Effect of multidisciplinary outpatient treatment after mild traumatic brain injury

A randomised controlled trial and prognostic factors for return to work

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Dissertation for the degree of philosophiae doctor (PhD)
at the University of Bergen

2016

Dissertation date: 10th June 2016

”It is not only the kind of injury that matters, but the kind of head”

Sir Charles Putnam Symonds, 1937

Contents

1. SCIENTIFIC ENVIRONMENT

This study was carried out at the Department of Physical Medicine and rehabilitation, Haukeland University Hospital, Bergen, Norway and the Department of Physical Medicine and Rehabilitation, Oslo University Hospital, Oslo, Norway, during the period 2009-2015. Scientific support has also been given by the staff at Department of Global Public Health and Primary Care, University of Bergen, Bergen, Norway, Faculty of Medicine, University of Oslo, Oslo, Norway and Centre for Clinical Research, Haukeland University Hospital, Bergen, Norway. Data was provided by Statistics Norway from the Norwegian Labour and Welfare Service.

This thesis is a part of the PhD programme at the Faculty of Medicine and Dentistry, Department of Global Public Health and Primary Care, University of Bergen.

2. ACKNOWLEDGEMENTS

There has been growing concern about the outcome and the rehabilitation offered for patients with brain injury over the last fifteen years. A consensus report *«Et reddet liv skal også leves»* from the Norwegian Directorate of Health from 2005 concluded that there was a need to organise follow-up visits at multidisciplinary outpatient clinics for patients with mild, moderate or severe traumatic brain injury. To improve their treatment, a national network of professionals treating patients with brain injury was established in 2005 under the leadership of Professor Erik Bautz-Holter. This project was a result of this national network and cooperation between Haukeland University Hospital and Oslo University Hospital.

I am grateful to all 353 patients who participated for their contributions and their willingness to participate in these studies.

My most sincere gratitude goes to my principal supervisor, Professor Jan Sture Skouen, MD, PhD, research leader at the Department of Physical Medicine and Rehabilitation, Haukeland University Hospital, and Department of Global Public Health and Primary Care, University of Bergen. He has been the principal investigator on this project. I greatly appreciate his enthusiasm and his encouragement of me to conduct this project. Throughout my education and career as a specialist in the Department of Physical Medicine and Rehabilitation, he has been an enthusiastic, knowledgeable and a motivating supervisor. Thank you, Sture!

I am very grateful to all the advice from my co-supervisor, Professor Emeritus Erik Bautz-Holter, MD, PhD, Department of Physical Medicine and Rehabilitation, Oslo University Hospital, and Faculty of Medicine, University of Oslo. After our first meeting in 2002, he challenged me and my department to improve the treatment of patients with traumatic brain injury. His long experience and reflective thoughts have been of great importance to the completion of this project. Thanks a lot, Erik!

I also thank my co-supervisor Professor Cecile Røe, MD, PhD, Head of the Department of Physical Medicine and Rehabilitation, Oslo University Hospital, and Faculty of Medicine, University of Oslo, for her substantial contribution to study conception, study design, data acquisition and data interpretation and for her extremely valuable feedback throughout this project. I especially thank her for

capacity and will to find good solutions for our project and manuscripts. My sincere thanks to Cecile!
I want to thank Biostatistician Jörg Aßmus, PhD, Centre for Clinical Research, Haukeland University Hospital, for his statistical analyses, good advice and admirable professionality and knowledge. Thank You, Jörg!
Thanks to co-author Torgeir Hellstrøm, MD, who has recruited the majority of the included patients at Oslo University Hospital. Thanks for all your work, feedback and important comments and suggestions to improve our manuscripts.
I want to acknowledge the multidisciplinary teams at Oslo University Hospital and Haukeland University Hospital. The development of this model of treatment has really been a team effort. The team members and collaborators are listed in Appendix. In particular, the team at Oslo University Hospital has been of great importance to the development of our multidisciplinary outpatient follow-up programme. Thanks to the multidisciplinary teams and to my friendly and valuable colleagues in Bergen who have contributed throughout this project: Kaia Frøyland, Gunvor Hjelmervik, Vibeche Thon Iversen, Ragnhild Lossius, Karin-Merete Marthinsen and Silje Karin Pedersen.

Karen Marie Haga, Secretary at the Neurosurgery Department, has been essential in providing the patient lists for potential participants from the acute ward at her department. I will like to thank, Professor Emeritus Knut Wester, MD, PhD and Terje Sundstøm, MD, PhD, Department of Neurosurgery, Haukeland University Hospital for their advices when this study was planned. Astrid Louise Grasdal, Dr. polit, Economist from University of Bergen, has contributed with her socio-economic considerations during the planning of this study. Silje Mæhle Haugland and Tone Brodal Mongstad have conducted the telephone interviews and the assessment of GOSE at follow-up. I also want to thank Unn H. Høydahl, Statistics Norway, who provided data from the Norwegian Labour and Welfare Service and integrated these data with the clinical data from this project.

During the study period, I have been supported by grants from The Norwegian Extra Foundation for Health and Rehabilitation, at which Personskadeforbundet LTN has supported applications for grants.

I want to thank my employer, the Department of Physical Medicine and Rehabilitation, Haukeland University Hospital, led by Clinic Director Margit Sørhus and the previous Head of the Outpatient Clinic Kjersti Sem Ringel, who gave me the opportunity to work on this project. Head Senior Consultant Mathias Hütler, MD, has been of great importance due to his interest, support, good advice and willingness to allow me to work on this project. Thank you so much, Matthias!

I also thank my good friend and colleague Thomas Kadar for his scientific advice, enthusiasm and daily visits to encourage me to complete this thesis.

Finally, I would like to thank my family. My mother Kirstina and father Johan, who died during the project period, thanks for your thoughtfulness and for teaching me to appreciate my daily work. My lovely and caring wife, Hege, has been of indescribable importance and has been my most important supporter throughout this project. My beloved encouraging boys, Knut, Haldor and Johan, who always are interested in my work (“almost” as much as soccer), I love you all, thank you!

Bergen, March 2016

Eirik Vikane

3. LIST OF ABBREVIATIONS

ACRM	American Congress of Rehabilitation Medicine
CONSORT	Consolidated Standards of Reporting Trials
CT	Computed Tomography
DAI	Diffuse Axonal Injury
GCS	Glasgow Coma Scale
GOSE	Glasgow Outcome Scale-Extended
GP	General Practitioner
HISS	Head Injury Severity Scale
ICD-10	International Classification of Diseases, 10th edition
ICF	International Classification of Functioning, Disability and Health
HAD	Hospital Anxiety and Depression Scale
MRI	Magnetic Resonance Imaging
MTBI	Mild Traumatic Brain Injury
NAV	The Norwegian Labour and Welfare Service
NRS	Numerical Rating Scale
OR	Odds Ratio
PCS	Post-concussion Symptoms
PGIC	Patient's Global Impression of Change
PTA	Posttraumatic Amnesia
PTSS-10	The Post-traumatic Stress Syndrome 10-Questions Inventory
RCT	Randomised Controlled Trial
RPQ	The Rivermead Post Concussion Symptoms Questionnaire
RTW	Return to Work
SF-36	The Short Form-36 Health Survey
SHC	The Subjective Health Complaints Questionnaire
SSB	Statistics Norway
SPSS	Statistical Package for the Social Sciences
STROBE	Strengthening the reporting of observational Studies in Epidemiology
TBI	Traumatic Brain Injury

WHO	The World Health Organization
WHO Task Force	The WHO Collaborating Centre Task Force on MTBI

4. LIST OF PUBLICATIONS

This thesis is based on the following papers, which will be referred to by their Roman numbers in the text.

I. Vikane E, Hellstrom T, Roe C, Bautz-Holter E, Assmus J, Skouen JS. **Missing a follow-up after mild traumatic brain injury-Does it matter?** *Brain Injury 2014; 28(11):1374-80.*

II. Vikane E, Hellstrøm T, Røe C, Bautz-Holter E, Aßmus J, Skouen JS. **Multidisciplinary outpatient treatment in patients with mild traumatic brain injury: a randomised controlled intervention study.** *Submitted to Brain Injury.*

III. Vikane E, Hellstrøm T, Røe C, Bautz-Holter E, Aßmus J, Skouen JS. **Predictors for return to work in subjects with mild traumatic brain injury.** *Behavioural Neurology* 2016*; Article ID 8026414, 10 pages, 2016. doi:10.1155/2016/8026414.*

5. SUMMARY

This thesis evaluates the efficacy of a multidisciplinary outpatient follow-up programme compared to follow-up by a general practitioner. Specifically, we explored the outcome and prognostic factors for outcome in patients with mild traumatic brain injury (MTBI). The majority of brain injury cases are MTBI, which has an overall favourable prognosis. However, a substantial subset of MTBI patients report symptoms and disability after injury. MTBI has been referred to as a “silent epidemic” because impairments in memory or cognition are often undetectable and its incidence is often underestimated. Cognitive problems together with physical, emotional and behavioural problems have an impact on participation and return to work (RTW). The current literature suggests education and reassurance as early interventions for MTBI after discharge from an emergency hospital. Multidisciplinary treatment is recommended for more complex cases of MTBI, but well-designed studies of the outcome and the efficacy of interventions in general and in promoting RTW in particular are still lacking.

In our study, approximately 30% of the patients did not attend a planned followed-up visit from six to eight weeks post-MTBI. Patients who did not attend this follow-up visit had less serious intracranial injuries and were more likely to RTW than patients who attended their follow-ups. Among the patients who attended their follow-ups, 25% were sick-listed, and this result indicates a need for follow-up care after MTBI in this group of patients. We found that the multidisciplinary outpatient follow-up programme focusing on providing greater understanding and reassurance of a favourable outcome for MTBI did not improve RTW, but may have reduced the development of PCS in a vulnerable group of patients. For the group of patients with persistent symptoms at two months post-MTBI, having been sick-listed within the year prior to injury, being sick-listed at two months post-MTBI, exhibiting severe or moderate disability at two months post-injury (GOSE) and experiencing psychological distress (HAD) were negative predictors of RTW. These findings support the contribution of pre-existing and comorbid conditions to outcomes after MTBI. Our results indicate that subsequent intervention studies should consider a different approach to promote RTW.

6. BACKGROUND

6.1. Introduction

Traumatic brain injury (TBI) is a major cause of disability worldwide [1]. Based on the clinical presentation and the level of consciousness after a TBI, the injury is usually classified as mild, moderate or severe [2]. From 70 to 90% of all hospital-treated brain injuries are mild TBI (MTBI) [3]. In a study in Norway, 86% of cases of hospitalisation for a TBI were classified as MTBI, and approximately 9 000 people experiencing MTBI are hospitalised each year in Norway [4, 5]. The overall prognosis after a MTBI is favourable, but 5%-20% of patients with MTBI may experience persistent problems [6, 7]. Because the incidence of MTBI is high, a substantial subset of patients report symptoms and disability after MTBI [6]. Therefore, the costs of MTBI are also high, with estimated annual cost in the United States of approximately $65 billion in 2009; thus, MTBI is regarded as a major public health problem [8]. TBI has been referred to as a “silent epidemic” because impairments in memory or cognition are often undetectable and its incidence is often underestimated [1, 9]. In addition to cognitive symptoms, physical, emotional and behavioural problems are quite common after MTBI [6]. These impairments heavily impact participation and RTW. The current literature suggests education and reassurance as early interventions for MTBI after discharge from an emergency hospital [10]. For more complex cases, specialised multidisciplinary treatment is recommended [11, 12]. Well-designed studies of the efficacy of interventions in general and for promoting RTW in particular are still lacking [7, 10, 12, 13]. The present thesis will evaluate the efficacy of a multidisciplinary follow-up programme and predictors associated with RTW.

6.2. Definition of traumatic brain injury

The Demographics and Clinical Assessment Working Group of the International and Interagency Initiative toward Common Data Elements for Research on Traumatic Brain Injury and Psychological Health proposed the following definition, *"TBI is defined as an alteration in brain function, or other evidence of brain pathology, caused by an external force"* [14]. The working group defined alteration in brain function as the appearance of one of the following clinical signs: any period of decreased or lost consciousness, loss of memory immediately before or after the injury, neurological deficits such as weakness, loss of balance, sensory loss, change in visual, speech or language function or any change in mental state such as confusion, disorientation or slowed thinking [14].

6.3. Classification of traumatic brain injury

TBI is classified in several ways, and during the past 50 years, there has been a change in the nomenclature from head injury to TBI [14]. Historically, TBI has been classified based on injury severity, pathoanatomy or physical mechanism [2]. Most clinical trials for MTBI have classified participants based on injury severity [15]. The most commonly used neurological injury severity scale to assess the depth and duration of impaired consciousness and coma in adults is the Glasgow Coma Scale (GCS), a 15-point clinical scale ranging from 3-15. The scores are based on three different behavioural responses, for which eye, verbal and motor responses are measured. Each level of response is graded according to a defined scale. Subscales for eye opening (1-4), verbal response (1-5) and best motor response (1-6) are developed [16, 17]. Patients with a GCS score of 13-15 are classified as MTBI, GCS score of 9-12 as moderate TBI or GCS score of 3-8 as severe TBI [18].

Pathoanatomical classification of MTBI is differentiated into complicated or uncomplicated injury. Complicated MTBI is characterised by the presence of a brain lesion or skull fracture on radiological examination demonstrating a structural injury in the brain that can explain the appearance of symptoms and loss of function after a TBI [19]. A structural TBI typically manifests from a contusion, haematoma or

diffuse axonal injury (DAI) [20]. A computed tomography (CT) scan is a fast and reliable tool that serves as the neuroimaging modality of choice to demonstrate complicated injuries in acute cases [21]. Magnetic resonance imaging (MRI) has been demonstrated to be more sensitive and specific than CT for detecting intracranial pathology, especially minor bleeding and DAI. Approximately 30% of patients with normal findings on CT exhibit intracranial injury on MRI [20]. A two-dimensional scale, the Head Injury Severity Scale (HISS), was developed by combining the injury severity based on GCS and the presence of complications such as an intracranial lesion or a brainstem haemorrhage [22]. The HISS is recommended and widely used in emergency care to differentiate and guide treatment for patients with different prognoses [22-24]. Finally, pathophysiology is used to classify or characterise patients with MTBI, but it has not been commonly used in clinical trials [2]. Classifying TBI according to pathophysiology may have prognostic value, and this approach is used in clinical triage. In the newly reviewed Scandinavian guidelines for head injuries, S100B, a biomarker for cerebral injury, is used in the decision algorithm to detect complications that require neurosurgical interventions [2, 25].

6.4. Definition of mild traumatic brain injury

According to the World Health Organization (WHO) Collaborating Centre Task Force on MTBI (WHO Task Force) definition from 2004, MTBI manifests as one or more of the following symptoms: confusion or disorientation, loss of consciousness for less than 30 minutes, loss of memory with post-traumatic amnesia (PTA) for less than 24 hours or transient neurological abnormalities. MTBI is defined as a GCS score from 13 to 15 at least 30 minutes after MTBI in an examination by a qualified health care provider [26]. Neurological abnormalities include seizures, intracranial lesions and neurological signs such as weakness, loss of balance, sensory loss, and changes in vision, speech or language [14, 26]. The symptoms of MTBI must not be a result of alcohol other substance use, other injuries, treatments or other problems such as psychological distress [26]. The International Collaboration on MTBI Prognosis recommends restricting the term MTBI to injuries caused by direct head trauma and excluding other aetiologies such as blasts and whiplash from the

definition of MTBI [15]. The WHO Task Force definition of MTBI is derived from the criteria recommended by the MTBI Committee of the Head Injury Interdisciplinary Special Interest Group of the American Congress of Rehabilitation Medicine (ACRM); there are only minor differences between these two definitions [27]. The ACRM suggests measuring the GCS just 30 minutes after injury, and the WHO Task Force suggests measuring the GCS at the first meeting by a professional health care provider at least 30 minutes after injury [26]. The ACRM defines altered mental status as being “dazed, disoriented or confused”, but the WHO Task Force did not include “dazed” in their definition [15]. Others have defined slowed thinking in addition to confusion and disorientation as a sign of altered mental status [14]. Finally, the WHO Task Force used the term “transient neurological abnormalities”, and the ACRM stated that neurological abnormalities “may or may not be transient” [15]. To achieve a standardised and comparable definition of MTBI, we have defined MTBI according to the recommendations from the WHO Task Force in the present work [26].

6.5. Epidemiology

The total incidence of TBI is difficult to assess, but the annual incidence of hospital-treated MTBI is approximately 100-300 patients per 100 000 people [3]. The actual rate of all MTBIs is most likely above 600 patients per 100 000 people [3]. The incidence of MTBI in a newly published study from New Zealand was 749 per 100 000 people, in which 95% of all TBI cases were MTBI [28]. Differences in the diagnostic criteria for MTBI and in the methods used to collect data related to the incidence of MTBI could explain the discrepancies in these estimates [29, 30].

The lowest incidence of MTBI or concussion in Scandinavia was reported in Finland, where approximately 55 per 100 000 people were hospitalised for MTBI in 2005 and the total incidence of MTBI in the population was approximately 160 per 100 000 [31, 32]. A study from Sweden has reported the highest incidence: in the total population, the incidence of MTBI was estimated to be approximately 540 per 100 000 in 1992-1993, and of these, approximately 200 per 100 000 people were admitted to a hospital [33].

In Norway, similar to other high-income countries, there has been a slight decrease in the incidence of hospital-treated MTBI in recent decades [34]. In 1974, the incidence of hospital-treated MTBI, classified as minor head injury, was approximately 210 per 100 000 people [35]. Heskestad et al. found in 2003 in Stavanger that approximately 125 per 100 000 people were hospitalised due to MTBI [36]. Finally, in 2005-2006, the incidence of hospital-treated MTBI in Oslo was approximately 72 per 100 000 people, with a male: female ratio of 1.8: 1.0 [4]. Andelic et al. and Heskestad et al. explained that the decrease in hospital-treated TBI over the last 30 years may be a result of improved traffic regulations and bike helmets, consequently preventing traffic accidents, and the use of clinical guidelines such as the Scandinavian guidelines for the management of head injuries [4, 36]. Heskestad et al. explained that the difference in the incidence of MTBI between Stavanger and Oslo may be a result of distinctions in the organisational structure of trauma care, as health care providers in Oslo can avoid hospitalising patients by observing them at an advanced outpatient clinic [36].

In Norway and the rest of Scandinavia, falls are the major cause of MTBI, accounting for over 50% of all MTBI cases, followed by traffic accidents and assaults, accounting for approximately 25% and 10% of MTBI cases, respectively [4, 36-38]. MTBI or concussion in sports is probably underreported, and studies from the USA indicate that 50% of these cases are not registered. In the USA, it is estimated that there is the same number of athletes per year who suffer a sports-related concussion as the number of patients who are diagnosed with a MTBI in an emergency room [18]. There is a variation of the mechanisms of MTBI according to age, and among young adults traffic accidents and assaults are most common [18]. Among children and elderly people, falls are a common cause of MTBI, and several studies have demonstrated an increased incidence of TBI the last decade among elderly persons [18, 31, 32, 36, 37]. In addition, the proportion of assaults in Norway has tended to be increased among younger hospitalised MTBI patients, and the overall proportion of such cases have increased from approximately 7% to 14% of all MTBI cases in recent decades [4, 36, 39, 40].

In a study from Oslo, 7% of patients hospitalised for MTBI had a contusion, 5% of patients had intracranial haemorrhage and 10% of the patients had a cranial fracture

[4]. A systematic review concluded that approximately 5% of hospital-admitted patients with a GCS score 15 and more than 30% of patients with a GCS score 13 had an intracranial abnormality [41].

6.6. Recovery after mild traumatic brain injury and development of post-concussion symptoms

Acute symptoms such as headache, fatigue, dizziness and cognitive impairment associated with pain, sleep disturbance and psychological distress are quite common [42, 43]. In the majority of subjects with MTBI, symptoms resolve within 12 months, but in a significant minority, symptoms persist. The symptoms following MTBI are described as post-concussion symptoms (PCS) [42, 44-46]. The estimated prevalence of PCS after MTBI is between 5% and 20% [7, 42, 47, 48]. Recently, published literature reported that PCS are not specific to MTBI but rather are more frequent among MTBI patients than among trauma-experiencing controls [42, 49]. Patients with more than three PCS after a head trauma are usually diagnosed with post-concussion syndrome [50]. Post-concussion syndrome is usually defined either according to the International Classification of Diseases, 10th edition (ICD-10) criteria or to the Diagnostic and Statistical Manual of Mental Disorders-4th Edition (DSM-IV). In addition to the presence of at least three PCS after a head trauma, DSM-IV requires that the symptoms have lasted for three months and have interfered with social, occupational or school functioning [50]. Furthermore, DSM-IV requires that memory or attention difficulties are verified on objective tests [50]. At present, there is no established consensus definition of post-concussion syndrome, and clinicians use different criteria when they diagnose patients with post-concussion syndrome [50]. Several Norwegian studies have used the ICD-10 criteria with a three-symptom criterion to define patients with post-concussion syndrome [51-53]. Using the ICD-10 criteria for post-concussion syndrome presents a risk of over-diagnosing the presence of post-concussion syndrome compared to the DSM-IV criteria, the use of which may under-diagnose this syndrome [51]. Using the ICD-10 criteria, the prevalence of post-concussion syndrome at 12 months post-MTBI among selected patients who were hospitalised

at two neurosurgical departments was estimated to be 27% and 40% in two Norwegian studies [51, 52].

PCS can be divided into somatic, cognitive and emotional complaints [54]. Typically, somatic PCS include headache, dizziness, nausea, fatigue, problems with vision, noise sensitivity and sleeping problems. Cognitive PCS include problems with concentration or memory and longer time to think, and emotional symptoms include depression, irritability, frustration and reduced tolerance to alcohol [44, 55]. MTBI may cause structural changes in the brain; injury-induced depolarisation of neurons, described as a neurometabolic cascade; or a psychological reaction that may cause persistent PCS [20]. There is an ongoing debate in the existing literature regarding whether PCS result from organic injury in the brain, psychological factors or both [56-58]. Persistent symptoms after MTBI are associated with pre-injury mental and physical health, injury-related stress and early post-injury cognitive impairment [42, 58]. A biopsychosocial model that includes pre-injury factors can best explain the development and maintenance of the PCS [11]. This model can also explain the multifactorial aetiology of persistent symptoms after MTBI [59].

Several investigations indicate that repeated injury within the first week after MTBI worsens neurocognitive function and may affect the severity of the brain injury [60]. There is uncertainty concerning the development of chronic or progressive neurobehavioral impairment after repeated MTBI [60, 61]. Clinically, two major presentations of chronic traumatic encephalopathy are described: one developing at a younger age involving behavioural and mood disturbance, and the other developing later in life involving cognitive impairment [62].

6.7. Prognosis and prognostic factors for return to work

The International Collaboration on MTBI Prognosis found in a systematic review that most workers RTW within three to six months after MTBI but that approximately 5-20% had persistent problems hindering RTW [7]. Because of varying inclusion criteria in cohort studies, patient characteristics, geographic regions, occupational categories, compensation systems and definitions of MTBI, RTW at one year post-MTBI varies from approximately 55% to 97% between studies [7, 63-65].

Prognostic studies of MTBI describe outcomes of patients with MTBI and describe which characteristics are associated with the outcomes. Prognostic factors can be divided into pre-injury factors, injury-related factors and post-injury factors. Unfavourable RTW is associated with pre-injury variables such as higher age, lower education level and occupational factors such as job independence and decision-making latitude [7, 63, 66-68]. Injury-related variables such as multiple bodily injuries have been demonstrated to negatively influence RTW. The connection between intracranial abnormalities on CT and RTW has been inconsistent to date [7, 63, 69]. Post-injury predictors after MTBI that have been negatively associated with RTW are nausea or vomiting on hospital admission, severe pain early after injury, fatigue, dizziness, various subjective symptoms, cognitive variables, financial compensation-seeking, and environmental factors such as social interaction [7, 63, 66-68, 70, 71]. Several authors have found that the total number of PCS and psychological symptoms post-injury reported at follow-up have a higher impact on RTW than the injury characteristics during the emergency stay [67, 72]. Because of the heterogeneity between prior studies, well-designed prognostic studies of long-term RTW after MTBI are needed [7]. Patients with persistent symptoms and functional impairments after MTBI may differ from the majority of patients who recover spontaneously. Therefore, it is also important to predict RTW for patients with remaining symptoms a few months post-injury [67, 72, 73]. Loss to follow-up is another common deficiency in the existing literature according to the WHO Task Force because it creates bias in the outcome [26]. Using data related to sick leave from a national register, missing data as a result of loss to follow-up or not attending a planned follow-up are avoided. Using data from a national register for sick leave may improve the outcome data and the identification of predictors of RTW after MTBI.

6.8. Rehabilitation

The WHO defined rehabilitation as *"The use of all means aimed at reducing the impact of disabling and handicapping conditions and at enabling people with disabilities to achieve optimal social integration"* [74]. Early detection of complications that require neurosurgical intervention is important to limit brain damage and improve functional outcome after MTBI [12]. According to the Scandinavian guidelines for acute management of MTBI, high-risk patients for complications after MTBI are investigated by performing a CT scan and are observed at a hospital for a minimum of 24 hours [25]. High-risk factors for complications are seizure after the injury, neurological deficits, clinical signs of a depressed or basal skull fracture, anticoagulant therapy, coagulation disorder, hydrocephalus treated with a shunt or two or more repeated vomiting episodes post-MTBI [25]. These guidelines also contain written discharge advice, in which patients receive information about the generally favourable outcome after MTBI and how to deal with possible complications [25]. A Cochrane report concluded that strong evidence indicated that the majority of patients with MTBI experienced a good recovery following the provision of appropriate information, without any additional specific intervention [75]. The International Collaboration on MTBI Prognosis concluded that some evidence supports the efficacy of early educational information that reassures patients with MTBI [10]. Despite the favourable outcome of MTBI for the majority of patients, a substantial group of patients report symptoms and disability after MTBI. To improve its outcome, several authors have suggested a planned follow-up visit after MTBI to screen for specific treatable conditions, such as depression, anxiety, or other modifiable factors [10, 76-78]. However, earlier studies produced conflicting results for early interventions after MTBI, probably because these studies included patients that would have recovered without any treatment [79-82]. Wade et al. found that an early intervention offered by a specialist service focused on providing information and advice significantly reduced social morbidity and the severity of PCS [79]. In contrast, other authors found no impact of cognitive-oriented counselling, advice, additional information or reassurance within three weeks after injury on PCS, social integration or quality of life [80-82]. To improve outcome and avoid persistent symptoms, several clinical recommendations and guidelines for MTBI have been developed in the last decade [10, 12, 21, 83, 84].

The newly revised Canadian guidelines used a modified Delphi process to create their recommendations based on a systematic review of the literature and on expert consensus [12]. The guidelines recommended an early evaluation of signs and symptoms combined with education focused on the normalisation of symptoms and reassurance of the expected favourable outcome within three months. In addition, there was a consensus for stress reduction and a gradual return to daily activities and work [12]. Treatment should be based on a biopsychosocial model, for which the International Classification of Functioning, Disability and Health (ICF) provides a useful framework for rehabilitation [12, 74]. Within the ICF framework, one can identify problems at the level of organ functioning, limitations in activities or restrictions in participation at work and can thereafter set realistic goals for the rehabilitation process [74]. In the Canadian guidelines, there is a consensus that somatic, cognitive or behavioural difficulties should be treated symptomatically and that a management strategy for each symptom must be considered. Based on consensus in the working group, specific guidelines were developed for several persistent conditions such as post-traumatic headache, sleep or wake disturbance, mental health disorders, cognitive dysfunction, visual dysfunction, vestibular dysfunction, fatigue, and return to activities such as work, school and sports [12]. There are multiple treatment options for persistent PCS. *Psychoeducation* is defined as a treatment that educates the patient about the expected symptoms, an interpretation of the symptoms and an explanation of how their complaints are being addressed [85]. *Cognitive rehabilitation* takes the form of either retraining in cognitive skills to improve functioning or training in compensatory strategies to overcome the impairments or adapt to the difficulties [85]. A more comprehensive, holistic neuropsychological rehabilitation programme addressing self-regulation of both cognitive and emotional processes to improve problem orientation and problem-solving skills seems to be effective after TBI [86]. *Psychotherapy* is an intervention for mental health disorders; examples of this form of treatment to improve mental health include cognitive behavioural therapy and other psychological methods such as metacognitive therapy. Finally, *integrated behavioural health treatment* usually involves a multidisciplinary approach that is a combination of the three above methods adapted for patients with comorbid behavioural conditions [85]. There is some limited evidence supporting the efficacy of the first three noted interventions for PCS, but to date, no controlled trial has

reported the efficacy of an integrated behavioural health treatment after MTBI [85]. In more complex cases and for patients with multiple impairments after a brain injury, multidisciplinary treatment is stated to be the best approach [11, 12, 75, 87]. Work disability is multifactorial in many cases, and a multidisciplinary treatment is recommended for individuals who have yet to RTW after MTBI [7, 12]. Multidisciplinary treatment involves teamwork between different professionals and the patient in which the output of the team is greater than the sum of the inputs by individual health care providers [74]. In TBI rehabilitation, the multidisciplinary team usually consists of a specialist in rehabilitation medicine, a neuro-psychologist, a physiotherapist, an occupational therapist, a speech therapist, a social worker and a nurse. A specialist in physical medicine and rehabilitation leads the multidisciplinary team in specialised medical rehabilitation. Together with the patients or their family, the team sets appropriate and realistic goals and coordinates a rehabilitation programme for the patients, who are evaluated and receive adjusted treatment on a regular basis. The process is patient-centred, and a rehabilitation plan is an important tool compiling the patient's problems, goals and possible interventions [74]. The rehabilitation process targets patient functioning, the environment and modifiable personal factors [74]. To date, there is little evidence in the literature supporting the efficacy of multidisciplinary treatment after a MTBI. Two randomised controlled trials (RCTs) showed that an early multidisciplinary intervention did not reduce PCS or improve RTW, probably because the studies included patients who might have recovered within a few weeks without any treatment [13, 88, 89]. A pilot RCT of a multidisciplinary intervention showed some promising results; in particular, this intervention protected against further development of psychological distress, and an another cohort comparison that included patients at four weeks post-MTBI improved RTW [90, 91]. Several authors have emphasised the need for well-designed treatment interventions to improve treatment and outcome after MTBI [10, 31, 78, 90-92]. It is recommended that additional studies should focus on the timing of the interventions, such as when patients report sustained complaints in the first one to three months after injury [26, 88]. It is a challenge to promptly identify persons with MTBI who are at risk to not RTW or to develop persistent PCS, and such patients are described as the "miserable minority" [48, 93]. Therefore, there is a need to identify patients requiring further follow-ups by improving outcome data and predictors for RTW as well as to evaluate the efficacy of multidisciplinary

treatment. In the present work, we have developed a holistic model for RTW among the vulnerable group of patients with persistent symptoms two months after a MTBI. The model was developed in a multidisciplinary outpatient clinic and was based on a biopsychosocial model within the framework of the ICF. For patients with persistent PCS, the treatment was individualised, and we used elements from integrated behavioural health treatment such as psychoeducation, cognitive rehabilitation and cognitive behavioural therapy when appropriate. The maim outcome variable was RTW.

7. AIMS OF THE STUDY

The purpose of this thesis was to evaluate the efficacy of a multidisciplinary outpatient follow-up programme compared to follow-up by a general practitioner (GP) and explore the outcome and prognostic factors of patients with MTBI.

Based on two prospective cohort studies of patients with MTBI and a randomised clinical trial, the specific aims of the 3 papers were as follows.

Paper I

> The aim of paper I was to identify whether clinical characteristics differed between patients who attended a planned follow-up session and those who did not. In addition, the aim was to examine the relationship between clinical characteristics from the emergency admittance, attendance at a planned follow-up service two months post-injury and RTW one year later.

Paper II

> The aim of paper II was to evaluate the efficacy of a multidisciplinary outpatient follow-up programme by comparing the results to a follow-up by a GP among patients who were sick-listed or at risk to be sick-listed with persistent PCS two months post-MTBI. The primary outcome was RTW, and the secondary outcomes were symptom burden, disability and the patients' impressions of changes at 12 months post-MTBI.

Paper III

> The objective of paper III was to identify which clinical characteristics predict RTW at 12 months post-MTBI for patients who either were sick-listed or at risk to be sick-listed with persistent PCS six to eight weeks post-MTBI.

8. MATERIALS AND METHODS

8.1. Study design

Paper I was a prospective cohort study of 343 patients with MTBI. Paper II was a prospective RCT with 151 patients. The participants were allocated to a multidisciplinary outpatient treatment programme or a follow-up session by a GP after a multidisciplinary examination. Paper III was a prospective cohort study with the same participants as those recruited for the study reported in paper II.

8.2. Population

Participants and settings:

In paper I, the patients with MTBI from Bergen and the surrounding area were admitted consecutively to the Department of Neurosurgery at Haukeland University Hospital, Bergen, Norway, from January 2009 to July 2011. In papers II and III, we recruited consecutive patients who were admitted for MTBI to the Department of Neurosurgery, Haukeland University Hospital, Norway, from January 2009 to January 2012 and to Oslo University Hospital, Norway, from January 2009 to July 2011, as shown in Figure 1. The patients were admitted either directly or from an emergency primary health care centre to a hospital. The patients were recruited from a mixed rural and urban community. The participants were restricted to inhabitants of Hordaland, Oslo and Akershus Counties, where the majority of the inhabitants are Norwegian residents (Caucasians). Patients diagnosed with ICD-10 code S06.0-S06.9 were considered to be eligible for inclusion in papers I-III. Because the primary outcome was RTW, the maximum age of the participants was set to 55 years to avoid any bias related to age. After discharge from the Department of Neurosurgery, further assessments were conducted at two outpatient rehabilitation clinics at Haukeland University Hospital, Norway, and Oslo University Hospital, Norway, until 12 months post-MTBI.

Inclusion criteria

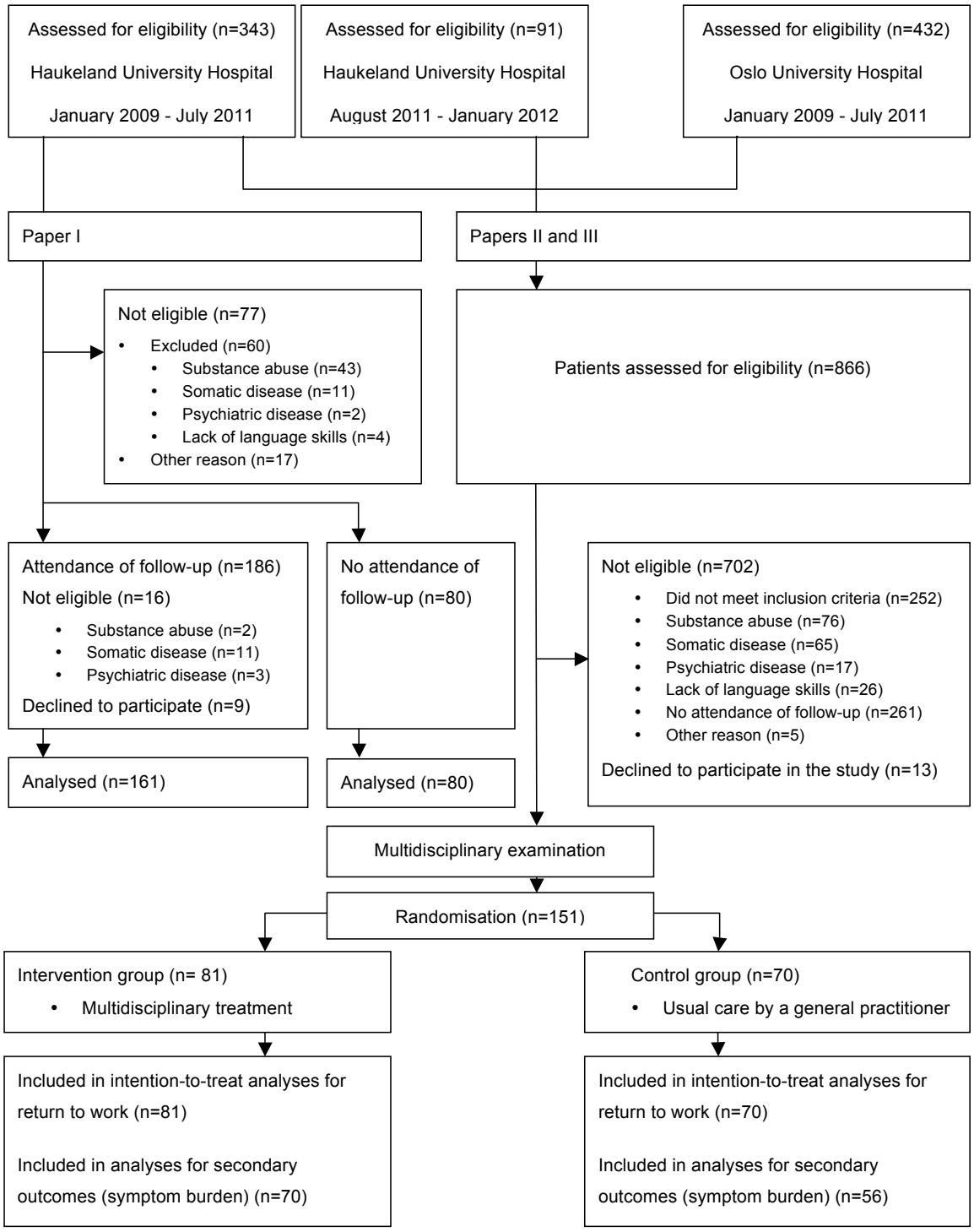
Adult patients aged 16-55 years who were hospitalised for five hours or longer (included in the inpatient statistics) with MTBI according to the WHO Task Force guidelines were included in these studies. MTBI is characterized by a GCS score between 13 and 15 after 30 minutes or the lowest score within the first 24 hours after injury, unconsciousness for less than 30 minutes and post-traumatic amnesia lasting less than 24 hours [26]. In papers II and III, we included patients with MTBI who either were sick-listed or at risk to be sick-listed with persistent PCS symptoms at six to eight weeks post-MTBI. Patients reporting substantial problems at work or with moderate disability according to the GOSE were defined as at risk to be sick-listed.

Exclusion criteria

Patients with psychiatric disease, major head trauma or other diseases that have a significant impact on working skills, were unemployed for the entirety of the last 6 months, lacked Norwegian language skills, or were out of work and diagnosed with substance abuse as stated in the medical records were excluded from the study.

A flow diagram for papers I, II and III is shown in Figure 1.

Figure 1 Flow Diagram for Papers I, II and III



8.3. Paper I

Procedures

When patients with MTBI were discharged from the hospital, they received an information pamphlet with information about their concussion and information about a planned follow-up consultation two months post-injury. Patients meeting the inclusion criteria received an appointment with a specialist in physical and rehabilitation medicine six to eight weeks after the injury.

Group allocation

Patients who failed to attend the follow-up session received a phone call and a new appointment by mail. Patients who failed to attend the follow-up session were classified as not attending follow-up. Patients in this study were categorised into two groups according to their attendance to the follow-up visit (AG) or not (NAG).

Baseline data

Age, gender, length of unconsciousness, amnesia, clinical status including GCS score, CT findings, alcohol intoxication, neck pain, headache, injury mechanisms and length of hospital stay were obtained from the medical records.

The presence of contusion, oedema, cerebral hematoma, epidural hematoma, subarachnoid haemorrhage or subdural hematoma on a CT scan was defined as intracranial pathology. Patients with more than one intracranial lesion on a CT scan were categorised as having multiple lesions. Based on the information from the medical records, patients who did not undergo a CT scan were defined as having no intracranial injury in the analysis. In addition, skull fracture and fracture of the cervical spine and face were documented. From an accredited third-party agency, Statistics Norway (SSB), we obtained data from the Norwegian Labour and Welfare

Service (NAV) related to the days sick-listed and the diagnosis for sick leave (one year prior to and the year following the injury). We defined all participants who were partly or completely sick-listed as not RTW in our analyses. Additional information about education level and income for both groups was obtained from SSB. The education levels at the time of injury were categorised as primary, secondary or higher education (more than 14 years of education).

Outcome variables

The main outcome was RTW. Independent of diagnosis, RTW was categorised as sick-listed or not twelve months after the injury.

Statistics

The statistical analyses were performed using IBM SPSS Statistics for Windows, Version 21.0 (IBM Corp., Armonk, NY). A statistician who did not participate in the treatment performed the statistical analyses. To compare the demographic and clinical characteristics between the AG and the NAG, the Chi-square test was used for categorical variables. We used the Mann-Whitney U Test for non-normally distributed continuous variables. Using logistic regression models, we predicted RTW at twelve months post-MTBI. Both the unadjusted models and a fully adjusted model were generated for all predictor variables of interest. Additionally, correlation analyses were performed for all predictor variables in the model. Based on these analyses, the final model was developed. The final model contained only statistically or clinically relevant variables and excluded predictors with fewer occurrences that could result in invalid measurements.

8.4. Paper II

Procedures

Six to eight weeks post-MTBI, the patients were offered a visit to a specialist in rehabilitation medicine according to a standardised protocol to collect a patient history and perform a clinical examination. The current extent of PCS, psychological complaints, disability and pain was measured using a self-report questionnaire. Patients who fulfilled the inclusion criteria for this study were offered a targeted multidisciplinary clinical examination two months post-MTBI. The team consisted of a specialist in rehabilitation medicine, a neuro-psychologist, an occupational therapist, a social worker, a nurse and a physiotherapist. Additional assessments, including a neuropsychological assessment, were performed by the team members to clarify the diagnosis, define the relationship to the employer or school, and identify working skills and routines in daily living. Feedback from the team with information concerning the expected favourable outcome and recommendations regarding gradual RTW was given immediately after the multidisciplinary examination. If needed, referral to other specialists or therapists was recommended. A report from the multidisciplinary examination at baseline was sent to the participant's GP. For both groups, the GPs were responsible for managing the participants' sick-leave certificates.

Randomisation

Between the multidisciplinary examination and the feedback from the team, the participants opened an envelope containing a card that informed them if they were recruited to the intervention or to regular care by their GP. The participants were randomised via simple randomisation using a 1:1 allocation ratio according to a computer-generated list of random number assignment generated by an independent researcher for each hospital. A person who did not participate in the study stored the lists, and envelopes with group allocations from the lists were produced. The allocation sequence was concealed from the multidisciplinary team.

Intervention

The multidisciplinary outpatient follow-up programme consisted of both individual contacts and a psycho-educational group intervention. The participants' capabilities and job demands were evaluated, and a plan for a gradual RTW or alternative activities was developed. The occupational therapist gave advice about using memory aids and structuring the day. The neuropsychologist cared for psychological distress or cognitive difficulties. Principles of cognitive behavioural treatment were used if appropriate. From each follow-up consultation, the GP received a report. Follow-ups within the first year after injury were tailored to the individual's needs and problems related to RTW and were continued as long as the participants were sick-listed. Meetings with the NAV or the employer to facilitate the patients' RTW were organised for only a few participants. The group intervention, which involved meetings once a week over a consecutive 4-week period, was conducted approximately between weeks nine and sixteen post-injury. The participants received information, addressed common problems and shared their experiences after MTBI. They discussed different strategies for lessening the impact of their injury and facilitating the process of RTW. Reasons for being physically active as a strategy for coping with their difficulties after TBI were addressed, and several exercises were performed.

Control group

After the multidisciplinary examination, the GP monitored the control group, which was offered typical, standard treatment that is not currently standardised in Norway. The recommendation from the multidisciplinary examination provided guidance for further treatment of the control group. The GP offered follow-ups and issued referrals to specialists, physiotherapists or other health care providers when needed.

Measures

Clinical and demographic data were obtained from the self-report questionnaire assessed at the first consultation six to eight weeks post-MTBI and from the medical records obtained during the patient's emergency stay. The presence of intracranial pathology was based on information from the acute CT scan and the medical records.

A standardised interview at the time of the first visit six to eight weeks post-MTBI was performed to measure PTA. The patients were asked retrospectively to recall known events. We dichotomised PTA into greater or less than one hour [94].

The participants received a questionnaire by mail at six and twelve months post-MTBI where the outcome measures and the treatment received were registered. The number of visits in the last six months for different types of treatment to different health professionals was categorised from no visits to more than six visits.

Outcomes

Days to sustainable RTW up to 12 months post-MTBI was the primary outcome measure. We defined number of days to sustainable RTW as the time until not receiving sick-leave benefits from the NAV for a period of five weeks post-MTBI. We used a period of five weeks to define sustainable RTW because a vacation period can last up to five weeks in Norway. If the participants received no sick-leave benefits from NAV, they were defined as RTW. If the participant was either partly or completely sick-listed, it was counted as a sick-listed day. Based on the diagnosis from the NAV, it was difficult to determine whether the sick leave was a result of the injury. Regardless of diagnosis, RTW was categorised as sick-listed or not. The number of days sick-listed in the first year after injury and RTW at twelve months after injury were recorded.

PCS, disability and the patient's impressions of changes were secondary outcomes.

The Rivermead Post Concussion Symptoms Questionnaire (RPQ): [44] a 16-item questionnaire of the most frequently reported brain injury-related symptoms that measures cognitive, emotional and physical symptoms. The patients' symptoms during the last 24 hours are compared with the pre-injury symptoms. The response to each item is rated on a 5-point Likert scale as follows: 0 = not experienced at all; 1 = a minor problem; 2 = a mild problem; 3 = a moderate problem; or 4 = a severe problem. The total number of symptoms rated above 1 are counted and summed as recommended by King et al. [44]. The RPQ is documented to have high reliability for PCS, although this measure lacks good validity [95]. Therefore, several authors argue against using the total sum score as recommended by King et al. [44, 95, 96]. Both the number of symptoms and a symptom-by-symptom comparison have been used as outcome measures [67, 72, 96]. In our study, we present both the total score and the number of symptoms as secondary outcomes.

GOSE: [97] an 8-point ordinal global scale for assessment of functioning in the areas of independence, work, social and leisure activities and participation in social life. The GOSE is a reliable and valid outcome measure used to evaluate patients after TBI [98, 99]. The scale is divided into upper (8) and lower (7) levels of good recovery, upper (6) and lower (5) levels of moderate disability, severe disability (3 and 4), vegetative state (2) and death (1).

Patient's Global Impression of Change (PGIC): [100] a 7-point categorical scale in which participants evaluate their overall change from the commencement of the study. Lower scores represent an improvement: very much improved (1), much improved (2), minimally improved (3), no change (4), minimally worse (5), much worse (6) and very much worse (7).

HAD: [101] a self-reported 14-item scale assessing states of depression (7 items) and anxiety (7 items). The patients rate each item using a 4-point scale from 0 to 3: 0 = no symptoms; 3 = a severe symptom or symptoms present most of the time. The subscale of anxiety and depression ranges from 0-21. A total score of 19 or higher using HAD was set as a cut-off for a mental disorder. For the subscales, 11

was set as a cut-off for anxiety and depression [102]. The HAD has been validated and documented to have high reliability for TBI [101, 103].

Sample size

The a priori power calculation was based on the variance in RTW in an earlier RCT [104]. Considering 15% differences in RTW between the groups, a significance level of 5% and a power of 90%, we needed 184 patients in each group.

Blinding

The baseline data were collected before randomisation, and the participants and the physicians were blinded to the allocation. Both the multidisciplinary team and the participants were aware of the randomisation during the feedback from the multidisciplinary examination two months post-injury. Postal self-report questionnaires were used to collect data at 12 months, and for the GOSE, an assistant who was blinded to the group allocation performed a telephone interview. The data were entered into the SPSS database by two independent persons unfamiliar with the aims and content of the study. Data concerning sick leave and other sickness benefits from one year before until one year after the injury was obtained from the NAV through an accredited third-party agency, SSB, which blinded the data before returning them to the first author. A statistician was responsible for the statistical analyses and control of the analyses in instances in which the work was performed by the first author. The statistician did not participate in the treatment programme and was blinded to the group allocation when the data were analysed.

Statistical method

Data analysis was completed using IBM SPSS Statistics for Windows, Version 22.0 (IBM Corp., Armonk, NY). The Chi-squared test for categorical variables and the

Mann-Whitney U test for continuous variables were used to compare the outcome data at the 12-month follow-up. A survival analysis was used to compare days to sustainable RTW in the two groups by landmarking at the randomisation time (i.e. patients who were sick-listed at 60 days after injury were included) [105]. The participants with 366 days of sick leave post-MTBI were censored. Finally, Kaplan-Meier analysis with the log-rank test was used, and we estimated a backward stepwise Cox regression for the intervention to adjust for effect modifiers, leading to the generation of a final model. To determine the effect modifiers, we estimated the crude model including only the intervention as a predictor as well as single-adjusted models including the intervention and one adjustment variable at a time among a pre-selected list of variables. Those variables which significantly changed the hazard ratio of the intervention effect in the single-adjusted models were included in the stepwise regression. The significance level was set at 0.05.

All of the participants who were randomised were analysed, including the participants who did not keep their appointments and those in the intervention group who did not receive treatment.

8.5. Paper III

We used the same procedure as described for paper II.

Measures

The primary outcome, RTW at 12 months post-MTBI, was the dependent variable. Data regarding sick leave one year before and the first year after the injury were collected from the NAV. Independent of diagnosis, the participants were categorised as sick-listed or not.

Pre-injury factors, injury-related factors and post-injury factors were examined as potential predictors for RTW at 12 months post-MTBI.

Pre-injury factors obtained from the self-report questionnaire at six to eight weeks post-MTBI consisted of age in years, sex, relationship status, number of children still living in the household, education level and employment status. Education level was categorised as lower or higher education, the latter of which was defined as 13 years or more of formal education. Information about smoking habits, alcohol consumption and previous diseases such as anxiety, depression, prior head injury, headache, neurological disease and other diseases was also obtained from the self-report questionnaire. We received information about previous sick leave from the NAV.

The injury mechanism was classified as traffic accident, fall, violence or other (sports), and these results were combined with occupational injuries obtained from the self-report questionnaire. From the medical records, we obtained information about GCS score, neurological status, headache, neck pain, alcohol intoxication, length of hospital stay during the emergency and CT findings. Findings on CT were categorised according to bleeding type, the presence of a contusion, injury location, and the presence of fractures of the skull, face and neck in the preliminary analysis. In the final analyses, we used the presence or absence of intracranial injury as

categories. PTA was assessed by performing a standardised interview six to eight weeks post-MTBI.

As described for paper II, post-injury factors were obtained from the self-report questionnaire at six to eight weeks post-MTBI.

RPQ was used to measure PCS. To predict RTW at 12 months post-MTBI, we used the total number of complaints with an RPQ score ≥ 2 six to eight weeks post-MTBI in our analyses.

The Post-Traumatic Stress Syndrome 10-Question Inventory (PTSS-10) is a self-reported inventory in which 10 separate items specific for post-traumatic stress disorder are rated from 1 to 7: 1 = never; 7 = always. Among persons who are traumatised, the PTSS-10 is reliable and valid tool for screening out patients at risk for psychiatric disorders [106-108]. We used the total score on the PTSS-10 in our analyses.

For psychiatric distress, we used the total overall score on the HAD in our analyses.

The subjective health complaints questionnaire (SHC) is a generic questionnaire that consists of 29 questions concerning severity and duration of subjective somatic and psychological complaints. The SHC is rated from 0 to 3: 0 = no, 1 = slight, 2 = moderate, and 3 = serious problems. The symptoms were categorised into five groups: flu (cold/flu and coughing), allergy (asthma, breathing difficulties, eczema, allergy and chest pain), musculoskeletal pain (headache, neck pain, upper back pain, lower back pain, arm pain, shoulder pain, migraine and leg pain during physical activity), gastrointestinal problems (heartburn, stomach discomfort, ulcer/non-ulcer dyspepsia, stomach pain, gas discomfort, diarrhoea and obstipation) and pseudo-neurology (extra heartbeats, heat flushes, sleep problems, tiredness, dizziness, anxiety and sadness/depression). The inventory has been validated to be reliable for scoring subjective health complaints [109, 110]. In our analyses, we used the total number of complaints from the SHC.

Pain in the head, pain in the neck and shoulders and pain in the back and legs were assessed using the numerical rating scale (NRS), in which pain is rated from 0,

representing no pain, to 10, representing the worst possible pain [111]. The NRS is a reliable, easy and commonly used measure of pain [112]. In the preliminary analyses, we used both the total score and the highest score on the NRS for pain in the head, the neck and the back. The location and number of painful areas was recorded using a pain drawing, which was graded from 0 to 10 painful areas. Higher scores indicated more widespread pain [113].

The GOSE, a measure of activities and participation, was scored by a physician as described above at baseline six to eight weeks post-MTBI before inclusion in the study. The scores were divided into good recovery (GOSE = 7 or 8), moderate disability (GOSE = 6) and severe or moderate disability (GOSE = 5 or less).

Participants had an expectation of a favourable outcome if they answered yes or reported recovery on the questionnaire. Participants answering no or who were not certain of their outcome were classified as having a negative expectation of outcome [114].

Statistical methods

To assess the predictors for RTW, we used a logistic regression model in which the dimensions were reduced in a stepwise manner. The unadjusted model for each of the pre-injury, injury-related and post-injury factors considering RTW as the outcome was estimated in the first step to detect all predictors associated with RTW. Then, in the second step, we estimated the fully adjusted model for all significant predictors according to the first step. To take into account potential confounding and to reflect all aspects of the study in the fully adjusted model, we ensured the inclusion of basic characteristics of the cohort in the model [115]. We therefore included age, sex and at least one representative for each of the predictor groups (pre-injury, injury related, and post-injury). The final model was estimated in the third step. To avoid multicollinearity, increase the power and improve the precision (SE, CI) of the estimated odds ratios (ORs), we developed the final model. In the final model, we included only the significant predictors from the fully adjusted model. For

missing data, we used pairwise deletion to ensure that we used all available data and achieved maximal power in the estimated models. For all analyses, the significance level was set to 0.05.

8.6. Ethics

The study was approved by The National Committees for Research Ethics in Norway and Norwegian Social Science Data Services, identifier NSD 20425. The study was conducted according to the Helsinki Declaration. Each patient provided informed consent to participate in studies II and III. In study I, only patients who attended their follow-ups provided an informed consent. In the study reported in paper I, patients who did not attend a follow-up visit received written information about the study and were given an opportunity to refuse to participate. The trial is registered in the ClinicalTrials.gov registry as NCT00869154.

9. SUMMARY OF RESULTS I-III

9.1. Paper I

Missing a follow-up after mild traumatic brain injury - Does it matter?

One hundred and sixty-one (67%) patients attended (AG) and 80 (33%) did not attend (NAG) their follow-up appointments, as shown in Figure 1. In the AG, 19% had intracranial pathology, and 9% had multiple lesions on their CT scans, compared to 5% and 1%, respectively, in the NAG (p=0.012). In the AG, 39% had consumed alcohol, compared to 62% in the NAG (p=0.001). The AG was older, with a median age of 31 years, compared to the NAG, with a median age of 25 years (p=0.022). No significant differences were detected between the groups concerning GCS, sex, education, cause of injury or sick leave before injury. Significantly fewer AG patients (83%) experienced RTW than the NAG (99%) at twelve months post-injury (p<0.001). Logistic regression analysis showed that follow-up attendance (odds ratio (OR)=16.89) and having been sick-listed within the last year before injury (OR=9.70) were negatively associated with RTW at twelve months post-injury. There was a nonsignificant trend toward an association between the presence of multiple lesions on the CT scan and RTW after MTBI (p=0.083). Skull fracture and cause of injury had no influence on outcome.

9.2. Paper II

Multidisciplinary outpatient treatment in patients with mild traumatic brain injury: a randomised controlled intervention study.

The number of days to sustainable RTW was 90 in the intervention group and 71 in the control group (p=0.375). The percentage of patients experiencing RTW at 12 months was 60% in the intervention group and 71% in the control group (p=0.173), and the median days sick-listed over the first year post-MTBI was 121 in the intervention group and 134 in the control group (p=0.617).

For the subgroup of patients who still were sick-listed according to the sick-leave register at baseline two months post-injury, there was no difference in days to sustainable RTW between the groups. Adjusted for anxiety, depression and PCS, the hazard ratio of the intervention for days to sustainable RTW was 0.48 (0.25, 0.91), which was significantly different from 1 (p=0.025). The number of PCS was fewer in the intervention group (6) than in the control group (8) at 12 months post-injury (p=0.041). No group differences were observed for disability (p=0.193) or patient's impression of change (p=0.285). Although this result was not significant, we noted a tendency of less frequent use of other health services (GPs, other specialists and physiotherapists) in the intervention group. Specifically, 51% of the patients in the intervention group reported no additional treatment during the first six months compared to 36% of the patients in the control group (p=0.199). From six to 12 months post-injury, the percentages of patients who reported receiving no additional treatment were 52% and 38% in the intervention and control groups, respectively (p=0.135).

9.3. Paper III

Predictors for return to work in subjects with mild traumatic brain injury.

We observed a significant negative association between RTW at 12 months and psychological distress (HAD), (OR 1.14 (1.1, 1.2)), severe and moderate disability at two-months post-MTBI (GOSE), being sick-listed at two months post-MTBI (OR 6.84 (2.3, 19.9)) and having been sick-listed within the last year before injury (OR 7.29 (2.6, 20.3)). None of the physical measures such as CT findings and different measures of pain were significantly associated with RTW.

10. DISCUSSION

10.1. Methodological considerations

10.1.1 General

The initial treatment by a specialist in rehabilitation medicine and the multidisciplinary examination were administered before randomisation at two months follow-up. During the multidisciplinary follow-ups and group interventions, the participants were not blinded, a common situation in clinical rehabilitation studies [86]. To improve the outcome data at 12 months post-MTBI, we used standardised postal self-report questionnaires. To avoid biases when analysing the registry data, the sick leave data from the NAV and the clinical data were linked and blinded by an accredited third-party agency, SSB. Assistants who entered the data into the SPSS database were blinded to the group allocation and were unfamiliar with the aims of the studies. Finally, the statistician who performed the analyses did not participate in the treatment programme and was blinded to the group allocation when the data were analysed.

The non-significant difference in outcome between the groups may be a result of little difference in the content of treatment offered between the groups. The follow-ups in the intervention group were individualised, and not all participants completed the group sessions. Both groups underwent a clinical examination by a specialist in rehabilitation medicine before the multidisciplinary examination consisting of a thorough examination, feedback and recommendations for further treatment. The intervention group then received individually tailored follow-up consultations and participated in four group sessions addressing RTW and coping strategies to lessen their symptoms after the injury. In the intervention group, 15 of the 17 participants who attended fewer than two individual follow-ups or group sessions terminated the programme as a result of their RTW. Therefore, most of the participants who were sick-listed and needed further treatment completed the multidisciplinary follow-up programme and received treatment that was distinct from follow-up by their GP.

In this model, we did not know the extent to which the GPs followed our recommendations concerning further treatment and sick leave. Greater cooperation

between the different stakeholders is therefore important in improving outcome. There was a tendency of less frequent use of other health services in the intervention group. Other authors have found less frequent health care use among patients or subgroups of patients receiving multidisciplinary treatment [90, 91]. This finding could be by chance, but the use of other health care services by patients receiving multidisciplinary treatment must be investigated in other studies.

The optimal timing for a multidisciplinary intervention is uncertain. Paniak et al. demonstrated little improvement between three and 12 months post-MTBI [80]. Others have concluded that patients with persistent symptoms differ from the majority of patients, who recover within three months [67, 70, 73]. Being sick-listed for longer than five months in Norway increases the probability of receiving a disability pension [116]. Our multidisciplinary follow-up programme may have been offered at the proper time, probably to the appropriate patients.

10.1.2 Study design

RCTs are the most stringent approach to determine whether a cause-effect relation exists between an intervention and an outcome. RCTs are considered to be the top of the hierarchy of research designs [117]. To improve the quality of RCT studies, the Consolidated Standards of Reporting Trials (CONSORT) was developed in 1996 and has been reviewed several times [118, 119]. The guidelines of CONSORT were followed in paper II. There was no difference in sustainable RTW, the primary outcome, between the groups, but additional analysis adjusted for HAD and RPQ scores demonstrated a significant difference in the hazard ratio for sustainable RTW in favour of the control group. This difference in the hazard ratio could be a result of selection bias between the groups. A minor limitation of the study is the use of a simple randomisation method with 1:1 allocation instead of block randomisation. This method was chosen due to an expected greater number of recruited patients than achieved. If small blocks with randomly selected block sizes were used, our less uneven numbers in the study arms could have been avoided, and the potential for selection bias would have been further reduced [120]. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement was

developed in 2007, and CONSORT was used as a model for these guidelines [121]. There are only minor differences between the CONSORT and STROBE guidelines, but separate guidelines for the intervention and procedures for randomisation are described in CONSORT. STROBE was followed to present the introduction, methods, results and discussion for the prospective cohort studies in papers I and III. A possible limitation of the predictor study reported in paper III was that the patients recruited were the same as those included in the intervention study reported in paper II. Our analysis did not reveal any association between the intervention and RTW, but we cannot exclude the possibility that the intervention had an impact on some of the patients.

10.1.3. External and internal validity

When we planned the trial, we discussed the controversy between a pragmatic trial and a more explanatory trial with strict criteria for inclusion and follow-up. Pragmatic trials are designed to evaluate the effectiveness of interventions in a real-life routine practice setting, whereas an explanatory trial tests an intervention under more standardised conditions and are therefore easier to replicate [122]. Selection bias may result from applying strict inclusion and exclusion criteria (internal validity), as only a small sample that may differ in clinical characteristics from the overall MTBI population could remain [123]. One strength of our cohort study reported in paper I was that we avoided a major selection bias by including all patients in the working population who were consecutively admitted to the Department of Neurosurgery, were hospitalised (for at least five hours) and met the standard definition of MTBI. In paper I, approximately 30% of the patients hospitalised for a MTBI were excluded because they were not working at the time of injury. In papers II and III, we selected a group of patients with more severe MTBI. To be included in papers II and III, the patients had to be sick-listed or at risk to be sick-listed with persistent symptoms six to eight weeks post-MTBI. Patients who reported substantial problems at work or moderate disability on the GOSE were defined to be at risk to be sick-listed. One limitation was that we did not use strict criteria for being at risk with a numerical cut-off value for inclusion, and this limitation could make our study slightly more difficult to replicate.

In choosing an individually tailored treatment for this heterogeneous group of patients, we were aware of the difficulties in judging the true impact of the intervention. However, we decided to design a more pragmatic trial that reflects clinical practice and that displays increased external validity. The study design of two centres at two different geographic locations in Norway may have increased the external validity, and the subgroup analyses performed did not show any differences between the centres. Our participants in and the studies are to some degree selected since they were recruited from two University Hospitals and at an age between16 to 55 years.

10.1.4. Measures

According to the guidelines for standardised outcome measures, ideally, all outcome measures should be evaluated and validated for the specific trial population, specific guidelines, the COSMIN (Consensus based Standards for the selection of health Measurement INstruments), have been developed for the selection of outcome measures in clinical trials [124, 125]. It was not possible to systematically select outcome measures beyond the scope of this thesis. In the present work, we used outcome measures that have been validated and recommended in systematic reviews [15, 126]. RTW is a measure of participation and is recommended as a social and economic outcome measure after MTBI [15, 126]. RTW is also stated to be a good indicator of the patient's well-being and adaption after a TBI [127]. RTW or sickness-related absence could be measured in several ways, and based on a review, five measures are suggested: frequency, length, incidence rate, cumulative incidence and duration [128]. Among these measures, we used frequency (number of persons experiencing RTW at 12 months post-MTBI) as the dependent variable for RTW in papers I and III. In paper II, we presented the frequency and length (number of days being sick-listed) in addition to the primary outcome, duration of absence (mean number of days absent, described as days to sustainable RTW). Based on the Norwegian holiday, which lasts for five weeks, we defined sustainable RTW as receiving no compensation for five weeks instead of a more commonly used period for four weeks [129]. According to this review, days to sustainable RTW is particularly suitable for comparing RTW between two groups in a RCT [128].

Although the median days to sustainable RTW was greater and the median number of days sick-listed was fewer in the intervention group than in the control group, there was no significant difference between the groups for these estimates of RTW. This result is in accordance with other studies that found high correlations between different definitions of RTW [129]. RTW at one year post-MTBI varies from approximately 55% to 97% between different patient populations [7, 63-65]. In paper I, in which all patients hospitalised for a MTBI were included, 88% experienced RTW, and in papers II and III, in which a subgroup of patients with persistent symptoms and disability at two months post-MTBI were included, only 66% experienced RTW at one year post-MTBI. We conducted the analyses according to the intention-to-treat principle by including all of the participants who were randomised in the analyses. One drawback to this method is that patients who do not complete the treatment were included in the analyses. We lacked data for secondary outcomes because only approximately 83% completed the follow-up questionnaires. It is well known that loss to follow-up or non-attendance could bias outcome in clinical studies [15, 26, 130]. Some authors have explained an unfavourable outcome after a multidisciplinary treatment as a result of selection bias, as the patients with the greatest complications attended the multidisciplinary treatment and the patients with less severe injuries and a favourable prognosis dropped out and did not attend their follow-ups, as reported in paper I [90]. One advantage of using sick leave data from a national registry was that we avoided missing data that could bias the results for RTW. To further avoid missing data, we received data related to sick leave in several forms from the SSB. However, there were some limitations to the sick leave data from the national registry. Sick leave data was not provided if the participants received benefits from the NAV for more than one year. If participants are sick-listed or disabled for one year, they receive a different benefit from the NAV termed a work assessment allowance (AAP) or a disability pension. All participants who received the benefit of AAP from the NAV were therefore defined to be sick-listed 12 months in advance [131]. From the sick leave data, we did not know whether the sick leave was a result of the MTBI. There was a significant difference in median days sick-listed from one year before the injury (0 days) to the first year post-MTBI (132 days); this result indicates that the increase in sick leave was a result of the MTBI. All participants who were either partly or completely sick-listed independent of diagnosis were defined as not RTW

in our analyses. Sick leave has a longitudinal and a vertical dimension with qualitative differences: length of being sick-listed and being partly or completed sick-listed, respectively [128]. A major limitation of our study was that we did not receive information about whether the participants were partly or completely sick-listed. From self-report questionnaires, we obtained data related to sick leave from 82% of the participants. In the intervention group, 18% of the participants reported in the questionnaire that they were 100% sick-listed at 12 months post-MTBI, compared to 25% of the participants in the control group. This difference was not significant, but the trend that participation in intervention group resulted in more persons working part-time instead of being completely sick-listed may be of clinical importance. Only information from sick leave certificates completed by a physician, manual-therapist or chiropractor is reported to the national registry. Short-term sick leave less than 16 days is missing, and we most likely missed information if the students were sick-listed for less than one year. A total of 16% of the participants in papers II and III were students, and in paper I, we did not have this information because participants who did not attended the planned follow-up were included. Regardless of occupational status, we used patients hospitalised for MTBI as a denominator when describing RTW in our studies. This choice is justified because the purpose of our study was to determine the efficacy of the health programme, not to obtain epidemiological data [128]. This is a limitation because students and unemployed participants must be disabled for one year to receive any benefits from the NAV [131]. In papers II and III, we excluded students and unemployed persons from additional unpublished analyses, but these results did not change our major findings or conclusion.

Cases of assault have been excluded from some reviews because recovery in these cases is complicated by litigation [7]. We did not find any association between assault and RTW in our prediction analyses, and our result is comparable to those of a study from England explaining that the difference in the association of RTW with litigation between Europe and USA is a result of different compensation cultures [91]. In Europe, payment for sick leave is provided by the state, and litigation is only involved in cases of traffic accidents or criminal acts. Another explanation may be early vocational rehabilitation and cooperation between the different stakeholders in Europe to maximise RTW [91]. To avoid any further

reduction of our sample size, we included students, unemployed persons and participants who were injured due to assault.

For the secondary outcome measures RPQ, PGIC, HAD and GOSE, from 79% to 83% completed these questionnaires at 12 months post-MTBI. Several working groups have recommended the GOSE as a core outcome measure in MTBI research [15, 126, 132]. The GOSE is also validated in a telephone interview format [133]. Assistants who were blinded to the group allocation performed the telephone interview in the present work. The GOSE is extensively used, but its scale is criticised for ceiling effects and may be insufficiently sensitive to functional changes in mild cases [126]. This is a limitation when evaluating outcome after MTBI. To simplify the analyses, it is recommended to dichotomise the GOSE score into favourable and unfavourable outcome [126]. To maintain some precision in our analyses, we categorised the GOSE into the three categories good recovery, moderate disability (upper levels of moderate disability) or severe disability including lower levels of moderate disability.

The RPQ is recommended for assessing PCS after MTBI [15, 126, 132]. However, the RPQ has been criticised for its lack of validity after MTBI, and several authors have therefore argued against using the total overall RPQ score as originally recommended [44, 95, 96]. PCS can be expressed in several ways, and in our RCT, we presented both the number of PCS and the total RPQ score as secondary outcomes [67, 72, 96, 134]. Some authors have stated a 15% reduction in the PCS score as a clinically relevant result, but this outcome measure remains to be sufficiently validated [135]. In paper III, we used the number of PCS to predict RTW at 12 months. Unpublished data of the total score of PCS instead of the number of PCS did not change our results. The psychological outcome measure HAD is validated, recommended and widely used in TBI research [103, 126]. The final secondary outcome measure used in the present work was the PGIC, a commonly used, valid instrument for patients with pain, although the PGIC has not been validated in patients with MTBI [100]. Our outcome measures represent different dimensions in the ICF framework, which includes body function, activity and participation. There is an overlap between the chosen outcome measures and the different dimensions in SF-36 (a measure of quality of life) in terms of health

problems, activities, pain, mental health and vitality. Therefore, we decided not to use SF-36 as an outcome measure in the present work [136].

One limitation of the injury-related factors in papers I and III was that clinical data were collected from the medical records, leading to imprecise and missing information. Strengths of the injury-related factors included that 145 (96%) of the participants underwent a CT scan. There is a strong indication that our results regarding intracranial findings are valid because up to 96% of the participants actually underwent a CT scan. We used a standardised interview and utilised the medical records from the emergency stay to assess PTA six to eight weeks post-MTBI. The neurosurgery departments used standardised monitoring curves to assess the GCS score, and this approach improves the quality of this measure.

10.1.5 Statistical considerations

A subgroup of all patients consecutively admitted to the hospitals for MTBI was recruited at two months post-MTBI, and we completed the study with fewer participants than estimated. The non-attending group was larger than expected, and it was not realistic to prolong the inclusion period for more than three years to increase the power of the study. Compared to our a priori power calculation, the study was inadequately powered for the primary outcome of RTW. This lack of power may lead to type 2 error, in which we may fail to reject a false null hypothesis. If there is an actual difference between the groups, a non-significant difference may be a result of a small sample size and insufficient power of the study. According to Stevens, this is not an issue if the sample is above 100 participants in each group, but it may lead to potential error in our study of 151 participants [137]. It appears that recruiting an adequate number of patients to achieve statistical power is a common problem in this type of study [13, 138]. If we had succeeded in recruiting a significant higher number of patients to the study, we could have achieved a more consistent difference between the groups. On the other hand, a too high number of patients that need to be treated for one to be benefit compared with a control has probably no clinical importance. Compared to other studies, our study was

adequately powered for evaluation of the secondary outcomes [89]. For sustainable RTW, we used non-parametric survival analyses and a backward stepwise Cox regression for the intervention to adjust for effect modifiers. We censored participants with 366 days of sick leave after the injury. There was no major difference in censoring between the two groups in the RCT, but one limitation was that only 78 participants were included in the final Cox regression model. Additionally, one drawback of non-parametric tests is an increased probability to fail to detect a true difference between the groups, referred to as type 2 error.

To predict RTW in papers I and III, we used a logistic regression model in which the dependent variable RTW was dichotomised. This approach simplifies the analyses, as we can consider non-normally distributed nominal and ordinal data as independent variables. This method may lead to loss of statistical power and increased probability for type 2 error. In the predictor study, presented in paper III, we missed approximately 10% of the cases in the adjusted model due to incomplete data from the self-report questionnaires at baseline. Statistical imputation is one method to handle missing data [115]. Even with statistical imputation, a few cases can bias the results if the cases are not missing at random in a small sample such as ours. Because of the uncertainty related to imputation, we decided not to use statistical imputation in our analyses. We cannot exclude selection bias due to missing data, but the power of the model was improved in the final model, in which the number of missing cases was reduced from 16 (11%) to 10 (7%).

10.2 General discussion

10.2.1 Return to work

There were no differences in days sick-listed, RTW at 12 months or sustainable RTW between the multidisciplinary outpatient follow-up programme and follow-up by the GP. When controlling for HAD and RPQ in an adjusted subgroup analysis for 78 of the patients who remained sick-listed (no sustainable RTW) at the time of randomisation, there was a difference in favour of the control group in the hazard ratio for days to sustainable RTW. One explanation for this result could be that RTW was delayed for many of the participants in the intervention, as they were sick-listed when participating in the group sessions. Several of the participants were prevented from participating in the first available group session, and RTW was then probably further delayed during the waiting period for the next group session.

The Norwegian welfare model compensates 100% of income, and there are regulations concerning job security [139, 140]. It is debated that such welfare arrangements may delay RTW and may even exclude patients on benefits from the job market because being out of work for a longer period increases the likelihood of receiving a disability pension [141]. Participating in a specialised care follow-up programme may justify being sick-listed, which leads to delayed RTW. Several authors have emphasized the role of expectations as a negative factor for RTW, but the evidence is limited [48, 142]. It is questionable whether excessive attention regarding symptoms and reduced focus on aspects concerning RTW could have produced negative expectations about the outcome of RTW in the intervention group. By focusing too much on difficulties in daily life as a consequence of symptoms and cognitive impairment after MTBI, the intervention could have had a negative impact on the belief in RTW. We found no association between expectations at two months post-injury and RTW, but we did not collect information about whether our treatment changed the patients' expectations about their ultimate outcome. Wade et al. improved participation in social activities in their RCT, and Radford et al. improved RTW in their cohort comparison study; however, to date, improved RTW after MTBI has not been documented in a multidisciplinary RCT [13, 79, 88, 90, 91]. In a qualitative study, several of the interviewed patients with a MTBI experienced RTW too early, their persistent symptoms affected their work capacity,

and the best time for RTW was difficult for the patients to determine [143]. Other authors have emphasised that prolonged activity restriction after MTBI may worsen outcome. Therefore, identifying the best intervention and time for RTW after MTBI remains an issue [144].

An earlier systematic review described three models of vocational rehabilitation after TBI: a programme-based vocational rehabilitation model, a supported employment model and a case-coordinated model [145, 146]. The *programme-based model* usually involves a structured rehabilitation programme of working skills, job training under supervision and assisted placement at the workplace. The *supported employment model* mainly consists of job training at work with long-term follow-up. In a *case-coordinated model*, the vocational rehabilitation is holistic and part of an individualised rehabilitation programme. The patients in this model are followed up by a coordinator who organises the different approaches for other medical services and vocational rehabilitation such as pre-job training, assisted job training and support at work [146]. Tyerman concluded that it remains necessary to conduct controlled clinical studies to evaluate the efficacy of these models for vocational rehabilitation after a TBI [146]. According to these models, our approach of vocational rehabilitation was most similar to a case-coordinated model in which a team member together with the patient produces an individualised plan for RTW and other activities that addresses the patient's problems, goals and possible interventions. The rehabilitation process was patient-centred, and the participants were held responsible for communication with their employer concerning RTW; standardised work visits were not included in our model. Team members participated in additional meetings with the employer or school to facilitate RTW for 5 participants (6%) in the intervention group. According to newly published literature, a structured RTW protocol including work visits and analysis for employability might be beneficial in vocational rehabilitation for patients with TBI, but this approach has not been evaluated [147, 148]. Van Velzen et al. recommended a step-by-step approach to facilitate RTW. The first step is to investigate the patient's work situation and goal for RTW. The second step includes a work visit to investigate the work requirements and provide information about the injury to the employer. At this step, the gap between work demands and patient capabilities is investigated. If RTW is possible, goals for vocational rehabilitation are created, and the employer is

informed about the plan for RTW or alternative job training. In the third step, the work training is performed. Every twelfth week, the capabilities of the patients are evaluated and new goals for RTW are set until the vocational rehabilitation is completed [147]. Finally, it is recommended that early vocational rehabilitation be integrated into the early rehabilitation process [147, 149].

We hypothesise that we recruited the most vulnerable patients for inclusion in the RCT: those who were sick-listed or at risk to be sick-listed at two months post-injury. We found that the sick leave trajectory of the subjects was a negative predictor for RTW at 12 months. These findings should be taken into consideration when offering vocational rehabilitation to patients with MTBI.

10.2.2 Post-concussion symptoms

The multidisciplinary outpatient follow-up programme may have reduced the development of PCS in a vulnerable group of patients. The multidisciplinary treatment focused on providing greater understanding and reassurance of a favourable outcome of MTBI. This information was repeated several times from different team members. This finding is in contradiction to earlier studies that have demonstrated that there is a low probability that repeating information or follow-ups early after the injury to all MTBI patients will improve their outcome [80, 89]. Compared to earlier studies, we recruited patients with more severe MTBI. The severity is indicated by the proportion of participants with PTA > 1 hour or intracranial injuries. Matuseviciene et al. reported intracranial lesions on CT in 10% of their cases compared to 27% in our study [13, 89]. Regarding the study by Wade et al., who found an effect of their intervention, concerning severity, 60% of their patients had PTA > 1 hour; thus, their sample was more comparable to ours [79]. Several authors argue that patients with persistent symptoms differ from patients who recover within few months post-MTBI [48, 67, 72, 73]. Both the severity of MTBI and the timing of our intervention, may explain the positive outcome for PCS in our intervention. PCS can be expressed as either the number of complaints or the total symptom score based on the severity and amount of common symptoms after MTBI [44, 95]. In our study, there was a significant difference between the groups only for

the number of PCS. The difference in total symptom score between the groups was consistent with the reduction in the number of complaints but was not significant. It could be debated whether the significant difference in the median number of PCS from 6 to 8 is of clinical importance. At present, there is no clear validated definition for a clinically relevant result. A reduction of 15% in the PCS score was previously stated to be of clinical importance [135]. Compared with this criterion, a reduction of two PCS is relevant. From a clinical perspective, we consider a reduction from 8 to 6 PCS as relevant because it probably reduces the total symptom burden for the patient. Notably, the effect of the intervention on the RPQ score was weak and would no longer be significant if the analysis were adjusted for multiple comparisons.

Finally, we do not know whether participants who did RTW developed more PCS as a result of higher demands at work. Because there was no significant difference in RTW at 12 months between the groups and there were fewer symptoms in the intervention group, the reduction in symptoms is most likely a result of the treatment received.

10.2.3 Association between psychological distress and return to work

In the RCT, there was no significant difference between the groups for the secondary outcomes HAD, GOSE and PGIC at 12 months post-MTBI. According to an earlier study, there were no change in psychological symptoms the first year after injury for hospitalised patients with MTBI [52]. In contrast, another study of a cohort in which 40% of the patients experienced MTBI found that a significant number of patients with TBI developed a psychiatric disorder within the first 6 months post-injury, and a systematic review found evidence for an increased risk of psychiatric disorders after MTBI [150, 151]. All participants in our study were screened for psychological distress, and a recommendation for psychological treatment was given if there was a clinical indication two months post-MTBI. Thus, both groups may have been offered psychological treatment to the same extent to avoid further development of psychiatric disorders. The HAD score at two months post-MTBI was an independent significant predictor of RTW at 12 months. There was a high

correlation between psychological distress (HAD), symptom burden (RPQ) and post-traumatic stress (PTSS-10), and care must be taken when interpreting these results in clinical practise. Our results resemble the findings of Guérin et al. and Nolin et al., in which the number of subjective symptoms, the including symptom burden and psychological distress, were associated with RTW several months post-MTBI [67, 72]. Our findings emphasise the importance of screening for psychological distress after MTBI.

10.2.4 Pre-injury and injury-related factors

In contradiction to earlier studies, we did not find any association between age, education and RTW [7, 63, 69, 152]. Similar to Stulemeijer et al., we excluded the oldest patients and avoided patients with poor prognosis in our study, and these discrepancies can explain this difference [69]. Most likely, our patients in paper III overestimated their formal education in self-report questionnaires, as 43% reported receiving higher education in this study, compared to 21% in paper I from the registry data. However, in line with the results presented in paper III, among all patients hospitalised with MTBI in study I, we did not find any association between education level and RTW.

In accordance with one earlier study, there was no association between injury-related factors such as intracranial lesions, PTA and GCS [69]. This result may be due to the recruitment of a specific group of patients with persistent symptoms six to eight weeks post-MTBI. Our findings are similar to those reported in the study of Nolin et al., in which the total number of symptoms several months post-MTBI was related to RTW [72]. Conversely, Waljas et al. recruited all patients with MTBI admitted to a hospital and found an association between intracranial injury and RTW, but our results are restricted to patients hospitalised with MTBI [63].

11. CONCLUSIONS

The present studies in papers I and III are two prospective cohort studies of patients with MTBI, in which we explored prognostic factors for RTW in patients with MTBI. Paper II was an RCT evaluating the efficacy of a multidisciplinary outpatient follow-up programme for patients with MTBI compared to follow-up by a GP.

Patients not attending the follow-up at two months post-MTBI had less intracranial injury and more favourable outcome concerning RTW. These patients most likely require less medical and rehabilitation support for their brain injury. A substantial group of patients who attended the planned follow-up were sick-listed, indicating the need for follow-up care after MTBI. Special care should be taken at follow-ups of patients who have pre-existing and comorbid conditions as well as those with intracranial pathology.

The multidisciplinary outpatient follow-up programme focusing on providing greater understanding and reassurance of a favourable outcome of MTBI did not improve RTW but appeared to reduce the development of PCS. Although this result was not significant, the intervention group tended to use other health services less often. Our results indicate that future intervention studies on multidisciplinary follow-up programs should focus on a different approach concerning RTW and with more focus on early vocational rehabilitation.

Four variables predicted RTW at 12 months among patients who either were sick-listed or at risk to be sick-listed with persistent PCS six to eight weeks post-MTBI. Having been sick-listed within the last year before injury, being sick-listed at two months post-MTB, having severe and moderate disability at two-months and exhibiting psychological distress were negative predictors of RTW at 12 months. There was a strong correlation between psychological distress, symptom burden and post-traumatic stress. None of the physical measures such as intracranial findings or different measures for pain were significantly associated with RTW. These findings strengthened our hypothesis that we recruited the most vulnerable patients for the RCT, i.e. those who were sick-listed or at risk to be sick-listed at two months post-injury.

12. IMPLICATIONS AND FUTURE RESEARCH

A standardised follow-up programme for all hospital-treated patients with MTBI is not recommended because a substantial group of patients with a favourable outcome did not attend their planned follow-up. Among hospitalised patients, as many as 30% were not working or studying when they were injured. Our findings in paper I demonstrate that both pre-existing or comorbid conditions and the severity of the injury may influence the outcome of RTW, and follow-up care is needed for a vulnerable group of patients.

Predictors for RTW in our study were early functional outcomes such as being sick-listed and disability at baseline six to eight weeks post-injury, as well as psychological distress and pre-injury variables such as having been sick-listed within the last year before injury. By including to a larger extent these predictors for RTW, vulnerable patients may be offered a more targeted multidisciplinary outpatient treatment to reduce their symptom burden.

The multidisciplinary outpatient follow-up programme focusing on providing greater understanding and reassurance of a favourable outcome for MTBI may have reduced the development of PCS, but the model must be developed further to improve RTW in the subgroup of patients with persistent symptoms two months post-MTBI. For these selected patients, standardised work visits and a plan for RTW must be conducted early in the rehabilitation process, and their progress must be evaluated on a regular basis. However, evaluation of the efficacy of this intervention in well-designed studies remains to be performed [147].

Although the optimal timing for a follow-up is uncertain, compared to other studies demonstrating no additional effect of an early intervention, a follow-up six to eight weeks post-injury may be reasonable for vulnerable patients [13, 88, 89].

Although the result was not significant, we noted that participation in the intervention group resulted in more persons working part-time instead of being completely sick-listed. This finding must be confirmed in other studies.

In accordance with other studies, we detected a tendency of less frequent use of other health care services among patients participating in the multidisciplinary follow-up programme [90, 91]. The use of other health care services by patients receiving multidisciplinary treatment compared to other interventions has to be further investigated.

We did not find any significant association between injury-related factors and RTW at 12 months. Our regression model was improved from an estimated pseudo-R^2 of 0.39 to 0.56 (Nagelkerke) when we included post-injury variables at two months post-MTBI in paper III, compared to using only pre-injury and injury-related variables in paper I. It appears that post-injury variables are more important than injury-related variables in predicting RTW in MTBI patients.

There is promising ongoing research in this field concerning injury-related factors. Traditionally, classifications based on the initial GCS score and findings on radiological examinations such as CT and MRI have many limitations, and there is a need for objective measures such as biomarkers that can be used to determine the outcome of individuals after MTBI [153]. More advanced MRI techniques, such as diffusion tensor imaging, susceptibility weighted imaging (blood oxygen level-dependent), functional MRI and magnetic resonance spectroscopy, have been developed. However, longitudinal clinical studies remain to be performed to validate the prognostic values of these techniques [154]. Combining different biomarkers in blood with these advanced MRI techniques has been suggested to improve the prognostic applicability of these measures [155].

Finally, prevention of brain injury is an important issue. Improved traffic regulations have reduced traffic accidents. One major cause of brain injury is falls, and cases of hospitalisation and death due to falls are increasing among the elderly population [31]. In addition, the proportion of assaults in Norway has increased among younger MTBI patients, and in paper I, 24% of all hospitalised patients with MTBI were caused by an assault. As many as 46% of all injured patients were intoxicated by alcohol. Specific regulations to prevent assaults should be taken into consideration, and precautions concerning falls among the elderly should have a high priority in the future.

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PAPERS I-III