Combined cognitive and vocational rehabilitation after mild-to-moderate traumatic brain injury

A randomized controlled trial

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Table of Contents

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Silje Christine Reistad Fure

Summary

Background: Many people sustain a traumatic brain injury (TBI) during their lifetime, and some struggle with returning to work afterwards. Returning to competitive employment and being a productive member of society is important for one's self-esteem and social life. It is also important to reduce societal costs after a TBI. Prolonged symptoms are often stated as the reason for difficulties with return to work (RTW), and existing research has mainly focused on finding treatments that reduce symptoms in these patients. However, treatments that sufficiently improve RTW rates are lacking. To date, there is sparse information on what characterizes patients who struggle with RTW after mild-to-moderate TBI. Furthermore, few well-controlled intervention studies have aimed to improve RTW outcomes in these patients. Regarding elements that may affect patients attempting to RTW, the focus has mainly been on factors related to patients and their injuries, while it seems reasonable to assume that factors related to the workplace and the psychosocial work environment also affect the RTW-process.

Aims: This thesis aimed to describe a sample of patients with mild-to-moderate TBI who were still symptomatic and struggled to RTW 8–12 weeks after injury, to evaluate the effectiveness of combined cognitive and vocational rehabilitation on RTW outcomes in these patients, and to examine the value of work-related factors on work participation after 1 year.

Materials and methods: A total of 116 patients were included as a part of a randomized controlled trial. Inclusion criteria included having sustained a mild or moderate TBI 8–12 weeks previously, being of working age (18–60 years), residing in Oslo or Akershus County, working at least 50% at the time of injury, and being at least 50% sick-listed at the time of inclusion due to post-concussion symptoms. Descriptive analyses of the patients' characteristics are presented. Multiple linear regression was applied to examine differences between patients with and without traumatic intracranial injury. Sixty patients were

randomized to receive Compensatory Cognitive Training and Supported Employment (CCT-SE) and 56 to receive treatment as usual (TAU). The two groups were followed up at inclusion and 3, 6, and 12 months after inclusion. Mixed-effect models were applied to compare the two groups' RTW outcomes. Multiple linear regression was also applied to build a prediction model with work participation at 1 year as a continuous endpoint.

Results: The sample reported a high symptom burden after injury. Patients with normal neuroimaging reported the highest symptom burden, while those with intracranial injuries had lower memory function. There were no differences in RTW outcomes at 12 months between the groups. Most had returned to work by 12 months (CCT-SE: 90%, TAU: 84%, p = .40), and all except three individuals were stably employed at that time. However, a higher proportion of patients in the CCT-SE group returned to work by the 3-month follow-up compared to the TAU group (81 vs. 60%, p = .02). In addition, 65% of patients in the CCT-SE group had returned to their pre-injury work level compared to 54% in the TAU group after 1 year. Predictability, quantitative demands, and rewards (recognition) in the workplace contributed to the best-fitting model, together with private or public employment, symptom burden at baseline, and sex. The best fitting model accounted for 25% of the variance in work participation at 1 year.

Conclusions: Subjective complaints do not necessarily co-vary with injury severity and the presence or absence of traumatic intracranial injury. Thus, these factors should not be the only consideration when planning treatment and follow-up after mild-to-moderate TBI. The CCT-SE intervention might help facilitate a more rapid RTW following mild-to-moderate TBI. The results also highlight the importance of considering work-related demands when treating patients with mild-to-moderate TBI.

Sammendrag

Bakgrunn: Mange opplever å få en traumatisk hodeskade i løpet av livet, og for noen av dem er det en utfordring å komme tilbake til arbeid. Tilbakeføring til arbeid er viktig for enkeltpersonens selvfølelse, sosiale liv og for å føle seg som et produktivt medlem av samfunnet. Det er også viktig for å redusere samfunnets utgifter knyttet til slike skader. Vedvarende symptomer er angitt som den viktigste årsaken til utfordringer knyttet til å gjenoppta arbeid og forskning på feltet har fokusert på å finne behandlinger som reduserer symptomene. Noen behandlinger er effektive mot symptomer, men de øker ikke tilbakeføring til arbeid. Det er i dag en mangel på informasjon om hva som kjennetegner pasientene som har utfordringer med å returnere til arbeid etter en lett eller moderat hodeskade. Videre er det også få velkontrollerte intervensjonsstudier som retter seg mot å forbedre arbeidsutkomme hos disse pasientene. Når man tidligere har sett på elementer som påvirker tilbakeføring til arbeid etter traumatiske hodeskader så har man fokusert på faktorer relatert til personen og skaden, mens det kan antas at også elementer knyttet til arbeidsplassen og det psykososiale arbeidsmiljøet påvirker denne prosessen.

Formål: Målet med denne avhandlingen er å beskrive et utvalg av pasienter med lett eller moderat traumatisk hodeskade som fortsatt har symptomer og utfordringer med tilbakeføring til jobb 8–12 uker etter skaden, å evaluere effekten av en kombinert kognitiv og arbeidsrettet rehabilitering på arbeidsrelaterte utkommemål hos disse pasientene og å undersøke påvirkningen av arbeidsrelaterte faktorer på arbeidsdeltagelse ett år etter inklusjon.

Materialer og metode: Inklusjonskriteriene var å ha fått en lett eller moderat traumatisk hodeskade 8–12 uker tidligere, være 18–60 år gammel, bo i Oslo eller tidligere Akershus fylke, være i minst 50% jobb på skadetidspunktet og sykemeldt minst 50% ved inklusjon grunnet post-commotio symptomer. Ett hundre og seksten pasienter ble inkludert og

deskriptiv analyse av pasientene ved oppstart av studien er presentert. Multippel lineær regresjon ble brukt til å sammenligne pasienter med og uten funn på CT/MR av hodet. Seksti pasienter ble randomisert til å motta kompensatorisk kognitiv trening og Supported Employment (CCT-SE), mens 56 mottok ordinær oppfølging (TAU). Blandede effekt modeller (mixed-effect models) ble anvendt for å sammenligne arbeidsutkomme mellom de to gruppene opp til ett år. Multippel lineær regresjon ble brukt for å bygge en prediksjonsmodell for arbeidsdeltagelse ett år etter inklusjon.

Resultat: Pasienter uten synlig intrakraniell skade på CT/MR rapporterte mest symptomer, mens pasienter med intrakraniell skade presterte dårligere på en test for verbal hukommelse. Det var ingen forskjell på hvor mange som var tilbake i jobb mellom de to gruppene ett år etter inklusjon. De fleste hadde returnert til arbeid etter ett år (CCT-SE: 90%, TAU: 84%, p = .40), og alle (unntatt 3) var da stabilt tilbake i arbeid. Det var i midlertidig en større andel av pasientene i CCT-SE gruppen som var tilbake i jobb etter 3 måneder sammenlignet med kontrollgruppen (CCT-SE: 81%, TAU: 60%, p = .02). I tillegg hadde 65% av pasientene i CCT-SE gruppen returnert til samme arbeidsgrad som før skaden etter ett år, mot kun 54% i TAU gruppen. Forutsigbarhet, kvantitative krav og belønninger (anerkjennelse) på arbeidsplassen bidro til den beste prediksjonsmodellen for arbeidsdeltagelse på ett år, sammen med sektor for ansettelse, symptombyrde ved studiens start og kjønn. Den beste modellen forklarte 25% av variasjonen i arbeidsdeltagelse på ett år.

Konklusjon: Subjektive plager varierer ikke nødvendigvis med alvorlighetsgrad av skade eller intrakraniell skade og man bør derfor vurdere flere faktorer enn dette når man planlegger oppfølging av pasienter etter lett eller moderat traumatisk hodeskade. Rehabilitering med CCT-SE kan hjelpe disse pasientene raskere tilbake i arbeid. Resultatene understreker også viktigheten av å vurdere arbeidsrelatert faktorer når man ønsker å hjelpe pasienter tilbake i jobb etter en lett eller moderat traumatisk hodeskade.

List of publications

The following publications form the basis of this thesis and will be referred to as papers I–III in the text:

I. Fure SCR, Howe EI, Spjelkavik Ø, Røe C, Rike PO, Olsen A, Ponsford J, Andelic N, Løvstad M. **Post-concussion symptoms three months after mild-to-moderate TBI: characteristics of sick-listed patients referred to specialized treatment and consequences of intracranial injury.** Brain Inj. 2021:1–11.

II. Fure SC, Howe EI, Andelic N, Brunborg C, Sveen U, Røe C, Rike PO, Olsen A, Spjelkavik Ø, Ugelstad H, Lu J, Ponsford J, Twamley EW, Hellstrøm T, Løvstad M. **Cognitive and vocational rehabilitation after mild-to-moderate traumatic brain injury: a randomised controlled trial.** Ann Phys Rehabil Med. 2021:101538.

III. Fure SCR, Howe EI, Andelic N, Brunborg C, Olsen A, Rike PO, Spjelkavik Ø, Enehaug H, Røe C, Løvstad M. **Workplace factors associated with return to work after mild-to-moderate traumatic brain injury.** *Submitted to the Journal of Head Trauma Rehabilitation in July 2021.*

Abbreviations

ACRM	American Congress of Rehabilitation Medicine
AFI	The Work Research Institute/Arbeidsforskningsinstituttet, Oslo Metropolitan University
AIS	Abbreviated injury score
CCT	Compensatory Cognitive Training
CCT-SE	Compensatory Cognitive Training and Supported Employment
CENTER-TBI	Collaborative European NeuroTrauma Effectiveness Research in Traumatic Brain Injury
CFQ	Cognitive Failure Questionnaire
COPSOQ-II	Copenhagen Psychosocial Questionnaire II – short version
CT	Computed tomography
DAI	Diffuse axonal injury
DKI	Diffuse kurtosis imaging
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
DTI	Diffuse tensor imaging
ED	Emergency department
EIVR	Early intervention vocational intervention
EQ VAS	EuroQol visual analog scale
FSS	Fatigue Severity Scale
GAD-7	Generalized Anxiety Disorder-7
GCS	Glasgow Coma Scale
GFAP	Glial fibrillary acidic protein
ICD-10	International Classification of Disease, Tenth Edition
ISI	Insomnia Severity Index
ISS	Injury Severity Score
LOC	Loss of consciousness
MRI	Magnetic resonance imaging
mTBI	Mild traumatic brain injury
NAV	The Norwegian Labour and Welfare Administration

OUH	Oslo University Hospital
PCS	Post-concussion symptoms
PHQ-9	Patient Health Questionnaire-9
PTA	Post-traumatic amnesia
PTSS-10	Post-traumatic Symptom Scale-10
QOLIBRI-OS	Quality of life after brain injury – overall scale
RCT	Randomized controlled trial
RPQ	Rivermead Post-concussion Symptom Questionnaire
RTW	Return to work
SE	Supported Employment
S100B	S100 calcium binding protein B
TAI	Traumatic axonal injury
TAU	Treatment as usual
TBI	Traumatic brain injury

1 Background

1.1 Introduction

Traumatic brain injury (TBI) is a cause of profound disability, with vast impact on individuals, their families, and society. Approximately 69 million people sustain a TBI each year (1), with an estimated 74–94% of these being classified as mild or moderate TBI (1-4). While the majority of patients with mild-to-moderate TBI recover within days to weeks, a subgroup of patients suffer from prolonged symptoms and require support and rehabilitation to return to everyday activities. This subgroup of patients accounts for 10–80% (5) of patients with a mild TBI (mTBI). This wide range is due to differences in the study methodologies and diagnostic criteria used in various studies. In the Norwegian setting, prolonged symptoms have been found in 27–40% of patients 1 year after mTBI (6, 7); however, there remains an unsatisfactory understanding of who these patients are and the causes of their protracted recovery.

The physical, cognitive, and emotional symptoms commonly experienced after TBI cause difficulties in several areas of patients' lives, including work participation (8). Returning to work after an injury is important for the wellbeing of patients with TBI, favorable in terms of societal costs, and represents a major goal within the field of rehabilitation. On average, ~40% of patients with TBI (all injury severities) return to work (RTW) after 1 year (9, 10). Among those with mTBI, a substantial proportion struggle to RTW for months and years after their injury. The size of the proportion varies in the literature, with 66–95% returning to work 1 year after mTBI (11, 12), while the RTW rate in Norway has been on the lower end of that range (66%) (12).

When searching for the causes of delayed RTW after TBI, the existing literature has mainly been preoccupied with the identification of personal and injury-related factors, while it is reasonable to assume that workplace-related factors also affect this process.

Multidisciplinary treatment is the current recommendation for follow-up among patients with mild-to-moderate TBI, and such comprehensive rehabilitation has been shown to improve symptoms after TBI. However, a reduction in symptom burden does not necessarily translate into more favorable RTW outcomes (13). The optimal treatment method for patients with prolonged symptoms remains unclear, while the need for new, well-designed intervention studies is pressing.

The current thesis describes the characteristics of patients with prolonged symptoms and difficulties in returning to work after mild-to-moderate TBI, examines the prognostic importance of work-related factors when returning to work, and evaluates the effect of a combined cognitive and vocational rehabilitation intervention on RTW outcomes.

1.2 Definition and classification of traumatic brain injury

TBI is most commonly defined as: "… *an alteration in brain function, or other evidence of brain pathology, caused by an external force*" (14). This definition is quite inclusive regarding the symptoms and mechanism of injury while also recognizing the difficulties related to previous definitions by encompassing injuries caused by an indirect force to the head (e.g., whiplash and blast injuries) (14), and simultaneously making a clear separation from non-traumatic brain pathologies.

Historically, TBIs have been classified by injury severity based on the Glasgow Coma Scale (GCS (15)) score. The GCS is a tool for assessing the level of consciousness (16) and consists of three subscales (eye opening, motor response, and verbal response) with a minimum score

of 3 (deep coma or brain-dead state) and a maximum score of 15 (fully awake and oriented) (15). Depending on the GCS score, a patient can be defined as having a mild (GCS 13–15), moderate (GCS 9–12), or severe TBI (GCS ≤ 8) (16).

Although the GCS is the most frequently used tool to classify TBI, it presents clinicians with certain challenges. For example, a considerable number of patients with TBI are under the influence of alcohol or other psychoactive substances when they sustain their injury. The number has been reported to be as high as 25–47 % of patients (17-19), and intoxication may confound the GCS score. Moreover, the routine pre-hospital sedation and intubation of patients with a seemingly serious head injury is commonly recommended, which also hampers the ability to establish a GCS score that represents the effect of the injury in isolation (19, 20).

Over time, other clinical signs have proven their importance as measures of TBI severity and have been included in the clinical evaluation of TBI. One such clinical factor is the duration of loss of consciousness (LOC), with longer periods of LOC being considered a sign of more severe injury (21). Likewise, the association between GCS, LOC, and the presence and duration of post-traumatic amnesia (PTA) was given attention, while the diagnostic and predictive properties of these clinical signs were also highlighted (22). While the term PTA is somewhat poorly defined, it commonly refers to a fluctuating alteration in consciousness after injury and comprises disorientation presenting together with disturbance of attention and memory (23, 24). In recent years, the term PTA has often been used interchangeably with post-traumatic confusional state in the clinical setting since this may better describe the ongoing clinical presentation (24, 25).

Currently, TBI severity classification is routinely performed based on injury severity, which is most commonly assessed using the GCS as well as the presence and duration of PTA and

LOC (see Table 1). Additionally, it often includes the presence or absence of intracranial injury on imaging of the head and focal neurologic deficits.

Table 1. Definition of injury severity in traumatic brain injuries. Adapted from The Little Black Book of Neuropsychology (26).

	Mild	Moderate	Severe
Glasgow Coma Scale score	13–15	9–12	3–8
Loss of consciousness	< 30 minutes	30 minutes–24 hours	> 24 hours
Post-traumatic amnesia	< 24 hours	1–7 days	> 7 days

In this thesis, the classification of mTBI is based on criteria developed by the American Congress of Rehabilitation Medicine (ACRM, (27)). These are frequently used within this field of research and represents the most widely accepted definition of mTBI (16). Their proposed criteria for mTBI involve a traumatically induced physiological disruption of brain function including at least one of the following: (1) LOC lasting less than 30 minutes; (2) PTA shorter than 24 hours; (3) alteration in mental state limited to GCS 13–15 thirty minutes after the injury; (4) focal neurological deficit(s) that may or may not be transient (27).

Further differentiation between patients with and without traumatic intracranial injury on head imaging after mTBI is common. Injuries with normal head computed tomography (CT) are classified as uncomplicated mTBI, while injuries with acute traumatic abnormalities on imaging are classified as complicated mTBI (28, 29). The proportion of intracranial injury on conventional neuroimaging in patients with mTBI is estimated to be 12–51% (3, 28, 30, 31). It is generally recognized that patients with an uncomplicated mTBI have a more preferable prognosis than patients with a complicated mTBI (28, 31). Of the patients admitted to Oslo University Hospital (OUH) with TBI and intracranial injury identified by neuroimaging, 46% had an mTBI (4), while the percentage of patients with mTBI is twice as higher when considering all hospital-admitted patients with TBI (3).

Another method of evaluating injury severity and describing injury type is the Abbreviated Injury Score (AIS, (32)). The AIS was developed in the mid-1960s and is an internationally recognized system for scoring of traumatic injuries in all body regions. Briefly, each injury is defined by body region (head, face, neck, thorax, abdomen, spine, upper extremity, lower extremity, external, or other), with each body region being given a score of 1–6 to indicate the level of trauma—with 1 representing "minor injury" and 6 indicating "unsurvivable injury" (33). The score for AIS Head can be used as an isolated measure of brain injury severity. Moreover, the AIS can be used to evaluate total injury severity across different types of injuries when utilized to calculate the Injury Severity Score (ISS, (34)). The ISS is calculated by taking the sum of the squares of the single highest AIS score in each of the three body regions with the worst injuries (35).

Additionally, pathoanatomical classification of TBI is routinely performed in cases where there is an intracranial injury present on CT or magnetic resonance imaging (MRI). This classification frequently makes distinctions between focal or diffuse brain injuries, and describes the type and number of lesions/hemorrhages while also recording the localization (right or left hemisphere and location in affected lobe(s)) of pathology. Scoring systems have been proposed for this purpose, including the Marshall Score for CT (36) and the Rotterdam CT scoring system (37), which are currently valuable in the early management of more severe TBIs. To date, the use of pathoanatomical classification is restricted by vast variation in the number, severity, and localization of lesions as well as the lack of research into its prognostic value (38). However, there is increasing evidence that more advanced imaging technologies may provide improved insights into mTBI. Research using advanced MRI methods such as diffuse kurtosis imaging (DKI) and diffuse tensor imaging (DTI) have demonstrated damage in the white matter of the brain not seen on conventional CT/MRI (39). These white matter changes are called traumatic axonal injuries (TAIs) or diffuse axonal injuries (DAIs), both of

which refer to axonal injury following TBI (40). TAIs are graded using three stages based on the location of lesions on an MRI (i.e., in lobar white matter (stage 1), in the corpus callosum (stage 2), or in the brainstem (stage 3)) (41), with each increase in stage being associated with an increased likelihood of an unfavorable outcome (42). Currently, TAI is routinely classified only after moderate and severe TBI. However, new studies examining the association between more subtle changes seen on advanced MRI and symptoms after mTBI indicate that there might also be predictive knowledge for outcome trajectories after mTBI if imaging is performed within 72 hours after injury (43).

Other future methods of classification may revolve around blood biomarkers. Although several biomarkers have been proposed and tested in recent years, this field remains relatively new and lacks a full consensus on which is the superior biomarker or how they should be utilized. In a report from the Collaborative European NeuroTrauma Effectiveness Research in Traumatic Brain Injury (CENTER-TBI) that examined six different biomarkers, glial-fibrillary-acidic-protein (GFAP) showed promise and outperformed clinical characteristics in predicting CT abnormalities in acute care (44). On the other hand, a living systematic review and meta-analysis from 2021 did not find sufficient evidence to support the clinical use of GFAP but concluded that S100 calcium binding protein B (S100B) can help clinicians distinguish which patients should undergo a CT scan after an mTBI (45). The S100B is also included in the Scandinavian guidelines for the management of minimal, mild, and moderate TBI in adults (46). However, the long-term prognostic value of biomarkers remains unknown (47).

In summary, although the classification method based on GCS is now widely acknowledged, it is not without flaws. Patients with TBI have vastly heterogeneous outcomes, which hampers aspects of both clinical care and research into this condition. The current unidimensional classification does not sufficiently discriminate between patients with different needs for

rehabilitation or those with different prognoses. This has led to the hypothesis that a multidimensional classifications system for TBI may be more beneficial in the future and can aid in resolving some of the heterogeneity observed today (47).

The challenges posed by different mechanisms of classification can confound the prediction of prognosis and may explain some of the heterogeneity presented in many studies. In the Scandinavian guidelines for management of TBI it is suggested that moderate TBI should be treated in the same fashion as mTBI, although being classified as more severe (46). This study follows this recommendation of treating mild and moderate TBIs similarly.

1.3 Pathophysiology of traumatic brain injury

The detailed pathophysiology of TBI is not fully understood. However, it is recognized that the injury occurs not only due to a direct impact but also due to complex vascular and cellular events that can result in further pathology (48). Briefly, the brain hits the inside of the cranium at the time of injury, causing damage to the brain. The injury may occur at the site of impact and/or the opposite location as the brain moves within the skull (coup-contrecoup injury), or rotational forces may stretch or tear the axons of white matter tracts, leading to a DAI/TAI. The impact causes a temporary disruption of cellular membranes and the release of neurotransmitters. It also causes a disturbance in the ionic equilibrium, with an increase in intracellular calcium and extracellular glutamate and potassium. This subsequently leads to an increase in cerebral glucose metabolism to fuel the sodium-potassium ATPase pumps as they work to regain ionic equilibrium. The increase in cerebral glucose metabolism is followed by a period of decreased metabolism, with the duration depending on the injury severity (48). The stretching or tearing of axons may also lead to disruption of the microtubules and damage to the cytoskeleton, which may degrade neuronal function. Furthermore, a TBI can trigger additional pathophysiological responses such as inflammatory and vascular changes, which—

together with the injury itself—create the neuropathology (49, 50). Cerebral blood flow is reduced in the early phase after a TBI, likely due to increased nitric oxide expression (49). Notably, this contributes to a further mismatch between energy demand and supply at the cellular level (48). Additionally, the inflammatory changes with cytokine upregulation and microglia activation add to the pathophysiology (48, 49). While some possible lines have been drawn between these physiological processes and post-concussion symptoms (48), the exact relationship remains unclear and is most likely multifactorial.

1.4 Epidemiology

TBI is a major cause of fatality and disability worldwide (51). However, the true incidence and prevalence of TBI have been notoriously difficult to determine since numbers vary between countries, regions, and study populations (52-54) and are generally acknowledged to be underestimated due to an unknown proportion of patients—particularly after mTBI—not presenting to the hospital (52). This point should be considered throughout this thesis. Some variation between countries is expected since incidence also depends on local risk factors, health regulations, work safety regulations, and common safety measures (e.g., seatbelt and helmet use, etc.). However, most discrepancies are likely to be caused by variability in data collection, case definition, and case ascertainment (2, 53, 55). The true incidence will likely never be known since it would be too comprehensive to examine. Nevertheless, estimates of TBI incidence and distribution across severity, age, and sex are essential for clinicians, researchers, and policymakers.

In a global systematic review and meta-analysis, Nguyen et al. (56) reported the pooled annual incidence proportion of all ages to be 295 per 100,000, with estimates ranging from 69 per 100,000 in a North American study up to 1750 per 100,000 in a study from New Zealand. The international pooled annual incidence proportion was 110 per 100,000 for pediatric

populations (< 15 years of age) and 166 per 100,000 for the elderly (> 65 years of age). Regarding sex differences, they found a pooled annual incidence proportion of 86 per 100,000 for females and 151 per 100,000 for males. Concerning injury severity, the annual incidence for mild, moderate, or severe TBI was 224, 23, and 13 per 100,000, respectively (56).

A living systematic review of TBI epidemiology in Europe (updated in 2021) reported the age-adjusted incidence for Europe to be 287 per 100,000 (53), with annual incidence rates by country varying from 47 per 100,000 (Spain) to 695 per 100,000 (the Republic of San Marino). Moreover, the reported proportion of injured males was consistently higher than that of females (55–80%) (53).

In the Norwegian context, TBI incidence rates have most commonly been presented as annual rates for hospitalized patients (83–157 per 100,000 (3, 57)) and hospital-referred patients (207–229 per 100,000 (57, 58)), with a male:female ratio of 1.8:1.0 (3, 58). The annual incidence of hospitalized patients with mTBI was 71 per 100,000 (3). Regardless of hospitalizing, the incidence of mTBI in adults has been estimated at 302 per 100,000 person-years (59), which is likely to be an underestimation since not all patients with mTBI were identified. The reported distribution of injury severity for hospitalized patients was 86% mild, 8% moderate, and 6% severe TBI (3).

Traffic accidents were previously the leading cause of TBI. However, falls are now the major cause worldwide, which presumably is due to increased traffic safety and greater human life expectancy resulting in more falls among the elderly (3, 53, 55, 57, 58). Among younger patients, violence seems to be increasing as a cause of TBI (60). This is unfortunate since TBIs resulting from violence are associated with a poorer prognosis.

In summary, mild and moderate TBI affects a substantial number of people and are one of the a major public health concern, also in Norway. The fact that a subgroup of these patients

report long-lasting symptoms interfering with their daily life activities, calls for better follow-up and treatement programmes. Thus, this will be the main focus of present thesis.

1.5 Post-concussion symptoms

Common symptoms following mTBI include physical (headache, dizziness/vertigo, vision or sleep disturbance, fatigue, hyperacusis, photosensitivity), cognitive (problems with mental efficiency, memory, attention, executive functioning), and emotional (depression, anxiety, restlessness, frustration, anger) symptoms (61). The majority of patients recover quickly (days to weeks) after an mTBI, with an estimated 20–40% of patients experiencing persisting post-concussion symptoms (PCS) lasting beyond 12 weeks (5, 7, 13, 28, 62). The variation in proportion with PCS is due to differences in definition, timing of controls, and other methodological discrepancies.

Patients with persisting symptoms after an mTBI are occasionally diagnosed with post-concussion syndrome. Although this syndrome has been defined in multiple ways (63), the most commonly used definition include having ≥3 PCS at least 3 months after sustaining an mTBI (64, 65). This resembles the definition proposed by the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV (64)), which requires an objectively measured cognitive impairment in addition to the duration of symptoms exceeding 3 months. Conversely, the definition of the International Classification of Disease, Tenth Edition (ICD-10 (66)) does not require an objectively measured cognitive impairment or any specific duration of symptoms and is thus regarded as more inclusive. The difference between these two classification systems has contributed to the confounding of diagnoses and research on post-concussion syndrome. In the new version of DSM, DSM-5 (67), there is no longer a definition of post-concussion syndrome. Instead, it contains a general description of neurocognitive disorder following TBI, which further complicates the use of the term post-

concussion syndrome. Additionally, the syndrome has been the subject of further debate since it is characterized by symptoms that are frequent in both non-brain injured trauma patients (5, 68) and the general population (69). When using the diagnostic criteria from the ICD-10, 31% of a healthy control sample met the criteria for post-concussion syndrome (70), which highlights a core problem in this field.

Notably, the patients included in this thesis were not diagnosed with post-concussion syndrome; however, they did suffer from PCS 8–12 weeks after TBI.

While PCS is most commonly referred to after mTBI, the symptoms as such occur after TBIs of all severities (71). In the Norwegian context, PCS 12 months post-injury have been reported to occur in 27% of patients after mTBI, 27% after moderate TBI, and 18% after severe TBI (7).

The development and maintenance of PCS are best understood when viewed in the context of the biopsychosocial model (72). The biopsychosocial model was proposed by Engel in 1977 in opposition to a strict biomedical model of disease (73), that focused solely on the biological aspects of illness. He argued that both somatic and mental illnesses (as was the dualistic view of that time) would be best understood if one considered not only the biomedical features but also the psychological and social aspects of the individual and illness. This model has propelled the field of TBI forward by inspiring both clinical approaches (e.g., multidisciplinary rehabilitation) and expanding the research to include psychosocial dimensions proven to be important in the follow-up and in long term prognosis after TBI (70, 74). Figure 1 illustrates some of the possible biopsychosocial elements that may influence the reporting of symptoms after TBI (75). The importance of the biopsychosocial model becomes increasingly clear when reviewing the predictors for PCS development after TBI (70).

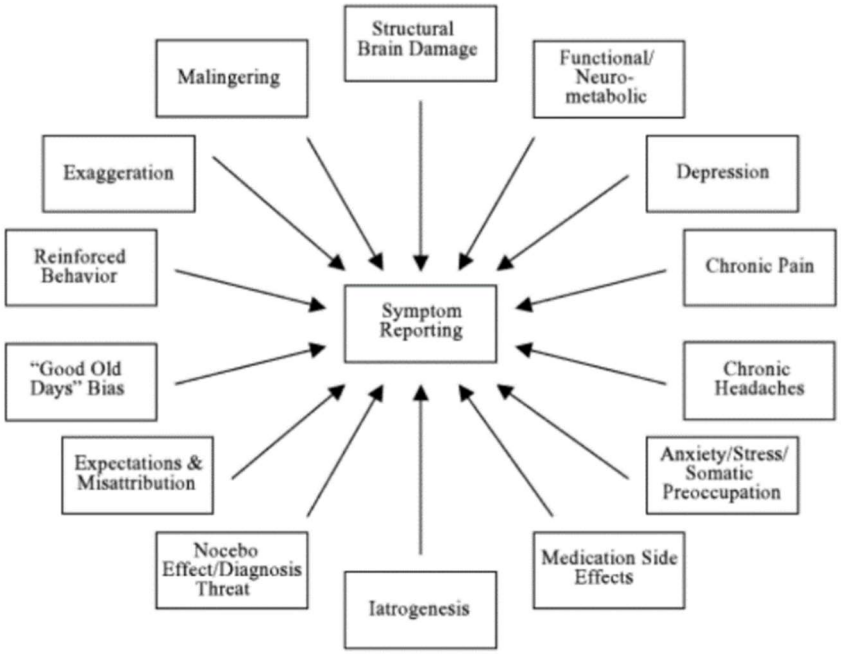

Figure 1. Possible biopsychosocial factors influencing PCS reporting. Reprinted with permission from Taylor & Francis Copy Clearance Center (75).

1.6 Prognostic factors for post-concussion symptom development

Intuitively, it seems reasonable to assume that patients with a more severe TBI will have a higher risk of developing PCS. However, upon reviewing the literature, it becomes clear that this association is not as obvious with regard to patients following mild and moderate TBI. Since injury-related factors do not satisfactorily predict clinical outcomes, a model consisting of several prognostic factors is assumed to be superior to any single prognostic factor (76). The literature on predictors for PCS is conflicting, which is partly due to the aforementioned discrepancies in the definition of PCS (62, 68, 77). The most examined predictive factors can be divided into pre-injury, injury-related, and post-injury-related factors.

Previously investigated pre-injury factors typically include characteristics such as age, gender, socioeconomic status, level of education, marital status, access to social support, involvement in legal proceedings, personality traits, and premorbid diseases, including previous history of

mental illness, substance abuse, TBI, and/or migraine. While the literature remains conflicting, gender, level of education, history of depression, anxiety, and other mental illnesses are often identified as the most robust pre-injury factors important to the development of PCS (5, 62, 71, 78-80). Therefore, this suggests that female gender, having a history of mental illness, and possessing a lower level of education increases the risk of PCS after TBI (5, 62, 65, 71, 78-80).

Commonly examined injury-related factors include mechanism of injury, injury severity (incl. GCS, LOC, and PTA), intracranial injury on neuroimaging, presence of extracranial injuries, acute symptom burden, and hospital admission. Studies have demonstrated that injury-related variables such as acute GCS, LOC, and PTA have some—yet limited—predictive value (81, 82). Additionally, there is evidence that the mechanism of injury (assault, in particular), extracranial injuries/multitrauma, and hospital admission predicts PCS (62, 70, 71). Regarding the presence of intracranial injury on neuroimaging (complicated mTBI), the results remain mixed, with some studies reporting no difference in clinical outcome between complicated and uncomplicated mTBI (70, 82, 83), while larger epidemiological studies report an increased occurrence of PCS and adverse outcomes in patients with complicated mTBI (28, 31, 71).

Post-injury factors that have demonstrated an association with PCS include a higher symptom burden (79) and impaired neuropsychological functioning early post-injury (77). Furthermore, emotional distress (symptoms of depression, anxiety, or post-traumatic stress) and maladaptive coping strategies shortly after injury have been reported as negative predictors of recovery 6 months after TBI (77, 84).

1.7 Return to work after traumatic brain injury

Helping patients return to stable employment is an important goal in the field of rehabilitation medicine. This outcome has positive consequences for patients' quality of life, self-esteem, and feeling of being a productive member of society (85). Additionally, increasing the proportion of patients returning to work after injury, and reducing the time until RTW, is important to minimize the societal cost of TBI and long-term disability.

As a result of divergent methodologies and definitions of both TBI and RTW, the percentage of patients returning to work after TBI varies between studies (86). For all TBI severities, numbers vary from 8 to 72% of patients returning to work, with a pooled estimate of ~40% (10, 87). For patients with moderate and severe TBI, the pooled estimate of the proportion returning to their pre-injury level of work is 33% (10). Among patients with mTBI, the RTW rate is higher, with an estimated 66–95% returning to work after 1 year (11, 12), which is comparable to the RTW rate in Norway at 66–85% after mTBI (12, 88, 89) and 53% returning to full-time work 1 year after moderate TBI (89).

After returning to competitive employment, even patients with mTBI can struggle to maintain stable employment and productivity. Kreutzer et al. reported that 27% of patients experienced difficulties with work stability 4 years after injury in a sample including all TBI severities (90), while another study demonstrated reduced work productivity 8 months after mTBI in 60% of patients who returned to work (91).

1.8 Prognostic factors for return to work

Returning to work is often associated with a lower symptom burden after TBI (92). Thus, the predictors for developing PCS and not returning to work overlap to some extent. However, the correlation between PCS and RTW is not as strong as one might expect. Traditionally, the most frequently studied predictors for RTW after TBI have been the same as those used to

predict PCS development and can likewise be divided into pre-injury, injury and post-injury-related (see Figure 2). Since these factors were previously accounted for (Section 1.6), this section will briefly report the traditional predictors for RTW and introduce some factors that have not been commonly examined.

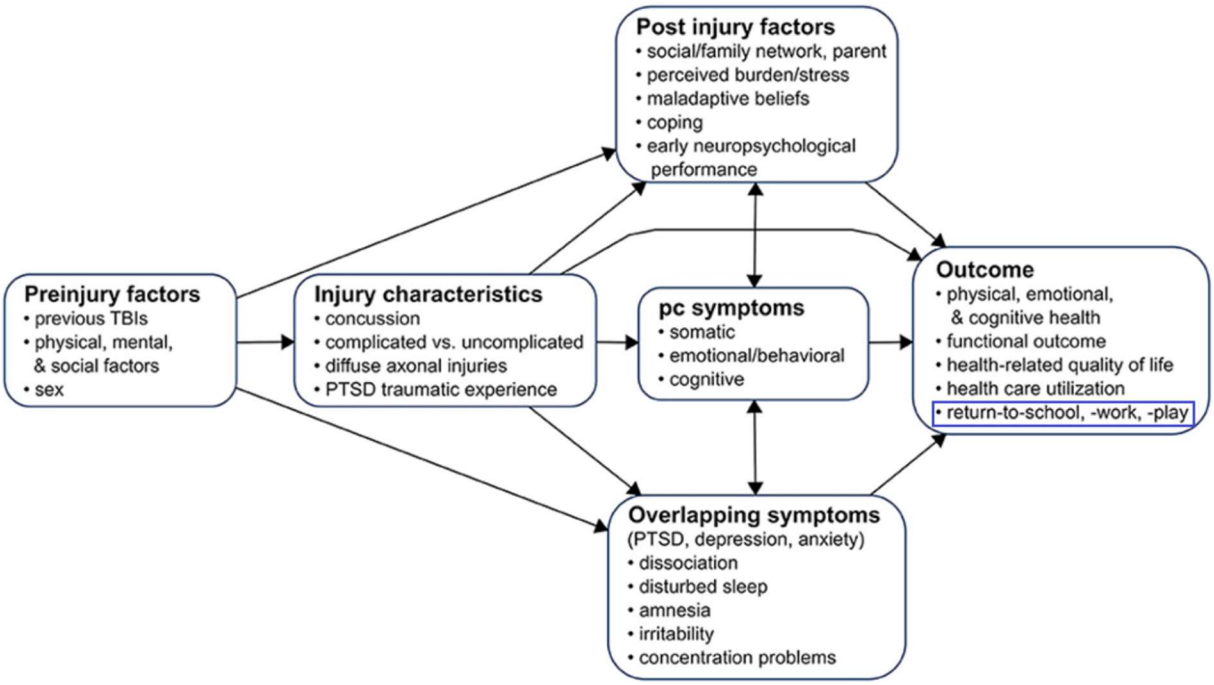

Figure 2. Biopsychosocial factors affecting outcomes after traumatic brain injury. Reprinted with permission from Frontiers in Neurology. **Copyright** © 2018 Polinder, Cnossen, Real, Covic, Gorbunova, Voormolen, Master, Haagsma, Diaz-Arrastia, and von Steinbuechel (5).

The pre-injury factors most often reported to be negatively associated with RTW after TBI include older age, being unmarried, having a lower educational level, substance abuse, and a history of depression, anxiety and other mental illnesses (13, 87, 93-99). Some studies found that being female was associated with poorer RTW; however, the overall picture seems to dispute this (78).

Of the injury-related predictors associated with a worse RTW outcome, the most commonly mentioned are injury severity (including GCS, PTA, and LOC), length of stay in hospital, and

extracranial injury/multitrauma (13, 87, 93, 99, 100). Additionally, a higher level of disability at discharge and violence as cause of injury negatively predict RTW after TBI (97).

Regarding post-injury factors, self-reported symptoms, cognitive difficulties, residual physical deficits, pain, and symptoms of depression, anxiety, and other mental illnesses negatively influence the likelihood of returning to work (13, 85, 87, 93, 100, 101).

However, when viewing factors related to RTW after TBI, it has been suggested that further insights might be gained by exploring predictors that are not only related to the patient and their injury. Returning to work is a complex process influenced by a multitude of factors and varying challenges depending on one's work tasks and workplaces, in addition to the individuals' symptoms. To improve occupational outcomes after TBI, it is necessary to acknowledge these aspects of the process. Therefore, further research regarding the predictive value of work-related factors has been called for (95, 102-104). This is partly due to these factors potentially being more easily amendable than personal or injury-related factors after a TBI has occurred.

Some work-related factors have already been examined to a certain extent, including the predictive value of being employed at the time of injury and the difference between having a white-collar (non-manual) or blue-collar (manual) job. The relative consensus is that being employed at the time of injury and having a white-collar job increased the likelihood of a good RTW outcome after TBI (95, 96, 99, 105). A systematic review from our research group regarding workplace characteristics associated with retaining employees after acquired brain injury (103) also reported a negative association between manual labor and work retention. Additionally, a positive relationship between working at a large enterprise (≥250 employees) and work retention was found. One of the included studies reported a U-shaped association between workload and work retention 6 months after injury (103).

Notably, the psychosocial aspects of one's workplace may be more easily adjusted after an injury than personal and injury-related factors. Psychosocial factors have been examined previously, but mainly in the general population and not specific to TBI. Independence and greater decision-making latitude has however been found to have a positive predictive value for RTW after TBI (106), while other psychosocial factors such as reward and recognition (107), work predictability (108), quality of leadership, and quantitative demands (109) have exhibited a predictive value for work participation in the general population, but have not yet been examined within the field of TBI.

1.9 Rehabilitation recommendations during study planning

When planning the current study, the recommended rehabilitation for patients with prolonged symptoms after TBI was multidisciplinary assessment and follow-up (110), with instructions for addressing various common PCS. This remains the recommendation to date. Comprehensive multidisciplinary follow-up appears sensible when viewing PCS after TBI from a biopsychosocial perspective. However, it has not always proved to be superior when compared to less time-consuming or costly follow-up programs (93). Moreover, the positive effect of the multidisciplinary follow-up on RTW rates has not been sufficiently demonstrated since a reduction of symptoms does not necessarily lead to RTW (91). In a randomized controlled trial (RCT) by Vikane et al. (12), patients were allocated to follow-up by a specialized multidisciplinary team or a general practitioner. After 1 year, the group receiving multidisciplinary follow-up reported fewer symptoms; however, there were no differences in RTW rates between the two groups (12). Considering the difficulties caused by cognitive symptoms when returning to work and the lack of improvement of RTW outcomes by the multidisciplinary follow-up, further research into possible interventions was called for.

1.10 Rehabilitation of cognitive symptoms for return to work

Cognitive symptoms are common after all severities of TBI and frequently include difficulties with processing speed, attention, memory, and executive functions. These symptoms have proven to be a hindrance when resuming competitive work after a TBI, in addition to the negative effect it has on patients (85). For this reason, cognitive rehabilitation has been proposed to improve cognitive complaints and functional level after TBI (111). Cicerone et al. (112 p1596) defined cognitive rehabilitation as "… a systematic, functionally oriented service of therapeutic activities that are based on assessment and understanding of the patient's brain-behavioral deficits". Additionally, they outlined four main approaches to cognitive interventions: 1) building on previously learned behaviour; 2) compensatory cognitive mechanisms; 3) external compensatory mechanisms or adapting the external environment; 4) aiding persons to adapt to their cognitive disability to improve the level of functioning and quality of life (112). Several systematic reviews have focused on the effect of cognitive rehabilitation after TBI to improve RTW. Some found cognitive rehabilitation to be efficient in facilitating RTW after TBI (85, 113) and Bayley et al. highlighted the potential of compensatory strategies (113), while a Cochrane review did not find improvement in RTW rates after cognitive rehabilitation among patients with TBI (8). Furthermore, a meta-analysis of RCTs examined the effect of occupation-based cognitive rehabilitation, which was defined as "…cognitive rehabilitation services that help clients participating in spontaneously meaningful activities" (114). This meta-analysis concluded that this type of rehabilitation had a small, but significant, positive effect on mental function and activities of daily living for patients after TBI (114).

1.11 Vocational rehabilitation

Since interventions aimed at improving clinical outcomes after TBI did not have the desired effect on RTW, more effort was placed on specific vocational interventions. Vocational rehabilitation can be defined as a rehabilitation approach that aims to improve vocational outcomes (i.e., RTW, stable employment, and work productivity) (115). There are mainly three broad categories of vocational rehabilitation described in the TBI literature. The first is a case-controlled method in which the vocational rehabilitation is integrated into a holistic rehabilitation plan and monitored by a case coordinator. The second is a program-based vocational rehabilitation method, which is a module-based program commonly including individualized work skill training, guided work trials, and assisted placement with transitional job support. The third category of vocational rehabilitation is Supported Employment (SE) with job placement, on-the-job training, and reinforcing work skills through on-the-job coaching as its cornerstones (115). A review of vocational rehabilitation after TBI from Fadyl et al. concluded that there was little evidence to distinguish the best method of vocational rehabilitation (115), while a more recent review found evidence supporting vocational rehabilitation after TBI while underlining the need for controlled studies and studies of cost-effectiveness (86). In 2016, Graham et al. published a systematic review of employment interventions for RTW after TBI (116). They aimed to review all RCTs that evaluated interventions to improve RTW in the working-age population after TBI. However, their extensive search resulted in only three studies being included. Notably, none of the included studies involved interventions that improved RTW when compared to their control groups, which further underlined the need for well-designed vocational intervention studies (116).
A recent scoping review with a wider perceptive (examining vocational rehabilitation after all types of acquired brain injury (104)) agreed with Fadyl et al.'s (115) assertion that there is still insufficient evidence to identify one "best practice" for vocational rehabilitation.

However, they highlighted some key features that may positively influence the outcome. First, a complex interaction of factors including the patient, stakeholders, work tasks, and the environment was noted, which emphasized the need to look beyond the patient and their individual symptoms after injury when delivering vocational rehabilitation. Second, the rehabilitation should focus on the patient's strengths, work, and environmental influences while working in tandem with an inter-disciplinary team. Third, the role of stakeholder engagement (including employers) was highlighted for successful RTW planning. Moreover, the early delivery of specialized vocational rehabilitation also increased the likelihood of returning to full-time work 1–2 years after injury (104).

2 Overview of thesis rationale

As delineated in the introduction, a substantial proportion of working-age individuals will sustain an mTBI during their lifetime, and some of them will struggle with the consequences for months or years. This places strains on patients and society that are not sufficiently managed to date. Additionally, there is no convincing evidence that comprehensive multidisciplinary treatment is efficient enough in helping patients return to competitive employment.

When planning the current study, there was a lack of evidence supporting vocational rehabilitation after mild-to-moderate TBI (116, 117). Furthermore, there have traditionally been weak collaborations between Norwegian rehabilitation services in the health sector, the Labour and Welfare Administration (NAV), and the workplaces. In the Norwegian context, a novel variation of vocational rehabilitation gained empirical support for patients with mental illness, with positive clinical and RTW outcomes (118). This approach involved SE and the "place-and-train" principles.

In line with this and with a focus on cognitive rehabilitation, Twamley et al. conducted a pilot RCT evaluating the effect of a compensatory cognitive training intervention in combination with SE for veterans with mild and moderate TBI (119). The participants were unemployed but wished to RTW. On average, ~ 4 years had passed since their most recent TBI. The 1-year follow-up revealed improvements in PCS and quality of life; however, no differences in the number of weeks worked during the study period (120). Thus, there was a need to replicate this study on a larger scale with a civilian sample in an early post-injury phase in a real-life competitive work setting and a different welfare system.

Essentially, there is a need for additional knowledge to identify characteristics of the patients that suffer persisting symptoms after mild-to-moderate TBI and struggle to return to work,

determine which work-related factors impact delayed RTW, and develop new well-designed intervention studies that combine the rehabilitation and vocational science perspectives in a multidisciplinary, cross-sectoral collaboration between health care services and the welfare system.

3 Aims

Paper I: Aims to describe the pre-injury, injury and post-injury characteristics of a subgroup of patients with mild-to-moderate TBI who remain symptomatic 8–12 weeks after injury, and to compare patients with and without traumatic intracranial injuries.

Paper II: Aims to evaluate whether a combined compensatory cognitive training and vocational rehabilitation is effective in improving return to work and work stability in patients with a protracted recovery after mild-to-moderate TBI.

Paper III: Aims to determine which factors predict work participation after 1 year in patients with mild-to-moderate TBI and persistent symptoms, with an emphasis on work-related factors.

4 Materials and methods

4.1 Trial design

This doctoral project was designed as an open-labeled two-armed RCT. The design per paper is as follows:

Paper I – A cross sectional cohort study describing the characteristics of patients at the time of baseline assessment (before the RCT), while also providing a comparison of patients with and without acute traumatic pathology on neuroimaging.

Paper II – A randomized controlled trial with two parallel intervention arms and a 1:1 allocation ratio, with follow-up 3, 6, and 12 months after inclusion.

Paper III – A longitudinal study examining work-related predictors for RTW 12 months after inclusion.

This doctoral thesis was part of a cross-sectoral research project that was a collaboration between Oslo University Hospital (OUH), Sunnaas Rehabilitation Hospital, the Work Research Institute (AFI) at Oslo Metropolitan University, and the Norwegian Labour and Welfare Administration (NAV). The overarching project aimed to examine the effectiveness of a combined cognitive and vocational intervention to improve RTW after mild-to-moderate TBI, with a qualitative process evaluation and a cost-effectiveness evaluation of the intervention. The project also included an earlier doctoral thesis (by Emilie Isager Howe) describing the RCT protocol (121), the feasibility of the CCT program (122), and interim trial results (123), while the current thesis describes the main RCT results including RTW trajectories over the first 12 months, along with sample characteristics and work-place related predictors of RTW.

4.2 Recruitment and setting

All patients were recruited from a specialized TBI-rehabilitation outpatient clinic at the Department of Physical Medicine and Rehabilitation, OUH, Oslo, Norway, between July 2017 and April 2019. Patients were referred to this clinic either after consultation with the Department of Neurosurgery, the Emergency Department, or their general practitioner. Eligible patients were identified by physiatrists at the outpatient clinic. The physiatrist informed the patients about the study (orally and in writing) and the included patients provided written informed consent either at this consultation or after a short period of deliberation. All patients included in this thesis were selected based on the criteria set to include patients in the RCT, which were as follows:

- The patients had sustained a mild or moderate TBI 8–12 weeks prior
- They were 18–60 years of age
- They worked ≥ 50% at the time of injury
- They were sick-listed ≥ 50% at inclusion due to post-concussion symptoms evaluated by the Rivermead Post-concussion Symptom Questionnaire (RPQ, (124))
- They resided in Oslo or Akershus County

The criteria proposed by the ACRM were used to diagnose mTBI (27), while the severity of mild-to-moderate TBI was limited to GCS 10–15, LOC < 24 hours, and PTA < 7 days. The most severe of the moderate TBIs (GCS 9) were excluded to obtain a more homogenous sample. Exclusion criteria were the inability to speak or read Norwegian, ongoing substance abuse, or a history of severe neurological or psychiatric illness.

4.3 Data collection

Data collection occurred at inclusion (8–12 weeks after injury) and 3, 6, and 12 months after inclusion. All follow-ups were at the same outpatient clinic at OUH, or via telephone at the patients' request. A medical doctor (the Ph.D. candidate) or a clinical psychologist (co-author EIH) performed baseline assessments. Follow-up assessments were performed by a physiatrist (3-month follow-up) and a psychologist (6- and 12-month follow-up).

4.4 Interventions

4.4.1 Combined cognitive and vocational intervention

The new intervention combined cognitive and vocational rehabilitation. The cognitive rehabilitation entailed Compensatory Cognitive Training (CCT), which was developed in the USA by Dr. Elisabeth Twamley (119, 120). The CCT manual was translated and amended to the Norwegian context after a feasibility study performed before the RCT (122). The translation and changes in the intervention were performed by researchers at the Dept. of Physical Medicine and Rehabilitation, OUH, and Sunnaas Rehabilitation Hospital, with permission from—and in collaboration with—Dr. Twamley. Representatives of The National Association for the Traumatically Injured (Personskadeforbundet LTN) provided user input for the manual. The training was group-based and included 5–7 participants per group. Each group attended one 2-hour session per week for 10 consecutive weeks. A clinical psychologist (co-author EIH) and a medical doctor (the Ph.D. candidate) delivered the cognitive intervention to the patients at the specialized TBI-rehabilitation outpatient clinic at OUH. Each CCT session covered a different topic and aimed to teach strategies for managing common symptoms after a mild-to-moderate TBI, with an emphasis on cognitive challenges, and psychoeducation (see Table 2 for the topics covered in each session). Additionally, the

Table 2. Overview of topics in the Compensatory Cognitive Training

Session	Topic	Examples of strategies
1	Course introduction and TBI information	Create a daily routine
2	Managing fatigue, sleep problems, headache, and tension	Mindfulness and sleep hygiene
3	Organization and prospective memory	Prioritizing and creating healthy habits
4	Organization and prospective memory (continued)	Calendar use and visualization
5	Attention and concentration	Self-talk and managing the environment
6	Learning and memory	Acronyms and creativity
7	Learning and memory (continued)	Overlearning and recall strategies
8	Planning and goal setting	Dividing large goals, keeping a planned schedule
9	Problem solving and cognitive flexibility	Six-step problem-solving method
10	Skill integration, review, and next steps	Applying strategies in everyday life

patients were provided with a pamphlet with information about TBI and audio files with relaxation exercises.

The vocational portion of the intervention was based on SE and the principles of "place-and-train". The SE Five-Stage process entails client engagement, vocational profiling, job finding, employer engagement, and on-/off-job support (125). In this study, all patients were employed at the time of injury and the focus was thus on stages 1 (client engagement), 4 (employer engagement), and 5 (on-/off-job support). The first session focused on gaining an overview of the patient's strengths and limitations, work tasks, and agreeing on a common goal between the job specialist and the patients. Follow-ups were customized based on the patients' needs, and could include consultations, guidance and advice, learning/training, work adaptation tasks, and assistive technology. The sessions included the employer, colleagues, or their local NAV contact. Each patient was followed up individually by a job specialist from the time of

inclusion until a maximum of 6 months after inclusion. The three employment specialists were occupational therapists or special educators working at NAV and had previous experience in working with patients with cognitive challenges after acquired brain injury. All employment specialists participated in formalized post-graduate SE education provided at Oslo Metropolitan University (126) prior to the intervention. Moreover, they received ongoing guidance from a SE educator, G. Wangen. The employment specialists aided the patients in returning to their competitive pre-injury employment through individual guidance sessions, guidance at their respective workplaces, and preferably in collaboration with the patients' employers. The patients also received the Norwegian statutory sick leave follow-up.

To ensure seamless cooperation between the job specialist and the health professionals delivering the CCT, a collaborative meeting was held every 3 weeks to calibrate their efforts and evaluations of each patient's progress. Senior researchers also participated in these meetings. Additionally, the job specialists each attended one cycle of 10 weeks with CCT to familiarize themselves with the cognitive portion of the intervention.
The job specialists had an average of three in-person meetings with each patient, and approximately one of the three was at the patient's workplace. On average, they had 10 telephone or e-mail consultations with each patient.

4.4.2 Treatment fidelity in the Compensatory Cognitive Training

During the intervention period, the Ph.D. candidates responsible for delivering the CCT were evaluated on their adherence to the manualized intervention. Fidelity rating was performed based on a publication by Winter et al. (127). Treatment fidelity was judged on six elements: a) explained the goal of the session clearly; b) utilized appropriate language and pace; c) exhibited sensitivity to the patients' responses; d) clearly responded to the patients' questions; e) demonstrated overall fidelity to the CCT manual; f) clearly explained the next step of the

intervention. The treatment fidelity rating was performed by two senior researchers (co-authors NA and ML) who attended 5% of the sessions. The two senior researchers scored the six elements as either poor, good, or excellent in each session they observed. Elements b, c, and f were rated as excellent, while items a, d, and e were rated as good.

4.4.3 Treatment as usual

The control group received treatment as usual (TAU) by a specialized TBI team at the TBI-rehabilitation outpatient clinic, OUH. This entailed an initial consultation with a physiatrist, who then referred patients to follow-up by other members of the team based on the patient's primary challenges. The TBI team consists of physiatrists/residents in physical medicine and rehabilitation, an occupational therapist, a physical therapist, a psychologist/neuropsychologist, and a social worker. Rehabilitation was thus tailored to each patients' needs and the duration of follow-up varied but was limited to 6 months after inclusion in the program. Some patients in the control group also attended four group sessions held by the health professionals in the TBI team, who provided information about TBI, cognitive and emotional problems after injury, common challenges in activities of daily life, participation in work and coping strategies as well as education in adjusted physical training. The patients also received the Norwegian statutory sick leave follow-up.

Patients in the control group were followed up for a median of 155 days, and 39 of the patients attended the group sessions described in the previous paragraph. All patients were consulted by a physiatrist at least once during the follow-up period, while 91% were consulted by an occupational therapist, 56% by a physical therapist, 38% by a clinical psychologist/neuropsychologist, and 36% by a social worker.

4.5 Measurements

4.5.1 Sociodemographic, injury-related, and work-related variables

Table 3 presents the sociodemographic, injury-related, and work-related characteristics presented in papers I–III. This information was collected from medical records and supplemented through baseline interviews with the patients.

4.5.2 Measures and instruments

Paper I

In addition to including the variables noted in Table 3, this paper presents the patients' previous history of disease and symptom burden after injury, as measured by questionnaires (Table 4) and a neuropsychological assessment (Table 5) at baseline.

History of previous diseases was self-reported through a structured interview at baseline in which the patients were asked whether they had previously suffered from a concussion/TBI, anxiety, depression, migraine/headache, cardiovascular disease, musculoskeletal disorder, gastrointestinal disorder, ADHD, dyslexia, or any other condition.

To ease comparisons with other studies, this paper reports several of the measurements recommended as common data elements for TBI, including RPQ, PHQ-9, QOLIBRI-OS, and the subtests of D-KEFS and WAIS-IV (128).

Table 3. Sociodemographic, injury-related, and work-related variables included in papers I–III

Variable	Paper I	Paper II	Paper III
Sociodemographic variables			
Age	✓	✓	✓
Sex	✓	✓	✓
Education	✓	✓	✓
Marital status	✓	✓	✓
Child(-ren) in household	✓	–	–
Injury-related variables			
Time since injury	–	✓	–
Cause of injury	✓	✓	✓
CT/MRI findings	✓	✓	✓
AIS Head	✓	–	–
Extracranial injury	✓	–	✓
Admitted to hospital	✓	–	–
GCS	✓	–	–
LOC	✓	✓	✓
PTA	✓	✓	✓
Injury severity	✓	✓	✓
Injured at workplace	✓	–	–
Under the influence of alcohol at time of injury	✓	–	–
Occupational variables			
Occupation type	✓	✓	✓
Permanent position	✓	✓	✓
Full-time position	✓	✓	✓
Private sector	–	✓	✓
Duration of employment	✓	✓	✓
Size of enterprise	–	–	✓
Sick-listed	✓	✓	–

AIS Head – Abbreviated Injury Scale Head, GCS – Glasgow Coma Scale, LOC – Loss of consciousness, PTA – Post-traumatic amnesia

Table 4. Questionnaires used in Paper I.

Questionnaire	Measuring variable	Cut-off score
Rivermead Post-concussion Symptoms Questionnaire (RPQ, (124))	Post-concussion symptoms	Mean reported
Patient Health Questionnaire (PHQ-9, (129))	Depression	≥10
Generalized Anxiety Disorder (GAD-7, (130))	Anxiety	≥10
Post-traumatic Symptom Scale-10 (PTSS-10, (131))	Post-traumatic stress	≥35
Fatigue Severity Scale (FFS, (132))	Fatigue	≥4
Insomnia Severity Index (ISI, (133))	Insomnia	>8
Quality of Life after Brain Injury Overall Scale (QOLIBRI-OS, (134))	Health-related quality of life	<52
EuroQol visual analog scale (EQ VAS, (135))	Health-related quality of life	<84
Cognitive Failures Questionnaire (CFQ, (136))	Cognitive function	Mean reported

Table 5. Neuropsychological tests used in Paper I.

Neuropsychological tests	
IQ	Prospective memory
Matrix reasoning (WAIS-IV, (137))	Memory for Intentions Screening Test (MIST, (138))
Block design (WAIS-IV, (137))	Processing speed and executive function
Vocabulary (WAIS-IV, (137))	Color Word Interference Test (D-KEFS, (139))
Similarities (WAIS-IV, (137))	Trail Making Test (D-KEFS, (139))
Verbal learning and memory	Coding (WAIS-IV, (137))
Total learning (CVLT-II, (140))	Ruff 2 and 7 Selective Attention Test (141)
Short-delay free recall (CVLT-II, (140))	
Long-delay free recall (CVLT-II, (140))	

Paper II

The primary outcome for this paper and the RCT was self-reported work participation at 12 months. Work participation was measured as the proportion of patients that had returned to any degree of competitive work at the 12-month follow-up.

Secondary outcomes were working hours per week (0–37.5 hours), work percentage (0–100%), work stability, and days from injury until return to pre-injury levels of work. Working hours per week were calculated from self-reported work percentage [(work percentage*37.5)/100]. Work stability was operationalized by dividing work percentage into four groups (0%, 1–49%, 50–79% and 80–100%), with patients remaining in the same group or moving to a higher group from one follow-up to the next being categorized as "stably employed", while patients moving to a lower group were categorized as "unstably employed". The necessary information was collected through structured interviews with the patients at baseline and the 3, 6, and 12-month follow-up assessments.

Paper III

The main outcome variable in this paper was self-reported work percentage (0–100%) 12 months after inclusion. The following variables from Table 3 were used as predictor variables in the analysis: age (years); sex (male/female); marital status (cohabitating/living alone); education (years); injury severity (mild/moderate); extracranial injury (yes/no); size of enterprise (number of employees); duration of employment (months); employment sector (public/private). The total RPQ score was used to represent symptom burden. Additionally, four scales from the Copenhagen Psychosocial Questionnaire – short version (COPSOQ-II, (142)) were included to reflect important aspects of the psychosocial work environment. The COPSOQ-II is based on seven major theories within occupational health psychology: 1) the job characteristics model; 2) the Michigan organizational stress model;

3) the demand-control-(support) model; 4) the sociotechnical approach; 5) the action-theoretical approach; 6) the effort-reward-imbalance model; 7) the vitamin model (143). The questionnaire is divided into 13 scales, with each scale consisting of 1–2 questions. Each question is scored from 0 ("To a very small extent" or "Never") to 4 ("To a very large extent" or "Always"), producing a total scale score of 0–8. The scales examined in Paper III were predictability, rewards (recognition), quantitative demands, and influence at work (decision authority). The patients completed the COPSOQ-II during their baseline assessment.

4.6 Sample size

Based on previous studies on occupational health care and RTW, an odds ratio of 2.0—or a 33% absolute difference—in RTW status between the CCT-SE and TAU groups was considered the minimum value of societal and clinical importance (120, 144). The total sample size was calculated by G*Power = 110, with 55 patients in each intervention arm, $\alpha = 0.05$, and a power level of 0.80. We estimated a loss to follow-up of 15% (145), thus requiring the inclusion of 125 patients. Due to a low dropout rate and the time restrictions of the study, participant inclusion ended in April 2019 with 116 participants included.

4.7 Randomization and blinding

Patients were randomized to the intervention group (CCT-SE) or the control group (TAU) in a 1:1 allocation ratio after baseline assessments in the RCT. Before the start of inclusion, an independent statistician made a computer-generated permuted block sequence with randomized block sizes (2, 4, 6, or 8). Then, a senior researcher—who was not involved in patient recruitment, intervention delivery, or patient assessment at any point—was in charge of group allocation. Outcome assessors were blinded to the group allocation. Blinding the patients or rehabilitation specialists delivering the treatments was not possible. Additionally,

the patients were given dummy identification numbers and allocation group in the database by an independent statistician, and group allocation was not revealed to the rehabilitation specialists (incl. the Ph.D. candidate) until the 12 months analyses had been performed.

4.8 Statistical methods

All statistical analyses were performed using IBM SPSS Statistics for Windows v. 25 or Stata v. 16. Descriptive analyses were used for baseline data and presented as a proportion (%) and frequency (n), using the mean (SD) or median (IQR/range), depending on the distribution. Sensitivity analyses were performed for all papers using the models run with 1,000 bootstrap samples. Statistical significance was set to < 0.05.

Paper I presented a descriptive analysis of the sample at baseline and compared symptoms in patients with and without traumatic intracranial injury on CT/MRI. When comparing patients with and without traumatic intracranial injuries, those that had not performed cerebral neuroimaging (n = 9) were excluded. Normally distributed data were analyzed using two-sample T-tests, while skewed data were analyzed using a Mann-Whitney U or Chi-squared test depending on whether the variable was continuous or categorical. Multiple linear regression analyses were then performed with the independent variables set as those significantly different between patients with and without intracranial injury. The presence or absence of injury on neuroimaging was set as a dependent variable, together with the two variables that were significantly different between the groups (i.e., previous mTBI and level of education).

In *Paper II,* mixed-effect logistic regression was used to evaluate proportions that had returned to work in the CCT-SE and TAU groups, while linear mixed-effect models were applied to analyze the working hours per week and work percentages between and within groups. The models allowed for a random intercept and random effect of time, while retaining

time and time-by-treatment as fixed effects. To adjust for potential baseline differences, the main effect of treatment was removed from the models. Kaplan-Meier curves and log-rank tests were used to analyze differences between the groups in days until returning to pre-injury work levels. The presence of intracranial abnormality and whether the patient was working at baseline were considered potential confounding factors and were adjusted for. An independent statistician who was blinded for the group allocation performed analyses on an intention-to-treat basis.

In *Paper III*, multiple linear regression was used to create the predictor models with a continuous independent variable (work percentage at 12 months). The missing values for work percentage at 12 months were handled by the last value carried forward, if available. Initially, a global model was built using expert opinions and previous literature. The global model was then reduced to the best-fitting model using manual backward elimination. At least one predictor per category was retained in the model, and an evaluation of the Akaike information criterion was performed at each step. No outliers were removed from the analysis since the objective was to construct a model for the heterogeneous group of patients after TBI. A best-fitting model for work percentage at 6 months was also made for comparison, using the same global model and procedure. The variance of work percentage explained by the models was represented by R^2 and adjusted R^2.

4.9 Ethics

This study was approved by the Regional Committee for Medical Research Ethics of South East Norway (2016/2038) and the protocol was registered at ClinicalTrials.gov (NCT03092713). The Research Council of Norway (256689/H10) provided funding for this research. Oral and written informed consent was retrieved from all participants and the study followed the ethical principles of the Helsinki Declaration. The study was also approved by

the Data protection representative of the health authority (Helseforetakets personvernombud ved OUS, no. 2016/19372). In this pragmatic clinical RCT, the patients' welfare was a priority. In cases where patients presented to the health professionals in the study with health care needs that would elicit a right to treatment in the Norwegian health system, appropriate referrals were ensured.

5 Main results

Of the 592 patients considered for eligibility, 432 were excluded because they did not match the inclusion criteria, while 39 declined to participate, and 5 were excluded for other reasons (see Figure 3 for a flowchart of the RCT recruitment process). The most frequent reasons for exclusion were > 12 weeks since injury (29%), not between 18–60 years of age (17%), and not on ≥ 50% sick leave at the time of assessment for inclusion (11%). Ethical regulations prohibited inquiries into why potential patients declined participation. However, of those who offered an explanation without being asked, most answered that the intervention was too time-consuming or that they did not feel they needed further follow-up. Due to a low dropout rate and the time restrictions of the study, participant inclusion ended in April 2019.

This resulted in 116 patients being included in the RCT (subsequently in papers I and II). Three patients were excluded from Paper III due to statistical considerations, resulting in 113 being included in the analyses. Table 6 presents the baseline characteristics for the 116 included patients.

5.1 Description of sample

Paper I presented the characteristics of the sample and compared patients with and without traumatic intracranial injury on CT/MRI. In total, 60% of the patients were women and the majority were employed in full-time positions working white-collar jobs. Mild TBI was diagnosed in 94% of the sample and intracranial injury in 23%.

5.2 Symptom burden

The patients collectively displayed a high symptom burden, with an average RPQ score of 28 (SD: 11). Fatigue, headache, and noise sensitivity were most frequently scored as moderate or severe problems by 75%, 64% and 54% of the sample, respectively. Concerning emotional

symptoms, 43% of the sample reported moderate to severe depressive symptoms (PHQ-9), 20% reported moderate to severe anxiety symptoms (GAD-7), and 20% scored above the established cut-off for post-traumatic stress symptoms (PTSS-10). Health-related quality of life was decreased, with 58% scoring below the threshold (QOLIBRI-OS < 52). The highest symptom burden was reported by patients with normal neuroimaging, with a difference in PCS (RPQ: $t(105) = 27$, $p < .01$), depressive symptoms (PHQ-9: $t(102) = 3.06$, $p < .01$), symptoms of post-traumatic stress (PTSS-10: $U = 649$, $p = .01$), and reduced health-related quality of life (QOLIBRI-OS: $t(100) = -3.9$, $p < .01$), while patients with intracranial injuries performed worse on a test for verbal memory (CVLT-II short-delay free recall: 55 vs. 60, $p = .04$).

5.3 Return to work outcomes

Of the 116 patients included, 60 were randomized to the CCT-SE group and 56 to the TAU group, as described in Paper II. There were no differences between the groups in RTW outcomes at 12 months. Most patients had returned to work by 12 months (CCT-SE: 90%, TAU: 84%, $p = .40$), and all except three of these individuals were stably employed at that time. However, a higher percentage of patients in the CCT-SE group returned to work by the 3 month follow-up when compared to the TAU group (81 vs. 60%, $p = .02$).

When assessing days until pre-injury work levels, 50% of the patients in the CCT-SE group had accomplished this by 365 days (SE: 25), while this took 415 days (SE: 14) for the TAU group. This 50-day difference between the groups was not statistically significant.

5.4 Predictors for work participation

Of the 116 patients included in the RCT, 113 were included in the analysis of work-related predictors for work participation at 12 months. Predictability, quantitative demands, and

rewards (recognition) in the workplace contributed to the best-fitting model together with sector of employment, symptom burden at baseline, and sex. The best-fitting model accounted for 25% of the variance in work participation at 1 year.

Figure 3. Flowchart of enrollment in the randomized controlled trial.

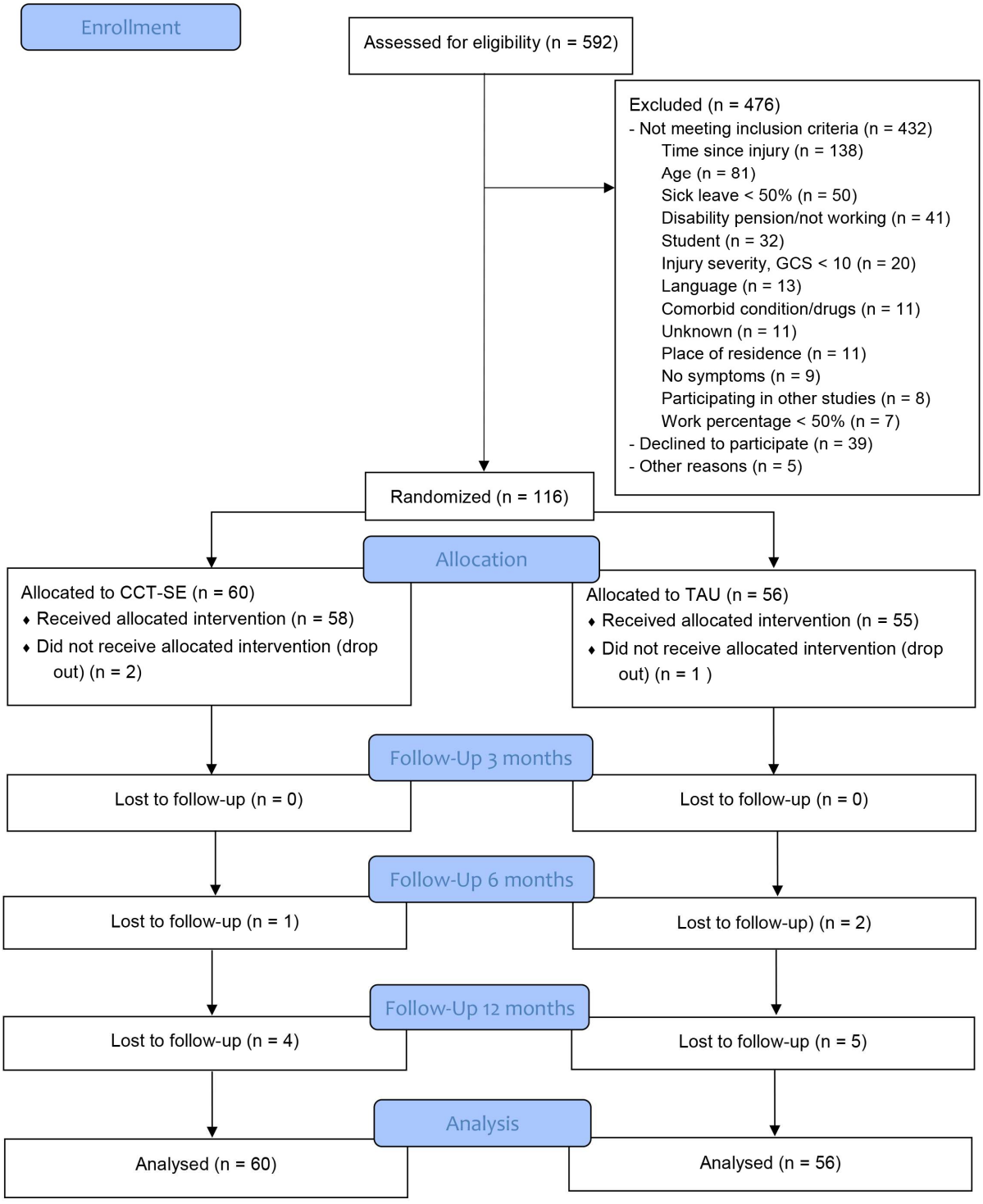

Table 6. Baseline characteristics of individuals with mild-to-moderate traumatic brain injury at 8 to 12 weeks post-injury by study group and for the total sample.

	n	CCT-SE (n = 60)	TAU (n = 56)	Total sample (n = 116)
Pre-injury factors				
Age, years, median (range)	60/56	42 (24–60)	44 (27–60)	43 (24–60)
Sex, female	60/56	33 (55)	36 (64)	69 (59)
Education, years, mean (SD)	60/56	16 (2)	16 (3)	16 (3)
Married/cohabitating	60/56	43 (72)	34 (61)	77 (66)
Child(-ren) in household	60/56	29 (48)	30 (54)	59 (51)
Self-reported history of				
Anxiety	60/56	3 (5)	3 (5)	6 (5)
Depression	60/56	11 (18)	6 (11)	17 (15)
Migraine/Headache	60/56	12 (20)	11 (20)	23 (20)
Previous concussion	60/56	32 (53)	18 (32)	50 (43)
≥ 2 previous concussions	59/56	10 (19)	8 (14)	18 (16)
Injury-related factors				
Cause of injury	60/56			
Falls		19 (31)	30 (54)	49 (42)
Traffic accidents		12 (20)	11 (20)	23 (20)
Sports		10 (17)	4 (7)	14 (12)
Violence		3 (5)	3 (5)	6 (5)
Exposure to inanimate objects		15 (25)	8 (14)	23 (20)
Unknown		1 (2)	0 (0)	1 (1)
CT/MRI findings, traumatic intracranial	60/56	11 (18)	16 (29)	27 (23)
AIS Head, median (range)	60/56	1 (1-4)	2 (1-4)	1 (1-4)
Extracranial injury	60/56	28 (47)	25 (45)	53 (46)
Injury severity based on ACRM criteria	60/56			
Mild		58 (97)	51 (91)	109 (94)
Moderate		2 (3)	5 (9)	7 (6)

Loss of consciousness (LOC)	60/56			
< 30 min		21 (35)	16 (29)	37 (32)
30 min–24 hr		1 (1)	2 (4)	3 (3)
No LOC		31 (52)	30 (53)	61 (52)
Not registered		7 (12)	8 (14)	15 (13)
Post-traumatic amnesia (PTA)	60/56			
< 1 hr		18 (30)	17 (31)	35 (30)
1–24 hr		7 (12)	9 (16)	16 (14)
25 hours–7 days		0 (0)	2 (4)	2 (2)
No PTA		25 (42)	26 (47)	51 (44)
Not registered		10 (16)	2 (2)	12 (10)
Injured at workplace	59/55	9 (15)	7 (13)	16 (14)
Under the influence of alcohol at time of injury	60/56	5 (8)	12 (21)	17 (15)
Work-related factors				
Occupation type, white-collar	60/56	53 (88)	50 (89)	103 (89)
Permanent position	60/56	56 (93)	49 (88)	105 (91)
Full-time position	60/56	55 (92)	48 (86)	103 (89)
Private sector	60/56	36 (60)	28 (50)	64 (55)
Duration of employment, months, median (range)	59/55	54 (0–408)	42 (0–480)	51 (0–480)
Size of enterprise	60/55			
Micro (1–9 employees)		4 (7)	5 (9)	9 (8)
Small (10–49 employees)		17 (28)	19 (34)	36 (31)
Medium (50–249 employees)		12 (20)	16 (28)	28 (24)
Large (≥ 250 employees)		27 (45)	16 (28)	43 (37)

Data are n (%) unless otherwise indicated. CCT-SE, Compensatory Cognitive Training and Supported Employment; TAU, treatment as usual; AIS head, Abbreviated Injury Scale Head.

6 Discussion

6.1 Methodological considerations

6.1.1 Internal and external validity

According to the 2010 CONSORT statement (146), external validity refers to the extent to which the results of a study can be generalized to other circumstances, while internal validity refers to the extent to which the design and conduct of a trial have minimized the risk of bias. Notably, sufficient internal validity is a prerequisite for evaluating external validity.

Internal validity

This thesis was derived from an RCT, which is the most rigorous scientific design to examine the effect of interventions since it attempts to eliminate the possibility of bias and thereby strengthens internal validity (147). To express internal validity, the following has been reported in the papers, as recommended (146): number of patients who completed the treatment as allocated, number of patients that did not complete treatment as allocated, including dropout rates and loss to follow-up.

There are four main types of bias that can negatively impact the internal validity of RCTs: selection bias, performance bias, detection bias, and attrition bias (148) (see Section 6.2.2 for a discussion on possible selection bias in this study). In an attempt to avoid performance bias (the care provided to the patients differs systematically between the groups), we aimed to deliver approximately the same amount of follow-up to patients in both treatment arms, and both groups were followed up for a maximum of 6 months. Moreover, both treatment groups received most of their intervention at the same outpatient clinic at OUH. Concerning detection bias (systematic differences in outcome assessments), the outcome assessors were blinded for group allocation and all patients had outcome assessments at the same time points and with identical content in the assessments. However, we cannot completely preclude that some

patients may have revealed their group allocation during the outcome assessment. With regard to attrition bias (loss to follow-up systematically differs between the intervention groups), this has been regarded as a non-issue in the present study since the loss to follow-up was low (8% at the 12-month follow-up, four patients in CCT-SE and five in TAU (149)). Consequently, steps were taken in an attempt to avoid various forms of bias in this study. However, chance errors (outcome variability due to chance alone) are more likely to occur in studies with smaller samples (148). To avoid chance errors, a power estimation was calculated before the start of inclusion (121).

External validity

In accordance with the CONSORT recommendations, detailed eligibility criteria, setting of data collection, number of people assessed for eligibility, details of interventions and administration of interventions, the definition of outcomes, and period of recruitment and follow-up were reported in the papers included in this thesis (146). The generalizability of the results are discussed in detail within the general discussion of Paper I (Section 6.2.1), which describes the selected sample. Briefly, the inclusion criteria (including restrictions based on age, work status, place of residence, and the presence of PCS 8–12 weeks after injury) limited the generalizability of the results. However, the results represent a working population of patients with mild-to-moderate TBI who sought treatment for symptoms 8–12 weeks after TBI, which provided information on the group of patients seen at rehabilitation facilities after the acute stage. Moreover, the sample represents patients with potential to resume their pre-injury occupation through rehabilitation due to their injury severity, being of working age and employed at the time of injury (117).

6.1.2 Study design

This thesis was based on a study designed as an RCT. This design is generally considered to be the most robust for evaluating the effect of an intervention and negating the effect of confounders (147). It was a pragmatic RCT in which the effectiveness of the intervention was evaluated in a real-world clinical setting, as opposed to an explanatory study where the intervention is tested under ideal circumstances (150). During the study planning process, it was discussed whether the RCT should include a treatment arm in addition to CCT-SE and TAU. An additional arm with patients who did not receive any follow-up would allow us to compare the effect of CCT-SE with the natural course of mild-to-moderate TBI. However, this did not seem ethical since there is a usual standard of care offered to these patients at the hospital where the study took place. Furthermore, it was suggested that additional interventions arms providing solely CCT and solely SE would enable us to discriminate which part of the CCT-SE intervention was most useful. Adding additional intervention arms to the RCT was not feasible due to the low incidence rate of mild-to-moderate TBI in our region combined with the time and budget restrictions of the study. Additionally, we anticipated that the combined cross-sectoral effort would involve synergies making the total effect to be both more than, and different from, the mere additive value of the two interventions in isolation, thus rendering the hypothetical extra intervention arms less informative.

Although RCTs are generally considered the superior method for demonstrating treatment efficacy, some have questioned whether it is the optimal research design for treatments within the field of rehabilitation. Turner-Stokes et al. (151) has called attention to the complexity of the interventions required and the heterogeneity of the patients, which together may cause the targeted relationships to be unpredictable on an individual basis. Their review highlights several challenges in the context of rehabilitation research, including a relatively small patient number, marked heterogeneity in relevant clinical characteristics, interventions, and

outcomes, and that the resources and duration required to observe effects often extends beyond those of any funded research project (151). They concluded that since the RCT-based literature does inform us of which rehabilitation treatment works best for which patient over time, practice-based evidence from large longitudinal cohort studies is required to define the effective service provision.

Papers I and III also utilized designs that were appropriate for their respective research questions. Paper I aimed to describe the sample at baseline and compare outcomes in patients with and without abnormal neuroimaging. This allowed for a cross-sectional description and the reporting of associations between the severity of injury and symptoms at baseline. Paper III aimed to examine the work-related predictors that affect work participation at 12 months. This was achieved by using baseline data with a longitudinal design that allowed for conclusions to be drawn concerning causal factors.

6.1.3 Inclusion criteria and study participants

The participants in this thesis were all recruited from the outpatient clinic at OUH. Paper I presents their characteristics as 60% female and—on average—highly educated with full-time, white-collar occupations. This is not entirely in line with the epidemiological studies on TBI where men usually are overrepresented, and TBIs are not typically more common in highly educated individuals (3, 56). The gender results may be explained by the fact that 10% more females are referred to the outpatient clinic (reference: personal communication with the quality registry at the outpatient clinic) and that women generally tend to seek health care more often than men (152). The patients had 16 years of formal education on average, which is high. This could be due to the population that the sample was collected from. The general population in Oslo has more years of education than the average citizen of Norway. In 2020, 61% of the population in Oslo aged 30–59 years had completed at least 3 years of

university/college education, while this number was 44% in the rest of Norway (153). Among those between 25–34 years of age, 69% in Oslo had completed at least 3 years of university/college (153).

A potential limitation of the study presented in Paper III is that it analyzed the same sample as in the RCT (Paper II). Although we found no significant differences between the groups with regard to work participation at 12 months, we cannot entirely exclude that the different intervention arms may have had an impact. However, in subsequent analyses, the treatment group was inserted into the prediction model and was found to have an insignificant effect on work participation at 12 months, thereby strengthening the view that work participation at 12 months was not dependent on the treatment received.

6.1.4 Outcome measures

In this thesis, outcome measures mainly relied on self-reported information collected from the participants as symptom burden and occupational information. This may be a limitation of this study since patients with TBI often report cognitive symptoms such as memory difficulties, which may increase the risk of collecting false values. However, the patients included in this study suffered from mild-to-moderate TBIs and had normal neurocognitive function on average. Therefore, we do not suspect that knowledge of their own current work status or symptom burden was affected.

As recommended by Graham et al. (116), the primary outcome measures in this study were proportion returned to competitive work, hours and percentage worked, work stability, and days until pre-injury work levels. In this study, patients were defined as returned to work if they had returned to work at any level, while nuance was provided by additionally collecting the other outcome measures. However, the definition of RTW varies substantially from study to study. For example, some authors have defined RTW as not receiving sick leave benefits

for 5 consecutive weeks (12) or working at least 12 hours per week (154), while others include studying or voluntary work as an occupation when reporting RTW (155, 156). In addition to the variation of inclusion criteria and timing of follow-up, these differences impede the comparison of results across studies with regard to RTW and work stability.

Some of the questionnaires included in this study overlapped on certain items. This is mainly relevant to the RPQ and PHQ-9 since some post-concussion symptoms (e.g., difficulties with sleep or concentration) overlap with symptoms of depression. This may have also affected the outcomes of GAD-7 and PTSS-10. It is important to note that these questionnaires are merely tools for screening symptom load. Diagnostic assessment requires the use of standardized diagnostic interviews such as the Mini International Neuropsychiatric Interview (M.I.N.I.), M.I.N.I. plus (157, 158), or the Structured Clinical Interview for DSM-5 Disorders (159) to confirm diagnoses. Importantly, the reported means above cut-off scores may have been inflated due to overlapping symptoms stemming from the TBI. Therefore, the results should be interpreted with caution.

6.1.5 Sample size

As mentioned in the methods section, the sample size was calculated with regard to the primary outcome measure (RTW proportion at 12 months). Based on existing literature, we aimed for a 33% absolute difference between the two intervention groups in the RCT to ensure clinical and societal importance. In retrospect, it became clear that this goal was set too high when considering this patient group. At the 12-month follow-up, 90% in the CCT-SE group and 84% in the TAU group had returned to work. The relatively small difference between the groups may be due to the pragmatic approach used in the study (including a comprehensive multidisciplinary follow-up such as TAU) and the natural recovery process of mild-to-moderate TBI. A post-hoc power calculation indicated that 478 patients would have

been required per group to reach the possibility of the estimated difference in this outcome measure. According to the quality registry at the Department of Physical Medicine and Rehabilitation at OUH, approximately 422 patients with TBI (all severities and ages) received follow-up at the TBI outpatient clinic in 2019. Among the patients of working age (18–65 years), 343 had an mTBI. Moreover, based on previous experience and research from the clinic, approximately 80% (274 patients) would have been eligible for inclusion into a study, whereof 30–40% would be expected to experience prolonged symptoms. This amounts to approximately 82–110 eligible patients per year. Considering the low TBI incidence in our region (3), we would have needed from 4.3 to 5.8 years to reach these numbers. However, this was not feasible given the budget and time constraints of this study.

6.1.6 Randomization and blinding

To ensure that no selection bias affected the randomization, the block sequences for randomization were constructed before inclusion to the study began. Furthermore, the senior researcher responsible for allocation was not involved in providing treatment, follow-ups, or analyses of data in the study. Group allocation was provided to the Ph.D. candidates in the study and the participants after completion of the baseline assessment.

The outcome assessors were blinded for group allocation and the patients were instructed not to reveal their allocated groups during follow-ups. However, this is difficult to control and some patients may have revealed their allocated group without our knowledge. The knowledge of group allocation may have led to bias in the assessors' interpretations of the results. However, the outcome assessors at 6 and 12 months follow-up were not a part of the study in any other capacity. Therefore, they had seemingly little motivation to skew the results in any direction. The rehabilitation specialists were not blinded for group allocation since they were responsible for the delivery of the interventions. This may have affected their

efforts or attitudes toward the treatment and subsequently affected the patients and outcomes. However, only blinding the outcome assessors has been suggested as preferential in pragmatic RCTs (150). As mentioned previously, the patients' identities were concealed in the database by an independent statistician, and was not revealed to the rehabilitation specialists (incl. the Ph.D. candidate) until the 12 month analyses had been performed.

6.1.7 Statistical analyses

The primary outcome and statistical analyses for this study were planned and published before the commencement of the trial (121), in line with recommendations in the CONSORT statement (146). All statistical analyses not mentioned in the protocol were likewise discussed with an independent statistician (co-author CB) to ensure that the optimal methods were correctly applied.

Paper I used descriptive analyses to present baseline information of the sample and compared symptom burden in patients with and without traumatic intracranial injury visible on CT/MRI.

In Paper II, multilevel mixed-effect models were built as per protocol and by the intention-to-treat principle. As recommended, the main effect of the treatment was removed from the analyses to correct for any potential differences at baseline (160), despite having an RCT design. Thus leaving the effect of treatment over time represented by the coefficient for the interaction of treatment and time.

Paper III utilized multiple linear regression to create a model for predicting work participation at 12 months after inclusion into the RCT. According to recommendations from the literature (161) and an independent statistician, a global model was first built using the variables assumed to be most influential on work participation after 12 months. These variables were chosen based on the literature and through discussions with experts in the field of rehabilitation as well as senior researchers at the Work Research Institute at Oslo

Metropolitan University. The global model was then reduced using the recommended (161) backward elimination until further removal of any variable would have degraded the model, as assessed by the Akaike information criterion in each step of the reduction.

6.2 General discussion

6.2.1 Characteristics of the study sample (Paper I)

Paper I aimed to characterize the sample included in this thesis. The rationale for this was the hypothesis that patients with protracted symptoms may differ from the overall TBI population. The patients in this sample were of working age and employed at the time of injury, excluding the pediatric population and the elderly. This provided the opportunity to describe the sample of patients who were experiencing symptoms 8–12 weeks after TBI, seeking treatment, and who likely aimed to RTW. In other words, we included those patients who are often seen in the rehabilitation setting after mild-to-moderate TBI.

Women were overrepresented in this sample compared to the general TBI population. Epidemiological studies of TBI have reported an estimated male-to-female ratio of 1.8:1.0 (3, 56), while this sample included approximately 60% women. While we cannot know the exact reasons for this overrepresentation, we are aware that women generally tend to seek health care services more often than men (152) and that the population this sample was recruited from also has more female patients than male patients. As previously mentioned, the quality registry from the outpatient clinic reported that approximately 10% more females than males are referred to the clinic (based on correspondence with the quality registry staff). Additionally, the development of PCS is more common in women than men (77). Why women report PCS more frequently is debated. In a CENTER-TBI study (162), differences in outcome between sexes after TBI were more pronounced in patients with mTBI when compared to moderate/severe TBI, and most pronounced in patients < 45 years and > 65

years. Outcomes after milder injuries may be more likely to be affected by differences in self-reporting, stress, and socioeconomic factors, that are commonly associated with sex (162). Some search for a biological/hormonal difference in injury response after TBI between the sexes as a means to explain why women report more symptoms (163). In addition to biological differences, men and women < 45 years may experience different challenges in everyday life, with women reporting to struggle with household duties as well as balancing rehabilitation after injury and domestic chores (162), which may negatively influence their quality of life and mental health after TBI.

Since the results of Paper I present atypical patient characteristics for the TBI population, one may argue that the results are not generalizable to all patients with mild-to-moderate TBI. While this is true, one may also argue that the importance of the results is enhanced for the same reasons. The aim of this study was not to confirm the commonly acknowledged characteristics of patients with TBI in general but to examine whether a sample of working age that remains symptomatic 8–12 weeks after TBI and seeks rehabilitation would differ from the main characteristics of patients with TBI. Thus, this study presents knowledge of a subgroup that is highly relevant to rehabilitation facilities working with patients after mild-to-moderate TBI.

6.2.2 Early outcomes after TBI with intracranial injury on CT/MRI (Paper I)

In the current sample, patients without traumatic abnormalities on neuroimaging reported more symptoms 8–12 weeks after TBI than those with abnormal results on CT/MRI. After controlling for differences between the two groups (previous mTBI and years of education), the patients without traumatic intracranial abnormalities still reported more post-concussion symptoms (RPQ), depressive symptoms (PHQ-9), symptoms of post-traumatic stress (PTSS-10), and lower health-related quality of life (QOLIBRI-OS).

At a group level, both those with and without intracranial injury performed within the normal range in the neuropsychological screening. However, the group with intracranial injury performed significantly worse on a test for verbal memory (CVLT-II short-delay free recall), which may indicate a relatively impaired memory function in this group. Yet, when controlling for differences between the groups (previous mTBI and years of education), the between-group difference in the verbal memory task was no longer significant.

The reporting of more symptoms in patients without abnormal CT/MRI is in line with the findings of some smaller studies (82, 164). However, large-scale studies have found more symptoms in patients with intracranial injury visible on neuroimaging (28, 165), and it is commonly recognized that the presence of intracranial injury on CT/MRI is associated with a worse outcome.

Possible explanations for why patients without traumatic intracranial injury report more symptoms in this sample are thoroughly discussed in Paper I. Briefly, this may be due to a selection bias, expectation bias, or somatization processes.

The potential selection bias stems from the routines for referral to the TBI outpatient clinic at OUH (from which the patients were recruited). Patients admitted to the neurosurgical department at OUH with an intracranial injury on CT/MRI are routinely referred to a follow-up at the TBI outpatient clinic 6–8 weeks after TBI (regardless of their symptom burden at the time), while patients externally referred to the outpatient clinic are often referred by their general practitioner due to ongoing symptoms. This may skew the proportions of patients in that patients with intracranial injury are referred even if they do not have symptoms. However, all included patients had a consultation with a physiatrist at the TBI outpatient clinic and were diagnosed with PCS 8–12 weeks after TBI before inclusion into the study, thereby eliminating the inclusion of asymptomatic patients.

The possible expectation bias is suspected in lieu of the clinical experience of the health professionals in the study. In our experience, patients with intracranial injury are more likely to be informed by health professionals in the acute phase that they had an injury that would take time to recover from and the patients therefore reported that the rate of recovery matched their expectations. On the other hand, the patients without intracranial injury were commonly informed that their symptoms would resolve within days/weeks and their frustration seemed to rise when their recovery did not match their expectations, based on information they received in the acute phase. This may have caused them to perceive their condition as relatively worse and resulted in higher self-reported symptoms. Importantly, this observation of a potential expectation bias is only reported by health professionals in contact with these patients and has not been systematically examined in this study. However, a qualitative paper describing the experiences of a subsample of the patients in this RCT is currently under review and supports the notion that the patients found it challenging to live with such a heterogeneous condition without a clear prognosis (166).

Lastly, a higher proportion of patients without intracranial injury reported having had previous mTBIs and higher levels of depressive and post-traumatic stress symptoms. Notably, the experiences from previous mTBIs might have altered the patients' expectations (167) and contributed to the misattribution of symptoms. Several studies have suggested that somatization may contribute to longstanding post-concussion symptoms (168-170), which may also have occurred in this study.

Richter et al. (43) reported imaging phenotypes on DTI that are associated with symptom burden after mTBI. Their results highlight that the abnormalities on DTI were detectable within 72 hours after injury, even when no changes were visible on conventional MRI. Furthermore, imaging performed earlier after mTBI (< 72 hours) seemed to hold the most predictive value, and patients with progressive changes on DTI also had worsening RPQ

scores. However, the changes in white matter likely vary due to both injury and host factors. To improve the role of ultra-early MRI, better detection of injury (e.g., multishell diffusion MRI), a larger number of patients, and more complex models for predicting outcomes are necessary (43).

In the future, further advancements in imaging technology might provide answers as to why some individuals without visible injury on conventional neuroimaging experience such a high symptom burden. Currently, it is assumed that the symptom burden in these patients is largely multifactorial and should be viewed in light of the biopsychosocial model.

6.2.3 Multi-sectoral collaboration (Paper II)

Traditionally, there has been poor collaboration between health care services, workplaces, and the labor and welfare sector. In day-to-day practice, the health care sector is mainly preoccupied with the illnesses of patients, while the labor and welfare administration and workplace are focused on the occupational status of patients. Notably, communication and cooperation between these entities have been lacking, which has resulted in a somewhat fragmented and suboptimal follow-up for patients.

The overarching study that this thesis is part of aimed to improve this cooperation while increasing knowledge and insights into each entity and simultaneously improving the follow-up for the patients. To achieve this, the health care personnel delivering the CCT had meetings with the job specialists providing the SE every 3 weeks throughout the intervention period to exchange information and coordinate their efforts for each patient. The job specialist further aimed to have at least one meeting with each patient's employer at the workplace to include the employer in the employees' rehabilitation plan. In this manner, the health care professionals were updated on their patients' occupational statuses, the job specialists were informed of medical recommendations regarding RTW for each patient, and the patients'

employers were informed regarding their condition and adjustment needs in the workplace to facilitate RTW.

The knowledge gained through this method of collaboration has provided further insights for the involved institutions and would benefit from further evolving the collaboration in the future. Although it may be a more time-consuming working method, it appears to result in a more coherent process for those involved. An article evaluating the cost-effectiveness of the RCT has been submitted but is not a part of this thesis. A detailed description of the patients' experiences of the RTW process in this study will also be published separately.

6.2.4 Interventions (Paper II)

In the RCT described in this thesis, the patients received either a combined cognitive and vocational intervention (CCT-SE) or the standard treatment for mild-to-moderate TBI at OUH (TAU).

Compensatory Cognitive Training

The CCT is based on CogSMART, a similar cognitive intervention that was also developed by Dr. Twamley in the USA. This intervention had previously been studied in a pilot RCT with unemployed veterans who sustained a mild-to-moderate TBI more than 4 years before receiving the intervention (119). They found no difference in RTW for this sample after 1 year but observed an improvement in post-concussion symptoms and quality of life (120). Cognitive symptoms have been linked to difficulties in maintaining a competitive job after TBI (171) and the CCT was implemented in this RCT to aid with these difficulties. The results of the RCT demonstrate that the intervention was effective in facilitating a more rapid RTW among patients. However, some elements related to the CCT are worth noting.

The CCT is a manualized intervention with specific topics for each of the 10 sessions, which mainly deal with compensatory strategies for various cognitive complaints. While delivering the intervention, there were some sessions where none of the patients in a group experienced problems with the topic at hand. Seeing as the intervention was delivered in a research setting, the intervention manual was followed rigorously regardless of the patients' specific complaints. In a clinical setting, adapting the intervention to the specific patients being treated should be considered to increase the relevance of the treatment to each individual and to reduce unnecessary effort for the therapists delivering the intervention. On the other hand, an advantage of the CCT intervention is precisely that it is manualized and designed to be delivered by different health professionals. However, individual tailoring of the CCT manual would require that the personnel delivering the manualized intervention have sufficient individual knowledge about the patients as well as the professional qualifications required to assess which patients may benefit from each of the compensatory strategies.

Furthermore, some patients experience oculovestibular symptoms (i.e., dizziness, nausea, blurry vision, disturbed sense of balance) after a mild or moderate TBI (172), and for some patients these are the most debilitating of their symptoms in their everyday life. This has led to specific intervention studies aiming to reduce these symptoms after TBI (173). However, in contrast to most other PCS, these symptoms are not included in the CCT manual and are consequently not addressed in this part of the intervention. In the current RCT, this was resolved by the patients receiving advice at their appointment with the physiatrist before inclusion to the RCT, as well as referral to treatment when necessary (i.e., to a physical therapist, ophthalmologist, or orthoptist).

Supported employment

The SE provided in the intervention group of the RCT deviated from standard SE delivery. SE has traditionally been provided to patients with mental illness and vocational disability (174,

175). In some instances, it has also been provided to individuals with intellectual disabilities (176) or substance abuse (177). It has typically been provided without a specific time frame and is often long-lasting or even without time limitation (178). In a multicentre RCT conducted in Norway, SE was provided to patients with common mental disorders (depression/anxiety) who struggled with work participation (175). In that study, SE was delivered together with cognitive behavioral therapy and compared to a control group receiving ordinary follow-up by their general practitioner, and could seek additional treatment as they pleased. This resulted in a higher RTW rate for patients receiving SE and cognitive behavioral therapy (175). In the current study, patients received selected elements from SE in the early phase after their injury, and for a maximum of 6 months after inclusion (121). Although this may have been sufficient for most patients, one can speculate that the time restriction may have impeded the RTW process for some patients. However, due to the time restrictions of the study, a 6-month limit was considered a necessary maximum. Additionally, the study aimed to compare two groups that received approximately the same amount and duration of the interventions, to minimize potential bias stemming from one group receiving a more comprehensive follow-up.

In this study, the patients were employed at the time of injury and were offered SE early in their sick leave period. Early specialized rehabilitation and early vocational rehabilitation after TBI has been shown to improve outcomes and be cost-effective (151, 179). This highlights the focus on early rehabilitation, which has been essential in this study and likely contributed to helping patients return to their competitive employments earlier.

Treatment as usual

TAU was the standard of care for patients at the TBI outpatient clinic and was very comprehensive in this study, with extensive follow-ups adjusted to the needs of the patient and some attending additional group sessions, as described in the Methods section. This

comprehensive control group is not necessarily representative of other rehabilitation facilities, neither in Norway nor internationally, and it might have contributed to the small difference between the two intervention groups with regard to the main RTW outcomes (180, 181).

6.2.5 Days until pre-injury work level (Paper II)

Mild-to-moderate TBI is a highly prevalent condition with a high impact on productivity loss and societal costs. In this context, it could be considered a more severe condition. Since TBI tends to affect young people, there is considerable potential societal monetary gain given that the intervention results in faster RTW. Cost-effectiveness studies of rehabilitation after TBI have most commonly focused on severe TBI (182, 183) and loss of production often accounts for most of the societal cost after TBI. The average cost of a new TBI in New Zealand was calculated at US $4,636 for mTBI and US $36,648 for moderate/severe TBI in 2010, with an estimated increase in these costs for 2020 (184). Although the cost per case was lower for mTBI, the total cost was three times higher for mTBI than for moderate/severe TBI due to the higher yearly incidence of mTBI (184). Since milder TBIs are markedly more frequent than severe TBI, it is reasonable to explore early rehabilitation after milder TBIs aiming to improve RTW and thus reduce the societal cost. In the current study, the findings of a 50-day difference in return to pre-injury work level and a 3-month between-group difference in the proportion of working patients suggested that the early intervention program for patients with mild and moderate TBI might be effective. As a result, a cost-effectiveness analysis of this study has been submitted for review.

Although the evidence for early vocational rehabilitation after TBI cannot clarify which program is superior or the optimal time of intervention, there is a relative consensus that some form of early intervention after injury is favorable (185). Notably, a review from 2021 developed a refined program theory of how early intervention vocational rehabilitation

(EIVR) works for individuals who recently sustained a TBI, acquired brain injury, or spinal cord injury (179). EIVR refers to vocational rehabilitation that starts within weeks of injury, often during the primary rehabilitation. Dunn et al. identified nine mechanisms that may improve vocational outcome (1 - ensuring rehabilitation teams' culture, 2 - fostering hope, 3 - exploring options, 4 - optimizing self-efficacy, 5 - maintaining worker identity, 6 - staying connected, 7 - setting goals, 8 - engaging employer, and 9 - flexing roles), with mechanisms 1–5 applicable to all patients, while mechanisms 6–9 only apply to patient employed at the time of injury (179). This newly developed program theory is of interest and should be explored in future studies.

6.2.6 Updated literature on RCTs aimed to improve return to work after TBI (Paper II)

Since commencing this study, a few RCTs describing cognitive or vocational interventions aimed at improving RTW after TBI have been published.

The results of a pilot feasibility RCT examining enhanced vocational rehabilitation for veterans with mTBI and mental illness was published in 2016 (186). The study included 18 veterans who were randomized to either a 12-week cognitive rehabilitation intervention embedded within vocational rehabilitation (n = 10) or supportive client-centered therapy with no focus on employment (n = 8). The intervention was found to be feasible and showed small to moderate effect sizes on RTW outcomes (186), thus warranting a large-scale trial.

An RCT from 2017 compared a cognitive behavioral intervention to telephone counseling early after mTBI (156). The patients were provided with either five sessions of cognitive behavioral therapy (39 patients) or five phone conversations (45 patients) starting 4–6 weeks after injury. They found no difference in RTW after 12 months, with an average of 66% of patients having returned to pre-injury work levels (156). This result is in line with the results

presented in this thesis, where 65% of the CCT-SE group and 54% of the TAU group had returned to pre-injury work levels after 12 months.

In 2018, the results of a feasibility study were published (154). With a focus on work retention 12 months after TBI, the study examined the feasibility of a multicentre RCT examining the clinical effectiveness and cost-effectiveness of an early specialist vocational rehabilitation in addition to usual care (n = 39) compared to usual care alone (n = 39). The study was found to be feasible, and 91% in the control group were competitively employed or studied full time after 12 months compared to 66% in the intervention group (154). The RTW findings in the control group of this feasibility study are comparable to the results from the current RCT in which 90% (CCT-SE) and 84% (TAU) had returned to work after 12 months. However, the definitions of RTW are not congruent and the results are therefore not directly comparable.

Additionally, a protocol for a pragmatic RCT examining the effect of a manual-based vocational rehabilitation program for patients after acquired brain injury was published in 2017 (187). To date, no results have been published from this Danish study.

6.2.7 Prognostic models for return to work after mild-to-moderate TBI (Paper III)

Paper III described the development of a prognostic model for RTW after mild-to-moderate TBI, with an expanded view on possible predicting factors—namely a focus on work-related factors. Prediction models for clinical outcomes after TBI using personal and injury-related factors have been thoroughly explored. A systematic review from 2020 examining prognostic models for clinical outcomes after moderate and severe TBI published from 2006 to 2018 reported on 67 different models, with age, pupil reactivity, and GCS score being the most commonly used predictors (188). However, prediction models for occupational outcomes are less common, with models including work-related factors being even less common.

A scoping review from 2021 examined the factors associated with sustaining work after acquired brain injury and included both quantitative and qualitative studies (189). In line with our statement on this topic, the quantitative studies focused on factors related to the patient, injury, and early functioning. However, the qualitative studies also highlighted the importance of work-related factors when aiming to sustain work after injury, including company size, having a supportive employer, and having the opportunity to prepare and plan work according to their own functional level (189). The scoping review called for results from the qualitative studies, including work descriptions and the psychosocial work environment, to be tested in hypothesis-driven longitudinal studies (189).

The innovative model constructed from this sample showed that sector of employment (private vs. public), predictability, quantitative demands, and rewards (recognition) in the workplace all predicted RTW at 12 months, which is in line with our hypothesis. These psychosocial factors are comparable to those described in the aforementioned scoping review (189). Additionally, sex and symptom burden at baseline (represented by RPQ score) added prognostic value to the model. The factors found to be of prognostic value (or not) are discussed in Paper III.

The best-fitting model explained 25% of the variance in work participation at 12 months, leaving 75% of the variance unexplained. Ideally, a prediction model would explain more than one-quarter of the variance in outcome. However, predictions involving people will often have to settle for explaining less than 50% due to the complexity of human behavior (190). Additionally, the group of patients sustaining TBIs are regarded as particularly heterogeneous compared to the population with other diseases or injuries, which further complicates predictions for individuals after TBI (116).

Prediction models are not currently part of TBI guidelines, neither for prognosis of clinical outcome nor RTW outcomes. Since the prediction model presented in this thesis is not

externally validated and devised on a relatively small sample, we do not conclude that this model should be implemented in clinical practice “as is”. Instead, it can serve as the foundation for a wider perspective of influencing factors that should be further explored to improve RTW after mild-to-moderate TBI.

7 Conclusions and future implications

7.1 Conclusions

The following conclusions can be drawn from the results of this thesis:

- Patients with post-concussion symptoms 8–12 weeks after mild-to-moderate TBI that seek treatment have different characteristics that may not be representative for all patients with mild-to-moderate TBI. Specifically, this group diverges in being predominately female, highly educated, and working white-collar jobs that are full-time and permanent positions.

- Subjective symptom burden at baseline in this sample is not only explained by injury severity and intracranial abnormalities, but also factors related to the individual, and this should be considered when planning follow-up and rehabilitation for these patients.

- The CCT-SE intervention applied in the first months after injury may improve early return to stable competitive work in patients after mild-to-moderate TBI, and thereby reduce the societal cost of TBI.

- Factors related to the work place (sector of employment) and psychosocial work environment (predictability, quantitative demands, and rewards (recognition)) should be considered when attempting to increase work participation after a mild-to-moderate TBI.

7.2 Future implications

The overarching collaboration between the health care sector, the Work Research Institute and the Norwegian Labour and Welfare Administration in this study is innovative and forward-thinking while simultaneously shedding light on a new form of collaboration that aims to improve outcomes for both the patients and society, by reducing the socioeconomic consequences of TBI. The knowledge gained through this collaboration should be explored further and could serve as the basis of a new method of cooperation between the health care and welfare sectors.

The characteristics of the subgroup of patients with mild-to-moderate TBI in this thesis present a somewhat adjusted view compared to the general characteristics of the TBI population acknowledged before the start of this doctoral project. This may aid clinicians in recognizing patients at risk of suffering from prolonged symptoms and delayed return to work, while providing further information to decision-makers when organizing health care services.

Since the CCT-SE accelerated RTW for patients after mild-to-moderate TBI, a cost-effectiveness analysis has been submitted for publication. Future studies could build on the positive effect of a combined cognitive and vocational intervention on RTW, perhaps with some adjustments to individual patients' needs with regard to the CCT manual and consider more focus on somatic symptoms including visual and vestibular complaints when appropriate.

In this study, SE was utilized in an original manner by starting the program early after injury and being limited to a maximum follow-up of 6 months. In line with the increasing focus on early rehabilitation and the positive results presented in this study, this variation in SE should be explored further. Furthermore, the intervention program has potential relevance for all patient groups in which cognitive symptoms complicate work participation. Thus, the project

can serve as a benchmark study regarding the efficacy of combined cognitive rehabilitation and supported employment efforts.

In line with the broader perspective of this research project, the data in this thesis also highlights that work-related factors are associated with return to work after TBI, as opposed to solely focusing on the patients and their injuries. Since the connection between the workplace, psychosocial work environment, and RTW after TBI remains quite uncharted territory, the results presented here may hopefully inspire further research into this important topic.

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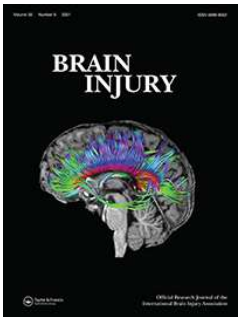
9 Appendix: Papers I-III

I



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Post-concussion symptoms three months after mild-to-moderate TBI: characteristics of sick-listed patients referred to specialized treatment and consequences of intracranial injury

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Post-concussion symptoms three months after mild-to-moderate TBI: characteristics of sick-listed patients referred to specialized treatment and consequences of intracranial injury

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ABSTRACT

Objective: To present pre-injury, injury-related, work-related and post-injury characteristics, and to compare patients with and without traumatic intracranial abnormalities, in a treatment-seeking sample with persistent post-concussion symptoms (PPCS) after mild-to-moderate TBI.

Methods: Cross-sectional design in the context of a specialized TBI outpatient clinic. Eligible patients were aged 18–60 years, employed ≥ 50% at time of injury, and sick listed ≥ 50% at inclusion due to PPCS. Data were collected 8–12 weeks after injury through review of medical records, semi-structured interviews, questionnaires, and neuropsychological screening.

Results: The study included 116 patients, of whom 60% were women, and predominantly white-collar workers in full-time positions. Ninety-four percent had a mild TBI, and 23% had intracranial abnormalities. The full sample reported high somatic, emotional, and cognitive symptom burden, and decreased health-related quality of life. Patients with normal CT/MRI results reported higher overall symptom burden, while patients with intracranial abnormalities had worse memory function.

Conclusion: Injury severity and traumatic intracranial radiological findings should not be the sole ground for planning of rehabilitation service provision in patients with PPCS, as subjective complaints do not necessarily co-vary with these variables.

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Introduction

The estimated annual incidence rate of traumatic brain injury (TBI) in the European Union is approximately 2.5 million (1). Most injuries are classified as mild (mTBI), accounting for 70–90% of all TBIs (2). Most patients recover within the first days to weeks after a mTBI (3), but a substantial proportion of patients experience persisting symptoms. Persistent post-concussion symptoms (PPCS) usually consist of a cluster of somatic, cognitive, and emotional symptoms. The patients in this study have not been defined to necessarily have post-concussion syndrome, but to have post-concussion symptoms lasting at least 3 months.

The exact incidence of patients with PPCS is unclear due to a lack of a universally acknowledged definition and diagnostic criteria, but it is estimated to occur in approximately 5–15% of the patients after mTBI (4). However, studies have reported rates of PPCS after mTBI as high as 40–45%, depending on which criteria are applied (5–7). Our understanding of PPCS is somewhat controversial, partly because the symptoms that define it (e.g. headache, fatigue, sleep disturbances) are common in the general population (6).

PPCS comprises a combination of somatic, emotional, and cognitive symptoms typically including headache, fatigue, sleep disturbances, balance disturbances, irritability, emotional lability, and impaired concentration and memory (8–10). The duration and character of these symptoms represents a considerable burden to the patients, their families, and the healthcare system. Return to work is one of the main challenges after TBI (11), with success rates varying from 12 to 70% (12). Even patients with mTBI may struggle to reach complete return to work as long as twelve months after injury (13). Problems with reattaining pre-injury occupational status may lead to reduced social integration and quality of life (14).

Injury-related variables alone, such as loss of consciousness (LOC), post-traumatic amnesia (PTA), and neuroimaging findings, have limited value for predicting symptom burden (15,16). Several studies have also examined the differences between patients with confirmed intracranial injury seen on cerebral computer tomography (CT) or magnetic resonance imaging (MRI) (complicated mTBI) and those without (uncomplicated mTBI) (5,17). However, PPCS also frequently occurs in patients without traumatic radiological abnormalities

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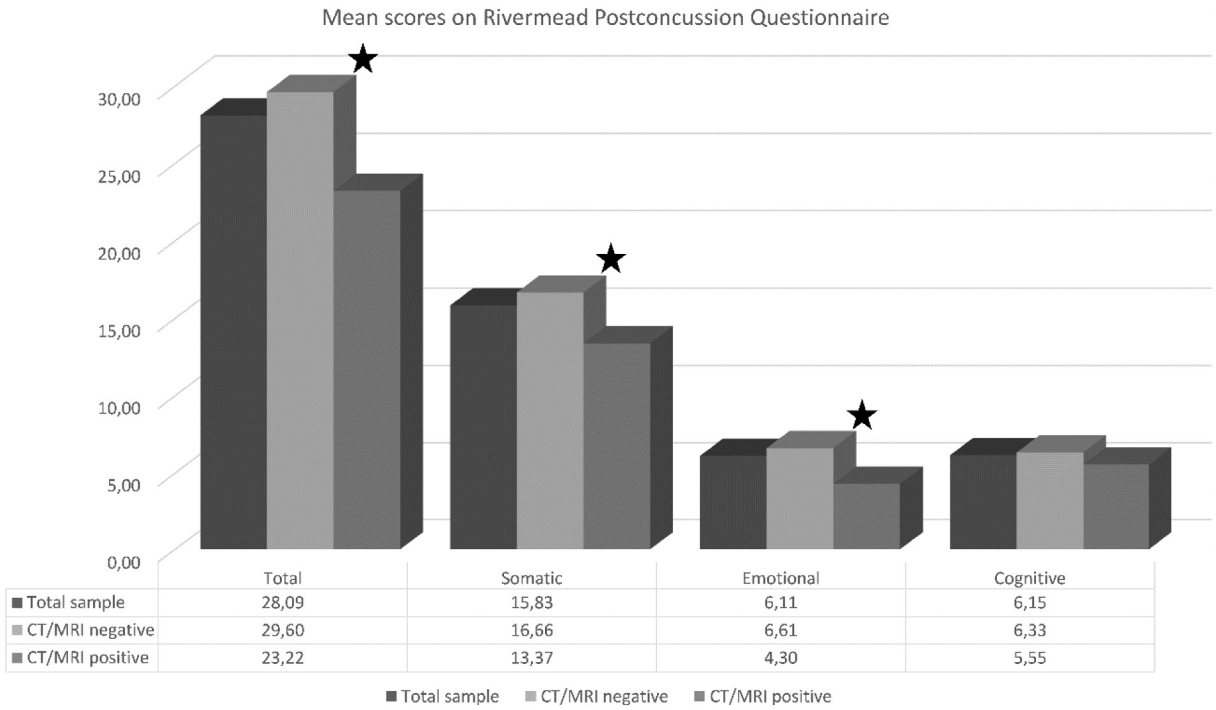

Figure 1. Mean scores on RPQ and its subscales from the total sample (green) and with the sample divided into patients without intracranial abnormalities (gray) and with intracranial abnormalities (blue). Stars mark significant differences between patients without and with intracranial abnormalities.

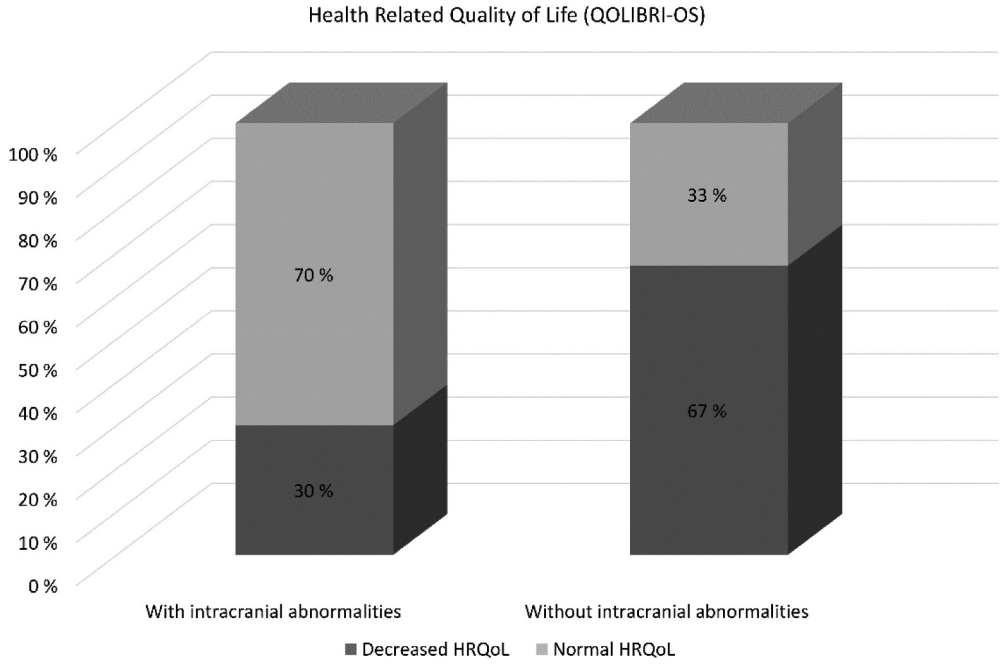

Figure 2. Health-Related Quality of Life as measured by QOLIBRI-OS, by patients with and without intracranial abnormalities.

(5,18). Some studies have shown lower levels of post-concussion symptoms in patients with uncomplicated mTBI compared to complicated mTBI and moderate TBI (5,19,20), while others have found no differences between the groups (17,21). Iverson et al. (16) found no significant difference in outcome when comparing complicated and uncomplicated mTBI, but effect sizes indicated more post-concussion and depressive symptoms in patients with uncomplicated mTBI. de Guise et al. (22) compared patients with and without radiological findings two weeks after injury and found more auditory and vestibular symptoms in the group with complicated mTBI, while the patients with uncomplicated mTBI reported more post-concussion symptoms. These findings are perplexing as it is intuitively expected that patients with more severe injuries also would report more symptoms.

Considering the complexity and lack of clear associations between injury-related variables and symptom burden (23), it is increasingly common to view PPCS from a biopsychosocial

perspective (24) where biological (i.e. brain injury), psychological (i.e. emotional state and personality), and social (i.e. participation and social support systems) factors are seen as interacting both in symptom development and maintenance (24). In this perspective, all these factors are also viewed as potential targets for intervention, as opposed to just biomedical factors.

The literature regarding predictors of PPCS is still conflicting, but in accordance with the biopsychosocial model, commonly identified prognostic factors include female gender, age, previous history of psychiatric problems, premorbid migraine/headache, previous TBIs, presence of LOC and PTA, and a higher symptom load in the acute phase (15,25–28).

Patients with PPCS represent a heterogeneous population and there is still uncertainty as to what typically characterizes these individuals. A better characterization of the population with PPCS is therefore important for several reasons. Identifying patients at risk will help medical personnel in stratification of patients to early interventions. Several larger studies provide epidemiological descriptions of patients with mild and moderate TBI. However, there is still a paucity of data specifically describing patients that do not fully recover, and subsequently are not able to return to work. As most patients recover, prospective observational studies typically end up having very limited sample sizes for studying this population. We therefore lack critical knowledge about these patients, who are the ones that are typically referred to specialist clinics for treatment and rehabilitation (29).

This study describes the characteristics (demographic, premorbid, injury-related, work-related and self-reported symptoms) of a group of patients with PPCS who are sick-listed and treatment-seeking. All patients had post-concussion symptoms 8–12 weeks after mild-to-moderate TBI and had not been able to return fully to preinjury occupational levels. The main aim of the study was to describe socio-demographics, pre-, and injury-related characteristics, and investigate differences in post-injury symptom burden between patients with and without traumatic intracranial injury.

Methods

Study design

This study presents baseline data from patients enrolled in an ongoing RCT, which examines the effect of a combined cognitive and vocational intervention in patients with mild-to-moderate TBI, who have not returned to work 8–12 weeks post-injury due to post-concussive symptoms (ClinicalTrials.gov: NCT03092713). A detailed description of the RCT study design can be found in Howe et al. (30). The Regional Committee for Medical and Health Ethics in South-Eastern Norway has approved the study (2016/2038). In the current study, we explore the characteristics of the sample *before randomization* to treatment or control group.

Study setting

Patients were referred from the neurosurgical department at Oslo University Hospital (OUH), their general practitioner, or the municipalities' emergency departments, to follow-up at a specialized TBI-outpatient clinic at the Department of Physical Medicine and Rehabilitation (PMR), OUH, between July 2017 and April 2019. OUH is the Level I trauma referral center of southeast Norway. It has a population base of approximately 2.9 million and includes the city of Oslo with 693.000 inhabitants (31), thus providing a sample that is both rural and urban, with predominantly Caucasian background. Approximately 600 patients with TBI of all severities are referred to the outpatient clinic annually.

Inclusion criteria and study participants

Patients were considered eligible if they were aged between 18 and 60 years; had sustained a mild or moderate TBI in the previous 8–12 weeks; resided in Oslo or Akershus County; worked at least 50% at time of injury; and were sick listed 50% or more due to post-concussion symptoms at time of inclusion, as assessed by the Rivermead Post-Concussion Symptoms Questionnaire (32). Severity of TBI was defined using criteria from the American Congress of Rehabilitation Medicine (ACRM) (33); Glasgow Coma Scale (GCS) 10–15 (34), LOC lasting less than 24 hours and PTA lasting less than 7 days. Five hundred and ninety-two potential study participants were identified, of whom 432 were not eligible and five were not included for other reasons. The most common reason for not being eligible was too long time since injury (n = 138), age <18 or >60 (n = 81), sick leave percentage <50% (n = 50) or not working at the time of injury (n = 41). Thirty-nine patients declined participation. Due to ethical considerations, the reason why they chose not to participate was not established. This resulted in 116 patients with mild and moderate TBI being included in the RCT, and thus in the current analysis. Patients were categorized depending on whether or not they had evidence of acute traumatic intracranial abnormalities on CT or MRI images of the head. This categorization was performed regardless of injury severity (mild/moderate) based on ACRM criteria, and we only included abnormalities that were related to the most recent trauma. According to Scandinavian guidelines, patients with mTBI and intracranial abnormalities should be considered, and treated, as having a moderate TBI (35). Exclusion criteria were a history of severe neurological or psychiatric illness, active substance abuse, or the inability to speak and read Norwegian.

Procedures

Potential participants were identified during follow-up at the outpatient clinic at OUH where a PMR physician provided them with oral and written information about the study and retrieved written consent. Alternatively, they were informed about the study, had a period of deliberation, and later consented via telephone contact. All consenting participants were invited to a baseline assessment 8–12 weeks after injury.

Measures

The assessment consisted of a clinical interview regarding preinjury, injury-, and work-related information,

questionnaires concerning post-concussion and emotional symptoms, and a neuropsychological screening.

Preinjury and work-related characteristics

Preinjury information was collected using a semi-structured interview where the following variables were recorded: age, sex, level of education, relationship status, number of children living at home, previous illnesses and TBIs, employment status and duration, type of occupation, and status of sick listing at the time of inclusion. Occupation type was divided into white collar (non-manual labor) or blue collar (manual labor). Employment status included full- or part-time position.

Injury-related measures

Results of CT/MRI caput and whether the participants had been hospitalized were retrieved from medical records. A medical doctor estimated Abbreviated Injury Scale-Head (AIS-H) (36) based on injury-related information from medical records according to the following definition: 1 – minor (no treatment needed), 2 – moderate (outpatient treatment), 3 – serious (non-ICU admission), 4 – severe (ICU observation and/or basic treatment), 5 – critical (requires intubation, mechanical ventilation, or vasopressors for blood support), 6 – unsurvivable. The remaining injury-related variables were collected from medical records and supplemented with information from the patient interview, if needed. These included mechanism of injury (falls, traffic accidents, sports, violence, or exposure to inanimate objects), level of consciousness shortly after the injury measured by GCS, duration of LOC and PTA, and whether it was a work-related injury. Information regarding alcohol and drug use at the time of injury was collected from medical records based on results of ethanol blood tests in the emergency department, physician verification following patient examination, or otherwise relied on self-reported information in the interviews.

Measures of post-injury symptoms and level of functioning

Post-concussion symptoms were measured with The Rivermead Post-Concussion Symptoms Questionnaire (RPQ) (32), where patients are asked to rate 16 post-concussion symptoms on a five-point Likert scale from 0 to 4, where 0 = "Not experienced," 1 = "No longer a problem," 2 = "Mild problem," 3 = "Moderate problem" and 4 = "Severe problem." The mean was calculated by adding all scores of 2–4 and dividing by number of items. The total mean is reported, along with the percentage of patients who scored ≥3 (indicating a moderate or severe problem) on single items.

Fatigue and sleep

Fatigue was measured using the Fatigue Severity Scale (FSS) (37), where patients score perceived fatigue during the last 2 weeks on 9 items with a 5 level Likert scale with higher scores indicating higher levels of fatigue. The percentage of patients reporting a score corresponding to moderate or severe fatigue are reported (i.e. ≥4) (38).

Insomnia was measured with the 7 – item Insomnia Severity Index (ISI) (39) that has a 5-point scale ranging from 0 ("none") to 4 ("very") which gives a total of 0–28 points with higher scores indicating more severe perceived insomnia. The established cut-off score is 8 points. Percentage of patients scoring above the cut-off is reported.

Emotional symptoms

Patient Health Questionnaire-9 (PHQ-9) (40) measured depressive symptoms in the sample with nine items that are scored from 0 ("not at all") to 3 ("nearly every day"). Percentage with a total score ≥10, indicating moderate to severe depressive symptoms is reported.

Generalized anxiety was measured using Generalized Anxiety Disorder-7 (GAD-7) (41) that has seven items, which are scored from 0 ("not at all") to 3 ("nearly every day"). A score ≥10 indicates moderate to severe generalized anxiety symptoms. The percentage of the sample reporting a sum of 10 or higher is reported.

The Posttraumatic Symptom Scale-10 (PTSS-10) (42) was used to measure post-traumatic symptomatology. It is a 10-item scale where the patients score on a Likert scale from 1 ("not at all/never") to 7 ("very often"). The percentage of patients reporting scores of 35 or more, corresponding to the clinical cutoff, is reported.

In this study, the internal consistency of the PHQ-9, GAD-7, and PTSS-10 was measured with Cronbach's alpha and was found to be good (Cronbach's α = 0.81, 0.88, and 0.86, respectively).

Health-related quality of life

The Quality of Life after Brain Injury Overall Scale (QOLIBRI-OS) (43) and EuroQol visual analog scale (EQ VAS) (44) were used to measure health-related quality of life (HRQoL). The QOLIBRI-OS consists of six items that are scored on a scale from 1 to 5, where 1 = "not at all satisfied", and 5 = "very satisfied." The cutoff for decreased quality of life on QOLIBRI-OS corresponds to a score below 52 (45). The mean score and proportional scoring below the cutoff is reported. With EQ VAS, the patients report their overall current health on a vertical visual analog scale from 0 ("the worst health you can imagine") to 100 ("the best health you can imagine"). The overall mean score is reported as well as the percentage of the sample scoring below cutoff (i.e. <84) from a population, which is similar in age and socioeconomic status, but generally healthy (46).

Cognitive function

The Cognitive Failures Questionnaire (CFQ) (47) was used to document perceived frequency of experiencing cognitive failure. There are 25 items rated from 0 ("never") to 4 ("very often") on a Likert scale. The overall mean (SD) is reported.

In addition, the patients underwent a neuropsychological screening. An IQ estimate was derived from the following four subtests of the Wechsler Adult Intelligence Scale – Fourth Edition (WAIS-IV) (48): Matrix Reasoning, Block Design, Vocabulary, Similarities. Verbal learning and memory were measured with the California Verbal Learning Test-Second Edition (CVLT-II), including measures of total learning (trials

1–5), short- and long delay-free recall (49). Prospective memory was screened using Memory for Intentions Screening Test (MIST) (50). Processing speed and executive function were measured using the Color Word Interference Test (CWIT) and the Trail Making Test (TMT) from the Delis–Kaplan Executive Function System (D-KEFS) (51), Coding from the WAIS-IV (48) and Ruff 2 and 7 Selective Attention Test (52). Validity was assessed using the Forced Choice Recognition index from CVLT-II (49). Standardized scores are reported. The results were considered within normal range if the score was ±1 SD from the mean in the normative sample.

Statistical analysis

All analyses were performed using IBM SPSS Statistics for Windows v. 25 (53) or Stata v. 16 (54). Descriptive analyses were performed for preinjury-, injury-related and post-injury characteristics, reporting proportions (%), number (n), and using mean (SD) when variables were normally distributed, and otherwise median (IQR). Patients lacking cerebral neuroimaging were excluded from the analysis that compared patients with and without traumatic intracranial injuries. Two-sample t-tests were applied for normally distributed variables and Mann–Whitney U or Chi-squared test for skewed data, for continuous and categorical variables, respectively. Further, the two patient groups were entered as an explanatory variable and analyzed against the dependent variables representing symptom burden. Potentially confounding variables (status of intracranial abnormality, previous mTBI, and level of education) were chosen from the literature and explored with multiple linear regression analyses, where we tested the scores that significantly differed between the groups on t-test or Mann–Whitney U-test. The necessary assumptions, including multicollinearity, were examined before conducting the regression analyses. To check for internal validity, sensitivity analyses were performed using the models run with 1,000 bootstrap samples. Significance level was set to $p < .05$.

Results

Sociodemographic characteristics

The patients had a mean age of 42 years (SD 9.8), 60% were women, and mean years of education were 16 (SD 2.5). Sixty-six percent were married or cohabitants and 51% had one or more children living in the household (See Table 1).

The patients predominantly worked full time (89%) and had permanent positions (91%) in white-collar occupations (89%). The median duration of employment at current workplace was 4.25 years (IQR 9.25 years). At inclusion, 81% of the patients were sick listed between 80% and 100%.

Self-reported premorbid conditions

The sample reported a history of the following pre-morbid conditions: anxiety 5%, depression 15%, migraine/headache 20%, cardiovascular disease 10%, musculoskeletal disorder 15%, gastrointestinal disorder 13%, ADHD 0.9%, and dyslexia 6%. Forty-three percent reported that they had previously suffered from at least one mTBI, of which 16% reported sustaining two or more previous mTBIs.

Injury-related factors

Of the 116 included patients, 94% were classified as having a mild TBI and 6% had a moderate TBI. The median GCS score was 15 (IQR 0). The mean AIS head score was 1.8 (SD .9), approaching a moderate level of injury. Forty-six percent sustained additional injuries in other body regions than the head. The most common were injuries to the face (15%), upper limbs (13%), lower limbs (11%), or neck (11%).

The most common cause of injury was falls, followed by traffic accidents, exposure to inanimate objects, sports, and violence. Alcohol intoxication at the time of injury was found in 15% of the patients. Twenty-two percent of the patients were admitted to a hospital, with an average length of stay of 1.4 days (SD 3.8).

Evidence of intracranial traumatic abnormalities on CT/MRI caput was seen in 23% of the patients, with one-third of the abnormalities being traumatic subarachnoid hemorrhage.

Post-concussion symptoms

The overall mean score on the RPQ was 28 (SD 11), indicating moderate to severe post-concussion symptoms. Fatigue (75%), headache (64%), and noise sensitivity (54%) were most frequently reported as moderate or severe problems on the somatic subscale of RPQ (cutoff ≥3). The most frequently reported emotional symptoms (cutoff ≥3) were feeling frustrated or impatient (51%) and depressed or tearful (29%). Poor concentration (48%) and taking longer to think (42%) were the most frequently reported moderate or severe cognitive problems (cutoff ≥3).

Fatigue and sleep

Moderate or severe fatigue (38) was reported by 78% of the patients on FSS, and 71% (n = 77/108) reported any (subthreshold to severe) degree of insomnia on the ISI (39).

Emotional symptoms

Forty-three percent of the patients reported moderate-to-severe depressive symptoms on PHQ-9. Twenty percent reported moderate-to-severe anxiety symptoms on GAD-7, and 20% reported scores above the clinical cutoff value (>35) on PTSS-10.

Health-related quality of life

Results from QOLIBRI-OS (45) showed mean scores of 45.7 (SD 22) with 58% (n = 67/115) of the individual scores corresponding to decreased HRQoL (score < 52). Mean score on the EQ VAS was 54.1 (SD 18) with 97% (n = 111/114) reporting decreased HRQoL when comparing to a healthy Swedish population, in the same age range, who scored a mean of 84 (46).

Self-reported and performance-based cognitive function

The total mean on the CFQ was 39 (SD 15), which is comparable to healthy controls in other studies (60,6263). The mean IQ score for the sample was 111 (SD 14). Neuropsychological

Table 1. Demographic, preinjury and injury-related characteristics 8–12 weeks post-injury.

Variable	n	With intracranial abnormalities n(%)	Normal CT/ MRI n(%)	Total sample n (%)
Preinjury factors				
Age, mean (SD)	116	45 (9)	42 (9)	42 (9.8)
Sex, female	116	12 (43)	52 (55)	69 (56)
Education, mean (SD)	116	15 (3)	16 (2)	16 (2.5)
Married/Cohabitant	116	20 (74)	50 (57)	77 (58)
Child(ren) in household	116	14 (51)	40 (49)	59 (50)
Self-reported history of				
Anxiety	116	2 (6)	4 (4)	6 (4)
Depression	116	4 (14)	12 (14)	17 (14)
Migraine/Headache	116	7 (25)	14 (17)	23 (19)
Previous concussion	115	6 (21)	38 (47)	49 (42)
≥2 previous concussions		0 (0)	16 (19)	18 (15)
Other somatic diseases	116	17 (57)	42 (52)	57 (48)
Injury-related factors				
Cause of injury	115			
Falls		18 (59)	27 (33)	49 (42)
Traffic accidents		4 (14)	17 (20)	23 (19)
Sports		3 (10)	10 (12)	14 (11)
Violence		2 (6)	4 (4)	6 (4)
Exposure to inanemate objects		0 (0)	21 (25)	23 (19)
CT/MRI findings, traumatic		27 (100)	80 (100)	27 (22)
Injury severity by ACRM criteria	116			
Mild		21 (78)	79 (99)	109 (94)
Moderate		6 (21)	1 (1)	7 (5)
Loss of consciousness (LOC)	115			
< 30 min		15 (60)	21 (25)	37 (31)
30 min – 24 hours		3 (10)	0 (0)	3 (3)
No LOC		5 (18)	49 (61)	61 (52)
Not registered		3 (10)	10 (12)	14 (11)
Post-traumatic amnesia (PTA)	115			
<1 hour		10 (36)	23 (28)	35 (29)
1 hour – 24 hours		10 (36)	6 (7)	16 (13)
25 hours – 7 days		2 (6)	0 (0)	2 (2)
No PTA		5 (18)	39 (48)	51 (43)
Not registered		0 (0)	11 (13)	11 (9)
Injured at workplace	114	3 (10)	11 (13)	16 (13)
Under the influence of alcohol at time of injury	116	8 (29)	9 (10)	17 (14)

test measures of memory, learning, attention, mental speed, and executive functioning provided mean scores within the normal range at the group level (see Table 2). All participants scored 16/16 on the CVLT-II forced recognition test, indicating valid test results.

Comparison of patients with and without traumatic intracranial injury

There were significant differences between patients with and without traumatic intracranial injury in total scores on the RPQ ($t(105) = 2.7$, $p < .01$), PHQ-9 ($t(102) = 3.06$, $p < .01$), PTSS-10 ($U = 649$, $p = .01$), ISI ($U = 688$, $p = .04$), EQ VAS ($t(103) = -2.18$, $p = .03$) and QOLIBRI-OS ($t(100) = -3.9$, $p < .01$). The difference was consistent in the direction of patients with a negative CT/MRI reporting higher symptom burden than those with intracranial abnormalities. There were no significant differences between the groups with respect to self-reported symptoms of anxiety, fatigue, or cognitive failures.

Regarding neuropsychological functioning, patients with intracranial abnormalities performed significantly worse than those without on verbal short delay-free recall on the CVLT-II ($t(104) = 2.3$, $p = .02$). See Table 3.

Patients with and without intracranial abnormalities were compared regarding pre-injury variables to exclude potential confounders. History of previous mTBI (X^2 (1, N = 115) = 4.3, $p = .03$) and level of education ($U = 694$, $p < .01$) were significantly different between the groups. Patients without intracranial abnormalities reported a higher percentage of previous mTBIs (48% vs. 22%) and a higher level of education (16 vs. 15 years). The groups did not differ with respect to sex, age, or previous depression, anxiety, or migraine/headache.

Status of intracranial abnormality remained the only significant explanatory variable (when running multiple linear regression analyses with status of intracranial abnormality, previous mTBI, and level of education inserted as explanatory

Table 2. Results of neuropsychological screening.

Neuropsychological tests	Standardized score Mean (SD)	Neuropsychological tests	Standardized score Mean (SD)
Psychomotor speed		**Executive functions**	
TMT[a] 1, 2 and 3	11 (3)	TMT[a] 4	10 (2)
TMT[a] 5	12 (2)	CWIT[2] 3 and 4	11 (3)
CWIT[2] 1	9 (3)		
CWIT[2] 2	10 (3)		
Coding[3]	11 (3)		
Attention and concentration		**Verbal abilities**	
Ruff 2 & 7 Total speed[4]	58 (11)	Vocabulary[3]	10 (2)
Ruff 2 & 7 Total accuracy[4]	48 (7)	Similarities[3]	12 (3)
Learning and memory		**Visuospatial abilities**	
CVLT-II[5] Total learning	60 (3)	Matrix Reasoning[3]	13 (3)
CVLT-II[5] Short delay free recall	56 (9)	Block Design[3]	11 (2)
CVLT-II[5] Long delay free recall	56 (9)		
Prospective memory		**General ability index (GAI)[3]**	111 (13)
MIST[6] Total PMT	67 (28)		

[a]Trail Making Test (TMT) from the Delis–Kaplan Executive Function System (D-KEFS), [2]Color Word Interference Test, [3]Wechler Adult Intelligence Scale 4th Edition, [4]The Ruff 2 & 7 Selective Attention Test, [5]Verbal Learning Test – II, [6]Memory for Intentions Test – Prospective Memory Test, [I]T-test.

Table 3. Multiple linear regression analyses.

Variabel	F	p	R^2	Coeff.	Beta	SE	t	P>|t|	95% CI
RPQ[1]	(3, 103) = 3.16	**0.028**	0.08						
Radiological Findings (Yes)				−7.42	−0.3	2.56	−2.90	**0.005**	−12.5, −2.35
Previous mTBI[4] (Yes)				−3.06	−0.14	2.14	−1.43	0.156	−7.29, 1.18
Years of education				−0.15	−0.3	0.45	−0.33	0.742	−1.04, 0.74
PHQ-9[2]	(3, 100) = 3.22	**0.026**	0.08						
Radiological Findings (Yes)				−3.41	−0.31	1.11	−3.06	**0.003**	−5.62, −1.2
Previous mTBI[4] (Yes)				−0.52	−0.06	0.93	−0.56	0.574	−2.37, 1.32
Years of education				−0.08	−0.04	0.2	−0.42	0.673	−0.47, 0.31
PTSS-10[3]	(3, 99) = 3.47	**0.019**	0.1						
Radiological Findings (Yes)				−7.18	−0.32	2.32	−3.10	**0.003**	−11.8, −2.58
Previous mTBI[4] (Yes)				−3.08	−0.16	1.95	−1.58	0.117	−6.95, 0.79
Years of education				−0.41	−0.1	0.41	−1.00	0.321	−1.22, 0.41
Insomnia Severity Index	(3, 95) = 1.74	0.163	0.05						
Radiological Findings (Yes)				−3.50	−0.25	1.58	−2.21	0.029	−6.65, −0.36
Previous mTBI[4] (Yes)				−0.1	−0.01	1.33	−0.07	0.942	−2.74. 2.55
Years of education				−0.25	−0.1	0.28	−0.91	0.366	−0.8, 0.3
QOLIBRI[5]	(3, 98) = 5.82	**0.001**	0.15						
Radiological Findings (Yes)				16.5	0.32	5.08	3.25	**0.002**	6.4, 26.54
Previous mTBI[4] (Yes)				−4.81	−0.1	4.16	−1.16	0.251	−13.6, 3.45
Years of education				0.91	−0.1	0.9	−1.02	0.309	−2.69, 0.86
EQ VAS[6]	(3, 101) = 1.64	0.18	0.05						
Radiological Findings (Yes)				8.27	0.2	4.4	1.86	0.066	−0.5, 17.1
Previous mTBI[4] (Yes)				−1.80	−0.05	3.73	−0.48	0.630	−9.2, 5.6
Years of education				−0.03	−0.004	0.78	−0.04	0.969	−1.6, 1.5

[1]Rivermead Post-concussion Questionnaire, [2]Patient Health Questionnaire-9, [3]Post-traumatic Symptoms Scale, [4]Mild Traumatic Brain Injury, [5]Quality of Life after Brain Injury, [6]EuroQol-5D Visual Analog Scale

variables) with respect to post-concussion symptoms (See Figure 1), depressive symptoms, post-traumatic stress symptoms, and HRQoL (QOLIBRI-OS, see Figure 2), still reflecting a significantly higher symptom burden in the group without intracranial abnormalities (see Table 4). The previous differences regarding sleep and HRQoL (EQ VAS) on the other hand, were no longer significant.

Likewise, we inserted the score for CVLT-II short delay-free recall as a dependent variable in a multiple linear regression analysis and status of intracranial abnormality, history of previous mTBI, and level of education as explanatory variables. In this case, the status of intracranial abnormality was no longer significant ($\beta = -.08$, $p = .4$).

Discussion

Here, we provide comprehensive data describing biopsychosocial characteristics in a well-defined subgroup of treatment-seeking patients with mild-to-moderate TBI who experience PPCS and have not been able to return to pre-injury work levels 8–12 weeks after injury. We also investigated whether patient characteristics differed for patients with and without traumatic intracranial injury. Patients with normal CT/MRI results reported higher overall symptom burden, while patients with intracranial abnormalities had worse memory function.

Patients in this study were predominantly female white-collar workers in full-time positions. Women are overrepresented in our sample. This is in line with other studies that also show that women tend to report more symptoms and seek healthcare services more often than men (64,65). Further, the sample was recruited from an urban population (Oslo) which is highly educated (56). Most patients were sick listed 80–100% and reported high somatic (fatigue, headache, noise sensitivity), emotional (feeling frustrated, depressed, anxious), and cognitive (poor concentration, taking longer to think) symptom burden 8–12 weeks after injury.

Patients with normal CT/MRI results reported higher levels of post-concussion symptoms, symptoms of depression and post-traumatic stress, and decreased health-related quality of life than patients with intracranial abnormalities. The fact that this absence of intracranial abnormality was associated with a higher symptom burden, and that the difference was still present when variables that systematically differed between the groups (i.e. previous mTBI and level of education) were controlled for, is somewhat paradoxical. In contrast, there was a difference in the opposite direction regarding neurocognitive function, as patients with intracranial abnormalities performed worse on a test of verbal memory compared to patients without, in univariate analysis.

Patients with normal CT/MRI results reporting more symptoms are contrary to findings in large-scale epidemiological studies (5,61). For example, Voormolen et al. (5) examined 1302 patients three months after complicated and uncomplicated mTBI and found that the presence of intracranial abnormalities on CT was a (weak) indicator for the occurrence of post-concussion symptoms. A study based on the TRACK-TBI data set (61) demonstrated the clinical relevance of early abnormal CT/MRI results after mTBI, with one or more brain contusion, or ≥4 foci of hemorrhagic axonal injury on MRI being associated with poorer 3-months outcome of global function as assessed with the Glasgow Outcome Scale – Extended. It is not completely clear why patients without intracranial abnormalities reported a higher symptom burden in the current sample, but there are a number of possible explanations. Firstly, there might be a subject expectation bias where patients with a normal CT/MRI expect a quick

Table 4. Neuropsychological screening of patients with and without intracranial abnormalities, standardized scores.

Neuropsychological test	p-value	Normal CT/ MRI, median (IQR)	With intracranial abnormalities, median (IQR)	U
Psychomotor speed				
Trail making test – 1	0.92	12 (3)	12 (63)	1027
Trail making test – 2	0.45	12 (63)	12 (63)	951
Trail making test – 3	0.32	12 (3)	12 (2)	848
Trail making test – 5	0.53	13 (1)	13 (2)	820
CWIT[a] – 1	0.72	10 (63)	9 (3)	904
CWIT[a] – 2	0.77	11 (3)	11 (3)	914
WAIS-IV[2] Coding	0.45	11 (63)	11 (2)	926
Attention and concentration				
Ruff 2 & 7[3] Total speed , mean (SD)	0.24	58 (10)	55 (11)	t(96) = 1.2
Ruff 2 & 7[3] Total accuracy	0.61	49.5 (10)	49 (8)	898
Learning and memory				
CVLT – II[4] Total learning , mean (SD)	0.06	61 (11)	55 (14)	t (105) = 1.9
CVLT – II[4] Short Delay Free Recall	**0.04**	60 (14)	55 (19)	782
CVLT – II[4] Long Delay Free Recall	0.06	60 (14)	55 (14)	823
Prospective memory				
MIST Total PMT[5]	0.71	69 (62)	73 (32)	953
Executive functions				
Trail making test – 4	0.19	11 (3)	11 (63)	863
CWIT[a] – 3	0.01	11 (3)	12.5 (3)	631
CWIT[a] – 4	0.07	11 (63)	12 (3)	699
Verbal abilities				
WAIS-IV[2] Vocabulary	0.17	10 (3)	10 (3)	857
WAIS-IV[2] Similarities	0.60	12 (4)	11 (4)	995
Visuospatial abilities				
WAIS-IV[2] Matrix Reasoning	0.87	13 (5.5)	13 (4)	1058
WAIS-IV[2] Block Design	0.53	11 (3.5)	11 (3)	994
General Ability Index (GAI)	0.41	114 (16.5)	112 (23)	916

[a]Color Word Interference Test, [2]Wechler Adult Intelligence Scale 4th Edition, [3]The Ruff 2 & 7 Selective Attention Test, [4]Verbal Learning Test – II, [5]Memory for Intentions Test – Prospective Memory Test, [t]T-test.

recovery, while patients with intracranial abnormalities accept a protracted recuperation, both relying on what they were told by healthcare professionals in the acute phase. The expectation of a quick recovery, and the following disappointment when this does not transpire, might have rendered the patients without intracranial abnormalities more impatient and frustrated with protracted symptoms. Consequently, they might have perceived their condition as relatively worse considering this, resulting in negative symptom development, and higher self-reported symptom levels (57,66).

Secondly, more patients without intracranial abnormalities reported previous mTBIs, and higher levels of depressive and post-traumatic stress symptoms. Experience of previous mTBIs may modify patient expectations (67), and support misattribution of nonspecific symptoms. Studies have indeed suggested that somatization may contribute to persistent symptoms after mTBI (55,58). Consequently, the burden of symptoms may be higher due to a combination of the post-concussion symptoms and somatization (57). However, the symptom burden in this sample was still high when controlling for previous patient-reported mTBIs and it is uncertain whether, and to what extent, potential somatization might have occurred in this study.

Thirdly, patients who are admitted to the neurosurgical department at OUH and have intracranial abnormalities are generally referred to follow-up at the specialized TBI outpatient clinic, from which the study participants were recruited six to eight weeks later, regardless of symptom burden. In comparison, patients with a normal CT/MRI are commonly referred to follow-up by their GP due to experiencing PPCS and decreased functional level. Therefore, selection bias resulting from differential referral practices in patients with and without intracranial injuries cannot be ruled out. On the other hand, all patients in this study had a consultation with a PMR physician and were found to be eligible for the study, which requires confirmation of PPCS at inclusion. Thus, the study did not include patients with intracranial abnormalities that did not experience PPCS. Regarding symptom burden, the fact that we included patients from the specialized outpatient clinic 8–12 weeks post-injury may explain why the results are not in line with those found in the epidemiological CENTER-TBI and TRACK-TBI studies (5,61). In these studies, all patients were included in the acute phase (and therefore regardless of symptom burden at 8–12 weeks). The sample with TBI that is presented in this study is therefore not expected to be representative of the population with mild-to-moderate TBI in general, but rather provides important insight regarding the subgroup of patients that develop PPCS and therefore seek treatment several weeks after the injury. These are exactly the patients that will present themselves to rehabilitations centers, and the current study represents one of very few studies examining the characteristics of this specific subgroup that runs a high risk of symptom chronicity.

A history of psychiatric illness is considered a risk factor in developing PPCS after mild-to-moderate TBI (28,59,68). Iverson et al. (15) performed a systematic review regarding predictors of clinical recovery from concussion including 101 full-text articles and 13 conference abstracts. The majority of included papers found a greater risk of persistent symptoms in patients with a pre-morbid psychiatric history. However, the review also confirmed that, as with other predictors in this field, the literature is mixed. In the current sample, the self-reported history of previous depression and anxiety did not exceed the lifetime prevalence in the Norwegian population (69). However, it cannot be ruled out that the patients in the current study may have underreported their previous psychiatric history, and the lack of predictive value of pre-morbid emotional problems should be interpreted with caution.

Patients who have a potential secondary financially gain may report higher level of disability (70). The rate of potential insurance claims in this sample is unknown. However, 16 patients suffered an occupational injury, which in Norway entails a more comprehensive welfare provision. These patients did not report more symptoms than the rest of the sample. Further, all patients receive 100% compensation of salary lost due to illness the first year after injury in workers'

compensation by the Norwegian welfare system. In light of this, we do not believe this was a major factor influencing the self-reported level of symptoms.

Almost half of the patients reported having previously sustained a mTBI, of whom as many as 16% reported sustaining several mTBIs in the past. This is another claimed predictor of PPCS (71,72), and the proportion of patients reporting at least one previous TBI does seem quite high in the current sample. However, having sustained previous mTBIs was not significantly associated with reporting a higher symptom burden in this study. Interestingly, Iverson et al. (15) likewise pointed out that most studies in their systematic review did not find an association between previous concussions and worse outcome. The existing literature is still conflicting on this matter, and more knowledge is required in order to conclude.

Limitations

The inclusion criteria reflect that this study utilizes a sample recruited to an RCT examining the effect of an intervention on return to work after mild-to-moderate TBI. The inclusion criteria, including restrictions in age, work status, and the presence of PPCS 8–12 weeks post-injury, limit the generalizability of the results. However, the results do represent the working population of patients with mild-to-moderate TBI who seek treatment for PPCS, thus giving more precise information concerning the group of patients which are exactly those the rehabilitation facilities need to reach with treatment after the acute stage. Furthermore, the sample represents patients with a potential to resume their pre-injury occupation, with potential reduction of societal costs related to TBI.

Additionally, we excluded nine patients from the comparison of outcomes in patients with and without intracranial abnormalities, as they did not have CT/MRI assessment after the injury. These are presumably the patients with least severe injuries, and excluding them may have affected the results.

Beyond the data reported here, additional data regarding results of neuromuscular examination, and possible vestibular or neuro-optometric impairments would have been useful.

Lastly, the prevalence of depressive symptoms in the study was measured using PHQ-9. Some of the symptoms of PPCS and depression overlap (consequently, so do some items on RPQ and PHQ-9) to such an extent that the results concerning depressive symptoms in this patient group need to be interpreted with a fair amount of caution, as scores on PHQ-9 may have been inflated by the PPCS. An overlap between symptoms of PPCS and emotional distress may also have affected the scores of anxiety symptoms (GAD-7) and post-traumatic stress symptoms (PTSS-10). The fact that premorbid conditions were based on self-report may have resulted in some bias colored by the current situation.

Clinical implications

This study examined the characteristics of treatment-seeking patients with PPCS after mild-to-moderate TBI 8–12 weeks post-injury. The results indicate that patients with a normal CT/MRI may have a symptom burden equal to, or even superior to, that of patients with intracranial abnormalities. Medical factors such as injury severity and radiological findings should therefore not be the sole ground for prioritizing rehabilitation services. Increased knowledge regarding patient's demographic and preinjury characteristic, combined with the level of symptoms reported by patients with and without intracranial abnormalities after injury, may support healthcare workers in better understanding the subgroup with protracted recovery and help predict which patients with mild-to-moderate TBI are at risk of experiencing PPCS. This is a prerequisite for the development of efficient and individualized treatment plans.

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Original article

Cognitive and vocational rehabilitation after mild-to-moderate traumatic brain injury: A randomised controlled trial

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ABSTRACT

Background: Returning to work is often a primary rehabilitation goal after traumatic brain injury (TBI). However, the evidence base for treatment options regarding return to work (RTW) and stable work maintenance remains scarce.
Objective: This study aimed to examine the effect of a combined cognitive and vocational intervention on work-related outcomes after mild-to-moderate TBI.
Methods: In this study, we compared 6 months of a combined compensatory cognitive training and supported employment (CCT-SE) intervention with 6 months of treatment as usual (TAU) in a randomised controlled trial to examine the effect on time to RTW, work percentage, hours worked per week and work stability. Eligible patients were those with mild-to-moderate TBI who were employed $\geq$ 50% at the time of injury, 18 to 60 years old and sick-listed $\geq$ 50% at 8 to 12 weeks after injury due to post-concussion symptoms, assessed by the Rivermead Post Concussion Symptoms Questionnaire. Both treatments were provided at the outpatient TBI department at Oslo University Hospital, and follow-ups were conducted at 3, 6 and 12 months after inclusion.
Results: We included 116 individuals, 60 randomised to CCT-SE and 56 to TAU. The groups did not differ in characteristics at the 12-month follow-up. Overall, a high proportion had returned to work at 12 months (CCT-SE, 90%; TAU, 84%, $P = 0.40$), and all except 3 were stably employed after the RTW. However, a significantly higher proportion of participants in the CCT-SE than TAU group had returned to stable employment at 3 months (81% vs. 60%, $P = 0.02$).
Conclusion: These results suggest that the CCT-SE intervention might help patients with mild-to-moderate TBI who are still sick-listed 8 to 12 weeks after injury in an earlier return to stable employment. However, the results should be replicated and a cost-benefit analysis performed before concluding.

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1. Introduction

Approximately 50 million people globally sustain a traumatic brain injury (TBI) each year [1]. Of these, roughly 90% are classified as mild TBI (mTBI) [2], with about 15% to 20% experiencing symptoms for more than 3 months [3]. Physical, cognitive and emotional symptoms affect patients, their families and their ability to remain competitively employed [4,5].

An estimated 18% to 60% of patients had a return to work (RTW) [6] after TBI. The vast variability of RTW rates is due to the inclusion of different TBI severities, follow-up times, sample sizes and definitions of RTW. One study of patients with mTBI without structured rehabilitation reported an RTW rate of 62% at 1 year after injury [7]. Several factors complicate the process of RTW. Some of the factors most often assessed are post-concussion symptoms, demographic factors, pre-injury occupational status, previous psychiatric history and injury severity [4,5].

The same factors that complicate RTW after TBI may also affect the ability to retain a stable work attachment. Concerning work stability, studies including individuals with intracranial injuries of all severity levels have reported that 34% to 55% found stable work after TBI [8,9]. With few studies reporting work stability after TBI and an inconsistent method of defining work stability, there is a definite lack of data concerning work stability, particularly after mild-to-moderate TBI.

A systematic review from 2016 found strong evidence supporting work-directed interventions combined with education/coaching for improving RTW outcomes after acquired brain injury [10]. Other systematic reviews examined the effect of cognitive rehabilitation on RTW after TBI; one supported the treatment methods, with particular emphasis on compensatory strategies [4], but others found no evidence of effect [11,12].

The diverging results concerning the effect of cognitive rehabilitation on RTW has led to an increased focus on vocational rehabilitation interventions provided at the workplace. In 2015, a multicentre, randomised controlled trial (RCT) of 1193 participants found that work-focused cognitive behavioural therapy combined with individual job support improved RTW proportions to some extent in patients with common mental disorders [13]. Likewise, there is some preliminary evidence supporting the use of supported employment in vocational rehabilitation after TBI [14].

In 2015, Twamley et al. [15] published 1-year follow-up results from a pilot RCT combining compensatory cognitive rehabilitation and supported employment in veterans with a history of mTBI. They observed no group differences in the attainment of competitive work but some improvement regarding symptoms and quality of life. These results require replication in larger-scale studies using a civilian sample.

The current study incorporated this knowledge in an RCT using a combined cognitive and vocational intervention to assess the effect on RTW and work stability in patients after mild-to-moderate TBI. The 3- and 6-month interim results of this study have been published [16]. We hypothesized that the intervention would result in a higher proportion of patients returning to stable competitive employment by the 12-month follow-up in addition to having a higher work percentage and more work hours per week as compared with the control group.

2. Methods

2.1. Study design

The study is a prospective RCT. Eligible patients were recruited from a specialised TBI-rehabilitation outpatient clinic at Oslo University Hospital and were randomised to the combined compensatory cognitive training and supported employment (CCT-SE) intervention or treatment as usual (TAU). The results of a feasibility study have been published previously [17]. Physiatrists at the Department of Physical Medicine and Rehabilitation of the hospital informed eligible patients about the study, and all participants provided written consent. Baseline assessments were performed 8 to 12 weeks after injury, with follow-up assessments at 3, 6 and 12 months after inclusion. The Regional Committee for Medical and Health Ethics in South-East Norway approved the trial (2016/2038), and the protocol was registered at ClinicalTrials.gov (NCT03092713) [18]. This study follows the CONSORT statement [19] and the ethical principles of the Helsinki declaration.

2.2. Participants

Eligible participants had sustained a mild-to-moderate TBI 8 to 12 weeks previously, lived in Oslo or Akershus county (approximately 1.3 million inhabitants; one-fourth of the Norwegian population), were of working age (18–60 years), were employed $\geq$ 50% at the time of injury and were sick-listed $\geq$ 50% at inclusion due to post-concussion symptoms assessed with the Rivermead Post Concussion Symptoms Questionnaire (RPQ) [20]. They were deemed as having post-concussion symptoms if at least one symptom was rated as $\geq$ 2. Mean total RPQ score at baseline was 28 (range 5-54). Classification of mTBI involved using the American Congress of Rehabilitation Medicine criteria [21]. Mild-to-moderate TBI was defined as Glasgow Coma Scale ([22]) 10–15, loss of consciousness $<$ 24 hr and post-traumatic amnesia $<$ 7 days. Exclusion criteria included progressive neurological disease, ongoing substance abuse and/or inability to speak or write Norwegian.

2.3. Interventions

2.3.1. CCT-SE

Participants in the intervention group received a combination of compensatory cognitive training (CCT [23]) and supported employment (SE [24]). CCT is a 10-week, group-based, manualized intervention with weekly sessions of 2 hr provided by a clinical psychologist and a physician. CCT aimed at teaching the participants compensatory strategies to help manage post-concussion symptoms, specifically focusing on strategies to alleviate cognitive symptoms. Topics in the sessions included headache, fatigue, difficulties with sleep, concentration, memory and executive function.

The vocational part of the intervention was based on SE in which a "place-and-train" method is adapted [25]: participants were supported by an employment specialist in returning to their current jobs by working at their actual, competitive, workplace. This part of the intervention was delivered individually, for a maximum of 6 months per participant, and administered by the Department of Vocational Rehabilitation, Norwegian Labour and Welfare Administration. The employment specialists attended all sessions of one CCT group to improve the integration of concepts from the CCT into the RTW process.

Monthly meetings were held during the intervention period and were attended by the CCT interventionists, employment specialists and at least one senior researcher to ensure optimal trans-sectoral collaboration and a shared understanding of the individual participants.

2.3.2. TAU

The control group received TAU for a maximum of 6 months after inclusion. At Oslo University Hospital, TAU entails treatment and follow-up from a specialised multidisciplinary TBI team at the TBI outpatient department. The participants received a

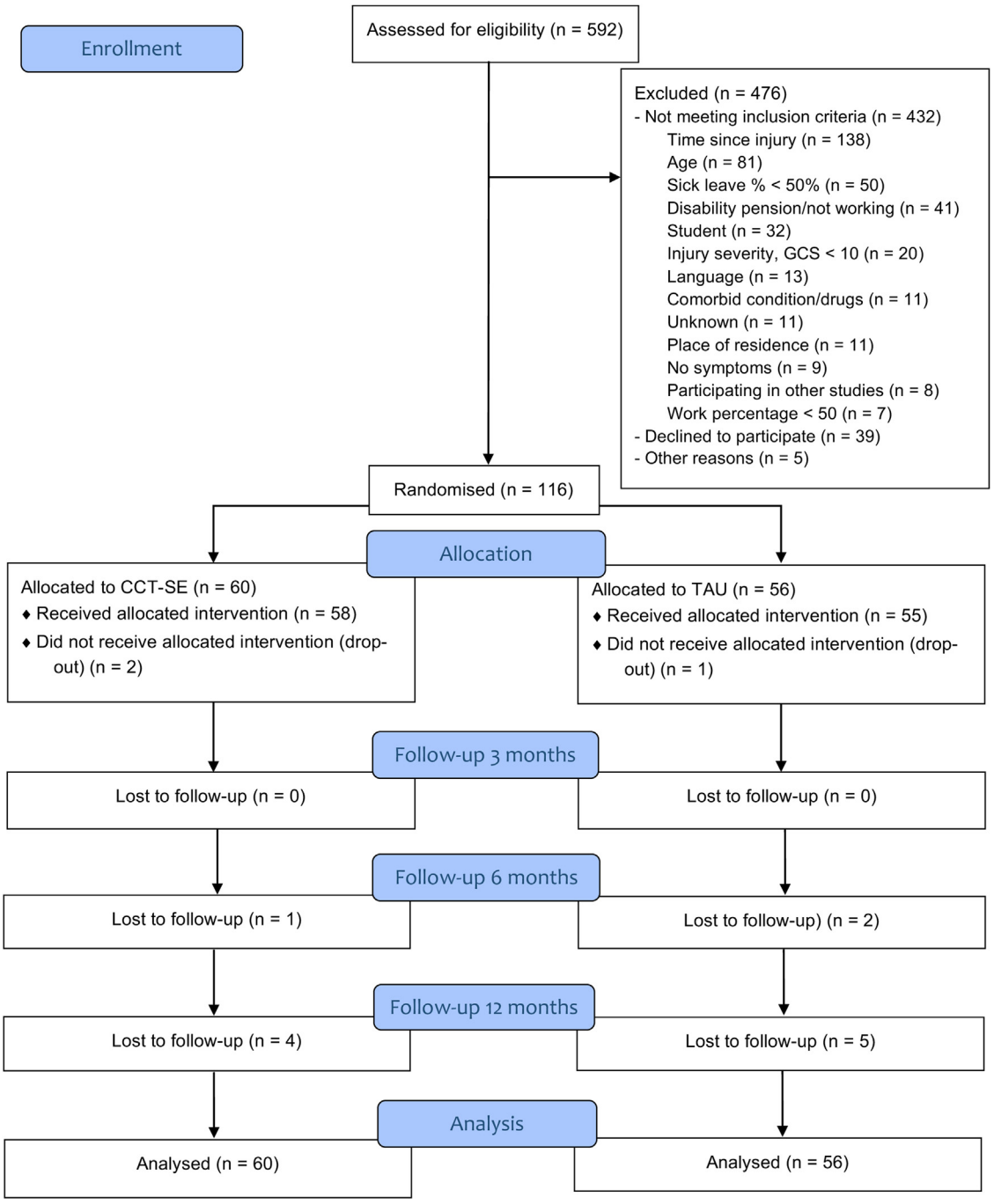

Fig. 1. Flow chart of inclusion and follow-up. CCT-SE, compensatory cognitive training and supported employment; GCS, Glasgow Coma Scale; TAU, treatment as usual.

consultation with a physiatrist and were referred to a physiatrist, physical therapist, occupational therapist, neuropsychologist or a social worker as required. Some participants were also offered participation in an educational group that focused on common problems after TBI and lasted for 2 hr per week for 4 weeks.

A detailed description of interventions in both treatment groups is in the study protocol [18].

2.4. Study outcomes

The primary outcome was self-reported work participation at the 12-month follow-up measured by the proportion of patients who had returned to work (0–100%). Furthermore, working hours per week (0–37.5 hr), work percentage (0–100%), work stability and self-reported time from injury to return to pre-injury work levels (in days) were secondary outcomes. Data were collected during appointments at the TBI outpatient clinic at inclusion and follow-up at 3, 6 and 12 months after inclusion. Working hours per week were calculated from work percentage [(work percentage * 37.5)/100]. To operationalise work stability, each participant was assigned a work category at each follow-up depending on their current work percentage (0%, $\leq$ 50%, 50–79% or 80–100%). Patients who moved to a lower work category from any follow-up to the next were classified as "unstably employed". Patients who maintained or improved their level of work participation were classified as "stably employed".

Table 1
Baseline characteristics of individuals with mild-to-moderate traumatic brain injury at 8 to 12 weeks post-injury by study group and for the total sample.

	n	CCT-SE (*n* = 60)	TAU (*n* = 56)	Total sample (*n* = 116)
Sociodemographic factors				
Age, years, median (range)	60/56	42 (24-60)	44 (27-60)	43 (24-60)
Sex, female	60/56	33 (55)	36 (64)	69 (59)
Education, years, mean (SD)	60/56	16 (2)	16 (3)	16 (3)
Married/cohabitating	60/56	43 (72)	34 (61)	77 (66)
Injury-related factors				
Cause of injury	60/56			
Falls		19 (31)	30 (54)	49 (42)
Traffic accidents		12 (20)	11 (20)	23 (20)
Sports		10 (17)	4 (7)	14 (12)
Violence		3 (5)	3 (5)	6 (5)
Exposure to inanimate objects		15 (25)	8 (14)	23 (20)
Unknown		1 (2)	0 (0)	1 (1)
CT/MRI findings, traumatic intracranial	60/56	11 (18)	16 (29)	27 (23)
Injury severity by ACRM criteria	60/56			
Mild		58 (97)	51 (91)	109 (94)
Moderate		2 (3)	5 (9)	7 (6)
Loss of consciousness (LOC)	60/56			
< 30 min		21 (35)	16 (29)	37 (32)
30 min–24 hr		1 (1)	2 (4)	3 (3)
No LOC		31 (52)	30 (53)	61 (52)
Not registered		7 (12)	8 (14)	15 (13)
Post-traumatic amnesia (PTA)	60/56			
< 1 hr		18 (30)	17 (31)	35 (30)
1–24 hr		7 (12)	9 (16)	16 (14)
25 hours–7 days		0 (0)	2 (4)	2 (2)
No PTA		25 (42)	26 (47)	51 (44)
Not registered		10 (16)	2 (2)	12 (10)
Work-related factors				
Occupation, white collar	60/56	53 (88)	50 (89)	103 (89)
Permanent position	60/56	56 (93)	49 (88)	105 (91)
Full-time position	60/56	55 (92)	48 (86)	103 (89)
Private sector	60/56	36 (60)	28 (50)	64 (55)
Duration of employment, months, median (range)	59/55	54 (0-408)	42 (0-480)	51 (0-480)

Data are *n* (%) unless otherwise indicated. CCT-SE: compensatory cognitive training and supported employment; TAU: treatment as usual.

2.5. Sample size

The sample size was calculated based on the proportions of RTW, aiming for a 33% absolute difference in RTW status between the 2 treatment groups at the 12-month follow-up [18]. From studies of occupational health care on RTW, we assumed that an odds ratio of 2.0 was the smallest clinical and societal relevant ratio [26]. This indicates that participants in the intervention group returned to work twice as quickly as participants in the control group. Assuming that two-thirds of the participants would achieve RTW during the follow-up, the sample size calculated with G*Power resulted in 110 patients, with 55 patients in each treatment group (α = 0.05, power level 80%). With an expected loss to follow-up of 15%, 125 participants were required.

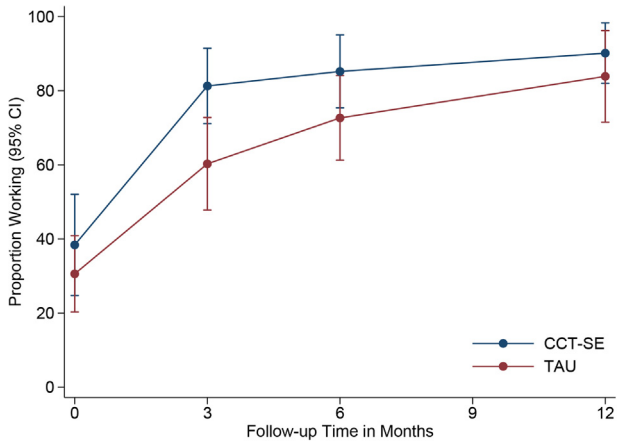

Fig. 2. Proportion of patients who returned to work after mild-to-moderate TBI. CCT-SE, compensatory cognitive training and supported employment; TAU, treatment as usual.

2.6. Randomisation and blinding

All included patients were randomised in a 1:1 ratio to one of the 2 treatment groups after baseline assessment. An independent statistician produced a computer-generated permuted block sequence with randomised block sizes (2, 4, 6 or 8) before starting inclusion. The researcher who was responsible for the allocation of patients to the treatment groups was not involved in patient recruitment or assessment. Outcome assessors were blinded to patient allocation. Blinding of rehabilitation specialists and patients was not possible.

2.7. Statistical analysis

Data analyses were performed with Stata 16. Descriptive methods were used to describe baseline and injury-related characteristics. A mixed-effects logistic regression was applied to evaluate the proportion of participants who had returned to work. Linear mixed-effects models were fitted to analyse working hours per week and work percentage between groups and within groups. Time and time-by-treatment interaction were fixed effects in all models, allowing a random intercept and random effect of time. The main effect of treatment was removed from the models to adjust for potential baseline differences. Differences between the groups in days to returning to pre-injury work levels were analysed by Kaplan–Meier curves and a log-rank test. The Kaplan–Meier curves were adjusted for the possible confounding effect of the presence of traumatic intracranial injury on CT/MRI or

whether the participants were working at baseline. Analyses were carried out on an intention-to-treat basis by an independent statistician who was blinded to group allocation. The level of significance was set at $P < 0.05$.

3. Results

Because of lower-than-expected loss to follow-up (6%) and the time limit of the study, the study inclusion, which began in July 2017, was terminated in April 2019 after inclusion of 121 patients (Fig. 1). Treatment in both groups was performed from August 2017 to November 2019. Five patients who initially consented to participate withdrew their consent before randomisation. Consequently, 116 participants were included in the analyses, 60 randomised to the CCT-SE group and 56 to TAU. Participants in the CCT-SE group were included at a mean (SD) of 77 (3) days after injury, and those in the TAU group at 68 (3) days after injury. Adherence to the CCT intervention was high. Three patients were absent from a total of 6 sessions, which resulted in a 99% attendance rate for the group [16].

Many included patients were female (59%), most were highly educated, and most had an mTBI (94%) (Table 1). The groups did not differ in baseline characteristics. A more comprehensive description of baseline characteristics is reported elsewhere, and a detailed description of the treatment received in both groups is reported in other publications from the project [16–18].

3.1. Proportion of patients returning to work

The proportion of patients returning to work at 3 months was higher in the CCT-SE than TAU group (mean 81% vs. 60%, mean between-group difference from baseline to 3 months 14%, 95% confidence interval [CI] 5; 32, $P = 0.02$) (Fig. 2). The control group had caught up with the treatment group by the 6- and 12-month follow-ups, and the mean between-group differences were no longer significant (−9% and −6%). In line with the finding that the RTW process mainly occurred within the first 3 months in the CCT-SE group, the within-group difference was significant only from baseline to 3 months for this group but was significant between all time points for the TAU group (see Table 2 for between- and within-group differences).

3.2. Working hours per week and work percentage

Linear mixed-effects models showed that the number of working hours per week and work percentage increased over time but did not significantly differ between groups.

3.3. Days until pre-injury work levels

Overall, 39 (65%) participants in the CCT-SE group and 30 (54%) in the TAU group returned to pre-injury work levels during the study period. Half of the patients were back to pre-injury levels within 365 days after injury in the CCT-SE group and by 415 days in the TAU group. The 50-day difference was not significant. The presence of traumatic intracranial abnormalities confounded the association between treatment groups and days before reaching pre-injury work levels and was adjusted for (Fig. 3). Adjustment for whether the patients were working at baseline did not affect this association (data not shown).

3.4. Work stability

Only 3 participants showed decreased work percentage category from 6 to 12 months, so most patients had stably

Table 2
Proportion working, work percentages and hours worked per week. Results from mixed-model analyses.

	Baseline	3 months	6 months	12 months	Within-group difference 0–3 months	Between-group difference 0–3 months	Within-group difference 3–6 months	Between-group difference 3–6 months	Within-group difference 6–12 months	Between-group difference 6–12 months
Proportion working										
CTT-SE	38 (25; 52)	81 (71; 92)	85 (75; 95)	90 (82; 98)	43 (29; 57) $P<0.001$	14 (-5; 32) $P=0.022$	4 (-6; 14) $P=0.434$	-9 (-24; 7) $P=0.164$	5 (-3; 13) $P=0.236$	-6 (-20; 7) $P=0.397$
TAU	31 (20; 41)	60 (48; 73)	73 (61; 84)	84 (72; 96)	29 (18; 42) $P<0.001$		13 (1; 24) $P<0.001$		11 (0; 22) $P<0.001$	
Work percentage										
CTT-SE	12 (6; 18)	34 (27; 40)	51 (43; 59)	77 (67; 88)	22 (14; 29) $P<0.001$	2 (-9; 12) $P=0.474$	17 (10; 24) $P<0.001$	0 (-11; 11) $P=0.518$	26 (19; 35) $P<0.001$	6 (-5; 18) $P=0.194$
TAU	10 (4; 16)	30 (23; 37)	47 (39; 55)	67 (56; 78)	20 (13; 28), $P<0.001$		17 (9; 24) $P<0.001$		20 (12; 29) $P<0.001$	
Hours worked per week										
CTT-SE	4.5 (2.3; 6.8)	12.6 (10.0; 15.2)	18.9 (15.9; 21.9)	28.9 (25.0; 32.8)	8.0 (5.3; 10.8) $P<0.001$	0.5 (-3.4; 4.5) $P=0.474$	6.4 (3.6; 9.1) $P<0.001$	0.1 (-3.9; 4.1) $P=0.518$	10.0 (7.0; 12.9) $P<0.001$	2.3 (-2.0; 6.6) $P=0.194$
TAU	3.7 (1.3; 6.0)	11.2 (8.6; 13.9)	17.5 (14.4; 20.6)	25.1 (21.1; 29.2)	7.5 (4.7; 10.4) $P<0.001$		6.3 (3.4; 9.2) $P<0.001$		7.6 (4.5; 10.7) $P<0.001$	

Data are mean (95% confidence interval). CCT-SE: compensatory cognitive training and supported employment; TAU: treatment as usual.

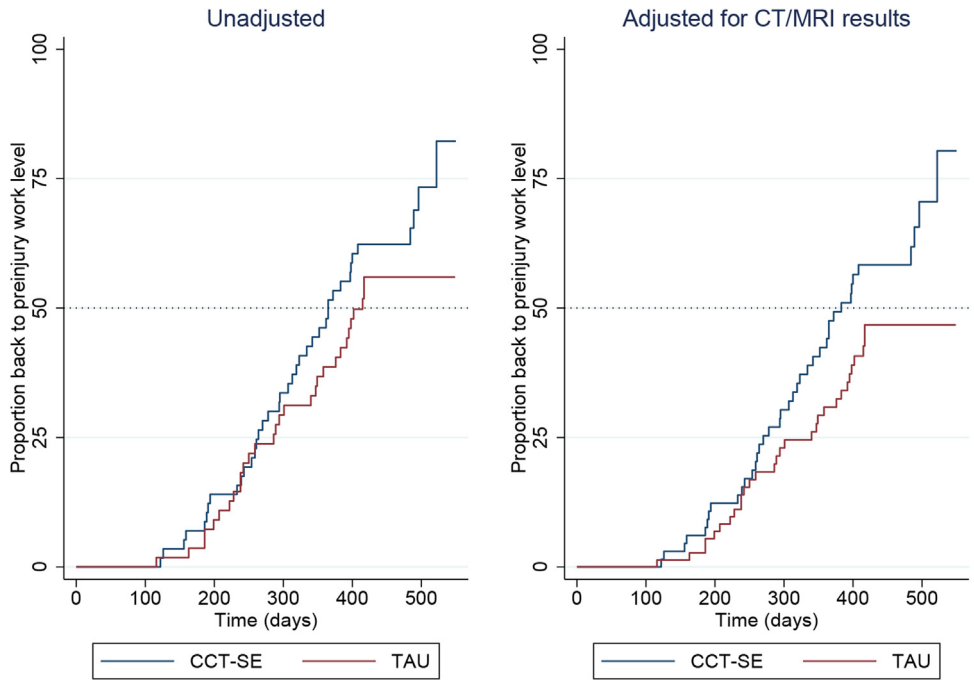

Fig. 3. Days to reach pre-injury work level by treatment group: unadjusted and adjusted for the presence of traumatic intracranial injury on CT/MRI. CCT-SE, compensatory cognitive training and supported employment; TAU, treatment as usual.

returned to work, regardless of group. From baseline to 3-month follow-up, 4 patients (CCT-SE: $n = 2$, TAU: $n = 2$) were unstably employed, and from 3 to 6-month follow-up, 6 (CCT-SE: $n = 2$, TAU: $n = 4$) were unstably employed. The group difference was not significant.

4. Discussion

This study examined the effectiveness of a pragmatic, cross-sectoral and innovative complex intervention (CCT-SE) on RTW in patients with mild-to-moderate TBI who were still symptomatic and on sick leave 8 to 12 weeks after injury. In contrast to our hypotheses, we found no differences in work outcomes between the CCT-SE and TAU groups at the 12-month follow-up. However, a significantly higher proportion of the CCT-SE group had returned to work after 3 months as compared with the TAU group, which suggests an early effect of the CCT-SE intervention on return to competitive work after mild-to-moderate TBI. We found no significant group differences in the other work-related outcomes. However, the median difference in time from injury to return to pre-injury work levels was 50 days, which supports accelerated RTW in the CCT-SE group. Overall, the within-group differences showed an improvement in all outcomes over time, and most patients in both groups were stably employed after an initial RTW.

Returning to work is a primary rehabilitation goal after TBI. Vocational rehabilitation may be challenging because of the heterogeneity of health-related TBI consequences and pre-morbid and contextual factors (i.e., personal and environmental factors). The literature has suggested focusing on both health and work factors, the involvement of the patient and employer, a combination of work-directed interventions [10], and the integration of these factors into early rehabilitation after TBI [27].

At the study planning time, evidence was lacking to support the effectiveness of vocational rehabilitation for people with mild-to-moderate TBI [5,28]. A novel approach to vocational rehabilitation, the "place-and-train" principles, involving SE, gained empirical support in the Norwegian context, with positive results for both work- and non-work-related outcomes for people with mental illness [25]. The present study was further inspired by Twamley et al. [15], who conducted a pilot study using the original CogSMART intervention combined with SE in veterans with mild-to-moderate TBI. The authors found improvement in affective post-concussion symptoms and quality of life but no significant improvement in RTW. The present study and Twamley et al. [15] used different inclusion criteria, such as time since injury (8–12 weeks vs. $>$ 4 years), tools used to determine impairment (the RPQ in the current sample vs. neuropsychological performance in the pilot study) and duration of SE support (6 vs. 12 months). Furthermore, our sample used the criterion of employment at the time of injury, whereas participants in the pilot study were unemployed but were motivated to return to work. Additionally, the sample in the current study was civilian; our study was conducted within a different governmental welfare system and included more than twice as many participants.

Of note, TAU in this study was relatively comprehensive. Vikane et al. [29] assessed the effect of the program constituting TAU in the current study compared to follow-up by a general practitioner for patients at risk or sick-listed with post-concussion symptoms at 2 months after mTBI. The group receiving follow-up care by a general practitioner also had a multidisciplinary examination with subsequent advice. The authors found that participants in the TAU program showed decreased symptom burden on the RPQ after 1 year, but the groups did not differ in days to sustainable RTW, so TAU was not effective for RTW.

However, the results of the 2 studies are not directly comparable. In the current study, TAU constituted the control group. Furthermore, the differences in inclusion criteria between the studies hamper comparisons, such as different severity levels (mild-to-moderate TBI vs. mTBI), time of inclusion (8–12 vs. 6–8 weeks after injury), age of sample (18–60 vs. 18–55 years) and whether the patients had been hospitalised (not necessarily vs. $\geq$ 5 hr). Additionally, Vikane et al. used a different definition of stable RTW than the current study and collected sick leave data

from a national registry [29]. Considering these differences, the high level of care received in TAU, with high attendance rate and low loss to follow-up, might still have affected the results and reduced the difference between the 2 treatment groups. Using a control group receiving a less-comprehensive follow-up might have resulted in a larger primary-outcome difference between the groups. A qualitative process evaluation that explores patients' experience with the RTW process will be published, in addition to the evaluation of clinical outcomes.

Overall rates of return to competitive employment (part or full time) at 12 months were high in both CCT-SE and TAU groups (90% and 84%). This finding may be explained in part by the context of the study, in addition to expected spontaneous recovery. The Norwegian welfare system includes measures to ensure a low unemployment rate, in addition to universally accessible, affordable and high-quality health care services. Furthermore, all patients in this study were employed $\geq$ 50% at the time of injury, which increases their likelihood of regaining employment after injury as compared with unemployed patients [5]. Conversely, only 65% of patients in the CCT-SE group and 54% in the TAU group had returned to their pre-injury work level at 12 months' follow-up. The Norwegian welfare system also includes a generous workers' compensation program that covers 100% of lost income for the first year of sick-listing and approximately 66% beyond the first year. The Organization for Economic Cooperation and Development has previously revealed that, of its member countries, Norway has the highest level of sick-listings and costs related to lost labour [13]. Reimbursement for the loss of income when sick-listed (i.e., up to 12 months) might have affected the patients' motivation to return quickly to full-time labour [5] and may, in general, hamper the efficacy of work-related interventions.

4.1. Strengths and limitations

The current study is a well-designed, innovative and cross-sectoral RCT examining RTW in a specific subsample of TBI patients with persistent symptoms. The risk of bias was minimised by the low loss to follow-up [30]. Because of the civilian sample, the results are more generalisable than those obtained from a sample of military veterans. The study was conducted in the context of generous income compensation during sick leave, thus potentially decreasing its generalisability to countries with other welfare systems because this may influence motivation for RTW and consequently RTW rates [5,31]. The generalisability should also be considered in light of the comprehensive multidisciplinary care received in TAU, which is not representative of the standard of care received at most other national or international facilities.

Atypically for the general TBI population, the sample was predominantly women, in white collar occupations, and full-time employees. However, this sample represents the patients after mild-to-moderate TBI with prolonged symptoms who are seeking treatment and reside in an urban area. Data from the Quality Registry at the TBI outpatient clinic show that 10% more female than male patients are referred for multidisciplinary follow-up (personal communication with Quality Registry staff).

The main outcomes were based on self-reported data, which could be considered a limitation if respondents report false values or do not remember correctly. However, the study participants had sustained mild-to-moderate TBI, and their knowledge of personal work-related data was not suspected to be notably affected.

The original sample size calculation was designed to detect a 33% absolute difference between the treatment groups in the proportion that returned to work at the 12-month follow-up. In previous work-related intervention studies on occupational back pain and mental disord, both 30% and 20% differences between groups in RTW were used [26,32]. In our study, we found only a 6% difference between groups at the 12-month follow-up. This finding could be related to the pragmatic context of the study (inclusion of the multidisciplinary follow-up as the TAU group) and the natural recovery process of mild-to-moderate TBI. However, the 50-day median difference in time from injury to return to pre-injury work levels might indicate an important effect of the CCT-SE intervention. This finding will be explored further in a study on the cost-effectiveness of this intervention.

5. Conclusions

The study results suggest that the combined cognitive and vocational intervention improved the early return to stable employment in patients with mild-to-moderate TBI. Expediting a stable RTW may substantially reduce costs related to lost labour after mild-to-moderate TBI, in addition to helping patients return to their pre-injury levels of functioning. The results of this study require replication, and a cost-benefit analysis should be performed before drawing a firm conclusion.

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Disclosure of interest

The authors declare that they have no competing interest.

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III

Workplace factors associated with return to work after mild-to-moderate traumatic brain injury

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Abstract:

Objective: Sociodemographic and injury-related predictors for return to work (RTW) after mild-to-moderate traumatic brain injury (TBI) have been extensively explored. However, there is a knowledge gap regarding work-related predictors of RTW. The main aim of this study was to explore work-related predictors of work participation 1 year after mild-to-moderate TBI.
Setting: Data was collected at inclusion, and 3, 6, and 12 months following inclusion at a specialized TBI rehabilitation outpatient clinic at Oslo University Hospital, Oslo, Norway.
Participants: Eligible patients had suffered a mild-to-moderate TBI 8–12 weeks previously, were employed ≥ 50% at time of injury, were between 18–60 years of age, and sick listed ≥ 50% at time of inclusion due to symptoms of TBI (based on Rivermead Post-Concussion Symptom Questionnaire). In total, 116 patients were included in a randomized controlled trial, of whom 113 were included in the 1-year analysis.
Design: Patients were originally included in a randomized controlled trial. There were no between-group differences in RTW after 1 year. Thus, the participants were analyzed as 1 cohort in this study.
Main measures: The primary outcome measure was work participation 1 year after study inclusion. Work-related predictors were chosen based on previous research and expert opinion and entered into a multivariable linear regression model. The model controlled for sociodemographic and injury-related factors.
Results: The best-fitting model explained 25% of variation in work participation at 1 year. Significant predictors were predictability, quantitative demands and rewards (recognition) at the workplace, private or public employment, symptom burden at baseline, and sex.
Conclusion: In this study, several work-related predictors outperformed some of the established sociodemographic and injury-related predictors of RTW after TBI, thus stressing the need for further focus and research on amendable predictors of RTW after mild-to-moderate TBI.

Keywords: Traumatic brain injury, prediction, post-concussion symptoms, concussion, mild-to-moderate TBI, return to work, vocational rehabilitation, workplace

Word count:

Abstract: 289 of 300

Main text: 3420 of 3500

Tables and figures: 5 of 5

References: 44 of 50

Introduction

Approximately 69 million people suffer a traumatic brain injury (TBI) globally each year[1], with ~ 92% classified as mild TBI (mTBI) or moderate TBI[1,2]. Most people recover quickly (days to weeks) after an mTBI, while some continue to experience somatic, cognitive, and emotional symptoms for a prolonged period. Regardless of injury severity, the typical symptoms (e.g., headache, fatigue, dizziness, difficulties with concentration and memory, sleep disturbances) often affect the person's day-to-day life and may hamper their ability to work[3]. Return to work (RTW) rates in patients with moderate and severe TBI vary between 35% and 50%[4] depending on study methodologies, including injury severity and time of data collection. For people with mTBI, the proportion of RTW is higher, with a RTW rate at 89% 12 months after injury[5]. However, in a cohort of participants with prolonged symptoms (resembling the current sample), the proportion that had returned to work after 1 year was 76%[6].

It is crucial to understand which patients are at risk of a less favorable outcome, including reduced work participation to provide optimal treatment and reduce the societal cost of TBI. The literature on predictors of RTW after TBI has most commonly focused on examining patient and injury characteristics[7,8]. These aspects have been thoroughly studied as predictors of clinical improvement and RTW. Different studies have found diverging results for the same predictors[9], but there is a relative consensus regarding the importance of factors such as age, injury severity, and premorbid psychiatric problems[8,10-15] as predictors of work-related outcomes.

Returning to stable work participation is a complex process[16] that relies on more than sociodemographic and injury-related circumstances. Factors related to the workplace also affect the individuals' likelihood of successful RTW after mild-to-moderate TBI[8,17], although they have been much less studied[18]. In contrast to demographic and injury-related factors,

work-related factors are more often modifiable and, consequently, a potential target for intervention to increase the likelihood of RTW after TBI. While some work-related factors, such as duration of employment and type and size of the enterprise, will be difficult to alter after a TBI, psychosocial workplace factors may be more easily amended.

In line with this, some studies highlight workplace psychosocial factors as important when attempting to RTW, often regardless of diagnosis. These include predictors such as greater independence and decision-making latitude[19,20], reward and recognition[21], work predictability[22], quality of leadership, and quantitative demands[20]. However, the relative influence of these factors is still uncharted territory, especially in quantitative research regarding specific diagnoses. Although studies have established these psychosocial factors to be important in reducing sick leave, it is reasonable to think that some psychosocial factors might be important for RTW regardless of diagnosis, whereas other factors might vary in importance depending on the specific diagnosis and symptoms (in this case, TBI).

Concerning workplace factors, type of occupation and pre-injury occupational status are 2 of the more examined work-related predictors[8,14], most commonly comparing manual (blue-collar) to non-manual (white-collar) occupations[23], and being employed previous to injury vs. not employed. A systematic review from 2020 by Alves et al.[18] examined work-related factors associated with RTW after acquired brain injury. They found moderate evidence that patients with a non-manual occupation are more likely to return to work. They also found an increased likelihood of returning to work if the patient works in a large enterprise (≥ 250 employees), but no relationship if the enterprise size exceeds 1,000 employees[18]. However, the main conclusion of the systematic review was that there is a pronounced lack of studies focusing on the predictive value of workplace-related factors on RTW after acquired brain injuries.

The present study, therefore, aimed to evaluate work-related predictors of RTW for patients with mild-to-moderate TBI 12 months after inclusion in a randomized controlled trial (RCT) comparing treatment as usual with a combined cognitive and vocational intervention. Based on previous studies, we hypothesized that work participation at 12-month follow-up would be associated with factors related to the psychosocial work environment and workplace, age, sex, education, marital status, injury severity, presence of extracranial injury, and symptom burden.

Method

Study design

This study includes a sample from an RCT with 1-year follow-up. The protocol and results from the RCT have been published previously[24-26]. The 116 patients were randomized to either combined cognitive and vocational intervention (n = 60) or treatment as usual (n = 56). No differences were found regarding RTW when the groups were compared at 12 months, and the participants are analyzed as 1 cohort in this study. The trial was registered in ClinicalTrial.gov (NCT03092713)[24], approved by the Regional Committee for Medical and Health Ethics in South-East Norway (2016/2038), and adhered to the Declaration of Helsinki.

Setting

Eligible patients were identified at a specialized TBI rehabilitation outpatient clinic at Oslo University Hospital (Oslo, Norway) between July 2017 and April 2019. After providing informed written consent, the patients attended a baseline assessment, followed by randomized group allocation and treatment for 6 months. Follow-up assessments were conducted at the outpatient clinic or by telephone 3, 6, and 12 months after inclusion.

Participants

Patients were eligible for inclusion[24] if they had suffered a mild or moderate TBI 8–12 weeks previously, were 18–60 years old, resided in Oslo or Akershus county, were employed ≥ 50 % at time of injury, and sick listed ≥ 50 % due to post-concussion symptoms as assessed by the Rivermead Post Concussion Symptoms Questionnaire (RPQ)[27] at time of inclusion. Mild-to-moderate TBI was defined as a Glasgow Coma Scale (GCS)[28] score of 10–15, loss of consciousness < 24 hours and post-traumatic amnesia (PTA) < 7 days. The criteria of the American Congress of Rehabilitation Medicine (ACRM) were used to classify mTBI[29]. Exclusion criteria were inability to speak or read Norwegian, progressive neurological disease, or ongoing substance abuse.

Outcome and predictor variables

The main outcome variable representing work participation (work percentage at 12 months, 0–100%) was collected by patients' self-report 12 months after study inclusion.

The predictor variables were chosen based on previous research[8,10-15,19-22] and expert opinion. Predictor data were collected at baseline through medical records and interviews with the patients and classified as work-related, sociodemographic, injury-related, or representing symptom burden.

The work-related predictors were number of employees in the enterprise, duration of employment (months), and whether the enterprise was in the public or private sector. Pre-injury occupational status was not included as a predictor because the sample was selected on the basis of being employed at the time of injury. Further, type of occupation was not entered into the model, as 89% of the sample had white-collar jobs.

A psychosocial risk assessment used selected items from the Copenhagen Psychosocial Questionnaire II – short version (COPSOQ II)[30] to represent aspects of the psychosocial workplace environment. This questionnaire was established based on core dimensions of 7

major theories in occupational health psychology[31]. The COPSOQ II is divided into 13 scales, each consisting of 1 or 2 items that are scored on a scale from 0 ("Never" or "To a very small extent") to 4 ("Always" or "To a very large extent"), giving a total scale score of 0–8. This study examined the scales termed Predictability, Quantitative demands, Rewards (Recognition), and Influence at work (Decision authority). See Appendix 1.

Sociodemographic variables included in the analyses were age (years), sex (male/female), marital status (cohabiting or single/living alone), and education (years).

Injury-related factors included TBI severity as assessed by ACRM criteria (mild/moderate TBI) and extracranial injury. Extracranial injuries were registered according to the affected body part and scored by severity using the Abbreviated Injury Scale[32] but were dichotomized to yes/no in these analyses. The total score on the RPQ was included to control for somatic, cognitive, and emotional symptom burden at baseline. The RPQ is a 16-item self-report measure of post-concussion symptoms scored on a 5-point Likert scale from 0 to 4, where 0 = "Not experienced", 1 = "No longer a problem", 2 = "Mild problem", 3 = "Moderate problem", and 4 = "Severe problem"[27].

Statistical analysis

All statistical analyses were performed using Stata version 16. Descriptive statistics were reported for baseline characteristics. In cases of missing work percentage data at 12 months follow-up, work percentage at 6 months was used (last value carried forward), if available. The predictor models were built using multivariable linear regression with a continuous endpoint (work percentage at 12 months). As per recommendation[33], a global model was built based on expert knowledge and previous research and then reduced using manual backward elimination until reaching the best-fitting model. However, at least 1 predictor per category (sociodemographic, injury-related, symptom burden, and work-related) was kept in the model.

An evaluation of the Akaike information criterion was performed at each step. For comparison, the global model was also reduced to a best-fitting model for work percentage at 6 months, using the same method. The amount of variance in work percentage explained by the model is represented by R^2 and adjusted R^2. Multicollinearity was checked for, using variable inflation factor and normality of the residuals controlled using a Q–Q plot. To check for internal validity, the models were run with 1,000 bootstrap repetitions. Statistical significance was set to $P < .05$.

Results

Of 116 participants randomized to the 2 intervention groups at baseline (See Figure 1, Flowchart), 110 attended the 6-month follow-up, and 107 attended the 1-year follow-up. The main outcome variable was missing for 9 participants. Of these, 6 had the 6-month work participation available. Sensitivity analysis showed insignificant differences in results before and after replacing the missing values. In total, 113 patients were included in the prediction analysis for work participation at 1 year and 110 for 6 months. The baseline characteristics of the sample are presented in Table 1 and thoroughly described elsewhere[34]. There were few missing items, with no variable missing more than 3%.

TABLE 1 AROUND HERE

Global prediction model

The global model contains the predictors deemed important for RTW at 1 year (see Table 2). The predictor values are presented in Tables 1 and 2. In the global model, sex, RPQ total score, employment in a private or public enterprise, and the workplace scales predictability and quantitative demands from COPSOQ were significant predictors for work participation at

1 year. The model explained 26% of the variance in work participation at 1 year. Bootstrapping analysis supported all statistically significant predictors in this model (sex −17, 95% CI −32 to −2, P = .03, RPQ total score −1, 95% CI −1 to −0.1, P =.03, private or public employment 18, 95% CI 4 to 32, P = .01, predictability 8, 95% CI 2 to 13, P < .01, quantitative demands 5, 95% CI 1 to 9, P = .03).

TABLE 2 AROUND HERE

Best-fitting prediction model

In the best-fitting model, the same factors (i.e., sex, RPQ total score, private/public enterprise, predictability, and quantitative demands) remained significant predictors for work participation at 1 year (Table 3). Bootstrapping analysis confirmed all statistically significant predictors (sex −16, 95% CI −30 to −3, P = .02, RPQ total score −1, 95% CI −1 to −0.1, P = .03, private or public employment 16, 95% CI 3 to 29, P = .02, predictability 8, 95% CI 3 to 13, P < .01, quantitative demands 5, 95% CI 1 to 9, P = .03). In addition, the scale rewards (recognition) had a P-value of .05 in the best-fitting model and a regression coefficient of −4, 95% CI −9 to −1, P < .04 in the bootstrapping analysis. The best-fitting model explained 25% of the variance on work participation at 1 year. Marital status did not contribute significantly, but the quality of the model was degraded if it was excluded. Extracranial injury was the factor closest to being significant among the injury-related predictors and was, therefore, kept in the model to include at least 1 variable representing each group of predictors.

TABLE 3 AROUND HERE

FIGURE 2 AROUND HERE

According to the estimates in the final prediction model (Figure 2), women worked 16% less than men did at 1 year. Employees in the public sector worked 16% more than those who

were privately employed. Further, an employee worked 8% more for each increase in predictability score at the workplace, and for each increase of 1 in the quantitative demands score, they worked 5% more. Additionally, the scale rewards (recognition) decreased the average work participation by 4% per increase of 1. Finally, for each increase of 1 in the total baseline RPQ score, they worked, on average, 1% less.

The best-fitting model for work participation at 6 months also contained total RPQ score (P = .02) and predictability (P < .01) at the workplace. Additional significant predictors were marital status (P < .01) and extracranial injury (P = .04). See Appendix 2.

Discussion

This study found that certain work-related factors outperformed some of the established sociodemographic and injury-related predictors of RTW after TBI, as only sex and post-concussion symptom burden remained significant factors in the best-fitting model. Employment in the private or public sector, predictability, quantitative demands, and rewards (recognition) at the workplace all predicted work participation at 1 year, in line with our assumptions.

Sex is a much-debated potential predictor for work participation after a TBI[9]. However, contrary to our findings, the consensus is that sex probably does not play an integral part in predicting RTW rates after TBI[8,35] but may contribute to predicting symptoms lasting more than 1 month[9,36]. The sample in this study was included specifically because they had symptoms lasting ≥ 8 weeks. That these patients were selected on the basis of prolonged symptoms may partially explain why women in this sample worked less than men.

As expected, we also found that a higher post-concussion symptom burden was negatively associated with work participation. Specifically, for each increase in total RPQ score, the sample worked 1% less. Symptom burden has previously been documented as associated with

RTW[37], and our results align with previous research and suggest that etiology-specific factors play a role.

When examining the structural work-related predictors, employment in the public or private sector had the greatest impact. As previously mentioned, work-related factors have not been studied meticulously[8,18], and the reason for the 16% increase of work participation in those publicly employed can only be hypothesized. A potential explanation might be the Norwegian working life model (IA Agreement)[38], in which most public enterprises in Norway take part. This agreement aims to "…improve the working environment, help bring employees back to work, prevent and reduce absence due to illness and prevent expulsion and withdrawal from working life"[38], and may make it easier for patients in the public sector to work with accommodations to their specific needs and to experience a greater sense of job security. However, an evaluation of an earlier version of the IA Agreement only found a small decrease in long-term sickness absence for women[39], whereas others only found a decrease among men working shifts[40]. Further, we have no measure of the quality or amount of work performed and cannot conclude that employees in the public sector accomplish more work. Possibly, patients in the public sector are simply allowed more time to perform the same amount of work than in the private sector.

As assumed, the amendable psychosocial workplace factors, predictability, quantitative demands, and rewards (recognition) predicted work participation at 1 year. This is particularly interesting as these factors may be intervened upon, even after the injury has occurred.

Previous findings suggest that predictability at the workplace decreases the number of absence days, regardless of diagnosis or profession[41]. This is in line with our results, in that higher predictability in work tasks facilitates higher work participation. This finding seems sensible for all employees, but perhaps particularly so for patients with TBI, due to typical

symptoms as fatigue, headache triggered by screen time, and problems with concentration, memory, and planning, which might leave them reliant on a predictable workday and the possibility of scheduling their work. Moreover, clinical experience suggests that many people who have sustained a TBI report reduced stress tolerance and may especially benefit from routines and structure, avoiding unforeseen changes, and high work stability. In turn, this may provide an opportunity to complete work tasks in a satisfactory manner, leading to a sense of achievement.

Concerning quantitative demands, it may be intuitive to think that a patient with a great workload may be hesitant to RTW with the fear of being overwhelmed and experiencing increased symptoms. However, our results show that a higher workload leads to increased work participation. This is in line with some previous research on quantitative demands, showing that medium to high quantitative demands were associated with a reduced risk of long-term sickness absence in a sample of 39 000 Danish workers[20]. It has been suggested that this is due to the increased workload serving as a challenge stressor that gives the employees more energy and contributes to increased motivation and work-related well-being[20], thus increasing work participation.

The importance of the scale rewards (recognition) at the workplace is also highlighted in this study. The findings were surprising and in contrast to previous research[21,42], in that high reward levels were associated with lower RTW. This finding may reflect that patients feel less pressure to RTW before they are ready if they believe the management understands their situation, appreciates their work, and treats them fairly at their workplace. This finding needs replication, and additional qualitative data from the RCT is under production.

Influence at work and decision-making latitude have previously been positively associated with higher work participation and lower risk of long-term sickness absence[20,41], also when

examining patients after mTBI[19]. For unknown reasons, this factor was not a predictor of RTW in this study. One could speculate this might be because this sample is highly educated, mostly employed in white-collar jobs, and thus has a high degree of decision authority at work. However, the average score of influence at work in this sample (4.3, SD 1.7) is comparable to the norm score from a Danish population (4.1, SD 1.8) and does not appear to be particularly high. The similar scores may be due to an overall well-regulated labor market and welfare system in the Scandinavian countries.

In opposition to our hypothesis, extracranial injuries did not predict work participation at 1 year. However, they predicted work participation at 6 months (Appendix 2), in line with previous research[12]. The impact of extracranial injuries at 6 months, and not at 12, likely reflects that the burden of these injuries is more pronounced earlier in the recovery process and then decreases with time since injury. However, others have found extracranial injuries to predict RTW at 1 year[43]. Thus, the results are divergent and underline the necessity for more research on the association between extracranial injuries and long-term work participation.

Limitations and strengths

While the best-fitting model explained 25% of the variance in work participation at 1 year, this still leaves 75% of the variance to be accounted for. Relevant factors that might account for some of the unexplained variance may include occupation type, premorbid psychiatric problems, substance abuse, length of stay in acute care, prior TBI, or other factors not yet explored. Sick leave in the year before injury and pre-injury work participation had low correlation with work participation at 1 year in this sample. RTW after TBI is influenced by a multitude of factors and is difficult to predict at both the individual and group levels. The sample size in this study limited the number of predictors in the model. However, while

previous studies have focused mainly on personal and injury-related factors, this study adds to the knowledge base identifying vocational predictors of work participation.

Additionally, the main outcome is self-reported, which may introduce some bias, but it is reasonable to believe that patients after mild-to-moderate TBI can provide valid information concerning their current work status[44].

To expand on the knowledge of work-related factors' impact on RTW, future studies may investigate further whether there are changes in work tasks or positions, or changes in jobs after a TBI, and may evaluate this with regard to psychosocial and organizational factors at the workplace.

Conclusion

This study examined predictors of work participation at 1 year after mild-to-moderate TBI. Sex, symptom burden, working in a public enterprise, and predictability and workload, along with recognition from management, predicted work participation, although not necessarily in the expected direction. This illustrates that several work-related factors outperformed some of the established sociodemographic and injury-related predictors of RTW after TBI, stressing the complexity of the RTW process and the need for further focus and research on amendable predictors of RTW after mild-to-moderate TBI.

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Appendices

Appendix 1. Scales and items from Copenhagen Psychosocial Questionnaire II – short version

Scale	Questions	Average score (SD)	Average values Danish employees (SD)
Predictability	- At your place of work, are you informed well in advance concerning for example important decisions, changes, or plans for the future? - Do you receive all the information you need in order to do your work well?	5.3 (1.3)	4.6 (1.7)
Quantitative demands	- Do you get behind with your work? - Do you have enough time for your work tasks?	3.9 (1.6)	3.3 (1.8)
Influence at work (Decision authority)	- Do you have a large degree of influence concerning your work? - Can you influence the amount of work assigned to you?	4.3 (1.7)	4.1 (1.8)
Rewards (Recognition)	- Is your work recognised and appreciated by the management? - Are you treated fairly at your workplace?	5.8 (1.9)	5.2 (1.6)

Appendix 2. Best fitting prediction model of work participation at 6 months.

Predictor	Coefficient	95% CI	*P*-value	R^2*
Constant[a]	54.4	26.3 to 82.5	<.01	
Marital status[b]	−21.0	−34.5 to −7.4	**<.01**	0.07
Extracranial injury[c]	−13.4	−26.3 to −0.6	**.04**	0.02
RPQ score	−0.7	−1.3 to −0.1	**.02**	0.07
Predictability	5.1	1.6 to 8.7	**<.01**	0.07
Total R^2				0.22
Adjusted R^2				0.19

*R^2 from univariate analyses, [a]Constant: Y-intercept of the model, [b]Marital status: 0 - Married/cohabitating; 1 - Single/living alone, [c]Extracranial injury: 0 – No; 1 – Yes.

Tables

Table 1. Baseline characteristics of individuals with mild-to-moderate traumatic brain injury at 8 to 12 weeks post-injury.

	Total sample (n = 113)
Sociodemographic factors	
Age, years, median (range)	42 (24–60)
Sex, female	66 (58)
Education, years, mean (SD)	16 (3)
Married/cohabitating	74 (65)
Injury-related factors	
Cause of injury	
Falls	49 (43)
Traffic accidents	21 (19)
Sports	14 (12)
Violence	6 (5)
Exposure to inanimate objects	22 (20)
Unknown	1 (1)
CT/MRI findings, traumatic intracranial	27 (24)
Injury severity by ACRM criteria	
Mild	106 (94)
Moderate	7 (6)
Loss of consciousness (LOC)	
Yes	40 (36)
No LOC	58 (51)
Not registered	15 (13)
Post-traumatic amnesia (PTA)	
Yes	52 (46)
No PTA	49 (43)
Not registered	12 (11)
Extracranial injury (yes)	51 (45)
Work-related factors	
Employed in private sector	63 (56)
Duration of employment, months, median (range)	54 (0–480)
Number of employees in enterprise, median (range)	70 (1–20000)
Occupation, white collar	100 (89)
Permanent position	102 (90)
Full-time position	100 (89)

Numbers are n (%).

Table 2. Global prediction model for work participation at 1 year

Predictor	Coefficient (estimate)	95% CI	*P*-value	R^2
Constant[a]	74.7	10.5 to 138.8	**.02**	0.26
Age	0.3	−0.6 to 1.1	.55	
Sex[b]	−17.0	−32.3 to −1.6	**.03**	
Marital status[c]	−12.1	−26.4 to 2.2	.10	
Injury severity[d]	−3.7	−34.4 to 27.0	.81	
Extracranial injury[e]	−5.3	−19.8 to 9.3	.47	
RPQ score	−0.7	−1.4 to −0.1	**.04**	
No. of employees	−0.1	−0.1 to 0.1	.63	
No. of months employed	−0.1	−0.1 to 0.1	.42	
Private or public sector[f]	17.7	2.9 to 32.6	**.02**	
Predictability	7.6	2.4 to 12.8	**<.01**	
Quantitative demands	4.9	0.4 to 9.5	**.03**	
Rewards (Recognition)	−4.4	−9.1 to 0.2	.06	
Influence at work	0.5	−4.1 to 5.0	.84	

[a]Constant: Y-intercept of the model, [b]Sex: 0 - Male; 1 – Female, [c]Marital status: 0 - Married/cohabitating; 1 - Single/living alone, [d]Injury severity: 0 – Mild; 1 – Moderate, [e]Extracranial injury: 0 – No; 1 – Yes, [f]Private or public sector: 0 - Private; 1 – Public.

Table 3. Best fitting prediction model of work participation at 1 year

Predictor	Coefficient (estimate)	95% CI	*P*-value	R^2*
Constant[a]	66.2	29.4 to 103.1	**<.01**	
Sex[b]	−16.0	−30.0 to −2.1	**.02**	0.04
Marital status[c]	−12.5	−26.2 to 1.4	.07	0.03
Extracranial injury[d]	−3.8	−17.0 to 9.4	.57	< 0.01
RPQ score	−0.7	−1.3 to −0.1	**.04**	0.05
Private or public sector[e]	15.8	2.3 to 29.3	**.02**	0.03
Predictability	7.9	3.3 to 12.6	**<.01**	0.06
Quantitative demands	4.5	0.4 to 8.7	**.03**	0.01
Rewards (Recognition)	−4.5	−9.0 to 0.1	.05	< 0.01
Total R^2				0.25
Adjusted R^2				0.20

*R^2 from univariate analyses, [a]Constant: Y-intercept of the model, [b]Sex: 0 - Male; 1 – Female, [c]Marital status: 0 - Married/cohabitating; 1 - Single/living alone, [d]Extracranial injury: 0 – No; 1 – Yes, [e]Private or public sector: 0 - Private; 1 – Public.

FIGURES

Figure 1. Flowchart

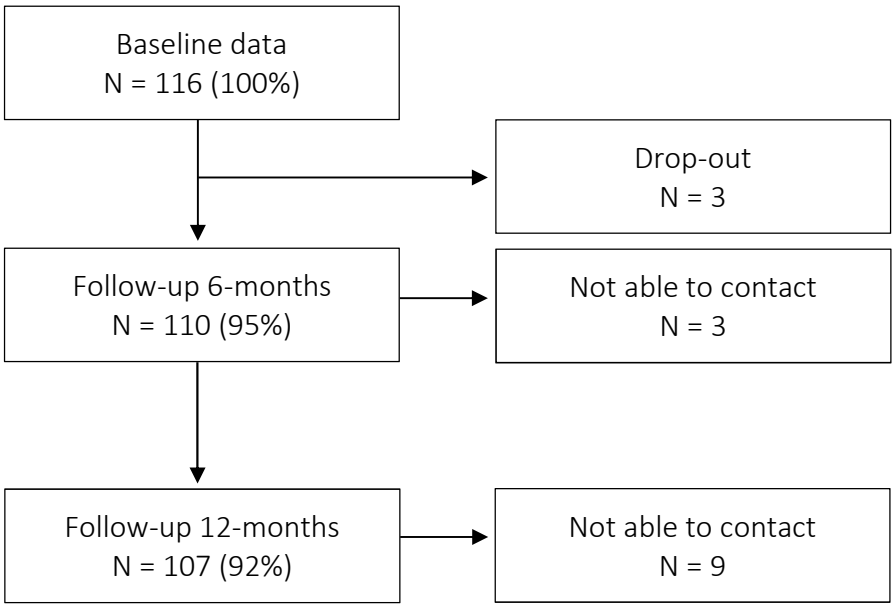

Figure 2. Linear regression estimates with 95% confidence intervals of the best fitting model to predict work participation at 1 year.