleep deprivation), the group mean score on hit reaction time was nearly 1 *SD* faster than the normative data provided with the CCPT, while at the same time, the number of commission errors was around the norm average. Also, the participants in our study had better scores on several baseline measures of health and sleep compared to norm samples [29] and comparable student samples [38].

Furthermore, the effect of sleep deprivation seemed to be dose dependent in our study, indicating that changes in emotional and cognitive functioning are more evident after several consecutive nights of sleep deprivation. Still, there are likely individual differences regarding sleep preference, resilience, habitual sleep duration, and other more stable dimensions at play in determining individual variation in vulnerability to mild–moderate sleep deprivation.

### Positive and negative affect

We observed a decrease in positive affect following sleep deprivation, but no change in negative affect after the sleep deprivation, which is in line with earlier laboratory findings [18, 19, 49]. In the present study, effects similar to those observed in earlier studies were revealed using a less-strict sleep restriction protocol. We also deployed individualized sleep deprivation time. This is important, as it suggests that small deviations from average total sleep time over consecutive days can cause a pronounced decline in experienced positive affect. We also observed that positive affect decreased at all the measurement times, also before the sleep deprivation, which may indicate that the effects were caused by being a part of the experiment (e.g. being less engaged upon repeated testing), and not merely the effects of partial sleep deprivation.

While our results are in line with other studies applying PANAS [18], they are somewhat in contrast to other previous studies reporting an increase in negative affect after sleep deprivation measured by Profile of Mood States (POMS) [13, 20, 21]. These two self-report measures therefore seem to capture different aspects of affective alteration following sleep deprivation. PANAS is designed to capture the presence or absence of active affects, and positive and negative affect are two distinct dimensions [36]. POMS assesses six dimensions of mood, five negative and one positive, which can be computed to one total mood disturbance score [50]. In our results, there was an interaction between positive and negative affect between visits. This can reflect distinct differences in how sleep deprivation influences positive and negative affect. Moreover, this demonstrates the importance of differentiating between positive and negative dimensions of affect in sleep deprivation studies. Altogether, our results lend support to studies indicating that the effect of sleep deprivation on negative affect is more dependent on the context than what is the case for positive affect [22, 23]. One night of total sleep deprivation leads to increased negative affect when the participants were exposed to a mild cognitive performance stressor [23]. However, in our study, we measured affect after performing the CCPT-3, which, for some, may also count as a mild cognitive performance stressor, and the reason we could not detect changes in negative affect after partial sleep deprivation in line with [23] may be due to differences in amount of sleep deprivation in our study compared to in [23], or because participants did not experience the CCPT-3 as a stressor because they are used to the test after taking it several times.

### Strengths, limitations, and suggestions for future research

The main strength of this study is the comprehensive design, including repeated measures using a combination of well-validated self-report, performance-based, and wearable sensor measures to study the effects of partial sleep deprivation in a naturalistic setting. Our study is the first to use a multiple baseline design; hence, we could use the participants as their own control. Moreover, our study is one of the few to investigate cognitive control function, subjective performance, exhaustion, and affect in the same study. A limitation with the present study is that the sleep deprivation condition was introduced at the same time in the protocol for everyone. One alternative approach could have been to use a crossover condition, where some participants had sleep deprivation at the beginning of the study period, while others experienced it at the end of the study period. This would provide us with different opportunities to adjust for order/practice effects. However, a disadvantage of crossover designs is that it is hard to estimate potential carryover effects. Importantly, as we tested the participants on three occasions (within-subject multiple baseline) before the sleep deprivation, we did have considerable control of the variance linked re-testing in our statistical analyses.

The study has a modest sample size, but still, our sample exceeds that of several previous similar studies [51–53]. Our sample comprises of mainly women (79%). Gender differences are therefore important to consider when interpreting interpretating our findings. Women seem to have higher vulnerability to both circadian and homeostatic influences following sleep deprivation compared to men measured in a laboratory setting [54]. In addition, women seem to experience more sleep difficulties, as well as more time awake during the night, and poorer sleep quality measured subjectively and with actigraphy compared to men [55], but still have better objectively measured sleep quality than men measured with polysomniography [56]. However, both sexes were included, and the distribution represents the sex distribution in many student groups cross-nationally.

## Conclusion

Short sleep duration is common in the adult population. We found that sleeping 1.5–2 hours less than usual for 3 days in a row in a home environment led to poorer cognitive control function measured at our lab in the morning. It also led to more exertion, poorer subjective performance, and reduced positive affect. These findings indicate that individuals become more impulsive after a period of short sleep. Moreover, we found that the participants had an increase in performance from the first baseline test to the third baseline test, but that 1 day of sleep deprivation overshadowed this effect, and the performance was further deteriorated after three nights of sleep deprivation. These findings highlight that even 1–2 hours less sleep for a few nights is associated with negative consequences. Also, these findings show that even a small lack of sleep may have important implications for everyday function and quality of life, such as social interaction, work efficiency, and traffic safety, especially in the early morning. Future research should focus on how such effects may vary with time of day and across different populations. It would also be interesting to see studies investigating how these effects can be remediated by psychological or medical interventions. Finally, we need knowledge determining the long-term accumulated effects and underlying biological mechanisms of mild–moderate partial sleep deprivation.

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*Conflict of interest statement*. None declared.

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# PAPER III

**Title:**

# Poor sleep quality is associated with greater negative consequences for neurocognitive and psychological health after mild traumatic brain injury than after orthopedic injury


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