# Prediction of outcome following mild traumatic brain injury

de Koning, Myrthe Elisabeth

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From care to recovery

**M.E. de Koning**

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ISBN digital version: 978-94-034-0074-7
ISBN printed version: 978-94-034-0075-4



Design cover illustration: Myrthe de Koning, Astrid van Til en Laura Vester
Layout: Sietske Nederhoff, www.persoonlijkproefschrift.nl
Printing: Ipskamp Printing, www.proefschriften.net

This research was financially supported by:

Junior Scientific Masterclass Groningen
Dutch Brain Foundation (Hersenstichting Nederland)
Graduate School of Medical Sciences/ Behavioural and Cognitive Neuroscience
University of Groningen

rijksuniversiteit
groningen

# Prediction of outcome following mild traumatic brain injury

From care to recovery

## Proefschrift

ter verkrijging van de graad van doctor
aan de Rijksuniversiteit Groningen
op gezag van de
rector magnificus prof. dr. E. Sterken
en volgens besluit van het College voor Promoties.

De openbare verdediging zal plaatsvinden op
woensdag 11 oktober 2017 om 16.15 door


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geboren op 11 oktober 1989
te Haarlemmermeer

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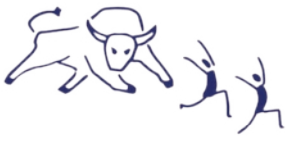
# General introduction

1



## GENERAL INTRODUCTION

Most people either know someone who has, or have themselves experienced mild traumatic brain injury (mTBI), commonly known as a concussion (in Dutch: hersenschudding). Historically, patients were advised to adhere to strict bed rest, especially during the first days of recovery.[1] This archaic view on the management of mTBI has long been abandoned. In general, patients recover within several weeks without any specific therapy. However, somehow a subgroup of mTBI patients continues to experience disabling problems months after injury limiting their daily activities. This dissertation sets out to explore these issues relating to the mTBI population, by addressing the role of injury characteristics, provided care, posttraumatic complaints, and psychological distress on the general outcome and specifically return to work up to one year after injury.



### Mild traumatic brain injury

Mild traumatic brain injury is defined as a "hit on the head by an external mechanical force, leading to a brain displacement inside the skull", resulting in a Glasgow Coma Scale (GCS) score of 13-15.[2,3] Differentiation between mTBI and head trauma without brain injury may be difficult, especially when a patient regained a maximum GCS after initial impairment. Therefore, the presence and duration of posttraumatic amnesia (PTA)[4] and loss of consciousness (LOC) in addition to the GCS, are required for the diagnosis of mTBI.[5,6] MTBI is a common disorder, affecting at least 600 per 100,000 persons per year.[5,7–10] Globally, road traffic accidents account for most of the traumatic brain injuries. In developing countries, the increasing use of motor vehicles contributes to rising incidence rates, whereas a constant decline of road traffic accidents is observed in industrialized countries in the past decades. It is in these countries that the ageing population is associated to more fall-related TBIs among the elderly, making falls the second most common cause for mTBI. Other major causes are interpersonal violence, recreational and sporting activities.[2] These injury etiologies explain the peak incidence of mTBI among children, young adults and elderly, with a male/female ratio of 3:1.[9] In approximately 30% of cases extra-cranial injuries such as limb fractures or internal injuries occur.[11–13]

### Posttraumatic complaints

Posttraumatic complaints (PTC) such as headache, dizziness, forgetfulness, and fatigue are relatively normal to experience the first days after injury, with a decline of complaints over time.[14] An estimated 15-25% of patients however – a group that is sometimes referred to as the *miserable minority* – develop chronic PTC that may persist up to years after injury.[15–18] The question comes to mind as to why some patients develop persistent PTC and others recover without complaints, and the answer remains an ongoing subject of debate. Persistent complaints have been tied to structural intracranial abnormalities. However, recent studies have been focusing more on pre-injury patient characteris-

tics in an attempt to explain the variation in outcome after seemingly identical traumas. Personality traits and psychological wellbeing have been indicated as important factors in adapting to complaints.[19–21] Seemingly, some patients are better able to cope with the consequences of an injury than others. Coping refers to the ability to adapt responses and regulate emotions after a distressing event. The use of active problem-directed coping styles have been linked to better outcome, whereas inadequate coping styles are linked to increased feelings of anxiety and depression, which in their turn have a strong relation to posttraumatic complaints.[22,23]

**Outcome of mTBI**

In the mid-20th century, clinicians and researchers started to reported that recovery of mTBI was not always without problems.[24] Physical, cognitive, and affective complaints as well as problems with returning to work or resuming other daily routines became a focus of research. Meanwhile, globally rising health care costs provided physicians, scientists and governments with incentives to study the societal financial burden of diseases. MTBI causes direct costs related to hospital admission but especially high indirect societal costs when patients struggle with work resumption, especially since many patients are within the working population.[25,26] The Glasgow Outcome Scale (GOS) is the most common applied measure for TBI outcome. Originally designed to measure outcomes in a multicenter study, it subsequently became the foremost measure to be used for comparison of outcomes on a global level.[27–29] Soon after the development of the scale, an extended 8-point version was developed to facilitate differentiation in the upper range of outcome (the GOS-extended, GOS-E). Outcome after mTBI is generally described as being either favorable or unfavorable. Some plea that given the lightness of the injury, mTBI patients should recover fully and therefore any GOS-E score below 8 is an unfavorable outcome.[30] However, most studies define scores from 1-6 as unfavorable, whereas 7 and 8 are considered favorable outcome.

**Return to work**

Apart from the GOS-E as a way of measuring outcome, an important parameter for recovery is return to pre-injury vocational activities. Successful return to work (RTW) has been associated with more positives outcomes in terms of quality of life, social integration and psychosocial health for both patients and significant others.[32–36] In terms of economic consequences of injury, loss of work productivity is considered to be the largest determinant of TBI-related costs.[25] Most patients with mTBI return to work within 3 to 6 months after injury, but approximately 5-20% continues to struggle with their vocational reintegration.[37] Furthermore, the majority of patients that do return to work still report complaints, raising the question whether these patients will develop problems in a later stage, outside the scope of most studies that are conducted between 3-6 months after injury. Return to work after mTBI is a multifactorial process in which patient characteristics (such as

age, gender, and education) and factors related to adaptation to injury (e.g. depression, posttraumatic stress, and coping) play a role.[14,37–39] In the transition from sick leave to complete work resumption not only are these aforementioned factors at hand but also occupational and environmental factors that may either advance or thwart endeavors to return to work.[40,41]

**Aftercare**

Brain trauma patients are generally assessed and treated according to regional protocols. For mTBI, multiple guidelines are available concerning management in the acute phase, for instance providing criteria for performing Computed Tomography scan (CT-scan) and/or hospital admission.[42–47] With regard to aftercare, guidelines provide generic advise on follow-up, since only few studies have been conducted on care after hospital discharge. Scheduled outpatient follow-up is advised after discharge from the ward, which would ideally prevent or reduce the chances for patients developing persistent PTC and disability.[48] Providing patients with adequate information with regard to their injury and its clinical course, is supposed to be the largest contributor of beneficial outcomes during follow-up.[49] Evidence supporting this theory however, is sparse, with few studies reporting on specialized follow-up and its influence on outcome.[32,50] In the absence of clinical risk factors or CT-abnormalities, patients are generally discharged home directly from the ED. Given the expectation of good recovery of these non-hospitalized patients, there is no recommendation of scheduled follow-up. In case of persistent complaints or problems when resuming activities, general practitioners may refer patients to the outpatient clinic. These general advises for follow-up have been part of European guidelines since 2002,[48] yet no studies have been published on guideline compliance or frequency of follow-up. Moreover, considering the economic burden of mTBI, it is important to assess which specialists mTBI patients consult in the sub-acute and chronic phase.

**General aim and outline of this dissertation**

All studies presented in this dissertation are part of the UPFRONT-study, which is described in detail in **chapter 2**. In **chapters 3 and 4** the aftercare is discussed for the entire mTBI population, and separately for non-hospitalized patients. In these chapters, outpatient follow-up is related to outcome in terms of GOS-E and posttraumatic complaints. The specificity of posttraumatic complaints and their relation to anxiety and depression is studied in **chapter 5**, by comparing mTBI patients with an orthopedic control group. In **chapter 6,** the influence of an acute alcohol intoxication on recovery is investigated. A multifactorial prediction model for successful return to work is proposed in **chapter 7.** The penultimate chapter of this dissertation, **chapter 8**, suggests an alternate approach to mTBI research**,** by investigating only those patients without complaints early after injury. A summary of the results and an integrated general discussion as well as future perspectives is provided in **chapter 9.**

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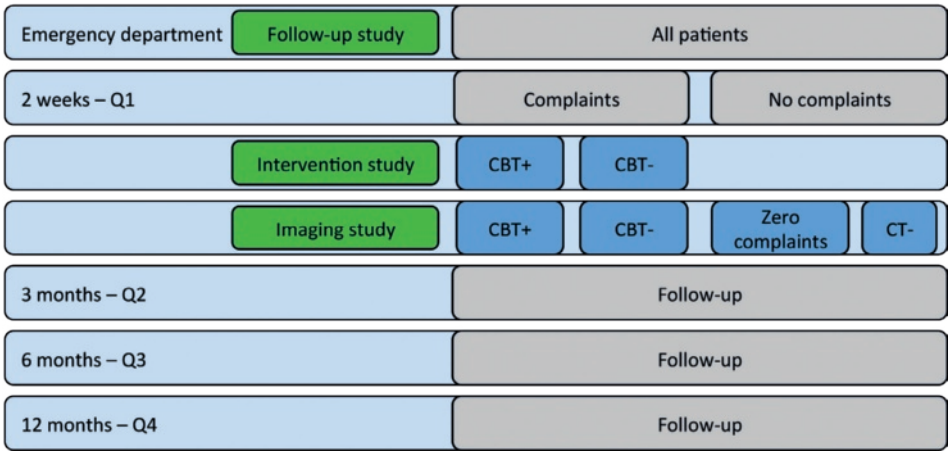
# UPFRONT-study

## UPFRONT-STUDY

All studies presented in this dissertation were part of the UPFRONT-study, in this chapter the methods will be described in detail. The UPFRONT-study is a prospective multicenter cohort study on mild traumatic brain injury (mTBI) with the aim to unravel the relation between adaptive deficits and long-term outcome. It is comprised of three separate projects; a clinical follow-up study of which this dissertation is a part of, an intervention study, and an imaging study. The interconnectedness of the studies and embedding in the UPFRONT-project are provided in Figure 1.

**Figure 1.** Graphic description of the three projects within the UPFRONT-study.




### Design and population

The UPFRONT-study started with inclusion of patients in January 2013 and ended in December 2015. Patients were included in three level-I trauma centers, spanning major regions in the Netherlands; The Elisabeth Hospital in Tilburg (EZH), the Medical Spectrum Twente in Enschede (MST) and the University Medical Center Groningen (UMCG). All patients with mTBI admitted to the Emergency Department (ED) of these three centers were screened for in- and exclusion criteria as provided in the section below.

Demographical and injury characteristics were obtained through medical records and injury severity scores (ISS) were calculated based on these records as a measure of extra-cranial injuries.[1] Presence of posttraumatic amnesia and loss of consciousness – being items in the standard neurological evaluation – were recorded. CT-scans were performed and assessed by a radiologist using the Marshall criteria.[2]

***Inclusion criteria***

- Mild traumatic brain injury as defined by a head trauma resulting in a GCS score of 13-15 at the ED with loss of consciousness (<30min) and/or posttraumatic amnesia (<24h);[3]
- Age of 16 years or older.

***Exclusion criteria***

- Chronic alcohol/drugs abuse;
- Previous TBI or psychiatric disease requiring admission;
- Major neurological disorder or dementia;
- Language barrier;
- No permanent home address.

Patients fulfilling these criteria were approached for participation by their treating physician upon discharge (either at the ED or after being admitted to the ward). They received an information leaflet on the study as well as general information on mTBI and recovery. Informed consent was obtained either by the treating physician or by one of the researchers via telephone in the week after discharge. For patients under 18 years of age, one of the parents or guardians also filled out the consent form.

**Follow-up**

Participants included in the UPFRONT-study received four follow-up questionnaires; 2 weeks, 3, 6, and 12 months after injury (i.e. T1-T4). Questionnaires were either sent by mail, or a digital version via e-mail, depending on patients' preference. Table 1 shows which questionnaires were applied at which time interval.

**Table 1.** Applied questionnaires on four measurement moments in the UPFRONT-study.

| Questionnaire | 2 wk. | 3 mo. | 6 mo. | 12 mo. |
|---|---|---|---|---|
| General information | X | | | |
| Return to work (RTW)[4] | X | X | X | X |
| Role resumption list (RRL)[5] | | | X | X |
| Head Injury Symptom Checklist (HISC)[6,7] | X | X | X | X |
| Hospital Anxiety and Depression Scale (HADS)[8] | X | X | X | X |
| Utrecht Coping List (UCL)[9] | X | | X | X |
| Impact of Event Scale[10] | X | | X | X |
| Dutch Multifactor Fatigue Scale (DMFS)[11] | | | | X |
| Checklist Individual Strength (CIS-20)[12] | X | X | X | X |
| Symptom Checklist (somatic scale, SCL-90)[13] | X | | X | |
| Dutch General Self Efficacy Scale (DGSES)[14] | X | | X | |
| Centrality of Events Scale (CES)[15] | | | | X |
| Glasgow Outcome Scale Extended (GOS-E)[16,17] | | | X | X |
| World Health Organization Quality of Life (WHO-QoL)[18] | | | | X |

**BOX I: INTERVENTION AND IMAGING STUDIES**

**Early intervention study of cognitive behavioral therapy (CBT)**

The aim of the intervention study was to assess whether early CBT reduces cognitive complaints with a positive effect on outcome defined by return to work. CBT was compared to a telephonic coaching condition. Patients reporting three or more complaints two weeks after injury were screened for participation in the intervention study. Additional inclusion criteria were age between 18-65 years and normal admission CT scan. Furthermore, patients had to have paid work or be studying at the time of their injury. After informed consent, patients were randomly assigned to the CBT or telephonic counseling group. The first group received 5 CBT group sessions, of which the protocol is described in detail elsewhere.[19] The telephonic counseling group received 5 calls during which only general advice was given.

**Relation between adaptive deficits and frontal network dysfunction by functional and structural imaging**

The imaging study aimed to unravel the relation between adaptive deficits and frontal network dysfunction, working with the hypothesis that the prefrontal cortex plays a key role in the regulation of adaptive responses to changes such as mTBI.[20] Patients were examined with fMRI and DTI-studies two times (approximately 4 weeks and 12 weeks) after injury to assess whether inadequate frontal network function is caused by functional or structural abnormalities. Participants in this study were all referred for neuropsychological assessment.

The imaging study was designed to form 4 groups as also displayed in figure 1:

- Group 1; patients from the CBT intervention study
- Group 2; patients from the telephonic counseling intervention study
- Group 3; patients with frontal abnormalities on admission CT irrespective of complaints;
- Group 4; patients with less than 3 complaints and no CT-abnormalities on ED admission.

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# Outpatient follow-up after mild traumatic brain injury: results of the UPFRONT-study

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Brain injury. 2017; 31(8):1102-8

## ABSTRACT

### Objective

To investigate outpatient follow-up after mild traumatic brain injury (mTBI) by various medical specialists, for both hospitalized and non-hospitalized patients, and to study guideline adherence regarding hospital admission.

### Methods

Patients (n=1151) with mTBI recruited from the Emergency Department received questionnaires two weeks (n=879), three months (n=780) and six months (n=668) after injury comprising outpatient follow-up by various health care providers, and outcome defined by the Glasgow Outcome Scale Extended (GOS-E) after six months.

### Results

Hospitalized patients (60%) were older (46.6±19.9 vs. 40.6±18.5 years), more severely injured (GCS<15, 50% vs. 13%) with more CT-abnormalities on admission (21% vs. 2%) compared to non-hospitalized patients ($p<0.01$). Almost half of patients visited a neurologist at the outpatient clinic within six months (60% of the hospitalized and 25% of the non-hospitalized patients ($c^2=67.10$, $p<0.01$)), and approximately ten percent consulted a psychiatrist/psychologist. Outcome was unfavourable (GOS-E<7) in 34% of hospitalized and 21% of non-hospitalized patients ($c^2=11.89$, $p<0.01$).

### Conclusion

Two third of all mTBI patients consult one or more specialists within six months after injury, with 30% having an unfavourable outcome. A quarter of non-hospitalized patients were seen at the outpatient neurology clinic, underling the importance of regular follow-up of mTBI patients irrespective of hospital admittance.

## INTRODUCTION

Traumatic brain injury (TBI) is one of the most common acute neurological disorders. In Europe, approximately 100-300 per 100,000 inhabitants are admitted to the Emergency Department (ED) annually, and the amount of TBI related hospital visits is increasing.[1,2] The associated direct healthcare costs for these hospital visits are estimated around €10 billion.[3] The majority of traumatic brain injuries (75-90%) are classified as mild TBI (mTBI),[1] and although most patients with mTBI recover within weeks to months without residual impairments, persistent complaints and delayed return to work occur in 15-20% of all cases.[4,5] However, it is unclear how frequently mTBI patients return to the outpatient clinic for follow-up in case of persistent complaints.



Most studies on outcome after mTBI do not differentiate between hospitalized and non-hospitalized patients, while there are clear differences between the groups. First, hospitalized patients are more severely injured,[6] and second, since guidelines recommend different aftercare following mTBI after hospitalization or direct discharge, it is probable that different follow-up pathways exist. The decision whether a mTBI patient has to be admitted to the hospital ward (or Intensive Care Unit) has been studied in various mTBI cohorts, which has led to European guidelines for ED treatment, admission and follow-up for this patient category.[6,7] Outpatient follow-up in the sub-acute phase after injury is recommended at least once for hospitalized patients. Conversely, for non-hospitalized patients specialized follow-up is only indicated when patients have persisting complaints interfering with daily activities. Although follow-up is indicated in the case of delayed recovery, it is not specified who is the most appropriate specialist to refer to and within which time frame after injury.

The aim of this study was to examine outpatient follow-up by various healthcare providers in a prospective cohort of patients with mild traumatic brain injury, up to 6 months after injury. Since hospital admission is closely related to follow-up, this was also investigated as part of this study. Given the assumed differences between hospitalized and non-hospitalized patients, we believe that it is relevant to determine care consumption and outcome separately for these subgroups of mTBI, to assess the clinical practice of aftercare for patients with mTBI.

## METHODS

### Participants

This study was part of a prospective multicenter cohort study on mTBI (UPFRONT-study). Patients were recruited from 2013-2015 at the ED of three participating trauma centres

in the Netherlands: University Medical Center Groningen (UMCG), Medical Spectrum Twente, and St. Elizabeth Hospital. All patients classified as mTBI according to the European Federation of Neurological Societies (EFNS) guidelines (i.e. GCS 13-15, PTA<24h and/or LOC< 30 minutes) were eligible for inclusion.[7] Patient and injury characteristics were obtained from medical records. Patients admitted to the hospital ward were defined as ***hospitalized***, patients discharged directly from the ED were defined as ***non-hospitalized***. The EFNS guideline for head injury treatment at the ED was applied in all participating centres. It comprises recommendations for treatment, discharge and follow-up, and describes criteria for hospital admittance. These criteria were used to evaluate the clinical practice of admission and follow-up in the UPFRONT-cohort.

CT-scans performed at the ED were classified according to the Marshall criteria,[8] scores were dichotomized into normal CT (score 1) and abnormal CT-scan (score 2-6). Abnormal scans included only trauma-related findings such as intracranial haemorrhage, contusions and oedema. Injury Severity Scores (ISS)[9] were calculated based on hospital records, to assess physical injuries.

Exclusion criteria were age under 16 years, substance abuse, language barrier and inability for follow-up. The study protocol was approved by the ethical committee of the UMCG. Informed consent was obtained from all participants, for patients with age of 16-18 years, a parent/guardian also completed the informed consent form.

**Measures**

Participants of the UPFRONT-study were asked to complete questionnaires two weeks, three months and six months after injury regarding outpatient clinic visits and specific questionnaires for complaints and mood. The questions on outpatient clinic visits were aimed specifically to obtain information on aftercare or follow-up related to the trauma.

*Head Injury Symptom Checklist (HISC).*[10,11] The HISC assesses posttraumatic complaints (PTCs) and is modified from the Rivermead Postconcussion Questionnaire.[12] The checklist addresses 21 PTCs such as headache, dizziness, forgetfulness and fatigue on a 3-point Likert scale, comparing complaints before and after injury.

*Hospital Anxiety and Depression Scale (HADS).*[13] Symptoms of anxiety and depression were measured by means of the HADS. This questionnaire consists of two subscales with seven questions each (score 1-4). Sum scores vary from 1-28, with the cut-off for anxiety and depression set on 8 or higher.

*Glasgow Outcome Scale Extended (GOS-E).*[14] Outcome was determined six months after injury with the GOS-E. The GOS-E consists of an 8-point scale, ranging from death (score 1) to complete recovery (score 8). Favourable outcome is defined by a GOS-E score 7-8, unfavourable outcome by a score of <7.

### Statistical analyses

The data were analyzed using SPSS 22.0. Baseline characteristics were compared between hospitalized and non-hospitalized patients using parametric (Student *t*-test) and non-parametric ($\chi^2$-test, Mann-Whitney *U* test) testing when appropriate. Guideline adherence was measured based on patient and injury characteristics. Follow-up visits at the outpatient clinic and outcome were described for the entire cohort and compared between hospitalized and non-hospitalized patients.

## RESULTS

In total, 1151 patients were included in the UPFRONT-study. Sixty percent of all patients were admitted to the hospital, mostly for one day (48%), with mean length of stay (LOS) of 3.4 days (±5.7). Figure 1 illustrates the distribution of participants among hospital admittance and discharge, and the number of complete information on pathways of care at different follow-up moments. Patients who did not complete the first questionnaire were significantly younger (37.5 vs. 46.2 years, p<0.005) than patients who completed the first questionnaire, other patient characteristics did not differ significantly. The mean age of the overall cohort was 44 years (±19.6), most patients were male, and mainly injured by a traffic accident or fall. All baseline, injury, and clinical characteristics are provided in table 1.



**Figure 1.** Flow schedule of follow-up for hospitalized and non-hospitalized patients.

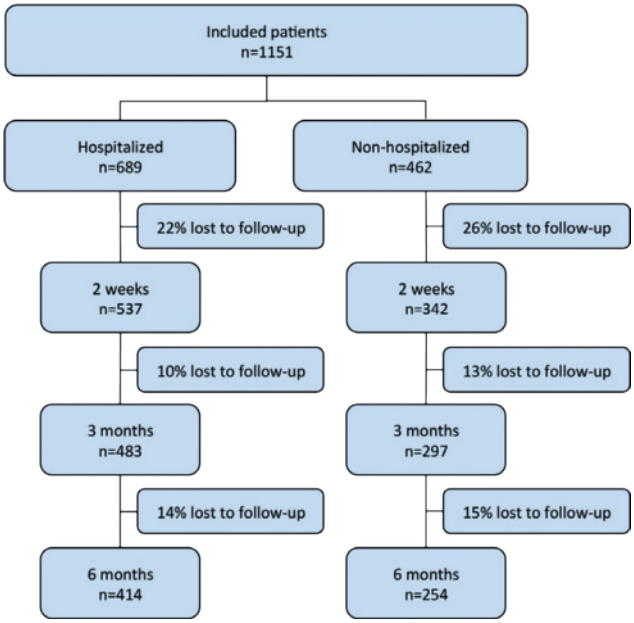


**Table 1.** Patient characteristics

| | All patients n=1151 | 1) Hospitalized n=689 | 2) Non-hospitalized n=462 | Difference 1-2 p-value |
|---|---|---|---|---|
| **Demographics** | | | | |
| Age, years, mean (SD) | 44.1 (19.6) | 46.6 (19.9) | 40.6 (18.5) | <0.005[a] |
| Male gender | 62 | 66 | 57 | 0.005[b] |
| Pre-injury employment status | | | | 0.076[c] |
| Working/student | 66 | 63 | 71 | |
| Not working | 34 | 37 | 29 | |
| **Injury characteristics** | | | | |
| Cause of injury | | | | < 0.005[c] |
| Traffic | | | | |
| Motor Vehicle Accident | 17 | 21 | 12 | |
| Bike accident | 29 | 30 | 28 | |
| Pedestrian | 3 | 4 | 3 | |
| Fall | 36 | 34 | 38 | |
| Assault | 8 | 5 | 12 | |
| Sport injury | 2 | 1 | 3 | |
| Other | 5 | 5 | 4 | |
| ISS score, mean (SD) | 7.2 (5.0) | 8.4 (5.8) | 5.2 (1.8) | < 0.005[a] |
| Alcohol usage day of injury | 35 | 38 | 32 | <0.005[b] |
| EMV score ED <15 | 35 | 50 | 13 | < 0.005[b] |
| Posttraumatic amnesia | | | | < 0.005[c] |
| None | 13 | 9 | 19 | |
| < 1 hour | 58 | 49 | 70 | |
| 1 hour – 1 day | 29 | 42 | 11 | |
| Loss of consciousness (yes) | 85 | 86 | 85 | 0.292[b] |
| CT-abnormalities | 14 | 21 | 2 | < 0.005[b] |

Data are represented by percentages if not specified otherwise.
[a] Student t test; [b] Pearson's χ–square test; [c] Mann-Whitney U test.

### Posttraumatic complaints

Two weeks after injury, patients had on average five PTCs, with no significant difference between hospitalized and non-hospitalized patients. The five most common complaints were: fatigue, headache, dizziness, increased need for sleep, and poor concentration. Of all patients, 16% scored above the cut-off value for depression, with no differences between hospitalized and non-hospitalized patients. In the non-hospitalized group a significant higher percentage of patients scored above the cut-off for anxiety, compared to hospitalized patients (23% vs. 16%, p=0.016). Six months after injury, 46% of non-hospitalized patients reported more than one PTC, compared to 61% of the hospitalized patients (p<0.001).

**Outpatient follow-up**

Almost all (98%) patients were discharged home either directly from the ED or hospital ward. A minority was discharged to a rehabilitation centre. Figure 2 presents outpatient follow-up visits for both hospitalized and non-hospitalized patients. Approximately half of patients visited a neurologist in the first six months after injury (60% of hospitalized and 25% of non-hospitalized patients, $c^2 = 67.1$, $p<.001$). Seven percent of the non-hospitalized and 12% of the hospitalized patients visited a psychiatrist or psychologist within six months after their injury.

**Figure 2.** Outpatient follow-up visits by different health care providers for hospitalized (A) and non-hospitalized (B) patients.

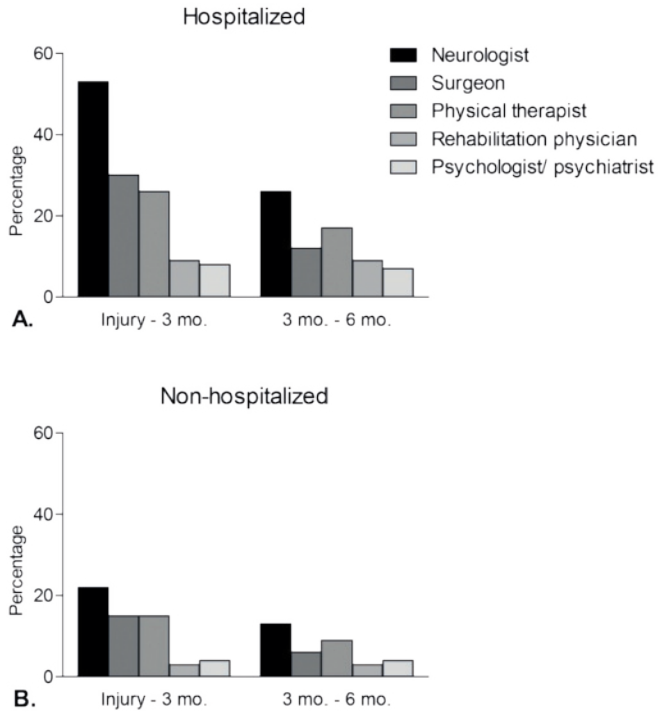
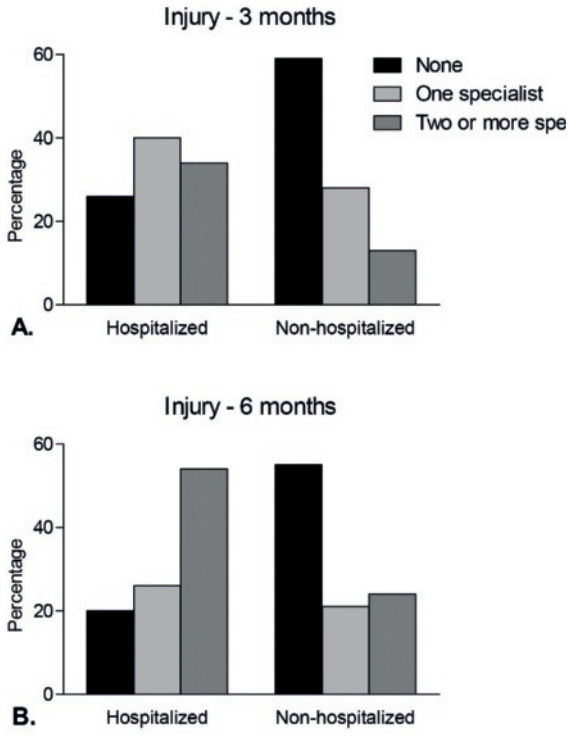



Figure 3 provides cumulative percentages of consulted specialists at each time interval. Most hospitalized patients were seen by one or several specialists within three months after injury, while more than half of the non-hospitalized patients did not consult a specialist. Six months after injury, 67% of the entire group had consulted at least one specialist (80% of hospitalized and 45% of non-hospitalized patients), with an average of five PTCs.

**Figure 3.** Cumulative number of consulted specialist up to three (A) and six (B) months after injury for hospitalized and non-hospitalized patients.



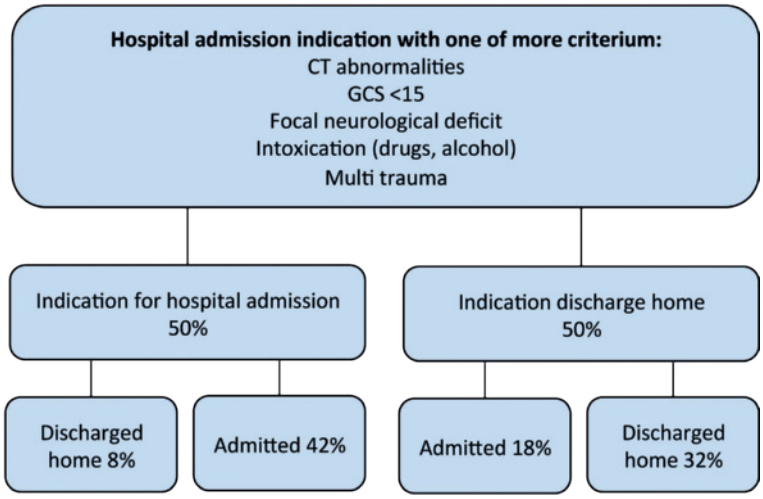

**Outcome**

Six months after injury, the majority of patients showed complete (GOS-E 8, 56%) or almost complete (GOS-E 7, 14%) recovery. Moderate disability (GOS-E 5-6) occurred in 22%, and severe disability (GOS-E <5) in 8% of cases. There were no significant within group differences with regard to the ISS. Outcome of non-hospitalized patients was significantly more often favourable than of hospitalized patients (79% vs. 66%, $c^2$ = 11.89, p <.001).

**Hospitalized vs. non-hospitalized patients**

Figure 4 illustrates guideline adherence for hospital admittance, fifty percent of patients met the criteria for hospital admission, the actual amount of admitted patients was 60%. Discharged patients who should have been admitted (n= 94, 8%) were relatively young (35.6 ±15.6 years), more often male (72%) and more often intoxicated with alcohol (50%). The category of admitted patients who were not indicated for admission (n= 207, 18%) were older (49.3 ±20.0 year), with mean LOS of 2.7 days (±6.4), 54% stayed for only one day.

**Figure 4.** Guideline adherence for hospital admittance.






## DISCUSSION

In this study we assessed outpatient follow-up after mild traumatic brain injury, separately for hospitalized and non-hospitalized patients. We found that two third of all patients were seen at least once at an outpatient clinic, mostly by neurologists. For non-hospitalized patients, the follow-up rate at neurologists of 25% in the first six months and unfavourable outcome in one in five of patients were unexpected findings that highlight the importance of follow-up for all mild TBI patients regardless of whether patients are admitted to the hospital.

We measured follow-up by different health care specialists up to six months after injury and demonstrated that two third of all patients in our cohort were seen at least once at the outpatient clinic, mostly by neurologists. A considerable part of both the hospitalized and non-hospitalized patients were seen by surgeons and physical therapists, indicating that physical injuries might require attention up to six month after injury. The mean injury severity score was comparable with findings of the TRACK-TBI study, demonstrating that physical problems and related treatments are part of the heterogeneous mTBI spectrum.[15] Most outpatient contacts declined over time, however, those with psychiatrists/psychologists showed a consult rate of approximately 10% after six months, a figure which was also observed in a recent study among moderate and severe TBI patients.[16] Although the reason of consultation (e.g. due to psychological problems or complaints of cognitive nature) was outside the scope of this study, this finding indicates that psychological problems are long lasting, and occur in patients with varying TBI severities. This

implicates that not the injury itself but also pre-injury characteristics might be involved in the development of these problems.[17,18]

More than half of the hospitalized patients consulted one or more specialist within six months after injury, probably due to problems on various levels of functioning (e.g. cognitive and physical). This is further supported by a reported average of five PTCs within different domains. Former studies have indicated that moderate and severe TBI patients often deal with various problems, and that rehabilitation physicians are important care providers in long-term aftercare for these patients.[16,19] We observed a relatively low follow-up rate with rehabilitation physicians. However, since persistent complaints and long-term vocational reintegration are a problem for a substantial part of the mTBI population,[20,21] rehabilitation physicians might become more involved in a later phase, outside the timeframe of the current study. Although guidelines specify that all patients who are admitted to the hospital should be seen at least once at the outpatient clinic, only 60% had visited a neurologist in the first six months after injury. An explanation for the fact that a large part was not seen for follow-up is that patients with a good recovery are expected not to feel the need for follow-up.[22]

Surprisingly, in the non-hospitalized cohort, 25% of all patients consulted a neurologist in the first six months after injury. This finding questions the clinical practise that only patients who are admitted to the ward should be seen for outpatient follow-up. Two weeks post-injury a comparable amount of PTCs were present in the two investigated groups. Yet, non-hospitalized patients were more often anxious, which might be related to uncertainty regarding the persistence of complaints.[23] The non-hospitalized patients, who are expected to make a full recovery and are not scheduled for regular follow-up, might feel a lack in opportunity to ask additional questions on expected recovery, despite the fact that an information leaflet was provided on discharge from the ED.[10,15] Whether intensified follow-up could help dealing with this uncertainty towards recovery is largely uninvestigated. Two recent papers reported on the effect of an information intervention aimed at high risk patients (≥ three complaints 10 days after injury), in which the authors conclude that the intervention had no effect on activity or participation nor on PTC level after three months.[24,25] Since we found no differences in the average number of complaints between our two groups after two weeks, it might be argued that the identification of at risk patients based on number of complaints is not appropriate for assessing need for outpatient follow-up. Other factors such as anxiety might be more accurate in the identification for specialized aftercare, but more research is needed in this area.[26]

In our cohort, 30% of patients had an unfavourable outcome six months after injury, which is comparable to earlier findings.[15] A recent study suggested that the relatively worse outcome for patients with mTBI, when compared to moderate TBI, is explained by

sickness awareness;[27] patients with mTBI are more aware of cognitive and behavioural disabilities and are therefore less satisfied with their outcome in comparison to more severely injured patients, who might be less aware of their problems. These mechanisms could also explain the unfavourable outcome in one in five of non-hospitalized patients; the awareness of their disabilities in combination with expectation of full recovery, which causes dissatisfaction with current levels of functioning.

The implication of the high rate of outpatient follow-up might be that aftercare should be scheduled for all patients irrespective of hospital admission. Although guidelines describe clear indications for hospital admission,[7] we found that hospital admission is not always guideline-based but varies according to clinical practice. Given the fact that mTBI guidelines for follow-up are solely based on hospital admission, and a substantial amount of non-hospitalized patients has an unfavourable outcome, a suggestion might be to alter the guidelines for follow-up, to ensure proper aftercare for all patients. Whether this aftercare should take place with follow-up at the outpatient clinic, within multidisciplinary teams or if phone counselling is sufficient, should be studied more extensively.



**Limitations**

Similar to most longitudinal mTBI studies, the generalizability of our findings are limited by selection bias related to dropout of patients. Research has shown that patients with good outcome are often lost to follow-up, which in our case could have led to an overestimation of outpatient visits and a bias towards worse outcome.[28,29] Another factor that questions the generalizability of our study is patient recruitment at the ED, while a part of the mTBI population does not consult any physician or only a general practitioner.[30,31] The burden of mTBI on society might be higher than estimated in the current and previous studies, if a part of this non-ED-visiting population also develops problems.

This study aimed at determining the aftercare of patients with mild traumatic brain injury, assessing follow-up by health care providers in different domains of care. However, we did not examine the reasons for outpatient follow-up, apart from it being trauma-related. We demonstrated that six months after injury many mTBI patients are still in the care system, with posttraumatic complaints within several domains. Future studies should point us in the direction as to whether different specialists are dealing with different problems, which might lead to more clear guidelines for scheduled follow-up and referral.

## CONCLUSIONS

In conclusion, the current study identified that 30% of all mTBI patients has an unfavourable outcome, and outpatient clinic visits are common. Even one in four of the non-hospitalized patients were seen by a neurologist in the first six months after injury and approximately ten percent of all patients needed psychological care. Specialized follow-up related to problems in the physical domain comprised another substantial part of follow-up for both hospitalized and non-hospitalized patients, even up to six months after injury. For clinical practice, current guidelines should also take into account non-hospitalized patients to ensure early identification of all at-risk mTBI patients who are in need of follow-up to prevent development of complaints and unfavourable outcome.

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# Non-hospitalized patients with mild traumatic brain injury: The forgotten minority

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Journal of Neurotrauma. 2017 Jan 1; 34(1):257-261

**ABSTRACT**

Non-hospitalized mild traumatic brain injury patients (mTBI) comprise a substantial part of the trauma population. For these patients, guidelines recommend specialized follow-up only in the case of persistent complaints or problems returning to previous activities. This study describes injury and outcome characteristics of non-hospitalized mTBI patients and the possibility of predicting which of the non-hospitalized patients will return to the outpatient neurology clinic. Data from all non-hospitalized mTBI patients (GCS 13-15, n=462) from a prospective follow-up study on mTBI (UPFRONT-study) conducted in three level-1 trauma centers were analyzed. At two weeks, three and six months after injury, patients completed questionnaires on posttraumatic complaints, depression, anxiety, outpatient follow-up, and resumption of activities. Most patients were male (57%), with a mean age of 40 years (range 16-91). Injuries were most often caused by traffic accidents (32%) or falls (39%). Six months after injury 36% showed incomplete recovery as defined by the GOSE. Twenty-five percent of the non-hospitalized patients returned to the outpatient neurology clinic within six months after injury, of which one third had not completely resumed pre-injury activities. Regression analyses showed an increased risk for outpatient follow-up for patients scoring above the cut-off value for anxiety (odds ratio [OR] =3.0), depression (OR 3.5), or both (OR 3.7) two weeks after injury. Our findings underline that clinicians and researchers should be aware of recovery for all mTBI patients, to prevent a forgotten minority.

## INTRODUCTION

Mild traumatic brain injury (mTBI) is one of the most common neurological disorders seen at the Emergency Department (ED).[1,2] After initial neurological examination to assess severity of injury and to identify possible risk factors for deterioration, approximately half of the patients is discharged home. In general, mTBI patients are expected to make a full recovery within weeks to months after injury, but approximately 15-20% develop persistent complaints and problems that interfere with resumption of previous activities.[3,4] Most outcome studies lack differentiation between hospitalized and non-hospitalized patients[5,6] or only include hospitalized patients.[7] Given the fact that non-hospitalized patients are among the mildest of the spectrum of mTBI, it can be expected that they show a better and faster recovery than hospitalized patients, however data supporting this assumption are not available.



Because of the expectation of good recovery, follow-up for non-hospitalized patients is only necessary in case of persistent complaints or problems resuming pre-injury activities according to current guidelines.[8,9] Conversely, these guidelines recommend that all admitted patients return at least once to the outpatient clinic, while it is acknowledged that only a part of this group will continue to experience persistent problems.[3,4] Although it might seem reasonable to assume that persistent complaints are more frequent in the hospitalized group (considering the higher likelihood of a more severe injury), the dichotomy of hospital admittance can be regarded as a rather over-simplified way of deciding who is in need of aftercare. Currently, it is unclear which of the non-hospitalized patients might need aftercare or specific advices on management of complaints. Hence, there is a need for additional information to find arguments that might add to this discussion on the clinical practice of care for non-hospitalized mTBI patients.

To this end, the goal of the current study was to describe the characteristics of non-hospitalized patients with mTBI to gain better understanding of the milder end of the spectrum of the mTBI population. In particular, the aim was to investigate which of the non-hospitalized patients returned to the outpatient neurological clinic to delineate this group of patients to identify the appropriate patient group in need for aftercare.

## METHODS

### Participants

This study was part of a prospective multi-center follow-up study (UPFRONT-study), comprising all mTBI patients above 15 years of age who presented at the ED of three level-1 trauma centers covering major mixed urban and rural regions in the Netherlands.

MTBI was defined by the attending neurologist or emergency physician by means of a Glasgow Coma Scale score (GCS) of 13-15, with posttraumatic amnesia (PTA)[10] of less than 24h and/or loss of consciousness (LOC) less than 30 minutes.[11] Exclusion criteria were: injury > 24h before ED visit, addiction to alcohol or drugs, severe comorbidity, psychiatric history for which the patient was admitted to a psychiatric hospital, and inability for follow-up (e.g. language barrier, homeless, living outside of referral region). For the current study, all patients admitted to the ward or ICU were excluded, leaving only those patients who were discharged directly from the ED. Hospital admission was based on clinical characteristics, defined by the European Federation Neurological Society (EFNS).[8] At the ED, brain CT-scan was performed and classified according to the Marshall criteria,[12] scores were dichotomized into normal CT (score 1) and abnormal CT-scan (score 2-6). Injury Severity Scores (ISS) were calculated based on hospital records.[13]

**Measures**

All participants of the UPFRONT-study received questionnaires at two weeks (T1), three months (T2) and six months (T3) after injury comprising items on complaints, mood and outcome. For the current study, the following questionnaires were used:

*Outpatient follow-up (T1-3):* At each time interval, patients were asked whether they visited one or several medical specialists (e.g. neurologist, surgeon). Patients were divided into groups based on outpatient follow-up with neurologists within six months after injury. Patients reporting outpatient follow-up at any moment were classified to the OFU group (with outpatient follow-up). Patients who completed all three measurements and reported no outpatient follow-up were classified as nOFU (no outpatient follow-up). In all cases, outpatient follow-up was initiated by the patients, and were referred to the outpatient clinic by a general practitioner.

*Head Injury Symptom Checklist (HISC) (T1-3):* The assessment of post-concussive complaints was done by means of a checklist,[4,14] comprising 21 common post-concussive complaints, which are scored on pre-injury and current levels. Dichotomized scores were calculated: 0= no increase and 1=any increase compared to pre-injury status.

*Hospital Anxiety and Depression Scale (HADS) (T1):* Feelings of anxiety and depression were measured using the HADS.[15] Both anxiety and depression are scored by means of seven questions on a 4-point Likert scale. The cut-off value is set at seven (range 0-28), above which patients are considered clinically depressed or anxious.

*Impact of event scale (IES) (T1):* To assess symptoms of post-traumatic stress patients completed the IES, which is a 15-item questionnaire with scores ranging from 0 to 5.[16,17] A cut-off value of 19 (range 0-75) is used to dichotomize patients into groups with and without serious symptoms of post-traumatic stress disorder.[18]

*Return to work (RTW) (T3):* Return to work was defined as "returning to previous vocational or educational activities". A return to work scale was applied for assessing partial or complete resumption, which was scored in 3 categories: 0= pre-injury work or study completely resumed, 1= pre-injury work or study partially resumed (i.e. work on a lower level or part time), 2= previous work or study not resumed. For analyses, we dichotomized scores into complete vs. incomplete and no resumption.
*Glasgow Outcome Scale Extended (GOS-E) (T3):* The Glasgow Outcome Scale defines outcome after TBI on an eight-point scale, ranging from death (score = 1) to complete recovery (score =8). Scores were dichotomized into complete recovery (score 8) and incomplete recovery (scores ≤7).[19,20]

**Statistical analyses**
Data was analyzed with SPSS 22.0 [IBM SPSS Statistics, SPSS Inc, Chicago, IL]. Patients and injury characteristics were compared using parametric (Student *t*-test) and non-parametric (Chi-square, Mann-U) testing. Prediction of group membership (OFU vs. nOFU) was done with univariate and multivariate binary logistic regression analyses.



## RESULTS

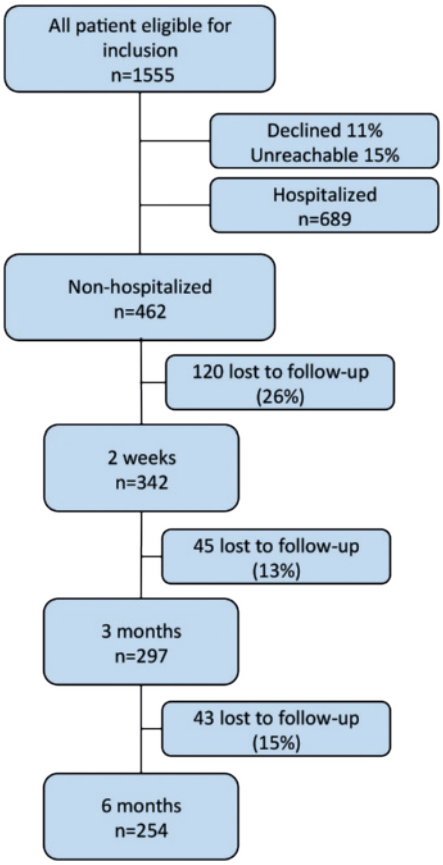
All mTBI patients arriving at the ED were screened for participation. In total, 25% was excluded based on various criteria: 5% alcohol/drug addiction, 10% psychiatric history, 5% inability for follow-up, 5% other reasons. Of those regarded eligible for inclusion (n=1555), 11% declined and 15% could not be contacted, leaving in total 1151 patients to be included in the UPFRONT-study, of which 40% (n=462) was discharged directly from the ED. Questionnaires were returned by 342 patients at two weeks, by 297 patients at three months and by 254 patients at six months (55%) after injury. Figure 1 shows a flowchart of all participants and follow-up moments. Patients who returned the first questionnaire (n=342) were older (42.6 (17.1) vs. 34.8 (18.6), $p<0.05$ and more often female (46% vs. 33%, $p=0.017$) than those who did not complete the first questionnaire (n=120). Table 1 provides patient and injury characteristics for the entire non-hospitalized group (n=462).

**Table 1.** Patient characteristics

| | All non-hospitalized patients (n=462) |
|---|---|
| **Patient characteristics** | |
| Age, years, mean (SD)<br>Range | 40.6 (18.5)<br>16-91 |
| Male gender | 57.4 |
| Pre-injury employment* | 70.9 |
| Retired | 13.4 |
| Unemployed | 15.7 |
| **Injury characteristics** | |
| Cause of injury | |
| Traffic | |
| Motor Vehicle Accident | 12 |
| Bicycle | 28 |
| Pedestrian | 2 |
| Fall/jump | 39 |
| Violence | 12 |
| Sport injury | 3 |
| Other | 4 |
| ISS score, mean (SD) | 5.22 (1.8) |
| Alcohol usage day of injury | 31.6 |
| GCS score | |
| 13 | 1 |
| 14 | 12 |
| 15 | 87 |
| Posttraumatic amnesia | |
| None | 19 |
| < 1 hour | 70 |
| 1 hour – 1 day | 11 |
| Loss of consciousness | 85 |
| CT-abnormalities | 2.0 |
| **Six month outcome** | |
| Number of complaints, mean (SD) | 3.6 (4.5) |
| Complete work resumption** | 86 |
| GOS-E, complete recovery | 64 |

Values are represented by percentages, if not specified otherwise.
*Pre-injury employment included vocational and educational activities.
** Only patients with pre-injury employment (n=160)
[a]Student-*t*-test; [b]Chi-square-test; [c]Mann-Whitney-U-test
ISS, Injury Severity Score; GCS, Glasgow Coma Scale; GOS-E, Glasgow Coma Scale Extended

**Figure 1.** Flow chart of all participants and follow-up moments**.**




In total, 291 patients provided information on outpatient follow-up with the neurologist, of which 25% returned to the outpatient clinic within six months after injury. None of the patient or injury characteristics described in table 1 differed between patients returning for follow-up (OFU, n=73) and patients not returning for follow-up (nOFU, n=218).

Outcome after six months was obtained for 81% of nOFU patients and 78% of OFU patients. Outpatient follow-up patients reported more complaints (6.0 (5.5) vs. 2.9 (3.8), $p<0.05$), a lower percentage of complete work resumption (67% vs. 90%, $p<0.05$), and a lower percentage of complete recovery according to GOS-E scores (49% vs. 69%, $p<0.05$) compared to nOFU patients. In total, 12 patients (4%) were involved in a case concerning litigation and/or compensation.

**Predictors for outpatient follow-up**

Patients returning for outpatient follow-up within six months after injury (OFU patients) were compared with patients who were not seen for follow-up (nOFU). Two weeks after

injury, OFU patients were more often depressed and anxious than nOFU patients (31% vs. 11%, p <0.001 and 37% vs. 17%, p <0.001). The groups did not differ significantly on the impact of event scale (46% vs. 34% above the cut-off, p=0.09) and amount of posttraumatic complaints after two weeks (6.3 vs. 5.2, p=0.09). The level of complete work resumption was also comparable between groups (57% vs. 60%, p=0.77). Univariate and multivariate logistic regression analyses with dependent variable outpatient follow-up and independent variables age, gender, anxiety, depression, post-concussive complaints and impact of event are summarized in Table 2.

**Table 2.** Univariate and multivariate logistic regression analyses with dependent variable outpatient follow-up

| | B(SE) | SE | P-value | Odds ratio (95% CI) |
|---|---|---|---|---|
| **Univariate regression** | | | | |
| Age | 0.003 | 0.01 | NS | 1.0 (1.0-1.0) |
| Gender | -0.517 | 0.22 | NS | 0.9 (0.5-1.5) |
| HADS, anxiety | 1.097 | 0.32 | 0.001 | 3.0 (1.6-5.6) |
| HADS, depression | 1.253 | 0.35 | <0.001 | 3.5 (1.8-7.0) |
| HADS, anxiety and depression | 1.301 | 0.39 | 0.001 | 3.7 (1.7-7.9) |
| Post-concussive complaints | 0.053 | 0.03 | NS | 1.1 (1.0-1.1) |
| Impact of Event scale | 0.012 | 0.01 | NS | 1.0 (1.0-1.0) |
| **Multivariate regression** | | | | |
| Constant | -1.462 | 0.18 | | |
| HADS, anxiety | 0.279 | 0.45 | NS | 1.3 (0.5-3.2) |
| HADS, depression | 1.097 | 0.471 | 0.02 | 3.0 (1.2-7.5) |

R2 = 0.05 (Cox & Snell), 0.07 (Nagelkerke). Model X2 (2) = 12.81, p = 0.002

## DISCUSSION

This paper focused on characteristics, outpatient follow-up and outcome of non-hospitalized mild traumatic brain injury patients. Six months after injury, outcome was not as good as we had expected. Patients had on average four posttraumatic complaints and 36% showed incomplete recovery as defined by the GOSE. Within six months after injury, one in four of the non-hospitalized patients returned to the outpatient neurology clinic of which one third had not completely resumed their pre-injury work or study. The patients seen at the outpatient clinic were more often depressed and/or anxious two weeks after injury, than those patients not seen at the outpatient clinic, while no differences were found in posttraumatic complaints or pre-injury (e.g. age, gender, employment status) and injury characteristics (e.g. GCS, ISS or PTA).

The finding that 25% of non-hospitalized patients presented themselves at the outpatient clinic within six months after injury is rather remarkable given the supposed good recovery of this patient group. Predicting which patients need outpatient follow-up is not possible already at the ED, since neither injury nor patient characteristics differed between OFU and nOFU patients. Two weeks after injury, both groups reported the same number of posttraumatic complaints and the same level of work resumption. However, patients seen for outpatient follow-up were more often depressed and/or anxious. Both variables showed a three-fold risk for outpatient follow-up in univariate regression. The higher odds ratio for depression, and the stronger effect over anxiety in the multivariate model shows that depression is a more important predictor in this respect, which has also been established in earlier studies.[21,22] A combination of both mood disorders showed an odds ratio of almost four, meaning that patients scoring above the cutoff for both anxiety and depression as early as two weeks after injury, have a four-times increased risk of returning to the outpatient clinic with delayed recovery.



Given the high incidence of mTBI, it would be of great value to timely identify which patients are in need for outpatient follow-up, especially since one in three of patients returning to the outpatient clinic had not resumed their vocational or educational activities after six months. Also, in the nOFU group, one in ten patients had failed to resume their pre-injury activities. The both groups combined shows that a substantial part of non-hospitalized patients who were employed before injury struggle with work or study resumption. This pattern was also demonstrated in GOS-E scores, were almost one third of the patients who were not seen for follow-up did not reach complete recovery within six months after injury. This indicates that problems not only arise in vocational reintegration, but also in overall outcome and resumption of social activities. The patients who returned for outpatient follow-up within six months after injury, were already two weeks after injury more anxious and depressed. Apparently, problems with resumption of previous activities become clear after a certain time interval post injury, during which the non-emotional distressed patients seem to recover. This suggests that patients have been struggling with their problems for a while, before seen by a neurologist with possible loss of work productivity that could have been prevented. Currently, outpatient follow-up is recommended for all hospitalized mTBI patients,[8] while for non-hospitalized patients specialized follow-up is restricted to those with persistent complaints or problems returning to previous activities. Since the outcome figures in our study are comparable to a recent study of mTBI, that included both hospitalized and non-hospitalized patients, we suggest it would be reasonable not to make such a considerable difference between these two groups when defining aftercare.[23]

Based on the finding that outcome for non-hospitalized patients is not always as good as expected, and that emotional distress two weeks after injury seems to be of influence,

we propose a change in clinical policy for non-hospitalized mTBI patients. We believe it could be feasible to contact all patients to assess posttraumatic complaints and feelings of depression and anxiety to identify at-risk patients for unfavorable outcome. Patients with posttraumatic complaints and an indication of emotional distress (based on the HADS questionnaire), should receive additional information on the course of recovery after mTBI. Telephonic aftercare in the sub-acute phase of mTBI and additional information on outcome and management of complaints has been shown to be productive in symptom reduction.[24,25] The most appropriate setting for information provision (e.g. during telephonic counseling or at the outpatient clinic) was not part of this study, and should be studied more extensively in the future. Although we realize that more extensive follow-up of mTBI patients might pose the risk of unnecessary care consumption, early signaling could on the long term not only reduce the indirect costs of mTBI due to lost work productivity, but might also prevent long-term outpatient follow-up visits and the associated diagnostic costs (i.e. Magnetic Resonance Imaging, Neuropsychological examination).

Although this study provides valuable information concerning outcome and follow-up of non-hospitalized mTBI patients, some considerations regarding the generalizability of our results should be taken into account. The admittance rate in our study was somewhat higher as compared to other mTBI studies,[26] probably related to the inclusion of physically injured patients, which comprised 15% of our cohort. Although this makes comparison between studies challenging, mTBI is often accompanied by non-head injuries, which makes the inclusion of these patients important when discussing the entire group. However, as a result of the exclusion criteria of the UPFRONT-study, patients with alcohol and/or drug abuse, and patients with a psychiatric history requiring admission were not included, mostly due to anticipated follow-up problems.[27] These patients also form an important subgroup of the mTBI population, with more problems recovering from their trauma than the general population. Although we acknowledge that including these patients would form a better representation of the entire mTBI spectrum, our results provide insight into a cohort of patients of varying ages that might benefit from early recognition of unfavorable recovery. Another generalization problem is related to patient drop-out in longitudinal follow-up studies which mostly concerns those with good recovery.[28] In our study, patients returning the first questionnaire were older and more often female, creating a possible bias in the results. Notwithstanding these limitations, we think to have provided valuable information that improves the understanding of the recovery trajectory of the entire spectrum of mTBI as our study is conducted among a large sample of mTBI patients, with acceptable dropout rates. With this study, we hope to increase awareness for non-hospitalized mTBI patients and plea for more research on outcome and treatment possibilities for this particular group of patients, a TBI minority that should not be forgotten.

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4

# Subacute posttraumatic complaints and psychological distress in trauma patients with or without mild traumatic brain injury

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Injury. 2016 Sept; 47(9):2041-2047

## ABSTRACT

### Objectives

To identify the frequency, nature and profile of complaints for trauma patients with and without mild traumatic brain injury (mTBI), and to assess their relation to anxiety and depression.

### Methods

A prospective cohort study in a level-one trauma centre was conducted. Mild traumatic brain injury patients and trauma controls were approached for participation. Two weeks after injury, The Head Injury Symptom Checklist (HISC) and the Hospital Anxiety and Depression Scale (HADS) were administered.

### Results

Two hundred seventy-two (272) patients with mTBI and 125 TC patients completed the questionnaires. Differences were demonstrated between the two trauma populations on frequency and nature of reported complaints. Ordinal common factor analysis on the mTBI scores yielded three factors: mental distress, physical discomfort, and sensory disbalance, which were all significantly correlated to anxiety and depression scores. Discriminant analyses identified a subset of complaints which could allocate almost 80% of patients to the correct group.

### Conclusions

Patients with mTBI showed a different pattern of complaints than orthopaedic control patients. A mental distress factor consisting of both somatic and cognitive complaints proved to be most discriminating and showed high correlations with anxiety and depression.

## INTRODUCTION

Traumatic brain injury (TBI) is considered a leading cause of death and disability worldwide. The majority of injuries consist of mild traumatic brain injuries (mTBIs), which is defined as a head injury caused by external physical force, resulting in a Glasgow Coma Scale Score of 13-15, with a short period of loss of consciousness (<15 minutes) and/or posttraumatic amnesia (<24 hours).[1] The incidence of mTBI is estimated at 100-200 per 100,000 individuals per year, with an increase in Emergency Department (ED) visits over the last years.[2,3] This increase in TBI related ED visits underlines the importance for physicians working at the ED to be aware of risk factors and outcome for mTBI. Most mTBI patients initially report posttraumatic complaints like headache, dizziness or forgetfulness, but recover within the first three months after injury without residual complaints. However, a subgroup of approximately 15-20% of cases, continues to experience posttraumatic complaints up to several months after sustaining an injury.[4–6]

Although these posttraumatic complaints are often attributed to brain injury, similar complaints are also commonly reported by uninjured individuals[7–9] and non-head injured trauma patients.[10,11] Several studies yielded evidence that experience of posttraumatic complaints might be influenced by several non-brain injury related factors including stress,[12] illness perception,[13] and symptom expectation.[14] It has been established that early psychological distress such as anxiety and depression is common after mTBI, and is associated with posttraumatic symptoms.[15,16] However, to which extent this relation between such complaints and anxiety and depression is also present in non-head injured patients has been poorly examined.

To obtain a better understanding of the construct of posttraumatic complaints, various research groups have performed factor analysis. Several studies have identified domains in which complaints tend to cluster, the 'complaint factors'. Yet the results of these studies failed to generate consistent results. Models of two, three or even four complaint factors have been suggested. Most studies describe at least one somatic/ physical domain, other proposed domains are related to cognitive or emotional/ affective complaints.[10,17–19] Apart from differences in identified domains, difficulties arise with complaints that fit in the cognitive as well as the emotional and somatic domain (e.g. sleep disturbances and fatigue). These inconsistencies with allocating complaints to certain domains indicates an overlap between complaints and clusters, which suggests that there might be a more general underlying construct. Complaints in the subacute phase after mTBI could be the result of a form of general (psychological) distress, instead of disturbances in cognitive or physical capacities. However, the relation between anxiety, depression and complaints in different domains remains largely unexamined in studies so far. The aforementioned find-

ings illustrate the proposed non-specific nature of posttraumatic complaints, and warrant further exploration of other underlying aspects.

Therefore, the purpose of this study was to investigate which complaints are more specific for mTBI patients in comparison to orthopaedic trauma control patients in the subacute phase (i.e. two weeks post-injury) and in particular to determine which combination of complaints indicates a disease specific profile for mild traumatic brain injury. In addition, test-retest reliability analyses were performed on data of healthy controls to assure the use of a stable measurement tool to assess posttraumatic complaints. We applied factor analysis to establish the underlying factors determining performance on the complaints list. Lastly, we examined the extent to which these factors were related to anxiety and depression to better understand the underlying construct of these disabling complaints.

## METHODS

### Participants

*Mild traumatic brain injuries (mTBI):* Patients were recruited from a prospective follow-up study on outcome in mTBI (UPFRONT-study), conducted in the University Medical Center Groningen (UMCG), a level I trauma centre. Patients were included at the ED between May 2013 and December 2014. MTBI was defined by the attending neurologist or ED physician by the following criteria: A head injury caused by external physical force resulting in a Glasgow Coma Scale (GCS) score of 13-15, loss of consciousness (LOC) of ≤ 15 minutes (documented, reported or self-reported) and/or posttraumatic amnesia (PTA) of ≤ 24 hours.[1]

*Trauma controls (TC):* Non-head-injured patients were recruited at the outpatient surgical clinic of the UMCG between June 2013 and October 2013. All patients who sustained a minor injury to an extremity (e.g. sprain or uncomplicated fracture of wrist or ankle), for which they had visited the ED less than 31 days previously were invited to complete the questionnaires at the outpatient clinic. Injury characteristics were gathered from medical records.

*Healthy controls (HC):* The volunteers for the healthy comparison group were recruited among working and social environment of the authors. Participants were asked to complete the questionnaire twice, with a two-week time interval, to determine test-retest reliability.

For all subgroups inclusion criteria were: age from 16-65 years and comprehension of the Dutch language. Participants were excluded based on the following criteria: a history of head injury (and concomitant head injury for the TC-group) requiring hospital admission, drug or alcohol addiction, psychiatric co-morbidity or unavailability for follow-up. This study was approved by the local ethical committee of the UMCG.

**Measures**

*Posttraumatic complaints*: the Head Injury Symptom Checklist (HISC)[20] contains 19 frequently reported complaints after traumatic brain injury. In addition, two non-posttraumatic complaints (itchiness and dry mouth) are assessed as an indicator of tendency to complain. The HISC scores each posttraumatic complaint on the pre-injury and current level with values ranging from 0 to 2 (never = 0, sometimes = 1, and often = 2). For each symptom a difference score is calculated by subtracting the pre-injury score from the current score. All resulted scores, to be denoted as complaints, were dichotomized into 0 (no increase in complaints) and 1 (any increase in complaints).

*Depression and anxiety*: Symptoms of depression and anxiety were assessed by means of the Hospital Anxiety and Depression Scale (HADS).[21] The HADS is a 14-item questionnaire, measuring 2 subscales (depression and anxiety) of 7 items each, resulting in a subscale score ranging from 0-21. A cut-off score of ≥ 8 is recommended for establishing the presence of both depression and anxiety.



**Statistical analyses**

The data were analyzed using SPSS (version 22.0). Demographic variables and injury characteristics of mTBI and TC patients were compared using parametric (Student *t*-test) and non-parametric (Mann-Whitney *U*-test, $\chi^2$-test) testing when appropriate. Test-retest analyses were performed by calculating kappa scores. Factor analysis was performed on the mTBI group. Because the data on complaints were dichotomous, we applied an exploratory ordinal common factor analysis with the software program FACTOR.[22] A polychoric parallel analysis with 95% boundary was used to indicate the number of factors, unweighted least squares as the method of extraction, with oblique rotation (Promin). Performing a separate analysis on the data of the TC patients does not allow a direct comparison between the factors found in both groups.[23] A discriminant analysis was performed to assess which complaints contributed most to group prediction. A cut-off of 0.4 was applied to determine which complaints were most discriminant in the function. With the most discriminating complaints an unweighted scale was constructed. A Receiver Operating Characteristic (ROC) analysis was performed to see how well group membership could be predicted. For all analyses, alpha was set at 0.05 two-sided.

## RESULTS

### Participants

During the inclusion period, 416 mTBI patients participated in the UPFRONT-study, of whom 272 patients completed both questionnaires. In the TC group, 205 non-head-injured patients were approached for participation, of whom 125 patients completed the questionnaires. Trauma control patients were most commonly treated for uncomplicated fractures (50%) and sprains (16%) in the upper (51%) or lower (46%) extremity. The mean interval between injury and follow-up was 16 days (SD 8.5 days), with a mean difference of 2 days between groups (mTBI 16 days vs. TC 14 days, p=0.001) Two weeks after injury, fifty percent of the mTBI patients had resumed their work or study, compared to 57% of the TC patients. Patient demographics and injury characteristics for both groups are summarized in Table 1.

### Posttraumatic complaints

Figure 1 depicts the percentage of patients reporting complaints two weeks after injury, expressed as percentages of the total groups. All complaints, except for itchiness (12% vs. 15%; p=0.342), arm pain (25% vs. 18%; p=0.119), trouble falling asleep (23% vs. 16%; p=0.120), and trouble sleeping through the night (27% vs. 22%; p=0.264) were reported significantly more often in the mTBI group. Missing scores varied from 0-2 percent, with the exception of alcohol intolerance, which was missing in 11% of the mTBI group.

**Figure 1.** Posttraumatic complaints two weeks after injury for mTBI and TC patients in percentages of the total group.

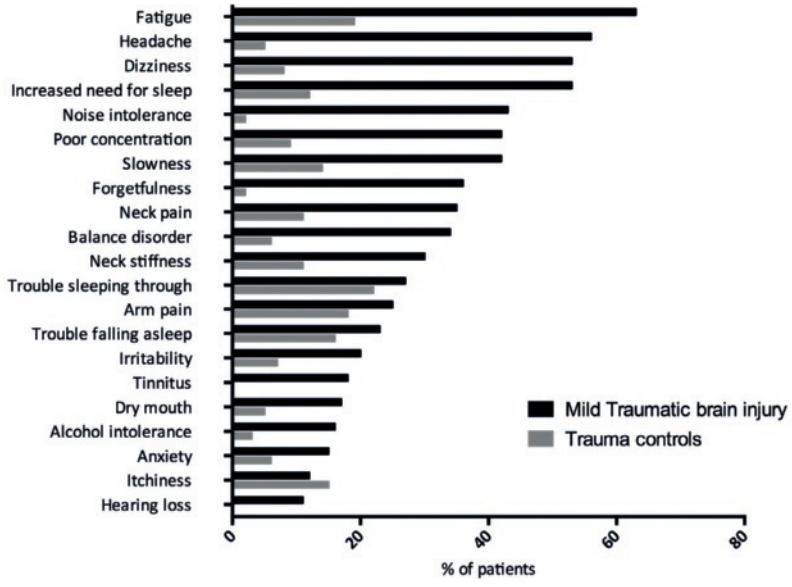


**Table 1.** Characteristics of patients with mild traumatic brain injury (mTBI) and trauma controls (TC).

| | 1) MTBI (N=272) | 2) TC (N= 125) | Difference 1-2 P-value |
|---|---|---|---|
| **Patient characteristics** | | | |
| Age, years, *mean (SD)* | 40.0 (15.4) | 35.8 (15.0) | 0.013[a] |
| Male gender | 171 (62.9) | 77 (60.6) | 0.809[b] |
| Employment status | | | 0.239[b] |
| Working/student | 223 (82.0) | 97 (77.6) | |
| Not working | 47 (17.3) | 28 (22.4) | |
| **Injury characteristics** | | | |
| Cause of injury | | | <0.001 [b] |
| Motor Vehicle Accident | 65 (23.9) | 5 (4.0) | |
| Fall/jump | 170 (62.5) | 45 (36.0) | |
| Violence | 13 (4.8) | 7 (5.6) | |
| Sport injury | 11 (4.0) | 25 (20.0) | |
| Other | 11 (4.0) | 43 (34.3) | |
| Day of injury alcohol intoxication | 102 (37.5) | 5 (4.0) | <0.001 [b] |
| Hospital admission | 143 (52.8) | 20 (16.0) | <0.001 [b] |
| Days admitted, *median (range)* | 2 (1 – 60) | 4 (1 – 18) | 0.002[c] |
| Posttraumatic amnesia | | | |
| None | 30 (11.0) | | |
| < 1 hour | 108 (39.7) | - | |
| 1 hour – 1 day | 91 (33.5) | - | |
| Unknown | 43 (15.8) | - | |
| Loss of consciousness (yes) | 189 (82.2) | - | |

Data are represented by numbers (percentages) if not specified otherwise
[a] Student t test; [b] Pearson's c-square test; [c] Mann-Whitney U test

### Healthy controls

Healthy controls (n=100) were invited to complete the HISC twice with a two-week time interval, in order to assess its test-retest reliability. Eighty percent of the participants returned two questionnaires within the given time frame. No significant differences were found in age, gender, and time interval between the healthy controls and the mTBI and TC group. Table 2 shows findings from test-retest analyses for each complaint.

**Table 2.** Test-retest analyses in healthy control subjects with a two-week time interval (n=80).

| Complaint | Kappa |
|---|---|
| Fatigue | 0.70** |
| Headache | 0.47** |
| Dizziness | 0.68** |
| Increased need for sleep | 0.62** |
| Poor concentration | 0.53** |
| Neck pain | 0.49** |
| Balance disorders | 0.61** |
| Slowness | 0.29** |
| Neck stiffness | 0.52** |
| Trouble sleeping through | 0.63** |
| Arm Pain | 0.71** |
| Trouble falling asleep | 0.99** |
| Forgetfulness | 0.74** |
| Tinnitus | 0.88** |
| Noise intolerance | 0.60** |
| Dry mouth | 0.73** |
| Alcohol intolerance | 0.63** |
| Irritability | 0.65** |
| Itching | 0.73** |
| Hearing loss | 0.50** |

** significant on the <0.01 level

### Factor analysis

Factor analysis was performed on HISC scores of 272 mTBI patients. Due to the high number of missing values on the question of alcohol intolerance, we excluded this question from the analysis. The remaining 20-symptoms formed a three-factor solution with eigenvalues of 7.27, 2.00 and 1.77. An oblique promin rotation was performed, which led to a 48.4% explanation of total variance. Table 3 provides factor loadings, explained variances, and inter-factor correlation coefficients. The factors were labelled as sensory disbalance, physical discomfort, and mental distress. Controlled severity scores for the mTBI and TC group were calculated for the factors, which were all significantly higher in the mTBI group.

**Table 3.** Factor analysis of the 20-item Head Injury Symptom Checklist for patients with mTBI 2 weeks after injury (n=272). Bold face loadings depict the complaints part of the three factors. Scale scores for each identified factor are provided for the mTBI and TC group.

| Symptom | Mental distress | Physical discomfort | Sensory disbalance |
|---|---|---|---|
| Dizziness | **0.940** | -0.302 | -0.060 |
| Slowness | **0.719** | 0.176 | 0.044 |
| Noise intolerance | **0.700** | 0.036 | 0.017 |
| Balance disorder | **0.679** | -0.266 | 0.228 |
| Fatigue | **0.654** | 0.111 | -0.045 |
| Headache | **0.645** | -0.139 | 0.067 |
| Poor concentration | **0.619** | 0.142 | 0.070 |
| Irritability | **0.599** | 0.100 | -0.063 |
| Forgetfulness | **0.572** | 0.069 | 0.176 |
| Anxiety | **0.530** | 0.194 | -0.057 |
| Increased need for sleep | **0.450** | 0.208 | -0.008 |
| Neck pain | 0.184 | **0.754** | -0.127 |
| Neck stiffness | -0.011 | **0.674** | 0.078 |
| Trouble sleeping through | -0.077 | **0.592** | 0.468 |
| Arm pain | -0.163 | **0.543** | 0.034 |
| Trouble falling asleep | 0.045 | **0.464** | 0.332 |
| Hearing loss | 0.010 | -0.006 | **0.819** |
| Tinnitus | 0.274 | -0.119 | **0.716** |
| Dry mouth | 0.284 | 0.105 | **0.319** |
| Itching | -0.162 | 0.296 | **0.313** |
| **Factor characteristics** | | | |
| Explained variance | 25.8% | 11.9% | 10.7% |
| Reliability estimate | 0.92 | 0.84 | 0.87 |
| **Inter-factor correlation matrix** | | | |
| Mental distress | 1.000 | | |
| Physical discomfort | 0.520 | 1.000 | |
| Sensory disbalance | 0.336 | 0.064 | 1.000 |
| **Scale scores for the identified factors** | | | |
| MTBI, *Mean (SD)* | 4.6 ± 3.3 | 1.4 ± 1.5 | 0.60 ± .94 |
| *Median (range)* | 4 (0-11) | 1 (0-5) | 0 (0-4) |
| TC, *Mean (SD)* | 0.9 ± 1.7 | 0.8 ± 1.3 | 0.20 ± 0.46 |
| ***Median (range)*** | 0 (0-10) | 0 (0-5) | 0 (0-2) |
| P-value difference[a] | <0.001 | <0.001 | <0.001 |

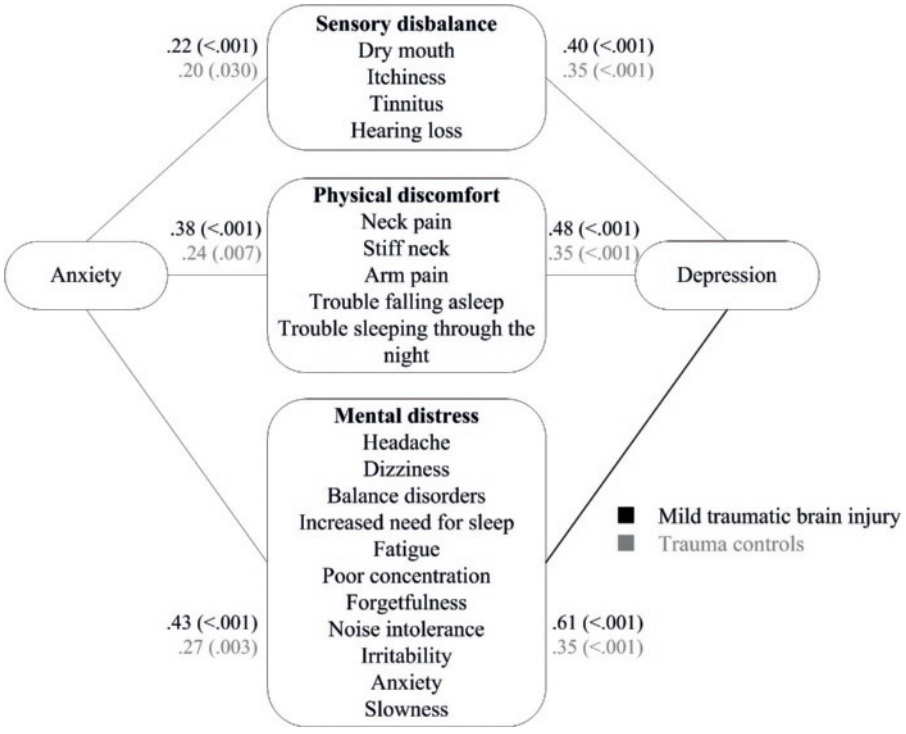
[a] Mann-Whitney U test

### Anxiety and depression

Scale scores were compared with anxiety and depression scores, for further exploration of the constructs of complaints. Mean HADS scores were significantly higher for the mTBI group compared to the TC group: anxiety (4.3 vs. 2.8; p <0.001) and depression (3.5 vs. 2.3; p=0.002). When applying the cut-off score of 8, 13% of patients with mTBI were defined as depressed, and 16% as anxious. In the TC group, 5% scored above the cut-off for depression and 5% above the cut-off for anxiety.

Figure 2 illustrates the correlations between the three factors and symptoms of anxiety and depression, for the mTBI and the TC group separately. Correlations with anxiety and depression scores did not differ significantly between the two groups for the first two factors, i.e. sensory disbalance (anxiety Z-score 0.22, p=0.83; depression Z-score 0.59, p=0.56) and physical discomfort (anxiety Z-score 1.43, p=0.15; depression Z-score 1.07, p=0.29), nor for anxiety with mental distress (Z-score 1.81, p=0.70). Only for the correlations between mental distress and depression a difference was found: the correlation was higher in the mTBI group (Z-score 3.15, p=0.002).

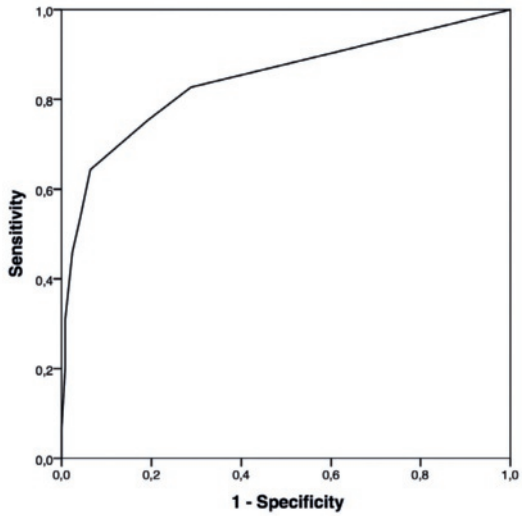
**Figure 2.** Correlations between total factors scores and HADS scores in patients with mTBI and trauma controls 2 weeks after injury.



### Discriminant and ROC analysis

A discriminant analysis was performed to assess which combination of complaints could optimally distinguish between the two groups. The most discriminating complaints appeared to be (with discriminant loadings): headache (0.73), dizziness (0.63), noise intolerance (0.60), fatigue (0.59), increased need for sleep (0.56), forgetfulness (0.52), poor concentration (0.47), and balance disorders (0.42). The predicted membership, as based on the classification equation, was correct for 78.8% of the patients, of which 77.6% of the mTBI patients, and 81.6% of the TC patients. The eight most discriminating complaints were used to construct an unweighted scale. The scale was added as a predictor for group membership in an ROC analysis. The ROC-curve is depicted in Figure 3 the area under the curve was 0.845 ($p<.05$). With a cut-off value of three complaints, the sensitivity was 64% and specificity was 94%.

**Figure 3.** Receiver Operating Characteristic curve for prediction of group membership (mTBI vs. TC) based on an unweighted scale constructed of most discriminating complaints.






## DISCUSSION

The main objective of this study was to identify differences in posttraumatic complaints between two cohorts of trauma patients comprising a group with brain injury and a non-brain injured trauma control group, focussing on frequency, clustering and relation with symptoms of anxiety and depression in the subacute phase after injury. In particular we aimed to find a specific profile to characterize the complaints of mTBI patients. The main finding was that most complaints were not only reported more often after mTBI, but also that they showed in combination a clearly different pattern when compared to

the trauma control group. Factor analysis on the complaints reported by mTBI patients revealed a three-factor structure with factors labelled as: mental distress, physical discomfort and sensory disbalance. Correlating these three factors with anxiety and depression in both groups showed that the relation was strongest in patients with mTBI, in particular the relation between symptoms of depression and mental distress. Based on discriminant analysis, a discriminant function combining several complaints could allocate almost 80% of patients to the correct group, with as most discriminating complaints those that were all part of the mental distress factor.

Previous studies on mTBI outcome have focused on nature, severity and specificity of posttraumatic complaints. Several cohorts of mTBI patients have been compared to orthopaedic trauma controls and healthy controls, with the consistent finding that complaints are common in all groups and thus not always mTBI specific.[5,11,16] These studies did not emphasize that although posttraumatic complaints occur also after non-head trauma, the pattern in this group is clearly different. We identified 15 complaints that were reported significantly more often in the mTBI group. The five most common symptoms in the mTBI group were fatigue (63%), headache (56%), dizziness (53%), increased need for sleep (53%), and noise intolerance (43%). A similar pattern of most frequent complaints was found in earlier research.[24,25] The pattern of most frequently mentioned complaints among trauma control patients was clearly different: this group scored highest on trouble sleeping through the night (22%), fatigue (19%), arm pain (18%), trouble falling asleep (16%), and itchiness (15%). The only overlapping complaint in these top-five complaints was fatigue. It seems likely that the mental/cognitive complaints in the mTBI group result in a mental fatigue, whereas the physical complaints in the TC group contribute to trouble falling asleep and sleeping through the night, thereby causing a more physical fatigue, which are considered distinctive features of fatigue.[26] Although these patterns are clearly different, both patient groups are limited in their return to daily activities. This indicates that complaints, whether they are of mental or physical nature, are problematic for a large group of ED-visiting patients. Since previous studies showed that complaints in the (sub)-acute phase are relevant for predictors for mTBI outcome, identifying the nature and profile of these complaints is of the utmost importance.

Through factor analysis on the mTBI data, three symptom factors were identified, with the “mental distress” factor accounting for the largest number of complaints and the largest amount of explained variance. Earlier studies have described smaller, more distinguishable domains such as the cognitive, somatic, or affective ones. Combinations of these domains are also common, depending on time of measurement and study cohort.[10,17] Complaints that are commonly described as being of cognitive nature (e.g. poor concentration, forgetfulness, and slowness in thinking) might become more apparent as a

separate subset of complaints when resuming previous activities such as work or study. For example, Lundin et al. found that poor memory and concentration were the most commonly reported symptoms three months after injury, whereas headache and dizziness were more prominent in the early phase, i.e. 1,7, and 14 days after injury.[27] The present study suggests that mental distress is an important underlying factor and influences functioning in the subacute phase after injury, causing the wide range of somatic, cognitive and affective complaints of mTBI patients. This hypothesis is supported by our findings on the correlations between the identified factors and anxiety and depression scores. The mental distress factor correlates strongly with anxiety and depression scores on the HADS in the mTBI group, especially when compared to the other factors and to the correlation within the TC group. The performed discriminant analysis provides additional support for the explanation of general mental distress causing complaints in the subacute phase: the participants of this study could be allocated to the correct group (i.e. mTBI or TC) in 79% of cases with the most differentiating complaints in this respect being all part of the mental distress factor. The most discriminating complaints were used to construct a scale for predicting group membership, which showed a good sensitivity and specificity in ROC analysis. These arguments all converge to the assumption that the subacute phase after mTBI is very different from the same period after a non-brain trauma. The differences are characterized by a distinguishable pattern of complaints and a stronger relation with symptoms of anxiety and depression in the mTBI group.



The physical discomfort factor consists of three complaints indicating soreness in the upper extremity or neck and two complaints of sleep disturbances. Neither the frequency of sleep disturbances nor arm pain differed significantly between the mTBI and TC group. However, more than half of the TC group suffered from an upper extremity injury which is most likely to explain the relatively high scores on arm pain, which is the third most common complaint in the TC group. The physical discomfort construct could explain the disturbances in sleeping (e.g. due to pain), which is supported by earlier research in which sleeping issues where found to be included in the general somatic factor, together with other physical complaints.[17,19] Caplan and colleagues, however, found difficulty falling/staying asleep to be part of the affective factor, indicating a psychological explanation.[28] This study was performed in a sample of US military soldiers, among whom PTSD is more common. PTSD is often accompanied by feelings of intrusion during night time,[29] which most likely provides the explanation for an affective factor including sleep disturbances.

We described a relatively new factor sensory disbalance, with itchiness, dry mouth, tinnitus and hearing loss. All four complaints were infrequently reported in both study groups, with a prevalence of zero in the TC group for the latter two. These two ear-related complaints had high loadings on this factor, whereas itchiness en dry mouth had low

loadings. Itchiness and dry mouth were introduced in the HISC to assess an increased tendency to complain, since these complaints are not considered to be related to the sustained brain trauma. We hypothesized that these complaints would correlate strongly with depression and anxiety scores on the HADS. However, the correlations found with the HADS were weak, which might be explained by the presence of the other two complaints of which this factor consists, which can be likely but infrequent consequences of brain injury. Furthermore, itchiness was a common complaint in the TC group probably due to treatment of various fractures with plaster, which commonly leads to dermal irritation. Moreover, both dry mouth and itchiness show loadings of comparable magnitudes on the mental distress and physical discomfort factors also, making interpretation of the factor more difficult. Hence, it may be the case that the specific combination of itchiness and dry mouth might be of use in assessing an increased tendency to complain for mTBI patients, but this conclusion cannot be drawn based on our present results.

This study was the first to relate different subsets of complaints (i.e. factors) with symptoms of anxiety and depression. Previous studies identified the importance of anxiety and depression in the development of complaints and outcome,[30–33] but failed to identify to which complaints these mood disorders are most strongly related. The influence of symptoms of anxiety and depression in the early phase after injury seems to play the most important role in the mental distress factor, especially after a mild traumatic brain injury. This factor consists of somatic, cognitive as well as affective complaints, which are all frequently reported after mTBI. Their co-occurrence with anxiety and depression indicates even stronger that mental distress is present in the sub-acute phase.

A high level of mental distress in the first few weeks after injury, could in turn cause a delayed recovery and return to functioning. This post-acute mental distress should be signalled within the first few weeks after injury, to offer timely counselling or treatment that might prevent persisting complaints and problems with reintegration in work, study or community.

**Limitations**

Although our study provides new information into the development of complaints in two trauma cohorts, some limitations must be taken into account.

The primary goal of our study was to examine whether a specific subset of complaints could be identified for patients with mild traumatic brain injury. Therefore, we included a sample of orthopaedic trauma patients from the ED, with an expected full recovery within weeks as control patients. Even though we aimed at including a cohort as similar as possible, the cause of injury differed between our study groups, and mTBI patients

were admitted to the hospital more often. However, other important parameters such as gender and pre-injury employment status did not differ between group, and the use of an orthopaedic trauma control group is widely accepted in mTBI research.[5,10,11,34]

We used a different questionnaire than the widely accepted RPQ. Although the HISC is derived from the RPQ, some questions were added or left out. Applying a different questionnaire in another language could lead to challenges when comparing results with previous or future research. The list has, however, been used in a clinical and research setting for many years,[20,30,35] and reported frequencies of complaints in our study were comparable to findings in similar study groups suggesting an adequate translation of complaints.[4,11] Lastly, test-retest analyses among healthy control subjects showed a high inter-item consistency, indicating a stable measurement tool. A cohort of mTBI or TC patients in the chronic phase after injury with stable complaints might have been more ideal to carry out these analyses on inter-item consistency. However former studies[7,8] have shown that healthy controls also report complaints in the posttraumatic spectrum and thereby may serve as a reliable group to investigate the consistency of the applied checklist.



Based on high rates of missing values on the question of decreased alcohol intolerance we decided to exclude this question for further analyses. The questionnaire does not offer a “not applicable” option and multiple patients indicated not to have drunk alcohol since their injury, making the tolerance impossible to assess. Furthermore, some questions might have been interpreted in different manners among patient groups. Slowness and fatigue could be viewed as either mental or physical complaints, which might provide for disturbed factors. Nevertheless, the general description of these common complaints could also be useful, as these complaints, whether they are of cognitive or physical nature, might both lead to disability and delayed return to work or study. An external independent validation in other study cohorts of the factors found in our analyses could give more insight into how robust these identified factor are, which could be the aim of future studies.

Another limitation in the interpretation of the reported complaints, which many mTBI researchers encounter, is the “good-old-days” bias, where patients perceive the pre-injury level of complaints on a lower level, leading to an overestimation of the difference with the current level.[36,37] Most studies only register the actual amount of complaints and with the use of the HISC we attempted to correct for this bias by requesting the patients to actually score the pre-injury level.

## CONCLUSIONS

This study demonstrated differences between two trauma populations on frequency, nature and pattern of reported complaints. The identified three-factor model in which complaints clustered in mTBI pertained to physical discomfort, mental distress, and sensory disbalance. The posttraumatic complaints that were most discriminating for the mTBI group were all part of the mental distress factor, which showed the highest correlation with depression. This indicates that the influence of especially depression but also anxiety is important after sustaining a trauma and that mental distress results in higher levels of complaints. Our findings provide valuable insight into a distinguishable subset of posttraumatic complaints occurring after a mild traumatic brain injury and might lead to intervention strategies aimed at decreasing psychological distress to enhance better functional outcome.

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# Acute alcohol intoxication in patients with mild traumatic brain injury: Characteristics, recovery and outcome

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Journal of Neurotrauma. 2016 Feb 15; 33(4):339-345

**ABSTRACT**

A substantial number of patients (30-50%) sustains a mild traumatic brain injury (mTBI) while they are under the influence of alcohol. An acute alcohol intoxication (AAI) at the time of injury has been subject of research in severe TBI, but little is known about the relation between AAI and mTBI. This study aimed to describe the characteristics of this intoxicated subgroup and evaluate recovery and outcome in comparison to sober mTBI patients. We included 528 mTBI patients (Glasgow Coma Scale [GCS] score 13-15) admitted to two level 1 trauma centers as part of a prospective follow-up study. We compared clinical characteristics, demographics and injury mechanism between groups. Post-concussive complaints, mood disorders and post-traumatic stress-related complaints were assessed at two weeks post- injury, and outcome at six months with the Glasgow Outcome Scale Extended (GOSE). 33% of the mTBI patients was intoxicated. Results showed that the intoxicated group was younger (36 vs. 40 years, p=.001), and were more frequently of male gender (78% vs. 60%, p<.001). The groups also differed in injury related characteristics, with intoxicated patients more frequently sustaining falls- or violence related injuries. The intoxicated group was assessed with a lower GCS score and had a higher hospital admission rate. However, at two weeks post-injury, intoxicated patients reported less complaints than the non-alcohol group and showed a better recovery at six months (average GOSE scores 7 vs. 7.3, p=.030). We conclude that AAI in mTBI represents a characteristically different group, which has implications for prevention measures as well as the course of recovery.

## INTRODUCTION

Traumatic brain injury is one of the most common neurological disorders, with mild traumatic brain injury (mTBI) accounting for approximately 80-90% of all cases.[1] Incidence rates of mTBI are estimated at 100-300/100,000 population, most frequently affecting males under 50 years of age.[2–4] Excessive alcohol consumption leading to acute alcohol intoxication (AAI) is associated with a higher risk of mTBI; up to 30-50% of all mTBIs are incurred when individuals are under the influence of alcohol.[5,6] These rates are not surprising, considering that AAI results in impaired decision making, impaired motor control, a lack of inhibitory control and an increased tendency for risk-taking that can lead to violent behavior or a vulnerability for victimization.[5,7] Whereas the majority of patients with mTBI shows a full recovery, 15%-25% of all cases continue to experience ongoing symptoms three months post-injury, causing considerable disability in daily life.[8] Considering the large proportion of patients with mTBI that are intoxicated at the time of injury, it is very important to study the characteristics of this subgroup and the influence of this pre-injury alcohol exposure on functional outcome.

Although there is a substantial body of research on the influence of alcohol on outcome in TBI and the potential underlying pathophysiological mechanisms, this literature mostly concerns patients with severe TBI or groups with varying severity. The results of these studies are inconsistent with both advantageous and disadvantageous effects of AAI on post-traumatic neural damage being reported with regard to mortality,[9,10] cognitive recovery,[11,12] and functional outcome.[13] This contradiction is also present in studies investigating the pathophysiological mechanism in severe TBI. Studies report both protective as harmful effects through either attenuation[14,15] or exacerbation[16] of the inflammatory responses.[14,15]



However, few patient studies have focused on the influence of alcohol on outcome in mild TBI specifically. In their paper on outcome prediction in mTBI, Jacobs and colleagues[17] found that besides age and extra cranial injuries, a day-of-injury alcohol intoxication was the strongest indicator of a more favorable functional outcome six months post-injury. This unexpected finding might be a result of an erroneous assessment of higher injury severity due to the intoxication than actually is the case.[18,19] However, evidence that AAI affects the initial severity assessment is inconclusive, as several studies report that AAI does not cause clinically significant changes in the GCS scores compared to sober TBI patients.[9,20,21] In animal studies, the neuroprotective effect of alcohol through attenuation of the inflammatory process for mTBI was studied, but results were inconclusive.[15]

Even though the direction of the effect is unclear, it can be hypothesized that intoxication at the time of injury could have a substantial influence on the outcome following TBI. Research on AAI in mTBI is scarce, and so far no attempt has been made to describe the characteristics of this subpopulation in mTBI. Currently, effects of AAI on outcome have mainly been demonstrated in experimental animal studies, which are not likely to match the mechanisms and outcomes of clinical mTBI.[22] It has been recognized that outcome in mTBI is strongly related to psychological factors such as emotional distress in the form of mood- or post-traumatic stress (PTSD)-related complaints.[23] With regard to the latter, AAI could play a role in the severity of these trauma induced complaints, by dampening the stress response.[24]

Therefore, the goal of this study was to compare mTBI patients with acute alcohol intoxication with sober mTBI patients, on clinical characteristics, demographics and injury mechanism. In addition, we investigated the influence of AAI on complaints, depression, anxiety and impact of events at two weeks post-injury and functional outcome at six months post-injury. Based on the findings of Jacobs and colleagues[17] we expected patients who were intoxicated to have a better outcome. Furthermore, we hypothesized that the protective effect of alcohol also influences the development of mood- and PTSD-related complaints.

## METHODS

### Design and setting

A prospective follow-up study on outcome in mTBI was conducted in two level I trauma centers: University Medical Center Groningen (UMCG) and St. Elisabeth Hospital Tilburg (EZH). Patients included received questionnaires two weeks and six months after injury. Demographic variables and injury characteristics were obtained from the hospital records. On admission, GCS scores were determined as part of the neurological examination. On the basis of these records, the Injury Severity Score (ISS) was determined.[25] A CT-scan of the brain was performed on admission and CT-abnormalities were defined by the Marshall score (category 1=no abnormalities, categories 2-6=abnormalities).[26]

### Participants

Patients with mTBI between 16 and 65 years of age admitted to the emergency departments (ED's) of the UMCG and EZH between February 2013 and October 2014 were included in this study. MTBI was defined as an injury to the head caused by external physical force resulting in: a Glasgow Coma Scale (GCS) score of 13-15, loss of consciousness( LOC) of ≤ 15 minutes (documented, reported or self-reported) and/or posttraumatic amnesia (PTA) of ≤ 24 hours. These criteria are in accordance with the recommended

guidelines of the WHO collaborating centre task force.[27] Patients suffering from a severe multi-trauma, chronic alcohol and/or drug abuse and major psychiatric or neurological disorders were excluded. Patients without a permanent home address were excluded due to anticipated follow-up difficulties.

The presence of an alcohol intoxication was assessed by emergency physicians according to the following criteria: recent ingestion of alcohol (by self-report or as reported by an observer), a physical exhibition of intoxication of the patient (e.g. slurred speech, alcohol odor) and if available, blood alcohol levels (BAL). Based on these criteria, patients were divided into four subgroups: (1) no alcohol consumption on the day of injury, (2) clear alcohol intoxication, (3) alcohol consumption on the day of injury but no clear intoxication, and (4) unknown. For comparative analyses, only the first two groups were used.

**Measures**

All measures were taken at two weeks post-injury, except for the GOSE which was determined six months post-injury.

*Post-concussive complaints*

The Head Injury Symptom Checklist contains the 21 most commonly described post-concussive symptoms. It is derived from the Rivermead Post-concussion Symptoms Questionnaire (RPQ),[28] which is the most common measure for post-concussive complaints. For all 21 complaints, a pre-injury and a current symptom level were indicated by the patient. Values range from 0 to 2 (0 = never, 1 = sometimes, 2 = often). The total amount of complaints (from 0 – 21) and the severity of complaints (0 – 42) can be determined.

*Depression and anxiety*

The presence or absence of depression and/ or anxiety was assessed by means of the Hospital Anxiety and Depression Scale (HADS).[29] The HADS is a 14-item questionnaire, containing two subscales (depression and anxiety) of seven items each. Items are rated on a scale from 0-3. A cut-off score of ≥ 8 was recommended for establishing the presence of both depression and anxiety. At this cut-off, an optimal balance between sensitivity and specificity (approximately 0.80) was established.[30]

*Posttraumatic stress*

The impact of event scale (IES) is a self-report measure of post-traumatic stress.[31] The IES consisted of 15 statements, with scores ranging from 0 to 5. Seven items on the scale concerned ‘intrusion’, which is described as strong waves of emotion towards the event. The other eight items were directed at symptoms of ‘avoidance’, staying away from reminders of the event. In a study by van der Ploeg and colleagues, support was found for the construct validity and an adequate reliability.[32]

*Secondary outcome measures*

The Extended version of the Glasgow Outcome Scale (GOSE)[33] provides eight categories of outcome ranging from 1 (= death), to 8 (= full recovery). A score of 7 or 8 is generally regarded as a good recovery. A structured questionnaire is used to determine the GOSE, which patients may either fill out at the outpatient clinic or at home. The GOSE has been found to be practical in use and to have a "very good" interrater-reliability (0.85).[33]

**Statistical Analysis**

The data were analyzed with SPSS 22.0, Armonk: NY, IBM corp. Differences in patient demographics and clinical characteristics between the intoxicated and the non-alcohol group were tested using the $C^2$ test (two-tailed) for categorical data, two sample Student's t-test for parametric data, and the Mann-Whitney U test for non-parametric data. Since there was a significant difference between the groups regarding gender and age, we included these variables as covariates in the two-week and six-month analyses. A one-way analysis of variance with covariates (ANCOVA) was used to compare groups. Post-hoc mean comparisons were performed using univariate tests under the Bonferroni criterion. Alpha was set at 0.05, two-sided.

## RESULTS

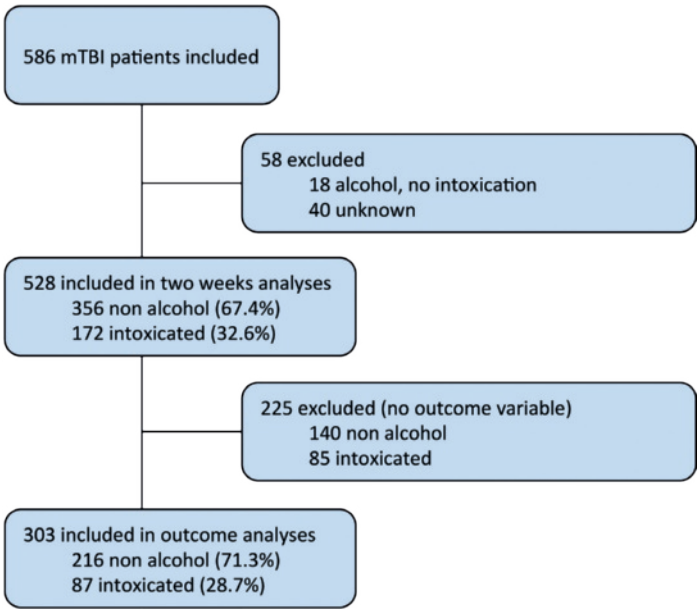
**Inclusion procedure and population**

Figure 1 shows the flowchart of included mTBI patients. Of the 586 mTBI patients fulfilling inclusion criteria, 18 patients falling under group 3 (alcohol consumed, no clear intoxication) and 40 patients falling under group 4 (intoxication unknown) were excluded from further analysis. Five hundred and twenty-eight patients filled out the baseline questionnaire and were included in the two-weeks post-injury analysis.

Six-month outcome scores were available for a subgroup of 303 patients of the final study population that filled out the two-week questionnaire. In this subgroup, 29% of the patients were intoxicated at time of injury, which was comparable to the two-week group (33% intoxicated). The non-alcohol patient group used in the outcome analysis did not differ significantly from the non-alcohol patient group included in the two-week analysis with regard to age, gender, educational level, GCS score, hospital admission, ISS and the presence of CT abnormalities. Likewise, the intoxicated patients in the outcome analysis did not differ from the intoxicated group from the two-week analysis on the same criteria. The intoxicated subgroup used in the outcome analysis was only slightly older than the group used in the two-week analysis (36.5 vs. 41.8 years, $p<.001$). With regard to the two participating trauma centers, no differences between these patients groups were found

on percentage of intoxicated patients ($c^2$ =3,61 (1), p=.058), hospital admittance rate ($c^2$ =0,71 (1), p=.399) and all of the two-weeks measures and six month outcome score.

**Figure 1.** Flowchart of inclusion procedures






**Mechanism of injury and clinical presentation**

Table 1 represents demographic and clinical characteristics for the total mTBI group and for the two subgroups (non-alcohol vs. intoxicated). Of the 528 patients, 172 patients (33%) were intoxicated at the time of injury. A comparison of the intoxicated group with the non-alcohol group shows significantly more males in the intoxicated group with a significantly lower age and GCS score. Of the total mTBI group, 306 patients were admitted to the hospital with an average of 3 days (range 1-60, SD=4,87). The group that was admitted to the hospital consisted out of significantly more intoxicated patients, although a significantly larger part of the intoxicated group was discharged after just one day (62% versus 39%). No significant differences were found with regard to the ISS and the presence of CT scan abnormalities.

Table 2 shows the injury mechanisms for the total mTBI group and for the two subgroups (intoxicated vs. non-alcohol). Significant differences in all trauma mechanisms were present. Compared to the non-alcohol group a higher percentage of injuries in the intoxicated group was caused by falls (77% vs. 55%) and violence (12% vs. 4%). Less traffic related causes like (car)collisions (9% vs. 32%) and less sports accidents (0% vs. 5%) were present in the intoxicated group when compared to the non-alcohol group.

**Table 1**. Patient demographic, clinical and premorbid characteristic

| Variable | mTBI total (n=528) | 1) No alcohol (n=356) | 2) Intoxication (n=172) | Difference 1-2 Statistic (df) | Difference 1-2 p |
|---|---|---|---|---|---|
| Male gender | 347 (65.7%) | 213 (59.8%) | 134 (77.9%) | $\chi^2$ =16,82 (1) | <.001 |
| Age | 38.8 (15.7), 16-65 | 40.28 (15.9), 16-65 | 35.73 (14.8), 16-65 | t=3.15 (526) | .002 |
| Education | 5.17 (2.3), 1-9 | 5.16 (2.3), 1-9 | 4.88 (2.2), 1-9 | | NS |
| GCS score | 14.5(0.6), 13-15 | 14.65 (0.6), 13-15 | 14.30 (0.7), 13-15 | z=-5.94(528) | <.001 |
| Hospital admission (yes) | 306 (58%) | 195 (54.8%) | 111 (64.5%) | $\chi^2$ =4.39 (1) | .039 |
| *If yes, more than 1 day* | 160 (53%) | 119 (61%) | 41 (38.5%) | $\chi^2$ =14.83 (1) | <.001 |
| ISS | 7.5 (4.9), 4-39 | 7.7 (5.0), 4-39 | 7.2 (4.8), 4-30 | | NS |
| CT abnormalities | 57 (11.9%) | 37 (11.3%) | 20 (12.1%) | | NS |
| Contusion | 22 (42.3%) | 13 (36.1%) | 9 (45%) | | NS |
| Hemorrhage | 46 (80.7%) | 29 (78.4%) | 17 (85%) | | NS |
| *Epidural* | 8 (14%) | 3 (8.1%) | 5 (25%) | | NS |
| *Subdural* | 11 (19.3%) | 10 (27%) | 1 (5%) | | NS |
| *Subarachnoid* | 27 (47.4%) | 16 (43.2%) | 11 (55%) | | NS |

Mean (SD) range, others Number (%)

**Table 2.** Mechanism of injury

| Variable | MTBI total (n=528) | 1) Non- alcohol (n=356) | 2) Intoxication (n=172) | Difference 1-2 X2 (df) | Difference 1-2 p |
|---|---|---|---|---|---|
| Mechanism of injury | | | | 56.68 (4) | <.001 |
| Falls | 328 (62.1%) | 196 (55.1%) | 132 (76.7%) | 24.09 (1) | <.001 |
| Collision | 131 (24.8%) | 115 (32.2%) | 16 (9.3%) | 32.56 (1) | <.001 |
| Violence | 35 (6.6%) | 14 (3.9%) | 21 (12.2%) | 12.89 (1) | <.001 |
| Sports | 16 (3%) | 16 (4.5%) | - | 7.93 (1) | .005 |
| Other | 17 (3.2%) | 15 (4.2%) | 2 (1.2%) | 3.43 (1) | .064 |

Number (%)

### Complaints at two weeks post-injury

ANCOVAs were conducted with the data on presence of AAI at the time of injury as the independent variable and self-reports of complaints, mood and impact of events at two weeks after the injury as dependent variables. Age, gender and GCS score were added as covariates (Table 3). The covariate Gender was significantly related to patients' self-report of total number and severity of complaints, the level of experienced anxiety and depression and impact of event. Females reported more, and more severe complaints, a higher level of experienced anxiety and depression and experienced a greater impact of event. The covariate GCS score was significantly related to patient's self-report of the total number and severity of complaints. Patients with a lower GCS score reported more and more severe complaints.

**Table 3.** ANCOVA for AAI on complaints, mood and impact of events at 2 weeks with covariates age, gender and GCS-score

| Variable | Df | F | p | Sign. Of covariates | | |
|---|---|---|---|---|---|---|
| | | | | Age | Gender | GCS-score |
| **Complaints (Total)** | | | | | | |
| Intoxication (AAI) | 1 | 7.28 | .007 | .200 | <.001 | .003 |
| Error | 369 | | | | | |
| Total | 374 | | | | | |
| **Complaints (Severity)** | | | | | | |
| Intoxication (AAI) | 1 | 7.53 | .006 | .310 | <.001 | .003 |
| Error | 369 | | | | | |
| Total | 374 | | | | | |
| **HADS Anxiety** | | | | | | |
| Intoxication (AAI) | 1 | 1.61 | .206 | .276 | <.001 | .819 |
| Error | 369 | | | | | |
| Total | 374 | | | | | |
| **HADS Depression** | | | | | | |
| Intoxication (AAI) | 1 | 4.49 | .035 | .371 | .002 | .147 |
| Error | 369 | | | | | |
| Total | 374 | | | | | |
| **Impact of events** | | | | | | |
| Intoxication (AAI) | 1 | .38 | .537 | .108 | .011 | .972 |
| Error | 369 | | | | | |
| Total | 374 | | | | | |

ANCOVA, analysis of covariance; AAI acute alcohol intoxication; GCS, Glasgow Coma Scale; HADS, Hospital Anxiety and Depression Scale.

After adjustment for age, gender and GCS score, a statistically significant difference in the number and severity of complaints two weeks post-injury was found between the non-alcohol and intoxicated group. Post hoc analysis (Bonferroni adjusted) showed that the number (6.4 vs. 5.1) and severity (6.3 vs. 8.1) of reported complaints two weeks post-injury was significantly higher in the non-alcohol group compared to the intoxicated group ($p$=.007 and $p$=.005, respectively). With regard to mood, we found a significant difference on the depression scale of the HADS, with intoxicated patients having a lower depression score than sober patients (2.9 vs. 4, p=.035) No significant differences were found between the non-alcohol group and the intoxicated group with regard to anxiety (3.8 vs. 4.6) and impact of events ( 15.7 vs. 15.6) two weeks post-injury.

**Table 4.** Complaints 2-weeks post-injury

| Variable<br>Complaints | mTBI total<br>(n=528) | 1) Non- alcohol<br>(n=356) | 2) Intoxication<br>(n=172) | Difference 1-2<br>$c^2$ | <br>p |
|---|---|---|---|---|---|
| **Somatic and cognitive** | | | | | |
| Headache | 227 (43%) | 162 (45.5%) | 65 (37.8%) | 2.82 (1) | .111 |
| Dizziness | 239 (45.3%) | 170 (47.8%) | 69 (40.1%) | 2.73 (1) | .113 |
| Balance disorders | 148 (28%) | 107 (30.1%) | 41 (23.8%) | 2.22 (1) | .148 |
| Drowsiness | 237 (44.9%) | 169 (47.3%) | 70 (40.5%) | 2.35 (1) | .136 |
| Fatigue | 263 (49.8%) | 199 (55.9%) | 64 (37.2%) | 16.20 (1) | **<.001** |
| Forgetfulness | 158 (29.9%) | 118 (33.1%) | 40 (23.3%) | 5.41 (1) | **.020** |
| Poor concentration | 184 (34.8%) | 149 (41.9%) | 35 (20.3%) | 23.62 (1) | **<.001** |
| Slowness | 165 (31.3%) | 135 (37.9%) | 30 (17.4%) | 22.64 (1) | **<.001** |
| Noise intolerance | 170 (32.2%) | 122 (34.3%) | 48 (27.9%) | 2.15 (1) | .164 |
| **Neck somatic** | | | | | |
| Neck pain | 143 (27.1%) | 110 (30.9%) | 33 (19.2%) | 8.06 (1) | **.005** |
| Neck Stiffness | 142 (26.9%) | 103 (28.9%) | 39 (22.7%) | 2.31 (1) | .129 |
| **Auditive** | | | | | |
| 'Tinnitus' | 79 (15%) | 60 (16.9%) | 19 (11%) | 3.07 (1) | .091 |
| Hearing loss | 39 (7.4%) | 27 (7.6%) | 12 (7%) | .063 (1) | .861 |
| **Emotional** | | | | | |
| Irritability | 95 (18%) | 71 (19.9%) | 24 (14%) | 2.82 (1) | .116 |
| Anxiety | 60 (11.4%) | 39 (11%) | 21 (12.2%) | .18 | .670 |
| Trouble falling asleep | 74 (14%) | 53 (14.9%) | 21 (12.2%) | .69 (1) | .406 |
| Trouble sleeping through | 91 (17.2% | 74 (20.8%) | 17 (9.9%) | 9.66 (1) | **.002** |
| **Non-posttraumatic** | | | | | |
| Dry mouth | 80 (15.2%) | 60 (16.9%) | 20 (11.6%) | 2.46 (1) | .117 |
| Arm pain | 104 (19.7%) | 85 (23.9%) | 19 (11%) | 12.07 (1) | **.001** |
| Itchiness | 40 (7.6%) | 31 (8.7%) | 9 (5.2%) | 2.00 (1) | .157 |

Number (%)

Table 4 represents the presence of the different complaints for the total mTBI group and the two subgroups (non-alcohol vs. intoxicated). Significant differences in different domains of complaints were present. Compared to the non-alcohol group a lower percentage of the intoxicated patients reported to experience fatigue (56% vs. 37%) poor concentration (42% vs. 20%), slowness (38% vs. 17%) and forgetfulness/memory problems (33% vs. 23%). The intoxicated group also reported having less problems sleeping through the night (21% vs. 10%) and had less complaints of pain in the neck- (31% vs. 19%) and arms (24% vs. 11%) when compared to the non-alcohol group.

**Six-month Outcome**

A GOSE score at six months was available for 305 patients. The scores ranged from 4 to 8. The majority of the patients reported a good recovery (score 7 and 8, 71%), 24% of patients a moderate disability and a minority a relatively severe disability (score 4, 5%) six months post-injury. To determine differences in outcome between groups, an ANCOVA was conducted with the presence of AAI at the time of injury as the independent variable and the score on the GOSE six months post-injury as the dependent variable (Table 5). Age, gender and GCS score were added as covariates and were significantly related to the GOSE score. A lower age, male gender and lower GCS score was associated with a better outcome. After adjustment for these variables, a significant difference in mean GOSE scores was present six months post-injury between the non-alcohol and intoxicated group (7 vs. 7.3, respectively). Intoxicated patients had a significantly higher outcome score than sober patients (p=.03).



**Table 5.** ANCOVA for AAI on GOSE scores at six months (outcome) with covariates age, gender and GCS score

| Variable | Df | F | p | Sign. Of covariates | | |
|---|---|---|---|---|---|---|
| GOSE | | | | Age | Gender | GCS score |
| Intoxication (AAI) | 1 | 4.75 | .030 | <.001 | .022 | .023 |
| Error | 298 | | | | | |
| Total | 303 | | | | | |

ANCOVA, analysis of covariance; AAI, acute alcohol intoxication; GOSE, Glasgow Outcome Scale Extended; GCS, Glasgow Coma Scale.

## DISCUSSION

Most clinical and laboratory studies investigating the effects of an acute alcohol intoxication (AAI) on outcome following traumatic brain injury have focused on severe TBI or groups with varying severity. This consecutive cohort study is one of the first to focus on AAI in amTBI population. We aimed to describe the characteristics of those mTBI patients that were clearly intoxicated with alcohol at the time of injury and compare this group to mTBI patients that had not consumed alcohol. The main findings comprise several differences in injury related characteristics between these groups. Moreover, we found that although intoxicated patients initially seem to have a more severe injury, they report less complaints at two weeks post-injury and have a better outcome six months post-injury.

In our study, we found that one-third of mTBI patients were intoxicated with alcohol at the time of injury, consistent with results reported in the literature.[5,6] Our results reveal important differences regarding injury related characteristics between the intoxicated and the non-alcohol group. The AAI group comprised mainly males and the group was significantly younger than the non-intoxicated group. This observation is in accord with studies describing that young males are more likely to engage in risk-taking behavior such as binge drinking.[5,34] The two groups differed in mechanism of injury as well, as intoxicated patients more frequently sustained falls- or violence related injuries than traffic- or sports related injuries. This is supported by existing literature showing that AAI raises the risk of injury through impaired motor control (e.g. falls) and interpersonal violence, especially in young males.[5,7] In our study cohort, further analysis of results showed that intoxicated patients are initially assessed with a lower GCS score and have a higher hospital admittance rate. However, this does not appear to be a precursor of a worse recovery. When controlling for age, gender and injury severity, the AAI group reports a lower number and less severe complaints two weeks post-injury. When looking at the specific complaints, the AAI group reports fewer complaints of fatigue, concentration, slowness, memory, neck- and arm pain, and sleeping through the night in comparison to the non-alcohol group. Moreover, AAI patients even have a better outcome six months post-injury when compared to the sober patients.

The apparent discrepancy between the initially worse clinical presentation of intoxicated patients and a more favorable outcome may be due to several underlying factors. First, several studies show that AAI can interfere with the initial assessment of injury severity.[17–19] Patients may be initially judged to have more severe brain injury, due to the central nervous system depressant effect of alcohol. This may lead to an erroneous impression of a more rapid improvement and better recovery. However, Lange and colleagues reported that GCS scores were only lowered by high BALs for patients with CT-abnormalities.[35] Considering the fact that only a minority of CT's from our patient group showed

abnormalities, an intoxication is not likely to have influenced the severity assessment in our patient population. Secondly, AAI can lead to an increased use of therapeutic and diagnostic procedures in the acute phase that may have an influence on outcome.[18] This is in line with our finding that intoxicated patients were admitted to the hospital more often. Moreover, a significantly higher number of these admitted intoxicated patients were discharged after just one day, suggesting that these were patients only admitted to "sleep off" their inebriation.[21]

Thirdly, AAI could have exerted a neuroprotective effect in the recovery process following mTBI. Using a rat model, Perez-Polo and colleagues demonstrated that the post-injury inflammatory processes seen in severe TBI are also present in mTBI, and therefore are also influenceable by alcohol.[22] However, several studies indicate that the effect of alcohol is dose-related, with only moderate concentrations being protective.[5,36] Considering the fact that we only included clearly intoxicated patients that had an excessive amount of alcohol, this would plead against this mechanism of protection. Moreover, two recent mouse studies on mTBI found no dose-dependent effects: there was no difference between moderate and excessive doses of alcohol intake on outcome.[19,37]
Our finding that differences in specific complaints are present between the intoxicated and non-alcohol group may provide more insight in the differences between these groups. Sleep dysfunction and fatigue are important complaints to assess since these may aggravate other symptoms and pain.[38] A higher percentage of the non-alcohol patients complain about fatigue and sleeping problems, which might partly explain the higher number of other complaints. Moreover, the non-alcohol group has more somatic complaints of neck- and arm pain, which has been suggested to be strongly related to preexistent stress levels and a neurotic personality that may influence the development of complaints.[38–41] A higher number of post-concussive complaints is also associated with mood disorders and PTSD.[38,42,43] Despite the fact that we found no differences in the presence of mood disorders and PTSD related complaints between the intoxicated and the non-alcohol group, the report of more and severe complaints by the non-alcohol group suggests that the impact of the trauma was bigger for this group. The trauma might have had a greater impact on sober patients because they experienced it more vividly in contrast to intoxicated patients of whom the intensity of the experience was dampened by alcohol.[24]



There are some limitations to this study. First, no objective measures such as blood alcohol levels (BAL) were obtained for the majority of patients. BAL is the currently accepted standard to measure alcohol exposure and is used to create a distinction in moderate and excessive alcohol use on the basis of legal limits. However, the clinical significance of these legal limit cut-offs is unknown, and does not take the variability of individual dependent effects of alcohol into account. Moreover, in several studies BALs

were obtained in less than half of the patients.[13] Furthermore, several studies report that BALs are not indispensable for an accurate distinction between intoxicated and sober patients. Mahler and colleagues found that emergency physicians were able to correctly identify significant alcohol exposure in blunt trauma patients 96% of the time.[44] In another study, Puljula and colleagues reported that in 95% of cases the initial judgement of intoxication by emergency physicians and nurses corresponded correctly with the obtained BALs.[34] This study included only patients who were assessed to be clearly intoxicated and compared to patients who had absolutely no alcohol. Patients who drank alcohol but were not intoxicated were excluded, which makes our study a solid comparison of intoxicated versus non-alcohol. The sample size included in the outcome analysis was smaller than the sample size at the two-week analysis. However, the two groups did not differ on the important clinical and injury characteristics. It is therefore unlikely that the smaller sample size would have had a negative effect on our comparison.

In summary, the current study demonstrates that AAI is inextricably linked to mTBI as part of the cause of injury and as a potential predictor for outcome. The AAI group seems a population to itself and differs from other mTBI patients on important aspects. The majority of intoxicated patients are young males, and the injury is more likely to be caused by falls or violence. Our results support the finding of a better outcome for mTBI patients that were intoxicated with alcohol. Intoxicated patients that initially appeared to have a worse clinical presentation, report a lower number of and less severe complaints after two weeks and have a better outcome after six months compared to non-alcohol patients. The clinical implication of our findings is that alcohol forms a high risk factor for the incidence of an mTBI, especially among adolescents and young adults. Routine assessment of recent alcohol use and precise registration of this information by clinicians and effective education targeted at this group might play an important role in the prevention of mTBI, reducing unnecessary hospital admission and related costs.

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# Prediction of return to work up to one year after mild traumatic brain injury: A multifactorial approach including occupational factors

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Accepted for publication in Neurology

## ABSTRACT

### Objective

To study return to work (RTW) after mild traumatic brain injury (mTBI) at 3, 6 and 12 months after injury, taking into account complete (cRTW), partial (pRTW) and no RTW (nRTW), thereby reporting on long-term sustainability of work. Furthermore, studying predictors for RTW at 6 and 12 months after injury with predictors in different categories (demographic factors, injury related factors, post-injury stressors, and occupational factors).

### Methods

Prospective longitudinal cohort-study (UPFRONT) including all patients with mTBI at the ED. Included patients received questionnaires at 2 weeks, 3,6, and 12 months after injury.

### Results

Rates of cRTW increased from 34% at 2 weeks to 84% at 12 months after injury, pRTW varied from 8-16% throughout the year. Patients shifted between all categories of work resumption, even after six months. With logistic regression we demonstrated that apart from previously identified predictors such as the presence of extra-cranial injuries, age, education, cause and severity of injury, and indicators of psychological distress, occupational factors were of influence for work resumption after 6 months, while at 12 months the model was solely based on the presence of extra-cranial injuries, and indicators of maladaptation after injury.

### Conclusion

RTW after mTBI is a gradual process, with shifts through different levels of RTW throughout the first year after injury. Patients resume activities despite posttraumatic complaints. These complaints, and the presence of signs of psychological distress already early after injury may help in predicting which patients will encounter problems with short and long-term RTW. Return to work is a multifactorial process, in which patient, injury and occupational factors play a role.

## INTRODUCTION

With an estimated incidence of 600 per 100,000 persons per year, mild traumatic brain injury (mTBI) is a major public health problem.[1] Especially during the first weeks of recovery, mTBI can have profound impact on daily functioning. Posttraumatic complaints (PTC) such as headache, dizziness or forgetfulness are reported by approximately 85% of patients during the first weeks after injury, and may interfere with daily routines.[2] Return to pre-injury vocational activities is an important parameter for outcome, and while it is acknowledged that most mTBI patients return to work (RTW) within weeks to months after injury, an estimated 5-20% struggles with work resumption in the chronic phase after 6 months post-injury.[3] This loss of work productivity accounts for a large part of mTBI related societal costs.[4] Therefore, being able to accurately predict already in an early phase after injury which patients will encounter problems with RTW is one of the most important endeavors in mTBI research.

In several reviews on the subject of RTW after mTBI it is concluded that RTW rates vary widely between studies,[3,4] mostly due to methodological differences. One of the contributors to heterogeneity of results is the applied criterion of work resumption; differences in levels of RTW are often not addressed. RTW may be defined as a complete resumption of pre-injury vocational activities, as a partial return at lower capacity, or as no return to work. Nevertheless, although this variation in methodology, multiple outcome studies led to the identification of factors influencing RTW in patients with mTBI as displayed in Table 1. Problems with work resumption are thought to be caused by both demographic factors (e.g. age, gender, educational level, and marital status) and injury characteristics (such as cause of injury, injury severity, presence of extra-cranial injuries, and CT-scan abnormalities) combined with post-injury stressors such as anxiety, depression and posttraumatic stress. Although it seems intuitive to consider also occupational factors in the prognostic models of RTW, these factors have received little attention over the years. Walker and colleagues reported that patients conducting pre-injury manual labor pre-injury were less likely to RTW when compared to skilled or professional/managerial functions, thereby demonstrating that work-related factors should be incorporated in prediction models.[5] In 2014, the WHO collaborating task force urged the need for more high quality research on occupational factors in relation to RTW after mTBI.[3]

Although it is acknowledged that a small percentage of patients does not return to work 1-2 years after injury, studies focusing on differences in predictors between short and long-term vocational integration are sparse.[6] Moreover, the majority of patients that resume work still report PTC, raising the question whether these patients will develop problems in a later phase, outside the scope of most studies conducted up to 6 months

after injury. Sustainability of employment is therefore another important question at hand, and it is debatable whether the same predictors apply for short- and long-term work resumption.

The objectives of this study on RTW after mTBI were twofold. The first aim was to identify RTW rates at 3, 6 and 12 months after injury. We focused not only on complete and no RTW, but also on partial RTW, thereby assessing long- and short term work resumption and sustainability over time. Second, we aimed to assess whether different predictors are related to RTW at 6 or 12 months after injury with a multifactorial approach studying predictors in different categories (i.e. demographic factors, injury related factors, post-injury stressors, and occupational factors).

**Table 1.** Predictors for RTW in 4 categories

| Demographic factors | Injury-related factors | Post-injury stressors | Occupational factors |
|---|---|---|---|
| Age[7–9] | Cause of injury[10] | Posttraumatic complaints[11,12] | Occupational category[5] |
| Gender[13] | Injury severity[14] | Psychological status[15,16] | Workplace and social support[17] |
| Education[18] | CT-scan results[7,18,19] | | |
| Marital status[17] | Concurrent symptoms[18] | | |
| | Extra-cranial injuries[20] | | |

## METHODS

### Design and setting

This study was part of a longitudinal multicenter cohort study (UPFRONT-study) on mTBI in three level-I trauma centers. Between 2013 and 2015, all patients with mTBI admitted to the Emergency Department (ED) were approached for participation in the UPFRONT study. MTBI was defined as an injury to the head resulting in a Glasgow Coma Scale (GCS) score of 13-15 and/or loss of consciousness <30min. Exclusion criteria were: previous TBI or psychiatric disease requiring hospital admission, inability for follow-up, and substance abuse.

Demographic variables and injury characteristics were obtained from medical records and Abbreviated Injury Scales were documented based on these records.[21] For the assessment of extra-cranial injuries, ISS scores were calculated with the exclusion of AIS Head. On admission GCS scores and presence of posttraumatic amnesia (PTA) and loss of consciousness (LOC) were obtained. CT-scans were assessed and scored using the Marshall criteria by a board certified radiologist.[22] For analyses, a dichotomization of

CT-scan results was applied (Marshall score of 1 = no abnormalities, Marshall score of 2-6 = CT-abnormalities). All patients included in the UPFRONT-study received questionnaires 2 weeks, 3,6 and 12 months after injury.

For the current study, only patients in the working age range in the Netherlands (from 18-65), who were employed at time of injury and completed at least one outcome measurement (at 6 or 12 months) were selected.

**Measures**

*Return to work.* Return to work (RTW) was scored in three categories: 0= pre-injury work not resumed (no RTW (nRTW)); 1= pre-injury work resumed on a lower level, or less amount of hours (partial RTW (pRTW)); 2= complete work resumption in the same capacity compared to pre-injury (complete RTW (cRTW)).[23] For logistic regression analyses, groups were dichotomized into no/partial RTW and complete RTW.

*Occupational factors.* Information on workplace in terms of occupational category, workload in hours/week, number of employees at this employer, and number of years patients had worked for this employer were obtained by questionnaires. Occupational categories were clustered in three levels: professional/managerial (e.g. executive, managerial function), skilled (e.g. sales, administrative support, repair), or manual labor (e.g. machine operators, private household, material moving), as also applied by Walker et al.[5]



*Posttraumatic complaints.* The Head Injury Symptom Checklist (HISC)[15,23] was derived from the Rivermead Post-concussion Questionnaire (RPQ),[24] and consists of 21 common PTCs such as headache, concentration problems, fatigue, and dizziness. Patients were asked to score complaints on a pre-injury and current level with values ranging from 0 to 2. Pre-injury scores were subtracted from current levels to create corrected scores. For analysis, corrected sum scores were calculated with a range from 0-21.

*Depression and anxiety.* The Hospital Anxiety and Depression Scale (HADS) was used to assess symptoms of anxiety and/or depression. The HADS is a 14-item questionnaire, with two subscales (HADS-A and HADS-D) of seven items each. Subscales are scored separately, with scores ranging from 0-21.[25]

*Post-traumatic stress.* For the assessment of posttraumatic stress, the Impact of Event Scale (IES) was applied.[26] Fifteen statements are scored on a range from 0-5, resulting in a maximum score of 75. Eight items on the scale measure “avoidance” – staying away from reminders of the event, the other seven items concern “intrusion”- strong waves of emotion towards the event. For analyses, the total sum score was calculated.

### Statistical analyses

Differences between the three groups (nRTW, pRTW and cRTW) were tested using parametric and non-parametric testing when appropriate. Post-hoc analyses to assess group differences were performed, using Bonferroni corrections. Logistic regression analyses were performed to predict return to work 6 and 12 months after injury (nRTW and pRTW vs. cRTW). Variables were included based on hypotheses according to existing literature, and selected using step-down variable selection, including all main effects and the interactions of education with occupational factors and ISS scores wit occupational factors, with Akaike's information criterion as stopping rule. In the regression analyses, for the predictor workload in hours/week, the nonlinear relationship with outcome could be approximated well with a restricted cubic spline with 3 knots.

Relationships between predictors and outcome of the resulting models were assessed with odds ratios (ORs) and graphical summaries. For continuous predictors, the ORs were scaled to correspond to a change from the 25th to the 75th percentile to facilitate interpretation. Subsequently, ROC-analyses were performed on both the 6-month and 12-month prediction model to calculate the area under the cure (AUC), We estimated the optimism by internal validation using 500 bootstrap samples. Logistic regression was performed in R version 3.3.2, with the *rms* package.[27] Missing values of predictors were imputed with singe imputation using *areImpute* function of the *Hmisc* package.

## RESULTS

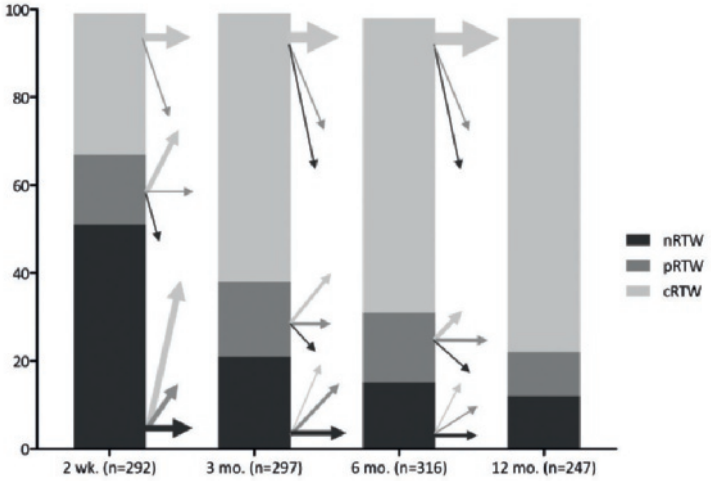
As illustrated in figure 1, of all patients included in the UPFRONT-study (n=1151), 81% was aged between 18-65 (n=928). Of those, 458 patients reported to have been employed at the time of injury. Patients with at least one outcome measurement (at 6 or 12 months after injury), were included resulting in 319 cases for analyses.

### Return to work

Figure 2 represents a flow schedule of work resumption throughout the study. The number of patients shifting from category is presented below the figure. Throughout the year, an increasing number of patients completely returned to work. A shift of patient between all categories was present, also 6 months after injury.

**Figure 1.** Flow schedule of included patients.


**Figure 2.** Flow schedule of work resumption.

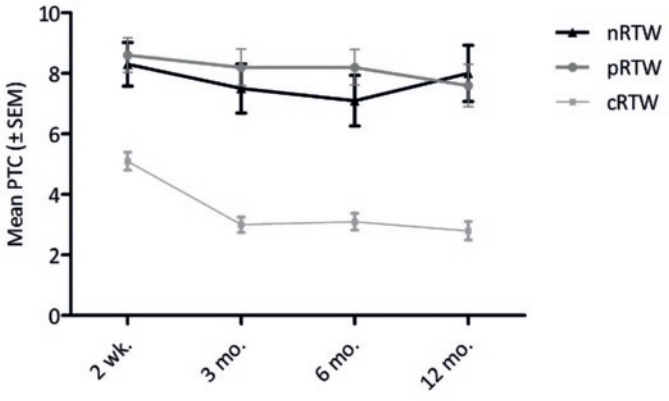



| | | | |
|---|---|---|---|
| Positive change in RTW status (up sloping arrows) | 117 | 47 | 41 |
| Negative change in RTW status (down sloping arrows) | 3 | 8 | 10 |

X-axis represents 4 measurement moments. The percentage of patients in three categories is represented by bars (y-axis, complete, partial or no work resumption). Arrows represent patient flow, with the thickness of the arrow corresponding with number of patients (the thicker the arrow, the more patients). Horizontal arrows represent patients that stay in the same category, whereas up- or down sloping arrows represent a shift in category. # Values represent number of patients.

In Figure 3 the mean number of posttraumatic complaints from 2 weeks – 12 months is depicted separately for nRTW, pRTW, and cRTW patients. At each time interval, significant differences were present between cRTW and pRTW and between cRTW and nRTW (all p-values < 0.001). No significant differences were present between pRTW and nRTW.

**Figure 3**. Posttraumatic complaints for all levels of work resumption through the first year after injury. SEM: Standard error of the mean.




**Group differences**

Six months after injury, 213 patients (67%) completely returned to work; 53 patients (17%) worked on a lower level or less amount of hours, and 50 patients (16%) did not return to work. In Table 2, groups are compared on demographic, injury, post-injury and occupational factors. Overall, nRTW patients were more severely injured (as indicated by GCS and ISS) and had more posttraumatic stressors two weeks after injury (complaints, anxiety, and depression) when compared to pRTW and cRTW patients.

**Table 2.** Patient characteristics of three RTW categories at 6 months post-injury.

| | 1= nRTW n=50 | 2= pRTW n=53 | 3= cRTW n=213 | Difference 1-2-3 Statistic (df) | P |
|---|---|---|---|---|---|
| **Demographics** | | | | | |
| Age, years, mean (SD) | 49.1 (11.0) | 44.6 (13.8) | 44.7 (12.1) | F= 2.72 (2) | NS |
| Male gender | 66 | 47 | 69 | X2= 9.18 (2) | 0.01 |
| Education, median (range) | 5 (2-7) | 5 (2.7) | 5 (2-7) | H= 4.76 (2) | NS |
| Partnered | 90 | 69 | 70 | X2= 2.47 (2) | NS |
| **Injury-related factors** | | | | | |
| MVA (yes) | 40 | 30 | 12 | X2= 27.43 | <0.001 |
| ISS score, mean (SD) | 12.2 (9.0) | 9.8 (6.3) | 6.7 (4.4) | F= 16.94 (2) | <0.001 |
| CT-abnormalities | 23 | 25 | 12 | X2= 13.94 (2) | 0.001 |
| Nausea or vomiting at ED | 28 | 36 | 32 | X2= 0.74 (2) | NS |
| Alcohol usage day of injury | 39 | 13 | 35 | X2= 10.48 (2) | 0.005 |
| GCS score | 14.3 (0.8) | 14.4 (0.6) | 14.6 (0.6) | H= 10.33 (2) | 0.006 |
| Posttraumatic amnesia | 84 | 90 | 89 | X2= 0.89 | NS |
| Loss of consciousness | 80 | 85 | 82 | X2= 0.37 | NS |
| **Occupational factors** | | | | | |
| Workload hours/week, mean (SD) | 33.2 (12.2) | 32.8 (8.1) | 34.3 (11.5) | F= 2.231 (2) | NS |
| Occupational category | | | | H=12.724 | 0.002 |
| Professional/managerial | 22 | 46 | 38 | | |
| Skilled | 49 | 48 | 54 | | |
| Manual labor | 29 | 6 | 8 | | |
| **Post-injury personal factors (2 weeks after injury)** | | | | | |
| PTC, mean (SD) | 8.3 (5.0) | 8.6 (4.1) | 5.1 (4.2) | F= 19.92 (2) | P<0.001 |
| HADS Anxiety, mean (SD) | 5.5 (4.5) | 4.6 (3.7) | 3.7 (3.3) | F= 5.04 | p=0.007 |
| HADS Depression, mean (SD) | 6.6 (5.4) | 5.2 (3.4) | 2.8 (3.3) | F= 21.44 | p<0.001 |
| Posttraumatic stress, mean (SD) | 20.8 (16.0) | 13.4 (12.5) | 12.9 (12.6) | F= 6.25 | p=0.002 |

All numbers are indicated as percentages, unless indicated otherwise.

### Predictors

For logistic regression analyses, RTW groups were dichotomized into complete vs. partial and no RTW, all variables displayed in table 2 were added to the analyses. Table 3 shows odds ratios (OR, with 95% CI) of the predictors in the final models for 6 month and 12 month RTW. Regarding the model for predicting 6 month RTW, three demographic variables (age, gender and education) and three injury related factors (being involved in an MVA, ISS score excluding head, and GCS score) were predictive for RTW. Furthermore, workload in hours/week and occupational category were of influence, with a non-linear effect of workload in hours/week and an interaction effect of education with occupational category (figures 4 and 5). However, there were only few manual laborers within the highest education group and few patients with professional/managerial function within the lowest education group. The number of PTC and score on HADS-D were also associated with lower odds of RTW. The area under the curve (AUC) of the final model was 0.82 in the sample with 0.02 optimism.

**Table 3.** Logistic regression analyses for 6 and 12 month RTW

| | | Odds ratios (95% CI) | |
|---|---|---|---|
| Predictor | Coding | 6 month RTW | 12 month RTW |
| **Demographics** | | | |
| Age | 56:36 | 0.59 (0.33-1.04) | - |
| Gender | Female:male | 0.45 (0.20-1.00) | - |
| Education (Verhage) | 5:4 | 1.37 (0.69 – 2.72) | - |
| **Injury characteristics** | | | |
| MVA (0=no) | Yes:no | 0.17 (0.07-0.40) | - |
| ISS excl head | 5:0 | 0.36 (0.20 – 0.65) | 0.42 (0.27-0.65) |
| GCS score | 15:13 | 2.56 (0.96-6.88) | - |
| **Occupational factors** | | | |
| Occupational category | Professional:skilled | 0.38 (0.15-0.98) | - |
| | Manual:skilled | 0.38 (0.12 -1.17) | - |
| Workload in hours/week | 40:28 | 1.25 (0.71 – 2.20) | - |
| **Two weeks after injury** | | | |
| HISC # of complaints | 9:2 | 0.44 (0.24-0.83) | 0.52 (0.24-1.11) |
| HADS depression | 5:1 | 0.56 (0.38-0.83) | 0.46 (0.29-0.73) |

**Figure 4.** Nonlinear effect of workload in hours/week for prediction of RTW at 6 months.

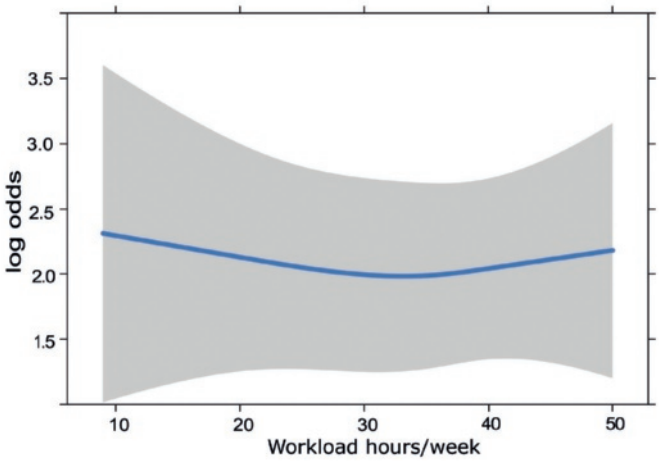
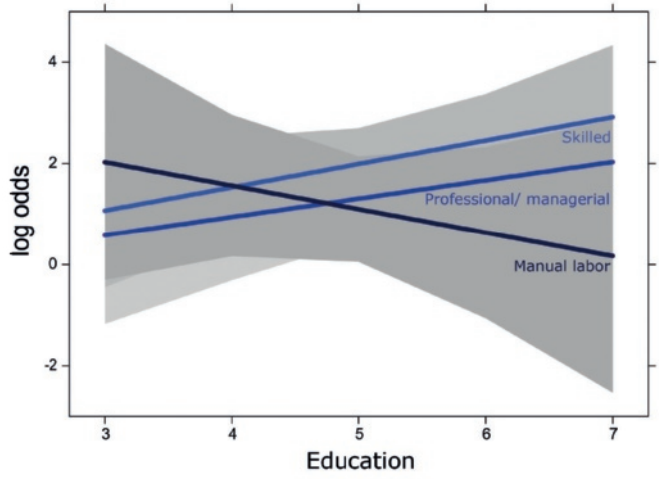



**Figure 5.** Interaction effect of education and occupational category prediction of RTW at 6 months.




At 12 months after injury, 77% completely returned to work. Predictors for incomplete long-term work resumption were extra-cranial injuries as defined by ISS, and the HADS-depression score and the number of PTC on the HISC after 2 weeks resulting in a prediction model with an AUC of 0.81 in the sample, with 0.01 optimism.

## DISCUSSION

The aims of this study on return to work after mTBI were twofold. First, we set out to explore the pathway of patient flow regarding levels of work resumption the first year after injury. We found that the percentage of patients that completely resumed their vocational activities (cRTW) increased from 34% at 2 weeks to 84% at 12 months after injury. The group of patients with partial work resumption (pRTW) was substantial, varying from 8-16% throughout the year. Interestingly, patients shifted between all categories of work resumption, even after six months, indicating that improvement or decline of functioning may take place at any time during the first year after injury. Second, we focused on finding predictors for 6 and 12-month work resumption, taking into account occupational factors such as workload in hours per week and occupational category. Apart from previously identified predictors such as the presence of extra-cranial injuries, age, education, cause and severity of injury, and indicators of psychological distress, occupational factors were found to be of influence for work resumption after six months, while at twelve months the model was solely based on the presence of extra-cranial injuries, and indicators of psychological distress early after injury.

Most studies report RTW as the first day back to work, but abstain from mentioning whether patients resumed work at the same capacity.[11,14,20] Therefore, in the current study we measured and reported RTW in three levels, thereby showing that several steps may be involved before complete RTW, and that around 10% of patients work at a partial level at 12 months after injury. Including these pRTW patients in cRTW,[20] or in nRTW figures[18] is an inadequate representation of RTW rates after mTBI. The few studies that did describe pRTW patients as a separate group, showed frequencies around 20%, comparable to our findings.[23,28] When comparing the three patient groups, we demonstrated that pRTW patients are in fact not always comparable to nRTW or cRTW patients, indicating they represent a separate subgroup and should deserve further scientific attention.

One of the major findings of this current study pertains to the issue of work sustainability: the shift in levels of RTW throughout the year. To our knowledge, this study is the first to describe patient flow over levels of work resumption throughout the first year after mTBI. Most patients shift to a “better” category (i.e. from nRTW to pRTW to cRTW), however at each measurement moment, some patients shift to a lower level of work. Job stability after mTBI is a sparsely researched subject. Most studies that addressed work sustainability investigate groups with various injury severities (i.e. ranging from mild-severe), limiting the possibility to draw conclusions regarding mTBI patients only.[29–32] From the current study we can conclude that not only for patients with moderate and severe TBI but also for mild TBI, problems may arise after the first day back to work. In other words, return to work

does not necessarily mean that patients stay at work or have resumed work on pre-injury levels. Important questions that remain to be studied are whether these patients can be identified in an earlier stage, to prevent problems in the chronic phase. An interesting method to approach this last question is to create groups based on stability of work. In several studies on job stability, occupational factors have been indicated as predictors for stable employment, thereby demonstrating the importance of including these factors in clinical studies.[29,32]

With logistic regression analyses, we developed a prediction model for RTW 6 months after injury. Several predictors that we identified have been shown to be of influence on work resumption in previous studies, such as age,[8] education,[18] extra-cranial injuries,[18] cause of injury,[10] and psychological status.[11,15] Furthermore, we found that women were less likely to return to work after six months when compared to men, an effect that has been subject to debate over the years.[3,13] Contrarily, we found no effect of several previously described predictors such as relationship status, CT-scan results, concurrent symptoms (i.e. nausea and vomiting), and day of injury alcohol intoxication.[18,33] However, we included several occupational factors that influenced the resulting prediction model. First, we added to the knowledge on the role of pre-injury occupational categories in RTW. As already described by Walker and colleagues, being employed as a manual laborer was associated with the lowest odds of return to work.[5] In our model, an interaction effect of education and occupational category was present. However, few manual laborers were educated on a high level, and few patients with managerial/professional function were lower educated, complicating extrapolation of results. Notwithstanding this limitation in our sample, we can support the hypothesis that occupational category is of influence of RTW. The second occupational factor we identified as a predictor in our model was workload in hours per week, which formed a non-linear U-shaped effect. Apparently, working approximately 32 hours per week is related to the lowest odds of RTW. It could be argued that those working a fulltime job (40h/week in the Netherlands), or even working more hours, have the strongest link with their workplace, relating to stronger feelings of responsibility. On the other side are those working less than 25h per week, possibly an amount of hours in which work and rest are perfectly combined. In this regard, it is important to assess whether other non-work related activities such as family life or recreational activities are affected by return to work, since cognitive and physical reserves might become exhausted. The latter is especially important given the fact that extra-cranial injuries were also predictive for RTW. Although the precise mechanism of occupational category and workload remain unclear, we can conclude that they – together with demographics, measures of injury severity, and signs of psychological distress – play a role in the multifactorial process of RTW, and should be taken into account when studying RTW after mTBI.

Regarding the prediction model for RTW 12 months after injury, the majority of effects we identified in the 6-month model disappeared. The only significant predictors left were extra-cranial injuries as defined by the ISS and the number of complaints (HISC) and level op depression (HADS-D) at two weeks after injury. Having sustained extra-cranial injuries proved predictive in both the 6-month and the 12-month model, indicating an important role for physical problems in vocational reintegration. The exact nature of these injuries that influence RTW should be studied more thoroughly to investigate possible targets for interventions. Both pRTW and nRTW patients reported on average 7 post-traumatic complaints throughout the year, raising the question why patients in the latter group did not return to work, while those in the former group manage to work at some extent. Personality traits and psychological wellbeing have been indicated as important factors of adapting to complaints. Apparently, indicators for psychological distress that can be measured early after injury are substantial contributors to long-term RTW and are more important than factors as age, education and severity of brain injury. A recent study demonstrated that cognitive complaints one month after injury are predictive for RTW 4 year after injury.[34] In the current study we demonstrated that the sum score of PTC after 2 weeks was predictive for 6-month and 12-month RTW, adding to the evidence that the factors that interfere with long-term work resumption can be identified already early after injury.

The results of the performed logistic regression clearly indicate that RTW after mTBI is a multifactorial process of which clinicians should be aware. Not only risk factors in patients demographic and injury characteristics should be signaled, but also – and maybe even more important – occupational factors and adaptive capacities.

**Limitations**

Although this study provided valuable contributions to the mTBI field, some limitations need to be addressed. First, we were not able to obtain RTW data from all patients included in the UPFRONT-study, and some of the patients included in the current RTW study were lost to follow-up between 6 and 12 months after injury, limiting the generalizability of results. Second, we did not report the exact reasoning for patients to work on for instance a lower level. Other factors, apart from the mTBI, might have caused the patient to work on a lower capacity. However, our cohort was prospectively followed and included a substantial amount of patients with RTW rates comparable to other studies, thereby indicating an adequate representation of the population. Third, we addressed the issue of levels of work resumption in the first part of this paper, however, for the prediction model we dichotomized RTW at 6 and 12 months. Although this approach facilitates the interpretation and applicability in clinical practice, a multinominal analysis with a larger study sample might be a better fit, especially since we identified several differences between pRTW and nRTW patients. Lastly, the long-term RTW assessment took place 1

year after injury, which could be considered as still relatively short-term. Future studies should therefore focus on the role of occupational factors up to many years after injury, to facilitate personalized advises for patients in an early stage after injury.

## CONCLUSIONS

This study on return to work provides valuable information on vocational rehabilitation after mild traumatic brain injury. We showed that a shift through categories took place throughout the year, and that patients resume activities even though they experience posttraumatic complaints. These complaints, and the presence of signs of psychological distress already early after injury may help in predicting which patients will encounter problems with short and long-term RTW. Last, we added to the evidence that occupational factors should be taken into account when advising patients on their work resumption and urge for more awareness of occupational factors among clinicians and researchers.

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# From miserable minority to the fortunate few: The other end of the mild traumatic brain injury spectrum

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## ABSTRACT

Traditionally, almost all research endeavors on mild traumatic brain injury (mTBI) have been focused on the patients with residual complaints or have a suboptimal recovery. This so-called “miserable minority” is studied to potentially find factors leading to an unsuccessful recovery. However, no study so far has zoomed in on the remarkable patients that report zero complaints early after injury, a group that we named the “fortunate few”. Because nothing is known about this group and their further recovery trajectory, this study, as part of the prospective UPFRONT-study, aimed to describe their demographic, clinical and premorbid characteristics and to examine whether they would remain asymptomatic throughout the first year after injury. Moreover, we investigated the influence of anxiety and depression (HADS) and determined outcome (GOS-E) and quality of life (WHOQOL-BREF) one year after injury. Our sample consisted of 70 mTBI patients (Glasgow Coma Scale [GCS] score 13-15). There was considerable heterogeneity in recovery in this group, as more than half of patients (57%) developed complaints at a later stage ($M=2$, $p<.001$). These secondary complaints were related to higher levels of anxiety ($M=3.2$, $p=.004$) and depression ($M=1.4$, $p=.002$), leading to less favorable outcome ($p=.014$) and a lower quality of life ($p=.006$) one year after injury. We therefore conclude that even part of the fortunate few, who seem fully recovered early after injury, may develop secondary complaints leading to unfavorable outcome and lower quality of life, warranting further research of this interesting group.

## INTRODUCTION

Research on mild traumatic brain injury (mTBI) particularly focuses on patients that show residual complaints or poor outcome.[1] However, no study so far has zoomed in on patients that report zero complaints at an early stage after injury. We argue that this is highly relevant, because these patients fall off the radar, with nothing known about their recovery trajectory. For example, it is not known whether these patients remain without complaints. Therefore, this group could be one of the missing links in the search for to factors leading to successful or unsuccessful recovery after mTBI.

It is uncommon to report no complaints after mTBI.[2–4] Interestingly, even healthy individuals without head injury often report similar complaints that are generally reported by mTBI patients, since these posttraumatic complaints (e.g. headache, concentration problems) are unspecific to mTBI.[3] Frequencies of patients with zero complaints range from 6% within the first two weeks to 20% at one year post-injury.[2,4] This implicates that this group is as big as the group reporting persistent complaints, also known as the 'miserable minority'.[1]

Thus, this seemingly remarkable group deserves further scientific attention, which was the goal of this short communication. Specifically, we questioned whether patients with zero complaints would remain asymptomatic throughout the first year, and examined the influence of anxiety and depression, that have been found to be related to chronic complaints. Secondly, we determined the rates of favourable outcome and quality of life at one year post-injury.



## METHODS

Participants were selected from the UPFRONT-study cohort, a prospective multicentre study on mTBI outcome in the Netherlands. At the emergency departments of three participating Level-1 Trauma centres, all mTBI patients aged 16 years or older were screened for inclusion. All patients meeting the inclusion and exclusion criteria were approached for participation. Detailed information on inclusion and exclusion can be found in a previous publication.[5] Written informed consent was obtained from all participants, in compliance with the ethical regulations of our institute.

All participants of the UPFRONT-study received questionnaires at 2 weeks, 3, 6 and 12 months after injury, measuring posttraumatic complaints, mood, and outcome. The following questionnaires were used for the current study:

*Head Injury Symptom Checklist* (HISC).[6] The HISC comprises 21 common posttraumatic complaints, which are rated on a pre-injury and post-injury level. For the current study, all participants that reported no complaints (i.e. compared to pre-injury) two weeks after injury were selected. This *no complaints* group was divided into two groups: (1) *Persistent no complaints (PnC):* participants that reported no complaints throughout the follow-up (on all time measurements up to 12 months); (2) *Secondary complaints (SC):* participants that started to report complaints during follow-up.

*Hospital Anxiety and Depression Scale* (HADS).[7] The HADS is a commonly applied measure to screen for anxiety and depression after head injury. It measures 2 subscales of 7 questions each, with scores ranging from 0-21.

*Glasgow Outcome Scale Extended (GOS-E):*[8] the GOS-E was administered as a measure of general functional outcome. The GOS-E defines outcome on an 8-point scale, ranging from dead (1) to complete recovery (8). Scores were dichotomized into incomplete recovery (scores 1-7) and complete recovery (8).

*World Health Organization Quality of Life scale abbreviated version (WHOQOL-BREF)*: Quality of life was measured with the Dutch version of the WHOQOL-BREF.[9] It contains 26 items, with scores ranging from 1-5 each. An overall Quality of Life score is calculated by summing up the first two items (overall quality of life and general health facet). The overall score, ranging from 2-10, was used as a general measure of quality of life.

Data were analyzed with the Statistical Package for the Social Sciences (SPSS 22.0, IBM SPSS Statistics, SPSS Inc, Chicago, IL). PnC and SC groups were compared using parametric (Student's t-test) and nonparametric tests ($\chi^2$, Mann–Whitney *U*). To investigate changes in HADS scores over time, a repeated measures ANOVA was performed on raw scores per subscale. Post-hoc mean comparisons were performed using univariate tests under the Bonferroni criterion. Alpha was set at 0.05, two-sided.

## RESULTS

A total of 119 mTBI patients, 10% of the entire population (n=1151), reported no complaints 2-weeks post-injury (total). We lost 49 patients (41%) to follow-up. Patients that dropped out were significantly younger than patients that filled out all their questionnaires (39.7 vs. 53.1, p<.001). Of the remaining patients, 30 (43%) remained without complaints over the course of one year after injury (PnC), while 40 patients (57%) developed secondary complaints (SC) over time (*M*=2, range 0-10, p<.001 at 3, 6 and 12 months). Table 1 shows a comparison of the PnC group with the SC group. The groups differed with respect to gender and educational level. Patients in the PnC group were significantly younger in comparison to those in the SC group (46.3 vs. 58.2). They also had a higher

educational level than the secondary complaints group (5.7 vs. 4.9). No differences were found between groups with regard to gender, psychiatric history and measures of injury severity (GCS, ISS and CT-abnormalities).

**Table 1.** Patient demographic, clinical and premorbid characteristics

| Variable | Total (n=119) | 1) PnC (n=30) | 2) SC (n=40) | Difference 1-2 statistic (df) | p |
|---|---|---|---|---|---|
| Male gender | 92 (77) | 25 (83) | 28 (70) | $\chi^2$=1.66 (1) | NS |
| Age | 47.6 (19.9) 16-89 | 46.3 (20.8) 17-88 | 58.2 (13.1) 23-79 | t=-2.74 (46) | .009 |
| Education | 5.3 (1.1) 3-7 | 5.7 (1) 3-7 | 4.9 (1.1) 3-7 | U=354,5 | .005 |
| GCS score | 14.6 (.67) 13-15 | 14.6 (.66) 13-15 | 14.7 (.45) 13-15 | U=591,5 | NS |
| Hospital admission (yes) | 57 (48) | 11 (36.7) | 23 (57.5) | $\chi^2$= 2.97 (1) | NS |
| ISS (Injury Severity Scale) | 6.2 (3.7) 0-19 | 5.1 (1.9) | 6.1 (3.9) | t=-1.23 (39) | NS |
| CT abnormalities | 9 (7.6) | 1 (3.3) | 3 (7.5) | $\chi^2$= .55 (1) | NS |
| Psychiatric history | 0 | 0 | 0 | | |

Mean (±SD), range; all others=number (%)

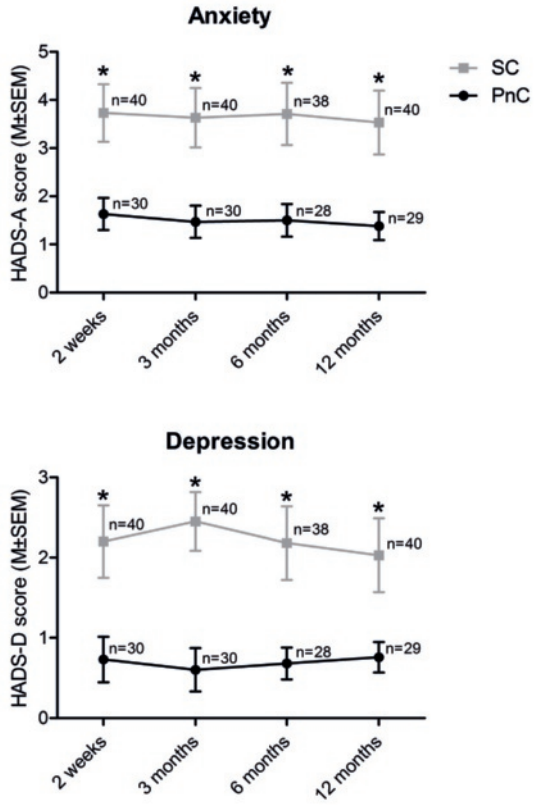
### Anxiety and depression

Patients in the PnC group had significantly lower HADS-A (*M*=3.2, p=.004) and HADS-D (*M*=1.4, p=.002) scores than the SC group (Figure 1). Post-hoc tests showed significant group differences at every time point. No significant effect was found for time or time x group interaction.

### Outcome and quality of life

At one year post-injury, 93% (n=26) of the PnC group showed favorable outcome compared to 68% (n=25) of the SC group ($\chi^2$=6.03, p=.014). Quality of life was also significantly higher in the PnC group compared to the SC group at one year post-injury (median: 9 vs. 8; *U*=343, p=.006).

**Figure 1.** Anxiety and depression scores over time in the PnC and SC groups




## DISCUSSION

This is the first study that describes the ten per cent of patients with mTBI that report zero complaints early after injury, a group that we named the "fortunate few". In current literature, it is generally assumed that these patients will remain without complaints and are therefore not followed-up. However, we observed that there exists considerable heterogeneity within this group, as more than half of these patients develop complaints at a later stage. These secondary complaints were related to higher levels of anxiety and depression, leading to less favorable outcome and a lower quality of life one year after injury. The patients that remained without complaints were younger and had a higher educational level when compared to the group that developed secondary complaints.

The far right end of the mTBI spectrum is constituted by the miserable minority, which is a group with persistent complaints and poor outcome.[1] This group is extensively studied;[10–12] however, little to nothing is known about the other end of the spectrum. This

is a remarkable gap in knowledge, considering that it may be just as atypical to report no complaints at all.[2] Moreover, the belief that these patients are fully recovered early after injury and will remain complaint free is presumptuous and incorrect. We found that no less than 50% of this group develops complaints at a later stage. Remarkably, this subgroup already showed signs of psychological distress, reflected by higher scores of anxiety and depression, at two weeks post-injury. The fact that we found that the group that remained without complaints was younger and had a higher educational level can be explained by the robust finding that a younger age is associated with good recovery after mTBI.[13] Higher educated patients may be better able to utilize adaptive coping strategies that prevent the secondary development of complaints.[14,15] Interestingly, when regarding the total fortunate few group, none of the patients of the total fortunate few group had a psychiatric history. This in accordance with the literature, which reports psychiatric history to be a common risk factor for developing persisting complaints.[1]

A limitation that needs to be addressed is the relatively large group of patients that was lost to follow-up. Although our dropout rate was comparable to other follow-up studies, we believe that the dropout of younger patients might have biased our results. It could be true that the percentage of patients that remain asymptomatic is larger than reflected by our results.

In conclusion, we demonstrated that some of the fortunate few, who seem fully recovered early after injury, may develop secondary complaints leading to poor outcome and lower quality of life. Therefore, the truly fortunate are in even fewer numbers than expected. We plead that more future mTBI research should be focused on early signs of psychological distress. This may be a better criterion to discern patients with optimal and non-optimal recovery than the presence of posttraumatic complaints, which holds important implications for clinical practice.

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8

# General discussion

# 9

## GENERAL DISCUSSION

This dissertation on mild traumatic brain injury aimed to study the role of posttraumatic complaints, psychological distress and the provided aftercare on general outcome and specifically return to work the first year after injury. All presented studies were part of a multicenter cohort study (UPFRONT) conducted between 2013 and 2015 in the Netherlands. In the following paragraphs, an integrated discussion of results and future perspectives is presented suggesting a different perspective on mTBI aftercare.

As can be observed from the cover of this thesis, mild traumatic brain injury encompasses a wide range of patients and causes of injury. For example the affected population comprises young healthy students falling off their bicycle in an intoxicated state, frail elderly stumbling on a slippery sidewalk, road traffic victims with extra-cranial injuries, and those with various recreational and sporting accidents. The heterogeneity the group impedes attempts of defining the specifics of necessary care in the different stages of recovery. Therefore a personalized approach of mTBI seems more fitting. Especially the subset of patients comprising up to 20% – occasionally referred to as the *miserable minority* – that report persistent complaints and struggle with resumption of pre-injury activities are the ones that should be targeted for interventions in an earlier stage. However, timely identification of these patients who are in need for follow-up and determining the appropriate aftercare is notoriously challenging.

As discussed in **chapters 3** and **4** of this dissertation, opting to provide patients with a form of aftercare is currently primarily based on the mere fact whether patients were or were not admitted to a hospital following injury.[1] It is remarkable to note that many studies do not report on their included patients in terms of hospitalization rates,[2–4] and those that do report admittance rates varying from 11 up to 45%.[5–8] In **chapter 3**, we showed that 60% of patients in the UPFRONT-cohort were admitted to the hospital, but guidelines for admission were not always followed as many cases of admission depended on the clinical presentation at hand. We zoomed in on the consulted medical specialists in the aftercare and found that 60% of hospitalized patients visit a neurologist in the first six months after injury, while according to guidelines all admitted patients should be followed-up. Other specialists involved in aftercare for all mTBI patients were those related to physical injuries (i.e. surgeons and physical therapists), rehabilitation physicians, psychologists and psychiatrists. Apparently, outpatient follow-up outside of the scope of the neurologist is relatively common, which raises questions whether comparable (after)care is provided by these specialists and if a more interdisciplinary approach might be more effective.

We were surprised to find that 25% of the non-hospitalized patients returned to the outpatient neurology clinic within 6 months after injury and chose to study this relatively unin-

vestigated group further in **chapter 4**. Initially, we hypothesized that non-hospitalized patients who did return to the outpatient clinic (OFU) were probably more severely injured when compared to their nOFU counterparts. Although characteristics related to injury severity have weak predictive value in terms of outcome,[9] it could be argued that premature discharge (either initiated by the patient or physician) might be related to unfavorable outcome and manifested by return to the outpatient clinic. Strikingly, we were unable to identify differences in any of the patient demographics or injury characteristics between OFU and nOFU patients. Two weeks after injury, however, a differentiation was discernible with regard to experienced psychological distress; symptoms of anxiety or depression early after injury were associated with higher odds of returning to the outpatient clinic. Signs of psychological distress such as anxiety or depression are associated with persistent posttraumatic complaints (PTC),[10–12] which tend to develop due to a combination of factors. The first being occurrence of brain injury itself as a trigger, with predisposing factors (e.g. maladaptive coping style) and post-injury stressors (e.g. anxiety and depression) explaining why in some patients complaints persist up to months after injury. These pre-injury personality factors and post-injury stressors might also explain why uninjured individuals and non-head injured trauma patients also occasionally report complaints that are often attributed to brain injury. In these cases, a non-head trauma or major life event may serve as a trigger for the development of complaints, resembling those of brain injury.[13–15]

Due to these aforementioned reasons, we aimed to investigate whether complaints reported after mTBI may be distinguished from trauma control patients regarding the nature (i.e. which specific complaints) and frequency in relation to anxiety and depression. We demonstrated in **chapter 5** that complaints reported after mTBI are also reported after orthopedic traumas. However, patients with mTBI not only reported more complaints than the control group, but also in a completely different pattern. Factor analyses yielded 3 factors, the biggest comprising cognitive and somatic complaints such as headache, poor concentration, and fatigue. This factor, which we summarized and labeled as *mental distress,* also showed the strongest correlation with depression and anxiety. This was especially the case for the mTBI group suggesting that the development of complaints – although variable in nature – could be seen as a manifestation of psychological distress. Our findings imply that the influence of psychological distress is more important after sustaining brain injury when compared to an orthopedic trauma. Injury to the head apparently causes an acute stress response, prompting the patient to adapt with the consequences of injury. Supported by the finding that an acute problem-focused coping style is related to better outcome when compared to a passive coping style,[16,17] it is concluded that some patients are better equipped to regulate the stress response after trauma leading to a better outcome.

In this regard, an interesting subgroup of mTBI patients are those with an acute alcohol intoxication (AAI), whom account for up to 30-50% of all mTBIs.[18] Given that an AAI may affect the stress response after injury by a dampened experience of trauma, and thereby possibly influence outcome,[19] we studied this subgroup in **chapter 6.** Approximately 30% of the UPFRONT-cohort was severely intoxicated during injury, mostly young males. When compared to the patients who sustained an injury while being sober, intoxicated patients reported a lower number of complaints and less symptoms of depression after two weeks, and they had a better outcome 6 months after injury. Furthermore, intoxicated patients were more often admitted to the hospital, but mostly just for one day of observation to "sleep it off". In **chapter 4,** we plead that the dichotomization for outpatient follow-up based on hospital admission is rather ambiguous and unfit for the heterogeneity of mTBI. Signs of psychological distress the first weeks after injury are probably more suitable for selecting patients in need of aftercare, as they are indications of adaptive disorders irrespective of the cause (e.g. structural abnormalities related to the injury or predisposing factors related to for instance maladaptive coping style).

When focusing on the societal consequences, persistent posttraumatic complaints after mTBI are the largest contributers of costs, due to loss of work productivity and sick leave.[20,21] Several studies have focused on finding predictors for return to work (RTW), with inconclusive results.[22–24] Although it would be intuitive to assume that the nature, load and satisfaction of employment are of influence in the process of work resumption after mTBI, prognostic models have mainly been focused on patient demographics and injury characteristics.[25] Furthermore, the levels of work resumption as defined by absent, partial or complete RTW are often unacknowledged and long-term work resumption (or sustainability of work) is largely understudied. In **chapter 7**, we aimed to address these issues by studying three levels of RTW (complete, partial, and no RTW) throughout the first year after injury. Interestingly, a lot of shifting took place in terms of the aforementioned status of RTW in the course of time – even after six months – indicating that a decline or improvement of functioning may take place outside the scope of most outcome studies. In the developed multifactorial prediction model we identified a substantial role of occupational factors on work resumption after 6 months, apart from the well-known predictors (e.g. age, cause of injury and extra-cranial injuries). Both occupational category and workload in hours/week were predictive for return to work. Occupations requiring manual labor had the lowest odds of RTW after six months, when compared to those of skilled or professional functions. Furthermore, the workload in hours per week showed a U-shaped effect, with the lowest odds of RTW on a 32-hour workweek. All physicians involved in the treatment of mTBI patients – which we studied in **chapter 3** – should be aware of these effects when advising patients on their recovery. In both the model for 6 and 12 months RTW, reporting of complaints and depression after 2 weeks were

related to lower odds of work resumption. It might be argued that the first measurement moment of the UPFRONT-study (after 2 weeks) is a relatively late interval to identify and possibly treat maladaptive disorders and predicting problems with RTW on the longer term. In a clinical setting, screening for problems at one week after injury might more fitting. However, an outpatient clinic visit one week after injury for all mTBI patients is not feasible. Studies have pointed out that telephonic follow-up could be effective in the prevention of persistent complaints after mTBI.[26] Therefore, mTBI might be a very suitable population for telephonic screening. The development of a personalized approach to assess whether and in which manner screening for maladaptive disorders is necessary, depending on patients' demographics, occupation, workload and adaptive capacities should therefore be a future goal for the mTBI field.

It seems applicable to propose an approach in which patients at-risk of unfavorable outcome based on signs of psychological distress are screened, including those who are without complaints early after injury; the *fortunate few* from **chapter 8.** In this chapter, we approached recovery of mTBI from a new perspective. Instead of focusing on the so-called *miserable minority* we studied patients that seem to recover very soon without impairments. Our ambition was to find characteristics in this subgroup that were protective of unfavorable outcome. However, our selected group of *fortunate few* was even smaller than we had anticipated. We were surprised to find that half of these supposedly fully recovered patients in an early stage developed secondary complaints in a later stage, affecting quality of life one year after injury. Patients developing secondary complaints reported more symptoms of anxiety and depression already 2 weeks after injury, showing the possibility of early identification even in those patients who would not meet the criteria for many interventions, since they are mostly based on the presence of posttraumatic complaints.[27]

The question remains whether this suggested change in practice to screen all mTBI patients for signs of maladaptation will lead to better outcomes. The key is early identification of at-risk patients to prevent instead of treat persistent complaints and unfavorable outcome. The first step is education as it has been shown that a reduction in posttraumatic complaints may be accomplished by providing information.[26,28] Adequately informing patients on recovery might recondition symptom expectation and illness perception of patients, both of which are known to influence psychological wellbeing.[29,30] Screening patients for psychological distress and adequately informing and reassuring them creates a threefold benefit of this approach: first, unnecessary consultation may be avoided for patients who were admitted to the hospital but recover without impairments. Second, non-hospitalized patients who feel the need to ask additional questions are provided with this opportunity during a telephonic follow-up, preventing negative symptom expectation.

Third, when deemed necessary patients are able to visit the outpatient clinic in an early phase after injury, thereby possibly preventing the development of chronic complaints and problems that limit the resumption of activities.

**Future perspectives**

As discussed throughout this dissertation, outcome following mTBI is a multifactorial process, on which we are gaining knowledge that provides new research angles as future perspectives on the mTBI research field.

For several decades, research has been focused on explanations for unfavorable outcome after mTBI. First endeavors for prediction models aimed to look at injury and patient characteristics such as GCS, CT-abnormalities, age and gender. When these models proved to be of insufficient accuracy, personality traits as coping style and psychological factors as anxiety and depression became an important scope. The bio-psychosocial model in combination with occupational factors has provided us with a good prediction model for RTW, leading to additional knowledge on recovery of mTBI. In the preceding paragraphs, we touched upon the suggestion that the provided care might also influence outcome. In case of a heterogenic disorder such as mTBI, guidelines are often unspecified for individual cases and the adherence varies.[31,32] Comparative Effectiveness Research (CER) is a way of identifying factors related to care that influence outcome. While conducting the UPFRONT-study we signaled differences in provided care between the three participating centers. Although all centers comply to the same guideline,[33] considerable differences were present in guideline adherence, clinical care, and follow-up. It is in our believe that the future of mTBI research should therefore not only focus on finding predictors in characteristics on a patient level, but also on differences and effectiveness of care systems.



In a time of globally rising health care costs, important questions pertain to the economic burden of disease and cost-effectiveness of treatments. The Dutch health care system, with its nationwide insurance and accessibility is consistently graded as among of best in the world.[34] The important role of general practitioners (GPs), who refer only 5-10% of their patients to in-hospital medical specialists, is one of the reasons for affordable healthcare. Most patients are treated within the GP practice, as probably also goes for a substantial part of the mTBI population. The advises for recovery, as provided by GPs are probably as important as those of the neurologists at the ED or at outpatient clinics. Even more so, since GPs are often better informed about a patients' background in terms of for instance family life and occupation. Little is known about how GPs assess and treat mTBI, for instance when they choose refer to either ED or outpatient clinic and how they advise patients in terms of recovery. The investigation of effectiveness of care systems should therefore not only focus on in-hospital treatment but also on the characteristics of the GP population and treatment.

Over the last decades, the ageing population has led to a shift towards older mTBI patients visiting the ED. Although the economic consequences in terms of work resumption do not apply to the elderly, it is easy to imagine the economic effects related to health-care costs within this population. Since higher age is associated with comorbidity and poly-pharmacy, more diagnostic procedures (e.g. CT-scans) are performed,[7,35] hospital admittance and longer length of stays are common, and concurrent injuries requiring surgical intervention and/or inpatient rehabilitation cause a rise in direct healthcare costs. Furthermore, although relatively new as a subject of TBI research, some associations between mTBI and the development of mild cognitive impairment and dementias have been proposed.[36,37] A recent publication on the late-life effects of TBI at older age combined three large prospective cohort studies and reported that TBI is related to Lewy body accumulation, progression of Parkinsonian features, and the risk of developing Parkinson disease.[38] The shift in the mTBI population and its effects on society urges an important task for governments and physicians related to fall prevention and long-term care solutions.[39]

These aforementioned suggestions for futures scopes on mTBI research will add to the increasing insights of the factors that are related to outcome after mTBI, leading eventually to the most effective care towards complete recovery after mild traumatic brain injury.

## CONCLUSION

In this dissertation we studied factors influencing general outcome and specifically return to work following mTBI. By investigating posttraumatic complaints, psychological distress and aftercare, and accounting for pre-injury adaptive capacities and occupational factors we contributed to the current body of work on the specifics of recovery after mTBI. Our findings indicate that adaptive disorders could and should be signaled early after injury, to ensure proper aftercare for the broad spectrum of mTBI patients that the heterogenic disorder entails.

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# Nederlandse samenvatting

## NEDERLANDSE SAMENVATTING

In Nederland worden jaarlijks zo'n 85.000 mensen op de spoedeisende hulp gezien met een traumatisch hersenletsel. De meerderheid hiervan betreft patiënten met een licht traumatisch hersenletsel (LTH). Men spreekt van een LTH wanneer een mechanische kracht invloed uitoefent op het hoofd, waarna een persoon een periode van maximaal een half uur buiten bewustzijn is en/of voor een periode van maximaal 24 uur geen nieuwe informatie opslaat (posttraumatische amnesie). De meeste patiënten herstellen vlot en zonder restproblemen van een dergelijk trauma, maar een minderheid van ongeveer 20% blijft kampen met posttraumatische klachten zoals hoofdpijn, concentratieproblemen en stemmingsstoornissen, en kunnen hierdoor niet goed de dagelijkse bezigheden hervatten. Hoewel er verschillende theorieën bestaan over de oorzaak van aanhoudende klachten, is niet goed bekend waarom patiënten met een ogenschijnlijk identiek trauma een compleet ander beloop van hun herstel kunnen hebben. Een centrale hypothese in de theorie over het herstel van patiënten na een LTH is dat adaptieve capaciteiten van belang zijn bij het al of niet persisteren van klachten. In andere woorden; de manier waarop patiënten omgaan met de gevolgen van het ongeval. Dit proefschrift beschrijft de uitkomst, en de factoren die hierop van invloed zijn, van LTH vanaf het eerste contact op de spoedeisende hulp, tot een jaar na het ongeval.

Het eerste hoofdstuk van dit proefschrift verschaft een algemene introductie over het onderwerp. Hierin wordt het kader van het onderzoek geschetst, en het overkoepelend doel van de studies beschreven in relatie tot eerder gepubliceerde artikelen. Hoofdstuk 2 beschrijft de methode van de UPFRONT-studie, het onderzoek waarop dit proefschrift is gebaseerd. Na de inclusieprocedure en follow-up momenten volgt een korte achtergrond van de verschillende deelprojecten van de studie.

In hoofdstuk 3 wordt een overzicht gegeven van de poliklinische vervolgafspraken die LTH patiënten doorlopen. Aangezien de huidige richtlijn van de Nederlandse Vereniging van Neurologie een onderscheid maakt tussen LTH patiënten die wel of niet in het ziekenhuis opgenomen zijn geweest, is deze follow-up studie ook gebaseerd op dit onderscheid. Twee-derde van alle LTH patiënten bezocht één of meer specialisten in de eerste zes maanden na het ongeval. Belangrijke specialisten in deze poliklinische follow-up waren de neuroloog, maar ook specialismen zoals de chirurgie of fysiotherapie waren frequent betrokken in de follow-up. Ook bleek dat ongeveer 10% van alle patiënten psychologische hulp zocht in de eerste zes maanden na het ongeval. Opvallend was dat van alle niet opgenomen patiënten, 25% nog eens werd teruggezien op de polikliniek neurologie in verband met aanhoudende klachten.

Hoofdstuk 4 borduurt voort op de bevinding van het voorgaande hoofdstuk dat een kwart van de niet opgenomen patiënten toch op enig moment terugkomt op de polikliniek Neurologie. Middels een regressieanalyse, een methode om uitkomsten te voorspellen op basis van verschillende variabelen, werd aangetoond dat patiënten die in een vroege fase na het ongeval hoger scoren op angst- en depressieschalen een grotere kans hebben op het terugkeren naar de polikliniek.

De hoofdstukken 3 en 4 onderstrepen het belang van follow-up van patiënten, niet zozeer gerelateerd aan een ziekenhuisopname, maar meer aan de hand van factoren die later vastlopen zouden kunnen voorspellen, zoals tekenen van stemmingsstoornissen als angst en depressie.

De studie die beschreven wordt in hoofdstuk 5 richt zich op de verschillen tussen twee soorten trauma patiënten. Enerzijds de LTH patiënten die deelnamen aan de UPFRONT-studie, en anderzijds patiënten die op de polikliniek traumatologie kwamen in verband met een licht (meestal orthopedisch) trauma zonder hersenletsel. Uit deze studie bleek dat beide groepen trauma-patiënten posttraumatische klachten rapporteren, maar dat deze bij LTH patiënten vaker voorkomen en ernstiger zijn. Met behulp van factoranalyse, een methode om verbanden tussen bepaalde items aan te tonen, bleken de klachten bij LTH patiënten volgens een specifiek patroon te verlopen. Dit patroon had een sterke correlatie met klachten van angst en depressie, wat erop wijst dat deze stemmingsstoornissen van groot belang zijn in het ontwikkelen of in stand houden van posttraumatische klachten na een LTH.

In hoofdstuk 6 werd een bijzondere populatie van de LTH patiënten beschreven, namelijk degenen die onder invloed waren van alcohol ten tijde van het ongeval. Vroegere studies zijn niet eenduidig over het beschermende dan wel schadelijke effect van alcohol op het aangedane brein. Het bleek dat patiënten onder invloed van alcohol minder klachten rapporteerden en een betere uitkomst na zes maanden hadden. Hieruit blijkt dat geïntoxiceerde patiënten een karakteristieke groep vormen, waarbij er wellicht een samenhang is met de herinneringen die patiënten hebben aan een trauma. Uit eerdere studies is gebleken dat tekenen van posttraumatische stress-stoornis het herstel na een LTH nadelig beïnvloeding. Mogelijk treden deze klachten bij geïntoxiceerde patiënten in mindere mate of hevigheid op, waardoor het herstel gunstiger verloopt.

Het hervatten van werkzaamheden is – gezien de vaak jonge populatie – een belangrijke uitkomstmaat na het oplopen van een LTH. In hoofdstuk 7 wordt de werkhervatting van onze populatie beschreven. Ten eerste werd aangetoond dat er door het jaar heen een verandering in het patroon van werkhervatting ontstaat, van niet- gedeeltelijk naar volle-

dige werkhervatting. Tevens zagen we dat patiënten het werk hervatten ondanks het rapporteren van klachten. Het beschreven predictiemodel voor zowel 6 maanden als 12 maanden na het ongeval toont aan dat deze klachten, samen met tekenen van psychologische belasting kunnen helpen voorspellen welke patiënten meer risico lopen op een problematische werkhervatting.

Hoofdstuk 8 beschrijft een totaal andere invalshoek in het onderzoek naar LTH. In plaats van de patiënten met klachten of suboptimaal herstel te bestuderen, werd er gekeken naar de patiënten die vroeg na het ongeval geen klachten rapporteren. Het bleek om ongeveer 10 procent van alle patiënten te gaan. Bij het volgen van deze patiënten gedurende het jaar na het ongeval, bleek de helft van hen alsnog klachten te ontwikkelen. Deze patiënten vertoonden vaak al tekenen van angst en depressie in een vroege fase na het ongeval, dus voordat ze klachten rapporteerden. Dit betekent dat er mogelijk al vroeg na het ongeval sprake is van verhoogde psychologische belasting, terwijl zich dit pas later kan uiten in het rapporteren van klachten.

Het laatste hoofdstuk van dit proefschrift beschrijft een algemene discussie van de bovengenoemde hoofdstukken. De bevinden worden in een breder kader besproken, en er worden perspectieven geboden voor toekomstig onderzoek naar licht traumatisch hersenletsel.

Samenvattend geeft dit proefschrift weer dat licht traumatisch hersenletsel een zeer heterogene groep patiënten omvat. In een grote populatie werden verschillende uitkomstmaten en factoren die hierop mogelijk van invloed zijn onderzocht. Uit deze studies is gebleken dat de ernst van het ongeval niet alleen bepalend is hoe patiënten herstellen. Ook de manier waarop patiënten omgaan met en zich aanpassen aan de gevolgen van het trauma zijn van belang voor het herstel. Om een adequate nazorg voor alle patiënten te garanderen is het dan ook van essentieel belang mogelijke problemen in deze adaptatie vroeg te signaleren.

# Dankwoord

## DANKWOORD

Een promotieonderzoek voer je niet alleen uit. In dit laatste hoofdstuk van mijn proefschrift maak ik met heel veel plezier gebruik van de gelegenheid om een aantal mensen te bedanken.

Hans en Myrthe, UPFRONT-maten, “eng hecht kliekje”. Wat zijn de afgelopen jaren snel gegaan! Ondanks dat ik door de coschappen soms even niet middenin het onderzoek zat, bleef de UPFRONT-continuïteit altijd gewaarborgd dankzij jullie inzet en “niet zeuren maar uitvoeren”-mentaliteit. Jullie hielden mij in deze jaren ook altijd scherp, wat ik als een van de belangrijkste redenen zie voor het tijdig afronden van dit proefschrift. We hebben met z’n drieën wat mooie momenten beleefd: etentjes in het Ghetto, de 10.30 koffie- en 15.00 cola-rondjes, vele aal-grappen op de UPFRONT-app, 5-meter lange palen in de Utrechtse gracht werpen, de IBIA in New Orléans samen met Anne en Sandra, eitjes tikken, de retreat in Den Andel waar hoofdstuk 8 tot stand is gekomen; de lijst is eindeloos. Het was al snel duidelijk dat we tijdens onze promoties als elkaars paranimfen zouden optreden en ik verheug mij ontzettend op de laatste verdediging uit dit drieluik!

Myrthe, behalve een gezellige collega werd je al snel een goede vriendin. Doordat we bij elkaar in de buurt wonen fietsen we meestal samen van de Hooghoudt naar huis. Tijdens deze fietstochten hebben we over het algemeen niet de meest serieuze gesprekken, maar kunnen we elkaar wel voorzien van nuttige tips. Hans en ik noemden jou vaak onze huispsycholoog, en hoewel ik niet voor Hans kan spreken, geldt voor mij dat je een bijzondere vriendin bent met ongekende kwaliteiten en inzichten waarmee je mij altijd aan het denken zet. Dit proefschrift is al naar de drukker op het moment dat jij jouw proefschrift verdedigt, maar ik weet zeker dat je het geweldig zult doen.
Hans, gelukkig was Scheens er om ons soms af te remmen in onze verregaande en overwegend ongepaste humor. Met veel bewondering heb ik gekeken naar hoe jij je met ogenschijnlijk gemak de “MRI-shizzle” eigen maakte. Het verbaasde mij niets dat jij jouw verdediging op geheel eigen stijl uitvoerde en er zo er niet alleen een interessante maar vooral ook een leuke gebeurtenis van maakte. Golden Boy, bedankt!
Ik wens jullie beiden alle goeds toe voor de toekomst, en ik hoop nog vaak met zulke bijzondere mensen te kunnen samenwerken.

Professor Spikman en Professor van der Naalt, beste Joke en Joukje. Een aantal jaar geleden hebben jullie met de UPFRONT een mooi project maar ook een ontzettend leuk team opgezet. Ieder bracht een eigen samenstelling aan karakter, kennis, inzicht en interesse in de mix. De drie proefschriften en vele publicaties die hier tot nu toe uit zijn voortgekomen zijn hiervan een mooi bewijs. Ook jullie beider benoeming tot hoogleraar

vond plaats in de tijdsspanne van dit project, en het is dan ook zeer passend dat jullie beiden als promotor (hebben) kunnen optreden tijdens onze promoties. De wekelijkse UPFRONT-overleggen waren behalve wetenschappelijk nuttig ook altijd gezellig. Buiten deze overleggen heb ik de borrels en etentjes bij jullie thuis, ergens in de stad of op congressen erg kunnen waarderen.

Joke, bedankt voor je altijd openstaande deur (behalve natuurlijk als er geschaatst kon worden). Ik heb veel geleerd van je commentaren op artikelen en kon altijd bouwen op je statistische suggesties, ook al betekende dit het opnieuw uitvoeren van analyses met voor mij onbekende softwarepakketten.
Joukje, tijdens mijn wetenschappelijke stage viel mij al op met hoeveel aandacht en plezier je verschillende studenten begeleidde, en ik heb veel geleerd van de manier waarop je dit aanpakt. Onze grotendeels overlappende copingstijlen maken dat we goed kunnen samenwerken, en ik hoop dat wij van deze samenwerking in de toekomst nog veel gebruik zullen maken.
Ik wil jullie beiden bedanken voor de prettige begeleiding waarin jullie mij de kans gaven mij te ontwikkelen als onderzoeker. Bovenal heb ik van de manier waarop jullie met elkaar samenwerken geleerd dat onderzoek altijd een team effort is, waarvoor ik jullie zeer dankbaar ben.

Leden leescommissie, Prof. Dr. H.P.H. Kremer, Prof. Dr. G.M. Ribbers, Prof. Dr. R.W.H.M. Ponds, bedankt voor het beoordelen van dit proefschrift.

Een klinische studie zonder deelnemers is onmogelijk. Ik wil daarom alle patiënten en gezonde controles bedanken voor hun deelname aan de UPFRONT-studie. Ook ben ik veel dank verschuldigd aan alle arts-assistenten voor hun inzet ten aanzien van de patiënteninclusie. Ook wil ik de JSM bedanken voor het honoreren van mijn MD/PhD aanvraag, waardoor ik de mogelijkheid kreeg dit promotieonderzoek uit te oefenen ten tijde van mijn studie Geneeskunde.

Het opzetten van een multicenter studie is binnen het onderzoek een uitdaging op zich. Gelukkig was er vanaf het begin een goede samenwerking tussen de deelnemende centra. Ik wil Dr. Gerwin Roks, Drs. Tansel Yilmaz (Elisabeth- TweeSteden Ziekenhuis, Tilburg) en Dr. Gerard Hageman (Medisch Spectrum Twente, Enschede) bedanken voor jullie enthousiaste betrokkenheid en gastvrije ontvangst bij de verscheidene bezoeken aan de ziekenhuizen om aanvullende gegevens te verzamelen.

Prof. Dr. M.E. Timmerman, beste Marieke. Bedankt voor je hulp met de hoofdstukken 5 en 7. De studie Geneeskunde staat helaas niet bekend om het uitvoerige statistiekonderwijs.

Gelukkig nam jij de tijd om de ingewikkelde modellen toe te lichten, en heb jij mij kennis leren maken met *R*, waarvoor dank.

Ook de studenten die door de jaren heen betrokken zijn geweest bij het project wil ik graag bedanken. Eline, jouw wetenschappelijke stage gaf interessante inzichten in verschillen in zorg tussen ziekenhuizen. Barzi, dankzij jouw inzet hebben we van het "Trauma Klachtenlijst paper" een mooi artikel kunnen schrijven. Dit uiteraard met de hulp van Dr. Mostafa El Moumni.

"Werken duurt lang, zorg dat het leuk is"
Deze bekende tegeltjeswijsheid is de basis voor het bedanken van de vele geweldige collega PhD's van de neuro(psycho)logie. Werken op V4 heeft de afgelopen jaren maar weinig als werk gevoeld. De vele gezellige momenten maakten het nooit vervelend om het UMCG binnen te stappen op maandagochtend. Door de dagelijkse NRC-puzzel, de lunch om 12.00 en koffie bij Vincent en Liban stond de klok alweer snel op Nacho's-met-Maallust-tijd in de Hooghoudt.
De Neuro-PhD groep heeft zich in de loop der jaren uitgebreid tot een zeer dynamische groep waarmee retreats, neuroklaasvieringen, noodstroomborrels, publicatieborrels en vele andere activiteiten georganiseerd worden. Gelukkig hebben ook de nieuwe (toekomstige) PhD's gezelligheid binnen de groep hoog in het vaandel staan. Arnoud, Madelein, Marja, Sygrid, Hans, Myrthe S., Robbert, Jonathan, Wieke, Anouk, Danique, Jeannette, Esther, Sanne, Roald, Ocatavio, Marenka, Marieke, Harmen, Jeffrey, Maraike, Gerrit, Marouska, Didin, Dan, Tinka; bedankt voor de mooie jaren!
Een bijzonder woord van dank aan de leden van de oude garde van V4.131, harde kern, schaduwgroep, vedettes, en puzzelaars; Bedankt voor de vriendschappen die zich ook buiten de muren van het ziekenhuis gevormd hebben en voorzetten. Ik hoop de komende jaren nog vele geplande of ongeplande (escalatie)borrels met jullie te mogen drinken, en dat ik met veel van jullie in de toekomst kan blijven samenwerken.

Astrid en Laura, het idee dat ik had voor de cover van dit proefschrift is dankzij jullie tot een prachtig eindresultaat gekomen, ik had mij het niet mooier kunnen voorstellen.

Een belangrijke factor in het intellectuele en creatieve proces waaraan een proefschrift wordt onderworpen, is de aanwezigheid van een breed en kleurrijk sociaal vangnet. Onderstaande woorden zijn gericht aan voor mij zeer dierbare vrienden en familie.

JC Moià, lieve meiden, bedankt voor de gezellige studentenjaren als *jaarclub van de eeuw* in Groningen en als hechte vriendengroep door heel Europa na onze studietijd. Behalve diepgaande gesprekken over de bijzondere momenten die we met elkaar meemaken

vind ik het erg fijn dat we als afwisseling ook (veel) niet-intellectuele gesprekken kunnen voeren.
Bernadette, van de Tellegenstraat tot onze verdedigingen in het Academiegebouw: bedankt voor je bijzondere vriendschap, het sparren over de uitdagingen van een MD/PhD-traject, samen lunchen en hardlopen, en natuurlijk de geweldige roadtrips naar congressen. Ik ben vereerd als paranimf te mogen optreden op 13 november.
Vakantiehuisclub; we hebben nog een aantal jaren om onze droom te verwezenlijken. Tot het zover is weet ik dat we nog veel mooie momenten tegemoet gaan!

Reza, Souri, en Pouya, bedankt voor jullie steun op afstand, de etentjes in Leeuwarden en voor jullie gezin waardoor Behrouz de bijzondere man is geworden die ik heb leren kennen.

Jos en Bernadette Bon. Bedankt voor jullie vriendschap vanaf mijn vroegste herinneringen en voor jullie betrokkenheid bij ons gezin. Lianne, als oudste vriendin heb je altijd een bijzondere plek in mijn leven. Ik verheug mij er ontzettend op mijn “neefje” te ontmoeten in oktober.

André en Zwannie. Hoewel Portugal een stuk verder weg is dan Bellingwolde blijft jullie interesse en enthousiasme altijd voelbaar aanwezig, bedankt voor jullie vriendschap.

Lieve mama en papa, hoe meer ik mijzelf ontwikkel, hoe meer eigenschappen ik van jullie in mijzelf herken. Pap, het doet mij ontzettend veel verdriet dat jij dit proefschrift niet kunt zien en niet aanwezig bent bij één van de belangrijkste mijlpalen in mijn carrière. Mama, bedankt dat je de herinnering aan papa levendig houdt, en altijd trots bent voor twee. De weekenden in Nieuw-Vennep voelen dankzij jou altijd als thuis. Lennard, onze sterke band is in mijn ogen niet alleen ontzettend bijzonder, maar hebben we grotendeels te danken aan het warme gezin waarin we zijn opgegroeid. Bedankt voor het altijd optreden als grote broer en de vurige discussies waarin je mij scherp houdt over de meest uiteenlopende onderwerpen.
Mama en Lennard, bedankt voor alles, ik zou mij geen beter gezin kunnen wensen.

Lieve Behrouz, de kracht van onze relatie heeft zich de afgelopen jaren keer op keer bewezen. Juist omdat we zo veel van elkaar verschillen en beiden een sterk gevoel van zelfstandigheid hebben passen we zo goed bij elkaar. Ik zou een tweede proefschrift kunnen schrijven gevuld met herinneringen waarvoor ik je zou willen bedanken, maar liever steek ik mijn tijd in het creëren van nieuwe.

- Myrthe de Koning -

# List of publications and Curriculum Vitae

## LIST OF PUBLICATIONS

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## CURRICULUM VITAE

Onze gangmaker Myrthe Elisabeth de Koning werd geboren in Nieuw Vennep op 11 oktober 1989. In dit dorp in de Haarlemmermeer woonde ze tot het moment dat ze ging studeren. Nadat ze in 2007 slaagde voor haar Gymnasium aan het Rijnlands Lyceum te Oegstgeest, werd ze uitgeloot voor de studie Geneeskunde. Ze besloot toen een reis te maken door Midden-Amerika. In 2008 werd ze tot haar grote blijdschap wél ingeloot aan de Rijksuniversiteit Groningen. Gedurende de Bachelorfase genoot ze met volle teugen van het studentenleven. Aan het begin van de masterfase startte ze met haar wetenschappelijke stage naar de ketenzorg van middelzwaar tot ernstig traumatisch hersenletsel. Dit gebeurde onder begeleiding van haar latere promotoren Joukje van der Naalt en Joke Spikman, ofwel; “de bazen”. In 2012 solliciteerde ze succesvol voor een MD/PhD traject, waardoor zij zich tot onze vreugde bij ons in de UPFRONT gelederen kon voegen. Zij doorliep gedurende deze periode ook haar coschappen, waarbij zij, heel bewonderenswaardig, altijd nauw betrokken bleef bij het onderzoek. Wij hadden het voorrecht om menig nationaal en internationaal congres met haar te bezoeken, waar zij met haar voordrachten telkens het publiek wist te interesseren en enthousiasmeren. Op 11 oktober zal ze haar proefschrift verdedigen en afstuderen aan de Rijksuniversiteit Groningen. Myrthe woont samen in Groningen met Behrouz Fard en Mojo Poes.

Hans van der Horn en Myrthe Scheenen